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Studies of the Tandem Mukaiyama Aldol-Lactonization (TMAL) Reaction: A Concise and Highly Diastereoselective Route to β-Lactones Applied to the Total Synthesis of the Potent Pancreatic Lipase Inhibitor, (-)-Panclicin D

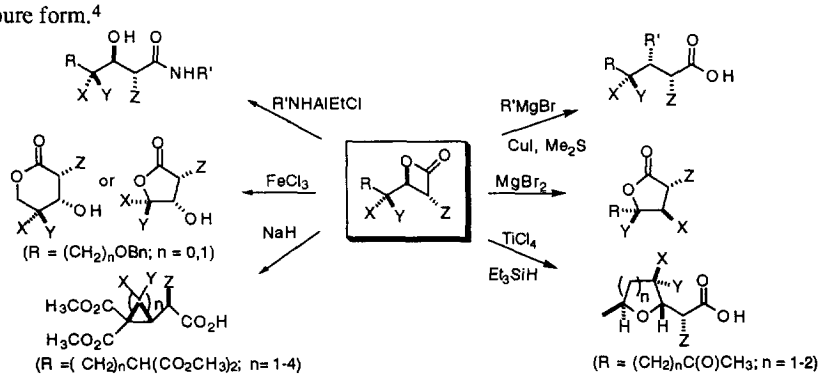
Hong Woon Yang, Cunxiang Zhao, and Daniel Romo*

Department of Chemistry, Texas A&M University, College Station, TX 77843-3255

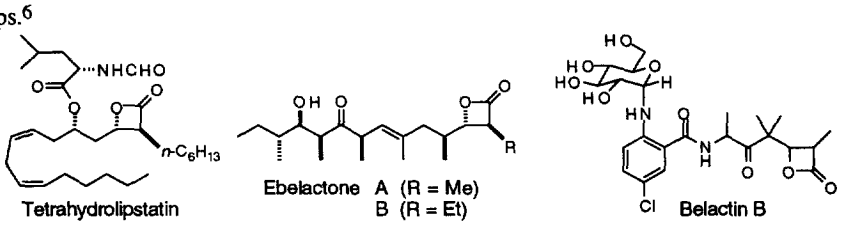
Abstract: A concise and highly diastereoselective route to β-lactones has been developed based on a tandem Mukaiyama aldol-lactonization employing thiopyridylsilylketene acetals and various aldehydes. (-) -Panclicin D, a potent pancreatic lipase inhibitor, was synthesized using this methodology. Recent optimization and extensions of this method are described which include variation of the silyl group and leaving group of the ketene acetal. © 1997 Elsevier Science Ltd.

Introduction

Despite the fact that β-lactones are versatile synthetic intermediates, as they undergo a variety of transformations in a stereospecific fashion,[1] their utilization in the context of natural product synthesis has been limited.[2] This is in stark contrast to epoxides which have become indispensable intermediates in synthesis.[3] The reason for this disparity is in part due to the lack of direct and general methods for the preparation of β-lactones in optically pure form.[4]



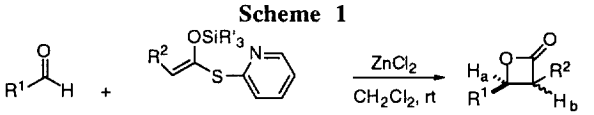
In addition, several structurally and biologically interesting natural products containing a β-lactone such as the tetrahydrolipstatins, the ebelactones and the belactins have been isolated.[5] However, while several of these naturally occurring β-lactones have been synthesized, assembly of the β-lactone moiety has typically required multiple steps.[6]



Furthermore, the utility of β-lactones as monomers for the synthesis of biodegradable polymers has also been studied extensively.[7] Recently, a copolymer of two β-lactone monomers, one incorporating the antibiotic chloroamphenicol, has been synthesized as a potential macromolecular prodrug for controlled drug release.[8]

Thus, inspired by the potential applications of optically pure β-lactones, we have initiated a program directed toward the development of concise enantio- and diastereoselective methods for their synthesis.[4e] In this regard, we recently described in preliminary form the development of a tandem Mukaiyama aldol-lactonization (TMAL hereafter)[9] reaction (Scheme 1) and its application to the first synthesis of the potent lipase inhibitor, (-)-panclicin D. This methodology builds on a single example of this reaction reported by Hirai[10] and compliments the tandem aldol-lactonizations recently reported by Danheiser[11] and Schick[12] employing enolates derived from various acid derivatives. Related reactions have also been employed for the single-pot synthesis of β-lactams by Hirai[10] and Cinquini and Cozzi.[13] Importantly, the TMAL reaction proceeds with high diastereoselectivity (>95% de) at ambient temperature. These reactions employ readily available thiopyridyl ketene acetals **2** and provide direct access to 3,4-disubstituted-β-lactones **3**. In this symposia-in-print, we report a full account of this work including recent improvements and extensions of this methodology.

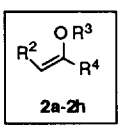
Scheme 1



1 **2** **3**

Discussion

For the purposes of optimization and extension of the TMAL reaction, we prepared a series of thiopyridyl ketene acetals **2a-2h**. The propionic acid derived ketene acetals **2b** and **2e** (R^2=Me) and α-benzyloxyketene acetal **2f** were prepared according to previously reported methods.[14] The triethylsilylketene acetal **2e** was obtained in 93% yield as an ~7:1 ratio of E/Z isomers (CIP rules). The acetic acid derived ketene acetals (R^2=H) were prepared from the corresponding thioesters upon treatment with the corresponding silyl triflate and Hunig's base.[15] Due to the instability of the triethylsilyl ketene acetals **2d** and **2e** to silica gel chromatography or distillation, these were typically used directly in the TMAL reaction without purification. These ketene acetals were contaminated with ~5-10% of triethylsilanol however this did not interfere with subsequent TMAL reactions.



2a-2h

2a: R^2 = H, R^3 = -Si(*t*-Bu)Me_2, R^4= 2-mercaptopyridine

2b: R^2 = Me, R^3 = -Si(*t*-Bu)Me_2, R^4 = 2-mercaptopyridine

2c: R^2 = H, R^3= -Si(*i*-Pr)$_3$, R^4 = 2-mercaptopyridine

2d: R^2 = H, R^3 = -$SiEt_3$, R^4 = 2-mercaptopyridine

2e: R^2 = Me, R^3 = -$SiEt_3$, R^4 = 2-mercaptopyridine

2f: R^2 = OBn, R^3 = -Si(*t*-Bu)Me_2, R^4 = 2-mercaptopyridine

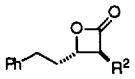
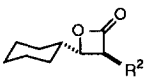
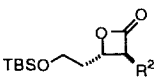
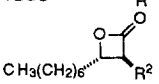
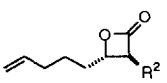
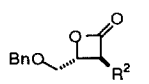
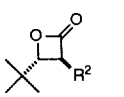
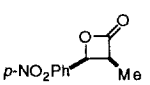
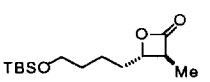
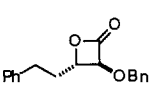
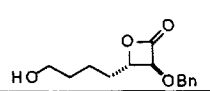
2g: R^2 = H, R^3 = -Si(*t*-Bu)Me_2, R^4 =

2h: R^2 = H, R^3 = -Si(*t*-Bu)Me_2, R^4 =

In our initial report, we employed the *t*-butyldimethylsilyl ketene acetals **2a** and **2b** and several β-lactones were prepared in fair to good yields (Table 1). The TMAL reaction is compatible with certain benzyl and silyl ethers (entries 5-6 and 11-12)[16] but α-substitution of the aldehyde leads to a dramatic reduction in conversion (entries 3 and 13). Use of benzaldehyde and cinnamaldehyde as substrates did not provide the corresponding β-lactone but instead gave predominantly aldol products in low yield.[17] Use of ketene acetal **2f**[14]

led to the benzyl-oxy β-lactones **3q-r** (entries 17-18). Treatment of the crude reaction mixtures with $CuBr_2$ or $KF{\bullet}2H_2O$ aided in separation of the β-lactone product from thioester and thioacetal (*vide infra*) by-products, respectively.

