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Selective Enzymatic Transformations of Itaconic Acid Derivatives: An Access to Potentially Useful Building Blocks

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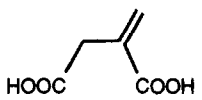
Abstract: Hydrolytic enzymes regioselectively catalyze the hydrolysis of diethyl itaconate **5a** to the monoester **5c** and opening of itaconic anhydride **6** to the regioisomeric monoester **5b** that was tranformed into the hydroxy esters **2**. This was used for the synthesis of β-methylene-γ-butyrolactone **7** and of the racemic epoxyalcohol **3**, that was resolved by a highly enantioselective *Pseudomonas fluorescens* lipase-catalyzed transesterification into (S)-**3** and (S)-**8** (90 and 86% ee, respectively).

Introduction

Itaconic acid **1** could constitute a versatile starting material for synthetically useful compounds, provided that regioselective transformations of the two carboxyl groups are available. For instance, the methene group can be the ideal precursor of an oxirane ring, which is, in turn, easily transformed into a numbers of derivatives.[1] This could be realized in principle by converting **1** through the proper hemiester into an unsaturated hydroxy ester **2**, that could be transformed into the epoxy alcohol **3**. This epoxidation could be carried out asymmetrically by the Sharpless method,[2] although an adverse effect of the ester group has been reported for this procedure.[3] The resolution of racemic **3** could be enzymatically accomplished as shown for other 2-substituted oxiranemethanols.[4] The compound **3** is related to citramalic acid **4**, a building block occurring in the natural chiral pool[5] already used as a chiral synthon.[6] We have studied various enzymatic transformations of itaconic acid **1** and compounds derived from it with the purpose of preparing synthetically useful polyfunctional building blocks.



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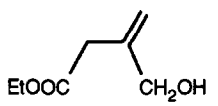

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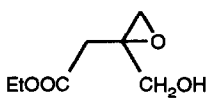

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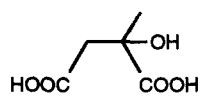
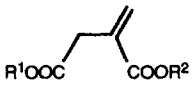


4

Monoesters of Itaconic Acid, Compounds 5b and 5c

The diester **5a** was prepared in a screw-top test tube at 150 °C (4 h, 95% yield), since the esterification with refluxing ethanol (2 h) in the presence of conc. H_2SO_4 affords the 4-ethyl ester **5b** as the main product (78% yield).[7]

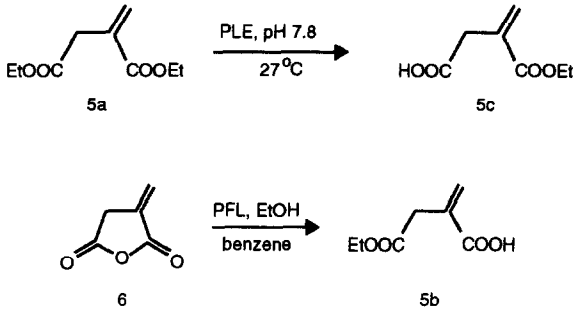


5

a. $R^1 = R^2 = C_2H_5$

b. $R^1 = C_2H_5$; $R^2 = H$ c. $R^1 = H$; $R^2 = C_2H_5$

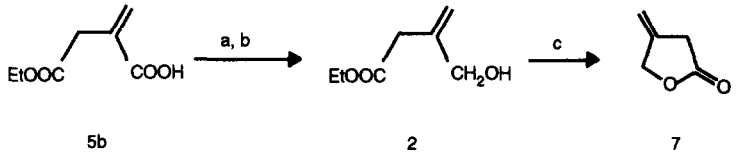
When the enzymatic hydrolysis of the diester **5a** was carried out in the presence of pig liver esterase (PLE)[8] the monoester **5c** was isolated as the only product (75% yield). Interestingly, when the *Pseudomonas fluorescens* lipase (PFL) was used as biocatalyst,[9] only a 1:1 mixture of esters **5b** and **5c** was obtained. Apparently, PLE is more sensitive than PFL to the presence of the methene group α to the ester moiety and exclusively hydrolyzes the more accessible 4-carboethoxy function. Another biocatalytic route to the monoesters **5b** or **5c** could rely on the enzymatic regioselective opening an anhydride.[10] Itaconic anhydride **6** chemically reacts with alcohols to afford 4-alkyl-itaconates[11] and we found that its reaction with ethanol in benzene in the presence of PFL afforded selectively (60% yield of isolated product) the 4-ethyl ester **5b** (Scheme 1).



