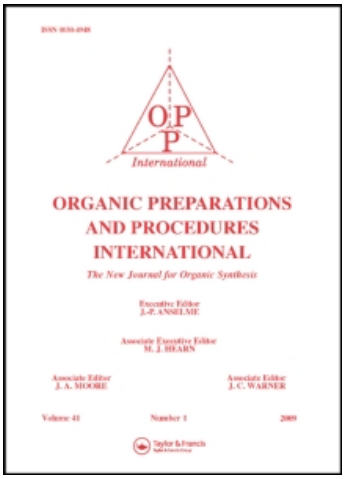

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ELECTROPHILE MEDIATED HETEROATOM CYCLIZATIONS ONTO C-C π-BONDS. PART 1: HALOGEN AND CHALCOGEN MEDIATED CYCLIZATION

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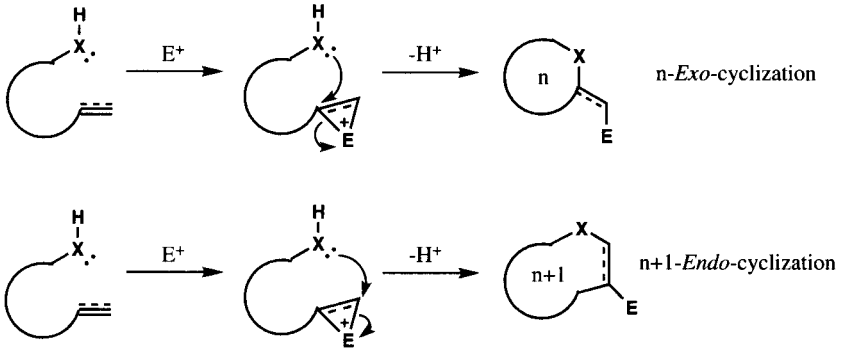
INTRODUCTION AND SCOPE

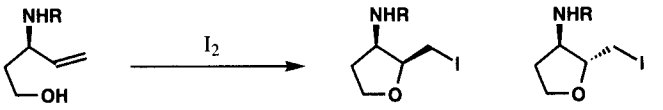
The functionalization of an unsaturated C-C linkage (alkene, alkyne or allene) by the addition of an onium ion forming electrophile followed by cleavage of the resulting onium ion with a nucleophilic reagent is a common and flexible method for the introduction of a plethora of functional groups into organic molecules. The strong stereoelectronic requirement for *trans*- addition of the electrophile and nucleophile coupled with the ability of a large number of heteroatom functional groups to act as the nucleophile in these processes, particularly in an intramolecular sense, has resulted in the exploitation of these reactions for the stereochemically controlled synthesis of a wide range of heterocyclic compounds.



Scheme 1

Cyclization may occur *via* either of a pair of regioisomeric transition states, the so called *exo*- and *endo*-cyclization modes, (*Scheme 1*), and control of regiochemistry in these reactions has been widely studied. The kinetic preference for one cyclization mode over another has been noted by many researchers who have demonstrated the overwhelming kinetic preference for 5-*endo* and 6-*exo* cyclization over their respective 4-*exo* and 7-*endo* alternatives; 5-*exo versus* 6-*endo* cyclization is less clear cut although 5-*exo* products usually predominate.

The π-facial selectivity in the onium ion forming step, and hence the product stereochemistry, is strongly influenced by an allylic heteroatom. The change from *trans*-selectivity to *cis*-selectivity in the cyclization of *N*-substituted 3-aminopent-4-en-1-ols (*Scheme 2*) has been rationalized in terms of steric control predominating in the former and electronic control, *via* π-$\sigma^*_{C(3)\text{-}N}$ interaction, in the latter.[1]



$R=SO_2CF_3$ 93 : 7
R=COMe 24 : 76

Scheme 2

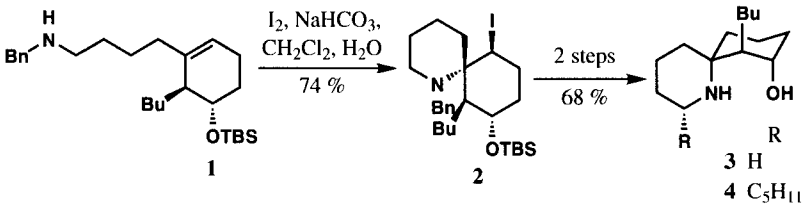
The halogenation, mercuration/hydration and selenylation of C=C and C≡C bonds are widely used in organic synthesis. Their cyclization variants involving the use of intramolecular nucleophiles (cyclofunctionalization reactions) remain the subject of considerable research and advances in this area have been highlighted previously in a number of excellent reports and reviews.[2-7] This review concentrates on the use of halogen and chalcogen containing species as electrophilic reagents with which to induce the cyclization of heteroatom functionality onto unsaturated C-C linkages. It represents a collation of the more important literature published in this area between 1989 and 1995 with particular emphasis being paid to the application of these methods in the syntheses of natural products and other related compounds possessing interesting biological properties.

I. CYCLIZATION ONTO ALKENES

1. Nitrogen Nucleophiles

a) Amines

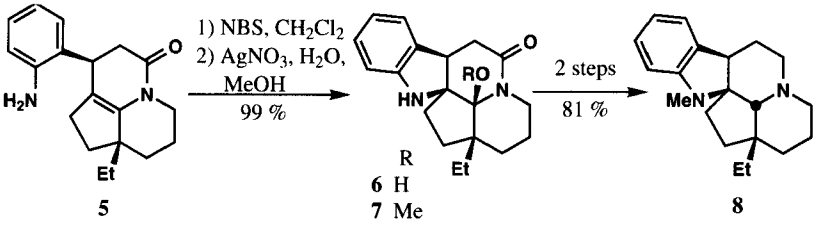
The synthetic utility of halogen sources for the cyclization of alkenylamines[8-16] has been elegantly exploited in the recent syntheses of several alkaloids, drugs and related compounds including quinolone derived antibacterials,[8] tricyclic non-competitive *N*-methyl-D-aspartic acid (NMDA) antagonists,[9] (±)-dependyl-perhydrohistrionicotoxin **3**,[10] (±)-aphanorphine,[11] (+)-croomine,[12] (±)-vallesamidine **8**,[13] and analogues of the novel antibiotic virantmycin.[14,15]



Tanner and Bäckvall[10] have utilized this chemistry in a synthesis of racemic dependyl-perhydrohistrionicotoxin **3** the key step involving the iodine mediated spirocyclization of the secondary amine **1** in basic, biphasic media. Thus **1** cyclized smoothly at room temperature over 3 hrs to yield the *trans*-iodoamine **2** (74%) which was transformed over two steps into the desired amino alcohol **3** (the dependyl analogue of the natural product **4**).

