Supplementary Information

Three-step alkylaminomethylative α,β-difunctionalization of enones

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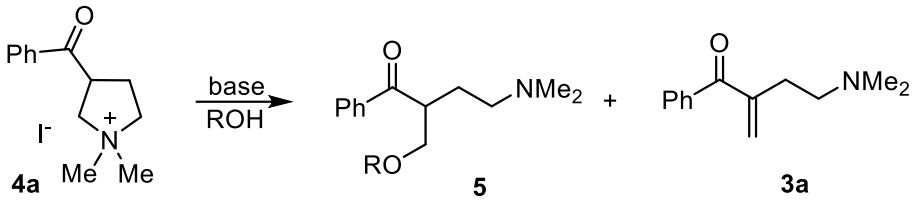
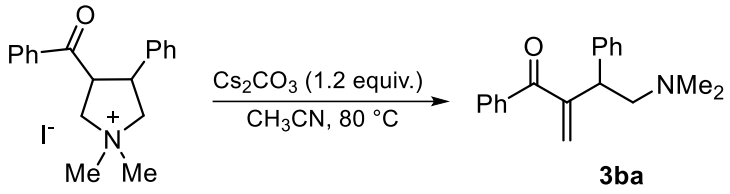
Optimization of the reaction conditions for the ring-cleavage of quaternary ammonium salts 4:



4a **5** **3a**

	Reaction Conditions	Result, **5** : **3a** (yield)
1	MeONa (1.2 equiv.), MeOH, 25 °C, 48 h	complex mixture
2	K_2CO_3 (1.05 equiv.), MeOH, 65 °C, 12 h	81 : 19 (**5**, 73%)
3	Cs_2CO_3 (1.05 equiv.), MeOH, 65 °C, 12 h	100 : 0 (**5**, 84%)
4	KOH (1.05 equiv.), MeOH, 60 °C, 17 h	97 : 3 (**5**, 68%)
5	KOH (1.05 equiv.), H_2O, 60 °C, 17 h	complex mixture
6	Cs_2CO_3 (2.0 equiv.), EtOH/H_2O (3:2), 65 °C, 12 h	no reaction
7	Cs_2CO_3 (1.05 equiv.), BnOH, 75 °C, 15 h	no reaction
8	Cs_2CO_3 (1.05 equiv.), iPrOH, 75 °C, 21 h	56 : 44
9	Cs_2CO_3 (1.05 equiv.), H_2O + 1,4-dioxane (3 : 2 mL), 65 °C, 12 h	complex mixture + starting quaternate
10	Cs_2CO_3 (1.05 equiv.), CH_3CN, 65 °C, 12 h	38% (**3a**)
11	Cs_2CO_3 (1.05 equiv.), CH_3CN, 80 °C, 40 h	30% (**3a**)
12	Cs_2CO_3 (1.05 equiv.), DMF, 100 °C, 3 h, then 65 °C, 12 h	52% (**3a**)
13	Cs_2CO_3 (1.05 equiv.), DMF, 100 °C, 4 h, then 65 °C, 12 h	28% (**3a**)
14	*t*BuOK (1.1 equiv.), DMSO, 25 °C, 24 h	complex mixture
15	NaH (1.3 equiv.), DMSO, 25 °C, 24 h	complex mixture

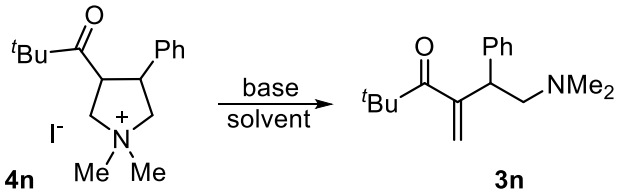
Optimization of the reaction conditions for the ring-cleavage without nucleophile:



4ba **3ba**

	Time, additive	Yield, **3ba**
1	3 h	47%
2	8 h	60%
3	15 h	53%
4	24 h	68%
5	48 h	84%
6	40 h	83%
7	3 h, DABCO (0.2 equiv.)	58%

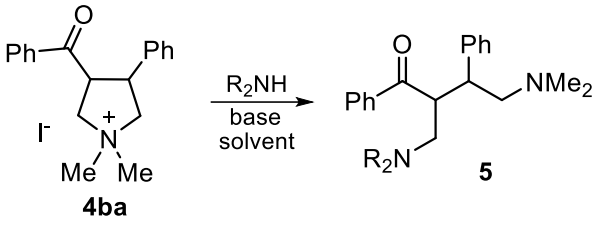
Optimization of the reaction conditions for the ring-cleavage of bulky substrate:



4n **3n**

	Reaction Conditions	Result
1	Cs_2CO_3 (1.05 equiv.), acetone cyanohydrin (2.5 equiv.), MeOH, 65 °C, 12 h	starting quaternate **4**
2	NaH (1.2 equiv.), DMSO, 80 °C, 24 h	complex mixture
3	NaH (1.2 equiv.), DMSO, 25 °C, 23 h	98%

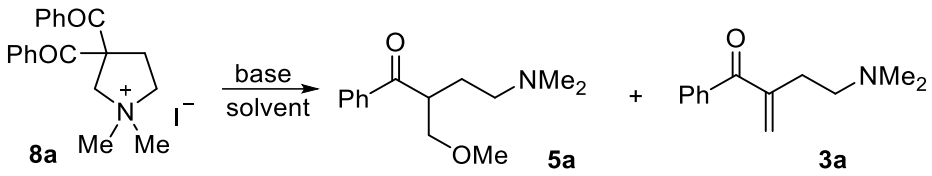
Optimization of the conditions for the reaction with amines:



4ba **5**

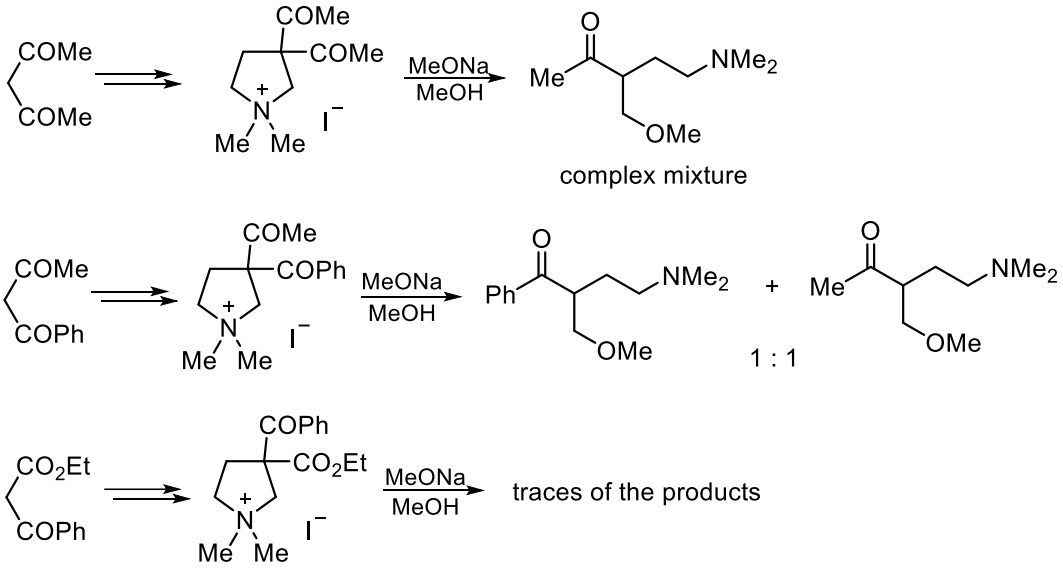
	Reaction Conditions	Result
1	piperidine (2 equiv.), Cs_2CO_3 (1.05 equiv.), MeOH, 65 °C, 12 h	83%, dr 17:83 (5% NMR yield of MeO-product)
2	piperidine (3 equiv.), Cs_2CO_3 (1.1 equiv.), CH_3CN, 80 °C, 2 h	93%, dr 18:82
3	aniline (3 equiv.), Cs_2CO_3 (1.05 equiv.), CH_3CN, 80 °C, 40 h	68%, dr 93:7
4	aniline (1.25 equiv.), Cs_2CO_3 (1.05 equiv.), CH_3CN, 80 °C, 15 h	69%, dr 93:7

Optimization of the conditions for the debenzoylation reaction:



	Reaction Conditions	Result, **5a** : **3a**
1	Cs_2CO_3 (2 equiv.), MeOH, 70 °C, 3 h	64 : 36
2	Cs_2CO_3 (2 equiv.), MeOH, 70 °C, 12 h	78 : 22 37% NMR yield (**5a**)
3	MeONa (1.2 equiv.), MeOH, 25 °C, 45 h	96 : 4 full conversion of **8a** 52% isolated yield (**5a**)
4	MeONa (5.0 equiv.), MeOH, 70 °C, 45 min	82 : 18 full conversion of **8a**
5	MeONa (1.2 equiv.), MeOH, 50 °C, 2 h	85 : 15 full conversion of **8a**

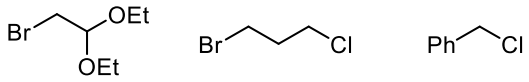
Investigation of other methylene-active compounds and the selectivity of the deacylation:



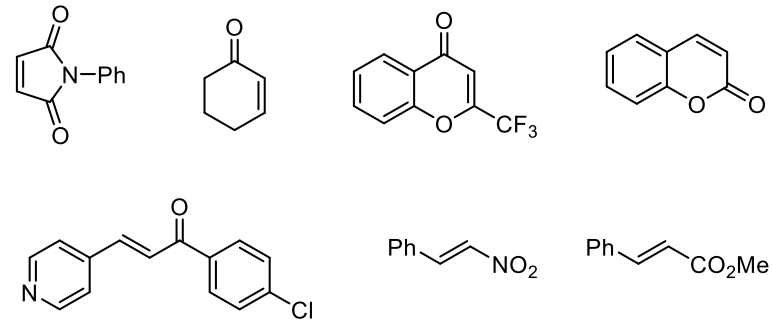
Unsuccessful reagents and substrates:

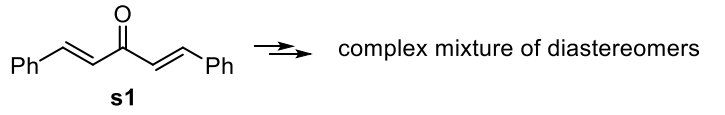
Nucleophiles: nitromethane, PhMgBr, sodium *p*-toluenesulfinate, phenol, NaN_3, 16M aqueous N_2H_4, malonamide, 3-oxo-3-phenylpropanoic acid, 5,5-dimethylcyclohexane-1,3-dione.

Poor reactive **alkyl halogenides**:

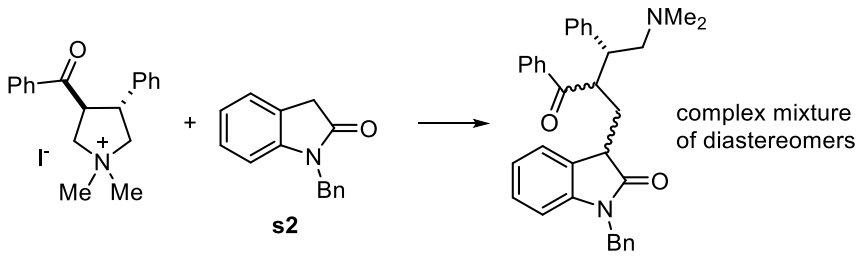


Substrates that provided quaternary ammonium salts in good to excellent yields, however their reaction in the ring-cleavage step resulted in a complex mixture of products:





s1

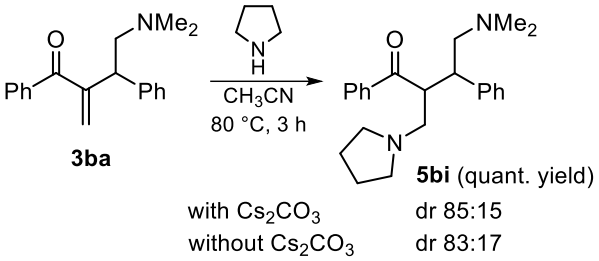


s2

An application of the dibenzylidene acetone (**s1**) resulted in a complex mixture of diastereomers due to the formation of two pyrrolidine cycles (double cycloaddition occurs even in the case of 1 equiv. of azomethine ylide, so the excess of azomethine ylide was used) and hence two reactive and four stereogenic centers. An application of unsymmetrical nucleophile such as *N*-benzyloxindole (**s2**) also resulted in a complex mixture of diastereomers.

Control experiments, presumable mechanisms and diastereoselectivity:

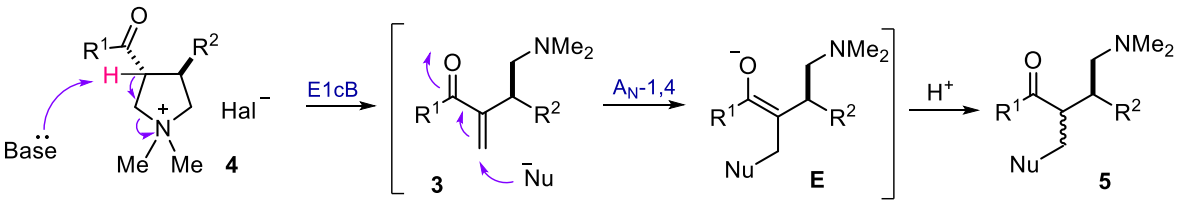
To get some insights into the selectivity of the process we performed the reaction of **3ba** with pyrrolidine in acetonitrile. It was found that the diastereoselectivity of the formation of product **5bi** remains on the same level as in the reaction of ammonium salt **4ba**. The presence of cesium carbonate did not make any effect on the process. These results additionally confirm the presence of the intermediate alkene **3ba**.



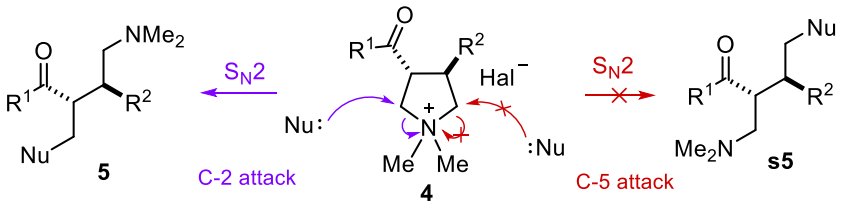
In this way, the presumable mechanism of the ring cleavage stage consists in the preliminary deprotonation of the acidic proton at the C-3 position of the pyrrolidine ammonium salt **4** by the inorganic base or amines, present in the reaction media, and elimination reaction leading to the intermediate terminal enone **3**. Subsequent Michael addition of the nucleophile provides the enolate **E**.

The presumable mechanism of the ring cleavage:

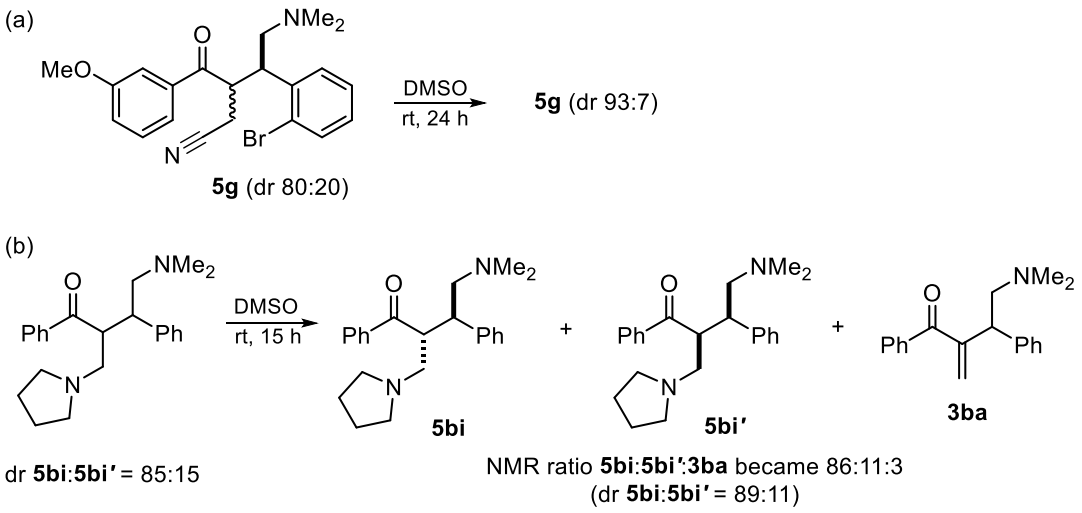
Elimination/Michael addition pathway



Direct S_N2 pathway

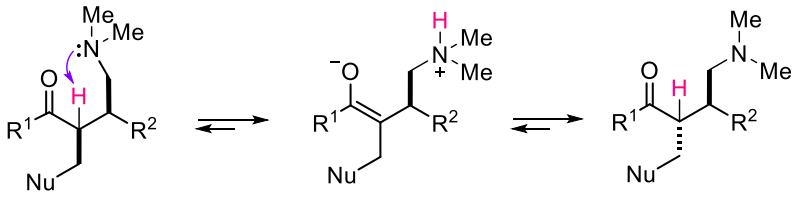


The alternative mechanism consists in the direct S_N2 attack of the strong nucleophile such as cyanide anion at C-2 atom of the pyrrolidine ammonium salt **4**. While such ring-opening of azaheterocyclic compounds are known in the literature (von Braun type reactions), the realization of this pathway is less probable due to the presence of an acidic proton at 3rd position of the pyrrolidine and basic reaction conditions. Additionally, such nucleophilic attack would take place at both α-positions of the quaternary ammonium salt – C-2 and C-5 atoms of the pyrrolidine, thus leading to the formation of a mixture of the corresponding products **5** and **s5**. However, we did not observe any traces of the alternative product **s5** of the attack at C-5 atom.



The stirring of the product **5g** in DMSO solution for 24 h resulted in the alteration of the diastereomeric ratio to 93:7 from 80:20. At the same time, treatment of the product **5bi** in DMSO at rt for 15 h resulted only in the insignificant decomposition to alkene **3ba**. These results indicate the equilibrium between the diastereomers in the solution and the ability to isomerize to less sterically hindered diastereomer. Apparently, the diastereoselectivity of the Michael addition of nucleophiles to the intermediates **3** is controlled by the reversible enolization in the presence of base or internal base (amino group) in a solution and results in the more thermodynamically expedient diastereoisomer.

The presumable mechanism of the diastereomeric isomerization:

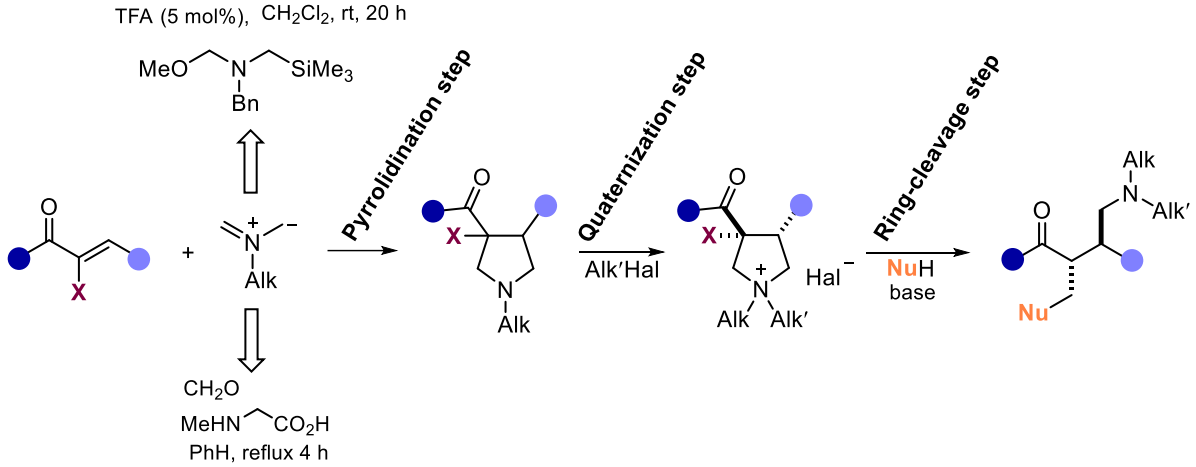


Materials and methods:

Starting materials, reagents, and solvents were purchased from commercial sources and used as received unless stated otherwise. All solvents used were dried and distilled per standard procedures. Dry cesium carbonate was applied. Alkyl halogenides was obtained from the commercial resources and was used after distillation. Starting enones **1** were purchased from commercial sources or synthesized according to the known literature procedures.

Purification of the reaction products was carried out by flash column chromatography using silica gel (40–63 µm, ASTM). Mixtures of chloroform/ethanol (95%) or dichloromethane/ethanol (95%) were used as eluents. ^{1}H and ^{13}C NMR spectra were recorded at 400/500 and 100/125 MHz, respectively; $CDCl_3$ or DMSO-d_6 were used as solvents. The chemical shifts are reported in ppm relative to internal standard TMS or to residual signals of the solvents. 2D NMR spectra were recorded at 600 MHz. The HRMS spectra were obtained using TOF mass spectrometer. Electrospray ionization with direct sample inlet (flow rate 240 µL/h) was used. The mass spectrometer was operating in positive mode in the mass range of 50–1550 Da.

General synthetic plan:



Corresponding quaternary ammonium salts **4** were obtained from enones or precursors of phenyl vinyl ketone via the pyrrolidination step and subsequent quaternization with alkyl halogenide: see **procedures A, B, C, D.**

Pyrrolidine ammonium salts **ring-cleavage** step was performed at 0.5 mmol scale according to the following ring-cleavage procedures: **General procedure RC** and **Procedures RC-Alc, RC-Am, RC-CN**.

General procedure RC for the **ring cleavage** of pyrrolidine ammonium salts**:**

Corresponding quaternary ammonium salt (0.5 mmol, 1.0 equiv.), dry cesium carbonate (1.05-1.2 equiv.), solvent (MeOH or CH_3CN, 3 mL) and nucleophile (1.0-3.0 equiv.) were sequentially added to the 10 mL pressure microwave vial equipped with a magnetic stirrer. The vial was sealed with cap and

heated in an oil bath for the indicated time (2-15 h) at 65 °C for MeOH and 80 °C for CH_3CN under vigorous stirring. The vial was cooled to room temperature and opened in a fume hood. The mixture was diluted with water (15 mL), extracted with CH_2Cl_2 (3×10 mL). Combined organic extracts were washed with water (3×10 mL), brine (10 mL), dried over sodium sulfate and evaporated under reduced pressure. The obtained products were purified by column chromatography or recrystallized.

By the nucleophile type:

Procedure RC-Alc for the ring-cleavage with **alcohol**:

Corresponding quaternary ammonium salt (0.5 mmol, 1.0 equiv.), dry cesium carbonate (171 mg, 0.53 mmol, 1.05 equiv.), MeOH (3 mL) were sequentially added to the 10 mL pressure microwave vial equipped with magnetic stirrer. Vial was sealed with cap and heated in an oil bath at 65 °C for 12 h under vigorous stirring.

Procedure RC-Am for the ring-cleavage with **amine**:

Corresponding quaternary ammonium salt (0.5 mmol, 1.0 equiv.), dry cesium carbonate (171 mg, 0.53 mmol, 1.05 equiv.), solvent (CH_3CN, 3 mL) and amine (1.2-3.0 equiv.) were sequentially added to the 10 mL pressure microwave vial equipped with magnetic stirrer. Vial was sealed with cap and heated in an oil bath at 80 °C for the indicated time (2-18 h) under vigorous stirring.

Note: For the secondary cyclic amines (piperidine, morpholine, pyrrolidine) the application of methanol as a solvent (heating in MeOH in an oil bath at 65 °C for 12-18 h) is possible and does not lead to the formation of sufficient amounts of MeO-product (in some cases up to 5% of MeO-product was detected by NMR ^1H analysis). In the case of aniline and cyclohexyl amine, the ratio of MeO- and RNH-products were up to 1:1. To prevent the competing MeO-product formation it is preferable to use CH_3CN as a solvent.

Procedure RC-CN for the ring-cleavage with **cyanide**:

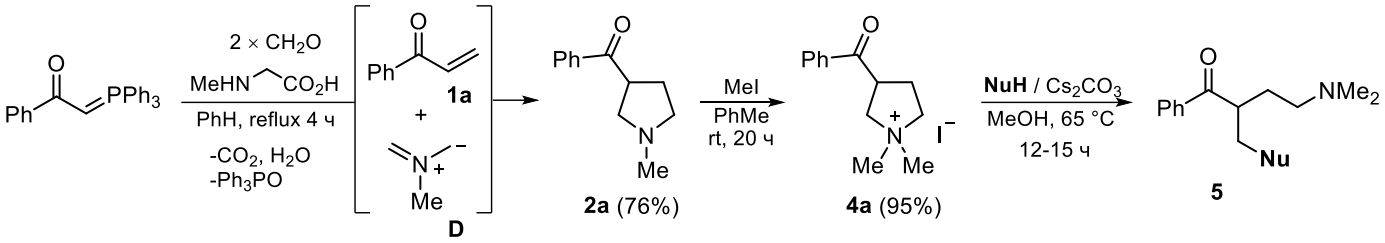
Caution! *Acetone cyanohydrin is extremely hazardous material. Procedure should be carried out in a good fume hood. Protective gloves and glasses are required at work. Formation of traces of hydrogen cyanide is possible.*

The reaction vials with acetone cyanohydrin should be ***carefully*** *sealed with cap and wrapped up with parafilm to prevent leakage. After the reaction, vials should be cooled to room temperature and opened* ***only*** *in a fine fume hood.*

Corresponding quaternary ammonium salt (0.5 mmol, 1.0 equiv.), dry cesium carbonate (171 mg, 0.53 mmol, 1.05 equiv.), MeOH (3 mL) and acetone cyanohydrin (106 mg, 1.25 mmol, 2.5 equiv.) were sequentially added to the 10 mL pressure microwave vial equipped with magnetic stirrer. Vial was sealed with cap and heated in an oil bath at 65 °C for 12 h under vigorous stirring.

Procedure A:

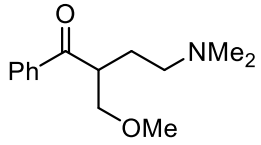
Application of (benzoylmethylene)triphenylphosphorane as the precursor of phenyl vinyl ketone:



3-Benzoyl-1-methylpyrrolidine **2a** could be obtained according to the literature procedure (*Tetrahedron Letters*, 2022, **111**, 154205).[ref1] To obtain quaternary ammonium salt **4a** we modified this procedure to one-pot cycloaddition/quaternization sequence:

A mixture of (benzoylmethylene)triphenylphosphorane (1140 mg, 3.0 mmol, 1.0 equiv.), finely ground *N*-methylglycine (401 mg, 4.5 mmol, 1.5 equiv.) and paraformaldehyde (75 mg, 7.5 mmol of formaldehyde, 2.5 equiv.) was refluxed in dry benzene (14 mL) in a 50 mL round-bottom flask fitted with a Dean-Stark trap for 4 h. The resulting mixture was cooled to room temperature and undissolved unreacted excess of *N*-methylglycine was filtered off. Methyl iodide (639 mg, 4.5 mmol, 1.5 equiv.) was added dropwise at room temperature to the resulting solution under constant stirring and the stirring continued overnight (15-24 h). The formed precipitate was filtered, washed with PhMe and dried at 65 °C. The resulting 3-benzoyl-1,1-dimethylpyrrolidin-1-ium iodide **4a** was obtained in 89% yield for two steps and was used further without additional purification.

Cleavage of the ammonium salt **4a** was performed according to the **general procedure RC** at 0.5 mmol scale.



4-(Dimethylamino)-2-(methoxymethyl)-1-phenylbutan-1-one (5aa)

Synthesized from (benzoylmethylene)triphenylphosphorane via the **procedures A** and then **RC-Alc.**

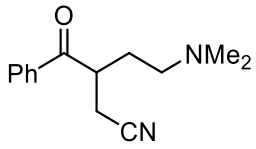
Product was purified by column chromatography (eluent: dichloromethane/methanol, from 100/6 to 100/10; R_f (dichloromethane/methanol, 10/1) = 0.12).

Light yellow oil. Yield: 88 mg (84% from quaternate; 75% yield for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.3, 1.3 Hz, 2H, PhH-2,6), 7.56 (tt, *J* = 7.4, 1.3 Hz, 1H, PhH-4), 7.47 (t, *J* = 7.6 Hz, 2H, PhH-3,5), 3.86 (dq, *J* = 8.4, 5.7 Hz, 1H, CHCOPh), 3.69 (dd, *J* = 9.1, 6.7 Hz, 1H, C*H*HOMe), 3.53 (dd, *J* = 9.1, 5.7 Hz, 1H, CH*H*OMe), 3.27 (s, 3H, OMe), 2.56–2.42 (m, 2H), 2.33 (s, 6H, NMe_2), 2.14–2.05 (m, 1H), 1.90–1.83 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.4 (C=O), 137.9 (C), 132.9 (CH), 128.6 (2CH), 128.4 (2CH), 74.5, 59.2, 57.2, 45.1 (NMe_2), 45.0, 27.8.

HRMS (ESI) calcd for $(C_{14}H_{22}NO_2)^+$ $[M+H]^+$: 236.1645, found: 236.1647.



3-Benzoyl-5-(dimethylamino)pentanenitrile (5ab)

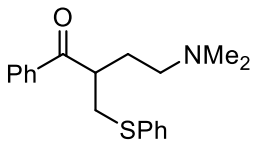
Synthesized from (benzoylmethylene)triphenylphosphorane via the **procedures A** and then **RC-CN.**

Light yellow oil.Yield: 99 mg (97% from quaternate; 86% yield for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.4, 1.2 Hz, 2H, PhH-2,6), 7.59 (tt, *J* = 7.4, 1.2 Hz, 1H, PhH-4), 7.49 (t, *J* = 7.7 Hz, 2H, PhH-3,5), 3.92 (p, *J* = 6.7 Hz, 1H, CHCOPh), 2.73 (dd, *J* = 16.8, 6.7 Hz, 1H, C*H*HCN), 2.66 (dd, *J* = 16.8, 7.1 Hz, 1H, CH*H*CN), 2.34–2.23 (m, 2H), 2.10 (s, 6H, NMe_2), 2.06–1.99 (m, 1H), 1.81 (dq, *J* = 14.2, 6.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.9 (C=O), 136.2 (C), 133.6 (CH), 128.9 (2CH), 128.5 (2CH), 118.7 (CN), 56.2 (*C*H_2N), 45.2 (NMe_2), 40.8 (*C*HBz), 30.5 (CH_2), 19.2 (*C*H_2CN).

HRMS (ESI) calcd for $(C_{14}H_{19}N_2O)^+$ $[M+H]^+$: 231.1492, found: 231.1505.



4-(Dimethylamino)-1-phenyl-2-((phenylthio)methyl)butan-1-one (5ac)

Synthesized from (benzoylmethylene)triphenylphosphorane via the **procedure A** and then **general procedure RC** applying PhSH (165 mg, 1.5 mmol, 3.0 equiv.), Cs_2CO_3 (325 mg, 1.0 mmol, 2.0 equiv.), MeOH, 65 °C, 15 h.

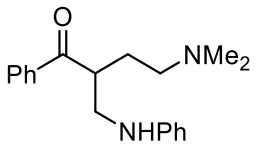
Product was purified by column chromatography (eluent: chloroform/ethanol, from 100/3 to 100/6; R_f (chloroform/ethanol, 100/6) = 0.27).

Colorless oil. Yield: 91 mg (65% from quaternate; 58% yield for 3 steps from alkene)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.4, 1.2 Hz, 2H, COPhH-2,6), 7.53 (tt, *J* = 7.4, 1.2 Hz, 1H, COPhH-4), 7.41 (t, *J* = 7.7 Hz, 2H, COPhH-3,5), 7.33–7.30 (m, 2H, SPhH), 7.29–7.25 (m, 2H, SPhH), 7.21–7.18 (m, 1H, SPhH), 3.79 (tdd, *J* = 7.6, 6.5, 5.2 Hz, 1H, CHCOPh), 3.31 (dd, *J* = 13.2, 7.6 Hz, 1H, C*H*HSPh), 3.08 (dd, *J* = 13.2, 6.5 Hz, 1H, CH*H*SPh), 2.26–2.17 (m, 2H), 2.08 (s, 6H, NMe_2), 2.05–1.96 (m, 1H), 1.85 (dtd, *J* = 11.8, 6.8, 5.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.2 (C=O), 137.5 (C), 136.2 (C), 133.0 (CH), 130.0 (2CH), 129.1 (2CH), 128.7 (2CH), 128.4 (2CH), 126.5 (CH), 57.0, 45.1 (NMe_2), 43.9, 36.4, 30.4.

HRMS (ESI) calcd for $(C_{19}H_{24}NOS)^+$ $[M+H]^+$: 314.1573, found: 314.1572.



4-(Dimethylamino)-1-phenyl-2-((phenylamino)methyl)butan-1-one (5ad)

Synthesized from (benzoylmethylene)triphenylphosphorane via the **procedures A** and then **RC-Am** applying $PhNH_2$ (140 mg, 1.5 mmol, 3.0 equiv.), Cs_2CO_3 (171 mg, 0.53 mmol, 1.05 equiv.), CH_3CN, 80 °C, 40 h.

Product was purified by column chromatography (eluent: chloroform/ethanol, from 100/4 to 100/7; R_f (chloroform/ethanol, 100/5) = 0.16).

Yellow oil. Yield: 101 mg (76% from quaternate; 68% yield for 3 steps from alkene).

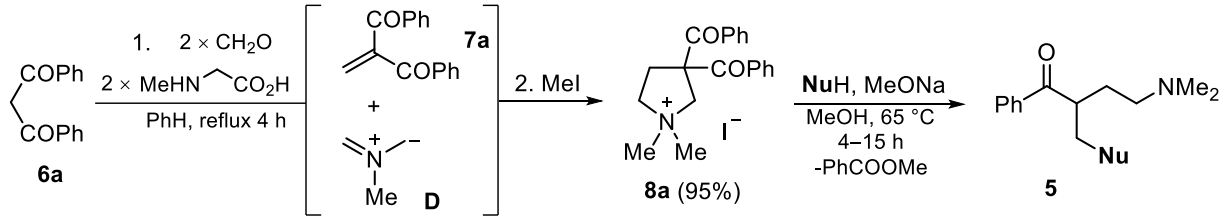
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.4, 1.2 Hz, 2H, COPhH-2,6), 7.54 (t, *J* = 7.4, 1.2 Hz, 1H, COPhH-4), 7.44 (t, *J* = 7.7 Hz, 2H, COPhH-3,5), 7.17–7.13 (m, 2H, NPhH-3,5), 6.68 (t, *J* = 7.3 Hz, 1H, NPhH-4), 6.57 (dd, *J* = 8.6, 1.0 Hz, 2H, NPhH-2,6), 4.18 (br s, 1H, N*H*Ph), 3.94–3.88 (m, 1H, C*H*COPh), 3.55 (dd, *J* = 13.0, 7.0 Hz, 1H, C*H*HNHPh), 3.32 (dd, *J* = 13.0, 5.4 Hz, 1H, CH*H*NHPh), 2.38–2.26 (m, 2H), 2.16 (s, 6H, NMe_2), 2.02 (dq, *J* = 14.2, 7.1 Hz, 1H), 1.75 (td, *J* = 13.1, 6.3 Hz, 1H).

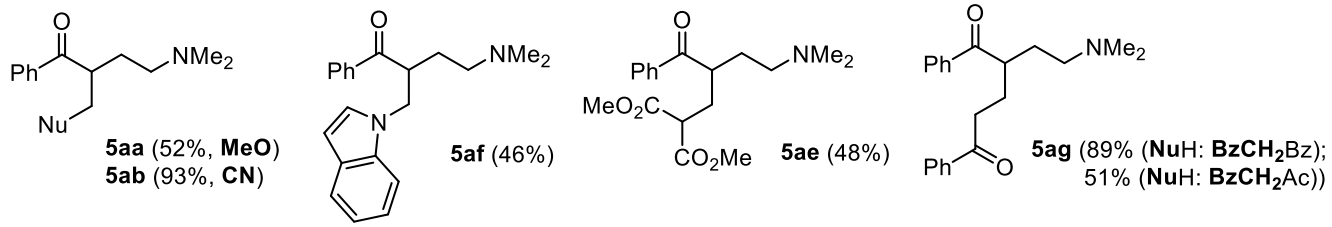
^{13}C NMR (126 MHz, $CDCl_3$) δ 203.3 (C=O), 148.1 (C), 137.5 (C), 133.1 (CH), 129.4 (2CH), 128.7 (2CH), 128.4 (2CH), 117.4 (CH), 112.9 (2CH), 57.3, 45.8, 45.3 (NMe_2), 44.1, 29.1.

HRMS (ESI) calcd for $(C_{19}H_{25}N_2O)^+$ $[M+H]^+$: 297.1961, found: 297.1960.

Procedure B:

Application of dibenzoylmethane as the precursor of phenyl vinyl ketone:





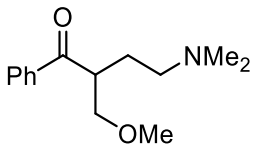
A mixture of 1,3-diphenylpropane-1,3-dione (**6a**) (2.24 g, 10.0 mmol, 1.0 equiv.), finely ground *N*-methylglycine (2.23 g, 25 mmol, 2.5 equiv.) and paraformaldehyde (750 mg, 25 mmol of formaldehyde, 2.5 equiv.) was refluxed in dry benzene (25 mL) in a 75 mL round-bottom flask fitted with a Dean-Stark trap for 4 h. The resulting mixture was cooled to room temperature and undissolved unreacted excess of *N*-methylglycine was filtered off. Methyl iodide (639 mg, 4.5 mmol, 1.5 equiv.) was added dropwise at room temperature to the resulting solution under constant stirring and the stirring continued overnight (15-24 h). The formed precipitate was filtered, washed with PhMe and dried at 65 °C to give 3,3-dibenzoyl-1,1-dimethylpyrrolidin-1-ium iodide (**8a**) in 95% yield. Ammonium salt was used further without additional purification.

Quaternary ammonium salt **8a** (0.5 mmol, 1.0 equiv.), MeOH (3 mL), corresponding nucleophile and freshly prepared MeONa (14 mg of Na (0.6 mmol, 1.2 equiv.) in 1 mL of MeOH, 0.6M solution) were sequentially added to the 10 mL pressure microwave vial equipped with a magnetic stirrer. Vial was sealed with cap and heated in an oil bath at 65 °C for 3–15 h under vigorous stirring. The vial was cooled to room temperature and opened in a fume hood. The mixture was diluted with water (15 mL), extracted with CH_2Cl_2 (3×10 mL). Combined organic extracts were washed with water (3×10 mL), brine (10 mL) and evaporated under reduced pressure.

Products 5aa, 5ab, 5ae, **5ag** were purified by an acid-base extraction:

The residue was extracted with cold 2 M HCl (12 mL). Water phase was washed with PhMe (2 × 7mL), basified with $NaHCO_3$ to pH = 8–9 and extracted with CH_2Cl_2 (3 × 7 mL). Combined organic extracts were washed with H_2O (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. Solvent was evaporated *in vacuo* and the product, if necessary, was purified by column chromatography.

Product **5af** (indole) were purified only by column chromatography without an acid base-extraction.

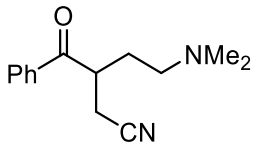


4-(Dimethylamino)-2-(methoxymethyl)-1-phenylbutan-1-one (5aa)

Synthesized from dibenzoylmethane according to the **procedure B** applying MeONa (1.2 equiv.), MeOH, 25 °C, 45 h.

Light yellow oil. Yield: 59 mg (52% from quaternate **8**; 49% for 3 steps from dibenzoylmethane).

The NMR data fully matched with the data of product **5aa,** obtained via the **procedure IA**.

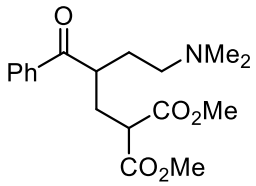


3-Benzoyl-5-(dimethylamino)pentanenitrile (5ab)

Synthesized from dibenzoylmethane according to the **procedure B** applying acetone cyanohydrin (85 mg, 1.0 mmol, 2.0 equiv.), MeONa (2.4 equiv.), MeOH, 65 °C, 4 h.

Light yellow oil. Yield: 101 mg (93% from quaternate; 88% for 3 steps from dibenzoylmethane).

The NMR data fully matched with the data of product **5ab,** obtained via the **procedure IC**.



Dimethyl 2-(2-benzoyl-4-(dimethylamino)butyl)malonate (5ae)

Synthesized from dibenzoylmethane according to the **procedure B** applying MeONa (1.2 equiv.), dimethyl malonate (79 mg, 0.6 mmol, 1.2 equiv.), MeOH, 65 °C, 3 h.

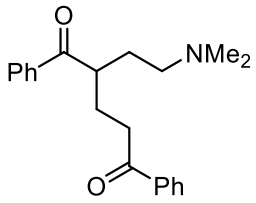
Product was purified by column chromatography (eluent: dichloromethane/methanol, from 100/4.5 to 100/10; R_f (dichloromethane/methanol, 100/10) = 0.57).

Yellow oil. Yield: 77 mg (48% from quaternate; 46% for 3 steps from dibenzoylmethane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.6 Hz, 2H, COPhH-2,6), 7.56 (t, *J* = 7.4 Hz, 1H, COPhH-4), 7.46 (t, *J* = 7.5 Hz, 2H, COPhH-3,5), 3.72 (s, 3H, CO_2Me), 3.65 (s, 3H, CO_2Me), 3.67–3.60 (m, 1H), 3.40 (dd, *J* = 8.9, 6.3 Hz, 1H, C**H**CO_2Me), 2.41 (ddd, *J* = 14.2, 8.9, 6.3 Hz, 1H), 2.28 (t, *J* = 7.2 Hz, 2H), 2.14 (s, 6H, NMe_2), 2.14–2.07 (m, 1H), 2.00–1.91 (m, 1H), 1.69–1.60 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.5 (Ph**C**=O), 169.7 (**C**O_2Me), 169.6 (**C**O_2Me), 137.2 (C), 133.2 (CH), 128.8 (2CH), 128.4 (2CH), 57.0, 52.7 (CO_2**Me**), 52.6 (CO_2**Me**), 49.5, 45.2 (NMe_2), 41.6, 30.9, 30.8.

HRMS (ESI) calcd for $(C_{18}H_{26}NO_5)^+$ $[M+H]^+$: 336.1805, found: 336.1805.



2-(2-(Dimethylamino)ethyl)-1,5-diphenylpentane-1,5-dione (5ag)

Synthesized from dibenzoylmethane according to the **procedure B** applying MeONa (1.2 equiv.), dibenzoylmethane (1.5 equiv.), MeOH, 65 °C, 4 h.

Product was purified by column chromatography (eluent: dichloromethane/methanol, from 100/6 to 100/10).

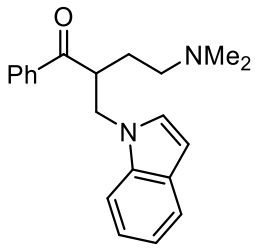
Yellow oil. Yield: 137 mg (89% from quaternate; 85% for 3 steps from dibenzoylmethane).

It was alternatively synthesized from dibenzoylmethane according to the **procedure B** applying MeONa (1.2 equiv.), benzoylacetone (1.75 equiv.), MeOH, 65 °C, 15 h in 48% overall yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.4, 1.2 Hz, 2H, COPhH-2,6), 7.89 (dd, *J* = 8.3, 1.2 Hz, 2H, COPh'H-2,6), 7.55 (t, *J* = 7.4 Hz, 1H COPhH-4), 7.53 (t, *J* = 7.4 Hz, 1H, COPh'H-4), 7.46 (t, *J* = 7.6 Hz, 2H, COPhH-3,5), 7.42 (t, *J* = 7.7 Hz, 2H, COPh'H-3,5), 3.71 (tt, *J* = 7.9, 5.4 Hz, 1H, C*H*COPh), 3.06 (ddd, *J* = 17.2, 8.5, 6.0 Hz, 1H), 2.89 (ddd, *J* = 17.2, 8.4, 6.4 Hz, 1H), 2.36 (t, *J* = 7.2 Hz, 2H, CH_2COPh'), 2.26–2.18 (m, 1H), 2.21 (s, 6H, NMe_2), 2.11–1.97 (m, 1H), 1.77–1.70 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5 (C=O), 199.8 (C=O), 137.4 (C), 136.9 (C), 133.19 (CH), 133.15 (CH), 128.8 (2CH), 128.7 (2CH), 128.4 (2CH), 128.1 (2CH), 57.3 (CH_2N), 45.1 (NMe_2), 43.3 (*C*HBz), 35.9 (*C*H_2Bz'), 30.1 (CH_2), 26.6 (CH_2).

HRMS (ESI) calcd for $(C_{21}H_{26}NO_2)^+$ $[M+H]^+$: 324.1958, found: 324.1965.



2-((1*H*-Indol-1-yl)methyl)-4-(dimethylamino)-1-phenylbutan-1-one (5af)

Synthesized from dibenzoylmethane according to the **procedure B** applying MeONa (1.2 equiv.), indole (1.5 equiv.), MeOH, 65 °C, 9 h.

Purified by column chromatography (eluent: dichloromethane/methanol, 100/8; R_f (dichloromethane/methanol, 100/8) = 0.29).

Light yellow oil. Yield: 70 mg (46% from quaternate; 44% for 3 steps from dibenzoylmethane).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 8.4, 1.2 Hz, 2H, COPhH-2,6), 7.56 (d, *J* = 7.8 Hz, 1H), 7.47 (tt, *J* = 6.9, 1.2 Hz, 1H, COPhH-4), 7.41 (dd, *J* = 8.2, 0.6 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 2H, COPhH-3,5), 7.22 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H), 7.08 (ddd, *J* = 7.8, 7.0, 0.8 Hz, 1H), 7.04 (d, *J* = 3.2 Hz, 1H, IndoleH-2), 6.37 (dd, *J* = 3.2, 0.6 Hz, 1H, IndoleH-3), 4.54 (dd, *J* = 14.3, 8.1 Hz, 1H, C***H***HNIndole), 4.30 (dd, *J* = 14.3, 6.1 Hz, 1H,

CH***H***NIndole), 4.15 (tt, *J* = 7.9, 5.8 Hz, 1H, C**H**COPh), 2.25 (t, *J* = 6.8 Hz, 2H, C**H$_2$**NMe$_2$), 2.07 (s, 6H, NMe$_2$), 2.02 (td, *J* = 14.6, 7.4 Hz, 1H, C***H***H), 1.68 (ddd, *J* = 13.9, 12.0, 6.4 Hz, 1H, CH***H***).

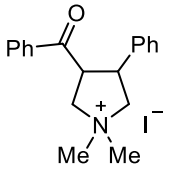
^{13}C NMR (126 MHz, $CDCl_3$) δ 202.2 (C=O), 137.4 (C), 136.1 (C), 133.1 (CH), 128.8 (C), 128.6 (2CH), 128.1 (2CH), 121.8 (CH), 121.2 (CH), 119.5 (CH), 109.4 (CH), 101.6 (CH), 56.9, 48.2, 45.1, 45.0 (NMe$_2$), 29.4 (one CH masked).

HRMS (ESI) calcd for $(C_{21}H_{25}N_2O)^+$ $[M+H]^+$: 321.1961, found: 321.1957.

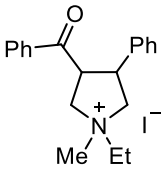
Procedure C for the synthesis of quaternary ammonium salts 4ba–bg from chalcone, azomethine ylides and alkyl halides:

A mixture of (*E*)-1,3-diphenylprop-2-en-1-one (2.5 g, 12.0 mmol, 1.0 equiv.), finely ground *N*-methylglycine (1.6 g, 18.0 mmol, 1.5 equiv.) and paraformaldehyde (0.83 g, 27.6 mmol of formaldehyde, 2.5 equiv.) was refluxed in a mixture of PhMe/MTBE (25 mL : 4 mL) in a 75 mL round-bottom flask fitted with a Dean-Stark trap (filled with PhMe) for 4 h. The resulting mixture was cooled to room temperature and undissolved unreacted excess of *N*-methylglycine was filtered off.

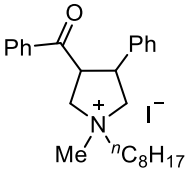
Methyl iodide (2.56 g, 18.0 mmol, 1.5 equiv.) was added dropwise at room temperature to the resulting solution under constant stirring and the stirring continued overnight (15-24 h). The formed precipitate was filtered, washed with PhMe and dried at 65 °C to give ammonium salt **4ba** in 97% yield starting from chalcone. Obtained 3-benzoyl-1,1-dimethylpyrrolidin-1-ium iodide was used further without additional purification.



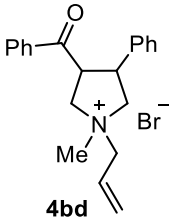
4ba



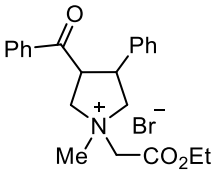
4bb



4bc



4bd

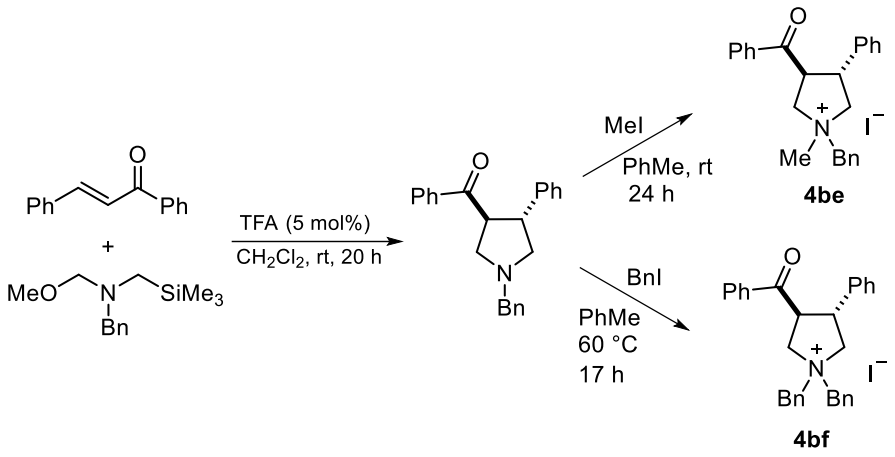


4bg

Other salts **4bb**–**bd, bg** were prepared according to the above procedure from **ethyl bromide (4bb), *n*-octyl iodide (4bc), allyl bromide (4bd)** and **ethyl bromoacetate (4bg)**. In case the formed precipitate is viscous oil or contain oily admixtures in it, the viscous oil was decantated form a solvent and was thoroughly rubbed with spatula in several portions of dry diethyl ether (at least 3-5 times × 10 mL) until it become solid. Then it was filtered off and dried in an oven at 60 °C.

In the case of ***n*-octyl iodide (4bc)**, the solution was left at stirring for 2 weeks. The obtained ammonium salt remained gummy viscous oil after the washing with ether. It was used as is after drying at vacuum.

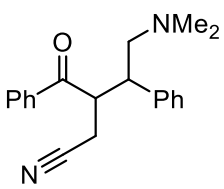
The ***N*-benzyl** substituted ammonium salts **4be** and **4bf** were obtained via the following procedure:



N-(Methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (782 mg, 3.3 mmol) was added to the solution of (*E*)-1,3-diphenylprop-2-en-1-one (624 mg, 3.0 mmol) in 10 mL CH_2Cl_2. The mixture was cooled to 0 °C and trifluoroacetic acid (17 mg, 0.15 mmol, 0.05 equiv.) in 1 mL of CH_2Cl_2 was added dropwise. The resulted solution was allowed to warm to rt and stirred for 20 h. The resulting solution was washed with aqueous $NaHCO_3$, water, brine and evaporated under reduced pressure to give ((3*S**,4*R**)-1-benzyl-4-phenylpyrrolidin-3-yl)(phenyl)methanone, which was used further as is.

The *N*-benzylpyrrolidine (511 mg, 1.5 mmol) was dissolved in PhMe (10 mL) and alkyl halogenide was added dropwise to the solution at stirring. In the case of **methyl iodide** (320 mg, 2.25 mmol, 1.5 equiv.), – the solution was stirred at rt for 24 h. In the case of **benzyl iodide** (850 mg, 3.9 mmol, 2.6 equiv.), the solution was heated at 60 °C for 17 h. The formed precipitate was filtered off, washed with PhMe and dried in an oven at 60 °C.

Ring cleavage of ammonium salts **4ba**-**bg,** derived from **chalcone**, with acetone cyanohydrin was performed according to the **procedure RC-CN** at 0.5 mmol scale to give products **5ba**-**5bg.**



3-Benzoyl-5-(dimethylamino)-4-phenylpentanenitrile (5ba)

Synthesized according to the **procedure C** applying chalcone (1.0 equiv.), *N*-methylglycine (1.5 equiv.), paraformaldehyde (2.5 equiv. of CH_2O) and then methyl iodide (1.5 equiv); 97% yield for 2 steps.

Ring-cleavage step according to the **procedure RC-CN** at 0.5 mmol scale: acetone cyanohydrin (2.5 equiv.), Cs_2CO_3 (1.05 equiv.) and MeOH, 65 °C, 12 h, 90% yield.

Diastereomeric ratio 96:4 (anti:syn).

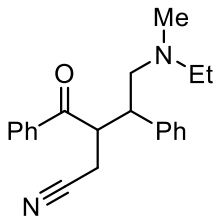
Light brown solid, mp 152–153 °C. Yield: 133 mg (90% from quaternate; 87% for 3 steps from chalcone).

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.1, 1.5 Hz, 2H, COPhH-2,6), 7.58–7.48 (m, 3H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 2H, PhH-2,6), 3.98 (td, *J* = 9.4, 4.1 Hz, 1H, C**H**COPh), 3.41 (ddd, *J* = 11.5, 9.2, 4.6 Hz, 1H, CHPh), 2.61 (dd, *J* = 12.8, 11.5 Hz, 1H, C***H***HNMe$_2$),

2.45 (dd, *J* = 16.7, 9.6 Hz, 1H, C***H***HCN), 2.40 (dd, *J* = 12.8, 4.6 Hz, 1H, CH***H***NMe_2), 2.20 (dd, *J* = 16.7, 4.1 Hz, 1H, CH***H***CN), 1.89 (s, 6H, NMe_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.1 (C=O), 139.1 (C), 138.3 (C), 132.4 (CH), 129.2 (2CH), 128.7 (2CH), 128.3 (2CH), 127.9 (CH), 127.6 (2CH), 118.4 (CN), 64.0, 48.3, 45.8, 44.3 (NMe_2), 18.8.

HRMS (ESI) calcd for $(C_{20}H_{23}N_2O)^+$ $[M+H]^+$: 307.1805, found: 307.1815.



3-Benzoyl-5-(ethyl(methyl)amino)-4-phenylpentanenitrile (5bb)

Synthesized according to the **procedure C** applying chalcone (1.0 equiv.), *N*-methylglycine (1.5 equiv.), paraformaldehyde (2.5 equiv. of CH_2O) and then ethyl iodide (1.5 equiv); 55% yield for 2 steps.

Ring-cleavage step according to the **procedure RC-CN** at 0.5 mmol scale: acetone cyanohydrin (2.5 equiv.), Cs_2CO_3 (1.05 equiv.) and MeOH, 65 °C, 12 h; 97% yield.

Diastereomeric ratio 90:10 before recrystallization.

Product was recrystallized from MeOH.

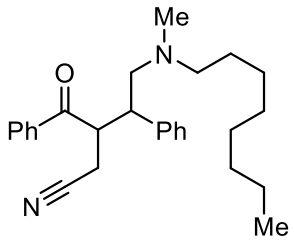
White solid, mp 99–101 °C, d.r. 96:4 (anti:syn).

Yield: 85 mg (97% from quaternate; 53% for 3 steps from chalcone).

Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.6 Hz, 2H, COPhH-2,6), 7.56 (t, *J* = 7.3 Hz, 1H, COPhH-4), 7.50 (t, *J* = 7.4 Hz, 2H, COPhH-3,5), 7.36 (t, *J* = 7.4 Hz, 2H, PhH-3,5), 7.29 (t, *J* = 7.3 Hz, 1H, PhH-4), 7.18 (d, *J* = 8.3 Hz, 2H, PhH-2,6), 4.01 (td, *J* = 9.3, 4.1 Hz, 1H, C**H**COPh), 3.45 (ddd, *J* = 11.7, 9.1, 4.4 Hz, 1H, C**H**Ph), 2.66 (dd, *J* = 12.9, 11.7 Hz, 1H, C***H***HN), 2.44 (dd, *J* = 12.9, 4.4 Hz, 1H, CH***H***N), 2.42 (dd, *J* = 16.8, 9.6 Hz, 1H, C***H***HCN), 2.26 (dq, *J* = 12.7, 7.1 Hz, 1H, NC***H***HCH_3), 2.21 (dd, *J* = 16.8, 4.1 Hz, 1H, CH***H***CN), 2.08 (dq, *J* = 12.7, 7.1 Hz, 1H, NCH***H***CH_3), 1.92 (s, 3H, NMe), 0.67 (t, *J* = 7.1 Hz, 3H, NCH_2**CH_3**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.4 (C=O), 139.3 (C), 138.0 (C), 132.6 (CH), 129.2 (2CH), 128.7 (2CH), 128.3 (2CH), 127.9 (2CH), 127.8 (CH), 118.4 (CN), 62.1, 51.2, 47.8, 45.6, 39.8, 18.7, 10.6 (NCH_2***C***H_3).

