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**-Supplementary Information-**

# An *ortho*-quinone methide based strategy towards the rubromycin spiroketal family

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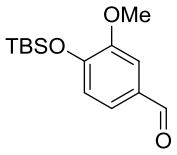
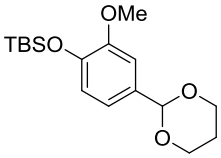
## General Details

Unless otherwise stated, commercially available reagents were used as supplied. All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an inert atmosphere of nitrogen or argon. Microwave heating was conducted in 10 mL thick walled microwave vials fitted with crimp top Teflon seals (CEM). Analytical thin-layer chromatography (TLC) was performed on silica gel plates (0.25 mm) precoated with a fluorescent indicator. Standard flash chromatography procedures were performed using Kieselgel 60 (40-63 μm) or with a Varian Superflash automated purification system. Petroleum refers to the fraction boiling between 40-60 °C. Infrared spectra were recorded in the range 4000-600 $cm^{-1}$, using a Bruker Tensor 37 FTIR machine equipped with a PIKE MIRacle ATR accessory. IR signals are reported in wavenumbers ($cm^{-1}$) and signal intensity is subjectively denoted br = broad, brs = broad (strong), brm = broad (medium) s = strong, m = medium and w = weak. Both $^{1}H$ and $^{13}C$ NMR spectra were recorded using either a Bruker AV400 NMR or AV600 spectrometer. Chemical shifts $\delta$ are reported in ppm (relative to $\delta_H$ $CHCl_3$ (7.27) and $\delta_C$ $CDCl_3$ (77.0) unless otherwise stated) and multiplicity of signals denoted: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet respectively with coupling constants ($J$) reported in hertz (Hz). Structural interpretations and assignments were made based upon COSY, HMQC, HMBC, DEPT 135, DEPT 90 and NOESY experiments. High resolution mass spectra (HRMS) were obtained by the EPSRC National Mass Service (Swansea) using a double focussing mass spectrometer (Finnigan MAT 95 XP).

## Experimental procedures and spectral data

**4-(*tert*-Butyldimethylsilyl)oxy)-3-methoxybenzaldehyde** (**11**).[1] 

$Et_3N$ (70 mL, 502 mmol, 1.5 equiv.) was added at 20 °C to a mixture of vanillin (50.0 g, 329 mmol, 1.0 equiv.), TBSCl (54.4 g, 361 mmol, 1.1 equiv.) and DMAP (0.1 g, 0.8 mmol, 0.25 mol %) in $CH_2Cl_2$ (750 mL). After stirring at r.t. for 24 h, the organic layer was washed with sat. aq. $NH_4Cl$ solution (2 × 500 mL). The separated organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography (25% EtOAc in petrol) afforded the aldehyde **11** as pale yellow oil (84.3 g, 96%); $R_f$ = 0.65 (25% EtOAc in petrol); $\nu_{max}$ (film)/cm$^{-1}$ 2958w and 2930w (C-H), 2857w ($OCH_3$), 1696s (C=O, aldehyde), 1593m (C=C), 1284m ($SiMe_2$), 1033m (Si-O), and 838m ($SiMe_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H, CHO), 7.40 (d, *J* = 1.8 Hz, 1H, ArCH), 7.36 (dd, *J* = 8.0 Hz, 1.8 Hz, 1H, ArCH), 6.96 (d, *J* = 8.0 Hz, 1H, ArCH), 3.87 (s, 3H, OMe), 1.00 (s, 9H, $SiMe_2{}^tBu$), 0.19 (s, 6H, $SiMe_2{}^tBu$); $^{13}$C NMR (100 MHz) δ 191.1 (CHO), 151.8 (*C*OMe), 151.5 (*C*OTBS), 131.1 (*C*CHO), 126.3 (ArCH), 120.9 (ArCH), 110.3 (ArCH), 55.6 (OMe), 25.7 (SiC(*C*$H_3$)$_3$), 18.7 (Si*C*($CH_3$)$_3$), −4.4 ($SiMe_2$); HRMS (CI) calc for $[C_{14}H_{23}O_3Si]^+$ 267.1412; found 267.1411 $[M+H]^+$; these spectroscopic data are in agreement with those previously reported.[1]

**(4-(1,3-Dioxan-2-yl)-2-methoxyphenoxy)(*tert*-butyl)dimethylsilane** (**12**).[1] 

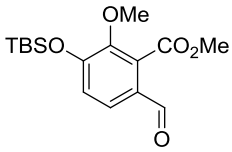
To a solution of aldehyde **11** (80.0 g, 246 mmol) in $CH_2Cl_2$ (210 mL) was added 1,3-propanediol (82 mL, 1.14 mol, 4.6 equiv.), $HC(OMe)_3$ (49 mL, 477 mmol, 1.9 equiv.) and *n*-$Bu_4NBr_3$ (7.6 g, 24.2 mmol, 0.01 equiv.) and the resultant mixture was stirred at 20 °C for 60 h. Sat. aq. $Na_2CO_3$ solution (250 mL) and $H_2O$ (250 mL) were added and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (200 mL) and the combined organic were dried over $MgSO_4$ and filtered before concentrating under reduced pressure. The residue was purified by flash chromatography (5% EtOAc in *n*-hexane) furnishing acetal **12**[1] as colourless oil (71.7 g, 22.1 mmol, 90%); $R_f$ = 0.64 (5% EtOAc in *n*-hexane); $\nu_{max}$ (film)/cm$^{-1}$ 2955w and 2929w (CH), 2855w ($OCH_3$), 1282m ($SiMe_2$), 1123m (SiO) and 838m ($SiMe_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.03 (d, *J* = 1.7 Hz, 1H, ArCH), 6.93 (dd, *J* = 8.2, 1.7 Hz, 1H, ArCH), 6.83 (d, *J* = 8.1 Hz, 1H, ArCH), 5.44 (s, 1H, *H*$CO_2$), 4.23 (dd, *J* = 11.2, 5.0 Hz, 2H, 2 × OC*H*$_a$H$_b$), 3.96-3.86 (m, 2H, 2 × OCH$_a$*H*$_b$), 3.82 (s, 3H, ArOMe), 2.08-2.22 (m, 1H, $OCH_2CH_aH_b$), 1.39 (m, 1H, $OCH_2CH_aH_b$), 0.99 (s, 9H, $SiMe_2t$-*Bu*), 0.16 (s, 6H, Si*Me*$_2$*t*-Bu); $^{13}$C NMR (100 MHz) δ 151.1 (*C*OMe), 145.6 (*C*OTBS), 132.6 (*C*$CHO_2$), 120.8 (ArCH), 118.8 (ArCH), 109.8 (ArCH), 101.9 (C*C*$HO_2$), 67.6 (2 × O*C*$H_2CH_2$), 55.6 (OMe), 25.9 (SiC(*C*$H_3$)$_3$), 25.9 (2 × $OCH_2CH_2$), 18.6 (Si*C*($CH_3$)$_3$), −4.5 ($SiMe_2$); HRMS (CI) calcd for $[C_{17}H_{29}O_4Si]^+$ 325.1826; found 325.1830 $[M+H]^+$; these spectroscopic data are in agreement with those previously reported.[1]

(1) M. Brasholz, X. Luan and H. Reißig, *Synthesis*, 2005, **20**, 3571.

**Methyl 3-((*tert*-butyldimethylsilyl)oxy)-6-(1,3-dioxan-2-yl)-2-methoxybenzoate (13).**[1] *n*-Butyllithum (59 mL, 146 mmol, 2.5 M in hexanes, 1.2 equiv.) was added to anhydrous cyclohexane (750 mL) at 2 °C before further cooling to –6 °C (external). Acetal **12** (39 g, 120 mmol, 1.0 equiv) was then added dropwise to the mixture and the reaction mixture was stirred at –6 °C for a further 10 hours. Methyl chloroformate (31 mL, 401 mmol, 3.3 equiv.) was added dropwise and the reaction was allowed to warm slowly to 10 °C over 16 h. The reaction mixture was quenched with sat. aq. $Na_2CO_3$ solution (200 mL), the layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 400 mL) and the combined organics were dried over $MgSO_4$ and concentrated under reduced pressure before the residue was purified by flash column chromatography (17% EtOAc in *n*-hexane) to give the benzoate **13**[1] as clear colourless solid (33.1 g, 72%); mp. 74-76 °C; [lit. 76-78 °C]; $R_f$ = 0.51 (17% EtOAc in *n*-hexane); $\nu_{max}$ (film)/cm$^{-1}$ 2951w and 2930w (CH), 2857w ($OCH_3$), 1724s (C=O, ester), 1599w (CO-O), 1492w, 1453w and 1437w (C=C), 1271s ($SiMe_2$), 1143m (SiO) and 838s ($SiMe_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, 1H, *J* = 8.6 Hz, ArCH), 6.87 (d, 1H, *J* = 8.6 Hz, ArCH), 5.55 (s, 1H, $CHO_2$), 4.21 (dd, J = 11.3, 1.2, 2H, 2 × $OCH_{a,}H_b$), 3.95-3.86 (m, 2H, 2 × $ROCH_{a,}H_b$), 3.89 (s, 3H, OMe), 3.81 (s, 3H, $CO_2Me$), 2.21-2.08 (m, 1H, $OCH_2CH_{a,}H_b$) 1.43-1.35 (m, 1H, $OCH_2CH_{a,}H_b$), 0.99 (s, 9H, $SiMe_2t$-*Bu*), 0.16 (s, 6H, $SiMe_2t$-Bu); $^{13}$C NMR (100 MHz) δ 167.9 (*C*$O_2$Me), 149.3 (*C*OMe), 148.3 (*C*OTBS), 129.6 (*C*$CHO_2$), 127.9 (*C*$CO_2$Me), 122.2 (ArCH), 122.0 (ArCH), 99.2 (C*C*$HO_2$), 67.4 (2 × O*C*$H_2CH_2$), 61.4 (OMe), 52.2 ($CO_2$*Me*), 25.8 (SiC(*C*$H_3$)$_3$), 25.7 (O*C*$H_2$*C*$H_2$), 18.5 (Si*C*($CH_3$)$_3$), –4.7 ($SiMe_2$); HRMS (CI) calcd for $[C_{19}H_{31}O_6Si]^+$ 383.1885; found 383.1884 $[M+H]^+$; these spectroscopic data are in agreement with those previously reported.[1]

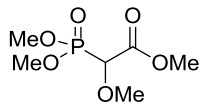
**Methyl 6-(1,3-dioxan-2-yl)-3-hydroxy-2-methoxybenzoate (14)**. To a solution of benzoate **13** (70 mg, 0.22 mmol.) in DMSO (1.4 mL) and $H_2O$ (79 µl, 4.4 mmol, 20 equiv.) was heated at 170 °C for 2 h. The reaction mixture was cooled to r.t. diluted with $Et_2O$ (10 mL) and washed with sat. aq. NaCl solution (5 × 6 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (25% EtOAc in petro) to give the *title compound* **14** as white solid (58 mg, 99%). Alternatively, to a solution of benzoate **13** (500 mg, 1.30 mmol) in THF (10 mL) was added TBAF (1 M in THF; 1.4 mL, 1.4 mmol, 1.1 equiv.) and stirred at r.t. for 60 min before addition of saturated aq. $NH_4Cl$ (10 mL). The mixture was extracted with $Et_2O$ (3 × 35 mL), dried over $MgSO_4$ before concentrating under reduced pressure. The residue was purified by flash column chromatography (25% EtOAc in petrol) to give the *title compound* **14** as white solid (344 mg, 98%); mp = 174-176 °C; $R_f$ = 0.21 (25% EtOAc in petrol); $\nu_{max}$ (film)/cm$^{-1}$ 3214br (-OH), 3006w, 2987w and 2924w (CH), 2857w ($OCH_3$), 1699s (C=O), 1587m (C=C); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, 1H, *J* = 8.5, 0.5 Hz, ArCH), 7.00 (d, 1H, *J* = 8.5 Hz, ArCH), 5.70 (brs, 1H, OH), 5.58 (s, 1H, $CHO_2$), 4.22 (ddd, *J* = 11.9, 5.0, 1.3 Hz, 2H, 2 × $OCH_{a,}H_bCH_2$), 3.92 (s, 3H, OMe), 3.91 (ddd, *J* = 12.3, 2.5, 1.3 Hz, 2H, 2 × $ROCH_{a,}H_bCH_2$), 3.85 (s, 3H, $CO_2Me$), 2.16 (dddd, *J* = 17.4, 13.2, 12.3, 5.0Hz, 1H, $OCH_2CH_{a,}H_b$), 1.41 (dddd, *J* = 13.5, 4.0, 2.5 Hz, 1.3 Hz, 1H, $OCH_2CH_{a,}H_b$); $^{13}$C NMR (100 MHz) δ 167.5 (*C*$O_2$Me), 149.2 (*C*OH), 144.3 (*C*OMe), 129.0 (*C*$CHO_2$), 126.0 (*C*$CO_2$Me), 122.9 (ArCH), 116.9 (ArCH), 99.1 (C*C*$HO_2$), 67.5 (2 × O*C*$H_2CH_2$), 62.6 (OMe), 52.5 ($CO_2$*Me*), 25.7 ($OCH_2$*C*$H_2$); HRMS (CI) calcd for $[C_{13}H_{17}O_6]^+$ 269.1020; found 269.1023 $[M+H]^+$.

**Methyl 3-((*tert*-butyldimethylsilyl)oxy)-6-formyl-2-methoxybenzoate** (**15**). To a solution of acetal




**13** (16.9 g, 44.2 mmol) in reagent grade THF (1.5 L) at –5 °C was added TMSOTf (8.4 mL, 46.4 mmol, 1.05 equiv.) dropwise and left to stir at that temperature for 15 minutes. $H_2O$ (8.8 mL, 489 mmol, 11.1 equiv.) was added dropwise to the reaction over 180 min (at which time TLC analysis indicated complete consumption of the starting material) before diluting the reaction mixture with EtOAc (1.5 L). Sat. aq. $Na_2CO_3$ solution (1.5 L) was then added to the solution. The layers were separated before further extraction of the aqueous layer with EtOAc (1.5 L). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure at 30 °C. The residue was purified by flash chromatography on silica gel (17% EtOAc in petroleum) to afford the *title compound* as pale yellow oil (13.2 g, 92%); $R_f$ = 0.41 (17% EtOAc in petroleum); $\nu_{max}$ (film)/cm$^{-1}$ 2952w and 2933w (CH), 2859w ($OCH_3$), 1737s (C=O, ester), 1695s (C=O, aldehyde), 1584m (CO-O), 1264s and 834s ($SiMe_2$) and 1138m (SiO); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H, CHO), 7.52 (d, 1H, *J* = 8.5, ArCH), 7.00 (d, 1H, *J* = 8.5, ArCH), 3.97 (s, 3H, OMe), 3.85 (s, 3H, $CO_2Me$), 1.02 (s, 9H, $SiMe_2$*t-Bu*), 0.25 (s, 6H, Si*Me*$_2$*t*-Bu); $^{13}$C NMR (100 MHz) δ 189.0 (*C*HO), 167.1 (*C*$O_2$Me), 154.8 (*C*OMe), 148.9 (*C*OTBS), 130.3 (*C*CHO), 128.9 (ArCH), 127.7 (*C*$CO_2$Me), 121.9 (ArCH), 61.8 (OMe), 52.9 ($CO_2$*Me*), 25.7 (SiC(*C*$H_3$)$_3$), 18.4 (Si*C*$(CH_3)_3$), –4.3 ($SiMe_2$); HRMS (CI) calcd for $[C_{16}H_{25}O_5Si]^+$ 325.1466; found 325.1467 $[M+H]^+$.

