JOC Article

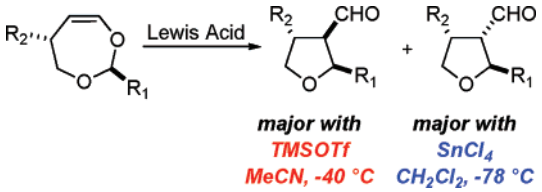
A Diastereoselective Ring Contraction of 1,3-Dioxepins to 2,3,4-Trisubstituted and Tetrasubstituted Tetrahydrofurans

Christopher G. Nasveschuk and Tomislav Rovis*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

rovis@lamar.colostate.edu

Received September 20, 2007



A modular and diastereoselective approach to 2,3,4-trisubstituted and tetrasubstituted tetrahydrofurans is reported. The use of dioxepins containing an embedded vinyl acetal functionality leads to a Lewis acid-mediated [1,3] ring contraction to afford tetrahydrofurans in good yield and excellent diastereoselectivity. The use of TMSOTf in MeCN leads to the 2,3-cis/3,4-trans diastereomer while $SnCl_4$ in CH_2Cl_2 provides the 2,3-trans/3,4-cis diastereomer. A variety of substituents are tolerated at each position. The presence of Lewis basic functionality under the $SnCl_4$ conditions alters the reaction favoring the diastereomer formed under the TMSOTf conditions. We present conclusive evidence that the products of each of these reactions are formed under kinetic control. We further provide stereochemical models consistent with each of these rearrangement reactions that account for the formation of the major diastereomer in each case.

Introduction

The transformation of a C−O bond to a C−C bond with control of configuration at the reactive carbon centers represents a significant challenge in synthesis. The Claisen rearrangement, a [3,3] rearrangement of allyl vinyl ethers, is one such strategy. It has been amply demonstrated that the use of chiral alcohol precursors in the Claisen and related rearrangements can be used to control stereocenters about the newly formed C−C bond via a stereochemical relay, taking advantage of the well-defined transition states inherent to this reaction. This strategy has been used to great effect in a variety of settings including the arena of complex molecule total synthesis.

In contrast, the use of this strategy in other rearrangement processes is less common. In particular, processes that occur stepwise rather than via concerted mechanisms have not been extensively illustrated to be susceptible to this stereochemical relay strategy. One example of the latter is the [1,3] O to C rearrangement of vinyl ethers, which can be initiated thermally or mediated by transition metals and Lewis acids.[1] Stimulated by our interest in expanding the repertoire of methods for use in the generation and control of C−C bonds and attendant stereochemistry, we initiated a program aimed at alleviating this deficiency. We were particularly intrigued by the use of Lewis acids in the process and the potential for absolute and relative control.

With this strategy in mind, our initial investigations were focused on the Ferrier-type rearrangement of vinyl acetals and we showed that solvent cage effects could be used to relay C−O stereochemistry to the newly formed C−C bond (eq 1).[2] The use of substituted enol ethers leads to the introduction of a second stereocenter in the process and we showed that in certain cases, useful levels of diastereoselectivity could be achieved (eq 2).[3] We later showed that allyl cations may be used as electrophile partners in this chemistry in spite of the competing [3,3] using a steric impediment to disfavor the Claisen (eq 3).[4] Alternately, the use of dihydrooxepins as substrates in this

(1) For some leading references of [1,3] rearrangements, see: (a) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455−1458. (b) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7559−7572. (c) Wang, S.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 5364−5371. (d) Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488−5489. For a recent review on the [1,3] rearrangement, see: Nasveschuk, C. G.; Rovis, T. *Org. Biomol. Chem.* **2008**, DOI: 10.1039/b714881j.

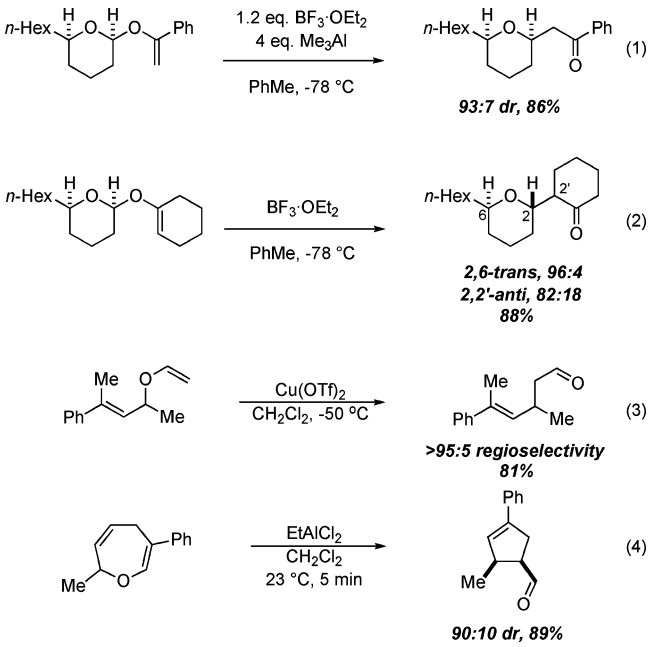
(2) (a) Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720−9721. (b) Zhang, Y.; Rovis, T. *Tetrahedron* **2003**, *59*, 8979.

