Supporting Information belonging to the manuscript:

The Synthesis of *o,p*-EDDHA and its detection as the Main Impurity in *o,o*-EDDHA Commercial Iron Chelates

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N-(2,2-Dimethoxyethyl)amino-(2-methoxyphenyl)acetic acid methyl ester, 7 (Figure 2). *1[st] Step:* Et_3N (7.5 mL, 53.9 mmol) was added over a solution of methyl *o*-methoxyphenylglycinate hydrochloride **5** (3.22 g, 17.79 mmol) in 50 mL of dry MeOH, under argon atmosphere at rt. The mixture was stirred for 30 min before 3.40 g (19.77 mmol) of dimethoxyacetaldehyde **6** (60 wt. % in H_2O) was added. After stirring at rt for 20 h, the solvents were removed under vacuum and the residue solved in CH_2Cl_2 and washed several times with water. The organic layer was dried over $MgSO_4$, filtered and concentrated to give 3.95 g (79%) of the corresponding imine as a yellow oil. IR (film) 1742, 1654 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.41 (d, J = 4.7 Hz, 1H), 7.40-7.18 (m, 2H), 6.93-6.80 (m, 2H), 5.43 (s, 1H), 4.70 (d, J = 4.7 Hz, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 3.36 (s, 3H), 3.29 (s, 3H). ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 171.4, 163.7, 156.8, 129.6, 129.1, 125.4, 121.0,

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110.9, 103.3, 69.2, 55.7, 54.3, 54.1, 52.5. Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N 4.98. Found: C, 59.53; H, 7.14; N, 4.63. *2nd Step:* A mixture of the imine obtained in the first step (3.12 g, 11.10 mmol), 5% Pd(C) (470 mg) and 100 mL of EtOH was hydrogenated at 50 p.s.i. for 24 h. The mixture was filtered and concentrated to provide 3.14 g (100%) of **7** as yellow oil. IR (film) 3342, 1740 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.29-7.17 (m, 2H), 6.92-6.80 (m, 2H), 4.67 (s, 1H), 4.43 (t, J = 5.6 Hz, 1H), 3.78 (s, 3H), 3.62 (s, 3H), 3.28 (s, 3H), 3.26 (s, 3H), 2.69 (dd, J = 12.0, 5.6 Hz, 1H), 2.53 (dd, J = 12.0, 5.6 Hz, 1H). ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 173.2, 157.1, 129.3, 128.8, 126.8, 120.9, 111.0, 103.8, 59.7, 55.6, 53.8, 53.7, 52.1, 48.8. Anal. Calcd. for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.57; H, 7.09; N, 4.62.

Compound 8 (Figure 2). *1st Step:* Acetic formic anhydride, freshly prepared by heating a mixture of Ac_2O (23.5 mL, 234.0 mmol) and formic acid (9.2 mL, 231.5 mmol) at 60 °C for 1h, were added over neat amine **7** (2.54 g, 8.97 mmol) at 0 °C. The mixture was stirred at 0 °C for 5 min and then for 10 min at rt, poured into a mixture of ice and water (200 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were extracted with a 10% solution of $NaHCO_3$ (3 x 90 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The expected formamide (2.56 g, 92%) was isolated as yellow oil. The NMR spectra showed that the compound was a mixture of rotamers. IR (film) 1749, 1670 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 8.13 (s, 0.6H), 8.06 (s, 0.4H), 7.38-6.83 (m, 4H), 6.21 (s, 0.6H), 5.39 (s, 0.4H), 4.27 (dd, J = 7.0, 3.7 Hz, 0.4H), 3.89 (dd, J = 5.0, 3.7 Hz, 0.6H), 3.76 (s, 3H), 3.74 (s, 1.5 H), 3.67 (s, 1.5H), 3.58 (dd, J = 6.3, 4.5 Hz, 0.8H), 3.42 (s, 0.2H), 3.35 (s, 1.5H), 3.32-3.27 (m, 0.4H), 3.26 (s, 1.5H), 3.25-3.17 (m, 0.2H), 3.16 (s, 1.5H), 3.14 (s, 1.5H), 3.13-3.06 (m, 0.4H). ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 171.2, 170.7, 164.6, 164.0, 157.4, 156.9, 131.0, 130.5, 130.3, 128.9, 128.7, 123.4, 122.2, 120.9, 120.4, 111.2, 111.0, 103.4, 103.2, 60.8, 55.4, 55.3, 55.0, 54.8, 54.7, 54.1, 52.3, 52.2, 47.8, 47.1. Anal. Calcd. for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N 4.50. Found: C, 58.21; H, 6.47; N, 4.17. *2nd Step*: A solution of the formamide obtained in the first step (2 g, 6.42 mmol) in dry CH_2Cl_2 (450 mL) was treated with $FeCl_3.6H_2O$ (80 g, 22.47 mmol) at reflux for 30 min under argon atmosphere. The reaction was then

