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β-LACTONES: INTERMEDIATES FOR NATURAL PRODUCT TOTAL SYNTHESIS AND NEW TRANSFORMATIONS

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Abstract – The exploration of β-lactone reactivity and transformations has continued since the first synthesis of these strained heterocycles by Einhorn in 1883. The principal reactivity modes of β-lactones include nucleophilic addition resulting in either acyl C2-O1 or alkyl C4-O1 cleavage, rearrangement leading to ring expansion, decarboxylation, and electrophilic reactions of β-lactone enolates. Recent advances in asymmetric β-lactone synthesis has led to further developments in the area of novel transformations of β-lactones and significantly increased applications in natural product total synthesis. The latter topic is the focus of this review and covers the period inclusive to the end of 2003.

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This paper is dedicated to Dr. Pierre Potier on the occasion of his 70th birthday.

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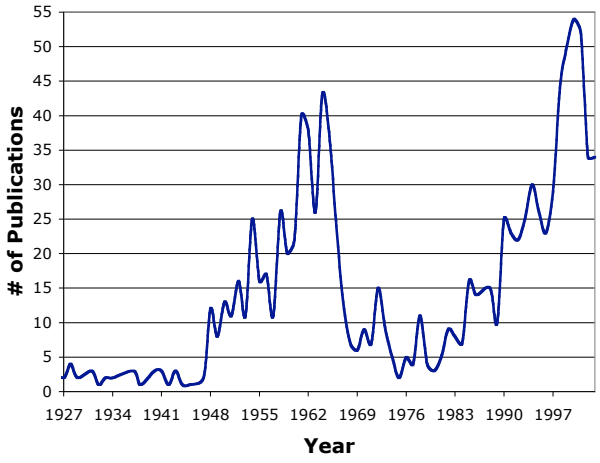
Despite the fact that the first β-lactone (2-oxetanone) synthesis was reported by Einhorn in 1883, these strained heterocycles have only recently received significant attention as synthetic intermediates.[1] One reason for this disparity is the lack of asymmetric methods for their synthesis.[2] In recent years, several advances in this area have begun to reveal the rich potential of the β-lactone nucleus as a valuable synthetic intermediate for natural and unnatural product synthesis. In addition, recently isolated, bioactive natural products possessing this structural motif are finding a utility as potent and sometimes specific inhibitors of protein function.[3] For example, Omuralide and the salinosporamides are highly potent and specific inhibitors of proteasome function.[4] This review briefly describes recent transformations of β-lactones described since 1993 when this subject was last reviewed[5] however, a primary focus is the application of these methods to the total synthesis of natural products, which has only occurred in the past 10 years. Natural products or precursors accessed *via* β-lactones as of 2003 are compiled in Figure 2. In line with this increased activity is the number of publications on the topic of "β-lactones" (Figure 1a) in the past decade. In the past two years a steady state of ~34 publications/year was reached following a record spike of publications numbering in the lower 50's in 1999-2001. A spike in activity (publications and patents-Figure 1b) also occurred in the 1950's to early 1970's, coinciding with the potential that β-lactones held as monomers for biodegradable polyesters useful as plastics and surgical materials.



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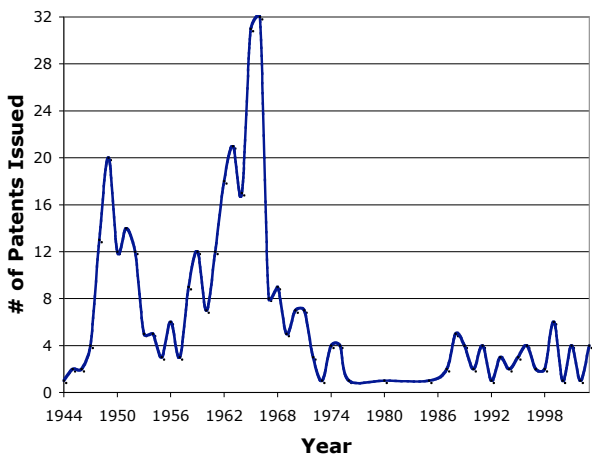


b)

Figure 1. Graphical data showing the number of (a) publications and (b) patents that include "beta-lactone" in the title or keyword by year inclusive to 2003 (source: SciFinder Scholar).

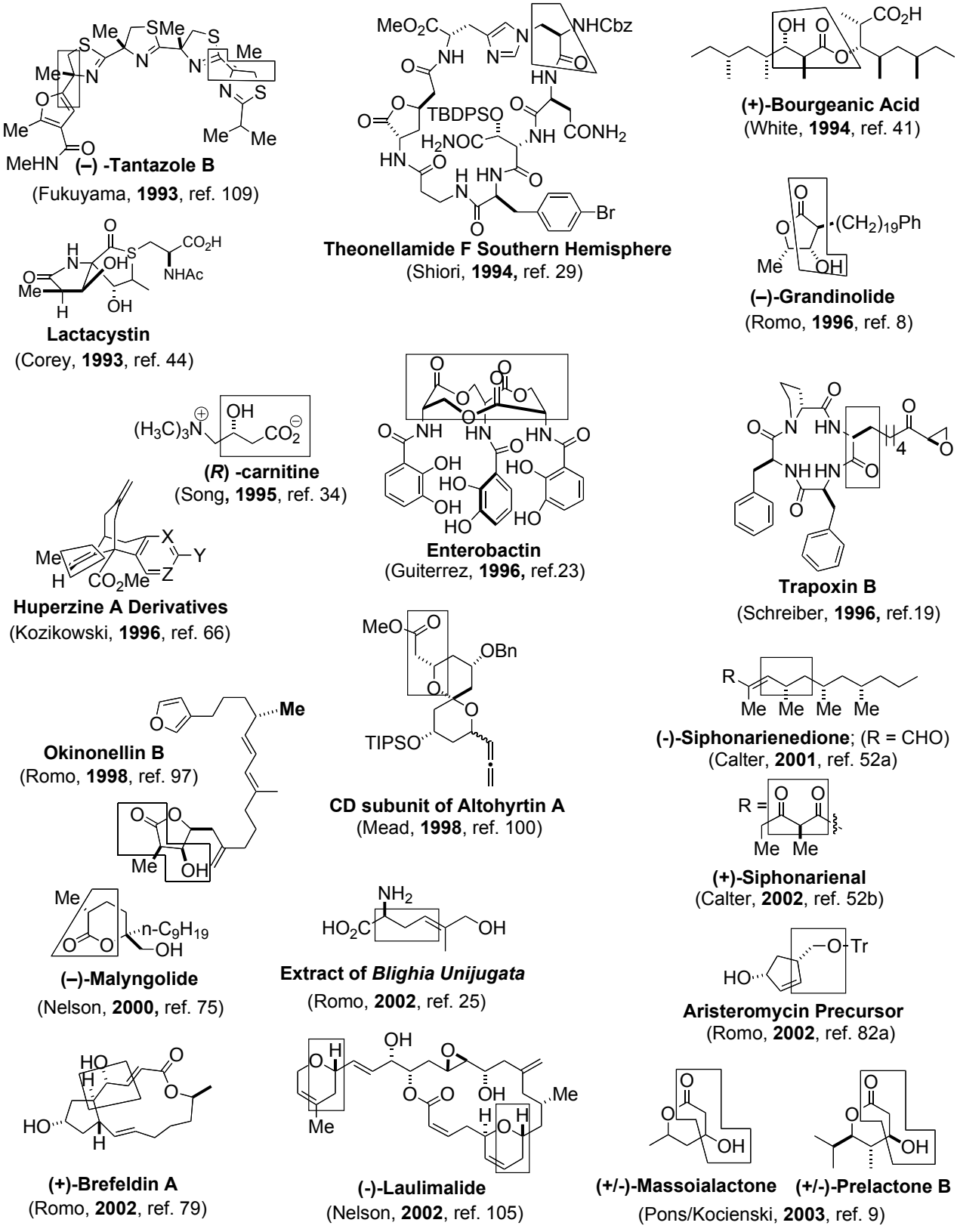


Figure 2. Natural products and precursors synthesized employing δ-lactone intermediates (atoms derived from the δ-lactone nucleus are boxed).

In the course of total syntheses and others studies, a variety of functional groups and ring systems have been accessed *via* δ-lactone intermediates. References included in this review are compiled in Table 1.

Table 1. Functional Arrays Accessible *via* β-Lactones

Functional Arrays Accessible *via* β-Lactones	Transformations of β-Lactones (ref #s.)					
	Alkyl C-O cleavage	Acyl C-O cleavage	Rrgmt.	Decarboxy-lation	Electrophilic addn.	Misc.
α-amino acids	13, 17, 19[NP], 27	17, 18, 22, 23,[NP] 25[NP]				
β-amino acids	27[NP], 28, 30					
α-hydroxy acids and esters		34[NP], 36-40, 41[NP]				
β-hydroxy thioesters		44[NP], 58				
β-hydroxy amides		45, 46, 50				
β-hydroxy ketones		51, 52[NP], 53[NP]				55
β-keto esters and β-keto amides		54				
1,3-diols		38				
β-thiol acids and esters	58					
β-halo acids and esters	59					
β-disubstituted carboxylic acids	61					
alkenes				63-65, 66[NP], 68, 69		
alkylidenecyclopropanes				70		
allylamines and sulfides				71		
α,β-unsaturated acids			10, 71			
allenes	75[NP]			73		
carbocycles	77, 78, 79[NP], 82[NP], 83	84		81	81	
epoxides	57					
2-methyleneoxetanes						16, 85, 86
substituted β-lactones					87[NP]	
tetrahydrofurans	59, 89[NP], 90					
γ-lactones		8[NP], 9[NP], 95, 96[NP]	7, 91, 92			
δ-lactones		8[NP], 9[NP]				
spirolactones	11	56	98			
spiroketals		99[NP], 100				
isochromans						78
butenolides			101			
3,6-dihydro-2*H*-pyran-2-ones			102			
2,3-dihydro-4*H*-pyrones			103, 104[NP]			
1,3-dioxan-4-ones					105	
1,3-dioxan-4,6-diones			106			
γ-lactams		107				
δ-lactams			11			
thiazolines	108[NP]					
oxazoles	108[NP]					

[NP] Designates reference to an application in or towards a natural product total synthesis.

This review is organized based on the type of functional arrays that are accessible from β-lactones. For each class of β-lactone derived products, new transformations involving the conversion of β-lactones to various functional arrays are described with a focus on the application of these methods to natural product

synthesis. Improved conditions and applications of previously developed β-lactone transformations are also briefly described.

2 GENERAL REACTIVITY OF β-LACTONES

The principal reactivity modes of β-lactones include cleavage of the acyl C2-O1 or alkyl C4-O1 bonds by nucleophiles, rearrangement leading to ring expansion, decarboxylation, and electrophilic reactions of β-lactone enolates (Figure 3).

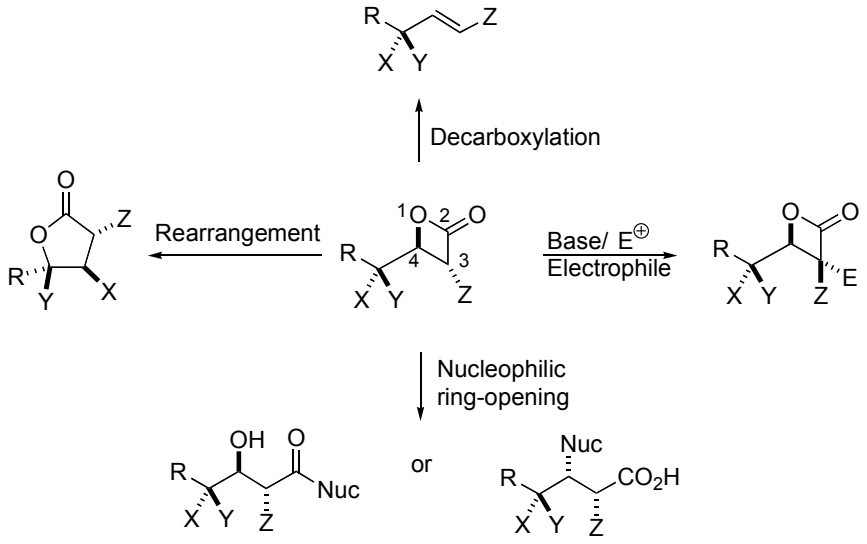


Figure 3. Primary Reactivity Modes of β-Lactones

2.1 DECARBOXYLATION

Decarboxylation of β-lactones can proceed *via* thermal decomposition, photolytic cleavage, or radical cleavage. These CO_2 extrusion reactions are in general stereospecific with complete transfer of stereochemistry of the β-lactone to the olefin *i.e*. *E*-olefins are obtained from *trans*-β-lactones and *Z*-olefins from *cis*-β-lactones (Figure 4).[6]

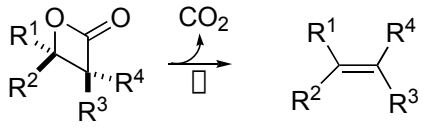


Figure 4. Decarboxylation of β-Lactones

2.2 REARRANGEMENT

When treated with various Lewis acids, β-lactones undergo non-concerted, dyotropic rearrangements to deliver butenolides or γ-lactones (Figure 5).[7] Lewis acids that promote this process include $MgBr_2$, $MgCl_2$, $TiCl_4$, $Ti(OiPr)_4$, BF_3, $FeBr_3$, $AlBr_3$, $SnCl_4$, $ZnCl_2$, and $Cu(acac)_2$.[5] γ-Lactones having

neighboring benzyl ethers can undergo ring expansion through a transacylation/debenzylation sequence in the presence of BF_3, BCl_3, or $FeCl_3$.[8] Recently, this process was extended to β-lactones with pendant silyl ethers.[9] α,β-Unsaturated acids can also be obtained *via* dyotropic rearrangements.[10] In a process not involving rearrangment but addition, SmI_2/NiI_2 promotes a coupling reaction between β-lactones and imines to form β-lactams in good yields.[11]

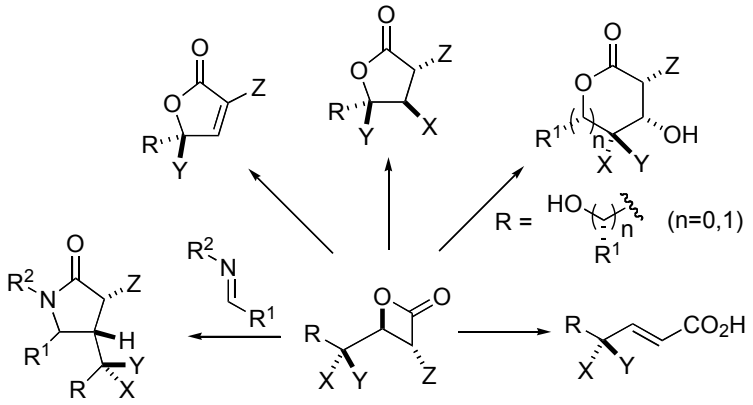


Figure 5. Rearrangements of β-Lactones

2.3 REACTION WITH NUCLEOPHILES

β-Lactones exhibit similar reactivities to epoxides due to their inherent ring strain (β-lactones, 22.8 kcal/mol; epoxides, 27.2 kcal/mol).[12] β-Lactones undergo facile nucleophilic attack leading to both C2-O1 bond (acyl C-O) and C4-O1 bond (alkyl C-O) cleavage, making these heterocycles versatile intermediates for a variety of transformations (Figure 6). In general, hard nucleophiles such as alkoxides, alkyllithiums, and Grignard reagents react with β-lactones to cleave the acyl C-O bond, while alkyl C-O cleavage occurs with soft nucleophiles including organocuprates, azides, halides, and thiolates.[5]

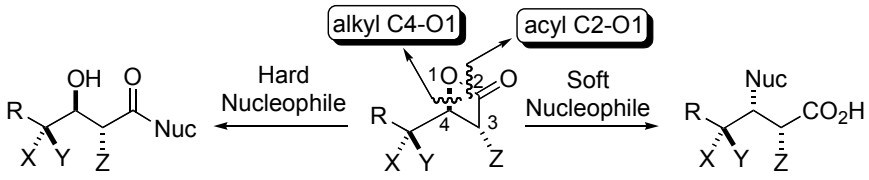


Figure 6. Nucleophilic Ring-opening of β-Lactones

2.3.1 Acyl C-O Cleavage

Acyl C-O cleavage of β-lactones with various nucleophiles provide aldol-type adducts including β-hydroxy acids, esters, amides, or ketones. Reductions of β-lactones with hydride sources (such as DIBAl-H, $LiAlH_4$, BH_3•DMS) usually result in acyl C-O cleavage to the corresponding diols. These

transformations have been studied extensively since these functional arrays are frequently found in natural products.

2.3.2 Alkyl C-O Cleavage

In addition to aldol adducts *via* acyl C-O cleavage, β-lactones can undergo alkyl C-O cleavage with various nucleophiles. The nucleophilic opening of serine and threonine β-lactones has found wide utility in the preparation of enantiopure amino acids and derivatives. [13] The intramolecular ring opening of β-lactones has provided new routes to larger rings including both carbocycles and heterocycles, and this mode of reactivity has often been exploited for natural product synthesis.

2.4 REACTION WITH ELECTROPHILES

Enolates of β-lactones can be formed at low temperature (–78 or –100 °C) and react with a variety of electrophiles in a highly diastereoselective fashion. The attack usually takes place opposite to the α-substituent for steric reasons (Figure 7).[14] While enolates of α-substituted β-lactones are surprisingly stable and react with electrophiles quite efficiently, alkylation of β-lactone enolates without α-substitution is difficult and often thwarted by side reactions such as self-acylation.[14b] Some success was achieved recently in a total synthesis of (+/-)-tetrahydrolipstatin using low temperature, inverse addition, and an allyl iodide as electrophile.[14c]

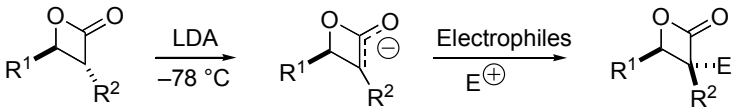


Figure 7. Diastereoselective Electrophilic Reactions of β-Lactones Enolates

2.5 MISCELLANEOUS

A few reactions are not readily classified into the above categories and thus are described separately below.