Heathcock has reported[13] the synthesis of racemic vallesamidine **8**, a key step in this elegant synthesis involving the NBS induced cyclization of the aniline intermediate **5**. Cyclization of **5**

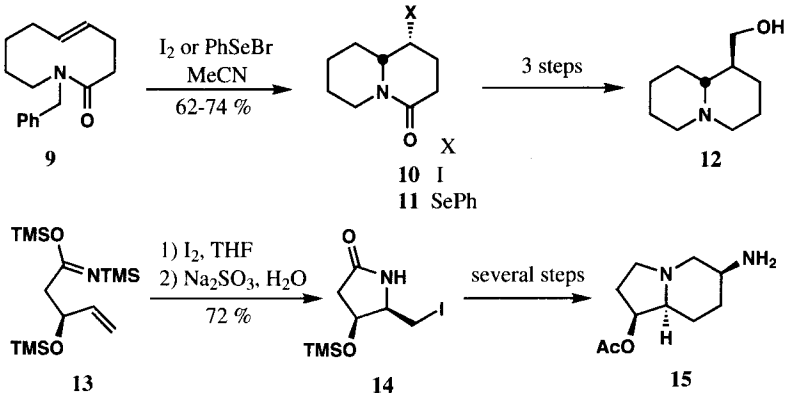
coupled with concomitant hydroxylation/methoxylation (using silver ion to precipitate bromide) resulted in the almost quantitative formation of hemiamidal **6** (79%) and amidal **7** (20%). Reductive methylation of **6** followed by amide reduction using $LiAlH_4$ allowed the formation of the 2,3,3-trialkylindoline alkaloid **8** (81%).



5 8

b) Amides, Carbamates, Sulfonamides, Ureas and Thioureas

Amides have been similarly cyclized[17-24] and this route to lactams has been utilized in the synthesis of several important alkaloids and related materials including (±)-epilupinine **12**,[17,18] and (-)-slaframine **15**,[19] as well as azabicyclo[3.1.1]heptane analogues of epibatidine[20] and novel heterocyclic lactams.[21]

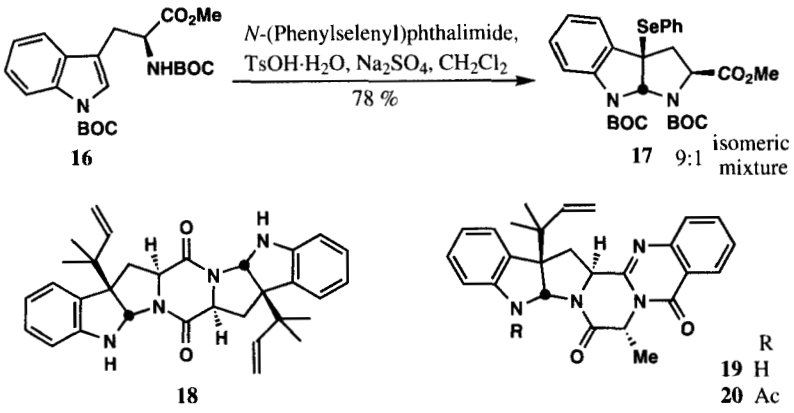


9 12 13 14 15

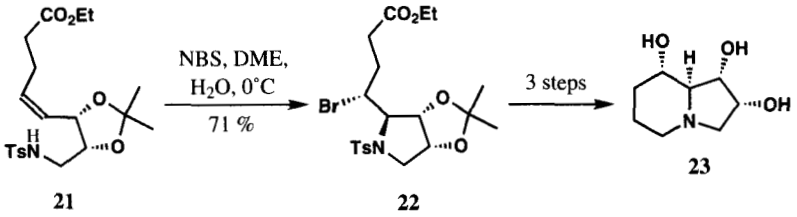
Iodine and selenium induced cyclization of the macrocyclic tertiary amide **9** occurred smoothly to afford **10** and **11** in good yield (62% and 74% respectively), iodide **10** being transformed over three steps to (±)-epilupinine **12**.[17,18] Similarly, iodine mediated cyclization of 3(*S*)-hydroxy-4-pentenamide[19] (as its tris-TMS derivative **13**) afforded the *cis*-substituted γ-lactam **14** (72%) which was successfully converted over several steps to (-)-slaframine **15**.

Carbamates have also been shown to be valuable substrates in these reactions.[23-29] Ward has shown[23,24] that unsaturated carbamates bearing allylic hydroxyl substituents can be cyclized with alkylselenium halides to afford 2,3-disubstituted pyrrolidines and piperidines. The allylic stereocenter has been shown to confer a fair degree of stereocontrol with *cis*-2,3 pyrolidines and *trans*-2,3-piperidines being the preferred stereoisomers.

Danishefsky has utilized the high yielding selenium induced cyclization[25] of the tryptophan derived carbamate **16** and has subsequently transformed the chiral tricycle **17** into amauromine **18**,

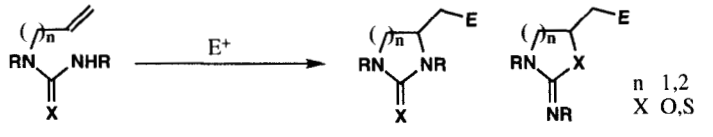


ardeemin **19** and *N*-acetylardeemin **20** (three naturally occurring indole alkaloids). Japanese workers[26] have shown that tellerium salts (PhTeOAc or $PhTeO_2CCF_3$) effect the cyclization of unsaturated carbamates. Halogens have been similarly utilized, Petter having described the low yielding NBS induced cyclization of a carbamate derivative of an unsaturated cyclopropylamine.[27]



Sulfonamides have been cyclized using either chalcogens[23,24] or halogens[30,31] and both *N*-bromosuccinimide and iodine have been utilized in the synthesis of polyhydroxylated indolizidine alkaloids[30] and related glycosidase inhibitors.[31] American workers have highlighted use of NBS in the synthesis of 8,8a-di-*epi*-swainsonine **23**. Cyclization of the 4-toluenesulfonamide derivative **21** occurred smoothly in aqueous 1,2-dimethoxyethane at 0° to afford the *N*-tosylpyrrolidine **22** (4:1 mixture of **22** and its stereoisomer, 71%) which was converted in three steps to **23**.[31]

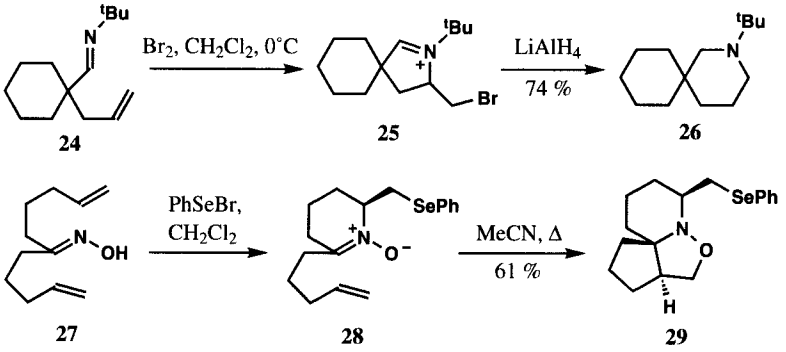
Ureas and thioureas[21,32-34] have been cyclized with NBS, iodine or organoselenium reagents to yield a series of novel nitrogen, oxygen and sulfur heterocycles. However, in many cases the products derived from these ambident nucleophiles comprise mixtures of heterocycles in which nucleophilic participation by nitrogen was accompanied by the alternative nucleophilic participation by oxygen or sulfur, (*Scheme 3*). Formation of the *O*-methyl isoureas or *S*-methyl isothioureas mostly obviated these problems.



Scheme 3

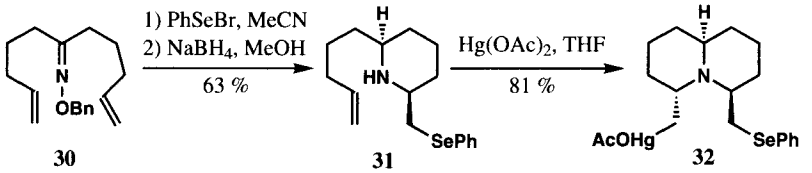
c) Imines, Oximes, Oxime Ethers and Hydroxamic Acids

Phenylselenium bromide[35,36] and halogen[36,37] have been used to induce the cyclization of *N*-alkylated γ,δ–alkenylimines yielding novel heterocyclic frameworks in high yield *via* the intermediacy of cyclic iminium ions. Sodium borohydride or lithium aluminum hydride reduction of these species affords saturated pyrrolidines and piperidines.



