2012

Synthesis of natural products and small molecules using quinones

Feng Liu
Iowa State University

Synthesis of natural products and small molecules using quinones

by

Feng Liu

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:

George A. Kraus, Major Professor

Robert S.Houk

Patricia A. Murphy

Arthur Winter

Yan Zhao

Iowa State University

Ames, Iowa

2012

TABLE OF CONTENTS

CHAPTER 4: Synthesis of Uliginosins A and B

CHAPTER 1: GENERAL INTRODUCTION

Total synthesis of biologically active natural products has been used for the discovery of new medicines. In collaboration with biology and medicinal chemistry, it has led to discovery and the ensuing syntheses of biologically potent natural products, which have been translated into drug applications.

In this thesis, we explored both total synthesis and methodology of several natural products and small molecules, especially using quinone as starting materials. Chapter 2 describes an efficient synthesis of Bauhinoxepin J and polyhydroxylated xanthones *via* intramolecular radical cyclization, and a novel method of facile oxidation of 1,4-hydroquinones to 1,4-benzoquinones by using N-Bromosuccinimide (NBS) was developed. Chapter 3 describes the direct synthesis of two ketone constituents, (Z)-tetradeca-8-en-11,13-diyn-2-one and (8Z,13Z)-pentadeca-8,13-dien-11-yn-2-one from *Echinacea pallida*. Chapter 4 describes a synthesis of Uliginosins A and B.

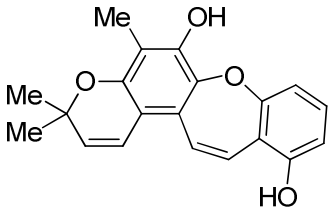
CHAPTER 2: Synthesis of Natural Products and Small Molecules Using Quinones

Part I: Concise Synthesis of Bauhinoxepin J Using Intramolecular Radical Cyclization

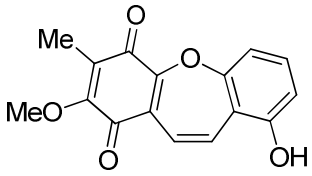
Introduction

In recent years scientists have discovered a number of biologically active natural products bearing the dibenz[*b*,*f*]oxepin skeleton. Those compounds have been isolated from plants which belong to the *Bauhinia* genus, particularly from *Bauhinia saccocalyx* and *Bauhinia purpurea.*[1–4] Several of these structurally unique natural products have been reported to exhibit attractive biological activities such as anti mycobacterial,[1,3] anti malarial,[1] anti fungal,[1] cytotoxic,[1,2,4] and anti-inflammatory[1] activities. Representative structures are showed in Figure 1. Bauhinoxepin A (**1**) was isolated by Kittakoop et al in 2004 from *B. saccocalyx* and shows anti mycobacterial activities with an MIC value of 6.25 μm.[3] Bauhiniastatin 1 (**2**) was isolated by Pettit et al from *Bauhinia purpurea*, exhibits significant growth inhibition against a mini-panel of human cancer cell lines, including the P388 cancer cell line.[2] Bauhinoxepin J (**3**) was isolated by Kittakoop et al from *B. purpurea* in 2007.[1] Although **3** appears to have a relatively simple structure, it exhibits remarkable biological activities including anti mycobacterial activity (MIC = 24.4 μm), anti malarial activity (IC_{50} = 5.8 μm), and tumor growth inhibitory activity (KB cells: IC_{50} = 10.5 μm; BC cells: IC_{50} = 12.1 μm).[1] Bulbophyol B (**4**), isolated from

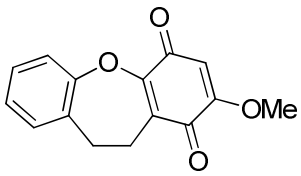
Bulbophyllum kwangtungense by Wu in 2006, displays growth inhibition against human epithelial carcinoma (HeLa) and human erythomyeloblastoid leukaemia (K562) cell lines in the low micromolar range.[4]



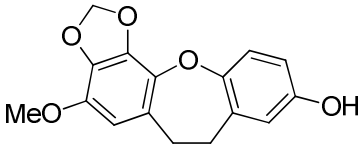
Bauhinoxepin A (1)



Bauhiniastatin 1 (2)



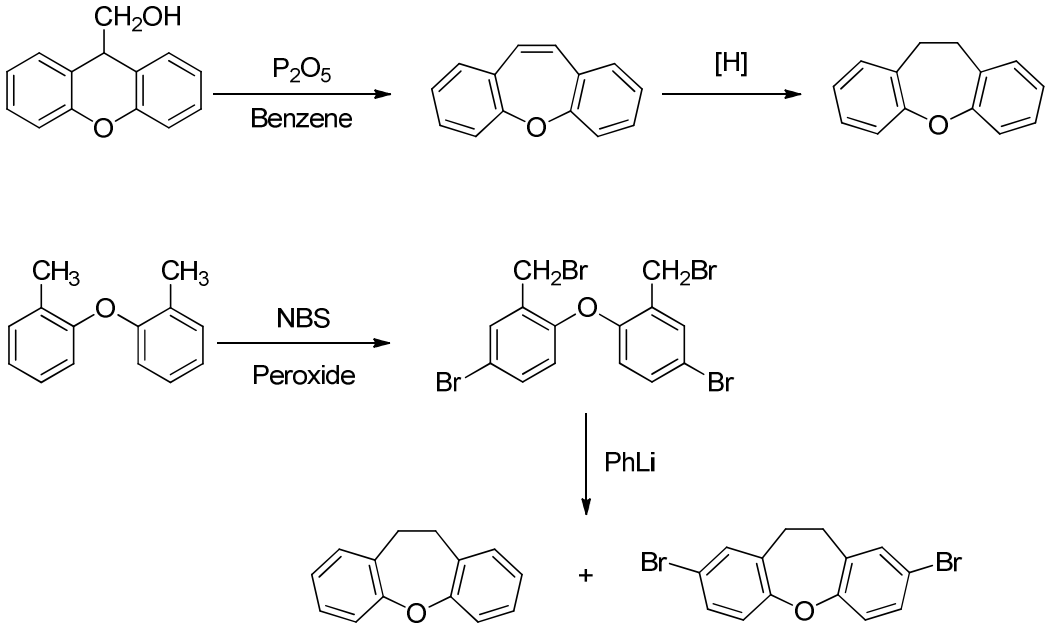
Bauhinoxepin J (3)



Bulbophyol B (4)

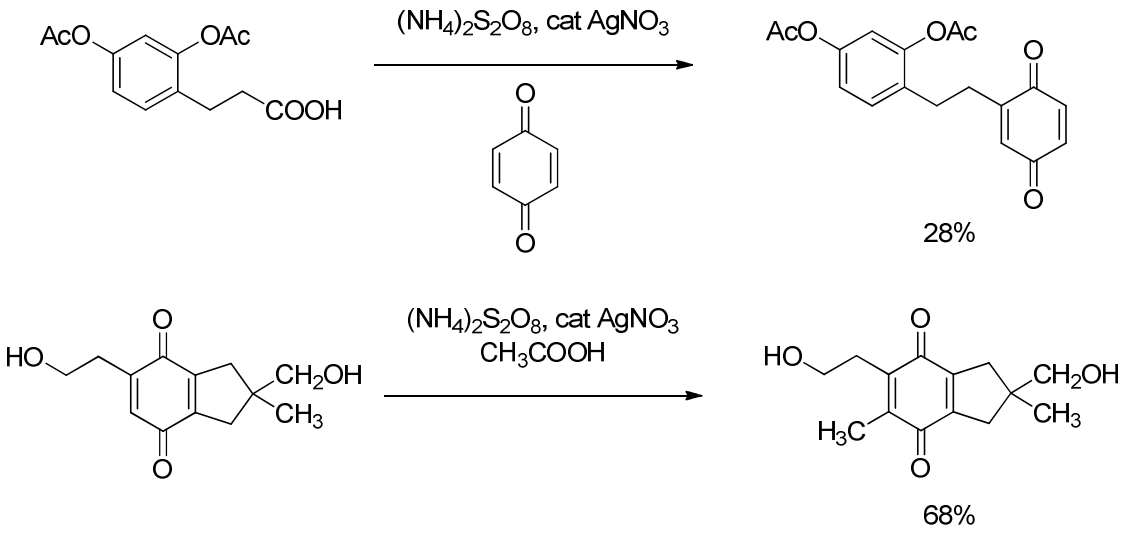
Figure 1

Bauhinoxepin J has a dihydrodibenzoxepin skeleton with a seven membered central ring flanked by a benzene ring on one side and a benzoquinone on the other. There have been two syntheses reported to make the dihydrodibenzoxepin skeleton. The first one involved acid-catalyzed rearrangement of xanthene-9-carbinol followed by reduction.[5] The second method entailed tetrabromination of 2,2´-dimethyldiphenyl ether with N-bromosuccinimide followed by cyclization (Scheme 1).[6]



Scheme 1

Kraus and coworkers have reported addition of radicals to substituted and unsubstituted quinones (Scheme 2).[7-8] The radical was generated by combination of ammonium persulfate in presence of a catalytic amount of silver nitrate.

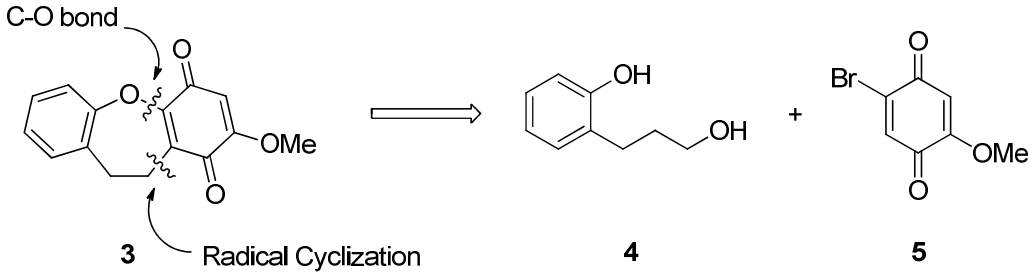


Scheme 2

Because of the benzoquinone part in Bauhinoxepin J and the above intermolecular radical addition to benzoquinones, we decided to apply intramolecular radical addition to benzoquinone as a key step to form Bauhinoxepin J. To the best of our knowledge, there is no evidence for the intramolecular radical addition to a quinone to make a seven membered ring.

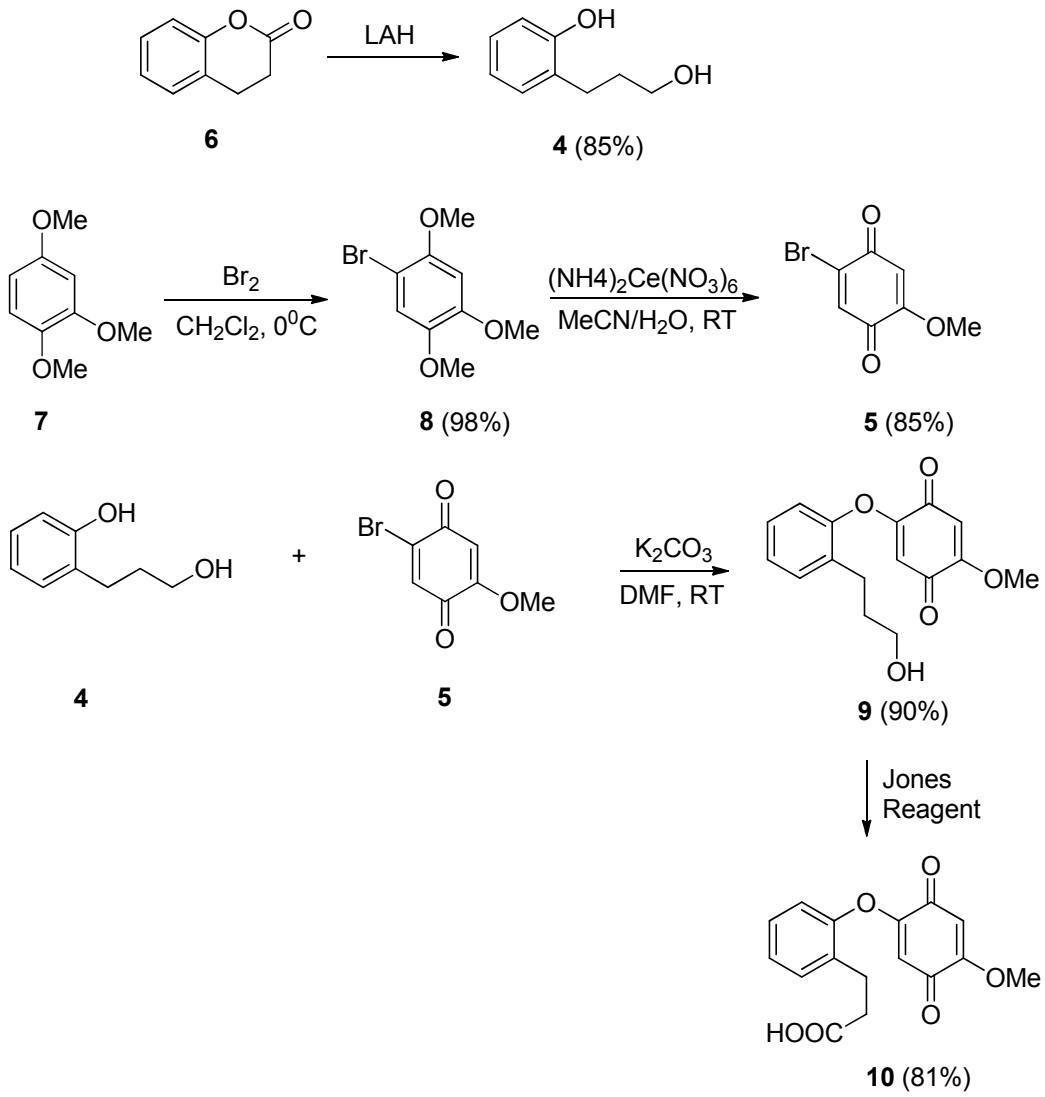
Results and Discussion

As shown in the retrosynthetic analysis, we envisioned that **3** could be assembled *via* C-O bond formation followed by radical cyclization. This pathway directed us to our starting materials: 2-(3-hydroxypropyl) phenol (**4**) and 2-bromo-5-methoxy-1,4-benzoquinone (**5**) (Scheme 3).



Scheme 3

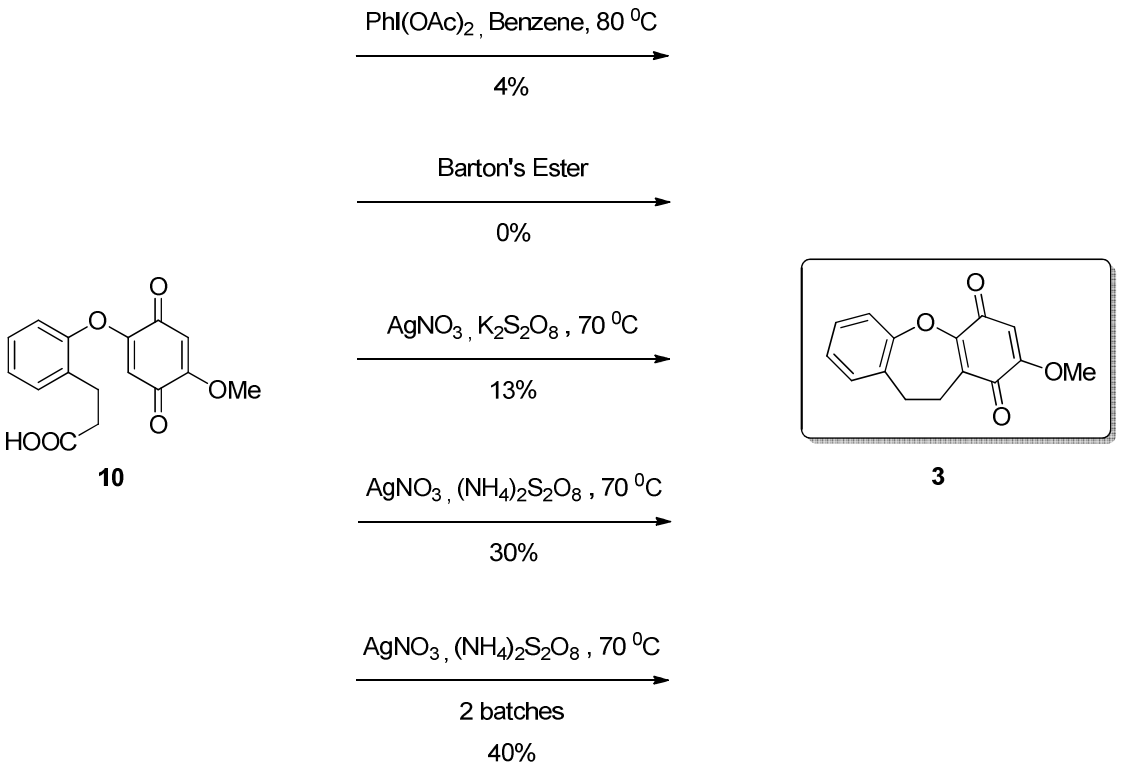
The diol **4** was prepared by treating dihydrocoumarin **6** with lithium aluminum hydride[9] and the benzoquinone **5** was made in two steps from 1,2,4 trimethoxybenzene **7**.[10-11] Coupling of **4** and **5** was achieved by using potassium carbonate as a base in DMF to give alcohol **9** in 90% yield. The primary alcohol **9** was then oxidized to the carboxylic acid **10** using Jones' reagent in 81% yield (Scheme 4).



Scheme 4

The stage was set for us to try the pivotal decarboxylative radical cyclization. First, we attempted to use phenyliodoso diacetate[12,13] to generate the radical from **10** (Scheme 5). To our disappointment, it provided a meager 4% yield of the target compound. We next employed the Barton ester[14,15] protocol. Unfortunately, this method did not provide any of the desired products. We then examined the silver catalyzed persulfate method developed by Torssell and by Minisci.[16-17] Fortunately, the use of ammonium persulfate with equivalent proportions of the silver salt afforded **3** in 30%

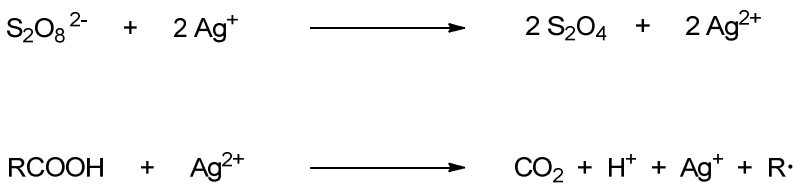
isolated yield as the only identifiable product. We also tried using potassium persulfate instead of ammonium persulfate; however, it provided only a 13% yield of **3**. The conditions of DeKimpe,[18] wherein both the silver salt and the persulfate were added in two portions, afforded **3** in 40% isolated yield. This constitutes a 25% overall yield of Bauhinoxepin J. The identity of synthetic Bauhinoxepin J (**3**) was confirmed by comparison of our ^{1}H NMR, ^{13}C NMR, LRMS, and HRMS data with the published spectra.



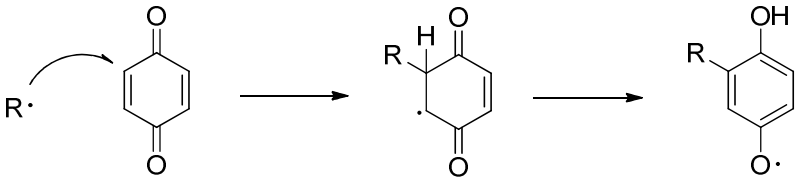
Scheme 5

The mechanism of silver (I) catalyzed persulfate reaction is shown below as proposed by Minisci.[17]

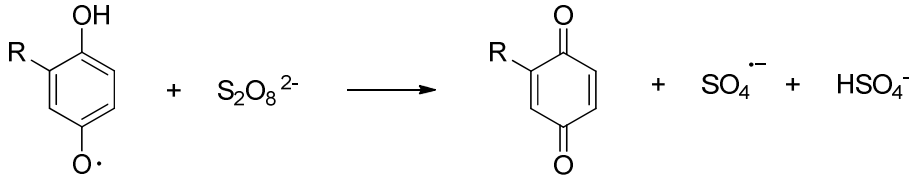
(i) Generation of carbon centered radical



(ii) Addition to quinone



(iii) Oxidation of the radical adduct in a redox chain



Conclusion

This represents the first total synthesis of Bauhinoxepin J (**3**). This synthesis features the first intramolecular radical addition to a quinone. This flexible and direct synthetic pathway will facilitate further biological evaluation of this little studied class of natural products.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or a Varian 400 MHz instrument. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra

were performed with a Finnegan TSQ700 mass spectrometer. Standard grade silica gel (60 Å, 32-63 μm) was used for flash column chromatography.

Compound 3

To a stirred solution of acid **10** (16 mg, 0.053 mmol) in 6 mL of 30% aq CH_3CN under argon was added silver nitrate (0.3 equiv). The mixture was heated to 65 °C and a solution of ammonium persulfate (1.3 equiv) in 2 mL of 30% aq CH_3CN was added dropwise for 20 min. The mixture was then stirred at 70 °C for 3 h. The mixture was cooled to 65 °C. An additional amount of silver nitrate (0.3 equiv) was added and a solution of ammonium persulfate (1.3 equiv) in 2 mL of 30% aq CH_3CN was added dropwise for 20 min. After an additional 3 h at 70 °C, the reaction mixture was cooled to room temperature and extracted with dichloromethane. The organic extracts were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified using flash chromatography on silica gel (1:1 hexanes:ethyl acetate) to obtain **3** (5.5 mg,40% yield).

^{1}H NMR (300 MHz, $CDCl_3$): 7.22–7.25 (m, 2H), 7.13–7.17 (m,2H), 5.90 (s, 1H), 3.83 (s, 3H), 3.06–3.09 (m, 2H), 2.81–2.85 (m, 2H).

^{13}C NMR(100 MHz, $CDCl_3$): 182.8, 181.9, 158.9, 155.7, 152.9, 133.2, 129.6, 128.0, 126.0,123.7, 121.2, 105.4, 56.7, 29.9, 26.5.

LRMS (EI): m/z 256 (M+, 100%), 241, 115,69; HRMS (EI) calcd for $C_{15}H_{12}O_4$: 256.0736, found: 256.0740.

Compound 4

To a suspension of lithium aluminum hydride (0.62 g, 16.2mmol) in diethyl ether (15 mL) at 0 °C, was added 3,4-dihydrocoumarin **6** (1.71 mL, 13.5mmol) in diethyl ether (15 mL). The reaction mixture was gently warmed to room temperature and then heated to reflux for 4 h, after which, it was cooled to room temperature. Then 0.6 mL water, 0.6 mL of 15% aqueous NaOH solution and 1.8 mL water were then added, successively, to quench the reaction. The resulting solution was diluted with ethyl acetate, washed with water and brine,successively. The organic layer was dried over Na_2SO_4, evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (dichloromethane : ethyl acetate = 4:1) to afford **4** (1.75 g, 85% yield).

^{1}H NMR (400MHz, $CDCl_3$): 7.14-7.10 (m, 2H), 7.05 (s, 1H), 6.90-6.84 (m, 2H), 3.66 (t, 2H, J = 6.0 Hz),2.79 (t, 2H, J = 6.8 Hz), 2.46 (s, 1H), 1.93-1.86 (m, 2H).

Compound 5

To a solution of **8** (1g, 4.05 mmol) in acetonitrile : water (1:2, 45 mL) was added ceric ammonium nitrate (6.0 g, 10.93mmol). After 3 h at room temperature, the reaction mixture was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (ethyl acetate) to afford **5** (0.75 g, 85% yield).

^{1}HNMR (400 MHz, CDCl3): 7.25 (s, 1H), 6.14 (s, 1H), 3.87 (s, 3H).

Compound 8

To a solution of **7** (1.0 g, 5.95 mmol) in dichloromethane (20 mL) at 0 °C was added bromine (0.34 mL, 6.54 mmol) in dichloromethane (5 mL). After stirring for 2.5 h at the same temperature, saturated aqueous sodium thiosulfate solution was added to quench the reaction. The resulting solution was diluted with dichloromethane, washed with water and brine, successively. The organic layer was dried Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 3:1) to afford **8** (1.44 g, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$) : 7.04 (s, 1H), 6.57 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H).

Compound 9

To a solution of **4** (220 mg, 1.44 mmol) in DMF (5 mL) was added potassium carbonate (200 mg, 1.44 mmol). After 30 min at room temperature , **5** (300 mg, 1.38 mmol) in DMF (10 mL) was added to the reaction mixture. The mixture was stirred at room temperature for additional 3.5 h upon which it was quenched with 1N HCl. The resulting solution was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 1:1) to afford **12** (358 mg, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 7.31 (dd, 1H, J = 6.8 Hz, 2.4 Hz), 7.28-7.21 (m, 2H), 7.00 (dd, 1H, J = 7.2 Hz, 2.0 Hz), 5.95 (s, 1H), 5.58 (s, 1H), 3.85 (s, 3H), 3.58 (s, 2H), 2.58 (t, 2H, J = 7.2 Hz) 2.23 (s, 1H), 1.83-1.77 (m, 2H).

^{13}C NMR (100 MHz , $CDCl_3$): 181.9, 181.7, 159.7, 158.9, 150.7, 133.8, 131.6, 128.1, 127.3, 121.1, 108.5, 105.7, 61.2, 56.9, 33.5, 25.8.

Compound 10

To a solution **9** (125 mg, 0.43 mmol) in acetone (10 mL) at 0 °C was added 8N Jones reagent (1.5 mL). The mixture was stirred at the same temperature for additional 3.5 h upon which 2-propanol was added to consume the excess Jones reagent. The solution was then evaporated *in vacuo*. The resulting residue was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (ethyl acetate) to afford **10** (105 mg, 81% yield).

^{1}H NMR (400MHz, $CDCl_3$): 7.31 (dd, 1H, J = 7.2 Hz, 1.6 Hz), 7.31-7.23 (m, 2H), 7.02 (dd, 1H, J = 8.0 Hz, 1.6 Hz), 5.97 (s, 1H), 5.58 (s, 1H), 3.88 (s, 3H), 2.85 (t, 2H, J = 7.6 Hz), 2.67 (t, 2H, J = 7.6 Hz).

