Pergamon

Tetrahedron 55 (1999) 6403–6434

TETRAHEDRON

Tetrahedron report number 492

Methods for the Synthesis of Optically Active β-Lactones (2-Oxetanones)

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Received 1 December 1998

Contents

1.	Introduction	6403
2.	Chiral Synthon Approaches	6405
	2.1. Lactonization of β-hydroxy acids via hydroxyl group activation	6405
	2.1.1. Serine	6405
	2.1.2. Malic acid	6406
	2.1.3. Other β-hydroxy acids	6407
	2.2. Lactonization of β-hydroxy acids via carboxyl group activation	6407
	2.3. Lactonization of β-diazo acids	6410
	2.3.1. Asparagine	6410
	2.4. Pyrolysis of 4-oxo-1,3-dioxanes	6410
	2.5. Lactonization of various β-halocarboxylic acids	6410
	2.5.1. Aspartic acid	6411
3.	Diastereoselective Routes	6412
	3.1. Substrate controlled strategies	6412
	3.1.1. Tandem aldol-lactonizations	6412
	3.1.2. Tandem Mukaiyama aldol-lactonizations	6413
	3.1.3. [2+2] Cycloadditions of ketenes and aldehydes	6415
	3.1.4. Carbon–hydrogen insertion of diazoacetates	6418
	3.2. Chiral auxiliary strategies	6419
4.	Enantioselective Routes	6420
	4.1. [2+2] Cycloadditions of ketenes and carbonyl compounds	6420
	4.1.1. Nucleophilic catalysis by alkaloid bases	6420
	4.1.2. Catalysis by Lewis acids	6422
	4.2. Asymmetric hydrogenation	6425
5.	Miscellaneous	6426
	5.1. Kinetic resolution	6426
	5.2. Topological resolution	6427
	5.3. Asymmetric desymmetrization	6427
6.	Summary and Outlook	6428

1. Introduction

Demand for the development of synthetic routes to optically active β-lactones (2-oxetanones) continues to grow due to the increase and reappraisal of their utility in synthetic methodology and natural product synthesis.[1] This is not surprising because β-lactones can be viewed as "activated aldol products" since they possess the

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PII: S0040-4020(99)00185-4

structural features of aldol products yet they also have the inherent reactivity due to strain reminiscent of epoxides (β-lactones, 22.8 kcal/mole; epoxides, 27.2 kcal/mole)[2] (Figure 1).

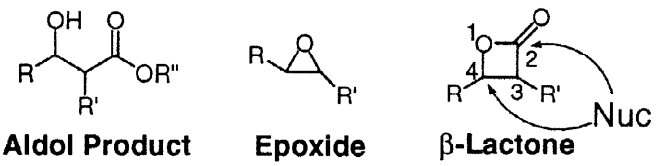
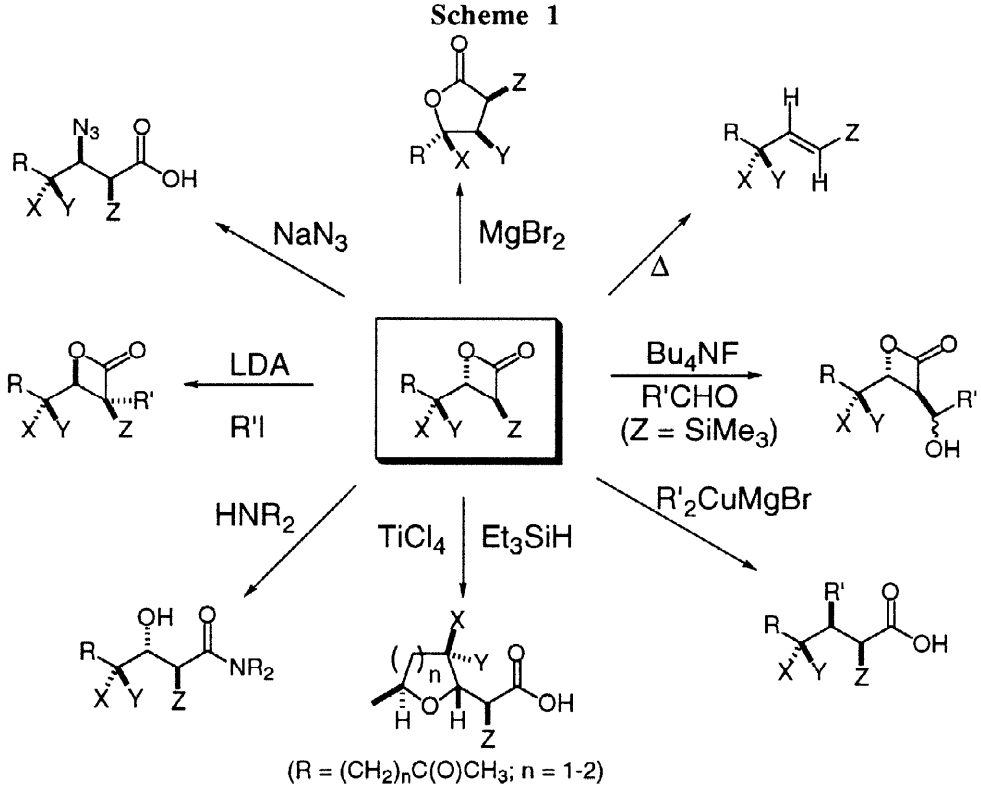


Figure 1. Comparison of Structure and Reactivity of β-Lactones to Aldols and Epoxides.

Asymmetric routes to aldols have been studied extensively as this is a common motif in many natural products. However, β-lactones have added utility in comparison to simple aldol products since they can undergo nucleophilic cleavage at both the C_2-O_1 bond (acyl-oxygen) as well as the C_4-O_1 (alkyl-oxygen) bond typically driven by release of ring strain (Figure 1). As a result, β-lactones undergo a number of interesting and useful stereospecific transformations making them versatile intermediates for organic synthesis (Scheme 1). Despite these facts, general methods for the direct synthesis of β-lactones in optically active form lag far behind those developed for epoxides and aldols.

Scheme 1



Several general reviews about β-lactones have appeared describing the racemic synthesis of β-lactones, their reactivity, and their transformations.[1,3,4,5] The synthesis of optically active β-lactones has not been reviewed to date and is thus the topic of this Tetrahedron Report. Optically active β-lactones are categorized according to the approach employed for introduction of chirality (chiral synthon, diastereoselective, enantioselective, and miscellaneous approaches) and then further divided according to the method employed in

their construction (e.g. lactonization, [2+2] cycloaddition, tandem aldol-lactonization, etc.). Most optically active β-lactones prepared in the course of a total synthesis are not included herein since these have been recently reviewed[6] although mention is made, in some cases, when the described methods have also been directly applied to natural product synthesis. In addition, it should be noted that this review is not intended to be exhaustive but rather to serve as a point of departure for chemists to find the most general and practical methods for the synthesis of optically active β-lactones reported up to 1998.

2. Chiral Synthon Approaches

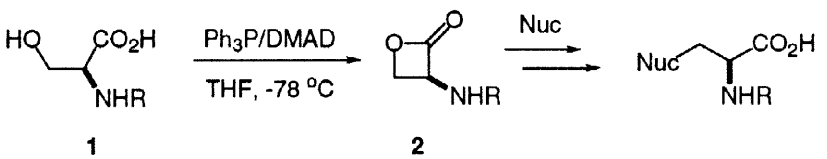
As one strategy for the synthesis of enantiomerically pure compounds, the chiral synthon approach has been widely applied in synthetic chemistry.[7] In general, the optically pure starting materials are readily obtained by resolution, asymmetric synthesis, or from nature. The preparation of optically active β-lactones using chiral synthons has been well developed. Most of the preparative methods for racemic β-lactone syntheses have been applied in chiral synthon strategies. Useful chiral templates for β-lactone synthesis include aspartic acid, asparagine, malic acid, serine, other β-hydroxy carboxylic acids, β-halocarboxylic acid salts, and 4-oxo-1,3-dioxanes. In most of these cases, the reaction conditions for the lactonization step are crucial for achieving high optical purities and yields. The preparation of β-lactones using β-hydroxy acids as starting materials is carried out via carboxyl group activation (retention of β-carbon stereochemistry) or hydroxyl group activation (inversion of β-carbon stereochemistry).

2.1. Lactonization of β-Hydroxy Acids via Hydroxyl Group Activation

2.1.1. Serine

Vederas and co-workers developed *N*-protected-α-amino β-lactones **2** as versatile intermediates for the synthesis of β-substituted-α-amino acids via ring opening reactions by various nucleophiles.[8] They achieved efficient formation of β-lactones **2** without racemization using modified Mitsunobu conditions (Scheme 2).

