Enantioselective Organocatalytic Michael Addition of Malonate Esters to Nitro Olefins Using Bifunctional Cinchonine Derivatives

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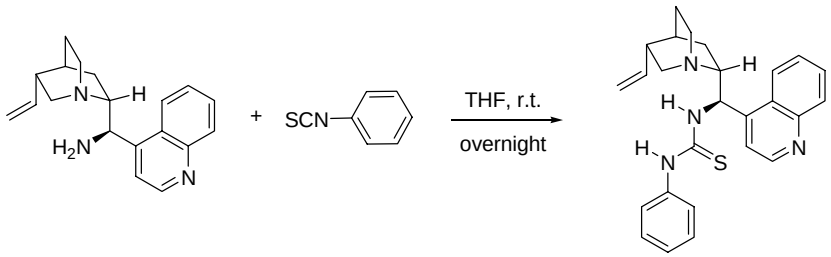
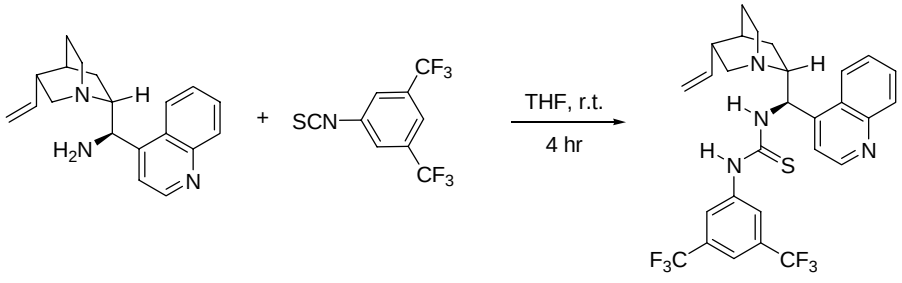
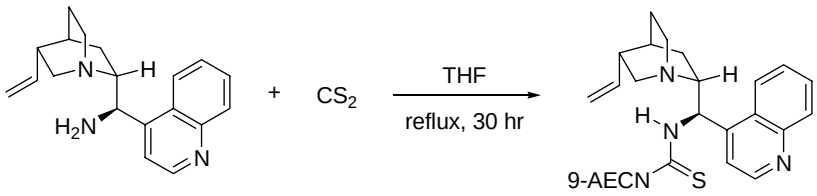
Procedure for preparing catalysts:



Phenyl isothiocyanate (0.81 g, 6.0 mmol) in dry THF (5 mL) was added slowly to the free 9-amino (deoxy) epicinchonine (1.46 g, 5.0 mmol) in dry THF (15 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature, and then concentrated under reduced pressure. The residue was purified by flash chromatography (elution gradient: ethyl acetate: methanol: triethylamine = 100: 2: 3 to 100: 10: 3) to afford the desired pruduct **1d** (1.78 g, 83 %) as white solid. $[\alpha]_D^{27}$ +298.1 (c 1.06, $CHCl_3$); ^{1}H-NMR (300 MHz, CD_3OD) δ_H 8.84 (m, 1 H), 8.67 (d, J = 8.2 Hz, 1 H), 8.09 (dd, J = 1.1, 8.5 Hz, 1 H), 7.83 (ddd, J = 1.4, 6.1, 8.4 Hz, 1 H), 7.72 (ddd, J = 1.4, 6.9, 8.3 Hz, 1 H), 7.61 (m, 1 H), 7.36 (m, 4 H), 7.19 (m, 1 H), 6.27 (d, J = 11.2 Hz, 1 H), 6.00 (ddd, J = 6.3, 10.5, 17.0 Hz, 1 H), 5.26 (dt, J = 1.6, 9.6 Hz, 1 H), 5.22 (dt, J = 1.6, 3.0 Hz, 1H), 3.35 (dp, J = 1.5, 3.2 Hz, 2H), 3.23 (dd, J = 8.3, 12.5 Hz, 2H), 3.03 (m, 3 H), 2.39 (dd, J = 7.2, 15.2 Hz, 1 H), 1.59 (dd, J = 8.7, 12.5 Hz, 3 H), 1.31 (dd, J = 8.4, 13.2 Hz, 1 H), 0.90 (t, J = 10.2 Hz, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ_C 182.7, 151.3, 150.8, 149.3, 142.0, 140.3, 131.3, 130.5, 130.3, 130.1, 129.4, 128.3, 126.8, 126.4, 125.5, 125.4, 121.4, 115.8, 62.3, 56.5, 53.2, 50.4, 40.8, 29.3, 27.7, 26. 5; IR (Nujol): v 3168, 1590, 1377 $cm^{-1;}$ ES-MS m/z 427 (100), ES+MS m/z 429 (100); HRMS (ESI) m/z calcd for ($C_{26}H_{29}N_4S_1$): 429.2107, found: 429.2108.



The free amine (1.00 g, 3.4 mmol) in dry THF (5 mL) was added slowly to 3, 5-bis(trifluomethyl) phenyl isothiocyanate (1.0 g, 3.7 mmol) in dry THF (2 mL) at 0 °C. The reaction mixture was stirred for 4 hours at room temperature, and then concentrated under reduced pressure. The residue was purified by flash chromatography (elution gradient: ethyl acetate: methanol: triethylamine = 100: 2: 3 to 100: 10: 3) to afford the desired pruduct **1e** (1.45 g, 94 %) as white amorphous solid. $[\alpha]_D^{25}$ +168.2 (c 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ_H 8.75 (t, *J* = 4.1 Hz, 1 H), 8.57 (t, *J* = 7.3 Hz, 1 H), 7.98 (t, *J* = 7.0 Hz, 2 H), 7.72 (dd, *J* = 6.0, 13.2 Hz, 1 H), 7.63 (m, 1 H), 7.53 (m, 2 H), 6.23 (d, *J* = 10.3 Hz, 1 H), 5.88 (ddd, *J* = 6.2, 10.5, 17.0 Hz, 1 H), 5.12 (dd, *J* = 9.7, 13.8 Hz, 1 H), 3.17 (m, 3 H), 2.95 (m, 3 H), 2.29 (dd, *J* = 6.8, 14.5 Hz, 1 H), 1.47 (m, 4 H), 1.17 (dt, *J* = 8.4, 9.9 Hz, 1 H), 0.82 (m, 2 H); ^{13}C NMR (125 MHz, CD_3OD) δ_C 183.0, 151.3, 149.4, 143.5, 142.0, 133.2 (q, *J* = 33.4 Hz, 2 C), 131.4, 130.3, 129.4, 128.4, 128.4, 126.4, 126.2, 124.0, 123. 9, 123.8, 118.2 (dd, 1 H, *J* = 4.0, 7.4 Hz, 2 C), 115.8, 62.2, 57.0, 57.0, 40.8, 40.8, 29.2, 27.7, 26.6; IR (Nujol): v 3244, 1634, 752, 681 cm^{-1}; ES-MS m/z 563 (100), ES+MS m/z 565, 587 (100); HRMS (ESI) m/z calcd for ($C_{28}H_{27}N_4F_6S_1$): 565.1855, found: 565.1855.

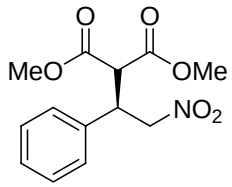


CS_2 (251μL, 4.15 mmol) was added slowly to the free amine (2.43 g, 8.3 mmol) in dry ethanol (5 mL). The reaction solution turned heterogeneous, and 15 mL dry ethanol was added. The mixture was refluxed for 30 hours, and concentrated under reduced pressure. The residue was purified by flash chromatography (elution gradient: ethyl acetate: methanol: triethylamine = 100: 2: 3 to 100: 10: 3) to afford the desired pruduct **1f** (1.34 g, 51 %) as pale yellow solid. $[\alpha]_D^{27}$ +318.4 (c 1.01, $CHCl_3$); ^{1}H-NMR (300 MHz, CD_3OD) δ_H 8.77 (d, *J* = 4.4 Hz, 2 H), 8.54 (d, *J* = 7.8 Hz, 2 H), 8.06 (d, *J* = 8.4 Hz, 2 H), 7.80 (m, 2 H), 7.65 (q, *J* = 7.4 Hz, 2 H), 7.45 (s, 2 H), 6.08 (d, *J* = 11.2 Hz, 2 H), 5.89 (ddd, *J* = 6.3, 10.6, 17.1 Hz, 2 H),

5.17 (dt, J = 1.5, 8.2 Hz, 2 H), 5.13 (d, J = 1.5 Hz, 2 H), 2.96 (m, 12 H), 2.32 (dd, J = 7.6, 15.7 Hz, 2 H), 1.55 (dd, J = 4.0, 14.0 Hz, 6 H), 1.18 (m, 4 H); ^{13}C NMR (125 MHz, CD_3OD) δ_C 184.1, 151.4, 151.4, 150.3, 150.3, 149.2, 149.2, 141.6, 141.6, 131.4, 131.4, 130.3, 130.3, 129.3, 129.3, 128.4, 128.4, 126.3, 126.3, 121.6, 121.6, 115.9, 115.9, 62.3, 62.3, 56.0, 56.0, 53.0, 53.0, 50.4, 50.4, 40.6, 40.6, 29.2, 29.2, 27.5, 27.5, 26.4, 26.4; IR (Nujol): v 3228, 1509 cm^{-1}; ES-MS m/z 627 (100), ES+MS m/z 630 (100); HRMS (ESI) m/z calcd for ($C_{39}H_{45}N_6S_1$): 629.3421, found: 629.3430.