^{13}C NMR (100 MHz , $CDCl_3$): 182.0, 181.4, 177.7, 159.6, 159.1, 150.8, 132.2, 131.2, 128.8, 127.3, 121.5, 108.8, 105.9, 56.9, 34.0, 25.0.

References

1. S. Boonphong, P. Puangsombat, A. Baramee, C. Mahidol, S. Ruchirawat, P. Kittakoop, *J. Nat. Prod.* **2007**, *70*, 795–801.
2. G. R. Pettit, A. Numata, C. Iwamoto, Y. Usami, T. Yamada, H. Ohishi, G. M. Cragg, *J. Nat. Prod.* **2006**, *69*, 323–327.

3. P. Kittakoop, S. Nopichai, N. Thongon, P. Charoenchai, Y. Thebtaranonth, *Helv. Chim. Acta.* **2004**, *87*, 175–179.
4. B. Wu, *Faming ZhuanliShengqingGongkaiShomingshu*, CN 1458155 A 20031126, **2003**.
5. Hess, B. A.; Bailey, A. S.; Boekelheide, V. *J. Am. Chem. Soc.* **1967**, *89*, 2746-2747.
6. Bergmann, E. D.; Shahak, I.; Aizenshtat, Z. *Tet. Lett.* **1968**, *31*, 3469-3470.
7. Kraus, G. A.; Kim, I. *Tetrahedron.* **2003**, *59*, 7935-7937.
8. Kraus, G. A.; Choudhury P. K. *Tetrahedron Lett.* **2001**, *42*, 6649-6650.
9. Botta, M.; Quici, S.; Pozzi, G.; Marzanni, G.; Pagliarin, R.; Barra, S.; Crich, S. G.*Organic &Biomolecular Chemistry.* **2004**, *2*, 570-577.
10. Hanbali, M.; Vela-Ruiz, M.; Bagnard, D.; Luu, B. *Bioorganic & Medicinal Chemistry Letters.* **2006**, *16*, 2637-2640.
11. Tohma, H.; Morioka, H.; Harayama, Y.; Hashizume, M.; Kita, Y. *Tetrahedron Letters.* **2001**, *42*, 6899-6902.
12. Togo, H.; Katohgi, M. *Synlett.* **2001**, 565.
13. Togo, H.; Aoki, M.; Kuramochi, T.; Yokoyama, M. *Perkin Trans. 1*. **1993**, 2417.
14. Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron*. **1989**, 45, 2615–2626.
15. Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron.* **1987**, 43, 5307–5314.
16. Jacobsen, N.; Torssell, K. *Justus Liebigs Ann. Chem.* **1972**, 763, 135–147.
17. Coppa, F.; Fontana, F.; Lazzarini, E.; Minisci, F. *Chem. Lett*. **1992**, 1299.
18. DeKimpe, Norbert, private communication.

Part II: Synthesis of PolyhydroxylatedXanthones via Acyl Radical Cyclizations and Facile Oxidation of 1,4-Hydroquinones to 1,4-Benzoquinones Using NBS

Introduction

Xanthones are found in many plants, including *Hypericum* and *Prunella* species. Many xanthones bearing hydroxyl substituents exhibit valuable biological activity.[1] Daviditin A (**1**) preserves endothelial dysfunction elicited by lysophosphatidyl choline (Fig. 1). The protective effect of daviditin A on the endothelium is related to reduction of asymmetric dimethylarginine concentration.[2] Xanthone **2** was shown to relax the corpus cavernosal smooth muscle by 97% compared to Viagra.[3] Bellidifolin (**3**) improved insulin resistance by enhancing insulin signaling.[4]

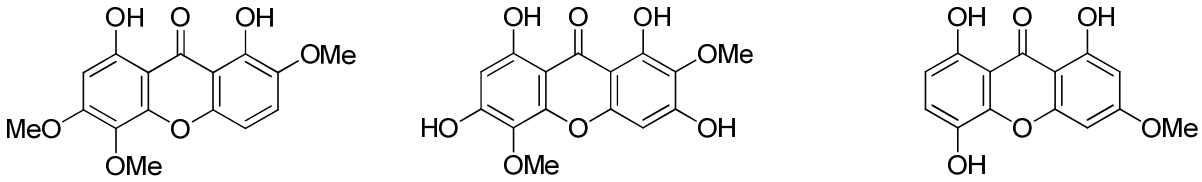


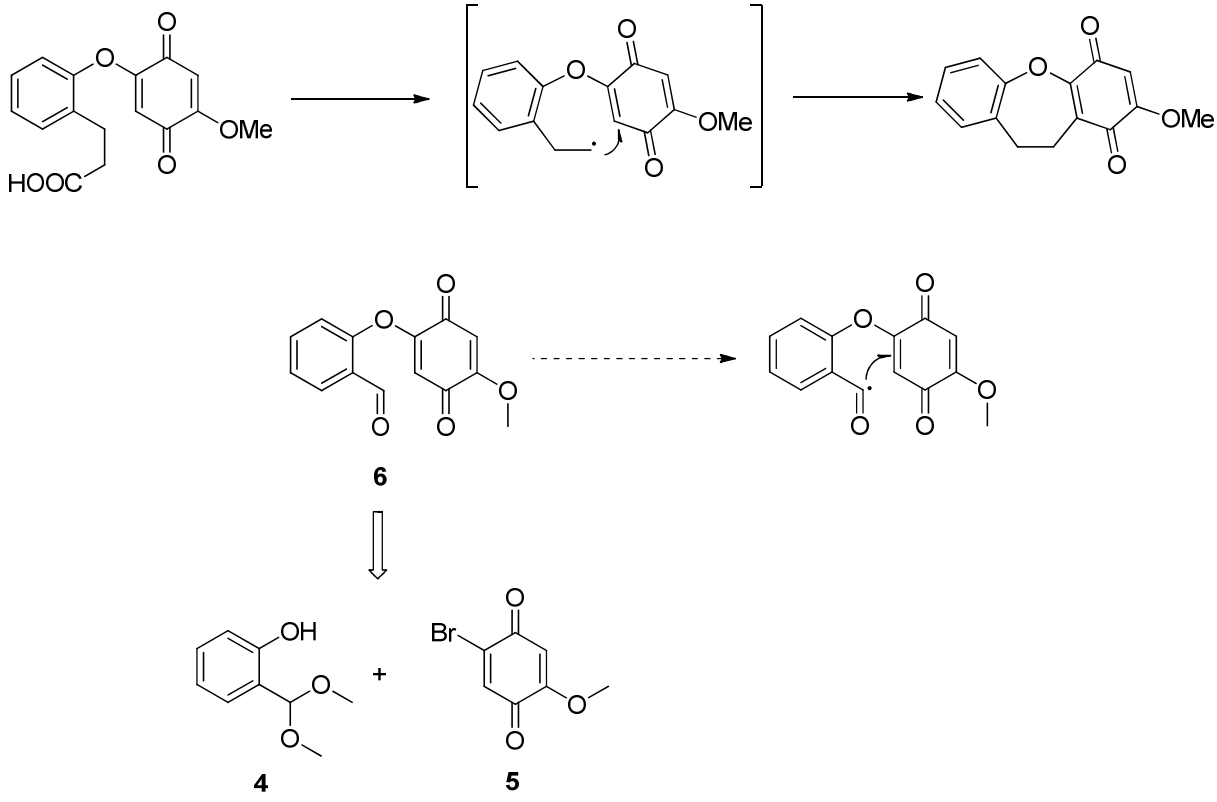
Figure 1

Because of the diverse biological activities of xanthones, several approaches have been reported.[5] Of these methods, Friedel–Crafts acylation/cyclization protocols[6] are the most commonly used methods. However, synthetic methods for highly hydroxylated xanthones are limited. Recently, Kraus developped a photo acylation reaction.[7] Okuma[8a]

and Larock[8b] reported benzyne additios. Snieckus[9a] and Argade[9b] employed directed metallations. We report herein a synthesis of polyhydroxylated xanthones employing acyl radical intermediates, meanwhile, we also found NBS can oxidize 1,4-hydroquinone to 1,4-benzoquinone.

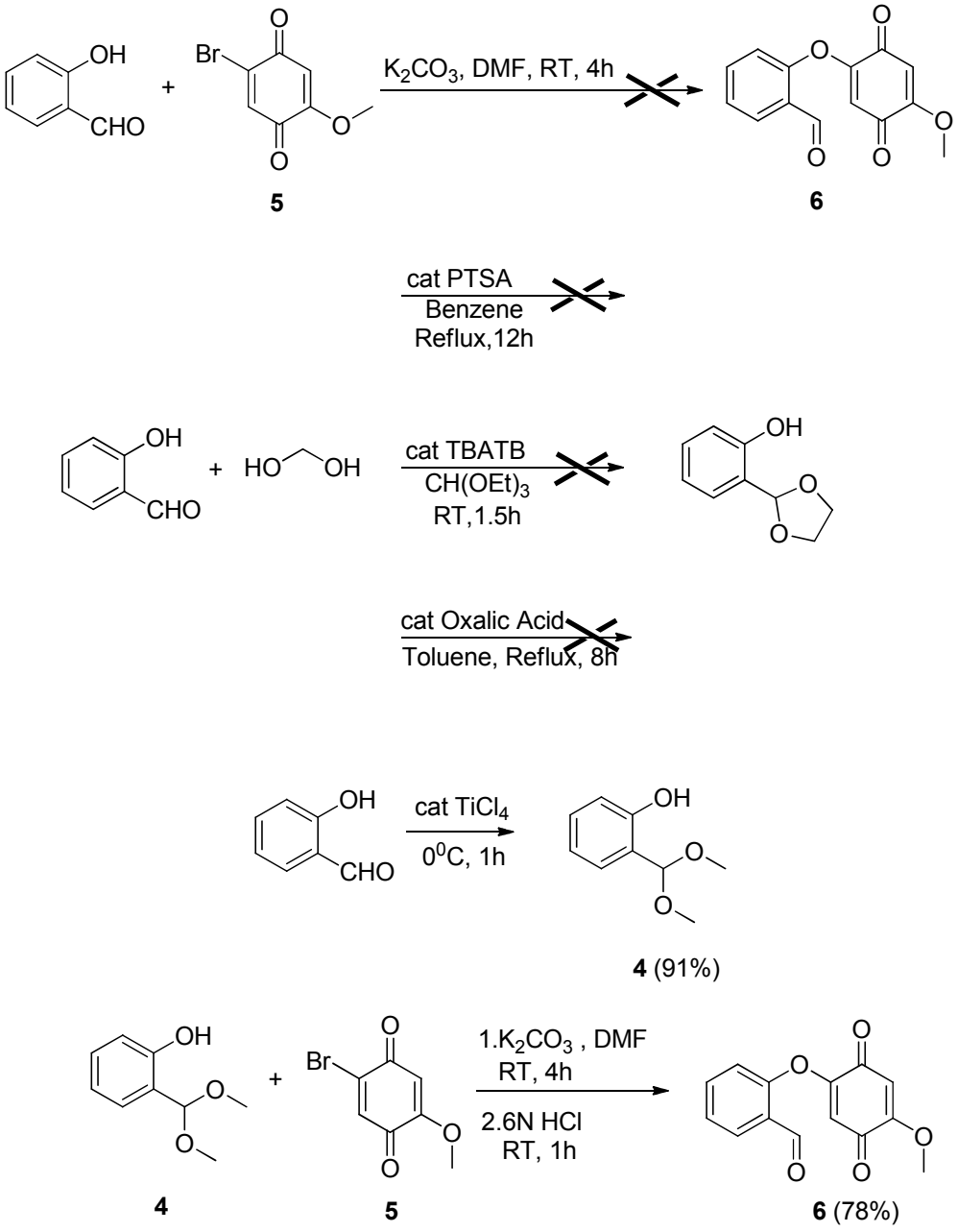
Results and Discussion

We recently reported that radicals generated by decarboxylationof an acid with persulfate underwent intramolecular cyclizationto a quinone, resulting in a direct synthesis of Bauhinoxepin J.[10] If an acyl radical could be generated from **6**,[11] the cyclization could lead to a direct synthesis of xanthones (Scheme 1). The quinone **6** can be synthesized by a coupling reaction of acetal **4** with bromoquinone **5**.



Scheme 1

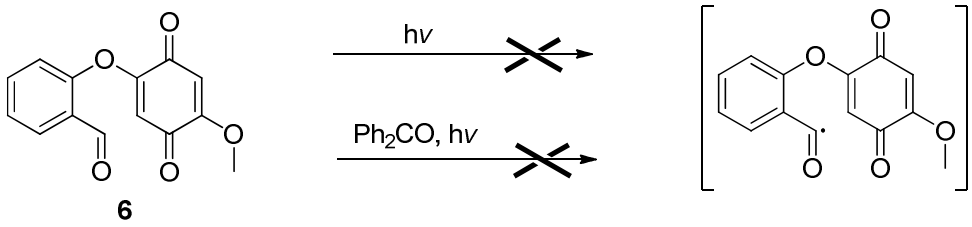
We first tried directly coupling salicyladehyde with bromoquinone **5** to generate quinone **6**, but the reaction failed (Scheme 2). Then we decided to protect carbonyl group first. All attempts to convert salicylaldehyde to a cyclic acetal failed.[12-14] Conversion of salicyladehyde to acylic acetal **4** was achieved by using $TiCl_4$ as a catalyst.[15] The reaction of acetal **4** with bromoquinone **5** andK_2CO_3 in DMF followed by HCl hydrolysis afforded quinone **6** in 78% yield.



Scheme 2

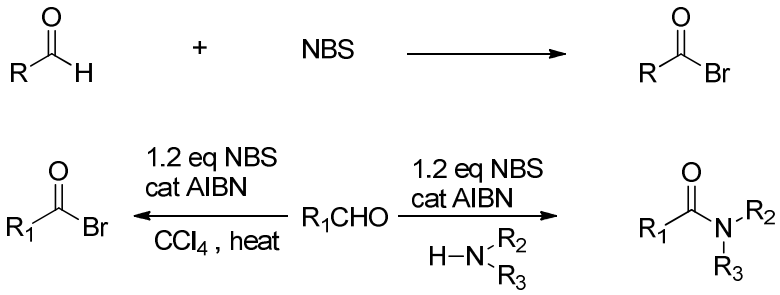
To the best of our knowledge, there have been no reports for the synthesis of xanthones from quinones such as **6**. Initially, we irradiated quinone **6** under conditions where an intramolecular hydrogen atom abstraction *via* an excited state quinone could lead to an acyl radical (scheme 3). Unfortunately, only starting material was recovered.

We next attempted to generate the acyl radical through hydrogen atom abstraction using the diradical of benzophenone, a strategy we had used successfully to generate acylhydroquinones.[16] This approach also failed.



Scheme 3

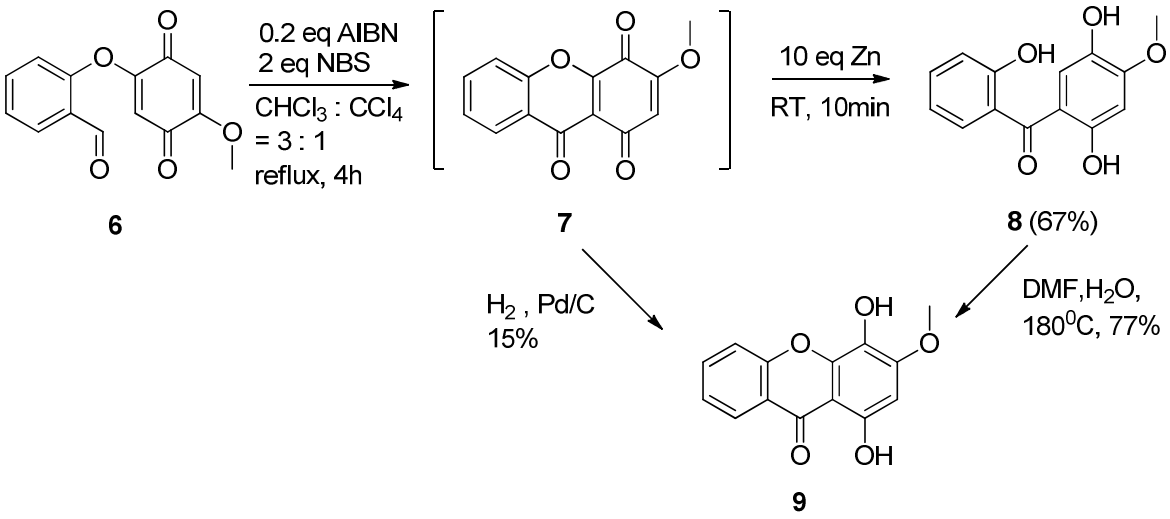
Cheung and later Marko reported that aryl aldehydes could be converted to acid bromides with NBS (Scheme 4).[17] Although this transformation has not been extensively studied, this reaction likely proceeds through an acyl radical intermediate.



Scheme 4

Treatment of quinone **6** with two equivalent of NBS and a catalytic amount of AIBN in $CHCl_3$ and CCl_4 produced xanthone **7** (scheme 5). A number of experiments were conducted to optimize thetransformation and it was found that two equivalents of NBS and 0.2 equiv of AIBN were necessary to achieve good conversion. Unfortunately, xanthone **7** was not stable to column chromatography. The xanthone **7** was reduced by catalytic hydrogenation to generate xanthone **9**, albeit in only 15% yield after two steps.

The structure of xanthone **9** was confirmed by X-ray spectroscopy (Fig. 2). Reduction of xanthone **7** with zinc in acetic acid afforded benzophenone **8** in 67% yield after two steps, whose structure was also determined by X-ray spectroscopy (Fig. 3). This appears to be the first example of xanthone cleavage under reductive conditions. Benzophenone **8** could be readily cyclized to form xanthone **9** by heating in aqueous DMF at 180 °C for 16 h in 77% yield.[7] Xanthone **9** is produced in an overall yield of 40%. Interestingly, benzophenone **8** is a natural product isolated from *Dalbergia cochinchinensis*.[18] This is the first report of its synthesis.



Scheme 5

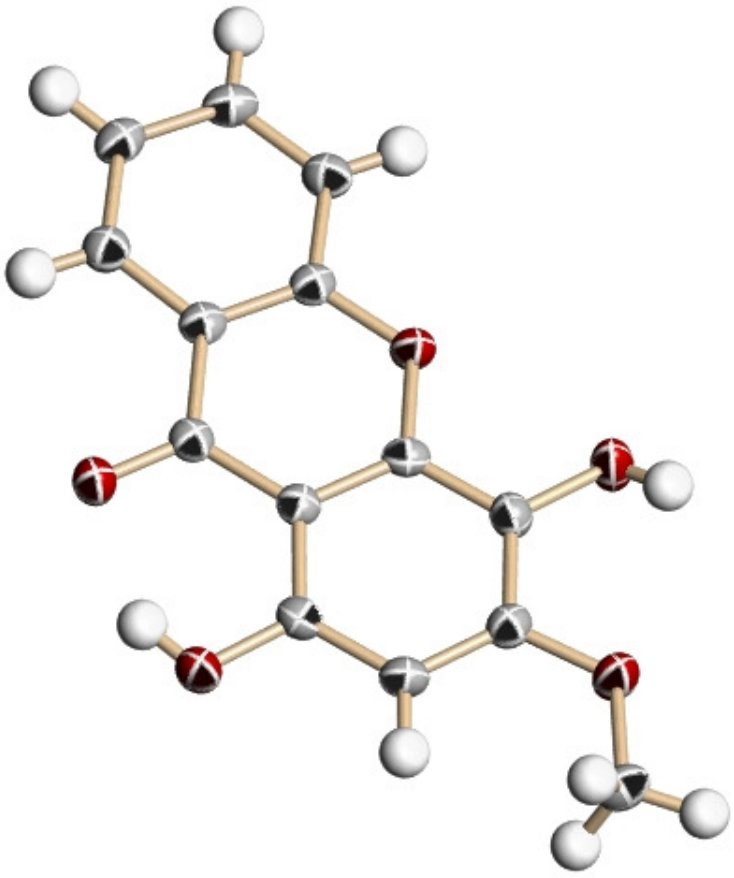


Figure 2

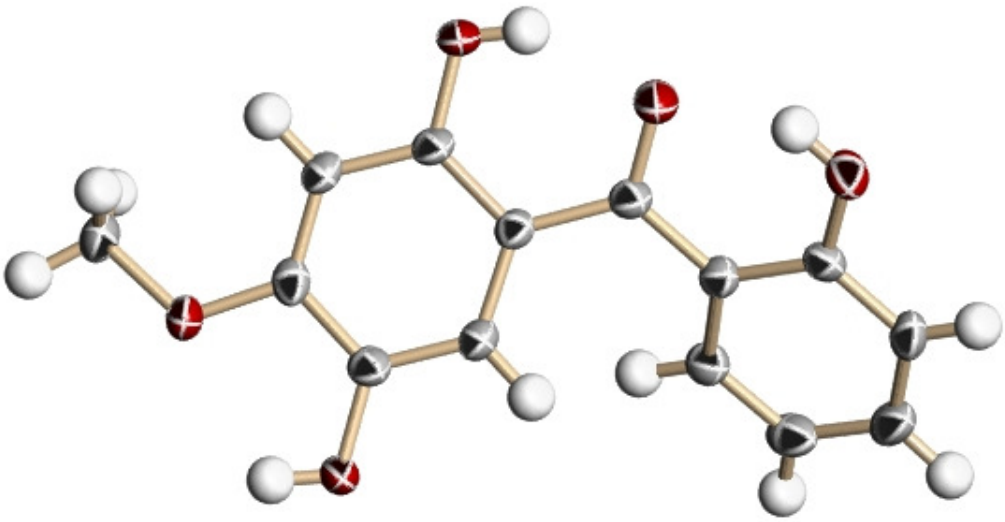
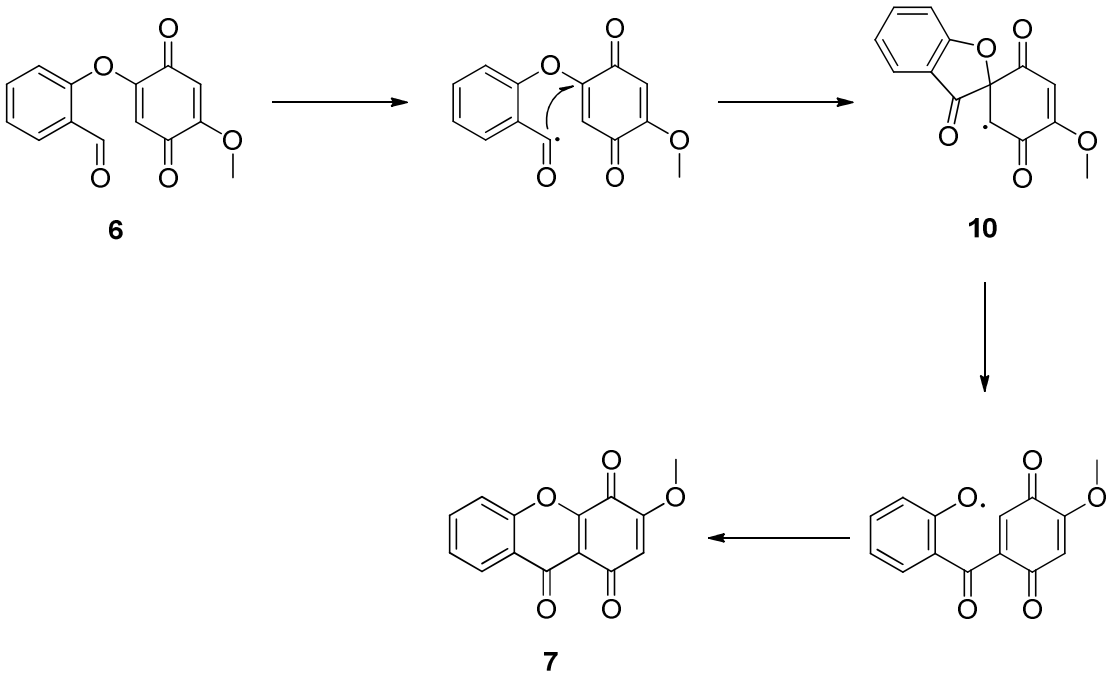


Figure 3

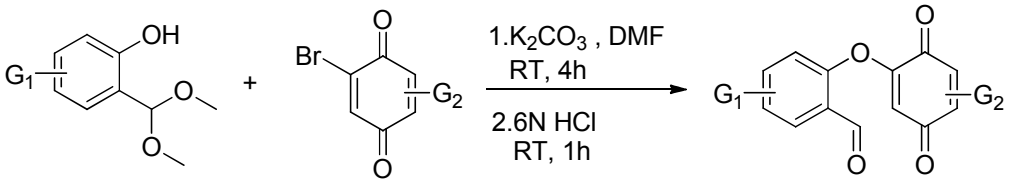
Moreover, this result was unexpected and suggests that production of xanthone **7** arises from a spirocyclic intermediate such as **10** that would result from a 5-exo-trig radical cyclization. Elimination of the phenoxide radical followed by cyclization and oxidation providesa route to **7** (Scheme 6). Attempts to isolate intermediates in the rearrangement by conducting the reaction using only one equivalent of NBS produced starting material plus a reduced yield of **7**. It is possible that the mechanism involves a 6-endo closure followed by arearrangement.



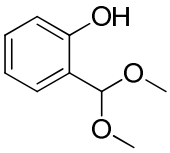
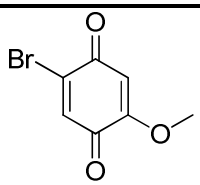
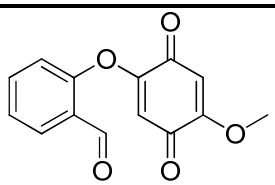
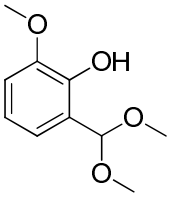
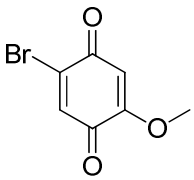
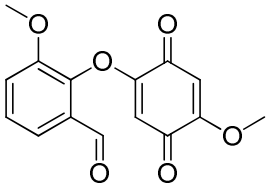
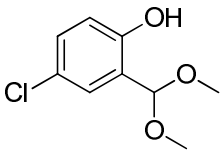
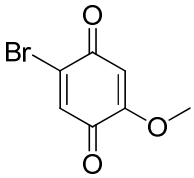
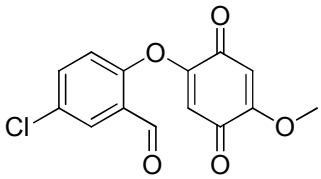
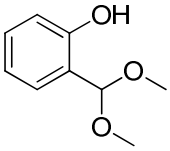
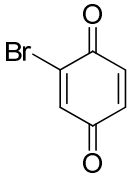
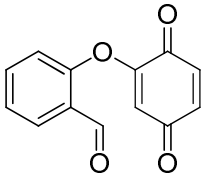
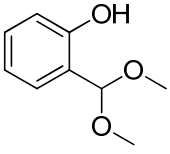
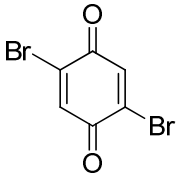
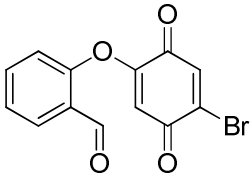
Scheme 6

This procedure was applied to other bromoquinones. The results in Table 1show the quinone precursors that were synthesized. The overall yields are in the range of 52–78%.

