SUPPORTING INFORMATION

The first stereoselective total synthesis of a new antitumour and anti-inflammatory neolignan, surinamensinol A

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Contents

General information:

The spectra were recorded with the following instruments; IR: Perkin-Elmer RX FT-IR spectrophotometer; ESIMS: VG-Autospec micromass spectrometer. ^{1}H NMR and ^{13} C NMR spectra were recorded on a 200 MHz and 50 MHz spectrometers using the solvent peak as internal reference ($CDCl_3$, δ H: 7.26; δ C: 77.0). Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated s = singlet, d = doublet, t = triplet, m = multiplet; coupling constants *(J)* are in Hz. ESIMS: VG-Autospec micromass. All reactions were monitored by thin-layer chromatography (TLC) using silica gel F_{254} pre-coated plates. Visualization was accomplished with UV-light or I_2 stain. Solvents for the catalytic reactions were technical grade. Solvents for chromatography (EtOAc, hexane) were technical grade. Organic extracts were dried over anhydrous Na_2SO_4.

Experimental Details:

1-(3,4,5-Trimethoxyphenyl)prop-2-en-1-ol (7)

To a stirred solution of 5 (2 g, 10.20 mmol) in dry THF a solution of vinyl magnesium bromide (1 M in THF, 10.20 mL) was added under N_2 atmosphere, at 0 °C, and the mixture was stirred at room temperature. After completion of reaction as indicated by TLC, the reaction mixture was quenched with the addition of sat. aq.NH_4Cl at 0 °C. The mixture was extracted with EtOAc (2 x 20 mL) and dried (anhy. Na_2SO_4). Evaporation of the solvent afforded the crude compound. The crude product on purification by column chromatography afforded pure 7 (1.94 g, 85%) as a light yellow liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.58 (2H, s), 6.01 (1H, m), 5.34 (1H, d, *J* = 16.0 Hz), 5.19-5.10 (2H, m), 3.84 (6H, s), 3.82 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.0, 139.9, 138.4, 136.8, 114.8, 102.8, 75.0, 60.5, 55.8; ESIMS: *m/z* 247 $[M + Na]^+$. Anal Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19%. Found: C, 64.24; H, 7.17%.

(*S*)-1-(3,4,5-Trimethoxyphenyl)prop-2-en-1-ol (8)

To 2- Iodoxybenzoic acid (4.3 g, 16.04 mmol), DMSO (4.0 mL) was added and stirred to get the clear solution, then a soln. of **7** (1.8 g, 8.03 mmol) in dry CH_2Cl_2 (20 mL) was added at 0 °C. The reaction was stirred at room temperature for 2 h, after completion of the reaction, mixture was filtered through a Celite pad, and washed with Et_2O (30 mL). The combined organic filtrates were washed with H_2O (10 mL) and dried (anhy. Na_2SO_4). Evaporation of the solvents resulted in the keto compound, which was used for selective reduction. The keto compound (1.5 g, 6.75 mmol) in dry THF was cooled to -40 °C and 1 M solution of (*R*)-(+)-2-methyl-CBS oxazaborolidine in toluene (0.6 mL, 2.02 mmol) was added under nitrogen atmosphere and stirred for 30 min. $BH_3.SMe_2$ (6.75 mL, 1M in THF, 6.75 mmol) was added and the entire mixture was stirred at room temperature for 30 min. After completion of reaction, the mixture was extracted with EtOAc (2 x 20 mL) and concentrated under reduced pressure to afford a crude product. The crude product on purification by column chromatography afforded pure **8** (1.06 g, 65%) with 91% *ee*, the enantiomeric purity of the compound was determined by Chiral PAK column with 10% IPA in hexane. $[\alpha]_D^{22}$ = -8.7 (c 1.0, $CHCl_3$). Spectral (^{1}H, ^{13}C NMR and MS) data of **8** were found to be same as those of **7**.

(*S*)-5-(1-(Benzyloxy)allyl)-1,2,3-trimethoxybenzene (9)

To a suspension of NaH (0.128 g, 7.01 mmol) in dry THF (5 mL) a solution of **8** (0.800 g, 3.57 mmol) in dry THF (10 mL) was added dropwise at 0 °C under nitrogen atmosphere. After stirring for 20 min, benzyl bromide (5 mL, 4.2 mmol) was added slowly drop by drop and the reaction mixture was stirred for 4 h at room temperature. After completion of the reaction, the mixture was quenched with saturated aq. NH_4Cl at 0 °C and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried (anhy. Na_2SO_4) and concentrated under reduced pressure. The crude product on purification by column chromatography afforded pure **9** (0.930 g, 83%) as a pale yellow liquid. $[\alpha]_D^{22}$ = -21.10 (c 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37-7.28 (5H, m), 6.58 (2H, s), 6.04-5.92 (1H, m), 5.34-5.21 (2H, m), 4.76 (1H, d, *J*

= 7.0 Hz), 4.54 (2H, s), 3.86 (6H, s), 3.85 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.2, 138.5, 138.3, 136.5, 133.3, 128.3, 127.6, 127.5, 116.4, 103.6, 81.9, 70.2, 60.8, 56.0; ESIMS: *m/z* 337 $[M + Na]^+$. Anal Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05%. Found: C, 72.61; H, 7.08%.

(2*S*,3*R*)-3-(Benzyloxy)-3-(3,4,5 trimethoxyphenyl) propane-1,2-diol (10)

A solution of *t*-BuOH/H_2O (1:1, 20 mL) was added to AD-mix-β (4.15 g) and stirred for 15 min at room temperature. Then it was cooled to 0 °C and **9** (0.9 g, 2.86 mmol) was added. The reaction mixture was stirred vigorously at 0 °C for 24 h, after completion of the reaction, monitored by TLC, the reaction mixture was quenched with solid Na_2SO_3 and the mixture was stirred at room temperature. The resultant mixture was filtered and the filtrate was extracted with EtOAc (2 x 20 mL) and the combined extracts were dried (anhy. Na_2SO_4) and concentrated under reduced pressure. The crude product on purification by column chromatography afforded pure **10** (0.647 g, 80%) as a yellow liquid. $[\alpha]_D^{22}$ = -52.3 (c 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48-7.37 (5H, m), 6.72 (2H, s), 4.64-4.58 (2H, m), 4.45 (2H, q, *J* = 12.0 Hz), 3.96 (9H, s), 3.91-3.45 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.0, 137.6, 137.5, 133.5, 128.1, 127.7, 127.5, 104.0, 81.9, 70.4, 63.2, 62.2, 60.4, 55.8; ESIMS: *m/z* 371 $[M + Na]^+$. Anal Calcd. for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94%. Found: C, 65.53; H, 6.91%.

(2*S*,3*R*)-3-(Benzyloxy)-2-hydroxy-3-(3,4,5-trimethoxy phenyl)propyl 4-methylbenzenesulfonate (11)

To ice cooled solution of **10** (0.6 g, 1.72 mmol) in dry CH_2Cl_2, Et_3N (0.24 mL, 1.72 mmol) was added and then p-TsCl (0.329 g, 1.72 mmol) and cat amount of DMAP were added. The mixture was stirred at room temperature for 12 h. After completion of the reaction, monitored by TLC, the solvent was evaporated and the crude product on purification by column chromatography afforded pure **11** (0.659 g, 76%) as a colorless oil. $[\alpha]_D^{22}$ = -15.4 (c 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75 (2H, d, *J* = 8.0 Hz), 7.35-7.21 (7H, m), 6.59 (2H, s), 4.51-4.23 (4H, m), 4.01-3.96 (2H, m), 3.86 (9H, s), 2.43 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.5, 148.0, 144.8, 137.9, 137.5, 137.3, 132.6, 129.7, 128.4, 127.9, 127.8, 104.1, 81.1, 73.2, 71.0, 69.6, 60.7, 56.1, 21.5; ESIMS: *m/z* 525 $[M + Na]^+$. Anal Calcd. for $C_{26}H_{30}O_8S$: C, 62.14; H, 6.02%. Found: C, 62.10; H, 6.05%.