Typical procedure for enantioselective Michael addition of malonate to nitroolefin:

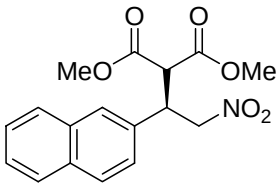
To a stirred solution of trans-β-nitrostyrene (59.6 mg, 0.40 mmol) and dimethyl malonate (3.0 equiv., 0.183 mL) in dry dichloromethane (0.40 mL) was added catalyst **1e** (0.1 equiv., 22.4 mg). After stirring for 30 hours, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (elution gradient: ethyl acetate: petroleum ether = 1:15 to 1:8) to afford desired Michael adduct **4a** (106.9 mg, 95%).



(R)-(-)-Methyl 2-carbomethoxy-4-nitro-3-phenyl-butyrate (R)-(-)-4a

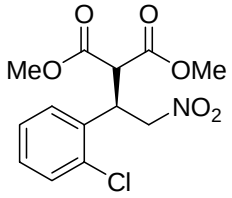
This product was obtained as a colorless solid in 95 % yield (106.9 mg) after flash chromatography (elution gradient: ethyl acetate: petroleum ether= 1:15 to 1:8) and 94 % ee as determined by HPLC analysis [Daicel chiralcel OD, hexane: IPA: methanol, 80: 20: 2, 0.9 mL/min, λ 220 nm, t (minor) = 13.8 min, t (major) = 16.7 min] at -20 °C for 30 hours. $[\alpha]_D^{26}$ -11.1 (c 1.30, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.12-7.00 (m, 5 H), 4.72-4.64 (m, 2 H), 4.03 (dt, J = 5.1, 9.0 Hz, 2 H), 3.65 (d, J = 9.1 Hz, 1 H), 3.56 (s, 3 H), 3.34 (s, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.2, 167.6, 136.5, 129.4, 128.8, 128.3, 77.2, 55.2, 53.4, 53.2, 43.4.

The absolute configuration of **(-)-4a** was determined to be **(R)** by comparing the optical rotation and the HPLC elution order with literature data. $[\alpha]_D^{26}$ -11.1 (c 1.30, $CHCl_3$) for 94% ee. [Lit. [1] (S)-(+), $[\alpha]_D^{25}$ +5.9 (c 1.02, $CHCl_3$), HPLC analysis [Daicel chiralcel OD, hexane: IPA, 70: 30, 0.9 mL/min, λ 220 nm, t (major) = 11.6 min, t (minor) = 13.7 min] for 96% ee; lit. [2] (S)-(+), $[\alpha]_D^{25}$ +4.4 (c 1.02, $CHCl_3$) for 93% ee].



(-)-Methyl 2-carbomethoxy-4-nitro-3-(2-naphthyl)-butyrate-(-)-4b

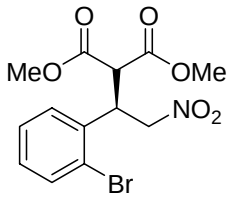
This product was obtained as a yellow solid in 83% yield (110 mg) after flash chromatography (elution gradient: ethyl acetate: petroleum ether = 1: 15 to 1: 8) and 89% ee as determined by HPLC analysis [Daicel chiralcel OJ, hexane: IPA: methanol, 80: 20: 2, 0.9 mL/min, λ 220 nm, t (minor) = 77.9 min, t (major) = 97.4 min] at -20 °C for 48 hours. $[\alpha]_D^{20.5}$ -2.91 (c 1.23, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.84 (m, 3 H), 7.73 (s, 1 H), 7.51 (m, 2 H), 7.37 (dd, *J* = 1.9, 8.5 Hz, 1 H), 5.03 (d, *J* = 7.3 Hz, 2 H), 4.45 (dt, *J* = 7.1, 8.7 Hz, 1 H), 4.01 (d, *J* = 9.0 Hz, 1 H), 3.80 (s, 3 H), 3.57 (s, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ_C 168.3, 167.7, 133.9, 133.7, 133.4, 129.4, 128.4, 128.1, 127.7, 127.0, 126.9, 125.5, 77.7, 55.2, 53.5, 53.3, 43.5.



(-)-Methyl 2-carbomethoxy-4-nitro-3-(2-chlorophenyl)-butyrate-(-)-4c

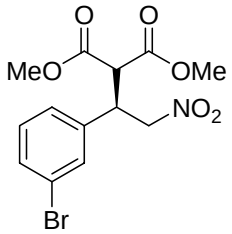
This product was obtained as a yellow oil in 99% yield (125 mg) after flash chromatography (elution gradient: ethyl acetate: petroleum ether = 1: 15 to 1: 8) and 94% ee as determined by HPLC analysis [Daicel chiralcel OD, hexane: IPA: methanol, 80: 20: 2, 1 mL/min, λ 220 nm, t (minor) = 10.1 min, t (major) = 25.2

min] at -20 °C for 30 hours. $[\alpha]_D^{20.5}$ -5.87 (c 1.09, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.44 (m, 1 H), 7.27 (m, 3 H), 5.15 (dd, *J* = 8.6, 13.7 Hz, 1 H), 4.99 (dd, *J* = 4.5, 13.7 Hz, 1 H), 4.79 (dt, *J* = 4.5, 8.5 Hz, 1 H), 4.15 (d, *J* = 8.4 Hz, 1 H), 3.76 (s, 1 H), 3.67 (s, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ_C 168.2, 167.7, 134.5, 134.0, 131.0, 130.0, 129.0, 127.7, 75.8, 53.4, 53.2, 53.2 39.8.



(-)-Methyl 2-carbomethoxy-4-nitro-3-(2-bromophenyl)-butyrate-(-)-4d

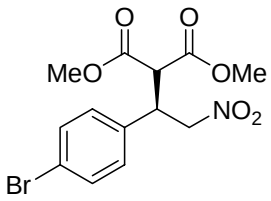
This product was obtained as a colorless oil in 95% yield (137 mg) after flash chromatography (elution gradient: ethyl acetate: petroleum ether = 1: 15 to 1:8) and 92% ee as determined by HPLC analysis [Daicel chiralcel OD, hexane: IPA, 70: 30, 1 mL/min, λ 220 nm, t (minor) = 9.1 min, t (major) = 18.1 min] at -20 °C for 30 hours. $[\alpha]_D^{20.5}$ -5.93 (c 1.08, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.64 (dd, *J* = 1.2, 8.0 Hz, 1 H), 7.31 (dt, *J* = 1.2, 7.7 Hz, 1 H), 7.26 (dd, *J* = 1.7, 7.8 Hz, 1 H), 7.19 (ddd, *J* = 1.8, 7.3, 8.0 Hz, 1 H), 5.16 (dd, *J* = 8.5, 13.7 Hz, 1 H), 4.99 (dd, *J* = 4.5, 13.8 Hz, 1 H), 4.80 (dt, *J* = 4.5, 8.2 Hz, 1 H), 4.14 (d, *J* = 7.9 Hz, 1 H), 3.76 (s, 3 H), 3.69 (s, 3 H); ^{13}C NMR (500 MHz, CDCl3) δ_C 168.2, 167.7, 135.7, 134.3, 130.2, 128.6, 128.4,125.2, 75.9, 53.5, 53.4, 53.4, 41.9.



(-)-Methyl 2-carbomethoxy-4-nitro-3-(3-bromophenyl)-butyrate-(-)-4e

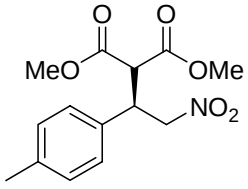
This product was obtained as a yellow solid in 85% yield (122 mg) after flash chromatography (elution gradient: ethyl acetate: petroleum ether = 1: 15 to 1: 8) and 90% ee as determined by HPLC analysis [Daicel chiralcel OJ, hexane: IPA:

methanol, 80: 20: 2, 1 mL/min, λ 220 nm, t (minor) = 35.4 min, t (major) = 45.9 min] at -20 °C for 30 hours. $[\alpha]_D^{20.5}$ -5.03 (c 1.43, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.45 (m, 1H), 7.42 (d, *J* = 1.6 Hz, 1 H), 7.21 (m, 2 H), 4.94 (dd, *J* = 5.0, 13.5 Hz, 1 H), 4.89 (dd, *J* = 9.1, 13.5 Hz, 1 H), 4.24 (dt, *J* = 5.0, 8.9 Hz, 1 H), 3.85 (d, *J* = 8.8, 1 H), 3.79 (s, 3 H), 3.63 (s, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ_C 168.0, 167.4, 138.9, 132.1, 131.5, 131.0, 126.9, 123.4, 77.3, 54.9, 53.6, 53.4, 42.9.



