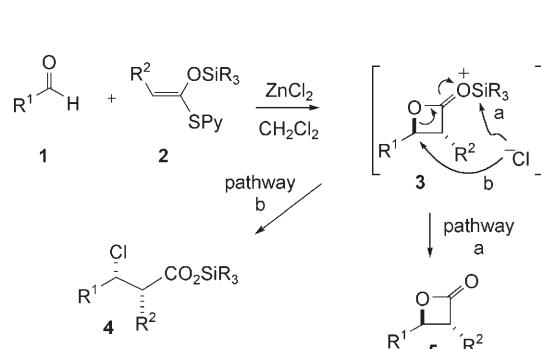


Highly Diastereoselective, Tandem, Three-Component Synthesis of Tetrahydrofurans from Ketoaldehydes via Silylated β -Lactone Intermediates**

T. Andrew Mitchell, Cunxiang Zhao, and Daniel Romo*

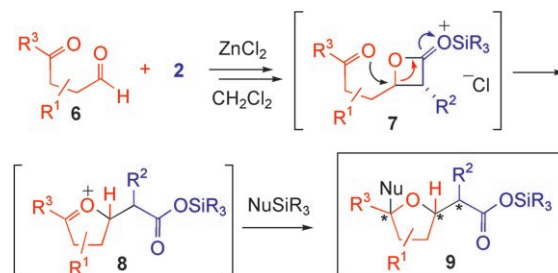
In memory of Albert I. Meyers

Processes that form multiple bonds and stereocenters in a single reaction, without the isolation of intermediates, are known as tandem, domino, multicomponent, or cascade reactions.^[1] They are powerful complexity-building reactions. We have developed stereoselective routes to both *cis*^[2] and *trans*^[3] β -lactones **5** through tandem Mukaiyama aldol-lactonization (TMAL) processes^[4] between thiopyridyl ketene acetal **2** and aldehyde **1** (Scheme 1, pathway a). This methodology has been utilized in total syntheses of (–)-panclicin D,^[5] orlistat and its congeners,^[6] okinonellins,^[7] brefeldin A,^[8] and belactosin C.^[9] In the course of these studies, we identified several by-products (e.g. β -chlorosilyl ester **4**; Scheme 1, pathway b) that led us to propose the silylated β -lactone intermediate **3** in the TMAL process. Thus we considered methods for intercepting these intermediates to enable the study of useful complexity-building processes.



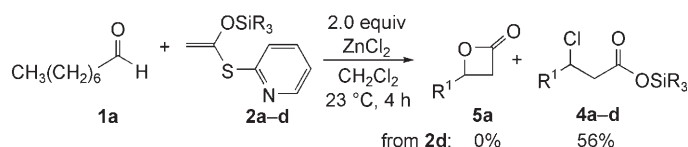
Scheme 1. Synthesis of β -lactone **5** (pathway a) or β -chloro silyl ester **4** (pathway b) via a postulated silylated β -lactone intermediate **3** in the tandem Mukaiyama aldol-lactonization process. Py = 2-pyridyl.

Mead and Pillai have reported Lewis acid promoted reductive cyclizations of simple keto- β -lactones for tetrahydrofuran (THF) synthesis. This approach suggested the possibility of utilizing aldehyde substrates bearing pendant ketones that could undergo reductive cyclization in the TMAL process (Scheme 2).^[10] The THF motif is commonly found in natural products, and while several approaches toward these heterocycles exist, many routes rely on C–O bond formation of relatively complex substrates or proceed through oxocarbenium ions derived from *O*-glycosides.^[11] Herein we describe the development of a tandem, three-component synthesis of THFs **9** from γ -ketoaldehydes **6**, thiopyridyl ketene acetals **2**, and silyl nucleophiles in which up to two C–C bonds, one C–O bond, and three new stereocenters are generated.



Scheme 2. Proposed three-component synthesis of tetrahydrofuran **9** from ketoaldehyde **6**, thiopyridyl ketene acetal **2**, and a silyl nucleophile via a postulated silylated β -lactone intermediate **7**.

Initially, we sought further evidence for the postulated intermediacy of the silylated β -lactone **3** in the TMAL process. Previously we reported a correlation between the size of the silyl group of ketene acetals **2a–c** and product distribution leading to either β -lactone **5a–c** (20–66%) or β -chlorosilyl esters **4a–c** (5–40%; Scheme 3).^[5] However, in



Scheme 3. Effect of varying the silyl group of ketene acetals **2a–d** on the product distribution of the TMAL process with octanal (**1a**). SiR₃: a: TES (triethylsilyl); b: TBS (*tert*-butyldimethylsilyl); c: TIPS (triisopropylsilyl); d: TBDPS (*tert*-butyldiphenylsilyl), R¹ = CH₃(CH₂)₆.