Scheme 1

The regioselectivity of this enzymatic reaction leads to the same monoester available by the chemical esterification of itaconic acid **1**,[11] whereas the monoester **5c** is biocatalytically available by the PLE-catalyzed hydrolysis of the diester **5a**.[12] The monoester **5b** was used as starting material for the preparation of the hydroxy ester **2** and for this purpose we had to reduce a carboxylic acid in the presence of

the ester and the methene moieties. Among many procedures adopted to achieve this transformation,[13] the most satisfactory in our hands was the reduction *in situ* with $NaBH_4$[14] of the mixed anhydride (ClCOOEt and Et_3N) prepared from **5b**.[15] The hydroxy ester **2** was used for the preparation of the racemic epoxy ester **3** and of β-methylene-γ-butyrolactone **7**. While α-methylene-γ-butyrolactone has been the target of several syntheses,[16] the β-methylene analog **7** is only available by a retrodienic thermolysis.[17] Cyclization (CF_3COOH in CH_2Cl_2) of the hydroxy ester **2** afforded the β-methylene lactone **7** in 80% yield (Scheme 2).



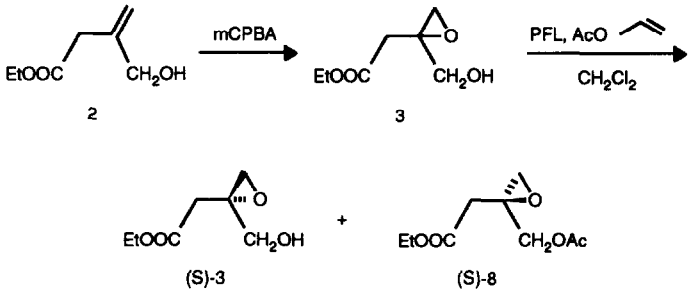
5b 2 7

a. ClCOOEt, Et_3N; b. $NaBH_4$; c. CF_3COOH, CH_2Cl_2

Scheme 2

PFL-catalyzed Resolution of Racemic Epoxyalcohol 3

For the preparation of the racemic epoxyalcohol **3** from the hydroxy ester **2** we could not use the *tert*-butyl hydroperoxide/vanadium acetylacetonate method[18] that we had conveniently used for the synthesis of other 2-substituted oxiranemethanols,[4] since the yields of the epoxyalcohol **3** were not reproducible. This was certainly due to the presence of the 4-carboethoxy moiety and is consistent with a

