Supporting Information

Bioinspired Route to Indanes and Cyclopentannulated Hetarenes *via* (3+2)-Cyclodimerization of Donor-Acceptor Cyclopropanes

Olga A. Ivanova,[a] Ekaterina M. Budynina,[a,b]* Dmitriy A. Skvortsov,[a] Michelle Limoge,[c] Andrei V. Bakin,[c] Alexey O. Chagarovskiy,[a,b] Igor V. Trushkov[a,b] and Mikhail Ya. Melnikov[a]

[a] Department of Chemistry, M. V. Lomonosov Moscow State University, Leninskie gory 1-3, Moscow 119991 Russia, e-mail: ekatbud@kinet.chem.msu.ru

[b] Federal Research Center of Pediatric Hematology, Oncology and Immunology named after Dmitrii Rogachev, Samory Mashela 1, Moscow 117997 Russia

[c] Department of Cancer Genetics, Roswell Park Cancer Institute, Elm and Carlton Sts. Buffalo, NY 14263

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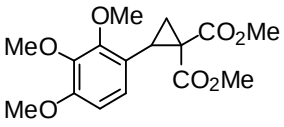
General Information

NMR spectra were acquired on Bruker Avance 600 spectrometer at room temperature; the chemical shifts δ were measured in ppm with respect to solvent (^{1}H: $CDCl_3$, δ = 7.27 ppm; ^{13}C: $CDCl_3$, δ = 77.00 ppm). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet. Coupling constants (*J*) are in Hertz. The structures of all compounds were elucidated with the aid of 1D NMR (^{1}H, ^{13}C) and 2D NMR (COSY ^{1}H–^{1}H, NOESY) spectroscopy. Infrared spectra were recorded on Thermo Nicolet IR200 FT-IR spectrometer. MALDI-TOF (Matrix Assisted Laser Desorption Ionization / Time of Flight) mass spectra were recorded on BrukerDaltonicsUltrafex II spectrometer in positive mode; anthracene or 1,8,9-trihydroxyanthracene were used as a matrix. LCMS spectra were acquired on Shimadzu HPLC chromatograph with Waters XBridge C18 3,5 µm (4.6 x 150 mm) column, PE SCIEX API-150EX mass detector (electrospray ionization) and Shimadzu (lmax 220 and 254 nm) UV-detector. High resolution and accurate mass measurements were carried out using a BrukermicrOTOF-Q^{TM} ESI-TOF (Electro Spray Ionization / Time of Flight) and Thermo Scientific* LTQ Orbitrap mass spectrometers. Elemental analyses were performed with Fisons EA-1108 CHNS elemental analyser instrument. Melting points (mp) are uncorrected and were measured on Electrothermal 9100 capillary melting point apparatus. X-Ray analysis was performed on STOE STADI VARI PILATUS-100K diffractometer. Analytical thin layer chromatography (TLC) was carried out with silica gel plates (silica gel 60, F_{254}, supported on aluminium); the revelation was done by UV lamp (365 nm) and chemical staining (iodine vapor and potassium permanganate solution in water). Column chromatography was performed on

silica gel 60 (230–400 mesh, Merck). Lewis acids ($Sn(OTf)_2$, $FeCl_3$, $ZnCl_2$) were commercially available. All the reactions were carried out using freshly distilled and dry solvents. Parent arylmethylidenemalonates and 2-aryl-1,1-cyclopropane diesters **1** were prepared by published procedures.[S1] Dimethyl [(*E*)-2-(2,3-dihydro-1,4-benzodioxin-6-yl)vinyl]malonate (**3a**) and dimethyl (*E*)-2-(4-methoxystyryl)malonate (**3b**) were synthesized according to procedure described earlier.[S2,S3] Quantum chemical calculations were performed using Gaussian 98 package.[S4]

Dimethyl 2-(2,3,4-trimethoxyphenyl)cyclopropane-1,1-dicarboxylate (1d)



Cyclopropane **1d** was obtained according to reported procedure[S1] from dimethyl 2-(2,3,4-trimethoxybenzylidene)malonate (3.10 g, 10 mmol), NaH (0.48 g, 12 mmol) and trimethylsulfoxonium iodide (2.64 g, 12 mmol), reaction time 2 h. Yield 2.53 g (78%); yellow oil; R_f 0.5 (diethyl ether).

^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.68 (dd, ^2J = 5.3, ^3J = 9.4 Hz, 1H, CH_2), 2.13 (dd, ^2J = 5.3, ^3J = 8.9 Hz, 1H, CH_2), 3.27 (dd, ^3J = 8.9, ^3J = 9.4 Hz, 1H, CH), 3.37 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.52 (d, ^3J = 8.6 Hz, 1H, Ar), 6.60 (d, ^3J = 8.6 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 18.34 (CH_2), 28.23 (CH), 36.91 (C), 52.21 (OCH_3), 52.73 (OCH_3), 55.87 (OCH_3), 60.79 (OCH_3), 60.84 (OCH_3), 106.28 (CH), 120.52 (C), 121.79 (CH), 141.95 (C), 153.22 (C), 153.74 (C), 167.23 (CO_2Me), 170.20 (CO_2Me);

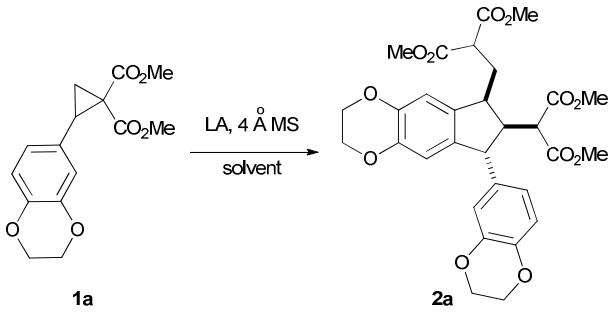
IR (film) 2970, 2855, 1740, 1600, 1510, 1470, 1450, 1420, 1380, 1340, 1290, 1220, 1140, 1110, 1070, 1030, 820 cm^{-1};

MALDI–TOF MS: *m*/*z* = 347 $[M+Na]^+$ (calcd. 347 for $C_{16}H_{20}NaO_7$);

Anal. Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.40; H, 6.17.

Optimization of the reaction conditions for (3+2)-cyclodimerization

Optimization of the reaction conditions was carried out for 3,4-dialkoxyphenyl-substituted cyclopropane **1a** as a model compound under variation of Lewis acids, solvent polarity and reaction temperature (see Table). The best yield of dimeric product **2a** was achieved when 0.2 M solution of **1a** in nitromethane was treated with 30 mol % of $Sn(OTf)_2$ followed by reflux (Entry 9).



1a **2a**

Entry	LA (mol %)	Solvent (c (mol/L))	Time (h)	T (°C)	Isolated yield (%)
1	$FeCl_3$ (100)	DCE (0.1)	2	reflux	-[a]
2	$SnCl_4$ (200)	$MeNO_2$ (0.2)	2	reflux	-[a]
3	$Sn(OTf)_2$ (10)	PhCl (0.2)	2	reflux	-[b]
4	$Sn(OTf)_2$ (10)	DCE (0.2)	2	reflux	15[c]
5	$Sn(OTf)_2$ (10)	$MeNO_2$ (0.1)	4	60	27
6	$Sn(OTf)_2$ (15)	$MeNO_2$ (0.1)	3	60	35
7	$Sn(OTf)_2$ (10)	$MeNO_2$ (0.2)	2	70	56
8	$Sn(OTf)_2$ (30)	$MeNO_2$ (0.2)	0.75	70	71
9	**$Sn(OTf)_2$ (30)**	**$MeNO_2$ (0.2)**	**0.5**	**reflux**	**80**

[a] Oligomeric and polymeric products were only formed. [b] Mixture of products containing no **2a** was formed. [c] Isomeric alkene **3a** was the main product.

General procedure for the $Sn(OTf)_2$-catalyzed cyclodimerization (method A)

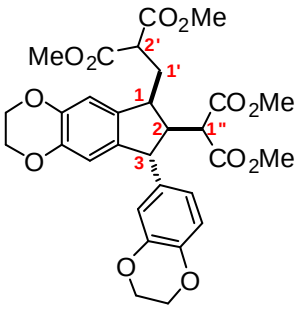
$Sn(OTf)_2$ (125 mg, 30 mol %) was added under argon atmosphere to a preheated up to 60 °C and vigorously stirred solution of cyclopropane **1** (1.0 mmol) in CH_3NO_2 (5 mL) containing 4 Å molecular sieves. The resulting mixture was refluxed for specified time and then poured into 5 mL of saturated aqueous $NaHCO_3$. After extraction with CH_2Cl_2 (3×2 mL), the combined organic fractions were washed with aqueous $NaHCO_3$ (3×2 mL) and aqueous Trilon B (2×2 mL). The organic layer was then dried with Na_2SO_4. The solvent was evaporated under vacuum, and the residue was purified by column chromatography (SiO_2, eluent – diethyl ether : petroleum ether, 3:1).

General procedure for the $Sn(OTf)_2$-catalyzed cross-dimerization (method B)

$Sn(OTf)_2$ (125 mg, 60 mol%) was added under argon atmosphere to a preheated up to 100 °C and vigorously stirred solution of cyclopropane **1** (0.5 mmol) and alkene **3** (0.5 mmol) in CH_3NO_2 (5 mL) containing 4 Å molecular sieves. The resulting mixture was refluxed for 0.5 h and then poured into 5 mL of saturated aqueous $NaHCO_3$. After extraction with CH_2Cl_2 (3×2

mL), the combined organic fractions were washed with aqueous $NaHCO_3$ (3×2 mL) and aqueous Trilon B (2×2 mL). The organic layer was then dried with Na_2SO_4. The solvent was evaporated under vacuum, and the residue was purified by column chromatography (SiO_2, eluent – diethyl ether : petroleum ether, 3:1).

Dimethyl {[(6*RS*,7*SR*,8*SR*)-8-(2,3-dihydro-1,4-benzodioxin-6-yl)-7-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-2,3,7,8-tetrahydro-6H-indeno[5,6-b][1,4]dioxin-6-yl}-methyl)malonate (2a)[S2]



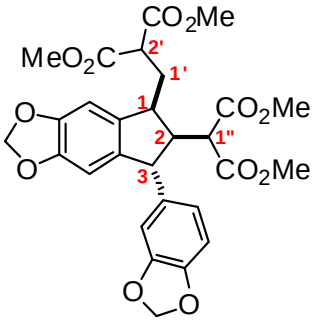
Cyclodimer **2a** was obtained according to method **A** from dimethyl 2-(2,3-dihydro-1,4-benzodioxin-6-yl)cyclopropane-1,1-dicarboxylate (**1a**) (292 mg, 1 mmol) under catalysis by $Sn(OTf)_2$ (125 mg, 0.3 mmol), reaction time 0.5 h. Yield 234 mg (80%); white foam; R_f 0.5 (diethyl ether); mp 170–171 °C.

^{1}H NMR ($CDCl_3$, 600 MHz)* δ = 1.70 (ddd, ^2J = 12.8, $^3J_{1',2'}$ = 3.6, $^3J_{1',1}$ = 12.5 Hz, 1H, C(1′)H_2), 2.04 (ddd, ^2J = 12.8, $^3J_{1',1}$ = 3.3, $^3J_{1',2'}$ = 11.8 Hz, 1H, C(1′)H_2), 3.09 (s, 3H, OCH_3), 3.21 (ddd, $^3J_{1',1}$ = 3.3, $^3J_{1,2}$ = 6.9, $^2J_{1',1}$ = 12.5 Hz, 1H, C(1)H), 3.29 (ddd, $^3J_{2,1}$ = 6.9, $^3J_{2,3}$ = 10.7, $^3J_{2,1''}$ = 11.3 Hz, 1H, C(2)H), 3.57 (dd, $^3J_{2',1'}$ = 3.6, $^3J_{2',1'}$ = 11.8 Hz, 1H, C(2′)H), 3.68 (s, 3H, OCH_3), 3.74 (d, $^3J_{1'',2}$ = 11.3 Hz, 1H, C(2)H), 3.77 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.00 (d, $^3J_{3,2}$ = 10.7 Hz, 1H, C(3)H), 4.18–4.27 (m, 8H, OCH_2), 6.18 (s, 1H, Ar), 6.60 (br. d, ^3J = 8.2 Hz, 1H, Ar), 6.62 (br. s, 1H, Ar), 6.76 (br. d, ^3J = 8.2 Hz, 1H, Ar), 6.78 (br. s, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 28.96 ($^1J_{CH}$ = 130 Hz, CH_2), 42.69 ($^1J_{CH}$ = 135 Hz, CH), 49.09 ($^1J_{CH}$ = 134 Hz, CH), 51.32 ($^1J_{CH}$ = 135 Hz, CH), 51.99 ($^1J_{CH}$ = 135 Hz, CH), 52.71 ($^1J_{CH}$ = 135 Hz, CH), 52.61 ($^1J_{CH}$ = 148 Hz, OCH_3), 52.74 ($^1J_{CH}$ = 148 Hz, 2×OCH_3), 52.78 ($^1J_{CH}$ = 148 Hz, OCH_3), 64.22 ($^1J_{CH}$ = 148 Hz, OCH_2), 64.26 ($^1J_{CH}$ = 148 Hz, OCH_2), 64.33 ($^1J_{CH}$ = 148 Hz, OCH_2), 64.37 ($^1J_{CH}$ = 148 Hz, OCH_2), 113.25 (CH, Ar), 114.15 (CH, Ar), 116.82 (CH, Ar), 117.94 (CH, Ar), 122.21 (CH, Ar), 134.76 (C, Ar), 136.23 (C, Ar), 139.70 (C, Ar), 142.25 (C, Ar), 142.31 (C, Ar), 143.09 (C, Ar), 143.12 (C, Ar), 168.09 (*C*O_2Me, Ar), 168.43 (*C*O_2Me), 169.49 (*C*O_2Me, Ar), 169.61 (*C*O_2Me);

IR (Nujol) 2960, 2870, 1730, 1510, 1470, 1380, 1290, 1160, 1080 cm^{-1}.

* Hereinafter atom numerations in NMR assignments and in structures were made identically and might not correspond to IUPAC name. It was made to simplify the comparison between spectral data for compounds **2a-i**.

Dimethyl ({(5*RS*,6*SR*,7*SR*)-7-(1,3-benzodioxol-5-yl)-6-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-yl}methyl)malonate (2b)



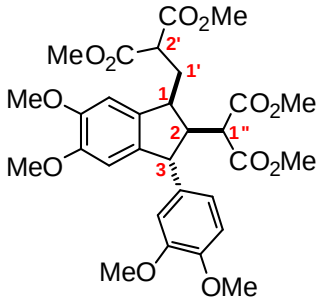
Cyclodimer **2b** was obtained according to method **A** from dimethyl 2-(1,3-benzodioxol-5-yl)cyclopropane-1,1-dicarboxylate (**1b**) (278 mg, 1 mmol) under catalysis by $Sn(OTf)_2$ (125 mg, 0.3 mmol), reaction time 0.5 h. Yield 186 mg (67%); white foam; R_f 0.68 (diethyl ether); mp 187–189 °C.

^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.74 (ddd, ^2J = 13.1, $^3J_{1',2'}$ = 3.7, $^3J_{1',1}$ = 12.5 Hz, 1H, C(1′)H$_2$), 2.08 (ddd, ^2J = 13.1, $^3J_{1',1}$ = 3.5, $^3J_{1',2'}$ = 11.9 Hz, 1H, C(1′)H$_2$), 3.13 (s, 3H, OCH_3), 3.25 (ddd, $^3J_{1,1'}$ = 3.5, $^3J_{1,2}$ = 6.9, $^3J_{1,1'}$ = 12.5 Hz, 1H, C(1)H), 3.32 (ddd, $^3J_{2,1}$ = 6.9, $^3J_{2,3}$ = 10.6, $^3J_{2,1''}$ = 11.0 Hz, 1H, C(2)H), 3.54 (dd, $^3J_{2',1'}$ = 3.7, $^3J_{2',1'}$ = 11.9 Hz, 1H, C(2′)H), 3.69 (s, 3H, OCH_3), 3.76 (d, $^3J_{1'',2}$ = 11.0 Hz, 1H, C(1′′)H), 3.77 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.06 (d, $^3J_{3,2}$ = 10.6 Hz, 1H, C(3)H), 5.87–5.94 (m, 4H, OCH_2O), 6.14 (br. s, 1H, Ar), 6.57 (d, ^4J = 1.7 Hz, 1H, Ar), 6.63 (dd, ^3J = 7.9, ^4J = 1.7 Hz, 1H, Ar), 6.72 (d, ^3J =7.9 Hz, 1H, Ar), 6.78 (br. s, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 29.17 ($^1J_{CH}$ = 131 Hz, CH_2), 42.99 ($^1J_{CH}$ = 136 Hz, CH), 49.21 ($^1J_{CH}$ = 134 Hz, CH), 51.71 ($^1J_{CH}$ = 129 Hz, CH), 51.99 ($^1J_{CH}$ = 147 Hz, OCH_3), 52.15 ($^1J_{CH}$ = 129 Hz, CH), 52.53 ($^1J_{CH}$ = 134 Hz, CH), 52.63 ($^1J_{CH}$ = 148 Hz, OCH_3), 52.65 ($^1J_{CH}$ = 148 Hz, OCH_3), 52.69 ($^1J_{CH}$ = 148 Hz, OCH_3), 100.92 (OCH_2O), 101.07 (OCH_2O), 105.24 (CH, Ar), 106.06 (CH, Ar), 107.72 (CH, Ar), 109.06 (CH, Ar), 122.83 (CH, Ar), 135.38 (C, Ar), 136.50 (C, Ar), 139.59 (C, Ar), 146.51 (C, Ar), 146.61 (C, Ar), 147.50 (C, Ar), 147.70 (C, Ar), 168.00 (*C*O_2Me, Ar), 168.35 (*C*O_2Me), 168.36 (*C*O_2Me, Ar), 169.46 (*C*O_2Me);

IR (Nujol) 2940, 2870, 1730, 1470, 1380, 1110, 1060, 950 cm^{-1};

ESI-HRMS: m/z = 579.1473 $[M+K]^+$ (calcd. 579.1462 for $C_{28}H_{28}KO_{12}$).