[*] Dr. T. A. Mitchell, Dr. C. Zhao, Prof. D. Romo
Department of Chemistry, Texas A&M University
P.O. Box 30012, College Station
TX 77842-3012 (USA)
Fax: (+1) 979-862-4880
E-mail: romo@tamu.edu
Homepage: <http://www.chem.tamu.edu/rgroup/romo>

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

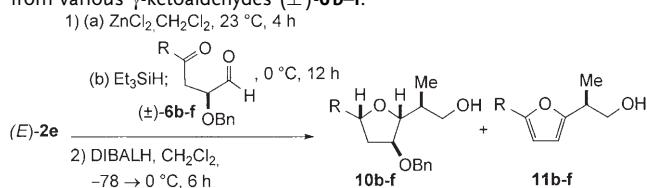
some cases the silyl esters **4a–c** were accompanied by the corresponding acids, thus raising the possibility of subsequent formation of silyl esters by a silylating agent generated in situ.^[10b] Use of the more robust TBDPS ketene acetal **2d** gave the β -chloro silyl ester **4d** exclusively, which was isolated in 56% yield with no acid detected by NMR analysis of the crude product. This result provides strong evidence for the silylated β -lactone intermediate **3** (Scheme 1).

With this result in hand, we began the study of the proposed tandem Mukaiyama aldol-lactonization/reductive cyclization process (called “the tandem process” throughout) by employing the more readily prepared TIPS (versus TBDPS) ketene acetal (*E*)-**2e** (*E/Z* 4:1) and racemic γ -ketoaldehyde ($\pm$)-**6a** (see the reaction in Table 1). The latter substrate was chosen to ensure high chelation-controlled selectivity in the initial Mukaiyama aldol reaction^[12] and high facial selectivity in the subsequent oxocarbenium reduction as predicted by the model of Woerpel and co-workers.^[13] The substrates, ketoaldehydes ($\pm$)-**6**, were prepared by oxidation of the corresponding diol.^[14] Building on our previous extensive studies of the TMAL process, we utilized precomplexation of the ketene acetal (*E*)-**2e** with ZnCl_2 , which modulates the Lewis acidity and increases the rate of the TMAL process.^[15] Direct reduction of the crude silyl ester (cf. **9**, Scheme 2) to the primary alcohol with DIBALH simplified the purification. Regardless of the amount of Et_3SiH used, our initial attempts unexpectedly delivered furan **11a** as the major product (Table 1, entries 1–4). Although initial yields of THF **10a** were unsatisfactory, only one diastereomer was observed as anticipated, based on chelation-controlled selectivity in the initial aldol/ $\text{S}_{\text{N}}2$ inversion during β -lactone ring opening, and the Woerpel model for oxocarbenium reduction. The relative configuration of **10a** was confirmed by X-ray analysis of the corresponding *para*-bromobenzoate.^[16] Initial reaction at 0 °C with warming to ambient temperature improved the ratio of **10a** to **11a**; however, the furan was still the major product (Table 1, entry 5). Increasing the amount of Lewis acid to 4.0 equivalents ultimately delivered **10a** as the major product in

substantially improved yield (42%; Table 1, entry 6). A large excess of ZnCl_2 and Et_3SiH led to **10a** with a greatly improved ratio to **11a** but in a slightly decreased yield (38%; Table 1, entry 7). Finally, optimal conditions were achieved at 0 °C using 4.0 equivalents of ZnCl_2 and 50 equivalents of Et_3SiH to deliver **10a** which was isolated in 54% yield (Table 1, entry 8). This overall yield corresponds to approximately 82% yield per step (over 4 steps), and includes subsequent reduction of the initially formed silyl ester (cf. **9**, Scheme 2).

Several substituted racemic γ -ketoaldehydes ($\pm$)-**6b–f** were also investigated and all gave similar overall yields for **10b–f** as well as high diastereoselectivity (Table 2).

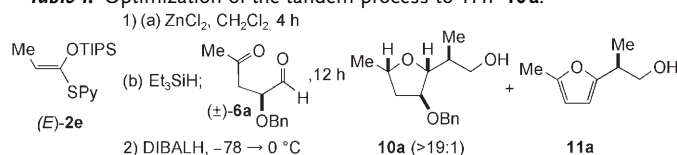
Table 2: Synthesis of tetrahydrofurans **10b–f** by the tandem process from various γ -ketoaldehydes ($\pm$)-**6b–f**.