Table 1. Reaction of **4** with **5** to Generate Quinone **6**

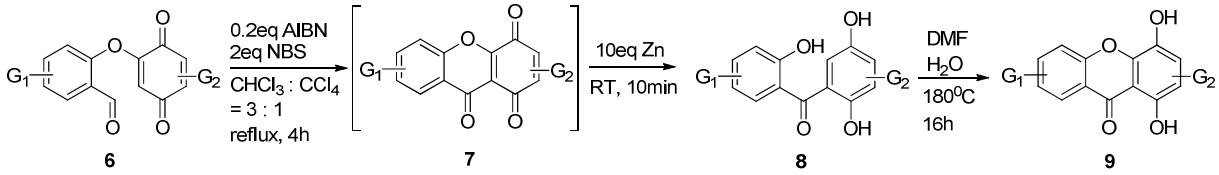


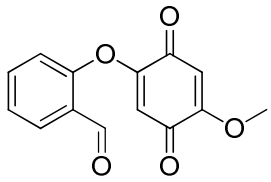
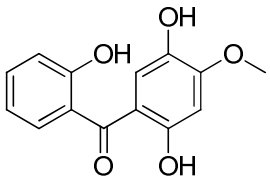
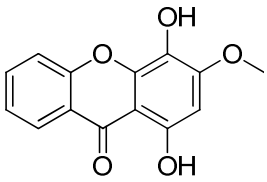
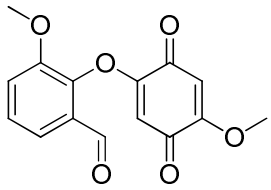
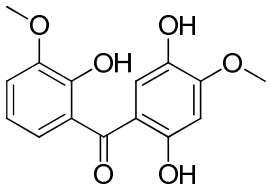
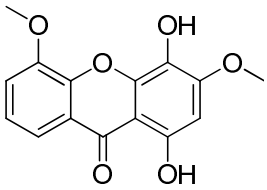
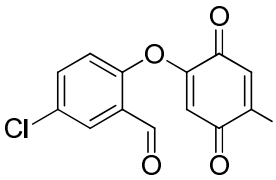
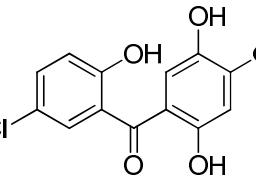
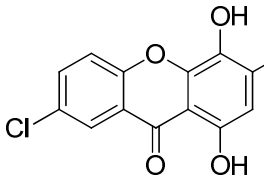
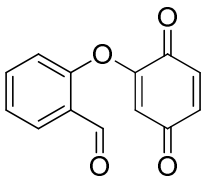
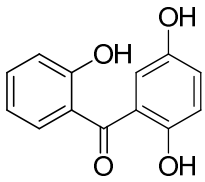
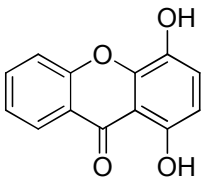
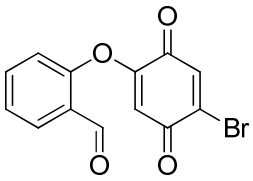
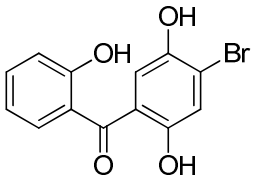
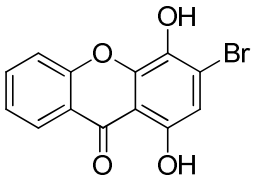
4 **5** **6**

Entry	4	5	6	Isolated Yield(%)
1				78
2				76
3				73
4				58
5				52

The xanthones in Table 2 were prepared from the corresponding quinones by cyclization with AIBN and NBS, reduction with zinc, and cyclization in DMF/water. The xanthone in entry 2 is a natural product isolated from *Centaurium erythraea*[19] that had not previously been synthesized. The overall yields for different xanthonesare 40% (entry 1), 36% (entry 2), 31% (entry 3), 29% (entry 4), and30% (entry 5).

Table 2. Reaction of Quinone **6** to Generate **8** and Xanthone **9**

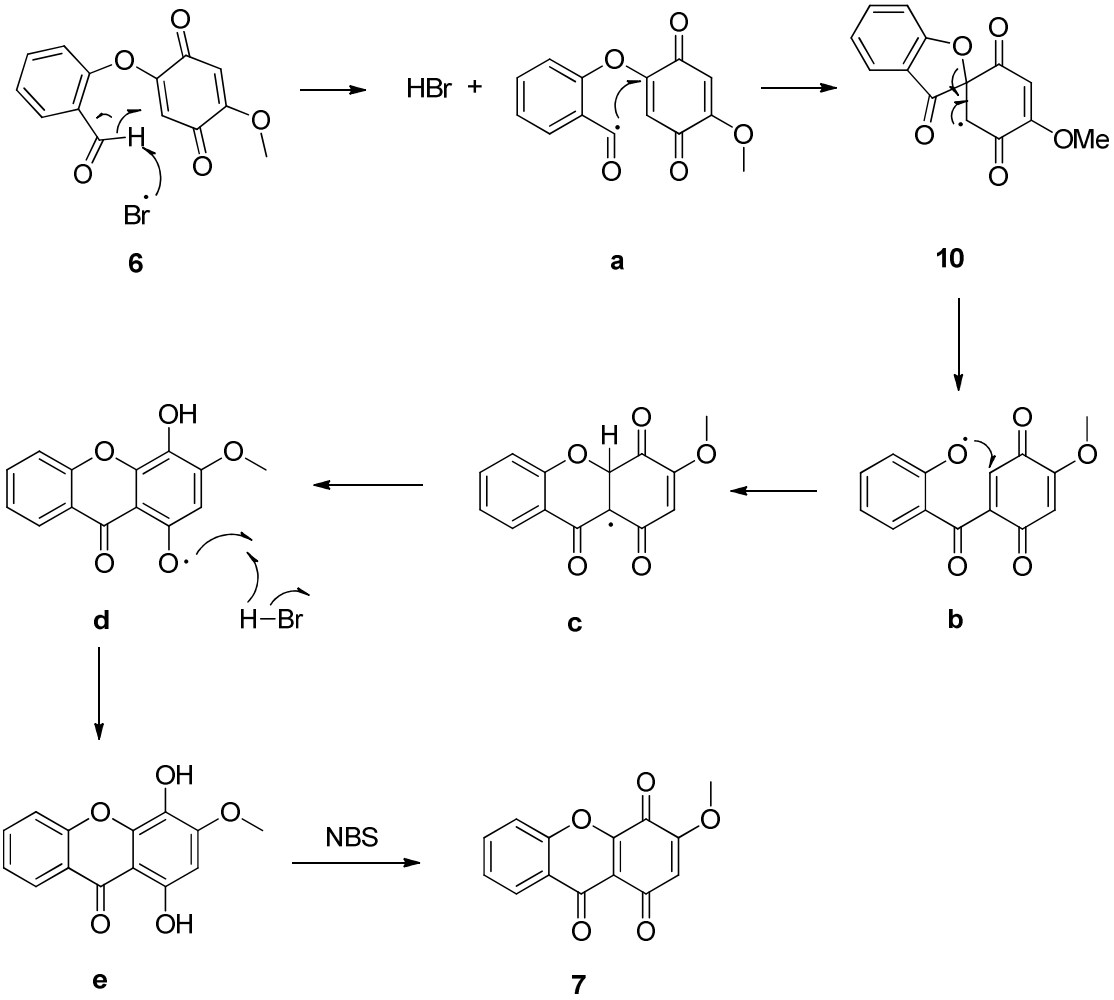


Entry	6	8[a]	Isolated Yield(%)	9[b]	Isolated Yield(%)
1			86		77
2			65		72
3			75		70
4			81		73
5			84		77

[a] Entry 1 is a natural product isolated from *Dalbergiacochinchinensis*.

[b] Entry 2 is a natural product isolated from *Centauriumerythraea*.

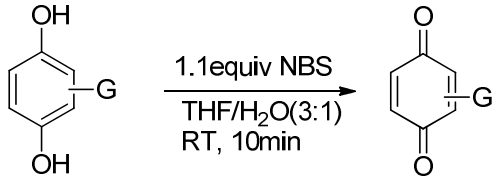
The proposed mechanism is shown below.

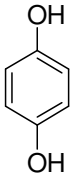
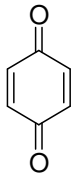
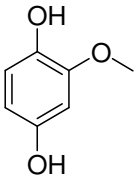
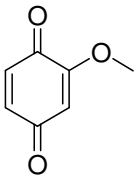
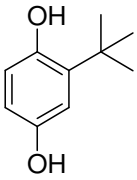
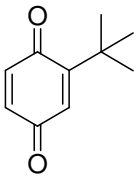
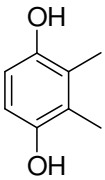
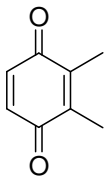


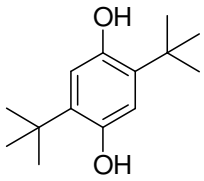
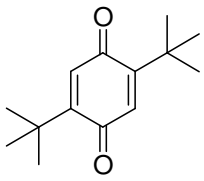
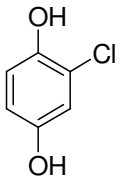
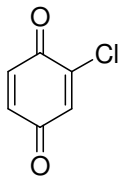
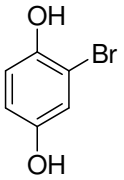
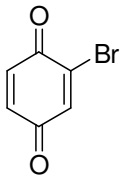
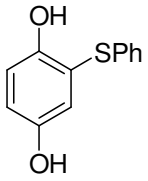
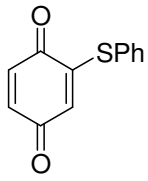
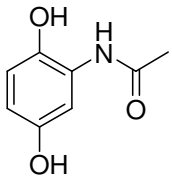
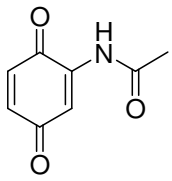
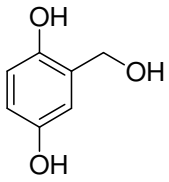
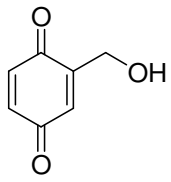
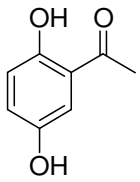
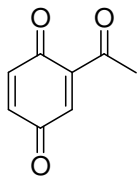
Based on the mechanism, we should get hydroxylated xanthone **e** directly. Unfortunately, attempts to isolate compound **e** failed. We finanlly obtained compound **7** instead. We realized maybe this result was due to oxidation of compound **e** by NBS.

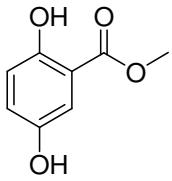
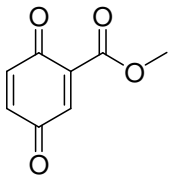
From compound **e** to compound **7**, only hydroquinone ring was changed to benzoquinone ring. Then we thouhgt, maybe NBS could oxidaze 1,4-hydroquinone to 1,4-benzoquinone. Interestingly, no one reported this result before. After many experiments, we found we could successfully oxidize 1,4-hydroquinone to 1,4-benzoquinone by using 1.1 equivalent NBS, THF and water as solvent. Table 3 showed the results.

Table 3. Oxidation of 1,4-Hydroquinone to 1,4-Benzoquinone



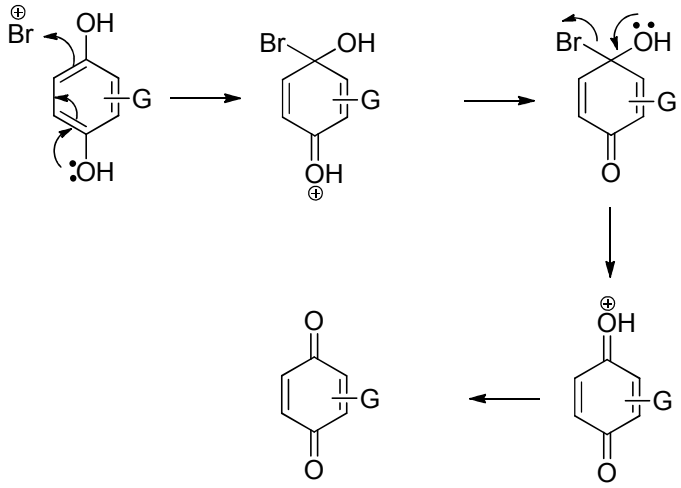
Entry	Starting Material	Product	Isolated Yield(%)
1			92
2			93
3			96
4			91

5			93
6			72
7			87
8			91
9			80
10			78
11			NR

12   NR

This method works fine for simple 1,4-hydroquinones with good yields. Entry **1** to entry **5** show that from the simplest 1,4-hydroquinone to di-substituted 1,4-hydroquinone, the yields are from 91% to 96%. This method also works fine for chloro (entry **6**) and bromo (entry **7**) substituted 1,4-hydroquinone, especially entry **7**. Because the 2-bromo-1,4-benzoquinone is really expensive, it is possible to make it with low price with this method. This method not only works for simple 1,4-hydroquinone, but also works for complicated 1,4-hydroquinone, entry **8** to **10**. Those related 1,4-benzoquinone are not easy to make. But by using NBS, it is easy to make them with good yields. When we tried β-keto 1,4-hydroquinone, entry **11** and **12**, both reactions failed. The reason is probably that both β-keto groups are electron withdrawing group which can result in electron deficient on the benzene ring.

The proposed mechanism is shown below.



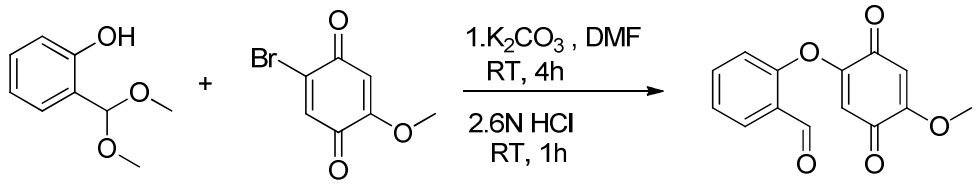
Conclusion

In summary, the first synthesis of xanthones by acyl radical chemistry has been achieved. Two natural products were synthesized. This novel approach will permit the direct synthesis of novel polyhydroxylated xanthones. And a new method of oxidation of 1,4-hydroquinone to 1,4-benzoquinone is developped.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. All ^{1}H and ^{13}C NMR spectra were recorded at 300 (400) MHz and 100 MHz respectively. High resolution mass spectra were recorded on a Q-TOF mass spectrometer. X-ray spectra were recorded by Bruker APEX2 CCD system . Standard grade silica gel (60 Å, 32-63 μm) was used for flash column chromatography.

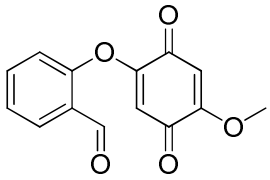
Representative procedure for quinone (6)



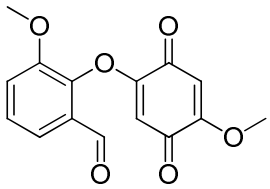
4 **5** **6**

To a solution of **4** (185 mg, 1.1 mmol) in 11 ml of dry DMF was added K_2CO_3 (152 mg, 1.1 mmol) at room temperature under argon. After stirring for 30 min, the solution of **5** (217 mg, 1.0 mmol) in 10 ml of dry DMF was added dropwise. The mixture was stirred for 3.5 hours. Then 4 ml of 6N HCl was added. After stirring for 1 hour, the

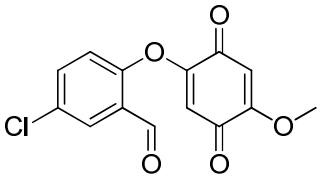
resulting mixture was extracted with ethyl acetate (3 × 10 ml). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. Residue was purified by column chromatography (Hexanes : EtOAc = 3:1) to give pure product.



Yield = 78%; ^{1}H NMR (300MHz, $CDCl_3$): 10.12 (s, 1H), 7.99-7.96 (dd, J=3.0, 6.0 Hz, 1H), 7.73-7.67 (dt, J=3.0, 9.0 Hz, 1H), 7.49-7.44 (t, J=6 Hz, 1H), 7.19-7.16 (d, J=9.0, 1H), 5.99 (s, 1H), 5.62 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): 187.7, 181.6, 180.7, 159.6, 159.3, 154.3, 136.3, 131.1, 127.9, 127.5, 122.3, 110.0, 105.9, 57.0.

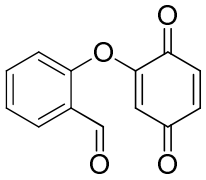


Yield = 76%; ^{1}H NMR (400MHz, $CDCl_3$): 10.11 (s, 1H), 7.51-7.49 (d, J=8.0 Hz, 1H), 7.40-7.36 (t, J=8.0 Hz, 1H), 7.26-7.24 (d, J=8.0 Hz, 1H), 5.96 (s, 1H), 5.53 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): 187.9, 181.8, 180.7, 159.5, 158.3, 151.1, 143.0, 129.0, 127.8, 121.0, 118.6, 109.2, 105.8, 56.9, 56.5.

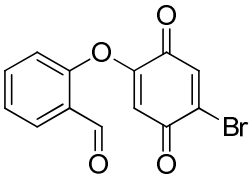


Yield = 73%; ^{1}H NMR (300MHz, $CDCl_3$): 10.08 (s, 1H), 7.93-7.92 (d, J=3.0 Hz, 1H),

7.65-7.62 (dd, J=3.0, 9.0 Hz, 1H), 7.14-7.11 (d, J=9.0 Hz, 1H), 5.98 (s, 1H), 5.67 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): 186.4, 181.3, 180.5, 159.6, 158.8, 152.9, 136.0, 133.4, 130.4, 128.8, 123.6, 110.6, 105.9, 57.0.

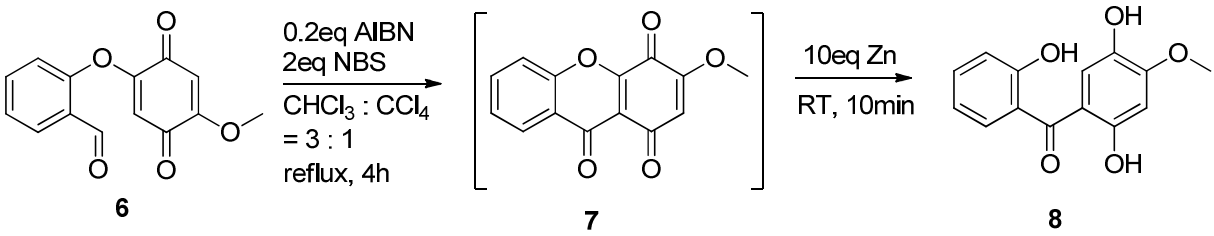


Yield = 58%; ^{1}H NMR (300MHz, $CDCl_3$): 10.12 (s, 1H), 7.99-7.96 (dd, J=3.0, 9.0 Hz, 1H), 7.73-7.67 (dt, J=3.0, 9.0 Hz, 1H), 7.49-7.44 (t, J=9.0 Hz, 1H), 7.18-7.15 (d, J=9.0 Hz, 1H), 6.86-6.83 (d, J=9.0 Hz, 1H), 6.77-6.73 (dd, J=3.0, 12.0 Hz, 1H), 5.70 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$): 187.8, 187.3, 180.9, 158.4, 154.1, 137.2, 136.3, 134.9, 131.2, 127.9, 127.4, 122.3, 112.3.

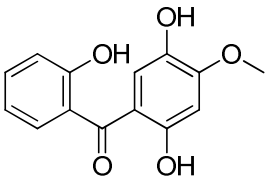


Yield = 52%; ^{1}H NMR (300MHz, $CDCl_3$): 10.09 (s, 1H), 7.99-7.96 (dd, J=3.0, 9.0 Hz, 1H), 7.74-7.68 (dt, J=3.0, 9.0 Hz, 1H), 7.52-7.47 (t, J=9.0 Hz, 1H), 7.35 (s, 1H), 7.19-7.16 (d, J=9.0 Hz, 1H), 5.86 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$): 187.7, 179.2, 178.4, 158.7, 153.5, 139.0, 136.4, 136.1, 131.8, 127.7, 122.3, 111.3, 111.2.

Representative procedure for benzophenone (8)

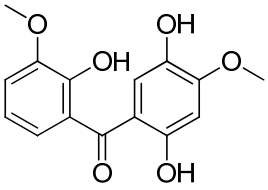


To the mixture of **6** (54 mg, 0.21 mmol), AIBN (7 mg, 0.042 mmol) and NBS (75 mg, 0.42 mmol) was added 2 ml of $CHCl_3$ and 6 ml of CCl_4 at room temperature under argon. The resulting mixture was boiled for 4 hours. After cooling to room temperature, the solvents were removed *in vacuo*. The residue was dissolved in 6 ml AcOH. After Zn metal powder (137 mg, 2.1 mmol) was added, the resulting mixture was stirred at room temperature for 10 min. The reaction mixture was filtered through celite and diluted with CH_2Cl_2, followed by washing twice with water. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. Residue was purified by column chromatography (Hexanes : EtOAc = 1:1) to give pure product.

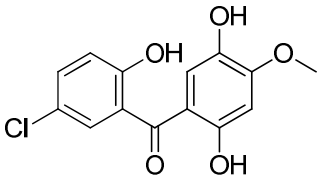


Yield = 86%. ^{1}H NMR and ^{13}C NMR are as same as reference.[1]

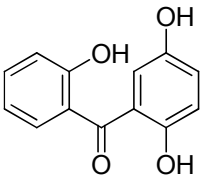
(1. Pathak, Vibha; Shirota, Osamu; Sekita, Setsuko; Hirayama, Yutaka; Hakamata, Yusuke; Hayashi, Tatsuo; Yanagawa, Takuma; Satake, Motoyoshii; *Phytochemistry*.**1997**, 46(7), 1219-1223.)



Yield = 65%; ^{1}H NMR (300MHz, DMSO-d_6): 12.18 (s, 1H), 9.29 (br s, 1H), 8.80 (br s, 1H), 7.13-7.09 (dd, J=3.0, 9.0 Hz, 1H), 6.92-6.87 (t, J=6.0 Hz, 1H), 6.81-6.78 (dd, J=3.0, 9.0 Hz, 1H), 6.68 (s, 1H), 6.56 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100MHz, DMSO-d_6): 199.8, 157.8, 155.8, 147.7, 143.6, 138.9, 126.3, 119.8, 119.2, 117.0, 113.3, 112.3, 100.1, 56.0, 55.9. HRMS (M-1) calcd for $C_{15}H_{13}O_6$: 289.0718; found: 289.0726.

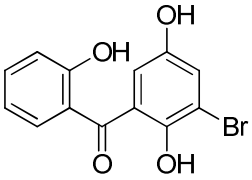


Yield = 75%; ^{1}H NMR (300MHz, DMSO-d_6): 7.40-7.36 (dd, J=3.0, 9.0 Hz, 1H), 7.28 (s, 1H), 6.99-6.96 (d, J=9.0 Hz, 1H), 6.68 (s, 1H), 6.56 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (100MHz, DMSO-d_6): 198.0, 158.0, 156.2, 153.3, 139.1, 131.0, 127.7, 122.4, 119.5, 118.0, 116.7, 112.0, 100.1, 56.0. HRMS (M-1) calcd for $C_{14}H_{10}ClO_5$: 293.0222; found: 293.0231.



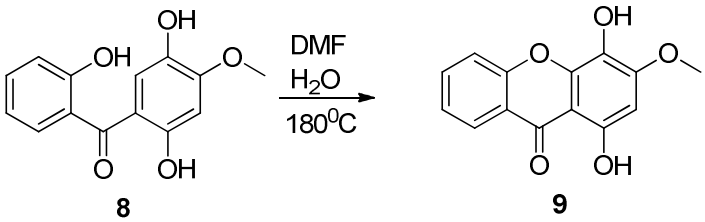
Yield = 81%; ^{1}H NMR (300MHz, DMSO-d_6): 10.83 (s, 1H), 10.57 (s, 1H), 9.83 (s, 1H), 7.49-7.43 (dt, J=3.0, 9.0 Hz, 1H), 7.36-7.33 (dd, J=3.0, 9.0 Hz, 1H), 7.00 (s, 1H), 6.97-

6.88 (m, 4H); ^{13}C NMR (100MHz, DMSO-d_6): 200.6, 157.6, 150.8, 145.5, 134.2, 131.0, 125.8, 123.3, 122.2, 119.1, 117.7, 117.4, 116.8. HRMS (M-1) calcd for $C_{13}H_9O_4$: 229.0506; found: 229.0508.



Yield = 84%; ^{1}H NMR (300MHz, $CDCl_3$): 7.63-7.60 (d, J=9.0 Hz, 1H), 7.55-7.49 (dt, J=3.0, 9.0 Hz, 1H), 7.27 (s, 1H), 7.25 (s, 1H), 7.09-7.06 (dd, J=3.0, 9.0 Hz, 1H), 6.97-6.92 (t, J=9.0 Hz, 1H); ^{13}C NMR (100MHz, DMSO-d_6): 201.4, 162.0, 155.2, 144.9, 136.5, 132.9, 125.8, 121.9, 120.1, 119.7, 119.3, 118.9, 118.4. HRMS (M-1) calcd for $C_{13}H_8BrO_4$: 306.9611; found: 306.9617.