2.5.1 Friedel-Crafts Reaction

The Lewis acid-mediated Friedel-Crafts reaction of arenes with β-lactones results in either alkylation or acylation depending on the nature of the arene, β-lactone, catalyst and reaction conditions employed in the reaction (Figure 8).[15]

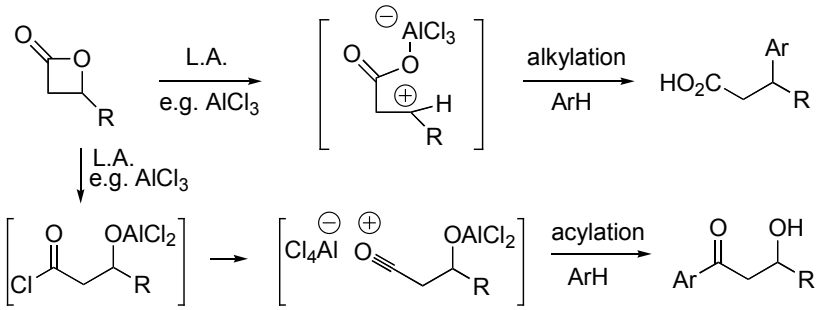


Figure 8. Friedel-Crafts Reactions with β-Lactones

2.5.2 Methylenation

Howell studied methylenation of β-lactones with both Tebbe's reagent and Petasis's reagent (Figure 9). [16] 2-Methyleneoxetanes were detected employing the Tebbe reagent, however isolation in significant quantities failed under various conditions. On the other hand, Petasis methylenation provided moderate to good yields of the desired product.

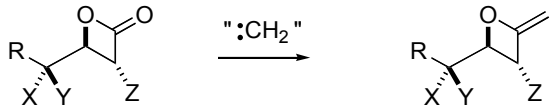


Figure 9. Methylenation of β-Lactones

FUNCTIONAL ARRAYS ACCESSIBLE *VIA* β-LACTONES

3.1 AMINO ACIDS

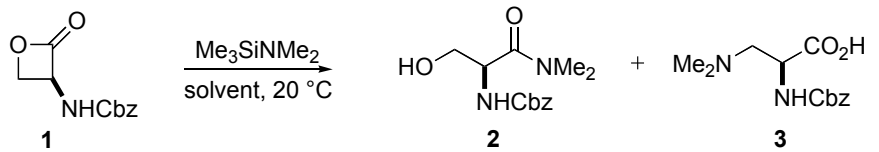
Vederas showed that β-amino-β-lactones, especially those derived from *N*-protected serine and threonine, are excellent precursors to unnatural β-amino acids *via* stereoselective, nucleophilic attack at the β-carbon.[13] On the other hand, nitrogen nucleophiles cleave optically active β-lactones *via* alkyl C-O cleavage delivering β-amino acids. This methodology is a highly versatile strategy for the preparation of β-amino acids not readily accessible by other methods. Several applications of the Vederas method have been applied to natural product synthesis and are described below.

3.1.1 β-Amino Acids

3.1.1.1 Ring Opening of β-Amino-β-Lactones

Vederas demonstrated that trimethylsilylamines are useful nucleophiles to form β-amino-L-alanine derivatives in good yields from Cbz-serine-β-lactone (**1**) (Table 2).[17] The product distribution between alkylation (C4-O1 cleavage) and acylation (C2-O1 cleavage) showed a high solvent dependency.

Table 2. Solvent Effects on Addition of Trimethylsilylamine to Serine β-Lactone



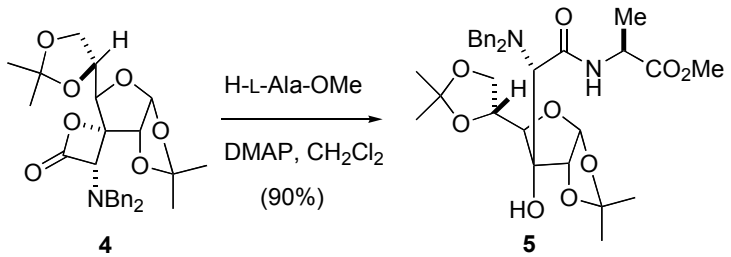
1 2 3

entry	solvent	product ratio: amide **2**	product ratio: amino acid **3**	% yield[a]
1	$CHCl_3$	80	20	88
2	CH_2Cl_2	65	35	85
3	$Cl(CH_2)_2Cl$	35	65	90
4	THF	20	80	92
5	MeCN	5	95	95

[a]Refers to combined yield of amide **2** and acid **3**.

The use of less polar solvents gave predominantly the amide (**2**) *via* acyl C-O cleavage (entries 1 and 2). On the other hand, use of polar aprotic solvents gave the amino acid (**3**) as the major product *via* alkyl C-O cleavage (entries 4 and 5). The authors suggested that the regioselectivity might be due to greater stabilization of charge separation in the transition state by the use of a more polar aprotic solvent, such as acetonitrile, as expected for an S_N2-like process.

Lavergne and co-workers coupled spirocyclic 2-oxetanones with various amino esters to form glycopeptides with complete stereocontrol.[18] The acylation of spirolactone (**4**) with alanine methyl ester employing DMAP as catalyst delivered glycopeptide (**5**) in 90% yield (Scheme 1).

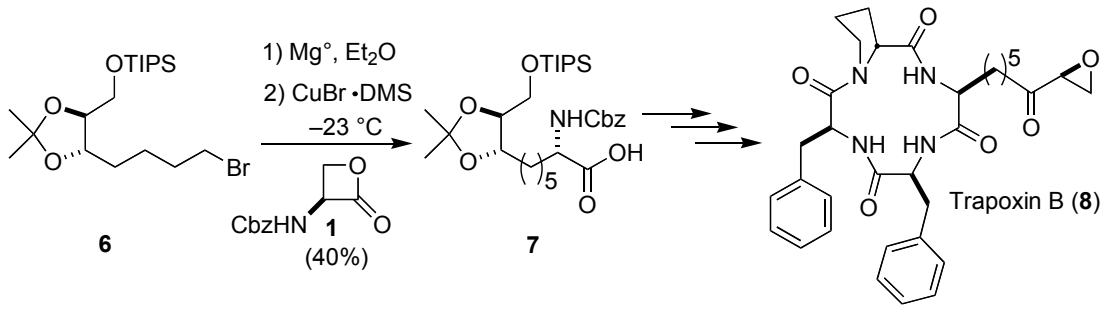


4 **5**

Scheme 1

- **Total Synthesis of Trapoxin B**

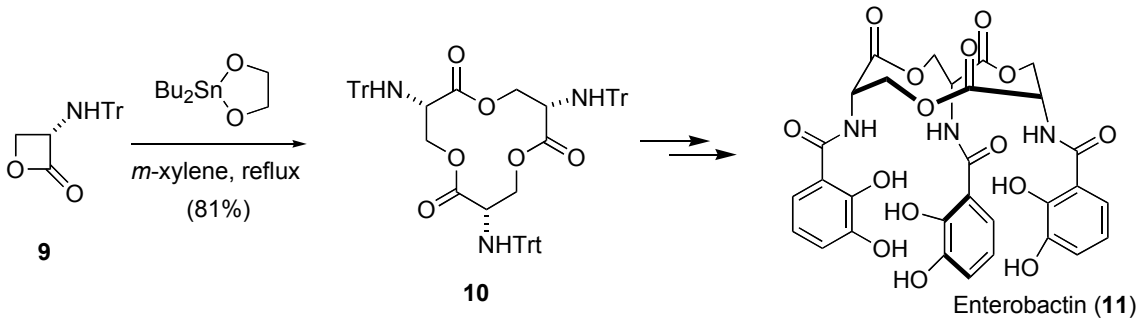
An organocuprate addition to Cbz-serine β-lactone (**1**) was utilized in the synthesis of the natural product trapoxin B (**8**) by Schreiber and co-workers (Scheme 2).[19] Trapoxin B is a cyclotetrapeptide isolated from the fungus *Helicoma ambiens* and found to alter mammalian cell growth and morphology by inhibition of histone deacetylase.[20] The reaction of the organocuprate derived from bromide (**6**) with β-lactone (**1**) gave acid (**7**) in 40% yield, employing the conditions of Vederas.[13b]



Scheme 2

- **Total Synthesis of Enterobactins**

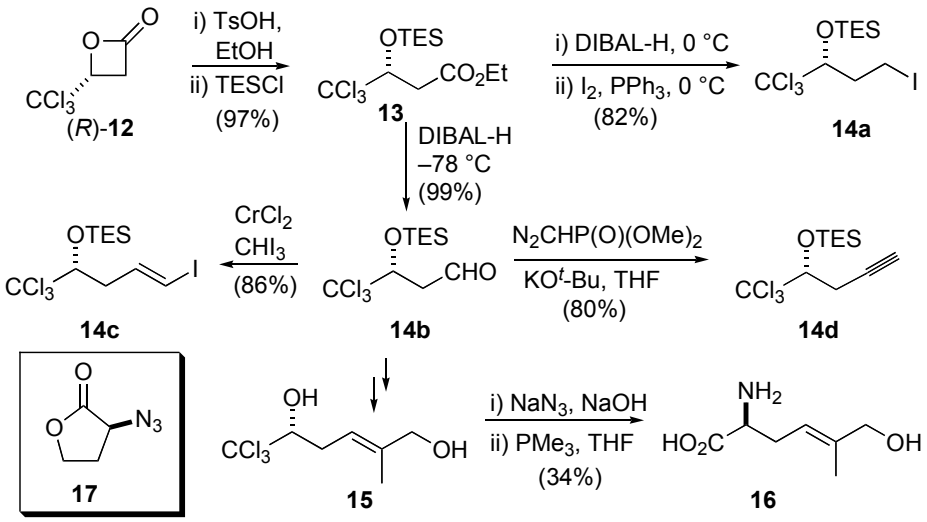
Enterobactin is produced by *E. coli* and other Gram-negative bacteria and exhibits the largest binding constant for ferric ion of any natural substance.[21] Shanzer and co-workers exploited the use of cyclic tin-oxygen compounds as templates to catalyze the self-condensation of β-lactones to macrocyclic products including the siderophore enterobactins.[22] Guiterrez and co-workers improved the trimerization step (**9** to **10**) to a remarkable 81% in contrast to 20-23% obtained by Shanzer (Scheme 3).[23] Further elaboration gave enantio-enterobactin (**11**) in good overall yield from D-serine derived β-lactone (**9**). The synthesis of enterobactin was also achieved starting from L-serine.



Scheme 3

3.1.1.2 Chiral Amino Acid Synthons from Trichloromethyl-β-lactones

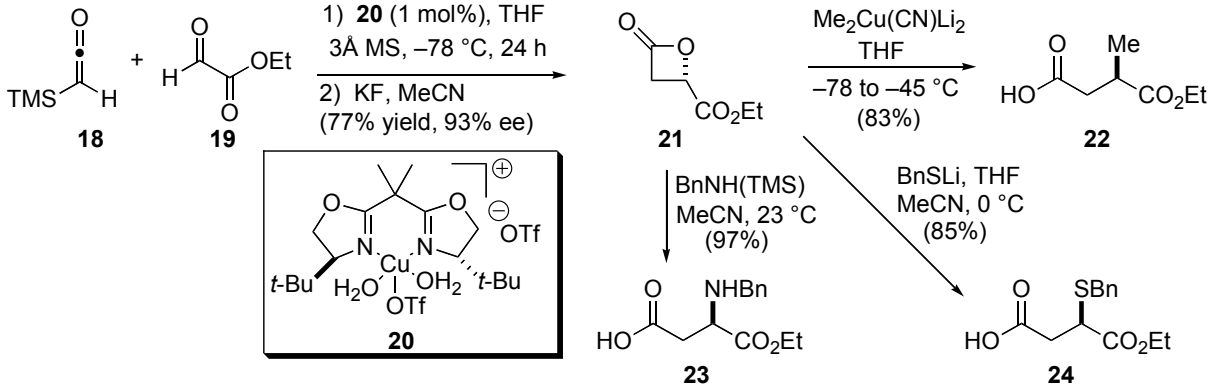
Romo and co-workers recently demonstrated that commercially available (*R*)- and (*S*)-4-trichloromethyl-β-lactones (**12**), available *via* the Wynberg process,[24] are useful precursors to β-amino acids (Scheme 4).[25] The amino acid functionality is masked as a trichloromethylcarbinol and can be readily unveiled under mild conditions as described by Corey.[26] The utility of this strategy was demonstrated by the synthesis of several amino acid chirons (**14a-d**), the synthesis of a naturally occurring β,γ–unsaturated amino acid (**16**) found in the seeds of *Blighia unijugata*, and the versatile, protected homoserine lactone (**17**).



Scheme 4

3.1.1.3 Amine Addition to β-Carboalkoxy-β-lactones

Evans and Janey applied C_2-symmetric Cu(II)-bis(oxazoline) complexes to catalyze enantioselective [2+2] cycloadditions between silylketenes and chelating carbonyl substrates (glyoxylates and β-keto esters) delivering β-carboalkoxy-β-lactones in excellent yields and selectivities.[27] β-Lactone (**21**) was transformed into the methyl-substituted carboxylic acid (**22**) by reaction with $Me_2Cu(CN)Li_2$, the protected aspartic acid (**23**) upon treatment with *N*-benzyl-*N*-trimethylsilylamine, and the benzylsulfide-substituted carboxylic acid (**24**) by attack of lithium benzyl sulfide (Scheme 5).



Scheme 5

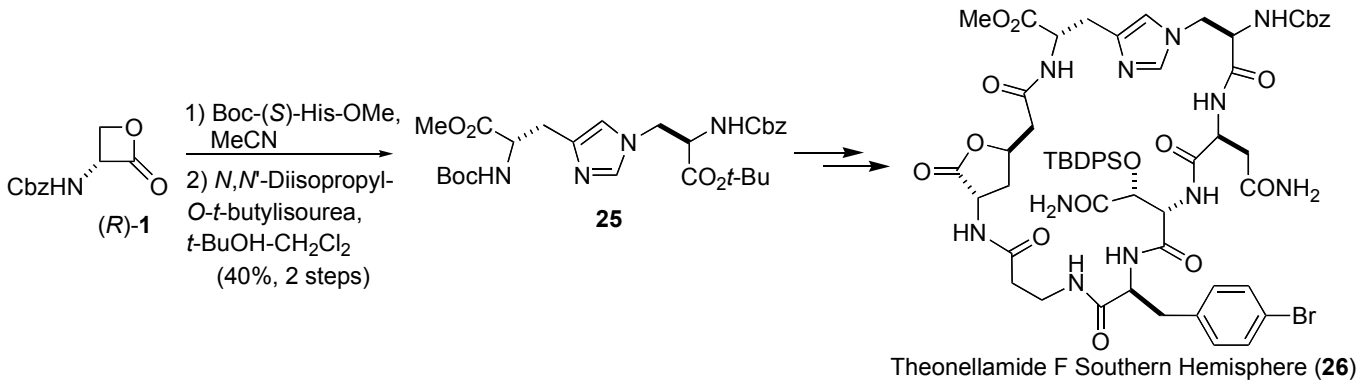
3.1.2 β-Amino Acids

3.1.2.1 Amine Addition

- **Studies towards Theonellamide F**

Isolated from the *Theonella* sponge, theonellamide F displays antifungal and cytotoxic activities.[28] In another application of the Vederas β-lactone approach to β-amino acids, Shioiri reported the synthesis of

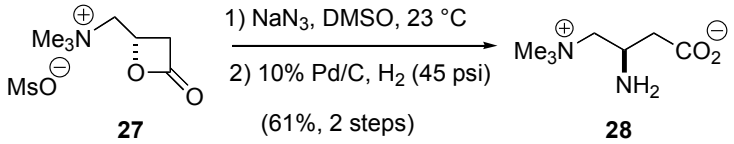
the southern hemisphere of theonellamide starting from serine β-lactone ((*R*)-**1**) (Scheme 6).[29] Lactone ((*R*)-**1**) was treated with Boc-(*S*)-His-OMe leading to alkyl C-O cleavage by the imidazole ring nitrogen. *tert*-Butylester formation with *N*,*N*'-diisopropyl-*O*-*t*-butylisourea delivered protected β-amino acid (**25**) in 40% yield for the two steps. This was further elaborated into the southern hemisphere (**26**) of theonellamide F.



Scheme 6

3.1.2.2 Azide Addition

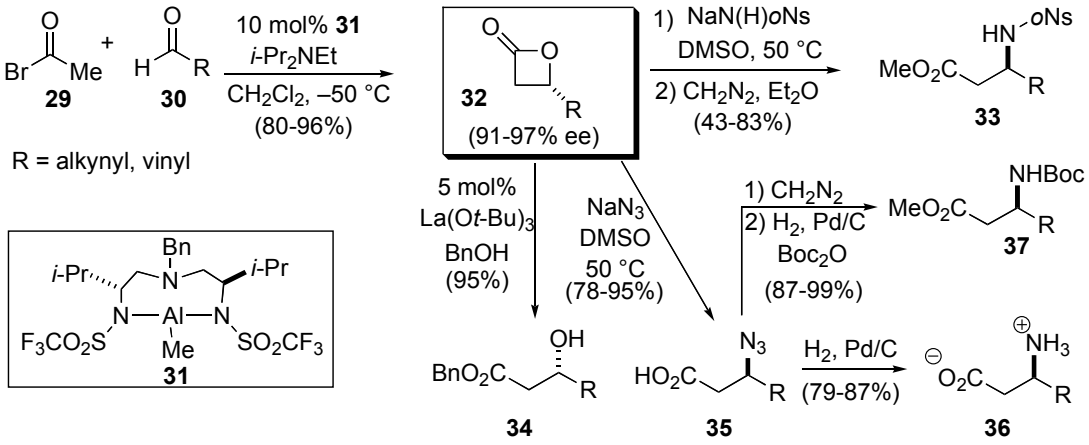
Giannessi and co-workers showed that β-lactone intermediates are useful for the synthesis of carnitine derivatives.[30] Alkyl C4-O1 cleavage of β-lactone (**27**) with sodium azide followed by azide reduction gave aminocarnitine (**28**) in >99% ee (Scheme 7).



Scheme 7

3.1.2.3 Sulfonamide Addition

Nelson and co-workers recently developed a novel Al(III) catalyzed, highly enantioselective approach to β-lactones *via* net addition of an acyl halide to an aldehyde proceeding by way of a [2+2] cycloaddition of a ketene and an aldehyde.[31] This process constitutes a major advance in the catalytic, asymmetric synthesis of β-lactones. Alkyl C-O cleavage of β-lactones (**32**) with azide smoothly promoted lactone ring opening to β-azido acids (**35**), which can be further reduced to β-amino acids (**36**) or derivatized to β-amino esters (**37**) (Scheme 8).[32] A La(O*t*-Bu)$_3$-catalyzed ring opening of the enantiomerically enriched β-lactones leads to the corresponding β-hydroxybenzyl esters (**34**) very efficiently and under mild conditions.[32a]



Scheme 8

These same authors also developed a useful new method for addition of protected nitrogen to β-lactone substrates. The sodium salt of *o*-nitrobenzenesulfonamide was employed as a nucleophile to cleave the alkyl C4-O1 bond of β-lactone (**32**) delivering *N*-nosyl–β-amino acid methyl esters (**33**). The sulfonamide protecting group was removed in 80-90% yield using the mild conditions of Fukuyama (PhSH, K_2CO_3, DMF).[33] Regioselectivity was good (alkyl C-O cleavage *vs* acyl C-O cleavage), except in the case of β-disubstituted β-lactones.