cooled to rt and neutralized with saturated $NaHCO_3$. The resultant emulsion was filtered and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with water, dried over $MgSO_4$, filtered and the solvent removed under vacuum. Finally, purification of the residue by filtration on silica gel (3:7, AcOEt : Hexane) gave 1.4 g (82%) of **8** as a very unstable oil. IR (film) 1747, 1736, 1676 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 9.17 (t, J = 1.4 Hz, 1H), 8.35 (s, 0.8H), 8.14 (s, 0.2H), 7.36-6.80 (m, 4H), 6.30 (s, 0.2H), 5.70 (s, 0.8H), 3.92 (dd, J = 18.0, 1.4 Hz, 1H), 3.90 (dd, J = 18.0, 1.4 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 198.4, 198.1, 170.8, 170.7, 164.0, 163.4, 157.4, 157.3, 131.6, 131.3, 129.2, 121.6, 121.4, 121.0, 111.4, 59.0, 55.7, 55.5, 54.5, 54.4, 52.8, 52.6, 51.4.

Synthesis of 10 (Figure 2). *1st Step:* A solution of methyl *p*-methoxyphenylglycinate (1.01 g, 5.16 mmol), obtained from its hydrochloride, in CH_2Cl_2 (10 mL) was added over a solution of the aldehyde **8** (1.37 g, 5.16 mmol) in 100 mL of CH_2Cl_2. Anhydrous $MgSO_4$ (8 g) was then added and the mixture stirred under argon for 20 h. The crude reaction was filtered and the solvent removed under vacuum. The corresponding imine (2.58 g) was obtained as an oil and used in the second step without further purification. ^1H NMR (200 MHz, $(CD_3)_2SO$) δ 8.19-8.08 (m, 1H), 7.26-6.67 (m, 9H), 6.21 (br s, 0.2H), 5.82-5.78 (m, 0.4H), 5.60-5.49 (m, 0.4H), 4.72-4.55 (m, 1H), 4.23-4.00 (m, 1H), 3.79-3.55 (m, 13H). *2nd Step:* A solution of the crude imine obtained in the first step (1.97 g, 4.45 mmol) in absolute EtOH (100 mL) and 5% Pd(C) (300 mg) was hydrogenated at 50 p.s.i. for 24 h. The mixture was filtered and the solvent removed under reduced presure. The residue was purified on silica gel (1:1, AcOEt : Hexane) leading to 1.28 g (oil, 65% from **8**) of formyl aminoester **10** as a diastereomeric mixture. IR (film) 3327, 1742, 1670 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 8.21 (s, 0.3H), 8.18 (s, 0.3H), 8.09 (s, 0.4H), 7.27-6.96 (m, 4H), 6.89-6.77 (m, 4H), 6.08 (s, 0.4H), 5.50 (s, 0.3H), 5.48 (s, 0.3H), 4.53 (s, 0.3H), 4.32 (s, 0.3H), 4.30 (s, 0.3H), 4.16 (s, 0.1H), 3.73-3.59 (m, 12 H), 3.47-3.02 (m, 2H), 2.74-2.19 (m, 3H). ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 174.5, 173.1, 173.0, 171.0, 170.7, 163.8, 159.3, 159.2, 157.4, 156.9, 132.2, 130.4, 130.2, 129.8, 129.7, 128.9, 128.6, 128.5, 128.4, 127.8, 122.5, 121.8, 120.8, 120.5, 114.0, 113.9, 113.8, 111.0, 110.8,

