PAPER

CoCl$_2$ catalysed decarboxylation-oxidation of mandelic acids by molecular oxygen

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A series of mandelic acid derivatives was oxidised by molecular oxygen using cobalt(II) chloride as the catalyst. Benzaldehyde and/or benzoic acid derivatives were obtained in high selectivities, depending on the aromatic ring substitution. Different oxidation mechanisms are operating, depending on the mandelic acid substitution.

Introduction

Cobalt complexes, and in particular cobalt(II) chloride, constitute versatile catalysts in organic synthesis[1] and have been used, for example, in the monohydroxylation of β-keto esters,[2] for the synthesis of β-amino alcohols from oxiranes[3] and for the acylation of anisole.[4]

In combination with molecular oxygen, the oxidation of alkenes to epoxides with cobalt complexes has been described with Schiff base ligands, cryptates or porphyrins.[5–8] Under O$_2$, the formation of cobalt(III) superoxo species, responsible for the oxidation of the alkenes, has been proposed. The oxidative cleavage of alkenes *versus* their epoxidation by a Co(II)/O$_2$ system has been studied for the cleavage of olefins into carbonyl derivatives[9] and for the oxidative cleavage of isoeugenol to vanillin.[10] The oxidative cleavage of α-diols has also been reported.[11] The same system has also been applied for the oxidation of alcohols to the corresponding carbonyl compounds,[7] for the oxidation of alkylbenzenes to carboxylic acids[12] and the oxidation of cyclic ethers to lactones.[13]
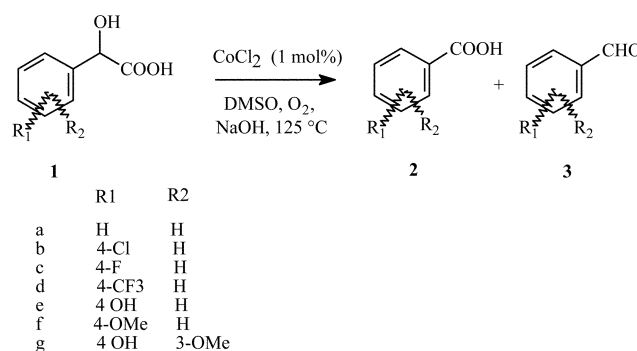
The oxidation of mandelic acids has been examined under a variety of systems.[14] However, the Co-catalysed oxidative decarboxylation of mandelic acid derivatives has not yet been reported. We present here our results on the use of the CoCl$_2$/O$_2$ system for the oxidation of such substrates. Moreover, we recently examined the use of Bi(0)/O$_2$ for the oxidation of α-ketols, and epoxides,[15] as well as for the oxidation of mandelic acids.[16,17] Some comparisons between both catalytic systems are presented.

Results and discussion

Oxidation of mandelic acid derivatives catalysed by CoCl$_2$/O$_2$

The oxidation of several mandelic acid derivatives (**1**) was examined under different reaction conditions, using CoCl$_2$ as the catalyst. As illustrated in Scheme 1, the oxidative cleavage of mandelic acids mainly affords benzoic acid derivatives (**2**) and/or benzaldehyde derivatives (**3**).

In a water medium at 80 °C, the conversion of **1a** was less than 5% after 24 h and in H$_2$O–NaOH or H$_2$O–AcOH media the conversion of **1a** was less than 18%. The best results were

	R1	R2
a	H	H
b	4-Cl	H
c	4-F	H
d	4-CF3	H
e	4 OH	H
f	4-OMe	H
g	4 OH	3-OMe

Scheme 1 Oxidation reaction of mandelic acid derivatives showing the numbering scheme

obtained in DMSO at 125 °C with 1 mol % catalyst under atmospheric O$_2$ pressure. It was observed that the oxidation reaction could be optimised by operating under basic conditions; the addition of 1.5 equiv. (*versus* substrate) of a 50% aqueous solution of sodium hydroxide afforded the best yields, as compared to the reaction in DMSO alone or with AcOH as the additive. Both DMSO and NaOH seem to play an important role in accelerating the oxidation. The results of the oxidation of several mandelic acid derivatives (**1**) under O$_2$ (1 atm) in a cobalt(II) chloride catalysed reaction are presented in Table 1.

Unsubstituted mandelic acid (**1a**) reacted smoothly, with a conversion of 42% after 24 h. No important evolution of the system was observed with longer reaction times. A 89:11 mixture of **2a** and **3a** was formed in 62% yield. The remaining product was phenylglyoxylic acid (**4a**), obtained in 38% yield.

