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A Stereocomplementary Approach to β-Lactones: Highly Diastereoselective Synthesis of *cis*-β-Lactones, a β-Chloro Acid, and a Tetrahydrofuran

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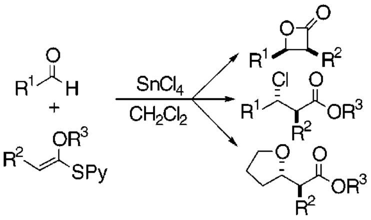
ABSTRACT



In the course of mechanistic studies of the $ZnCl_2$-mediated tandem Mukaiyama aldol–lactonization reaction of aldehydes and thiopyridyl ketene acetals, a stereocomplementary reaction employing $SnCl_4$ was discovered. This method provides a highly diastereoselective entry to *cis*-1,2-disubstituted β-lactones as well as a β-chloro carboxylic acid and a tetrahydrofuran. The former products were obtained by varying the reaction temperature. The latter product was obtained when the aldehyde substrate bore a pendant silyl ether.

A number of stereoselective routes to β-lactones have been reported recently.[1] One method that we have developed in our lab is the tandem Mukaiyama aldol−lactonization (TMAL) reaction which provides a highly diastereoselective approach to *trans*-1,2-disubstituted β-lactones.[2] We, and others,[3] have used this reaction to access a variety of racemic and optically active β-lactones including natural[1] and unnatural products.[3a,4] During our mechanistic studies of the $ZnCl_2$-mediated tandem Mukaiyama aldol−lactonization reaction,[5] we determined that bidentate chelation between $ZnCl_2$ and the thiopyridyl group of ketene acetals was an important factor in promoting the lactonization step. With this in mind, we searched the literature for Lewis acids that were capable of bidentate chelation with 2-mercaptopyridine. We found that $SnCl_4$ was known to form a bidentate chelate with this ligand,[6] and so we studied its reaction with thiopyridyl ketene acetals and aldehydes. Herein we report that $SnCl_4$ promotes a low-temperature, net TMAL reaction (−78 °C) of thiopyridyl ketene acetals and aldehydes. *Importantly, this provides a stereocomplementary route to β-lactones as it delivers cis-1,2-disubstituted β-lactones in contrast to the use of $ZnCl_2$ as Lewis acid* (Scheme 1*).* We have also found that by simply warming the reaction to 0

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[1] For reviews including methods for the synthesis of racemic and optically active β-lactones, see: (a) Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441−449. (b) Pommier, A.; Pons, J.-M. *Synthesis* **1995**, 729−744. (c) Lowe, C.; Vederas, J. C. *Org. Prep. Proc. Int.* **1995**, *27*, 305−346. (d) Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403−6434. For some related and complementary methods for the stereoselective synthesis of β-lactones, see: (e) Danheiser, R. L.; Nowick, J. S.; Lee, J. H.; Miller, R. F.; Huboux, A. H. *Org. Synth.* **1996**, *73*, 61−72. (f) Danheiser, R. L.; Lee, T. W.; Menichincheri, M.; Brunelli, S.; Nishiuchi, M. *Synlett* **1997**, 469−470. (g) Wedler, C.; Schick, H. *Org. Synth.* **1998**, *75*, 116−123 and references cited.

[2] (a) Yang, H. W.; Romo, D. *J. Org. Chem.* **1997**, *38*, 44−5. (b) Yang, H. W.; Zhao, C. X.; Romo, D. *Tetrahedron* **1997**, *53*, 16471−16488.

[3] (a) Romo, D.; Harrison, P. H. M.; Jenkins, S. I.; Riddoch, R. W.; Park, K.; Yang, H. W.; Zhao, C.; Wright, G. D. *Bioorg. Med. Chem.* **1998**, *6*, 1255−1272. (b) Dollinger, L. M.; Howell, A. R. *J. Org. Chem.* **1998**, *63*, 6782−6783.

[4] Yang, H. W.; Romo, D. *J. Org. Chem.* **1998**, *63*, 1344−1347.

[5] Zhao, C.; Romo, D., manuscript submitted.

[6] Masaki, M.; Matsunami, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3274−3279.