HRMS (ESI) calcd for $(C_{21}H_{25}N_2O)^+$ $[M+H]^+$: 321.1961, found: 321.1975.



3-Benzoyl-5-(methyl(octyl)amino)-4-phenylpentanenitrile (5bc)

Synthesized according to the **procedure C** applying chalcone (1.0 equiv.), *N*-methylglycine (1.5 equiv.), paraformaldehyde (2.5 equiv. of CH_2O) and then *n*-octyl iodide (1.3 equiv), 2 weeks, rt; 49% yield for 2 steps.

Ring-cleavage step according to the **procedure RC-CN** at 0.5 mmol scale: acetone cyanohydrin (3.3 equiv.), Cs_2CO_3 (1.05 equiv.) and MeOH, 65 °C, 18 h; 82% yield.

Purified by column chromatography (eluent: chloroform/hexane 2:1; R_f (chloroform) = 0.42).

Product was crystallized from MeOH.

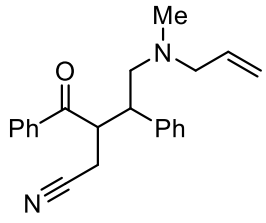
Diastereomeric ratio 96:4 (anti:syn).

White crystals, mp 84–85 °C. Yield: 81 mg (82% from quaternate; 40% for 3 steps from chalcone).

Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 2H, COPhH-2,6), 7.56 (t, *J* = 7.3 Hz, 1H, COPhH-4), 7.50 (t, *J* = 7.4 Hz, 2H, COPhH-3,5), 7.35 (t, *J* = 7.4 Hz, 2H, PhH-3,5), 7.29 (t, *J* = 7.3 Hz, 1H, PhH-4), 7.16 (d, *J* = 7.2 Hz, 2H, PhH-2,6), 4.03 (td, *J* = 9.1, 4.1 Hz, 1H, C**H**COPh), 3.44 (ddd, *J* = 11.7, 8.7, 4.3 Hz, 1H, C**H**Ph), 2.68 (dd, *J* = 12.6, 11.7 Hz, 1H, C***H***HN), 2.45 (dd, *J* = 12.6, 4.3 Hz, 1H, CH***H***N), 2.43 (dd, *J* = 16.6, 9.6 Hz, 1H, C***H***HCN), 2.21 (dd, *J* = 16.6, 4.1 Hz, 1H, CH***H***CN), 2.15 (ddd, *J* = 12.2, 10.3, 4.8 Hz, 1H, NC***H***HCH$_2$), 2.01 (ddd, *J* = 12.2, 10.3, 4.8 Hz, 1H, NCH***H***CH$_2$), 1.94 (s, 3H, NMe), 1.31–0.94 (m, 12H), 0.88 (t, *J* = 7.2 Hz, 3H, CH$_2$CH$_2$C***H$_3$***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.6 (C=O), 139.3 (C), 137.9 (C), 132.7 (CH), 129.2 (2CH), 128.7 (2CH), 128.4 (2CH), 128.0 (2CH), 127.8 (CH), 118.4 (CN), 62.5, 58.0, 47.6, 45.6, 40.5, 31.9, 29.6, 29.4, 27.6, 25.9, 22.8, 18.6, 14.2 (CH_3).

HRMS (ESI) calcd for $(C_{27}H_{37}N_2O)^+$ $[M+H]^+$: 405.2900, found: 405.2909.



5-(Allyl(methyl)amino)-3-benzoyl-4-phenylpentanenitrile (5bd)

Synthesized according to the **procedure C** applying chalcone (1.0 equiv.), *N*-methylglycine (1.5 equiv.), paraformaldehyde (2.5 equiv. of CH_2O) and then allyl bromide (1.2 equiv); 72% yield for 2 steps.

Ring-cleavage step according to the **procedure RC-CN** at 0.5 mmol scale: acetone cyanohydrin (2.5 equiv.), Cs_2CO_3 (1.05 equiv.) and MeOH, 65 °C, 12 h; 97% yield.

Diastereomeric ratio 89:11 (anti:syn).

Beige crystals, mp 96–98 °C. Yield: 116 mg (97% from quaternate; 70% for 3 steps from chalcone).

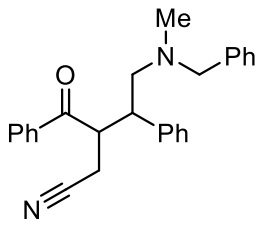
Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.8 Hz, 2H, COPhH-2,6), 7.57 (t, *J* = 7.3 Hz, 1H, COPhH-4), 7.52 (t, *J* = 7.4 Hz, 2H, COPhH-3,5), 7.36 (t, *J* = 7.4 Hz, 2H, Ph′H-3,5), 7.29 (t, *J* = 7.3 Hz, 1H, Ph′H-4), 7.16 (d, *J* = 8.3 Hz, 2H, Ph′H-2,6), 5.37–5.28 (m, 1H, NCH$_2$C***H***=CH$_2$), 5.01 (br s, 1H, NCH$_2$CH=C***H***H), 4.99 (d, *J* = 8.0, 1.8 Hz, 1H, NCH$_2$CH=CH***H***), 4.03 (td, *J* = 9.2, 4.0 Hz, 1H, C**H**COPh), 3.45 (ddd, *J* = 11.5, 8.8, 4.4 Hz, 1H, C**H**Ph), 2.83 (dd, *J* = 13.5, 6.3 Hz, 1H, NC***H***HC=), 2.71 (dd, *J* = 13.0, 11.5 Hz, 1H, C***H***HN), 2.66 (dd, *J* = 13.5, 7.1 Hz, 1H, NCH***H***C=), 2.43 (dd, *J* = 16.7, 9.4 Hz, 1H, C***H***HCN), 2.43 (dd, *J* = 13.0, 4.4 Hz, 1H, CH***H***N), 2.21 (dd, *J* = 16.7, 4.0 Hz, 1H, CH***H***CN), 1.95 (s, 3H, NMe).

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9 (C=O), 139.2 (C), 137.9 (C), 134.5 (CH), 132.7 (CH), 129.2 (2CH), 128.8 (2CH), 128.3 (2CH), 128.0 (2CH), 127.9 (CH), 118.3 (CN), 118.1, 61.5, 60.6, 47.5, 45.7, 40.9, 18.6.

Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.2 Hz, 2H, COPhH-2,6), 7.58–7.54 (m, 1H, COPhH-4), 7.46 (t, *J* = 7.7 Hz, 2H, COPhH-3,5), 7.28–7.25 (m, 2H, Ph′H-3,5), 7.21 (t, *J* = 7.3 Hz, 1H, Ph′H-4), 7.09 (d, *J* = 8.4 Hz, 2H, Ph′H-2,6), 5.79–5.69 (m, 1H, NCH$_2$C***H***=CH$_2$), 5.14–5.09 (m, 2H, NCH$_2$CH=C**H$_2$**), 4.21 (dt, *J* = 7.7, 5.8 Hz, 1H, C**H**COPh), 3.54–3.48 (m, 1H, C**H**Ph), 2.93 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.88–2.84 (m, 1H), 2.80–2.72 (m, 1H), 2.49–2.45 (m, 1H), 2.06 (s, 3H, NMe).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.2 (C=O), 139.5 (C), 137.5 (C), 135.1 (CH), 133.3 (CH), 128.8 (2CH), 128.5 (2CH), 128.4 (2CH), 127.6 (CH), 118.3 (2CH), 118.0 (CN), 61.0, 58.5, 47.2, 45.3, 41.7, 17.1 (one C masked).

HRMS (ESI) calcd for $(C_{22}H_{25}N_2O)^+$ $[M+H]^+$: 333.1961, found: 333.1956.



3-Benzoyl-5-(benzyl(methyl)amino)-4-phenylpentanenitrile (5be)

Synthesized according to the **procedure C** applying chalcone (1.0 equiv.), *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (1.1 equiv.), trifluoroacetic acid (0.05 equiv.), DCM, 0 °C to rt, overnight; and then methyl iodide (1.5 equiv); 77% yield for 2 steps.

Ring-cleavage step according to the **procedure RC-CN** at 0.5 mmol scale: acetone cyanohydrin (2.5 equiv.), Cs_2CO_3 (1.05 equiv.) and MeOH, 65 °C, 16 h; 80% yield.

Purified by column chromatography (eluent: dichloromethane; R_f (dichloromethane/ethanol, 100/1) = 0.66).

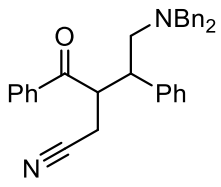
Diastereomeric ratio 87:13.

Yellow viscous oil. Yield: 118 mg (80% from quaternate; 62% for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 2H, COPhH-2,6), 7.61 (t, *J* = 7.4 Hz, 1H, COPhH-4), 7.52 (t, *J* = 7.7 Hz, 2H, COPhH-3,5), 7.34–7.22 (m, 6H), 7.06–7.00 (m, 4H), 4.16 (ddd, *J* = 9.7, 7.3, 4.0 Hz, 1H, C**H**COPh), 3.51–3.41 (m, 1H, C**H**Ph), 3.46 (d, *J* = 13.1 Hz, 1H, NC***H***HPh), 3.30 (d, *J* = 13.1 Hz, 1H, NCH***H***Ph), 2.81 (dd, *J* = 12.8, 10.9 Hz, 1H, C***H***HN), 2.44 (dd, *J* = 12.8, 4.8 Hz, 1H, CH***H***N), 2.37 (dd, *J* = 16.6, 9.7 Hz, 1H, C***H***HCN), 2.07 (s, 3H, NMe), 2.03 (dd, *J* = 16.6, 4.0 Hz, 1H, CH***H***CN).

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.1 (C=O), 138.8 (C), 138.0 (C), 137.2 (C), 133.2 (CH), 129.3 (2CH), 129.0 (2CH), 129.0 (2CH), 128.4 (4CH), 128.3 (2CH), 127.8 (CH), 127.3 (CH), 118.5 (CN), 62.4, 60.5, 46.3, 45.8, 41.7, 17.6.

HRMS (ESI) calcd for $(C_{26}H_{27}N_2O)^+$ $[M+H]^+$: 383.2118, found: 383.2123.



3-Benzoyl-5-(dibenzylamino)-4-phenylpentanenitrile (5bf)

Synthesized according to the **procedure C** applying chalcone (1.0 equiv.), *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (1.1 equiv.), trifluoroacetic acid (0.05 equiv.), DCM, 0 °C to rt, overnight; and then benzyl iodide (2.6 equiv), 60 °C, 17 h; 70% yield for 2 steps.

Ring-cleavage step according to the **procedure RC-CN** at 0.5 mmol scale: acetone cyanohydrin (2.5 equiv.), Cs_2CO_3 (1.05 equiv.) and MeOH, 65 °C, 12 h; 69% yield.

Diastereomeric ratio 77:23 **(3*R**, 4*R**) : (3*S**:4*R**)** in the crude mixture (syn:anti).

Purified by column chromatography (eluent: chloroform/*n*-C_6H_{14}, 1/1; R_f (chloroform/*n*-C_6H_{14}, 1/1) = 0.15) to give dr 80:20, yellow amorphous solid.

Purification by recrystallization from MeOH provided mixture of diastereomers - 90:10 (syn:anti).

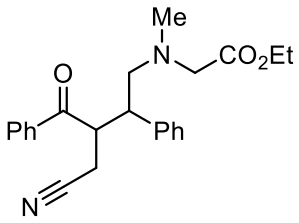
Major diastereomer (3*R*, 4R)**: white crystals, mp 164–165 °C.

Yield: 110 mg (69% from quaternate; 48% for 3 steps from chalcone).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.3 Hz, 2H, COPhH-2,6), 7.59 (t, *J* = 7.4 Hz, 1H, COPhH-4), 7.40 (t, *J* = 7.8 Hz, 2H, COPhH-3,5), 7.35–7.31 (m, 4H), 7.30–7.22 (m, 9H), 6.82–6.78 (m, 2H), 4.23 (ddd, *J* = 10.5, 6.3, 3.4 Hz, 1H, C**H**COPh), 3.68 (d, *J* = 13.7 Hz, 2H, 2×NC***H***HPh), 3.52–3.47 (m, 1H, C**H**Ph), 3.46 (d, *J* = 13.7 Hz, 2H, 2×NCH***H***Ph), 2.79 (dd, *J* = 13.0, 8.9 Hz, 1H, C***H***HN), 2.60 (dd, *J* = 13.0, 6.6 Hz, 1H, CH***H***N), 2.27 (dd, *J* = 16.3, 10.5 Hz, 1H, C***H***HCN), 1.77 (dd, *J* = 16.3, 3.4 Hz, 1H, CH***H***CN).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.4 (C=O), 138.7 (2C), 138.2 (C), 136.4 (C), 133.8 (CH), 129.1 (2CH), 128.9 (4CH), 128.7 (4CH), 128.6 (4CH), 128.5 (2CH), 127.7 (CH), 127.4 (2CH), 118.5 (CN), 58.7 (2×CH_2Ph), 55.9, 45.9, 45.2, 16.4 (one C masked).

HRMS (ESI) calcd for $(C_{32}H_{31}N_2O)^+$ $[M+H]^+$: 459.2431, found: 459.2439.



Ethyl *N*-(-3-(cyanomethyl)-4-oxo-2,4-diphenylbutyl)-*N*-methylglycinate (5bg)

Synthesized according to the **procedure C** applying chalcone (1.0 equiv.), *N*-methylglycine (1.5 equiv.), paraformaldehyde (2.5 equiv. of CH_2O) and then ethyl 2-bromoacetate (1.5 equiv), 48 h, rt; 75% yield for 2 steps.

Ring-cleavage step according to the **procedure RC-CN** at 0.5 mmol scale: acetone cyanohydrin (2.5 equiv.), Cs_2CO_3 (1.05 equiv.) and CH_3CN, 65 °C, 12 h; 95% yield.

Purified by column chromatography (eluent: chloroform/hexane 2:1; R_f (chloroform) = 0.42).

Diastereomeric ratio 85:15 (anti:syn).

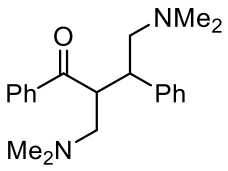
Product was crystallized from EtOAc/*n*-C_6H_{14} (1:6) to give single major diastereomer.

White solid, mp 126–127 °C. Yield: 134 mg (95% from quaternate; 71% for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.6 Hz, 2H, COPhH-2,6), 7.57 (t, *J* = 7.3 Hz, 1H, COPhH-4), 7.52 (t, *J* = 7.3 Hz, 2H, COPhH-3,5), 7.36 (t, *J* = 7.3 Hz, 2H, PhH-3,5), 7.29 (t, *J* = 7.3 Hz, 1H, PhH-4), 7.17 (d, *J* = 8.4 Hz, 2H, PhH-2,6), 4.10–4.04 (m, 1H, C**H**COPh), 4.07 (q, *J* = 7.2 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 3.44 (ddd, *J* = 11.5, 8.9, 4.5 Hz, 1H, C**H**Ph), 2.94 (dd, *J* = 13.3, 4.5 Hz, 1H, C***H***HN), 2.86 (d, *J* = 17.3 Hz, 1H, NC***H***HCO_2Et), 2.79 (dd, *J* = 13.3, 11.5 Hz, 1H, CH***H***N), 2.79 (d, *J* = 17.3 Hz, 1H, NCH***H***CO_2Et), 2.43 (dd, *J* = 16.7, 9.5 Hz, 1H, C***H***HCN), 2.24 (dd, *J* = 16.7, 4.2 Hz, 1H, CH***H***CN), 2.12 (s, 3H, NMe), 1.19 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.6 (C=O), 170.9 (***C***$O_2CH_2CH_3$), 138.8 (C), 137.7 (C), 132.7 (CH), 129.2 (2CH), 128.9 (2CH), 128.4 (2CH), 127.9 (CH), 127.7 (2CH), 118.4 (CN), 60.7, 60.4, 57.4, 48.0, 45.2, 40.3, 18.7, 14.3 ($CO_2CH_2\boldsymbol{C}H_3$).

HRMS (ESI) calcd for $(C_{23}H_{27}N_2O_3)^+$ $[M+H]^+$: 379.2016, found: 379.2008.



4-(Dimethylamino)-2-((dimethylamino)methyl)-1,3-diphenylbutan-1-one (5bh)

Synthesized according to the **procedure C** from (*E*)-1,3-diphenylprop-2-en-1-one; 97% yield.

Ring-cleavage step according to the **procedure RC-Am** at 0.5 mmol scale: 33% aqueous solution of $HNMe_2$ (10.0 equiv.), Cs_2CO_3 (1.1 equiv.) and CH_3CN, 80 °C, 3 h; yield 95%.

Diastereomeric ratio 82:18 (anti:syn).

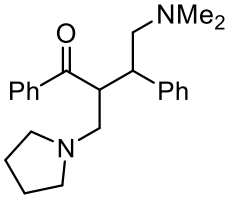
Product was recrystallized from EtOAc/*n*-C_6H_{14} to give single major diastereomer.

Colorless crystals, mp 128–133 °C. Yield: 149 mg (95% from quaternate; 92% for 3 steps from alkene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.8, 1.7 Hz, 2H, COPhH-2,6), 7.51–7.43 (m, 3H), 7.32 (t, *J* = 7.3 Hz, 2H, PhH-3,5), 7.26–7.21 (m, 1H), 7.20 (d, *J* = 8.1 Hz, 2H, PhH-2,6), 3.91 (ddd, *J* = 10.7, 9.6, 3.5 Hz, 1H, C**H**COPh), 3.26 (td, *J* = 9.6, 5.8 Hz, 1H, C**H**Ph), 2.74 (dd, *J* = 12.1, 10.7 Hz, 1H C***H***HN), 2.51 (dd, *J* = 12.5, 9.8 Hz, 1H, C***H***HN), 2.37 (dd, *J* = 12.5, 5.8 Hz, 1H, CH***H***N), 2.01 (s, 6H, NMe_2), 1.96 (dd, *J* = 12.1, 3.5 Hz, 1H, CH***H***N), 1.88 (s, 6H, NMe_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.9 (C=O), 141.7 (C), 140.0 (C), 131.5 (CH), 128.7 (2CH), 128.3 (2CH), 128.2 (2CH), 127.6 (2CH), 126.9 (CH), 65.0, 62.3, 48.0, 47.4, 46.1 (NMe_2), 44.6 (NMe_2).

HRMS (ESI) calcd for $(C_{21}H_{29}N_2O)^+$ $[M+H]^+$: 325.2274, found: 325.2278.



4-(Dimethylamino)-1,3-diphenyl-2-(pyrrolidin-1-ylmethyl)butan-1-one (5bi)

Synthesized according to the **procedure C** from (*E*)-1,3-diphenylprop-2-en-1-one; 97% yield.

Ring-cleavage step according to the **procedure RC-Am** at 0.5 mmol scale: pyrrolidine (3.0 equiv.), Cs_2CO_3 (1.1 equiv.) and CH_3CN, 80 °C, 2.5 h; yield 81%.

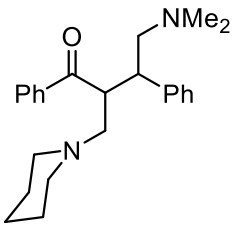
Mixture of diastereomers (dr 79:21 anti:syn), beige solid, mp 111–113 °C.

Product was recrystallized from $CHCl_3$/*n*-C_6H_{14} or MeOH to give single major anti-diastereomer, beige solid, mp 117–118 °C. Yield: 138 mg (81% from quaternate; 79% for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.0, 1.2 Hz, 2H, COPhH-2,6), 7.51–7.43 (m, 3H, COPhH-3,4,5), 7.31 (t, *J* = 7.4 Hz, 2H, Ph'H-3,5), 7.23 (t, *J* = 7.4 Hz, 1H, Ph'H-4), 7.21 (d, *J* = 8.3 Hz, 2H, Ph'H-2,6), 3.91 (td, *J* = 10.2, 3.6 Hz, 1H, C**H**COPh), 3.29 (td, *J* = 9.6, 5.9 Hz, 1H, C**H**Ph), 2.85 (dd, *J* = 12.0, 10.7 Hz, 1H, C***H***HNPyrr), 2.51 (dd, *J* = 12.5, 9.6 Hz, 1H, C***H***HNMe$_2$), 2.38 (dd, *J* = 12.5, 5.9 Hz, 1H, CH***H***NMe$_2$), 2.34–2.28 (m, 2H), 2.24–2.18 (m, 2H), 2.17 (dd, *J* = 12.0, 3.6 Hz, 1H, CH***H***NPyrr), 1.88 (s, 6H, NMe_2), 1.54–1.43 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.3 (C=O), 141.9 (C), 140.1 (C), 131.5 (CH), 128.7 (2CH), 128.28 (2CH), 128.25 (2CH), 127.6 (2CH), 126.8 (CH), 65.1, 58.7, 54.6 (2NCH_2), 49.5, 47.5, 44.7 (NMe_2), 23.7 (2CH_2).

HRMS (ESI) calcd for $(C_{23}H_{31}N_2O)^+$ $[M+H]^+$: 351.2431, found: 351.2441.



4-(Dimethylamino)-1,3-diphenyl-2-(piperidin-1-ylmethyl)butan-1-one (5bj)

Synthesized according to the **procedure C** from (*E*)-1,3-diphenylprop-2-en-1-one; 97% yield.

Ring-cleavage step according to the **procedure RC-Am** at 0.5 mmol scale: piperidine (3.0 equiv.), Cs_2CO_3 (1.1 equiv.) and CH_3CN, 80 °C, 2 h; yield 93%.

Diastereomeric ratio 83:17 (anti:syn).

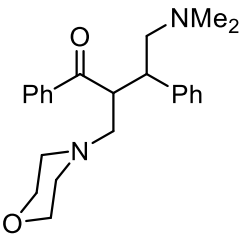
Product was recrystallized from MeOH to give single major anti-diastereomer.

Beige solid, mp 124–125 °C. Yield: 164 mg (93% from quaternate; 90% for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.1, 1.5 Hz, 2H, COPhH-2,6), 7.50–7.42 (m, 3H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.24–7.19 (m, 3H), 3.90 (td, *J* = 10.3, 4.0 Hz, 1H, C**H**COPh), 3.31 (td, *J* = 9.6, 6.0 Hz, 1H, C**H**Ph), 2.60 (dd, *J* = 12.5, 10.6 Hz, 1H), 2.49 (dd, *J* = 12.5, 9.6 Hz, 1H), 2.38 (dd, *J* = 12.5, 6.0 Hz, 1H), 2.30–2.23 (m, 2H), 2.08–2.02 (m, 2H), 2.04 (dd, *J* = 12.5, 4.0 Hz, 1H), 1.91 (s, 6H, NMe_2), 1.31–1.22 (m, 2H), 1.22–1.14 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 202.1 (C=O), 141.9 (C), 140.6 (C), 131.2 (CH), 128.6 (2CH), 128.3 (2CH), 128.1 (2CH), 127.7 (2CH), 126.8 (CH), 65.4, 61.8, 55.0 (CH_2), 48.1, 47.0, 44.8 (NMe_2), 26.0 ($2CH_2$), 24.4. (one CH_2 is masked).

HRMS (ESI) calcd for $(C_{24}H_{33}N_2O)^+$ $[M+H]^+$: 365.2587, found: 365.2578.



4-(Dimethylamino)-2-(morpholinomethyl)-1,3-diphenylbutan-1-one (5bk)

Synthesized according to the **procedure C** from (*E*)-1,3-diphenylprop-2-en-1-one; 97% yield.

Ring-cleavage step according to the **procedure RC-Am** at 0.5 mmol scale: morpholine (3.0 equiv.), Cs_2CO_3 (1.1 equiv.) and MeOH, 65 °C, 18 h; yield 84%.

Diastereomeric ratio 85:15 (anti:syn).

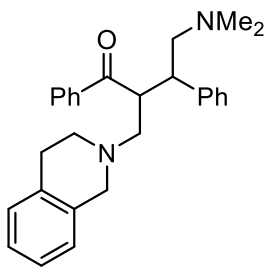
Product was recrystallized from MeOH to give single major anti-diastereomer.

Beige solid, mp 134–135 °C. Yield: 149 mg (84% from quaternate; 81% for 3 steps from alkene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.1, 1.6 Hz, 2H, COPhH-2,6), 7.50–7.43 (m, 3H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.26–7.19 (m, 3H), 3.90 (ddd, *J* = 10.7, 9.7, 4.0 Hz, 1H, C**H**COPh), 3.41–3.31 (m, 3H), 3.31–3.24 (m, 2H), 2.64 (dd, *J* = 12.5, 10.7 Hz, 1H, C***H***HNMorph), 2.52 (dd, *J* = 12.5, 10.1 Hz, 1H, C***H***HNMe$_2$), 2.38 (dd, *J* = 12.5, 5.6 Hz, 1H, CH***H***NMe$_2$), 2.34–2.28 (m, 2H), 2.15–2.09 (m, 2H), 2.08 (dd, *J* = 12.5, 4.0 Hz, 1H, CH***H***NMorph), 1.90 (s, 6H, NMe_2).

^{13}C NMR (151 MHz, $CDCl_3$) δ 201.2 (C=O), 141.6 (C), 140.5 (C), 131.4 (CH), 128.8 (2CH), 128.21 (2CH), 128.17 (2CH), 127.6 (2CH), 127.0 (CH), 66.9 ($2CH_2$), 65.5, 61.3, 53.9, 47.7, 47.0, 44.7 (NMe_2). (one CH_2 is masked).

HRMS (ESI) calcd for $(C_{23}H_{31}N_2O_2)^+$ $[M+H]^+$: 367.2380, found: 367.2392.



2-((3,4-Dihydroisoquinolin-2(1*H*)-yl)methyl)-4-(dimethylamino)-1,3-diphenylbutan-1-one (5bl)

Synthesized according to the **procedure C** from (*E*)-1,3-diphenylprop-2-en-1-one; 97% yield.

Ring-cleavage step according to the **procedure RC-Am** at 0.5 mmol scale: 1,2,3,4-tetrahydroisoquinoline (1.3 equiv.), Cs_2CO_3 (1.1 equiv.) and CH_3CN, 80 °C, 2.5 h; yield 81%.

Diastereomeric ratio 88:12 (anti:syn).

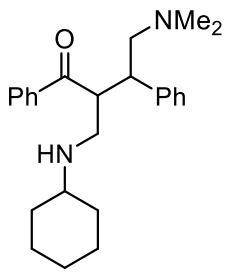
Product was recrystallized from MeOH to give dr 96:4 (anti:syn).

White crystals, mp 142–143 °C. Yield: 163 mg (81% from quaternate; 79% for 3 steps from alkene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.1, 1.4 Hz, 2H, COPhH-2,6), 7.47–7.38 (m, 3H), 7.36–7.31 (m, 2H), 7.26–7.22 (m, 3H), 7.02–6.98 (m, 2H), 6.92 (dd, *J* = 5.0, 4.0 Hz, 1H), 6.85 (dd, *J* = 5.0, 4.0 Hz, 1H), 4.04 (td, *J* = 10.0, 3.8 Hz, 1H, C**H**COPh), 3.45 (d, *J* = 15.0 Hz, 1H, THIQ-1-C***H***HN), 3.38 (d, *J* = 15.0 Hz, 1H, THIQ-1-CH***H***N), 3.36 (td, *J* = 9.3, 5.3 Hz, 1H, C**H**Ph), 2.85 (dd, *J* = 12.5, 10.6 Hz, 1H), 2.77–2.70 (m, 1H), 2.59–2.50 (m, 2H), 2.49–2.40 (m, 1H), 2.40 (dd, *J* = 12.5, 5.7 Hz, 1H), 2.34–2.28 (m, 1H), 2.25 (dd, *J* = 12.5, 3.8 Hz, 1H, CH***H***N^{THIQ}), 1.91 (s, 6H, NMe_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.2 (C=O), 141.7 (C), 140.2 (C), 135.3 (C), 134.6 (C), 131.4 (CH), 128.7 (2CH), 128.5 (CH), 128.3 (2CH), 128.2 (2CH), 127.6 (2CH), 126.9 (CH), 126.4 (CH), 125.8 (CH), 125.4 (CH), 65.3, 60.6, 56.8, 50.8, 48.0, 47.2, 44.7 (NMe_2), 29.2.

HRMS (ESI) calcd for $(C_{28}H_{33}N_2O)^+$ $[M+H]^+$: 413.2587, found: 413.2602.



2-((Cyclohexylamino)methyl)-4-(dimethylamino)-1,3-diphenylbutan-1-one (5bm)

Synthesized according to the **procedure C** from (*E*)-1,3-diphenylprop-2-en-1-one; 97% yield.

Ring-cleavage step according to the **procedure RC-Am** at 0.5 mmol scale: cyclohexylamine carbonate (2.0 equiv.), Cs_2CO_3 (3.0 equiv.) and CH_3CN, 80 °C, 8 h; yield 92%.

Diastereomeric ratio 81:19 (anti:syn).

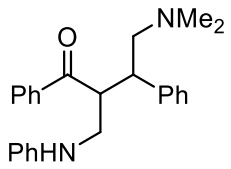
Product was recrystallized from $CHCl_3$/*n*-C_6H_{14} to give single major anti-diastereomer.

White needles, mp 112–115 °C. Yield: 169 mg (92% from quaternate; 89% for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 2H, COPhH-2,6), 7.52–7.44 (m, 3H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.28–7.22 (m, 3H), 3.80 (ddd, *J* = 9.8, 8.4, 4.4 Hz, 1H, C**H**COPh), 3.42 (td, *J* = 9.9, 5.8 Hz, 1H, C**H**Ph), 2.76 (dd, *J* = 11.8, 8.3 Hz, 1H), 2.51–2.45 (m, 2H), 2.39 (dd, *J* = 12.5, 5.8 Hz, 1H), 2.08 (tt, *J* = 10.3, 3.4 Hz, 1H), 1.88 (s, 6H, NMe_2), 1.58–1.50 (m, 3H), 1.50–1.44 (m, 2H), 1.12–0.96 (m, 3H), 0.81–0.70 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.5 (C=O), 141.5 (C), 139.8 (C), 131.7 (CH), 128.7 (2CH), 128.39 (2CH), 128.36 (2CH), 127.7 (2CH), 127.0 (CH), 65.0, 56.6, 50.8, 48.7, 47.4, 44.6 (NMe_2), 33.4, 33.2, 26.2, 25.0, 24.9.

HRMS (ESI) calcd for $(C_{25}H_{35}N_2O)^+$ $[M+H]^+$: 379.2744, found: 379.2744.



4-(Dimethylamino)-1,3-diphenyl-2-((phenylamino)methyl)butan-1-one (5bn)

Synthesized according to the **procedure C** from (*E*)-1,3-diphenylprop-2-en-1-one; 97% yield.

Ring-cleavage step according to the **procedure RC-Am** at 0.5 mmol scale: $PhNH_2$ (1.25 equiv.), Cs_2CO_3 (1.05 equiv.) and CH_3CN, 80 °C, 15 h; yield 69%.

Product was recrystallized from $CHCl_3$/*n*-C_6H_{14} (1/20 v/v).

Diastereomeric ratio 93:7 (anti:syn).

Beige solid, mp 124–126 °C. Yield: 125 mg (69% from quaternate; 67% for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.6 Hz, 2H, COPhH-2,6), 7.47 (t, *J* = 7.3 Hz, 1H, COPhH-4), 7.42–7.35 (m, 4H), 7.31–7.27 (m, 3H), 7.07–7.03 (m, 2H, NPhH-3,5), 6.62 (t, *J* = 7.3 Hz, 1H, NPhH-4), 6.26 (d, *J* = 7.8 Hz, 2H, NPhH-2,6), 3.95 (ddd, *J* = 10.1, 8.3, 4.1 Hz, 1H, C**H**COPh), 3.66–3.60 (m, 1H), 3.51 (td, *J* = 10.4, 5.2 Hz, 1H), 3.30–3.23 (m, 1H), 3.05 (br d, *J* = 13.5 Hz, 1H), 2.52 (dd, *J* = 12.5, 10.8 Hz, 1H, C***H***HNMe$_2$), 2.40 (dd, *J* = 12.5, 5.2 Hz, 1H, CH***H***NMe$_2$), 1.86 (s, 6H, NMe_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7 (C=O), 147.8 (C), 141.0 (C), 139.5 (C), 131.8 (CH), 129.2 (2CH), 128.9 (2CH), 128.4 (2CH), 128.3 (2CH), 127.4 (2CH), 127.3 (CH), 117.2 (CH), 113.0 (2CH), 64.8, 48.9, 47.4, 45.3, 44.4 (NMe_2).

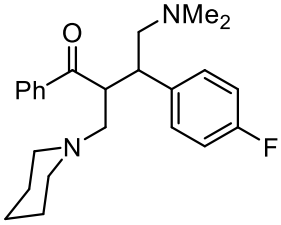
HRMS (ESI) calcd for $(C_{25}H_{29}N_2O)^+$ $[M+H]^+$: 373.2274, found: 373.2264.

General procedure D for the heteromethylation of various enones **1**:

A mixture of enone (4.0 mmol, 1.0 equiv.), finely ground *N*-methylglycine (534 mg, 6.0 mmol, 1.5 equiv.) and paraformaldehyde (276 mg, 9.2 mmol of formaldehyde, 2.3 equiv.) was refluxed in benzene (12 mL) in a 50 mL round-bottom flask fitted with a Dean-Stark trap for 4 h. The resulting mixture was cooled to room temperature and undissolved unreacted excess of *N*-methylglycine was filtered off. **Methyl iodide** (852 mg, 6.0 mmol, 1.5 equiv.) was added dropwise at room temperature to the resulting solution under constant stirring and the stirring continued overnight (15-24 h). The formed precipitate was filtered, washed with PhMe and dried at 60 °C to give the desired ammonium salt.

In case the formed precipitate is viscous oil or contain oily admixtures in it, solvent was decantated from the viscous oil and it was thoroughly rubbed with spatula in several portions of dry diethyl ether (at least 3-5 times × 10 mL) until it become solid. Then it was filtered off and dried in an oven at 60 °C to give the desired ammonium salt.

The latter was used further without additional purification in **ring-cleavage procedures RC (RC-Alc, RC-Am, RC-CN)**.



4-(Dimethylamino)-3-(4-fluorophenyl)-1-phenyl-2-(piperidin-1-ylmethyl)butan-1-one (5c)

Synthesized according to the **procedure D** from (*E*)-3-(4-fluorophenyl)-1-phenylprop-2-en-1-one; quantitative yield.

Ring-cleavage step according to the **procedure RC-Am** at 0.5 mmol scale: piperidine (3.0 equiv.), Cs_2CO_3 (1.1 equiv.) and CH_3CN, 80 °C, 2 h; yield 84%.

Diastereomeric ratio 79:21 (anti:syn)

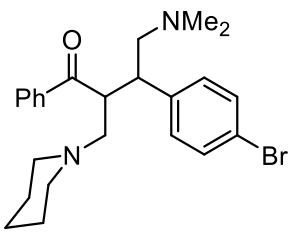
Product was recrystallized from MeOH to give single major anti-diastereomer.

White solid, mp 124–125 °C. Yield: 160 mg (84% for 3 steps from alkene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.3 Hz, 2H, COPhH-2,6), 7.52–7.42 (m, 3H), 7.16 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.00 (t, *J* = 8.6 Hz, 2H), 3.87 (td, *J* = 10.0, 4.3 Hz, 1H, C**H**COPh), 3.30 (td, *J* = 9.2, 6.4 Hz, 1H, C**H**Ar), 2.57 (dd, *J* = 12.5, 10.4 Hz, 1H), 2.46 (dd, *J* = 12.5, 9.2 Hz, 1H), 2.38 (dd, *J* = 12.5, 6.4 Hz, 1H), 2.28–2.21 (m, 2H), 2.10–2.03 (m, 2H), 2.03 (dd, *J* = 12.5, 4.2 Hz, 1H), 1.93 (s, 6H, NMe_2), 1.31–1.13 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.0 (C=O), 161.7 (d, *J* = 244.5 Hz, C-F), 140.3 (C), 137.5 (d, *J* = 3.2 Hz, $2Ar^FC$), 131.5 (CH), 129.6 (d, *J* = 7.9 Hz, $2Ar^FCH$), 128.2 (2CH), 127.8 (2CH), 115.4 (d, *J* = 21.1 Hz, $2Ar^FCH$), 65.2, 61.5, 55.0 ($2NCH_2$), 48.1, 46.1, 44.9 (NMe_2), 26.0 ($2CH_2$), 24.3.

HRMS (ESI) calcd for $(C_{24}H_{32}FN_2O)^+$ $[M+H]^+$: 383.2493, found: 383.2496.



3-(4-Bromophenyl)-4-(dimethylamino)-1-phenyl-2-(piperidin-1-ylmethyl)butan-1-one (5d)

Synthesized according to the **procedure D** from (*E*)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one; 89% yield.

Ring-cleavage step according to the **procedure RC-Am** at 0.5 mmol scale: piperidine (3.0 equiv.), Cs_2CO_3 (1.1 equiv.) and MeOH, 65 °C, 18 h; yield 71%.

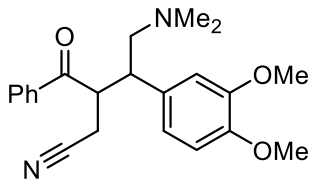
Diastereomeric ratio 93:7 (anti:syn).

Product was recrystallized from MeOH to give single major anti-diastereomer.

White crystals, mp 150–151 °C. Yield: 140 mg (71% from quaternate; 63% for 3 steps from alkene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.1, 1.4 Hz, 2H, COPhH-2,6), 7.52–7.41 (m, 3H, PhH), 7.43 (d, *J* = 8.4 Hz, 2H, Ar^{Br}H-2,6), 7.09 (d, *J* = 8.4 Hz, 2H, Ar^{Br}H-3,5), 3.87 (td, *J* = 10.0, 4.3 Hz, 1H, CHCOPh), 3.28 (td, *J* = 9.2, 6.6 Hz, 1H, CHAr), 2.56 (dd, *J* = 12.5, 10.4 Hz, 1H), 2.45 (dd, *J* = 12.4, 9.0 Hz, 1H), 2.38 (dd, *J* = 12.4, 6.6 Hz, 1H), 2.29–2.21 (m, 2H), 2.10–2.03 (m, 2H), 2.03 (dd, *J* = 12.5, 4.3 Hz, 1H), 1.92 (s, 6H, NMe_2), 1.32–1.12 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.9 (C=O), 140.9 (C), 140.2 (C), 131.7 (2CH), 131.5 (CH), 130.0 (2CH), 128.2 (2CH), 127.8 (2CH), 120.5 (C), 65.0, 61.5, 55.0 ($2NCH_2$), 47.8, 46.3, 44.9 (NMe_2), 26.0 ($2CH_2$), 24.3. HRMS (ESI) calcd for $(C_{24}H_{32}BrN_2O)^+$ $[M+H]^+$: 443.1693, found: 443.1692.



3-Benzoyl-4-(3,4-dimethoxyphenyl)-5-(dimethylamino)pentanenitrile (5ea)

Synthesized according to the **procedure D** from (*E*)-3-(3,4-dimethoxyphenyl)-1-phenylprop-2-en-1-one; quantitative yield.

Ring-cleavage step according to the **procedure RC-CN** at 0.5 mmol scale: acetone cyanohydrin (2.5 equiv.), Cs_2CO_3 (1.05 equiv.) and MeOH, 65 °C, 12 h; 75% yield.

Purified by column chromatography (eluent: dichloromethane/methanol from 100:1 to 100:5; R_f (dichloromethane/methanol, 100/5) = 0.49 and 0.72).

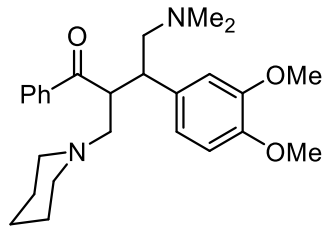
Diastereomeric ratio 89:11 (anti:syn).

Beige solid, mp 118–119 °C. Yield: 135 mg (75% from quaternate; 75% for 3 steps from enone).

Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.9 Hz, 2H, COPhH-2,6), 7.57–7.53 (m, 1H, COPhH-4), 7.51 (t, *J* = 7.2 Hz, 2H, COPhH-3,5), 6.85 (d, *J* = 8.2 Hz, 1H, ArH-5), 6.73 (dd, *J* = 8.2, 2.0 Hz, 1H, ArH-6), 6.65 (d, *J* = 2.0 Hz, 1H, ArH-2), 3.93 (td, *J* = 9.2, 4.2 Hz, 1H, C**H**COPh), 3.90 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.37 (ddd, *J* = 11.4, 8.9, 4.7 Hz, 1H, C**H**Ar), 2.60 (dd, *J* = 12.7, 11.4 Hz, 1H, C***H***HNMe$_2$), 2.44 (dd, *J* = 16.8, 9.4 Hz, 1H, C***H***HCN), 2.40 (dd, *J* = 12.7, 4.7 Hz, 1H, CH***H***NMe$_2$), 2.24 (dd, *J* = 16.8, 4.2 Hz, 1H, CH***H***CN), 1.92 (s, 6H, NMe_2).

Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.3, 1.2 Hz, 0.26H, COPhH-2,6), 7.57–7.53 (m, 0.13H), 7.46 (t, *J* = 7.7 Hz, 0.26H, COPhH-3,5), 6.74 (d, *J* = 8.2 Hz, 0.13H, ArH-5), 6.63 (dd, *J* = 8.2, 2.0 Hz, 0.13H, ArH-6), 6.53 (d, *J* = 2.0 Hz, 0.13H, ArH-2), 4.26 (td, *J* = 7.1, 5.6 Hz, 0.13H, C**H**COPh), 3.83 (s, 0.39H, OMe), 3.80 (s, 0.39H, OMe), 3.40–3.34 (m, 0.13H, C**H**Ar), 2.81 (dd, *J* = 16.8, 6.9 Hz, 0.13H, C***H***HCN), 2.72 (dd, *J* = 16.8, 7.3 Hz, 0.13H, CH***H***CN), 2.63 (dd, *J* = 12.6, 10.5 Hz, 0.13H, C***H***HNMe$_2$), 2.31 (dd, *J* = 12.6, 5.1 Hz, 0.13H, CH***H***NMe$_2$), 2.15 (s, 0.8H, NMe_2).

Major diastereomer: ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.3 (C=O), 149.4 (C-O), 148.6 (C-O), 138.2 (C), 132.4 (CH), 131.5 (C), 128.7 (2CH), 127.6 (2CH), 120.1 (CH), 118.5 (CN), 111.8 (CH), 111.7 (CH), 64.0, 56.14 (OMe), 56.05 (OMe), 47.7, 46.1, 44.4 (NMe_2), 18.7 (***C***H_2CN). Signals of **minor diastereomer** are masked**.** HRMS (ESI) calcd for $(C_{22}H_{27}N_2O_3)^+$ $[M+H]^+$: 367.2016, found: 367.2021.



3-(3,4-Dimethoxyphenyl)-4-(dimethylamino)-1-phenyl-2-(piperidin-1-ylmethyl)butan-1-one (5eb)

Synthesized according to the **procedure D** from (*E*)-3-(3,4-dimethoxyphenyl)-1-phenylprop-2-en-1-one; quantitative yield.

Ring-cleavage step according to the **procedure RC-Am** at 0.5 mmol scale: piperidine (3.0 equiv.), Cs_2CO_3 (1.1 equiv.) and MeOH, 65 °C, 18 h; yield 69%.

Diastereomeric ratio 80:20 (anti:syn).

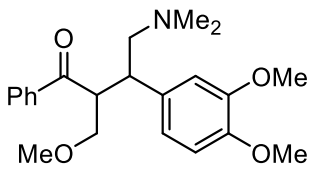
Product was recrystallized from MeOH to give single major anti-diastereomer.

White crystals, mp 120–122 °C. Yield: 146 mg (69% for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.3, 1.6 Hz, 2H, COPhH-2,6), 7.50–7.42 (m, 3H), 6.82 (d, *J* = 8.2 Hz, 1H, ArH-5), 6.74 (dd, *J* = 8.2, 1.9 Hz, 1H, ArH-6), 6.70 (d, *J* = 1.9 Hz, 1H, ArH-2), 3.89 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.84 (td, *J* = 10.1, 4.1 Hz, 1H, C**H**COPh), 3.26 (td, *J* = 9.4, 6.1 Hz, 1H, C**H**Ar), 2.59 (dd, *J* = 12.5, 10.5 Hz, 1H), 2.47 (dd, *J* = 12.5, 9.5 Hz, 1H), 2.38 (dd, *J* = 12.5, 6.1 Hz, 1H), 2.30–2.24 (m, 2H), 2.08 (dd, *J* = 12.5, 4.1 Hz, 1H), 2.11–2.04 (m, 2H), 1.93 (s, 6H, NMe_2), 1.31–1.24 (m, 2H), 1.23–1.16 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.2 (C=O), 149.0 (C–O), 147.8 (C–O), 140.5 (C), 134.4 (C), 131.3 (CH), 128.1 (2CH), 127.7 (2CH), 120.2 (CH), 111.5 (CH), 111.4 (CH), 65.3, 61.7, 56.1 (OMe), 56.0 (OMe), 55.0 ($2CH_2$), 48.3, 46.6, 44.9 (NMe_2), 26.0 ($2CH_2$), 24.4.

HRMS (ESI) calcd for $(C_{26}H_{37}N_2O_3)^+$ $[M+H]^+$: 425.2799, found: 425.2785.



3-(3,4-Dimethoxyphenyl)-4-(dimethylamino)-2-(methoxymethyl)-1-phenylbutan-1-one (5ec)

Synthesized according to the **procedure D** from (*E*)-3-(3,4-dimethoxyphenyl)-1-phenylprop-2-en-1-one; quantitative yield.

Ring-cleavage step according to the **procedure RC-Alc** at 0.5 mmol scale: K_2CO_3 (1.1 equiv.) and MeOH, 65 °C, 24 h; yield 48%.

Purified by column chromatography (eluent: dichloromethane/methanol from 100:5; R_f (dichloromethane/methanol, 10/1) = 0.19 and 0.51).

Diastereomeric ratio 91:9 (anti:syn).

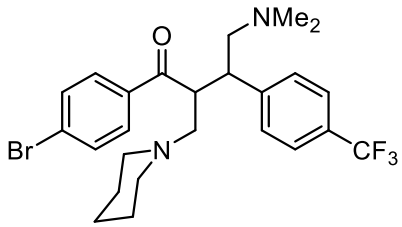
Light yellow amorphous solid. Yield: 89 mg (48% for 3 steps from enone).

Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.1, 1.5 Hz, 2H, COPhH-2,6), 7.51–7.43 (m, 3H), 6.84 (d, *J* = 8.2 Hz, 1H, ArH-5), 6.79 (dd, *J* = 8.2, 2.0 Hz, 1H, ArH-6), 6.73 (d, *J* = 2.0 Hz, 1H, ArH-2), 3.91 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.85 (td, *J* = 10.1, 4.2 Hz, 1H, C**H**COPh), 3.46 (dd, *J* = 9.8, 8.8 Hz, 1H, C***H***HO), 3.34 (td, *J* = 9.9, 6.0 Hz, 1H, C**H**Ar), 3.13 (dd, *J* = 8.8, 4.2 Hz, 1H, CH***H***O), 3.07 (s, 3H, CH_2O**Me**), 2.43 (dd, *J* = 12.5, 9.7 Hz, 1H, C***H***HN), 2.37 (dd, *J* = 12.5, 6.0 Hz, 1H, CH***H***N), 1.88 (s, 6H, NMe_2).

Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.3, 1.2 Hz, 2H, COPhH-2,6), 7.35 (t, *J* = 7.7 Hz, 2H, COPhH-3,5), 6.67 (d, *J* = 8.2 Hz, 1H, ArH-5), 6.64 (dd, *J* = 8.2, 1.8 Hz, 1H, ArH-6), 6.59 (d, *J* = 1.8 Hz, 1H, ArH-2), 4.12 (td, *J* = 7.7, 5.9 Hz, 1H, C**H**COPh), 3.77 (s, 3H, OMe), 3.76–3.71 (m, 2H), 3.73 (s, 3H, OMe), 3.29 (s, 3H, CH_2O**Me**), 3.25 (q, *J* = 7.6 Hz, 1H), 2.58 (dd, *J* = 12.4, 7.3 Hz, 1H, C***H***HN), 2.51 (dd, *J* = 12.4, 7.9 Hz, 1H, CH***H***N), 2.16 (s, 6H, NMe_2). COPhH-4 is masked.

Major diastereomer: ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.9 (**C**OPh), 149.1 (C-O), 148.0 (C-O), 140.2 (C), 133.7 (C), 131.5 (CH), 128.3 (2CH), 127.6 (2CH), 120.0 (CH), 111.5 (CH), 111.3 (CH), 74.9 (OCH_2), 65.2, 59.2, 56.1 (OMe), 56.0 (OMe), 50.7, 45.9, 44.5 (NMe_2). Most of the signals of the **minor diastereomer** are masked.

HRMS (ESI) calcd for $(C_{22}H_{30}NO_4)^+$ $[M+H]^+$: 372.2169, found: 372.2176.



1-(4-Bromophenyl)-4-(dimethylamino)-2-(piperidin-1-ylmethyl)-3-(4-(trifluoromethyl)phenyl)butan-1-one (5f)

Synthesized according to the **procedure D** from (*E*)-1-(4-bromophenyl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one; quantitative yield.

Ring-cleavage step according to the **procedure RC-Am** at 0.5 mmol scale: piperidine (3.0 equiv.), Cs_2CO_3 (1.1 equiv.) and CH_3CN, 80 °C, 3 h; yield 81%.

Diastereomeric ratio 93:7 (anti:syn).

Product was recrystallized from EtOAc/*n*-C_6H_{14} to give single major anti-diastereomer.

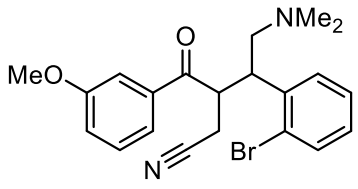
White solid, mp 164–165 °C. Yield: 207 mg (81% for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 3.83 (td, *J* = 10.2, 4.1 Hz, 1H, C**H**COAr), 3.40 (td, *J* = 9.9, 5.6 Hz, 1H, C**H**Ar'), 2.54 (dd, *J* = 12.5, 10.7 Hz, 1H), 2.46 (dd, *J* = 12.5, 10.1 Hz, 1H), 2.35 (dd, *J* = 12.6, 5.6 Hz, 1H, C***H***HNMe$_2$), 2.28–2.22 (m, 2H), 2.08–2.02 (m, 2H), 1.98 (dd, *J* = 12.6, 4.1 Hz, 1H, CH***H***NPiper), 1.90 (s, 6H, NMe_2), 1.30–1.13 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.0 (COAr), 145.8 (C), 139.2 (C), 131.4 (2CH), 129.2 (2CH), 129.20 (q, $J_{C\text{-}F}$ = 32.4 Hz), 128.6 (2CH), 126.2 (C), 125.65 (q, $J_{C\text{-}F}$ = 3.7 Hz, *C*CF_3), 124.34 (q, $J_{C\text{-}F}$ = 271.9 Hz, CF_3), 65.3, 61.7, 55.0 ($2CH_2$), 47.9, 47.0, 44.7 (NMe_2), 26.0 ($2CH_2$), 24.3 (CH_2).

HRMS (ESI) calcd for $(C_{25}H_{31}BrF_3N_2O)^+$ $[M+H]^+$: 511.1566, found: 511.1573.

4-(2-Bromophenyl)-5-(dimethylamino)-3-(3-methoxybenzoyl)pentanenitrile (5g)



Synthesized according to the **procedure D** from (*E*)-3-(2-bromophenyl)-1-(3-methoxyphenyl)prop-2-en-1-one; 79% yield.

Ring-cleavage step according to the **procedure RC-CN** at 0.5 mmol scale: acetone cyanohydrin (2.5 equiv.), Cs_2CO_3 (1.05 equiv.) and MeOH, 65 °C, 12 h; 80% yield.

Purified by column chromatography (eluent: chloroform/hexane 4:1; R_f (chloroform/ethanol, 100/5) = 0.29+0.43).

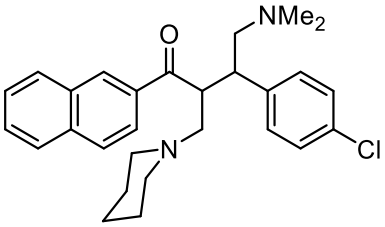
Diastereomeric ratio 80:20 (anti:syn). Diastereomeric ratio changed upon storage in DMSO solution at rt for 1 day to 93:7 (anti:syn).

Beige solid, mp 116–118 °C. Yield: 130 mg (80% from quaternate; 63% for 3 steps from alkene).

Major diastereomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74 (d, *J* = 7.3 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.64 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.55 (s, 1H), 7.50–7.41 (m, 2H), 7.23 (td, *J* = 8.0, 1.4 Hz, 1H), 7.17 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.28 (td, *J* = 10.2, 3.8 Hz, 1H, C**H**COAr), 3.95 (td, *J* = 10.3, 4.4 Hz, 1H, C**H**Ar), 3.85 (s, 3H, OMe), 2.49–2.41 (m, 1H, C***H***HN), 2.41 (dd, *J* = 17.0, 9.5 Hz, 2H, C***H***HCN), 2.30 (dd, *J* = 17.0, 3.8 Hz, 1H, CH***H***CN), 2.19 (dd, *J* = 12.6, 4.4 Hz, 1H, CH***H***N), 1.76 (s, 6H, NMe_2).

^{13}C NMR (126 MHz, DMSO) δ 195.2 (**C**OAr), 159.4, 139.5, 138.6, 132.8, 129.5, 129.0, 128.3, 125.2, 120.0, 118.2, 117.7 (CN), 112.4 (C-Br), 63.3, 55.3 (OMe), 46.2, 43.4 (NMe_2), 43.3, 18.5 (**C**H_2CN).

HRMS (ESI) calcd for $(C_{21}H_{24}BrN_2O_2)^+$ $[M+H]^+$: 415.1016, found: 415.1020.



3-(4-Chlorophenyl)-4-(dimethylamino)-1-(naphthalen-2-yl)-2-(piperidin-1-ylmethyl)butan-1-one (5ha)

Synthesized according to the **procedure D** from (*E*)-3-(4-chlorophenyl)-1-(naphthalen-2-yl)prop-2-en-1-one; quantitative yield. **Ring-cleavage step** according to the **procedure RC-Am** at 0.5 mmol scale: piperidine (3.0 equiv.), Cs_2CO_3 (1.1 equiv.) and MeOH, 65 °C, 18 h; yield 74%.

Diastereomeric ratio > 95:5 (anti:syn).

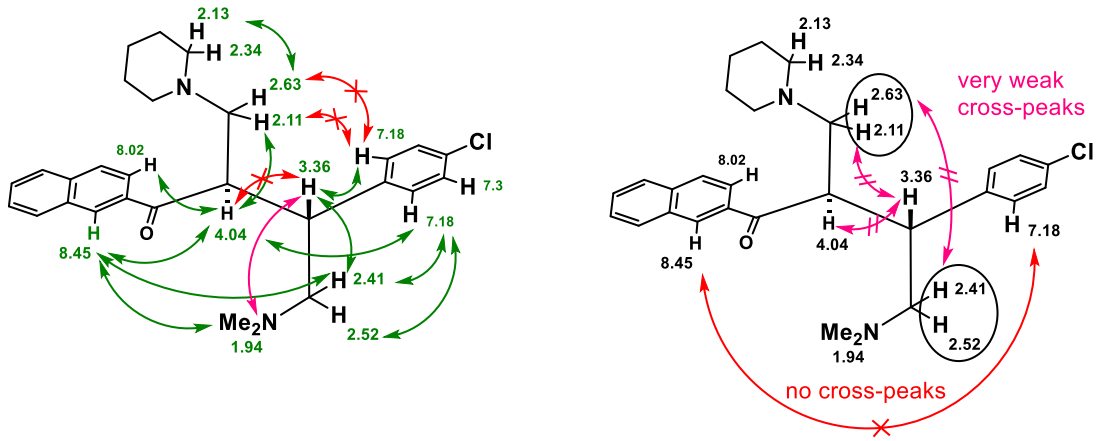
Product was recrystallized from MeOH/$CHCl_3$ to give single major anti-diastereomer.

White solid, mp 158–159 °C. Yield: 166 mg (74% for 3 steps from alkene).