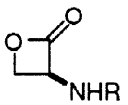
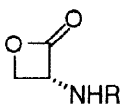
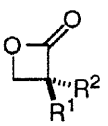
Scheme 2



1 **2**

Optically pure *N*-benzyloxycarbonyl or *N-tert*-butoxycarbonyl substituted serines **1** underwent facile cyclization with the preformed adduct of triphenylphosphine and dimethyl azodicarboxylate (DMAD) at -78 °C in good yields (Table 1).[8a] Mechanistic studies by Vederas using ^{2}H and ^{18}O labeled β-hydroxy acids have indicated that these reactions proceed via hydroxyl group activation.[8b] The utility of the derived *N*-protected-β-lactones has been demonstrated in the synthesis of many unnatural amino acids,[9] of β-lactone containing natural products,[6] and of several natural product syntheses including theonellamide, trapoxin B, and tantazole B.[10]

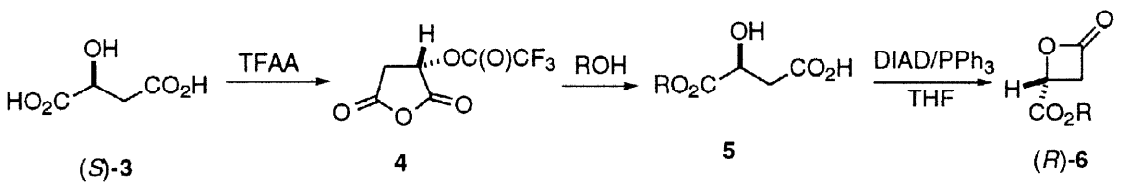
Table 1. Optically Pure β-Lactones Prepared from Serine

entry	β-lactone (**2**)			% yield	config. (C3)	ref.
			R			
1			Cbz	76	*S*	8c
2			Boc	72	*S*	8a
3			C(O)Bn	77	*S*	8c
			R			
4			Cbz	81	*R*	8c
5			Boc	84	*R*	11
		R^1	R^2			
6		NBn•Cbz	H	71	*S*	8c
7		H	NBn•Cbz	71	*R*	8c

2.1.2. Malic Acid

One route to β-lactones to be used as monomers for the synthesis of biodegradable polymers begins with (*S*)-malic acid (**3**). Guérin and co-workers reported a novel synthesis of optically active 4-benzyloxy- and 4-alkyloxycarbonyl β-lactones **6** with very high optical purity (>98% ee) via Mitsunobu cyclization of malate monoesters **5** (Scheme 3).[12]

Scheme 3

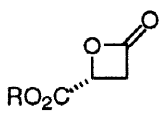
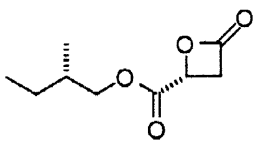


(*S*)-**3** **4** **5** (*R*)-**6**

Their synthesis began with (*S*)-malic acid (**3**) as a chiral synthon. In the presence of trifluoroacetic anhydride (TFAA), optically pure (*S*)-malic acid was converted to the corresponding malic acid anhydride **4**. Treatment of this intermediate with anhydrous alcohols provided the optically pure monoesters **5** with high regioselectivity. Finally, the monoesters **5** were lactonized using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine to afford (*R*)-alkyl malolactonates **6** in good yield and in high optical purity (98% ee).

The observed (4*R*)-configuration in the product β-lactones **6** was attributed to inversion of the β-stereocenter in the monoesters **5** via hydroxyl group activation. This method generally provided excellent optical purity (>98% ee) for all cases reported (Table 2). The low isolated yields were attributed to thermal decomposition of the β-lactones during further purification by vacuum distillation.

Table 2. Optically Active β-Lactones Prepared from Malic Acid

entry	β-lactone	R	% ee	% yield[a]	config.(C4)	ref.
1		Bn	>98	59(11)	*R*	12
2		Me	>98	56(24)	*R*	12
3		Et	>98	NR	*R*	13
4		*n*-Pr	>98	NR	*R*	13
5			>98	62(20)	*R*	12

[a]Yield is after column chromatography. Yield in parenthesis is after column chromatography followed by distillation. NR = not reported.

2.1.3. Other β-Hydroxy Acids

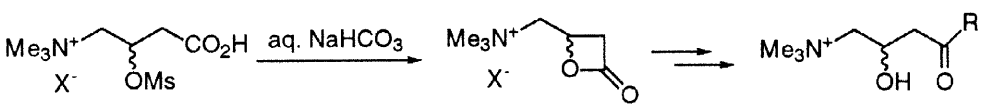
Lenz and co-workers prepared (*S*)-butyrolactone **10** in >97% ee from (*R*)-β-*O*-mesylbutyric acid (**9**) under basic aqueous conditions (Scheme 4).[14] In their synthesis, the starting material, methyl (*R*)-β-hydroxybutyrate (**8**) was prepared by methanolysis of poly[(*R*)-β-hydroxybutyrate] (**7**), a bacterial product.[15]

Scheme 4

7 **8** **9** **10**

In their studies of a β-lactone route to carnitine and derivatives, Giannessi and co-workers utilized (*S*)- and (*R*)-carnitine mesylates **11** for the formation of the corresponding β-lactones **12** by lactonization through an inversion process.[16] These β-lactones were subsequently converted to a variety of carnitine derivatives via *O*-acyl fission (Scheme 5).

Scheme 5



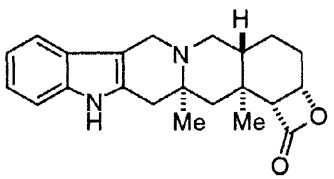
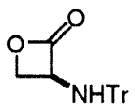
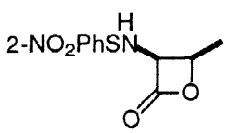
(*R*) or (*S*)-**11** (*R*) or (*S*)-**12** (>99% ee)

2.2. Lactonization of β-Hydroxy Acids via Carboxyl Group Activation

The lactonization of β-hydroxy acids via carboxyl group activation has been known since the late 1950's. Early application of this strategy for the preparation of β-lactones through a carboxylic anhydride intermediate[17] or by use of *N*,*N*-diisopropylcarbodiimide[18a] generally provided low yields. However, the subsequent

discovery of new peptide coupling reagents made this route more popular for the preparation of β-lactones. In general, these reactions lead to net retention of stereochemistry since they proceed by carboxyl group activation. Optically active β-lactones prepared by this method are shown in Table 3. Employing the coupling reagent, bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOPCl), this strategy has been applied to the total synthesis of a proteasome inhibitor, lactacystin, and analogs.[19]

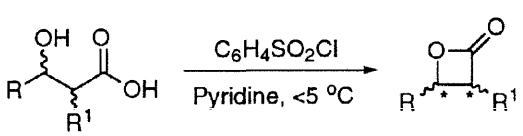
Table 3. Optically Active β-Lactones Prepared by Carboxyl Group Activation

entry	β-lactone	reagents[a]	% yield	config. (C3,C4)	ref.
1		$ClCO_2Et$	35	3*R*,4*S*	17
2		DIC	15	3*S*	18a
3		DIC, DMAP	26	3*S*	18b
4		DCC	10	3*S*	18c
5		BOPCl, Et_3N	95	3*S*	18d
6		MsCl, Py, K_2CO_3[b]	23	3*S*,4*R*	20

[a]DIC = *N*,*N*-diisopropylcarbodiimide. DMAP = *N*,*N*-dimethylaminopyridine. DCC = *N*,*N*-dicyclohexylcarbodiimide. BOPCl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride. [b]The cyclization precursor was a benzylhydroxamate, rather than the carboxylic acid, derived from *N*-(*o*-nitrophenylsulfenyl)-*l*-threonine.

A versatile method for carboxyl group activation of β-hydroxy acids **13** for the synthesis of β-lactones **14** was developed by Adam and coworkers (Scheme 6). They reported the formation of β-lactones via intramolecular cyclization of β-hydroxy acids **13** using benzenesulfonyl chloride in pyridine at low temperature (< 5 °C).[21] In this method, at least one C3-substituent ($R_1 \neq H$) is necessary for efficient cyclization, suggestive of the requirement of the Thorpe-Ingold (gem-dialkyl) effect for efficient lactonizations. The stereochemistry of the β-carbon center was retained as expected for carboxyl group activation. Adam's procedure has become one of the most widely used preparative methods for optically active β-lactones and racemic β-lactones (Table 4). Many total syntheses of naturally occurring β-lactones have been accomplished employing this method for construction of the β-lactone ring.[6, 22]

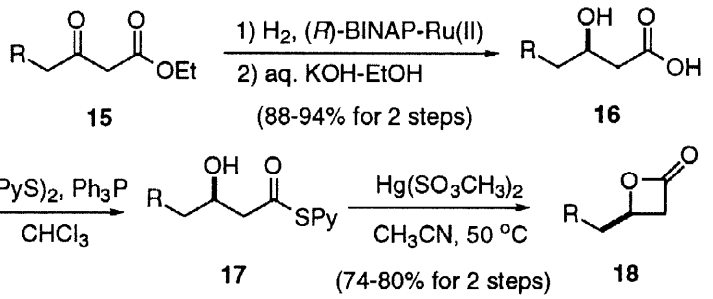
Scheme 6



13 **14**

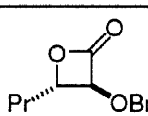
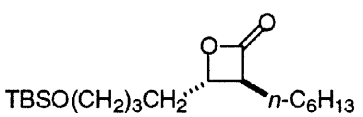
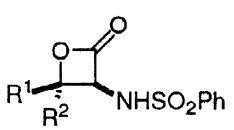
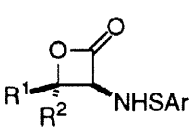
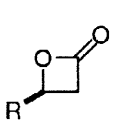
Roelens and co-workers developed a general method for the synthesis of optically pure β-lactones employing modified Masamune conditions with thioesters (Scheme 7).[23] Optically pure hydroxy acids **16** were obtained by asymmetric hydrogenation of β-ketoesters **15**, available in two steps from acid chlorides, using Noyori's BINAP-Ru(II) catalyst. After conversion to the corresponding thiopyridyl esters **17**, application of modified Masamune conditions provided enantiomerically pure β-lactones **18** (Table 4). While this method allows access to a number of 4-substituted β-lactones, the number of steps involved and the use of Hg(II) salts detracts from the practicality of this methodology.

