Vinylogous and Stereoselective Domino Synthesis of Pyrano[2,3-c]pyrroles from Alkylidene Meldrum's acids

Mariia Savchuk,[a] Giang Vo-Thanh,[b] Sylvain Oudeyer,[a] Hélène Beucher [a]

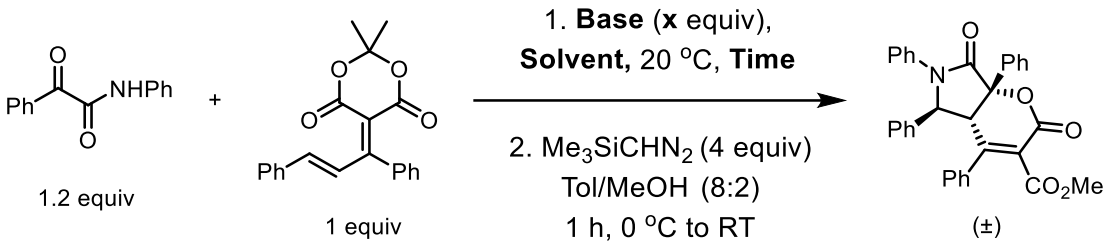
and Jean-François Brière*[a]

[a] University of Rouen-Normandy, INSA Rouen, UNIROUEN, CNRS, COBRA, 76000 Rouen, France;
[b] Institut de Chimie Moléculaire et des Matériaux d'Orsay. CNRS UMR 8182, Université Paris Saclay, 91405 Orsay Cedex, France.

I. General information

Reactions were performed using oven dried glassware under the inert atmosphere of nitrogen. Unless otherwise noted, all reagent-grade chemicals and solvents were obtained from commercial suppliers and were used as received. THF, Toluene, MeCN and CH_2Cl_2 were dried over MBRAUN MB SPS-800 Apparatus. Reactions were monitored by thin-layer chromatography with silica gel 60 F254 pre-coated aluminium plates (0.25 mm). Visualization was performed under UV light, phosphomolybdic acid or $KMnO_4$ oxidation. Chromatographic purification of compounds was achieved with 60 silica gel (40-63 μm). Melting points were measured on a WME Köfler hot-stage (Stuart SMP3) and are uncorrected. Infrared spectra (IR) were recorded on a PerkinElmer Spectrum 100 Series FT-IR spectrometer. Liquids and solids were applied on the Single Reflection Attenuated Total Reflectance (ATR) Accessories. Data are reported in cm^{-1}. ^{1}H Spectra (300 MHz or 400 Mhz), ^{13}C NMR spectra (75 MHz or 101 Mhz) and ^{19}F NMR (376 MHz) were recorded on a Bruker Avance 300 or NEO400As. Processing and analysis of the spectra were performed by MestReNova 12.0.1 on a PC workstation. Data appear in the following order: chemical shifts in ppm which were referenced to the internal solvent signal, number of protons, multiplicity (*s*, singlet; *d*, doublet; *t*, triplet; *q*, quadruplet; *dd*, doublet of doublet, *ddd*, doublet of doublet of doublet, *dt*, doublet of triplet; *ddt*, doublet of doublet of triplet, *td*, triplet of doublet; *tdd*, triplet of doublet of doublet; *m*, multiplet, AB_q, AB system) and coupling constant *J* in Hertz. Accurate Mass measurements (HRMS) were performed by the Mass Spectrometry Laboratory of the University of Rouen and were recorded with a Waters LCT 1er XR spectrometer.

II. Optimization of the reaction conditions



In order to evaluate the ability of a given base to promote the Aza-Michael addition reaction, 2 equiv of inorganic base were used for the preliminary investigations. At least 1.2 equiv of base are required to completely deprotonate the given amount of α-keto amide substrate. Only the Cs_2CO_3 was sufficiently strong to facilitate the Aza-Michael addition/aldol condensation process (*entries 1-4*). Shorter reaction times were applied to investigate the amount of base required (*entry 5-6*), where the best performance was achieved with the two equivalents of base.

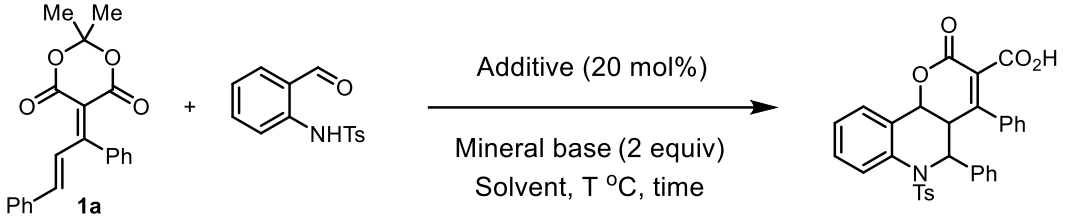
At last, the solvent effect was studied (*entry 7-11*) by applying one equivalent of Cs_2CO_3. With the best solvent (ACN) and 1.2 equiv of the base, the reaction was complete after the 1 hour of stirring at room temperature (*entry 12*). These optimum conditions were used for the scope of this domino process.

Entry	Base	Equiv	Solvent	T, °C	Time, h	Conversion [a], %	Isolated Yield [b], %
1.	Cs_2CO_3	2	DCM	20	16	100	*n.d.*
2.	Na_2CO_3	2	DCM	20	16	0	-
3.	K_2CO_3	2	DCM	20	16	0	-
4.	K_3PO_4	2	DCM	20	16	0	-
5.	Cs_2CO_3	2	DCM	20	5	82	*n.d.*
6.	Cs_2CO_3	1	DCM	20	5	36	*n.d.*
7.	Cs_2CO_3	0.2	DCM	20	5	0	-
8.	Cs_2CO_3	1	THF	20	5	45	45
9.	Cs_2CO_3	1	ACN	20	5	89	81
10.	Cs_2CO_3	1	Toluene	20	5	30	*n.d.*
11.	Cs_2CO_3	1	EtOAc	20	5	54	*n.d.*
12.	Cs_2CO_3	1.2	ACN	20	1	100	97

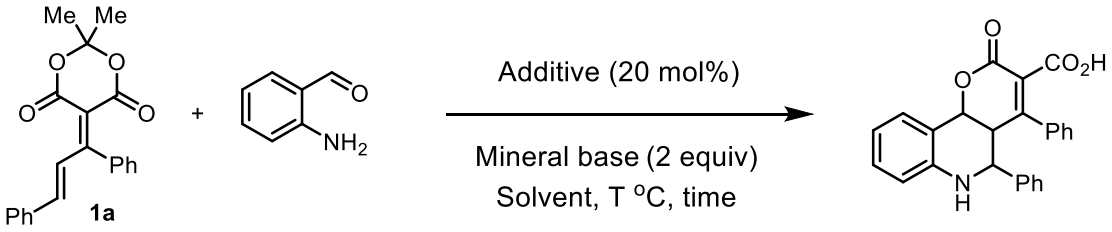
[a] Conversion was determined on a crude acid by the integration of the crude ^{1}H-NMR; [b] Isolated yield was determined on the methyl ester after the purification by column chromatography, recrystallization or washing with Et_2O; *n.d.* - for non-determined value.

III. Aza-nucleophiles investigated in the VMAC reaction

Preliminary investigations of several type of aza-nucleophiles (representative examples), known to be competent for a domino aza-Michael-aldol reaction, [1] were evaluation with vinylogous alkylidene Meldrum's acid **1a**. Eventually, none of them display the excellent reactivity of the α-ketoamides like **2a**.

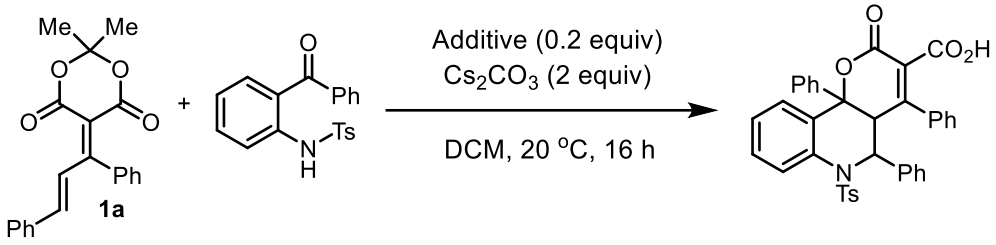


Entry	Additive	Base	Solvent	Time, h	T, °C	Conversion, %
1.	Quinuclidine	Na_2CO_3 in NaCl	Toluene	5	20	0
2.	Quinuclidine	Na_2CO_3 in NaCl	Toluene	16	50	0
3.	$BnEt_3N^+Cl^-$	Cs_2CO_3	Toluene	16	20	0
4.	$BnEt_3N^+Cl^-$	Cs_2CO_3	THF	16	20	0
5.	DBU	Cs_2CO_3	Toluene	16	20	0

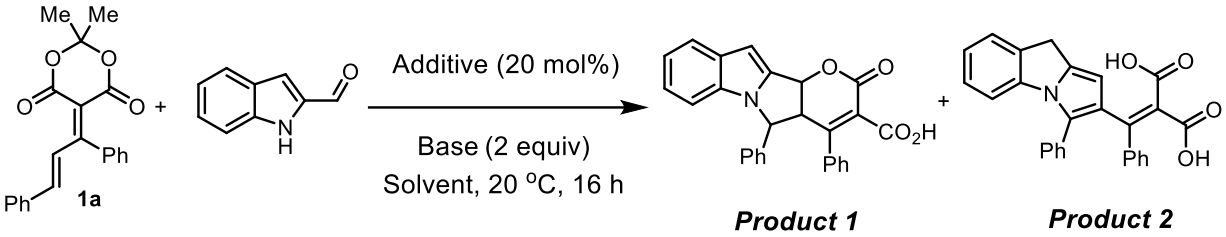


Entry	Additive	Base	Solvent	Time, h	T, °C	Conversion, %
1.	Quinuclidine	Na_2CO_3 in NaCl	Toluene	5	20	*degrad. of SM*
2.	DABCO	Na_2CO_3 in NaCl	Toluene	16	50	*degrad. of SM*
3.	$BnEt_3N^+Cl^-$	Cs_2CO_3	Toluene	16	20	*degrad. of SM*

[1] Song, Y.-X.; Du, D.-M. *Adv. Synth. Catal.* **2021**, *363*, 4667-4694.



Entry	Additive	Base	Solvent	Time, h	T, °C	Conversion, %
1.	Quinuclidine	Cs_2CO_3	DCM	16	20	0
2.	DBU	Cs_2CO_3	DCM	16	20	0
3.	-	Cs_2CO_3	DCM	16	20	0



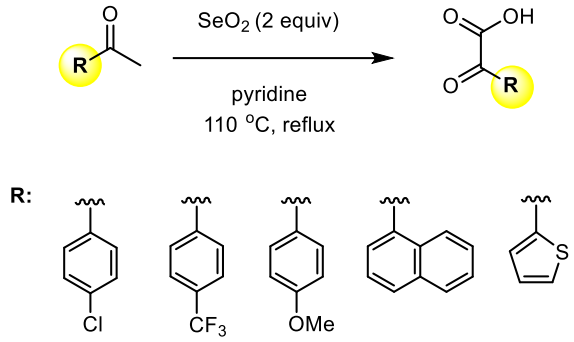
Entry	Additive	Base	Solvent	Conversion, % *Product 1* [a]	Conversion, % *Product 2*
1.	-	Cs_2CO_3	THF	28	51
2.	-	Cs_2CO_3	Toluene	28	6
3.	-	Cs_2CO_3	DCM	16	18
4.	-	K_3PO_4	DCM	0	0
5.	-	K_3PO_4	Toluene	0	0
6.	Quinuclidine	Cs_2CO_3	THF	8	92
7.	Quinuclidine	Cs_2CO_3	Toluene	25	4
8.	Quinuclidine	Cs_2CO_3	ACN	67	33
9.	Quinuclidine	Cs_2CO_3	ACN	49	40
10.	Quinuclidine	-	THF	0	0
11.	DBU	Cs_2CO_3	Toluene	36	12
12.	$BnEt_3N^+Cl^-$	Cs_2CO_3	Toluene	74	5
13.	$BnEt_3N^+Cl^-$	K_3PO_4	DCM	40 [b]	3
14.	$BnEt_3N^+Cl^-$	Cs_2CO_3	DCM	36 [c]	9
15.	$BnEt_3N^+Cl^-$	K_3PO_4	ACN	40 [d]	-

[a] Product **1** is unstable in the presence of the base and decompose, mainly to give a Product **2**, and cannot be stored for a long time (and partially decompose on the silica gel column); [b] Isolated yield for the methylated product is 40%; [c] Isolated yield for the methylated product is 36%; [d] Isolated yield for the methylated product is 40%.

IV. Experimental procedures

IV.1 synthesis of α-ketoamides (2)

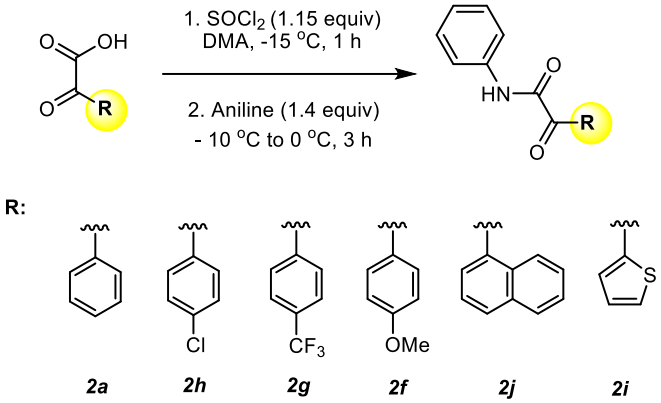
General procedure for the preparation of α-keto acids



α-keto acids commercially available or, otherwise, they were prepared according to the previously developed synthetic procedures.[2] In a dry flask equipped with reflux condenser, the corresponding aryl-ketone (1 equiv) and selenium dioxide (2 equiv) were added under the inert atmosphere, followed by anhydrous pyridine (5 mL). The reaction mixture was then stirred at 110 °C for 16 hours. After completion of the reaction, the solution was filtered on Celite and the residue was washed with EtOAc. The filtrate was treated with 1M aqueous NaOH (3 x 20 mL) and the aqueous layers were separated. Then the corresponding aqueous layers were acidified with 1M aqueous HCl to the pH=1.5. The mixture was then extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to provide the corresponding α-keto acid. Obtained acids were used without further purification for the next step.

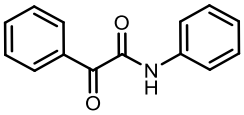
[2] Guillemard, G.; Colobert, F.; Wencel-Delord, J. *Adv. Synth. Catal.* **2018**, 4184-4190.

General procedure for the preparation of α-keto amides (2)



α-keto amides were prepared according to the previously developed procedures.[3] To a solution of α-keto acid (1 equiv) in *N*,*N*-dimethylacetamide (5 mL) cooled to −15 °C, $SOCl_2$ (1.15 equiv) was added dropwise. After stirring for 1 h at this temperature, aniline (1.4 equiv) was added and the mixture was stirred for 3 h at the temperatures between −10 °C and 0 °C, then poured onto a H_2O and stirred at rt overnight. The solid formed was dissolved in Et_2O or EtOAc and then extracted with the same solvent (3 × 20 mL). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo before the purification by flash column chromatography (pentane:Et_2O or PE:EtOAc).

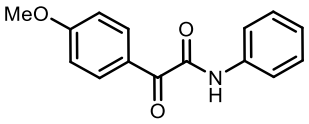
2-oxo-N,2-diphenylacetamide (*2a*)



Obtained according to the general procedure for the α-keto amides preparation as a light yellow solid **2a** after the column chromatography with Pentane/Et_2O as an eluent (625 mg, 82% yield). **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 8.94 (s, 1H), 8.50 – 8.36 (m, 2H), 7.78 – 7.62 (m, 3H), 7.59 – 7.48 (m, 2H), 7.48 – 7.35 (m, 2H), 7.25 – 7.17 (m, 1H). ^{1}H-NMR data is in agreement with the previously reported.[3]

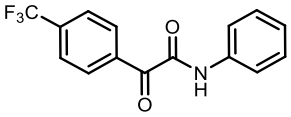
[3] Joie, C.; Deckers, K.; Enders, D. *Synthesis* **2014**, 799–808.

2-(4-methoxyphenyl)-2-oxo-N-phenylacetamide (*2f*)



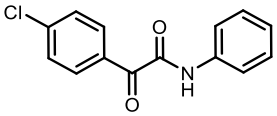
Obtained according to the general procedure for the α-keto amides preparation as a light yellow solid **2f** after the column chromatography with Pentane/Et_2O as an eluent (401 mg, 59% yield in two steps). **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 9.00 (s, 1H), 8.56 – 8.48 (m, 2H), 7.74 – 7.66 (m, 2H), 7.47 – 7.33 (m, 2H), 7.23 – 7.16 (m, 1H), 7.05 – 6.93 (m, 2H). ^{1}H-NMR data is in a well-agreement with the previously reported.[3]

2-oxo-N-phenyl-2-(4-(trifluoromethyl)phenyl)acetamide (*2g*)



Obtained according to the general procedure for the α-keto amides preparation as a yellow solid **2g** after the column chromatography with PE/Et_2O as an eluent (380 mg, 49% yield in two steps). **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 8.93 (s, 1H), 8.59 – 8.49 (m, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.74 – 7.67 (m, 2H), 7.47 – 7.38 (m, 2H), 7.25 – 7.19 (m, 1H). ^{1}H-NMR data is in a well-agreement with the previously reported.[4]

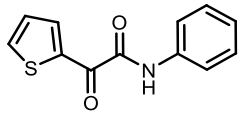
2-(4-chlorophenyl)-2-oxo-N-phenylacetamide (*2h*)



Obtained according to the general procedure for the α-keto amides preparation as a light yellow solid **2h** after the column chromatography with Pentane/Et_2O as an eluent (646 mg, 65% yield in two steps). **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 8.94 (s, 1H), 8.50 – 8.33 (m, 2H), 7.75 – 7.63 (m, 2H), 7.54 – 7.46 (m, 2H), 7.46 – 7.36 (m, 2H), 7.25 – 7.16 (m, 1H). ^{1}H-NMR data is in agreement with the previously reported.[5]

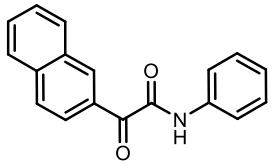
[4] Sagadevan, A.; Ragupathi, A.; Lin, C.-C.; Hwu, J.R.; Hwang, K.C. *Green Chem*. **2015**, 1113-1119.
[5] Shao, J.; Huang, X.; Wang, S.; Liu, B.; Xu, B. *Tetrahedron* **2012**, 573-579.

2-oxo-N-phenyl-2-(thiophen-2-yl)acetamide (*2i*)



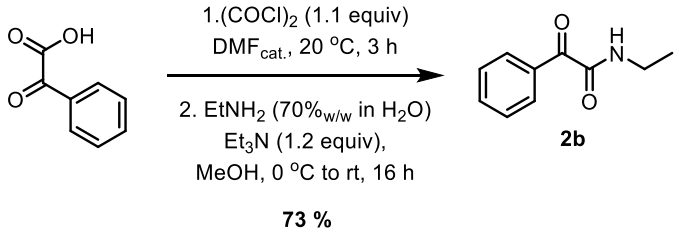
Obtained according to the general procedure for the α-keto amides synthesis as a yellow solid **2i** after the column chromatography with PE/EtOAc as an eluent (567 mg, 74% yield in two steps). **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 9.10 (s, 1H), 8.49 (d, *J* = 3.9 Hz, 1H), 7.89 (d, *J* = 4.9 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.45 – 7.36 (m, 2H), 7.23 (m, 2H). ^{1}H-NMR data is in a well-agreement with the previously reported.[4]

2-(naphthalen-2-yl)-2-oxo-N-phenylacetamide (*2j*)



Obtained according to the general procedure for the α-keto amides preparation as a yellow solid **2j** after the column chromatography with Pentane/Et_2O as an eluent (394 mg, 54% yield in two steps). **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 9.34 – 9.29 (m, 1H), 9.03 (s, 1H), 8.26 (dd, *J* = 8.7, 1.7 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.97 – 7.86 (m, 2H), 7.78 – 7.71 (m, 2H), 7.70 – 7.62 (m, 1H), 7.62 – 7.54 (m, 1H), 7.47 – 7.39 (m, 2H), 7.22 (t, *J* = 7.4 Hz, 1H). ^{1}H-NMR data is in a well-agreement with the previously reported.[4]

General procedure for the preparation of the N-ethyl-2-oxo-2-phenylacetamide (2b)

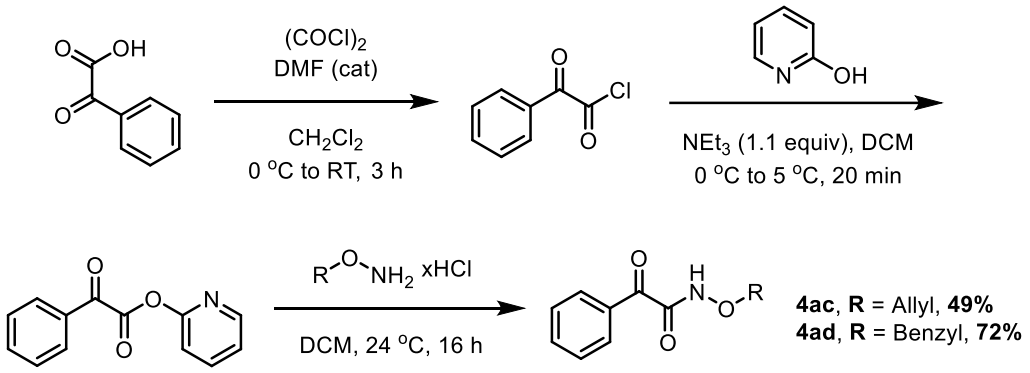


73 %

To a stirred solution of phenylglyoxylic acid (1 equiv) in DCM, the solution of oxalyl chloride (1.1 equiv) was added dropwise at 0 °C under the inert atmosphere, followed with the drop of DMF as a catalyst. Then a reaction mixture was stirred for 3h at the room temperature, until the evolution of gas was not observed. After the reaction was complete, all the volatiles were removed under the vacuum. Obtained phenyl glyoxylic acid chloride was suspensed in MeOH and the solution of $EtNH_2$ (70%$_{w/w}$ in H_2O, 1.4 equiv) was added added at 0-5 °C, followed with the distilled NEt_3 (1.2 equiv). Then the reaction mixture was left to warm and stir overnight,

diluted with water and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with HCl (3 M), $NaHCO_{3(sat.)}$, dried over $MgSO_4$ and evaporated under reduced pressure. Purification on silica gel column with the PE:EtOAc as an eluent provided a desired product **2b** with the 73% yield (259 mg) as the yellowish oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.38 – 8.31 (m, 2H), 7.67 – 7.58 (m, 1H), 7.52 – 7.44 (m, 2H), 7.06 (s, 1H), 3.50 – 3.38 (m, 2H), 1.26 (t, *J* = 7.3 Hz, 3H). Data is in a well agreement with the previously reported.[6]

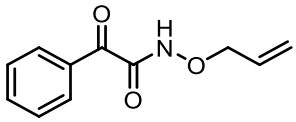
General Procedure for the preparation of N-Alkoxy-α-oxoarylacetamides (2c) and (2d)



N-Alkoxy-α-oxoarylacetamides were obtained according to the procedure reported by Geffken and Haerting.[7] To a stirred solution of phenylglyoxylic acid (1 equiv) in DCM, the solution of oxalyl chloride (1.1 equiv) was added dropwise at 0 °C under the inert atmosphere, followed by the drop of DMF as a catalyst. Then a reaction mixture was stirred for 3h at the room temperature, until the evolution of the gas was not observed. After the temperature of the reaction mixture was again decreased to 0 °C, and the 2-pyridone (1 equiv) and triethylamine (1.2 equiv) were added slowly. A reaction mixture was left stirring for 10 minutes at ambient temperature, followed by the addition of the O-alkylhydroxylamine (1 equiv in 5 mL of DCM) and left stirring overnight. Diethyl ether was added and the mixture was washed with HCl (3 M), $NaHCO_3$ dried over $MgSO_4$ and evaporated. The residues were purified by Silica gel column with PE : Acetone or PE : EtOAc as an eluent providing the desired products as the yellowish oils (R=Allyl ***2c***: 337 mg, 49% with the 93% purity after the purification; R=Bn ***2d***: 612 mg, 72%).

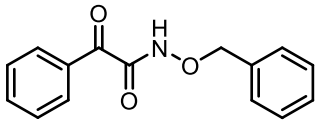
[6] Rajasekhara, R.; Selvaraj, S.; Anju, C. *Synth. Commun.* **2012**, 3493–3503.
[7] Geffken, D.; Haerting, M. *Synth. Comm.* **1996**, 4153–4156.

N-(allyloxy)-2-oxo-2-phenylacetamide (*2c*)



N-(allyloxy)-2-oxo-2-phenylacetamide was ***2c*** obtained according to the general procedure for the preparation of N-Alkoxy-α-oxoarylacetamides as a yellow oil after the purification by column chromatography (337 mg, 49% with the 93% purity). **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 9.30 (s, 1H), 8.38 – 8.24 (m, 2H), 7.72 – 7.61 (m, 1H), 7.56 – 7.46 (m, 2H), 6.14 – 5.94 (m, 1H), 5.50 – 5.35 (m, 2H), 4.61 – 4.43 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ_C 187.1 (C), 159.2 (C), 134.9 (CH), 133.0 (C), 131.5 (CH), 131.0 (CH), 128.7 (CH), 121.7 (CH_2), 77.8 (CH_2). **IR (neat)** ν_{max} 3188, 2985, 1658, 1596, 1579, 1492, 1449, 1420, 1342, 1319, 1289, 1218, 1179, 1160, 1064, 1026, 1000, 975, 931, 906, 845, 809, 746, 676, 614, 515, 452 cm^{-1}. *Thus far we were unable to obtain any correct analyses by mass spectrometry due to instability issue of this compound.*

N-(benzyloxy)-2-oxo-2-phenylacetamide (*2d*)

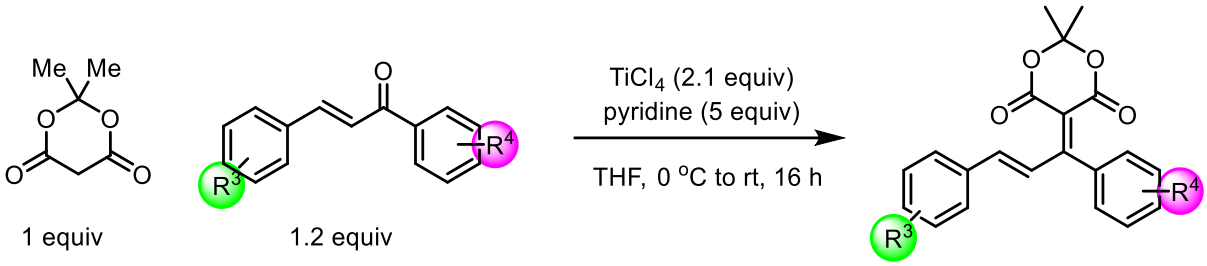


N-(benzyloxy)-2-oxo-2-phenylacetamide was ***2d*** obtained according to the general procedure for the preparation of N-Alkoxy-α-oxoarylacetamides as a yellow oil after the purification by column chromatography (612 mg, 72%). **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 9.19 (s, 1H), 8.33 – 8.17 (m, 2H), 7.72 – 7.60 (m, 1H), 7.56 – 7.31 (m, 7H), 5.05 (s, 2H). In a well agreement with the previously reported data.[8]

[8] Bera, T.; Singh, B.; Jana, M.; Saha, J. *Chem. Commun*. **2022**, 7538-7541.