**Methyl (Dimethylphosphono)methoxyacetate**[2] To methyl bromomethoxyacetate[3] (26.3 g, 144




mmol, 1.0 equiv.) was cautiously added trimethyl phosphite (18 mL, 153 mmol, 1.1 equiv.) dropwise at r.t. (**CAUTION**! This reaction is extremely exothermic, take care to add trimethyl phosphite dropwise at r.t.) and the resultant, gently bubbling mixture was stirred at r.t for 20 min before heating at 185 °C for 5 h. The cooled reaction mixture was distilled under reduced pressure (111-112 °C/0.1 mbar) to afford the title compound as clear colourless oil (30.5 g, 99%); $\nu_{max}$ (film)/cm$^{-1}$ 2900w ($CO_2C$-$H_3$), 2853w and 2849w ($OCH_3$), 1750s (C=O), 1262s (P=O); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.25 (d, *J* = 19.5 Hz, 1H, PCH), 3.86 (d, *J* = 5.2 Hz, 3H, POMe), 3.84 (s, 3H, OMe), 3.83 (d, *J* = 5.2 Hz, 3H, POMe), 3.52 (d, *J* = 0.5 Hz, 3H, $CO_2$*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.3 (*C*$O_2$Me), 78.8 (d, *J* = 158.3 Hz, (PCH), 60.3 (d, *J* = 12.9 Hz, CO*Me*), 54.2 (d, *J* = 8.0 Hz, POMe), 54.1 (d, *J* = 8.0 Hz, POMe), 52.8 ($CO_2$*Me*); $^{31}$P (161.9, MHz, $CDCl_3$) δ = 16.3 (P=O); HRMS (CI) calcd for $[C_6H_{14}O_6P]^+$ 213.0528; found 213.0519 $[M+H]^+$; these spectroscopic data are in agreement with those previously reported.[2]

(2) V. Guay and P. Brassard, *Synthesis*, 1987, **3**, 294.

(3) Prepared according to S. Gagliardi, G. Nadler, E. Consolandi, C. Parini, M. Morvan, M. Legave, P. Belfiore, A. Zocchetti, G. D. Clarke, I. James, P.. Nambi, M. Gowen and C. Farina, *J. Med. Chem.* 1998**, 41**, 1568. (**CAUTION**, this reaction is extremely exothermic, take care to heat the reaction gently in a vessel using methyl methoxyacetate (20.0 g) and $CCl_4$ (250 ml), a vessel no smaller than 2 litres with extremely efficient vapour release/cooling was needed)

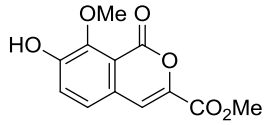
**(*E/Z*)-Methyl-3-((*tert*-butyldimethylsilyl)oxy)-6-(2,3-dimethoxy-3-oxoprop-1-en-1-yl)-2-methoxy benzoate** (**16**). To a solution of $(MeO)_2P(O)CH(OMe)CO_2Me$ (3.5 g, 16.5 mmol, 1.3 equiv.) in THF (40 mL) was added NaHMDS (2 M in THF, 8.6 mL, 17.1 mmol, 1.35 equiv.) dropwise at −78 °C over 10 min before stirring at this temperature for 20 min. A solution of aldehyde **15** (4.10 g, 12.7 mmol) in THF (20 mL) was added dropwise and the reaction mixture was allowed to slowly warm to 20 °C and stirred for 16 h. Sat. aq. $NH_4Cl$ (45 mL) was was added and the reaction mixture was extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure to afford the *title compound* as pale yellow oil, an inseparable mixture of (*E:Z*; 1:5) isomers[4] (5.0 g, 12.2 mmol, 96%). $R_f$ = 0.28 (EtOAc;Petroleum 1:19); $\nu_{max}$ (film)/cm$^{-1}$ 2953w and 2931w (CH), 2858w ($OCH_3$), 1722s (C=O, ester), 1636w (C=C, conj), 1590m (CO-O), 1484m (C=C), 1236s and 836s ($SiMe_2$) and 1138m (SiO); HRMS (CI) calcd for $[C_{19}H_{28}O_7N_1Si_1]^+$ 428.2099; found $[M+NH_4]^+$ 428.099; (*Z*)-isomer**:** $^1$H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 1H, *J* = 8.63, ArCH), 6.91 (d, 1H, *J* = 8.63, ArCH), 6.83 (s, 1H, *H*C=$C_{quat.}$), 3.95 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.82 (s, 3H, $CO_2Me$), 3.73 (s, 3H, $CO_2Me$), 1.02 (s, 9H, $SiMe_2$*t-Bu*), 0.22 (s, 6H, Si*Me*$_2$*t*-Bu); $^{13}$C NMR (100) MHz, $CDCl_3$) δ 167.7 (*C*$O_2$Me), 164.6 (*C*$O_2$Me), 149.3 (*C*OMe), 148.1 (Ar$C_{quat.}$), 145.6 (*C*OTBS), 130.6 (Ar$C_{quat.}$), 126.3 (ArCH), 124.3 (HC=$C_{quat.}$), 122.3 (ArCH), 119.4 (H*C*=$C_{quat.}$), 61.3 (OMe), 59.3 (OMe), 52.4 ($CO_2$*Me*), 52.2 ($CO_2$*Me*), 29.5 (SiC(*C*$H_3$)$_3$), 18.2 (Si*C*$(CH_3)_3$), −4.49 ($SiMe_2$); (*E*)-isomer: $^1$H NMR (400 MHz, $CDCl_3$) δ = 6.84-6.79 (m, 2H, 2 × ArCH), 6.11 (s, 1H, *H*C=$C_{quat.}$), 3.85 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.69 (s, 3H, $CO_2Me$), 3.60 (s, 3H, $CO_2Me$), 1.00 (s, 9H, $SiMe_2$*t-Bu*), 0.19 (s, 6H, Si*Me*$_2$*t*-Bu); $^{13}$C NMR (100.0 MHz, $CDCl_3$) δ 167.8 (*C*$O_2$Me), 163.9 (*C*$O_2$Me), 148.3 (*C*OMe), 147.9 (Ar*C*$_{quat.}$), 147.9 (*C*OTBS), 128.9 (Ar$C_{quat.}$), 126.5 (HC=*C*$_{quat.}$), 125.2 (ArCH), 122.1 (ArCH), 107.0 (H*C*=$C_{quat.}$), 61.3 (OMe), 56.0 (OMe), 52.1 ($CO_2$*Me*), 52.0 ($CO_2$*Me*), 25.7 (SiC(*C*$H_3$)$_3$), 18.2 (Si*C*$(CH_3)_3$), -4.6 ($SiMe_2$).

**(*E/Z*)-Methyl 6-(2,3-dimethoxy-3-oxoprop-1-en-1-yl)-3-hydroxy-2-methoxybenzoate** (**17**). To a solution of phenoxysilane **16** (340 mg, 0.82 mmol) in THF (3.5 mL) was added TBAF (1 M in THF; 1.05 mL, 1.05 mmol, 1.28 equiv) and the reaction was stirred at 20 °C for 30 min before addition of sat. aq. $NH_4Cl$ solution (5 mL). The mixture was extracted with $Et_2O$ (3 × 20 mL), dried over $MgSO_4$ and filtered before being concentrated under reduced pressure. The residue purified by flash coloumn chromatography (25% EtOAc in petroleum) to give the *title compound*, an inseparable mixture of (*E:Z*; 1:5) isomers,[4] as pale yellow oil (238 mg, 97%). Stereochemical assignments were made on the basis of NOESY experiments and correllation of chemical shifts of closely related literature compounds.[4f] (*E:Z*; 1:5) as pale yellow oil; $R_f$ = 0.23 (11% EtOAc in petrol); $\nu_{max}$ (film)/cm$^{-1}$ 3283br (OH), 2998w and 2939w (CH), 2834w ($OCH_3$), 1730s and 1701s (C=O, ester), 1629 (C=C, conj.) 1573m (C=C), 1275s and 1063 (C-O-$CH_3$); HRMS (CI) calcd for $[C_{14}H_{17}O_7]^+$ 297.0972; found 297.0696 $[M+H]^+$; (*Z*)-isomer: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, 1H, *J* = 7.50, ArCH), 7.03 (d, 1H, *J* = 7.5, ArCH), 6.88 (s, 1H, *H*C=$C_{quat.}$) 5.89 (brs, 1H, OH), 3.97 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.83 (s, 3H, $CO_2Me$), 3.71 (s, 3H, $CO_2Me$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.8 (*C*$O_2$Me), 165.2 (*C*$O_2$Me), 149.7 (*C*OH), 146.0 (*C*OMe), 127.6 (ArCH), 124.2 (HC=*C*$_{quat.}$), 120.0 (ArCH),

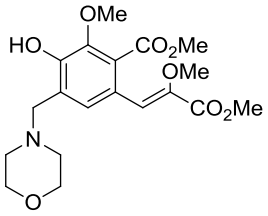
(4) Stereochemical assignments were made on the basis of NOESY experiments and correllation of chemical shifts of the closely related compounds found in reference 1 (SI).

117.8 (H*C*=$C_{quat.}$), 62.9 (OMe), 59.9 (OMe), 53.2 ($CO_2Me$), 52.7 ($CO_2Me$); (*E*)-isomer: $^1$H NMR (400 MHz, $CDCl_3$) δ 6.85-6.78 (m, 2H, ArCH), 6.12 (s, 1H, *H*C=$C_{quat.}$), 5.85 (brs, 1H, OH), 3.87 (s, 3H,OMe), 3.84 (s, 3H, OMe), 3.70 (s, 3H, $CO_2Me$), 3.61 (s, 3H, $CO_2Me$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.8 (*C*$O_2$Me), 164.1 (*C*$O_2$Me), 148.2 (*C*OH), 147.0 (*C*OMe), 128.76 (Ar$C_{quat.}$), 128.2 (CH=*C*$_{quat.}$), 125.7 (ArCH), 122.7 (ArCH), 107.1 (H*C*=$C_{quat.}$), 63.0 (OMe), 56.3 (OMe), 52.4 ($CO_2Me$), 52.0 ($CO_2Me$).

**Methyl 7-hydroxy-8-methoxy-1-oxo-1H-isochromene-3-carboxylate** (**18**). A solution of phenol **17** (100 mg, 0.34 mmol) and *p*-TSA monohydrate (66 mg, 0.35 mmol, 1.02 equiv.) in PhMe (2 ml) was heated in a crimp sealed microwave vial at 135 °C for 21 h. The reaction mixture was then slowly cooled to –25 °C and the duly formed creamy precipitate was filtered and washed with cold $Et_2O$ (15 mL). The resultant white solid was purified by flash column chromatography (20% EtOAc in petrol) to give the *title compound* **18** as pale white powder (80 mg, 94%); mp = 136-138 °C; $R_f$ = 0.21 (20% EtOAc in petrol); $\nu_{max}$ (film)/cm$^{-1}$ 3241br (-OH), 3083w (CH), 2944w (OCH), 1695 (C=O ester), 1592m, 15992m, 1509m, 1494m (C=C), 1306s (-O-H) 1237s and 1071s (C-O-$CH_3$); $^1$H NMR (400 MHz, $d_6$-DMSO) δ 10.36 (brs, 1H, COH), 7.58 (s, 1H, C*H*=$C_{quat.}$), 7.51 (d, 1H, *J* = 8.49, ArCH), 7.42 (d, 1H, *J* = 8.49, ArCH), 3.85 (s, 3H, OMe), 3.80 (s, 3H, $CO_2Me$); $^{13}$C NMR (100MHz, $d_6$-DMSO) δ 160.3 (*C*$O_2$Me), 156.8 (Ar*C*$CO_2$), 153.2 (*C*OH), 148.3 (*C*OMe), 139.7 (CH=*C*$_{quat.}$), 127.7 (Ar$C_{quat.}$), 124.9 (ArCH), 124.4 (ArCH), 116.3 (Ar$C_{quat.}$), 112.9 (*C*H=$C_{quat.}$), 60.9 (OMe), 52.50 ($CO_2$*Me*); HRMS (EI) calcd for $[C_{12}H_{11}O_6]^+$251.0550; found $[M+H]^+$ 251.0552.




**Methyl 6-(2,3-dimethoxy-3-oxoprop-1-en-1-yl)-3-hydroxy-2-methoxy-4-(morpholinomethyl) benzoate** (**20**). To a solution of phenol **17** (50 mg, 0.17 mmol) in MeCN (1 mL) was added 4-methylenemorpholin-4-ium chloride[5] (46 mg, 0.34 mmol, 2.0 equiv.), the vial was crimp sealed and then heated at 150 °C for 16 h. The resultant clear yellow solution was allowed to cool to r.t. and then diluted with EtOAc (10 mL) and filtered before being concentrated under reduced pressure. The residue, a pale yellow oil, was purified by flash column chromatography (33% EtOAc in petroleum) to give the *title compound* **20** (*E*:*Z*; 16:84)[6] as clear colourless oil which solidified to a clear wax upon storage at –5 °C (61 mg, 91%). Alternatively, a solution of paraformaldehyde (101 mg, 3.9 mmol, 2.0 equiv.) and morpholine (0.3 mL, 3.9 mmol, 2.0 equiv.) in acetic acid (6 mL) was stirred at 20 °C for 24 h before addition of phenol **17** (574 mg, 1.9 mmol, 1.0 equiv.). The vial was crimp sealed then heated at 130 °C for 16 h. The clear yellow solution was allowed to cool to r.t. and filtered before being concentrated under reduced pressure. The residue, a pale yellow oil, was purified by flash column chromatography (33% EtOAc in petroleum) to give the *title compound* **20** (*E*:*Z*; 13:87) as clear colourless oil which solidified to a clear wax upon storage at –5 °C (76.5 mg, quant); mp = 22-23 °C; $R_f$ = 0.23 (10% MeCN in $CH_2Cl_2$); $\nu_{max}$ (film)/cm$^{-1}$ 2948w (CH), 2841w ($OCH_3$), 1726s (C=O, ester), 1636m (C=C,




(5) (a) H. Sliwa and D. Blondeau, *Heterocycles*, **1981**, 16, 2159-2167. (b). R. Hernández-Altamirano, V. Y. Mena-Cervantes, S. Perez-Miranda, F. J. Fernández, C. A. Flores-Sandoval, V. Barba, H. I. Beltrán and L. S. Zamudio-Rivera, *Green Chem.*, **2010**, 12, 1036-1048.
(6) Stereochemical assignments were made on the basis of nOe experiments.

conj.), 1450m (C-H), 1274s and 1057s (C-O-$CH_3$); HRMS (CI) calcd for $[C_{19}H_{26}O_8N_1]^+$ 396.1653; found 396.1653 $[M+H]^+$; (*Z*)-isomer: $^1$H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H, OH), 6.62 (s, 1H, ArCH), 6.09 (s, 1H, *H*C=$C_{quant.}$), 3.92 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.78-3.75 (m, 4H, 2 × $NCH_2CH_2O$), 3.71-3.68 (brs, 5H, 1 × $CO_2$Me and $CCH_2$), 3.63 (s, 3H, $CO_2$Me), 2.57 (brs, 4H, 2 × $OCH_2CH_2N$); $^{13}$C NMR (100 MHz) δ 167.8 (*C*$O_2$Me), 163.9 (*C*$O_2$Me), 149.7 (ArOH), 147.8 (*Ar*OMe), 144.9 (CH=*C*$_{quant.}$), 124.7 (ArCH), 124.5 (Ar$C_{quant.}$), 123.6 (Ar$C_{quant.}$), 122.9 (Ar$C_{quant.}$), 107.1 (*CH*=$C_{quant.}$), 66.7 (2 × $RNCH_2CH_2O$), 61.60 (*C*$H_2$N), 61.20 (OMe), 55.98 (OMe), 52.86 (2 × $OCH_2CH_2N$), 52.11 ($CO_2$*Me*), 51.96 ($CO_2$*Me*); (*E)*-isomer: δ $^1$H NMR (400 MHz, $CDCl_3$) δ = 9.87 (s, 1H, OH), 7.62 (s, 1H, ArCH), 6.81 (s, 1H, Ar*H*C=$CR_2$), 3.95 (s, 3H, OMe), 3.94 (s, 2H, Ar$CH_2$), 3.91 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.76-3.73 (m, 4H, 2 × $NCH_2CH_2O$), 3.72 (s, 3H, OMe), 2.57 (brs, 4H, 2 × $OCH_2CH_2N$).