(3) Frein, J. D.; Rovis, T. *Tetrahedron* **2006**, *62*, 4573−4583.

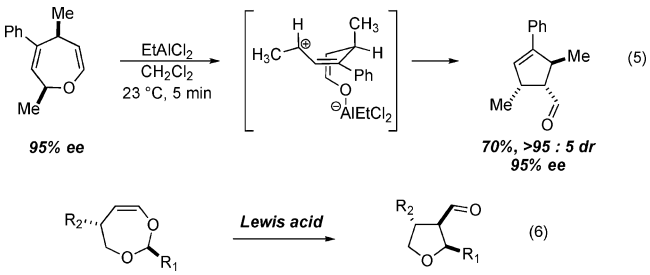
(4) Nasveschuk, C. G.; Rovis, T. *Org. Lett.* **2005**, *7*, 2173−2176.

10.1021/jo702071v CCC: $40.75
Published on Web 12/19/2007

reaction also leads to exclusive [1,3] rearrangement with good levels of diastereocontrol (eq 4).[5] Here, the [3,3] process generates a vinyl cyclopropane carboxaldehyde and thus is thermodynamically disfavored relative to the cyclopentene carboxaldehyde product.



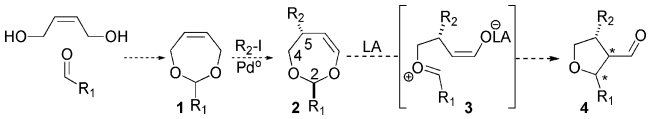
During our studies of 2,5-dihydrooxepins we found that a preexisting stereocenter exerts a positive influence on the diastereoselectivity of the reaction (eq 5). We hypothesized that this effect would be operative in other [1,3] ring contractions, and investigated 1,3-dioxepins as precursors to tetrahydrofurans (eq 6), a common motif in natural products.[6,7]



Linchpin strategies that rapidly assemble densely functionalized tetrahydrofurans are particularly attractive and some recent advances have emerged.[8] These include Pd-catalyzed oxyarylation of alkenes, [3+2] annulation of aldehydes, and intramolecular oxocarbenium ion allylation.[9] We envisioned a complementary method in which *cis*-1,4-butenediol could be used as a platform for the construction of a tetrahydrofuran (Scheme 1). Functionalization of a 1,3-dioxepin could be coupled with an olefin migration to provide a vinyl acetal such as **2**.[10] Subsequent Lewis acid-induced ring contraction of **2** should provide 2,3,4-trisubstituted tetrahydrofurans.

Some precedent in the literature suggested that this approach should be feasible. In the course of extensive contributions to the chemistry of vinyl acetals,[11] Frauenrath has shown that 2,4-