Table 1. Synthesis of Racemic β-Lactones **3** via TMAL Reaction of Aldehydes and *t*-Butyl dimethylsilyl Ketene Acetals **2** (Scheme 1)

entry	β-lactones	R^2	cmpd. no.	ketene acetal	rxn time (h)	trans/cis ratio[a]	yield(%)
1		Me	**3a**	**2b**	22	37:1	57
2		H	**3b**	**2a**	5	-	53
3		Me	**3c**	**2b**	45	>19:1	16
4		H	**3d**	**2a**	5	-	52
5		Me	**3e**	**2b**	24	>19:1	51
6		H	**3f**	**2a**	24	-	31
7		Me	**3g**	**2b**	23	>19:1	42[b]
8		H	**3h**	**2a**	2.5	-	35
9		Me	**3i**	**2b**	23	>19:1	35[c]
10		H	**3j**	**2a**	23	-	24[c]
11		Me	**3k**	**2b**	24	>19:1	74
12		H	**3l**	**2a**	18	-	70
13		Me	**3m**	**2b**	48	-	0
14		H	**3n**	**2a**	4.5	-	42[c]
15		-	**3o**	**2b**	25	<1:19	36
16		-	**3p**	**2b**	40	>19:1	47
17		-	**3q**	**2f**	48	>19:1	61
18		-	**3r**	**2f**	45	>19:1	22[d]

[a]Determined or estimated by analysis of the crude reaction mixtures by 200 or 300 MHz ^1H NMR. [b]A 2.5:1 mixture of trans/cis-β-lactones was previously obtained for this β-lactone by the method of Danheiser (ref. 11a). [c]These β-lactones were volatile and not readily separated from *t*-butyldimethylsilanol. [d]This is a three step yield including Swern oxidation of 5-*t*-butyldimethylsiloxypentanol, TMAL reaction, and desilylation.

The stereochemistry of the β-lactones **3** was readily assigned by inspection of the coupling constants of the C3, C4 protons of the β-lactone ring ($J_{Ha, Hb}$ ~6 Hz for cis, 4-4.5 Hz for trans, Scheme 1).[18] In the case of β-lactone **3o**, further verification of the anomalous stereochemistry was obtained by single crystal X-ray analysis which verified that the cis stereochemistry was indeed obtained with *p*-nitrobenzaldehyde (Figure).[19]

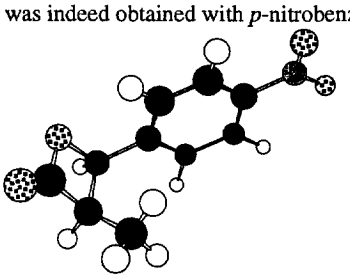
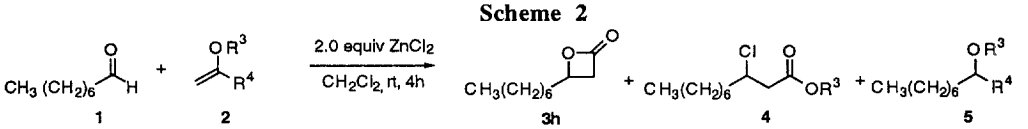


Figure. Chem3D representation of single crystal x-ray structure of β-lactone *cis*-**3o**.

In efforts to optimize the TMAL reaction, the reactions employing octanal and hydrocinnamaldehyde with the silylketene acetal **2a** were chosen as model reactions and studied in some detail under a set of standard conditions. It was found that in the reaction of octanal with ketene acetal **2a**, in addition to recovered aldehyde and the desired β-lactone **3h**, two other products were isolated from the crude reaction mixtures prior to treatment with $CuBr_2$ or KF. Interestingly, these were determined to be the β-chloroester **4** (R^3 = TBS) and the silylated hemithioacetal **5** (R^3 = *t*-$BuMe_2Si$, R^4 = SPy). The characterization of the former was more readily done on the more robust, corresponding triisopropylsilylester **4** (R^3 = *i*-Pr_3Si). Similar products were also detected in reactions with hydrocinnamaldehyde. Thus, a systematic study of reaction parameters was undertaken to provide insight into the mechanism of this transformation and minimize the formation of these by-products.

Scheme 2



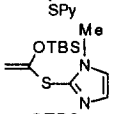
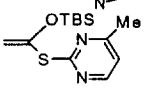
Several reaction parameters were studied. Use of the polar aprotic, donor solvent, acetonitrile, which was expected to stabilize potentially charged intermediates and solubilize $ZnCl_2$, gave only traces of β-lactone under the normal reaction conditions. The use of diethylether which also led to complete dissolution of $ZnCl_2$ led to lower yields of β-lactone within the same reaction time. Raising the reaction temperature to reflux in CH_2Cl_2 led to the chloroesters as the major products. Varying the injection order, in efforts to reduce the possibility of forming the silylthioacetal **5**, by adding the aldehyde as a CH_2Cl_2 solution by syringe pump over a period of 8 h to a CH_2Cl_2 solution of the ketene acetal and $ZnCl_2$, decreased the amount of silylthioacetal **5** formed but did not improve the yield of β-lactone **3h**. Increasing the equivalents of $ZnCl_2$ employed had no effect on the yield due to its low solubility in CH_2Cl_2.

The effect of changing the leaving group of the thiopyridyl ketene acetal was studied next in efforts to improve the efficiency of the lactonization step. We have determined that the nitrogen of the pyridine ring is important for efficient lactonization and high stereoselectivity since reactions employing phenylthioester ketene acetals led to low yields of a 1:1 mixture of cis/trans β-lactones. The 2-mercapto-3-methylpyrimidine (**2g**) and 2-mercapto-3-

methylimidazole (**2h**) ketene acetals were therefore examined since it was expected that these groups would lead to increased potential for chelation with divalent zinc. However, in both cases, the rate of the initial aldol reaction was reduced significantly and in the case of ketene acetal **2g**, no β-lactone was obtained after the standard reaction time of 4 hours (Table 2). The reduced nucleophilicity of ketene acetals **2g** and **2h** may be attributed to the strong electron withdrawing nature of the pyrimidine and imidazole rings.

The steric bulk of the protecting group was next varied to study its effect on the reaction outcome and this was found to have a profound effect on both yield and in some cases, reaction rate. The TMAL reactions were carried out using octanal and various silylketene acetals (Table 2, entries 1-3). As can be seen, yields of β-lactone dropped drastically and larger quantities of chloroester **4** were obtained when employing the triisopropyl silylketene acetal **2c**. In contrast, the use of the triethylsilylketene acetal **2d** led to a significant increase in the yield of β-lactone. The improved yields appear to be due to improved efficiency in the lactonization or subsequent step since the ratio of aldol products **4** detected in the crude reaction mixtures were reduced significantly.

Table 2. Effect of Varying the Silyl and Thiol Group of the Ketene Acetal on the TMAL Reaction Employing Octanal (Scheme 2)

entry	ketene acetal	cmpd. no.	ratio (**3h**:**4**: **5**)[a]	% yield (**3h**)[b]
1		**2c**	1 : 2 : trace	20%
2		**2a**	7 : 1 : 1.5	53%
3		**2d**	4 : trace : 1	66%
4		**2g**	-	0
5		**2h**	-	trace

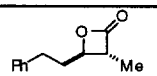
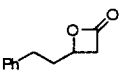
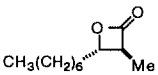
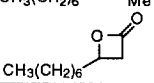
[a]Ratios determined by ^{1}H-NMR (200 MHz) of the crude reaction mixtures or by isolation. [b]In all these reactions, varying amounts (~10%) of unreacted aldehyde were detected in the crude reaction mixtures.

Thus, employing triethylsilyl ketene acetals **2d** and **2e** in the TMAL reaction led to yield increases of 13-30% (Table 3). In some cases shorter reaction times (entry 3 vs 4) with only slight diminution in selectivity (entry 1 vs 2) was possible in comparison to the same reactions employing the *t*-butyldimethylsilylketene acetals **2a-b**.

To demonstrate the utility of this methodology for natural product synthesis, we targeted a recently isolated β-lactone natural product, (-)-panclicin D,[20] which has twice the inhibitory activity towards pancreatic lipase compared to the recently approved anti obesity agent, tetrahydrolipstatin (Orlistat).[21] Several members of this family of lipase inhibitors have been synthesized[5] and an elegant approach involving a [2+2] cycloaddition to construct the β-lactones found in lipstatin and tetrahydrolipstatin was recently reported by Kocienski and Pons.[6] Our synthesis of (-)-panclicin D commenced with a Brown asymmetric allylation of *n*-octanal using *d*-*B*-allyldiisopinocampheylborane (^{d}Ipc$_2$BAll)[22] to give the (R)-homoallylic alcohol **6** in 55% yield and 92% ee(Scheme 3).[23] The (R)-enantiomer was utilized since it had been determined in the racemic series that the TMAL reaction provided the anti relative stereochemistry. Therefore, in order to obtain the required syn relative

stereochemistry found in (-)-panclicin D, the (R)- enantiomer was required followed by a Mitsunobu reaction to invert this stereochemistry. Protection of alcohol **7** followed by ozonolysis provided the aldehyde **9** in 88% yield (2 steps). Application of the tandem aldol-lactonization to this aldehyde and ketene thioacetal **10** proceeded

