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On the Reaction of (*S*)-Trifluoroacetoxysuccinic Anhydride with Amines to Produce Hydroxysuccinamic (Malamic) Acid Derivatives

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Abstract. L-Malic acid (**2**) reacts with trifluoroacetic anhydride under anhydrous conditions to give (*S*)-trifluoroacetoxysuccinic acid anhydride (**3**). The anhydride **3** undergoes regioselective ring opening with an excess of anilines or primary aliphatic amines leading to *N*-substituted-(*S*)-3-hydroxysuccinamic acids (**4a–g**). Structural elucidation of the reaction products **4a–g** was based on analytical and spectroscopic data and on an X-ray structure analysis of **4b**. Secondary aliphatic amines react with **3** by condensation and subsequent elimination to furnish *N*,*N*'-disubstituted fumaric acid amides **5a**, **b**. Some *N*-substituted-2-hydroxysuccinamic acids (**7a**,**b**) were also prepared for spectral comparison with the 3-hydroxy compounds.

A novel natural product isolated from a *Justicia* plant species [1] was recently proven by total synthesis to have structure **1** [2]. An attempt at complete structural elucidation by spectroscopy alone was not successful because these methods did not unequivocally establish the position of the OH group in the hydroxysuccinic (malic) acid side chain. Although a few simpler monoamides related to **1** were known from the literature, none of the publications dealing with these compounds described their spectroscopic data (NMR, IR) in sufficient detail for comparison with the natural product. Thus, in addition to the total synthesis of **1** [2], we explored in some detail regiospecific syntheses of *N*-aryl-2- and *N*-aryl-3-hydroxysuccinamic acids (**4**,**7**).

Activated anhydrides or derivatives of malic acid (**2**) are useful precursors for the coupling with nucleophiles like amines to form such products [3–7]. Rankin *et al.* described the cleavage of the D,L-malic acid chloralide by anilines at reflux temperature (in benzene) to give **4** [3]. (*S*)-Trifluoroacetoxysuccinic acid anhydride (**3**), obtained from reaction of L-malic acid (**2**) with trifluoroacetic anhydride, has been used for the coupling with dry ammonia gas [7], and *n*-octyl- or benzylamine [4, 5].

Herein, we report further exploration of this method and show that **3** can be regioselectively converted with anilines into a series of *N*-aryl-3-hydroxysuccinamic acids (**4**) at low temperature (0 °C). For purposes of spectral comparison with these compounds, we have prepared 2-hydroxy derivatives (**7**) by an independent method.

Results and Discussion

L-Malic acid (**2**) was converted to its anhydride trifluoroacetate (**3**) by reaction with trifluoroacetic anhydride at 0 °C. Treatment of **3** with an excess of several anilines (in THF solution), gave *N*-substituted aryl-(*S*)-3-hydroxysuccinamic acids (**4a–g**) as the only products. The strongly electron withdrawing trifluoroacetyl group (CF_3CO) activated the anhydride (**3**) and promoted nucleophilic attack of the amine at the neighboring carbon. Under weakly basic conditions the trifluoroacetate is unstable, with the CF_3CO-moiety acting as a good leaving group for this reaction (Scheme 1). Furthermore, ammonia [7] and primary and aliphatic amines

