A modular approach to the synthesis of 2,3,4-trisubstituted tetrahydrofurans†

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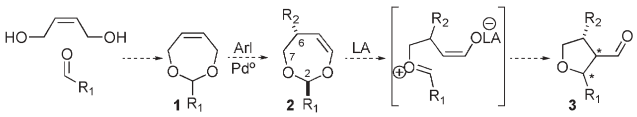
A highly diastereoselective Lewis acid-mediated [1,3] rearrangement of 1,3-dioxepins is the key step along a modular route to 2,3,4-trisubstituted tetrahydrofurans.

Convergent and modular approaches towards the synthesis of stereochemically complex small molecules are of paramount importance in synthetic organic chemistry. As part of a program to determine synthetically valuable applications of [1,3] O to C rearrangements[1] we became interested in 1,3-dioxepins as precursors to tetrahydrofurans, an increasingly significant motif in natural products.[2] Linchpin strategies that rapidly assemble densely functionalized tetrahydrofurans are particularly attractive and some recent advances have emerged.[3,4] Using *cis*-1,4-butenediol as a platform for the rapid assembly of a tetrahydrofuran (Scheme 1), we speculated that functionalization of a 1,3-dioxepin could be coupled with an olefin migration to provide a vinyl acetal such as **2**. Subsequent Lewis acid-induced ring contraction of **2** should provide 2,3,4-trisubstituted tetrahydrofurans.

Some precedent in the literature suggests this approach should be feasible. In the course of extensive contributions to the chemistry of vinyl acetals,[5] Frauenrath has shown that a 2,7-disubstituted dioxepin **4** undergoes ring contraction in good yield with varying diastereoselectivity dependent on starting material stereochemistry.[6] Takano has illustrated an elegant approach to furofuran lignan (±)-asarinin using a Heck reaction of a 1,3-dioxepin followed by ring contraction of **6** (Scheme 2).[7] We decided to evaluate the generality of these isolated examples and the viability of this sequence as an approach to a diverse substitution pattern about a tetrahydrofuran core.

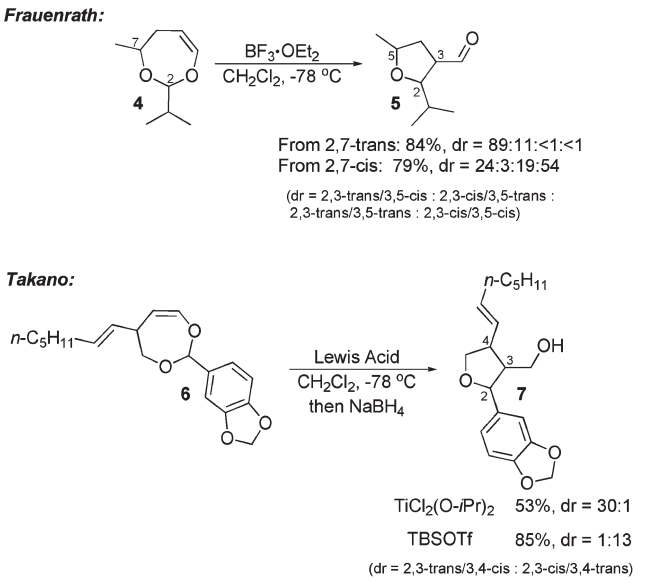
The condensation of *cis*-butenediol with aldehydes is well precedented.[5–7] With the requisite achiral 1,3-dioxepins in hand, we required a bond-forming event that would disrupt the symmetry of the molecule and form the vinyl acetal necessary for the [1,3] rearrangement. A number of workers have examined the asymmetric Heck reaction of methylene and isopropylidene acetals of butenediol, which made this process particularly appealing for our purposes. Unfortunately, Heck reactions using reported conditions with substrates such as **1** tended to be messy, and were plagued by prohibitively long reaction times and low conversions.[8] A survey of established Heck reaction conditions revealed that the desired coupling of aryl iodides and 1,3-dioxepins proceeds well under Jeffery's conditions.[9]



Scheme 1 General synthetic approach.

With an efficient route to 1,3-dioxepins, we began to evaluate conditions to effect a diastereoselective [1,3] rearrangement. We hypothesized that the selectivities observed in Takano's work were a function of the π-donating ability of the substituent at the 2-position of the 1,3-dioxepin. Indeed, when **8**, **10**, and **12** are subjected to $TiCl_2(O\text{-}iPr)_2$, the corresponding tetrahydrofurans may be isolated in good yield and diastereoselectivity (Table 1, entries 1, 3, 4). Consistent with this hypothesis, all four diastereomers are obtained in significant amounts when simple alkyl substitution is present at the acetal position (entry 5). Takano reported that rearrangement of **6** in the presence of TBSOTf provides a different diastereomer of **7**, relative to that obtained under the $TiCl_2(O\text{-}iPr)_2$ conditions (Scheme 2). This reaction, however, is very sensitive to the substitution pattern. Treatment of **8** and **14** with TBSOTf provides **9** and **15** in poor diastereoselectivity (entries 2 and 6). These results suggest that the reported reaction conditions lack generality.