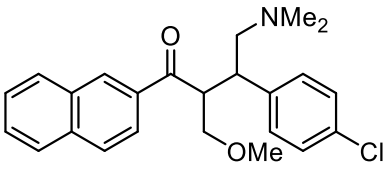
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H, Naph**H**-1), 8.02 (dd, *J* = 8.6, 1.6 Hz, 1H, Naph**H**-3), 7.98 (d, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 1H, Naph**H**-4), 7.89 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.60–7.53 (m, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 4.02 (td, *J* = 9.9, 4.1 Hz, 1H, C**H**CONaph), 3.36 (td, *J* = 9.3, 6.2 Hz, 1H, C**H**Ar), 2.63 (dd, *J* = 12.6, 10.3 Hz, 1H, C***H***HNPiper), 2.50 (dd, *J* = 12.5, 9.4 Hz, 1H, C***H***HNMe_2), 2.39 (dd, *J* = 12.5, 6.2 Hz, 1H, CH***H***NMe_2), 2.35–2.28 (m, 2H), 2.15–2.07 (m, 2H), 2.09 (dd, *J* = 12.6, 4.1 Hz, 1H, CH***H***NPiper), 1.92 (s, 6H, NMe_2), 1.30–1.24 (m, 2H), 1.23–1.16 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.7 (C=O), 140.4 (C), 137.8 (C), 135.0 (C), 132.8 (C), 132.5 (C), 129.7 (2CH), 129.6 (CH), 128.8 (2CH), 128.5 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 126.5 (CH), 124.6 (CH), 65.1, 61.5, 55.1 ($2CH_2$), 48.2, 46.5, 44.9 (NMe_2), 26.0 ($2CH_2$), 24.3.

HRMS (ESI) calcd for $(C_{28}H_{34}ClN_2O)^+$ $[M+H]^+$: 449.2354, found: 449.2345.



^{1}H–^{1}H NOESY of 5ha



3-(4-Chlorophenyl)-4-(dimethylamino)-2-(methoxymethyl)-1-(naphthalen-2-yl)butan-1-one (5hb)

Synthesized according to the **procedure D** from (*E*)-3-(4-chlorophenyl)-1-(naphthalen-2-yl)prop-2-en-1-one; quantitative yield.

Ring-cleavage step according to the **procedure RC-Alc** at 0.5 mmol scale: Cs_2CO_3 (1.1 equiv.) and MeOH, 65 °C, 24 h; yield 70%.

Diastereomeric ratio 91:9 (anti:syn).

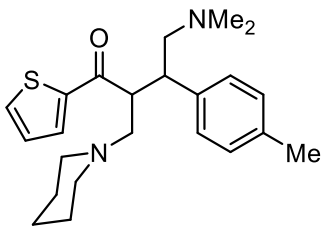
Product was recrystallized from MeOH.

Yellow amorphous solid, mp 133–134 °C. Yield: 139 mg (70% for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 1H, Naph**H**-1), 8.04 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.91–7.85 (m, 2H), 7.59–7.52 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 4.04 (td, *J* = 9.9, 4.2 Hz, 1H, C**H**CONaphth), 3.50 (dd, *J* = 9.6, 8.8 Hz, 1H, C***H***HOMe), 3.43 (td, *J* = 9.8, 6.0 Hz, 1H, C**H**Ar), 3.16 (dd, *J* = 8.8, 4.2 Hz, 1H, CH***H***OMe), 3.07 (s, 3H, OMe), 2.46 (dd, *J* = 12.6, 9.7 Hz, 1H, C***H***HN), 2.38 (dd, *J* = 12.6, 6.0 Hz, 1H, CH***H***N), 1.87 (s, 6H, NMe_2).

^{13}C NMR (151 MHz, $CDCl_3$) δ 199.5 (CONaph), 139.7, 137.4, 135.1, 132.78, 132.76, 129.6, 129.5 (2CH), 129.0 (2CH), 128.6, 128.1, 127.9, 127.8, 126.5, 124.3, 74.5, 65.1, 59.2, 50.4, 45.7, 44.6.

HRMS (ESI) calcd for $(C_{24}H_{27}ClNO_2)^+$ $[M+H]^+$: 396.1725, found: 396.1712.



4-(Dimethylamino)-2-(piperidin-1-ylmethyl)-1-(thiophen-2-yl)-3-(*p*-tolyl)butan-1-one (5i)

Synthesized according to the **procedure D** from (*E*)-1-(thiophen-2-yl)-3-(*p*-tolyl)prop-2-en-1-one; quantitative yield.

Ring-cleavage step according to the **procedure RC-Am** at 0.5 mmol scale:

piperidine (3.0 equiv.), Cs_2CO_3 (1.1 equiv.) and MeOH, 65 °C, 18 h; yield 75%.

Diastereomeric ratio 90:10 (anti:syn).

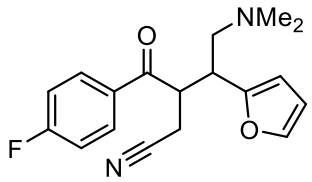
Product was recrystallized from MeOH to give single major anti-diastereomer.

White solid, mp 172–173 °C. Yield: 144 mg (75% for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 3.1, 0.7 Hz, 1H), 7.54 (dd, *J* = 4.9, 0.7 Hz, 1H), 7.13–7.09 (m, 3H), 7.08 (d, *J* = 8.1 Hz, 2H), 3.65 (td, *J* = 10.1, 3.8 Hz, 1H, C**H**Thenoyl), 3.23 (dt, *J* = 10.4, 8.5 Hz, 1H, C**H**Ar), 2.62 (dd, *J* = 12.5, 10.7 Hz, 1H), 2.45 (dd, *J* = 12.5, 8.5 Hz, 1H, C***H***HNMe$_2$), 2.42 (dd, *J* = 12.5, 6.8 Hz, 1H), 2.32 (s, 3H, Me), 2.35–2.28 (m, 2H), 2.11–2.05 (m, 2H), 2.06 (dd, *J* = 12.5, 3.8 Hz, 1H, CH***H***NPiper), 1.95 (s, 6H, NMe$_2$), 1.36–1.27 (m, 2H), 1.26–1.18 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.8 (C=O), 148.0 (C), 138.7 (C), 136.3 (C), 131.5 (CH), 129.5 (CH), 129.3 (2CH), 128.0 (2CH), 127.6 (CH), 65.0, 61.2, 54.9 (2CH$_2$), 50.7, 46.3, 44.8 (NMe$_2$), 26.1 (2CH$_2$), 24.4, 21.2 (Me).

HRMS (ESI) calcd for $(C_{23}H_{33}N_2OS)^+$ $[M+H]^+$: 385.2308, found: 385.2312.



5-(Dimethylamino)-3-(4-fluorobenzoyl)-4-(furan-2-yl)pentanenitrile (5j)

Synthesized according to the **procedure D** from (*E*)-1-(4-fluorophenyl)-3-(furan-2-yl)prop-2-en-1-one; quantitative yield.

Ring-cleavage step according to the **procedure RC-CN** at 0.5 mmol scale: acetone cyanohydrin (2.5 equiv.), Cs_2CO_3 (1.05 equiv.) and MeOH, 65 °C, 12 h; 71% yield.

Diastereomeric ratio 81:19 (anti:syn).

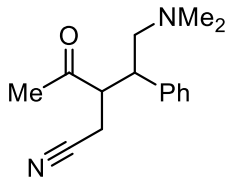
Product was recrystallized from MeOH/H_2O to give dr 99:1 (anti:syn).

Light brown crystals, mp 88–89 °C. Yield: 112 mg (71 % for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.8, 5.4 Hz, 2H, COArH-2,6), 7.38 (d, *J* = 1.7 Hz, 1H), 7.17 (t, *J* = 8.6 Hz, 1H), 6.32 (dd, *J* = 3.1, 1.7 Hz, 1H), 6.16 (d, *J* = 3.1 Hz, 1H), 3.98 (td, *J* = 8.7, 4.8 Hz, 1H, C**H**COAr), 3.55 (ddd, *J* = 11.4, 8.5, 4.7 Hz, 1H, C**H**Het), 2.70 (dd, *J* = 12.9, 11.4 Hz, 1H, C***H***HN), 2.49 (dd, *J* = 16.8, 8.9 Hz, 1H, C***H***HCN), 2.44 (dd, *J* = 12.9, 4.7 Hz, 1H, CH***H***N), 2.26 (dd, *J* = 16.8, 4.8 Hz, 1H, CH***H***CN), 1.94 (s, 6H, NMe$_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.4 (COAr), 165.4 (d, $J_{C\text{-}F}$ = 254.1 Hz, C-F), 152.5 (C), 142.5 (CH), 134.1 (d, $J_{C\text{-}F}$ = 3.1 Hz), 130.2 (d, $J_{C\text{-}F}$ = 9.2 Hz), 118.2 (CN), 115.8 (d, $J_{C\text{-}F}$ = 21.9 Hz), 110.5 (CH), 108.5 (CH), 61.3, 44.8, 44.5 (NMe$_2$), 41.5, 18.3 (**C**H$_2$CN).

HRMS (ESI) calcd for $(C_{18}H_{20}FN_2O_2)^+$ $[M+H]^+$: 315.1503, found: 315.1508.



3-Acetyl-5-(dimethylamino)-4-phenylpentanenitrile (5k)

Synthesized according to the **procedure D** from (*E*)-4-phenylbut-3-en-2-one; 77% yield.

Ring-cleavage step according to the **procedure RC-CN** at 0.5 mmol scale: acetone cyanohydrin (2.5 equiv.), Cs_2CO_3 (1.05 equiv.) and MeOH, 65 °C, 6 h; 71% yield.

Purified by column chromatography (eluent: chloroform/ethanol, from 100/1 to 100/2; R_f (chloroform/ethanol, 100/6) = 0.46+0.58).

Diastereomeric ratio 83:17.

Light yellow viscous oil. Yield: 67 mg (71% from quaternate; 55% for 3 steps from alkene).

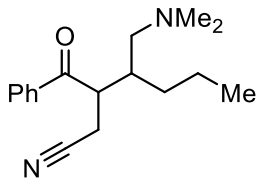
Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.31 (m, 2H), 7.30–7.25 (m, 1H), 7.15–7.11 (m, 2H), 3.19 (td, *J* = 10.3, 4.4 Hz, 1H, C**H**Ph), 3.02 (td, *J* = 10.4, 3.8 Hz, 1H, C**H**COMe), 2.59 (dd, *J* = 12.6, 11.3 Hz, 1H, C***H***HN), 2.37 (s, 3H, COMe), 2.36 (dd, *J* = 12.6, 4.4 Hz, 1H, CH***H***N), 2.23 (dd, *J* = 16.7, 10.6 Hz, 1H, C***H***HCN), 2.15 (s, 6H, NMe_2), 2.02 (dd, *J* = 16.7, 3.8 Hz, 1H, CH***H***CN).

^{13}C NMR (126 MHz, $CDCl_3$) δ 205.0 (**C**OMe), 139.3 (C), 129.3 (2CH), 128.1 (2CH), 127.8 (CH), 118.3 (CN), 64.8, 52.6, 47.5, 45.03 (NMe_2), 32.1 (CO**Me**), 18.9 (***C***H_2CN).

Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.31 (m, 0.2H), 7.30–7.25 (m, 0.4H), 7.15–7.11 (m, 0.4H), 3.31–3.26 (m, 0.2H), 3.24–3.20 (m, 0.2H), 2.71 (dd, *J* = 12.7, 9.5 Hz, 0.2H, C***H***HN), 2.67 (dd, *J* = 16.6, 5.4 Hz, 0.2H, C***H***HCN), 2.64 (dd, *J* = 16.6, 8.6 Hz, 0.2H, CH***H***CN), 2.46 (dd, *J* = 12.7, 5.3 Hz, 0.2H, CH***H***N), 2.22 (s, 1.2H, NMe_2), 2.06 (s, 0.6H, COMe).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.1 (**C**OMe), 139.7 (C), 129.0 (2CH), 128.2 (2CH), 127.7 (CH), 119.0 (CN), 61.7, 53.6, 45.6 (NMe_2), 44.97, 30.7, 16.5.

HRMS (ESI) calcd for $(C_{15}H_{21}N_2O)^+$ $[M+H]^+$: 245.1648, found: 245.1643.



3-Benzoyl-4-((dimethylamino)methyl)heptanenitrile (5l)

Synthesized according to the **procedure D** from (*E*)-1-phenylhex-2-en-1-one; 47% yield.

Ring-cleavage step according to the **procedure RC-CN** at 0.5 mmol scale: acetone cyanohydrin (2.5 equiv.), Cs_2CO_3 (1.05 equiv.) and MeOH, 65 °C, 24 h; 62% yield.

Diastereomeric ratio 64:36.

Purified by column chromatography (eluent: dichloromethane/ethanol, 100/1; R_f (dichloromethane/ethanol, 100/3) = 0.61).

Light yellow viscous oil. Yield: 40 mg (62% from quaternate; 29% for 3 steps from alkene).

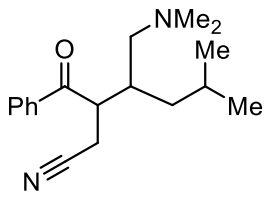
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99–7.94 (m, 2H), 7.59–7.55 (m, 1H), 7.51–7.45 (m, 2H), 4.21 (ddd, *J* = 8.7, 5.0, 4.0 Hz, 0.64H, C**H**Bz **major d**), 4.14 (td, *J* = 7.2, 3.2 Hz, 0.36H, C**H**Bz **minor d**), 2.80 (dd, *J* = 16.9, 7.3 Hz, 1H, 0.36H, C***H***HCN **minor d**), 2.78 (dd, *J* = 16.7, 8.7 Hz, 1H, 0.64H, C***H***HCN **major d**), 2.65 (dd, *J* = 16.9, 7.0 Hz, 1H, 0.36H, CH***H***CN **minor d**), 2.47 (dd, *J* = 16.7, 5.1 Hz, 0.64H, CH***H***CN **major d**), 2.34–2.28 (m,

0.7H), 2.20 (dd, *J* = 12.9, 4.1 Hz, 0.64H), 2.17 (s, 3.84H, NMe_2 **major d**), 2.14–2.08 (m, 0.36H, 4-CH **minor d**), 2.08–2.01 (m, 0.64H, 4-CH **major d**), 2.02 (s, 2.16H, NMe_2 **minor d**), 1.99–1.96 (m, 0.7H), 1.44–1.17 (m, 3H), 1.12–0.95 (m, 1.84H), 0.92 (t, *J* = 7.1 Hz, 1.08H, $CH_2C\boldsymbol{H_3}$ **minor d**), 0.76 (t, *J* = 7.1 Hz, 1.9H, $CH_2C\boldsymbol{H_3}$ **major d**).

Major diastereomer: ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.5 (C=O), 136.4 (C), 133.1 (CH), 128.8 (2CH), 128.4 (2CH), 119.7 (CN), 61.8, 45.7 (NMe_2), 44.8, 38.4, 30.1, 20.6, 14.23, 14.17.

Minor diastereomer: ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.9 (C=O), 137.5 (C), 133.3 (CH), 128.7 (2CH), 128.6 (2CH), 119.6 (CN), 60.5, 45.3 (NMe_2), 44.2, 38.8, 32.0, 21.1, 16.4, 14.3.

HRMS (ESI) calcd for $(C_{17}H_{25}N_2O)^+$ $[M+H]^+$: 273.1962, found: 273.1963.



3-Benzoyl-4-((dimethylamino)methyl)-6-methylheptanenitrile (5m)

Synthesized according to the **procedure D** from (*E*)-5-methyl-1-phenylhex-2-en-1-one; 48% yield.

Ring-cleavage step according to the **procedure RC-CN** at 0.5 mmol scale: acetone cyanohydrin (2.5 equiv.), Cs_2CO_3 (1.05 equiv.) and MeOH, 65 °C, 24 h; 56% yield.

Diastereomeric ratio 67:33 in the crude mixture.

Purified by column chromatography (eluent: chloroform; R_f (chloroform/ethanol, 100/5) = 0.3).

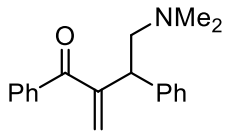
Diastereomeric ratio 75:25.

Light yellow viscous oil. Yield: 38 mg (56% from quaternate; 27% for 3 steps from alkene).

^1H NMR (500 MHz, $CDCl_3$) δ 7.98–7.95 (m, 2H, **major+minor d**), 7.59–7.55 (m, 1H, **major+minor d**), 7.50–7.45 (m, 2H, **major+minor d**), 4.26 (ddd, *J* = 8.5, 5.2, 3.5 Hz, 0.75H, C**H**Bz **major d**), 4.16 (td, *J* = 7.2, 3.0 Hz, 0.25H, C**H**Bz **minor d**), 2.78 (dd, *J* = 16.9, 7.0 Hz, 0.25H, C***H***HCN **minor d**), 2.77 (dd, *J* = 16.7, 8.5 Hz, 0.75H, C***H***HCN **major d**), 2.64 (dd, *J* = 16.9, 7.4 Hz, 0.25H, CH***H***CN **minor d**), 2.45 (dd, *J* = 16.7, 5.2 Hz, 0.75 H, CH***H***CN **major d**), 2.34–2.29 (m, 1H), 2.20 (s, 4.5H, NMe_2 **major d**), 2.16 (dd, *J* = 12.9, 3.9 Hz, 0.75H, C***H***HN **major d**), 2.11–2.04 (m, 1H, **major+minor d**), 2.03 (s, 1.5H, NMe_2 **minor d**), 1.67–1.60 (m, 0.25H, min d), 1.49–1.40 (m, 0.75H, **major d**), 1.24–1.18 (m, 0.25H, **minor d**), 0.99–0.90 (m, 3.5H, **major+minor d**), 0.78 (d, *J* = 6.5 Hz, 2.25H, **major d**), 0.56 (d, *J* = 6.5 Hz, 2.25H, **major d**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.1 (C=O **minor**), 199.7 (C=O **major**), 137.7 (C **minor**), 136.4 (C **major**), 133.3 (2CH **minor**), 133.2 (CH **major**), 128.8 (2CH **major**), 128.7 (2CH **minor**), 128.6 (2CH **minor**), 128.4 (2CH **major**), 119.8 (CN **major**), 119.6 (CN **minor**), 61.9 (**major**), 60.6 (**minor**), 45.8, 45.2, 45.0, 44.1, 38.8 (**minor**), 36.9 (**major**), 36.5 (**minor**), 36.1 (**major**), 25.7 (**minor**), 25.6 (**major**), 23.8 (**major**), 23.4 (**minor**), 22.2 (**minor**), 21.5 (**major**), 16.6 (**minor**), 13.9 (**major**).

HRMS (ESI) calcd for $(C_{18}H_{27}N_2O)^+$ $[M+H]^+$: 287.2118, found: 287.2127.



4-(Dimethylamino)-2-methylene-1,3-diphenylbutan-1-one (3ba)

Synthesized according to the **procedure C** from (*E*)-1,3-diphenylprop-2-en-1-one; 97% yield.

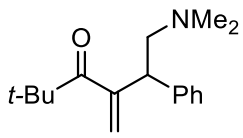
Ring-cleavage step according to the **procedure RC** at 4.0 mmol scale: Cs_2CO_3 (1.05 equiv.) and CH_3CN, 80 °C, 40 h; yield 83%.

Light brown solid, mp 73–76 °C. Yield: 899 mg (81% for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 8.3, 1.3 Hz, 2H, COPhH-2,6), 7.49 (t, *J* = 7.4 Hz, 1H, COPhH-4), 7.39 (t, *J* = 7.6 Hz, 2H, COPhH-3,5), 7.33–7.29 (m, 4H), 7.23–7.19 (m, 1H, PhH-4), 5.66 (d, *J* = 0.9 Hz, 1H, =C***H***H), 5.60 (s, 1H, =CH***H***), 4.40 (dd, *J* = 9.3, 6.7 Hz, 1H, C**H**Ph), 2.86 (dd, *J* = 12.2, 9.3 Hz, 1H, C***H***HNMe$_2$), 2.65 (dd, *J* = 12.2, 6.7 Hz, 1H, CH***H***NMe$_2$), 2.21 (s, 6H, NMe$_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.5 (C=O), 150.6 (C), 141.3 (C), 138.1 (C), 132.1, 129.8 (2CH), 128.7 (2CH), 128.4 (2CH), 128.1 (2CH), 126.8, 124.1, 63.4, 45.5 (NMe$_2$), 45.3.

HRMS (ESI) calcd for $(C_{19}H_{22}NO)^+$ $[M+H]^+$: 280.1696, found: 280.1698.



6-(Dimethylamino)-2,2-dimethyl-4-methylene-5-phenylhexan-3-one (3n)

Synthesized according to the **procedure D** from (*E*)-4,4-dimethyl-1-phenylpent-1-en-3-one; 74% yield.

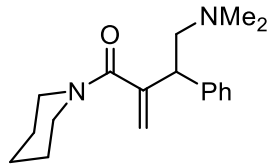
Ring-cleavage step: corresponding quaternary ammonium salt (0.5 mmol) was added to the suspension of NaH (0.6 mmol, 1.2 equiv., 60% suspension in mineral oil) in DMSO (3 mL) at 25 °C. The resulting mixture was left at stirring under argon atmosphere for 23 h at 25 °C. The mixture was diluted with water (10 mL), extracted with CH_2Cl_2 (2×10 mL). Combined organic extracts were washed with water (2×10 mL), brine (10 mL), dried over sodium sulfate and evaporated under reduced pressure to give the desired product in 98% yield.

Light red viscous oil. Yield: 95 mg (98% yield from quaternate; 73% yield for 3 steps from alkene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 7.23–7.17 (m, 3H), 5.51 (s, 1H, =C***H***H), 5.21 (d, *J* = 1.2 Hz, 1H, =CH***H***), 4.10 (dd, *J* = 9.5, 6.4 Hz, 1H, C**H**Ph), 2.73 (dd, *J* = 12.2, 9.5 Hz, 1H, C***H***HNMe$_2$), 2.51 (dd, *J* = 12.2, 6.4 Hz, 1H, CH***H***NMe$_2$), 2.20 (s, 6H, NMe$_2$), 1.14 (s, 9H, *t*Bu).

^{13}C NMR (126 MHz, $CDCl_3$) δ 211.1 (***C***O*t*Bu), 150.6 (C), 141.4 (C), 128.6 (2CH), 128.5 (2CH), 126.8 (CH), 116.7 (=CH_2), 63.4, 46.8, 45.7 (NMe$_2$), 43.9 (***C***Me$_3$), 28.5 (3***C***H$_3$).

HRMS (ESI) calcd for $(C_{17}H_{26}NO)^+$ $[M+H]^+$: 260.2009, found: 260.2015.



4-(Dimethylamino)-2-methylene-3-phenyl-1-(piperidin-1-yl)butan-1-one (3o)

Synthesized according to the **procedure D** from (*E*)-3-phenyl-1-(piperidin-1-yl)prop-2-en-1-one.

First step: (*E*)-3-phenyl-1-(piperidin-1-yl)prop-2-en-1-one (1.0 equiv.), sarcosine (1.5 equiv.), paraformaldehyde (2.3 equiv. of CH_2O), PhH, reflux with Dean-Stark trap, 4 h, 75% yield.

Second step: methyl iodide (1.5 equiv), PhMe/CH_2Cl_2 (v/v 3/2), rt, 24 h; 68% yield.

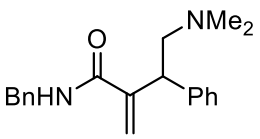
Ring-cleavage step according to the method described for **3m**: MeONa (1.2 equiv.) and MeOH, 65 °C, 12 h; yield 87%.

Beige solid, mp 85–87 °C. Yield: 63 mg (87% yield from quaternate; 44% yield for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.23 (m, 4H), 7.19 (t, *J* = 7.0 Hz, 1H, PhH-4), 5.15 (s, 1H, =C***H***H), 5.03 (s, 1H, =CH***H***), 3.94 (t, *J* = 7.9 Hz, 1H, C**H**Ph), 3.54 (br s, 1H), 3.38 (br s, 1H), 3.22–3.05 (m, 2H), 2.83 (dd, *J* = 12.3, 8.4 Hz, 1H, C***H***HN), 2.79 (dd, *J* = 12.3, 7.4 Hz, 1H, CH***H***N), 2.22 (s, 6H, NMe_2), 1.51–1.33 (m, 4H), 1.09 (br s, 1H), 0.95 (br s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3 (N-C=O), 146.3 (C), 140.6 (C), 128.6 (2CH), 128.4 (2CH), 126.9 (CH), 113.5 (=CH_2), 62.7, 48.1, 47.8, 45.9 (NMe_2), 42.4, 26.0, 25.6, 24.6.

HRMS (ESI) calcd for $(C_{18}H_{27}N_2O)^+$ $[M+H]^+$: 287.2118, found: 287.2116.



***N*-Benzyl-4-(dimethylamino)-2-methylene-3-phenylbutanamide (3p)**

Synthesized according to the **procedure D** from *N*-benzylcinnamamide.

First step: *N*-benzylcinnamamide (1.0 equiv.), sarcosine (1.5 equiv.), paraformaldehyde (2.3 equiv. of CH_2O), PhH, reflux with Dean-Stark trap, 4 h, 72% yield.

Second step: methyl iodide (1.5 equiv), PhMe/CH_2Cl_2 (v/v 3/1), rt, 24 h; 93% yield.

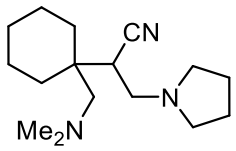
Ring-cleavage step: corresponding quaternary ammonium salt (0.5 mmol, 1.0 equiv.), MeOH (3 mL) and freshly prepared MeONa (14 mg of Na (0.6 mmol, 1.2 equiv.) in 1 mL of MeOH, 0.6M solution) were sequentially added to the 10 mL pressure microwave vial equipped with a magnetic stirrer. Vial was sealed with cap and heated in an oil bath at 65 °C for 12 h under vigorous stirring. The vial was cooled to room temperature and opened in a fume hood. The mixture was diluted with water (15 mL), extracted with CH_2Cl_2 (3×10 mL). Combined organic extracts were washed with water (3×10 mL), brine (10 mL) and evaporated under reduced pressure to give the desired product in 86% yield.

Beige solid, mp 98–99 °C. Yield: 89 mg (86% yield from quaternate; 58% yield for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (br s, 1H, NH), 7.32–7.21 (m, 8H), 7.16 (d, *J* = 6.8 Hz, 2H), 5.81 (s, 1H, =C***H***H), 5.23 (s, 1H, =CH***H***), 4.47 (dd, *J* = 14.7, 5.6 Hz, 1H, PhC***H***HNC=O), 4.40 (dd, *J* = 14.7, 5.3 Hz, 1H, PhCH***H***NC=O), 3.99 (dd, *J* = 8.8, 5.6 Hz, 1H, CHPh'), 2.84 (dd, *J* = 12.4, 8.8 Hz, 1H, C***H***HNMe_2), 2.63 (dd, *J* = 12.4, 5.6 Hz, 1H, CH***H***NMe_2), 2.16 (s, 6H, NMe_2).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.1 (N-C=O), 148.3 (C), 141.9 (C), 138.5 (C), 128.7 (4CH), 128.2 (2CH), 127.9 (2CH), 127.4 (CH), 126.9 (CH), 119.3 (=CH_2), 64.3, 45.9, 45.5 (NMe_2), 43.9.

HRMS (ESI) calcd for $(C_{20}H_{25}N_2O)^+$ $[M+H]^+$: 309.1961, found: 309.1975.



2-(1-((Dimethylamino)methyl)cyclohexyl)-3-(pyrrolidin-1-yl)propanenitrile (11)

Corresponding quaternary ammonium salt **10** was synthesized according to the **procedure D** from ethyl 2-cyano-2-cyclohexylideneacetate, 74% yield.

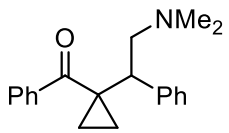
Ring-cleavage step: a mixture of the salt **10** (1.0 mmol), pyrrolidine (3.0 equiv.), KOH (3.0 equiv.) and MeOH (6 mL) was heated in a sealed vial in an oil bath at 65 °C for 46 h under constant stirring. Usual work-up and purification by column chromatography (eluent: chloroform/ethanol, from 100/1 to 100/10; R_f (chloroform/ethanol, 100/5) = 0.3) provided product **11** in 70% yield.

Light yellow oil. Yield: 136 mg (70% from quaternate; 52% yield for 3 steps from alkene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.16 (dd, *J* = 11.0, 3.7 Hz, 1H, C***H***HN), 2.87 (t, *J* = 11.5 Hz, 1H, CH***H***N), 2.67–2.60 (m, 2H), 2.59–2.54 (m, 2H), 2.51 (dd, *J* = 12.0, 3.7 Hz, 1H, C**H**CN), 2.42 (d, *J* = 14.4 Hz, 1H, C***H***HNMe$_2$), 2.36 (d, *J* = 14.4 Hz, 1H, CH***H***NMe$_2$), 2.31 (s, 6H, NMe$_2$), 1.84–1.75 (m, 4H), 1.64–1.58 (m, 1H), 1.53–1.44 (m, 8H), 1.40–1.31 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 122.2 (CN), 62.8, 54.5 (2C), 53.0, 48.9 (2C), 40.1, 38.7, 32.0, 31.5, 25.8, 23.7 (2C), 21.6 (2C).

HRMS (ESI) calcd for $(C_{16}H_{30}N_3)^+$ $[M+H]^+$: 264.2434, found: 264.2441.



(1-(2-(Dimethylamino)-1-phenylethyl)cyclopropyl)(phenyl)methanone (12)

NaH (52 mg of 60% dispersion in mineral oil, 1.3 mmol of NaH) was placed in a Schlenk-tube under argon atmosphere. Dry dimethylsulfoxide (2 mL) was added via syringe at room temperature and the resulting suspension was stirred at rt for 40 min. A solution of 4-(dimethylamino)-2-methylene-1,3-diphenylbutan-1-one **3ba** (196 mg, 0.7 mmol) in dry DMSO (4 mL) was added drop-wise via syringe to the suspension of NaH in DMSO. The resulting mixture was heated in an oil bath at 60 °C for 1.5 h. Then it was quenched with water (20 mL) and extracted with EtOAc (3×10 mL). Organic extracts were washed water (10 mL), brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give cyclopropane.

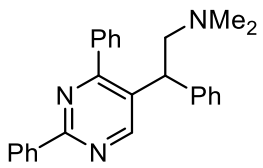
Purified by column chromatography (eluent: chloroform/ethanol, 100/1; R_f (chloroform/ethanol, 100/5) = 0.55).

Colorless viscous oil. Yield: 185 mg (90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.9, 1.6 Hz, 2H, COPhH-2,6), 7.48–7.43 (m, 3H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.1 –7.11 (m, 2H, Ph'H-2,6), 3.83 (dd, *J* = 8.6, 6.1 Hz, 1H, C**H**Ph), 2.61 (dd, *J* = 12.5, 8.6 Hz, 1H, C***H***HNMe$_2$), 2.56 (dd, *J* = 12.5, 6.1 Hz, 1H, CH***H***NMe$_2$), 1.92 (s, 6H, NMe$_2$), 1.35 (ddd, *J* = 10.1, 6.0, 4.7 Hz, 1H, C***H***HCH$_2$), 0.73 (ddd, *J* = 10.1, 6.0, 4.0 Hz, 1H, CH***H***CH$_2$), 0.61 (ddd, *J* = 8.9, 6.0, 4.7 Hz, 1H, CH$_2$C***H***H), 0.52 (ddd, *J* = 8.9, 6.0, 4.0 Hz, 1H, CH$_2$CH***H***).

^{13}C NMR (151 MHz, $CDCl_3$) δ 201.1 (C=O), 139.1 (C), 138.4 (C), 131.2 (CH), 129.1 (2CH), 128.5 (2CH), 128.3 (2CH), 128.2 (2CH), 127.1 (CH), 62.9, 45.3 (NMe$_2$), 44.2, 34.0, 12.1, 4.6.

HRMS (ESI) calcd for $(C_{20}H_{24}NO)^+$ [M+H]$^+$: 294.1852, found: 294.1848.



2-(2,4-Diphenylpyrimidin-5-yl)-N,N-dimethyl-2-phenylethan-1-amine (13)

Benzamidine hydrochloride (56 mg, 0.36 mmol) and sodium acetate (30 mg, 0.36 mmol) were sequentially added to the solution of 4-(dimethylamino)-2-methylene-1,3-diphenylbutan-1-one **3ba** (84 mg, 0.3 mmol) in dry dimethylsulfoxide (2 mL). The resulting mixture was heated in an oil bath at 140 °C for 15 h, quenched with water (10 mL), neutralized with $NaHCO_3$ and extracted with dichloromethane (2×10 mL). Organic extracts were washed with $NaHCO_3$ solution, water (3×10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give pyrimidine.

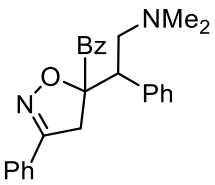
Purified by column chromatography (eluent: *n*-C_6H_{14}/ethyl acetate, 10/4; R_f (*n*-C_6H_{14}/ethyl acetate, 1/1) = 0.63).

Beige viscous oil. Yield: 99 mg (87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H, HetH-6), 8.50–8.47 (m, 2H), 7.48–7.41 (m, 8H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 7.3 Hz, 2H), 4.36 (dd, *J* = 9.8, 6.6 Hz, 1H, CH), 2.97 (dd, *J* = 12.8, 9.8 Hz, 1H, C***H***HNMe$_2$), 2.68 (dd, *J* = 12.8, 6.6 Hz, 1H, CH***H***NMe$_2$), 2.10 (s, 6H, NMe$_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6 (C), 162.2 (C), 158.0 (CH), 142.2 (C), 138.6 (C), 137.8 (C), 130.7 (C), 130.5 (CH), 129.1 (CH), 129.0 (2CH), 128.9 (2CH), 128.6 (2CH), 128.4 (2CH), 128.3 (2CH), 128.2 (2CH), 126.9 (CH), 64.9, 45.5 (NMe$_2$), 43.1.

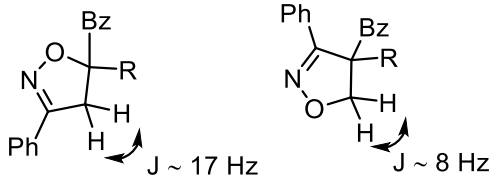
HRMS (ESI) calcd for $(C_{26}H_{26}N_3)^+$ [M+H]$^+$: 380.2121, found: 380.2119.



(5-(2-(Dimethylamino)-1-phenylethyl)-3-phenyl-4,5-dihydroisoxazol-5-yl)(phenyl)methanone (14)

N-Hydroxybenzimidoyl chloride (86 mg, 0.55 mmol) and triethylamine (58 mg, 0.58 mmol) were sequentially added to the solution of 4-(dimethylamino)-2-methylene-1,3-diphenylbutan-1-one **3ba** (140 mg, 0.5 mmol) in dry dichloromethane (6 mL). The resulting mixture was stirred at room temperature for 3 days, washed with water (2 × 6 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a mixture of two diastereomers 60:40. The latter were partially separated by column chromatography (eluent: chloroform/*n*-C_6H_{14}, from 2/1 to 100/0).

Colorless viscous oil. Yield: 140 mg (70%).



The regiochemistry of the product was assigned based on the J-coupling constant of the CHH-protons of the methylene group of isoxazoline ring.[ref2]

Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 2H, COPhH-2,6), 7.54 (dd, *J* = 7.7, 1.5 Hz, 2H, N=CPhH-2,6), 7.46 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.36–7.31 (m, 4H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 4.09 (d, *J* = 17.2 Hz, 1H, C***H***HC=N), 3.94 (dd, *J* = 9.0, 5.2 Hz, 1H, C**H**Ph), 3.70 (d, *J* = 17.2 Hz, 1H, CH***H***C=N), 2.76 (dd, *J* = 13.3, 9.0 Hz, 1H, C***H***HNMe$_2$), 2.63 (dd, *J* = 13.3, 5.2 Hz, 1H, CH***H***NMe$_2$), 1.94 (s, 6H, NMe$_2$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 197.4 (C=O), 157.1 (C=N), 138.0, 136.1, 132.1, 130.3, 129.74 (2CH), 129.70 (2CH), 129.2 (C), 128.7 (2CH), 128.3 (2CH), 128.1 (2CH), 127.5, 126.8 (2CH), 97.9, 59.8, 49.3, 45.0 (NMe$_2$), 40.4 (C).

Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.1, 1.5 Hz, 2H, COPhH-2,6), 7.45 (t, *J* = 7.2 Hz, 1H), 7.43–7.37 (m, 6H), 7.33–7.23 (m, 5H), 7.18 (t, *J* = 7.3 Hz, 1H), 4.03 (dd, *J* = 11.5, 5.3 Hz, 1H, C**H**Ph), 3.45 (d, *J* = 17.8 Hz, 1H, C***H***HC=N), 3.35 (d, *J* = 17.8 Hz, 1H, CH***H***C=N), 3.21 (dd, *J* = 12.8, 11.5 Hz, 1H, C***H***HNMe$_2$), 2.46 (dd, *J* = 12.8, 5.3 Hz, 1H, CH***H***NMe$_2$), 1.99 (s, 6H, NMe$_2$).

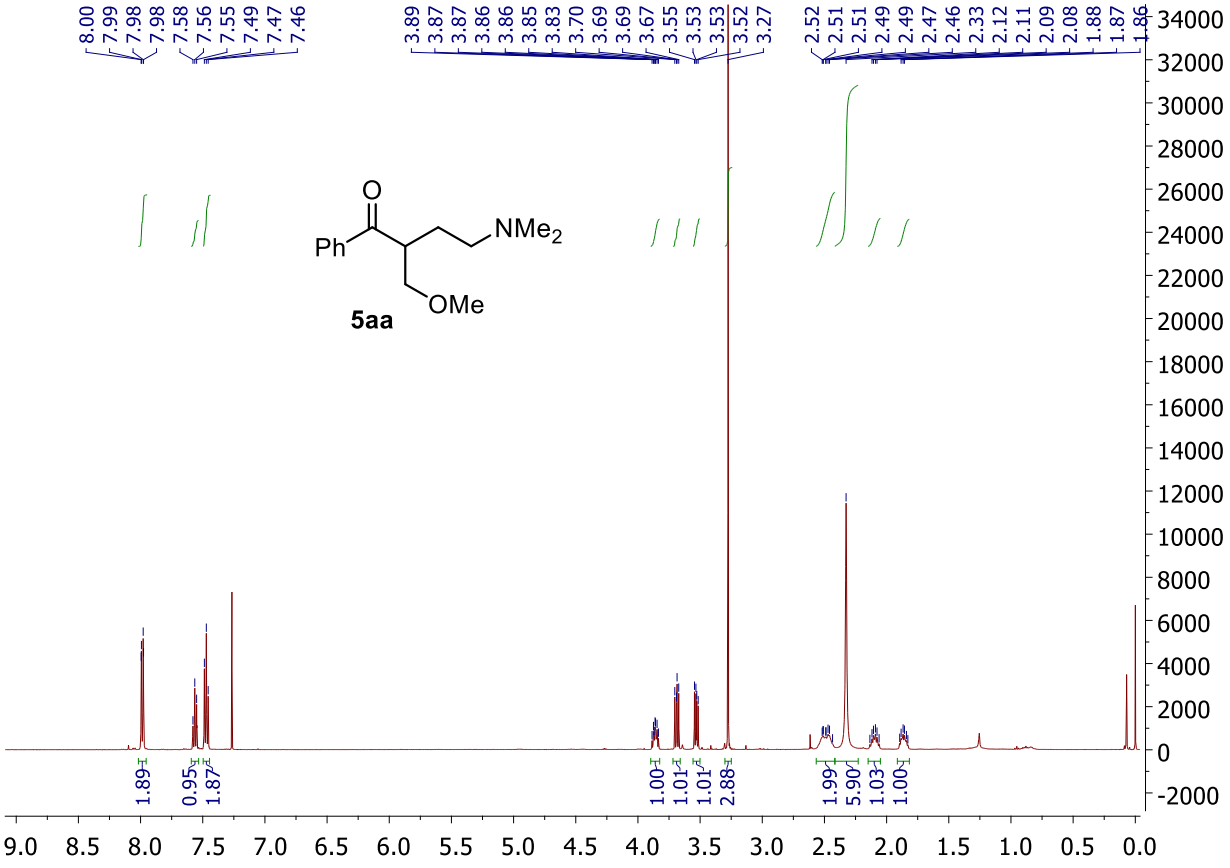
^{13}C NMR (151 MHz, $CDCl_3$) δ 199.3 (C=O), 157.1 (C=N), 138.0, 137.2, 131.5, 130.3 (CH), 129.7 (2CH), 129.3 (2CH), 128.9 (C), 128.7 (3CH), 127.9 (2CH), 127.8 (C), 126.7 (2CH), 96.3, 60.3, 52.1, 44.9, 44.5 (NMe$_2$).

HRMS (ESI) calcd for $(C_{26}H_{27}N_2O_2)^+$ $[M+H]^+$: 399.2067, found: 399.2057.

References:

