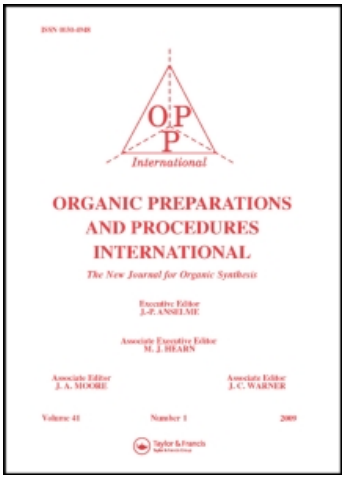

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SYNTHESIS AND CLEAVAGE OF LACTONES AND THIOLACTONES. APPLICATIONS IN ORGANIC SYNTHESIS. A REVIEW

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SYNTHESIS AND CLEAVAGE OF LACTONES AND THIOLACTONES. APPLICATIONS IN ORGANIC SYNTHESIS. A REVIEW

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The review is dedicated to Dr. Oliver E. Edwards on the occasion of his 87th anniversary.

SYNTHESIS AND CLEAVAGE OF LACTONES AND THIOLACTONES. APPLICATIONS IN ORGANIC SYNTHESIS. A REVIEW

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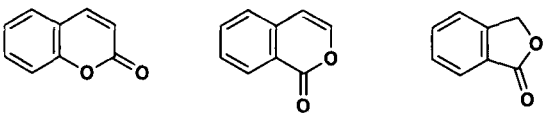
INTRODUCTION

Lactones are a special group of intramolecular esters characterized by enhanced reactivity and extraordinary synthetic utility.[1-7]

Scheme 1 **1**

Lactones are cyclic esters derived from aliphatic hydroxy acids (*Scheme 1*) and are named by adding "-olide" to the name of the hydrocarbon with the same number of carbon atoms, *e.g.* 3-propanolide (**1**, n = 2) or 4-butanolide (**1**, n = 3). Names derived from trivial names of non-hydroxylated carboxylic acids are also used, *e.g.* γ-butyrolactone (**1**, n = 3), δ-valerolactone (**1**, n = 4). Names based on the nomenclature of heterocycles may also be used for lactones. Thus, γ-butyrolactone is named tetrahydro-2-furanone or dihydro-2(3*H*)-furanone and δ-valerolactone (5-pentanolide) is named tetrahydro-2-pyrone. Trivial names, which are considered to pertain to the small heterocycles such as coumarin **2**, isocoumarin **3** and phthalide **4**, are encountered.



2 **3** **4**

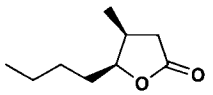
Fig. 1

α-Lactones (**1**, n = 1), being strained three-membered ring compounds, are considered unstable and have been postulated as synthetic intermediates in a number of reactions, for example in the ozonolysis of ketenes and photo-decomposition of β-peroxy lactones.[8,9] Interestingly, perfluorodialkyl α-lactones are stable at –20°C and have been isolated and character-

ized.[8,10] β-Lactones (**1**, n = 2) also have inherent reactivity due to angle and torsional strain of the four-membered ring. As a result, β-lactones undergo a number of useful transformations that make them versatile intermediates for organic synthesis.[11,12] Synthetically useful reactions of β-lactones are for example: thermal decarboxylation at temperatures up to 160°C to give olefins, Lewis acid promoted rearrangement leading to γ-lactones, nucleophilic ring-opening by oxygen-alkyl or oxygen-acyl bond cleavage, reaction with Grignard, organolithium and organocuprate reagents and also with other organometallic nucleophiles, ring opening with ylides, rearrangement leading to ring expansion and electrophilic reaction of β-lactone enolate. Excellent review articles by Pommier and Pons[11,13] and Yang and Romo[12] and Robin and Rousseau[14] on the synthesis and transformations of β-lactones have been published. A review of β-lactones as reactive intermediates for natural product total synthesis has also appeared.[15]

The most stable are γ-lactones (**1**, n = 3) and δ-lactones (**1**, n = 4). The high rate of ring closure observed in the five-membered ring is due to a relatively low activation enthalpy, which reflects the low strain in the ring. As a consequence, most naturally occurring lactones contain stable five- or six-membered rings. Seven-membered lactones, which have shown various interesting biological activities, are however difficult to prepare by conventional methods.[16] A typical lactone, γ-butyrolactone is one of the major industrial chemicals with application in the production of pharmaceuticals, pesticides and petrochemicals and can be used as a raw material for making α-pyrrolidone, vitamin B_1, cyclopropamine and butyric acid to name only a few.

Lactones are important contributors to the flavour of many fruits and dairy products. "Whiskey lactone" (*cis*- and *trans*-3-methyl-4-octanolide) **5** and **6**, for example, also known as "oak" lactone, can be found in spirits and wines.[17,18] Very common flavor compounds used in the perfume and food industries[19] are low molecular weight lactones. γ-Lactones[3] are also useful intermediates in the synthesis of many classes of natural products[19,20] such as antibiotics, lignans, pheromones, alkaloids, antileukemics, etc.



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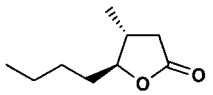

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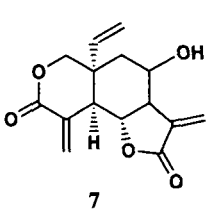
Fig. 2

It is well known that the α-methylene carbonyl moiety is a characteristic feature of many biologically active substances. α-Methylene-γ-lactones that belong to this class of compounds have received much attention due to the broad spectrum of biological activity exibited by natural products containing this structural feature.[21-27] These electrophilic lactones have antitumor, cytoxic, phytotoxic, antiinflammatory, antibacterial, antifungal and plant growth inhibitory properties. One interesting example is vernolepin **7**,[28] a sesquiterpene tumor inhibitor, which possesses-in addition to the α-methylene-γ-lactone structural feature-an α-methylene-δ-lactone moiety. Another natural compound is parthenin **8**[28] exhibiting anti-allergenic activity.



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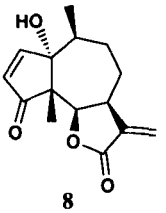

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Fig. 3

In synthesis, α-methylenation of the pre-formed lactone ring has frequently been applied[29] for example in the synthesis of vernolepin, frullanolide and eriolanin. Sesquiterpene lactones with *cis*-and *trans*-fused α-methylene-γ-lactone moieties are a rapidly expanding group of natural products comprising ca. 2000 compounds.[30] Some of them have been shown to possess important biological activity.[30-33] High insect antifeedant activity has been reported for natural sesquiterpene lactones isolated from plants and also for synthetic terpenoid lactones.[34-37] The interest in natural and synthetic compounds has contributed to the development of effective and versatile syntheses of α-methylene-γ-lactones. Synthetic procedures used for the preparation of α-methylene-γ-lactones are presented in reviews published in 1975[38] and 1986[39] and in recent articles by Collins[40-43] and Laduwahetty.[44]

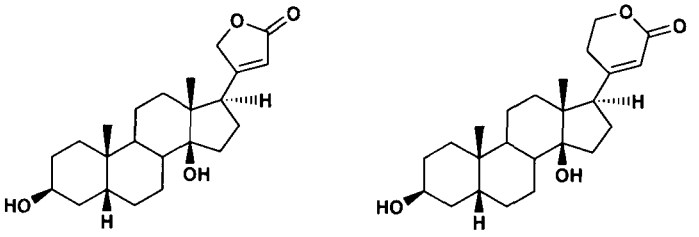
Butenolides, a family of unsaturated lactones, are often encountered among fungi, bacteria and marine organisms called gorgonians[45] and exhibit diverse biological activities.[46] Compounds belonging to this class are usually referred to as α,β-and β,γ-butenolides, **9** and **10**, respectively.

9 **10**

Fig. 4

Many unsaturated natural lactones[5] exhibit cytotoxic and/or antitumor activity. Most of them are α-methylene-γ-lactones, however some 5- and 6-membered endocyclic α,β-unsaturated lactones, for example cardenolides, bufadienolides and withanolides, are also biologically active. Therefore, much effort has been devoted to the synthesis of these compounds and their analogs.[47] Cardenolides[48-50] and bufadienolides[51,52] constitute an important group widely distributed in plants. These steroid conjugates are called cardiac glucosides due to their cardiotonic activity.[49] Digitoxygenin **11**[50,53] obtained from *digitalis* and bufalin **12** are typical aglycones. Cardiac glucosides have been used for centuries to treat heart failure. These compounds and their analogs are synthesized from pregnane derivatives and are considered to be "the most ingested drugs in medicine".[49,54]

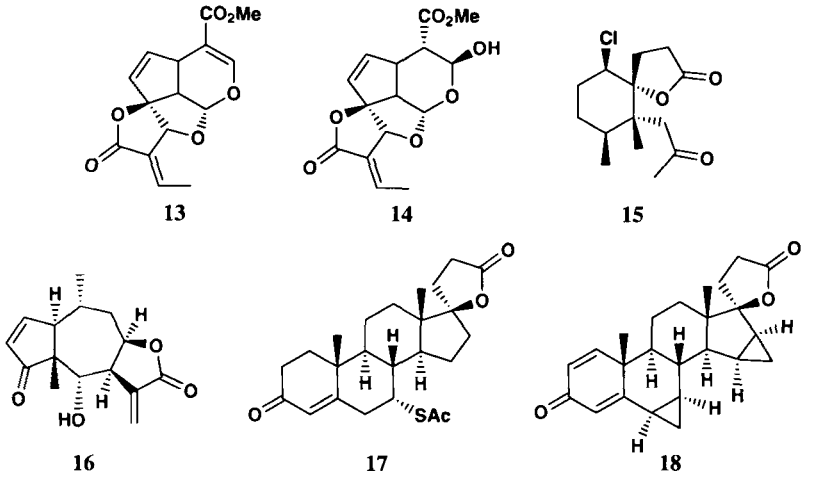
Another interesting group are spirolactones,[55,56] many of them also biologically active.[32,57] Antitumor and antimicrobial agent plumericin **13**, antileukemic iridoid allamandin **14**, and some norsequiterpenoids *e.g.* napalilactone **15**,[57] are examples of naturally occurring



11 12

Fig. 5

spirolactones. Some steroidal spirolactones have antitumor and anti-aldosterone activity, like helanalin **16**,[58] spironolactone **17**[59,60] and spirorenone **18**,[61] respectively. Synthetic approaches to γ- and δ-spirolactones have been reported.[57,62]



13 14 15

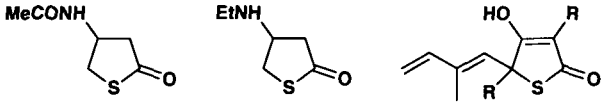
16 17 18

Fig. 6

A large group of natural products are medium ring lactones with the ring size between 8 and 11.[63] Macrocyclic lactones (macrolides)[64,65] are most often 12-, 14- or 16-membered ring compounds [**1**, n = 11, 13, 15]. In macrolide antibiotic erythromycin A, for example, two sugar residues are linked to a 14-membered macrocyclic lactone ring. Larger ring (26-38 membered) polyene macrolides are naturally occurring antifungal agents.[66]

Because of the broad spectrum of biological activity of lactones, their industrial application and enormous synthetic utility, the synthesis of lactones has been extensively investigated. In this review, only the most convenient and general methods used for the preparation of lactones will be summarized. The common occurence of lactones in nature, their diverse chemical properties, high reactivity and diverse transformations are the reason for their extensive application in organic synthesis. Among other reactions, the cleavage of the lactone ring has been most often used in laboratory synthesis of organic compounds and in industrial processes.[67] Cleavage of the lactone ring proceeds under diverse experimental conditions with a variety of reagents, therefore, chemoselectivity of these reactions is frequently observed.

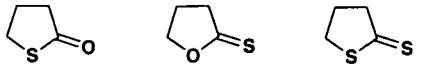
Another interesting group are thio analogs of lactones. In general, small ring heterocycles, and sulfur compounds in particular, are synthetically and biologically important. They are found in fruits and vegetables[68,69] being among the most important and potent flavor compounds,[70] for example, of blackcurrant and grapefruit.[70,71] Thiolactones are often key intermediates in the synthesis of biologically active compounds[72,73] like (+)-biotin,[74-80] anti-HIV agents,[81,82] adenosine receptor antagonists[83] and, for example, intermediates in the synthesis of Raloxifene analogs, potential candidates for the prevention of breast cancer, for control of uterine cancer, and treatment of Alzheimer's disease.[84] In recent years a number of natural products containing a thiolactone moiety have been isolated. Some of them, like thiolactones **19** and **20** and thiolactomycin **21** and thiotetramycin **22** have shown antibiotic activity.[85]



19 **20** **21** R = Me
22 R = Et

Fig. 7

Thio-analogs of lactones, thio- **23**, thiono- **24** and dithiolactones **25** are by far less investigated than lactones themselves. However, homocysteine (2-amino-4-mercaptobutyric acid) and homocysteine thiolactone are molecules of extraordinary biological and biomedical significance.[86] Owing to their important biochemical properties, macrocyclic thiolactones are under intense investigation.[87] Thio- and thionolactones are also versatile intermediates for organic synthesis.[88] In the synthesis of various types of heterocyclic organic compounds, lactones and thiolactones are useful starting materials.[89]



23 **24** **25**

Fig. 8

γ-Thiolactone reactivity results from their lactone character and sulfur content. While β-thiolactones, due to their easy alkylation, have been shown to be of synthetic importance,[90] α-thiolactones, by analogy to α-lactones, are described as intermediates.[91] However, the synthesis of stable α,α-disubstituted α-thiolactones has been reported.[92]

The chemistry of thiolactones, and cleavage reactions in particular, is in many aspects analogous to the behavior of lactones. The specificity of thiolactone reactivity is associated with high nucleophilicity of sulfur. Only selected chemical reactions proceeding with cleavage of the thiolactone ring are included in this review and mainly the five-membered thio-analogs of lactones are considered.

The intention of the authors is to present the main types of reactions accompanied with cleavage of the lactone and thiolactone ring and give emphasis to the reagents used, reaction conditions and synthetic applicability of these processes to the preparation of important organic target molecules. Since the literature concerning cleavage of lactones and thio analogs is enormous, the authors are aware that the review will not provide a complete coverage of the topic. Therefore, any omission of papers dealing with reactivity of lactones and thiolactones is not intentional.

1. SYNTHESIS OF LACTONES. GENERAL METHODS

1. Introduction

Over the years, much attention has been focused on lactone synthesis. Methods for the synthesis of lactones of various types have been reviewed by many authors. The review articles on lactone synthesis are those by Kano[3] and Rousseau.[63] A comprehensive review of lactone synthesis by Wolfe and Ogliaruso appeared in supplement B of Patai "*The chemistry of acid derivatives*" Part 2, published in 1979.[2] There, the reader will find references to previous reviews and an extensive list of publications. Selected chapters of "*March's Advanced Organic Chemistry*" are another excellent source of references on the subject.[1]

In recent years, new methodologies have been developed for selective and effective synthesis of lactones. The new chemistry applied to the synthesis of lactones includes ring-closing methathesis for macrolide construction, palladium catalyzed couplings, carbonylation reaction to incorporate carbon monoxide as the lactone carbonyl as well as enzyme or enzyme mimic catalyzed Baeyer-Villiger oxidations of ketones. Insertion reactions of metal carbenoids has been found valuable for preparating small, medium and large ring lactones. The new methodologies enabled the synthesis of multiply-substituted biologically active complex lactones with high degrees of stereocontrol. These aspects of contemporary lactone synthesis are discussed in detail in excellent review articles by Collins[40-43] and Laduwahetty.[44] In these reviews the reader will find nearly six hundred references pertaining to the synthesis of mono-, bi- and polycyclic lactones as well as medium-ring lactones, spirolactones and macrolides. Seven-membered ring lactones are difficult to synthesize by conventional methods and are prepared mostly by metal-catalyzed reactions.[16] The synthesis of macrocyclic lactones (macrolides) has also been specifically reviewed.[64,65,93,94]

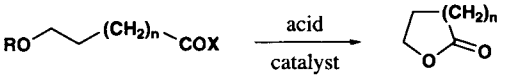
Chiral γ-butyrolactone derivatives have been prepared by enantioselective synthesis from small substrates of natural origin like amino acids, L-ascorbic acid, tartaric acids, monosaccharides or other chiral substrates like sulfoxides, epoxides, or substituted acetylenic acids. Enzymatic reactions, like reduction, oxidation and hydrolysis, have also been applied in the preparation of chiral lactones.[19] However, this aspect of the lactone chemistry will not be reviewed. Some limitations of the subject surveyed have been necessary; accordingly, only the basic, general methods, both classical and recently published, which are of practical importance and may be applied for the synthesis of lactones, will be included in the brief overview of lactone

synthesis. The review focuses mainly on γ-lactones; however, some aspects of β-, δ-, ε- and ω-lactones are also included. Short comments on the scope and limitation of a particular reaction will also be provided.

2. Cyclizations

a) Cyclization of Hydroxyacids and Hydroxyacid Derivatives

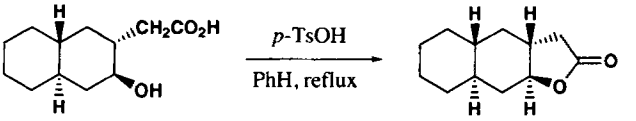
As lactones are intramolecular esters, a useful method for their preparation involves cyclization of hydroxyacids[95-97] or hydroxyacid derivatives - esters and amides - with a free or protected hydroxyl group such as tetrahydropyranyl (THP) or silyl ether (SiR_3).[98-101] Analogously to ester formation[1] these reactions are acid-catalyzed (*Scheme 2*), and various mineral acids have been used as catalyst. In addition to most frequently used mineral acids, camphor sulfonic acid,[102] *p*-toluenesulfonic acid[103,104] and pyridinium *p*-toluenesulfonate, among others, have been used as catalysts. The maximum rate of cyclization was observed in the formation of γ-butyrolactone and it decreased dramatically toward the 8-membered ring lactone.[63] For the unhindered system, γ-hydroxycarboxylates spontaneously cyclize to lactones, especially in the presence of a catalytic amount of mineral acid. Cyclization leading to γ-lactones proceeded usually in good to excellent yield.



n = 0-3; X = OH, OR, NR_2; R = H, THP, SiR_3

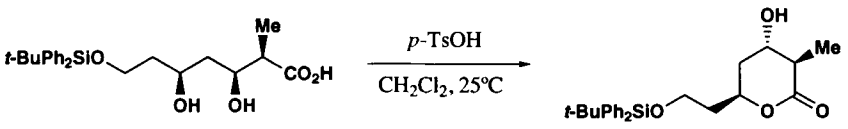
Scheme 2

Lactonization of hydroxy acid **26** proceeded readily when it was heated for 10 minutes in benzene solution containing traces of *p*-toluenesulfonic acid (*p*-TsOH)[105] to give **27** in 97% yield (*Scheme 3*).



26 **Scheme 3** **27** (97%)

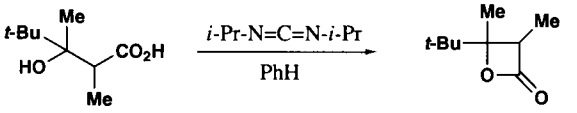
β,δ-Dihydroxy carboxylic acid **28** cyclizes to δ-lactone **29** in 85% yield (*Scheme 4*).[106]



28 **Scheme 4** **29** (85%)

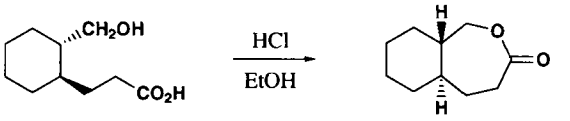
The lactonization of hydroxy carboxylic acids in the presence of mineral acid or on heating can, in general, only be applied to the preparation of γ- and δ-lactones. β-Hydroxy

acids cyclize only in special cases when there is relief from steric compression as in the case of **30**, giving **31** in 61% yield upon reaction with *N,N'*-diisopropylcarbodiimide in benzene (*Scheme 5*).[107]



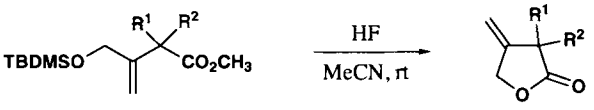
30 **Scheme 5** **31** (61%)

Occasionally, good yields of seven-membered lactones have been observed (*Scheme 6*), *e.g.* **33** from ε-hydroxy acid **32**.[108]



32 **Scheme 6** **33** (72%)

Hydroxy acids and hydroxy esters protected as tetrahydropyranyl (THP),[83] tributylsilyl (TBS),[96,97] benzyloxymethyl (BOM)[78] and *t*-butyldimethylsilyl (TBDMS) ethers[98,99] are hydrolyzed under the influence of an acid prior to cyclization to a lactone. For example, the easily prepared acrylate derivative **34** can easily be transformed to β-methylene-γ-butyrolactones **35a-c** in excellent yield (*Scheme 7*).[99]

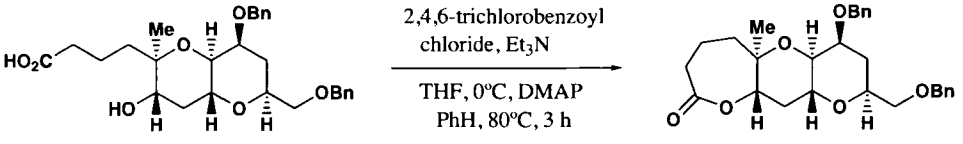


34 **35**

a) R^1, R^2 = Me (92%); *b)* R^1, R^2 = *i*-Pr (94%); *c)* R^1, R^2 = -$(CH_2)_3$- (92%)

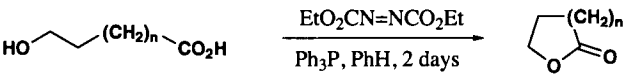
Scheme 7

Under Yamaguchi lactonization conditions (2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0°C, then 4-dimethylaminopyridine, benzene, 80°C) medium and large ring lactones have been prepared from ω-hydroxy acids in excellent yield (>80%).[96] The method has been found effective in the synthesis of multifunctional marine natural products (*Scheme 8*). For example, hydroxy acid **36** gave tricyclic lactone **37** in nearly quantitative yield.[96]



36 **Scheme 8** **37** (97%)

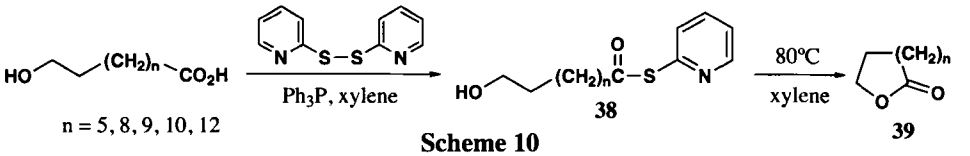
Lactonization of long-chain ω-hydroxy acids proceeds also under dehydrating conditions in the presence of the Mitsunobu reagent (*Scheme 9*).[109]



n = 3 (40%); n = 9 (60%)

Scheme 9

Macrolactonization of ω-hydroxy acids also occurs effectively on treatment with 2,2'-dipyridyl disulfide followed by thermolysis of intermediate ω-hydroxy-2-pyridyl thiolesters **38** in xylene (*Scheme 10*).[110] The isolated yields of macrolides are in the range of 47-80%, with the exception of the highly strained nine-membered ring (**39**, n = 5, 8% yield).[111]

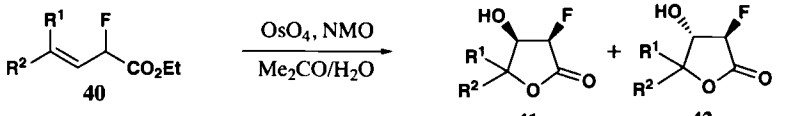


n = 5, 8, 9, 10, 12

Scheme 10

b) The Sharpless Asymmetric Dihydroxylation of Unsaturated Carboxylic Acids

The osmylation of β,γ-unsaturated esters **40** in the presence of *N*-methylmorpholine oxide (NMO) to the respective diol is followed by direct lactonization leading to the formation of β-hydroxy-γ-butyrolactones as a mixture of stereoisomers **41** and **42** (*Scheme 11*).[112]

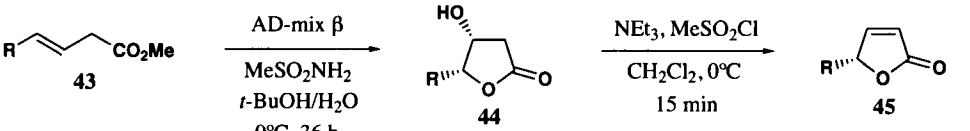


$R^1 = R^2 = Et$
$R^1, R^2 = -(CH_2)_5-$

	41	**42**
	54%	22%
	48%	31%

Scheme 11

The Sharpless asymmetric dihydroxylation of the β,γ- and γ,δ-unsaturated ester employing AD-mix α[101] or AD-mix β[40] followed by *in situ* cyclization of the resulting diol-ester furnished optically active hydroxy γ-lactones which have often been used for the preparation of optically active butenolides.[12,101,113-115] For example, the synthesis of optically active β-hydroxy-γ-lactones **44** and butenolides **45** from β,γ-unsaturated ester **43** has been reported (*Scheme 12*).[113]

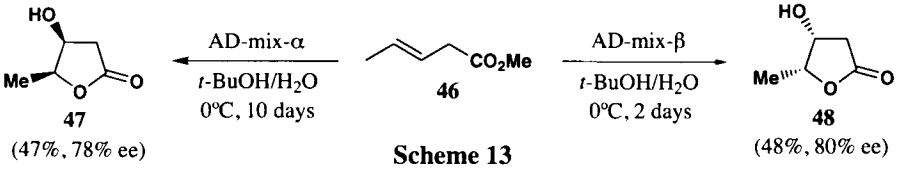


R = *n*-Bu, CH_2OSi*t*-$BuMe_2$

	44		**45**
R	yield (%)	ee(%)	yield (%)
n-Bu	92	97	87
CH_2OSi*t*-$BuMe_2$	88	92	72

Scheme 12

S,S- and *R,R*-β-Hydroxylactones, **47** and **48**, were obtained from the *trans* unsaturated ester **46** with AD-mix-α or AD-mix-β, respectively, in good yield and up to 80% ee (*Scheme 13*).[114]

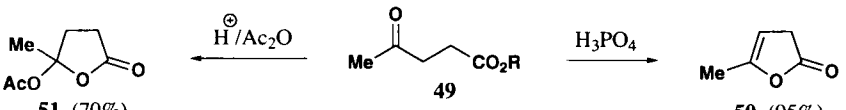


47 (47%, 78% ee) **46** **48** (48%, 80% ee)

Scheme 13

c) Cyclization of Aldehyde and Ketocarboxylic Acids

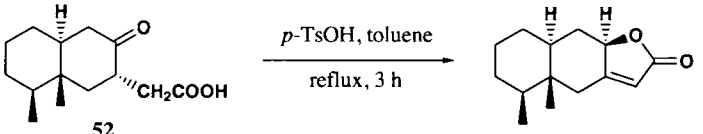
Carboxylic acids and esters containing an aldehyde or ketone carbonyl function at the γ- or δ-position often provide good yields of unsaturated lactones (enol lactones) upon treatment with various acid catalysts. As an example, cyclization of levulinic ester **49** to the α-angelica lactone **50** is presented (*Scheme 14*).[116] The cyclization carried out in the presence of acetic anhydride afforded acetoxy-γ-lactone **51**.[117]



51 (70%) **49** **50** (95%)

Scheme 14

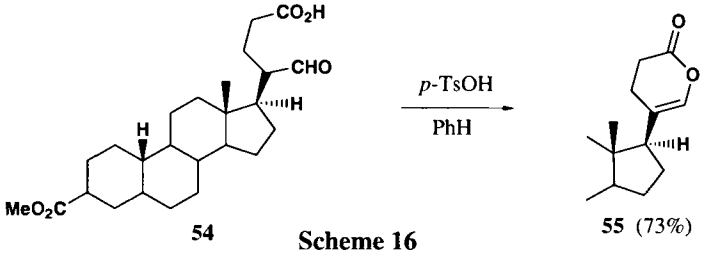
Another typical cyclization of *trans*-fused keto acid **52** in the presence of *p*-toluenesulfonic acid in toluene afforded (±)-11-demethyltetrahydroligularenolide **53** in 94% yield (*Scheme 15*).[118]



52 **53** (94%)

Scheme 15

Acid-catalyzed cyclization of the aldehyde carboxylic acid **54** has been used in the synthesis of bufadienolide **55** (*Scheme 16*).[119]

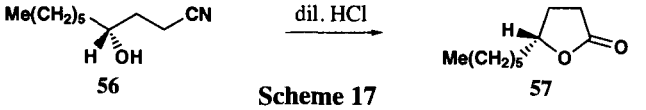


54 **55** (73%)

Scheme 16

d) Cyclization of Hydroxynitriles

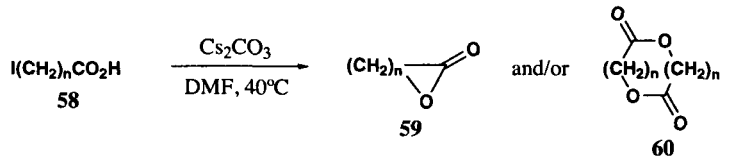
Nitriles with appropriately placed hydroxy groups are also potential substrates for the preparation of lactones under acidic conditions. For example, the reaction of 4-hydroxydecanitrile **56** in the presence of dilute HCl afforded γ-decalactone **57** in quantitative yield (*Scheme 17*).[120]



56 **Scheme 17** **57**

e) Cyclization of Haloacids

The reaction of cesium salts of ω-halo carboxylic acids **58** gives lactones **59** and/or their dimers **60** (*Scheme 18*). The structure of the product largely depends on the ring size of the lactone. The method was reported to be particularly effective for the preparation of macrolides (**59**, n = 10-15) from ω-iodo carboxylic acids. For lower homologues (n = 5, 8) only dimers have been isolated in 88 and 95% yield, respectively.[121]



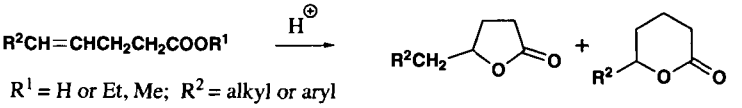
58 **59** **60**

n = 10	33%	54%
n = 11	62%	30%
n = 12	77%	18%
n = 13	72%	13%
n = 14	83%	17%
n = 15	85%	15%

Scheme 18

f) Cyclization of Unsaturated Carboxylic Acids, Esters and Amides

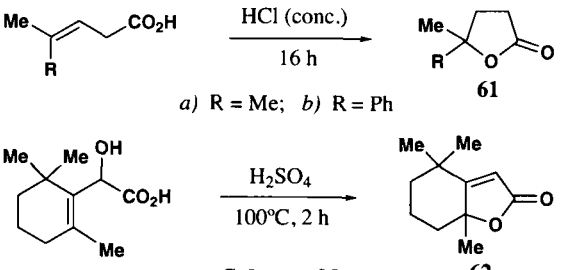
Lactones have been prepared from various unsaturated acids and esters[2,100] upon treatment with acids (*Scheme 19*). The method has largely been applied to the formation of γ-and/or δ-lactones.