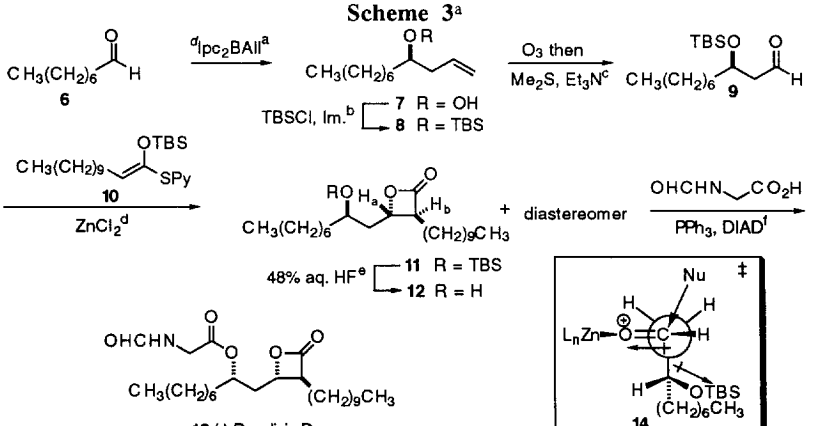
Table 3. Comparison of the Use of *t*-Butyldimethylsilyl and Triethylsilyl Ketene Acetals in the TMAL Reaction.

entry	β-lactones	cmpd. no.	ketene acetal	rxn time (h)	trans/ cis ratio[a]	% yield
1		**3a**	**2b**	22	37:1	57
2			**2e**	22	17:1	**70**
3		**3b**	**2a**	5	-	53
4			**2d**	4	-	**66**
5		**3g**	**2b**	23	>19:1	42
6			**2e**	23	39:1	**60**
7		**3h**	**2a**	2.5	-	35
8			**2d**	4	-	**65**

[a]Determined or estimated by analysis of the crude reaction mixtures by ^{1}H NMR or by GC analysis.

smoothly to give the β-lactones **11** as a 9.3:1 mixture of diastereomers (300 MHz ^{1}H NMR). These were directly desilylated to afford the more readily purified, diastereomeric hydroxy β-lactones **12** (53% overall), which were separable by flash chromatography. ^{1}H-NMR analysis confirmed that the major diastereomer **12** possessed a *trans*-substituted-β-lactone ($J_{Ha,\ Hb}$ = 4.2 Hz) as expected and the relative stereochemistry was subsequently determined to be anti by conversion to (-)-panclicin D. Mitsunobu reaction employing N-formyl glycine provided synthetic (-)-panclicin D **13** which displayed spectral and physical properties that matched those of the natural product ($[\alpha]^D_{20}$ = -23.0 (*c* 0.30, CHCl3); lit. $[\alpha]^D_{20}$ = -23 (*c* 0.30, CHCl3)).[20b] This synthesis constitutes one of the most concise and efficient routes to this class of lipase inhibitors (6 steps, 20% overall yield from *n*-octanal) and is readily adapted to prepare any member of this family.

Scheme 3[a]



[a](a) Et_2O,-100 → -48°C, (55%, 92% ee) (b) DMF, 23°C, (95%) (c) MeOH-CH_2Cl_2, -78°C then 23°C, (93%) (d) CH_2Cl_2, 23°C, 61h (9.3:1 dr) (e) CH_3CN, 0→ 23°C, (53%, 2 steps) (f) THF, 0→23°C, (88%)

A rationale for the high relative stereoinduction obtained in the TMAL reaction employed in the panclicin D synthesis is proposed. Although the product is formally a "chelation-controlled product", Keck has provided experimental evidence that indicates a *t*-butyldimethylsilyl ether is not capable of serving as a ligand for a bidentate Lewis acid such as $SnCl_4$ or $MgBr_2$.[24] A more probable rationale is based on a model for 1,3-asymmetric induction recently proposed by Evans and coworkers.[25] Their proposed model is based on both experimental and computational data and derives from consideration of both steric and electrostatic effects of the complexed aldehyde. Thus, transition state **14** based on Evans' model reasonably explains the predominance (9:1 dr) of the anti (relative stereoselection) stereoisomer **11** obtained in the TMAL reaction. This transition state minimizes steric interactions by adopting the preferred staggered aldehyde conformation and may also benefit from favorable electrostatic interactions between the polarized carbonyl carbon and the β-heteroatom substituent.[25]

Regarding the internal stereoselection, Choo and Suh have recently reported that Mukaiyama aldol reactions of thiopyridyl silylketene acetals with the bidentate Lewis acid $TiCl_4$ lead to exclusive formation of the *syn*-aldols independent of the geometry of the ketene acetal (stereoconvergent).[15] Choo proposed cyclic transition states to explain the high syn selectivity (internal) for these titanium mediated aldol reactions. These workers proposed the involvement of the pyridine nitrogen in addition to the silyl ether oxygen in chelation to titanium. However, in the present reaction employing $ZnCl_2$, which is also capable of bidentate chelation, the trans-β-lactone derived from the *anti*-aldol is the major product obtained for all aldehydes studied with the exception of *p*-nitrobenzaldehyde. We are using the data presented here in addition to ongoing mechanistic studies to define a possible reaction pathway for this interesting transformation and this will be reported in due course.

In conclusion, we have found that the $ZnCl_2$-mediated TMAL reaction provides the highest yields of β-lactones employing triethylsilylketene acetals in contrast to other more robust silyl groups. α-Heteroatom-substituted thiopyridylsilylketene acetals also participate in the TMAL reaction. The TMAL reaction proceeds efficiently with aliphatic aldehydes and *p*-nitrobenzaldehyde but provides mainly aldol products employing benzaldehyde or cinnamaldehyde. The simplicity and high diastereoselectivity of the TMAL reaction should make it the method of choice for preparing various *trans*-3,4-disubstituted-β-lactones. The ready availability of stereodefined β-lactones by this method should lead to increased opportunities for deployment of these versatile intermediates in synthesis. In addition to mechanistic studies of this reaction, we are continuing to apply the TMAL reaction to the synthesis of a variety of optically pure β-lactones and to utilize these versatile intermediates in natural product synthesis.

Experimental

General

All reactions were carried out under N_2 in oven-dried glassware unless noted otherwise. Methylene chloride was distilled from CaH_2 immediately prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone ketyl radical immediately prior to use. Other solvents used were also dried and distilled according to standard procedures prior to use. Flash column chromatography was done using Baxter S/P Silica Gel 60Å (23-400 Mesh ASTM). Thin layer chromatography was done using EM silica gel 60F glass plates (0.25 mm). 2-Mercaptopyridine, silyl triflates, and silyl chlorides were purchased from Aldrich Chemical Co. or Acros and used as received. Anhydrous $ZnCl_2$ (Aldrich) was fused under high vacuum prior to use. All aldehydes were distilled

(Kughelrohr distillation) or purified by flash chromatography (silica gel) immediately prior to use. The thiopyridyl esters were prepared from the corresponding acid chlorides and 2-mercaptopyridine by a previously reported method.[26] Propionic acid derived ketene acetals **2b**[14a] and **2f**[14b] were prepared according to known methods. Mass spectra were obtained on a VG Analytical 70S high resolution, double focusing, sectored (EB) mass spectrometer at the Center for Chemical Characterization and Analysis (Texas A&M). GC analyses were performed on a Hewlett-Packard 5880A gas chromatograph equipped with an FID detector and a 20 M 30%*t*-butyldimethylsilyl-β-cyclodextrin in OV1701 column kindly provided by Prof. Gyula Vigh (Texas A&M).[23] IR spectra were recorded on a Nicolet Impact 410DSP. ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer (300 MHz) or a Varian XL 200E spectrometer (200 MHz) and chemical shifts are reported in ppm using tetramethylsilane (δ 0.0) or residual $CHCl_3$ (δ 7.26) as internal reference. ^{13}C NMR spectra were recorded on a Varian VXR-300 (75 MHz) or Varian XL 200E (50 MHz) and chemical shifts are reported in ppm using $CDCl_3$ (δ 77.0) as internal reference.

General Procedure for the Synthesis of Acetic Acid Derived Ketene Acetals as Described for Thioketene Acetal 2a: *S*-2-Pyridyl ethanethioate (4.42 g, 28.85 mmol) was dried azeotropically with xylenes. After purging with N_2, 96 mL of CH_2Cl_2 and 7.04 mL of diisopropylethyl amine (40.4 mmol) was added and the mixture was cooled to 0 °C. After 10 minutes, 2.95 mL of TBSOTf (34.62 mmol) was added dropwise. After 3 h, an additional 0.4 mL of diisopropylethyl amine and 0.6 mL of TBSOTf were added. The resulting reaction mixture was stirred for 43.5 h at 0 ~ 5 °C and quenched with pH 7 buffer at that temperature. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered and then concentrated in vacuo to give a mixture of a crystalline solid and an oil. The mixture was redissolved into hexanes and filtered to remove the crystalline solid. The resulting oil was purified by distillation (110-113 °C/0.75 mm Hg) to afford 6.24 g (81%) of ketene acetal **2a.** Data not previously reported or different from that previously reported is given: ^{1}H NMR (200 MHz, $CDCl_3$) 8.44-8.48(m, 1H), 7.52-7.61(m, 1H), 7.37-7.42(m, 1H), 7.01-7.08(m, 1H), 4.91(d, J = 1.0 Hz, 1H), 4.80(d, J = 1.0 Hz, 1H), 0.82(s, 9H), 0.14(s, 6H).