The utility of the optically active β-azido acids (**35**) as building blocks for peptide synthesis was demonstrated in the synthesis of a tri-β-peptide using the iteration of the azide reduction-amine acylation sequence.[32b]

3.2 ALDOL ADDUCTS

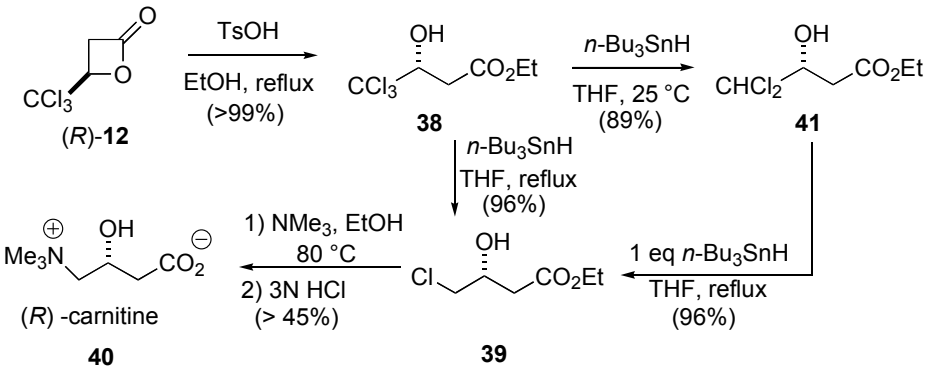
β-Lactones can be viewed as masked aldol adducts with the added advantage of inherent reactivity due to ring strain. Several types of β-lactones can now be synthesized with high stereoselectivity and can be transformed with high stereospecificity, making them useful alternative chiral aldol synthons.

3.2.1 β-Hydroxy Acids and Esters

3.2.1.1 Alcoholysis

Song and co-workers developed an efficient method for the preparation of (*R*)–carnitine (**40**) by way of a β-lactone intermediate.[34] (*R*)-Carnitine (vitamin B_T) regulates the transport of long-chain fatty acids through mitochondrial membranes and plays an important role in human metabolism.[35] The process involved acyl C-O cleavage of commercially available β-lactone (**12**) with acidic ethanol to produce β-

hydroxy ester (**38**) in excellent yield (Scheme 9). Controlled dechlorination with tributyltin hydride gave either the monochlorinated product **39** or the mono-dechlorinated product (**41**), depending on the reaction temperature.

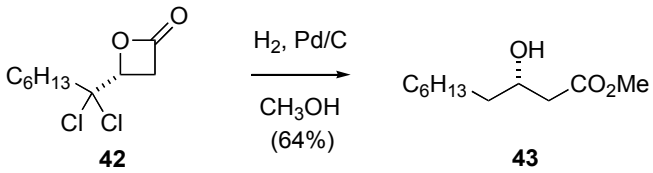


Scheme 9

3.2.1.2 Hydrogenolysis

In a subsequent report, Song and Choi found that β-lactone (**12**) could be directly converted to ester (**39**) by a selective hydrogenation using Pd-C/KOAc in EtOH.[36] Proper choices of catalyst and base were crucial for controlled dechlorination. Hydrogenation of β-lactone (**12**) with Pd-C/NEt_3, PtO_2/KOAc, or Raney Ni/KOAc in EtOH delivered mono-dechlorinated product (**41**) in high yields.

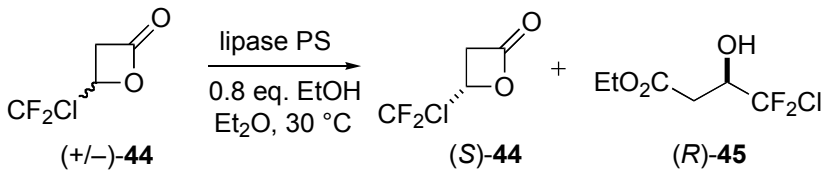
In a related process, Wynberg developed a two-step method to convert β-lactone (**42**) to β-hydroxy ester (**43**).[37] More recently, Romo and Tennyson demonstrated that this process could also be performed in a single pot (Scheme 10). [38]



Scheme 10

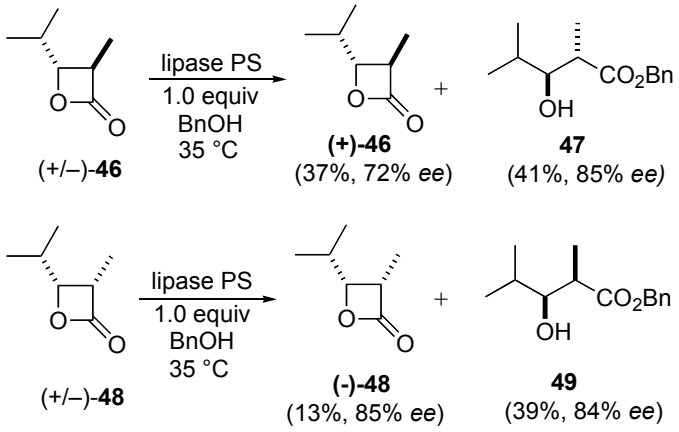
3.2.1.3 Kinetic Resolution

Fujisawa and co-workers employed a lipase to achieve an enzymatic kinetic resolution of racemic fluorinated β-lactones by conversion to the corresponding ethyl ester (Scheme 11).[39] Treatment of racemic β-lactone (**44**) with lipase PS and ethanol in ether gave the (*S*)- β-lactone (**44**) in 97% *ee* (43% yield), and the (*R*)- β-hydroxy ester (**45**) in 81% *ee* (40% yield).



Scheme 11

Yamamoto and co-workers found that lipase PS promoted the enantioselective transesterification of 3,4-dialkyl-β-lactones (Scheme 12).[40] Racemic *trans*-β-lactone (**46**) gave β-lactone ((+)-**46**) (3*R*,4*R*) in 72% *ee* (37% yield) and β-hydroxy ester (**47**) in 85% *ee* (41% yield). Similarly, racemic *cis*-β-lactone (**48**) under the same conditions gave (3*S*,4*R*) β-lactone ((-)-**48**) in 85% *ee* (13% yield) and β-hydroxy ester (**49**) in 84% *ee* (39% yield).

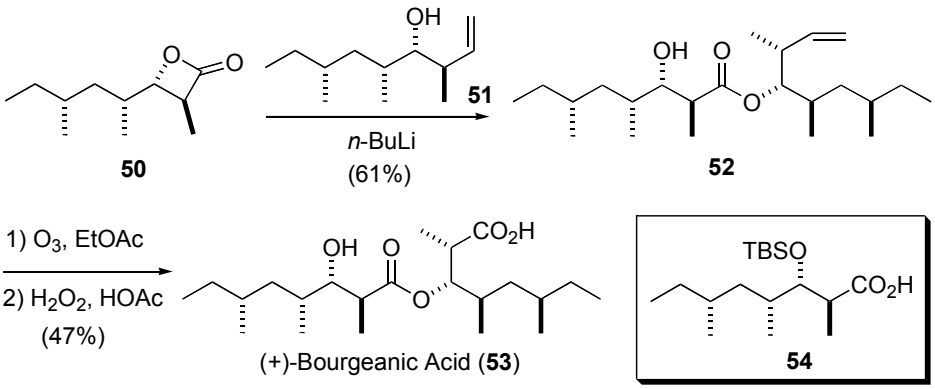


Scheme 12

3.2.1.4 Acylation

- **Total Synthesis of (+)-Bourgeanic Acid**

White and Johnson's synthesis of (+)-bourgeanic acid (**53**) involved acylation of a highly hindered secondary alcohol with a β-lactone intermediate.[41] Bourgeanic acid, isolated from several *Romalina* species of lichen, was the first isolated member of a new class of naturally occurring aliphatic depsipeptides.[42] β-Lactone (**50**) was utilized as an acylating agent for the lithioalkoxide derived from alcohol (**51**) to give ester (**52**) in 61% yield (Scheme 13) when typical methods for coupling acid (**54**) failed. However, this tactic has not always proven successful.[43] The superior reactivity of the lithio alkoxide over other alkali metal alkoxide derivatives of alcohol (**51**) appears to be related to both the coordination of lithium to the β-lactone carbonyl and the enhancement of nucleophilicity. A related intramolecular reaction involving a thiol nucleophile and a β-lactone as an acylating agent was employed by Corey in his total synthesis of the proteasome inhibitor, lactacystin (see Figure 2).[44]

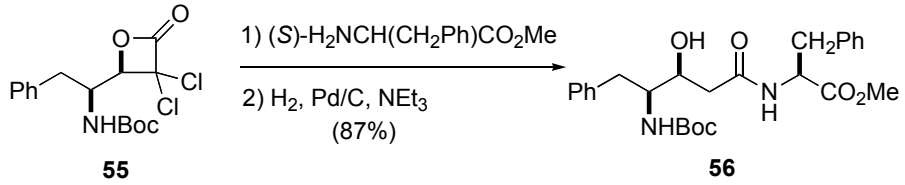


Scheme 13

3.2.2 β-Hydroxy Amides

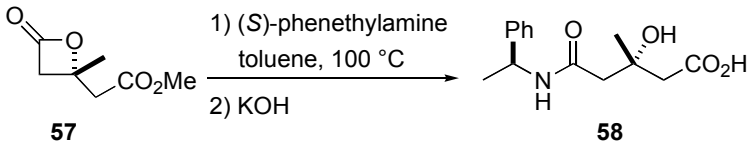
3.2.2.1 Acyl C-O Cleavage by Amines

Palomo and co-workers made excellent use of α,α-dichlorinated β-lactones obtained by [2+2] cycloaddition of dichloroketenes and optically pure α-amino aldehydes for the synthesis of peptide mimics.[45] (*S*)-Phenylalanine was used as an amine nucleophile to cleave the acyl C-O bond in **55** delivering an intermediate chlorinated amide in excellent yield (Scheme 14). Subsequent dehalogenation produced peptide mimic **56** in 87% overall yield from β-lactone (**55**).



Scheme 14

Shirahama and co-workers employed a β-lactone intermediate to synthesize chiral HMGA (3-hydroxy-3-methylglutaric acid) esters and amides.[46] HMGA is an important intermediate in the biosynthesis of terpenoids, steroids, and carotenoids.[47] β-Lactone (**57**) underwent acyl C-O cleavage with (*S*)-phenethylamine to yield acid (**58**) after hydrolysis (Scheme 15). Several natural products possess related HMGA fragments such as fasciculol D and dicrotaline.

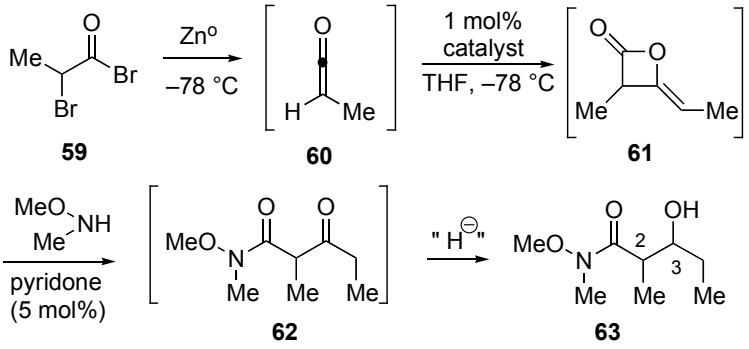


Scheme 15

3.2.2.2 Tandem Amine Addition-Reduction

Calter developed a novel catalytic, asymmetric ketene dimerization process of methylketene leading to 4-methylene-2-oxetanones (**61**) in high enantiomeric purity.[48] The ketene dimer (**61**) was not isolated but directly ring-opened with *N*-methyl-*N*-methoxyamine with pyridone as catalyst. Reduction of the resulting configurationally stable β-keto amide (due to incipient $A^{1,3}$ strain in enol tautomers[49]) provided an elegant, one-pot synthesis of all four possible stereoisomers of dipropionate synthon (**63**) from bromopropionyl bromide (**59**) (Table 3).[50]

Table 3. One-Pot Asymmetric Synthesis of All Four Isomers



59 **60** **61** **62** **63**

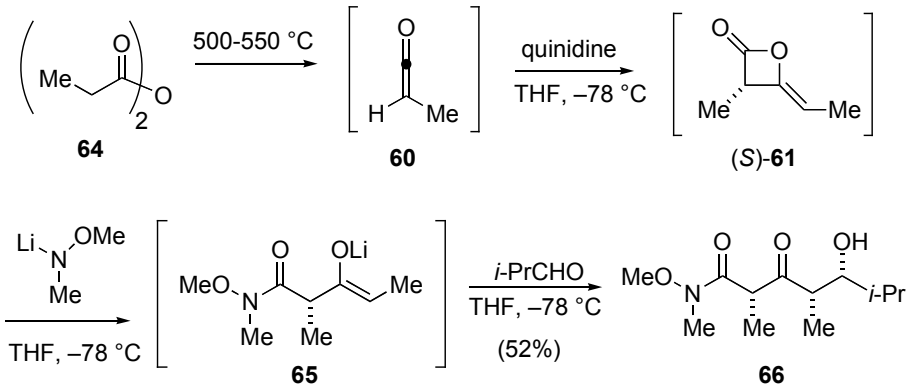
Catalyst	Reduction conditions[a]	% ee of **63** (configuration)	% Yield of **63**[b]
quinidine	A	99 (2*S*, 3*S*)	40
quinidine	B	99 (2*S*, 3*R*)	46
TMS-quinidine	A	95 (2*R*, 3*R*)	40
TMS-quinidine	B	95 (2*R*, 3*S*)	46

[a]A = $KB(H)Et_3$, THF, –78 °C, *anti*/*syn* = 99:1; B = $Zn(OTf)_2$, $NaBH_4$, THF, –78 °C, *syn*/*anti* = 98.5:1.5. [b]Overall yield from **59**.

3.2.3 β-Hydroxy Ketones

3.2.3.1 Tandem Amine Addition-Aldol Reaction

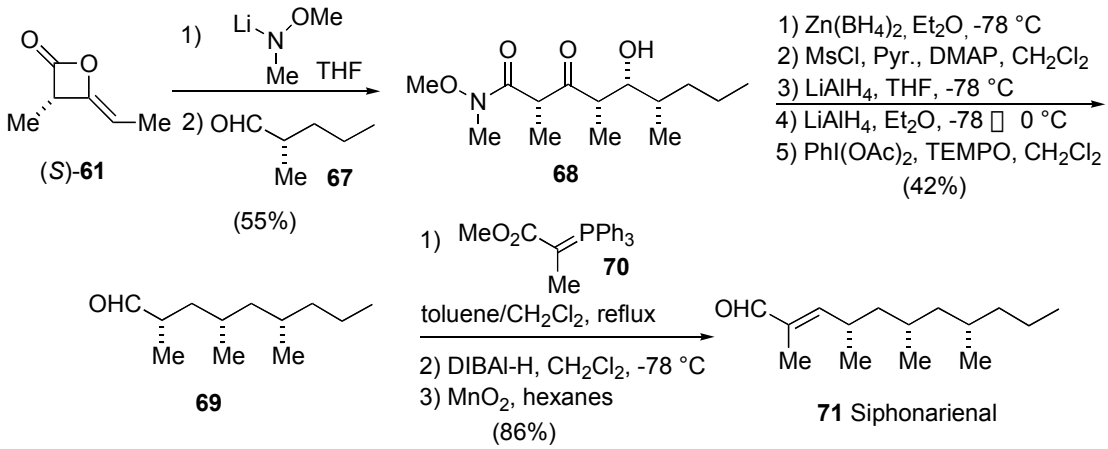
More recently, Calter extended the methodology to the asymmetric synthesis of polypropionates.[51] The dimer ((*S*)-**61**) was again obtained by asymmetric dimerization of methylketene but this time derived from thermolysis of propionic anhydride. Direct treatment of dimer (**61**) with the lithium amide of *N*,*O*-dimethylhydroxylamine, followed by addition of isobutyraldehyde led to an *in situ* aldol process to give polypropionate (**66**) in 52% yield and a *syn*,*syn*:*anti*,*syn* ratio of 95:5 (Scheme 16). This is a useful and concise route to polypropionate synthons.



Scheme 16

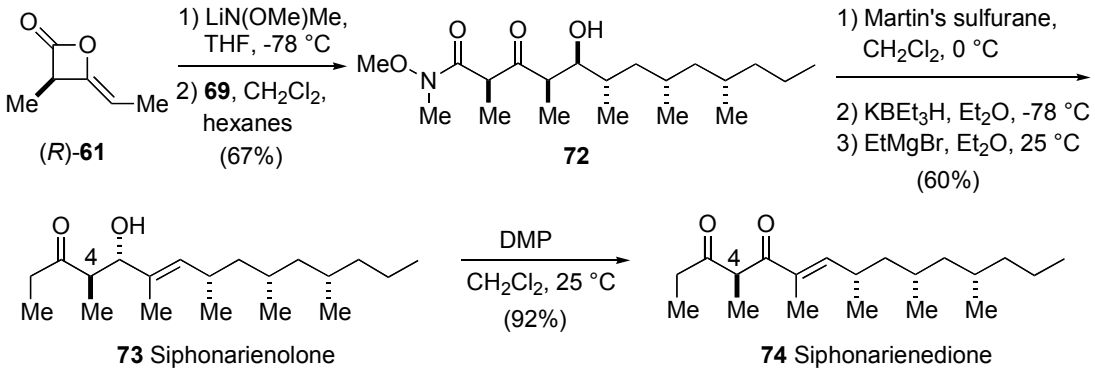
- **Total Synthesis of Siphonarienes**

Calter and co-workers applied this methodology to the asymmetric synthesis of marine derived polypropionates, the siphonarienes. Aldol reaction between aldehyde (**67**) and enolate (**65**) derived from (*S*)-**61** gave **68** in 55% yield with very high diastereoselectivity (>19:1) setting all three methyl-bearing stereocenters of siphonarienal (**71**) in one pot (Scheme 17).[52a] Deoxygenation and chain homologation delivered siphonarienal (**71**) in 10 steps from ketene dimer (**61**).



