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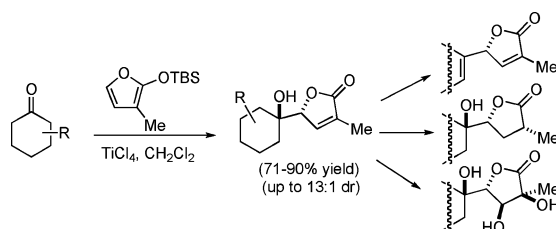
Ke Kong and Daniel Romo*

Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, Texas 77842-3012

romo@mail.chem.tamu.edu

Received March 3, 2006

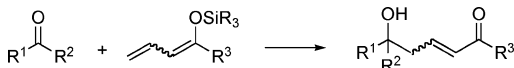
ABSTRACT



Vinylogous Mukaiyama aldol reactions employing silyloxyfurans and substituted cyclic ketones are described. These annulations proceed with moderate to good diastereoselectivity. The potential application of this process to the synthesis of butenolide and γ -lactone containing natural products was demonstrated by further transformations of the addition products.

The Mukaiyama aldol reaction is one of the most important carbon–carbon bond forming processes in an organic chemist's repertoire. The vinylogous version of this process is an important extension and provides a concise entry to the δ -hydroxy- α,β -unsaturated carbonyl motif (Scheme 1).¹

Scheme 1. Vinylogous Mukaiyama Aldol Reaction



Furthermore, the addition of dienolsilanes to carbonyls or imines has been widely used in organic synthesis.¹ Considering the significance of this process, it is surprising that there are only scant reports of dienolsilane additions to nonsymmetric ketones.² This is in sharp contrast with aldehydes which have been extensively explored as substrates for the

vinylogous Mukaiyama aldol addition.^{1a} Presumably, low reactivity and low diastereoselectivity have hampered the use of ketones as electrophiles.³ Because ketones are less reactive than aldehydes toward nucleophilic addition, highly electrophilic ketones, such as pyruvate esters, have been used for vinylogous Mukaiyama aldol reactions.^{2b–d} Because of the greater difficulty of differentiating diastereotopic faces of ketones compared to aldehydes, the addition of silyloxyfurans to aliphatic ketones proceeded with only moderate diastereoselectivity in the absence of external chiral ligands.^{2a} One solution to overcome this difficulty was the use of tetrionic acid derived dianions.⁴ In this case, a chelation-controlled process allowed the addition to proceed with good diastereoselectivity.

(2) (a) Jefford, C. W.; Jaggi, D.; Bernardinelli, G.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, 28, 4041. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, 121, 686. (c) Naito, S.; Escobar, M.; Kym, P. R.; Liars, S.; Martin, S. F. *J. Org. Chem.* **2002**, 67, 4200. (d) Le, J. C.-D.; Pagenkopf, B. L. *Org. Lett.* **2004**, 6, 4097.

(3) (a) For a discussion of the low reactivity of ketones as electrophiles, see: Betancort, J. M.; Garcia, C.; Walsh, P. J. *Synlett* **2004**, 749. (b) In a recent review of allylmetal additions to carbonyl compounds, only two pages were dedicated to ketones. See: Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, 103, 2763.

(1) For recent reviews, see: (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, 100, 1929. (b) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, 44, 4682. (c) Kalesse, M. *Top. Curr. Chem.* **2005**, 244, 43.

In connection with our studies toward gymnodimine (**5**),⁵ we were attracted to the possibility of directly appending a butenolide to a cyclic ketone by a vinylogous Mukaiyama aldol reaction of a silyloxyfuran (Figure 1, highlighted in

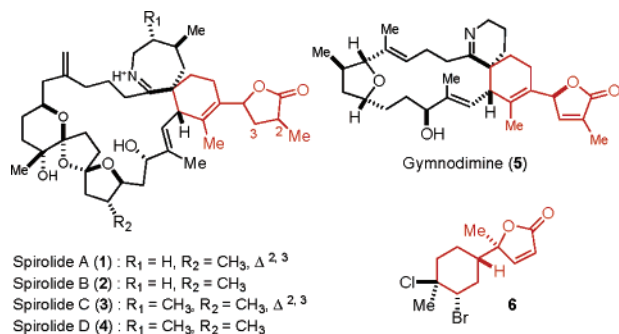


Figure 1. Butenolide/ γ -lactone (highlighted in red) containing natural products.

red). We reasoned that diastereoselectivity might be achieved with *unsymmetric cyclic ketones* because of the conformational rigidity of such substrates leading to better facial differentiation with respect to both the ketone and the dienolsilane nucleophile. This process would provide a concise strategy for appending butenolides and γ -lactones in natural products possessing such arrays, such as the spirolides **1–4**,⁶ gymnodimine (**5**),⁷ and the unnamed marine metabolite **6**.⁸ Herein, we disclose our studies of silyloxyfuran additions to substituted cyclic ketones that proceed with moderate to high diastereoselectivity and subsequent transformations of the butenolides.