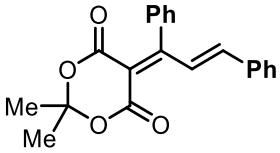
IV.2 Synthesis of vinylogous alkylidene Meldrum's acid derivatives (1)

General Procedure for the preparation of Alkylidene Meldrum's Acids (1)



Vinylogous alkylidene Meldrum's acid were synthesized following the reported procedure and the corresponding references were mentioned when the molecules were known (*vide infra*).[9] $TiCl_4$•2THF complex suspension was prepared by dropwise addition of $TiCl_4$ (2.1 equiv) to anhydrous THF (0.5 M) at 0 °C under inert atmosphere. Then a solution of Meldrum's acid (1.0 equiv) and enone (1.2 equiv) in anhydrous THF (1.0 M) under Ar atmosphere was added to the $TiCl_4$•2THF complex suspension. Pyridine (5.0 equiv) was eventually added, and the mixture was stirred at rt for 16 h. The reaction was quenched at 0 °C by addition of water (4 mL), then it was washed with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was then purified either by trituration or flash column chromatography over silica gel.

(*E*)-5-(1,3-diphenylallylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (*1a*)

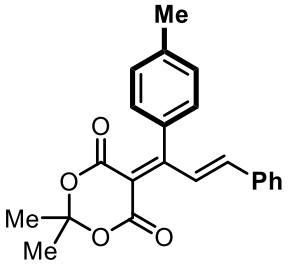


^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.70 (d, *J* = 15.9 Hz, 1H), 7.53–7.45 (m, 5H), 7.39–7.35 (m, 3H), 7.22–7.18 (m, 2H), 6.71 (d, *J* = 15.9 Hz, 1H), 1.83 (s, 6H). ^{1}H-NMR data is in a well-agreement with the previously reported ones.[10]

[9] (a) Baxter, G. J.; Brown, R. F. C. *Aust. J. Chem.* **1975** *28*, 1551. (b) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774.

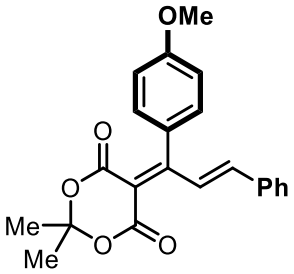
[10] Milbeo, P.; Lebrêne, A.; Savchuk, M.; Vo-Thanh, G.; Oudeyer, S.; Beucher, H.; Brière, J.-F. *Chem. Eur. J.* **2023**, pp.e202301311.

(*E*)-2,2-dimethyl-5-(1-(4-methylphenyl)-3-phenylallylidene)-1,3-dioxane-4,6-dione (*1b*)



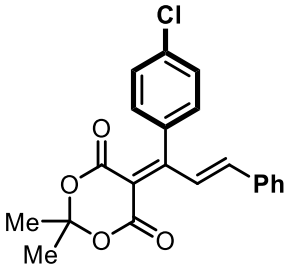
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.70 (d, *J* = 15.8 Hz, 1H), 7.57–7.48 (m, 2H), 7.41–7.33 (m, 3H), 7.30–7.23 (m, 2H), 7.13–7.07 (m, 2H), 6.75 (d, *J* = 15.8 Hz, 1H), 2.44 (s, 3H), 1.83 (s, 6H). ^{1}H-NMR data is in a well-agreement with the previously reported ones.[10]

(*E*)-5-(1-(4-methoxyphenyl)-3-phenylallylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (*1c*)



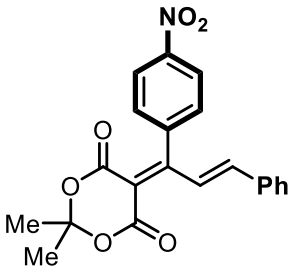
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.68 (d, *J* = 15.7 Hz, 1H), 7.58–7.49 (m, 2H), 7.42–7.33 (m, 3H), 7.22–7.11 (m, 2H), 7.03–6.93 (m, 2H), 6.77 (d, *J* = 15.8 Hz, 1H), 3.88 (s, 3H), 1.83 (s, 6H). ^{1}H-NMR data is in a well-agreement with the previously reported ones.[10]

(*E*)-5-(1-(4-chlorophenyl)-3-phenylallylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (*1d*)



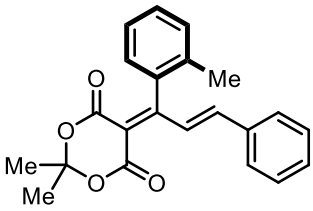
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.68 (d, *J* = 15.8 Hz, 1H), 7.56–7.48 (m, 2H), 7.48–7.43 (m, 2H), 7.41–7.35 (m, 3H), 7.19–7.08 (m, 2H), 6.69 (d, *J* = 15.8 Hz, 1H), 1.82 (s, 6H). ^{1}H-NMR data is in a well-agreement with the previously reported ones.[10]

(*E*)-2,2-dimethyl-5-(1-(4-nitrophenyl)-3-phenylallylidene)-1,3-dioxane-4,6-dione (*1e*)



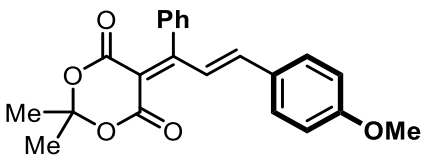
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.72 (d, *J* = 16.0 Hz, 1H), 8.36–8.32 (m, 2H), 7.52-7.49 (m, 2H), 7.41–7.36 (m, 5H), 6.58 (d, *J* = 16.0 Hz, 1H), 1.83 (s, 6H). ^{1}H-NMR data is in a well-agreement with the previously reported ones.[10]

(E)-2,2-dimethyl-5-(3-phenyl-1-(o-tolyl)allylidene)-1,3-dioxane-4,6-dione (*1f*)



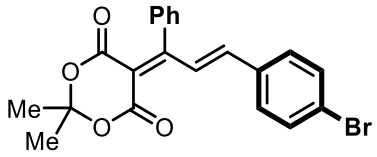
The compound was prepared according to the standard procedure for the Alkylidene Meldrum's Acid synthesis. The title product **1f** was obtained with an 11% isolated yield (m=84 mg), as a yellow solid after the purification by column chromatography (PE:EtOAc = 80:20). **Mp** = 141-143 ^{o}C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 8.63 (d, *J* = 15.7 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.42 – 7.32 (m, 4H), 7.31 – 7.26 (m, 1H), 7.26 – 7.23 (m, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 15.7 Hz, 1H), 2.20 (s, 3H), 1.84 (s, 3H), 1.77 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ_C 167.0 (C), 161.8 (C), 160.3 (C), 149.6 (CH), 136.7 (C), 135.6 (C), 135.5 (C), 131.1 (CH), 130.1 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 127.0 (CH), 126.7 (CH), 125.7 (CH), 113.9 (C), 103.8 (C), 27.7 (CH_3), 27.4 (CH_3), 19.7 (CH_3). **IR (neat)** ν_{max} 1726, 1602, 1572, 1544, 1446, 1393, 1312, 1269, 1278, 1217, 1197, 1082, 1018, 999, 977, 928, 875, 866, 836, 766, 757, 730, 694, 637, 561, 519, 499, 472, 433, 416 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{22}H_{20}O_4Na^+$ 371.1259; Found 371.1257.

(*E*)-5-(3-(4-methoxyphenyl)-1-phenylallylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (*1g*)



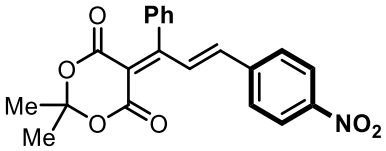
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.63 (d, *J* = 15.7 Hz, 1H), 7.49–7.43 (m, 5H), 7.21–7.17 (m, 2H), 6.90–6.85 (m, 2H), 6.68 (d, *J* = 15.7 Hz, 1H), 3.84 (s, 3H), 1.82 (s, 6H). ^{1}H-NMR data is in a well-agreement with the previously reported ones.[10]

(*E*)-5-(3-(4-bromophenyl)-1-phenylallylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (*1h*)



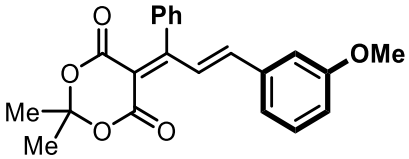
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.67 (d, *J* = 15.8 Hz, 1H), 7.53–7.43 (m, 5H), 7.40–7.33 (m, 2H), 7.21–7.14 (m, 2H), 6.62 (d, *J* = 15.8 Hz, 1H), 1.83 (s, 6H). ^{1}H-NMR data is in a well-agreement with the previously reported ones.[10]

(*E*)-2,2-dimethyl-5-(3-(4-nitrophenyl)-1-phenylallylidene)-1,3-dioxane-4,6-dione (*1i*)



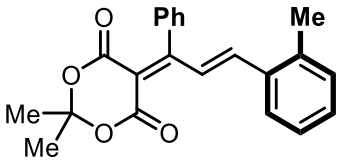
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.76 (d, *J* = 15.9 Hz, 1H), 8.27–8.15 (m, 2H), 7.71–7.58 (m, 2H), 7.55–7.44 (m, 3H), 7.24–7.16 (m, 2H), 6.70 (d, *J* = 15.9 Hz, 1H), 1.84 (s, 6H). ^{1}H-NMR data is in a well-agreement with the previously reported ones.[10]

(*E*)-5-(3-(3-methoxyphenyl)-1-phenylallylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (*1j*)



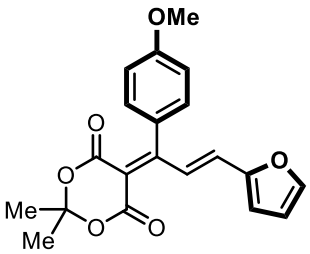
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.68 (d, *J* = 15.8 Hz, 1H), 7.51–7.42 (m, 3H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.23–7.16 (m, 2H), 7.13–7.07 (m, 1H), 7.02–6.98 (m, 1H), 6.96–6.89 (m, 1H), 6.67 (d, *J* = 15.8 Hz, 1H), 3.82 (s, 3H), 1.83 (s, 6H). ^{1}H-NMR data is in a well-agreement with the previously reported ones.[10]

(*E*)-2,2-dimethyl-5-(3-(2-methylphenyl)-1-phenylallylidene)-1,3-dioxane-4,6-dione (*1k*)



^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.60 (d, *J* = 15.7 Hz, 1H), 7.78–7.69 (m, 1H), 7.52–7.40 (m, 3H), 7.26–7.17 (m, 4H), 7.17–7.10 (m, 1H), 7.01 (d, *J* = 15.7 Hz, 1H), 2.10 (s, 3H), 1.83 (s, 6H). ^{1}H-NMR data is in a well-agreement with the previously reported ones.[9]

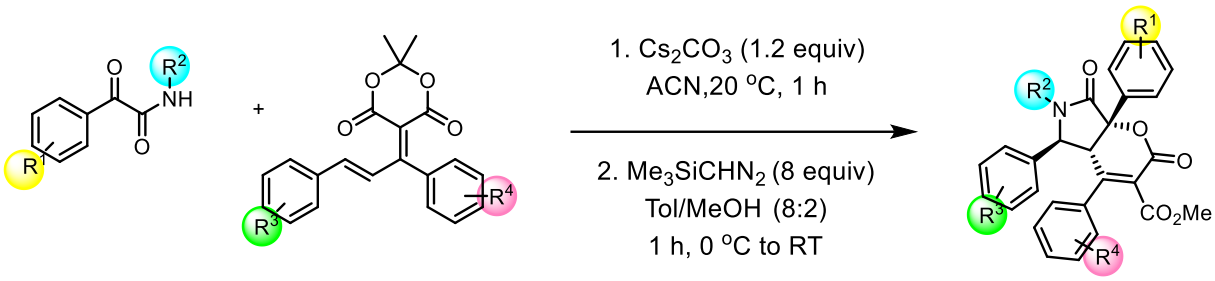
(E)-5-(3-(furan-2-yl)-1-(4-methoxyphenyl)allylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (*1l*)



^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.50 (d, *J* = 15.5 Hz, 1H), 7.56 (d, *J* = 1.8 Hz, 1H), 7.19–7.08 (m, 2H), 7.02–6.91 (m, 2H), 6.61 (d, *J* = 3.4 Hz, 1H), 6.52 (d, *J* = 15.5 Hz, 1H), 6.48 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.87 (s, 3H), 1.81 (s, 6H). ^{1}H-NMR data is in a well-agreement with the previously reported ones.[10]

IV.3 Synthesis of the aza-VMAC reaction product (4)

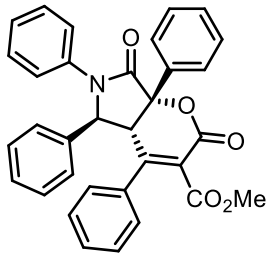
General procedure for the domino aza-Michael-aldol-cyclocondensation reaction



α-ketoamide (1.2 equiv) and alkylidene Meldrum's acid **MA** (1.0 equiv) were dissolved in anhydrous acetonitrile (1.5 mL, 0.04 M) under inert atmosphere. Then the Cs_2CO_3 (1.2 equiv) was added, the tube was sealed and the resulting heterogeneous mixture was vigorously stirred at 20 °C for the given time (around 1 h) under inert atmosphere. After the reaction was quenched by dropwise addition of HCl (2 mL, 1 M in H_2O) and diluted with EtOAc (4 mL). The organic phases were washed with HCl 1M (2 × 3 mL) and the combined aqueous phases were extracted twice with EtOAc (2 × 3 mL), dried over $MgSO_4$ and concentrated under a reduced pressure. The resulting crude was used without further purification in the methylation step.

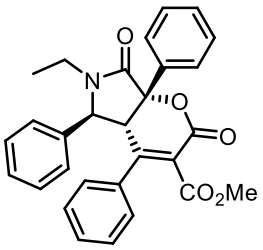
A solution of the crude carboxylic acid in PhMe/MeOH (2.0 mL, 80:20 v/v) was cooled down to 0 °C with an iced bath and then the trimethylsilyldiazomethane (8 equiv, 2 M in hexane) was added dropwise. The reaction mixture was stirred at 0 °C for 15 min then at room temperature for 15 min. The excess of $TMSCHN_2$ was quenched by dropwise addition of acetic acid at 0 °C. Then the mixture was stirred at 0 °C for 5 min, then at room temperature for 10 min. After that the reaction mixture was diluted with EtOAc, washed with water (2 × 3 mL), $NaHCO_3$ (1 × 3 mL) and brine (1 × 3 mL), dried over $MgSO_4$ and concentrated under the reduced pressure. The crude mixture was purified by flash column chromatography with the PE:EtOAc as an eluent.

(±) Methyl 2,7-dioxo-4,5,6,7a-tetraphenyl-2,4a,5,6,7,7a-hexahydropyrano [2,3-c]pyrrole-3-carboxylate (*4aa*)



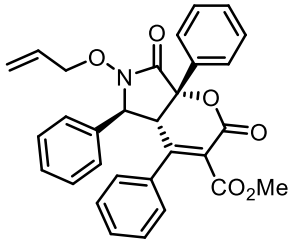
The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1a** (24.7 mg, 0.07 mmol, 1.0 equiv) and α-ketoamide **2a** (20 mg, 0.09 mmol, 1.2 equiv) in ACN (0.04 M). The crude product was obtained diastereomerically pure (100% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4aa** (35 mg, 92%). The compound can be also purified by washing with Et_2O with the 97% yield. The reaction was performed on 1 mmol scale as well. Purification was done by washing with Et_2O (434 mg, 84%) and then the filtrate was evaporated and purified by silica gel column (49 mg, 10%). The desired product was isolated with 94% yield total. **Mp** = 256-257 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 7.66 – 7.58 (m, 2H), 7.57 – 7.41 (m, 3H), 7.32 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 7.14 – 7.04 (m, 3H), 7.02 – 6.89 (m, 7H), 5.28 (d, *J* = 7.9 Hz, 1H), 3.96 (d, *J* = 8.0 Hz, 1H), 3.64 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 167.8 (C), 164.9 (C), 159.4 (C), 152.0 (C), 136.6 (C), 136.4 (C), 136.3 (C), 134.8 (C), 130.7 (CH), 129.5 (CH), 129.2 (CH), 128.9 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 127.3 (CH), 127.1 (CH), 126.5 (CH), 126.2 (CH), 124.0 (CH), 123.8 (C), 86.4 (C), 67.0 (CH), 53.0 (CH_3), 52.5 (CH). **IR (neat)** ν_{max} 1746, 1722, 1634, 1598, 1494, 1447, 1432, 1379, 1355, 1312, 1284, 1193, 1139, 1112, 1076, 1066, 1044, 997, 968, 931, 828, 793, 777, 762, 749, 727, 712, 691, 619, 610, 590, 564, 533, 501, 488, 425 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + H]^+$ Calcd for $C_{33}H_{26}NO_5^+$ 516.1811; Found 516.1828.

(±) Methyl 6-ethyl-2,7-dioxo-4,5,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4ab)



The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1a** (20.4 mg, 0.06 mmol, 1.0 equiv) and α-ketoamide **2b** (13 mg, 0.07 mmol, 1.2 equiv) in ACN (0.04 M) after the overnight stirring with the 2 equiv of Cs_2CO_3 as a base. The crude product was obtained diastereomerically pure (74% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4ab** (21 mg, 73%). **Mp** = 73-76 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.59 – 7.52 (m, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.45 – 7.38 (m, 1H), 7.20 – 7.09 (m, 4H), 7.05 (t, *J* = 7.6 Hz, 2H), 7.02 – 6.95 (m, 2H), 6.95 – 6.88 (m, 2H), 4.67 (d, *J* = 8.0 Hz, 1H), 3.83 (h, *J* = 7.0 Hz, 1H), 3.76 (d, *J* = 8.0 Hz, 1H), 3.61 (s, 3H), 2.72 (h, *J* = 6.7 Hz, 1H), 1.03 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ_C 168.5 (C), 164.9 (C), 159.5 (C), 152.2 (C), 136.8 (C), 136.2 (C), 134.8 (C), 130.5 (CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.6 (CH), 127.2 (CH), 125.9 (CH), 123.3 (C), 86.2 (C), 65.3 (CH), 53.0 (CH), 52.9 (CH_3), 36.5 (CH_2), 12.0 (CH_3). **IR (neat)** ν_{max} 1744, 1712, 1596, 1414, 1369, 1307, 1282, 1233, 1138, 1066, 1042, 929, 838, 750, 697, 641, 610, 514, 426, 406 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{29}H_{25}NO_5Na^+$ 490.1630; Found 490.1620.

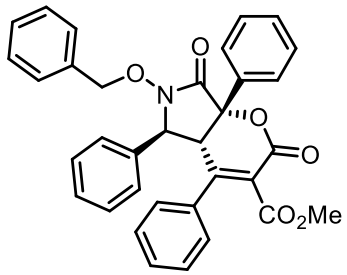
(±) Methyl 6-(allyloxy)-2,7-dioxo-4,5,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c] pyrrole-3-carboxylate (*4ac*)



The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1a** (27.2 mg, 0.08 mmol, 1.0 equiv) and α-ketoamide **2c** (21.3 mg, 0.098 mmol, 1.2 equiv, 94% pure) in ACN (0.04 M) after 1 h stirring. The crude product was

obtained diastereomerically pure (100% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4ac** (32.6 mg, 81%). **Mp** = 170-173 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 7.59 – 7.39 (m, 5H), 7.23 – 7.00 (m, 8H), 6.91 (d, *J* = 7.7 Hz, 2H), 5.84 (m, *J* = 16.9, 6.7 Hz, 1H), 5.38 – 5.22 (m, 2H), 4.83 (d, *J* = 8.1 Hz, 1H), 4.55 – 4.41 (m, 1H), 4.39 – 4.26 (m, 1H), 3.81 (d, *J* = 8.2 Hz, 1H), 3.61 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 164.6 (C), 164.6 (C), 159.0 (C), 151.3 (C), 136.2 (C), 134.9 (C), 134.5 (C), 131.7 (CH), 130.6 (CH), 129.6 (CH), 129.3 (CH), 129.2 (CH), 128.9 (CH), 128.7 (CH), 127.5 (CH), 127.3 (CH), 125.8 (CH), 123.6 (C), 122.1 (CH_2), 83.8 (C), 76.6 (CH_2), 66.3 (CH), 52.9 (CH_3), 50.7 (CH). **IR (neat)** ν_{max} 2955, 1741, 1707, 1617, 1497, 1459, 1447, 1432, 1368, 1311, 1279, 1244, 1204, 1184, 1092, 1081, 1054, 1030, 999, 983, 935, 911, 879, 839, 799, 779, 771, 714, 662, 646, 619, 605, 593, 521, 498, 477, 448, 436, 419 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + H]^+$ Calcd for $C_{30}H_{26}NO_6^+$ 496.1760; Found 496.1759. $[M + Na]^+$ Calcd for $C_{30}H_{25}NO_6Na^+$ 518.1580; Found 518.1577. $[M + K]^+$ Calcd for $C_{30}H_{25}NO_6K^+$ 534.1319; Found 534.1315.

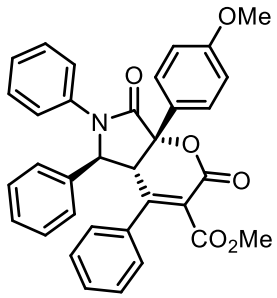
(±) Methyl 6-(benzyloxy)-7a-(4-methoxyphenyl)-2,7-dioxo-4,5-diphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c] pyrrole-3-carboxylate (*4ad*)



The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1a** (21.8 mg, 0.07 mmol, 1.0 equiv) and α-ketoamide **2c** (20 mg, 0.08 mmol, 1.2 equiv) in ACN (0.04 M) after 1h stirring. The crude product was obtained diastereomerically pure (94% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4ad** (26.2 mg, 74%). **Mp** = 167-168 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 7.50 – 7.34 (m, 5H), 7.34 – 7.24 (m, 3H), 7.20 (s, 1H), 7.18 – 7.15 (m, 1H), 7.13 – 6.99 (m, 4H), 6.99 – 6.92 (m, 2H), 6.80 – 6.69 (m, 4H), 5.14 (d, *J* = 10.6 Hz, 1H), 4.74 (d, *J* = 10.6 Hz, 1H), 3.98 (d, *J* = 8.0 Hz, 1H), 3.62 (d, *J* = 8.0 Hz, 1H), 3.53 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 164.6 (C), 164.0 (C), 158.9 (C), 151.3 (C), 136.3 (C), 135.0 (C), 134.4 (C), 134.3 (C), 130.6 (CH), 130.4 (CH), 129.5 (CH), 129.3 (CH), 129.0 (CH), 128.8 (CH), 128.8 (CH), 128.6 (CH), 127.3 (CH), 127.2 (CH), 125.8 (CH), 123.4

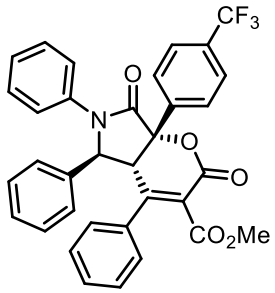
(C), 83.8 (C), 77.0 (CH_2), 66.7 (CH), 52.9 (CH_3), 50.8 (CH). **IR (neat)** ν_{max} 1734, 1496, 1448, 1364, 1309, 1283, 1243, 1091, 1079, 1051, 1031, 908, 801, 751, 696, 643, 599, 506, 438, 409 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{34}H_{27}NO_6Na^+$ 568.1736; Found 568.1720.

(±) Methyl 7a-(4-methoxyphenyl)-2,7-dioxo-4,5,6-triphenyl-2,4a,5,6,7,7a-hexahydropyrano [2,3-c]pyrrole-3-carboxylate (*4af*)



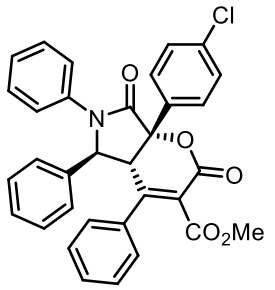
The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1a** (21.8 mg, 0.07 mmol, 1.0 equiv) and α-ketoamide **2f** (20 mg, 0.08 mmol, 1.2 equiv) in ACN (0.04 M) after 1h of reaction. The crude product was obtained diastereomerically pure. Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product **4af** as a white powder (33 mg, 93%, >99% dr). It is also possible to recrystallize the product from EtOAc/pentane. **Mp** = 203 – 209 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.60 – 7.52 (m, 2H), 7.30 – 7.26 (m, 2H), 7.24 – 7.17 (m, 3H), 7.15 – 7.04 (m, 3H), 7.03 – 6.95 (m, 7H), 6.94 – 6.90 (m, 2H), 5.26 (d, *J* = 7.8 Hz, 1H), 3.95 (d, *J* = 7.9 Hz, 1H), 3.84 (s, 3H), 3.63 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ_C 167.9 (C), 165.2 (C), 159.5 (C), 152.1 (C), 141.3 (C), 136.7 (C), 136.5 (C), 136.3 (C), 131.9 (C), 129.5 (CH), 129.4 (CH), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 127.4 (CH), 127.1 (CH), 126.4 (CH), 126.3 (CH), 123.93 (CH), 123.0 (C), 86.3 (C), 67.1 (CH), 52.9 (CH_3), 52.3 (CH), 21.4 (CH_3). **IR (neat)** ν_{max} 1717, 1611, 1515, 1495, 1459, 1435, 1364, 1311, 1284, 1237, 1182, 1140, 1068, 1043, 1025, 968, 920, 837, 816, 766, 743, 690, 580, 559, 527, 505, 463, 417 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{34}H_{27}NO_6Na^+$ 568.1736; Found 568.1733.

(±) Methyl 2,7-dioxo-4,5,6-triphenyl-7a-(4-(trifluoromethyl)phenyl)-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (*4ag*)



The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1a** (19 mg, 0.06 mmol, 1.0 equiv) and α-ketoamide **2g** (20 mg, 0.07 mmol, 1.2 equiv) in ACN (0.04 M) after 1h of reaction. The crude product was obtained diastereomerically pure (100% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4ag** (29.3 mg, 88%). **Mp** = 198 – 203 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.83 – 7.71 (m, 4H), 7.31 – 7.26 (m, 2H), 7.25 – 7.18 (m, 3H), 7.15 – 7.06 (m, 3H), 7.04 – 6.91 (m, 7H), 5.30 (d, *J* = 7.9 Hz, 1H), 3.95 (d, *J* = 7.9 Hz, 1H), 3.65 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ_C 167.3 (C), 164.6 (C), 159.0 (C), 151.8 (C), 140.2 (C), 136.2 (C), 134.5 (C), 131.5 (q, *J* = 33.9 Hz, $^2J_{C-F}$), 130.9 (CH), 129.0 (CH), 128.9 (CH), 128.9 (CH), 128.8 (CH), 127.3 (CH), 127.1 (CH), 126.8 (CH), 126.7 (CH), 126.3 (q, *J* = 3.7 Hz, $^3J_{C-F}$), 124.0 (CH), 123.98 (q, *J* = 272.4 Hz, $^1J_{C-F}$), 123.7 (C), 86.0 (C), 67.2 (CH), 53.0 (CH_3), 52.3 (CH). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -62.85. **IR (neat)** ν_{max} 1718, 1598, 1494, 1436, 1364, 1324, 1236, 1168, 1124, 1068, 1043, 1015, 845, 759, 693, 595, 565, 513, 443, 406 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{34}H_{24}NO_5F_3Na^+$ 606.1504; Found 606.1503.

