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Practical Synthesis of Optically Active α,α-Disubstituted Malonamic Acids through Asymmetric Hydrolysis of Malonamide Derivatives with *Rhodococcus* sp. CGMCC 0497

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Received November 12, 2002

Abstract: A variety of α,α-disubstituted malonamides undergo enantioselective hydrolysis with *Rhodococcus* sp. CGMCC 0497 to give challenging enantiopure α,α-disubstituted malonamic acids with up to >99% enantiomeric excesses and 98% chemical yields. The enantioselectivity originated from the effects of a highly enantioselective amidase. The products could be converted to valuable (*R*)- or (*S*)-α,α-dialkylated amino acids after routine conversions.

Nitrile-converting enzymes have been known for several decades[1] and demonstrated great potential in organic synthesis and chemical industry,[2] but the substrates studied are still very limited and the ability of the enzymes to catalyze stereoselective conversion remains largely unexploited.[3,4] So far, most studies focus on the enantioselective conversion of racemic nitriles, such as α-alkyl nitriles,[5a,5b] α-hydroxy nitriles,[5c,5d] α-acyloxy nitriles,[5e] α-amino nitriles,[5f,5g] and *β*-acetoxy nitriles,[5h] while only a few focus on prochiral nitriles especially malononitrile derivatives.[6,7]

In our previous studies, the strain *Rhodococcus* sp. CGMCC 0497 has been screened out in our laboratory and proved to be a powerful nitrile hydratase/amidase-containing microorganism. It has also been demonstrated that the strain was an efficient enantioselective biocatalytic system and was able to transform a variety of α-substituted arylacetonitriles into optically pure α-substituted arylacetamides and α-substituted arylacetic acid such as the famous nonsteroidal antiinflammatory drug (*S*)-naproxen with excellent enantiomeric excesses.[8] We recently have focused our attention on the asymmetric hydrolysis of prochiral α,α-disubstituted malononitriles, owing to the interest in the synthesis of enantiopure α,α-dialkylated α-amino acids through enzymatic method.

This class of nonproteinogenic α-amino acids has attracted increasing attention in recent years due to their potential to induce particular conformations when incorporated into a polypeptidic chain. They can therefore be used as enzyme inhibitors and offer opportunities for drug discovery.[9] However, compared to the synthesis of optically active α-monosubstituted amino acids, highly efficient methods to the asymmetric synthesis of α,α-dialkylated α-amino acids are relatively rare and their extensive use is limited by the availability of enantiopure compounds in large scale.[10] Considered to be an attractive approach, enzyme-catalyzed resolution has been successfully applied to the production of α-monosubstituted amino acid, but the attempt to extending the methodology to α,α-dialkylated α-amino acids was not satisfying, because the process is generally slow and less stereoselective and the undesired enantiomer cannot be racemized.[10] In this paper, we report a practical enzymatic method for the synthesis of optically pure α,α-disubstituted malonamic acids, precursors of α,α-dialkylated α-amino acids, by asymmetric hydrolysis of diamides with *Rhodococcus* sp. CGMCC 0497.

Yokoyama et al. have reported the hydrolysis of prochiral disubstituted malononitriles by *Rhodococcus rhodochrous* ATCC 21197, but the substrate was limited to 2-butyl-2-methylmalononitrile.[7] In our study, first, dinitriles were used as substrate. In accordance with the literature, 2-butyl-2-methylmalononitrile can be converted to (*R*)-2-butyl-2-methylmalonamic acid neatly by *Rhodococcus* sp. CGMCC 0497. However, when 2-benzyl-2-methyl-malononitrile **1** was used as substrate (0.125% w/v), most probably due to the steric hindrance, the products isolated were a complex mixture of hydrolysis intermediates (Scheme 1). After 66 h, the reaction give

