Supporting information for

An efficient total synthesis of leukotriene B_4

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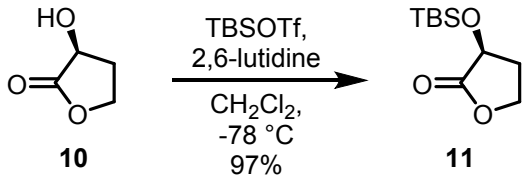
Table of Contents:

General Information

Unless stated otherwise, all commercially available reagents and solvents were used in the form they were supplied without any further purification. The stated yields are based on isolated material. All reactions were performed under an argon atmosphere using Schlenk techniques. Reaction flasks were covered with aluminium foil during reactions and storage to minimize exposure to light. Thin layer chromatography was performed on silica gel 60 F_{254} aluminum-backed plates fabricated by Merck. Flash column chromatography was performed on silica gel 60 (40-63 μm) produced by Merck. NMR spectra were recorded on a Bruker AVI600, Bruker AVII400 or a Bruker DPX300 spectrometer at 600 MHz, 400 MHz or 300 MHz respectively for ^{1}H NMR and at 150 MHz, 100 MHz or 75 MHz respectively for ^{13}C NMR. Coupling constants (*J*) are reported in hertz and chemical shifts are reported in parts per million (δ) relative to the central residual protium solvent resonance in ^{1}H NMR ($CDCl_3$ = δ

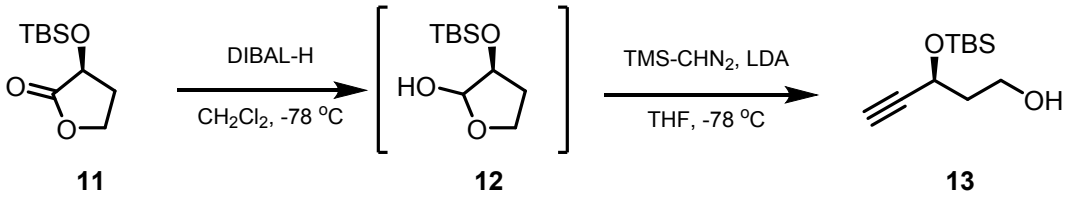
7.26, DMSO-d_6 = δ 2.50 and MeOD-d_4 = δ 3.31) and the central carbon solvent resonance in ^{13}C NMR ($CDCl_3$ = δ 77.00 ppm, DMSO-d_6 = δ 39.43 and MeOD-d_4 = δ 49.00). Mass spectra were recorded at 70 eV on Waters Prospec Q spectrometer using EI, ES or CI as the methods of ionization. High resolution mass spectra were recorded on Waters Prospec Q spectrometer using EI or ES as the methods of ionization. Optical rotations were measured using a 1 mL cell with a 1.0 dm path length on a Perkin Elmer 341 polarimeter. HPLC analyses were performed on an Agilent Technologies 1200 Series instrument with diode array detector set at 254 nm and equipped with a C_{18} stationary phase (Eclipse XDB-C18 5µm 4.6 × 150 mm), applying the conditions stated. The UV/Vis spectra from 190-900 nm were recorded using a Biochrom Libra S32PC spectrometer using quartz cuvettes. Diastereomeric ratios reported in this paper have not been validated by calibration, please see reference Wernerova and Hudlicky[1] for discussions and guidelines.

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)dihydrofuran-2(3*H*)-one (11).



Following the procedure reported by Corey and coworkers,[2] alcohol **10** (5.00 g, 49.0 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (250 mL) under argon. The solution was cooled to -78 °C and after ten minutes, 2.6-lutidine (17 mL, 14.0 mmol, 3.0 eq.) was added. After an additional ten minutes, TBSOTf (11.0 g, 49.0 mmol, 1.0 eq.) was added dropwise. The reaction mixture was stirred at -78 °C and it was allowed to reach room temperature over night. Sat. aq. NH_4Cl (50 mL) was added and the layers were separated. The aq. layer was extracted with CH_2Cl_2 (3×25 mL) and the combined organic layers were dried (Na_2SO_4). The solvent was removed *in vacuo* and the crude product was purified by flash chromatography on silica gel (hexane, then hexane/EtOAc 8:2) to afford the desired product **11** as a colourless oil. All spectroscopic and physical data were in full agreement with those reported in the literature.[3] Yield: 10.0 g (97%); TLC (hexane/EtOAc 8:2, $KMnO_4$ stain): R_f = 0.29 $[\alpha]_D^{20}$ = -31 (c = 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 – 4.32 (m, 2H), 4.21 – 4.12 (m, 1H), 2.49 – 2.39 (m, 1H), 2.27 – 2.12 (m, 1H), 0.89 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 68.3, 64.8, 32.4, 25.7, 18.3, -4.6, -5.2.

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)pent-4-yn-1-ol (13).



11 **12** **13**

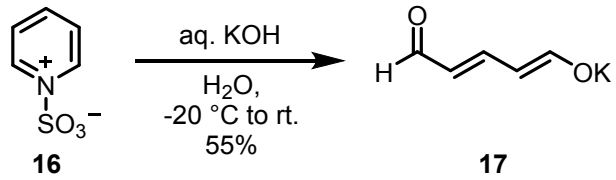
57% over the two steps

TBS-protected lactone **11** (1.50 g, 6.90 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (75 mL) and cooled to -78 °C. DIBAL-H (8.30 mL, 1.0 M in CH_2Cl_2, 8.30 mmol, 1.2 eq.) was added dropewise and the solution was stirred until completion by TLC (hexane/EtOAc 6:4) (~ two hours) at -78 °C. The reaction was stirred for another 30 minutes before a solution of sat. aq. Rochelle-salt (30 mL) was added. The reaction was allowed to reach rt. The layers were separated and the aq. layer was extracted with CH_2Cl_2 (3×35 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude lactol was azetroped with 2-Me-THF before beeing dissolved in THF (18 mL). LDA (17 mL, 1.0 M in THF/hexane) was diluted with THF (20 mL) and cooled to -78 °C. TMS-diazomethane (4.10 mL, 2.0 M in Et_2O) was added and the mixture was stirred for 30 minutes. To this solution, the THF-solution containing the crude lactol **12** was added as quickly as possible without allowing the reaction mixture to warm too much, and the combined mixture stirred for another two hours at -78 °C. The cooling bath was removed and the reaction was allowed to reach rt. slowly and then stirred for 30 minutes at rt. The solution was carefully quenched with sat. aq. NH_4Cl (20 mL). The layers were separated and the aq. layer was extracted with Et_2O (3×20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc 8:2) to afford the desired product **13** as a colourless oil in 57% yield (0.85 g) from lactone **10**; Spectroscopic and physical data were in agreement with those reported in the literature.[4, 5]

20

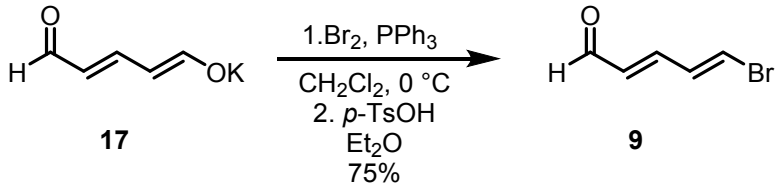
TLC (hexane/EtOAc 8:2, $KMnO_4$ stain): R_f = 0.21; $[\alpha]^D$ = -55 (c = 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (ddd, *J* = 7.0, 5.1, 2.1 Hz, 1H), 3.89 (ddd, *J* = 11.8, 7.6, 4.2 Hz, 1H), 3.75 (ddd, *J* = 10.9, 6.1, 4.5 Hz, 1H), 2.47 (bs, 1H), 2.42 (d, *J* = 2.1 Hz, 1H), 2.02 – 1.82 (m, 2H), 0.88 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 84.8, 73.2, 61.8, 59.8, 40.2, 25.8, 18.2 (3C), -4.5, -5.1.

Potassium (1*E*,3*E*)-5-oxopenta-1,3-dien-1-olate (17).



