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Graphical Abstract

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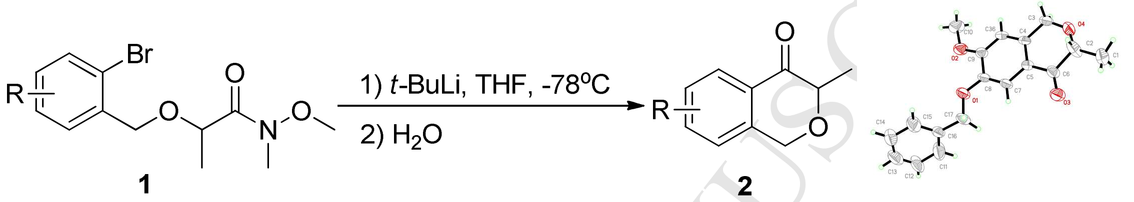

Short reaction time: 1 min.
Yields: 79%-95%.

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ABSTRACT

The synthesis of 4-isochromanones via Parham-type cyclization with Weinreb amide as the internal electrophilic group, *t*-BuLi as the lithium reagent was described. The reaction was efficient and could be completed in one minute. The application scope of this new protocol was investigated and the desired products could be obtained in good to excellent yields. Besides, the synthetic potential of this method was further demonstrated by the synthesis of natural product (±)-XJP, which was obtained in 6 steps with overall yield up to 54%.

1. Introduction

The 4-isochromanones were one kind of important scaffolds that present in some natural products such as (±)-7, 8- dihydroxy-3-methylisochroman-4-one [(±)-XJP], which exhibiting favorable pharmacological properties including antioxidant, antitumour, antibacterial activities,[1-5] and also used as key intermediates in the synthesis of natural product pentalongin derivatives.[6,7] Consequently, the synthesis of 4-isochromanones was of great interest in the field of organic chemistry and medicinal chemistry. The preparation of 4-isochromanones was conventionally carried out by Perkin condensation, Dieckmann condensation, and intramolecular Friedel–Crafts reaction.[8] Additionally, methods reported lately in the literatures for the preparation of 4-isochromanones involve Friedel–Crafts acylation of chromium-carbene-complex-derived ketenes;[9] Heck reactions followed by oxidative cleavage reactions to form the skeleton;[7] Organolithium compounds addition reaction;[10] AuCl$_3$ catalyzed cascade triggered by an internal nucleophile.[11] However, these methods generally suffered from some limitations such as low yields, multi-step reactions or expensive transition metal catalysts.

The Parham cyclization, which was the intramolecular cylization of aryllithium and an internal electrophile, has been used for the assembling of a wide array of carbo- and heterocyclic systems.[12-16] This strategy has been successfully employed in our previous work to construct 4-isochromanone skeleton with carboxylic acid as the internal electrophilic group in a total synthesis endeavor. [17] However, due to the low yield and the prolonged reaction time, the application of this reaction was restricted on our subsequent research. So it was necessary to improve this method by further efforts. It was found that the Weinreb amides were much more effective electrophiles than carboxylic acids in Parham cyclizations in some cases.[18-20] Also, there were some benefits of Weinreb amide, such as stability, ease of preparation, few side-reaction during nucleophilic addition.[21,22] Based on the findings, we investigated the feasibility of the synthesis of 4-isochromanones via Parham-type cyclization with Weinreb amides.

2. Results and discussion

In this protocol, an aryllithium generated by lithium–halogen exchange was expected to undergo an intramolecular cyclization on to the electrophilic group of the aromatic ring to provide the target compound. In order to study the influences of the electrophilic group as well as the lithium reagent on the Parham-type cyclization, the reaction profiles of substrates using different type of groups as internal electrophiles were investigated. As shown in Table 1, the internal electrophiles and the lithium reagents both played crucial roles in the reaction. When the precursors were carboxylic acid and ester, the yields were very low compared with the precursors with amides as internal

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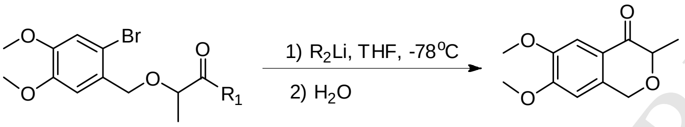
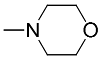
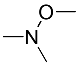
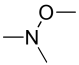
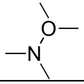
electrophiles. It should be noted that the cyclization reaction of precursor with Weinreb amide completed in just one mintute, which was much faster than the precursor with morpholine (Entrys 1-4). Moreover, it was interesting that the reaction was sensitive to the lithium reagents. The desired product was obtained in excellent yield when using *t*-BuLi as the lithium reagent, however, the use of *n*-BuLi was less successful and led to butylated byproduct. Obviously, the steric effect was the key reason of the different profiles of the reactions. Thus, a more bulky and less nucleophilic reagent MesLi was chosen for the lithium–halogen exchange. However, MesLi led to incomplete conversion even with prolonged reaction time (Entrys 4-6). The best condition was the compound with Weinreb amide as the precursor and *t*-BuLi as the lithium reagent (Entry 4). The use of Weinreb amide as internal electrophiles clearly promoted the reaction. This observation was explained by a complex-induced proximity effect (CIPE).[23-25] Lithium–halogen exchange could be favored first by coordination of the organolithium to the amide group, and then the relatively stable internal chelate tetrahedral intermediate formed after cyclization was favored to the reaction, as depicted in Scheme 1.

Table 1. Optimization of the substrates and lithium reagents.[a]

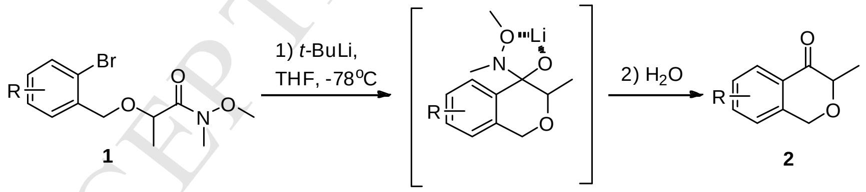


Entry	R_1	R_2Li	Time	Yield[b](%)
1	$-OCH_2CH_3$	*t*-BuLi	4 h	Trace
2	-OH	*t*-BuLi	4 h	50
3		*t*-BuLi	4 h	87[c]
4		*t*-BuLi	1 min	91
5		*n*-BuLi	1 min	42
6		Mes-Li	4 h	70

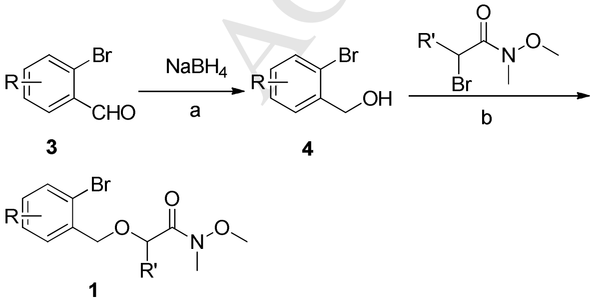
[a] Reagents and conditions: 1.2 equiv of *n*-BuLi (1.2 equiv of Mes-Li or 2.2 equiv of *t*-BuLi), and 1.0 equiv of substrate in THF, -78 °C, then H_2O.

[b] Isolated yields.

[c] The starting material cannot converse completely even with prolonged reaction time.



Scheme 1. The internal chelate after cyclization

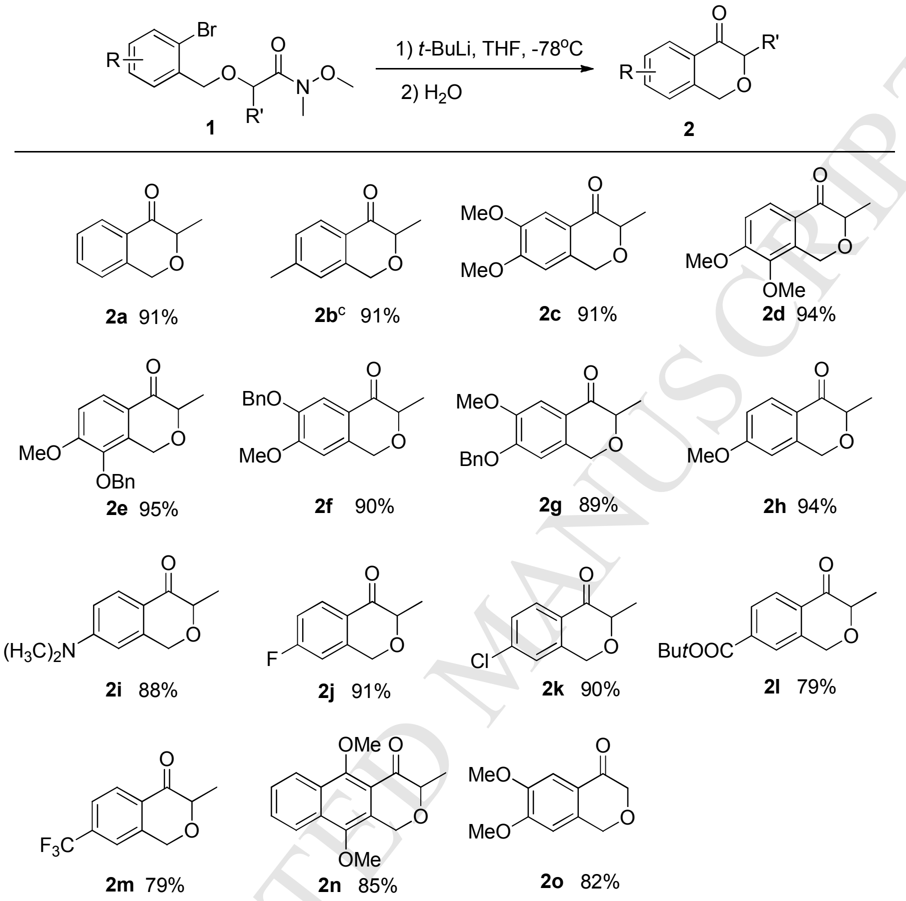


Reagents and conditions: (a) $NaBH_4$, rt, MeOH, 10 min, 95%-99% yields; (b) NaH, rt, dry DMF, 30 min, 90%-99% yields.

Scheme 2. Synthesis of the precursors with Weinreb amides **1**.

Subsequently, the application scope of this new protocol was investigated. Firstly, the precursors of Weinreb amides **1** were prepared by alkylation of the corresponding (2-bromophenyl) methanol **4** with 2-bromo-N-methoxy-*N*-methylacetamide[26] under standard conditions in excellent yields (Scheme 2). Then we applied the optimized condition to various substituted precursors for exploring the substrate scope. As shown in Table 2, in general, the precursors tested could be smoothly converted to the desired products in good to excellent yields regardless of the different substitutions on the aromatic ring. Clearly, substrates with electron-donating groups on the aromatic ring gave better yields than electron-withdrawing groups. The substrates bearing methyl, methoxy, benzyloxy, dimethylamino groups gave the corresponding products in 88%-94% yields (**2b-2i**), while the cyclizations of the substrates with trifluoromethyl group and ester group on the aromatic rings took place in moderate yields (**2l**-**2m**). The products with fluoro- and chloro-groups were obtained in 90%-91% yields (**2j**-**2k**). Interestingly, electron-donating groups at C6 position on the aromatic ring seemed to favor the reaction (**2c** vs **2d**, **2e** vs **2f**, **2g**). It was worth noting that the compound **2n** was a key intermediate in synthesis of 3-methylpentalongin, from which we could easily synthesize the final product via the reported route.[7] Additionally, the product **2f** was confirmed by NMR, MS analysis along with X-ray diffraction determination (Fig. 1). When we changed the 3-methyl group by hydrogen atom, the desired product was also obtained in 82% yield (**2o**). However, we still could not get the precursor of **1** according to the Scheme 2 when the 3-methyl group was replaced with aromatic groups such as a phenyl group.

Table 2. Preparation of 4-isochromanones[a,b]



[a] Reagents and conditions: 2.2 equiv of *t*-BuLi, and 1.0 equiv of **1** in THF, -78 °C, 1 min.

[b] Isolated yields.

[c] 3.0 equiv *t*-BuLi was required.

Then, the protocol found here was applied to the synthesis of natural product (±)-XJP. (±)-XJP was a structurally unique 4-isochromanone compound recently isolated from the peel of *Musa sapientum* L., and was endowed with potent anti-hypertensive activity. Although the total synthesis has been achieved via different synthetic routes, the overall yield were not satisfying[17, 28-29]. Herein, we would like to report the synthesis of the (±)-XJP via the new explored methodology (Scheme 2).

The synthesis was started with the bromobenzyl alcohol **8**, which was synthesized from the commercially available benzaldehyde **5** via a routine synthesis in 88% overall yield in three steps[30, 31]. The precursor with Weinreb amide **9** was prepared by alkylation of the corresponding (2-bromophenyl) methanol **8** with 2-bromo-*N*-methoxy-*N*-methyl propanamide under standard condition in 95% yield. With the compound **9** in hand we turned our attention to the construction of the skeleton of isochroman-4-one. Gratifyingly, the cyclization reaction following the previously described annulation protocol proceeded

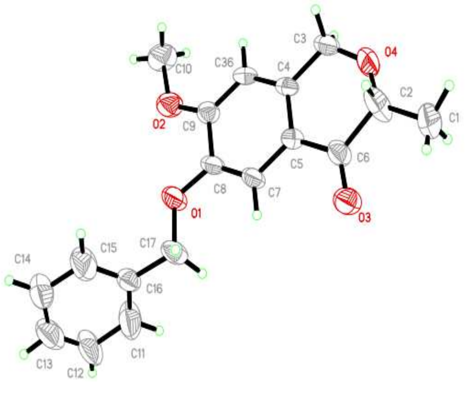
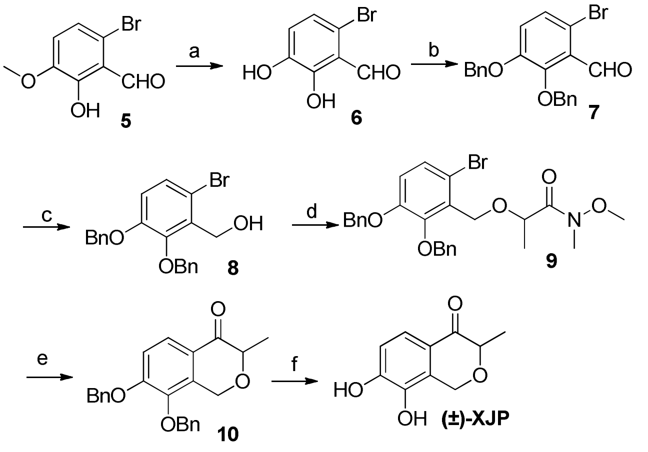


Figure 1. X-ray crystal structure of **2f**.

smoothly to afford the 4-isochromanone **10** in 93% yield, which was then converted to (±)-XJP via a deprotection operation. The synthesis was accomplished efficiently in 6 steps with overall yield up to 54%.



Reagents and conditions: (a) BBr_3, 0 ^{o}C, dry CH_2Cl_2, 3 h, 95% yield; (b) BnBr/K_2CO_3/KI, DMF, 80 ^{o}C, overnight, 96% yield; (c) $NaBH_4$, MeOH, rt, 30 min, 96% yield; (d) 2-bromo-*N*-methoxy-*N*-methylpropanamide, NaH, rt, dry DMF, 30 min, 95% yield; (e) *t*-BuLi -78 ^{o}C, 1 min, then H_2O, 93% yield; (f) Pd-C/H_2, THF, rt, 4 h, 70% yield.

Scheme 3. The synthetic route toward **(±)-XJP**

3. Conclusion

In summary, we have developed a practical and efficient protocol to synthesize the 4-isochromanones via Parham-type cyclization with Weinreb amide as the precursors. The reaction proceeded in one minute and produced 4-isochromanones in good to excellent yields. Additionally, the synthetic potential of this method was further demonstrated by the synthesis of natural product (±)-XJP in 6 steps with overall yield up to 54%.

4. Experimental section

4.1. General

All commercially available starting materials and solvents were reagent grade and used without further purification unless otherwise noted. Anhydrous DMF was obtained by distillation over CaH_2 and anhydrous THF was obtained by distillation over Na. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-300 spectrometers, and were referenced to the residual peaks of $CHCl_3$ at 7.26 ppm or DMSO-d_6 at 2.50 ppm (^{1}H NMR) and $CDCl_3$ at 77.23 ppm or DMSO-d_6 at 39.52 ppm (^{13}C NMR). Chemical shifts (δ) were reported relative to residual protic solvent signals. HRMS was performed on an Agilent 6530 Q-TOF mass spectrometer, and ESI-MS was carried out on an Agilent 6120 mass spectrometer. TLC was performed on Huanghai HSGF 254 silica gel plates (China). Silica gel 60 H (200-300 mesh), manufactured by Qingdao Haiyang Chemical Group Co., Ltd (China) was used for general chromatography.

4.2. Typical procedure for the synthesis of 4-isochromanones

To a solution of precursors with Weinreb amides **1a-1n** (1 mmol) in dry THF (10 mL), *t*-BuLi (2.2 mmol) was added at -78 ^{o}C, and after 1 min, the reaction was quenched by the addition of sat. NH_4Cl (10 mL). Ethyl acetate (15 mL) was added, the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography afforded **2a**–**2n**.

*4.2.1 3-methylisochroman-4-one (**2a**)* White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 7.6 Hz, 1H), 7.40 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 4.77 (s, 3H), 4.10 (q, *J* = 6.6 Hz, 1H), 1.38 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 195.81, 142.03, 133.79, 129.15, 127.61, 126.57, 124.32, 78.38, 66.83, 15.69; MS-ESI: (ESI, pos.ion) m/z: 163.1 $[M+H]^+$; HRMS (ESI) calculated for $C_{10}H_{11}O_2$ $[M+H]^+$ 163.0759, found 163.0744.

*4.2.2 3,7-dimethylisochroman-4-one (**2b**)* White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (s, 1H), 7.22 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 4.75 (s, 2H), 4.09 (q, *J* = 6.6 Hz, 1H), 2.26 (s, 3H), 1.39 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 196.11, 139.22, 137.43, 134.70, 129.00, 126.70, 124.25, 78.38, 66.75, 21.04, 15.74; MS-ESI: (ESI, pos.ion) m/z: 177.1 $[M+H]^+$; HRMS (ESI) calculated for $C_{10}H_{11}O_2$ $[M+H]^+$ 177.0916, found 177.0925.

*4.2.3 6,7-dimethoxy-3-methylisochroman-4-one (**2c**)* White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 (s, 1H), 7.31 (s, 1H), 4.85 (s, 1H), 4.22 (q, *J* = 6.6 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 1.51 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.72, 153.91, 148.59, 136.93, 122.31, 107.82, 105.83, 77.83, 66.43, 56.09, 55.97, 15.79; MS-ESI: (ESI, pos.ion) m/z: 222.9 $[M+H]^+$; HRMS (ESI) calculated for $C_{12}H_{15}O_4$ $[M+H]^+$ 223.0965, found 223.0974.

*4.2.4 7,8-dimethoxy-3-methylisochroman-4-one (**2d**)* White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 8.6 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 5.14 (d, *J* = 15.8 Hz, 1H), 4.80 (d, *J* = 15.8 Hz, 1H), 4.19 (q, *J* = 6.6 Hz, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 1.50 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.93, 156.85, 135.86, 124.08, 123.06, 111.12, 77.73, 62.84, 60.56, 55.89, 15.68; MS-ESI: (ESI, pos.ion) m/z: 222.9 $[M+H]^+$; HRMS (ESI) calculated for $C_{12}H_{15}O_4$ $[M+H]^+$ 223.0965, found 223.0972.

*4.2.5 8-(benzyloxy)-7-methoxy-3-methylisochroman-4-one (**2e**)* White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 8.6 Hz, 1H), 7.38-7.34 (m, 5H), 6.97 (d, *J* = 8.6 Hz, 1H), 5.07-4.95 (m, 3H), 4.50 (d, *J* = 15.8 Hz, 1H), 4.80 (d, *J* = 15.8 Hz, 1H), 4.09 (q, *J* = 6.6 Hz, 1H), 3.97 (s, 3H), 1.43 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.90, 156.88, 141.75, 137.08, 136.40, 128.54, 128.46, 128.37, 124.16, 124.12, 123.09, 111.15, 77.60, 74.80, 74.76, 63.03, 55.91, 15.60; MS-ESI: (ESI, pos.ion) m/z: 299.1 $[M+H]^+$; HRMS (ESI) calculated for $C_{18}H_{18}O_4Na$ $[M+Na]^+$ 321.1097, found 321.1112.

*4.2.6 6-(benzyloxy)-7-methoxy-3-methylisochroman-4-one (**2f**)* White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 (s, 1H), 7.47-7.26 (m, 5H), 6.61 (s, 1H), 5.16 (s, 2H), 4.84 (s, 2H), 4.19 (q, *J* = 6.6 Hz, 1H), 3.92 (s, 3H), 1.49 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.77, 154.57, 147.81, 137.23, 136.33, 128.64, 128.11, 127.55, 122.33, 110.02, 106.18, 77.98, 70.84, 66.60, 56.22, 15.88; MS-ESI: (ESI, pos.ion) m/z: 299.1 $[M+H]^+$; HRMS (ESI) calculated for $C_{18}H_{18}O_4Na$ $[M+Na]^+$ 321.1097, found 321.1110.

*4.2.7 7-(benzyloxy)-6-methoxy-3-methylisochroman-4-one (**2g**)* White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52 (s, 1H), 7.45-7.28 (m, 5H), 6.64 (s, 1H), 5.22 (s, 2H), 4.81 (m, 2H), 4.22 (q, *J* = 6.6 Hz, 1H), 3.93 (s, 3H), 1.51 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.85, 153.17, 149.20, 136.73, 135.90, 128.73, 128.23, 127.19, 122.67, 77.96, 70.86, 66.47, 56.11, 15.87; MS-ESI: (ESI, pos.ion) m/z: 299.1 $[M+H]^+$; HRMS (ESI) calculated for $C_{18}H_{18}O_4Na$ $[M+Na]^+$ 321.1097, found 321.1109.

