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Asymmetric Synthesis of Cyclic Hydroxy Ketones Derived from Enol Ethers via Sharpless Asymmetric Dihydroxylation. A Study in the Correlation of the Enol Ether Chain Length and Enantioselectivity

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The Sharpless asymmetric dihydroxylation reaction of enol ethers derived from their corresponding cyclic ketones, gave α-hydroxyketones with high enantioselectivity. The enantiomeric excess was found to be proportional to the length of the unbranched enol ether chain with a maximum ee for the pentyl enol ether. An efficient synthesis of α-hydroxy chromanone in >90% ee was demonstrated using this method.

Introduction

α-Hydroxy ketones are important synthons for the chiral synthesis of natural products, fine chemicals, and medicines.[1] Previously, Sharpless showed that they can be synthesized from methyl and *tert*-butyldimethylsilyl (TBDMS) enol ethers of open-chain hydrocarbons[2] and also methyl and TBDMS enol ethers of cyclic ketones[3] using the osmium-catalyzed asymmetric dihydroxylation (AD) reaction.[4]

We had been looking for a new efficient chiral preparation of α-hydroxy ketone **3** as an intermediate to *cis*-aminochromanol (**5**)[5] (Scheme 1), an important class of amino alcohol for the development of biologically active compounds. When we investigated the Sharpless AD reaction as a possible method for producing **3**, we discovered a correlation between the enol ether chain length and enantioselectivity. In this paper, we present a study of the Sharpless AD reaction of enol ethers derived from cyclic ketones that examines this correlation. The results of this study have produced a general method for the asymmetric synthesis of cyclic hydroxy ketones and an efficient new preparative method for the synthesis of **3**.

Results and Discussion

Our approach to hydroxychromanone (**3**) and its conversion to *cis*-aminochromanol (**5**) are outlined in Scheme **1**. The methyl enol ether **2a** was prepared as described in the literature[2] by heating the ketone **1** with trimethylorthoformate, excess methanol, and catalytic *p*-toluenesulfonic acid followed by slow distillation.

Our initial asymmetric dihydroxylation reactions required double the suggested quantity[2] of the commercially available AD *β*-mixture along with additive methanesulfonamide, in a 50/50 mixture of acetonitrile/water at 0 °C 18 h for completion. (*R*)-α-Hydroxy chromanone (**3**) was produced in 66% LC assay yield and 82% ee. The AD α-mixture was used on the TBDMS enol ether of chromanone, yielding the (*S*)-α-hydroxy ketone in 81% LC assay yield and 58% ee. In addition to the modest induction, this method was impractical because for each gram of **2a**, 13 g of reagent and 65 mL of solvent were required.

Better yields and a more practical process were obtained when we directly prepared the Sharpless AD *β*-mixture with a few modifications.[6] As reported in the literature, the use of sodium persulfate as a co-oxidant requires catalytic amounts of potassium ferricyanide.[7] By applying this method, we were able to reduce the amount of potassium ferricyanide from 6 to 0.2 equiv by using only 1.5 equiv of sodium persulfate (for each gram of **2a**, now only 6 g of reagents and 24 mL of solvent were required). When applied to the methyl enol ether of chromanone, the assay yield increased to 90% with the ee at 83% (*R*).

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(5) For literature on work previously performed on the synthesis of *cis*-aminochromanol, see: (a) Davies, I. W.; Taylor, M.; Marcoux, J. F.; Matty, L.; Wu, J.; Hughes, D.; Reider, P. J. *Tetrahedron Lett.* **2000**, *41*, 8021. (b) Hansen, K. B.; Rabbat, P.; Springfield, S. A.; Devine, P. N.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 8743.

(6) For 5 mmol of enol ether, the AD-mixture contained $K_3Fe(CN)_6$ (329 mg, 1 mmol), $Na_2S_2O_8$ (1.79 g, 7.5 mmol), K_2CO_3 (4.15 g, 30 mmol), $(DHQD)_2PHAL$ for the *β*-mixture or $(DHQ)_2PHAL$ for the α-mixture (77.9 mg, 0.1 mmol), $K_2OsO_4 \cdot 2H_2O$ (18.4 mg, 0.05 mmol), and $CH_3SO_2NH_2$ (500 mg, 5.25 mmol).