The method has proved particularly suitable for the synthesis of spirocyclic amines. Imine **24** cyclized readily to **25** when treated with bromine (CH_2Cl_2, 0°). Reduction then afforded the 2-azaspiro[5.5]-decane **26** (74% over the two steps); this skeleton has been reported as a subunit of several alkaloids.

Grigg and co-workers have shown that chalcogens (PhSeBr and PhSeOTf)[38] and halogens (NBS and iodine)[39] can induce the cyclization of suitably unsaturated oximes to afford nitrone intermediates that undergo rapid 1,3-dipolar cycloaddition reactions to yield complex spiro and fused heterocycles which are precursors of complex spiro-amino alcohols (after reduction of the relatively labile N-O bond). Thus oxime **27**, when treated with PhSeBr, cyclizes to the nitrone **28** which affords the complex tricyclic isoxazolidine **29** in good yield (61% from **27**). Italian workers have also noted the propensity for selenium based electrophiles [$(PhSe)_2SO_4$] to induce the cyclization of unsaturated oximes to afford cyclic nitrones.[40]



The selenium induced cyclization of unsaturated oxime ethers has been recently highlighted[41,42] as a flexible route to both pyrrolidines and piperidines. Unlike the cyclization of oximes, these processes do not suffer from the drawback of the possible intervention of the oxime oxygen atom as an alternative nucleophile and so do not result in the formation of 1,2-oxazine byproducts.[38-40]

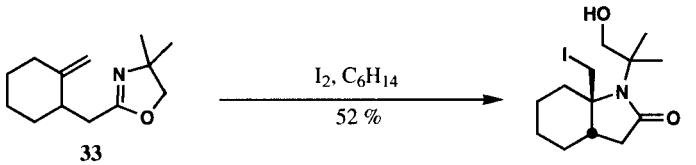
Grigg's group has shown[41] that suitably unsaturated oxime *O*-allyl and *O*-benzyl ethers undergo selenium mediated cyclization with concomitant bromide induced loss of either acrolein or

benzaldehyde to afford a cyclic iminium ion, reduction with a hydride source affording the corresponding secondary amine. Thus oxime ether **30** cyclized to afford amine **31** (63%) which underwent mercury induced cyclization to afford the bicyclic tertiary amine **32** (81%). This approach thus extends the imine cyclization methodology of De Kimpe's group[35-37] that appears to require an *N*-alkylated imine and so necessarily produces only monocyclic tertiary amines.

Tiecco and Testaferri have since shown[42] that, in the absence of other internal C=C bonds, *O*-allyl oxime ethers cyclize upon treatment with electrophilic selenium. Hydrolytic workup furnishes isoxazolidines containing a free NH group; extension of these ideas by the same workers to the *O*-allyl ethers[43] and *C*-allylated derivatives of hydroxamic acids[44] afforded similar selenylated *N*-acylisoxazolidines and *N*-hydroxy-2-pyrrolidinone ring systems.

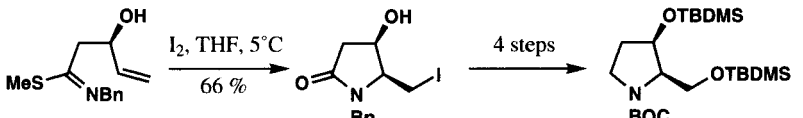
d) Oxazolines, Imidates, Thioimidates and Amidines

Unsaturated oxazolines have been shown to be useful synthetic precursors of lactams. Iodine mediated cyclization of a series of olefinic oxazolines afforded γ-lactams in good to high yield with high levels of stereoselectivity in many cases.[45] For example, oxazoline **33** cyclized smoothly under the influence of iodine in hexane to afford the synthetically useful bicyclic lactam **34** after hydrolytic workup.



33 34

N-Substituted *O*-allyl imidates and amidines have been similarly cyclized using benzeneselenenyl halides,[46] the products after hydrolysis being important in that they contain 1,2,3-related alcohol, selenide and amino derived functionalities.



35 36 37

The iodine induced cyclization of unsaturated thioimidates has been studied by Takahata and Mamose[47-49] who have shown that γ,δ-olefinic thioimidates can be readily transformed into a series of stereospecifically functionalized γ-lactams which are precursors of several naturally occurring alkaloids, α-amino acids and related compounds.[47,48] Nucleophilic participation by the sulfur atom was avoided by initial formation of the *S*-methyl ether; thus thioether **35** cyclized smoothly to afford (after hydrolytic workup) the *cis*-4,5-disubstituted lactam **36** which was converted to lactam **37** (a precursor to (-)-detoxinine) over four steps. Similar reactions involving related thioimidate *S*-methyl ethers has allowed the synthesis of a wide range of biologically active molecules such as slaframine and 3-hydroxy glutamic acid.

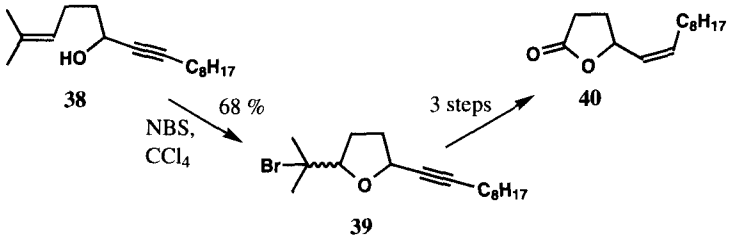
Similar procedures using iodine as an electrophile have been applied by the same group[49] to δ,ε-olefinic thioimidate *S*-methyl ethers and have allowed the synthesis of a series of stereospecifically substituted δ-lactams of use in the synthesis of alkaloids such as coniine and solenopsin.

2. Oxygen Nucleophiles

a) Alcohols and Phenols

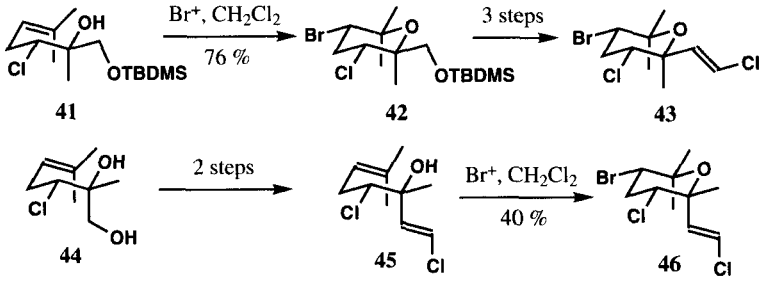
Sources of electrophilic halogen[1,29,50-114] and chalcogen[22,28,29,75-80,115-147] have been extensively utilized by numerous research groups to induce the cyclization of a wide variety of alkenols. Much work has concentrated on the use of either of these flexible series of reagents to synthesize specifically substituted tetrahydrofurans.[149] Amongst the halogens, sources of electrophilic chlorine have been only fleetingly investigated,[50,52] however both bromonium ion[29,50,52-78] and iodonium ion sources[29,76-112] have been extensively studied. Particular emphasis has been placed both upon cyclization regio- and stereo-selectivity in terms of ring size and substitution pattern and on the control of absolute stereochemistry. The factors that control these processes (e.g. the steric[149] and electronic[1] effects of allylic substituents) show the expected sensitivity to substrate structure.

