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SYNTHESIS OF POLYDENTATE LIGANDS CONTAINING AMIDES AND THIOLS FOR BIOMIMETIC METAL COMPLEXES

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SYNTHESIS OF POLYDENTATE LIGANDS CONTAINING AMIDES AND THIOLS FOR BIOMIMETIC METAL COMPLEXES

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ABSTRACT

Three pentadentate "N_2S_3" and one tetradentate "N_2S_2" new ligands with "N" = CO*N*H and "S" = *S*H have been synthesized. The key step is the direct diamide formation from the malonyl diester and the amines in the presence of trimethylaluminum.

Nitrile hydratases (NHases) are metalloenzymes that contain a non-heme iron(III) or a non-corrinoid cobalt(III) and catalyze the hydration of nitriles to amides.[1–3] Recent x-ray crystallographic structures of NHases from *Rhodococcus* sp.R312 and *Rhodococcus* sp.N771 indicated that the iron(III) is coordinated to two nitrogen atoms from peptide bonds of the main chain and three cystein sulfur atoms, two of which are post-translationally oxidized to cystein sulfinic (RSO_2^-) and sulfenic (RSO^-) moieties.[4,5] Despite the structural information brought by x-ray diffraction data, post-translational oxidation of bound cysteins remains to be

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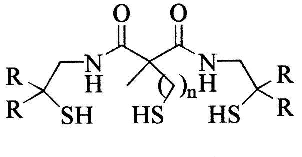
understood and it is not yet clear how NHases work. The study of relevant mimetic complexes should help to answer these questions.

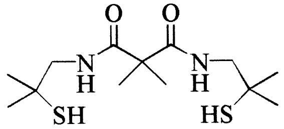
As part of our research program directed toward the synthesis of biomimetic complexes of NHases, different iron(III) and cobalt(III) complexes with thiolato and N-carboxamido ligands were to be studied. Recently, some model complexes of NHases have been reported,[6–8] but none of them has the N_2S_3 (with "N" = CO*N*H and "S" = *S*H) coordination sphere present in the enzyme metal center. One of the major reasons for this lack is probably the synthetic difficulty to accede to N_2S_3 ligands. To our knowledge, the synthesis of polydentate ligands containing two amide and three thiol groups has not been reported so far. Only a N_2S_2 ligand similar to **4** has been prepared in low yield (37%).[9]

In this paper we report the synthesis of the following three N_2S_3 ligands **1–3** and the N_2S_2 ligand **4** (Fig. 1).

Our first route to the formation of the diamide moiety consisted of a classical double-coupling reaction between a diacid and two equivalents of an amino compound. The diacid **8** was prepared in good yield by condensation of diethyl 2-methylmalonate (**6**) with benzylchloromethylsulfide (**5**) in anhydrous DMF in the presence of sodium hydride, followed by a double saponification (Scheme 1). **5** was prepared by a smooth and high-yielding method from bromochloromethane, benzyl mercaptan, and potassium hydroxide using triethylbenzylammonium chloride (TEBAC),[10] as phase-transfer catalyst. It was more satisfactory than using benzyl mercaptan and 1,3,5-trioxane in the presence of hydrogenchloride (gas).[11]