SCHEME 1



SCHEME 2

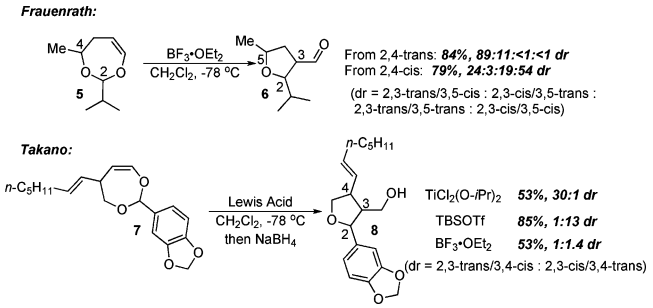
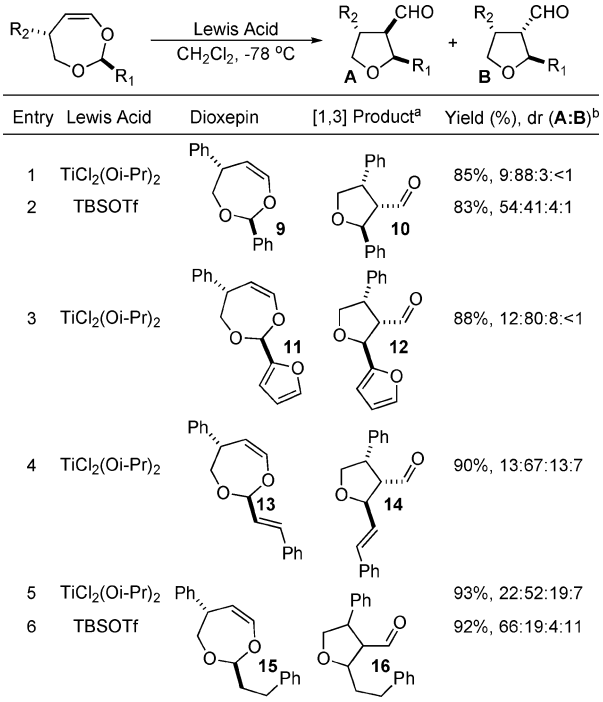


TABLE 1. Evaluation of Takano's Conditions



[a] Relative stereochemistry was assigned by NOE experiments. [b] The 2,3-cis/3,4-cis and 2,3-trans/3,4-trans diastereomers are not shown.

(5) Nasveschuk, C. G.; Rovis, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3264−3267.

(6) Reviews: (a) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407−2473. (b) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301−2323. For a review of lignan natural products, see: (c) Ward, R. S. *Nat. Prod. Rep.* **1997**, *16*, 75−96.

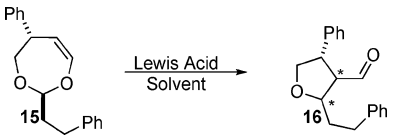
(7) For a review of methods for the synthesis of furofuran lignans, see: Brown, R.; Swain, N. A. *Synthesis* **2004**, 811−827.

(8) Oxidative cyclization: (a) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3371−3373. (b) Takacs, J. M.; Schroeder, S. D.; Han, J.; Gifford, M.; Jiang, X.; Saleh, T.; Vayalakkada, S.; Yap, A. H. *Org. Lett.* **2003**, *5*, 3595−3598. (c) Hartung, J.; Drees, S.; Greb, M.; Schmidt, P.; Svoboda, I.; Feuss, H.; Murso, A.; Stalke, D. *Eur. J. Org. Chem.* **2003**, 2388−2408. Epoxide ring opening: (d) Makosza, M.; Barbasiewicz, M.; Krajewski, D. *Org. Lett.* **2005**, *7*, 2945−2948.

(9) Pd-catalyzed oxy-arylation of alkenes: (a) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099−3107. [3+2] annulation of aldehydes: (b) Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R.-A.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245−4248. Intramolecular oxocarbenium ion allylation: (c) Cassidy, J. H.; Marsden, S. P.; Stemp, G. *Synlett* **1997**, 1411−1413.

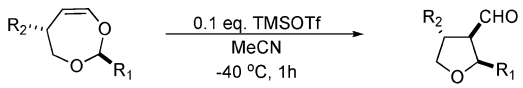
(10) Nasveschuk, C. G.; Frein, J. D.; Jui, N. T.; Rovis, T. *Org. Lett.* **2007**, *9*, 5099−5102.

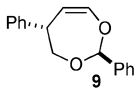
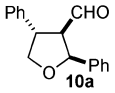
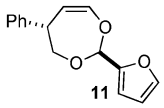
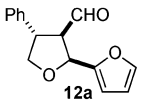
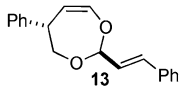
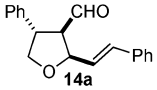
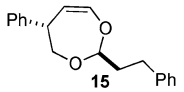
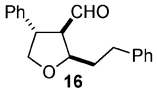
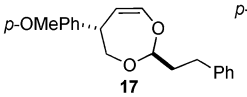
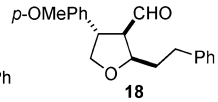
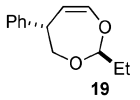
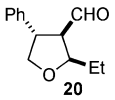
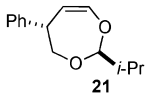
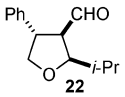
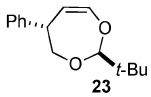
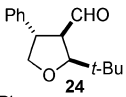
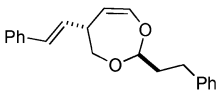
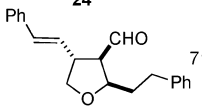
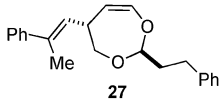
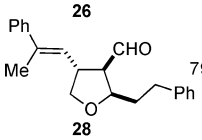
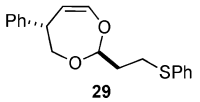
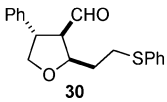
TABLE 2. Lewis Acid Screen



