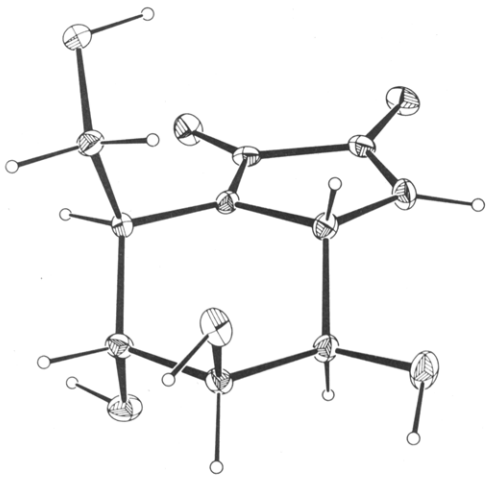

Figure 1. Molecular structure of 1 by an ORTEP drawing.

the fact that 1 showed inhibitory activity against α-mannosidase,[6] to be the same as those of mannose. The relative stereochemistry of kifunensine has thus been deduced to be as shown in 1.

For the confirmation of the presumed structure and determination of its stereochemistry, a single-crystal X-ray analysis was undertaken using crystals of 1: monoclinic, space group $P2_1$; unit cell a = 7.934 (2), b = 6.634 (1), and c = 8.933 (3) Å; β = 101.59 (3)°; V = 460.6 (2) Å^3; Z = 2, D_x = 1.68 g cm^{-3}. Intensities were measured with $2\theta/\omega$ scan mode using graphite-monochromated Mo Kα radiation (λ = 0.71069 Å). The structure was determined by the direct method (MULTAN 84) and successive block-diagonal least-squares and Fourier syntheses. Parameters were refined by using anisotropic temperature factors to R = 0.047 for 1273 reflections used ($F_o \geq 3\sigma(F_o)$). A perspective drawing of the structure of 1 is given in Figure 1. The structure of kifunensine was thus defined to be 1 (relative configuration). The absolute stereochemistry of 1 was presumed, on the basis of its biological activity (α-mannosidase inhibition), to be the D form.[10]

Kifunensine corresponds to a cyclic oxamide derivative of 1-amino-substituted mannojirimycin.[11,12] Because of its novel structure and interesting biological activity, kifunensine represents a unique 1,5-iminopyranose and provides a new insight into the chemistry and biochemistry of this class of compounds.

Supplementary Material Available: Details of the X-ray crystal analysis of 1 including tables of fractional coordinates, thermal parameters, bond lengths, and bond angles (5 pages). Ordering information is given on any current masthead page.

(10) Very recently, we have completed a synthesis of kifunensine from D-mannosamine, confirming its absolute structure. Details will be reported in due course.

(11) Mannojirimycin (nojirimycin B): Niwa, T.; Tsuruoka, T.; Goi, H.; Kodama, Y.; Itoh, J.; Inoue, S.; Yamada, Y.; Niida, T.; Nobe, M.; Ogawa, Y. *J. Antibiot.* **1984**, *37*, 1579.

(12) For a review on 1,5-iminopyranoses and 1,4-iminofuranoses, see: Fleet, G. W. J. *Spec. Publ. Royal Chem. Soc.* **1988**, No. 65, 149.

Studies on the Mechanism of the Asymmetric Epoxidation: A Ligand Variation Approach†

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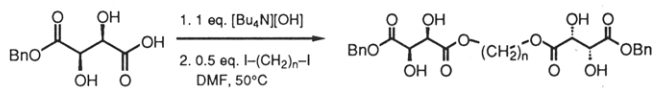
Summary: The application of linked bis-tartrate esters as ligands for the titanium-mediated asymmetric epoxidation is studied in order to gain information about the structure of the active catalytic species. The results obtained argue against the sole intermediacy of monomeric titanium–tartrate in the parent system.

