An Exceptionally Mild Catalytic Thioester Aldol Reaction Inspired By Polyketide Biosynthesis

Gojko Lalic, Allen D. Aloise, and Matthew D. Shair*

*Department of Chemistry and Chemical Biology
Harvard University
Cambridge, Massachusetts 02138*

Supporting Information

Experimental Section

General procedures: Unless otherwise noted, reactions were performed in oven dry glassware, under an atmosphere of argon. Flash column chromatography was performed using a HPFC Biotage system (Biotage Inc.) with pre-packed FLASH silica gel columns.

Materials: Unless otherwise noted solvents used were purified by passage through two packed columns of neutral alumina on a solvent dispensing system. Commercially available compounds were used without purification. TLC analyses were performed on 250 μ m Silica Gel 60F₂₅₄ plates purchased from EM Science.

Instruments: IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. ¹H and ¹³C NMR spectra were recorded on a Varian INOVA500 or Mercury400 spectrometer. Chemical shifts for proton and carbon resonances are reported in ppm (δ) relative to chloroform (δ 7.26, 77.07 respectively). HPLC analyses were performed on a HP 1100 series instrument using the indicated column.

General procedure for the preparation of malonic acid half thioesters (2) and (3):¹ To a solution of ethyl polyphosphate (PPE) (15 g) in CHCl₃ (60 mL) and THF (10 mL) was added malonic or methylmalonic acid (100 mmol, 4 equiv). To the resulting white suspension was added the benzyl mercaptan (25 mmol, 1 equiv) via syringe. The reaction was stirred at 25°C for 40 hr, diluted with Et₂O (200 mL), and extracted with saturated aq. NaHCO₃ (3X). The aqueous extracts were acidified with 10% HCl to a pH=1-2 and then extracted with CHCl₃ (2X). The organic layers were concentrated to a yellow oil and then purified via silica gel chromatography (1:1 EtOAc/hexane) to afford a yellow oil which solidified to a white solid upon standing.

General procedure for the catalytic acetate aldol reaction (Table 1): Aldol reactions were performed in capped glass vials that were not treated or dried prior to the experiments. No measures were taken to protect the reactions from the air. To a stirred solution of malonic acid half benzylthioester (0.5 mmol, 1.0 equiv) in THF (5 mL, solvent stored in a vial without protection from the air before use) at 23°C was added 5-methoxybenzimidazole (0.11 mmol, 0.22 equiv) and Cu(2-ethylhexanoate)₂ (0.1 mmol, 0.2 equiv). After the reaction became homogenous (~1 min) aldehyde

(0.5 mmol, 1.0 equiv) was added. The solution was stirred at 23°C for the period of time indicated in Table 1 and quenched with a 0.5 M HCl solution. The resulting solution was diluted with EtOAc and washed successively with 0.5 M HCl, saturated aq. NaHCO₃, and brine. The organic layer was dried over oven dried Na₂SO₄, filtered through cotton, and concentrated under reduced pressure. The product was purified using continuous gradient flash column chromatography.

Table 1, Entry 1

3-Hydroxy-5-phenyl-pentanethioic acid S-benzyl ester: Obtained as a colorless oil in 82% yield. FTIR (neat, cm⁻¹) 3437 (b), 3027, 2926, 1683, 1494, 1451, 1071; ¹H NMR (500 MHz, CDCl₃) δ 7.29-7.15 (m, 10H), 4.11 (s, 2H), 4.10-4.04 (m, 1H), 2.90-2.60 (m, 5H), 1.85-1.68 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 198.7, 141.5, 137.2, 128.8, 128.7, 128.5, 127.4, 126.0, 67.9, 50.4, 38.1, 33.3, 31.7; MS (APCI⁺) calcd for C₁₈H₂₁O₂S (M+H)⁺: 301.1, found 301.0.