**Methyl 3-acetoxy-4-(acetoxymethyl)-6-(2,3-dimethoxy-3-oxoprop-1-en-1-yl)-2-methoxy benzoate** (**21**)**.** To a solution of **20** (100 mg, 0.25 mmol, 1.0 equiv.) in $Ac_2O$ (2 mL, 21.2 mmol, 84.6 equiv), the reaction was crimp sealed then heated at 155 °C for 24 h. Once cooled the solution was added to MeOH (10 mL) and concentrated under reduced pressure. The residue, a light brown oil was purified by flash column chromatography (5% MeCN in $CH_2Cl_2$) to give the *title compound* **21** (*E*:*Z*; 1:4)[6] as pale yellow oil (89 mg, 84%); $R_f$ = 0.26 (5% MeCN in $CH_2Cl_2$); $\nu_{max}$ (film)/cm$^{-1}$ 2953w (CH), a 2851w ($OCH_3$), 1770m (C=O, ester), 1727s (C=O, ester), 1635m (C=C, conj.), 1454m (C-H), 1221s, 1183s and 1154s (C-O-$CH_3$); HRMS (CI) calcd for $[C_{19}H_{26}O_{10}N_1]^+$ 428.1551; found 428.1551 $[M+NH_4]^+$; (*Z*)-isomer: $^1$H NMR (400 MHz, $CDCl_3$) 7.01 (s, 1H, ArCH), 6.13 (s, H, C*H*=$C_{quant.}$), 5.02 (s, 2H, C$H_2$OAc), 3.85 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.72 (s, 3H, $CO_2$Me), 3.61 (s, 3H, $CO_2$Me), 2.33 (s, 3H, OAc), 2.06 (s, 3H, OAc); $^{13}$C NMR (100 MHz) δ 171.1 (O*C*OMe), 168.8 (O*C*OMe), 167.3 (*C*$O_2$Me), 164.8 (*C*$O_2$Me), 150.2 (*C*OMe), 147.8 (CH=*C*$_{quant.}$), 142.9 (*C*OAc), 132.3 (ArCH), 131.9 (Ar$_{quat.}$), 130.4 (Ar$_{quat.}$), 127.1 (Ar$_{quat.}$), 118.8 (*C*H=$C_{quant.}$), 62.9 (OMe), 61.6 ($CH_2$OAc), 60.3 (OMe), 53.3 ($CO_2$*Me*), 53.0 ($CO_2$*Me*), 21.4 (OCO*Me*), 21.1 (OCO*Me*); **(*E*)-isomer:** $^1$H NMR (400 MHz, $CDCl_3$) δ $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.91 (s, 1H, ArCH), 6.86 (s, H, C*H*=$C_{quant.}$), 5.05 (s, 2H, C$H_2$OAc), 3.93 (s, 3H, OMe), 3.83 (s, 6H, 1 × OMe, 1 × $CO_2$Me), 3.74 (s, 3H, $CO_2$Me), 2.35 (s, 3H, OAc), 2.09 (s, 3H, OAc); $^{13}$C NMR (100 MHz) δ 171.1 (O*C*OMe), 168.9 (O*C*OMe), 167.4 (*C*$O_2$Me), 164.1 (*C*$O_2$Me), 150.3 (*C*OMe), 149.2 (CH=*C*$_{quant.}$), 141.9 (*C*OAc), 133.0 (ArCH), 130.2 ($CH_2$), 128.8 (Ar$C_{quant.}$), 127.1 (Ar$C_{quant.}$), 118.8 (*C*H=$C_{quant.}$), 62.8 (OMe), 61.4 (Ar$CH_2$), 56.7 (OMe), 53.0 ($CO_2$*Me*), 52.8 ($CO_2$*Me*), 21.4 (CO*Me*), 21.1 (CO*Me*).

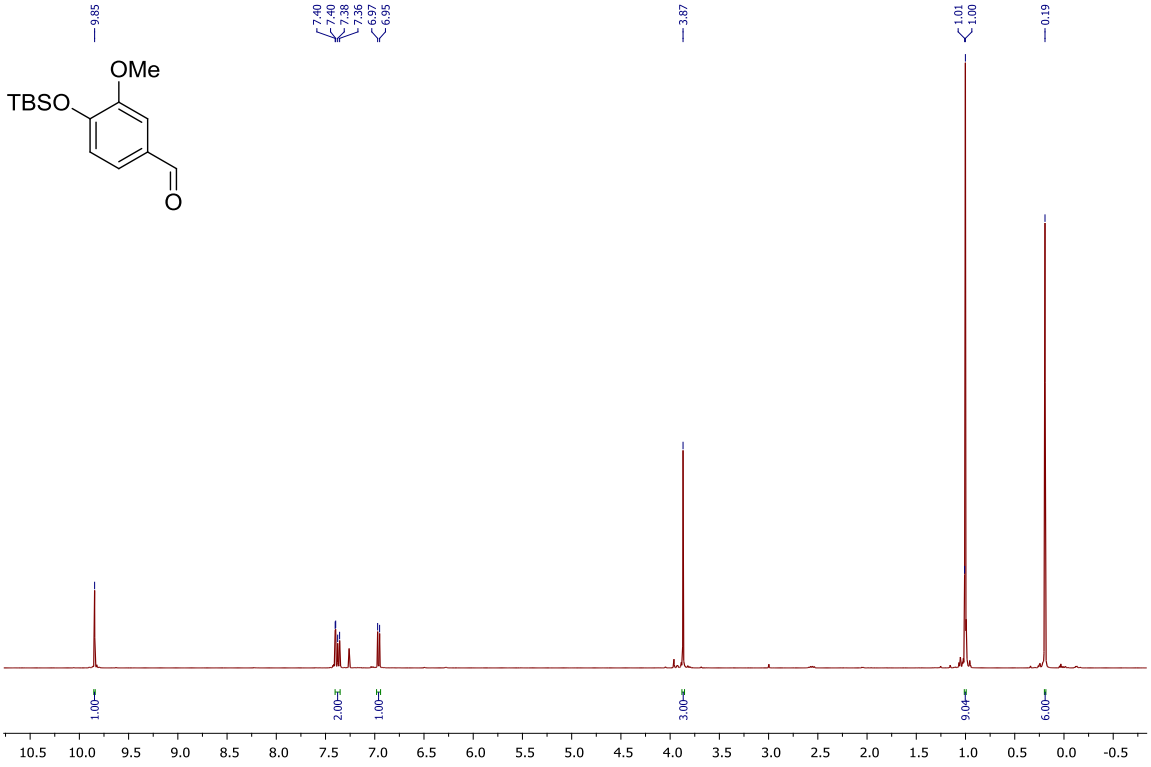
**Methyl 6-((*Z*)-2,3-dimethoxy-3-oxoprop-1-en-1-yl)-8-methoxy-3,3a,4,9a-tetrahydro-2H-furo[2,3 -b]chromene-7-carboxylate** ((±)-**24**). To a solution of amine **20** (20 mg, 51 μmol, 1.0 equiv.) dissolved in PhMe (0.2 ml) was added MeI (0.1 M in PhMe, 0.5 ml, 50 μmol, 0.99 equiv). The reaction was stirred at r.t. for 2 h, at which time TLC analysis indicated complete consumption of the starting material. 2,3-Dihydrofuran (0.38 μl, 0.5 mmol, 10.0 equiv.) was added and the crimp sealed reaction mixture was heated at 130 °C for 16 h in a microwave reactor. The reaction mixture was cooled to r.t., diluted with EtOAc (3 mL) and filtered through a short pad of silica (d = 1 cm × h = 0.5 cm). The filtrate was concentrated under reduced

pressure and the residue purified by flash column chromatography (25% EtOAc in petrol) to give the *title compound* **24** clear colourless oil (12.4 mg, 0.033 mmol, 65%). Alternatively, a solution of amine **20** (20 mg, 51 μmol, 1.0 equiv.) was dissolved in 2,3-dihydrofuran (0.10 mL, 6.81 mmol). The crimp sealed mixture was heated at 130 °C for 16 h. The cooled reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography (1→10% $Et_2O$ in petrol) to give the *title compound* **24** as clear colourless oil (14.0 mg, 35 μmol, 70%); $R_f$ = 0.19 (25% EtOAc in petrol); $\nu_{max}$ (film)/cm$^{-1}$ 2938w and 2924w (CH), 2854 (O-C-$H_3$), 1724s (2 × C=O, ester), 1645w (O-CO), 1452m, and 1438m (C=C); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H, ArCH), 6.78 (s, 1H, CH=$C_{quat.}$), 5.71 (d, *J* = 5.3 Hz, 1H, $O_2CH$), 3.98-3.88 (m, 2H, $OCH_2$), 3.87 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.75 (s, 3H, $CO_2Me$), 3.66 (s, 3H, $CO_2Me$), 3.01 (dd, *J* = 15.9, 5.3 Hz, 1H, $O_2CHCH$), 2.78-2.72 (m, 1H, Ar$H_aH_b$), 2.68 (dd, *J* = 15.9, 2.6 Hz, 1H, Ar$H_aH_b$), 2.03-1.96 (m, 1H, $OCH_2CH_aH_b$), 1.62-1.57 (m, 1H, $OCH_2CH_aH_b$); $^{13}$C NMR (100 MHz) δ 164.5 ($CO_2$Me), 163.5 ($CO_2$Me), 153.1 (COMe), 148.3 (CH=$C_{quat.}$), 142.0 (Ar$C_{quat.}$), 129.8 (Ar$C_{quat.}$), 127.2 (Ar$C_{quat.}$), 119.0 (Ar$C_{quat.}$), 103.6 (CH=$C_{quat.}$), 103.2 ($O_2$CH), 74.5 ($OCH_2$), 67.0 (OMe), 66.1 (OMe), 61.9 ($CO_2Me$), 59.6 ($CO_2Me$), 52.8 ($O_2CHCH$), 30.7 ($OCH_2CH_2$), 29.8 ($CH_2$); The $^{13}$C NMR spectrum could not be clearly distinguished from the major (*Z*)-isomer; HRMS (EI) calcd for $[C_{19}H_{26}O_8N]^+$ 396.1653; found 396.1654 $[M+NH_4]^+$.

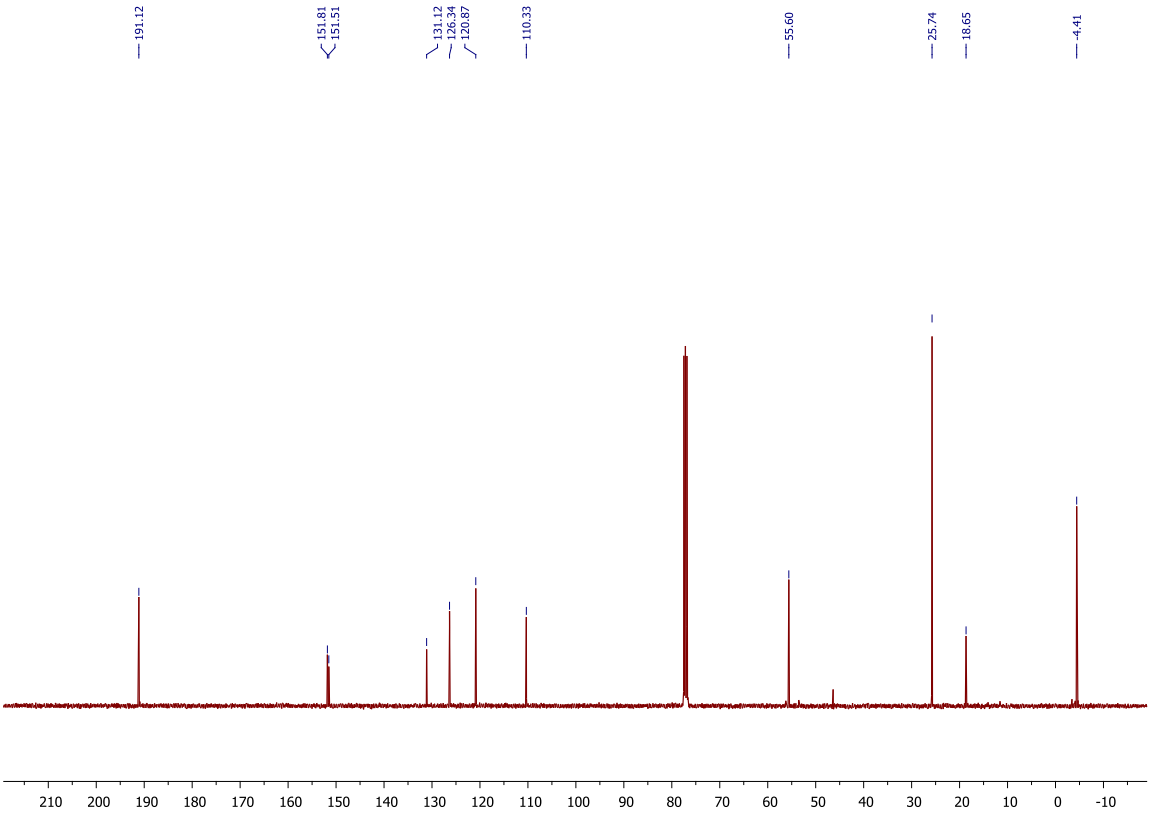
**Methyl 6-(2,3-dimethoxy-3-oxoprop-1-en-1-yl)-8-methoxy-5'-oxo-4',5'-dihydro-3'H-spiro[chroman-2,2'-furan]-7-carboxylate** ((±)-**26**). Amine **20** (20 mg, 51 μmol) was dissolved in γ-methylene-γ-butyrolactone (0.10 mL, 1.12 mmol) and the crimp sealed reaction mixture was heated at 130 C for 16 h in a microwave reactor. The reaction mixture was then cooled to r.t., and purified by flash column chromatography (1→10% EtOAc in petrol) to give *spiroketal* **26** (*E*:*Z*; 1:3) as clear colourless oil (14.2 mg, 64%); $R_f$ = 0.15 (10% $Et_2O$ in petrol); $\nu_{max}$ (film)/cm$^{-1}$ 2939w and 2930w (CH), 2854 (O-C-$H_3$), 1792s and 1725s (C=O, ester), 1645w (O-CO), 1567m, 1475m, 1440m, 1436m (C=C); (*Z*)-isomer: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H, ArCH), 6.81 (s, 1H, CH=$C_{quat.}$), 3.96 (s, 3H, OMe), 3.91 (s, 3H, OMe), 3.82 (s, 3H, $CO_2Me$), 3.74 (s, 3H, $CO_2Me$), 3.09-2.94 (m, 2H, $CH_2$), 2.72-2.52 (m, 2H, $CH_2$), 2.41-2.23 (m, 2H, $CH_2$), 2.19-2.08 (m, 1H, C$H_aH_b$), 2.04 (m, 1H, $CH_aH_b$); $^{13}$C NMR (100 MHz) δ 173.5 ($CO_2$), 167.2 ($CO_2$Me), 164.3 ($CO_2$Me), 147.3 (RH=$C_{quat.}$), 146.2 (COMe), 142.2 (Ar$C_{quat.}$), 125.5 (Ar$C_{quat.}$), 125.4 (Ar$C_{quat.}$), 124.9 (ArCH), 118.6 (CH=$C_{quat.}$), 109.0 (spiro-C), 61.9 (OMe), 59.4 (OMe), 52.6 ($CO_2Me$), 52.3 ($CO_2Me$), 38.8 ($CH_2$), 32.9 ($CH_2$), 26.9 ($CH_2$), 25.7 ($CH_2$); (*E*)-isomer: $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.65 (s, 1H, ArCH), 6.84 (s, 1H, CH=$C_{quat.}$), 3.93 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.81 (s, 3H, $CO_2Me$), 3.72 (s, 3H, $CO_2Me$), 3.09-2.94 (m, 2H, $CH_2$), 2.72-2.52 (m, 2H, $CH_2$), 2.41-2.23 (m, 2H, $CH_2$), 2.19-2.08 (m, 1H, C$H_aH_b$), 2.04 (m, 1H, $CH_aH_b$); The $^{13}$C NMR spectrum could not be clearly distinguished from the major (*Z*)-isomer. HRMS (EI) calcd for $[C_{20}H_{23}O_9]^+$ 407.1337; found 407.1339 $[M+H]^+$.