1. E. M. Buev, P. A. Khardina, V. S. Moshkin and V. Y. Sosnovskikh, *Tetrahedron Lett*., 2022, **111**, 154205.

2. (a) A. Corsaro, U. Chiacchio, G. Perrini, P. Caramella and F. M. Albini, *J. Heterocyclic Chem*, 1989, **26**, 1691–1699; (b) P. Yu. Ushakov, E. A. Khatuntseva, Y. V. Nelyubina, A. A. Tabolin, S. L. Ioffe and A. Yu. Sukhorukov, *Adv. Synth. Catal*., 2019, **361**, 5322–5327.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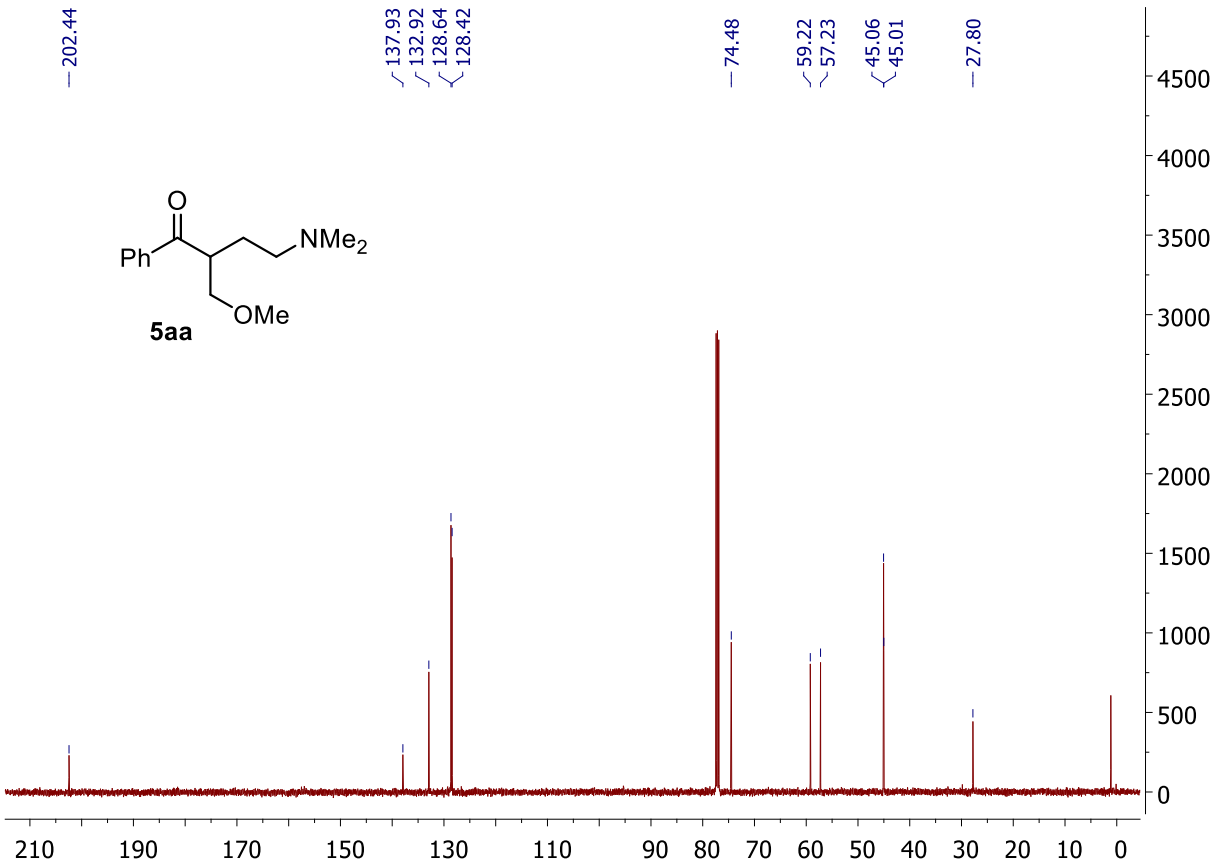
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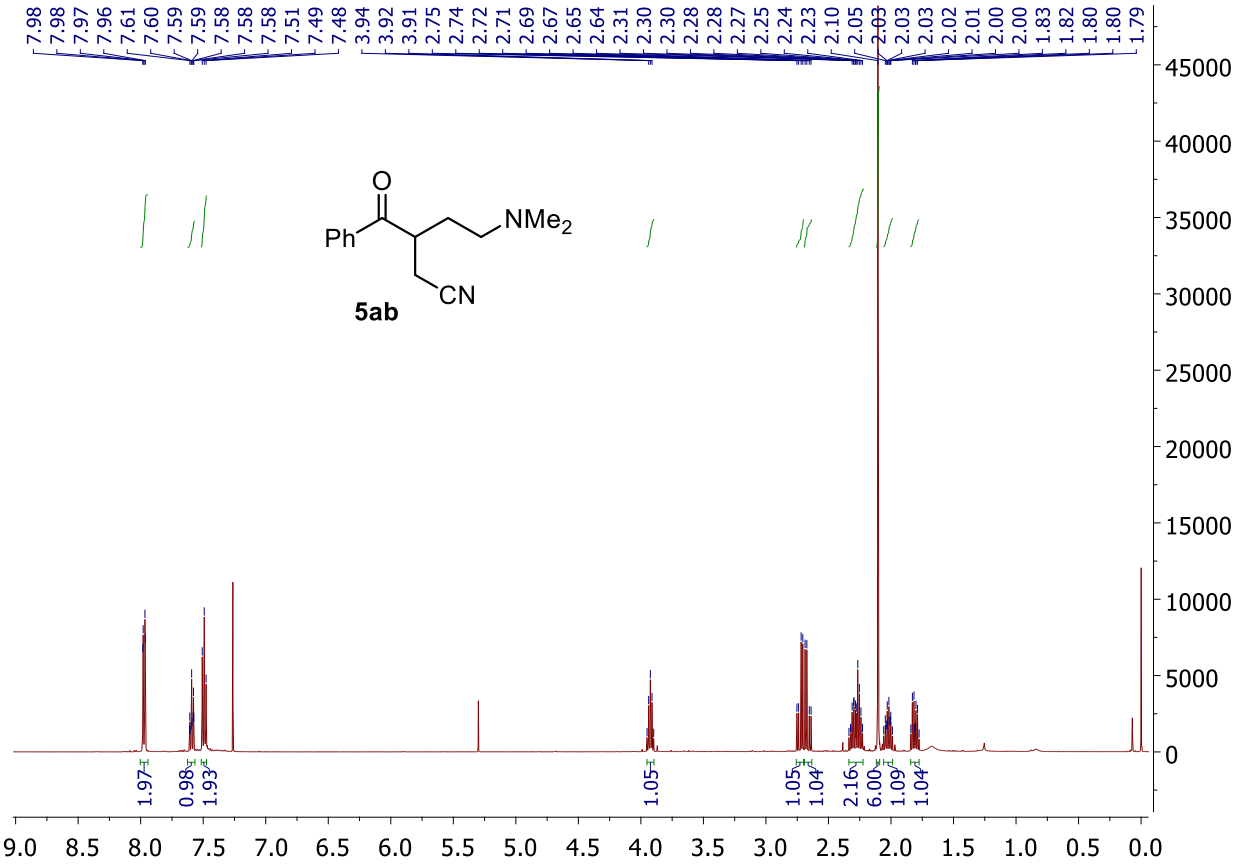
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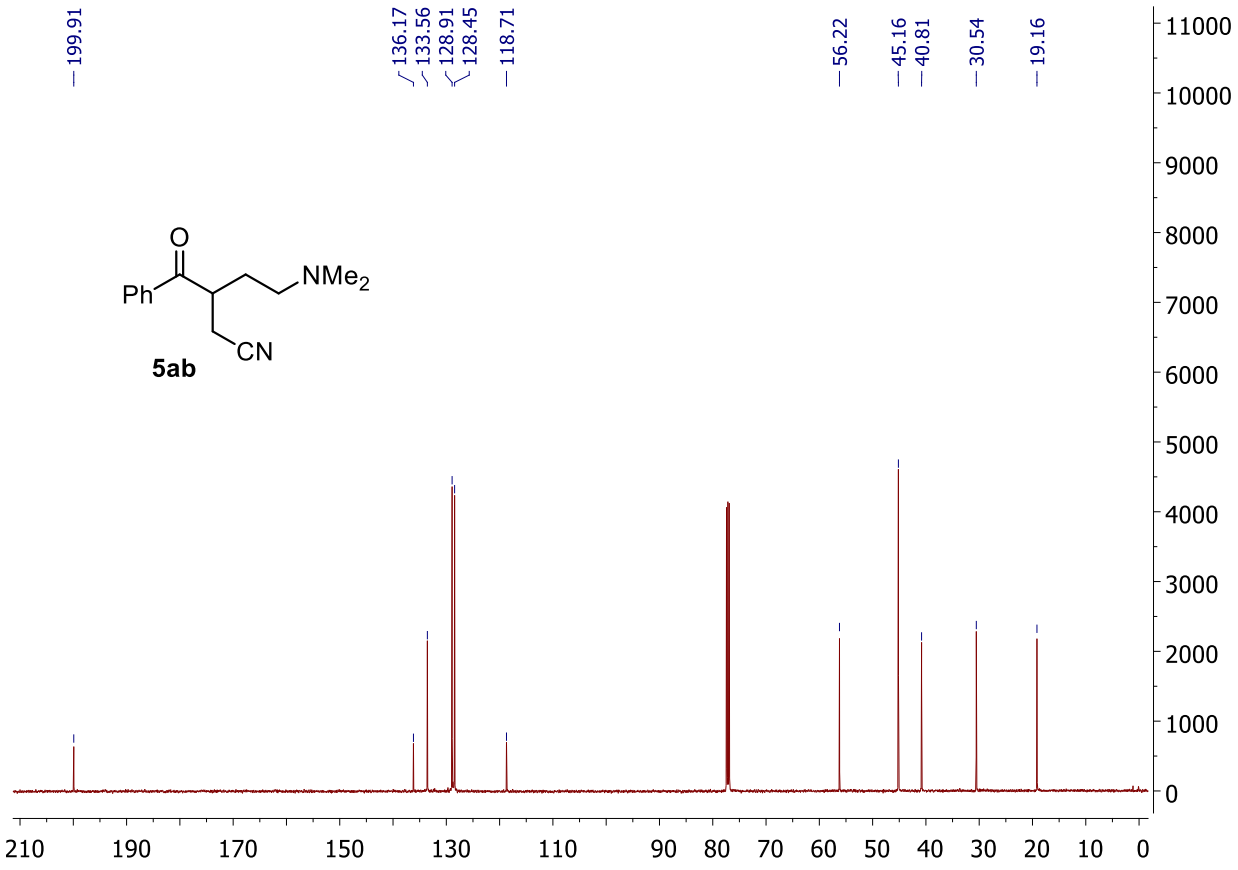
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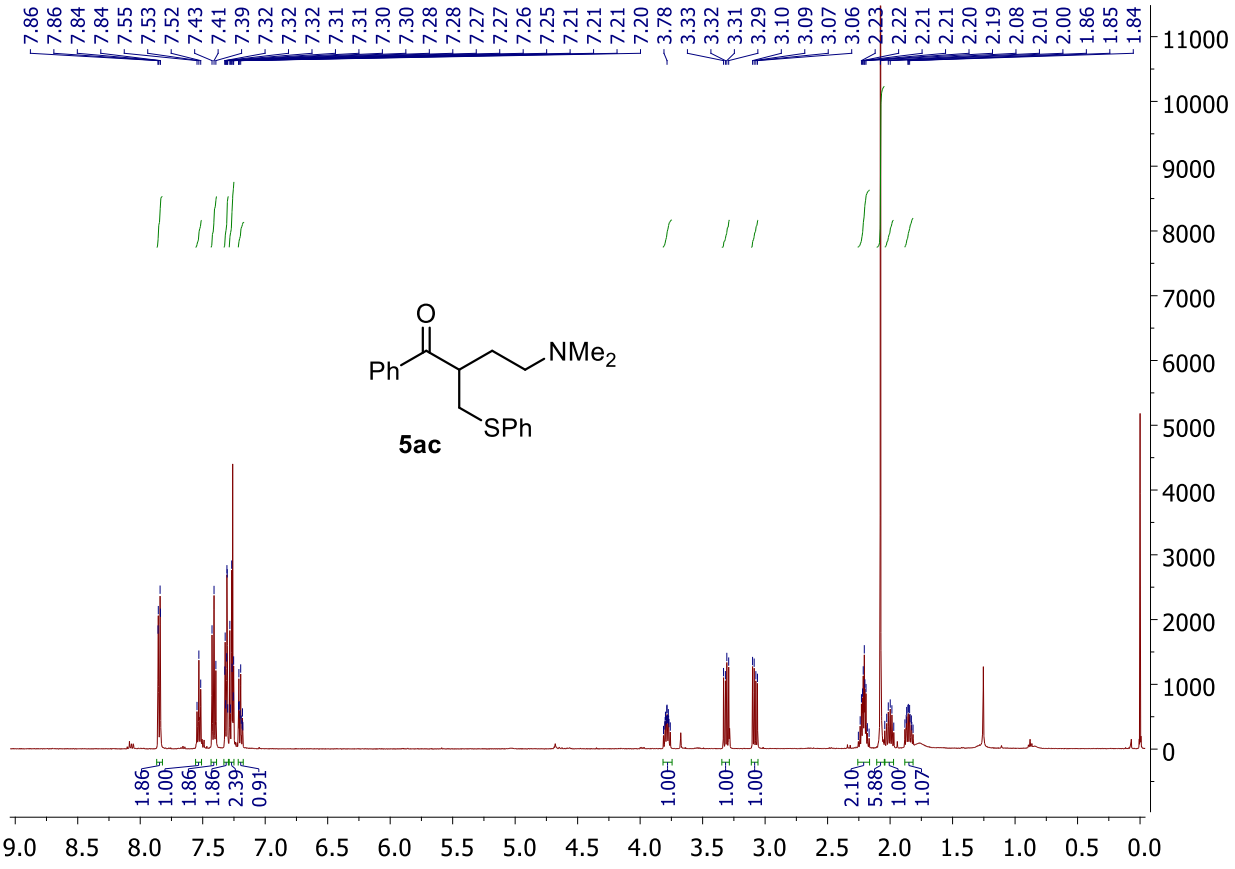
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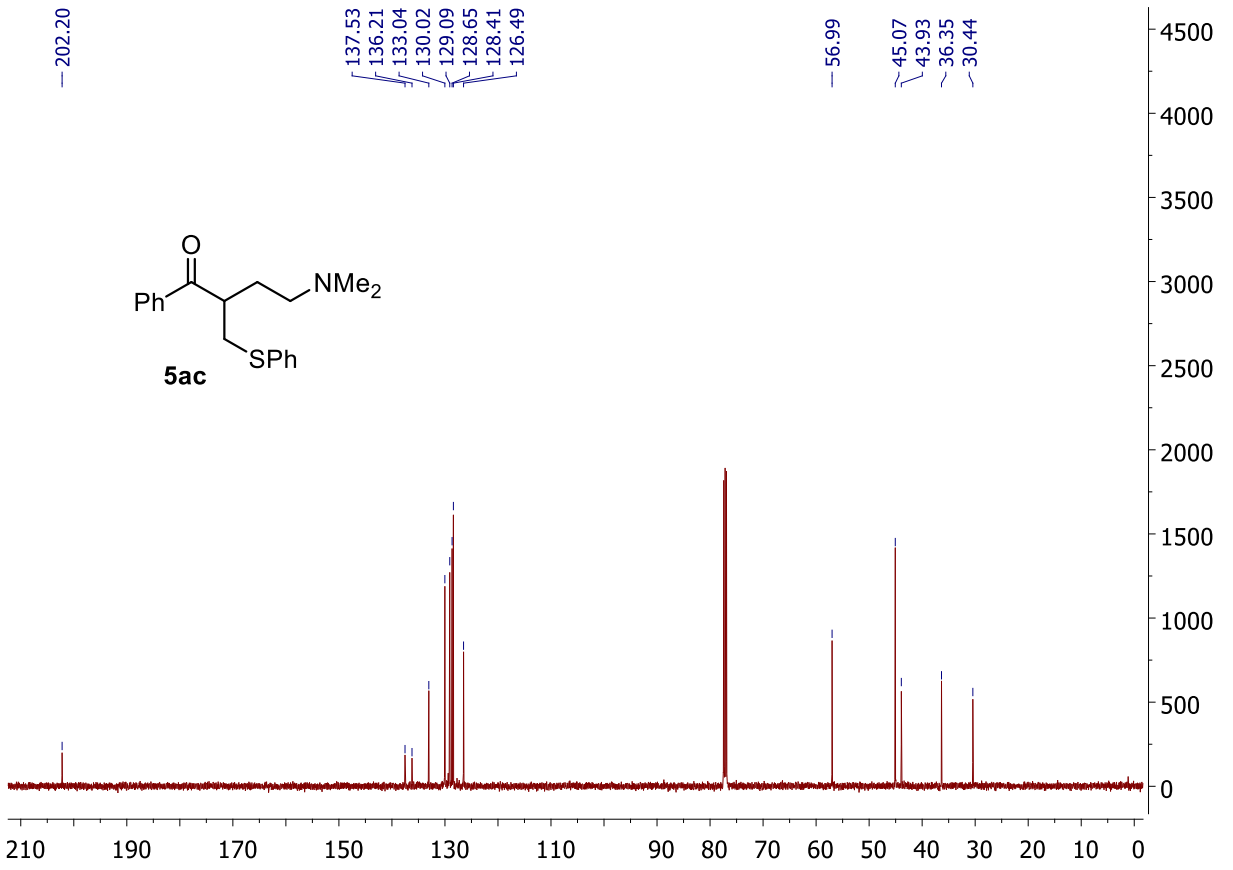
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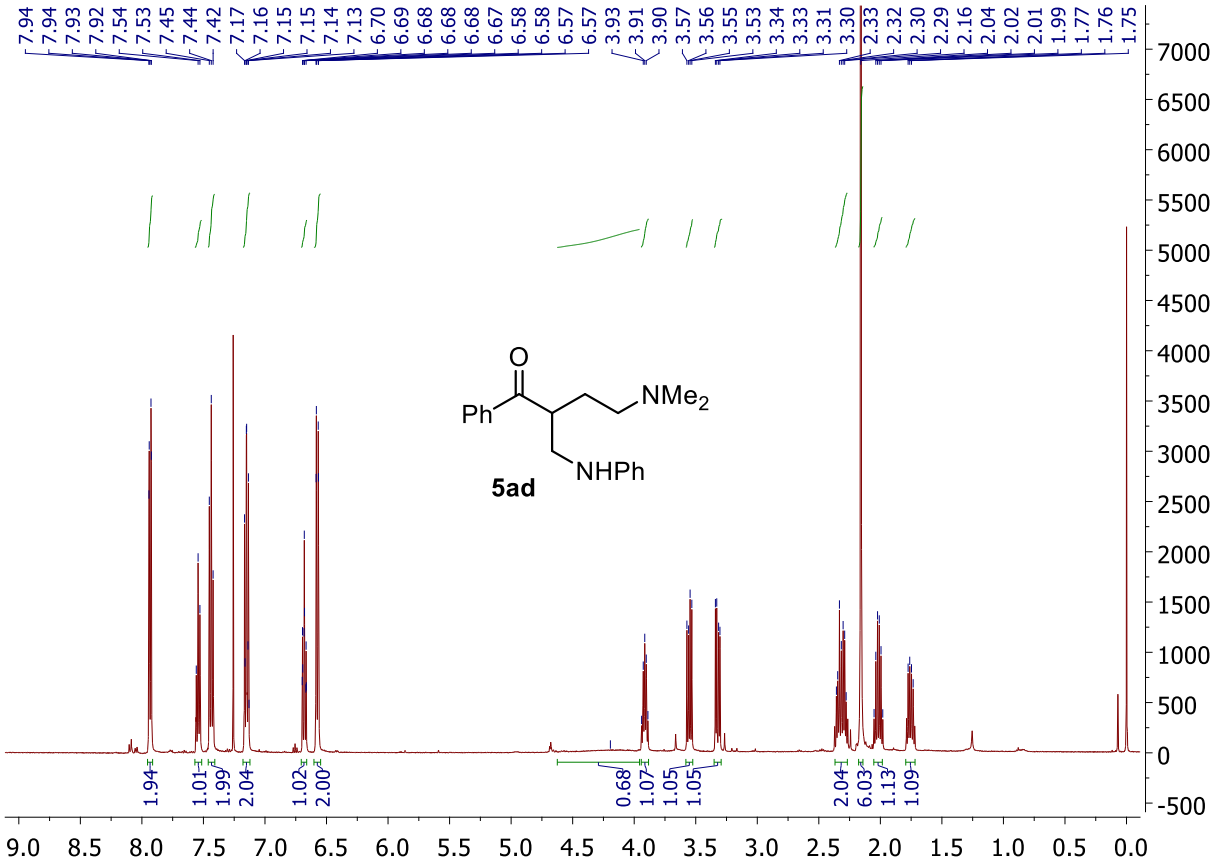
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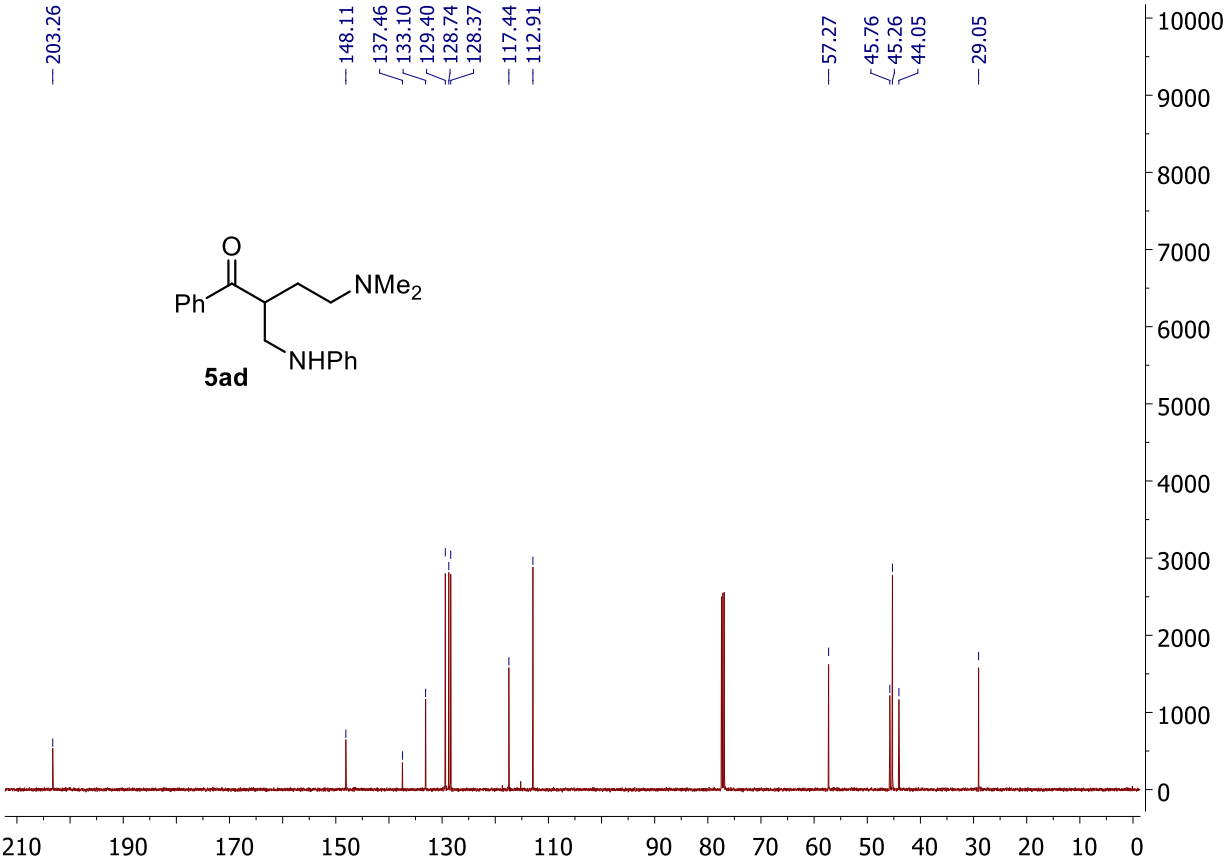
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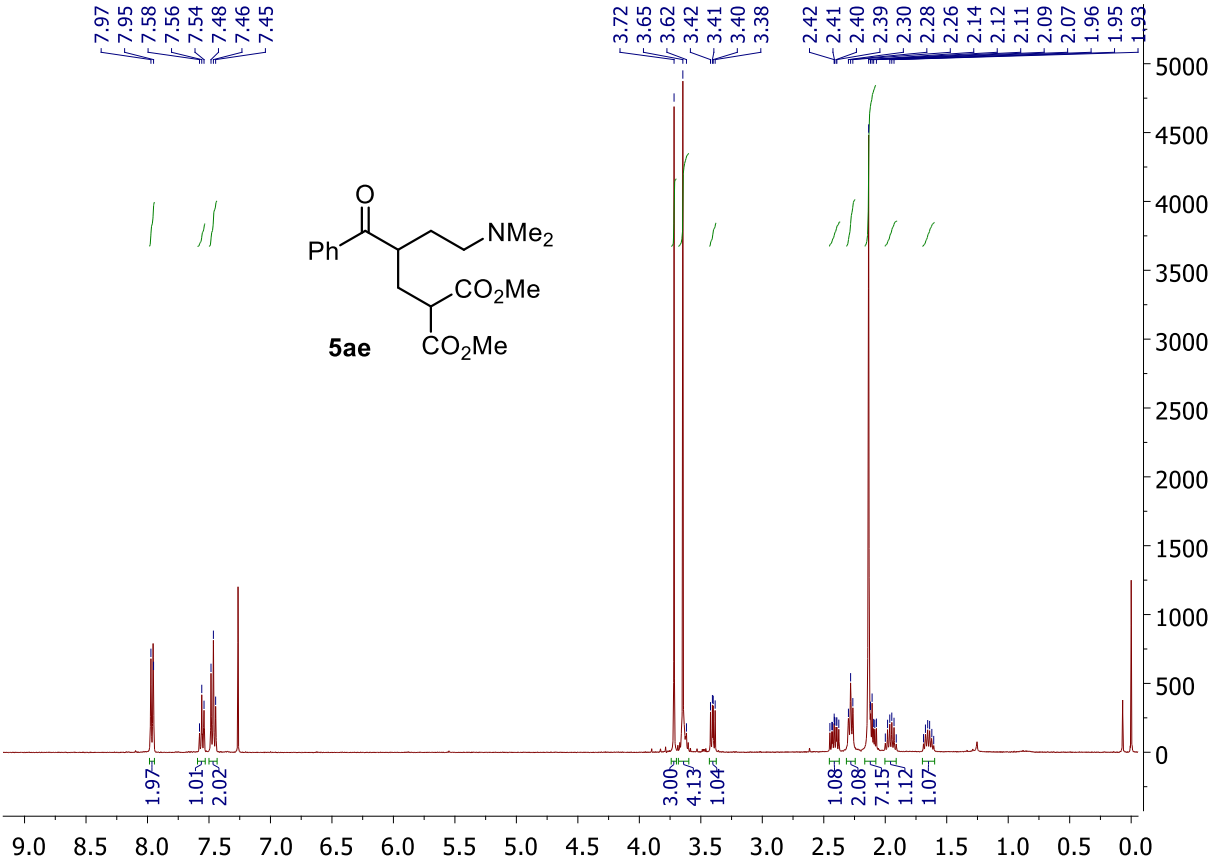
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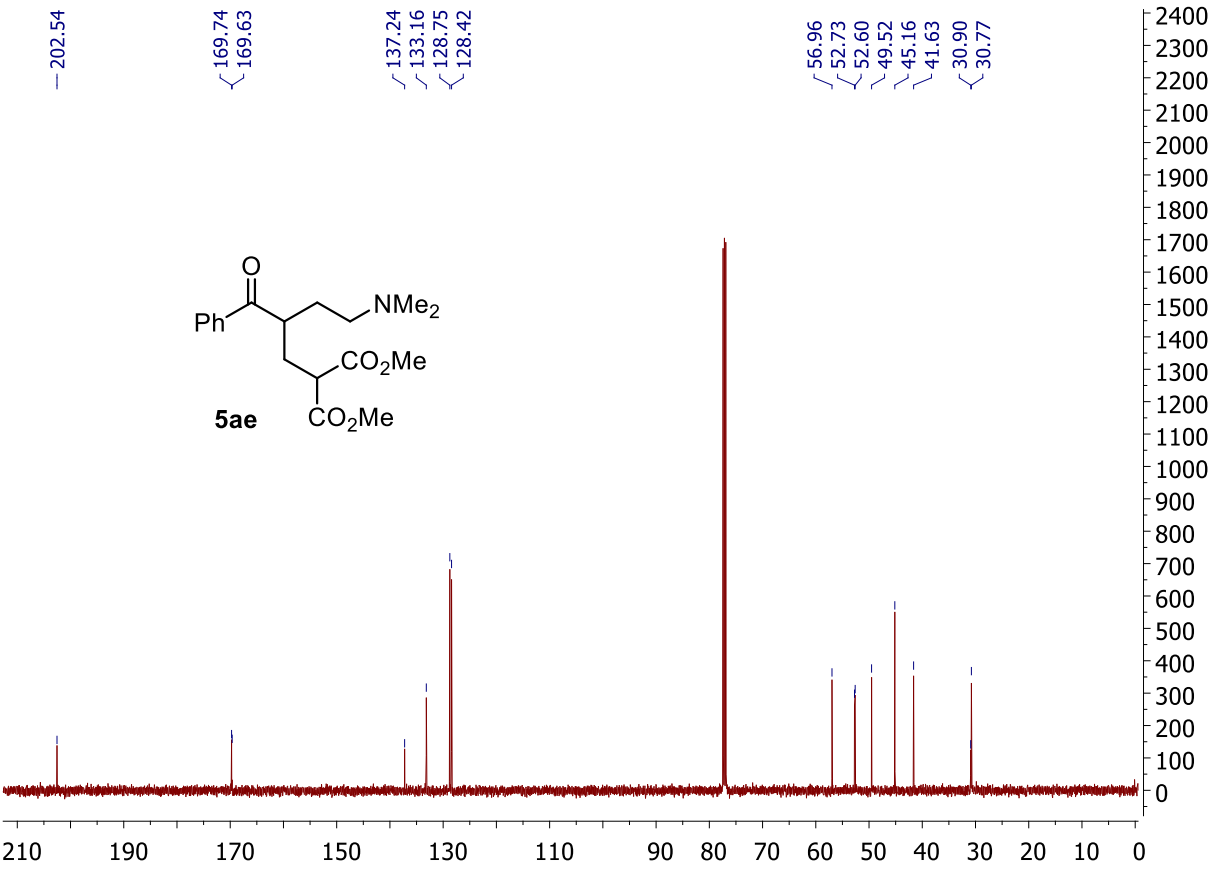
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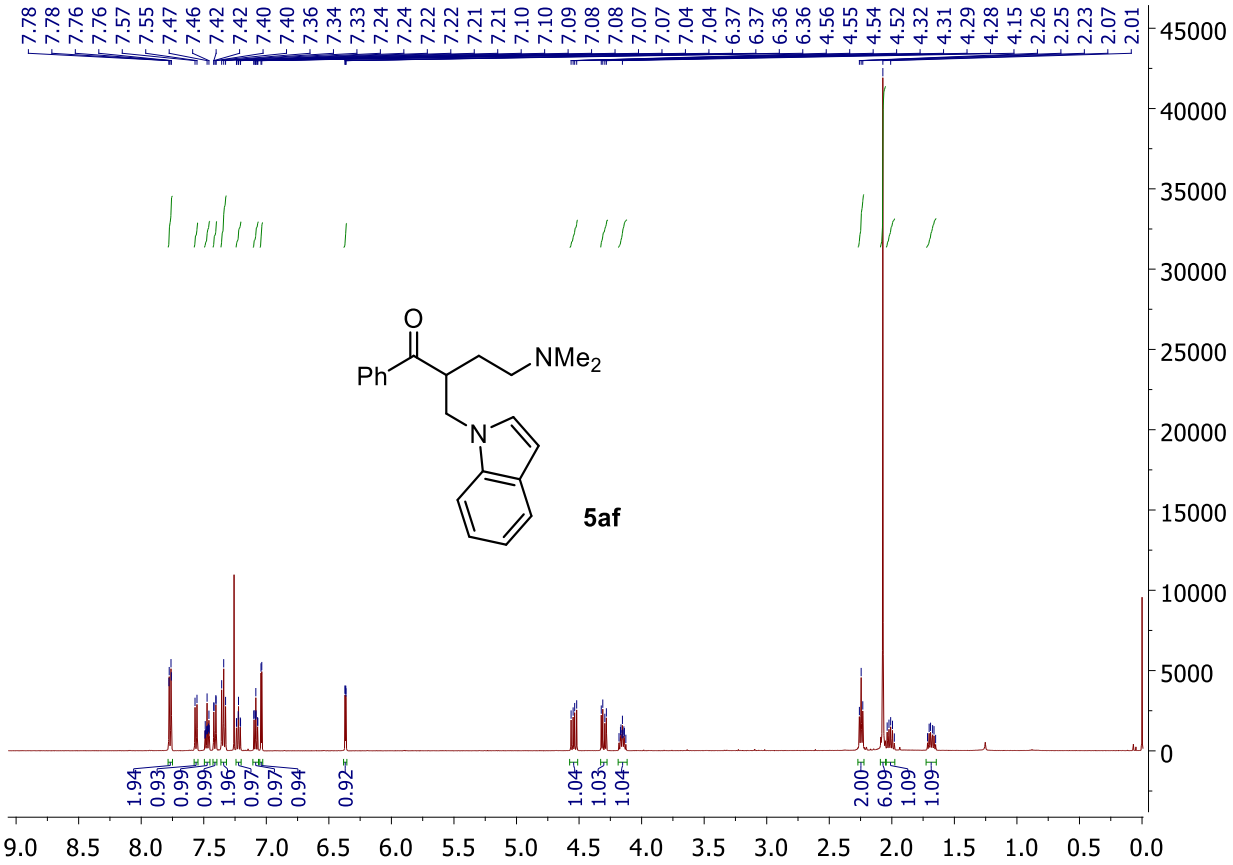
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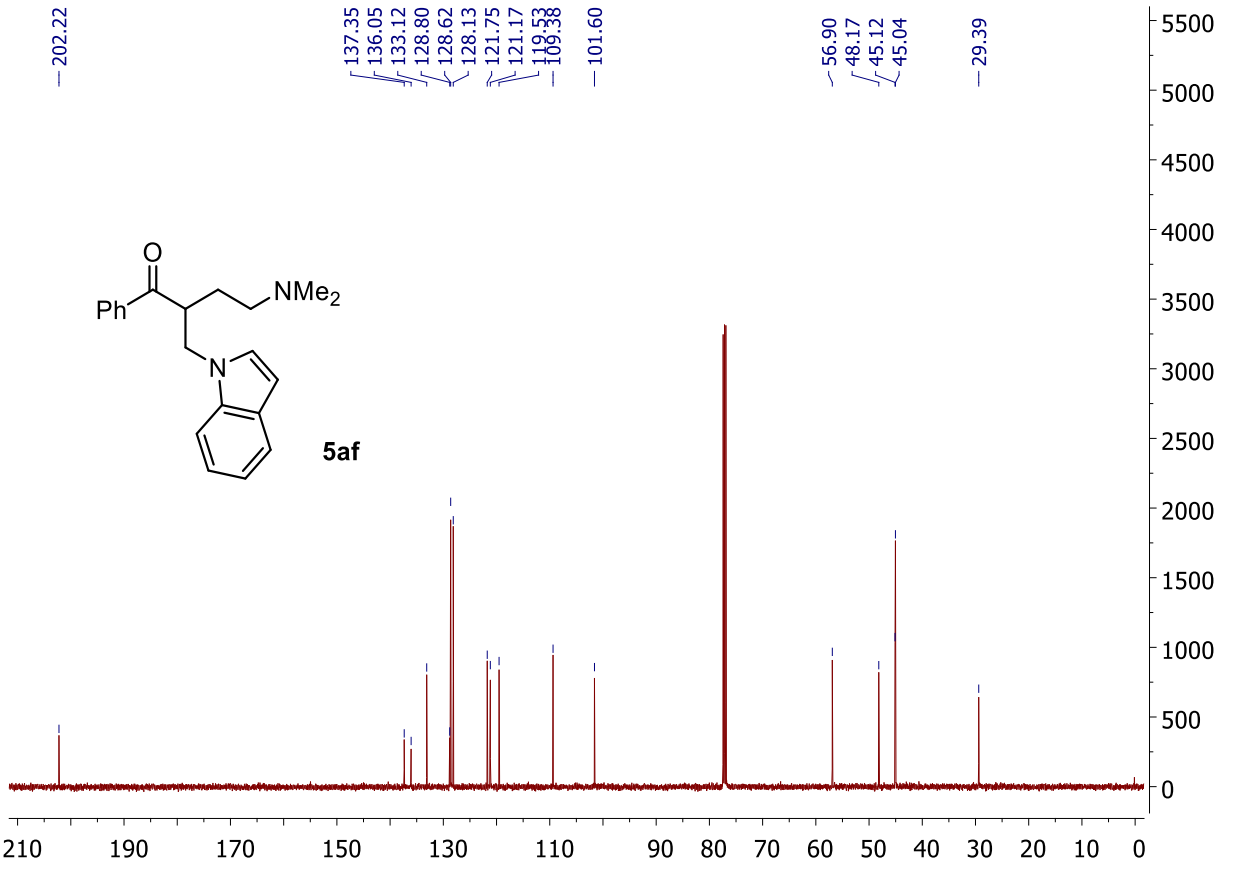
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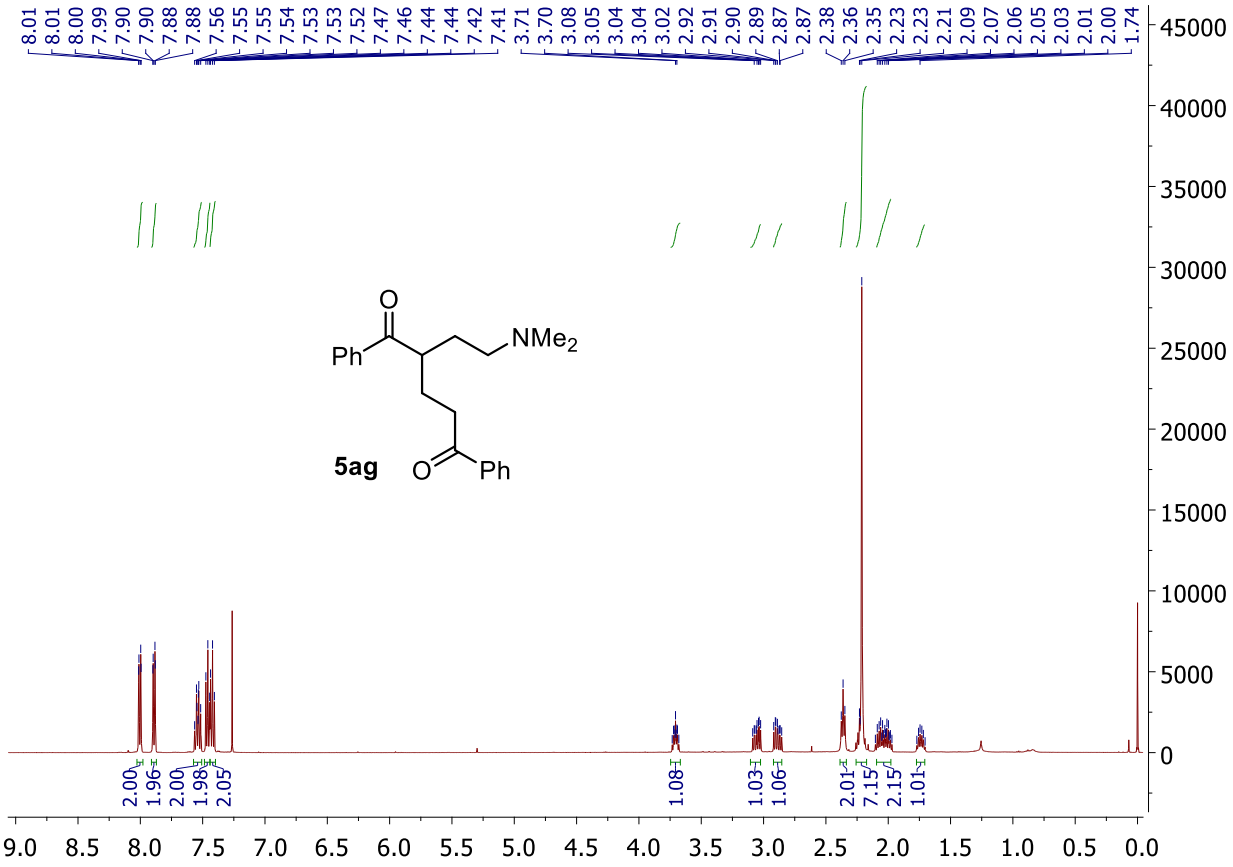
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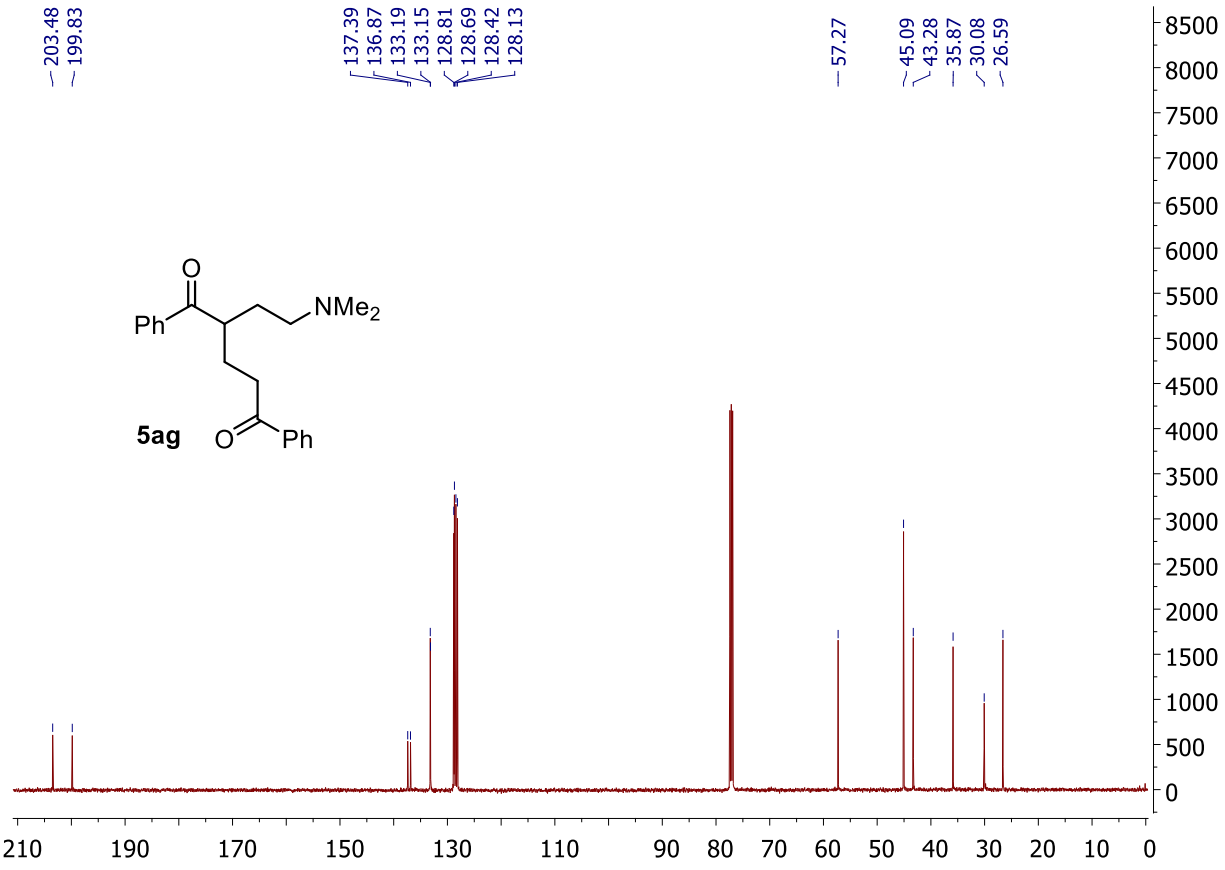
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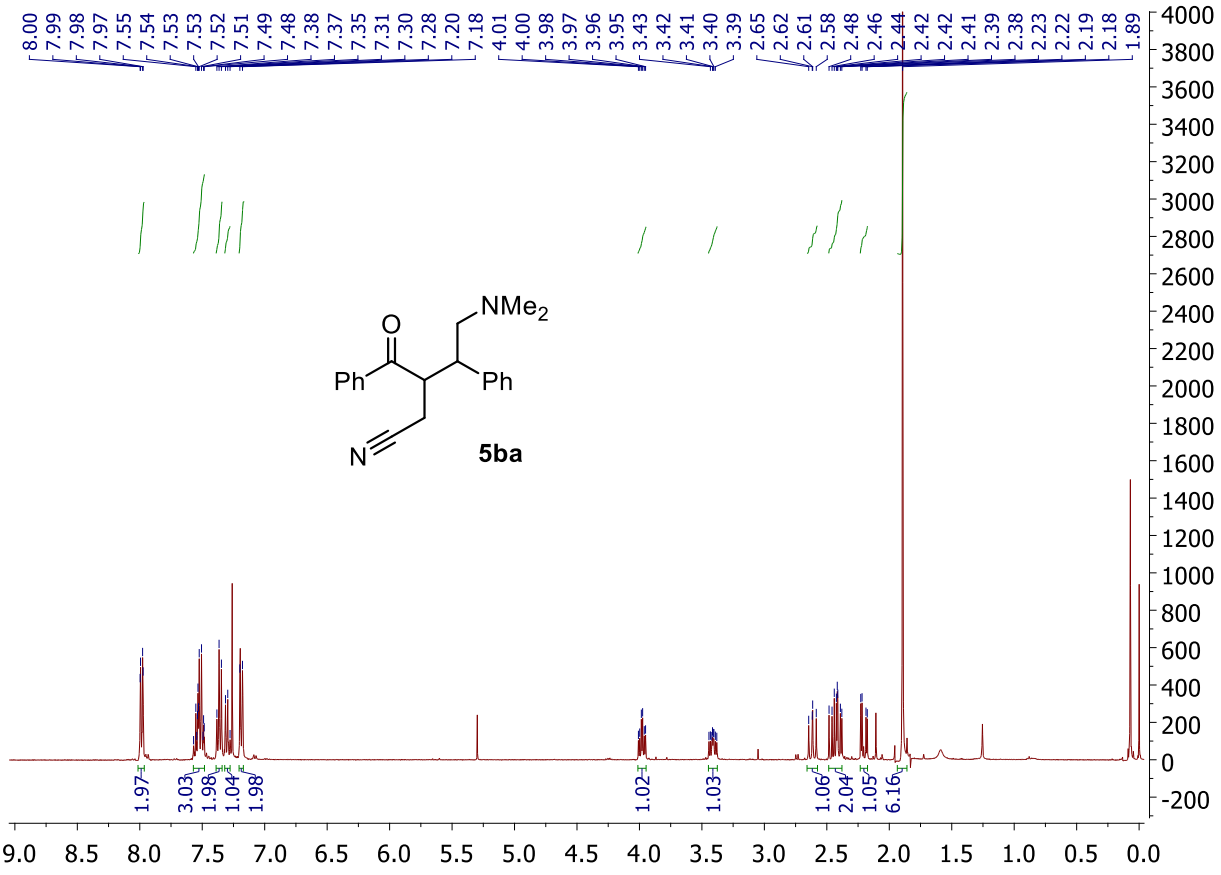
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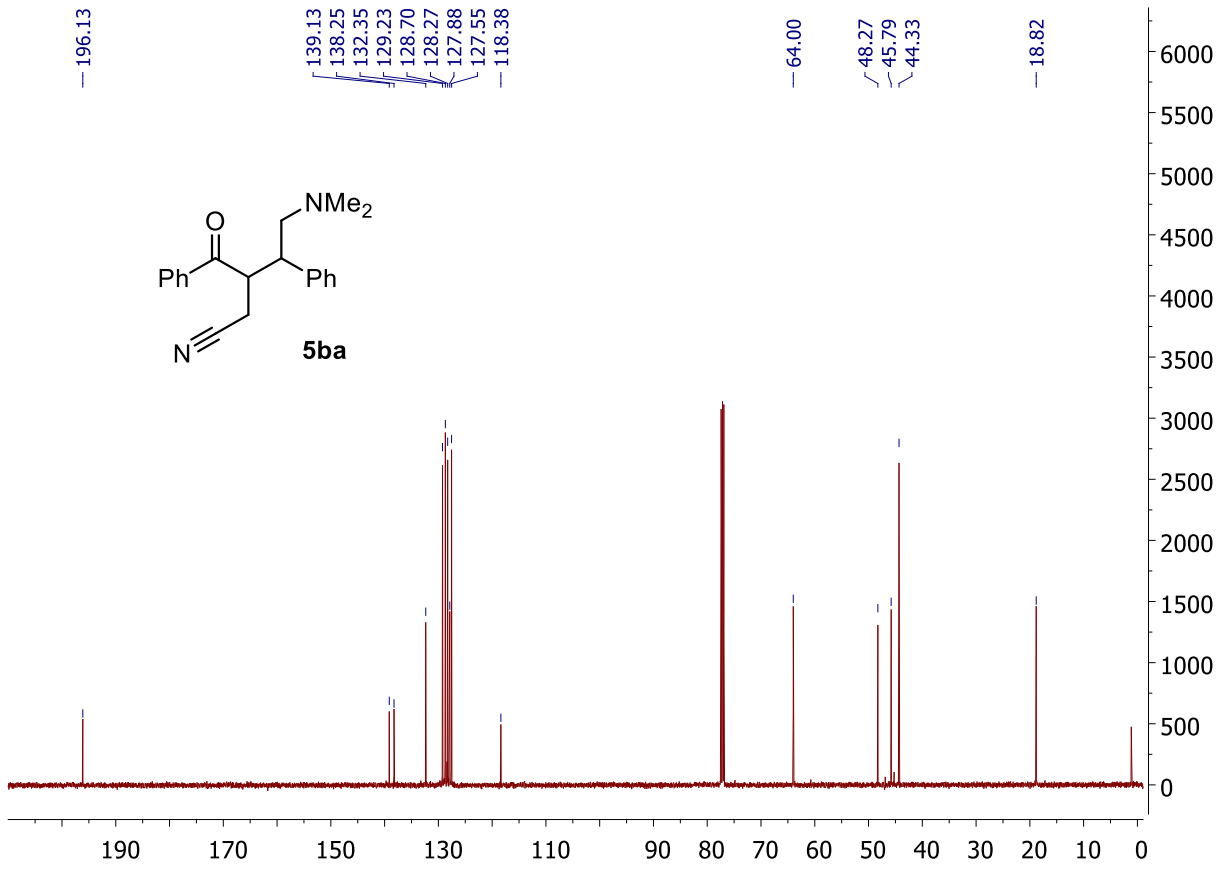
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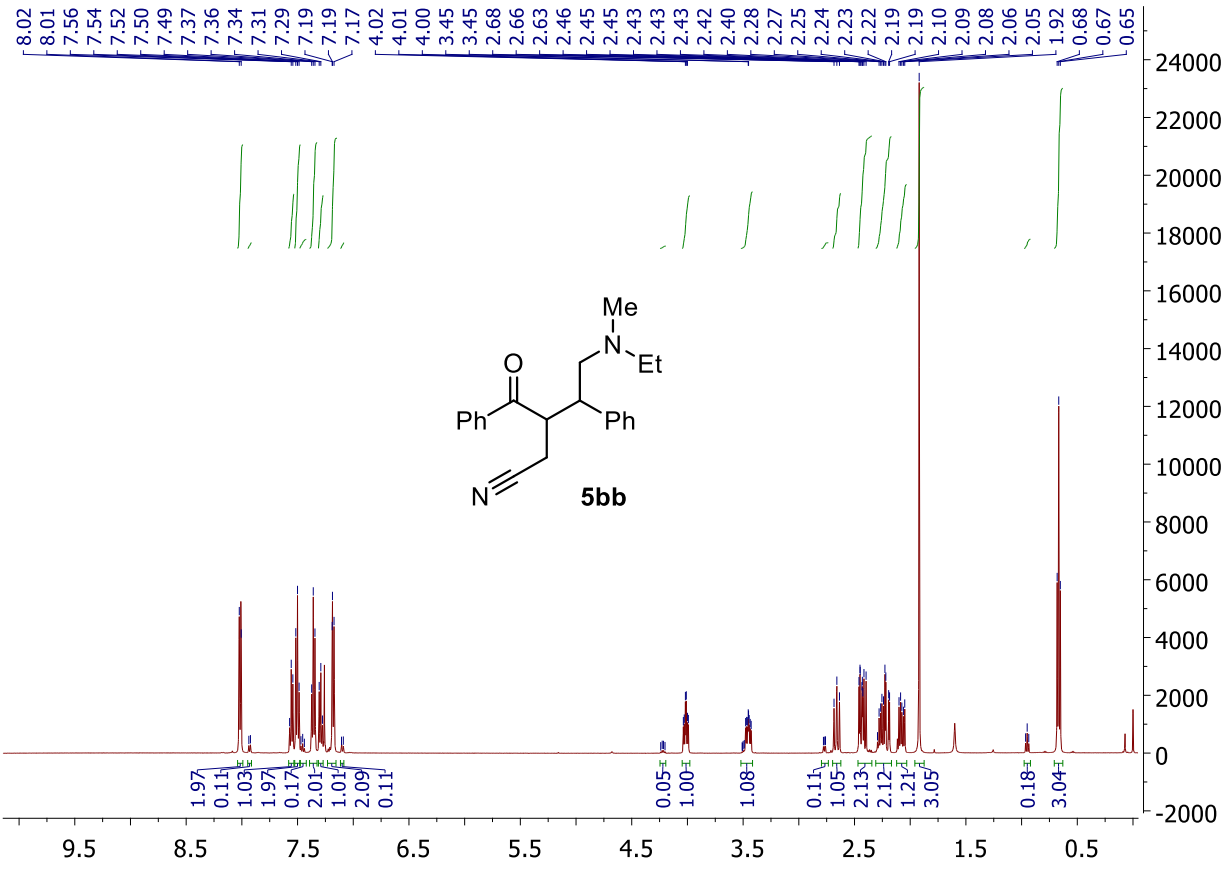
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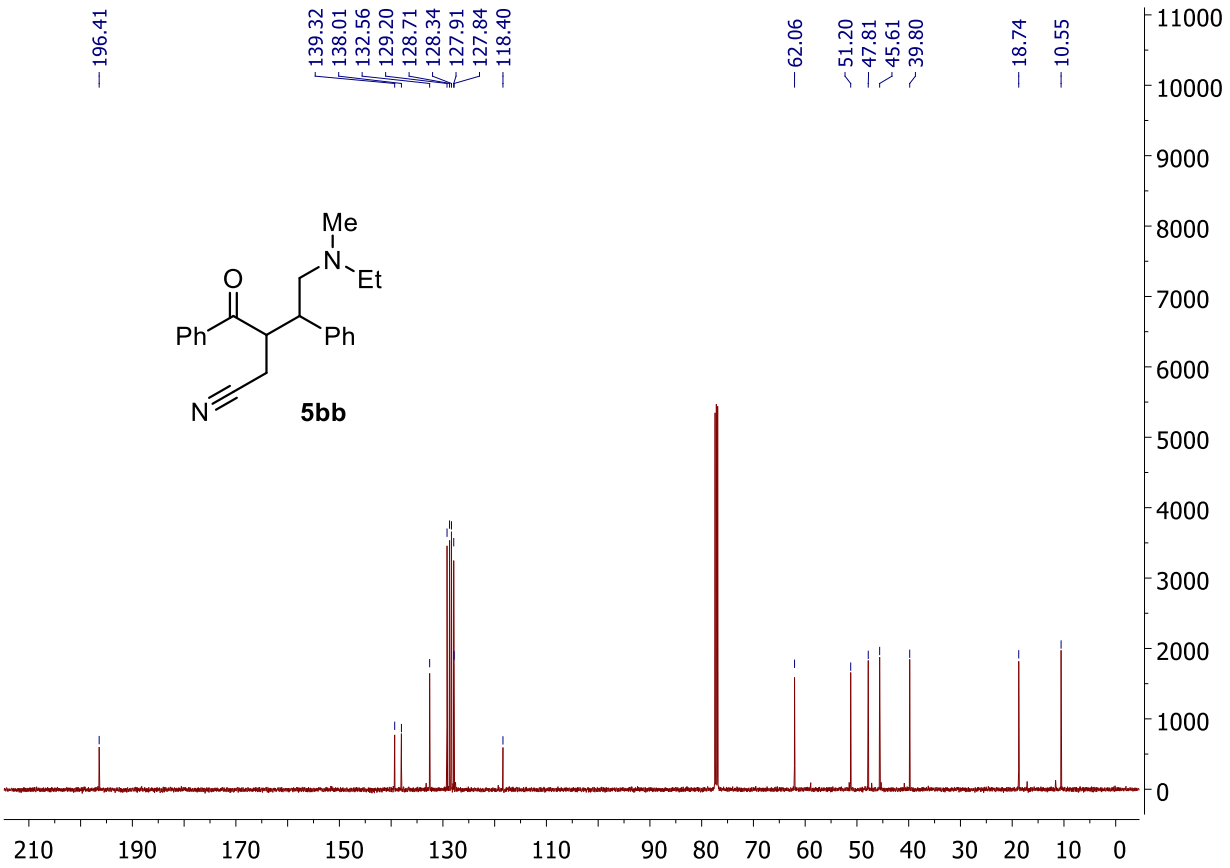
