A Highly Diastereoselective, Tandem Mukaiyama Aldol-Lactonization Route to *β*-Lactones: Application to a Concise Synthesis of the Potent Pancreatic Lipase Inhibitor, (−)-Panclicin D

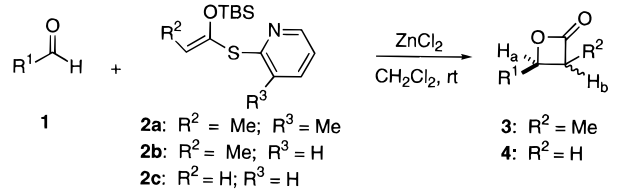
Hong Woon Yang and Daniel Romo*

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

Received October 17, 1996

β-Lactones (2-oxetanones) have recently emerged as important synthetic targets due to their occurrence in a variety of natural products, their utility as versatile synthetic intermediates, and their use as monomers for the preparation of biodegradable polymers.[1] As part of a program directed toward the asymmetric synthesis and the development of new transformations of *β*-lactones, we have been searching for general and efficient diastereo- and enantioselective methods for their preparation. In connection with these studies, we now report on an exceptional tandem aldol-lactonization process that provides direct access to achiral and chiral 3,4-disubstituted-*β*-lactones with high stereoselectivity.[2] This method builds on work recently reported by Hirai and co-workers[3] and compliments the tandem aldol-lactonizations recently reported by Danheiser[4] and Schick[5] employing enolates derived from various acid derivatives. The latter methods provide good yields of *β*-lactones from ketones and some aldehydes; however, the stereoselectivity of these reactions with aldehydes appears to be highly dependent on the substitution of the thiol ester and aldehyde employed. In contrast, the tandem Mukaiyama aldol-lactonizations reported herein employing readily available ketene thioacetals **2b** and **2c**[6] and both racemic and optically active aldehydes *proceed at ambient temperature with high levels of stereocontrol* (Scheme 1).[7] In addition, this process provides the first general route to α-unsubstituted-*β*-lactones by a tandem-aldol lactonization sequence in contrast to previous methods.[5] The utility of this method is demonstrated by a concise synthesis of (−)-panclicin D,[8] a recently isolated pancreatic lipase inhibitor with twice the inhibitory activity of the recently approved antiobesity agent tetrahydrolipstatin (Orlistat).[9]

Scheme 1



1

2a: R^2 = Me; R^3 = Me
2b: R^2 = Me; R^3 = H
2c: R^2 = H; R^3 = H

3: R^2 = Me
4: R^2 = H

Treatment of various aldehydes in a methylene chloride slurry of freshly fused $ZnCl_2$ with the readily available ketene thioacetal **2b** gave almost exclusively the *trans*-α-methyl *β*-lactones **3a**−**f** in moderate to good yields (Table 1).[10] Purification of the *β*-lactones was simplified in some cases by treatment of the reaction mixture with $CuBr_2$ followed by hydrolysis which removed both unreacted ketene thioacetal and any thiol ester formed during the reaction.[11] 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 ($J_{Ha,Hb} \sim 6$ Hz for cis, 4−4.5 Hz for trans).[12] The stereochemical outcome of these reactions is in accord with previous reports of Mukaiyama aldol reactions employing ketene thioacetals which proceed through open transition states.[13] An exception is the reaction with *p*-nitrobenzaldehyde which is the single example of *β*-lactone synthesis reported by Hirai. In this case, the methyl-substituted ketene thioacetal **2a** was employed and the *cis*-substituted *β*-lactone **3h** was the only product isolated (23% yield).[3a] We obtained the same *β*-lactone employing ketene thioacetal **2b** (Table 1, entry 15), and the cis stereochemical outcome was verified by single crystal X-ray analysis.[14] This intriguing reversal in stereoselectivity with *p*-nitrobenzaldehyde is consistent with a recent report of $TiCl_4$-mediated aldol condensations of benzaldehyde and ketene thioacetals;[7] however, a rationalization of the stereochemical outcome in the present reaction involving $ZnCl_2$ must await further studies. As mentioned above, the present tandem reaction can also be applied to the synthesis of α-unsubstituted *β*-lactones **4a**−**g** using the acetic acid derived ketene thioacetal **2c** (Table 1).