The large number of natural products with diverse and significant biological properties containing tetrahydrofuran or tetrahydropyran ring systems has prompted applications of halonium ion mediated cyclization of alkenols to the syntheses of such targets. Bromonium ion sources have allowed the preparation of many of these, amongst them the Japanese beetle pheromone,[53] terpenes and related compounds,[55-57,61] laurencin and related red-algal metabolites[58-60] (using an interesting enzymic source or Br^+) and more complex bridged ethers[62,64-65] as well as a host of medicinally useful skeletal systems.[66-74]

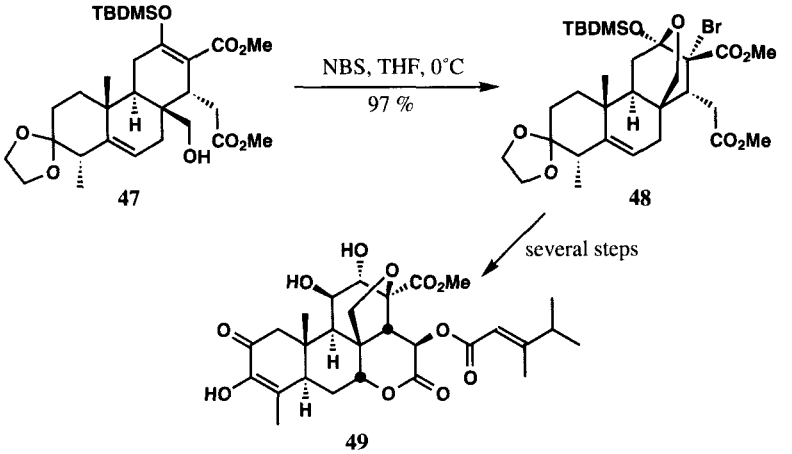


The NBS cyclization of alkenols has been applied to butanolide synthesis such as the γ-lactone **40** (a pheromone from the Japanese beetle);[53] NBS induced cyclization of alkenol **38** afforded an isomeric mixture of the bromides **39** (68%) which was converted over three steps to the desired unsaturated lactone **40**.

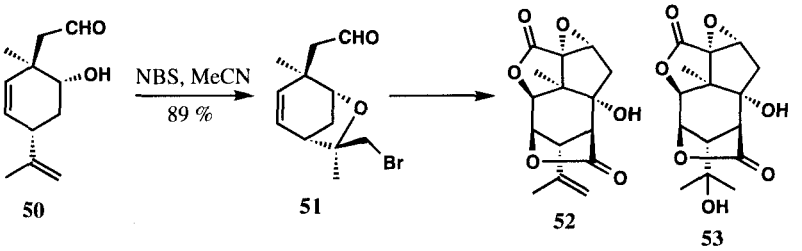
Jung and Lew[55,56] have developed interesting routes to cytotoxic halogenated monoterpenes aplysiapyranoids A and D. Their strategy involves the 2,4,4,6-tetrabromo-cyclohexa-2,5-dienone (TBCO, a source of Br^+) mediated cyclization of unsaturated alcohols. Treatment of **41** with the brominating agent in dichloromethane afforded high yields of **42** which was cleanly tranformed into aplysiapyranoid A **43** over three steps.[55] Homologation of **44** gave alcohol **45** which cyclized to afford aplysiapyranoid D **46**.[56]



The effectiveness of electrophile induced heteroatom cyclization for the construction of bridged rings is illustrated by the total synthesis of (±)-bruceantin **49** using a high yielding bromoetherification procedure to develop the desired complex polycyclic framework.[57] Advanced intermediate **47** cyclized readily over 2 hrs to afford the crystalline bromoether **48** which rearranged under basic conditions to afford the required bicyclo[3.2.1]octane subunit. Several further synthetic transformations afforded the natural product **49** in racemic form.

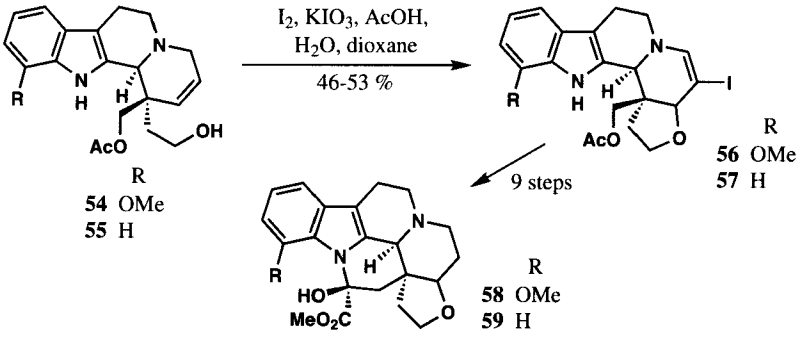


An NBS induced bridged-ring forming cyclization forms part of an enantiospecific synthesis of both the highly toxic GABA antagonist (-)-picrotoxinin **52** and its non-toxic hydrated derivative (-)-picrotin **53**.[62] Cyclization of homochiral **50** in acetonitrile afforded bromoether **51** (89%) which was transformed over several steps to afford both **52** and **53**.

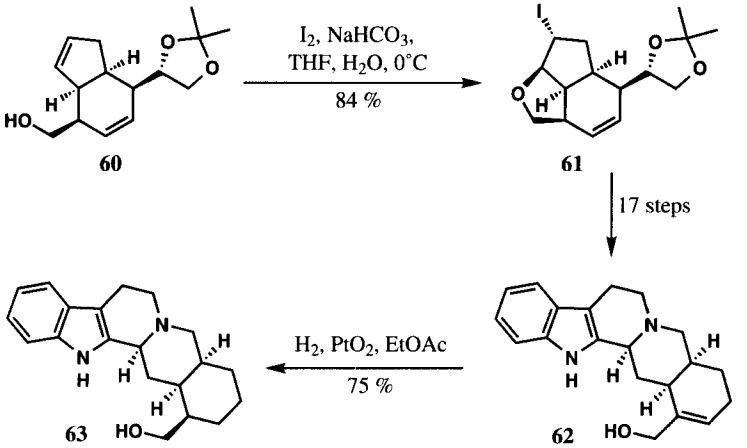


Iodonium ion mediated cyclizations of alkenols have been utilized in the syntheses of many natural products including the indole alkaloid (±)-cuanzine[82] and its 12-desmethoxy derivative,[81] the

novel α-yohimbane alkaloids (-)-nitraraine and (-)-dihydonitranane,[83] homochiral fluorinated analogues of muscarine,[84] a series of novel 13-oxaprostanoids,[85] the C_{17}-C_{22} subunit of the Ca^{2+} and Mg^{2+} transporting polyether antibiotic ionomycin,[86] derivatives of the potent immunosuppressant agent FK506,[87,88] and a series of novel blood platelet aggregation inhibitors.[89] In addition a wide variety of simpler cyclic structures have been prepared by these means.[90-112]

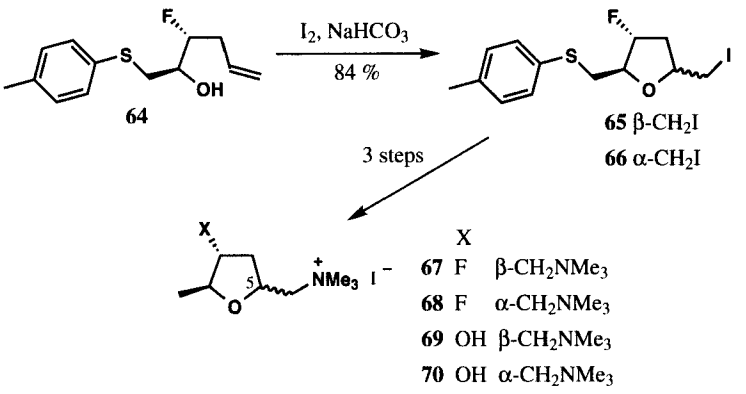


Langlois has utilized iodine mediated cyclization coupled with product oxidation as a key step in the syntheses of (±)-cuanzine **58** and its 12-desmethoxy analogue **59**.[81,82] The advanced intermediates **54** and **55** were oxidatively cyclized to **56** and **57** (I_2, KIO_3) in an aqueous acetic acid/dioxane mixture. Further manipulations afforded the desired natural products **58** and **59**.