R^1 = H or Et, Me; R^2 = alkyl or aryl

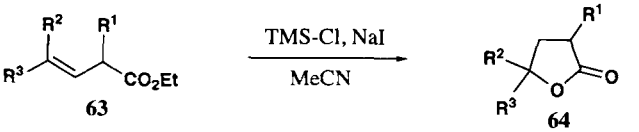
Scheme 19

For example, acid-catalyzed cyclization of 4-methyl- and of 4-phenylpent-3-enoic acid gave 4,4-dimethyl- and 4-methyl-4-phenylbutyrolactone **61a**[122] and **61b**[123], respectively in quantitative yields. In a similar reaction 2,6,6-trimethylcyclohexene-1-glycolic acid was cyclized to γ-lactone **62** with concomitant dehydration of the secondary hydroxyl group (*Scheme 20*).[124]



Scheme 20

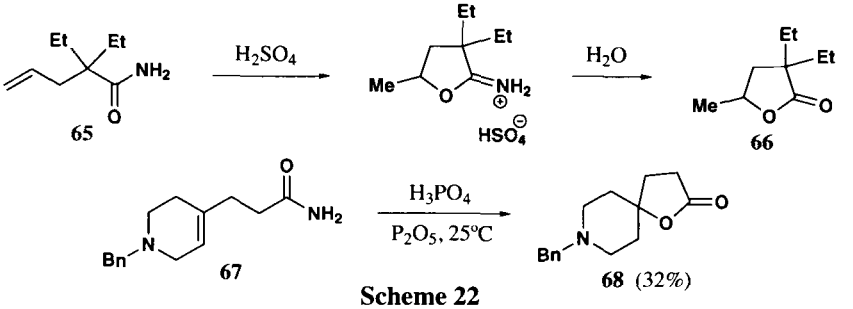
Lactonization has also been observed when β,γ-unsaturated esters **63** were treated with trimethylsilyl iodide (TMS-I) in acetonitrile. γ-Lactones **64** have been isolated in 67-87% yield (*Scheme 21*).[125] α-Alkylidene lactones have also been prepared by this method starting from α-alkylidene β,γ-unsaturated esters.[125]



R^1 = H, R^2, R^3 = -$(CH_2)_5$- (82%); R^1 = Me, R^2, R^3 = -$(CH_2)_5$- (67%);
R^1 = Me, R^2, R^3 = -$(CH_2)_4$- (75%); R^1 = H, R^2 = R^3 = Me (87%)

Scheme 21

Reaction of unsaturated amide **65** with sulfuric acid gave the intermediate immonium salt which could be hydrolyzed into lactone **66**.[126] Polyphosphoric acid was also reported as catalyst for the cyclization of unsaturated amide **67** to spirolactone **68** (*Scheme 22*).[127]

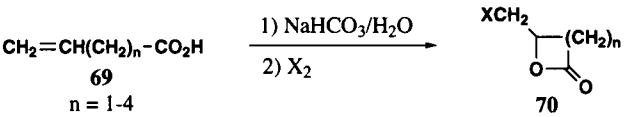


Scheme 22

g) Halolactonization of Unsaturated Carboxylic Acids, Esters and Amides

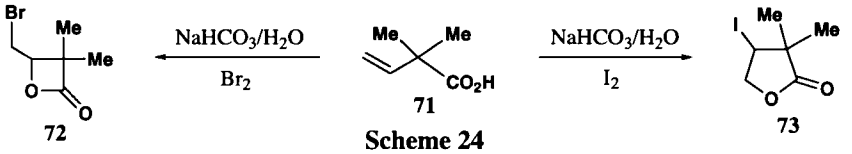
One of the most widely employed methods of lactone synthesis is the electrophile-induced ring closure of unsaturated carboxylic acids. Halolactonization and selenolactonization are probably the most frequently used methods. A review concerning various aspects of cyclo-functionalization has recently appeared.[128] In general, halolactonization of 4,5-ene-carboxylic

acids gives γ-lactones, and that of 5,6-ene-carboxylic acids gives δ-lactones.[129] The reaction of unsaturated carboxylic acids **69** with Br_2 or I_2 in the presence or absence of base affords halolactones **70** (*Scheme 23*).[129] Two alternative mechanisms have been proposed for reactions carried out in polar and aprotic neutral solvents.[129]



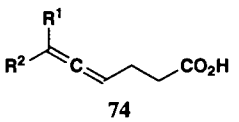
Scheme 23

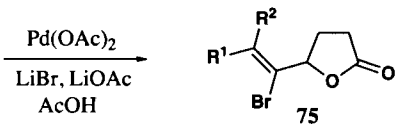
Formation of either cyclic halonium species for reaction in protic solvents or a concerted addition of halogen and carboxyl oxygen to the double bond in aprotic neutral solvents like ether and acetonitrile has been postulated.[129] For symmetrically substituted olefins, the order of preference is: β-lactone > γ-lactone > δ-lactone >> ε-lactone. For instance, the irreversible bromolactonization ($NaHCO_3$ in H_2O, Br_2) of **71** furnishes β-lactone **72**, whereas reversible iodolactonization ($NaHCO_3$ in H_2O, I_2, 24 h) leads to γ-lactone **73** (*Scheme 24*).[129]



Scheme 24

The regiochemistry of halolactonization is generally consistent with Markownikov's rule and depends also on lactone stability. *N*-Bromosuccinimide in DMF as a source of positive bromine in bromolactonization has been used.[130] High yield palladium(II) catalyzed intramolecular bromolactonization of allenic acids **74** to γ-substituted lactones **75** has also been reported,[131] and selected examples are shown in *Scheme 25*. The reaction has been performed in the presence of lithium bromide and palladium acetate as catalyst and in the presence of *p*-benzoquinone or copper(II) acetate as reoxidants.[131] The reaction proceeds by sequential nucleophilic attack of the external (Br^-) and internal carboxylate nucleophiles on the (π-allene) and (π-allyl) palladium complexes.[131]

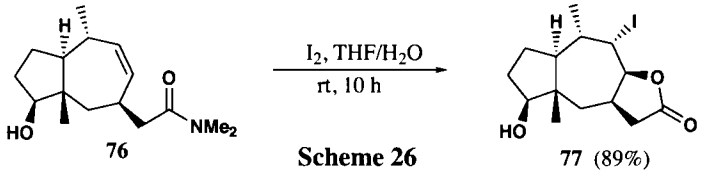




	Yield (%)	Z / E
$R^1 = C_5H_{11}$, $R^2 = H$	84	92:8
$R^1 = i$-Pr, $R^2 = H$	90	37:63
$R^1 = R^2 = Me$	74	
$R^1 = Me$, $R^2 = Et$	67	59:41

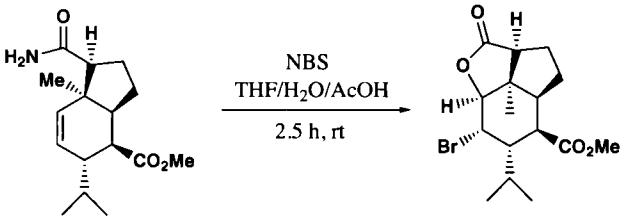
Scheme 25

The efficient and frequently used method of lactone synthesis is iodolactonization of *N,N*-dialkyl γ,δ-unsaturated amides. In a typical procedure iodine in tetrahydrofuran-water mixture was used in preparation of lactone **77** from *N,N*-dimethylamide **76** (*Scheme 26*).[132]



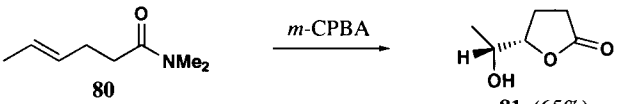
76 **Scheme 26** **77** (89%)

The reaction was also carried out in dimethoxyethane.[133] In a similar reaction, bromination of unsaturated amide **78** with *N*-bromosuccinimide (NBS) led to lactone **79** in 87% yield (*Scheme 27*).[134]



78 **Scheme 27** **79** (87%)

Electrophilic cyclizations involving epoxidation of an unsaturated amide followed by the epoxide ring opening were also reported. As an example the synthesis of lactone **81** from amide **80** upon treatment with *m*-chloroperbenzoic acid (*m*-CPBA) in 65% yield is shown in *Scheme 28*.[135]

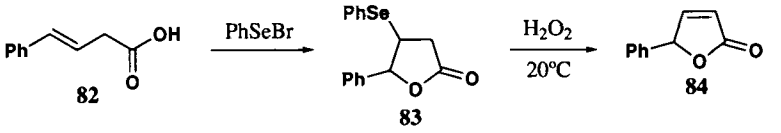


80 **Scheme 28** **81** (65%)

In some electrophilic cyclizations of unsaturated amides a competitive formation of lactones and lactams was observed.[136] The dual reactivity appears to depend on two factors, the nature of the elctrophile and the reaction conditions. A review on electrophilic cyclization of unsaturated amides has recently been published.[136]

h) Selenolactonization of Unsaturated Carboxylic Acids, Esters and Amides

Selenolactonization of unsaturated carboxylic acids[128,137-141] and esters[140,142] has been effected with phenyl selenyl bromide, chloride and triflate[137] as reagent in polar (H_2O, MeOH) and unpolar (CH_2Cl_2) solvents. For instance, the reaction of acid **82** with phenylselenyl bromide in water afforded selenolactone **83** in 49% yield, while the reaction in methylene chloride gave quantitative yield of **83** (*Scheme 29*).[138] Similarly, oxidative deselenylation of **83** gave superior yields of butenolide **84** when carried out in methylene chloride.[138,139] The reaction on solid

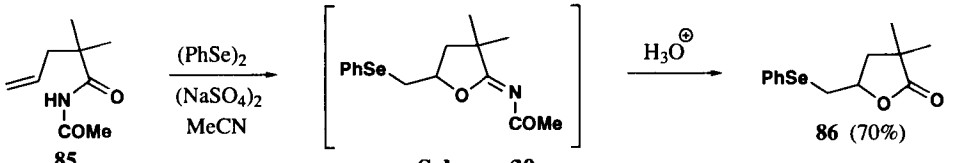


in H_2O	49%	77%
in CH_2Cl_2	100%	90%

Scheme 29

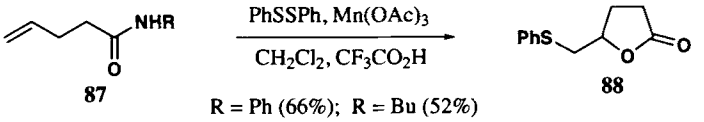
support[138] and asymmetric inter- and intramolecular selenolactonization have recently been reported.[137,139]

Electrophilic cyclization of *N*-alkyl unsaturated amides *via* phenylsulfenylation affords lactones in high yield. Reaction of *N*-acyl unsaturated amide **85** with diphenyldiselenide and sodium persulfate in acetonitrile gave lactone **86** in 70% yield (*Scheme 30*).[143]



Scheme 30

Sulfenylation of unsaturated amide **87** with diphenydisulfide in the presence of manganic acetate to give lactone **88** was also described (*Scheme 31*).[144]



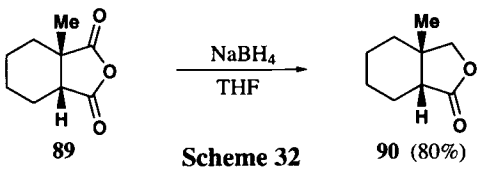
R = Ph (66%); R = Bu (52%)

Scheme 31

3. Reductions

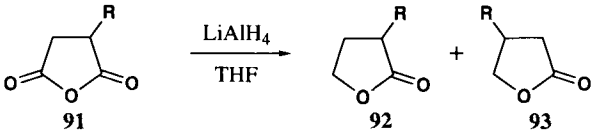
a) Reduction of Cyclic Anhydrides

A variety of reagents such as sodium borohydride, lithium aluminum hydride, lithium tri-*tert*-butoxyaluminumhydride, sodium in ethanol and zinc in acetic acid have been used to reduce numerous acid anhydrides to lactones.[145,146] The reduction of a number of cyclic anhydrides with $NaBH_4$ gave γ- and δ-lactones in good to excellent yield (51-97%).[146] Unsymmetrical anhydrides, *e.g.* **89**, usually undergo reduction with sodium borohydride in tetrahydrofuran or dimethylformamide[146] at the more hindered carbonyl, as shown in *Scheme 32*.[146] The fused



Scheme 32

lactone **90** was isolated in 80% yield. In the same reduction, when $NaBH_4$ was replaced by $NaBH(OMe)_3$, the yield of **90** was 78%.[146] In contrast, however, the regioselectivity of the reduction with LAH is poor and mixtures of α- and β-substituted γ-lactones **92** and **93** are obtained from substituted succinic anhydride **91** (*Scheme 33*)[145]



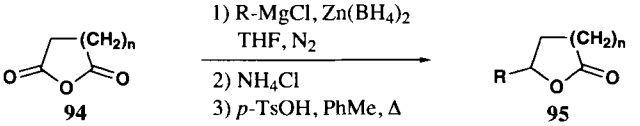
91 **92** **93**

R = Me (69%, **92**:**93** = 1:2.2); R = Ph (72%, **92**:**93** = 3:2)

Scheme 33

b) Reductive Alkylation of Anhydrides

Reductive alkylation of anhydrides **94** with a mixture of Grignard reagent and zinc borohydride[147] followed by cyclization of the intermediate hydroxy acids under moderate acidic conditions has been used for the synthesis of monosubstituted lactones **95**. Overall yields are only moderate (*Scheme 34*); however, due to the simplicity and availability of the starting materials, the reaction could be of interest to prepare related monosubstituted lactones. The yields of δ-lactones were even lower (15%).[147]



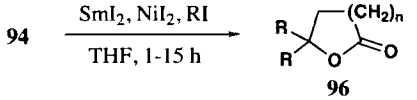
94 **95**

R = Ph, n = 1 (44%); R = $PhCH_2$, n = 1 (16%);
R = C_8H_{17}, n = 1 (28%); R = $PhCH_2$, n = 2 (15%)

Scheme 34

c) Barbier Alkylation of Anhydrides

Cyclic acid anhydrides, like succinic and glutaric anhydrides and some of their derivatives, undergo fast Barbier-type reactions mediated by samarium(II) iodide in the presence of catalytic amounts of nickel(II) iodide[148] or indium[149] to give γ,γ-disubstituted lactones **96** in high yields (*Scheme 35*). Without the nickel salt catalyst no reaction occurred.[148]

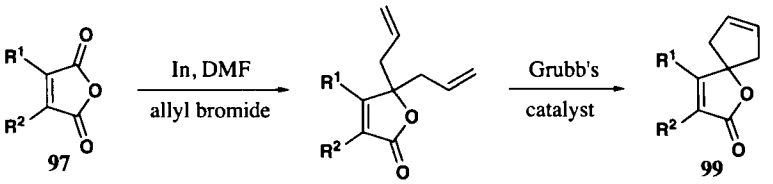


96

R = C_2H_5, n = 1 (92%); R = *n*-C_7H_{15}, n = 1 (95%);
R = allyl, n = 1 (80%); R = cyclohexyl, n = 1 (75%);
R = *n*-C_4H_9, n = 2 (95%); R = allyl, n = 2 (75%);
R = *n*-$C_{12}H_{25}$, n = 2 (72%)

Scheme 35

The allylation reaction of cyclic anhydrides **97** with allyl bromide in dimethylformamide in the presence of indium metal resulted in the formation of diallyl γ-lactones **98** in good yields (*Scheme 36*).[149] The ring-closing metathesis of lactone-dienes **98** provides a general synthetic method for spirolactones **99**.



97 → 98 → 99

	98	99
$R^1 = R^2 = H$	64%	87%
$R^1, R^2 = -(CH_2)_4-$	57%	52%
$R^1, R^2 = -CH=CH-CH=CH$	80%	92%

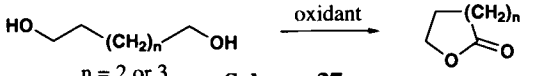
Scheme 36

4. Oxidations

A simple and generally applied lactone synthesis is the oxidation of various functional groups. Several miscellaneous types of compounds, such as diols, olefins, ketones and ethers, can be converted to lactones by oxidation reactions employing a variety of reagents.

a) Oxidation of Diols

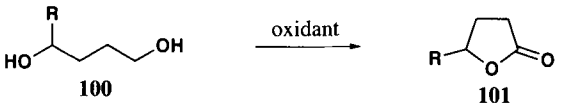
Alkanediols, mostly 1,4- and 1,5-diols, in which at least one OH group is primary, have been oxidized to lactones[2] (*Scheme 37*) by chromium and manganese oxidizing reagents including: copper chromite, chromic acid, manganese dioxide, and potassium permanganate.[150]



Scheme 37

Other oxidants like silver carbonate on celite,[151] nickel(II) bromide-benzoyl peroxide,[152] trityl tetrafluoroborate,[153] *N*-haloamides,[154] ruthenium[155,156] and palladium[157] complexes and sodium bromite[158,159] have also been used for this purpose. Oxidations have been carried out in solvents of various polarities, like acetone, methylene chloride, chloroform, carbon tetrachloride, acetonitrile, benzene and pyridine usually in satisfactory yields.

New reagent systems for high yield oxidation of 1,4-diols have been reported in recent years. These include: amino alcohol-based iridium bifunctional complex,[160] trichloroisocyanuric acid-pyridine,[161] 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)/*N*-chlorosuccinimide/tetrabutylammonium iodide (TBAI)/CH_2Cl_2[162] and tetrapropylammonium perruthenate(VII)/4-methylmorpholine *N*-oxide/CH_2Cl_2.[163] Selected oxidations of 1,4-diol **100** to γ-lactone **101** are shown in *Scheme 38*.



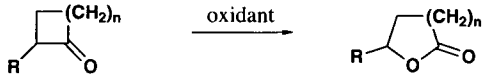
100 101

R	conditions	yield (%)	ref.
H	$RuH_2(PPh_3)_4$/toluene/Me_2CO	90	156
Me	ibid	96	
H	NCS/CH_2Cl_2	88	154
C_6H_5	TEMPO/NCS/TBAI/CH_2Cl_2	97	162

Scheme 38

b) Oxidation of Cyclic Ketones to Lactones (Baeyer-Villiger Reaction)

The Baeyer-Villiger (B-V) reaction[2,164-169] has become one of the most well-known and widely applied reactions in organic synthesis. Oxidation of cyclic ketones to lactones appears to be one of the most frequently used synthetic routes to γ- and δ-lactones (*Scheme 39*). The regiochemistry[170] of the reaction is highly predictable with the following migratory aptitude: tertiary

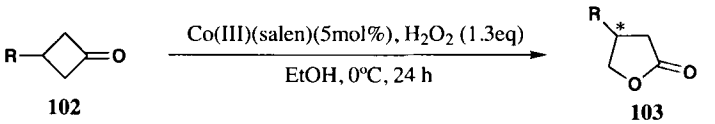


R = alkyl or aryl
n = 1-2

Scheme 39

alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl > primary alkyl > CH_3. Primary and secondary stereoelectronic effects that suppressed the intrinsic migratory aptitudes have also been proposed for the explanation of experimental results.[170] The reaction is generally stereoselective; that is, the migrating group retains its configuration. A wide range of oxidants may be used with their activity decreasing in the order: CF_3CO_3H > monopermaleic acid > monoperphthalic acid > 3,5-dinitroperbenzoic acid > *p*-nitroperbenzoic acid > *m*-chloroperbenzoic acid ~ $HCO_3H > C_6H_5CO_3H > CH_3CO_3H >> H_2O_2 >$ *t*-BuOOH.