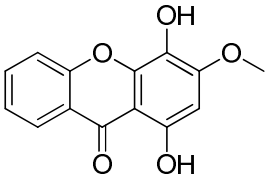
Representative procedure for xanthone (9)



8 **9**

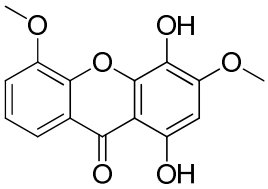
To **8** (23 mg, 0.088 mmol) in a sealable tube was added 1.7ml of DMF and 2.7 ml of H_2O. The resulting mixture was heated at 180°C for 16 hours. After cooling to room temperature, the reaction mixture was diluted with EtOAc followed by washing twice with water. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. Residue was purified by column chromatography (Hexanes : EtOAc

= 1:1) to give pure product.



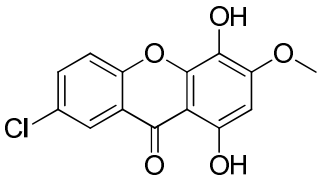
Yield = 77%; ^{1}H NMR (300MHz, DMSO-d_6): 12.40 (s, 1H), 8.90 (br s, 1H), 8.16-8.13 (dd, J=3.0, 9.0 Hz, 1H), 7.90-7.84 (dt, J=3.0, 9.0 Hz, 1H), 7.63-7.61 (d, J=6 Hz, 1H), 7.49-7.44 (t, J=6.0 Hz, 1H), 6.58 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (100MHz, DMSO-d_6): 180.6, 155.8, 155.6, 154.7, 143.9, 135.9, 126.0, 125.3, 124.2, 119.6, 117.8, 102.5, 94.7, 56.4.

HRMS (M-1) calcd for $C_{14}H_9O_5$: 257.0455; found: 257.0452.

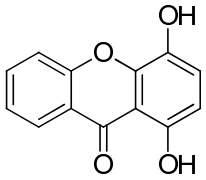


Yield = 72%; ^{1}H NMR (300MHz, DMSO-d_6): 12.44 (s, 1H), 8.75 (br s, 1H), 7.69-7.66 (dd, J=3.0, 9.0 Hz, 1H), 7.53-7.49 (dd, J=3.0, 9.0 Hz, 1H), 7.40-7.35 (t, J=6.0 Hz, 1H), 6.59 (s,1H), 3.98 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (100MHz, DMSO-d_6): 180.7, 155.9, 154.7, 148.2, 145.8, 144.1, 126.1, 123.8, 120.3, 116.9, 115.8, 102.5, 94.7, 56.5, 56.3.

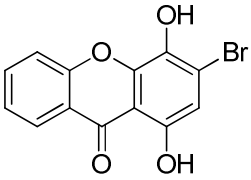
HRMS (M-1) calcd for $C_{15}H_{11}O_6$: 287.0561; found: 287.0567.



Yield = 70%; ^{1}H NMR (300MHz, DMSO-d_6): 12.17 (s, 1H), 8.97 (br s, 1H), 8.07-8.06 (d, J=3.0 Hz, 1H), 7.92-7.88 (dd, J=3.0, 9.0 Hz, 1H), 7.68-7.65 (d, J=9.0 Hz, 1H), 6.61 (s, 1H), 3.94 (s, 3H); ^{13}C NMR (100MHz, DMSO-d_6): 56.6, 95.1, 102.4, 120.4, 120.8, 124.3, 126.2, 128.5, 135.6, 143.7, 154.3, 154.8, 156.2, 179.5. HRMS (M-1) calcd for $C_{14}H_8ClO_5$: 291.0066; found: 291.0072.



Yield = 73%; ^{1}H NMR (300MHz, DMSO-d_6): 11.84 (s, 1H), 9.72 (br s, 1H), 8.20-8.17 (dd, J=3.0, 9.0 Hz, 1H), 7.95-7.89 (dt, J=3.0, 9.0 Hz, 1H), 7.68-7.66 (d, J=6.0 Hz, 1H), 7.53-7.48 (t, J=9.0 Hz, 1H), 7.31-7.28 (d, J=9.0 Hz, 1H), 6.68-6.66 (d, J=6.0 Hz, 1H); ^{13}C NMR (100MHz, DMSO-d_6): 181.9, 155.6, 152.4, 143.7, 137.4, 136.4, 125.5, 124.5, 123.7, 119.8, 118.2, 114.9, 109.0. HRMS (M-1) calcd for $C_{13}H_7O_4$: 227.0350; found: 227.0356.

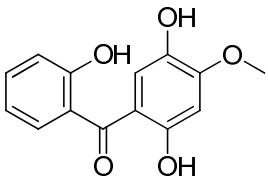


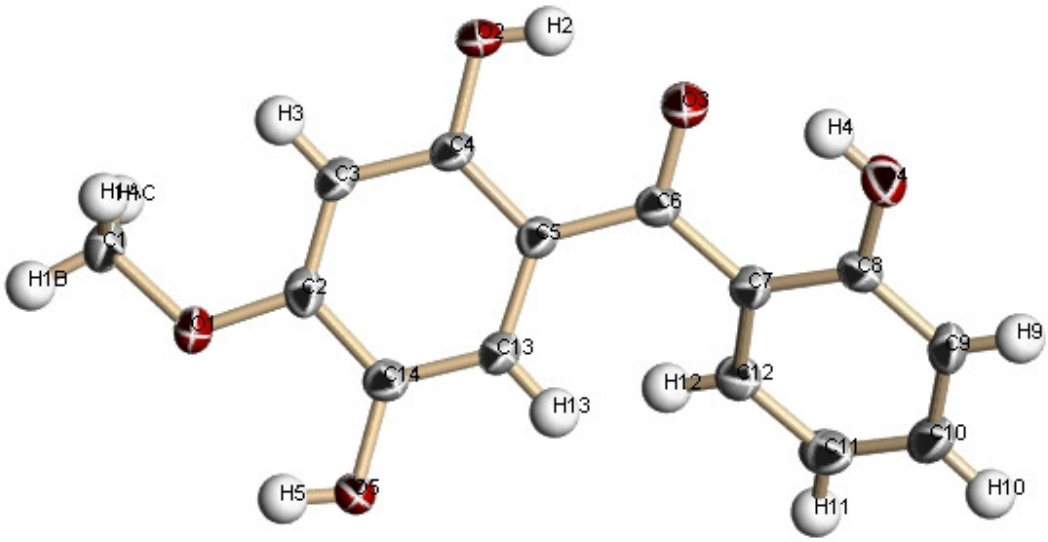
Yield = 77%; ^{1}H NMR (300MHz, DMSO-d_6): 11.91 (br s, 1H), 8.20-8.16 (dd, J=3.0, 9.0 Hz, 1H), 7.98-7.92 (dt, J=3.0, 9.0 Hz, 1H), 7.68-7.66 (d, J=6.0 Hz, 1H), 7.56-7.50 (dt,

J=3.0, 9.0 Hz, 1H), 7.02 (s, 1H), 6.88 (s, 1H); ^{13}C NMR (100MHz, DMSO-d_6): 181.5, 155.3, 152.5, 136.6, 135.3, 125.4, 124.9, 119.8, 119.5, 118.1, 112.5, 109.7, 108.2. HRMS (M-1) calcd for $C_{13}H_6BrO_4$: 304.9455; found: 304.9457.

X-Ray Data

1. Benzophenone **8**





A yellow plate-like specimen of $C_{14}H_{12}O_5$, approximate dimensions 0.05 mm x 0.10 mm x 0.29 mm, was used for the X-ray crystallographic analysis. Crystal was selected under the microscope and covered with PARATONE oil. After that sample was mounted in diffractometer under the stream of cold nitrogen. The X-ray intensity data were measured using BRUKER APEX2 CCD diffractometer.

The total exposure time was 8.97 hours. The frames were integrated with the Bruker

SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 8268 reflections to a maximum θ angle of 25.07° (0.84 Å resolution), of which 2056 were independent (average redundancy 4.021, completeness = 99.9%, R_{int} = 6.42%, R_{sig} = 5.50%) and 1390 (67.61%) were greater than $2\sigma(F^2)$. The final cell constants of a = 9.957(4) Å, b = 3.8623(15) Å, c = 30.418(13) Å, β = 97.709(5)°, volume = 1159.2(8) $Å^3$, are based upon the refinement of the XYZ-centroids of 1169 reflections above 20 σ(I) with 5.229° < 2θ < 44.30°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.813. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9676 and 0.9943.

All non-hydrogen atoms were refined in full-matrix anisotropic approximation based on F^2 . All expected hydrogen atoms were placed on a calculated positions and were refined in isotropic approximation using "riding" model. The U_{iso}(H) values have been set at 1.2 - 1.5 times the U_{eq} value of the carrier atom. with 176 variables converged at R1 = 5.66%, for the observed data and wR2 = 14.02% for all data. The goodness-of-fit was 1.046. The largest peak in the final difference electron density synthesis was 0.264 $e^-/Å^3$ and the largest hole was -0.235 $e^-/Å^3$ with an RMS deviation of 0.060 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.491 g/cm^3 and F(000), 544 e^-.

Table 1. Sample and crystal data for Benzophenone8.

Chemical formula	$C_{14}H_{12}O_5$
Formula weight	260.24
Temperature	173(2) K
Wavelength	0.71073 Å

Crystal size	0.05 x 0.10 x 0.29 mm	
Crystal habit	yellow plate	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 9.957(4) Å	α = 90°
	b = 3.8623(15) Å	β = 97.709(5)°
	c = 30.418(13) Å	γ = 90°
Volume	1159.2(8) $Å^3$	
Z	4	
Density (calculated)	1.491 Mg/cm^3	
Absorption coefficient	0.114 mm^{-1}	
F(000)	544	

Table 2. Data collection and structure refinement for Benzophenone8.

Theta range for data collection	1.35 to 25.07°	
Index ranges	-11<=h<=11, -4<=k<=4, -36<=l<=36	
Reflections collected	8268	
Independent reflections	2056 [R(int) = 0.0642]	
Coverage of independent reflections	99.9%	
Absorption correction	multi-scan	
Max. and min. transmission	0.9943 and 0.9676	
Structure solution technique	direct methods	
Structure solution program	SHELXS-97 (Sheldrick, 2008)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-97 (Sheldrick, 2008)	
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	2056 / 0 / 176	
Goodness-of-fit on F^2	1.046	
Δ/σ_{max}	0.001	
Final R indices	1390 data; I>2σ(I)	R1 = 0.0566, wR2 = 0.1264
	all data	R1 = 0.0911, wR2 = 0.1402

Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0494P)^2+1.4709P]$ where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole	0.264 and -0.235 eÅ^{-3}
R.M.S. deviation from mean	0.060 eÅ^{-3}

Table 3. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å^2) for Benzophenone8.

U(eq) is defined as one third of the trace of the orthogonalizedU_{ij} tensor.

	x/a	y/b	z/c	U(eq)
O1	0.1737(2)	0.5995(6)	0.92261(7)	0.0290(6)
O2	0.6455(2)	0.8167(6)	0.96285(7)	0.0315(6)
O3	0.8047(2)	0.5550(7)	0.91270(7)	0.0361(6)
O4	0.9572(2)	0.2118(7)	0.86563(7)	0.0333(6)
O5	0.2227(2)	0.2734(7)	0.84832(7)	0.0310(6)
C1	0.1417(3)	0.7741(9)	0.96110(11)	0.0319(8)
C2	0.3058(3)	0.5889(8)	0.91532(10)	0.0235(7)
C3	0.4127(3)	0.7185(8)	0.94397(10)	0.0227(7)
C4	0.5437(3)	0.6883(8)	0.93331(9)	0.0224(7)
C5	0.5683(3)	0.5329(8)	0.89302(9)	0.0201(7)
C6	0.7063(3)	0.5111(8)	0.88220(10)	0.0233(7)
C7	0.7360(3)	0.4384(8)	0.83702(10)	0.0232(7)
C8	0.8608(3)	0.2861(8)	0.83088(10)	0.0242(7)
C9	0.8897(3)	0.2065(9)	0.78884(11)	0.0290(8)
C10	0.7991(3)	0.2871(10)	0.75218(11)	0.0358(9)
C11	0.6795(3)	0.4616(9)	0.75720(11)	0.0322(8)
C12	0.6488(3)	0.5328(9)	0.79883(10)	0.0255(7)
C13	0.4558(3)	0.3930(8)	0.86548(10)	0.0223(7)
C14	0.3272(3)	0.4191(8)	0.87609(10)	0.0231(7)

Table 4. Bond lengths (Å) for Benzophenone8.

O1-C2	1.364(4)	O1-C1	1.424(4)
O2-C4	1.355(4)	O2-H2	0.84
O3-C6	1.267(4)	O4-C8	1.360(4)
O4-H4	0.84	O5-C14	1.370(4)

O5-H5	0.84	C1-H1A	0.98
C1-H1B	0.98	C1-H1C	0.98
C2-C3	1.376(4)	C2-C14	1.402(4)
C3-C4	1.391(4)	C3-H3	0.95
C4-C5	1.415(4)	C5-C13	1.413(4)
C5-C6	1.458(4)	C6-C7	1.471(4)
C7-C12	1.402(4)	C7-C8	1.409(4)
C8-C9	1.382(4)	C9-C10	1.373(5)
C9-H9	0.95	C10-C11	1.395(5)
C10-H10	0.95	C11-C12	1.370(4)
C11-H11	0.95	C12-H12	0.95
C13-C14	1.366(4)	C13-H13	0.95

Table 5. Bond angles (°) for Benzophenone8.

C2-O1-C1	118.3(2)	C4-O2-H2	109.5
C8-O4-H4	109.5	C14-O5-H5	109.5
O1-C1-H1A	109.5	O1-C1-H1B	109.5
H1A-C1-H1B	109.5	O1-C1-H1C	109.5
H1A-C1-H1C	109.5	H1B-C1-H1C	109.5
O1-C2-C3	124.5(3)	O1-C2-C14	114.3(3)
C3-C2-C14	121.1(3)	C2-C3-C4	119.4(3)
C2-C3-H3	120.3	C4-C3-H3	120.3
O2-C4-C3	117.2(3)	O2-C4-C5	121.9(3)
C3-C4-C5	120.9(3)	C13-C5-C4	117.4(3)
C13-C5-C6	122.7(3)	C4-C5-C6	119.8(3)
O3-C6-C5	119.1(3)	O3-C6-C7	118.5(3)
C5-C6-C7	122.4(3)	C12-C7-C8	117.2(3)
C12-C7-C6	123.0(3)	C8-C7-C6	119.7(3)
O4-C8-C9	117.3(3)	O4-C8-C7	121.9(3)
C9-C8-C7	120.8(3)	C10-C9-C8	120.3(3)
C10-C9-H9	119.8	C8-C9-H9	119.8
C9-C10-C11	119.9(3)	C9-C10-H10	120.0
C11-C10-H10	120.0	C12-C11-C10	119.8(3)
C12-C11-H11	120.1	C10-C11-H11	120.1
C11-C12-C7	121.6(3)	C11-C12-H12	119.2
C7-C12-H12	119.2	C14-C13-C5	121.7(3)
C14-C13-H13	119.2	C5-C13-H13	119.2
C13-C14-O5	118.8(3)	C13-C14-C2	119.3(3)

O5-C14-C2 121.8(3)

Table 6. Anisotropic atomic displacement parameters ($Å^2$) for Benzophenone8.

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

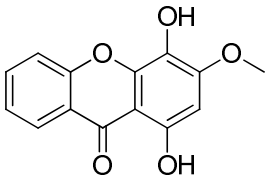
	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0211(12)	0.0428(14)	0.0243(12)	-0.0067(11)	0.0073(9)	0.0006(10)
O2	0.0234(12)	0.0499(15)	0.0205(12)	-0.0117(11)	0.0002(10)	-0.0046(12)
O3	0.0239(12)	0.0605(17)	0.0235(13)	-0.0080(12)	0.0014(10)	-0.0012(12)
O4	0.0210(12)	0.0523(16)	0.0262(13)	0.0017(12)	0.0024(10)	0.0038(11)
O5	0.0189(11)	0.0521(16)	0.0224(12)	-0.0102(11)	0.0039(9)	-0.0062(11)
C1	0.0297(18)	0.039(2)	0.0295(19)	-0.0084(17)	0.0124(15)	-0.0010(16)
C2	0.0215(17)	0.0290(18)	0.0211(17)	0.0053(15)	0.0067(13)	0.0026(14)
C3	0.0277(17)	0.0259(18)	0.0153(16)	-0.0004(14)	0.0058(13)	0.0007(14)
C4	0.0253(17)	0.0285(17)	0.0134(16)	-0.0008(14)	0.0019(13)	-0.0018(14)
C5	0.0215(16)	0.0223(16)	0.0167(16)	0.0002(13)	0.0031(13)	0.0011(13)
C6	0.0239(17)	0.0267(18)	0.0189(17)	-0.0010(14)	0.0016(14)	-0.0020(14)
C7	0.0227(17)	0.0265(17)	0.0209(17)	-0.0009(14)	0.0053(13)	-0.0035(14)
C8	0.0203(16)	0.0285(18)	0.0236(17)	-0.0018(15)	0.0020(13)	-0.0054(14)
C9	0.0262(17)	0.034(2)	0.0297(19)	-0.0042(16)	0.0142(15)	-0.0055(15)
C10	0.037(2)	0.049(2)	0.0229(18)	-0.0083(17)	0.0124(16)	-0.0149(18)
C11	0.034(2)	0.042(2)	0.0203(18)	0.0027(16)	0.0021(14)	-0.0116(17)
C12	0.0244(17)	0.0298(18)	0.0224(18)	0.0008(15)	0.0036(14)	-0.0037(15)
C13	0.0246(17)	0.0254(18)	0.0176(16)	-0.0011(14)	0.0056(13)	0.0002(13)

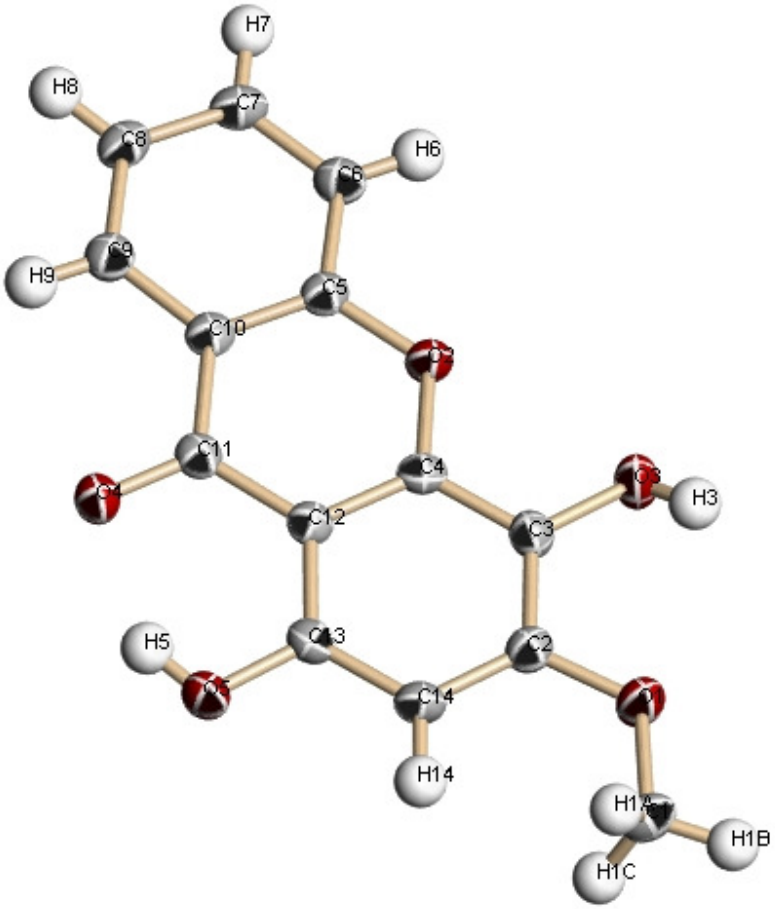
	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C14	0.0237(17)	0.0274(17)	0.0178(17)	0.0007(14)	0.0013(13)	-0.0016(14)

Table 7. Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å^2) for Benzophenone8.

	x/a	y/b	z/c	U(eq)
H2	0.7204	0.7575	0.9554	0.047
H4	0.9360	0.3030	0.8888	0.05
H5	0.1512	0.2846	0.8601	0.047
H1A	0.1863	0.6566	0.9877	0.048
H1B	0.0434	0.7716	0.9613	0.048
H1C	0.1736	1.0141	0.9608	0.048
H3	0.3971	0.8278	0.9708	0.027
H9	0.9728	0.0956	0.7853	0.035
H10	0.8178	0.2240	0.7234	0.043
H11	0.6194	0.5310	0.7318	0.039
H12	0.5665	0.6489	0.8019	0.031
H13	0.4700	0.2778	0.8389	0.027

2. Xanthone**9**





A yellow block-like specimen of $C_{14}H_{10}O_5$, approximate dimensions 0.10 mm x 0.13 mm x 0.31 mm, was used for the X-ray crystallographic analysis. Crystal was selected under the microscope and covered with PARATONE oil. After that sample was mounted in diffractometer under the stream of cold nitrogen. The X-ray intensity data were measured using BRUKER APEX2 CCD diffractometer.

The total exposure time was 8.98 hours. The frames were integrated with the Bruker

SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 8733 reflections to a maximum θ angle of 28.53° (0.74 Å resolution), of which 2574 were independent (average redundancy 3.393, completeness = 92.6%, R_{int} = 3.24%, R_{sig} = 3.51%) and 1877 (72.92%) were greater than $2\sigma(F^2)$. The final cell constants of a = 8.268(3) Å, b = 4.8051(19) Å, c = 27.536(11) Å, β = 91.174(4)°, volume = 1093.7(8) $Å^3$, are based upon the refinement of the XYZ-centroids of 2349 reflections above 20 σ(I) with 5.696° < 2θ < 55.52°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.780. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9636 and 0.9880.

All non-hydrogen atoms were refined in full-matrix anisotropic approximation based on F^2 . All expected hydrogen atoms were placed on a calculated positions and were refined in isotropic approximation using "riding" model. The U_{iso}(H) values have been set at 1.2 - 1.5 times the U_{eq} value of the carrier atom. with 175 variables converged at R1 = 4.38%, for the observed data and wR2 = 13.92% for all data. The goodness-of-fit was 0.950. The largest peak in the final difference electron density synthesis was 0.257 $e^-/Å^3$ and the largest hole was -0.245 $e^-/Å^3$ with an RMS deviation of 0.052 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.568 g/cm^3 and F(000), 536 e^-.

Table 1. Sample and crystal data for Xanthone9.

Chemical formula	$C_{14}H_{10}O_5$
Formula weight	258.22
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal size	0.10 x 0.13 x 0.31 mm

Crystal habit	yellow block	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 8.268(3) Å	α = 90°
	b = 4.8051(19) Å	β = 91.174(4)°
	c = 27.536(11) Å	γ = 90°
Volume	1093.7(8) $Å^3$	
Z	4	
Density (calculated)	1.568 Mg/cm^3	
Absorption coefficient	0.121 mm^{-1}	
F(000)	536	

Table 2. Data collection and structure refinement for Xanthone9.

Theta range for data collection	1.48 to 28.53°	
Index ranges	-10<=h<=11, -6<=k<=6, -37<=l<=36	
Reflections collected	8733	
Independent reflections	2574 [R(int) = 0.0324]	
Coverage of independent reflections	92.6%	
Absorption correction	multi-scan	
Max. and min. transmission	0.9880 and 0.9636	
Structure solution technique	direct methods	
Structure solution program	SHELXS-97 (Sheldrick, 2008)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-97 (Sheldrick, 2008)	
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	2574 / 0 / 175	
Goodness-of-fit on F^2	0.950	
Final R indices	1877 data; I>2σ(I)	R1 = 0.0438, wR2 = 0.1223
	all data	R1 = 0.0662, wR2 = 0.1392
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0869P)^2+0.2651P]$	

	where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole	0.257 and -0.245 eÅ^{-3}
R.M.S. deviation from mean	0.052 eÅ^{-3}

Table 3. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å^2) for Xanthone9.

U(eq) is defined as one third of the trace of the orthogonalizedU_{ij} tensor.

	x/a	y/b	z/c	U(eq)
O1	0.72057(14)	0.2127(3)	0.42467(5)	0.0300(3)
O2	0.01459(13)	0.5936(2)	0.33145(4)	0.0237(3)
O3	0.73622(15)	0.8314(3)	0.35324(5)	0.0314(3)
O4	0.44465(14)	0.7914(3)	0.40097(4)	0.0269(3)
O5	0.29353(14)	0.1533(3)	0.45272(5)	0.0297(3)
C1	0.7054(2)	0.4096(4)	0.46361(7)	0.0305(4)
C2	0.8696(2)	0.1086(4)	0.41577(6)	0.0230(4)
C3	0.8719(2)	0.9083(4)	0.37884(6)	0.0227(4)
C4	0.0185(2)	0.7881(3)	0.36795(6)	0.0203(3)
C5	0.1548(2)	0.4599(3)	0.31956(6)	0.0209(3)
C6	0.1403(2)	0.2653(3)	0.28203(6)	0.0254(4)
C7	0.2760(2)	0.1203(4)	0.26834(6)	0.0272(4)
C8	0.4250(2)	0.1642(4)	0.29192(6)	0.0266(4)
C9	0.4388(2)	0.3588(4)	0.32863(6)	0.0252(4)
C10	0.3034(2)	0.5129(3)	0.34260(6)	0.0214(4)
C11	0.31352(19)	0.7268(3)	0.38033(6)	0.0211(4)
C12	0.16380(19)	0.8608(3)	0.39239(6)	0.0198(3)
C13	0.1571(2)	0.0691(3)	0.42881(6)	0.0228(4)
C14	0.0110(2)	0.1892(3)	0.44049(6)	0.0245(4)

Table 4. Bond lengths (Å) for Xanthone9.

