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Optically Active α-Acetoxycarboxylic Acids and α-Hydroxycarboxylic Acids by Enzyme-Aided Syntheses

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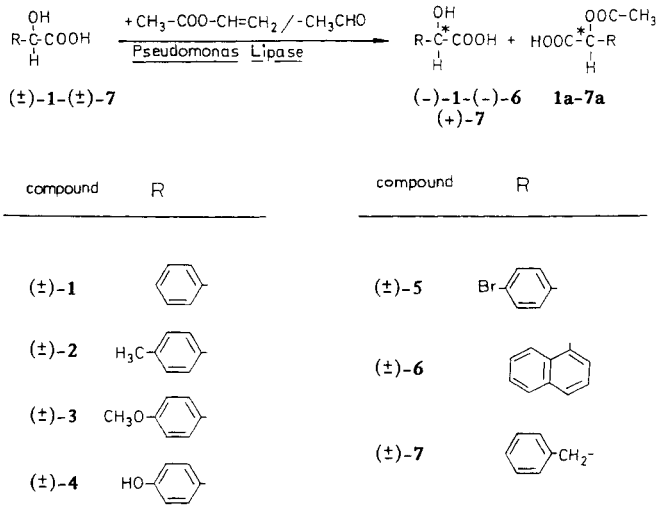
Enantiomerically pure O-acetylmandelic acid and optically active mandelic acid are interesting organic intermediates. E.g. they have been used for the syntheses of chiral ligands and as chiral auxiliaries for the resolution of racemic amines [1, 2]. A. Mosandl et al. synthesized the enantiomers of oct-1-en-3-ol by reductive cleavage of their corresponding diastereomeric esters of (S)-(+)-O-acetylmandelic acid [3]. The optically active α-acetoxycarboxylic acids are usually prepared by acetylation of one of the enantiomers of the α-hydroxycarboxylic acid with acetyl chloride for example, and the optically active α-hydroxy-carboxylic acids are classically gained by the separation of the diastereomeric salts of optically active bases. In the last few years a lot of enzyme-catalyzed reactions have been reported for the syntheses of optically active α-hydroxcarboxylic acids [4, 5, 6], but to our knowledge the enantioselective enzyme-aided esterification of the α-hydroxy group in mandelic acid has not yet been reported, although this can be regarded today as a standard reaction in organic syntheses. In connection with our works about syntheses of optically active aliphatic alcohols [7] we were interested in an easy and short synthesis of enantiomeric pure O-acetylmandelic acid.

We here present a new one-pot one-step synthesis of S-(+)-O-acetylmandelic acid from racemic mandelic acid as starting material by an enzyme-aided process.

The reaction was achieved in organic solvents with vinyl acetate as acetylation agent and *Pseudomonas sp. lipase* (Röhm GmbH) as catalyst. Because of the little solubility of the mandelic acid in nonpolar organic solvents which are usually used in enzyme-aided syntheses, we applied the more polar acetone or mixtures of acetone and toluene for the reactions. As we found the strongly polar solvent did not affect the activity of the enzyme, which we used two to three times. And surprisingly we also found no inhibition of the enzyme by the free carboxylic group of the substrate. No intermolecular esterification of two molecules of mandelic acid has been observed neither. The reaction has been completed during 24 hrs. with high optical and chemical yield.

The process is not limited to mandelic acid. We were also able to synthesize the optically active O-acetyl derivatives **2a** – **7a**. Beside the O-acetyl derivatives we isolated in all cases the opposite enantiomers of the α-hydroxy acids (−)-**1** – (−)-**6**, (+)-**7** which have not been acetylated during the reactions and which show high optical activity too.



Present investigations show that the acetylated mandelic acid derivatives **4a** and **5a** seem to be very good derivatization agents for the determination of the optically purity of aliphatic alcohols via their diastereoisomeric esters by HPLC [8].

The method is also useful for the large scale syntheses of the described acids. In an upscaled reaction we were able to prepare multigrams of S-(+)-O-acetylmandelic acid beside multigrams of R-(−)-mandelic acid.

We find, that the new described method is the most easy direct access to optically active α-acetoxycarboxylic acids and optically active α-hydroxy carboxylic acids.

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Experimental

The microanalyses were performed by the Institut für Brennstoffchemie und Physikalisch-Chemische Verfahrenstechnik der Technischen Hochschule Aachen on a Carlo Erba 1106 apparatus. – Melting points (not corrected): Kofler hot-stage. – Optical rotations: Polartronic E, Schmidt + Haensch. – Column chromatography: silica gel 60 (Merck), solvents: trichloromethane/acetic acid (80:20,v/v). – Enzyme: *Pseudomonas sp. lipase* (Röhm GmbH, Darmstadt, Germany), activity: 23 U/mg, tributyrine.

