Synthetic Methods

Stereoselective Lewis Acid Mediated [1,3] Ring Contraction of 2,5-Dihydrooxepins as a Route to Polysubstituted Cyclopentenes**

*Christopher G. Nasveschuk and Tomislav Rovis**

The Diels–Alder reaction is a cornerstone of organic synthesis, and its ability to enable the production of cyclohexenes in a stereocontrolled manner is unparalleled. In contrast, no method exists for the synthesis of cyclopentanes that matches the scope and power of the Diels–Alder reaction in spite of the prevalence of these ring systems in natural products. Among numerous methods that have been used to target these cores, vinylcyclopropane ring-expansion strategies have been intensively investigated and have provided some spectacular successes.[1,2] Nevertheless, most reports result in mono- or disubstituted cyclopentanes and cyclopentenes, while approaches to polysubstituted systems are rare.[3] We were interested in addressing this deficiency and developing a diastereoselective approach to tri-, tetra-, and pentasubstituted cyclopentanes from readily available precursors, and herein we report our results.

We have previously reported the [1,3] rearrangement of vinyl acetals which proceeds through a metalloenolate and oxocarbenium ion pair.[4] To extend this concept to other stabilized cations, we initiated a program to study the [1,3] rearrangement of allylvinyl ethers that would form a metalloenolate and an allylic cation ion pair under Lewis acidic conditions. However, we were mindful that these substrates could also undergo a Lewis acid (LA) accelerated Claisen rearrangement, which if concerted, would form the [3,3] rearrangement product exclusively.[5] A number of workers have documented that the Lewis acid mediated Claisen rearrangement proceeds stepwise[6] and occasionally provides the [1,3] adduct with some selectivity.[7] To favor the [1,3] over the [3,3] product, we envisioned that a cyclic allylvinyl ether or 2,5-dihydrooxepin could provide access to densely functionalized cyclopentenes under ionizing conditions as the [3,3] rearrangement should be disfavored because of ring strain in the cyclopropane product [Eq. (1)]. We report the successful implementation of this strategy, in which a unique Lewis acid promoted ring contraction of 2,5-dihydrooxepins to cyclopentenes was used.

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[**] Financial support was provided by the National Institute of General Medical Sciences (GM65407). We also thank Merck Research Laboratories, GlaxoSmithKline, Amgen, and Eli Lilly for unrestricted support. We thank Professor Andre Charette (Montreal) for helpful discussions.

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

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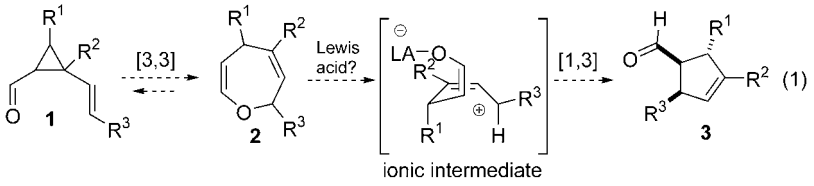
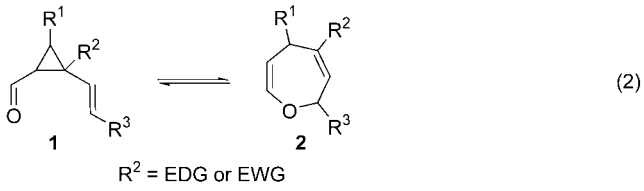
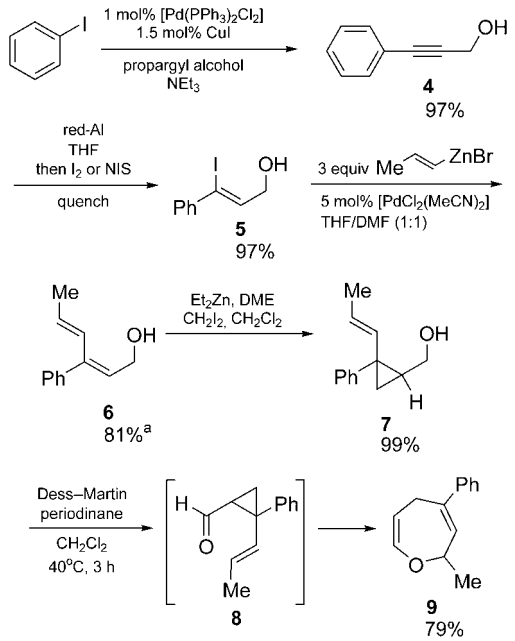


Despite their apparent complexity, 2,5-dihydrooxepins are readily prepared by a retro-Claisen reaction of the corresponding cyclopropyl aldehyde **1**, itself available by a modular approach using established methods (see below).[8,9] An equilibrium between **1** and **2** has been predicted computationally,[10] and may be shifted towards the 2,5-dihydrooxepin with π-stabilizing substituents [Eq. (2); EDG = electron-donating group, EWG = electron-withdrawing group].[9]



(2)