Scheme 17

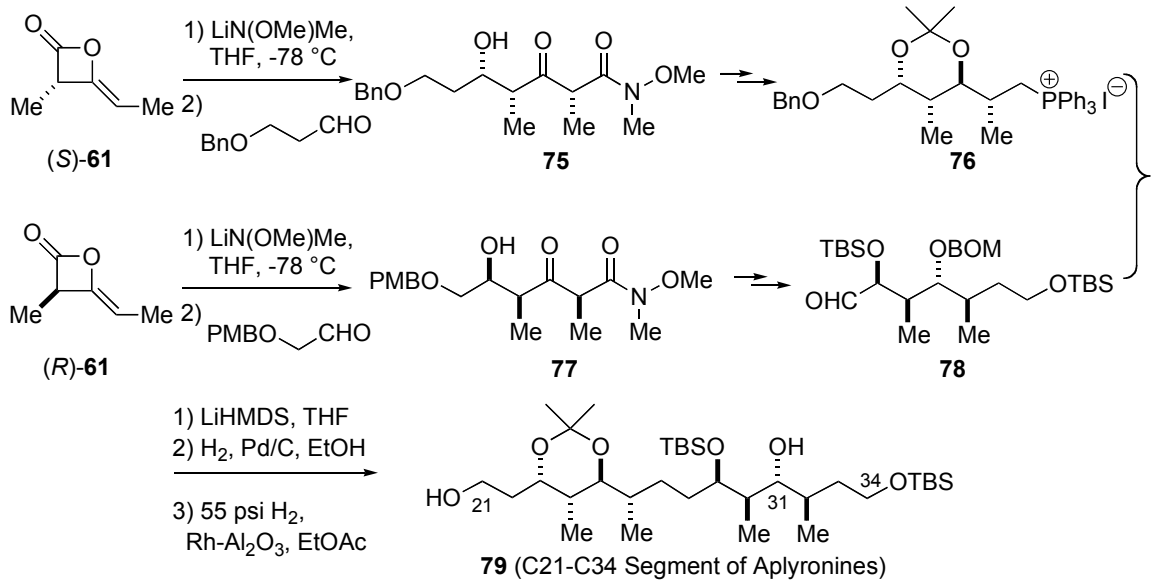
The same intermediate (**69**) was also used in the first total synthesis of siphonarienolone (**73**) and siphonarienedinone (**74**) by the same methodology (Scheme 18).[52b] Several C4-diastereomers were also prepared from (*S*)-**61**, allowing unambiguous reassignment of the stereochemistry of the siphonarienes.



Scheme 18

- **Synthesis of the C_{21}-C_{34}-segment of Aplyronines**

Calter and Guo further demonstrated the utility of the tandem amine addition-aldol reaction in asymmetric polypropionate synthesis by preparing the C21-C34-segment of aplyronines, a family of polyketide natural products exhibiting strong cytotoxicity towards a variety of cancer lines.[53,54] Both **75** and **77** were derived from ketene dimer (**61**), and were converted to advanced intermediates (**76**) and (**78**) *via* distereoselective reduction and functional group manipulation (Scheme 19). Wittig reaction between **76** and **78** afforded a *Z*-olefin in good yield (81%) and high selectivity. Subsequent hydrogenation gave diol (**79**), the C21-C34 synthon of aplyronines.

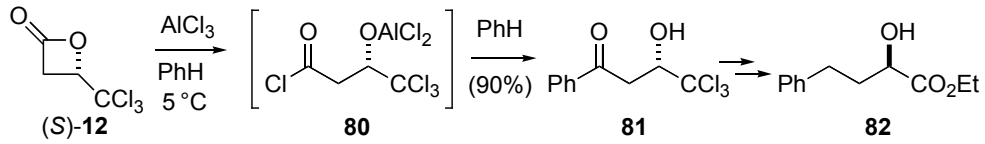


Scheme 19

3.2.3.2 Friedel-Crafts Acylation

Fujisawa and Wynberg reported a facile synthesis of (*S*)-□-hydroxy-□-trichloromethylated aromatic ketones *via* Friedel-Crafts acylation involving cleavage of the C2-O bond.[55] For example, reaction of □-

trichloromethyl-β-propiolactone (**12**) with $AlCl_3$ (3.75 equiv) in benzene gave the butanone (**81**) in 90% yield (Scheme 20).

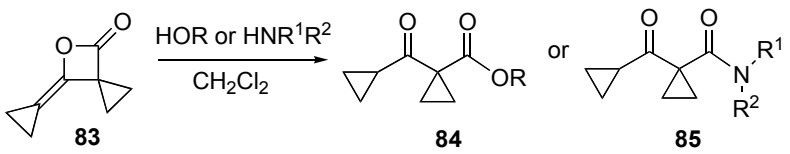


Scheme 20

This reaction was proposed to involve Lewis acid induced acyl C1-O cleavage to form the intermediate acid chloride (**80**), which then undergoes Friedel-Crafts acylation with benzene to deliver the aryl ketone (**81**). However, direct generation of a β-alkoxyacylium ion would also appear possible. Other β-hydroxy aromatic ketones were also obtained in good yields (68-74%) with anisole, *m*-xylene, mesitylene, and *N*-methylpyrrole as nucleophiles. Butanone (**81**) was converted to ethyl ester (**82**) by reduction of the ketone and hydrolysis of the trichloromethylcarbinol. The latter proceeded with inversion of configuration in good overall yield. The ester (**82**) is a precursor to enalapril, an angiotensin converting enzyme (ACE) inhibitor.

3.2.4 β-Keto Esters and β-Ketoamides

Hoffman and co-workers reported that alcohols and amines effectively cleave the acyl C1-O bond of spirocyclic lactone (**83**), a highly strained molecule having the shortest cyclopropylidene double bond (1.287Å) reported to date (Scheme 21).[56] The acylated derivatives (**84**) and (**85**) showed enhanced lipophilicity because enolizations of the β-ketoamides and esters were precluded by their structure.

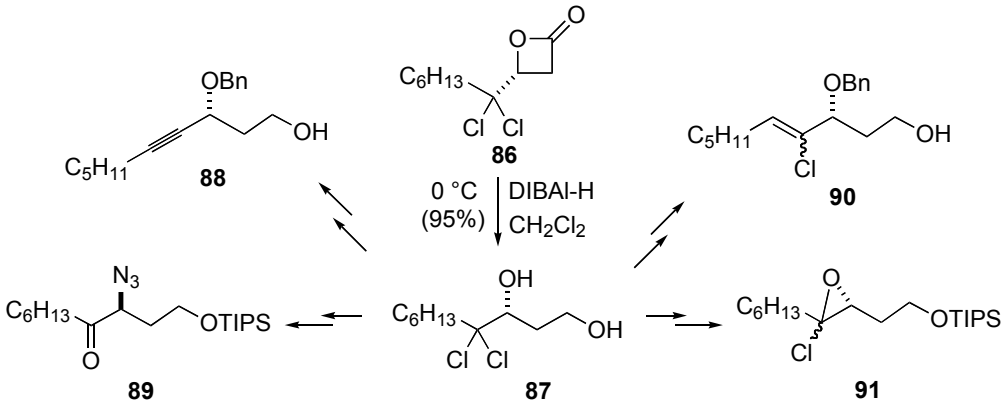


Scheme 21

3.2.5 1,3-Diols

In analogy to esters, β-lactones can be reduced to give diols with a variety of common reducing agents including DIBAl-H, $LiAlH_4$, and BH_3•DMS. Romo and Tennyson employed DIBAl-H reduction of β-lactones, first reported by Fujisawa,[57] to reduce β-lactone (**86**) to the corresponding diol (**87**) in excellent

yield (Scheme 22).[38] Transformation of this versatile intermediate into a number of useful chiral synthons including propargylic benzyl ether (**88**), α-azido ketone (**89**), vinyl chloride (**90**) and chloro epoxide (**91**) were also reported.



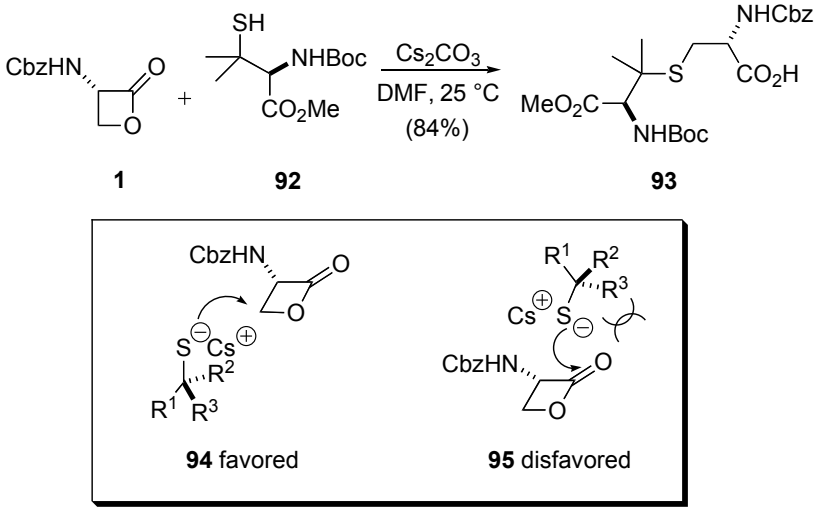
Scheme 22

α-FUNCTIONALIZED ACIDS AND ESTERS

3.3.1 α-Thiol Acids and Esters

- **Synthesis of Lanthionines**

Goodman and co-workers investigated the addition of thiols to serine-derived β-lactones to generate protected stereoisomeric lanthionines.[58a] They found that cesium thiolates of α,α-disubstituted cysteine derivatives (such as **92**) led to efficient carbon-sulfur bond formation *via* alkyl C4-O cleavage of β-lactone (**1**) (Scheme 23). Other conditions including normal organic and inorganic bases in different

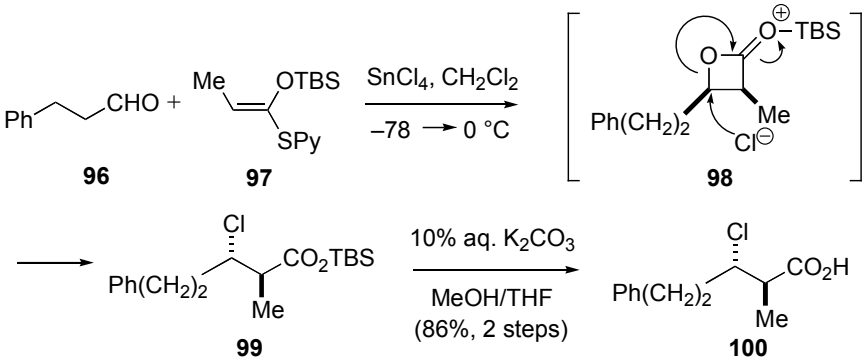


Scheme 23

solvents at various temperatures resulted in exclusive formation of the corresponding thioester *via* acyl C2-O cleavage. The authors proposed that approach of the tertiary thiolate anions of α,α-disubstituted cysteine derivatives to the carbonyl carbon of the β-lactone is blocked for steric reasons (**94** *vs* **95**). Undoubtedly, the enhanced softness of the cesium thiolates also contributes to the regioselectivity observed. More recently, the authors extended the chemistry to the synthesis of β-methylcysteine and β-methyllanthionine derivatives.[58b] Replacing the Cbz protecting group with the larger Fmoc group was found to completely suppress thioester formation.

3.3.2 β-Halo Acids and Esters

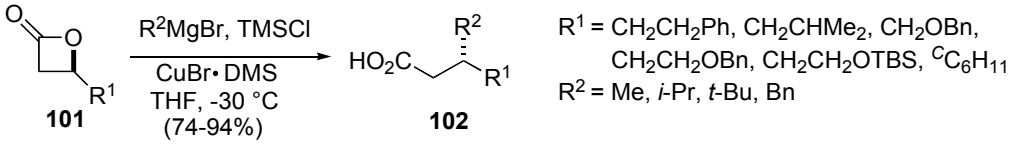
Romo and co-workers reported the highly diastereoselective (>19:1) formation of a β-chloro acid (**99**) by way of a presumed β-lactone intermediate (**98**) (Scheme 24).[59] This $SnCl_4$-mediated net Mukaiyama aldol-lactonization presumably affords silylated β-lactone intermediate (**98**), which undergoes alkyl C4-O cleavage by chloride ion. This methodology offers a practical stereocontrolled route to β-chloro carboxylic acids from aldehydes.



Scheme 24

3.3.3 α-Substituted Carboxylic Acids

Building on the previous work of Fujisawa,[60] Nelson and co-workers optimized the Grignard-mediated ring opening (alkyl C-O) of optically active β-lactones as a generally useful asymmetric synthesis of α-disubstituted carboxylic acids (**102**) and as an alternative to conjugate addition.[61] Stoichiometric amounts of CuBr and TMSCl are important for achieving consistently high reaction yields (Scheme 25). This represents a general alternative to asymmetric conjugate addition reactions. This reaction appears insensitive to the steric environment of both the lactone, as exemplified by a *cis*-3,4-disubstituted β-lactone, and the nucleophile, as *t*-butylmagnesium bromide reacted efficiently. Unfortunately, phenyl and vinyl derived organometallic reagents do not participate in this process.

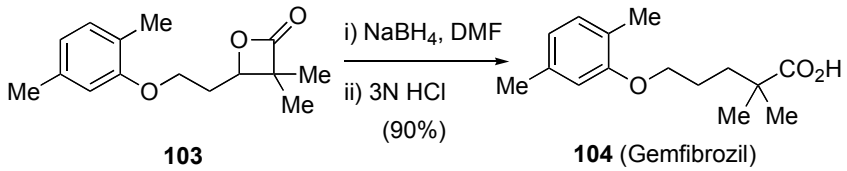


Scheme 25

3.3.4 Miscellaneous

- **Synthesis of Gemfibrozil**

A β-lactone intermediate was employed in the synthesis of the anti-hyperlipoproteinemic agent gemfibrozil.[62] Wang and co-workers performed reduction of intermediate lactone (**103**) with sodium borohydride to afford gemfibrozil (**104**) in 90% yield (Scheme 26). It is interesting to note that hydride attack occurred at the β-carbon (C4-O cleavage), presumably due to the β-disubstitution adjacent to the carbonyl and use of the polar solvent DMF. Hydrogenolysis also afforded the same product (**104**) in 70% yield using either Raney nickel, palladium (10%) on charcoal, or palladium hydroxide (20%) on charcoal.



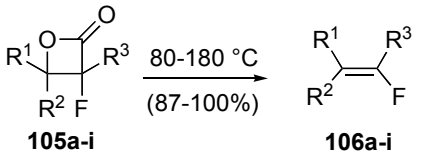
Scheme 26

3.4 ALKENES AND ALLENES

3.4.1 Alkenes

3.4.1.1 Thermal Decarboxylation

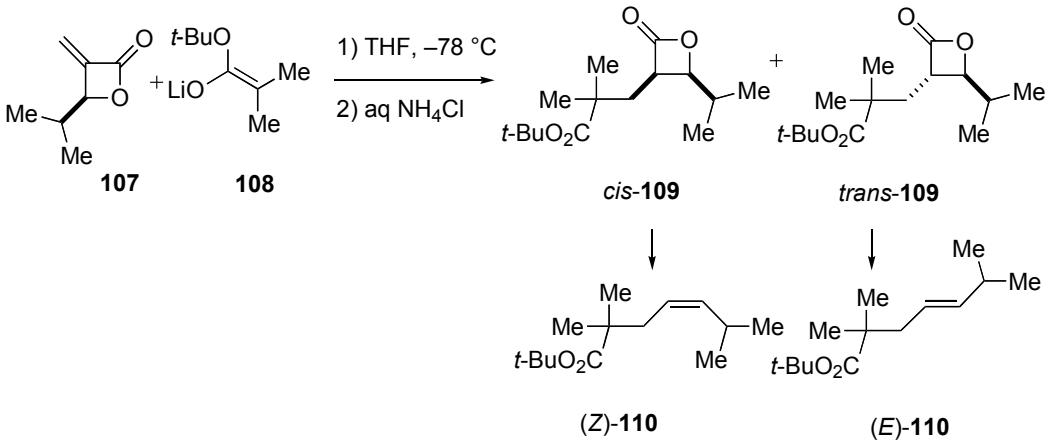
Dolbier and co-workers prepared 1,1-diflouroalkenes and 1-fluoroalkenes *via* stereospecific decarboxylation of the corresponding β-lactones in excellent yield.[63] Fluoroalkenes (**106**) were obtained by heating β-lactones (**105**) between 80-180 °C (Scheme 27).



	a	b	c	d	e	f	g	h	i
R^1	Me	Et	Ph	Bn	Bn	Ph	Ph	Bn	Ph
R^2	Me	Et	Bn	Bn	Ph	Me	Ph	Bn	Bn
R^3	F	F	F	F	H	H	H	H	H

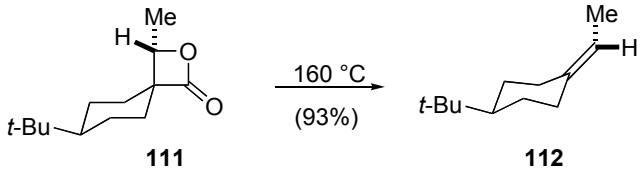
Scheme 27

Adam and co-workers found that conjugate addition of enolates to β-methylene-γ-lactones followed by decarboxylation gave β,γ-unsaturated esters.[64] Reaction of Michael acceptor (**107**) with enolate (**108**) gave γ-lactones (**109**) in a 16:84 ratio (*cis*/*trans*), favoring the *trans* diastereomer (Scheme 28). This was followed by stereospecific, thermal decarboxylation to produce β,γ-unsaturated esters (**110**) with *E*/*Z* selectivities mirroring the stereochemistry of the starting γ-lactones. This overall process represents a complementary approach to β,γ-unsaturated esters accessible *via* Claisen rearrangements.



Scheme 28

Mulzer and Speck prepared (*R*)-1-*t*-butyl-4-ethylidenecyclohexane (**112**) with >98% ee in gram quantities from 4-*t*-butylcyclohexanecarboxylic acid *via* the optically active γ-lactone (**111**) (Scheme 29).[65] This process illustrates a new approach to axially chiral olefins.