The Baeyer-Villiger oxidations catalyzed by complex catalytic systems,[169,171-173] mediated by enzymes[174-177] and carried out in ionic liquids[178] have also been reported. In recent years much effort has been directed toward the development of metal assisted asymmetric B-V reactions.[179-187] As an example, asymmetric B-V of 3-phenylcyclobutanone **102** to β-substituted lactone **103** using Co(salen) as the catalyst has been shown (*Scheme 40*). Urea-hydrogen



102 103

R = *p*- ClC_6H_4 (76%, 75% ee)
R = *p*- $MeOC_6H_4$ (75%, 78% ee)

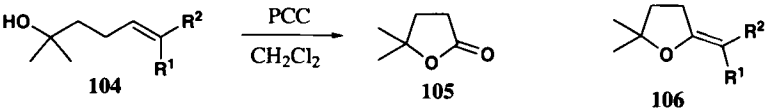
Scheme 40

peroxide complex or 30% hydrogen peroxide served as effective oxidants in solvents like CH_2Cl_2, THF, MeCN, EtOH, MeOH, hexane, benzene and toluene.[179]

Given the volume of research conducted on B-V reaction, only the most representative references are included.

c) Oxidative Cyclization of γ-Hydroxyolefins

γ-Hydroxyolefins are also good substrates for the preparation of γ-lactones. Various oxidative cyclizations of γ-hydroxy olefins **104a-c** to γ-lactones **105a-c** (*Scheme 41*) have been described using oxo-chromium(VI) reagents such as pyridinium chlorochromate (PCC), pyridinium dichromate,[188] or chromic acid.[189] Enol ethers **106a-c** have been postulated as the likely intermediates[188] in the reaction. The yield of the product depends strongly on the structure of the starting hydroxy olefin **104**, *e.g.* the trisubstituted olefin **104c** gives lactone **105c** in only 18% yield.[188]

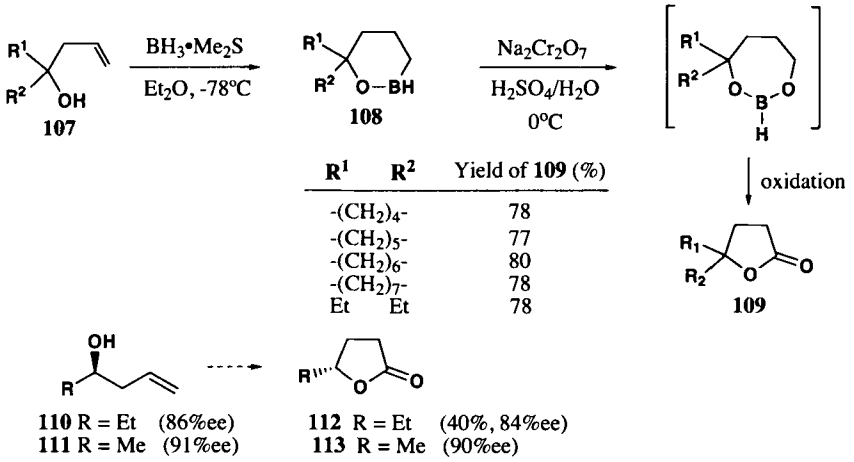


104 **105** **106**

a) $R^1 = R^2 = H$ (53%); *b)* $R^1 = Me, R^2 = H$ (46%); *c)* $R^1 = R^2 = Me$ (18%)

Scheme 41

Homoallylic alcohols **107** have been transformed to γ-lactones **109** by hydroboration-oxidation sequence in 70-83% yield (*Scheme 42*). The key step involves oxidation of the stable intermediate organoborane derivative **108** with chromic acid to lactones **109**. This one-pot synthesis has also been applied to the preparation of optically active lactones **112** and **113** from chiral substrates **110** and **111**, respectively. The reaction occurred with high *ee* indicating that there was virtually no loss of optical activity at the chiral center.[189]



107 **108**

R^1	R^2	Yield of **109** (%)
-$(CH_2)_4$-		78
-$(CH_2)_5$-		77
-$(CH_2)_6$-		80
-$(CH_2)_7$-		78
Et	Et	78

109

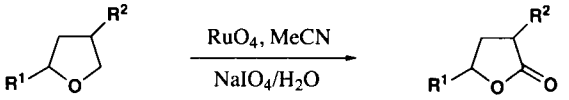
110 R = Et (86%ee)
111 R = Me (91%ee)

112 R = Et (40%, 84%ee)
113 R = Me (90%ee)

Scheme 42

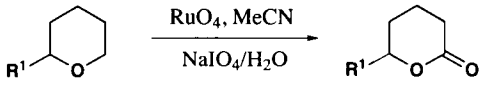
d) Oxidation of Cyclic Ethers

Ruthenium tetroxide, employed under either stoichiometric or catalytic procedure, is an effective reagent for the conversion of an aliphatic ether to the corresponding ester[190] or lactone[191] in good yields. Stoichiometric oxidation of 5- and 6-membered cyclic ethers **114** and **116** with RuO_4 afforded respective lactones **115** and **117** (*Scheme 43*) in 41-65% yield.[191] When two-phase catalytic oxidation procedure was used, the corresponding diacids were formed, presumably through intermediacy of ω-hydroxy acids.[191] Chromium trioxide in acetic anhydride has also been found effective for the oxidation of fused tetrahydrofuran to γ-lactone.[192] In steroids, 17-spirolactones are prepared from 17-spiroethers upon oxidation with *t*-butyl chromate in carbon tetrachloride-acetic acid-acetic anhydride mixture in over 40% yield after recrystallization.[193]



114 **115**

$R^1 = R^2 = H$ (65%); $R^1 = H$, $R^2 = Me$ (63%); $R^1 = Me$, $R^2 = H$ (59%)



116 **117**

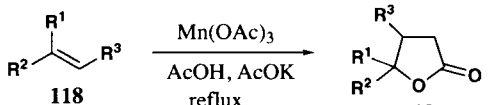
R = H (47%); R = Me (41%)

Scheme 43

Trimethylsilylnitrate-chromium trioxide, trimethylsilyl nitrate-DMSO[194] and titanium silicates[195] reagent systems were also effective for the one-step conversion of cyclic ethers to lactones. The reported yields for the conversion of tetrahydrofuran and tetrahydropyran were in the range of 40-65%.

e) Oxidation of Olefins

Olefins react with a variety of carboxylic acids in the presence of metal salts (M = Mn^{3+}, Ce^{4+}, V^{5+}) to give γ-lactones.[196-198] High to moderate yields of lactones were obtained from both internal and terminal olefins.[198] For example, manganic acetate in acetic acid reacts with olefins **118** by a free radical pathway leading to γ–butyrolactones **119** in generally excellent yields (*Scheme 44*).[196]

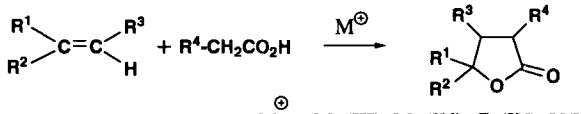


118 **119**

$R^1 = C_6H_5$, $R^2 = H$, $R^3 = Me$ (79%); $R^1 = C_6H_5$, $R^2 = Me$, $R^3 = H$ (74%);
$R^1 = C_6H_{13}$, $R^2 = R^3 = H$ (74%); $R^1 = H$, $R^2 = R^3 = C_3H_7$ (44%);
$R^1 = C_6H_5$, $R^2 = R^3 = H$ (60%)

Scheme 44

Various other metal oxidants like activated manganese(IV) oxide, manganic(III) acetate, cerium(IV) acetate and ammonium vanadate(V) have been effective in this transformation (*Scheme 45*). In lactone synthesis, it was found advantageous to add 10-30% potassium acetate or other carboxylate salt to the reaction mixture.[198] The addition of acetate ion shortened the reaction time by raising the reflux temperature of the reaction mixture and decreased the formation of the side-products resulting in higher lactone yields. Acetic, propionic and cyanoacetic acids have been successfully utilized for the preparation of γ-lactones from unhindered olefins in 41-79% yield. Isobutyric and succinic acids gave also lactones, albeit in low yield (25%).[198]



$M^{\oplus}$ = Mn(III), Mn(IV), Ce(IV), V(V)

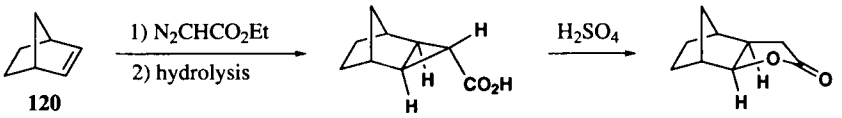
R^1 = alkyl or phenyl; R^2 = H or alkyl;
R^3 = H or alkyl or phenyl; R^4 = H or Me or CN or CH_2CO_2H

Scheme 45

5. Miscellaneous Reactions

a) Cyclopropanecarboxylic Acid Rearrangement

Cyclopropane carboxylic acids, readily available by the addition of carbalkoxy carbenes to olefins, undergo thermal and/or acid-catalyzed rearrangement to lactones on treatment with mineral acids (H_2SO_4, HBr)[199-201] in variable yields. Thus, cyclopropane carboxylic acid **121** prepared from norbornene **120** afforded lactone **122** upon treatment with sulfuric acid in 48% yield (*Scheme 46*).[199]

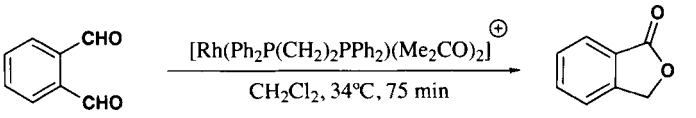


120 **121** **122** (48%)

Scheme 46

b) Catalytic Ring Closure of 1,4-Dialdehydes

A practical and mild catalytic method of converting aliphatic and aromatic 1,4-dialdehydes to γ-lactones in a Cannizzaro-type reaction has been reported.[202] A series of rhodium-diphosphine complexes [Rh(diphosphine)(acetone)$_2$]$^+$ was tested. For example, *o*-phthaldialdehyde **123** was completely and cleanly converted to lactone **124** with the use of a catalyst precursor [Rh($Ph_2P(CH_2)_2PPh_2$)]$_2$(ClO_4)$_2$ in methylene chloride solution (*Scheme 47*).[202] Other phosphine ligands examined were $Ph_2P(CH_2)_3PPh_2$, $(C_6H_{11})_2P(CH_2)_2P(C_6H_{11})_2$, ($p$-$CF_3C_6H_4)_2P(CH_2)_2P(p$-$CF_3C_6H_4)_2$, and $Ph_2P(CH_2)_4PPh_2$.



123 124 quantitative yield

Scheme 47

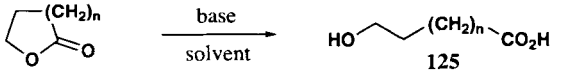
II. CLEAVAGE OF LACTONES

1. Hydrolysis

a) Base-catalyzed Hydrolysis of Lactones

The high susceptibility of lactones toward nucleophiles makes the base-catalyzed hydrolysis the most frequently used cleavage reaction of lactones. Alkali metal hydroxides: NaOH,[203-208] KOH,[209-220] LiOH[221] and carbonates K_2CO_3,[207,222-224] Na_2CO_3[207,224] and $NaHCO_3$[225] are the reagents of choice. Water solutions of ammonia[226] and triethylamine have also been used occasionally. Lactone hydrolysis under basic conditions usually proceeds in alcohols (MeOH, EtOH), acetone, acetonitrile, water or mixtures of these solvents. Aqueous tetrahydrofuran and dimethyl sulfoxide have also been used.

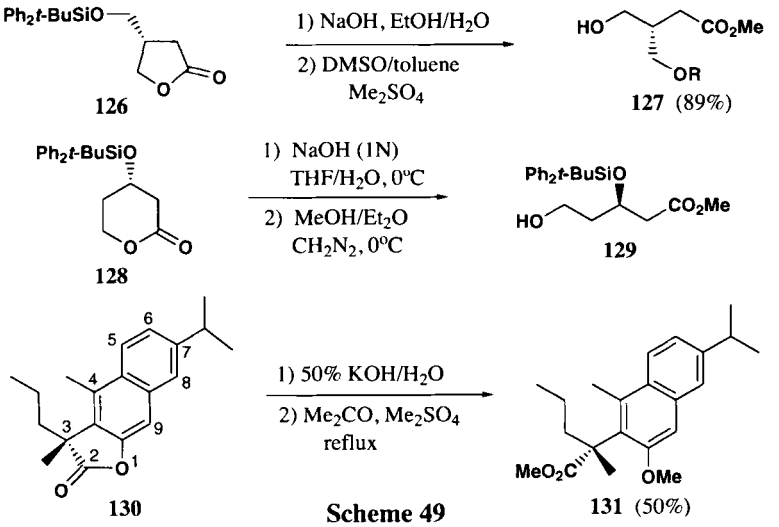
In the case of 5- and 6-membered ring lactones[204,209] the resulting product hydroxy-acids **125** (*Scheme 48*) undergo facile recyclization in the course of isolation and/or purification. In order to prevent this unwanted reaction, the crude hydroxy acid is esterified by treatment with



n = 1 or 2 125

Scheme 48

diazomethane,[203,204,208,219] methyl sulfate,[81,209] methyl iodide[220] or benzyl bromide.[214,215,220] Several examples are shown in *Scheme 49*. In two step reaction hydroxy esters **127** and **129** were



126 127 (89%)

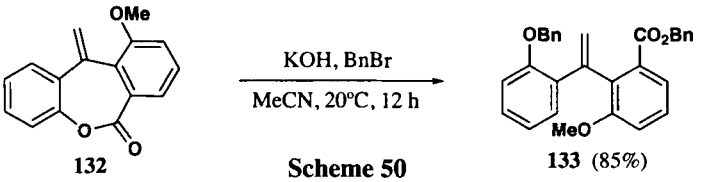
128 129

130 131 (50%)

Scheme 49

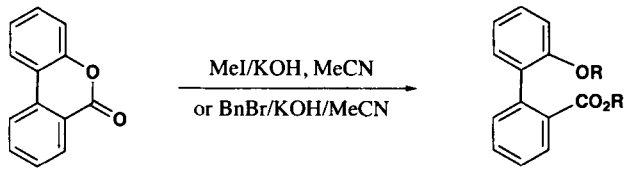
obtained from **126**[81] and **128**,[204] respectively, in excellent yield. Ether-ester **131** was obtained from aromatic lactone **130** in 50% yield.

Recyclization was also prevented when the alkali carboxylate, produced by the base-catalyzed ring opening of 7-membered lactone **132**, was esterified with benzyl bromide to give **133** in 85% yield (*Scheme 50*).[220] The hydrolysis was carried out in the presence of excess benzyl bromide[215] or the isolated sodium salt was alkylated in the next step.[5]



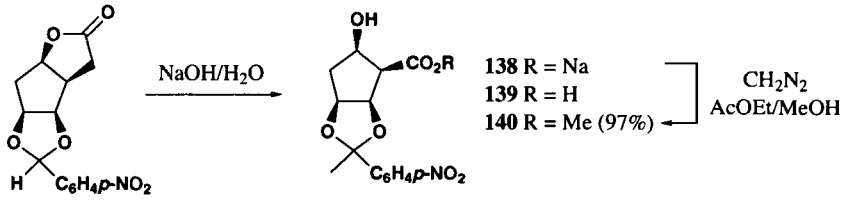
132 **Scheme 50** **133** (85%)

Similarly, opening of the lactone ring in **134** with potassium hydroxide in the presence of methyl iodide or benzyl bromide afforded biphenyl carboxylates **135** and **136**, respectively, in excellent yield (*Scheme 51*).[220]



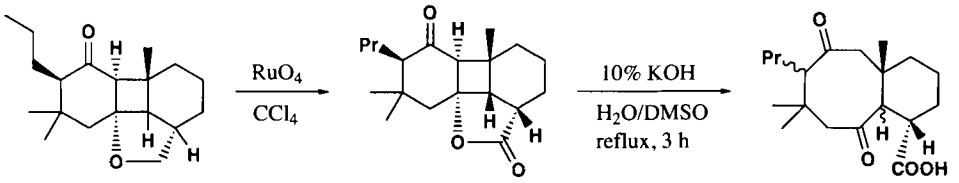
134 **Scheme 51** **135** R = Me (95%); **136** R = Bn (83%)

In some cases the cyclization of a hydroxy acid could be suppressed.[203,214] Thus, the hydrolysis of lactone **137** with sodium hydroxide gave sodium salt of hydroxyacid **138**. The free hydroxy acid **139** was obtained when solution of **138** was acidified with saturated potassium hydrogen sulfate solution (*Scheme 52*). However, all attempts to oxidize **139** to the respective ketone have failed, because it underwent fast lactonization. Esterification of **139** with diazomethane in AcOEt/MeOH solution gave hydroxy ester **140** in 97% yield.[203]



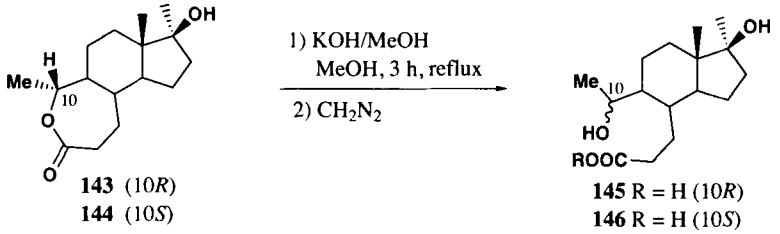
137 **Scheme 52**

In the course of synthetic work toward compounds with the taxane skeleton, the hydrolysis of lactone **141** was accompanied by cleavage of the cyclobutane ring in a retroaldol reaction to afford **142**, an 8-membered ring system fused with the cyclohexane ring (*Scheme 53*).[210]



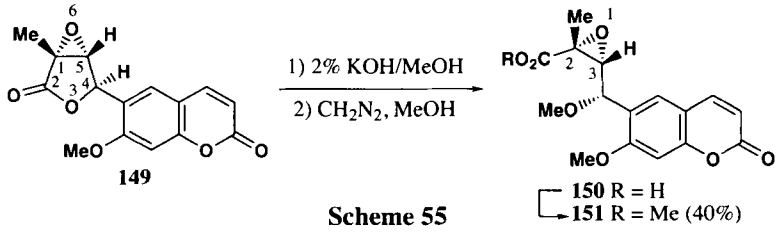
Scheme 53

Epimeric lactones **143** and **144**, prepared from 17α-methyltestosterone, were hydrolyzed in alcoholic KOH to dihydroxyacids **145** and **146**, which exhibited strong tendency toward recyclization. These were immediately esterified by treatment with diazomethane to afford **147** and **148** (*Scheme 54*).[217]



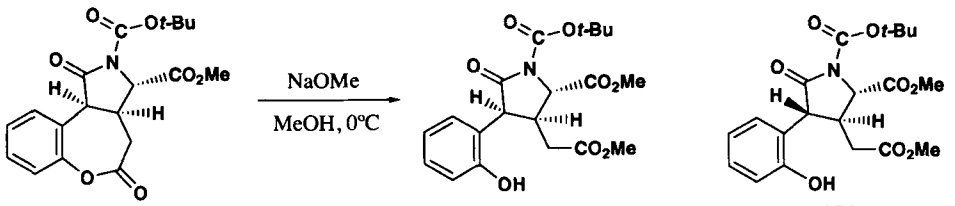
Scheme 54

Selective opening of the five-membered lactone ring of micromelin **149** under very mild conditions with one equivalent of base added proceeded without opening the coumarin lactone ring. The crude methoxy acid **150** was treated with diazomethane and isolated as methyl ester **151** (*Scheme 55*).[216]



Scheme 55

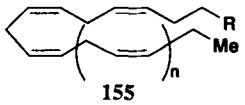
Lactone rings are particularly easily cleaved upon treatment with alkali metal alkoxides.[206,227-230] Sodium methoxide is the reagent of choice for the hydrolysis. Reaction of lactone **152** using sodium methoxide in methanol at 0°C afforded phenol-ester **153** in 85% yield. Formation of methyl ester **153** in this reaction is advantageous, since the recyclization is then avoided (*Scheme 56*).[227] When lithium hydroxide in tetrahydrofuran–water at 20°C was used followed by treatment with diazomethane in Et_2O, lactone **152** afforded a 5:1 mixture of *cis*- and *trans*-isomers, **153** and **154**, respectively, in 47% yield of two steps.



152 **153** (85%) **154**

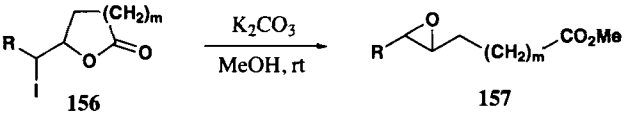
Scheme 56

In the synthesis of polyunsaturated sulfur and oxygen-containing fatty acids **155c-f** related to eicosapentaenoic **155a** and docosahexaenoic acid **155b**, iodolactones **156a** and **156b**, formed from respective acids, were hydrolyzed with methanolic potassium carbonate to furnish important intermediate epoxides **157a** and **157b**, respectively (*Scheme 57*).[223] The synthesis based on the degradation of naturally occurring fatty acids **155a** and **155b** competes well with those based on multi-step construction of the acids from simple starting material. The complete conservation of the *Z*-configuration of the appropriate double bonds originating from the substrate fatty acids is an additional advantage.



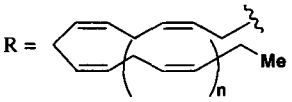
155

a) n = 2, R = CH_2CO_2H; *b)* n = 3, R = CO_2H; *c)* n = 1, R = SCH_2CO_2Me;
d) n = 1, R = OCH_2CO_2Et; *e)* n = 2, R = SCH_2CO_2Me; *f)* n = 2, R = OCH_2CO_2Et



156 **157**

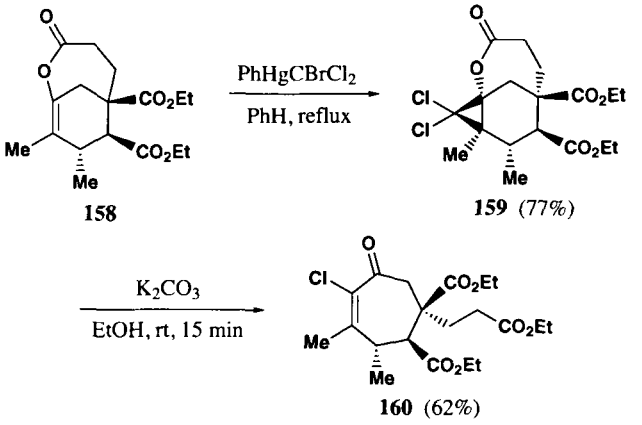
a) n = 1, m = 2 (85%); *b)* n = 2, m = 1 (89%)



Scheme 57

Upon treatment of dichlorocyclopropane lactone **159** with ethanolic K_2CO_3, a stereo-controlled ring expansion to 2-chlorocycloheptenone **160** was observed (*Scheme 58*).[224] Thus the dichlorocyclopropanation of the unsaturated lactone **158** followed by hydrolysis provides a versatile synthetic way to functionalized 2-chlorocycloheptenones. The internal bond cleavage was postulated to be initiated by the ionization of the cyclopropyl C-Cl bond prior to the lactone cleavage.[224]

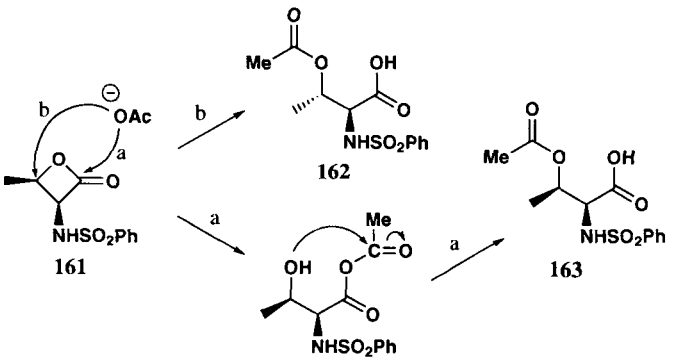
The synthesis and nucleophilic ring opening of optically pure *N*-protected α-amino-β-alkyl-β-lactones has been investigated. Reaction of the protected threonine β-lactone **161** with sodium acetate in acetic acid produced diastereoisomeric acetates **162** and **163** in 1:7 ratio with



158 159 (77%) 160 (62%)

Scheme 58

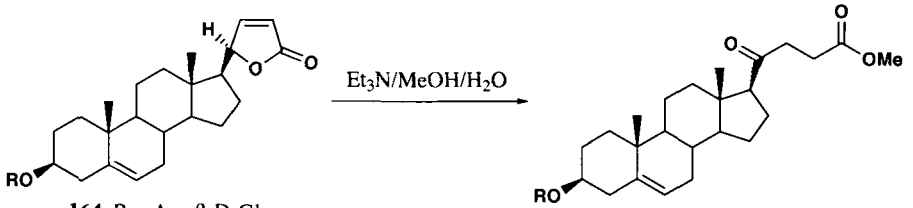
the predominant nucleophilic attack at the carbonyl carbon of the β-lactone (*Scheme 59*, path a). Formation of **163** in the second step is explained by a probable intramolecular acyl transfer to the β-oxygen.[231]



161 162 163

Scheme 59

The hydrolysis of lactones can also be carried out in methanolic or aqueous ammonia[226] or triethylamine.[232] Mild hydrolysis of lactone **164** in triethylamine-methanol-water mixture afforded the 3-glucoside of methyl 21-nor-20-oxo-5-cholen-24-oate **166** (*Scheme 60*).[232] A similar reaction of the free alcohol **165** followed by acetylation (Ac_2O/Py) resulted in the isolation of compound **167** in 50% yield.[232]



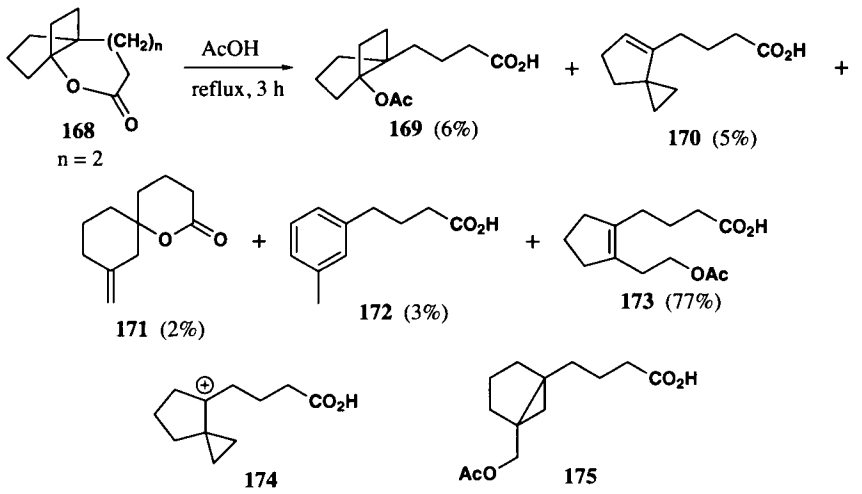
164 R = Ac_4-β-D-Glc
165 R = H

166 R = β-D-Glc (87%)
167 R = Ac (50%)

Scheme 60

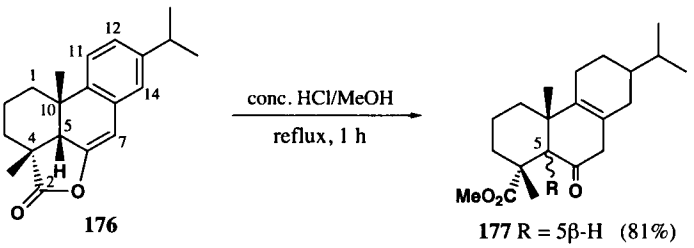
b) Acid-catalyzed Hydrolysis of Lactones

Acid-catalyzed hydrolysis of lactones is frequently used in organic synthesis; however, side reactions, such as isomerization, are often observed under acidic conditions. The hydrolysis of a lactone accompanied by extensive isomerization is exemplified by the cleavage of [5.3.2]propella-ε-lactone **168** (n = 2) in refluxing acetic acid.[233] The five products **169-173** were obtained in 93% combined yield. The thermodynamically most stable 1,2-disubstituted cyclopentene **173** was the major product (77%). Its formation was suggested to proceed by the formation of cyclopropylcarbinyl cation intermediate **174** followed by a nucleophilic attack on the cyclopropane ring, concerted with ring cleavage and/or rearrangement. Intermediate acid **175** has been postulated to account for the formation of compounds **171** and **172** (*Scheme 61*).[233] Interestingly, the corresponding δ-lactone **168** (n = 1) was recovered unchanged under similar conditions.[233]



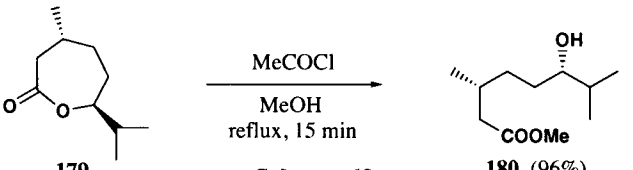
Scheme 61

Methanolysis of lactone **176** with concentrated hydrochloric acid in refluxing methanol afforded *cis*-fused A/B keto ester **177**[209] while 5α isomer **178** was not observed at all (*Scheme 62*). On the other hand, the corresponding A/B *trans* keto ester **178** could not be epimerized to **177** under similar conditions.[209]



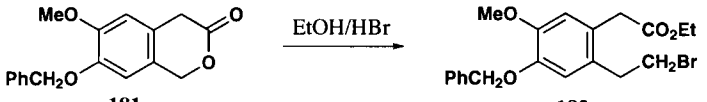
Scheme 62

In the synthesis of the ring D building block of vitamin D_3 from menthol, an acid-catalyzed cleavage of the 7-membered lactone was used (*Scheme 63*). Thus, treatment of lactone **179,** which is easily accessible from natural (-)-menthol, with a catalytic amount of acetyl chloride in methanol afforded hydroxy-methyl ester **180**, in 96% yield. The compound was used for the synthesis of the CD-fragment of 24*S*-hydroxy vitamin D_3.[234]



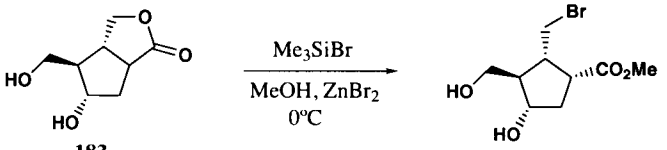
179 **Scheme 63** **180** (96%)

In reactions catalyzed by Brønsted or Lewis acids, for example zinc bromide[235] and zinc chloride,[236] cleavage of lactones leading to ω-bromoesters has also been effected. The synthesis of *N*-benzyltetrahydroisoquinoline alkaloid corgoine[237] involved formation of bromoester **182** from lactone **181** in the crucial step (*Scheme 64*). A group of naturally occurring *N*-benzyltetrahydroisoquinoline alkaloids has been synthesized, employing this reaction.[237]



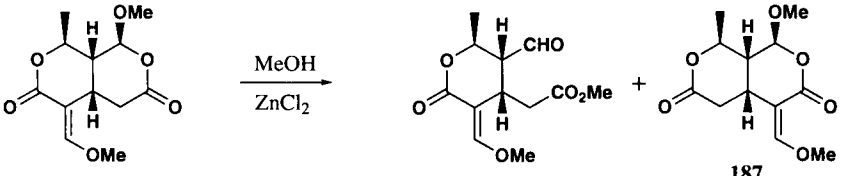
181 **Scheme 64** **182**

Bicyclic lactone **183** was the key intermediate in the synthesis of carbocyclic nucleosides. The reaction of **183** with trimethylsilyl bromide (*Scheme 65*), catalyzed by zinc bromide in methanol, afforded the relatively unstable γ-bromo ester **184**.[235]



183 **Scheme 65** **184** (70%)

In the synthesis of natural iridoid xylomollin[236] various zinc salts were found to be effective in transforming *cis*-fused bislactone **185** into what appeared to be a thermodynamic mixture of **186** and **173** (*Scheme 66*). Either of these compounds **185**, **186** and **187** reverted to

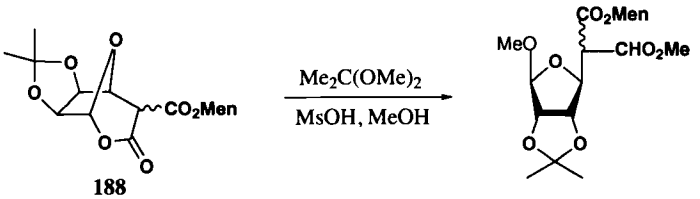


185 **186** **187**

Scheme 66

approximately the same mixture (1:4.5:1.4, respectively) when subjected to the same reaction conditions.[236]

The reported synthesis of branched-chain sugar derivatives was based on the selective ring-opening of lactone **188** which on treatment with methanesulfonic acid in methanol/2,2-dimethoxypropane gave L-β-ribofuranose derivative **189** (*Scheme 67*) as a 1:1 mixture of C(5) epimers, in 85% yield.[238]



188
Men = menthyl

Scheme 67

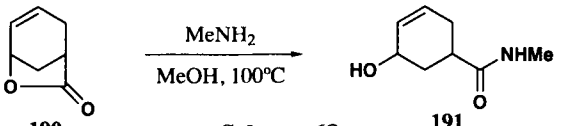
189 (85%)

2. Reaction with Miscellaneous Nucleophiles

a) N-Nucleophiles

The mode of lactone ring-opening appears to be very sensitive to the particular nucleophile, solvent and reaction conditions. Among all of the methods available for cleavage of lactones, ammonolysis has been relatively popular. Lactones upon reaction with ammonia,[206,239,240] primary amines such as methylamine,[206,241,242] *n*-butylamine,[207] benzylamine[231,243-245] as well as secondary amines[206,246,247] are converted to amides or hydroxyamides.