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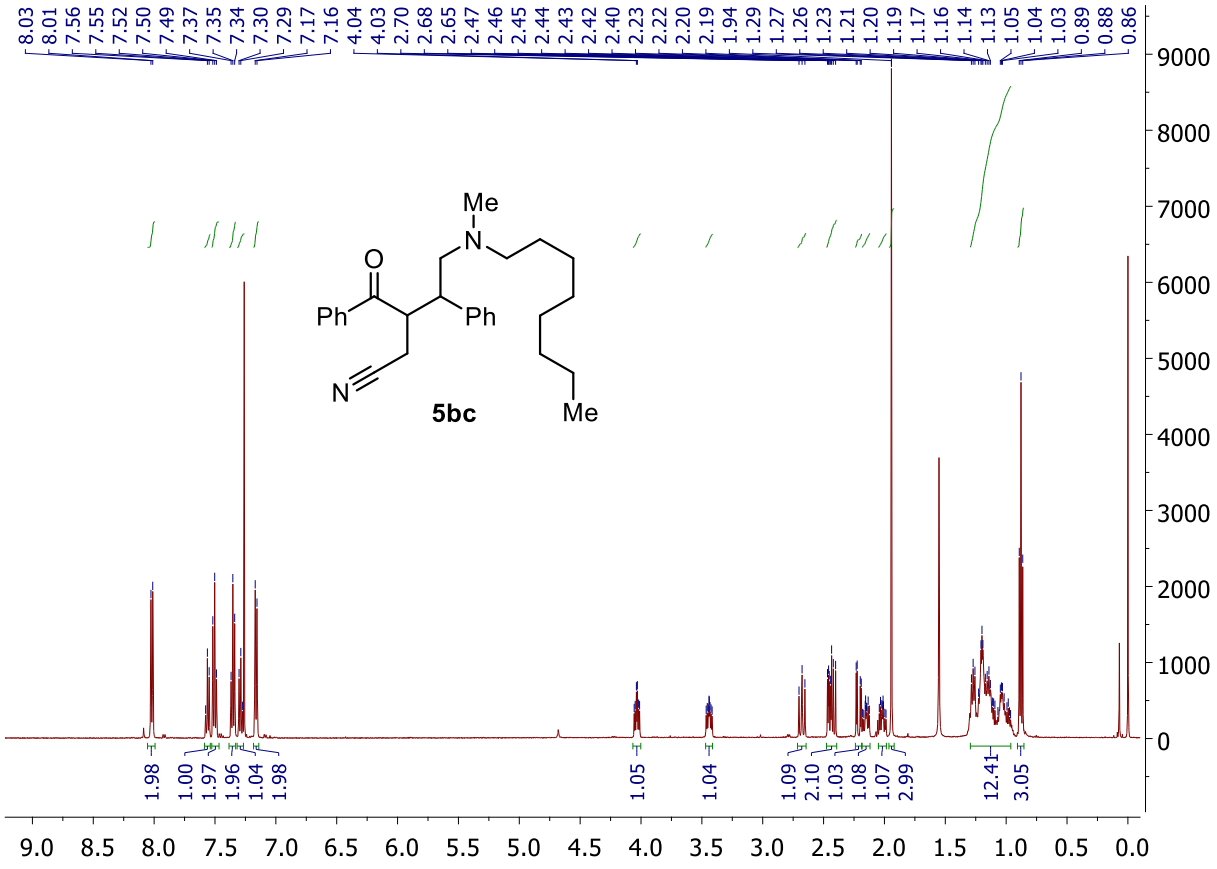
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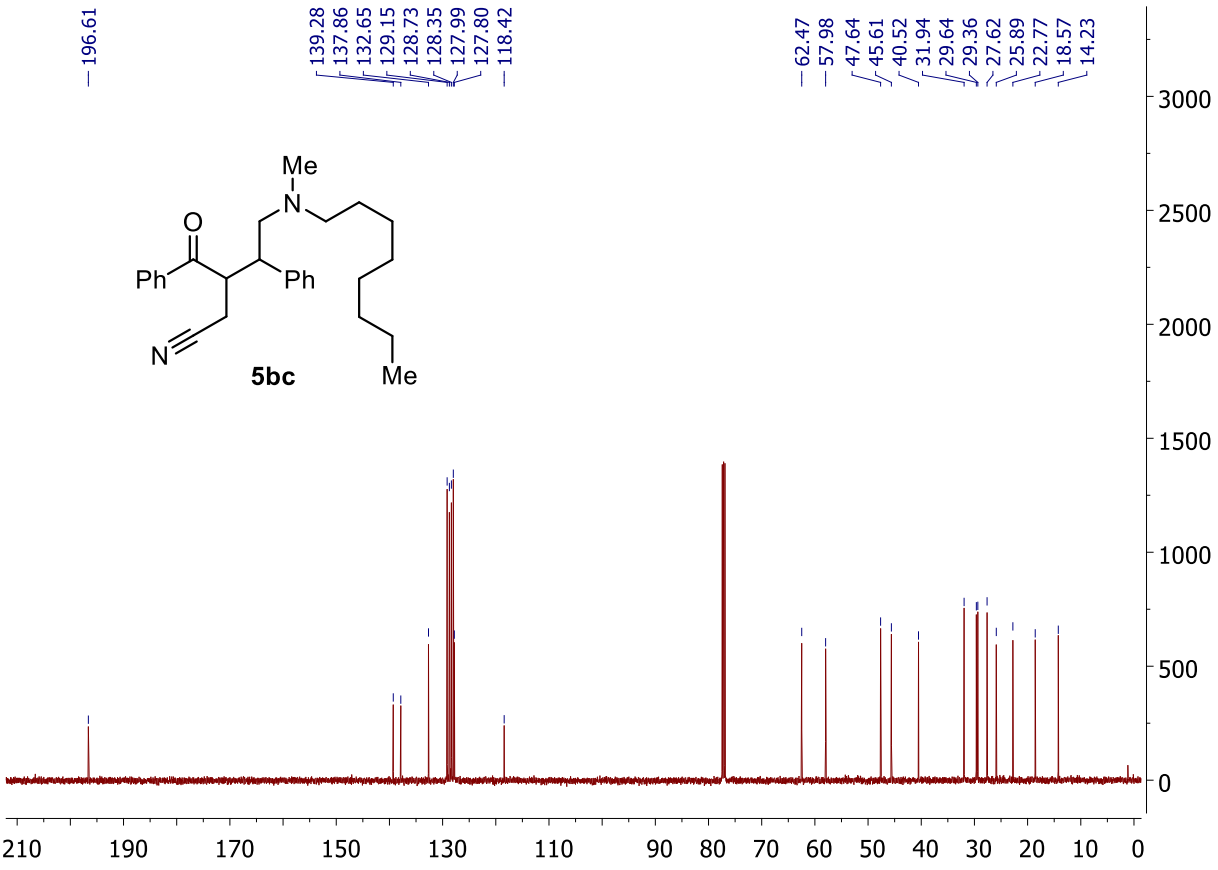
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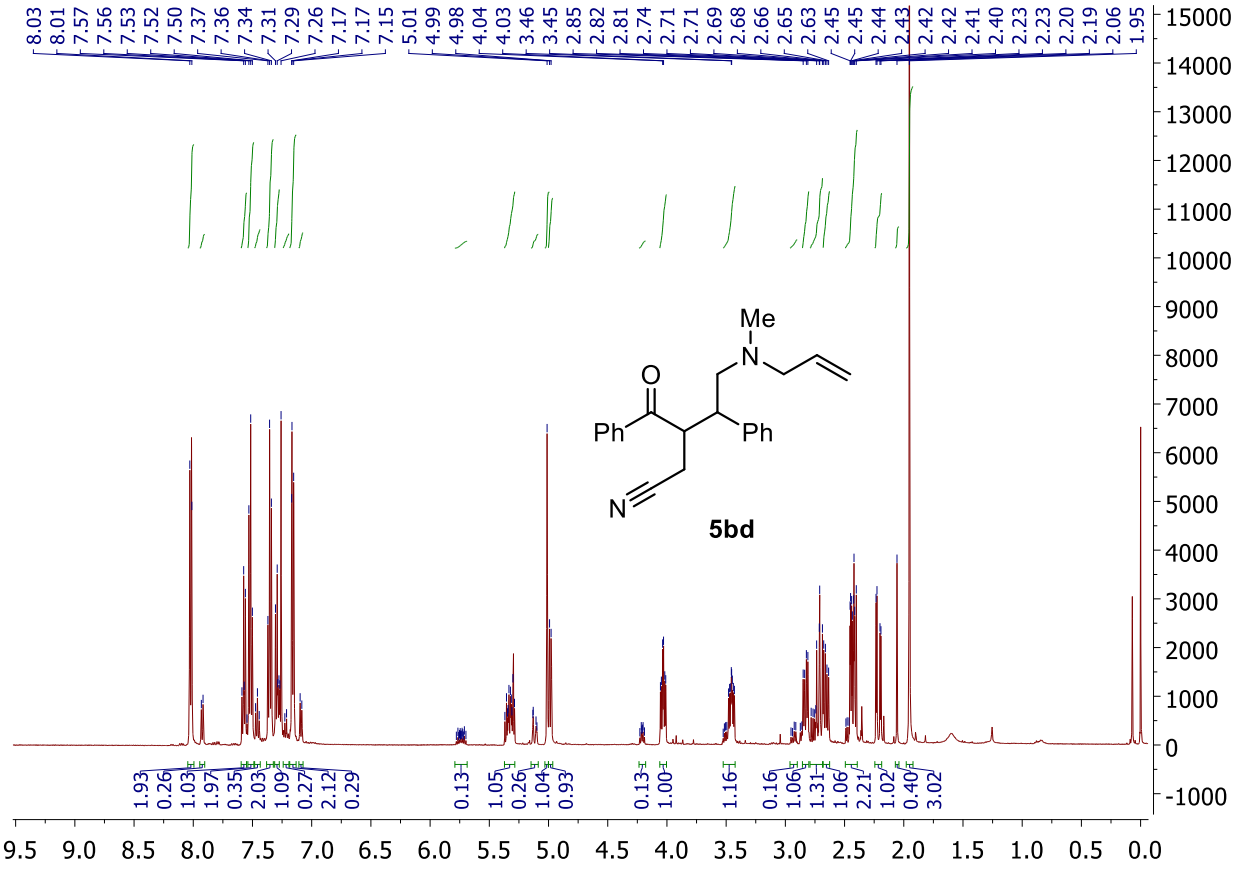
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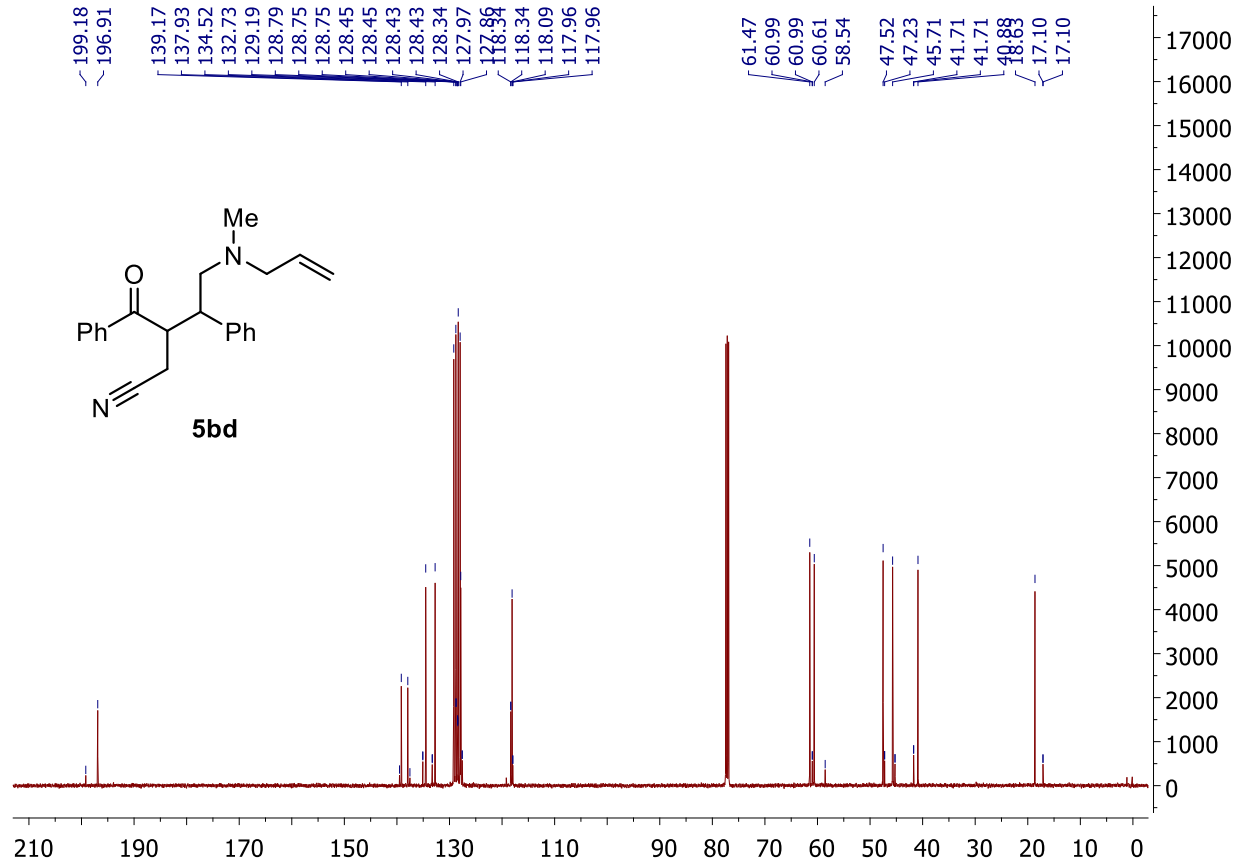
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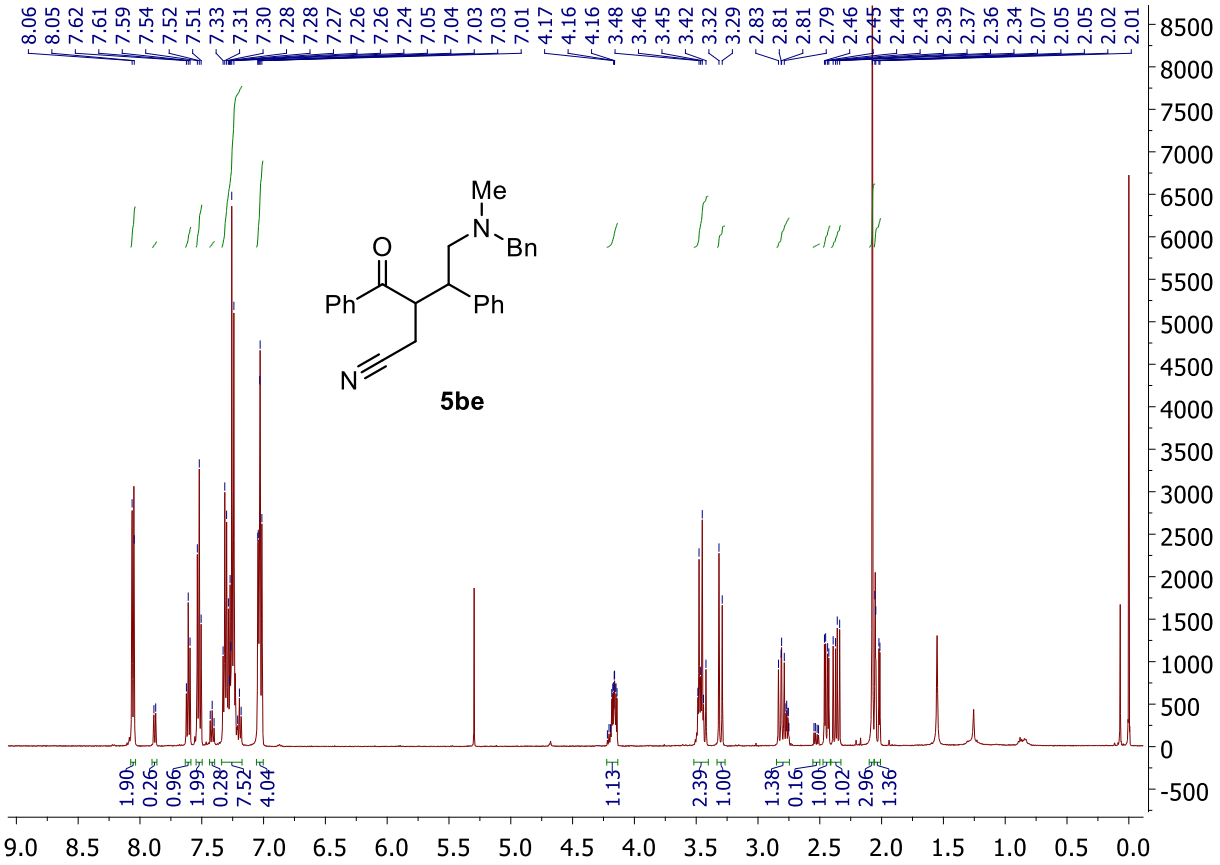
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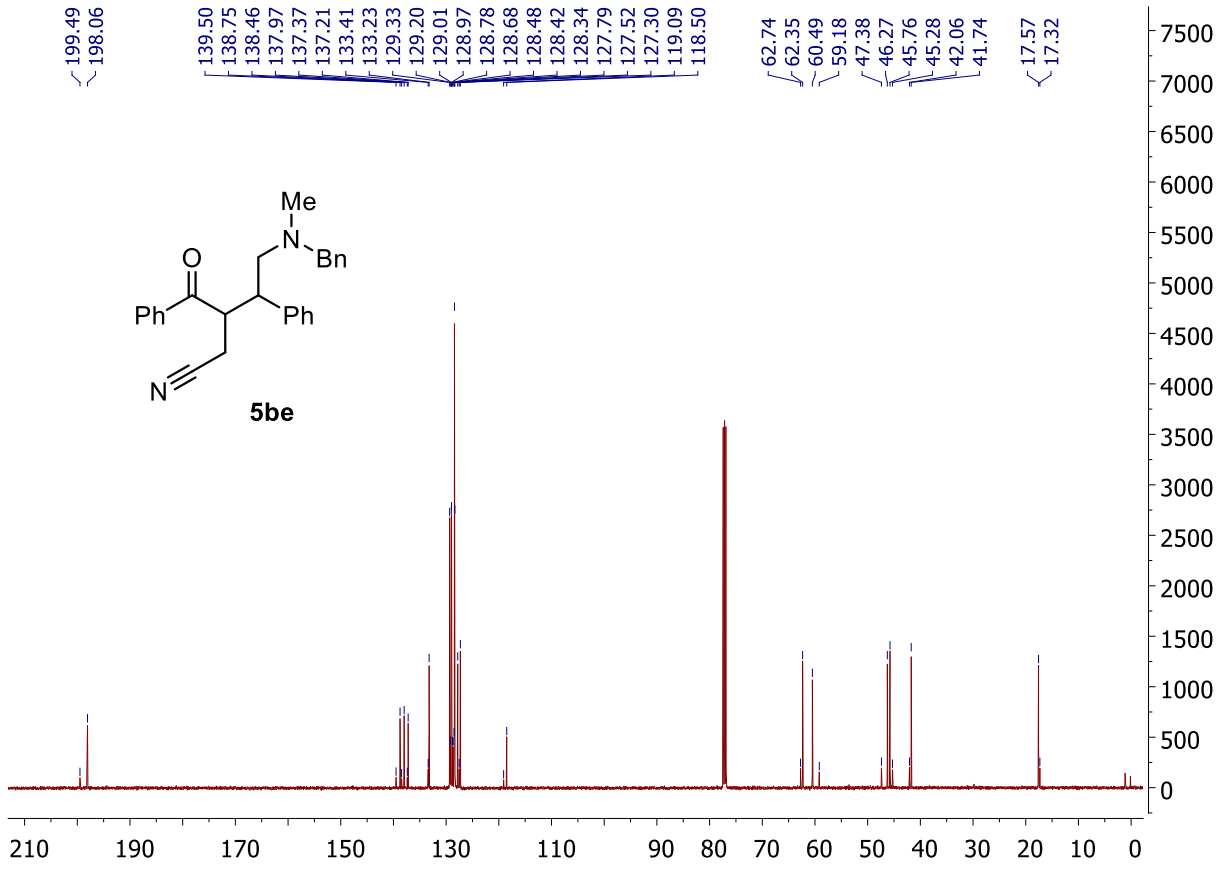
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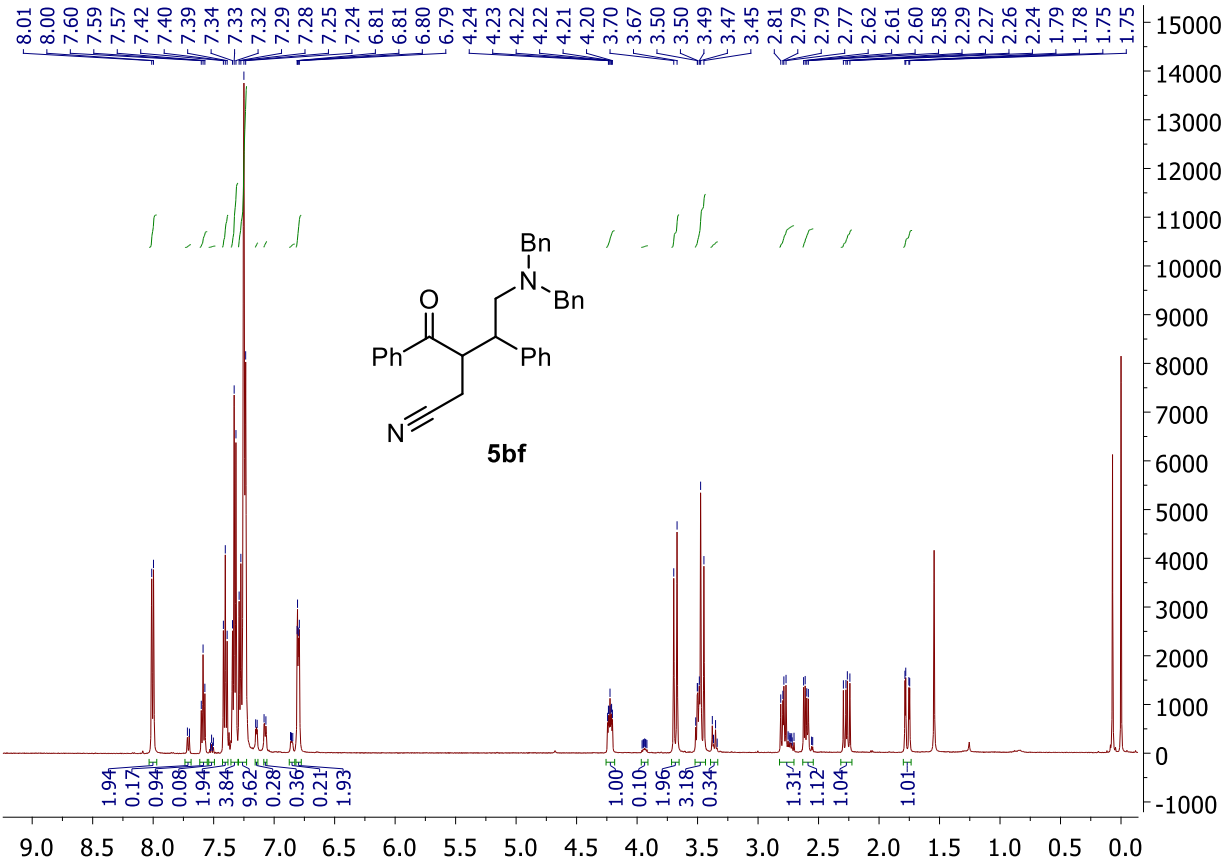
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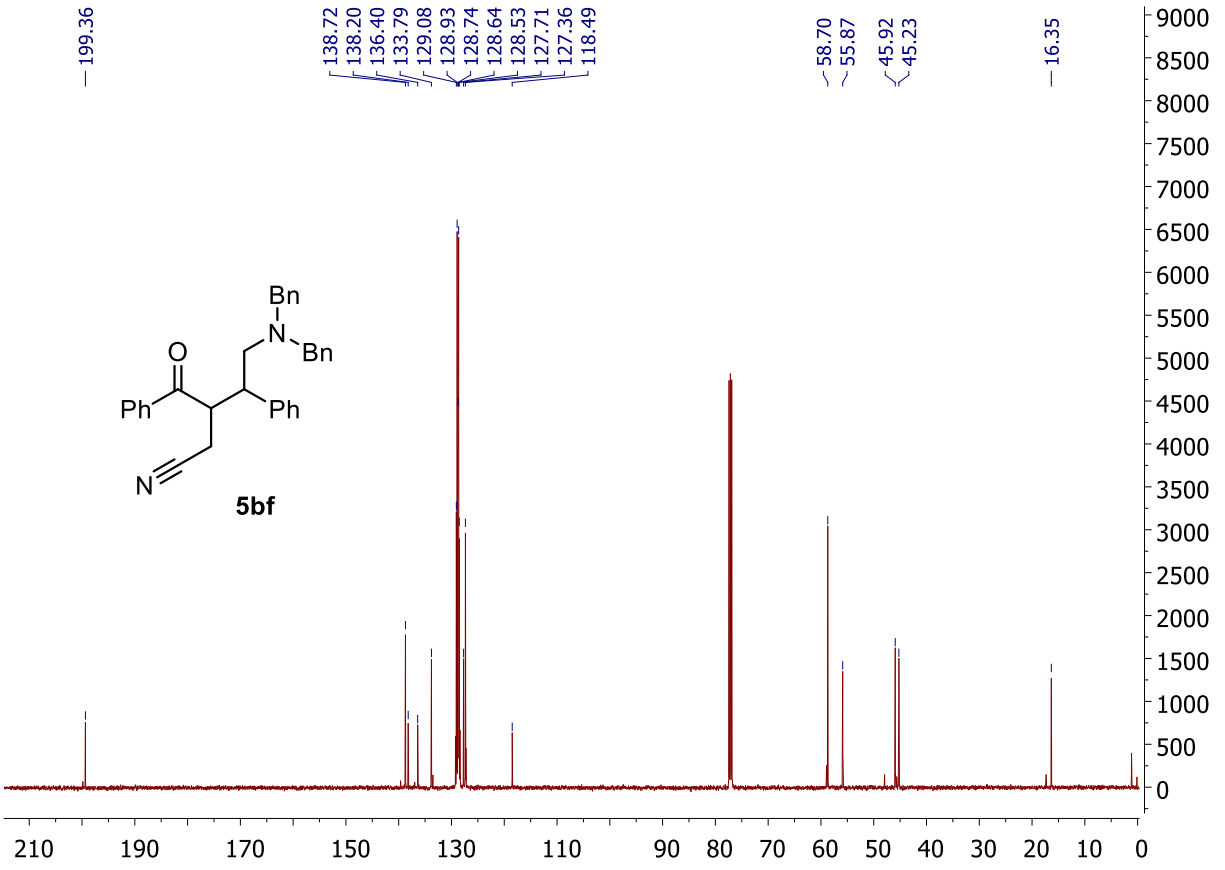
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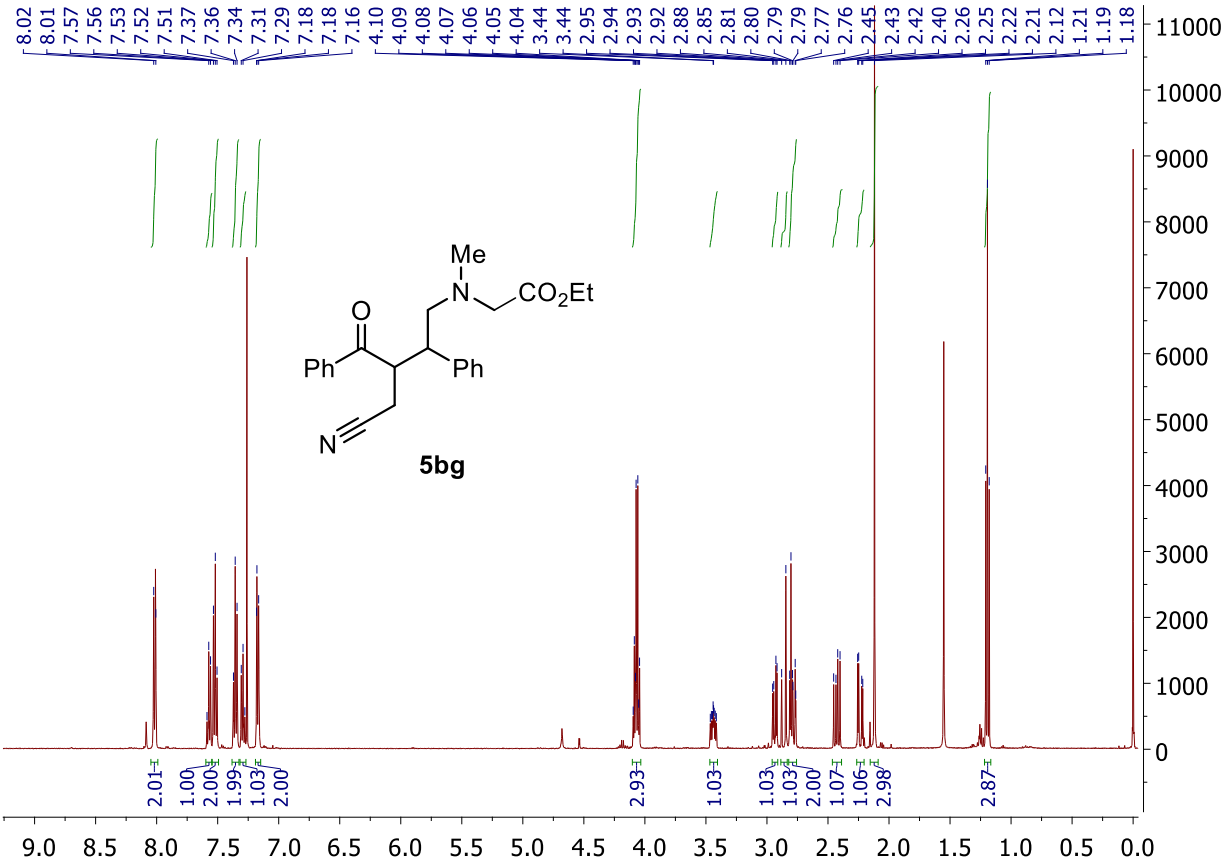
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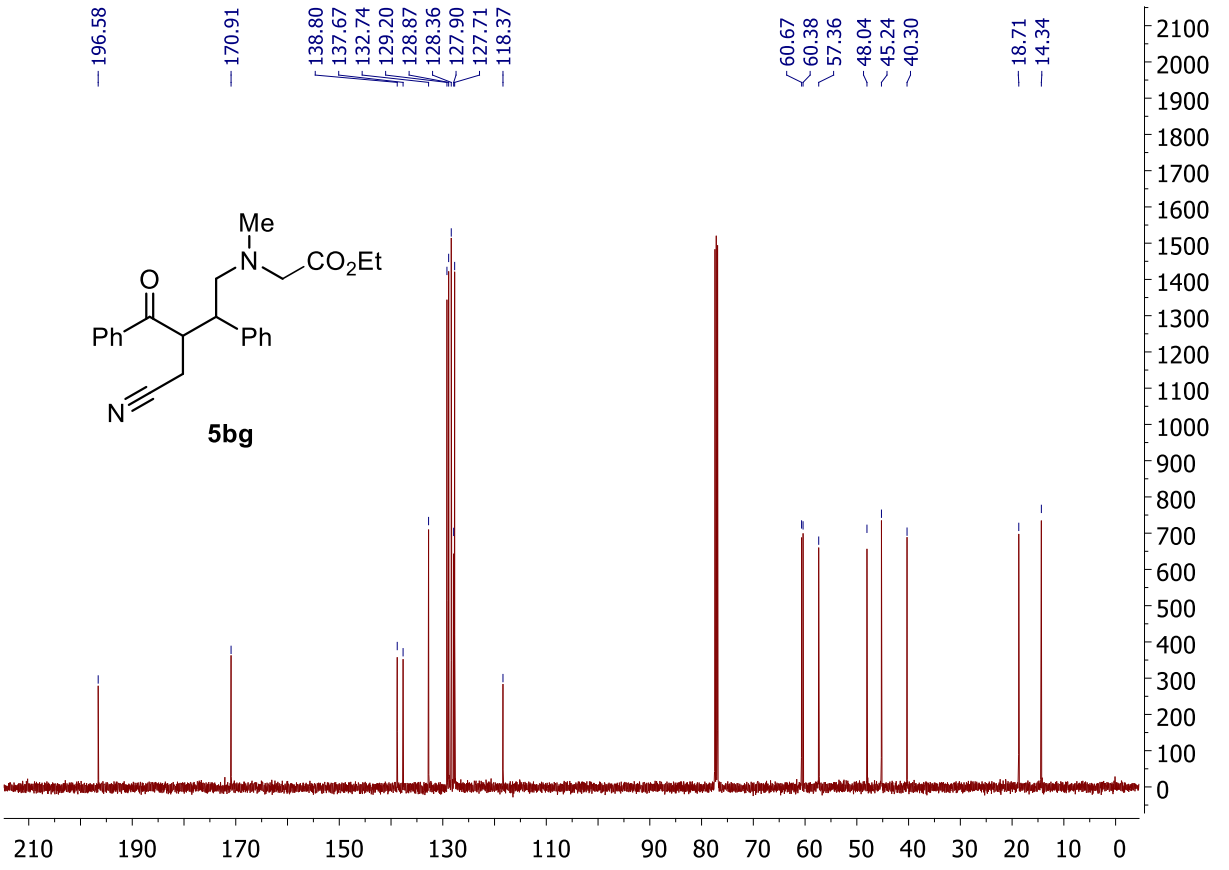
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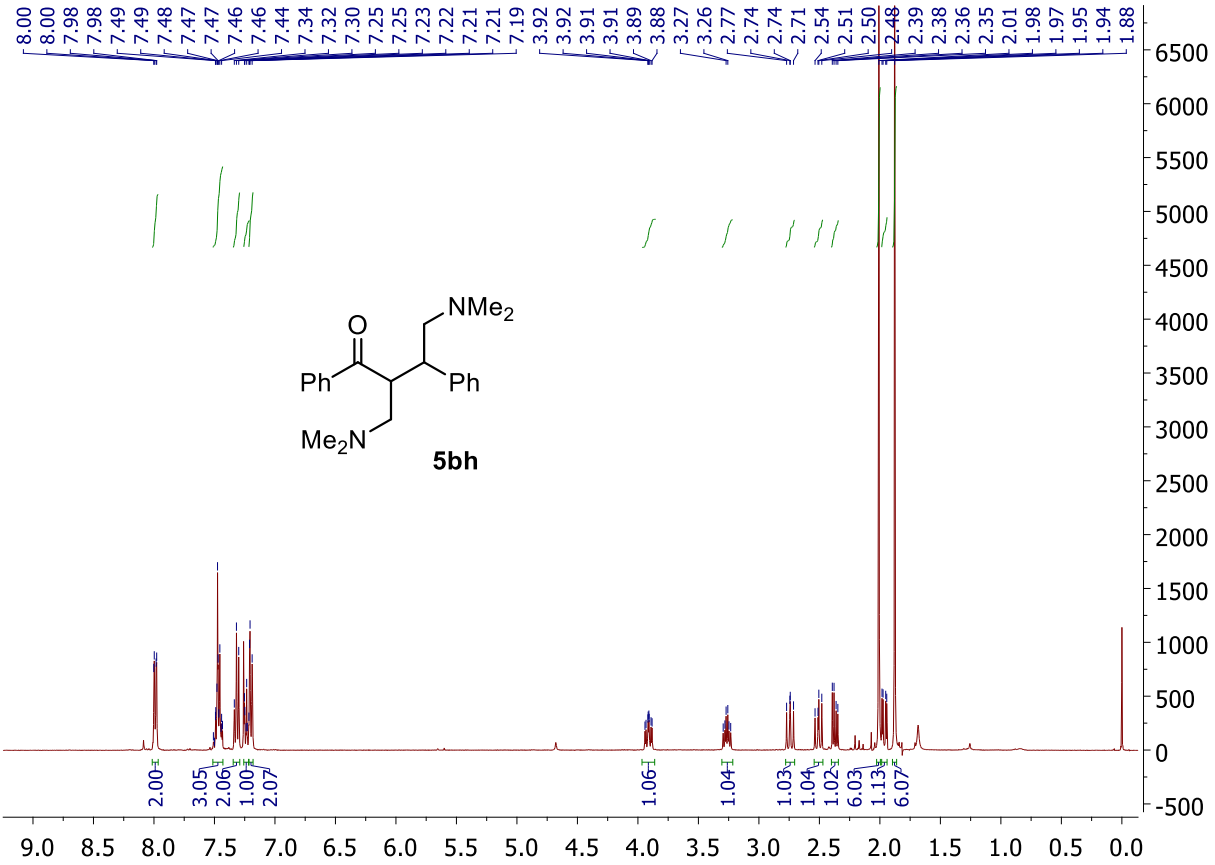
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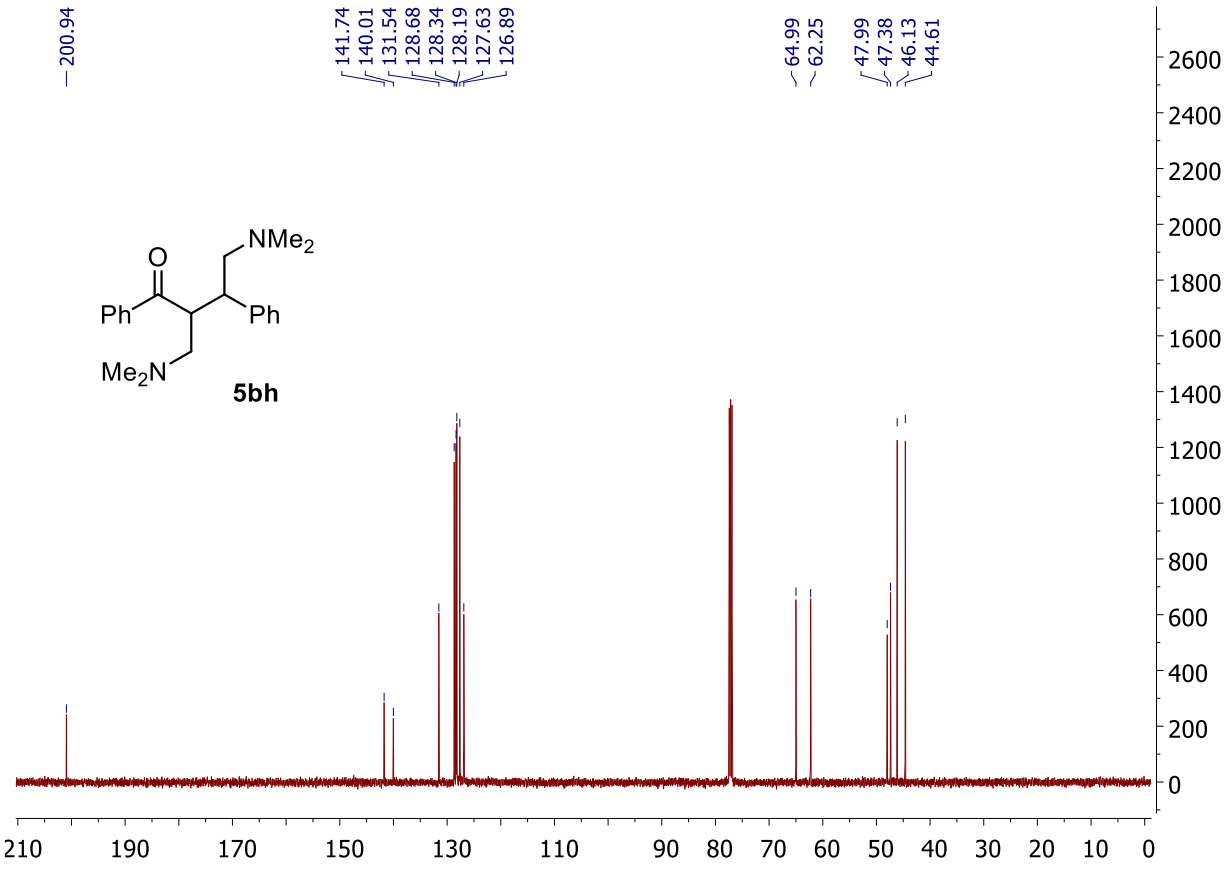
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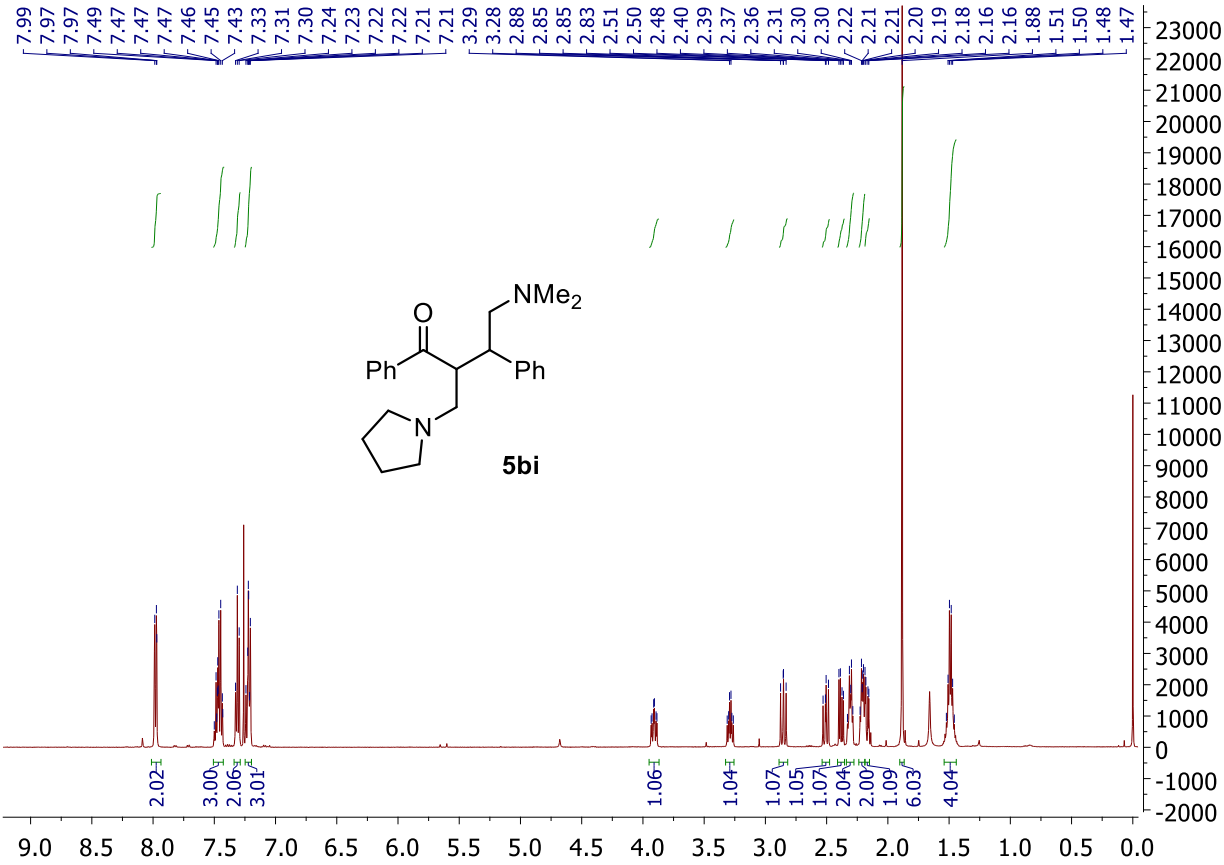
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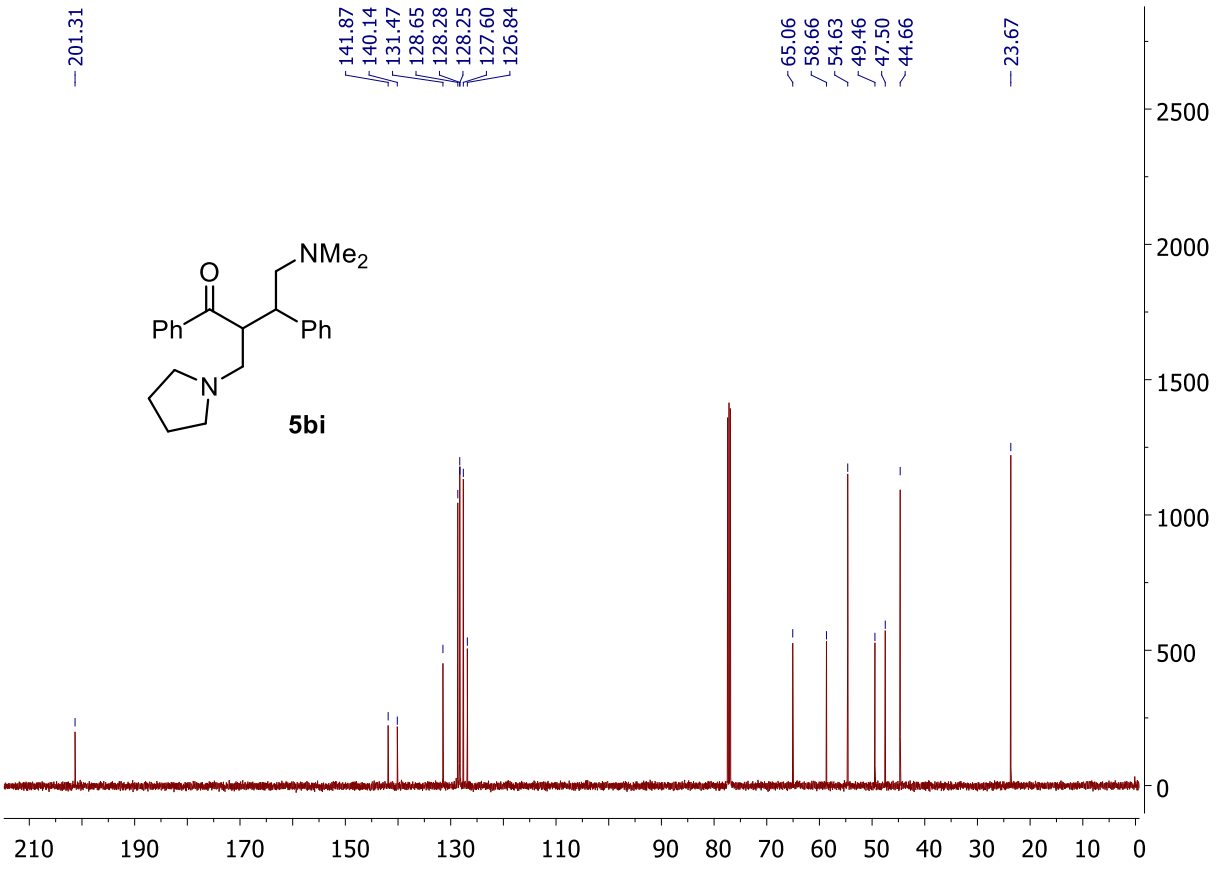
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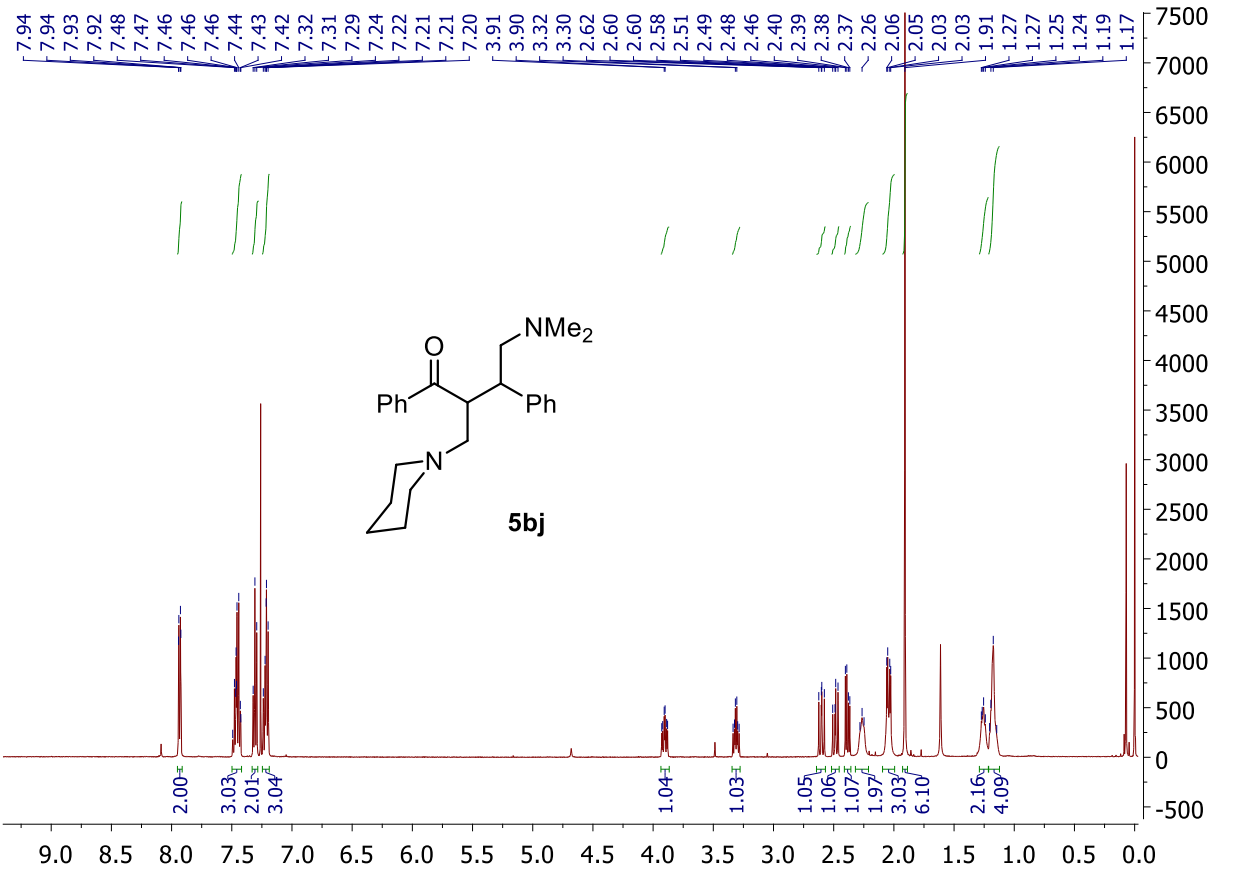
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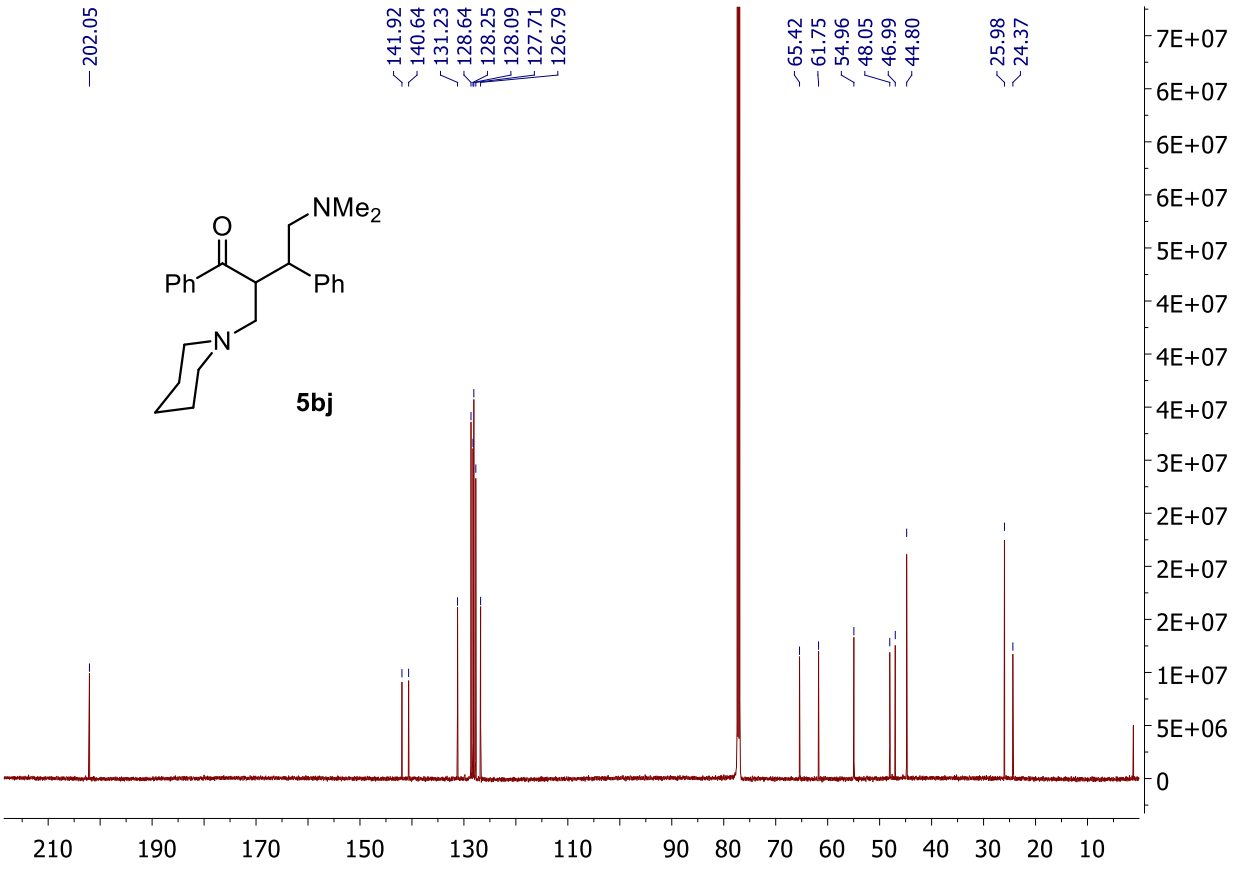
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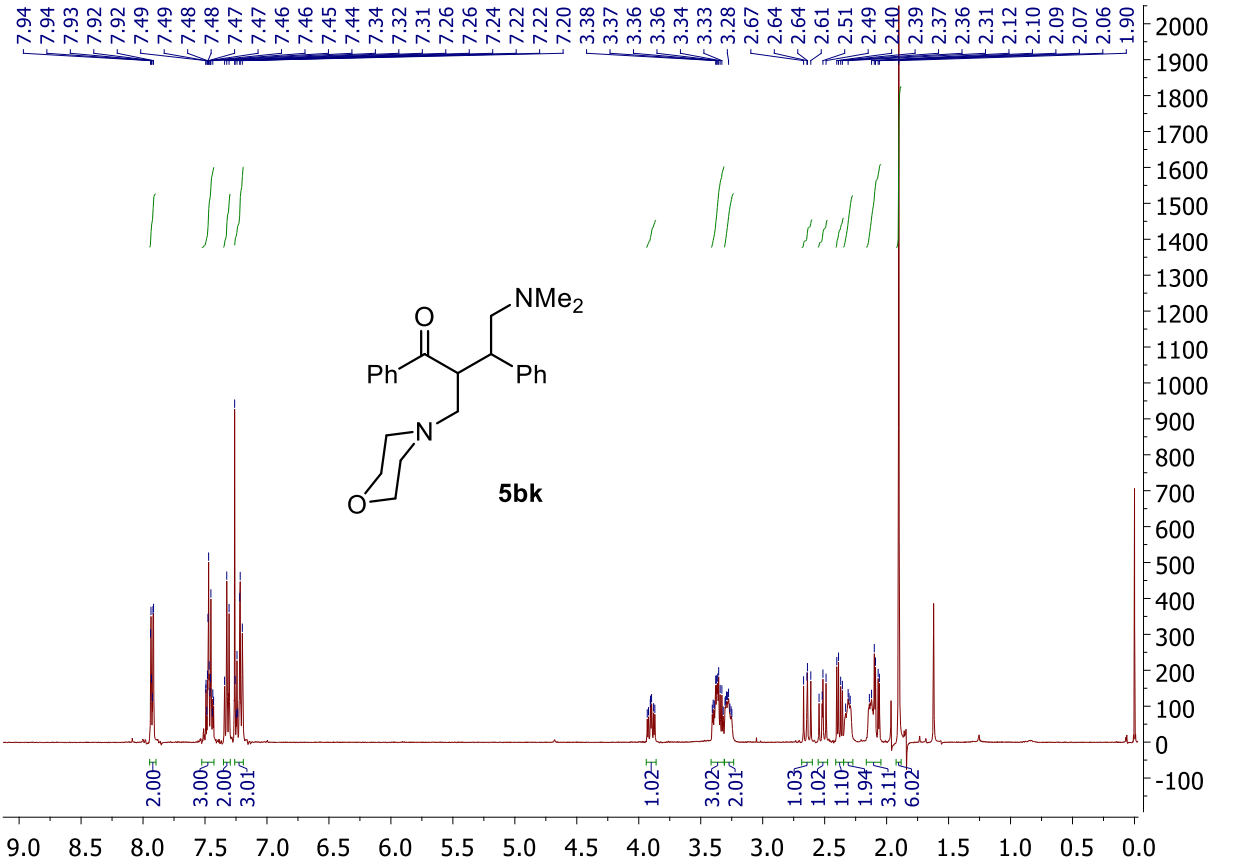
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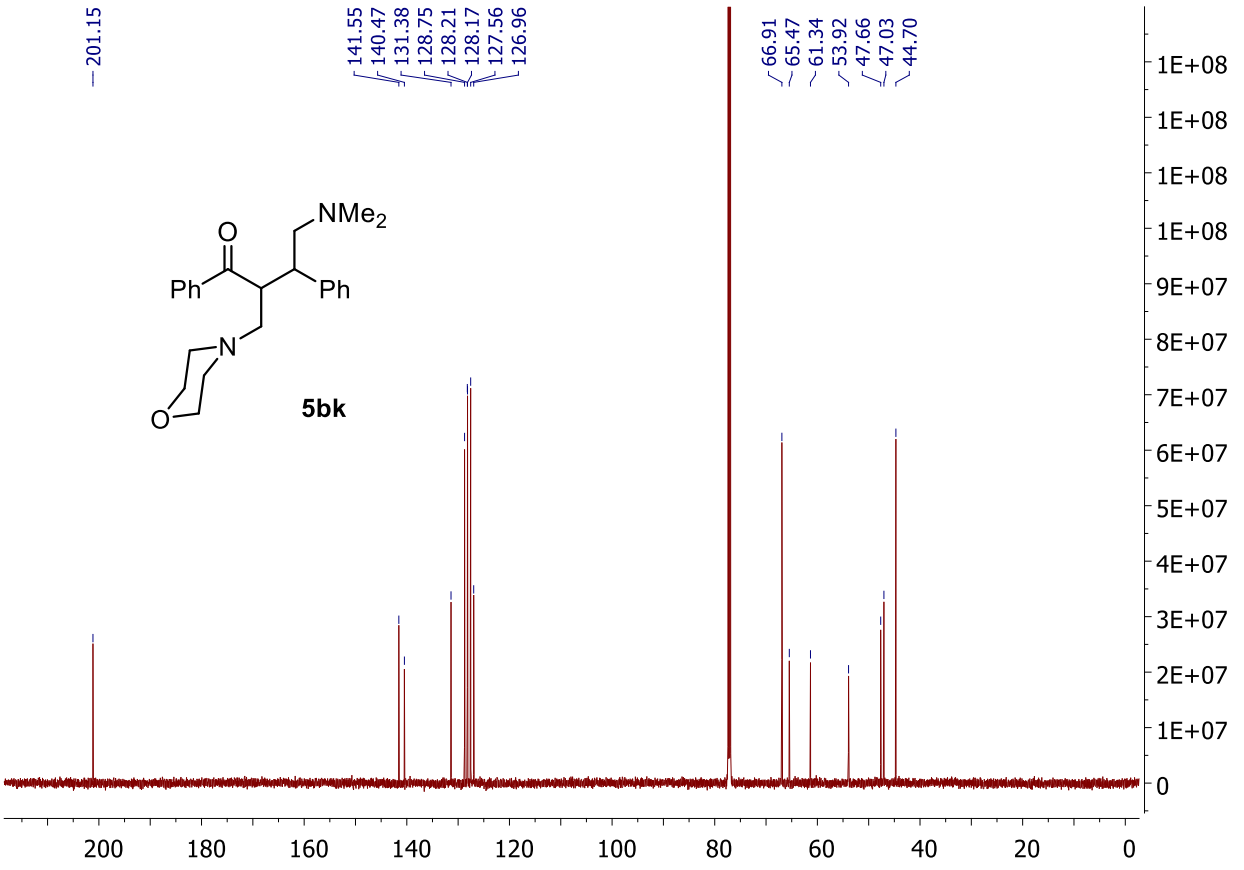
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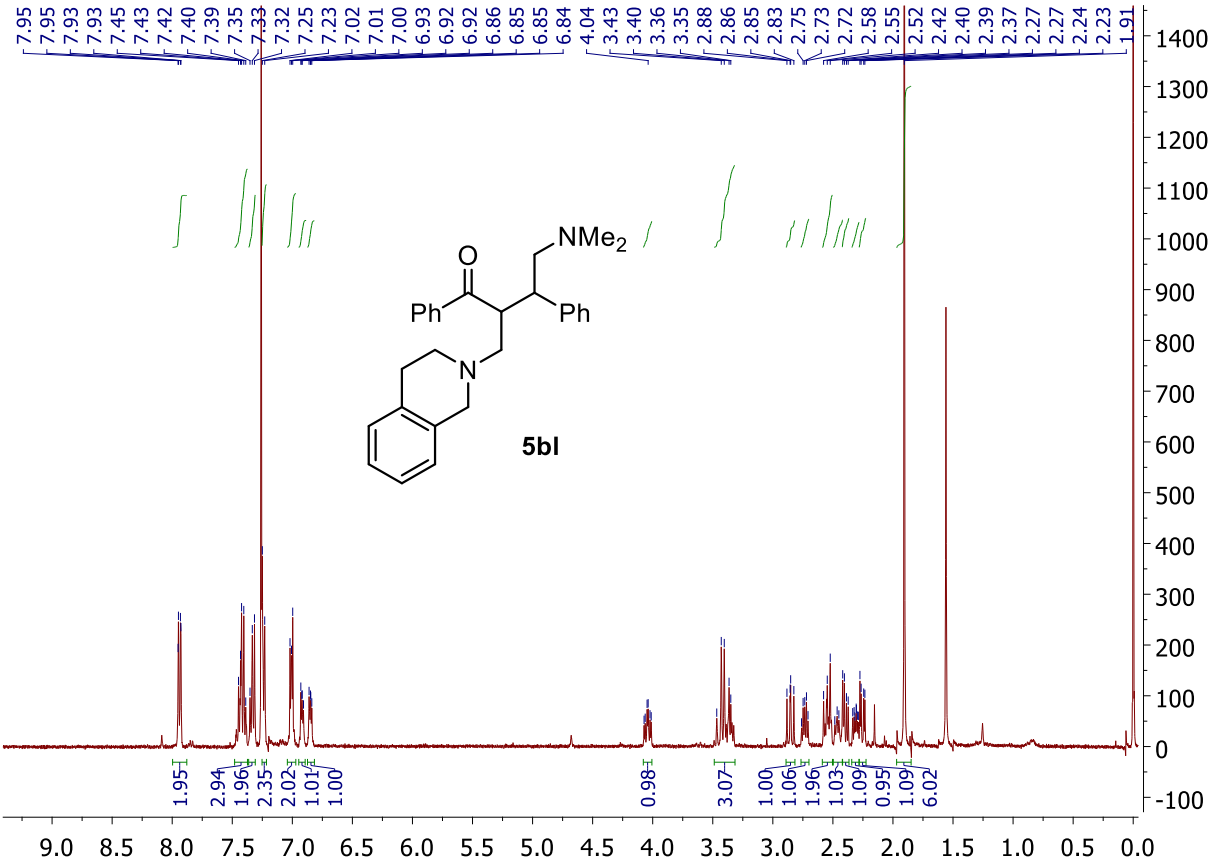
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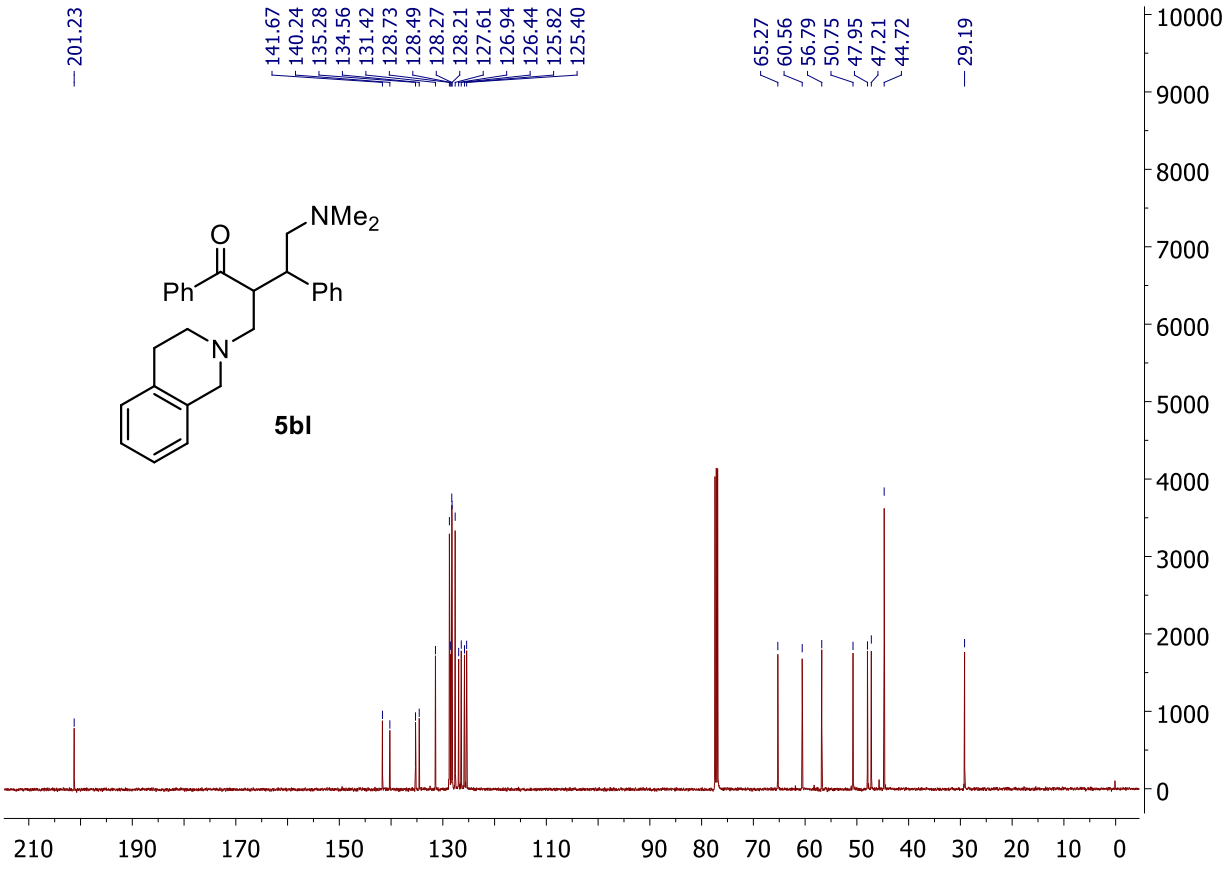