Table 1 Analytical and spectral data of **4a–g**, **7a**, **b**

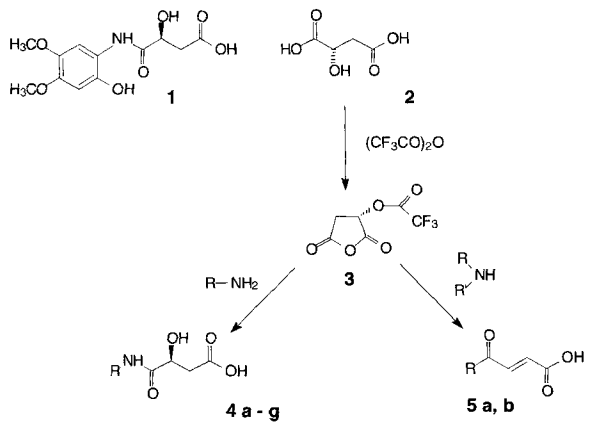
	Formula (mol.weight)	Analysis %Calcd./Found C, H, N	IR ν (cm^{-1}) [a] COOH, NH	^1H NMR [b] δ (ppm), J (Hz)	^{13}C NMR [b] δ(ppm)
4a	$C_{10}H_{11}NO_4$ (209.20)	57.41, 5.30, 6.70 57.64, 5.33, 6.62	1718 1554	2.49 (dd, 1H, J=8.4, 15.6, CH_2), 2.73 (dd, 1H, J=4.2, 15.6, CH_2), 4.41 (dd, 1H, J = 4.2, 8.4, CH), 7.05 (t, 1H, J=7.4, CH_{aryl}), 7.30 (t, 2H, J=8,0, CH_{aryl}), 7.70 (d, 2H, J=8.4, CH_{aryl}), 9.75 (bs, 1H, NH)	39.6 (CH_2), 68,9 (CH), 119.6 (C_o), 123.5 (C_p), 128.6 (C_m), 138.6 (C_i), 171.8 (C=O), 172.1 (C=O).
4b	$C_{12}H_{15}NO_6$ (269.25)	53.53, 5.62, 5.20 53.06, 5.38, 5.18	1723 1551	2.47 (dd, 1H, J=8.4, 15.6, CH_2), 2.72 (dd, 1H, J=3.9, 15.6, CH_2), 3.70 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.37 (dd, 1H, J=4.2, 8.4, CH), 6.87 (d, 1H, J=8.7, CH_{aryl}), 7.26 (dd, 1H, J=2.4, 8.4, CH_{aryl}), 7.42 (d, 1H, J=2.4, CH_{aryl}), 9.59 (bs, 1H NH)	39.6 (CH_2), 55.4 (OCH_3), 55.7 (OCH_3), 68.9 (CH), 104.9 (C_o), 111.5, 112.0 ($C_{o'}$, $C_{m'}$), 132.2 (C_i), 145.0 (C_p), 148.5 (C_m), 171.3 (C=O), 172.1 (C=O).
4c	$C_{11}H_{11}NO_6$ (253.21)	52.18, 4.38, 5.53 52.28, 4.33, 5.68	1720 1543	2.46 (dd, 1H, J=8.7, 15.6, CH_2), 2.70 (dd, 1H, J=4.2, 15.6, CH_2), 4.36 (dd, 1H, J=3.6, 4.5, CH) 5.97 (s, 2H, OCH_2O), 6.84 (d, 1H, J=8,4, CH_{aryl}), 7.15 (dd, 1H, J=2.1, 8.4, CH_{aryl}), 7.38 (d 1H, J=2.1, CH_{aryl}), 9.68 (bs, 1H, NH),	39.6 (CH_2), 68.9 (CH), 100.9 (OCH_2O), 101.7 (C_o), 107.9 ($C_{o'}$), 112,5 ($C_{m'}$), 133.0 (C_i), 143.0 (C_p), 146.9 (C_m), 171.4 (C=O), 172.1 (C=O).
4d	$C_{10}H_{10}N_2O_6$ (254.20)	47.25, 11.02, 3.97 47.20, 10.85, 3.81	1714 1542	2.55 (dd, 1H, J=8.0, 15.7, CH_2), 2.74 (dd, J=4.6, 1H, 15.7, CH_2), 4.45 (dd, 1H, J=4.6, 7.8, CH), 7.99 (d, 2H, J=9.6, CH_{aryl}), 8.20 (d, 2H, J=9.3, CH_{aryl}), 10.42 (s, 1H, NH)	39.4 (CH_2), 69.0 (CH), 100.9 (OCH_2O), 1017 (C_o), 124.8 (C_m), 142.5 (C_p), 144.9 (C_i), 172.0 (C=O), 173.0 (C=O).