Some limitations of the present method were noted. In the case of pivalaldehyde, the reaction only proceeds when the acetal **2c** is employed (*cf.* entries 13, 14). When this aldol-lactonization procedure was applied to α,*β*-unsaturated aldehydes and some aromatic aldehydes no *β*-lactones were isolated, but instead olefinic products derived from apparent *in situ* elimination of the *β*-lactones were detected in the crude reaction mixtures.[15] In

* To whom correpondence should be addressed: Tel: 409-845-9571; Fax: 409-845-4719; E-mail: romo@chemvx.tamu.edu.

(1) (a) For a recent review of *β*-lactone chemistry, see: Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441−449. For recent reviews of *β*-lactone-containing natural products, see: (b) Lowe, C.; Vederas, J. *Org. Prep. Proced. Int.* **1995**, *27*, 305−346. (c) Pommier, A.; Pons, J.-M. *Synthesis* **1995**, 729−744. (d) For a lead reference to polymers derived from *β*-lactones, see: Jedlinski, Z.; Kurcok, P.; Kowalczuk, M.; Matuszowicz, A.; Dubois, P.; Jerome, R.; Kricheldorf, H. R. *Macromolecules* **1995**, *28*, 7276−7280.

(2) Reetz, M. T.; Schmitz, A.; Holdgrun, X. *Tetrahedron Lett.* **1989**, *30*, 5421−5424.

(3) (a) Hirai, K.; Homma, H.; Mikoshiba, I. *Heterocycles* **1994**, *38*, 281−282. (b) For related work involving the one-step synthesis of *β*-lactams, see: Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *Tetrahedron* **1996**, *52*, 2573−2582.

(4) (a) Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1991**, *56*, 1176−1185. (b) Danheiser, R. L.; Nowick, J. S.; Lee, J. H.; Miller, R. F.; Huboux, A. H. *Org. Synth.* **1995**, *73*, 61.

(5) Wedler, C.; Kleiner, K.; Kunath, A.; Schick, H. *Liebigs. Ann.* **1996**, 881−885 and references cited.

(6) The ketene thioacetals **2b** (∼20:1 *Z*(O):*E*(O)) and **2c** are readily prepared from the corresponding acids in two steps by standard acylation and silylation, see: Hirai, K.; Iwano, Y.; Mikoshiba, I.; Koyama, H.; Nishi, T. *Heterocycles* **1994**, *38*, 277−280 and ref 3b.

(7) For a recent report of the use of ketene thiopyridylacetals in aldol reactions, see: Suh, K.-H.; Choo, D.-J. *Tetrahedron Lett.* **1995**, *36*, 6109−6112.

(8) Isolation and biological activity: (a) Yoshinari, K.; Aoki, N.; Ohtsuka, T.; Nakayama, N.; Itezono, Y.; Mutoh, M.; Watanabe, J.; Yokose, K. *J. Antibiot.* **1994**, *47*, 1376−1384. Structure determination: (b) Mutoh, M.; Nakada, N.; Matsukuma, S.; Ohshima, S.; Yoshinari, K.; Watanabe, J.; Arisawa, M. *J. Antibiot.* **1994**, *47*, 1369−1375.

(9) Zhi, J.; Melia, A. T.; Guerciolini, R.; Chung, J.; Kinberg, J.; Hauptman, J. B.; Patel, I. H. *Clin. Pharm. Ther.* **1994**, *56*, 82.

(10) A general procedure for the tandem Mukaiyama aldol-lactonization can be found in the supporting information.