Dimethyl ({1*RS*,2*SR*,3*SR*)-3-(3,4-dimethoxyphenyl)-5,6-dimethoxy-2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-2,3-dihydro-1*H*-inden-1-yl}methyl)malonate (2c)



Cyclodimer **2c** was obtained *via* two alternative ways:

according to method **A** from dimethyl 2-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate (**1c**) (294 mg, 1 mmol) under catalysis by $Sn(OTf)_2$ (125 mg, 0.3 mmol), reaction time 2 h. Yield 200 mg (68%).

according to method **B** from dimethyl 2-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate (**1c**) (147 mg, 0.5 mmol) and dimethyl (*E*)-

(3,4-dimethoxystyryl)malonate (**3c**) (147 mg, 0.5 mmol) under catalysis by $Sn(OTf)_2$ (125 mg, 0.3 mmol). Yield 256 mg (87%).

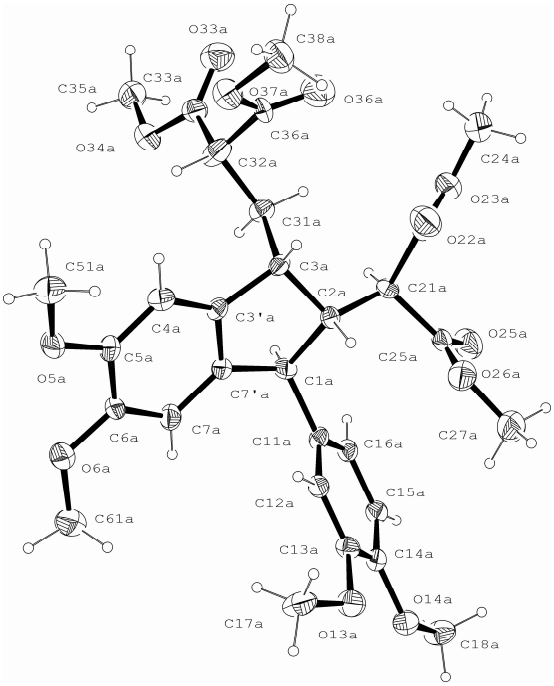
White foam; R_f 0.30 (diethyl ether); mp 78–80 °C.

^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.77–1.83 (m, 1H, C(1′)H_2), 2.04–2.12 (m, 1H, C(1′)H_2), 3.03 (s, 3H, OCH_3), 3.30–3.38 (m, 2H, 2CH), 3.57 (dd, $^3J_{2',1'}$ = 3.9, $^3J_{2',1'}$ = 11.7 Hz, 1H, C(2′)H), 3.68 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.86 (d, $^3J_{1'',2}$ = 8.6 Hz, 1H, C(1″)H), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.00 (d, $^3J_{3,2}$ = 10.2 Hz, 1H, C(3)H), 6.17 (s, 1H, Ar), 6.61 (br. s, 1H, Ar), 6.73 (dd, ^3J = 8.4, ^4J = 2.0 Hz, 1H, Ar), 6.81 (d, ^3J = 8.4 Hz, 1H, Ar), 6.89 (br. s, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 28.71 (CH_2), 42.67 (CH), 49.11 (CH), 51.28 (CH), 51.64 (CH), 51.93 (CH), 52.24 (4×OCH_3), 55.43 (OCH_3), 55.47 (OCH_3), 55.58 (2×OCH_3), 107.41 (CH, Ar), 107.87 (CH, Ar), 110.18 (CH, Ar), 111.47 (CH, Ar), 121.46 (CH, Ar), 133.56 (C, Ar), 134.81 (C, Ar), 137.85 (C, Ar), 147.43 (C, Ar), 147.58 (C, Ar), 148.30 (C, Ar), 148.43 (C, Ar), 167.61 (*C*O_2Me, Ar), 168.07 (*C*O_2Me), 169.01 (*C*O_2Me, Ar), 169.09 (*C*O_2Me);

IR (Nujol) 3000, 2950, 2840, 1730, 1490, 1410, 1220, 1200, 1110, 990 cm^{-1};

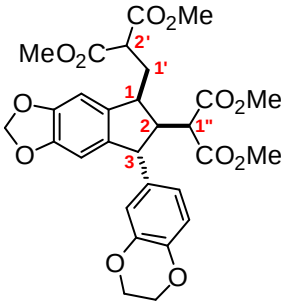
ESI-HRMS: m/z = 589.2280 $[M+H]^+$ (calcd. 589.2274 for $C_{30}H_{37}O_{12}$).

Anal. Calcd. for $C_{30}H_{36}O_{12}$: C, 61.22; H, 6.16. Found: C, 61.37; H, 6.09.



Molecular structure (ORTEP-3[S5]) from single crystal X-ray study of **2c**

Dimethyl ({(5*RS*,6*SR*,7*SR*)-7-(2,3-dihydro-1,4-benzodioxin-6-yl)-6-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-yl}methyl)malonate (2d)



Cross-dimer **2d** was obtained according to method **B** from dimethyl 2-(1,3-benzodioxol-5-yl)cyclopropane-1,1-dicarboxylate (**1b**) (139 mg, 0.5 mmol) and dimethyl [(*E*)-2-(2,3-dihydro-1,4-benzodioxin-6-yl)vinyl]malonate (**3a**) (146 mg, 0.5 mmol) under catalysis by $Sn(OTf)_2$ (125 mg, 0.3 mmol). Yield 205 mg (72%); white foam; R_f 0.58 (diethyl ether); mp 85–87 °C.

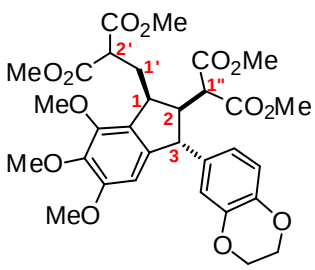
^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.74 (ddd, ^2J = 13.4, $^3J_{1',2'}$ = 3.7, $^3J_{1',1}$ = 12.4 Hz, 1H, C(1′)H$_2$), 2.07 (ddd, ^2J = 13.4, $^3J_{1',1}$ = 3.3, $^3J_{1',2'}$ = 11.9 Hz, 1H, C(1′)H$_2$), 3.12 (s, 3H, OCH_3), 3.24 (ddd, $^3J_{1,1'}$ = 3.3, $^3J_{1,2}$ = 6.9, $^3J_{1,1'}$ = 12.4 Hz, 1H, C(1)H), 3.33 (ddd, $^3J_{2,1}$ = 6.9, $^3J_{2,3}$ = 10.7, $^3J_{2,1''}$ = 11.0 Hz, 1H, C(2)H), 3.55 (dd, $^3J_{2',1'}$ = 3.7 Hz, $^3J_{2',1'}$ = 11.9 Hz, 1H, C(2′)H), 3.70 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.79 (d, $^3J_{1'',2}$ = 11.0 Hz, 1H, C(1′′)H), 3.85 (s, 3H, OCH_3), 4.02 (d, $^3J_{3,2}$ = 10.7 Hz, 1H, C(3)H), 4.24 (s, 4H, OCH_2CH_2O), 5.90 (AB-system, ^2J = 13.2, OCH_2O), 6.15 (br. s, 1H, Ar), 6.62 (dd, ^3J = 8.2, ^4J = 2.0 Hz, 1H, Ar), 6.64 (d, ^4J = 2.0 Hz, 1H, Ar), 6.78 (br. s, 1H, Ar), 6.79 (d, ^3J = 8.2 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 29.17 ($^1J_{CH}$ = 131 Hz, CH_2), 43.00 ($^1J_{CH}$ = 136 Hz, CH), 49.22 ($^1J_{CH}$ = 135 Hz, CH), 51.60 ($^1J_{CH}$ = 139 Hz, CH), 51.75 ($^1J_{CH}$ = 131 Hz, CH), 51.93 ($^1J_{CH}$ = 147 Hz, OCH_3), 52.57 ($^1J_{CH}$ = 132 Hz, CH), 52.65 ($^1J_{CH}$ = 148 Hz, OCH_3), 52.67 ($^1J_{CH}$ = 148 Hz, 2×OCH_3), 64.34 ($^1J_{CH}$ = 149 Hz, OCH_2), 64.37 ($^1J_{CH}$ = 150 Hz, OCH_2), 101.05 (OCH_2O), 105.20 (CH, Ar), 106.15 (CH, Ar), 116.88 (CH, Ar), 117.97 (CH, Ar), 122.22 (CH, Ar), 134.77 (C, Ar), 136.44 (C, Ar), 139.74 (C, Ar), 142.42 (C, Ar), 143.21 (C, Ar), 146.55 (C, Ar), 147.26 (C, Ar), 168.01 (*C*O_2Me), 168.39 (*C*O_2Me), 169.40 (*C*O_2Me), 169.49 (*C*O_2Me);

IR (Nujol) 2940, 2880, 1750, 1735, 1720, 1470, 1380, 1320, 1270, 1210, 1170, 1160, 1050, 950, 800, 780 cm^{-1};

MALDI–TOF MS: *m*/*z* = 593 $[M+Na]^+$ (calcd. 593 for $C_{29}H_{30}NaO_{12}$);

Anal. Calcd. for $C_{29}H_{30}O_{12}$: C, 61.05; H, 5.30. Found: C, 61.21; H, 5.30.

Dimethyl ({(1*RS*,2*SR*,3*SR*)-3-(2,3-dihydro-1,4-benzodioxin-6-yl)-5,6,7-trimethoxy-2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-2,3-dihydro-1*H*-inden-1-yl}methyl)malonate (2e)



Cross-dimer **2e** was obtained according to method **B** from dimethyl 2-(2,3,4-trimethoxyphenyl)cyclopropane-1,1-dicarboxylate (**1d**) (162 mg, 0.5 mmol) and dimethyl [(*E*)-2-(2,3-dihydro-1,4-benzodioxin-6-

yl)vinyl]malonate (**3a**) (146 mg, 0.5 mmol) under catalysis by $Sn(OTf)_2$ (125 mg, 0.3 mmol). Yield 225 mg (73%); white foam; R_f 0.65 (diethyl ether); mp 84–85 °C.

^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.62–1.68 (m, 1H, C(1′)H_2), 2.10–2.17 (m, 1H, C(1′)H_2), 3.09 (s, 3H, OCH_3), 3.27 (ddd, $^3J_{3,2}$ = 6.8, ^3J = 11.2, ^3J = 11.4 Hz, 1H, C(2)H), 3.62 (s, 6H, OCH_3), 3.64–3.69 (m, 2H, CH), 3.73 (d, $^3J_{1'',2}$ = 12.0 Hz, 1H, C(1″)H), 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.01 (d, $^3J_{3,2}$ = 11.0 Hz, 1H, C(3)H), 4.18–4.22 (m, 4H, OCH_2CH_2O), 5.93 (br. s, 1H, CH, Ar), 6.59 (br. d, ^3J = 8.1 Hz, 1H, Ar), 6.62 (br. s, 1H, CH, Ar), 6.75 (d, ^3J = 8.1 Hz, 1H, Ar);

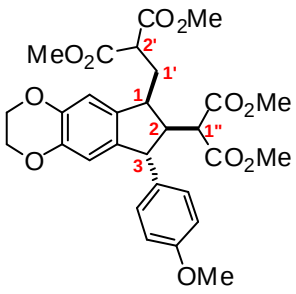
^{13}C NMR ($CDCl_3$, 150 MHz) δ = 29.43 ($^1J_{CH}$ = 130 Hz, CH_2), 40.71 ($^1J_{CH}$ = 137 Hz, CH), 49.19 ($^1J_{CH}$ = 134 Hz, CH), 51.78 ($^1J_{CH}$ = 137 Hz, CH), 51.87 ($^1J_{CH}$ = 147 Hz, OCH_3), 52.29 ($^1J_{CH}$ = 147 Hz, OCH_3), 52.34 ($^1J_{CH}$ = 137 Hz, CH), 52.47 ($^1J_{CH}$ = 147 Hz, OCH_3), 52.75 ($^1J_{CH}$ = 134 Hz, CH), 52.79 ($^1J_{CH}$ = 148 Hz, OCH_3), 56.15 ($^1J_{CH}$ = 144 Hz, OCH_3), 60.73 ($^1J_{CH}$ = 145 Hz, OCH_3), 60.89 ($^1J_{CH}$ = 143 Hz, OCH_3), 64.30 ($^1J_{CH}$ = 148 Hz, OCH_2), 64.34 ($^1J_{CH}$ = 148 Hz, OCH_2), 104.45 (CH, Ar), 116.82 (CH, Ar), 118.16 (CH, Ar), 122.36 (CH, Ar), 128.85 (C, Ar), 134.36 (C, Ar), 140.47 (C, Ar), 142.37 (2×C, Ar), 143.11 (C, Ar), 148.92 (C, Ar), 153.57 (C, Ar), 167.97 (CO_2Me), 168.31 (CO_2Me), 169.45 (CO_2Me), 170.35 (CO_2Me);

IR (Nujol) 2980, 2950, 2870, 1750, 1740, 1590, 1510, 1470, 1380, 1290, 1170, 1130, 1080, 730 cm^{-1};

MALDI–TOF MS: m/z = 616 $[M]^+$ (calcd. 616 for $C_{31}H_{36}O_{13}$);

Anal. Calcd. for $C_{31}H_{36}O_{13}$: C, 60.38; H, 5.88. Found: C, 60.25; H, 5.74.

Dimethyl {[(6*RS*,7*SR*,8*SR*)-7-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-8-(4-methoxyphenyl)-2,3,7,8-tetrahydro-6H-indeno[5,6-b][1,4]dioxin-6-yl}methyl)malonate (2f)



Cross-dimer **2f** was obtained according to method **B** from dimethyl 2-(2,3-dihydro-1,4-benzodioxin-6-yl)cyclopropane-1,1-dicarboxylate (**1a**) (146 mg, 1 mmol) and dimethyl (*E*)-2-(4-methoxystyryl)malonate (**3b**) (132 mg, 0.5 mmol) under catalysis by $Sn(OTf)_2$ (125 mg, 0.3 mmol). Yield 214 mg (77%); white foam; R_f 0.7 (diethyl ether); mp 152-153 °C.

^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.73 (ddd, ^2J = 13.0, $^3J_{1',2'}$ = 3.6, $^3J_{1',1}$ = 12.5 Hz, 1H, C(1′)H_2), 2.06 (ddd, ^2J = 13.0, $^3J_{1',1}$ = 3.4, $^3J_{1',2'}$ = 11.8 Hz, 1H, C(1′)H_2), 2.98 (s, 3H, OCH_3), 3.24 (ddd, $^3J_{1,1'}$ = 3.4, $^3J_{1,2}$ = 6.9, $^3J_{1,1'}$ = 12.5 Hz, 1H, C(1)H), 3.33 (ddd, $^3J_{2,1}$ = 6.9, $^3J_{2,3}$ = 10.7, $^3J_{2,1''}$ = 11.0 Hz, 1H, C(2)H), 3.54 (dd, $^3J_{2',1'}$ = 3.6, $^3J_{2',1'}$ = 11.8 Hz, 1H, C(2′)H), 3.68 (s, 3H, OCH_3), 3.75 (d, $^3J_{1'',2}$ = 11.0 Hz, 1H, C(1″)H), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3),

3.83 (s, 3H, OCH_3), 4.06 (d, $^3J_{3,2}$ = 10.7 Hz, 1H, C(3)H), 4.15–4.21 (m, 4H, OCH_2CH_2O), 6.12 (br. s, 1H, Ar), 6.79 (br. s, 1H, Ar), 6.81 (d, ^3J = 8.6 Hz, 2H, Ar), 7.04 (d, ^3J = 8.6 Hz, 2H, Ar);

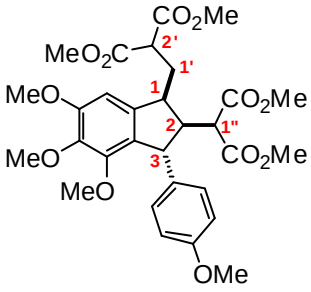
^{13}C NMR ($CDCl_3$, 150 MHz) δ = 28.93 ($^1J_{CH}$ = 131 Hz, CH_2), 42.75 ($^1J_{CH}$ = 137 Hz, CH), 49.16 ($^1J_{CH}$ = 132 Hz, CH), 51.31 ($^1J_{CH}$ = 139 Hz, CH), 51.45 ($^1J_{CH}$ = 131 Hz, CH), 51.96 ($^1J_{CH}$ = 147 Hz, OCH_3), 52.57 ($^1J_{CH}$ = 131 Hz, CH), 52.59 ($^1J_{CH}$ = 148 Hz, OCH_3), 52.65 ($^1J_{CH}$ = 148 Hz, OCH_3), 52.69 ($^1J_{CH}$ = 148 Hz, OCH_3), 55.25 ($^1J_{CH}$ = 144 Hz, OCH_3), 64.19 ($^1J_{CH}$ = 147 Hz, OCH_2), 64.24 ($^1J_{CH}$ = 147 Hz, OCH_2), 113.27 (CH, Ar), 113.61 (2×CH, Ar), 114.03 (CH, Ar), 130.23 (2×CH, Ar), 133.46 (C, Ar), 136.27 (C, Ar), 139.99 (C, Ar), 142.27 (C, Ar), 143.13 (C, Ar), 158.49 (C, Ar), 168.02 (CO_2Me), 168.39 (CO_2Me), 169.41 (CO_2Me), 169.54 (CO_2Me);

IR (Nujol) 2980, 2950, 2870, 1735, 1470, 1380, 1330, 1310, 1250, 1220, 1170, 1080, 1050, 740 cm^{-1};

MALDI–TOF MS: m/z = 579 $[M+Na]^+$ (calcd. 579 for $C_{29}H_{32}NaO_{11}$);

Anal. Calcd. for $C_{29}H_{32}O_{11}$: C, 62.58; H, 5.80. Found: C, 62.42; H, 5.73.