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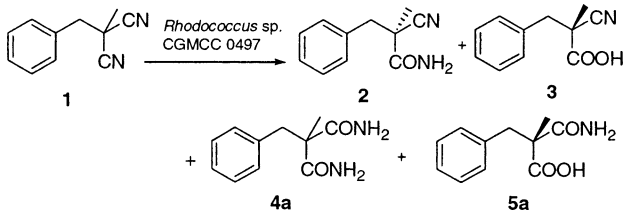
10.1021/jo026691u CCC: $25.00
Published on Web 02/14/2003

SCHEME 1. Hydrolysis of α-Benzyl-α-methyl Malononitrile 1



a mixture of (*S*)-2-cyano-2-methyl-3-phenylpropanamide **2** (56%, 93% ee), (*R*)-2-cyano-2-methyl-3-phenylpropanoic acid **3** (33%, 52% ee), and 2-benzyl-2-methyl-malonamide **4a** (8%). Similar results were obtained for the hydrolysis of 2-(2′-chlorobenzyl)-2-methylmalononitrile, 2-(3′-chlorobenzyl)-2-methylmalononitrile, 2-(4′-chlorobenzyl)-2-methylmalononitrile, and 2-(4′-methoxybenzyl)-2-methylmalononitrile. By prolonging the reaction time of **1** to 112 h, the mixture converted to (*R*)-2-benzyl-2-methylmalonamic acid **5a** (52%, 95% ee) and **3** (44%, 1.2% ee). The high enantiomeric excess of **5a** encouraged us to explore a new approach to improve its chemical yield.

It is well-known that enzyme-catalyzed hydrolysis of nitriles proceeds by two routes: by nitrilase or by a combination of nitrile hydratase (NHase) and amidase through an intermediate amide.[4] *Rodococcus* sp. CGMCC 0497 acts mainly by the latter route. It is clear that 2-benzyl-2-methylmalonamic acid **5a** may be derived in two ways: one involved 2-cyano-2-methyl-3-phenylpropionic acid **3** by NHase and the other involved 2-benzyl-2-methylmalonamide **4a** by amidase. Further experiments were carried out using racemic **3a** and **4a** as substrates, respectively (0.125% w/v). The transformation of racemic **3a** did not occur at all after 1 day and **3a** was recovered quantitively, while the diamide **4a** was converted to **5a** in >99% yield and 94% ee, which demonstrated that **5a** was derived mostly from diamide **4a** with high efficiency and enantioselectivity.

It is especially noticeable that, using **4a** as substrate, the reaction concentration could reach to 1% (w/v) and **5a** was achieved in 95% yield and 97% ee after 1 day at 30 °C with *Rodococcus* sp. CGMCC 0497. Compared to the above-mentioned hydrolysis of **1**, the hydrolysis of **4a** was much faster and more efficient. The quantitive conversion of **4a** to **5a** made recrystallization feasible for the purification process and flash chromatograph could be avoided, which made large-scale production possible. Moreover, α,α-disubstituted malonamides can be easily synthesized from the corresponding malonamic acid diesters by routine reactions.[11] Since α,α-disubstituted malonamides have advantages over the corresponding dinitriles as substrates in the production α,α-disubstituted malonamic acids, the asymmetric hydrolysis of α,α-disubstituted malonamides instead of malononitriles was investigated with whole cells of *Rodococcus* sp. CGMCC 0497. To the best of our knowledge, the study on the asymmetric desymmetrization of α,α-disubstituted malonamides to afford optically pure malonamic acid derivatives is very rare and the catalytic method directly to the enantiopure α,α-disubstituted malonamic acids has never been reported. The characteristics of the two functional groups of the amide acid enable the conversion to both enantiomers of amino acids in 100% theoretic yield.