Entry	Ketoaldehyde	Major adduct	10/11 ^[a]	Yield [%] ^[b]	d.r. ^[a]
1	($\pm$)- 6b		1.3:1	42	> 19:1
2	($\pm$)- 6c		2.3:1	52	> 19:1
3	($\pm$)- 6d		3.0:1	49	> 19:1
4	($\pm$)- 6e		3.5:1	54	> 19:1
5	($\pm$)- 6f		2.2:1	49 ^[c]	> 19:1

[a] Determined by ^1H NMR spectroscopic analysis (300 MHz) of the crude product. [b] Yield of isolated product (over 2 steps). [c] The reaction mixture for the DIBALH reduction was slowly warmed from $-78 \rightarrow -30^\circ\text{C}$ over 6 h to prevent cleavage of the PMB group. PMB = *para*-methoxybenzyl.

Table 1: Optimization of the tandem process to THF **10a**.

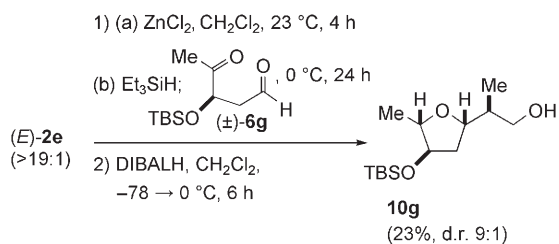


Entry	ZnCl_2 [equiv]	(<i>E</i>)- 2e [equiv]	Et_3SiH [equiv]	<i>T</i> [°C]	10a/11a ^[a] (% yield 10a) ^[b]
1	2.0	2.0	0.0	23	only 11a (0)
2	2.0	2.0	2.0	23	1.0:3.5 (11)
3	2.0	2.0	10.0	23	1.0:3.5 (9)
4	2.0	2.0	50.0	23	1.0:3.5 (10)
5	2.0	2.0	10.0	0 $\rightarrow$ 23	1.0:2.0 (24)
6	4.0	1.2	10.0	0 $\rightarrow$ 23	2.0:1.0 (42)
7	8.0	1.2	100.0	0 $\rightarrow$ 23	9.0:1.0 (38)
8	4.0	1.2	50.0	0	6.2:1.0 (54)

[a] Determined by ^1H NMR spectroscopic analysis (300 MHz) of the crude product. [b] Yield of isolated product (over 2 steps). Bn = benzyl, DIBALH = diisobutylaluminum hydride.

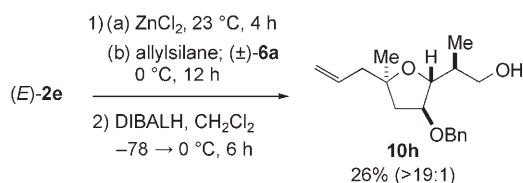
The tandem process was also successful with β -oxygenated ketoaldehydes (for example **6g**) and ketene acetal (*E*)-**2e** (*E/Z* > 19:1) and gave good diastereoselectivity (d.r. 9:1) for the desired THF **10g**, albeit with a reduced yield (Scheme 4). The stereochemical outcome of the initial Mukaiyama aldol reaction was consistent with the model proposed by Evans et al.^[17] for additions to β -silyloxy aldehydes, and was as observed in previous TMAL reactions.^[5,6]

Pleasingly, allylsilane could also be utilized as the nucleophilic component to deliver **10h** as a single diastereo-



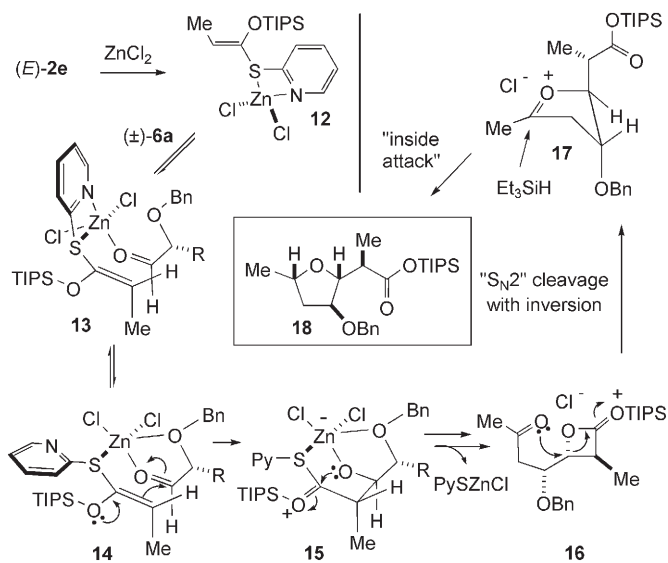
Scheme 4. The tandem process with a β -silyloxy aldehyde ($\pm$)-**6g**.

mer, accompanied by increased quantities of **11a** (Scheme 5). Importantly, an additional C–C bond is constructed with excellent stereocontrol of the resulting quaternary center.