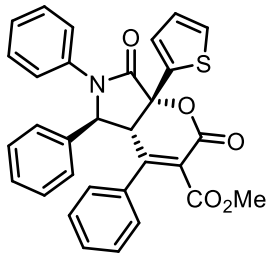
(±) Methyl 7a-(4-chlorophenyl)-2,7-dioxo-4,5,6-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (*4ah*)



The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1a** (21.5 mg, 0.06 mmol, 1.0 equiv) and α-ketoamide **2h** (20 mg,

0.08 mmol, 1.2 equiv) in ACN (0.03M). The crude product was obtained diastereomerically pure (100% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4ah** (33.0 mg, 93%). **Mp** = 223 - 226 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.59 – 7.53 (m, 2H), 7.52 – 7.45 (m, 2H), 7.31 – 7.26 (m, 2H), 7.25 – 7.18 (m, 3H), 7.15 – 7.05 (m, 3H), 7.04 – 6.90 (m, 7H), 5.28 (d, *J* = 7.9 Hz, 1H), 3.91 (d, *J* = 7.9 Hz, 1H), 3.64 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ_C 167.5 (C), 164.7 (C), 159.1 (C), 151.9 (C), 136.3 (C), 135.8 (C), 134.7 (C), 130.8 (CH), 129.5 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 127.8 (CH), 127.3 (CH), 127.1 (CH), 126.6 (CH), 123.9 (CH), 123.8 (C), 85.9 (C), 67.0 (CH), 53.0 (CH_3), 52.2 (CH). **IR (neat)** ν_{max} 1755, 1722, 1495, 1359, 1312, 1236, 1066, 1046, 1012, 808, 761, 721, 693, 569, 514, 476, 420, 407 cm^{-1}. **HRMS (ESI/TOF) m/z:** $[M + Na]^+$ Calcd for $C_{33}H_{24}NO_5{}^{35}ClNa^+$ 572.1241; Found 572.1221; $[M + Na]^+$ Calcd for $C_{33}H_{24}NO_5{}^{37}ClNa^+$ 574.1211; Found 574.1226.

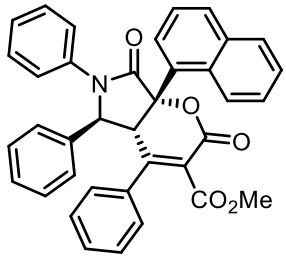
(±) Methyl 2,7-dioxo-4,5,6-triphenyl-7a-(thiophen-2-yl)-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (*4ai*)



The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1a** (26.5 mg, 0.08 mmol, 1.0 equiv) and α-ketoamide **2i** (22 mg, 0.1 mmol, 1.2 equiv) in ACN (0.04 M) after 1h of reaction. The crude product was obtained diastereomerically pure (84% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4ai** (31.2 mg, 75%). **Mp** = 239 – 242 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.53 – 7.50 (m, 1H), 7.48 – 7.45 (m, 1H), 7.28 – 7.26 (m, 1H), 7.26 – 7.17 (m, 4H), 7.17 – 7.04 (m, 6H), 7.01 – 6.91 (m, 3H), 6.90 – 6.83 (m, 2H), 5.23 (d, *J* = 7.7 Hz, 1H), 4.05 (d, *J* = 7.7 Hz, 1H), 3.65 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ_C 166.8 (C), 164.9 (C), 158.8 (C), 152.2 (C), 138.3 (C), 136.3 (C), 136.2 (C), 134.8 (C), 130.8 (CH), 128.94 (CH), 128.89 (CH), 128.79 (CH), 128.6 (CH) , 128.1 (CH), 128.1 (CH), 127.6 (CH), 127.4 (CH), 127.1 (CH), 126.6 (CH), 124.0 (C), 123.9 (CH), 83.1 (C), 66.9 (CH), 53.0 (CH_3), 52.1 (CH). **IR (neat)** ν_{max} 1750, 1725, 1623, 1598, 1494, 1432, 1361, 1380, 1351, 1311,

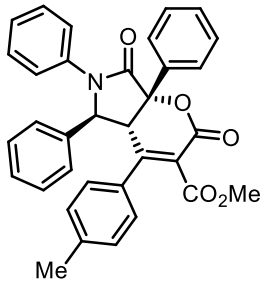
1237, 1075, 1065, 996, 910, 762, 724, 691, 580, 556, 405 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{31}H_{23}NO_5SNa^+$ 544.1195; Found 544.1193.

(±) Methyl 7a-(naphthalen-1-yl)-2,7-dioxo-4,5,6-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (*4aj*)



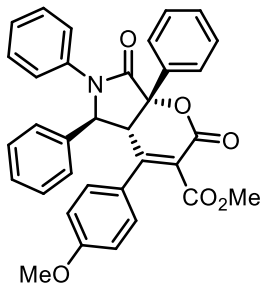
The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1a** (20.2 mg, 0.06 mmol, 1.0 equiv) and α-ketoamide **2j** (20 mg, 0.07 mmol, 1.2 equiv) in ACN (0.04 M) after 1h of reaction. The crude product was obtained diastereomerically pure (100% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4aj** (30.5 mg, 89%). **Mp** = 181 – 183 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 8.08 (s, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.96 – 7.86 (m, 2H), 7.68 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.60 – 7.51 (m, 2H), 7.35 – 7.29 (m, 2H), 7.25 – 7.16 (m, 3H), 7.08 (t, *J* = 7.6 Hz, 3H), 7.03 – 6.94 (m, 7H), 5.33 (d, *J* = 7.9 Hz, 1H), 4.08 (d, *J* = 7.9 Hz, 1H), 3.61 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ_C 167.9 (C), 164.8 (C), 159.4 (C), 152.1 (C), 136.6 (C), 136.4 (C), 134.9 (C), 133.6 (C), 133.5 (C), 133.1 (C), 130.7 (CH), 129.4 (CH), 128.9 (CH), 128.9 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 127.8 (CH), 127.3 (CH), 127.1 (CH), 127.0 (CH), 126.5 (CH), 126.3 (CH), 124.0 (CH), 123.8 (C), 122.9 (CH), 86.7 (C), 67.2 (CH), 52.9 (CH_3), 52.6 (CH). **IR (neat)** ν_{max} 1750, 1711, 1598, 1497, 1458, 1445, 1431, 1367, 1310, 1282, 1233, 1068, 1045, 927, 813, 760, 752, 730, 713, 693, 639, 573, 553, 476, 410 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{37}H_{27}NO_5Na^+$ 588.1787; Found 588.1788.

(±) Methyl 2,7-dioxo-4,6,7a-triphenyl-5-(p-tolyl)-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (*4ba*)



The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1b** (25.8 mg, 0.07 mmol, 1.0 equiv) and α-ketoamide **2a** (20 mg, 0.09 mmol, 1.2 equiv) in ACN (0.05 M) after 1h of reaction. The crude product was obtained diastereomerically pure (100% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4ba** (33.4 mg, 85%). **Mp** = 257 – 259 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.65 – 7.57 (m, 2H), 7.54 – 7.47 (m, 2H), 7.47 – 7.40 (m, 1H), 7.32 – 7.27 (m, 2H), 7.25 – 7.17 (m, 2H), 7.10 – 7.04 (m, 1H), 7.04 – 6.96 (m, 3H), 6.96 – 6.91 (m, 2H), 6.91 – 6.80 (m, 4H), 5.26 (d, *J* = 7.9 Hz, 1H), 3.95 (d, *J* = 7.9 Hz, 1H), 3.66 (s, 3H), 2.22 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ_C 167.9 (C), 165.2 (C), 159.5 (C), 152.1 (C), 141.3 (C), 136.7 (C), 136.5 (C), 136.3 (C), 131.9 (C), 129.5 (CH), 129.4 (CH), 129.2 (CH), 128.9 (CH), 128.8 (C), 128.5 (CH), 127.4 (CH), 127.1 (CH), 126.4 (CH), 126.3 (CH), 123.9 (CH), 123.0 (C), 86.3 (C), 67.1 (CH), 52.9 (CH_3), 52.3 (CH), 21.4 (CH_3). **IR (neat)** ν_{max} 1737, 1715, 1632, 1599, 1496, 1459, 1432, 1376, 1364, 1310, 1282, 1237, 1200, 1141, 1077, 1031, 1001, 968, 931, 830, 793, 752, 741, 730, 692, 567, 551, 406 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{34}H_{27}NO_5Na^+$ 552.1787; Found 552.1776.

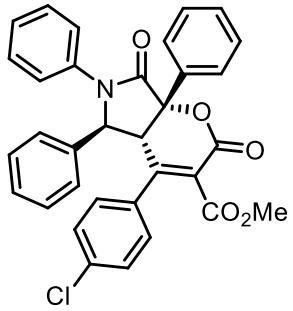
(±) Methyl 4-(4-methoxyphenyl)-2,7-dioxo-5,6,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano [2,3-c]pyrrole-3-carboxylate (*4ca*)



The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1c** (27.0 mg, 0.07 mmol, 1.0 equiv) and α-ketoamide **2a** (20 mg,

0.09 mmol, 1.2 equiv) in ACN (0.05 M) after 1h of reaction. The crude product was obtained diastereomerically pure (100% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4ca** (34.0 mg, 84%). **Mp** = 239 – 242 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.64 – 7.56 (m, 2H), 7.54 – 7.47 (m, 2H), 7.47 – 7.40 (m, 1H), 7.32 – 7.27 (m, 2H), 7.25 – 7.18 (m, 2H), 7.11 – 7.06 (m, 1H), 7.06 – 6.99 (m, 3H), 6.98 – 6.93 (m, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 6.58 (d, *J* = 8.8 Hz, 2H), 5.26 (d, *J* = 8.0 Hz, 1H), 3.94 (d, *J* = 8.0 Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ_C 167.9 (C), 165.5 (C), 161.7 (C), 159.7 (C), 151.5 (C), 136.9 (C), 136.5 (C), 136.3 (C), 129.5 (CH), 129.28, 129.2 (CH), 128.9 (CH), 128.9 (CH), 128.5 (CH), 127.1 (CH), 126.9 (C), 126.4 (CH), 126.3 (CH), 123.9 (CH), 122.1 (C), 114.2 (CH), 86.2 (C), 67.2 (CH), 55.5 (CH_3), 53.0 (CH_3), 52.3 (CH). **IR (neat)** ν_{max} 1750, 1712, 1603, 1512, 1495, 1460, 1433, 1371, 1317, 1258, 1231, 1212, 1182, 1076, 1031, 911, 841, 786, 724, 705, 691, 575, 555, 517, 472, 414 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{34}H_{27}NO_6Na^+$ 568.1736; Found 568.1721.

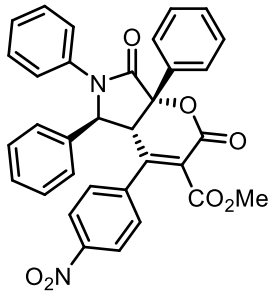
(±) Methyl 4-(4-chlorophenyl)-2,7-dioxo-5,6,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (*4da*)



The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1d** (27.3 mg, 0.07 mmol, 1.0 equiv) and α-ketoamide **2a** (20 mg, 0.09 mmol, 1.2 equiv) in ACN (0.05 M) after 1h of reaction. The crude product was obtained diastereomerically pure (100% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4da** (26.0 mg, 64%). **Mp** = 234 – 237 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.62 – 7.56 (m, 2H), 7.55 – 7.49 (m, 2H), 7.49 – 7.43 (m, 1H), 7.30 – 7.26 (m, 2H), 7.25 – 7.19 (m, 2H), 7.11 – 7.01 (m, 6H), 6.99 – 6.93 (m, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.26 (d, *J* = 8.1 Hz, 1H), 3.87 (d, *J* = 8.1 Hz, 1H), 3.67 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ_C 167.7 (C), 164.6 (C), 159.2 (C), 150.5 (C), 137.0 (C), 136.5 (C), 136.3 (C), 136.1 (C), 133.2 (C), 129.6 (CH), 129.3 (CH), 129.1 (CH), 129.0 (CH), 128.9

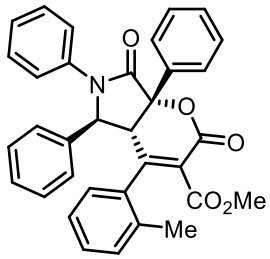
(CH), 128.8 (CH), 128.8 (CH), 127.1 (CH), 126.6 (CH), 126.1 (CH), 124.2 (C), 124.0 (CH), 86.4 (C), 67.0 (CH), 53.1 (CH_3), 52.8 (CH). **IR (neat)** ν_{max} 1755, 1714, 1634, 1593, 1494, 1459, 1448, 1435, 1384, 1368, 1312, 1230, 1214, 1127, 1077, 1047, 911, 807, 771, 749, 722, 730, 693, 565, 515, 462, 483, 442, 406 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{33}H_{24}NO_5Na^{35}Cl^+$ 572.1241; Found 572.1228.

(±) Methyl 4-(4-nitrophenyl)-2,7-dioxo-5,6,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (*4ea*)



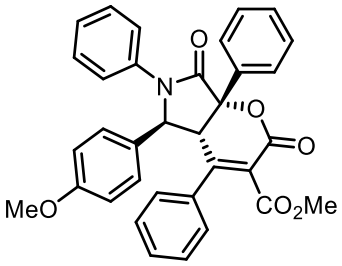
The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1e** (28.1 mg, 0.07 mmol, 1.0 equiv) and α-ketoamide **2a** (20 mg, 0.09 mmol, 1.2 equiv) in ACN (0.05 M) after 1h of reaction. The crude product was obtained diastereomerically pure (82% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4ea** (22.0 mg, 53%). **Mp** = 275 – 278 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.93 (d, *J* = 8.8 Hz, 2H), 7.63 – 7.46 (m, 5H), 7.26 – 7.19 (m, 4H), 7.14 – 6.98 (m, 8H), 5.29 (d, *J* = 8.2 Hz, 1H), 3.86 (d, *J* = 8.2 Hz, 1H), 3.66 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ_C 167.4 (C), 163.9 (C), 158.7 (C), 149.3 (C), 148.5 (C), 141.1 (C), 136.1 (C), 136.0 (C), 135.8 (C), 129.8 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 128.5 (CH), 127.2 (CH), 126.8 (CH), 126.0 (CH), 124.2 (CH), 123.7 (CH), 86.7 (C), 67.0 (CH), 53.4 (CH), 53.3 (CH_3). **IR (neat)** ν_{max} 1751, 1714, 1531, 1346, 1089, 911, 728, 693, 566, 449, 419 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{33}H_{24}N_2O_7Na^+$ 583.1481; Found 583.1471.

(±) Methyl 2,7-dioxo-5,6,7a-triphenyl-4-(o-tolyl)-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (*4fa*)



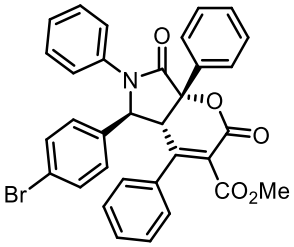
The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1f** (25.8 mg, 0.07 mmol, 1.0 equiv) and α-ketoamide **2a** (20 mg, 0.09 mmol, 1.2 equiv) in ACN (0.04 M) after 1h of reaction. The crude acid product was obtained as a mixture of two diastereoisomers (88% conversion, 50:50 dr, as measured by ^{1}H NMR), which are believed to be two atropoisomers. An evolution of the ratio to 80:20 was observed after methylation. Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4fa** (27.0 mg, 69%). **Mp** = 251-254 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.59 – 7.38 (m, 5H), 7.37 – 7.27 (m, 2H), 7.25 – 7.19 (m, 2H), 7.18 – 7.06 (m, 2H), 7.05 – 6.95 (m, 5H), 6.94 – 6.74 (m, 3H), 5.31 (d, *J* = 7.4 Hz, 0.8H*maj.*), 5.21 (br.d, *J* = 4.7 Hz, 0.2H *min.*), 4.04 (br.d, *J* = 4.1 Hz, 0.2H *min.*), 3.77 (d, *J* = 7.4 Hz, 0.8H *maj.*), 3.54 (s, 3H), 2.15 (s, 0.6H *min.*), 1.52 (s, 2.4H *maj.*). **^{13}C NMR (101 MHz, $CDCl_3$):** δ_C 168.1 (C), 164.0 (C), 159.0 (C), 154.3 (C), 137.0 (C), 136.4 (C), 136.2 (C), 134.2 (C), 134.0 (C), 130.7 (CH), 129.7 (CH), 129.4 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 127.5 (CH), 126.7 (CH), 126.0 (CH), 125.9 (C), 125.4 (CH), 124.4 (CH), 123.0 (C), 87.0 (C), 67.0 ($CH_{maj.}$), 64.6 ($CH_{min.}$), 53.6 ($CH_{3min.}$), 52.7 ($CH_{3maj.}$), 52.6 (CH), 20.1 ($CH_{3min.}$), 18.8 ($CH_{3maj.,}$). **IR (neat)** ν_{max} 1733, 1751, 1705, 1494, 1432, 1362, 1314, 1236, 1201, 1071, 998, 828, 758, 746, 701, 691, 669, 617, 568, 537, 510, 447, 427, 404 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M+Na]^+$ Calcd for $C_{34}H_{27}NO_5Na^+$ 552.1787; Found 552.1782.

(±) Methyl 5-(4-methoxyphenyl)-2,7-dioxo-4,6,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano [2,3-c]pyrrole-3-carboxylate (*4ga*)



The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1g** (27.0 mg, 0.07 mmol, 1.0 equiv) and α-ketoamide **2a** (20 mg, 0.09 mmol, 1.2 equiv) in ACN (0.05 M) after 1h of reaction. The crude product was obtained diastereomerically pure (87% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4ga** (30.4 mg, 75%). **Mp** = 243-246 °C. **^{1}H NMR (400 MHz, CDCl$_3$):** δ_H 7.65 – 7.58 (m, 2H), 7.55 – 7.48 (m, 2H), 7.48 – 7.42 (m, 1H), 7.30 – 7.27 (m, 1H), 7.25 – 7.18 (m, 3H), 7.16 – 7.05 (m, 4H), 7.02 – 6.94 (m, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.50 (d, *J* = 8.6 Hz, 2H), 5.23 (d, *J* = 7.9 Hz, 1H), 3.92 (d, *J* = 8.0 Hz, 1H), 3.66 – 3.60 (m, 6H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ_C 167.8 (C), 164.9 (C), 159.6 (C), 159.4 (C), 152.2 (C), 136.5 (C), 136.4 (C), 135.0 (C), 130.6 (CH), 129.5 (CH), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.3 (CH), 127.3 (CH), 126.5 (CH), 126.2 (CH), 124.1 (CH), 123.7 (C), 114.3 (CH), 86.4 (C), 66.6 (CH), 55.3 (CH_3), 52.9 (CH_3), 52.6 (CH). **IR (neat)** ν_{max} 1748, 1717, 1614, 1516, 1495, 1447, 1363, 1310, 1234, 1176, 1069, 1045, 1031, 969, 913, 845, 797, 779, 751, 734, 724, 691, 591, 553, 512, 474, 429 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + H]^+$ Calcd for $C_{34}H_{28}NO_6^+$ 546.1917; Found 546.1909. $[M + Na]^+$ Calcd for $C_{34}H_{27}NO_6Na^+$ 568.1736; Found 568.1717.

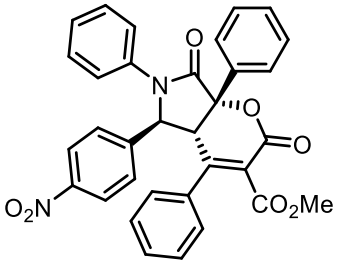
(±) Methyl 5-(4-bromophenyl)-2,7-dioxo-4,6,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (*4ha*)



The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1h** (30.6 mg, 0.07 mmol, 1.0 equiv) and α-ketoamide **2a** (20 mg,

0.09 mmol, 1.2 equiv) in ACN (0.05 M) after 1h of reaction. The crude product was obtained diastereomerically pure (100% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4ha** (27.3 mg, 62%). **Mp** = 283 – 286 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.64 – 7.58 (m, 2H), 7.56 – 7.49 (m, 2H), 7.49 – 7.43 (m, 1H), 7.31 – 7.27 (m, 1H), 7.26 – 7.20 (m, 4H), 7.18 – 7.13 (m, 2H), 7.13 – 7.06 (m, 3H), 7.04 – 6.98 (m, 2H), 6.82 – 6.75 (m, 2H), 5.24 (d, *J* = 7.9 Hz, 1H), 3.90 (d, *J* = 7.9 Hz, 1H), 3.64 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)**: δ_C 167.8 (C), 164.7 (C), 159.2 (C), 151.5 (C), 136.22 (C), 136.17 (C), 135.8 (C), 134.7 (C), 132.0 (CH), 130.9 (CH), 129.7 (CH), 129.3 (CH), 129.1 (CH), 128.9 (CH), 128.5 (CH), 127.3 (CH), 126.7 (CH), 126.1 (CH), 123.9 (CH), 122.5 (C), 86.1 (C), 66.3 (CH), 53.0 (CH_3), 52.3 (CH). **IR (neat)** ν_{max} 1748, 1724, 1494, 1349, 1312, 1236, 1071, 829, 747, 731, 691, 572, 447, 413 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{33}H_{24}NO_5Na^{79}Br^+$ 616.0736; Found 616.0713; $[M + Na]^+$ Calcd for $C_{33}H_{24}NO_5Na^{81}Br^+$ 618.0715; Found 618.0703.

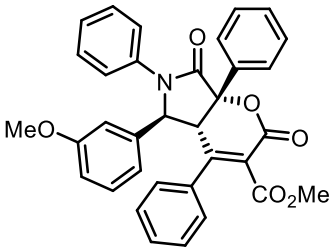
(±) Methyl 5-(4-nitrophenyl)-2,7-dioxo-4,6,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (*4ia*)



The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1i** (28.1 mg, 0.07 mmol, 1.0 equiv) and α-ketoamide **2a** (20 mg, 0.09 mmol, 1.2 equiv) in ACN (0.05 M) after 1h of reaction. The crude product was obtained diastereomerically pure (100% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4ia** (26.0 mg, 63%). **Mp** = 235 – 238 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.81 (d, *J* = 8.6 Hz, 2H), 7.65 – 7.59 (m, 2H), 7.58 – 7.51 (m, 2H), 7.51 – 7.44 (m, 1H), 7.29 – 7.27 (m, 1H), 7.26 – 7.21 (m, 4H), 7.18 – 7.03 (m, 7H), 5.43 (d, *J* = 7.9 Hz, 1H), 3.93 (d, *J* = 7.9 Hz, 1H), 3.63 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)**: δ_C 167.7 (C), 164.5 (C), 159.0 (C), 150.7 (C), 147.6 (C), 144.2 (C), 136.0 (C), 135.9 (C), 134.5 (C), 131.2 (CH), 129.8 (CH), 129.4, (CH), 129.3 (CH), 129.1 (CH), 127.9 (CH), 127.3 (CH), 126.9 (CH), 126.1 (CH), 124.1 (C), 123.9 (CH), 123.6 (CH), 85.9 (C), 65.8 (CH), 53.1

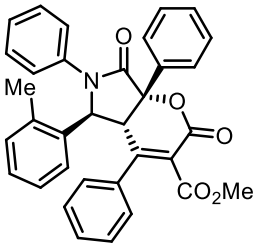
(CH_3), 52.2 (CH). **IR (neat)** ν_{max} 1726, 1599, 1522, 1494, 1446, 1347, 1312, 1285, 1237, 1071, 1044, 1001, 928, 860, 829, 777, 746, 714, 694, 592, 573, 516, 447, 426 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{33}H_{24}N_2O_7Na^+$ 583.1481; Found 583.1469.

(±) Methyl 5-(3-methoxyphenyl)-2,7-dioxo-4,6,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano [2,3-c]pyrrole-3-carboxylate (*4ja*)



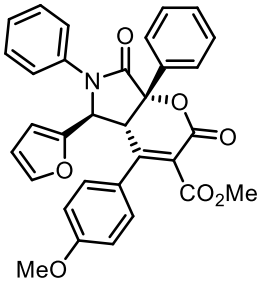
The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1j** (30.6 mg, 0.07 mmol, 1.0 equiv) and α-ketoamide **2a** (20 mg, 0.09 mmol, 1.2 equiv) in ACN (0.05 M) after 1h of reaction. The crude product was obtained diastereomerically pure (100% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4ja** (34.0 mg, 84%). **Mp** = 220 – 225 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.64 – 7.58 (m, 2H), 7.55 – 7.48 (m, 2H), 7.48 – 7.41 (m, 1H), 7.33 – 7.28 (m, 2H), 7.26 – 7.19 (m, 3H), 7.17 – 7.06 (m, 3H), 7.05 – 6.98 (m, 2H), 6.91 (t, *J* = 7.9 Hz, 1H), 6.58 – 6.48 (m, 2H), 6.42 (s, 1H), 5.23 (d, *J* = 7.8 Hz, 1H), 3.97 (d, *J* = 7.8 Hz, 1H), 3.64 (s, 3H), 3.57 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ_C 167.8 (C), 164.9 (C), 159.7 (C), 159.3 (C), 151.9 (C), 138.3 (C), 136.5 (C), 136.3(C), 134.9 (C), 130.7 (CH), 130.1 (CH), 129.5 (CH), 129.2 (CH), 128.9 (CH), 128.7 (CH), 127.3 (CH), 126.5 (CH), 126.2 (CH), 123.8(CH), 123.8 (CH), 119.1 (CH), 113.7 (CH), 113.1 (CH), 86.3 (C), 66.8 (CH), 55.2 (CH_3), 52.9 (CH_3), 52.2 (CH). **IR (neat)** ν_{max} 1749, 1721, 1603, 1496, 1446, 1433, 1367, 1311, 1288, 1263, 1233, 1190, 1158, 1136, 1069, 1044, 1001, 929, 913, 888, 838, 824, 778, 763, 749, 726, 690, 566, 515, 481, 404 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{34}H_{27}NO_6Na^+$ 568.1736; Found 568.1719.

(±) Methyl 2,7-dioxo-5,6,7a-triphenyl-4-(o-tolyl)-2,4a,5,6,7,7a-hexahydropyrano[2,3-c] pyrrole -3-carboxylate (*4ka*)



The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1k** (25.8 mg, 0.07 mmol, 1.0 equiv) and α-ketoamide **2a** (20 mg, 0.09 mmol, 1.2 equiv) in ACN (0.05 M) after 1 h of reaction. The crude product was obtained diastereomerically pure (95% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a white powder **4ka** (30.3 mg, 77%). **Mp** = 227 -231 ^{o}C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.64 – 7.57 (m, 2H), 7.54 – 7.47 (m, 2H), 7.47 – 7.40 (m, 1H), 7.25 – 7.13 (m, 6H), 7.12 – 6.99 (m, 4H), 6.97 – 6.86 (m, 3H), 6.81 – 6.73 (m, 1H), 5.60 (d, *J* = 7.9 Hz, 1H), 4.02 (d, *J* = 7.2 Hz, 1H), 3.66 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 167.7 (C), 165.1 (C), 159.6 (C), 151.6 (C), 136.5 (C), 135.8 (C), 134.4 (C), 130.9 (CH), 129.5 (CH), 129.2 (CH), 128.9(CH), 128.6 (CH), 127.3 (CH), 127.1 (CH), 126.5 (CH), 126.3 (CH), 123. 9 (CH), 123.7 (C), 86.80 (C), 53.0 (CH_3), 19.7 (CH_3). **IR (neat)** ν_{max} 1750, 1718, 1618, 1598, 1494, 1446, 1432, 1379, 1354, 1310, 1284, 1226, 1198, 1140, 1113, 1100, 1076, 1067, 1043, 915, 764, 750, 730, 723, 692, 574, 503, 476, 426 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{34}H_{27}NO_5Na^+$ 552.1787; Found 552.1776.