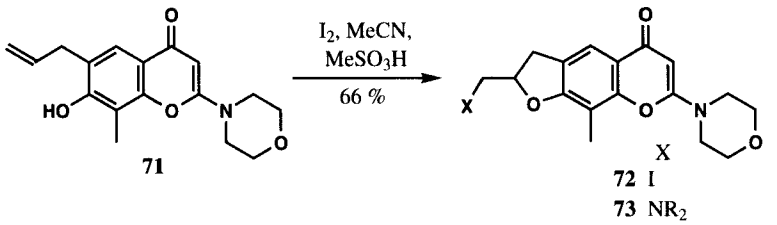


Iodine mediated cyclization of **60** afforded a single iodide **61** in high yield which was transformed over seventeen steps to the structure proposed for the novel α-yohimbane alkaloid (-)-nitraraine and '(-)-dihydronitraraine' **63**. Spectral properties for both **62** and **63** were not consistent with those described for the natural products adding weight to the theory that their structures have previously been wrongly assigned.[83]

Iodoetherification has been used to prepare 3α-fluorinated analogues of both muscarine **69** and *allo*-muscarine **70**.[84] The homochiral fluorinated sulfide **64** cyclized regiospecifically, but with

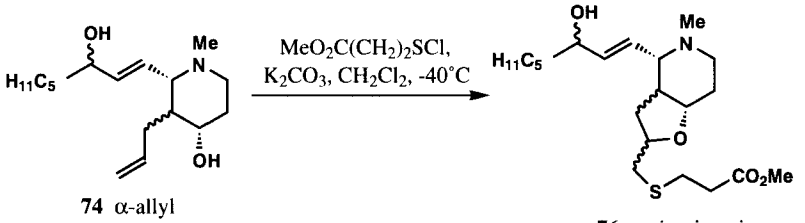


little stereoselectivity, to afford a chromatographically separable 3:2 mixture of tetrahydrofuranyl iodides **65** and **66** (84%) which were each transformed over three steps to the 3α-fluoro analogues **67** and **68** of the natural products **69** and **70**.



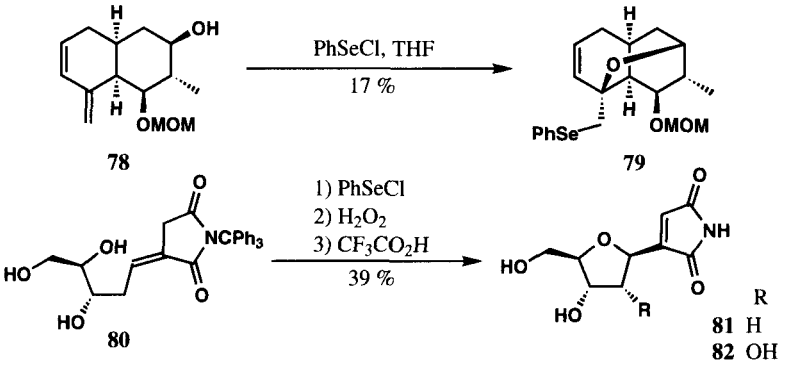
Iodine mediated cyclization of 2-allylphenols has been utilized by workers at Upjohn to prepare a series of 2-morpholinochromanones that show blood platelet aggregation inhibitory properties.[89] Cyclization of phenol **71** (iodine in acidic acetonitrile) afforded the cyclic iodide **72** which was aminated to afford a series of tertiary amines **73**, the thiomorpholine derivative in particular showing good aggregation inhibitory activity.

Unlike selenium sources which have been extensively explored as electrophilic reagents,[75-80,123-143] sources of electrophilic sulfur[115-122] like those of tellurium[122,144-146] have only been sparingly investigated as electrophilic reagents with which to cyclize unsaturated alcohols.



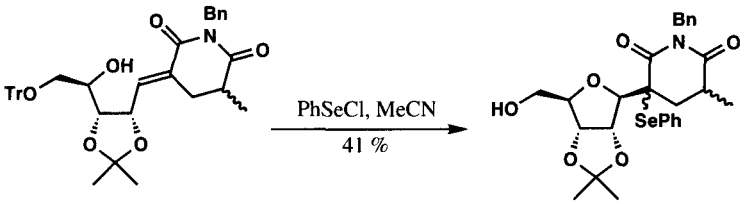
Sulfur, mostly in the form of sulphenyl chlorides, has been used to prepare some novel aza-prostacyclin analogues[115] and a series of novel sulfur containing diuretics.[117] For the former, French

workers have described the cyclization of the piperidinyl alcohols **74**. For example, treatment of **74** and **75** with the propanoate derived sulphenyl chloride in basic dichloromethane at low temperature afforded the cyclized products **76** and **77** (no yields were reported).[115]



78 79 80

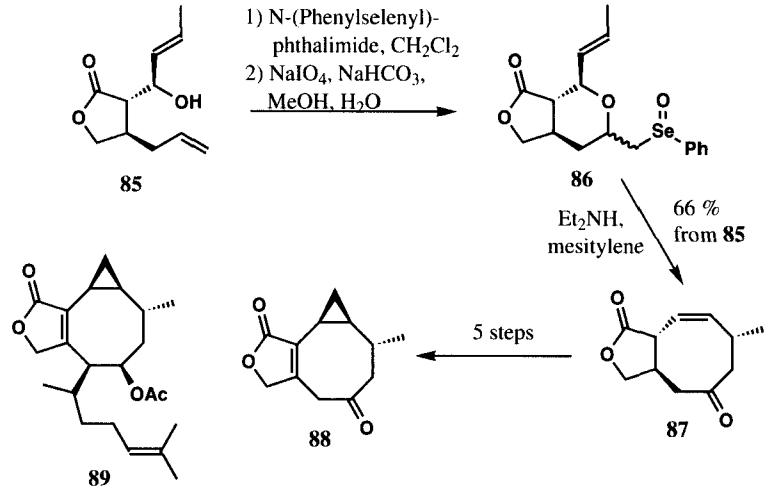
The versatility of selenium mediated cyclization attests both to the reactivity of such electrophiles and the ease of subsequent removal of selenium. Kallmerten has successfully utilized electrophilic selenium in a synthesis of the oxa-bridged octalin system of a macrolide antibiotic;[123] treatment of **78** with PhSeCl in tetrahydrofuran afforded the required tricycle **79** albeit in low yield.



