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Ring expansion of *trans*-divinyl ethylene oxide by oxonium ylide [2,3] sigmatropic rearrangement

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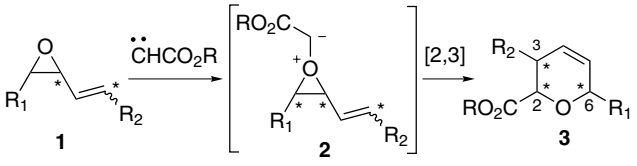
Abstract—Oxonium ylide [2,3] sigmatropic rearrangement of *trans*-divinyl ethylene oxide is observed upon its exposure to ethyl or *t*-butyl diazoacetate in the presence of either Rh(II) or Cu(II) catalysts to produce *cis*-6-vinyl-3,6-dihydropyran-2-carboxylates.

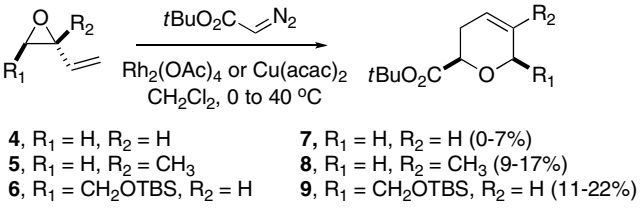
The widespread presence of functionalized dihydropyran rings in biologically active natural products has stimulated the development of a wide range of synthetic approaches for their preparation.[1] Some of the most general methods for the stereocontrolled synthesis of polysubstituted dihydropyrans include hetero Diels–Alder cycloaddition,[2] dioxanone Claisen rearrangement,[3] ring closing metathesis,[4] vinyl-silane terminated oxycarbenium cyclization,[5] and intramolecular allylsilane addition.[6]

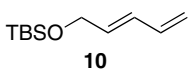
We envisioned a synthetic approach, outlined in Scheme 1, based on application of the well-studied [2,3] sigmatropic rearrangement of oxonium ylides derived from allylic ethers to vinyl epoxides.[7,8] Exposure of a vinyl epoxide, such as **1**, to a carbenoid would produce an oxonium ylide intermediate (**2**), which is poised to undergo the [2,3] rearrangement. During studies on Cu-catalyzed reactions of diazomethane with vinyloxirane, Kapps and Kirmse first observed rearrangement of this type to produce 5,6-dihydro-2*H*-pyran in low yield.[9] Independent studies by Somfai and Coldham have demonstrated the viability of the analogous aza-[2,3] Wittig rearrangement of vinyl aziridines for the preparation of tetrahydropyridines.[10] Successful extension of this ring expansion strategy would provide a general approach to the synthesis of stereodefined dihydropyrans with the 2,3- and 2,6-stereochemical relationships resulting from chirality transfer during the concerted rearrangement.

Our initial attempts to perform the rearrangement focused on vinyl epoxides **4**–**6** (Scheme 2). Epoxides **4** and **5** are commercially available and **6** was prepared from 1,4-pentadien-3-ol following known protocol.[11] Treatment with *t*-butyl diazoacetate in the presence of either $Rh_2(OAc)_4$ or $Cu(acac)_2$ to catalyze diazodecomposition at temperatures ranging from 0 °C to 40 °C led



Scheme 1. Dihydropyran synthesis by vinyl epoxide ring expansion.





Scheme 2. Reactions of vinyl epoxides with Rh or Cu carbenoids.