Interestingly, better conversions were obtained with substituted mandelic acids, either with electron-donating or with electron-withdrawing substituents. Thus, the reactivity of *p*-chloro-, *p*-fluoro- and *p*-trifluoromethylmandelic acids (**1b**–**1d**) possessing electron-withdrawing substituents was examined; these substrates afforded conversions of 75–100% after 24 h. A clean reaction with a quantitative yield of the corresponding benzoic acids (**2b**–**2d**) and benzaldehydes (**3b**–**3d**) was obtained. However, the selectivity **2:3** was very dependent on the nature of the substituents. Thus, for *p*-fluoro- and

Table 1 Oxidation of mandelic acid derivatives by molecular oxygen, catalysed by cobalt(II) chloride (1 mol %) in DMSO–NaOH at 125 °C

Substrate	Reaction time/h	% Conversion of **1**	% Yield[a] of **2** + **3**	% Selectivity **2:3**
1a	24	42	62	89:11
1b	24	75	100	29:71
1c	24	98	100	82:18
1d	24	100	100	83:17
1e	0.5	97	57	1:99
1f	8	62	88	16:84
1g	2	100	85	1:99

[a] Yield of products calculated on converted substrate.

Scheme 2 Mechanistic pathways for the oxidation of mandelic acids

catalysed by CoCl$_2$. These reactions were carried out for unsubstituted **1a**, for the mandelic acid derivative **1f** with an electron-rich aryl ring and for **1d**, with an electron-poor aryl moiety.

(a) Oxidation of mandelic acid, benzaldehyde and phenylglyoxylic acid. With 1 mol % of CoCl$_2$ in DMSO–NaOH at 125 °C, unsubstituted mandelic acid (**1a**) was 35% converted after 2 h to yield benzoic acid (**2a**) and phenylglyoxylic acid (**4a**) with a selectivity of 57:43. After 24 h, the conversion of **1a** was of 42% and some benzaldehyde (**3a**) was present, with a **2a**:**3a**:**4a** selectivity of 55:7:38 (Scheme 3).

Both benzaldehyde (**3a**) and ketoacid (**4a**), possible intermediates in the formation of benzoic acid (**2a**), were subjected to oxidation under the same conditions. The oxidation of **3a** afforded a complete conversion after 2 h, with the formation of 30% of **2a** and 70% of a sulfoxide derivative (**5a**) issued from the reaction of **3a** and DMSO. However, compound **5a** was not isolated during the oxidation of **1a**.

The oxidation of ketoacid **4a** occurred at a slow rate and gave a conversion of only 16% after 2 h, with the exclusive formation of **2a**. The conversion of **4a** reached 37% after 24 h. The slow oxidation of **4a** is in agreement with the fact it was isolated in 38–43% selectivity from the oxidation of **1a**.

Taking into consideration the data of Scheme 3 and the fact that the sulfoxide derivative **5a** was not formed during the oxidation of **1a**, the mechanism of formation of **2a** from **1a** by the CoCl$_2$ system can occur through the two different pathways "a" and "b" of Scheme 2. The main pathway "b" involves a first oxidation of **1a** to aldehyde **3a**, followed by its further and rapid oxidation into **2a**. Surprisingly, in this oxidation process from **1a** compound **5a** is not observed. Possibly the