4e	$C_{10}H_{12}N_2O_4$ (224.22)	53.57, 5.40, 12.49 52.65, 5.38, 11.99	1670 –	2.41 (dd, 1H, J=8.7, 15.6, CH_2), 2.69 (dd, 1H, J=3.9, 15.6, CH_2), 4.32 (dd, 1H, J=3.9, 8.4, CH), 6.49 (d, 2H, J=8.4, CH_{aryl}), 7.30 (d, 2H, J=8.4, CH_{aryl}), 9.30 (bs, 1H, NH)	68.9 (CH), 113.7 (C_o), 121.2 (C_m), 127.7 (C_i), 145.0 (C_p), 170,6 (C=O), 172.2 (C=O), (the signal for the CH_2 overlapped with the solvent signal).
4f	$C_8H_{15}NO_4$ (189.21)	50.78, 8.00, 7.40 50.47, 8.19, 7.18	1718 1548	[c] 0.93 (t, 3H, J=7.1, CH_3), 1.35 (m, 2H, CH_2), 1.51 (m, 2H, CH_2), 2.67 (dd, 1H, J = 8.4, 16.8, CH_2), 2.99 (dd, 1H, J=3.6, 16.8, CH_2), 3.27 (dd, 2H, J=6.9, 13.2, CH_2), 4.52 (dd, 1H, J=3.6, 8.4, CH), 7.16 (t, 1H, J=6.0, NH)	[c] 13.6 (CH_3), 19.9 (CH_2), 31.2 (CH_2), 38.9 (CH_2), 39.1 (CH_2), 68.1 (CH), 173.5 (C=O), 175.3 (C=O).
4g	$C_{13}N_{17}NO_5$ (267.28)	58.42, 6.41, 5.24 58.17, 6.44, 5.02	1716 1544	[d] 2.48 (dd, 1H, J=9.0, 16.0, CH_2), 2.74 (t, 2H, J=7.2, CH_2), 2.76 (dd, 1H, J=3.5, 16.0, CH_2), 3.41 (m, 2H, J=7.2, CH_2), 3.75 (s, 3H, OCH_3), 6.84 (d, 2H, J=8.4, CH_{aryl}), 7.14 (d, 2H, J=8.4, CH_{aryl}), 7.82[b] (t, 1H, J=5.5, NH)	[d] 35.8 (CH_2), 40.5 (CH_2), 41.9 (CH_2), 55.8 (OCH_3), 69.9 (CH), 115.1 (C_m), 130.9 (C_o), 132.4 (C_i), 159.9 (C_p), 174.7 (C=O), 175.9 (C=O).
7a	$C_{10}H_{11}NO_4$ (209.20)	–	1730 1550	2.59 (dd, 1H, J=8.1, 14.7, CH_2), 2.69 (dd, 1H, J=4.8, 14.7, CH_2), 4.40 (dd, 1H, J=4.8, 8.1, CH), 7.02 (t, 1H, J=7.2, CH_{aryl}), 7.28 (t, 2H, J=7.8, CH_{aryl}), 7.59 (d, 1H, J=7.8, CH_{aryl}), 9.94 (bs, 1H, NH) [e]	41.4 (CH_2), 67.2 (CH), 119.0 (C_o), 123.1 (C_p), 128.6 (C_m), 139.1 (C_i), 168.3 (C=O), 174.9 (C=O).
7b	$C_{12}H_{15}NO_6$ (269.25)	–	1736 1544	2.57 (dd, 1H, J=8.4, 14.7, CH_2), 2.68 (dd, 1H, J=4.5, 14.7, CH_2), 3.70 (s, 3H, OCH_3), 4.40 (dd, 1H, J=4.5, 8.4, CH), 6.86 (d, 1H, J=8.7, CH_{aryl}), 7.08 (dd, 1H, J=2.4, 8.7, CH_{aryl}), 7.34 (d, 1H, J=2.4, CH_{aryl}), 9.82 (bs, 1H, NH)	41.4 (CH_2), 55.4 (OCH_3), 55.8 (OCH_3), 67.3 (CH), 104.3 (C_o), 111.0, 112.1 ($C_{o'}$, $C_{m'}$), 133.0 (C_i), 144.8 (C_p), 148.6 (C_m), 168.0 (C=O), 175.2 (C=O).