Dimethyl ({(1*RS*,2*SR*,3*SR*)-4,5,6-trimethoxy-2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]- 3-(4-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl}methyl)malonate (2g)



Cross-dimer **2g** was obtained according to method **B** from dimethyl 2-(3,4,5-trimethoxyphenyl)cyclopropane-1,1-dicarboxylate (**1e**) (162 mg, 1 mmol) and dimethyl (*E*)-2-(4-methoxystyryl)malonate (**3b**) (132 mg, 0.5 mmol) under catalysis by $Sn(OTf)_2$ (125 mg, 0.3 mmol). Yield 238 mg (81%); white foam; R_f 0.32 (diethyl ether : petroleum ether); mp 51-53 °C.

^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.81–1.86 (m, 1H, C(1′)H_2), 2.04–2.09 (m, 1H, C(1′)H_2), 3.03 (s, 3H, OCH_3), 3.15 (s, 3H, OCH_3), 3.26–3.32 (m, 2H, CH), 3.47 (dd, $^3J_{2',1'}$ = 5.0, $^3J_{2',1'}$ = 10.6 Hz, 1H, C(2′)H), 3.65 (s, 3H, OCH_3), 3.70 (d, $^3J_{1'',2}$ = 9.5 Hz, 1H, C(1″)H), 3.74 (s, 9H, OCH_3), 3.80 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.27 (d, $^3J_{3,2}$ = 7.9 Hz, 1H, C(3)H), 6.62 (br. s, 1H, Ar), 6.78 (d, ^3J = 8.4 Hz, 2H, Ar), 7.08 (d, ^3J = 8.4 Hz, 2H, Ar);

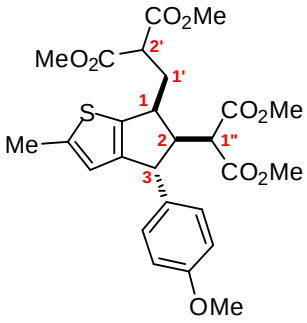
^{13}C NMR ($CDCl_3$, 150 MHz) δ = 29.05 ($^1J_{CH}$ = 131 Hz, CH_2), 44.56 ($^1J_{CH}$ = 136 Hz, CH), 49.56 ($^1J_{CH}$ = 136 Hz, CH), 49.99 ($^1J_{CH}$ = 131 Hz, CH), 51.67 ($^1J_{CH}$ = 139 Hz, CH), 52.01 ($^1J_{CH}$ = 147 Hz, OCH_3), 52.12 ($^1J_{CH}$ = 134 Hz, CH), 52.64 ($^1J_{CH}$ = 148 Hz, 3×OCH_3), 55.22 ($^1J_{CH}$ = 144 Hz, OCH_3), 56.10 ($^1J_{CH}$ = 144 Hz, OCH_3), 59.68 ($^1J_{CH}$ = 144 Hz, OCH_3), 60.62 ($^1J_{CH}$ = 144 Hz, OCH_3), 103.46 (CH, Ar), 113.27 (2×CH, Ar), 129.66 (2×CH, Ar), 130.10 (C, Ar), 134.83 (C, Ar), 139.44 (C, Ar), 141.74 (C, Ar), 150.50 (C, Ar), 153.18 (C, Ar), 158.17 (C, Ar), 168.12 (CO_2Me), 168.71 (CO_2Me), 169.42 (CO_2Me), 169.46 (CO_2Me);

IR (film) 2980, 2950, 2900, 2870, 1750, 1740, 1470, 1460, 1380, 1310, 1260, 1180, 1125, 1050, 735 cm^{-1};

MALDI–TOF MS: *m*/*z* = 611 $[M+Na]^+$ (calcd. 611 for $C_{30}H_{36}NaO_{12}$);

Anal. Calcd. for $C_{30}H_{36}O_{12}$: C, 61.22; H, 6.16. Found: C, 61.29; H, 6.18.

Dimethyl {[(4*RS*,5*RS*,6*SR*)-5-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-4-(4-methoxyphenyl)-2-methyl-5,6-dihydro-4*H*-cyclopenta[*b*]thien-6-yl]methyl}malonate (2h)



Cross-dimer **2h** was obtained according to method **B** from dimethyl 2-(5-methylthiophen-2-yl)cyclopropane-1,1-dicarboxylate (**1f**) (127 mg, 1 mmol) and dimethyl (*E*)-2-(4-methoxystyryl)malonate (**3b**) (132 mg, 0.5 mmol) under catalysis by $Sn(OTf)_2$ (125 mg, 0.3 mmol). Yield 153 mg (59%); yellowish foam; R_f 0.75 (diethyl ether); mp 57-59 °C.

^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.78 (ddd, ^2J = 12.8, $^3J_{1',2'}$ = 3.5, $^3J_{1',1}$ = 12.5 Hz, 1H, C(1′)H_2), 2.05 (ddd, ^2J = 12.8, $^3J_{1',1}$ = 3.2, $^3J_{1',2'}$ = 12.3 Hz, 1H, C(1′)H_2), 2.36 (s, 3H, CH_3), 3.03 (s, 3H, OCH_3), 3.40–3.44 (m, 1H, CH), 3.57–3.62 (m, 1H, CH), 3.67 (dd, $^3J_{2',1'}$ = 3.5, $^3J_{2',1'}$ = 12.3 Hz, 1H, C(2′)H), 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.79 (d, $^3J_{1'',2}$ = 11.6 Hz, 1H, C(1′′)H), 3.82 (s, 3H, OCH_3), 4.03 (d, $^3J_{3,2}$ = 9.6 Hz, 1H, C(3)H), 6.06 (br. s, 1H, Th), 6.81 (d, ^3J = 8.6 Hz, 2H, Ar), 7.07 (d, ^3J = 8.6 Hz, 2H, Ar);

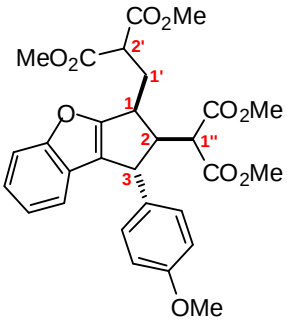
^{13}C NMR ($CDCl_3$, 150 MHz) δ = 15.91 ($^1J_{CH}$ = 128 Hz, CH_3), 29.89 ($^1J_{CH}$ = 131 Hz, CH_2), 41.57 ($^1J_{CH}$ = 138 Hz, CH), 48.94 ($^1J_{CH}$ = 133 Hz, CH), 49.64 ($^1J_{CH}$ = 131 Hz, CH), 52.02 ($^1J_{CH}$ = 148 Hz, OCH_3), 52.60 ($^1J_{CH}$ = 147 Hz, OCH_3), 52.63 ($^1J_{CH}$ = 148 Hz, OCH_3), 52.72 ($^1J_{CH}$ = 148 Hz, OCH_3), 52.79 ($^1J_{CH}$ = 131 Hz, CH), 55.13 ($^1J_{CH}$ = 137 Hz, CH), 55.24 ($^1J_{CH}$ = 144 Hz, OCH_3), 113.55 (2×CH, Ar), 120.35 (CH, Ar), 129.62 (2×CH, Ar), 133.72 (C, Ar), 138.99 (C, Ar), 142.88 (C, Ar), 148.91 (C, Ar), 158.45 (C, Ar), 167.84 (CO_2Me), 168.36 (CO_2Me), 169.25 (CO_2Me), 169.40 (CO_2Me);

IR (film) 3020, 2965, 2860, 1760, 1740, 1610, 1520, 1450, 1310, 1270, 1160, 1040, 840, 805, 770 cm^{-1};

MALDI–TOF MS: *m*/*z* = 541 $[M+Na]^+$ (calcd. 541 for $C_{26}H_{30}NaO_9S$);

Anal. Calcd. for $C_{26}H_{30}O_9S$: C, 60.22; H, 5.83. Found: C, 60.20; H, 6.06.

Dimethyl {[(1*RS*,2*SR*,3*SR*)-2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-3-yl]methyl}malonate (2i)



Cross-dimer **2i** was obtained according to method **B** from dimethyl 2-(1-benzofuran-2-yl)cyclopropane-1,1-dicarboxylate (**1g**) (137 mg, 1 mmol) and dimethyl (*E*)-2-(4-methoxystyryl)malonate (**3b**) (132 mg, 0.5 mmol) under catalysis by $Sn(OTf)_2$ (125 mg, 0.3 mmol). Yield 113 mg (42%); yellowish foam; R_f 0.35 (diethyl ether); mp 118–120 °C.

^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.94 (ddd, ^2J = 13.1, $^3J_{1',2'}$ = 3.5, $^3J_{1',1}$ = 12.2 Hz, 1H, C(1′)H$_2$), 2.18 (ddd, ^2J = 13.1, $^3J_{1',1}$ = 3.4, $^3J_{1',2'}$ = 11.2 Hz, 1H, C(1′)H$_2$), 3.13 (s, 3H, OCH_3), 3.59–3.63 (m, 1H, C(1)H), 3.72–3.76 (m, 1H, C(2)H), 3.70 (s, 3H, OCH_3), 3.76 (dd, $^3J_{2',1'}$ = 3.5, $^3J_{2',1'}$ = 11.2 Hz, 1H, C(2′)H), 3.795 (s, 3H, OCH_3), 3.803 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.85 (d, $^3J_{1'',2}$ = 11.4 Hz, 1H, C(1′′)H), 4.23 (d, $^3J_{3,2}$ = 8.7, ^5J = 1.6 Hz, 1H, C(3)H), 6.82 (br. d, ^3J = 8.2 Hz, 1H, CH, Ar), 6.84 (d, ^3J = 8.7 Hz, 2H, Ar), 7.04 (dd, ^3J = 7.8 Hz, ^3J = 8.2 Hz, 1H, Ar), 7.18 (d, ^3J = 8.7 Hz, 2H, Ar), 7.17–7.21 (m, 1H, Ar), 7.46 (br. d, ^3J = 8.2 Hz, 1H, CH, Ar);

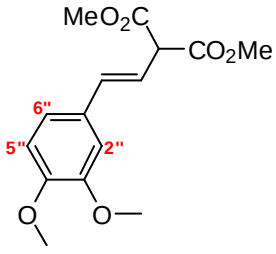
^{13}C NMR ($CDCl_3$, 150 MHz) δ = 29.36 ($^1J_{CH}$ = 133 Hz, CH_2), 38.93 ($^1J_{CH}$ = 141 Hz, CH), 44.87 ($^1J_{CH}$ = 132 Hz, CH), 49.67 ($^1J_{CH}$ = 134 Hz, CH), 52.16 ($^1J_{CH}$ = 148 Hz, OCH_3), 52.66 ($^1J_{CH}$ = 134 Hz, CH), 52.69 ($^1J_{CH}$ = 148 Hz, OCH_3), 52.71 ($^1J_{CH}$ = 148 Hz, OCH_3), 52.84 ($^1J_{CH}$ = 148 Hz, OCH_3), 54.74 ($^1J_{CH}$ = 137 Hz, CH), 55.25 ($^1J_{CH}$ = 144 Hz, OCH_3), 112.03 (CH, Ar), 113.71 (2×CH, Ar), 119.11 (CH, Ar), 122.80 (CH, Ar), 123.35 (CH, Ar), 123.76 (C, Ar), 125.10 (C, Ar), 129.44 (2×CH, Ar), 132.72 (C, Ar), 158.62 (C, Ar), 159.81 (C, Ar), 162.24 (C, Ar), 167.71 (*C*O_2Me), 168.35 (*C*O_2Me), 169.17 (*C*O_2Me), 169.28 (*C*O_2Me);

IR (Nujol) 2970, 2950, 2870, 1760, 1740, 1470, 1450, 1270, 1160, 1050, 800, 770 cm^{-1};

MALDI–TOF MS: *m*/*z* = 561 $[M+Na]^+$ (calcd. 561 for $C_{29}H_{30}NaO_{10}$);

Anal. Calcd. for $C_{29}H_{30}O_{10}$: C, 64.68; H, 5.61. Found: C, 64.62; H, 5.37.

Dimethyl (*E*)-(3,4-dimethoxystyryl)malonate (3c)



$Sn(OTf)_2$ (33 mg, 10 mol%) was added to a preheated up to 110 °C (oil bath) and vigorously stirred solution of cyclopropane **1c** (230 mg, 0.79 mmol) in chlorobenzene (10 mL) containing molecular sieves 4 Å under argon atmosphere. The resulting mixture was stirred at this temperature for 2.5 h, allowed to cool to room temperature and poured into saturated aqueous solution of $NaHCO_3$ (10 mL). After extraction with CH_2Cl_2 (3×5 mL), the combined organic fractions were washed with aqueous solution of Trilon B (3×5 mL) and water (2×5 mL).

The organic layer was then dried with Na_2SO_4. The solvent was evaporated under vacuum, and the residue was purified by column chromatography (SiO_2, eluent: diethyl ether : petroleum ether, 2:1) to yield **3c** (145 mg, 63%) as white solid; mp 73–75 °C; R_f 0.40 (dietyl ether: petroleum ether, 1:1).

^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.79 (s, 6H, 2×OCH_3), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.21 (d, ^3J = 9.2 Hz, 1H, C(2)H), 6.27 (dd, ^3J = 15.8, ^3J = 9.2 Hz, 1H, C(1′)H), 6.53 (d, ^3J = 15.8 Hz, 1H, C(2′)H), 6.81 (d, ^3J = 8.3 Hz, 1H, C(5″)H), 6.93 (dd, ^3J = 8.3, ^4J = 2.0 Hz, 1H, C(6″)H), 6.98 (d, ^4J = 2.0 Hz, 1H, C(2″)H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 52.83 ($^1J_{CH}$ = 148 Hz, 2×OCH_3), 55.56 ($^1J_{CH}$ = 133 Hz, CH), 55.88 (OCH_3), 55.92 (OCH_3), 108.78 (CH), 111.04 (CH), 118.52 (CH), 120.21 (CH), 129.08 (C, Ar), 135.01 (CH, Ar), 149.10 (C, Ar), 149.34 (C, Ar), 168.55 (2×CO_2Me);

IR (Nujol) 3008, 2956, 2838, 1747, 1727, 1514, 1520, 1464, 1433, 1309, 1267, 1191, 1157, 1141, 1020, 968, 804 cm^{-1};

ESI-MS: *m/z* (%) = 295 $[M+H]^+$ (calcd. 295 for $C_{15}H_{19}O_6$);

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 61.67; H, 5.79.

Cell assays

HEK-293, MCF7 and SiHa cell lines

The cytotoxicity of tested compounds was assessed using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay[S6] with some modifications. 4000 cells per well were plated out in 100 mL of DMEM media containing 10% FBS in 96-well plate and incubated at 37 °C in 5% CO_2 incubator for 24 h. Then 10 mL of water-DMSO solution of tested compound was added to the cells (DMSO concentration in the media was kept below 1%) in such way that effective concentrations of studied compounds were in a range of 50 nM to 100 mM (eight dilutions). Doxorubicin (3 nM to 6 mM) was used as a control. After incubation for 72 h 10 mL MTT solution in PBS (5 mg/ml) was added, cells were incubated for 2 h. Medium was removed and 100 mL of DMSO was added. Samples were incubated for 15 min with shaking to completely solubilize formazan. Cell survival was measured spectrophotometrically at 565 nm.

MDA-MB-231-EGFP and MCF10A cell lines

MDA-MB-231-EGFP and MCF10A cells were seeded 10K and 5K (respectively) per well in 100 µL in central 10 columns of 96-well plates. PBS was added to outer 2 columns of plates. Plates were incubated at 37 °C overnight. The next day, 9 serial dilutions of each inhibitor were made in appropriate media at 2X the desired final concentration. 100 µL of media (for control) or inhibitor dilution was added to appropriate wells (Final concentrations: 100 µM, 50 µM, 10 µM, 5 µM, 1 µM, 500 nM, 100 nM, 50 nM, 10 nM, 0 nM = control). Plates were incubated at 37 °C for 48 hours. Plates were taken from the incubator, media was removed and excess media was removed by aggressively patting dry. 100 µL of 1% Methylene Blue in 50% methanol: 50% water was added to each well. Plates were incubated on rocker at room temperature for 5 minutes to fix and stain cells. Stain was removed and plates were submerged in distilled water to rinse 6 times, changing the water after the third rinse. Plates were air-dried on the benchtop. 100 µL of 1% SDS in PBS was added to each well and placed on rocker to solubilize cells until uniform color was reached. The absorbance of each plate was read at 650 nm. Background absorbance of 1% SDS in PBS only was subtracted from each value. IC_{50} was determined using Four Parameter Logistic Standard Curves Analysis in SigmaPlot Data Analysis Software.

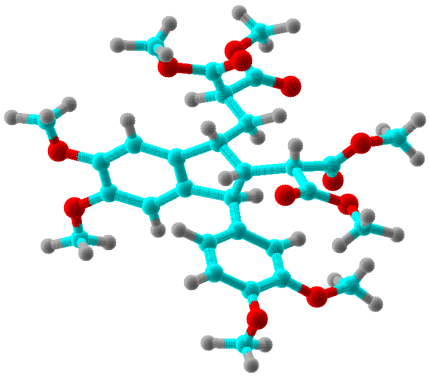
Table Cytotoxicity of dimers **2a-i**

	IC_{50}			
2	HEK-293	MCF7	SiHa	MDA Mb-231
a	8.7	24.5	-[a]	33.5
b	13.2	31.7	55.0	35.1
c	43	91.4	59.0	-[a]
d	12.6	48.3	-[a]	-[a]
e	-[a]	44.0	-[b]	-[b]
f	-[a]	88.2	-[b]	-[a]
g	75.9	62.7	-[b]	-[b]
h	-[a]	53.5	-[b]	-[b]
i	-[a]	61.4	-[a]	-[b]

[a] IC_{50} > 100 µM. [b] Not tested.