## NMR Spectra

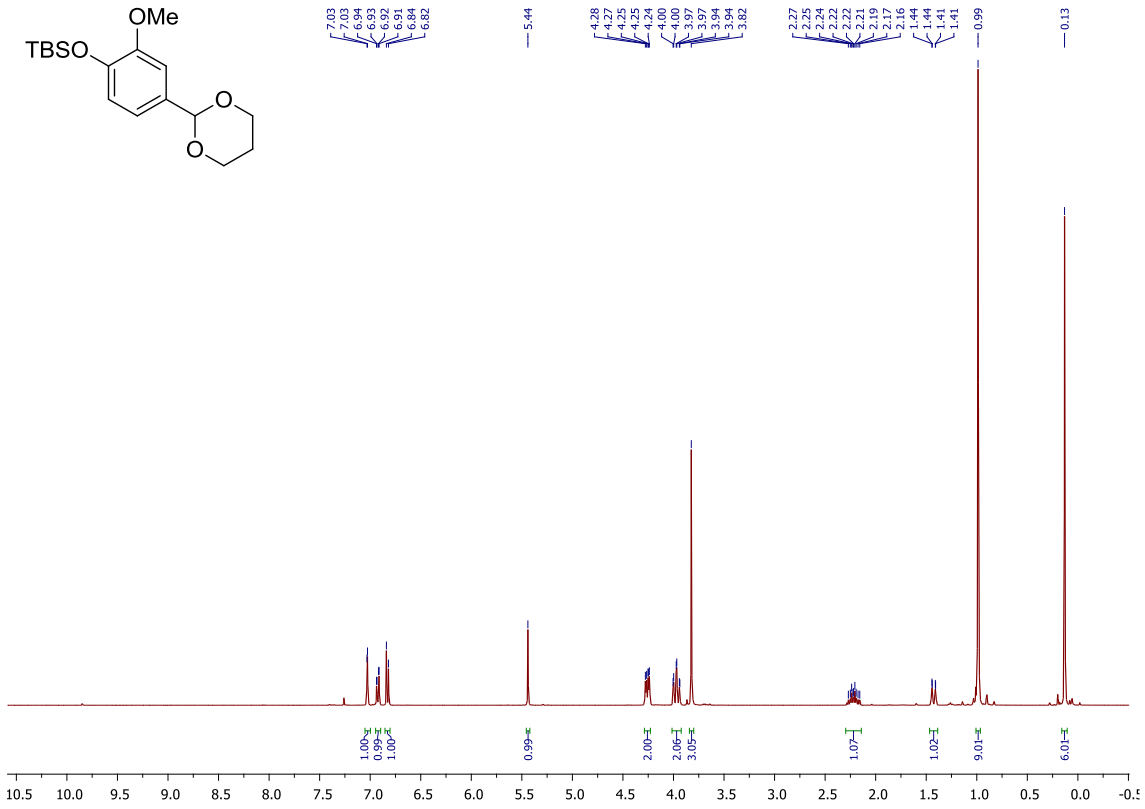
### $^{1}$H NMR Spectrum (Compound 11)



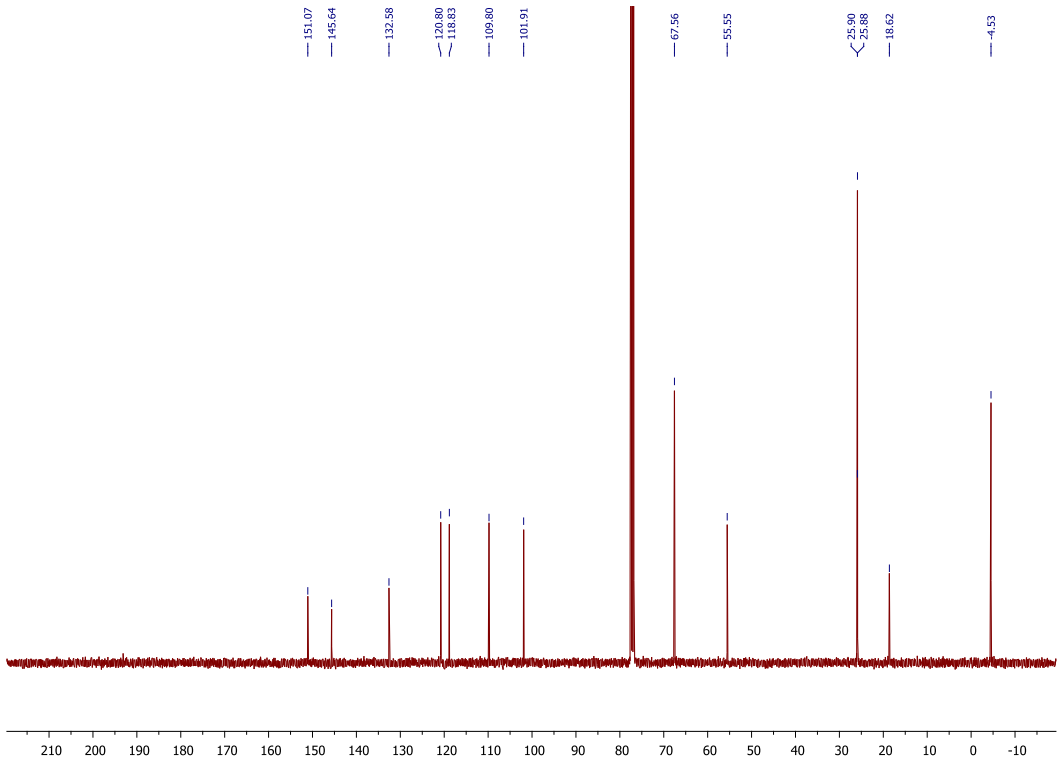

### $^{13}$C NMR Spectrum (Compound 11)



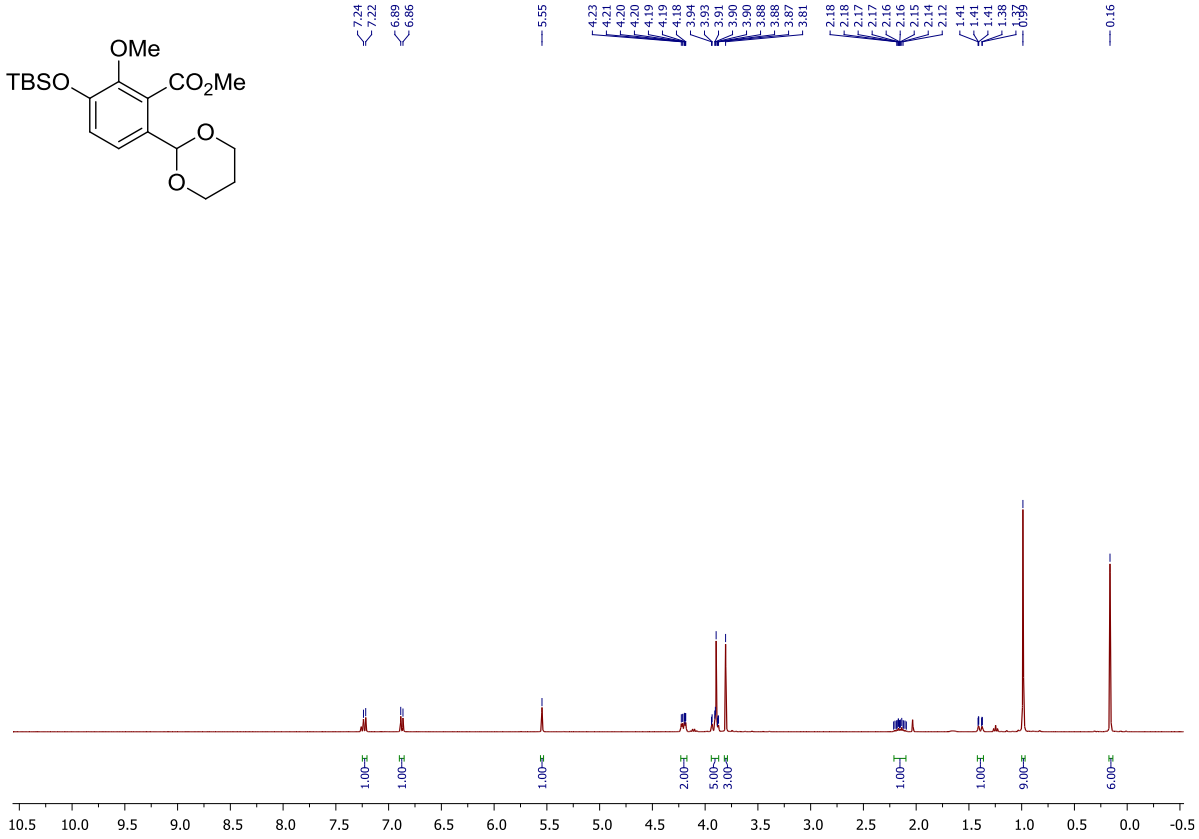
## $^{1}$H NMR Spectrum (Compound 12)



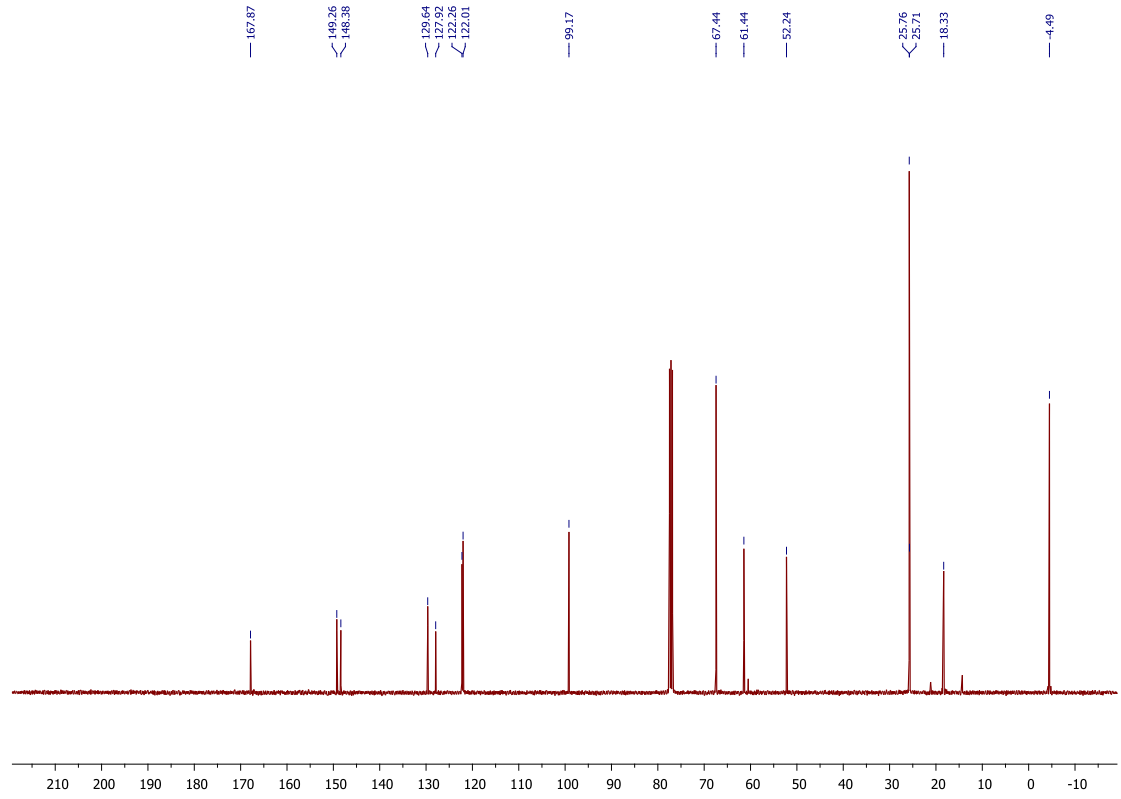

## $^{13}$C NMR Spectrum (Compound 12)



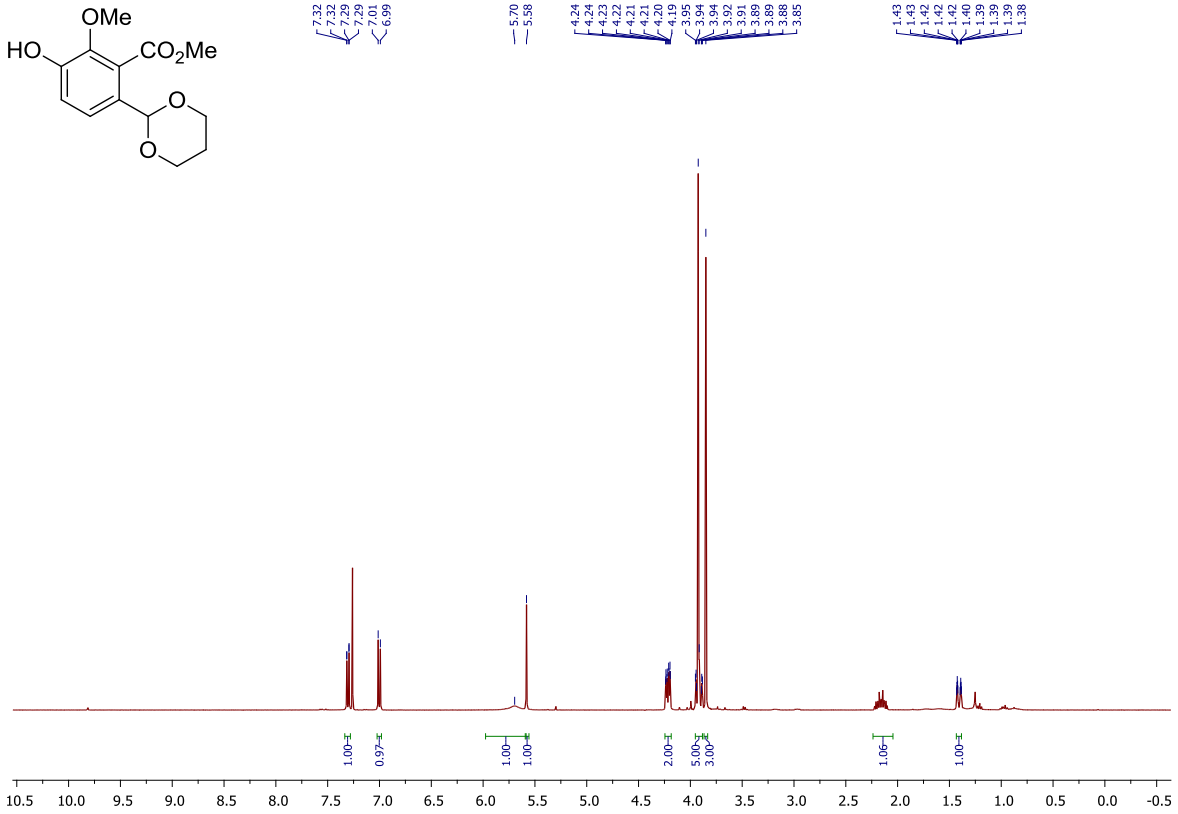
## $^{1}$H NMR Spectrum (Compound 13)