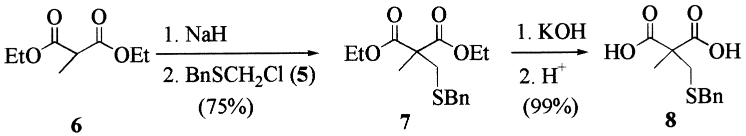


1 n = 1, R = Me
2 n = 2, R = Me
3 n = 1, R = H



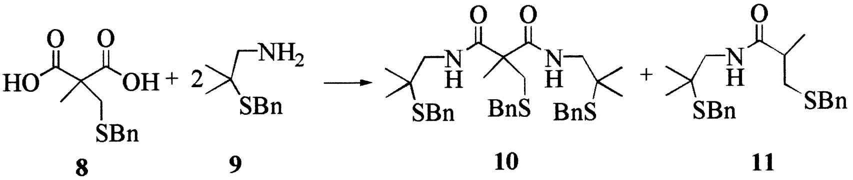
4

Figure 1. N_2S_3 and N_2S_2 ligands



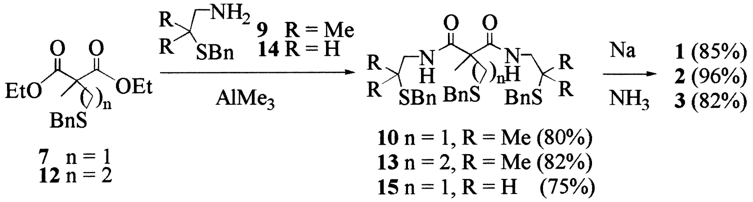
Scheme 1.

The diacid **8**, converted in situ into the dicarbonylchloride ($SOCl_2$) and then treated with **9**[12] in the presence of Et_3N in CH_2Cl_2 at 25°C gave the desired diamide **10** in 53% yield; surprisingly, the side-product **11**, resulting from the fragmentation of the malonic function was also formed in 18% yield (Scheme 2); Lower temperature (0°C) gave the mixture **10**:**11** in a 85:15 ratio. Other conventional coupling reagents[13] such as 1,3-diclohexylcarbodiimide (DCC) and DCC / 1-hydroxybenzotriazole (HOBt) gave similar results. Carbonyldiimidazole (CDI) gave the monoamide **11** (65% yield) as the only isolable product. All efforts to separate the diamide **10** from the monoamide **11** failed. Even after total deprotection of the thiol groups, the two compounds remained unseparable.



Scheme 2.

Since we needed highly pure ligands for metal complexation, the presence of the monoamide was not acceptable. Another strategy was then adopted. The direct amidation of the diester **7** by the amine **9** in the presence of trimethylaluminum[14] in anhydrous CH_2Cl_2 at 40°C afforded the diamide **10** as the unique product in 80% yield (Scheme 3). This reaction is very sensitive to higher temperature: the use of toluene at 80°C for 72 h gave exclusively the monoamide **11** in 60% yield.

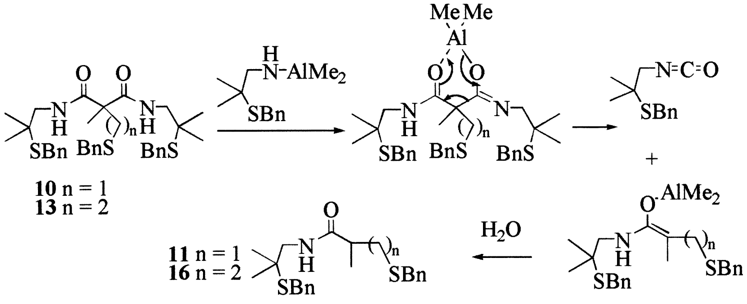


Scheme 3.

The procedure was successfully applied to the diester **12** and the amine **9** to afford the diamide **13** in 82% yield. The corresponding monoamide **16** (*vide infra*) was also obtained when the reaction was conducted in toluene at 80°C. A third diamide **15** was prepared from **7** and **14** in good yield following the same methodology.

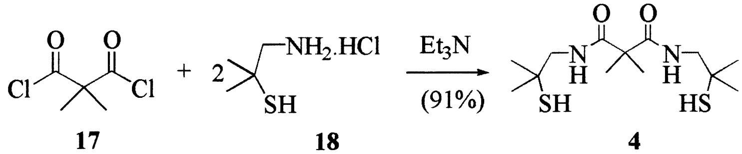
The three N_2S_3 ligands **1**, **2**, and **3** were obtained, respectively, by debenzylation of **10**, **13**, and **15** with sodium in liquid ammonia and anhydrous THF in good yields (Scheme 3).

The formation of the monoamides **11** and **16** is tentatively assigned to a fragmentation of the malonic diamide under basic conditions assisted by aluminum (Scheme 4).



Scheme 4.

Finally, the preparation of the N_2S_2 ligand **4** was rather straightforward from dimethylmalonyl dichloride (**17**) and 1-amino-2-methyl-2-propanethiol hydrochloride (**18**) with triethylamine in anhydrous CH_2Cl_2 in 91% yield (Scheme 5). No trace of monoamide was detected under these conditions.