[a] NaCl film [b] In DMSO-d_6 [c] In $CDCl_3$ [d] In MeOD [e] ^1H NMR data in agreement with the literature [3].

react under same conditions to afford **4** pro-ducts. By way of contrast secondary amines (such as diisopropylamine and dicyclohexylamine), with higher pK_a values, react after initial amide formation, *via* elimination to form fumaric acid amides **5a**,**b**.

The novel products **4a–g** could be isolated in a pure state by vacuum liquid chromatography on silica in good to moderate yields. Characterization was performed by analytical as well as spectroscopic data (Table 1).

The NMR and IR data of the condensation product obtained by the reaction of anhydride **3** with aniline are in agreement with the literature [3]. In the ^1H NMR



4	R	5	R
a	C_6H_5	a	$(i\text{-}C_3H_7)_2N$
b	3.4-$(CH_3O)_2C_6H_3$	b	$(cyc\text{-}C_6H_{11})_2N$
c	3.4-$(CH_2OCH_2)C_6H_3$		
d	4-$(NO_2)C_6H_4$		
e	4-$(NH_2)C_6H_4$		
f	$n\text{-}C_4H_7$		
g	4-$(CH_3O)C_6H_4CH_2CH_2$		

Scheme 1

spectrum of the *N*-substituted 3-hydroxysuccinamic acids (**4**) the signal for the CH_2 (two double doublets) appeared between 2.45–2.75 ppm. The double doublet at δ 4.4 ppm is typical for the CH. The IR band at around 1720 cm^{-1} is characteristic for the COOH group in these compounds. For the *N*-aryl-(*S*)-3-hydroxysuccinamic acids (**4**) we found $[\alpha]_D$ values of −50 to −55° (c 0.98, MeOH). Although the method of synthesis and previous work [6, 7] was probably sufficient to establish the regiochemical outcome of these reactions, a single crystal X-ray diffraction experiment on **4b** confirmed the result.

Less basic amines (*e.g.* diphenylamine) do not react with anhydride **3** under the described reaction conditions. Amines with two or more *N* (or OH)-functionalities (*o*-phenylendiamine, 2-aminopyridine) react in a more complex manner to give a product mixture. In this case the one basic functionality has to be protected or can be introduce later (*via* hydrogenation of *N*-(4-nitrophenyl)-(*S*)-3-hydroxysuccinamic acid **4d** to the aniline **4e**, for example). Acid sensitive protection groups, such as the TBDMS group, are stable if water is excluded as was shown in the total synthesis of **1** [2].

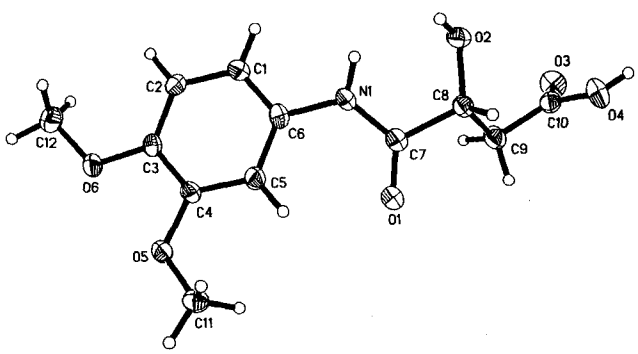
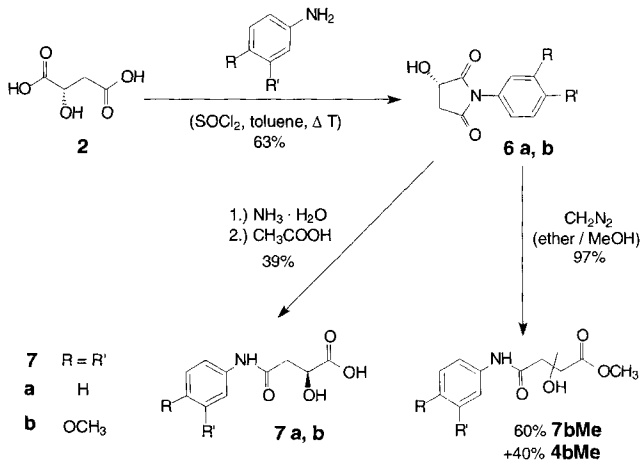


