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Vinylogous hydrazone strategy for the organocatalytic alkylation of heteroaromatic aldehydes derivatives

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Contents

1. General methods

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. Thin layer chromatography was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation. Silica gel (Silica gel 60, 230-400 mesh, Fluka) was used for column chromatography. NMR spectra were acquired on a Bruker Ultra Shield 700 instrument, running at 700 MHz for ^{1}H and 176 MHz for ^{13}C, respectively. Chemical shifts (δ) were reported as part per million (ppm) in δ scale relative to residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.00 ppm for ^{13}C NMR). Coupling constants (*J*) were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were obtained on Bruker Maxis Impact spectrometer using electrospray (ES+) ionization. Optical rotations were measured on a Perkin-Elmer 241 polarimeter and $[\alpha]_D$ values are given in $deg \bullet cm \bullet g^{-1} \bullet dm^{-1}$; concentration *c* is listed in $g \bullet (100\ mL)^{-1}$. The enantiomeric ratio (er) of the products were determined by Ultra Performance Convergence Chromatography (UPC[2]) using Daicel Chiralpak IA, IB, IC and IG columns as chiral stationary phases. Melting points were uncorrected. Cinnamaldehydes[1] and hydrazones[2] were synthesized according to the literature procedures and compounds described in the literature were characterized by comparison of their ^{1}H and ^{13}C NMR spectra to the previously reported data.

[1] N. Daubresse, C. Francesch and C. Rolando, *Tetrahedron*, 1998, **54**, 10761.

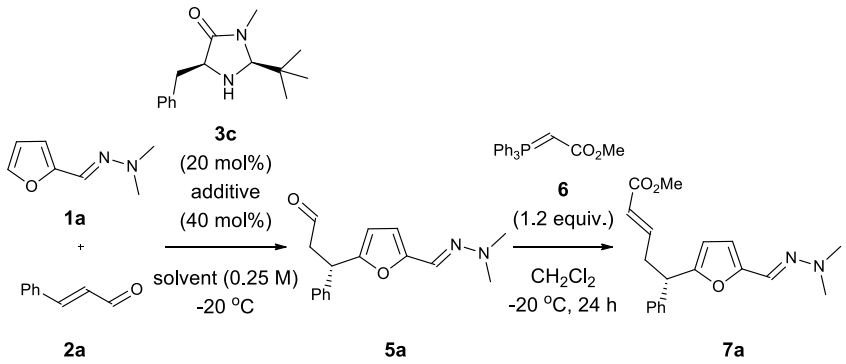
[2] A. Ros, B. Estepa, R. López-Rodríguez, E. Álvarez, R, Fernández and J. M. Lassaletta, *Angew. Chem. Int. Ed.*, 2011, **50**, 1724.

2. Additional screening results for the asymmetric alkylation of hydrazones derived from heteroaromatic aldehydes

2.1. General procedure for optimization studies

To a stirred solution of 2-furfural *N*,*N*-dimethylhydrazone **1a** (1.2 equiv., 0.06 mmol, 8.3 mg) and cinnamaldehyde **2a** (1.0 equiv., 0.05 mmol, 6.6 mg) in appropriate solvent (0.2 mL), catalyst **3** (0.2 equiv., 0.01 mmol) and acidic additive (0.4 equiv., 0.02 mmol) were added at indicated temperature. The resulting mixture was stirred overnight. After completion of the addition reaction, cold dichloromethane (0.5 mL) and methyl(triphenylphosphoranylidene)acetate **6** (1.5 equiv., 0.075 mmol, 25 mg) were added. The mixture was stirred at -20 °C overnight. The reaction mixture was directly purified by column chromatography (hexane/diethyl ether 4:1) to give **7a** as a colorless oil.

2.2. Additive screening and relative substrate ratio effect on the asymmetric alkylation of hydrazones derived from heteroaromatic aldehydes

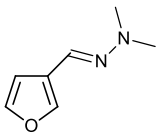


	Solvent	Add.	Conv. [%][a]	er.[b]
1	PhMe	TFA	>95 (95)	98:2
2	CH_2Cl_2	TFA	82	93:7
3	CH_2Cl_2	TFMSA	>95 (88)	82:18
4	CH_2Cl_2	*p*-TsOH	62	n.d.
5	CH_2Cl_2	*o*-F-BzOH	45	n.d.
5[c]	CH_2Cl_2	TFA	70	n.d.

[a] Conversion as determined by ^{1}H NMR of a crude reaction mixture. Isolated yield is given in parentheses. [b] Determined by a chiral stationary phase UPC[2]. [c] Reaction performed using of hydrazone **1a** (1 equiv., 0.05 mmol).

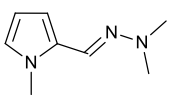
3. Synthesis of hydrazones 1b-d

3-Furfural *N*,*N*-dimethylhydrazone (**1b**)



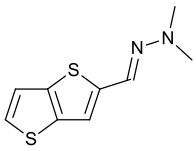
The suspension of furan-3-carboxaldehyde (192 mg, 2 mmol), *N*,*N*-dimethylhydrazine (180 mg, 3 mmol, 228 µl) and $MgSO_4$ (1.2 g, 10 mmol) in CH_2Cl_2 (6 mL) was stirred at room temperature overnight. The reaction mixture was filtered and solid was washed with aid of CH_2Cl_2. After evaporation of the solvent, crude product was purified by flash column chromatography (hexane/diethyl ether 4:1) to give **1b** (227 mg, 82%) as a colorless liquid. R_f = 0.28 (hexane/diethyl ether 2:1); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.52 (br s, 1H), 7.36 – 7.35 (m, 1H), 7.22 (br s, 1H), 6.72 – 6.71 (m, 1H), 2.89 (s, 6H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 143.3, 140.5, 125.9, 124.7, 107.6, 42.9 (2C); HRMS (ES+): calcd. for: $C_7H_{10}N_2O$ $[M+H]^+$ 139.0907, found 139.0909.

1-Methylpyrrole-2-carbaldehyde *N*,*N*-dimethylhydrazone (**1c**)



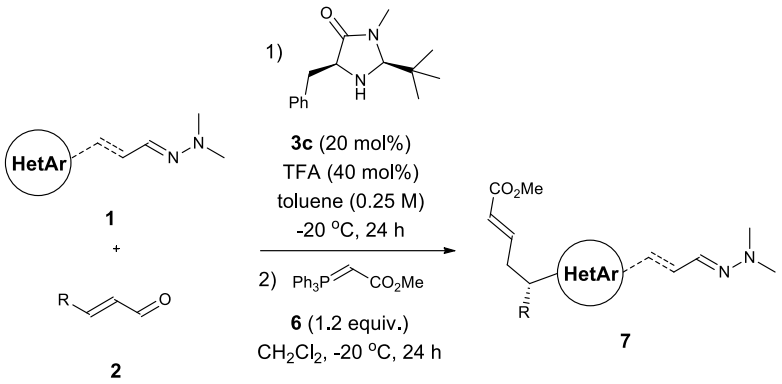
The suspension of 1-methylpyrrole-2-carbaldehyde (110 mg, 1 mmol, 108.6 µl), *N*,*N*-dimethylhydrazine (90 mg, 1.5 mmol, 114 µl) and $MgSO_4$ (0.6 g, 5 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature overnight. The reaction mixture was filtered and solid was washed with aid of CH_2Cl_2. After evaporation of the solvent, crude product was purified by flash column chromatography (hexane/diethyl ether 4:1) to give **1c** (227 mg, 82%) as a colorless liquid. R_f = 0.29 (hexane/diethyl ether 2:1); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.34 (s, 1H), 6.60 – 6.58 (m, 1H), 6.27 (dd, J = 3.7, 1.8 Hz, 1H), 6.11 (dd, J = 3.7, 2.6 Hz, 1H), 3.85 (s, 3H), 2.87 – 2.84 (m, 6H). ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 129.8, 128.9, 125.0, 110.7, 107.5, 43.2 (2C), 36.3; HRMS (ES+): calcd. for: $C_8H_{13}N_3$ $[M+H]^+$ 152.1208, found 152.1206.

Thieno[3,2-*b*]thiophene-2-carbaldehyde *N*,*N*-dimethylhydrazone (**1d**)



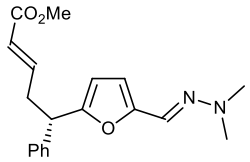
The suspension of thieno[3,2-*b*]thiophene-2-carbaldehyde (28 mg, 0.17 mmol), *N*,*N*-dimethylhydrazine (15 mg, 0.25 mmol) and $MgSO_4$ (168 mg, 0.34 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature overnight. The reaction mixture was filtered and solid was washed with aid of CH_2Cl_2. After evaporation of the solvent, crude product was purified by flash column chromatography (hexane/diethyl ether 1:1) to give **1d** (30 mg, 86%) as a yellow amorphous solid. R_f = 0.29 (hexane/diethyl ether 1:1); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.41 – 7.39 (m, 1H), 7.30 (d, *J* = 5.2 Hz, 1H), 7.19 (dd, *J* = 5.2 Hz, *J* = 0.6 Hz, 1H), 7.12 (s, 1H), 2.98 (s, 6H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 145.3, 139.1, 137.9, 127.4, 126.6, 119.8, 116.5, 42.8 (2C); HRMS (ES+): calcd. for: $C_9H_{10}N_2S_2$ $[M+H]^+$ 211.0408, found 211.0409.

4. Asymmetric alkylation of hydrazones 1 derived from heteroaromatic aldehydes with α,β-unsaturated aldehydes 2 – general procedure



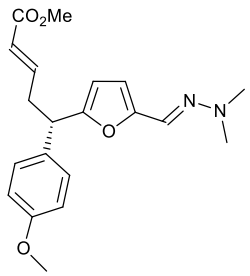
To a stirred solution of the corresponding *N*,*N*-dimethylhydrazone **1** (1.2 equiv., 0.12 mmol) and α,β-unsaturated aldehyde **2** (1.0 equiv., 0.1 mmol) in toluene (0.4 mL) (2*S*,5*S*)-(−)-2-*tert*-butyl-3-methyl-5-benzyl-4-imidazolidinone **3c** (0.2 equiv., 0.02 mmol, 4.9 mg) and trifluoroacetic acid (0.4 equiv., 0.04 mmol, 4.6 mg) were added at -20 °C. The resulting yellow solution was stirred overnight. After completion of the addition reaction, cold dichloromethane (1 mL) and methyl(triphenylphosphoranylidene)acetate (1.5 equiv., 0.15 mmol, 50 mg) were added. The mixture was stirred at -20 °C overnight. The reaction mixture was directly purified by column chromatography (hexane/diethyl ether 4:1) to give products **7a-l**.

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-phenylpent-2-enoate (**7a**)



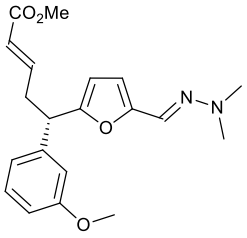
Following the general procedure product **7a** was isolated in 95% yield (31.9 mg) as colorless oil. R_f = 0.41 (hexane/diethyl ether 1:1); $[\alpha]_D^{25}$= -27.2 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.33 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 7.06 (s, 1H), 6.86 (dt, *J* = 15.6 Hz, *J* = 7.1 Hz, 1H), 6.32 (d, *J* = 3.3 Hz, 1H), 6.03 (dd, *J* = 3.3 Hz, *J* = 0.8 Hz, 1H), 5.82 (dt, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 4.16 (t, *J* = 7.7 Hz, 1H), 3.68 (s, *J* = 2.3 Hz, 3H), 3.05 – 3.00 (m, 1H), 2.92 (s, 6H), 2.81 (ddd, *J* = 8.4 Hz, *J* = 6.8 Hz, *J* = 3.1 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.7, 156.0, 151.6, 146.3, 141.1, 128.6 (2C), 127.9 (2C), 127.0, 123.8, 122.8, 108.1, 107.3, 51.4, 44.5, 42.7 (2C), 37.5; HRMS (ES+): calcd. for: $C_{16}H_{18}N_2O_2$ $[M+H]^+$ 327.1709, found 327.1708; the er was determined by UPC^2 using a chiral Chiralpack IA gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 2.93 min, τ_{minor} = 3.06 min, (98:2 er).

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(4-methoxyphenyl)pent-2-enoate (**7b**)



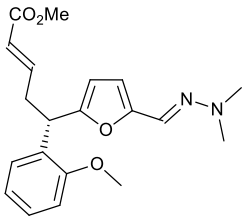
Following the general procedure product **7b** was isolated in 88% yield as yellowish oil. R_f = 0.22 (hexane/diethyl ether 1:1); $[\alpha]_D^{25}$= -28.3 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.15 – 7.13 (m, 2H), 7.06 (s, 1H), 6.87 – 6.83 (m, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.31 (d, *J* = 3.3 Hz, 1H), 5.99 (dd, *J* = 3.3 Hz, *J* = 0.8 Hz, 1H), 5.81 (dt, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 4.11 (t, *J* = 7.7 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.01 (dtd, *J* = 14.9 Hz, *J* = 7.1 Hz, *J* = 1.5 Hz, 1H), 2.92 (s, 6H), 2.79 – 2.74 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.9, 158.7, 156.7, 151.7, 146.6, 133.3, 129.0 (2C), 124.0, 122.9, 114.2 (2C), 108.1, 107.4, 55.4, 51.6, 43.9, 42.9 (2C), 37.9; HRMS (ES+): calcd. for: $C_{20}H_{24}N_2O_4$ $[M+H]^+$ 357.1814, found 357.1816; the er was determined by UPC^2 using a chiral Chiralpack IB gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 4.54 min, τ_{minor} = 3.86 min, (94.5:4.5 er).

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(3-methoxyphenyl)pent-2-enoate (**7c**)



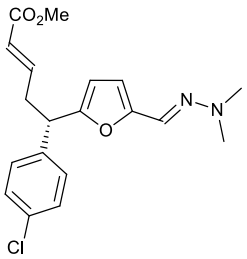
Following the general procedure product **7c** was isolated in 85 % yield as colorless oil. R_f = 0.27 (hexane/diethyl ether 2:1); $[\alpha]_D^{25}$= 30.0 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = (t, *J* = 7.9 Hz, 1H), 7.06 (s, 1H), 6.86 (dt, *J* = 15.6 Hz, *J* = 7.1 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.79 – 6.75 (m, 2H), 6.32 (d, *J* = 3.3 Hz, 1H), 6.04 (dd, *J* = 3.3 Hz, *J* = 0.7 Hz, 1H), 5.82 (dt, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 4.12 (t, *J* = 7.7 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.01 (dtd, *J* = 16.2 Hz, *J* = 7.3 Hz, *J* = 1.5 Hz, 1H), 2.93 – 2.91 (m, 6H), 2.82 – 2.77 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.7, 159.80, 155.8, 151.6, 146.2, 142.7, 129.6, 123.8, 122.8, 120.3, 113.8, 112.2, 108.1, 107.2, 55.2, 51.4, 44.5, 42.7 (2C), 37.5; HRMS (ES+): calcd. for: $C_{20}H_{24}N_2O_4$ $[M+H]^+$ 357.1814, found 357.1814; the er was determined by UPC^2 using a chiral Chiralpack IA gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 3.22 min, τ_{minor} = 3.12 min, (97:3 er).

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(2-methoxyphenyl)pent-2-enoate (**7d**)



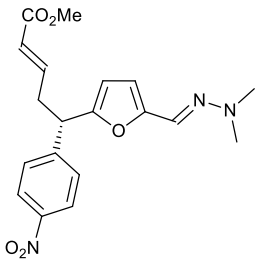
Following the modified general procedure (Wittig reaction performed at room temperature) product **7d** was isolated in 95% yield as colorless oil. R_f = 0.20 (hexane/diethyl ether 1:1); $[\alpha]_D^{25}$= 6.4 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.19 (ddd, *J* = 8.1 Hz, *J* = 7.5 Hz, *J* = 1.7 Hz, 1H), 7.09 – 7.07 (m, 2H), 6.94 – 6.85 (m, 3H), 6.35 (d, *J* = 3.3 Hz, 1H), 6.07 (dd, *J* = 3.3 Hz, *J* = 0.7 Hz, 1H), 5.81 (dt, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 4.70 (t, *J* = 7.5 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 2.95 – 2.92 (m, 1H), 2.91 (s, 6H), 2.82 – 2.75 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.9, 156.7, 156.0, 151.4, 147.1, 129.8, 128.2, 127.9, 124.1, 122.2, 120.7, 110.7, 108.4, 107.2, 55.4, 51.3, 42.8 (2C), 37.0, 36.6; HRMS (ES+): calcd. for: $C_{20}H_{24}N_2O_4$ $[M+H]^+$ 357.1814, found 357.1817; the er was determined by UPC^2 using a chiral Chiralpack IB gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 3.82 min, τ_{minor} = 3.44 min, (91:9 er).

(*S*,*E*)-Methyl 5-(4-chlorophenyl)-5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)pent-2-enoate (**7e**)



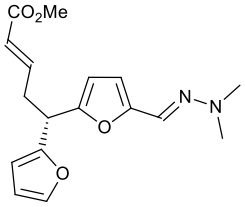
Following the general procedure product **7e** was isolated in 97% yield as colorless oil. R_f = 0.31 (hexane/diethyl ether 1:1); $[\alpha]_D^{25}$= -31.8 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.28 – 7.26 (m, 2H), 7.18 – 7.14 (m, 2H), 7.04 (s, 1H), 6.82 (dt, *J* = 15.6 Hz, *J* = 7.1 Hz, 1H), 6.31 (d, *J* = 3.3 Hz, 1H), 6.03 (dd, *J* = 3.3 Hz, *J* = 0.7 Hz, 1H), 5.81 (dt, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 4.14 (t, *J* = 7.7 Hz, 1H), 3.68 (s, 3H), 3.04 – 2.98 (m, 1H), 2.93 (s, 6H), 2.79 – 2.73 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.6, 155.3, 151.9, 145.7, 139.6, 132.8, 129.2 (2C), 128.8 (2C), 123.4, 123.1, 108.2, 107.2, 51.4, 43.9, 42.7 (2C), 37.4; HRMS (ES+): calcd. for: $C_{19}H_{21}ClN_2O_3$ $[M+H]^+$ 361.1309, found 361.1311; the er was determined by UPC^2 using a chiral Chiralpack IB gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 4.78 min, τ_{minor} = 3.83 min, (98:2 er).

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(4-nitrophenyl)pent-2-enoate (**7f**)



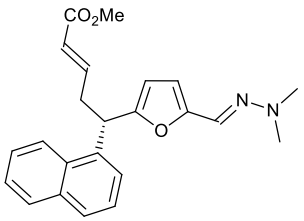
Following the general procedure product **7f** was isolated in 93% yield as colorless oil. R_f = 0.16 (hexane/diethyl ether 1:1); $[\alpha]_D^{25}$= -31.5 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 8.18 – 8.14 (m, 2H), 7.42 – 7.37 (m, 2H), 7.02 (s, 1H), 6.81 (dt, *J* = 15.6 Hz, *J* = 7.2 Hz, 1H), 6.32 (d, *J* = 3.3 Hz, 1H), 6.11 (dd, *J* = 3.3 Hz, *J* = 0.7 Hz, 1H), 5.82 (dt, *J* =15.6 Hz, *J* = 1.4 Hz, 1H), 4.28 (t, *J* = 7.7 Hz, 1H), 3.68 (s, 3H), 3.10 – 3.01 (m, 1H), 2.93 (s, 6H), 2.84 – 2.77 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.3, 153.8, 152.3, 148.6, 147.0, 144.8, 128.8 (2C), 123.9 (2C), 123.5, 122.8, 108.7, 107.1, 51.5, 44.3, 42.6 (2C), 37.0; HRMS (ES+): calcd. for: $C_{19}H_{21}N_3O_5$ $[M+H]^+$ 372.1614, found 372.1616; the er was determined by UPC^2 using a chiral Chiralpack IB gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 5.36 min, τ_{minor} = 4.68 min, (99:1 er).

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(furan-2-yl)pent-2-enoate (**7g**)



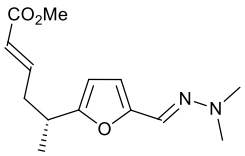
Following the general procedure product **7g** was isolated in 85% yield as yellowish oil. R_f = 0.27 (hexane/diethyl ether 1:1); $[\alpha]_D^{25}$= -27.6 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.34 (dd, *J* = 1.8 Hz, *J* = 0.8 Hz, 1H), 7.07 (s, 1H), 6.87 (dt, *J* = 15.6 Hz, *J* = 7.2 Hz, 1H), 6.32 (d, *J* = 3.3 Hz, 1H), 6.29 (dd, *J* = 3.2 Hz, *J* = 1.9 Hz, 1H), 6.10 (dt, *J* = 3.1 Hz, *J* = 0.6 Hz, 1H), 6.07 (dd, *J* = 3.3 Hz, *J* = 0.6 Hz, 1H), 5.84 (dt, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 4.30 (t, *J* = 7.4 Hz, 1H), 3.69 (s, 3H), 2.94 (s, 6H), 2.97 – 2.88 (m, 2H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.6, 153.6, 153.5, 151.6, 145.6, 141.7, 123.6, 123.0, 110.3, 108.3, 107.4, 106.7, 51.4, 42.7 (2C), 38.2, 35.6; HRMS (ES+): calcd. for: $C_{17}H_{20}N_2O_4$ $[M+H]^+$ 317.1508, found 317.1509; the er was determined by UPC^2 using a chiral Chiralpack IB gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 3.53 min, τ_{minor} = 3.14 min, (91:9 er).

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(naphthalen-1-yl)pent-2-enoate (**7h**)



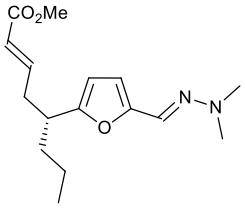
Following the general procedure product **7h** was isolated in 92% yield as colorless oil. R_f = 0.2 (hexane/diethyl ether 4:1); $[\alpha]_D^{25}$= 48.8 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.33 (d, *J* = 7.1 Hz, 1H), 7.07 (s, 1H), 6.97 (dt, *J* = 15.5 Hz, *J* = 7.0 Hz, 1H), 6.34 (d, *J* = 3.3 Hz, 1H), 6.04 (d, *J* = 3.2 Hz, 1H), 5.89 (d, *J* = 15.7 Hz, 1H), 5.03 (t, *J* = 7.4 Hz, 1H), 3.67 (s, 3H), 3.17 – 3.12 (m, 1H), 3.02 – 2.98 (m, 1H), 2.92 (s, 6H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.7, 155.6, 151.7, 146.4, 137.0, 134.1, 131.3, 129.0, 127.7, 126.3, 125.6 125.5, 124.9, 123.7, 122.9, 122.7, 109.0, 107.4, 51.4, 42.7 (2C), 39.7, 37.0; HRMS (ES+): calcd. for: $C_{23}H_{24}N_2O_3$ $[M+H]^+$ 377.1914, found 377.1913; the er was determined by UPC^2 using a chiral Chiralpack IB gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 4.54 min, τ_{minor} = 5.20 min, (96:4 er).

(*R*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)hex-2-enoate (**7i**)



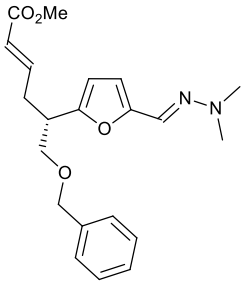
Following the general procedure product **7i** was isolated in 85% yield as yellowish oil. R_f = 0.24 (hexane/diethyl ether 2:1); $[\alpha]_D^{25}$= 57.6 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.09 (s, 1H), 6.90 (ddd, *J* = 15.5 Hz, *J* = 7.6 Hz, *J* = 7.1 Hz, 1H), 6.30 (d, *J* = 3.3 Hz, 1H), 6.01 (dd, *J* = 3.3 Hz, *J* = 0.9 Hz, 1H), 5.84 (dt, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 3.71 (s, 3H), 3.05 (dt, *J* = 12.7 Hz, *J* = 6.4 Hz, 1H), 2.94 – 2.93 (m, 6H), 2.68 – 2.63 (m, 1H), 2.44 – 2.39 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.8, 158.7, 150.9, 146.7, 124.1, 122.7, 107.7, 106.0, 51.4, 42.8 (2C), 38.2, 32.4, 18.4; HRMS (ES+): calcd. for: $C_{14}H_{20}N_2O_3$ $[M+H]^+$ 265.1610, found 265.1611; the er was determined by UPC^2 using a chiral Chiralpack IB gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 3.09 min, τ_{minor} = 3.25 min, (96:4 er).

(*R*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)oct-2-enoate (**7j**)



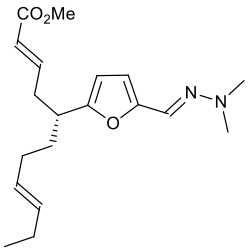
Following the general procedure product **7j** was isolated in 81% yield as colorless oil. R_f = 0.41 (hexane/diethyl ether 1:1); $[\alpha]_D^{25}$= -7.8 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.10 (s, 1H), 6.87 (dt, *J* = 15.6 Hz, *J* = 7.3 Hz, 1H), 6.32 (d, *J* = 3.3 Hz, 1H), 6.01 (d, *J* = 3.3 Hz, 1H), 5.81 (dt, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 3.70 (s, 3H), 2.93 (s, 6H), 2.93 – 2.89 (m, 1H), 2.57 (dtd, *J* = 8.8 Hz, *J* = 7.2 Hz, *J* = 1.5 Hz, 1H), 2.52 – 2.47 (m, 1H), 1.83 – 1.83 (m, 1H), 1.67 – 1.61 (m, 1H), 1.59 – 1.55 (m, 1H), 1.32 – 1.25 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.8, 157.4, 151.0, 147.0, 124.2, 122.5, 107.5, 107.1, 51.4, 42.8 (2C), 38.0, 36.6, 35.6, 20.3, 13.9; HRMS (ES+): calcd. for: $C_{16}H_{24}N_2O_3$ $[M+H]^+$ 293.1908, found 293.1906; the er was determined by UPC^2 using a chiral Chiralpack IB gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 3.05 min, τ_{minor} = 2.94 min, (98:2 er).

(*S*,*E*)-Methyl 6-(benzyloxy)-5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)hex-2-enoate (**7k**)



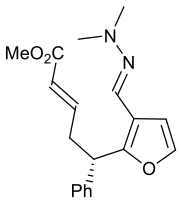
Following the general procedure product **7k** was isolated in 91% yield as colorless oil. R_f = 0.3 (hexan/diethyl ether 1:1); $[\alpha]_D^{25}$= -11.8 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.35 – 7.31 (m, 2H), 7.31 – 7.26 (m, 3H), 7.08 (s, 1H), 6.90 (dt, *J* = 15.6 Hz, *J* = 7.3 Hz, 1H), 6.31 (d, *J* = 3.3 Hz, 1H), 6.09 (dd, *J* = 3.3 Hz, *J* = 0.5 Hz, 1H), 5.83 (dt, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 4.50 (s, 2H), 3.72 – 3.67 (m, 1H), 3.70 (s, 3H), 3.59 (dd, *J* = 9.4 Hz, *J* = 7.3 Hz, 1H), 3.28 – 3.22 (m, 1H), 2.94 (s, 6H), 2.72 (dddd, *J* = 14.7 Hz, *J* = 7.4 Hz, *J* = 5.9 Hz, *J* = 1.5 Hz, 1H), 2.66 – 2.59 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.7, 154.5, 151.2, 146.5, 138.2, 128.4 (2C), 127.6 (2C), 127.6, 123.9, 122.7, 108.0, 107.6, 73.1, 71.4, 51.3, 42.8 (2C), 38.8, 33.2; HRMS (ES+): calcd. for: $C_{21}H_{26}N_2O_4$ $[M+H]^+$ 371.1981, found 371.1982; the er was determined by UPC^2 using a chiral Chiralpack IB gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 4.08 min, τ_{minor} = 3.87 min, (97:3 er).

(*R*,2*E*,8*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)undeca-2,8-dienoate (**7l**)



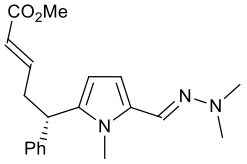
Following the general procedure product **7l** was isolated in 96% yield as yellowish oil. R_f = 0.20 (hexane/diethyl ether 1:1); $[\alpha]_D^{25}$= 14.3 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.09 (s, 1H), 6.88 – 6.83 (m, 1H), 6.32 (d, *J* = 3.3 Hz, 1H), 6.02 (d, *J* = 3.3 Hz, 1H), 5.82 – 5.78 (m, 1H), 5.39 – 5.33 (m, 1H), 5.30 – 5.24 (m, 1H), 3.69 (s, 3H), 2.93 (s, 6H), 2.96 – 2.90 (m, 1H), 2.57 (dtd, *J* = 8.5 Hz, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 2.53 – 2.45 (m, 1H), 2.04 – 1.93 (m, 4H), 1.75 – 1.69 (m, 1H), 1.66 – 1.59 (m, 1H), 0.92 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.8, 156.9, 151.1, 146.8, 132.4, 128.1, 124.2, 122.6, 107.4 (2C), 51.4, 42.8 (2C), 37.7, 36.7, 33.4, 24.7, 20.5, 14.3; HRMS (ES+): calcd. for: $C_{19}H_{28}N_2O_3$ $[M+H]^+$ 333.2178, found 333.2178; the er was determined by UPC^2 using a chiral Chiralpack IB gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 3.15 min, τ_{minor} = 3.00 min, (98:2 er).

(*S*,*E*)-Methyl 5-(3-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-phenylpent-2-enoate (**7m**)



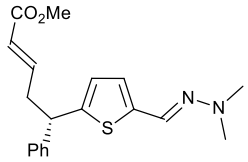
Following the modified general procedure (alkylation reaction performed at -30 °C for 72 h) product **7m** was isolated in 71% yield as a colorless oil. R_f = 0.17 (hexane/diethyl ether 2:1); $[\alpha]_D^{25}$= -28.8 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.31 – 7.27 (m, 5H), 7.22 – 7.19 (m, 1H), 7.03 (s, 1H), 6.86 (ddd, *J* = 15.6 Hz, *J* = 8.8 Hz, *J* = 5.5 Hz, 1H), 6.59 (d, *J* = 1.9 Hz, 1H), 5.82 (dt, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 4.41 (dd, *J* = 8.5 Hz, *J* = 7.1 Hz, 1H), 3.68 (s, 3H), 3.11 – 3.05 (m, 1H), 2.90 (dtd, *J* = 8.6 Hz, *J* = 7.1 Hz, *J* = 1.5 Hz, 1H), 2.84 (s, 6H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.7, 152.1, 146.3, 141.5, 141.3, 128.6 (2C), 127.7 (2C), 126.8, 126.1, 122.7, 119.1, 108.9, 51.4, 42.9 (2C), 42.8, 36.9; HRMS (ES+): calcd. for: $C_{19}H_{22}N_2O_3$ $[M+H]^+$ 327.1707, found 327.1705; the er was determined by UPC^2 using a chiral Chiralpack IA gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 2.73 min, τ_{minor} = 2.43 min, (86:14 er).

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)-1-methyl-1*H*-pyrrol-2-yl)-5-phenylpent-2-enoate (**7n**)



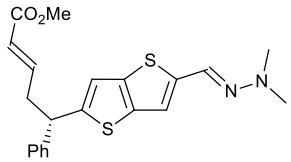
Following the modified general procedure (alkylation reaction performed at -30 °C for 20 h, Wittig olefination performed at 0 °C) product **7n** was isolated in 70% yield as colorless, amorphous crystals. R_f = 0.3 (hexane/diethyl ether 1:1); $[\alpha]_D^{25}$= -14.0 (CH_2Cl_2); mp = 95 °C; ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.28 – 7.25 (m, 3H), 7.20 – 7.16 (m, 1H), 7.10 (dd, *J* = 8.0, 1.0 Hz, 2H), 6.93 (dt, *J* = 15.6, 7.1 Hz, 1H), 6.27 (d, *J* = 3.8 Hz, 1H), 6.13 (dd, *J* = 3.8, 0.4 Hz, 1H), 5.82 (dt, *J* = 15.6, 1.4 Hz, 1H), 4.03 (t, *J* = 7.6 Hz, 1H), 3.69 (s, 3H), 3.53 (s, 3H), 2.96 (dtd, *J* = 8.7, 7.6, 1.5 Hz, 1H), 2.80 (s, 6H), 2.75 (dtd, *J* = 8.7, 7.3, 1.5 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.7, 146.9, 142.5, 136.8, 130.1, 129.5, 128.7 (2C), 127.8 (2C), 126.7, 122.6, 110.0, 106.6, 51.4, 43.2 (2C), 43.1, 39.1, 32.4; HRMS (ES+): calcd. for: $C_{20}H_{25}N_3O_2$ $[M+Na]^+$ 362.1844, found 362.1847; the er was determined by UPC^2 using a chiral Chiralpack IA gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 3.00 min, τ_{minor} = 3.12 min, (95:5 er).

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)thiophen-2-yl)-5-phenylpent-2-enoate (**7o**)



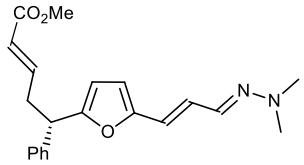
Following the modified general procedure (alkylation reaction performed in 1,2-dichloroethane at room temperature for 72 h, Wittig olefination performed in 1,2-dichloroethane at room temperature for 20 h) product **7o** was isolated in 52% yield as a yellowish oil. R_f = 0.25 (hexane/diethyl ether 1:1); $[\alpha]_D^{25}$= 6.2 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.32 (s, 1H), 7.31 – 7.28 (m, 2H), 7.26 (s, *J* = 1.0 Hz, 1H), 7.25 (br s, 1H), 7.23 – 7.19 (m, 1H), 6.87 (dt, *J* = 15.6 Hz, *J* = 7.1 Hz, 1H), 6.78 (d, *J* = 3.6 Hz, 1H), 6.69 (dd, *J* = 3.6 Hz, *J* = 0.8 Hz, 1H), 5.83 (dt, *J* = 15.6 Hz, *J* = 1.4 Hz, 1H), 4.24 (t, *J* = 7.7 Hz, 1H), 3.68 (s, 3H), 3.00 (dtd, *J* = 8.8 Hz, *J* = 7.4 Hz, *J* = 1.5 Hz, 1H), 2.94 – 2.90 (m, 1H), 2.89 (s, 6H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.7, 146.6, 146.3, 143.1, 141.3, 128.7 (2C), 128.0, 127.6 (2C), 126.9, 124.3, 124.3, 122.9, 51.4, 46.4, 42.9 (2C), 39.6; HRMS (ES+): calcd. for: $C_{19}H_{22}N_2O_2S$ $[M+Na]^+$ 365.1349, found 365.1351; the er was determined by UPC^2 using a chiral Chiralpack IG gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 3.63 min, τ_{minor} = 3.90 min, (96:4 er).

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)thieno[3,2-*b*]thiophen-2-yl)-5-phenylpent-2-enoate (**7p**)



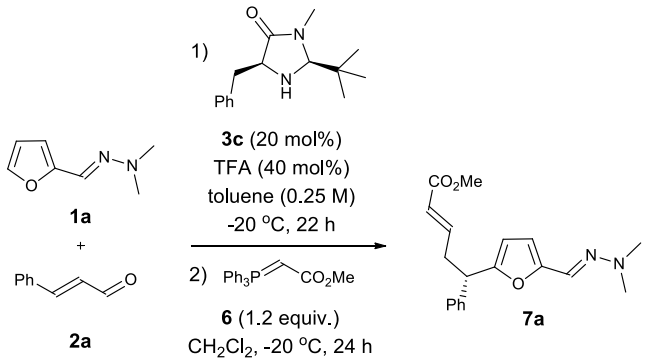
Following the modified general procedure (alkylation reaction performed in 1,2-dichloroethane at room temperature for 72 h, Wittig olefination performed in 1,2-dichloroethane at room temperature for 20 h) product **7p** was isolated in 48% yield as a yellow amorphous solid. R_f = 0.2 (hexane/diethyl ether 2:1); $[\alpha]_D^{25}$= 25.9 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.36 (s, 1H), 7.35 – 7.30 (m, 2H), 7.30 – 7.27 (m, 2H), 7.26 – 7.22 (m, 1H), 7.01 (s, 1H), 6.93 (s, 1H), 6.89 (dt, *J* = 15.6 Hz, *J* = 7.1 Hz, 1H), 5.86 (dt, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 4.32 (t, *J* = 7.7 Hz, 1H), 3.68 (s, 3H), 3.05 (dtd, *J* = 8.7 Hz, *J* = 7.3 Hz, *J* = 1.5 Hz, 1H), 3.00 – 2.96 (m, 1H), 2.95 (s, 6H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.6, 149.7, 146.0, 144.1, 142.7, 137.8, 137.2, 128.8 (2C), 127.6 (2C), 127.7, 127.2, 123.1, 117.1, 116.7, 51.4, 47.0, 42.8 (2C), 39.5; HRMS (ES+): calcd. for: $C_{21}H_{22}N_2O_2S_2$ $[M+Na]^+$ 421.1049, found 421.1051; the er was determined by UPC^2 using a chiral Chiralpack IG gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 4.97 min, τ_{minor} = 5.81 min, (94:6 er).