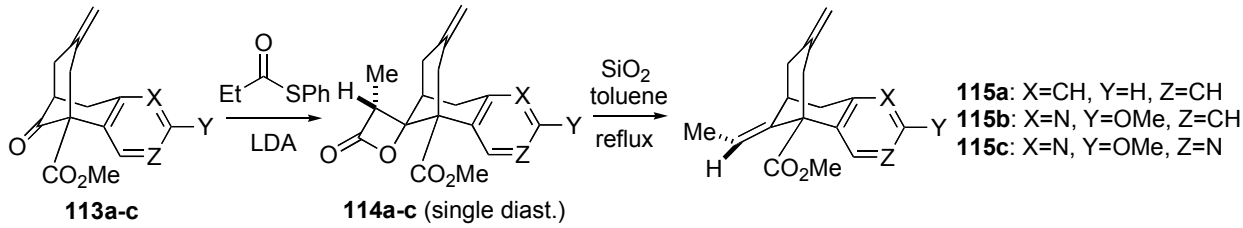


Scheme 29

- **Synthesis of Huperzine Analogs**

Kozikowski and co-workers utilized thermal decarboxylation of γ-lactones (**114a-c**) in the synthesis of modified heterocyclic analogues of huperzine A,[66] a natural product lead for psychotherapeutic agents for the treatment of Alzheimer's disease. After several olefination methods were studied unsuccessfully on this system, the method of Danheiser[67] applied to ketones (**113a-c**) proceeding through a reversible aldol process, provided γ-lactones (**114a-c**) with high diastereoselectivity (Scheme 30). Subsequent stereospecific, thermal decarboxylation provided several pyrimidone and pyrazole analogues (**115a-c**) of huperzine A. This application nicely demonstrates the utility of γ-lactones as precursors to stereodefined

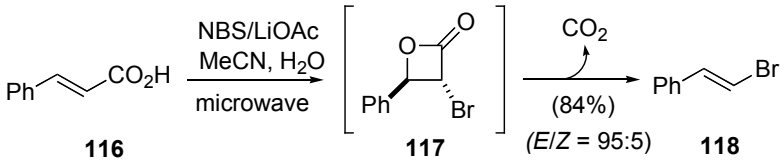
trisubstituted olefins *via* decarboxylation and as a two-step alternative to Wittig olefinations wherein the aldol-like stereoselectivity during β-lactone formation is translated into olefin stereochemistry. Interestingly, given the high stereospecifity of the decarboxylation process, the β-lactone intermediates provided an alternative and more easily determined proof of olefin stereochemistry.



Scheme 30

3.4.1.2 Photolytic Cleavage

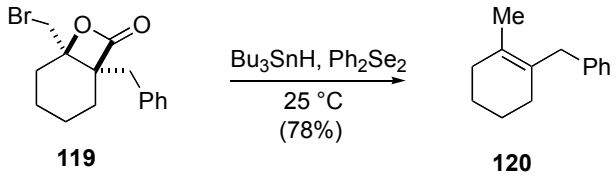
Tokuda and co-workers prepared (*E*)- β-arylvinyl halides *via* 2-oxetanones in good yields and excellent selectivity.[68] Under microwave irradiation, halolactonization of alkenoic acid (**116**) with *N*-bromosuccinimide produced β-lactone (**117**) (Scheme 31). Under the reaction conditions, the β-lactone intermediate fragments with loss of CO_2 to deliver vinyl bromide (**117**) in 84% yield with high *E*/*Z* selectivity.



Scheme 31

3.4.1.3 Radical Cleavage

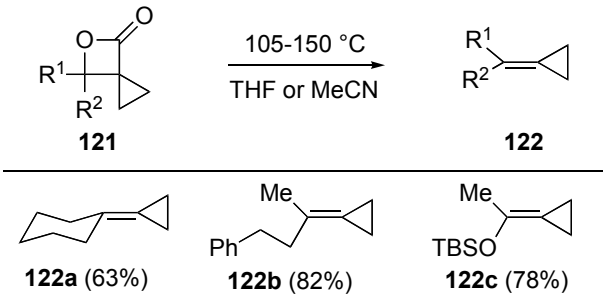
Crich and Mo showed that free-radical reactions of β-bromo-β-lactones mediated by catalytic benzeneselenol (generated *in situ* from Bu_3SnH and Ph_2Se_2) gave decarboxylated products in good yield (Scheme 32).[69] The authors noted that treatment of lactone (**119**) with tributyltin hydride and AIBN alone was not effective.



Scheme 32

3.4.2 Alkylidenecyclopropanes

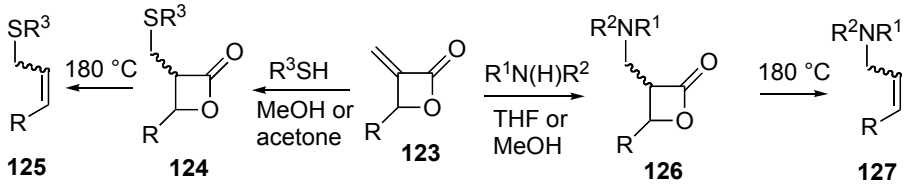
Danheiser and co-workers developed a novel method for the synthesis of alkylidenecyclopropanes (**122**)[70] *via* thermal decarboxylation of β-spirocyclopropyl-β-lactones (**121**). These β-lactones are available *via* aldol-lactonization reactions of thiophenyl ester enolates and ketones developed by the same group (Scheme 33).[67] Alkylidenecyclopropanes (**122a-c**) were obtained in this manner in good yields. The latter compounds are useful synthons for the synthesis of five and seven membered carbocycles *via* cycloaddition reactions



Scheme 33

3.4.3 Allylamines and Sulfides

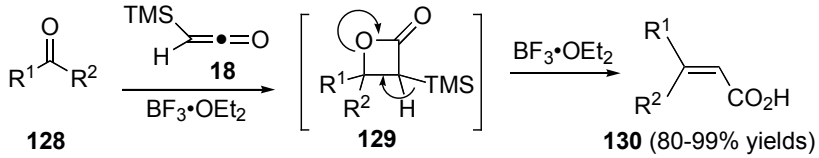
Adam and co-workers showed that β-thio- and β-amino γ-lactones are formed in moderate to excellent yields (64%-99%) by conjugate addition of thiol and amine nucleophiles to β-methylene-γ-lactones (**123**) (Scheme 34).[71] These intermediates underwent thermal decarboxylation to provide allylic sulfides (**125**) and allylamines (**127**) in moderate to good yields. The solvents employed had profound effects on the stereoselectivity of the Michael addition. *trans*-γ-Lactones were the major products in protic solvent like MeOH, while considerable amounts of the *cis* isomers were formed in aprotic solvents such as THF, acetone, and CCl_4. The authors suggested that nucleophilic addition and protonation could take place concurrently in an antiperiplanar fashion in protic solvent, leading to the *trans* isomers. Again, this methodology constitutes an alternative to the conventional Wittig olefination.



Scheme 34

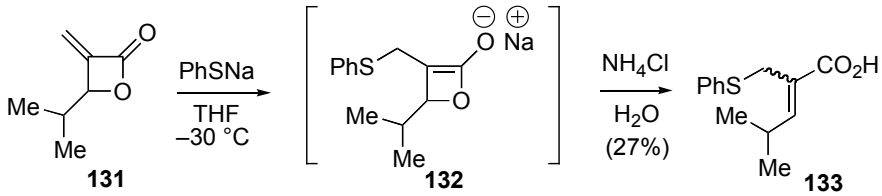
3.4.4 β,γ-Unsaturated Acids

Trimethylsilyl-β-lactones are useful precursors for β,γ-unsaturated acids. Black and co-workers developed these rearrangements as a strategy for carbonyl homologations.[10] Cycloaddition between aldehydes or ketones and trimethylsilylketene mediated by BF_3•OEt_2 gave β-lactone intermediates (**129**), which spontaneously rearranged to β,γ-unsaturated acids (**130**) in excellent yields (Scheme 35).



Scheme 35

Adam and co-workers also demonstrated that treatment of α-methylene-β-lactone (**131**) with the sodium salt of thiophenol gave acrylic acid (**133**) after mild aqueous acid treatment (Scheme 36).[71] The reaction presumably involves initial conjugate addition of the sodium salt followed by ring fragmentation by a process not involving β-elimination, a process forbidden for β-lactones due to incorrect orbital alignment as first noted by Mulzer.[72]



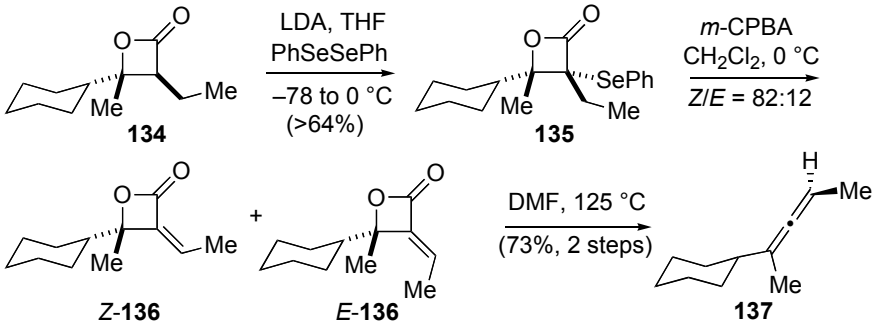
Scheme 36

3.4.5 Allenes

3.4.5.1 Thermal Decarboxylation of α-Alkylidene-β-lactones

Danheiser and co-workers showed that thermal decarboxylation of α-alkylidene-β-lactones, available *via* a selenation/oxidation/elimination sequence, gave allenes such as **137** in good yield.[73] Noteworthy is that electrophilic attack on the enolate derived from trisubstituted β-lactones (**134**) occurs mainly *cis* to the larger α-substitutuent (Scheme 37). This was postulated to be due to developing eclipsing interaction between the α-ethyl group and the β-cyclohexyl group and points to a possible late transition state in these reactions.[70] β-Lactone (**135**) was obtained as a single diastereomer and furnished an 82:12 mixture of the *Z*/*E* ethylidene-β-lactones (**136**) upon treatment with *m*-CPBA. Decarboxylation of β-

lactones (**136**) by heating in DMF and following distillation gave allene (**137**) in good overall yield. This methodology provides a unique approach to substituted allenes.

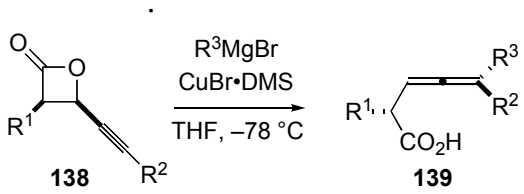


Scheme 37

3.4.5.2 S_N2' Addition of Cuprates to β-Alkynyl-γ-lactones

Building on initial studies of Fujisawa on racemic substrates,[74] Nelson and Wan recently explored SN2' addition of cuprates to optically active β-alkynyl-γ-lactones to give allenes (**139**) with excellent enantiopurity (Table 4). [75] The stereochemical outcome is consistent with *anti*- 1,3-substitution as expected.[76]

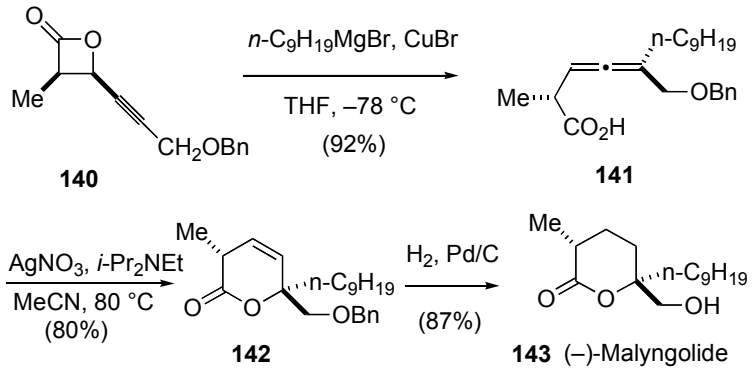
Table 4. Allenes *via* S_N2' Addition of Cuprates to β-Alkynyl-γ-lactones



Entry	R^1	R^2	R^3	% Yield (%ee)
1	H	CH_2Bn	$CHMe_2$	92 (92)
2	H	CH_2Bn	$CH_2CH_2CHCH_2$	94 (93)
3	H	CH_2Bn	$(CH_2)_{10}CH_3$	90 (92)
4	H	CH_2Bn	Ph	93
5	H	CH_2Bn	Me	92 (93)
6	H	CH_2Bn	*t*-Bu	93
7	Me	$(CH_2)_2OPMB$	Me	88 (90)
8	Bn	$SiMe_3$	Me	80
9	H	CH_2Bn	CH_2CO_2t-Bu	84 (83)
10	H	CH_2Bn	CH_2CN	79 (90)

- **Total Synthesis of (–)-Malyngolide**

This latter chiral allene synthesis was then applied to a concise and stereocontrolled synthesis of (–)-malyngolide (**143**).[75] Optically active β-lactone (**140**) was treated with *n*-C_9H_{19}MgBr in the presence of catalytic CuBr to form allene (**141**) in 92% yield (Scheme 38). This was followed by silver(I)-promoted cyclization to the γ-lactone (**142**). Hydrogenolysis of the benzyl ether was accompanied by saturation of the alkene delivering the antibiotic natural product, (–)-malyngolide (**143**), in 87% yield.

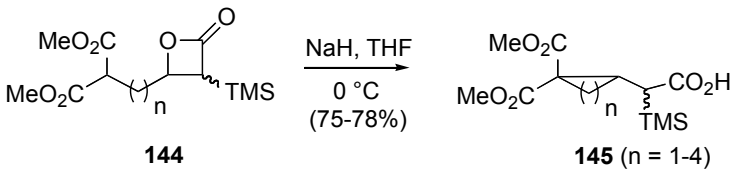


Scheme 38

3.5 CARBOCYCLES

3.5.1 Intramolecular Carbanion Additions

Mead and co-workers prepared several carbocyclic ring systems by intramolecular addition of stabilized carbanions to β-trimethylsilyl-γ-lactones with exclusive regioselectivity for alkyl C4-O bond scission.[77] Reaction of malonate substituted γ-lactones (**144**) with sodium hydride in THF gave the corresponding 3-6 membered carbocycles (**145**) in good yields (Scheme 39).

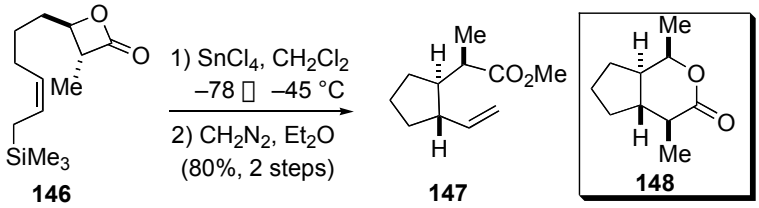


Scheme 39

3.5.2 Intramolecular Allylsilane Additions

Functionalized cyclopentanes are structural features in many natural products. Romo and Zhao reported a cyclopentane synthesis involving intramolecular allylsilane additions to γ-lactones.[78] Intramolecular

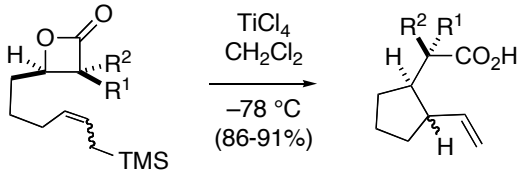
alkyl C4-O cleavage of β-lactone (**146**) mediated by $SnCl_4$ led to *trans*- cyclopentane (**147**) as the major isomer (10:1, *trans*/*cis*) in good yield after esterification (Scheme 40). Interestingly, a bicyclic lactone (**148**) derived from bis-cyclization was isolated in 35% yield when the reaction was warmed to 25 °C.



Scheme 40

In further studies of this process toward brefeldin A (*vide infra*), $TiCl_4$ was found to provide the highest yields for this cyclization.[79] *trans*-β-Lactones (**149b**) were found to give opposite and increased diastereoselectivity relative to *cis*-β-lactones (**149a**) (Table 5) in this cyclization. The *Z*/*E* geometry of the allylsilane had no effect on the stereochemical outcome.

Table 5. Effect of β-Lactone and Allylsilane Steroechemistry on the Stereoselectivity of Cyclopentane Formation



149a: R^1=Me, R^2=H
149b: R^1=H, R^2=Me

150a: R^1=Me, R^2=H
150b: R^1=H, R^2=Me

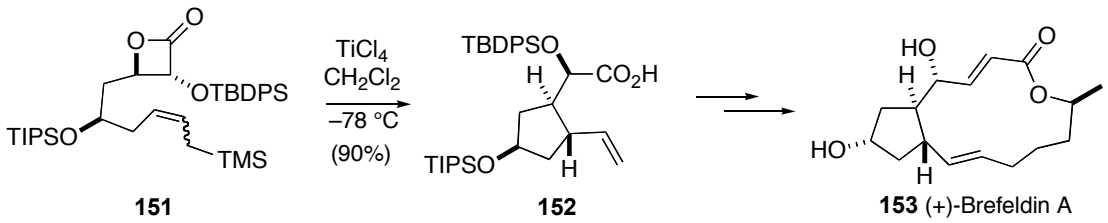
Compound	*Z*/*E*	*trans*/*cis*
149a	1:1	2:3
”	4:1	2:3
”	8:1	2:3
149b	1:2	10:1
”	4:1	10:1
”	ND[a]	10:1

[a]ND: not determined but the *E*-isomer was the major diastereomer.

- **Total Synthesis of (+)-Brefeldin A**

The utility of this cyclopentane synthesis was demonstrated in a total synthesis of (+)-brefeldin A,[79] a fungal metabolite displaying potent antitumor, antifungal, antiviral, antimitotic, and immunosuppressive activities.[80] Cyclization of β-lactone (**151**) with $TiCl_4$ smoothly delivered the desired *trans*-fused

cyclopentane (**152**) as a single diastereomer (>19: 1, 500 MHz NMR) with inversion of configuration at the α-carbon (Scheme 41). Synthesis of brefeldin A (**153**) from cyclopentane (**152**) required an additional eight steps and included a complex cross-metathesis and an intramolecular Horner-Wadsworth-Emmons macrocyclization.