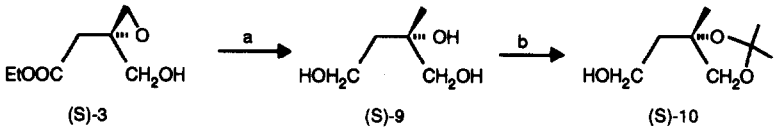


2 3

(S)-3 (S)-8

Scheme 3

similar observation on the adverse effect of an ester group during the *tert*-butyl hydroperoxide/titanium isopropoxide procedure for an asymmetric Sharpless epoxidation.[3] In view of the potential problems to be faced performing the Sharpless epoxidation of an unsaturated hydroxy ester such as **2**, enzymatic resolution of racemic **3** could be more useful. We were able to epoxidize the methylene group in the compound **2** with *m*-chloroperbenzoic acid (58% yield) and the racemic epoxyalcohol was subjected to a PFL-catalyzed resolution (Scheme 3). The transesterification was carried out with vinyl acetate in chloroform with PFL[19] and furnished in two separate incubations[20] (-)-**3** (30% yield) and (+)-acetate **8** (36%). For the evaluation of the enantiomeric excess (ee) by ^{1}H-NMR spectroscopy, we prepared the MTPA ester,[21] thus establishing for compound (-)-**3** a 90% ee. For the assignment of the configuration, the epoxyalcohol was converted into the known compound **10**. It should also be recalled that the triol **9** as well as its acetonide **10** are derived from citramalic acid **4** and already have been used as chiral building blocks.[22] The $LiAlH_4$ reduction of the (-)-**3** afforded the triol **9**, which was converted into the (S)-(-)-acetonide **10** in 18% overall yield (Scheme 4).



(S)-3 (S)-9 (S)-10

a. $LiAlH_4$, THF; b. CH_3COCH_3, PTSA

Scheme 4

The sign and the value of the optical rotation of this sample allowed us to establish the (S)-configuration to the starting (-)-**3**.[23] Finally, a sample of (S)-(-)-**3** was acetylated to the corresponding (R)-(-)-acetate **8**.[24] Since the (+)-acetate **8** was enzymatically prepared, this is the acetate of the (R)-epoxyalcohol **3**, namely the (S)-(+)-acetate **8**[24] with 86% ee.

Conclusions

We have shown that selective enzymatic transformations of itaconic acid **1** make this compound the ideal precursor of a number of polyfunctional building blocks, as already shown in a few cases also chemically. We have prepared the monoester **5b** by a regioselective PFL-catalyzed opening of itaconic anhydride **6** with ethanol in benzene and the enzymatic hydrolysis of the diester **5a** can afford the regioisomeric monoester **5c**. The latest compound can be reduced with $NaBH_4$ *via* a mixed anhydride to the hydroxy ester **2**, that in turn can be chemically converted to the β-methylene lactone **7**. The epoxidation of the compound **2** with *m*-chloroperbenzoic acid gives the racemic epoxy alcohol **3**, which is enzymatically resolved into (S)-(-)-**3** (90% ee) and its enantiomeric acetate (S)-(+)-**8** (86% ee). Both compounds are structurally related to citramalic acid, as shown by the conversion of (S)-(-)-**3** into the (S)-(-)-acetonide **10**.

Experimental Section

Pseudomonas fluorescens lipase (PFL), solvents and reagents were from Fluka (Switzerland). Pig liver esterase (PLE) was purchased from Boehringer Mannheim (Germany). The enzymes were used without further purification. As a general procedure, after the extraction of the products in a given solvent, the organic solution was dried on sodium sulfate, the solvent removed at reduced pressure and the mixture of products purified as described below. Analytical TLC were performed on silica gel Merck 60 F254 plates and column chromatographies on silica gel Merck (230-400), unless differently indicated. GLC analyses were performed on a Hewlett Packard gaschromatograph (Mod. 5890/II) equipped with a fused silica capillary column (HP-5). Distillations for analytical purposes were carried on a glass tube oven Büchi GKR-50. The 60 MHz (on a Varian EM 60, $SiMe_4$ as internal standard) and the 500 MHz (on a Bruker AM-500) ^{1}H-NMR spectra were recorded for solutions in $CDCl_3$. Optical rotations were measured on a Perkin-Elmer polarimeter (Mod. 241).

2-Methylene succinic acid, diethyl ester 5a. A solution of itaconic acid **1** (20 g, 0.154 mol) in ethanol (150 mL) containing a few drops of conc. sulfuric acid was kept at 150 °C in a screw-top test tube for 4 h. The mixture was neutralized with a saturated sodium hydrogen carbonate and ethanol was removed at reduced pressure. Addition of saturated sodium hydrogen carbonate, extraction with dichloromethane (3 x 70 mL), washing of the organic solution with water and standard work-up afforded essentially pure **5a** (27 g, 95%). B.p. 120 °C (0.6 mm Hg); ^{1}H-NMR δ 1.1-1.5 (t+t, 6 H, CH_3CH_2); 3.4 (s, 2 H, CH_2CO); 4.0-4.5 (q+q, 4 H, CH_2CH_3); 5.80 (s, 1 H, *CH*=); 6.45 (s, 1 H, *CH*=). Anal. Calcd. for $C_9H_{14}O_4$: C, 58.06; H, 7.58. Found: C, 58.14; H, 7.66.