83 84

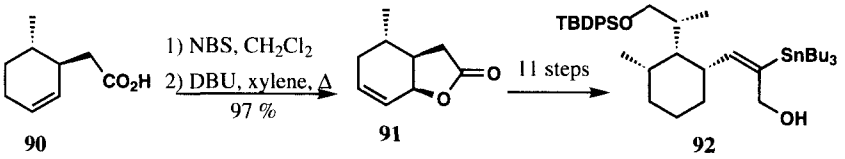
Electrophilic selenium has also found application in the synthesis of nucleoside analogues.[124,126] Cyclization of alcohol **80** followed by selenide oxidation, subsequent selenoxide elimination and acid catalyzed detritylation afforded **81**, the 2'-deoxy analogue of showdomycin **82**.[124] Dutch workers[126] have reported a similar approach to the synthesis of glutarimide *C*-nucleosides, treatment of **83** with PhSeCl in acetonitrile afforded the desired cyclized product **84** (41 %).

An enantiospecific synthesis of the tricyclic core of acetoxycrenulide **89** developed by Paquette relies on an intramolecular selenoetherification, selenoxide elimination and Claisen rearrangement sequence.[127] Treatment of lactone **85** with $PhSe^+$ in dichloromethane followed by selenide oxidation afforded selenoxide **86** which upon heating underwent selenoxide elimination with concomitant Claisen rearrangement to afford the 10-oxabicyclo[6.3.0]-undecene ring structure **87** that was subsequently converted to **88** the tricyclic core of acetoxycrenulide **89**.

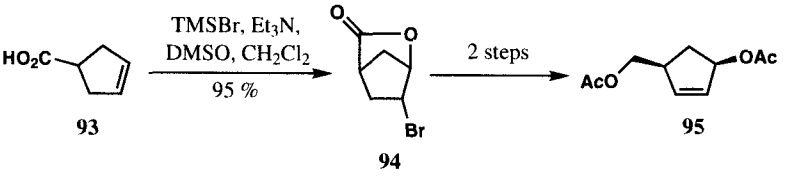


b) Carboxylic Acids

Lactonization mediated by an electrophilic halogen or chalcogen source is well established, especially in those cases involving the use of bromine,[150-156] iodine[77,157-177] and selenium.[22,28,129,133,140,142,143,176-178] The use of both electrophilic sulfur and tellurium are less well developed.[118,122]

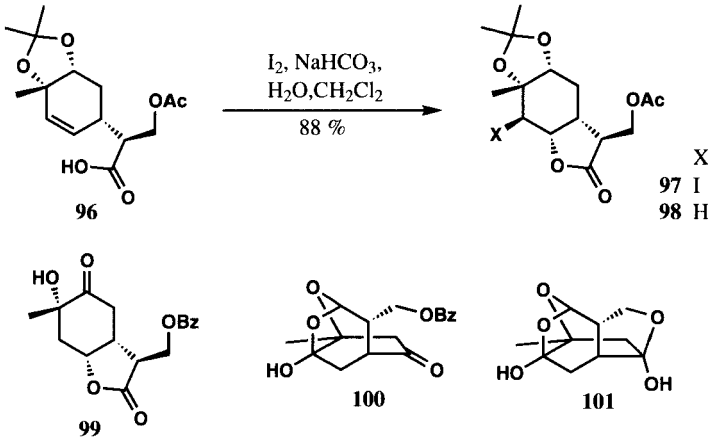


Bromine has found use in syntheses of the tetrahydropyran portion of the ionophore antibiotic tetronomycin,[150] carbocyclic nucleosides *pseudo*-ribofuranosides,[151] a tripeptide equivalent of the right half of the macrocyclic polypeptide echinocandin[152] and a heavily functionalized β-lactone.[153] Semmelhack[150] has prepared stannane **92** (an equivalent of the tetrahydropyran portion of tetronomysin) by lactonization of the unsaturated acid **90**; base catalyzed elimination of hydrogen bromide from **91**. Subsequent manipulation afforded **92**.

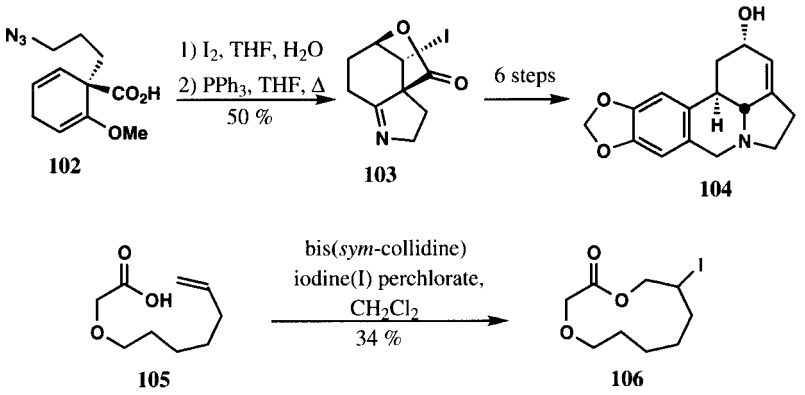


The unsaturated diacetate **95** is available by a simple three stage procedure involving bromolactonization of acid **93** under Iwata's conditions.[155] The resulting bromolactone **94** was reduced and treated with acetic anhydride and base to afford high yields of **95** (a key intermediate in the synthesis of *pseudo*-ribofuranosides and carbocyclic nucleosides).[151]

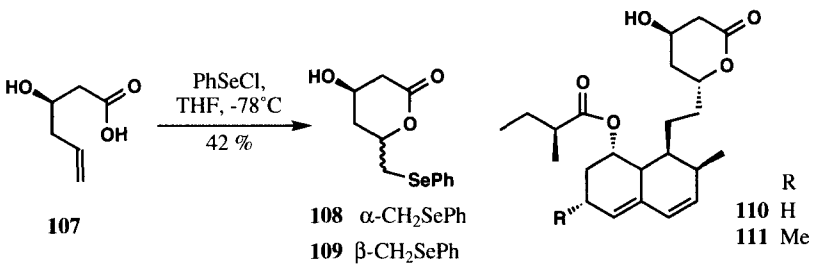
Iodolactonization has been successfully utilized in syntheses of a plethora of natural products and related compounds including the monoterpene paeonilactones A-C,[157,162] (+)-phyllanthocin,[158] a synthon for the A ring of a series of vitamin D_3 metabolites,[159,176] the C_{27}-C_{38} segment of the halichondrins,[160] (+)-paeoniflorigenone,[162] precursors to the zoanthamine alkaloids,[163] (+)-1-deoxylycorine,[164] cadambine,[165] (-)-(6*R*)-massoialactone[166] and analogues of mevinic acid.[177]



Japanese workers have explored the use of iodolactonization in the synthesis of some pharmacologically active monoterpenes from *Paeoniae Radix*.[162] Acid **96** [ten steps from natural (-)-carvone] was cleanly lactonized to yield a single iodide **97** (88%) which afforded **98** upon radical reduction (Bu_3SnH, AIBN; 93%); tricycle **98** was then converted to (+)-paeonilactone C **99**, (+)-paeoniflorigenone **100** and (+)-paeonisuffral **101**.



A short and elegant synthesis of (+)-1-deoxylycorine **104**[164] employs iodolactonization of **102** followed by Staudinger reduction of the azide functionality to afford imine **103** (50%) which was transformed over a further six steps into the natural product **104**. Iodolactonization has recently been shown to be useful for the synthesis of medium ring polyethers;[169] acid **105** afforded moderate yields of the eleven membered lactone **106** when treated with electrophilic iodine in dichloromethane.