64.6, 64.2, 64.1, 59.8, 57.9, 55.3, 55.1, 54.3, 52.4, 52.3, 52.2, 52.0, 46.2, 46.0, 45.9, 45.0, 43.7. Anal. Calcd. for $C_{23}H_{28}N_2O_7$: C, 62.15; H, 6.35; N 6.30. Found: C, 62.34; H, 6.05; N, 6.06.

Synthesis of o,p-EDDHA, 3 (Figure 2). *1st Step*: 12M HCl (4.5 mL, 54 mmol) was added over 790 mg (1.78 mmol) of **9** and stirred at 60-70 °C for 3h. The mixture was allowed to reach rt, then the solvent was removed under vacuum and the residue dried several times with acetone in a rotary evaporator, to give 690 mg (96%) of the expected amino acid as a 1:1 mixture of diastereoisomers and as a beige solid. IR (KBr) 3384, 2937, 1736 cm^{-1}. ^1H NMR (200 MHz, $(CD_3)_2SO$) δ 8.86 (br s, 1H), 7.47-7.40 (m, 4H), 7.12-6.96 (m, 4H), 5.41 (d, *J* = 3.5 Hz ,0.2H), 5.24 (d, *J* = 4.5 Hz, 0.7H), 5.09 (d, *J* = 3.0 Hz ,0.8H), 4.98 (br s, 0.3H), 3.79 (s, 1.5 H), 3.78 (s, 1.5H), 3.76 (s, 1.5H), 3.75 (s, 1.5H), 3.39-3.03 (m, 4H). ^{13}C NMR (50.03 MHz, $(CD_3)_2SO$) δ 169.6, 168.8, 168.6, 160.1, 159.7, 157.2, 131.5, 130.6, 130.4, 129.5, 125.1, 122.4, 120.7, 118.5, 114.4, 114.1, 111.7, 61.7, 57.6, 55.8, 55.3, 54.8, 53.0, 41.3, 40.8. Anal. Calcd. for $C_{20}H_{26}N_2O_6Cl_2$: C, 52.07; H, 5.68; N 6.07. Found: C, 51.88; H, 5.97; N, 5.73. *2nd Step*: HBr (48%) (3 mL, 26.75 mmol) was added over the product obtained in the first step (490 mg, 1.07 mmol) and refluxed for 2 h. The resultant solution was allowed to reach rt and then the solvent was removed under vacuum and the residue dried several times with acetone in a rotary evaporator. After drying under vacuum, *o,p*-EDDHA **3** (530 mg, 95%, dihydrobromide) was isolated as a 1:1 mixture of diasteroisomers and as a pink solid. IR (KBr) 3384, 2920, 1735 cm^{-1}. ^1H NMR (200 MHz, $(CD_3)_2SO$) δ 9.81 (br s, 1H), 8.62 (br s, 1H), 7.49-7.32 (m, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.14-6.91 (m, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 5.35 (br s, 0.2H), 5.27 (d, *J* = 2.7 Hz, 0.5H), 5.12 (br s, 0.8H), 4.96 (br s, 0.5), 3.20-2.87 (m, 4H). ^{13}C NMR (50.03 MHz, $(CD_3)_2SO$) δ 170.2, 169.6, 169.3, 158.8, 158.3, 157.2, 155.8, 131.7, 131.3, 130.9, 130.3, 129.5, 123.3, 120.8, 119.5, 117.2, 115.9, 115.7, 111.9, 62.1, 58.7, 58.5, 55.9, 55.1, 41.6. ^1H NMR (200 MHz, D_2O-Na_2CO_3) δ 6.96-6.72 (m, 4H), 6.54-6.34 (m, 4H), 4.17 (s, 1H), 3.75 (s, 1H), 2.56-2.39 (m, 4H). ^{13}C NMR (50.03 MHz, D_2O-Na_2CO_3) δ 179.9, 177.7, 159.3, 131.2, 130.6, 129.9, 129.2, 127.1, 124.0, 118.3, 117.9, 66.9, 64.3, 45.4, 45.1. Anal. Calcd. for $C_{18}H_{22}N_2O_6Br_2$: C, 41.40; H, 4.25; N 5.36. Found: C, 41.13; H, 4.46; N, 5.01.