Scheme 7



15 **16** **17** **18**

Table 4. Optically Pure β-Lactones Prepared by Adam's or Roelens' Procedures

entry	β-lactone			% yield	config. (C3,C4)	method[a]	ref.
1				72	3*S*,4*S*	A	24
2				70	3*S*,4*S*	A	25
		R^1	R^2				
3		Me	H	54	3*S*,4*R*	A	26
4		H	Me	55	3*S*,4*S*	A	26
5		Et	H	39	3*S*,4*R*	A	26
		R^1	R^2				
6		Me	H	56	3*S*,4*R*	A	27
7	Ar = 2-NO_2Ph	H	Me	45	3*S*,4*S*	A	27
		R					
8		$PhCH_2$		78	4*R*	B	23
9		4-MeO-$PhCH_2$		80	4*R*	B	23
10		3,4-$(MeO)_2$-$PhCH_2$		74	4*R*	B	23

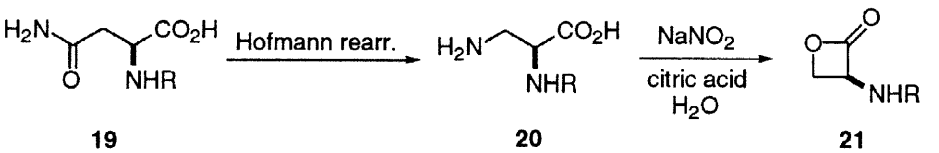
[a]Method A: Adam's procedure (ref. 21). Method B: Roelens' procedure (ref. 23).

2.3. Lactonization of β-Diazo Acids

2.3.1. Asparagine

One useful route to α-amino protected β-lactones was reported by Miyoshi and co-workers. This method involved the synthesis of *l*-α-*N*-tosylamino-β-propiolactones **21** from *l*-*N*-tosylamino-asparagines **19** (Scheme 8).[28a]

Scheme 8



19 **20** **21**

This transformation consists of a Hofmann rearrangement and a diazotization followed by an in situ cyclization. This methodology was utilized for the synthesis of β-lactones (Table 5) that were subsequently employed as starting materials for the synthesis of (*S*)-seryl peptides by ring opening with various amino or peptide esters.[28b]

Table 5. Optically Active β-Lactones **21** Prepared from Asparagine

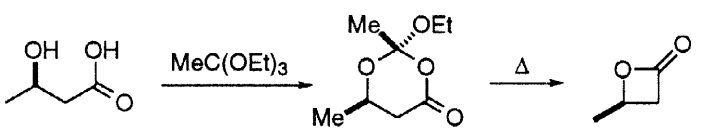
entry	R	% yield	config.(C3)[a]	ref.
1	*p*-MePhSO$_2$	56	*S*	28a
2	*p*-MeOPhSO$_2$	62	*S*	28b
3	PhSO$_2$	28	*S*	28b
4	*p*-ClPhSO$_2$	52	*S*	28b

[a]Optical purities were not reported.

2.4. Pyrolysis of 4-Oxo-1,3-dioxanes

Blume reported a new route to β-lactones *via* ring contraction of 4-oxo-1,3-dioxanes.[29] Later, Seebach and Griesbeck employed this method for the synthesis of (*S*)-4-methyloxetan-2-one (**24**) (Scheme 9).[30] The 1,3-dioxan-4-one **23** was prepared from (*R*)-3-hydroxybutanoic acid (**22**) and pyrolyzed to the β-lactone **24**. This β-lactone was utilized for the preparation of enantiomerically pure (*S*)-3-hydroxybutanoic acid (ent-**22**) through basic hydrolysis of β-lactone **24** indicating that pyrolysis proceeds by inversion at C3.

Scheme 9

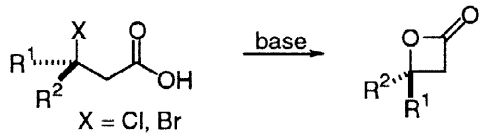


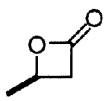
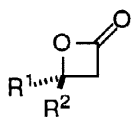
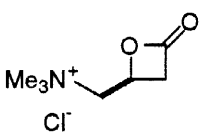
22 **23** **24**

2.5. Lactonization of Various β-Halocarboxylic Acids

The intramolecular lactonization of β-halocarboxylic acid salts under basic conditions is the oldest preparative method for β-lactone synthesis. Einhorn reported the first example of this reaction in 1883 as a route to 4-(2-nitrophenyl)oxetan-2-one from the corresponding β-bromocarboxylic acid salt precursor.[31] Several optically active β-lactones have been prepared from chiral β-halocarboxylic acids in this manner (Table 6).

Table 6. Optically Active β-Lactones Prepared from β-Halocarboxylic Acids



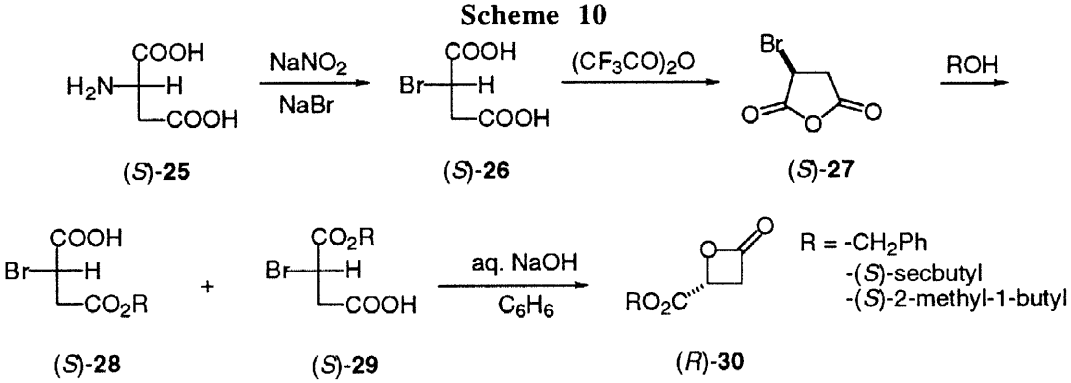
entry	β-lactone			% ee	% yield	config. (C4)	ref.
1				83(90)[a]	72	*R*	32a
2				73	NR[b]	*R*	32b
		R^1	R^2				
3		Me	Et	NR[b]	NR[b]	*R*	33
4		Et	Me	NR[b]	56	*S*	33
5				NR[b]	65[c]	*S*	16a

[a]% ee in parentheses refers to optical purity of the starting β-bromobutyric acid. Enantiomeric excess was determined after conversion of the β-lactone to citronellic acid. [b]NR = not reported. [c]NMR yield.

2.5.1. Aspartic Acid

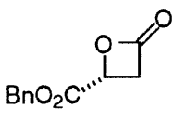
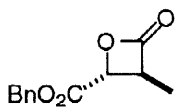
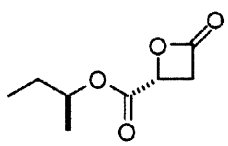
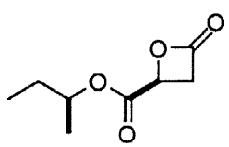
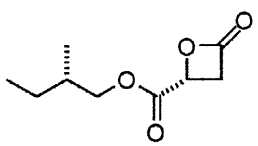
Chiral β-substituted β-lactones are considered useful monomers for the synthesis of biodegradable polymers via ring opening polymerization or copolymerization. The chirality of the polymer is known to play an important role in biodegradability and tacticity. However, β-substituted β-lactones could not be prepared by the well-known route based on optically active β-bromosuccinic acids due to racemization during the ring closure step.[34] In 1985, Guérin and co-workers reported a new, improved route to the desired β-lactones from readily available *l*-aspartic acid (Scheme 10).[34,35] *l*-Aspartic acid (**25**) was converted to *l*-bromosuccinic acid (**26**) by a diazotization/bromination sequence with retention of configuration. The bromosuccinic anhydride **27** was then obtained by treatment with trifluoroacetic anhydride. Alcoholysis provided monoalkyl esters **28** and **29** and subsequent base induced lactonization gave optically enriched β-lactones **30** via inversion at C3 (Table 7).

Scheme 10



Subsequently, Guerin and co-workers found that these transformations can proceed, in some cases, with little or no loss of optical purity but generally in low overall yield. However, the optical purity was highly dependent on the reaction temperature of the lactonization step (entries 1 and 2, Table 7).[35]

Table 7. Optically Active β-Lactones Prepared from Aspartic Acid

entry	β-lactone (**30**)	selectivity	% yield[a]	config. (C3,C4)	ref.
1		80% ee (50 °C)	5[b]	4*R*	34
2		95% ee (35 °C)	NR	4*R*	35
3		>99% ee	39[c]	3*S*,4*R*	36
4		20% de	NR	4*R*	37
5		20% de	NR	4*S*	37
6		84% de	NR	4*R*	13

[a]NR = not reported. [b]Overall yield (see Scheme 10). [c]Yield is for the lactonization step only.

3. Diastereoselective Routes

Diastereoselective routes for the asymmetric synthesis of β-lactones reported to date can be categorized into three strategies: (1) aldol-lactonizations (2) Lewis acid-mediated approaches including tandem Mukaiyama aldol-lactonizations and [2+2] cycloadditions and (3) chiral auxiliary strategies employing transition metal complexes. Both substrate and reagent controlled strategies have been employed.