*4.2.8 7-methoxy-3-methylisochroman-4-one (**2h**)* Colorless oil; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.93 (d, *J* = 8.6 Hz, 1H), 6.83 (dd, *J* = 8.6 Hz, 2.4 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 4.81 (s, 1H), 4.24 (q, *J* = 6.6 Hz, 1H), 3.81 (s, 3H), 1.45 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 194.74, 163.92, 144.48, 129.22, 122.72, 114.05, 108.32, 78.26, 66.91, 55.50, 15.73; MS-ESI: (ESI, pos.ion) m/z: 193.1 [M+H]$^+$; HRMS (ESI) calculated for $C_{12}H_{15}O_4$ [M+H]$^+$ 193.0865, found 193.0845.

*4.2.9 7-(dimethylamino)-3-methylisochroman-4-one (**2i**)* Yellow solid; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.89 (d, *J* = 8.8 Hz, 1H), 6.61 (dd, *J* = 8.9 Hz, 2.5 Hz, 1H), 6.26 (d, *J* = 2.4 Hz, 1H), 4.81 (s, 2H), 4.19 (q, *J* = 6.6 Hz, 1H), 3.04 (s, 3H), 1.48 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 194.40, 153.67, 144.02, 128.87, 117.86, 110.94, 104.73, 78.25, 67.31, 40.05, 16.04; MS-ESI: (ESI, pos.ion) m/z: 205.8 [M+H]$^+$; HRMS (ESI) calculated for $C_{12}H_{15}NO_2Na$ [M+Na]$^+$ 228.1000, found 228.0986.

*4.2.10 7-fluoro-3-methylisochroman-4-one (**2j**)* Yellow solid; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.08 (dd, *J* = 8.6 Hz, 2.4 Hz, 1H), 7.08 (td, *J* = 8.6 Hz, 2.4 Hz, 1H), 6.89 (dd, *J* = 8.6 Hz, 2.4 Hz, 1H), 4.91 (s, 2H), 4.25 (q, *J* = 6.6 Hz, 1H), 1.52 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 194.40, 167.48, 164.08, 145.11, 144.99, 130.08, 129.95, 125.94, 115.49, 115.19, 111.22, 110.92, 78.33, 66.61, 66.59, 15.58; MS-ESI: (ESI, pos.ion) m/z: 181.1 [M+H]$^+$; HRMS (ESI) calculated for $C_{10}H_{10}FO_2$ [M+H]$^+$ 181.0665, found 181.0655.

*4.2.11 7-chloro-3-methylisochroman-4-one (**2k**)* White solid; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.96 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H), 7.20 (s, 1H), 4.89 (s, 2H), 4.24 (q, *J* = 6.6 Hz, 1H), 1.51 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 194.86, 143.57, 140.22, 128.51, 128.25, 127.70, 124.45, 78.47, 66.48, 15.64; MS-ESI: (ESI, pos.ion) m/z: 197.0 [M+H]$^+$; HRMS (ESI) calculated for $C_{10}H_{10}ClO_2$ [M+H]$^+$ 197.0369, found 197.0356.

*4.2.12 3-methyl-7-(trifluoromethyl)isochroman-4-one (**2m**)* White solid; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.15 (d, *J* = 8.2 Hz, 1H), 7.65 (dd, *J* = 8.2 Hz, 0.6 Hz, 1H), 7.49 (s, 1H), 4.98 (s, 2H), 4.29 (q, *J* = 6.6 Hz, 1H), 1.53 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 194.80, 142.57, 136.23, 131.71, 127.50, 124.55, 124.50, 121.70, 121.65, 78.57, 66.68, 15.54; MS-ESI: (ESI, pos.ion) m/z: 231.1 [M+H]$^+$; HRMS (ESI) calculated for $C_{11}H_{10}F_3O_2$ [M+H]$^+$ 231.0633, found 231.0629.

*4.2.13 5,10-dimethoxy-3-methyl-1H-benzo[g]isochromen-4(3H)-one (**2n**)* Yellow solid; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.36 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H,), 7.66 (m, 2H), 5.31 (d, *J* = 15.0 Hz, 1H), 4.80 (d, *J* = 15.0 Hz, 1H), 4.22 (q, *J* = 6.6 Hz, 1H), 4.01 (s, 3H), 3.87 (s, 3H), 1.55 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ:195.71, 155.70, 146.50, 131.57, 129.52, 129.18, 128.09, 126.72, 125.00, 121.98; MS-ESI: (ESI, pos.ion) m/z: 272.9 [M+H]$^+$; HRMS (ESI) calculated for $C_{16}H_{16}NaO_4$ [M+Na]$^+$ 295.0941, found 295.0945.

*4.2.14 6,7-dimethoxyisochroman-4-one (**2o**)* Yellow solid; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.41 (s, 1H), 6.57 (s, 1H), 4.76 (s, 2H), 4.24 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 192.73, 154.23, 148.76, 136.78, 122.72 107.52, 106.06, 72.91, 67.54, 56.18, 56.05; MS-ESI: (ESI, pos.ion) m/z: 208.92 [M+H]$^+$; HRMS (ESI) calculated for $C_{11}H_{12}O_4$ [M+H]$^+$ 209.0736, found 209.0750.

4.3. Procedure for total synthesis of (±)-XJP

*4.3.1 2-((2,3-bis(benzyloxy)-6-bromobenzyl)oxy)-N-methoxy-N-methyl propanamide (**9**)*. A 50 ml round bottom flask was charged with compound **8** (5 mmol) and argonated. Anhydride DMF (20 ml) was added with stirring, and to the stirred solution 2-bromo-N-methoxy-N-methyl propanamide (7.5 mmol) was added. The mixture was cooled with ice-water bath and sodium hydride (15 mmol) was added with stirring. Cooling bath was removed and the mixture was stirred at rt for further 30 min. The reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were washed with brine, dried with Na$_2$SO$_4$ and evaporated. The residue was separated with column chromatography to afford **9** in 95% yield. Colorless oil; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.45-7.24 (m, 11H), 6.83 (d, *J* = 8.8 Hz, 1H), 5.06 (s, 2H), 5.04 (s, 2H), 4.85 (d, *J* = 10.2 Hz, 1H), 4.57 (d, *J* = 10.2 Hz, 1H),4.39 (q, *J* = 6.6 Hz, 1H), 3.52 (s, 3H), 3.11 (s, 3H), 1.45 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 151.54, 148.75, 137.32, 136.43, 131.77, 128.86, 128.65, 128.36, 128.22, 128.11, 127.60, 116.97, 115.37, 76.13, 71.84, 70.99, 65.55, 61.13, 32.24, 18.03; MS-ESI: (ESI, pos.ion) m/z: 514.1 [M+H]$^+$; HRMS (ESI) calcd for $C_{26}H_{29}BrNO_5$ [M+H]$^+$ 514.1224, found 514.1212.

*4.3.2 7,8-bis(benzyloxy)-3-methylisochroman-4-one (**10**)* To a solution of precursor **9** (1 mmol) in dry THF (10 mL), *t*-BuLi (2.2 mmol) was added at -78 ^{o}C, and after 1 min, the reaction was quenched by the addition of sat. NH$_4$Cl (10 mL). Ethyl acetate (15 mL) was added, the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Flash column chromatography afforded **10** in 93% yield. White solid; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.81 (d, *J* = 8.7 Hz, 1H), 7.47-7.32 (m, 10H), 7.03 (d, *J* = 8.7 Hz, 1H), 5.23 (s, 2H), 5.09-4.98 (m, 3H), 4.54 (d, *J* = 15.9 Hz, 1H), 4.10 (q, *J* = 6.9 Hz, 1H), 1.45 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 194.92, 155.98, 142.16, 137.00, 136.64, 135.94, 128.77, 128.59, 128.54, 128.40, 127.52, 124.04, 123.37, 112.61, 77.66, 74.88, 70.82, 63.09, 15.64; MS-ESI: (ESI, pos.ion) m/z: 397.1 [M+Na]$^+$; HRMS (ESI) calcd for $C_{24}H_{22}NaO_4$ [M+Na]$^+$ 397.1410, found 397.1415.

*4.3.3 (±)-7, 8-dihydroxy-3-methylisochroman-4-one [**(±)-XJP**]* To a solution of 7, 8-bis (benzyloxy)-3-methylisochroman-4-one **10** (0.26 mmol) in THF (5 mL) was added Pd-C (0.02 g, 10%) and the mixture was stirred under H$_2$ atmosphere for 4 h at room temperature. Then the reaction solution was passed through a short diatomite pad and washed with THF. The combined organic phase was concentrated *in vacuo*, and the residue was purified by a short silica gel column chromatography to give **(±)-XJP** in 70% yield. White solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.47 (s, 1H), 8.96 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 4.92 (d, *J* = 15.6 Hz, 1H), 4.69 (d, *J* = 15.6 Hz, 1H), 4.21 (q, *J* = 6.6 Hz, 1H), 1.31 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 194.45, 150.46, 139.43, 129.95, 121.31, 118.61, 114.26, 76.44, 62.27, 15.50. MS-ESI: (ESI, neg.ion) m/z: 193.0 [M-H]$^-$; HRMS (ESI) calcd for $C_{10}H_9O_4$ [M-H]$^-$ 193.0506, found 193.0501.

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Supplementary Material

Supplementary data and compound characterizations associated with this article can be found in the online version at ______.

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Electronic Supporting Information (ESI) for:

An efficient synthesis of 4-isochromanones via Parham-type cyclization with Weinreb amide

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Contents	**Page**
X-ray Structure and data of **2f**	S2-S18
^{1}H-NMR and ^{13}C-NMR Spectra	S19-S35

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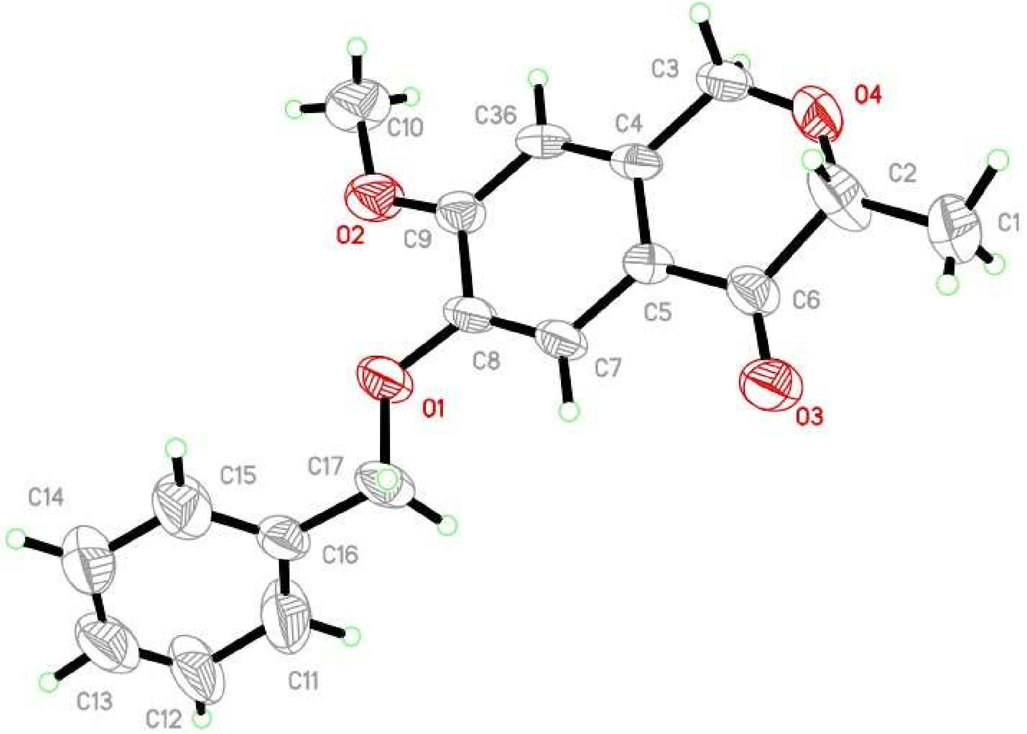

Contents:

Table S1 - Crystal Data and Details of the Structure Determination

Table S2 - Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms

Table S3 - Hydrogen Atom Positions and Isotropic Displacement Parameters

Table S4 - (An)isotropic Displacement Parameters

Table S5 - Bond Distances (Angstrom)

Table S6 - Bond Angles (Degrees)

Table S7 - Torsion Angles (Degrees)

Table S8 - Contact Distances(Angstrom)

Table S9 - Hydrogen Bonds (Angstrom, Deg)

Table S1 - Crystal Data and Details of the Structure Determination

Formula	C18 H18 O4
Formula Weight	298.32
Crystal System	Triclinic
Space group	P-1 (No. 2)
a, b, c [Angstrom]	8.734(6) 12.109(8) 14.722(10)
alpha, beta, gamma [deg]	98.844(10) 92.973(11) 96.98(1)
V [Ang**3]	1523.1(18)
Z	4
D(calc) [g/cm**3]	1.301
Mu(MoKa) [/mm]	0.091
F(000)	632
Crystal Size [mm]	0.22 x 0.24 x 0.27
Data Collection	
Temperature (K)	296
Radiation [Angstrom]	MoKa 0.71073
Theta Min-Max [Deg]	2.0, 25.0
Dataset	-10: 10 ; -14: 13 ; -17: 12
Tot., Uniq. Data, R(int)	8087, 5267, 0.054
Observed data [I > 2.0 sigma(I)]	2993
Refinement	
Nref, Npar	5267, 390
R, wR2, S	0.1228, 0.3238, 1.09
w = 1/[\s^2^(Fo^2^)+(0.0000P)^2^+14.0000P] where P=(Fo^2^+2Fc^2^)/	
Max. and Av. Shift/Error	0.05, 0.00
Min. and Max. Resd. Dens. [e/Ang^3]	-0.77, 0.98

Table S2 - Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms

Atom	x	y	z	U(eq) [Ang^2]
O1	0.0599(5)	0.7569(3)	0.7357(2)	0.0906(14)
O2	-0.1297(5)	0.5767(3)	0.7194(3)	0.0961(14)
O3	0.1428(5)	0.8882(3)	1.0851(2)	0.0991(14)
O4	-0.1087(8)	0.6647(4)	1.1295(3)	0.185(2)
C1	0.0397(11)	0.8111(6)	1.2413(4)	0.137(4)
C2	-0.0021(7)	0.7442(6)	1.1504(4)	0.103(2)
C3	-0.1576(6)	0.5994(4)	1.0507(4)	0.0724(16)
C4	-0.0992(5)	0.6430(3)	0.9695(3)	0.0565(16)
C5	0.0037(5)	0.7411(3)	0.9803(3)	0.0543(14)
C6	0.0560(6)	0.8010(4)	1.0722(3)	0.0696(16)
C7	0.0572(6)	0.7813(4)	0.9007(3)	0.0672(16)
C8	0.0154(7)	0.7259(4)	0.8167(3)	0.0722(18)
C9	-0.0914(6)	0.6255(4)	0.8047(3)	0.0654(17)
C10	-0.2312(8)	0.4769(5)	0.6997(5)	0.110(3)
C11	0.1747(10)	0.9544(6)	0.6130(5)	0.141(3)
C12	0.2076(9)	0.9762(6)	0.5229(4)	0.127(3)
C13	0.2871(9)	0.9070(6)	0.4796(5)	0.120(3)
C14	0.3289(9)	0.8110(7)	0.5065(5)	0.125(3)
C15	0.2932(9)	0.7936(6)	0.5962(4)	0.112(3)
C16	0.2114(7)	0.8683(4)	0.6477(3)	0.0752(19)
C17	0.1778(7)	0.8529(5)	0.7437(3)	0.0866(19)
C36	-0.1496(6)	0.5877(4)	0.8816(3)	0.0626(16)
O5	0.3769(5)	0.2179(3)	0.2768(2)	0.0920(14)
O6	0.5648(5)	0.3884(3)	0.2559(2)	0.0857(14)
O7	0.6175(5)	0.3483(3)	-0.0929(2)	0.0930(14)
O8	0.3578(7)	0.1044(4)	-0.1369(3)	0.151(2)

C18	0.4943(11)	0.1934(7)	-0.2467(4)	0.161(4)
C19	0.4725(8)	0.1734(5)	-0.1529(4)	0.095(2)
C20	0.5393(6)	0.2648(4)	-0.0766(3)	0.0731(19)
C21	0.4939(5)	0.2513(4)	0.0159(3)	0.0542(14)
C22	0.3953(6)	0.1603(4)	0.0280(3)	0.0641(16)
C23	0.3294(7)	0.0714(4)	-0.0544(4)	0.0790(19)
C24	0.3547(6)	0.1438(4)	0.1152(3)	0.0631(16)
C25	0.4123(6)	0.2249(4)	0.1897(3)	0.0700(18)
C26	0.5159(6)	0.3178(4)	0.1774(3)	0.0648(16)
C27	0.2902(9)	0.1188(5)	0.2943(4)	0.118(3)
C28	0.6814(7)	0.4825(4)	0.2515(4)	0.0851(19)
C29	0.7171(6)	0.5437(3)	0.3439(3)	0.114(2)
C30	0.8707(6)	0.5896(5)	0.3660(4)	0.198(2)
C31	0.9164(8)	0.6484(7)	0.4538(5)	0.207(3)
C32	0.8085(11)	0.6613(6)	0.5196(4)	0.180(3)
C33	0.6549(10)	0.6154(6)	0.4974(4)	0.200(2)
C34	0.6092(7)	0.5566(5)	0.4096(4)	0.190(3)
C35	0.5536(6)	0.3290(4)	0.0912(3)	0.0667(16)

Table S3 - Hydrogen Atom Positions and Isotropic Displacement Parameters

Atom	x	y	z	U(iso) [Ang^2]
----	---	---	---	-----------
H1A	-0.03220	0.86440	1.25440	0.2050
H1B	0.14220	0.85060	1.24260	0.2050
H1C	0.03680	0.76220	1.28690	0.2050
H2	0.08090	0.69690	1.15240	0.1240
H3A	-0.26980	0.59030	1.04500	0.0870
H3B	-0.12600	0.52550	1.05160	0.0870
H7	0.12380	0.84860	0.90760	0.0800
H10A	-0.18940	0.41950	0.72790	0.1640

H10B	-0.24510	0.45330	0.63420	0.1640
H10C	-0.32920	0.48890	0.72350	0.1640
H11	0.12330	1.00580	0.64930	0.1690
H12	0.17370	1.03580	0.49810	0.1530
H13	0.32040	0.92340	0.42360	0.1440
H14	0.37800	0.76020	0.46810	0.1500
H15	0.32430	0.73250	0.62020	0.1350
H17A	0.27020	0.83940	0.77740	0.1040
H17B	0.14130	0.91960	0.77600	0.1040
H36	-0.22360	0.52430	0.87420	0.0750
H18A	0.44790	0.12850	-0.28950	0.2410
H18B	0.60280	0.20690	-0.25500	0.2410
H18C	0.44640	0.25800	-0.25740	0.2410
H19	0.55250	0.12380	-0.14870	0.1140
H23A	0.37410	0.00250	-0.05080	0.0950
H23B	0.21860	0.05490	-0.05100	0.0950
H24	0.29010	0.07970	0.12340	0.0760
H27A	0.19660	0.10310	0.25480	0.1770
H27B	0.26530	0.12840	0.35750	0.1770
H27C	0.34970	0.05710	0.28240	0.1770
H28A	0.64310	0.53120	0.21150	0.1020
H28B	0.77350	0.45560	0.22700	0.1020
H30	0.94290	0.58100	0.32210	0.2380
H31	1.01920	0.67910	0.46860	0.2480
H32	0.83910	0.70060	0.57830	0.2150
H33	0.58270	0.62400	0.54140	0.2400
H34	0.50650	0.52590	0.39480	0.2280
H35	0.62190	0.39100	0.08260	0.0800

Table S4 - (An)isotropic Displacement Parameters

Atom	U(1,1) or U	U(2,2)	U(3,3)	U(2,3)	U(1,3)	U(1,2)
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O1	0.118(3)	0.084(2)	0.0574(19)	0.0153(17)	0.004(2)	-0.040(2)
O2	0.126(3)	0.074(2)	0.076(2)	0.0088(19)	-0.005(2)	-0.027(2)
O3	0.132(3)	0.087(2)	0.064(2)	0.0178(18)	-0.019(2)	-0.039(2)
O4	0.337(6)	0.100(3)	0.094(3)	-0.005(2)	0.110(3)	-0.076(4)
C1	0.237(9)	0.111(5)	0.065(4)	0.018(4)	0.029(5)	0.023(6)
C2	0.083(4)	0.159(5)	0.067(3)	0.047(3)	-0.002(3)	-0.021(4)
C3	0.078(3)	0.054(2)	0.095(3)	0.032(2)	0.031(3)	0.012(2)
C4	0.057(3)	0.043(2)	0.075(3)	0.0252(19)	0.012(2)	0.0056(19)
C5	0.055(3)	0.047(2)	0.061(2)	0.0154(19)	0.000(2)	0.001(2)
C6	0.077(3)	0.076(3)	0.055(2)	0.023(2)	-0.003(2)	-0.005(3)
C7	0.076(3)	0.061(2)	0.063(3)	0.024(2)	0.008(2)	-0.016(2)
C8	0.099(4)	0.051(2)	0.064(3)	0.022(2)	0.007(3)	-0.017(3)
C9	0.074(3)	0.057(3)	0.061(3)	0.012(2)	-0.004(2)	-0.008(2)
C10	0.120(5)	0.084(4)	0.102(4)	-0.002(3)	-0.025(4)	-0.041(4)
C11	0.225(7)	0.136(5)	0.092(4)	0.043(4)	0.069(5)	0.084(5)
C12	0.167(6)	0.147(5)	0.099(4)	0.072(3)	0.062(4)	0.056(5)
C13	0.139(6)	0.134(5)	0.095(4)	0.053(4)	0.029(4)	-0.004(5)
C14	0.147(6)	0.134(6)	0.088(4)	0.004(4)	0.042(4)	0.002(5)
C15	0.148(6)	0.120(5)	0.080(4)	0.040(3)	0.023(4)	0.029(5)
C16	0.096(4)	0.068(3)	0.061(3)	0.022(2)	0.008(3)	-0.007(3)
C17	0.103(4)	0.089(3)	0.054(3)	0.019(2)	-0.010(3)	-0.045(3)
C36	0.064(3)	0.041(2)	0.082(3)	0.020(2)	0.004(2)	-0.008(2)
O5	0.134(3)	0.069(2)	0.071(2)	0.0172(17)	0.032(2)	-0.013(2)
O6	0.116(3)	0.072(2)	0.0584(19)	0.0060(17)	0.0131(19)	-0.028(2)
O7	0.121(3)	0.076(2)	0.075(2)	0.0141(18)	0.027(2)	-0.026(2)
O8	0.223(5)	0.116(3)	0.079(3)	0.001(2)	0.012(3)	-0.093(3)
C18	0.224(9)	0.163(7)	0.063(4)	-0.001(4)	0.013(5)	-0.078(6)