Ketene Acetal 2c: This ketene acetal was prepared according to the general procedure using *S*-2-Pyridyl ethanethioate (473 mg, 3.1 mmol, 1.0 equiv), diisopropylethyl amine (806 µl, 1.5 equiv) and TIPSOTf (906 µl, 1.2 equiv) in 15 mL CH_2Cl_2. Workup followed by purification by flash chromatography (silica gel deactived with 2% triethylamine) gave 863 mg (90%) of ketene acetal **2c** as a colorless oil: R_f 0.53 (20% ethyl acetate/hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.40-8.44 (m, 1H); 7.49-7.58 (m, 1H), 7.38-7.43 (m, 1H), 6.97-7.04 (m, 1H), 4.88 (d, J=1.1 Hz, 1H), 4.81 (d, J=1.1 Hz, 1H), 0.97-1.34 (m, 21H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.6, 149.8, 149.5, 136.5, 123.4, 120.2, 102.8, 17.7, 12.4; IR (thin film) 2947, 1602 cm-1; FAB HRMS Calcd for $C_{16}H_{28}NOSSi$ [M+H]: 310.1661. Found 310.1688.

Ketene Acetal 2d: Prepared according to the general procedure using *S*-2-Pyridyl ethanethioate (5.59g, 36.5mmol, 1.0 equiv), diisopropylethylamine (9.53 mL, 1.5 equiv) and TESOTf (9.90 mL, 1.2 equiv) in 70 mL CH_2Cl_2. Workup followed by drying and concentration in vacuo gave 9.70 g of crude ketene acetal **2d** (98%) as a yellow oil. Due to its instability to silica gel chromatography and distillation, this ketene acetal which was typically ~85% pure was directly employed in TMAL reactions without further purification. Analysis by 300 MHz ^{1}H NMR showed the presence of triethylsilanol and some unreacted thioester but these impurities were found to have no effect on the subsequent TMAL reaction. A small amount was purified on a deactivated silica gel column (2%

Et_3N) for characterization purposes: R_f 0.54 (20% ethyl acetate/hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ 8.41-8.44 (m, 1H), 7.48-7.59 (m, 1H), 7.35-7.40 (m, 1H), 6.97-7.04 (m, 1H),4.87 (d, J =1.0 Hz, 1H), 4.79 (d, J =1.0 Hz, 1H), 0.75-1.00 (m, 9H), 0.50-0.75 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.3, 149.6, 149.2, 136.4, 123.2, 120.2, 103.1, 6.4, 4.6; IR (thin film) 3074, 1702, 1603 cm^{-1}; FAB HRMS Calcd for $C_{13}H_{22}NOSSi$ [M+H]: 268.1191. Found 268.1196.

Ketene Acetal 2e: This ketene acetal was prepared according to the method of Hirai[14a] using *S*-2-Pyridyl propanethioate (4.80 g, 28.7 mmol, 1.0 equiv), hexamethyldisilazane (7.30 mL, 33.9 mmol, 1.2 equiv), *n*-BuLi (14.0 mL of a 2.50 M soln in hexane, 35.0 mmol, 1.2 equiv), TESCl (8.59 g, 57.0 mmol, 2.0 equiv), triethylamine (8.0 mL, 57.4 mmol, 2.0 equiv), DMF (4.4 mL, 56.8 mmol, 2.0 equiv) in 72 mL THF. This gave 8.13 g (~100%, ~81% purity contaminated with triethylsilanol which did not interfere with subsequent reactions) of crude ketene acetal **2e** as a yellow oil. Due to its instability to silica gel chromatography and distillation this ketene acetal was directly employed in TMAL reactions without further purification. A small amount was purified on a deactivated silica gel column (2% Et_3N) for characterization purposes: R_f 0.52 (20% ethyl acetate/hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ 8.39-8.42 (m, 1H), 7.47-7.58 (m, 1H), 7.28-7.33 (m, 1H), 6.93-7.00 (m, 1H), 5.41 (q, J=3.4 Hz, 1H), 1.71 (d, J=3.4 Hz, 3H), 0.80-0.88 (m, 9H), 0.57-0.68 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 106.8, 149.5, 149.4, 136.4, 121.5, 119.6, 118.1, 12.2, 6.4, 5.0; IR (thin film) 2949, 1634 cm^{-1}; FAB HRMS Calcd for $C_{14}H_{24}NOSSi$ [M+H]: 282.1348. Found 282.1375.

Ketene Acetal 2g: Prepared according to the general procedure using *S*-2-(4-methyl)pyrimidyl ethanethioate (409 mg, 2.4 mmol, 1.0 equiv), diisopropylethylamine (0.64 mL, 1.5 equiv) and TESOTf (0.67 mL, 1.2 equiv) in 10 mL CH_2Cl_2. Workup followed by drying and concentration in vacuo gave 697 mg (102%, contaminated with triethysilanol) of crude ketene acetal **2g** as a yellow oil: R_f 0.33 (20% ethyl acetate/hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ 8.40 (d, 1H), 6.85 (d, 1H), 4.93 (s, 1H), 4.82 (s, 1H), 2.45 (s, 3H), 0.84 (s, 9H), 0.16 (s, 6H).

Ketene Acetal 2h: Prepared according to the general procedure using *S*-2-(1-methyl)imidazoyl ethanethioate (173 mg,1.1 mmol, 1.0 equiv), diisopropylethylamine (0.29 mL, 1.5 equiv) and TESOTf (0.30 mL, 1.2 equiv) in 6 mL CH_2Cl_2. Workup followed by drying and concentration in vacuo gave 335 mg of crude ketene acetal **2h** as a yellow oil which was contaminated with triethylsilanol but could be used directly in subsequent reactions: R_f 0.61 (50% ethyl acetate/hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ 6.93 (d, J =2.5 Hz, 1H), 6.65 (d, J =2.5 Hz, 1H), 5.45 (d, J =2.6 Hz, 1H), 4.49 (d, J =2.6 Hz, 1H), 3.60 (s, 3H), 0.94 (s, 9H), 0.23 (s, 6H).

General Procedure for TMAL Reaction: Anhydrous $ZnCl_2$ (1.2-2.0 equiv) was freshly fused at ~0.5 mm Hg and after cooling to ambient temperature, CH_2Cl_2 (appropriate volume to make the final concentration of aldehyde in CH_2Cl_2 ~0.15 M) was added. The aldehyde (1.0 equiv) was then added neat or as a CH_2Cl_2 solution at room temperature. After stirring for 15 minutes, the thiopyridylketene acetal (1.1-1.2 equiv) was added neat. The fused $ZnCl_2$ was broken up using the end of a syringe needle. The suspension was stirred vigorously for the time indicated in the Tables. As the reaction proceeds, the bright yellow heterogeneous mixture in most cases becomes homogeneous with concurrent formation of a bright yellow precipitate.

Work-up Procedure A: (For β-lactones with R_f similar to thioester by-product.) After addition of pH 7 buffer, the mixture was stirred vigorously for 10 min and filtered through Celite with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, filtered, taken up in CH_2Cl_2 (appropriate volume to make the final concentration ~0.15 M) and directly treated with $CuBr_2$ (1.3 equiv relative to ketene acetal). The resulting suspension was stirred for 1.5 h, filtered through Celite, and washed with 10% aq K_2CO_3 and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product which was purified by flash chromatography (silica gel).

Work-up Procedure B: (For β-lactones with R_f similar to thioacetal by-product.) The reaction mixture was diluted with diethyl ether and then filtered through Celite with more diethyl ether. The combined organics were washed with water and brine then dried over Na_2SO_4. After removal of the solvent in vacuo the residue was dissolved in acetonitrile and treated with $KF \cdot 2H_2O$ with vigorous stirring for 2h. The mixture was filtered through florisil with diethyl ether. Removal of the solvent in vacuo was followed by purification by flash chromatography (silica gel).

Using the general procedure described above, β-lactones **3a-3r** were prepared in the reaction times and diastereoselectivities indicated in the Tables.

***trans*-(+/-)-3-Methyl-4-(2-phenylethyl)oxetan-2-one (3a):** This β-lactone was prepared from hydrocinnamaldehyde (0.26 mL, ~90% purity, 2.0 mmol, 1.0 equiv) and ketene acetal **2e** (676 mg, 2.4 mmol, 1.2 equiv, corrected for ~87% purity) using 545 mg of $ZnCl_2$ (4.0 mmol, 2.0 equiv) in 15 mL of CH_2Cl_2. Workup (procedure B) followed by purification by flash chromatography (1:19 ethyl acetate/hexanes) gave 267 mg (70%) of β-lactone **3a** as a colorless oil: R_f 0.49 (1:4 ethyl acetate/hexanes); IR(thin film) 2935, 1818 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 7.17-7.36 (m, 5H), 4.15-4.19 (m, 1H), 3.20 (qd, J = 3.9, 7.5 Hz, 1H), 2.62-2.90 (m, 2H), 1.98-2.28 (m, 2H), 1.32 (d, J = 7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.7, 139.9, 128.5, 128.2, 126.2, 78.5, 50.7, 35.6, 31.1, 12.3; FAB HRMS Calcd for $C_{12}H_{14}O_2$ [M+H]: 191.1072. Found: 191.1061. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.91; H, 7.37.