Results of geometry optimization for two diastereomers of 2c at B3LYP/6-311G** level

1,2-*cis*-2,3-*trans*-**2c**



E = -2068.0821428 (rel E = 0 kJ/mol)

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
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4	6	0	0.400954	-2.684042	0.069121
5	6	0	0.394665	-1.356415	-0.371506
6	6	0	1.370856	-0.895789	-1.236301
7	6	0	-0.582244	-0.259379	0.019007
8	6	0	1.222638	0.582807	-1.521020
9	6	0	-0.239500	0.870053	-1.015652
10	6	0	-2.037463	-0.705449	0.033663
11	6	0	-2.813016	-0.545442	1.191995
12	6	0	-4.145821	-0.941781	1.239003
13	6	0	-4.735154	-1.537202	0.099423
14	6	0	-3.962873	-1.708845	-1.045536
15	6	0	-2.627802	-1.297221	-1.078006
16	8	0	3.379026	-3.976674	-1.565694
17	8	0	1.533463	-4.845957	0.024566
18	6	0	2.369708	1.428088	-0.915315
19	6	0	-0.483686	2.314705	-0.528677
20	8	0	-4.964724	-0.785580	2.316449
21	8	0	-6.043975	-1.894165	0.226448
22	6	0	4.430208	-3.548587	-2.421382
23	6	0	0.540170	-5.389249	0.879320
24	6	0	-6.681190	-2.501124	-0.885665
25	6	0	-4.426748	-0.172688	3.480702
26	6	0	-0.328914	3.319240	-1.671830
27	8	0	-0.133008	3.050819	-2.829382
28	8	0	-0.438198	4.575306	-1.201899
29	6	0	-0.323601	5.625268	-2.179767
30	6	0	-1.853284	2.505299	0.121849
31	8	0	-2.042134	2.586311	1.309666
32	8	0	-2.824037	2.564280	-0.804967
33	6	0	-4.168583	2.725818	-0.313002
34	6	0	2.714854	1.169158	0.566920
35	6	0	3.729073	0.037508	0.734694

36	8	0	4.724428	-0.087891	0.064951
37	8	0	3.374607	-0.794425	1.725084
38	6	0	4.265387	-1.900110	1.969763
39	6	0	3.231053	2.447464	1.238061
40	8	0	2.934266	3.566161	0.902781
41	8	0	4.019905	2.171204	2.289780
42	6	0	4.519177	3.308750	3.020202
43	1	0	3.149298	-1.384728	-2.350825
44	1	0	-0.378510	-3.034061	0.732723
45	1	0	-0.342391	0.088236	1.032529
46	1	0	1.249194	0.787716	-2.594036
47	1	0	-0.890784	0.717770	-1.878853
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50	1	0	-2.050559	-1.454996	-1.981820
51	1	0	2.152616	2.489706	-1.034333
52	1	0	3.278155	1.242376	-1.494327
53	1	0	0.230717	2.596459	0.246474
54	1	0	5.091083	-4.407281	-2.528444
55	1	0	4.051033	-3.259246	-3.408246
56	1	0	4.984905	-2.710779	-1.985214
57	1	0	0.820581	-6.429880	1.035017
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59	1	0	-0.454172	-5.345817	0.420487
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63	1	0	-5.248924	-0.122675	4.192830
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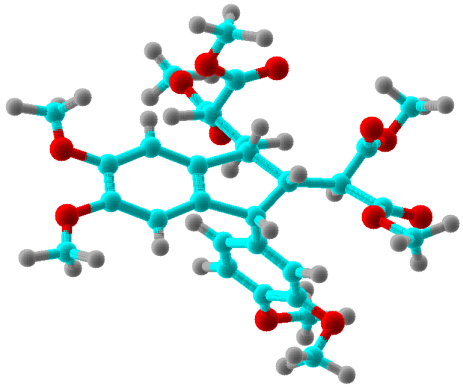
66	1	0	-0.441386	6.552471	-1.624013
67	1	0	0.653513	5.589117	-2.663208
68	1	0	-1.102876	5.526291	-2.936927
69	1	0	-4.789613	2.824176	-1.200230
70	1	0	-4.464594	1.850074	0.264410
71	1	0	-4.238513	3.618430	0.309912
72	1	0	1.825489	0.892562	1.140265
73	1	0	3.893288	-2.375502	2.874410
74	1	0	5.285781	-1.542559	2.110233
75	1	0	4.232803	-2.600796	1.134387
76	1	0	5.139828	2.894162	3.810854
77	1	0	3.691901	3.882954	3.439356
78	1	0	5.107110	3.951768	2.364414

1,2-*cis*-2,3-*cis*-**2c**



E = -2068.0760338 (rel E = 16.0 kJ/mol)

Standard orientation:

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2	6	0	-2.289578	3.478984	-0.610318
3	6	0	-1.008672	4.090257	-0.679211
4	6	0	0.126257	3.298577	-0.814903
5	6	0	0.000493	1.906145	-0.868892
6	6	0	-1.244974	1.305787	-0.771378
7	6	0	1.110258	0.893952	-1.076605
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9	6	0	0.277003	-0.385027	-1.474483
10	6	0	2.087629	0.767297	0.089136
11	6	0	3.430054	0.469072	-0.171721
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13	6	0	2.633191	0.811150	2.454485
14	6	0	4.364251	0.329578	0.850768
15	6	0	3.957504	0.476819	2.186296
16	6	0	-1.316244	-0.885975	0.555355
17	6	0	-2.750088	-0.813229	1.105720
18	6	0	-3.712711	-1.588667	0.214493
19	8	0	-3.604492	-2.760926	-0.046965
20	8	0	-4.687092	-0.800953	-0.279035
21	6	0	-5.634539	-1.453921	-1.148823
22	6	0	-2.818632	-1.357592	2.532794
23	8	0	-1.873806	-1.582029	3.241554
24	8	0	-4.100759	-1.519462	2.916406
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38	8	0	4.847913	0.350121	3.228510

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61	1	0	3.520478	-0.628398	-4.678396
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63	1	0	3.494652	-2.390595	-4.356828
64	1	0	-0.828336	-5.684609	-0.373509
65	1	0	-0.783671	-5.333837	-2.131630
66	1	0	-2.026539	-4.568792	-1.098623
67	1	0	-5.320878	4.649631	-0.393458
68	1	0	-4.789936	3.146892	0.403634
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76	1	0	5.992831	-0.931281	4.308629
77	1	0	5.814985	-1.396508	2.592585
78	1	0	4.460356	-1.638443	3.733716

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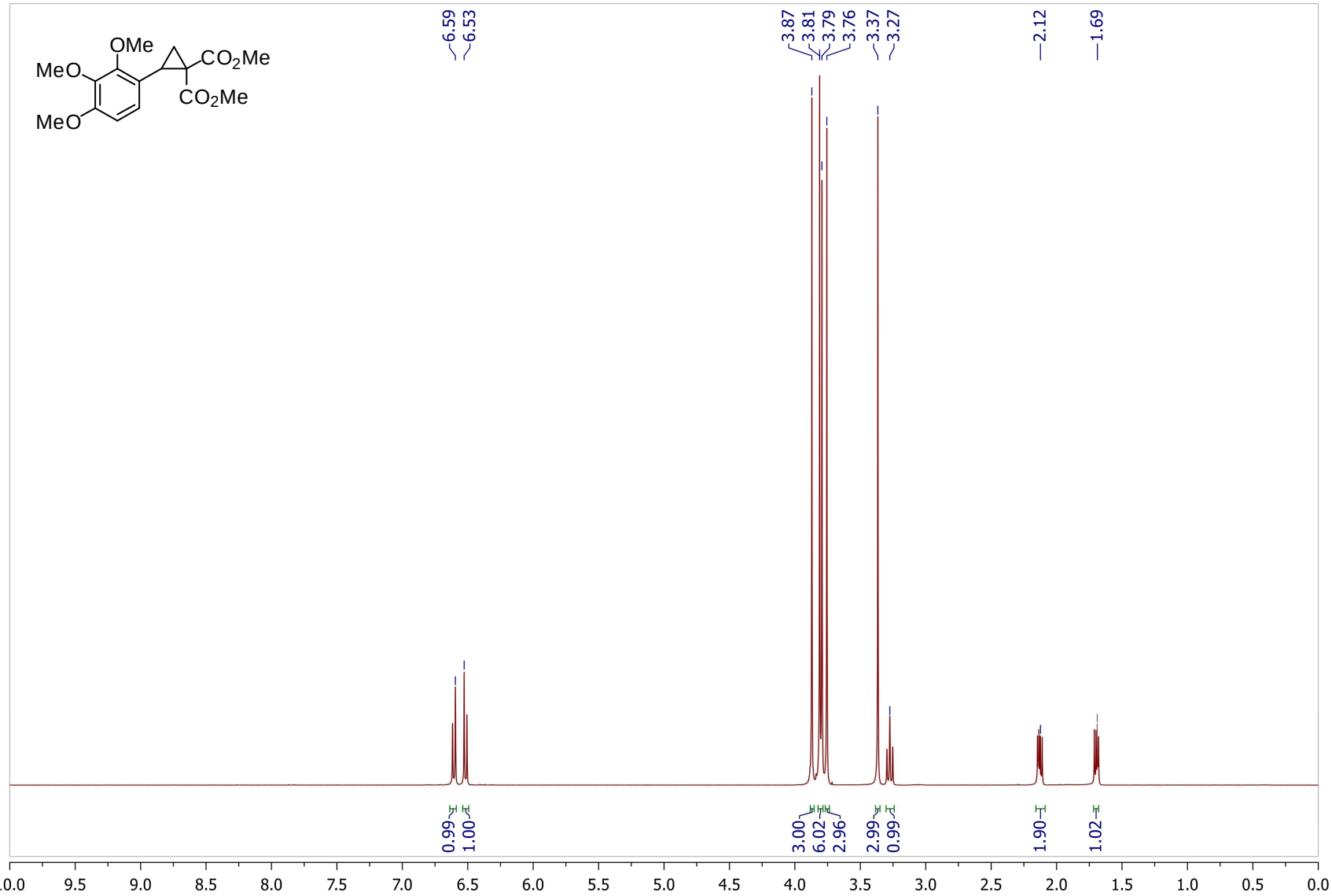
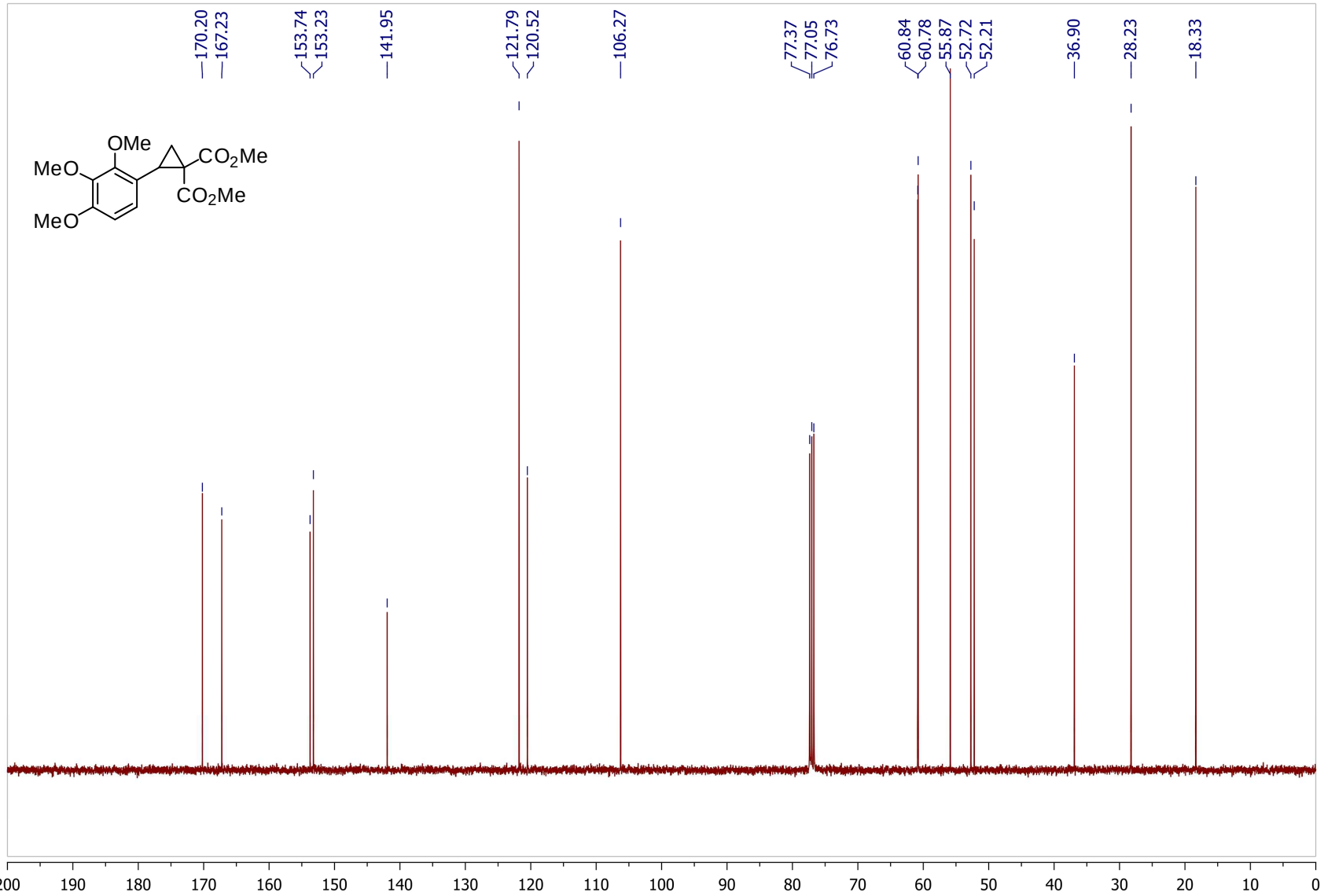
Dimethyl 2-(2,3,4-trimethoxyphenyl)cyclopropane-1,1-dicarboxylate (1d)

^{1}H NMR ($CDCl_3$, 600 MHz)



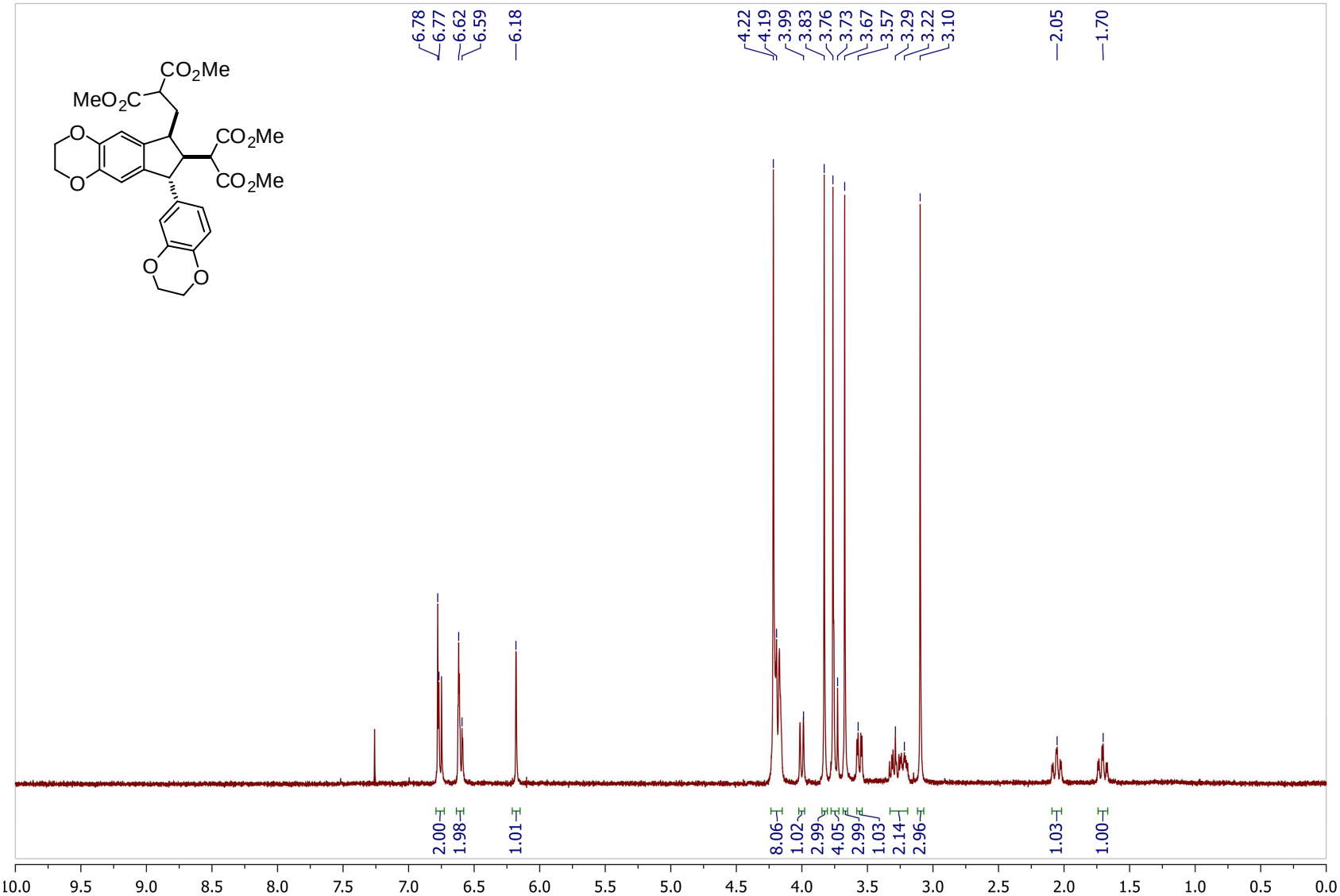
Dimethyl 2-(2,3,4-trimethoxyphenyl)cyclopropane-1,1-dicarboxylate (1d)