(-)-Methyl 2-carbomethoxy-4-nitro-3-(4-bromophenyl)-butyrate-(-)-4f

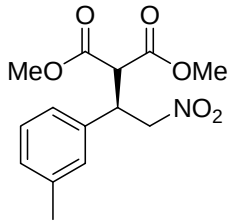
This product was obtained as a colorless solid in 87% yield (125 mg) after flash chromatography (elution gradient: ethyl acetate: petroleum ether = 1: 15 to 1: 8) and 90% ee as determined by HPLC analysis [Daicel chiralcel OD, hexane: IPA, 60: 40, 1 mL/min, λ 220 nm, t (minor) = 10.0 min, t (major) = 13.3 min] at -20 °C for 48 hours. $[\alpha]_D^{20.5}$ -2.87 (c 1.54, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.49 (d, *J* = 8.5 Hz, 2 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 4.93 (dd, *J* = 4.9, 13.3 Hz, 1H), 4.87 (dd, *J* = 9.2, 13.3 Hz, 1 H), 4.24 (dt, *J* = 5.0, 9.1 Hz, 1 H), 3.85 (d, *J* = 9.0 Hz, 1 H), 3.79 (s, 3 H), 3.62 (s, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ_C 168.0, 167.4, 135.6, 132.7, 130.0, 123.0, 77.5, 54.9, 53.6, 53.4, 42.8.



(+)-Methyl 2-carbomethoxy-4-nitro-3-(4-methylphenyl)-butyrate-(+)-4g

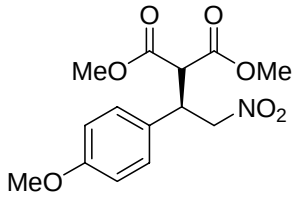
This product was obtained as a white solid in 82% yield (97 mg) after flash chromatography (elution gradient: ethyl acetate: petroleum ether = 1: 15 to 1: 8) and 92% ee as determined by HPLC analysis [Daicel chiralcel OD, hexane: IPA: methanol, 98: 2: 0.5, 1 mL/min, λ 220 nm, t (minor) = 33.2 min, t (major) = 40.2

min] at -20 °C for 48 hours. $[\alpha]_D^{20.5}$ +2.28 (c 1.23, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.15 (m, 4 H), 4.93 (dd, *J* = 5.1, 13.1 Hz, 1 H), 4.88 (dd, *J* = 9.0, 13.1 Hz, 1 H), 4.23 (ddd, *J* = 5.19, 5.12, 5.15 Hz, 1 H), 3.87 (d, *J* = 9.0 Hz, 1 H), 3.79 (s, 3 H), 3.60 (s, 3 H), 2.33 (s, 3 H); ^{13}C NMR (500 MHz, $CHCl_3$) δ_C 168.2, 167.8, 134.5, 134.0, 131.0, 130.0, 129.0, 127.7, 75.9, 53.4, 53.3, 39.8.



(-)-Methyl 2-carbomethoxy-4-nitro-3-(3-methylphenyl)-butyrate-(-)-4h

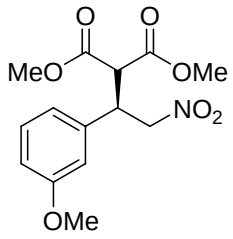
This product was obtained as a yellow oil in 92% yield (109 mg) after flash chromatography (elution gradient: ethyl acetate: petroleum ether = 1: 15 to 1: 8) and 91% ee as determined by HPLC analysis [Daicel chiralcel OD, hexane: IPA: methanol, 98: 2: 0.5, 1 mL /min, λ 220 nm, t (minor) = 27.8 min, t (major) = 32.5 min] at -20 °C for 52 hours. $[\alpha]_D^{20.5}$ -1.31 (c 1.23, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.23 (t, *J* = 7.55, 1 H), 7.11 (d, *J* = 7.33, 1 H), 7.05 (s, 1 H), 7.04 (d, *J* = 7.88, 1 H), 4.94 (dd, *J* = 5.4, 13.4 Hz, 1 H), 4.90 (dd, *J* = 8.8, 13.3 Hz, 1 H) 4.26-4.21 (ddd, *J* = 5.3, 5.3, 5.3, 1 H), 3.79 (s, 3 H), 3.60 (s, 3 H), 2.35 (s, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ_C 168.3, 167.7, 139.1, 136.5, 129.6, 129.3, 129.0, 125.1, 77.8, 55.2, 53.4, 55.3, 43.3, 21.8.



(-)-Methyl 2-carbomethoxy-4-nitro-3-(4-methoxy phenyl)-butyrate-(-)-4i.

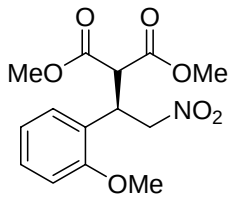
This product was obtained as a colorless oil in 96 % yield (119.0 mg) after flash chromatography (elution gradient: ethyl acetate: petroleum ether = 1: 15 to 1: 8) and 92 % ee as determined by HPLC analysis [Daicel chiralcel OD, hexane: IPA, 60: 40, 1 mL/min, λ 220 nm, t (minor) = 9.6 min, t (major) = 11.7 min] at -20 °C

for 30 hours. $[\alpha]_D^{20.5}$ -9.7 (c 1.49, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.08-7.06 (m, 2 H), 6.77-6.76 (m, 2 H), 4.82 (dd, *J* = 5.0, 13.0 Hz, 1 H), 4.75 (dd, *J* = 9.2, 13.0 Hz, 1 H), 4.12 (dt, *J* = 5.0, 9.2 Hz, 1 H), 3.76 (d, *J* = 9.2 Hz, 1 H), 3.70 (s, 3 H), 3.69 (s, 3 H), 3.50 (s, 3 H), ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.3, 167.7, 159.8, 129.4, 129.4, 128.3, 114.8, 114.8, 78.1, 55.6, 55.3, 53.4, 53.2, 42.7.



(-)-Methyl 2-carbomethoxy-4-nitro-3-(3-methoxy phenyl)-butyrate-(-)-4j

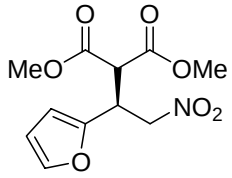
This product was obtained as a colorless solid in 97 % yield (120.7 mg) after flash chromatography (elution gradient: ethyl acetate: petroleum ether = 1: 15 to 1: 8) and 91 % ee as determined by HPLC analysis [Daicel chiralcel OD, hexane: IPA: methanol, 98: 2: 0.5, 0.9 mL/min, λ 220 nm, t (major) = 59.8 min, t (minor) = 72.5 min] at -20 °C for 30 hours. $[\alpha]_D^{20.5}$ -10.5 (c 1.37, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.16 (t, *J* =7.9 Hz 1 H), 6.74 (m, 2H), 6.69 (m, 1 H), 4.84 (dd, *J* = 5.2, 13.3 Hz, 1 H), 4.80 (dd, *J* = 8.8, 13.3 Hz, 1 H), 4.14 (dt, *J* = 5.2, 8.8 Hz, 1 H), 3.79 (d, *J* = 8.9 Hz, 1 H), 3.70 (s, 3 H), 3.68 (s, 3 H), 3.52 (s, 3 H), ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.3, 167.6, 160.3, 138.1, 130.5, 120.2, 114.3, 114.0, 77.7, 55.6, 55.1, 53.4, 53.3, 43.3.



(-)-Methyl 2-carbomethoxy-4-nitro-3-(2-methoxy phenyl)-butyrate-(-)-4k

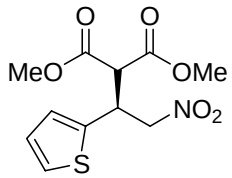
This product was obtained as a colorless solid in 96 % (118.9 mg) yield after flash chromatography (elution gradient: ethyl acetate: petroleum ether = 1: 15 to 1: 8) and 97 % ee as determined by HPLC analysis [Daicel chiralcel OD, hexane:

IPA, 60:40, 1 mL /min, λ 220 nm, t (minor) = 6.2 min, t (major) = 8.0 min] at -20 °C for 30 hours. $[\alpha]_D^{20.5}$ -27.6 (c 1.42, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.19 (m,1 H), 7.07 (dd, *J* =1.6, 7.7 Hz, 1 H), 6.81 (m, 2 H), 4.96 (dd, *J* = 9.0, 13.1 Hz, 1 H), 4.82 (dd, *J* = 4.6, 13.1 Hz, 1 H), 4.33 (dd, *J* = 4.6, 13.1 Hz, 1 H), 4.11 (d, *J* = 9.9 Hz, 1 H), 3.80 (s, 3 H), 3.68 (s, 3 H), 3.44 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.8, 168.0, 157.7, 130.9, 130.1, 124.0, 121.3, 111.5, 76.4, 55.8, 53.3, 53.0, 52.9, 40.7.



(+)-Methyl 2-carbomethoxy-4-nitro-3-(2-furyl)-butyrate (+)-4l

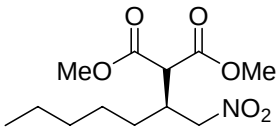
This product was obtained as a yellow oil in 93 % yield (100.7 mg) after flash chromatography (elution gradient: ethyl acetate: petroleum ether = 1: 15 to 1: 8) and 95 % ee as determined by HPLC analysis [Daicel chiralcel OD, hexane:IPA, 60: 40, 1 mL/min, λ 220 nm, t (minor) = 6.5 min, t (major) = 15.0 min] at -20 °C for 30 hours. $[\alpha]_D^{20.5}$ +7.1 (c 1.46, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.28 (m, 1 H), 6.22 (dd, *J* =1.9, 3.2 Hz, 1 H), 6.15 (d, *J* = 3.3 Hz, 1 H), 4.87-4.79 (m, 2 H), 4.32 (dt, *J* = 5.0, 8.1 Hz, 1 H), 3.88 (d, *J* = 7.8 Hz, 1 H), 3.69 (s, 3 H), 3.62 (s 3 H); ^{13}C NMR (125 MHz, CDCl3) δ_C 167.9, 167.6, 149.8, 143.3, 111.0, 108.8, 75.7, 53.5, 53.4, 53.1, 37.2.