(11) Kim, S.; Lee, J. I. *J. Org. Chem.* **1984**, *49*, 1712−1716.

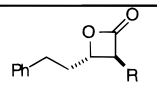
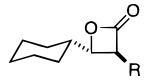
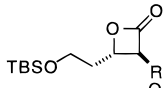
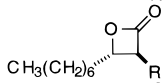
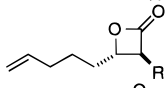
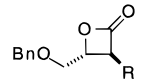
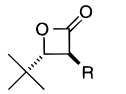
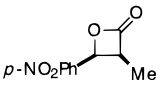
(12) Mulzer, J.; Zippel, M.; Bruntrup, G.; Segner, J.; Finke, J. *Liebigs Ann. Chem.* **1980**, 1108.

(13) Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893−909.

(14) The X-ray data of *β*-lactone **3h** has been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

S0022-3263(96)01948-2 CCC: $14.00

Table 1. Synthesis of Racemic β-Lactones 3 and 4 via Tandem Aldol-Lactonization of Aldehydes and Ketene Acetals 2b and 2c

entry	β-lactones	R	prod.	rxn time (h)	trans/cis ratio[a]	yield
1		Me	**3a**	22	37:1	57
2		H	**4a**	5	-	53
3		Me	**3b**	45	>19:1	16
4		H	**4b**	5	-	52
5		Me	**3c**	24	>19:1	51
6		H	**4c**	24	-	31
7		Me	**3d**	23	>19:1	42[b]
8		H	**4d**	2.5	-	35
9		Me	**3e**	23	>19:1	35[c]
10		H	**4e**	23	-	24[c]
11		Me	**3f**	24	>19:1	74
12		H	**4f**	18	-	70
13		Me	**3g**	48	-	0
14		H	**4g**	4.5	-	42[c]
15		-	**3h**	25	<1:19	36

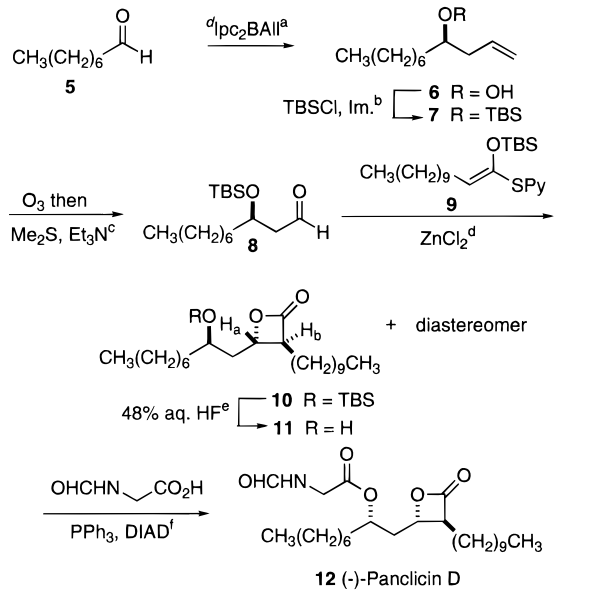
[a] Determined or estimated by analysis of the crude reaction mixtures by 200 or 300 MHz ^{1}H NMR. [b] A 2.5:1 mixture of trans/cis-β-lactones was previously obtained for this β-lactone by the method of Danheiser (ref. 4a). [c] These β-lactones were volatile and not readily separated from *t*-butyldimethylsilanol.

addition, while some aldehydes bearing pendant protected alcohols provided the desired β-lactones, others gave products resulting from further reaction of the presumed β-lactone intermediate.[16]

