Dual Mechanisms of Acid-Catalyzed Rearrangement of Enol Ester Epoxides: Enantioselective Formation of α-Acyloxy Ketones

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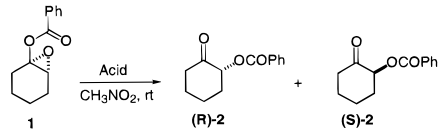
Enol ester epoxides can rearrange to α-acyloxy ketones or aldehydes under thermal or acidic conditions.[1,2] Investigations of these rearrangements have largely been carried out on steroids,[2a,b,d,g,h,k,l,n] and the mechanistic conclusions have been based on stereochemical analysis of the diastereomeric products. Rearrangements under thermal conditions proceed via intramolecular migration of the acyloxy group with inversion of configuration at the carbon to which the acyloxy group migrates.[2a,g] In contrast, most acid-catalyzed rearrangements occur with retention of configuration.[2b,h,k,l] While the proposed mechanisms have provided reasonable explanations for the observed stereochemistry in these cases, some uncertainty remains.[3] Recently, we reported the enantioselective epoxidation of enol esters using a fructose-derived ketone as catalyst.[4] The availability of enantiomerically enriched enol ester epoxides prompted us to study the factors involved in the rearrangements of these epoxides under acidic conditions with the aim of developing a route to enantiomerically enriched α-acyloxy ketones.[5] Herein we wish to report our preliminary studies in this area.

Our studies started with (*R*,*R*)-1-benzoyloxy-1,2-epoxycyclohexane (**1**) as a test substrate (Scheme 1). Treating epoxide **1** with protic acids such as *p*-TsOH led to a facile rearrangement with retention of configuration (Table 1, entry 1). The reaction was complete within 10 min as monitored by TLC, and the product showed only a 3% decrease in ee compared to the starting epoxide. In addition to catalysis by protic acids, we found that this rearrangement could also be catalyzed by Lewis acids. Interestingly, the ee of the product varied dramatically with the Lewis acids. For example, 85% ee was obtained for the product when $Sn(OTf)_2$ was employed (Table 1, entry 2), but only 15% ee was obtained when $La(OTf)_3$ was used (Table 1, entry 4). *Strikingly, it was found that the S isomer (inverted product) actually became the major product with certain Lewis acids (Table 1, entries 6−12).* High enantioselectivities (80−91% ee) were obtained with $YbCl_3$, $ErCl_3$, $AlMe_3$, and silica gel[6] (Table 1, entries 6, 8, 9, and 12).

Scheme 1



The results presented in Table 1 indicate that there are two distinct pathways involved in the acid-catalyzed rearrangement of enol ester epoxides, leading to two different enantiomers. Although a full understanding of the factors controlling this competition has not been attained, the acidity of the catalyst seems to play an important role. For example, when $Yb(OTf)_3$ was used as the catalyst, the *R* enantiomer of the rearranged product was obtained in 66% ee (Table 1, entry 5). On the other hand, when a notably weaker Lewis acid $YbCl_3$ was used, the *S* enantiomer was obtained in 82% ee (Table 1, entry 6). Pathways **a** and **b** outlined in Scheme 2 provide plausible mechanisms for the results. In pathway **a**, the complexation of a strong acid to the epoxide oxygen of **3** leads to cleavage of the C_1−O bond to form carbocation intermediate **5**. Subsequent acyl migration with retention of configuration gives acyloxy ketone **6**. In pathway **b**, the complexation of a weak acid to **3** weakens both epoxide bonds, facilitating acyloxy migration with inversion of configuration (**7**).[7,8]

The discovery of the two different rearrangement pathways prompted us to investigate more substrates to test the generality. Of particular interest was the possibility of generating either enantiomer of an acyloxy ketone in high ee from a single enantiomerically enriched enol ester epoxide. As shown in Table 2, *p*-TsOH proved to be an effective catalyst for rearrangement via pathway **a** for a variety of epoxides, giving products with retention of configuration in high stereospecificity. In most cases,

(1) For leading reviews on enol ester epoxide rearrangements, see: (a) McDonald, R. N. *Mech. Mol. Migr.* **1971**, *3*, 67−107. (b) Riehl, J.-J.; Casara, P.; Fourgerousse, A. *C. R. Acad. Sci. Paris, Ser. C* **1974**, *279*, 79−82.