Scheme 5.

Preliminary results using these ligands are already interesting: ligand **1**, upon deprotonation and complexation with Fe(III), followed by spontaneous air oxidation, afforded a pentacoordinated complex, with one sulfinato ligand (RSO_2^-) $[(N_2S_2S\{O\}O)Fe]^{2-}$. It is the first example of an *O*-sulfinato-iron(III) complex obtained by O_2 oxidation of a thiolato ligand.[15] Ligand **4**, upon deprotonation and complexation with Co(III), gave a rather rare, tetracoordinated, square-planar $[(N_2S_2)Co]^-$ complex.[16] Other iron(III) or cobalt(III) complexes using **1–4** as ligands are currently under investigation.

EXPERIMENTAL

Benzylchloromethylsulfide ($BnSCH_2Cl$) (**5**): To a solution of benzylthiol (15.6 g, 0.126 mol) in CH_2ClBr (1 L) were added successively triethylbenzylammonium chloride (TEBAC, 3.05 g, 0.013 mol) and a fine powder of potassium hydroxide (10.2 g, 0.182 mol) under argon. After vigorous stirring at room temperature for 1 h, a saturated aq. solution of NH_4Cl was added to the mixture to reach $pH \cong 7$, the organic layer was washed with water (100 mL), dried (Na_2SO_4), and evaporated to afford $BnSCH_2Cl$ (**5**) as a pure (NMR), colorless oil (21.8 g, 100%). This product was used in the next step without further purification. ^1H NMR (250 MHz, $CDCl_3$): δ 7.34–7.26 (m, 5 H, Ar), 4.54 (s, 2H, SCH_2Cl), 3.89 (s, 2H CH_2Ph).

Diethyl 2-(benzylthiomethyl)-2-methylmalonate (**7**): NaH (60% in mineral oil, 556 mg, 13.9 mmol) was added in small portions under Ar to a solution of $BnSCH_2Cl$ (**5**) (2.168 g, 12.6 mmol) and diethyl 2-methylmalonate (**6**) (2.19 g, 12.6 mmol) in anhydrous DMF (55 mL) cooled to −10°C. After 1.5 h at −10°C and 16 h at 25°C, aq. HCl 1M was added to reach $pH \cong 7$ and the solvents were evaporated under reduced pressure. Water (30 ml) was added and the mixture extracted with Et_2O (3 × 30 mL). The organic layer was washed with water (2 × 20 mL) dried (Na_2SO_4), and evaporated. The crude product was purified by chromatography over silica gel (1:9 EtOAc-cyclohexane) to afford 7 as a colorless oil (2.93 g, 75%). ^1H NMR (250 MHz, $CDCl_3$): δ 7.29–7.19 (m, 5H, Ar), 4.15 (q, 4H, $J = 7.1$ Hz, OCH_2CH_3), 3.70 (s, 2H, SCH_2Ph), 2.97 (s, 2H, CH_2S), 1.45 (s, 3H, CH_3), 1.21 (t, 6H, OCH_2CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 171.06 (CO), 138.01 (Ar-C), 128.87 (Ar-CH), 128.45 (Ar-CH), 127.05 (Ar-CH), 61.48 (OCH_2CH_3), 54.81 ($C(CO)_2$), 37.95 (SCH_2Ph), 37.11 (SCH_2), 19.72 (CH_3), 13.94 (OCH_2CH_3); MS (CI/NH_3): 311 (MH^+), 328 ($M+NH_4^+$); IR ($CHCl_3$): ν 1730 cm^{-1} (CO); Anal. calc. for $C_{16}H_{22}O_4S$ (310.42): C 61.91, H 7.14. Found: C 61.98, H 7.28.