The stability of the oxocarbenium ion intermediate appears to be the key to synthetically useful diastereoselectivities in the [1,3] ring contraction of 1,3-dioxepins. With that in mind we decided to



Scheme 2 Previous reports.

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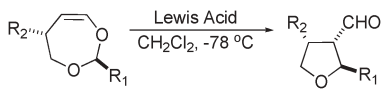
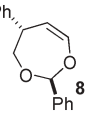
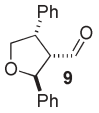
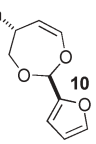
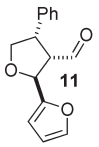
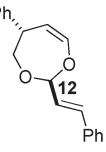
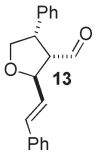
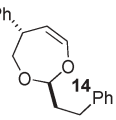
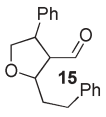
Table 1 Oxocarbenium ion stabilization



Entry	Lewis acid	Dioxepin	[1,3] Product[a]	Yield (%), dr
1	$TiCl_2(O\textit{i}\text{-}Pr)_2$			85%, 9 : 88 : 3 : <1
2	TBSOTf			83%, 4 : 41 : 54 : 1
3	$TiCl_2(O\textit{i}\text{-}Pr)_2$			88%, 12 : 80 : 8 : <1
4	$TiCl_2(O\textit{i}\text{-}Pr)_2$			90%, 13 : 67 : 13 : 7
5	$TiCl_2(O\textit{i}\text{-}Pr)_2$			93%, 7 : 19 : 22 : 52
6	TBSOTf			92%, 66 : 19 : 4 : 11

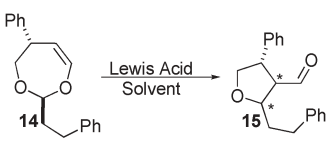
[a] Relative stereochemistry was assigned by NOE experiments.

reinvestigate this transformation in an effort to identify a more general protocol. A brief screen of the conversion of **14** to **15** was executed employing several Lewis acids in CH_2Cl_2 at −78 °C. As illustrated in Table 2, Lewis acid-induced rearrangement provides tetrahydrofuran products in good chemical yield; however, poor diastereoselectivities are observed (entries 1–3).

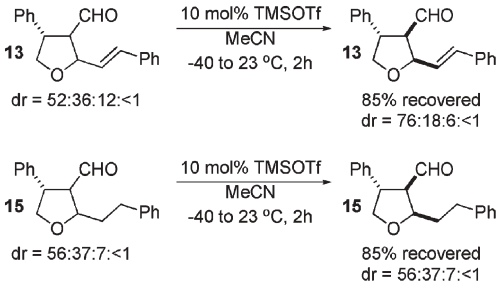
It has been reported that oxocarbenium ion reactivity can be tuned *via* solvent stabilization.[10] We hypothesized that a polar aprotic solvent would stabilize the transient acyclic oxocarbenium ion generated upon Lewis acid-induced ionization and serve to enhance the diastereoselectivity of this process. We were delighted to find that 10 mol% TMSOTf in MeCN provided 2,3-*cis*/3,4-*trans* adduct **15** in good yield and excellent diastereoselectivity (Table 2, entry 4).

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 **13**, formed *via* a different route, was subjected to the optimized conditions and

Table 2 [1,3] Ring contraction optimization

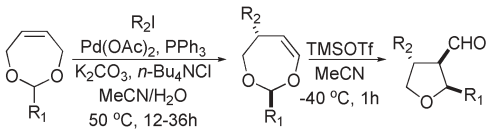


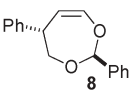
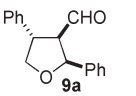
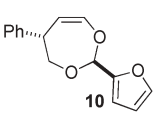
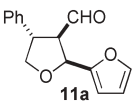
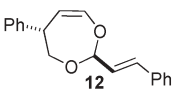
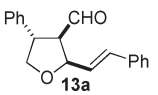
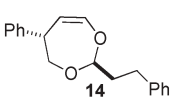
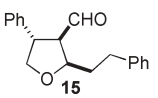
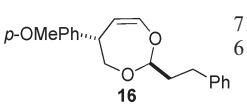
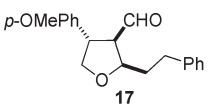
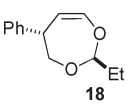
Entry	Lewis acid	Eq.	Solvent	T (°C)	dr	Yield (%)
1	$BF_3{\cdot}OEt_2$	0.1	CH_2Cl_2	−78	62 : 24 : 3 : 11	93
2	Et_2AlCl	1.05	CH_2Cl_2	−78	17 : 21 : 13 : 49	98
3	TMSOTf	0.1	CH_2Cl_2	−78	55 : 33 : 6 : 8	80
4	TMSOTf	0.1	MeCN	−40	91 : 5 : 4 : <1	85



Scheme 3 Epimerization study.