^{13}C NMR ($CDCl_3$, 150 MHz)



Dimethyl {[(6*RS*,7*SR*,8*SR*)-8-(2,3-dihydro-1,4-benzodioxin-6-yl)-7-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-2,3,7,8-tetrahydro-6H-indeno[5,6-b][1,4]dioxin-6-yl}-methyl)malonate (2a)

^{1}H NMR ($CDCl_3$, 600 MHz)



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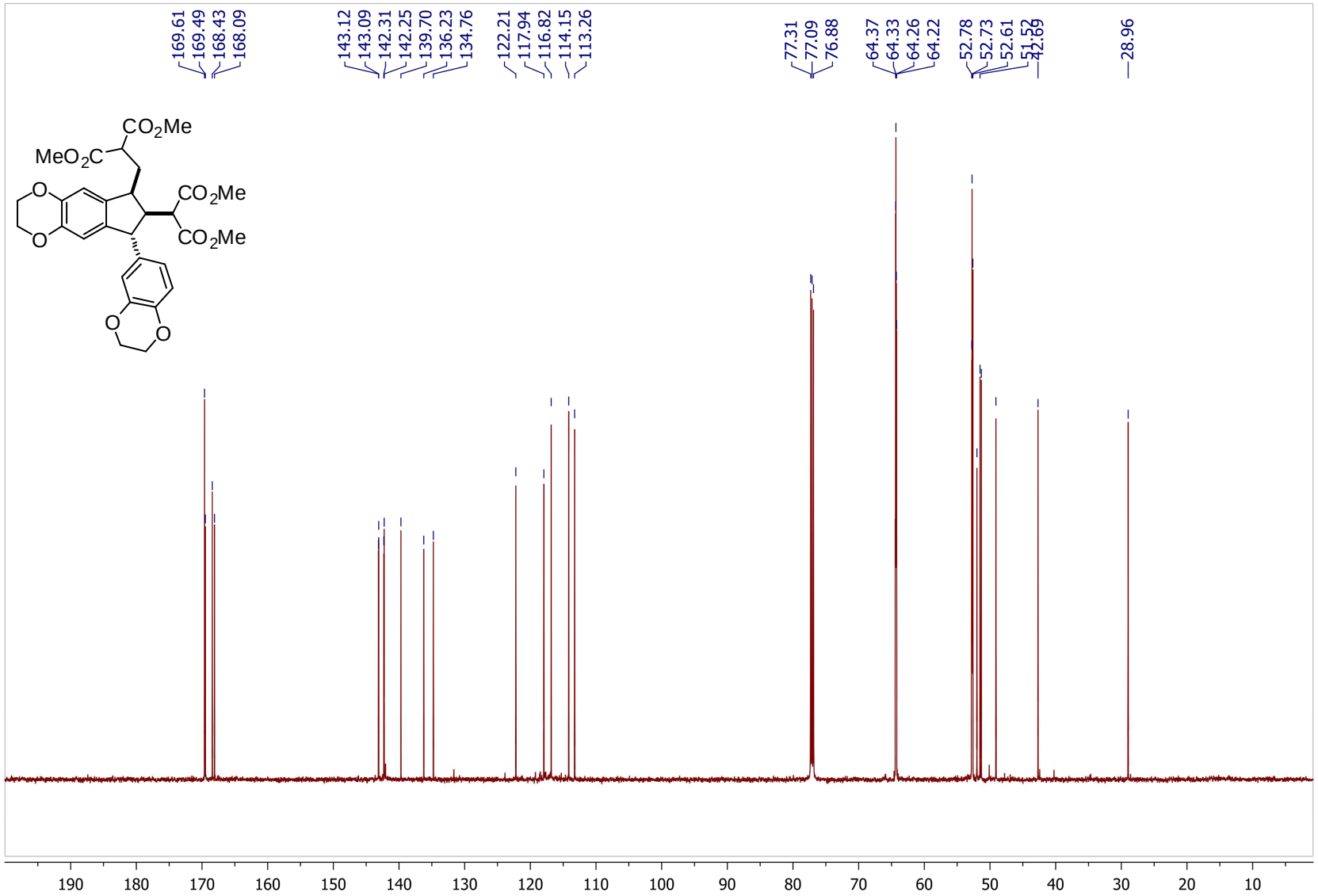
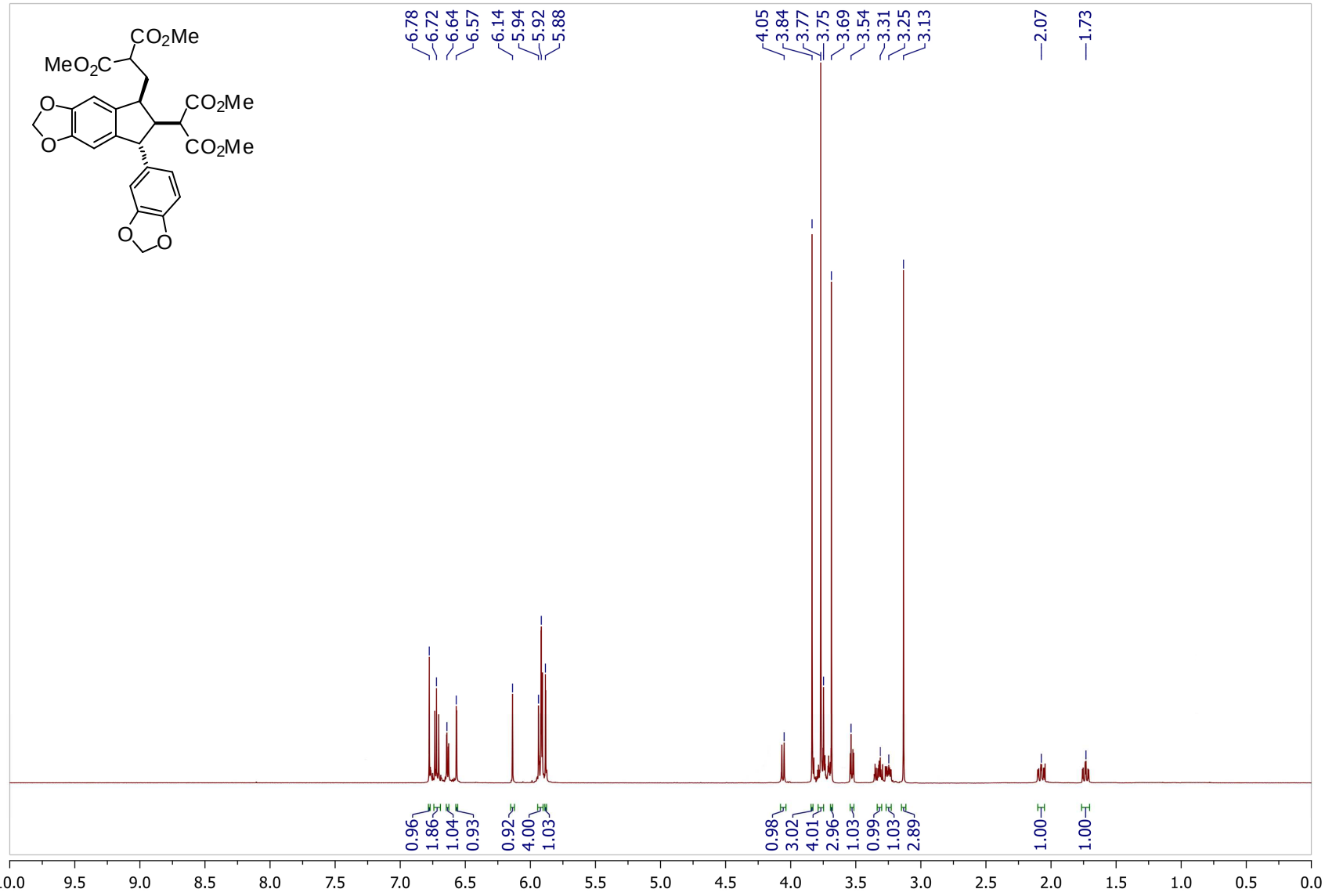
^{13}C NMR ($CDCl_3$, 150 MHz)



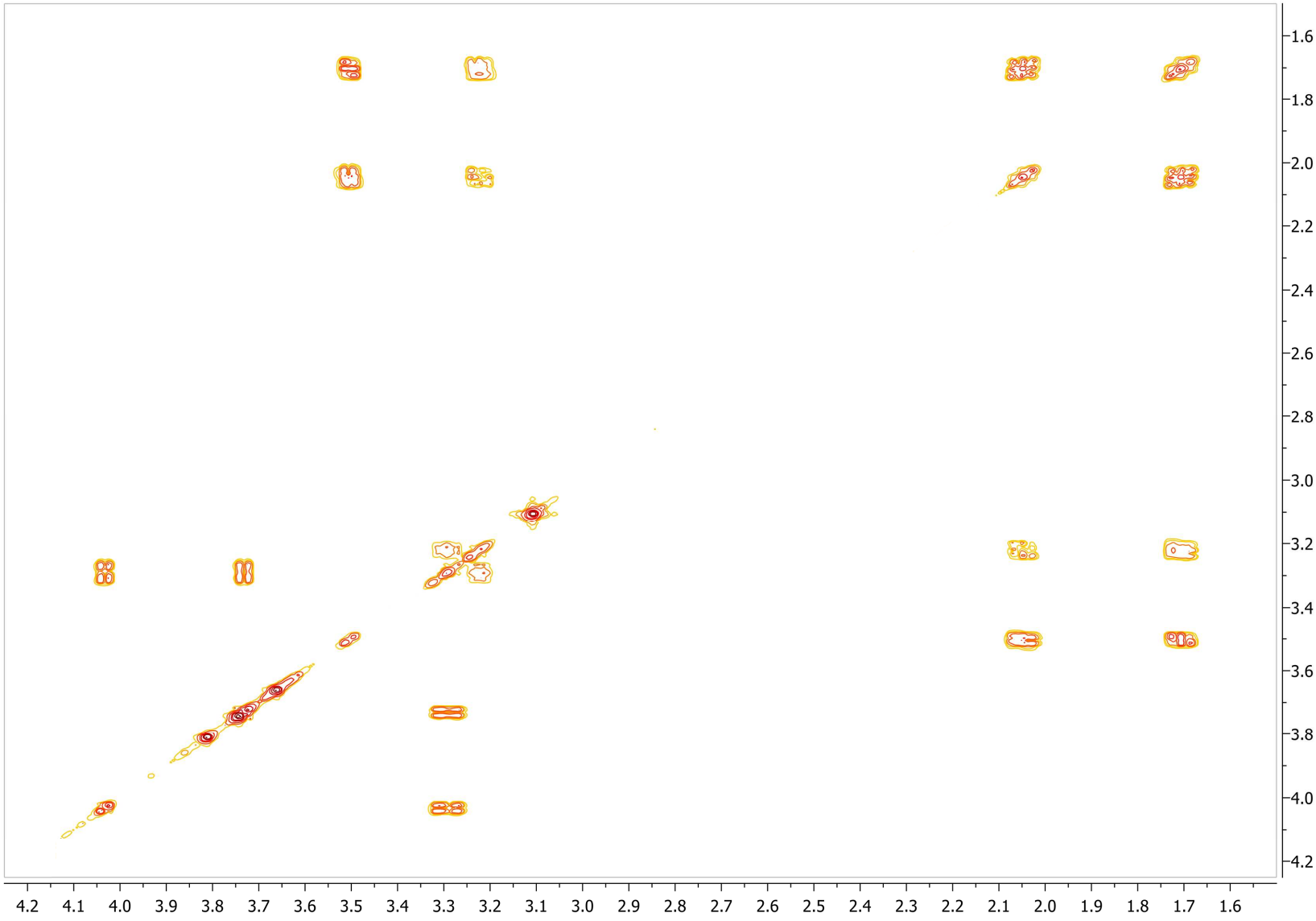
Dimethyl ({(5*RS*,6*SR*,7*SR*)-7-(1,3-benzodioxol-5-yl)-6-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-yl}methyl)malonate (2b)

^{1}H NMR ($CDCl_3$, 600 MHz)



Dimethyl ({(5*RS*,6*SR*,7*SR*)-7-(1,3-benzodioxol-5-yl)-6-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-yl}methyl)malonate (2b)

COSY ^{1}H-^{1}H



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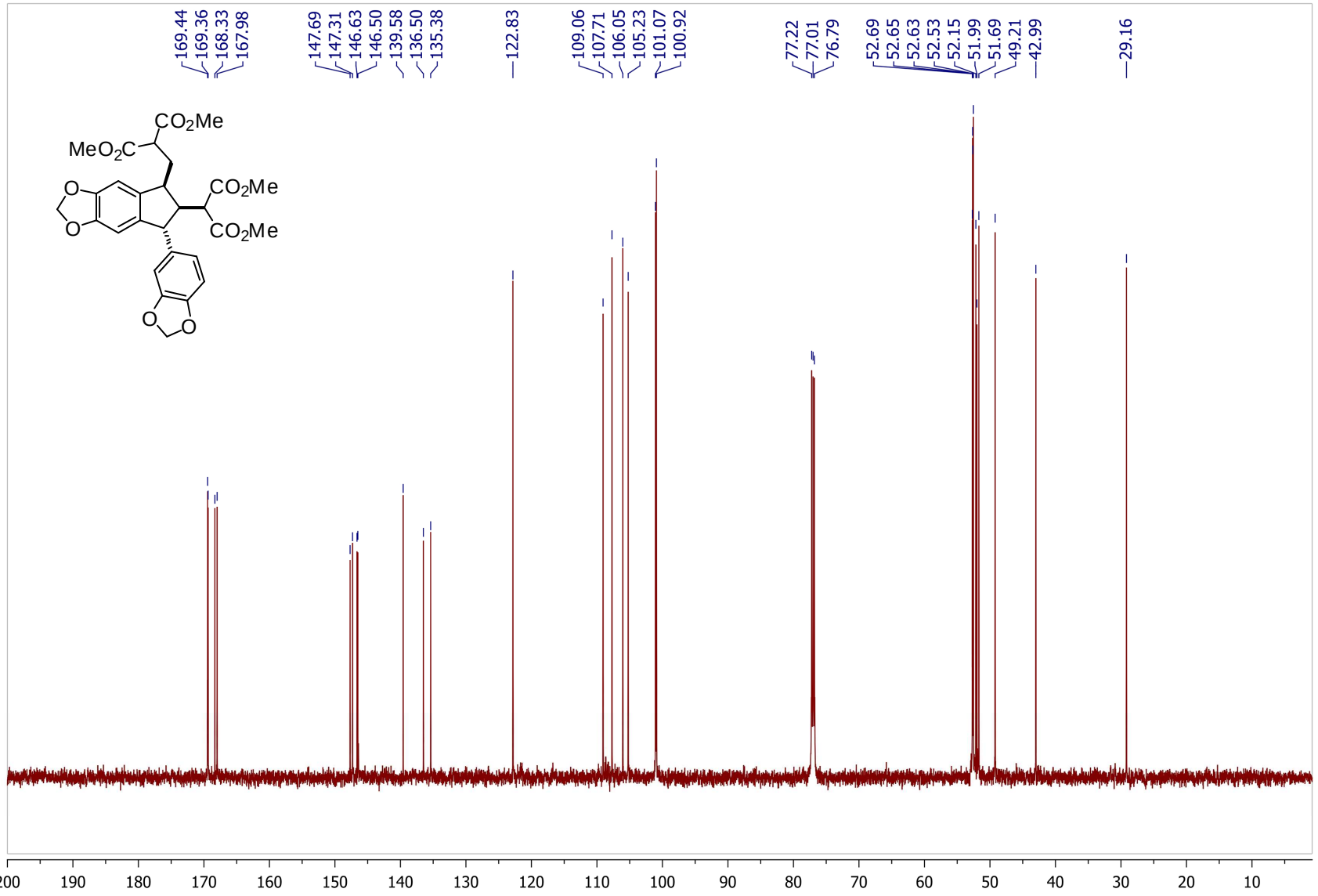
^{13}C NMR ($CDCl_3$, 150 MHz)