General procedure for the preparations of (−)-1 to (−)-6, (+)-7 and 1a to 7a

To the (±)-α-hydroxycarboxylic acid (±)-**1** – (±)-**7** (0.015 mol) was added toluene (30 ml) and acetone (10 – 20 ml) until the acid has dissolved. The temperature was adjusted to 37 °C and 3 g of lipase (*Pseudomonas sp.*, Röhm GmbH, 23 U/mg, tributyrin) was added, followed by the addition of 3 ml (2.8 g, 0.033 mol) vinyl acetate, The mixture was stirred for 24 hours. After cooling to room temperature the enzyme was filtered off, washed two times with acetone (20 ml), dried, and stored for reuse. The filtrate was concentrated in the vacuum to 10 ml, and then cooled to −20 °C for 12 to 20 hrs., until crallization of the α-hydroxyacid has completed. The crystals were filtered off, washed with ice-cold toluene (20 – 30 ml) and recrystallized from toluene. The filtrate was first shaken with 2 × 20 ml hydrochloric acid (20 %), and then with 2 × 30 ml aqueous potassium carbonate (10 %). To the combined potassium carbonate layers was added dropwise conc. HCl until the O-acetyl acid seperates as crystals or as oil. In case of an oily precipitate the whole mixture was freezed, and then warmed up to room temperature. In most cases the O-acetyl derivative has then crystallized. The crystals were filtered off, washed salt free with water, recrystallized from water and dried in the desiccator.

*R-(−)-Mandelic acid [(−)-**1**)]* and S-(+)-O-acetylmandelic acid (**1a**)

2.3 g (0.015 mol) (±)-**1** have been treated according to the general procedure. To remove all crystal water **1a** has to dry in the desiccator (P_4O_{10}) at least for 2 days.
(−)-**1**: Yield 0.94 g (82 %), m.p. 131 – 133 °C (toluene), (ref. [9] 131 – 133 °C),
$[\alpha]_D^{20} = -155.8$ (c = 2.3, water)⟨ref. [9] $[\alpha]_D^{20} = -157.5$ (c = 2.5, water)⟩.

$C_8H_8O_3$	Calcd.	C 63.2	H 5.4
(152.1)	Found	C 63.1	H 5.4

1a: Yield 0.80 g (55 %), m.p. 98 °C (water), (ref. [10] 95 – 97 °C), $[\alpha]_D^{20} = +152.4$ (c = 2.3, acetone)⟨ref. [10] $[\alpha]_D^{20} = +148.0$ (c = 1.9, acetone)⟩.

$C_{10}H_{10}O_4$	Calcd.	C 61.9	H 5.2
(194.2)	Found	C 61.8	H 5.4

*Large scale preparation of R-(−)-**1** and* **1a**: 50.2 g (0.33 mol) mandelic acid, 200 ml acetone, 100 ml toluene, 64.6 ml (60.3 g, 0.7 mol) vinyl acetate, 50 g *Pseudomonas lipase* were treated as described in the general procedure.

*Isolation of R-(−)-**1***: After removal of the enzyme the filtrate was concentrated to 100 ml. After cooling to −20 °C for 10 hrs. the mandelic acid was filtered off and washed three times with 50 ml ice cold toluene. The filtrate was concentrated to 50 ml and cooled down to −20 °C for 24 hrs. again, to crystallize all the mandelic acid. The two crops were recrystallized from toluene. Yield: 23 g (92 %), m.p. 133 °C, $[\alpha]_D^{20} = -153.0$ (c = 1.0, water).
Isolation of **1a**: The toluene solution which contained **1a** was diluted with toluene until 100 ml and than shaked two times with 30 ml HCl (20 %). The O-acetylmandelic acid was than extracted with 3 × 50 ml potassium carbonate (20 %). Acidification of the aqueous solution afforded the acid which was purified by crystallisation from water. Yield: 27 g (84 %), m.p. 93 – 94 °C, $[\alpha]_D^{20}$: +149.5 (c = 1.0, acetone).

*(−)-p-Methylmandelic acid (−)-2 and (+)-p-Methyl-O-acetylmandelic acid **2a***

2.5 g (0.015 mol) (±)-**2** have been treated according to the general procedure.
(−)-**2**: Yield 0.8 g (64 %), m.p. 131 °C (toluene), (ref. [11] 131 °C), $[\alpha]_D^{20} = -147.0$ (c = 1.5, acetone) ⟨ref. [11] $[\alpha]_D^{20} = -148.0$ (acetone)⟩.

$C_9H_{10}O_3$	Calcd.	C 65.1	H 6.1
(166.2)	Found	C 65.1	H 6.1

2a: Yield 0.65 g (42 %), m.p. 89 – 90 °C (water), $[\alpha]_D^{20} = +153.5$ (c = 1.5, acetone).

$C_{11}H_{12}O_4$	Calcd.	C 63.5	H 5.8
(208.2)	Found	C 63.3	H 5.9

(−)-p-Methoxymandelic acid (−)-3 and (+)-p-Methoxy-O-acetylmandelic acid (**3a**)

2.73 g (0.015 mol) (±)-**3** have been treated as described in the general procedure. To remove all the crystal water **3a** has to dry for two days in the desiccator (P_4O_{10}).
(−)-**3**: Yield 0.94 g (69 %), m.p. 104 °C (toluene), (ref. [12] 104 – 105 °C, $[\alpha]_D^{20} = -145.5$ (c = 2.1, water) ⟨ref. [12] $[\alpha]_D^{20} = -146.5$ (c = 2.4, water)⟩.