(+)-Methyl 2-carbomethoxy-4-nitro-3-(2-thienyl)-butyrate (+)-4m

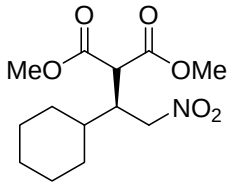
This product was obtained as a yellow oil in 87 % yield (98.9 mg) after flash chromatography (elution gradient: ethyl acetate: petroleum ether = 1:15 to 1: 8) and 94 % ee as determined by HPLC analysis [Daicel chiralcel OD, hexane: IPA, 60: 40, 1 mL /min, λ 220 nm, t (major) = 8.4 min, t (minor) = 14.1 min] at -20 °C

for 30 hours. $[\alpha]_D^{20.5}$ +10.1 (c 1.19, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.16 (dd, J = 1.2, 5.0 Hz, 1 H), 6.88 (dd, J =1.0, 3.3 Hz, 1 H), 6.86 (dd, J = 3.6, 5.0 Hz, 1 H), 4.88 (dd, J = 4.7, 12.8 Hz, 1 H), 4.84 (dd, J = 7.6, 12.8 Hz, 1 H), 4.50 (dt, J = 5.4, 8.0 Hz, 1 H), 3.85 (d, J = 7.8 Hz, 1 H), 3.70 (s 3 H), 3.61 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.0, 167.5, 138.8, 127.5, 127.2, 126.1, 78.2, 55.7, 53.5, 53.5, 38.8.



(-)-Methyl 2-carbomethoxy-3-nitromethyloctanoate (-)-4n

This product was obtained as an colorless oil in 81 % yield (89.2 mg) after flash chromatography (elution gradient: ethyl acetate: petroleum ether = 1:20) and 86 % ee as determined by HPLC analysis [Daicel chiralcel OD-H, hexane: IPA, 95:5, 1 mL /min, λ 215 nm, t (minor) = 7.3 min, t (major) = 12.5 min] at -20 °C for 72 hours. $[\alpha]_D^{25}$ -4.8 (c 1.16, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 4.56 (dd, J = 5.1, 13.4 Hz, 1 H), 4.38 (dd, J =6.8, 13.4 Hz, 1 H), 3.62 (s, 3 H), 3.62 (s, 3 H), 3.53 (d, J = 5.8 Hz, 1 H), 2.78-272 (m, 1 H), 1.32-1.28 (m, 2 H), 1.24-1.12 (m, 6 H), 0.73 (s, J = 6.9 Hz,1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.8, 168.6, 77.0, 53.3, 53.2, 52.7, 37.4, 31.8, 30.3, 26.7, 22.8, 14.3.



(-)-Methyl 2-carbomethoxy-4-nitro-3-cyclohexylbutyrate (-)-4o

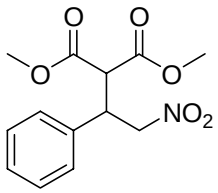
This product was obtained as a colorless oil in 82 % yield (94.0 mg) after flash chromatography (elution gradient: ethyl acetate: toluene = 1:20) and 82 % ee as determined by HPLC analysis [Daicel chiralcel OD-H, hexane: IPA, 90: 10, 0.5 mL /min, λ 220 nm, t (minor) = 11.9 min, t (major) = 21.5 min] at r.t. for 31 hours. $[\alpha]_D^{25}$ -7.9 (c 1.42, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 4.53 (dd, J = 6.5, 14.6

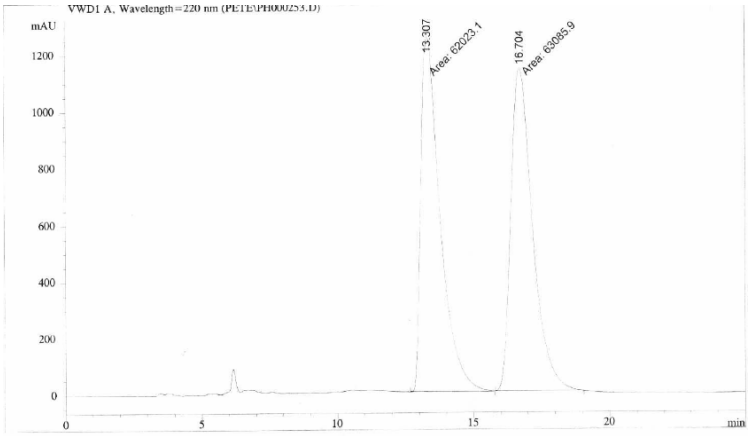
Hz 1H,) 3.67 (m, 7 H) 2.80 (ddd, J = 4.8, 6.5, 11.2 Hz, 1 H) 1.62 (m, 5 H) 1.36 (m, 1 H) 1.08 (m, 3 H) 0.91 (m, 2 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ_C 169.4, 169.0, 75.8, 53.4, 53.2, 51.4, 42.6, 40.0, 30.6, 30.2, 26.7, 26.6, 26.4.

References

1 H. M. Li, Y. Wang, L. Tang and L. Deng, *J. Am. Chem. Soc*. 2004, **126**, 9906

2 J. G. Ji, D. M. Barnes, J. Zhang, S. A. King, S. J. Wittenberger and H. E. Morton, *J. Am. Chem. Soc*. 1999, **121**, 10215





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Dilution : 1.0000

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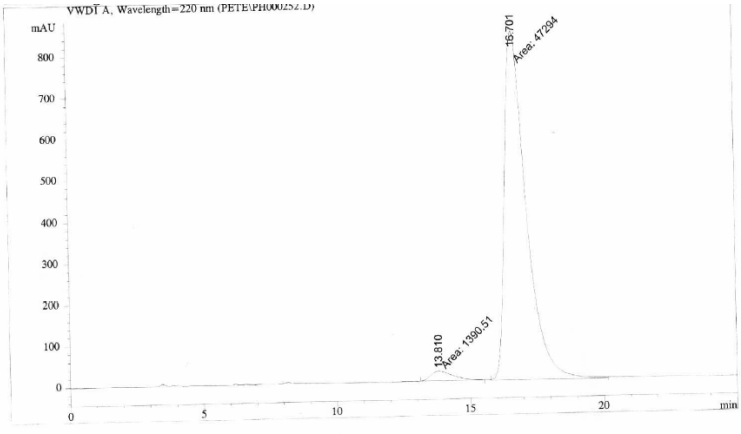

Area Percent Report

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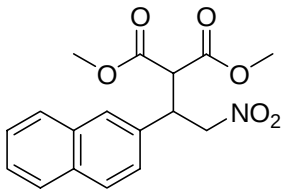

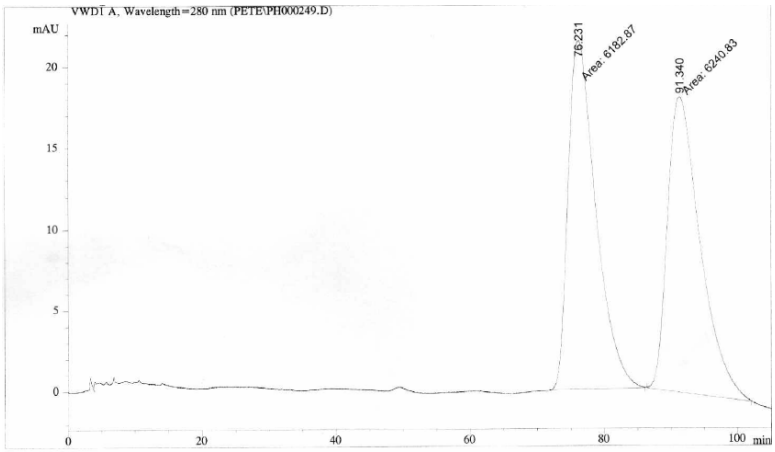


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Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=280 nm

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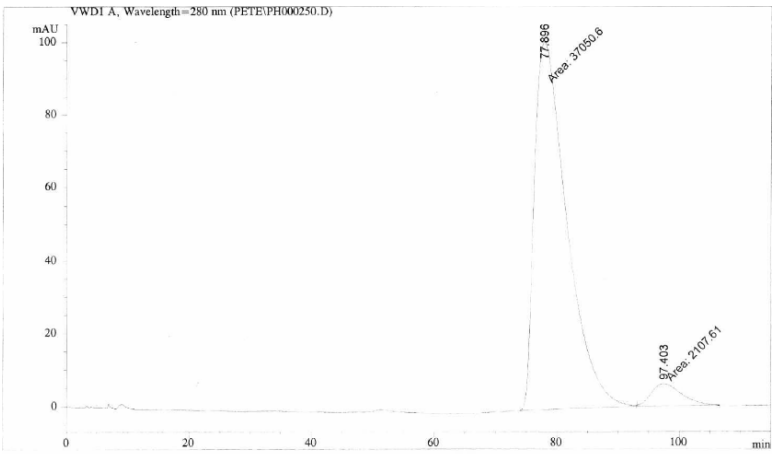