2-methyl-2-(benzylthiomethyl)-malonic diacid (**8**): Aq. 2M potassium hydroxide solution (58 mL) was added to a solution of the diester **7** (1.085 g, 3.5 mmol) in ethanol (95%, 80 ml). After 3 days at 25°C, ethanol was evaporated and aq. 1M HCl was added at 0°C to reach $pH \cong 1$. The mixture was extracted with Et_2O (3 × 100 mL). The organic layer was washed with aq. saturated NaCl (50 ml), dried (Na_2SO_4), and evaporated to afford **8** as a pure (NMR), colorless solid (882 mg, 99%). ^1H NMR (250 MHz, $CDCl_3$): δ 8.96 (s br., 2H, D_2O exchangeable, OH), 7.29–7.17 (m, 5H, Ar), 3.73 (s, 2H, SCH_2Ph), 2.98 (s, 2H, SCH_2), 1.52 (s, 3H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 177.03 (CO), 137.61 (Ar-C), 128.94 (Ar-CH), 128.56 (Ar-CH), 127.24 (Ar-CH), 55.18 ($C(CO)_2$), 38.05 (SCH_2Ph), 36.51 (SCH_2), 19.66 (CH_3); MS (CI/NH_3): 228 ($M-CO_2+NH_4^+$); IR ($CHCl_3$): ν 3680, 3500 cm^{-1} (OH), 1710, 1720 cm^{-1} (CO); Anal. calc. for $C_{12}H_{14}O_4S$ (254.31): C 56.68, H 5.55, S 12.61. Found: C 56.71, H 5.59, S 12.41.

Diethyl 2-(2-benzylthioethyl)-2-methylmalonate (**12**): NaH (60% in mineral oil, 1 g, 25 mmol) was added in small portions under Ar to a solution of benzylthiol (2.912 g, 23.5 mmol) in anhydrous DMF (20 mL) cooled to −10°C (ice–NaCl bath). After 0.5 h at −10°C, the mixture was added dropwise to a solution of the diethyl 2-(2-bromoethyl)-2-methylmalonate[17] (6.504 g, 23.1 mmol) in anhydrous DMF (20 mL) at 0°C. After 16 h at 25°C, aq. HCl 1M was added to the reaction to reach pH $\cong$ 1 and the solvents were evaporated under reduced pressure. Water (50 mL) was added and the mixture extracted with EtOAc (2 × 100 mL). The organic layer was washed with water (2 × 50 mL), dried (Na_2SO_4), and evaporated. The crude product was purified by chromatography on silica gel (1:1 CH_2Cl_2-cyclohexane) to afford **12** as a colorless oil (5.781 g, 77%). ^1H NMR (250 MHz, $CDCl_3$): δ 7.29–7.20 (m, 5H, Ar), 4.13 (q, 4H, $J = 7.1$ Hz, OCH_2CH_3), 3.70 (s, 2H, SCH_2Ph), 2.37–2.31 (m, 2H, CH_2CH_2S), 2.10–2.15 (m, 2H, CH_2CH_2S), 1.35 (s, 3H, CH_3), 1.20 (t, 6H, OCH_2CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 171.73 (CO), 138.19 (Ar-C), 128.84 (Ar-CH), 128.44 (Ar-CH), 126.96 (Ar-CH), 61.31 (OCH_2CH_3), 53.39 ($C(CO)_2$), 35.96, 35.63 (SCH_2Ph, SCH_2), 26.01 (CH_2CH_2S), 19.89 (CH_3), 13.94 (OCH_2CH_3); MS (CI/NH_3): 342 ($M+NH_4^+$), 325 (MH^+); IR ($CHCl_3$): ν 1728 cm^{-1} (CO); High Resolution MS calc. for $C_{17}H_{25}O_4S$ (M^+): 325.1474. Found: 325.1478.

General Procedure for the Synthesis of Diamides

A solution of trimethylaluminum in heptane (2M, 7.2 mL, 14.4 mmol) was added dropwise under argon to a solution of the amino compound (11 mmol) in anhydrous CH_2Cl_2 (5 mL) cooled to −15°C. After stirring at 25°C until no more methane evolved, the reaction was cooled to 0°C and a solution of the starting diester (3.7 mmol) in anhydrous CH_2Cl_2 (3 mL) was added. After 48 h at 40°C (bath), the mixture cooled to −15°C was carefully acidified by conc. HCl (pH $\cong$ 1), extracted with EtOAc (3 × 40 mL), and the combined organic layers were washed with satured aq. $NaHCO_3$ (to pH 8), and water (2 × 20 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography on silica gel (1:4 EtOAc-cyclohexane) to afford the corresponding diamide as a colorless oil. All of the following compounds were prepared according to this procedure.