C19	0.116(5)	0.087(4)	0.072(3)	-0.012(3)	0.025(3)	-0.007(4)
C20	0.083(4)	0.066(3)	0.066(3)	0.005(2)	0.015(3)	-0.004(3)
C21	0.045(2)	0.051(2)	0.063(3)	0.010(2)	-0.001(2)	-0.007(2)
C22	0.074(3)	0.041(2)	0.076(3)	0.006(2)	0.002(3)	0.008(2)
C23	0.081(4)	0.068(3)	0.080(3)	0.007(3)	-0.010(3)	-0.009(3)
C24	0.060(3)	0.049(2)	0.078(3)	0.011(2)	0.007(2)	-0.004(2)
C25	0.089(4)	0.049(2)	0.076(3)	0.023(2)	0.018(3)	0.004(2)
C26	0.067(3)	0.052(2)	0.071(3)	0.007(2)	0.008(2)	-0.007(2)
C27	0.199(6)	0.063(3)	0.095(4)	0.023(3)	0.066(4)	-0.010(4)
C28	0.112(4)	0.072(3)	0.061(3)	0.008(3)	-0.001(3)	-0.023(3)
C29	0.165(4)	0.085(4)	0.103(3)	0.042(3)	0.023(3)	0.016(4)
C30	0.187(3)	0.213(5)	0.179(4)	-0.003(4)	0.020(3)	0.006(4)
C31	0.192(4)	0.224(5)	0.185(4)	-0.007(4)	0.011(3)	0.002(4)
C32	0.186(4)	0.171(5)	0.171(4)	0.004(4)	0.018(3)	0.009(4)
C33	0.195(3)	0.222(5)	0.170(4)	-0.020(4)	0.023(3)	0.037(4)
C34	0.183(4)	0.210(5)	0.167(4)	-0.015(4)	0.023(3)	0.041(4)
C35	0.088(3)	0.046(2)	0.064(3)	0.010(2)	0.021(2)	-0.007(2)

Table S5 - Bond Distances (Angstrom)

O1	-C8	1.365(6)	C14	-C15	1.413(10)
O1	-C17	1.442(7)	C15	-C16	1.381(9)
O2	-C9	1.311(6)	C16	-C17	1.493(7)
O2	-C10	1.391(8)	C1	-H1A	0.9600
O3	-C6	1.206(6)	C1	-H1B	0.9600
O4	-C2	1.245(9)	C1	-H1C	0.9600
O4	-C3	1.318(7)	C2	-H2	0.9800
O5	-C25	1.347(5)	C3	-H3B	0.9700
O5	-C27	1.405(8)	C3	-H3A	0.9700
O6	-C28	1.445(7)	C7	-H7	0.9300
O6	-C26	1.344(6)	C10	-H10C	0.9600
O7	-C20	1.213(6)	C10	-H10A	0.9600

O8	-C19	1.280(9)	C10	-H10B	0.9600
O8	-C23	1.361(7)	C11	-H11	0.9300
C1	-C2	1.458(9)	C12	-H12	0.9300
C2	-C6	1.508(8)	C13	-H13	0.9300
C3	-C4	1.470(7)	C14	-H14	0.9300
C4	-C5	1.383(6)	C15	-H15	0.9300
C4	-C36	1.386(6)	C17	-H17A	0.9700
C5	-C6	1.456(6)	C17	-H17B	0.9700
C5	-C7	1.416(6)	C36	-H36	0.9300
C7	-C8	1.323(6)	C18	-C19	1.456(9)
C8	-C9	1.422(7)	C19	-C20	1.490(8)
C9	-C36	1.383(7)	C20	-C21	1.465(6)
C11	-C12	1.429(10)	C21	-C22	1.354(7)
C11	-C16	1.296(9)	C21	-C35	1.373(6)
C12	-C13	1.270(11)	C22	-C23	1.529(7)
C13	-C14	1.368(11)	C22	-C24	1.387(6)
C24	-C25	1.383(7)	C23	-H23A	0.9700
C25	-C26	1.396(7)	C23	-H23B	0.9700
C26	-C35	1.350(6)	C24	-H24	0.9300
C28	-C29	1.445(7)	C27	-H27A	0.9600
C29	-C30	1.390(7)	C27	-H27B	0.9600
C29	-C34	1.390(8)	C27	-H27C	0.9600
C30	-C31	1.390(9)	C28	-H28A	0.9700
C31	-C32	1.391(11)	C28	-H28B	0.9700
C32	-C33	1.390(13)	C30	-H30	0.9300
C33	-C34	1.390(9)	C31	-H31	0.9300
C18	-H18A	0.9600	C32	-H32	0.9300
C18	-H18B	0.9600	C33	-H33	0.9300
C18	-H18C	0.9600	C34	-H34	0.9300
C19	-H19	0.9800	C35	-H35	0.9300

Table S6 - Bond Angles (Degrees)

C8	-O1	-C17	116.0(4)	C12	-C13	-C14	127.0(7)
C9	-O2	-C10	121.0(5)	C13	-C14	-C15	116.1(7)
C2	-O4	-C3	132.3(6)	C14	-C15	-C16	119.2(6)
C25	-O5	-C27	118.7(4)	C15	-C16	-C17	119.6(5)
C26	-O6	-C28	118.2(4)	C11	-C16	-C17	121.8(6)
C19	-O8	-C23	126.3(5)	C11	-C16	-C15	118.5(6)
C1	-C2	-C6	113.9(6)	O1	-C17	-C16	106.5(4)
O4	-C2	-C1	126.9(6)	C4	-C36	-C9	120.9(4)
O4	-C2	-C6	116.2(5)	C2	-C1	-H1A	110.00
O4	-C3	-C4	113.8(4)	H1A	-C1	-H1C	109.00
C3	-C4	-C5	120.2(4)	H1B	-C1	-H1C	109.00
C3	-C4	-C36	120.3(4)	C2	-C1	-H1C	109.00
C5	-C4	-C36	119.5(4)	H1A	-C1	-H1B	110.00
C4	-C5	-C7	118.8(4)	C2	-C1	-H1B	110.00
C4	-C5	-C6	120.1(4)	O4	-C2	-H2	96.00
C6	-C5	-C7	121.0(4)	C1	-C2	-H2	96.00
C2	-C6	-C5	115.1(4)	C6	-C2	-H2	96.00
O3	-C6	-C5	122.6(4)	C4	-C3	-H3B	109.00
O3	-C6	-C2	122.3(4)	H3A	-C3	-H3B	108.00
C5	-C7	-C8	121.9(5)	C4	-C3	-H3A	109.00
O1	-C8	-C7	126.7(5)	O4	-C3	-H3A	109.00
O1	-C8	-C9	113.5(4)	O4	-C3	-H3B	109.00
C7	-C8	-C9	119.7(4)	C5	-C7	-H7	119.00
C8	-C9	-C36	119.0(4)	C8	-C7	-H7	119.00
O2	-C9	-C8	116.2(4)	O2	-C10	-H10A	109.00
O2	-C9	-C36	124.8(5)	H10A	-C10	-H10C	109.00
C12	-C11	-C16	124.7(7)	H10B	-C10	-H10C	109.00
C11	-C12	-C13	114.2(7)	O2	-C10	-H10C	110.00
H10A	-C10	-H10B	109.00	C21	-C22	-C23	120.5(4)

O2	-C10	-H10B	110.00	C21	-C22	-C24	121.1(4)
C12	-C11	-H11	118.00	C23	-C22	-C24	118.4(4)
C16	-C11	-H11	118.00	O8	-C23	-C22	113.0(4)
C13	-C12	-H12	123.00	C22	-C24	-C25	118.5(5)
C11	-C12	-H12	123.00	O5	-C25	-C24	123.0(4)
C12	-C13	-H13	116.00	O5	-C25	-C26	116.6(4)
C14	-C13	-H13	117.00	C24	-C25	-C26	120.4(4)
C13	-C14	-H14	122.00	O6	-C26	-C25	113.9(4)
C15	-C14	-H14	122.00	O6	-C26	-C35	127.3(5)
C14	-C15	-H15	120.00	C25	-C26	-C35	118.7(4)
C16	-C15	-H15	120.00	O6	-C28	-C29	107.8(4)
C16	-C17	-H17B	110.00	C28	-C29	-C30	115.9(5)
H17A	-C17	-H17B	109.00	C28	-C29	-C34	124.1(5)
O1	-C17	-H17B	110.00	C30	-C29	-C34	120.0(5)
C16	-C17	-H17A	110.00	C29	-C30	-C31	120.0(5)
O1	-C17	-H17A	110.00	C30	-C31	-C32	120.0(7)
C4	-C36	-H36	120.00	C31	-C32	-C33	119.9(6)
C9	-C36	-H36	120.00	C32	-C33	-C34	120.1(6)
O8	-C19	-C18	119.9(6)	C29	-C34	-C33	120.0(6)
O8	-C19	-C20	118.0(5)	C21	-C35	-C26	121.8(5)
C18	-C19	-C20	117.2(6)	C19	-C18	-H18A	109.00
O7	-C20	-C19	120.6(4)	C19	-C18	-H18B	109.00
O7	-C20	-C21	123.2(4)	C19	-C18	-H18C	109.00
C19	-C20	-C21	116.1(4)	H18A	-C18	-H18B	109.00
C20	-C21	-C22	120.1(4)	H18A	-C18	-H18C	109.00
C20	-C21	-C35	120.5(4)	H18B	-C18	-H18C	109.00
C22	-C21	-C35	119.4(4)	O8	-C19	-H19	97.00
C18	-C19	-H19	97.00	O6	-C28	-H28B	110.00
C20	-C19	-H19	97.00	C29	-C28	-H28A	110.00
O8	-C23	-H23A	109.00	C29	-C28	-H28B	110.00

O8	-C23	-H23B	109.00	H28A	-C28	-H28B	108.00
C22	-C23	-H23A	109.00	C29	-C30	-H30	120.00
C22	-C23	-H23B	109.00	C31	-C30	-H30	120.00
H23A	-C23	-H23B	108.00	C30	-C31	-H31	120.00
C22	-C24	-H24	121.00	C32	-C31	-H31	120.00
C25	-C24	-H24	121.00	C31	-C32	-H32	120.00
O5	-C27	-H27A	109.00	C33	-C32	-H32	120.00
O5	-C27	-H27B	110.00	C32	-C33	-H33	120.00
O5	-C27	-H27C	109.00	C34	-C33	-H33	120.00
H27A	-C27	-H27B	110.00	C29	-C34	-H34	120.00
H27A	-C27	-H27C	109.00	C33	-C34	-H34	120.00
H27B	-C27	-H27C	109.00	C21	-C35	-H35	119.00
O6	-C28	-H28A	110.00	C26	-C35	-H35	119.00

Table S7 - Torsion Angles (Degrees)

C17	-O1	-C8	-C7	7.5(8)
C17	-O1	-C8	-C9	-175.1(5)
C8	-O1	-C17	-C16	178.0(5)
C10	-O2	-C9	-C36	-2.7(8)
C10	-O2	-C9	-C8	178.8(5)
C2	-O4	-C3	-C4	-15.4(10)
C3	-O4	-C2	-C1	179.4(7)
C3	-O4	-C2	-C6	20.3(11)
C27	-O5	-C25	-C24	6.5(8)
C27	-O5	-C25	-C26	-171.5(5)
C26	-O6	-C28	-C29	-178.6(4)
C28	-O6	-C26	-C35	-6.1(8)
C28	-O6	-C26	-C25	175.3(5)
C23	-O8	-C19	-C18	174.9(6)
C19	-O8	-C23	-C22	28.1(9)

C23	-O8	-C19	-C20	-30.6(9)
C1	-C2	-C6	-C5	-174.4(6)
O4	-C2	-C6	-O3	169.3(6)
O4	-C2	-C6	-C5	-12.6(8)
C1	-C2	-C6	-O3	7.5(9)
O4	-C3	-C4	-C36	-175.3(5)
O4	-C3	-C4	-C5	3.1(7)
C36	-C4	-C5	-C7	-1.2(6)
C3	-C4	-C5	-C6	0.7(6)
C5	-C4	-C36	-C9	3.9(7)
C36	-C4	-C5	-C6	179.1(4)
C3	-C4	-C5	-C7	-179.7(4)
C3	-C4	-C36	-C9	-177.6(5)
C4	-C5	-C7	-C8	-2.2(7)
C7	-C5	-C6	-C2	-176.0(5)
C6	-C5	-C7	-C8	177.5(5)
C4	-C5	-C6	-C2	3.7(7)
C7	-C5	-C6	-O3	2.1(8)
C4	-C5	-C6	-O3	-178.2(5)
C5	-C7	-C8	-C9	2.8(8)
C5	-C7	-C8	-O1	-180.0(5)
O1	-C8	-C9	-O2	1.0(7)
C7	-C8	-C9	-C36	0.0(8)
C7	-C8	-C9	-O2	178.6(5)
O1	-C8	-C9	-C36	-177.6(5)
C8	-C9	-C36	-C4	-3.3(8)
O2	-C9	-C36	-C4	178.2(5)
C12	-C11	-C16	-C15	2.5(12)
C16	-C11	-C12	-C13	-4.5(12)
C12	-C11	-C16	-C17	178.0(7)

C11	-C12	-C13	-C14	6.9(12)
C12	-C13	-C14	-C15	-7.0(13)
C13	-C14	-C15	-C16	4.2(11)
C14	-C15	-C16	-C11	-2.4(10)
C14	-C15	-C16	-C17	-177.9(6)
C15	-C16	-C17	-O1	-73.1(7)
C11	-C16	-C17	-O1	111.5(7)
C18	-C19	-C20	-O7	-5.1(9)
O8	-C19	-C20	-C21	14.8(8)
O8	-C19	-C20	-O7	-160.3(6)
C18	-C19	-C20	-C21	170.0(6)
C19	-C20	-C21	-C35	177.7(5)
O7	-C20	-C21	-C22	174.2(5)
O7	-C20	-C21	-C35	-7.4(8)
C19	-C20	-C21	-C22	-0.7(7)
C35	-C21	-C22	-C23	-178.9(5)
C20	-C21	-C22	-C23	-0.5(7)
C20	-C21	-C22	-C24	177.8(5)
C20	-C21	-C35	-C26	-178.9(5)
C35	-C21	-C22	-C24	-0.6(8)
C22	-C21	-C35	-C26	-0.5(8)
C24	-C22	-C23	-O8	170.7(5)
C23	-C22	-C24	-C25	-179.1(5)
C21	-C22	-C23	-O8	-11.0(8)
C21	-C22	-C24	-C25	2.6(8)
C22	-C24	-C25	-O5	178.5(5)
C22	-C24	-C25	-C26	-3.6(8)
O5	-C25	-C26	-O6	-0.6(7)
C24	-C25	-C26	-C35	2.6(8)
C24	-C25	-C26	-O6	-178.6(5)

O5	-C25	-C26	-C35	-179.3(5)
O6	-C26	-C35	-C21	-179.1(5)
C25	-C26	-C35	-C21	-0.5(8)
O6	-C28	-C29	-C30	144.0(5)
O6	-C28	-C29	-C34	-34.9(7)
C28	-C29	-C30	-C31	-179.0(6)
C34	-C29	-C30	-C31	0.0(8)
C28	-C29	-C34	-C33	178.9(5)
C30	-C29	-C34	-C33	0.0(8)
C29	-C30	-C31	-C32	0.0(10)
C30	-C31	-C32	-C33	-0.1(11)
C31	-C32	-C33	-C34	0.1(11)
C32	-C33	-C34	-C29	0.0(10)

Table S8 - Contact Distances(Angstrom)

O1	.O2	2.546(6)	C10	.C30_b	3.492(9)
O2	.O1	2.546(6)	C15	.O5_b	3.382(9)
O2	.C32_a	3.300(8)	C24	.O3_k	3.362(7)
O2	.C30_b	3.373(7)	C25	.C9_i	3.515(8)
O3	.C24_c	3.362(7)	C30	.C10_h	3.492(9)
O5	.C15_h	3.382(9)	C30	.O2_h	3.373(7)
O5	.O6	2.545(6)	C32	.O2_m	3.300(8)
O6	.O5	2.545(6)	C33	.C34_b	3.401(10)
O7	.C36_j	3.415(7)	C34	.C10_i	3.546(10)
O1	.H32_a	2.8800	C34	.C33_b	3.401(10)
O2	.H32_a	2.7600	C36	.O7_e	3.415(7)
O2	.H30_b	2.6800	C1	.H11_d	3.0700
O3	.H24_c	2.4800	C3	.H35_e	3.0900
O3	.H7	2.5800	C4	.H3B_f	3.0000
O3	.H19_b	2.8000	C4	.H2	2.9900

O3	.H1B	2.4300
O5	.H15_h	2.9000
O6	.H15_h	2.7200
O6	.H34	2.5500
O6	.H10C_i	2.6800
O7	.H18B	2.7000
O7	.H18C	2.7800
O7	.H2_h	2.9100
O7	.H36_j	2.5200
O7	.H35	2.5500
O8	.H17B_k	2.8400
C9	.C25_g	3.515(8)
C10	.C34_g	3.546(10)
C23	.H7_k	3.0100
C24	.H27A	2.6100
C24	.H27C	2.8200
C25	.H17A_h	3.0100
C26	.H17A_h	2.9500
C27	.H24	2.4900
C27	.H32_b	3.0200
C28	.H35	2.5600
C30	.H1C_j	2.8300
C32	.H27B_b	3.0500
C33	.H34_b	2.8100
C34	.H10C_i	2.9900
C34	.H33_b	2.8000
C35	.H28A	2.7900
C35	.H28B	2.8200
C36	.H10A	2.7800
C36	.H10C	2.7600
C7	.H17A	2.7700
C7	.H17B	2.7400
C8	.H28B_b	3.0500
C9	.H28B_b	3.0900
C10	.H34_g	2.7100
C10	.H36	2.5400
C10	.H30_b	2.7200
C14	.H31_a	2.9500
C15	.H31_a	3.0200
C17	.H7	2.4900
C21	.H3A_i	3.0900
C22	.H19	3.0000
C22	.H23A_l	3.0300
H7	.C23_c	3.0100
H7	.O3	2.5800
H7	.H23B_c	2.5000
H7	.H17A	2.3500
H7	.H17B	2.2400
H10A	.H30_b	2.3100
H10A	.C36	2.7800
H10A	.H36	2.3800
H10B	.H34_g	2.3500
H10C	.O6_g	2.6800
H10C	.C34_g	2.9900
H10C	.H34_g	2.2400
H10C	.H36	2.3100
H10C	.C36	2.7600
H11	.C1_d	3.0700
H11	.H17B	2.2800
H11	.H1A_d	2.2000

H1A	.H11_d	2.2000	H15	.O5_b	2.9000
H1B	.O3	2.4300	H15	.H17A	2.5700
H1B	.H18B_b	2.4200	H15	.O6_b	2.7200
H1C	.C30_e	2.8300	H17A	.H7	2.3500
H1C	.H30_e	2.3900	H17A	.H15	2.5700
H2	.O7_b	2.9100	H17A	.C7	2.7700
H2	.C4	2.9900	H17A	.C26_b	2.9500
H3A	.C21_g	3.0900	H17A	.C25_b	3.0100
H3A	.H36	2.5900	H17B	.O8_c	2.8400
H3B	.C4_f	3.0000	H17B	.H11	2.2800
H7	.C17	2.4900	H17B	.H7	2.2400
H17B	.C7	2.7400	H30	.C10_h	2.7200
H18B	.O7	2.7000	H30	.H28B	2.2500
H18B	.H1B_h	2.4200	H30	.O2_h	2.6800
H18C	.O7	2.7800	H30	.H10A_h	2.3100
H19	.C22	3.0000	H31	.C15_m	3.0200
H19	.O3_h	2.8000	H31	.C14_m	2.9500
H23A	.C22_l	3.0300	H32	.O2_m	2.7600
H23B	.H24	2.5700	H32	.O1_m	2.8800
H23B	.H7_k	2.5000	H32	.C27_b	3.0200
H24	.C27	2.4900	H32	.H27B_b	2.4400
H24	.O3_k	2.4800	H33	.C34_b	2.8000
H24	.H27C	2.4400	H33	.H34_b	2.2500
H24	.H23B	2.5700	H34	.C10_i	2.7100
H24	.H27A	2.1300	H34	.C33_b	2.8100
H27A	.H24	2.1300	H34	.H10C_i	2.2400
H27A	.C24	2.6100	H34	.H33_b	2.2500
H27B	.C32_b	3.0500	H34	.H10B_i	2.3500
H27B	.H32_b	2.4400	H34	.O6	2.5500
H27C	.C24	2.8200	H35	.H28B	2.4100

H27C	.H24	2.4400	H35	.H28A	2.3300
H28A	.C35	2.7900	H35	.O7	2.5500
H28A	.H35	2.3300	H35	.C3_j	3.0900
H28B	.H30	2.2500	H35	.C28	2.5600
H28B	.C35	2.8200	H36	.H3A	2.5900
H28B	.C9_h	3.0900	H36	.H10A	2.3800
H28B	.H35	2.4100	H36	.H10C	2.3100
H28B	.C8_h	3.0500	H36	.C10	2.5400
H30	.H1C_j	2.3900	H36	.O7_e	2.5200

Table S9 - Hydrogen Bonds (Angstrom, Deg)

C1	-- H1B	.. O3	0.9600	2.4300	2.764(8)	100.00	.
C24	-- H24	.. O3	0.9300	2.4800	3.362(7)	158.00	1_544
C36	-- H36	.. O7	0.9300	2.5200	3.415(7)	161.00	1_456