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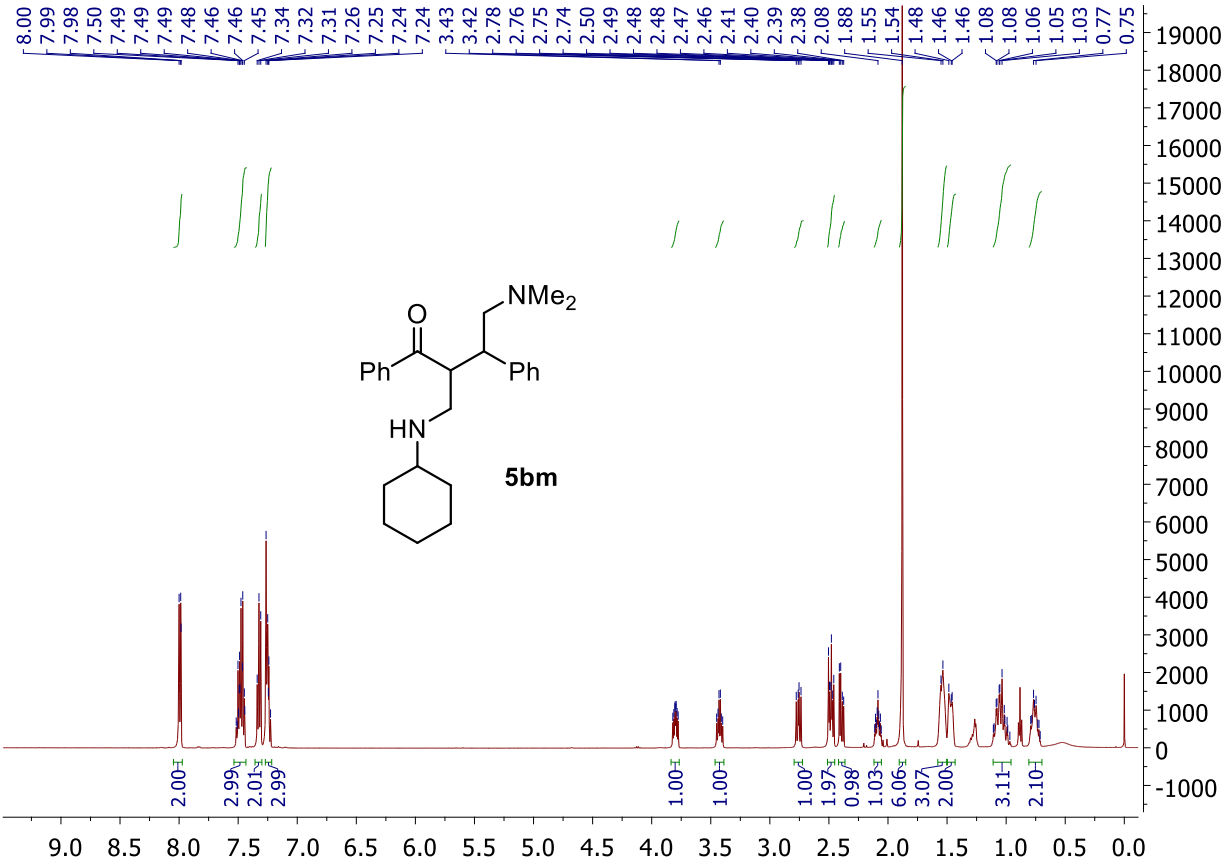
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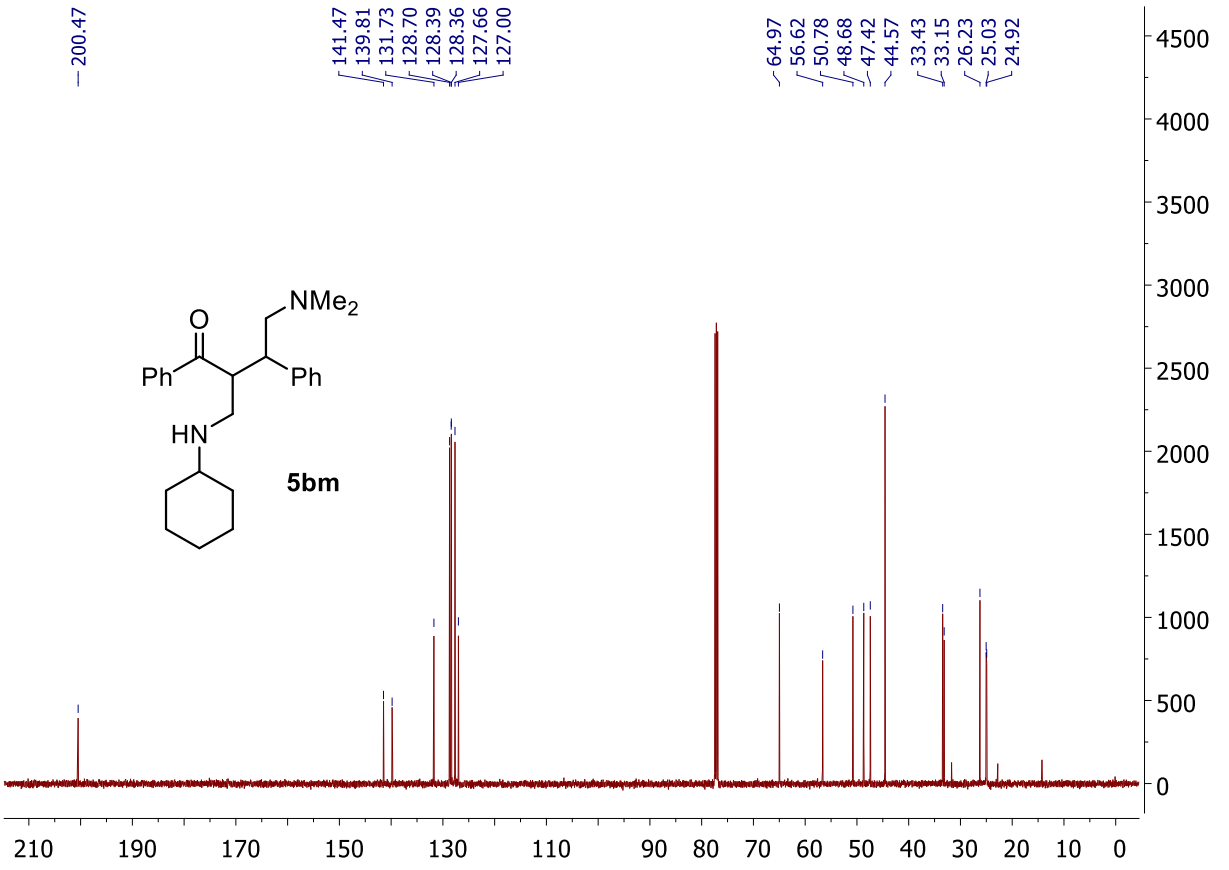
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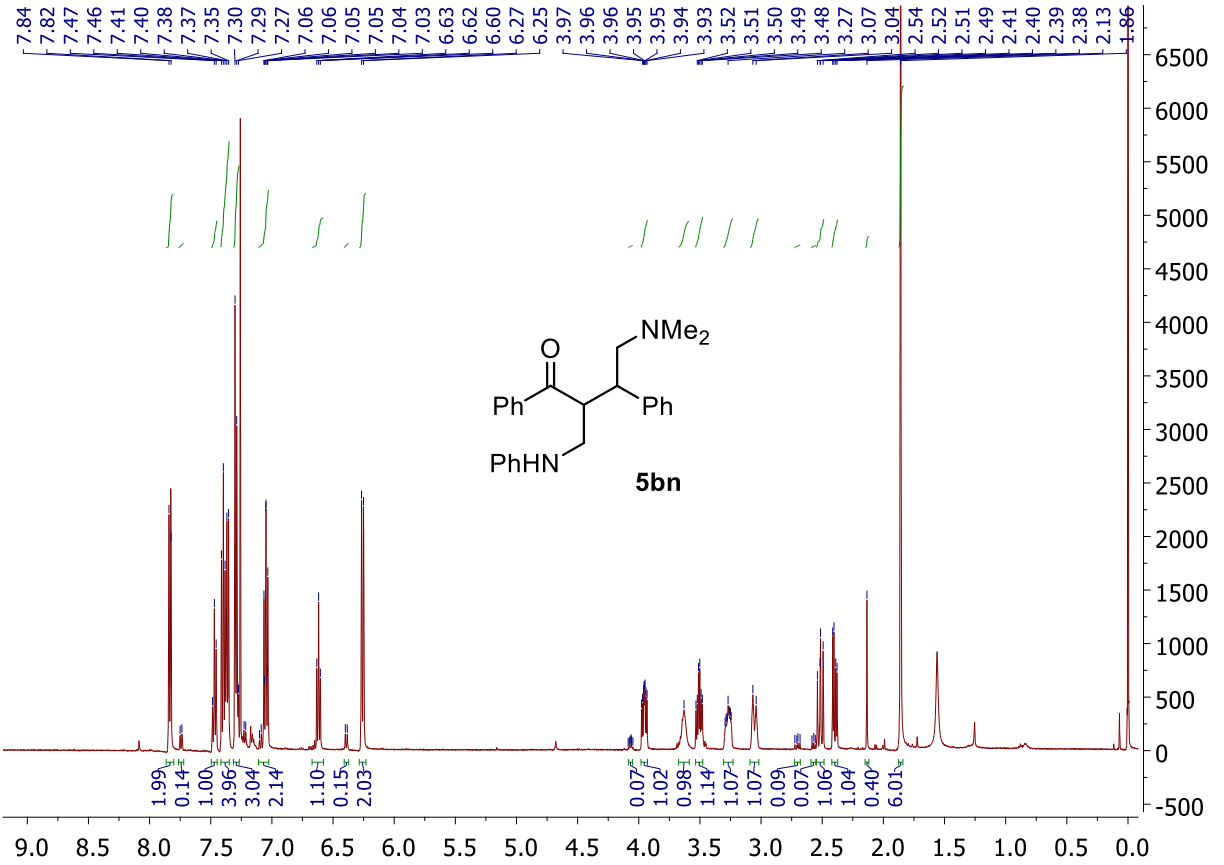
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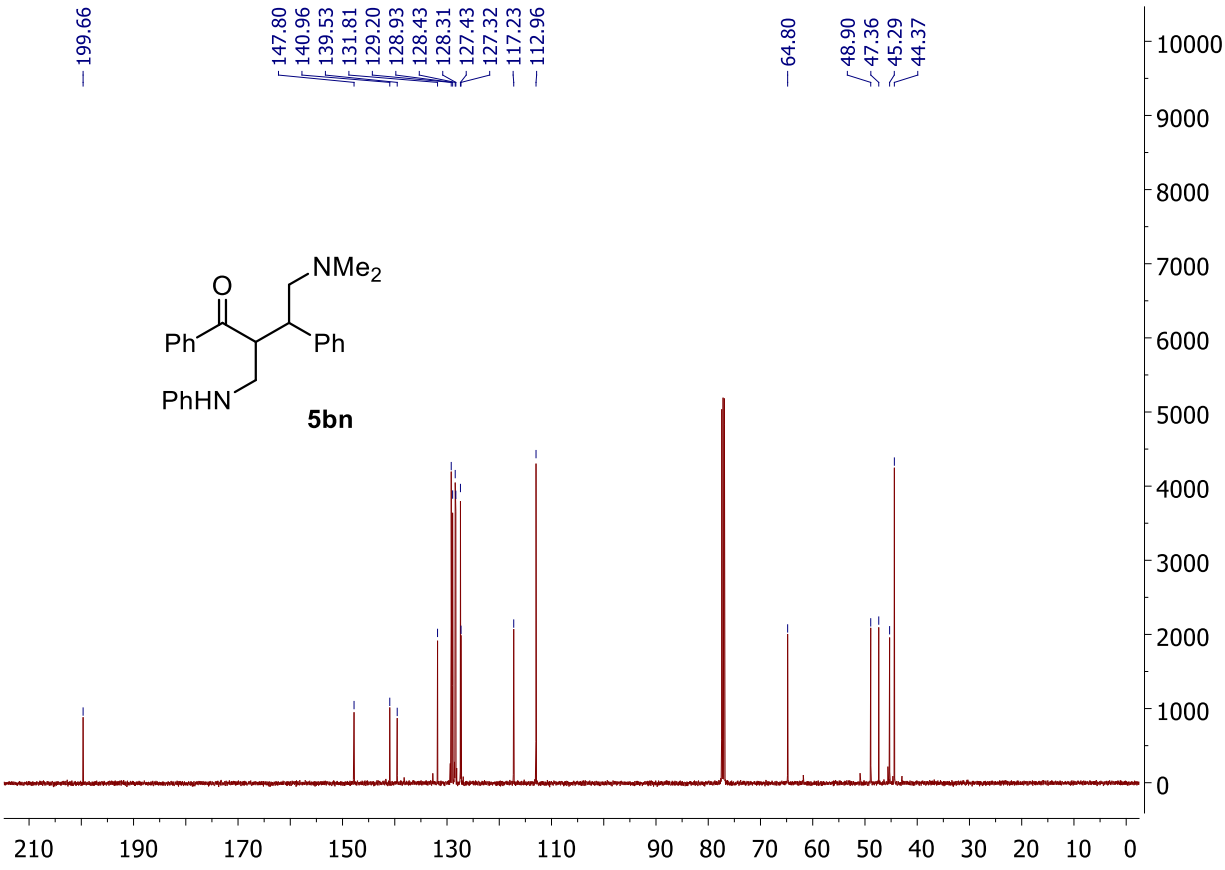
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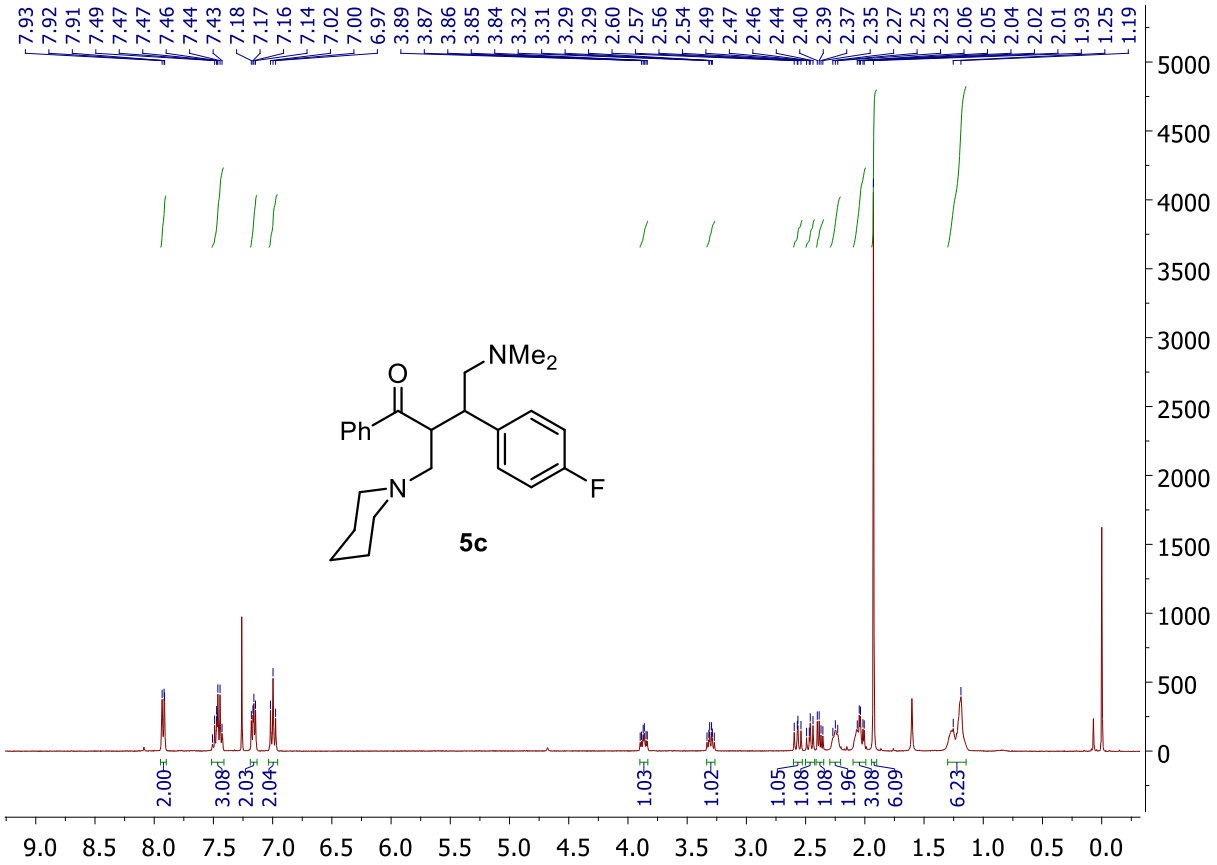
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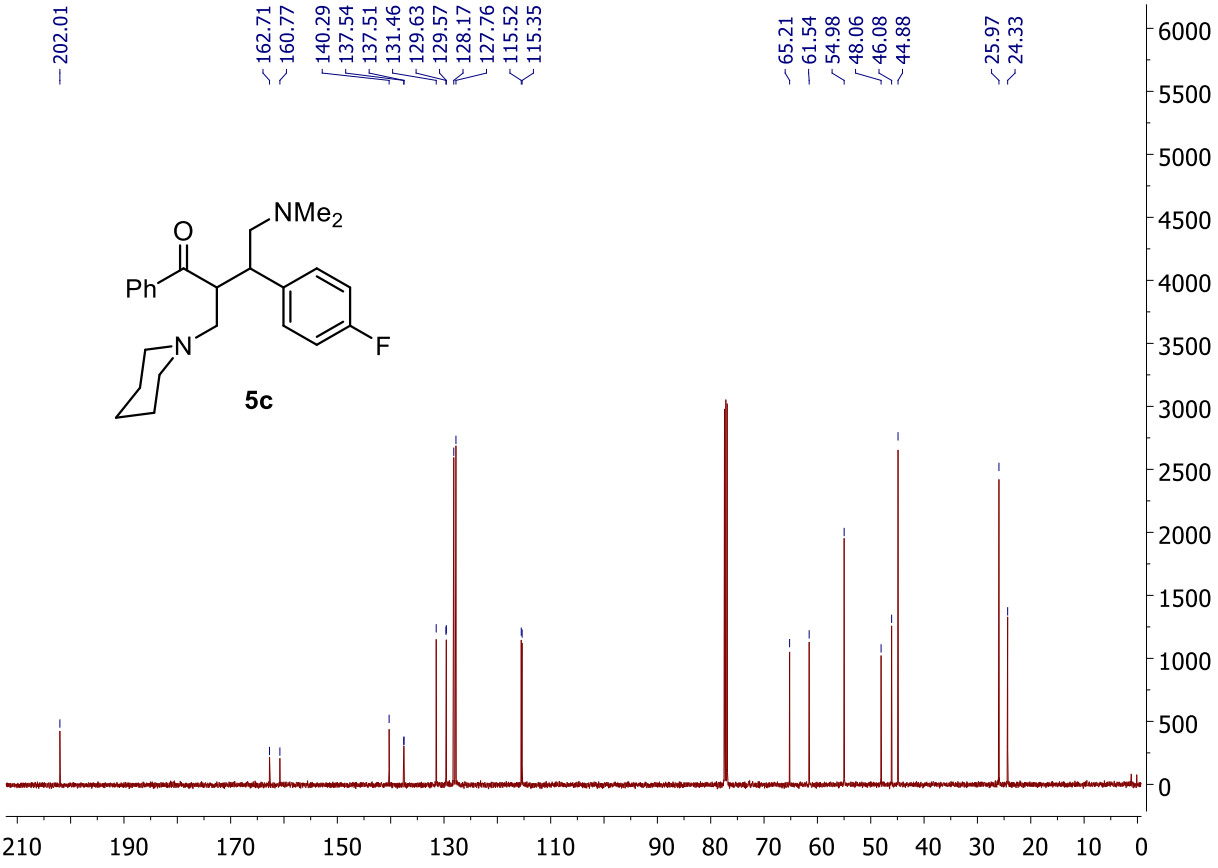
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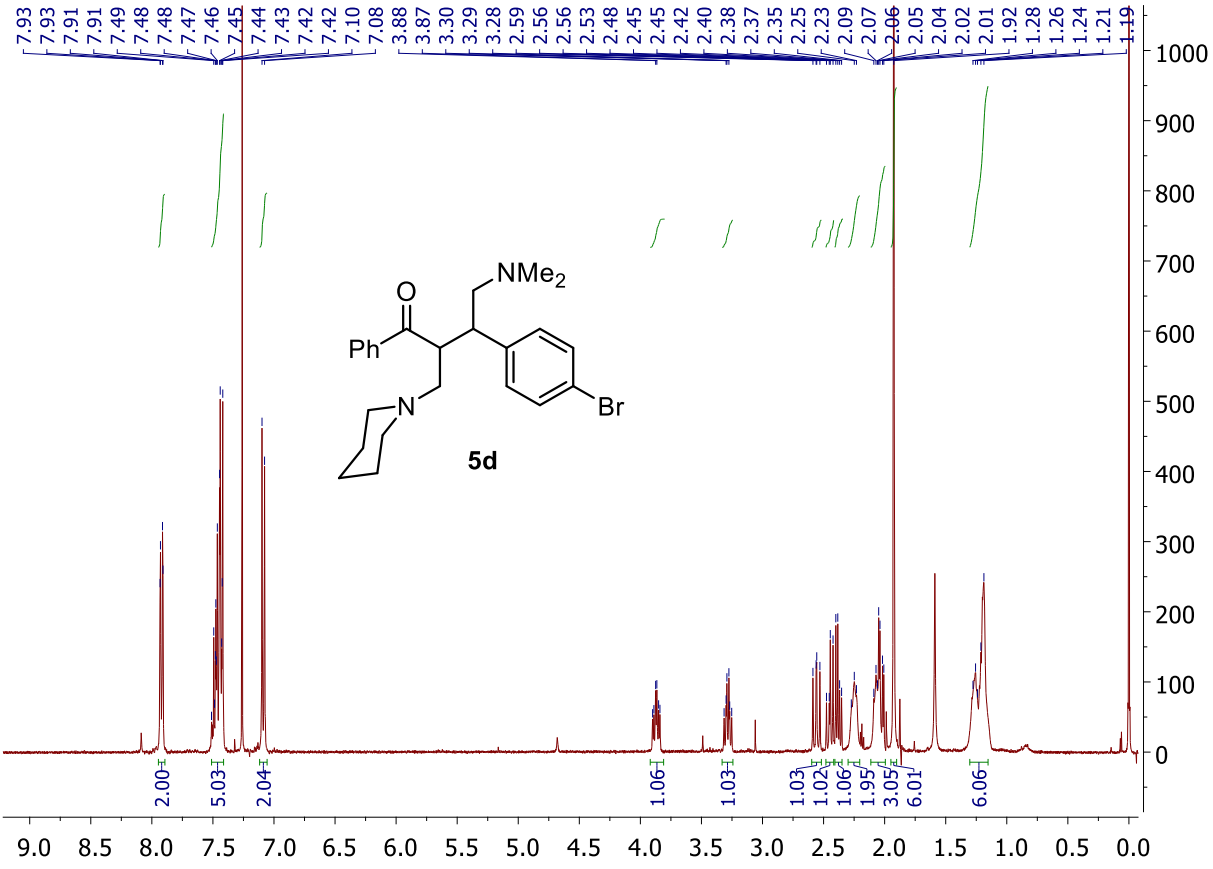
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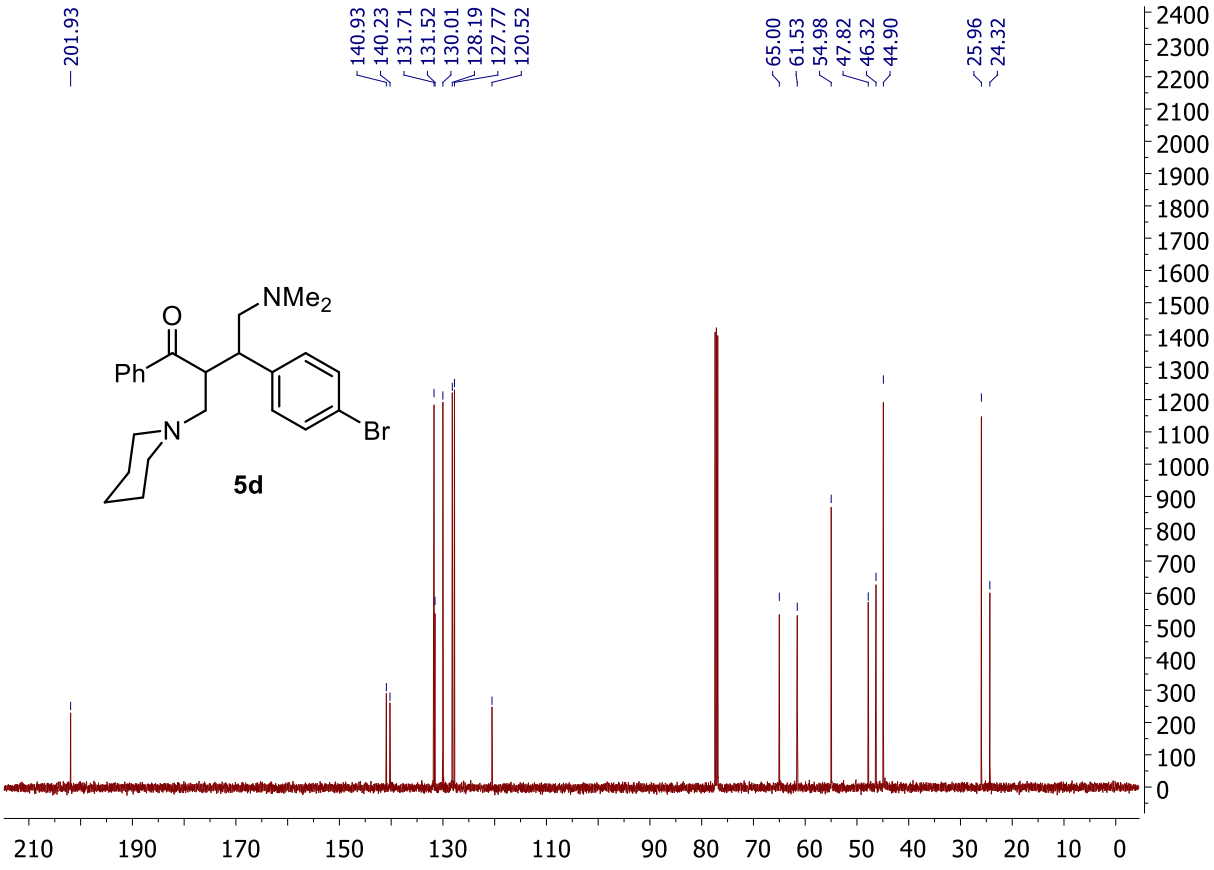
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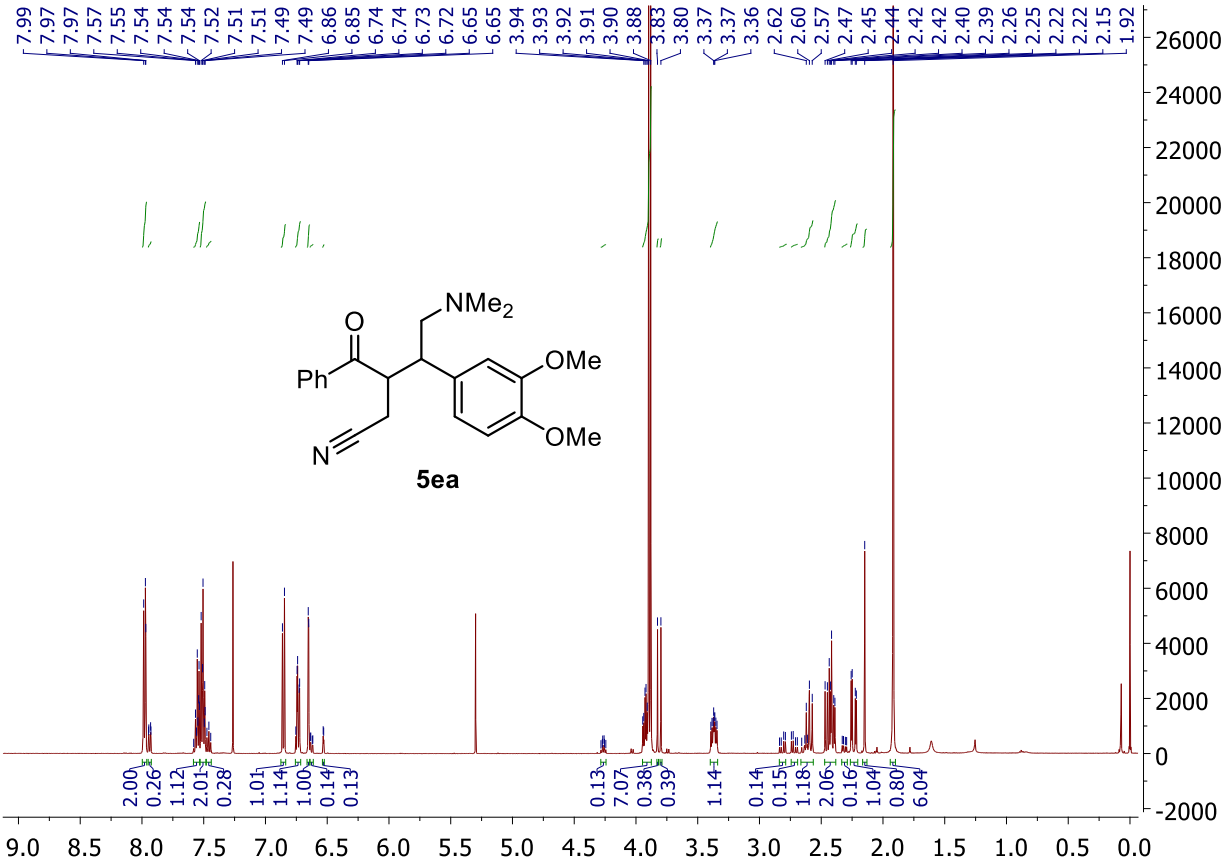
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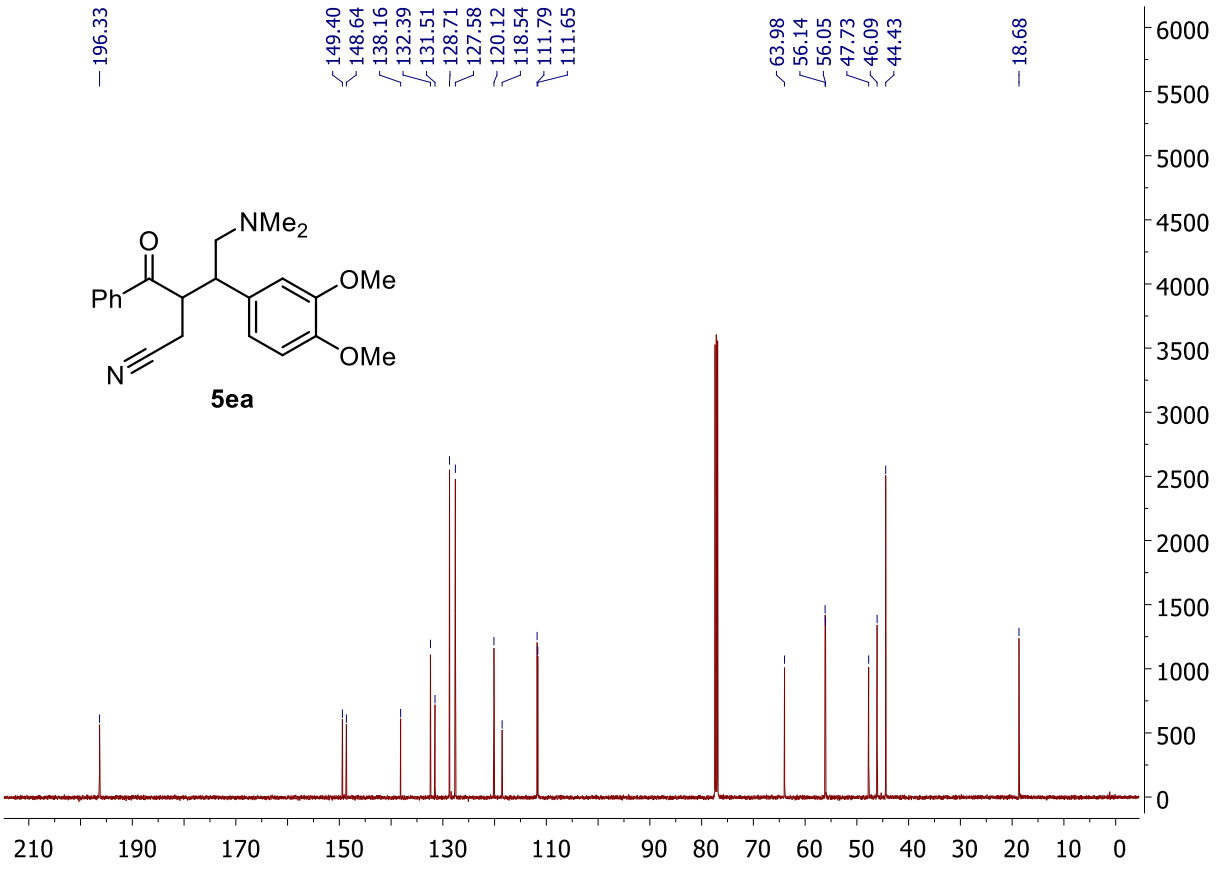
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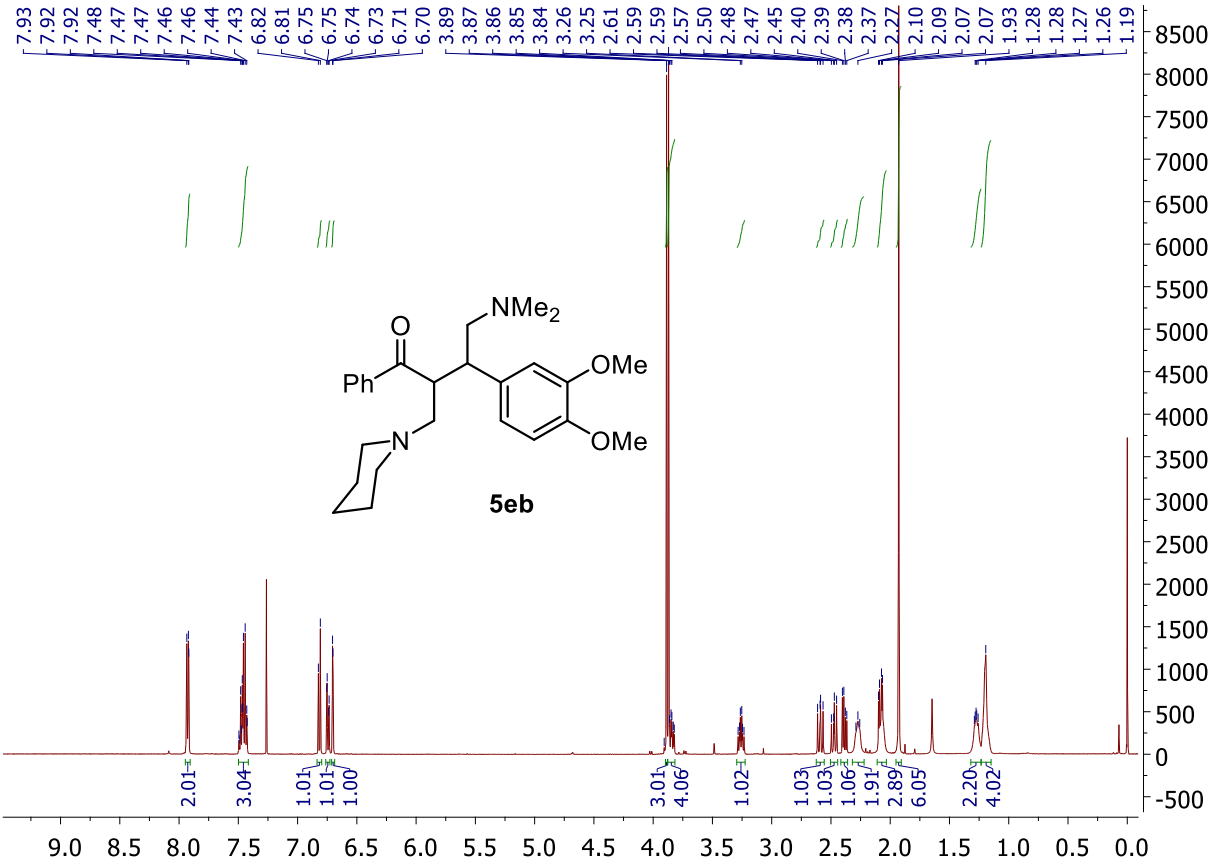
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NMe2
O
Ph
OMe
OMe
N
5eb
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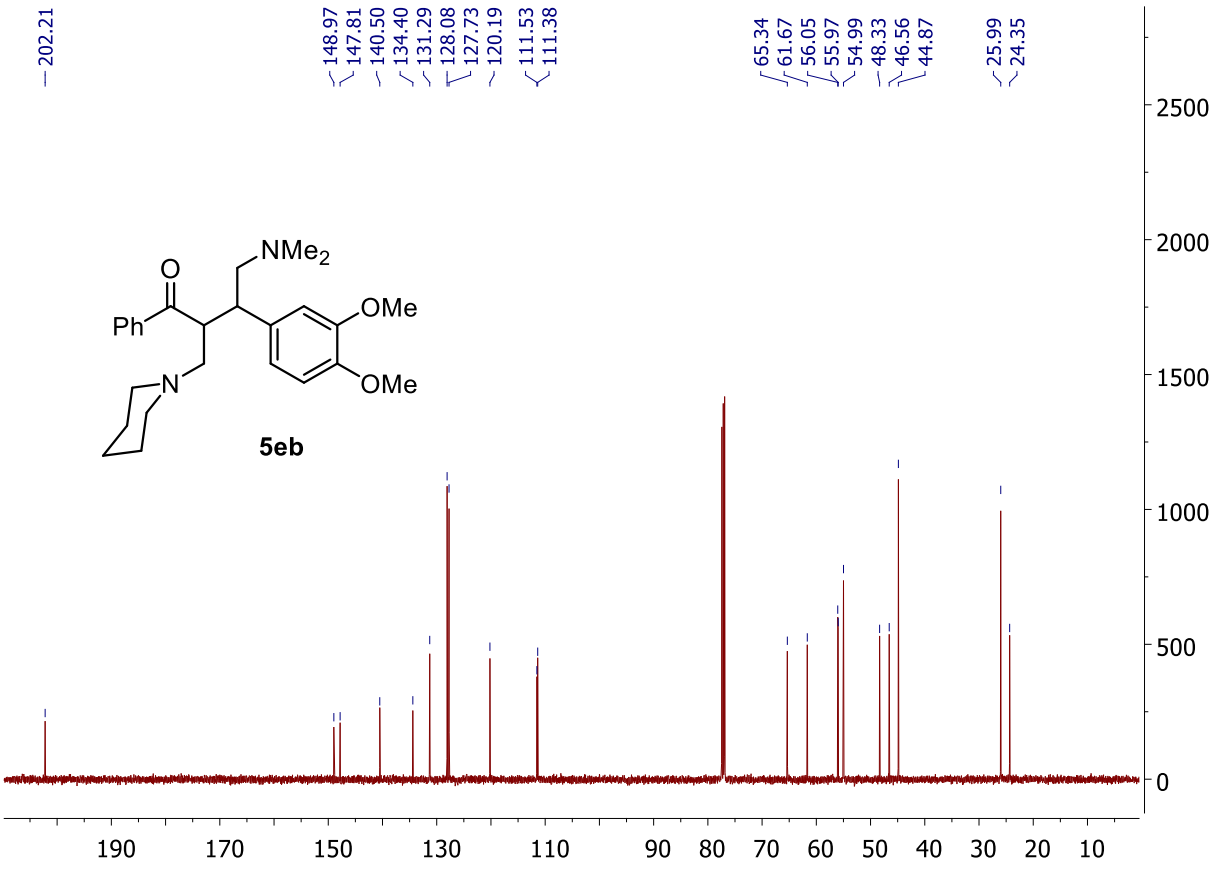
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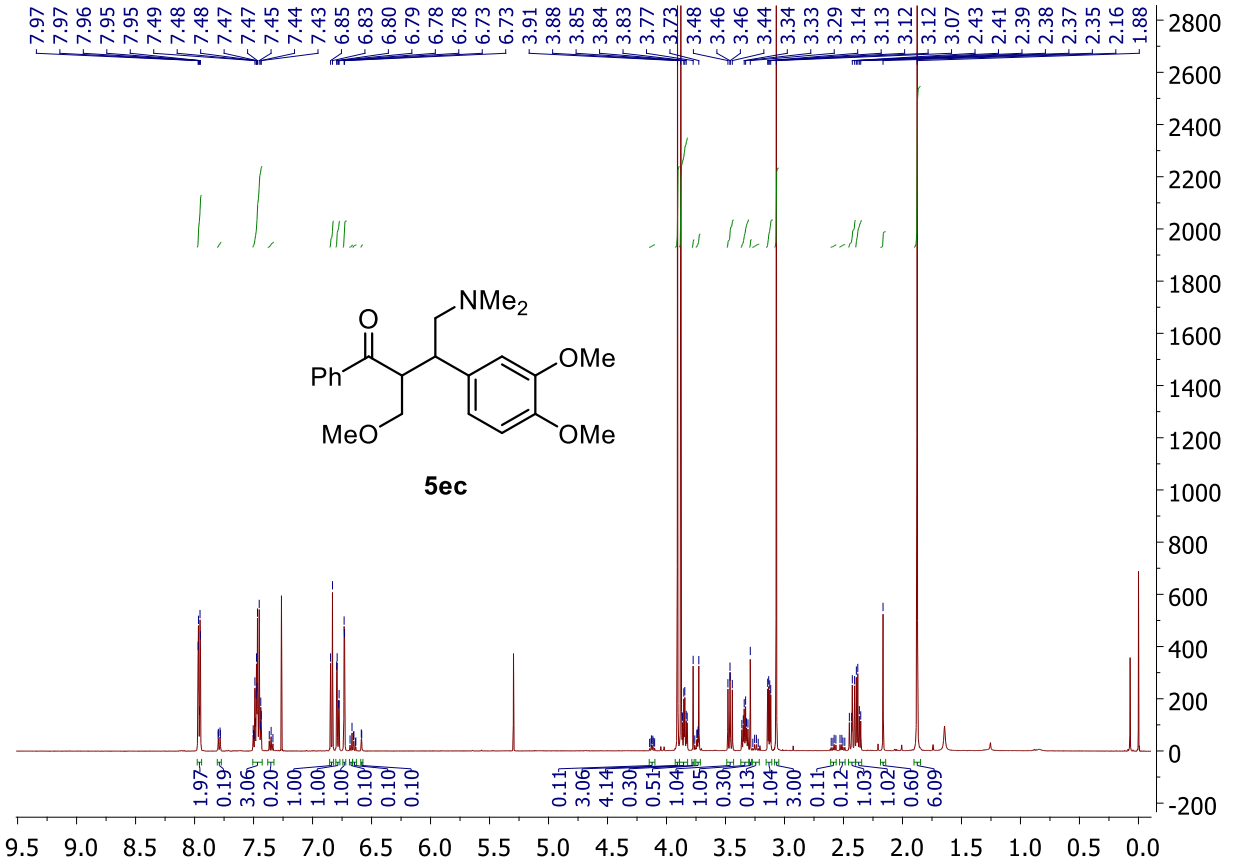
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MeO
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5ec
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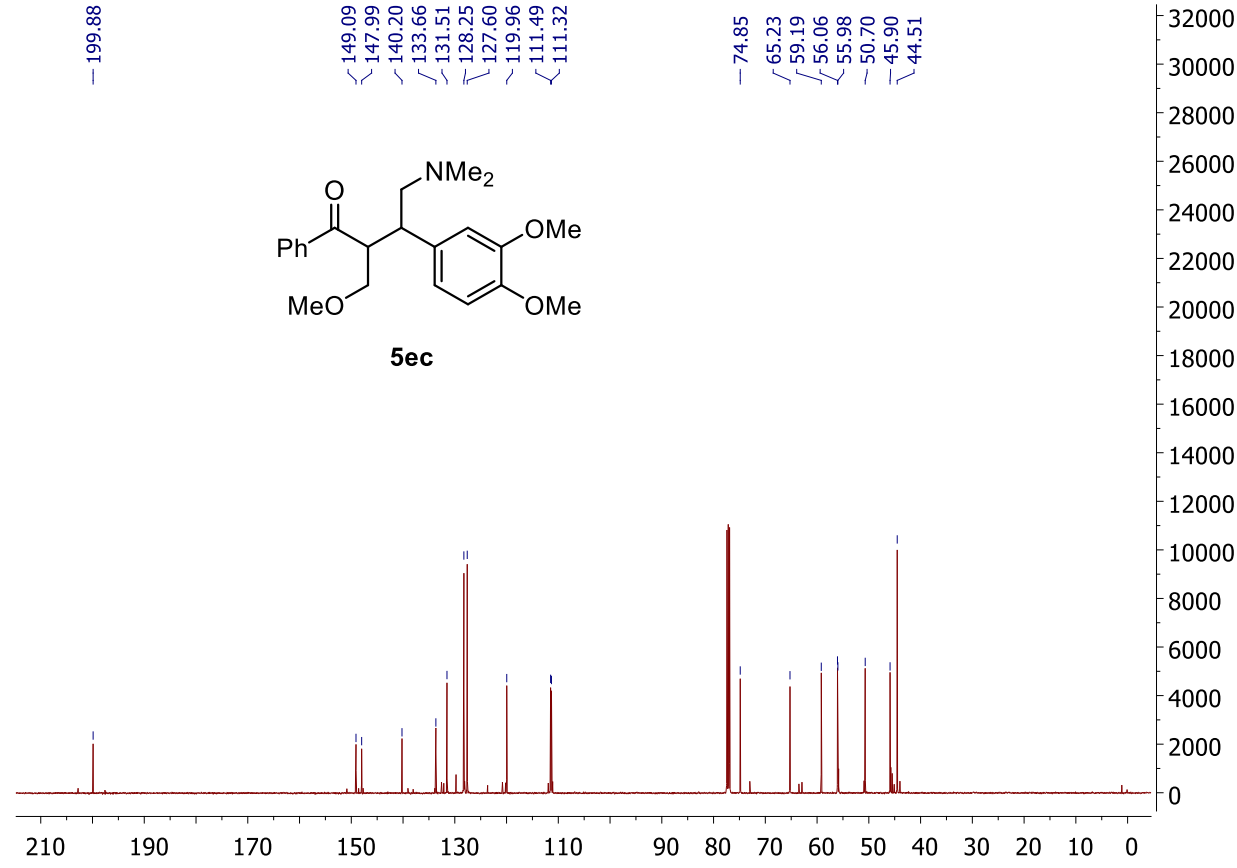
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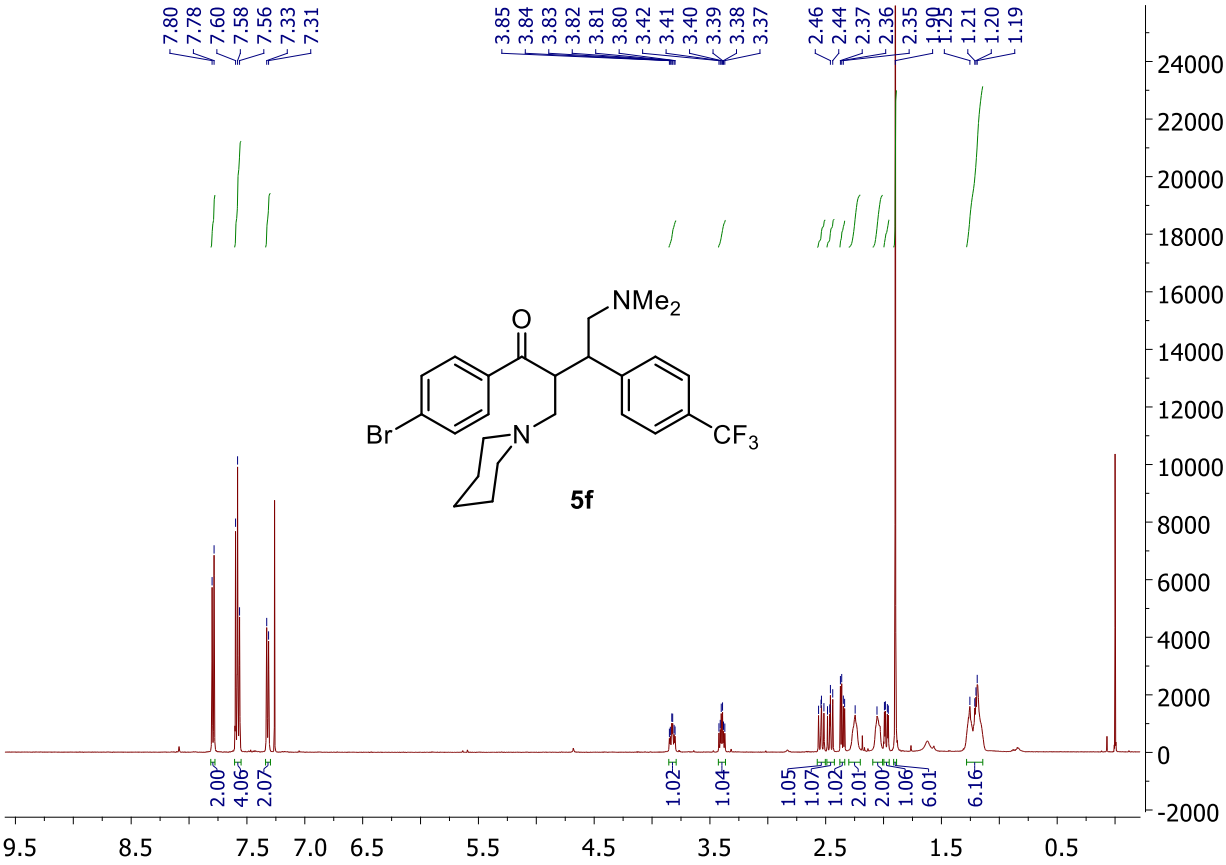
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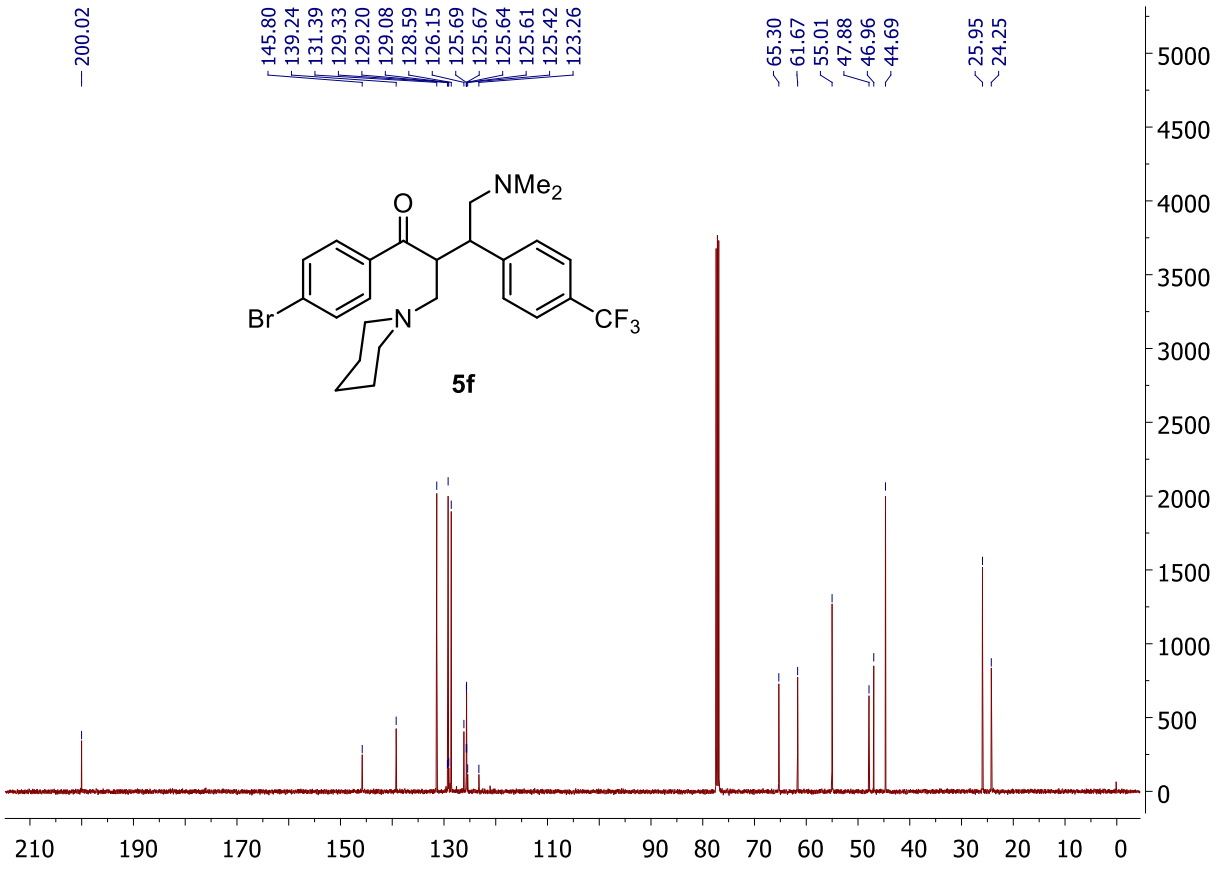
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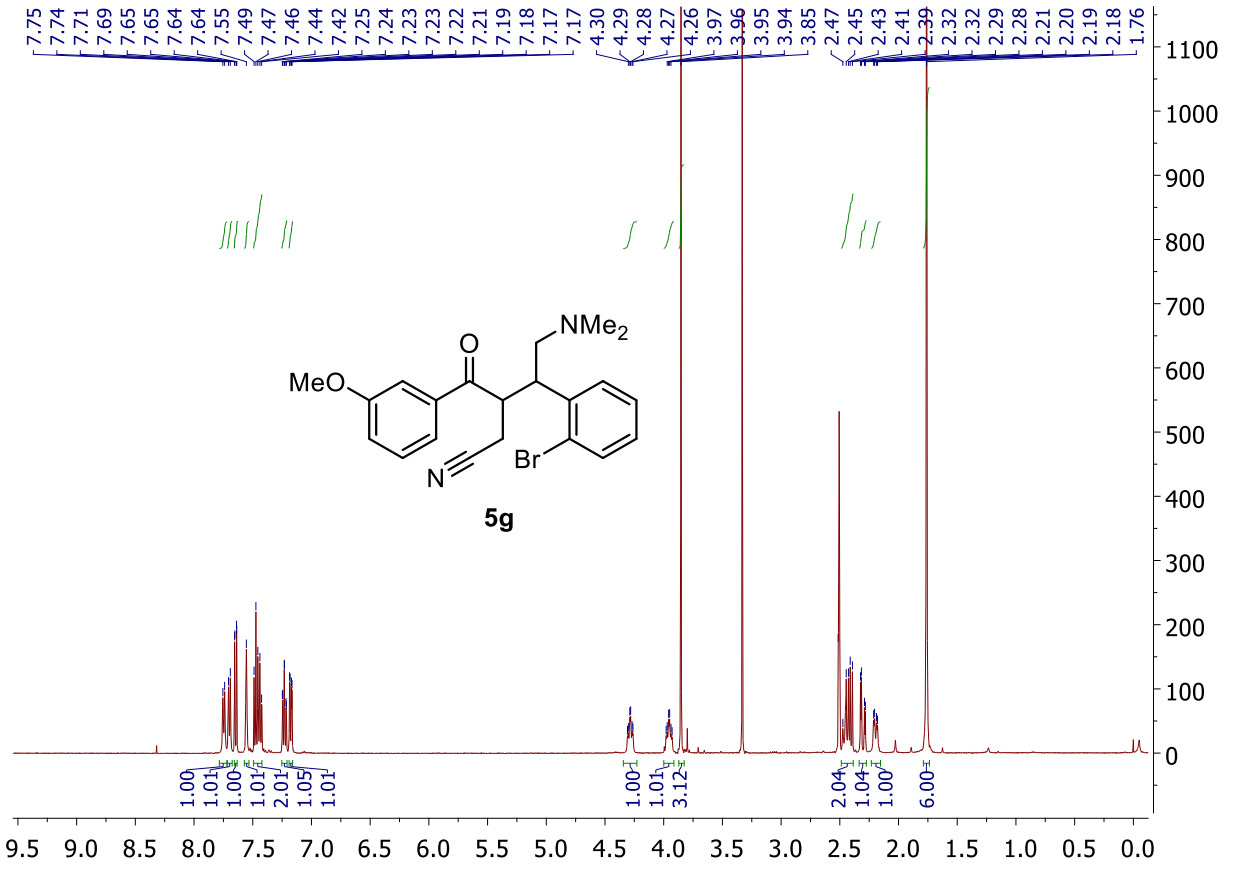
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1.00 1.01 1.00 1.01 2.01 1.05 1.01 1.00 1.01 3.12 2.04 1.04 1.00 6.00
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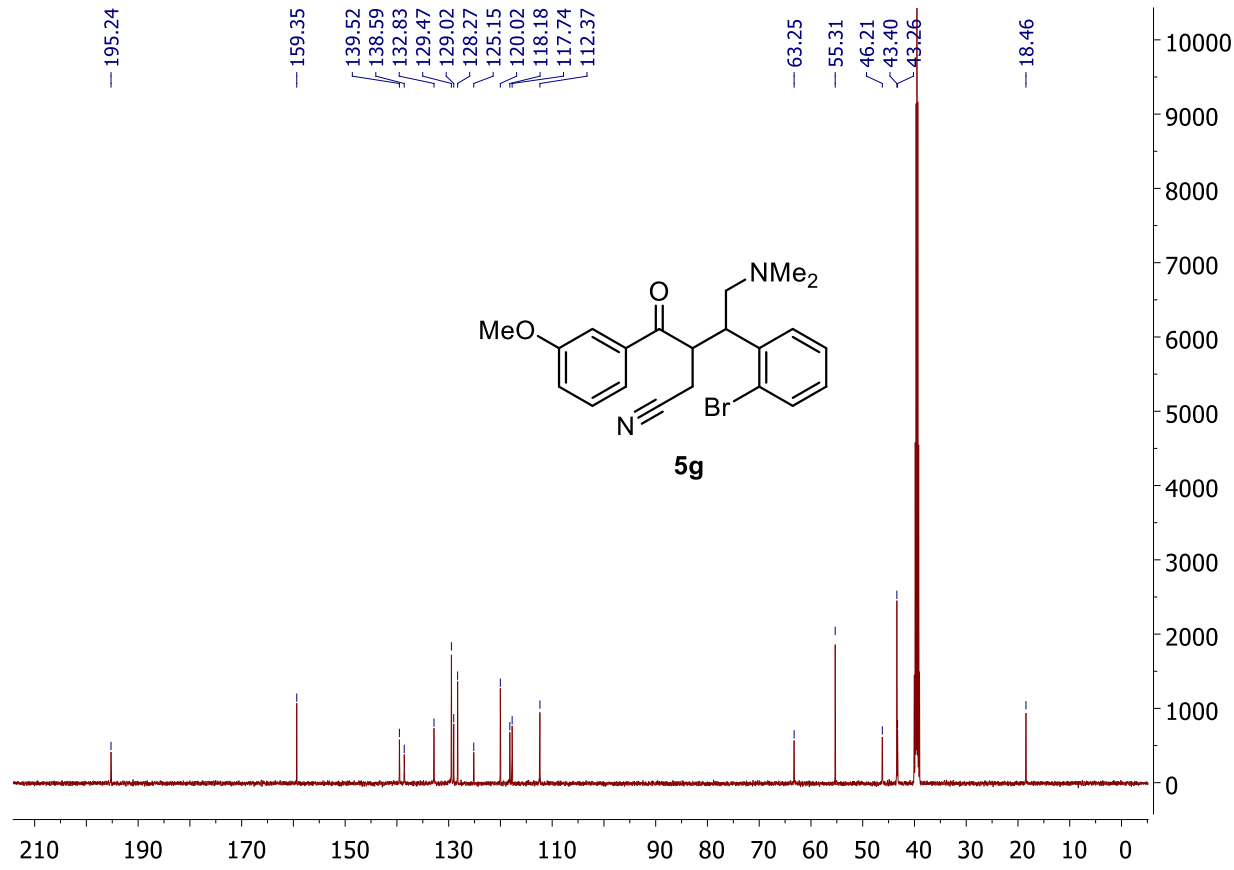