(*S*,*E*)-Methyl 5-(5-((1*E*,3*E*)-3-(2,2-dimethylhydrazono)prop-1-en-1-yl)furan-2-yl)-5-phenylpent-2-enoate (**7q**)



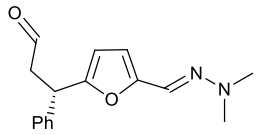
Following the modified general procedure (alkylation reaction performed for 48 h) product **7q** was isolated in 76% yield as a colorless oil. R_f = 0.16 (hexane/diethyl ether 2:1); $[\alpha]_D^{25}$= 47.6 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.30 (t, *J* = 7.6 Hz, 2H), 7.23 (dd, *J* = 16.7, 7.7 Hz, 3H), 7.04 (d, *J* = 9.3 Hz, 1H), 6.86 (dt, *J* = 15.4, 7.2 Hz, 1H), 6.77 (dd, *J* = 15.8, 9.2 Hz, 1H), 6.32 (d, *J* = 15.8 Hz, 1H), 6.15 (d, *J* = 3.2 Hz, 1H), 6.02 (d, *J* = 3.2 Hz, 1H), 5.82 (d, *J* = 15.6 Hz, 1H), 4.07 (t, *J* = 7.7 Hz, 1H), 3.68 (s, 3H), 3.02 (dtd, *J* = 8.6, 7.6, 1.3 Hz, 1H), 2.91 (s, 6H), 2.84 – 2.78 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.6, 156.1, 152.5, 146.2, 141.1, 134.8, 128.6 (2C), 127.7 (2C), 127.0, 125.6, 122.8, 119.1, 108.8, 108.3, 51.4, 44.8, 42.7 (2C), 37.3; HRMS (ES+): calcd. for: $C_{21}H_{24}N_2O_3$ $[M+Na]^+$ 375.4251, found 375.4248; the er was determined by UPC^2 using a chiral Chiralpack IB gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 4.16 min, τ_{minor} = 3.75 min, (93:7 er).

5. Synthesis of (*S*,*E*)-methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-phenylpent-2-enoate (7a) – 1 mmol scale experiment



To a stirred solution of the corresponding *N*,*N*-dimethylhydrazone **1** (1.2 equiv., 1.2 mmol) and *trans*-cinnamaldehyde **2** (1.0 equiv., 1 mmol, 132 mg) in toluene (4 mL) (2*S*,5*S*)-(−)-2-*tert*-butyl-3-methyl-5-benzyl-4-imidazolidinone **3c** (0.2 equiv., 0.2 mmol, 49 mg) and trifluoroacetic acid (0.4 equiv., 0.4 mmol, 46 mg) were added at -20 °C. The resulting solution was stirred for 22h. After completion of the addition reaction, cold dichloromethane (10 mL) and methyl(triphenyl-phosphoranylidene)acetate (1.5 equiv., 1.5 mmol, 500 mg) were added. The mixture was stirred at -20 °C for 24h. After evaporation of solvents the reaction mixture was purified by column chromatography (hexane/diethyl ether 4:1) to give product **7a** in 91% yield (97:3 er). NMR and UPCC data were in accordance with previously obtained results.

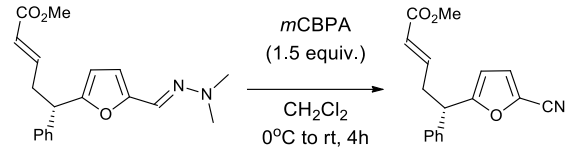
6. Synthesis and isolation of (*S*,*E*)-3-(5-((2,2-dimethylhydrazono)methyl)furan-2-yl)-3-phenylpropanal (5a)



To a stirred solution of 2-furfural *N*,*N*-dimethylhydrazone **1a** (24.9 mg, 0.18 mmol) and cinnamaldehyde **2a** (19.8 mg, 0.15 mmol) in toluene (0.6 mL) (2*S*,5*S*)-(−)-2-*tert*-Butyl-3-methyl-5-benzyl-4-imidazolidinone **3c** (7.5 mg, 0.03 mmol) and trifluoroacetic acid (6.9 mg, 0.06 mmol) were added at -20 °C. The resulting yellow solution was stirred overnight. The reaction mixture was directly purified by flash column chromatography (hexane/diethyl ether 2:1) to give **5a** (35 mg, 93%) as a colorless liquid. R_f = 0.26 (hexane/diethyl ether 1:1); $[\alpha]_D^{25}$= -25.5 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 9.74 (t, *J* = 1.7 Hz, 1H), 7.47 (s, 1H), 7.34 – 7.30 (m, 2H), 7.27 – 7.26 (m, 1H), 7.26 – 7.23 (m, 2H), 6.48 (d, *J* = 3.4 Hz, 1H), 6.06 (dd, *J* = 3.4 Hz, *J* = 0.9 Hz, 1H), 4.67 (t, *J* = 7.5 Hz, 1H), 3.24 (ddd, *J* = 17.3 Hz, *J* = 7.5 Hz, *J* = 1.8 Hz, 1H), 3.04 (ddd, *J* = 17.3 Hz, *J* = 7.6 Hz, *J* = 1.7 Hz, 1H), 2.96 (s, 6H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 200.3, 155.3, 151.9, 140.8, 128.7 (2C), 127.8 (2C), 127.1, 123.5, 108.4, 107.1, 48.4, 42.7 (2C), 39.4; HRMS (ES+): calcd. for: $C_{19}H_{22}N_2O_3$ $[M+H]^+$ 271.1500, found 271.1502; the er was determined by UPC[2] using a chiral Chiralpack IB gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 4.01 min, τ_{minor} = 3.41 min, (3:97 er).

7. Unmasking of hydrazone in 7a

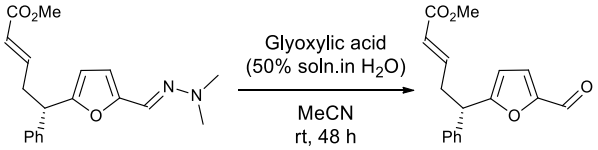
Synthesis of (*S*,*E*)-methyl 5-(5-cyanofuran-2-yl)-5-phenylpent-2-enoate (**8a**)



7a **8a**

Reaction was carried out following the modified literature procedure.[3] To a stirred solution of **7a** (32.6 mg, 0.1 mmol) in CH_2Cl_2 (1 mL), mCBPA (34 mg, 0.15 mmol, 77% mCPBA was used) in CH_2Cl_2 (3 mL) was added dropwise at 0 °C. Then the reaction mixture was stirred at room temperature. After full consumption of starting material **7a** (as indicated by TLC analysis, about 4 h) K_2CO_3 (69 mg, 0.5 mmol) was added in one portion and reaction mixture was stirred for a few minutes in an open flask. The reaction mixture was filtered and solid was washed with CH_2Cl_2 (5 mL). After evaporation of the solvent crude product was purified by flash column chromatography ($CHCl_3$) to give nitrile **8a** (26.1 mg, 95%) as a colorless oil. R_f = 0.45 (chloroform); $[\alpha]_D^{25}$= 35.3 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 7.36 – 7.32 (m, 2H), 7.30 – 7.26 (m, 1H), 7.23 – 7.20 (m, 2H), 7.00 (d, *J* = 3.6 Hz, 1H), 6.80 (dt, *J* = 15.6 Hz, *J* = 7.1 Hz, 1H), 6.17 (dd, *J* = 3.6 Hz, *J* = 0.7 Hz, 1H), 5.84 (dt, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 4.14 (t, *J* = 7.7 Hz, 1H), 3.69 (s, 3H), 3.02 (dtd, *J* = 8.9 Hz, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H), 2.86 (dddd, *J* = 14.9 Hz, *J* = 7.9 Hz, *J* = 7.0 Hz, *J* = 1.6 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 166.4, 162.2, 144.8, 139.4, 129.0 (2C), 127.7, 127.6 (2C), 125.3, 123.5, 122.9, 111.6, 108.1, 51.5, 44.7, 36.8; HRMS (ES+): calcd. for: $C_{17}H_{15}NO_3$ $[M+Na]^+$ 304.0950, found 304.0951; the er was determined by UPC[2] using a chiral Chiralpack IC gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.2 mL/min; τ_{major} = 3.17 min, τ_{minor} = 3.11 min, (97:3 er).

Synthesis of (*S*,*E*)-methyl 5-(5-formylfuran-2-yl)-5-phenylpent-2-enoate (**9a**)



7a **9a**

Reaction was carried out in the modified literature procedure.[4] To a stirred solution of **7a** (0.1 mmol, 32.6 mg) in MeCN (0.2 mL) 50% glyoxylic acid in H_2O (0.4 mL) was added and reaction mixture was stirred for 48 h. After this time water (5 mL) was added and resulting mixture was extracted with CH_2Cl_2 (3x10 mL). Combined organic layers were dried over anhydrous $MgSO_4$, filtered and solvents were evaporated. Crude product was purified by flash chromatography (dichloromethane/hexanes 90:10 *v/v*) to obtain aldehyde **9a** (24.1 mg, 85%) as a colorless oil. R_f = 0.1 (dichloromethane); $[\alpha]_D^{25}$= 12.2 (CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 9.55 (s, 1H), 7.35 – 7.31 (m, 2H), 7.27 (dt, *J* = 3.8, 1.6 Hz, 1H), 7.25 (dt, *J* = 3.0, 1.8 Hz, 2H), 7.15 (d, *J* = 3.6 Hz, 1H), 6.82 (dt, *J* = 15.6, 7.1 Hz, 1H), 6.26 (dd, *J* = 3.6, 0.5 Hz, 1H), 5.84 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.20 (t, *J* = 7.7 Hz, 1H), 3.68 (s, 3H), 3.09 (dtd, *J* = 8.8, 7.4, 1.5 Hz, 1H), 2.88 (dddd, *J* = 16.5, 8.2, 7.1, 1.5 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 177.2, 166.4, 163.3, 152.3, 145.0 (2C), 139.5, 128.9 (2C), 127.8 (2C), 127.6, 123.4, 109.5, 51.5, 44.9, 36.9; HRMS (ES+): calcd. for: $C_{17}H_{16}O_4$ $[M+Na]^+$ 307.0946, found 307.0946; the er was determined by UPC[2] using a chiral Chiralpack IG gradient from 100% CO_2 up to 40%; MeOH, 2.2 mL/min; τ_{major} = 2.70 min, τ_{minor} = 2.83 min, (97:3 er).

[3] J. Młochowski, K. Kloc and E. Kubicz, *J. Prakt. Chem.*, 1994, **336**, 467.

[4] R. J. Petroski, *Synth. Commun.*, 2006, **36**, 1727.

8. Crystal and X-ray data for (*S*,*E*)-methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)-1-methyl-1*H*-pyrrol-2-yl)-5-phenylpent-2-enoate (7n)

The single-crystal X-ray diffraction study at room temperature revealed that compound **7n** ($C_{20}H_{25}N_3O_2$) crystallizes in the non-centrosymmetric triclinic space group *P*1 (Z = 1) (Figure S1).

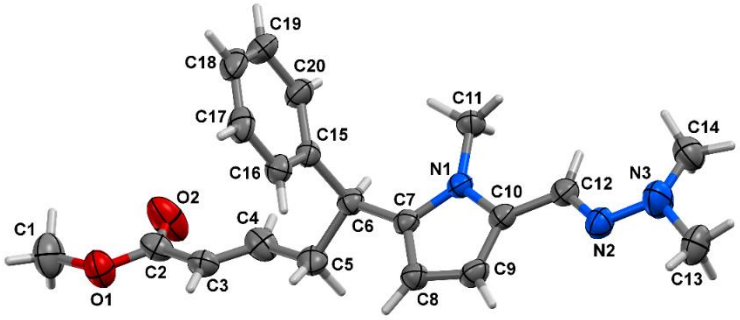


Figure S1. The molecular structure of the compound **7n** at room temperature, with atom numbering. The displacement ellipsoids are drawn at the 30% probability level.

Single crystal X-ray diffraction analysis was performed at 293 K by the ω-scan technique on a RIGAKU XtaLAB Synergy, Dualflex, Pilatus 300K diffractometer[5] with PhotonJet micro-focus X-ray Source Cu-Kα (λ = 1.54184 Å). Data collection, cell refinement, data reduction and absorption correction were performed using CrysAlis PRO software[5]. The crystal structure was solved by using direct methods with the SHELXT 2018/2 program[6]. Atomic scattering factors were taken from the International Tables for X-ray Crystallography. Positional parameters of non-H-atoms were refined by a full-matrix least-squares method on F^2 with anisotropic thermal parameters by using the SHELXL 2018/3 program[7]. All hydrogen atoms were found from the difference Fourier maps and for further calculations they were positioned geometrically in calculated positions (C–H = 0.93–0.97 Å) and constrained to ride on their parent atoms with isotropic displacement parameters set to 1.2-1.5 times the U_{eq} of the parent atom.

7n: Formula $C_{20}H_{25}N_3O_2$, triclinic, space group *P*1, *Z* = 1, unit cell constants *a* = 6.4512(1), *b* = 8.5325(2), *c* = 8.7429(2) Å, α = 91.537(2), β = 93.551(2), γ = 91.604(2)°, *V* = 479.943(17) Å^3. A total of 9488 reflections angles in the range of 5.07 to 66.60° were collected of which 3227 were unique (R_{int} = 1.26%) and 3193 of these were greater than 2σ(I). The final anisotropic full-matrix least-squares refinement on F^2 with 231 parameters converged at R_1 = 3.50% and wR_2 = 9.26% for all data. The largest peak in the final difference electron density synthesis was 0.224 e Å^{-3} and the largest hole was -0.178 e Å^{-3}. The goodness-of-fit was 1.044. The absolute configuration was determined from anomalous scattering, by calculating the *x* Flack parameter[8] of -0.02(6) using 1485 quotients.

CCDC 2064989 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

[5] O. D. Rigaku. CrysAlis PRO. Rigaku Oxford Diffraction Ltd, Yarnton, Oxfordshire, England, 2019.

[6] G. M. Sheldrick, *Acta Cryst.*, 2015, **A71**, 3.

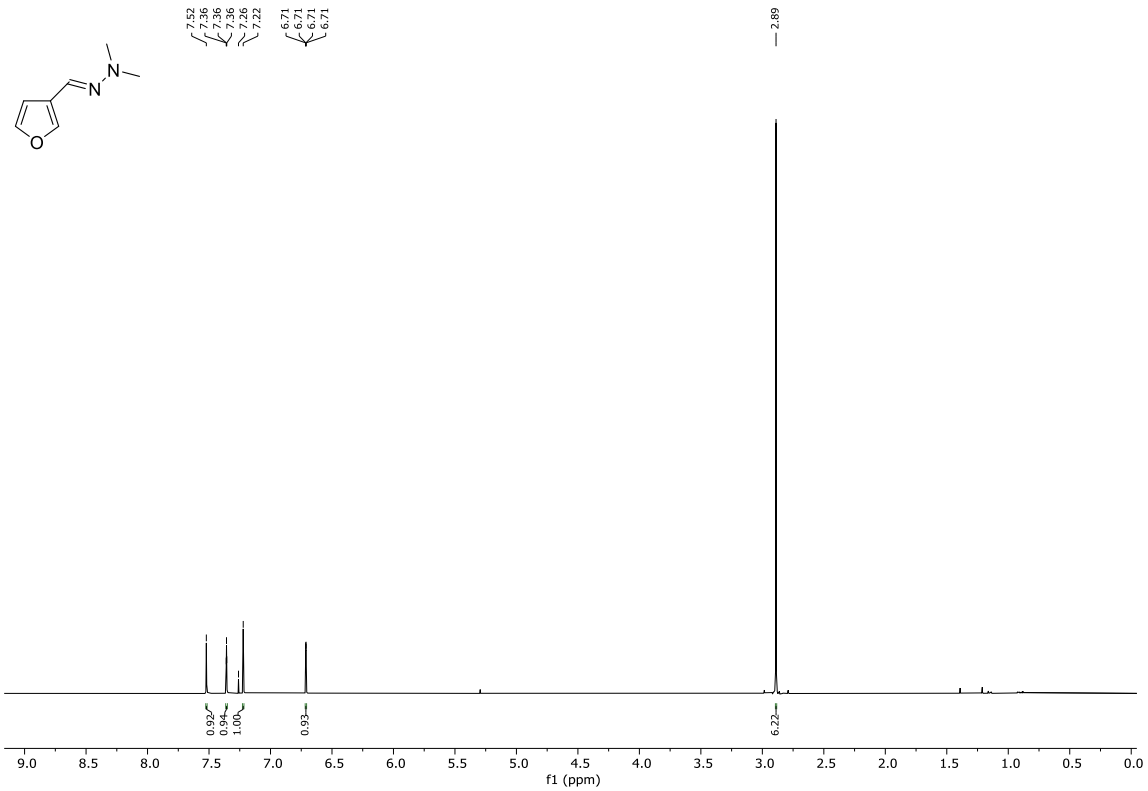
[7] G. M. Sheldrick, *Acta Cryst.*, 2015, **C71**, 3.

[8] S. Parsons, H. D. Flack and T. Wagner, *Acta Cryst.*, 2013, **B69**, 249.

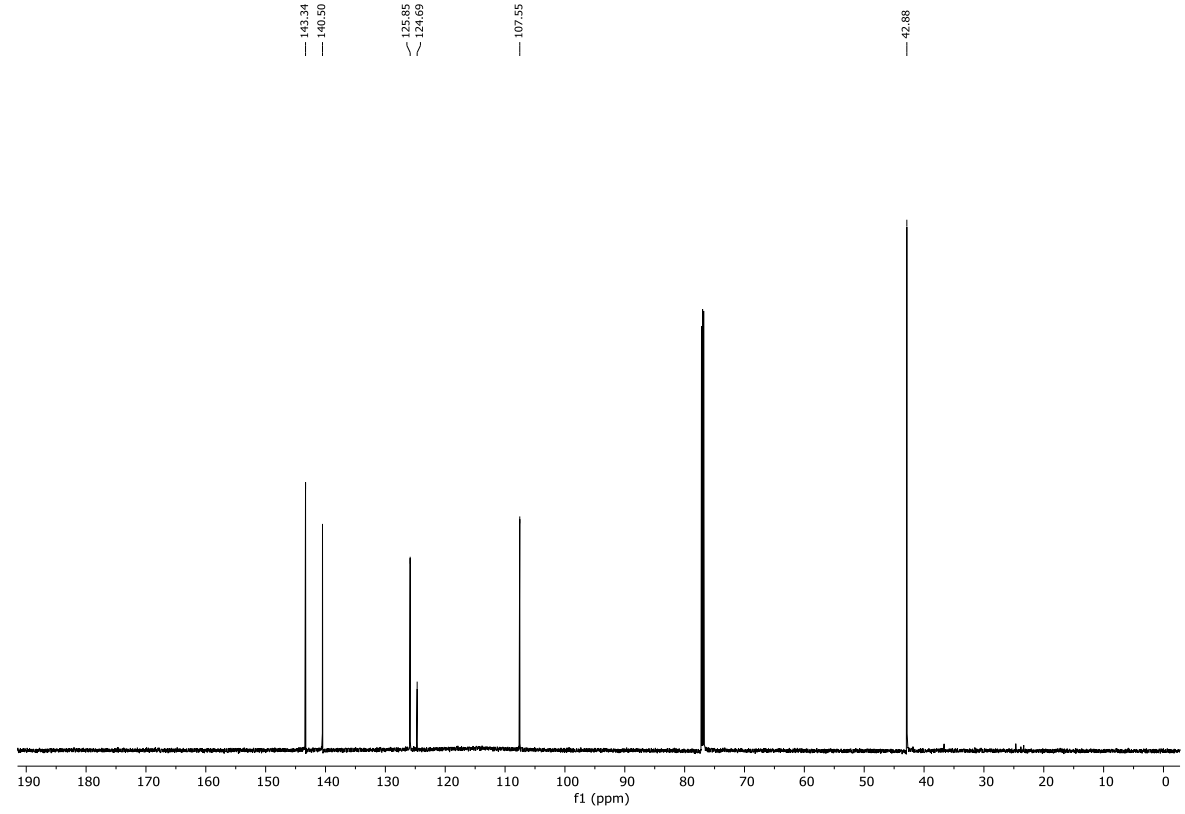
9. NMR data

3-Furfural *N*,*N*-dimethylhydrazone (**1b**)

^{1}H NMR

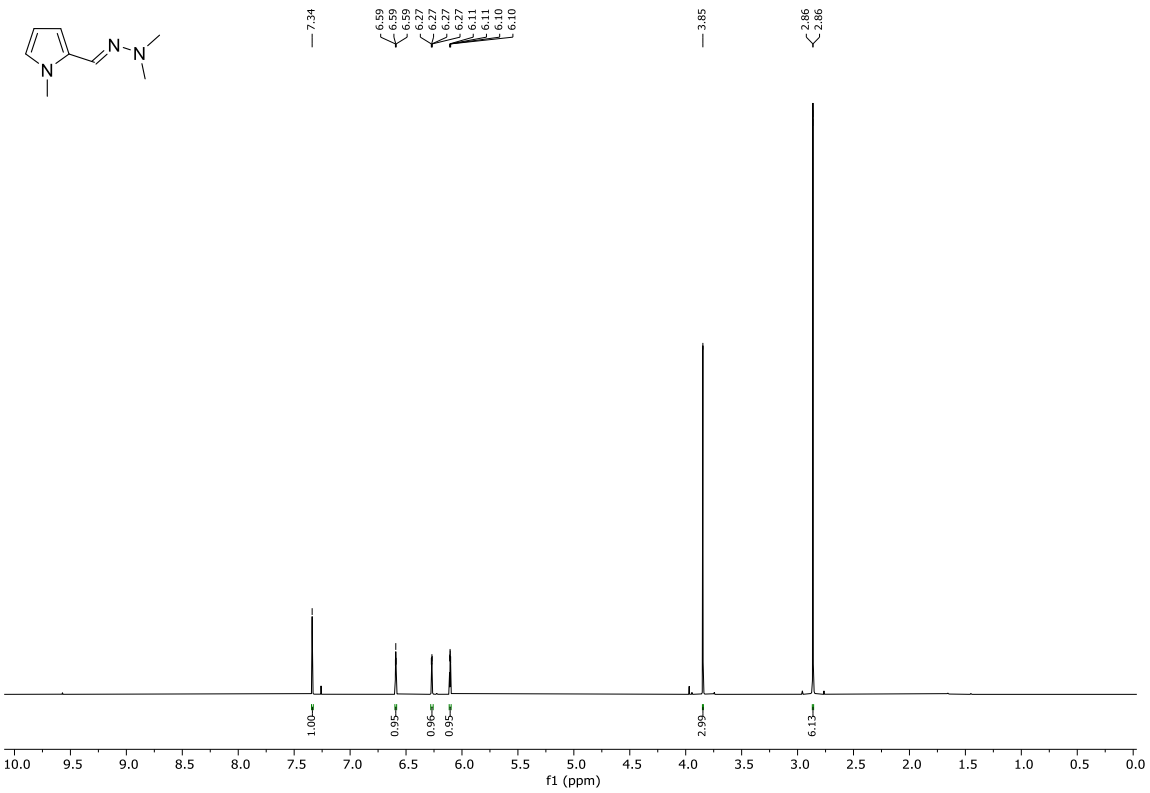


^{13}C NMR

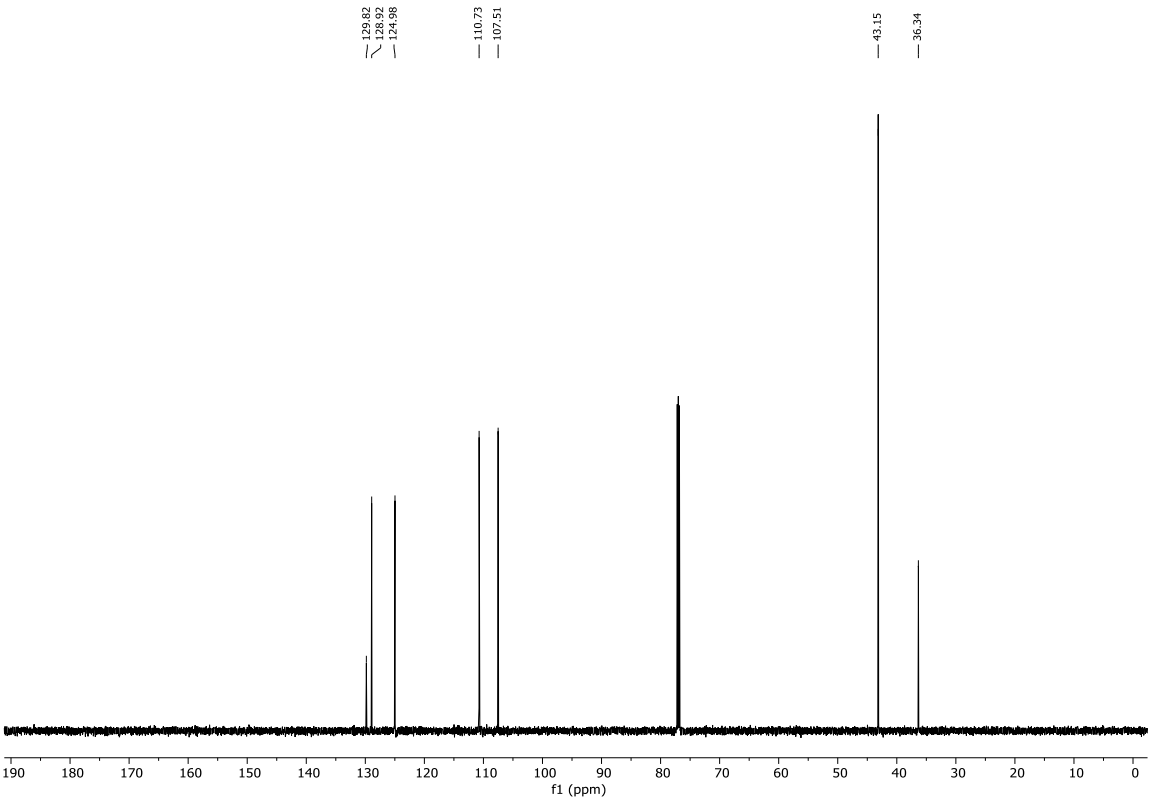


1-Methylpyrrole-2-carbaldehyde *N*,*N*-dimethylhydrazone (**1c**)

^{1}H NMR

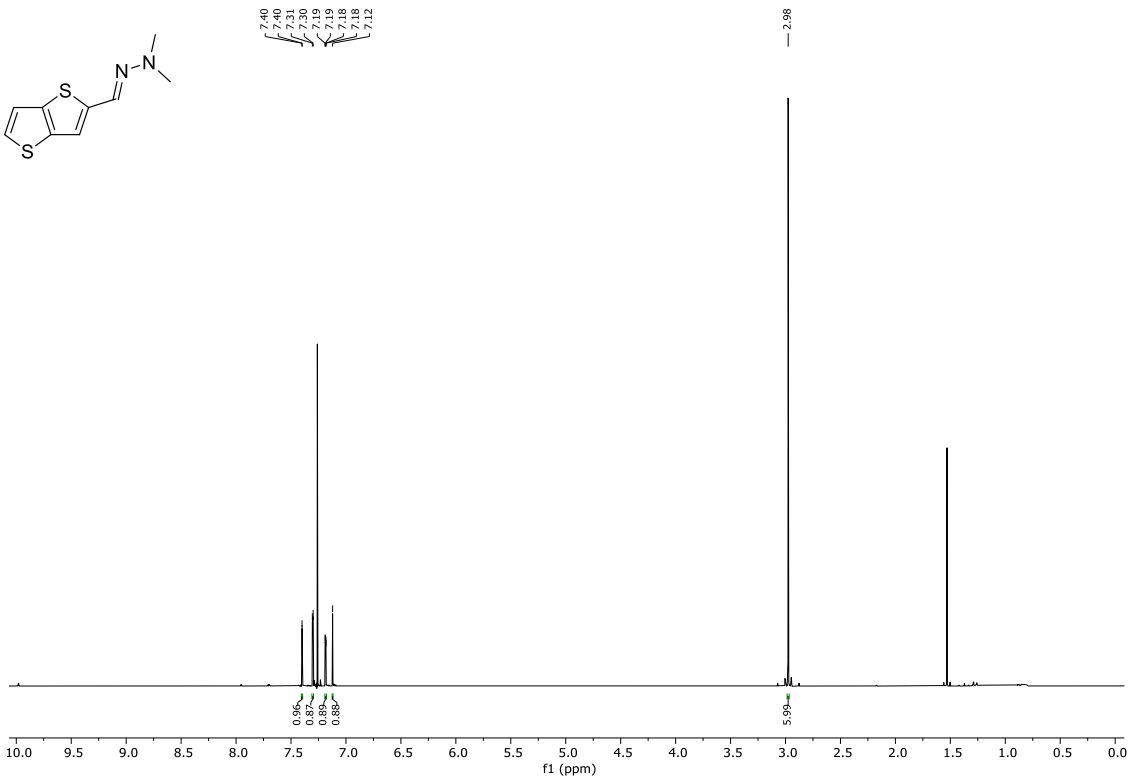


^{13}C NMR

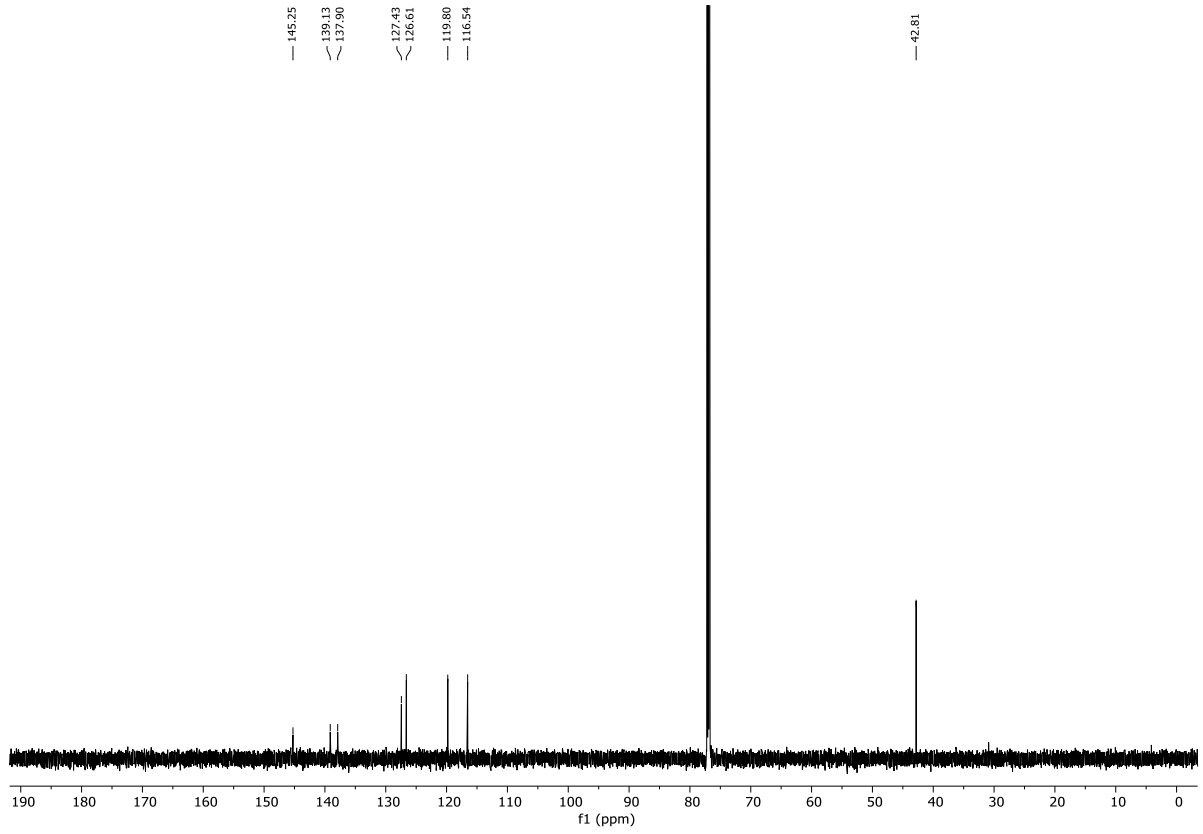


Thieno[3,2-b]thiophene-2-carbaldehyde *N*,*N*-dimethylhydrazone (**1d**)

^{1}H NMR

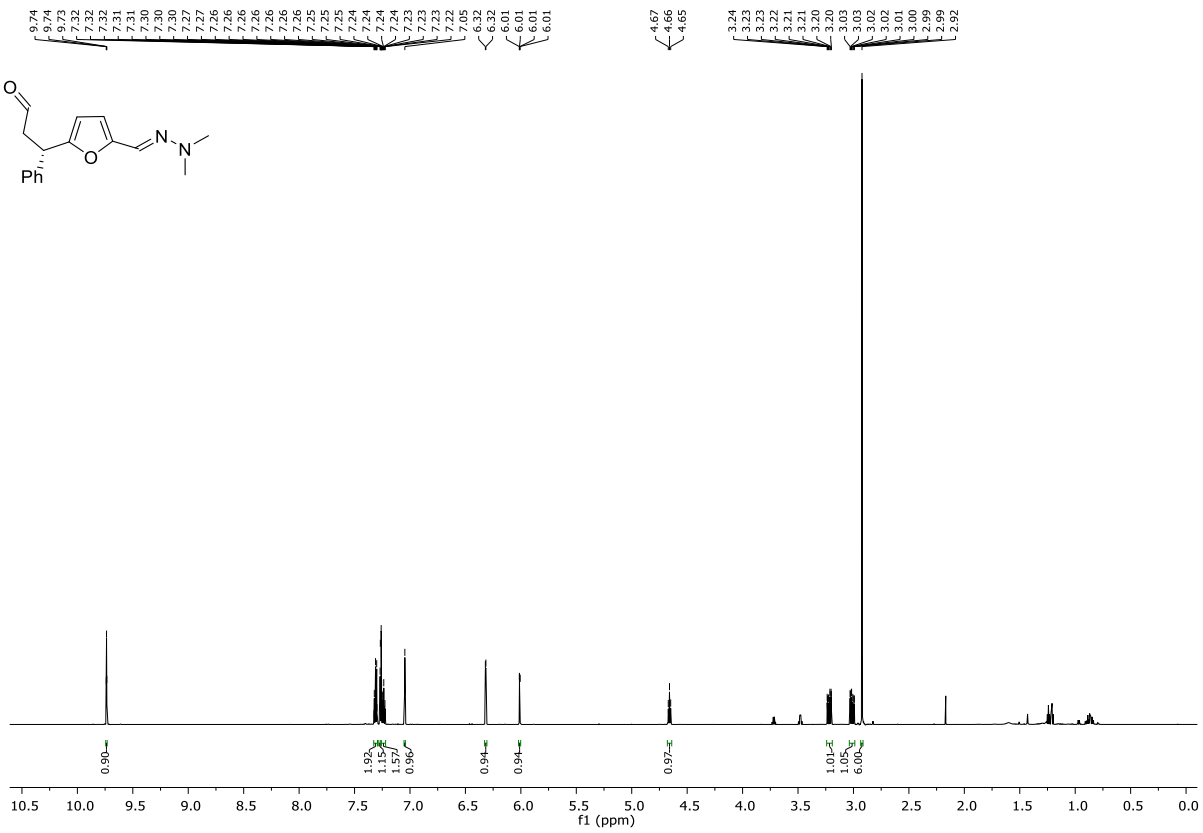


^{13}C NMR

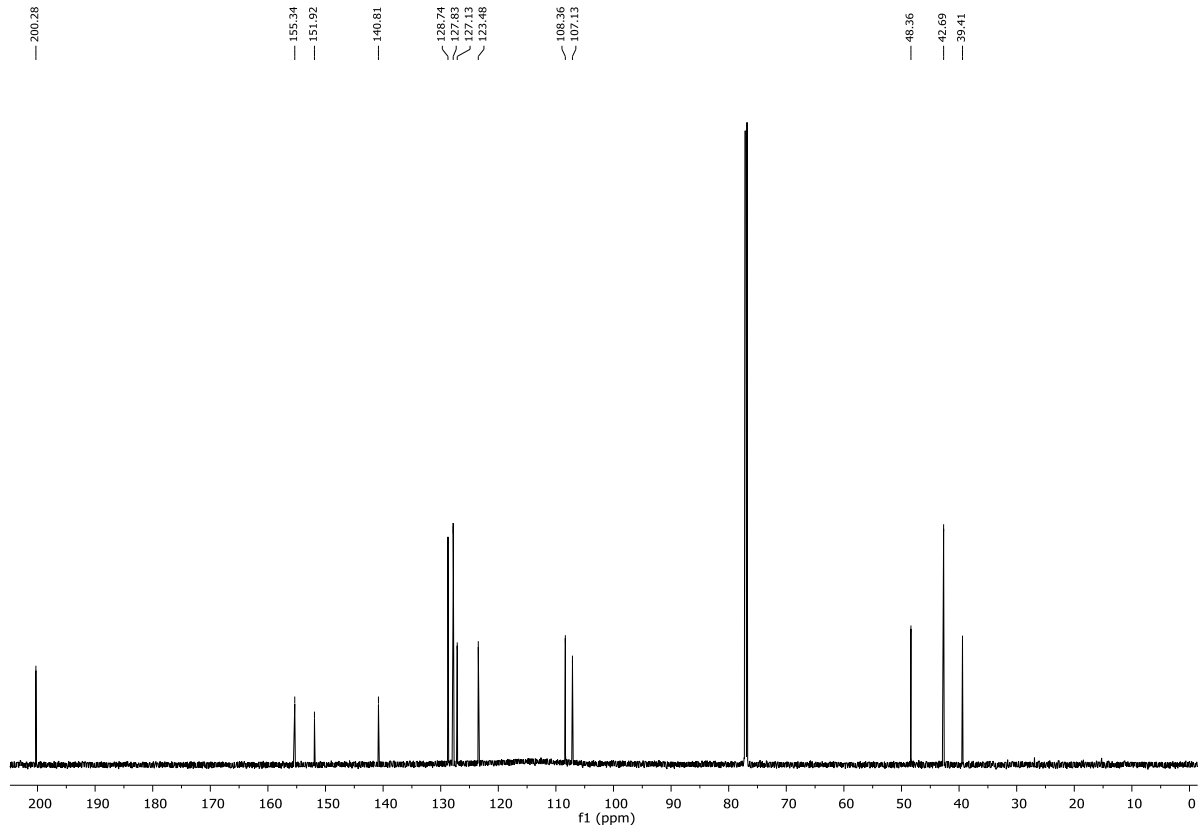


(*S*,*E*)-3-(5-((2,2-Dimethylhydrazono)methyl)furan-2-yl)-3-phenylpropanal (**5a**)