Translation of Symmetry Code to Equiv.Pos

a =[1455.00] = [1_455] =-1+x,y,z

b =[2666.00] = [2_666] =1-x,1-y,1-z

c =[1566.00] = [1_566] =x,1+y,1+z

d =[2577.00] = [2_577] =-x,2-y,2-z

e =[1456.00] = [1_456] =-1+x,y,1+z

f =[2567.00] = [2_567] =-x,1-y,2-z

g =[2566.00] = [2_566] =-x,1-y,1-z

h =[2666.00] = [2_666] =1-x,1-y,1-z

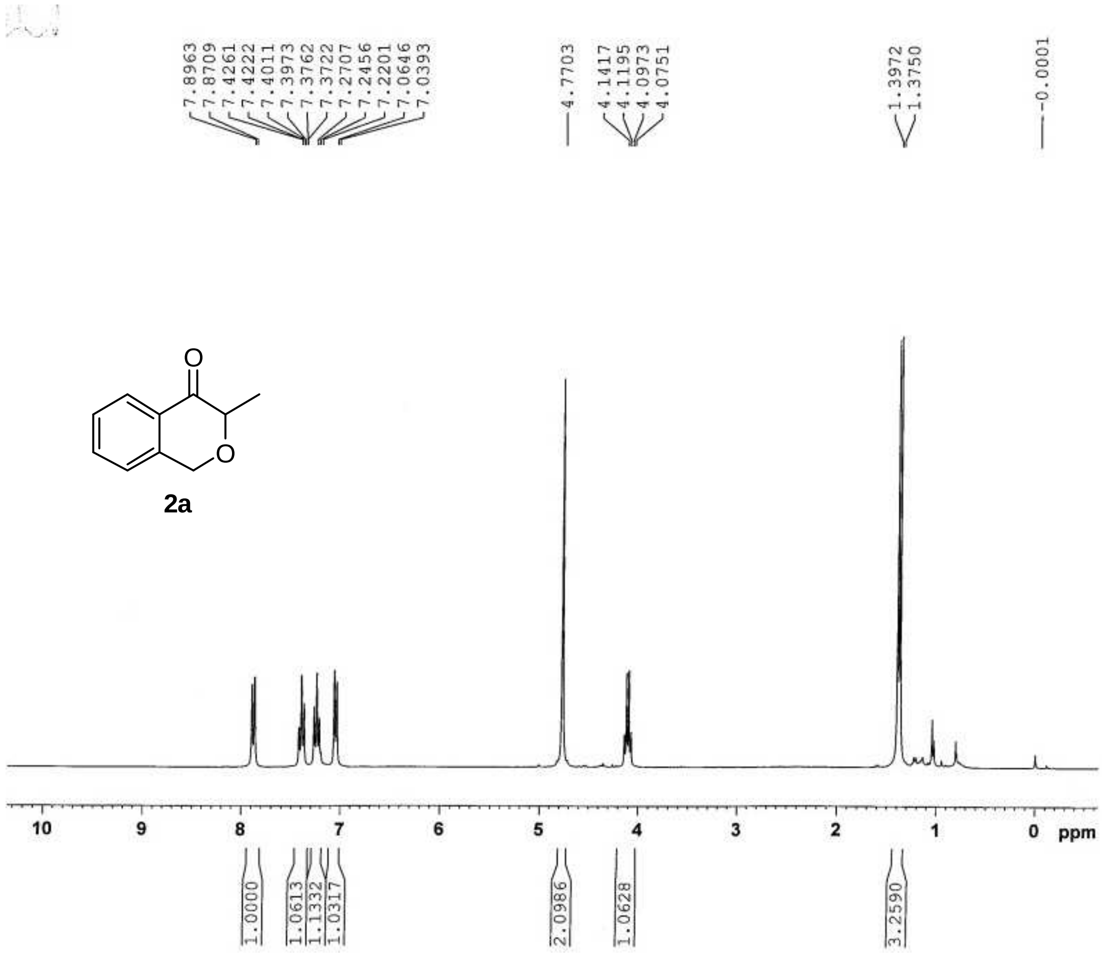
i =[2566.00] = [2_566] =-x,1-y,1-z

j =[1654.00] = [1_654] =1+x,y,-1+z

k =[1544.00] = [1_544] =x,-1+y,-1+z

l =[2655.00] = [2_655] =1-x,-y,-z

m =[1655.00] = [1_655] =1+x,y,z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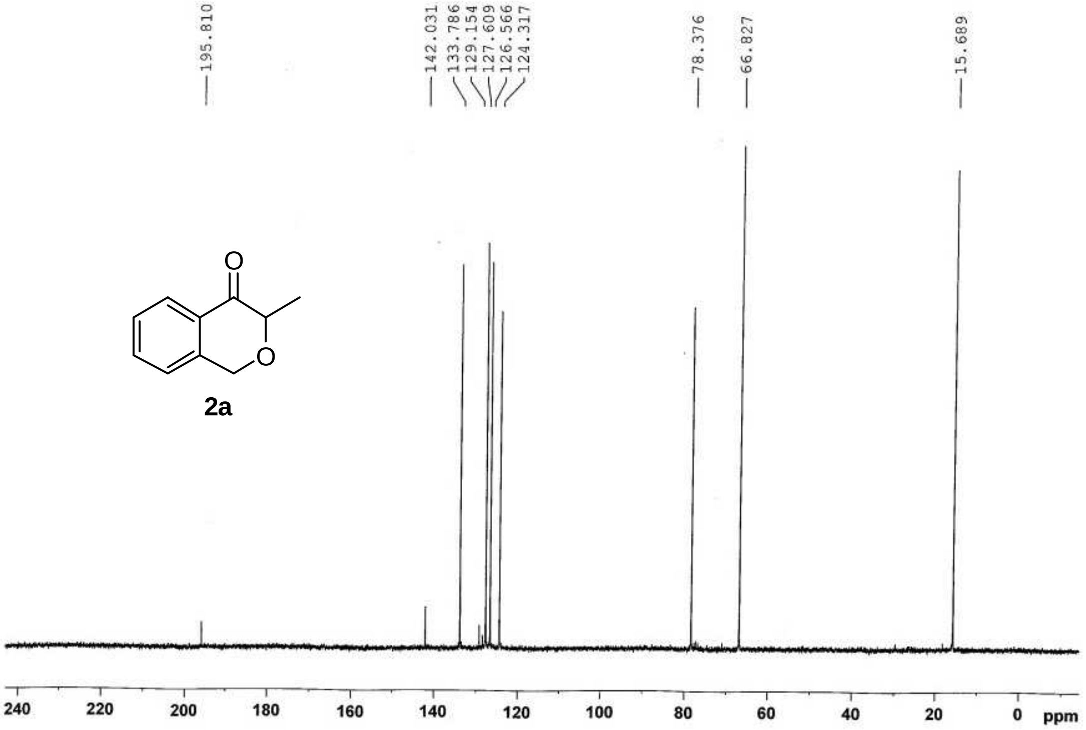
7.3762
7.3722
7.2707
7.2456
7.2201
7.0646
7.0393
4.7703
4.1417
4.1195
4.0973
4.0751
1.3972
1.3750
-0.0001
O
O
2a
10
9
8
7
6
5
4
3
2
1
0
ppm
1.0000
1.0613
1.1332
1.0317
2.0986
1.0628
3.2590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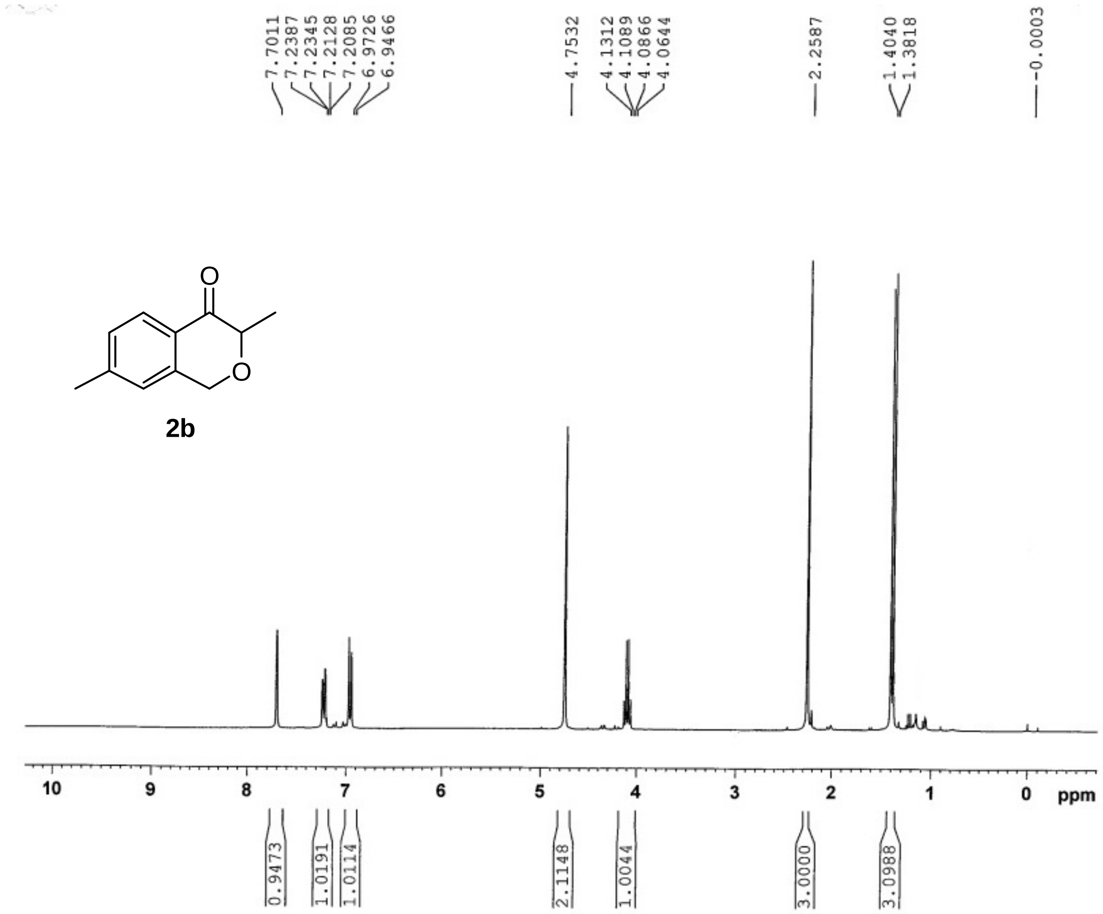
142.031
133.786
129.154
127.609
126.566
124.317
78.376
66.827
15.689
O
O
2a
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm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7.2345
7.2128
7.2085
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6.9466
4.7532
4.1312
4.1089
4.0866
4.0644
2.2587
1.4040
1.3818
-0.0003
O
O
2b
10
9
8
7
6
5
4
3
2
1
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ppm
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1.0191
1.0114
2.1148
1.0044
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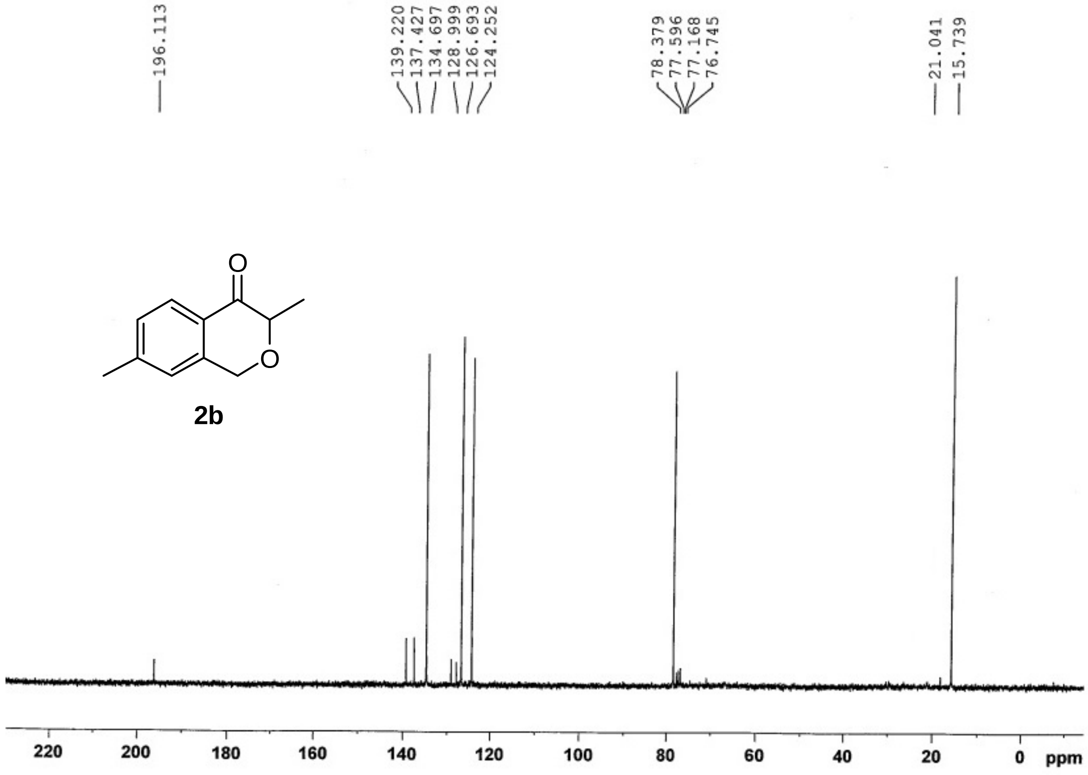
3.0988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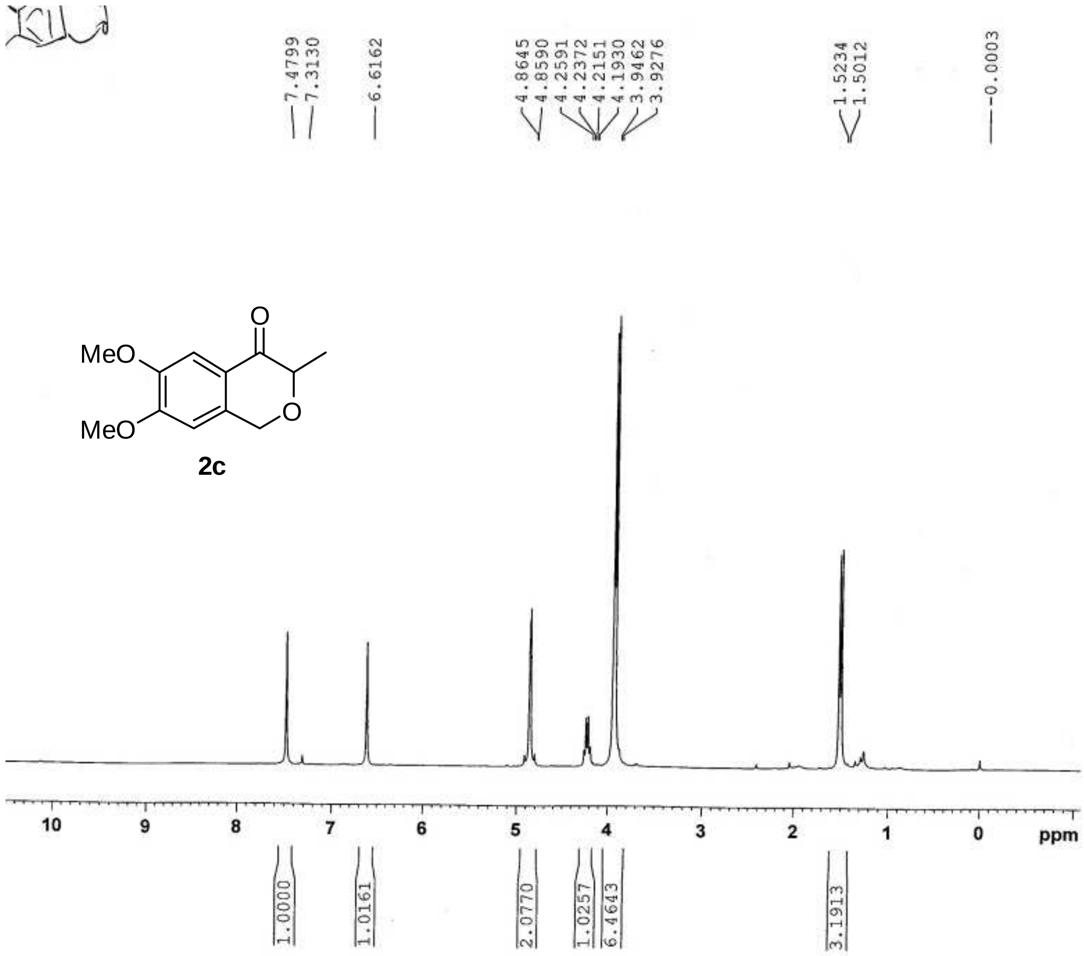
126.693
124.252
78.379
77.596
77.168
76.745
21.041
15.739
O
O
2b
220
200
180
160
140
120
100
80
60
40
20
0
ppm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3.9276
1.5234
1.5012
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MeO
MeO
O
O
2c
10
9
8
7
6
5
4
3
2
1
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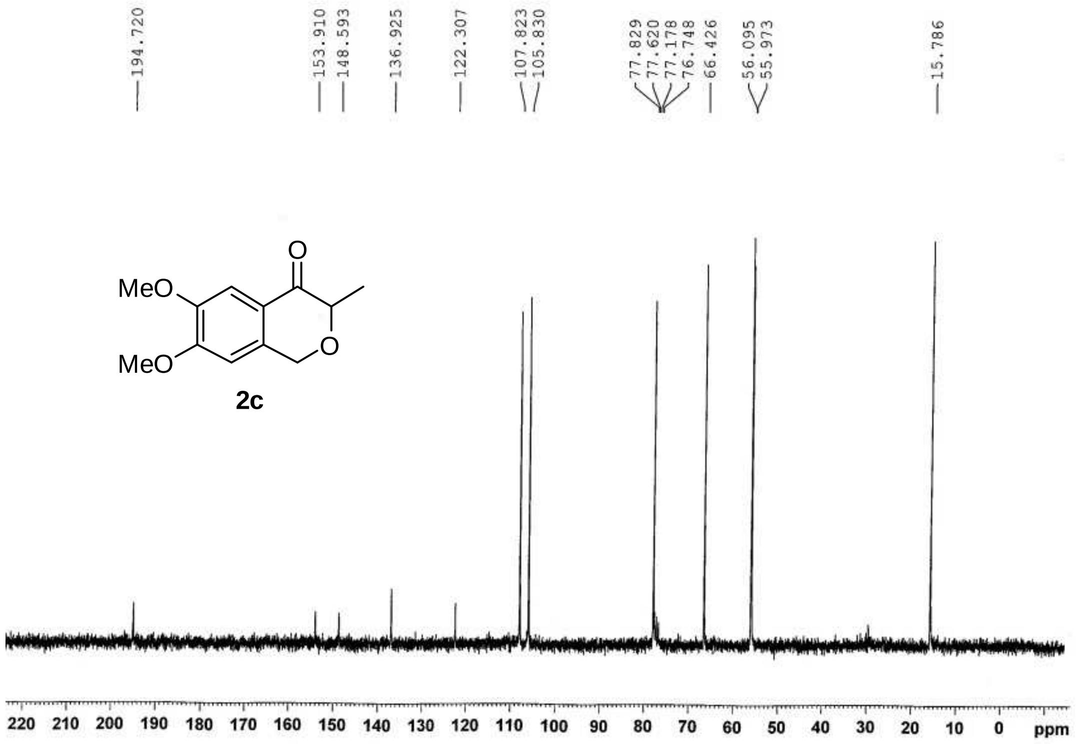
3.1913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66.426
56.095
55.973
15.786
MeO
MeO
O
O
2c
220
210
200
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180
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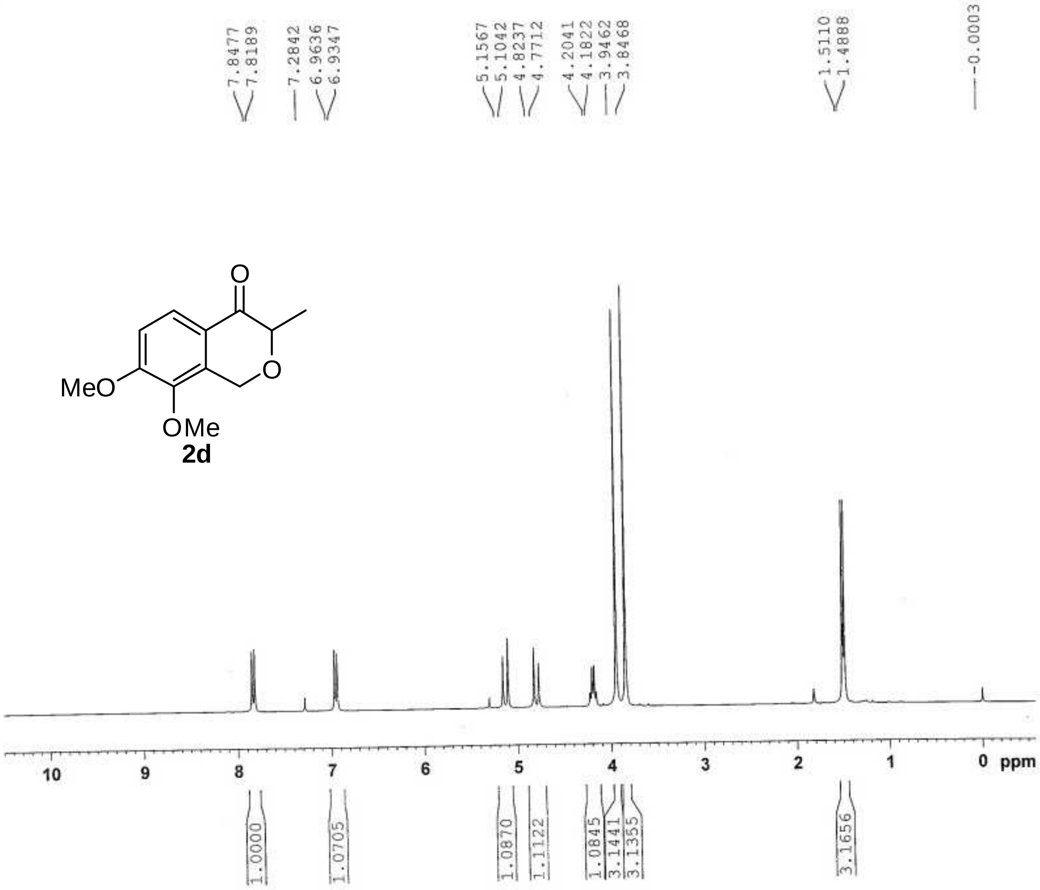
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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5.1042
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4.1822