107

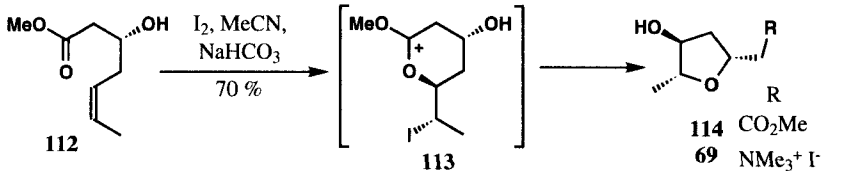
108 α-CH_2SePh
109 β-CH_2SePh

110 H
111 Me

Natural product synthesis by selenolactonization has been less well explored. Amongst the few recent examples, British workers have demonstrated the synthetic utility of selenium in the synthesis of chiral mevinic acid analogues.[177] Selenium induced kinetically controlled cyclization of the β-hydroxy acid **107** (from baker's yeast reduction of the corresponding ketone) at low temperature afforded a 10:1 mixture of the cyclic selenides **108** and **109**. Naturally occurring mevinic acids include (+)-compactin **110** and (+)-mevinolin **111**, both of which are effective as inhibitors of human cholesterol biosynthesis.

c) Amides, Carbamates, Carbonates, Esters and Ureas

These carboxylic acid derivatives in conjunction with electrophilic halogen (particularly iodine) and chalcogen (chiefly selenium) have been utilized for the construction of a number of interesting compounds[11,22,32,33,90,96,179-189] including (-)-muscarine,[179] (-)-anisomycin,[181] *cis*- and *trans*-4-hydroxy-L-proline,[183] the tetrahydropyran subunit of the polyether nigericin[184] and the C_{14}-C_{25} spiroketal subunit of calyculin.[187]



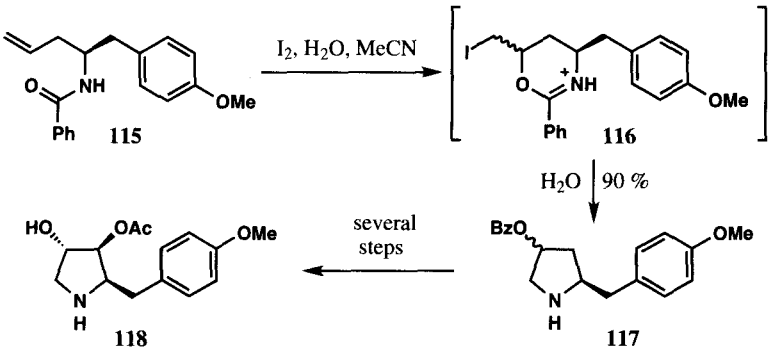
112

113

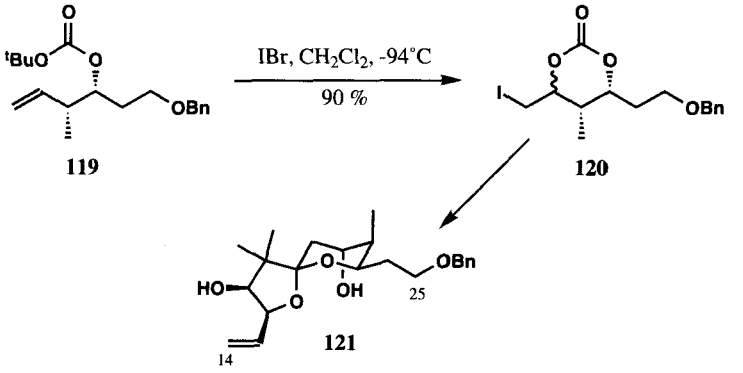
114 CO_2Me
69 $NMe_3^+ I^-$

Knight's group[179] have used iodine mediated cyclization of an unsaturated ester to develop a short route to (-)-muscarine **69** (the unnatural enantiomer). Treatment of *cis*-alkenyl ester **112** with iodine in dry acetonitrile under basic conditions resulted in an unusual 6-*exo*-cyclization to **113** *via* interception of the intermediate iodonium ion by the ester group. Addition of water followed by intramolecular iodide displacement by the alcoholic functionality afforded the cyclic hydroxyester **114** (70%) which was subsequently converted to **69**.

Japanese workers[181] have developed a short synthesis of (-)-anisomycin **118** involving iodocyclization of unsaturated amide **115**. Treatment of **115** with iodine in wet acetonitrile afforded the amine **117** presumably *via* hydrolysis of the cyclic oximinium ion **116** followed by displacement of iodide by the amine so liberated; amine **117** was readily converted over several steps into the natural product **118**.

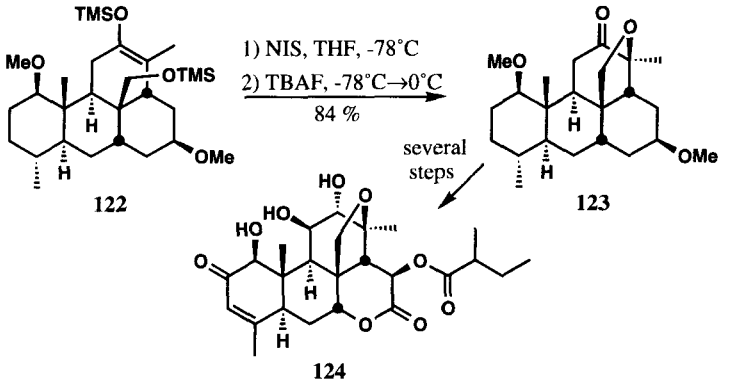


Iodocyclization of the appropriate carbonate provides access to the C_{14}-C_{25} spiroketal subunit of calyculin.[187] Treatment of the unsaturated carbonate **119** with iodine monobromide at low temperature affords high yields of the cyclic carbonate **120**; further synthetic elaboration of **120** gave the required subunit **121**.



d) Ethers and Silyl Ethers

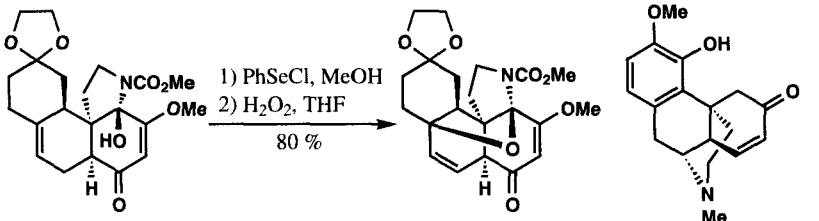
Small or activated ethers (e.g. methyl, benzyl or *tert*-butyl)[29,65,114,131,146,190-192] and silyl ethers[65,114,131,192] have been cyclized using a variety of electrophilic reagents. Steroidal methyl ethers[75] have been cyclized with sources of bromine and iodine, aryltellurium trichlorides cyclize benzyl ethers[146] and French workers have described the iodine mediated cyclization of *tert*-butyl ethers.[191,192]



This type of cyclization has been under utilized in natural product synthesis although 2,6-dichlorobenzyl ethers have been utilized in recent syntheses of (+)-muscarine **69**[190] whilst treatment of the silyl ether **122** with *N*-iodosuccinimide at low temperature (in a manner analogous to that for cyclization of alcohol **47** highlighted in section 2.2.1 for the synthesis of tetrahydropyran **48**) followed by *in situ* desilylation afforded the pentacyclic ketone **123** (84%) which was successfully transformed over several steps to simalikalactone D **124**.[193]

e) Miscellaneous

A variety of electrophilic species have been used to induce cyclization of other functional groups containing nucleophilic oxygen including a wide variety of ketones and β-keto esters,[22,140-142,194,195] oximes,[38,39] hydroxamic acids,[43,44] epoxides,[196] hydroperoxides,[197] hemiamidals,[198] acetals and ketals,[131,199-201] and isoxazolines.[202-205]



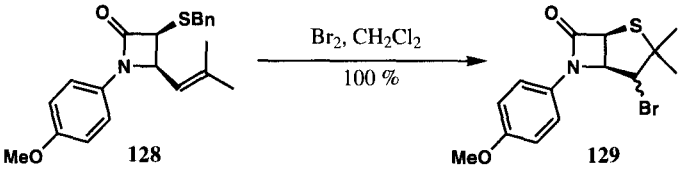
125 126 127

Tius and Kerr have described the use of a hemiamidal cyclization in the synthesis of the morphinan alkaloid (±)-thebainone A **127**.[199] Treatment of the hemiamidal **125** with PhSeCl in methanol resulted in cyclization to afford the selenoether which was oxidized at selenium to afford **126** after selenoxide elimination. Several further synthetic steps allowed the synthesis of the desired alkaloid **127** as well as constituting formal syntheses of both racemic β-thebainone A and morphine.