Guided by the structure of gymnodimine, we chose 2-methylcyclohexanone (**7a**) and 3-methyl-2-(*tert*-butyldimethyl)silyloxy furan (**8a**)⁹ as model substrates. We were pleased to find that vinylogous Mukaiyama aldol addition afforded the δ -silyloxy and δ -hydroxy butenolides **9a/9b** in good yield and diastereoselectivity in the presence of a variety of Lewis acids (Table 1). The presence of alcohol product **9b** suggests that silylation of the aldolate intermediate is slow compared to addition, proceeding either by inter- or intramolecular silicon transfer. Thus, following initial metal-catalyzed addition, subsequent silicon-catalyzed addition may become the predominant reaction pathway as previously reported for Mukaiyama aldol additions (Table 1, entries 1–3).¹⁰ In most cases, good diastereoselectivity was observed leading to only two adducts out of four possible

Table 1. Vinylogous Mukaiyama Aldol Reaction of Ketone **7a** with Silyloxy Furan **8a**: Effect of Lewis Acids

entry	conditions	% yield 9a (9b) ^a	dr ^b
1	BF ₃ ·OEt ₂ , –78 °C	67 (17)	10:1
2	TiCl ₄ , –78 °C	70 (9)	9:1
3	SnCl ₄ , –78 °C	58 (13)	9:1
4	ZnBr ₂ , –20 °C ^c	(~20)	2:2:1:1
5	TMSOTf, –78 °C	16 (69)	11:1

^a Refers to isolated, purified yields. ^b Determined on the crude reaction mixture by ¹H NMR (500 MHz) integration of H_a for both **9a** and **9b**. ^c 1.0 equiv of Lewis acid was employed.

stereoisomers for all Lewis acids screened. An exception was ZnBr₂ which led to poor diastereoselectivity and conversion (Table 1, entry 4). The relative stereochemistry of the major diastereomer **9b** and minor diastereomer *epi*-**9b** was unambiguously established by X-ray crystallographic analysis (Figure 2). Apparently, during this reaction, the silyloxyfuran

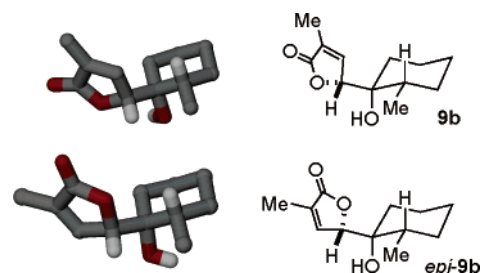


Figure 2. X-ray structures (POV chem rendering) of δ -hydroxy butenolide **9b** and *epi*-**9b**.

8a approaches the cyclic ketone **7a** in a facially selective manner to avoid 1,3-diaxial interactions. Consistent with the Jefford and Brown model,¹¹ a Diels–Alder reaction-like transition arrangement between the silyloxy furan and the ketone (*si/si* face, **A**, Figure 3) leads to the syn adducts **9a/9b**, and the *si/re* face approach (**B**) is less favorable because of interactions of the α -methyl substituent of the ketone **7a** with the C4 hydrogen of the silyloxy furan **8a**.