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Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=280 nm

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
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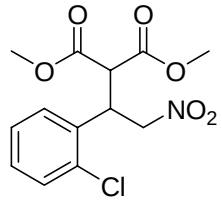

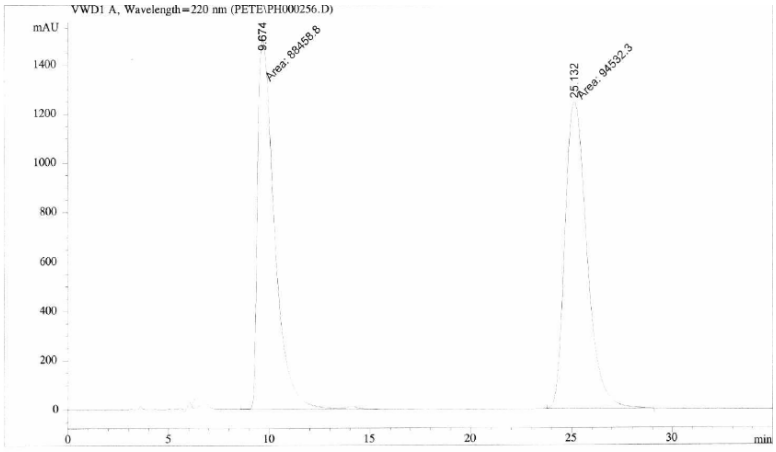


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Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
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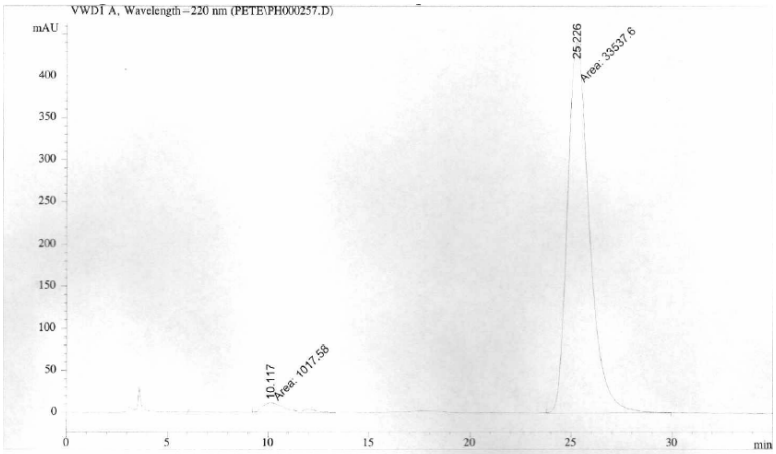


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Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
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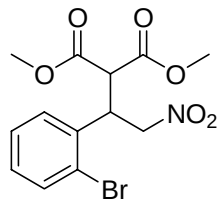

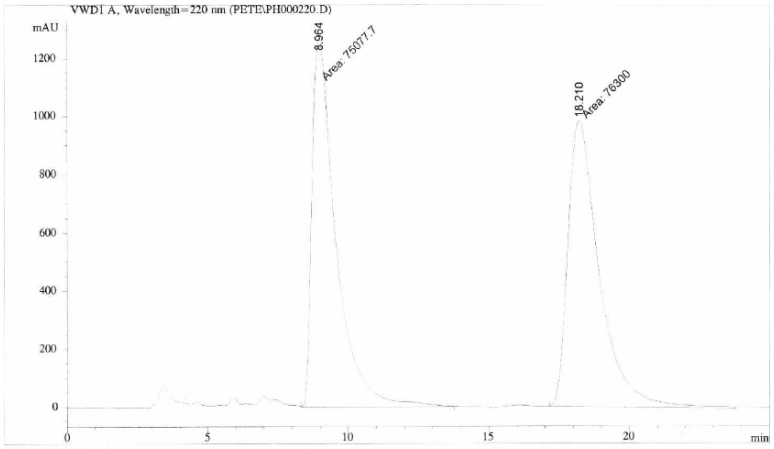

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Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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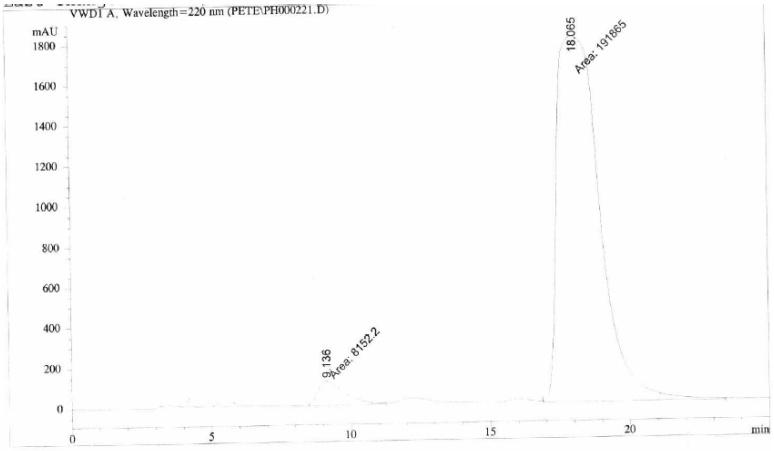

Area Percent Report

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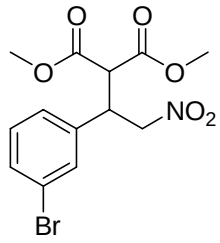
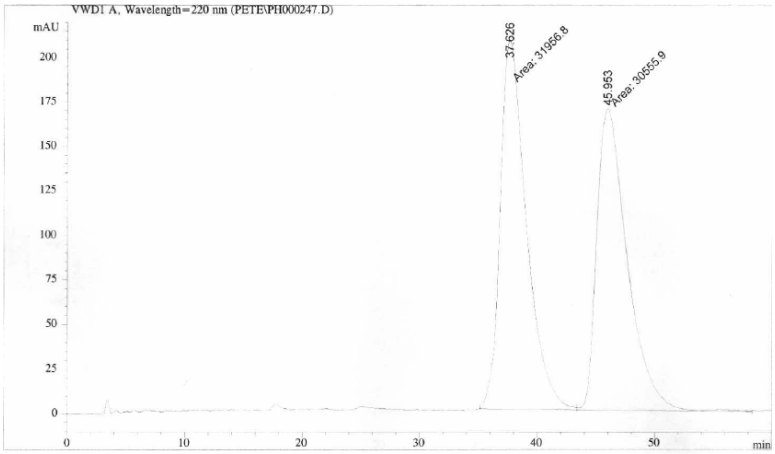
Dilution : 1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.136	MM	1.1231	8152.19922	120.98145	4.0757
2	18.065	MM	1.7657	1.91865e5	1811.05432	95.9243





Area Percent Report

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Dilution : 1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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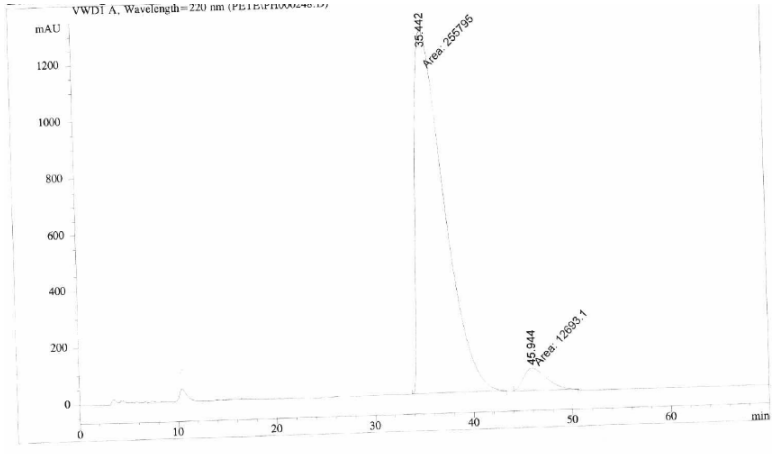

Area Percent Report

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Dilution : 1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.442	MM	3.3222	2.55795e5	1283.24915	95.2724
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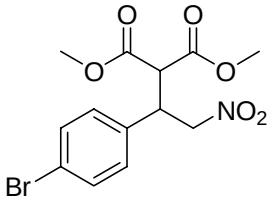