N,N′-bis-(2-benzylthio-2-methylpropyl)-2-(benzylthiomethyl)-2-methylmalonyl diamide (**10**): from **7** (450 mg, 1.45 mmol) and amine **9** (850 mg, 4.4 mmol); yield 706 mg (80%); ^1H NMR (250 MHz, $CDCl_3$): δ 7.31–7.19 (m, 17H, Ar+NH), 3.72 (s, 2H, SCH_2Ph), 3.69 (s, 4H, 2 × SCH_2Ph), 3.25

(d, 4H, $J = 5.7$ Hz, 2 × CH_2N), 2.97 (s, 2H, CH_2S), 1.48 (s, 3H, CH_3), 1.26 (s, 12H, 4 × CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 171.58 (CO), 137.87 (Ar-C) 137.80 (Ar-C), 128.77 (CH-Ar), 128.63 (CH-Ar), 128.37 (CH-Ar), 126.83 (CH-Ar), 54.18 ($C(CO)_2$), 47.61 (NCH_2), 46.35 (Me_2CS), 39.72 (CH_2S), 37.70 (CH_2SCH_2Ph), 32.72 (Me_2CSCH_2Ph), 26.48 (4 × CH_3), 19.76 (CH_3); MS (CI/NH_3): 609 (MH^+); High Resolution MS (CI/CH_4): m/z calc. for $C_{34}H_{45}N_2O_2S_3$ (MH^+): 609.2643, found: 609.2641.

N,N′-bis-(2-benzylthio-2-methylpropyl)-2-(2-benzylthioethyl)-2-methylmalonyl diamide (**13**): from **12** (1.192 g, 3.7 mmol) and amine **9** (2.112 g, 11 mmol); yield 1.872 g (82%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.35–7.20 (m, 15H, Ar), 7.02 (t, 2H, $J = 6.8$ Hz, D_2O exchangeable, NH), 3.67 (s, 4H, 2 × SCH_2Ph), 3.66 (s, 2H, SCH_2Ph), 3.20 (d, 4H, CH_2N), 2.33–2.27 (m, 2H, CH_2CH_2S), 2.12–2.06 (m, 2H, CH_2CR_2S), 1.32 (s, 3H, CH_3), 1.22 (s, 12H, 4 × CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 172.32 (CO), 138.17 (Ar-C), 128.90 (CH-Ar), 128.80 (CH-Ar), 128.62 (CH-Ar), 128.44 (CH-Ar), 127.07 (CH-Ar), 126.94 (CH-Ar), 53.23 ($C(CO)_2$), 47.71 (NCH_2), 46.58 (Me_2CS), 39.07 (CH_2S), 36.09 (CH_2CH_2S), 32.72 (SCH_2Ph), 26.69 (4 × CH_3), 18.90 (CH_3); MS (CI/NH_3): 623 (MH^+); IR ($CHCl_3$): ν 1670 cm^{-1} (CO); High Resolution MS (CI/CH_4): m/z calc. for $C_{35}H_{47}N_2O_2S_3$ (MH^+): 623.2800. Found: 623.2802.

N,N′-bis-(2-benzylthioethyl-2-(benzylthiomethyl)-2-methylmalonyl diamide (**15**): from **7** (500 mg, 1.61 mmol) and amine **14** (685 mg, 4.10 mmol); yield 670 mg (75%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.29–7.17 (m, 15H, Ar), 7.03 (t, 2H, $J = 4.9$ Hz, D_2O exchangeable, NH), 3.70 (s, 2H, SCH_2Ph), 3.68 (s, 4H, 2 × $CH_2CH_2SCH_2Ph$), 3.35 (m, 4H, 2 × CH_2N), 2.93 (s, 2H, CH_2S), 2.52 (t, 4H, $J = 6.5$ Hz, 2 × CH_2CH_2S), 1.45 (s, 3H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$: δ 171.89 (CO), 137.99 (Ar-C), 128.95 (CH-Ar), 128.84 (CH-Ar), 127.16 (CH-Ar), 54.20 ($C(CO)_2$), 39.70 (CH_2S), 38.40 (2 × SCH_2Ph), 37.88 (SCH_2Ph), 35.77 (NCH_2), 30.81 (2 × CH_2S), 20.24 (CH_3); MS (CI/NH_3): 553 (MH^+); High Resolution MS (CI/CH_4): m/z calc. for $C_{30}H_{37}N_2O_2S_3$ (MH^+): 553.2017; found: 553.2018.