Fig.1 X-Ray structure of **4b**; selected bond lengths (Å) and angles (°): N1–C7 1.357 (4), C7–C8 1.538 (3), O2–C8 1.426 (3), C8–C9 1.535 (4); N1–C7–C8 114.3 (2), O2–C8–C7 113.9 (2), O2–C8–C9 111.2 (2), C9–C8–C7 107.2 (2)

The synthesis of the *N*-aryl-2-hydroxysuccinamic acids (**7a,b**) was achieved by reaction of an *N*-aryl-2-hydroxysuccinimide (**6**) with aqueous ammonia solution and treatment of the formed ammonium salt with acid as described previously [3, 9]. The imide **6** can easily prepared from *L*-malic acid (**2**) and an aniline at reflux temperature in toluene in the presence of small amounts of $SOCl_2$ (Scheme 2). This conversion of the imide **6** to the *N*-aryl-2-hydroxysuccinamic acids (**7**) was always accompanied by small amounts of the *N*-aryl-3-hydroxysuccinamic acid isomer **4** (**7**:**4** = 90:10; detected by ^1H NMR). Both products can be separated by chromatographic methods. Ring opening of the imide **6b** occurred by reaction with CH_2N_2 in ether solution (in the presence of MeOH) to give a mixture of the methyl esters of **7b** and **4b**, but with lower chemoselectivity (**7bMe**: **4bMe** = 60:40).

The ^1H and ^{13}C NMR spectra of the *N*-aryl-2- and *N*-aryl-3-hydroxysuccinamic acids (**7** and **4**) were extremely similar, and it would be difficult to determine, which was which unless both were available. As earlier



Scheme 2

described, **7** and **4** might be distinguishable by comparison of their pK_a values [9]. The IR COOH-band for the *N*-aryl-2-hydroxysuccinamic acids (**7**) occurred at 1730–1740 cm^{-1}, while those for **4** derivatives were slightly lower (Table1). There appeared to be a significant difference between the isomers **4** and **7** in the mass spectra, where there was an intense peak for loss of water for **7** compared to isomer **4**.

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Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker ACF 300 or a Varian JS 300 spectrometer. Chemical shifts are reported in units of δ (ppm), and the solvent was used as an internal reference; DMSO-d_6 (^1H: $\delta = 2.50$; ^{13}C: $\delta = 39.51$), $CDCl_3$ (^1H: $\delta = 7.27$; ^{13}C: $\delta = 77.00$), and MeOD (^1H: $\delta = 3.31$; ^{13}C: $\delta = 49.15$). IR spectra were recorded as NaCl films on a Perkin-Elmer (1600 Series FTIR) spectrometer. Optical rotations were measured with a Rudolph Research Autopol III polarimeter. Elemental analysis were performed by Desert Analytics (Tucson, Arizona, USA). Mass spectra were measured on a VG 7070 and a HP 5989A mass spectrometer by the UCR Mass Spectroscopic Facility (University of California, Riverside). The X-Ray structure analysis of **4b** was performed on a Bruker AXS SMART CCD diffractometer ($MoK_\alpha = 0.71073$ Å). The structure was based on 4042 unique reflections, and solution and refinement were via the SHELXTL-plus system [10].