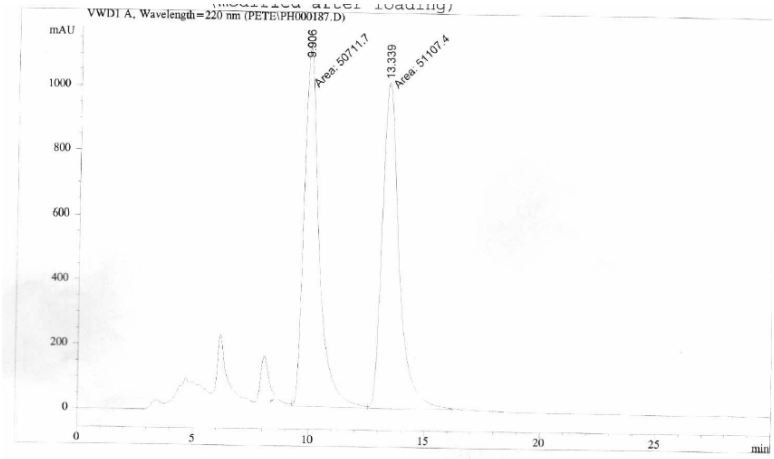


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Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
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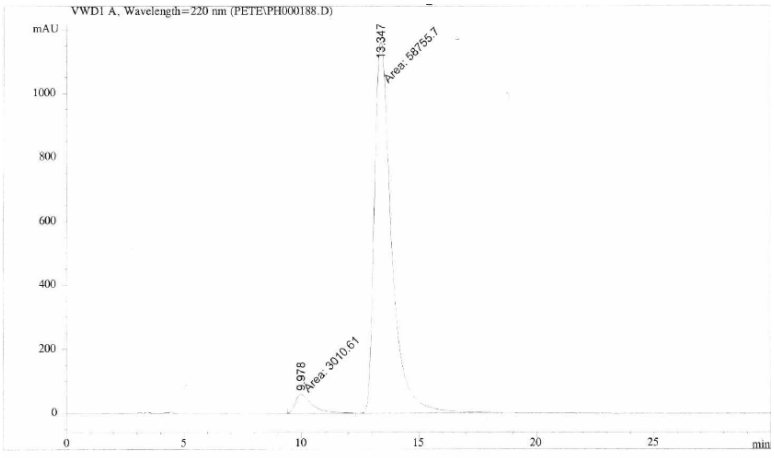


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]      %
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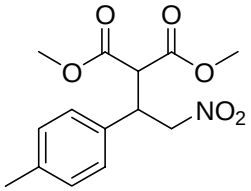

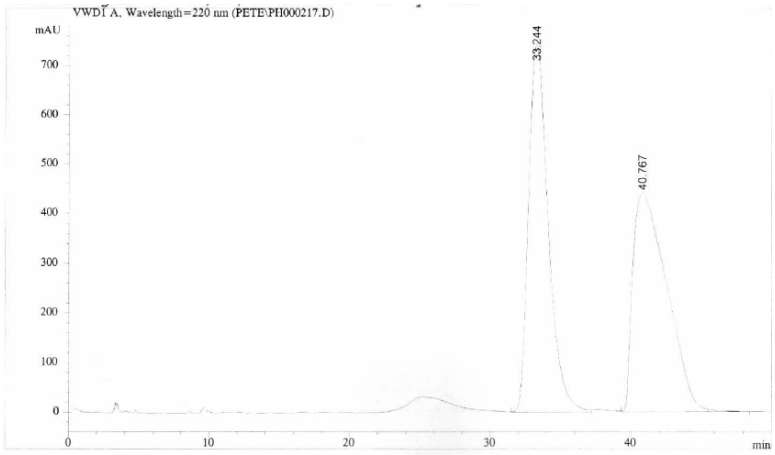


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Sorted By             :      Signal
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Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
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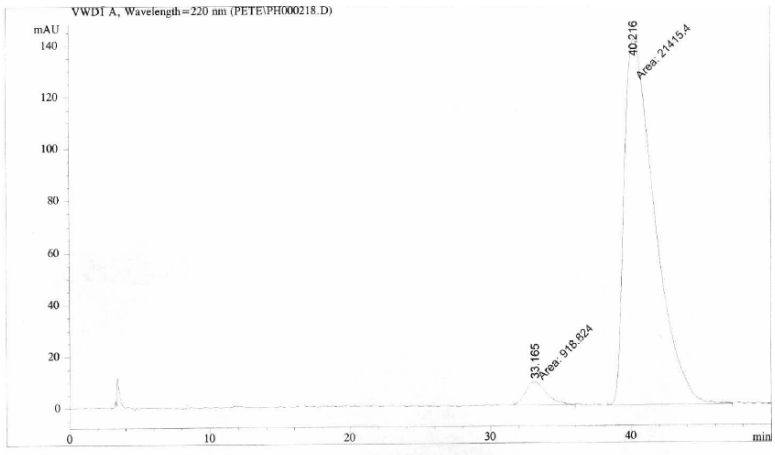


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                      Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
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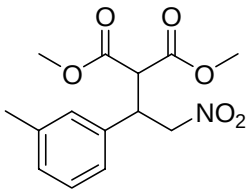
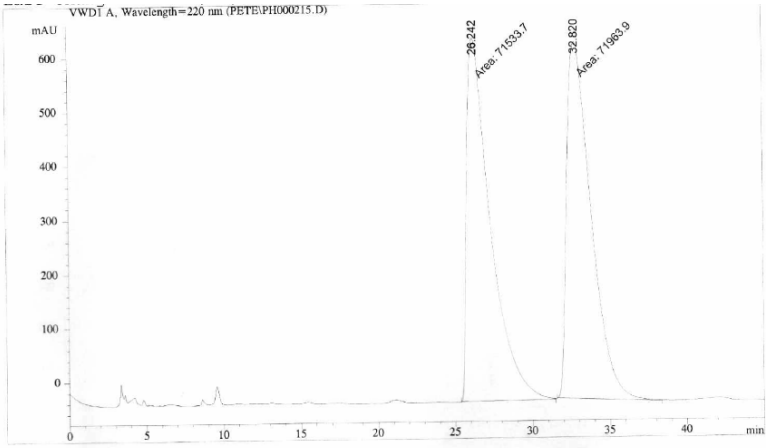
   2  40.216 MM    2.5302 2.14154e4   141.06815  95.8860
```



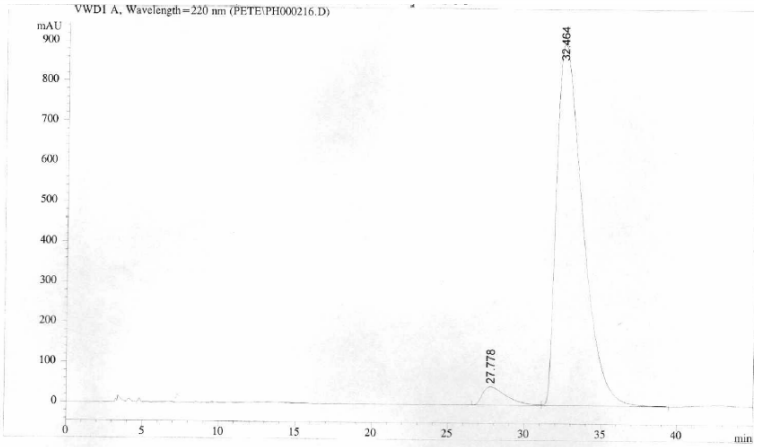



```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  26.242 MM    1.7735 7.15337e4   672.23975  49.8501
   2  32.820 MM    1.8149 7.19639e4   660.85565  50.1499
```

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================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  27.778 VV    1.6436 5022.93604   45.65321   4.4719
   2  32.464 VV    1.8207 1.07299e5   901.45801  95.5281
```
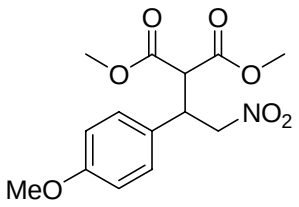
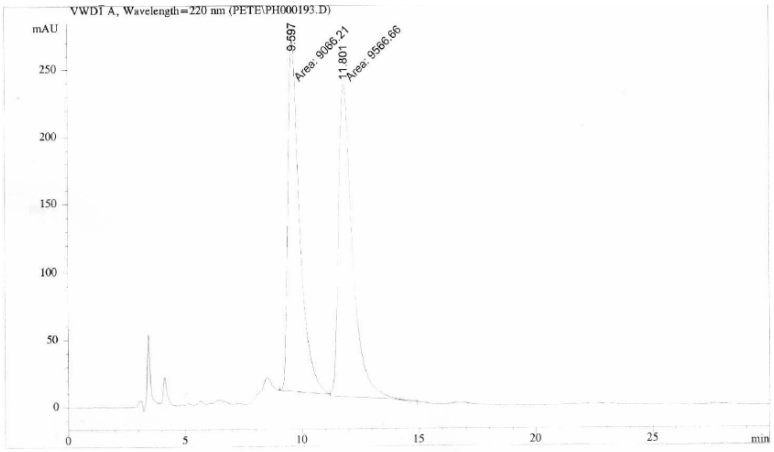



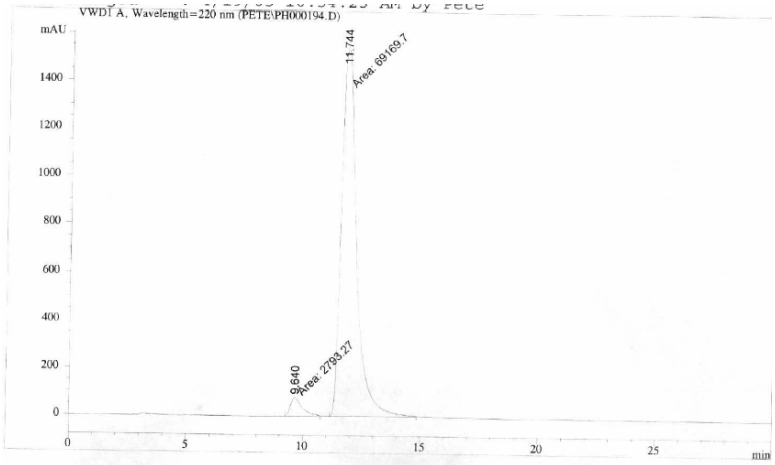


Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.597	MM	0.5809	9066.21387	260.13983	48.6571
2	11.801	MM	0.6877	9566.65820	231.83745	51.3429