General Procedure for Debenzylation

Sodium (~1.6 g, 70 mmol) was added in small portions to a solution of benzylated diamide (10.2 mmol) in anhydrous THF (50 mL) and liquid ammonia (100 mL) until the deep blue color remained for 15 min. After addition of solid ammonium chloride (6 g, 112 mmol) and evaporation of ammonia under Ar, the mixture, cooled to 0°C, was acidified by aq. 2M HCl (pH ≅ 1), extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with saturated aq. NaCl, dried ($MgSO_4$), and evaporated.

The crude product was purified by chromatography on silica gel (1:1 EtOAc-cyclohexane) to afford the corresponding tris-thiol as a colorless solid. All of the following compounds were prepared according to this procedure.

N,N′-bis-(2-mercapto-2-methylpropyl)-2-(mercaptomethyl)-2-methylmalonyl diamide (**1**): from **10** (6.2 g, 10.2 mmol); yield 2.95 g (85%); m.p. (cyclohexane): 84°C; ^1H NMR (250 MHz, Me_2SO-d_6): δ 7.83 (t, 2H, $J = 5.5$ Hz, D_2O exchangeable, NH), 3.25 (m, 4H, CH_2N), 3.01 (d, 2H, $J = 8.4$ Hz, $C\mathit{H}_2SH$), 2.72 (s, 2H, D_2O exchangeable, $Me_2CS\mathit{H}$), 2.15 (t, 1H. D_2O exchangeable, $CH_2S\mathit{H}$), 1.42 (s, 3H, CH_3), 1.24 (s, 12H, $4 \times CH_3$); ^{13}C NMR (63 MHz, $CDCl_3$: δ 171.61 (CO), 55.48 ($\mathit{C}(CO)_2$), 52.44 (NCH_2), 45.16 ($Me_2\mathit{C}SH$), 33.05 (CH_2S), 29.96 ($4 \times CH_3$); 19.46 (CH_3), MS (CI/NH_3): 339 (MH^+); IR ($CHCl_3$): ν 1675 cm^{-1} (CO), 3440, 3330 cm^{-1} ($CO\mathit{NH}$); High Resolution MS (CI/CH_4): m/z calc. for $C_{13}H_{27}N_2O_2S_3$ (MH^+): 339.1235; found: 339.1234.

N,N′-bis-(2-mercapto-2-methylpropyl)-2-(2-mercaptoethyl)-2-methylmalonyl diamide (**2**): from **13** (1.793 g, 2.9 mmol); yield 975 mg (96%); m.p. (cyclohexane): 93°C; ^1H NMR (250 MHz, $CDCl_3$): δ 7.16 (t, 2H, $J = 6.1$ Hz, D_2O exchangeable, NH), 3.32 (d, 4H, $2 \times C\mathit{H}_2NH$), 2.53–2.44 (m, 2H, $CH_2C\mathit{H}_2S$), 2.24–2.17 (m, 2H, $C\mathit{H}_2CH_2S$), 1.63 (s, 2H, D_2O exchangeable, $2 \times Me_2CS\mathit{H}$), 1.49 (s, 3H, CH_3), 1.42 (t, 1H, $J = 7.9$ Hz, D_2O exchangeable, $CH_2\mathit{S}H$), 1.32 (s, 12H, $4 \times CH_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ 172.26 (CO), 53.51 ($\mathit{C}(CO)_2$), 52.30 (CH_2N), 45.08 ($Me_2\mathit{C}S$), 43.86 (CH_2S), 29.92 ($4 \times CH_3$), 20.12 ($\mathit{C}H_2CH_2S$), 19.06 (CH_3); MS (CI/NH_3): 353 (MH^+); High Resolution MS (CI/CH_4): m/z calc. For $C_{14}H_{29}N_2O_2S_3$ (MH^+): 353.1391. Found: 353.1379.