entry	Lewis acid	equiv	solvent	*T* (°C)	dr	yield (%)
1	BF_3•OEt_2	0.1	CH_2Cl_2	−78	62:24:3:11	93
2	$TiCl_2$(Oi-Pr)$_2$	1.1	CH_2Cl_2	−78	52:22:19:7	93
3	TMSOTf	0.1	CH_2Cl_2	−78	55:33:6:8	80
4	TMSOTf	0.1	MeCN	−40	91:5:4:<1	85

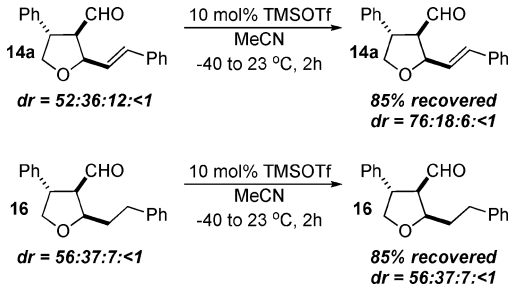
TABLE 3. Reaction Scope



Entry	Dioxepin	[1,3] Product	Yield (%), dr
1	 **9**	 **10a**	70, 94:5:1:<1
2	 **11**	 **12a**	94, 95:5:<1:<1
3	 **13**	 **14a**	88, 96:3:1:<1
4	 **15**	 **16**	85, 96:3:1:<1
5	 **17**	 **18**	84, 91:6:2:1
6	 **19**	 **20**	97, 90:7:2:<1
7	 **21**	 **22**	83, 85:10:5:<1
8	 **23**	 **24**	55, 70:18:12:<1
9	 **25**	 **26**	71, 93:6:1:<1
10	 **27**	 **28**	79, 83:17:<1:<1
11	 **29**	 **30**	68, 83:13:4:<1

disubstituted dioxepin **5** undergoes ring contraction in good yield with varying diastereoselectivity dependent on starting material

SCHEME 3



stereochemistry.[12] Takano has illustrated an elegant approach to the furofuran lignan (±)-asarinin using a Heck reaction of a 1,3-dioxepin followed by ring contraction of **7** (Scheme 2).[13] To our knowledge, substrates **5** and **7** are the only two examples of a [1,3] ring contraction of a 1,3-dioxepin to produce trisubstituted tetrahydrofurans. In particular, we wondered whether there were structural parameters that would be key in determining the efficiency and selectivity that could be attained. We endeavored to expand the scope of this approach to the tetrahydrofuran framework and recently reported a general and modular approach for the synthesis to the 2,3-cis/3,4-trans tetrahydrofuran diastereomer.[14] Herein we report a full account of our research in this area.

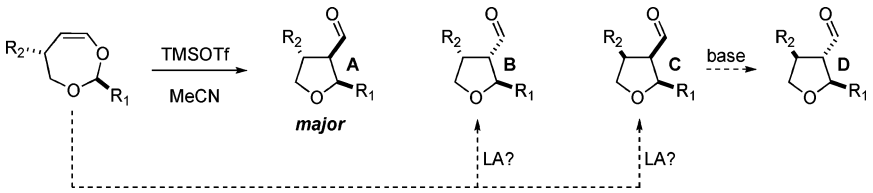
Results and Discussion

The [1,3] ring contraction of 1,3-dioxepins has been proposed to proceed by initial coordination of the Lewis acid to the vinyl acetal oxygen, followed by ionization to produce a metalloenolate and oxocarbenium ion **3**, which then collapse to form the tetrahydrofuran product **4** (Scheme 1). In light of the mechanism there are two ways to approach the development of this reaction that should have a direct effect on the diastereoselectivity in the tetrahydrofuran product: (1) an analysis of the substitution at the 2-position of the 1,3-dioxepin, which directly affects the stability and lifetime of the oxocarbenium ion intermediate, and (2) changing the Lewis acid to alter the nucleophilicity of the resultant metalloenolate. Frauenrath's work illustrated that simple alkyl substitution at the 2-postion of the dioxepin can lead to mixtures of all four tetrahydrofuran diastereomers. Takano's work showed that changing the Lewis acid had a pronounced effect on the diastereoselectivity of the reaction: $TiCl_2$(O-*i*Pr)$_2$ produced the 2,3-trans/3,4-cis stereochemistry and TBSOTf gave the 2,3-cis/3,4-trans stereochemistry (Scheme 2).