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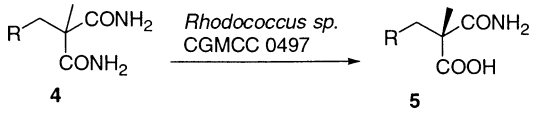
TABLE 1. Enantioselective Hydrolysis of Various α-Substituted-α-methylmalonamides by *Rhodococcus* sp. CGMCC 0497

entry[a]	substrate	R	*T* (°C)	Yield (%)	ee (%)[b]
1	**4a**	C_6H_5	30	94	97
2	**4a**	C_6H_5	20	94	97
3	**4b**	*o*-ClC_6H_4	30	94	97[c]
4	**4b**	*o*-ClC_6H_4	20	92	97[c]
5	**4c**	*m*-ClC_6H_4	30	94	95
6	**4c**	*m*-ClC_6H_4	20	91	96
7	**4d**	*p*-ClC_6H_4	30	92	>99
8	**4d**	*p*-ClC_6H_4	20	95	>99
9	**4e**	*p*-$CH_3C_6H_4$	30	97	>99
10	**4e**	*p*-$CH_3C_6H_4$	20	98	>99
11	**4f**	*p*-$MeOC_6H_4$	30	95	>99[c]
12	**4f**	*p*-$MeOC_6H_4$	20	93	>99[c]
13	**4g**	*p*-FC_6H_4	30	95	>99
14	**4g**	*p*-FC_6H_4	20	95	>99
15	**4h**	*p*-BrC_6H_4	30	97	>99
16	**4h**	*p*-BrC_6H_4	20	94	>99
17	**4i**	$C_6H_5CH_2$	30	94	>99
18	**4i**	$C_6H_5CH_2$	20	92	>99
19	**4j**	C_3H_7	30	94	91[c]

[a] Carried out for 1 day with a substrate concentration of 2.5 g/L. [b] Determined by HPLC on a Chiralpak AS column with hexane/2-propanol mixtures unless stated otherwise. [c] Determined by HPLC on a Chiralcel OJ column.

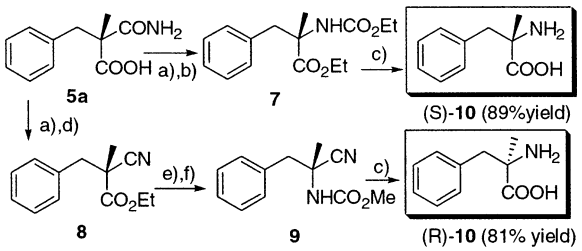
SCHEME 2. Asymmetric Hydrolysis of α,α-Disubstituted Malonamides 4



The results of the enantioselective hydrolysis of various α,α-disubstituted malonamides by *Rhodococcus* sp. CGMCC 0497 at 20 or 30 °C are summarized in Table 1. As shown, in all cases, the enzymes maintain high activity at 20 and 30 °C and the reactions proceeded smoothly and completely during 1 day (Scheme 2). Excellent enantioselectivities and isolated yields were obtained with a variety of substrates. *Rhodococcus* sp. CGMCC 0497 tolerates aromatic ring substituents in the ortho-, meta-, and para-positions. All para-substituted substrates gave products with excellent enantiomeric excesses of >99%, slightly higher than ortho and meta ones. With a monosubstituted benzene ring, **4i** gave product **5i** with >99% ee, while **4a** gave product **5a** with 97% ee. Dialkyl-substituted malonamide **4j** gave product **5j** with a slightly lower ee of 91%.

The hydrolysis of all the above substrates was neat and concordant. However, the effects between the substrates and enzymes in *Rhodococcus* sp. CGMCC 0497 are very complex. When 2-benzyl-2-ethylmalonamide **4k** and 2-butyl-2-ethylmalonamide **4l** were subjected to the reaction, there were only trace products observed after 2 days, while the hydrolysis of 2-allyl-2-benzylmalonamide **4m** gave the deamidized product 2-allylphenylpropionate **6** in a yield of 78% after 4 days. It seemed that the results were not only induced by steric hindrance but by an electronic effect of the substrates as well. Other enzymes in the whole cell may also come into effect under certain