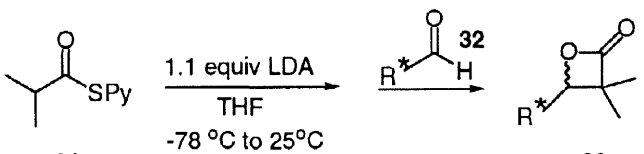
3.1. Substrate Controlled Strategies

3.1.1. Tandem Aldol-Lactonizations

Recently, Cossio and co-workers applied Danheiser's aldol-lactonization methodology for β-lactone synthesis[38] to optically pure aldehydes **32** bearing α-stereogenic centers using the lithium enolate of thiopyridyl isobutyrate **31** (Scheme 11).[39] In most cases, they obtained β-lactones resulting from non-chelation controlled addition as major products (>98:2) except in the case of the *t*-butyldimethylsilyl protected, mandelic acid derived aldehyde (Table 8, entry 1). They also found that the use of enolates derived from thiopyridyl isobutyrate **31** afforded the best results in terms of stereoselectivities and yields. The latter result possibly reflecting the requirements of a gem-dialkyl effect for efficient lactonization as described above and previously noted in related

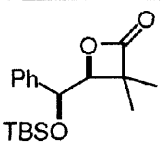
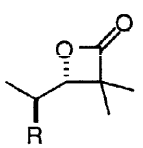
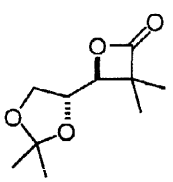
reactions.[40] Only α,α-dimethyl-substituted β-lactones have been synthesized to date using this methodology (Table 8). Another aldol-lactonization process involving a chiral oxazaphophorinane was reported by Evans and Gordon. However, the only β-lactone reported, (*S*)-3-methyl-4-phenyl-2-oxetanone, was not isolated but rather directly hydrolyzed.[38b]

Scheme 11



31 **33**

Table 8. Optically Active β-Lactones Prepared by the Tandem Aldol-Lactonization

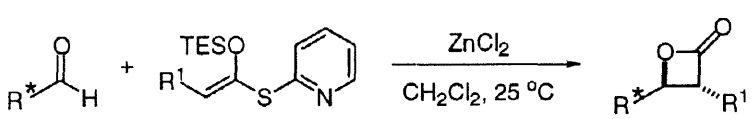
entry	β-lactone (**33**)	R	*anti/syn*	% yield	config.(C4)
1			12:88	41	*S*
2		OBn	>98:2	39-61	*R*
3		NBn_2	>98:2	61[a]	*R*
4			>98:2	38-55	*S*

[a]Yield as determined by ^1H NMR.

3.1.2. Tandem Mukaiyama Aldol-Lactonizations

Recently, Romo and Yang applied the tandem Mukaiyama aldol-lactonization (TMAL) reaction[41] to a variety of optically active aldehydes (Scheme 12).[42] High internal (*trans/cis*) and relative (*syn/anti*) stereoselectivity for the propionate ketene acetal **34** (R^1 = Me) was obtained (Table 9). In most cases, less than 2% racemization of α-epimerizable aldehydes was observed despite the fact that these reactions are conducted at 25° C in the presence of a potential base (thiopyridyl group) and a Lewis acid. This methodology was exploited in a concise synthesis of the potent pancreatic lipase inhibitor, (-)-panclicin D.[41b,c]

Scheme 12

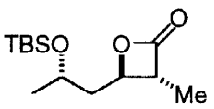
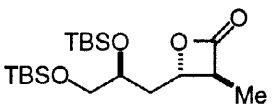
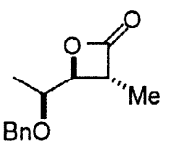
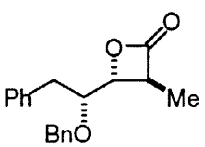
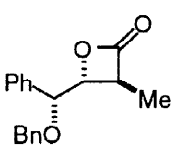
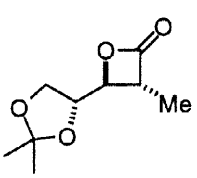
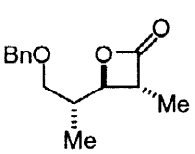
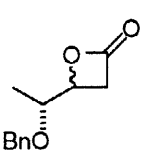
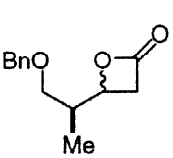


R^1 = H, Me

32 **34** **35**

Interestingly, in contrast to Cossio's results, the stereochemistry of the major diastereomer obtained with α-benzyloxy aldehydes (Table 9, entries 3-5) is consistent with a chelation-controlled aldol reaction.

Table 9. Optically Active β-Lactones Prepared by the TMAL Reaction

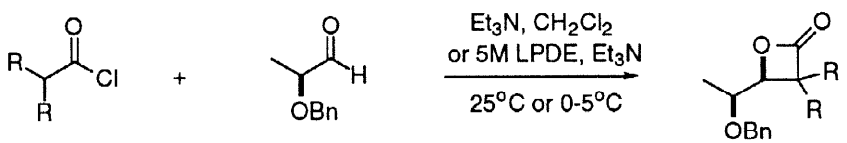
entry	β-lactone	% ee	*trans/ cis*	*syn/ anti*	% yield	config. (C3,C4)
1		85[a]	>19:1	1:9.1	62	3*R*,4*R*
2		98	>19:1	1:4.8	46	3*S*,4*S*
3		96	>19:1	20:1	69	3*R*,4*S*
4		98	>19:1	22:1	63	3*S*,4*R*
5		69	>19:1	>19:1	50	3*S*,4*R*
6		99	3.6:1	<1:19	82	3*R*,4*S*
7		99	>19:1	1:1.9	29	3*R*,4*R*
8[b]		ND[c]	-	1:1.6	64	4*S*[d]
9[b]		ND[c]	-	1:1.4	55	4*R*[d]

[a]The starting aldehyde had an optical purity of 85% ee. [b]Acetate ketene acetal **34** (R^1 = H) was used. [c]ND = not determined. [d]Configuration is for major *anti*-β-lactone.

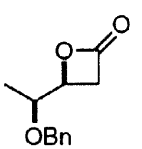
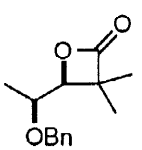
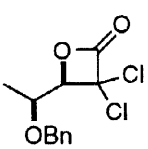
3.1.3. [2+2] Cycloadditions of Ketenes and Aldehydes

Although the [2+2] cycloaddition of carbonyl compounds and ketenes has been known since 1911,[43] it has only recently been utilized to prepare β-lactones in optically active form. Both thermal, catalyzed and purely thermal versions of this cycloaddition are known. A large body of recent theoretical work points to the concerted, asynchronous nature of Lewis acid catalyzed versions of these cycloadditions which likely involve a nucleophilic ketene adding to a Lewis acid-activated aldehyde.[44] Cossio and co-workers recently performed computational and experimental studies of both the thermal and the presumed Li(I)-catalyzed [2+2] cycloaddition of methylketene and dichloroketene with chiral aldehydes (Table 10).[45] These workers concluded based on their computational work that these cycloadditions take place through a concerted, asynchronous [$\pi 2_S + (\pi 2_S + \pi 2_S)$] mechanism as has been commonly proposed for these apparent symmetry forbidden cycloadditions. In most cases, a single stereoisomer was obtained in the thermal or 5 M lithium perchlorate in diethylether (5M LPDE) promoted cycloadditions and is consistent with non-Felkin or the Cram chelate model, respectively, leading to the same sense of stereocontrol. This methodology was applied to a total synthesis of (+)-angelica lactone.[45]

Table 10. Optically Active β-Lactones Prepared by Thermal or 5M LPDE-Promoted [2+2] Cycloadditions



R = H, Me, Cl

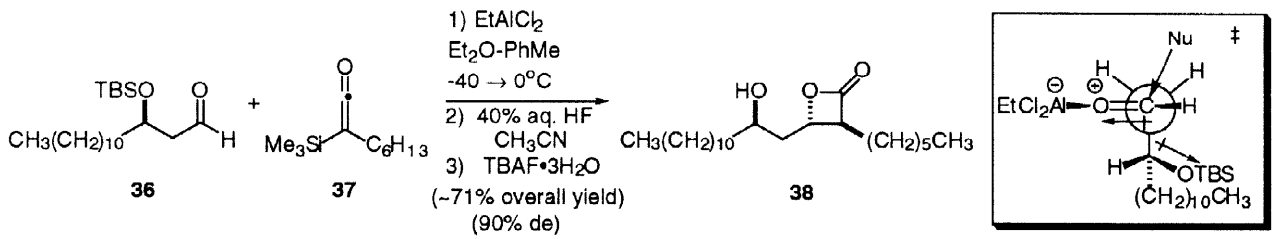
entry	β-lactone[a]	% yield	Config. C(4)
1		55[b]	*S*
2		58	*S*
3		70	*R*

[a]The stereoisomers shown were reported to be the only ones detectable by 300MHz ^{1}H NMR analysis of the crude reaction mixtures. [b]Yield includes a subsequent dyotropic rearrangment with $MgBr_2$ to the corresponding γ-lactone.