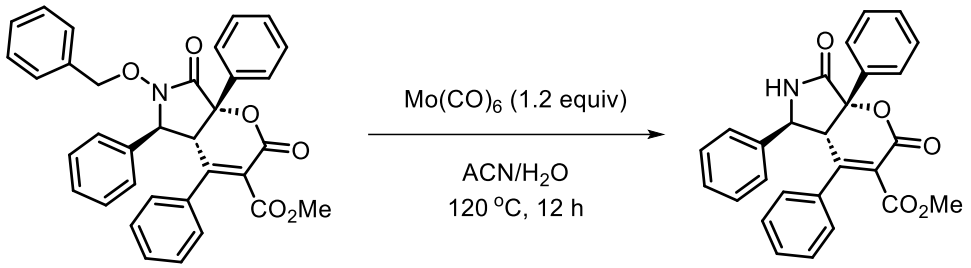
(±) Methyl 5-(furan-2-yl)-4-(4-methoxyphenyl)-2,7-dioxo-6,7a-diphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (*4la*)



The title compound was prepared according to the above representative procedure from alkylidene Meldrum's acid **1l** (26.2 mg, 0.06 mmol, 1.0 equiv) and α-ketoamide **2a** (20 mg, 0.07 mmol, 1.2 equiv) in ACN (0.04 M) after 1h of reaction. The crude product was obtained

diastereomerically pure (91% conversion, >99% dr). Flash column chromatography over silica gel (PE/EtOAc 80:20 v/v, then pure EtOAc) afforded the desired product as a brown powder **4la** (29.7 mg, 75%). **Mp** = 248 – 251 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.67 – 7.59 (m, 2H), 7.54 – 7.47 (m, 2H), 7.47 – 7.40 (m, 1H), 7.31 – 7.27 (m, 2H), 7.23 (s, 1H), 7.20 – 7.14 (m, 3H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.02 – 5.94 (m, 1H), 5.94 – 5.87 (m, 1H), 5.19 (d, *J* = 8.2 Hz, 1H), 4.39 (d, *J* = 8.2 Hz, 1H), 3.75 (s, 3H), 3.67 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ_C 167.5 (C), 165.4 (C), 161.6 (C), 159.7 (C), 151.5 (C), 147.2 (C), 143.4 (CH), 136.4 (C), 136.2 (C), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 127.4 (CH), 126.9 (C), 126.3 (CH), 125.1 (CH), 122.2 (C), 114.3 (CH), 112.6 (CH), 110.8 (CH), 85.9 (C), 61.0 (CH), 55.5 (CH_3), 52.9 (CH_3), 47.8 (CH). **IR (neat)** ν_{max} 1729, 1699, 1603, 1514, 1594, 1420, 1376, 1363, 1299, 1260, 1195, 1178, 1122, 1074, 1019, 831, 767, 740, 694, 623, 566, 482, 413 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{32}H_{25}NO_7Na^+$ 558.1529; Found 558.1522.

IV.4 Synthetic transformation of precursor 4ad



4ad **4ae**

According to the previously developed by Saha's protocol.[11] To a solution of OBn-pyrrolidone ***4ad*** (25 mg, 0.046 mmol, 1.0 equiv) in acetonitrile/water (9 : 1, 10.0 mL), $Mo(CO)_6$ (14.5 mg, 0.055 mmol, 1.2 equiv) was added and the reaction was stirred at 120 °C under argon atmosphere for 12 h. After cooling to room temperature, the mixture was filtered through celite and thoroughly washed with ethyl acetate. Combined filtrate was concentrated in *vacuo*, and crude residue was purified by silica gel column chromatography (1 :1 EtOAc : hexane) to afford a product **4ae** in 76 % (15.3 mg) yield. **Mp**= 165-269 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.59 – 7.40 (m, 5H), 7.22 – 7.03 (m, 8H), 6.92 (d, *J* = 7.7 Hz, 2H), 6.49 (s, 1H), 4.80 (d, *J* = 8.0 Hz, 1H), 3.79 (d, *J* = 8.1 Hz, 1H), 3.62 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ_C 170.4 (C), 164.8 (C), 159.5 (C), 151.9 (C), 137.3 (C), 136.0 (C), 134.8 (C), 130.7 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 127.3 (CH), 126.6 (CH), 125.9 (CH), 123.5 (C), 86.4 (C), 62.1 (CH), 54.9 (CH), 52.9 (CH_3). **IR (neat)** ν_{max} 3238, 2953, 1716, 1627, 1496, 1446, 1435, 1368, 1307, 1282, 1241, 1133, 1070, 1036, 1020, 1001, 849, 816, 798, 752, 695, 621, 611, 545, 522, 504, 419 cm^{-1}. **HRMS (ESI/TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{27}H_{21}NO_5Na^+$ 462.1317; Found 462.1304.

[11] Bera, T.; Singh, B.; Gandon, V.; Saha, J. *Chem. Eur. J.* **2022**, e202201208.

V. X-Ray diffraction analysis

Data collection

The crystal structure of **4aa** [$C_{33}H_{25}NO_5$] has been determined from single crystal X-Ray diffraction (CCDC2328277). The chosen crystal was stuck on a glass fibre and mounted on a kappa goniometer of a Bruker D8-VENTURE diffractometer equipped with a PHOTON area detector. A series of exposures were recorded, corresponding to 99 % completeness with 5 average redundancy.

The cell parameters and the orientation matrix of the crystal were preliminary determined by using APEX Software.[12] Data integration and global cell refinement were performed with SAINT Software.[13] Intensities were corrected for Lorentz, polarisation, decay and absorption effects (SADABS Software)[12] and reduced to F_O^2. The program package WinGX[14] was used for space group determination, structure solution and refinement.

Data refinement

The standard space group *P-1* (n°2) was determined from systematic extinctions and relative F_O^2 of equivalent reflections. The structure was solved by direct methods.[15] Anisotropic displacement parameters were refined for all non-hydrogen atoms. Every Hydrogen atoms were located from subsequent difference Fourier syntheses and placed with geometrical constraints (SHELXL).[14] The final cycle of full-matrix least-square refinement on F^2 was based on 9145 observed reflections and 354 variable parameters and converged with unweighted and weighted agreement factors of: R1 = 0.0520, wR2 = 0.1389 for 7346 reflections with $I>2\sigma I$ and R1 = 0.0655, wR2 = 0.1512 for all data.

Chemical Formula	$C_{33}H_{25}NO_5$
Molecular Weight / $g.mol^{-1}$	515.54

[12] APEX. V2022.10-1

[13] a) SAINT V8.40B Bruker AXS LLC.219; b) SADABS – 2016/2 – Bruker AXS area detector scaling and absorption correction.

[14] WinGX: Version 2023.1: An integrated system of Windows Programs for the solution, refinement and analysis of *Single Crystal X-Ray Diffraction Data* by Louis J. Farrugia, Dept. of chemistry, University of Glasgow. L. J. Farrugia (**2012**) *J. Appl. Cryst.* 45, 849-854.

[15] Include in WinGX suite: - SIR 92: A. Altomare, G. Cascarano, C. Giacovazzo and A. Guagliardi, *J. Appl. Crystallogr.* **1994**, 27, 435; -SHELX & SHELXTL program: G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, 64, 112-122.

Crystal System	Triclinic
Space Group	*P*-1
Z , Z' (asymmetric units per unit cell)	2, 1
a / *Å*	10.1201(2)
b / *Å*	11.3054(3)
c / *Å*	13.5515(3)
α / °	70.3700(10)
β / °	72.4580(10)
γ / °	67.8020(10)
V / $Å^3$	1324.77(5)
d_{calc} / $g.cm^{-3}$	1.292
F(000) / e^-	540
Absorption coefficient μ (Mo$K\alpha_1$) / mm^{-1}	0.087

Structural description

The compound crystallizes in triclinic space group P-1. The asymmetric unit is composed of one compound molecule (**Figure 1**). The cohesion of the packing is ensured by means of π interactions (in T shape or $\pi\pi$). The distance between aromatic ring are at circa 4,0Å.

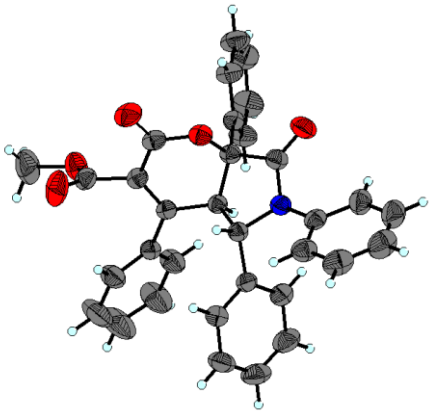


Figure 1. Asymmetric unit in thermal ellipsoidal representation (50% of probability) using the following colour code: C, grey; H, light blue; O, red; N, deep blue.

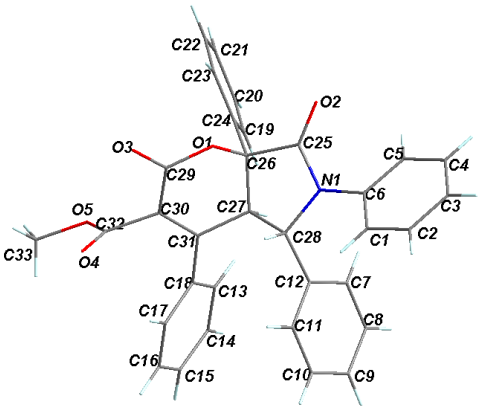


Figure 2. Asymmetric unit with labels

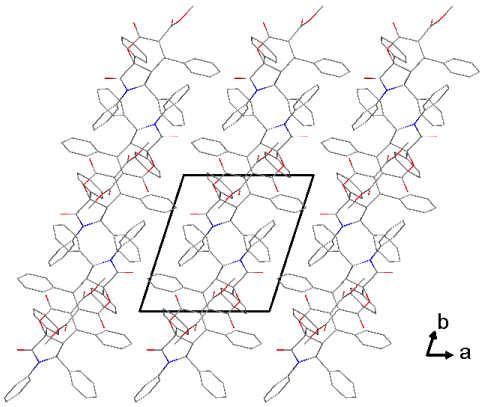


Figure 3. Projection along c

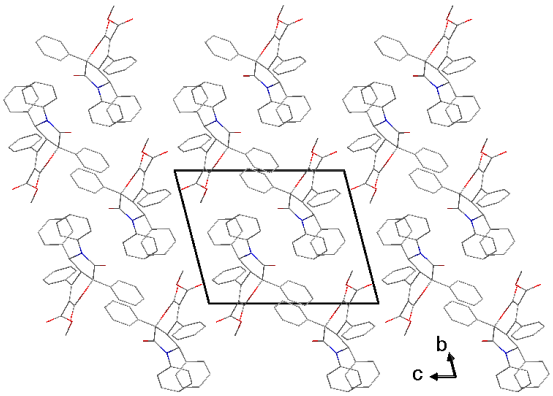


Figure 4. Projection along a

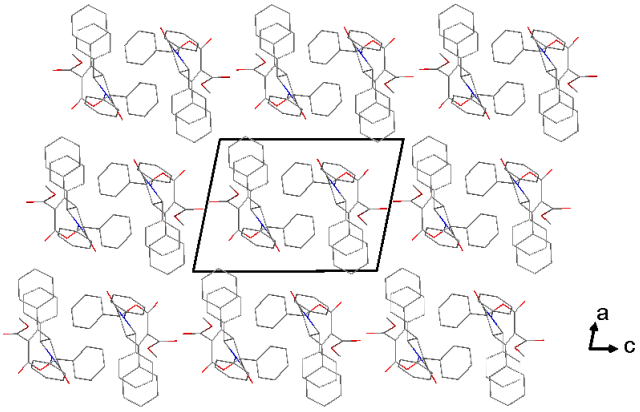
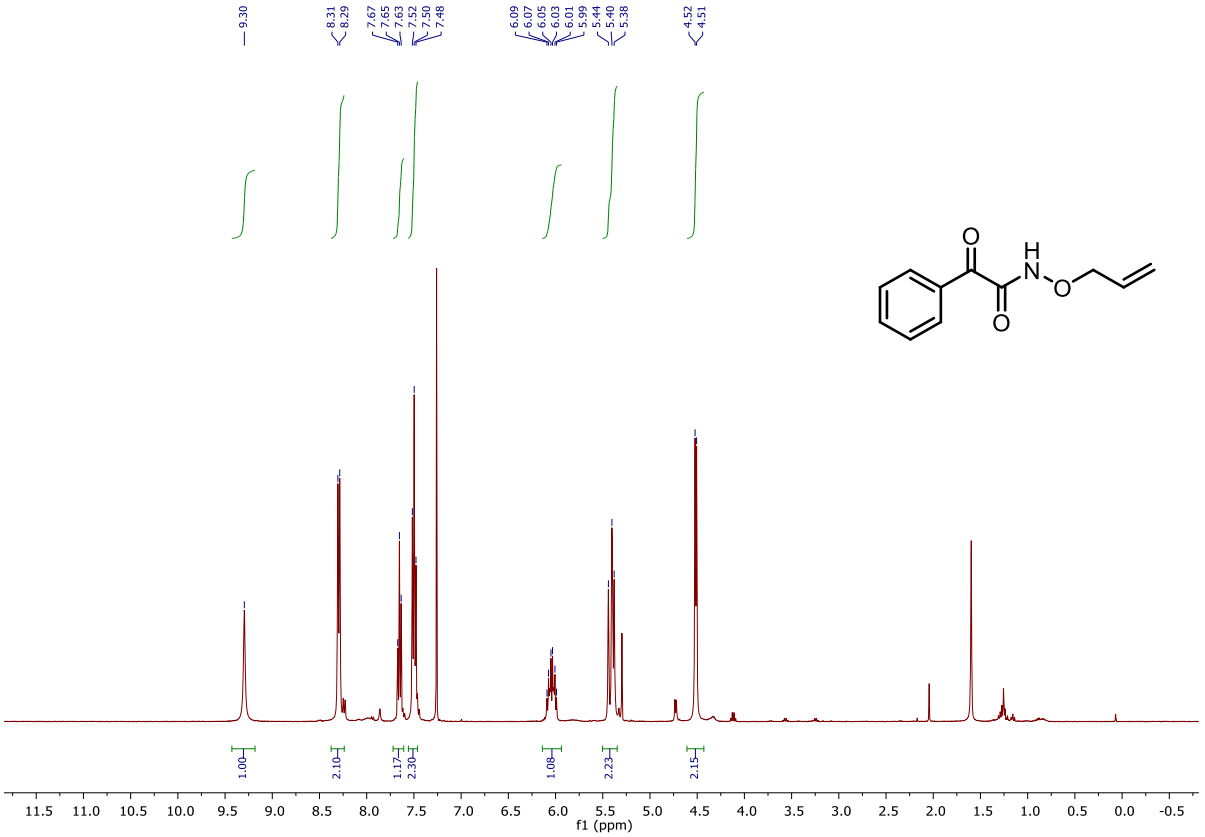
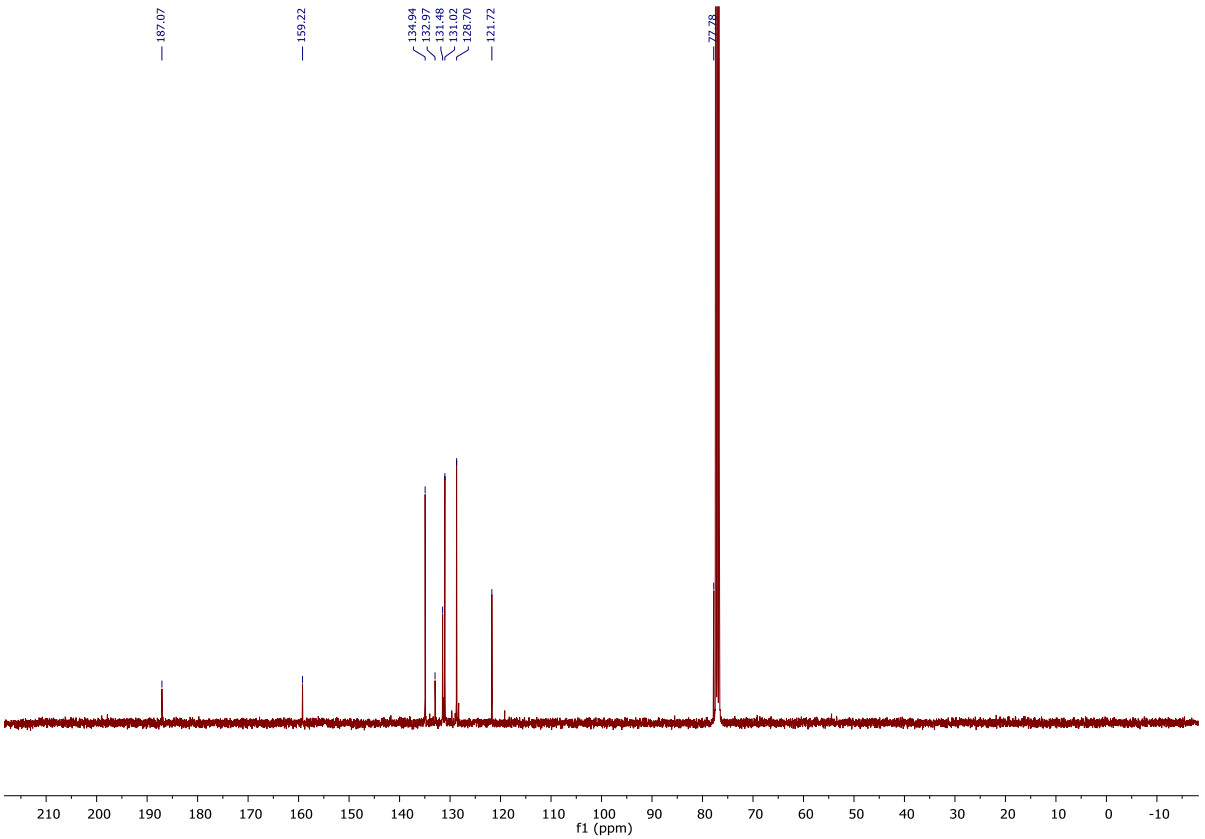


Figure 5. Projection along b

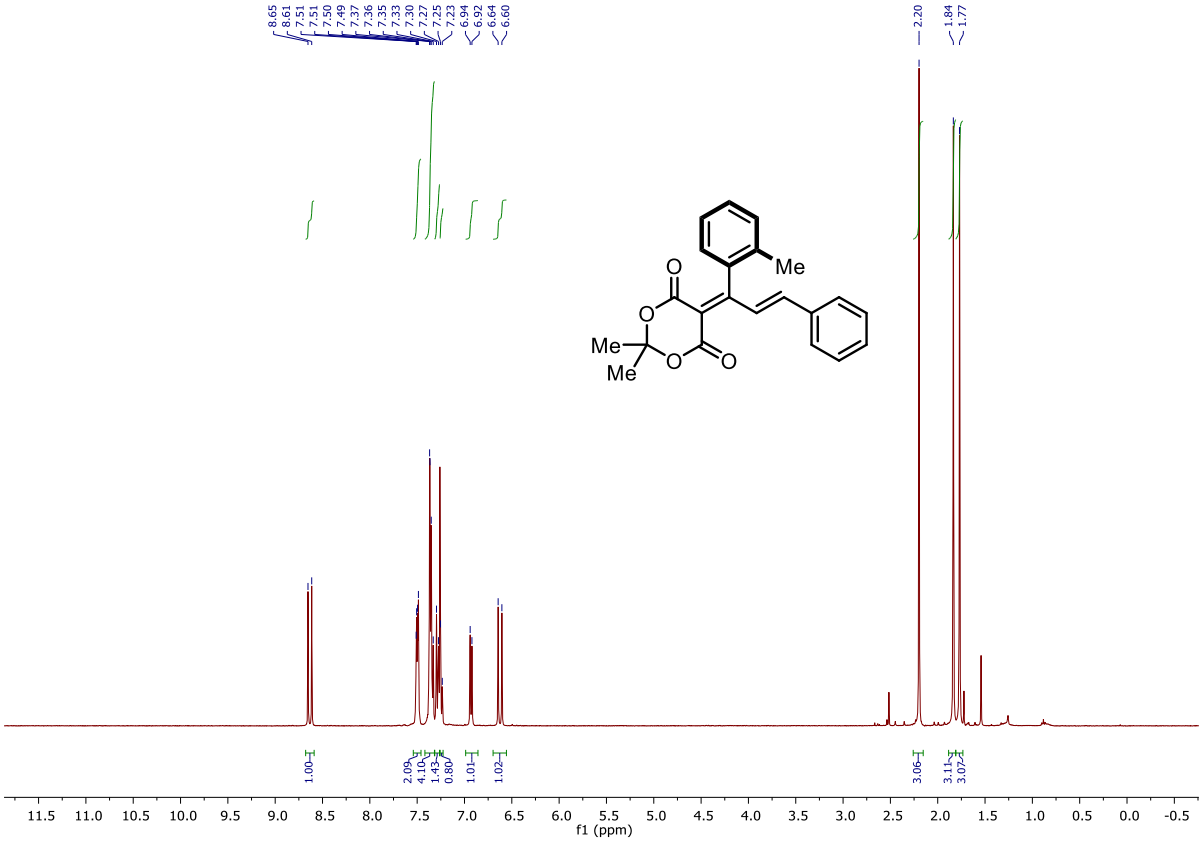
VI. NMR spectra

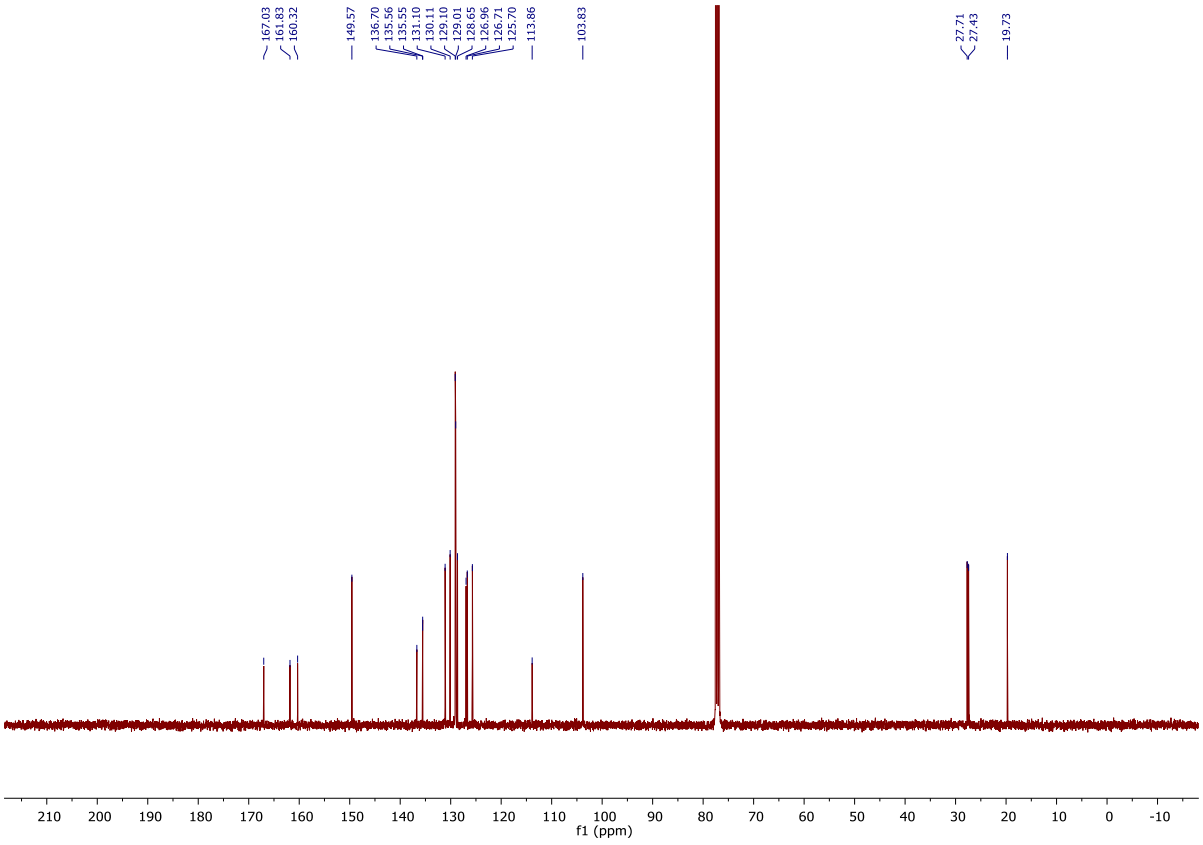
N-(allyloxy)-2-oxo-2-phenylacetamide (2c)



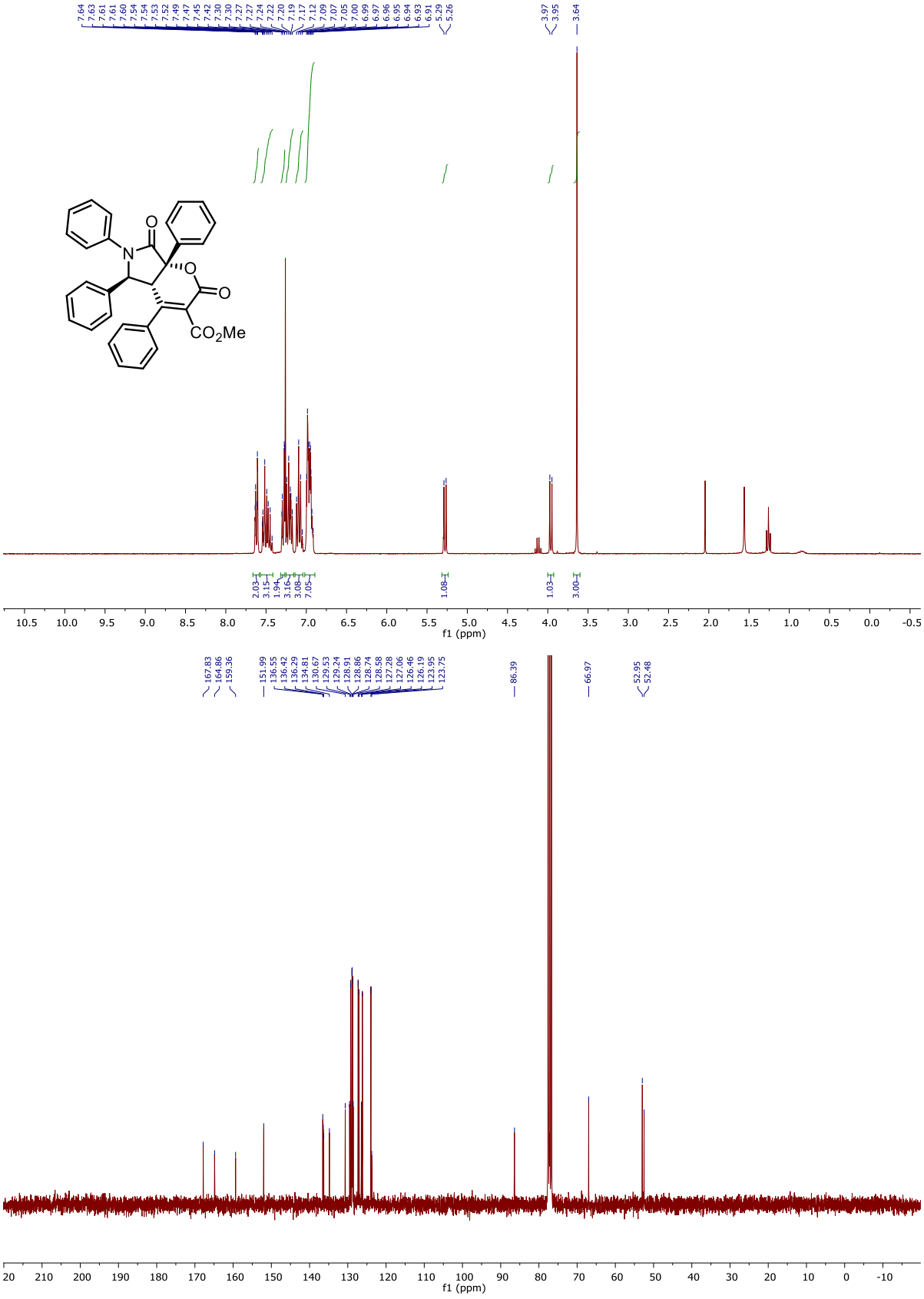


(E)-2,2-dimethyl-5-(3-phenyl-1-(o-tolyl)allylidene)-1,3-dioxane-4,6-dione (1f)