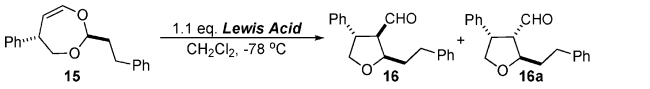
In light of this precedent, we hypothesized that π-donation of the substituent at the 2-position of the 1,3-dioxepin would be key in obtaining synthetically useful diastereoselectivities and began our studies by evaluating the generality of Takano's conditions through manipulation of substitution at the 2-position of the dioxepin. To this end, **9**, **11**, and **13** were subjected to Takano's conditions (stoichiometric $TiCl_2$(O-*i*Pr)$_2$ in CH_2Cl_2 at −78 °C). As expected, the corresponding tetrahydrofurans were isolated in good yield and diastereoselectivity (Table 1, entries 1, 3, and 4). However, and consistent with our hypothesis, all four diastereomers are obtained in significant amounts when simple alkyl substitution is present at the acetal position (entry

(11) Frauenrath, H. *Synthesis* **1989**, 721−734.
(12) Frauenrath, H.; Runsink, J. *J. Org. Chem.* **1987**, *52*, 2707−2712.
(13) Takano, S.; Samizu, K.; Ogasawara, K. *Synlett* **1993**, 785−787.
(14) Nasveschuk, C. G.; Jui, N. T.; Rovis, T. *Chem. Commun.* **2006**, 3119−3121.

SCHEME 4



SCHEME 5



Entry	Lewis acid	Yield (%)	dr (**16**:**16a**:other isomers)
1	$TiCl_2(Oi\text{-}Pr)_2$	*93*	*22:52:19:7*
2	$SnCl_4$	*89*	*10:81:9:<1*

5). The minor diastereomer produced from these reactions is the 2,3-cis/3,4-trans tetrahydrofuran.

Takano also reported that ring contraction in the presence of TBSOTf provides the 2,3-cis/3,4-trans diastereomeric tetrahydrofuran. This reaction, however, is very sensitive to the nature of the 2-substitutent. Treatment of **9** and **15** with TBSOTf provides **10** and **16** in poor diastereoselectivity (entries 2 and 6). These results suggest that the reported conditions are not general.

Consistent with our initial hypothesis, the lifetime and inherent stability of the oxocarbenium intermediate appears to be the key in accessing synthetically useful levels of diastereoselection in the ring contraction of 1,3-dioxepins. With this in mind we decided to pursue a more general protocol. A brief Lewis acid screen for the conversion of **15** to **16** was conducted in CH_2Cl_2 at −78 °C. Conventional conditions for the Lewis acid-mediated processes did produce tetrahydrofuran products albeit with poor diastereoselectivity (Table 2, entries 1−3).

It has been reported that oxocarbenium ion reactivity can be tuned by judicious choice of solvent.[15] We hypothesized that a polar aprotic solvent would stabilize the transient acyclic oxocarbenium ion generated upon Lewis acid ionization of the 1,3-dioxepin, and would serve to enhance the diastereoselectivity of this process. We were pleased to find that 10 mol % TMSOTf in MeCN at −40 °C provides the 2,3-cis/3,4-trans adduct **16** in good yield and excellent diastereoselectivity (Table 2, entry 4).[16]

The substrate scope for the TMSOTf-MeCN conditions is broad and provides functionalized tetrahydrofurans in uniformly high diastereoselectivity. The highest levels of diastereoselection are observed for substrates that possess aromatic or alkene substitution at the 2-position (Table 3, entries 1−3). Branched 2-alkyl substitution results in diminishing diastereoselectivity with increasing steric bulk (entries 6−8). The reaction is also tolerant of Lewis basic functionality (entries 2 and 11). Di- and trisubstituted olefins at the dioxepin 5-position also provide tetrahydrofurans in good yield and selectivity (entries 9 and 10).