Table 1, Entry 2

3-Hydroxy-4-methyl-pentanethioic acid S-benzyl ester: Obtained as a colorless oil in 85% yield. FTIR (neat, cm⁻¹) 3457 (b), 3063, 3030, 2961, 2874, 1679, 1051, 997; ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.25 (m, 5H), 4.18-4.12 (m, 2H), 3.88-3.84 (m, 1H), 2.75 (dd, *J*₁ = 15.5 Hz, *J*₂ = 3 Hz, 1H), 2.68 (dd, *J*₁ = 15.5 Hz, *J*₂ = 9 Hz, 1H), 1.75-1.69 (m, 1H), 0.95-0.92 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 199.1, 137.2, 128.8, 128.7, 127.3, 73.2, 47.6, 33.3, 33.2, 18.3, 17.5; MS (APCI⁺) calcd for C₁₃H₁₉O₂S (M+H)⁺: 239.1, found 239.1.

Table 1, Entry 3

3-Benzylsulfanylcarbonyl-2-hydroxy-propionic acid ethyl ester: Obtained as a colorless oil in 97% yield. FTIR (neat, cm⁻¹) 3478 (b), 3030, 2982, 2930, 1733, 1684, 1496, 1454, 1203, 1098, 1044; ¹H NMR (500 MHz, CDCl₃) δ 7.25-7.20 (m, 5H), 4.49 (dd, *J*₁ = 6.5 Hz, *J*₂ = 4 Hz, 1H), 4.23-4.18 (m, 2H), 4.12-4.11 (m, 2H), 3.06 (dd, *J*₁ = 16 Hz, *J*₂ = 4.5 Hz, 1H), 2.97 (dd, *J*₁ = 16 Hz, *J*₂ = 6.5 Hz, 1H), 1.23 (t, *J*₁ = 7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 195.6, 173.2, 137.0, 128.8, 128.6, 127.3, 67.3, 62.1, 47.1, 33.3, 14.0

Table 1, Entry 4

3-Cyclohexyl-3-hydroxy-thiopropionic acid S-benzyl ester: Obtained as a colorless oil in 81% yield. FTIR (neat, cm⁻¹) 3462 (b), 2924, 1684, 1451, 1039; ¹H NMR (500 MHz, CDCl₃) δ 7.29-7.20 (m, 5H), 4.15-4.08 (m, 2H), 3.83-3.80 (m, 1H), 2.74 (dd, *J*₁ = 16 Hz, *J*₂ = 3 Hz, 1H), 2.67 (dd, *J*₁ = 16 Hz, *J*₂ = 9 Hz, 1H), 2.56 (bs, 1H), 1.81-1.69 (m, 3H), 1.64-1.61 (m, 2H), 1.34-1.30 (m, 1H), 1.22-0.95 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 199.2, 137.2, 128.8, 128.6, 127.3, 72.7, 47.8, 43.1, 33.2, 28.8, 28.0, 26.3, 26.1, 26.0; MS (APCI⁺) calcd for C₁₆H₂₃O₂S (M+H)⁺: 279.1, found 279.0.

Table 1, Entry 5

3-Hydroxy-3-(tetrahydro-furan-3-yl)-thiopropionic acid S-benzyl ester: Obtained as a 1:1 mixture of isomers and as a colorless oil in 70% yield. FTIR (neat, cm⁻¹) 3409 (b), 2974, 2927, 2864, 1686, 1115, 1070, 1028; ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.24 (m, 10H), 4.19-4.12 (m, 4H), 4.04-3.71 (m, 10H), 3.54 (dd, *J*₁ = 8 Hz, *J*₂ = 7 Hz, 1H), 2.84 (dd, *J*₁ = 16 Hz, *J*₂ = 2.5 Hz, 1H), 2.73-2.68 (m, 3H), 2.33-2.27 (m, 2H), 2.04-1.84 (m, 2H), 1.58-1.54 (m, 1H), ¹³C NMR (100 MHz, CDCl₃) δ 198.8, 198.6, 137.0, 128.8, 128.7, 127.5, 71.2, 70.5, 70.1, 69.8, 68.3, 68.2, 49.1, 49.0, 44.6, 44.5, 33.4, 28.9, 28.0; MS (APCI⁺) calcd for C₁₄H₁₉O₃S (M+H)⁺: 267.1, found 267.0.