(+/-)-4-(2-Phenyethyl)oxetan-2-one (3b): This β-lactone was prepared from hydrocinnamaldehyde (0.26 mL, 90% purity, 2.0 mmol, 1.0 equiv) and ketene acetal **2d** (642 mg, 2.4 mmol, 1.2 equiv, corrected for ~85% purity) using 545 mg of $ZnCl_2$ (4.0 mmol, 2.0 equiv) in 15 mL of CH_2Cl_2. Workup (procedure B) followed by purification by flash chromatography (1:19 ethyl acetate/hexanes) gave 227 mg (65%) of β-lactone **3b** as a colorless oil: R_f 0.35 (1:4 ethyl acetate/hexanes); IR (thin film) 2931, 1818 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.15-7.36 (m, 5H), 4.44-4.55 (m, 1H), 3.48 (dd, J= 5.7, 16.3 Hz, 1H), 3.03 (dd, J= 4.3, 16.3 Hz, 1H), 2.64-2.91 (m, 2H), 1.97-2.30 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.1, 139.9, 128.5, 128.3, 126.3, 70.3, 42.7, 36.2, 31.1; FAB HRMS Calcd for $C_{11}H_{12}O_2$ [M+Na]: 199.0735. Found: 199.0750. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.72; H, 6.90.

***trans*-(+/-)-4-Cyclohexyl-3-methyloxetan-2-one (3c):** This β-lactone was prepared from cyclohexanecarboxaldehyde (0.22 mL, 1.77 mmol, 1.0 equiv) and ketene acetal **2b** (541 mg, 1.92 mmol, 1.1

equiv) using 361 mg of $ZnCl_2$ (2.59 mmol, 1.5 equiv) in 12 mL of CH_2Cl_2. Workup (procedure A) followed by purification by flash chromatography (1:15 ethyl acetate/hexanes) gave 48 mg (16 %) of β-lactone **3c**[27] as a colorless oil. Data not previously reported is given: R_f 0.32 (1:15 ethyl acetate/hexanes); IR (thin film) 2929, 1818 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.87 (dd, J = 4.1, 8.3 Hz, 1H), 3.28 (qd, J = 4.1, 7.5 Hz, 1H), 1.87-2.00 (m, 1H), 1.40-1.87 (m, 4H), 1.37 (d, J = 7.5, 3H), 0.90-1.40 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.2, 83.2, 48.9, 41.7, 28.4, 27.0, 25.9, 25.3, 25.0, 12.8; FAB HRMS Calcd for $C_{10}H_{16}O_2$ [M+Na]: 191.1048. Found: 191.1052. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.38; H, 9.55.

(+/-)-4-Cyclohexyloxetan-2-one (3d): This β-lactone was prepared from cyclohexanecarboxaldehyde (0.22 mL, 1.77 mmol, 1.0 equiv) and ketene acetal **2a** (528 mg, 1.97 mmol, 1.1 equiv) using 351 mg of $ZnCl_2$ (2.52 mmol, 1.42 equiv) in 12 mL of CH_2Cl_2. Workup (procedure A) followed by purification by flash chromatography (1:4 ethyl acetate/hexanes) gave 141 mg (52%) of β-lactone **3d**[28] as a colorless oil. Data not previously reported is given: R_f 0.32 (1:9 ethyl acetate/hexanes); IR (thin film) 2929, 1832 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.15-4.25 (m, 1H), 3.43 (dd, J = 5.8, 16.3 Hz, 1H), 3.11 (dd, J = 4.4, 16.3 Hz, 1H), 1.52-1.97 (m, 6H), 0.90-1.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.5, 74.7, 41.7, 40.7, 27.9, 26.9, 25.7, 25.1, 24.9; FAB HRMS Calcd for $C_9H_{14}O_2$ [M+H]: 155.1072. Found: 155.1081. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.34; H, 9.22.

***trans*-(+/-)-4-(2-tert-Butyldimethylsiloxyethyl)-3-methyloxetan-2-one (3e):** This β-lactone was prepared from 3-*tert*-butyldimethylsiloxypropanal (102 mg, 0.54 mmol, 1.0 equiv) and ketene acetal **2b** (173 mg, 0.61 mmol, 1.1 equiv) using 110 mg of $ZnCl_2$ (0.79 mmol, 1.5 equiv) in 4 mL of CH_2Cl_2. Workup (procedure A) followed by purification by flash chromatography (1:19 diethyl ether/pentane) gave 67 mg (51%) of β-lactone **3e** as a colorless oil: R_f 0.38 (1:9 ethyl acetate/hexanes); IR (thin film) 2958, 1830 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.34 (dt, J= 4.0, 6.7, 1H), 3.67-3.85 (m, 2H), 3.37 (qd, J = 4.0, 7.5 Hz, 1H), 1.89-2.15 (m, 2H), 1.39 (d, J = 7.5, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.1, 77.5, 58.9, 50.9, 36.9, 25.8, 18.1, 12.3, -5.5; FAB HRMS Calcd for $C_{12}H_{24}O_3Si$ [M+H] 245.1573. Found: 245.1573. Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 59.14; H, 9.95.

(+/-)-4-(2-*tert*-Butyldimethylsiloxyethyl) oxetan-2-one (3f): This β-lactone was prepared from 3-*tert*-butyldimethylsiloxypropanal (99 mg, 0.53 mmol, 1.0 equiv) and ketene acetal **2a** (155 mg, 0.57 mmol, 1.1 equiv) using 103 mg of $ZnCl_2$ (0.73 mmol, 1.4 equiv) in 4.0 mL of CH_2Cl_2. Workup (procedure A) followed by purification by flash chromatography (1:12 diethyl ether/pentane) and Kughelrohr distillation gave 38 mg (31%) of β-lactone **3f** as a colorless oil: R_f 0.20 (1:9 ethyl acetate/hexanes); IR (thin film) 2957, 1825 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.63-4.76 (m, 1H), 3.74-3.80 (m, 1H), 3.55 (dd, J = 5.8, 16.4 Hz, 1H), 3.21 (dd, = 4.3, 16.4 1H), 1.90-2.11 (m, 2H), 0.89 (s, 9H), 0.058 (s, 6H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 168.4, 69.1, 58.8, 43.2, 37.3, 25.8, 18.2, -5.53, -5.55; FAB HRMS Calcd for $C_{11}H_{22}O_3Si$ [M+H]: 231.1416. Found: 231.1437.

***trans*-(+/-)-4-Heptyl-3-methyloxetan-2-one (3g):** This β-lactone was prepared from octanal (0.31 mL, 2.0 mmol, 1.0 equiv) and ketene acetal **2e** (676 mg, 2.4 mmol, 1.2 equiv, corrected for 85% purity) using 545 mg of $ZnCl_2$ (4.0 mmol, 2.0 equiv) in 15 mL of CH_2Cl_2. Workup (procedure B) followed by purification by flash

chromatography (1:19 ethyl acetate/hexanes) gave 221 mg (60%) of β-lactone **3g** as a colorless oil which exhibited physical and spectral data that matched those reported by Danheiser and Nowick.[11a]

(+/-)-4-Heptyloxetan-2-one (3h): This β-lactone was prepared from octanal (0.31 mL, 2.0 mmol, 1.0 equiv) and ketene acetal **2d** (645 mg, 2.4 mmol, 1.2 equiv, corrected for 85% purity) using 545 mg of $ZnCl_2$ (4.0 mmol, 2.0 equiv) in 15 mL of CH_2Cl_2. Workup (procedure B) followed by purification by flash chromatography (1:19 ethyl acetate/hexanes) gave 222 mg (65%) of β-lactone **3h**[29] as a colorless oil. Data not previously reported is given: R_f 0.27 (1:9 ethyl acetate/hexanes), IR (thin film) 2929, 1830 cm^{-1}; ^1H NMR(200 MHz, $CDCl_3$) δ 4.45-4.57(m, 1H), 3.51(dd, J = 5.7, 16.2 Hz, 1H), 3.05(dd, J = 4.2, 16.2, 1H), 1.65-1.93 (m, 2H), 1.20-1.50 (m, 10H), 0.89 (t, J = 6.9, 3H); ^{13}C NMR(50 MHz, $CDCl_3$) δ 168.3, 71.3, 42.8, 34.6, 31.6, 29.1, 29.0, 24.9, 22.5, 14.0; FAB HRMS Calcd for $C_{10}H_{18}O_2$ [M+H]: 171.1385. Found: 171.1371. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.45; H, 10.62.