Synthesis of aminonitrile* 12 *(Figure 3). *1st Step:* A 100 mL round bottomed flask equipped with a Dean-Stark apparatus and a reflux condenser, was charged with a solution of amine **11** (5.08 g, 31.75 mmol) in dry benzene (40 mL), *o*-anisaldehyde (4.32 g, 31.75 mmol) and a catalytic amount of anhydrous $ZnCl_2$ (molten and dried before use). The reaction was refluxed for 12 h, then cooled to rt, filtered off and the solvent removed under vacuum. The corresponding imine (8.80 g, 99%) was obtained as yellow oil. IR (film) 3354, 1697, 1637 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.83 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.34-7.25 (m, 1H), 6.84 (m, 2H), 5.19 (br s, 1H), 3.77 (s, 3H), 3.63-3.57 (m, 2H), 3.41-3.30 (m, 2H), 1.34 (s, 9H). ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 159.0, 156.1, 132.3, 127.4, 124.5, 120.9, 111.2, 79.4, 61.2, 55.6, 28.5. Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N 10.06. Found: C, 64.89; H, 8.25; N, 9.77. *2nd Step*: TMSCN (6.09 mL, 48.55 mmol) was added over a solution of the imine obtained in the first step (9 g, 32.37 mmol) in anhydrous THF (35 mL), at rt under argon atmosphere. After stirring for 42 h at rt the reaction was cooled on an ice bath and 10 mL of saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (50 mL x 2) and the combined organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Aminonitrile **12** (9.20 g, 93%) was obtained as a yellow oil and was used in the next step without further purification. IR (film) 3342, 2251, 1701 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.36-7.26 (m, 2H), 6.97-6.86 (m, 2H), 4.92 (br s, 1H), 4.82 (s, 1H), 3.81 (s, 3H), 3.25-3.16 (m, 2H), 2.98-2.70 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 156.7, 156.1, 130.6, 128.6, 123.2, 121.0, 119.0, 111.3, 79.3, 55.7, 49.7, 47.1, 28.4.

Synthesis of 13 (Figure 3): Acetic formic anhydride, freshly prepared by heating a mixture of Ac_2O (2.49 mL, 24.89 mmol) and formic acid (0.97 mL, 24.70 mmol) at 60 °C for 1h, was added over neat nitrile **12** (580 mg, 1.90 mmol) at 0 °C. The mixture was stirred at 0 °C for 5 min and then for 1 h at rt. Absolute MeOH (15 mL) was added, the resultant solution cooled to -17 °C and HCl gas bubbled through until the solution was saturated. The mixture was allowed to stir at rt for 1 h and then quenched with water (1 mL) and left to stir for another 12 h. The crude was concentrated under reduced pressure, dissolved in the minimum amount of MeOH and precipitated with acetone.

The solid was filtered, washed with acetone and dried under vacuum, to yield 310 mg (55%) of amide **13** as a white solid. This compound was isolated as dihydrochloride. m.p. 115-117 °C. IR (KBr) 3414, 3321, 3281, 1703 cm^{-1}. ^1H NMR (200 MHz, $(CD_3)_2SO$) δ 9.98 (br s, 0.5H), 9.76 (br s, 0.5H), 8.54 (br s, 4H), 7.67 (br s, 2H), 7.47-7.40 (m, 2H), 7.14-6.97 (m, 2H), 5.13 (s, 1H), 3.83 (s, 3H), 3.10-2.95 (m, 4H). ^{13}C NMR (50.03 MHz, $(CD_3)_2SO$) δ 167.7, 157.1, 131.2, 129.3, 120.6, 119.0, 111.6, 57.1, 55.7, 42.4, 34.8. Anal. Calcd. for $C_{11}H_{19}N_3O_2Cl_2$: C, 44.61; H, 6.47; N 14.19. Found: C, 44.45; H, 6.82; N, 13.79.

