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Enzymatic resolution of substituted mandelic acids

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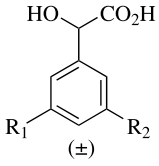
Abstract—A series of substituted mandelic acids were prepared and subjected to enzymatic resolution utilizing Lipase PS 'Amano'.

The kinetic resolution of racemic substrates by enzyme catalysis, especially efficient processes for lipase-catalyzed hydrolysis of esters and acylation of secondary alcohols, has become a standard reaction in organic synthesis.[1] During the course of our studies, we required the use of several enantiomerically pure substituted mandelic acids. Attempts to resolve several of these mandelic acids with various chiral amines via their diastereomeric salts were unsuccessful.[2] We report herein, the successful enzymatic resolution of racemic 3- and 3,5-substituted mandelic acids **1**–**6** (Fig. 1) with Lipase PS 'Amano'.[3–5]

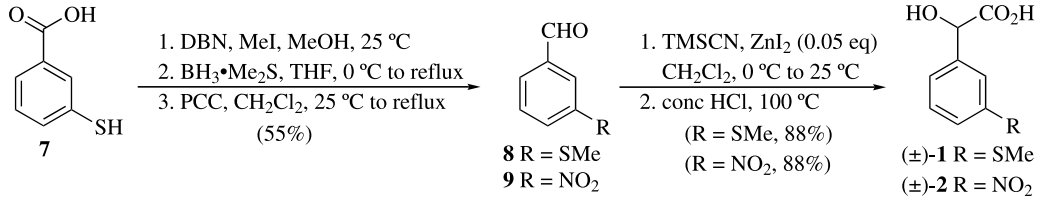


1 R_1 = H; R_2 = SMe
2 R_1 = H; R_2 = NO_2
3 R_1 = Cl; R_2 = NO_2
4 R_1 = Cl; R_2 = NMe_2
5 R_1 = CF_3; R_2 = NMe_2
6 R_1 = Cl; R_2 = pyrrole

Figure 1.

The syntheses of the mandelic acids are outlined in Schemes 1–3. Conversion of 3-mercaptobenzoic acid (**7**) to 3-(methylthio)benzaldehyde (**8**) was accomplished in a straightforward manner (Scheme 1). Subsequent cyanohydrin formation and acidic hydrolysis provided racemic 3-(methylthio)mandelic acid (**1**). 3-Nitromandelic acid (**2**) was prepared in a similar manner starting from 3-nitrobenzaldehyde (**9**).

The preparations of mandelic acids **3**, **4** and **6** began with 3,5-dinitrobenzene (Scheme 2). Thus, reduction of the carboxylic acid followed by selective reduction of one of the nitro groups provided nitrobenzene **12**.[6] Generation of the diazonium salt followed by treatment with a mixture of copper(I) chloride and copper(II) chloride gave chlorobenzene **13**. Aldehyde formation followed by generation of the cyanohydrin and acidic hydrolysis provided 3-chloro-5-nitromandelic acid (**3**). Reductive amination of chlorobenzene **13** in a one-pot/two-step procedure gave the dimethylamino analogue **14**, which was converted to 3-chloro-5-dimethylaminomandelic acid (**4**) using the standard procedures.



Scheme 1.

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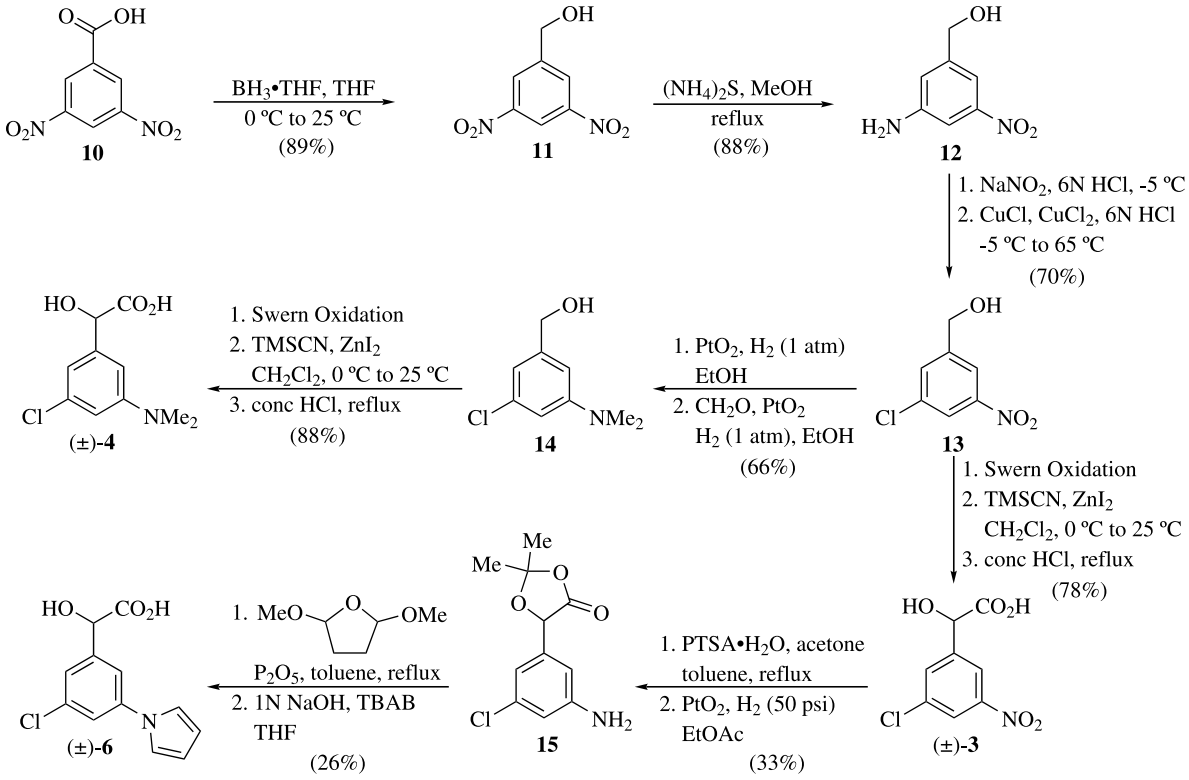
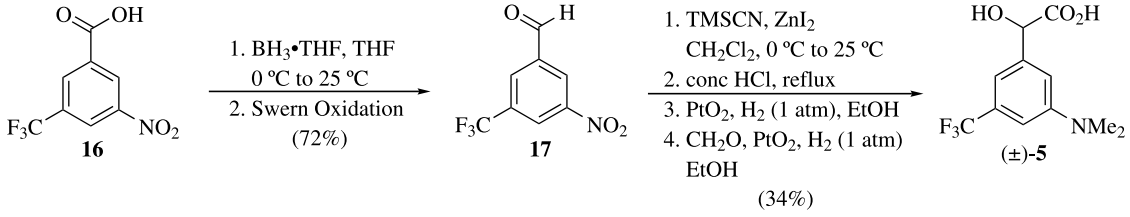
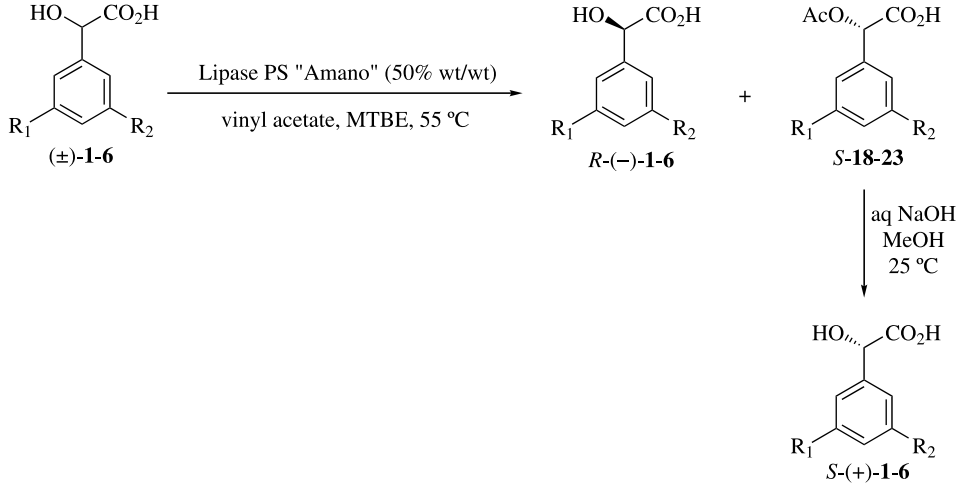


Scheme 2.



Scheme 3.

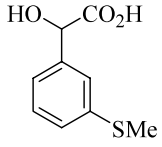
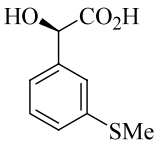
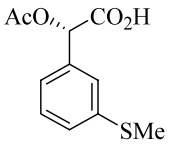
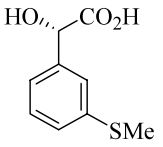
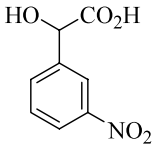
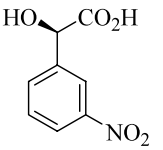
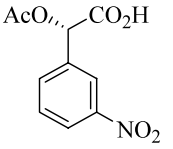
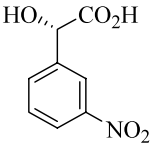
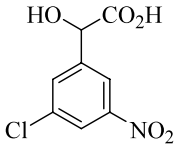
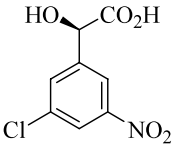
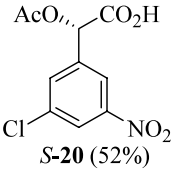
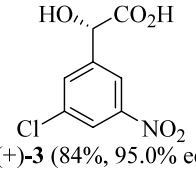
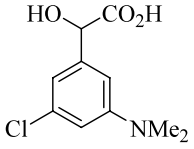
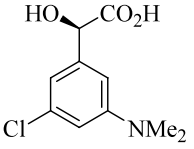
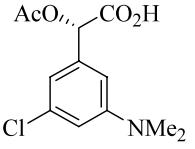
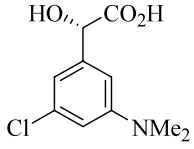
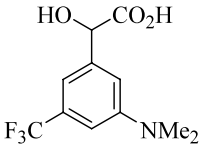
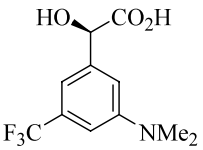
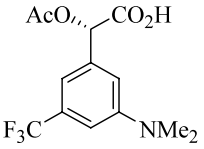
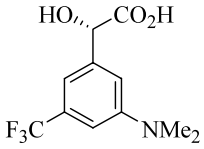
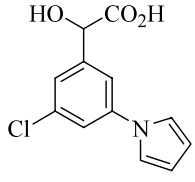
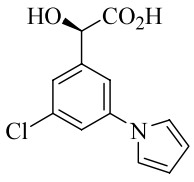
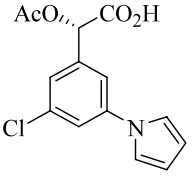
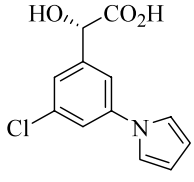


Scheme 4.

By protecting mandelic acid **3** as the corresponding acetonide derivative, it was possible to carry out the nitro group reduction and subsequent derivatization to the pyrrole.[7] Deprotection under basic conditions provided 3-chloro-5-(pyrrole-1-yl)mandelic acid (**6**).

3-Dimethylamino-5-(trifluoromethyl)mandelic acid (**5**) was prepared using similar methodology starting with benzoic acid **16** (Scheme 3). In this case, it was shown that the reductive amination of the preformed mandelic acid could be carried out without any difficulties.

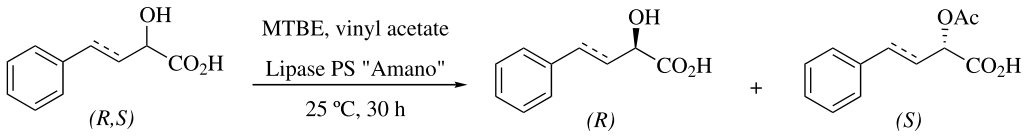
Table 1. Enzymatic resolution of racemic mandelic acids with lipase PS 'Amano'[a]

Substrate	*R*-(−)-Alcohol (Yield, % ee)[b]	*S*-Acetate (Yield)[c] $\xrightarrow[\text{MeOH}]{\text{NaOH}}$	*S*-(+)-Alcohol (Yield, % ee)[b]
 (±)-**1**	 *R*-(−)-**1** (32%, 96.0% ee)	 *S*-**18** (35%)	 *S*-(+)-**1** (86%, 96.2% ee)
 (±)-**2**	 *R*-(−)-**2** (46%, 97.7% ee)	 *S*-**19**(35%)	 *S*-(+)-**2** (88%, 95.7% ee)
 (±)-**3**	 *R*-(−)-**3** (42%, 99.0% ee)	 *S*-**20** (52%)	 *S*-(+)-**3** (84%, 95.0% ee)
 (±)-**4**	 *R*-(−)-**4** (40%, 97.9% ee)	 *S*-**21** (38%)	 *S*-(+)-**4** (87%, 99.0% ee)
 (±)-**5**	 *R*-(−)-**5** (27%, >99% ee)	 *S*-**22** (49%)	 *S*-(+)-**5** (67%, 96.2% ee)
 (±)-**6**	 *R*-(−)-**6** (38%, 98.0% ee)	 *S*-**23** (42%)	 *S*-(+)-**6** (84%, 91.8% ee)

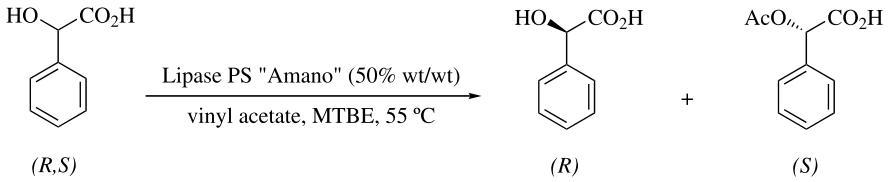
[a]These reactions were run with 50% wt/wt of Lipase PS "Amano" in the presence of vinyl acetate in *tert*-butyl methyl ether at 55 °C.

[b]The enantiomeric excesses were determined on a Chiralcel OD HPLC column eluting with hexanes:ethanol:TFA or hexanes:isopropanol:TFA (90:10:0.5 or 95:5:0.5) at 1.0 mL/min flow rate and UV detection at 228 nm.

[c]The enantiomeric excesses were not determined on the *S*-acetates **18-23**, but the enantiomeric excesses of hydrolysis products *S*-(+)-**1-6** were determined.



Scheme 5.



Scheme 6.

The enzymatic resolution of the racemic mandelic acids was then studied. Mandelic acids **1**–**6** were resolved with Lipase PS 'Amano' (50% wt/wt) in the presence of excess vinyl acetate in *tert*-butyl methyl ether at 55°C, with the reaction progress monitored by HPLC, to afford *R*-(−)-alcohols **1**–**6** and *S*-acetates **18**–**23** (Scheme 4). These resolutions proved to be quite general for various substituents, giving reasonable yields and selectivity in greater than 95% ee (Table 1).[8] The *S*-acetates **18**–**23** were hydrolyzed under basic conditions (NaOH, methanol) in a separate manipulation to provide *S*-(+)-alcohols **1**–**6** without any racemization (as confirmed by chiral HPLC analyses).

The stereochemical assignments of the products were initially made based on the work described by Chadha et al., where 2-hydroxy-4-phenylbutanoic acid and an unsaturated isomer were resolved utilizing Lipase PS 'Amano' (Scheme 5).[3]

Later studies in our laboratory using commercial supplies of each enantiomer of mandelic acid confirmed that the (*S*)-enantiomer of mandelic acid was preferentially acylated by Lipase PS 'Amano' as shown by chiral HPLC analyses (Scheme 6).

A representative procedure for enzymatic resolution of racemic mandelic acids follows: A mixture of (±)-**1** (2.0 g, 10.1 mmol), Lipase PS 'Amano' (1.0 g), and vinyl acetate (5.0 mL) in *tert*-butyl methyl ether (5.0 mL) was heated at 55°C for 24 h. The reaction was filtered and the filter cake was washed with ethyl acetate (100 mL). The filtrate was concentrated in vacuo and chromatographed on silica gel, eluting with chloroform:methanol:concentrated ammonium hydroxide (6:3:1) to afford *R*-(−)-**1** (630 mg, 32%) as a yellow oil and *S*-**18** (850 mg, 35%) as a tan solid.[8,9] HPLC Analysis of *R*-(−)-**1**: 98.6% purity, 96.0% ee, Chiralcel OD Column (95:5:0.5 hexanes/ethanol/TFA mobile phase, 1.0 mL/min flow rate, UV detector at 228 nm).

In summary, chiral resolutions of substituted racemic mandelic acids were achieved using Lipase PS 'Amano'. In this way, both the *R*-(−)- and *S*-(+)-alcohols were obtained in optical purities of >95% ee. The reaction has proven to be quite general on a multi-gram scale with both electron withdrawing and electron donating groups tolerated on the aromatic ring. This has allowed synthetic efforts toward the substituted mandelic acids to consider all means available followed by a straightforward enzymatic resolution to give the individual enantiomers. The utility of these compounds in further syntheses will be reported in due course.

Acknowledgements

We thank AstraZeneca for the opportunity to collaborate on this project and subsequently publish this body of work.

References

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3. For an example of the enzymatic resolution of an α-hydroxy carboxylic acid using Lipase PS 'Amano', see: Chadha, A.; Manohar, M. *Tetrahedron: Asymmetry* **1995**, *6*, 651.
4. Lipase PS 'Amano' (*Pseudomonas cepacia*; Lot No. LPSAW09505) was purchased from Amano Pharmaceutical Co., Ltd, Nagoya, Japan.
5. For examples of the use of enzymes in the resolution of mandelic acid and mandelate esters, see: (a) Strauss, U. T.; Faber, K. *Tetrahedron: Asymmetry* **1999**, *10*, 4079; (b) Zhang, W.; Wang, P. G. *J. Org. Chem.* **2000**, *65*, 4732; (c) Queiroz, N.; da Graça Nascimento, M. *Tetrahedron Lett.* **2002**, *43*, 5225.

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7. Fang, Y.; Leysen, D.; Ottenheijm, H. C. J. *Synth. Commun.* **1995**, *25*, 1857.
8. For additional experimental details, including spectroscopic data, and additional examples, see: Inghardt, T.; Nyström, J.-E. World Patent WO 0042059, 2000.
9. Depending on the chromatography eluents used and the drying time, products may have been isolated as their ammonium salts. When necessary, salts were neutralized in a separatory funnel with aqueous acid or by passing through a weakly acidic ion exchange resin.