3-Methyl-4-(4-pentenyl)oxetan-2-one (3i): This β-lactone was prepared from 4-pentenal (99 mg, 0.95 mmol, 1.0 equiv) and ketene acetal **2a** (351 mg, 1.13 mmol, 1.2 equiv) using 198 mg of $ZnCl_2$ (1.42 mmol, 1.5 equiv) in 7 mL of CH_2Cl_2. Workup (procedure A) followed by purification by flash chromatography (1:9 ethyl acetate/hexanes) and then Kughelrohr distillation to remove remaining *tert*-butydimethylsilanol gave 52 mg (35%) of β-lactone **3i** as a colorless oil: R_f 0.41 (1:6 ethyl acetate/hexanes); IR (thin film) 2931, 1822 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.79 (ddt, J=16.9, 10.1, 6.6 Hz, 1H), 4.96-5.09 (m, 2H), 4.18 (dt, J = 6.6, 4.1 Hz, 1H), 3.23 (dq, J = 7.6, 4.1 Hz, 1H), 2.06-2.18 (m, 2H), 1.45-1.96 (m, 4H), 1.39 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 137.7, 115.4, 79.4, 50.7, 33.5, 33.1, 24.2, 12.5.

4-(4-Pentenyl)oxetan-2-one (3j): This β-lactone was prepared from 4-pentenal (161 mg, 1.54 mmol, 1.0 equiv) and ketene acetal **2a** (498 mg, 1.77 mmol, 1.2 equiv) using 298 mg of $ZnCl_2$ (2.14 mmol, 1.4 equiv) in 10 mL of CH_2Cl_2. Workup (procedure A) followed by purification by flash chromatography (1:9 ethyl acetate/hexanes) gave 52 mg (24%) of β-lactone **3j** as a colorless oil: R_f 0.26 (1:9 ethyl acetate/hexanes); IR (thin film) 2972, 1826 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.79 (ddt, J = 17.0, 10.2, 6.6 Hz, 1H), 4.96-5.09 (m, 2H), 4.46-4.58 (m, 1H), 3.52 (dd, J = 16.2, 5.8 Hz, 1H), 3.06 (dd, J = 16.2, 4.3 Hz, 1H), 2.07-2.19 (m, 2H), 1.37-1.97 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 137.6, 115.4, 71.1, 42.8, 34.0, 33.0, 24.1.

***trans*-(+/-)-4-(Benzyloxymethyl)-3-methyloxetan-2-one (3k):** This β-lactone was prepared from benzyloxyethanal (150 mg, 1.00 mmol, 1.0 equiv) and ketene acetal **2b** (343 mg, 1.11 mmol, 1.1 equiv) using 193 mg of $ZnCl_2$ (1.45 mmol, 1.5 equiv) in 7 mL of CH_2Cl_2. Workup (procedure A) followed by purification by flash chromatography (1:5 ethyl acetate/hexanes) gave 153 mg (74%) of β-lactone **3k** as a colorless oil: R_f 0.58 (1:2 ethyl acetate/hexanes); IR (thin film) 2971, 1823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.39 (m, 5H), 4.60 (s, 2H), 4.34 (app q, J = 4.2 Hz, 1H), 3.80 (dd, J = 3.0, 11.4 Hz, 1H), 3.73 (dd, J = 4.5, 11.4 Hz, 1H), 3.59 (dq, J = 4.2, 7.5 Hz, 1H), 1.40 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 137.3, 128.4, 127.9, 127.6, 77.2, 73.6, 68.9, 47.2, 12.1; FAB HRMS Calcd for $C_{12}H_{14}O_3$ [M+H]: 207.1021. Found: 207.1039. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.03; H, 6.88.

(+/-)-4-(Benzyloxymethyl)oxetan-2-one (3l): This β-lactone was prepared from benzyloxyethanal (150 mg, 1.00 mmol, 1.0 equiv) and ketene acetal **2b** (310 mg, 1.10 mmol, 1.1 equiv) using 188 mg of $ZnCl_2$ (1.35 mmol, 1.35 equiv) in 7 mL of CH_2Cl_2. Workup (procedure A) followed by purification by flash chromatography (1:4 ethyl acetate/hexanes) gave 134 mg (70%) of β-lactone **3l** as a colorless oil: R_f 0.42 (1:2 ethyl acetate/hexanes); IR (thin film) 3082, 1826 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.31-7.36 (m, 5H), 4.56-4.71 (m, 3H), 3.82 (dd, *J*= 3.2, 11.6 Hz, 1H), 3.71 (dd, *J*= 4.3, 11.6 Hz, 1H), 3.48 (dd, *J*= 5.5, 16.2 Hz, 1H), 3.39 (dd, *J*= 4.9, 16.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 137.3, 128.5, 127.9, 127.7, 73.6, 69.3, 69.2, 39.7; FAB HRMS Calcd for $C_{11}H_{12}O_3$ [M+H]: 193.0865. Found: 193.0882.

(+/-)-4-*tert*-Butyloxetan-2-one (3n): This β-lactone was prepared from pivaldehyde (0.26 ml, 2.32 mmol, 1.0 equiv) and ketene acetal **2a** (676 mg, 2.53 mmol, 1.1 equiv) using 441 mg of $ZnCl_2$ (3.17 mmol, 1.4 equiv) in 15 mL of CH_2Cl_2. Workup (procedure A) followed by purification by flash chromatography (1:10 ether/pentane) gave 126 mg (42%) of β-lactone **3n** as a colorless oil. Spectral data for this compound matched that previously reported.[30]

(+/-)-*cis*-3-Methyl-4-*p*-nitrophenyloxetan-2-one (3o): This β-lactone was prepared from *p*-nitrobenzaldehyde (100 mg, 0.65 mmol, 1.0 equiv) and ketene acetal **2b** (193 mg, 0.69 mmol, 1.1 equiv) using 125 mg of $ZnCl_2$ (0.90 mmol, 1.4 equiv) in 5 mL of CH_2Cl_2. Workup (procedure A) followed by purification by flash chromatography (1:4 ethyl acetate/hexanes) gave 48 mg (36 %) of β-lactone **3o** as a crystalline solid. An x-ray quality crystal was obtained by recrystallization from chloroform/hexanes. ^1H-NMR and IR data for this compound matched that previously reported.[10] Additional data for this compound, not reported previously, follows: R_f 0.20 (1:4 ethyl acetate/hexanes); m. p. 103-104 °C ($CHCl_3$/hexanes); IR (CH_2Cl_2) 2985, 1832 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.28-8.35 (m, 2H), 7.47-7.55 (m, 2H), 5.74 (d, *J*=6.7, 1H), 4.71 (qd, *J*= 6.6, 7.8 Hz, 1H), 0.95 (d, *J*=7.8, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 148.0, 141.9, 126.5, 123.9, 74.0, 50.7, 9.7; EI HRMS Calcd for $C_{10}H_9NO_4$ [M+H]: 207.0532. Found: 207.0527.

***trans*-(+/-)-4-(4-*t*-Butyldimethylsilyloxybutyl)-3-methyloxetan-2-one (3p):** This β-lactone was prepared from 5-t-butyldimethylsilyloxypentanal (1.00 g, 4.6 mmol, 1.0 equiv), ketene acetal **2b** (1.55 g, 5.5 mmol, 1.2 equiv) and $ZnCl_2$ (1.25 g, 9.2 mmol, 2.0 equiv) in 30 mL CH_2Cl_2. Work-up (procedure A) followed by purification by gravity chromatography (5% ethyl acetate/hexanes) gave 574 mg of β-lactone **3p** as a colorless oil (46% yield): R_f 0.30 (80:20-hexane:ethyl acetate); ^1H NMR (200 MHz, $CDCl_3$) δ 4.16 (td, *J* =6.5, 4.1 Hz, 1H), 3.61 (t, *J* =6.0 Hz, 2H), 3.20 (dq, *J* =4.1, 7.5 Hz, 1H), 1.63-1.95 (m, 2H), 1.38-1.62 (m, 4H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 172.0, 79.5, 62.6, 50.7, 33.9, 32.2, 25.9, 21.5, 18.3, 12.5, -1.2; IR (thin film) 2935, 1823 cm^{-1}; FAB HRMS Calcd for $C_{14}H_{28}O_3Si$ [M+Na]: 295.1705. Found: 295.1721. Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36. Found: C, 61.62; H,10.29.