Glutaconaldehyde potassium salt **17** was prepared from commercially available pyridinium-1-sulfonate (**16**) according to the procedure of Becher.[6] Pyridinium-1-sulfonate **16** (60.8 g, 0.38 mol, 1.0 eq.) was added to a solution of KOH (87.5 g, 1.56 mol, 4.1 eq.) in H_2O (210 mL). The solution was stirred and cooled to −20 °C. After one hour, the temperature was slowly raised to 20 °C over four hours. The mixture was heated to 30–40 °C for 30 minutes and then cooled to 5 °C. The crude product that precipitated was filtered, washed with acetone (2×80 mL) and dried in the air, giving red-brown crystals. MeOH (1.40 L) was added to the crude product and the mixture was heated to reflux before activated carbon (2.80 g) was added. The carbon was filtered off and the filtrate was concentrated under reduced pressure to a volume of ~ 55 mL. The pale yellow crystals of glutaconaldehyde potassium salt **17** were collected, washed with acetone and dried. All spectroscopic and physical data were in full agreement with those reported in the literature.[6] Yield: 28.5 g (55%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.67 (d, J = 9.2 Hz, 2H), 7.04 (t, J = 12.9 Hz, 1H), 5.10 (dd, J = 13.0, 9.1 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 184.4 (2C), 159.8, 106.2 (2C).

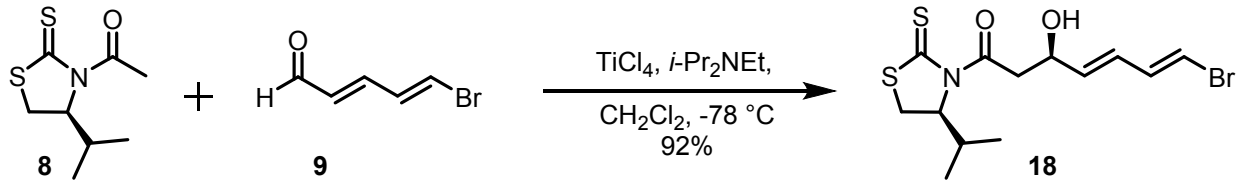
(2*E*,4*E*)-5-Bromopenta-2,4-dienal (9).



Bromopentadienal **9** was prepared by the bromination of glutaconaldehyde potassium salt **17** according to the protocol reported by Duhamel *et al*.[7] Bromine (12.6 g, 78.8 mmol, 1.2 eq.) was added dropwise to a solution of triphenylphosphine (21,5 g, 81.9 mmol, 1.2 eq.) in CH_2Cl_2 (320 mL) at 0 °C. The reaction mixture was stirred for four hours at ambient temperature. The black/red-brown crude product was filtered trough a pad of silica giving a yellow oil which was futher purified by flash chromatography on silica gel (hexane/EtOAc 9:1) to affording a mixture of the *E*,*E*- and the *E*,*Z*-isomer (3:1). The mixture was dissolved in Et_2O (125 mL). *p*-TsOH (600 mL) was added and the solution was stirred for five minutes before being concentrated *in vacuo*. The slurry was dissolved in Et_2O (30.0 mL), filtered trough

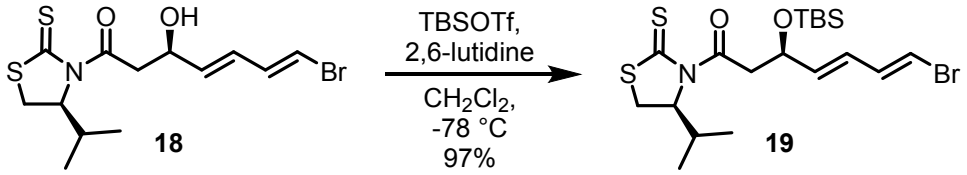
a pad of silica and consentrated *in vacuo* to afford the product **9** as a yellow oil. All spectroscopic and physical data were in agreement with those reported in the literature.[7] Yield: 8.10 g (75%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (d, *J* = 7.8 Hz, 1H), 7.07 – 6.90 (m, 3H), 6.24 – 6.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3, 147.9, 135.7, 132.0, 120.0.

(*R*,4*E*,6*E*)-7-Bromo-3-hydroxy-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)hepta-4,6-dien-1-one (18)



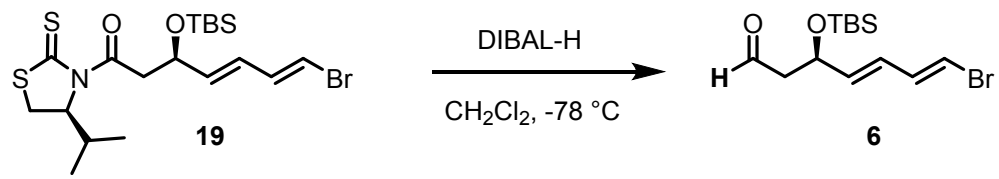
The (*R*)-aldol product **18** was prepared according to the procedure of Olivo and coworkers.[8] To a solution of *N*-acetylthiazolidinethione **8** (5.0 g, 24.6 mmol, 1.0 eq.) in CH_2Cl_2 (245 mL), $TiCl_4$ (4.66 g, 1.0M in CH_2Cl_2, 24.6 mmol, 1.0 eq.) was added at -78 °C and stirred for five minutes. Hünig's base (3.81 g, 29.5 mmol, 1.2 eq.) in CH_2Cl_2 (61 mL) was added and the solution was stirred for 30 min at -78 °C, whereupon the freshly prepared aldehyde **9** (3.56 g, 22.1 mmol, 0.90 eq.) in CH_2Cl_2 (61 mL) was added dropwise. The mixture was stirred for one hour at -78 °C and then quenched with half aq. saturated NH_4Cl (100 mL), before it was warmed to room temperature. The layers were separated and the aq. layer was extracted with CH_2Cl_2 (80 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 7:3) to afford the product **18** as a yellow oil. All spectroscopic and physical data were in full agreement with those reported in the literature.[8] Yield: 7.41 g (92%); $[\alpha]_D^{20}$ = 271 (c = 0.13, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (dd, *J* = 13.5, 10.8 Hz, 1H), 6.35 (d, *J* = 13.6 Hz, 1H), 6.26 (ddd, *J* = 15.3, 10.8, 1.5 Hz, 1H), 5.79 (dd, *J* = 15.3, 5.4 Hz, 1H), 5.16 (dd, *J* = 7.8, 6.4 Hz, 1H), 4.76–4.65 (m, 1H), 3.70 (dd, *J* = 17.6, 3.1 Hz, 1H), 3.53 (dd, *J* = 11.5, 7.9 Hz, 1H), 3.29 (dd, *J* = 17.6, 8.6 Hz, 1H), 3.04 (dd, *J* = 11.6, 1.1 Hz, 1H), 2.93 (d, *J* = 4.5 Hz, 1H), 2.36 (dq, *J* = 13.6, 6.8 Hz, 1H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.1, 172.3, 136.7, 134.8, 128.0, 109.6, 71.5, 68.1, 45.1, 31.0, 30.8, 19.2, 18.0. The diastereomeric ratio (15.3:1) of the crude product was determined by HPLC analysis (Eclipse XDB-C18, MeOH/H_2O 70:30, 1.0 mL/min, t_r(minor) = 8.65 min and t_r(major) = 10.85 min).

(*R*,4*E*,6*E*)-7-Bromo-3-((*tert*-butyldimethylsilyl)oxy)-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)hepta-4,6-dien-1-one (19).



Following the procedure reported by Corey and coworkers,[2] the aldol product **18** (3.30 g, 9.10 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (90 mL) under argon. The solution was cooled to -78 °C, and after ten minutes, 2.6-lutidine (2.91 g, 27.2 mmol, 3.0 eq.) was added. After an additional ten minutes, TBSOTf (3.11 g, 11.8 mmol, 1.3 eq.) was added dropwise. The reaction mixture was stirred at -78 °C for two hours. Sat. aq. NH_4Cl (80 mL) was added and the layers were separated. The aq. layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (hexane/EtOAc 98:2) to afford the desired product **19** as a yellow oil. All spectroscopic and physical data were in full agreement with those reported in the literature.[9] Yield: 4.21 g (97%); $[\alpha]_D^{20}$ = 263 (c = 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (dd, *J* = 13.4, 10.7 Hz, 1H), 6.31 (d, *J* = 13.5 Hz, 1H), 6.15 (dd, *J* = 15.5, 11.1 Hz, 1H), 5.79 (dd, *J* = 14.9, 6.6 Hz, 1H), 5.04 (t, *J* = 7.0 Hz, 1H), 4.75 (q, *J* = 6.4 Hz, 1H), 3.64 (dd, *J* = 16.6, 7.8 Hz, 1H), 3.47 (dd, *J* = 10.9, 7.9 Hz, 1H), 3.21 (dd, *J* = 16.4, 4.6 Hz, 1H), 3.03 (d, *J* = 11.6 Hz, 1H), 2.48 – 2.26 (m, 1H), 1.06 (d, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 170.9, 136.8, 127.4, 109.1, 71.8, 69.8, 46.2, 31.0, 30.9, 25.9 (3C), 19.3, 18.2, 17.9, -4.2, -4.8.

(*R*,4*E*,6*E*)-7-Bromo-3-((*tert*-butyldimethylsilyl)oxy)hepta-4,6-dienal (6).



Aldehyde **6** was prepared by a DIBAL-H reduction of the protected thiazolidinethione **19** according to the procedure of Olivo *et al*.[9] DIBAL-H (2.50 mL, 1.0 M in hexane, 1.2 eq.) was added to a stirred solution of thiazolidinethione **19** (1.00 g, 2.08 mmol, 1.0 eq.) in CH_2Cl_2 (40 mL) at -78 °C. The mixture

was stirred for three hours and then quenched with sat. aq. $NaHCO_3$ (20 mL). The cooling bath was removed and solid Na-K tartrate (~ 0.70 g) (Rochelle-salt) was added and stirring was continued for another 40 min. Et_2O (70 mL) was added. The layers were separated and the aq. layer was extracted with Et_2O (3×60 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc 95:5) to afford the title compound **6** as yellow oil. All spectroscopic and physical data were in full agreement with those reported in the literature.[9] $[\alpha]_D^{20}$ = 32 (c = 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 2.2 Hz, 1H), 6.69 (dd, *J* = 13.4, 10.8 Hz, 1H), 6.33 (d, *J* = 13.6 Hz, 1H), 6.16 (ddd, *J* = 15.2, 10.6, 1.3 Hz, 1H), 5.75 (ddd, *J* = 15.3, 5.9, 0.8 Hz, 1H), 4.66 (dd, *J* = 6.8, 5.5 Hz, 1H), 2.75 – 2.41 (m, 2H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 136.6, 136.1, 127.6, 109.6, 68.5, 51.4, 25.9, 14.3, -4.2, -4.9.

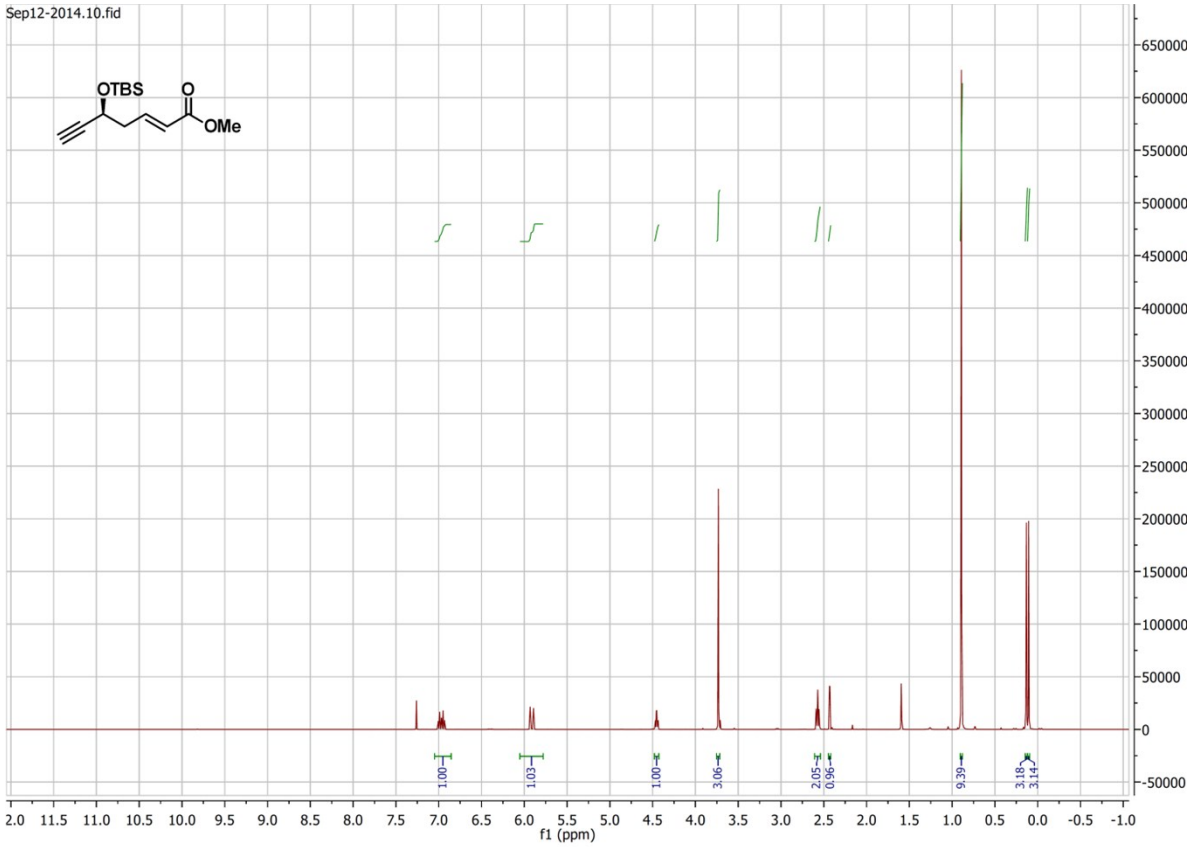


Figure S-3 ^{1}H NMR spectrum of compound **15**.

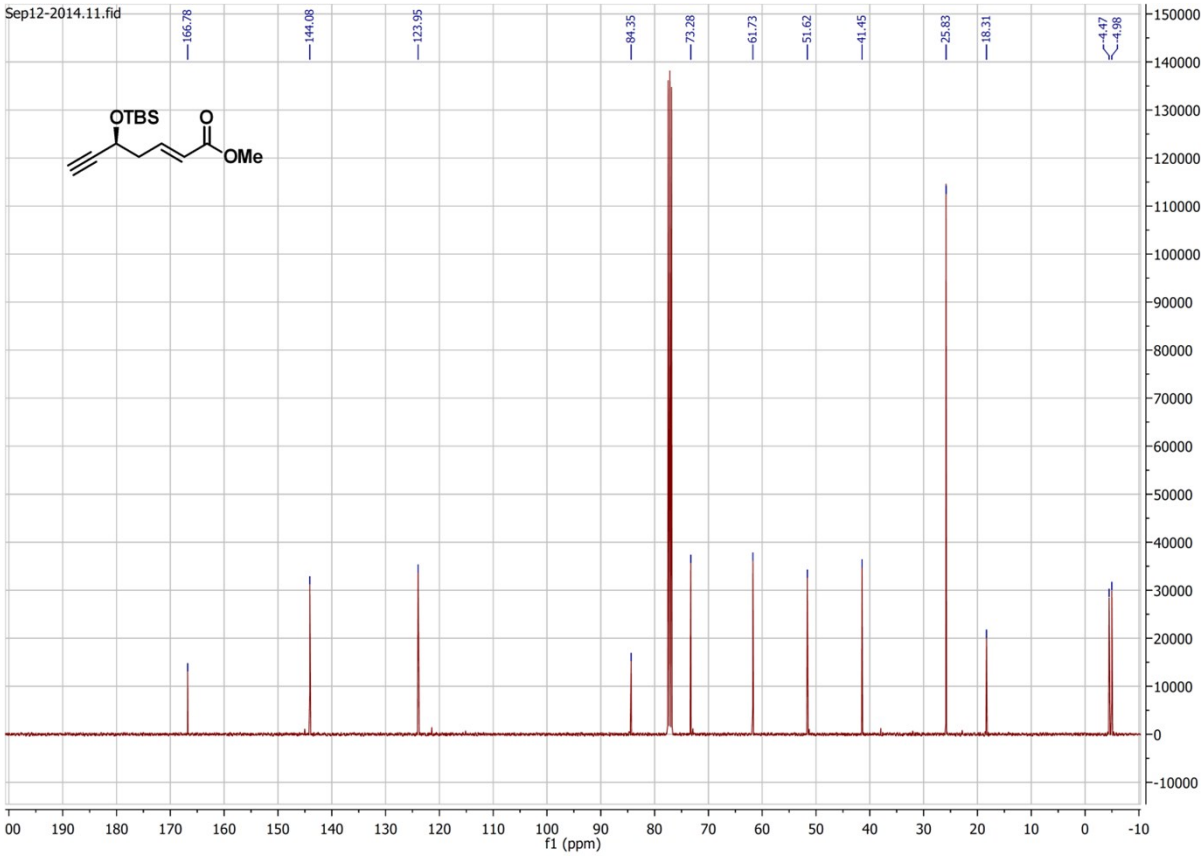


Figure S-4 ^{13}C NMR spectrum of compound **15**.

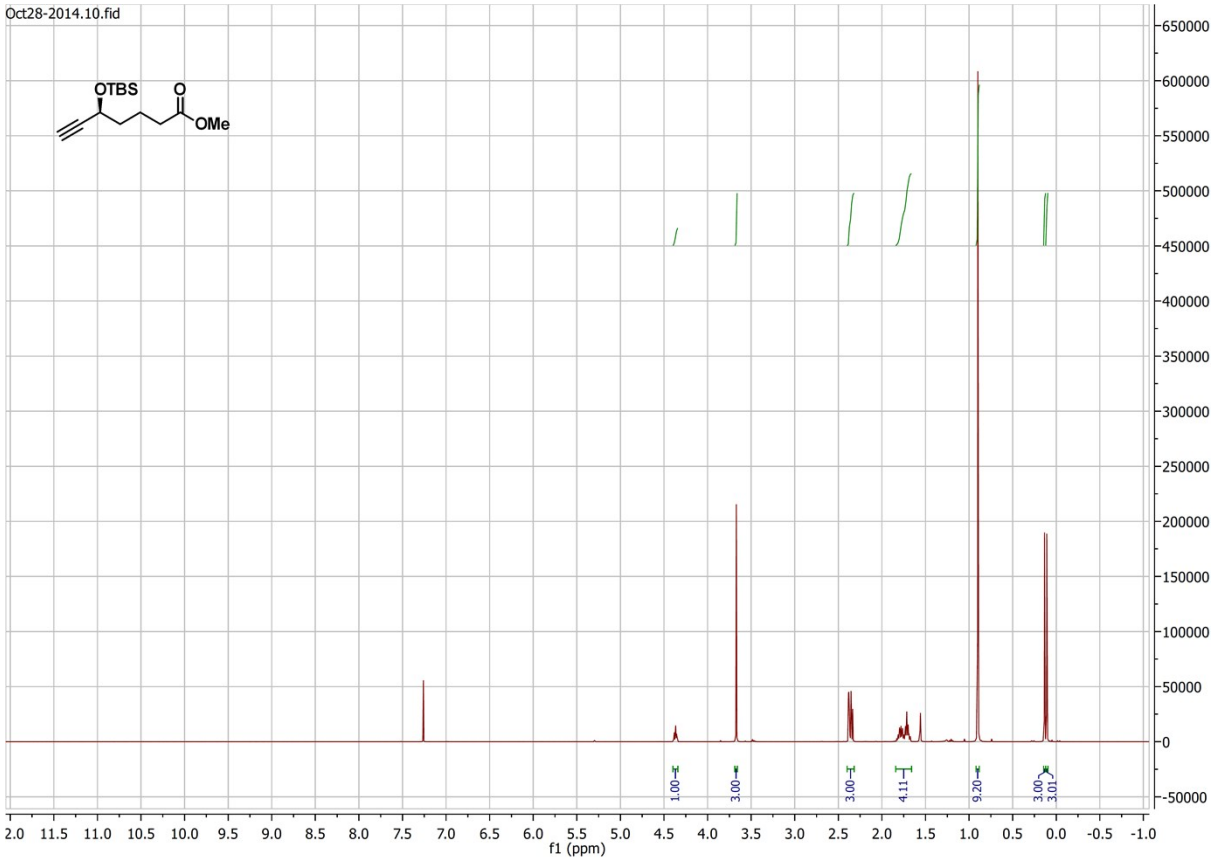


Figure S-5 ^{1}H NMR spectrum of compound **7**.

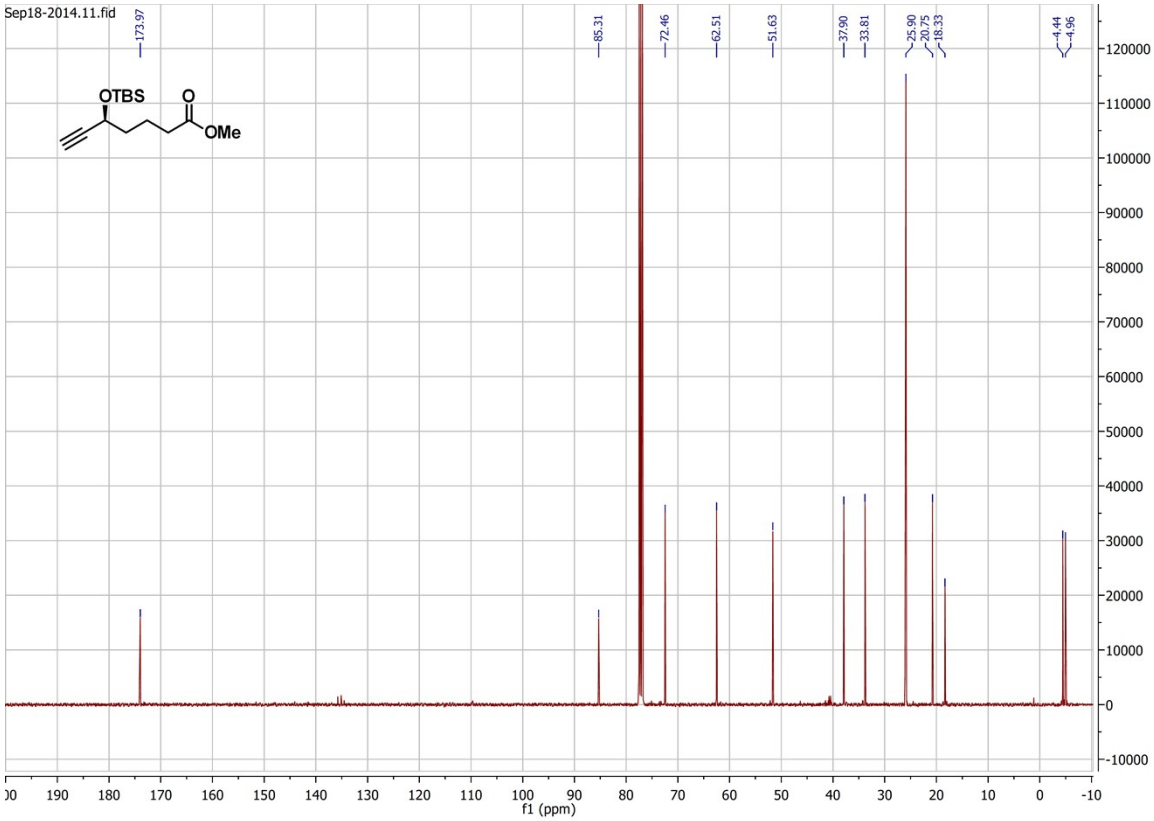


Figure S-6 ^{13}C NMR spectrum of compound **7**.

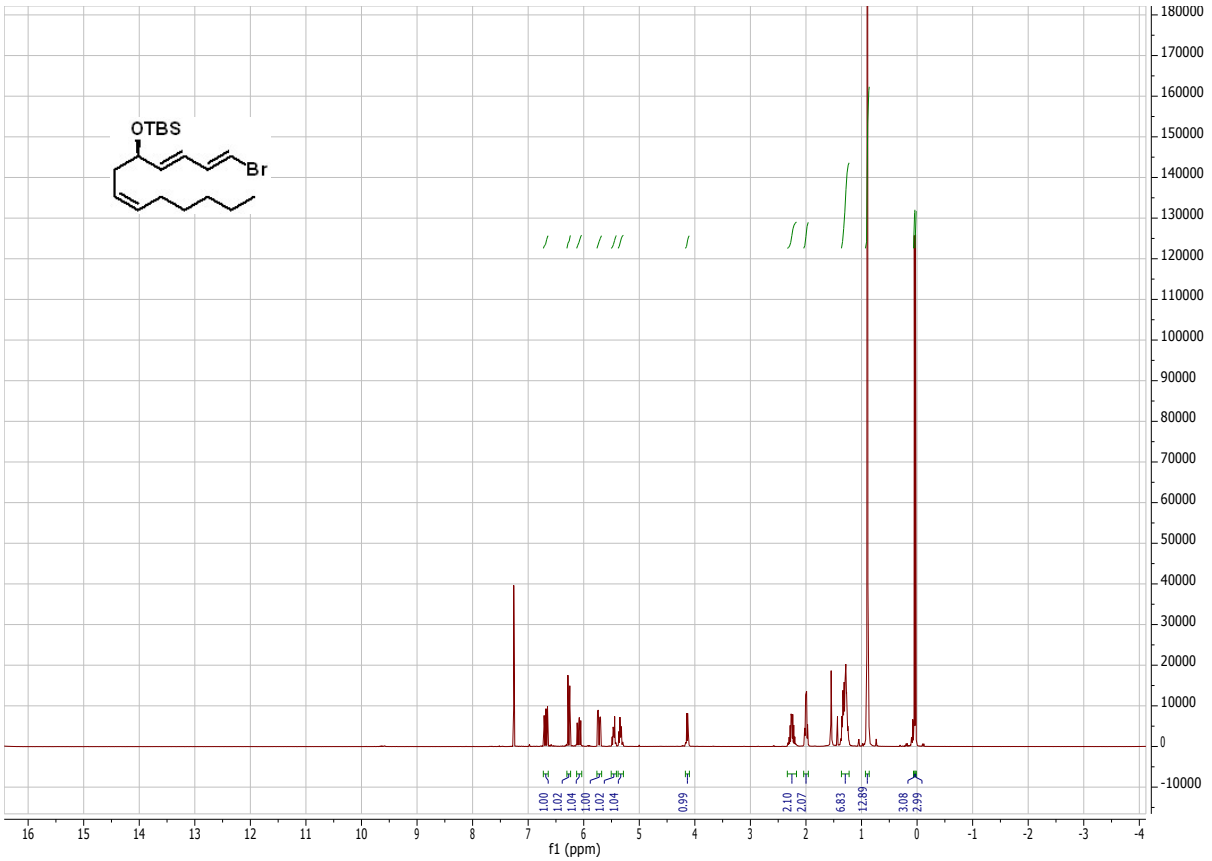


Figure S-1 ^{1}H NMR spectrum of compound **20**.

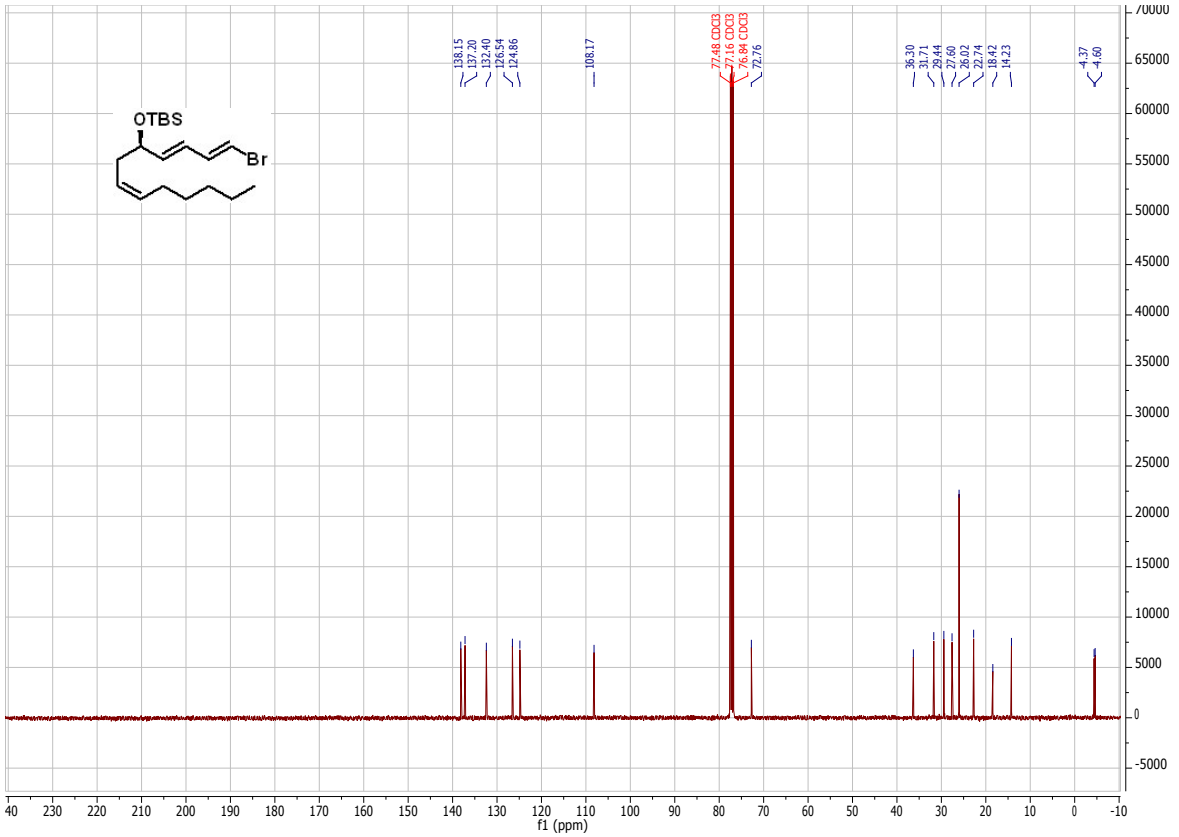


Figure S-2 ^{13}C NMR spectrum of compound **20**.

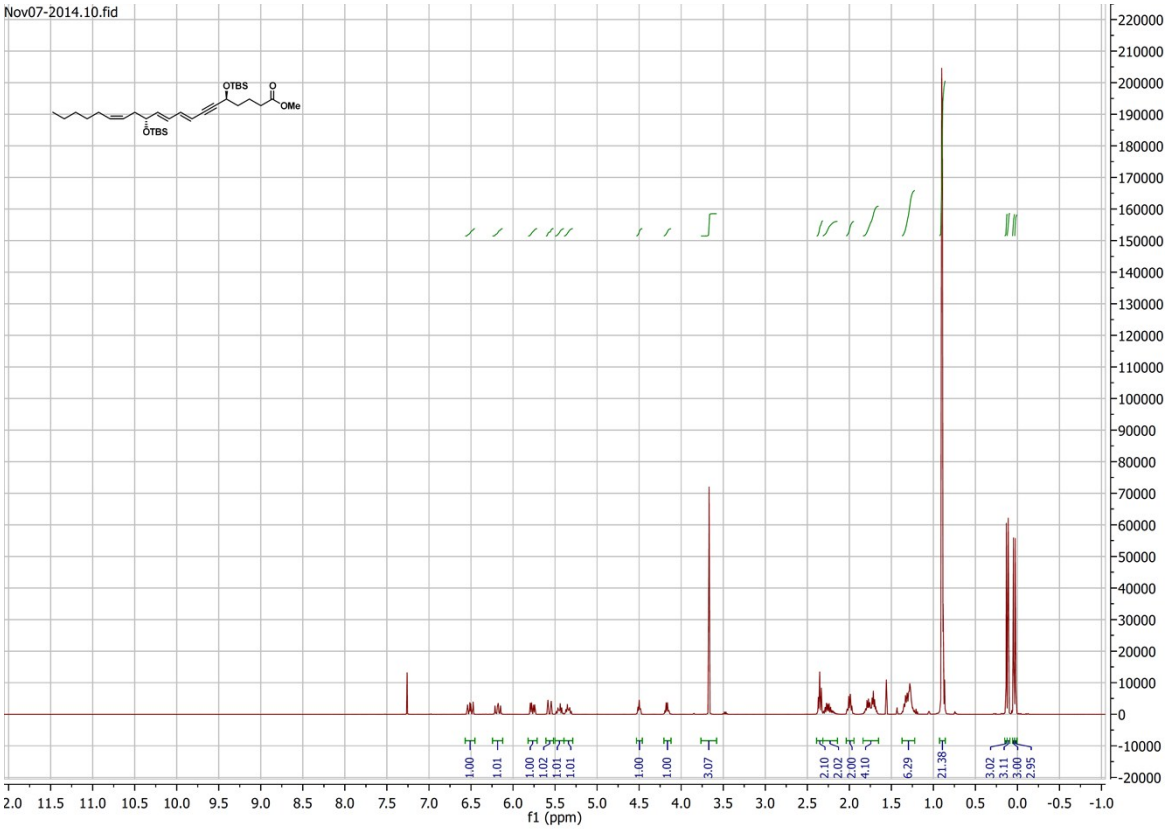


Figure S-7 ^{1}H NMR spectrum of compound **21**.

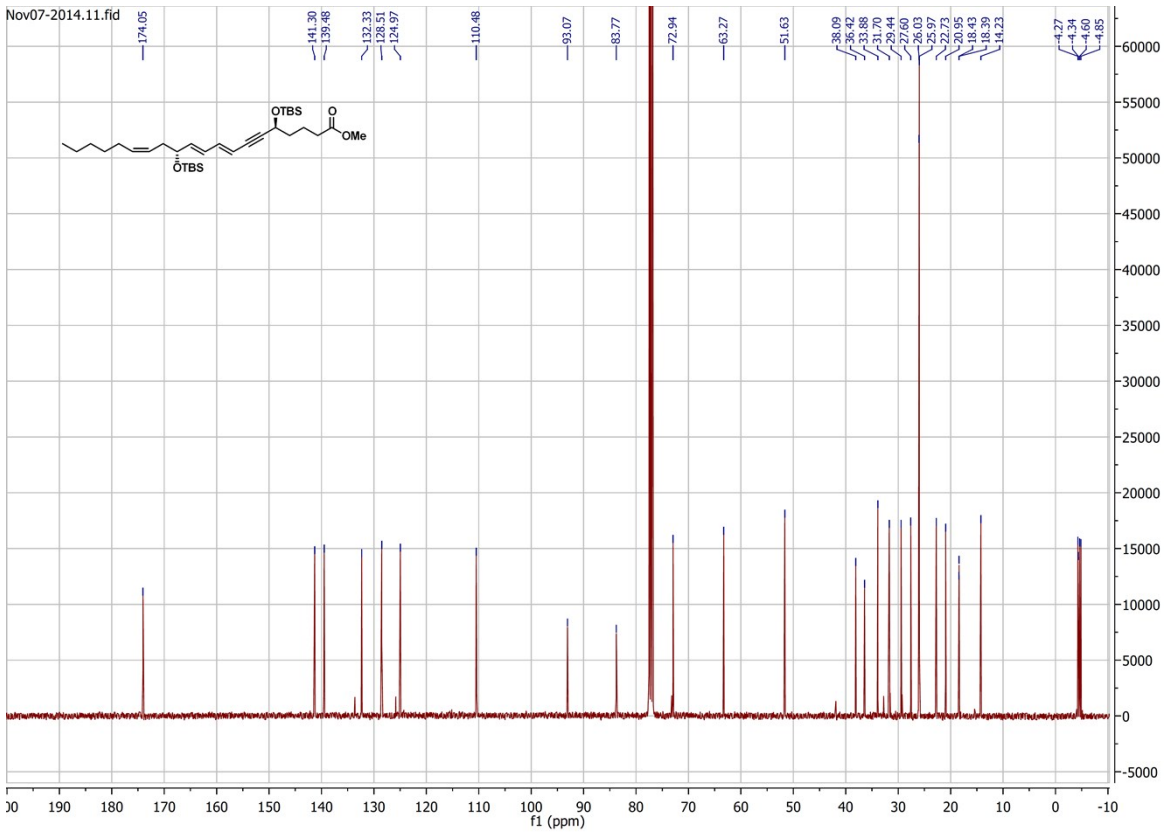


Figure S-8 ^{13}C NMR spectrum of compound **21**.

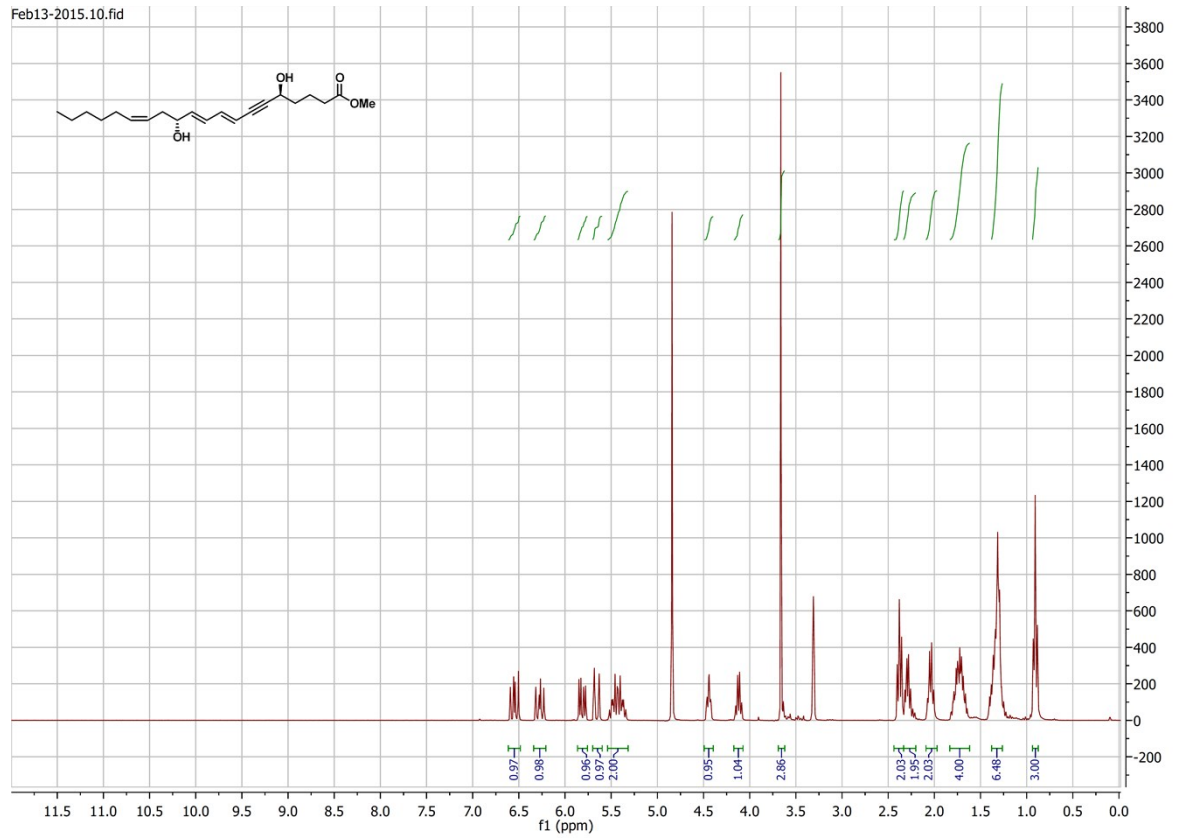


Figure S-9 ^{1}H NMR spectrum of compound **22**.

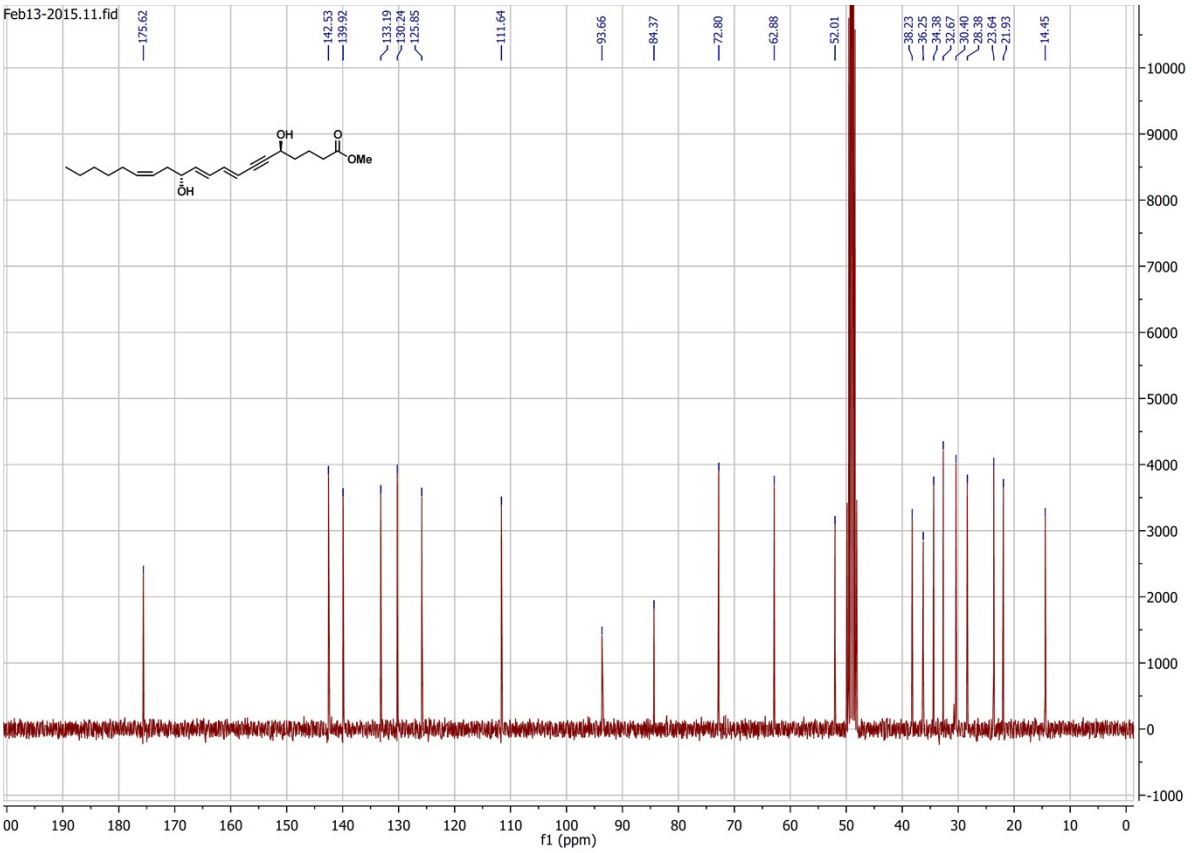


Figure S-10 ^{13}C NMR spectrum of compound **22**.

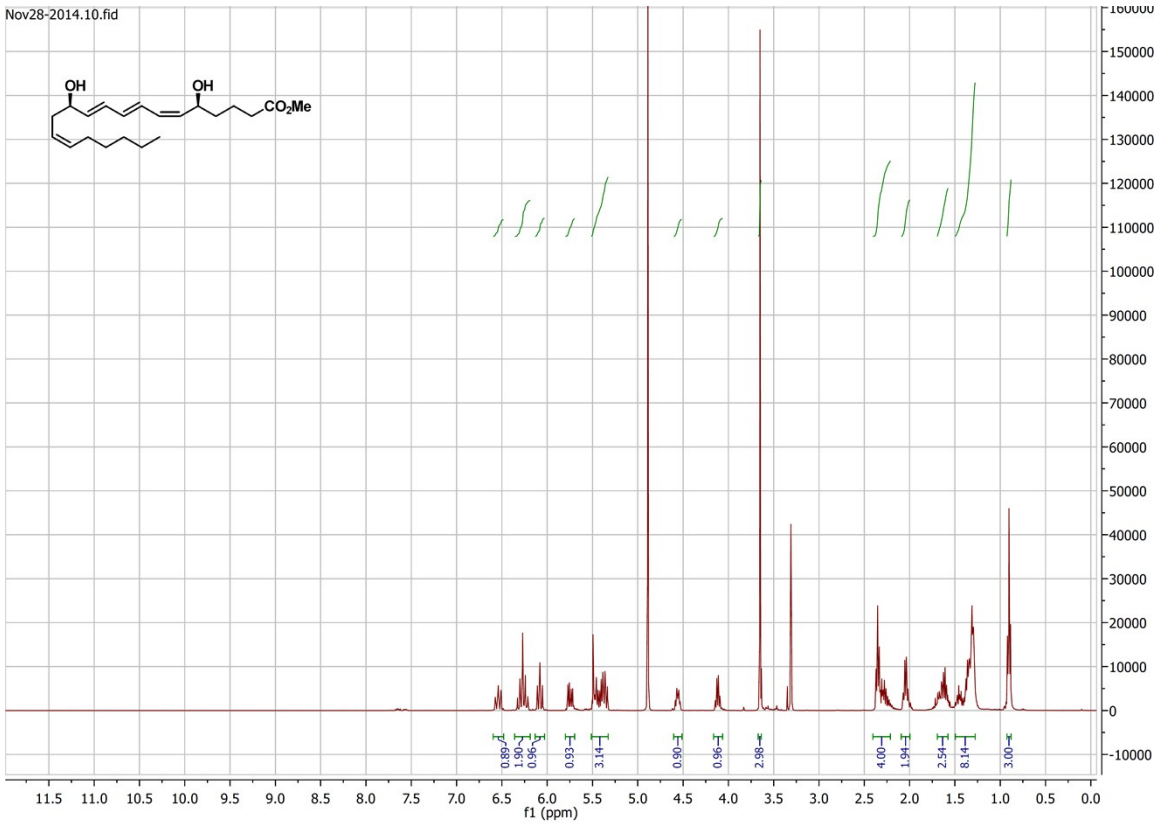


Figure S-11 ^{1}H NMR spectrum of compound **23**.

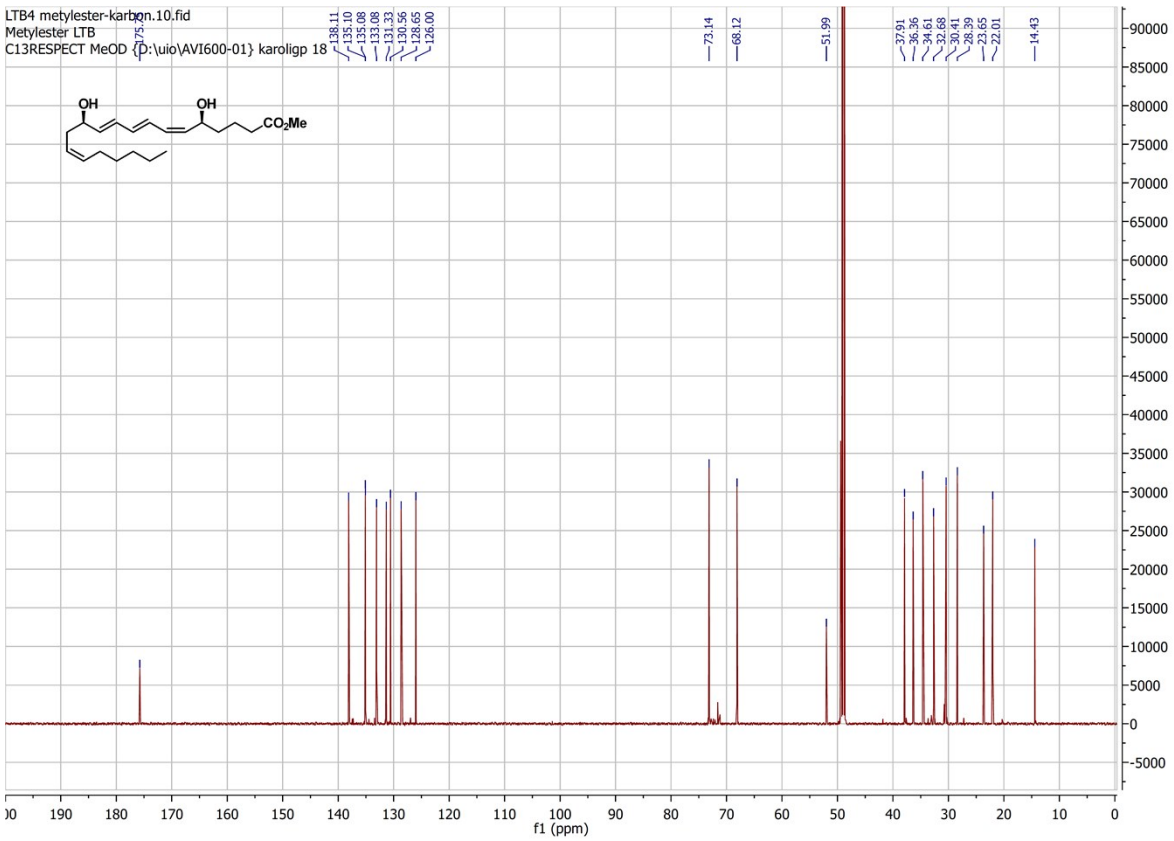


Figure S-12 ^{13}C NMR spectrum of compound **23**.