Sir: Determination of the structure of the active species in any catalytic cycle is extremely difficult. The possibility of catalytic activity being derived solely from a minor species must be dealt with as unambiguously as is possible.[1] This paper details the synthesis of three linked bis-tartrate ligands and their use in epoxidation reactions to gain information about the structure of the active catalytic species in the titanium-mediated asymmetric epoxidation/kinetic resolution.[2]

The mechanism of the asymmetric epoxidation has been studied in detail in our laboratories.[3] A broad range of experimental data suggest that the predominant (~90%) species in solution generated by the addition of 1 equiv of dialkyl tartrate to a titanium alkoxide has a structure 1, analogous to the solid-state structure of a related derivative[4] (Figure 1). Kinetic studies support the hypothesis of epoxidation by such a species, and a stereochemical model has been developed to rationalize the observed sense and degree of asymmetric epoxidation and kinetic resolution.[5] However, one mechanistic possibility

Scheme I



3

4, n = 3, 51%

5, n = 4, 81%

6, n = 5, 84%

† This paper is dedicated to Dr. Günther Ohloff on the happy occasion of his 65th birthday.

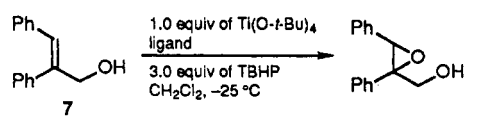
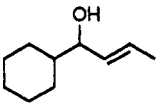
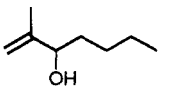
(1) Extensive studies of the rhodium–bisphosphine catalyzed asymmetric hydrogenation of α-aminoacrylic acid derivatives revealed that the major product (>60:1) was derived from the minor (~9%) alkyl hydride intermediate (see: Halpern, J. *Science* **1982**, *217*, 401).

(2) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. (c) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922. (d) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(3) (a) Woodard, S. S. Ph.D. Dissertation, Stanford University, Stanford, CA, 1981. (b) Sharpless, K. B.; Woodard, S. S.; Finn, M. G. *Pure Appl. Chem.* **1983**, *55*, 1823. (c) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 8. (d) Finn, M. G. Ph.D. Dissertation, Massachusetts Institute of Technology, Cambridge, MA, 1985. (e) Carlier, P. R.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 2978. (f) Burns, C. J.; Martin, C. A.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 2826.

0022-3263/89/1954-4016$01.50/0

Table I. Epoxidation Results

asymmetric epoxidation		kinetic resolution efficiencies (k_f/k_s)[b]		
 7			 8	 9
		ligand[a]		
(+)-DET (1.2 equiv)	>98 (2*S*)	DMT	19	–
(+)-**4** (0.6 equiv)	88 (2*S*)	DET	36	52[c]
(+)-**5** (0.6 equiv)	91 (2*S*)	DIPT	104	138
(+)-**6** (0.6 equiv)	94 (2*S*)	**4**	1.3[d]	5.9[d]
		5	1.2[d]	5.3[d]

[a] TBHP = *tert*-butyl hydroperoxide, DMT = dimethyl tartrate, DET = diethyl tartrate, DIPT = diisopropyl tartrate. [b] Values for DMT, DET, and DIPT reported in ref 3a, measured at −20 °C unless otherwise noted. [c] Measurements performed at 0 °C. [d] Reaction performed at −25 °C.

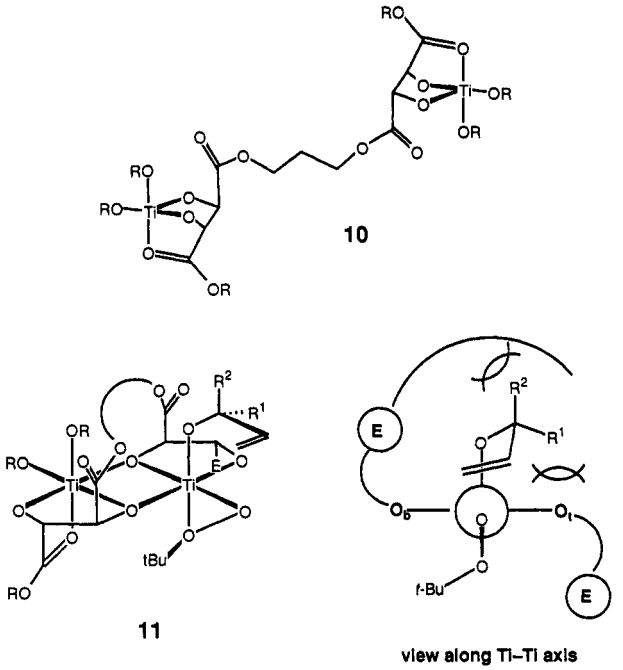


Figure 1.

we sought to rule out was epoxidation solely by a monomeric titanium–tartrate species **2**, present in a small equilibrium amount. The fact that the reaction is first-order with respect to the titanium–tartrate catalyst over a 10-fold range in concentration argues against the sole intermediacy of a monomeric titanium–tartrate.[6] However, the solution equilibria may be quite complex. Hence the failure to observe deviation from first-order behavior within this concentration range is less than definitive evidence. Therefore we sought to provide evidence of another kind by designing ligands that would allow experimental discrimination between epoxidation by monomer and dimer.