SCHEME 3. Synthesis of either (*R*)- or (*S*)-α,α-Dialkylated Amino Acid[a]



[a] Conditions: (a) DMF, EtBr, K_2CO_3, rt; (b) DMF, $Hg(OAc)_2$, NBS, EtOH, rt; (c) 20% HCl, reflux; (d) P_2O_5, toluene; (e) 3 N NaOH, THF, rt; (f) $SOCl_2$, NaN_3, MeOH.

conditions. Substrates **4a-4j**, with methyl group as one of the two substituents at the α-position, are more favorable in the hydrolysis reaction, and **4m**, with unsaturated allyl group, may result in side reactions. Our further work will be focused on the modification of the strain at the molecular level in order to enhance its adaptability toward diamide substrates.

The products of the enantioselective hydrolysis of α,α-disubstituted malononitriles, (*R*)-α,α-disubstituted malonamic acids **5**, could afford either (*R*)- or (*S*)-α,α-dialkylated amino acids after routine conversion. For example, (*R*)-2-benzyl-2-methylmalonamic acid **5a** was transferred to (*R*)-**10** or (*S*)-**10**. (Scheme 3). α-Methylphenylalanine **10** is an efficient *β*-turn and helix former, much better than its nonmethylated parent compound phenylalanine.[9]

In conclusion, we have demonstrated a successful asymmetric hydrolysis of α,α-disubstituted malonamides to afford enantiopure (*R*)-α,α-disubstituted malonamic acids using the strain *Rodococcus* sp. CGMCC 0497 at 20 or 30 °C. The products can be converted to valuable products such as either (*R*)- or (*S*)-α,α-dialkylated amino acids or other biologically active compounds.[12] The mild and practical reaction condition, high substrate concentration, and excellent enantioselectivity and chemical yield as well as the convenient purification procedure provide a good prerequisite for large-scale production. Currently, the applications of the technologies of cell immobilization and bisphasic systems in enzymatic hydrolysis of diamides are being actively investigated in this laboratory, and we believe that the method could be developed into a valuable alternative for both enantiomers of α,α-dialkylated amino acids.

Experimental Section

General Procedure for α,α-Disubstituted Malonamic Acids (5) and Determination of Enantiomeric Excess. A suspension of 5 g of washed wet cells of *Rodococcus* sp. CGMCC 0497 (available from the China General Microbiological Culture Colletion Center) and 40 mL of 0.1 mM potassium phosphate buffer (pH = 7.0) was incubated at 30 or 20 °C for 30 min with continuous magnetic stirring before the addition of **4** (100−400 mg in 100−200 μL DMSO). The reaction was quenched with 3 N HCl after 1 day and centrifuged. The resulting supernatant was extracted with ethyl acetate and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography on silica gel (elutent, petroleum ether/EtOAc/AcOH 100:100:1) or recrystallization (CH_2Cl_2/PE). To a solution of α,α-disubstituted malonamic acid **5** (0.1 mmol, obtained from flash chromatography) in DMF (0.1 mL) was added bromoethane or iodomethane (2 mmol) and anhydrous K_2CO_3 (2 mmol). The reaction was carried out at room temperature for 1 day to achieve the esters, and the esters were subjected to chiral HPLC.

(*R*)-2-Benzyl-2-methyl-malonamic acid 5a: white solid, mp 117.9−118.9 °C, lit.[12] mp 120−121 °C; $[\alpha]^{15}_D$ −15.01 (*c* 1.07, MeOH), 94% ee {lit.[12] $[\alpha]_D$ −4.4 (*c* 0.5, MeOH), *R*}; ^{1}H NMR (300 MHz, [D$_6$]acetone) δ 7.29−7.19 (m, 5H), 3.61 (br s, 3H), 3.25 (d, 1H, *J* = 13.8 Hz), 3.20 (d, 1H, *J* = 13.5 Hz), 1.37 (s, 3H); IR (KBr): *ν* 3423, 3204 (NH), 3034 (br OH), 1745, 1659 (C=O); MS *m*/*z* (%) 207 (M^+, 2), 91 (100).