N,N′-bis-(2-mercaptoethyl)-2-(mercaptomethyl)-2-(methylmalonyl diamide (**3**): from **15** (639 mg, 1.16 mmol); yield 266 mg (82%); m.p. (cyclohexane): 88°C; ^1H NMR (250 MHz, $CDCl_3$): δ 7.17 (s br, 2H, D_2O exchangeable, NH), 3.44–3.36 (m, 4H, $2 \times CH_2N$), 2.95 (d, 2H, $J = 9.0$ Hz, CH_2S), 2.67–2.59 (m, 4H, $2 \times CH_2C\mathit{H}_2S$), 1.61 (t, 1H, D_2O exchangeable, SH), 1.48 (s, 3H, CH_3), 1.37 (t, 2H, $J = 8.4$ Hz, D_2O exchangeable, $2 \times$ SH); ^{13}C NMR (63 MHz, $CDCl_3$): δ 171.63 (CO), 55.15 ($\mathit{C}(CO)_2$), 42.57 (CH_2N), 33.01 (CH_2S), 24.25 ($2 \times CH_2S$), 19.16 (CH_3); MS (CI/NH_3). 283 (MH^+); High Resolution MS (CI/CH_4) m/z calc. For $C_9H_{19}N_2O_2S_3$ (MH^+): 283.0609. Found: 283.0604.

N-(2-benzylthio-2-methylpropyl)-1-benzylthio-2-methylpropionamide (**11**): Carbonyldiimidazole (CDI, 163 mg, 1 mmol) was added at room temperature under argon to a solution of the diacid **8** (116 mg, 0.457 mmol) in anhydrous THE (2 mL). After vigorous stirring at room temperature for 30 min, a solution of the amine **9** (95 mg, 1 mmol) in anhydrous THF (2 mL) was added to the mixture. After 3 days at room temperature, aq. HCl 1M was added to reach pH ≅ 1 and the product extracted with EtOAc (3 × 30 mL). The organic layer was washed with water (20 mL), saturated aq. $NaHCO_3$ (pH ≅ 10), saturated aq. NaCl (20 mL), dried ($MgSO_4$), and evaporated to afford **11** as a pure (NMR), colorless oil (114 mg, 65%). ^{1}H NMR (250 MHz, $CDCl_3$): δ7.33–7.20 (m, 10H, Ar), 5.80 (s br, 1H, NH), 3.69 (s, 4H, 2 × $SC\mathit{H}_2Ph$), 3.25–3.20 (m, 2H, CH_2N), 2.71 (dd, 1H, $J_{AB} = 13.1$ Hz $J = 8.1$ Hz, $BnSC\mathit{H}_AH_B$), 2.42 (dd, 1H, $J = 5.9$ Hz, $SCH_A\mathit{H}_B$), 2.19 (m, 1H, $C(O)C\mathit{H}CH_3$), 1.23 (s, 6H, 2 × CH_3), 1.11 (d, 3H, $J = 7$ Hz, $CHC\mathit{H}_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ 174.55 (CO), 138.24 (Ar-C), 138.04 (Ar-C), 128.66 (Ar-CH), 128.43 (Ar-CH), 128.35 (Ar-CH), 126.88 (Ar-CH), 47.11 (Me_2CS), 46.59 (CH_2N), 41.50 (*C*HCO), 36.83 (S*C*H_2Ph), 35.18 (S*C*H_2Ph), 32.63 (CH_2S), 26.53 (2 × CH_3), 17.50 (*C*H_3CH); MS (CI/NH_3): 388 (MH^+); High Resolution MS (CI/CH_4): *m*/*z* calc. for $C_{22}H_{30}NOS_2$ (MH^+): 388.1769. Found: 388.1764.