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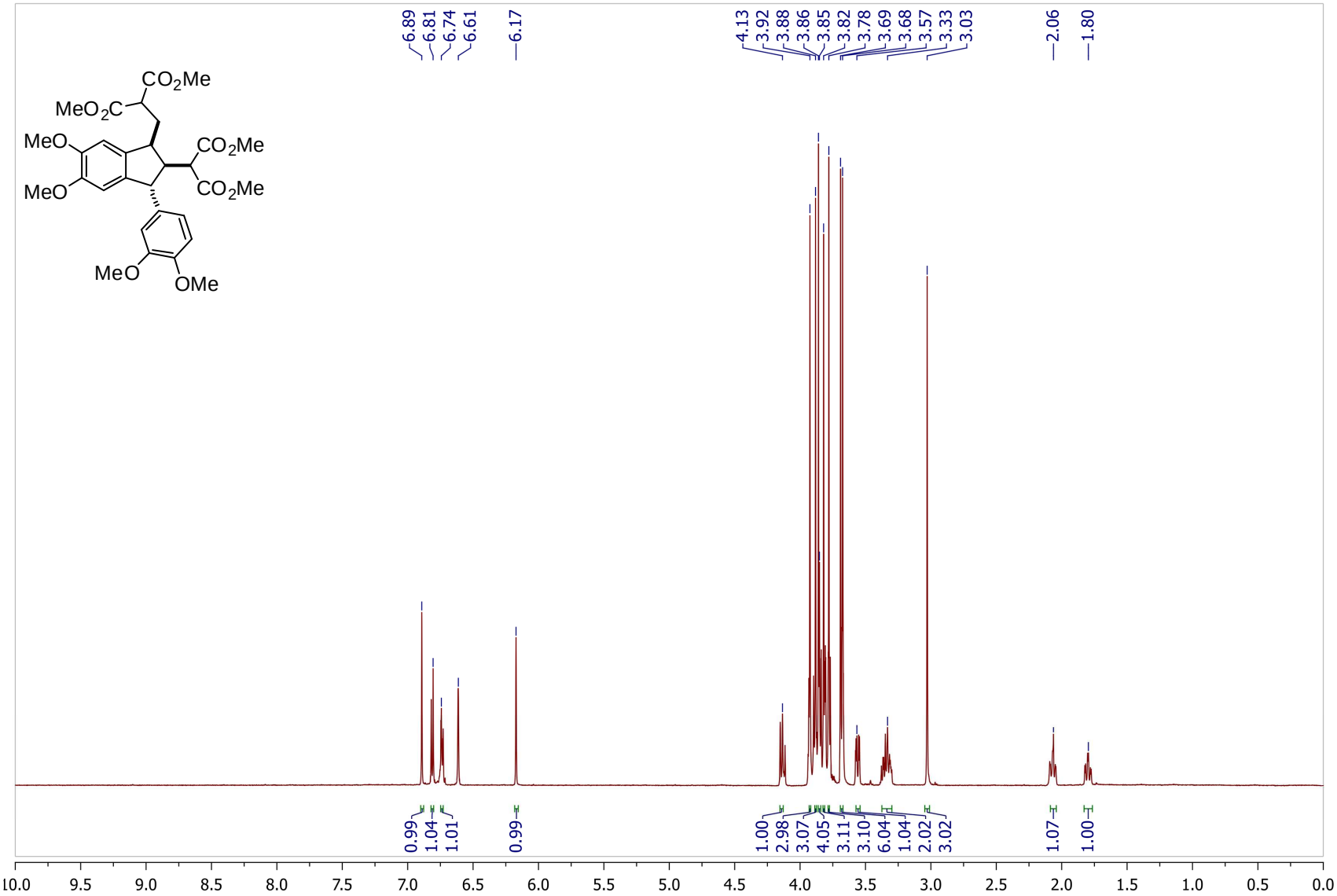
^{1}H NMR ($CDCl_3$, 600 MHz)



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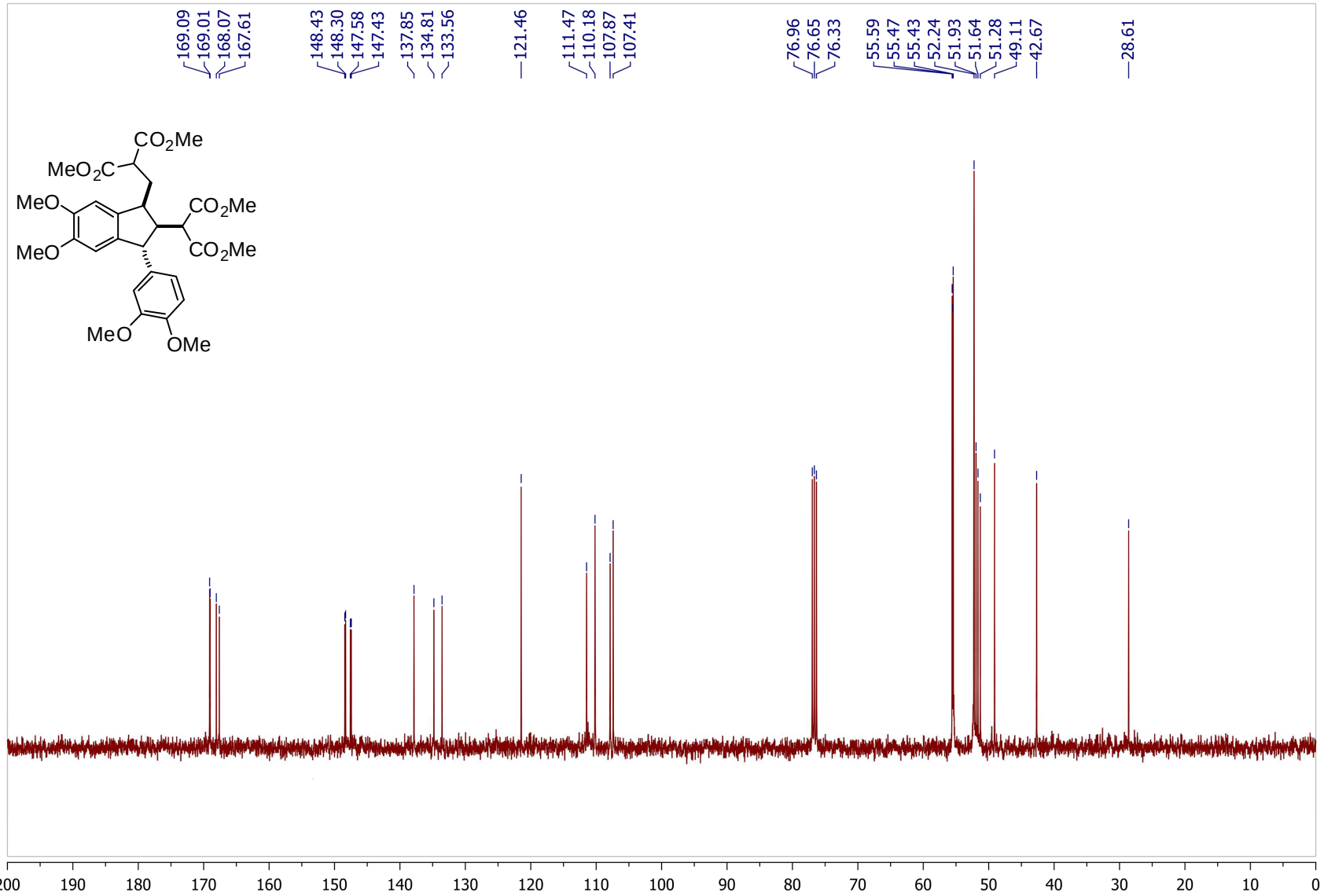
^{13}C NMR ($CDCl_3$, 150 MHz)



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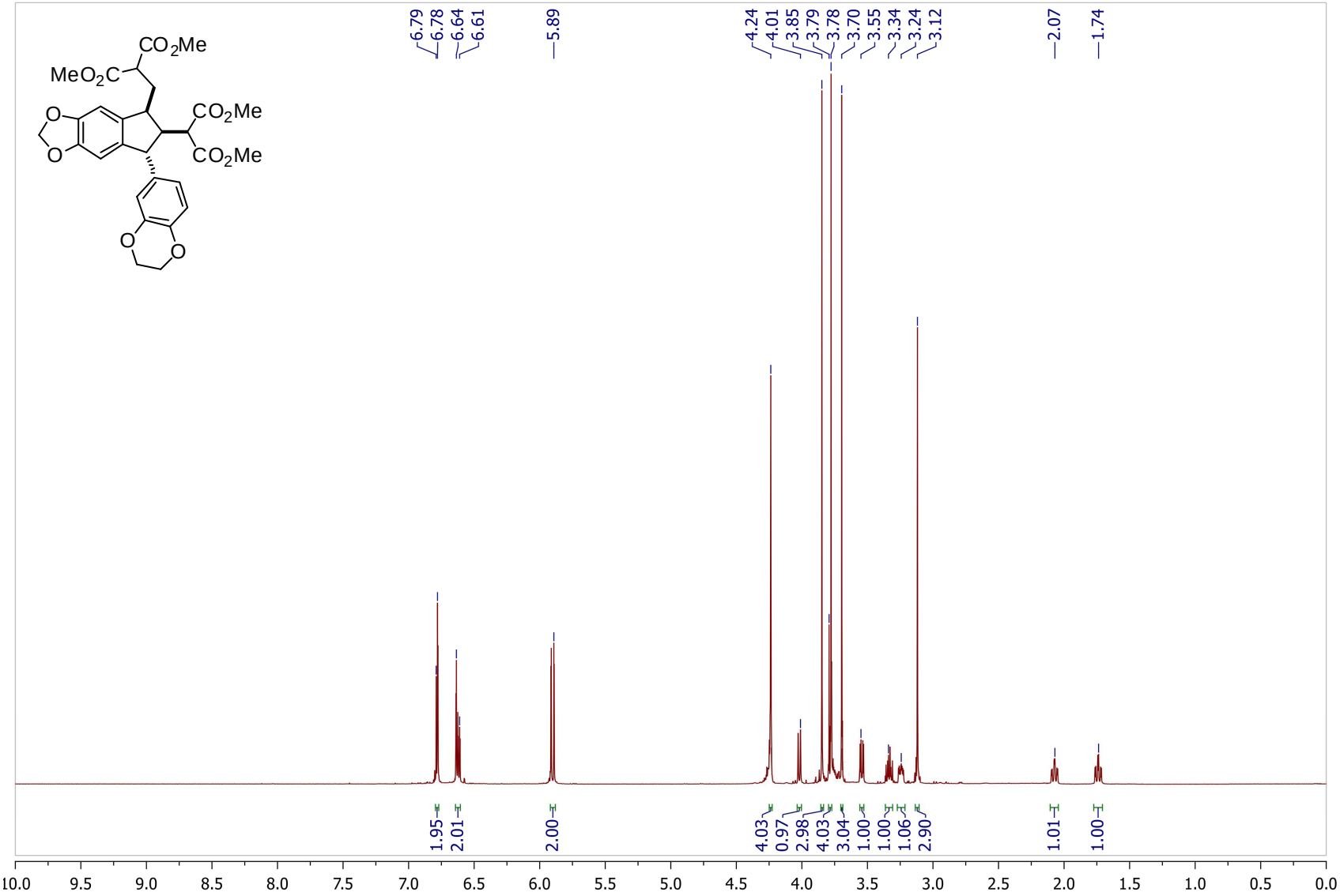
^{1}H NMR ($CDCl_3$, 600 MHz)



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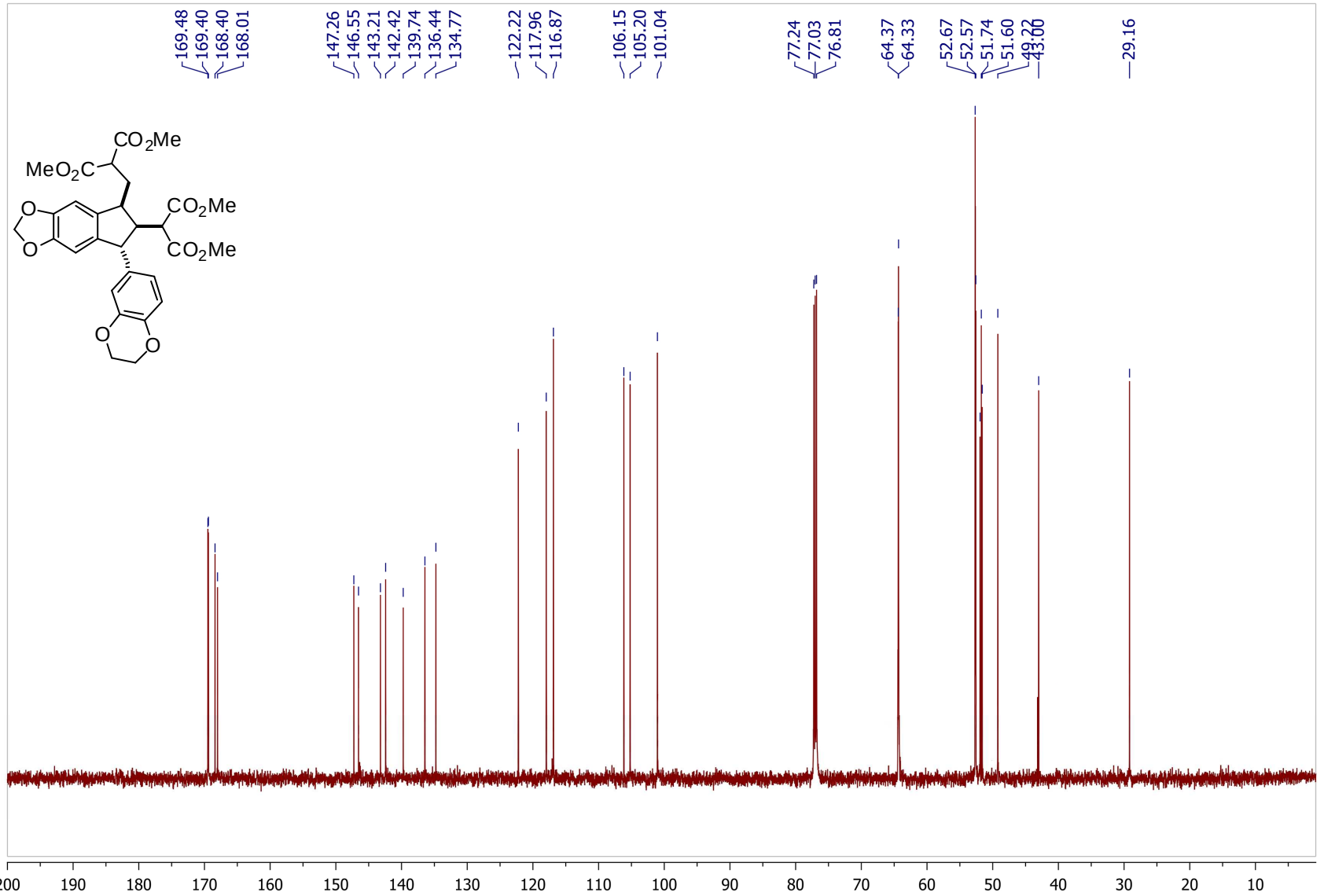
^{13}C NMR ($CDCl_3$, 150 MHz)



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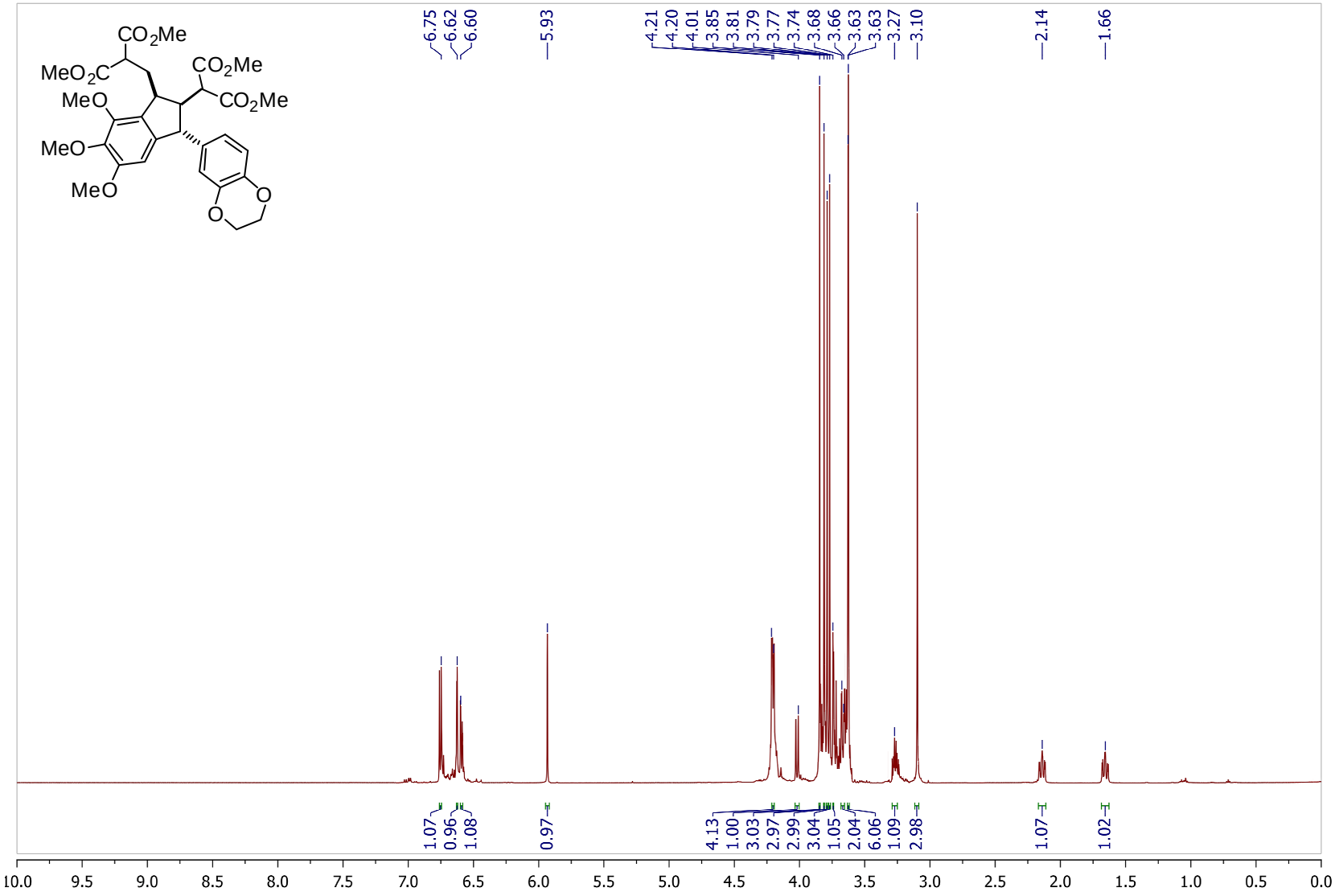
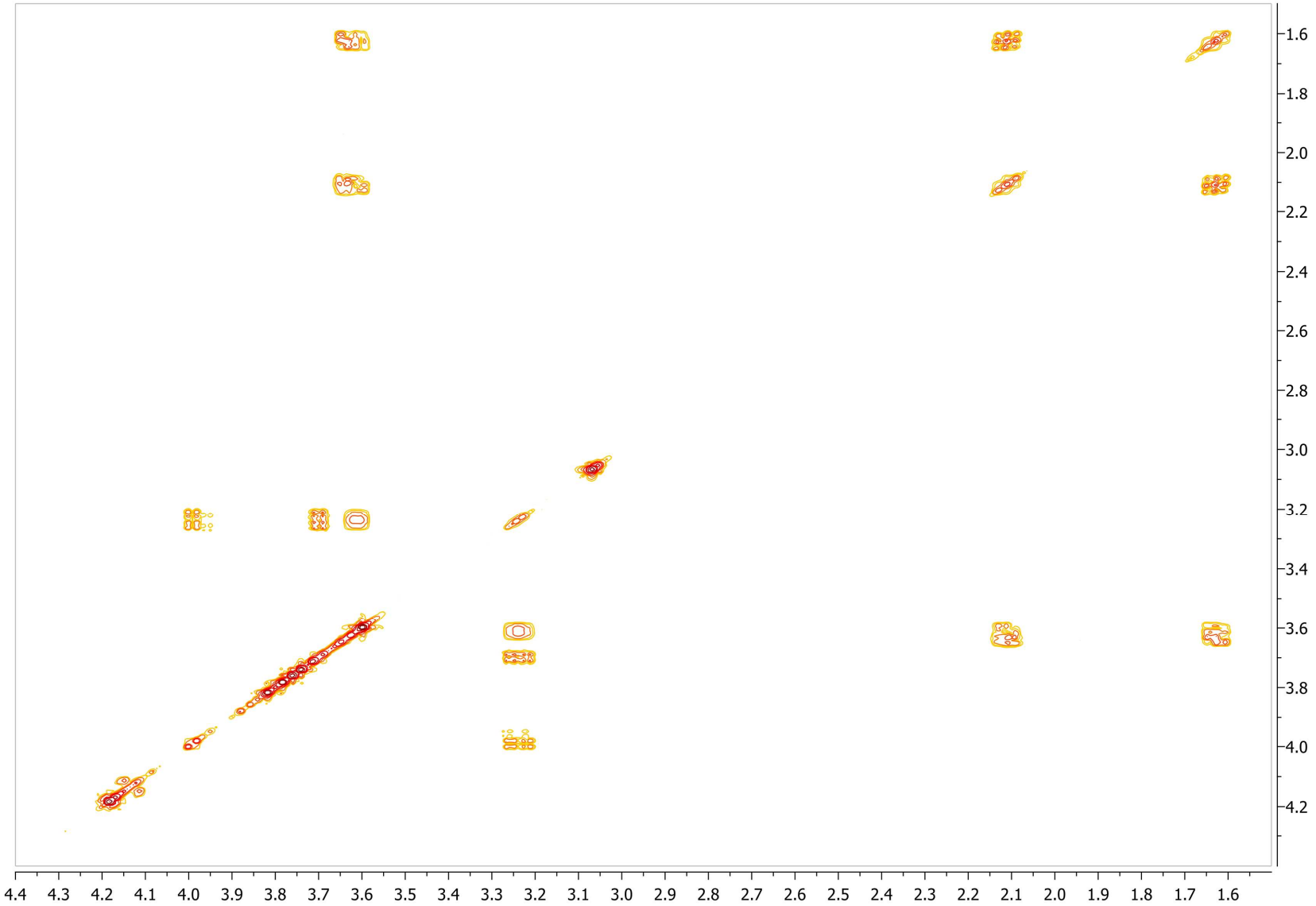
^{1}H NMR ($CDCl_3$, 600 MHz)