(*S*)-2-Ethoxycarbonylamino-2-methyl-3-phenylpropanoic Acid Ethyl Ester 7. To a solution of (*R*)-2-benzyl-2-methylmalonamic acid **5a** (33 mg, 0.16 mmol) in dry DMF (0.3 mL) were added ethyl bromide (0.32 mmol) and solid K_2CO_3 (0.32 mmol) at room temperature. After 24 h, the resulting mixture was poured into water, extracted with ether, washed, and dried on Na_2SO_4. The solvent was removed under reduced pressure and the resulting product was purified by flash chromatograph (98% yield). The product was dissolved in dry DMF (1.5 mL). $Hg(OAc)_2$ (61 mg, 0.19 mmol), dry ethanol (220 mg, 5 mmol), and NBS (37 mg, 0.21 mmol) were added at room temperature. After 16 h, the resulting mixture was poured into water, extracted with ether, washed, and dried on Na_2SO_4. The solvent was removed under reduced pressure and the resulting product was purified by flash chromatograph to afford (*S*)-**7** (96% yield): oil; $[\alpha]^{18}_D$ +31.02 (*c* 2.15, $CHCl_3$); the enantiomeric excess was determined by HPLC on a Chiralcel OD column with hexane/2-propanol mixtures 8:2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.23(m, 3H), 7.08−7.05(m, 2H), 5.37 (brs, 1H), 4.27−4.10 (m, 4H), 3.43 (d, 1H, *J* = 13.8 Hz), 3.18 (d, 1H, *J* = 13.2 Hz), 1.64 (s, 3H), 1.33−1.23 (m, 6H); IR (film) *ν* 3358 (NH), 1721 (C=O), 704; MS *m*/*z* (%) 279 (M^+, 0.8), 234 (2.5), 206 (M^+ − COOEt, 43.3), 190 (28.0), 188 (100), 142 (53.5), 116 (53.6), 91 (58.8), 88 (35.7), 42 (43.0); HRMS calcd for $(C_{15}H_{21}NO_4)^+$ 279.14706, found 279.15017.

(*R*)-2-Cyano-2-methyl-3-phenylpropionic Acid Ethyl Ester 8.[13] To a solution of (*R*)-2-benzyl-2-methylmalonamic acid **5a** (33 mg, 0.16 mmol) in dry DMF (0.3 mL) were added ethyl bromide (0.32 mmol), and solid K_2CO_3 (0.32 mmol) at room temperature. After 24 h, the resulting mixture was poured into water, extracted with ether, washed, and dried on Na_2SO_4. The solvent was removed under reduced pressure and the resulting product was purified by flash chromatograph (98% yield). The product was dissolved in dry toluene (2 mL). Phosphorus pentoxide (0.3 mmol) was added. The resulting mixture was refluxed for 4 h, cooled to room temperature, poured into water, and extracted with ethyl acetate. The solvent was removed under reduced pressure and the resulting product was purified by flash chromatograph to afford (*R*)-**8** (93% yield): oil; $[\alpha]^{25}_D$ −23.8 (*c* 0.51, $CHCl_3$); the enantiomeric excess was determined by HPLC on a Chiralcel OJ column with hexane/2-propanol mixtures 9:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.23 (m, 5H), 4.19 (q, 2H, *J* = 7.2 Hz), 3.23 (d, 1H, *J* = 13.5 Hz), 3.08 (d, 1H, *J* = 13.5 Hz), 1.62 (s, 3H), 1.24 (t, 3H, *J* = 7.1 Hz); IR (film) *ν* 2245 (CN), 1743 (C=O); MS *m*/*z* (%) 217 (M^+, 3), 144 (M^+ − COOEt, 5), 91 (100).