Table 1, Entry 6

3-Hydroxy-hept-6-ynethioic acid S-benzyl ester: Obtained as a colorless oil in 65% yield. FTIR (neat, cm^{-1}) 3293, 3062, 3029, 2923, 2117, 1679, 1496, 1453, 1071, 993; ^1H NMR (500 MHz, CDCl_3) δ 7.32-7.24 (m, 5H), 4.25-4.21 (m, 1H), 4.18-4.12 (m, 2H), 2.83 (bs, 1H), 2.79 (dd, $J_1 = 16$ Hz, $J_2 = 4$ Hz, 1H), 2.74 (dd, $J_1 = 16$ Hz, $J_2 = 8$ Hz, 1H), 2.37-2.33 (m, 2H), 1.98-1.96 (m, 1H), 1.72-1.65 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 198.5, 137.1, 128.8, 128.7, 127.4, 83.6, 69.0, 67.3, 50.2, 34.8, 33.3, 14.7; MS (APCI $^+$) calcd for $\text{C}_{14}\text{H}_{17}\text{O}_2\text{S}$ ($\text{M}+\text{H}$) $^+$: 249.1, found 249.0.

Table 1, Entry 7

3-Hydroxy-3-phenyl-thiopropionic acid S-benzyl ester: Obtained as a colorless oil in 22% yield. FTIR (neat, cm^{-1}) 3454 (b), 1680, 1495, 1453, 1054, 1027, 979; ^1H NMR (500 MHz, CDCl_3) δ 7.36-7.26 (m, 10H), 5.21 (dd, $J_1 = 9$ Hz, $J_2 = 3.5$ Hz, 1H), 4.20-4.15 (m, 2H), 3.03 (dd, $J_1 = 16$ Hz, $J_2 = 9$ Hz, 1H), 2.94 (dd, $J_1 = 16$ Hz, $J_2 = 3.5$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 198.4, 142.5, 137.3, 129.1, 128.9, 128.8, 128.2, 127.6, 125.9, 71.1, 52.5, 33.6; MS (EI $^+$) calcd for $\text{C}_{16}\text{H}_{14}\text{OS}$ ($\text{M}-\text{H}_2\text{O}$) $^+$: 254.0, found 253.8.

Table 1, Entry 8

3-Hydroxy-3-(3-nitro-phenyl)-thiopropionic acid S-benzyl ester: Obtained as a colorless oil in 82% yield. FTIR (neat, cm^{-1}) 3508 (b), 3087, 3030, 2926, 1679, 1526, 1348, 1065; ^1H NMR (500 MHz, CDCl_3) δ 8.27 (s, 1H), 8.16 (dd, $J_1 = 8$ Hz, $J_2 = 2$ Hz, 1H), 7.71 (d, $J = 8$ Hz, 1H), 7.53 (t, $J = 8$ Hz, 1H), 7.30-7.27 (m, 5H), 5.32-5.30 (m, 1H), 4.22-4.16 (m, 2H), 3.43 (d, 3.5 Hz, 1H(OH)), 3.03-3.05 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 197.9, 148.4, 144.2, 136.7, 131.7, 129.6, 128.8, 128.7, 127.5, 122.8, 120.8, 69.8, 51.7, 33.4; MS (EI $^+$) calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_4\text{S}$ (M) $^+$: 317.1, found 316.7.