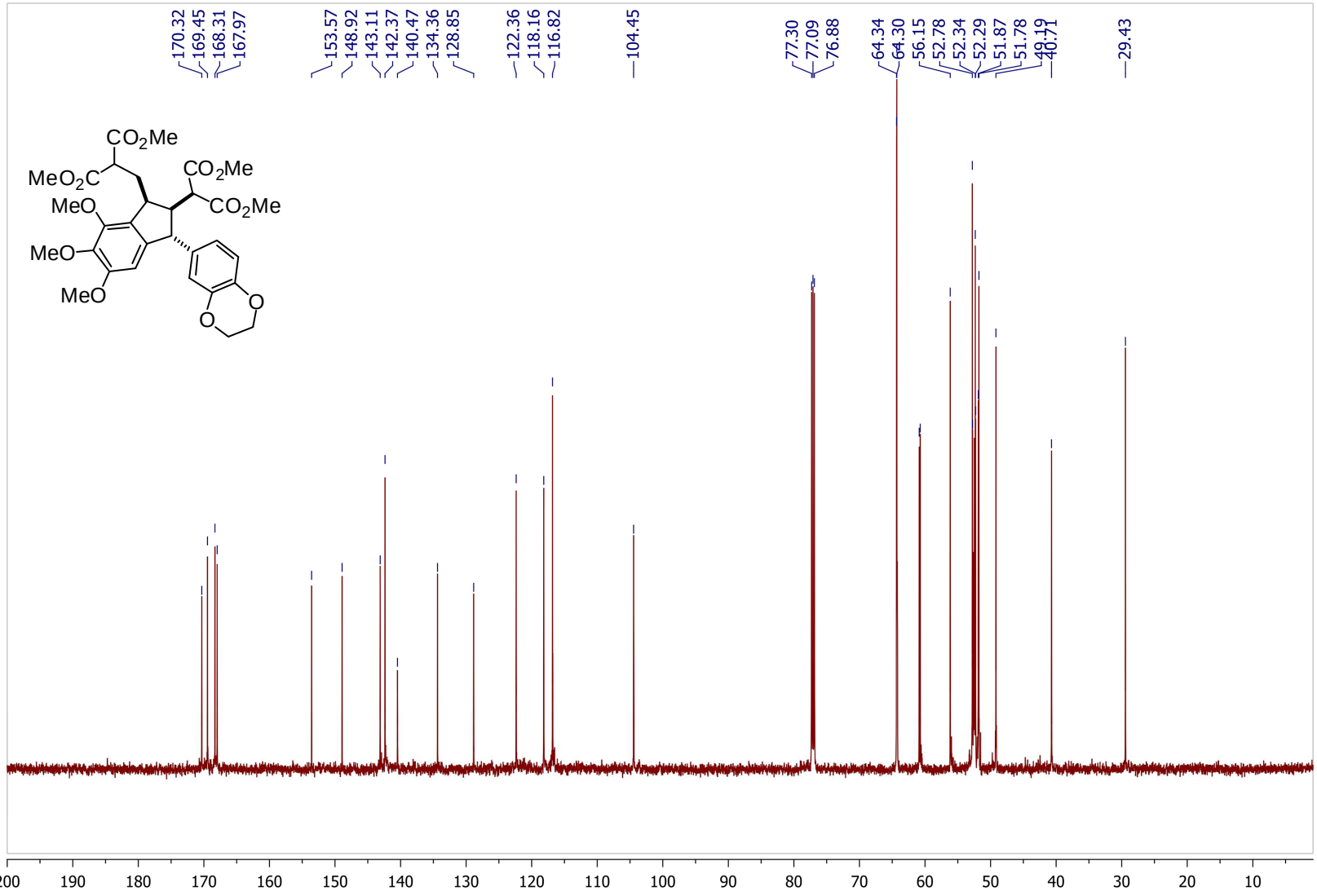
Dimethyl ({(1*RS*,2*SR*,3*SR*)-3-(2,3-dihydro-1,4-benzodioxin-6-yl)-5,6,7-trimethoxy-2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-2,3-dihydro-1*H*-inden-1-yl}methyl)malonate (2e)

COSY ^{1}H-^{1}H



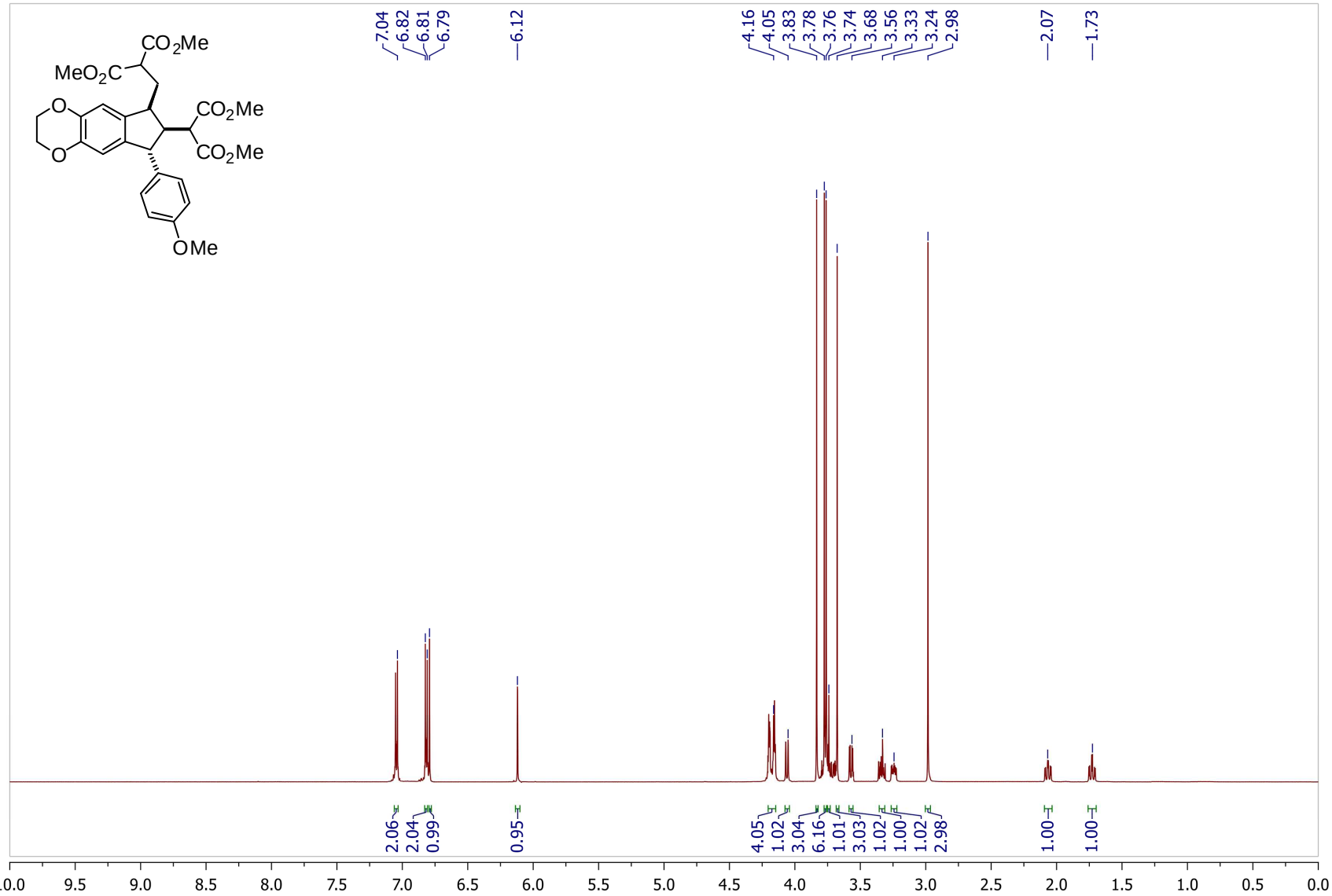
Dimethyl ({(1*RS*,2*SR*,3*SR*)-3-(2,3-dihydro-1,4-benzodioxin-6-yl)-5,6,7-trimethoxy-2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-2,3-dihydro-1*H*-inden-1-yl}methyl)malonate (2e)

^{13}C NMR ($CDCl_3$, 150 MHz)



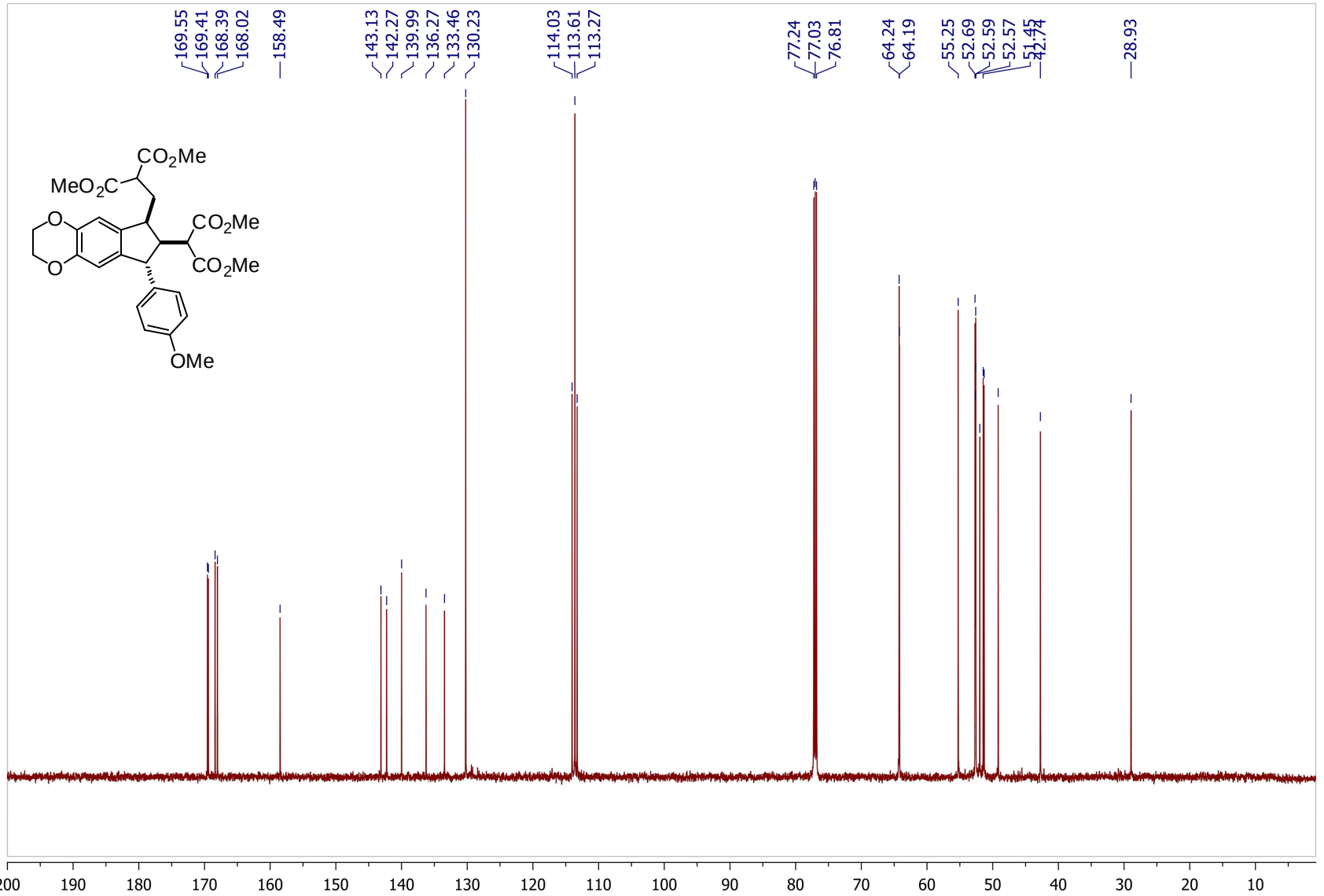
Dimethyl {[(6*RS*,7*SR*,8*SR*)-7-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-8-(4-methoxyphenyl)-2,3,7,8-tetrahydro-6H-indeno[5,6-b][1,4]dioxin-6-yl}methyl)malonate (2f)

^{1}H NMR ($CDCl_3$, 600 MHz)



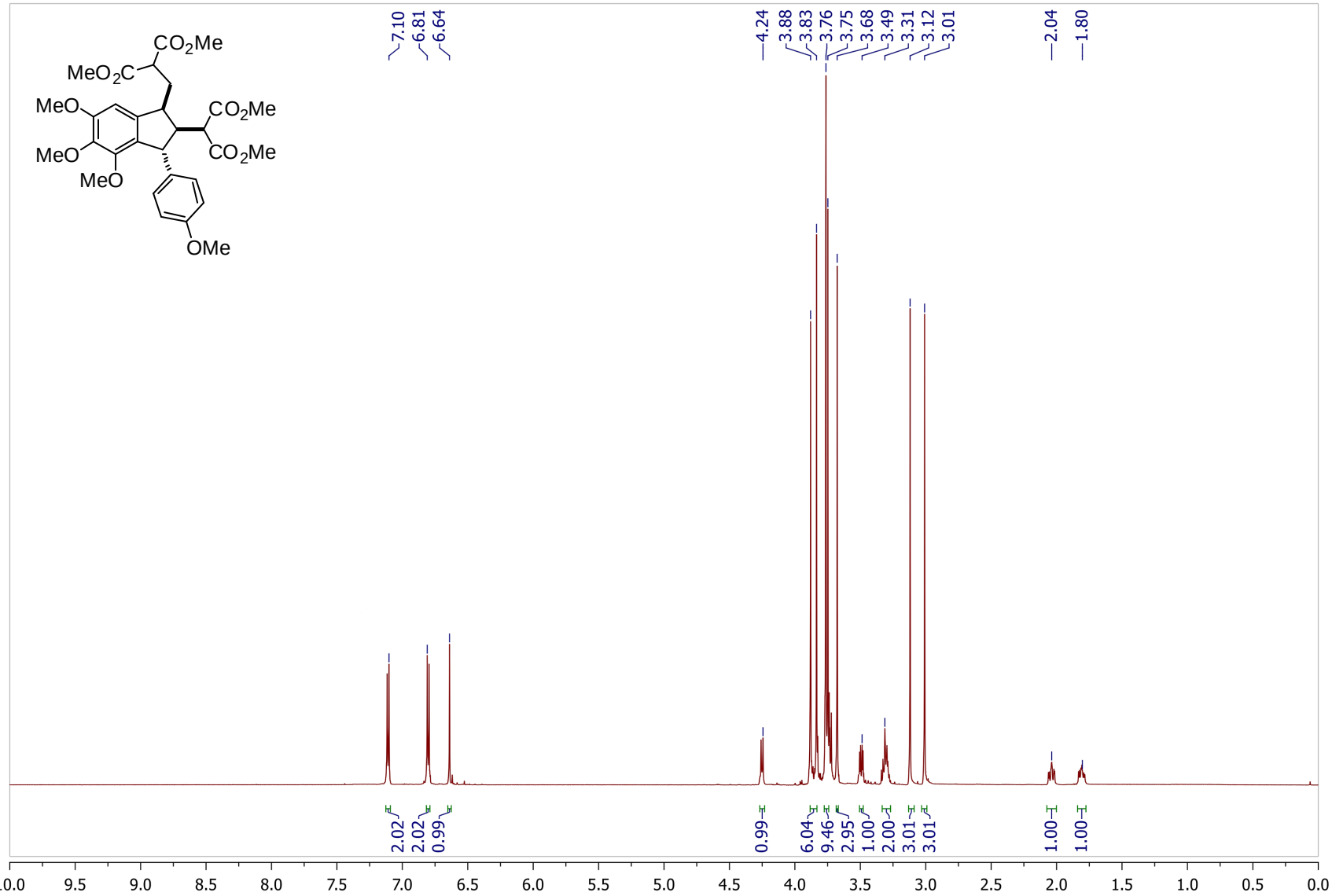
Dimethyl {[(6*RS*,7*SR*,8*SR*)-7-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-8-(4-methoxyphenyl)-2,3,7,8-tetrahydro-6H-indeno[5,6-b][1,4]dioxin-6-yl}methyl)malonate (2f)