O1-C2	1.357(2)	O1-C1	1.437(2)
O2-C5	1.371(2)	O2-C4	1.3723(19)
O3-C3	1.363(2)	O3-H3	0.84
O4-C11	1.253(2)	O5-C13	1.356(2)
O5-H5	0.84	C1-H1A	0.98

C1-H1B	0.98	C1-H1C	0.98
C2-C14	1.396(2)	C2-C3	1.401(2)
C3-C4	1.382(2)	C4-C12	1.409(2)
C5-C10	1.394(2)	C5-C6	1.397(2)
C6-C7	1.380(2)	C6-H6	0.95
C7-C8	1.397(3)	C7-H7	0.95
C8-C9	1.380(2)	C8-H8	0.95
C9-C10	1.403(2)	C9-H9	0.95
C10-C11	1.463(2)	C11-C12	1.440(2)
C12-C13	1.419(2)	C13-C14	1.383(2)
C14-H14	0.95		

Table 5. Bond angles (°) for Xanthone9.

C2-O1-C1	118.10(13)	C5-O2-C4	119.10(13)
C3-O3-H3	109.5	C13-O5-H5	109.5
O1-C1-H1A	109.5	O1-C1-H1B	109.5
H1A-C1-H1B	109.5	O1-C1-H1C	109.5
H1A-C1-H1C	109.5	H1B-C1-H1C	109.5
O1-C2-C14	124.35(15)	O1-C2-C3	114.23(14)
C14-C2-C3	121.41(15)	O3-C3-C4	119.39(15)
O3-C3-C2	122.57(15)	C4-C3-C2	118.03(15)
O2-C4-C3	115.84(14)	O2-C4-C12	121.75(14)
C3-C4-C12	122.41(15)	O2-C5-C10	123.17(15)
O2-C5-C6	115.44(14)	C10-C5-C6	121.38(15)
C7-C6-C5	118.81(16)	C7-C6-H6	120.6
C5-C6-H6	120.6	C6-C7-C8	120.72(16)
C6-C7-H7	119.6	C8-C7-H7	119.6
C9-C8-C7	120.13(16)	C9-C8-H8	119.9
C7-C8-H8	119.9	C8-C9-C10	120.25(16)
C8-C9-H9	119.9	C10-C9-H9	119.9
C5-C10-C9	118.65(15)	C5-C10-C11	119.27(15)
C9-C10-C11	122.08(15)	O4-C11-C12	121.64(15)
O4-C11-C10	122.19(15)	C12-C11-C10	116.16(14)
C4-C12-C13	117.87(15)	C4-C12-C11	120.48(15)
C13-C12-C11	121.65(14)	O5-C13-C14	118.97(15)
O5-C13-C12	120.62(15)	C14-C13-C12	120.41(15)
C13-C14-C2	119.85(15)	C13-C14-H14	120.1

C2-C14-H14 120.1

Table 6. Anisotropic atomic displacement parameters (Å^2) for Xanthone9.

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0247(6)	0.0339(7)	0.0314(7)	-0.0113(5)	0.0006(5)	0.0051(5)
O2	0.0238(6)	0.0234(6)	0.0241(6)	-0.0061(5)	-0.0006(4)	0.0018(5)
O3	0.0206(6)	0.0421(8)	0.0315(7)	-0.0129(6)	-0.0001(5)	0.0003(5)
O4	0.0216(6)	0.0295(7)	0.0294(6)	-0.0038(5)	-0.0014(5)	-0.0004(5)
O5	0.0244(6)	0.0315(7)	0.0329(7)	-0.0111(5)	-0.0031(5)	-0.0010(5)
C1	0.0347(10)	0.0297(10)	0.0274(9)	-0.0056(7)	0.0060(7)	0.0056(8)
C2	0.0236(8)	0.0227(8)	0.0230(8)	0.0003(6)	0.0029(6)	0.0017(6)
C3	0.0200(8)	0.0244(8)	0.0235(8)	-0.0009(7)	-0.0005(6)	-0.0014(6)
C4	0.0267(8)	0.0171(8)	0.0174(8)	-0.0002(6)	0.0024(6)	-0.0009(6)
C5	0.0241(8)	0.0177(8)	0.0210(8)	0.0027(6)	0.0039(6)	-0.0003(6)
C6	0.0297(9)	0.0232(9)	0.0232(8)	-0.0006(7)	-0.0014(7)	-0.0007(7)
C7	0.0366(10)	0.0218(8)	0.0233(8)	-0.0022(7)	0.0034(7)	0.0009(7)
C8	0.0293(9)	0.0229(9)	0.0280(9)	0.0018(7)	0.0072(7)	0.0038(7)
C9	0.0260(9)	0.0225(8)	0.0271(9)	0.0024(7)	0.0014(7)	-0.0002(7)
C10	0.0259(9)	0.0180(8)	0.0203(8)	0.0032(6)	0.0024(6)	-0.0001(6)
C11	0.0227(8)	0.0194(8)	0.0212(8)	0.0032(6)	0.0013(6)	-

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
						0.0020(6)
C12	0.0217(8)	0.0185(8)	0.0192(8)	0.0020(6)	0.0014(6)	-0.0017(6)
C13	0.0249(8)	0.0215(8)	0.0219(8)	-0.0003(6)	-0.0006(6)	-0.0034(6)
C14	0.0288(9)	0.0210(8)	0.0237(8)	-0.0042(7)	0.0009(7)	-0.0005(7)

Table 7. Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å^2) for Xanthone9.

	x/a	y/b	z/c	U(eq)
H3	-0.3444	0.8422	0.3712	0.047
H5	0.3729	1.0619	0.4428	0.044
H1A	-0.2585	1.3233	0.4942	0.046
H1B	-0.4080	1.4664	0.4661	0.046
H1C	-0.2277	1.5732	0.4571	0.046
H6	0.0388	0.2335	0.2662	0.03
H7	0.2680	-0.0109	0.2426	0.033
H8	0.5170	0.0600	0.2827	0.032
H9	0.5405	0.3885	0.3445	0.03
H14	0.0069	1.3264	0.4653	0.029

References

1. Demirkiran, O. *Top. Heterocycl. Chem.* **2007**, 9, 139–178.
2. Jiang, D.-J.; Jiang, J.-L.; Tan, G.-S.; Du, Y.-H.; Xu, K.-P.; Li, Y.-J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2003**, 367, 600–606.
3. Meyer, J. J. Marion.; Rakuambo, N. C.; Hussein, A. A. *J. Ethnopharmacol.* **2008**, 119(3), 599–603.

4. Tian, L.-Y.; Bai, X.; Chen, X.-H.; Fang, J.-B.; Liu, S.-H.; Chen, J.-C. *Phytomedicine.* **2010**, 17, 533–539.

5. Sousa, M. E.; Pinto, M. M. M. *Curr. Med. Chem.* **2005**, 12, 2447–2479.

6. Pedro, M.; Cerqueria, F.; Sousa, M. E.; Nascimento, M. S. J.; Pinto, M. *Bioorg. Med. Chem.* **2002**, 10, 3725.

7. Kraus, G. A.; Mengwasser, J. *Molecules*. **2009**, 14, 2857–2861.

8. (a) Okuma, K.; Nojima, A.; Matsunaga, N.; Shioji, K. *Org. Lett.* **2009**, 11, 169–171; (b) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, 12, 3117–3119.

9. (a) MacNeil, S. L.; Gray, M.; Gusev, D. G.; Briggs, L. E.; Snieckus, V. *J. Org. Chem.* **2008**, 73, 9710–9719; (b) Mondal, M.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2006**, 71, 4992–4995.

10. Kraus, G. A.; Thite, A.; Liu, F. *Tetrahedron Lett.* **2009**, 50, 5303–5304.

11. Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, 99, 1991–2069.

12. Donald L. Jameson; Sharon E. Hilgen; Conrad E. Hummel; Susan L. Pichla; T*etrahedron Letters,* **1989**, 1609-12.

13. Rangam Gopinath; Sk. Jiaul Haque; Bhisma K. Patel; *JOC,* **2002**, 5842-5845.

14. KREUTZER, Kristina, Ann; TAM, Wilson; GARNER, J., Michael; BOYLES, John, Ronald; *PCT Int. Appl.,* **2001021580**.

15. Clerici, A.; Pastori, N.; Porta, *O. Tetrahedron.* **1998**, 54, 15679–15690.

16. (a) Kraus, G. A.; Kirihara, M.; Wu, Y. *ACS Symposium Series*. **1994**, 577(Benign byDesign), 76–83.; (b) Kraus, G. A.; Liu, P. *Tetrahedron Lett.* **1994**, 35, 7723–7726.

17. (a) Cheung, Y.-F. *Tetrahedron Lett.* **1979**, 3809–3810; (b) Marko, I. E.; Mekhalfia, A. *Tetrahedron Lett.* **1990**, 31, 7237.

18. Pathak, V.; Shirota, O.; Sekita, S.; Hirayama, Y.; Hakamata, Y.; Hayashi, T.; Yanagawa, T.; Satake, M. *Phytochemistry.* **1997**, 46, 1219–1223.

19. Neshta, N. M.; Glyzin, V. I.; Patudin, A. V. *Khimiya Prirodnykh Soedinenii.* **1984**, 110.

CHAPTER 3: The Preparation of Ketone Constituents from *Echinacea pallida*

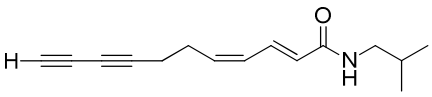
Introduction

Echinacea is a genus of herbaceous flowering plants in the daisy family, *Asteraceae*. The nine species it contains are commonly called purple coneflowers, but only three of these are used for medicinal purposes. *Echinacea angustifolia*, *Echinacea pallida*, and *Echinacea purpurea* are the main *Echinacea* species and have been used to treat infections and enhance the immune system.[1] *Echinacea* has ranked among the leading botanical supplements sold worldwide. Commercial *Echinacea* is often a mixture of species and there is no standardization of the chemical components. There are some differences in the constituents of *Echinacea* across the species and their respective plant parts (Table1).

Table 1. Major constituents of *Echinacea* species used medicinally[2]

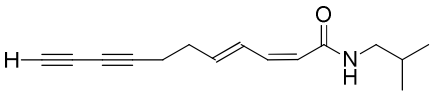
Species	Plant part	Constituents	Comment
Echinacea purpurea	Aerial parts	Alkamides; caffeic acid esters, mainly cichoric acid; polysaccharides; polyacetylenes	Echinacoside is not present
Echinacea angustifolia	Roots	Alkamides; caffeic acid esters, particularly echinacoside; cynarin; polysaccharides; polyacetylenes	Cynarin is characteristic of *E. angustifolia*
Echinacea pallida	Roots	Caffeic acid esters, particularly echinacoside; polysaccharides; polyacetylenes (distinctive series)	Alkamides largely absent

Alkamides are main components of *Echinacea angustifolia* and *Echinacea purpurea*, in which mainly isobutylamides of straight chain fatty acids with double bonds and triple bonds. Bohlmann and Bauer have revealed the structure, chemistry and biological activities of these alkamides.[3] Alkamide constituents in *Echinacea*are shown in Figure 1.[4] The major constituents of*Echinacea pallid*a are ketonecompounds which are shown in Figure 2.[5]



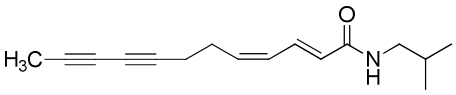
1

(2*E*,4*Z*)-*N*-isobutylundeca-2,4-dien-8,10-diynamide



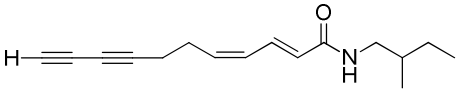
2

(2*Z*,4*E*)-*N*-isobutylundeca-2,4-dien-8,10-diynamide



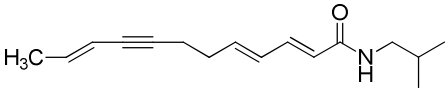
3

(2*E*,4*Z*)-*N*-isobutyldodeca-2,4-dien-8,10-diynamide



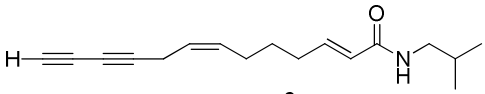
4

(2*E*,4*Z*)-*N*-(2-methylbutyl)undeca-2,4-dien-8,10-diynamide



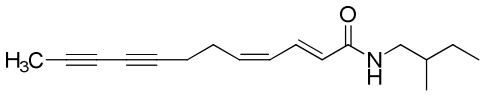
5

(2*E*,4*E*,10*E*)-*N*-isobutyldodeca-2,4,10-trien-8-ynamide



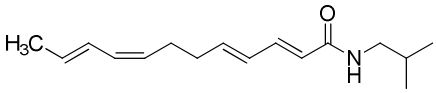
6

(2*E*,7*Z*)-*N*-isobutyltrideca-2,7-dien-10,12-diynamide



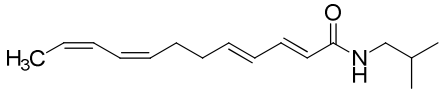
7

(2*E*,4*Z*)-*N*-(2-methylbutyl)dodeca-2,4-dien-8,10-diynamide



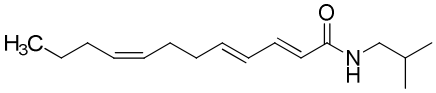
8

(2*E*,4*E*,8*Z*,10*E*)-*N*-isobutyldodeca-2,4,8,10-tetraenamide



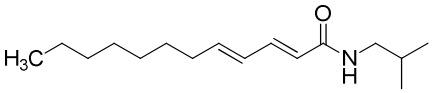
9

(2*E*,4*E*,8*Z*,10*Z*)-*N*-isobutyldodeca-2,4,8,10-tetraenamide



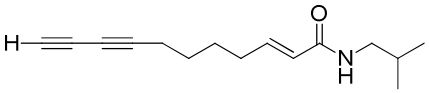
10

(2*E*,4*E*,8*Z*)-*N*-isobutyldodeca-2,4,8-trienamide



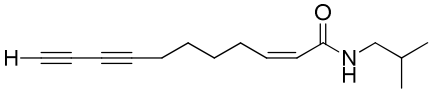
11

(2*E*,4*E*)-*N*-isobutyldodeca-2,4-dienamide



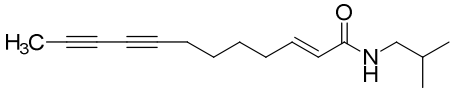
12

(*E*)-*N*-isobutylundeca-2-en-8,10-diynamide



13

(*Z*)-*N*-isobutylundeca-2-en-8,10-diynamide



14

(*E*)-*N*-isobutyldodeca-2-en-8,10-diynamide

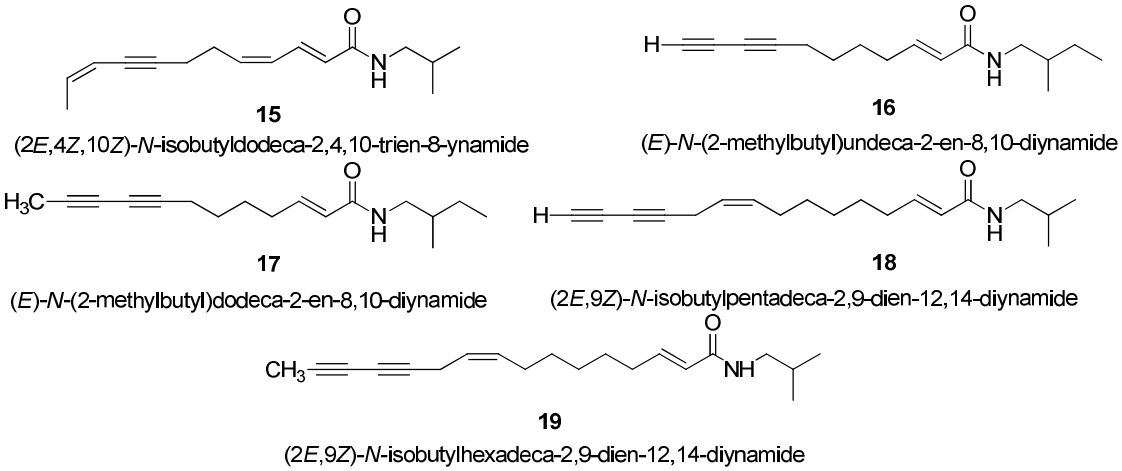


Figure 1. Main alkamides in *Echinacea* species

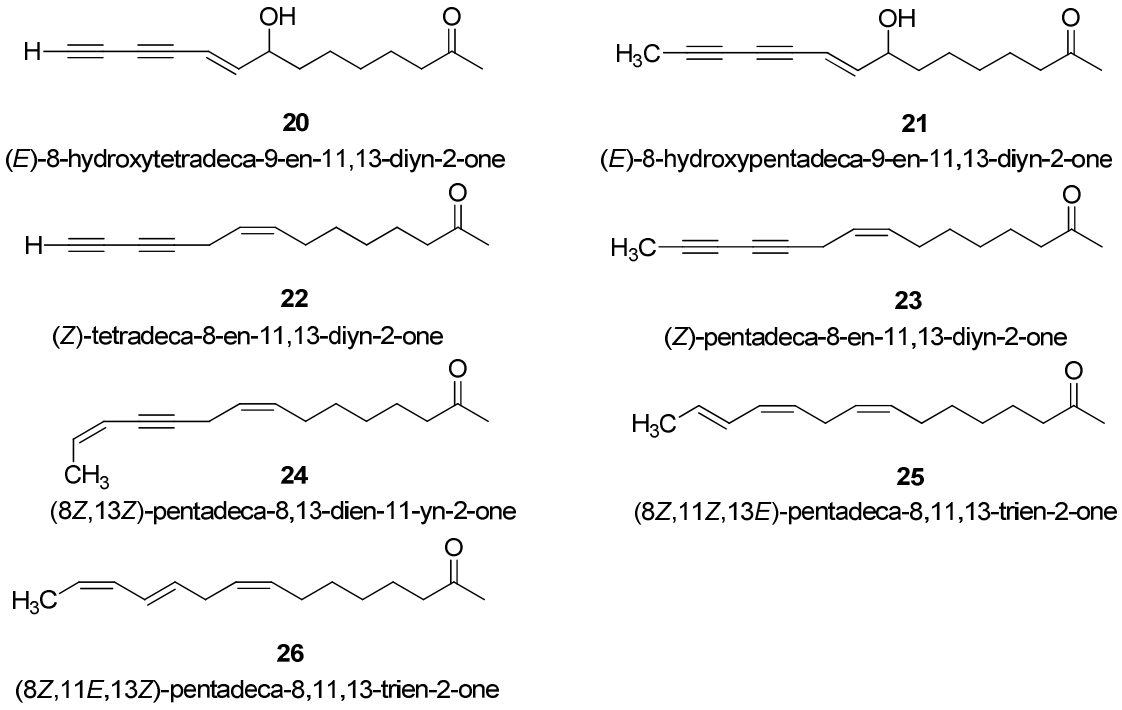
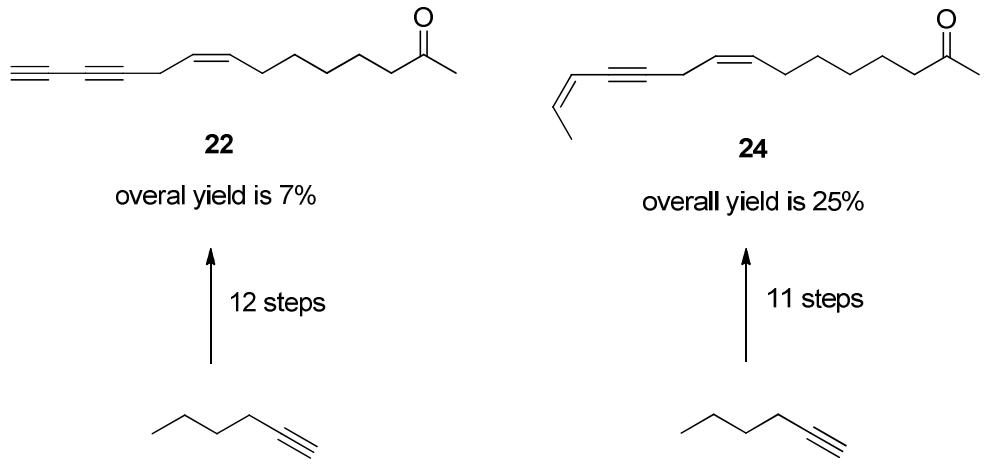


Figure 2. Ketones in *Echinacea pallida*

Ketones **22** and **24** from *Echinacea pallida* exhibit a range of biological activities.[6] Recently, Chicca and co-workers reported that **24** showed a concentration

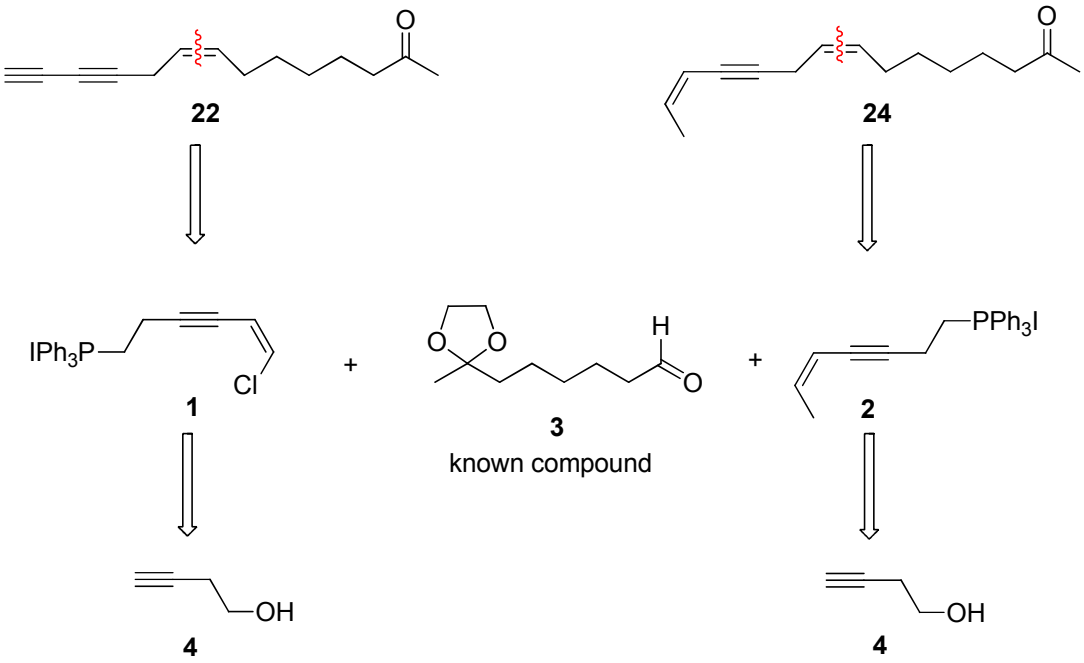
dependent cytotoxicity on several human cancer cell lines, including leukemia (Jurkat and HL-60), breast carcinoma (MCF-7), and melanoma (MeWo) cells.[7] Binns has reported that the ketones from *Echinacea pallida* are potent antifungal agents.[8] Related acetylenic ketones have been reported by Bohlmannin Centaurea ferox roots.[9] Despite the potential value of theketones from *Echinacea pallida*, few reports of synthesis of authentic standards or analogs have been reported. Crombie and co-workers reported the first syntheses of related amides using organometallic coupling reactions.[10] Wailes has also reported the synthesis of related dienamides.[11] Kraus reported the synthesis of ketone **22**[12] in 2005 and Benvenuti and Prati reported a clever synthesis of ketone **24** in 2008.[13] Both strategies chose 1-hexyne as the same starting material and took 12 steps and 11 steps with the overall yields 7% and 25% (Scheme 1) respectively. The number of steps and low overall yield limited the amount of both ketones that could be prepared for biological testing. We report herein a more efficient synthesis *via* a phosphonium salt route.



Scheme 1

Results and Discussion

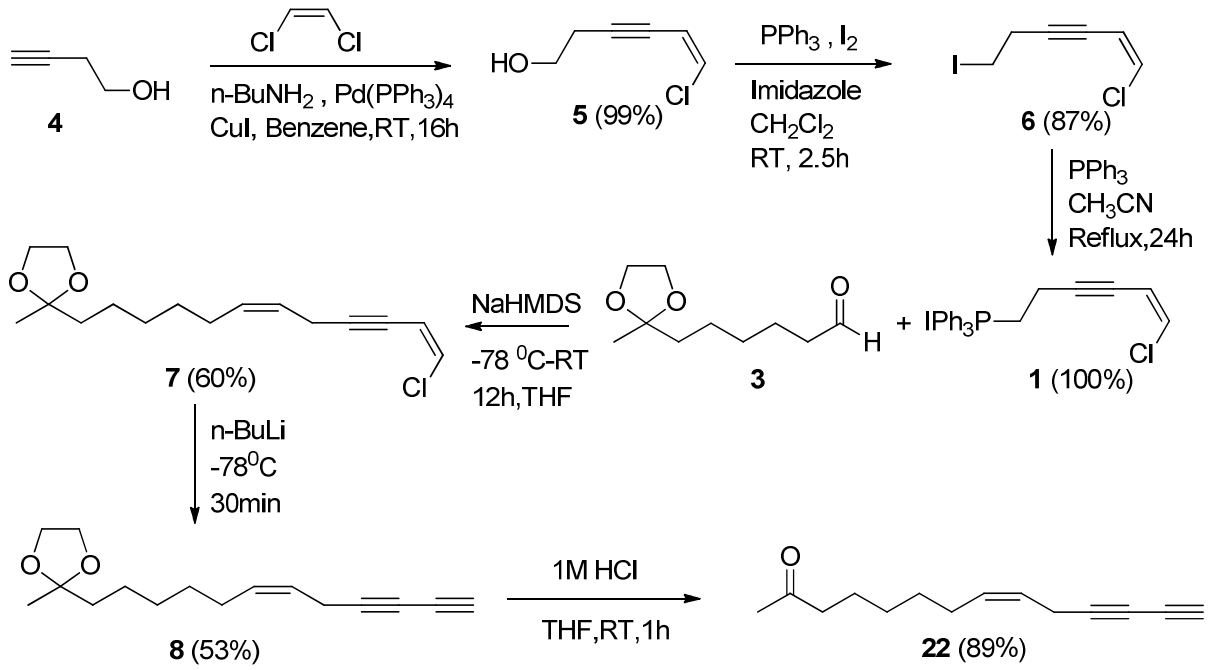
Due to the similarity of ketone **22** and **24**, we thought we could synthesize both compounds by the same strategy. Retro-synthetic analysis is shown in Scheme 2. We chose Wittig reaction as a key step for synthesizing **22** and **24** by coupling of different phosphonium salts **1** and **2** with the same aldehyde **3**.[14] Phosphonium salts **1** and **2** were eventually from the same starting material **4**.