3. Sulfur Nucleophiles

a) Sulfides and Thioketals

Sources of electrophilic halogen (Br_2, I_2, $C_5H_5NBr_3$) effect the cyclization of alkenyl sulfides and thioketals.[189,206-209] Substrates containing the sensitive β-lactam ring can be employed in such processes. Thus treatment of β-lactam **128** with bromine in dichloromethane resulted in the quantitative cyclization to afford the novel penicillin analogue **129** as a 5:1 epimeric mixture of α- and β-bromo isomers.[208]



128 129

b) Thioureas

Thioureas have been cyclized through sulfur onto intramolecular alkenes using iodine in dichloromethane to afford dihydrothiazoles and dihydrothiazines.[34]

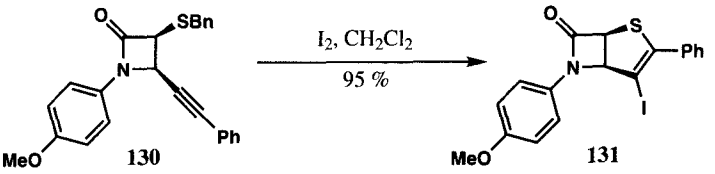
II. CYCLIZATION ONTO ALKYNES

1. Oxygen Nucleophiles (Carboxylic Acids)

Little research has been carried out in this area although the kinetics of iodocyclization have been reported[210] and Back has described[143] the cyclization of 5-pentynoic acid induced by benzeneselenenyl 4-toluenesulfonate to afford an unsaturated γ-lactone (16% yield).

2. Sulfur Nucleophiles (Sulfides and Thioketals)

Alkynyl sulfides and thioketals have been cyclized using bromine,[207,208,211] iodine,[207,208,209,211] and phenylsulphenyl chloride.[211] Turos' group have described the use of halogens to prepare five-, six- and seven-membered sulfur containing heterocycles[207] from alkynyl sulfides and have applied analogous methodology to a series of β-lactam sulfides. Thus treatment of benzyl sulfide **130** with iodine in dichloromethane resulted in rapid 5-*endo*-dig cyclization to afford the penem analogue **131**.



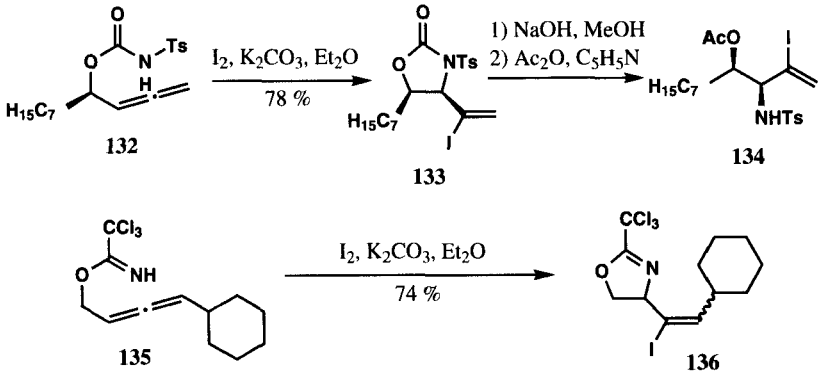
Japanese workers have recently described the synthesis of *S*-phenyl benzothiophenium salts by the cyclization of 2-alkynyl diarylsulfides using Br_2 and PhSCl (81-85% yields).[211]

III. CYCLIZATION ONTO ALLENES

1. Nitrogen Nucleophiles (Carbamates and Imidates)

Friesen and co-workers have developed methodology to allow the iodocyclization of suitably unsaturated allenic carbamates and imidates[212-214] allowing ready access to 1,2-amino alcohols containing neighboring alkene functionality.

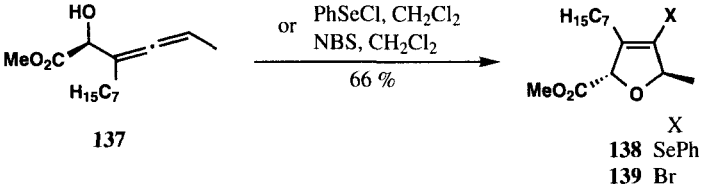
Treatment of allenyl carbamate **132** with iodine and potassium carbonate in diethyl ether afforded the cyclized product **133** in high yield; subsequent carbamate hydrolysis followed by acetylation afforded the versatile amino alcohol derivative **134**.[212] In a later paper,[213] the same workers described the ozonolysis of compounds related to **134** to afford α-amino-β-hydroxy acids. Allenic imidates have been cyclized under similar conditions, imidate **135** reacted smoothly with iodine to afford the cyclic 1,2-amino alcohol derivative **136** in good yield as a 19:1 mixture of (*Z*)- and (*E*)-isomers.[214]



2. Oxygen Nucleophiles

a) Alcohols

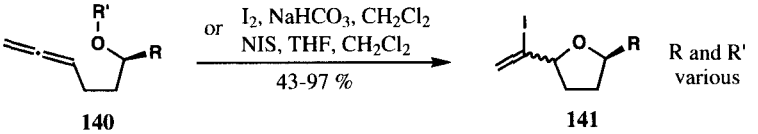
Little work has been reported concerning the cyclization of allenic alcohols using halogen or chalcogen sources.[215,216] Marshall has shown that allenic alcohols can be cyclized with both *N*-bromocuccinimide and phenylselenenyl chloride to afford highly substituted 2,5-dihydrofurans.[215] Treatment of allenol **137** with either PhSeCl or NBS in dichloromethane at room temperature resulted in rapid cyclization to afford 2,3,4,5-tetra-substituted 2,5-dihydrofurans **138** and **139** in good yield; in the case of selenium induced cyclization, small amounts (17%) of the alternative non-cyclized product resulting from the addition of phenylselenenyl chloride across the terminal olefin of the allene moiety were formed.



Walkup utilized similar conditions with iodine or *N*-iodosuccinimide as electrophiles to prepare tetrahydrofurans in good yields but with only moderate levels of stereoselectivity.[216]

b) Ethers and Silyl Ethers

Allenic ethers and silyl ethers cyclize in a manner similar to the corresponding alcohols but with much enhanced levels of stereoselectivity.[216] Treatment of ethers or silyl ethers **140** with electrophilic iodine (I_2 or NIS) resulted in cyclization to tetrahydrofurans **141** (*cis:trans* ratios of up to 98:2); such compounds have been highlighted as useful precursors of many tetrahydrofuran containing natural products including nucleosides, nucleotides and polyether antibiotics.



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