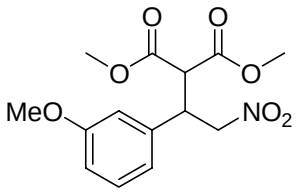


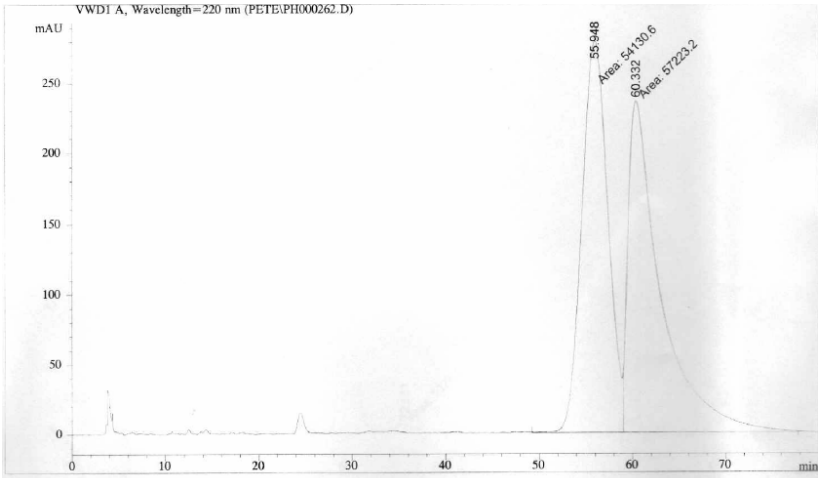
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

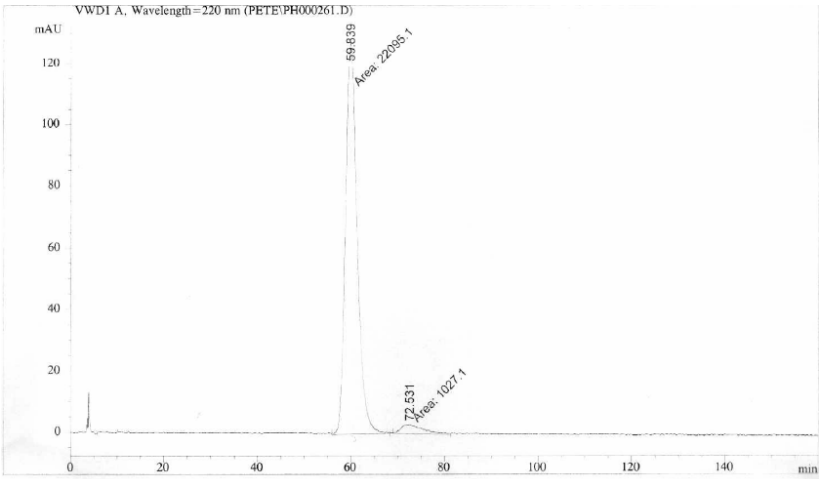
Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.640	MM	0.5949	2793.27124	78.26107	3.8815
2	11.744	MM	0.7452	6.91697e4	1546.99915	96.1185

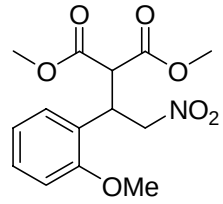


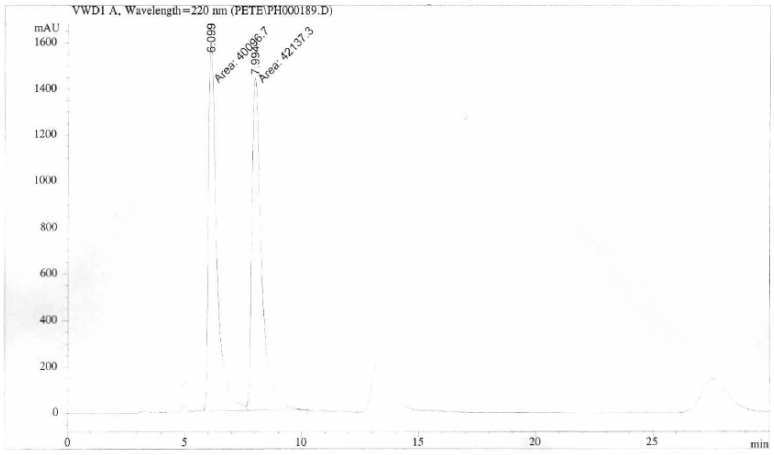



```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  55.948 MF    3.2341 5.41306e4   278.95352  48.6114
   2  60.332 FM    4.0429 5.72232e4   235.90164  51.3886
```

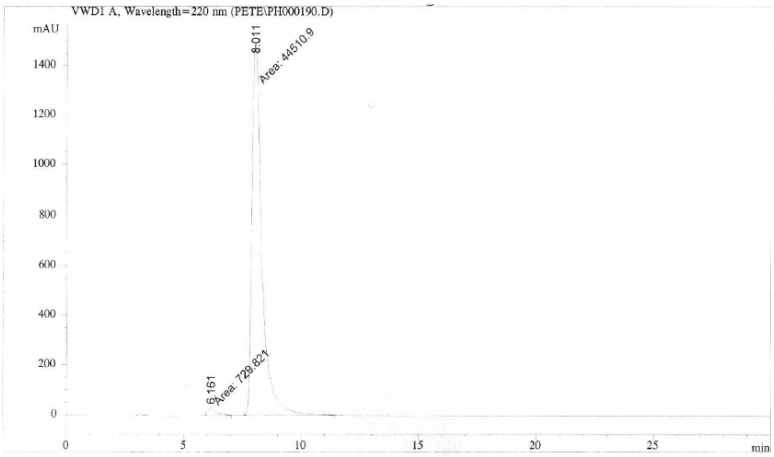



```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  59.839 MM    2.8891 2.20951e4   127.46130  95.5580
   2  72.531 MM    5.6524 1027.09546    3.02850   4.4420
```

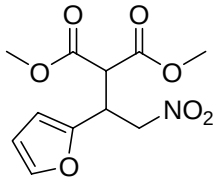


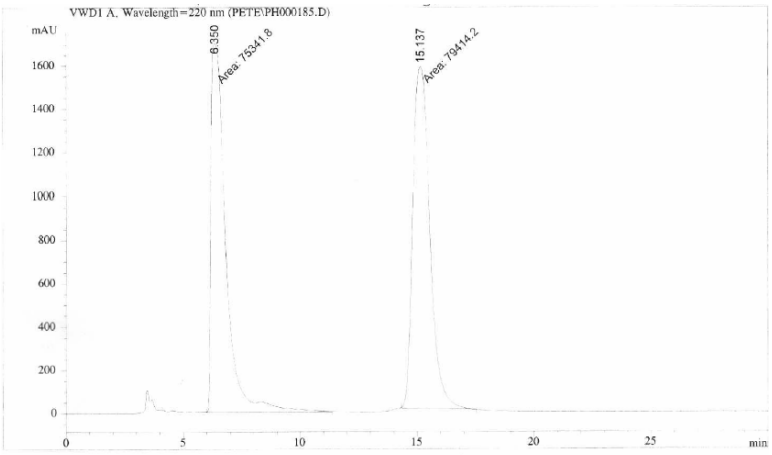



```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1   6.099 MF    0.4189 4.00967e4  1595.31189  48.7593
   2   7.994 FM    0.4893 4.21373e4  1435.16614  51.2407
```

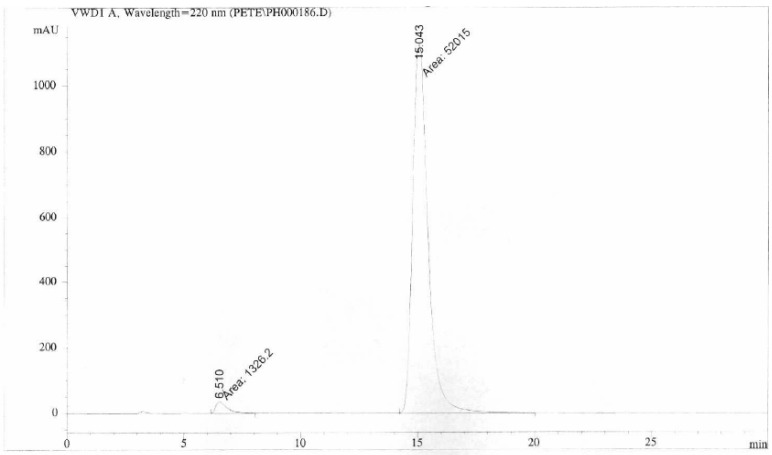



```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1   6.161 MM    0.3755  729.82062   32.39339   1.6132
   2   8.011 MM    0.4960 4.45109e4  1495.80017  98.3868
```