Scheme 2 Retrosynthesis

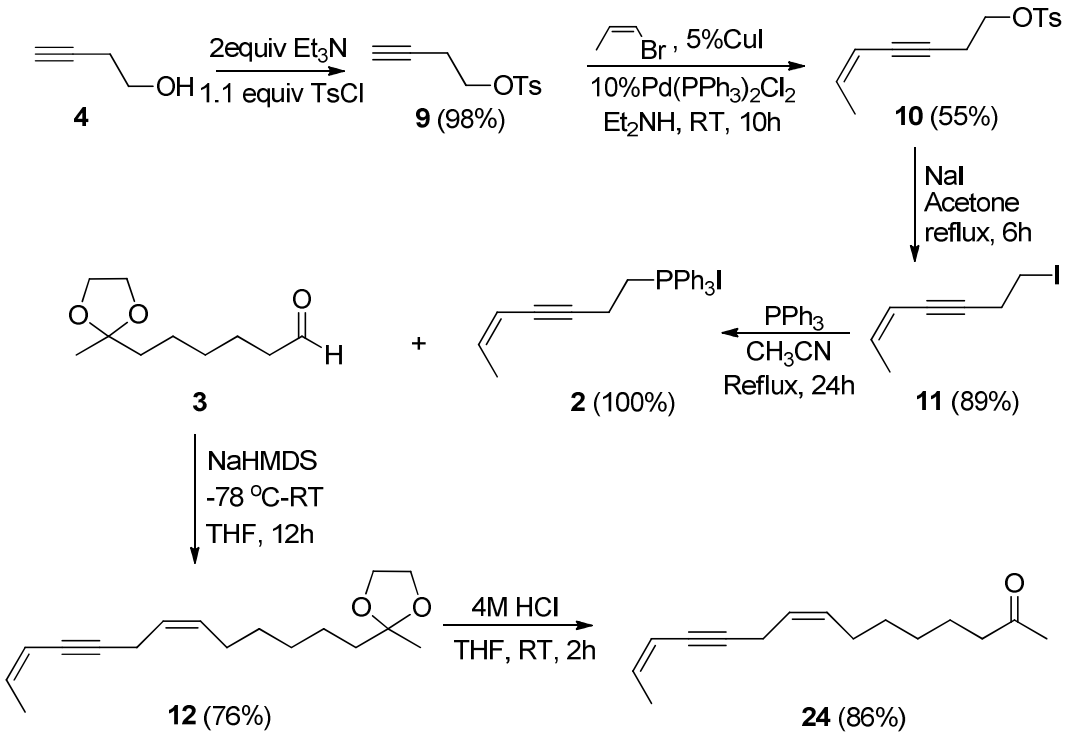
Alcohol **5**, prepared in one step from **4** by the method of Kende,[15] was converted into phosphonium salt **1** in two steps. Phosphonium salt **1** underwent an exclusively cis-selective Wittig reaction[15] with aldehyde **3** to generate a dieneyne **7** in 60% yields. Transformation of the chloroalkene into anacetylene using n-Butyl lithium at -78°C[16] was a clean reaction. There was no evidence of products derived from deprotonation of the

methylene group between theacetylene and the alkene. The ketal protecting group was removed with HCl, providing ketone **22** in 24% overall yield from **4** over six steps (Scheme 3).



Scheme 3 Synthesis of Ketone **22**

Tosylate **9**, prepared in one step from 4,[17] was coupled with cis-1-bromopropene afforded tosylate **10** that could be converted into phosphonium salt **11** in two steps. The cis-selective Wittig reaction of **2** with aldehyde **3** gave ketal **12** in 76% yield. Hydrolysis of ketal **12** with HCl produced ketone **24** in 31% overall yield from **4** over six steps (Scheme 3).



Scheme 4 Synthesis of Ketone **24**

Conclusion

The strategy described above represents a significant improvement over the previous synthetic routes. The route to ketones **22** and **24** is direct and quite flexible with regard to the introduction of additional functional groups.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. All ^{1}H and ^{13}C NMR spectra were recorded at 300MHz and 100 MHz respectively. High resolution mass spectra were recorded on a Q-TOF mass spectrometer.Standard grade silica gel (60 Å, 32-63 μm) was used for flash column chromatography.

Compound 1

To 7 mL of dry dichloromethane were added in order: triphenylphosphine (473 mg, 1.8mmol), imidazole (123 mg, 1.8 mmol), and iodine (458 mg, 1.8 mmol). A solution of compound **5** (217mg,1.6 mmol) in 7 mL of dry dichloromethane was added. The mixture was stirred at room temperature under argon for 2.5 h. The solvent was removed *in vacuo* and the residue was purified by silica gel flash chromatography (Hexanes/EtOAc = 1:1) to give the iodide (335 mg, 87% yield). A solution of the iodide (335 mg,1.4 mmol) and triphenylphosphine (367 mg,1.4 mmol) in 10 mL of acetonitrile was boiled for 24 h. The solvent was removed *in vacuo* to give compound **1** (711 mg, 100% yield). Compound **1** is pure enough for next one without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): 2.83-2.95 (m, 2H), 3.77-3.85 (m,2H), 5.35-5.38 (d, J=9.0 Hz, 1H), 6.09-6.11 (d, J=6.0 Hz, 1H),7.54-7.74 (m, 15H).

Compound 2

A solution of compound **10** (116 mg, 0.44 mmol) and NaI (116 mg, 0.77 mmol) in 12 mL of acetone was boiled for 6 h. After cooling to room temperature, the solution was treated with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After removing solvents *in vacuo*, the residue was purified by flash chromatography (Hexanes/EtOAc = 4:1) to give theiodide (86 mg, 89% yield). A solution of the iodide (85 mg,0.39 mmol) and triphenylphosphine (102 mg, 0.39 mmol) in 5 mL of acetonitrile was boiled for 24 h. The solvent was removed *in vacuo* to give compound **11** (188 mg, 100% yield). Compound **11** is pure enough for next one without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): 1.46-1.49 (dd, J=3.0, 6.0 Hz, 3H),2.78-2.89 (m, 2H), 3.71-3.79(m, 2H), 4.82-4.85 (d, J=9.0 Hz, 1H),5.58-5.69 (m, 1H), 7.52-7.70 (m, 15H).

Compound 7

To a solution of compound **1** (241 mg, 0.50 mmol) in 7 mL of dry THF was added 1.0 M sodium bis(trimethylsilyl)amide (NaHMDS) (0.5 mL) at -78 °C under argon. The mixture was stirred at -78 °C for 20 min. A solution of compound **3** (79 mg, 0.46 mmol) in 3 mL of dry THF was added. The mixture was warmed to room temperature in 1.5 h and stirred at room temperature for 12 h. Saturated NH_4Cl solution was added to quench the reaction. The aqueous layer was extracted three times with 5 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4. After removing solvents *in vacuo*, the residue was purified by preparative TLC (hexanes/EtOAc = 10:1) to give compound **7** (56 mg, 60% yield).

^{1}H NMR (300 MHz, $CDCl_3$): 1.30-1.43 (m, 9H), 1.58-1.65 (m,2H), 2.03-2.09 (m, 2H),3.13-3.14 (d, J=3.0 Hz, 2H), 3.88-3.98 (m,4H), 5.41-5.54 (m, 2H), 5.82-5.86 (m, 1H),6.28-6.31 (d, J=9.0 Hz,1H).

^{13}C NMR (100 MHz, $CDCl_3$): 18.3, 24.0, 24.2, 27.4, 29.5, 29.7,39.4, 64.8, 74.5, 97.5, 110.3,112.6, 123.6, 127.2, 132.5.

HRMS (M+1):calculated for $C_{16}H_{24}ClO_2$: 283.1459; found: 283.1458.

Compound 10

To a solution of cis-1-bromo-1-propene (0.51 mL, 6 mmol) in12 mL of Et_2NH were added CuI (60 mg, 0.3 mmol) and $Pd(PPh_3)_2Cl_2$ (421 mg, 0.6 mmol) at room

temperature under argon.The mixture was stirred at room temperature for 5 min. A solutionof compound **9** (1344mg, 6 mmol) in 18 mL of Et_2NH was added. The mixture was stirred at room temperature for 10 h. The solution was treated with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After removing solvents *in vacuo*, the residue was purified by flash chromatography (Hexanes/EtOAc = 4:1) to give compound **10** (872 mg, 55% yield).

^1H NMR (300 MHz, $CDCl_3$): 1.75-1.77 (d, J=6.0 Hz, 3H), 2.41 (s,3H), 2.65-2.71 (td, J=3.0, 9.0Hz, 2H), 4.06-4.11 (t, J=9.0 Hz, 2H),5.31-5.37 (m, 1H), 5.84-5.94 (m, 1H), 7.30-7.33 (d, J=9.0Hz, 2H),7.75-7.78 (d, J=9.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 15.9, 20.5,21.7, 68.0, 79.4, 88.3, 109.7, 128.0, 130.0, 132.9,138.5, 145.0.

HRMS(M+1): calculated for $C_{14}H_{17}O_3S$: 265.0893; found: 265.0890.

Compound 12

To a solution of compound **2** (188 mg, 0.39 mmol) in 5 mL of dry THF was added 1.0M sodium bis(trimethylsilyl)amide (NaHMDS) (0.4 mL) at -78 °C under argon. The mixture was stirredat -78 °C for 20 min. A solution of compound **3** (118 mg,0.63 mmol) in 3 mL of dry THF was added. The mixture was warmed to room temperature in 1.5 h and stirred at room temperature for 12 h. Saturated NH_4Cl solution was added to quench reaction. The aqueous layerwas extracted three times with 5 mL of ethyl acetate. The combined organic layers were driedover Na_2SO_4. After removing solvents *in vacuo*, the residue was purified by preparative TLC (Hexanes/EtOAc = 4:1) to give compound **12** (78 mg,76% yield).

^{1}H NMR (300 MHz, $CDCl_3$): 1.30-1.42 (m, 9H), 1.59-1.64 (m,2H),1.82-1.85 (dd, J=3.0, 6.0 Hz,3H), 2.02-2.08 (m, 2H), 3.08-3.09(d, J=3.0 Hz, 2H), 3.87-3.97 (m, 4H), 5.42-5.47 (m, 3H),5.83-5.93(m, 1H).

^{13}C NMR (100 MHz, CDCl3): 16.0, 18.2, 23.9, 24.2, 27.9, 29.5,29.7, 39.4, 64.8, 77.1, 93.2,110.3, 110.5, 124.5, 131.8, 137.4.

HRMS(M+1): calculated for $C_{17}H_{27}O_2$: 263.2006; found: 263.2004.

Ketone 22

To a solution of compound **7** (56 mg, 0.2 mmol) in 3 mL of dry THF was added 2.5 M n-BuLi (0.08 mL) at -78° C under argon. The mixture was stirred at -78 °C for 30 min. Saturated NH_4Cl solution was added to quench reaction. The aqueous layer was extracted three times with 5 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4. After removing solvents *in vacuo*, the residue was purified by silica gel flash chromatography (Hexanes/EtOAc = 4:1) to give compound **8** (26 mg, 53% yield). To the solution of compound **8** (26 mg, 0.11 mmol) in 1.5 mL of THF was added 1.5 mL of 1 N HCl. The mixture was stirred at room temperature for 1 h and quenched with water. The aqueous layer was extracted three times with 5 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4. After removing solvents *in vacuo*, the residue was purified by flash chromatography (Hexanes/EtOAc = 4:1) to give compound **22** (19 mg, 89% yield). Both ^{1}H and ^{13}C NMR spectra of **22** were identical to spectra reported in the literature.[12]

Ketone 24

To the solution of compound **12** (78 mg, 0.3 mmol) in 4 mL of THF was added 4 mL of 1N HCl. The mixture was stirred at room temperature for 1 h. Water was added to quench thereaction. The aqueous layer was extracted three times with 5 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4. After removing solvents *in vacuo*, the residue was purified by flash chromatography (Hexanes/EtOAc = 4:1) to give compound **24** (56 mg, 86%yield). Both ^{1}H and ^{13}C NMR spectra of **24** were identical to spectra reported in the literature.[13]

References

1. *Herbal Drugs and Phytopharmaceuticals. A Handbook for Practice on a ScientificBasis, 3rd ed.* Wichtl, M., Ed.; Medpharm Scientific: Stuttgart, **2004**.
2. Barnes, J. *Pharm. J.* **2002**, 269, 716–718.
3. (a)Bauer, R. Chemistry, pharmacology and clinical applications of *Echinacea* products. In: Mazza G., Oomah B.D., Herbs, Botanicals & Teas. Lancaster, Pennsylvania, **2000**, 45-73. (b) Bauer, R; Remiger, P; Wagner, H. *Phytochemistry,* **1989**, 28(2) 505-508. (c)Bauer, R; Remiger, P; Wagner, H. *Phytochemistry*, **1988**, 27(7), 2339-2342.
4. Bauer, R; Remiger, P. *Planta Med.* **1989**, 55, 367–371.
5. Bauer, R; Woelkart, K. *Encyclopedia of Dietary Supplements,* **2005**, 177-187.
6. La Lone, C. A.; Huang, N.; Rizshsky, L.; Yum, M.-Y.; Singh, N.; Hauck, C.; Nikolau, B. J.; Wurtele, E. S.; Kohut, M. L.; Murphy, P. A.; Birt, D. F. *J. Agric. Food Chem.* **2010**, 58, 8573-8584.

7. Chicca, A.; Adinolfi, B.; Pellati, F.; Orlandini, G.; Benvenuti, S.; Nieri, P. *Planta Med.* **2010**, 76, 444-446.

8. Binns, S. E.; Purgina, B.; Bergeron, C.; Smith, M. L.; Ball, L.; Baum, B. R.; Arnason, J. T. *Planta Med.* **2000**, 66, 241-244.

9. Bohlmann, F.; Rode, K. M.; Zdero, C. *Chem. Ber.* **1966**, 99, 3544-3551.

10. (a) Crombie, L.; Harper, S. H. *Nature*, **1949**, 164, 1053-1054. (b) Crombie, L.; Manzoor-I-Khuda,M. *J. Chem. Soc.* **1957**, 2767-2777. (c) Crombie, L.; Fisher, D. *TetrahedronLett.* **1985**, 26, 2481-2484. (d) Crombie, L.; Horsham, M. A.; Blade, R. J. *TetrahedronLett.* **1987**, 28, 4879-4882.

11. Wailes, P. C. *Aust. J. Chem.* **1959**, 12, 173-189.

12. Kraus, G. A.; Bae, J.; Schuster, J. *Synthesis,* **2005**, 3502-3504.

13. Morandi, S.; Pellati, F.; Benvenuti, S.; Prati, F. *Tetrahedron*, **2008**, 64, 6324-6328.

14. Birch, A. J.; Mani, N. S.; Subba Rao, G. S. R. *J. Chem. Soc., Perkin Trans. 1: Org. Bio-Org. Chem.* **1990**, 5, 1423-1427.

15. Kende, A. S.; Smith, C. A. *J. Org. Chem.* **1988**, 53, 2655-2657.

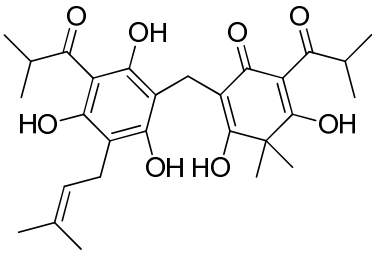
16. Rubin, Y.; Knobler, C. B.; Diederich, F. *J. Am. Chem. Soc.* **1990**, 112, 1607-1617.

17. Finaru, A.; Berthault, A.; Besson, T.; Guillaumet, G.; Berteina-Raboin, S. *Tetrahedron Lett.* **2002**, 43, 787-790.

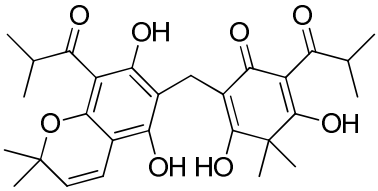
CHAPTER 4: Synthesis of Uliginosins A and B

Introduction

Uliginosin A (**1**) and Uliginosin B (**2**) shown in Figure 1 are acyl phloroglucinols present in *Hypericum gentianoides*.[1-3] These acyl phloroglucinols showed antibacterial activity against *Bacillus subtilis*,[4-6] *Staphylococcus aureus* and antifungal activity against *Trichophyton mentagrophytes*.[3] Recently, Hillwig[7] reported that both compounds exhibit anti-inflammatory and anti-HIV activity. Because *H. gentianoides* is not a common species and can be difficult to grow, the availability of quantities of **1** and **2** depends on the development of an efficient synthetic route. In 1978 Meikel and Stevens reported the synthesis of **1**[8-9] and achieved the synthesis of **2**[10-11] by oxidation of **1** with DDQ in 8% yield. Unfortunately, we were unable to reproduce the synthesis of **1** due to the limited experimental detail. We describe herein a general route for the synthesis of both compounds in improved yields from a common intermediate.



1

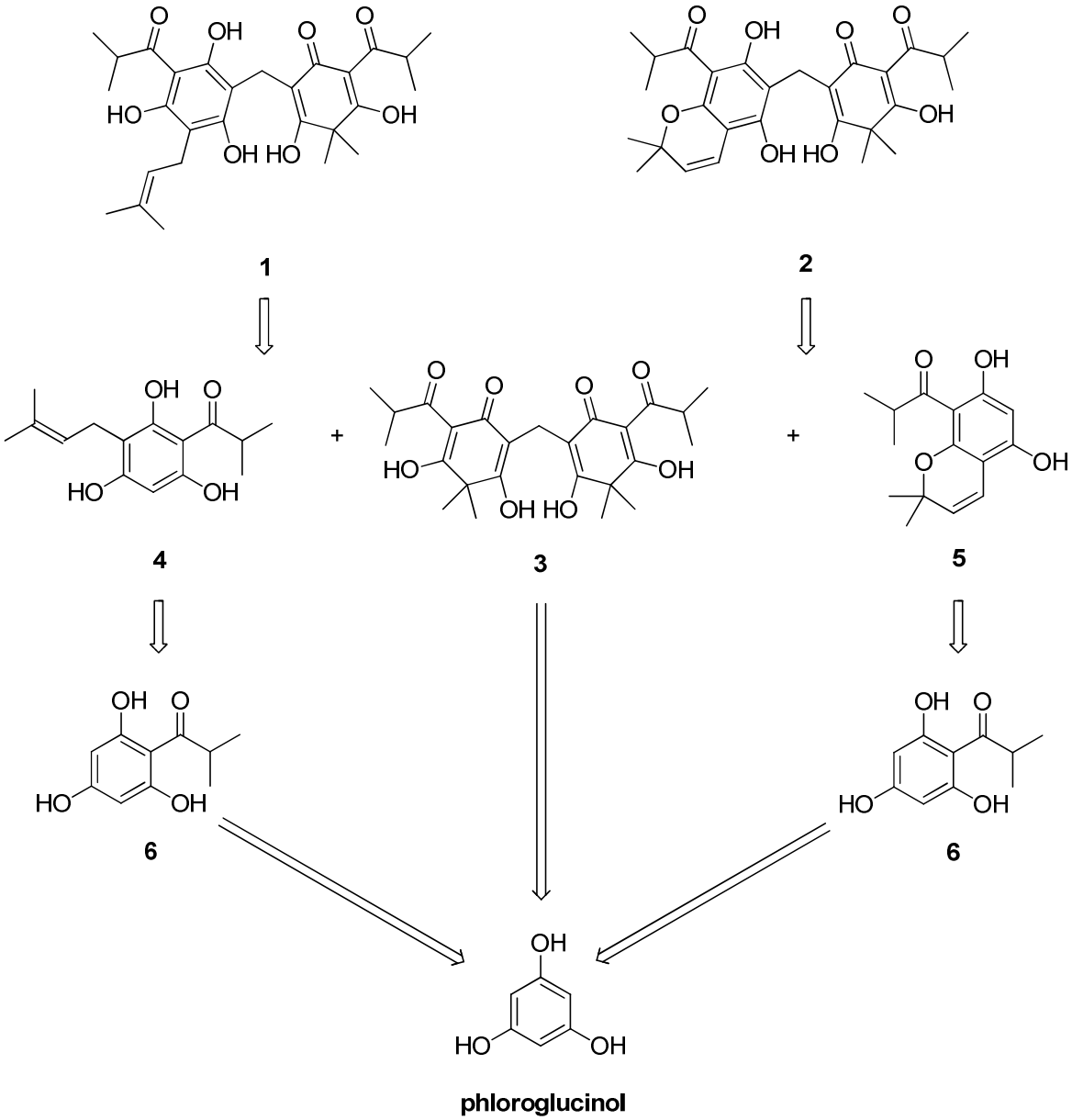


2

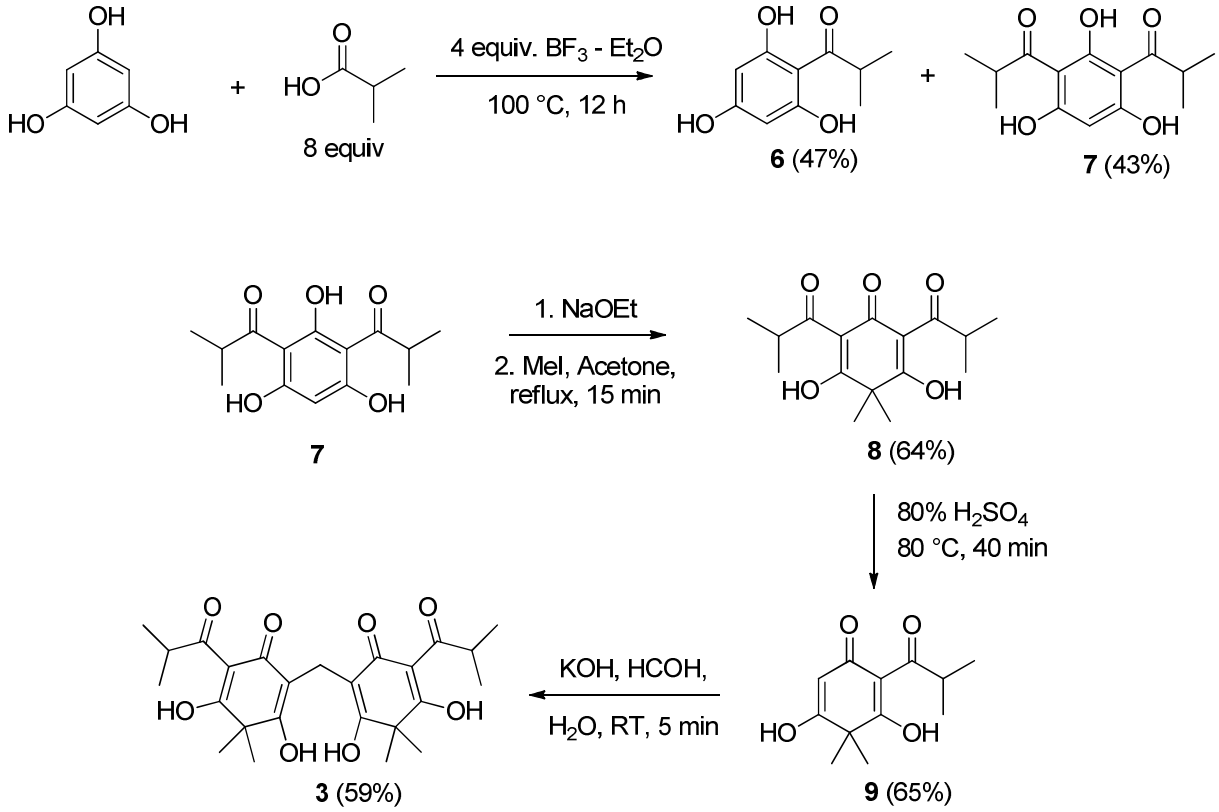
Figure 1 Structures of **1** and **2**

Results and Discussion

Compounds **1** and **2** are from the coupling reactions of **3**[12] with prenyl ketone **4** and benzopyran **5** respectively (Scheme 1). Prenyl ketone **4** and benzopyran **5** are from the same compound **6**. Compound **3** and **6** are eventually from phloroglucinol. Scheme 2 showed how to make compound **3**.