10.1021/ol990860o CCC: $18.00

Scheme 1. Stereocomplementary Synthesis of β-Lactones by Use of $ZnCl_2$ or $SnCl_4$

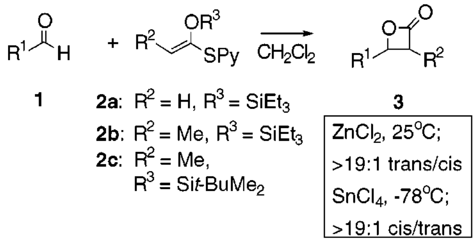


Table 1. Synthesis of 1,2-Disubstituted and Monosubstituted β-Lactones **3** via the $SnCl_4$-Promoted Reaction of Aldehydes **1** and Ketene Acetals **2**

entry[a]	β-lactone	R^1	R^2	*cis*/*trans* ratio[b]	yield, %[c,d]
1	**3a**	$Ph(CH_2)_2$	Me	>19:1	62
2	**3b**	$Ph(CH_2)_2$	H		32 (66)
3	**3c**	*p*-NO_2Ph	Me	>19:1	66
4	**3d**	$CH_3(CH_2)_6$	Me	>19:1	64
5	**3e**	cyclo-C_6H_{11}	Me	2.3:1	9
6	**3f**	cyclo-C_6H_{11}	H		40 (52)
7	**3g**	*t*-Bu	Me	<1:19	5[e]
8	**3h**	(*S*)-$CH_3CH(OTBS)CH_2$	Me	>19:1[f]	81

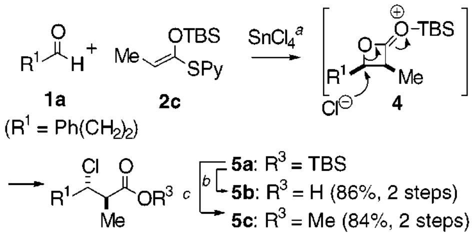
[a] Ketene acetal **2b** was employed in all entries except 2 and 6 for which **2a** was employed. [b] Estimated by analysis of crude reaction mixtures by 300 MHz ^{1}H NMR. In most cases, the *trans* isomers were undetectable. [c] Yields refer to the isolated and purified (flash chromatography) major diastereomer. Starting aldehyde accounts for the mass balance. [d] Yields given in parentheses are those obtained using $ZnCl_2$ (see ref 2b). [e] Estimated by analysis of the crude reaction mixture by 300 MHz ^{1}H NMR. [f] The relative stereoselectivity was 3.3:1 (GC). The stereochemistry (*syn*/*anti*) of the major diastereomer has not been determined.

°C, diastereomerically pure β-chloro carboxylic acids can be obtained. A tetrahydrofuran could also be obtained when 4-*tert*-butyldimethylsiloxybutanal is employed as substrate. To the best of our knowledge, there are no general, highly diastereoselective methods for the synthesis of *cis*-1,2-dialkyl-substituted β-lactones. The [2 + 2] cycloaddition of silylketenes and aldehydes promoted by bulky Lewis acids provides α-trialkysilyl-β-alkyl β-lactones with high cis selectivity;[7] however, subsequent alkylative desilylation delivers the thermodynamically preferred *trans*-dialkyl-substituted β-lactone.[8]

Initially, only low yields of β-lactone were obtained (10−30%) using the conditions we had previously employed for the $ZnCl_2$-mediated TMAL reaction with the exception of temperature (−78 vs 25 °C).[2] After some experimentation, we determined that the best results were obtained by slow addition of $SnCl_4$ to a mixture of the ketene acetal and aldehyde. In a typical experiment, a CH_2Cl_2 solution of $SnCl_4$ (1 M, 1.2 equiv) was added via syringe pump over a period of ~1 h to a cooled (−78 °C) CH_2Cl_2 solution of the aldehyde (1.0 equiv, ~0.2 M in CH_2Cl_2) and thiopyridylketene acetal (1.2 equiv). After stirring for 2 h, the reaction was quenched at −78 °C and filtered through Celite, and the organics were separated and dried. Direct treatment of the crude reaction mixture with $CuBr_2$-facilitated removal of the thiopyridyl ester byproduct by conversion to the carboxylic acid.[9] In this way, several *cis*-1,2-disubstituted β-lactones were prepared (Table 1) including a chiral β-lactone (entry 8). In most cases, very high cis diastereoselectivity was observed with exceptions being cyclohexanecarboxaldehyde which gave only a 2.3:1 ratio of *cis*/*trans* isomers (entry 5) and pivaldehyde which gave exclusively the *trans*-β-lactone (entry 7). Furthermore, α-substitution of the aldehyde also leads to a dramatic decrease in the yield of β-lactone as previously observed in the $ZnCl_2$-mediated TMAL reaction.[2] As in the $ZnCl_2$-promoted TMAL reaction, unreacted aldehyde accounted for the majority of the material balance, and benzaldehyde and anisaldehyde were found to be unreactive. In contrast to the $ZnCl_2$-mediated TMAL reaction, lower yields were obtained with acetate ketene acetal **2a** compared to propionate ketene acetal **2b** and this is due in part to the generation of the corresponding thiopyridyl silyl acetal derived from the aldehyde substrate.