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SCHEME 1

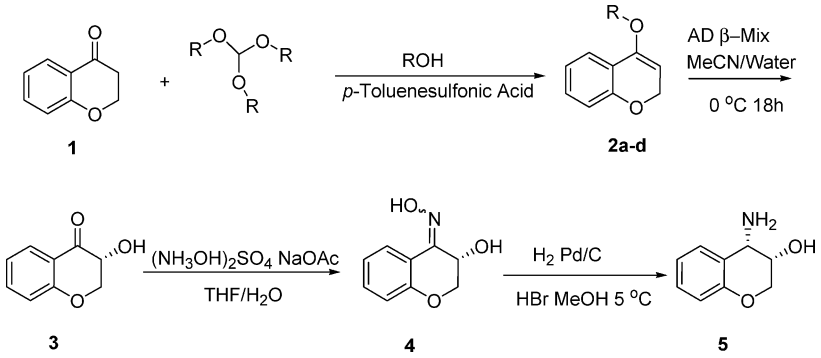
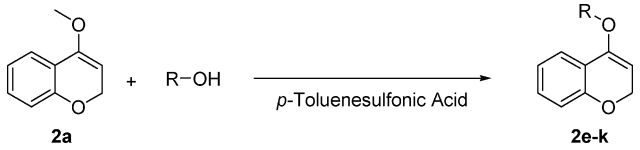


TABLE 1. AD of Enol Ethers with Modified α- and *β*-Mixtures

			yield %[8]		ee %	
entry	compd	R	α-mixture	*β*-mixture	α-mixture	*β*-mixture
1	**2a**	methyl[a]	69	90	66 (*S*)	83 (*R*)
2	**2b**	ethyl[a]		75		89 (*R*)
3	**2c**	propyl[a]		87		92 (*R*)
4	**2d**	butyl[a]	73	74	80 (*S*)	92 (*R*)
5	**2e**	pentyl	77	99	92 (*S*)	94 (*R*)
6	**2f**	decyl		49		95 (*R*)
7	**2g**	isopropyl	91	70	12 (*S*)	20 (*R*)
8	**2h**	isobutyl		59		86 (*R*)
9	**2i**	isopentyl		23		76 (*R*)
10	**2j**	methoxy ethyl		75		84 (*R*)
11	**2k**	benzyl		94		64 (*R*)
12	**6a**	methyl[a]	88	89	92 (*S*)	93 (*R*)
13	**6b**	propyl		79		94 (*R*)
14	**6c**	pentyl	53	82	96 (*S*)	97 (*R*)
15	**6d**	isopropyl	68	85	26 (*S*)	36 (*R*)
16	**6e**	isobutyl		95		94 (*R*)
17	**6f**	phenyl		70		38 (*R*)
18	**8a**	methyl[a]	80	87	74 (*S*)	83 (*R*)
19	**8b**	propyl		99		93 (*R*)
20	**8c**	pentyl	53	25	94 (*S*)	92 (*R*)
21	**8d**	isopropyl	68	89	26 (*S*)	36 (*R*)
22	**10a**	methyl[a]	48	47	76 (*R*)	79 (*S*)
23	**10b**	pentyl	49	31	90 (*R*)	92 (*S*)
24	**12a**	methyl[a]	49	78	83 (*R*)	87 (*S*)
25	**12b**	pentyl	47	50	92 (*R*)	90 (*S*)

[a] Enol ethers that were made according to ref 2.