Table 1, Entry 9

(S2): To a solution of **S1** (105.0 mg, 0.349 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) at 0°C was added Hunig's base (128 μl , 0.734 mmol, 2.1 equiv) followed by methoxymethylchloride (53 μl , 0.699 mmol, 2.0 equiv) and 4-(dimethylamino)pyridine (8.5 mg, 0.069 mmol, 0.2 equiv). The solution was stirred at 23°C for 12 h. The reaction mixture was diluted with EtOAc and washed successively with 0.5 M HCl, saturated aq. NaHCO_3 , and brine. The organic layer was dried over oven dried Na_2SO_4 , filtered through cotton, and concentrated under reduced pressure. The product was purified using continuous gradient flash column chromatography (0-15% EtOAc in hexane) to yield 113.2 mg of the product **S2** as a colorless oil (94% yield). FTIR (neat, cm^{-1}) 2930, 1685, 1495, 1454, 1147, 1098, 1030, 917; ^1H NMR (500 MHz, CDCl_3) δ 7.29-7.16 (m, 10H), 4.64 (d, $J = 7$ Hz, 1H), 4.63 (d, $J = 7$ Hz, 1H), 4.13 (s, 2H), 4.10-4.06 (m, 1H), 3.35 (s, 3H), 2.92 (dd, $J_1 = 15$ Hz, $J_2 = 7$ Hz, 1H), 2.77-2.71 (m, 2H), 2.67-2.61 (m, 1H), 1.91-1.85 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 196.2, 141.5, 137.4, 128.8, 128.5, 128.3, 128.2, 127.2, 125.9, 96.1, 74.4, 55.7, 49.0, 36.5, 33.3, 31.3; MS (ES $^+$) calcd for $\text{C}_{20}\text{H}_{24}\text{O}_3\text{SNa}$ ($\text{M}+\text{Na}$) $^+$: 367.1, found 367.3.

(S3): To a solution of **S2** (103.4 mg, 0.309 mmol, 1.0 equiv) in CH₂Cl₂ (3.0 mL) at -78°C was added diisobutylaluminum hydride (1 M solution in hexane) (386 mL, 0.386 mmol, 1.25 equiv). After 10 min the reaction was quenched with Rochelle's salt and warmed to room temperature. The reaction mixture was diluted with EtOAc and washed successively with Rochelle's salt and brine. The organic layer was dried over oven dried Na₂SO₄, filtered through cotton, and concentrated under reduced pressure. The product was purified through a plug of Florisil, using 20 mL of hexane to separate non polar impurities and 20 mL of EtOAc to elute product, yielding 72.1 mg of the crude product **S3** as a colorless oil. Product **S3** was used in the next step without further purification.

3-Hydroxy-5-methoxymethoxy-7-phenyl-heptanethioic acid S-benzyl ester: The reaction was performed on a 0.31 mmol scale. The product was obtained as a colorless oil in 74% yield based on the theoretical yield for the previous reaction (see procedure for **S3**). Diastereoisomers (1.28:1 ratio) were separated by preparative HPLC (Zorbax CN 9.4 mm column with gradient 5-20% EtOAc in hexane over 20 min).

Major diastereoisomer: FTIR (neat, cm⁻¹) 3459 (b), 2938, 1684, 1454, 1147, 1096, 1071, 1028; ¹H NMR (500 MHz, CDCl₃) δ 7.29-7.18 (m, 10H), 4.69 (s, 2H), 4.40-4.36 (s, 1H), 4.19-4.12 (m, 2H), 3.89-3.86 (m, 1H), 3.42 (s, 3H), 2.79 (dd, *J*₁ = 15.5 Hz, *J*₂ = 8.5 Hz, 1H), 2.73-2.63 (m, 3H), 2.17-2.15 (m, 1H), 1.94-1.81 (m, 2H), 1.72-1.64 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 197.7, 141.8, 137.3, 128.8, 128.6, 128.4, 128.3, 127.3, 125.9, 96.6, 75.4, 65.2, 56.0, 50.8, 41.0, 36.7, 33.3, 31.5; MS (APCI⁺) calcd for C₂₂H₂₉O₄S (M+H)⁺: 389.2, found 388.9