(+/-)-4-(2-Phenylethyl)-3-benzyloxyoxetan-2-one (3q): This β-lactone was prepared from hydrocinnamaldehyde (132 µl, 1.0 mmol, 1.0 equiv) and ketene acetal **2f** (1.02 g, mixture of E/Z isomers, ~1.3 mmol of Z isomer, ~1.3 equiv) in 7 ml CH_2Cl_2 by the general procedure. Workup (procedure A) followed by purification by flash chromatography (1:3 chloroform/hexanes) gave 171 mg (61%) of β-lactone **3q** as a colorless oil: R_f 0.24 (50% chloroform/hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ 7.10-7.50 (m, *J*=7 8 Hz, 10H), 4.82 (d, *J*=11.6 Hz, 1H), 4.55

(d, *J*=11.6 Hz, 1H), 4.53 (d, *J*=3.6 Hz, 1H), 4.39-4.50 (m, *J*=3 Hz, 1H), 2.55-2.83 (m, *J*=5 Hz, 2H), 1.77-2.22 (m, *J*=4 Hz, 2H), ; ^{13}C NMR (200 MHz, $CDCl_3$) δ 168.0, 139.8, 136.2, 128.7, 128.63, 128.57, 128.4, 128.3, 126.4, 85.2, 79.1, 72.9, 34.1, 31.1; IR (thin film) 2927, 1835 cm^{-1}; FAB HRMS Calcd for $C_{18}H_{18}O_3$ [M+Na]: 305.1154. Found 305.1166.

(+/-)-4-(4-Hydroxybutyl)-2-benzyloxyoxetan-2-one (3r): This β-lactone was prepared from 5-t-butyldimethylsilyloxypentanol (from monosilylation of 1,4, butanediol[31]) by Swern oxidation. The crude aldehyde was used in the TMAL reaction due to its instability to silica gel.

The aldol-lactonization was carried out according to the general procedure using the crude 5-*t*-butyldimethylsilyloxypentanal (3.25 g, 15 mmol, 1.0 equiv), ketene acetal **2b** (6.73 g, 18 mmol, 1.2 equiv) and $ZnCl_2$ (4.20 g, 30 mmol, 2.0 equiv) in 75 ml CH_2Cl_2. Work-up (procedure A) gave 2.45 g of crude β-lactone as a bright yellow oil and this was directly carried on to the desilylation step.

To the *t*-butyldimethyl silylether (2.45 g, 6.7 mmol, 1.0 equiv) in 40 ml THF was added hydrogen fluoride•pyridine (2.66 g, 26.9 mmol, 4 equiv) at ambient temperature. After stirring for 1h, the reaction mixture was diluted with ethyl acetate. The organics were washed with water, satd. $NaHCO_3$, water, brine and then dried over Na_2SO_4. Removal of the solvent followed by flash chromatography (10% ethyl acetate in hexanes) gave 0.83 g (22% yield for 3 steps) of β-lactone **3r** as a colorless oil: R_f 0.30 (50% ethyl acetate/hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ 7.33 (s, 5H), 4.81 (d, *J*=11.7 Hz, 1H), 4.58 (d, *J*=11.7 Hz, 1H), 4.55 (d, *J*=3.6 Hz, 1H), 4.38-4.50 (m, 1H), 3.56 (t, *J*=6.2 Hz, 2H), 2.20-2.50 (broad, *J*=10 Hz, 1H), 1.25-1.85 (m, 6H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 168.3, 136.2, 128.7, 128.5, 128.2, 85.2, 80.1, 72.8, 62.0, 32.0, 31.8, 21.3; IR (thin film) 2935, 1827 cm^{-1}; FAB HRMS Calcd for $C_{14}H_{18}O_4$ [M+Na]: 273.1103. Found 273.1105.

Tri*iso*propylsilyl 3-chlorodecanoate (4) (R^3 = Si(*i*-Pr)$_3$): Colorless oil: R_f 0.64 (20% ethyl acetate/hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ 4.27 (m, 1H), 2.77 (d, *J*=6.9Hz, 2H), 1.19-1.81 (m, 15H), 1.07 (d, *J*=6.9Hz, 18H), 0.87 (m, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.1, 58.3, 45.2, 38.0, 31.7, 29.1, 28.9, 26.3, 22.6, 17.7, 14.1, 11.9; IR (thin film) 2924, 1722 cm^{-1}; HRMS Calcd for $C_{19}H_{39}ClO_2Si$[M+H]: 363.2486. Found 363.2480.

Thiopyridyl silyloxyacetal (5) (R^3 = SiMe$_2$*t*-Bu, R^4 = SPy): Bright yellow oil: R_f 0.44 (20% ethyl acetate/hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ 7.90-7.95 (m, 1H), 7.56-7.62 (m, 1H), 7.07-7.15 (m, 2H), 6.67 (t, *J*=6.8Hz, 1H), 1.00-2.00 (m, 12H), 0.81-0.90 (m, 12H), 0.13 (s, 3H), -0.10 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 178.4, 135.9, 135.4, 133.5, 113.1, 85.5, 37.1, 31.7, 29.12, 29.05, 25.6, 24.6, 22.6, 17.8, 14.1, -5.12, -5.18; IR (thin film) 2928, 1621 cm^{-1}; HRMS Calcd for $C_{19}H_{36}NOSSi$[M+H]: 354.2283. Found 354.2274.

***d*-*B*-Allyldiisopinocampheylborane (^{d}Ipc$_2$BAll)**:[22] To a solution (-)-*B*-methoxydiisopinocam-phenylborane (4.75 g, 15.0 mmol) in ether (20 mL) was added allylmagnesium bromide (15 mL, 15 mmol, 1M solution in ether) at 0° C. The resulting slurry was stirred for 1.5 h at room temperature, centrifuged under N_2 (after transfer to test tubes via cannula), transferred to a round-bottom flask via cannula, concentrated in vacuo, dissolved into pentane, transferred to a test tube via cannula, centrifuged again, and finally concentrated for 1 h under vacuum (~10 mm Hg). The residue was taken up into pentane, filtered through a fritted glass funnel under N_2, and once again concentrated under vacuum (10 mmHg, 0.5 h and then ~0.5 mmHg, 0.5 h) to give "salt-free" ^{d}Ipc$_2$BAll (4.59 g, 14.1 mmol) as an almost clear oil.

(*R*)-1-Undecen-4-ol (7): To a solution of ^{d}Ipc$_2$BAll (4.59 g, 14.1 mmol) in ether (20 mL) at -100°C was added a precooled (-78 °C) solution of n-octanal (2.21 mL, 14.0 mmol) in ether (40 mL) along the sides of the flask. The resulting reaction mixture was stirred for 1 hr at -100°C and then warmed to -48 °C, and stirred for an additional 19 h at that temperature. The reaction was quenched by addition of 1.0 mL of methanol. The resulting mixture was warmed to room temperature, treated with 3N NaOH (10 mL) and 30% H_2O_2 (20 mL), and then refluxed for 3 h. The organic layer was separated and the aqueous layer was washed with ether (1x30 mL). The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by flash chromatography (1:15 ethyl acetate/hexanes) to afford 1.33 g (55%) of the known[32] alcohol **7** as a colorless oil that gave spectral data that correlated with that previously reported (92% ee, chiral GC analysis). Data not previously reported or different from that previously reported is given: R_f 0.34 (1:9 ethyl acetate/hexanes); $[\alpha]^{26}_D$ +7.11 (*c* 1.02, $CHCl_3$), lit.[38c] $[\alpha]^{25}_D$ +6.51 (*c* 1.04, $CHCl_3$).

(*R*)-Silyl ether (8): To a solution of (*R*)-1-undecen-4-ol **7** (1.22 g, 7.16 mmol) and imidazole (0.54 g, 7.85 mmol) in DMF (3.7 mL) was added TBSCl (1.19 g, 7.82 mmol) as a solution of 4 mL of DMF at room temperature. The resulting mixture was stirred overnight, diluted with ether (50 mL), washed with brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and finally purified by flash chromatography (hexanes) to give 1.93g (95%) of (*R*)-silyl ether **8** as a colorless oil: R_f 0.68 (hexanes); $[\alpha]^{26}_D$ +13.6 (*c* 1.03, $CHCl_3$); IR (thin film) 2929, 2857 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.71-5.92 (m, 1H), 5.01-5.09 (m, 1H), 4.98-4.99 (m, 1H), 3.62-3.73 (m, 1H), 2.16-2.24 (m, 2H), 1.20-1.45 (m, 12H), 0.85-0.90 (m, 12H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 116.5, 72.0, 41.9, 36.8, 31.8, 29.7, 29.3, 25.9, 25.3, 22.6, 18.1, 14.1, -4.4, -4.5; Anal. Calcd for $C_{17}H_{36}OSi$: C, 71.76; H, 12.75. Found: C, 71.67; H, 12.70.