p-trifluoromethylmandelic acids (**1c** and **1d**) the corresponding benzoic acid derivatives **2c** and **2d** were formed as the major compounds in 82–83% selectivities. In contrast, for *p*-chloromandelic acid (**1b**) the main product was *p*-chlorobenzaldehyde (**3b**) with a selectivity of 71%.
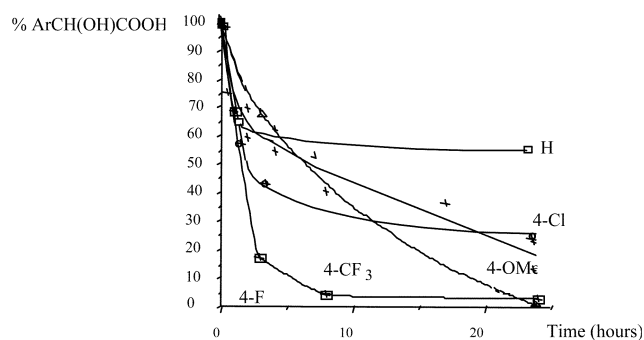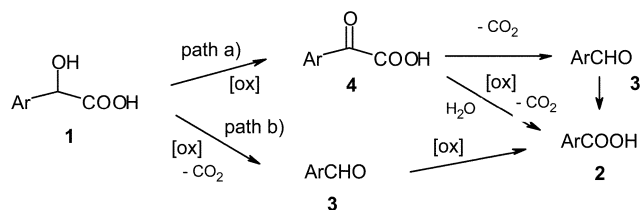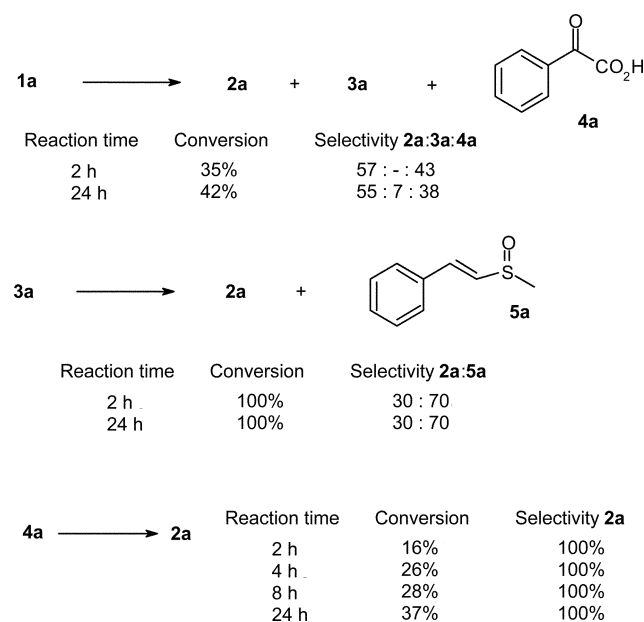
The reactivity was enhanced with electron-rich substituents (**1e**–**1g**). *p*-Hydroxymandelic acid (**1e**) was converted in 0.5 h and vanillic acid (**1g**) in 2 h. Yields of **2** + **3** of 57–88% was accounted for by the presence of some polymeric material in the cases of **1e** and **1g** and of an additional ketoacid derivative (**4f**, 12%), in the case of **1f**. The selectivities **2:3** were here in favour of the formation of the corresponding aldehydes **3e**–**3g**, with **2:3** ratios up to 1:99 in the cases of 4-hydroxymandelic acid (**1e**) and vanillic acid (**1g**). In the case of the *p*-methoxy substituent in **1f**, the selectivity towards the aldehyde **3f** was 84%.

The kinetics of the consumption of different mandelic acid derivatives is presented in Fig. 1

Mechanistic considerations

The reactivity and selectivity differences observed for the oxidation of mandelic acid derivatives are probably due to different mechanisms operating in the oxidative Co catalysed system. The oxidation of mandelic acids to the corresponding benzoic acids and/or benzaldehyde derivatives involves an oxidative decarboxylation reaction, which can occur *via* paths "a" or "b" shown in Scheme 2. Thus, derivatives **1** can be oxidised to the corresponding α-ketoacids **4** *via* path "a", with further decarboxylation to aldehydes **3** or oxidative decarboxylation to benzoic acids **2**.

Alternatively, following path "b", the oxidative decarboxylation of **1** can directly afford aldehydes **3**, which may be further oxidised to acids **2**. In order to determine the main reaction pathways for the differently substituted mandelic acid derivatives, mechanistic studies were carried out on the oxidation of substrates **1**, as well as on the oxidation of the corresponding benzaldehydes **3** and ketoacid derivatives **4**,

Fig. 1 Kinetics of the oxidation of mandelic acid derivatives by the catalytic system CoCl$_2$/O$_2$ in DMSO–NaOH at 125 °C

Scheme 3 Oxidation of mandelic acid (**1a**), benzaldehyde (**3a**) and phenylglyoxylic acid (**4a**) catalysed by CoCl$_2$

rapid oxidation of the intermediate aldehyde species prevents the formation of **5a**.

In competitive pathway "a", phenylglyoxylic acid (**4a**) is formed and accumulated and is only slowly oxidised into **2a**. This pathway "a" is to be considered as a minor contribution, as illustrated in Scheme 4.

(b) Oxidation of 4-methoxymandelic acid, 4-anisaldehyde and 4-methoxyphenylglyoxylic acid. The oxidation of 4-methoxy substituted mandelic acid (**1f**) mainly afforded the corresponding aldehyde derivative **3f** with a conversion of 62% after 8 h and a selectivity **2f**:**3f**:**4f** of 14:74:12. As shown in Fig. 2, the oxidation of 4-anisaldehyde (**3f**) was much faster than that of 4-methoxymandelic acid (**1f**). Interestingly, the oxidation of 4-methoxyphenylglyoxylic acid (**4f**) was very slow.