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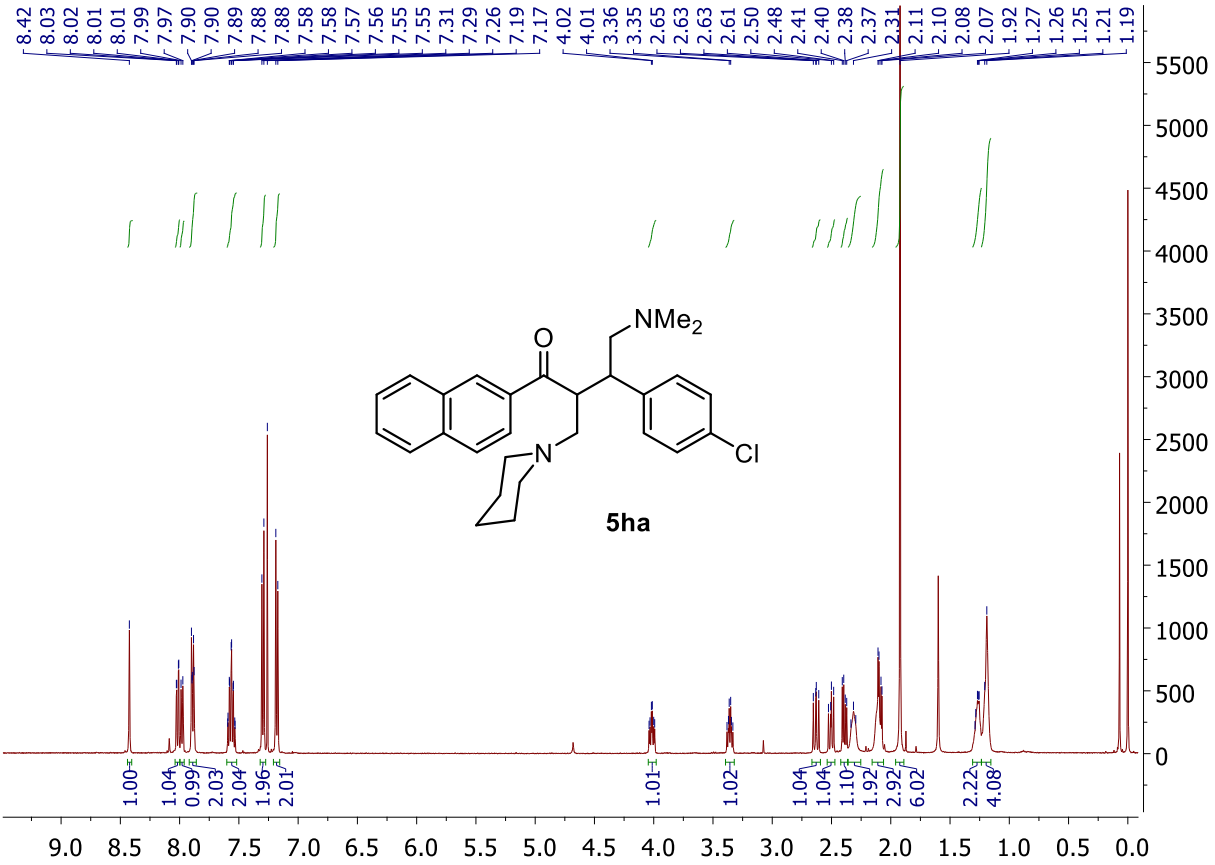
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Cl
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9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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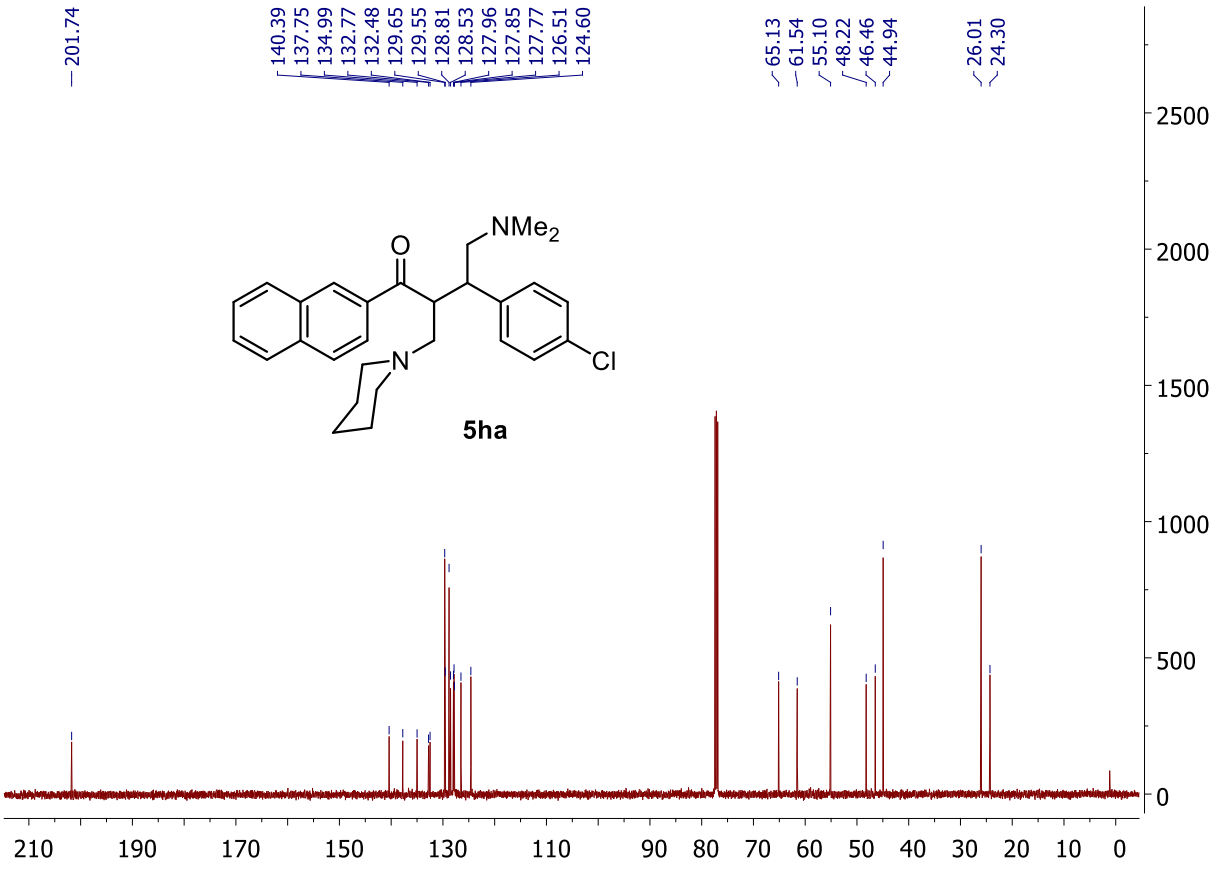
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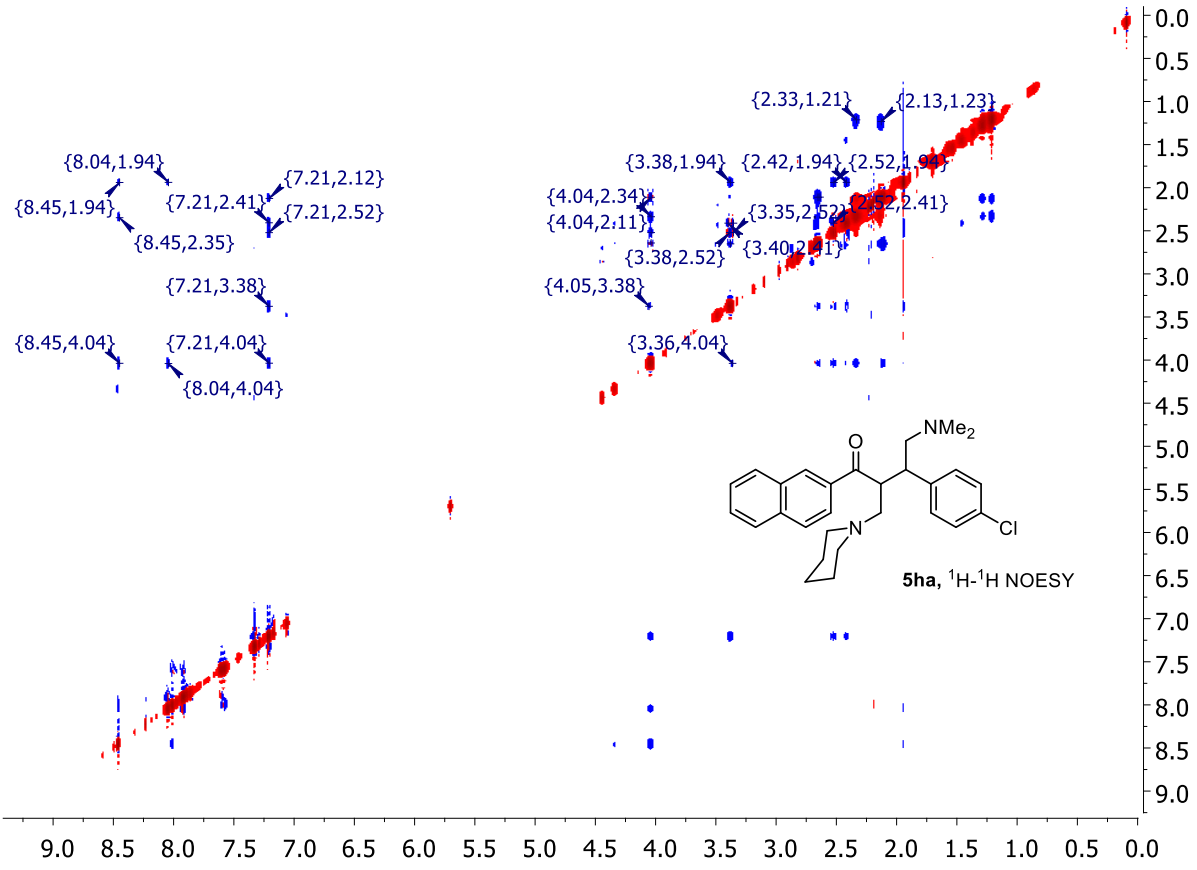
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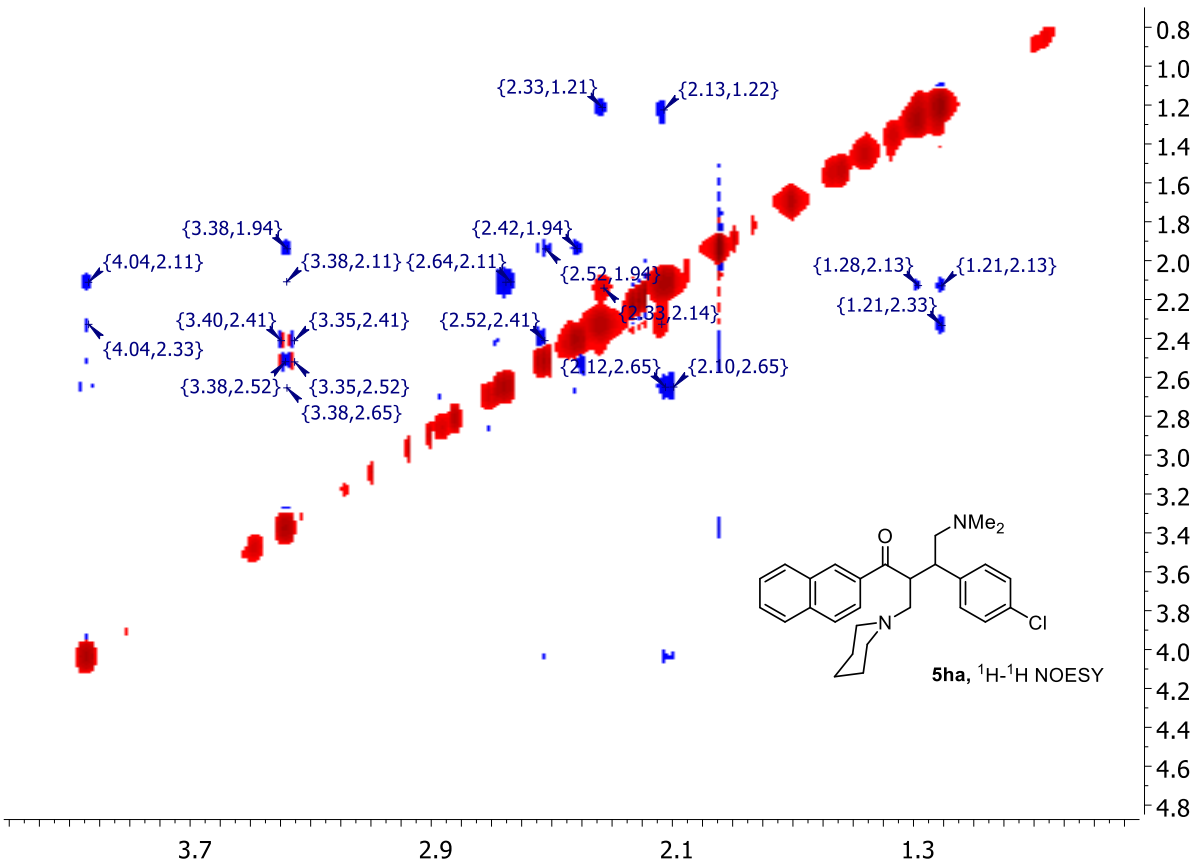
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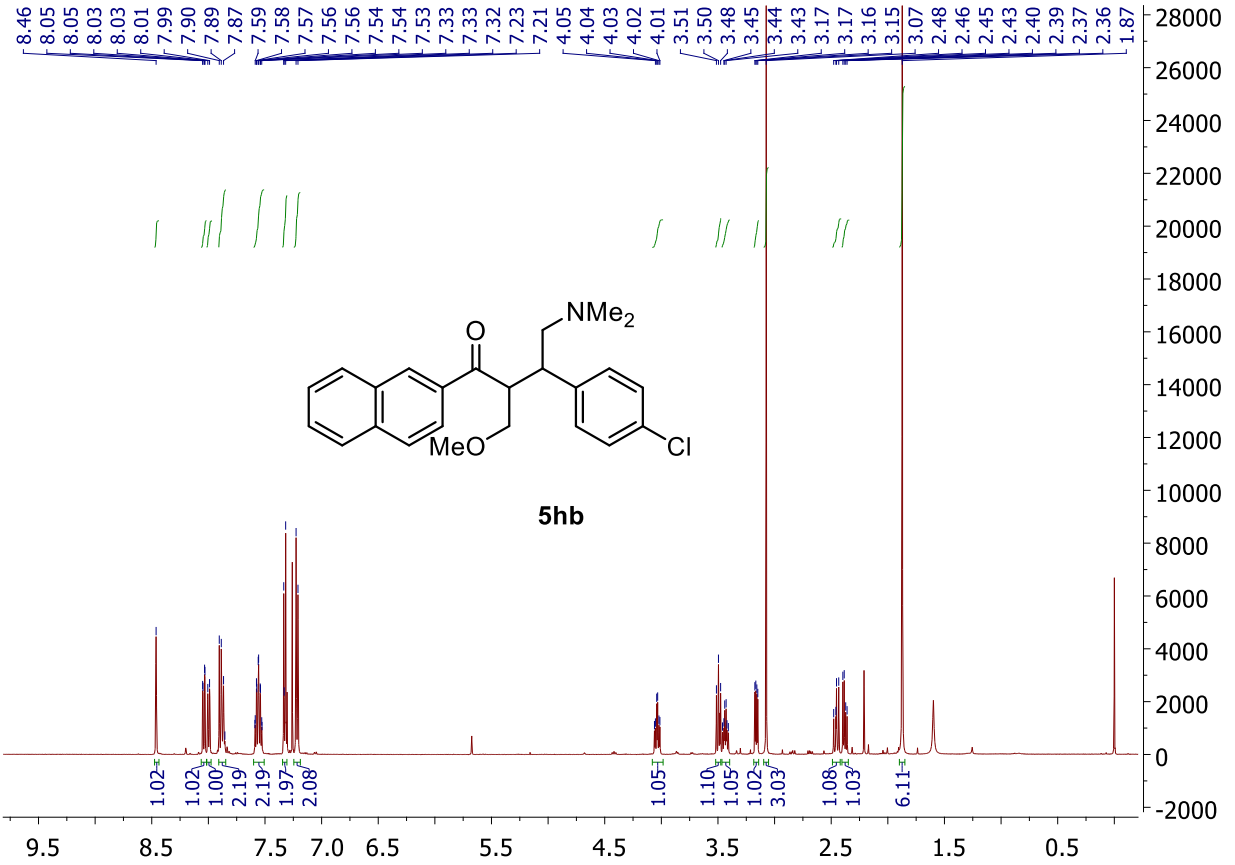
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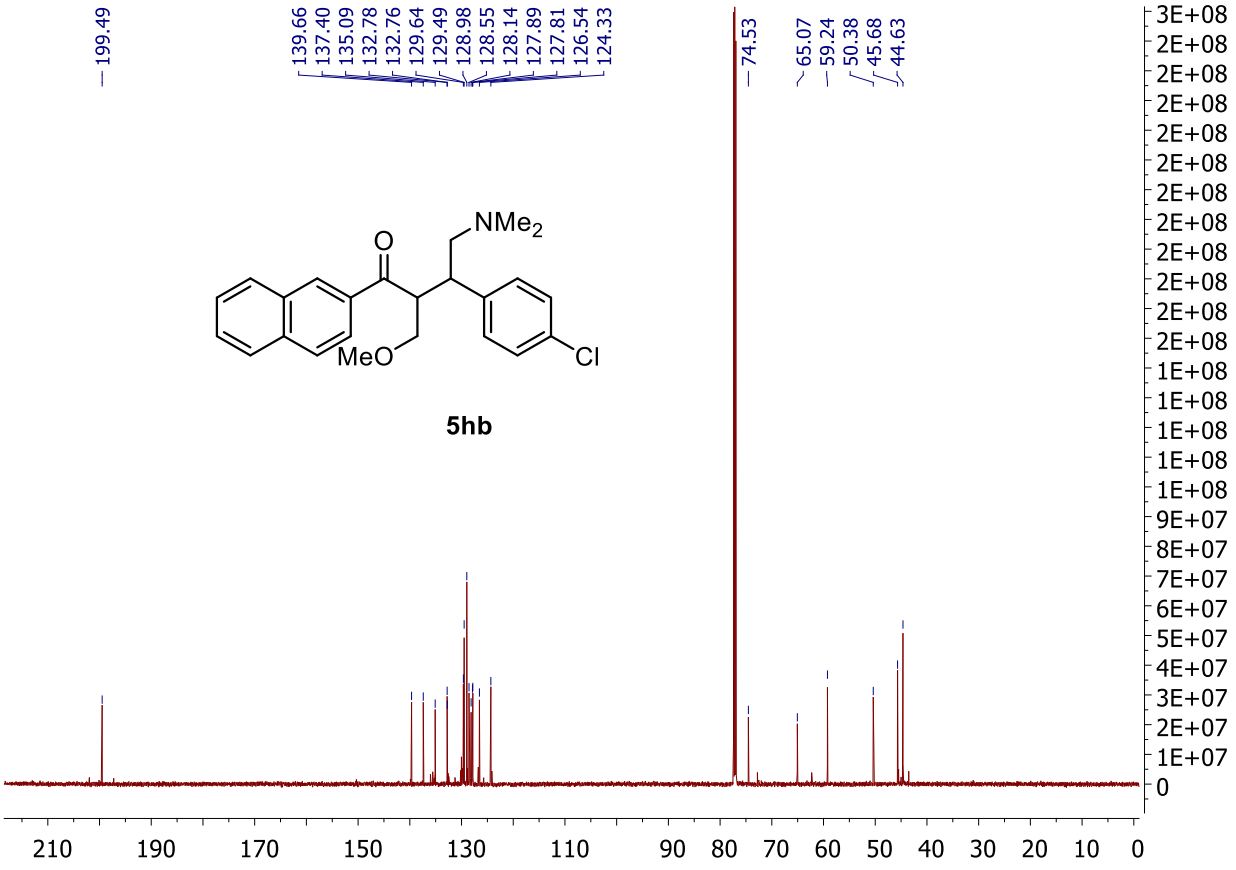
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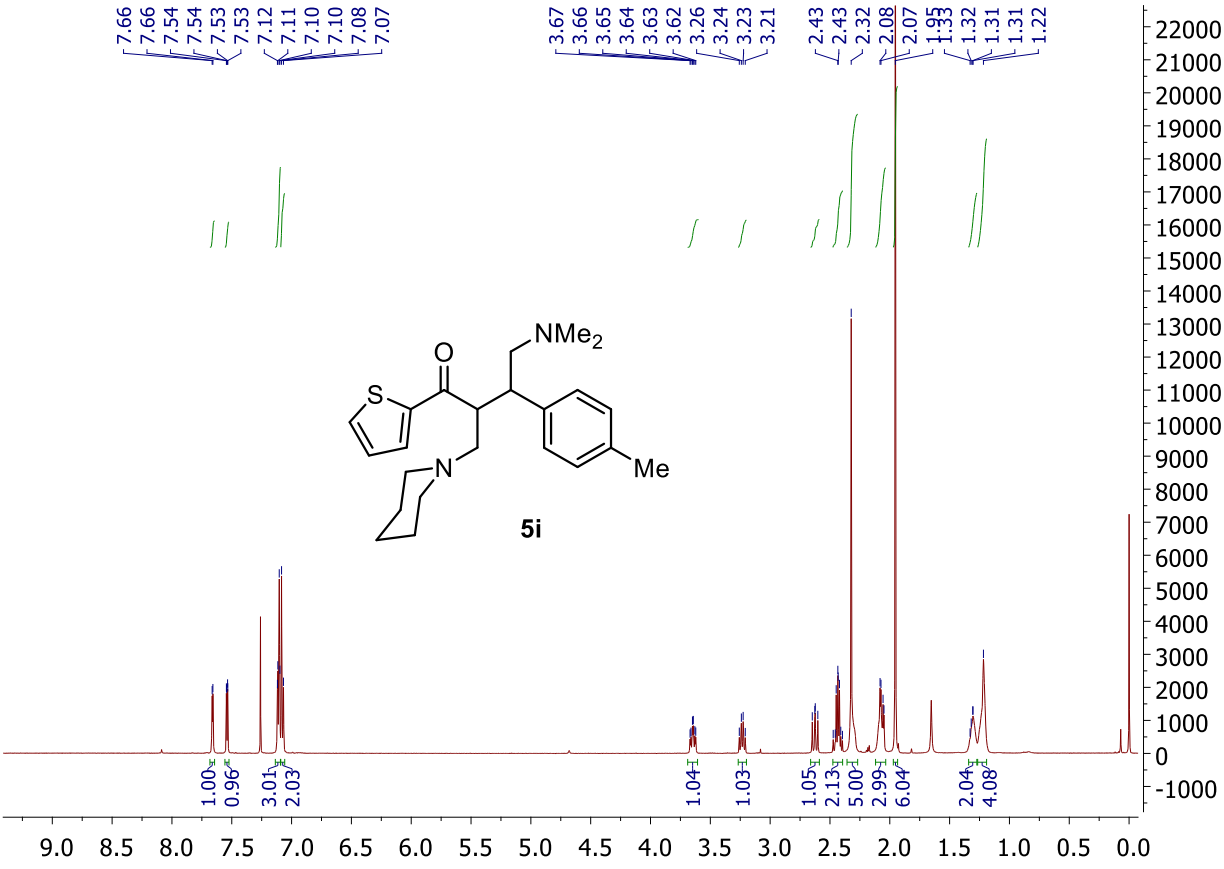
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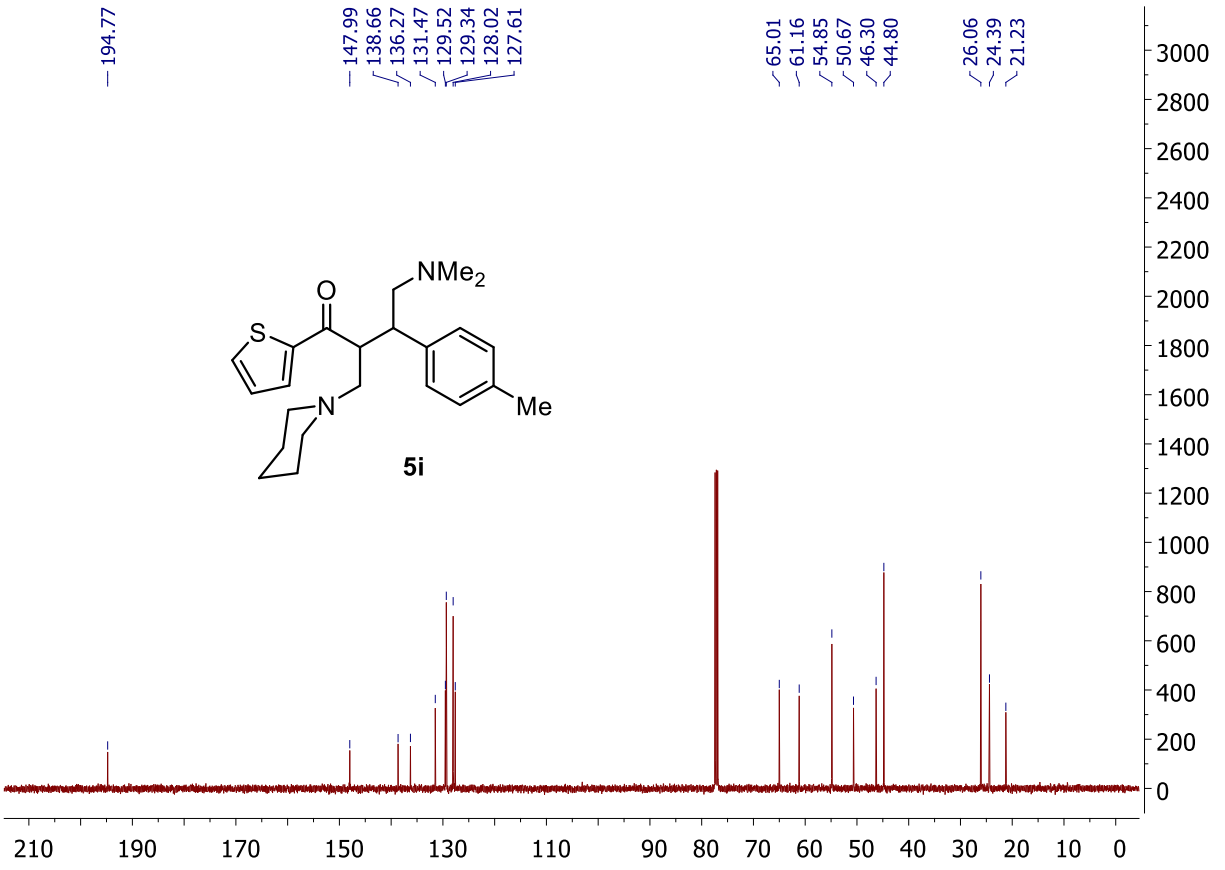
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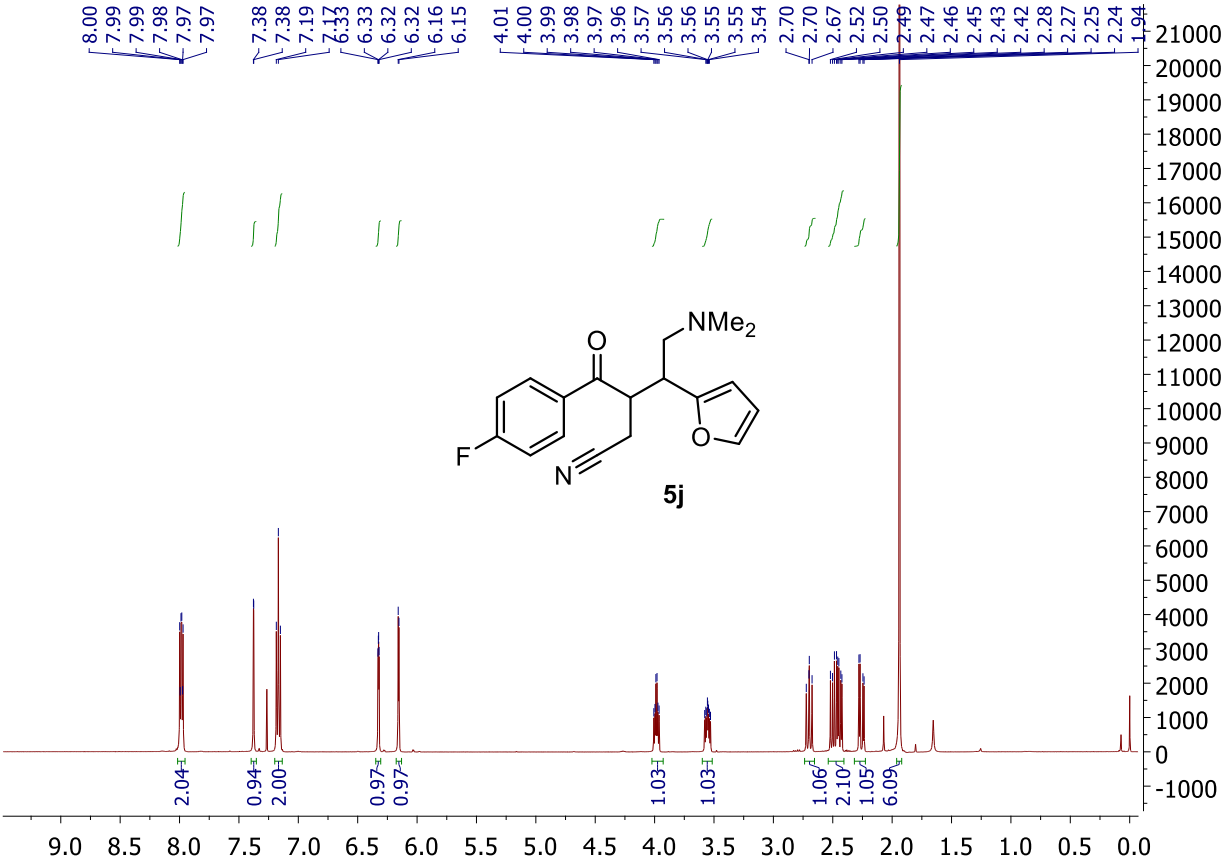
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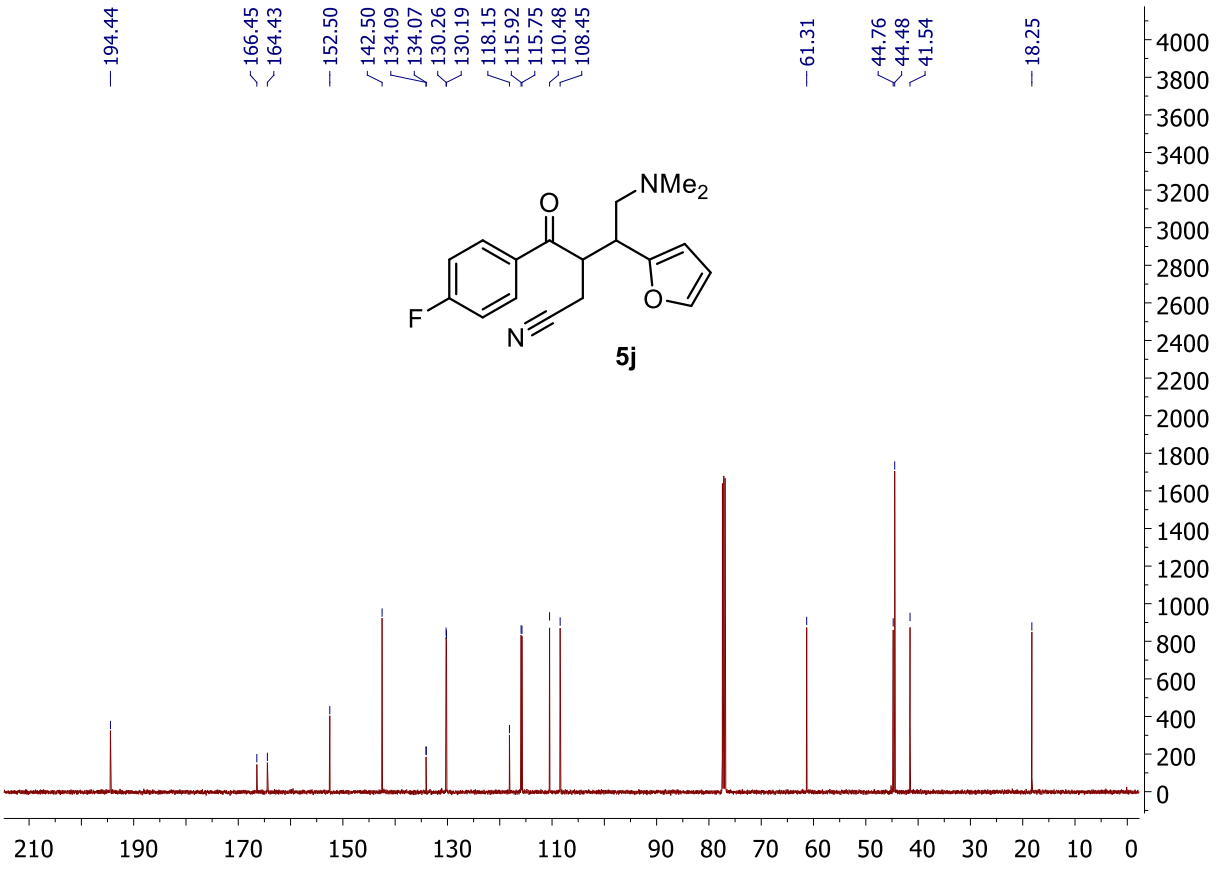
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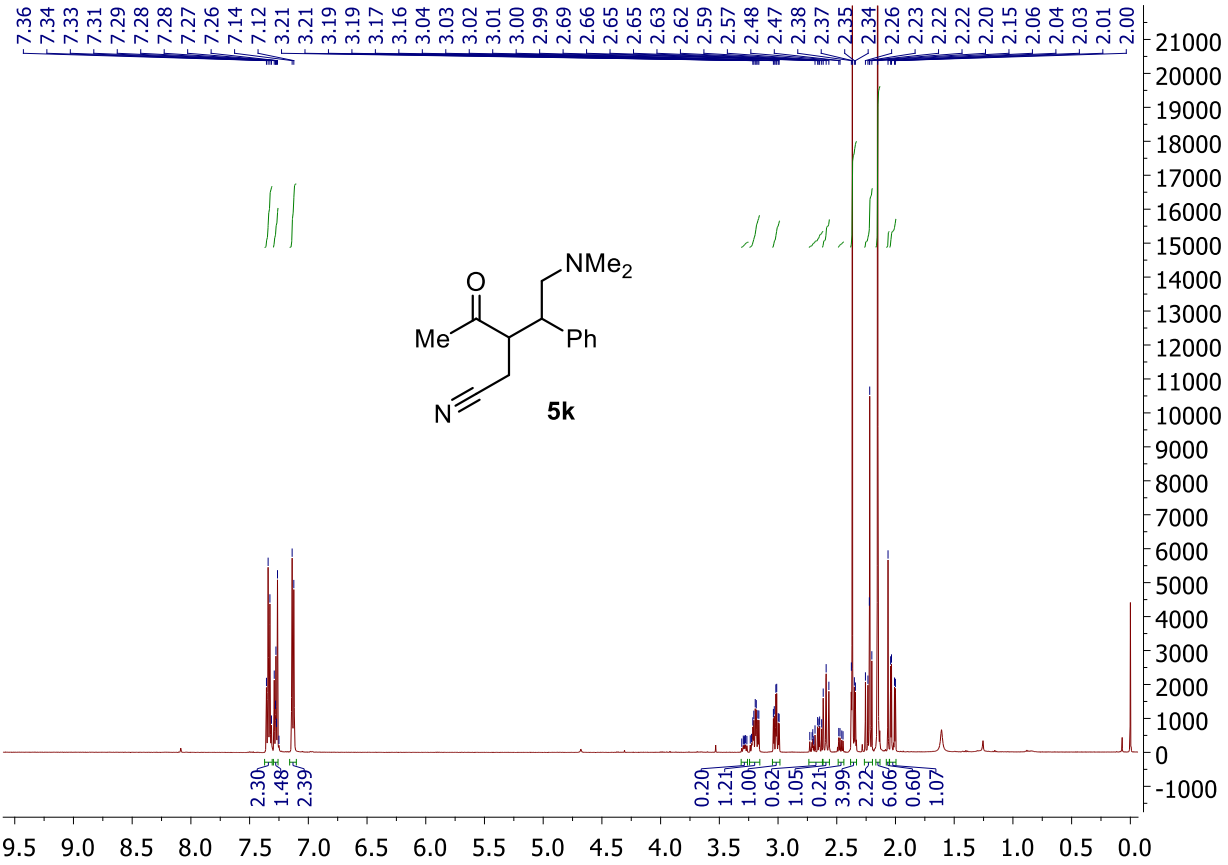
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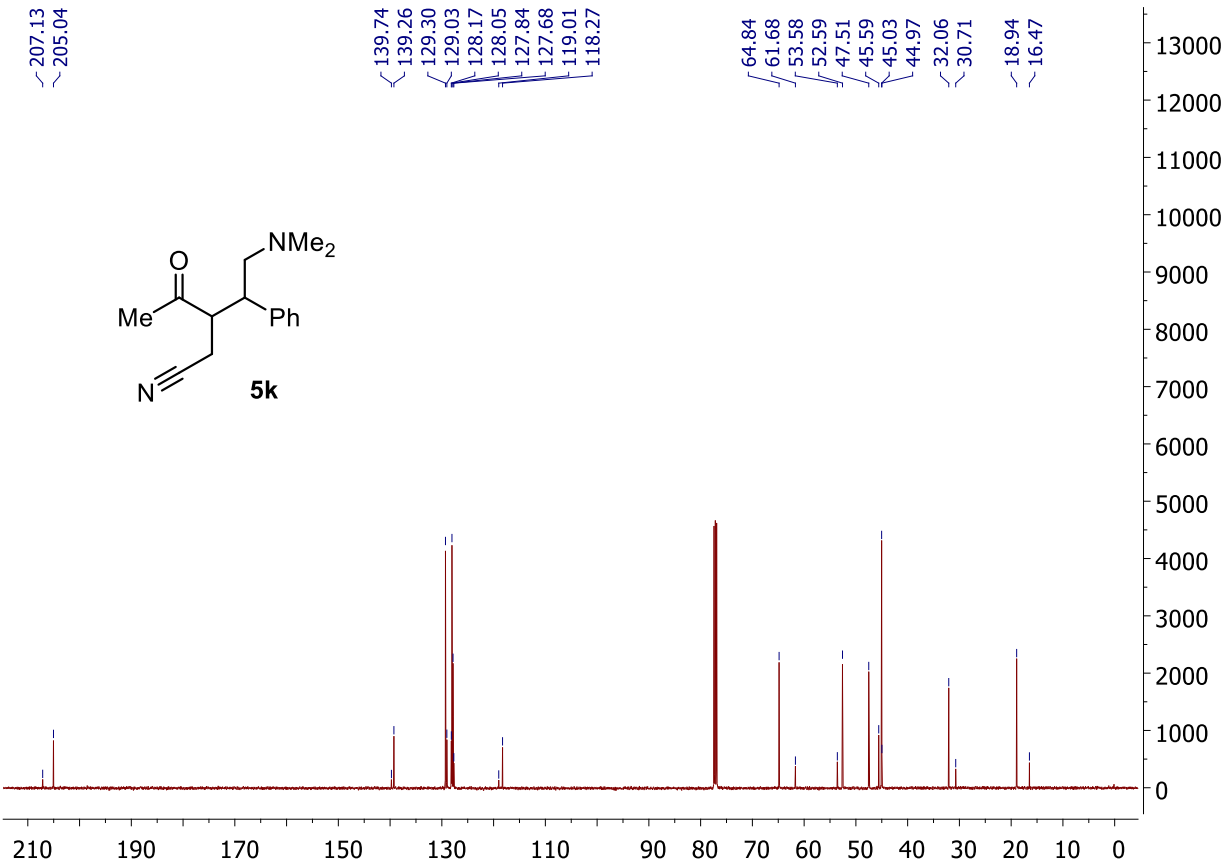
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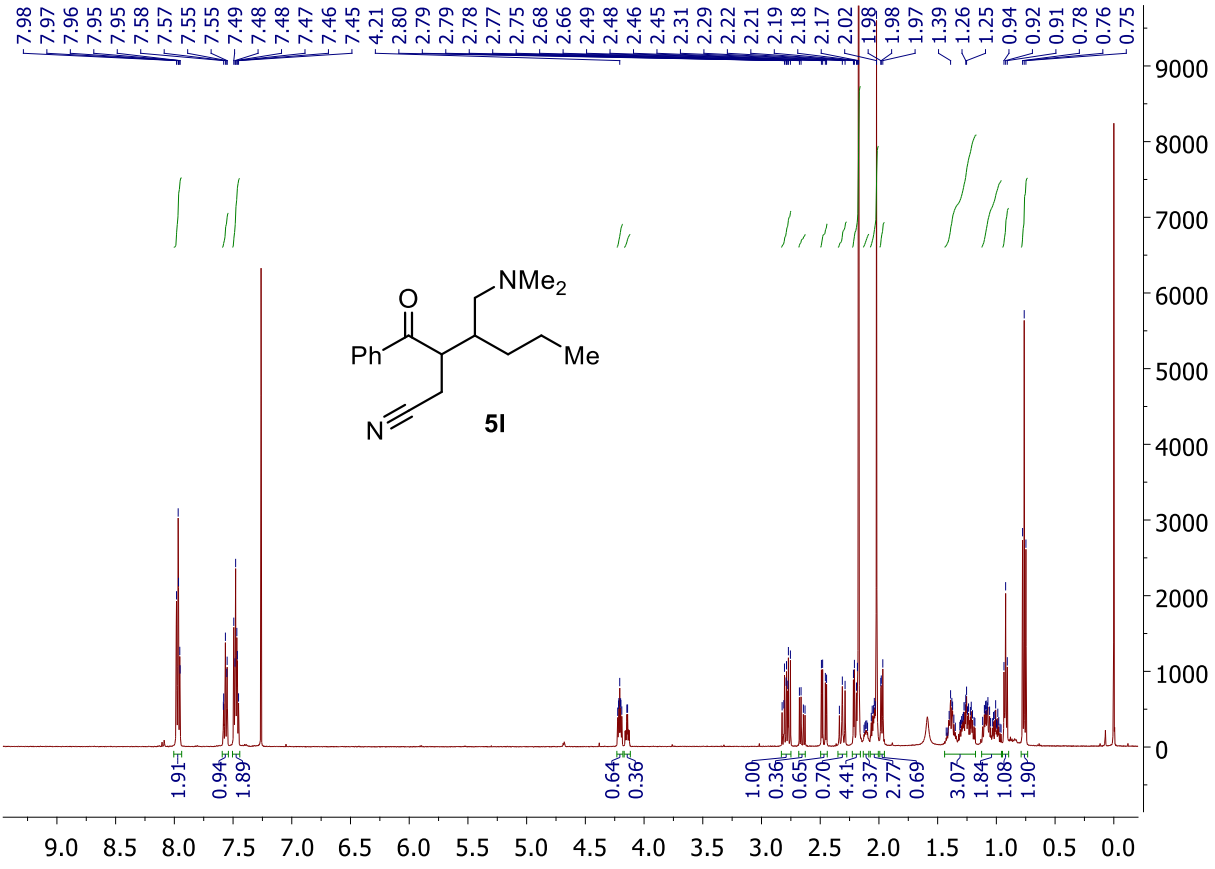
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Ph
Me
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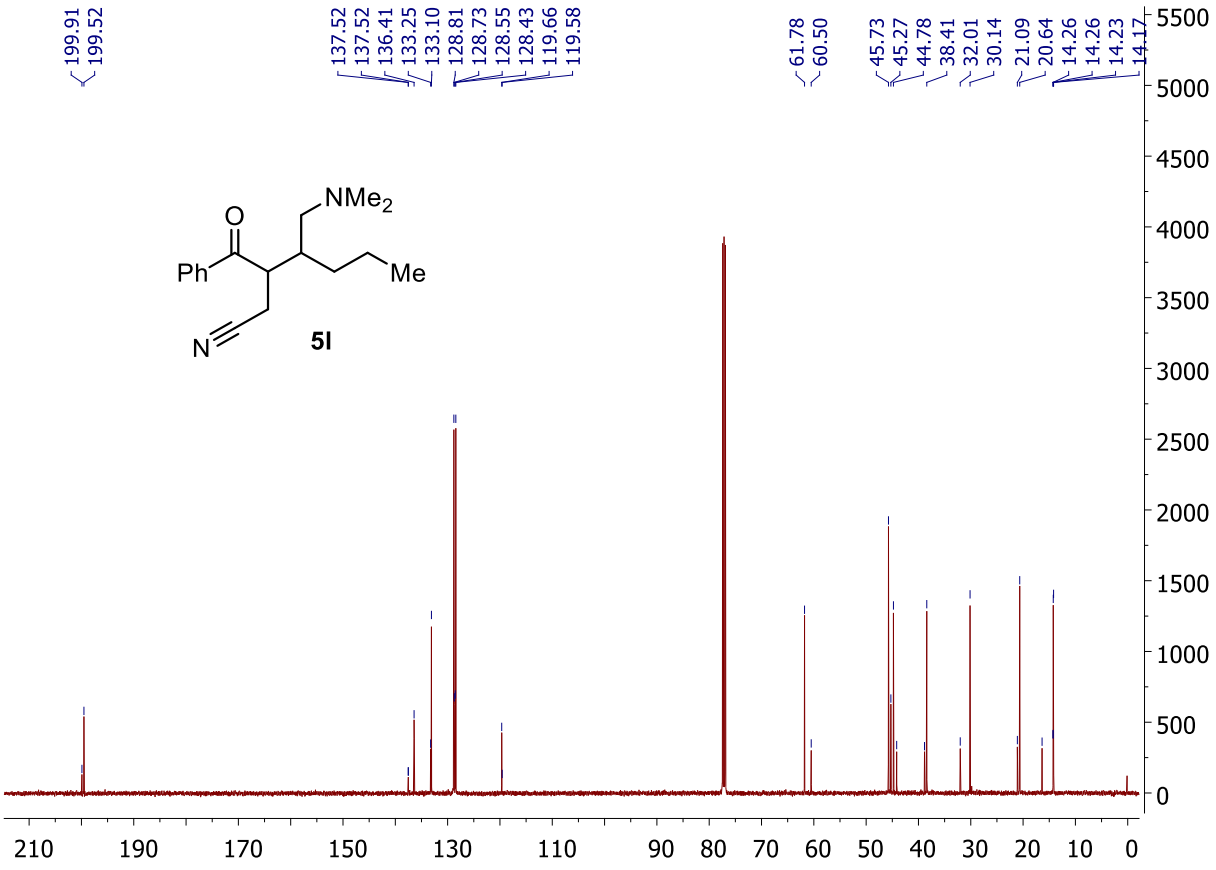
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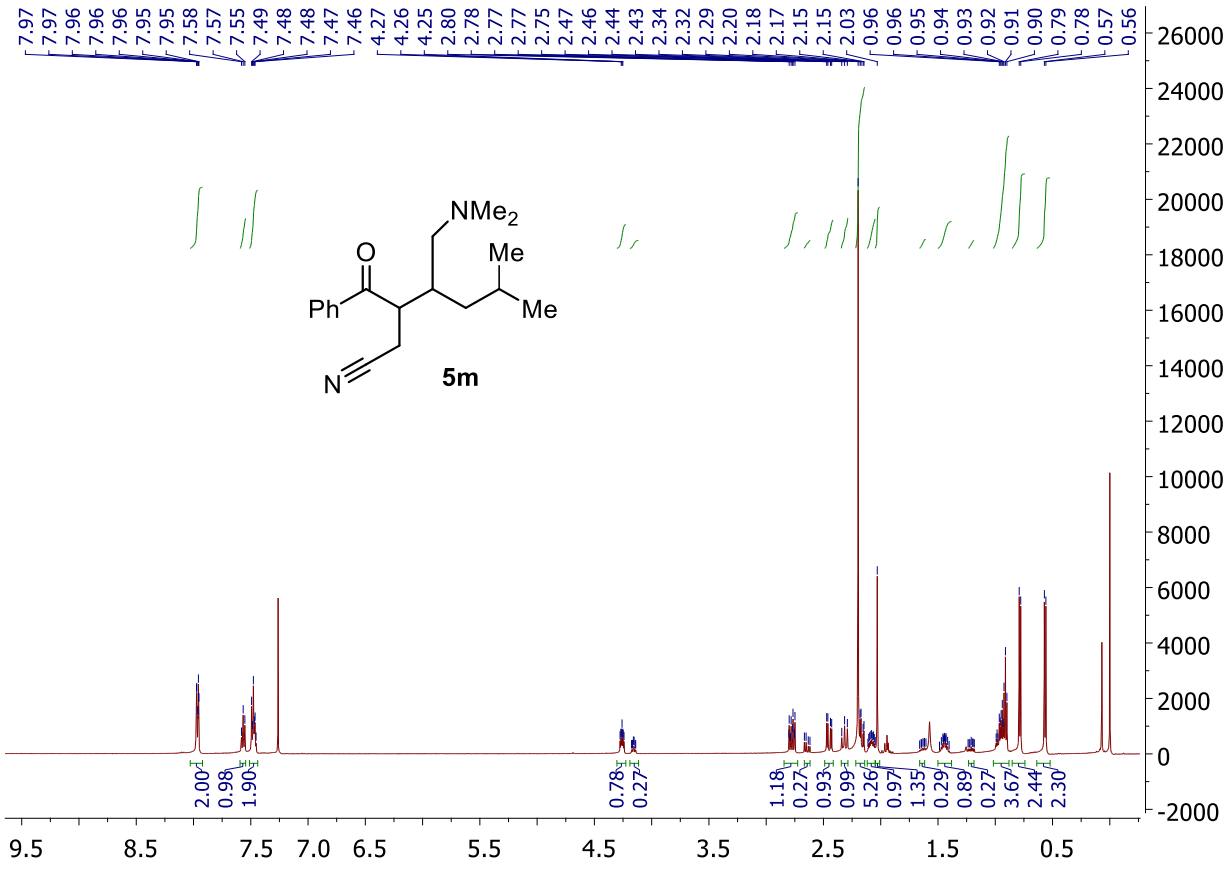
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Me
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N
5m
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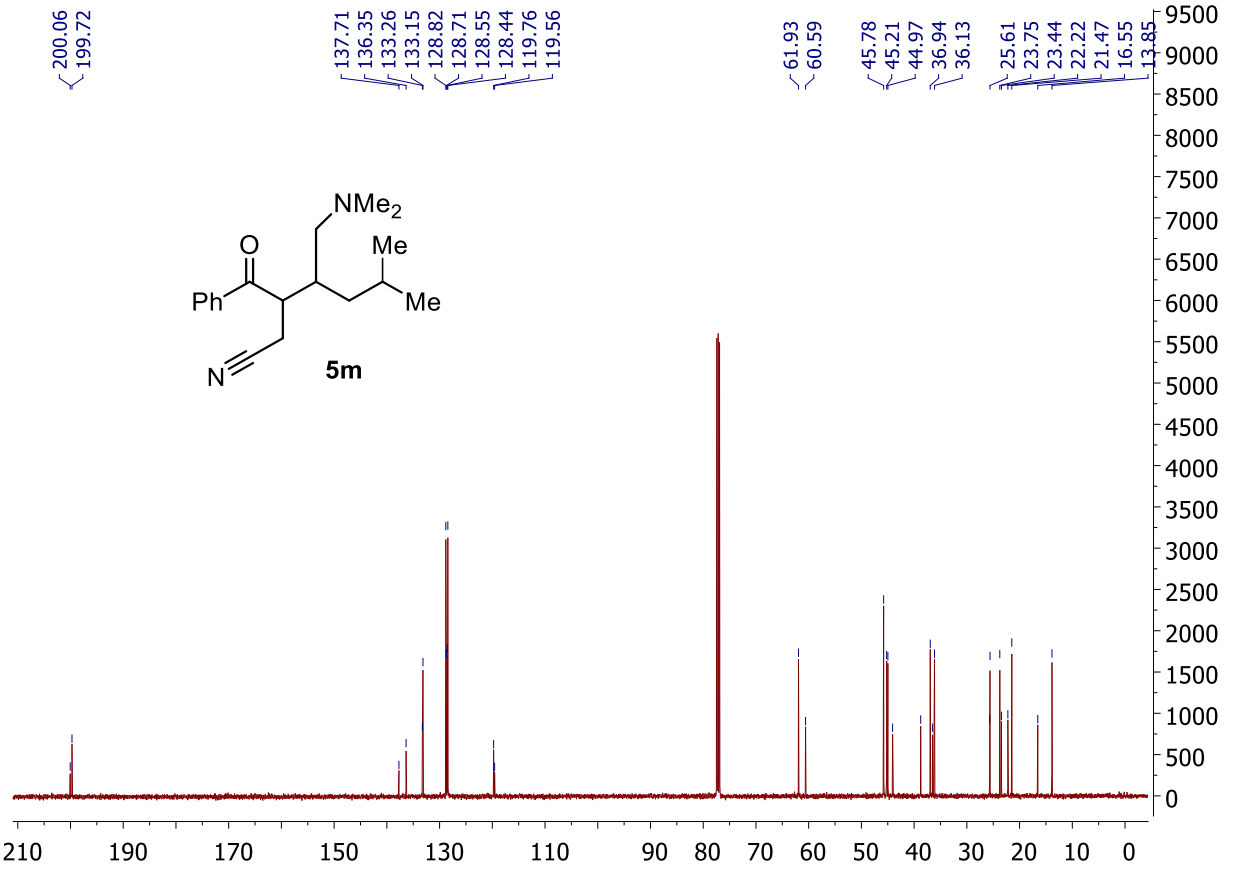
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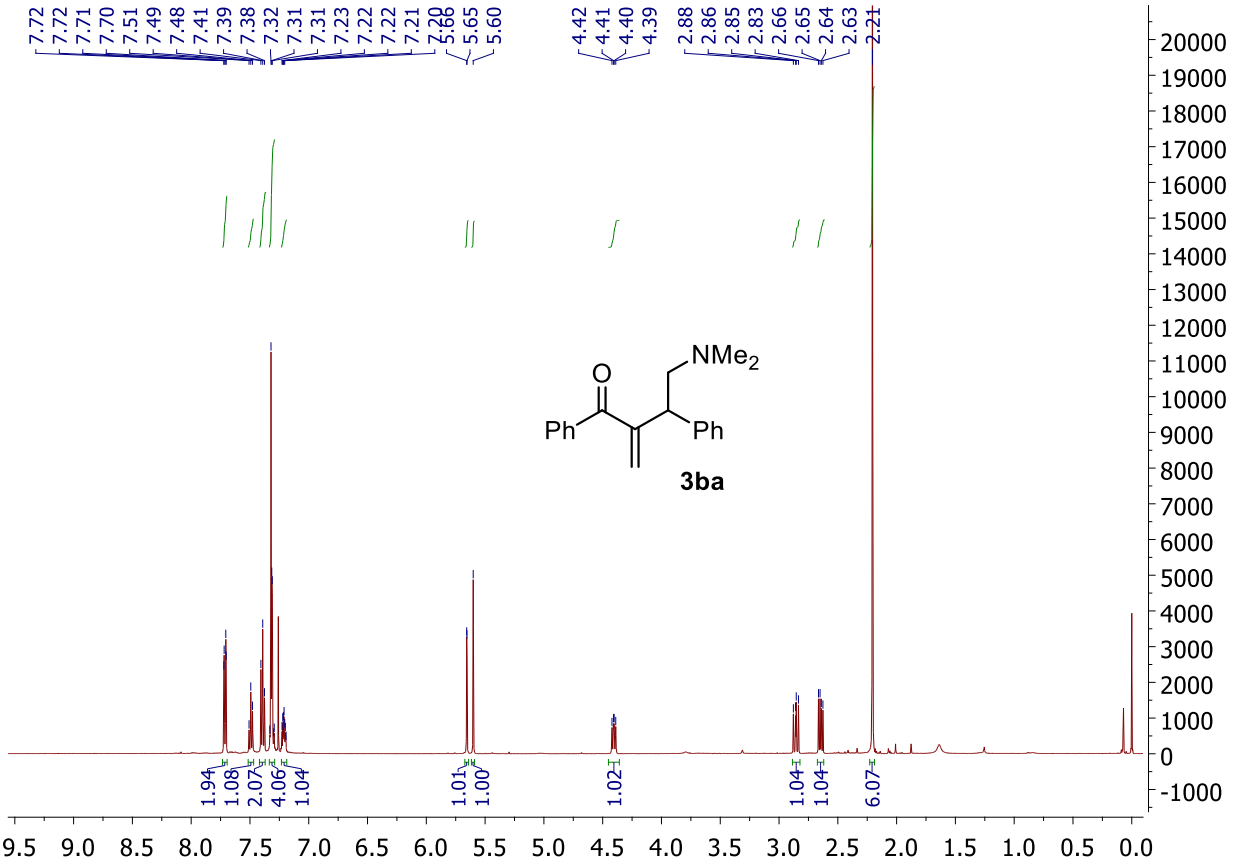