Lactone aminolysis, apparently a simple transformation, generally requires rather harsh conditions, such as high temperature and/or strong catalyst and long reaction times. Furthermore, a large excess of amine is frequently used. For example, when lactone **190** was treated with methanolic methylamine at 100°C, a nearly quantitative yield of amide **191** was obtained (*Scheme 68*).[241]

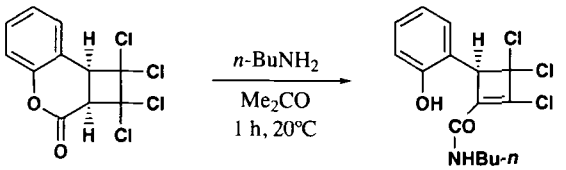


190

Scheme 68

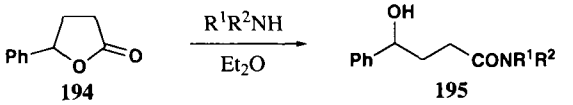
191

However, the aminolysis of 5-membered lactones was also carried out under mild conditions in $MeNH_2$-THF at 4°C for 15 min[242] or in $MeNH_2$-H_2O solution at room temperature.[206] In general, cleavage reactions are sensitive to amine basicity and the amount of the nucleophile used. Mild conditions, such as *n*-butylamine in acetone or dioxane at room temperature, were also effective for cleavage of aromatic 6-membered lactone **192**. Product **193** was obtained in the yield of 48-100%, depending on the concentration of the added amine (*Scheme 69*).[207] The reactions of ammonia and 1° and 2° amines, for example cyclohexylamine, benzylamine, dimethylamine, piperidine, morpholine, with γ-phenyl-γ–butyrolactone **194** have been



192 **Scheme 69** 193

shown to produce γ-hydroxy-γ-phenylbutyramides **195** (*Scheme 70*).[248] α-Morpholino-γ-phenyl-γ-butyrolactone has been found to be resistant to ring opening by 2° amines, while benzylamine and cyclohexylamine react to produce the corresponding amides of α-morpholino-γ-hydroxy-γ-phenylbutyric acid in 63% and 36% yield, respectively.[248]

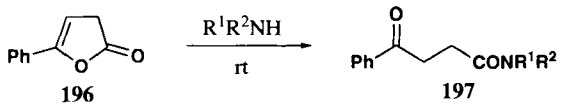


194 195

R^1 = H, R^2 = C_6H_{11} (88%); R^1 = H, R^2 = $CH_2C_6H_5$ (92%); R^1 = R^2 = CH_3 (27%); R^1, R^2 = $(CH_2)_5$ (33%); R^1, R^2 = C_4H_8O (morpholine) (85%)

Scheme 70

In reactions of primary and secondary amines with 4-phenyl-3-butenolide **196** (*Scheme 71*), several amides of β-benzoylpropionic acid **197** have been prepared.[248]



196 197

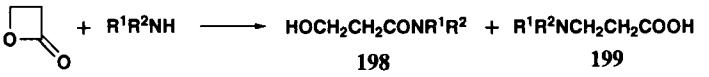
R^1 =H, R^2 = $CH_2C_6H_5$ (80%); R^1 = H, R^2 = cyclohexyl (50%); R^1 = R^2 = CH_3 (69%); R^1 = CH_3, R^2 = $CH_2C_6H_5$ (98%)

Scheme 71

In contrast to the five-membered ring lactones which are cleaved at the oxygen-acyl bond upon nucleophilic attack, β-lactones undergo oxygen-acyl or oxygen alkyl bond cleavage.[245] The strained β-propiolactone reacts with ammonia and most 1° and 2° amines to give both amides **198** and amino acids **199** (*Scheme 72*).[249] The two competing reactions have been found to vary with the amine, the solvent (H_2O or Et_2O or MeCN) and the reaction conditions. Selected examples are shown in *Scheme 72*. With few exceptions, water was the best solvent for amide formation and acetonitrile the best for amino acid.

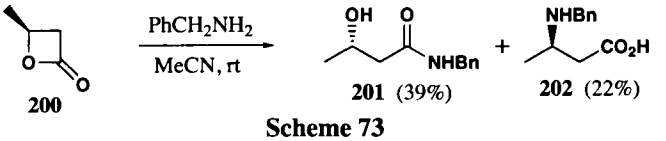
Ring opening of (*S*)-β-butyrolactone **200** with benzylamine[245] occurs primarily at the carbonyl to form amide **201** (39%) and amino acid **202** (22%) (*Scheme 73*). Ring opening of lactone **203**, the derivative of *N*-protected L-threonine, with benzylamine in acetonitrile (*Scheme 74*) occurs at the carbonyl to form amide **204** in 72% yield.[231]

Tertiary amines react with β-propiolactone in non-aqueous solvents to form betaines.[249]

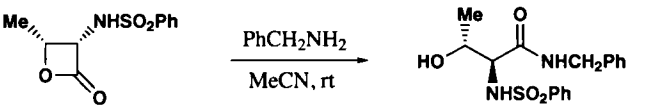


R^1, R^2	Solvent	Amide **198** (%)	Amino acid **199** (%)
H, H	H_2O	90	
	MeCN		97
Et, H	H_2O	97	
	Et_2O	76	
	MeCN		87
$C_6H_5CH_2$, H	H_2O	51	
	MeCN		94
	Et_2O	44	11
Et, Et	H_2O	80	
	MeCN	70	

Scheme 72

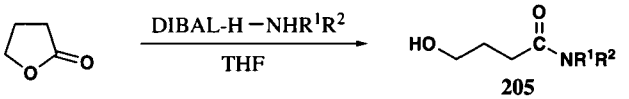


Scheme 73



Scheme 74

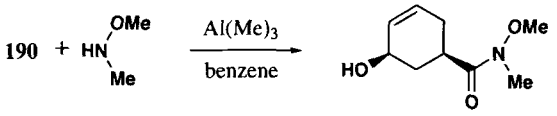
The reaction of γ-butyrolactone with organoaluminum species generated from diisobutylaluminum hydride (DIBAL-H) and 1° or 2° amines has also provided a convenient and mild method for efficient preparation of γ-hydroxyamides. The reaction of γ-butyrolactone with benzylamine at 45°C for 24 h afforded amide **205a** in 98% yield. The same reaction in the presence of DIBAL-H at room temperature (*Scheme 75*) gave **205a** after 30 min in 98% yield, while the reaction with *i*-pentylamine gave amide **205b** in 95% yield. The reaction of γ-butyrolactone with organoaluminum reagent derived from 2° amine (*e.g.* diethylamine) required gentle heating or treatment with DIBAL-H–NHR^1R^2·HCl complex. The yield of **205c** was 72 or 94%, respectively.[250]



a) R^1 = H, R^2 = $C_6H_5CH_2$ (98%); *b)* R^1 = H, R^2 = *i*-C_5H_{11} (95%); *c)* R^1 = R^2 = Et (94%); *d)* R^1 = OMe, R^2 = Me (92%)

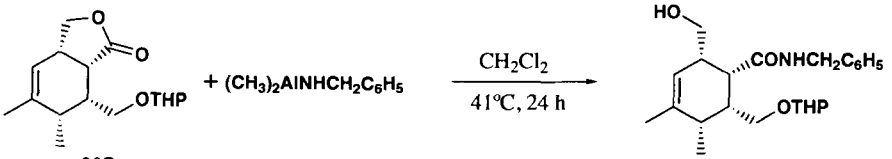
Scheme 75

The method has also been applied for the synthesis of Weinreb amides **205d**, which are important intermediates for the preparation of aldehydes and ketones.[251] Previously, the synthesis of *N*-methoxy-*N*-methylamide **206** in the reaction of lactone **190** with aluminum amide derived from *N,O*-dimethylhydroxylamine was reported (*Scheme 76*).[252,253]



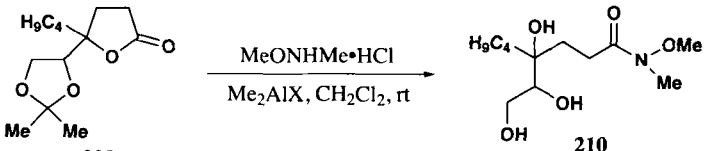
Scheme 76 **206** (91%)

The reaction of a dimethylaluminum amide species with lactone **207**, under very mild reaction conditions produces hydroxyamide **208** in high yield (*Scheme 77*).[254] The dimethylaluminum amide can be generated *in situ* from trimethylaluminum with ammonia or primary and secondary amines. The reaction was also performed with a series of esters and was reported as a general method for the conversion of esters to amides.



207 **Scheme 77** **208** (80%)

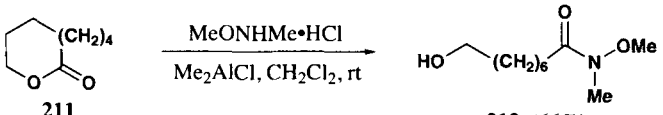
In the aminolysis of variously substituted lactones, trimethylaluminum-*N,O*-dimethylhydroxylamine has been used. However, the reaction gave unsatisfactory results in the case of sterically hindered lactones.[255] In contrast, a smooth and efficient reaction of γ-lactone **209** with dimethylaluminum chloride and *N,O*-dimethylhydroxylamine hydrochloride to give **210a** has been described (*Scheme 78*).[255] The reaction with trimethylaluminum afforded **210b** in only 55% yield.



209 **210**

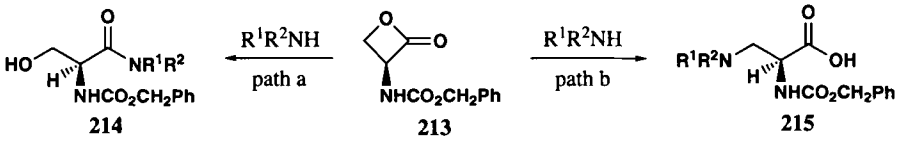
Scheme 78 *a)* X = Cl (94%); *b)* X = Me (55%)

The reaction appears to be of a general type since 9-membered lactone **211** (*Scheme 79*) gave 66% yield of hydroxyamide **212** under similar conditions.[256]



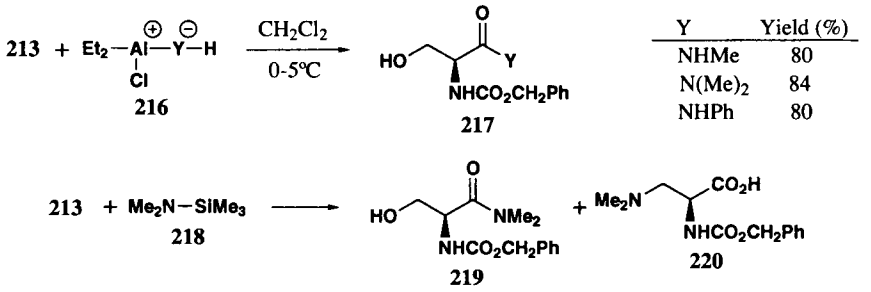
211 **Scheme 79** **212** (66%)

Reactions of nitrogen nucleophiles with serine β-lactone **213**[257,258] can generate a mixture of products: amide **214** arising from acyl-oxygen cleavage (*Scheme 80*, path a) and amino acid **215** arising from alkyl-oxygen cleavage (*Scheme 80*, path b). The mode of ring-opening is reported to be very sensitive not only to the particular nucleophile, but also to the solvent and reaction conditions.[259]



Scheme 80

The ring opening of *N*-carbobenzyloxy-L-serine-β-lactone **213** by diethylaluminum chloride-amine complex **216** and by *N,N*-dimethyl-*N*-(trimethylsilyl)amine **218** afforded good yield of L-serinamides **217** and a mixture of amide **219** and β-amino-L-alanine derivatives **220**, respectively (*Scheme 81*).[259] The regioselectivity of the reaction was influenced by the nature of the nucleophile, the solvent and the catalyst (Lewis acid or metal ion). Thus, in the reaction with amine **218** acyl-oxygen cleavage product **219** prevailed in $CHCl_3$, while alkyl-oxygen cleavage leading to β-amino-L-alanine derivative **220** occured in MeCN.[259]

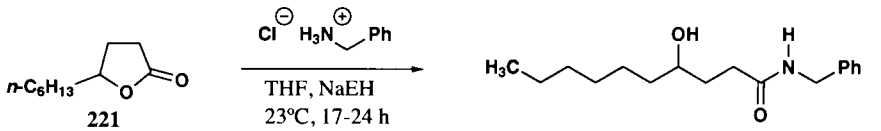


Y	Yield (%)
NHMe	80
$N(Me)_2$	84
NHPh	80

Reaction conditions	Product ratio Amide **219**	Amino acid **220**	Yield (%)
$CHCl_3$, 20°C, 3 h	80	20	88
CH_2Cl_2, 20°C, 1 h	65	35	85
$(CH_2)_2Cl_2$, 20°C, 1 h	35	65	90
THF, 20°C, 8 h	20	80	92
MeCN, 20°C, 4 h	5	95	95

Scheme 81

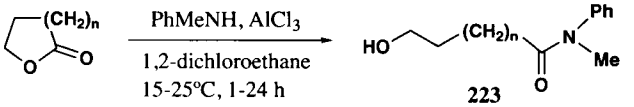
Another general method for mild aminolysis of 4- to 6-membered lactones by using sodium 2-ethylhexanoate (NaEH) has also been reported.[244] The reagent served as a base and a catalyst in high yield aminolysis of lactones *e.g.* **221** by benzylamine hydrochloride (*Scheme 82*) to give hydroxyamide **222** in high yield. The nearly neutral pH conditions should make this method applicable for acid or base sensitive substrates. Compared with γ-lactones, β- and



Scheme 82

δ-lactones were much more reactive and required 4h reaction time and gave the product with over 90% yield.[244]

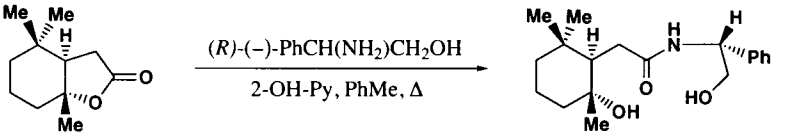
1° and 2° aliphatic or aromatic amines react cleanly with medium-sized ring lactones in the presence of aluminum chloride to afford ω-hydroxyalkyl amides **223** in the yield in most cases exceeding 70%.[247] As an example, the reaction of γ-, δ- and ε-lactones with phenylmethylamine is shown (*Scheme 83*). In the absence of aluminum chloride little or no reaction was observed. The other Lewis acids examined, like $AlCl_3$, $TiCl_4$, $FeCl_3$, $BF_3{\cdot}Et_2O$, with the exception of $ZrCl_4$, gave poor results.



n = 3 (66%); n = 4 (74%); n = 5 (66%)

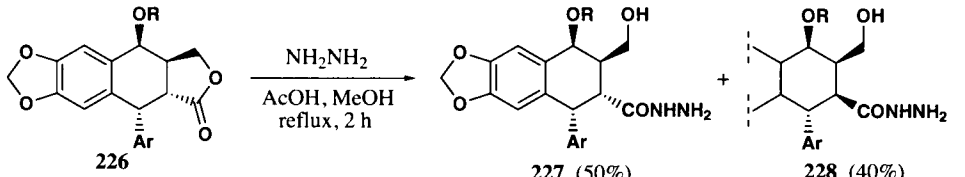
Scheme 83

Another aminolysis of γ-lactones promoted by 2-hydroxypyridine (2-OH-Py) acting as a bifunctional base-acid catalyst[260] has also been reported.[261-264] The γ-hydroxyamides (4-hydroxybutyramides) have been obtained in over 80% yield. For example, (+)-*trans*-tetrahydroactinidiolide **224** was cleaved with (*R*)-(−)-α-phenylglycinol in the presence of 2- hydroxypyridine to hydroxy amide **225** (*Scheme 84*).[261]



Scheme 84

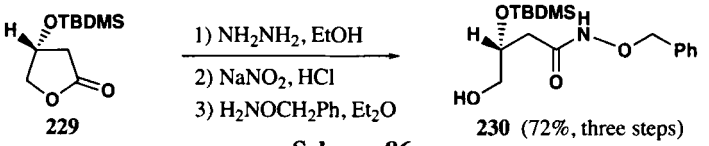
Hydrazine was found to be another effective nucleophile for cleavage of lactones. In the synthesis of a lactam analog of antitumor agent etoposide, the reaction of lactone **226** with hydrazine in refluxing MeOH/AcOH provided a mixture of *trans*- (**227**) and *cis*-hydrazide (**228**) (*Scheme 85*).[265] Interestingly, a direct conversion of lactone **226** to a lactam using NH_3 and heat



R = β-D-4,6-O-ethylidene glucose
Ar = 3,5-dimethoxy-4-hydroxyphenyl

Scheme 85

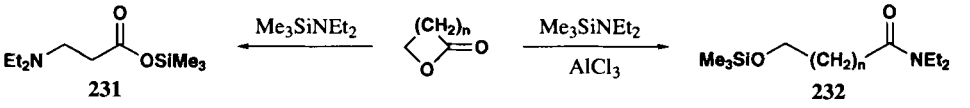
was unsuccessful. Similarly, cleavage of lactone **229** with hydrazine monohydrate in EtOH gave rise to the hydrazide, which was further converted to hydroxamate **230** (*Scheme 86*).[266]



229 **230** (72%, three steps)

Scheme 86

The regioselectivity observed in lactone cleavage with diethylaminotrimethylsilane was dependent on ring size and sensitive to the type of catalyst used. Whereas β-propiolactone reacted in the absence of a catalyst to give β-amino acid derivative **231**, the less strained lactones (n = 2 or 3) gave, under $AlCl_3$ catalysis, ω-siloxyamides **232** (*Scheme 87*).[267]



231 n = 1 (78%) n = 1-3 **232** n = 2 (60%); n = 3 (40%)

Scheme 87

The regioselectivity was also observed in the ring-opening reactions of lactones with alkylaminostannanes. *N,N*-Diethylaminotrimethylstannane **233** and piperidinotrimethyl-stannane **234** induce regioselective ring-opening in β-propiolactone, γ-butyrolactone, δ-valerolactone and ε-caprolactone by means of acyl-oxygen bond fission to give the corresponding ω-stannyloxyamides **235** in good yields (*Scheme 88*).[267,268] Both organometallic reagents, dialkylaminosilanes and dialkylaminostannanes are also effective reagents for cleavage of oxiranes and oxetanes to difunctional organic compounds.[267]

233 $R^1 = R^2 = Et$
234 $R^1, R^2 = -(CH_2)_5-$

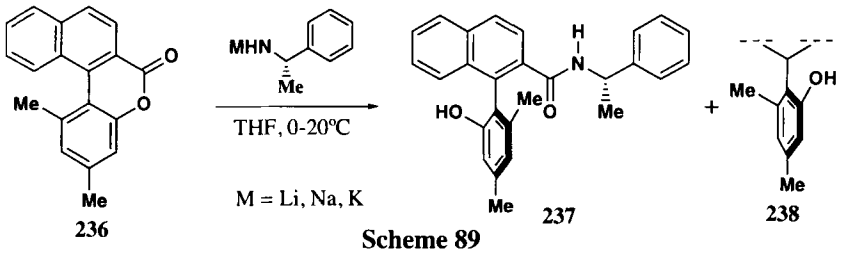
235

n = 1	$R^1 = R^2 = Et$	(95%)	n = 3	$R^1 = R^2 = Et$	(71%)
	$R^1, R^2 = -(CH_2)_5-$	(96%)		$R^1, R^2 = -(CH_2)_5-$	(77%)
n = 2	$R^1 = R^2 = Et$	(90%)	n = 4	$R^1 = R^2 = Et$	(90%)
	$R^1, R^2 = -(CH_2)_5-$	(89%)		$R^1, R^2 = -(CH_2)_5-$	(92%)

Scheme 88

b) Chiral N-Nucleophiles

Atroposelective ring cleavage reactions of lactone-bridged biaryls with chiral metal amides to axially chiral biaryl target molecules has been extensively studied. An excellent review article on the subject appeared in 1999.[269] As an example, a reaction of lactone **236** with chiral 1-phenylethylamine salt is presented (*Scheme 89*). The ratio of *M*- and *P*-atropoisomers strongly



Scheme 89

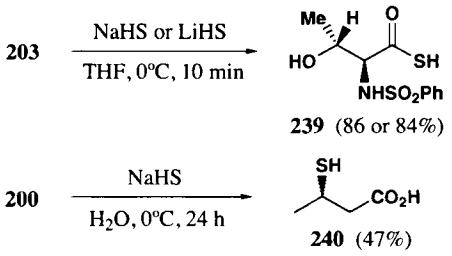
depends on the metal used. The best results were obtained with potassium amide and the ratio of **237**:**238** was 95:5.