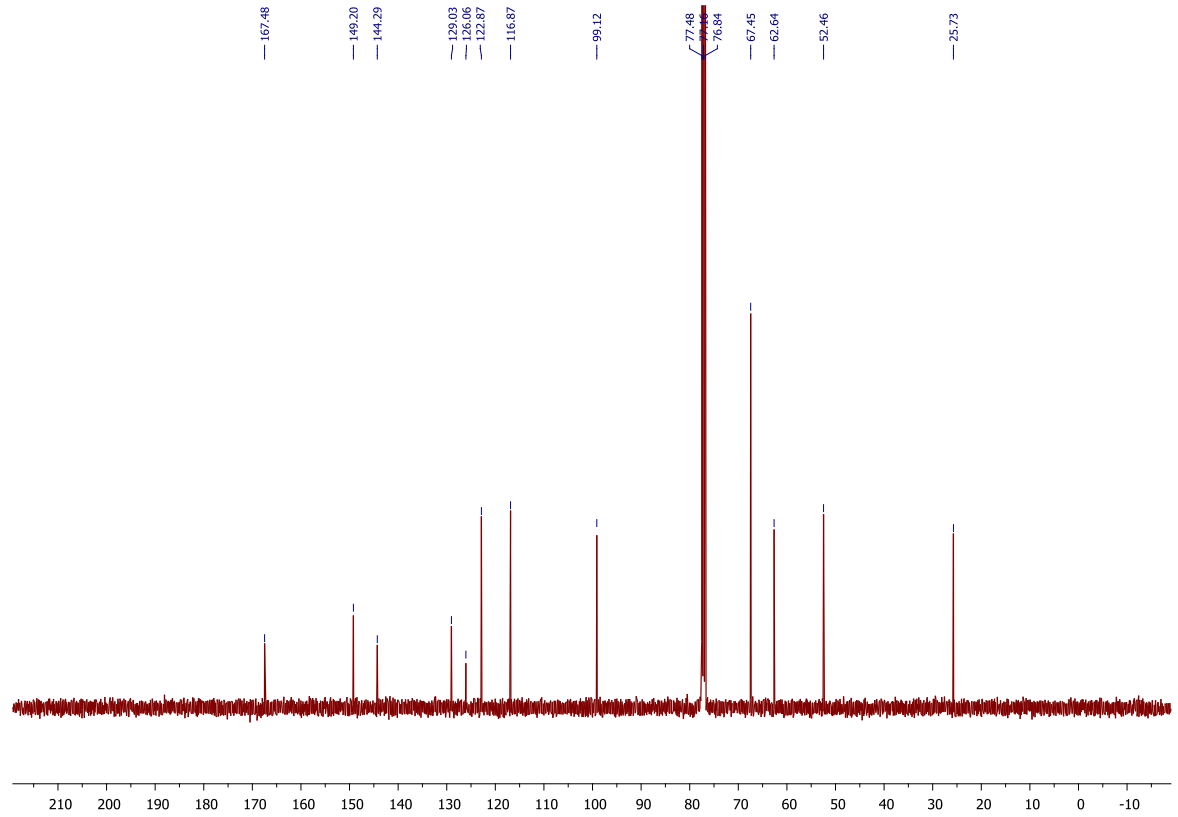

## $^{13}$C NMR Spectrum (Compound 13)



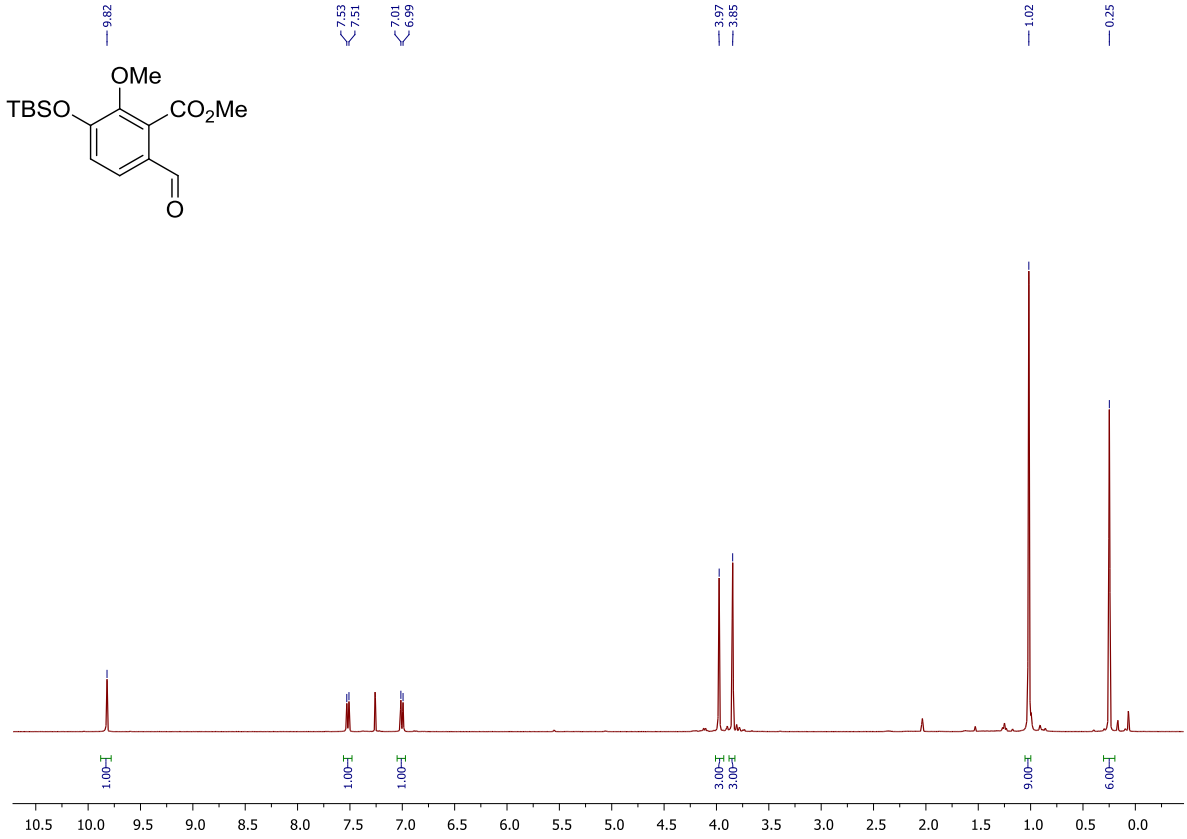
## $^{1}$H NMR Spectrum (Compound 14)



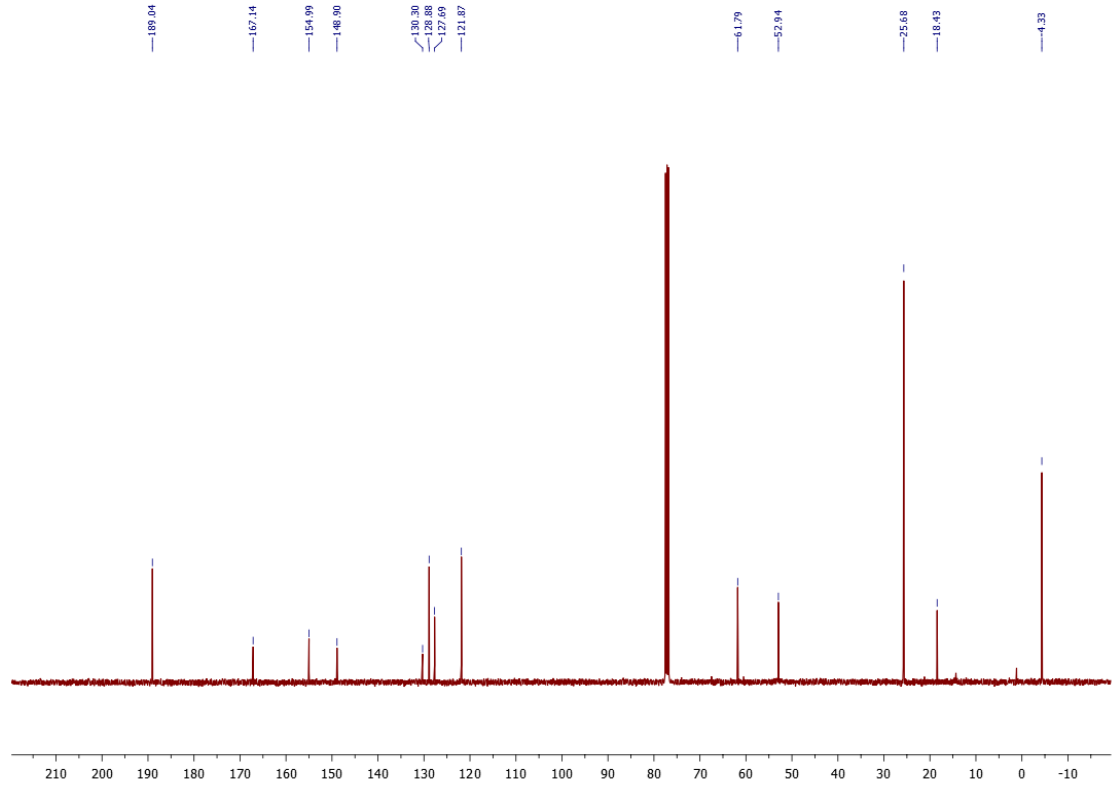

## $^{13}$C NMR Spectrum (Compound 14)



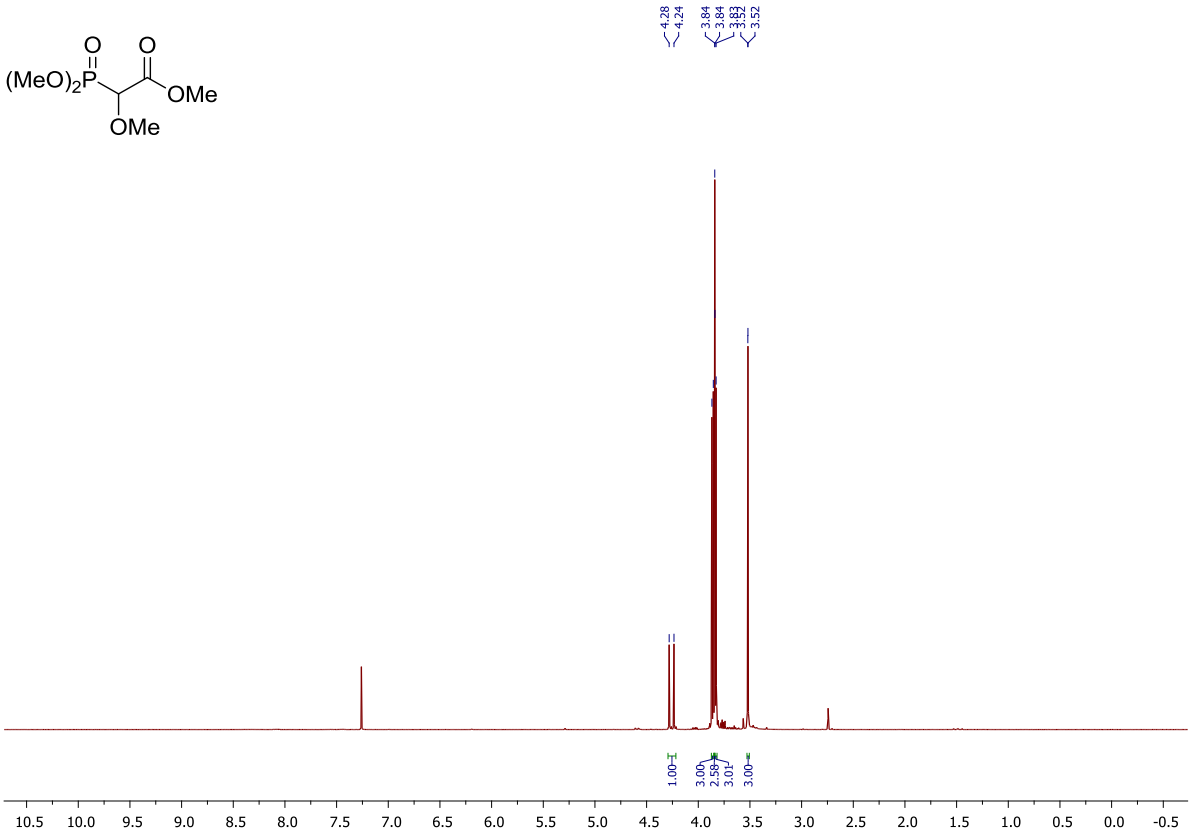
## $^{1}$H NMR Spectrum (Compound 15)