To further elucidate the contributing factors that determine the diastereoselectivity of this reaction, a control experiment was designed (Scheme 3). A mixture of diastereomers of **14**, formed via a different route, were subjected to the optimized conditions and returned **14** with enhanced diastereoselectivity. This result suggests that ring opening/epimerization may be responsible for the high levels of diastereoselection found for substrates with π-donating substituents at the 2-position. Interestingly, the reaction conditions do not provide diastereomeric enrichment in the case of **16**, implying that its formation is not reversible and the selectivities for substrates with alkyl substitution are kinetic in origin.

Having developed a general, catalytic, and diastereoselective ring contraction of 1,3-dioxepin derivatives to the corresponding 2,3-cis/3,4-trans tetrahydrofurans (Scheme 4, **A**) we desired access to one of the other three possible diastereomers. Presumably, **B** or **C** could be produced by Lewis acid-mediated ring contraction and **D** could by made by epimerization of **C**. Stabilization of the oxocarbenium ion intermediate by solvent (MeCN) was crucial in providing access to **A**; we therefore hypothesized that **B** or **C** could be formed under conditions that provide a more reactive oxocarbenium−metalloenolate ion pair.

By using Takano's conditions as a starting point, a brief Lewis acid screen revealed that stoichiometric $SnCl_4$ promotes the rearrangement of **15** to **16a** in good yield and good 2,3-trans/3,4-cis diastereoselectivity (Scheme 5, entry 2).

The substrate scope for these conditions is general and proceeds in excellent diastereoselectivity provided that there is an aromatic or branched alkyl group at the 2-position of the dioxepin (Table 4, entries 1 and 2). The reaction also proceeds with good chemo- and diastereoselectively in the face of a possible [1,2] alkyl shift. Cyclobutanes (entries 3−7), cyclopropanes (entries 8 and 9), and cyclopentanes (entry 10) survive under the optimized conditions to provide 2-cycloalkyl tetrahy-

SCHEME 6

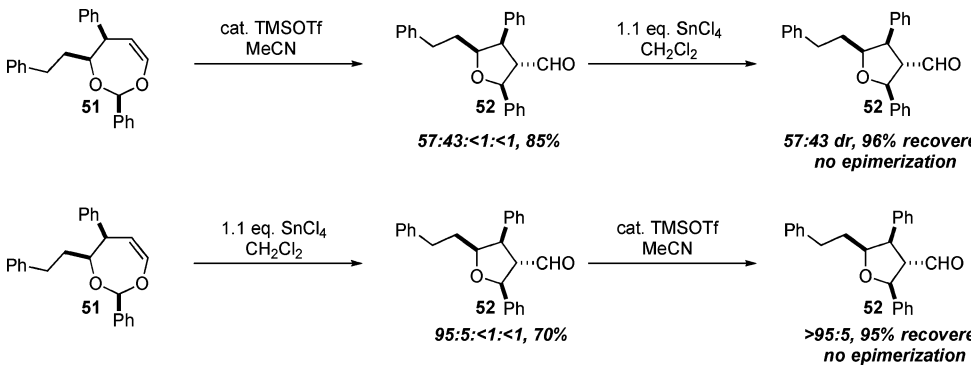
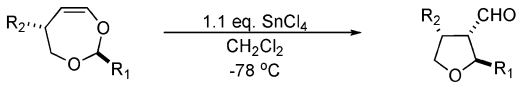
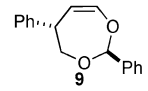
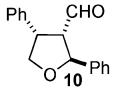
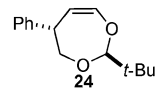
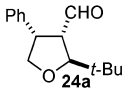
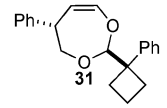
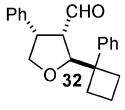
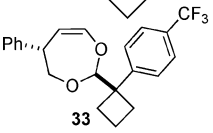
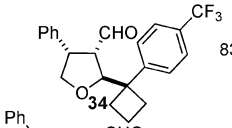
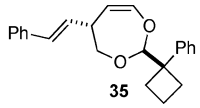
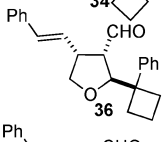
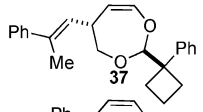
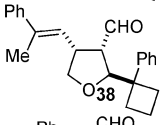
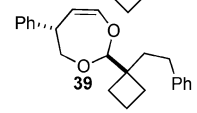
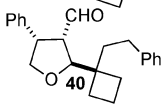
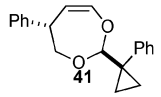
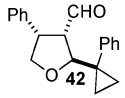
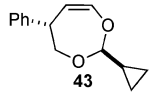
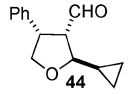
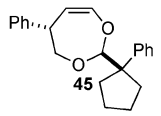
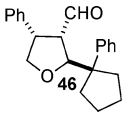