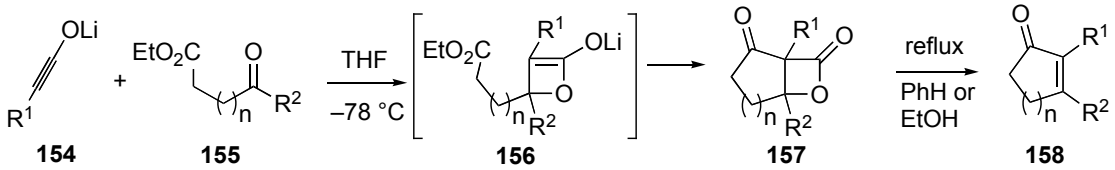


Scheme 41

3.5.3 Tandem [2+2] Cycloaddition-Dieckmann Condensation with Ynolate Anions

Shindo and co-workers reported a novel, tandem [2 + 2] cycloaddition Dieckmann condensation route to cycloalkenones and naphthalenes *via* α-lactone intermediates.[81] The [2 + 2] cycloaddition of ynolate anions (**154**) with β- or γ-keto esters (**155**), gave α-lactone enolates (**156**) initiating a Dieckmann condensation, and ultimately leading to bicyclic-α-lactones (**157**). Acid-catalyzed decarboxylation of these intermediates produced 2,3-disubstituted cyclopentanones and cyclohexanones (**158**) (Table 6).

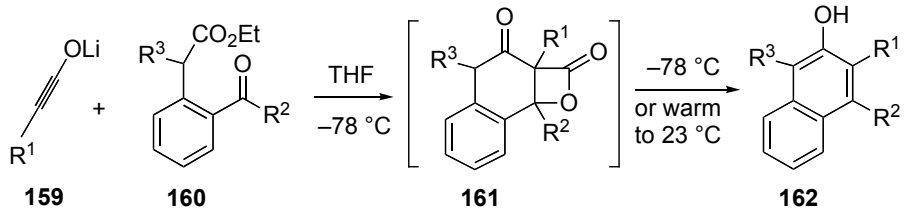
Table 6. Cycloalkenones *via* Tandem [2+2] Cycloaddition-Dieckmann Condensation



Entry	R^1	R^2	n	Decarboxylation	% Yield
1	Bu	Ph	2	SiO_2/PhH	74
2	Me	Ph	2	SiO_2/PhH	89
3	Bu	Me	2	HCl/EtOH	89
4	Me	Me	2	SiO_2/PhH	54
5	Bu	Ph	1	HCl/EtOH	89
6	Bu	Me	1	SiO_2/PhH	83
7	Me	Ph	1	HCl/EtOH	84
8	Me	$Et_2OC(CH_2)_2$–	1	HCl/EtOH	60

In a useful extension of this methodology, these authors developed a one-pot synthesis of highly substituted naphthalenes (**162**) not readily available *via* conventional methods (Table 7).[81b]

Table 7. Naphthalenes *via* Tandem [2+2] Cycloaddition-Dieckmann Condensation

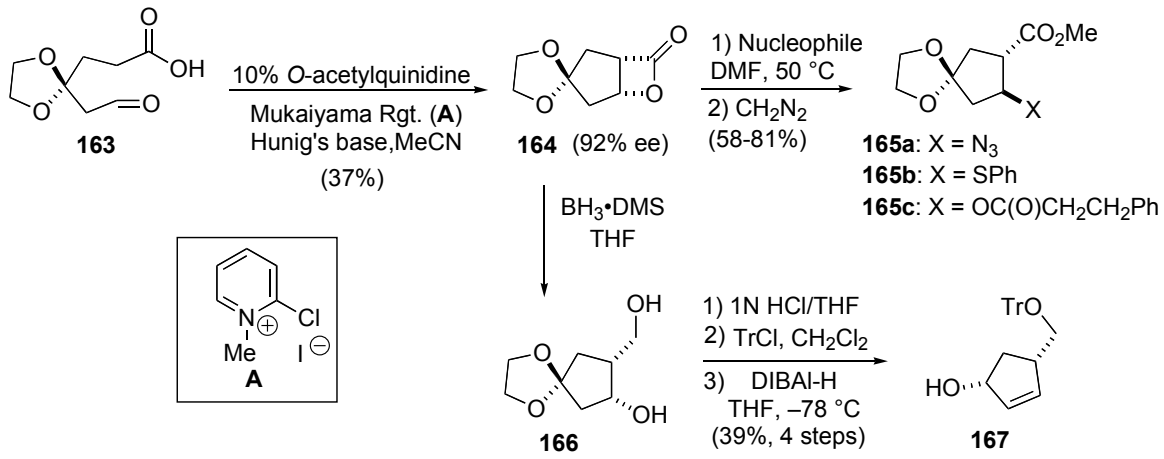


159 **160** **161** **162**

Entry	R^1	R^2	R^3	% Yield
1	Me	Me	H	74
2	Me	Et	H	89
3	Me	*i*-Pr	H	89
4	Me	Ph	H	54
5	Me	1-naphthyl	H	89
6	Bu	Me	H	83
7	Bu	Ph	H	83
8	*c*-Hex	Me	H	84
9	Me	Ph	Me	60

3.5.4 Nucleophilic Opening of Bicyclic β-Lactones

Romo and co-workers developed a catalytic, asymmetric approach to carbocycle-fused β-lactones (e.g. **164**) *via* an intramolecular, nucleophile-catalyzed aldol-lactonization (NCAL) process (Scheme 42).[82] These bicyclic β-lactones undergo facile ring cleavage under mild conditions *via* both acyl C1-O and alkyl C4-O bond cleavage.[83] Alkyl C4-O cleavage with azide, thiol, and carboxylate in DMF leads to a variety of *trans*-β-substituted cyclopentane esters (**165a-c**) following esterification. Cs_2CO_3 greatly accelerated the nucleophilic addition in the case of thiophenol and hydrocinnamic acid. Cleavage of the acyl C1-O bond with hydroxylamines proceeds at ambient temperature and reductive cleavage is readily accomplished with boron or aluminum reducing agents. The utility of these bicyclic β-lactones was demonstrated by conversion of **164** to cyclopentenol (**167**), a key intermediate in the synthesis of the antiviral carbocyclic nucleoside, (-)-aristeromycin.[84]

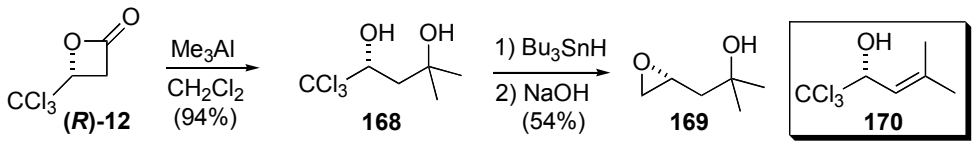


Scheme 42

3.6 OXYGEN-CONTAINING HETEROCYCLES

3.6.1 Epoxides

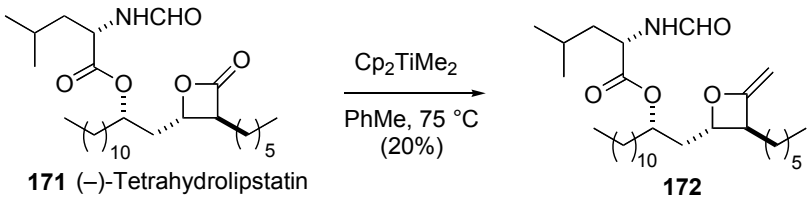
Fujisawa and co-workers performed an acyl C1-O cleavage reaction of commercially available β-trichloromethyl-β-propiolactone (**12**) with Me_3Al delivering optically active diol (**168**) in excellent yield (Scheme 43).[57] Controlled dechlorination with tributyltin hydride gave the chlorohydrin, which was converted to epoxide (**169**) by treatment with NaOH. Alternatively, dehydration of diol (**168**) with $CuSO_4$ on SiO_2 in refluxing toluene gave alkene product (**170**) in 53% yield.



Scheme 43

3.6.2 2-Methyleneoxetanes

Howell and co-workers employed the Petasis reagent to convert a variety of β-lactones to 2-methyleneoxetanes, a relatively unexplored class of strained heterocycles.[16] The Petasis reaction also proceeded with unprotected (–)-tetrahydrolipstatin (**171**), an anti-obesity drug marketed by Hoffmann-La Roche under the name Xenical® (Orlistat®), in an unoptimized 20% yield affording the corresponding 2-methyleneoxetane analog (**172**) (Scheme 44). [85] This derivative exhibited comparable inhibition activity toward porcine pancreatic lipase as Orlistat®.



171 (–)-Tetrahydrolipstatin **172**

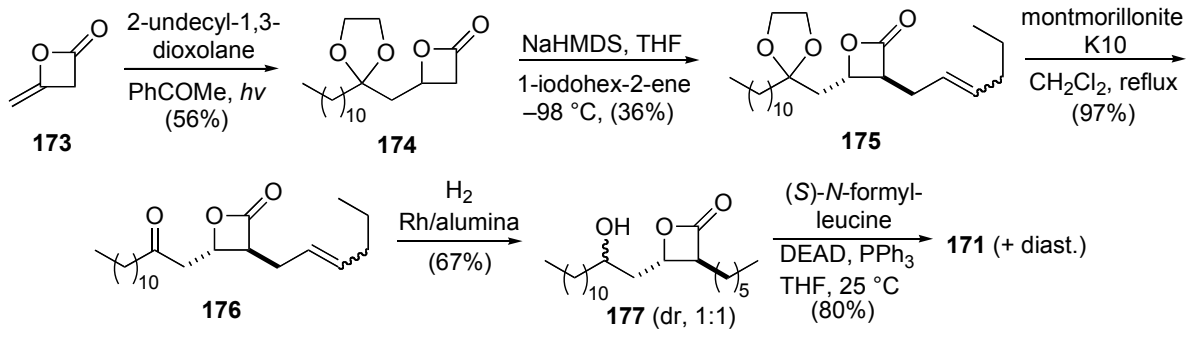
Scheme 44

One noteworthy feature of the Petasis methylenation is the observed chemoselectivity. It was found that the β-lactone carbonyl was preferred over alkenes, esters, carbamates, and most remarkably ketones.[86] Unprotected hydroxyl groups are tolerated except at proximal position.

3.6.3 Substituted β-Lactones *via* Alkylation

- **Total Synthesis of (–)-Tetrahydrolipstatin**

Alkylation of α-unsubstituted β-lactones is typically problematic due to competing self-condensation *via* Claisen processes as noted above. Parsons and Cowell recently overcame this difficulty to some degree in a concise synthesis of (–)-tetrahydrolipstatin (**171**).[87] Notably, β-lactone (**174**) was prepared by a novel photoalkylation of diketene (**173**) (Scheme 45). Sodium hexamethyldisilazide was found to be the optimal base and the alkylation was realized with 1-iodohex-2-ene as electrophile. Iodohexane was found to be insufficiently reactive to compete with self-acylation in accordance with Hanessian's findings in contrast to the more reactive allylic iodide.[88] β-Lactone (**174**) was converted to (–)-tetrahydrolipstatin in three steps (26% overall yield) involving hydrogenation with 5% rhodium on alumina, which also reduced the ketone (**175**) to a 1:1 mixture of diastereomeric alcohols (**176**) but without concomitant reduction of the β-lactone. Subsequent Mitsunobu reaction with *N*-formylleucine gave Orlistat® (**171**) and its C6 epimer in a 1:1 ratio. Importantly, this synthesis demonstrated a number of reactions and conditions that are compatible with the β-lactone nucleus.



173 **174** **175** **176** **177** (dr, 1:1)

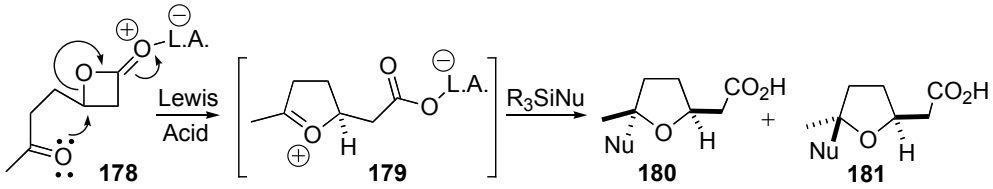
Scheme 45

3.6.4 Tetrahydrofurans

3.6.4.1 Intramolecular Ketone Additions

Mead and co-workers considered the use of β-lactones for the synthesis of 2,5-disubstituted tetrahydrofurans, which are ubiquitous substructures in natural products.[89] Lewis acid-mediated cyclization of a pendant ketone afforded the presumed oxocarbenium ion (**179**) *via* alkyl C4-O cleavage of β-lactone (**178**) (Table 8). Subsequent capture by various silane reagents gave *cis* tetrahydrofurans (**180**) as the major products. Concentration and temperature were determined to be the major factors controlling selectivity. Titanium tetrachloride provided the highest yields and superior selectivities (Table 8, entries 1, 7 and 9), while triethylsilane gave greater selectivity and yield when compared to the bulkier triphenylsilane (Table 8, entry 1 vs. entry 2).

Table 8. Synthesis of 2,5-Disubstituted Tetrahydrofurans *via* β-Lactones

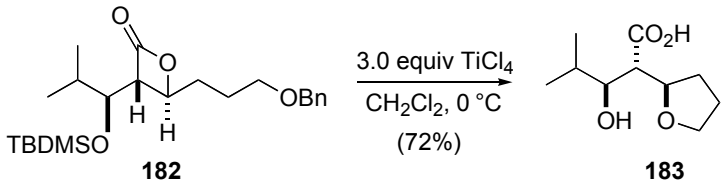


entry	L.A.	R_3SiNu	**180**:**181**	% yield
1	$TiCl_4$	Et_3SiH	85:15	82
2	$TiCl_4$	Ph_3SiH	42:58	60
3	$BF_3•OEt_2$	Et_3SiH	74:26	70
4	$BF_3•OEt_2$	Ph_3SiH	60:40	69
5	$MeAlCl_2$	Et_3SiH	85:15	45
6	Et_2AlCl	Et_3SiH	80:20	47
7	$TiCl_4$	TMS-allyl	80:20	77
8	$BF_3•OEt_2$	TMS-allyl	68:32	68
9	$TiCl_4$	TMSCN	88:12	77
10	$BF_3•OEt_2$	TMSCN	76:24	65

3.6.4.2 Intramolecular Benzyl Ether Additions

Mead and Park developed another method for tetrahydrofuran synthesis *via* β-lactone intermediates in studies directed toward the synthesis of the pamamycin polyether antibiotics.[90] Upon treatment with titanium tetrachloride, an intramolecular nucleophilic attack of the pendant benzyl ether resulted in alkyl C-O cleavage of β-lactone (**182**) with concomitant debenzylation and desilylation to give

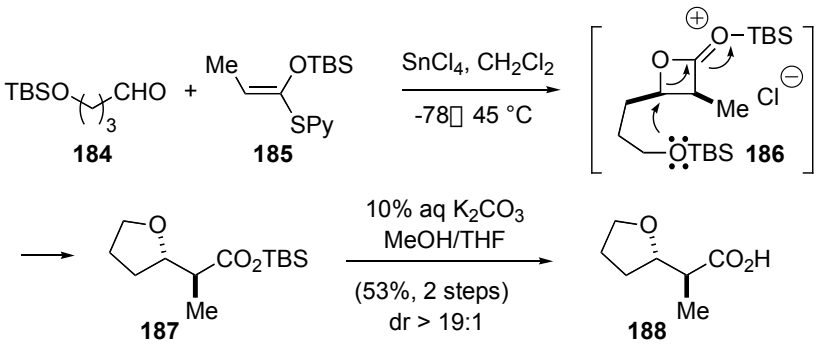
tetrahydrofuran (**183**) in good yield (Scheme 46). This reaction was found to proceed with inversion of configuration at the □-carbon.



Scheme 46

3.6.4.3 Intramolecular Silyl Ether Additions

Romo and co-workers discovered the formation of a tetrahydrofuran during a $SnCl_4$-mediated synthesis of *cis*-□-lactones.[59] Reaction of aldehyde (**184**) with thiopyridyl keteneacetal (**185**) in the presence of tin tetrachloride was proposed to initially form the silylated *cis*-□-lactone (**186**), which then underwent cyclization to deliver the tetrahydrofuran (**187**) with excellent (> 19:1) diastereoselectivity (Scheme 47). The stereochemical outcome is consistent with a *cis*-□-lactone intermediate undergoing S_N2-type inversion during alkyl C-O cleavage to the tetrahydrofuran.



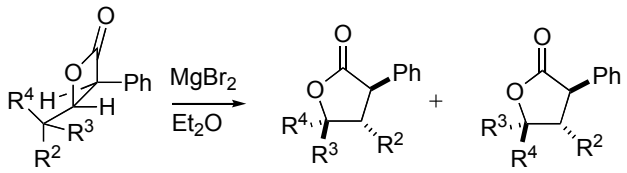
Scheme 47

3.6.5 □- and □-Lactones

3.6.5.1 Dyotropic Rearrangement

Mulzer reported the dyotropic ring expansion of □-lactones to form □-lactones in excellent yield (Table 9).[7] This procedure involves treatment of the □-lactone (**189**) with $MgBr_2$ in Et_2O at 25-30 °C for 12-60 hours.

Table 9. Dyotropic Ring Expansion of Substituted β-Lactones



entry	R^2	R^3	R^4	**190a** : **190b**	% yield
1	Ph	Me	OMe	78:22	96
2	Ph	OMe	Me	22:78	97
3	Ph	Me	H	97: 3	96
4	Ph	H	Me	85:15	95
5	OBn	*t*-Bu	Me	>99: 1	86
6	OBn	Me	Et	>99: 1	99
7	OBn	Et	Me	>99: 1	99

The reaction can proceed *via* a concerted or stepwise mechanism, as shown in Figure 10. In a concerted mechanism, only β-lactone (**190a**) should arise where the alkyl C-O bond is cleaved simultaneously with migration of R^2. The stepwise process can also deliver β-lactone (**190a**), but it can also undergo bond rotation prior to formation of lactone (**190b**). The observed formation of lactone (**190b**) provided the first evidence for a stepwise mechanism for this previously accepted concerted process.[91] The migratory aptitude of substituents were also established to be in the order of π-donor > *n*-donor > σ-donor.