N-(2-benzylthio-2-methylpropyl)-1-benzylthio-3-methylbutyramide (**16**): A solution of trimethylaluminum in heptane (2M, 7.5 mL, 15 mmol) was added dropwise under argon to a solution of the amine **9** (2.11 g, 10.8 mmol) in anhydrous toluene (7 mL) cooled to −15°C. After stirring at 25°C until no more methane evolved, the reaction, cooled to 0°C, was added a solution of the diester **12** (1 g, 3.09 mmol) in anhydrous toluene (4 ml). After 48 h at reflux, the mixture, cooled to −15°C, was carefully acidified by aq. 2M HCl (pH ≅ 1), extracted with EtOAc (3 × 40 mL), and the combined organic layers were washed with saturated aq. $NaHCO_3$ (to pH 8), and water (2 × 20 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography on silica gel (3:7 EtOAc-cyclohexane) to give the monoamide **16** as a pale-yellow oil (590 mg, 48%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.36–7.20 (m, 10H, Ar), 5.76 (t, 1H, $J = 5.8$ Hz, NH), 3.68 (s, 2H, SCH_2Ph), 3.67 (s, 2H, SCH_2Ph), 3.20 (d, 2H, NCH_2), 2.45–2.26 (m, 4H, $C\mathit{H}_2C\mathit{H}_2S$), 1.93 (m, 1H, $C(O)C\mathit{H}CH_3$), 1.25 (s, 6H, 2 × CH_3), 1.07 (d, 3H, $J = 6.9$ Hz, $CHC\mathit{H}_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ 175.59 (CO), 138.21 (Ar-C), 128.82 (Ar-CH), 128.67 (Ar-CH), 128.67 (Ar-CH), 128.49 (Ar-CH), 127.61 (Ar-CH), 127.13 (Ar-CH), 126.96 (Ar-CH), 47.14 (CH_2N), 46.81 (Me_2CS), 40.20 (CHCO), 36.12 (CH_2S), 33.18 (S*C*H_2Ph), 32.87 (S*C*H_2Ph), 29.27 (*C*H_2CH_2S), 26.76 (CH_3), 26.69 (CH_3), 17.86 (*C*H_3CH); MS (CI/NH_3): 402 (MH^+); High Resolution MS (CI/CH_4): *m*/*z* calc. for $C_{23}R_{32}NOS_2$ (MH^+): 402.1925. Found: 402.1929.

N,N′ bis-(2-mercapto-2-methylpropyl)-2,2-dimethylmalonyl diamide (**4**): To a suspension of 1-amino-2-methyl-2-propanethiol hydrochloride (**18**) (184 mg, 1.3 mmol) in anhydrous CH_2Cl_2 (5 mL) were added successively triethylamine (346 µL, 2.49 mmol) and dimethylmalonyl dichloride (**17**) (100 mg, 0.592 mmol) at 0°C under argon. After vigorous stirring at room temperature for 16 h, aq. HCl 1M was added to the mixture to reach pH ≅ 1 and the product extracted with CH_2Cl_2 (2 × 20 ml). The organic layer was washed with saturated aq. $NaHCO_3$ (10 ml), water (10 ml), dried ($MgSO_4$), and evaporated to afford **4** as a pure (NMR), colorless solid (165 mg, 91%). m.p. (cyclohexane) 92°C; ^1H NMR (250 MHz, Me_2SO-d_6): δ 7.60 (t, 2H, $J = 6.3$ Hz, D_2O exchangeable, NH), 3.22 (d, 4H, CH_2N), 2.71 (s, 2H, D_2O exchangeable, SH), 1.35 (s, 6H, 2 × CH_3), 1.22 (s, 12H, 4 × CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 173.41 (CO), 52.09 (CH_2) 49.35 ($C(CO)_2$), 45.09 (Me_2CSH), 29.72 (4 × CH_3), 23.90 (2 × CH_3); MS (CI/NH_3): 307 (MH^+); IR ($CHCl_3$): ν 3320, 3450 cm^{-1} (CO*NH*), 1670 cm^{-1} (CO); Anal. calc. for $C_{13}H_{26}N_2O_2S_2$ (306.49): C 50.95, H 8.55, N 9.14. Found: C 50.97, H 8.59, N 9.25.

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