$C_9H_{10}O_4$	Calcd.	C 59.3	H 5.5
(182.2)	Found	C 59.4	H 5.8

3a: Yield 0.66 g (39 %), m.p. 65 °C (water), $[\alpha]_D^{20} = +157.0$ (c = 0.5, acetone).

$C_{11}H_{12}O_5$	Calcd.	C 58.9	H 5.4
(224.2)	Found	C 58.6	H 5.4

(−)-p-Hydroxymandelic acid (−)-4 and (+)-p-Hydroxy-O-acetylmandelic acid (**4a**)

2.5 g (0.015 mol (±)-**4** have been treated as described in the general procedure, but as solvent 40 ml acetone was used solely. (−)-**4** and **4a** have been seperated by column chromatography [column: 70 × 2.5 cm, silica gel 60 Merck, $CHCl_3$/AcOH (80/20, v/v)], (−)-**4** was crystallized from water.
(−)-**4**: Yield 0.63 g (45 %), m.p. 112 °C (water), $[\alpha]_D^{20} = -123.4$ (c = 0.3 in water).

$C_8H_8O_4 * H_2O$	Calcd.	C 51.6	H 5.4
(186.1)	Found	C 52.0	H 5.4

4a: Yield 0.47 g (30 %), m.p. 130 – 132 °C (water), $[\alpha]_D^{20} = +154.6$ (c = 0.8 in acetone).

$C_{10}H_{10}O_5$	Calcd.	C 57.1	H 4.8
(210.2)	Found	C 56.8	H 4.8

(–)-p-Bromomandelic acid (–)-5 and (+)-p-Bromo-O-acetylmandelic acid (**5a**)

3.47 g (0.015 mol) (±)-**5** have been treated as described in the general procedure.
(–)-**5**: Yield 1.18 g (68 %), m.p. 130 – 132 °C (toluene), (ref. [13] 131 °C), $[\alpha]_D^{20} = -111.0$ (c = 0.8, acetone) ⟨ref. [13] $[\alpha]_D^{20} = -115.0$ (c = 0.6, acetone)⟩.

$C_8H_7BrO_3$	Calcd.	C 41.6	H 3.1
(231.05)	Found	C 42.0	H 3.0

5a: Yield 1.13 g (55 %), m.p. 147 – 148 °C (water), $[\alpha]_D^{20} = +123.5$ (c = 0.54 in acetone).

$C_{10}H_9BrO_4$	Calcd.	C 44.0	H 3.3
(273.09)	Found	C 44.0	H 3.3

(–)-α-Hydroxy-α-(1-naphthyl)acetic acid (–)-*6 and (+)-α-*Acetoxy-α-(1-naphthyl)acetic acid (**6a**)

3.03 g (0.015 mol) (±)-**6** have been treated as described in the general procedure with the following changes: to remove all the acid (–)-**6** from the toluene solution, cooling to –20 °C has to repeat after filtration of the first crop. The combined two precipitates are than purified by crystallization from water plus a little charcoal. If no crystallization of **6a** occurs it has to be scratched with a glass rod for about 30 to 60 minutes.
(–)-**6**: Yield 0.91 g (60 %), m.p. 123 °C (water), (ref.[14] 124 – 125 °C), $[\alpha]_D^{20} = -185.9$ (c = 1.2, acetone) ⟨ref. [14]$[\alpha]_D^{20} = -187.4$ (c = 3.0, acetone)⟩.

$C_{12}H_{10}O_3$	Calcd.	C 71.3	H 5.0
(202.2)	Found	C 71.2	H 5.0

6a: Yield 0.73 g (40 %), m.p. 134 – 135 °C (water), $[\alpha]_D^{20} = +191.0$ (c = 1.6, acetone).

$C_{14}H_{12}O_4$	Calcd.	C 68.8	H 5.0
(244.2)	Found	C 68.9	H 5.0

(+)-2-Hydroxy-3-phenylpropionic acid (+)-*7* and (–)-2-Acetoxy-3-phenylpropionic acid (**7a**)

2.49 g (±)-**7** have been treated as described in the general procedure. **7a** has been only isolated as a viscous slightly brown oil.

(+)-**7**: Yield 0.89 g (71 %), m.p. 123 °C (toluene), (ref. [15] 124 °C), $[\alpha]_D^{20} = +24.0$ (c = 1.5 in water) ⟨ref [14] $[\alpha]_D^{20} = +22.2$ (c = 0.8 in water)⟩.

$C_9H_{10}O_3$	Calcd.	C 65.1	H 6.1
(166.2)	Found	C 64.8	H 6.0

7a: Yield 0.86 g (55 %) ⟨impure brownish oil, $[\alpha]_D^{20} = -10.5$ (c = 1.5, acetone)⟩.

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