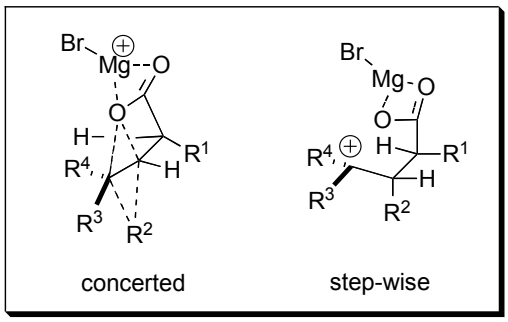
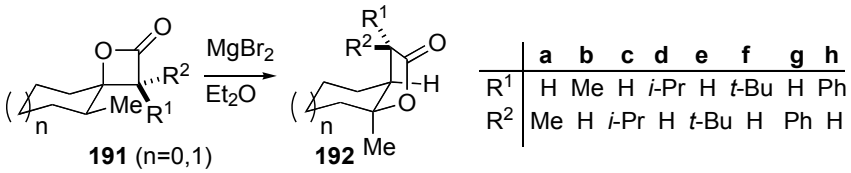


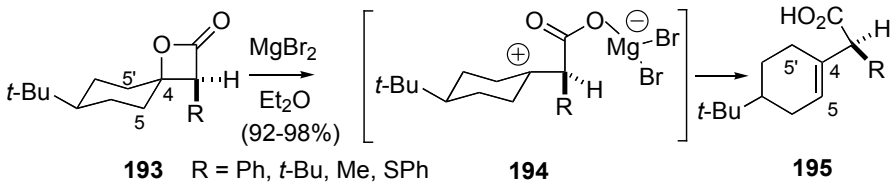
Figure 10. Possible Mechanistic Pathways for Dyotropic Ring Expansion of β-Lactones

Treatment of spirocyclic β-lactones with $MgBr_2$ in ether can give rise to two possible products, a β-lactone or a β,γ-unsaturated acid, depending on the starting β-lactone.[92] When β-lactones (**191**) were subjected to the reaction conditions, the β-lactones (**192**) were isolated in 68-98% yield (Scheme 48).



Scheme 48

However, treatment of β-lactones (**193**) under the same conditions gave the unsaturated carboxylic acids (**195**) in excellent yield (Scheme 49). It was found that both the C4 and C5 substituents influenced product distribution. While solvents were found to have little effect, Lewis acids had considerable effect on the relative migratory aptitude of C_5 substituents.[92]

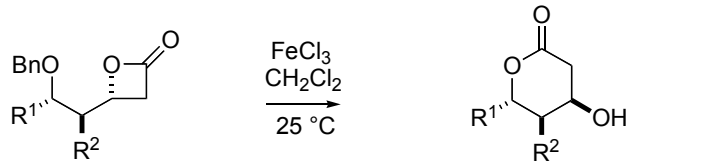


Scheme 49

Black's group also studied similarly substituted β-lactones in dyotropic rearrangements to *cis*-fused β-lactones. The reaction dependence on relative stabilities of the intermediate carbocations and the orientation of migrating bonds required to achieve an *anti*-periplanar relationship were studied.[91]

3.6.5.2 Tandem Transacylation/Deprotection of β-Lactones with Pendant Ethers

Romo and Zemribo demonstrated that β- and γ-lactones can be prepared from β-lactones bearing pendant benzyl ethers *via* a tandem transacylation/debenzylation pathway.[8] Optically active β-lactones (**196**) were obtained in high diastereoselectivity *via* the chelation-controlled [2 + 2] cycloadditions of silylketene and optically active aldehydes.[93] Building on prior work by Ganem who developed a method for conversion of benzyl ethers to the corresponding acetates,[94] $FeCl_3$ was employed to promote the tandem transacylation/debenzylation of β-lactones (**196**) to afford γ-lactones (**197**) in good yields (Scheme 50). In an attempt to minimize the formation of benzylated lactones obtained as minor byproducts (~8%), other Lewis acids including BF_3•OEt_2 and $MgBr_2$•OEt_2 were also studied but proved inferior to $FeCl_3$. Finally, improved selectivity (>19:1 *versus* 8.5:1, debenzylated *vs*. benzylated) for alcohol **197a** was realized using tetrabutylammonium iodide as a nucleophilic additive to the Fe(III)–mediated reaction by presumed interception of the benzyl cation formed in the reaction.

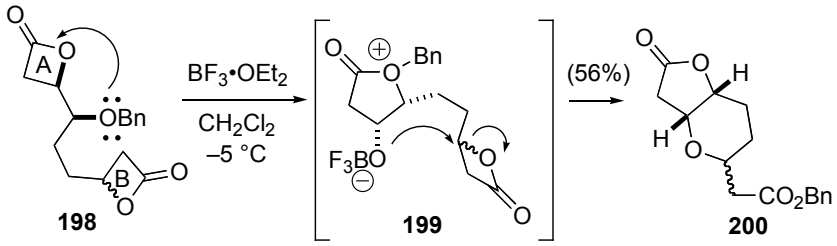


196a R^1 = H, R^2 =Me
196b R^1 = Me, R^2 = H

197a R^1 = H, R^2 =Me (68%)
197b R^1 = Me, R^2 = H (64%)

Scheme 50

In a study aimed at exploring the competition between alkyl C4-O alkyl cleavage and acyl C1-O cleavage, Mead and co-workers found that treatment of bis-β-lactone (**198**) with BF_3•OEt_2 gave the bicyclic β-lactone (**200**) in 56% yield (Scheme 51).[95] The authors speculate that benzyl ether oxygen addition to β-lactone ring **A** in substrate (**198**) leads to selective intramolecular acyl C_1-O cleavage to deliver intermediate (**199**). The resulting alkoxide presumably then adds to β-lactone ring **B** at the alkyl C-O bond producing *cis*-bicyclic β-lactone (**200**).

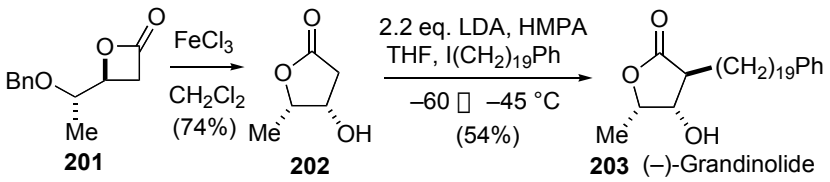


198 **199** **200**

Scheme 51

- **Total Synthesis of (–)-Grandinolide**

Romo and Zemribo applied the transacylation/debenzylation process to a concise synthesis of (–)-grandinolide,[8] a bark extract from the South American tree *Iryanthera grandis*. Treatment of β-lactone (**201**) with $FeCl_3$ in CH_2Cl_2 gave γ-lactone (**202**) in 74% yield (Scheme 52). A subsequent *anti*-selective α-alkylation with 1-iodo-19-phenylnonadecane delivered (-)-grandinolide (**203**) in 54% yield.



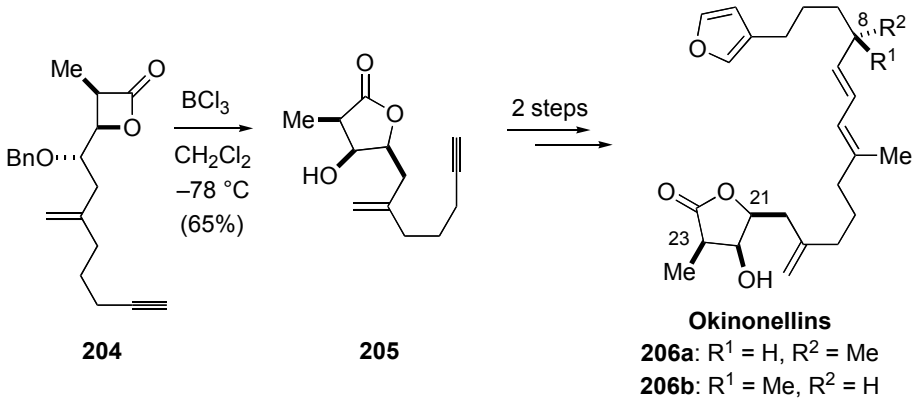
201 **202** **203** (–)-Grandinolide

Scheme 52

- **Total Synthesis of Okinonellin B**

The tandem acylation/debenzylation was also employed by the same group to prepare two diastereomers of the marine cytotoxin, okinonellin B.[96] These metabolites belong to a family of marine

furanosesterterpenes that exhibit antibacterial, cytotoxic and antispasmodic activity.[97] The total synthesis involved a transacylation/debenzylation of a more elaborate β-lactone (**204**) with BCl_3 in CH_2Cl_2 at 25 °C to deliver the β-lactone (**205**) in 65% yield (Scheme 53). This butyrolactone was transformed in two additional steps to deliver two diastereomers of okinonellin B (**206a-b**). The relative stereochemistry between the butyrolactone and C8-methyl group in addition to the absolute stereochemistry remain unknown due to a lack of the natural product for comparative purposes.



204 **205**

Okinonellins

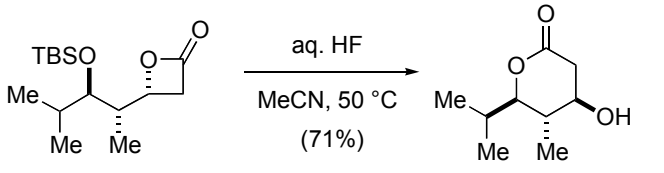
206a: R^1 = H, R^2 = Me

206b: R^1 = Me, R^2 = H

Scheme 53

- **Total Synthesis of Prelactone B**

Pons' group reported an aqueous HF-promoted translactonization of siloxy β-lactones to γ- and δ-lactones in the synthesis of (±)-prelactone B (**208**).[14c] Translactonization of β-lactone (**207**) along with its diastereomers (7:2:1) provided a 71% yield of (±)-prelactone B (**208**) and two inseparable diastereomers (5.7:1:1, Scheme 54). β-Trimethylsilyl-β-lactones were also found to participate in Peterson-type eliminations under the same conditions leading exclusively to α,β-unsaturated γ- and δ-lactones including racemic massoialactone (see Figure 2).



207 **208** Prelactone B

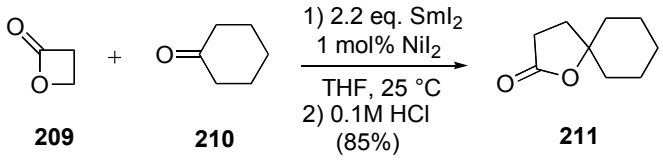
Scheme 54

3.6.6 Spirolactones

3.6.6.1 SmI_2/NiI_2–Mediated Rearrangement

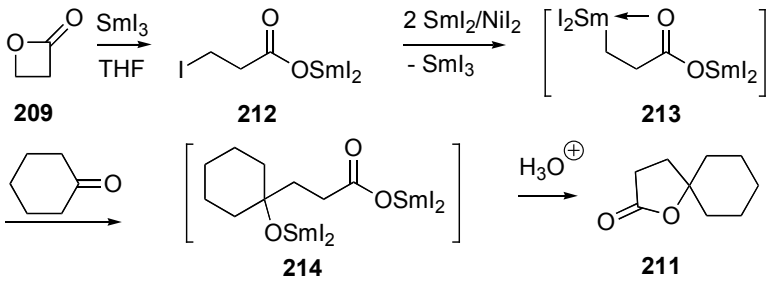
Namy and Machrouhi showed that SmI_2/NiI_2 is an excellent system for the coupling of β-lactones to ketones and aldehydes to form spiro-γ-lactones in good yields.[11] For example, treatment of β-

propiolactone and cyclohexanone (**210**) with SmI_2 and catalytic NiI_2 gave the β-lactone (**194**) (Scheme 55).



Scheme 55

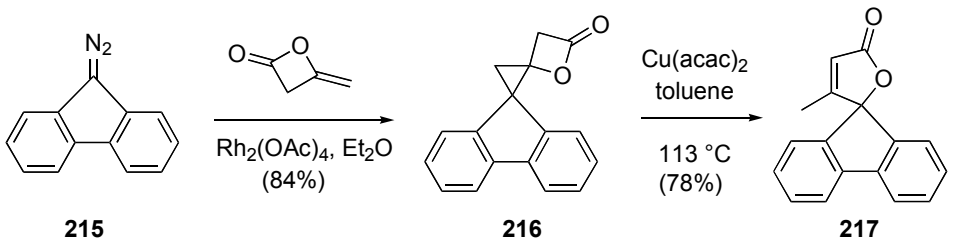
A possible mechanism proposed by the authors involves ring-opening of the β-propiolactone (**209**) by Sm(III) to generate iodo samarium carboxylate (**212**). Subsequent conversion to the samarium homoenolate (**213**) with Sm(II), followed by addition to cyclohexanone delivers the samarium alkoxy carboxylate (**214**). This intermediate undergoes cyclization to yield the spirolactone (**211**) upon acidic work-up (Scheme 56). This intriguing process enables a net insertion of a carbonyl carbon into the alkyl C3-O bond of a β-lactone.



Scheme 56

3.6.6.2 Cyclopropanation with Diazo Compounds

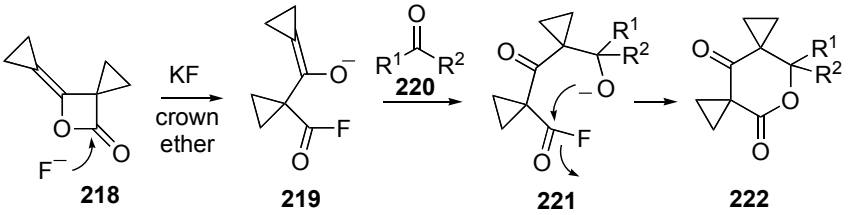
Geraghty and co-workers showed that β-methylene-γ-lactone reacts with diazo compounds to form cyclopropyl spiro-γ-lactones in good yields.[98] Rhodium-catalyzed decomposition of **215** in the presence of diketene led to clean formation of spiro lactone (**216**). Rearrangement to furanone (**217**) occurred upon heating in the presence of $Cu(acac)_2$ (Scheme 57). A mechanism involving insertion of the metal into the alkyl C-O bond of the β-lactone was proposed to explain the observations including regiochemistry. Similarly, pyranones and benzofurans were obtained *via* cyclopropyl spiro-γ-lactone intermediates in good yields.

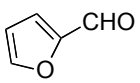
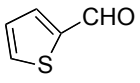
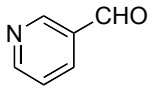
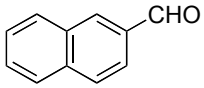
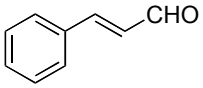
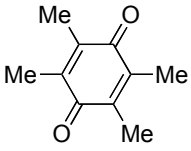
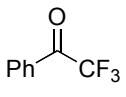


Scheme 57

3.6.6.3 Fluoride-Catalyzed Reaction with Electrophiles

Hoffmann and co-workers exploited a fluoride ion-catalyzed reaction of α-methylene-β-lactones with electrophiles.[56] The resulting crystalline β-keto-δ-valerolactones (**222**) are of potential interest in medicinal and agricultural chemistry (Scheme 58).



220	CCl_3CHO	PhCHO			
(yield of **222**)	(37%)	(37%)	(48%)	(40%)	(11%)
220					
(yield of **222**)	(23%)	(17%)	(37%)	(45%)	

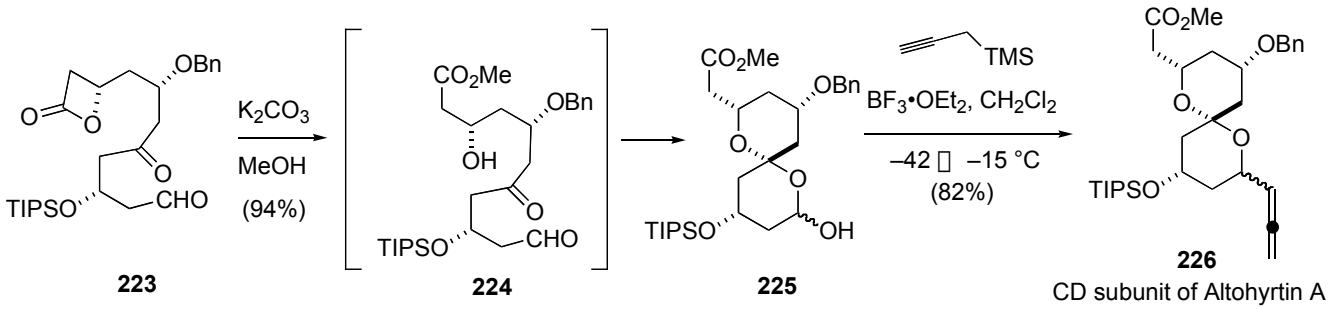
Scheme 58

3.6.7 SPIROKETAL

- **Studies towards Altohyrtin A**

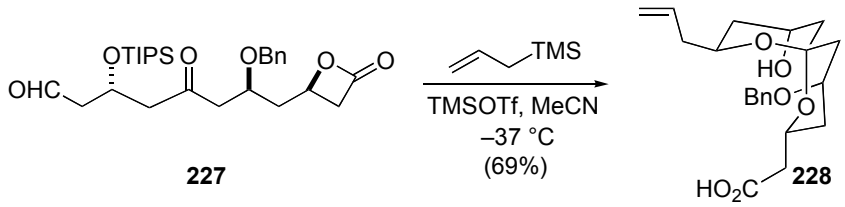
The synthesis of spiroketals has drawn much attention due to the number of natural products possessing this functionality, such as the recently isolated marine natural products altohyrtin and spongistatin. Mead and Zemribo developed an approach to the CD subunit of altohyrtin A,[99] an agent displaying remarkable antineoplastic activity. Methanolysis of γ-lactone (**223**) released δ-hydroxy ester (**224**),

from which a series of thermodynamically-driven cyclizations ensued producing the spiroketal (**225**) (□:□ = 7:1) in excellent yield (Scheme 59). Subsequent treatment with propargylsilane and BF_3•OEt_2 provided the allene (**226**) (□:□ = 1.6:1) comprising the CD subunit of altohyrtin.



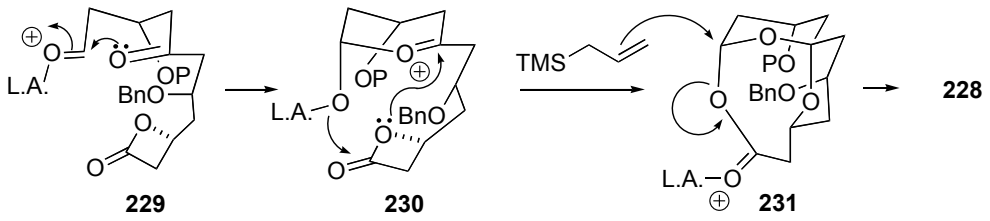
Scheme 59

Mead and Zemribo subsequently reported that spiroketals could be prepared stereospecifically from the Lewis acid mediated attack of an allyl nucleophile on a tricyclic diacetal intermediate, ultimately derived from a □-lactone.[100] Spiroketal (**228**) closely resembles the AB subunit of altohyrtin A (Scheme 60).