Table 2 presents the results obtained for the oxidations of **1f**, **3f** and **4f** catalysed by $CoCl_2$. As already observed for the oxidation of **3a**, the oxidation of 4-anisaldehyde (**3f**), which was completely converted in 2 h, afforded mainly the sulfoxide derivative **5f** (analogous to **5a** in Scheme 3) in 90% yield while 4-methoxybenzoic acid (**2f**) was only formed in 10% yield. The sulfoxide derivative **5f** was not observed during the oxidation of **1f**.

Our data of Fig. 2 and Table 2 indicate that the $CoCl_2$ catalysed oxidation of 4-methoxymandelic acid (**1f**) should mainly proceed through mechanistic pathway "b" in Scheme 2, involving the direct formation of 4-anisaldehyde (**3f**). The carboxylic acid **2f** should be formed from the oxidation of **3f**. The ketoacid **4f** is not a plausible intermediate in the oxidation of **1f** to **3f** or to **2f**.

(c) Oxidation of 4-trifluoromethylmandelic acid, 4-trifluoromethylbenzaldehyde and 4-trifluoromethylphenylglyoxylic acid. In order to examine the relative reaction rates of a mandelic acid derivative with electron-withdrawing substituents, the oxidation of 4-trifluoromethylmandelic acid (**1d**) was compared to that of 4-trifluoromethylbenzaldehyde (**3d**) and 4-trifluoromethylphenylglyoxylic acid (**4d**). As shown in Fig. 3, both the aldehyde **3d** and the ketoacid **4d** reacted faster than **1d**. The results of the oxidation of **1d**, **3d** and **4d** are summarised in Table 3.

The oxidation of 4-trifluoromethylbenzaldehyde (**3d**) gave 60% of 4-trifluoromethylbenzoic acid (**2d**) after complete conversion in 2 h. The oxidation of 4-trifluoromethylphenylglyoxylic acid (**4d**) afforded exclusively the carboxylic acid **2d** with a conversion of 75% after 7 h. In the case of the oxidation of **1d** to **2d** by $CoCl_2$ occurring with 83% selectivity, both mechanisms, either *via* path "a" or path "b" in Scheme 2 are compatible with the available data.

We can conclude that the Co-catalysed oxidative decarboxylation of derivatives **1** gives rise to the reaction products **2** and **3** in very different ratios, ranging from 1:99 to 89:11, depending on the substrate substitution. The reaction follows different pathways depending on the nature of the aryl group. Thus, for the methoxy-substituted **1f**, the aldehyde **3f** was selectively obtained following mainly path "b". For unsubstituted **1a** or for CF_3-substituted **1d** the carboxylic acids **2a** and **2d** were the main reaction products, respectively, and both pathways "a" and "b" are operative.
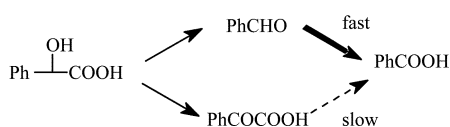
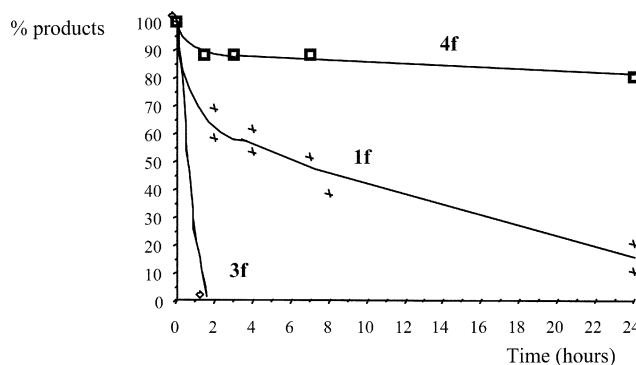**Scheme 4** Mechanistic pathways for the oxidation of mandelic acid (**1a**) catalysed by $CoCl_2$

Fig. 2 Oxidation of 4-methoxymandelic acid (**1f**), 4-anisaldehyde (**3f**) and 4-methoxyphenylglyoxylic acid (**4f**) catalysed by $CoCl_2$

Table 2 Oxidation of 4-methoxymandelic acid (**1f**), 4-anisaldehyde (**3f**) and 4-methoxyphenylglyoxylic acid (**4f**) catalysed by $CoCl_2$