TABLE 4. Reaction Scope



Entry	Dioxepin	[1,3] Product	Yield (%), dr
1			87, 95:5:<1:<1
2			89, 88:12:<1:<1
3			86, 92:8:<1:<1
4			83, 82:9:6:3
5			83, 95:5:<1:<1
6			80, 86:14:<1:<1
7			92, 84:16:<1:<1
8			90, 89:11:<1:<1
9			87, 95:5:<1:<1
10			96, 91:9:<1:<1

drofuran products in good yield and diastereoselectivity. In all cases the minor diastereomer formed is the 2,3-cis/3,4-trans tetrahydrofuran.

Additional Lewis basic functionality in the 1,3-dioxepin enables the production of the 2,3-cis/3,4-trans tetrahydrofuran. Substrates with ether (**47**) and hydroxyl (**49**) Lewis basic functionality, when exposed to the optimized $SnCl_4$ rearrangement conditions, produce tetrahydrofuran **48** and tetrahydrofuran-lactol **50** in good yield and diastereoselectivity (eqs 7 and 8). We suggest these products arise from initial Lewis acid

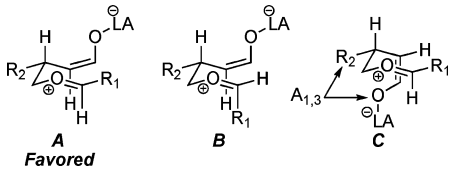


FIGURE 1. Stereochemical model for TMSOTf conditions.

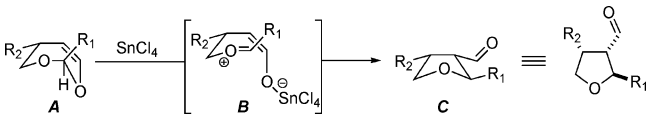
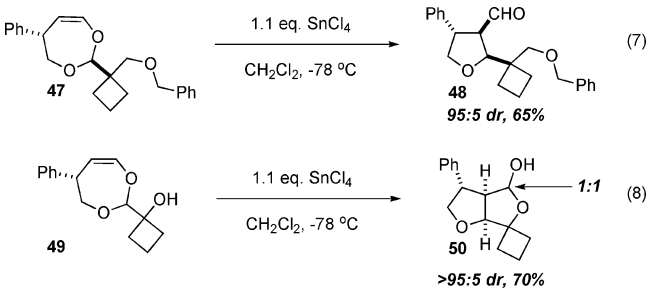


FIGURE 2. Stereochemical model for $SnCl_4$ conditions.

chelation between the ether or free hydroxyl oxygen and the vinyl ether oxygen of the 1,3-dioxepin.



Tetrasubstituted tetrahydrofuran scaffolds can also be accessed by using this methodology. Ring contraction of **51** in the presence of catalytic amounts of TMSOTf in MeCN produces the desired tetrahydrofuran in good yield but with poor diastereoselectivity (Scheme 6). However, rearrangement of **51** in the presence of $SnCl_4$ provided tetrasubstituted tetrahydrofuran **52** in excellent yield and exceptional diastereoselectivity. No diastereomeric enrichment or epimerization was observed when **52** was exposed to $SnCl_4$ in CH_2Cl_2. The same is true for the TMSOTf-MeCN conditions, showing that the selectivities obtained under both reaction conditions are kinetic and do not arise from initial unselective alkylation followed by an epimerization event. These results also suggest that the reversibility previously discussed is a function of the substitution present on the tetrahydrofuran (Scheme 3).

Stereochemical Models

As can be seen above, solvent and electronic stabilization of the oxocarbenium ion independently increase the selectivity of the [1,3] ring contraction. These effects proved to be synergistic, leading to exceptional levels of diastereoselection for the 2,3-cis/3,4-trans tetrahydrofuran in the presence of TMSOTf in MeCN. The relative configuration in the 2,3,4-trisubstituted tetrahydrofuran products can be rationalized with our proposed stereochemical model (Figure 1). Although the stereochemical relationship is primarily controlled via the pre-existing stereocenter at the 5-position of the 1,3-dioxepin (**A**, Figure 1), the stereochemical fidelity of the 1,3-ring contraction is influenced by the type of substitution and not the relative stereochemistry at the acetal position (**A** vs **B**, Figure 1). Furthermore, there is an interplay of energy minimization brought about by the potential relief of $A_{1,3}$ strain between R_2 (Figure 1, **C**) and the substituents R_1 and R_2 occupying pseudoequatorial positions (**A** vs **B**, Figure 1).