Preparation of the *N*-Substituted (*S*)-3-Hydroxysuccinamic Acids (4a–g)

To *L*-Malic acid (2.0 g, 14.92 mmol) was added dropwise at 0 °C trifluoroacetic anhydride (7.44 g, 35.42 mmol). After stirring for 1 h at 0 °C, the excess of TFAA was distilled off at room temperature under reduced pressure and the white residue dried in vacuum (for about 1 h). The resulting anhydride (**3**) was dissolved at 0 °C in 25 ml dry THF and a solution of the amine (29.83 mmol) added dropwise. The reaction mixture was stirred for 1 h at 0 °C and a further 1 h at room temperature. After removing the solvent by rotaevaporation the pure product was obtained by vacuum liquid chromatography (VLC) [8] on silica (40 g silica gel (Sigma), corn size: 10–40 μ; *n*-hexane/EtOAc as eluent, with increasing concentrations of EtOAc). If required the reaction product recrystallized from EtOH/*n*-hexane (addition of little amounts of charcoal).

(S)-3-Hydroxy-N-phenylsuccinamic Acid (**4a**)

Yield 57%, *m.p.* 118–120 °C. – $[\alpha]_D^{25}$ –57.0° (c 0.98, MeOH); IR data have been identical with the literature data of the (*R,S*)-form [3]. – MS (EI): *m/z* (%) = 209 (M^+), 120 (13), 93 (100), 90 (25), 77 (20).

N-(3,4-Dimethoxyphenyl)-(S)-3-hydroxysuccinamic Acid (**4b**)

Yield 39%, *m.p.* 124–126 °C. – $[\alpha]_D^{25}$ –51.6° (c 0.98, MeOH). – MS (EI): *m/z* (%) = 269 (75, M^+), 251 (18, $M - H_2O$), 153 (100), 138 (75), 110 (25). A hot saturated solution of **4b** overlayered with *n*-hexane gave, after 1d, pink crystals suitable for X-ray diffraction analysis. Crystals ($C_{12}H_{15}NO_6$) were monoclinic, space group $p2_1$, unicell dimension a = 9.9442 (8) Å, $\alpha = 90°$, b = 5.5846 (5) Å, $\beta = 109.4580$ (10)°, c = 11.6060 (10) Å, $\gamma = 90°$, Z = 607.72 Å^3, $\rho = 1.471$ mg/m^3, $\mu = 0.119$ mm^{-1}, $T = 163$ K.

N-(3,4-Methylenedioxyphenyl)-(S)-3-hydroxysuccinamic Acid (**4c**)

Yield 52%, *m.p.* 139–141 °C. – $[\alpha]_D^{25}$ –53.9° (c 0.98, MeOH). – MS (CI^+): *m/z* (%) = 254 (98, MH^+), 238 (10), 225 (5), 208 (5), 138 (100), 110 (3), 95 (3).

N-(4-Nitrophenyl)-(S)-3-hydroxysuccinamic Acid (**4d**)

Yield 56%, *m.p.* 187–189 °C. – $[\alpha]_D^{25}$ –55.0 (c 0.98, MeOH). – MS (EI): *m/z* (%) = 254 (100, M^+), 236 (4, $M - H_2O$), 208 (26), 165 (27), 149 (30), 138 (99), 122 (16), 108 (49), 89 (28), 71 (41).

N-(4-Aminophenyl)-(S)-3-hydroxysuccinamic Acid (**4e**)

Compound **4d** (0.50 g, 1.97 mmol) was hydrogenated in THF (50 ml) for 12 h in the presence of Pd/C (0.25 g, 10% Pd). After filtration of the catalyst over Celite and evaporation of the solvent, the product recrystallized from EtOH. Yield 66%; *m.p.* >300 °C (dec.). – MS (EI): *m/z* (%) 224 (52, M^+), 206 (10, $M - H_2O$), 134 (11), 108 (100), 107 (48), 91 (6), 80 (18).

N-(n-Butyl)-(S)-3-hydroxysuccinamic Acid (**4f**)

Yield 62%, *m.p.* 55–56 °C. – $[\alpha]_D^{25}$ –41.7° (c 0.99, MeOH). – MS (EI): *m/z* (%) = 190 (99, MH^+), 172 (100, $MH^+ - H_2O$), 154 (49).