PLE-catalyzed hydrolysis of the diester 5a. The diester **5a** (0.9 g, 4.83 mmol) was suspended in 0.1 M solution of potassium dihydrogen phosphate (2.1 mL) and PLE (0.9 mL, 10 mg/mL, 130 U/mg) was added. The pH was kept at 7.8 by sequentially addition of 1 N sodium hydroxide. When the calculated amount of base (3.84 mL corresponding to a 80 % conversion of diester) was added, the mixture was acidified with N HCl (pH 2). After addition of sodium chloride and extraction with diethyl ether (3 x 3 mL) the organic phase was treated with a solution of sodium hydrogen carbonate and after usual work-up the unreacted diester (0.135 g, 15%) was recovered. The aqueous phase was acidified (pH 4) and the products extracted with diethyl ether (3 x 3 mL). The monoester **5c** was obtained after usual work-up (0.57 g, 75 % yield from the diester **5a**). ^{1}H-NMR δ 1.30 (t, 3 H, CH_3CH_2); 3.40 (s, 2 H, CH_2CO); 4.40 (q, 2 H, CH_2CH_3); 5.85 (s, 1 H, *CH*=); 6.50 (s, 1 H, *CH*=); 8.40-9,30 (m, 1 H, exchangeable). The 500 MHz ^{1}H-NMR spectrum showed the signals of the protons of double bond at 5.715 and at 6.330 ppm. The signals at 5.810 and 6.435 assigned to the 4-ethyl ester were undetectable.

PFL-catalyzed esterification of itaconic anhydride 6. To a solution of itaconic anhydride **6** (0.3 g, 2.67 mmol) in dry benzene (4.4 mL) and ethanol (0.155 mL, 2.65 mmol), PFL (8.34 mg, 264 units, 31.5 U/mg) was added. The progress of the reaction was monitored by TLC (toluene/ethyl acetate, 7/3). After 10 h an additional amount of PFL (8 mg) was added and the reaction was stopped removing the enzyme by filtration (24 h). Evaporation of the solvent and column chromatography (elution with hexane/ethyl acetate 7:3) afforded the pure monoester **5b** (0.25 g, 60 %), that was crystallized from dichloromethane - hexane; m.p. 55-57 °C; ^{1}H-NMR δ 1.25 (t, 3 H, CH_3CH_2); 3.40 (s, 2 H, CH_2-C=); 4.25 (q, 2 H, CH_2CH_3); 5.95 (s, 1 H, *CH*=); 6.60 (s, 1 H, *CH*=); 11.30-11.70 (m, 1 H, exchangeable). Anal. Calcd. for $C_7H_{10}O_4$: C, 53.17; H, 6.38. Found: C, 53.24; H, 6.46.

Ethyl 3-methylene-4-hydroxy butyrate 2. To a solution of the monoester **5b** (5 g, 31.6 mmol) in dry