(2) For examples of acid-catalyzed and thermal rearrangements of enol ester epoxides, see: (a) Soloway, A. H.; Considine, W. J.; Fukushima, D. K.; Gallagher, T. F. *J. Am. Chem. Soc.* **1954**, *76*, 2941−2943. (b) Leeds, N. S.; Fukushima, D. K.; Gallagher, T. F. *J. Am. Chem. Soc.* **1954**, *76*, 2943−2948. (c) Gardner, P. D. *J. Am. Chem. Soc.* **1956**, *78*, 3421−3424. (d) Johnson, W. S.; Gastambide, B.; Pappo, R. *J. Am. Chem. Soc.* **1957**, *79*, 1991−1994. (e) Shine, H. J.; Hunt, G. E. *J. Am. Chem. Soc.* **1958**, *80*, 2434−2435. (f) House, H. O.; Thompson, H. W. *J. Org. Chem.* **1961**, *26*, 3729−3734. (g) Williamson, K. L.; Johnson, W. S. *J. Org. Chem.* **1961**, *26*, 4563−4569. (h) Nambara, T.; Fishman, J. *J. Org. Chem.* **1962**, *27*, 2131−2135. (i) Draper, A. L.; Heilman, W. J.; Schaeffer, W. E.; Shine, H. J.; Shoolery, J. N. *J. Org. Chem.* **1962**, *27*, 2727−2729. (j) Riehl, J.-J.; Lehn, J.-M.; Hemmert, F. *Bull. Soc. Chim. Fr.* **1963**, 224−227. (k) Rhone, J. R.; Huffman, M. N. *Tetrahedron Lett.* **1965**, 1395−1398. (l) Williamson, K. L.; Coburn, J. I.; Herr, M. F. *J. Org. Chem.* **1967**, *32*, 3934−3937 (m) McDonald, R. N.; Tabor, T. E. *J. Am. Chem. Soc.* **1967**, *89*, 6573−6578. (n) Smith, S. C.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 6379−6380.

(3) For example, it was observed that treating an enol ester epoxide of epiandrosterone acetate with silicic acid at 50 °C for 17 h led to the formation of a mixture α and *β* epimeric 16-acetoxy ketones with a ratio of 1.8:1 in a 16.7% isolated yield (see ref 2d). The α isomer resulted from a rearrangement with retention of configuration, and the *β* isomer resulted from a rearrangement with inversion. On the basis of the observation that the α and *β* isomers did not undergo isomerization under the reaction conditions, it was suggested that these two isomers came from two competing reactions. However, it is not clear whether these two reactions were induced by acid alone or both acid and heat since the reaction was carried out at 50 °C.

(4) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819−7822.

(5) For leading references on nonenzymatic synthesis of enantiomerically enriched hydroxyketones and their derivatives, see: (a) Enders, D.; Bhushan, V. *Tetrahedron Lett.* **1988**, *29*, 2437−2440. (b) Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679−6690. (c) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919−934. (d) Hashiyama, T.; Morikawa, K.; Sharpless, K. B. *J. Org. Chem.* **1992**, *57*, 5067−5068. (e) Reddy, D. R.; Thornton, E. R. *J. Chem. Soc., Chem. Commun.* **1992**, 172−173. (f) D'Accolti, L.; Detomaso, A.; Fusco, C.; Rosa, A.; Curci, R. *J. Org. Chem.* **1993**, *58*, 3600−3601. (g) Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, *35*, 669−672. (h) Fududa, T.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 4389−4392. (i) Adam, W.; Fell, R. T.; Stegmann, V. R.; Saha-Moller, C. R. *J. Am. Chem. Soc.* **1998**, *120*, 708−714.

(6) For examples of silica gel catalyzed rearrangements, see refs 2a, b, and d. Both inversion and retention of configuration were reported.

(7) While the acidity of the catalyst is an important factor affecting the competition of the two pathways, the size and the coordination number of the Lewis acid could also be important. Full elucidation of these factors awaits further studies.