Minor diastereoisomer: FTIR (neat, cm⁻¹) 3469 (b), 2942, 1684, 1496, 1454, 1147, 1028; ¹H NMR (500 MHz, CDCl₃) δ 7.26-7.14 (m, 10H), 4.67 (d, *J* = 7 Hz, 1H), 4.63 (d, *J* = 7 Hz, 1H), 4.26-4.21 (m, 1H), 4.15-4.09 (m, 2H), 3.82-3.79 (m, 1H), 3.37 (s, 3H), 2.78-2.69 (m, 2H), 2.63-2.60 (m, 2H), 2.14-2.12 (m, 1H), 1.87-1.76 (m, 3H), 1.68-1.65 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 197.8, 141.8, 137.2, 128.8, 128.6, 128.4, 128.3, 127.3, 125.9, 95.4, 76.3, 67.4, 55.9, 50.7, 40.7, 36.1, 33.3, 31.1; HRMS (ES⁺) calcd for C₂₂H₂₈O₄SN⁺: 411.1606, found 411.1619.

3-Hydroxy-2-methyl-5-phenyl-pentanethioic acid S-benzyl ester (5): This reaction was performed in a capped glass vial that was not treated or dried prior to the experiment. No measures were taken to protect the reaction from the air. To a solution of methyl malonic acid half benzylthioester (**3**) (25.3 mg, 0.113 mmol, 1 equiv) in THF (1.1 mL) was added dihydrocinnamaldehyde (30 mg, 0.226 mmol, 2 equiv), 5-methoxybenzimidazole (3.3 mg, 0.023 mmol, 0.2 equiv), and Cu(2-ethylhexanoate)₂ (7.9 mg, 0.023 mmol, 0.2 equiv). The green solution was stirred at 23°C for 18.5 hr, diluted with EtOAc, and washed successively with 0.5 M HCl, saturated aq. NaHCO₃, and brine. The organic layer was dried over MgSO₄, filtered, and concentrated to a yellow oil. Silica gel chromatography (0 to 18% EtOAc/hexane continuous gradient) afforded **5** as a yellow oil (18.4 mg, 52%) and a 7.3 : 1 *syn/anti* mixture of diastereomers. R_f = 0.23 (20% EtOAc/hexane); FTIR (neat, cm⁻¹) 3453, 2927, 1677, 1495, 1454; ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.18 (m, 10H), 4.14 (s, 2H, minor isomer), 4.13 (s, 2H, major isomer), 3.95 (dt, *J* = 9.5, 4 Hz, 1H, major isomer) 3.76-3.70 (m, 1H, minor isomer), 2.88-2.82 (m, 1H), 2.74-2.69 (m, 1H), 2.68-2.62 (m, 1H), 2.43 (br s, 1H), 1.85-1.77 (m, 1H), 1.71-1.64 (m, 1H) 1.26 (d, *J* = 7 Hz, 3H, minor isomer) 1.25 (d, *J* = 7 Hz, 3H, major isomer); ¹³C NMR (100 MHz, CDCl₃) δ 203.6, 141.9, 137.4, 129.0, 128.9, 128.7, 127.6, 126.2, 71.6, 53.2, 36.1, 33.4, 32.5, 11.8; HRMS (ES⁺) calcd for C₁₉H₂₃O₂S (M+H)⁺: 315.1419, found 315.1411.