(*R*)-2-Methoxycarbonylamino-2-methyl-3-phenylpropanonitrile 9. To a solution of (*R*)-2-cyano-2-methyl-3-phenylpropionic acid ethyl ester **7** (0.27 mmol) in THF (1.5 mL) was added 3 N NaOH (1.5 mL). The mixture was stirred at room temperature for 30 min and then acidified, extracted with ethyl acetate, and dried on $MgSO_4$. After evaporation, the residue was purified by flash chromatograph. To the product was added $SOCl_2$ (0.3 mL) and the reaction mixture was stirred at 40 °C for 3 h. The excess $SOCl_2$ was removed at reduced pressure. The residue was dissolved in cyclohexane and evaporated again. The acid chloride was then cooled to room temperature and dissolved in dry acetone (1 mL). Then a solution of sodium azide (26 mg, 0.4 mmol) in water (0.2 mL) was added and the stirring was continued for 1 h. The mixture was poured into water, extracted with ether, and dried on $MgSO_4$. After filtration dry methanol

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(1 mL) was added. The solution was stirred at 80 °C for 2 h and evaporated for flash chromatograph to afford (*R*)-**9** (94% yield): white solid, lit.[14] mp 81 °C; $[\alpha]^{22}_D$ −46.6 (*c* 0.798, $CHCl_3$) {lit.[14] $[\alpha]_D$ −46.1 (*c* 2, $CHCl_3$), *S*}; the enantiomeric excess was determined by HPLC on a Chiralcel OJ column with hexane/2-propanol mixtures 9:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.34 (m, 3H), 7.30−7.27 (m, 2H), 4.94 (brs, 1H), 3.74 (s, 3H), 3.29 (d, 1H, J = 13.8 Hz), 3.19 (d, 1H, J = 13.5 Hz), 1.66 (s, 3H); IR (KBr) ν 3325 (NH), 2240 (CN), 1699 (C═O); MS *m*/*z* (%) 219 (M^+ + 1, 8), 218 (M^+, 15), 192 (M^+ − CN, 99), 91 (100).

(*S*) And (*R*)-α-Methylphenylalanine 10. (*S*)-2-Ethoxycarbonylamino-2-methyl-3-phenylpropanoic acid ethyl ester **7** or (*R*)-2-methoxycarbonylamino-2-methyl-3-phenylpropanonitrile **9** (0.13 mmol) was hydrolyzed by refluxing for 3 h with 20% aqueous hydrochloric acid (3 mL). The solution was evaporated under vacuum. To the residue was added distilled water (3 mL) and the solution was evaporated again. The residue was purified by Dowex 50 × 2−400 ion-exchange resin to yield 95% of a white powder: $[\alpha]^{17}_D$ −22.0 (*c* 0.61, H_2O), *S*; $[\alpha]^{17}_D$ +21.8 (*c* 0.73, H_2O), *R* {lit.[15] $[\alpha]_D$ −22 (*c* 1, H_2O), *S*}; ^{1}H NMR (300 MHz, D_2O) δ 7.22−7.19 (m, 3H), 7.10−7.07 (m, 2H), 3.11 (d, 1H, J = 14.4 Hz), 2.79 (d, 1H, J = 14.4 Hz), 1.37 (s, 3H); IR (KBr) 2500−3300, 1650 (C═O); MS (ESI) 202 ([M + Na]$^+$), 180 ([M + H]$^+$).

Acknowledgment. We are grateful to the National Science Foundation of China (Grant No. 20032020) for financial support. We also thank Prof. Lijun Xia and Miss Zuoding Ding for technical assistance.

Supporting Information Available: Experiment procedures and full characterization for compounds **1**−**3, 4a**−**4m, 5b**−**5j, 6.** This material is available free of charge via the Internet at http://pubs.acs.org.

JO026691U

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