Table 3 Reaction sequence scope



Entry	R_1, R_2	Yield (%), dr	[1,3] Product	Yield (%), dr
1	**8**; R_1 = Ph, R_2 = Ph	75, (87 : 13)		70, (94 : 5 : 1 : <1)
2	**10**; R_1 = 2-Furyl, R_2 = Ph	65, (87 : 13)		94, (>95 : 5 : <1:<1)
3	**12**; R_1 = CHCHPh, R_2 = Ph	71, (83 : 17)		88, (96 : 3 : 1 : <1)
4	**14**; R_1 = CH_2CH_2Ph, R_2 = Ph	65, (85 : 15)		85, (96 : 3 : 1 : <1)
5	**16**; R_1 = CH_2CH_2Ph, R_2 = *p*-OMePh	59, (85 : 15)		84, (91 : 6 : 2 : 1)
6	**18**; R_1 = Et, R_2 = Ph	64, (85 : 15)		97, (90 : 7 : 2 : <1)
7	**20**; R_1 = *i*-Pr, R_2 = Ph	67, (85 : 15)		83, (85 : 10 : 5 : <1)
8	**22**; R_1 = *t*-Bu, R_2 = Ph	68, (83 : 17)		55, (70 : 18 : 12 : <1)
9	**24**; R_1 = CH_2CH_2Ph, R_2 = CHCHPh	42, (79 : 21)		71, (93 : 6 : 1 : <1)
10	**26**; R_1 = CH_2CH_2Ph, R_2 = $CHC(CH_3)Ph$	71, (78 : 22)		79, (83 : 17 : < 1 : <1)
11	**28**; R_1 = CH_2CH_2SPh, R_2 = Ph	59, (83 : 17)		68, (83 : 13 : 4 : <1)

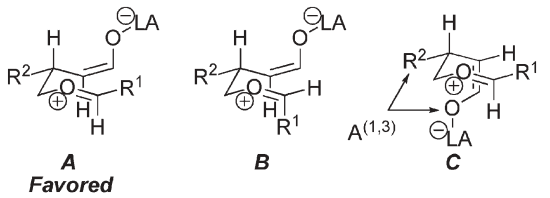


Fig. 1 Proposed stereochemical model for the diastereoselective ring contraction. Pseudoequatorial disposition of the substituents and minimization of $A^{(1,3)}$ strain suggests A should be favored, rationalizing the observed stereochemistry.

returned **13** with enhanced dr. Interestingly, the reaction conditions do not provide diastereomeric enrichment in the case of **15**, which suggests that its formation is not reversible and the selectivities for substrates with alkyl substitution at the 2-position are kinetic in origin.

With optimized rearrangement conditions in hand, we set out to evaluate the full scope of this modular sequence. The Heck reaction provides a variety of 1,3-dioxepins in good yields and moderate diastereoselectivity. Aromatic, alkenyl, and trisubstituted alkenyl iodides couple efficiently (Table 3).[11] Cinnamaldehyde-derived 1,3-dioxepin (**12**) chemoselectively undergoes cross-coupling at the *cis* alkene in preference to the *trans*-styrenyl alkene (entry 3).

We have shown that *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 in the presence of MeCN (Table 3, entries 1–3). High diastereoselectivity is also observed for dioxepins containing heteroatoms in the side chain (entries 2, 11). Di- and tri-substituted olefins at the dioxepin 6-position also provide tetrahydrofurans in good yield and selectivity (entries 9, 10). Branched 2-alkyl substitution results in diminishing diastereoselectivity with increasing steric bulk (entries 7–8, *vide infra*).

The relative configuration in the 2,3,4-trisubstituted tetrahydrofuran products can be rationalized with our proposed stereochemical model (Fig. 1). While the diastereochemical relationship is primarily controlled *via* the pre-existing stereocenter at the 6-position of the 1,3-dioxepin (A, Fig. 1), the stereochemical fidelity of the 1,3-ring contraction is influenced by the type of substitution and not the relative stereochemistry (of the Heck reaction) at the acetal position (A *vs* B, Fig. 1). Furthermore, we believe there is interplay of energy minimization brought about by potential relief of $A^{(1,3)}$ strain between R^2 and the metalloenolate (C, Fig. 1) and the substituents R^1 and R^2 occupying pseudo-equatorial positions (A *vs* B, Fig. 1).

In conclusion, we have further defined the scope of this useful strategy for the stereoselective synthesis of 2,3,4-trisubsituted tetrahydrofurans. It has been identified that both electronic and solvent stabilization of the oxocarbenium ion intermediate are crucial in obtaining optimal diastereomeric ratios. Studies into the asymmetric variant of this sequence are currently underway.

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11 Conversion falters in the presence of sterically encumbering aromatic iodides. For example, Heck reaction with **1** and 2,6-dimethyliodobenzene proceeded with 10% conversion by ^{1}H NMR after 1 week under the optimized conditions.