Ring-opening reaction of biaryl lactones has been carried out with a variety of chiral *N*-, *O*- and *C*-nucleophiles.[269] The reactions were found to be strongly dependent on the metal counter ion of the deprotonated nucleophile. The method has been successfuly applied to the synthesis of a series of natural products, for example naphthylisoquinoline alkaloids, mastigophorenes A and B, dimeric sesquiterpenes and phenylanthraquinone-knipholone.[269]

c) Sulfur and Selenium Nucleophiles

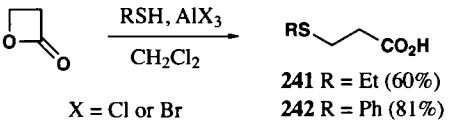
The high reactivity of strained β-lactones toward thiophenol and sodium thiophenoxide was recognized as early as in 1949.[270] β-Propiolactone reacts much more rapidly with thiophenol than it does with phenol (1h vs. 6 hrs) and the yield of β-thiophenoxypropionic acid is higer (49 vs 24%).[270] The reaction of alkyl- and aryl thiols with β-lactones is slow and synthetically not important.[245] While the strained β-lactone ring is subjected to ring opening by nucleophilic attack at the β-carbon atom, powerful nucleophiles, *e.g.* RS^-,[271,272] are generally required for ring opening of the larger lactones resulting with the cleavage of the ω-carbon-oxygen bond. LiHS, NaHS[231] and Na_2S[245] are reagents of choice for the effective cleavage of β-lactones to afford products forming through alkyl-oxy[231] and /or alkyl-acyl[245] attack of the nucleophile

High yield (> 80%) of (2*S*,3*R*)-2[(phenylsulfonyl)amino]-3-hydroxybutanethioic acid **239** was obtained in the reaction of β-lactone **203** derived from L-threonine with NaHS or LiHS while (*S*)-β-methyl-β-propiolactone [(*S*)-4-methyloxetan-2-one)] **200** upon treatment with aqueous NaHS gave (*R*)-3-mercaptobutanoic acid **240** in 47% yield (*Scheme 90*).[245]



Scheme 90

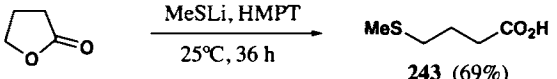
The highly strained β-propiolactone reacted readily with ethane- and benzenethiol in the presence of $AlCl_3$ or $AlBr_3$ to give high yield of 3-(ethylthio)- **241** and 3-(phenylthio)-propionic acid **240** in 60 and 81% yield, respectively (*Scheme 91*).[273] Sodium or lithium thioalkoxides, in contrast to sodium thiophenoxide, are effective reagents for the cleavage of lactones, as shown in the reaction of γ-butyrolactone with lithium thiomethoxide leading to 4-(methylthio)butyric acid **243** (*Scheme 92*).[274]



X = Cl or Br

241 R = Et (60%)
242 R = Ph (81%)

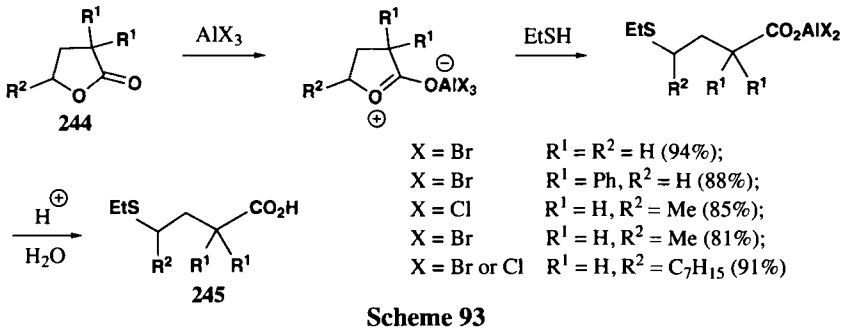
Scheme 91



243 (69%)

Scheme 92

Another interesting example is the conversion of lactones **244** to ω-alkylthio- and ω-arylthiocarboxylic acids **245** in high yield through ω-carbon-oxygen bond cleavage when they are treated with aluminum halide and alkane or arene thiols.[273,275] Selected examples of the reaction are shown (*Scheme 93*).[273]



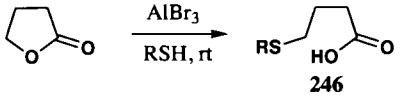
244

245

X = Br	$R^1 = R^2 = H$ (94%);
X = Br	R^1 = Ph, R^2 = H (88%);
X = Cl	R^1 = H, R^2 = Me (85%);
X = Br	R^1 = H, R^2 = Me (81%);
X = Br or Cl	R^1 = H, $R^2 = C_7H_{15}$ (91%)

Scheme 93

Cleavage of γ-butyrolactone using aluminum bromide (2.2-1.8 molar equivalents) and ethane, *n*-propane, *i*-propane and *i*-butanethiol afforded the respective γ-(alkylthio)butyric acid **246** in excellent yield (*Scheme 94*).[273]



246

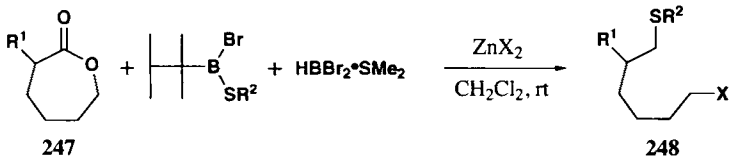
R	Yield (%)
n-Pr	92
i-Pr	93
i-Bu	83

Scheme 94

Primary and secondary alkanethiol reacted more efficiently than benzenethiol, which required longer reaction times.[273] The reagent system AlX_3-thiol is characteristic of only a selective *O*-alkyl cleavage for all of the β-, γ-, δ- and ε-lactones investigated.[273] The method

gave better results in comparison with a procedure in which lithium thiomethoxide has been used.[274] The resulting ω-alkylthio and ω-arylthio carboxylic acid can recyclize to the respective alkylthio or arylthiolactones. For instance, 4-(phenylthio)butanoic acid and 5-(phenylthio)pentanoic acid can be recyclized to 4-(phenylthio)-γ-butyrolactone and 5-(phenylthio)-δ-valerolactone, respectively.[276]

Lactones, *e.g.* **247** are effectively converted to ω-bromoalkyl sulfides **248** in reaction with an equimolar mixture of phenyl or *n*-butyl thexylbromothioborinate and dibromoborane-dimethyl sulfide (*Scheme 95*) in the presence of zinc halides.[277] Nucleophilic cleavage of the alkyl-oxygen bond by the halide ion was considered as the crucial step in the reaction. The method worked well with 7- and 8-membered as well as macrocyclic lactones. The reaction of γ-butyro- and δ-valerolactone with phenyl sulfide afforded the corresponding ω-bromoalkyl sulfide in only 25% yield.[277]

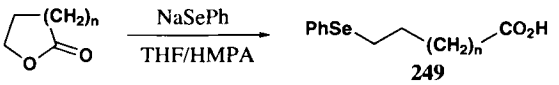


247 **248**

R^1 = H, R^2 = C_6H_5, X = Br (72%); R^1 = H, R^2 = *n*-Bu, X = Br (68%);
R^1 = H, R^2 = C_6H_5, X = I (71%); R^1 = H, R^2 = *n*-Bu, X = I (59%);
R^1 = H, R^2 = C_6H_5, X = I (62%); R^1 = Me, R^2 = *n*-Bu, X = Br (67%)

Scheme 95

Phenylselenide anion, a powerful non-basic nucleophile, has been used for the conversion of lactones into ω-phenylselenocarboxylic acids in an S_N2-type cleavage reaction. In medium size ring lactones, the alkyl-oxygen bond is cleaved to give ω-phenylselenyl acids **249** upon reaction with sodium or lithium phenylselenide in THF/HMPA solution (*Scheme 96*).[271]



249

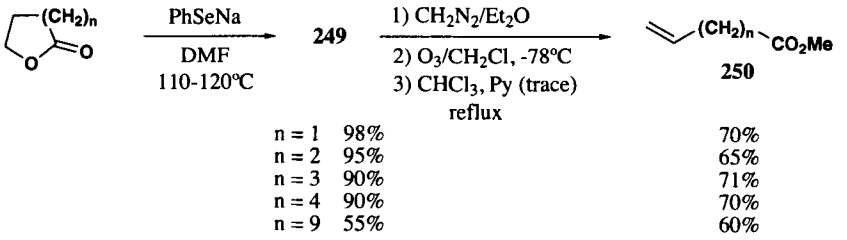
n = 1 (85%), n = 2 (85%), n = 3 (20%)

Scheme 96

The cleavage of several other γ-lactones proceeded in at least 75% yield. Steric crowding at the γ-carbon in γ-butyrolactone (*n*-hexyl or dimethyl substitution) lowers the yield remarkably to 20%.[272,278] The reaction was sensitive to the degree of solvation of the phenylselenide anion and the following reactivity gradient was established: NaSePh/18-Crown-6/THF > NaSePh/HMPA/THF > LiSePh/HMPA/THF > LiSePh/THF ~ LiSePh/diethyl ether ~ PhSeSePh/$NaBH_4$/THF/EtOH. The sodium phenyl selenide-borane complex, formed in the reaction of diphenyl diselenide with sodium borohydride in EtOH/THF, has been found unreactive. It has also been reported that the more ionic sodium phenyl selenide is significantly more reactive

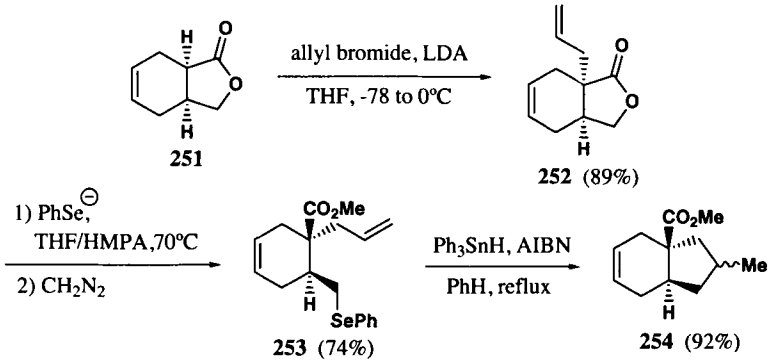
than its lithium counterpart.[272,278] Thus, reaction of valerolactone with lithium phenyl selenide in THF/HMPA for 3 h gave **249** (n = 2) in 33% yield.[278]

ω-Phenylselenylcarboxylic acids are in general useful synthetic precursors of ω-vinyl carboxylic acids. Thus, the conversion of lactones to ω-phenyl selenyl carboxylic acids **249**, achieved by S_N2-type reaction of sodium phenylselenide in HMPA or DMF, is followed by further oxidation-elimination to the final products, ω-vinylcarboxylic acids **250** (*Scheme 97*).[272]



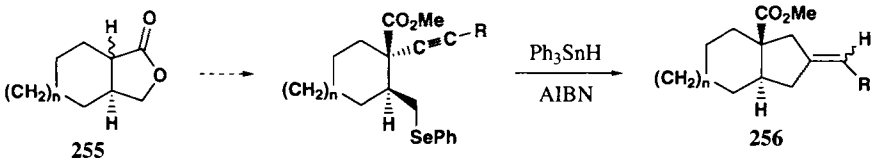
Scheme 97

The esterification of ω-phenylselenylcarboxylic acids before the oxidation step has been found essential. Otherwise, the selenoxide derived from selenide **249** (n = 2) undergoes rearrangement to yield δ-valerolactone.[271]



Scheme 98

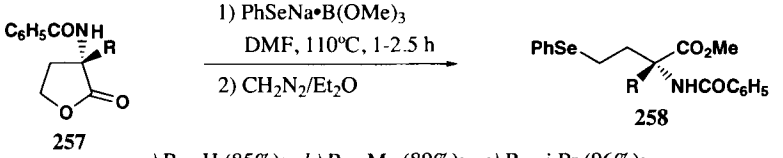
The phenylselenylation of lactones followed by radical cyclization was also used in the synthesis of bicyclic compounds (*Scheme 98*).[279,280] Alkylation of the enolate derived from bicyclic lactone **251** with allyl bromide furnished lactone **252** which upon cleavage with sodium phenylselenide (NaSePh), generated from diphenyl diselenide and sodium hydride, and esterification with diazomethane gave unsaturated selenide **253**. Treatment of selenide **253** with triphenyl stannane/2,2'-azobis(isobutyronitrile) (AIBN) furnished *trans*-ring-fused bicyclic compound **254**.[279,280] A series of bicyclic lactones have been examined. When 3-substituted prop-2-ynylic bromides were used as the alkylating agents for a series of saturated bicyclic lactones **255** (n = 1-3), alkylidene bicyclic compounds **256** were obtained in a similar sequence of reactions in at least 41% overall yield (*Scheme 99*).[280]



overall yield
n = 1 R = Ph (85%); n = 1 R = Pr (55%);
n = 2 R = Pr (56%); n = 3 R = Pr (43%)

Scheme 99

In a similar fashion, γ-lactones, derivatives of *N*-benzoylhomoserine, were effectively cleaved to the corresponding α-(2-phenylseleno)ethyl amino acids, upon action of a complex formed from diphenyldiselenide and sodium trimethoxyborohydride (*Scheme 100*).[281] The complex prepared from diphenyl diselenide with $NaBH_4$ was less effective and the uncomplexed sodium phenyl selenide gave no reaction product. α-Unsubstituted **257** (R = H) and α-methyl substituted *N*-benzylhomoserine lactone **257** (R = Me) were cleaved with the reagent

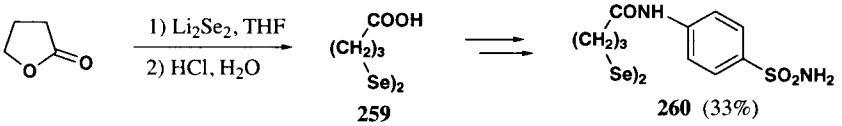


a) R = H (85%); *b)* R = Me (89%); *c)* R = *i*-Pr (96%);
d) R = $C_6H_5CH_2$ (97%); *e)* R = CH_2CH_2O*t*-Bu (87%)

Scheme 100

prepared from sodium borohydride and diphenyl diselenide to give compound **258a** and **258b** in 85% and 89% yield. However, the transformation of homoserine lactones bearing bulkier or more highly functionalized α-substituents to compounds **258c-258e** requires a more reactive complex to be used. The chemistry described above provides convenient access to α-(2-phenylseleno)ethyl amino acids and provides a key transformation for the synthetic approach to α-vinyl amino acids.[281]

In a synthesis of potential antiviral agents and cytokine inducers **260**, γ-butyrolactone was converted to 4,4'-diselenobisbutyric acid **259** by treatment with dilithium diselenide, generated *in situ* from elemental lithium and selenium (*Scheme 101*).[282]



Scheme 101

3. Reduction of Lactones

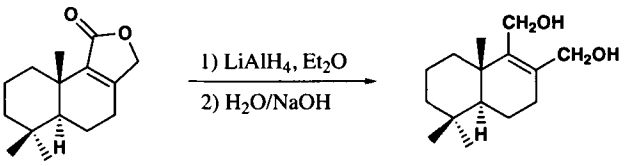
a) Reduction with Metal Hydrides

Nucleophilic reducing agents, such as sodium borohydride, lithium aluminum hydride and other complex metal hydrides are widely used for the reduction of organic compound

groups.[283] Hydrides are usually the reagents of choice for reductions of several organic functional groups. The reducing characteristics of the parent hydrides differ because of their structural variations and can be modified by changing the reaction conditions.[283] Among many hydrides currently in use for reductions, $LiAlH_4$ is an exceptionally powerful reducing agent for lactones, while $NaBH_4$, being a very mild reducing agent, reacts slowly. Lithium aluminium hydride reduces lactones to the respective 1,ω-diols (*Scheme 102*), usually isolated in excellent yield.

Scheme 102

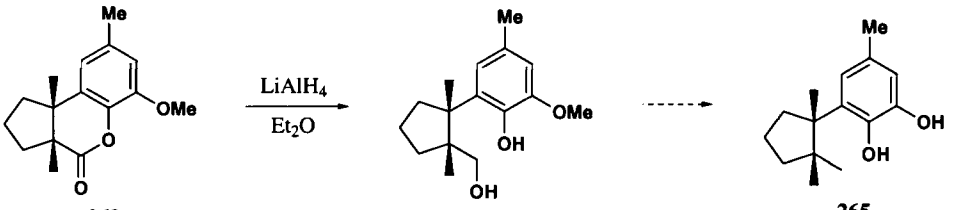
The literature on this subject is enormous and only some selected examples are presented. The $LiAlH_4$ reductions were carried out with aliphatic,[284-287] aromatic,[288-291] and unsaturated[292] lactones. Reduction of lactones being derivatives of various natural products, such as sugars,[293] sesquiterpenes[294-296] and diterpenes,[297,298] steroids,[299-301] alkaloids,[302] and macrocyclic compounds[303] has also been reported. Reduction of isodrimenin **261**[296] to diol **262**, which is an intermediate in the synthesis of physiologically active drimanic sequitriterpenes, is presented (*Scheme 103*).



261 **262** (90%)

Scheme 103

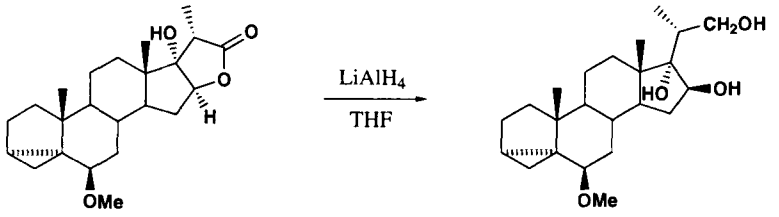
Herbertenediol **265**, a monomeric half of the axially chiral "dimeric sesquiterpenes" exhibiting nerve growth stimulating activity, was synthesized from diol **264** available through the reduction of lactone **263** with lithium aluminum hydride (*Scheme 104*).[295]



263 **264** (97%) **265**

Scheme 104

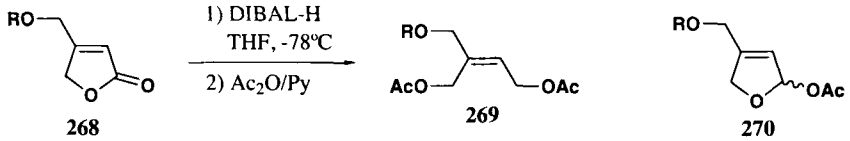
Recently, the reductive cleavage of steroid lactone **266** to diol **267** by $LiAlH_4$ (100% yield) has been described. The diol has been used as an intermediate in the course of an attempted synthesis of a strongly cytostatic saponin OSW-1 (*Scheme 105*).[300]



266 **267** (100%)

Scheme 105

Some reductions of lactones require complex reducing agents like Red/Al [sodium *bis*(methoxyethoxy)aluminumhydride],[289,291,301] L-Selectride (lithium tri-*sec*-butylborohydride),[289,291] and DIBAL-H (diisobutylaluminum hydride).[81,96] In the synthesis of dideoxydidehydronucleosides, potent anti-HIV agents, linear allylic acetate **269** was obtained by DIBAL-H reduction of unsaturated lactone **268** and acylation of the resulting diol (*Scheme 106*).[81] The expected unsaturated lactol acetate **270** was not formed.



268 **269** **270**

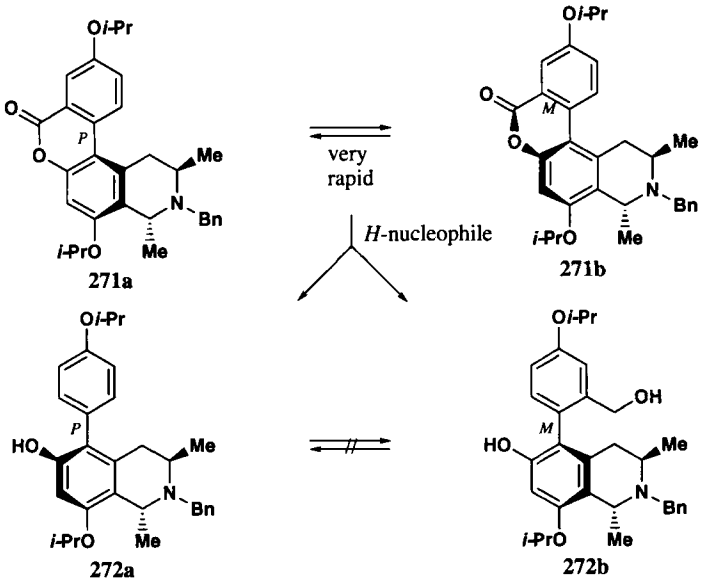
R = $SiPh_2$-*t*-Bu

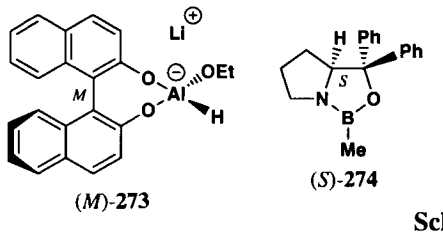
Scheme 106

Atroposelective lactone ring cleavage reactions have been extensively studied as a route to axially chiral biaryls.[269,288,289,291,304,305] The reduction of lactone-bridged biaryl compounds giving *M*- and *P*-atropoisomeric alcohols in high diastereoselectivity with Red/Al, $LiAlH_4$, L-Selectride, borane activated by oxazaborolidine and with chiral *H*-nucleophiles has been reported. Thus, reductive ring cleavage of lactone **271** proceeded in good yields and gave quite high diastereoselectivities already with achiral hydride transfer reagents, interestingly always with the *M*-configured diol **272b** as the main atropoisomeric product (up to 83:17 for L-Selectride). Selected examples are shown in *Scheme 107*.[289]

Sodium borohydride is considered essentially inert toward functional groups other than the carbonyl group in aldehydes and ketones.[283] However, some γ-lactones are reduced by $NaBH_4$[283,306,307] even under mild conditions (*Scheme 108*).[307] As an example, reduction of α-hydroxy-γ-lactone **275** to tetrol derivative **276** with sodium borohydride in tetrahydrofuran-water (4:1) mixture in over 65% yield is presented. Interestingly, the reduction of lactones which lack the α-hydroxy group, for example **277**, to the respective triol derivative, required the $BH_3 \cdot Me_2S$ complex or LAH as a reducing agent.[307]

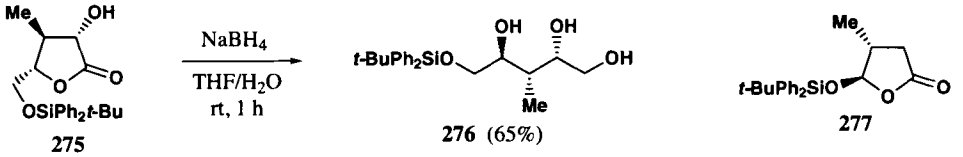
The reduction of ketal-lactone **279** to cyclic ethers **278** and **280** required $NaBH_4$ in the presence of $BF_3 \cdot Et_2O$ or $AlCl_3$ in boiling THF (*Scheme 109*). The regioselectivity of the reductive cleavage was strongly influenced by the nature of the Lewis acid added.[306] The reaction with



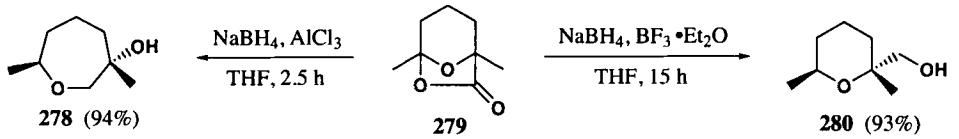


H-nucleophile	(M):(P)	Yield (%)
1 RedAl	69:31	87
2 LAH	73:27	76
3 L-Selectride	83:17	83
4 (*M*)-BINAL-H [(*M*)-**273**] (rt)	96:4	57
5 (*S*)-**274**·BH_3, 0°C	6:94	58
6 (*R*)-**274**·BH_3, -30°C	67:33	97

Scheme 107



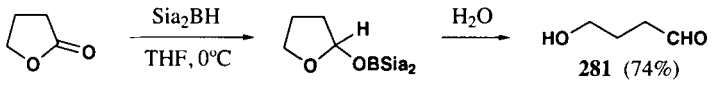
Scheme 108



Scheme 109

several other Lewis acids such as $TiCl_4$ and $ZnCl_2$ and other hydride sources like DIBAL-H, $NaBH_3CN$, Et_3SiH and $LiAlH_4$ instead of $NaBH_4$ gave negative results.

One of the major applications of disiamylborane [*bis*-(3-methyl-2-butyl)borane, Sia_2BH], in addition to the selective hydroboration of olefins, is the rapid reduction of γ-lactones to γ-hydroxyaldehydes. For example, γ-butyrolactone upon reduction gave 3-hydroxybutyric aldehyde **281** in 74% yield (*Scheme 110*).[308] The reaction appears to be quite general and

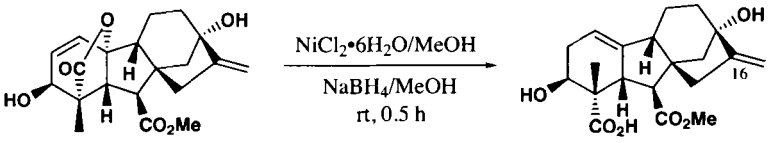


Scheme 110

provides a simple and convenient route to these reactive substances.[283,308,309] However, the corresponding reduction with borane went rapidly past this stage to yield predominantly the diol. A number of interesting applications of disiamylborane for selective reduction of lactones have been reported.[308] It has also been observed that esters are not reduced by this reagent under standard conditions.

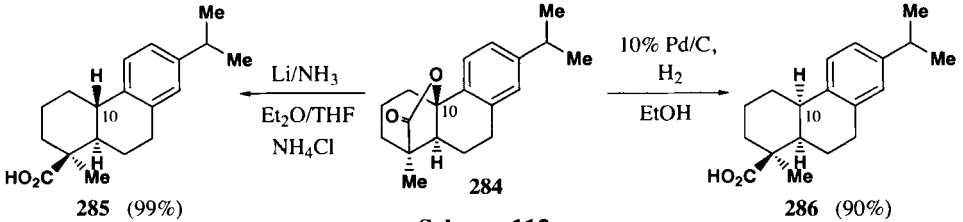
b) Miscellaneous Reductions

Cleavage of lactones under hydrogenolytic conditions is activated by the presence of an allylic double bond in the substrate, as illustrated in the following example. Thus, in the reduction of the allylic lactone functionality of gibberellin GA_3 **282**, nickel boride generated *in situ* was an effective reducing agent (*Scheme 111*).[310] The quantitative formation of compound **283** proceeded without reduction of the C(16) methylene group and the reaction was selective, although there were three allylic functional groups in **282**. Other reducing systems such as Li/liquid NH_3/*t*-BuOH or H_2/Pd-$BaCO_3$/piperidine, previously effective for reduction of analogous allylic lactones, were found to be inefficient.



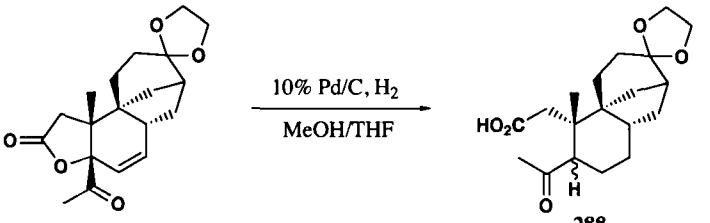
Scheme 111

Hydrogenolysis of the diterpenoid lactone **284** with lithium in liquid ammonia in the presence of NH_4Cl afforded carboxylic acid **285** with complete retention of stereochemistry at the benzylic asymmetric center (C-10). In contrast, inversion of configuration at C(10) was a result of catalytic hydrogenolysis (Pd-C) of lactone **284** carried out in the presence of palladium on carbon catalyst in ethanol to give carboxylic acid **286** (*Scheme 112*). These results are in conformity with the earlier observations for similar substrates.[311]



Scheme 112

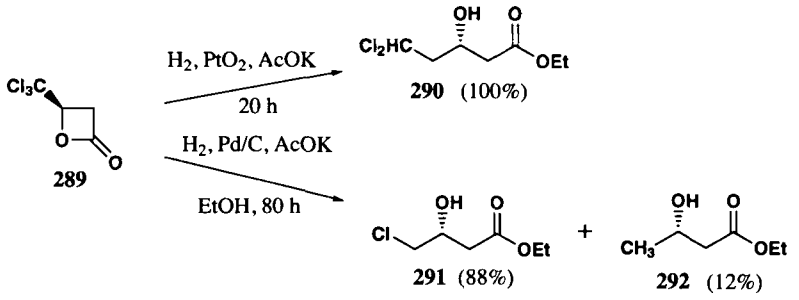
In the construction of ring A of diterpene stemodinone, simultaneous hydrogenolysis of allylic lactone **287** and hydrogenation of the olefin proceeded to give a diastereoisomeric mixture of keto acid **288** (*Scheme 113*).[312]



287 **288**

Scheme 113

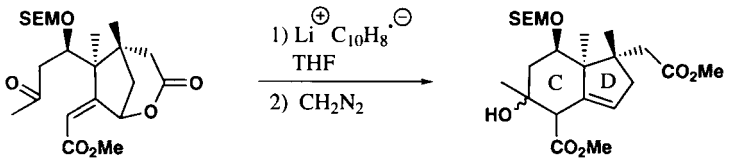
In the synthesis of biologically active γ-amino-β-hydroxy acids, catalytic hydrogenation of lactone **289** under various conditions was examined.[313] The reductions were carried out in EtOH under hydrogen atmosphere using catalysts such as Pd/C, PtO_2 and Ra-Ni in the presence of bases such as NEt_3 or AcOK. Compound **290** was formed as the major or only product when Pt/AcOK, Pd/C-NEt_3 or Pd/C-AcOK catalysts were used. In the presence of the Pd/C-AcOK catalyst, prolonged time reaction gave **291** (88% yield, *Scheme 114*) accompanied by completely dehalogenated product **292** (12% yield).[313]



289

Scheme 114

The reductive cyclization of allylic lactone **293** in the presence of two mole equivalents of lithium naphthalenide in THF at –78°C followed by the esterification of the carboxylic acid with diazomethane gave bicyclic diester **294**, the CD-ring fragment of natural triterpene glycinoeclepin A, in 50% yield (*Scheme 115*). The reductive cleavage of the lactone ring which proceeded with the assistance of the allylic double bond was followed by the base catalyzed intramolecular aldol-type condensation resulting in the formation of ring C of compound **294**. In the first step, one-electron transfer is followed by the fission of the lactone C-O bond to form a radical carboxylate which reacts with another electron to form an enolate ready for intramolecular condensation.[314] Similar transformation was observed when dimethylcuprate in THF at –78°C was used.[314] Efficient lactone cleavage-ring closing with formation (72% yield) of indene diester derivative similar to **294** was also observed when dimethylcuprate in THF at –78°C was used.[314]