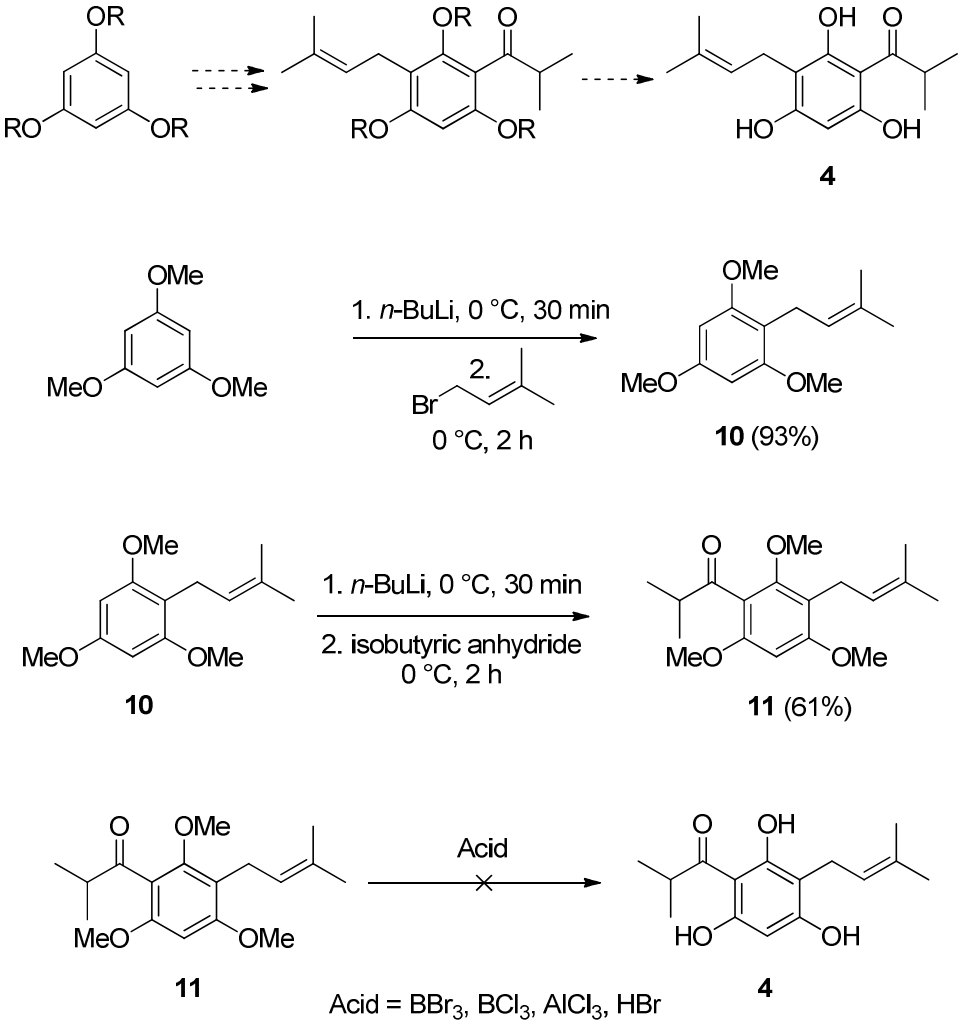


Scheme 1



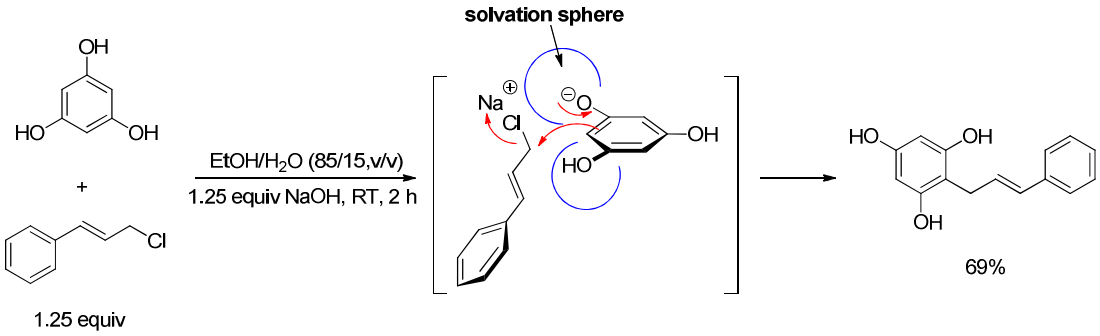
Scheme 2

The synthesis of Uliginosin A (**1**) required the reaction of prenyl ketone **4** with **3**. Although two syntheses of prenyl ketone **4** had been reported,[13-14] the prenylation of isobutyrylphloroglucinol proved difficult, affording multiple products with a variety of bases (NaH, NaOMe and KOH).[13,15,16] A new strategy was decided to protect three hydroxy groups first, then two metal hydrogen exchange reactons followed by deprotection to generate prenyl ketone **4** (Scheme 3). We chose 1,3,5-trimethoxybenzene as starting material. Metal hydrogen exchange followed by prenylation and another metal hydrogen exanchge followed by acylation generated compound **8** in good yields. But the demethylation proved diffcult, all attemps failed using Lewis acids and mineral acids.



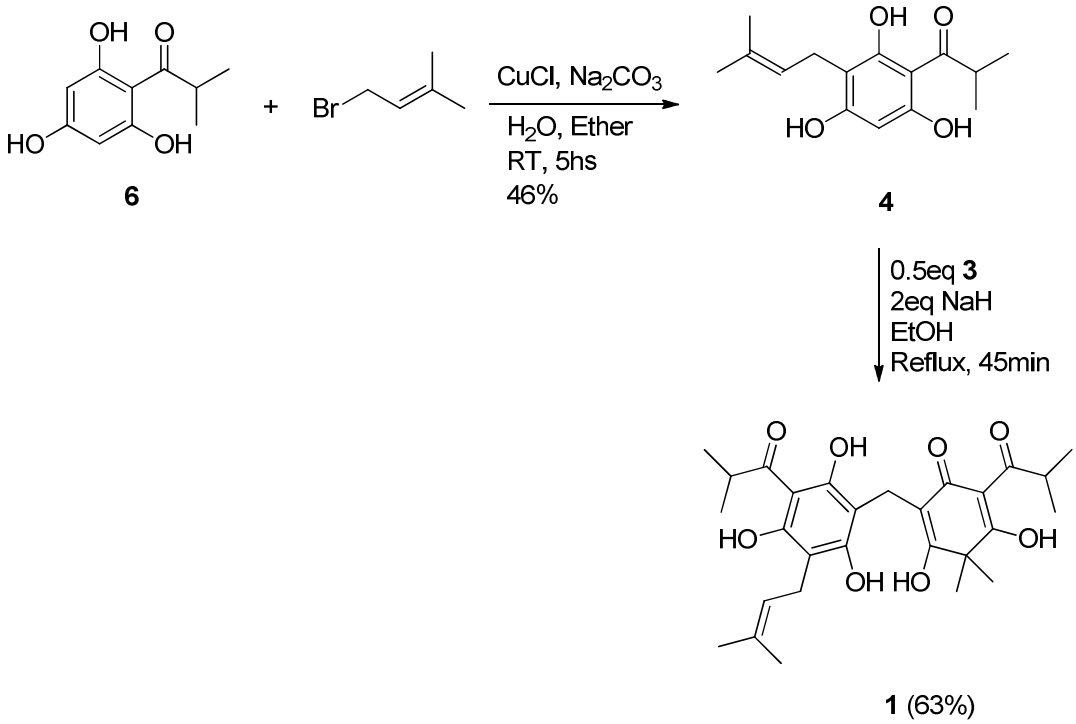
Scheme 3

Wagner and Mioskowski[17] mentioned an interesting reaction. They carried out cinnamylation of phloroglucinol in aqueous solution by using NaOH as a base, they could get C-alkylation product exclusively in good yields (Scheme 4). After deprotonation of phloroglucinol in aqueous solution, the anion was surrounded with water, so the O-alkylation could not happen. Only C-alkylation could occur.



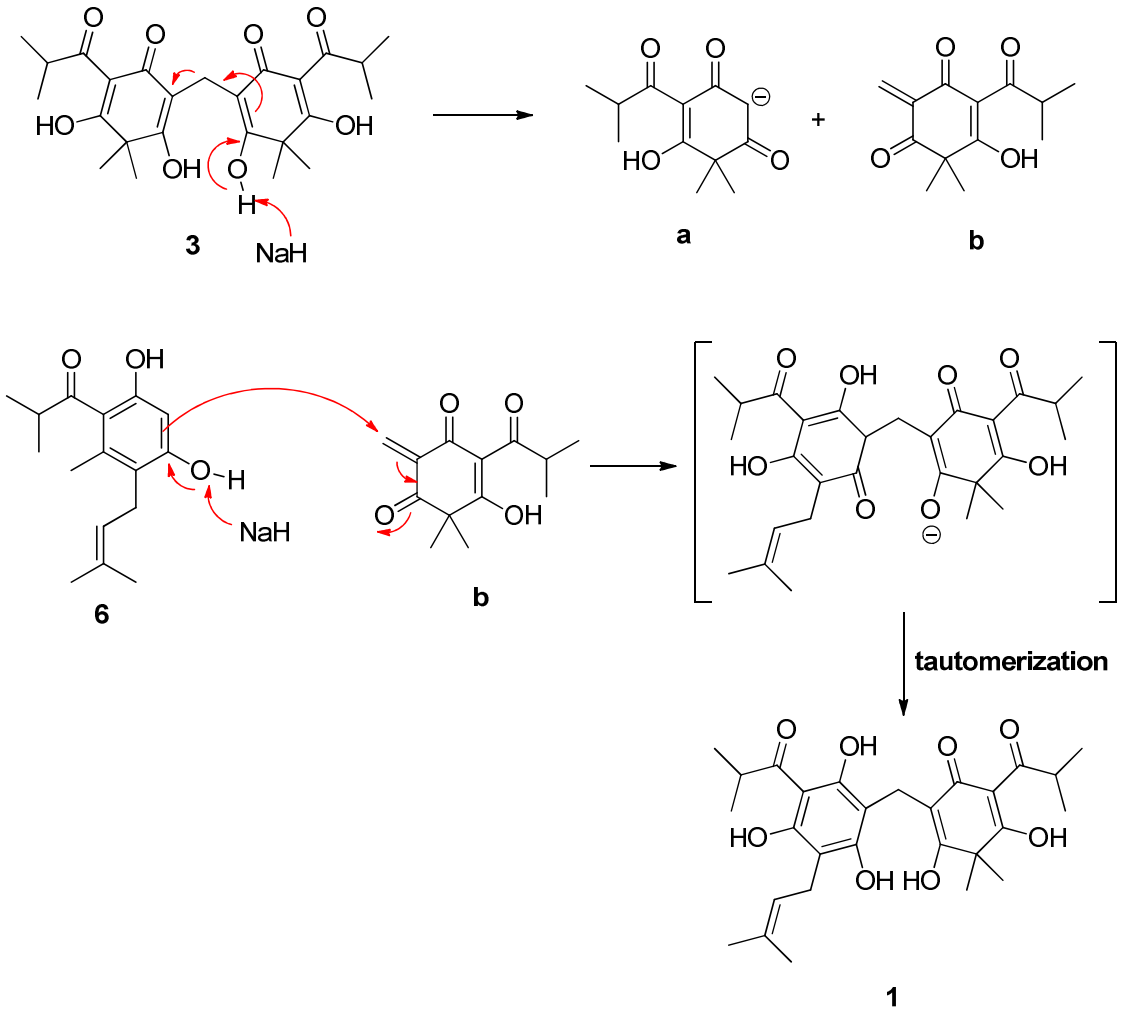
Scheme 4

Based on this idea, after trying different reaction conditions, the reaction of isobutyryl-phloroglucinol with prenyl bromide at room temperature in ether and saturated aqueous Na_2CO_3 with copper (I) chloride as catalyst reproducibly provided a 46% yield of prenyl ketone **4** (Scheme 5). Initially, the connection of **4** with **3** failed, in part because of the limited experimental details in the Meikel and Stevens paper. After many experiments, the key coupling of **4** and **3** to generate Uliginosin A (**1**) was achieved in 63% yields. The crucial experimental parameters were found to be the number of equivalents of the base and the temperature.



Scheme 5

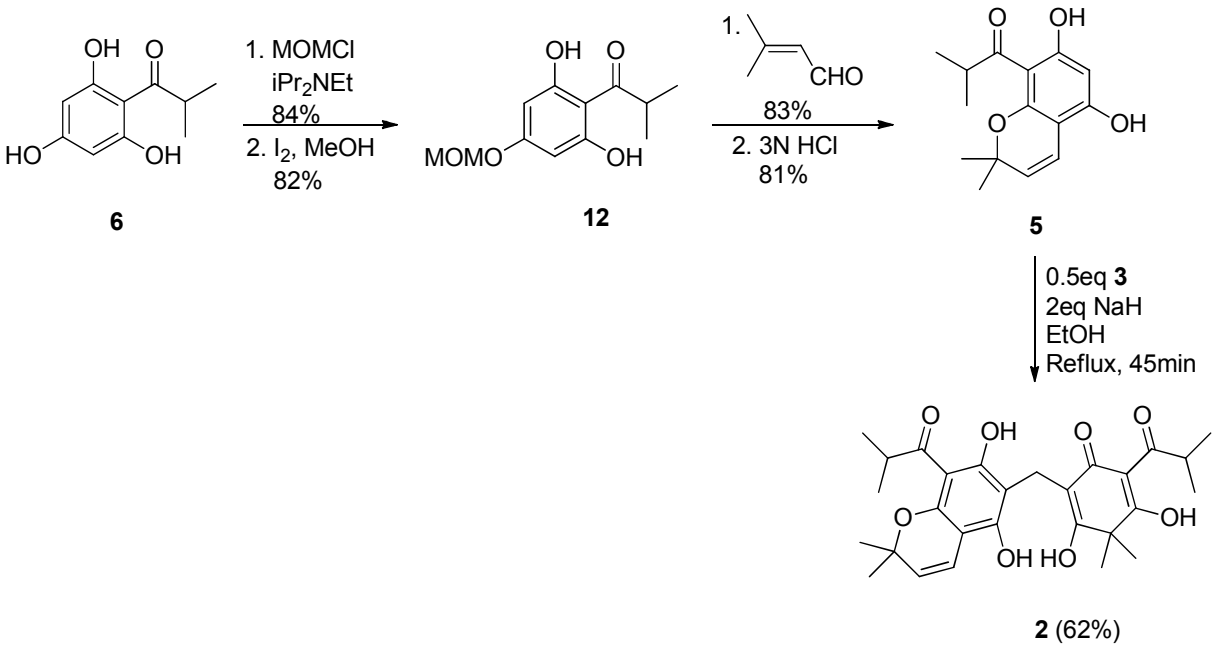
Scheme 6 showed the possible mechanism.



Scheme 6

Benzopyran **5** was prepared by a route used by our group for the synthesis of acyl benzopyrans[18] (Scheme 7). Ketone **7** was generated by protection of two hydroxyl groups of compound **6** with MOMCl, followed by selective deprotection of one MOM group with iodine. Base induced cyclization of ketone **7** with 3-methyl-2-butenal and deprotection with HCl afforded benzopyran **5**. The reaction of benzopyran **5** with **3**

afforded Uliginosin B (**2**) in 62% yields.



Scheme 7

Conclusion

In summary, direct and reproducible syntheses of Uliginosins A and B were achieved. The direct prenylation of isobutyrylphloroglucinol was solved. The availability of these commonly occurring acyl phloroglucinols will permit additional studies of their biological activity.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. All ^{1}H and ^{13}C NMR spectra were recorded at 300MHz and 100 MHz respectively.Standard grade silica gel (60 Å, 32-63 μm) was used for flash

column chromatography.

Compound 1

To a mixture of compound **3** (25 mg, 0.095 mmol), **4** (22 mg, 0.048 mmol) and NaH (8 mg, 0.192 mmol) was added 3 mL of EtOH. The resulting mixture was boiled for 45 min. After cooling to room temperature, the solvent was removed in *vacuo*. After acidifying with 3N HCl, the aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic layers were washed by brine and dried over Na_2SO_4. The solvent was removed in *vacuo*. The residue was purified by silica gel chromatography (Hexanes:EtOAc = 1:1) to give Uliginosin A (**1**) (15 mg, 63% yield). The proton and carbon NMR were identical to the literature spectra.[6]

Compound 2

To a mixture of compound **5** (30 mg, 0.065 mmol), **3** (36 mg, 0.13 mmol) and NaH (11 mg, 0.26 mmol) was added 3mL of EtOH. The resulting mixture was boiled for 45 min. After cooling to room temperature, the solvent was removed in *vacuo*. After acidifying by 3N HCl, EtOAc (5mL × 3) was added to extract. The combined organic layers were washed by brine and dried over Na_2SO_4. The solvent was removed in *vacuo*. The residue was purified by silica gel chromatography (Hexanes:EtOAc = 5:1) to give Uliginosin B (**2**) (20 mg, 62% yield). The proton and carbon NMR were identical to the literature spectra.[19]

Compound 4

Prenyl bromide (0.08 mL, 0.6 mmol) was added to a two-phase mixture consisting of isobutyrylphloroglucinol (58 mg, 0.29 mmol) and CuCl (2 mg, 0.02 mmol) in ether (3 mL) and saturated aqueous Na_2CO_3 (3 mL). The mixture was stirred vigorously for 5 h at room temperature. After acidifying with 3N HCl, the aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic layers were washed by brine and dried over Na_2SO_4. The solvent was removed in *vacuo*. The residue was purified by silica gel chromatography (Hexanes:EtOAc = 3:1) to give pure **4** (35 mg, 46% yield).

Compound 5

The solution of **12** (69 mg, 0.28 mmol) and 3-methyl-2-butenal (0.07 mL, 0.7 mmol) in 5mL of pyridine was boiled for 16 h. After cooling to room temperature, the solvent was removed in *vacuo*. The residue was purified by silica gel chromatography (Hexanes:EtOAc = 5:1) to give the MOM ether of **12** (71 mg, 83% yield). To a solution of the MOM ether of **12** (120 mg, 0.39 mmol) in 20 mL of MeOH was added 1.3 mL of 3N HCl. The resulting mixture was boiled for 25 min. After cooling to room temperature, the solvent was removed in *vacuo*. The residue was purified by preparative TLC (Hexanes:EtOAc = 5:1) to give pure **5** (83 mg, 81% yield).

^{1}H NMR: 6.55-6.59(1H, d, J=12.0 Hz), 5.94(1H, s), 5.41-5.44(1H, d, J=9.0 Hz), 3.81-3.90(1H, m), 1.49(6H, s), 1.17-1.20(6H, d, J=9.0 Hz).

^{13}C NMR (100MHz): 19.6, 28.0, 39.4, 78.3, 96.4, 102.3, 105.2, 116.7, 124.6, 156.7, 158.5, 166.2, 210.8.

Compound 12

To a solution of isobutyrylphloroglucinol (257 mg, 1.3 mmol) in 5 mL of CH_2Cl_2 was added diisopropylethylamine (0.68mL, 3.9 mmol) at 0 °C. Chloromethylmethylether (2.6 mmol) was then added. The mixture was stirred at 0 °C for 2 h. Water was added to quench the reaction. CH_2Cl_2 (5 mL × 3) was added to extract. The combined organic layers were washed by brine and dried over Na_2SO_4. The solvent was removed in *vacuo*. The residue was purified by silica gel chromatography (Hexanes:EtOAc = 1:1) to give the 2,4-Bis-MOM ether of isobutyrylphloroglucinol (310 mg, 84% yield). To a solution of the 2,4-Bis-MOM ether of isobutyrylphloroglucinol (428 mg, 1.5 mmol) in 15 mL of MeOH was added I_2 (150 mg) at room temperature. The resulting mixture was stirred at room temperature for 16 h. Saturated aqueous $Na_2S_2O_3$ solution was added followed by EtOAc (10 mL × 3). The combined organic layers were washed by brine and dried over Na_2SO_4. The solvent was removed in *vacuo*. The residue was purified by silica gel chromatography (Hexanes:EtOAc = 1:1) to give **12** (295 mg, 82% yield).

^{1}H NMR (300MHz): 6.08(2H, s), 5.14(2H, s), 3.86-3.95(1H, m), 3.45(3H, s), 1.17-1.19(6H, d, J=6.0 Hz).

^{13}C NMR (100MHz): 19.4, 39.6, 56.6, 94.0, 96.3, 105.0, 163.2, 163.4, 211.3.

References

1. Nor C, Bernardi AP, Machado HJS, Schripsema J, Rech SB, von Poser GL. *Natural Product Commun*. **2008**, 3(2), 237-240.
2. Ferraz ABF, Schripsema J, Pohlmann AR, von Poser GL. *Biochem. Systematics Ecol*. **2002**, 30(10), 989-991.

3. Taylor HL, Brooker RM. *Lloydia*, **1969**, 32(2), 217-219.
4. Franca HS, Kuster RM, Rito, P, Passos de Oliveira A, Teixeira LA, Rocha L.*Quimica Nova*, **2009**, 32(5), 1103-1106.
5. Dall'Agnol R, Ferraz A, Bernardi AP, Albring D, Nor C, Schapoval EES, von Poser GL.*Phytotherapy Research*, **2005**, 19(4), 291-293.
6. Rocha L, Marston A, Potterat O, Auxiliadora M, Kaplan C, Stoeckli-Evans H,Hostettmann K. *Phytochemistry*, **1995**, 40(5), 1447-52.
7. Hillwig ML. *US 7854946 B1 20101221,* **2010**
8. Meikle T, Stevens R.*J. Chem. Soc. Chem. Commun*., **1972**, 123-124.
9. Meikle T, Stevens R. *Perkin Transactions, 1*, **1978**, 1303-1312.
10. Meikle T, Stevens R. *Tetrahedron Letters*, **1972**, 4787-4788.
11. Meikle T, Stevens R. *Perkin Transactions, 1*, **1979**, 2563-2573.
12. Penttila A, Sundman J. *Acta Chemica Scandinavica*., **1964**, 344-52.
13. Kuhnke J, Bohlmann F. *Tetrahedron Letters*, **1985**, 26(33), 3955-3958.
14. Boubakir Z, Beuerle T, Liu, B, Beerhues L. *Phytochemistry*, **2005**, 66(1), 51-57.
15. Shigeyuki MIZOBUCHI, Yuko SATO. *Agric. Biol. Chem.* **1985**, *49*, 719
16. Suen-Ying Fung, Johannes Brussee, Rob A. M. van der Hoeven, Wilfried M. A. Niessen, Johannes J. C. Scheffer, Robert Verpoorte. *J. Nat. Prod.* **1994**, *57*, 452
17. Arnaud Gissot, Alain Wagnera, Charles Mioskowskia. *Tetrahedron,* **2004**, 6807-6812.
18. Kanthasamy AG, Kraus GA, Anantharam, V. U.S. Pat. Appl. Publ. **2011**, US20110112182 A1 20110512.
19. Parker WL, Johnson F. *JACS*, **1968**, 90(17), 4716–4723.

CHAPTER 5: GENERAL CONCLUSIONS

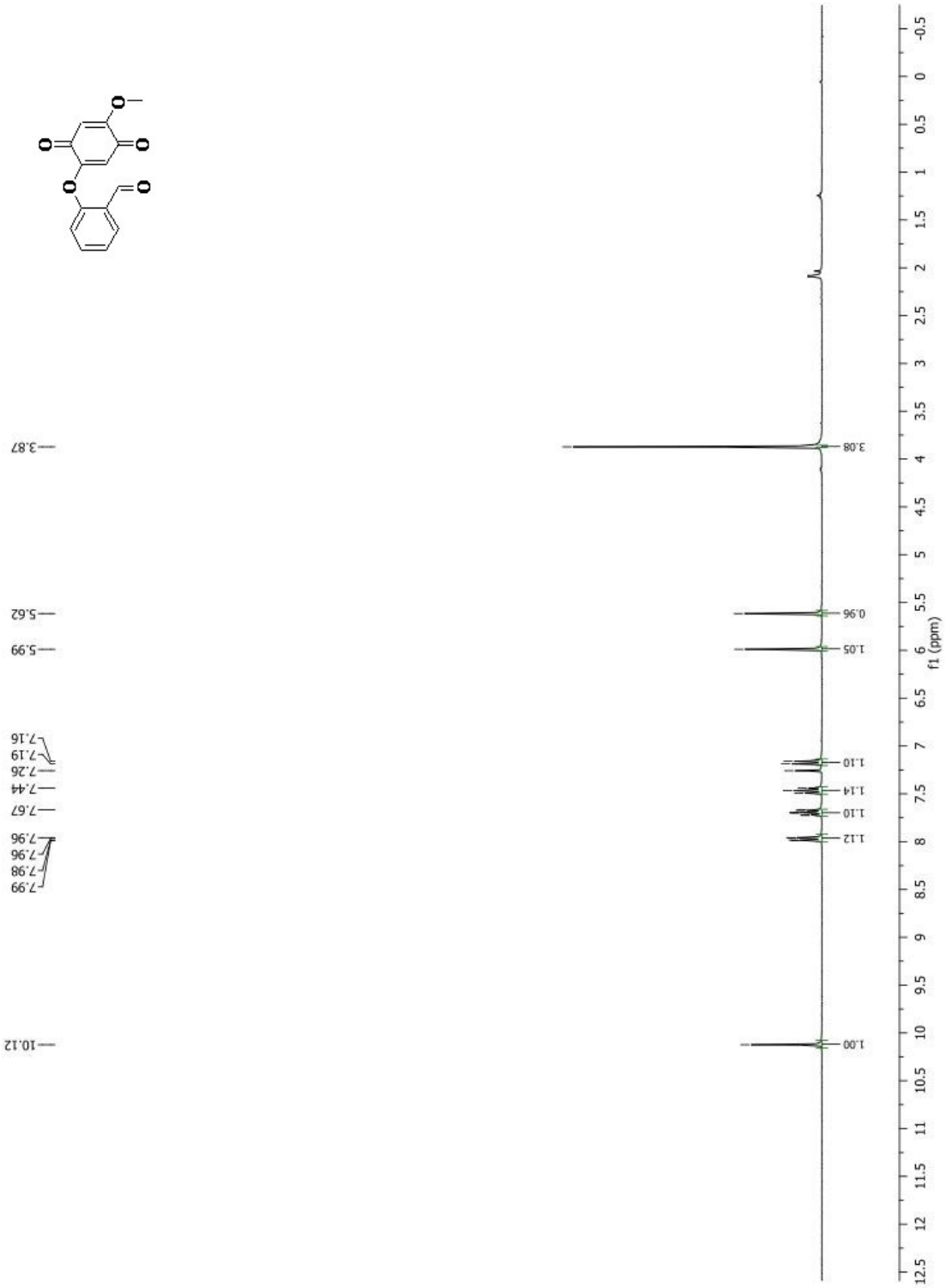
In this dissertation, syntheses of some biologically active natural products have been studied. During this process, novel synthetic methodologies have been developed.