Kocienski and Pons reported the first diastereoselective [2+2] cycloaddition of ketenes and aldehydes and this reaction has been employed in the total synthesis of several β-lactone containing natural and unnatural

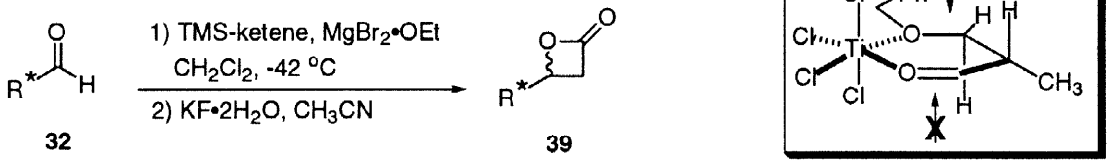
products including (-)-tetrahydrolipstatin,[46a] (-)-lipstatin,[46b] and panclicins A-E.[46c] In the case of (-)-tetrahydrolipstatin, these workers employed $EtAlCl_2$ for the cycloaddition of *n*-hexyl trimethylsilylketene (**37**) and 3-(*R*)-(*t*-butyldimethylsiloxy)tetradecanal (**36**) (Scheme 13). The desired β-lactone **38** was obtained after desilylation and separation from the other three diastereomers produced. The stereochemical outcome is consistent with a chelation-controlled addition but this mechanism is not likely with the "monocoordinate" Lewis acid $EtAlCl_2$.[47] Kocienski and Pons ascribed the stereochemical outcome of this cycloaddition to an electrostatic interaction model[46a,c] but it should be noted that this outcome is also consistent with recent models for 1,3-asymmetric induction proposed by Evans and coworkers for monocoordinate Lewis acids which minimize non-bonded interactions and benefit from cancellation of dipoles (Scheme 13).[48]

Scheme 13



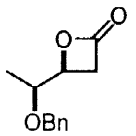
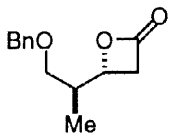
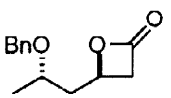
Romo and Zemribo reported the asymmetric synthesis of β-lactones via a chelation-controlled [2+2] cycloaddition strategy employing trimethylsilylketene (TMS-ketene) and optically pure aldehydes (Scheme 14).[49] This methodology, in conjunction with a tandem transacylation-debenzylation of β-lactones, was applied to a synthesis of (-)-grandinolide.[50]

Scheme 14



β-Lactones **39** were obtained after desilylation of the intermediate α-silyl β-lactones. Among the Lewis acids studied, $MgBr_2•OEt_2$ provided the best diastereoselectivities and yields (Table 11). The diastereoselectivity was explained by invoking the chelation-control model (Scheme 14) which Keck proposed for titanium and magnesium Lewis acids based on NMR studies.[51] Subsequently, Mead and coworkers improved the diastereoselectivities for both α- and β-chelation control in this cycloaddition (>98% de) by performing the reaction at -60°C.[52]

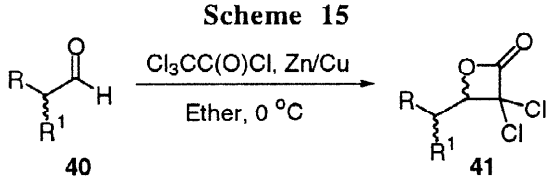
Table 11. Optically Active β-Lactones Prepared by Chelation-controlled [2+2] Cycloaddition of TMS-Ketene and Chiral Aldehydes

entry	β-lactone	% de	% yield[a]	config.(C4)
1		86[b]	86	*S*
2		96(88)[c]	86	*R*
3		~70	84	*R*

[a]Yield is for the two steps of [2+2] cycloaddition followed by desilylation. [b]Optical purity was not rigorously determined. [c]Enantiomeric excess is given in parenthesis as determined by Mosher ester analysis of the alcohol derived from debenzylation.

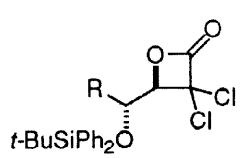
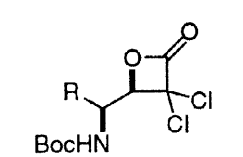
Palomo and co-workers reported diastereoselective [2+2] cycloadditions involving dichloroketene and α-oxy- and α-aminoaldehydes (Scheme 15).[53a] They generated dichloroketene in situ by treatment of trichloroacetyl chloride with Zn/Cu couple. In every case, only a single diastereomer was obtained (Table 12). Dechlorination was achieved by hydrogenolysis either directly on the crude cycloaddition products or after further manipulation of the α,α-dichloro-β-lactones. Subsequently, the Palomo group elegantly showed the utility of the derived α,α-dichloro-β-lactones as acylating agents for α-amino acid esters as a route to γ-amino β-hydroxy and β, β-dihydroxy acids.[53b]

Scheme 15



40 **41**

Table 12. β-Lactones Prepared by [2+2] Cycloaddition of Dichloroketene and Chiral Aldehydes

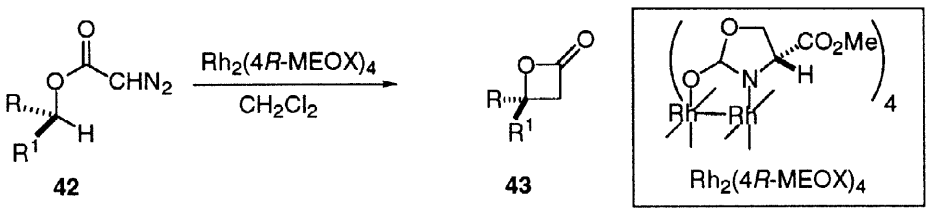
entry	β-lactone		% yield	config.(C4)
		R		
1		Me	85	*R*
2		*i*-Pr	65	*R*
3		*i*-Bu	55	*R*
4		Ph	NR[a]	*R*
		R		
5		$PhCH_2$	44	*R*
6		*i*-Pr	35[b]	*R*

[a]NR = not reported. [b]Overall yield for [2+2] cycloaddition followed by transacylation to a γ-lactam.

3.1.4. Carbon-Hydrogen Insertion of Diazoacetates

In the course of exploration of catalysts for intramolecular carbon-hydrogen insertion reactions of chiral diazoacetates **42**, Doyle and co-workers observed that β-lactones **43** were, in some cases, the major products obtained from several possible C-H insertion products (Scheme 16).[54]

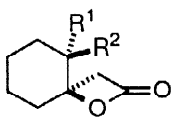
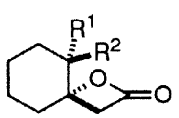
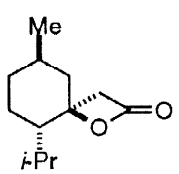
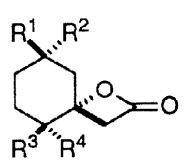
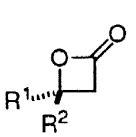
Scheme 16



42 **43**

However, the synthesis of β-lactones by this method is not yet synthetically useful because of very low yields due to formation of other C-H insertion products. In general, higher yields were obtained for acyclic diazoacetates than for cyclic diazoacetates (*cf.* Table 13, entries 8 and 9 vs entries 1-7).

Table 13. Optically Pure β-Lactones Prepared by C-H Insertion of Chiral Diazoacetates

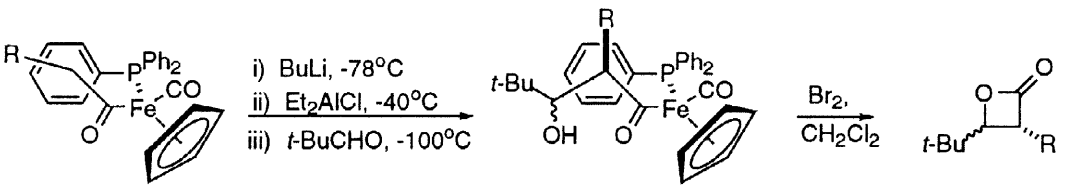
entry	β-lactone					% yield	% ee[a, b]	config.(C4)
		R^1	R^2					
1		H	Me			26	>99	*R*
2		Me	H			18	ND	*R*
		R^1	R^2					
3		Me	H			8	NR	*S*
4		H	Me			7	ND	*S*
5						18	ND	*S*
		R^1	R^2	R^3	R^4			
6		H	Me	*i*-Pr	H	11	ND	*R*
7		Me	H	H	*i*-Pr	25	ND	*R*
		R^1	R^2					
8		Me	*n*-Hexyl			49	NR	*R*
9		*n*-Hexyl	Me			45	NR	*S*

[a]ND = not determined due to instability of β-lactone product. [b]NR = not reported.

3.2. Chiral Auxiliary Strategies

In connection with earlier work involving highly stereoselective addition of enolates derived from a chiral iron acyl complex to aldehydes,[55] Davies and co-workers reported a novel transformation of β-hydroxy acyl iron complexes to optically pure β-lactones via oxidative decomplexation (Scheme 17).[56]

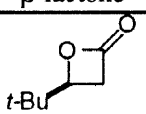
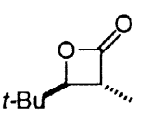
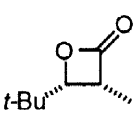
Scheme 17



44 **45** **46**

Addition of the diethylaluminum enolate derived from the enantiomerically pure iron acetyl complex **44** to pivalaldehyde stereoselectively provided β-hydroxy acyl complexes **45** as single diastereomers (>100:1 by ^{1}H NMR). The aldol product was then converted to enantiomerically pure β-lactones **46** by oxidative decomplexation with bromine (Table 14). Interestingly, *trans*- or *cis*-3,4-disubstituted β-lactones **46** (R = Me) could be obtained in a highly stereoselective manner by simply changing from an aluminum to a copper enolate (entries 2 and 3, Table 14). This methodology was successfully applied to the synthesis of (-)-tetrahydrolipstatin.[56b]

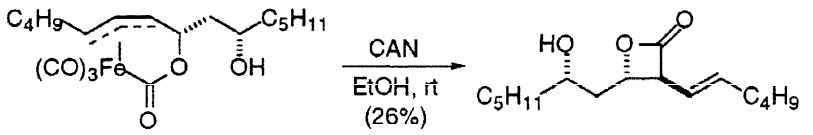
Table 14. Optically Pure β-Lactones Prepared via Chiral Acyl Iron Complexes

entry	β-lactone	% yield[a]	% ee[b]	Config. (C3, C4)
1		58	>98	4*S*
2		59	>98	3*R*, 4*S*
3		44	>98	3*R*, 4*R*

[a]Yield is for the two steps of aldol reaction and oxidative decomplexation. [b]% ee is assumed to be >99% ee based on diastereomeric purity of the precursor.