^{13}C NMR ($CDCl_3$, 150 MHz)



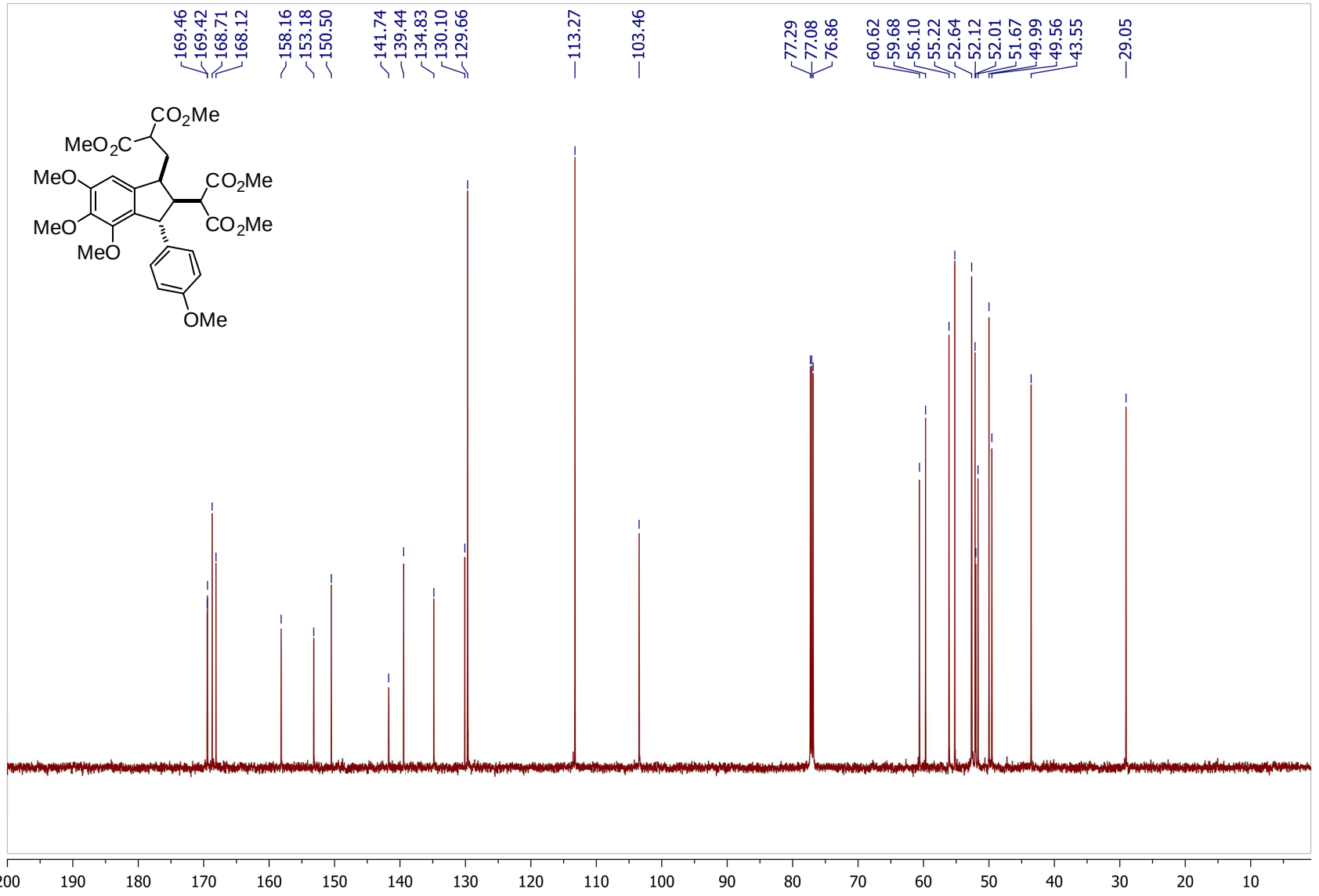
Dimethyl ({(1*RS*,2*SR*,3*SR*)-4,5,6-trimethoxy-2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]- 3-(4-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl}methyl)malonate (2g)

^{1}H NMR ($CDCl_3$, 600 MHz)



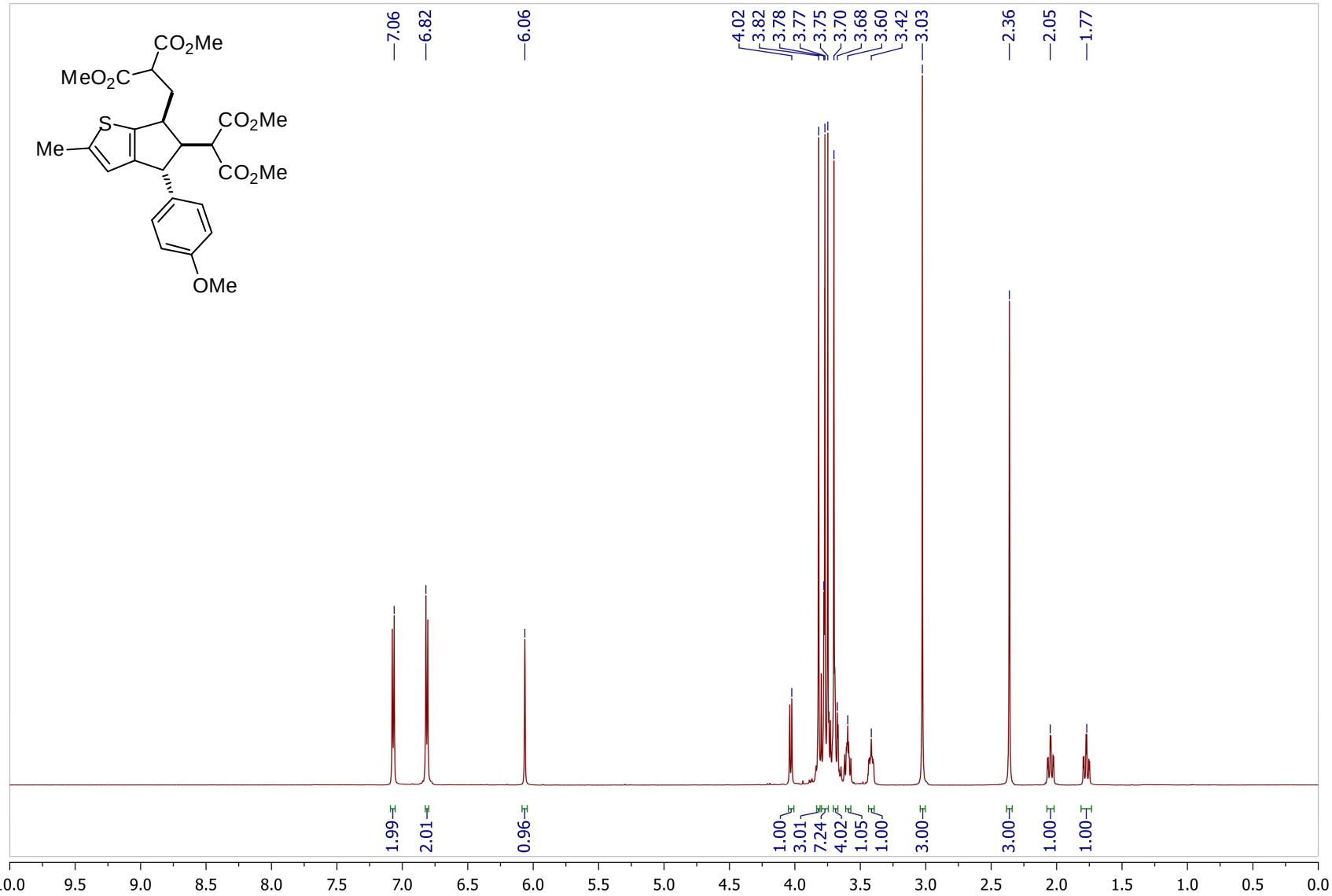
Dimethyl ({(1*RS*,2*SR*,3*SR*)-4,5,6-trimethoxy-2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]- 3-(4-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl}methyl)malonate (2g)

^{13}C NMR ($CDCl_3$, 150 MHz)



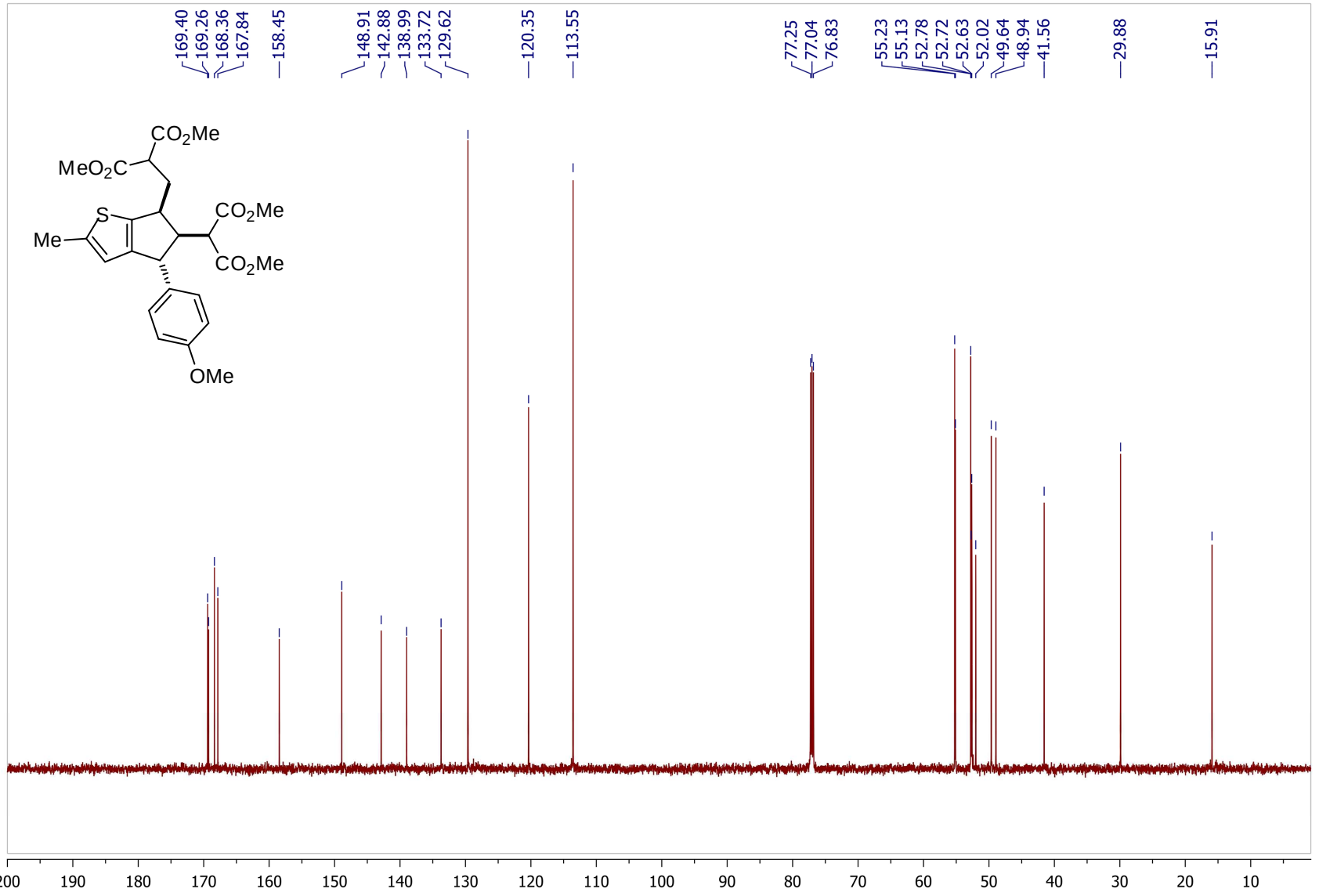
Dimethyl {[(4*RS*,5*RS*,6*SR*)-5-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-4-(4-methoxyphenyl)-2-methyl-5,6-dihydro-4*H*-cyclopenta[*b*]thien-6-yl]methyl}malonate (2h)

^{1}H NMR ($CDCl_3$, 600 MHz)



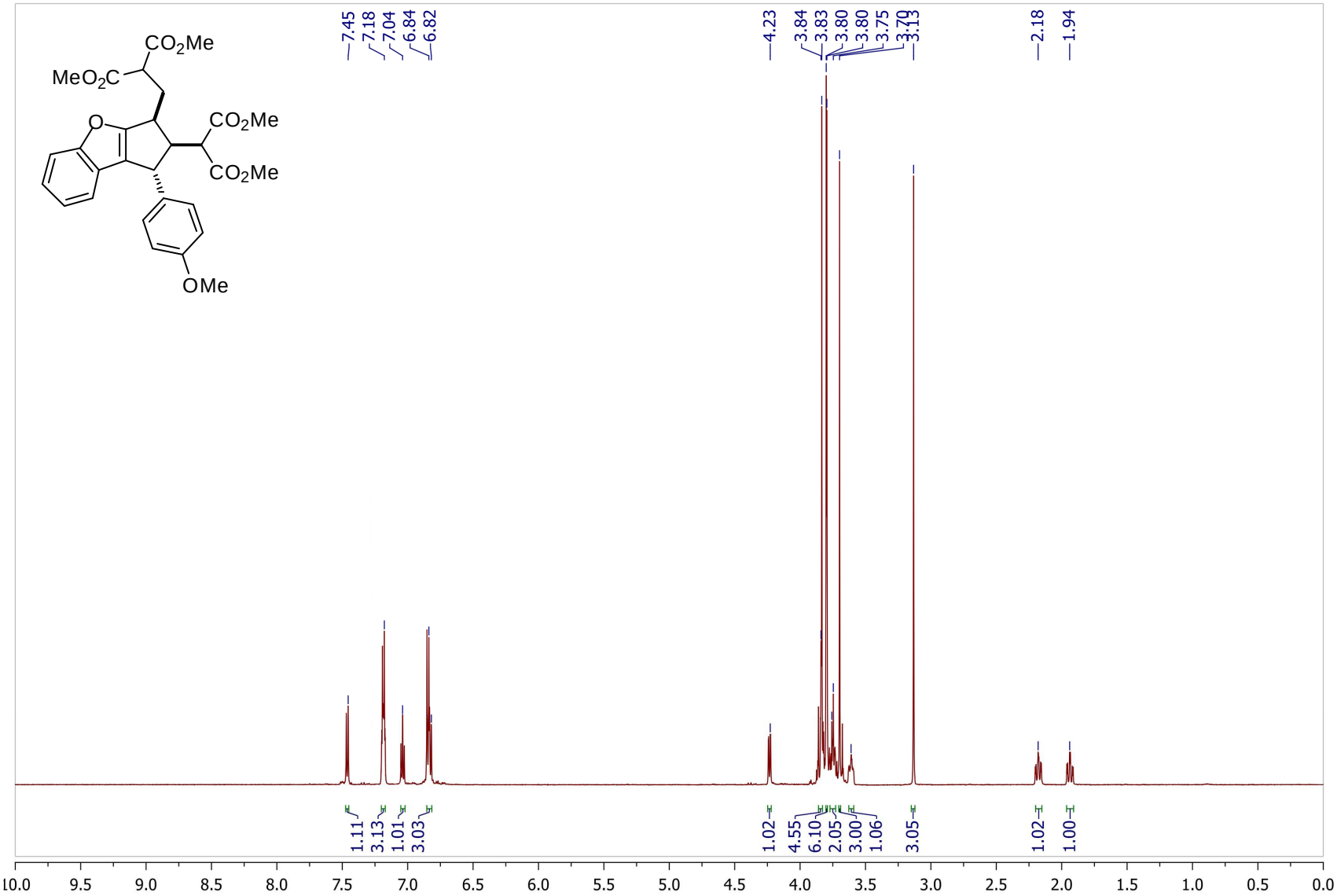
Dimethyl {[(4*RS*,5*RS*,6*SR*)-5-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-4-(4-methoxyphenyl)-2-methyl-5,6-dihydro-4*H*-cyclopenta[*b*]thien-6-yl]methyl}malonate (2h)

^{13}C NMR ($CDCl_3$, 150 MHz)



Dimethyl {[(1*RS*,2*SR*,3*SR*)-2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-3-yl]methyl}malonate (2i)

^{1}H NMR ($CDCl_3$, 600 MHz)



Dimethyl {[(1*RS*,2*SR*,3*SR*)-2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethyl]-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-3-yl]methyl}malonate (2i)

^{13}C NMR ($CDCl_3$, 150 MHz)