SCHEME 2

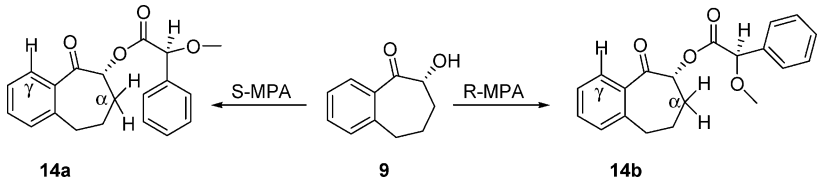


On the basis of the literature, we did not expect to see much variation of enantioselectivity with the ether chain length. However, we decided to examine this by preparing enol ethers **2a**−**k** (Table 1). The ethyl, propyl, and butyl enol ethers were prepared as stated above via the trialkylorthoformate method. When this method was applied to the higher boiling alcohols, the reactions were very sluggish and incomplete. Attempts to make the isopropyl enol ether of chromanone (**2g**) gave no reaction. This problem was resolved by implementing a simple exchange reaction (Scheme 2). The methyl enol ether **2a** was heated with an excess of the higher alcohol and catalytic *p*-toluenesulfonic acid while distilling off methanol. Fractional distillation gave the desired higher enol ethers in moderate to good yields. Enol ether **2g** was isolated in 87% yield. Yields of pure enol ethers of chain length pentyl and higher were lower (e.g., pentyl = 50% yield) because of mixed fractions and large pot residues due to polymerization.

The enol ethers **2a**−**k** (Table 1, entries 1−11) were hydroxylated using the modified *β*-mixture conditions. Surprisingly, a steady increase in enantiomeric excess from 83 to 94% was observed with enol ethers from methyl to pentyl (entries 1−5). Any further increase in chain length gave no significant improvement in enantioselectivity, as demonstrated by the decyl enol ether, with only a 1% increase in ee (entry 6).

When the modified AD *β*-mixture was applied to **2g** (entry 7), the ee decreased dramatically to 20%, indicating that branching of the alkyl group is not advantageous to enantioselectivity. When the branching occurred after the C1 position, the ee recovered to a level comparable to the unbranched cases. This is demonstrated by the isobutyl ether (86% ee) (entry 8) and the isopentyl ether (76% ee) (entry 9). However, the enantioselectivity of the branched enols did not exceed that of the unbranched enols.

SCHEME 3. Absolute Configuration Determination via MPA Ester Derivatization of 9



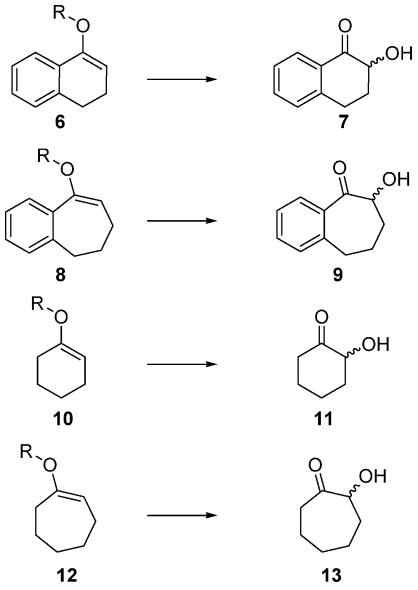


FIGURE 1. Enol Ethers to α-Hydroxy Ketones With Modified AD Conditions.

Replacement of one of the carbon atoms in the enol chain with a heteroatom reduced the selectivity, as demonstrated by comparing the methoxyethyl ether (84% ee) (entry 10) with the butyl ether (92% ee) (entry 4). Finally, when the modified AD *β*-mixture was applied to the benzyl ether, the enantiomeric excess was a modest 64% (entry 11), indicating again that branching can be deleterious to the enantioselectivity. The same trends were observed with the α-mixture but with an even greater range of ee when going from the methyl (66% ee) (entry 1) to the pentyl (92% ee) (entry 5). The isopropyl ether gave nearly racemic hydroxyketone with an ee of just 12% (entry 7).

These results show that optimal enantioselectivity was obtained with the pentyl enol ether, giving a yield of 99% and an ee of 94%. The decrease in quantity of reagents by 80%, along with the high yield and high ee, made the Sharpless AD reaction a useful, preparative method for the production of either enantiomer of α-hydroxychromanone.