Synthesis of compound 14 (Figure 3). *1st Step:* Et_3N (2.48 mL, 17.88 mmol) was added over a solution of **13** (882 mg, 2.98 mmol) in dry MeOH (20 mL), under argon atmosphere at rt. The mixture was stirred for 30 min and then, *p*-anisaldehyde (405 mg, 2.98 mmol) in 2 mL of MeOH was added. The mixture was stirred for 20 h at rt. The solvents were removed under vacuum, the residue was dissolved in the minimum amount of CH_2Cl_2 and Et_2O was added until precipitation. The crude was filtered and the solvents were removed under vacuum to give 630 mg (62%) of the expected imine as oil. The NMR spectra showed that the imine was a mixture of rotamers. IR (film) 3421, 3346, 3215, 1683, 1647 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 8.18 (s, 0.45H), 8.10 (s, 0.55H), 7.61 (dd, J = 8.8, 3.4 Hz, 2H), 7.28-7.22 (m, 2H), 6.91-6.81 (m, 4H), 6.17 (br s, 0.45H), 4.46 (s, 0.55H), 3.85 (s, 1.35H), 3.80 (s, 1.65H), 3.79 (s, 1.65H), 3.74 (s, 1.35H), 3.67-3.61 (m, 2H), 2.91 (t, J = 5.8 Hz 2H). ^{13}C NMR (50.03 MHz, $CDCl_3$) δ. 175.7, 164.6, 161.9, 161.7, 156.9, 132.0, 130.0, 129.6, 129.3, 127.9, 120.9, 114.3, 114.0, 111.0, 62.0, 61.7, 61.2, 55.6, 55.5, 55.3, 49.1, 45.9. Anal. Calcd. for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N 12.31. Found: C, 67.11; H, 6.58; N, 12.72. *2nd Step:* TMSCN (0.32 mL, 2.59 mmol) was added over a solution of the imine obtained in the first step (590 mg, 1.73 mmol) in anhydrous THF (5 mL), at rt under argon atmosphere. After stirring at rt for 42 h, the crude was cooled on an ice bath and 1 mL of saturated NH_4Cl solution was added. The mixture was diluted with 5 mL of water, extracted with Et_2O (10 mL x 2) and the combined organic layers were washed with water, dried over$MgSO_4$, filtered and concentrated under reduced pressure. Compound **14** (660 mg, 72%) was obtained as yellow oil and was used in the next step without

further purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28-7.03 (m, 4H), 6.88-6.63 (m, 4H), 4.72 (br s, 0.8H), 4.65 (br s, 0.2H), 4.61 (s, 0.2H), 4.44 (d, J = 1.9 Hz, 0.4H), 4.29 (d, J = 2.2 Hz, 0.4H), 3.80 (s, 6H), 3.92-2.74 (m, 4H), 2.26 (br s, 2H).

Synthesis of o,p-methoxy-EDDHA, 15 (Figure 3). Acetic formic anhydride, freshly prepared by heating a mixture of Ac_2O (0.81 mL, 20.28 mmol) and formic acid (2.10 mL, 20.96 mmol) at 60 °C for 1h, was added over neat nitrile **14** (590 mg, 1.60 mmol) at 0 °C. The mixture was stirred at 0 °C for 5 min and then for 1 h at rt. 12M HCl (4.0 mL, 48.00 mmol) was added over the solution that was stirred at 60 - 70 °C for 3h. The mixture was allowed to cool to rt and after removing the solvent under vacuum, 480 mg (60%, dihydrochloride) of *o,p*-methoxy-EDDHA **15** was obtained as a 1:1 mixture of diastereoisomers and as an orange solid. The spectroscopical data of this product were identical to those of the compound obtained by hydrolysis of **10** with HCl.

Synthesis of ethylenediamino-bis-phenylacetic acid. The preparation of this compound was effected following the route depicted in Figure 6.