The utility of this methodology is demonstrated by an extremely concise total synthesis of (−)-panclicin D. The synthesis began with a Brown asymmetric allylation of *n*-octanal using *d*-*B*-allyldiisopinocampheylborane (^{d}Ipc$_2$BAll)[17] to give the homoallylic alcohol **6** in 55% yield and 92% ee (Scheme 2).[18] Alcohol protection followed by ozonolysis provided the aldehyde **8** in 88% yield (two steps). Application of the tandem aldol-lactonization to this aldehyde and ketene thioacetal **9**[19] proceeded smoothly to give the β-lactones **10** as a 9.3:1 mixture of diastereomers. These were directly desilylated to afford the more readily purified, hydroxy β-lactones **11**, that were separable by flash chromatography, in 53% overall yield from aldehyde **8**. As expected, the major diastereomer **11** possessed a *trans*-substituted β-lactone ($J_{Ha,Hb}$ = 4.2 Hz), and the relative stereochemistry was subsequently determined to be anti by conversion to (−)-panclicin D. Mitsunobu reaction employing *N*-formylglycine provided synthetic (−)-panclicin D (**12**) which displayed spectral and physical properties that matched those of the natural product ($[\alpha]^{20}_D = -23.0$ (*c* 0.30, $CHCl_3$); lit. $[\alpha]^{20}_D = -23$ (*c* 0.30, $CHCl_3$)).[8b] This synthesis constitutes one of the most concise and efficient routes to this class of lipase inhibitors (six steps, 20% overall yield from *n*-octanal) and is readily adapted to prepare any member of this family.

In conclusion, we have found that the $ZnCl_2$-mediated tandem aldol-lactonization reaction provides an expedient, mild, and highly stereoselective route to β-lactones from aldehydes and readily available ketene thiopyridylacetals. The simplicity and high diastereoselectivity should make this procedure the method of choice for preparing various *trans*-3,4-disubstituted β-lactones as demonstrated by the first total synthesis of (−)-panclicin D. We are presently seeking to further optimize this aldol-lactonization sequence, and the results of these studies will be described in a full account of this work.

Scheme 2[a]



[a] (a) Et_2O,-100°C → -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°C → 23°C, (53%, 2 steps) (f) THF,0°C→ 23°C, (88%)

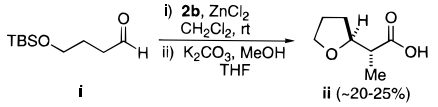
Acknowledgment. Support of this work by the NSF in the form of a Minority Planning Grant (CHE 9510566) and a CAREER award (CHE 9624532) to D.R. is gratefully acknowledged. Dr. N. Nakada and Mr. K. Yoshinari from Nippon Roche (Japan) kindly provided spectral data of natural (−)-panclicin D. We thank Dr. Lloyd Sumner and Dr. Barbara Wolfe for obtaining mass spectral analysis, and Dr. Joe Reibenspies for performing the X-ray analysis.

Supporting Information Available: Experimental procedures including synthesis and characterization of all new compounds reported herein; chiral GC traces of alcohol **6** and spectral data of selected β-lactones and natural and synthetic (−)-panclicin D (25 pages).

JO9619488

(15) A related process has been previously observed in Al-catalyzed [2 + 2] cycloadditions of ketenes and both aromatic and α,β-unsaturated aldehydes: Concepcion, A. B.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1995**, *51*, 4011−4020.

(16) A rather interesting result is observed in reaction of aldehyde **i** under typical aldol-lactonization conditions. This gave the tetrahydrofuran **ii** as predominantly one diastereomer (>19:1, 200 MHz ^{1}H NMR, cf. Mead, K. T.; Park, M. *J. Org. Chem.* **1992**, *57*, 2511−2514). The relative stereochemistry has not been determined at this time but is based on the expected, initially formed *trans*-β-lactone undergoing an inversion process during intramolecular cyclization of the pendant ether (unpublished results of M. Scott Champ).



(17) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401−404.

(18) Enantiomeric excess was determined by GC analysis using a *t*-BuMe_2Si β-cylodextrin column: Shitangkoon, A.; Vigh, G. *J. Chromatogr. A* **1996**, 31−42.

(19) This ketene acetal was prepared in three steps from lauric acid. See supporting information for experimental details.