3-Benzylsulfanylcabonyl-2-hydroxy-butyric acid ethyl ester (7): This reaction was performed in a capped glass vial that was not treated or dried prior to the experiment. No measures were taken to

protect the reaction from the air. To a solution of methyl malonic acid half benzylthioester (**3**) (112 mg, 0.5 mmol, 1.5 equiv) in THF (3.3 mL) was added a 50% solution of ethyl glyoxalate in toluene (66 μ L, 0.33 mmol, 1.0 equiv), 5-methoxybenzimidazole (9.9 mg, 0.067 mmol, 0.2 equiv), and Cu(2-ethylhexanoate)₂ (23 mg, 0.067 mmol, 0.2 equiv). The green solution was stirred at 23°C for 1 hr, diluted with EtOAc, and washed successively with 0.5 M HCl, saturated aq. NaHCO₃, and brine. The organic layer was dried over MgSO₄, filtered, and concentrated to a yellow oil. Silica gel chromatography (0 to 30% EtOAc/hexane continuous gradient) afforded **7** as a yellow oil (76.7 mg, 82%) and a 7.5 : 1 *syn/anti* mixture of diastereomers. *R*_f = 0.64 (50% EtOAc/hexane); FTIR (neat, cm⁻¹) 3487, 2926, 1733, 1680, 1454; ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.23 (m, 5H), 4.60 (d, *J* = 3.5 Hz, 1H), 4.25 (q, *J* = 7.5 Hz, 2H), 4.16 (d, *J* = 3.5 Hz, 2H, major isomer), 4.13 (d, *J* = 3 Hz, 2H, minor isomer), 3.18-3.13 (m, 1H, minor isomer), 3.11-3.06 (m, 1H, major isomer), 3.02 (br s, 1H), 1.37 (d, *J* = 7.5, 3H, minor isomer), 1.28 (t, *J* = 7 Hz, 3H), 1.25 (d, *J* = 7 Hz, 3H, major isomer); ¹³C NMR (100 MHz, CDCl₃) δ 200.1, 173.3, 137.4, 129.1, 128.9, 127.6, 72.9 (minor isomer), 71.7 (major isomer), 62.5, 51.3, 33.5 (major isomer), 33.4 (minor isomer), 14.4 (major isomer), 14.0 (minor isomer), 11.6; HRMS (ES⁺) calcd for C₁₄H₁₉O₃S (M+H)⁺: 283.1004, found 283.1017.

Determination of diastereoselectivity: Diastereomeric ratios were determined by ¹H NMR spectroscopy. Spectral assignment of *syn* and *anti* isomers was accomplished by comparison to authentic samples of both the *syn* and *anti* diastereomers of 3-hydroxy-2-methyl-5-phenylpentanethioic acid *S*-phenyl ester independently synthesized according to published procedures.² Assignments were in agreement with established trends in the ¹H and ¹³C NMR resonances of aldol adducts.³

Crossover experiment:

This reaction was performed in a capped glass vial that was not treated or dried prior to the experiment. No measures were taken to protect the reaction from the air. To a solution of **S4** (38.2 mg, 0.127 mmol, 1.0 equiv) in THF (1.3 mL) was added **S5** (31 μ L, 0.254 mmol, 2.0 equiv) followed by Cu(2-ethylhexanoate)₂ (10.1 mg, 0.025 mmol, 0.20 equiv) and 5-methoxybenzimidazole (4.1 mg, 0.028 mmol, 0.22 equiv). The solution was stirred at room temperature for 15 h and quenched with 0.5 M HCl. The resulting solution was diluted with EtOAc and washed successively with 0.5 M HCl, saturated aq. NaHCO₃, and brine. The organic layer was dried over oven dried Na₂SO₄, filtered through cotton, and concentrated under reduced pressure. The crude ¹H NMR revealed no crossover product.

(1) Imamoto, T.; Kodera, M.; Yokoyama, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2303.

(2) *syn*: Hirama, M.; Garvey, D. S.; Lu, L. D.-L.; Masamune, S. *Tetrahedron Lett.* **1979**, *41*, 3937. *anti*: Hirama, M.; Masamune, S. *Tetrahedron Lett.* **1979**, *24*, 2225.

(3) Heathcock, C. H. "The Aldol Addition Reaction" in *Asymmetric Synth.*; Ed. Morrison, James D., 1984, Vol. 3, p. 111.