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## Enantioselective synthesis of $\alpha$ -hydroxyacids through oxidation of terminal alkenes with AD-mix/TEMPO

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## Abstract

 $\alpha$ -Hydroxyacids can be enantioselectively prepared by means of a two-step oxidation process, involving first the asymmetric dihydroxylation of a terminal alkene and subsequent oxidation with TEMPO/NaOCl/NaClO<sub>2</sub> in good to excellent yields. No fragmentation of the glycol intermediate was detected. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: TEMPO; asymmetric dihydroxylation; α-hydroxyacids; oxidation.

In the course of our research programme aimed at the synthesis of eudesmanolides from *Umbelliferae* plants, we envisaged the retrosynthetic analysis depicted in Fig. 1, to access the  $\alpha$ -hydroxy- $\gamma$ -lactone moiety.

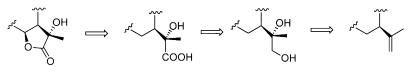


Fig. 1.

As is well known, 1,2-diols are very prone to undergo fragmentation reactions under oxidative conditions. However, if these conditions were mild enough, their oxidation would provide us with the required  $\alpha$ -hydroxyacids in a simple manner. Being aware of such a difficulty, we undertook a search for a method which allowed the oxidation of glycols while avoiding the oxidative cleavage of the molecule.

 $\alpha$ -Hydroxyacids are important in the field of organic synthesis for several reasons.<sup>1</sup> For instance, mandelic acid and many of its derivatives are used as chiral intermediates and resolving agents of alcohols and amines.<sup>2</sup> The *C*<sub>2</sub>-symmetry backbone of tartaric acid has long been recognised as a valuable chiral ligand in numerous asymmetric processes, especially the Sharpless epoxidation.<sup>3</sup> MTPA (Mosher's

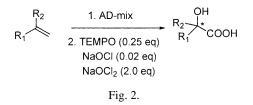
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reagent) and MPA have been used in the determination of the absolute configuration of amines and secondary alcohols by NMR.<sup>4</sup>  $\alpha$ -Hydroxyacids also find applications in the cosmetics industry as antiageing factors.<sup>5</sup>

Even though several synthetic routes have been developed,<sup>6</sup>  $\alpha$ -hydroxyacids are usually obtained from natural sources, either directly or after some transformations.

Since the asymmetric dihydroxylation of a terminal double bond provides an optically active glycol, we thought that subsequent oxidation of the primary alcohol would produce the corresponding homochiral  $\alpha$ -hydroxyacid (Fig. 2).



The Sharpless asymmetric dihydroxylation (AD) is a well-known process. The availability of the ADmix ( $\alpha$  and  $\beta$ ), the high enantiomeric excess and the simplicity of the work-up make this reaction an excellent choice to provide optically active material for many synthetic processes.<sup>7</sup>

The problem is in the oxidation of the glycol. As was previously pointed out, oxidation of the primary alcohol in the presence of a vicinal tertiary alcohol leads in most cases to fragmentation of the molecule. Any oxidation process involving esters of metals as intermediates (M=Cr, Mn, Os, Ru) leads to decarboxylative rearrangements. We tried different oxidation reagents. The Swern oxidation produced in most substrates an intractable mixture of products. The NMR analysis of this mixture displayed the presence of the aldehyde proton, but any attempt at isolation was unsuccessful.<sup>8</sup> IBX oxidation<sup>9</sup> led us to the same result. Dess–Martin periodinane is described to fragment glycols<sup>9</sup> and oxidation with NaOCl/NaOCl<sub>2</sub> also gave negative results.

Our attention was then drawn to a paper by Zhao et al., which described the oxidation of primary alcohols to carboxylic acids with sodium chlorite catalysed by TEMPO and bleach.<sup>10</sup> The TEMPO radical is oxidised to an *N*-oxoammonium ion which is the active species in the oxidation of the primary alcohol. The proposed mechanism suggested to us that no fragmentation product should be produced. This fact prompted us to investigate the oxidation of the glycols under those conditions. To our delight, we observed that in most cases, the oxidation proceeded smoothly yielding the  $\alpha$ -hydroxyacids in good yields. In many cases, the reaction needed to be mildly heated to reach completion. The results are displayed in Table 1. The nature of the terminal alkene prevents epimerisation at the carbon bearing the tertiary hydroxyl group, as no hydrogen is available at that position to be removed. The *ee/de* are thus determined by the effectiveness of the Sharpless asymmetric dihydroxylations.<sup>11</sup>

The presence of an electron-withdrawing group enhances the yield of the process, as observed in entries 1 and 2. Entry 2 accounts for the preparation of the precursor of the Mosher's reagent. The oxidation is also possible when the aromatic ring bears an amino group, as long as it is protected (entry 3). As expected, when no acetate group was present, the yields lowered to 25-30%. Marked differences were observed for the benzyl methacrylate (entry 6) when treated with AD-mix- $\alpha$  (good yield in the TEMPO oxidation step, 85%) or AD-mix- $\beta$  (only moderate yield, 51%), but in both cases, the dicarboxylic derivative could be isolated.<sup>12</sup> Finally, entries 7 and 8 constitute two interesting examples. In both cases, the major diastereomer was the same for any oxidising mixture. In the case of the 6-hydroxy-cyperone (entry 8), we were surprised that the allylic secondary alcohol remained unaltered, allowing after lactonisation, the synthesis of several 11-hydroxy-eudesmanolides.

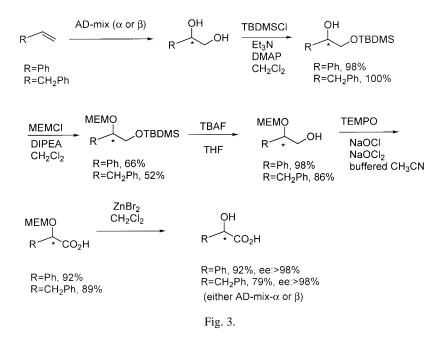
Table 1

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Entry	Starting Material	Product	Yield AD <sup>a</sup>	Yield of TEMPO oxidation (ee or de)
1	CH <sub>3</sub> Ph	CH₃ Ph- ←OH ★ COOH	AD-mix α: 100% AD-mix β: <u>9</u> 6%	60% ( <i>ee</i> .>98%) 68% ( <i>ee</i> . 79%)
2	CF <sub>3</sub> Ph	CF <sub>3</sub> Ph-+OH COOH	AD-mix α: 77% AD-mix β: 65%	80% (ee. 96%) 80% (ee. 50%)
3	AcNH	AcNH OH * COOH	AD-mix α: 80% AD-mix β: 60%	67% <sup>b</sup> 57% <sup>b</sup>
4		соон ОН	AD-mix α: 80% AD-mix β: 95%	69% <sup>c</sup> 79% <sup>c</sup>
5		соон	AD-mix α: 100% AD-mix β: 88%	73% (ee. 74%) 91% (ee. 79%)
6	OBn	HOOC * OBn	AD-mix α: 85% AD-mix β: 86%	85% <sup>b</sup> 51% <sup>b</sup>
7	X	Соон	AD-mix α: 92% AD-mix β: 86%	73% ( <i>de</i> . 40%) <sup>d</sup> 71% ( <i>de</i> . 78%) <sup>d</sup>
8 0 <sup>-</sup>		он соон	AD-mix α: 87% AD-mix β: 77%	54% ( <i>de.</i> >98%) <sup>d</sup> 62% ( <i>de.</i> >98%) <sup>d</sup>

<sup>a</sup> The absolute configuration can easily be deduced by applying the mnemonic rule developed by Sharpless. See i.e. ref. 7. <sup>b</sup>Unable to determine its optical purity. Produced an intractable mixture upon treatment with several coupling reagents. <sup>c</sup> Dihydrocarvone was used as a mixture of isomers. <sup>d</sup> Both AD-mixes led to the same diastereomer as the major compound.

This procedure could even be successfully applied when the double bond is monosubstituted as long as some precautions are taken. When the glycols from styrene and allylbenzene were submitted to the same conditions, cleavage of the diol was observed. Nevertheless this problem was easily solved by the selective protection of the secondary hydroxyl group (Fig. 3). This route provided us with optically active mandelic and phenyllactic acids.



In conclusion, this procedure allows for the direct and easy conversion of terminal alkenes into optically active  $\alpha$ -hydroxyacids avoiding the common glycol cleavage observed in this kind of substrate under most oxidative conditions. In this way, valuable compounds like mandelic, atrolactic or phenyllactic acids can easily be synthesised.

*General procedure*. The general procedure is based on those described by Sharpless (AD)<sup>11</sup> and Anelli (TEMPO),<sup>13</sup> although some modifications were introduced: 1 mmol of olefin was dissolved in *t*-BuOH:H<sub>2</sub>O (1:1, 10 mL) and 1.49 g of AD-mix was added. The mixture was stirred at rt for 18 h. Then, the reaction was quenched by adding 500 mg of sodium sulfite and it was stirred for 10 min. *t*-BuOH was removed under vacuum and the aqueous layer was extracted with EtOAc (25 ml×3). The organic layer was dried over sodium sulfate and the solvent was removed under vacuum. The resulting residue was dissolved in acetonitrile (5 mL) and sodium phosphate buffer (4 mL, pH=6.5). Then, 0.25 mmol of TEMPO, sodium chlorite (2 mmol) and diluted bleach (0.02 mmol, 4% active chlorine) were added and the mixture was heated to 55°C.

After four days, the reaction was allowed to cool down to rt and water (10 mL) was added. The pH was set to 8 with 1N NaOH and cool aqueous sodium sulfite (0.4 g in 8 ml of water) was added. The pH was lowered to 2 with 1N HCl and the mixture was extracted with EtOAc (25 ml×3). The organic layer was dried over sodium sulfate and the solvent removed by rotary evaporation. The resulting crude mixtures contained only the desired  $\alpha$ -hydroxyacids, although in some cases some TEMPO-derived impurities remained.

The optical purity was determined by esterification of the resulting  $\alpha$ -hydroxyacid with (+)-menthol using O,O'-di(2-pyridyl) thiocarbonate (DPTC) as coupling reagent.<sup>14</sup>

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