3.9462
3.8468
1.5110
1.4888
-0.0003
O
MeO
O
OMe
2d
10
9
8
7
6
5
4
3
2
1
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ppm
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1.1122
1.0845
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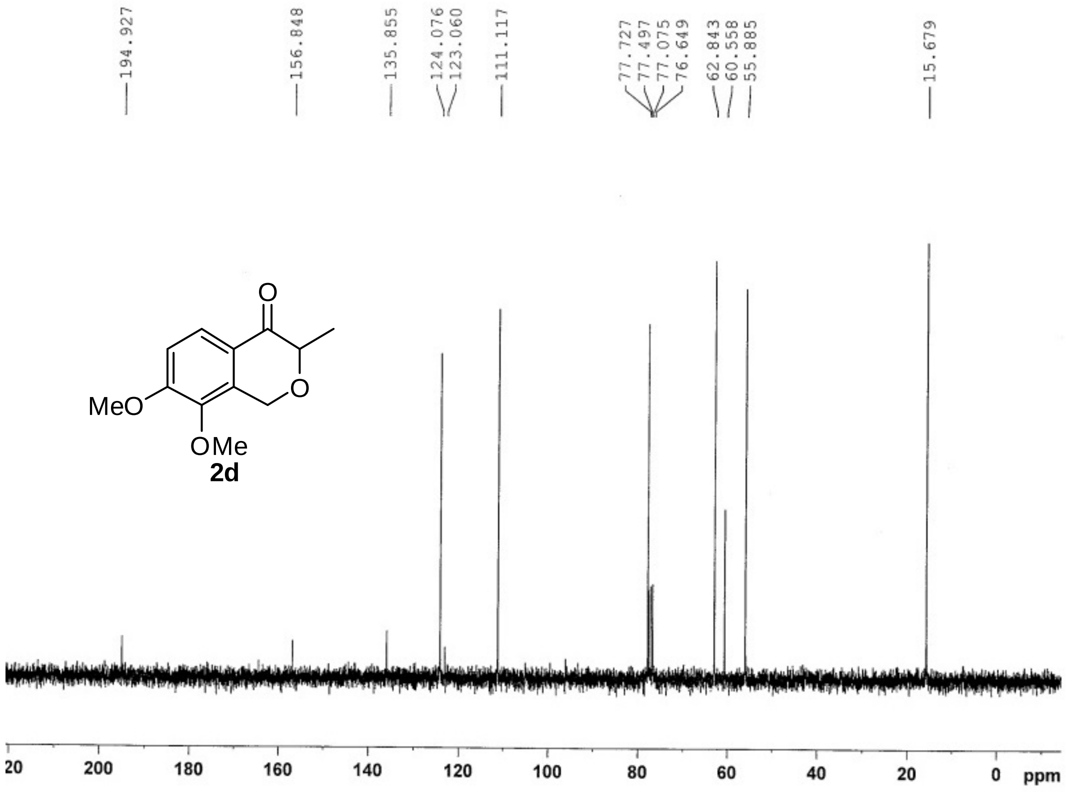
3.1355
3.1656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55.885
15.679
O
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O
OMe
2d
20
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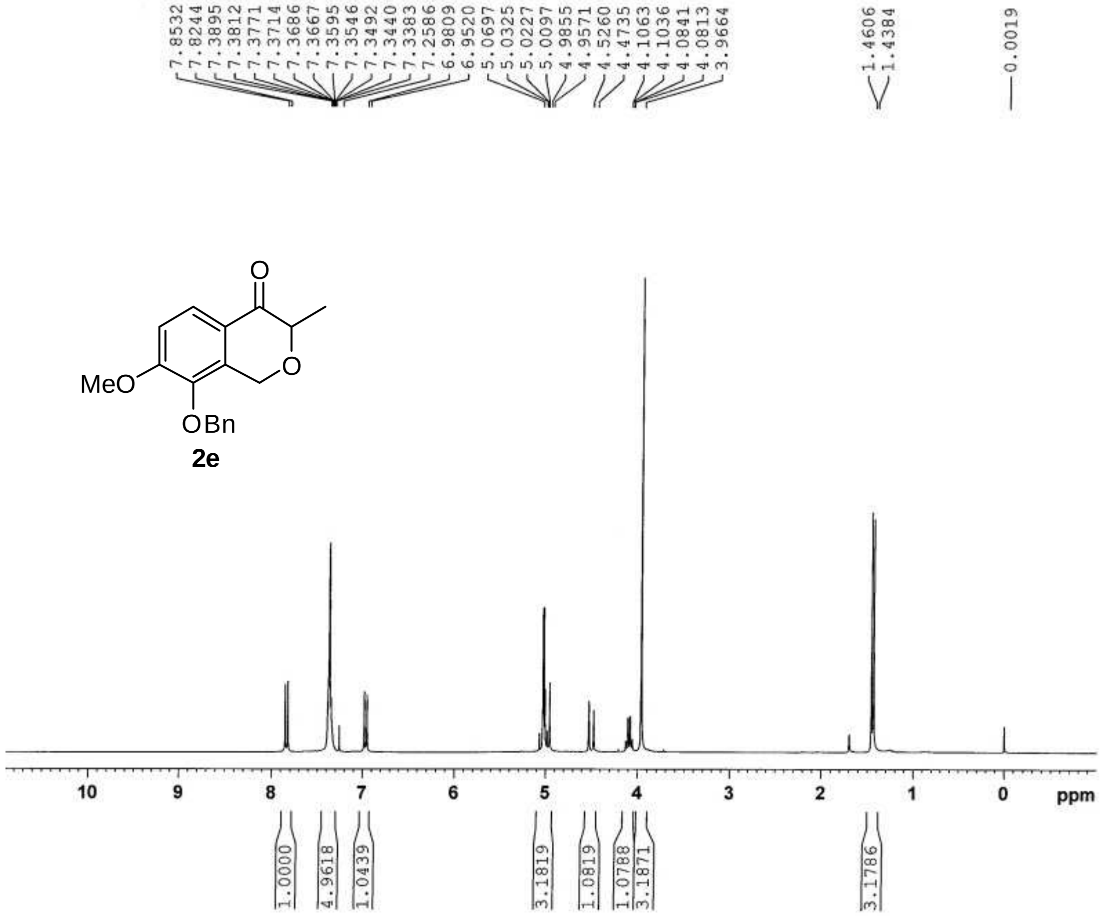
140
120
100
80
60
40
20
0
ppm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7.3440
7.3383
7.2586
6.9809
6.9520
5.0697
5.0325
5.0227
5.0097
4.9855
4.9571
4.5260
4.4735
4.1063
4.1036
4.0841
4.0813
3.9664
1.4606
1.4384
0.0019
O
MeO
O
OBn
2e
10
9
8
7
6
5
4
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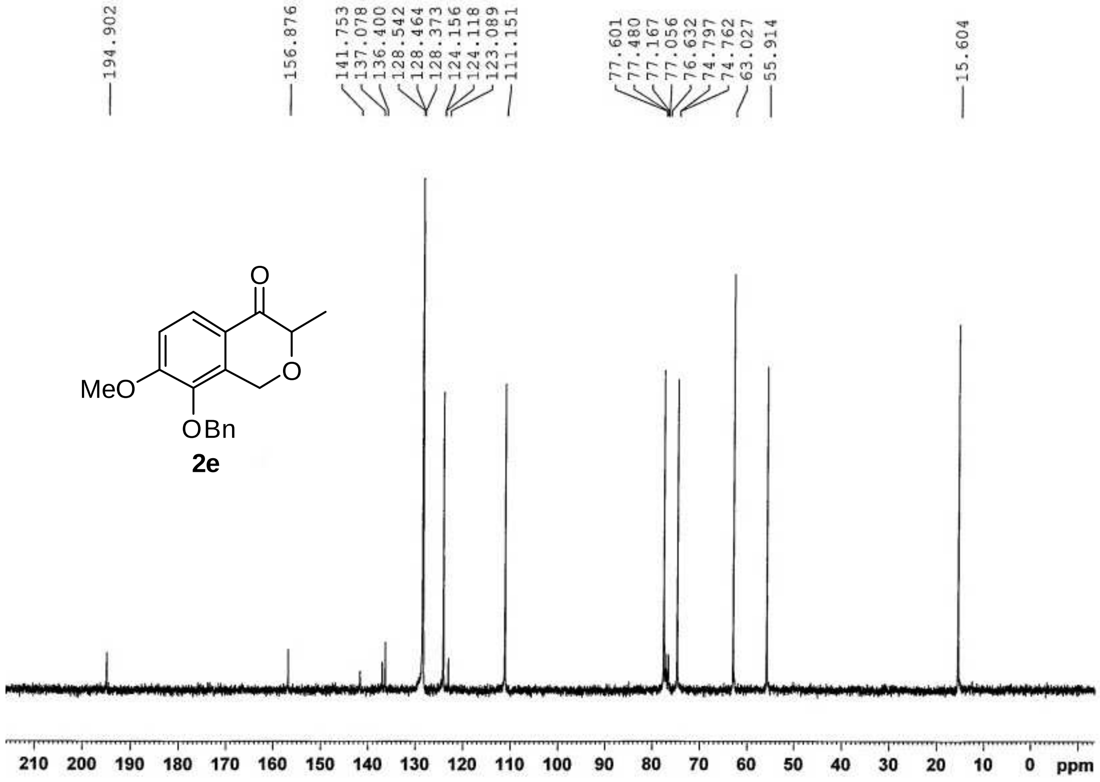
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77.480
77.167
77.056
76.632
74.797
74.762
63.027
55.914
15.604
O
MeO
O
OBn
2e
210
200
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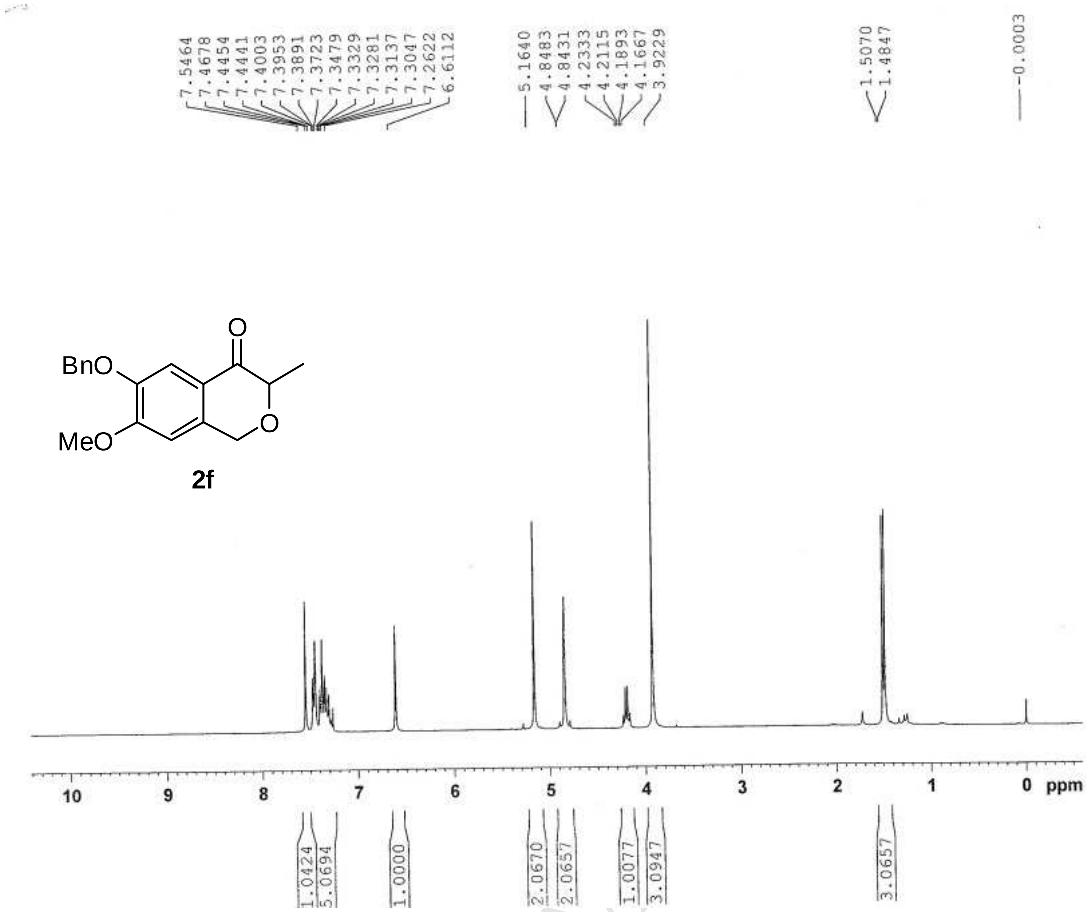
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O
2f
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6
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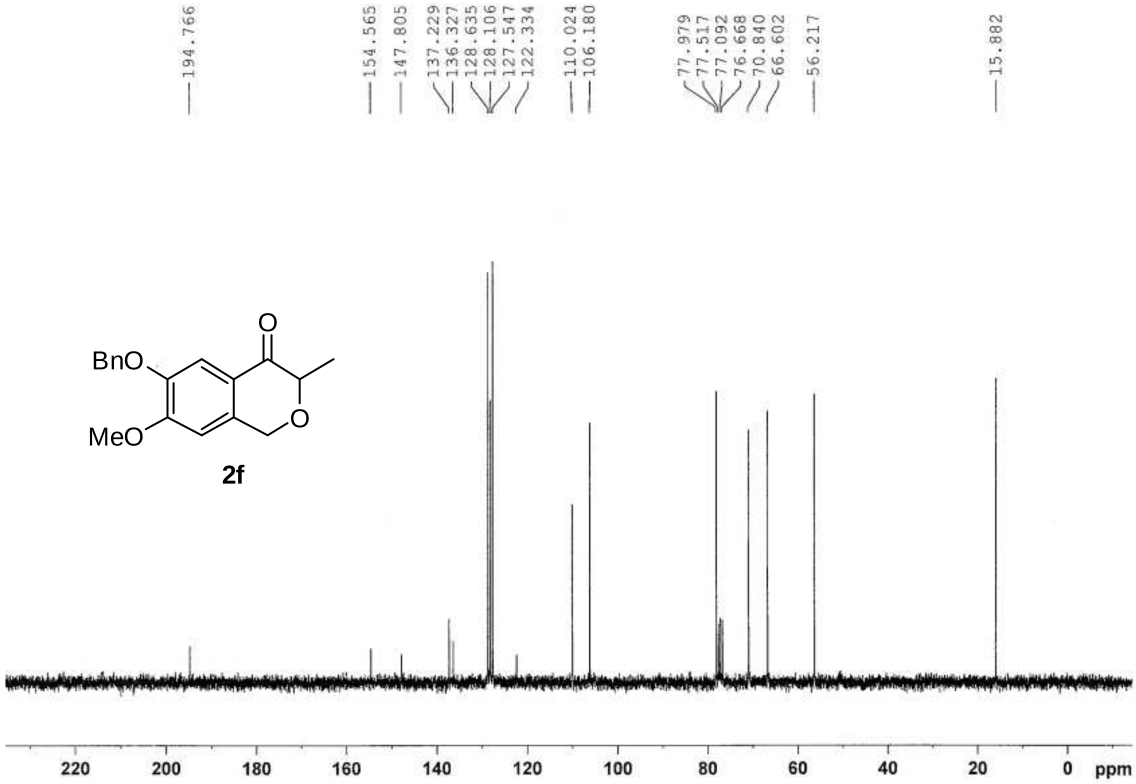
3.0657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77.517
77.092
76.668
70.840
66.602
56.217
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O
O
2f
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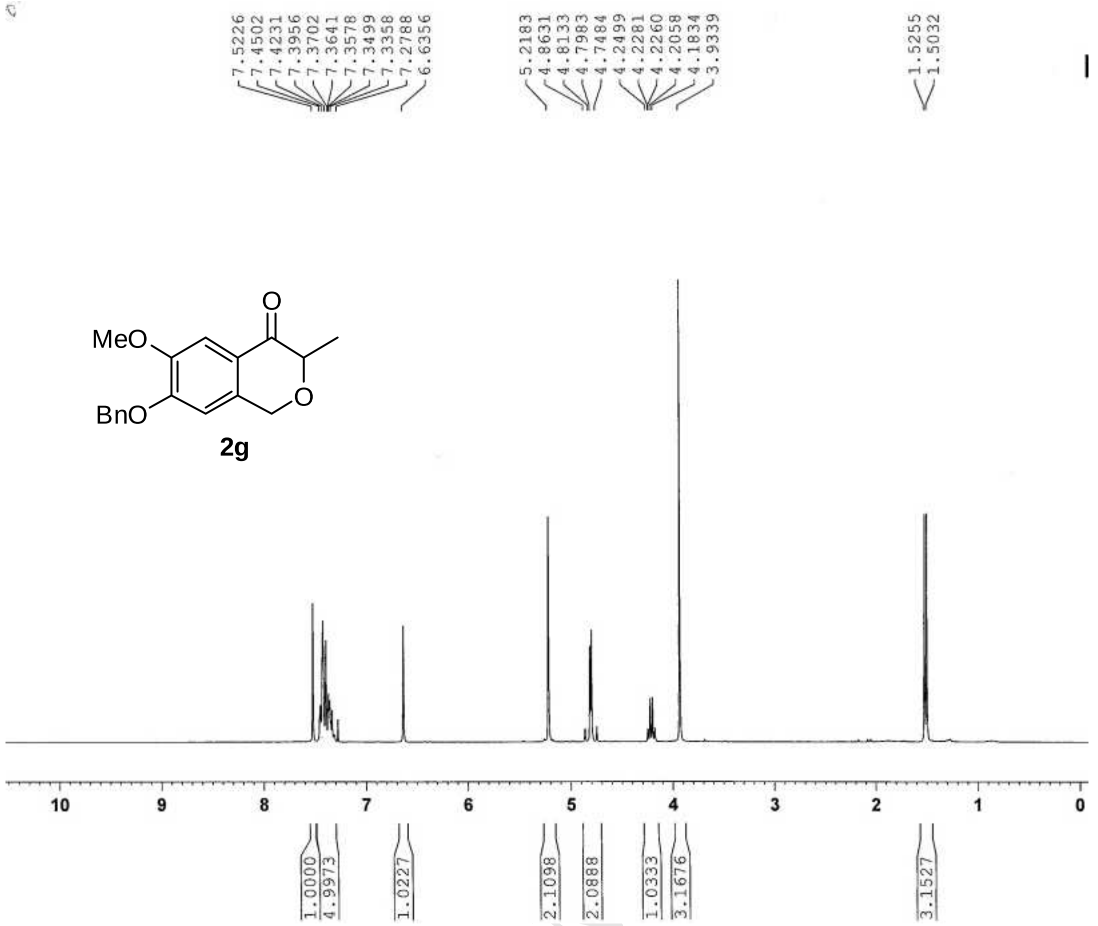
120
100
80
60
40
20
0
ppm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5.2183
4.8631
4.8133
4.7983
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4.2499
4.2281
4.2260
4.2058
4.1834
3.9339
1.5255
1.5032
MeO
BnO
O
O
2g
10
9
8
7
6
5
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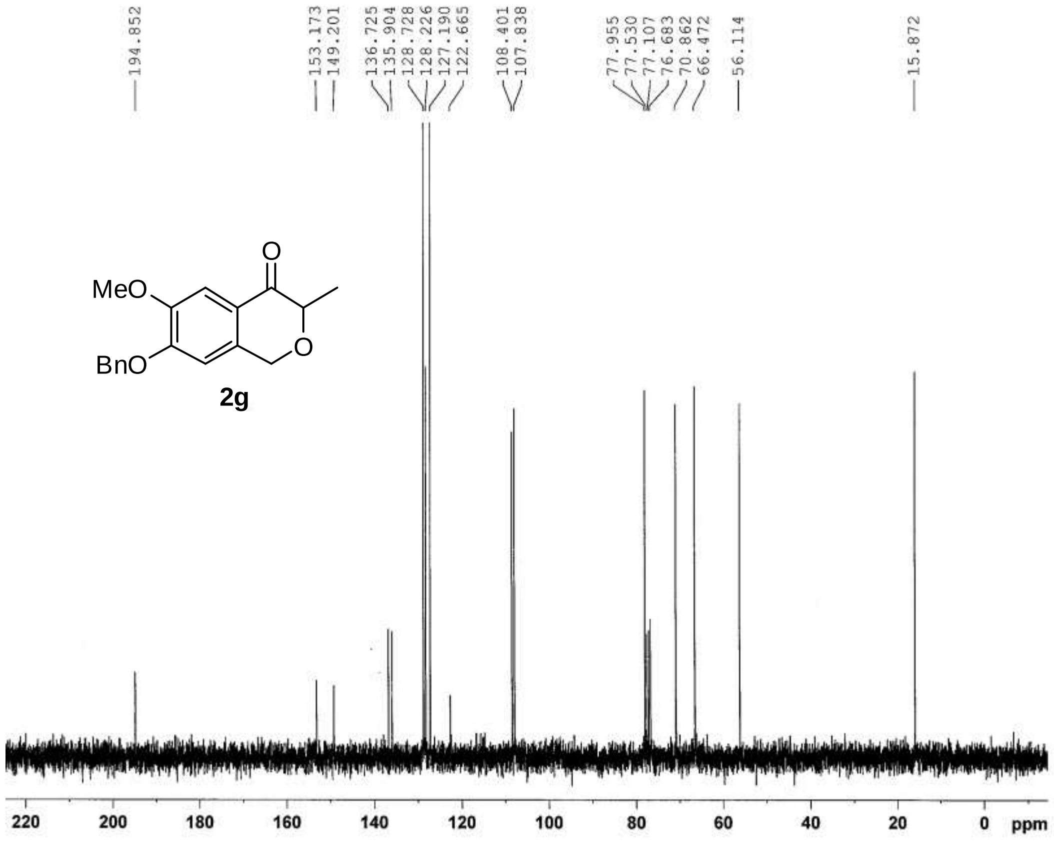
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77.107
76.683
70.862
66.472
56.114
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O
O
2g
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40
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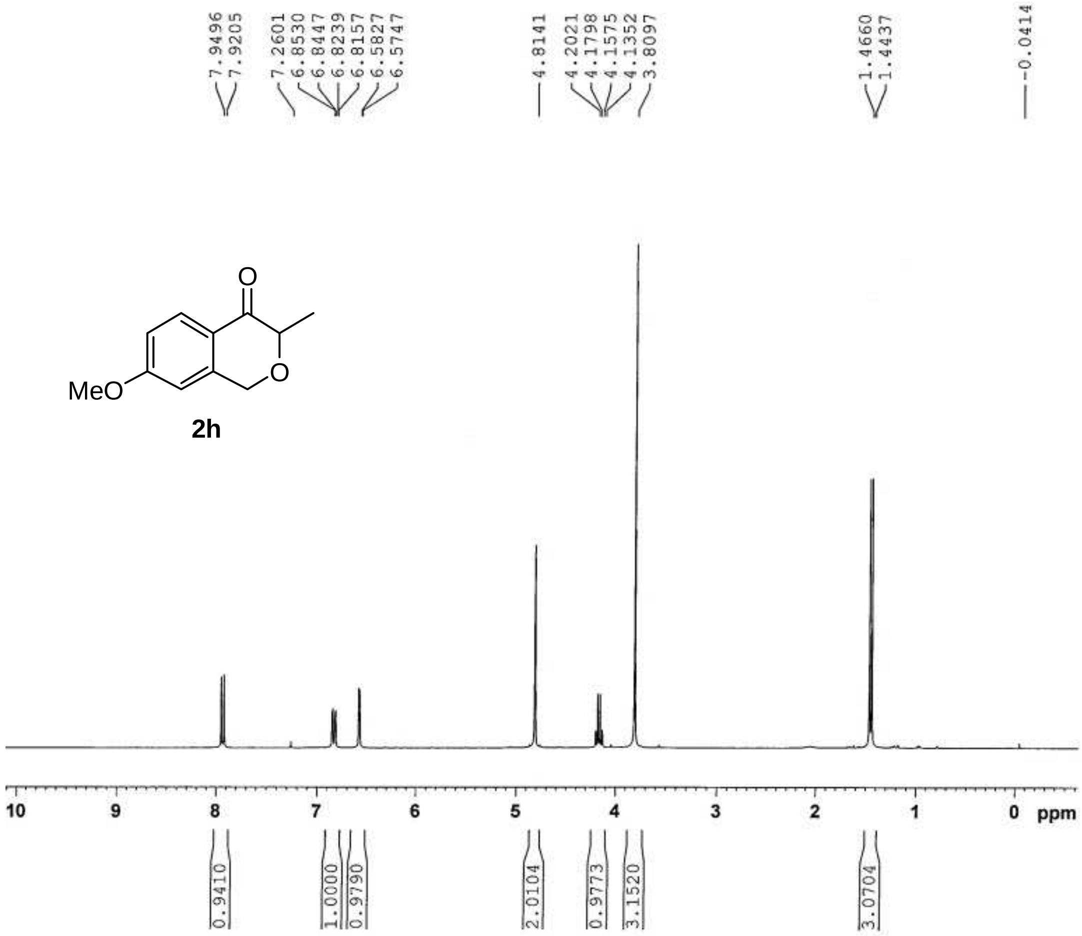
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4.1798
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1.4660
1.4437
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O
O