Scheme 5. Use of allyltrimethylsilane as the nucleophile leading to formation of a quaternary carbon in the tandem process.

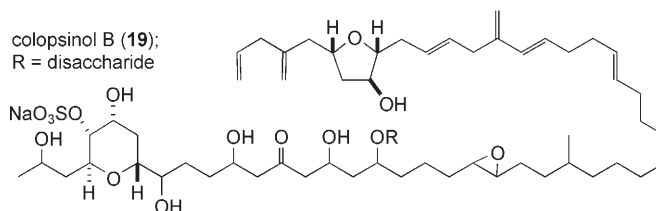
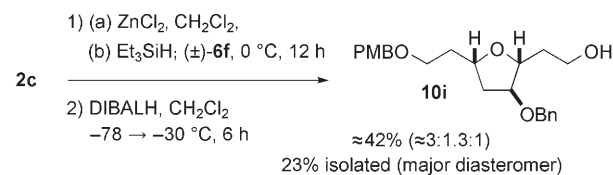
A mechanistic pathway that rationalizes the stereochemical outcome of this tandem process is proposed based on the current experimental evidence for a chelation-controlled TMAL process,^[12,15] as well as the Woerpel model for oxocarbenium reductions^[13] (Scheme 6). Precoordination of ZnCl_2 and ketene acetal **2e** leads to the tetrahedral complex **12**.^[18] Initial monodentate coordination with the α -benzyloxy aldehyde ($\pm$)-**6a** leads to a trigonal-bipyramidal complex **13**,^[19] which involves bidentate chelation of zinc(II) with the thiopyridyl group.^[20] A highly ordered, boatlike transition state **14** is generated by ligand rearrangement and leads to bidentate coordination of the aldehyde ($\pm$)-**6a**.



Scheme 6. Mechanistic proposal for the tandem Mukaiyama aldol-lactonization/reductive cyclization process. $\text{R} = \text{CH}_2\text{C}(\text{O})\text{CH}_3$.

Subsequent chelation-controlled addition leads to the observed high diastereoselectivity in the aldol step providing silylated β -lactone **16**. Subsequent alkyl C–O cleavage with inversion delivers **17**. Oxocarbenium **17** adopts the stereo-electronically favorable envelope conformation with the benzyloxy substituent in a pseudoaxial orientation and reduction occurs from the “inside” of the envelope, as predicted by the Woerpel model,^[13] to finally give silyl ester **18**.

To highlight the utility of this methodology, we synthesized the THF fragment of colopsinol B (**19**) (Scheme 7).^[21] Thus, α -benzyloxy- γ -ketoaldehyde ($\pm$)-**6f** was utilized, under typical conditions with acetate ketene acetal **2c**, to deliver the



Scheme 7. Synthesis of the THF fragment **10i** of colopsinol B (**19**) by employing the tandem process.

alcohol **10i** as a mixture of diastereomers ($\approx 3:1.3:1$, $\approx 42\%$). This outcome was expected because of the low diastereoselectivity in the initial aldol step. However, the major diastereomer could be readily separated and was isolated in 23% yield ($\approx 70\%$ per step over 4 steps). The configuration of **10i** was confirmed by coupling constant and nOe analysis, and these data also correlated well with that reported for the THF unit of colopsinol B (**19**).^[16]

In summary, we have developed a diastereoselective, three-component synthesis of substituted THF units that employ γ -ketoaldehydes, ketene acetals, and silyl nucleophiles and that proceeds through silylated β -lactone intermediates. The overall efficiency for α -benzyloxy- γ -ketoaldehydes is good, with typical yields in the range of 42 to 54%, which corresponds to $\approx 82\%$ yield per step for the tandem, three-component process and the subsequent reduction. The observed high diastereoselectivity and relative stereochemical induction are consistent with a boat transition state arrangement in the TMAL process, $\text{S}_{\text{N}}2$ opening of the intermediate β -lactone by the pendant ketone, and the Woerpel model for “inside attack” of five-membered oxocarbenium ions. The rapid assembly of a THF fragment of colopsinol B from simple starting materials demonstrates the utility of this methodology.

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