Substrate	Time/h	% Conversion	Products	% Product yield
3f	2	100	**2f**	10
			5f	90
4f	24	20	**2f**	100
1f	8	62	**2f**	14
			3f	74
			4f	12

Comparative studies between the oxidation of mandelic acid derivatives under molecular oxygen catalysed by $CoCl_2$ and by Bi(0)

The oxidative decarboxylation of substrates **1** has been recently examined in a Bi(0) catalysed reaction in the presence of molecular oxygen in DMSO–AcOH.[16] As in the Co catalysed oxidation, compounds **2** and **3** were obtained with selectivities depending on the substitution on the aryl ring. However, on comparing both catalytic systems, we observed that the reactions do not always afford the same main product for the same substituent. In order to better compare the $CoCl_2$ and the Bi(0) systems for the oxidation of **1**, Table 4 summarises the results obtained in the Bi(0) catalysed reactions, including conversions, yields of **2** and **3** and selectivities.

The comparison of the data of Tables 1 and 4 indicates that from the point of view of the reaction rate and conversion, metallic bismuth is a slightly more efficient catalyst than $CoCl_2$ for the oxidation of **1a**, **1f** and **1g**. Similar reactivities were observed for the oxidation of 4-trifluoromethylmandelic acid (**1d**). For the remaining cases, $CoCl_2$ showed a better catalytic activity than Bi(0).
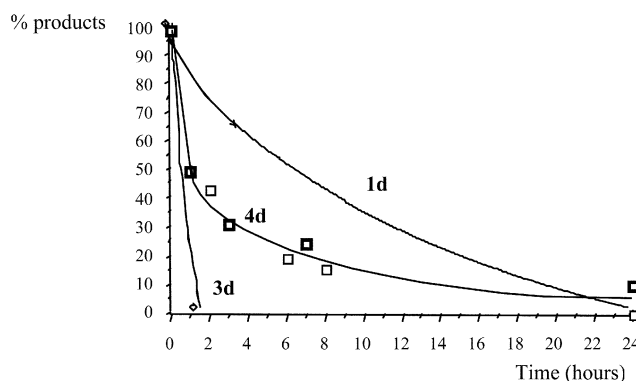
Fig. 3 Oxidation of 4-trifluoromethylmandelic acid (**1d**), 4-trifluoromethylbenzaldehyde (**3d**) and 4-trifluoromethylphenylglyoxylic acid (**4d**) catalysed by $CoCl_2$

Table 3 Oxidation of 4-trifluoromethylmandelic acid (**1d**), 4-trifluoro-methylbenzaldehyde (**3d**) and 4-trifluoromethylphenylglyoxylic acid (**4d**) catalysed by CoCl$_2$

Substrate	Time/h	% Conversion	Products	% Product yield
3d	2	100	**2d**	60
4d	7	75	**2d**	100
1d	24	100	**2d**	83
			3d	17

Table 4 Oxidation of mandelic acid derivatives **1** catalysed by Bi(0)[16]

| Substrate	Time/h	% Conversion of **1**	% Yield[a] of **2** + **3**	% Selectivity **2:3**
1a	24	54	87	93:7
1b	24	56	98	98:2
1c	24	72	97	97:3
1d	24	97	99	99:1
1e	6	100	98	23:77
1f	6	77	98	62:38
1g	0.6	97	98	13:87

[a] Yield of products calculated on converted substrate.

However, important changes in the selectivities of both Bi(0) and Co(II) catalysed reactions were observed. When benzalde-hyde derivatives **3** are the main compounds formed, as in the case of **1e** and **1g**, a better selectivity is obtained with CoCl$_2$ as compared to Bi(0). On the contrary, when benzoic acid deri-vatives **2** are the main products as in the oxidation of **1a**, **1c** and **1d**, better selectivities towards **2** are obtained with Bi(0).

In two cases, the selectivity of the two catalytic systems is completely reversed. Thus, for the oxidation of 4-chloro- and 4-methoxymandelic acid (**1b** and **1f**, respectively), the CoCl$_2$ catalysed oxidation affords mainly the corresponding benzal-dehyde derivatives **3b** and **3f**, whereas in the Bi(0) catalysed oxidation, the corresponding benzoic acid derivatives **2b** and **2f** are selectively obtained. With the Co(II) system, 4-chloro-benzaldehyde (**3b**) and 4-anisadehyde (**3f**) are formed with 71% and 84% selectivities, respectively. With the Bi catalytic system, 4-chloro- and 4-methoxybenzoic acids (**2b** and **2f**) are formed in 98% and 62% yields, respectively.