***Imine*17.** 682 mg (3.93 mmol)of dimethoxyacetaldehyde **6** (60 wt. % in H_2O) were added to a solution of 650 mg (3.93 mmol) of methyl phenylglycinate **16** (obtained from its hydrochloride) in 50 mL of dry MeOH. The mixture was stirred for 20 h under argon atmosphere at rt. Elimination of the volatile under vacuum gave 970 mg (98%) of **17** as a yellow oil. IR (film) 1736, 1689 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45 (d, J = 4.7 Hz, 1H), 7.33-7.27 (m, 5H), 5.00 (s, 1H), 4.72 (d, J = 4.7 Hz, 1H), 3.67 (s, 3H), 3.37 (s, 3H), 3.31 (s, 3H). ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 170.9, 163.7, 137.0, 128.9, 128.4, 127.9, 103.2, 75.7, 54.3, 54.2, 52.6. Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N 5.57. Found: C, 62.38; H, 6.49; N, 5.92.

***N-(2,2-Dimethoxyethyl)aminophenylacetic acid methyl ester,* 18.** A mixture of imine **17** (970 mg, 3.86 mmol), 5% Pd(C) (140 mg) and 30 mL of EtOH was hydrogenated at 50 p.s.i. for 24 h. The mixture was filtered and concentrated to provide 910 mg (93%) of **18** as a yellow oil. IR (film) 3344, 1740 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 6.01 (br s, 1H), 4.64 (s, 1H),

4.52 (t, J = 5.4 Hz, 1H), 3.64 (s, 3H), 3.31 (s, 3H), 3.28 (s, 3H), 2.73 (d, J = 5.4 Hz, 2H). ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 173.2, 137.8, 128.9, 128.3, 127.6, 103.8, 65.3, 54.0, 53.9, 52.4, 48.8. Anal. Calcd. for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N 5.53. Found: C, 61.48; H, 7.85; N, 5.21.

***Formylation of* 18**. Acetic formic anhydride, freshly prepared by heating a mixture of Ac_2O (3.2 mL, 31.96 mmol) and formic acid (1.4 mL, 31.72 mmol) at 60 °C for 1h, were added over neat amine **18** (310 mg, 1.22 mmol) at 0 °C. The mixture was stirred at 0 °C for 5 min and then for 10 min at rt, poured into a mixture of ice and water (20 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were extracted with a 10% solution of $NaHCO_3$ (3 x 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. A mixture of rotamers of formamide **19** (260 g,76%) was isolated as a yellow oil. IR (film) 1747, 1674 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.15 (s, 0.7H), 8.04 (s, 0.3H), 7.36-7.16 (m, 5H), 6.09 (s, 0.7H), 5.27 (s, 0.3H), 4.32 (t, J = 5.5 Hz, 0.3H), 3.77 (s, 0.9H), 3.71 (s, 2.1H), 3.67-3.54 (m, 0.7H), 3.49-3.41 (m, 0.8H), 3.36 (s, 0.9 H), 3.28 (s, 0.9H), 3.24-3.14 (m, 1.2H), 3.12 (s, 2.1H), 3.11 (s, 2.1H). ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 170.6, 164.9, 164.3, 134.7, 133.9, 129.5, 129.3, 129.2, 129.1, 129.0, 128.4, 103.4, 103.3, 66.0, 58.6, 55.6, 55.2, 55.0, 54.9, 52.8, 52.6, 47.8, 47.5. Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N 4.98. Found: C, 59.93; H, 7.16; N, 4.59.