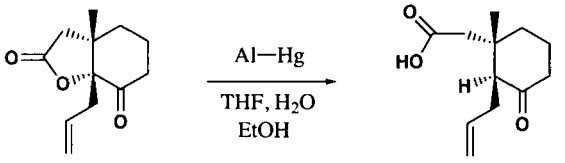
293

SEM = $CH_2OCH_2CH_2SiMe_3$

Scheme 115

294 (50%)

In carbonyl-assisted reduction, bicyclic keto-lactone **295** reacted with aluminum amalgam to produce **296** as an almost pure *trans* isomer (*Scheme 116*). The reduction of **295** with calcium in liquid ammonia gave a 3.5 : 1 mixture of the *trans*- and *cis*-isomers.[315] Under substantially more basic conditions of calcium in liquid ammonia, intermolecular protonation of the intermediate enolate competes with an intramolecular process in which proton is delivered from the α-oriented carboxyl group.[315]

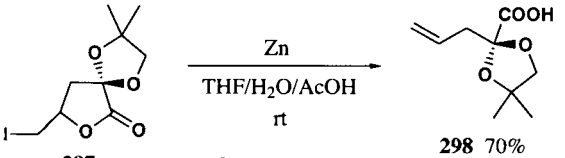


295

Scheme 116

296 (88%)

It is well known that reductive fragmentation of 6-bromo-6-deoxyglucosides with zinc in ethanol or with *n*-butyllithium in tetrahydrofuran results in the formation of 5,6-dideoxyhex-5-enoses.[316-319] In a similar reaction, the reductive dehalogenation of iodo-γ-lactone **297** afforded unsaturated carboxylic acid derivative **298** (*Scheme 117*).[320]



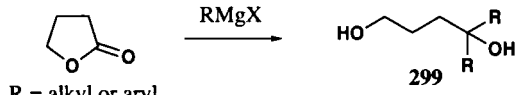
297

Scheme 117

298 70%

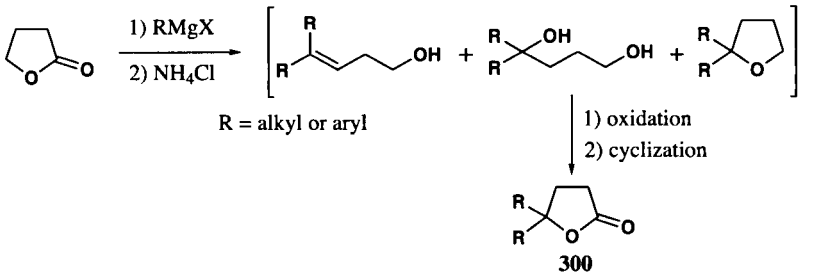
4. Reactions with Organometallics

The opening of the lactone ring *via* nucleophilic addition at the carbonyl residue affords access to a variety of adducts depending on the choice of nucleophile. The reaction of lactones with organometallic reagents is a useful tool for the homologation of the carbon chain, and the expected product of the addition of a Grignard reagent to the carbonyl group of γ-lactone is a dialkylated diol **299** (*Scheme 118*). The side-products of the reaction result from a single Grignard addition.[321] The Grignard reagents used in the reactions of lactones were prepared from alkyl,[322] allyl,[321] aryl-alkyl[322] or aryl[323] halides. In a typical reaction, γ-butyrolactone reacts with an alkyl or aryl Grignard reagent to afford a mixture of dialkylated products



Scheme 118

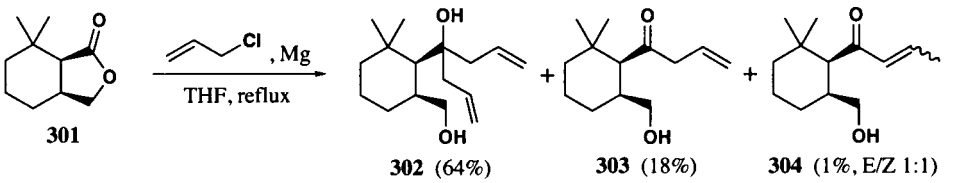
which after oxidation and cyclization give γ,γ-dialkyl- or γ,γ-diaryllactone **300** in good yield (*Scheme 119*). The following oxidants were used: 65% HNO_3, Ag_2CO_3, $K_2Cr_2O_7$, CrO_3, MnO_2, $KMnO_4$.[322]



RMgX: MeMgI, EtMgBr, *n*-BuMgBr, PhMgBr, $PhCH_2MgCl$, 1-naphthyl-MgBr

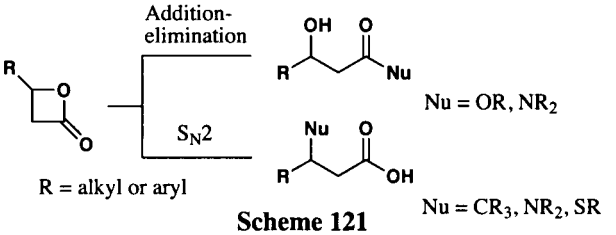
Scheme 119

In the synthesis of γ-damascone, *cis*-lactone **301** upon treatment with allylmagnesium chloride in refluxing THF afforded diol **302** in 64% yield. The other isolated side-products included compounds derived from mono-Grignard addition, hydroxy ketones **303** and **304** in 18% and 1% yields, respectively (*Scheme 120*).[321]



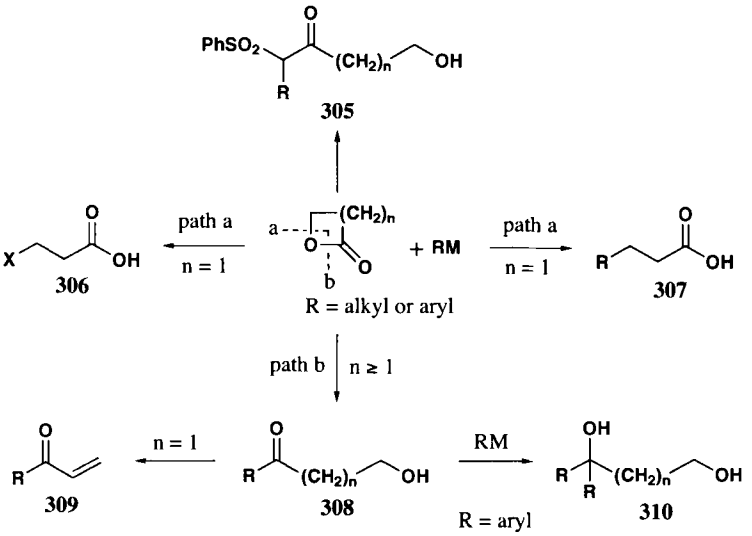
Scheme 120

The S_N2 ring-opening of bifunctional electrophilic β-lactones provides an access to a variety of versatile synthetic building blocks.[324] Depending on the nucleophile reactivity, addition-elimination or scission of the C_{alkyl}-O bond in an S_N2 reaction are the main pathways (*Scheme 121*).



Scheme 121

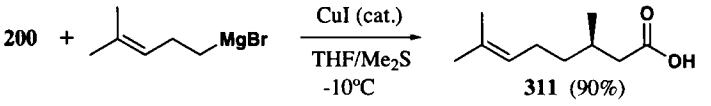
It has also been reported[324] that alkyl Grignard-mediated β-lactone ring opening is virtually insensitive to the steric environment of both the lactone electrophile and the nucleophilic carbon atom. In contrast, sp^2-hybridized nucleophiles, including vinyl- and phenyl-derived organometallics, do not undergo efficient S_N2 lactone ring opening.[324] In this process, the ring opening of the lactone can follow pathway *a* or *b* (*Scheme 122*), depending on the ring size and the nature of organometallic reagent RM.[325] For example, sterically constrained β-lactones react with lithium, magnesium and cadmium organometallics to give β-halopropionic acid **306** (X = Cl or Br), carboxylic acid **307**, β-hydroxyketone **308** (n=1-3), vinyl ketone **309** (R = aryl) and diol **310** (n = 2, 3), depending on the reagent and reaction conditions (*Scheme 122*). Homologous



Scheme 122

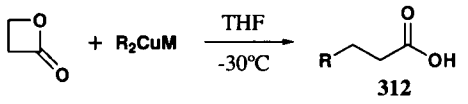
saturated lactones (n = 2 or 3) (*Scheme 122*, path b) commonly undergo a double organometallic attack to give mainly diols **310** (R = aryl, n = 2, 3) *via* intermediate hydroxy ketones **308**. Substituted γ-hydroxyketones **308** (n = 2) were prepared from the respective γ-lactones by reaction with *n*-BuLi in Et_2O or THF at –90°C. The reaction of β-propiolactone, δ-valerolactone and ε-caprolactone with *n*-butyllithium in ether and in THF at –90°C gave essentially negative results.[325] The reaction of 4-, 6- and 7-membered lactones with dilithio sulfones as organometallic reagents generated from alkyl phenyl sulfone and BuLi gave ω-hydroxy-β-keto sulfones **305** (n = 1, 3, 4; R = H or alkyl).[325]

β-Butyrolactones have been found to undergo regioselective S_N2 ring opening with alkyl Grignard reagents in the presence of a Cu(I) catalyst.[324,326] For example, in the synthesis of optically active terpenes citronellol and pulegone, (*R*)-β-methyl-β-propiolactone **200** easily prepared from 3-bromobutyric acid gave citronellic acid **311** in an S_N2 type ring opening with homoprenyl magnesium bromide in the presence of copper(I) salt (*Scheme 123*).[326]



Scheme 123

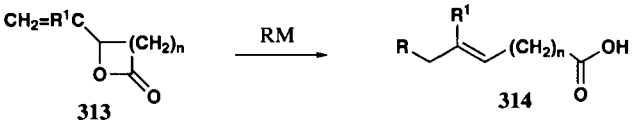
β-Propiolactone reacts also with various organocuprates to give β-substituted propionic acids **312** in high yields (*Scheme 124*).[327] In the reaction of lithium or bromomagnesium dimethyl cuprate with β-propiolactone in THF at –30°C, butyric acid was obtained in 70 and 86% yield, respectively. In general, it seems that halomagnesium cuprates gave better yields of products than respective lithium cuprate reagents (*Scheme 124*).[327]



R	M	Yield (%)
Me	Li	70
Me	MgBr	86
n-Bu	Li	83
n-Bu	MgBr	92
i-Pr	MgBr	79
Ph	Li	20
Ph	MgBr	80

Scheme 124

Regio- and stereoselective ring opening of β-, γ- and δ-lactones **313** with unsaturated substituents at the ω-position using organocopper reagents such as halomagnesium diorganocuprates or Grignard reagents in the presence of copper(I) iodide is a synthetic method for the preparation of (*E*)-3-, (*E*)-4- and (*E*)-5-alkenoic acids **314** (*Scheme 125*) *via* S_N2' reaction pathway.[328] In all reactions the *E*-isomer was found to be the major one, however, in most of the cases described up to 20% of the *Z*-isomer was detected.



n = 1 RM = MeMgBr/CuI, Me_2CuMgX, BuMgBr/CuI, R^1 = H, Me, Cl (70-96%);
n = 2 RM = BuMgBr/CuI, R^1 = H (93%);
n = 3 RM = BuMgBr/CuI, R^1 = H (95%)

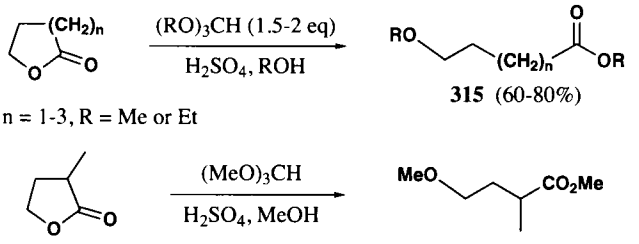
Scheme 125

Reports on cleavage of lactones with germanium and zirconium organometallics have also appeared.[329,330]

5. Miscellaneous Methods for Lactone Ring-cleavage

The high reactivity of lactones makes them susceptible to a great variety of reagents providing an effective method of synthesizing a specific target compound in a high yield reaction. Some examples are presented below.

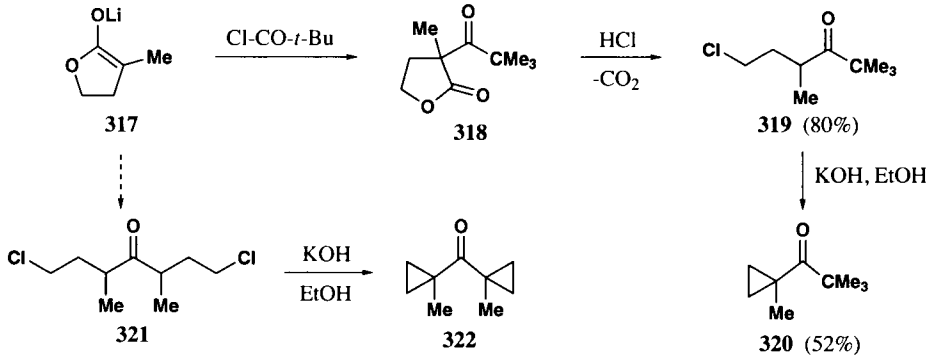
A one-step synthesis of ester-ethers **315** from γ-, δ- and ε-lactones has been reported.[331] This simple transformation requires treatment of a solution of the lactone and trialkylorthoformate in methanol or ethanol with a catalytic amount of acid (*Scheme 126*). Sulfuric, methanesulfonic, trifluoromethanesulfonic and perchloric acids are effective catalysts for this transformation.



Scheme 126

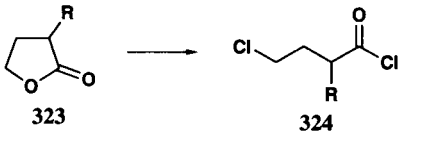
Reactions were generally complete in 3-8 h depending on the amount of acid catalyst added. Both γ- and δ-lactones are transformed in excellent yield (over 80%),[331] while ε-caprolactone gave the respective product in lower yield (61%). In the case of β-propiolactone decomposition products dominate the reaction mixture. In some reactions near quantitative yields are occasionally observed, *e.g.* **316**, whereas the sterically hindered substrates 2,2-diphenyl-γ-butyrolactone and 2β-hydroxy-3,3-diphenyl-γ-butyrolactone produced only trace amounts of the desired product. Other orthoesters including trimethyl orthoacetate, orthobutanoate, and orthobenzoate were used; however, less than 50% conversion was observed, even when large excess of the reagent was used.[331]

Lithium enolates of γ-lactones, *e.g.* **317**, are easily acylated in the α position to give 2-acyl-2-alkyl-4-butanolides **318**. The subsequent ring opening of **318** with HCl allows preparation of γ-chloroketone **319** which can be cyclized to 1-alkyl-1-acylcyclopropane derivatives **320** (*Scheme 127*).[332] The described methodology has also been applied to the synthesis of dicyclopropyl ketones. For example, 2-methyl-4-butanolide was transformed to dicyclopropyl ketone **322** *via* the intermediate **321** in over 50% overall yield.



Scheme 127

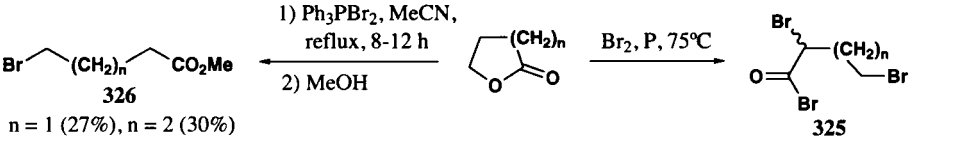
ω-Haloalkylcarboxylic acids are important bifunctional synthons which can function as alkylating agents. These compounds may be prepared from lactones and general methods of preparation of ω-halocarboxylic acids and their derivatives have been described.[333] α-Alkyl substituted γ-butyrolactone **323** can be cleaved to synthetically useful γ-chloroacyl chlorides **324** (*Scheme 128*).[332] For example, the 4-chloro-2-methylbutanoyl chloride (**324**, R = Me) was obtained in 80% yield from lactone **323** (R = Me) upon reaction with anhydrous zinc chloride in thionyl chloride solution. Sterically hindered lactone **323** (R = *t*-Bu) treated with zinc chloride in phosphorous pentachloride gave pure acid chloride **324** (R = *t*-Bu), albeit in 24% yield.[332]



323	Reagent	**324** Yield (%)
R = Me	$ZnCl_2$, $SOCl_2$, 65°C, 65 h	80
R = *t*-Bu	$ZnCl_2$, PCl_5, 100°C	24

Scheme 128

2,ω-Dibromoacyl bromides **325** can be prepared in good yield in the reaction of five- to eight-membered ring lactones with red phosphorus and bromine at room temperature and then with an additional equivalent of bromine at 75°C (*Scheme 129*).[334] In another reaction, lactone cleavage with



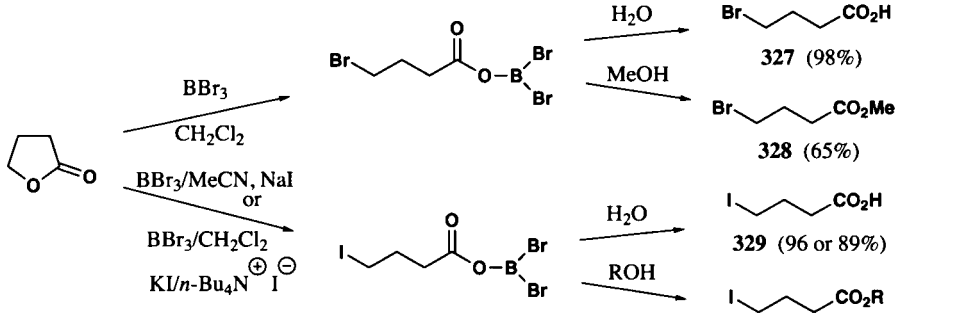
n = 1 (27%), n = 2 (30%)
n = 3 (34%), n = 4 (27%)

n = 1 (68%), n = 2 (55%)
n = 3 (78%)

Scheme 129

triphenylphosphine dibromide in refluxing acetonitrile afforded ω-bromoacyl bromides which were subsequently treated with dry methanol to give ω-bromomethyl esters **326** (*Scheme 129*), though yields were low, usually because of polymerization and tar formation.[335]

Lactones also react with boron tribromide in acetonitrile or methylene chloride to afford the corresponding ω-bromoalkylcarboxylic acids **327** and esters **328**, depending on the quenching procedure, in good yield. In the presence of iodide ion the corresponding ω-iodoalkylcarboxylic acids and esters are obtained (*Scheme 130*).[333] In a similar reaction, ω-iodocarboxylic acids **329** and esters **330** are

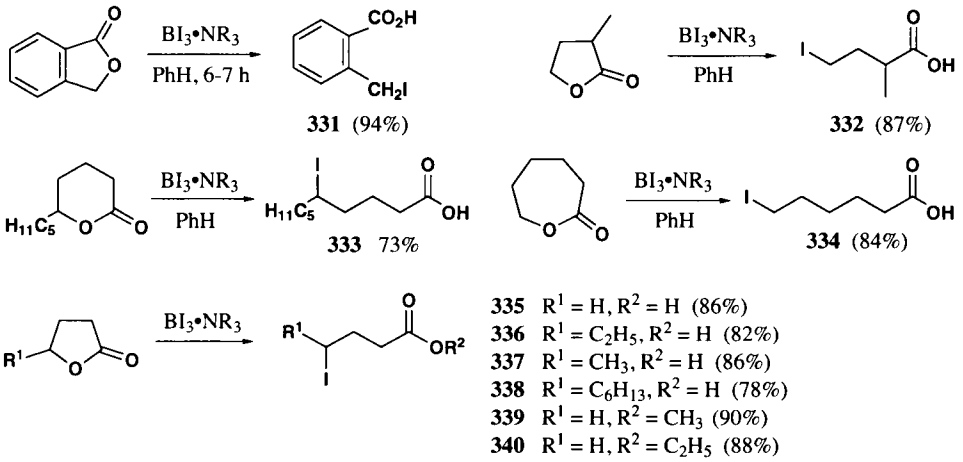


Scheme 130

R = Me (62%), R = *i*-Pr (55%)

prepared under homogenous (boron tribromide, sodium iodide in acetonitrile) or heterogenous phase transfer conditions (boron tribromide, potassium iodide in the presence of tetra-*n*-butylammonium iodide) (*Scheme 130*).[333] Four-, six- and seven-membered lactones under the above conditions afforded the respective ω-bromo and/or ω-iodo carboxylic acids in over 80% yield.[333]

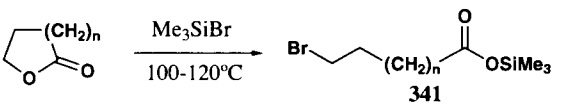
The use of a complex of triiodoborane and *N,N*-diethylaniline (NR_3) for the preparation of ω-iodocarboxylic acids and esters from γ-, δ-, and ε-lactones has also been reported.[336] The reaction is carried out in benzene and quenched with water or alcohol (MeOH, EtOH) to give acids **331-338** or esters **339** and **340** (*Scheme 131*). The products were obtained in very good yield, exceeding 80% in most cases. The esters can also be converted with thionyl chloride directly into ω-halocarbonyl chlorides.[337] ω-Bromo- and ω-iodocarboxylic acids have also been prepared under phase transfer conditions.[333]



335 $R^1 = H, R^2 = H$ (86%)
336 $R^1 = C_2H_5, R^2 = H$ (82%)
337 $R^1 = CH_3, R^2 = H$ (86%)
338 $R^1 = C_6H_{13}, R^2 = H$ (78%)
339 $R^1 = H, R^2 = CH_3$ (90%)
340 $R^1 = H, R^2 = C_2H_5$ (88%)

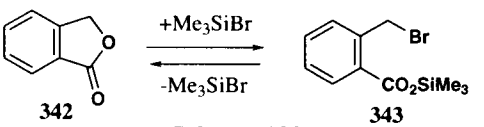
Scheme 131

Silyl esters of ω-bromo- and ω-iodocarboxylic acids are useful alkylating reagents, affording access to a wide range of compounds, including ω-hydroxy, ω-mercapto- and ω-amino acid derivatives. It is known that trimethylsilyl bromide fails to react with aliphatic esters; however, β-, γ-, δ- and ε-lactones undergo complete ring opening on treatment with this reagent at elevated temperatures to produce silyl esters of ω-bromocarboxylic acids **341** (n = 0-3) in excellent yields (*Scheme 132*).[337] In the case of aromatic lactone **342**, only equilibrium with ca. 30% of **343** was achieved.[337]



341

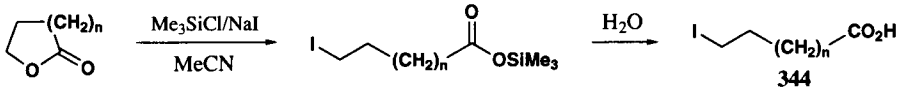
n = 0 (79%), n = 1 (86%), n = 2 (90%), n = 3 (96%)



342 **343**

Scheme 132

β-, γ- and δ-Lactones undergo ready cleavage on heating under reflux with trimethylsilyl chloride/sodium iodide in acetonitrile to provide, after hydrolytic workup, the corresponding iodoalkyl carboxylic acids **344** (n = 0-2) in 81, 79 and 84% yield, respectively (*Scheme 133*).[338] β-Butyrolactone reacted somewhat faster than γ-butyrolactone.

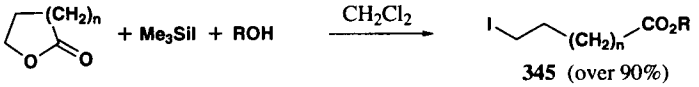


344

n = 0 (81%), n = 1 (79%), n = 2 (84%)

Scheme 133

Another synthetically useful transformation is the one-pot reaction of lactones with freshly distilled trimethylsilyl iodide (TMS-I) in dichloromethane. The reaction carried out in the presence of an alcohol provides a short and convenient way to iodoalkyl esters **345** in over 90% yield (*Scheme 134*).[339] The resulting ω-iodoesters are important intermediates in organic synthesis acting as alkylating reagents. In some reactions sequential addition was preferred. Thus, the reaction of lactones with TMS-I (one equivalent) in CH_2Cl_2 gave an iodoacid intermediate which upon addition of the alcohol and additional TMS-I (0.5 equivalent) afforded iodoalkyl ester in over 90% yield. No *t*-butyl ester formation was observed in the reaction of γ-butyrolactone.[339]

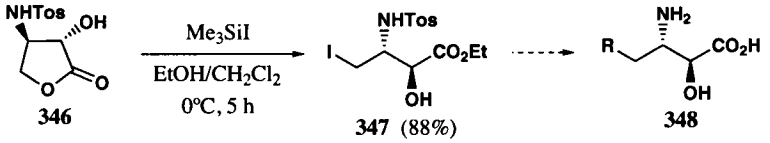


345 (over 90%)

n = 0-3; R = Et, Me, *i*-C_3H_7, *i*-C_4H_9, $C_6H_5CH_2$, *n*-C_3H_7

Scheme 134

(*S*)-Aspartic acid was transformed into the *trans*-hydroxy-*N*-tosylaminolactone **346** in a series of reactions. The opening of this lactone by treatment with TMS-I afforded homoserine derivative **347** in high yield (*Scheme 135*).[340] Iodo ester **347** was alkylated and deprotected in three steps to give 4-alkyl-3-amino-2-hydroxybutyric acids **348** in over 70% yield for each step.[340] α-Hydroxy-β-amino acids[341,342] are important constituents of a variety of biologically active compounds,[340,341] precursors of β-lactam and aminoglycoside antibiotics, constituents of biologically active peptides with antimicrobial and antitumor properties and of synthetic protease inhibitors.[340]

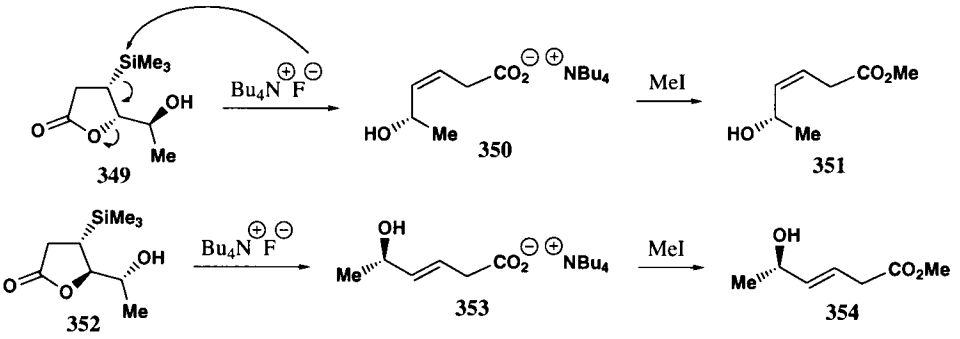


346 **347** (88%) **348**

R = Me (87%); R = Et (72%); R = *n*-Bu (77%); R = $C_6H_5CH_2$ (79%)

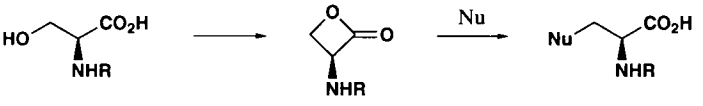
Scheme 135

Fluoride-mediated desilylation of hydroxylactones **349** and **352** was accompanied by ring cleavage leading to the corresponding *cis*- and *trans*-olefinic carboxylates **350** and **353**, respectively (*Scheme 136*).[343,344] These, on treatment with methyl iodide, gave the corresponding methyl esters, **351** and **354**.