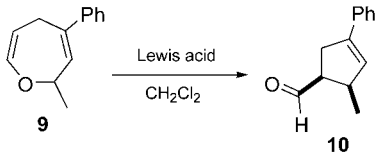
We began our investigations by developing a highly modular approach to the 2,5-dihydrooxepin skeleton. A representative synthesis is illustrated in Scheme 1. A Sonogashira cross-coupling between propargyl alcohol and aryl halides provided **4**.[11] Selective formation of the (*Z*)-vinyl iodide **5** was effected with red-Al/I_2,[12] and a Negishi coupling was then employed to insert an additional alkene.[13] A directed Simmons–Smith cyclopropanation afforded **7** in near quantitative yield as a single regioisomer.[14] We felt that **7** could be converted into **9** in a one-pot oxidation/retro-Claisen sequence and, after some optimization, it was found that 1.5 equivalents of the Dess–Martin periodinane in CH_2Cl_2 at 40 °C provided the desired 2,5-dihydrooxepin. The nature of the equilibrium meant that the unrearranged aldehyde **8** could be isolated and subsequently converted into **9** by heating overnight in toluene at 110 °C.



Scheme 1. Synthetic approach to the 2,5-dihydrooxepins.

With a convergent approach to the requisite 2,5-dihydrooxepins in hand, we began our studies on the stereoselective [1,3] ring contraction by conducting a brief screen of Lewis acids. $Cu(OTf)_2$, $TiCl_4$, and $SnCl_4$ yielded no product under a variety of conditions (Table 1, entries 1–3). In the presence of $EtAlCl_2$ (entries 4–6), the starting material was consumed with the formation of uncharacterized oligomeric products. We hypothesized that this could happen in one of two ways: 1) vinyl ether **9** could polymerize before ionization of the C–O bond or 2) the zwitterionic intermediate generated from the ionization of C–O is stable enough so that intramolecular ring closure is slower than the bimolecular reaction. Thus, cyclopentene **10** was isolated in 89% yield with 90:10 (*cis*/*trans*) selectivity (entry 7) when **9** was subjected to dilute Lewis acid at ambient temperature. We further note that slow addition of dilute 2,5-dihydrooxepin to the Lewis acid generally provides an incremental increase in selectivity (entry 8).

Table 1: Optimization of [1,3] ring contraction.



Entry	Lewis acid	Conditions	Yield [%] (*cis*/*trans*)
1	$Cu(OTf)_2$	various	NP[a]
2	$TiCl_4$	various	NP[a]
3	$SnCl_4$	various	NP[a]
4	$EtAlCl_2$	0.1 M, −78 °C, 30 min	NP[a]
5	$EtAlCl_2$	0.1 M, 23 °C, 30 min	NP[a]
6	$EtAlCl_2$	0.001 M, −78 °C, 60 min	NP[a]
7	$EtAlCl_2$	0.001 M, 23 °C, 5 min	89 (90:10)
8	$EtAlCl_2$	0.02 M, 23 °C, 5 min[b]	53 (93:7)

[a] Starting material consumed. [b] Slow addition of substrate to dilute Lewis acid. NP = no product.

We then evaluated the scope of the [1,3] ring contraction of the 2,5-dihydrooxepins. Electron-donating and electron-withdrawing groups in the *para* position of the aromatic ring are tolerated and give products in comparable yield and selectivity (Table 2, entries 1–3). Additional substitution on the dihydrooxepin unit is well-tolerated, with substrate **15** furnishing tetrasubstituted cyclopentene **16** in good selectivity. An increase in the steric bulk of the substituent from a methyl group (**9**) to a phenethyl group (**17**) or protected alcohol (**19**) results in a slight decrease in the yield and selectivity, but still provides synthetically useful amounts of product. Lastly, the use of aldehyde **21** as a substrate indicates

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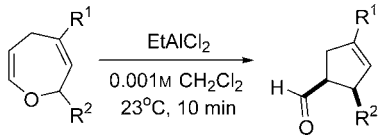
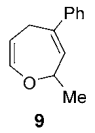
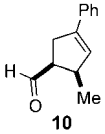
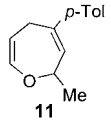
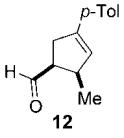
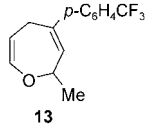
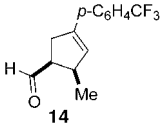
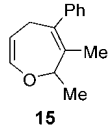
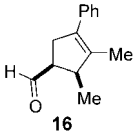
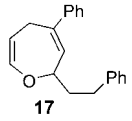
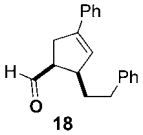
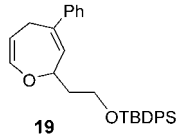
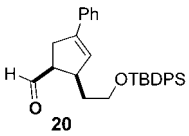
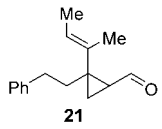
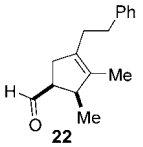
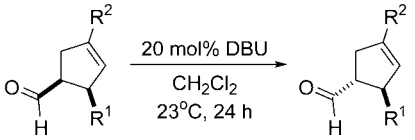
Table 2: Reaction scope.