2h
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8
7
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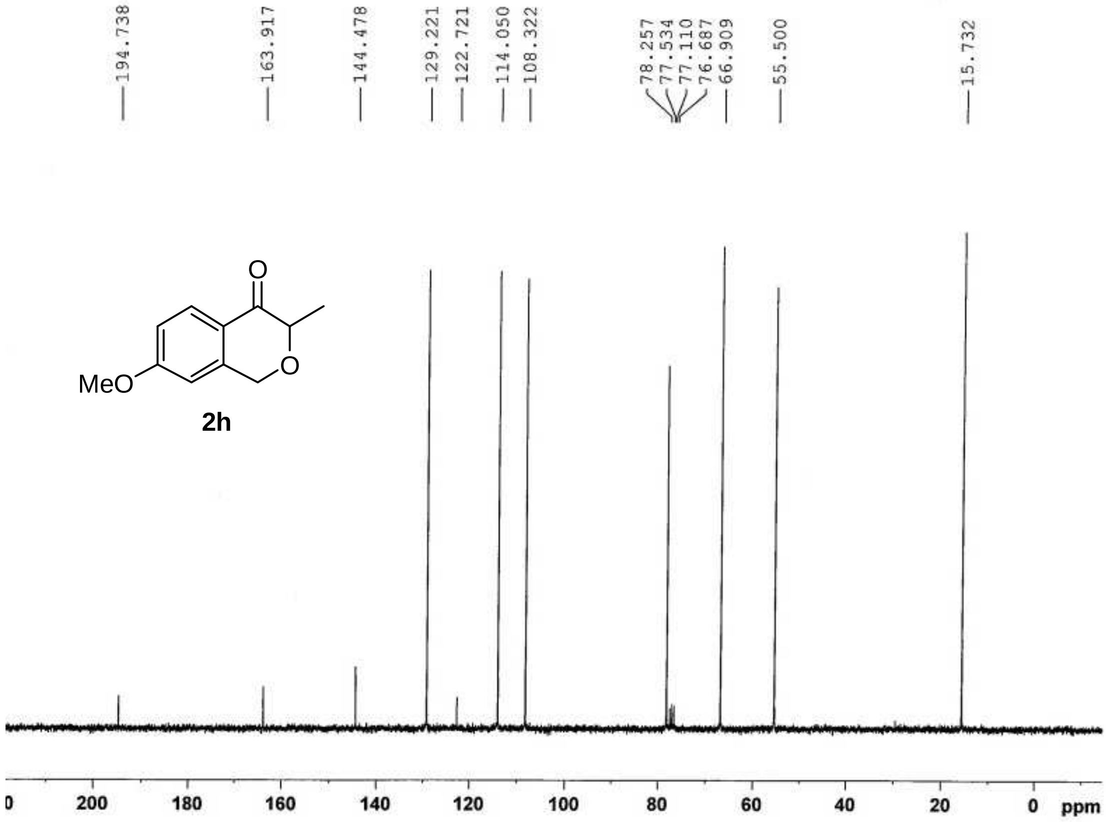
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MeO
O
O
2h
200
180
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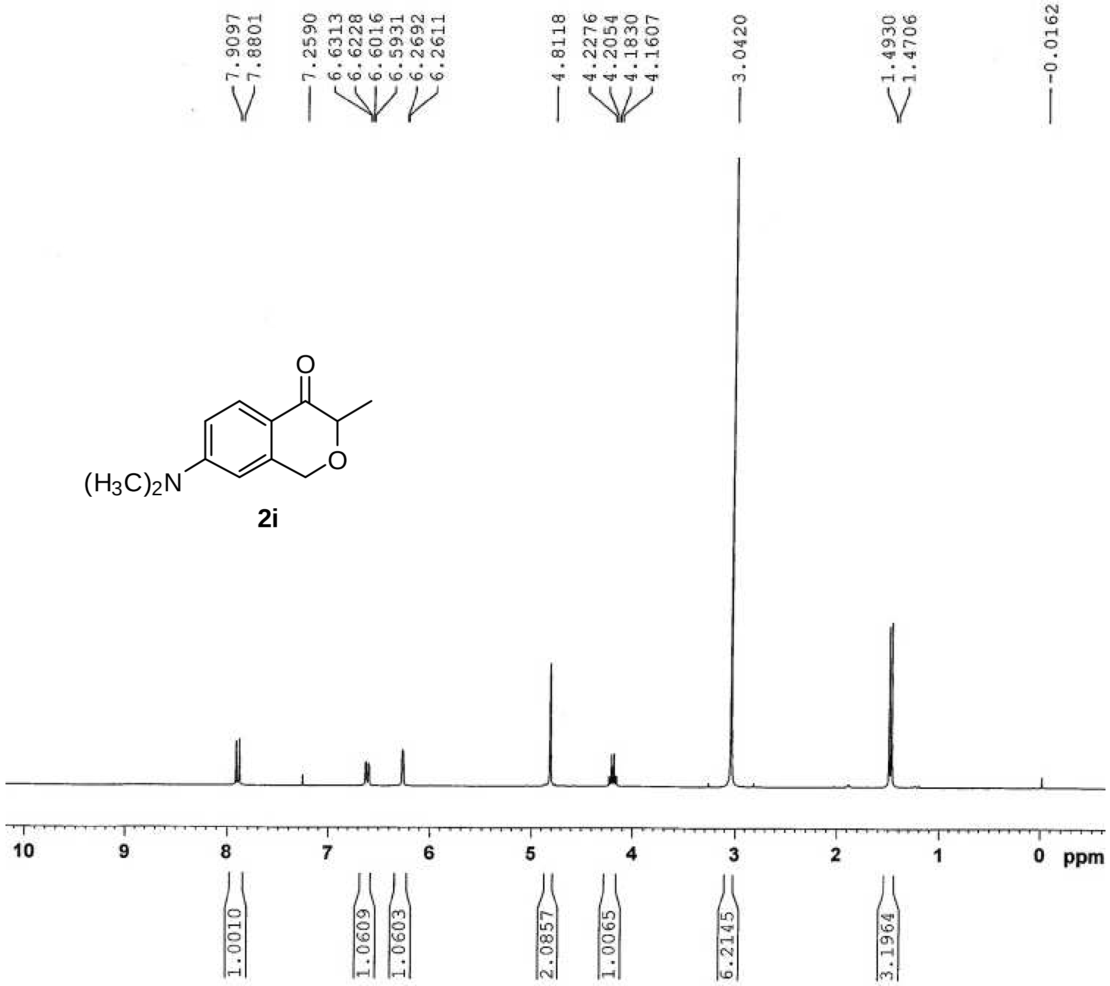
ppm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4.2054
4.1830
4.1607
3.0420
1.4930
1.4706
-0.0162
O
O
(H3C)2N
2i
10
9
8
7
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5
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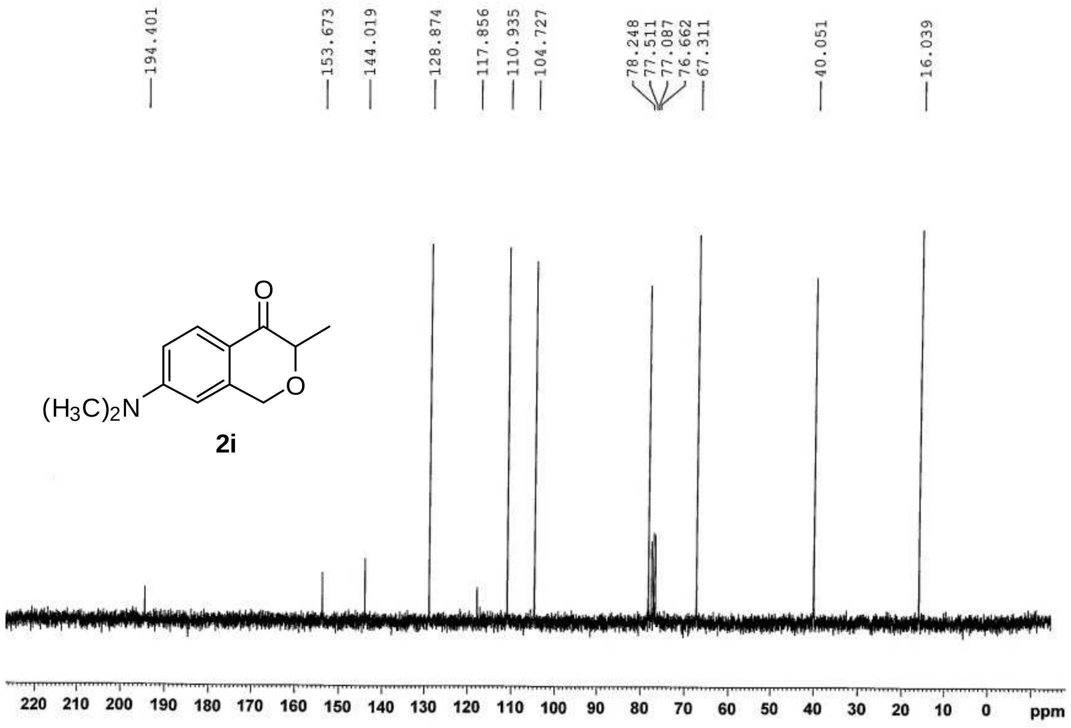
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40.051
16.039
O
O
(H3C)2N
2i
220
210
200
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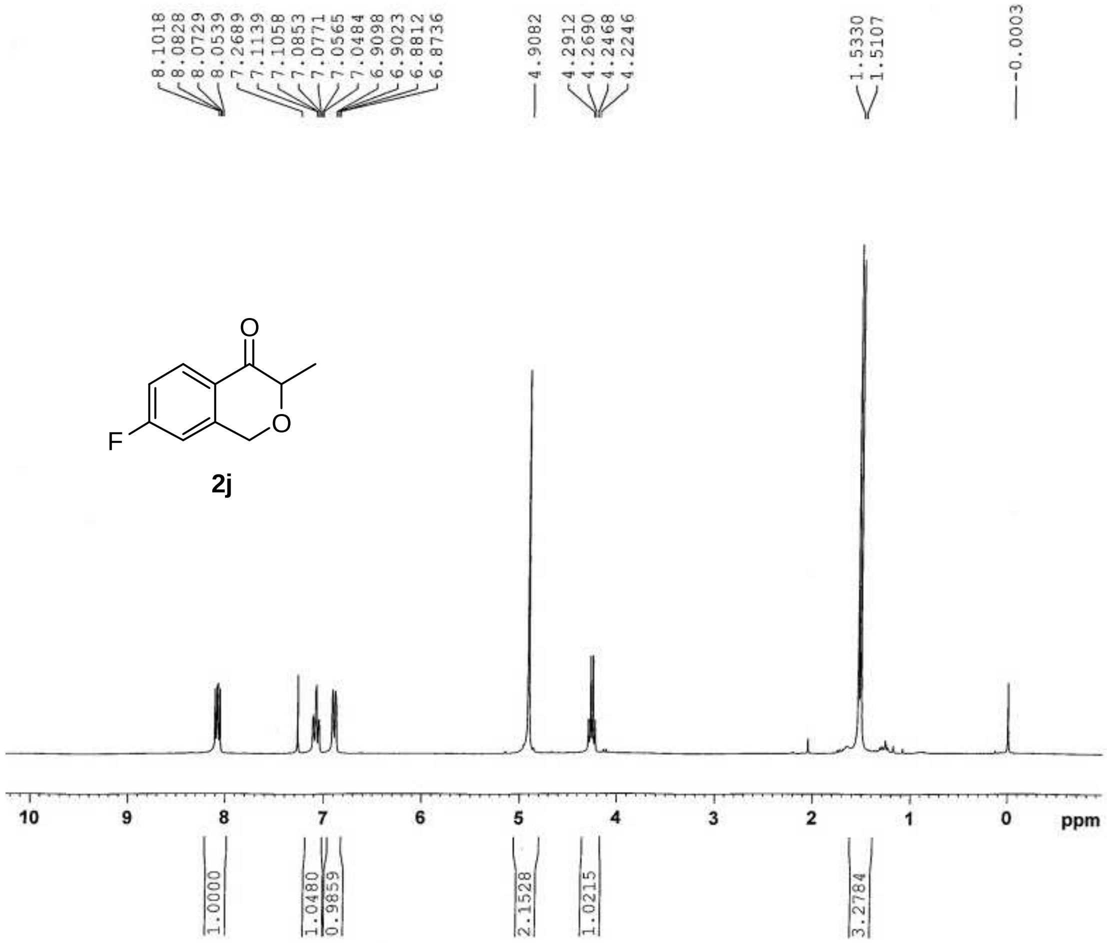
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6.8736
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O
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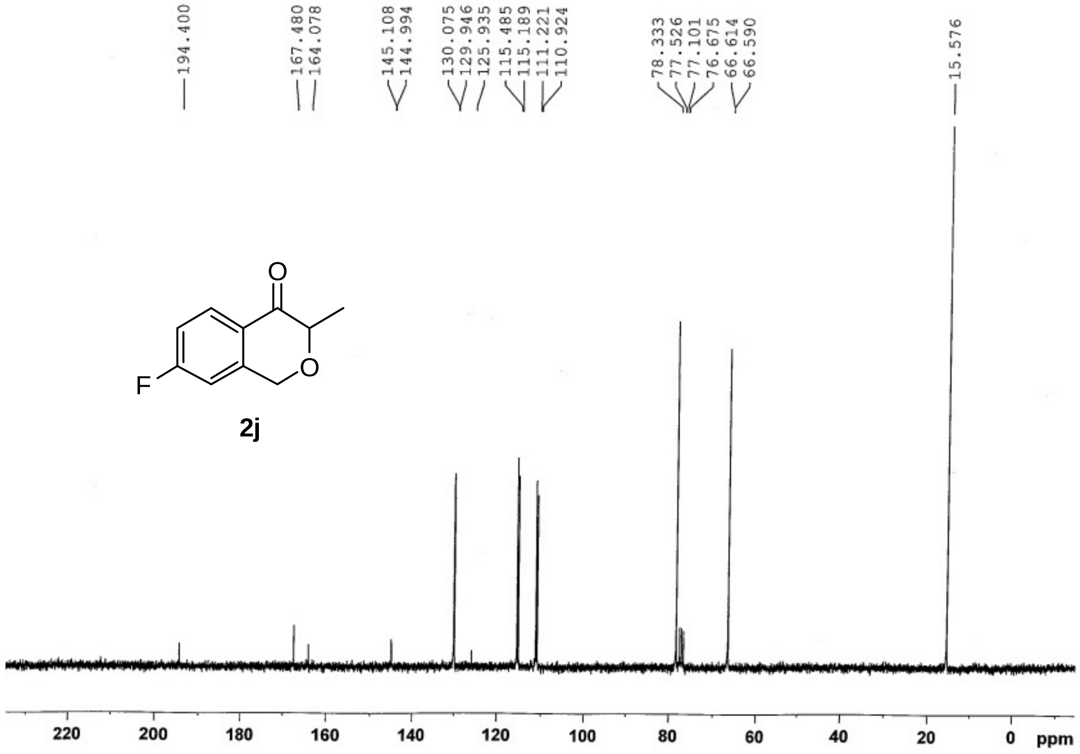
3.2784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125.935
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115.189
111.221
110.924
78.333
77.526
77.101
76.675
66.614
66.590
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O
F
2j
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200
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120
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40
20
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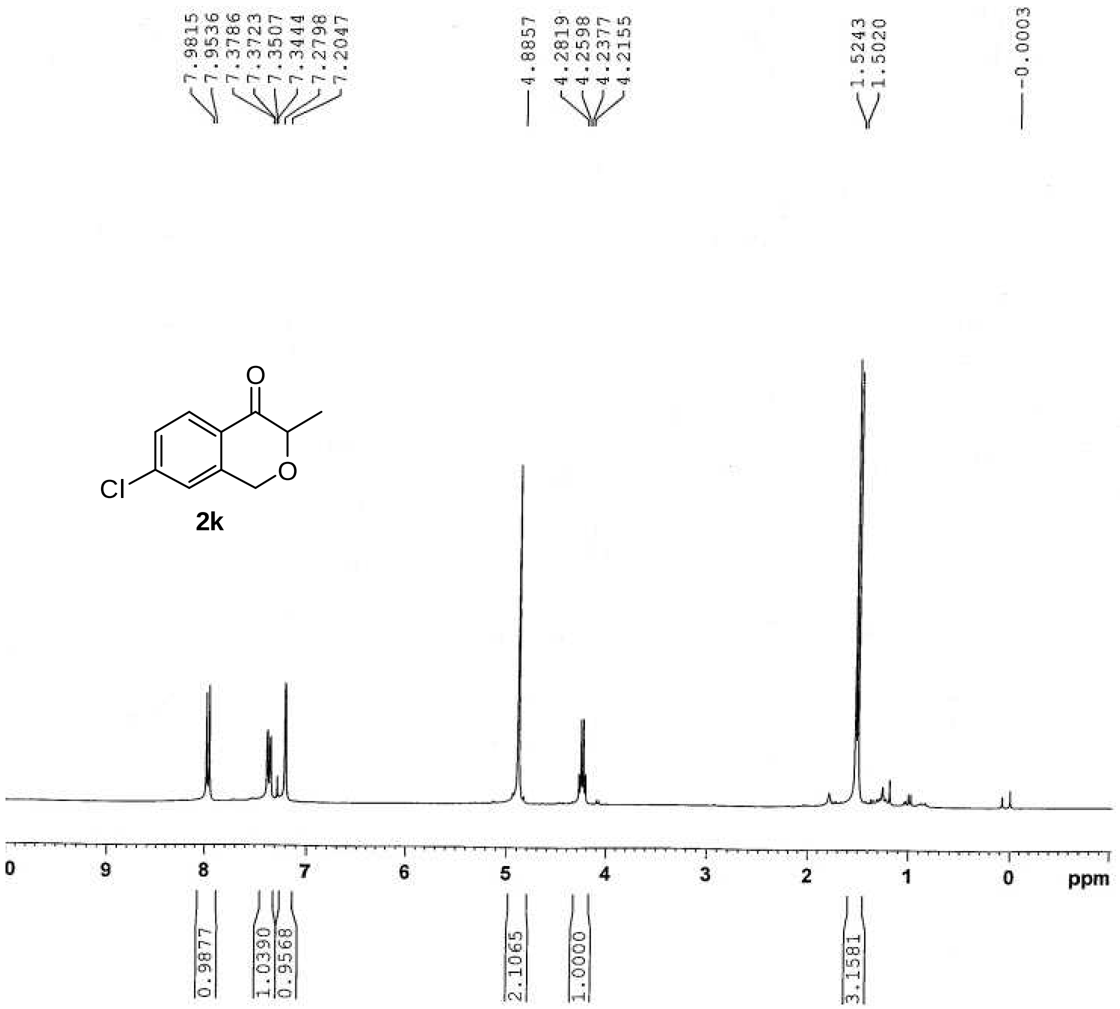
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4.2598
4.2377
4.2155
1.5243
1.5020
-0.0003
O
O
Cl
2k
0
9
8
7
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5
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3
2
1
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ppm
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0.9568
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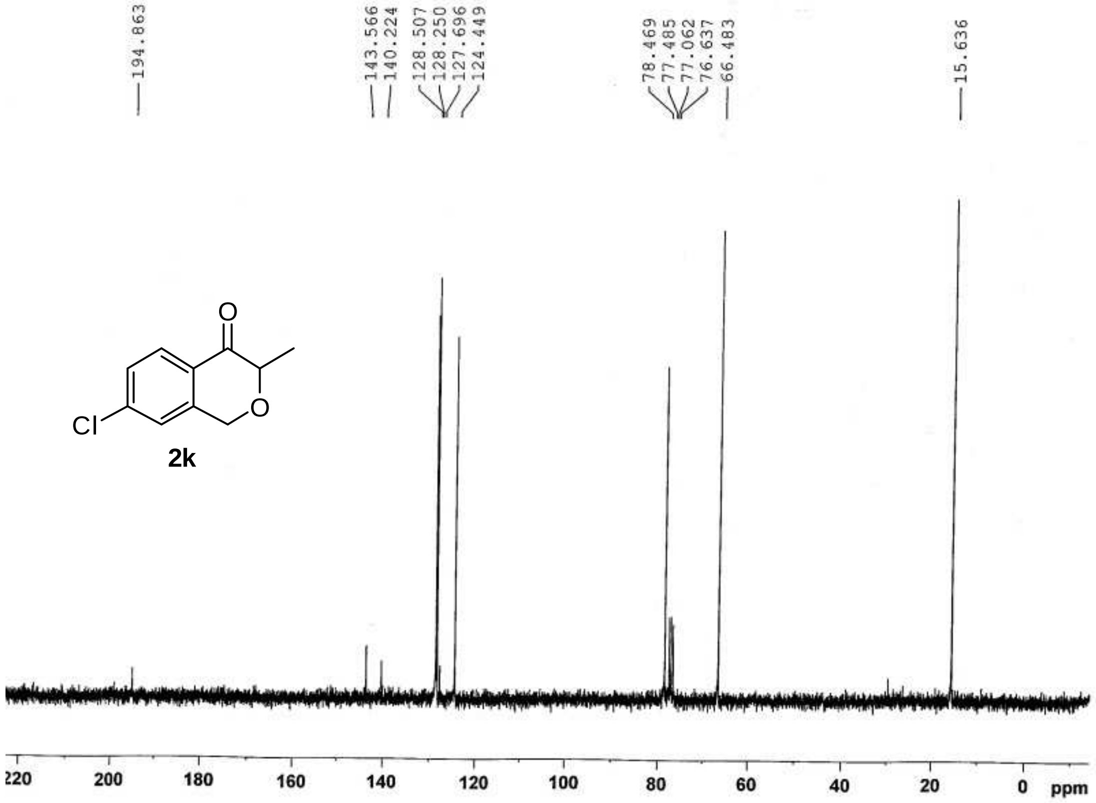
3.1581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140.224
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128.250
127.696
124.449
78.469
77.485
77.062
76.637
66.483
15.636
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O
Cl
2k
220
200
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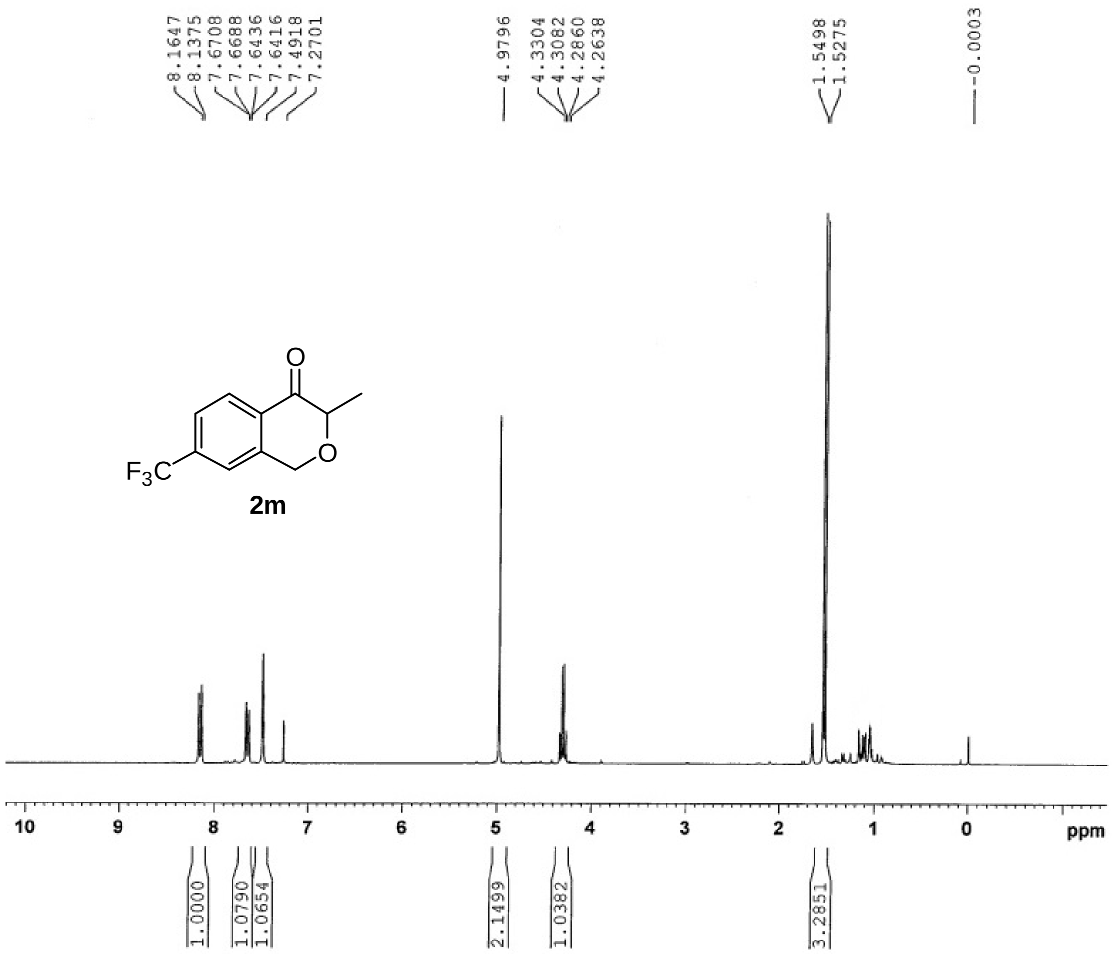
160
140
120
100
80
60
40
20
0
ppm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7.6708