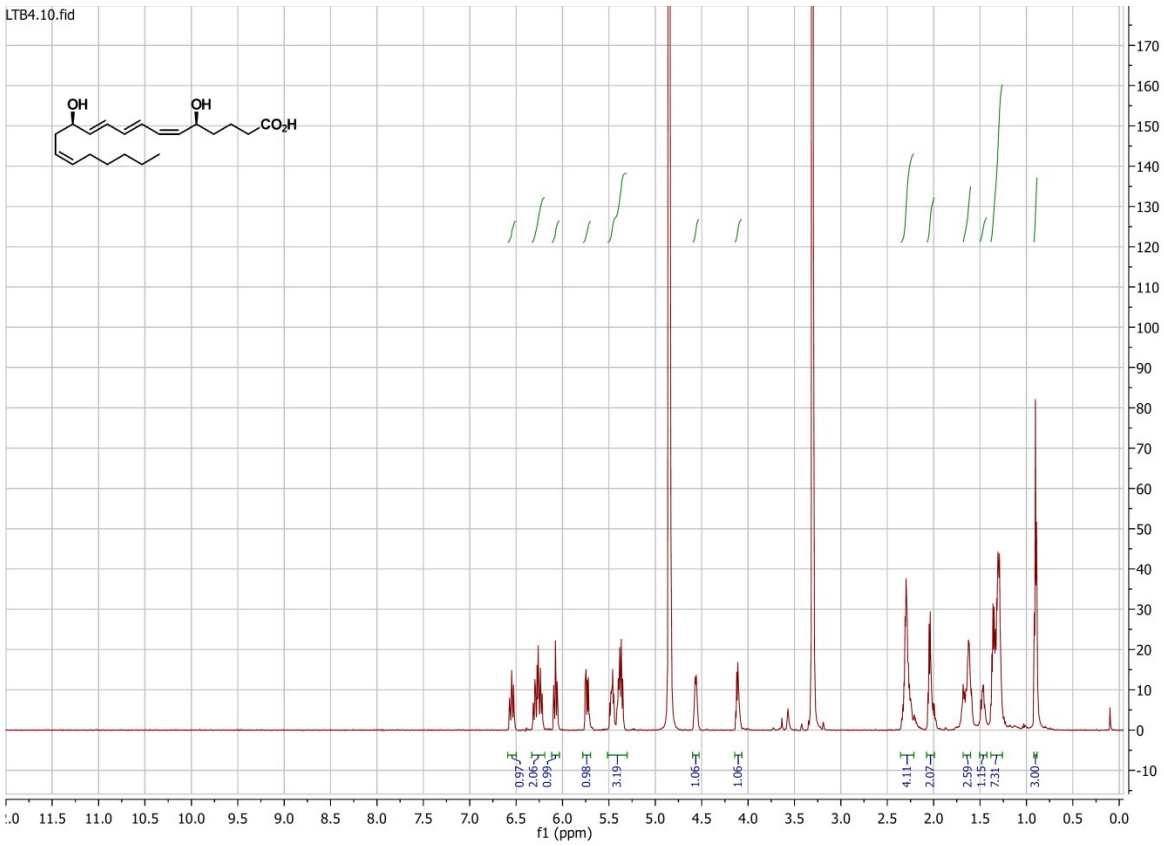


Figure S-13 ^{1}H NMR spectrum of LTB_4 (**1**).

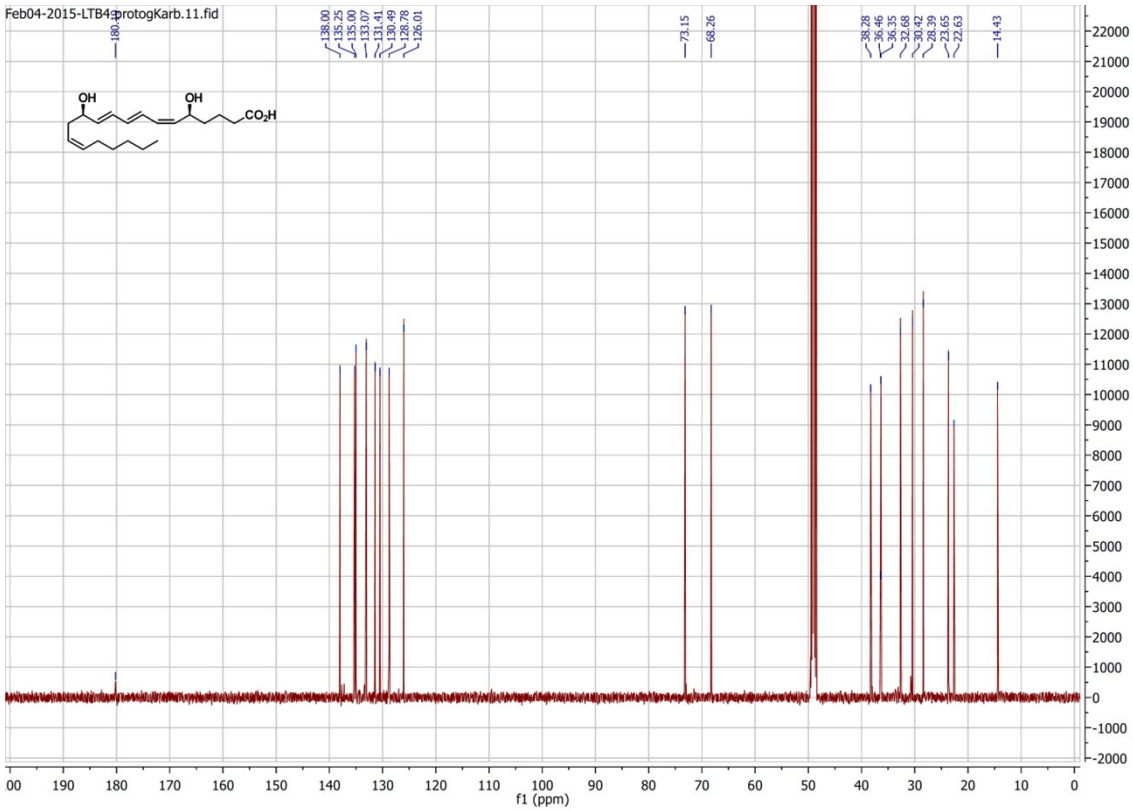


Figure S-14 ^{13}C NMR spectrum of LTB_4 (**1**).

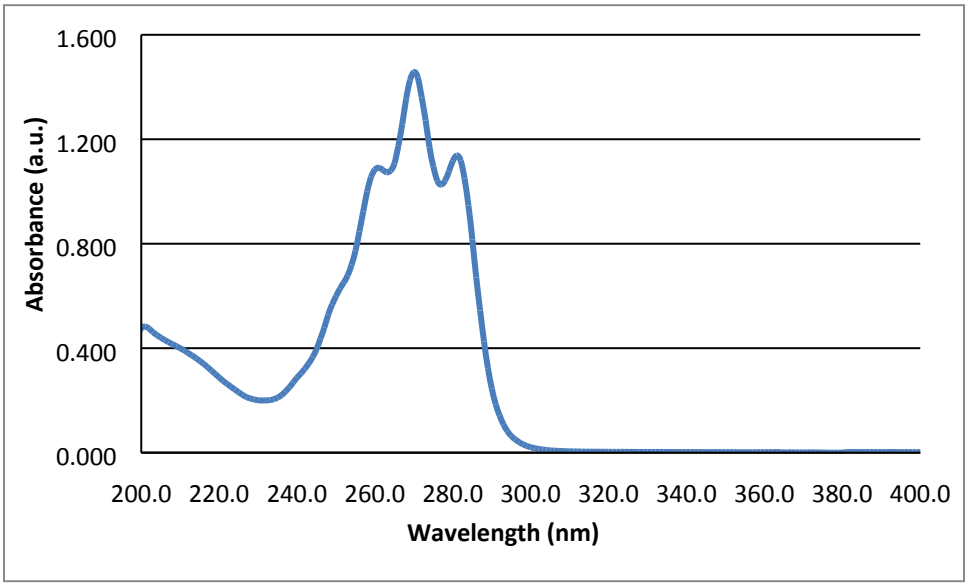


Figure S-15 UV-Vis chromatogram of the methyl ester **23**.

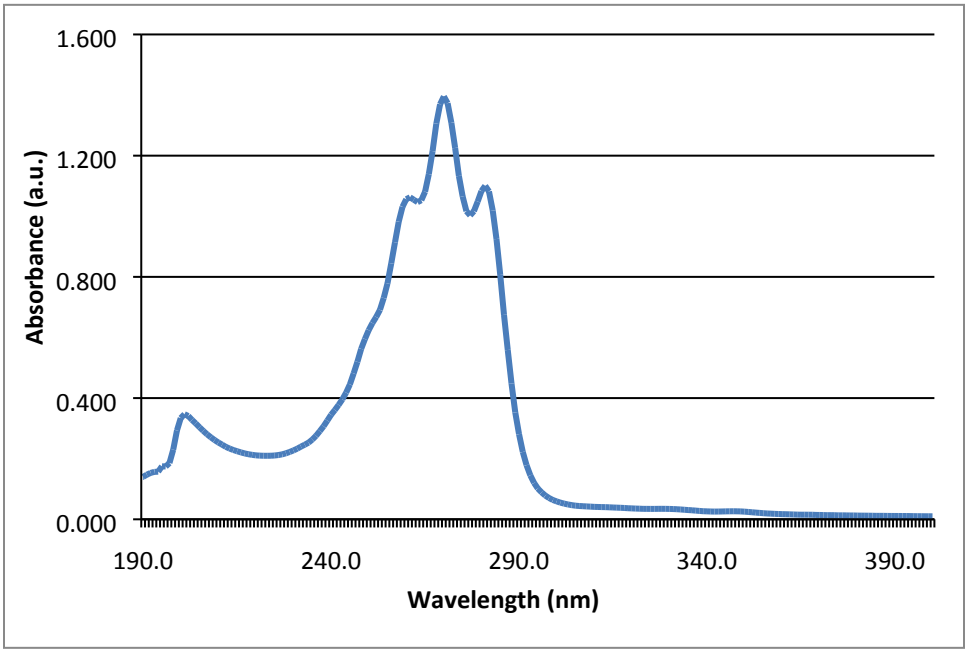


Figure S-16 UV-Vis chromatogram of LTB_4 (**1**).

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