Scheme 60

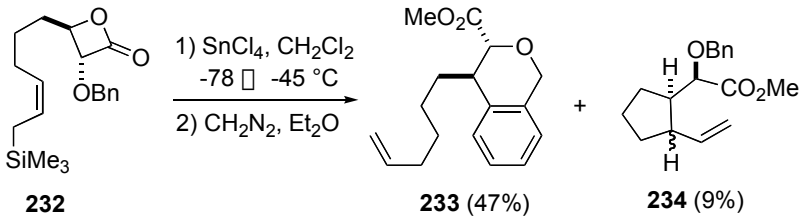
The high selectivity (single isomer) was rationalized by initial attack of the ketone oxygen on the activated aldehyde to yield oxocarbenium ion (**230**) followed by acyl C1-O cleavage of the □-lactone and subsequent cyclization to the tricyclic diacetal intermediate (**231**) (Scheme 61). Exclusive equatorial attack of the allylsilane nucleophile then delivers spiroketal (**228**).



Scheme 61

3.6.8 Isochromans

During their studies of intramolecular allylsilane additions to β-lactones, Romo and Zhao discovered the first example of an intramolecular Friedel-Crafts alkylation of β-lactones.[78] This unexpected reaction gave isochroman (**233**) as a single diastereoisomer, accompanied with minimal amount of desired cyclopentane (**234**) (Scheme 62). Although the relative stereochemistry of **233** was not rigorously determined, this novel process provides a new and unusual diastereoselective route to isochromans.

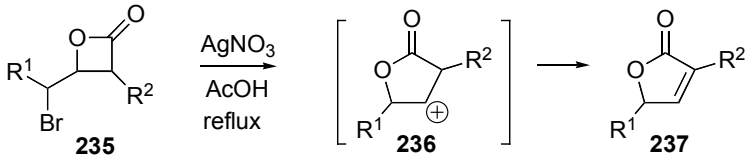


Scheme 62

3.6.9 Butenolides

Black and co-workers developed a method for the synthesis of substituted butenolides (**237**) in a single step from brominated β-lactones (**235**), available *via* bromolactonization (Table 10).[101] The proposed mechanism involves a stepwise dyotropic rearrangement of the β-lactone ring presumably proceeding through the carbocation (**236**) and ultimately resulting in ring expansion to γ-lactones (**237**).

Table 10. Butenolide Synthesis *via* Brominated β-Lactones

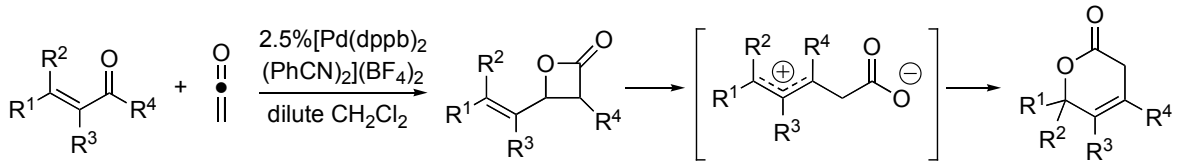


entry	R^1	R^2	% yield
1	H	H	53
2	H	Me	59
3	H	*i*-Pr	52
4	H	Bn	52
5	H	Bu	50
6	Et	H	31
7	Et	Et	64
8	Et	*i*-Pr	65
9	Et	Bn	60

3.6.10 3,6-Dihydro-2*H*-pyran-2-ones

Hattori and co-workers described the synthesis of 3,6-dihydro-*2H*-pyran-2-ones *via* tandem Pd(II)-catalyzed [2 + 2] cycloaddition-allylic rearrangement of ketene with β,γ-unsaturated aldehydes and ketones.[102] The intermediate β-lactones (**239**) underwent allylic arrangement to 3,6-dihydro-*2H*-pyran-2-ones **241** except in the case of entries 1-3, which gave only β-lactone **239** in excellent yield under the reaction conditions (Table 11). Methyl vinyl ketones also afforded β-lactones, though in poor yields, along with recovered ketones (Table 11, entries 12-14). The authors suggested a zwitterionic intermediate (**240**) for the allylic arrangement, due to the observation that BF_3•OEt_2 catalyzed the same rearrangement to give **241d** (Table 11, entry 4), *albeit* in 13% yield. Considerable amounts (28%) of diene were obtained from decarboxylation in the reaction of ketene with aldehyde (**238f**) (Table 11, entry 6).

Table 11. 3,6-Dihydro-2*H*-pyran-2-ones *via* Tandem [2+2] Cycloaddition-Allylic Rearrangement



238 **239** **240** **241**

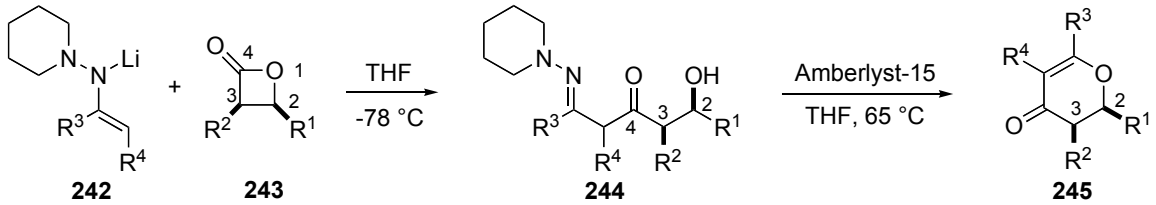
entry	aldehyde/ketones	R^1	R^2	R^3	R^4	% yield
1	**238a**	H	H	H	H	96 (**239a**)
2	**238b**	H	H	Br	H	93 (**239b**)
3	**238c**	H	H	Me	H	96 (**239c**)
4	**238d**	Me	H	H	H	70 (**241d**)
5	**238e**	Ph	H	H	H	77 (**241e**)
6	**238f**	*p*-$NO_2C_6H_4$	H	H	H	36 (**241f**)
7	**238g**	Pr	H	H	H	58 (**241g**)
8	**238h**	Pentyl	H	H	H	58 (**241h**)
9	**238i**	Me	Me	H	H	31 (**241i**)
10	**238j**	Pr	H	Et	H	66 (**241j**)
11	**238k**	R^1, $R^2 = (CH_2)_4$		H	H	52 (**241k**)
12	**238l**	H	H	H	Me	7 (**241l**)
13	**238m**	Me	H	H	Me	19 (**241m**)
14	**238n**	Ph	H	H	Me	18 (**241n**)

3.6.11 2,3-Dihydro-4*H*-pyrones

Nelson and co-workers reported that hydrazone anion-mediated β-lactone ring opening and ensuing cyclization-dehydroamination of the derived β-keto hydrazone affords 2,3-dihydro-4*H*-pyrones.[103]

Piperidine-derived hydrazones were deprotonated with LDA to generate anions (**242**), which reacted with optically active β-lactones (**243**), obtained by catalytic, asymmetric acyl halide-aldehyde cyclocondensation reactions,[31] to afford δ-keto hydrazones (**244**) (Table 12). Reflux in THF with Amberlyst-15® resin gave 2,3-dihydro-4*H*-pyrones (**245**) in good yields. Optically active 3,4-disubstituted β-lactone (**243e**) also underwent analogous lactone to dihydropyrone interconversion to afford 2,3-disubstituted dihydropyrone (**245i**), but with partial epimerization at C3 (Table 12, entry 9). This transformation of β-lactones provides a complementary route to hetero Diels-Alder cycloadducts for the preparation of 2,3-dihydro-4*H*-pyrones, which are useful building blocks for the synthesis of pyran-containing natural products.

Table 12. 2,3-Dihydro-4*H*-pyrones from Optically Active β-Lactones



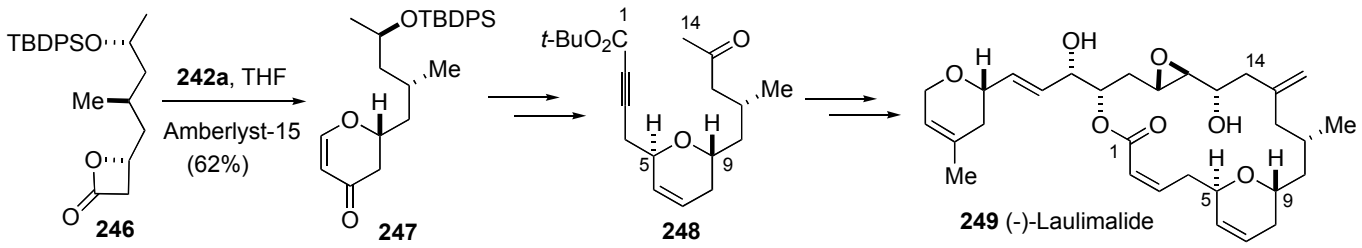
242 **243** **244** **245**

entry	β-lactones (% *ee*)	R^1	R^2	R^3	R^4	% yield
1	**243a** (91% *ee*)	CH_2CH_2Ph	H	H	H	78 (**245a**)
2	**243b** (90% *ee*)	$C{\equiv}CSiMe_3$	H	H	H	72 (**245b**)
3	**243c** (90% *ee*)	$(CH_2)_8CH{=}CH_2$	H	H	H	81 (**245c**)
4	**243d** (91% *ee*)	CH_2OBn	H	H	H	75 (**245d**)
5	**243a** (91% *ee*)	CH_2CH_2Ph	H	H	Me	74 (**245e**)
6	**243a** (91% *ee*)	CH_2CH_2Ph	H	Et	H	78 (**245f**)
7	**243b** (90% *ee*)	$C{\equiv}CSiMe_3$	H	Et	H	68 (**245g**)
8	**243d** (91% *ee*)	CH_2OBn	H	Et	H	76 (**245h**)
9	**243e** (93% *ee*)	Me	CH_2OBn	H	H	NR[a] (3:1, *syn*/*anti*) (**245i**)

[a]NR = Not reported.

- **Total synthesis of (-)-Laulimalide**

Nelson's group then applied this methodology to an elegant, asymmetric synthesis of (-)-laulimalide, with extensive use of their group's β-lactone synthesis and subsequent transformations.[104] Reaction of β-lactone (**246**) and hydrazone anion (**242a**) ($R^3 = R^4 = H$) delivered dihydropyrone (**247**) in 62% yield (Scheme 63). Further elaboration resulted in the total synthesis of (-)-laulimalide (**249**). A similar strategy was employed to construct the second dihydropyran present in the natural product.

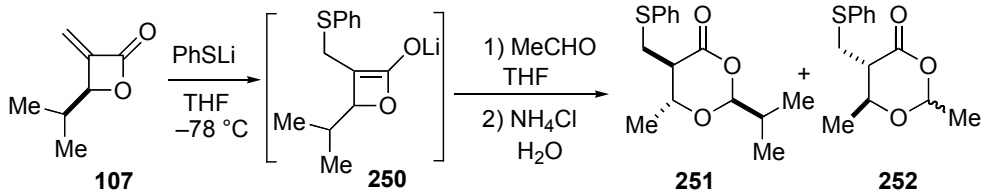


Scheme 63

3.6.12 1,3-Dioxan-4-ones

Adam and Nava-Salgado reported an unusual aldol reorganization process involving a complex cascade of aldol additions, retroaldol cleavages and translactonizations.[105] Condensation of the lithium enolate (**250**), generated from conjugate addition of lithium thiophenolate to β-methylene-γ-lactone (**107**), with acetaldehyde gave the 1,3-dioxan-4-ones (**251**) and (**252**) (Table 13). The product ratio was dependent on the amount of acetaldehyde employed and reaction temperature.

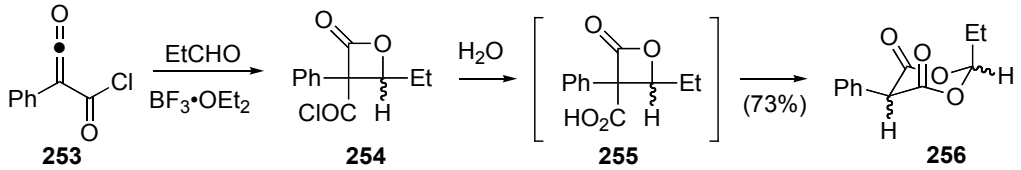
Table 13. 1,3-Dioxan-4-ones *via* β-Lactone Intermediate



entry	MeCHO (equiv)	temp (°C)	ratio (**251**:**252**)	% yield
1	0.9	–78 → 20	58:42	41
2	1.5	–78 → –40	50:50	40
3	1.5	–78 → 20	34:66	63
4	2.0	–78 → 20	0:100	55

3.6.13 1,3-Dioxane-4,6-diones

Saidi and co-workers developed a one-pot procedure for the synthesis of 5-phenyl-1,3-dioxane-4,6-dione derivatives *via* expansion of β-lactone intermediates.[106] Following Lewis acid catalyzed [2+2] cycloaddition of ketene (**253**) and propionaldehyde to give β-lactone (**254**), hydrolysis led to a spontaneous presumably acid-catalyzed rearrangement to give 5-phenyl-1,3-dioxane-4,6-dione (**256**) in 73% yield (Scheme 64). Several aldehydes and ketones were studied and the corresponding 5-phenyl-1,3-dioxane-4,6-diones were obtained in fair to good yields.

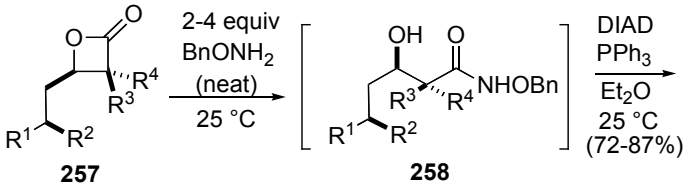


Scheme 64

3.7 NITROGEN-CONTAINING HETEROCYCLES

3.7.1 β-Lactams

β-Lactams are versatile intermediates in organic synthesis and are substructures of many antibiotics. Romo and Yang demonstrated a single-pot, mild conversion of β-lactones to β-lactams.[107] The procedure involves initial acyl C-O cleavage of β-lactone (**257**) by stirring neat with *O*-benzylhydroxylamine to form the *N*-benzyloxyhydroxamic acid derivative (**258**). In a single pot, the crude product is subjected to Mitsunobu-Miller conditions to provide β-lactams (**259**). A number of β-lactams were prepared in this fashion and selected examples are shown (Scheme 65). The Mitsunobu reactions occur with inversion of configuration at the β-carbon as expected, and the β-lactams were isolated in moderate to good overall yields (72-87%) with excellent transfer of chirality.

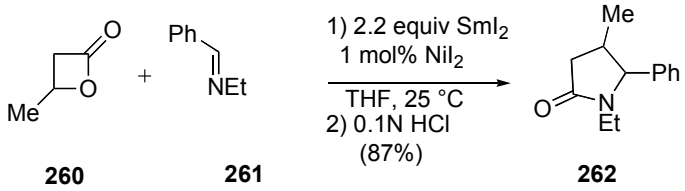


	a	b	c	d
R^1	Ph	Ph	Ph	Me
R^2	H	H	H	OTBS
R^3	H	H	Me	H
R^4	H	Me	H	Me

Scheme 65

3.7.2 β-Lactams

In a reaction analogous to that described earlier for coupling to carbonyl compounds, Namy and Machrouhi used a SmI_2/NiI_2 system in the coupling of β-lactones and imines to form β-lactams in good yields.[11] For example, reaction of β-lactone (**260**) with imine (**261**) gave β-lactam (**262**) followed by acid catalyzed lactamization in 87% yield (Scheme 66).



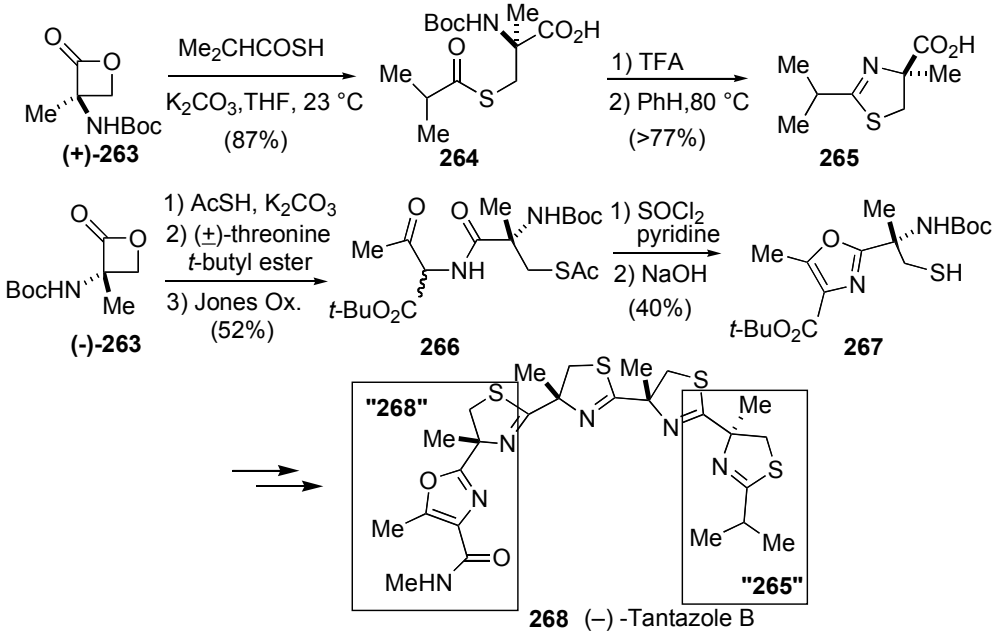
Scheme 66

3.7.3 Thiazolines and Oxazoles

- **Total Synthesis of (–)-Tantazole B**

Fukuyama and Xu elegantly utilized thiol additions to β-methylserine-derived β-lactones (**263**) and (**266**) (alkyl C4-O cleavage) in the first total synthesis of (–)-tantazole B (**268**) (Scheme 67).[108] Further

transformations of β-lactones (**263**) led to both thiazoline (**265**) and oxazole (**267**) which were then incorporated into the final target (as shown in boxes, respectively). Tantazole B and other members of the family exhibit selective cytotoxicity against murine solid tumors.



Scheme 67

4 SUMMARY AND OUTLOOK

β-Lactone transformations continue to draw great interest and this has increased in recent years due to the discovery of methods for their synthesis in optically active form.[2] These versatile heterocycles undergo a variety of novel and useful transformations, due to their inherent ring strain, making them useful chiral synthons (Table 1). Several of these transformations have been applied to the synthesis of bioactive natural products (Figure 1). However, while the chemistry of β-lactones has attracted greater interest in recent years, it would appear that the full synthetic utility of these heterocycles has yet to be exploited and further novel transformations should be expected in the future. Thus, great opportunities and lots of excitement lie ahead in the discovery of new transformations of β-lactones and their application to organic synthesis. β-Lactones will continue to receive much attention for the rational design of novel methodology and subsequent application to natural product endeavors.

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