The scope of the reaction was explored by use of other ketone substrates. Although TMSOTf gave the best yield and diastereoselectivity on the model substrate, further experiments indicated that TiCl₄ had greater substrate generality

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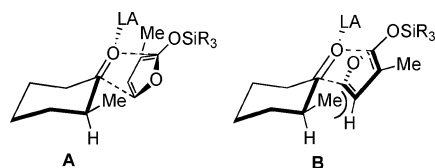


Figure 3. Models rationalizing the stereochemical outcome of vinylogous Mukaiyama aldol addition between 2-methylcyclohexanone (**7a**) and silyloxy furan **8a**.

and promoted the addition reaction even at $-78\text{ }^{\circ}\text{C}$. Moreover, Ti(IV) complexes constitute a well-studied platform for asymmetric processes,^{1b} thus providing impetus for utilizing this Lewis acid in subsequent studies. Addition proceeded with various α -substituted cyclohexanones in good yields with moderate to high diastereoselectivity (Table 2, entries 1–5). A pendant ester was tolerated (Table 2, entry 2), and bicyclic ketones, such as norcamphor and *trans*-decalone, also provided good diastereoselectivities as expected (Table 2, entries 3 and 4). The relative stereochemistry of the major adducts **9e** and **9f** was confirmed by X-ray crystallography (Figure 4). However, the addition reaction was susceptible to steric factors, as evidenced by the finding that although norcamphor reacted efficiently (Table 2, entry 3) camphor was totally inert even at elevated temperatures for extended times (not shown). From these examples, it appears that the α -substituent is indeed responsible for high diastereoselectivity because 3-methyl cyclohexanone and 4-*tert*-butylcyclohexanone provided good yields but poor diastereoselectivities (Table 2, entries 6 and 7). This is easily understood because the lack of the unfavorable interaction with the α -methyl group reduces the energy difference of these two diastereomeric transition-state arrangements (Figure 3, **A** vs **B**). The conformational flexibility and the absence of prominent 1,3-diaxial interactions likely account for the poor diastereoselectivity leading to three diastereomers when 2-methyl cyclopentanone was used as the substrate (Table 2, entry 8).

The silyloxyfuran partner could also be varied (Table 3). Unsubstituted silyloxyfuran **8b** and 4-methylsilyloxy furan **8c** both reacted to give the addition adducts in good yield and diastereoselectivity (Table 3, entries 1 and 2). The relative stereochemistry of the major diastereomers of adducts **9k** and **9l** was verified by X-ray crystallography.¹² The fact that the reaction of 4-methylsilyloxy furan **8c** provided only one detectable diastereomer further validated the stereochemical models described previously (Figure 3). In this case, unfavorable steric interactions as in **B** (Figure 3) would be more prominent when a vinylic hydrogen is substituted by a methyl group. Interestingly, the addition of 5-methylsilyloxy furan **8d** to ketone **7a** occurred at the α -position leading to adduct **9m** (Table 3, entry 3). Because with silyloxyfuran substrates γ -addition is favored electronically in Lewis acid promoted vinylogous Mukaiyama aldol additions,^{1b} steric effects must be responsible for this reversal of regioselectivity.¹³

Table 2. Substrate Scope of the Vinylogous Mukaiyama Aldol Addition of Silyloxyfuran **8a** and Various Cyclic Ketones

entry	Lewis acid	product	% yield ^d	dr ^e
1 ^a	TiCl ₄ (3 equiv)		14 (63)	10:1
2 ^a	TiCl ₄ (3 equiv)		48 (28)	13:1
3 ^b	TiCl ₄ (3 equiv)		56 (34)	5:1
4 ^b	TiCl ₄ (3 equiv)		50 (31)	9:1
5 ^a	TiCl ₄ (3 equiv)		34 (42)	10:1
6 ^c	TMSOTf (0.4 equiv)		33 (66)	1.5:1.5 :1:1
7 ^b	TMSOTf (0.4 equiv)		19 (70)	1.7:1
8 ^c	TiCl ₄ (0.4 equiv)		47 (7)	3.6:2.3 :1

^a The relative stereochemistry of the product is predicted by the Jefford and Brown (ref 11) model in analogy to **9a** (only the major diastereomer is depicted). ^b The relative stereochemistry of the major product was established by X-ray crystallographic analysis (see Figure 4). ^c The stereochemistry of the major adduct was not determined. ^d Refers to isolated, purified yields. Yields in parentheses refer to the nonsilylated adduct. ^e Determined on the crude reaction mixture by ¹H NMR (500 MHz) integration of H_a for combined silylated and nonsilylated adducts.

The presence of the alkene in δ -hydroxy butenolide adducts **9a**–**9m** allows for further functionalization to motifs related to those found in natural products (Figure 1). Hydrogenation of butenolide **9b** afforded γ -lactone **10** in excellent yield as a single diastereomer (Scheme 2). Dihydroxylation provided triol **11** with excellent diastereoselectivity. Dehydration using thionyl chloride/pyridine conditions¹⁴ led to cyclohexene **12** with moderate regioselectivity

(12) See Supporting Information for details.