tetrahydrofuran (30 mL), triethylamine (3.19 g, 31.6 mmol) was added. The mixture was cooled with an ice bath and a solution of ethyl chloroformate (3.4 g, 31.6 mmol) in dry tetrahydrofuran (10 mL) was added dropwise. The reaction was kept under stirring at 0 °C for 0.5 h and then the salts were removed by filtration. The resulting clear solution was added to sodium borohydride (2.2 g, 58 mmol) in water (15 mL) cooled at 10 °C. After 2 h under stirring at 10 °C, the mixture was acidified with 3N HCl. By extraction with diethyl ether (3 x 30 mL) and usual work-up, a mixture of the hydroxy ester **2** and the corresponding saturated alcohol (10%) was obtained (3 g) that was used as such for the epoxidation step. A sample (1 g) was purified by column chromatography (elution with hexane/diethyl ether, 6:4) to yield 0.43 g of pure hydroxy ester **2**. B. p. 145 °C (6 mmHg) ; ^{1}H-NMR δ 1.30 (t, 3H, CH_3CH_2); 3.20 (s, 2 H, CH_2CO); 3.95-4.50 (m, 5 H, OCH_2CH_3, CH_2OH and H exchangeable with ^2H_2O); 5.20 (s, 1 H, *CH*=); 5.35 (s, 1 H, *CH*=). Anal. Calcd. for $C_7H_{12}O_3$: C, 58.33; H, 8.39. Found: C, 58.41; H, 8.50.

β-Methylene-γ-butyrolactone 7. The hydroxy ester **2** (0.1 g, 0.69 mmol) was dissolved in dichloromethane (0.5 mL) and a catalytic amount of trifluoroacetic acid was added. The mixture was kept at room temperature overnight and then the acid was neutralized with a saturated sodium hydrogen carbonate solution and the organic phase separated. After usual work-up, the lactone **8** was obtained essentially pure (0.054 g, 80%). A few attempts to distil this sample afforded the isomeric β-methyl butenolide.[17] ^{1}H-NMR δ 3.20-3.45 (m, 2 H, CH_2CO); 4.00-4.70 (m, 2 H, CH_2O); 4.90-5.10 (m, 1 H, *CH*=); 5.15-5.35 (m, 1 H, *CH*=).

Ethyl 3,4-epoxy-3-methanol butanoate 3. To a solution of the crude hydroxyester **2** (3 g, containing 10% of saturated ester, 17.7 mmol) in dichloromethane (30 mL), *meta*-chloroperbenzoic acid (6.7 g, 55% in water, 21.3 mmol) was added. The reaction mixture was kept at room temperature for 24 h under stirring. The precipitate was removed by filtration and the organic phase washed with a 12 % ammonium hydroxide solution and water. After the usual work-up, the crude mixture (3.56 g) was purified by chromatography. Elution with hexane/ethyl acetate (7:3) afforded the epoxyalcohol **3** (1.64 g, 58% yield). B.p. 83-85 °C (0.1 mmHg); ^{1}H-NMR 1.30 (t, 3 H, CH_3CH_2); 2.40-2.60 (m, 1 H, exchangeable with ^2H_2O); 2.60-3.25 (m+s, 4 H, CH_2O and CH_2CO); 3.90 (q, 2 H, CH_2OH); 4.30 (q, 2 H, CH_2CH_3). Anal. Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.56; H, 7.62.

Enzymatic transesterification of the epoxyalcohol 3. The epoxyalcohol **3** (1.2 g, 7.5 mmol) was dissolved in chloroform (13 mL) and vinyl acetate (3.28 mL, 3 g, 34.8 mmol) was added. After addition of PFL (32.8 mg, 31.5 U/mg), the mixture was kept at 30 °C for a time depending on the desired ratio of alcohol/acetate. The extent of the reaction was monitored on GLC. When the desired conversion was reached, the enzyme was filtered off and the solvent evaporated. The products were separated by chromatography (silica gel 1/30). At 36% conversion (0.5 h), the acetate **8** was recovered by elution with hexane/ethyl acetate (8:2) (31%, $[\alpha]_D$ +10.7, *c* 1.83 in $CHCl_3$). B.p. 145 °C (3 mm Hg); ^{1}H-NMR δ 1.30 (t, 3 H, CH_3CH_2); 2.10 (s, 3H, CH_3CO); 2.55-3.25 (m+s, 4 H, CH_2CO and CH_2O); 4.00-4.50 (m, 4 H, CH_2CH_3 and CH_2OAc). Anal. Calcd. for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.54; H, 7.08. In another experiment at 70 % conversion to the acetate (1.25 h), the epoxyalcohol **3** was isolated by elution with hexane/ethyl acetate (6:4) (30%, $[\alpha]_D$ -15.56, *c* 1.83 in $CHCl_3$) with chemico-physical properties in agreement with those of racemic **3**.