^{1}H NMR

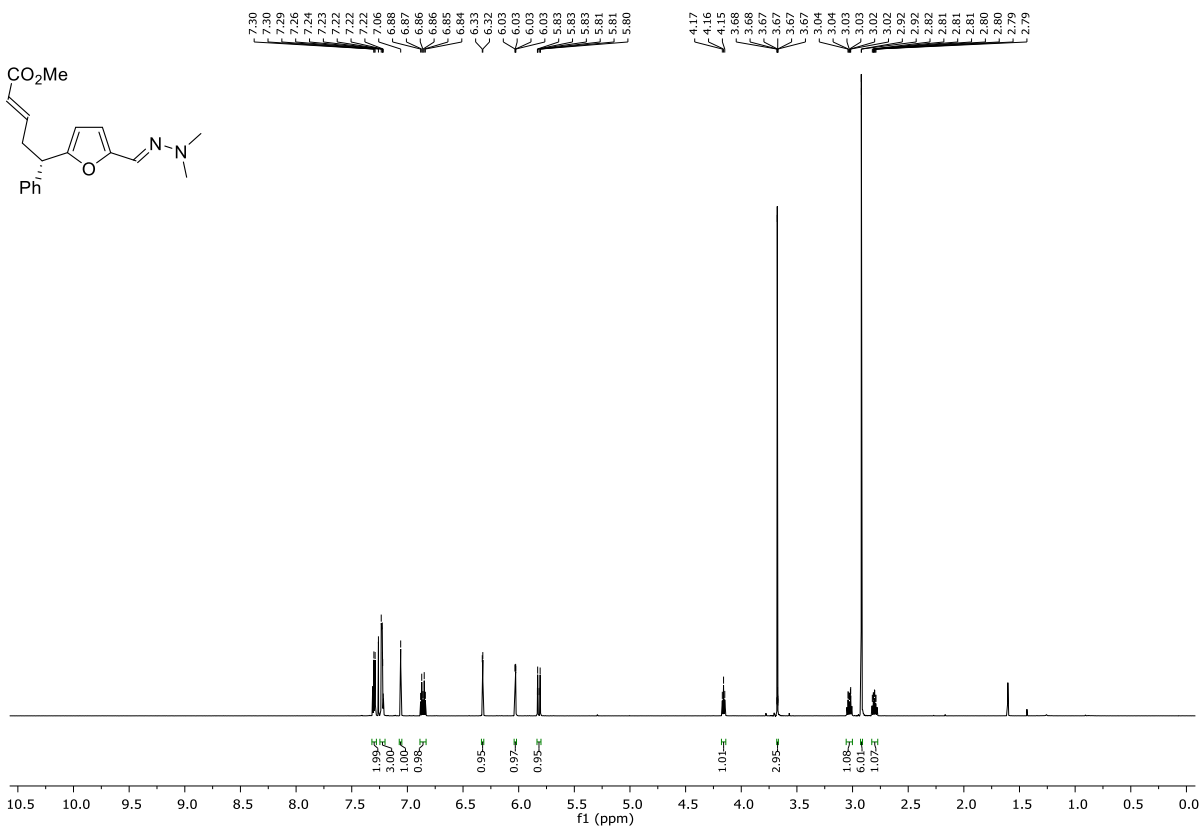


^{13}C NMR

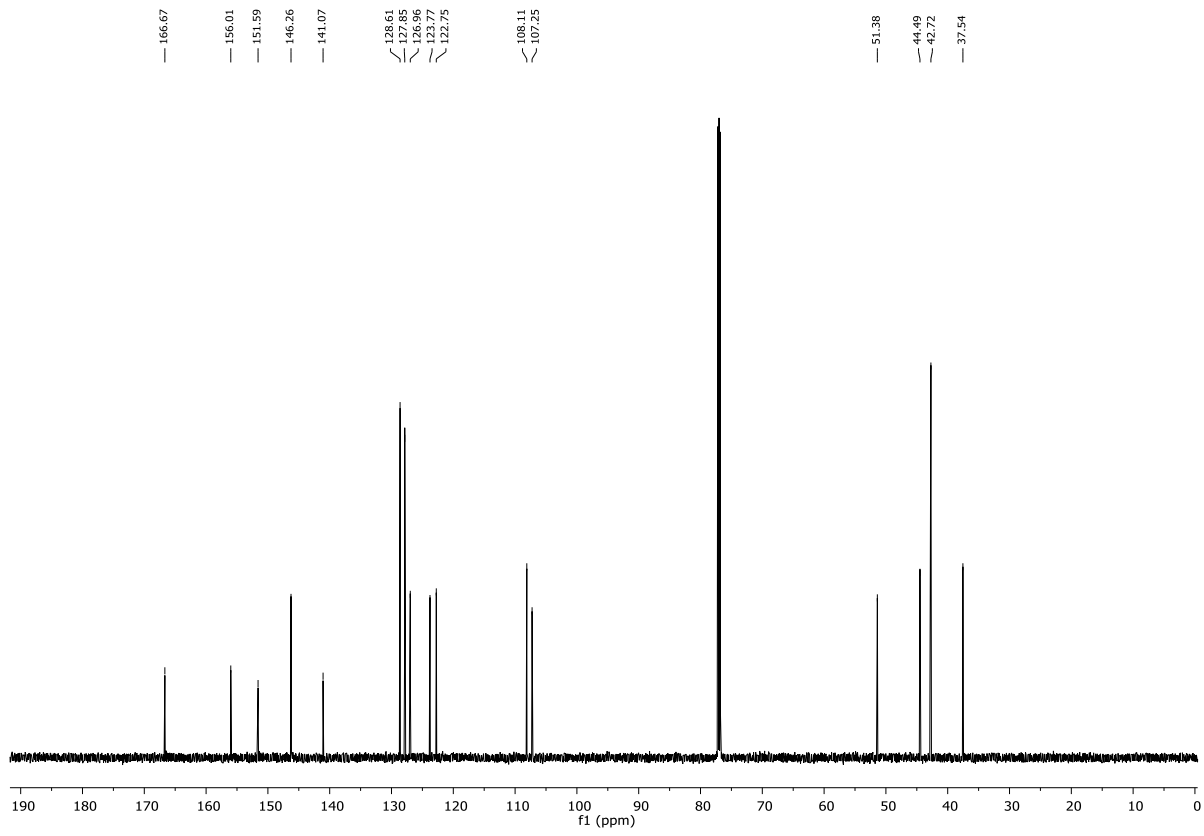


(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-phenylpent-2-enoate (**7a**)

^{1}H NMR

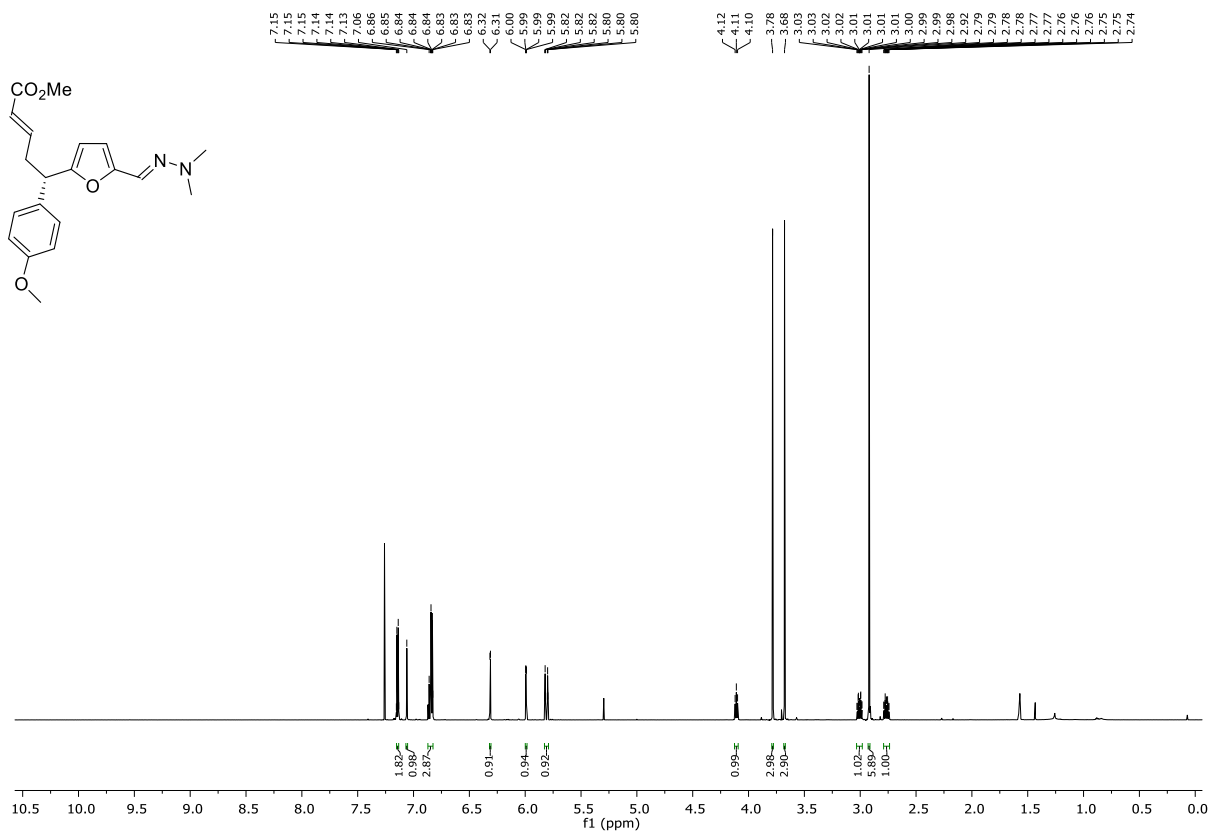


^{13}C NMR

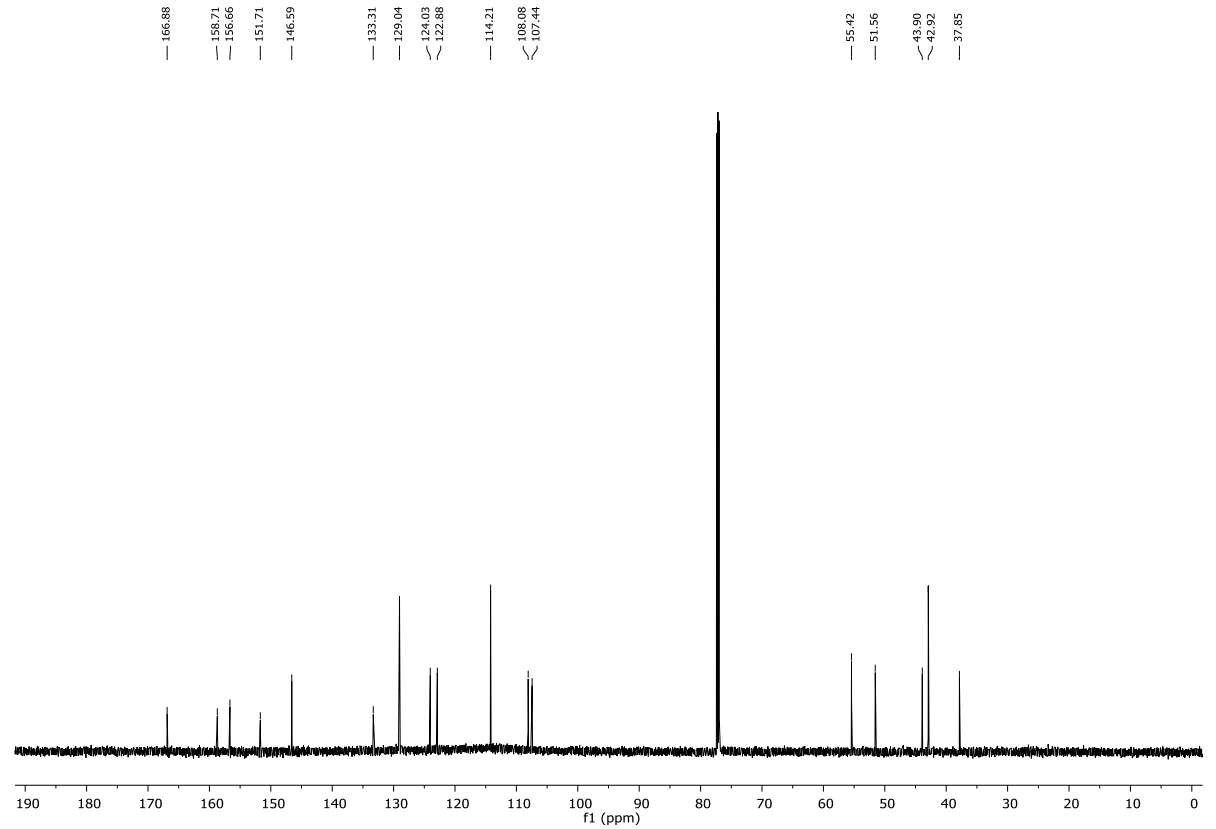


(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(4-methoxyphenyl)pent-2-enoate (**7b**)

^{1}H NMR

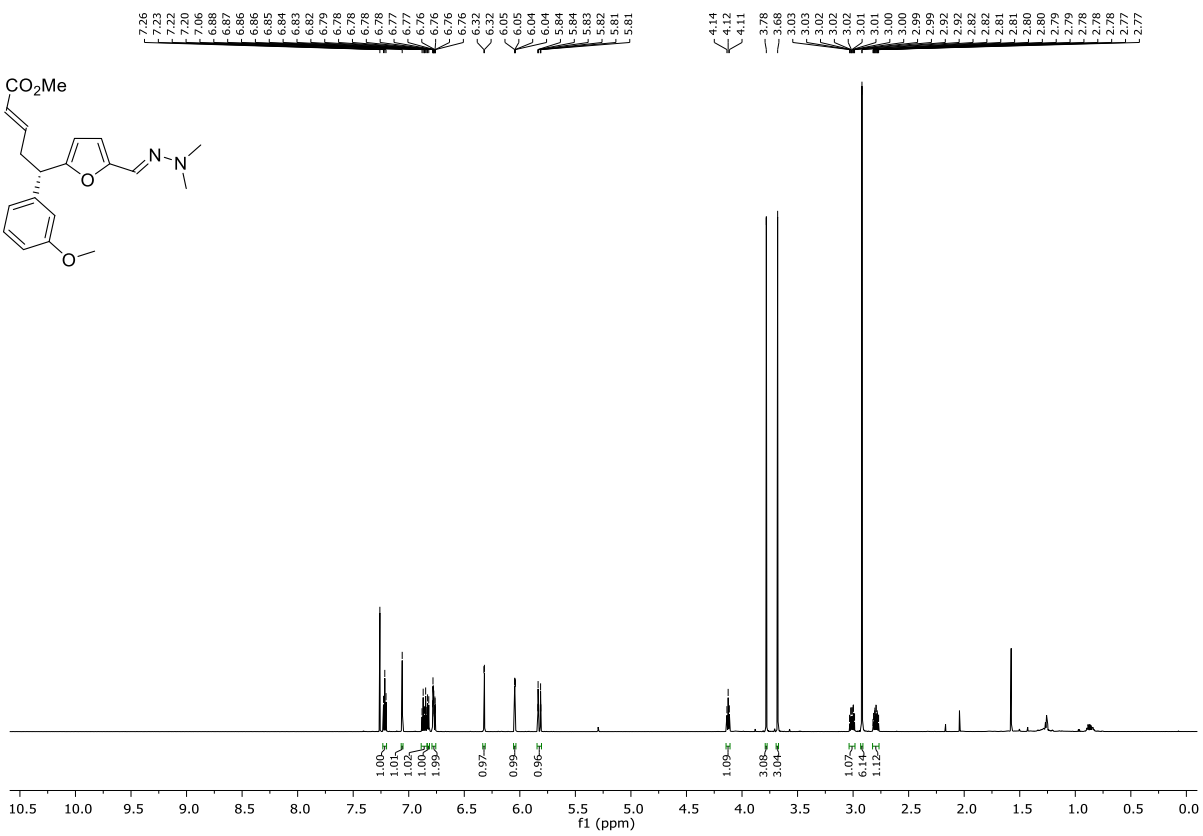


^{13}C NMR

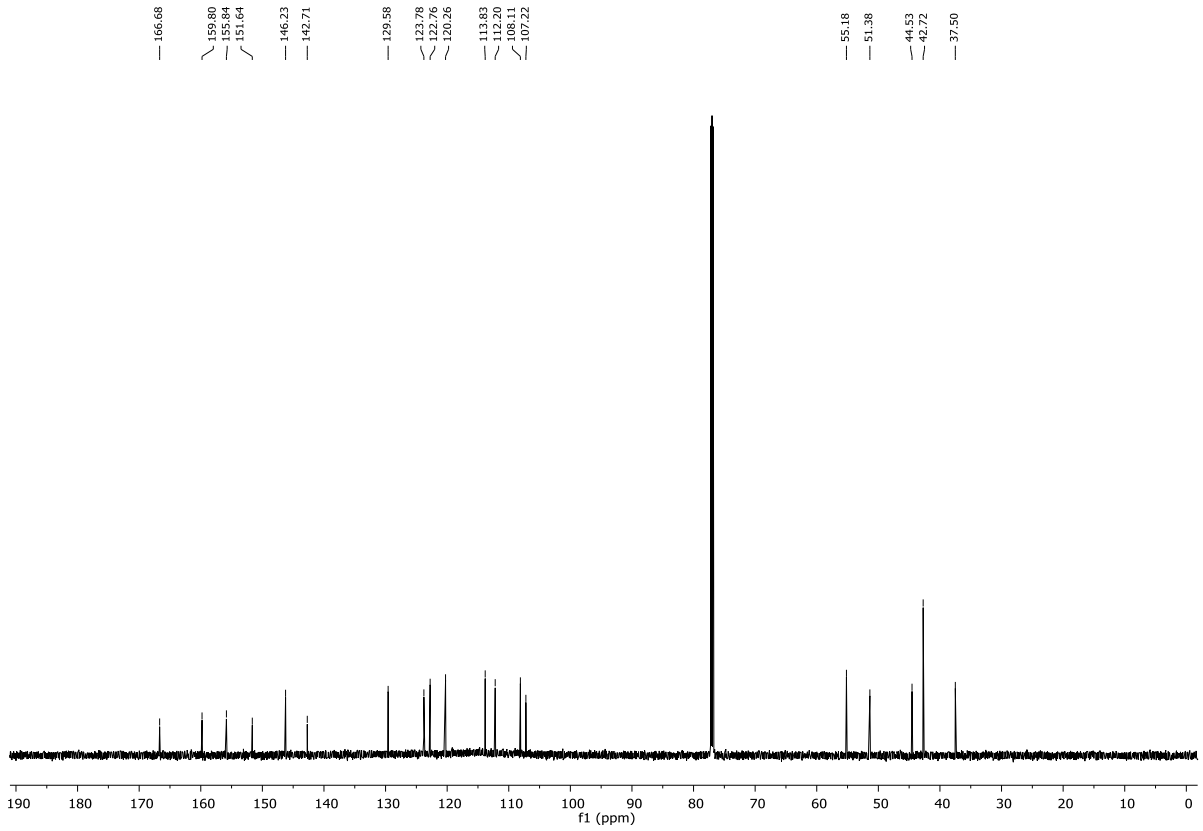


(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(3-methoxyphenyl)pent-2-enoate (**7c**)

^{1}H NMR

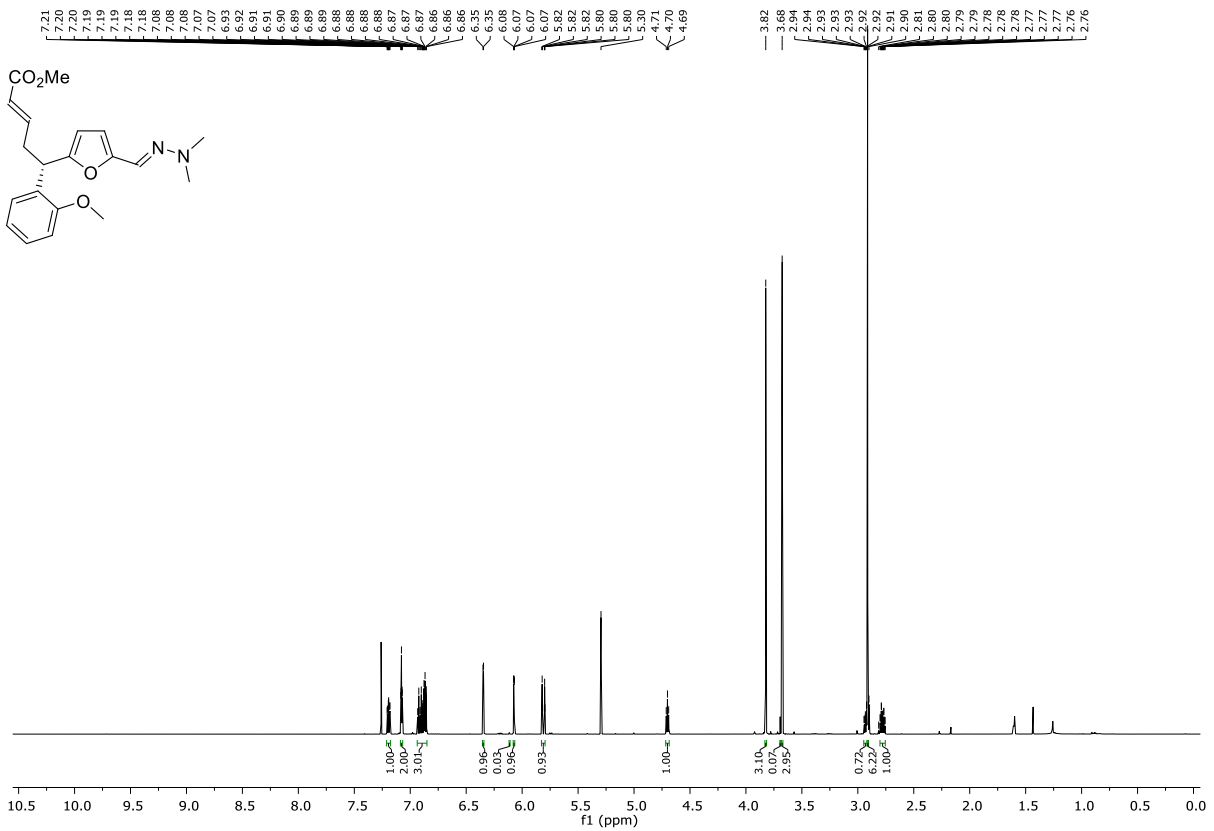


^{13}C NMR

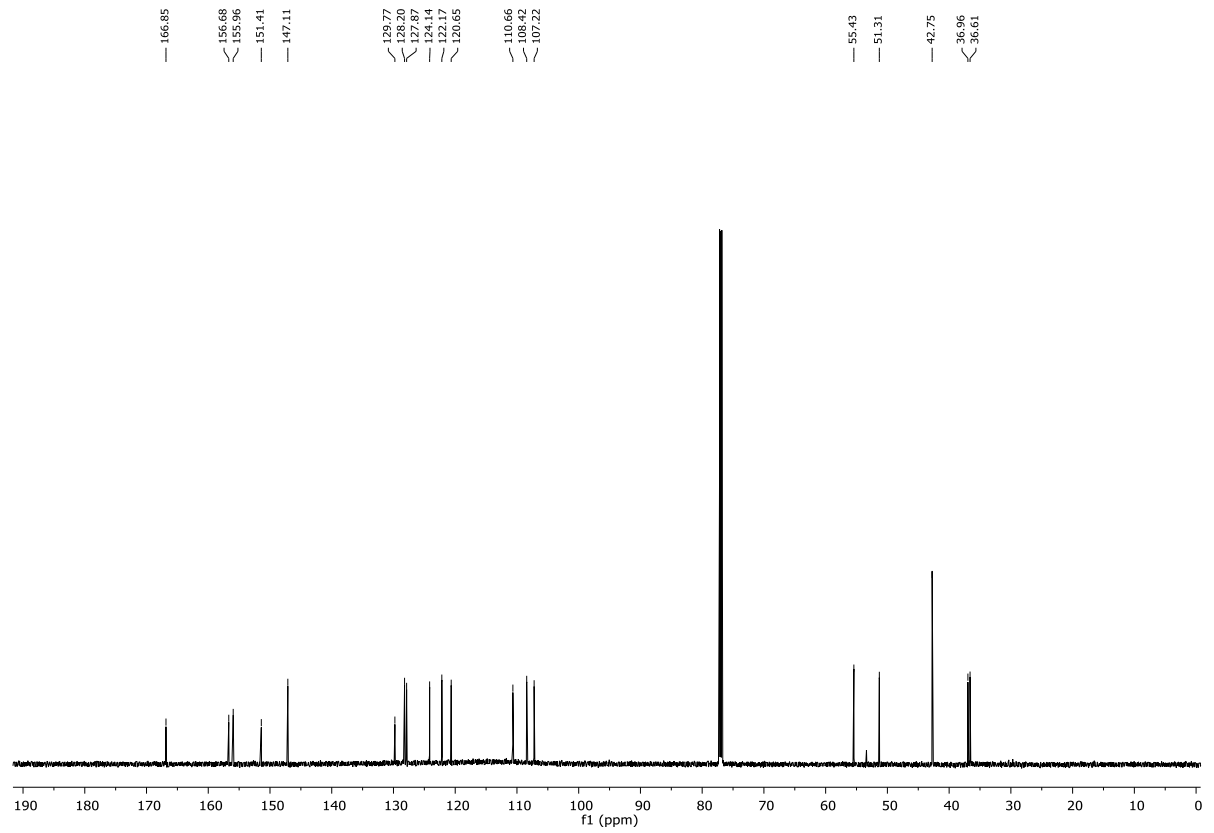


(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(2-methoxyphenyl)pent-2-enoate (**7d**)

^{1}H NMR

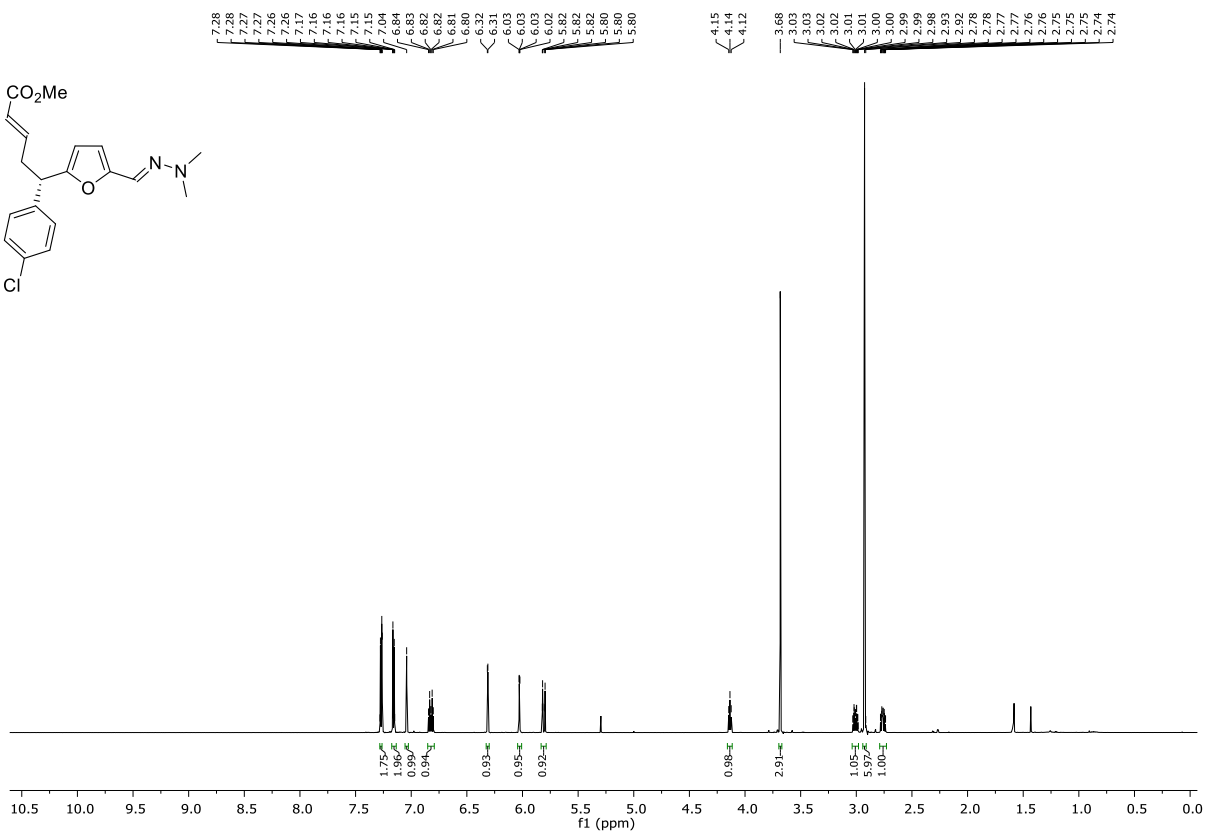


^{13}C NMR

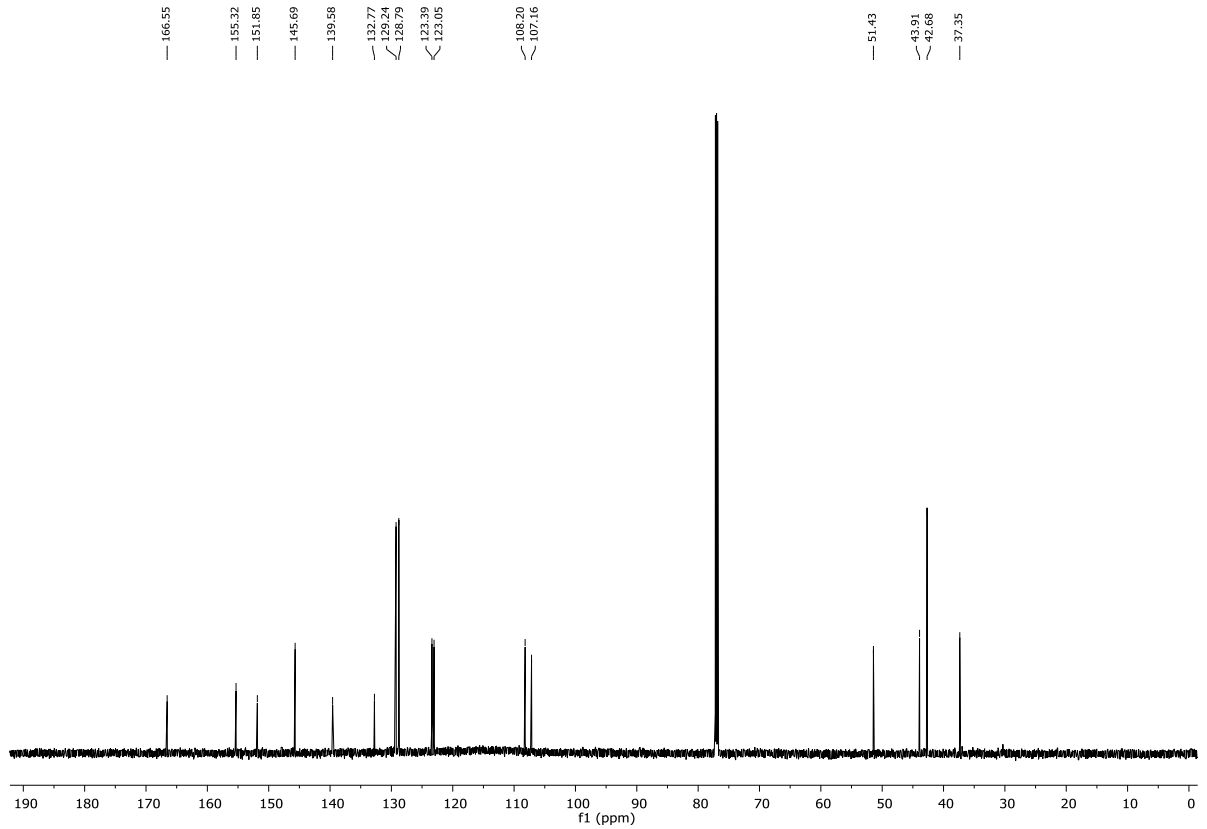


(*S*,*E*)-Methyl 5-(4-chlorophenyl)-5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)pent-2-enoate (**7e**)

^{1}H NMR

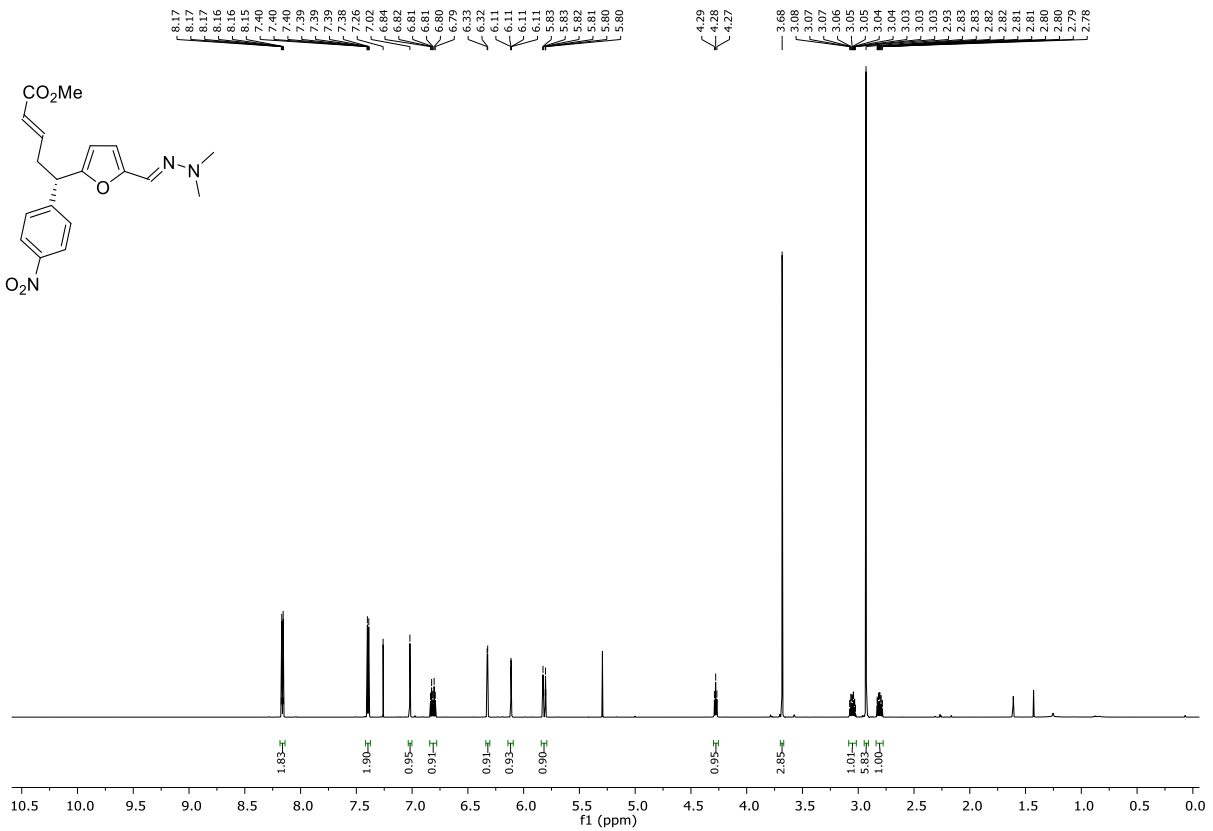


^{13}C NMR

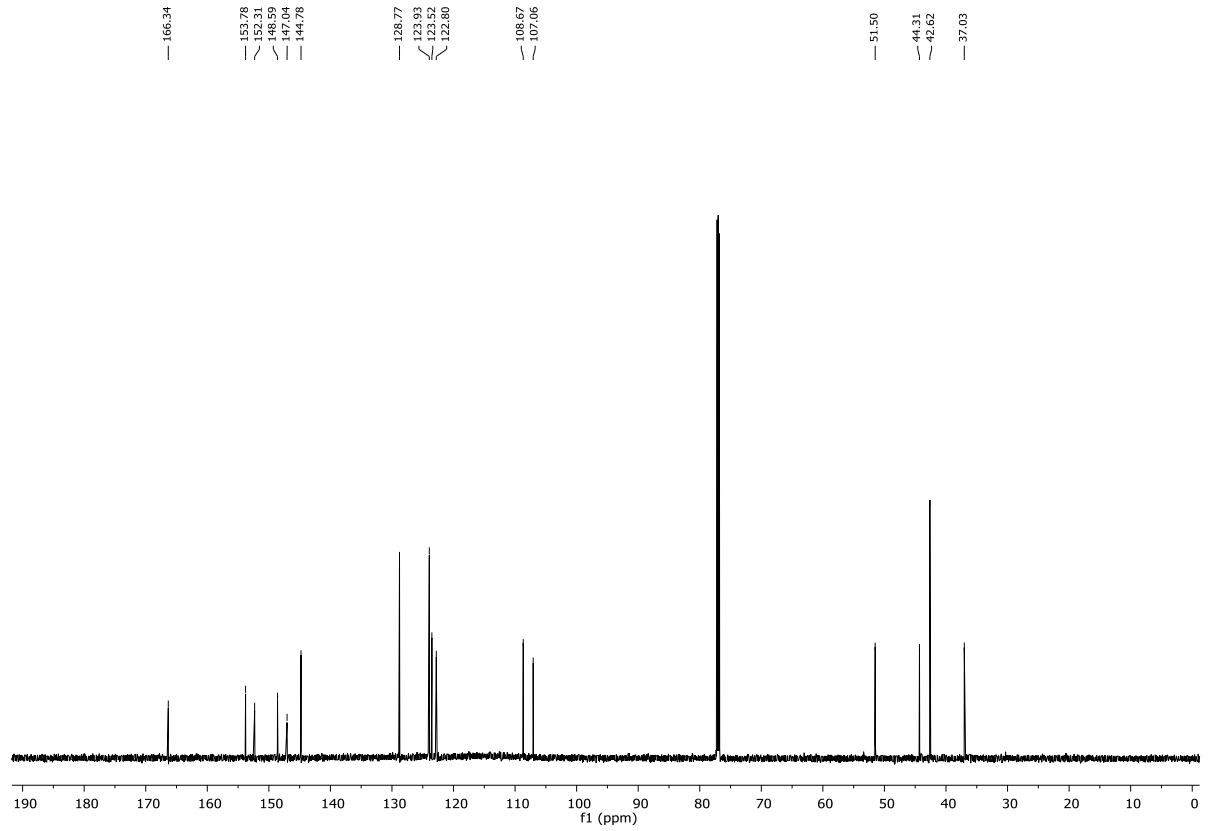


(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(4-nitrophenyl)pent-2-enoate (**7f**)