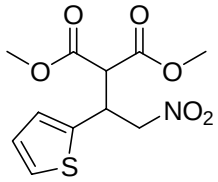


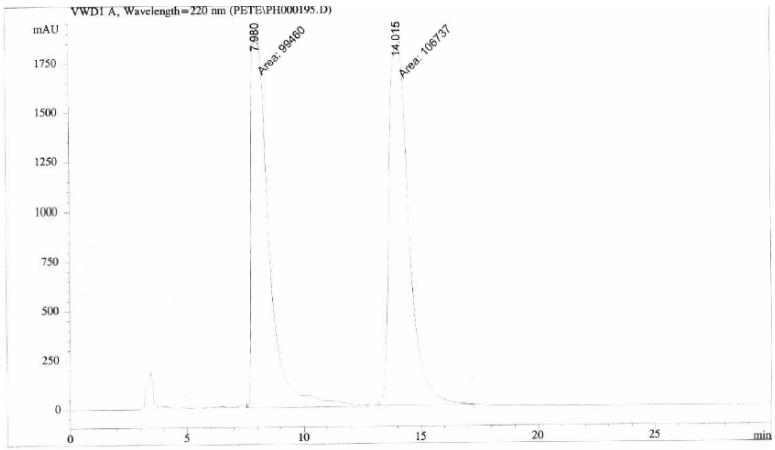



```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1   6.350 MM    0.7381 7.53418e4  1701.17725  48.6843
   2  15.137 MM    0.8410 7.94142e4  1573.71814  51.3157
```

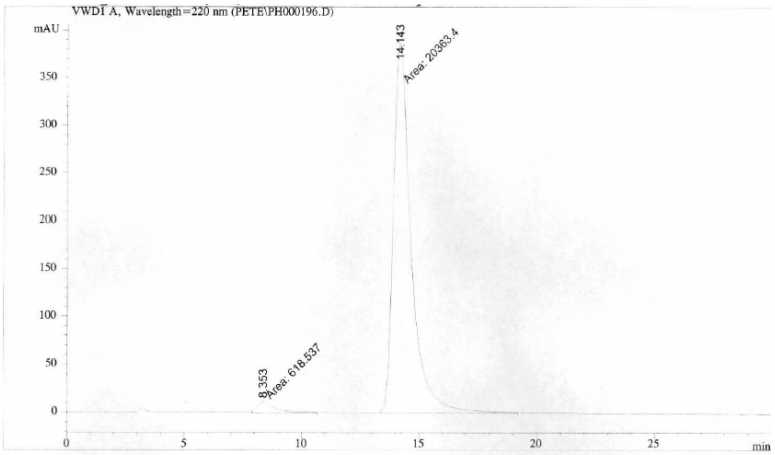



```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1   6.510 MM    0.6153 1326.20117   35.92173   2.4863
   2  15.043 MM    0.7648 5.20150e4  1133.51819  97.5137
```

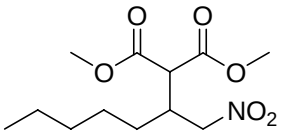


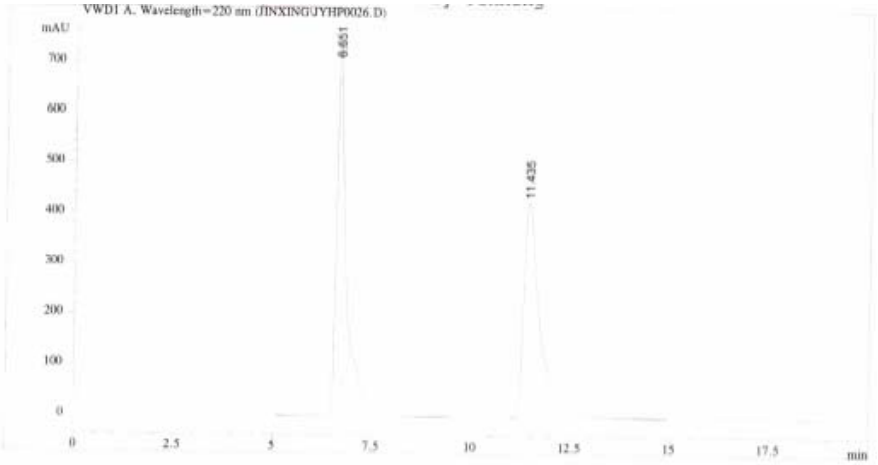



```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.980 MM    0.8948 9.94600e4  1852.50488  48.2355
   2  14.015 MM    0.9841 1.06737e5  1807.72339  51.7645
```




```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.353 MM    0.8843  618.53711   11.65816   2.9480
   2  14.143 MM    0.8754 2.03634e4   387.71878  97.0520
```



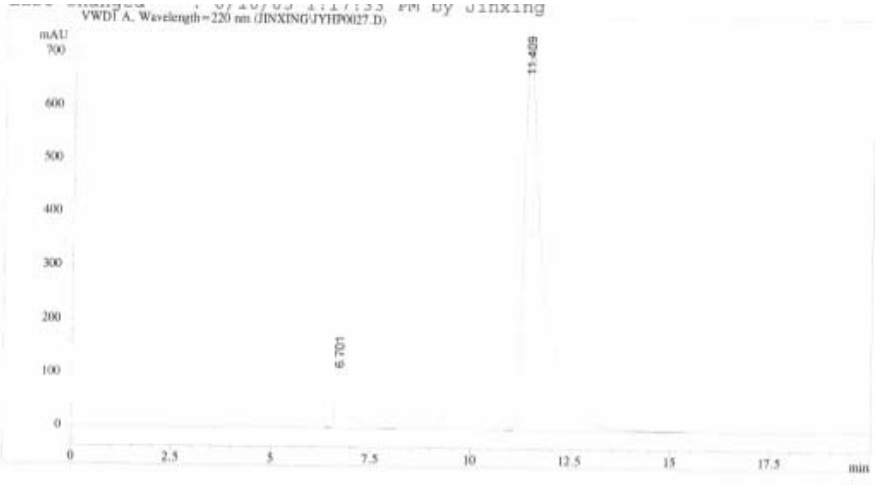


Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.651	VB	0.2601	1.31221e4	721.90820	49.6882
2	11.435	VB	0.4431	1.32868e4	426.91190	50.3118

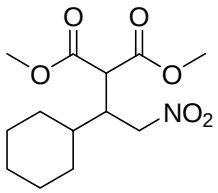


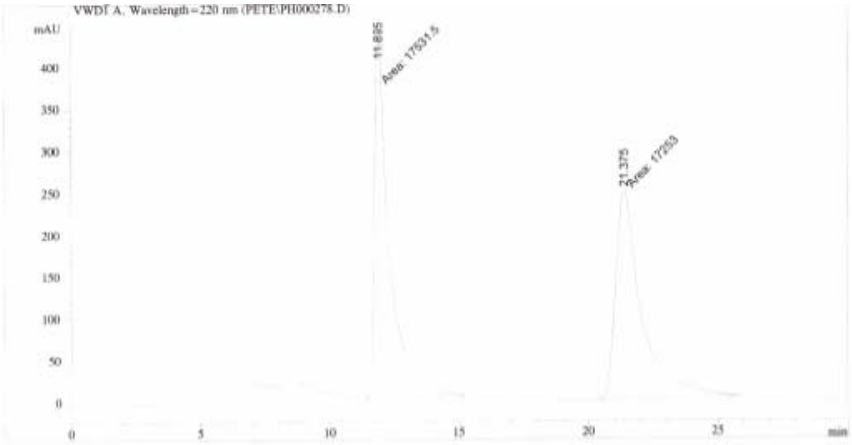
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.701	VB	0.2545	1896.43774	107.16307	7.1166
2	11.409	VB	0.5051	2.47515e4	705.94135	92.8834



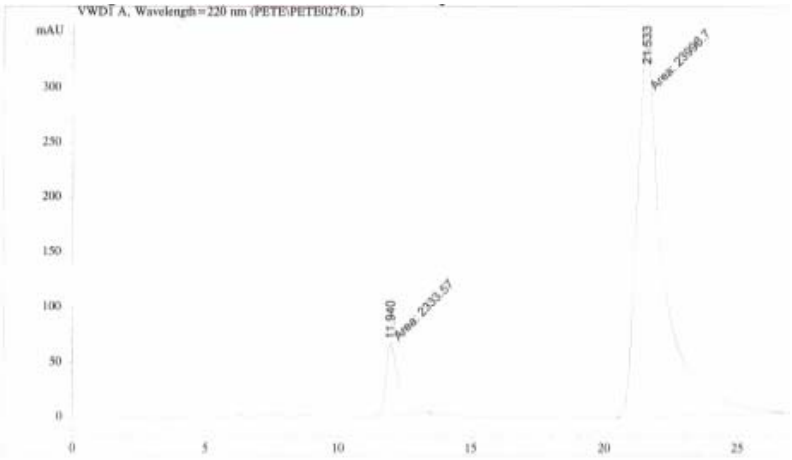


Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.895	MM	0.6046	1.75315e4	426.82263	50.4004
2	21.375	MM	1.1540	1.72530e4	249.17342	49.5996



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.940	MM	0.5850	2333.56738	66.48462	8.0627
2	21.533	MM	1.1774	2.39967e4	339.67120	91.1373