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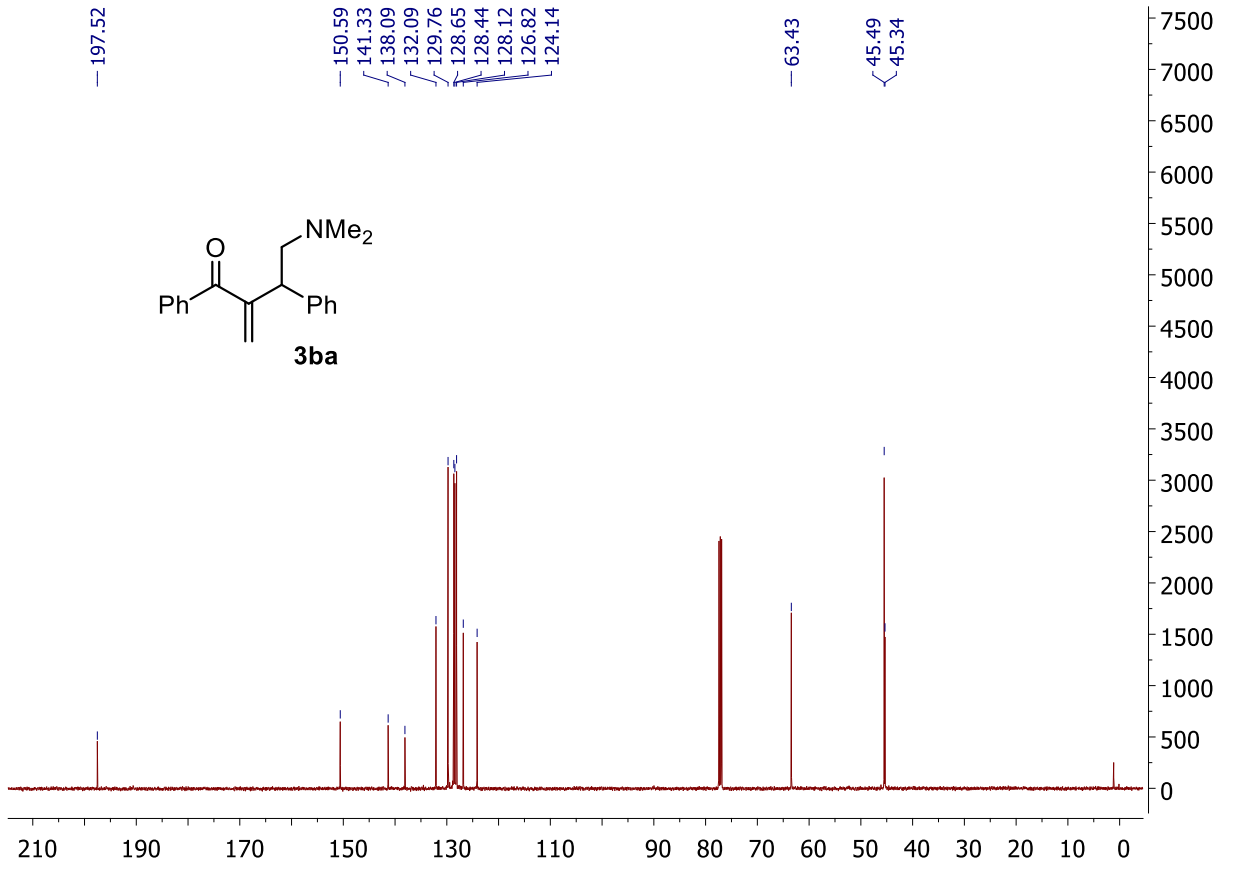
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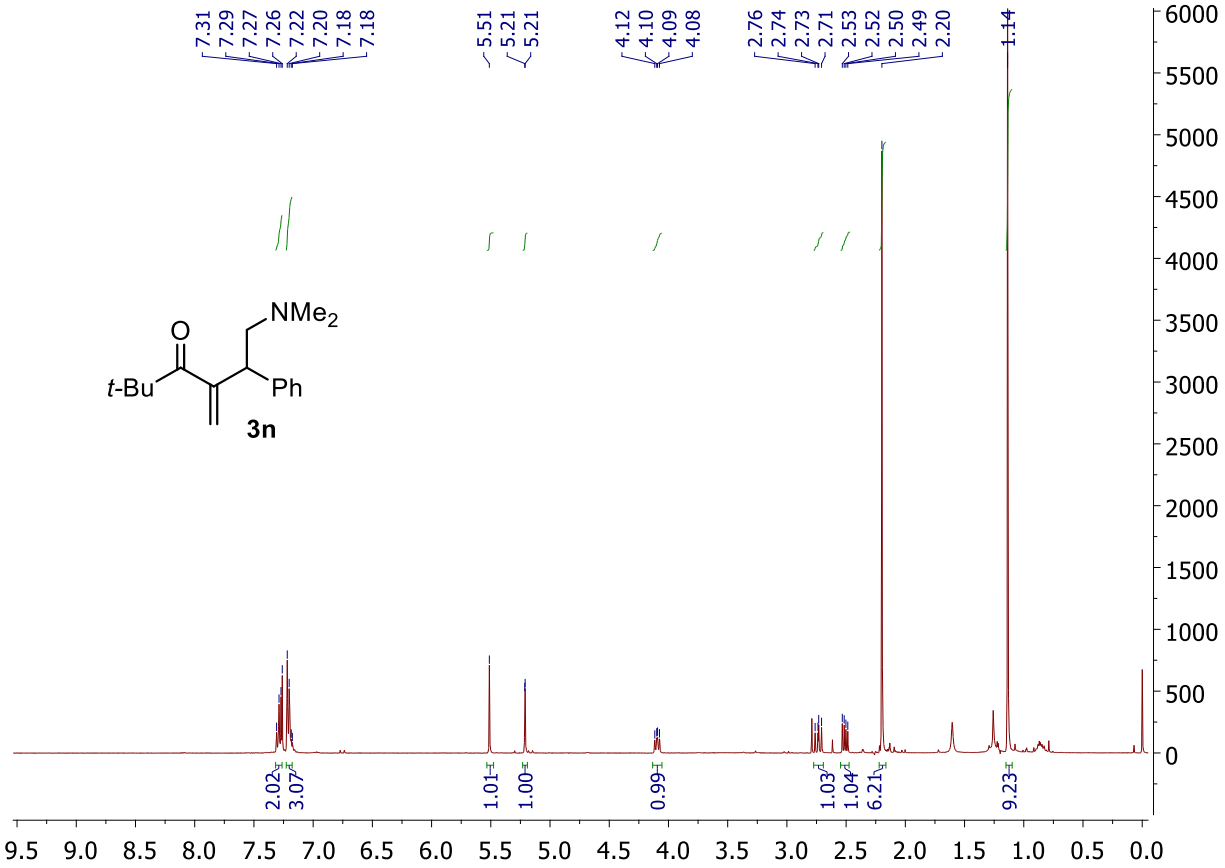
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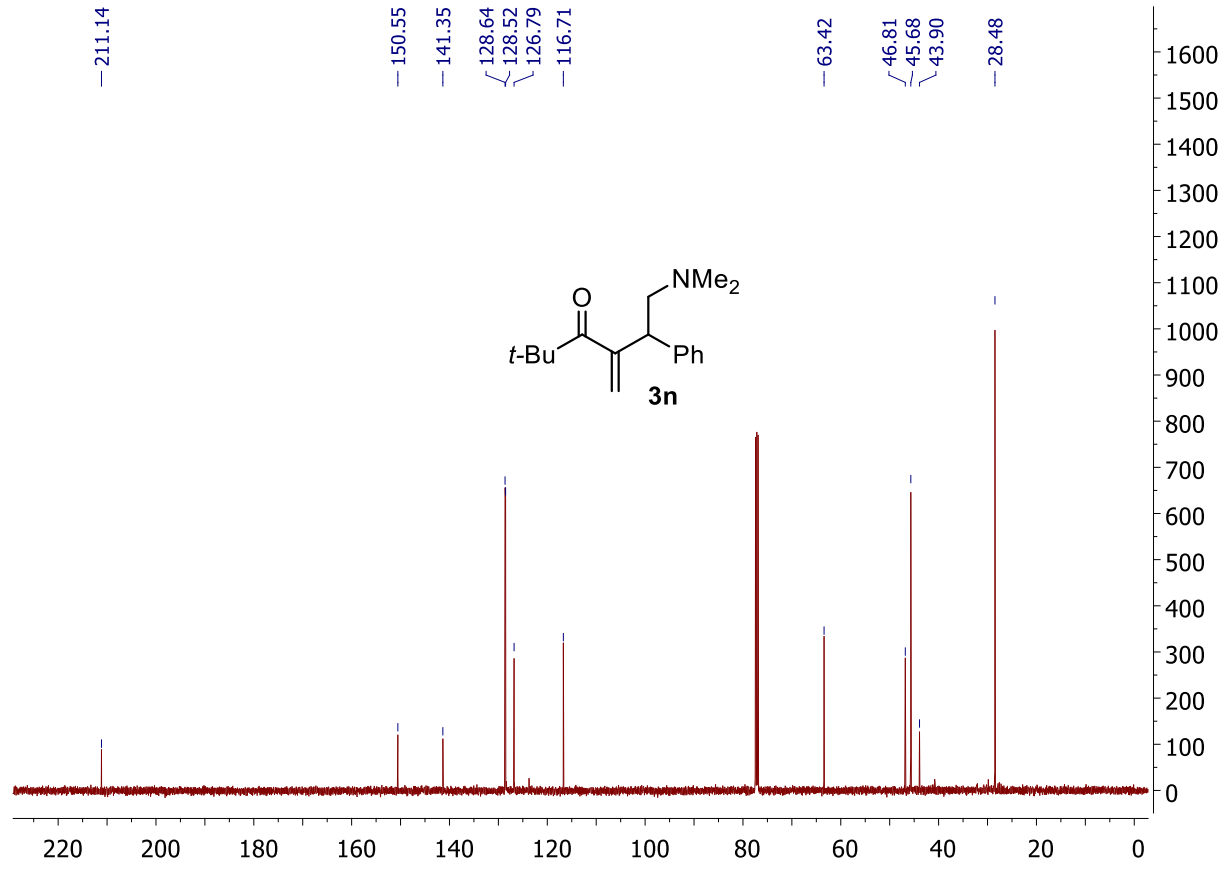
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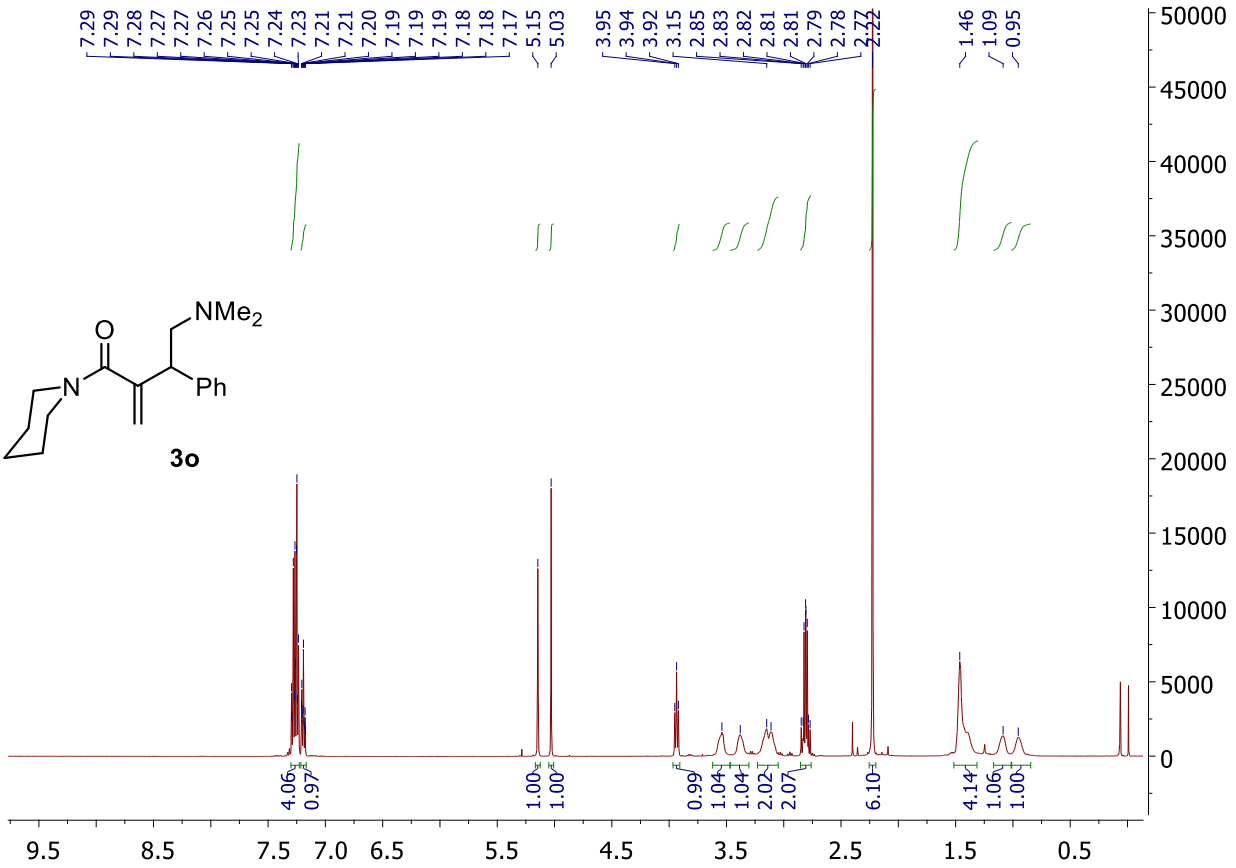
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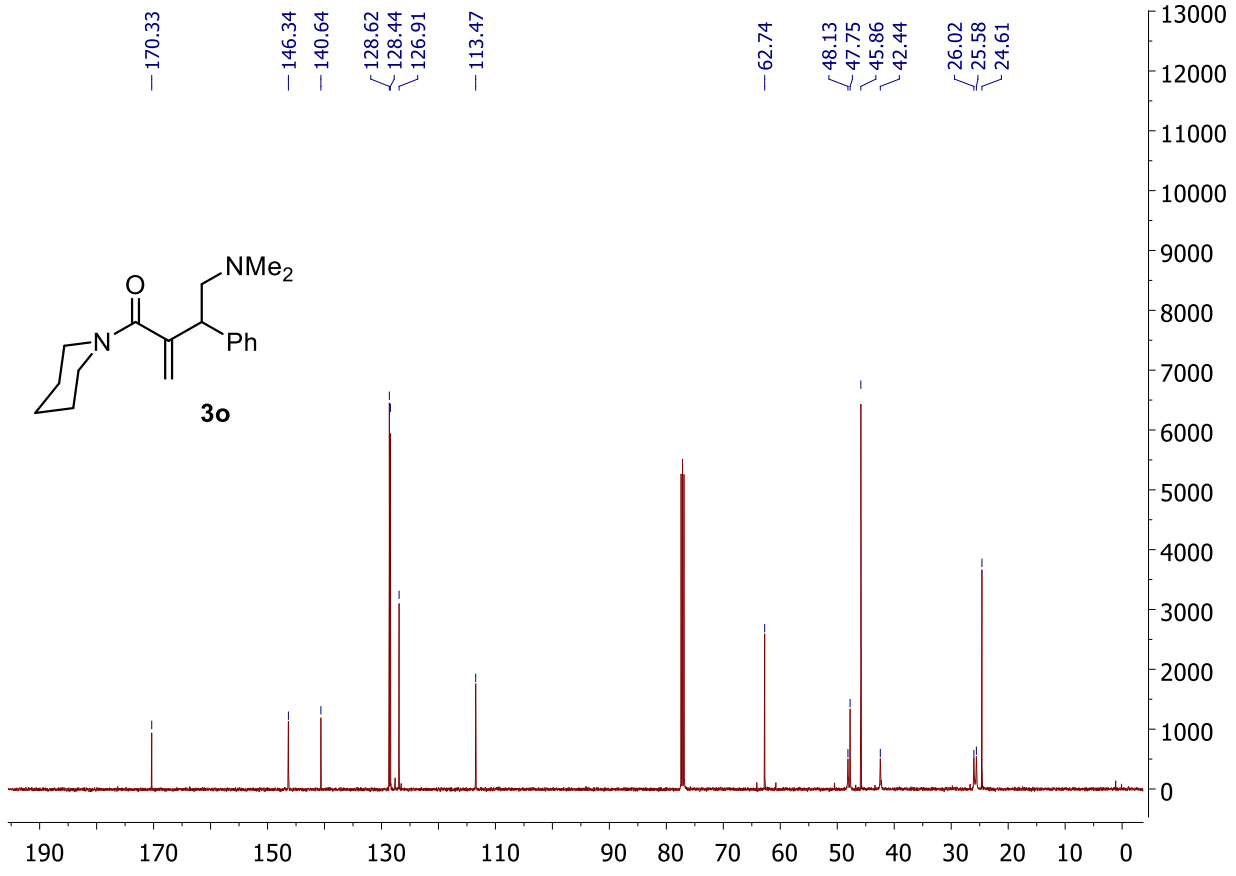
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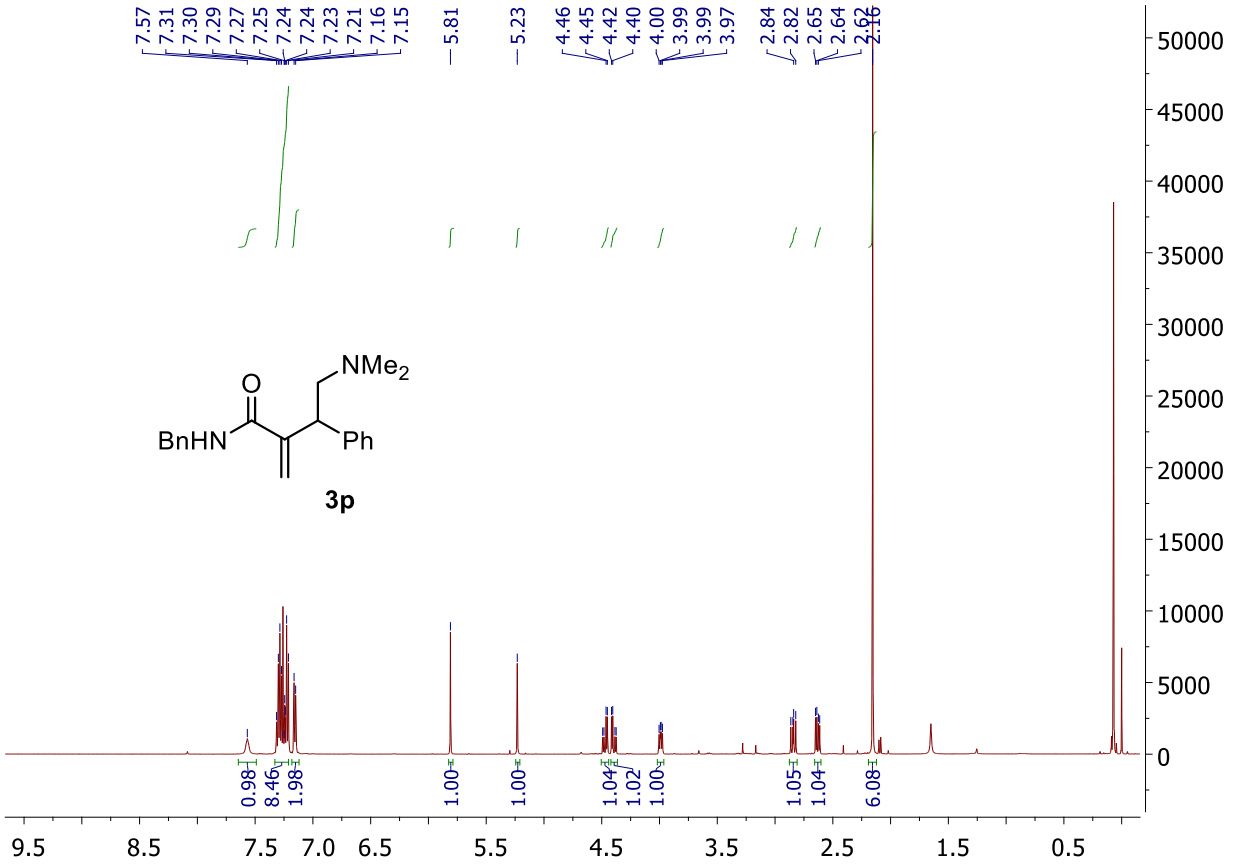
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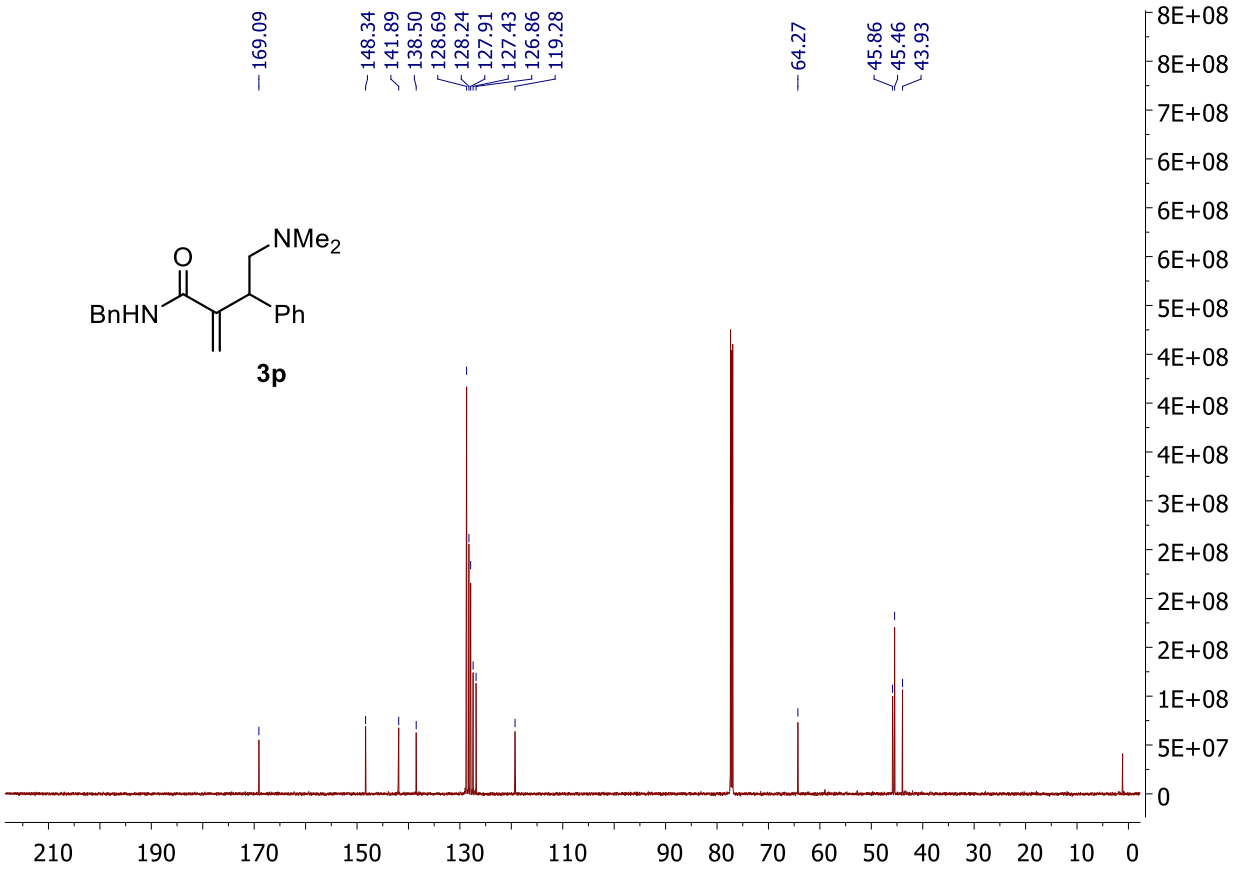
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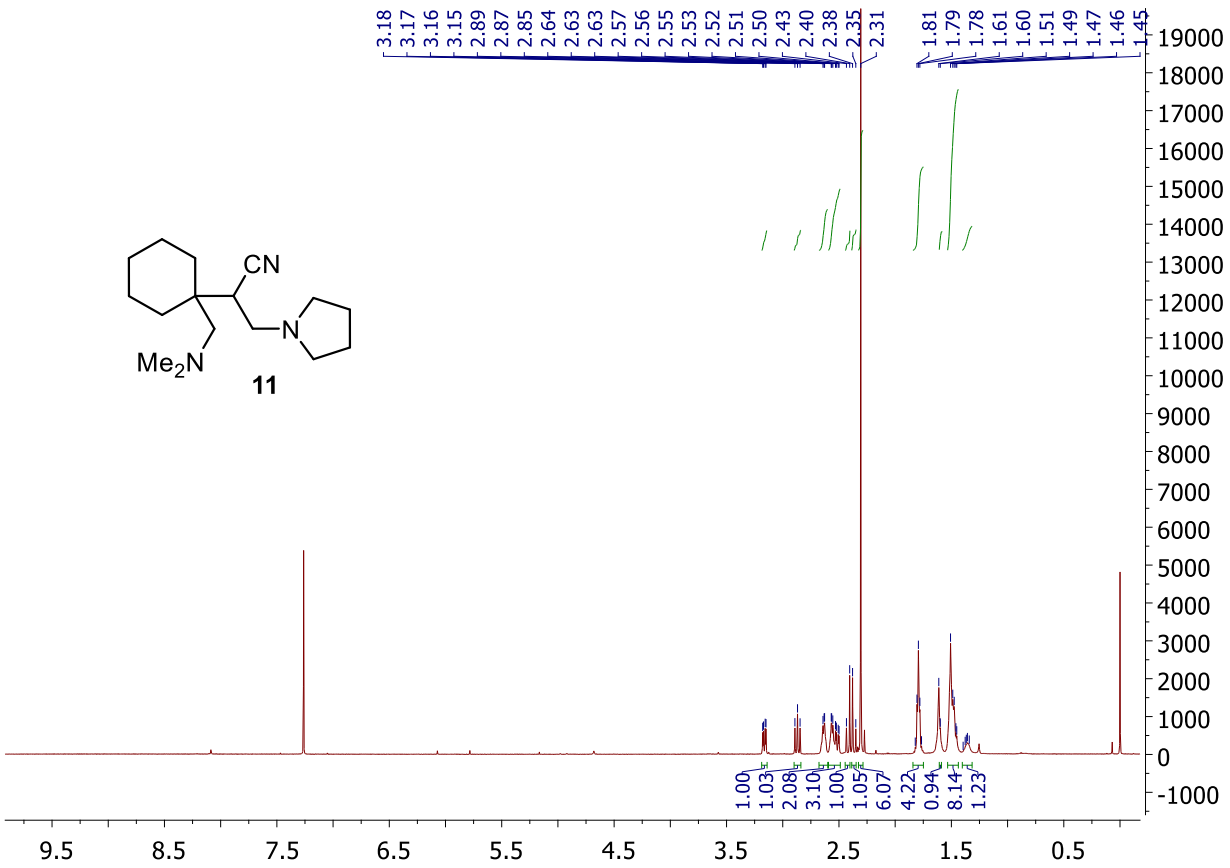
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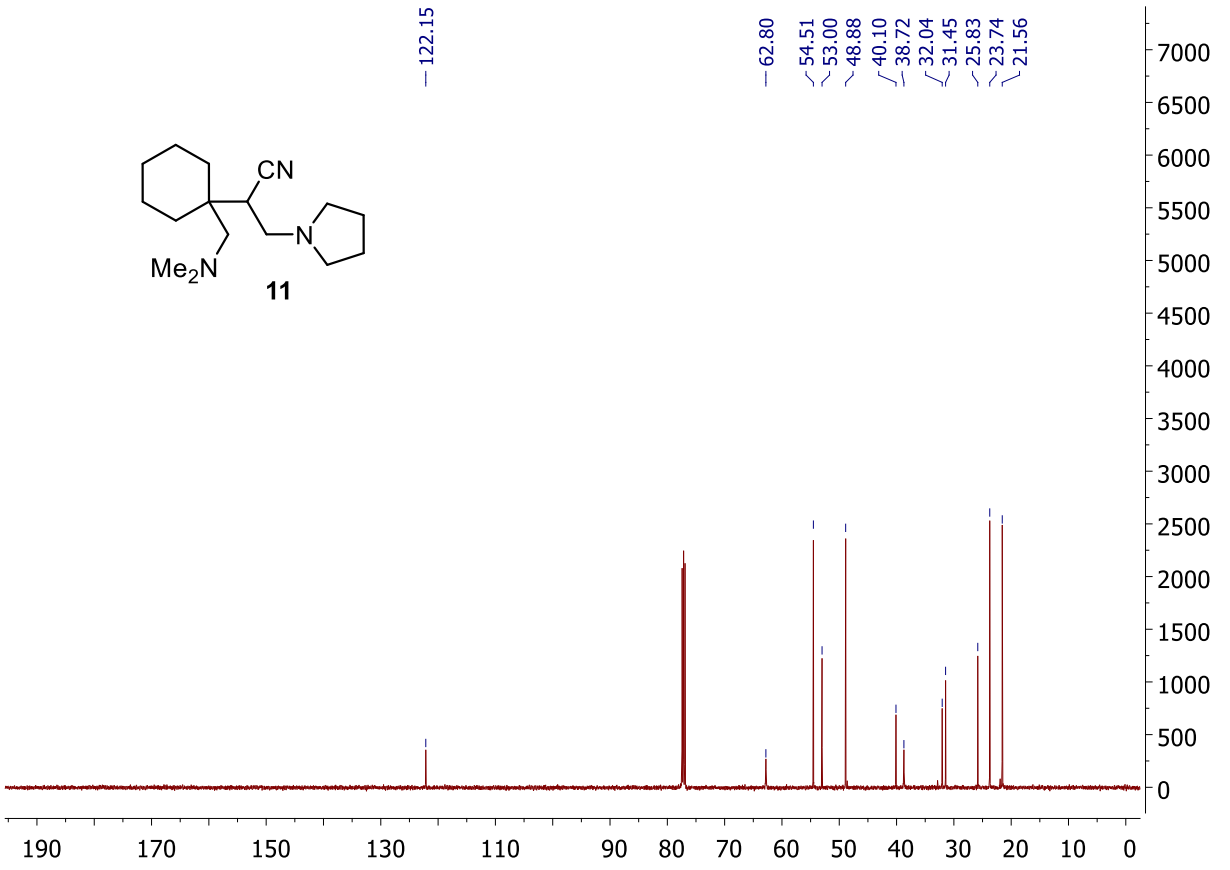
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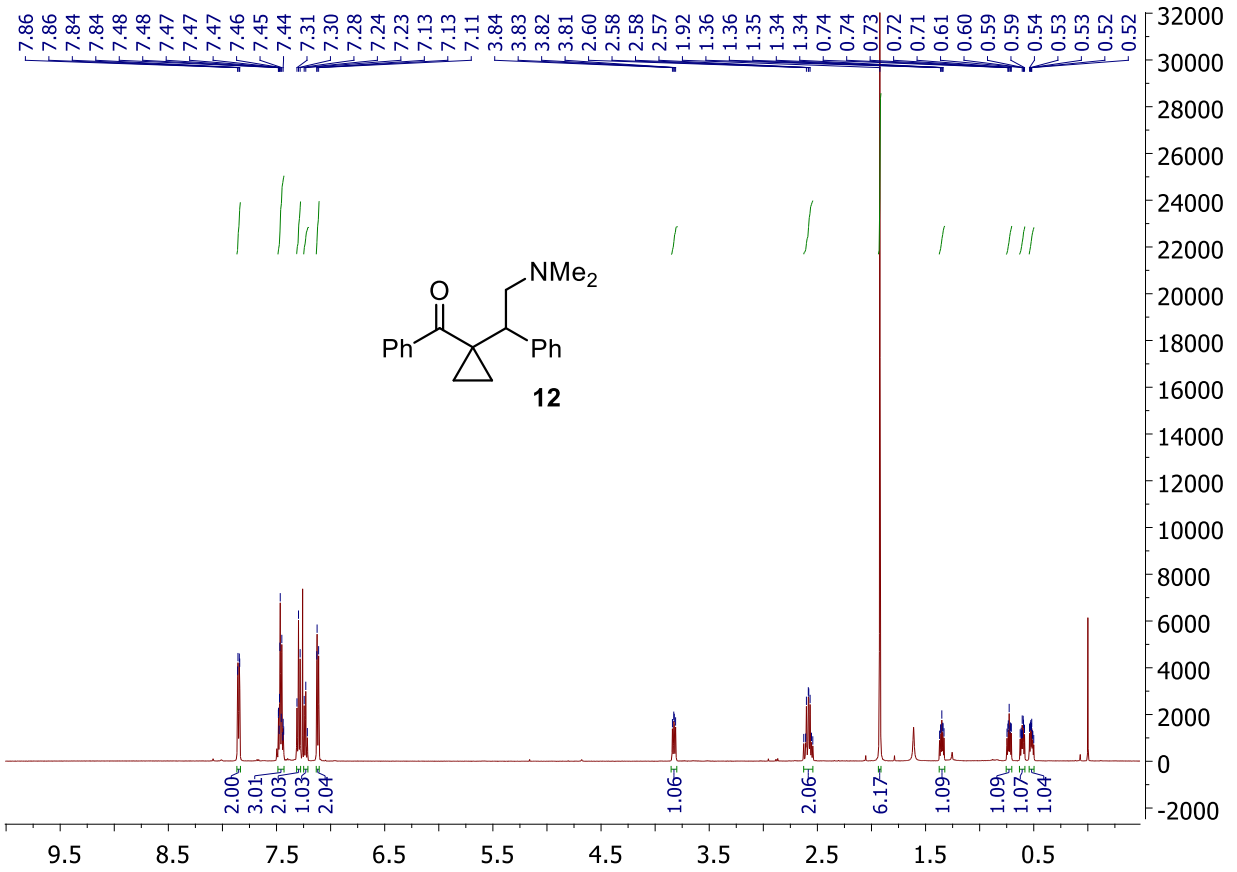
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O
Ph
Ph
12
2.00 3.01 2.03 1.03 2.04 1.06 2.06 6.17 1.09 1.09 1.07 1.04
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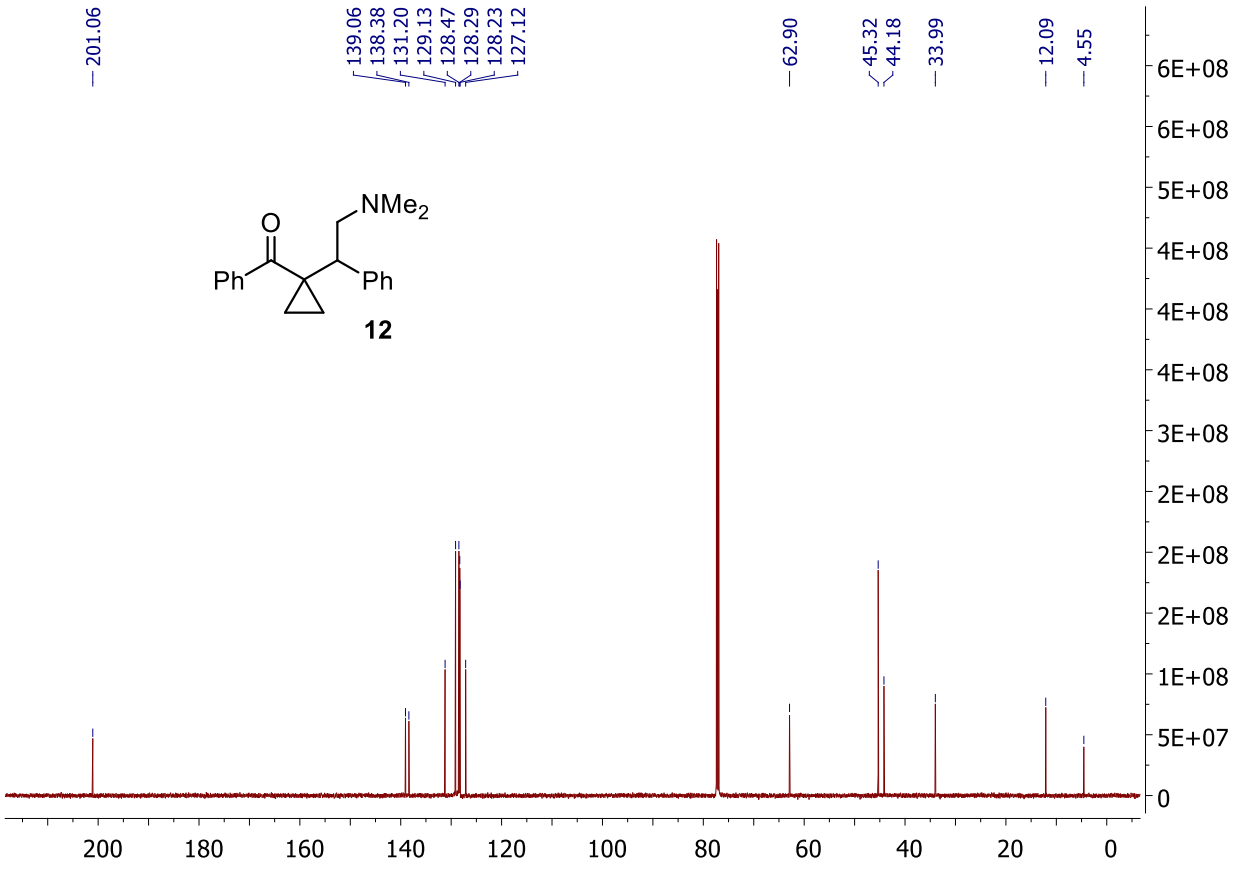
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12
6E+08 6E+08 5E+08 4E+08 4E+08 4E+08 3E+08 2E+08 2E+08 2E+08 1E+08 5E+07 0
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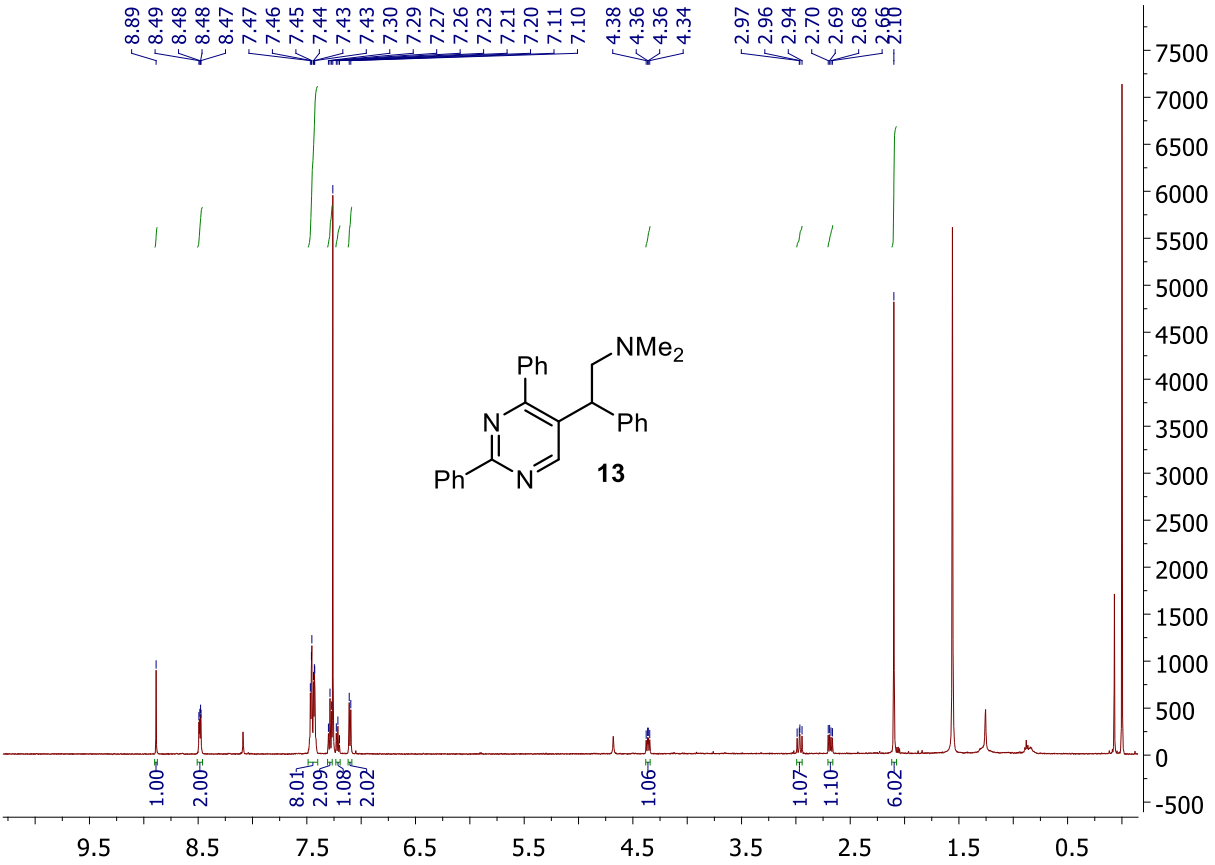
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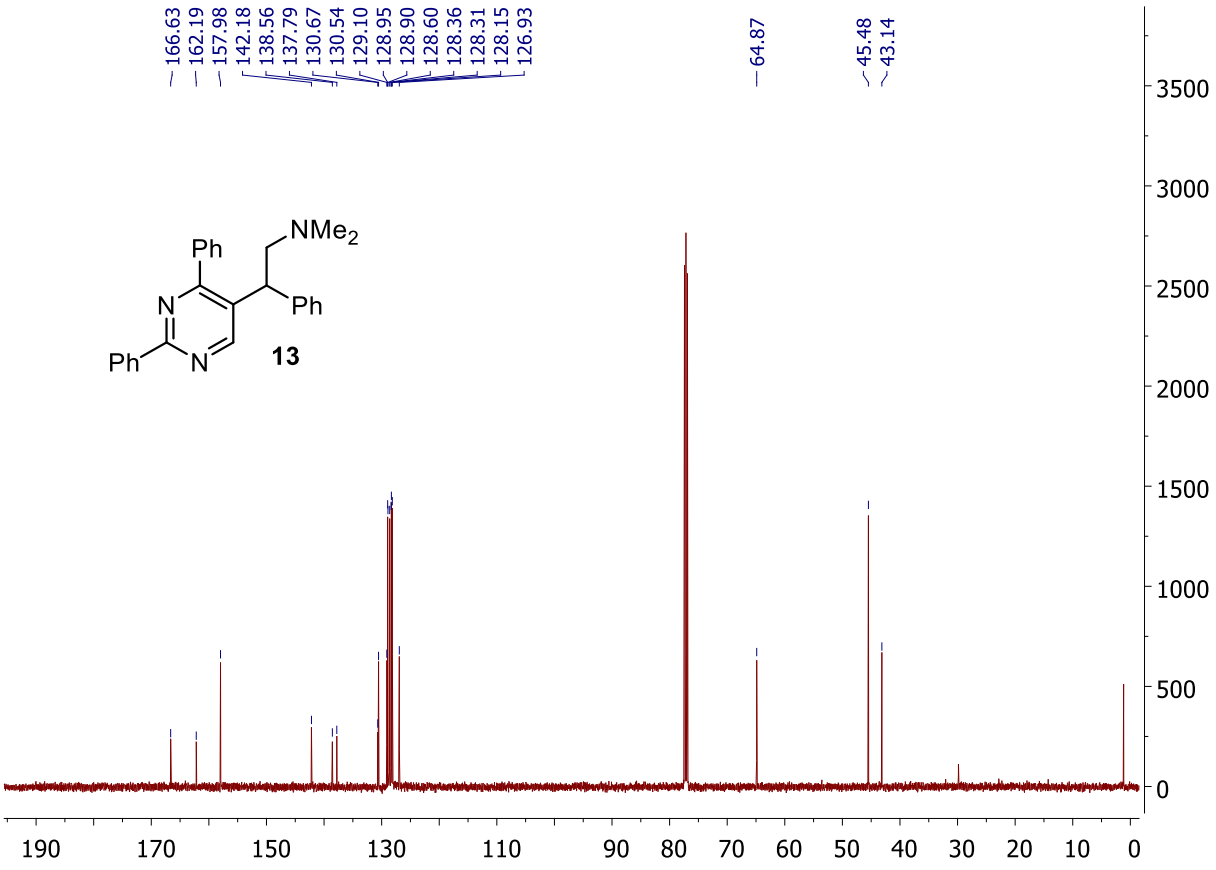
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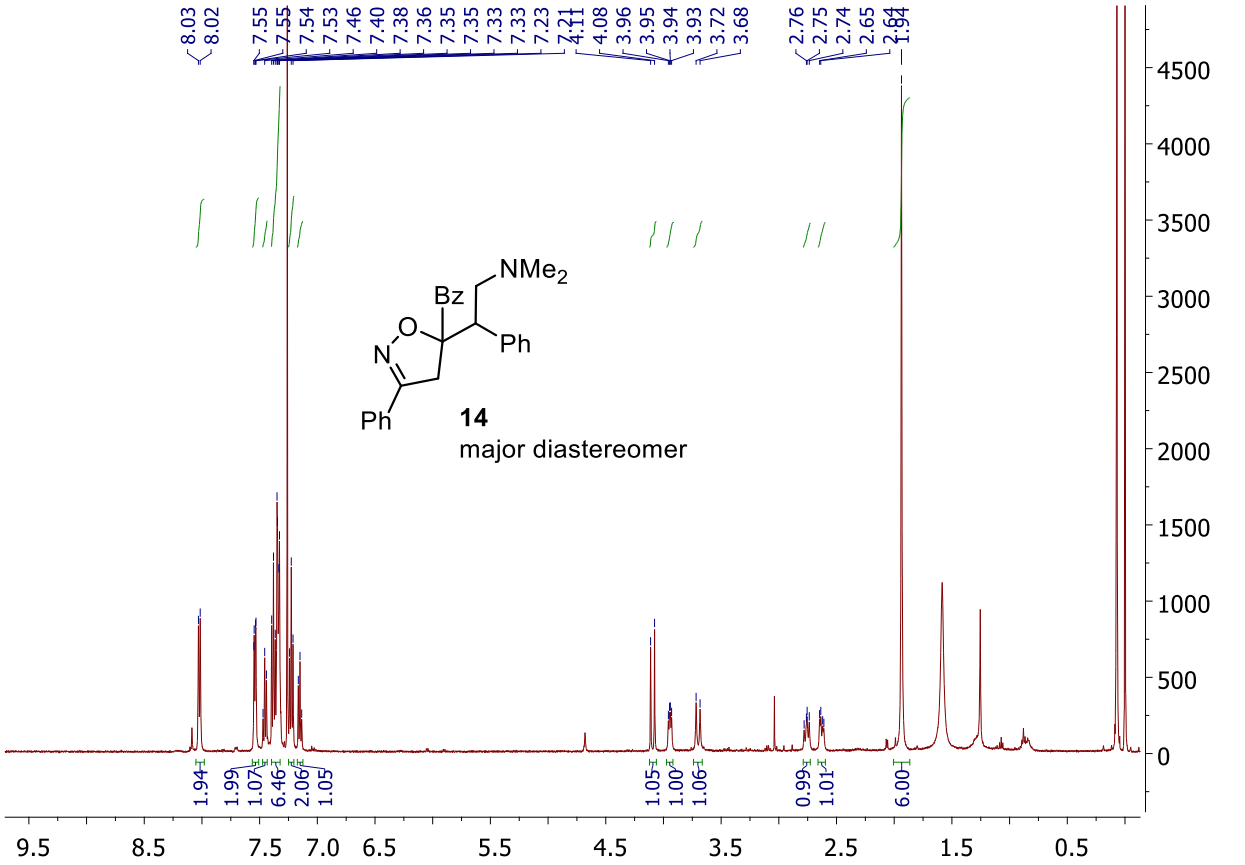
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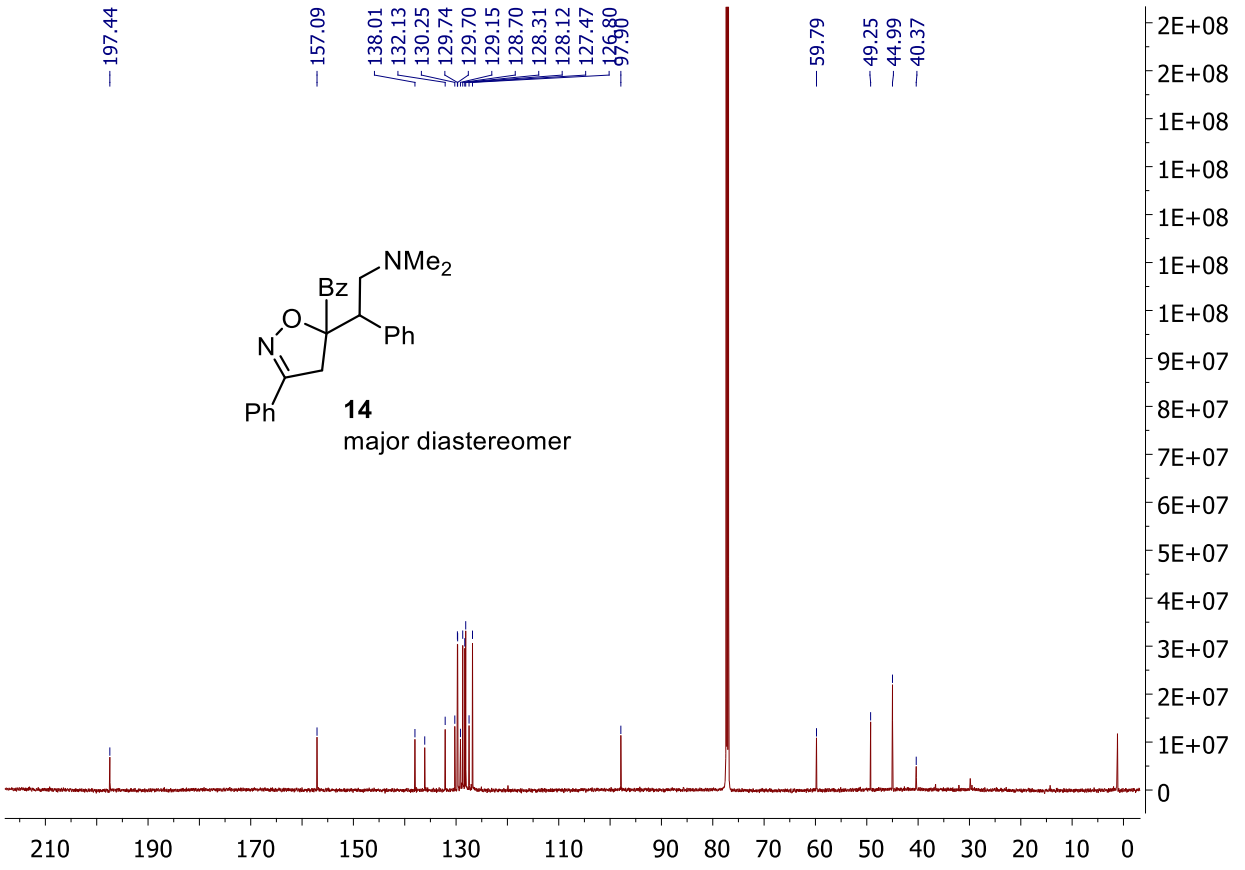
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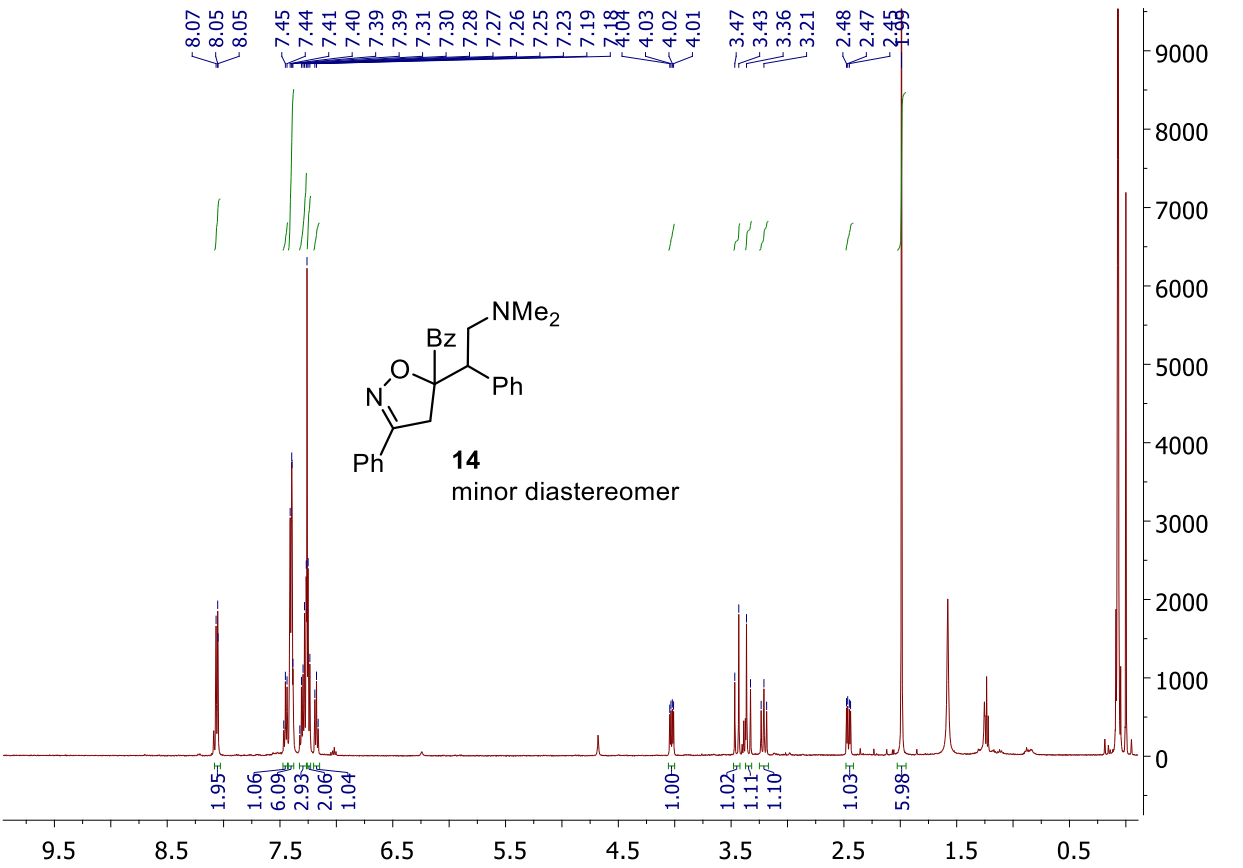
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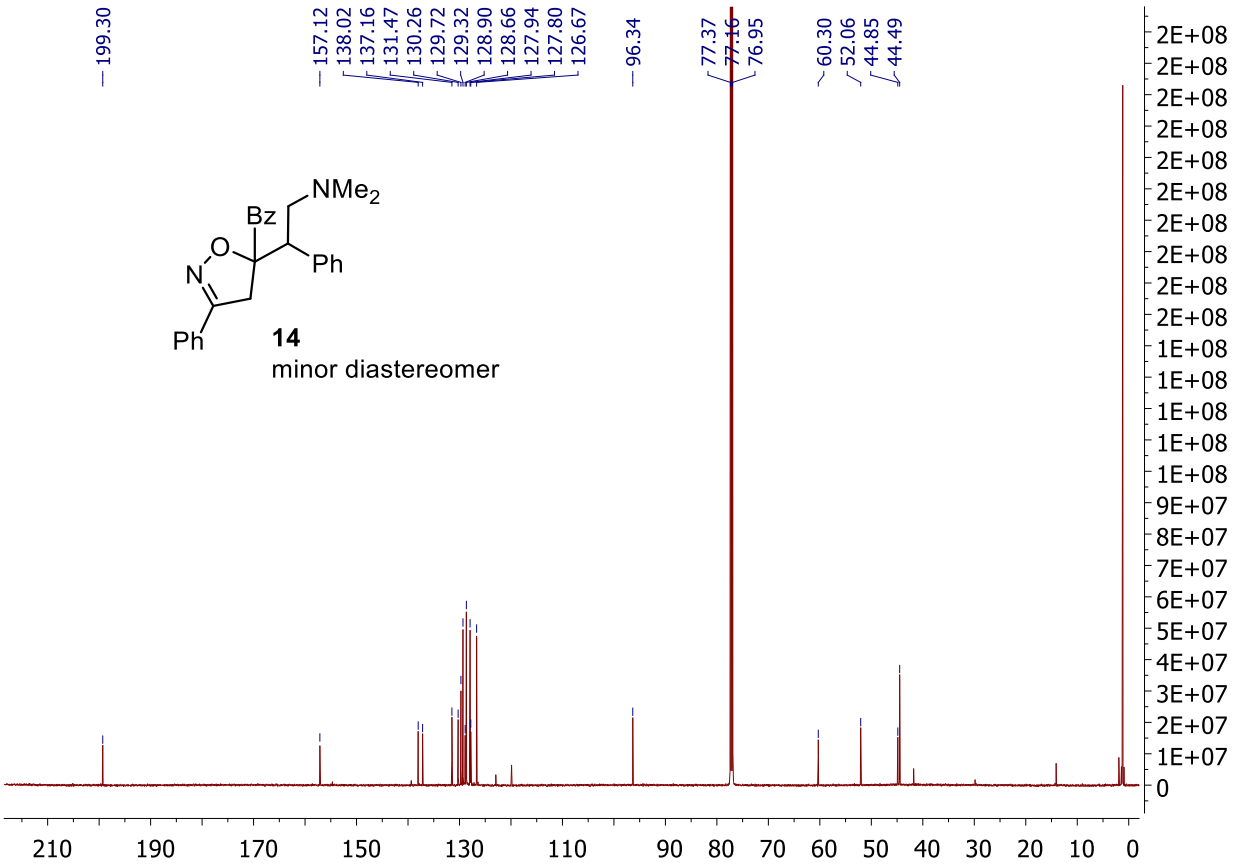
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