^{1}H NMR

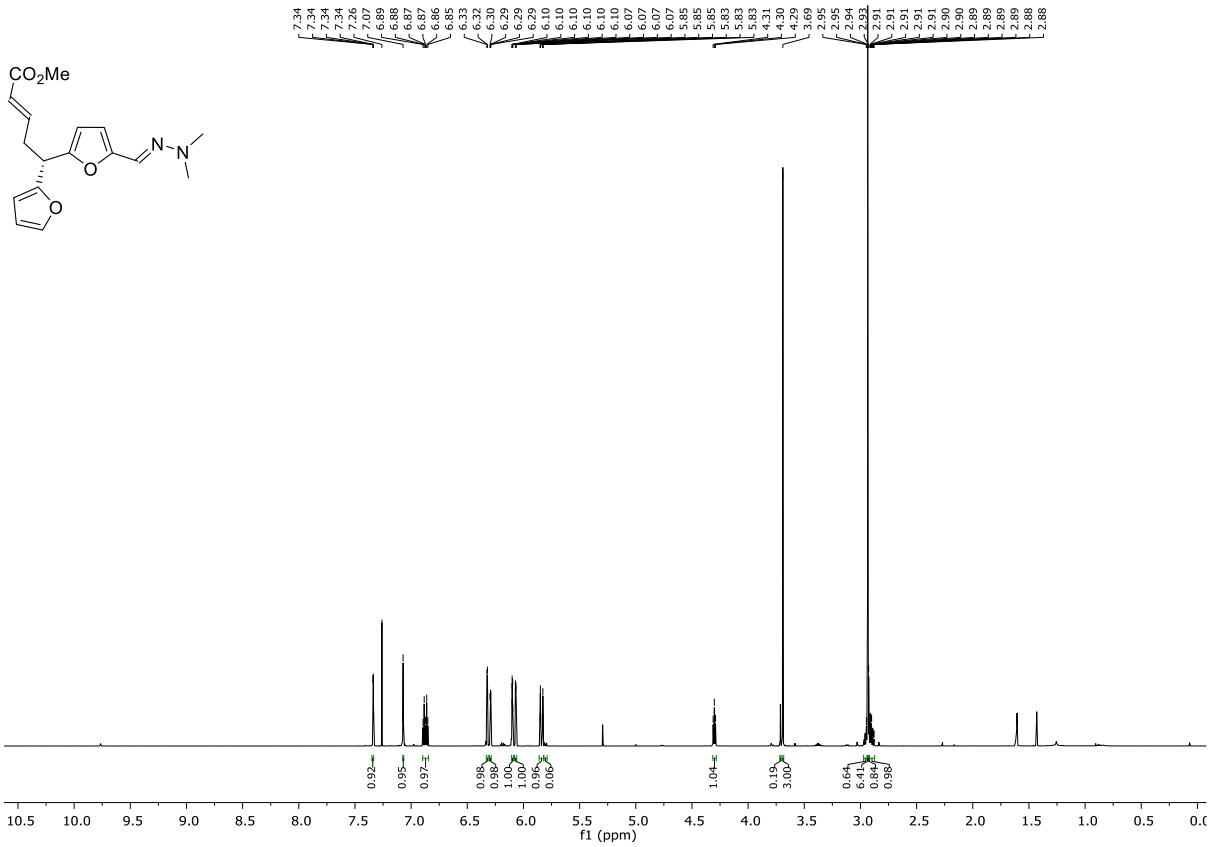


^{13}C NMR

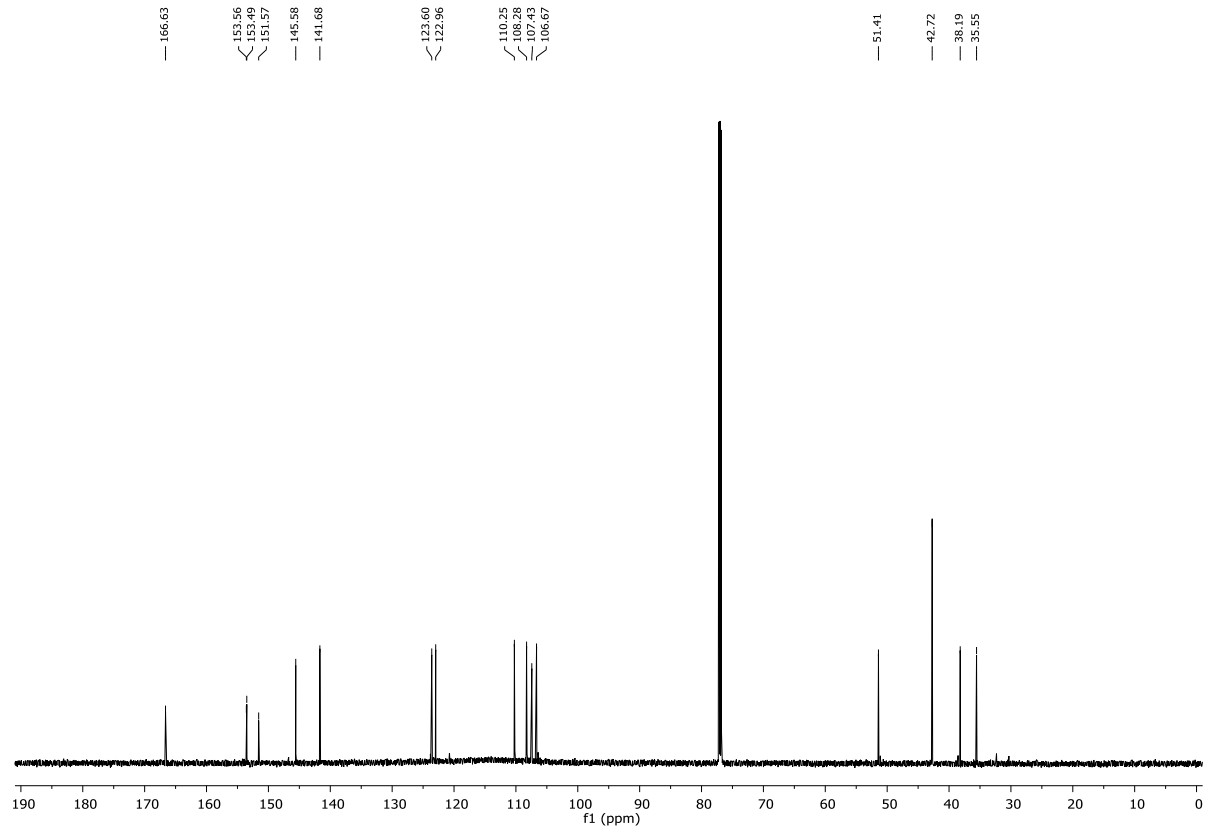


(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(furan-2-yl)pent-2-enoate (**7g**)

^{1}H NMR

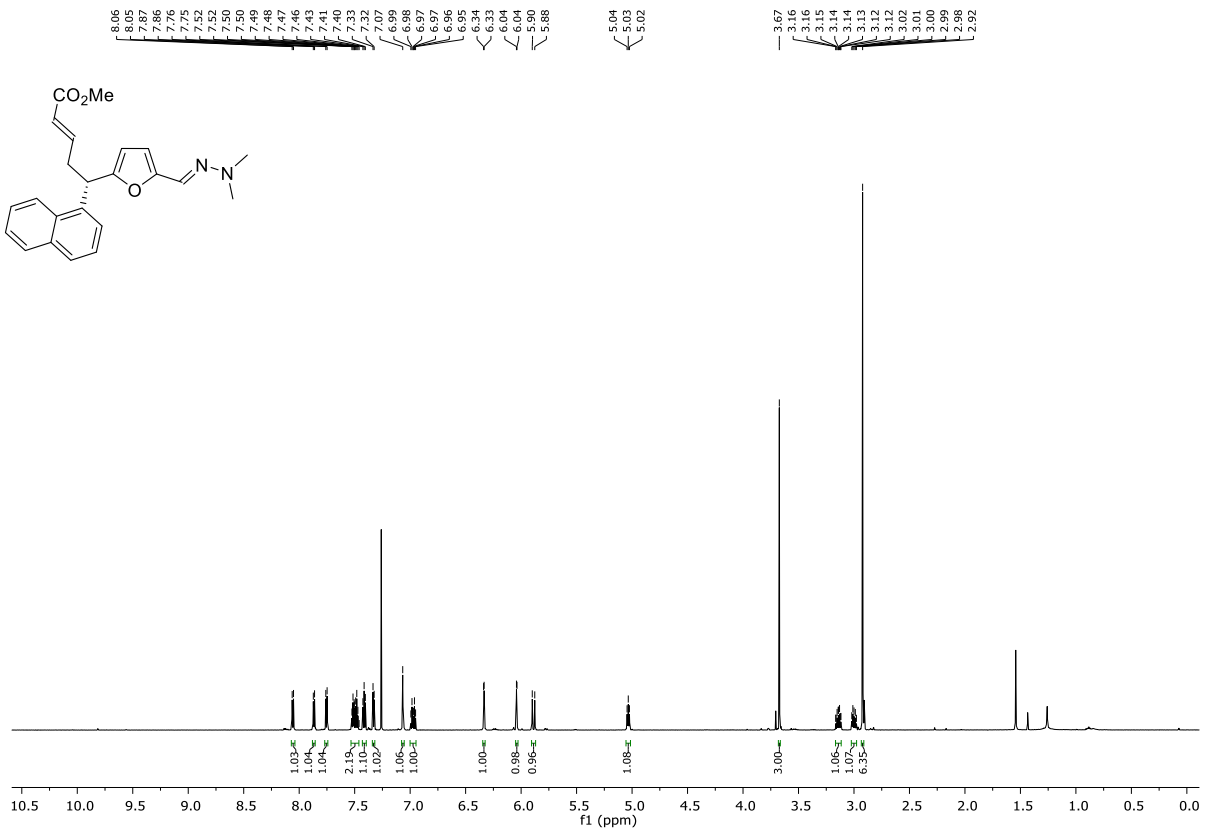


^{13}C NMR

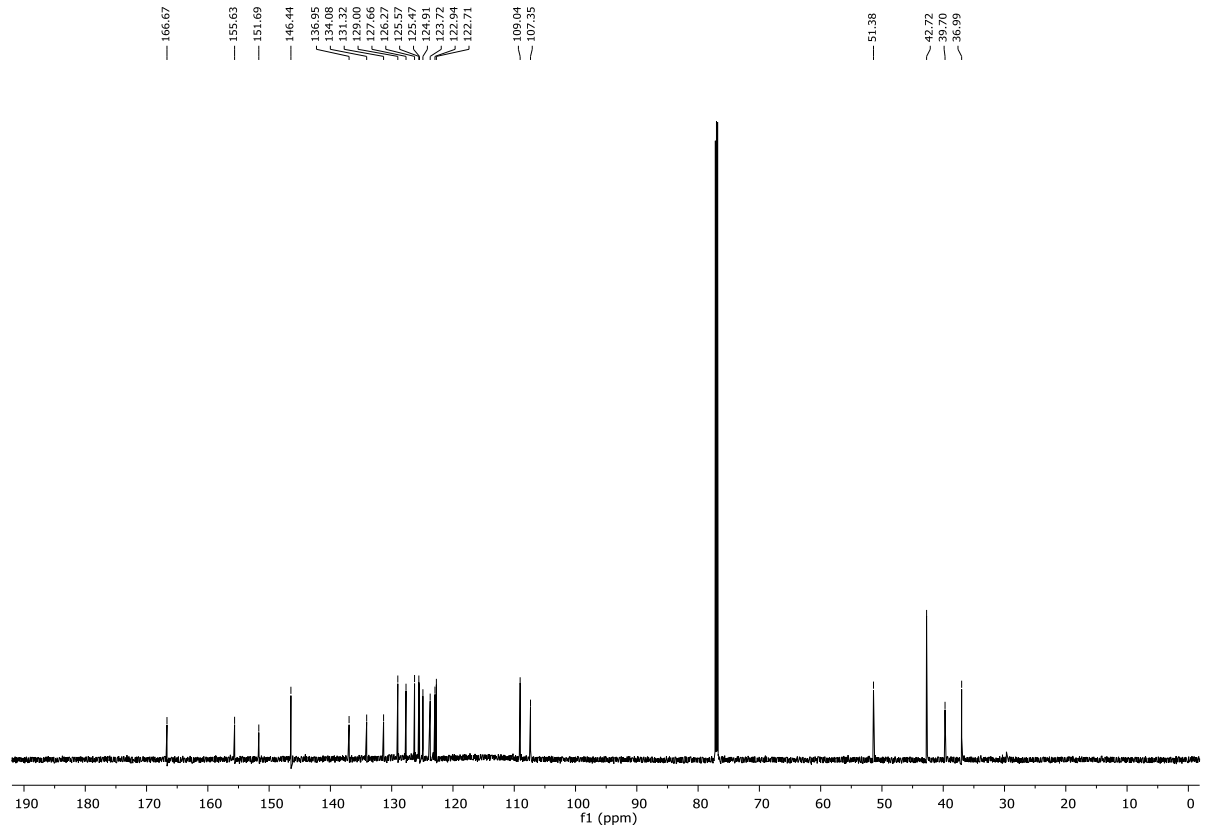


(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(naphthalen-1-yl)pent-2-enoate (**7h**)

^{1}H NMR

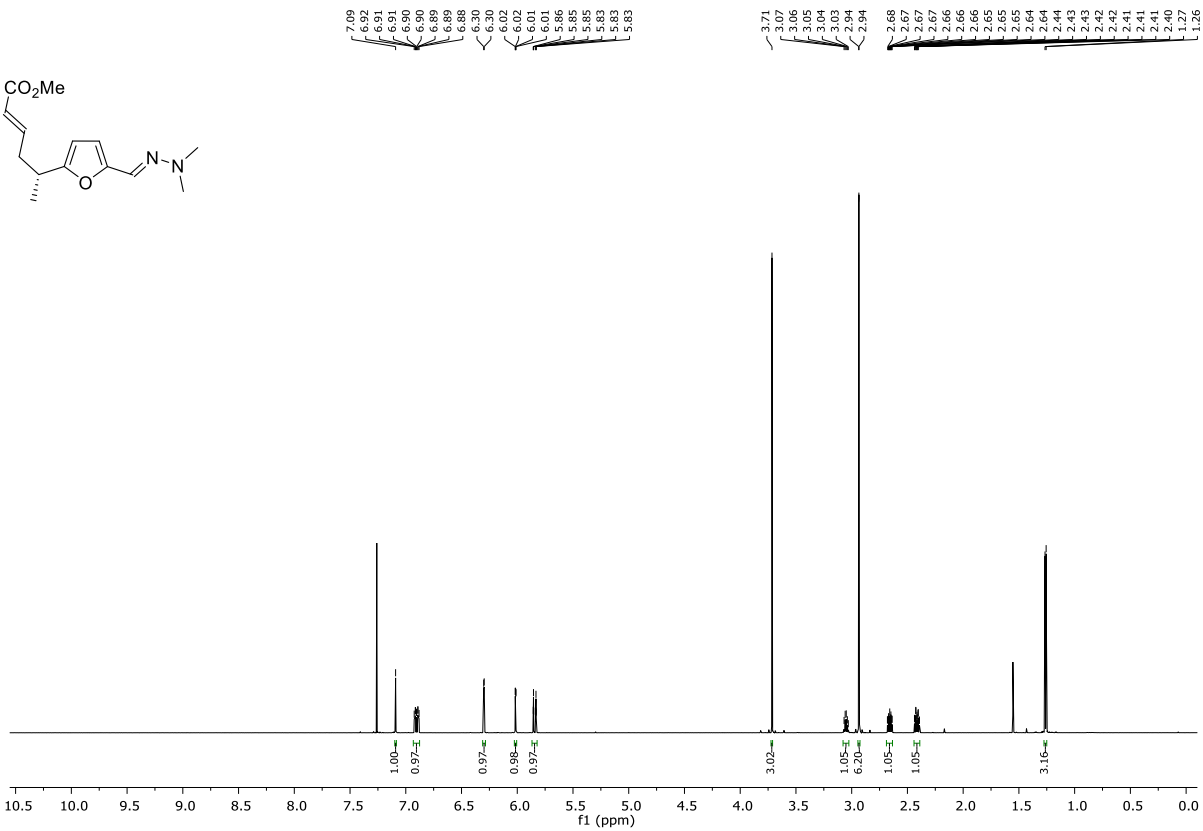


^{13}C NMR

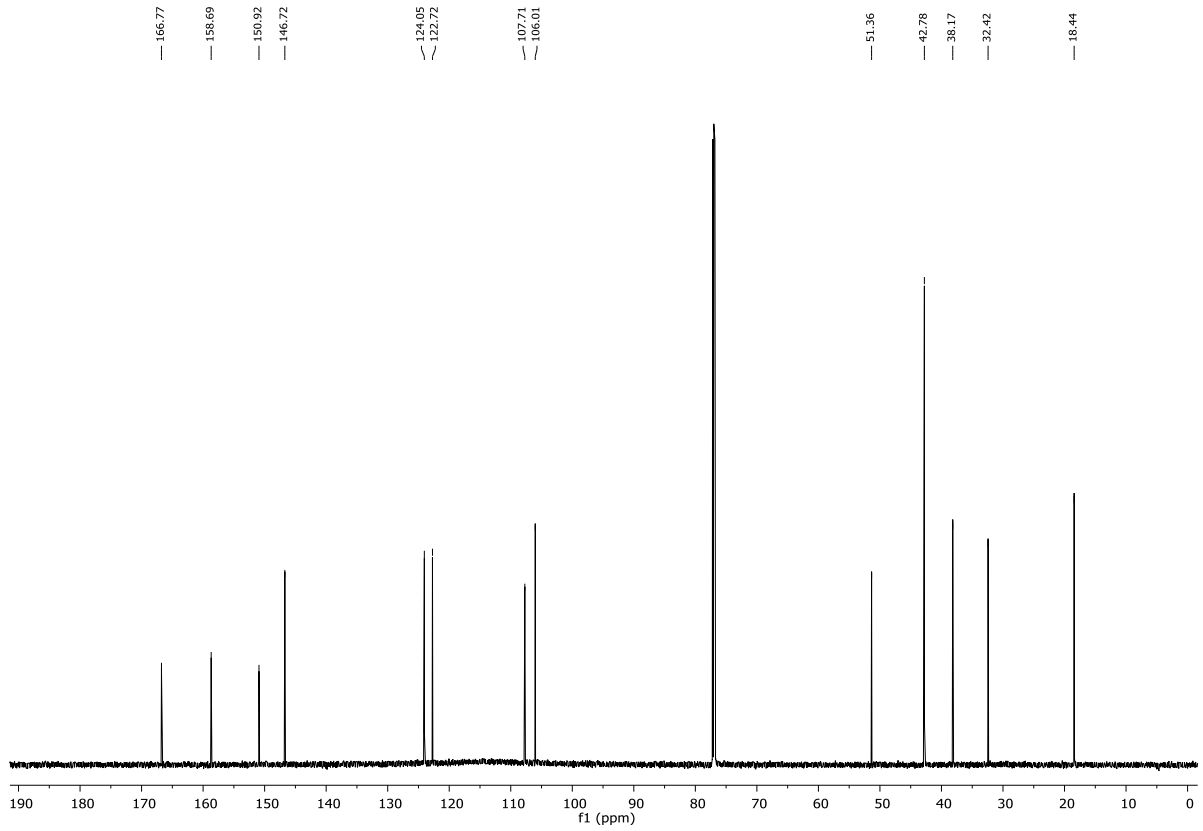


(*R*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)hex-2-enoate (**7i**)

^{1}H NMR

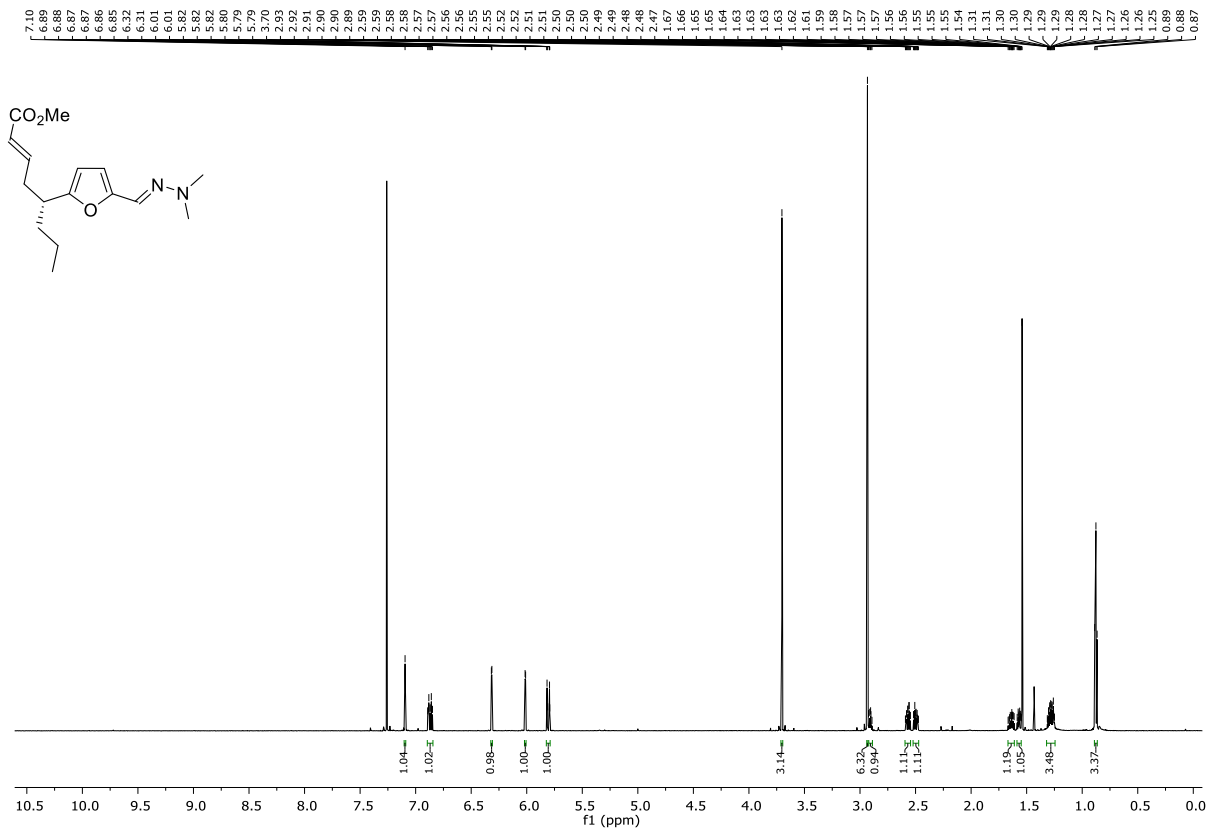


^{13}C NMR

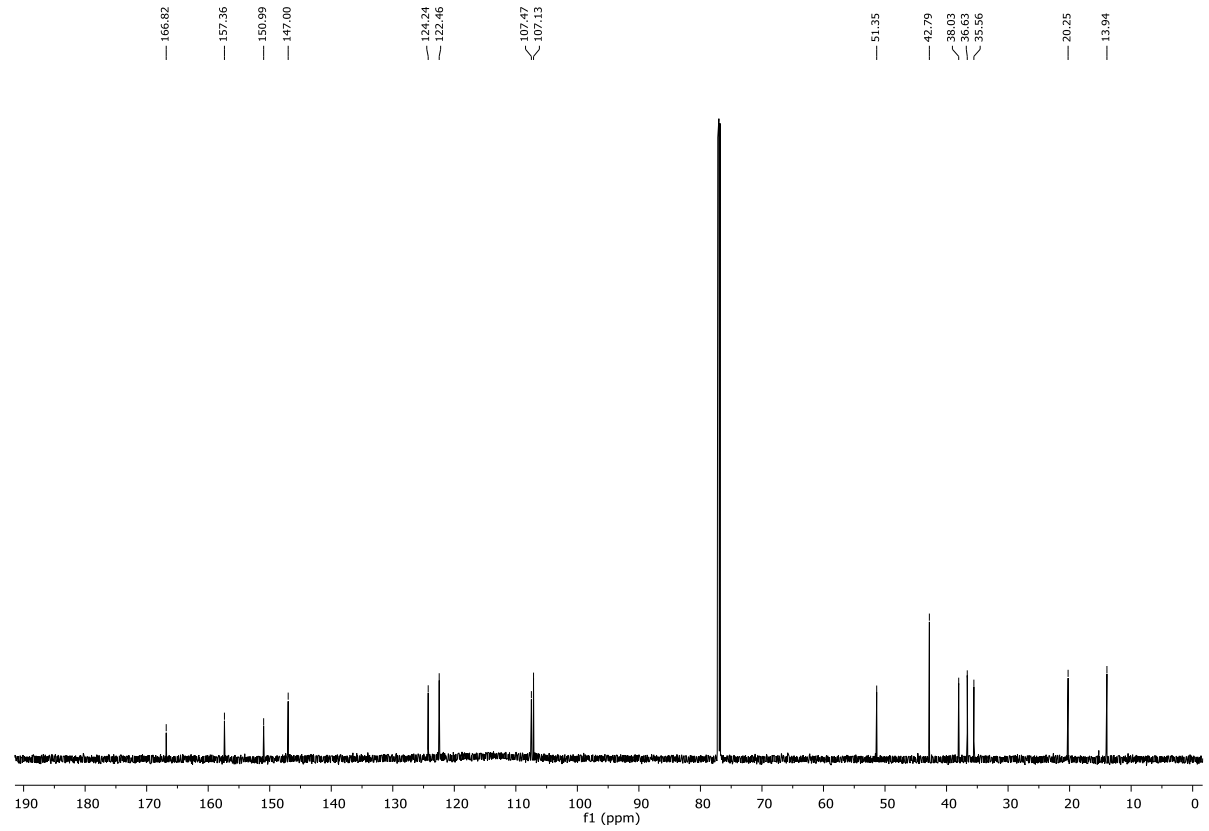


(*R*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)oct-2-enoate (**7j**)

^{1}H NMR

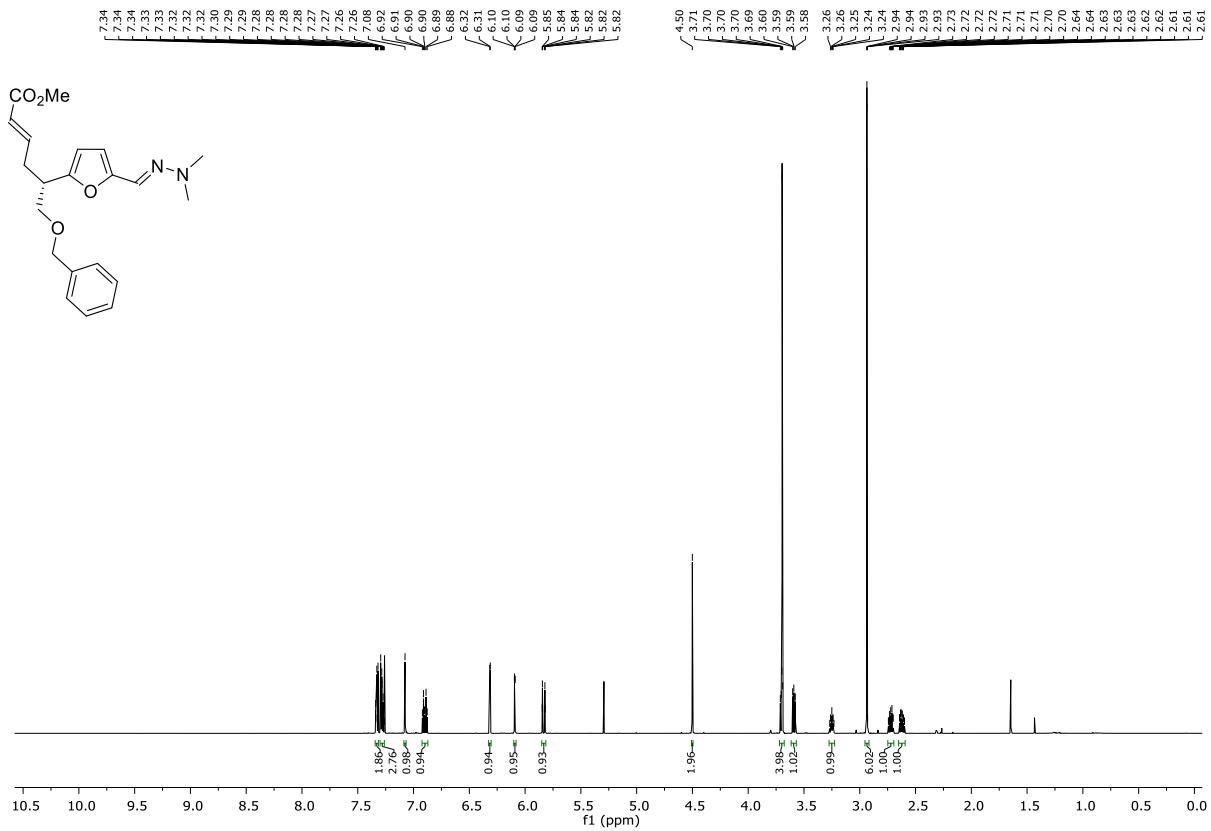


^{13}C NMR

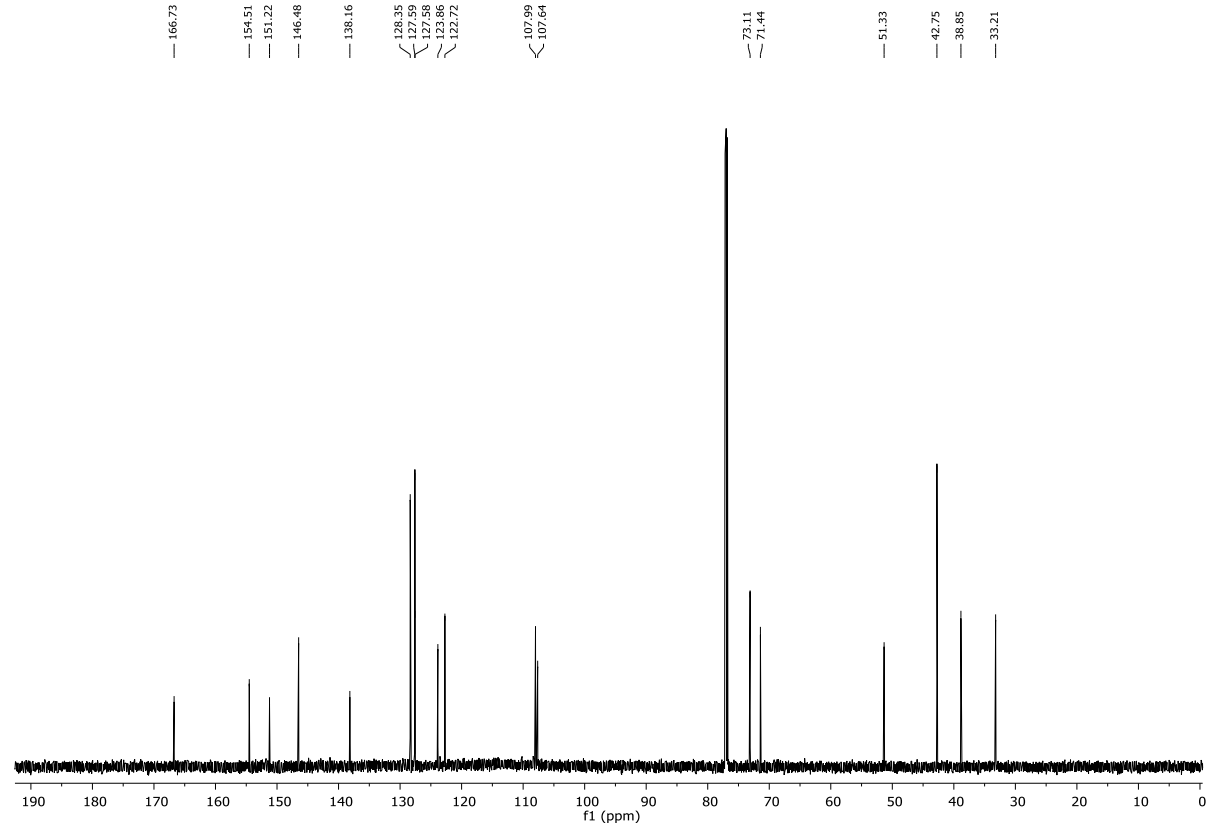


(*S*,*E*)-Methyl 6-(benzyloxy)-5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)hex-2-enoate (**7k**)