If the temperature of the reaction after complete addition of $SnCl_4$ was allowed to rise above −78 °C, varying amounts of β-chloro silyl esters (i.e., **5a**) were produced. Subsequently, we found that if the TBS−ketene acetal **2c** was employed and the reaction was allowed to slowly warm to 0 °C after complete addition of $SnCl_4$, the β-chlorosilyl ester **5a** could be obtained in high yield (Scheme 2).[10] In practice, the unstable silyl ester **5a** was not isolated but rather directly treated with a basic methanol solution to deliver the crystalline β-chloro carboxylic acid **5b** or subjected to Fischer esterification to deliver the β-chloro methyl ester **5c**.

Scheme 2. Diastereoseletive Synthesis of β-Chloro Carboxylic Acid Derivatives from Hydrocinnamaldehyde and Thiopyridyl Ketene Acetals[a]



[a] (a) CH_2Cl_2, −78 → 0 °C; (b) 10% aqueous K_2CO_3, MeOH, THF, 25 °C; (c) catalytic H_2SO_4, MeOH, reflux.

We currently favor a mechanism for formation of this product that proceeds through the silylated β-lactone inter-

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[7] Concepcion, A. B.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1995**, *51*, 4011−4020.

[8] (a) Mead, K. T.; Yang, H. L. *Tetrahedron Lett.* **1989**, *30*, 6829−6832. (b) Mead, K. T.; Park, M. *J. Org. Chem.* **1992**, *57*, 2511−2514.

[9] Kim, S.; Lee, J. I. *J. Org. Chem.* **1984**, *49*, 1712−1716.

[10] The cleavage of β-lactones to β-chloro and β-bromo carboxylic acids is known, see: (a) Pu, Y.; Martin, F. M.; Vederas, J. C. *J. Org. Chem.* **1991**, *56*, 1280−1283. (b) Labrouillere, M.; Le Roux, C.; Oussaid, A.; Gaspard-Iloughmane, H.; Dubac, J. *Bull. Soc. Chim. Fr.* **1995**, *132*, 522−530. (c) Kricheldorf, H. R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 689−690.

mediate **4** in analogy to the same intermediate proposed in the $ZnCl_2$-mediated reaction.[5] This mechanism is supported by the generation of the silyl ester rather than the carboxylic acid, the fact that use of the TBS−ketene acetal leads to higher yields of β-chloro silyl esters,[11] and the high diastereoselectivity observed for this product. The fact that this reaction proceeds with complete inversion of configuration, with respect to the initially formed *cis*-β-lactone, lends further support for this mechanism. The stereochemistry of β-chloro acid **5b** was verified by single-crystal X-ray analysis (Figure 1).

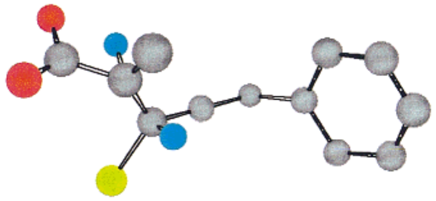
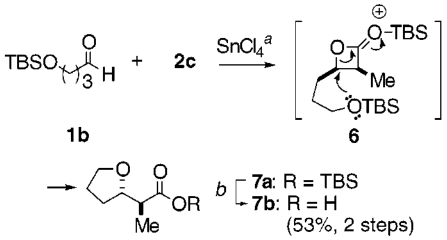


Figure 1. Chem3D representation of the single-crystal X-ray structure of β-chloro carboxylic acid **5b** (hydrogen atoms are omitted for clarity except at stereogenic centers).