Keywords: Oxonium ylide; [2,3] Sigmatropic rearrangement; Dihydropyran synthesis.
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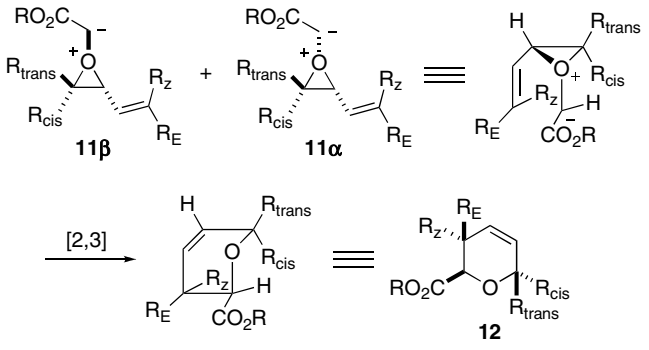
to poor yields of the expected dihydropyrans **7**–**9**. Oxetane products arising from [1,2] Stevens rearrangement were also produced in low yield. A maximum yield of 22% of dihydropyran **9** was observed upon reaction of **6** using 10 mol % $Cu(acac)_2$ at room temperature. In reactions of **6**, diene **10** was isolated as the major product in yields of 51–74%, and in reactions of **4** and **5**, low mass recoveries can be explained by the formation of volatile diene products. These results are consistent with a study by Martin and Ganem in which they reported deoxygenation of epoxides by treatment with dimethyl diazomalonate and $Rh_2(OAc)_4$ at 80 °C.[12] We were disappointed to find deoxygenation to be favored over rearrangement for epoxides **4**–**6**; however, the formation of dihydropyrans (albeit in low yield) did provide evidence that the desired rearrangement pathway could compete.

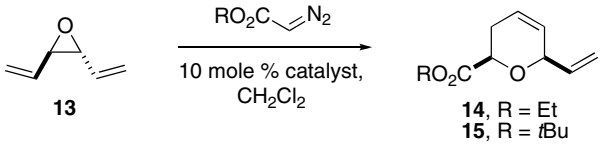
We suspected that the outcomes observed in the reactions of **4**–**6** were, at least partly, due to the stereochemistry of complexation between the Lewis basic epoxide oxygen and the Lewis acidic carbenoid carbon. Ylide formation can occur on either the β-face of the epoxide to produce **11β** or the α-face to produce **11α** (Scheme 3). Whether ylide formation is kinetically or thermodynamically controlled, the ratio of **11β**:**11α** is likely to be dictated by the nature of the epoxide substituents.[13] It was expected that the oxonium ylide rearrangement would proceed via a boat-like transition state similar to that invoked to rationalize the stereochemical outcome of vinyl aziridine rearrangements.[10] In this model, only **11α**, with the cis relationship between the carbenoid carbon and vinyl substituent required for effective orbital overlap, is capable of undergoing rearrangement, while both **11β** and **11α** are capable of deoxygenation. The poor yields of dihydropyrans **7**–**9** and the modest enhancements in yields as the size of the substituent trans to the vinyl group is increased from epoxides **4**–**6** can then be explained as results of steric influences in ylide formation. The exclusive formation of **6** as the 2,6-cis diastereomer is also consistent with the transition state shown in Scheme 3 in which the carbo *t*-butoxy substituent on the carbenoid carbon adopts the *exo* orientation to minimize steric interactions.

With this analysis in mind, we chose to examine the rearrangement of *trans*-divinyl ethylene oxide (**13**, Table 1) which was prepared from *meso*-1,5-hexadiene-3,4-diol



Scheme 3. Transition state model for rearrangement.

Table 1. [2,3] Rearrangement of **13**[15]



Entry	R	Catalyst	Temperature (°C)	Yield[a] (%)
1	*t*-Bu	$Rh_2(OAc)_4$	40	33
2	Et	$Rh_2(OAc)_4$	40	31
3	*t*-Bu	$Cu(acac)_2$	40	50
4	Et	$Cu(acac)_2$	40	51
5	*t*-Bu	$Cu(hfacac)_2$	40	71
6	Et	$Cu(hfacac)_2$	40	68
7	*t*-Bu	$Cu(hfacac)_2$	24	72
8	*t*-Bu	$Cu(hfacac)_2$	0	69
9	*t*-Bu	$Cu(hfacac)_2$	−10	62
10	*t*-Bu	$Cu(hfacac)_2$	−30	44

[a] Isolated yield after purification by column chromatography.