N-(4-Methoxyphenethyl)-(S)-3-hydroxysuccinamic Acid (**4g**)

Yield 69%, *m.p.* 86–90 °C. – $[\alpha]_D^{25}$ –26.9° (c 0.98, MeOH). – MS(EI): *m/z* (%) = 268 (81, MH^+), 250 (37, $MH^+ - H_2O$), 135 (100), 105 (11).

N,N'-Disubstituted Fumaric Acid Amides (**5a,b**)

The compounds **5a,b** were obtained analogously to the procedure for the preparation of the *N*-substituted *L*-malic acid derivatives (**4**).

N,N'-Diisopropylfumaric Acid Amide (**5a**)

Yield 31%, *m.p.* 111–113 °C. – IR: $\nu_{max}/cm^{-1} = 2983, 2638, 1722, 1593, 1451, 1367, 1236, 1137, 829$. – ^1H NMR (DMSO-d_6): δ/ppm = 1.10 (d, 6H, $J = 6.6$ Hz, CH_3), 1.33 (d, 6H, $J = 6.6$ Hz, CH_3), 3.47 (sept, 1H, $J = 6.6$ Hz, CH), 3.85 (sept, 1H, $J = 6.6$ Hz, CH), 5.80 (d, 1H, $J_{trans} = 12.0$ Hz, CH), 6.68 (d, 1H, $J_{trans} = 12.0$ Hz, CH), 12.56 (bs, 1H, OH). – MS (EI): *m/z* (%) = 199 (3, M^+), 181 (18, $M - H_2O$), 156 (6), 138 (7), 112 (10), 100 (33), 99 (34), 86 (100), 58 (44).

$C_{10}H_{17}NO_3$	Calcd.:	C 60.28	H 8.60	N 7.03
(199.25)	Found:	C 60.23	H 8.51	N 7.05.

N,N'-Dicyclohexylfumaric Acid Amide (**5b**)

Yield 41%, *m.p.* 149 °C. – IR: $\nu_{max}/cm^{-1} = 2929, 2855, 1716, 1616, 1446, 1207, 1170, 894$. – ^1H NMR (DMSO-d_6): δ/ppm = 1.15 (m, 6H, CH_2), 1.48 (m, 6H, CH_2), 1.69 (m, 6H, CH_2), 2.32 (m, 2H, CH_2), 3.02 (m, 1H, CH), 3.40 (m, 1H, CH), 5.79 (d, 1H, $J_{trans} = 12.3$ Hz, CH), 6.69 (d, 1H, $J_{trans} = 12.3$ Hz, CH), 12.50 (bs, 1H, OH). – MS (EI): *m/z* (%) = 280 (100, MH^+), 198 (34), 182 (48), 180 (20).

$C_{16}H_{25}NO_3$	Calcd.:	C 68.79	H 9.02	N 5.01
(279.38)	Found:	C 68.65	H 9.18	N 4.81.

(R,S)-2-Hydroxy-N-phenylsuccinimide (**6a**) and *N-(3,4-Dimethoxyphenyl)-(S)-2-hydroxysuccinimide* (**6b**)

A mixture of *L*- (or *D,L*-) malic acid (4.97 g, 37.10 mmol), the aniline (35.3 mmol), $SOCl_2$ (6 drops) and 200 ml toluene was refluxed for 12 h on a Dean-Stark water separator. After cooling to room temperature, the precipitated product (**6**) was filtered off and recrystallized from EtOH. **6a**. – Yield: 63%, *m.p.* 176–