During their total synthesis of (-)-valilactone, Ley and coworkers reported the formation of the β-lactone intermediate **48** via oxidation of chiral π-allytricarbonyliron lactone complex **47**. The utility of these complexes was previously demonstrated for the preparation of racemic β- or δ-lactones from vinyloxiranes by the Ley group (Scheme 18).[57]

Scheme 18



47 48

4. Enantioselective Routes

In contrast to the synthesis of other versatile functional groups, direct enantioselective routes to β-lactones have not been well developed. To date, only a few approaches have been reported including chiral Lewis acid promoted [2+2] cycloadditions, chiral nucleophile catalyzed net [2+2] cycloadditions, and asymmetric hydrogenation of β-ketoesters.

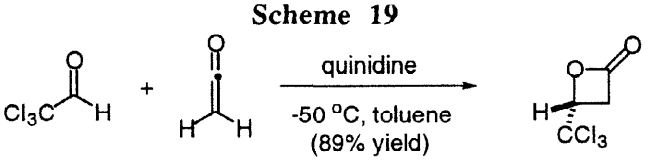
4.1. [2+2] Cycloadditions of Ketenes and Carbonyl Compounds

The [2+2] cycloadditions of ketene or silylketenes with carbonyl compounds reported to date can be divided into two categories according to the types of catalysts employed: (1) Nucleophile-promoted net [2+2] cycloadditions and (2) Lewis acid catalyzed [2+2] cycloadditions.

4.1.1. Nucleophilic Catalysis by Alkaloid Bases

One of the earliest and most remarkable advances in the field of asymmetric catalysis was achieved by Wynberg and Staring for the synthesis of optically active β-lactones. They reported the formation of β-lactone **51** in excellent yield and optical purity by the net [2+2] cycloaddition of ketene **50** with chloral **49** promoted by 1-2 mol% of quinidine via nucleophilic catalysis (Scheme 19).[58] This transformation is thought to involve an ammonium enolate intermediate and proceed by way of an aldol-lactonization process.[58d] This methodology was employed to access optically pure natural and unnatural malic acid.

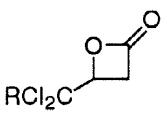
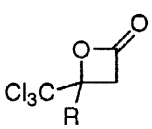
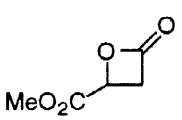
Scheme 19



49 50 (*R*)-(-)-51

Later, Wynberg investigated other carbonyl compounds in this reaction using quinidine and quinine as the chiral catalysts.[58b] Moderate to excellent enantioselectivities (45-98% ee) and poor to excellent yields (1-95%) were observed for various carbonyl compounds (Table 15). Wynberg and coworkers determined that only activated aldehydes or ketones participate in this aldol-lactonization severely limiting the scope of this methodology. However, this methodology has been used extensively. The preparation of 4-carbomethoxy-2-oxetanones was achieved in 36-72% by [2+2] cycloaddition of methyl glyoxylate with ketene using quinine and quinidine (entry 14, Table 15).[59] Recently, Song and co-workers reported the use of polymer bound cinchona alkaloids as catalysts for the preparation of the (*S*) and (*R*)-β-lactones **51**.[60] These trichloro β-lactones have been utilized as intermediates in the synthesis of optically active carnitines (entry 2 and 3, Table 15).[61]

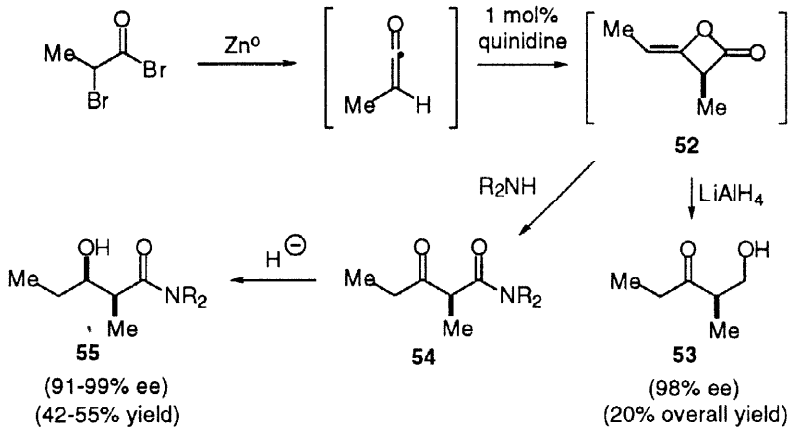
Table 15. Optically Active β-Lactones Prepared by Net [2+2] Cycloadditions Promoted by Alkaloid Bases

entry	β-lactone		% ee[a]	% yield[a]	config. (C4)	method[a,b]	ref.
		R					
1		Cl	98(76)	89(NR[c])	*R*(*S*)	A(B)	58a
2		Cl	59(25)	73(71)	*R*(*S*)	C(D)	60
3		Cl	27(22)	66(60)	*R*(*S*)	E(F)	60
4		H	45	67	*R*	A	58b
5		Me	91(76)	95	R(*S*)	A(B)	58b
6		Et	89(70)	87(NR[c])	*R* (*S*)	A(B)	58b
7		*n*-Pr	92	100	*R*	A	58c
8		*n*-Hex	92	100	*R*	A	58c
9		Ph	90(68)	89(NR[c])	*R*(*S*)	A(B)	58b
		R					
10		Me	94(85)	72	*R*(*S*)	A(B)	58b
11		Et	NR[c]	1-2	NR	A(B)	58b
12		*p*-ClPh	90(65)	68	*R*(*S*)	A(B)	58b
13		*p*-NO_2Ph	89(65)	95	*R*(*S*)	A(B)	58b
14			72(36)	32(35)	*R*(*S*)	A(B)	59

[a]Values of % ee and yield in addition to absolute configuration and method employed for the enantiomeric β-lactone are given in parentheses. [b]Method is classified by type of alkaloid base used: method A: quinidine, method B: quinine; method C: poly(quinidine-*co*-acrylonitrile); method D: poly(quinine-*co*-acrylonitrile); method E: poly(cinchonine-*co*-acrylonitrile); method F: poly(cinchonidine-*co*-acrylonitrile). [c]NR = not reported.

Calter reported an interesting catalytic, asymmetric dimerization of methylketene catalyzed by cinchona alkaloids (Scheme 20).[62a] The optically active β-methylene-β-lactone **52** was not isolated but directly reduced to the alcohol **53** due to its volatility and instability. Either enantiomer of **55** was prepared by judicious choice of the chiral amine nucleophile with high enantioselectivity. More recently, the Calter group has expanded the utility of the β-lactone **52** by trapping it with various amines and performing substrate-controlled reductions of β-ketoamide **53** leading to all four possible isomers of the dipropionate synthon **55**.[62b]

Scheme 20

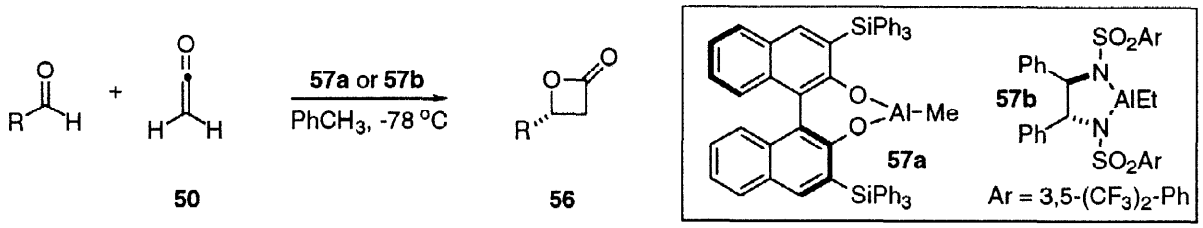


4.1.2. Catalysis by Lewis Acids

In 1994, Miyano and co-workers reported the first asymmetric [2+2] cycloaddition of ketene with aldehydes mediated by stoichiometric amounts of chiral aluminum-binaphthol complexes.[63a] They obtained poor to moderate enantioselectivities (17-56% ee) and low to excellent yields (33-91% GC yields). Subsequently, this group also reported the first catalytic, asymmetric [2+2] cycloaddition promoted by 10 mol% of aluminum-bissulfonamide complexes.[63b] A variety of β-lactones were obtained in good yields but with varying degrees of enantioselectivity (14-74% ee) (Table 16).

The [2+2] cycloaddition of silylketenes with aldehydes catalyzed by Lewis acids has also been studied as a route to optically active β-lactones. The intrinsic stability of silylketenes makes them more easily handled relative to the parent ketene.[64] Studies by the Kocienski and Pons groups involved the use of 30 mol% of Al-bissulfonamide-based catalysts previously used by Miyano for [2+2] cycloadditions with ketene.[65] Low to good enantioselectivity was achieved (36-83% ee) for the *cis* silylated β-lactones **58** and moderate to excellent diastereoselectivities (*cis*/*trans* = 69:31 to 99:1) (Table 17). This methodology has been recently applied to an asymmetric synthesis of the HMG-CoA synthase inhibitor, 1233A.[66]

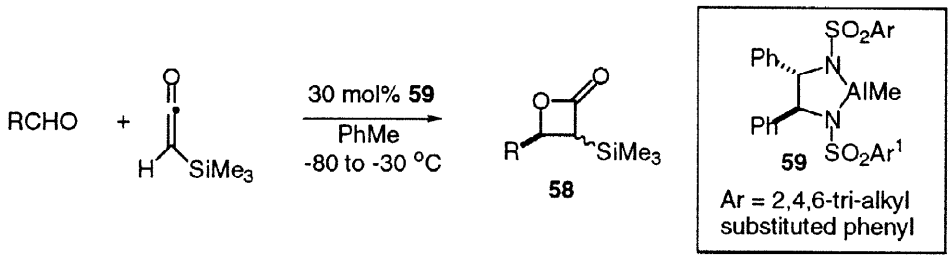
Table 16. Optically Active β-Lactones **56** Prepared by Stoichiometric and Sub-stoichiometric Amounts of Chiral Binaphthol **57a** or Bis-sulfonamide **57b**



entry	R	% ee	% yield[a]	config.(C4)	method[b]	ref.
1	Me	23	78	*S*	A	63a
2	Me	30	59	*S*	B	63b
3	Et	56	67	*S*	A	63a
4	Et	33	77	*S*	B	63b
5	*n*-Pr	45	69	*S*	A	63a
6	*n*-Bu	17	80	*S*	A	63a
7	*n*-Bu	41	82	*S*	B	63b
8	*i*-Pr	28	59	*R*	A	63a
9	*i*-Pr	56	76	*R*	B	63b
10	*t*-Bu	65	77	*R*	B	63b
11	Ph	21	76	*S*	A	63a
12	Ph	14	11	*R*	B	63b
13	Cyclohexyl	74	75	*R*	B	63b

[a]GC yields. [b]Method A: stoichiometric amount of Al-binaphthol-based Lewis acid **57a** was used. Method B: 20 mol% of Al-bissulfonamide based Lewis acid **57b** was used.