As summarized in Table 1, the method is applicable for the enantioselective hydroxylation of enol ethers derived from other cyclic ketones (Figure 1) such as tetralone and benzosuberone with the same effect of chain length and branching of the alkyl group as **2**. The pentyl enol ethers **6c** and **8c** gave excellent enantioselectivity with ees of 97 and 92%, respectively. Interestingly, the phenyl ether **6f** (entry 17) with branching occurring at C1 gave an enantiomeric excess of the same magnitude as the isopropyl ether **6d** (entry 15).

Racemic α-hydroxycyclohexanone is a commercially available reagent used as a building block in organic synthesis. There are no simple efficient methods for the asymmetric synthesis of either enantiomer. Therefore, it was rewarding to observe that our method is applicable to the synthesis of α-hydroxycyclohexanone (**11**) and α-hydroxycycloheptanone (**13**). The α-hydroxy ketones were produced in good ee with the α- and *β*-mixtures. The pentyl enol ethers **10b** and **12b** gave an enantiomeric excess ≥ 90%.

TABLE 2. Chemical Shifts of α- and *γ*-Protons of MPA Esters

compd	δ (*R*,*R*)- or (*S*,*S*)-MPA ester	δ (*R*,*S*)- or (*S*,*R*)-MPA ester	$\Delta\delta$ (*R*,*S*)- or (*S*,*R*)-
3 α 1H	4.55	4.39	0.16
3 α 1H	4.45	4.27	0.18
3 *γ* 1H	7.85	7.90	−0.05
7 α 1H	3.07	3.01	0.06
7 α 1H	2.30	2.20	0.10
7 *γ* 1H	8.00	8.04	−0.04
9 α 1H	2.22	2.08	0.14
9 α 1H	2.09	1.98	0.11
9 *γ* 1H	7.65	7.44	−0.09

Absolute Configuration. Absolute configurations for **3**,[5b] **7**,[9] and **11**[10] have been reported in the literature. The absolute configuration of **9** was assumed on the basis of the following supportive data.

The SFC retention time profile of compounds **3** and **7** showed that the (*R*)-enantiomers eluted later than the (*S*)-enantiomers. We therefore extrapolated that compound **9**, being structurally similar to **3** and **7**, would have an analogous SFC profile, with the (*R*)-enantiomer being the later elutant.

Derivatization experiments were carried out on **9** on the basis of the work of Riguera.[11] He showed that the absolute configuration of secondary alcohols can be deduced by ^{1}H NMR by esterifying both alcohol enantiomers with either (*R*)- or (*S*)-methoxyphenylacetic acid (MPA) (Scheme 3). Comparisons of the adjacent protons of the MPA ester bearing a carbon determine the configurations as shown by his mnemonic. The results of these experiments were consistent with the same experiments as carried out on hydroxy ketones **3** and **7** with known configurations (Table 2).

The absolute configuration of **13**, made with the *β*-mixture, was designated (*S*)- on the basis of the assumption of analogous chiral GC retention times and optical rotations with the known (*S*)-α-hydroxycyclohexanone, also made with the *β*-mixture.

(8) Standard conditions were used for all AD reactions; therefore, the yields were not optimized.

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(10) Lee, L. G.; Whitesides, G. M. *J. Org. Chem.* **1986**, *51*, 25.

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Conclusion

We have shown that the Sharpless AD reaction, with a few modifications, gives α-hydroxyketones from enol ethers of cyclic ketones, with high enantioselectivity. The degree of the enantiomeric excess is proportional to the length of the unbranched enol ether chain, giving optimum enantioselectivity with the pentyl moiety. Branching of the enol ether chain results in decreased selectivity, especially with branching at the C1 carbon. These results led to an efficient scalable synthesis of α-hydroxy chromanone (99% yield, 94% ee), a precursor of *cis*-aminochromanol, an important amino alcohol for the synthesis of vital biologically active compounds. The method has also been shown to be effective for the production of other enantiomerically enriched α-hydroxy ketones including (*R*)- and (*S*)-α-hydroxycyclohexanone, an important building block in organic synthesis.