^{1}H NMR

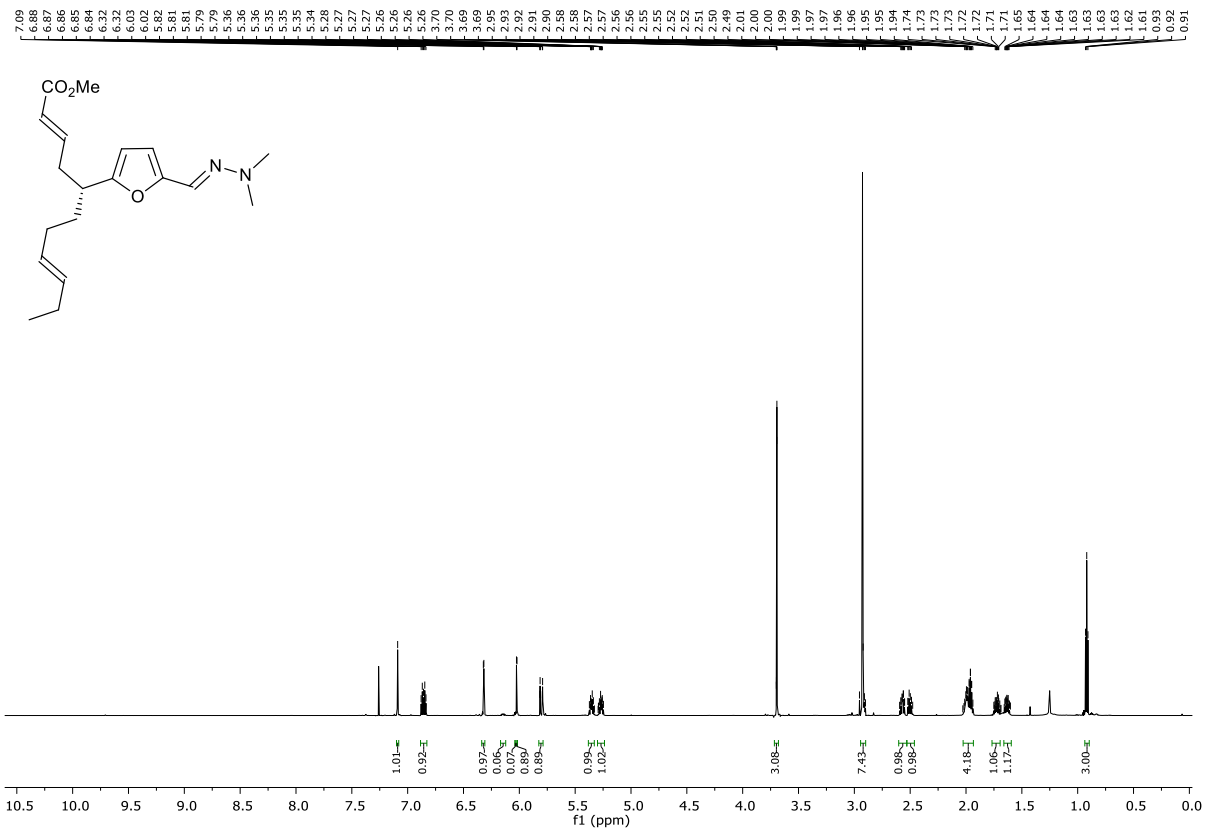


^{13}C NMR

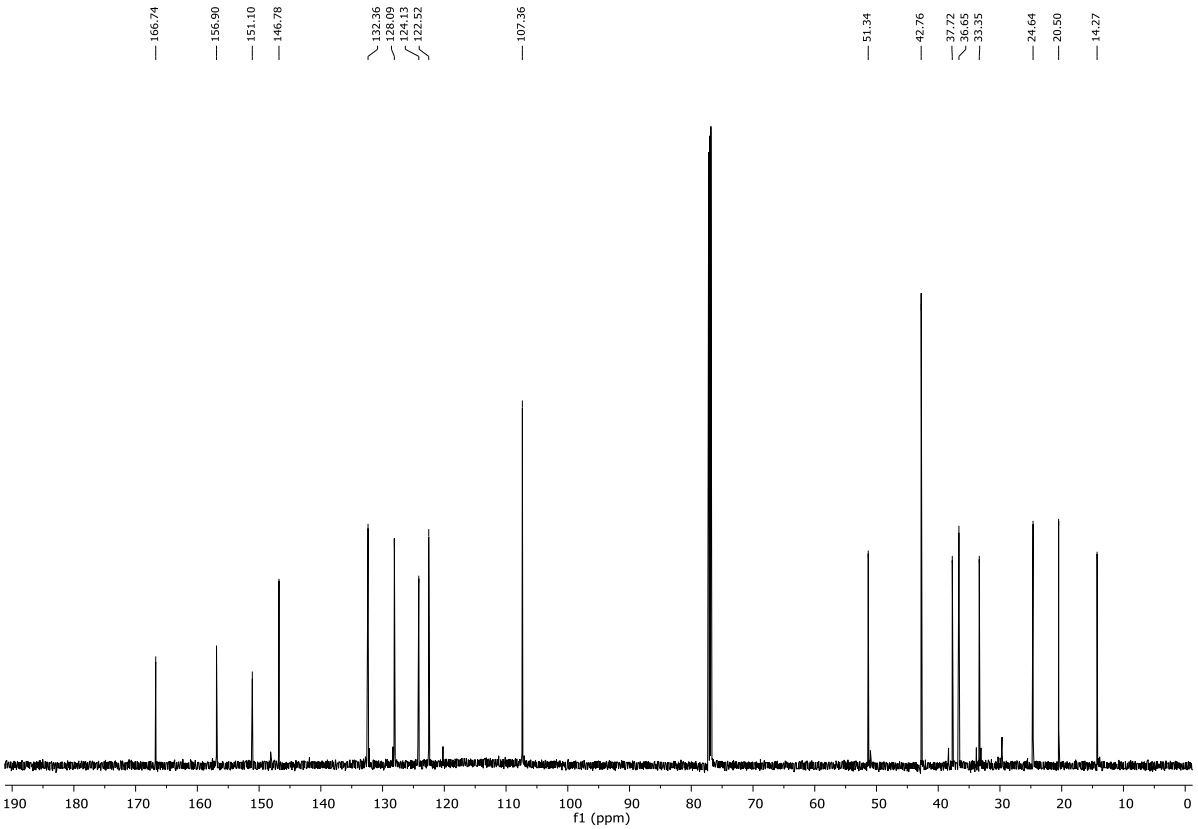


(*R*,2*E*,8*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)undeca-2,8-dienoate (**7l**)

^{1}H NMR

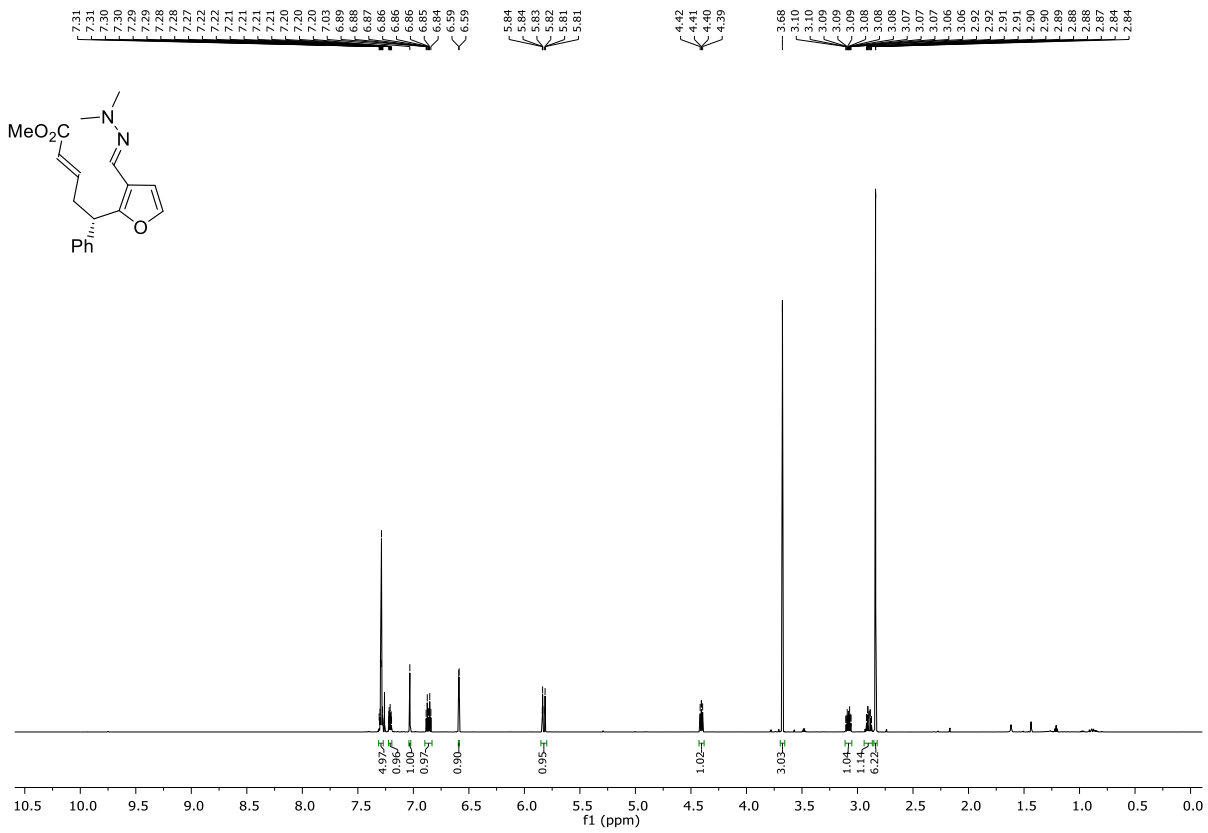


^{13}C NMR

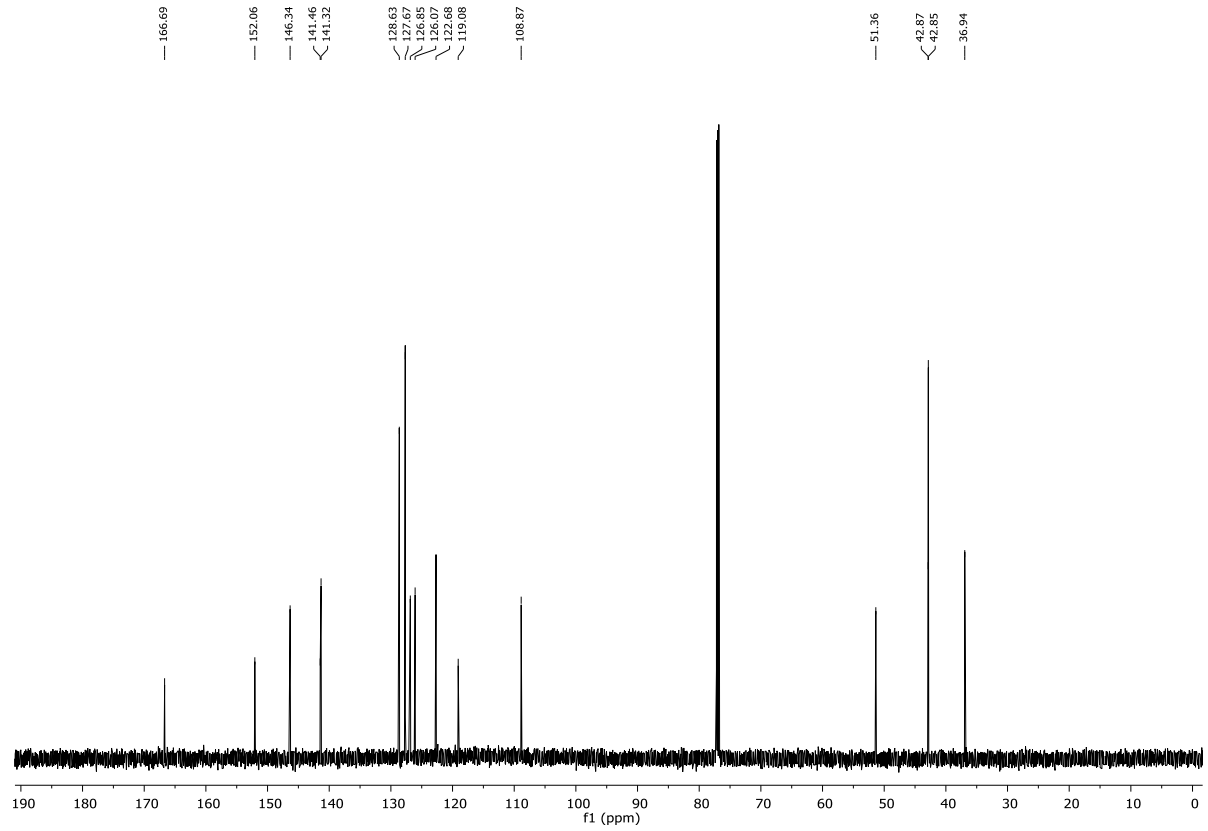


(*S*,*E*)-Methyl 5-(3-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-phenylpent-2-enoate (**7m**)

^{1}H NMR

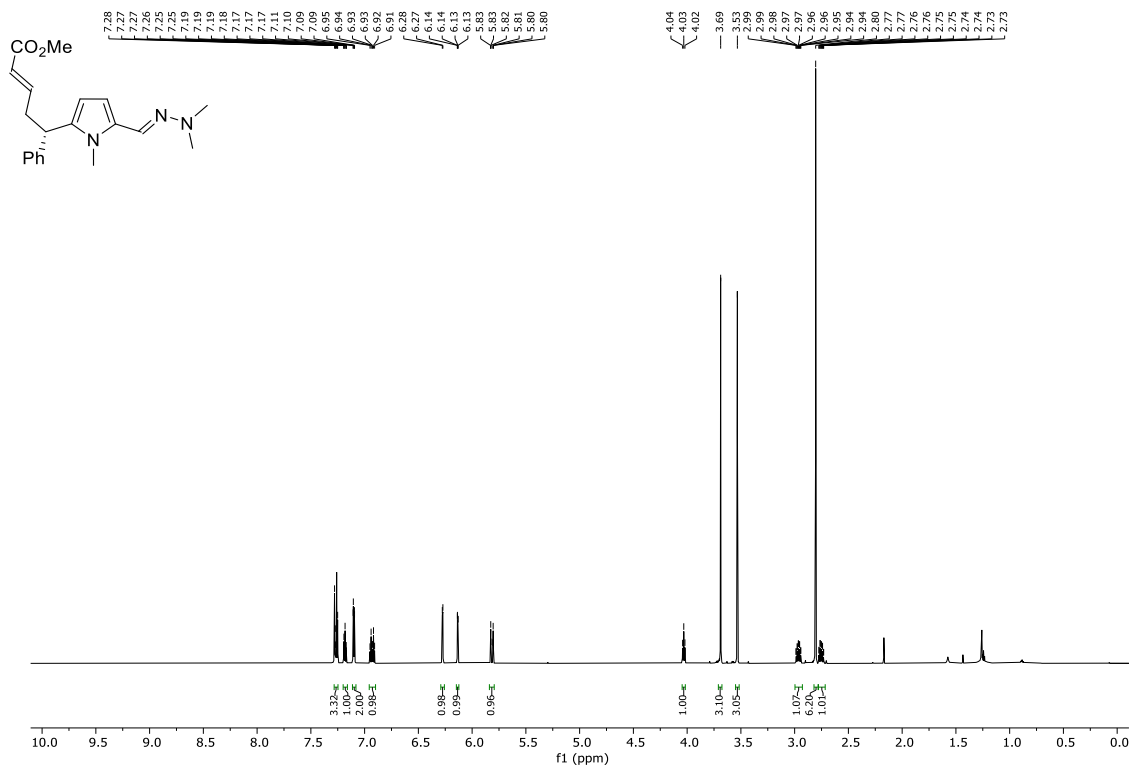


^{13}C NMR

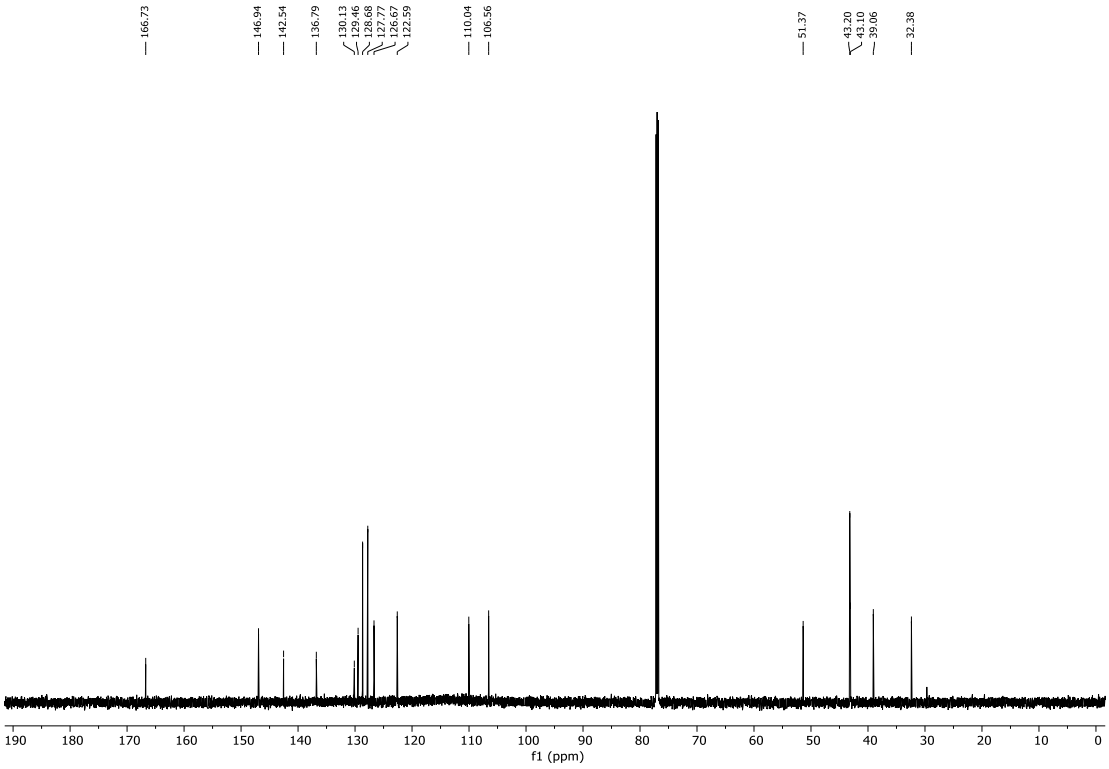


(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)-1-methyl-1*H*-pyrrol-2-yl)-5-phenylpent-2-enoate (**7n**)

^{1}H NMR

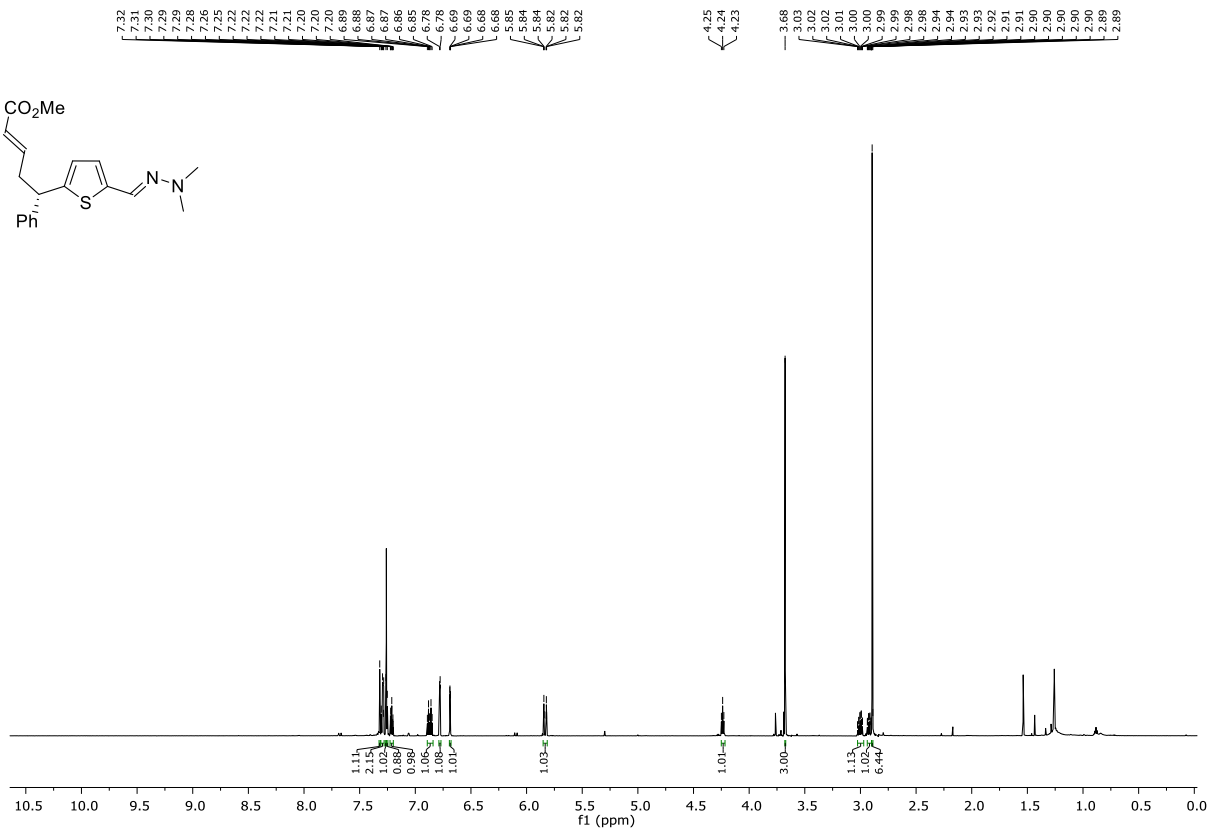


^{13}C NMR

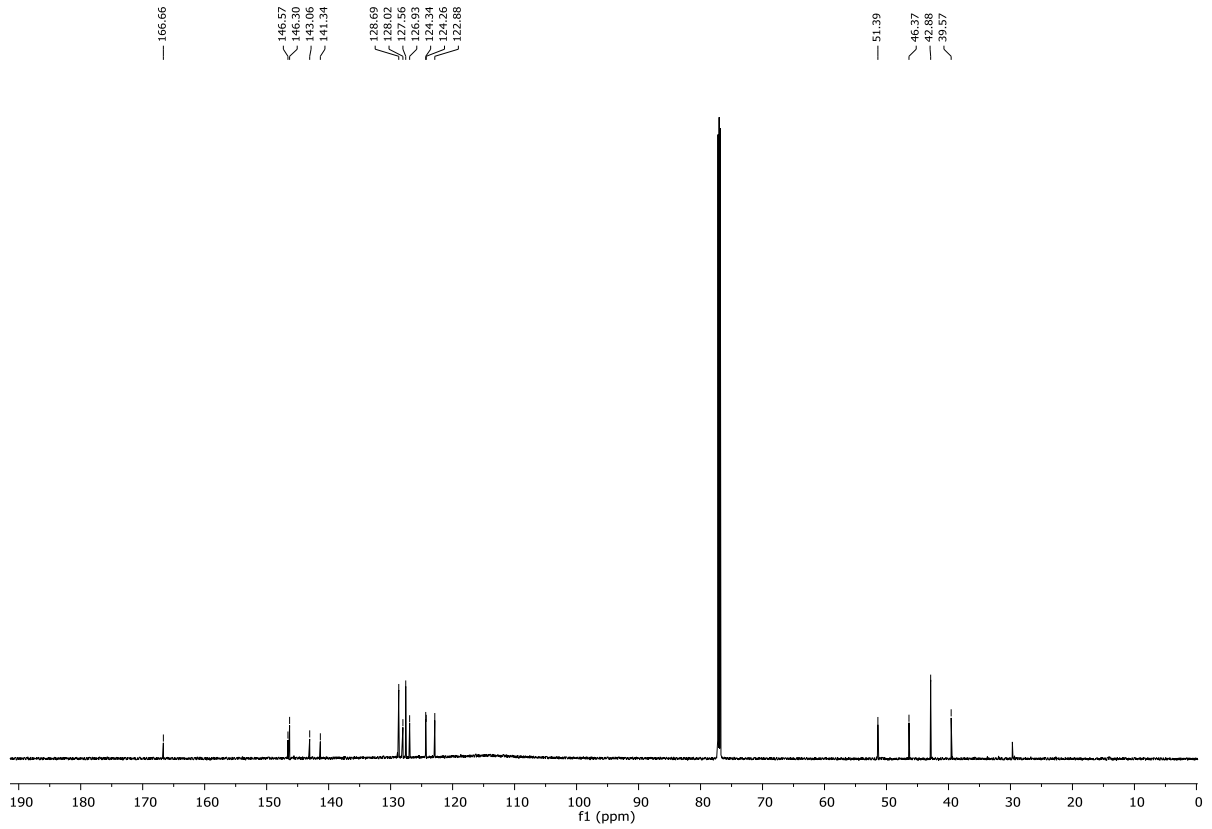


(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)thiophen-2-yl)-5-phenylpent-2-enoate (**7o**)

^{1}H NMR

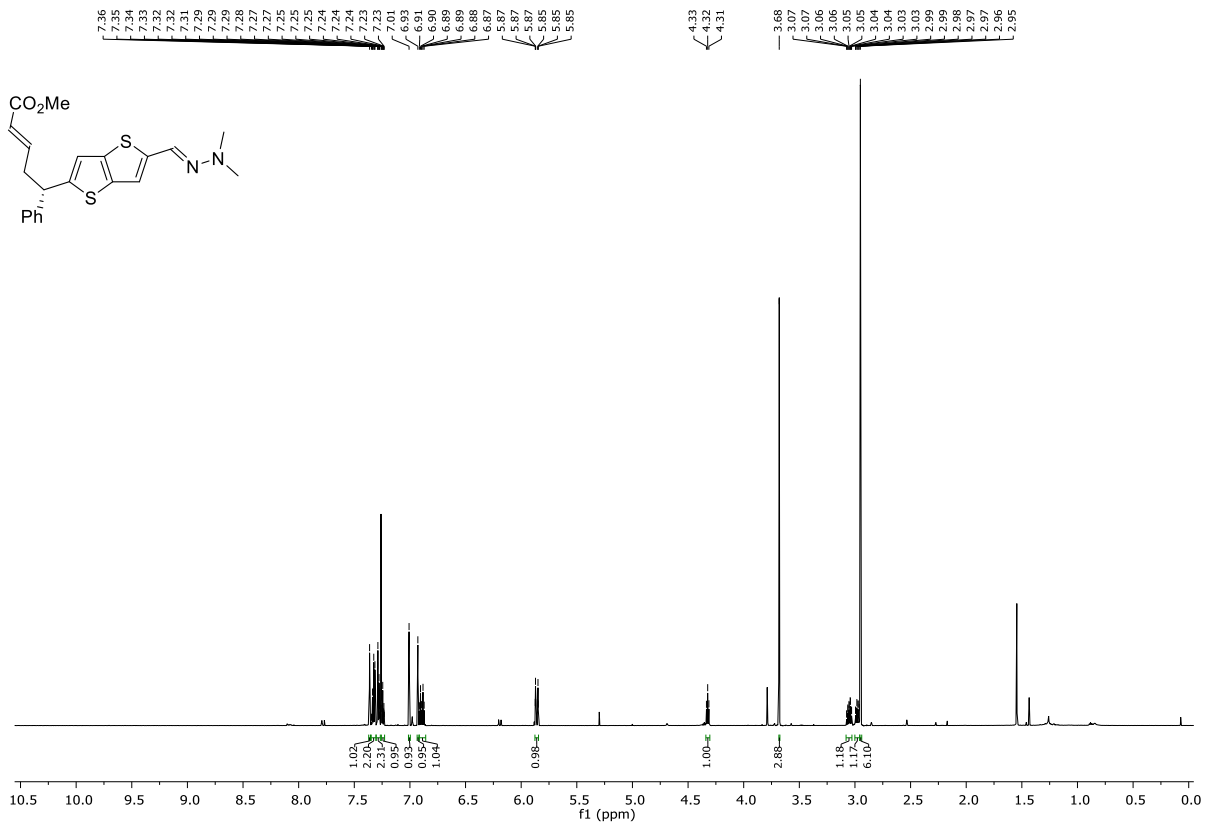


^{13}C NMR

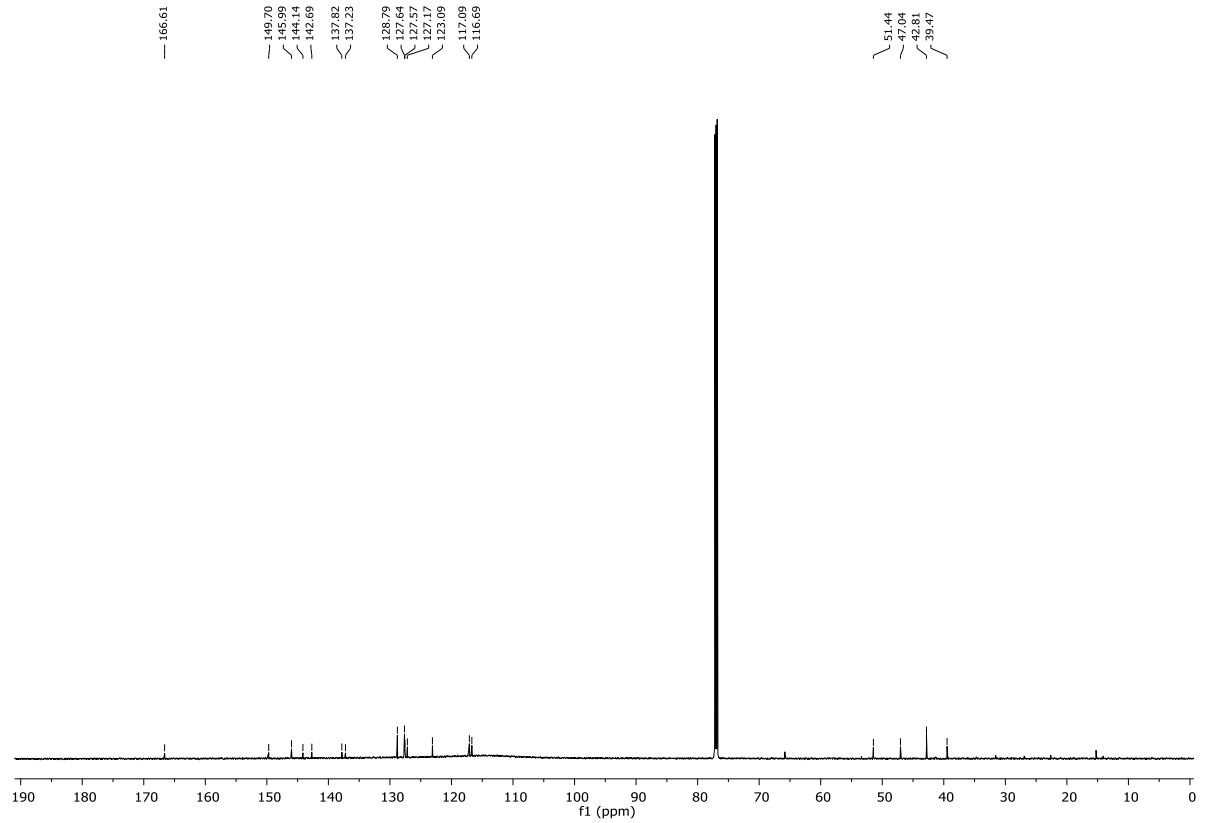


(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)thieno[3,2-*b*]thiophen-2-yl)-5-phenylpent-2-enoate (**7p**)

^{1}H NMR

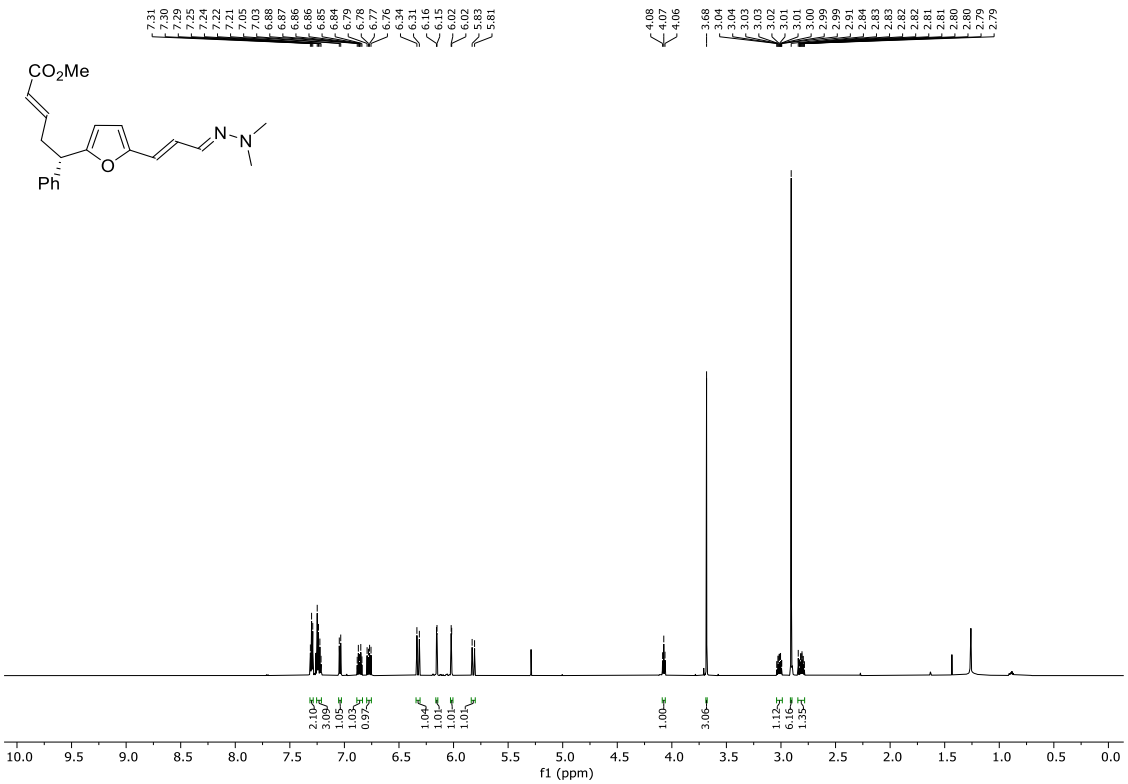


^{13}C NMR

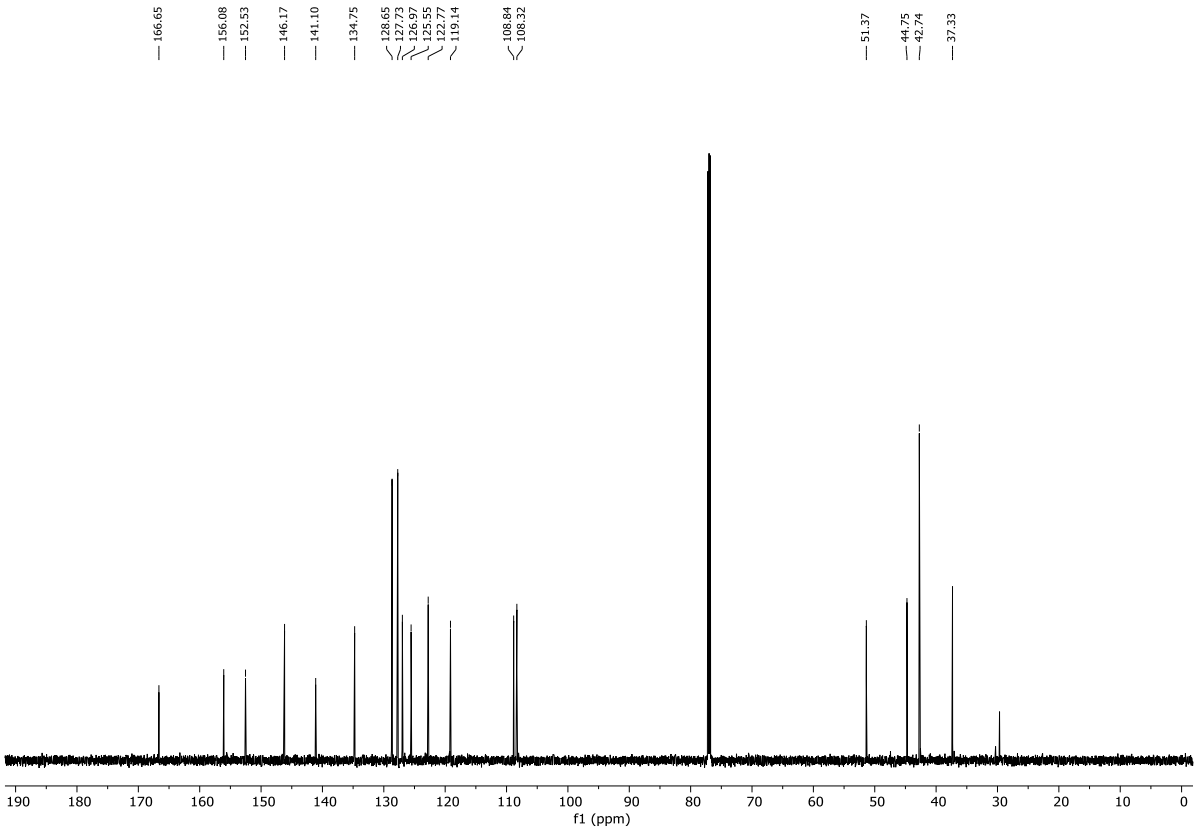


(*S*,*E*)-Methyl 5-(5-((1*E*,3*E*)-3-(2,2-dimethylhydrazono)prop-1-en-1-yl)furan-2-yl)-5-phenylpent-2-enoate (**7q**)