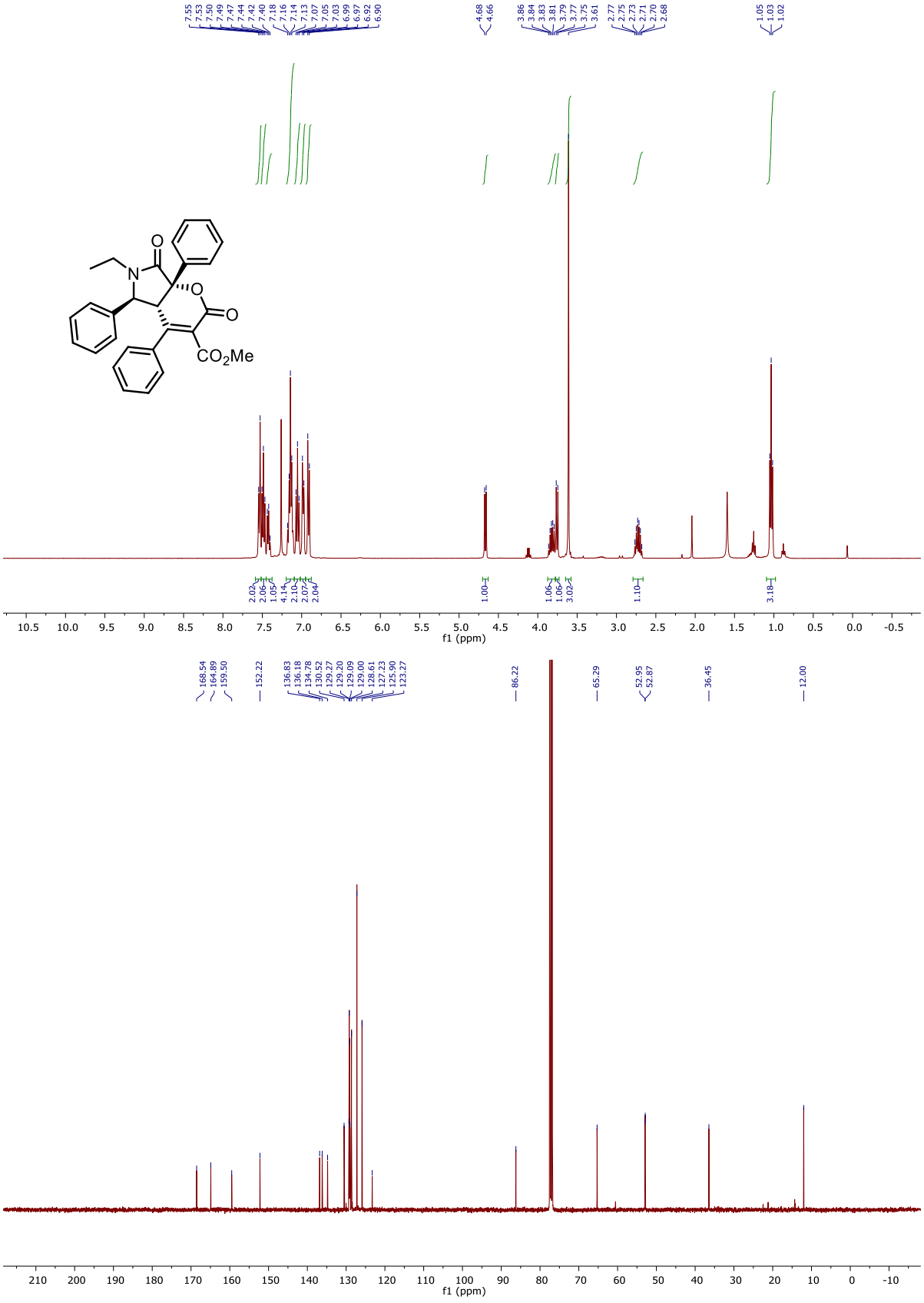




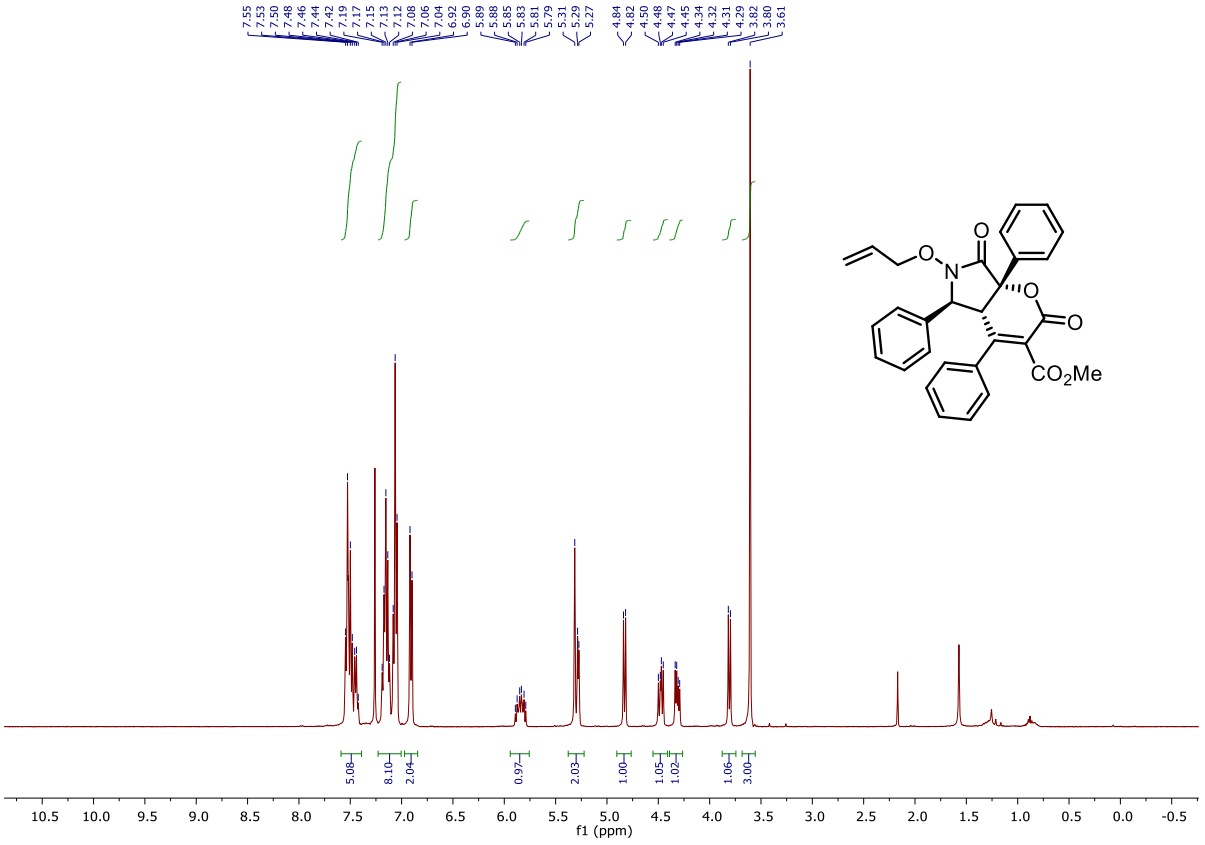
(±) Methyl 2,7-dioxo-4,5,6,7a-tetraphenyl-2,4a,5,6,7,7a-hexahydropyrano [2,3-c]pyrrole-3- carboxylate (4aa)

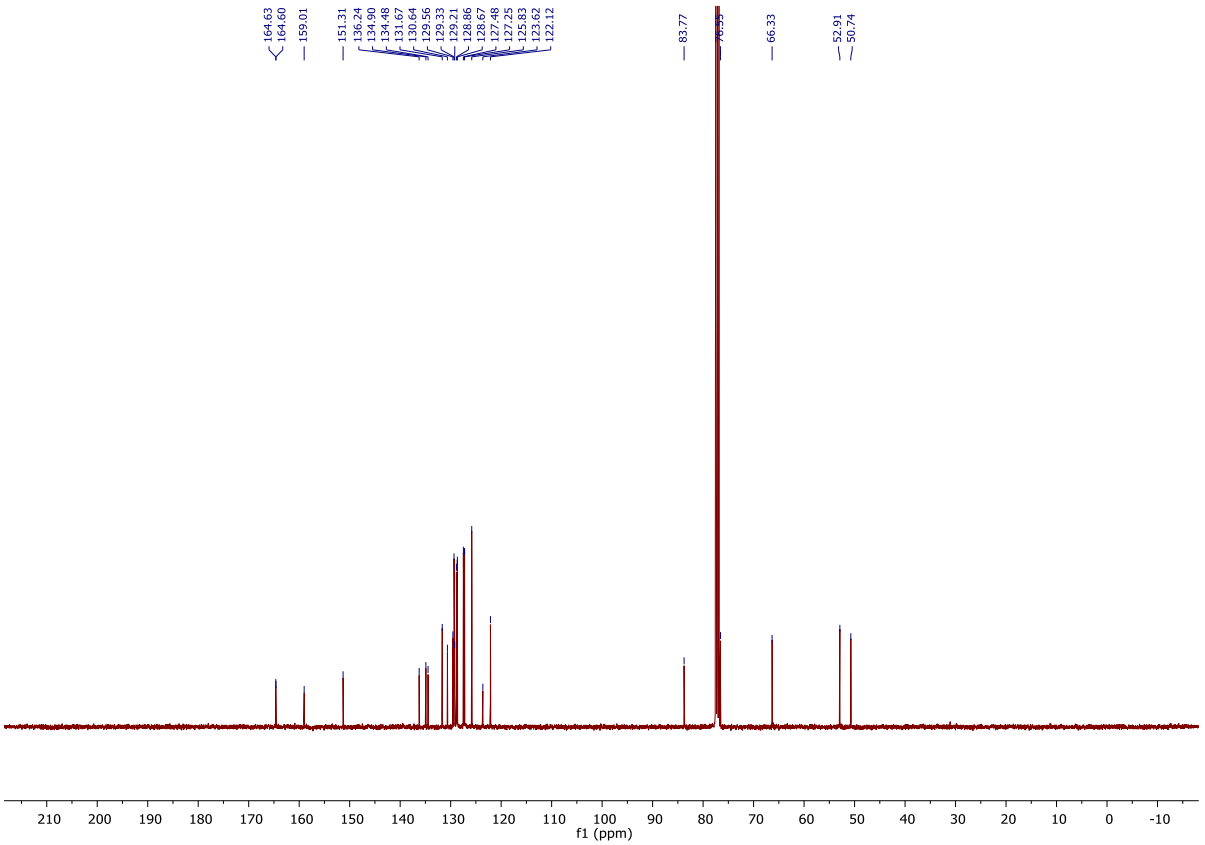


(±) Methyl 6-ethyl-2,7-dioxo-4,5,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4ab)

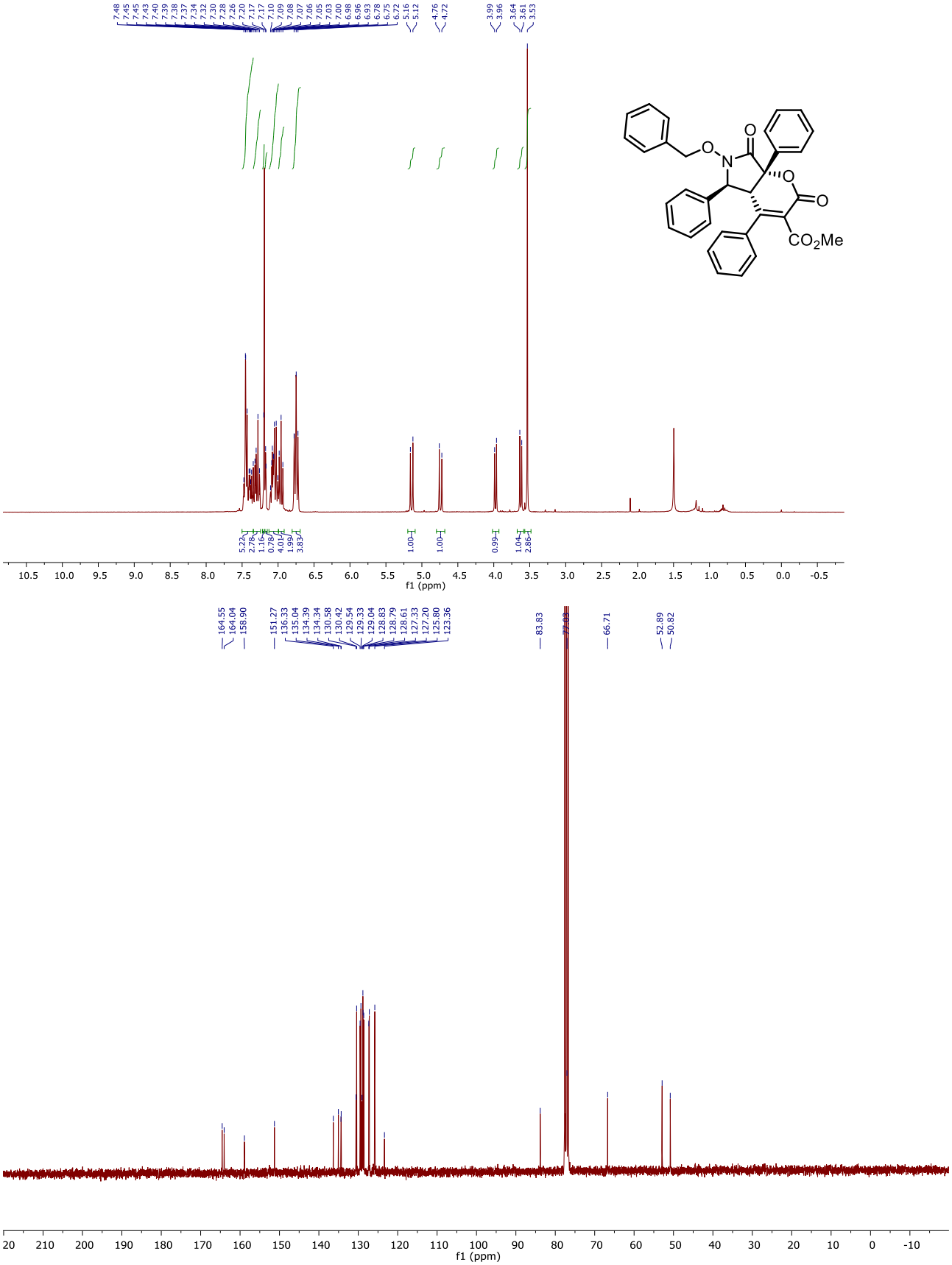


(±) Methyl 6-(allyloxy)-2,7-dioxo-4,5,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4ac)

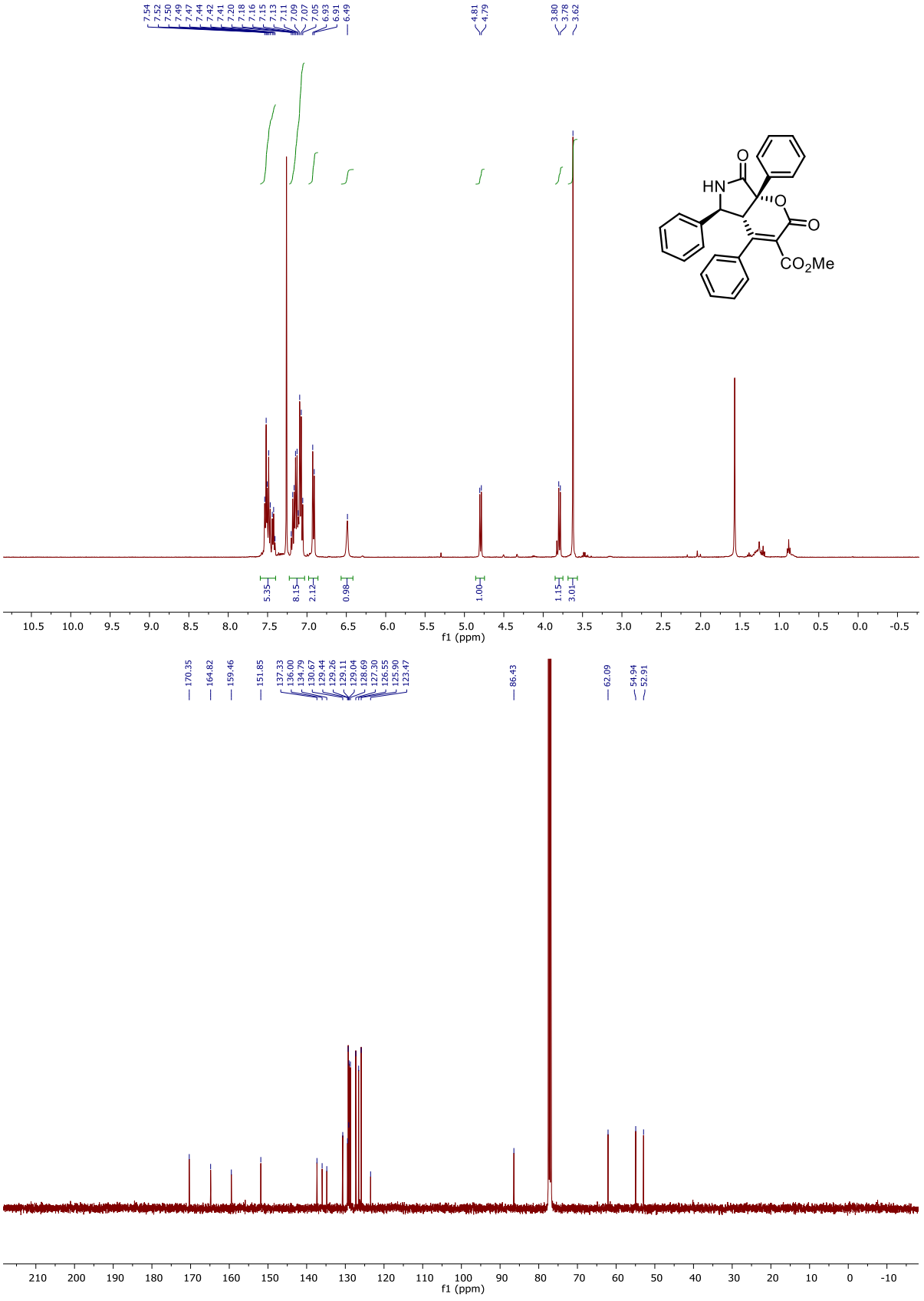




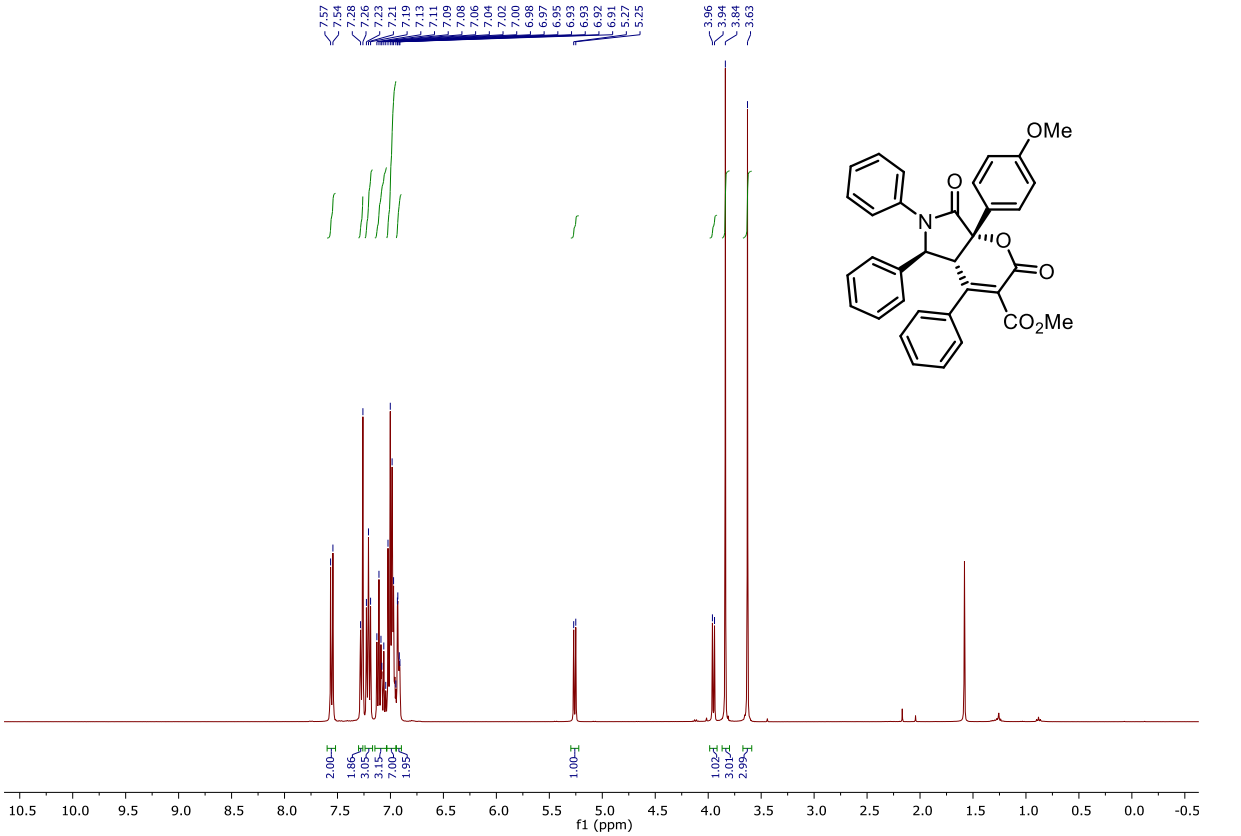
(±) Methyl 6-(benzyloxy)-7a-(4-methoxyphenyl)-2,7-dioxo-4,5-diphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c] pyrrole-3-carboxylate (4ad)

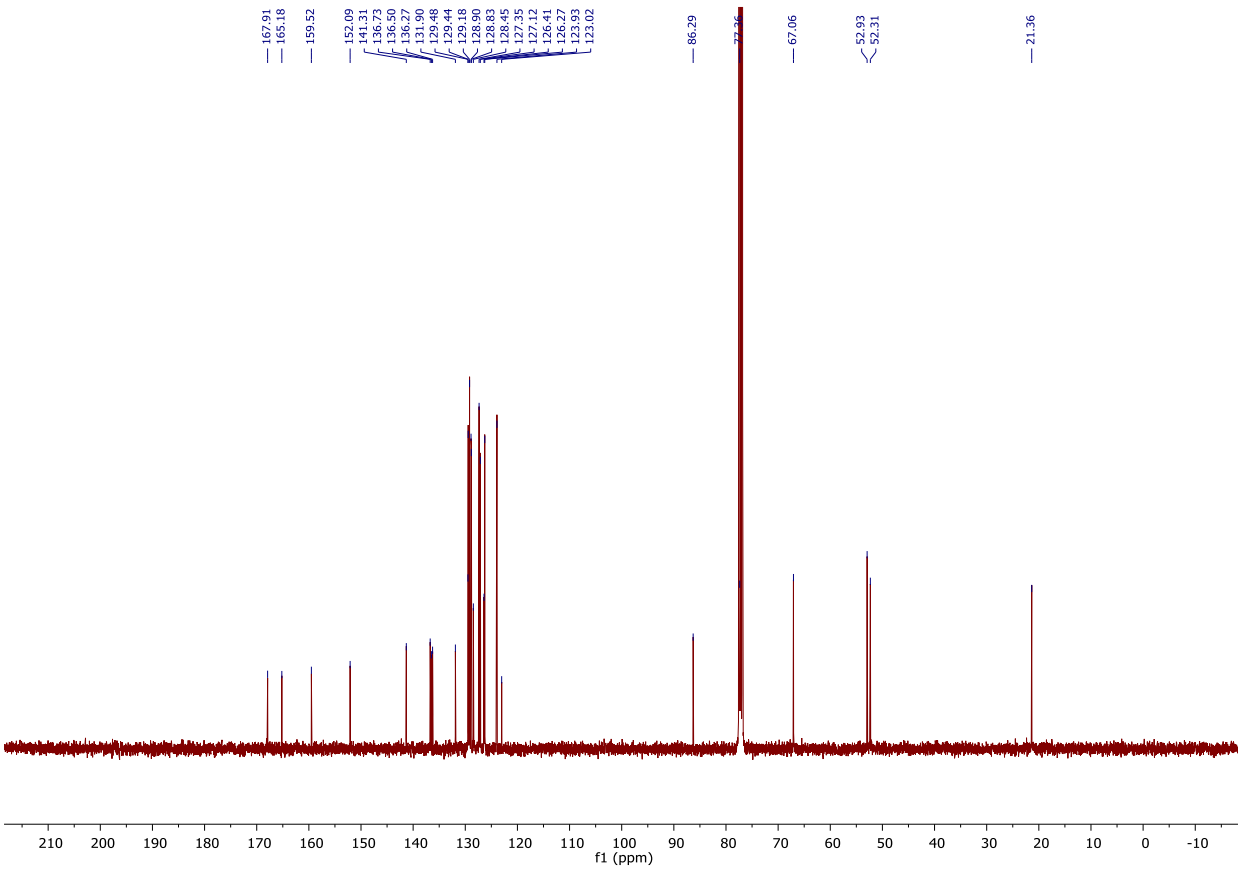


(±) Methyl 2,7-dioxo-4,5,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4ae)