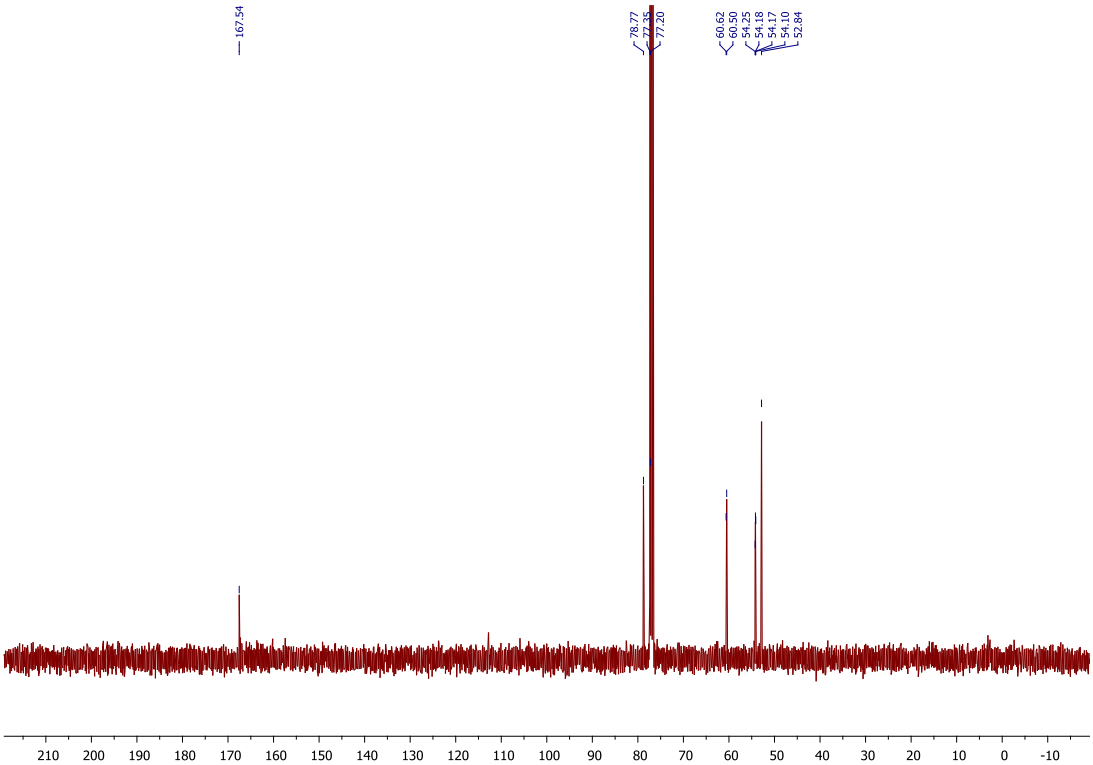

## $^{13}$C NMR Spectrum (Compound 15)



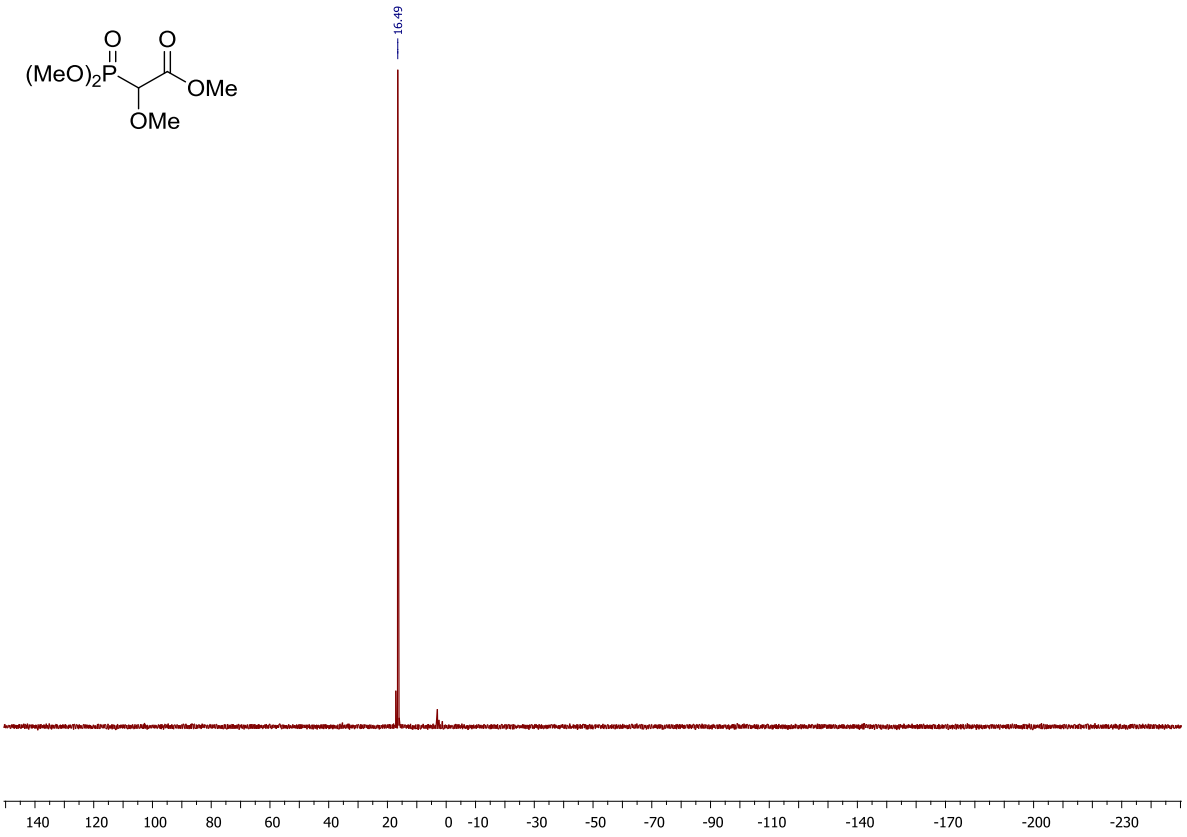
## $^{1}$H NMR Spectrum



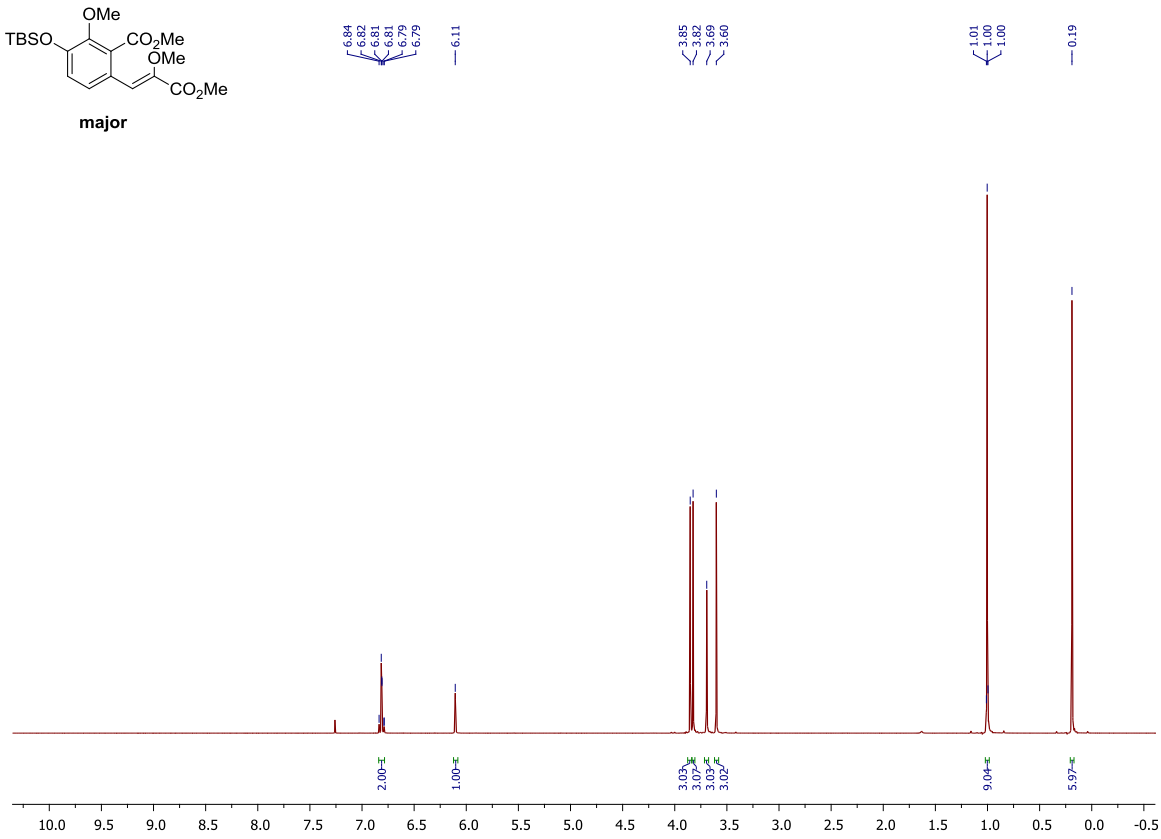

## $^{13}$C NMR Spectrum



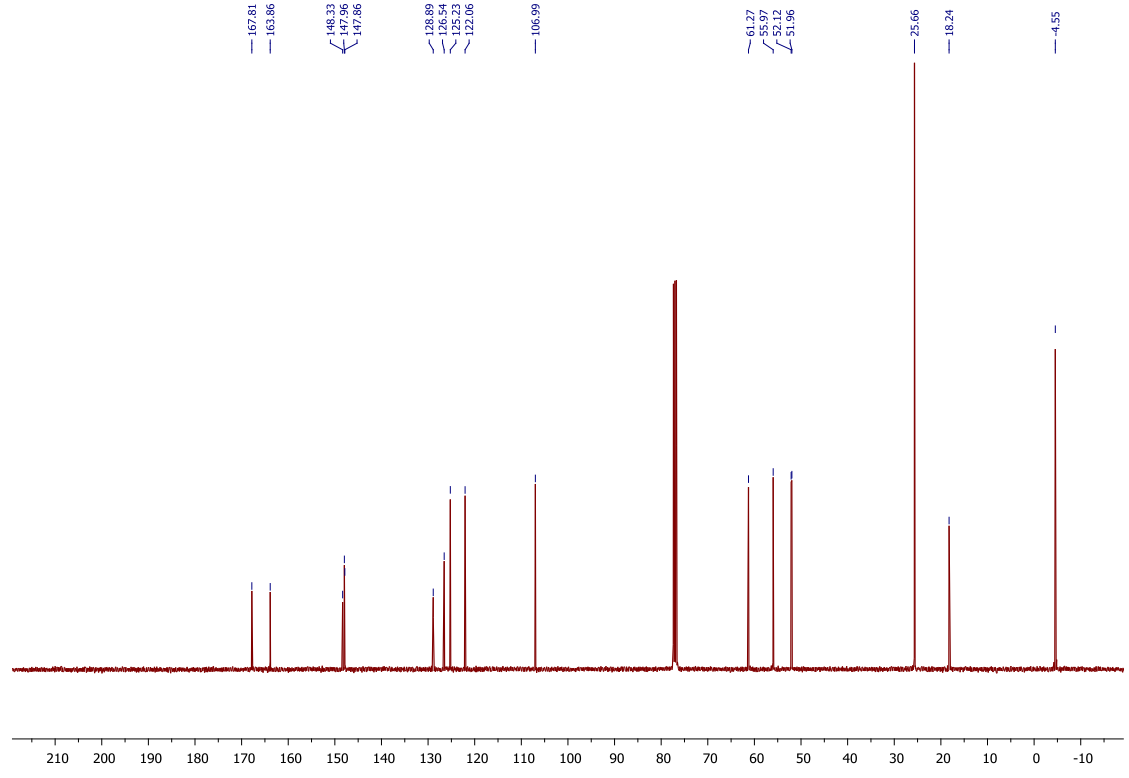
## $^{31}$P NMR Spectrum



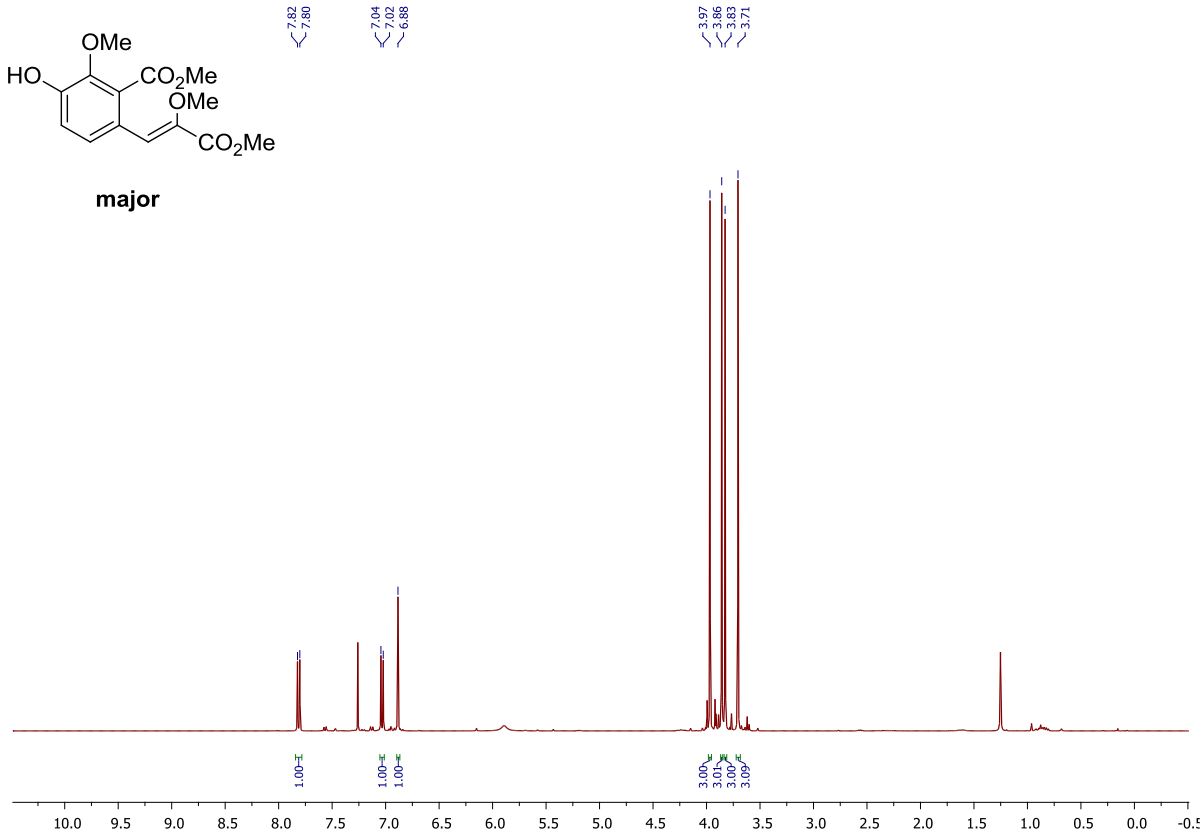
## $^{1}$H NMR Spectrum (Compound 16; *Z*-isomer highlighted)