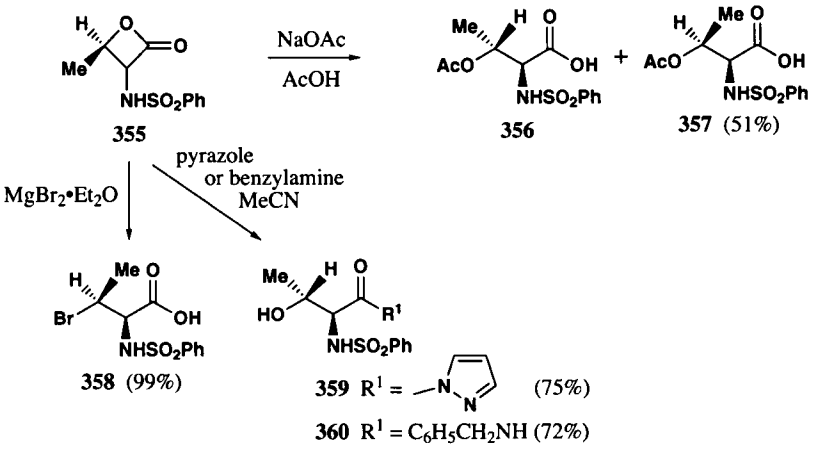
Scheme 136

Synthesis and reactivity of β-lactones derived from amino acids has been intensively investigated.[231,345] An *N*-protected derivative of serine, for example, can be cyclized under modified Mitsunobu conditions to β-lactones which afford access to stereochemically pure α-amino acids upon reaction with a variety of carbon or heteroatom (nitrogen, oxygen, halogen, sulfur) nucleophiles (*Scheme 137*).[257,345]



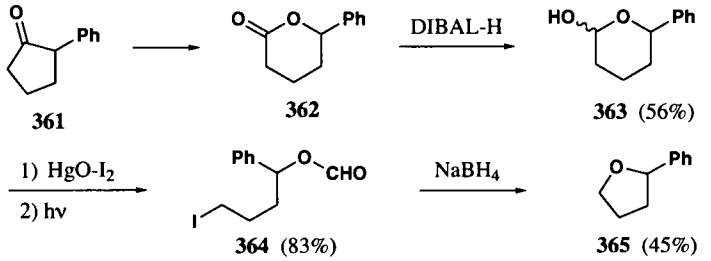
Scheme 137

In a similar fashion cleavage of α-amino-β-lactone **355** derived from threonine with various nucleophiles provides an effective method for synthesizing optically active *N*-protected α-amino acids.[231] The reactions with thiourea, LiHS or NaHS, pyrrazole, benzylamine, EtMgCl/CuBr·Me_2S, $MgBr_2 \cdot Et_2O$, $MgI_2 \cdot Et_2O$, $MgCl_2 \cdot Et_2O/Bu_4NCl$ as nucleophilic reagents have been reported.[231] Reaction of **355** with sodium acetate in acetic acid produced diastereoisomeric acetates **356** and **357** in 7:1 ratio (51% yield) (*Scheme 138*). The reaction of phenylsulfonyl derivatives of threonine **355** and of allo-threonine with anhydrous magnesium halides (chlorides, bromides, iodides) proceeded at the β-carbon to give single isomers of β-haloamino acid derivatives, for example **358** (99% yield). However, under the action of LiHS, NaHS and *N*-nucleophiles ring opening occurred primarily (if not exclusively) at the carbonyl carbon of the β-lactone. For example, the reaction of **355** with nitrogen nucleophiles like pyrazole and benzylamine gave amides **359** and **360** in 75% and 72% yield, respectively.[231] Apparently, the additional steric and/or electron-withdrawing effect of the α-nitrogen substituent on the β-lactone ring was responsible for the altering of the course of reaction from that observed with less-substituted β-butyrolactone and serine β-lactones.[231]



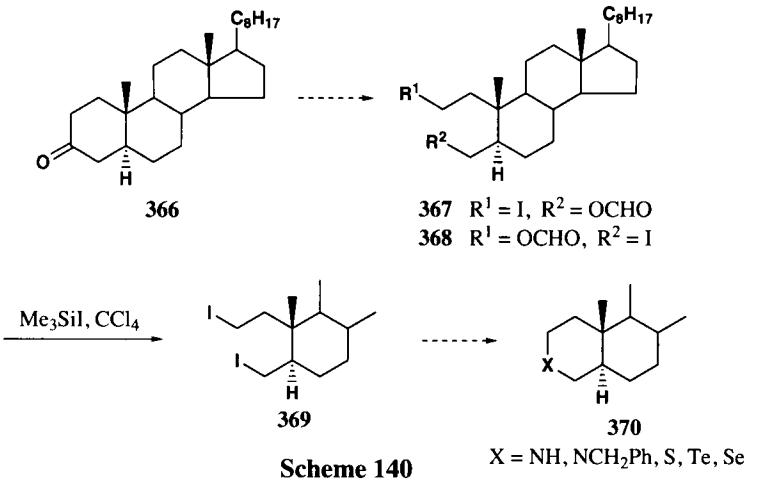
Scheme 138

Another interesting reaction involving lactones as intermediates is a general method for replacing the carbonyl group of cyclopentanone with an oxygen atom to give a corresponding tetrahydrofuran ring *via* a regioselective β-scission of alkoxyl radicals.[346] In the synthesis of natural lignans, the transformation of cyclopentanone **361** to tetrahydrofuran ring compound **365** *via* δ-lactone **362** has been elaborated. The crucial steps involve reduction of lactone **362** with DIBAL-H to lactol **363** and a regioselective β-scission of the alkoxyl radical generated from hypoiodite derived from lactol **363** to give iodoformate **364** (*Scheme 139*).[346] The method has been succesfully applied to the synthesis of oxasteroids from the corresponding cyclic ketones.[347-349]



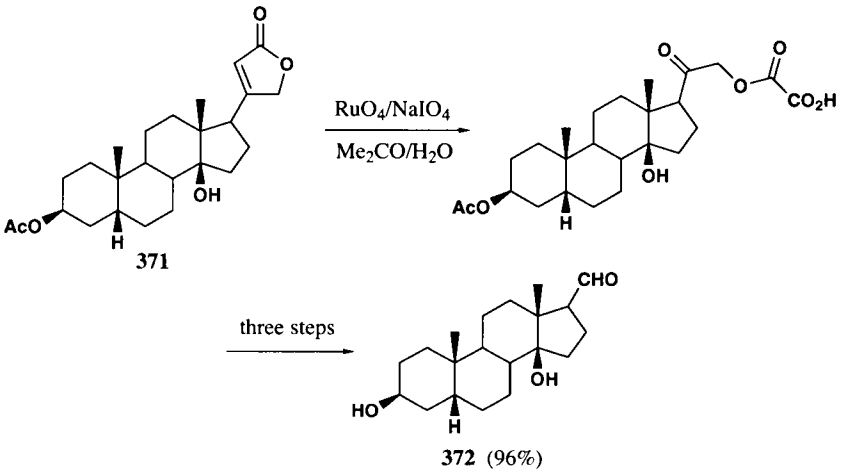
Scheme 139

This methodology has been applied to the synthesis of various heterocyclic compounds.[349] In steroids, for example, iodo formates **367** and **368**, prepared in three steps from 5α-cholestan-3-one **366**, upon reaction with trimethylsilyl iodide were transformed into the corresponding diiodide **369**, a crucial intermediate. This on treatment with either primary amines, sodium sulfide, sodium telluride or potassium selenocyanates readily afforded 3-aza-3-thia- or 3-tellura- and 3-selena-5α-cholestanes **370** (*Scheme 140*).[349] This versatile substitution of the carbonyl group of ketones by a heteroatom *via* intermediate lactones has also been applied to the synthesis of 16-thia-, 16-aza- and 16-selena-5α-androstanes from 5α-androstan-16-one.[349] Preparation of B- and C-ring heterosteroids has been described as well.[349]



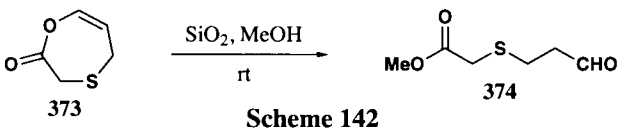
Scheme 140

Unsaturated lactones undergo typical oxidative cleavage. In the synthesis of 3β,14β-dihydroxy-5β-androstane-17β-carboxaldehyde **372**, a valuable intermediate in the synthesis of semisynthetic digitalis-like compounds, cleavage of the unsaturated lactone ring of digitoxigenin 3-acetate **371** was effected by $RuO_4/NaIO_4$ as oxidant (*Scheme 141*). The reaction was an alternative to potentially hazardous ozonolysis carried out in a pilot plant scale.[350]



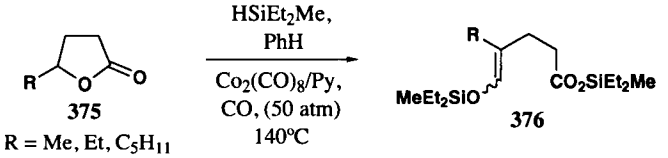
Scheme 141

Enol lactones are very labile compounds easily cleaved to the corresponding ester-aldehydes or ester-ketones. The labile enol thialactone **373** undergoes cleavage in MeOH containing silica gel at room temperature to give ester-aldehyde **374** (*Scheme 142*).[351]



Scheme 142

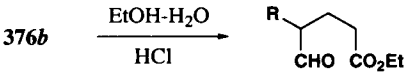
In the catalytic reactions of substituted γ-lactones **375** with hydrosilane and carbon monoxide in the presence of $Co_2(CO)_8$ under elevated pressure and temperature, a silyloxymethylidene group was incorporated to produce enol silyl ethers **376**, valuable synthetic intermediates in good yield.[352] Selected examples are shown in *Scheme 143*. The leaving group in the carbon-oxygen bond cleavage remained in the product as the silyl ester functionality. Desilylation of **376b** upon reaction with aqueous hydrochloric acid in ethanol afforded 1,5-aldehyde ester **377** in 90% yield.[352]



375 **376**

R = Me, Et, C_5H_{11}

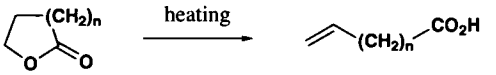
a) R = Me (87%); *b)* R = Et (67%); *c)* R = C_5H_{11} (81%)



376*b* **377** (90%)

Scheme 143

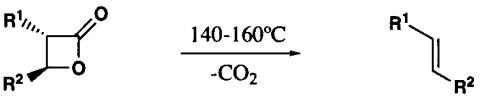
Thermolysis is another method of lactone ring cleavage. Lactones undergo thermal decomposition depending on the ring size of the substrate. Thus, lactones containing more than six atoms in the ring pyrolyze at temperatures over 520°C to give unsaturated acids.[353] For example, ten- and twelve- membered ring lactones **378** and **379** gave 8-nonenoic and 10-hendecenoic acids **380** and **381** in 92 and 86% yield, respectively (*Scheme 144*).[354]



378 n = 6 **380** (92%)
379 n = 8 **381** (86%)

Scheme 144

On the other hand relatively unstable β-lactones undergo elimination of CO_2 to give olefins.[354-356] It has also been shown that β-lactones containing bulky alkyl groups, *e.g.* *t*-butyl and/or 1-adamantyl, are decarboxylated at temperatures of 140-180°C to the corresponding olefins **382** with retention of initial geometry and without double bond isomerization (*Scheme 145*). The yields are in the range of 82-100%.[357]

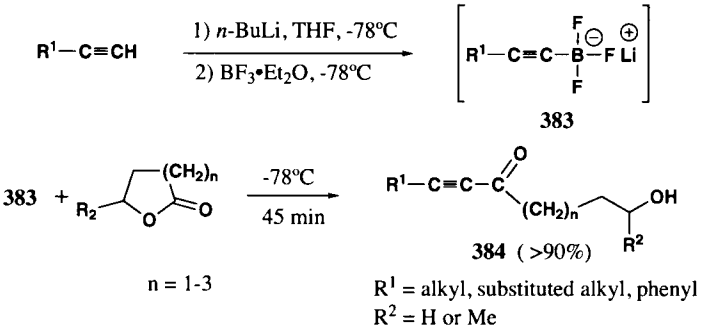


R^1 = *t*-Bu or 1-adamantyl **382**
R^2 = *t*-Bu or 1-adamantyl

Scheme 145

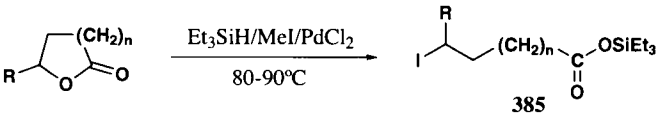
In contrast, 5-membered ring γ-butyrolactone shows two modes of decomposition, a decarbonylation reaction which gives CO, ethene and formaldehyde, and decarboxylation giving CO_2 and propene.[358] Alkynyltrifluoroborate salts **383**, readily generated *in situ* by the addition of

$BF_3{\cdot}OEt_2$ to alkynyllithiums, were shown to mediate the regioselective cleavage of 5-, 6-, and 7-membered lactones to afford substituted α-alkynones **384** in yields exceeding 90% in most cases. (*Scheme 146*).[359] The inherent ability of α-alkynones to undergo nucleophilic addition and cyclizations makes these compounds very useful intermediates in the synthesis of a wide range of more elaborated targets such as heterocycles, nucleosides, pheromones, drugs, and other bioactive compounds.[359]



Scheme 146

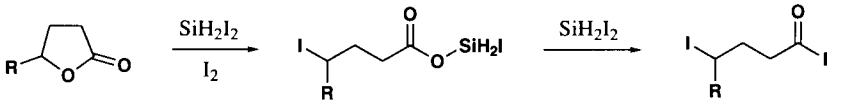
The ring opening of γ-, δ- and ε-lactones with triethylsilane (Et_3SiH)/alkyl halide/$PdCl_2$ reagents[360] is a reaction leading to synthetically useful silyl ω-halocarboxylates **385** in yields which depend on the ring size of the lactone (*Scheme 147*).[360] In a similar fashion, bromosilation of γ-, δ- and ε- lactones was achieved with the use of Et_3SiH/allyl bromide/$PdCl_2$ as the reagent[360] in 74, 79 and 75% yield, respectively. The products thus obtained were useful starting materials for *O*-silyl protected amino acids. However, the attempted iodosilation of unsaturated lactones, *e.g.* 2-furanone with Et_3SiH/MeI($PdCl_2$), was unsuccessful.



n = 1 R = H (68%); n = 2 R = H (88%); n = 3 R = H (68%);
n = 1 R = Me (87%); n = 2 R = Me (60%)

Scheme 147

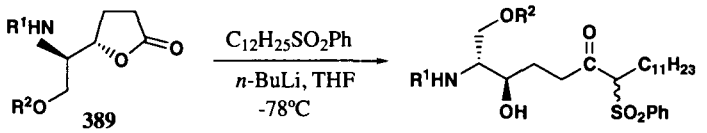
The ring opening of γ-butyrolactone with diiodosilane (SiH_2I_2)[361] afforded silyl 4-iodobutyrate **386** in quantitative yield. The (trimethylsilyl)-4-iodobutyrate has been formed in a similar manner. Hovewer, the second step occurred only with SiH_2I_2 and iodine to afford 4-iodobutyryl iodide **388** in 91% yield (*Scheme 148*). Interestingly, γ-valerolactone reacts slower and requires higher temperature for 80% conversion to **387** in 6h.



386 R = H
387 R = Me
388 R = H (91%)

Scheme 148

In the synthesis of piperidine alkaloids, nucleophilic opening of the γ-substituted γ-lactone **389** was also achieved with $C_{12}H_{25}SO_2Ph$ and *n*-BuLi to afford intermediate **390** (*Scheme 149*).[101]



Scheme 149

Ring cleavage-polymerization of β- and ε-lactones to polyesters catalyzed by (tetraphenylporphyrinato)aluminum chloride, alkoxide and phenoxide[362] or potassium naphthalenide[363] has been reported.

III. SYNTHESIS OF THIOLACTONES – AN OVERVIEW

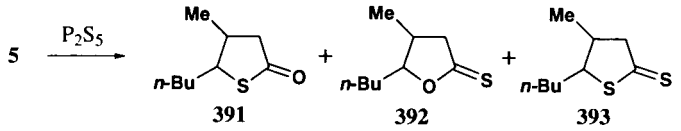
1. Introduction

Thiolactones are compounds valuable in synthesis[73] being also of biological significance.[364] For example, a new antibiotic thiolactomycin **21** contains a unique thiolactonic structure and shows activity against many species of microorganisms.[364] Thio- and thionolactones are used as versatile intermediates in organic synthesis.[88] For example, thionolactones are substrates for the construction of medium and large ring ethers in which organometallic addition, methyl iodide trapping of the intermediate hemithioketal and Ph_3SnH-AIBN reduction of the methyl thioketal intermediate are the crucial steps.[88] In contrast to this behavior of thionolactones, direct nucleophilic addition to medium and large ring lactones generally results in rupture of the ring due to the high reactivity of the tetrahedral intermediate obtained through the initial addition of the nucleophile to the sp^2 carbon of the lactone. α-Thiolactones as synthetic intermediates have also been postulated.[91]

Chemical synthesis of sulfur analogs of lactones has been an area of interest to synthetic organic chemists for over a century. In general, small ring thiolactones can be prepared by the addition of thioacetic acid to β,γ- or γ,δ-unsaturated carboxylic acids[90] and the synthesis of γ-thiobutyrolactone was carried out by pyrolysis of γ-mercaptobutyric acid in 78% yield.[90] Preparation of macrocyclic thiolactones has also been reported.[365-367] The use of phosphorus pentasulfide[368,369] as a reagent for the effective conversion of carbonyl to thiocarbonyl compounds has been the subject of continued investigation since it was first reported in 1869 by Henry[370] and by Wislicenus.[371] The usual procedure, which involves boiling in toluene,[372,373] xylene,[372,373] MeCN[373] or ethyl benzene[372] as solvent, normally requires a large excess of reagent and long reaction times and results in quite variable yields. The thionation reaction carried out in CH_2Cl_2 at room temperature[374] and in solvent-free conditions under microwave irradiation has also been reported.[69,375]

2. Oxygen-sulfur Exchange in Lactones

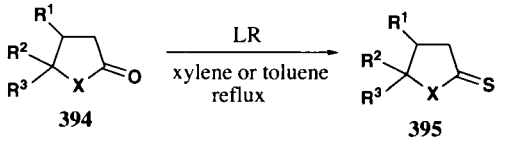
Small and medium ring lactones undergo thionation more readily than acyclic esters.[373] The reaction of "whiskey lactone" **5** with P_4S_{10} heated to 140-150°C for 10 min. and to 180-200°C for another 10-20 min. afforded a mixture of all three types of sulfur-containing lactones, *i.e.* thio- **391**, thiono- **392**, and dithio-lactones **393** (*Scheme 150*).[71,376] Selectivity of the reaction with P_2S_5 strongly depends on temperature and time. The compounds are of similar polarity and often could not be separated sufficiently.[71,377]



Scheme 150

2,4-*bis*(*p*-Methoxyphenyl)-1,3-dithiaphosphetane 2,4-disulfide, known as Lawesson's reagent (LR),[68,69,71,82,96,97,372-376,378-383] has been commonly used for the efficient conversion of oxygen functionalites into their thio analogs.[376,384] Recently, a review of Jesberger, Davis and Barner on the application of Lawesson's reagent has been published.[385]

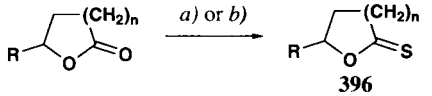
Simple substituted γ-lactones **394** gave the corresponding thionolactones **395** upon reaction with LR in refluxing xylene or toluene in high yields (*Scheme 151*).[376] A combination of P_4S_{10} reagent and hexamethyldisiloxane (HMDO) converts lactones to thionolactones **396** in yields comparable to or superior to those obtained with Lawesson's reagent or with P_4S_{10} alone (*Scheme 152*).[372,373] High



X	R^1	R^2	R^3	Yield (%)
O	H	H	H	98
O	CN	Me	Me	90
O	*i*-Pr	Me	Me	66
O	H	Me	H	97

Scheme 151

yields of thionolactones (>85%) as the nearly exclusive product from γ-alkyl substituted γ-butyrolactones were also achieved when LR-HMDO 1:1 mixture was used under microwave irradiation.[69] However, when LR alone or P_4S_{10}/HMDO mixture was used, appreciable amounts (up to 14%) of dithiolactone were detected.[69] Oxygen-sulfur exchange in lactones[70,74-78,386] can also be efficiently conducted with the aid of several sulfur-introducing reagents: thiourea/HBr,[70] $Na_2S{\cdot}9H_2O$-THF/H_2O,[75] potassium ethylthioxanthogenate in DMF,[76] potassium thioacetate in DMF,[74,78,387] potassium methylthioxanthogenate in dimethylacetamide.[77]

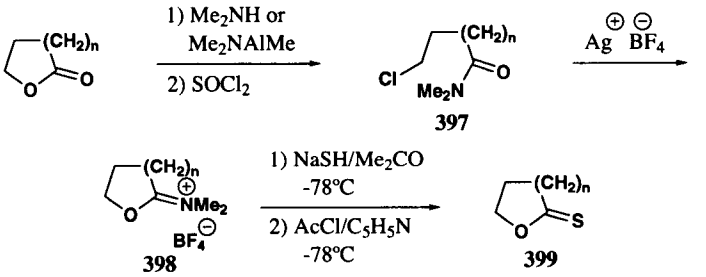


a) P_4S_{10}/HMDO/MeCN
b) LR (solvent)

n = 1	R = Me	*a)*	(87%)
		b) (PhMe)	(85%)
n = 2	R = H	*a)*	(82%)
		b) (MeCN)	(71%)
n = 3	R = H	*a)*	(82%)
		b) (PhMe)	(73%)

Scheme 152

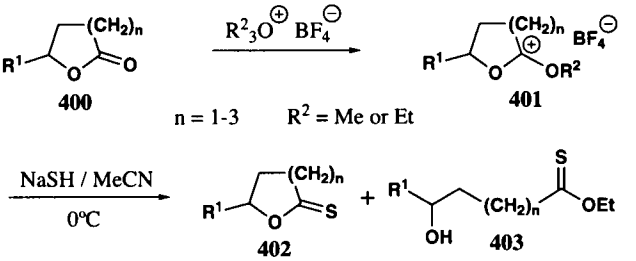
A preparative route to five-, six-, and seven-membered thionolactones **399** by a two-step, low temperature sulfhydrolysis-acetylation of *N,N*-dimethyliminolactonium salts **398** has been reported.[388] Compounds **398** were prepared in two steps from lactones *via* chloro-amides **397** (*Scheme 153*).



n = 1 (78%); n = 2 (43%); n = 3 (84%)

Scheme 153

A shorter and more convenient route to thiolactones was the *O*-alkylation of lactones **400** with Meerwein's salts $R_3O^+ BF_4^-$ (R=Me or Et) followed by treatment of the resulting *O*-alkyllactonium tetrafluoroborate salts **401** with Na_2S[380] or anhydrous sodium hydrosulfide in acetonitrile at 0°C. This led to five-, six-, and seven-membered thionolactones **402** (*Scheme 154*).[386] As by-products, the respective hydroxythionoesters **403** were isolated in yields up to 49%. The method is also adaptable to the conversion of macrocyclic lactones to the corresponding thionolactones.[386]

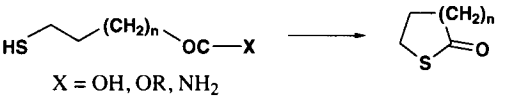


n = 1 R^1 = H	(90%)	-
n = 1 R^1 = Me	(78%)	(10%)
n = 2 R^1 = H	(54%)	(40%)
n = 2 R^1 = Et	(43%)	(49%)
n = 3 R^1 = H	(44%)	(17%)

Scheme 154

3. Cyclization of γ-Thiolcarboxylic Acids and Derivatives

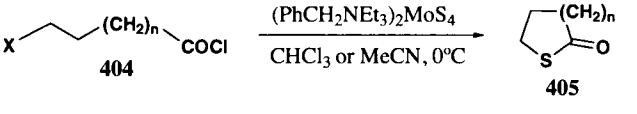
The cyclization of γ-thiol carboxylic acids,[389-396] esters[81,83,397] and amides[398,399] provides an effective and widely applied method for synthesizing thiolactones (*Scheme 155*). Cyclizations are carried out under a variety of conditions, mostly in the presence of acidic[392,394-398] or basic[83,391] reagents.



Scheme 155

4. Conversion of ω-Haloacid Chlorides to Thiolactones

An interesting sulfur transfer reaction mediated by benzyltriethylammonium tetrathiomolybdate $[(PhCH_2NEt_3)_2MoS_4]$ converts ω-halo acid halides **404** to the corresponding thiolactones **405** in moderate to good yields in one step (*Scheme 156*).[90]



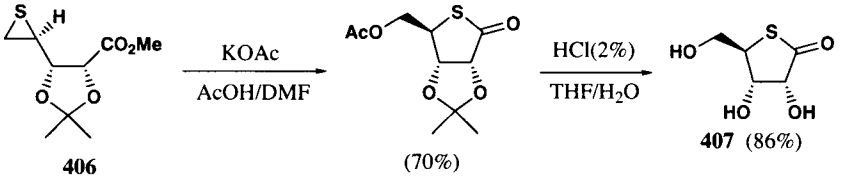
n = 0 X = I
n = 1, 2, 3, 10 X = Br

n = 0 (30%); n = 1 (65%);
n = 2 (77%); n = 3 (13%);
n = 10 (31%)

Scheme 156

5. Cyclization of Thiiranecarboxylic Esters

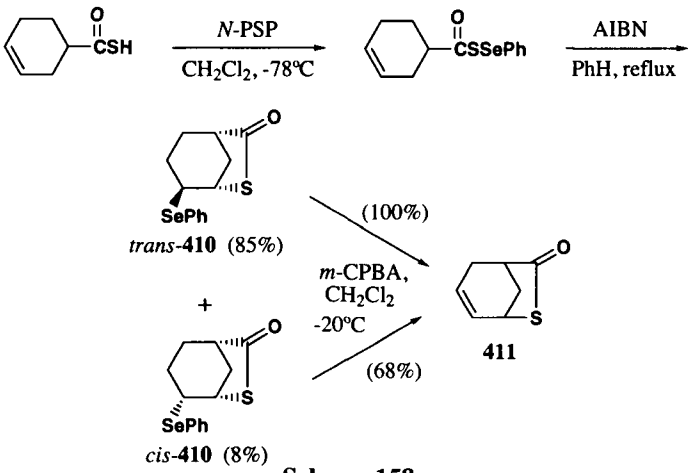
The synthesis of aldopentono-1,4-thiolactones by regioselective thiirane ring opening and thiolactonization can be accomplished on treatment of thiirane ester **406** with potassium acetate in AcOH/DMF mixture, at reflux temperature (*Scheme 157*).[400,401] Thus, 4-thio-*D*-ribono-1,4-lactone **407** has been prepared from *D*-gulono-1,4-lactone in few steps *via* thiirane ester **406**.[400]



Scheme 157

6. Selenothiolactonization of Selenosulfides

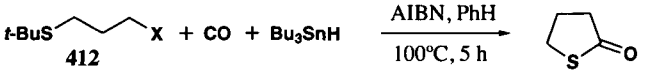
S-Acyl phenylselenosulfides, for example **409**, prepared from unsaturated thiocarboxylic acid **408**, on treatment with *N*-phenylselenophtalimide (*N*-PSP) undergo radical cyclization upon reaction with 2,2'-azobis(isobutyronitrile) (AIBN) in refluxing benzene to afford selenothiolactones **410**.[72] In the next step, unsaturated thiolactone **411** was exclusively formed by the oxidative removal of the phenylseleno group with m-chloroperbenzoic acid in methylene chloride at –20°C, while the thiolactone sulfur was not affected (*Scheme 158*).[72] The selenolactonization proceeds in high yield (81-93%) with the yield and regiochemistry of the *syn*-elimination of PhSeOH depending on the stereochemistry of phenyl selenothiolactone **410**.