***Deprotection of* 19.** A solution of formamide **19** (110 mg, 0.39 mmol) in dry CH_2Cl_2 (30 mL) was treated with $FeCl_3.6H_2O$ (370 mg, 1.36 mmol) at reflux for 30 min under argon atmosphere. The reaction was then cooled to rt and neutralized with saturated $NaHCO_3$. The resultant emulsion was filtered off, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with water, dried over $MgSO_4$, filtered and the solvent removed under vacuum. Finally, purification of the residue by filtration on silica gel (3:7, AcOEt : Hexane) gave 70 mg (76%) of **20** as a very unstable oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.27 (s, 0.6H), 9.18 (s, 0.4H), 8.35 (s, 0.6H), 8.14 (s, 0.4H), 7.37-7.30 (m, 2H), 7.19-7.15 (m, 3H), 6.27 (s, 0.4H), 5.44 (s, 0.6H), 3.94-3.92 (m, 2H), 3.78 (s, 1.8H), 3.73 (s, 1.2H).

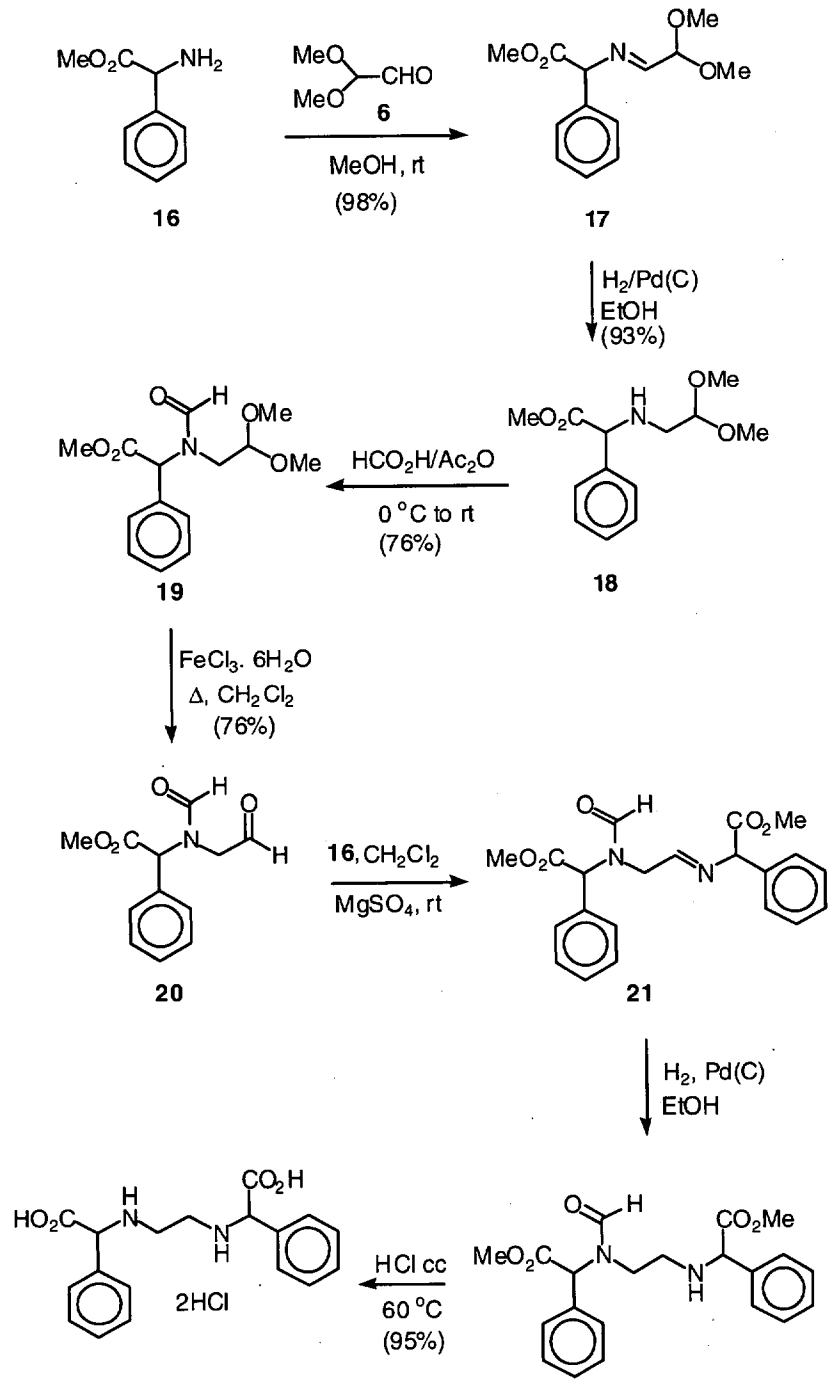
***Synthesis of* 21.** A solution of methyl phenylglycinate **16** (185 mg, 1.12 mmol), obtained from its hydrochloride, in 1 mL of CH_2Cl_2, was added over a solution of the aldehyde **20** (263 mg, 1.12 mmol) in 25 mL of CH_2Cl_2 at rt and under argon atmosphere. Anhydrous $MgSO_4$ (2 g) was then added and the mixture stirred under argon for 20 h. The crude reaction was filtered and the solvent removed under reduced pressure, leading to 410 mg of imine **21** as an oil, that was employed in the following step without purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.18-7.98 (m, 2H), 7.40-7.04 (m, 10H), 6.09-5.77 (m, 0.6H), 5.68-5.51 (m, 0.3H), 5.33-5.30 (m, 0.1H), 4.78-3.91 (m, 3H), 3.71-3.58 (m, 6H).