(8) To test whether the rearrangements proceed intermolecularly or intramolecularly, crossover experiments were carried out using a mixture of 1-acetoxy-1,2-epoxycyclohexane and 1-benzoyloxy-1,2-epoxycycloheptane as substrates under acidic conditions (*p*-TsOH, $YbCl_3$, $AlMe_3$, silica gel). In the case of *p*-TsOH, small amounts of crossover products (2-benzoyloxycyclohexanone and 2-acetoxycycloheptanone) were detected by GC and ^1H NMR. The amounts of these products were found to be concentration dependent (ca 6.8% at substrate concentration of 0.64 M and ca. 1.7% at substrate concentration of 0.018 M). In the cases of $YbCl_3$, $AlMe_3$, and Silica gel, the crossover products were found to be minimal (less than 0.5% at substrate concentration of 0.64 M and less than 0.2% at substrate concentration of 0.018 M) (for details see Supporting Information). All of these results suggest that the acid-catalyzed rearrangements proceed predominantly in an intramolecular fashion, particularly for pathway **b**. Further experiments with enantiomerically enriched enol ester epoxides showed that the enantioselectivities of the rearranged products were not affected by the substrate concentrations.

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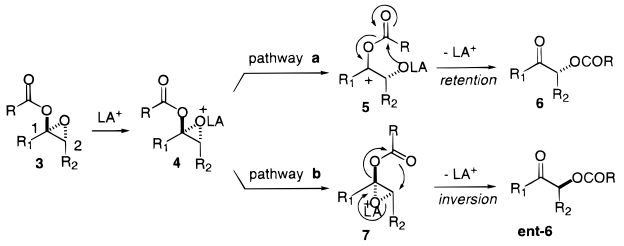
Table 1. Effects of Different Acid Catalysts on the Rearrangement of (*R,R*)-1-Benzoyloxy-1,2-epoxycyclohexane (**1**)[a]

entry	acid	*t* (min)	ee% (**1**)[b]	ee% (**2**)[b]	yield(%)[c]
1	*p*-TsOH	10	93	90 (R)	89
2	$Sn(OTf)_2$	10	93	85 (R)	84
3	$AlCl_3$	1	92	26 (R)	74
4	$La(OTf)_3$	40	93	15 (R)	88
5	$Yb(OTf)_3$	5	92	66 (R)	67
6	$YbCl_3$	90	93	82 (S)	76
7	$ZnBr_2$	10	93	12 (S)	48
8	$ErCl_3$	90	90	80 (S)	73
9	$AlMe_3$	5	91	87 (S)	85
10	$AlEt_2Cl$	17	91	67 (S)	54
11	$AlEtCl_2$	10	91	30 (S)	41
12	Silica gel	720	92	91 (S)	83

[a] All reactions were carried out in nitromethane under anhydrous conditions at room temperature using 10 mol % acid catalyst except entry 12 where 5−10 times (by weight) silica gel (Davisil 35−60 mesh, pH 7.0) was used. Epoxide **1** was freshly made and stored at −20 °C prior to use to avoid decomposition. [b] The enantiomeric excess was determined by HPLC (Chiracel OD). The absolute configuration of **2** was determined by comparing HPLC chromatograms with the authentic sample prepared from commercially available (*R,R*)-1,2-*trans*-cyclohexanediol. [c] Isolated yield.

Scheme 2



the resulting α-acyloxy ketones were crystalline, and the enantiomeric excess could be further enhanced by recrystallization. To test the generality of the rearrangement via pathway **b**, silica gel, $YbCl_3$, and $AlMe_3$ were used (Table 2). In most cases the isomer with inverted configuration was the major product;[9] however, in two cases (Table 2, entries 6 and 7) the rearrangement proceeded with retention of configuration. The preference for pathway **a** with these benzylic epoxides is probably due to a stabilized carbocation intermediate **5**.

In summary, a detailed study of enantiomerically enriched enol ester epoxides has shown that the acid-catalyzed rearrangement of these epoxides operates through two distinct pathways, one with retention of configuration and the other with inversion. Acidity of the catalyst is one important factor, with strong acids favoring retention of configuration and weak acids favoring inversion. *In addition to the mechanistic significance, the elucidation of the dual pathways for the acid-catalyzed enol ester epoxide rearrangement also provides the flexibility to synthesize either enantiomer of α-acyloxy ketone from one enantiomer of an enol ester epoxide by judicious choice of reaction conditions* (Scheme 3).

(9) We found that the thermal rearrangement of these epoxides could also lead to the formation of the inverted product with high stereospecificity when the rearrangements were carried out in sealed tubes at high temperature (160−190 °C) in vacuo. Since the Lewis acid-catalyzed rearrangement can be conveniently carried out at room temperature, it provides a mild method to obtain the inverted product, particularly for systems which are thermally sensitive.