^{1}H NMR

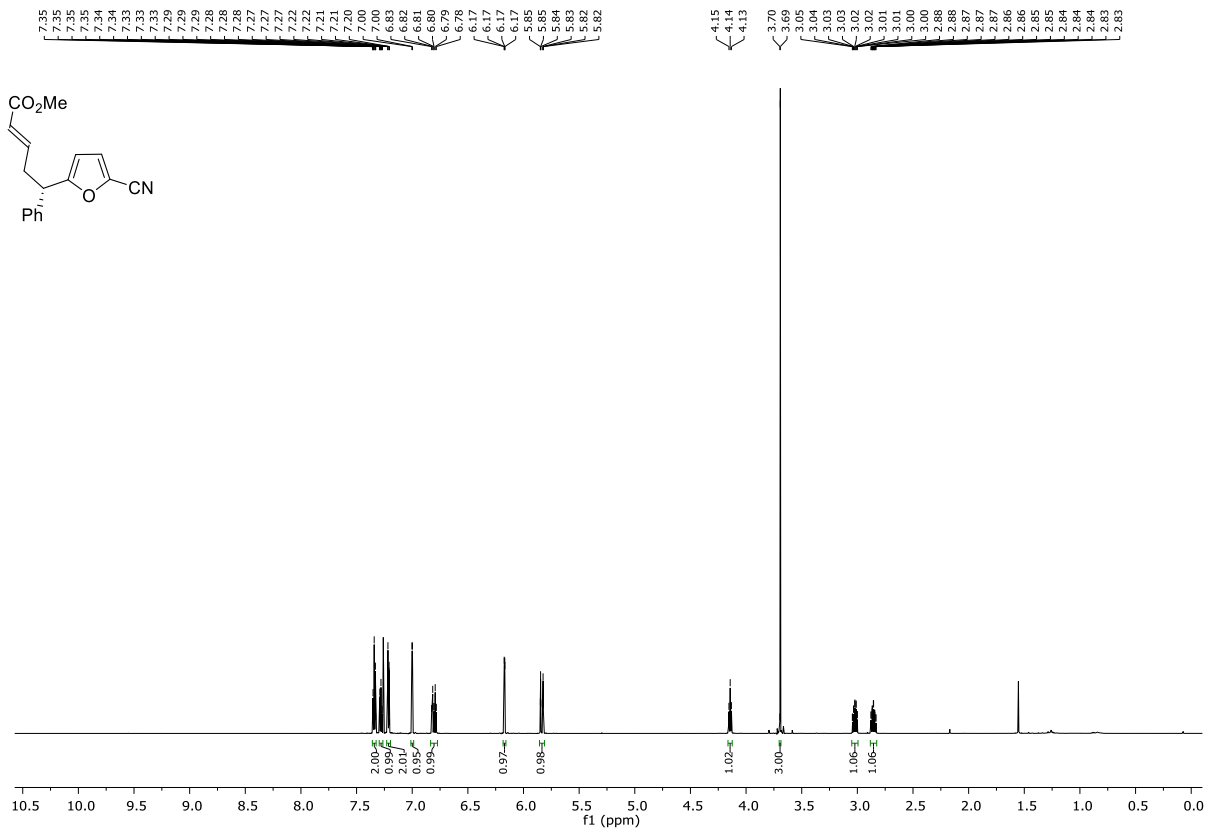


^{13}C NMR

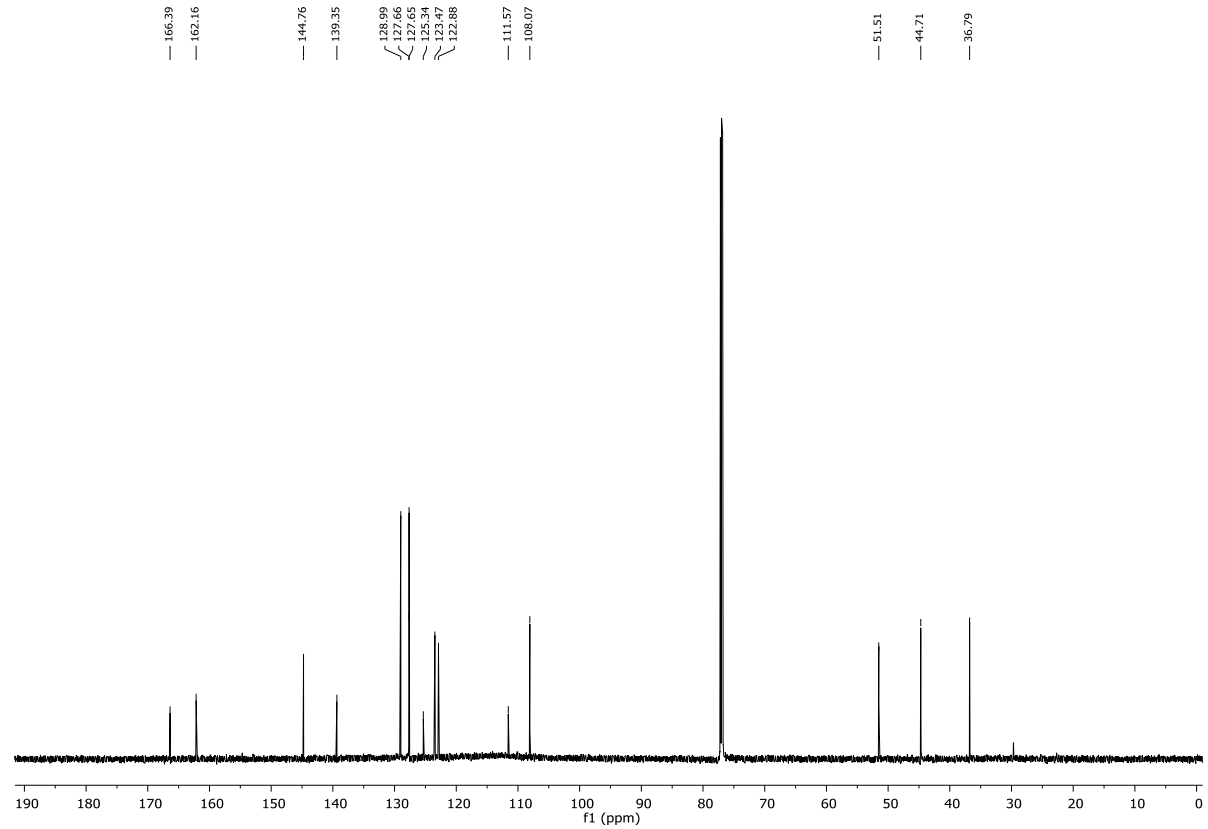


(*S*,*E*)-Methyl 5-(5-cyanofuran-2-yl)-5-phenylpent-2-enoate (**8a**)

^{1}H NMR

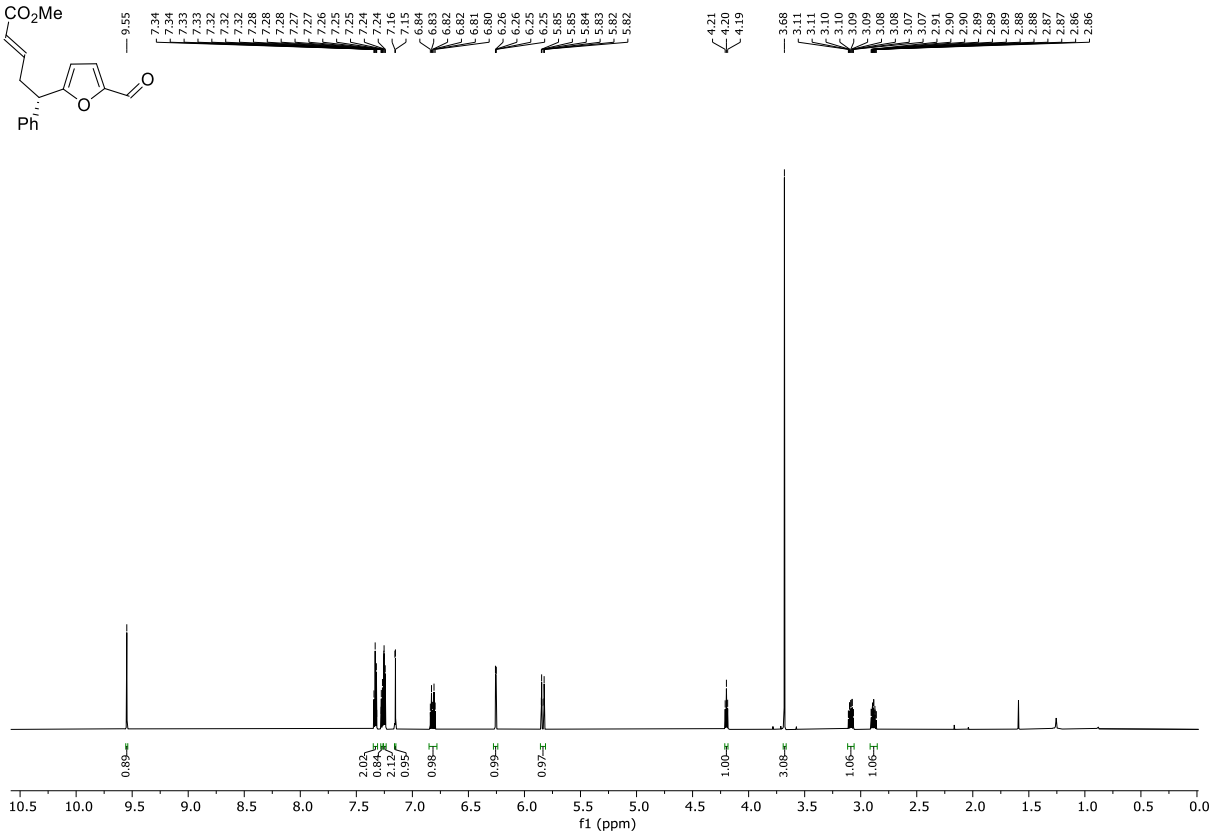


^{13}C NMR

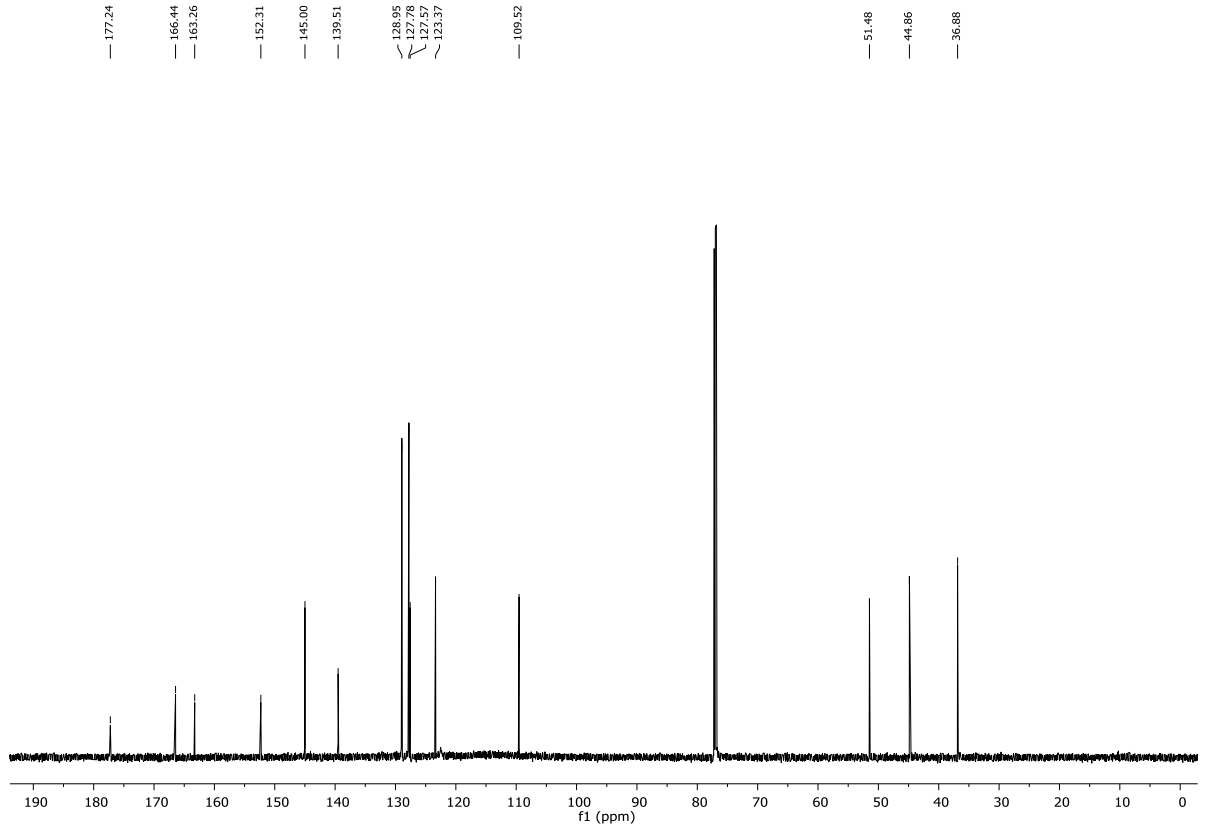


(*S*,*E*)-Methyl 5-(5-formylfuran-2-yl)-5-phenylpent-2-enoate (**9a**)

^{1}H NMR



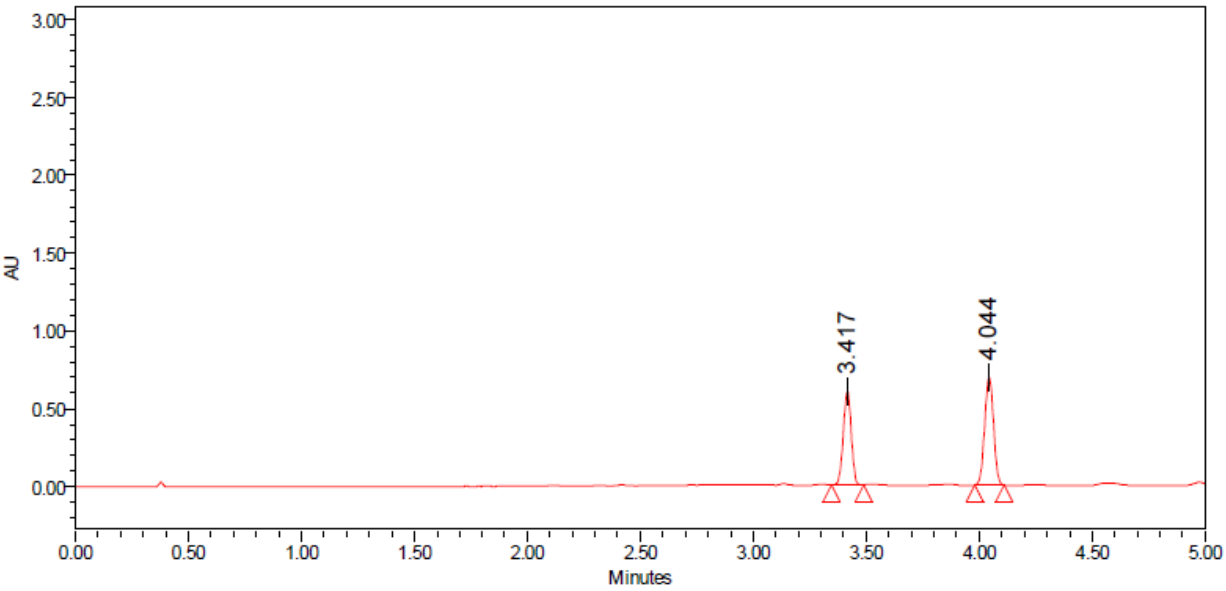
^{13}C NMR



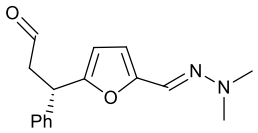
10. UPC² Traces

(*S*,*E*)-3-(5-((2,2-Dimethylhydrazono)methyl)furan-2-yl)-3-phenylpropanal (**5a**)

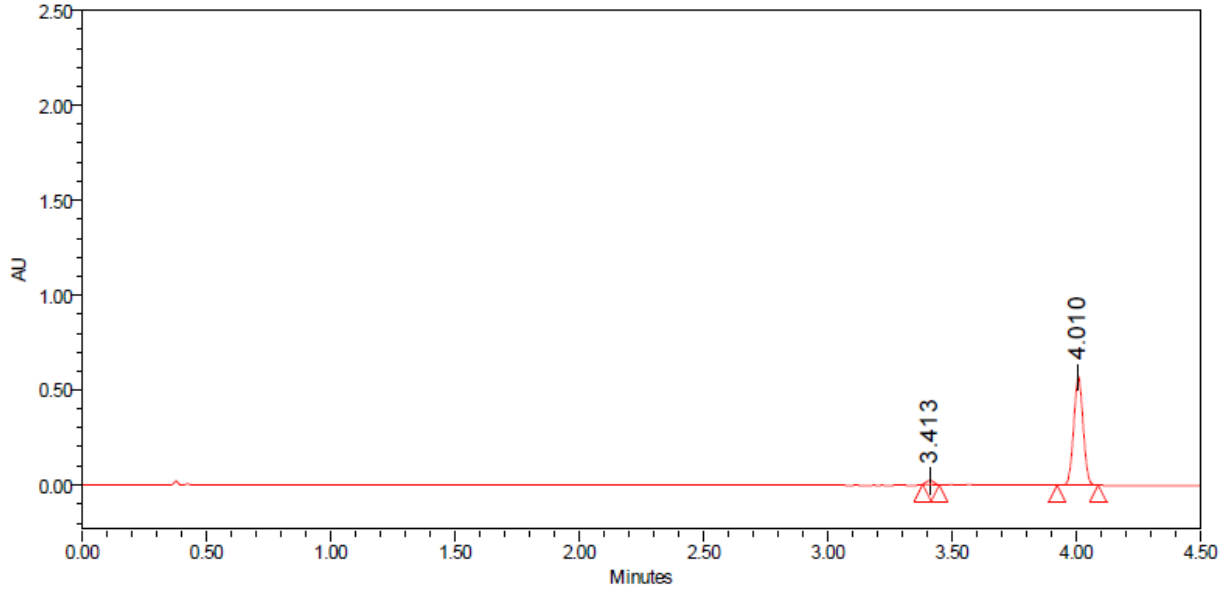
Racemic sample



Enantiomerically enriched sample



5a

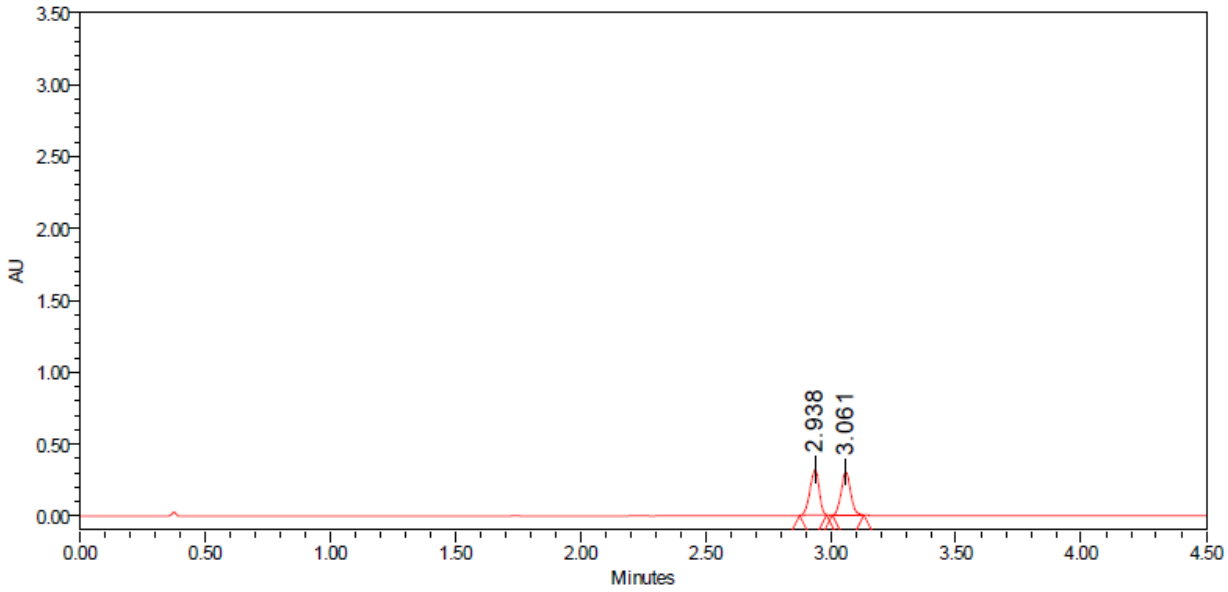


Peak Results

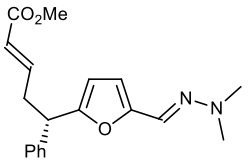
	RT	% Area
1	3.413	2.80
2	4.010	97.20

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-phenylpent-2-enoate (**7a**)

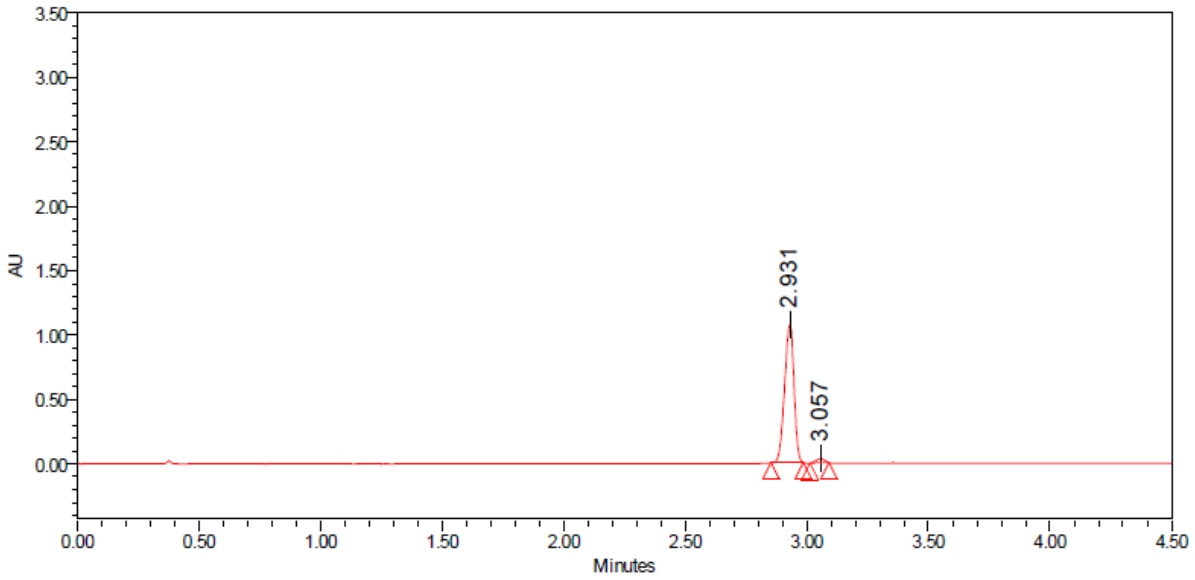
Racemic sample



Enantiomerically enriched sample



7a

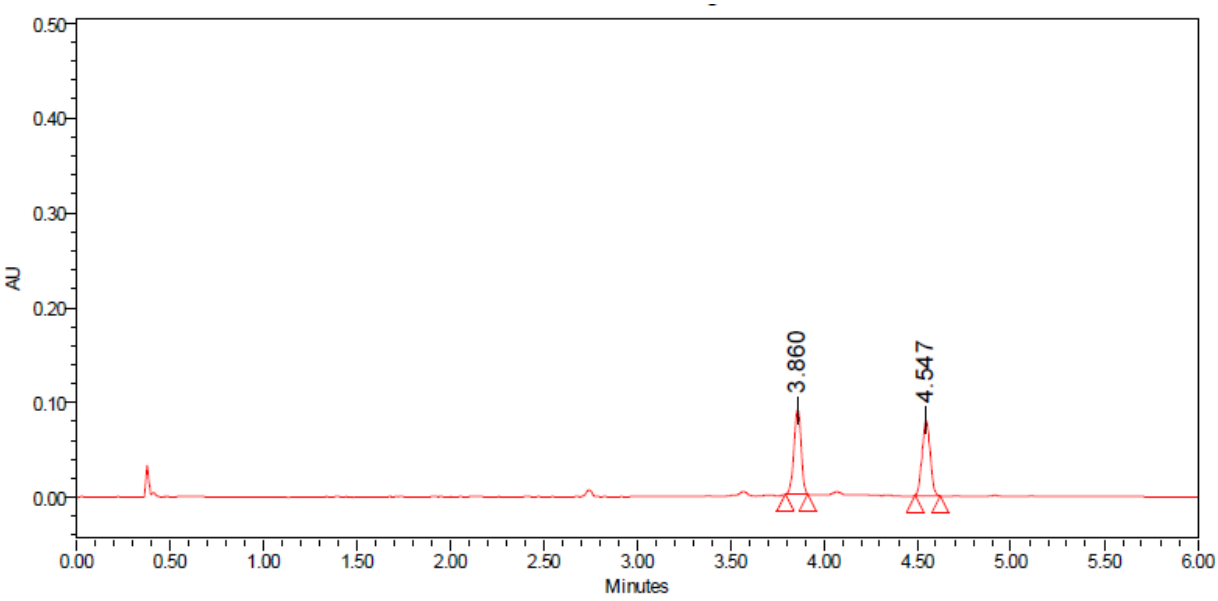


Peak Results

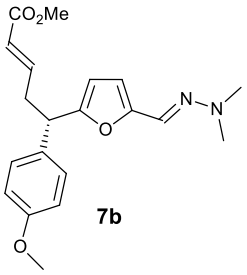
	RT	% Area
1	2.931	97.58
2	3.057	2.42

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(4-methoxyphenyl)pent-2-enoate (**7b**)

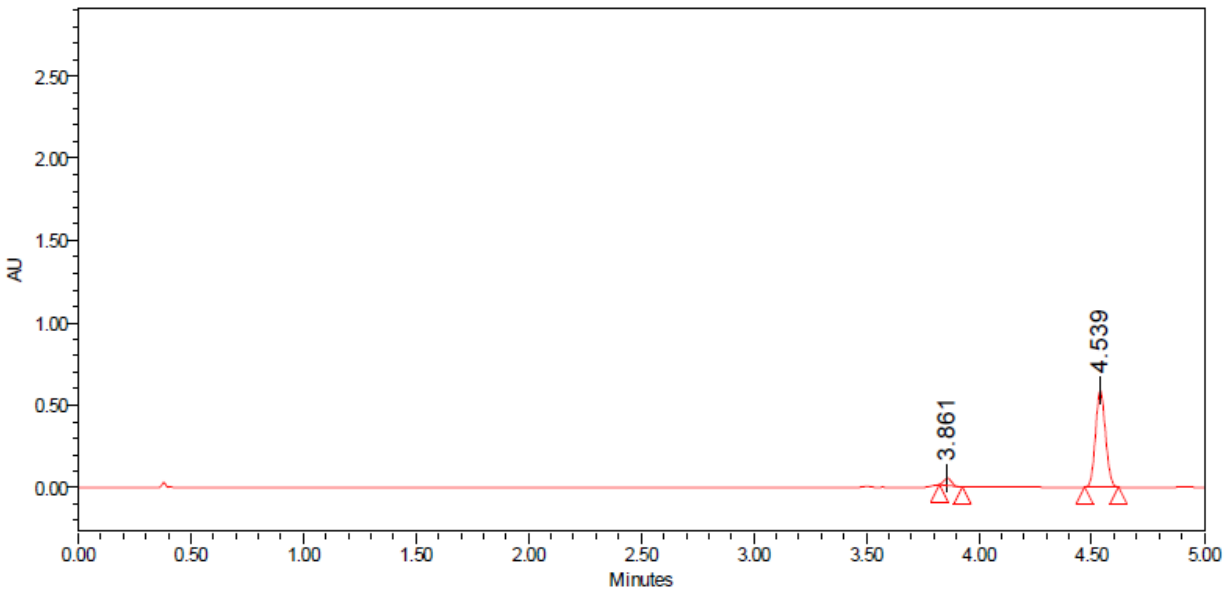
Racemic sample



Enantiomerically enriched sample



7b

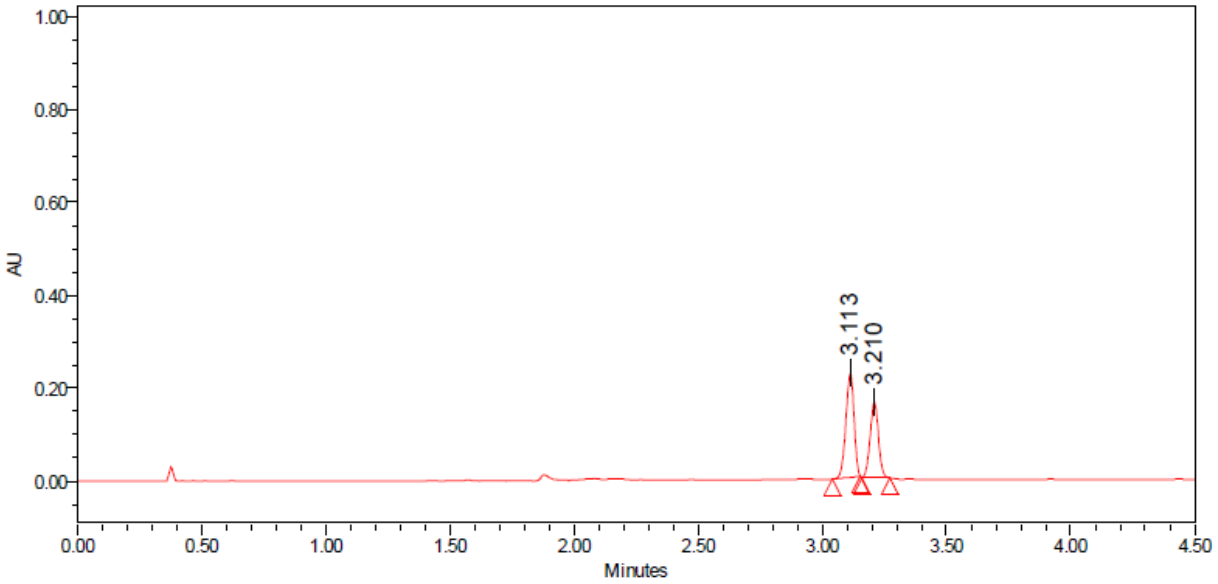


Peak Results

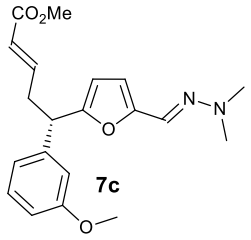
	RT	% Area
1	3.861	5.55
2	4.539	94.45

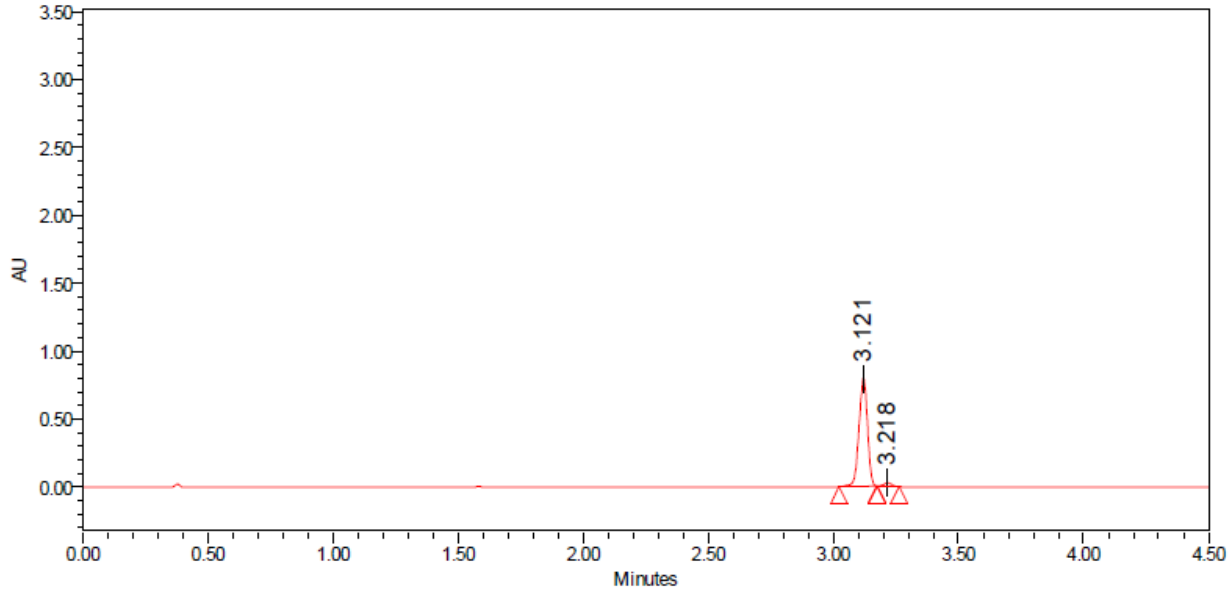
(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(3-methoxyphenyl)pent-2-enoate (**7c**)

Racemic sample



Enantiomerically enriched sample



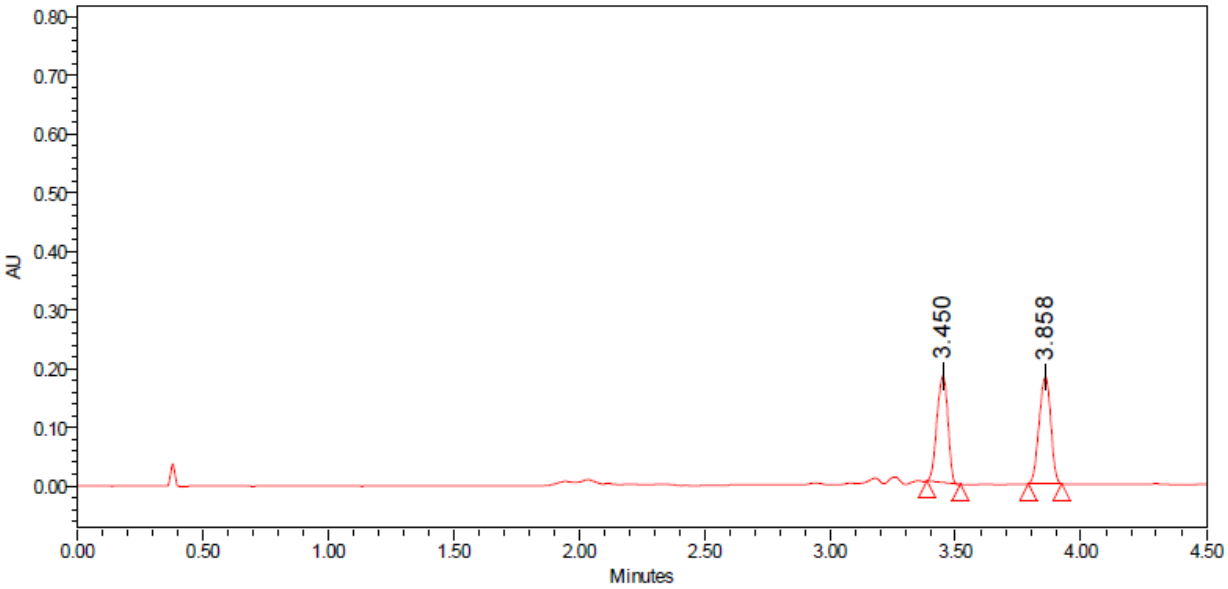


Peak Results

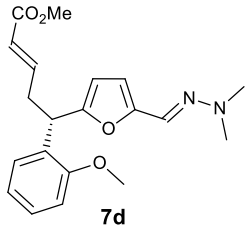
	RT	% Area
1	3.121	97.09
2	3.218	2.91

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(2-methoxyphenyl)pent-2-enoate (**7d**)

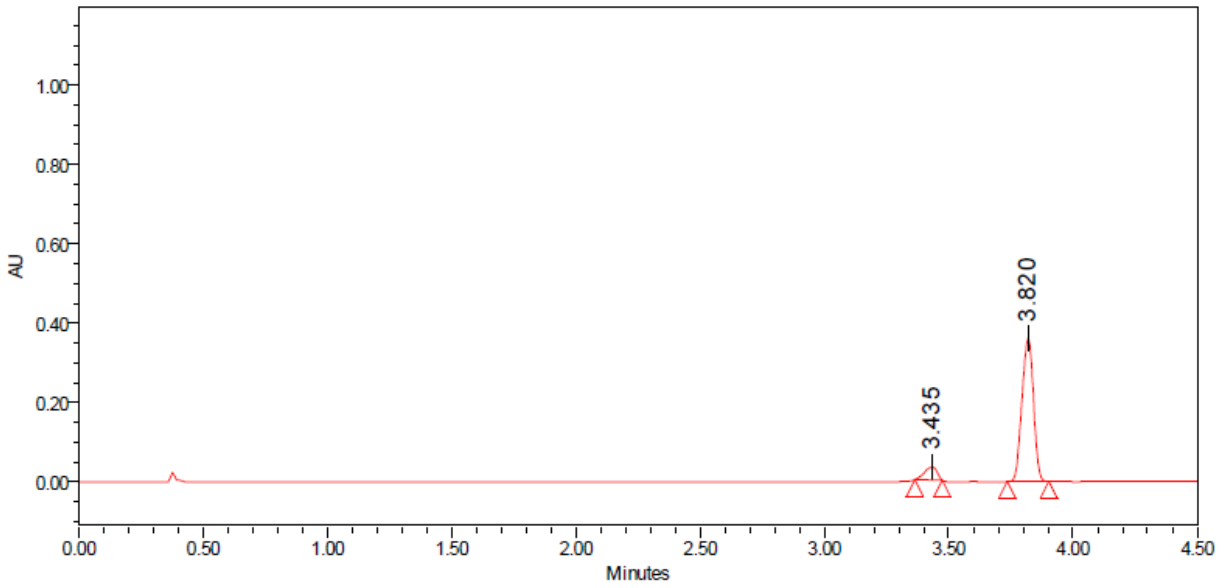
Racemic sample



Enantiomerically enriched sample



7d

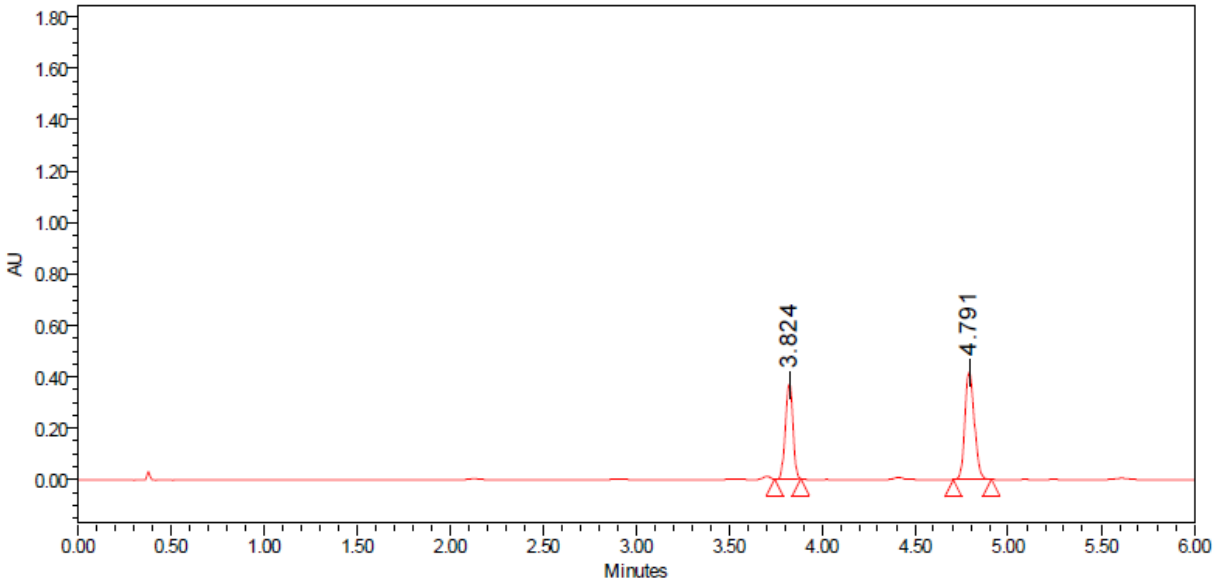


Peak Results

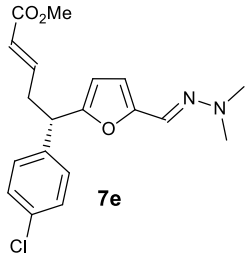
	RT	% Area
1	3.435	8.98
2	3.820	91.02

(*S*,*E*)-Methyl 5-(4-chlorophenyl)-5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)pent-2-enoate (**7e**)