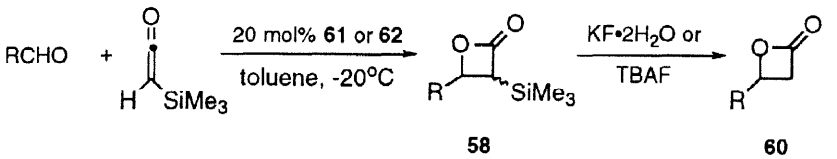
Table 17. Optically Active α-Trimethylsilyl β-Lactones **58** Prepared by [2+2] Cycloaddition of TMS-ketene with Various Aldehydes Employing the Al-bissulfonamide-based Lewis Acid **59**



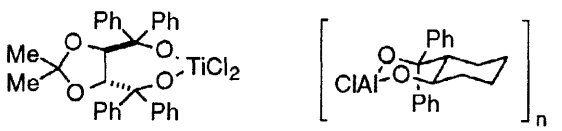
entry	R	*cis/trans* (**58**)	% ee (*cis*-**58**)	% yield	config. (C3,C4)
1	$PhCH_2$	75:25	82	72	3*S*,4*R*
2	*p*-MeOPhCH_2	99:1	83	77	3*S*,4*R*
3	*c*-C_6H_{11}	69:31	67	43	3*S*,4*R*
4	$PhCH_2CH_2$	94:6	36	82	3*S*,4*R*
5	$C_{11}H_{23}$	94:6	47	67	3*S*,4*R*

Romo and coworkers have also studied the [2+2] cycloaddition of trimethylsilyl ketene and various aldehydes. They found that titanium[67a] and aluminum [67b] based chiral Lewis acids gave the best reactivity and selectivity of the Lewis acids studied. The cycloaddition led to exclusive formation of the *cis* silylated β-lactones **58** in most cases as has previously been observed when bulky achiral Lewis acids were employed in this cycloaddition.[68] Low to good enantioselectivity (9-85% ee) and moderate to good yields (45-78%, two steps) were obtained after desilylation (Table 18). The highest enantioselectivity observed to date for α-unsubstituted, aliphatic aldehydes (Table 18, entry 2) was obtained using the novel Lewis acid **62**. The structure of this Lewis acid was not rigorously determined and the representation shown by structure **62** is only meant to show the presumed Lewis acid stoichiometry. However, preliminary work by these authors based on ^{27}Al NMR indicates that this catalyst may exist as two species, one of which is a dimer.[67b] Some of the optically active β-lactones described in this report were used to probe the active site of HMG-CoA synthase.[67b]

Table 18. Optically Active β-Lactones Prepared by [2+2] Cycloaddition of TMS-ketene with Aldehydes Employing Ti-TADDOL and Al-Diol Chiral Lewis Acids **61** and **62**



58 60



61 62

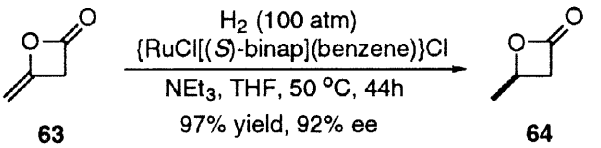
entry	R	*cis/trans* (**58**)	% ee (**60**)[a]	% yield (**60**)[b]	config.(C4)[c]	method[d]	ref.
1	*n*-Bu	34:1	41	49	ND	A	67a
2	*n*-Bu	>99:1	85[e]	86	*R*	B	67b
3	Ph	>99:1	28[e]	82	ND	B	67b
	p-NO_2Ph	>19:1	21	71	ND	A	67a
4	$PhCH_2$	9:1	9	58	*R*	A	67a
5	$PhCH_2$	>19:1	75	45	*R*	B	67b
6	$PhCH_2CH_2$	>19:1	41[f]	78	*S*	A	67a
7	$PhCH_2CH_2$	>19:1	36	60	*S*	B	67b
8	*c*-C_6H_{11}	>19:1	80	66	*S*	A	67a
9	*c*-C_6H_{11}	>99:1	84[e]	83	*S*	B	67b
10	$BnO(CH_2)_4$	19:1	45[f]	76	ND	A	67a
11	$TBSO(CH_2)_5$	>19:1	46	55	ND	B	67b
12	CH_2=$CH(CH_2)_7$	>19:1	22	71	ND	B	67b
13	$(CH_3CH_2)_2CH$	>19:1	56	46	ND	B	67b

[a]% ee was measured after desilylation of α-trimethylsilyl-β-lactones **58** to give β-lactones **60**. [b]Yield is for 2 steps. [c]ND = not determined. [d]Ti-TADDOL-based Lewis acid **61** was employed in method A. Al-based Lewis acid **62** was employed in method B. [e]% ee is for β-lactone **58**. [f]% ee was measured for the β-lactone **60** derived from desilylation of pure *cis*-silylated-β-lactones **58**.

4.2. Asymmetric Hydrogenation

Both enantiomers of 4-methyloxetan-2-one (**64**) have been synthesized in up to 92% ee by the asymmetric hydrogenation of diketene **63** employing a catalytic amount (0.1-0.2 mol%) of binap-Ru(II) complexes in the presence of triethylamine (Scheme 21).[69] β-Lactone **64** has been utilized as a starting material for an important biodegradable polymer, poly[(*R*)-3-hydroxybutyrate], via ring opening polymerization.[70]

Scheme 21



63 64

Several catalyst complexes were observed by ^{31}P NMR analysis and thus the exact structure of the active catalyst has not been established. Triethylamine was found to be a critical additive (0.5 to 0.9 equiv. relative to Ru(II)) in this reaction to prevent polymerization of diketene and to control competitive hydrogenolysis leading to butyric acid.[70]

The procedure of Roelens[23] described above (Section 2.2; see Scheme 7 and Table 4) which employs an asymmetric Noyori hydrogenation of β-ketoesters as the stereochemical setting step also falls into the category of enantioselective routes. This is one of the most general routes reported to date and is thus mentioned here again.

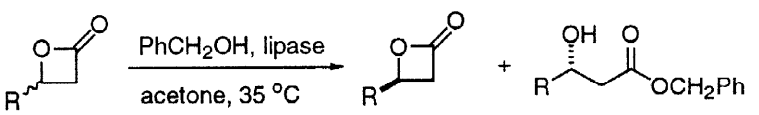
5. Miscellaneous

Other approaches for the synthesis of optically active β-lactones which do not fall into the categories described above are described below. These can be classified into kinetic resolution, topological resolution, and asymmetric desymmetrization.

5.1. Kinetic Resolution

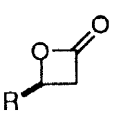
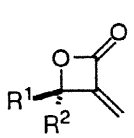
In 1995, Yamamoto and coworkers reported the preparation of optically active 4-alkyloxetan-2-ones by lipase-promoted transesterification.[71a] Racemic β-lactone **65** in the presence of benzyl alcohol and porcine pancreas lipase provided optically active β-lactones **66** and benzyl-3-hydroxy butyrates **67** (Scheme 22, Table 19). This methodology was also applied to the resolution of α-methylene β-lactones (Table 19, entries 4 and 5)[71b] and more recently to the synthesis of chlorodifluoromethyl substituted β-lactones.[71c]

Scheme 22



(+/-)-**65** (*R*)-(+)-**66** (*S*)-(+)-**67**

Table 19. Optically Active β-Lactones Prepared by Kinetic Resolution with Porcine Pancreas Lipase