(10) Nicolosi, G.; Patti, A.; Piattelli, M.; Sanfilippo, C. *Tetrahedron: Asymmetry* **1995**, *6*, 519−524.

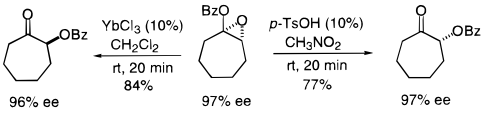
(11) Naemura, K. Wakebe, T.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 2585−2595.

Table 2. Examples of *p*-TsOH-, Silica gel-, $YbCl_3$-, or $AlMe_3$-Catalyzed Rearrangements of Enol Ester Epoxides[a]

entry	epoxide	acid	time (h)	epoxide ee (%)[d]	product ee (%)[e]	yield (%)[j]
1		*p*-TsOH	0.2	93	90 (99) (R)[f]	89
		silica gel	12	92	91 (S)	83
		$YbCl_3$	0.5	92	88 (S)	73
		$AlMe_3$	0.1	91	87 (S)	85
2		*p*-TsOH	0.1	93	93 (99) (R)[f]	70
		silica gel	19	93	88 (S)	87
		$AlMe_3$	0.1	91	85 (S)	85
3		*p*-TsOH	0.3	92	87 (99) (R)[f]	72
		silica gel	12	92	90 (S)	95
		$YbCl_3$	0.5	92	94 (S)	79
		$AlMe_3$	0.2	92	89 (S)	90
4		*p*-TsOH	0.3	97	97 (R)[g]	77
		silica gel	48	97	97 (S)	70
		$YbCl_3$	0.3	97	96 (S)	84
		$AlMe_3$	0.2	97	69 (S)	91
5[l]		*p*-TsOH	2	94	90 (99) (R)[h]	68
		$YbCl_3$	3	94	77 (S)	87
		$AlMe_3$[b]	0.1	94	69 (S)	79
6[l]		*p*-TsOH	0.3	94	94 (R)[i]	72
		$AlMe_3$[c]	5	94	90 (R)	71
7		*p*-TsOH	0.05	99	99 (R)[g]	79
		silica gel	48	99	38 (R)	45[k]
		$YbCl_3$	2.5	99	57 (R)	87
		$AlMe_3$	0.1	99	93 (R)	81

[a] All reactions were carried out at room temperature with 10 mol % *p*-TsOH (dried by azeotropic removal of its hydrate) in dry CH_3NO_2, or 5−10 times (by weight) silica gel (Davisil 35−60 mesh, pH 7.0) in CH_3NO_2, or 10 mol % $YbCl_3$ in CH_2Cl_2, or 10 mol % $AlMe_3$ in CH_3NO_2 unless otherwise noted. [b] 100 mol % $AlMe_3$ was used. [c] 20 mol % $AlMe_3$ was used. [d] Enantioselectivity was determined by chiral HPLC (Chiralcel OD) except entries 3 and 6 where enantioselectivity was determined by ^1H NMR shift analysis with $Eu(hfc)_3$. For determining absolute configuration of these epoxides see ref 4. [e] Enantioselectivity was determined by chiral HPLC (Chiralcel OD) except entry 3 where enantioselectivity was determined by ^1H NMR shift analysis with $Eu(hfc)_3$. The values in parentheses are the ee's after recrystallization. [f] The absolute configurations were determined by comparing HPLC chromatograms (entries 1 and 2) or ^1H NMR shift analysis using $Eu(hfc)_3$ (entry 3) with the authentic sample prepared from commercially available (*R,R*)-1,2-*trans*-cyclohexanediol. [g] The α-acyloxy ketones were hydrolyzed to α-hydroxy ketones, and the absolute configurations were determined by comparing the measured optical rotations of the α-hydroxy ketones with the literature (see: refs 10 and 11). [h] The absolute configuration was tentatively assigned by analogy. [i] The absolute configuration was determined by comparing the measured optical rotation with the literature (see: ref 5a). [j] Isolated yield. [k] Conversion determined by the ^1H NMR of the crude reaction mixture. [l] No reaction was found with silica gel.

Scheme 3



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Supporting Information Available: The characterization of enol ester epoxides and α-acyloxy ketones, the NMR spectral and HPLC data for the determination of the enantiomeric excess of these compounds, and the crossover experimental data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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