178 °C; the IR and ^{1}H NMR data have been consistent with the literature [3]. **6b**, – Yield: 44%, *m.p.* 180–182 °C. – $[\alpha]_D^{25}$ –31.0° (c 0.98, MeOH). – IR: ν_{max}/cm^{-1} = 3475, 2940, 1715, 1516, 1261, 1187, 1022, 764. – ^{1}H NMR (DMSO-d_6): δ/ppm = 2.59 (dd, 1H, J = 4.8, 17.7 Hz, CH_2), 3.11 (dd, 1H, J = 8.4, 17.7 Hz, CH_2), 3.72 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.64 (dddd, 1H, J = 4.8, 6.6, 8.4 Hz, CH), 6.20 (d, 1H, J = 6.6 Hz, OH), 6.78 (dd, 1H, J = 2.4, 8.4 Hz, aromat. CH), 6.84 (d, 1H, J = 2.1 Hz, aromat. CH), 7.04 (d, 1H, J = 8.4 Hz, aromat. CH). – MS (EI): *m/z* (%) = 251 (100, M^+), 179 (42), 164 (43), 152 (20), 138 (32), 136 (27), 121 (11), 110 (21), 108 (16), 93 (45), 80 (19), 71 (31).

$C_{12}H_{13}NO_5$	Calcd.:	C 57.37	H 5.22	N 5.57
(251.24)	Found:	C 57.00	H 5.29	N 5.50.

(R,S)-2-Hydroxy-N-phenylsuccinamic Acid (**7a**)

Prepared *via* a literature procedure [3], *m.p.* 141–143 °C (*m.p.*$_{Lit.}$ 141 °C); the IR and ^{1}H-NMR data were in agreement with the lit. [3]. – MS (EI): *m/z* (%) = 209 (4, M^+), 191 (52, M – H_2O), 119 (78), 93 (100), 77 (11).

N-(3,4-Dimethoxyphenyl)-(S)-2-hydroxysuccinamic Acid (**7b**)

The imide **6b** (1.50 g, 5.97 mmol) was dissolved in 30 ml 30% aqueous NH_3 solution (510,8 mmol). After 10 min at room temp, was diluted with water (75 ml) and then heated to boiling temp. (1 min.). After cooling, the NH_3 was removed by rotaevaporation. Acetic acid was added (75 ml, 40%), and the mixture extracted with EtOAc (5 × 50 ml). The EtOAc extract was dried (Na_2SO_4), and the solvent removed by rotaevaporation. The residue (containing: 87% **7b** + 13% **4b**, by ^{1}H NMR) was purified by VLC (*n*-hexane/EtOAc, gradient EtOAc) to yield **7b** (39%), *m.p.* 120–24 °C. – MS (EI): *m/z* (%) = 269 (75, M^+), 251 (100, M – H_2O), 233 (35), 153 (44), 138 (51), 110 (26), 95 (5).

Methylesters **4b** *Me* and **7b** *Me*

Compound **4b** (66.5 mg, 0.247 mmol), MeOH (5ml) and a CH_2N_2 solution in ether (generated from *N*-methyl-*N*-nitrosourea [11]) (50 ml, ≈ 0.8 g CH_2N_2, 19.03 mmol) was stirred for 1 h. The solvent evaporation yielded **4bMe** (97%). – ^{1}H NMR ($CDCl_3$): δ/ppm = 2.77 (dd, 1H, J = 8.4, 17.1 Hz, CH_2), 3.03 (dd, 1H, J = 3.5, 17.1 Hz, CH_2), 3.71 (s, 3H, $COOCH_3$), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.56 (m, 1H, CH), 6.77 (d, 1H, J = 8.4 Hz, aromat. CH), 6.94 (dd, 1H, J = 2.4, 8.4 Hz, aromat. CH), 7.33 (d, 1H, J = 2.4 Hz, aromat. CH), 8.63 (bs, 1H, NH).

7bMe was obtained by an analogous procedure. – Yield: 96%. – ^{1}H NMR ($CDCl_3$): δ/ppm = 2.78 (dd, 1H, J = 7.2, 15.5 Hz, CH_2), 2.86 (dd, 1H, J = 4.5, 15.5 Hz, CH_2), 3.78 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.57 (m, 1H, CH), 6.73 (d, 1H, J = 8.7 Hz, aromat. CH), 6.87 (dd, 1H, J = 2.1, 8.7 Hz, aromat. CH), 7.25 (d, 1H, J = 2.1 Hz, aromat. CH), 8.17 (bs, 1H, NH).

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