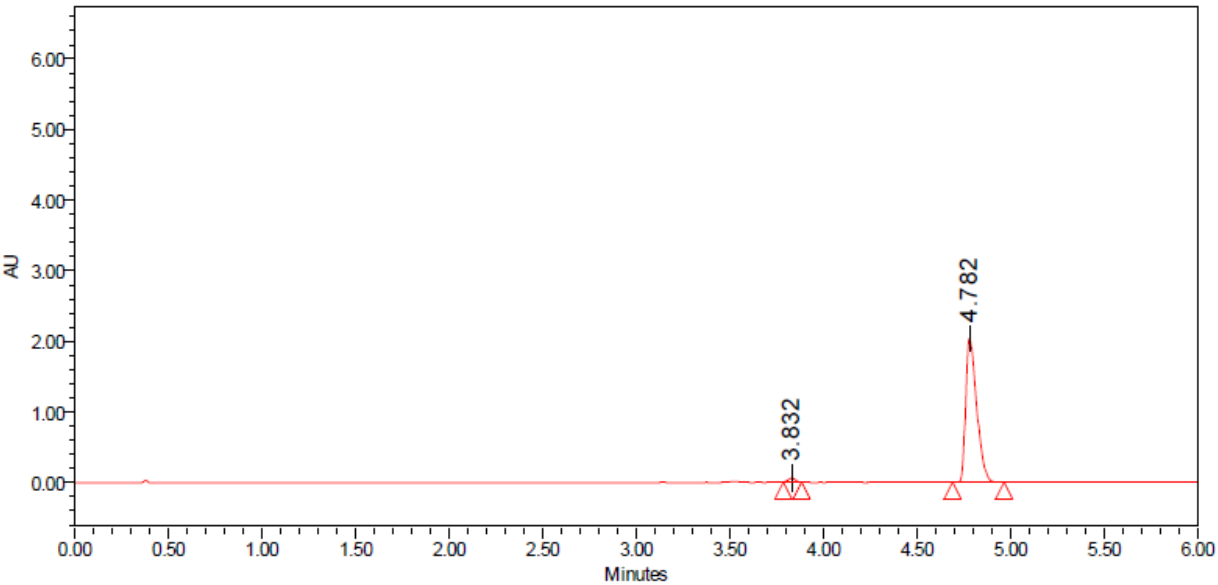
Racemic sample



Enantiomerically enriched sample



7e

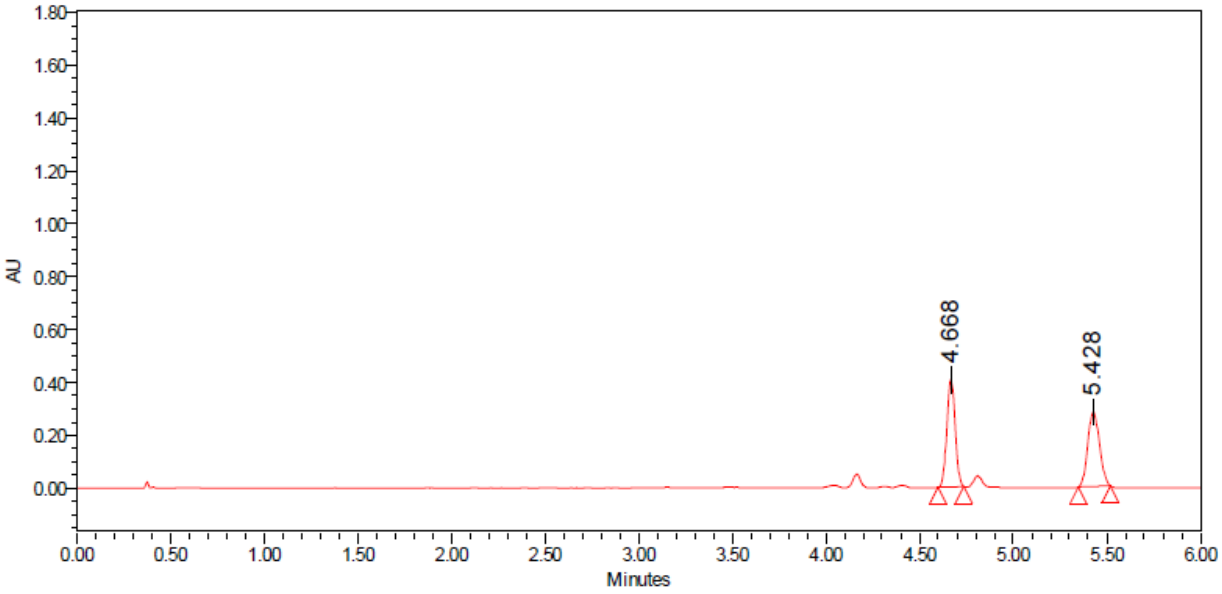


Peak Results

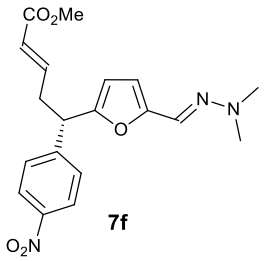
	RT	% Area
1	3.832	1.69
2	4.782	98.31

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(4-nitrophenyl)pent-2-enoate (**7f**)

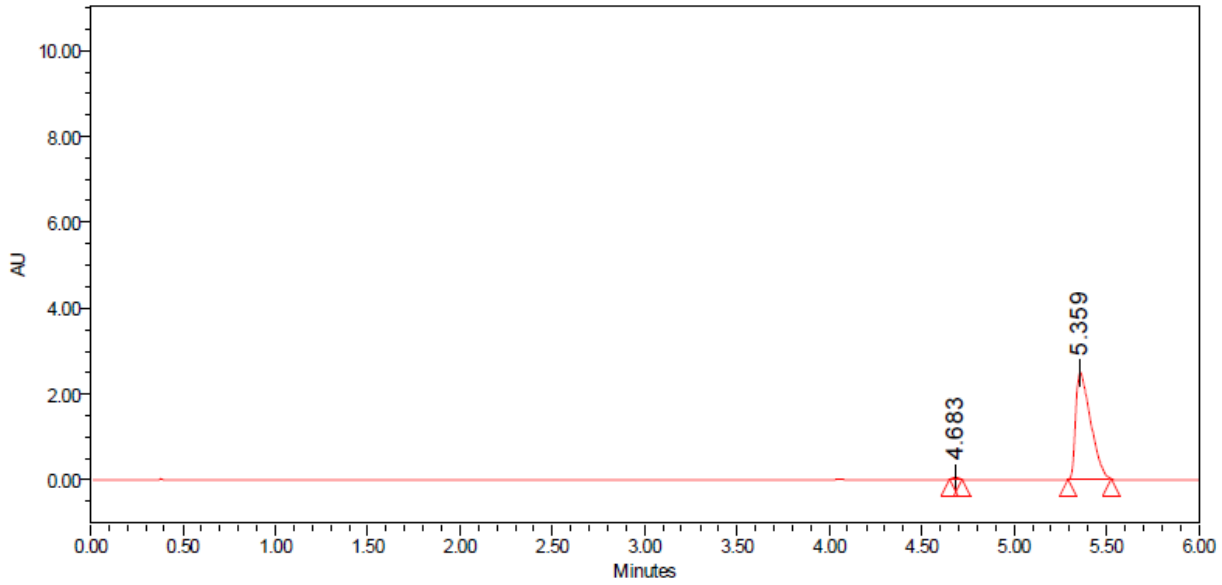
Racemic sample



Enantiomerically enriched sample



7f

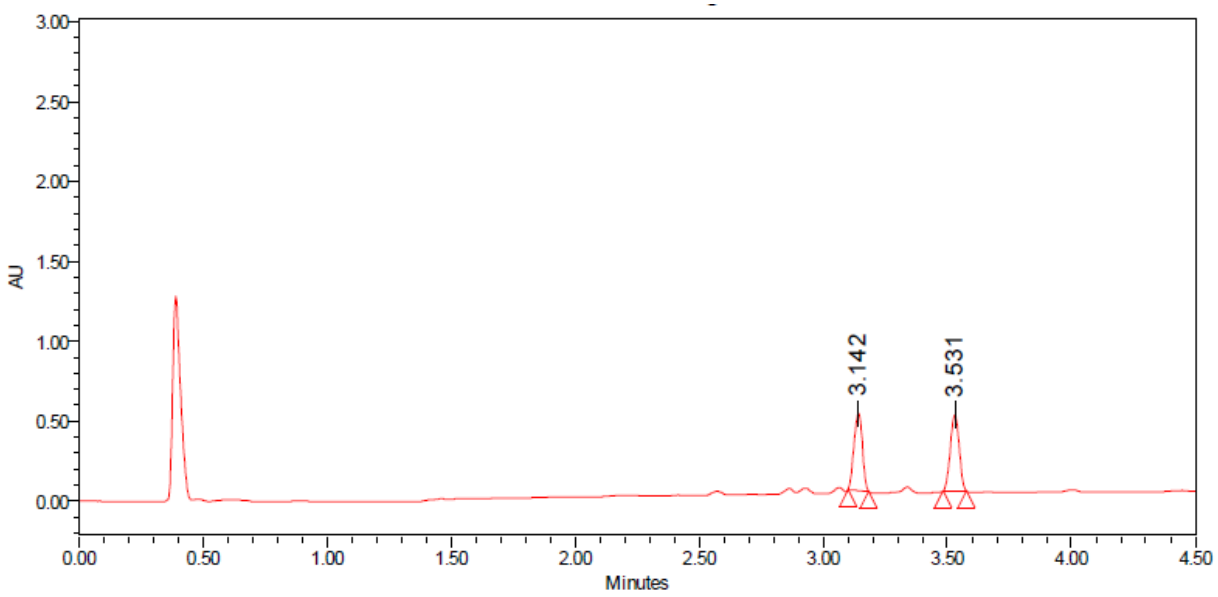


Peak Results

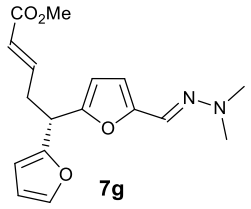
	RT	% Area
1	4.683	0.77
2	5.359	99.23

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(furan-2-yl)pent-2-enoate (**7g**)

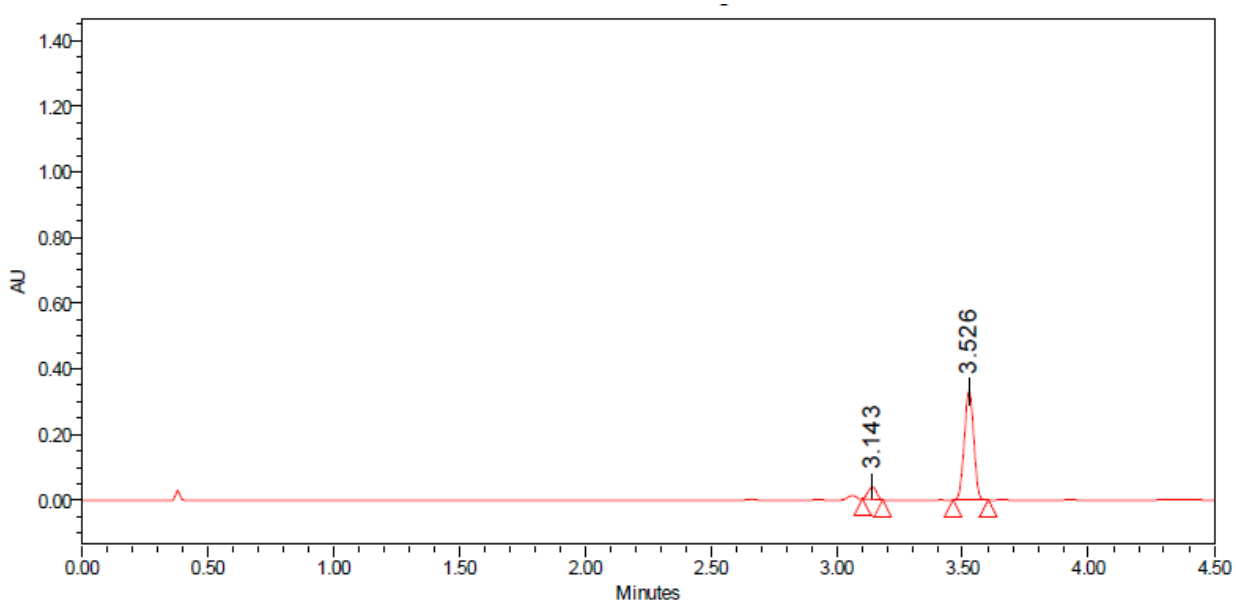
Racemic sample



Enantiomerically enriched sample



7g

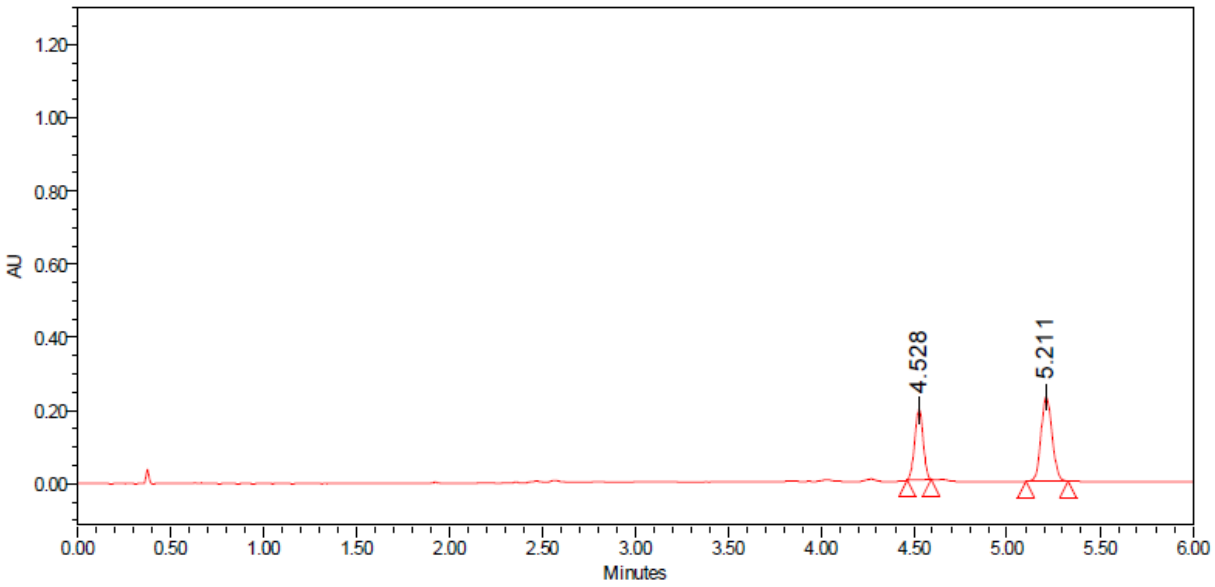


Peak Results

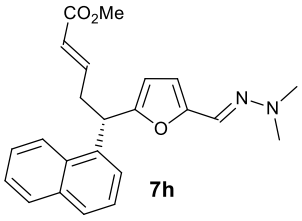
	RT	% Area
1	3.143	9.20
2	3.526	90.80

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-(naphthalen-1-yl)pent-2-enoate (**7h**)

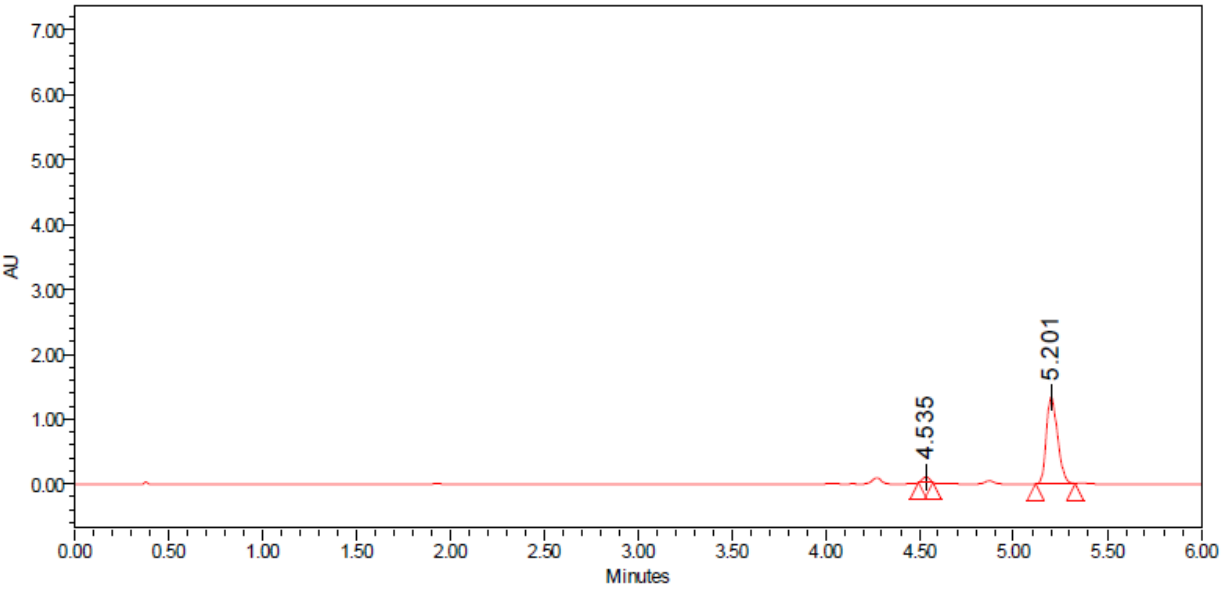
Racemic sample



Enantiomerically enriched sample



7h

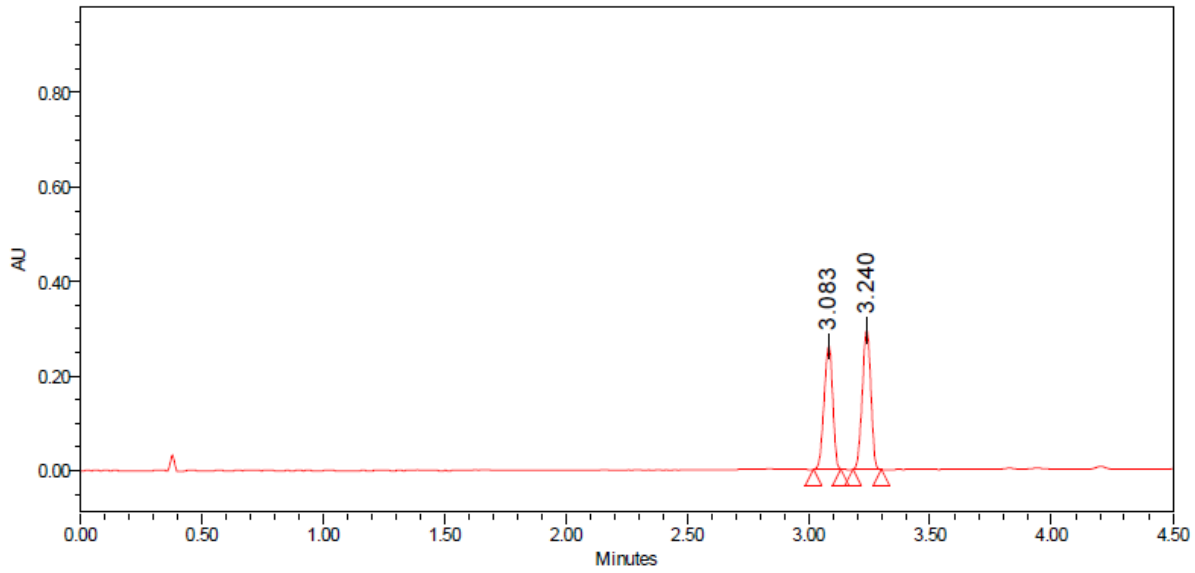


Peak Results

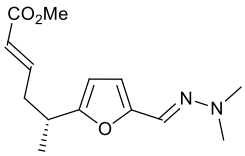
	RT	% Area
1	4.535	3.76
2	5.201	96.24

(*R*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)hex-2-enoate (**7i**)

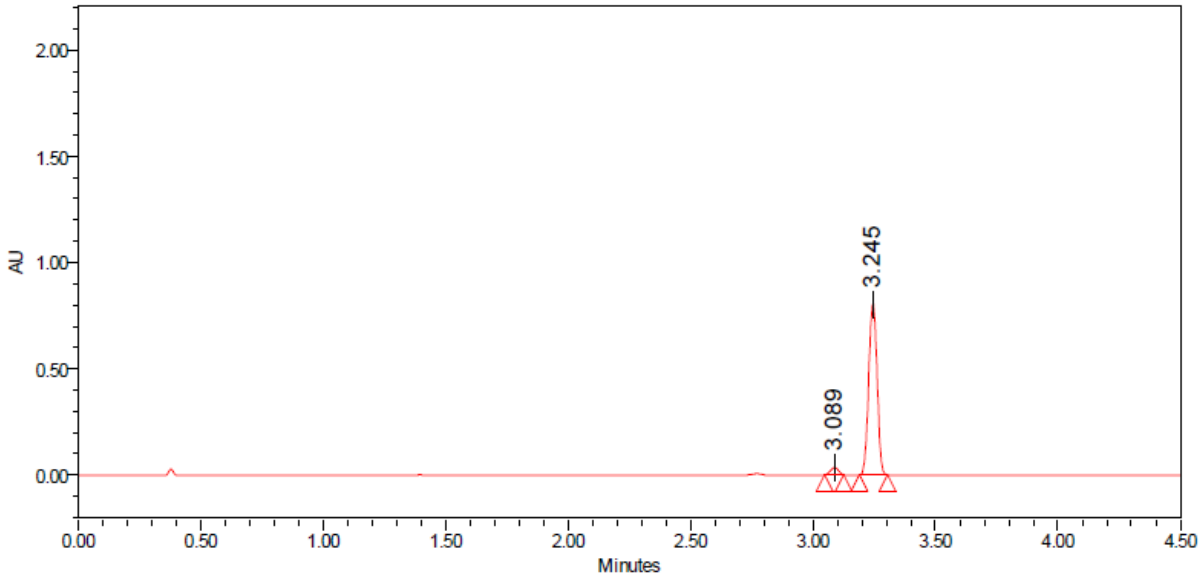
Racemic sample



Enantiomerically enriched sample



7i

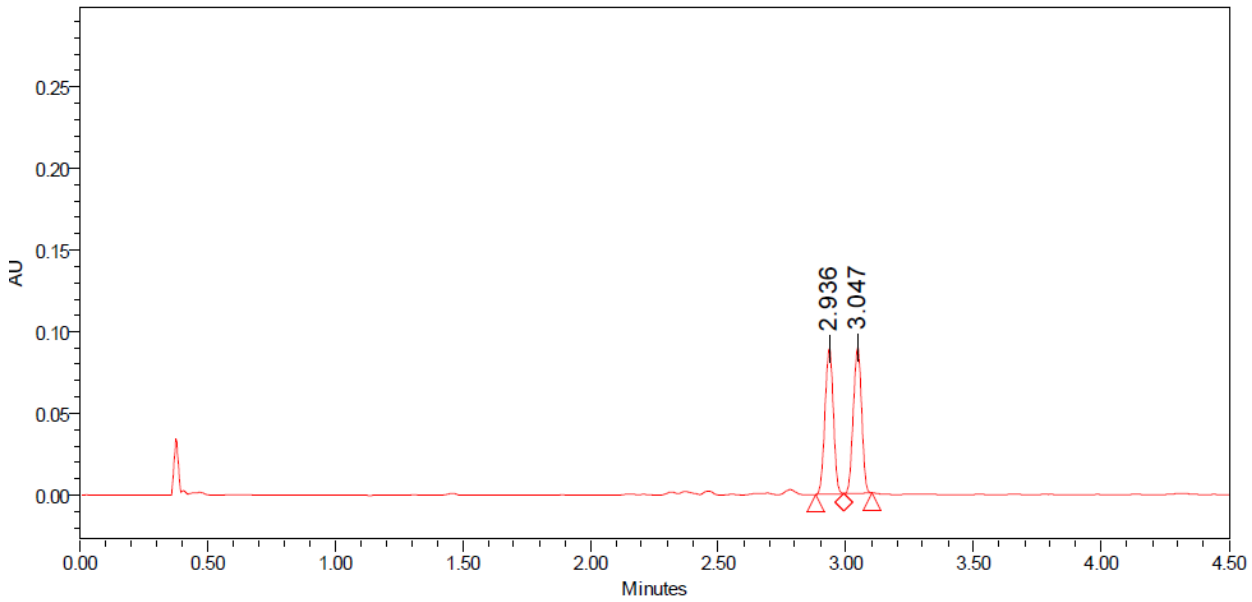


Peak Results

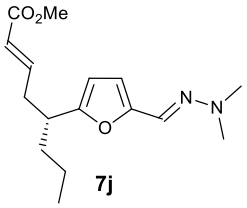
	RT	% Area
1	3.089	3.96
2	3.245	96.04

(*R*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)oct-2-enoate (**7j**)

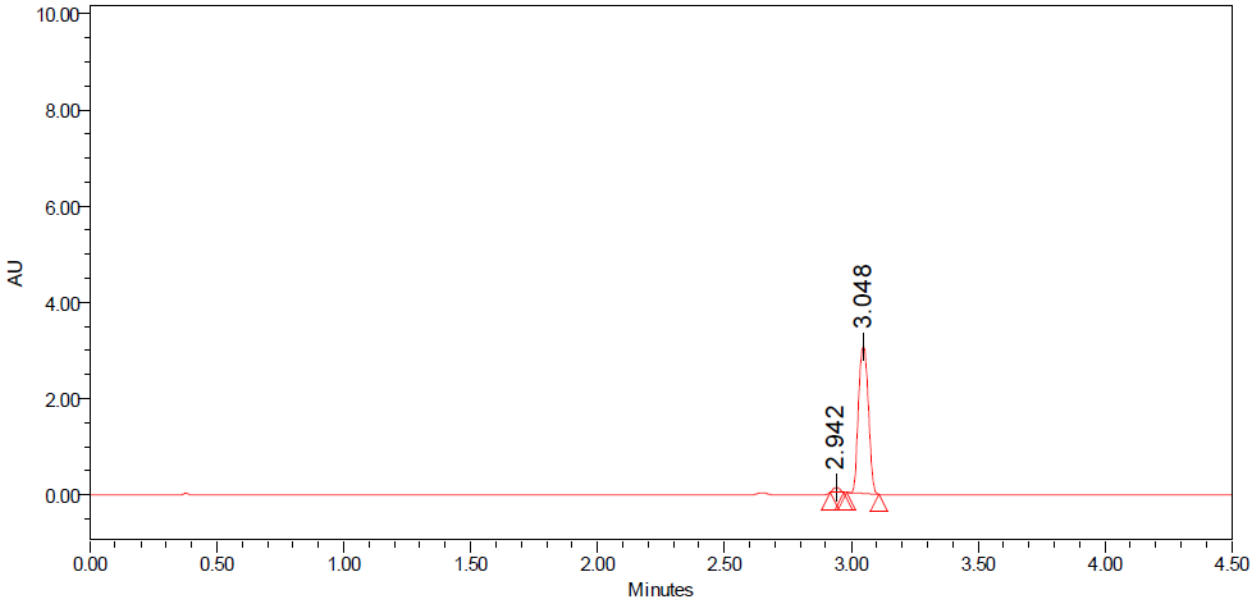
Racemic sample



Enantiomerically enriched sample



7j

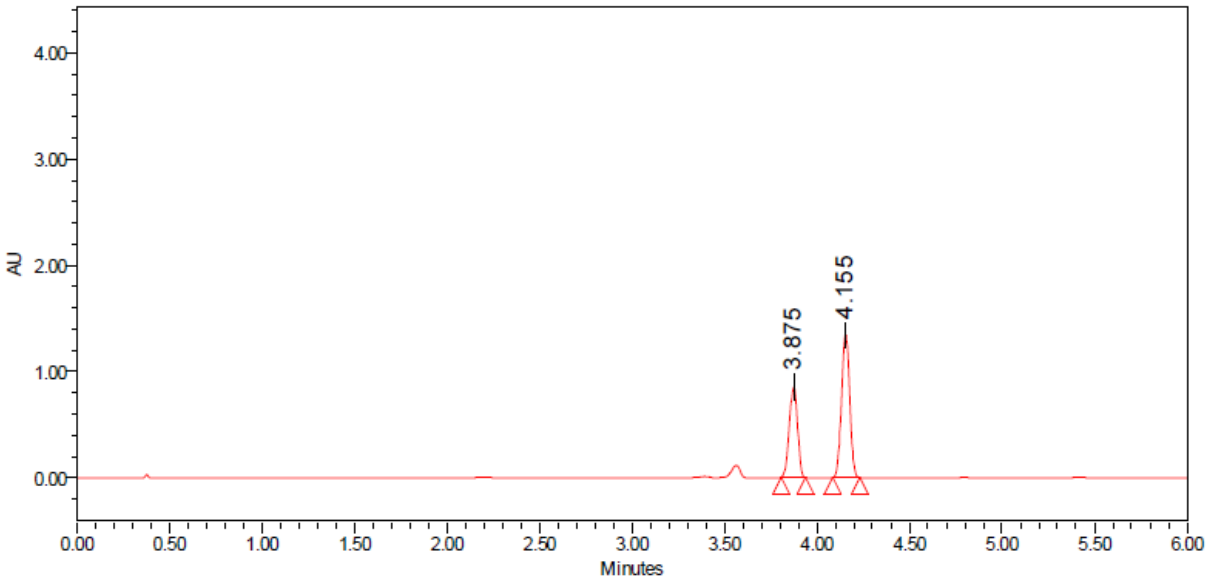


Peak Results

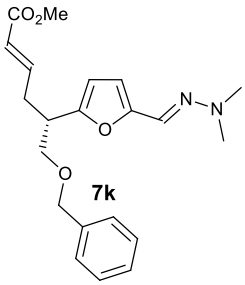
	RT	% Area
1	2.942	2.27
2	3.048	97.73

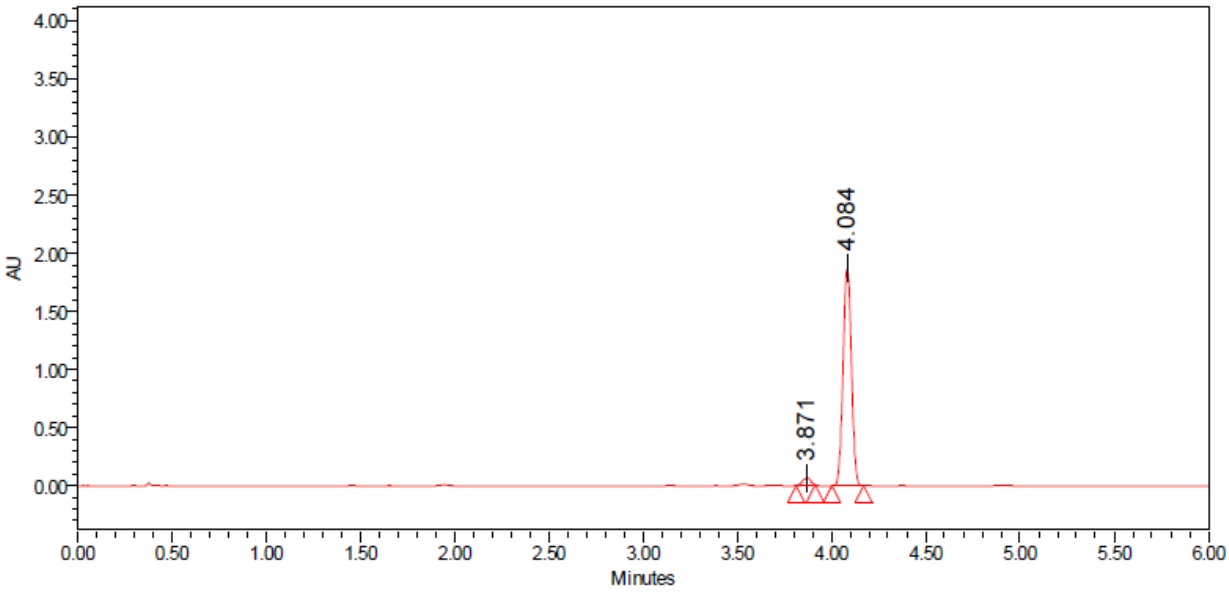
(*S*,*E*)-Methyl 6-(benzyloxy)-5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)hex-2-enoate (**7k**)

Racemic sample



Enantiomerically enriched sample



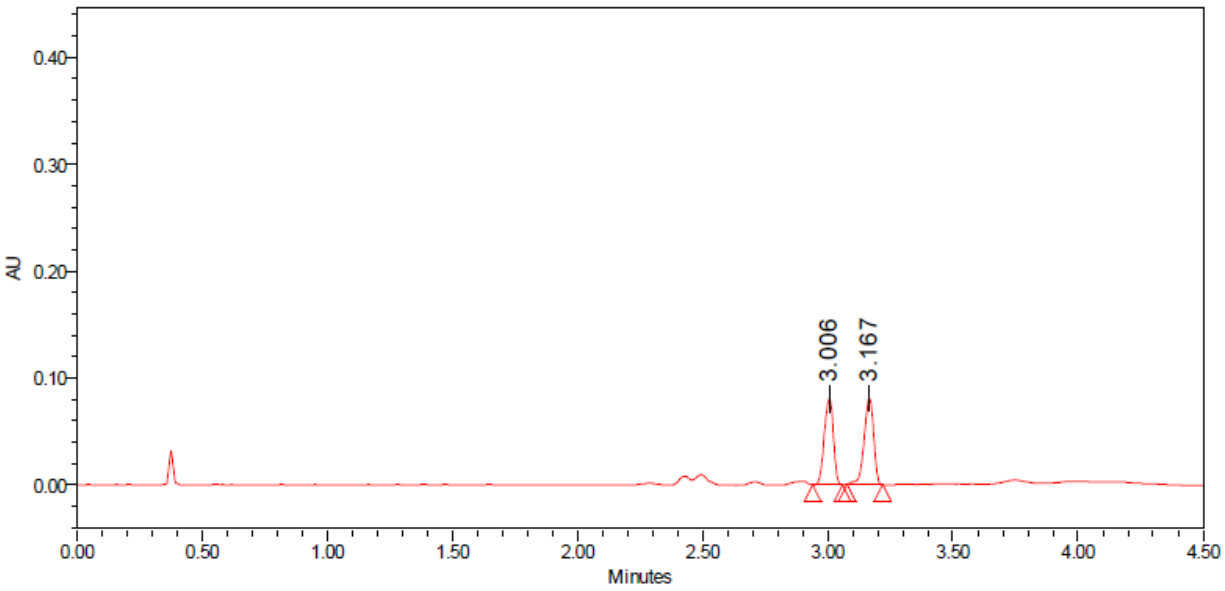


Peak Results

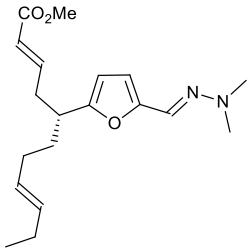
	RT	% Area
1	3.871	3.18
2	4.084	96.82

(*R*,2*E*,8*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)undeca-2,8-dienoate (**7l**)