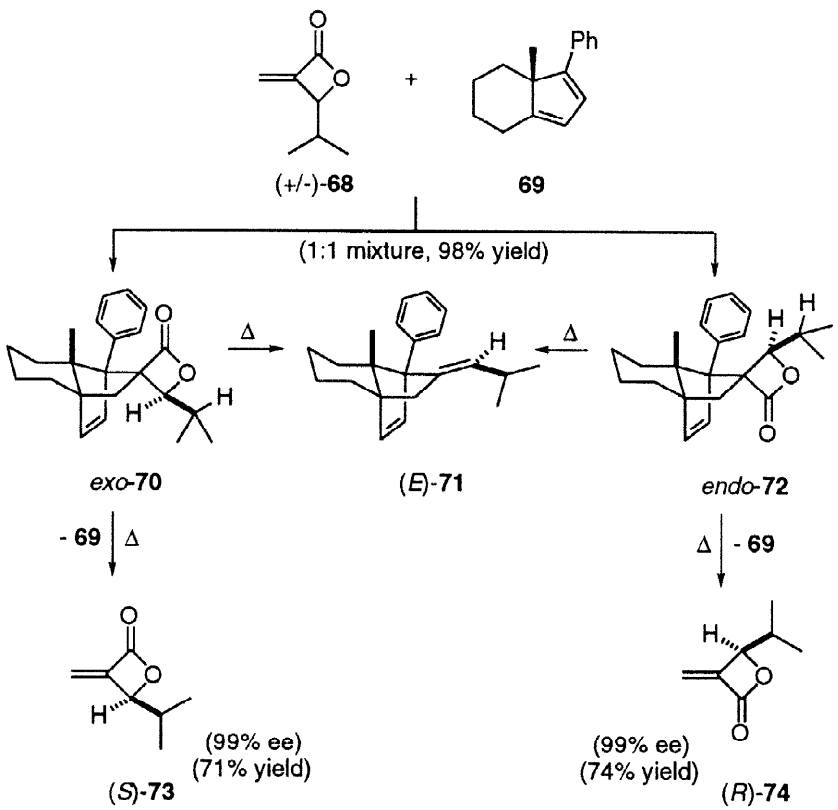
entry	β-lactone			% ee	% yield	config. (C4)	ref.
			R				
1			Me	96	36	*R*	71a
2			*n*-Pr	75	42	*R*	71a
3			*i*-Pr	95	41	*S*	71a
		R^1	R^2				
4		Me	H	99	NR	*R*	71b
5		H	*i*-Pr	>99	NR	*S*	71b

[a] NR = Not reported.

5.2. Topological Resolution

A chiral discrimination reaction that differentiates enantiotopic faces during product formation has been applied to the resolution of racemic β-lactones. Winterfeldt, Adam, and coworkers succeeded in obtaining optically pure β-lactones via a Diels-Alder / retro-Diels-Alder sequence using chiral cyclopentadiene **69** (Scheme 23).[72] The *exo* and *endo* Diels-Alder products **70** and **72** were separated by column chromatography and then submitted to flash vacuum pyrolysis to afford enantiomeric β-lactones **73** and **74**. The diene **69** could also be recovered along with approximately 5% of the olefin **71** derived from carbon dioxide elimination from the β-lactones.

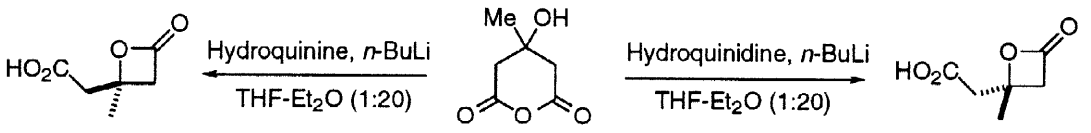
Scheme 23



5.3. Asymmetric Desymmetrization

In the course of the preparation of chiral HMGA (3-hydroxy-3-methylglutaric acid) esters and amides, (*R*)- and (*S*)-β-carboxymethyl-β-methyl-β-lactones were utilized as efficient acylating agents. They were prepared from racemic HMGA anhydride **75** via asymmetric desymmetrization with hydroquinine or hydroquinidine (Scheme 24).[73] This process involves an enantioselective transacylation proceeding by way of a presumed acylammonium intermediate.

Scheme 24



76 (>90% ee) (70% yield)

75

77 (>90% ee) (70% yield)

6. Summary and Outlook

While several routes for the asymmetric synthesis of β-lactones have been developed, many of them lack generality and practicality. The majority of procedures that have been developed involve chiral synthons or diastereoselective reactions which by the nature of these strategies lack generality. However, the chiral synthon methods developed by Vederas[8,9] involving the conversion of various amino acids to β-lactones has great synthetic potential and has been applied widely.[10] In this regard, lactonizations of chiral β-hydroxy acids have often been used to form β-lactones employing Adam's procedure,[21] various coupling agents (e.g. BOPCl) or the Mitsunobu procedure. This method is limited by the availability of the requisite chiral β-hydroxy acid and the appropriate degree of α- and β-substitution (gem-dialkyl effect) to ensure efficient lactonization. In the area of diastereoselective reactions, the most general procedures are those which do not require a high degree of substitution for efficient lactonization (i.e. apparent absence of a gem-dialkyl effect) and these include [2+2] cycloadditions of ketenes and aldehydes[46,49,50,53] and tandem Mukaiyama aldol-lactonizations with thiopyridylketene acetals and aldehydes.[41,42] Thus, if one is interested in introducing a β-lactone into a given substrate using substrate control, a directing group, typically an adjacent alkoxy group, can be used to obtain good stereochemical induction based on the Felkin, Evans, or Cram-chelate models employing these methods.

Further behind in development are general and practical, catalytic, asymmetric routes to β-lactones. This deficiency along with the the utility of β-lactones as versatile inetermediates, the discovery of new transformations of β-lactones, the isolation of novel β-lactone-containing natural products, and the need for biodegradable polymers with specific characteristics and functional arrays will undoubtedly continue to spur research in this area. The most promising methods studied to date which will likely see further development in the future include Lewis acid catalyzed [2+2] cycloadditions,[63-67] nucleophile catalyzed-net [2+2] cycloadditions building on the work of Wynberg,[58-62] and Lewis acid promoted tandem Mukaiyama aldol-lactonizations. The [2+2] cycloaddition route developed by Wynberg provides a high yielding and highly enantioselective route to various β-lactones but suffers from the requirement of electron poor aldehydes and is thus quite limited in scope. A more general approach, which suffers from a lengthy procedure and the use of mercury salts for the lactonization step, is the method developed by Roelens and coworkers employing a Noyori hydrogenation of a β-ketoester as the key stereochemical setting step. Therefore, at the present writing, these methods represent the best enantioselective routes to β-lactones.

Thus, great opportunities exist for the development of concise and general catalytic, asymmetric routes to β-lactones. Having achieved this goal, it should be expected that in the future, β-lactones may become as often

employed in natural and unnatural product synthesis as aldol products or epoxides. In this way, these strained heterocycles may take a more prominent role as versatile chiral synthons in organic synthesis.

We are grateful to the NSF (Planning Grant and CAREER Award to D. R.), the Alfred P. Sloan Foundation, and Zeneca Pharmaceuticals for generous financial support. The authors wish to extend thanks to the reviewers for their careful review of the manuscript and their insightful comments.

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Biographical sketch

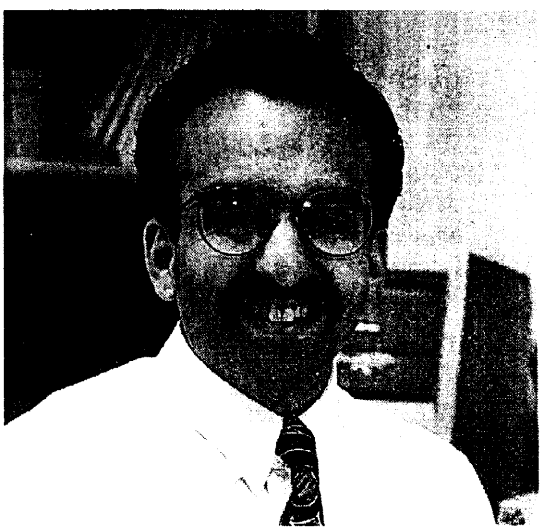
Hong Woon Yang

Daniel Romo

Hong Woon Yang was born in Seoul, Korea. He received his B.S. degree in Chemistry in 1987 from Seoul National University and his M.S. degree in Chemistry in 1991 from Pohang University of Science and Technology under the direction of Professor Sung Kee Chung. In August, 1998, he received his Ph.D. degree in Chemistry under Professor Daniel Romo at Texas A&M University. His doctorate research focused on the development of concise, stereoselective routes to β-lactones and their application to natural product synthesis. He will begin his postdoctoral studies with Professor Gary H. Posner at Johns Hopkins University in March of 1999.

Biographical sketch

Hong Woon Yang



Daniel Romo

Hong Woon Yang was born in Seoul, Korea. He received his B.S. degree in Chemistry in 1987 from Seoul National University and his M.S. degree in Chemistry in 1991 from Pohang University of Science and Technology under the direction of Professor Sung Kee Chung. In August, 1998, he received his Ph.D. degree in Chemistry under Professor Daniel Romo at Texas A&M University. His doctorate research focused on the development of concise, stereoselective routes to β-lactones and their application to natural product synthesis. He will begin his postdoctoral studies with Professor Gary H. Posner at Johns Hopkins University in March of 1999.

Daniel Romo was born in 1964 in San Antonio, Texas and obtained his B.A. in chemistry/biology from Texas A&M University in 1986. His graduate studies as a National Science Foundation Minority Graduate Fellow were carried out under the supervision of Professor Albert I. Meyers at Colorado State University. After completing his Ph. D. studies in 1991, he went to Harvard as an American Cancer Society Postdoctoral Fellow working in the laboratory of Professor Stuart L. Schreiber. In 1993, he returned to Texas A&M University where he is currently an assistant professor of chemistry. At the heart of his research interests is the total synthesis of natural products that have unique and complex structure and display significant and specific physiological activity. His target driven projects focus on structure elucidation, total synthesis, and mechanism of action studies of these natural products. His methodology driven projects focus on the development of stereoselective methods for the preparation of β-lactones (2-oxetanones), the discovery of new transformations of these heterocycles, and the subsequent application of these methods to natural product synthesis. His awards include a National Science Foundation CAREER award (1995), an Alfred P. Sloan Fellowship (1997), a Zeneca Award for Excellence in Chemistry (1998), and the College of Science Montague Scholar Award administered by the Center for Teaching Excellence at Texas A&M (1997-98).