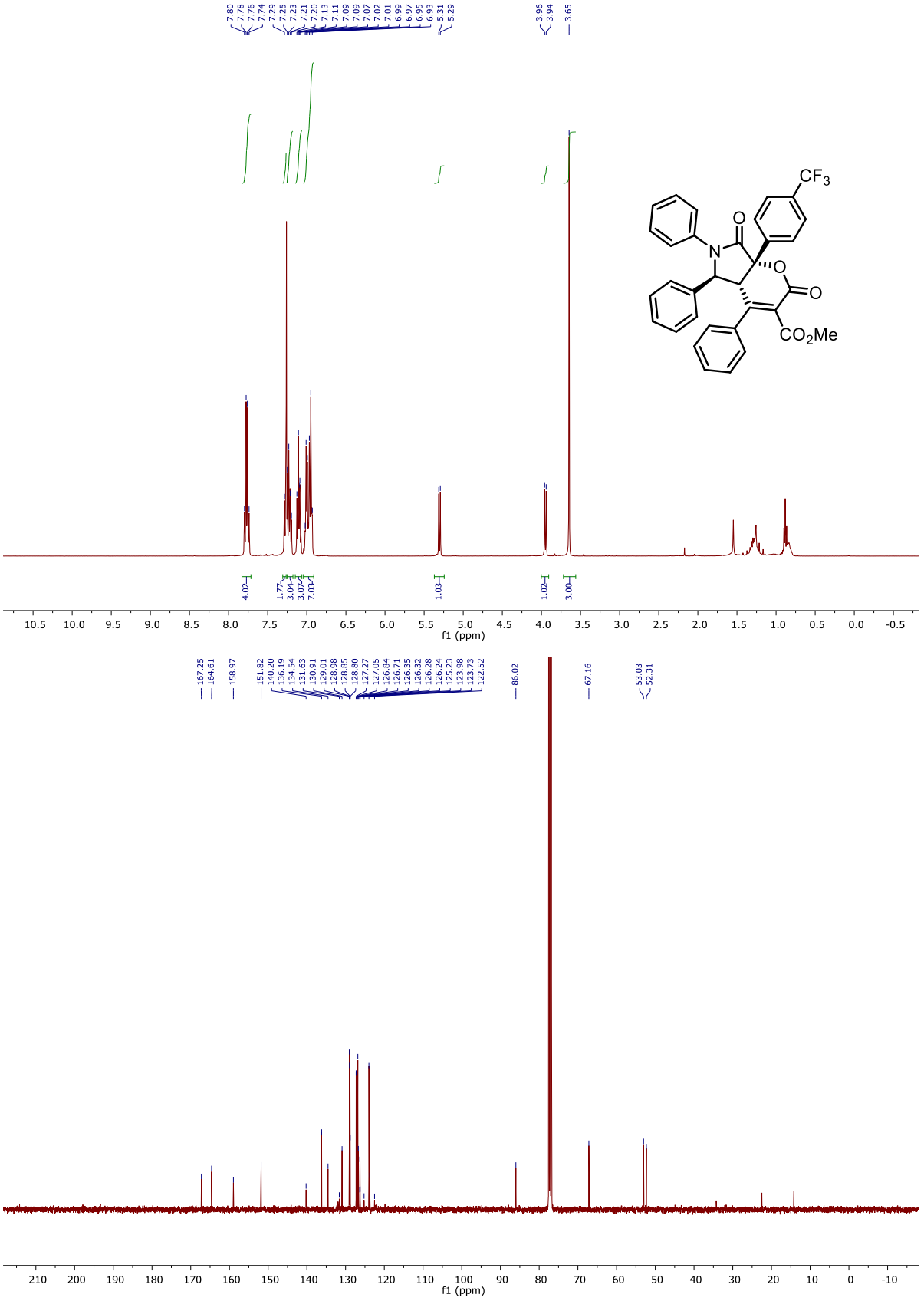


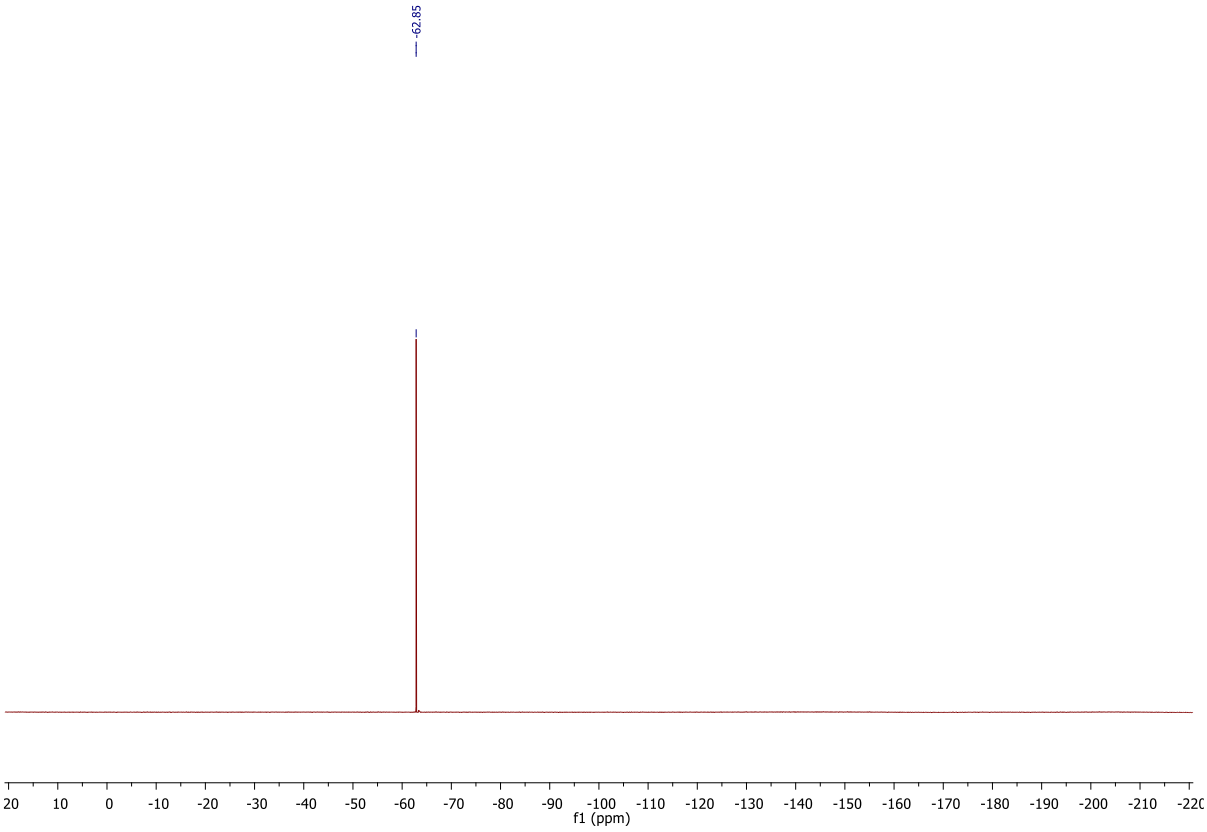
(±) Methyl 7a-(4-methoxyphenyl)-2,7-dioxo-4,5,6-triphenyl-2,4a,5,6,7,7a-hexahydropyrano [2,3-c]pyrrole-3-carboxylate (4af)



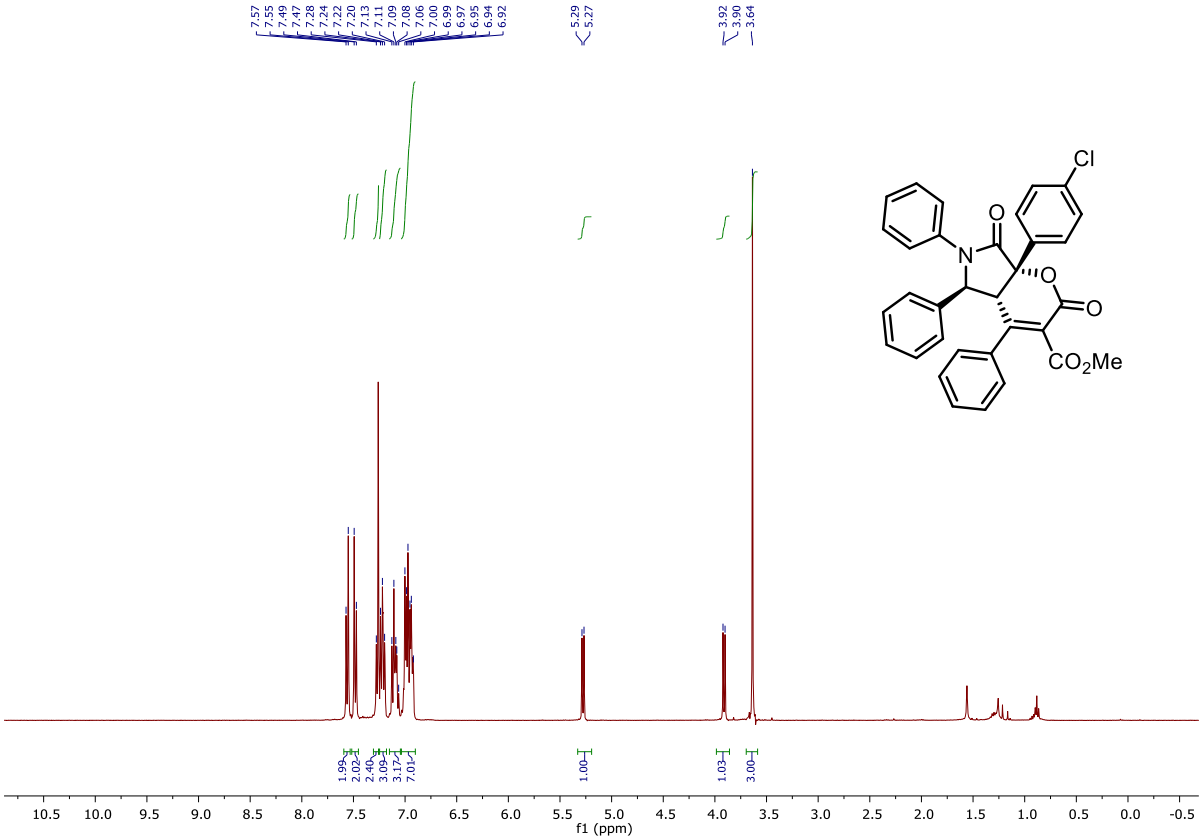


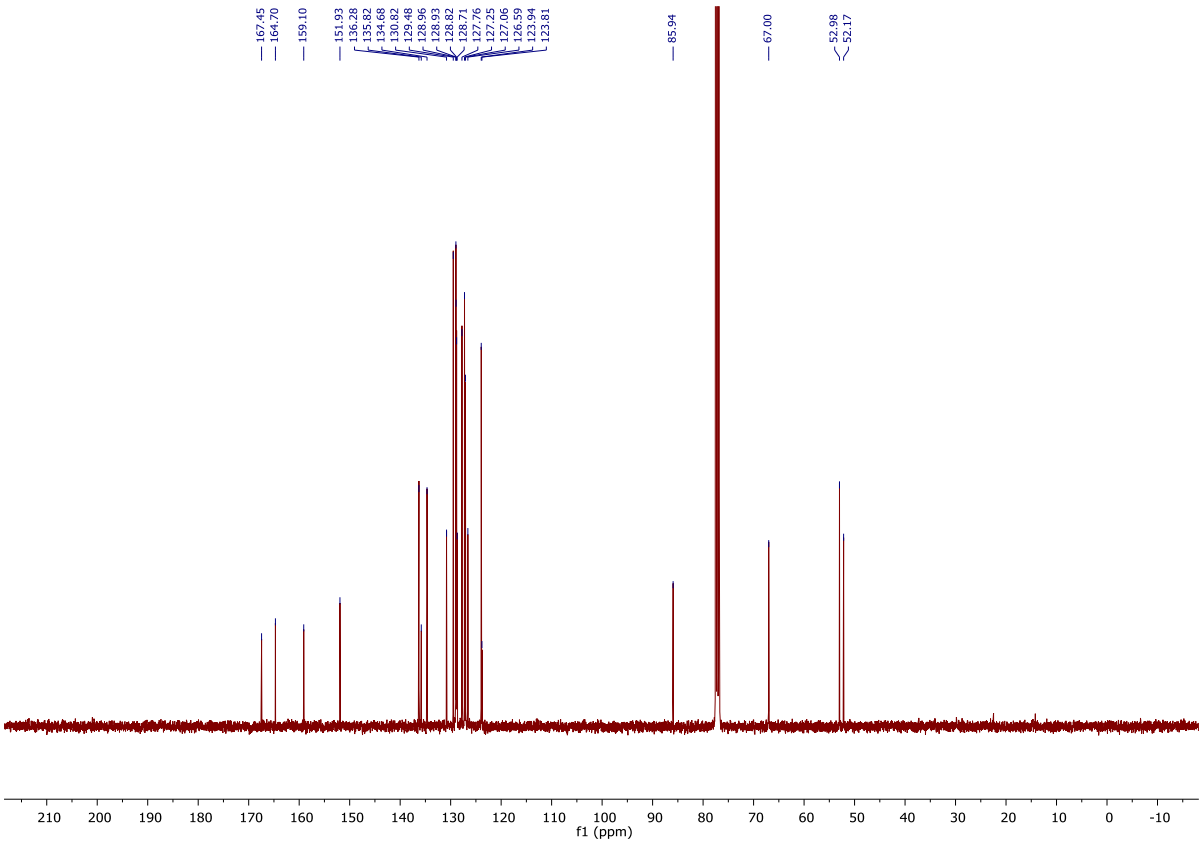
(±) Methyl 2,7-dioxo-4,5,6-triphenyl-7a-(4-(trifluoromethyl)phenyl)-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4ag)



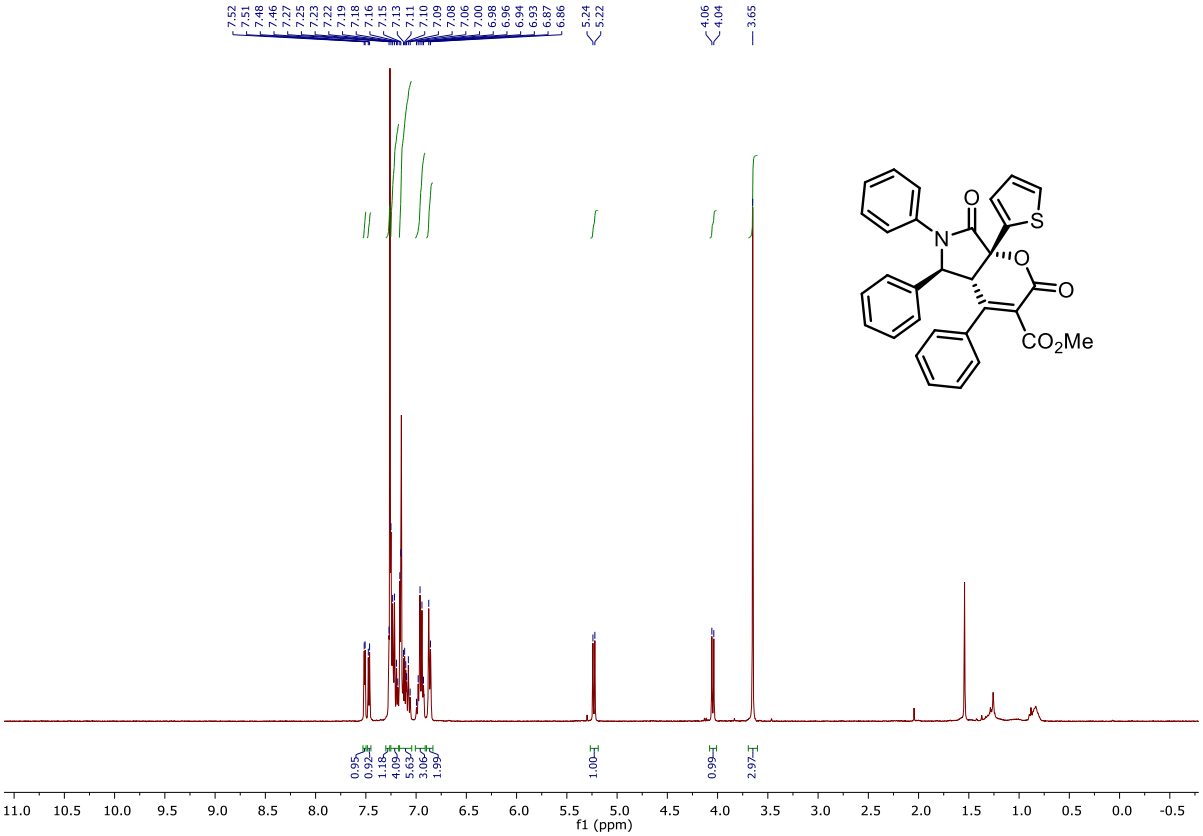

-62.85
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

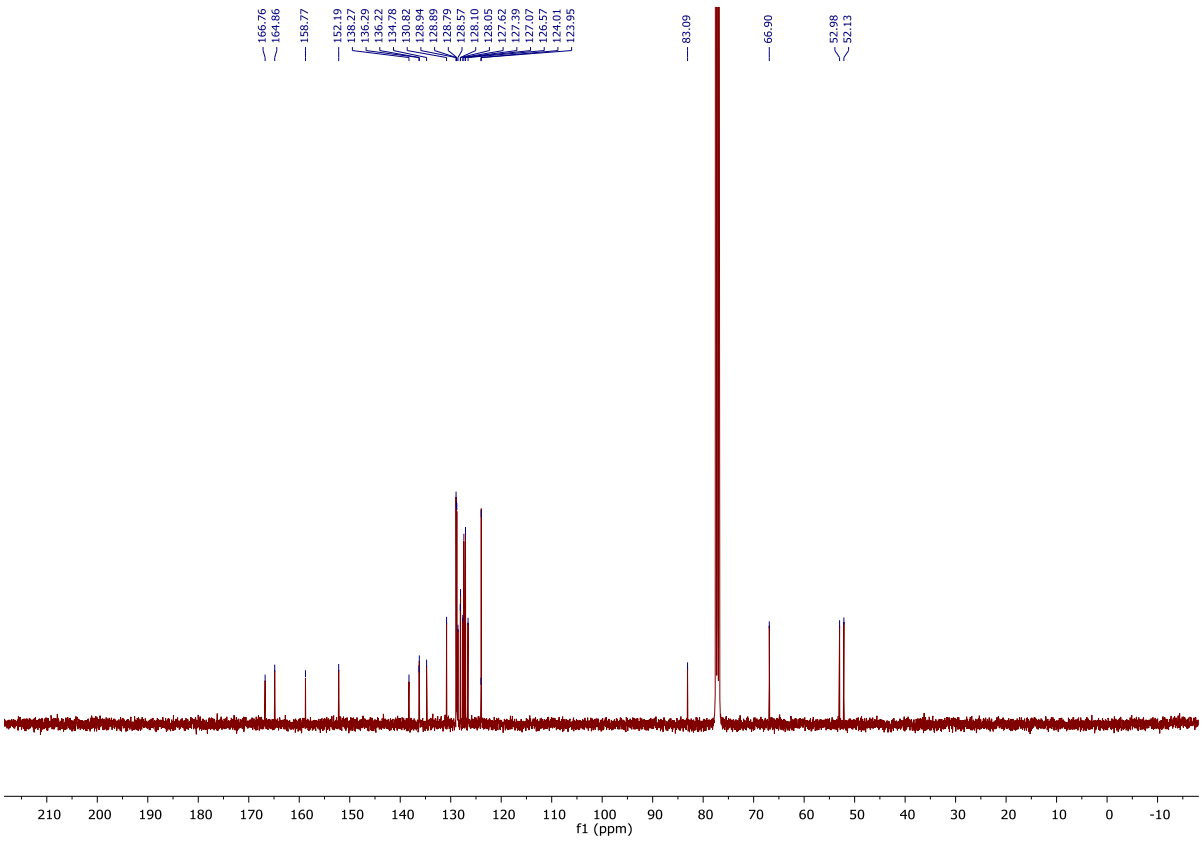
(±) Methyl 7a-(4-chlorophenyl)-2,7-dioxo-4,5,6-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4ah)



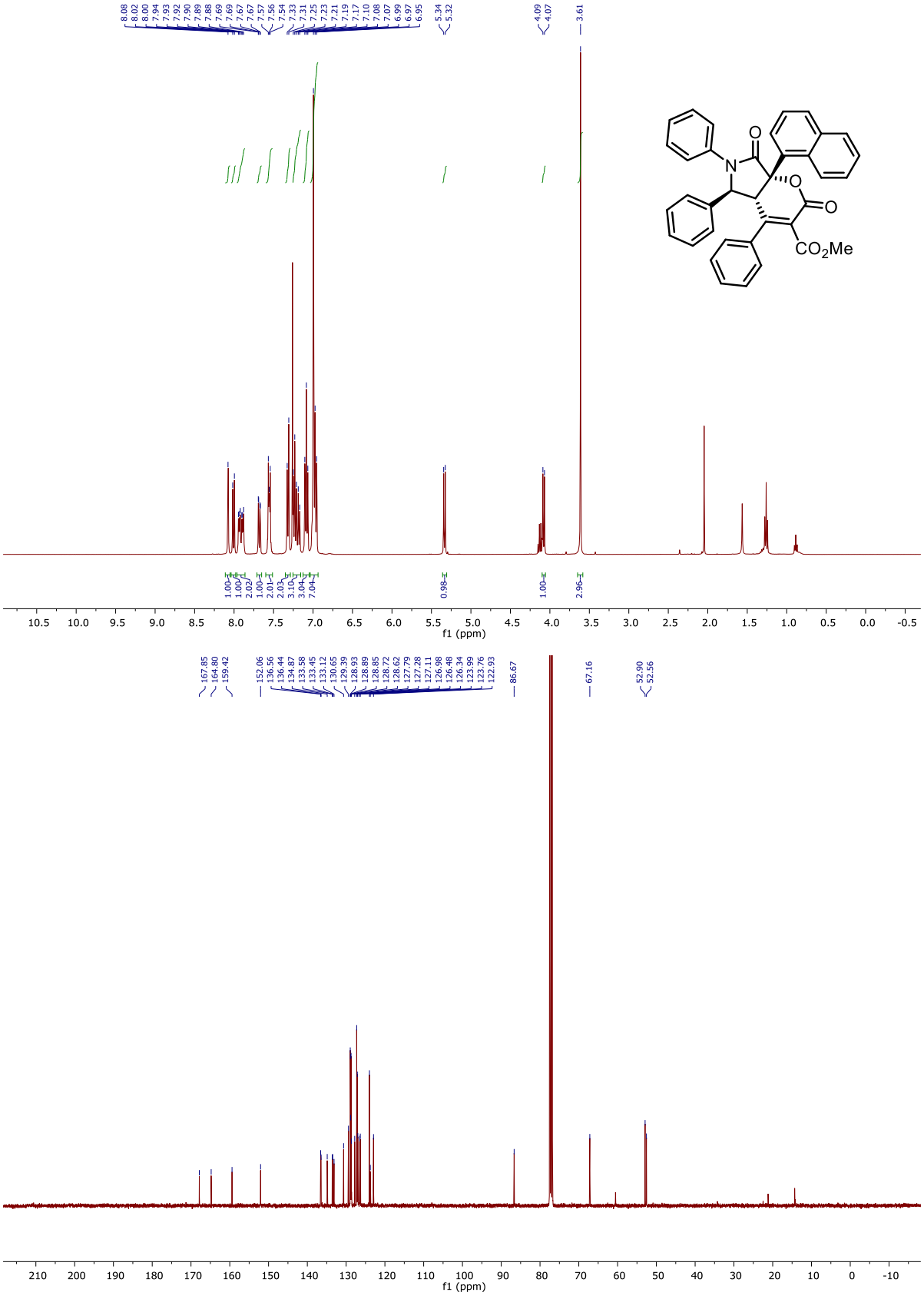


(±) Methyl 2,7-dioxo-4,5,6-triphenyl-7a-(thiophen-2-yl)-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4ai)

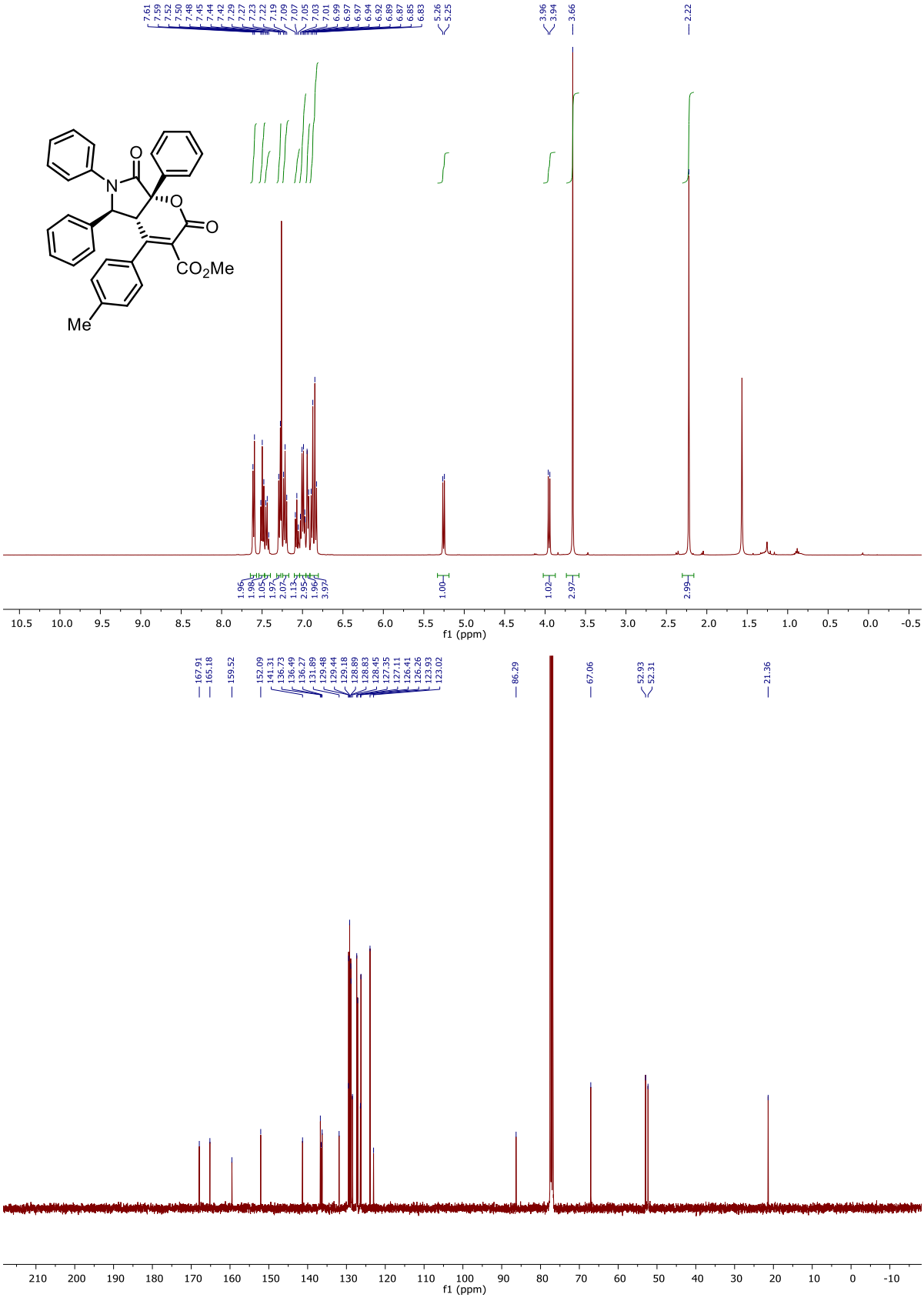




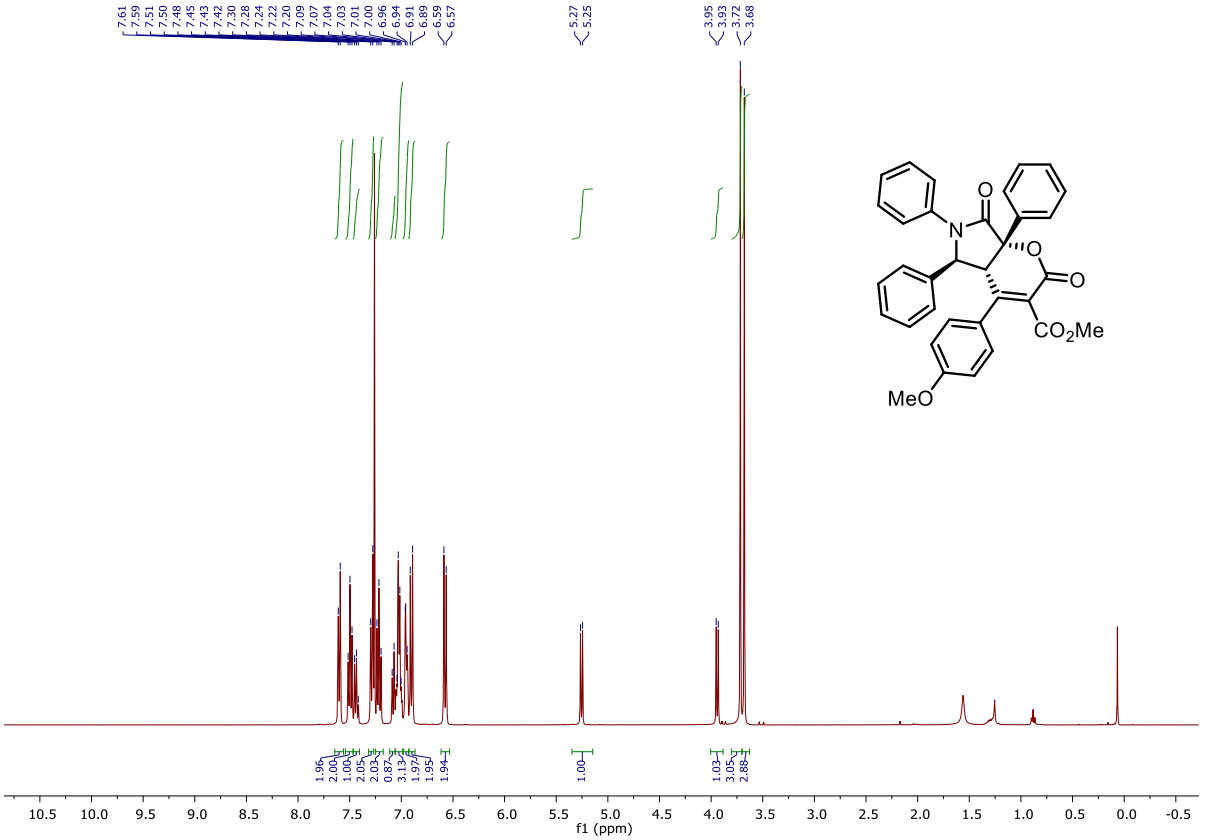
(±) Methyl 7a-(naphthalen-1-yl)-2,7-dioxo-4,5,6-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4aj)