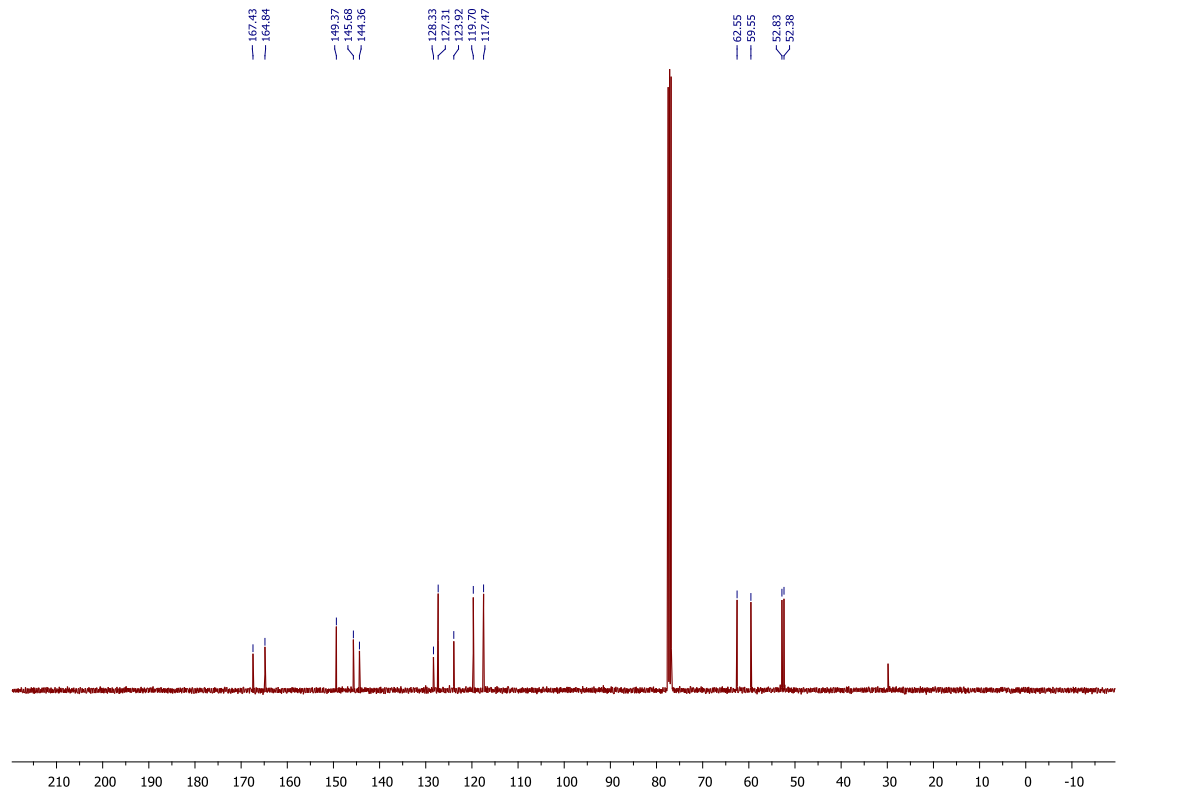

## $^{13}$C NMR Spectrum (Compound 16; *Z*-isomer highlighted)



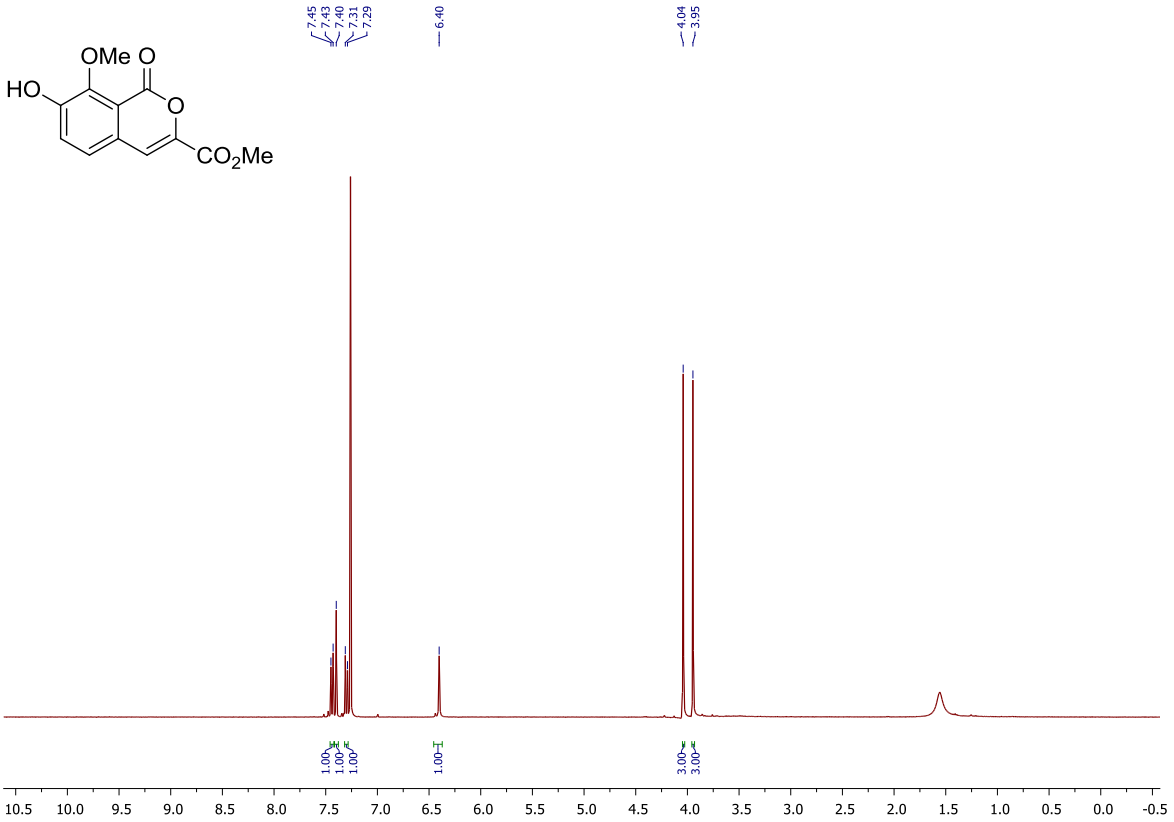
## $^{1}$H NMR Spectrum (Compound 17; *Z*-isomer highlighted)



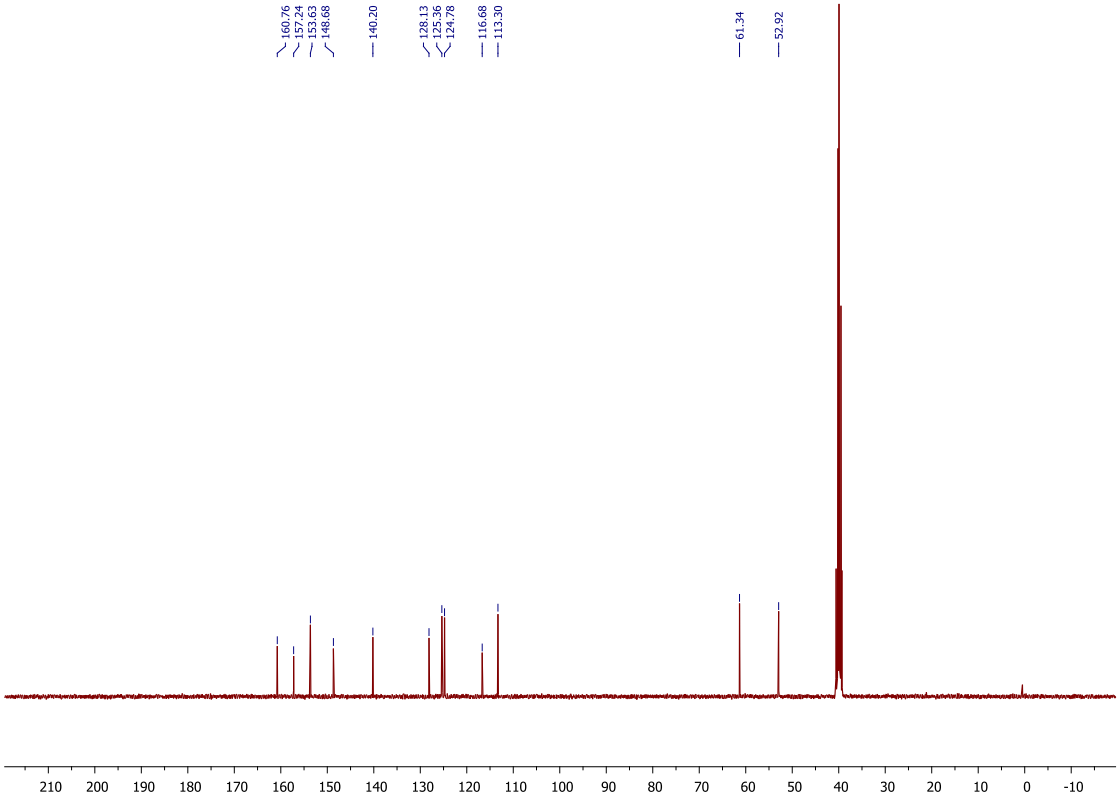

## $^{13}$C NMR Spectrum (Compound 17; *Z*-isomer highlighted)



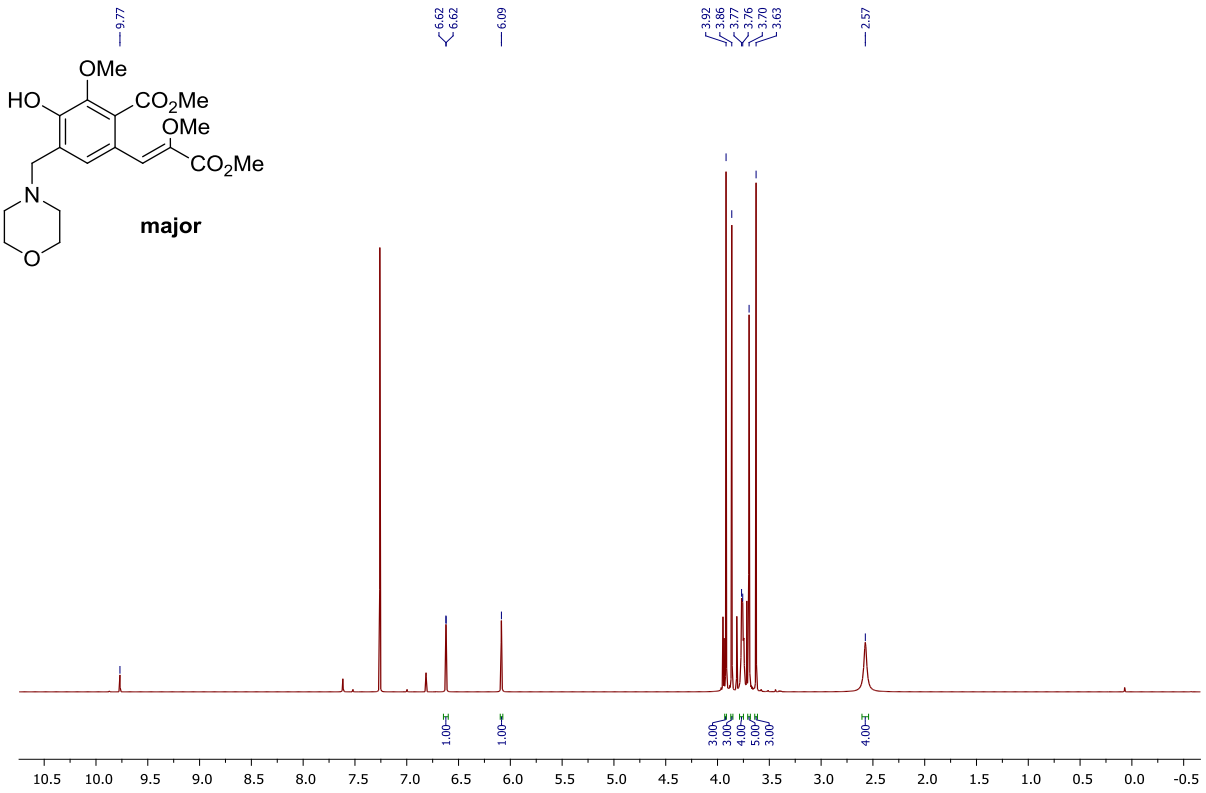
## $^{1}$H NMR Spectrum (Compound 18)



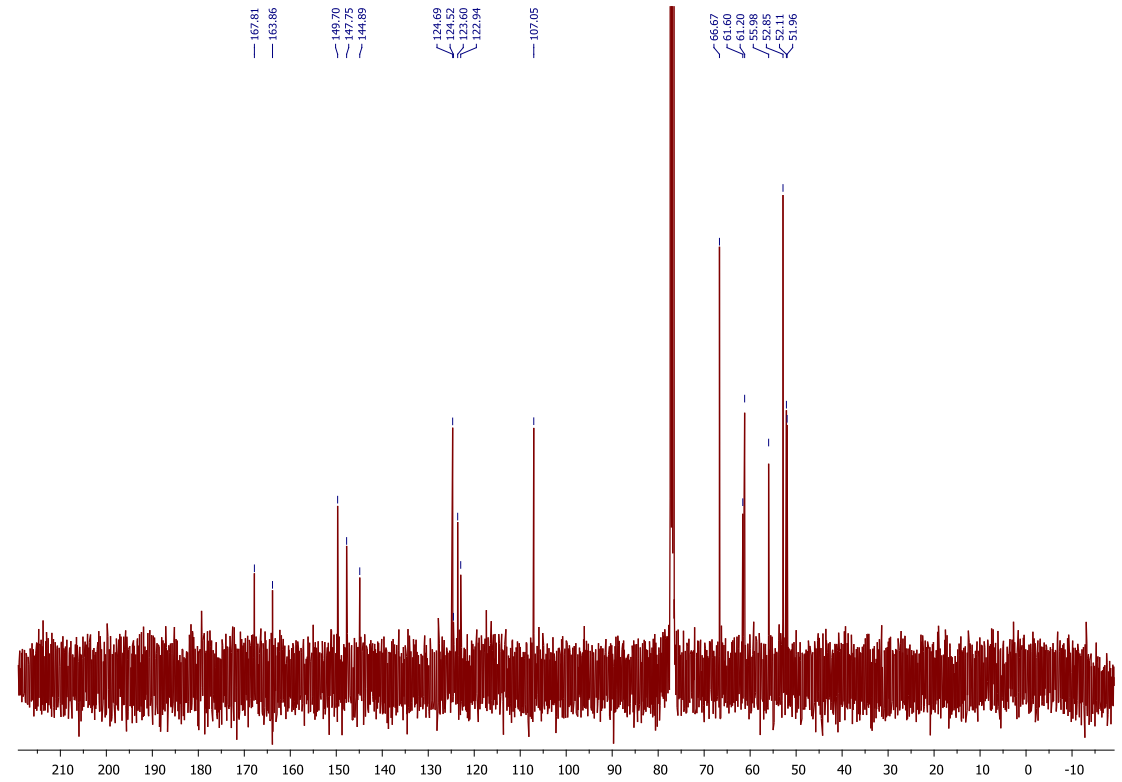

## $^{13}$C NMR Spectrum (Compound 18)



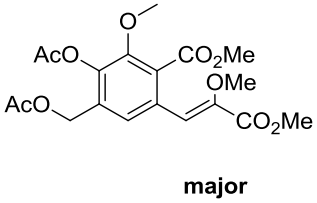
## $^{1}$H NMR Spectrum (Compound 20; *Z*-isomer highlighted)




## $^{13}$C NMR Spectrum (Compound 20)



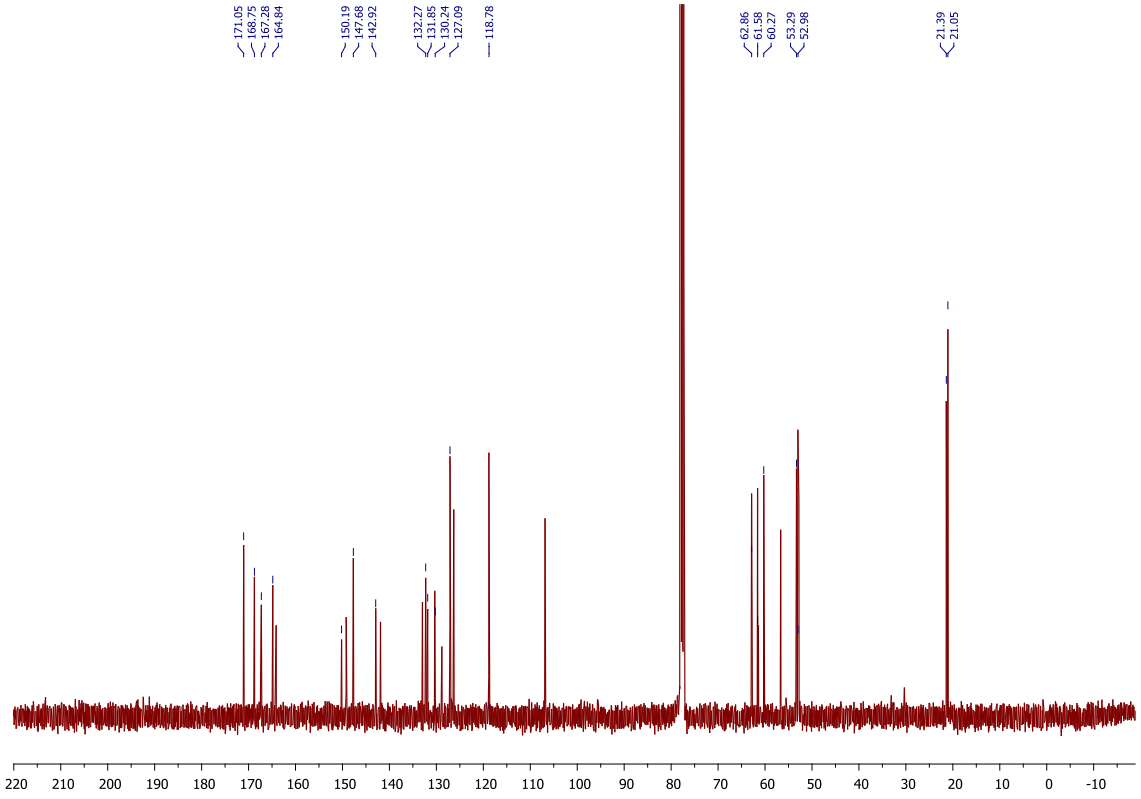
## $^{1}$H NMR Spectrum (Compound 21; *Z*-isomer highlighted)