(1*R*,2*S*)-1-(Benzyloxy)-1-(3,4,5 trimethoxyphenyl) propan-2-ol (3)

To LAH (0.181 g, 4.7 mmol), dry THF (5 mL) was added at 0 °C and then a solution of **11** (0.6 g, 1.19 mmol) in dry THF (10 mL) was added dropwise at 0 °C under nitrogen atmosphere. The mixture was stirred at reflux for 12 h. After completion of the reaction, monitored by TLC, the reaction mixture was cooled to 0 °C and quenched with aq Na_2SO_4 paste and stirred at room temperature. The mixture was filtered through a pad of Celite, and washed with hot EtOAc (20 mL). The filtrate was washed with brine (2 x 10 mL), dried (anhy. Na_2SO_4), and evaporated under reduced pressure. The crude product on purification by column chromatography afforded pure **3** (0.517 g, 89%) as a brown liquid. $[\alpha]_D^{22}$ = − 38.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39-7.30 (5H, m), 6.59 (2H, s), 4.52 (2H, q, *J* = 12.0 Hz); 4.33 (1H, m), 4.17 (1H, d, *J* = 7.0 Hz); 3.86 (9H, s), 1.21 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.3, 148.0, 137.1, 133.5, 128.5, 128.0, 127.9, 104.6, 87.6, 71.3, 70.8, 60.0, 56.1, 18.4; ESIMS: *m/z* 355 $[M + Na]^+$. Anal Calcd. for $C_{19}H_{24}O_5$: C, 68.66; H, 7.28%. Found: C, 68.64; H, 7.29%.

(*E*)-ethyl 3-(4-Hydroxy-3-methoxyphenyl)acrylate (12)

To a stirred solution of **6** (1.0 g, 6.57 mmol) in benzene (10 mL), ethyl (triphenyl phosphornylidene) acetate (3.43 g, 9.85 mmol) was added and the mixture was heated to reflux for 4 h. After completion of the reaction as indicated by the TLC, the mixture was concentrated in vacuo to give the crude residue. The residue on purification by column chromatography afforded pure **12** (1.18 g, 81%) as a yellowish solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.07-6.90 (4H, m), 6.29 (1H, d, *J* = 15.0 Hz), 4.26 (2H, q, *J* = 8.0 Hz), 3.83 (3H, s), 1.33 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.3, 148.2, 147.5, 146.9, 128.5,

127.2, 114.8, 114.6, 109.5, 60.2, 55.9, 14.2; ESIMS: *m/z* 245 $[M + Na]^+$. Anal Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35%. Found: C, 64.87; H, 6.31%.

3-(4-(Benzyloxy)-3-methoxyphenyl)propan-1-ol (13)

To the compound **12** (1.1 g, 4.95 mmol) in MeOH $NiCl_2 \cdot 6H_2O$ (0.235 g, 0.98 mmol) was added. The reaction mixture was cooled to 0 °C and $NaBH_4$ (0.376 g, 9.89 mmol) was added in small portions. The reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, as indicated by the TLC, the reaction was quenched with addition of sat. aq. NH_4Cl at 0 °C. Methanol was removed under reduced pressure. The mixture was extracted with EtOAc (2 x 20 mL) and dried (anhy. Na_2SO_4). Evaporation of the solvents afforded a crude compound. The free hydroxy group of the compound was protected as benzyl ether as fallows.

To NaH (0.160 g, 6.6 mmol), dry THF (10 mL) was added at 0 °C. To this suspension a solution of the above hydroxy compound (1.0 g, 4.46 mmol) in dry THF (5 mL) was added at 0 °C under nitrogen atmosphere. After stirring for 15 min, benzyl bromide (0.58 mL 4.90 mmol) was added slowly drop by drop and the reaction mixture was stirred for 4 h at room temperature. After completion of reaction, the mixture was cooled to 0 °C and quenched with sat. aq. NH_4Cl and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried (anhy. Na_2SO_4) and concentrated under reduced pressure. The crude was subjected to reduction with LAH.

To LAH (0.174 g, 4.57 mmol) at 0 ^{0}C slowly dry THF (10 mL) was added and then a solution of the above ester compound (1.2 g, 3.82 mmol) in dry THF (5 mL) was added dropwise at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 1 h. After completion of the reaction, monitored by TLC, the reaction mixture was cooled to 0 °C and quenched with aq. Na_2SO_4 paste and allowed to stir at room temperature. The mixture was filtered through a pad of Celite, and washed with hot EtOAc (30 mL). The filtrate was washed with brine (2 x 10 mL), dried (anh. Na_2SO_4), and evaporated under reduced pressure. The crude product on purification by column chromatography afforded pure **13** (0.897 g, 67%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45-7.25 (5H, m), 6.81-6.64 (3H, m), 5.12 (2H, s), 3.87 (3H, s), 3.65 (2H, t, *J* = 7.0 Hz), 2.64 (2H, t, *J* = 8.0 Hz), 1.91-1.81 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.5, 146.1, 137.1, 135.1, 128.4, 127.7, 127.2, 120.0, 114.1, 112.2, 71.1, 62.1, 55.8, 34.2, 31.5; ESIMS: *m/z* 295 $[M + Na]^+$. Anal Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40%. Found: C, 74.95; H, 7.43%.

(3-(4-(Benzyloxy)-3-methoxyphenyl)propoxy)(tert-butyl)dimethylsilane (14)

To the compound **13** (0.8 g, 2.94 mmol) in dry CH_2Cl_2, imidazole (0.400 g, 5.88 mmol) and TBDMS-Cl (0.754 g, 4.99 mmol) were added sequentially at 0 °C. After stirring for 5 min, DMAP (catalytic amount) was added to the reaction mixture and stirring was continued for 4 h at room temperature. After completion of the reaction monitored by TLC, the reaction mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried (anhy. Na_2SO_4) and concentrated in vacuo. The crude product on purification by column chromatography afforded pure **14** (1.08 g, 95%) as a yellow liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.59-7.36 (5H, m), 6.95-6.78 (3H, m), 5.25 (2H, s), 4.00 (3H, s), 3.77 (2H, t, *J* = 7.0 Hz), 2.76 (2H, t, *J* = 7.0 Hz), 2.0-1.91 (2H, m), 1.06 (9H, s), 0.20 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.4, 146.1, 137.3, 135.4, 128.3, 127.5, 127.1, 120.1, 114.2, 112.3, 71.1, 62.1, 55.8, 34.4, 31.5, 25.8, 18.2, -5.3; ESIMS: *m/z* 410 $[M + Na]^+$. Anal Calcd. for $C_{23}H_{34}O_3Si$: C, 71.46; H, 8.86%. Found: C, 71.43; H, 8.83%.

4-(3-(tert-Butyldimethylsilyloxy)propyl)-2-methoxy phenol (4)

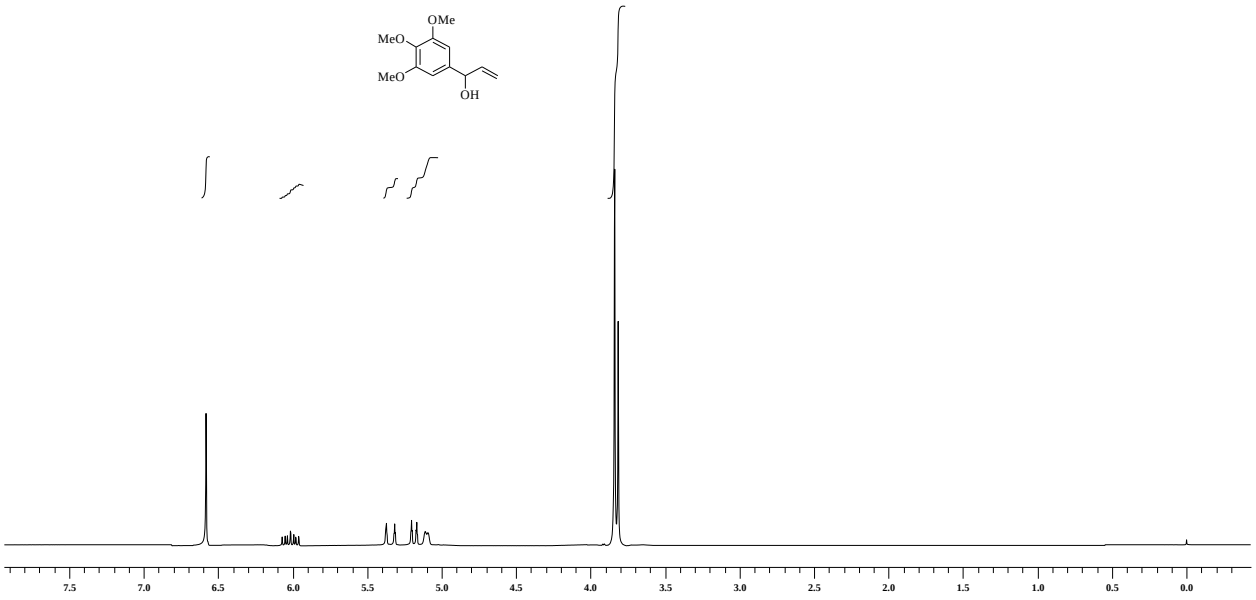
To the compound **14** (0.9 g, 2.32 mmol) in EtOAc (10 mL) catalytic amount of Pd/C was added and the mixture was stirred for 2 h under hydrogen atmosphere (1 atm). After completion of reaction monitored by TLC, the reaction mixture was filtered and concentrated under reduced pressure to give the crude product. The crude product on purification by column chromatography afforded pure **4** (0.626 g, 91%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.89-6.79 (3H, m), 3.89 (3H,

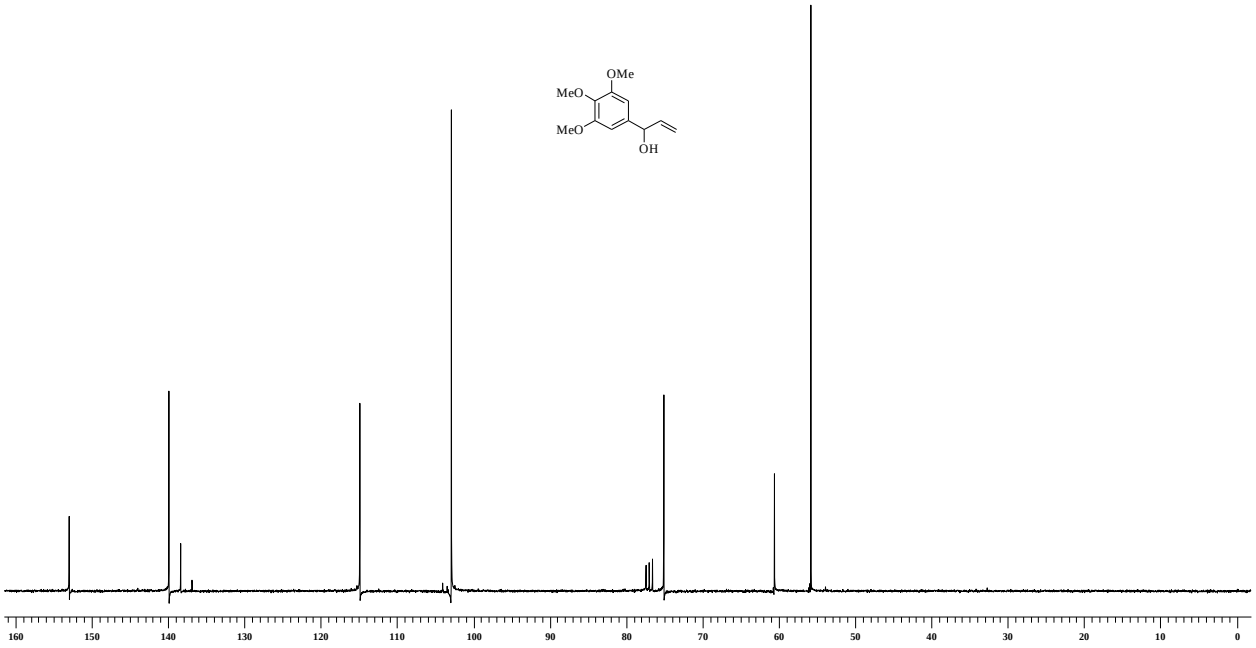
s), 3.61 (2H, t, *J* = 7.0 Hz), 2.60 (2H, t, *J* = 7.0 Hz), 1.99-1.85 (2H, m), 0.91 (9H, s), 0.10 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.6, 146.1, 135.6, 120.2, 114.2, 112.7, 62.1, 55.8, 34.5, 31.4, 25.9, 18.1, -5.3; ESIMS: *m/z* 319 $[M + Na]^+$. Anal Calcd. for $C_{16}H_{28}O_3Si$: C, 64.82; H, 9.52%. Found: C, 64.86; H, 9.50%.

1*R*,2*R*)-2-(4-(3-Hydroxypropyl)2methoxyphenoxy)-1-(3,4,5-trimethoxyphenyl)propan-1-ol (1)

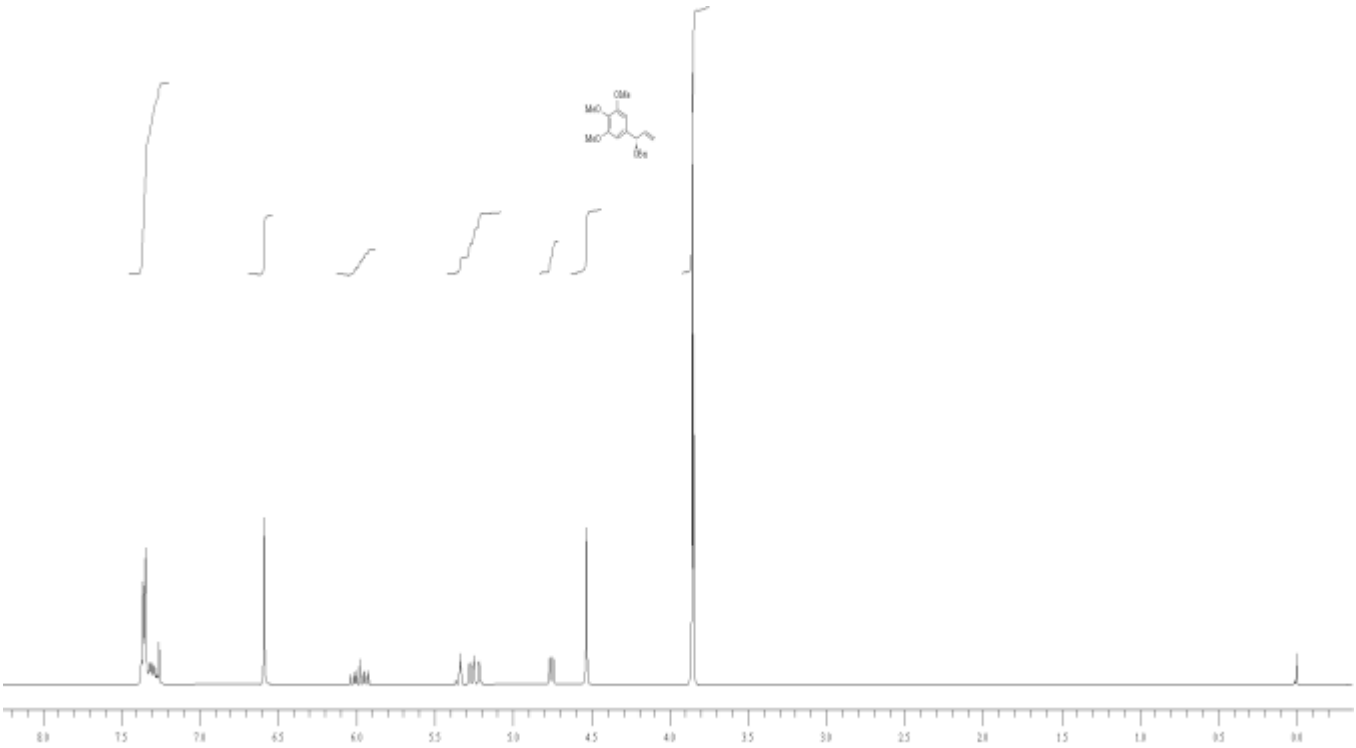
A mixture of 0.500 g **3** (1.5 mmol), 0.534 g **4** (1.8 mmol), 0.512 g triphenylphosphine (1.95 mmol), and 0.38 mL diethyl azodicarboxylate (1.95 mmol) in 20 mL anhydrous THF was heated to reflux for 24 h under nitrogen atmosphere. The mixture was concentrated under reduced pressure. This residue was dissolved in MeOH and then cat. amount of *p*-TsOH was added. The mixture was stirred at room temperature. After completion of reaction, MeOH was evaporated and the reaction mixture was extracted with EtOAc (2 x10 mL). The combined organic extracts were washed with brine, dried (anhy. Na_2SO_4) and concentrated in vacuo. This crude material was hydrogenated in the presence of 10% Pd/C and yielded the target molecule **1** (0.244 g, 40%) (as a colorless liquid), with 90% *ee*, the enantiomeric purity of the compound was determined by Chiral PAK column, with 20% IPA in hexane. $([\alpha]_D^{22} = -59.1$ (*c* = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.91 (1H, d, *J* = 8.0 Hz), 6.76 (1H, d, *J* = 2.0 Hz), 6.72 (1H, dd, *J* = 8.0, 2.0 Hz), 6.60 (2H, s), 4.60 (1H, d, *J* = 7.0 Hz), 4.05 (1H, m), 3.87 (9H, s), 3.85 (3H, s), 3.68 (2H, t, *J* = 7.0 Hz), 2.63 (2H, t, *J* = 7.0 Hz), 1.92-1.80 (2H, m), 1.20 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.2, 150.5, 145.2, 138.0, 137.2, 135.2, 121.0, 119.3, 112.4, 104.5, 83.1, 77.4, 62.2, 56.0, 34.2, 31.9, 16.9 (In the ^{13}C NMR spectral data there are little deviations in the singal values (two peaks are differing by +/- 1.0 - 2.0 ppm and five peaks by +/- 0.3 - 0.6 ppm), compared to those for natural product. These deviations, perhaps, may be due to the recording of the spectrum at different concentrstion to Ref. 1, at different temperature or with $CDCl_3$ with a trace of water); ESIMS: *m/z* 429 $[M + Na]^+$. Anal Calcd. for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44%. Found: C, 65.05; H, 7.48%.

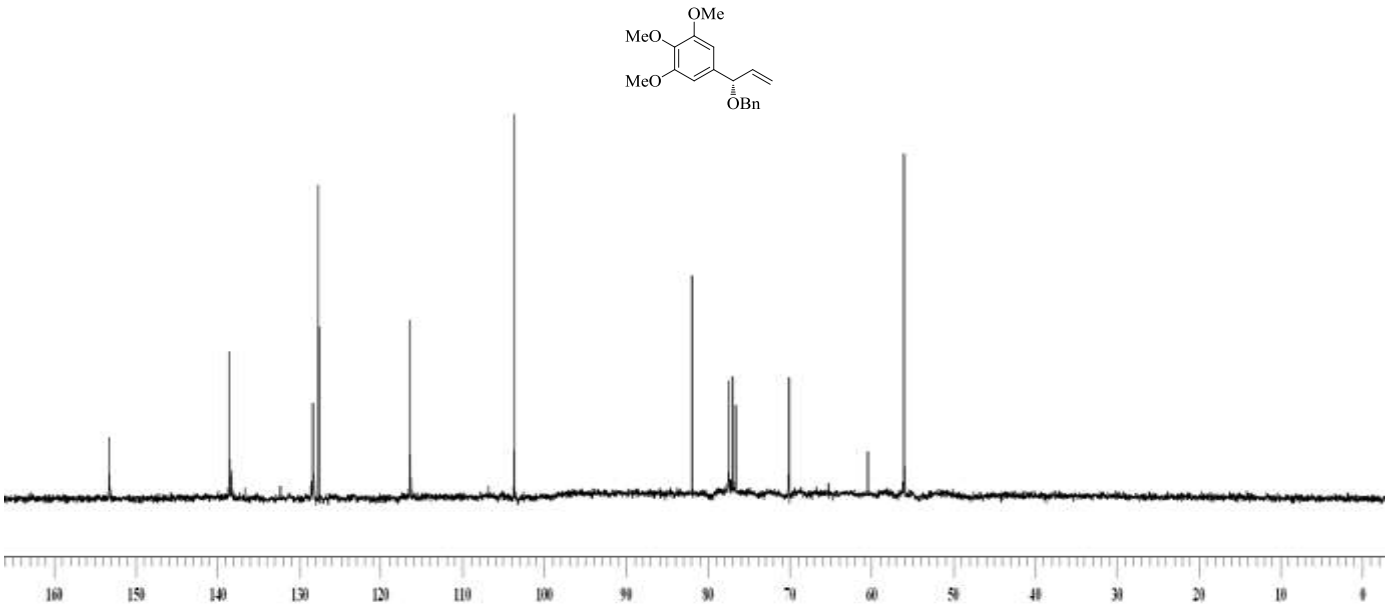
1-(3,4,5-Trimethoxyphenyl)prop-2-en-1-ol (7)



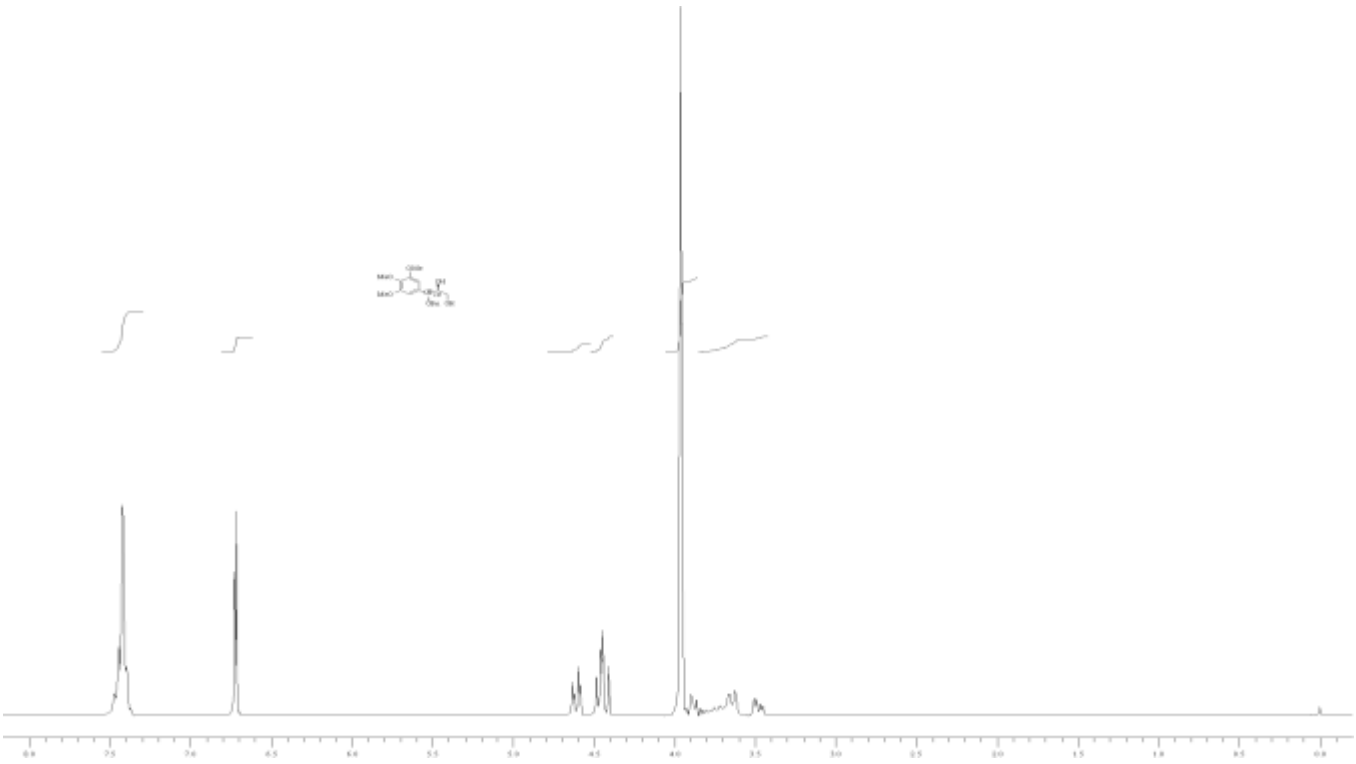


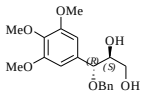
(*S*)-5-(1-(Benzyloxy)allyl)-1,2,3-trimethoxybenzene (9)

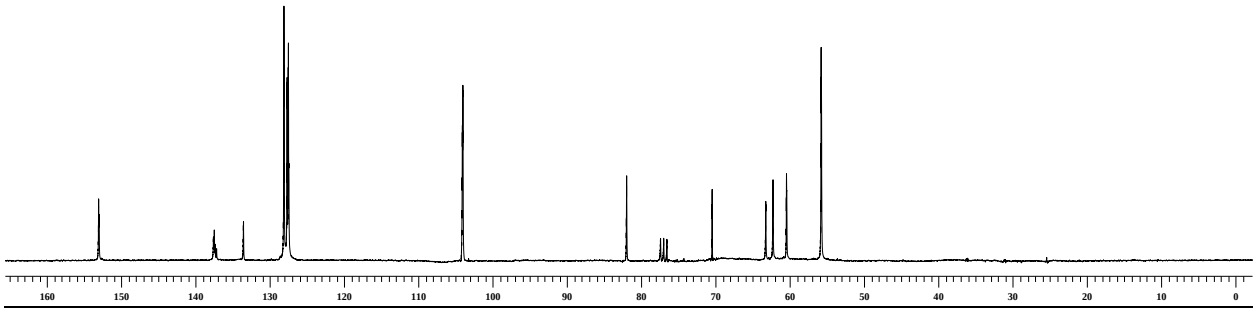




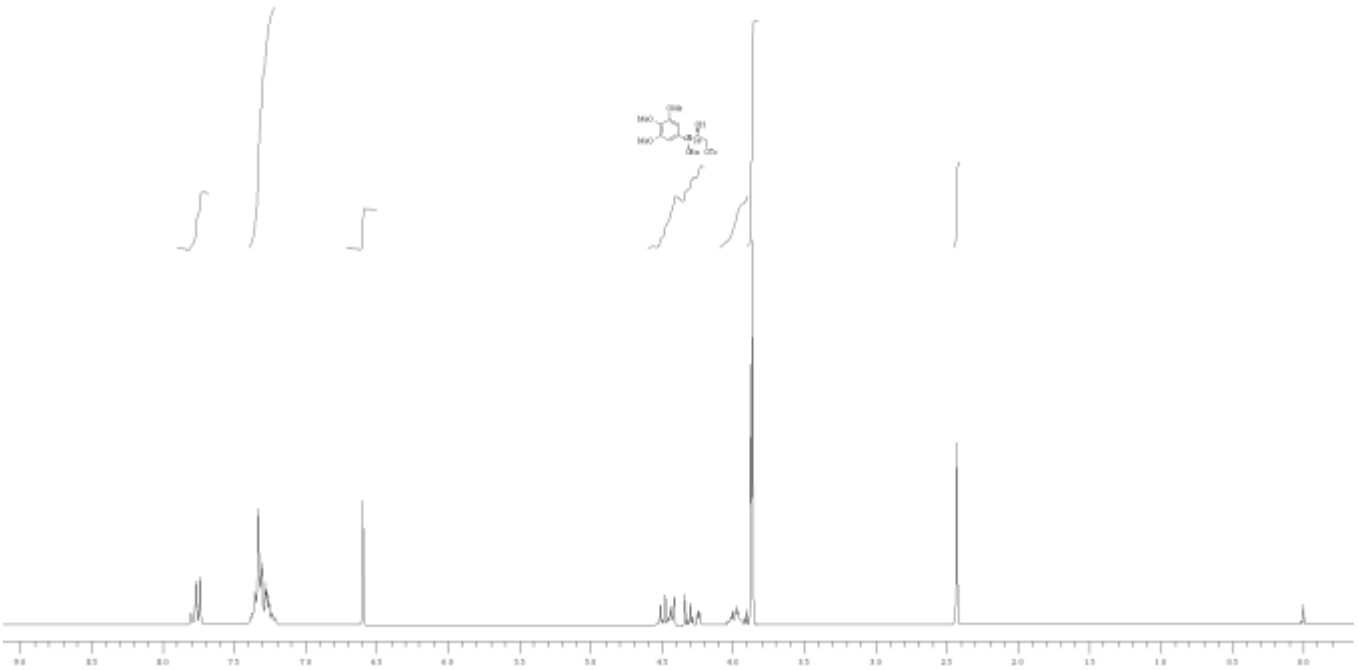
(2*S*,3*R*)-3-(Benzyloxy)-3-(3,4,5 trimethoxyphenyl) propane-1,2-diol (10)

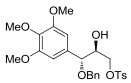


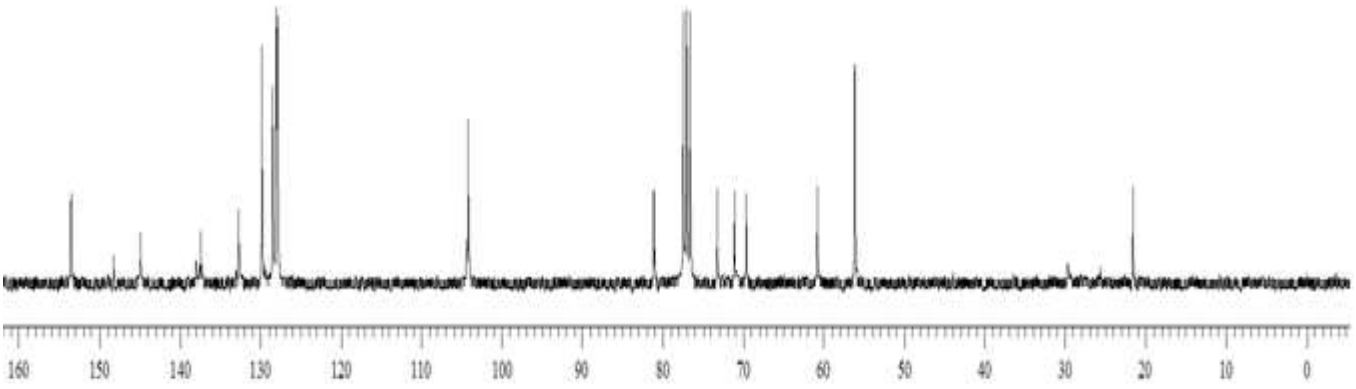




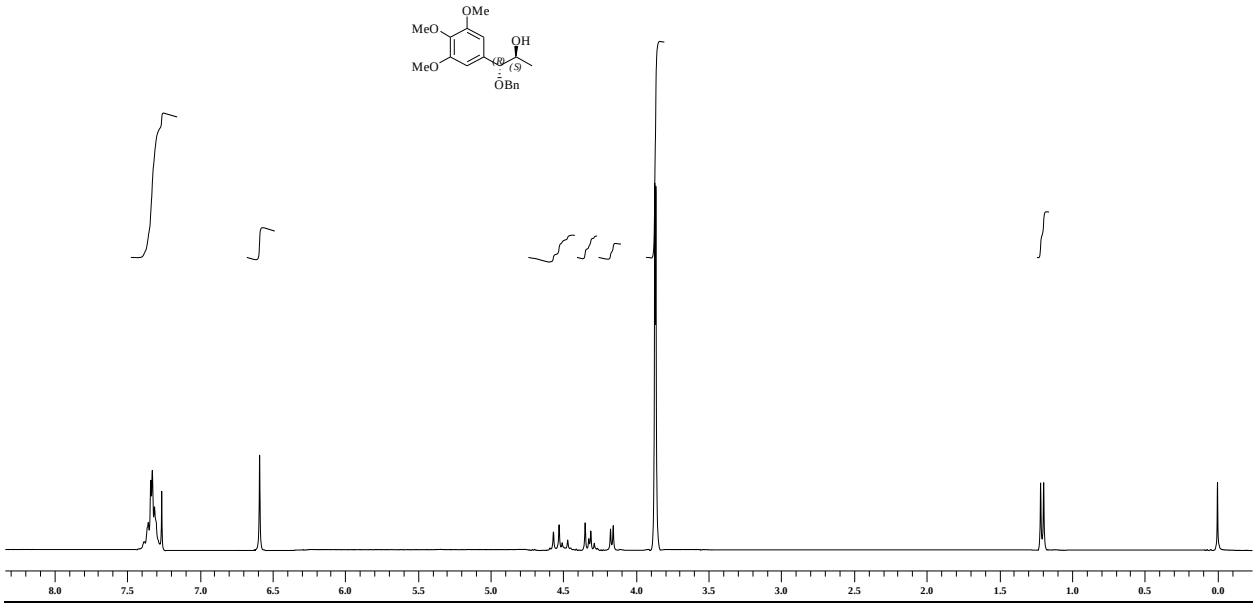
(2*S*,3*R*)-3-(Benzyloxy)-2-hydroxy-3-(3,4,5-trimethoxy phenyl)propyl 4-methylbenzenesulfonate (11)

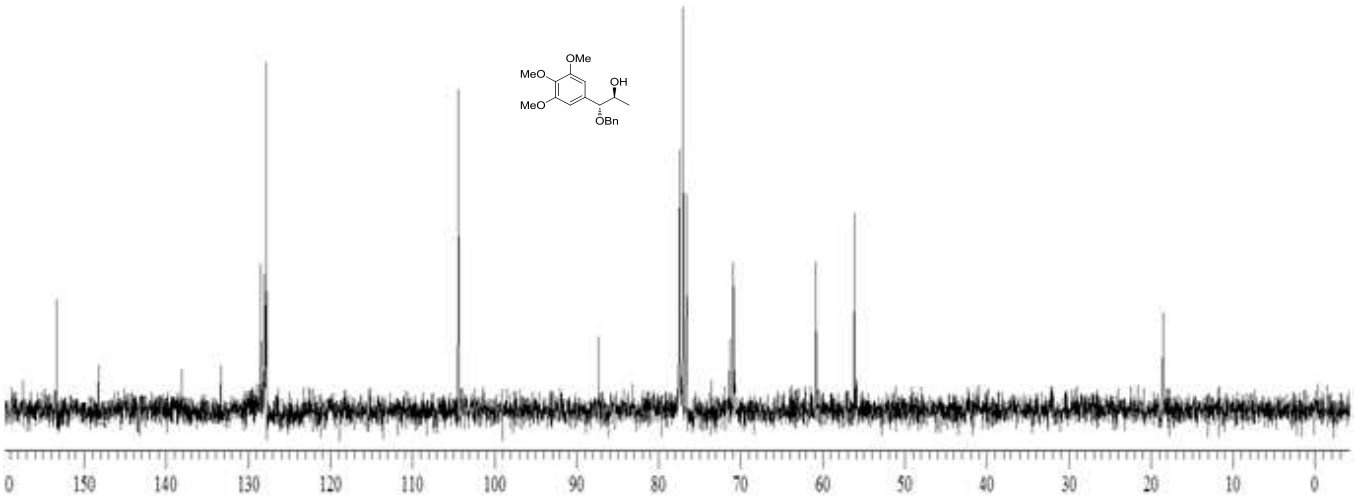




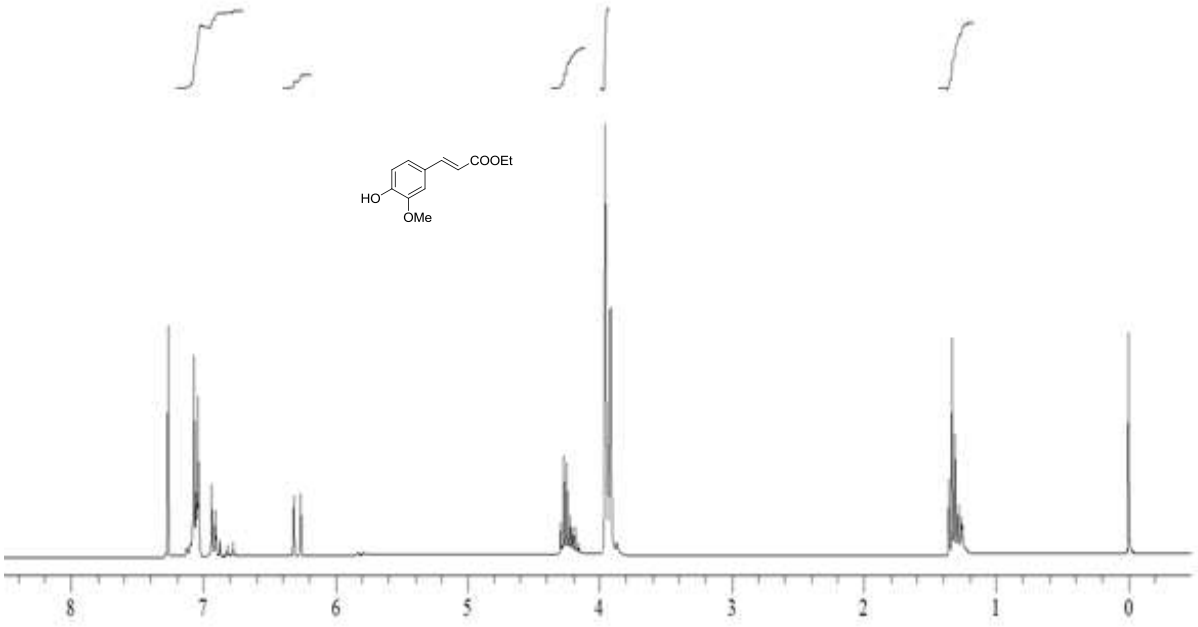


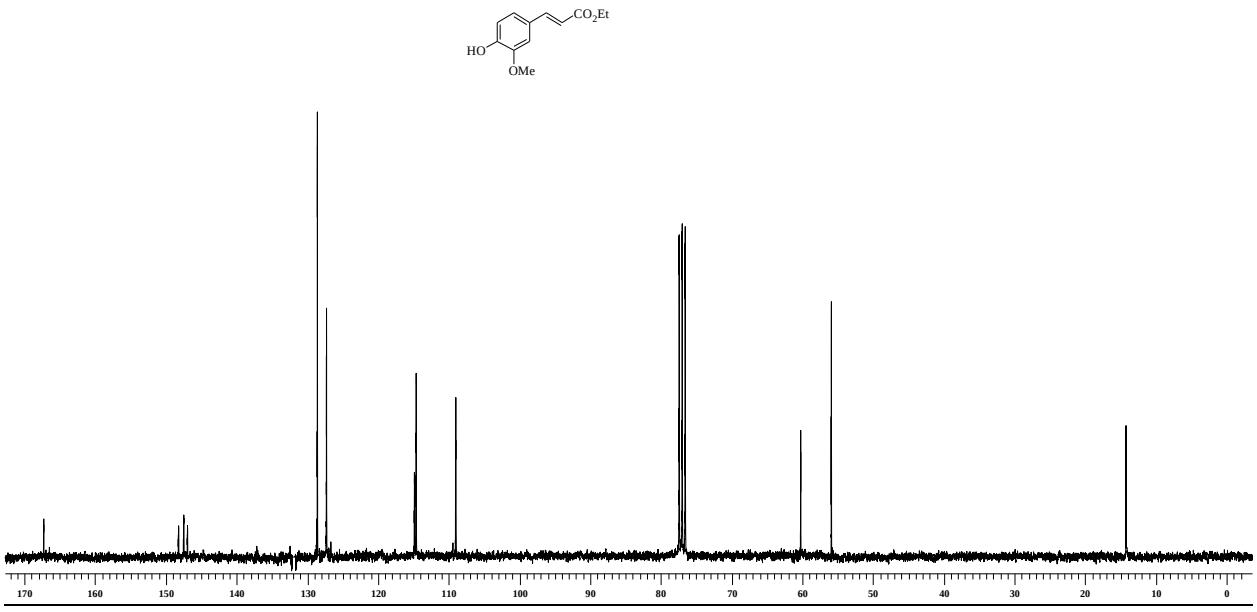
(1*R*,2*S*)-1-(Benzyloxy)-1-(3,4,5 trimethoxyphenyl) propan-2-ol (3)



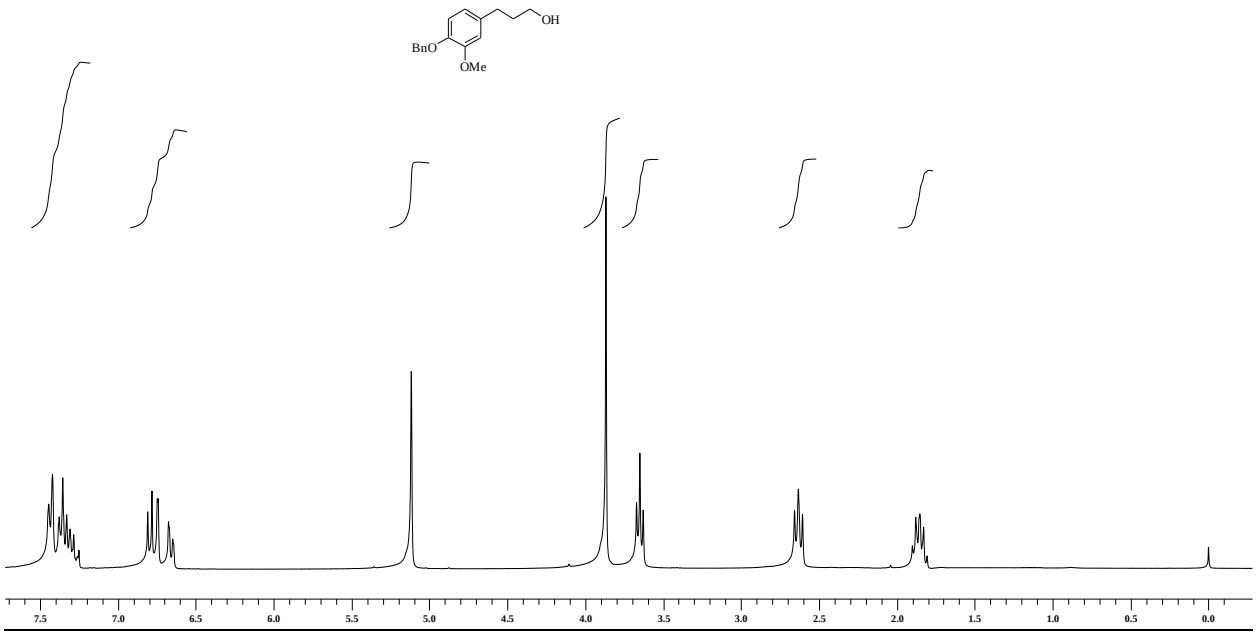


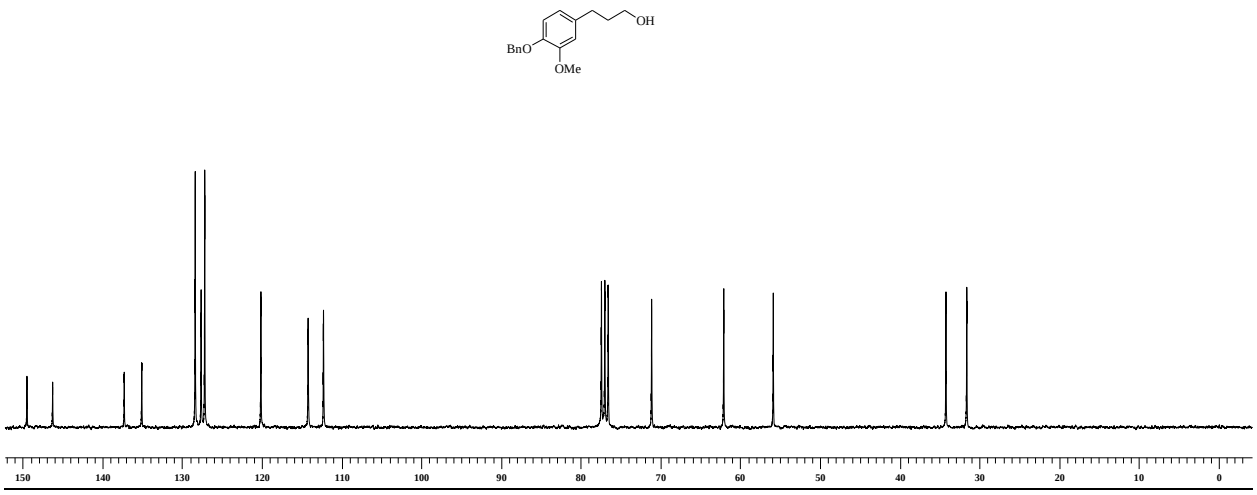
(*E*)-ethyl 3-(4-Hydroxy-3-methoxyphenyl)acrylate (12)