(*R*)-Aldehyde (9): Ozone was bubbled into a stirred MeOH-$CHCl_2$ (1:1, 35 mL) solution of 0.91 g of (*R*)-silyl ether **8** (3.20 mmol) at -78 °C until the blue color persisted for ~4 min. Methyl sulfide (7.0 mL, 94.4 mmol) and triethylamine (0.7 mL, 4.97 mmol) were added and the cooling bath was removed. The reaction mixture was warmed to room temperature, stirred overnight, concentrated in vacuo. Purification by flash chromatography (1:29 ethyl acetate/hexanes) afforded 860 mg (93%) of (*R*)-aldehyde **9** as a colorless oil: R_f 0.37 (1:29 ethyl acetate: hexane); $[\alpha]^{26}_D$ -5.77 (*c* 1.04, $CHCl_3$); IR (thin film) 2933, 1726 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.81 (t, *J* = 2.5 Hz, 1H), 4.18 (quint., *J* = 5.8 Hz, 1H), 2.51 (dd, *J* = 2.5 and 5.7 Hz, 2H), 1.45-1.55 (m, 2H), 1.20-1.35 (m, 8H), 0.80-0.90 (m, 14H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 68.2, 50.8, 37.8, 31.7, 29.5, 29.2, 25.7, 25.1, 22.6, 17.9, 14.1, -4.5, -4.7; FAB HRMS Calcd for $C_{14}H_{31}OSi$ [M^+-C_2H_3O]: 243.2144. Found 243.2153.

Thiopyridyl ketene acetal (10): To a solution of lauric acid (3.00 g, 14.7 mmol) in 6 mL of $SOCl_2$ (81.4 mmol) was added three drops of DMF. The resulting mixture was refluxed for 3 hours. Residual $SOCl_2$ was removed in vacuo then 4 mL of benzene was added and then the process was repeated. The resulting acid chloride was diluted with 10 mL of CH_2Cl_2. To a solution of 2-mercaptopyridine (1.73 g, 15.4 mmol) and Et_3N (2.40 mL, 17.0 mmol) in 30 mL of CH_2Cl_2 was added a solution of acid chloride in 10 mL of CH_2Cl_2 at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was quenched by careful addition of water. The organic layer was separated, washed with 5% NaOH (3 x 100 mL), brine, dried over $MgSO_4$,

filtered, concentrated in vacuo, and purified by flash chromatography (1:10 → 1:9 ethyl acetate/hexanes) to give 3.38 g (78%) of *S*-2-pyridyl dodecanethioate. R_f 0.54 (1:4 ethyl acetate/hexanes); IR (thin film) 3047, 2919, 1707 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.60-8.64 (m, 1H), 7.70-7.78 (m, 1H), 7.59-7.64 (m, 1H), 7.25-7.31 (m, 1H), 2.70 (t, *J* = 7.2 Hz, 2H), 1.73 (m, 2H), 1.20-1.40 (m, 16H), 0.88 (t, *J* = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2, 151.4, 150.1, 136.9, 129.9, 123.2, 44.0, 31.7, 29.4, 29.2, 29.1, 29.0, 28.7, 25.2, 22.5, 13.9; EI HRMS Calcd for $C_{17}H_{27}NOS$ [M^+]: 293.1813. Found: 293.1838.

To a solution of hexamethyldisilazane (1.18 mL, 5.58 mmol) in 10 mL of THF was added n-BuLi (2.33 mL, 5.58 mmol, 2.40 M in hexane) at room temperature. After 30 minutes, the reaction mixture was cooled to -78 °C. To this solution of LiHMDS was added DMF (0.72 mL, 9.30 mmol), Et_3N (1.30 mL, 9.30 mmol), and then TBSCl (1.40 g, 4.77 mmol) in 2.5 mL of THF and finally *S*-2-pyridyl dodecanethioate (1.40 g, 4.77 mmol) in 2.5 mL of THF at that temperature. After an additional 30 minutes, ethyl acetate was added, and then the organic phase was washed with brine twice, dried over Na_2SO_4, filtered, and concentrated to afford crude material. Purification by flash chromatography (hexanes → 5 → 10% ethyl acetate/hexanes) gave 1.44 g (74%) of thiopyridyl ketene acetal **10** as a yellow oil: R_f 0.73 (1:4 ethyl acetate/hexanes); IR (thin film) 3042, 2924 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.40-8.43 (m, 1H), 7.50-7.59 (m, 1H), 7.30-7.35 (m, 1H), 6.95-7.02 (m, 1H), 5.40 (t, *J* = 7.3 Hz, 1H), 2.13-2.20 (m, 2H), 1.20-1.42 (m, 16H), 0.83-0.90 (m, 12H), 0.080 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.51, 149.31, 139.17, 136.41, 124.12, 121.36, 119.52, 31.88, 29.61, 29.58, 29.42, 29.34, 29.31, 29.12, 26.73, 25.61, 22.65, 18.04, 14.09, -4.45. Anal. Calcd for $C_{23}H_{41}NOSSi$: C, 67.75; H, 10.14. Found: C, 67.82; H, 10.16.

(3*S*,4*S*)-3-Decyl-4-[(*R*)-2-hydroxynonyl]oxetan-2-one (12): The tandem aldol-lactonization was carried out according to the general procedure using $ZnCl_2$ (642.1 mg, 4.62 mmol), (*R*)-aldehyde **9** (400 mg, 1.40 mmol), and thiopyridyl ketene acetal **10** (794 mg, 1.95 mmol), and for 61 hrs. The reaction was worked up by the general work-up procedure. Integration of the crude reaction mixture in d_6-benzene (400 MHz ^1H NMR) showed a 9.3:1 diastereomeric ratio of β-lactone products. However, the crude product **11** was not purified but taken directly to the desilylation step.To a solution of the crude reaction mixture in 24 ml of CH_3CN was added aqueous 1.4 mL of HF (48%, 38.6 mmol) at 0 °C. The reaction mixture was stirred for 2 h at that temperature and then warmed to room temperature. After stirring for 1 h, ether (25 mL) was added and the organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo. The resulting faint yellow oil was redissolved into hexanes, washed with 3% ice-cold NaOH (2x20 mL), brine, and then dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (1:9 ethyl acetate/hexanes) gave 94 mg (19%) of diastereomerically pure β-lactone **12** as a crystalline solid and 168 mg (34%) of a mixture of β-lactone **12** and a diastereomeric β-lactone (53% total yield for 2 steps). The stereochemistry of the minor diastereomer has not been rigorously determined. Data for the major diastereomer is given: R_f 0.24 (1:9 ethyl acetate/hexanes); $[\alpha]^{26}_D$ -51.6 (*c* 0.31, $CHCl_3$); IR (KBr) 2916, 1814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.50 (app quint. *J* = 4.2 Hz, 1H), 3.77-3.84 (m, 1H), 3.26 (ddd, *J* = 4.0, 6.9, 8.2 Hz, 1H), 1.70-1.95 (m, 4H), 1.26-1.50 (m, 28H), 0.885 (t, *J* = 7.2 Hz, 3H), 0.881 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.72 75.61, 68.31, 56.44, 41.77, 38.01, 31.82, 31.71, 29.50, 29.46, 29.41, 29.26, 29.16, 27.64, 26.73, 25.35, 22.60, 22.57, 14.04, 14.01. FAB HRMS Calcd for $C_{22}H_{42}O_3$ [M+H]: 355.3212. Found: 355.3232.

(-)-Panclicin D (13): A mixture of (3*S*,4*S*)-3-decyl-4-[(*R*)-2-hydroxynonyl]oxetan-2-one **12** (79.6 mg, 0.22 mmol), N-formylglycine (80.9 mg, 0.78 mmol), and Ph_3P (174.8 mg, 0.66 mmol) was azeotroped with 1 mL of xylene under high vacuum. The mixture was charged with 2.5 mL of THF and then DIAD (0.137 mL, 0.66 mmol) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 hours. The reaction mixture was concentrated in vacuo. After removing triphenyl phosphine oxide by flash chromatography (1:2 ethyl acetate/hexanes), final purification was done by flash chromatography using THF/chloroforom/hexanes (0.4:1:3) to give 85.6 mg (88%) of (-)-panclicin D **13** as a colorless oil: R_f 0.26 (1:2 ethyl acetate/hexanes); $[\alpha]^{26}_D$ -23 (*c* 0.30, $CHCl_3$), lit.[20b] $[\alpha]^{25}_D$ -23 (*c* 0.30, $CHCl_3$); IR (thin film) 1818, 1748, 1686, 1674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25-8.26 (m, 1H), 6.18 (br s, 1H), 5.10-5.16 (m, 1H), 4.33 (dt, *J* = 4.4, 8.0 Hz, 1H), 4.13 (ddd, *J* = 0.4, 5.2, 18.4 Hz, 1H), 4.03 (ddd, *J* = 0.4, 5.2, 18.4 Hz, 1H), 3.21 (ddd, *J* = 4.0, 7.2, 8.0 Hz, 1H), 2.14 (dt, *J* = 8.0, 15.2 Hz, 1H), 2.02 (dt, *J* = 4.4, 15.2 Hz, 1H), 1.55-1.85 (m, 4H), 1.26-1.45 (m, 26H), 0.88 (t, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.88, 169.16, 161.07, 75.05, 72.89, 56.92, 40.01, 38.77, 33.98, 31.80, 31.63, 29.46, 29.42, 29.21, 29.14, 28.99, 27.50, 26.71, 25.07, 22.59, 22.52, 14.03, 13.98. FAB HRMS Calcd for $C_{25}H_{45}O_5N$ [M+H]: 440.3376. Found: 440.3355.

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