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7.6436
7.6416
7.4918
7.2701
4.9796
4.3304
4.3082
4.2860
4.2638
1.5498
1.5275
-0.0003
O
F3C
O
2m
10
9
8
7
6
5
4
3
2
1
0
ppm
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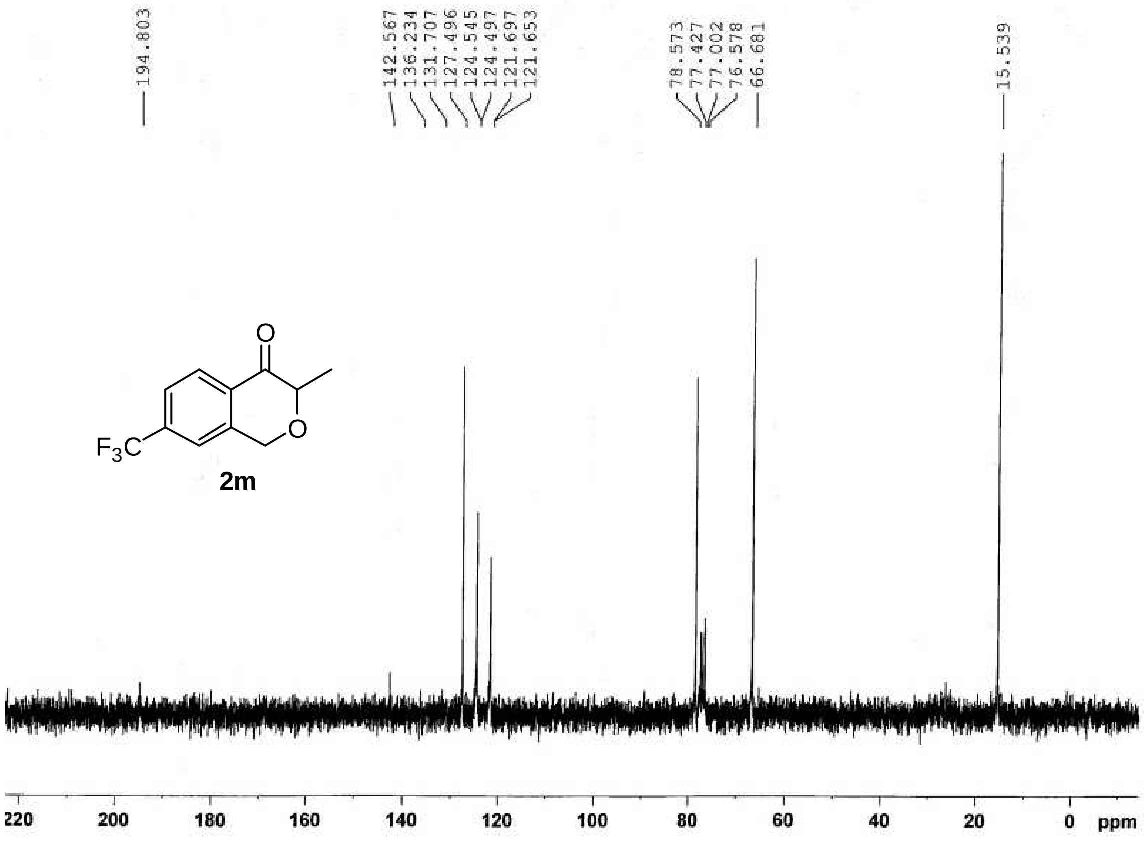
1.0790
1.0654
2.1499
1.0382
3.2851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127.496
124.545
124.497
121.697
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78.573
77.427
77.002
76.578
66.681
15.539
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O
2m
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200
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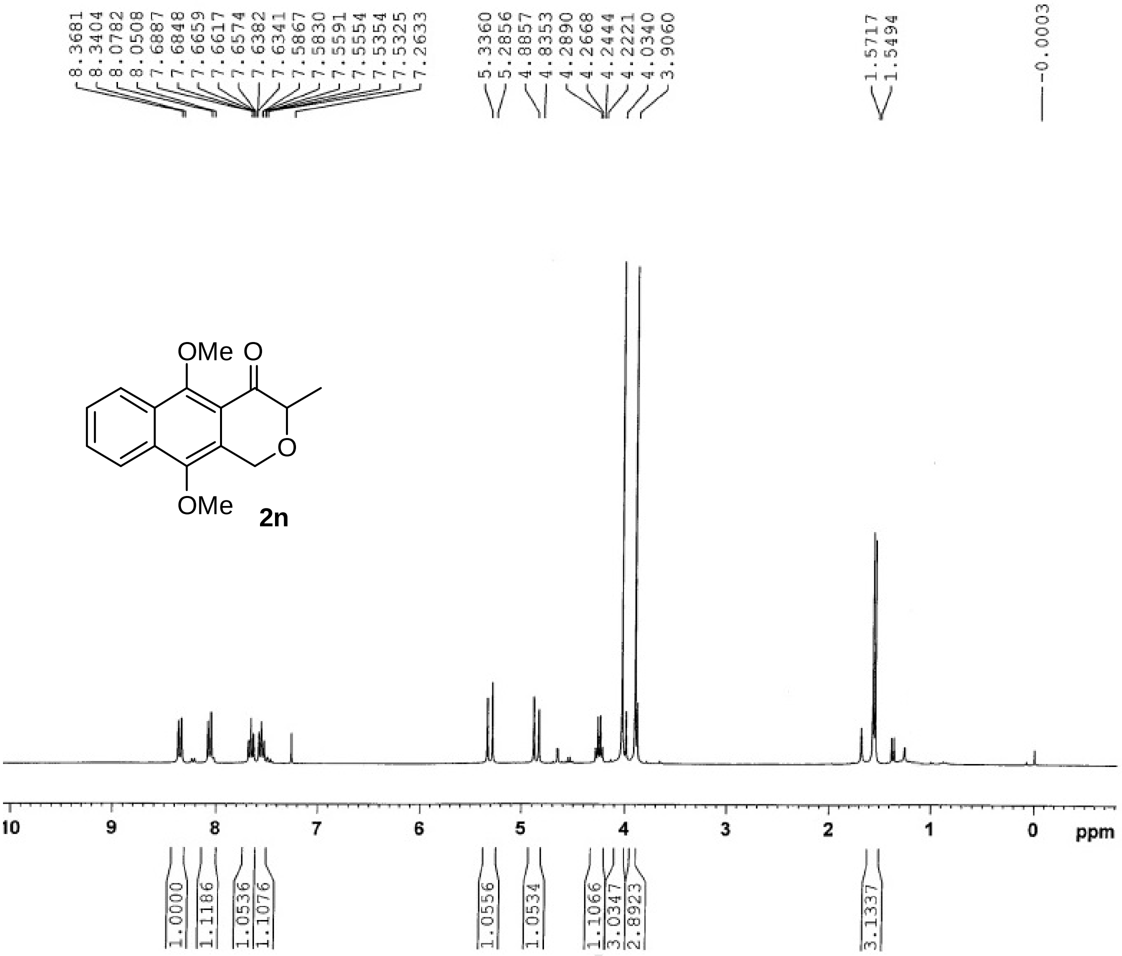
40
20
0
ppm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8.0782
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7.6341
7.5867
7.5830
7.5591
7.5554
7.5354
7.5325
7.2633
5.3360
5.2856
4.8857
4.8353
4.2890
4.2668
4.2444
4.2221
4.0340
3.9060
1.5717
1.5494
-0.0003
OMe
O
O
OMe
2n
10
9
8
7
6
5
4
3
2
1
0
ppm
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1.0556
1.0534
1.1066
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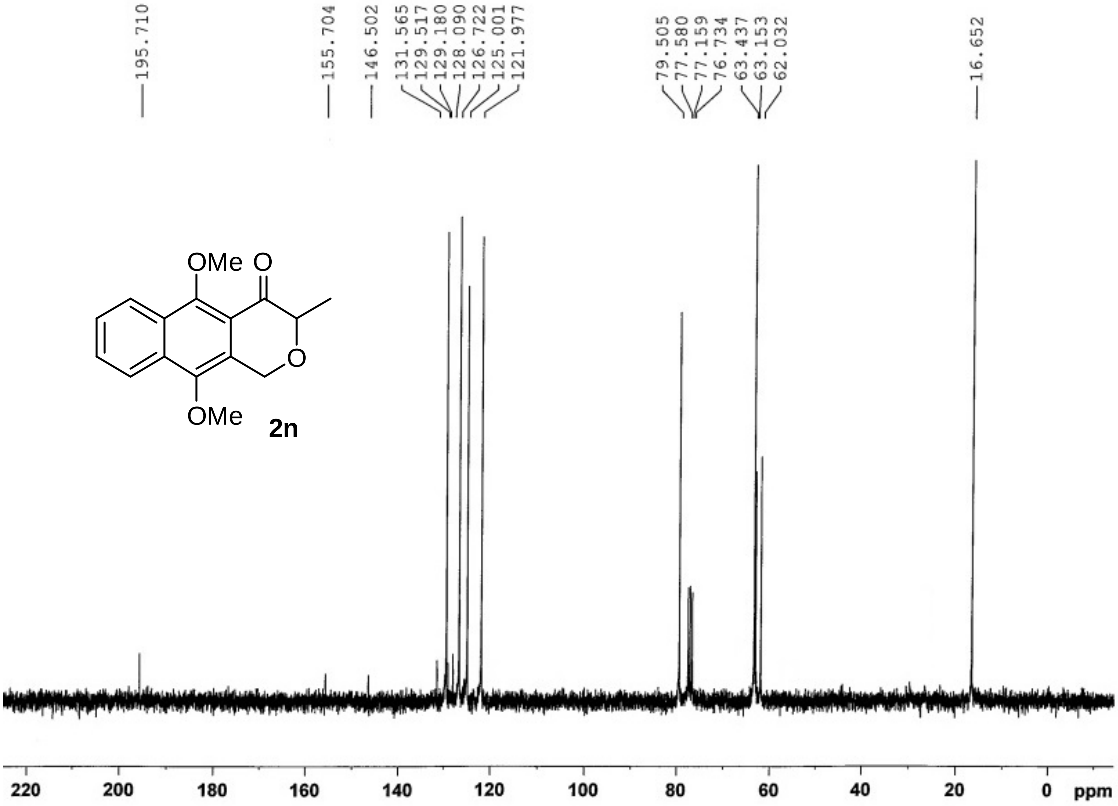
3.1337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146.502
131.565
129.517
129.180
128.090
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125.001
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77.580
77.159
76.734
63.437
63.153
62.032
16.652
OMe
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OMe
2n
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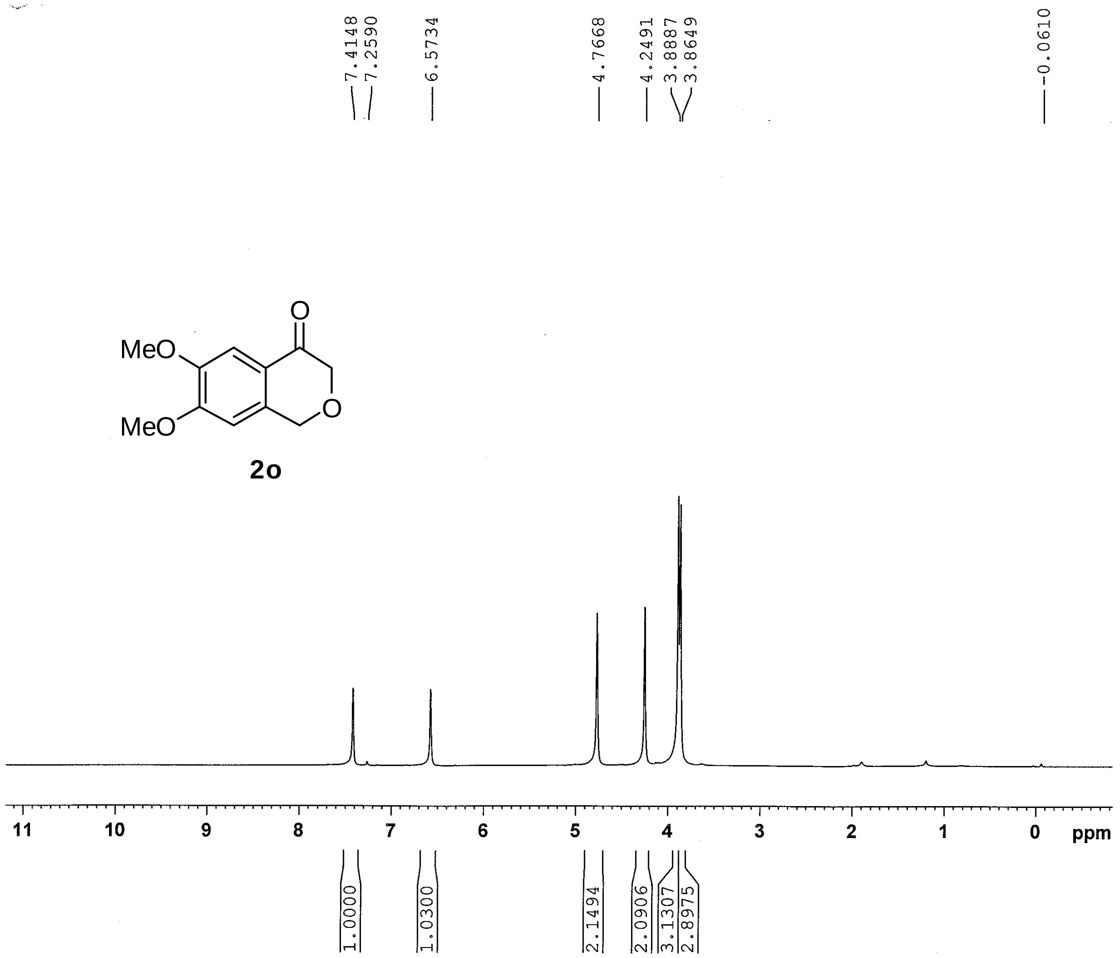
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6.5734
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4.2491
3.8887
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-0.0610
MeO
MeO
O
O
2o
11
10
9
8
7
6
5
4
3
2
1
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ppm
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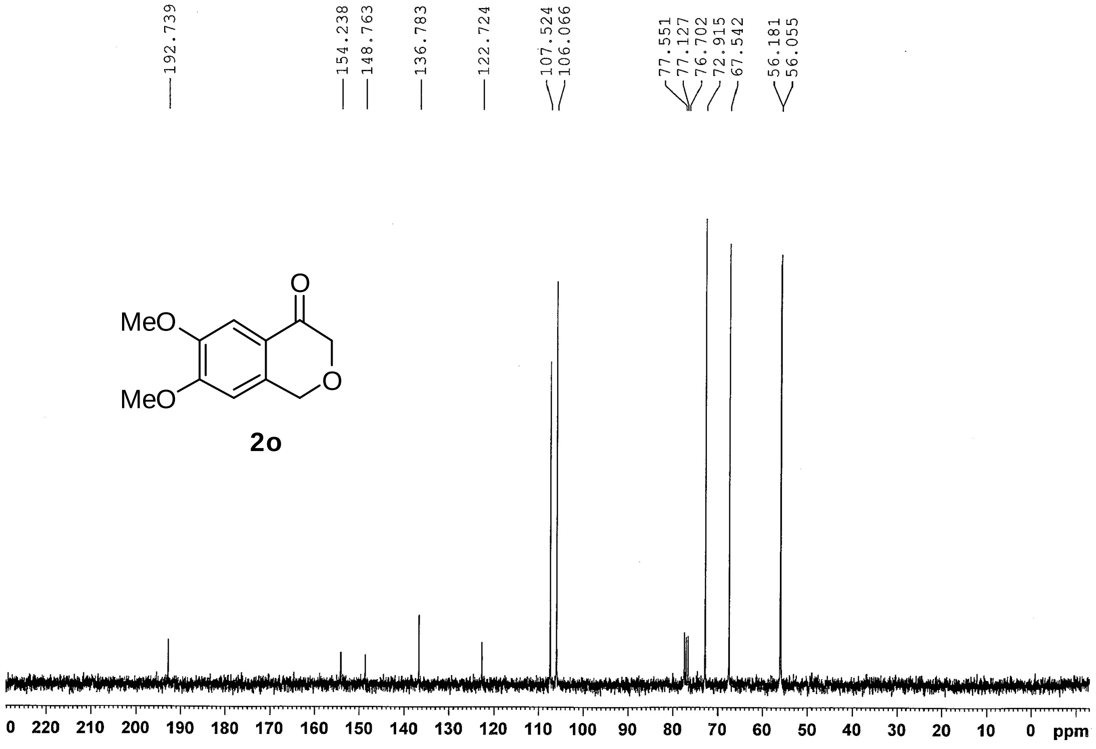
2.8975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148.763
136.783
122.724
107.524
106.066
77.551
77.127
76.702
72.915
67.542
56.181
56.055
MeO
MeO
O
O
2o
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
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60
50
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20
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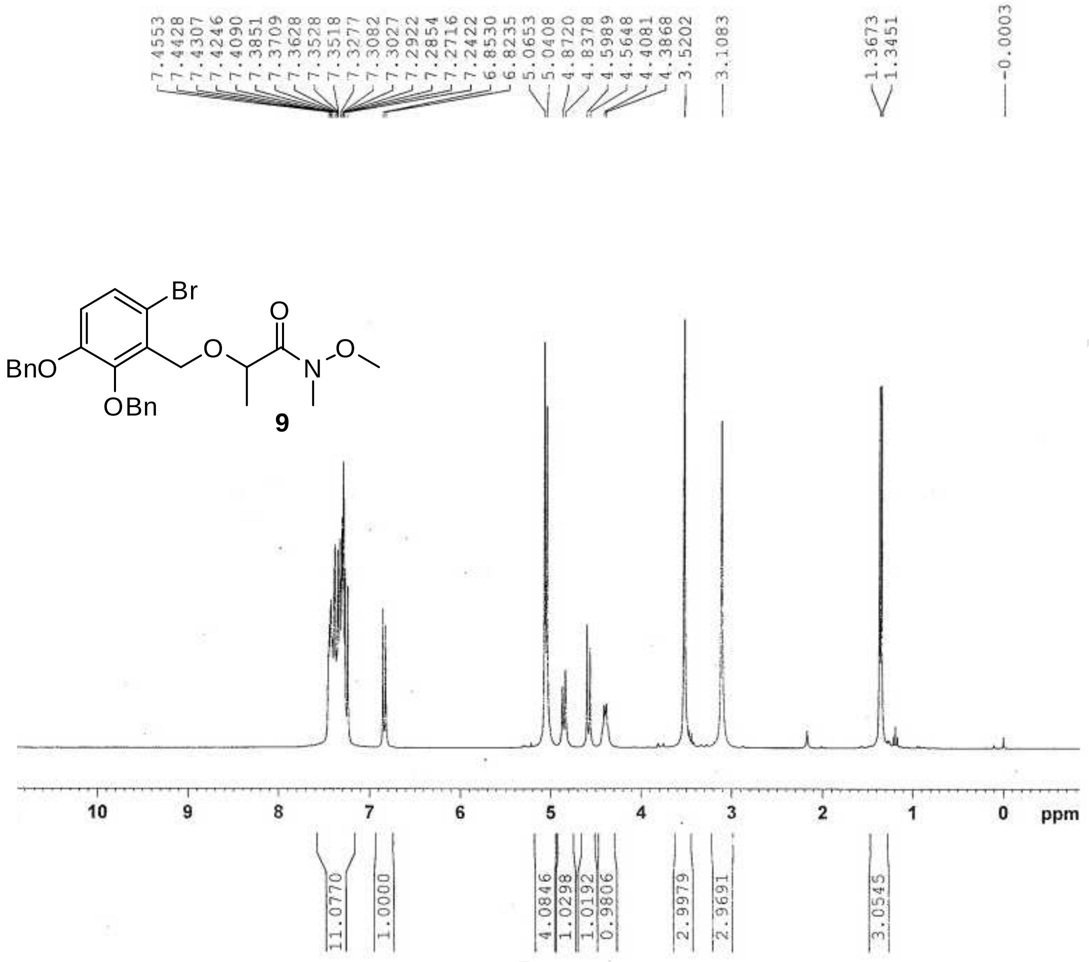
0