The ee of the (-)-**3** was established by the analysis of the 500 MHz ^{1}H-NMR spectrum of the (R)-MTPA ester. To a solution of the epoxyalcohol **3** (0.02 g, 0.125 mmol) in dry pyridine (0.36 mL) and carbon tetrachloride (0.36 mL), (S)-MTPA chloride (0.043 g) was added and the mixture was kept at room

temperature overnight. The reaction was treated with 3-dimethylamino-1-propylamine (0.022 mL) under stirring for 10 min., then dichloromethane (1 mL) was added and the organic phase was washed with 1N HCl, saturated sodium carbonate solution and water. After usual work-up, the (R)-MTPA ester was recovered and in the recorded spectrum the signal due to the protons of methylene group at position 1 was constituted by two couples of doublets centered at 4.27, 4.35, 4.67 and 4.71 ppm. In the spectrum of (R)-MTPA ester of racemic epoxyalcohol **3** the four doublets showed the same intensity. In the case of the derivative from the (-)-epoxyalcohol **3**, the doublets at 4.27 and 4.35, as the doublets at 4.71 and 4.67 ppm, were in a ratio of 5:95. The ee of the (+)-acetate **8** was established treating the (-)-epoxyalcohol **3** ($[\alpha]_D$ -15.56, 90 % ee) with acetic anydride in pyridine to afford the acetate **8** that showed $[\alpha]_D$ -11.2.

Preparation of (S)-(-)-2-methyl-1,2,4-butanetriol 1,2-acetonide 10. The epoxyalcohol **3** (0.35 g, 2.19 mmol) was dissolved in dry tetrahydrofuran (4 mL) and the solution was added dropwise to a suspension of lithium aluminum hydride (0.51 g, 13.4 mmol) in tetrahydrofuran (11 mL). The progress of the reaction was monitored by TLC ($CHCl_3/CH_3OH$, 9/1) until disappareance of the starting material. Water (0.5 mL), 15 % sodium hydroxide solution (0.5 mL) and water (1.5 mL) were sequentially added. The precipitate was filtered through a Celite pad and the solvent was evaporated at reduced pressure. The crude triol **9** (0.190 g) was dissolved in acetone (12 mL), a catalytic amount of *p*-toluensulfonic acid was added, and the mixture was kept overnight at room temperature. The acid was neutralized with a saturated solution of sodium hydrogen carbonate and the solvent evaporated at reduced pressure. The crude acetonide **10** (0.140 g) was purified by column chromatography (neutral aluminum oxide, activity III) by elution with hexane/diethyl ether (9:1) to afford pure compound **10** (0.062 g, 18 % from epoxyalcohol **3**). ^{1}H-NMR δ 1.25-1.55 (m, 9 H, CH_3); 1.55-2.05 (m, 2 H, CH_2); 2.30-2.90 (m, 1 H, exchangeable with ^2H_2O); 3.60-4.10 (m+s, 4 H, CH_2OH and CH_2OC); $[\alpha]_D$ -6.7 (*c* 1.67 in $CHCl_3$). The α_D reported in the literature[6a] for the (S)-(-)-acetonide **10** from (S)-(+)-citramalic acid **4** is -9.6 (*c* 1.67 in $CHCl_3$). The (R)-MTPA ester of the (-)-acetonide **10** (0.015 g, 0.094 mmol) was prepared as described for the MTPA ester of compound **3**. The ee of the optically active acetonide **10** was established by ^{1}H-NMR 500 MHz spectrum. The signal due to the protons of methylene group of the acetonide ring was constituted by four doublets beetwen 3.575 and 3.755 ppm in the case of the racemic compound. For the optically active compound, the four doublets were in a ratio of 85:15.

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24. Due to the relative priorities of the groups, the (S)-acetate **8** is in fact the acetate of the (R)-alcohol **3**.

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