Tetrahydrofuran silyl ester **7a** was obtained when silyl ether-substituted aldehyde **1b** was employed and the reaction was allowed to warm to −45 °C (Scheme 3).[12] This product was also more easily isolated after conversion to carboxylic acid **7b** (53% yield, unoptimized). Once again, high diastereoselectivity (>19:1, 300 MHz ^{1}H NMR) is observed for this product. The stereochemical outcome (anti as depicted) is again consistent with an initially formed *cis*-β-lactone undergoing inversion of configuration at the β-carbon during cyclization through the intermediate silylated β-lactone **6**. In this case, the stereochemical outcome was confirmed by comparison to known carboxylic acid **7b**.[13]

Scheme 3. Diastereoselective Synthesis of a Tetrahydrofuran from an Aldehyde and a Thiopyridyl Ketene Acetal[a]



[a] (a) CH_2Cl_2, $-78 \rightarrow -45$ °C; (b) 10% aqueous K_2CO_3, MeOH, THF, 25 °C.

While it is tempting to suggest that the present reaction proceeds via a TMAL mechanism, several observations are inconsistent with those made in the $ZnCl_2$-mediated TMAL reaction. Another possible mechanism is a [2 + 2] cycloaddition involving an in situ generated, silylated ketene. This could potentially be derived from the silylketene acetal by $SnCl_4$-assisted loss of the thiopryidyl group. Further studies will be required to distinguish between the possible mechanisms.

In summary, an $SnCl_4$-mediated reaction between aldehydes and a thiopyridyl ketene acetal has been discovered that provides a highly diastereoselective entry to *cis*-1,2-disubstituted β-lactones. A limitation is that α-substitution of the aldehyde leads to reduced yields and reduced or, in some cases, reversed diastereoselectivity. This method provides a stereocomplementary approach to β-lactones since the $ZnCl_2$-mediated TMAL reaction allows access to *trans*-1,2-dialkyl-substituted β-lactones. By raising the reaction temperature to 0 °C and using TBS rather than TES−ketene acetals, a subsequent in situ reaction ensues leading to β-chloro carboxylic acids. This transformation provides a concise, stereoselective route to β-chloro carboxylic acids, a class of compounds for which there are only few approaches.[14] In addition, the use of a silyl ether substituted aldehyde substrate led to the formation of a tetrahydrofuran product. We are searching for other suitable nucleophiles that are capable of trapping the proposed silylated β-lactone intermediate (i.e., **4**).

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Supporting Information Available: Experimental procedures and characterization data for all new compounds; ^{1}H and ^{13}C NMR spectra for compounds **3a**,**d**,**e**,**h**, **5b**,**c**, and **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added in Proof: A Lewis acid-catalyzed [2 + 2] cycloaddition approach to *cis*-1,2-dialkyl-substituted β-lactones (92−94% de) has recently appeared (ref 15).

OL990860O

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[11] Use of the TES−ketene acetal **2b** leads to greater amounts of β-lactone at the expense of β-chloro silyl ester. This is consistent with competitive attack of chloride ion at the β-carbon rather than silicon since a bulkier silyl group should divert attack to the β-carbon.

[12] For related stepwise routes to tetrahydrofurans, see: White, D.; Zemribo, R.; Mead, K. T. *Tetrahedron Lett.* **1997**, *38*, 2223−2226 and references cited.

[13] (a) Mikami, K.; Shimizu, M. *Tetrahedron* **1996**, *52*, 7287−7296. (b) See ref 8a.

[14] For some approaches to β-chloro carboxylic acids, see: (a) Le Roux, C.; Gaspard-Iloughmane, H.; Dubac, J. *J. Org. Chem.* **1994**, *59*, 2238−2240 and references cited. (b) Bellassoued, M.; Dubois, J.-E.; Bertounesque, E. *Tetrahedron Lett.* **1988**, *29*, 1275−1278. (c) Also see ref 10.

[15] Nelson, S. G.; Wan, Z.; Peelen, T. J.; Spencer, K. L. *Tetrahedron Lett.* **1999**, *40*, 6535−6539.