***Synthesis of aminoester* 22.** A solution of crude imine **21** (410 mg, 1.07 mmol) in absolute EtOH (30 mL) and 5% Pd(C) (60 mg) was hydrogenated at 50 p.s.i. for 24 h. The mixture was filtered and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel (2:3, AcOEt : Hexane) leading to 330 mg (oil, 75% from **21**) of formyl bis-aminoester **22** as a mixture of rotamers. IR (film) 3344, 1741, 1668 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.16 (s, 0.4H), 8.15 (s, 0.3H), 8.07 (s, 0.3H), 7.26-7.07 (m, 10H), 5.82 (s, 0.7H), 5.28 (s, 0.3H), 4.21 (d, J = 3.2 Hz, 0.3H), 4.09 (d, J = 4.4 Hz, 0.7H), 3.65 (s, 0.7H), 3.63 (s, 1.6H), 3.61 (s, 0.7H), 3.53 (s, 3H), 3.46-3.06 (m, 2H), 2.56-1.95 (m, 3H). ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 173.3, 173.1, 173.0, 170.7, 170.6, 170.5, 164.1, 164.0, 163.8, 138.1, 138.0, 137.9, 134.3, 133.6, 133.5, 129.4, 129.2, 129.0, 128.9, 128.8, 128.7, 128.5, 128.2, 128.1, 128.0, 127.5, 127.4, 126.9, 65.4, 65.3, 65.2, 65.1, 65.0, 59.4, 59.3, 58.8, 52.7, 52.5, 52.3, 52.2, 46.5, 46.4, 46.1, 45.6, 44.3. Anal. Calcd. for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N 7.29. Found: C, 65.83; H, 6.36; N, 6.87.

Synthesis of ethylenediamine-bis-phenylacetic acid. A solution of **22** (280 mg, 0.73 mmol) in 12M HCl (1.4 mL, 16.80 mmol) was refluxed for 3 h. The solution was allowed to reach rt , the solvent removed under vacuum and the residue dried several times with acetone in a rotary evaporator to give 300 mg (95%) of ethylenediamine-*bis*-phenylacetic acid as a beige solid and as a 1:1 mixture of diasteromers. This compound was obtained as dihydrochloride. IR (KBr) 3421, 2930, 1737 cm^{-1}. ^{1}H NMR (200 MHz, $(CD_3)_2SO$) δ 7.60-7.51 (m, 10H), 5.26 (s, 2H), 3.35-3.14 (m,

4H). ^{13}C NMR (50.03 MHz, $(CD_3)_2SO$) δ 168.5, 130.5, 129.9, 129.7, 129.0, 128.8, 128.0, 62.2, 40.9. Anal. Calcd. for $C_{18}H_{22}N_2O_4Cl_2$: C, 53.88; H, 5.53; N 6.98. Found: C, 54.21; H, 5.71; N, 6.59.

Figure 6



ethylenediamine-bis-phenylacetic acid

22 (75% two steps)