Experimental Section

General Procedure for Enol Ethers 2e−k, 6b−f, 8b−d, 10b, and 12b. Preparation of 4-Isopropoxy-2*H*-chromene (2g). Methyl enol (**2a**) (10.0 g, 61.7 mmol), 2-propanol (10 mL), and *p*-toluenesulfonic acid monohydrate (20 mg, 1.105 mmol) were combined and heated at 80 °C for 2 h. The temperature was increased to 110 °C allowing the low-boiling components to distill. A concentric tube column distillation head was used to collect 10.2 g of a clear colorless oil containing 78 mol % **2g** at 112 °C and 4 Torr: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (d, J = 6.1, 6H), 4.4 (m, 1H), 4.74 (t, J = 3.9, 1H), 4.88 (d, J = 3.9, 2H), 6.85 (dd, J = 8.1, 1.0, 1H), 6.95 (td, J = 7.5, 1.1 1H), 7.19 (td, J = 7.7, 1.7, 1H), 7.49 (dd, J = 7.7, 1.7 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8, 65.8, 69.1, 90.4, 115.6, 120.9, 121.3, 122.5, 129.6, 148.1, 155.7; GCMS *m*/*z* 190, 147, 121, 91, 65.

General Procedure for α-Hydroxy Ketones 3, 7, 9, 11, and 13. Preparation of (*R*)-α-Hydroxychromanone (3) from 1a. A slurry of $K_3Fe(CN)_6$ (1.65 g, 5.0 mmol), $Na_2S_2O_8$ (8.95 g, 37.5 mmol), K_2CO_3 (20.8 g, 150 mmol), $K_2OsO_4 \cdot 2H_2O$ (92 mg, 0.25 mmol), $CH_3SO_2NH_2$ (2.5 g, 26.3 mmol), and $(DHQD)_2PHAL$ (390 mg, 0.50 mmol) in CH_3CN (50 mL) and water (50 mL) was aged at 0 °C for 10 min. To the slurry was added the methyl enol ether **2a** (4.05 g, 25 mmol), and the mixture was aged overnight at 0 °C. Methyl *tert*-butyl ether (MTBE) (50 mL) and 20% brine solution (50 mL) were added, and the layers were separated. The aqueous layer was back-extracted with MTBE (50 mL) and the combined organic layers were washed with 20% brine solution. The organic layer was dried with Na_2SO_4 and stripped of solvents to give **3** as a yellow oil (3.65 g, 22.5 mmol). $[\alpha]^{20}_D$ +71.25 ($CHCl_3$); SFC retention times, 7.6 min for the (*R*)-enantiomer and 6.7 min for the (*S*)-enantiomer. Isolation of **3** as a white crystalline solid was achieved by crystallization from ethyl acetate and hexanes.

(6*R*)-5-Oxo-6,7,8,9-tetrahydro-5*H*-benzo[*a*][7]annulen-6-yl (2*S*)-(Methyloxy)(phenyl)ethanoate (14a): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (m, 1H), 1.98 (m, 1H), 2.04 (m, 1H), 2.08 (m, 1H), 2.95 (m, 2H), 3.46 (s, 3H), 4.40 (s, 1H), 5.42 (m,-1H), 7.19 (d, J = 7.6, 1H), 7.30 (t, J = 7.6, 1H), 7.35 (om, 3H), 7.41 (td, J = 7.6, 1.5, 1H), 7.45 (m,2H), 7.74 (dd, J = 7.6, 1.5, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.3, 28.9, 34.0, 57.5, 78.3, 82.2, 126.7, 127.3, 128.6, 128.7, 129.2, 129.9, 132.1, 136.1, 136.5, 141.4, 169.9, 199.1.

Supporting Information Available: General experimental procedure, product data for compounds **2b**−**f**, **2h**−**k**, **7**, **6a**−**f**, **8a**−**d**, **9**, **10a**,**b**, **11**, **12a**,**b**, **13**, **14b**, **15a**,**b**, and **16a**,**b**, and copies of ^{1}H and ^{13}C NMR spectra for compounds **2**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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