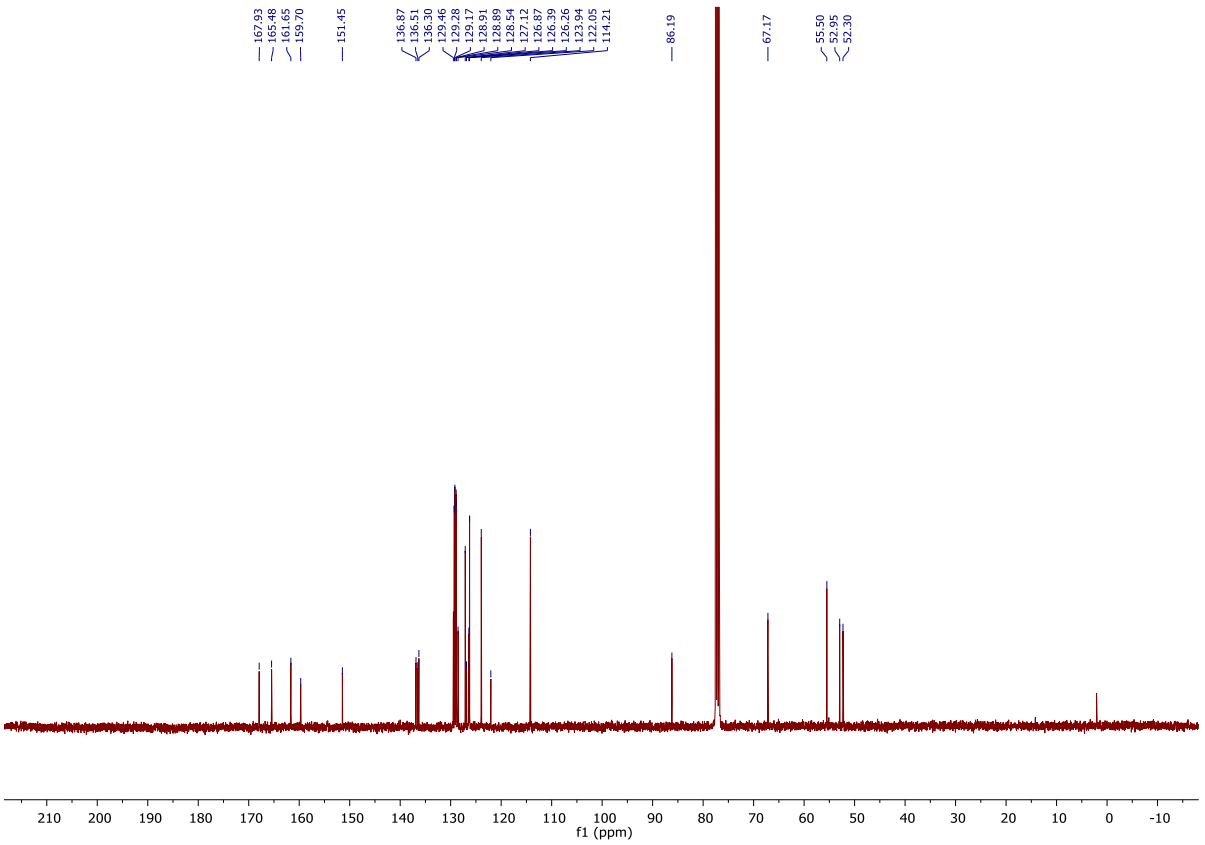


(±) Methyl 2,7-dioxo-4,6,7a-triphenyl-5-(p-tolyl)-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4ba)

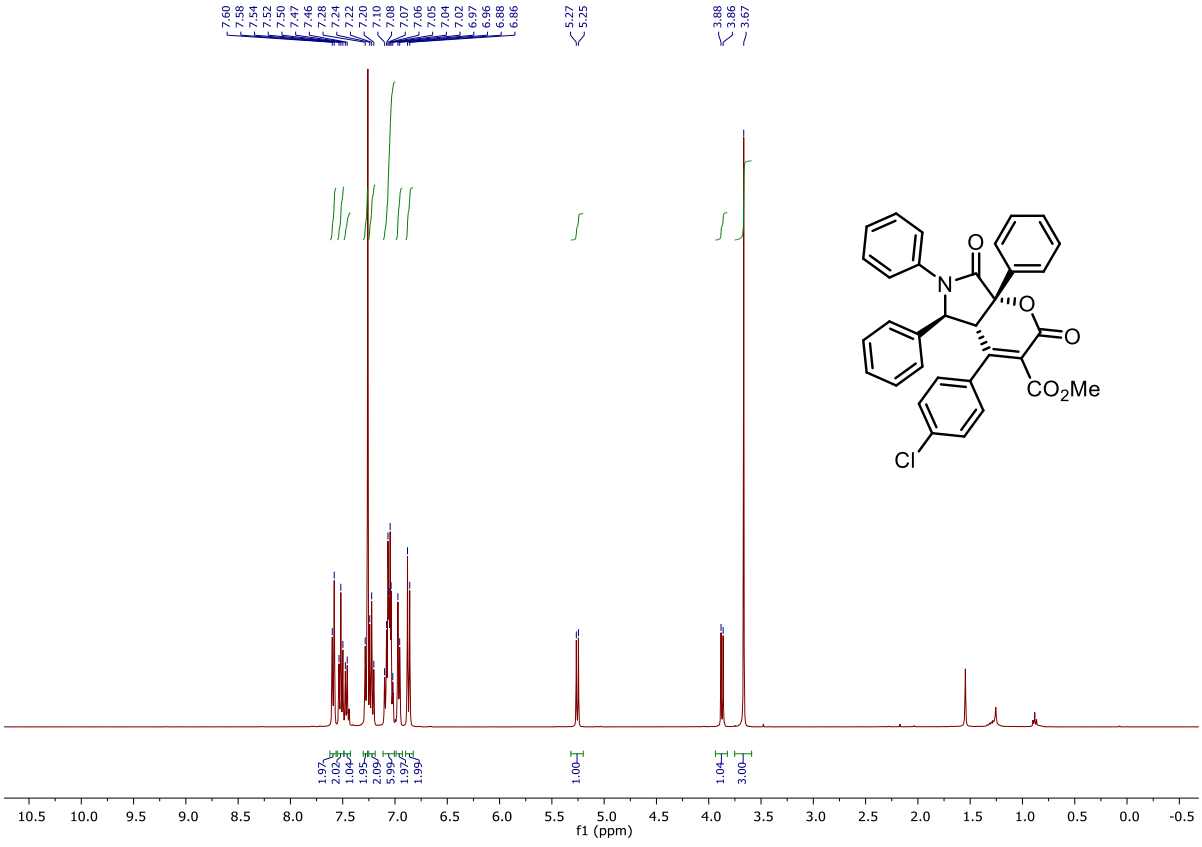


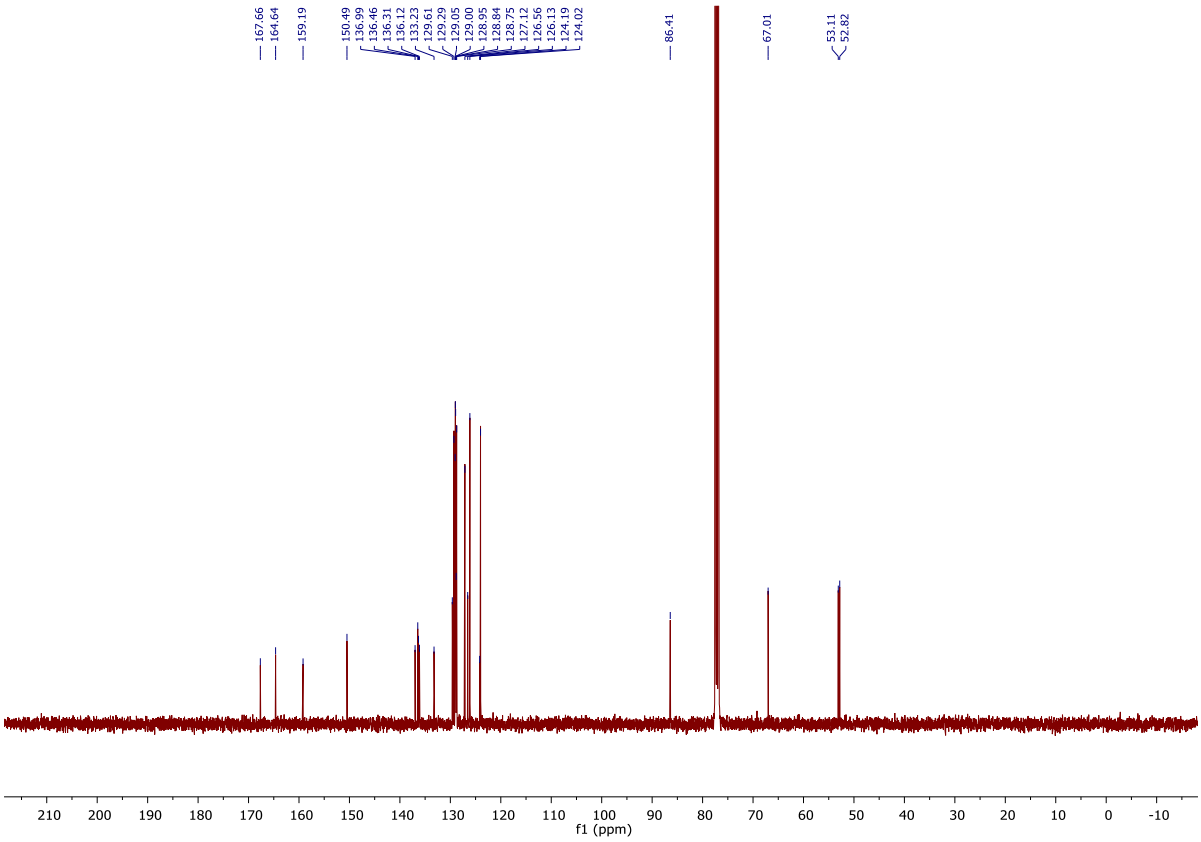
(±) Methyl 4-(4-methoxyphenyl)-2,7-dioxo-5,6,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4ca)



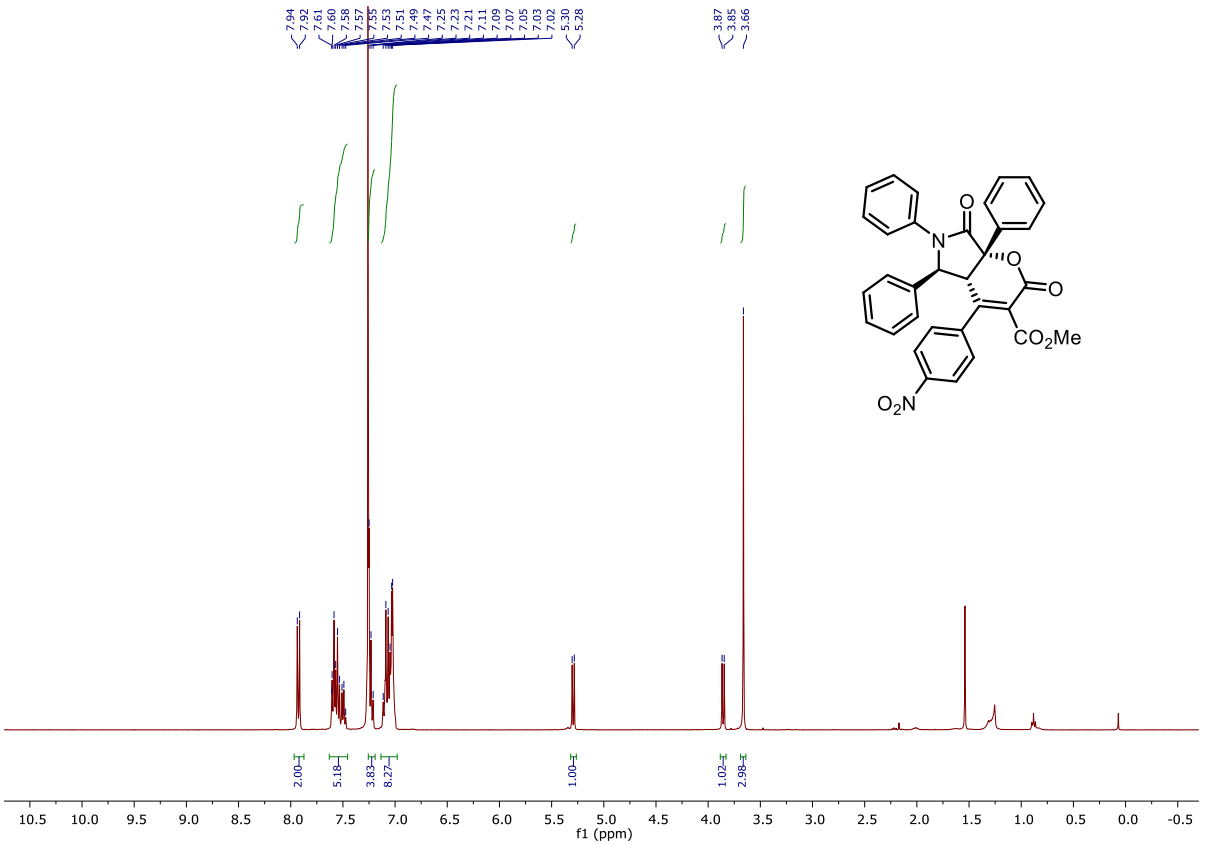


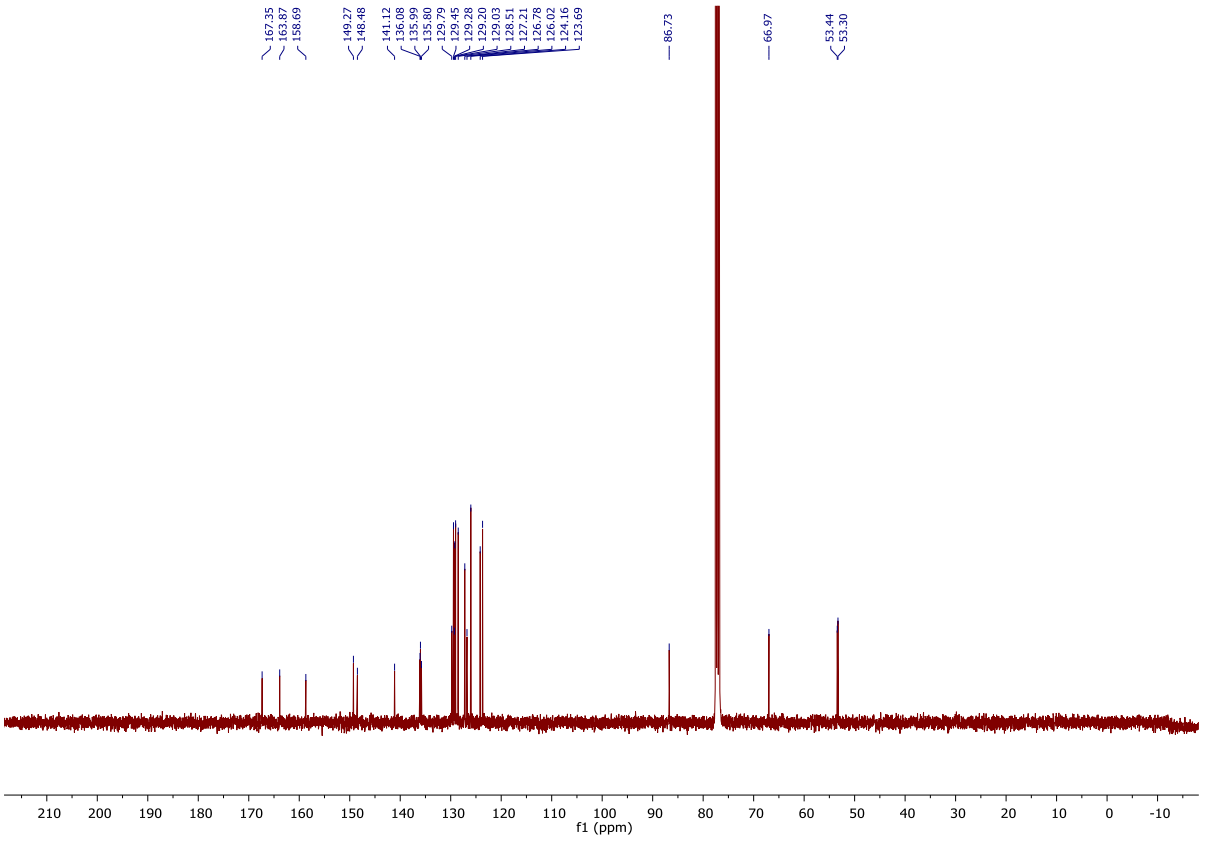
(±) Methyl 4-(4-chlorophenyl)-2,7-dioxo-5,6,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4da)



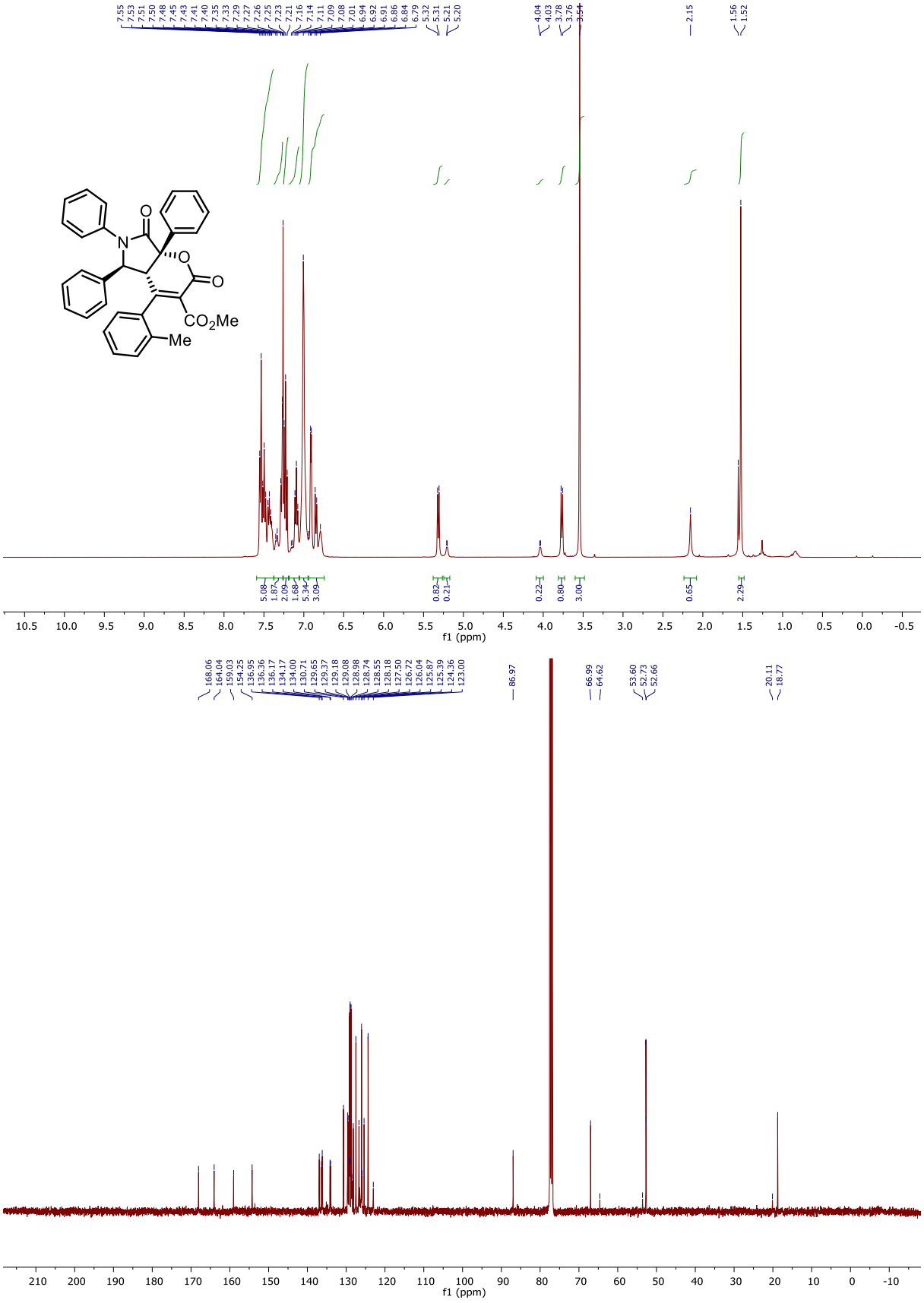


(±) Methyl 4-(4-nitrophenyl)-2,7-dioxo-5,6,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4ea)

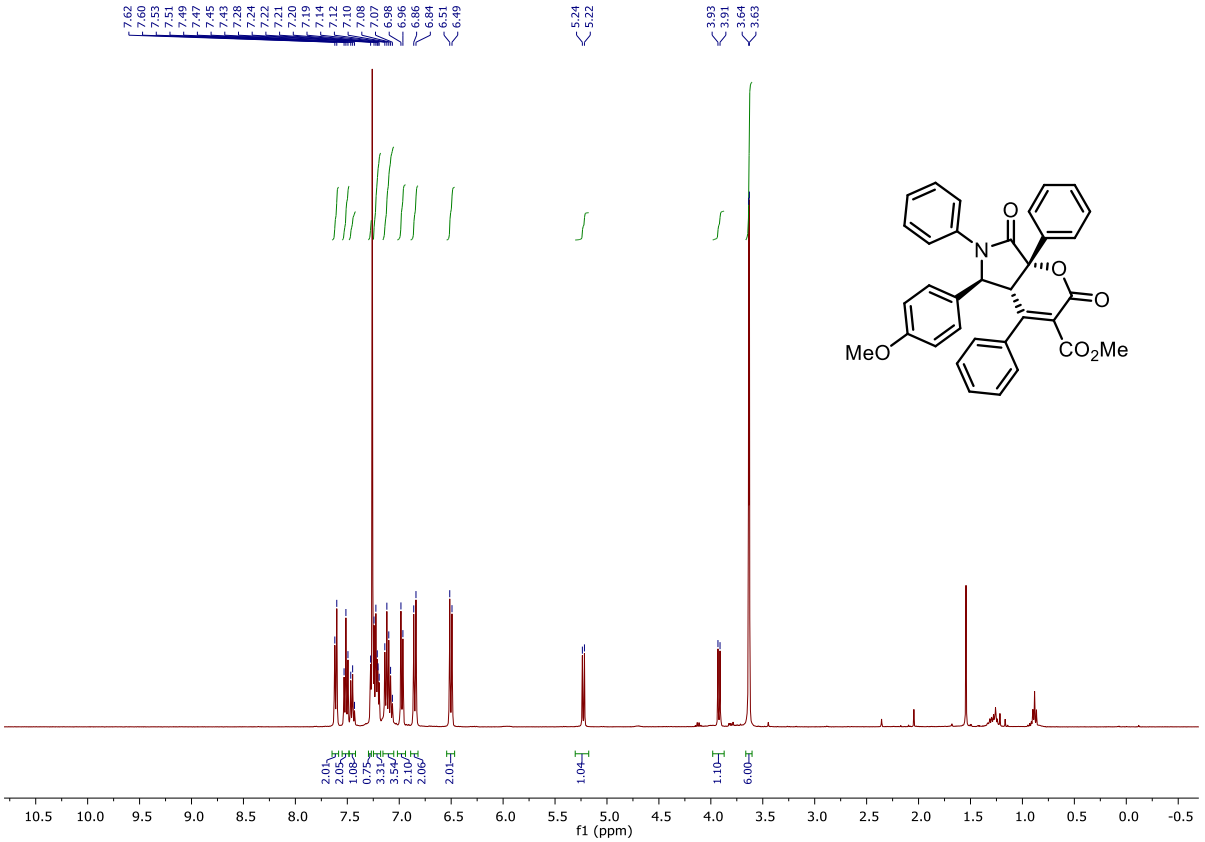


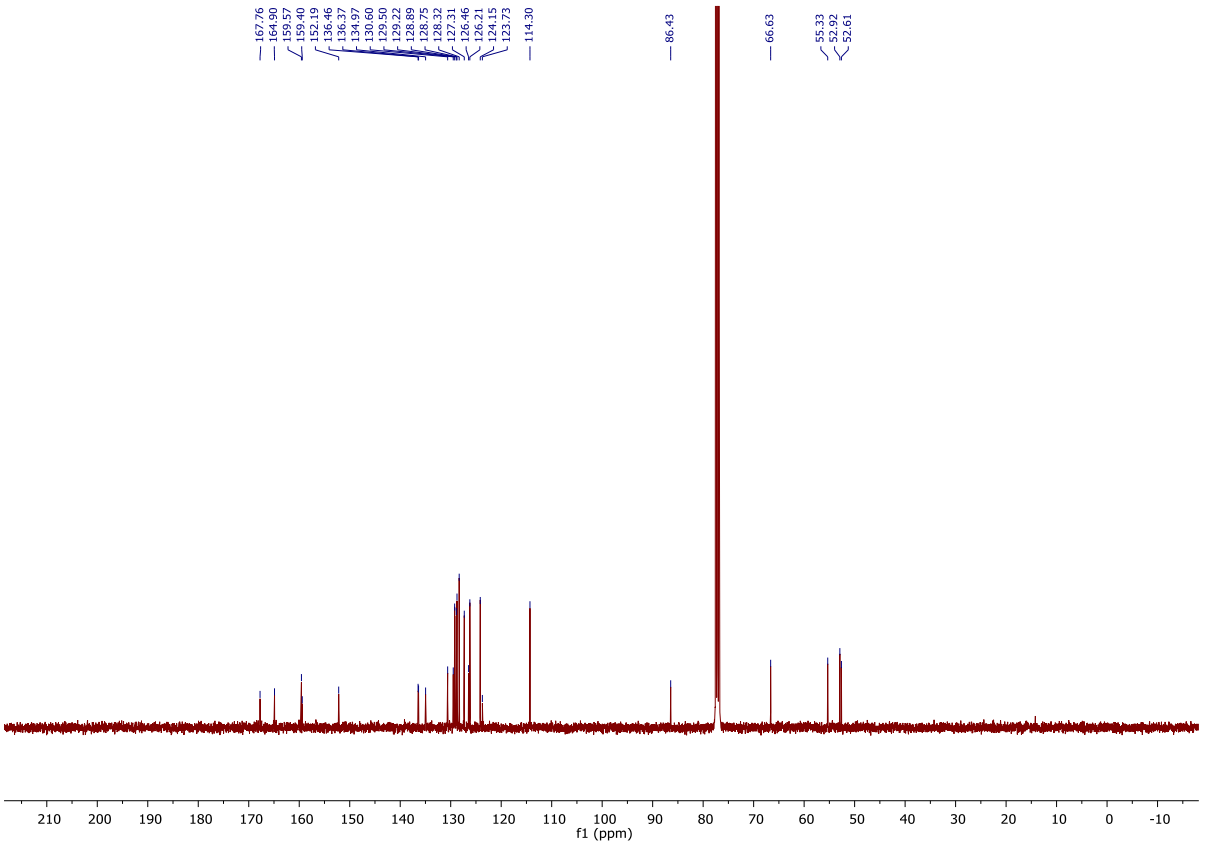


(±) Methyl 2,7-dioxo-5,6,7a-triphenyl-4-(o-tolyl)-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4fa)