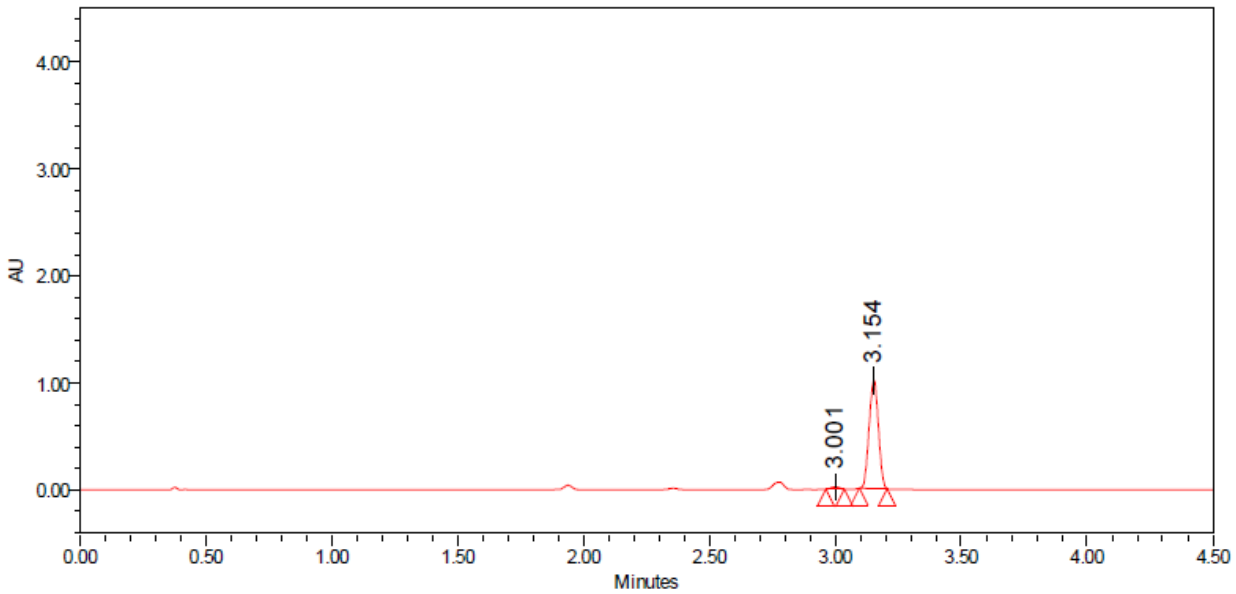
Racemic sample



Enantiomerically enriched sample



7l

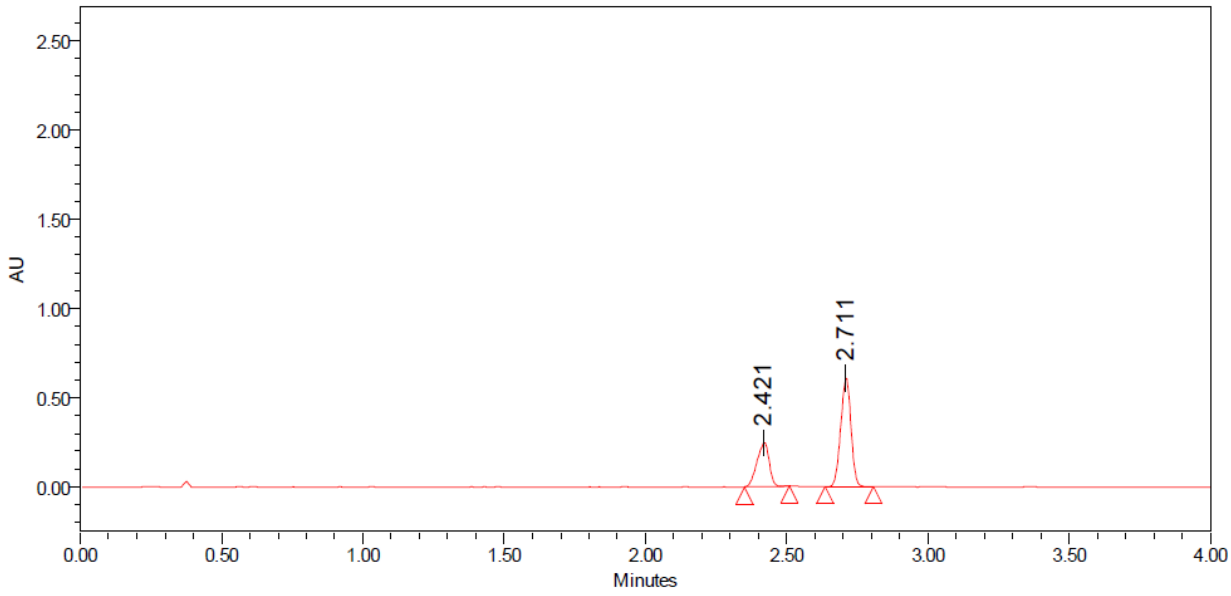


Peak Results

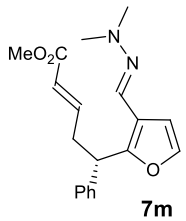
	RT	% Area
1	3.001	2.06
2	3.154	97.94

(*S*,*E*)-Methyl 5-(3-((*E*)-(2,2-dimethylhydrazono)methyl)furan-2-yl)-5-phenylpent-2-enoate (**7m**)

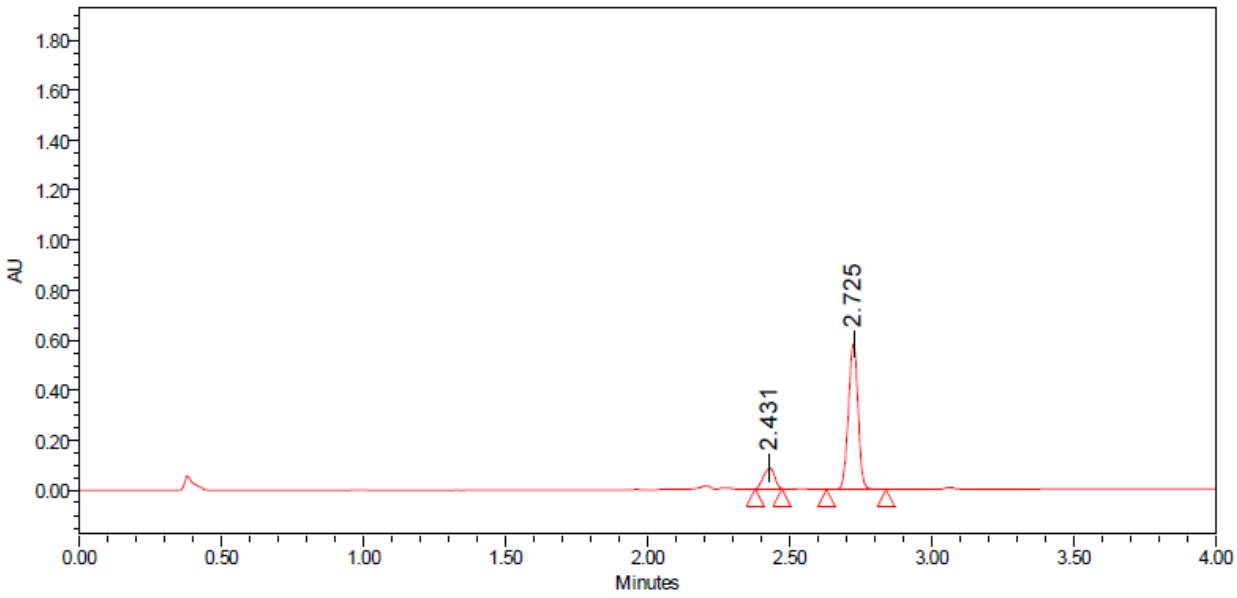
Racemic sample



Enantiomerically enriched sample



7m

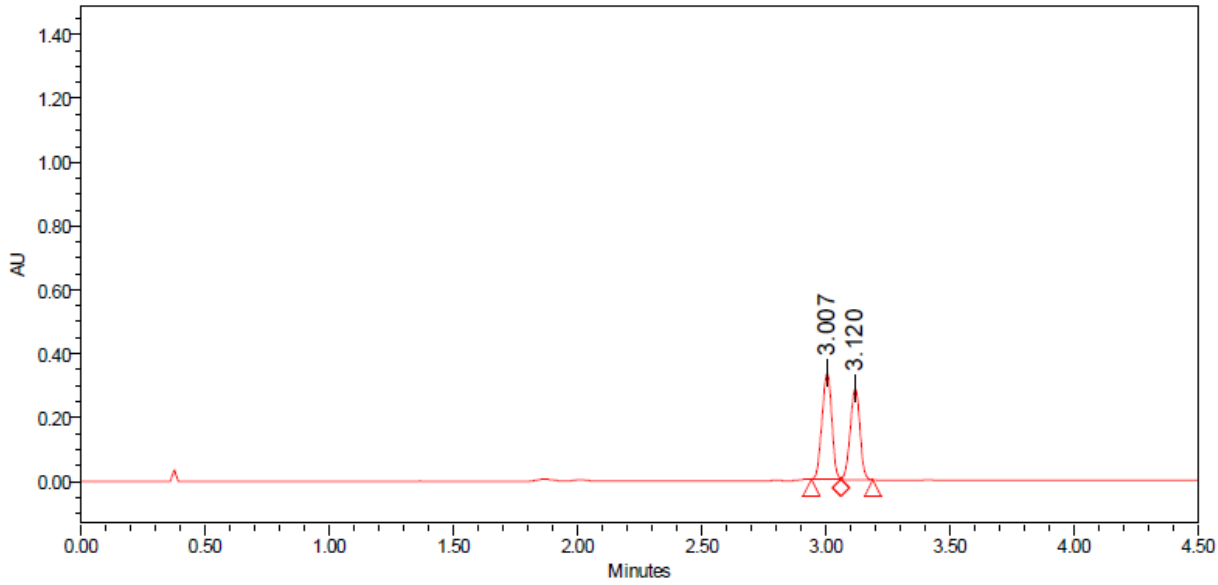


Peak Results

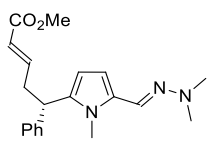
	RT	% Area
1	2.431	13.99
2	2.725	86.01

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)-1-methyl-1*H*-pyrrol-2-yl)-5-phenylpent-2-enoate (**7n**)

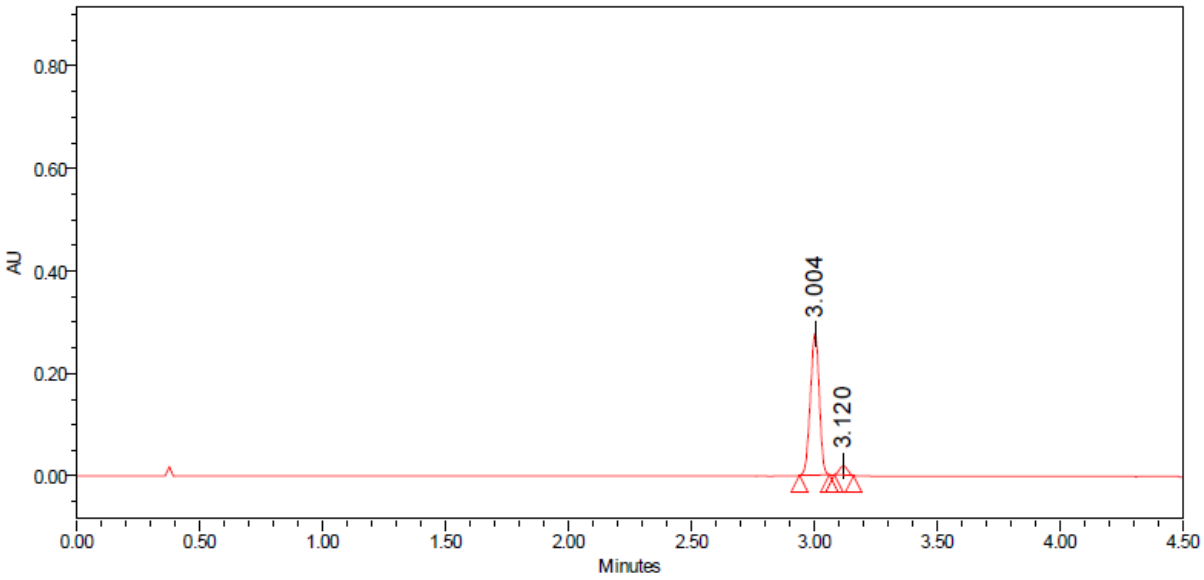
Racemic sample



Enantiomerically enriched sample



7n

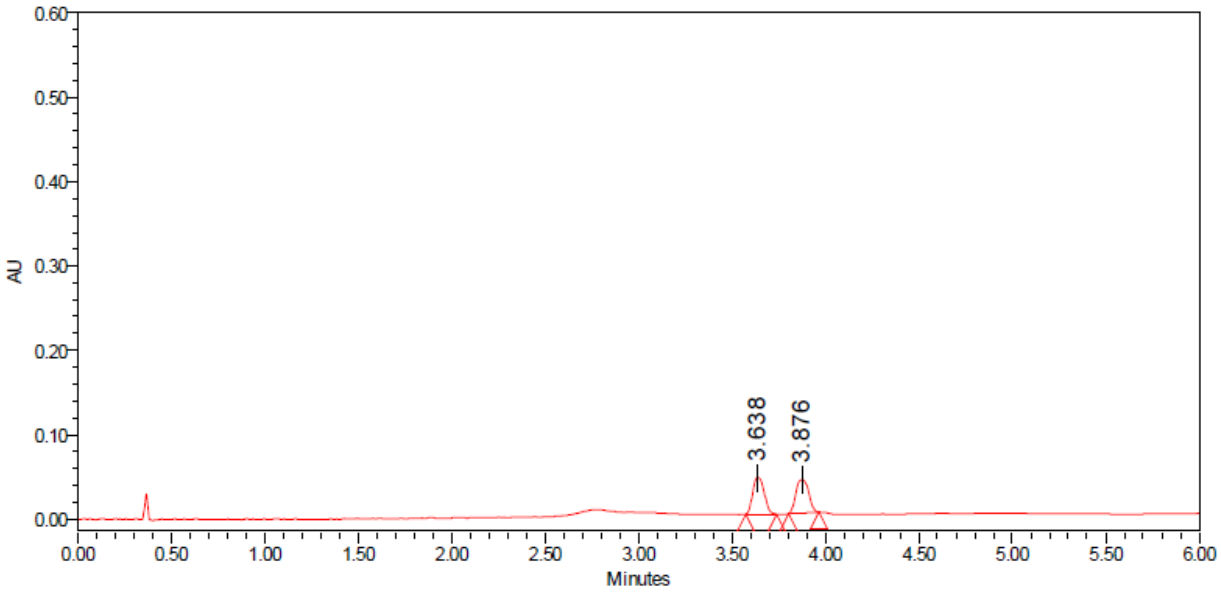


Peak Results

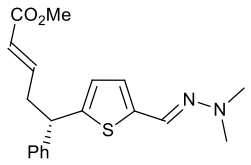
	RT	% Area
1	3.004	94.70
2	3.120	5.30

(*S*,*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)thiophen-2-yl)-5-phenylpent-2-enoate (**7o**)

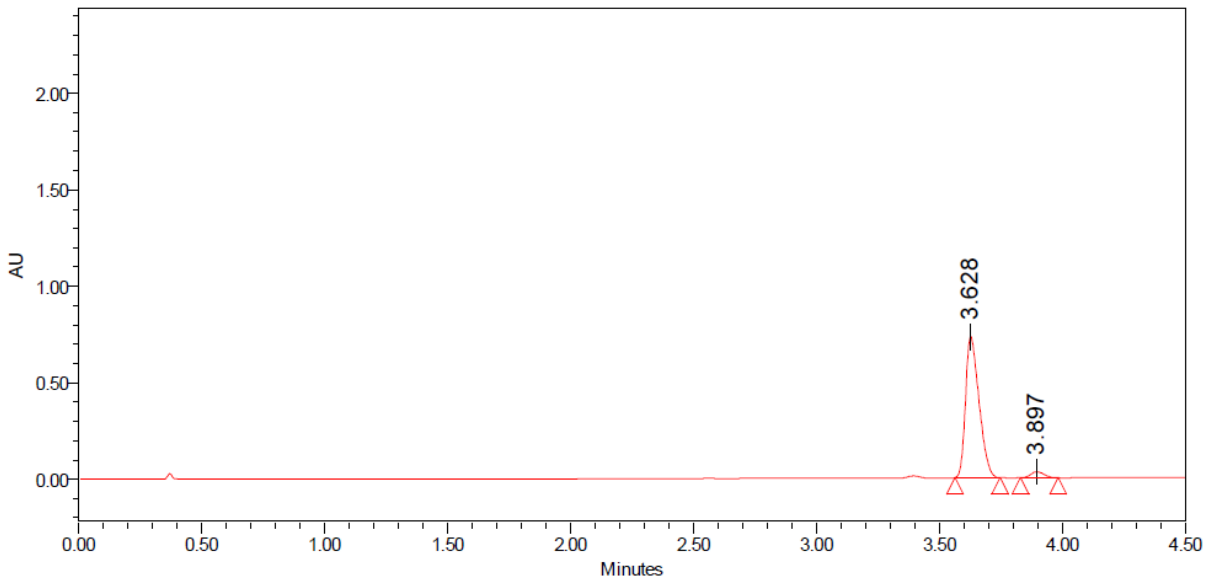
Racemic sample



Enantiomerically enriched sample



7o

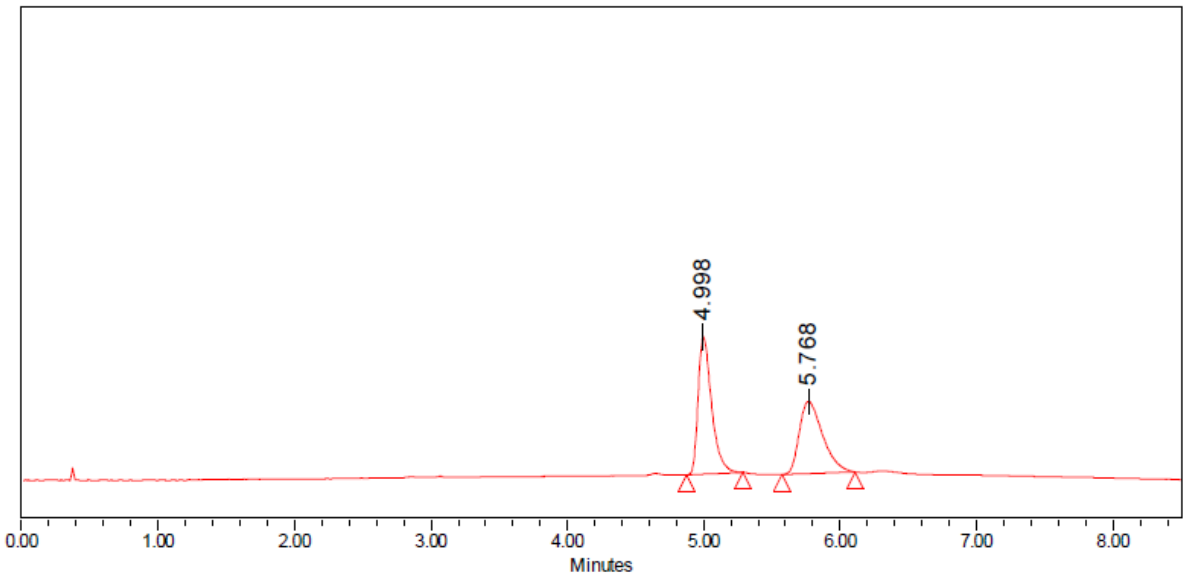


Peak Results

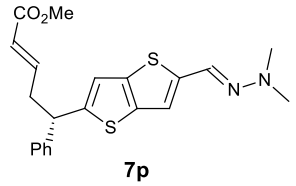
	RT	% Area
1	3.628	96.03
2	3.897	3.97

(*S*)-(*E*)-Methyl 5-(5-((*E*)-(2,2-dimethylhydrazono)methyl)thieno[3,2-*b*]thiophen-2-yl)-5-phenylpent-2-enoate (**7p**)

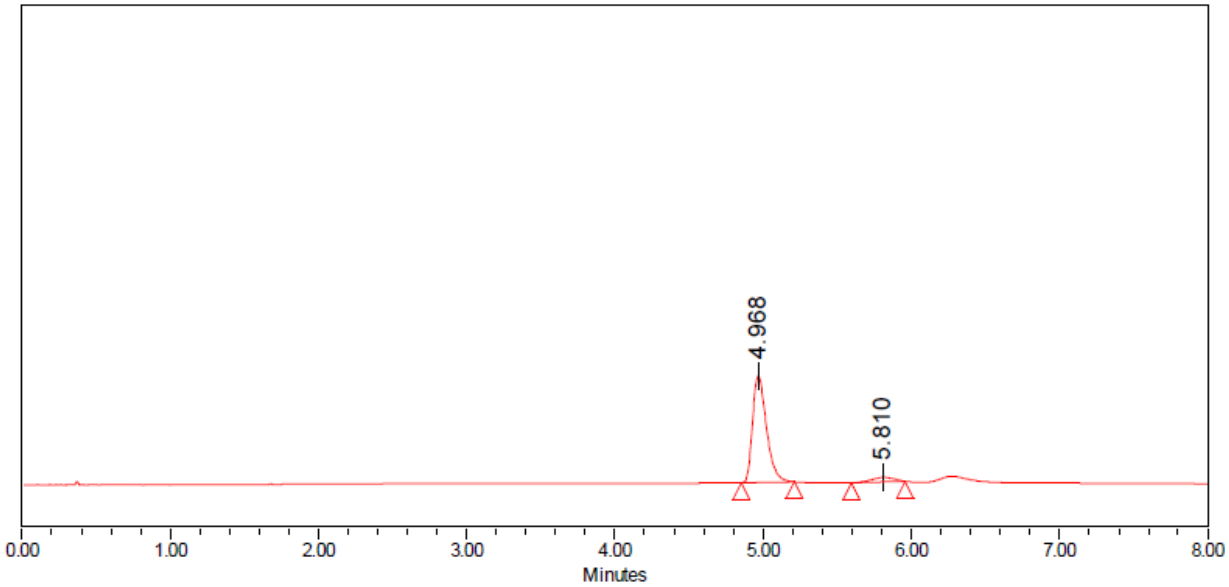
Racemic sample



Enantiomerically enriched sample



7p

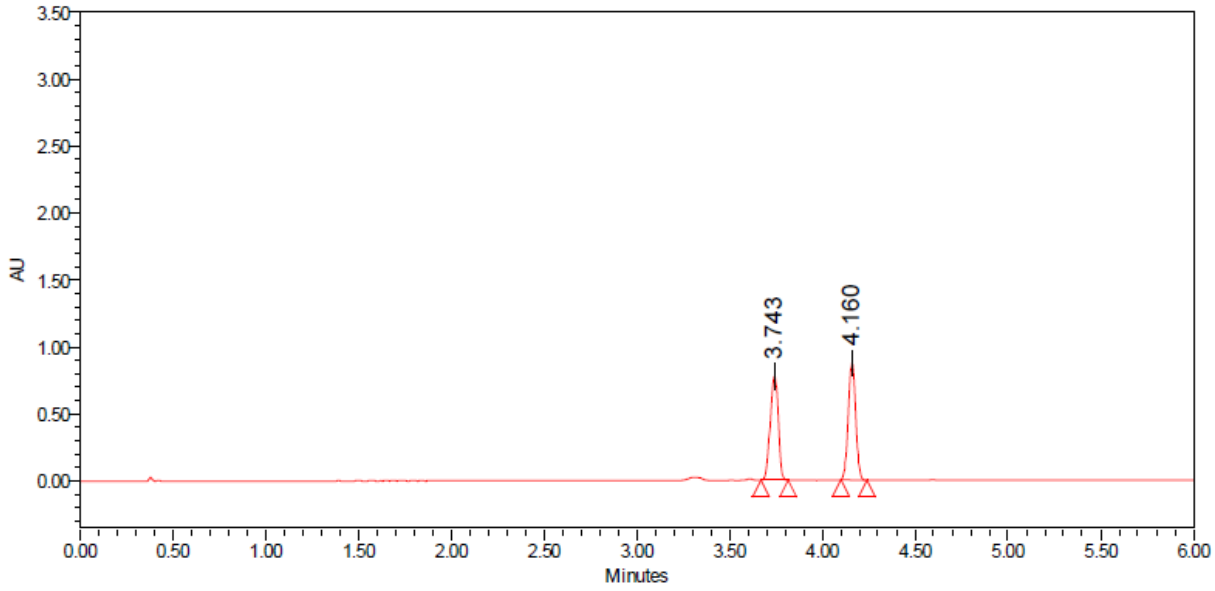


Peak Results

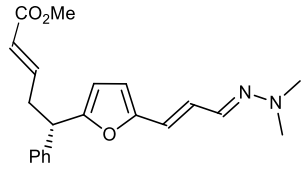
	RT	% Area
1	4.968	93.57
2	5.810	6.43

(*S*,*E*)-Methyl 5-(5-((1*E*,3*E*)-3-(2,2-dimethylhydrazono)prop-1-en-1-yl)furan-2-yl)-5-phenylpent-2-enoate (**7q**)

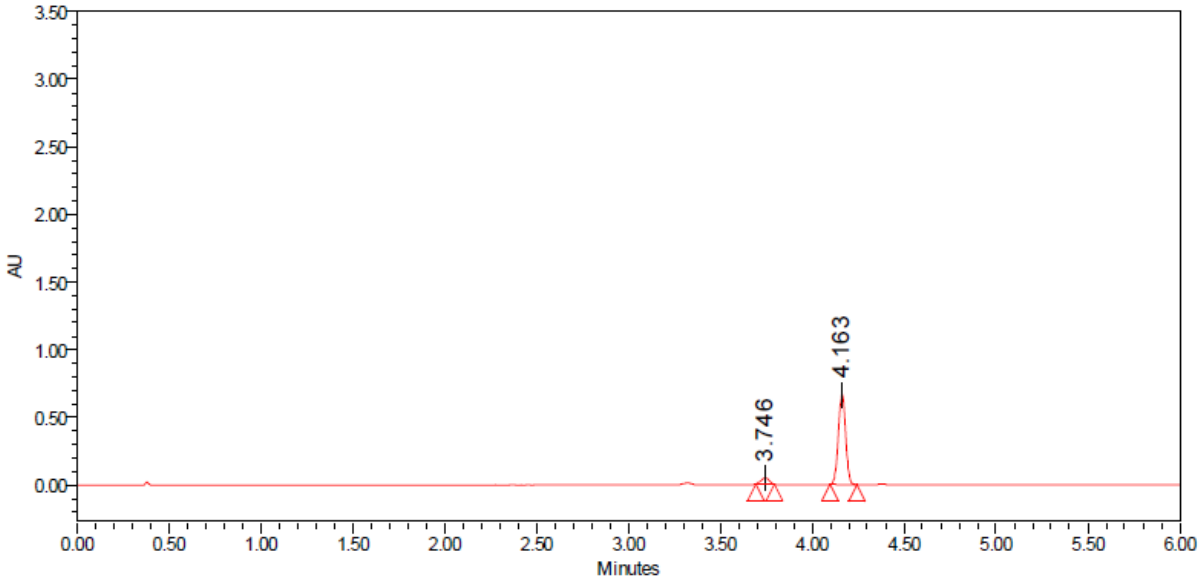
Racemic sample



Enantiomerically enriched sample



7q

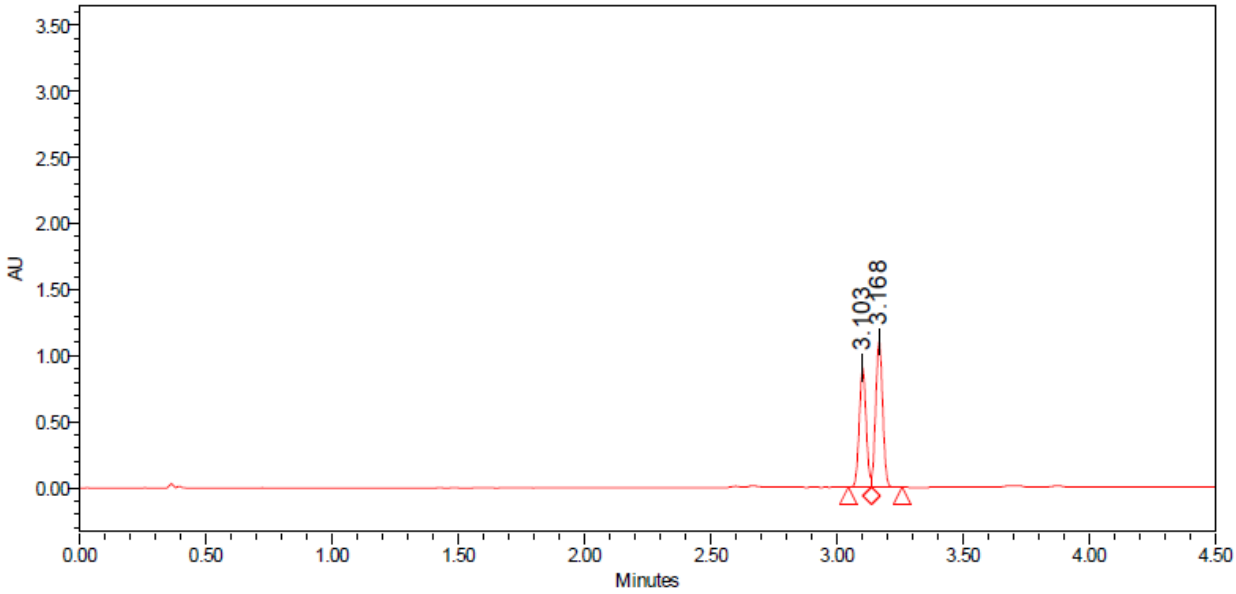


Peak Results

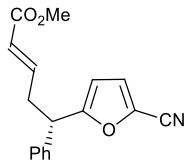
	RT	% Area
1	3.746	7.08
2	4.163	92.92

(*S*,*E*)-Methyl 5-(5-cyanofuran-2-yl)-5-phenylpent-2-enoate (**8a**)

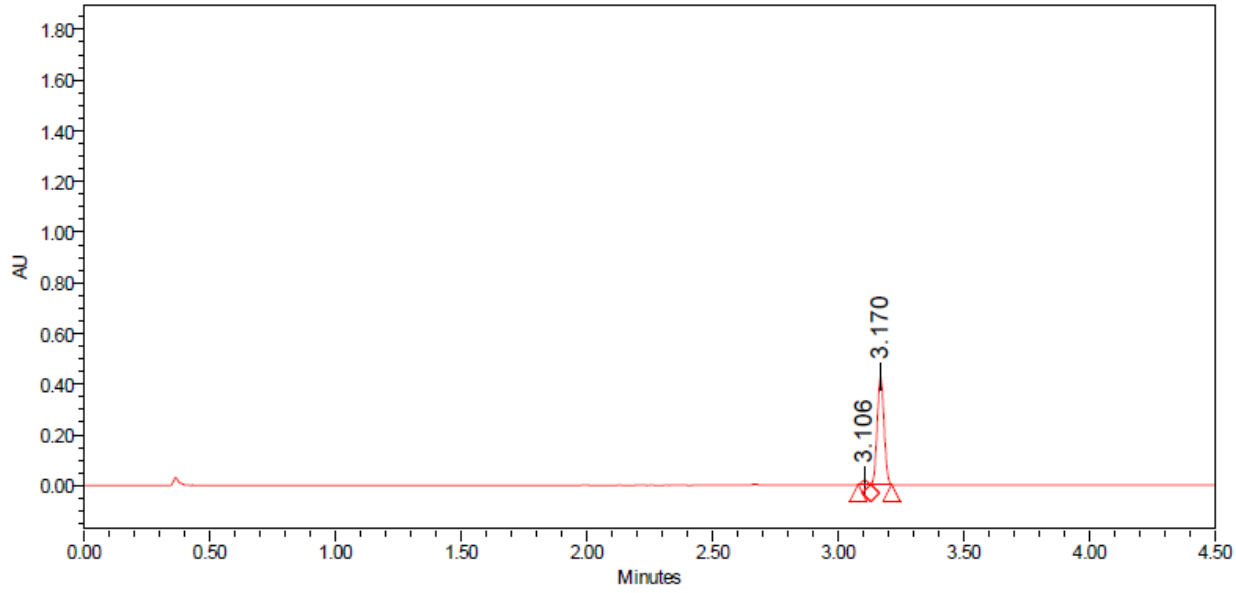
Racemic sample



Enantiomerically enriched sample



8a

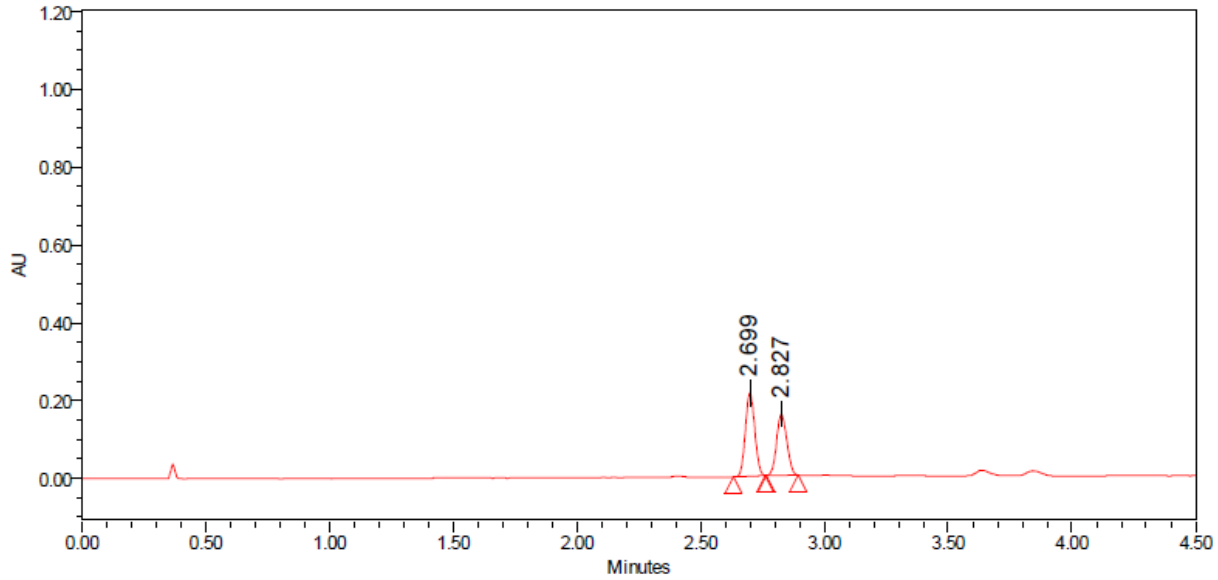


Peak Results

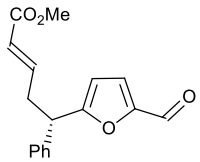
	RT	% Area
1	3.106	3.34
2	3.170	96.66

(*S*,*E*)-Methyl 5-(5-formylfuran-2-yl)-5-phenylpent-2-enoate (**9a**)

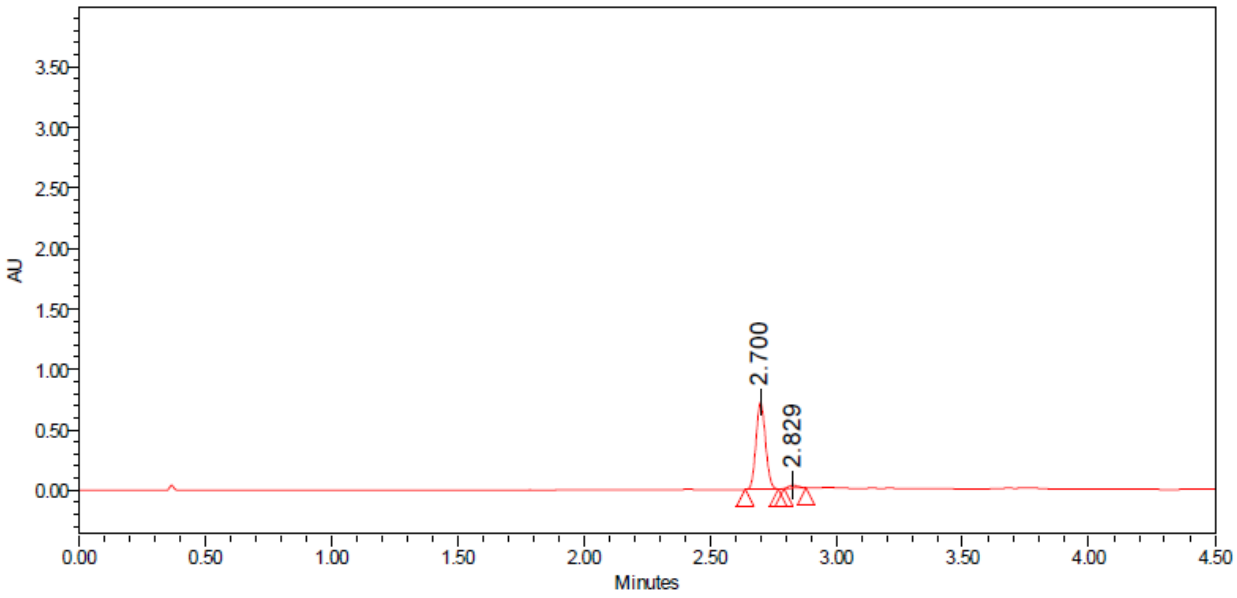
Racemic sample



Enantiomerically enriched sample



9a



Peak Results

	RT	% Area
1	2.700	96.81
2	2.829	3.19