Scheme 158

7. Intramolecular Homolytic Substitution by Acyl Radicals at Sulfur

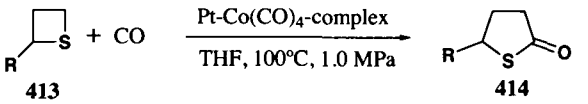
γ-Thiolactones are efficiently prepared by the reaction of 3-(*t*-butylthio)propyl derivatives **412** and carbon monoxide in the presence of tributyltin hydride and a catalytic quantity of AIBN (*Scheme 159*). The intramolecular homolytic substitution by acyl radical at the sulfur atom with the extrusion of *tert*-butyl radical is the key to the sequence.[402] In a similar reaction, α-methyl, β-butyl and γ-methyl-γ-thiolactones have also been prepared in 64, 86 and 75% yield.[402]



Scheme 159

8. Catalytic Carbonylation of Thietanes

γ-Substituted γ-thiobutyrolactones **414** have been prepared by catalytic carbonylation of thietanes **413** promoted by organoplatinum-cobalt heterodinuclear complexes (*Scheme 160*) involving CO insertion into the less substituted C-S bond of thietane in tetrahydrofuran at 100°C and under high pressure.[403]

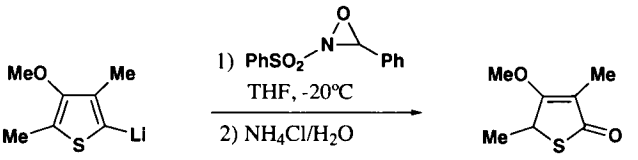


R = H (99%); R = Me (89%)

Scheme 160

9. Hydroxylation of Thiophenes

The oxidation of substituted thiophene derivative **415** with 2-(phenylsulfonyl)-3-phenyloxaziridine affords thiolactone derivative **416** in 59% yield (*Scheme 161*).[85]

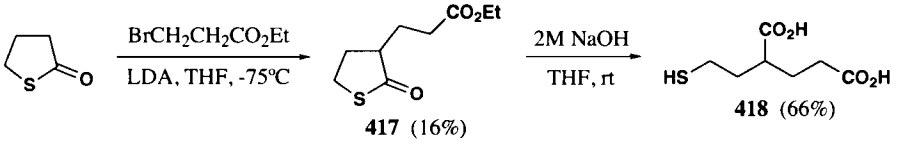


415 **Scheme 161** **416** (59%)

IV. CLEAVAGE OF THIOLACTONES

1. Base- and Acid-catalyzed Hydrolysis of Thiolactones

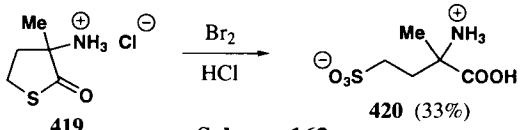
In analogy to lactones, their thio-analogs undergo acid-[404] and base-catalyzed hydrolysis under similar experimental conditions. In the far more frequently reported base-catalyzed reactions, NaOH,[404-414] KOH,[383,397,415,416] NaOMe,[417,418] are used and reactions are carried out in water, ethanol, methanol, dimethylsulfoxide, tetrahydrofuran, acetonitrile, dimethylformamide, dioxane and mixtures of these solvents. As an example, the synthesis of 2-(2-mercaptoethyl)pentanedioic acid **418**, the inhibitor of glutamate carboxypeptidase, is shown. It was synthesized by alkylation of γ-thiobutyrolactone with ethyl 3-bromopropionate in the presence of lithium diisopropylamide (LDA) followed by base-mediated hydrolysis of alkylated thiolactone **417** (*Scheme 162*).[412]



417 (16%) **418** (66%)

Scheme 162

In an acid-catalyzed reaction, racemic α-methylhomocysteine thiolactone **419** undergoes oxidative ring opening by bromine to the corresponding sulfonic acid **420** (*Scheme 163*).[396]

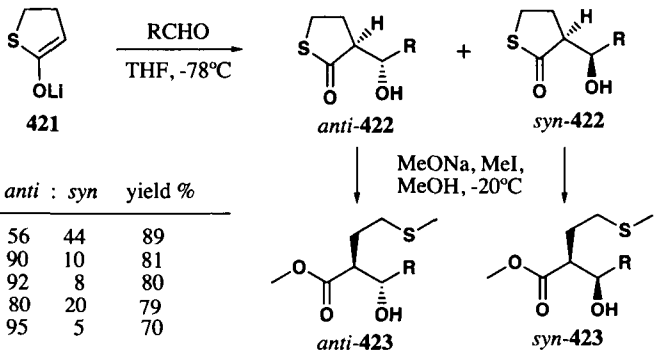


419 **420** (33%)

Scheme 163

2. Hydrolysis – *S*-Alkylation of Thiolactones

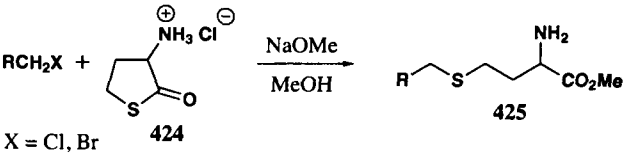
The hydrolysis of thiolactones under basic conditions is often carried out in the presence of an alkylating agent. As a result of the high nucleophilicity of sulfur, *S*-alkylated compounds are the final products of these reactions. The following examples illustrate this behavior. Aldol reactions of lithium enolates **421**, derived from γ-thiobutyrolactone, with aliphatic and aromatic aldehydes gave *anti* and *syn* adducts **422**. All the isolated *anti* and *syn* diastereoisomers were separately converted in ≥90% yield and without detectable epimerization to methyl esters **423** by treatment with MeONa (2 mol. equiv.) and MeI (3 mol. equiv.) in methanol at –20°C (*Scheme 164*).[418]



R	*anti* : *syn*		yield %
Ph	56	44	89
i-Pr	90	10	81
C_6H_{11}	92	8	80
n-C_6H_{13}	80	20	79
t-Bu	95	5	70

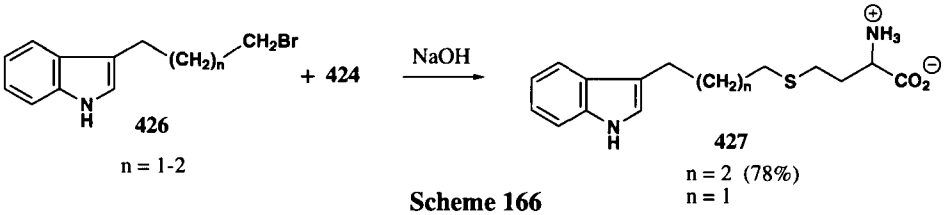
Scheme 164

A simple method for the synthesis of *S*-alkylhomocysteines **425** by the reaction of homocysteine thiolactone **424** with primary alkyl halides in sodium methoxide solution in 50-97% yield has been reported (*Scheme 165*).[417,419]



Scheme 165

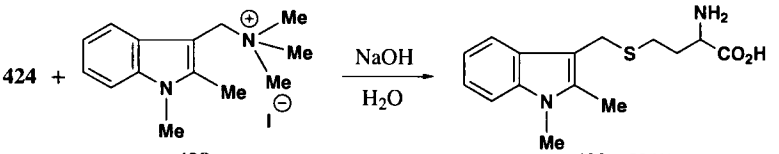
The hydrolysis-alkylation procedure has also been used in the reaction of homocysteine thiolactone hydrochloride **424** with 4-(3-indolyl)but-1-yl bromide **426** to give homocysteine derivative **427** (*Scheme 166*).[406,407]



Scheme 166

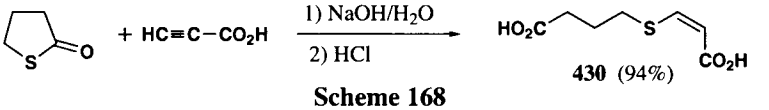
The basic hydrolysis of D,L-homocysteine thiolactone hydrochloride **424** accompanied by the alkylation of the thiol group was also reported as a key step in the synthesis of a novel antiviral agent *S*-adenosyl-D,L-homocysteine.[408,414] As a nucleophile, 5'-chloro-5'-deoxy-3-deazaadenosine[408] was used for the synthesis of *S*-(3-deazaadenosyl)-L-homocysteine.[414]

Preparation of *S*-(3-indolylmethyl) derivatives of homocysteine **429** from homocysteine thiolactone hydrochloride **424** and 1,2-dimethylgramine methiodide **428** has been reported (*Scheme 167*).[406]



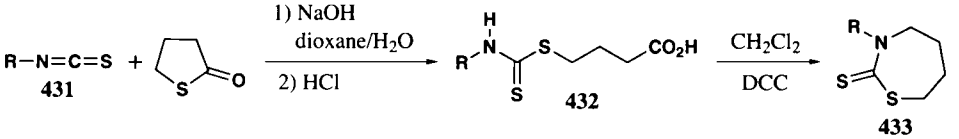
Scheme 167

Another example of the base catalyzed opening of thiolactone is the reaction of γ-thiobutyrolactone with propiolic acid which under basic conditions (NaOH) gave *cis*-3-(3'-carboxypropylthio)acrylic acid **430** (*Scheme 168*), an intermediate in the synthesis of β-lactam antibiotics.[411] Product **430** was isolated in 94% yield and contained less than 5% of the *trans* isomer.[411]



Scheme 168

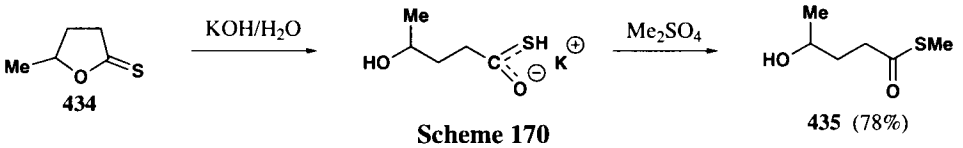
The reaction of electrophilic alkylisothiocyanates **431** with γ-thiobutyrolactone in alkaline medium yielded, after acidification, 4-thiocarbamoylthiobutyric acids **432** (*Scheme 169*). The yields were over 60% in most cases. Compounds **432** are cyclized to 3-substituted-2-thioxo-1,3-thiazepan-4-one **433**, cyclic dithiourethanes with a 7-membered ring system.[413] *N,N'*-Dicyclohexylcarbodiimide (DCC)/4-pyrrolidinopyridine in 10:1 ratio proved the best for the cyclization of **432** to **433** in moderate to high yields.[413] Most aromatic isocyanates gave appreciably lower yields of **433** (~20%).



R = alkyl, aryl, cyclohexyl, phenyl, *o*-, *m*-, *p*-tolyl, halophenyl, nitrophenyl, 1-naphthyl

Scheme 169

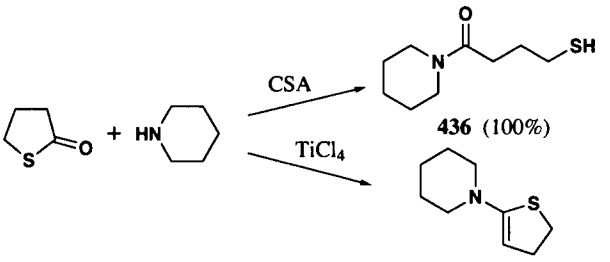
The hydrolysis of thiono-γ-valerolactone **434** with potassium hydroxide followed by methylation with dimethylsulfate affords methyl thioester **435** (*Scheme 170*).[383]



Scheme 170

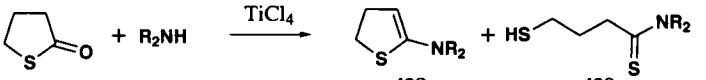
3. *N*-Nucleophiles

The reaction of γ-thiobutyrolactone and piperidine catalyzed by camphorsulfonic acid (CSA) promoted the formation of thiol-amide **436** (*Scheme 171*).[420] However, the same reaction catalyzed by titanium(IV) chloride enabled isolation of *S,N*-ketene acetal **437** in 71% yield. The compound was air- and moisture sensitive and appeared to be the first example of acyclic *S,N*-ketene acetal which is unstabilized by an electron-withdrawing group at the β-position.[420]



Scheme 171

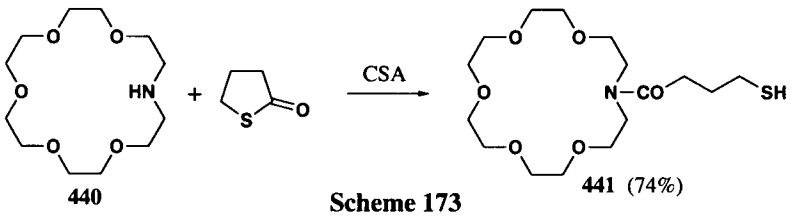
Other secondary amines under similar conditions gave mixtures of *S,N*-ketene acetal **438** and the ring opened amide **439** (*Scheme 172*).[420]



R_2NH	relative ratio of products (%)	
piperidine	>95	<5
pyrrolidine	0	100
diethylamine	70	30
morpholine	25	75

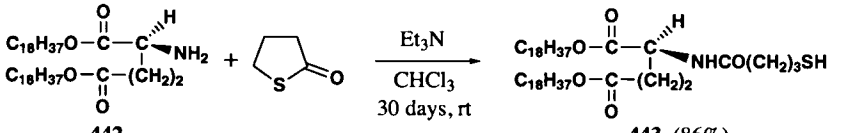
Scheme 172

N-(4-Mercaptobutanoyl)-aza-18-crown-6 **441**, starting material for the preparation of self-assembled monolayers applied in electroanalytical chemistry, has been prepared by the reaction of the nucleophilic 1-aza-18-crown-6 **440** with γ-thiobutyrolactone in refluxing toluene containing catalytic amounts of CSA in 74% yield (*Scheme 173*).[421]



Scheme 173

A slow base-catalyzed reaction of γ-thiobutyrolactone with L-glutamic ester **442** gave **443**, a dioctadecyl L-glutamate-derived anionic amphiphile which forms bilayer membranes (*Scheme 174*).[422]



Scheme 174

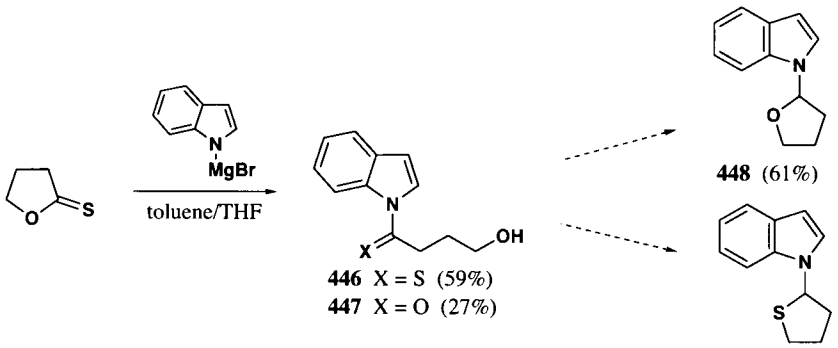
Amines are reported to open *N*-acyl-D,L-homocysteine thiolactone **444** to **445** quantitatively.[423] Similarly, thiolactones **444** can react with amino acids to form a peptide bond (*Scheme 175*). The hydrolytic opening of the thiolactone ring can be suppressed in favor of aminolysis by using low temperatures, since the temperature coefficient of the rate of aminolysis has been found to be exceptionally small.[424] Compounds containing primary amino groups can be thiolated rapidly at pH 7.5-8 by *N*-acetylhomocysteine thiolactone **444** (R = Me) using catalysis by Ag^+ and imidazole.[425] The ring opening of α,α-disubstituted γ-thiobutyrolactone has also been achieved by means of a Hg-assisted [$Hg(CF_3CO_2)_2$] reaction in the presence of benzyl amine.[426]

R = Me, R = C_6H_5; R^1 = alkyl or amino acid residue

Scheme 175

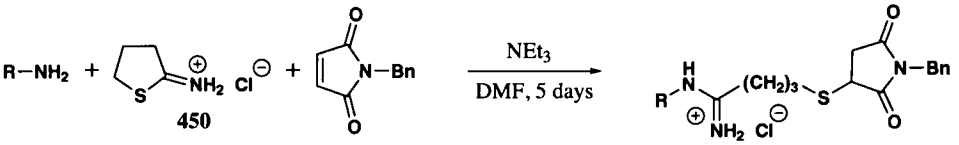
N-Acetylhomocysteine thiolactone **444** (R = Me) has been frequently used to introduce a thiol functionality into small molecules and macromolecules for a variety of biologically important purposes. Thiolation for labeling proteins was described in 1969.[425] For example, modification of proteins used in enzyme immunoassays by reaction with **444** (R = Me) has been described.[423] The nucleophilic sulfhydryl group can also be incorporated into the antibiotic tobramycin by treatment with racemic thiolactone **444** (R = Me).[423] The thiolation of aminoglycosides, muramyl dipeptides, serum albumin, enzymes, albumin microspheres, cell surface carbohydrates, lactoglobulin, oligonucleotides and amino lipids has been reported.[423,427-430]

The thioacylation of amines with thionolactone is another synthetically useful reaction. Thus, thionobutyrolactone reacted with indolylmagnesium bromide to give the desired indole ω-hydroxythioamide **446** with amide **447** as a side product (*Scheme 176*).[431] The resulting ω-hydroxythioamides *e.g.* **446** are efficiently converted to *N*-glycoside analogs **448** or 2-substituted tetrahydrothiophenes **449**.[431]



Scheme 176

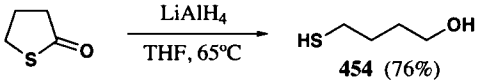
β-Glycosylamidine as a ligand for affinity chromatography has been prepared in the tandem nucleophilic opening of 2-iminothiolane hydrochloride **450**. Thus, the reaction of β-glucosyl- or β-galactosylamine with **450** was accompanied by electrophilic attack of *N*-benzylmaleimide to afford β-glucosyl- and β-galactosylamidines **451** and **452** in 69% and 55% yield, respectively. The same one-pot procedure using γ-thiobutyrolactone in place of **450** gave in a slow reaction β-glucosylamide **453** in 28% yield.[432] In the tandem nucleophilic opening of γ-thiobutyrolactone, the reaction with β-glucosylamine was accompanied by electrophilic attack of *N*-benzylmaleimide to afford β-glucosylamide **451** (*Scheme 177*).[432]



Scheme 177

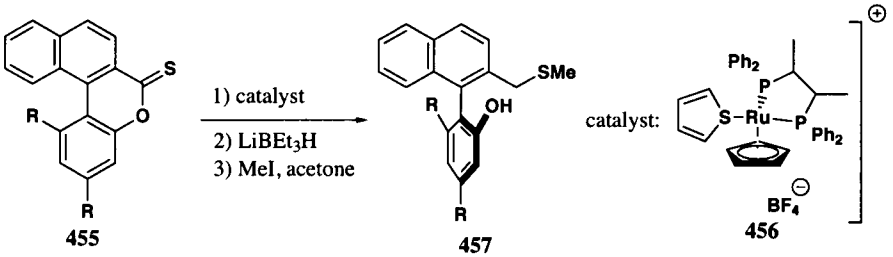
4. Miscellaneous Reactions

α,ω-Hydroxyalkanethiols have an extensive scope of applications and are used in organic synthesis as intermediates, in electrochemistry as monolayers on gold electrodes, in cancer radiotherapy[433] and as elements of biosensors.[365] An important compound, 4-mercapto-1-butanol **454** was obtained in the reduction of γ-thiobutyrolactone with lithium aluminum hydride in tetrahydrofuran in 76% yield (*Scheme 178*).[433]



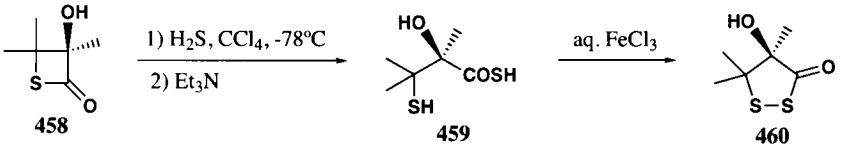
Scheme 178

The reductive ring opening of biaryl thionolactones with the aid of transition metal complexes has also been reported.[290,434] Atroposelective nucleophilic ring cleavage reactions of configurationally unstable biaryl thionolactones **455** assisted by ruthenium complex **456** at –78°C afforded axially chiral thioethers **457** with enantiomeric ratios of up to 92:8. At higher temperatures (0° or 23°C), the ratio was close to 1:1.[434] The intermediate thionolactone-ruthenium complexes were reduced with achiral ($LiBEt_3H$) or chiral [(M)-BINAL-H] H-nucleophiles (*Scheme 179*).



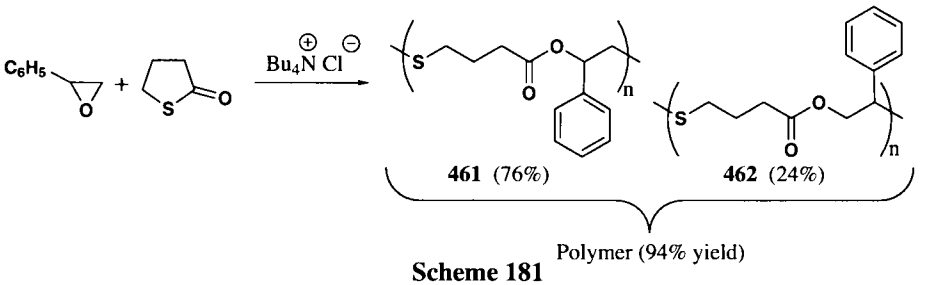
Scheme 179

The 1,2-dithiolane system is available by the cleavage-recyclization of the β-thiolactone. Thus, the reaction of β-thiopropiolactone derivative **458** with hydrogen sulfide and triethylamine in carbon tetrachloride at –78°C has been described to afford thiol thioacid **459** (*Scheme 180*) which underwent smooth oxidative cyclization to 1,2-dithiolane **460**, a fragment found in the antitumor antibiotic leinamycin.[394,435]



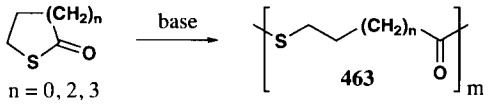
Scheme 180

The tetrabutylammonium chloride catalyzed alternating copolymerization of styrene oxide with γ-thiobutyrolactone produced the corresponding polymer (*Scheme 181*) in 94% yield.[436] The β-cleavage product **461** of thiolactone and α-adduct **462** were formed in the ratio of 76:24, reflecting the effects associated with higher electrophilicity and steric hindrance of α-carbon on styrene oxide. Other epoxides such as butyl glycidyl ether and 1,2-hexene oxide afforded products of β-cleavage of the oxirane in 100% yield.[436]



Scheme 181

In the absence of water and oxygen ε–thiocaprolactone polymerized by a base-catalyzed ring-opening reaction to linear polymer **463** (n = 3). In general, the reaction required elevated temperatures (110-180°C) and prolonged reaction time (15-40 h) to result in over 80% conversion (*Scheme 182*).[437]

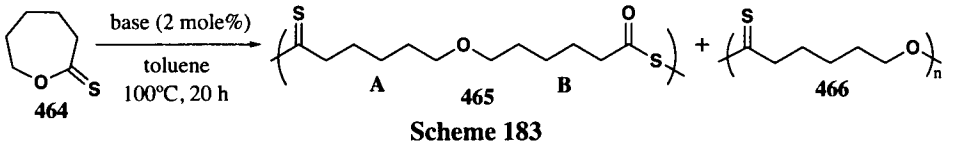


Scheme 182

When potassium *t*-butoxide (0.47 mole %), *n*-butyl lithium (1.0 mole %) or sodium dispersion (1.6 mole %) were used as initiator conversion of ε-thiocaprolactone was 100, 86 and 77%, respectively. No thermal polymerization took place at the temperatures employed in the absence of ionic initiators. The potassium *t*-butoxide catalyzed reaction of δ-thiovalerolactone to polymer **463** (n

= 2) resulted in 21% conversion. Under the same conditions γ-thiobutyrolactone did not polymerize.[437] However, the polymerization of β-thiolactone and α,α-disubstituted β-thiolactone by heating with trace of water or in the presence of a basic catalyst has been reported.[438]

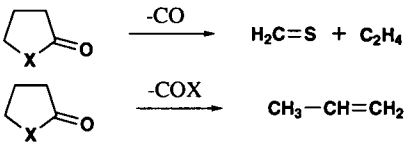
The anionic ring-opening polymerization of ε-thionocaprolactone **464** has also been examined.[439] When organolithiums (MeLi, *n*-BuLi, *sec*-BuLi, *t*-BuLi, PhLi), Grignard reagents (MeMgCl, *t*-BuMgCl) or lithium *t*-butoxide were used as initiators, the corresponding polythiocarboxylic-*O*-ester **466** was selectively formed and 100% conversion was observed. However, when potassium *t*-butoxide and 1,8-diazabicyclo[5.4.0]undec-7-one (DBU) were used, the corresponding polythiocarboxylic-*S*-ester **465** predominantly formed with the A and B unit ratio of 37:63 and 11:89, respectively (*Scheme 183*).[439]



Scheme 183

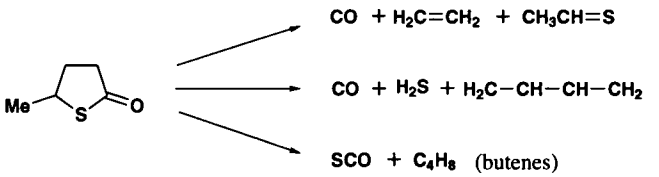
Ethyl lithiodiazoacetate[435] and oxiranes[436] have been reported as effective catalysts for the cleavage of thiolactones to afford alternating copolymers.

γ-Butyrolactone and γ-thiobutyrolactone show two modes of thermal decomposition, a decarbonylation reaction which gives CO, ethene and formaldehyde (or thioformaldehyde) and decarboxylation giving CO_2 (or COS) and propene. Decarboxylation has been found to be the main reaction for the lactone, and decarbonylation the main reaction for the sulfur analog (*Scheme 184*).[358]



Scheme 184

Under pyrolytic conditions at temperatures above 840°C the modes of thermal decomposition of γ-thiovalerolactone, α-methyl- γ-thiovalerolactone and β-methyl- γ-thiovalerolactone have also been determined.[355] The reaction of γ-thiovalerolactone proceded with the loss of carbon monoxide or carbonyl sulfide (*Scheme 185*).[355]



Scheme 185

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