as previously reported.[14] Due to the C_2-symmetry of **13**, only one oxonium ylide intermediate is possible thus removing the potential for unproductive ylide formation. As such, we felt that epoxide **13** was more likely to undergo successful rearrangement than those previously studied, since the outcome of its reaction would reflect only the relative reactivity of the oxonium ylide for rearrangement versus deoxygenation. We were gratified to find that treatment of **13** with ethyl or *t*-butyl diazoacetate in the presence of Rh(II) or Cu(II) catalysts gave serviceable yields of dihydropyrans **14** and **15**, respectively, and our results are shown in Table 1.[15] There was no discernable yield difference between reactions of ethyl and *t*-buyl diazoacetate; however, we did observe a marked influence on the choice of catalyst on the efficiency of the rearrangement. Specifically, we found Cu(II) catalysts to be more effective at promoting rearrangement than the widely used $Rh_2(OAc)_4$. Previous reports on oxonium ylide rearrangements have also made note of significant catalyst effects on reactivity.[8a,16] $Cu(hfacac)_2$ was found to catalyze the rearrangement most effectively providing a maximum 72% yield of **15** (entry 7). Yields showed little to no temperature dependence in the range of 0–40 °C for the reaction of **13** with *t*-butyl diazoacetate catalyzed by $Cu(hfacac)_2$, but we did find that yields were decreased at lower temperatures (entries 9 and 10). Structural assignments were made by correlation to previously reported ^1H and ^{13}C NMR data for **15**.[17] Both **14** and **15** were isolated as single stereoisomers with the *cis*-2,6 relationship which conforms to our transition state model.

In conclusion, we have demonstrated a viable approach to the synthesis of 2,6-*cis* substituted dihydropyrans **14** and **15** by [2,3] sigmatropic rearrangement of oxonium ylides derived from *trans*-divinyl ethylene oxide (**13**). Although the scope of this strategy is limited by competitive deoxygenation, we have shown that rearrangement can be promoted by appropriate choice of substrate. Application of this methodology to the synthesis of optically active dihydropyrans and in natural product synthesis will be reported in due course.

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15. *General procedure for Cu(hfacac)$_2$ catalyzed rearrangement.* To a solution of epoxide **13** (104.5 mg, 1.09 mmol) and Cu(hfacac)$_2$ (52.0 mg, 0.110 mmol) in 9 mL CH_2Cl_2 at room temperature was added *t*-butyl diazoacetate (186.3 mg, 1.31 mmol) in 2 mL of CH_2Cl_2 via a syringe pump. Upon complete consumption of **13**, as determined by TLC, the reaction was quenched by addition of 0.5 M K_2CO_3. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (9:1 hexanes/EtOAc) gave 165.0 mg (72%) of dihydropyran **15** as a white solid. Data for **15**: mp = 53–55 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.88 (ddd, $J = 17.4$, 10.4, 6.2 Hz, 1H) 5.85 (m, 1H); 5.65 (m, 1H); 5.34 (dt, $J = 17.4$, 1 Hz, 1H); 5.19 (dt, $J = 10.4$, 1 Hz, 1H); 4.68 (m, 1H); 4.15 (dd, $J = 10.3$, 4.5 Hz, 1H); 2.40–2.19 (m, 2H); 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.4, 136.9, 128.9, 124.1, 117.8, 83.1, 76.9, 71.7, 27.3, 27.0; HRMS calcd for $C_{12}H_{19}O_3$ (MH^+) 211.1334, found 211.1329. Data for **14**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89 (ddd, $J = 17.1$, 10.5, 6.2 Hz, 1H) 5.86 (m, 1H); 5.65 (m, 1H); 5.30 (dt, $J = 17.1$, 1 Hz, 1H); 5.21 (dt, $J = 10.5$, 1 Hz, 1H); 4.59 (m, 1H); 4.10 (dd, $J = 10.3$, 4.4 Hz, 1H); 4.06 (q, $J = 6.9$ Hz, 2H); 2.45–2.24 (m, 2H); 1.25 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.8, 137.4, 128.9, 122.9, 118.8, 82.9, 76.7, 61.9, 27.6, 16.1; HRMS calcd for $C_{10}H_{15}O_3$ (MH^+) 183.1021, found 183.1022.
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