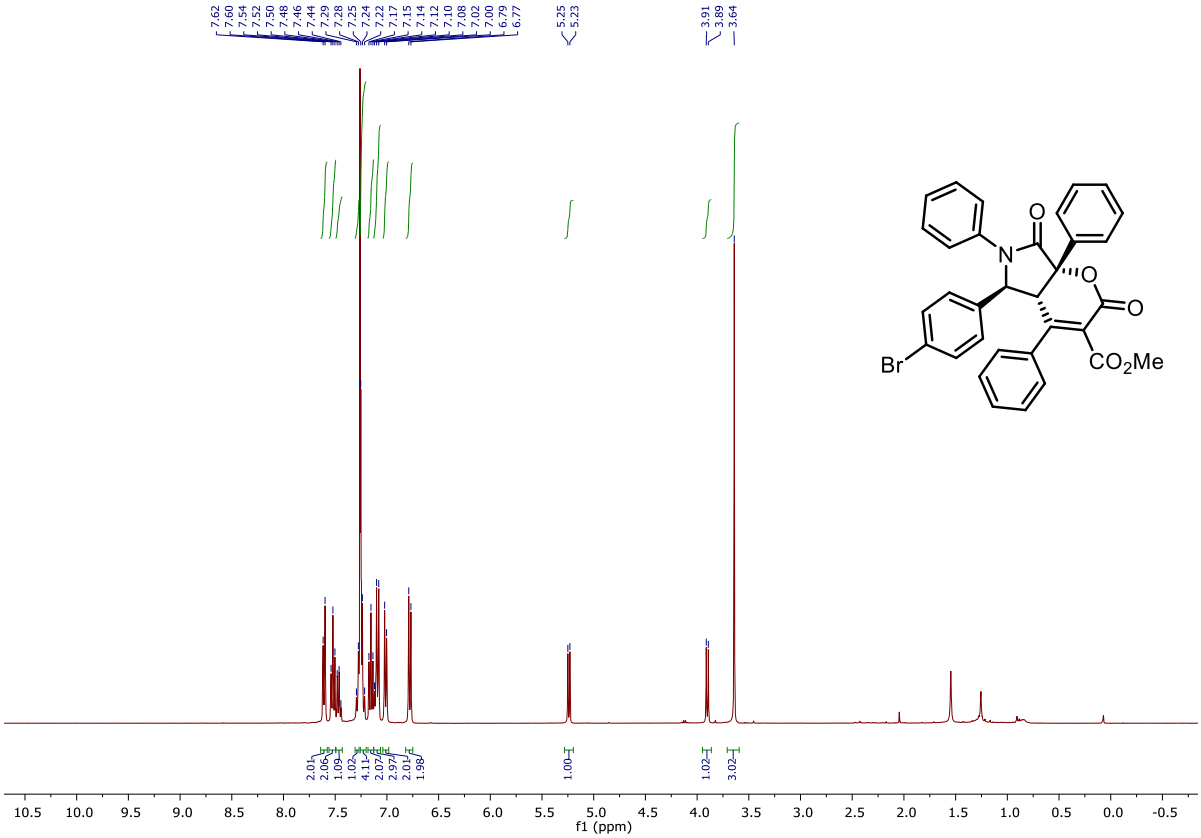


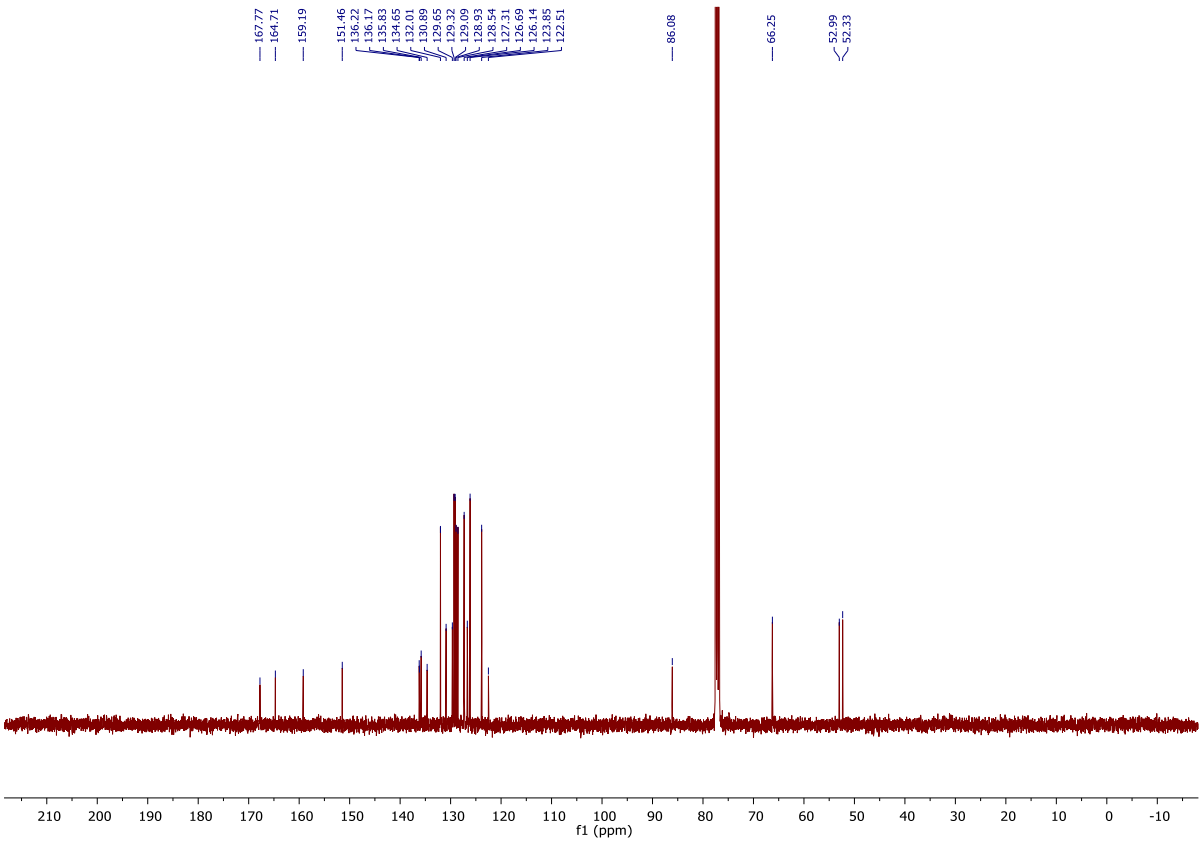
(±) Methyl 5-(4-methoxyphenyl)-2,7-dioxo-4,6,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4ga)



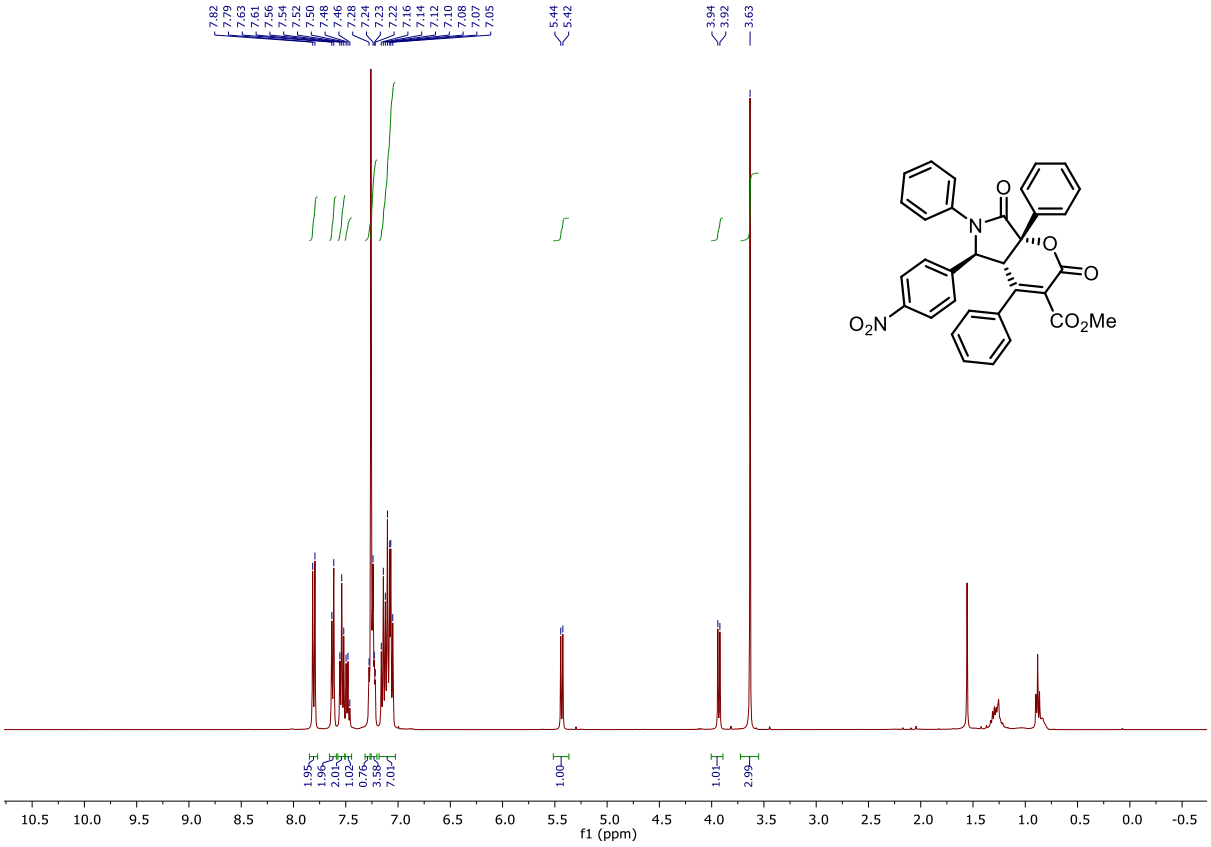


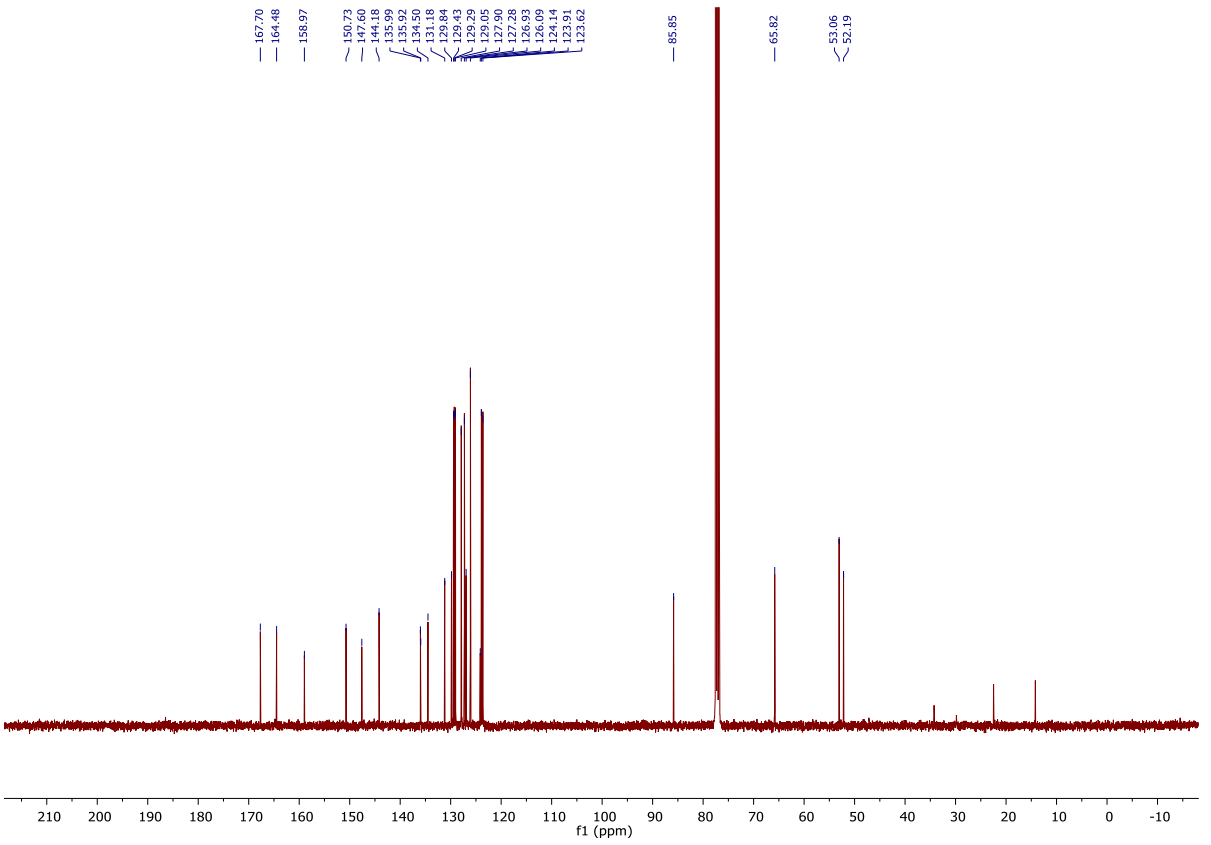
(±) Methyl 5-(4-bromophenyl)-2,7-dioxo-4,6,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4ha)



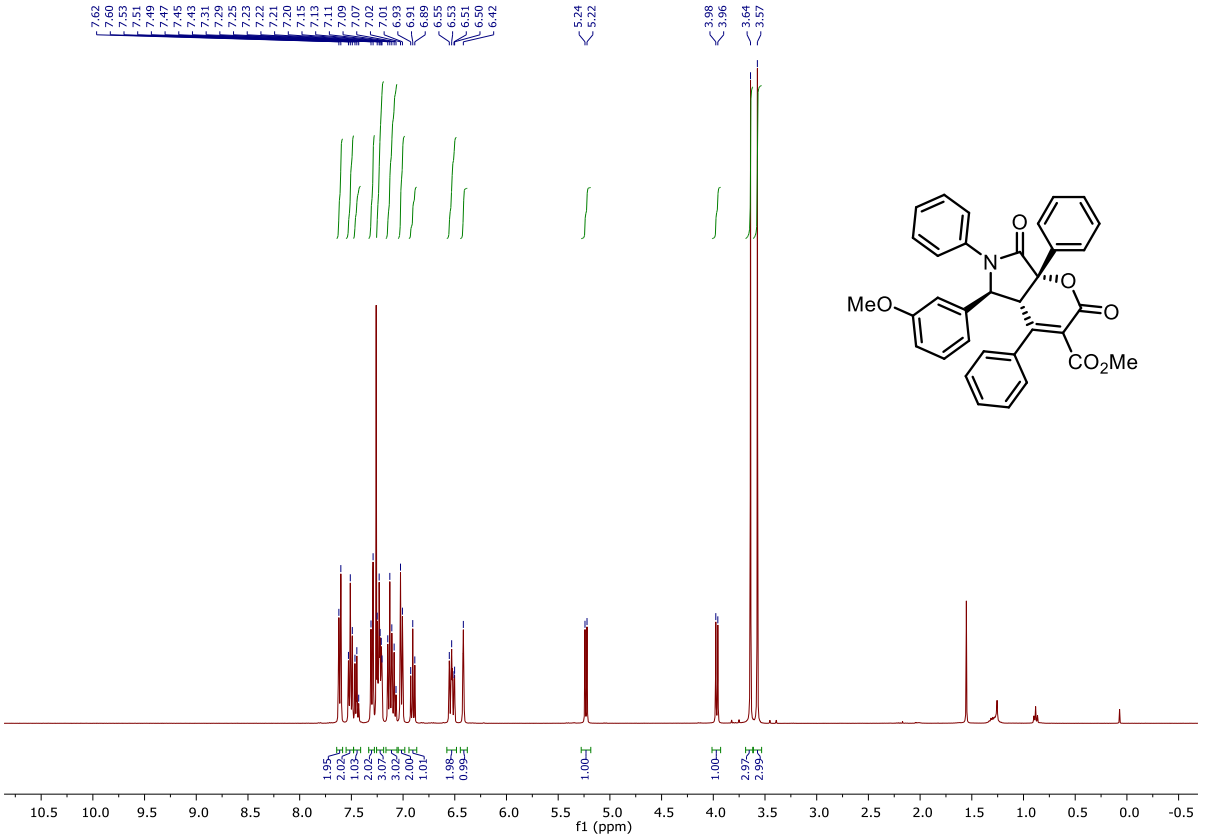


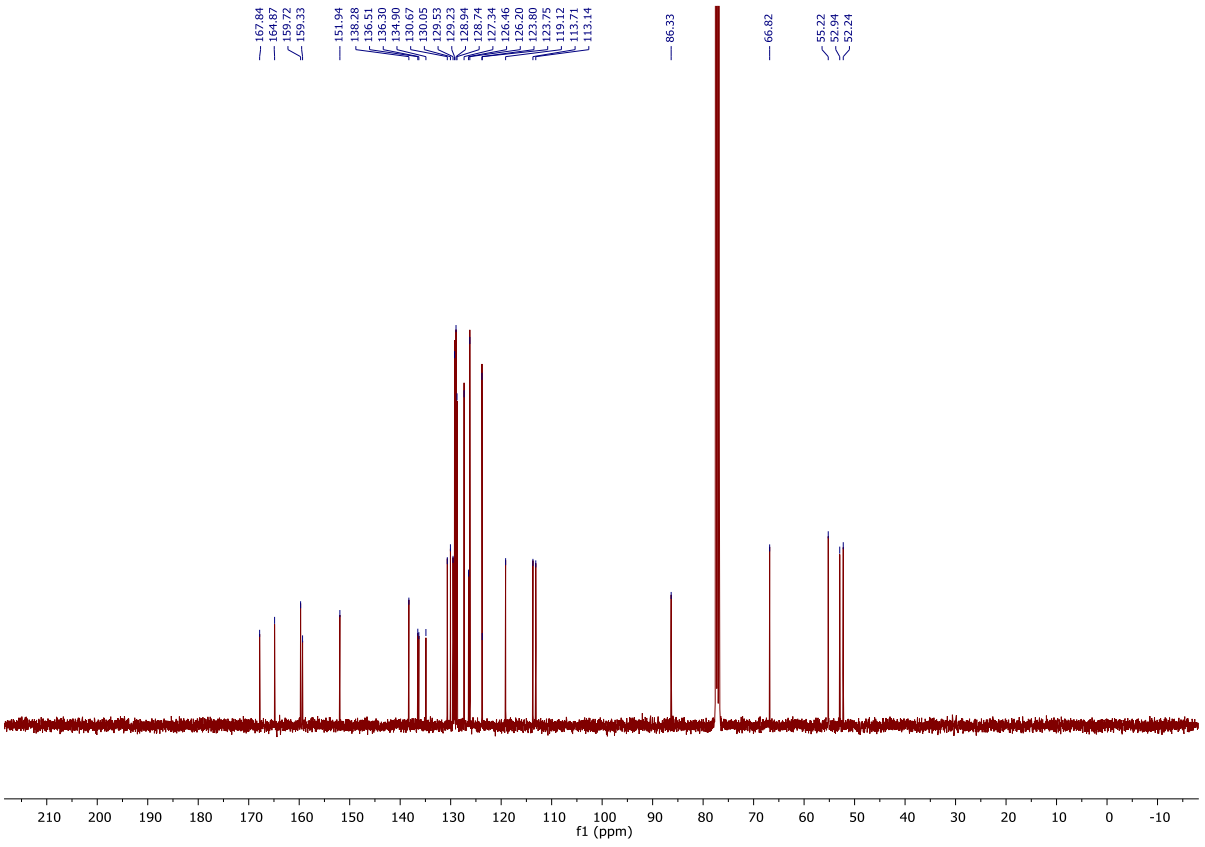
(±) Methyl 5-(4-nitrophenyl)-2,7-dioxo-4,6,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4ia)



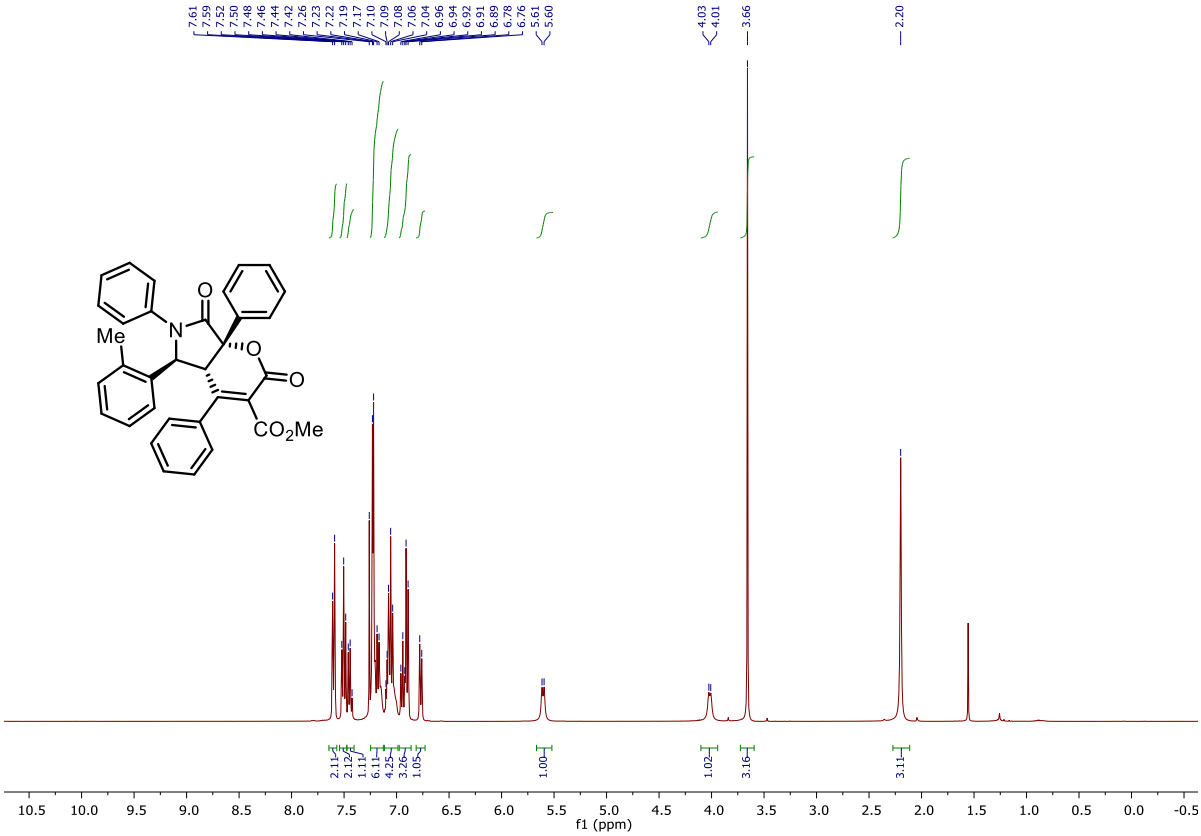


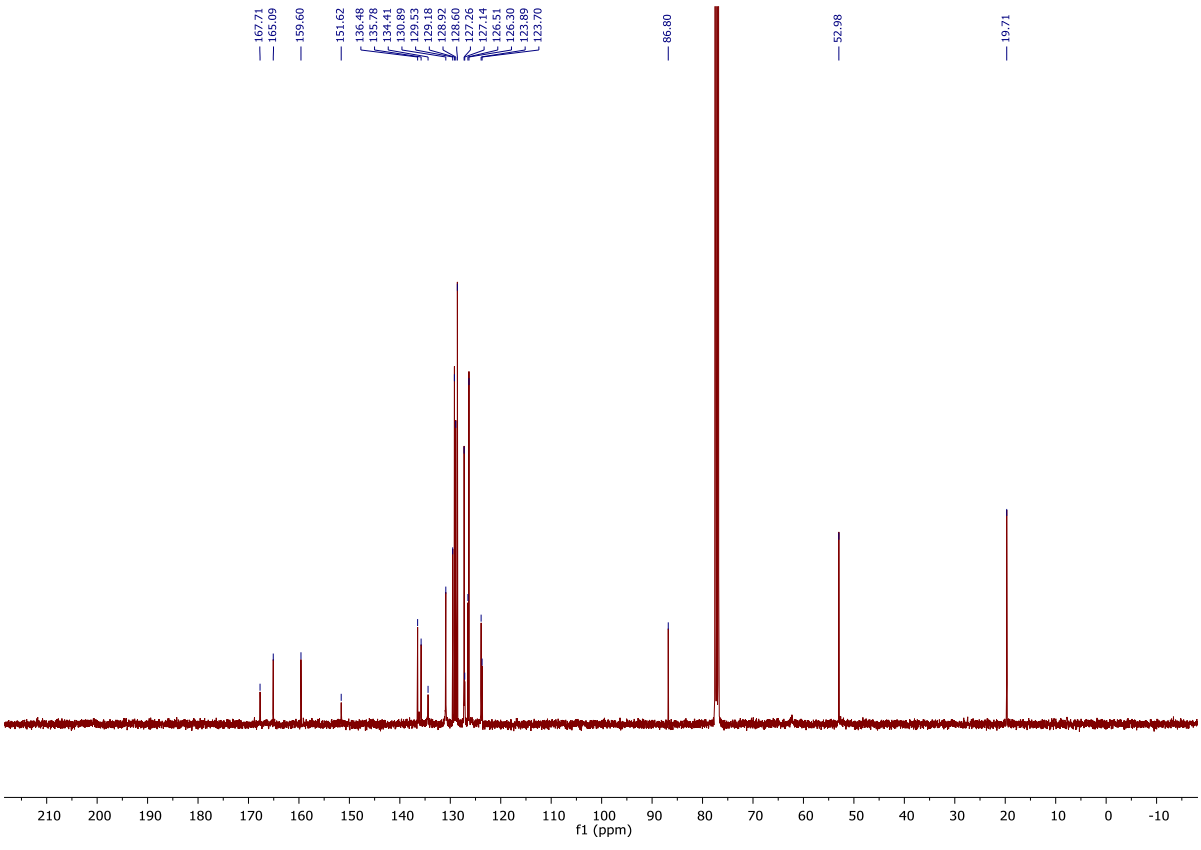
(±) Methyl 5-(3-methoxyphenyl)-2,7-dioxo-4,6,7a-triphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4ja)





(±) Methyl 2,7-dioxo-5,6,7a-triphenyl-4-(o-tolyl)-2,4a,5,6,7,7a-hexahydropyrano[2,3-c] pyrrole -3-carboxylate (4ka)





(±) Methyl 5-(furan-2-yl)-4-(4-methoxyphenyl)-2,7-dioxo-6,7a-diphenyl-2,4a,5,6,7,7a-hexahydropyrano[2,3-c]pyrrole-3-carboxylate (4la)