(15) (a) Pougny, J.-R.; Sinaÿ, P. *Tetrahedron Lett.* **1976**, *17*, 4073−4076. (b) Ratcliffe, A. J.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 747−750. (c) Marra, A.; Esnault, J.; Veyrières, A.; Sinaÿ, P. *J. Am. Chem. Soc.* **1992**, *114*, 6354−6360.

(16) See the Supporting Information for stereochemical assignment by NOE experiments.

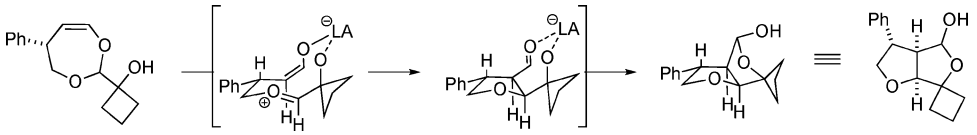


FIGURE 3. Stereochemical model for chelation control.

The 2,3-trans/3,4-cis tetrahydrofurans, formed under the $SnCl_4$ conditions, can be rationalized by a different stereochemical model. Assuming that the *E*-oxocarbenium ion is formed by ionization of the acetal, a boat-like early transition state leads to the observed stereochemistry in the tetrahydrofuran product (Figure 2, **B**). The R_1 and R_2 substituents occupy equatorial positions, which minimize their steric interactions. Although the tin alkoxide occupies an axial position, the steric interaction with R_1 is minimal. This transition state structure may also benefit from an electrostatic stabilization between the tin alkoxide and the oxocarbenium ion, which could help to stabilize the boat-like transition state.

The 2,3-cis/3,4-trans tetrahydrofuran diastereomers **48** and **50** produced under the $SnCl_4$ conditions can be rationalized by a chelation-controlled stereochemical model (Figure 3). After ionization, the Lewis acid remains chelated to the Lewis basic functionality, which orients the enolate and oxocarbenium ion appropriately to furnish the cis stereochemistry.

In summary, we have developed a modular and diastereodivergent [1,3] ring contraction of 1,3-dioxepins. The diastereoselectivity of the [1,3] rearrangement is controlled by the combination of Lewis acid and solvent. TMSOTf in MeCN leads to the formation of the 2,3-cis/3,4-trans diastereomer while $SnCl_4$ in CH_2Cl_2 provides the 2,3-trans/3,4-cis diastereomer. The application of this method to the synthesis of tetrahydrofuran-containing natural products is ongoing.

Experimental Section

General Procedure A for the [1,3] Ring Contraction of 1,3-Dioxepins. A flame-dried round-bottomed flask was charged with 1,3-dioxepin (1 equiv, 0.5 mmol) and freshly distilled MeCN (10 mL) and cooled to −40 °C. TMSOTf (0.05 equiv, 0.2 M solution in MeCN) was added dropwise and the reaction was monitored by TLC. Upon disappearance of 1,3-dioxepin (typically 1 h) the reaction was quenched with 0.5 mL of saturated aq NH_4Cl and then extracted with ether. $MgSO_4$ was added and the reaction was mixed for 15 min, then filtered through a pad of celite, and the solvent was removed in vacuo. The product was purified by silica gel column chromatography, using 9:1−3:1 Hex:EtOAc as eluent.

General Procedure B for the [1,3] Ring Contraction of 1,3-Dioxepins. A flame-dried round-bottomed flask was charged with CH_2Cl_2 (5 mL) and 1.1 equiv of $SnCl_4$ then cooled to −78 °C. The 1,3-dioxepin (0.25 mmol) was then added dropwise and the reaction was monitored by TLC. Upon disappearance of the 1,3-dioxepin (typically 15 min) the reaction was quenched with 0.5 mL of saturated aq NH_4Cl and then extracted with ether. The organic layer was washed twice with H_2O and once with brine and then dried over $MgSO_4$. After filtration, the solvents were removed in vacuo. The product was purified by silica gel column chromatography, using 9:1−3:1, Hex:EtOAc as eluent.

Acknowledgment. We thank Eli Lilly, Boehringer Ingelheim, and Johnson & Johnson for support. T.R. is a fellow of the Alfred P. Sloan Foundation and thanks the Monfort Family Foundation for a Monfort Professorship.

Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702071V