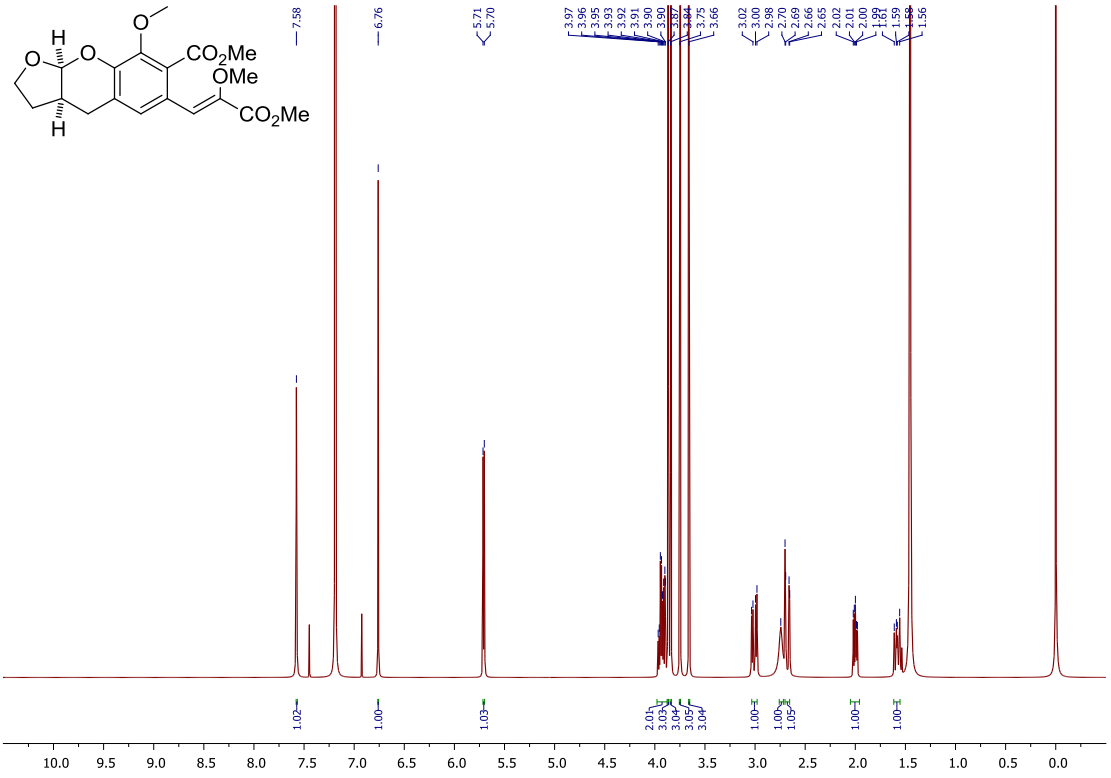

major



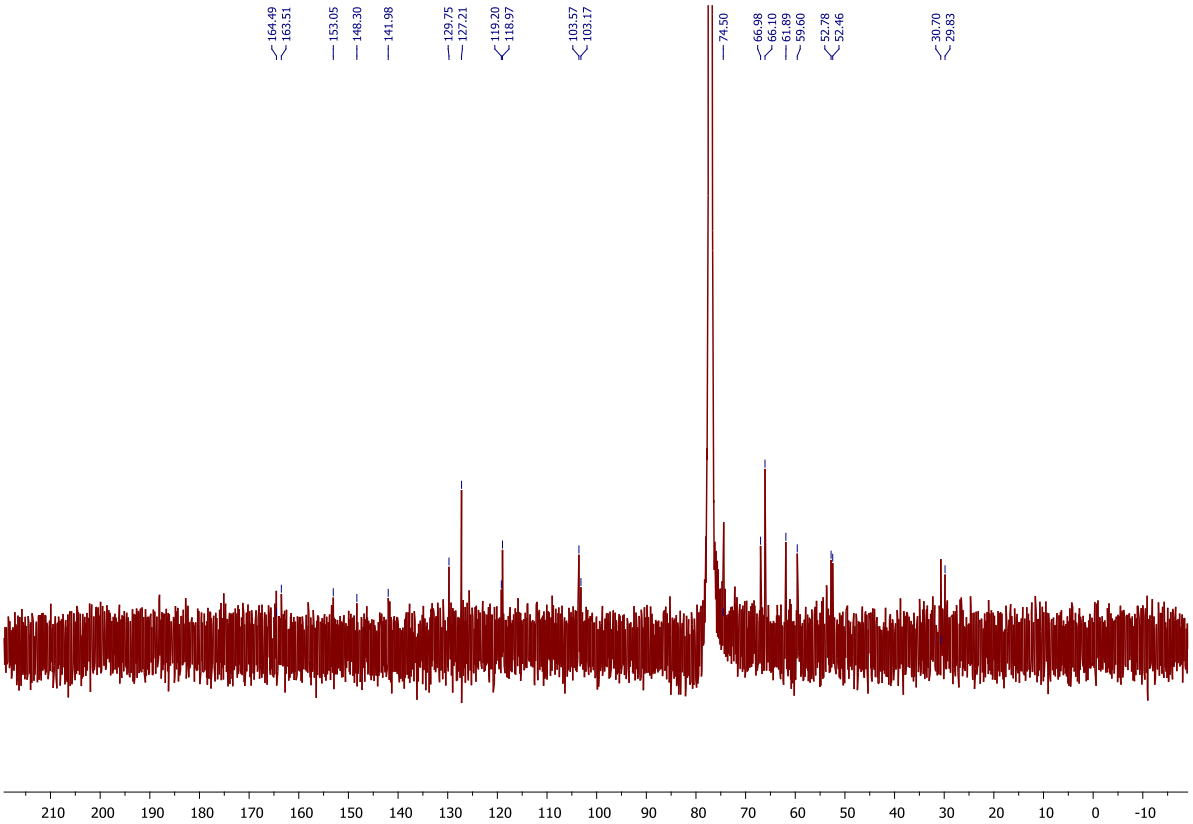

## $^{13}$C NMR Spectrum (Compound 21; *Z*-isomer highlighted)



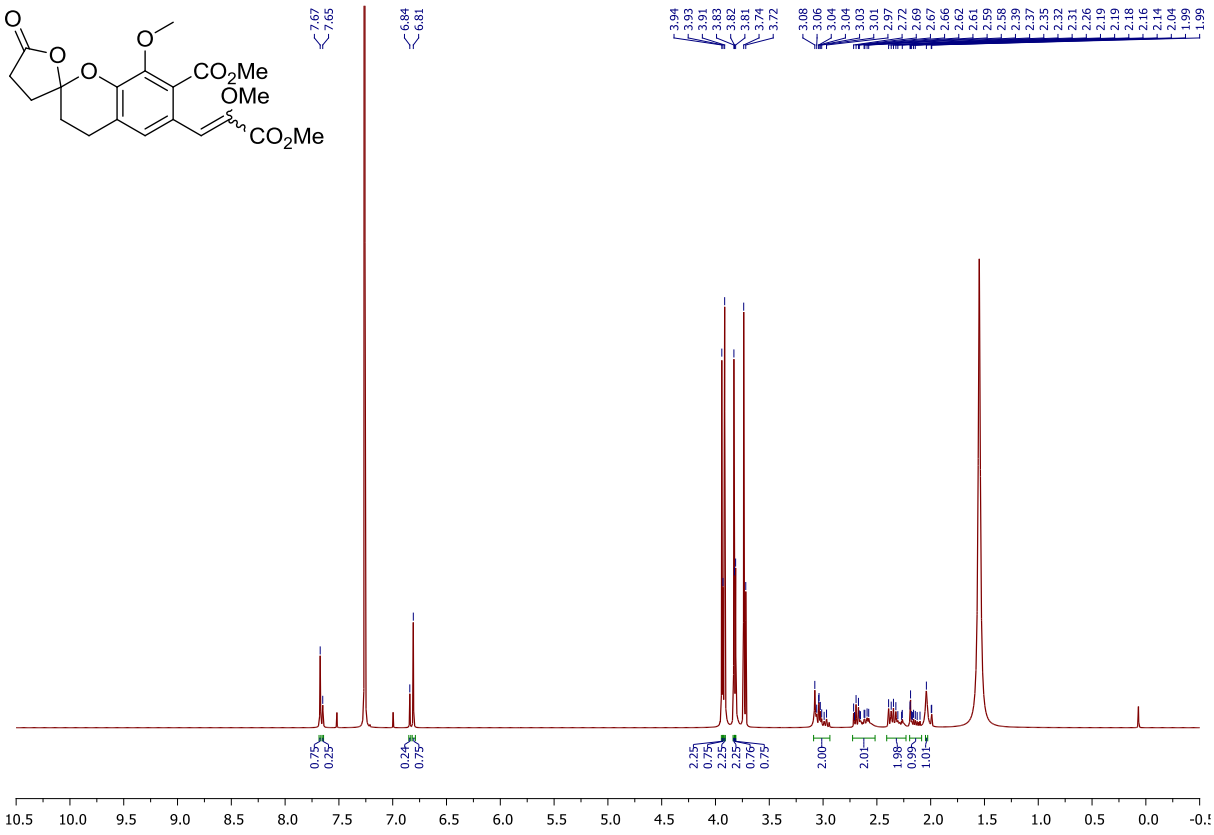
## $^{1}$H NMR Spectrum (Compound (±)-24)



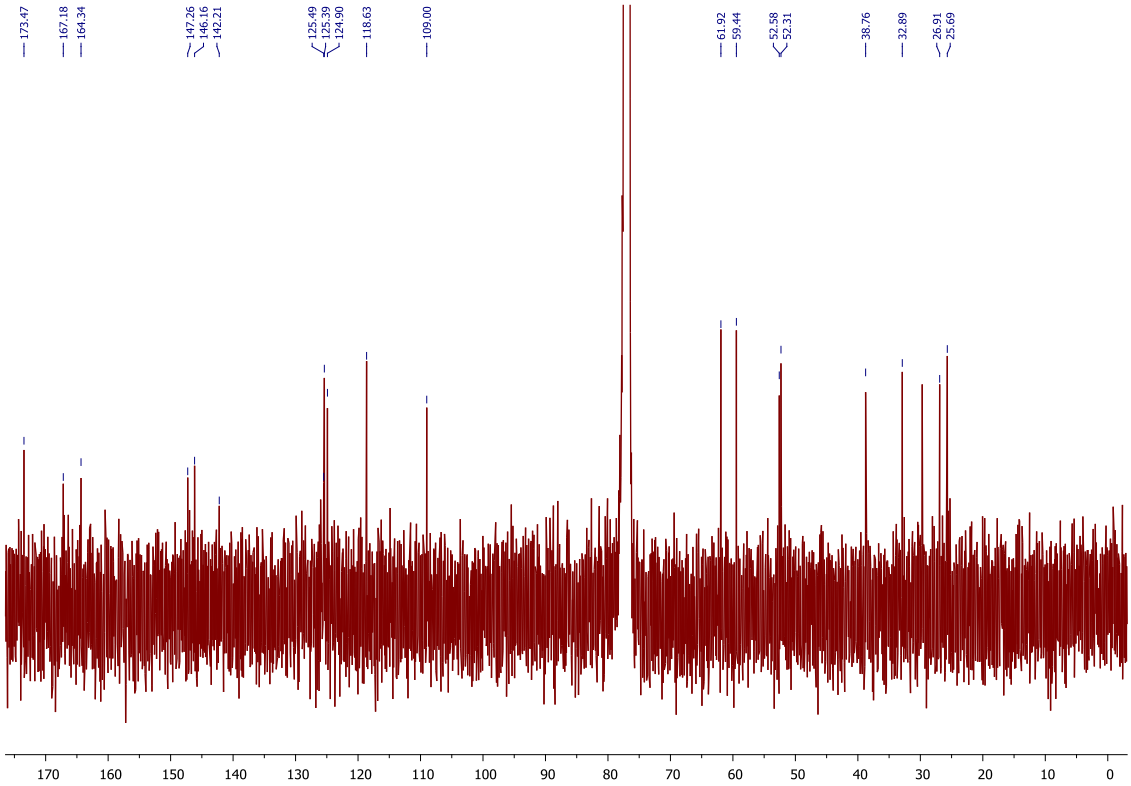

## $^{13}$C NMR Spectrum (Compound (±)-24)



## $^{1}$H NMR Spectrum (Compound (±)-26)

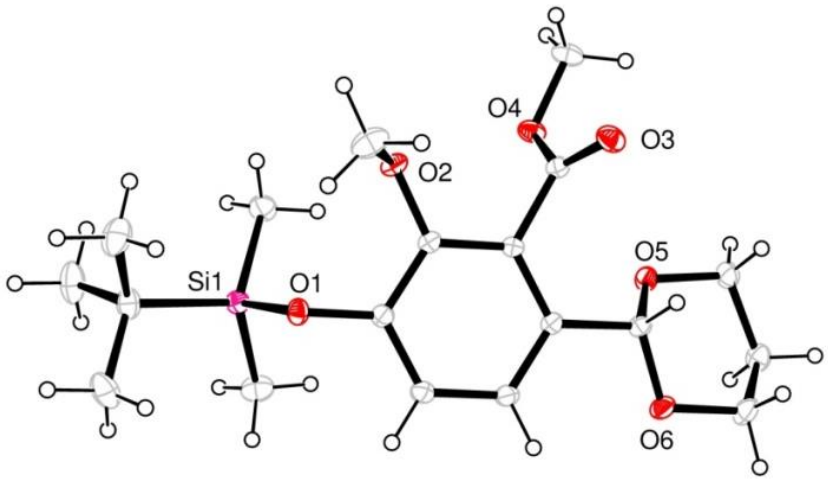



## $^{13}$C NMR Spectrum (Compound (±)-26)



## X-ray data

Ortep plot of compound **13** with ellipsoids shown at 30% probability. Data for this compound is available via the Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk) as CCDC 1420253.




| | |
|---|---|
| Empirical formula | C19 H30 O6 Si |
| Formula weight | 382.52 |
| Temperature | 100(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | -P 2ybc |
| Unit cell dimensions | a = 14.6051(10)Å a = 90° |
| | b = 15.8731(11)Å b = 97.9860(10)° |
| | c = 8.9463(6)Å g = 90° |
| Volume | 2053.9(2) $Å^3$ |
| Z | 4 |
| Density | 1.237 $Mg/m^3$ |
| Absorption coefficient | 0.145 $mm^{-1}$ |
| F(000) | 824 |
| Crystal size | 0.40 × 0.10 × 0.10 $mm^3$ |
| Theta range for data collection | 2.57 to 34.99° |
| Index ranges | –23<=h<=23, 25–<=k<=24, –14<=l<=7 |
| Reflections collected | 8987 |
| Independent reflections | 43509 [R(int) = 0.0304] |
| Completeness to theta = 25.00° | 99.3% |
| Absorption correction | Multiscan |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data/restraints/parameters | 8987/0/242 |
| Goodness-of-fit $F^2$ | 1.025 |
| Final R indices [I.2sigma(I)] | R1 = 0.0421, wR2 = 0.1192 |

| | |
|---|---|
| R indices (all data) | R1 = 0.0590, wR2 = 0.1329 |
| Largest diff. peak and hole | 1.474 and -0.383e.Å$^{-3}$ |