The desired linked bis-tartrate ligands **4–6** were synthesized by alkylation[7] of monobenzyltartaric acid **3** (Scheme I). The ligands proved labile to transesterification at room temperature in the presence of Ti(O-*i*-Pr)$_4$, but showed no sign of transesterification after 24 h at room temperature in the presence of Ti(O-*t*-Bu)$_4$. As it has been demonstrated that the rate of epoxidation is much faster than transesterification under the conditions of the reaction,[8] the integrity of the ligand during the epoxidation seemed assured. The ligands could always be recovered in greater than 90% yield after the reaction, lending credence to this hypothesis.[9] Preliminary efforts directed toward characterization of the Ti(O-*t*-Bu)$_4$ complexes of ligands **4–6** suggested that the binding mode adopted by these ligands is similar to that of the parent dialkyl tartrates.[10] Ligands **4–6** were then tested for their efficacy in asymmetric epoxidation and kinetic resolution using Ti(O-*t*-Bu)$_4$ as the precatalyst.[11] The titanium complexes derived from ligands **4–6** mediate high levels of asymmetric induction (88–94% ee, 2*S*) in the epoxidation of **7**, though not quite as high as the parent catalyst. The titanium complex derived from **6** also epoxides 2-undecen-1-ol in 88% ee (2*S*) under both stoichiometric and catalytic (5%) conditions. Thus it appears that the active catalytic species in the linked-tartrate manifold is very similar structurally to that in the parent system.

In contrast, however, the linked tartrate derived catalyst does not mediate efficient kinetic resolution of secondary allylic alcohols **8** and **9** (k_f/k_s = 1 to 6).[12] Prior to this study, no titanium tartrate catalyst had been examined that performed asymmetric epoxidation without simultaneously kinetically resolving secondary allylic alcohols. This decoupling of asymmetric epoxidation and kinetic resolution *activities* is thus unprecedented and quite significant.

(4) (a) Williams, I. D.; Pedersen, S. F.; Sharpless, K. B.; Lippard, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 6430. (b) For X-ray structures of three other titanium–tartrate species, see: Pedersen, S. F.; Dewan, J. C.; Eckman, R. R.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1279.

(5) For a full description of the stereochemical model for the asymmetric epoxidation and kinetic resolution see ref 3c, p 278–287.

(6) See ref 3c.

(7) Wagenknecht, J. H.; Baizer, J. L. *Synth. Commun.* **1972**, *2*, 215.

(8) See ref 3c.

(9) Recovery of the ligand in 90% yield of course does not rule out the possibility of sole catalysis by a minor transesterified species. However, note that transesterification would give rise to a titanium–tartrate complex derived from monomeric tartrates. Such a catalyst would be expected to efficiently mediate both asymmetric epoxidation and kinetic resolution of secondary allylic alcohols. Since this is not what is observed (vide infra), it is likely that the ligand maintains its integrity in the active species.

(10) IR spectroscopy confirmed the binding of all the ligand hydroxyls and showed the presence of both bound and unbound carbonyls. ^{1}H and ^{13}C NMR spectra of the complexes were poorly resolved, but were not inconsistent with the proposed structure. The molecularity of the Ti(O-*t*-Bu)$_4$ complex of ligand **5** was determined by the Signer method (see ref 3c) to be 1.2 ± 0.1, consistent with the predominance of 2:1 Ti:ligand species.

(11) The reactions were performed at −25 °C in CH_2Cl_2 with 100% catalyst, at substrate concentrations <0.1 M. In each case 0.6 equiv of the bis-tartrate ligand were used.

(12) Relative rates of epoxidation of the fast and slow enantiomers were calculated by means of an equation relating the percent ee of the remaining starting material and the percent conversion of the reaction:

$$k_f/k_s = \ln [(1 - c)(1 - ee)]/\ln [(1 - c)(1 + ee)]$$

(See ref 2b).