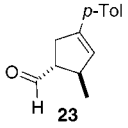
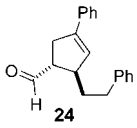


Entry	substrate	Product	Yield [%]	*cis*/*trans*
1	 **9**	 **10**	89	90:10
2	 **11**	 **12**	85	93:7
3	 **13**	 **14**	75	87:13
4	 **15**	 **16**	58	88:12
5	 **17**	 **18**	73	85:15
6	 **19**	 **20**	52	85:15
7	 **21**	 **22**	59	89:11

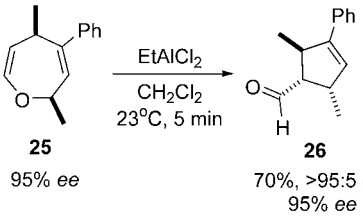
p-Tol = *para*-toluene, TBDPS = *tert*-butyldiphenylsilyl.

Table 3: Aldehyde epimerization.



Entry	Substrate (R^1, R^2)	Product	Yield [%]	*cis*/*trans*
1	**12** (Me, *p*-Tol)	 **23**	68	12:88
2	**18** ($-CH_2CH_2Ph$, Ph)	 **24**	81	3:97

jected to the optimized reaction conditions, **26** was isolated in 70% yield and 95% *ee* [Eq. (3)]. The pre-existing stereo-



(3)

center controls the diastereoselective course of the reaction, and the observed selectivity can be rationalized by our proposed model (Figure 1). There is an interplay of minimi-

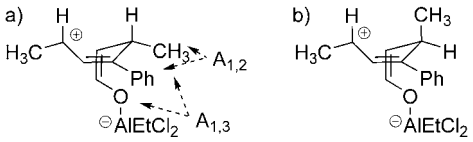
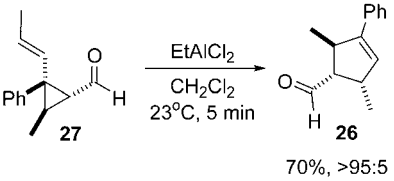


Figure 1. Proposed stereochemical model for the diastereoselective rearrangement of **25**. a) Minimization of the $A_{1,2}$ and $A_{1,3}$ strains and b) the favored model brought about by this process.

that formation of the dihydrooxepin is not necessary to achieve reaction. Furthermore, this substrate lacks the aryl stabilization evident in the other substrates, thus suggesting that aliphatic stabilization is sufficient in some cases. These disubstituted cyclopentene carboxaldehydes are readily epimerized[14] to form the *trans* diastereomer upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; Table 3, entries 1 and 2).

A considerable advantage of this method is the ability to introduce substitution at every position of the dihydrooxepin ring. With this approach in mind, we sought to apply the protocol of Charette et al.[15] as a means of introducing further substitutents onto the cyclopropane and affording a tetrasubstituted cyclopentene on [1,3] rearrangement. 2,5-Dihydrooxepin **25** was synthesized in an enantioenriched form using the Charette–Simmons–Smith protocol.[15] When **25** was subzation between the $A_{1,2}$ strain, between the phenyl group on the allyl cation and the adjacent methyl, and the $A_{1,3}$ strain, between the alkoxide on the enolate and the methyl group, that presumably leads to the observed levels of diastereoselectivity.

As noted above, we may also use the aldehydes as precursors for the rearrangement [Table 2, entry 7; Eq. (4)].



(4)

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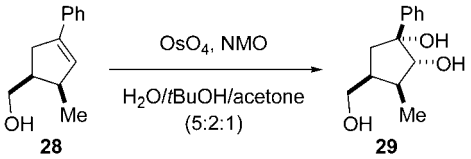
We suggest that this arises from the initial Lewis acid catalyzed retro-Claisen rearrangement that gives the 2,5-dihydrooxepin prior to [1,3] bond migration. Another possibility is that the Lewis acid accelerates the Claisen/retro-Claisen equilibrium so that a Curtin–Hammett situation is formed where the cyclopentene product is siphoned off from either the 2,5-dihydrooxepin or the cyclopropyl aldehyde. Although the exact mechanism at this stage remains unclear, this observation makes the overall procedure operationally simpler.

The presence of the olefin in the cyclopentene allows for further diastereoselective functionalization. We investigated one such approach and found that diastereoselective dihydroxylation produces a pentasubstituted cyclopentane in modest yield but excellent selectivity [Eq. (5), NMO = 4-methylmorphoöine *N*-oxide].[16]



(5)

In summary, we have developed a novel room-temperature Lewis acid mediated diastereoselective [1,3] ring contraction of 2,5-dihydrooxepins. Our modular approach to these seven-membered heterocycles allows for the installation of a variety of groups at every position. The reaction provides access to *cis* and *trans* cyclopentene carboxaldehydes with good selectivities, and can lead to tetrasubstituted cyclopentenes in high enantiomeric excess and diastereoselectivity.

Received: January 11, 2005
Published online: April 21, 2005

Keywords: cyclopentenes · diastereoselectivity · Lewis acids · rearrangement · ring contraction

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