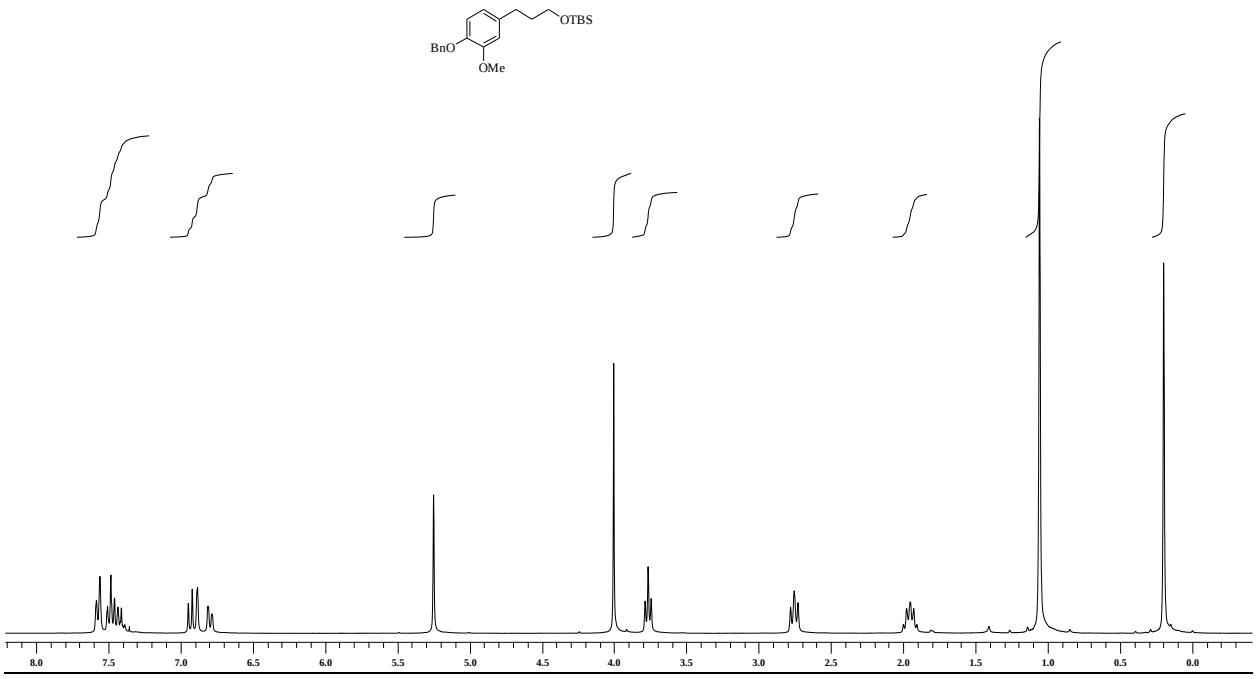


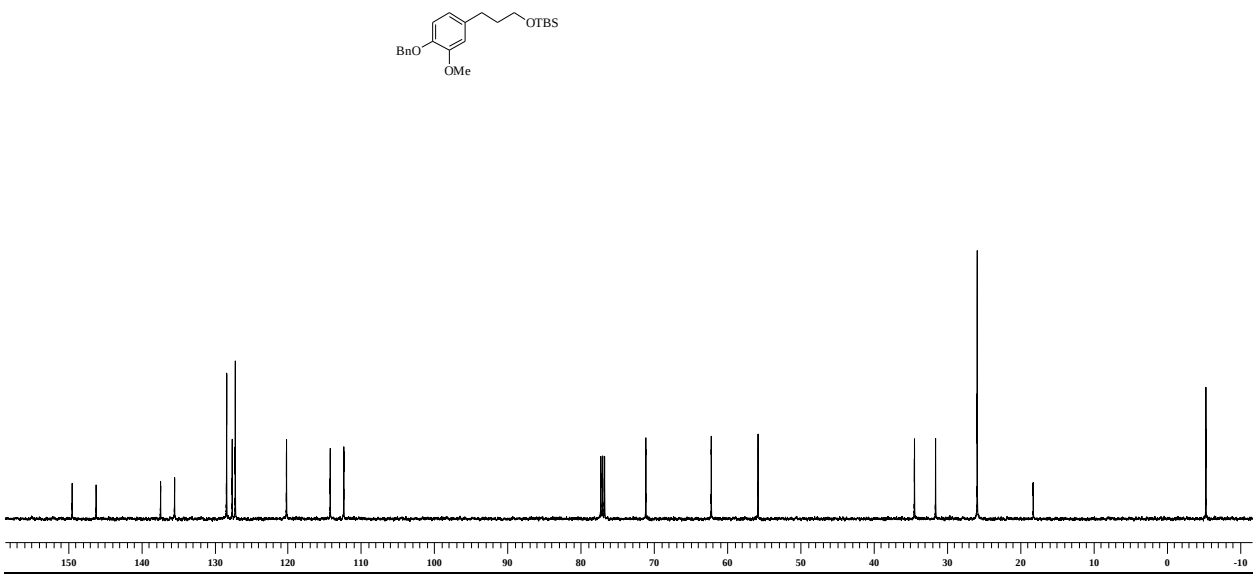
3-(4-(Benzyloxy)-3-methoxyphenyl)propan-1-ol (13)



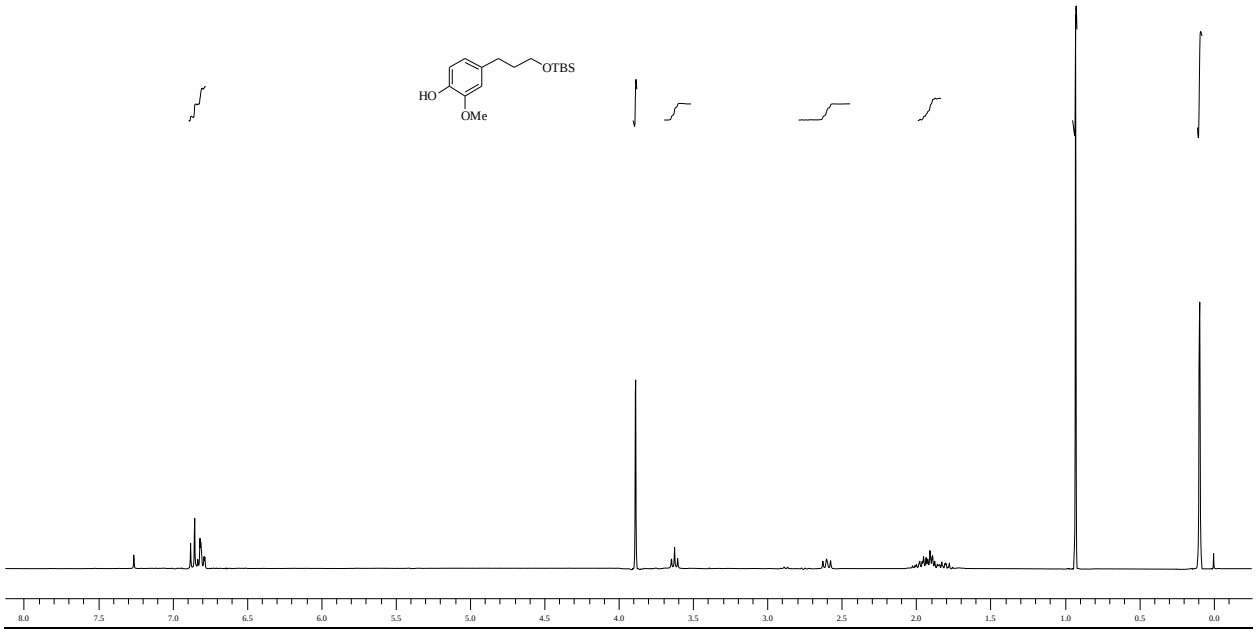


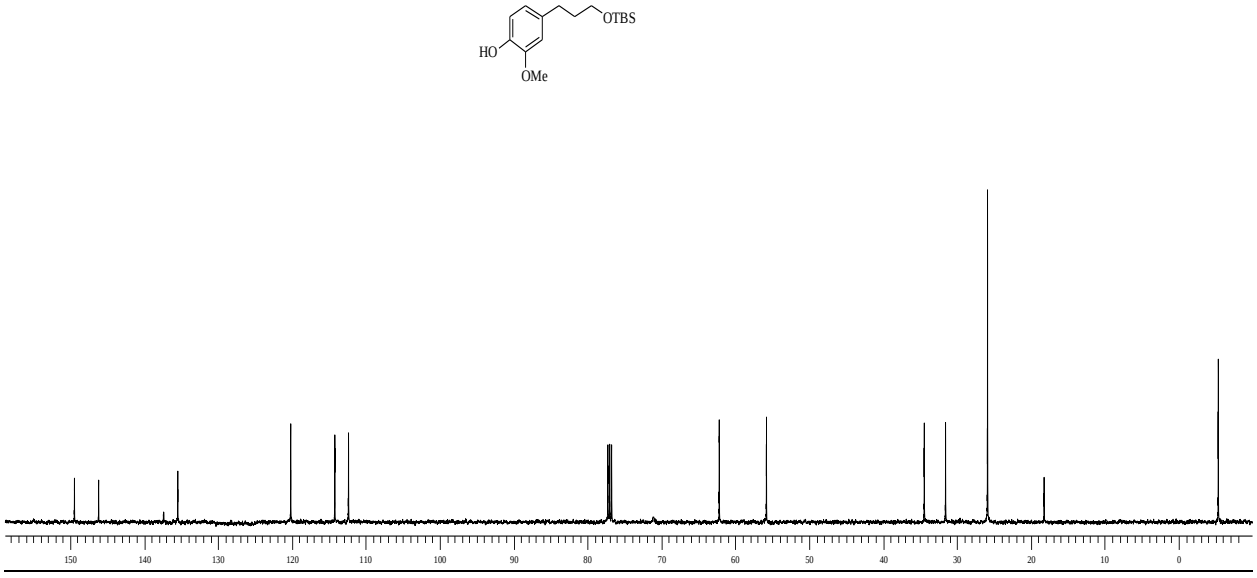
(3-(4-(Benzyloxy)-3-methoxyphenyl)propoxy)(tert-butyl)dimethylsilane (14)





4-(3-(tert-Butyldimethylsilyloxy)propyl)-2-methoxy phenol (4)





(1*R*,2*R*)-2-(4-(3-Hydroxypropyl)2methoxyphenoxy)-1-(3,4,5-trimethoxyphenyl)propan-1-ol (1)