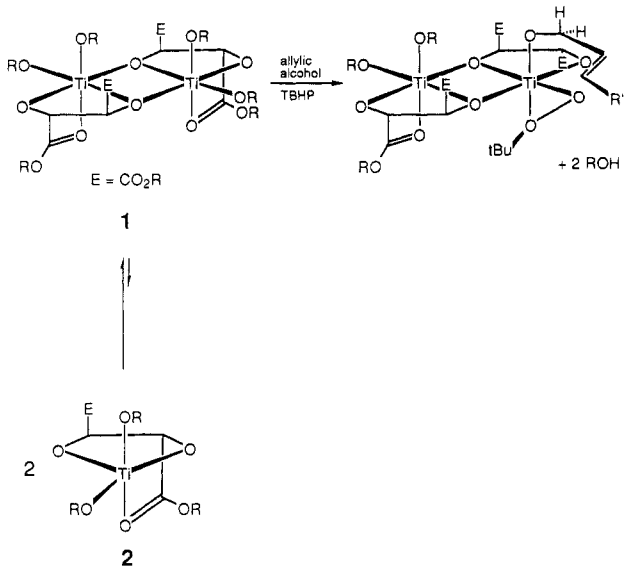


Figure 2.

On the basis of our stereochemical model, kinetic resolution is easier to account for than asymmetric epoxidation, as the former is merely a consequence of the steric disposition of the tartrate ligand around each titanium center. Additional stereoelectronic factors must be invoked in order to rationalize enantiofacially selective epoxidation.[13] Support for this unified model of kinetic resolution/asymmetric epoxidation is given by the observation of reasonable kinetic resolution (k_f/k_s = 16) but low levels of diastereoselectivity (60/40) in the epoxidation of cis secondary allylic alcohols.[14] Therefore it is likely that the perturbation induced by the inclusion of the link did not compromise the fundamental recognition characteristics of the catalyst but diminished its tolerance for substrate variation (primary vs secondary allylic alcohols).

Now let us consider how the structures of the possible catalytic species could affect the asymmetric epoxidation/kinetic resolution behavior of titanium tartrate. If epoxidation occurs solely via the intermediacy of a monomeric titanium–tartrate in the parent system, then epoxidation in the linked tartrate manifold would likely occur through a species such as **10** (Figure 2). The link between the ester groups in structure **10** is remote from the individual reaction sites and does not constrain optimization of the ideal coordination geometry enjoyed by **2**. Thus one would expect a species such as **10** to behave similarly in all respects to a catalyst derived from monomeric dialkyl tartrates. The inability of the linked tartrate derived catalyst to mediate efficient kinetic resolution of secondary allylic alcohols thus argues against the sole intermediacy of **10** and against epoxidation exclusively by monomeric titanium–tartrate in the parent system.

The behavior of the linked tartrate derived catalyst can be rationalized if the catalyst reacts in the familiar dimer conformation **11**, as the bridge could quite conceivably perturb the ideal coordination geometry of the allylic alcohol. In this regard secondary allylic alcohols would be more affected by the bridge than primary allylic alcohols, simply by virtue of greater steric bulk at the carbinol carbon. Examination of molecular models indicates that while epoxidation of primary allylic alcohols ($R^1 = R^2 =$ H) could proceed largely unperturbed, the presence of the bridge would impede reaction of the fast enantiomer (R^1 = H, R^2 = alkyl) of a secondary allylic alcohol, due to nonbonded steric interactions absent in the parent catalyst.[15] The rate of epoxidation of the slow enantiomer (R^1 = alkyl, R^2 = H) would be largely unchanged, thus decreasing the kinetic resolution efficiency k_f/k_s.

Acknowledgment. We thank the National Institutes of Health (Grant GM-28384) and the National Science Foundation (Grant CHE-8303355) for generous support of this work.

Supplementary Material Available: Experimental details and spectral data for compounds **3–6** (5 pages). Ordering information is given on any current masthead page.

(13) Besides attainment of the optimum S_N2-like olefin–peroxide bond trajectory, the most likely stereoelectronic effects are believed to be a preference for a spiro (vs planar) arrangement of the η^2-alkyl peroxide and olefin and a low (i.e. 0–30°) O–C_1/C_2–C_3 dihedral angle of the allylic alkoxide.

(14) See ref 3c.

(15) It should be noted that as the exact details of catalyst loading are not known, the reactants could conceivably load on the opposite side of the Ti_2O_2 plane from the link. However, it is hard to imagine how such an arrangement would adversely affect kinetic resolution, and it is precisely that adverse effect that we are trying to explain.