ppm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7.4307
7.4246
7.4090
7.3851
7.3709
7.3628
7.3528
7.3518
7.3277
7.3082
7.3027
7.2922
7.2854
7.2716
7.2422
6.8530
6.8235
5.0653
5.0408
4.8720
4.8378
4.5989
4.5648
4.4081
4.3868
3.5202
3.1083
1.3673
1.3451
-0.0003
Br
O
BnO
O
N
O
OBn
9
10
9
8
7
6
5
4
3
2
1
0
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0.9806
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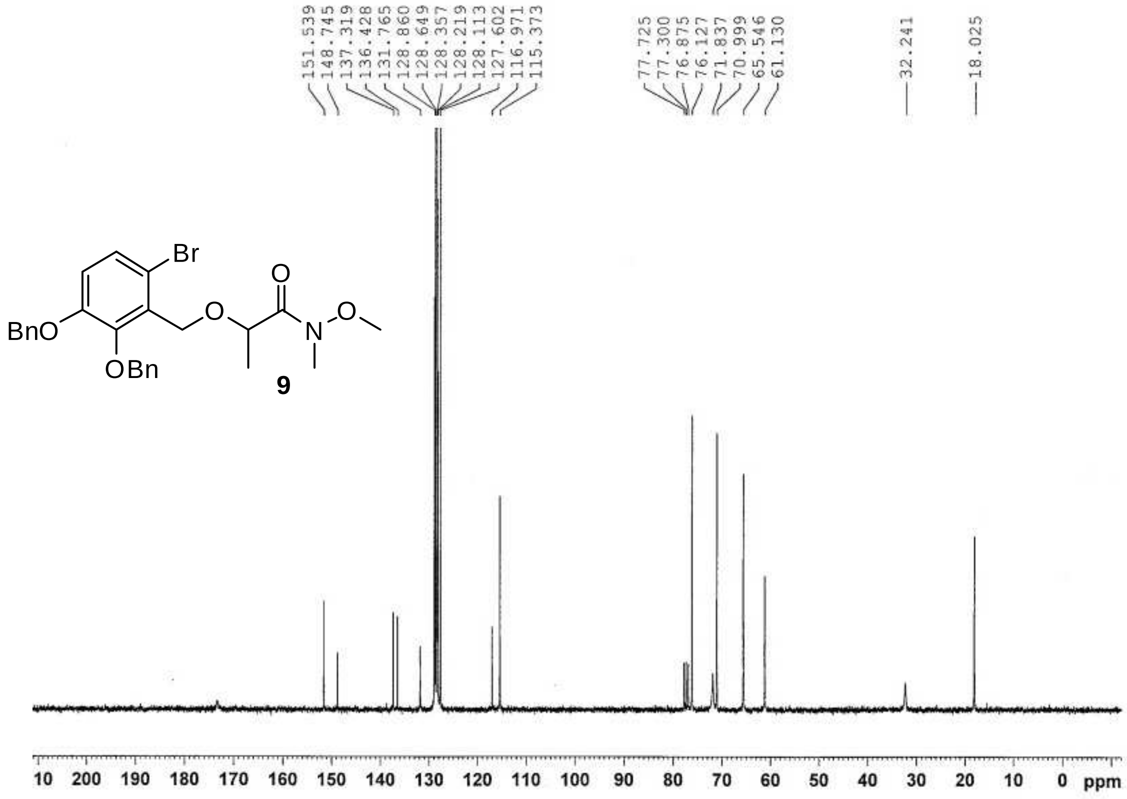
2.9691
3.0545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128.860
128.649
128.357
128.219
128.113
127.602
116.971
115.373
77.725
77.300
76.875
76.127
71.837
70.999
65.546
61.130
32.241
18.025
Br
O
BnO
O
N
O
OBn
9
10
200
190
180
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150
140
130
120
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50
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20
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0
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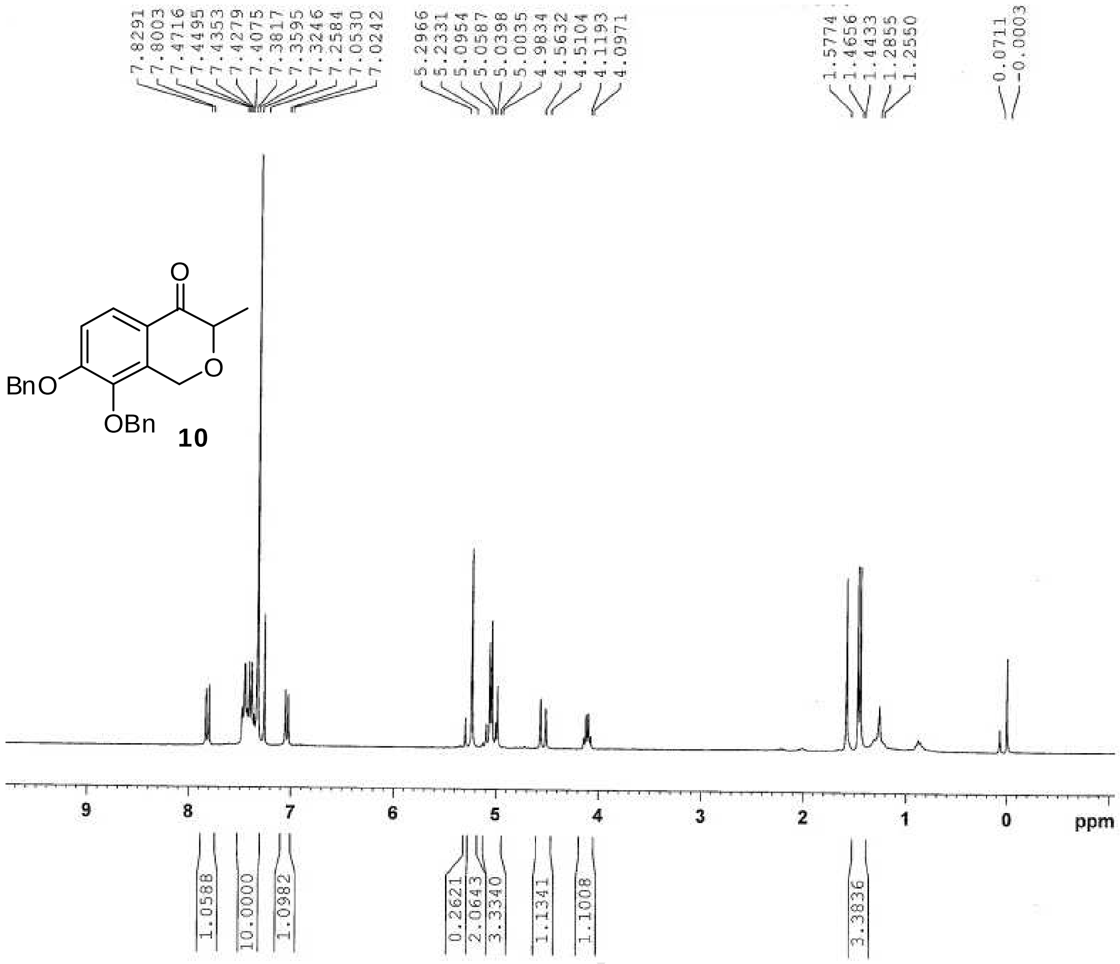
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7.4279
7.4075
7.3817
7.3595
7.3246
7.2584
7.0530
7.0242
5.2966
5.2331
5.0954
5.0587
5.0398
5.0035
4.9834
4.5632
4.5104
4.1193
4.0971
1.5774
1.4656
1.4433
1.2855
1.2550
0.0711
-0.0003
O
O
BnO
OBn
10
9
8
7
6
5
4
3
2
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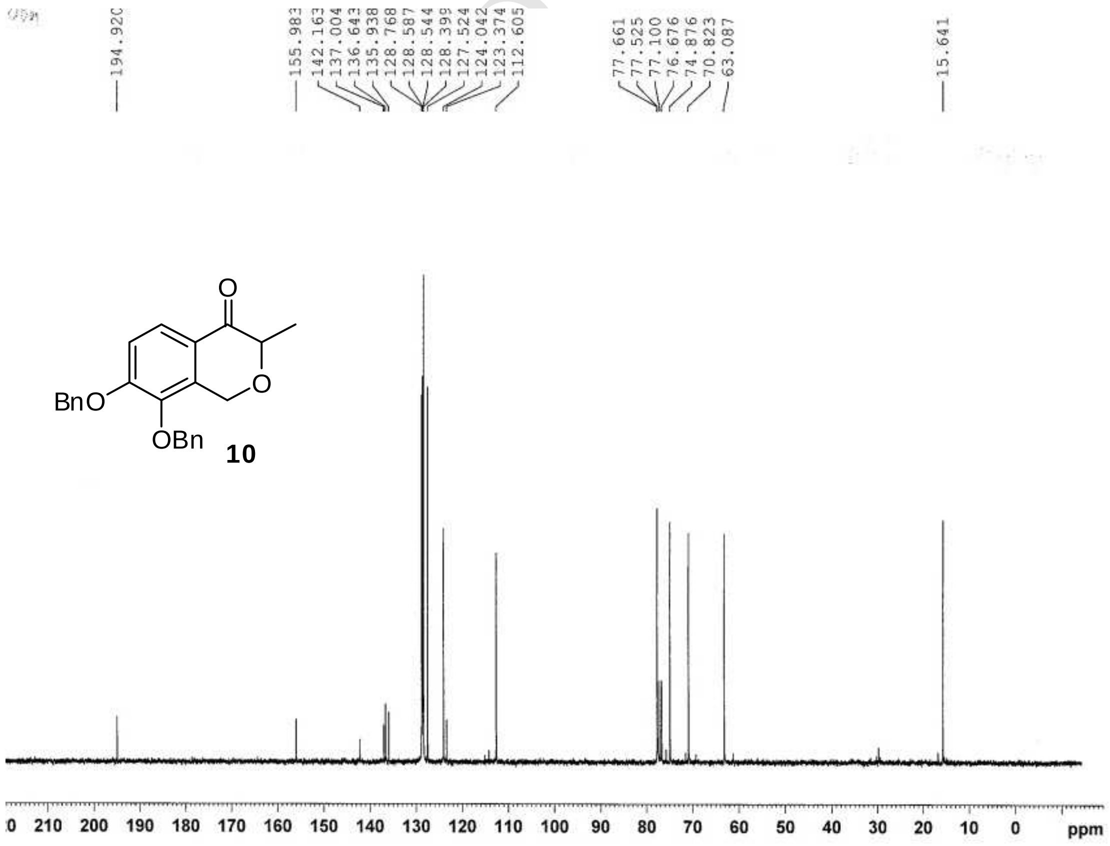
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123.374
112.605
77.661
77.525
77.100
76.676
74.876
70.823
63.087
15.641
O
O
BnO
OBn
10
210
200
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140
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120
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60
50
40
30
20
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0
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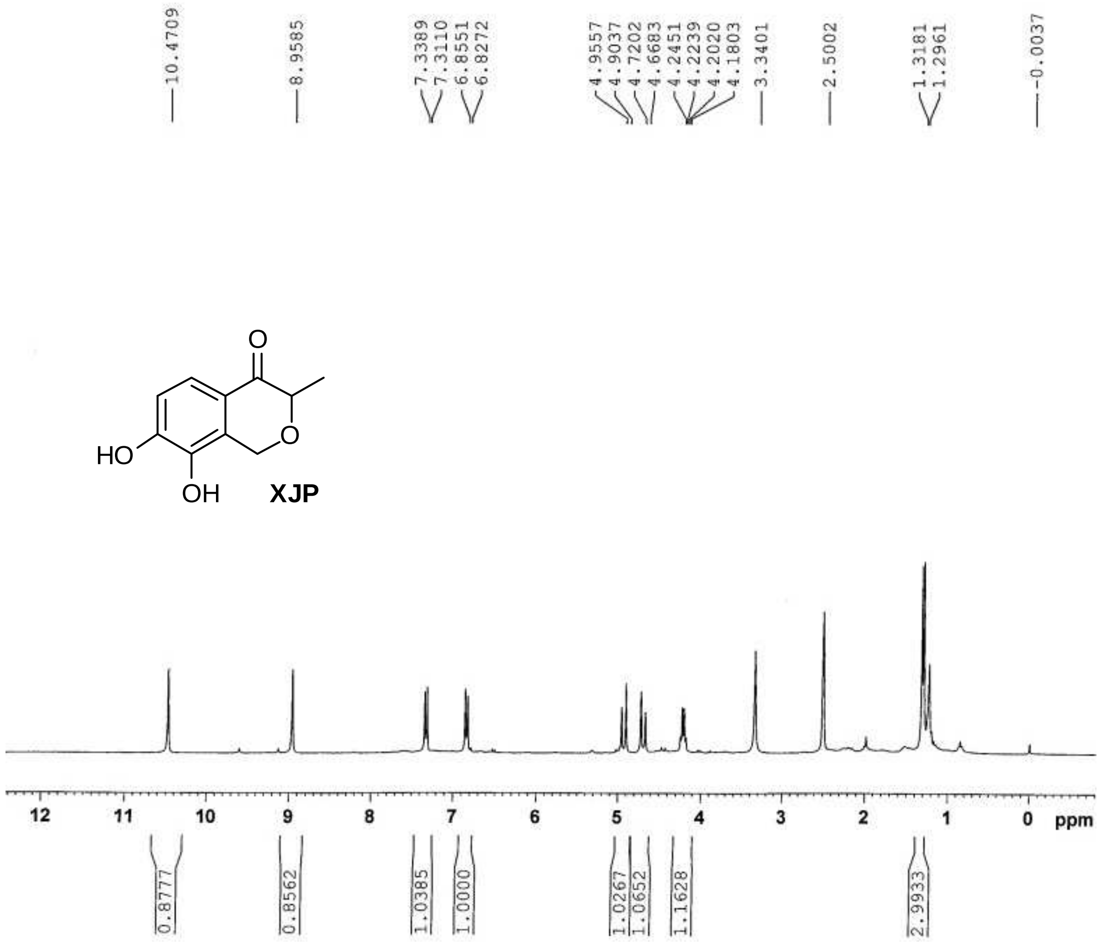
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4.7202
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4.2451
4.2239
4.2020
4.1803
3.3401
2.5002
1.3181
1.2961
-0.0037
O
HO
OH
O
XJP
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
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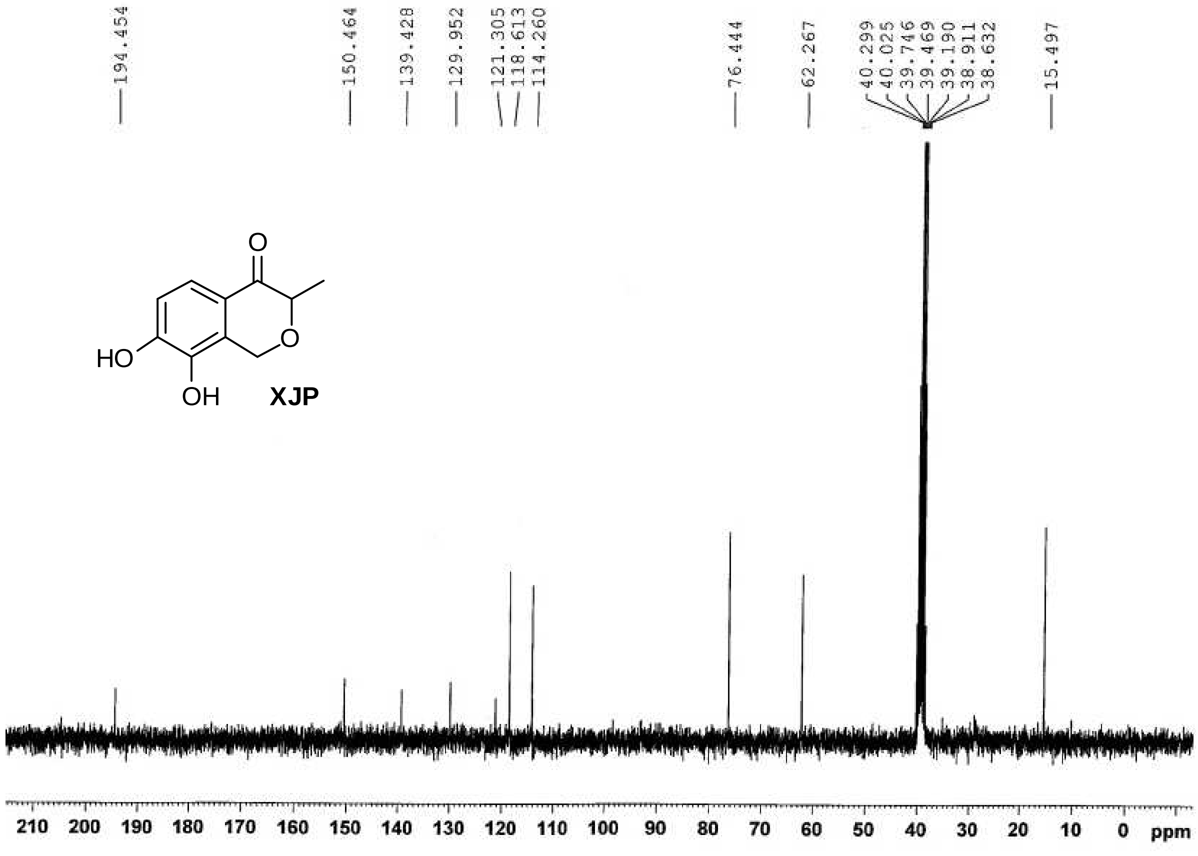
2.9933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121.305
118.613
114.260
76.444
62.267
40.299
40.025
39.746
39.469
39.190
38.911
38.632
15.497
O
HO
OH
O
XJP
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm