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STEREOSELECTIVE ACETOXYLATION OF CHIRAL PHENYLACETIC ESTERS

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Summary : Asymmetric oxidation of substituted phenylacetic acids was performed using D.D.Q. as oxidizing reagent. The formation of a donor-acceptor intermediate complex between substrate and reagent accounted for the d.e. observed and the configuration of the major products obtained.

Optically active α hydroxy carboxylic compounds are versatile chiral building blocks for asymmetric synthesis[1] and are important structural subunits of natural products[2]. These products have been obtained by chemical[3a] or biochemical[3b] reduction of α keto esters, by selective oxidation of one enantiomer of racemic 1,2-diols using enzymes as shown by WONG[5] or from chiral glyoxylates via an asymmetric Ene Reaction as shown by WHITESELL[4]. Using more accessible carboxylic acids as precursors however, is a more interesting strategy and direct hydroxylation of chiral enolates with dibenzylperoxydicarbonates[6], molybdenum peroxo complexes[7], sulfonyloxaziridine derivatives[8] or of chiral E-silyl ketene acetals with lead tetracetate[9] has been successfully performed using this route. Recent reports indicate that the control of the approach of aromatic substrates can be obtained by a donor-acceptor interaction between the substrate (acting as donor) and an electron deficient reagent (acting as acceptor). Regio and chemoselective chlorination[10], bromination[11] and nitration[12] of aromatic substrates were successfully obtained using this methodology[13]. D.D.Q is known to form charge transfer complexes readily and its use as oxidation reagent for chiral ester or amide derivatives was shown to be diastereoselective[14]. Formation of a donor-acceptor intermediate complex during the course of the reaction was responsible for the deep coloration (red to blue) which vanished at the end of the reaction and permitted diastereoselective oxidation at room temperature, in a protic solvent.

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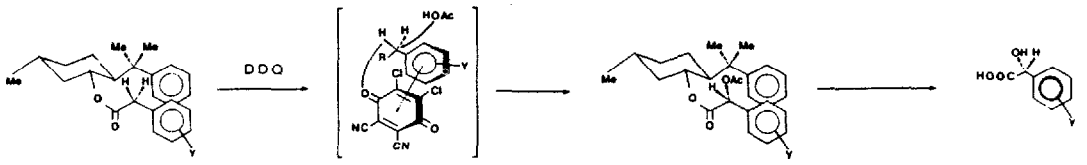
In the present work we describe the formation of various substituted mandelic acids using this methodology. We first studied the effect of various inductors on the diastereoselection of the acetoxylation reaction using D.D.Q. as oxidizing agent (table I).

	Chemical yield 2	d.e.	Configuration of the major isomer 3
(-) Menthyl	80 %	20 %	-
(+) Bornyl	80 %	5 %	R
(-) Isobornyl	80 %	54 %	R
(-) 8-phényl menthyl	60 %	62 %	R
(±) Phényl-2 cyclohexyl	86 %	13 %	-

Table I. Acetoxylation of chiral-4-isopropyloxy-phenylacetates : Influence of inductor structure on diastereoselectivity.

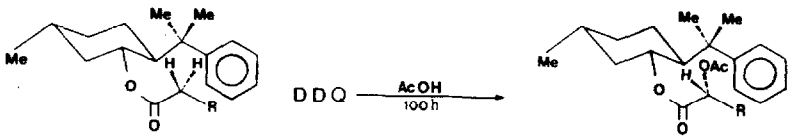
The rate and diastereoselectivity of oxidation by D.D.Q. are mainly dependent on the diastereofacial bulking of the inductor as demonstrated by the differences observed for d.e. using (+) bornyl-ester (5 % d.e.) and (-) isobornyl-ester (54 % d.e.). The use of chiral inductors such as (-) 8-phenyl menthol[15] which specifically hinder or block a substrate face, permitted good control of the approach of the reagent during the formation of the donor-acceptor interaction and accounted for the higher induction observed. The donor-acceptor complex was formed at the less hindered face of the substrate during the course of this reaction and permitted selective removal of one of the diastereotopic hydrogens from prochiral methylene. The nucleophilic attack by acetic acid occurred at the opposite more hindered face. As would be expected with a π stacking model[16] when (-) 8-phenyl menthol and (-) isoborneol were used as inductors, the R substituted mandelic acid was obtained after hydrolysis (scheme 1).

Few or no epimerisation was observed[6,17]. This absolute configuration is identical of that obtained by hydride reduction of phenyl-glyoxylate of 8-phenyl menthol analog[18]. During such reduction reaction the C-H bond is formed by nucleophilic attack on the less hindered face and then the alcool function appears on the more hindered face. Conversely the oxidation by DDQ occurs via concerted hydride abstraction on the less hindered face and solvolysis on the more hindered face as previously described[20].



Scheme I. Asymmetric oxidation of (-) 8-phenyl-menthyl phenylacetates.

We believe that the asymmetric center is created in two distinct steps. The formation of a donor-acceptor interaction between the two reagents occurs in the first, the geometry of the complex being highly dependent on the inductor structure. Hydrogen atom removal by D.D.Q. and simultaneous introduction of the acetoxy group from the bulkier opposite face occur in the second step. The observed final induction is the result of the combined diastereoselection of the two processes.



Entry	R	c.y.	Configuration* of the major product	d.e.**
1	4- Isopropyloxyphenyl	60 %	R	62 %
2	4- Methoxyphenyl	52 %	R	67 %
3	3,4- Dimethoxyphenyl	91 %	R	65 %
4	3,4,5-Dimethoxyphenyl	74 %	R	65 %
5	3,4-(Methylenedioxy) phenyl	82 %	R	66 %
6	3,4-(Ethylenedioxy) phenyl	82 %	R	65 %

* The configuration of 4-methoxy and 3,4-dimethoxy mandelic acid derivatives were determined after hydrolysis of acetoxylated products (NaOH 2N, 0°C) and by comparison of specific rotation with literature data. ** Determined by HPLC and ^{1}HNMR

Table II. Acetoxylation of substituted (-) 8-phenyl-menthyl phenylacetates : Influence of the electron releasing substituent on reaction selectivity.

As shown in table II, additional electron releasing substituents exerted little or no influence on the enantiomeric excess obtained (table II, entries 2, 3, 4). The only difference between the substrates given in table II was related to the strength of the donor-

acceptor interaction of the intermediate complexes formed according to scheme 1. This observation suggests that the formation of donor-acceptor interactions is not the limiting step for the diastereoselectivity of the oxidation. For increased or better conserved induction, the second step of the reaction must occur as quickly as possible within a tighly bound complex (scheme 1). The results presented here demonstrate the efficiency of our method for asymmetric synthesis of substituted mandelic acids in mild conditions nevertheless. The advantage of this strategy lies in the fact that no enolate or ketene acetal formation is required. The observed induction is comparable with previously published data on chemical reduction of α carbonyl esters or amides[19]. In addition, this method[21] is particularly convenient for hydroxylation of electron rich phenyl acetic derivatives. This is of interest, for only poor results are obtained with the other methods mentioned above.

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