(13) This reversal has been noted previously in additions to aldehydes. See: Redero, E.; Sandoval, C.; Bermejo, F. *Tetrahedron* **2001**, *57*, 9597. We thank a reviewer for bringing this work to our attention.

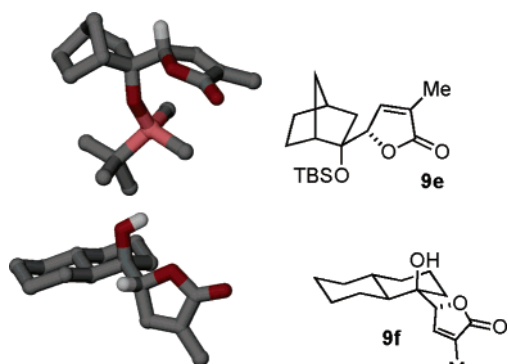


Figure 4. Stereochemical verification of the Mukaiyama aldol adducts **9e** and **9f** by X-ray analysis (POV chem rendering).

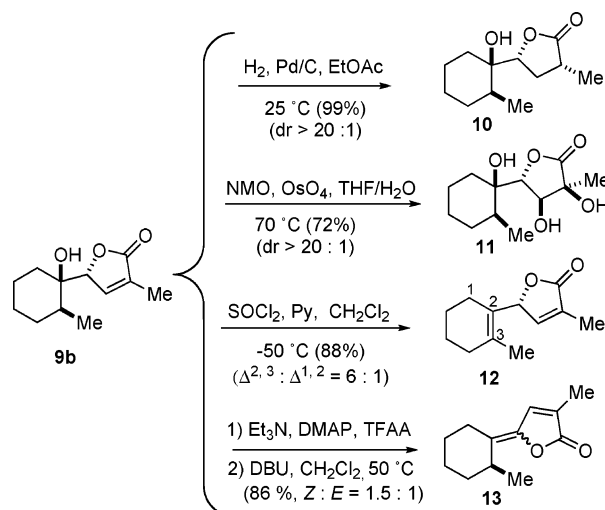
(6:1), the major isomer being a substructure of gymnodimine and spirolides A and C (Figure 1). Alternatively, treatment of the butenolide **9b** derived trifluoroacetate led to exocyclic elimination adduct **13** as a mixture of *E/Z* isomers. Stereo-

Table 3. Scope of the Mukaiyama Aldol Addition: Reaction of Various Silyloxyfurans **8b–d** with Ketone **7a**

entry	silyloxyfurans	% yield ^a	dr ^b
1		 9k : R' = TBS (64%) R' = H (6%)	10:1 ^c
2		 9l : R' = TIPS (66%) R' = H (30%)	>20:1 ^c
3		 9m (53%)	2:1

^a Refers to isolated, purified yields. ^b Determined on the crude reaction mixtures by ¹H NMR. ^c Relative stereochemistry of the major diastereomer was verified by X-ray analysis (see Supporting Information).

Scheme 2. Further Transformations of Butenolide **9b**



chemical assignments were made on the basis of nOe and literature precedent.¹²

In conclusion, efficient, diastereoselective, vinylogous Mukaiyama aldol additions of silyloxy furans to unsymmetrically substituted cyclic ketones are described. In general, 2-substituted cyclohexanones and bicyclic ketones provided good levels of diastereoselectivity. Poor diastereoselectivity was observed when cyclopentanone and 3- or 4-substituted cyclohexanones were employed as substrates. The butenolide adducts were transformed into motifs common to several natural products, thus this strategy provides a useful method for appending butenolides and γ -lactones onto cyclic ketones. Further studies of this process including application to the synthesis of gymnodimine are ongoing and will be reported in due course.

Acknowledgment. We thank the NIH (GM52964), the Welch Foundation (A-1280), TAMU Life Sciences Task Force, and Pfizer for support of these investigations. We thank Dr. Ziad Moussa for helpful discussions and Dr. Nattamai Bhuvanesh and Dr. Joseph Reibenspies (TAMU) for X-ray structural analyses.

Supporting Information Available: Experimental procedures and characterization data for compounds **9a–g**, **9i**, **9k–m**, and **10–13**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) For a related example, see: Kido, F.; Fujishita, T.; Tsutsumi, K.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1975**, 337.