Scheme 5 illustrates the fact that the oxidation of **1b** can be oriented towards the formation of either **2b** or **3b**, according to the nature of the catalytic system. Thus, **2b** or **3b** can be selec-tively obtained by using the Bi(0) or the Co(II) systems, respec-tively. A similar Scheme 6 can be proposed for the oxidation of **1f**, indicating that either the aldehyde **3f** or the carboxylic acid **2f** can be selectively obtained with CoCl$_2$ or Bi(0) as the catalyst, respectively, though with a lesser selectivity.

For the Bi(0) catalysed oxidations, path "a" *via* the ketoacid **4** (Scheme 2) was shown to be the main pathway followed for the oxidation of **1a** and **1d** to the corresponding carboxylic acids **2a** and **2d**.
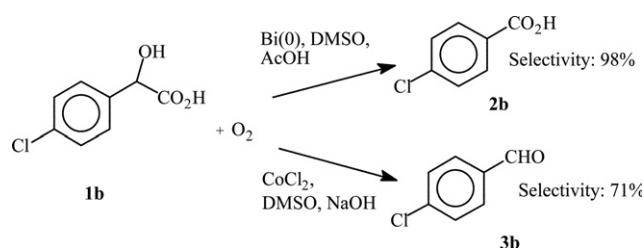
Scheme 5 Selectivity in the oxidation of 4-chloromandelic acid (**1b**) with two different catalytic systems
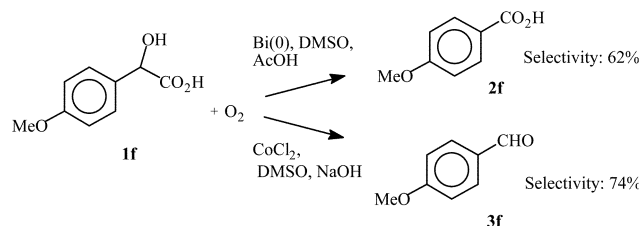
Scheme 6 Selectivity in the oxidation of 4-methoxymandelic acid (**1f**) with two different catalytic systems

Conclusions

The CoCl$_2$/O$_2$ system in DMSO–NaOH constitutes a novel and efficient catalytic system for the oxidative decarboxylation of mandelic acid derivatives. Benzoic acids or benzaldehyde derivatives are obtained selectively, depending on the substitu-ents present on the aromatic ring. In the reactivity examined for a series of *para*-substituted mandelic acids, it was observed that for OH, OMe and Cl substituents, the oxidation led to selective formation of the corresponding aldehydes **3**. In con-trast, for H, F and CF$_3$ substituents, the corresponding carboxylic acids **2** were formed in selectivities higher than 80%. The cobalt(II) chloride catalysed oxidation of mandelic acid derivatives is proposed to follow different mechanistic pathways, depending on the substitution on the aryl ring.

Interestingly, comparison of the oxidation of the same substrates by a Bi(0)/O$_2$ system presents some similarities, although in the cases of 4-chloromandelic acid and 4-methoxy-mandelic acid, the main products obtained were different and the selectivities **2:3** were completely reversed.

Experimental

Commercially available products were used without further purification. HPLC analysis was effectuated with a Waters Millipore apparatus, with a μ-Bondapack C18 Waters 9 μm, 30 cm × 3.9 mm column. The eluent was a 80:20 mixture of H$_2$O–MeOH with H$_3$PO$_4$ (0.5%). The elution was carried out at 1 mL min^{-1} in isocratic mode and the products were detected by UV at $\lambda = 256$ nm.

General oxidation procedure

The reactions were carried out under 1 atm molecular oxygen. Mandelic acid or one of its derivatives (2 mmol) was dissolved in DMSO (5 mL) in the presence of anhydrous CoCl$_2$ (0.02 mmol) and NaOH (3 mmol of a 50% aqueous solution). The mixture was stirred at 125 °C and the consumption of the start-ing material was followed by HPLC and/or by ^{1}H NMR. The crude reaction mixture was hydrolysed with 5 mL aqueous 1 M HCl solution saturated with NaCl and extracted with ethyl acetate (5 × 10 mL). Organic layers were collected and washed twice with an aqueous 0.1 M HCl solution saturated with NaCl, dried over MgSO$_4$ and filtered off. The products were analysed and quantified by HPLC and by ^{1}H NMR and their spectral data compared to those of authentic samples.

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