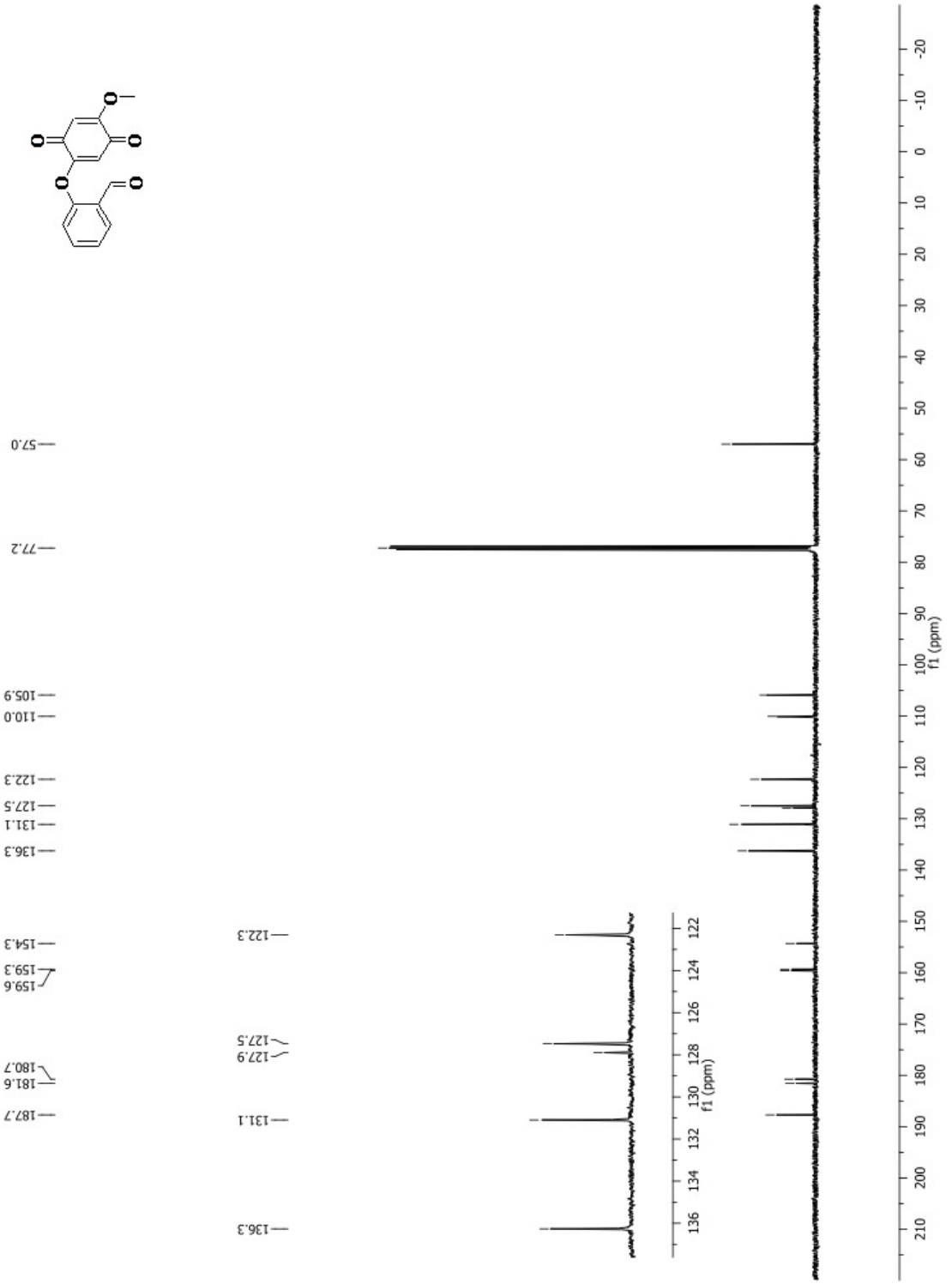
Chapter 2 describes an efficient synthesis of Bauhinoxepin J and polyhydroxylated xanthones *via* intramolecular radical cyclization as a key step. Two new natural products were first made during synthesis of polyhydroxylated xanthones. Based on the mechanism proposed from synthesis of polyhydroxylated xanthones, a noval method of facile oxidation of 1,4-hydroquinones to 1,4-benzoquinones by using NBS was developped.

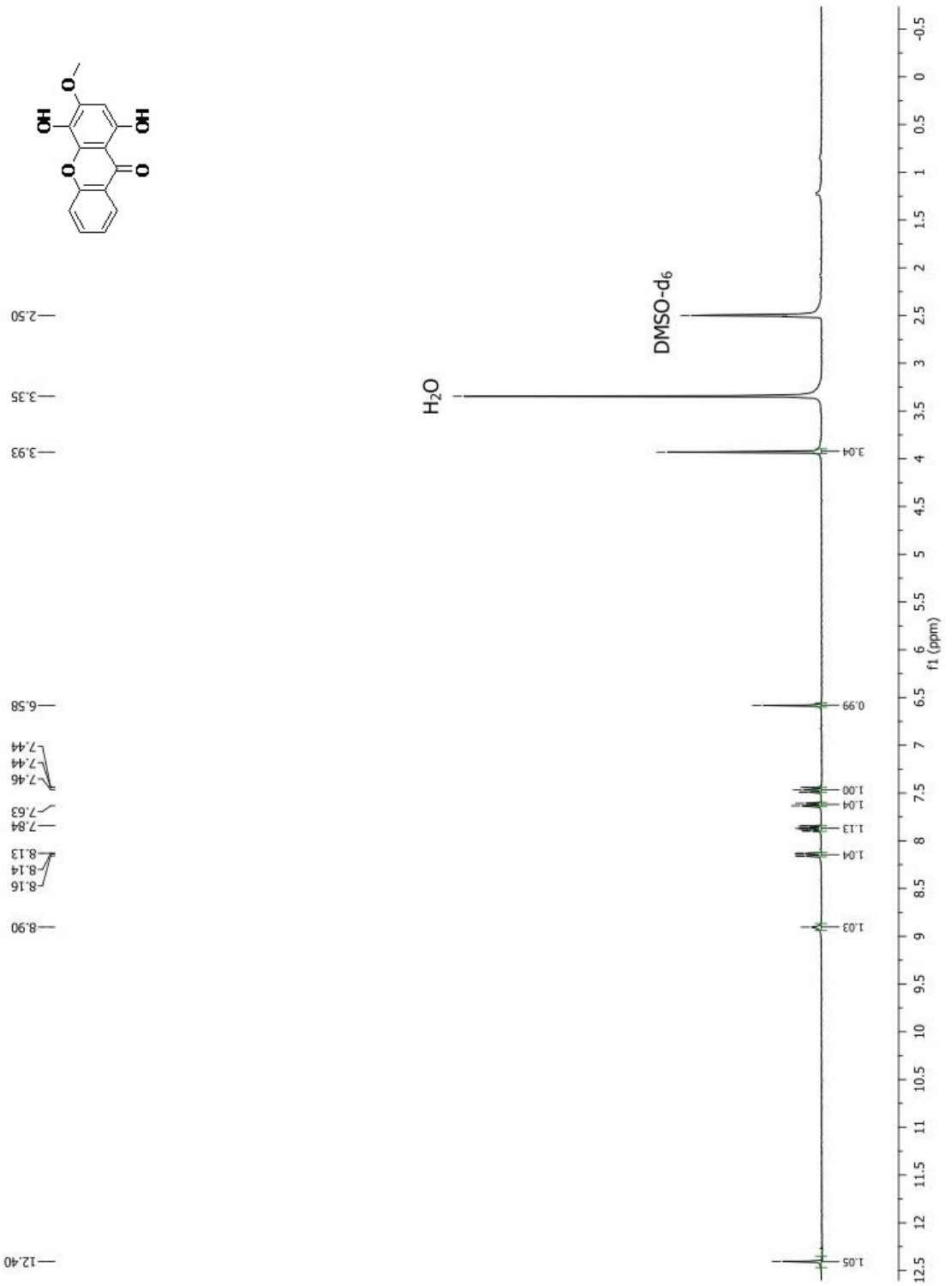
Chapter 3 describes a new, efficient and straightforward formal total synthesis of two ketone constituents, (Z)-tetradeca-8-en-11,13-diyn-2-one and (8Z,13Z)-pentadeca-8,13-dien-11-yn-2-one from *Echinacea pallida*, employing Wittig reaction as a key step to generate cis double bonds.

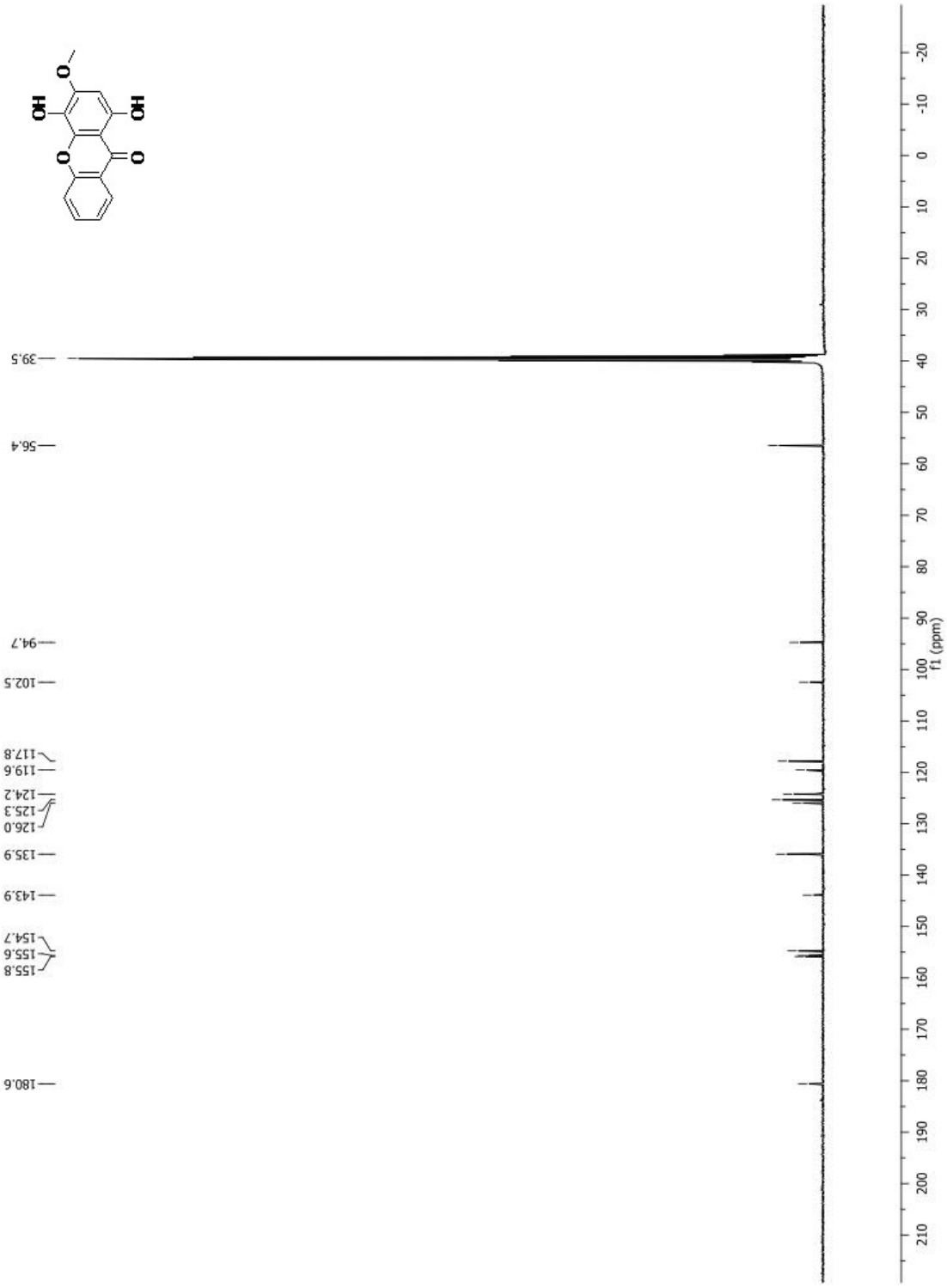
Chapter 4 illustrates a direct route for the synthesis of Uliginosins A and B by using the same strategy. This strategy led to successful synthesis of two natural products in a straightforward fashion.

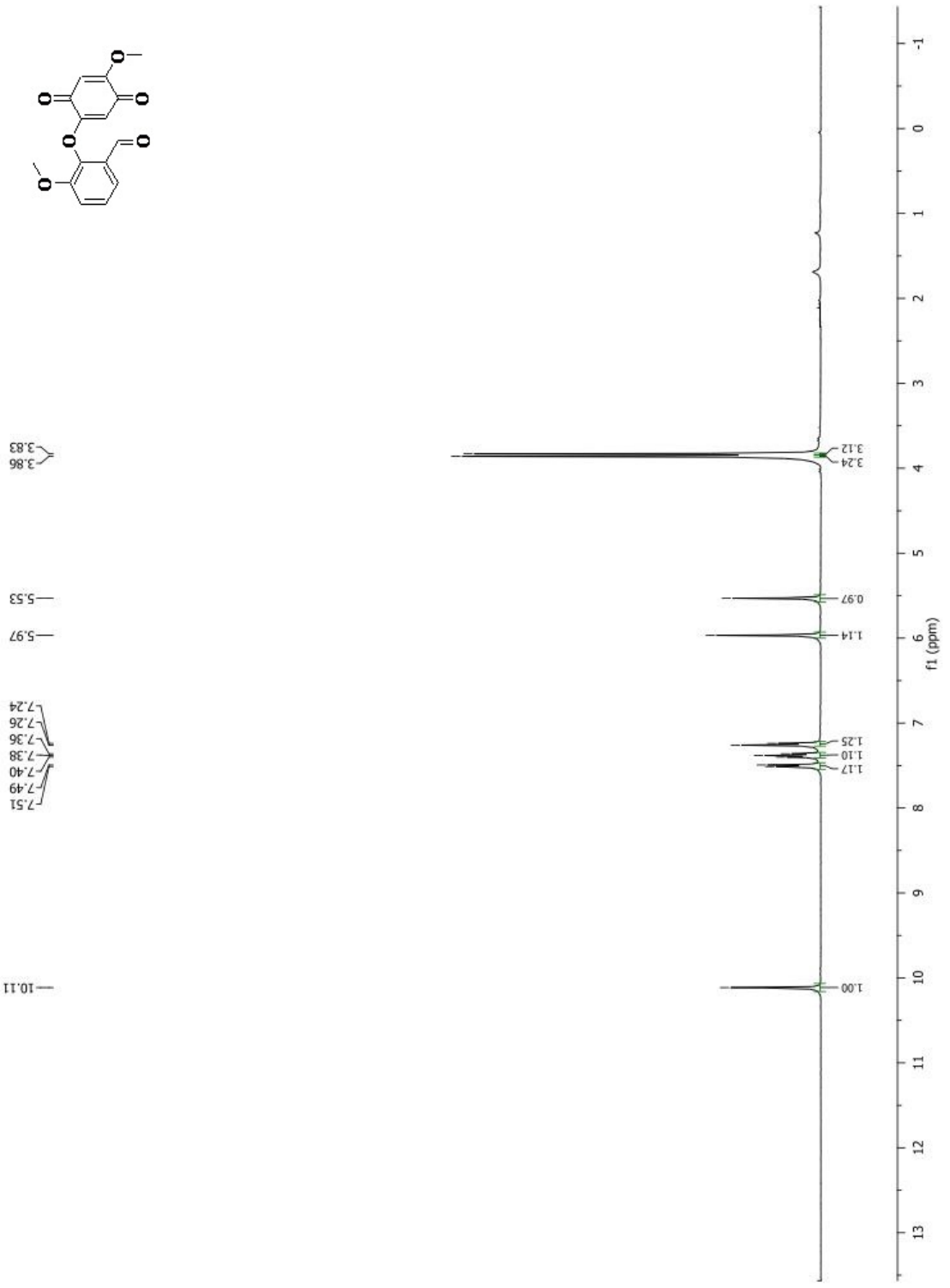
APPENDIX: ^{1}H and ^{13}C NMR Spectra

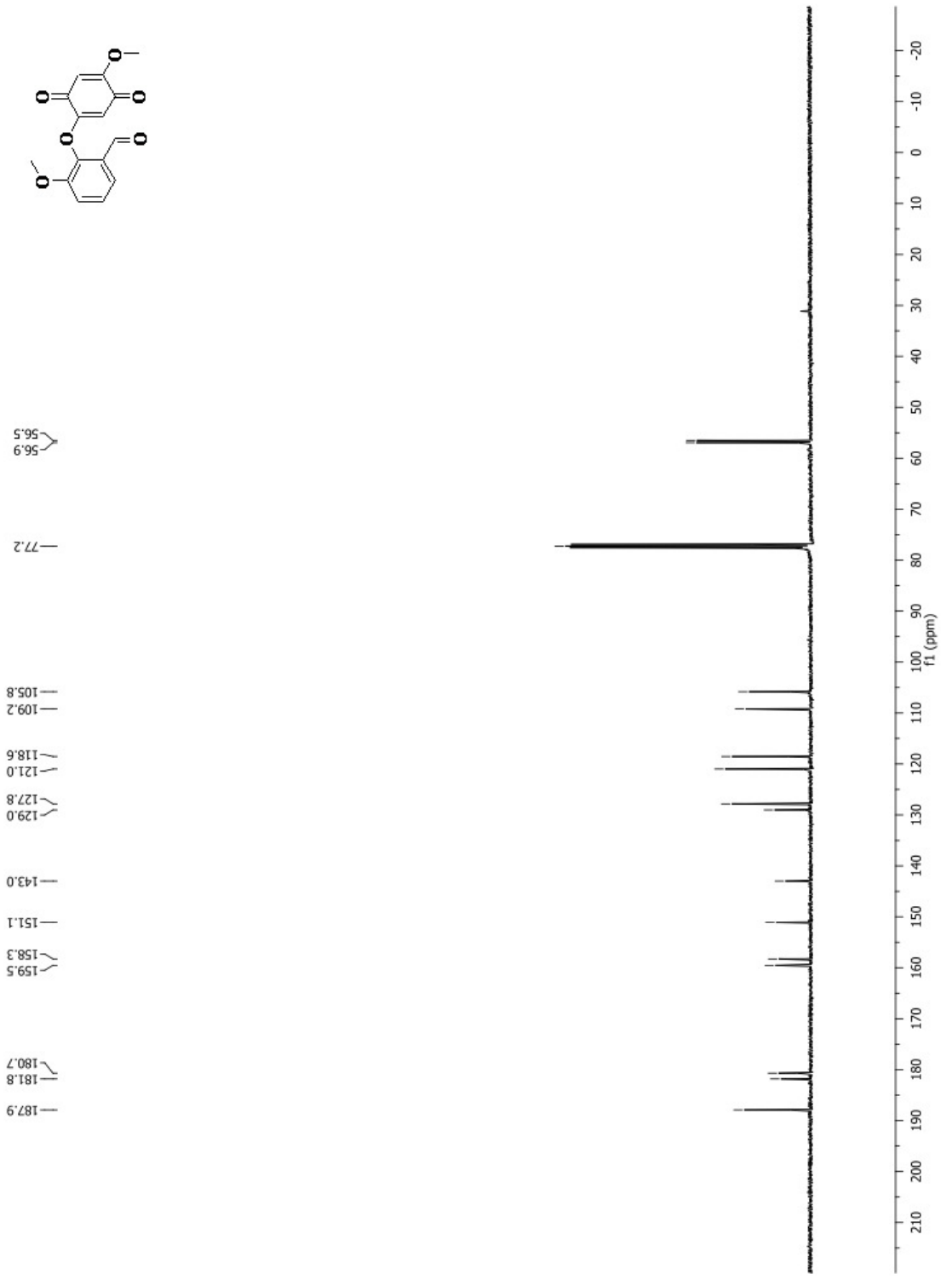


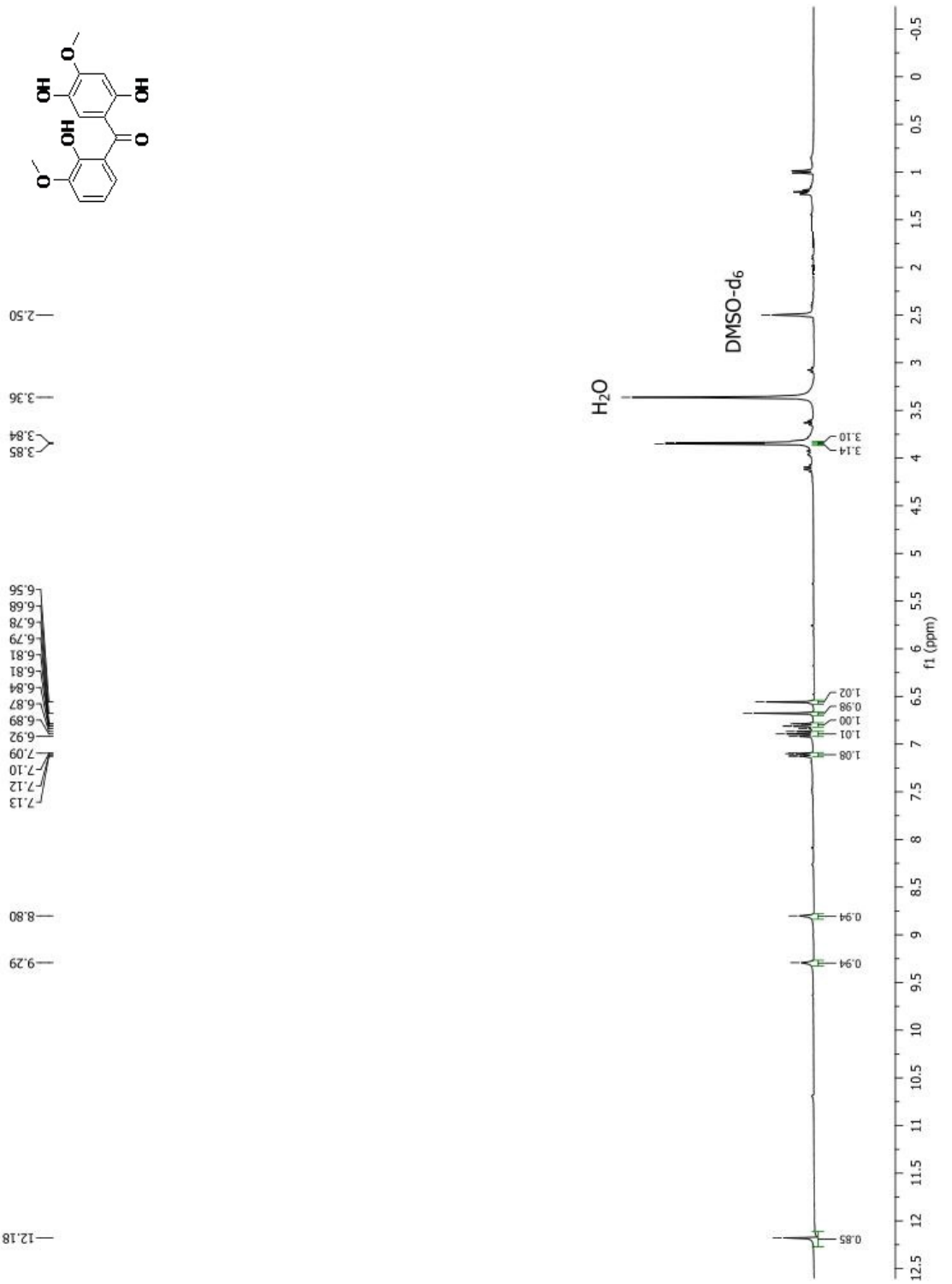


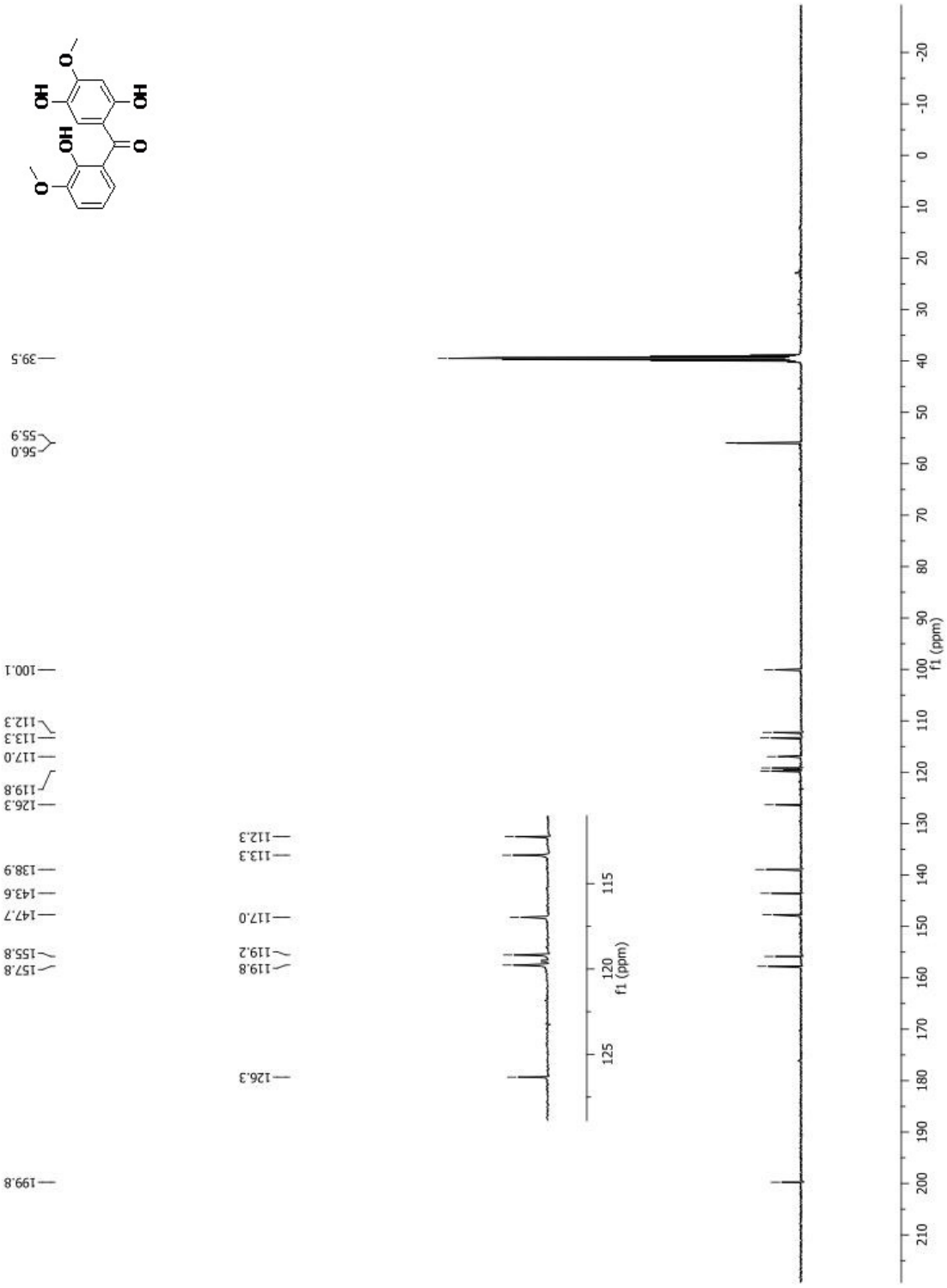


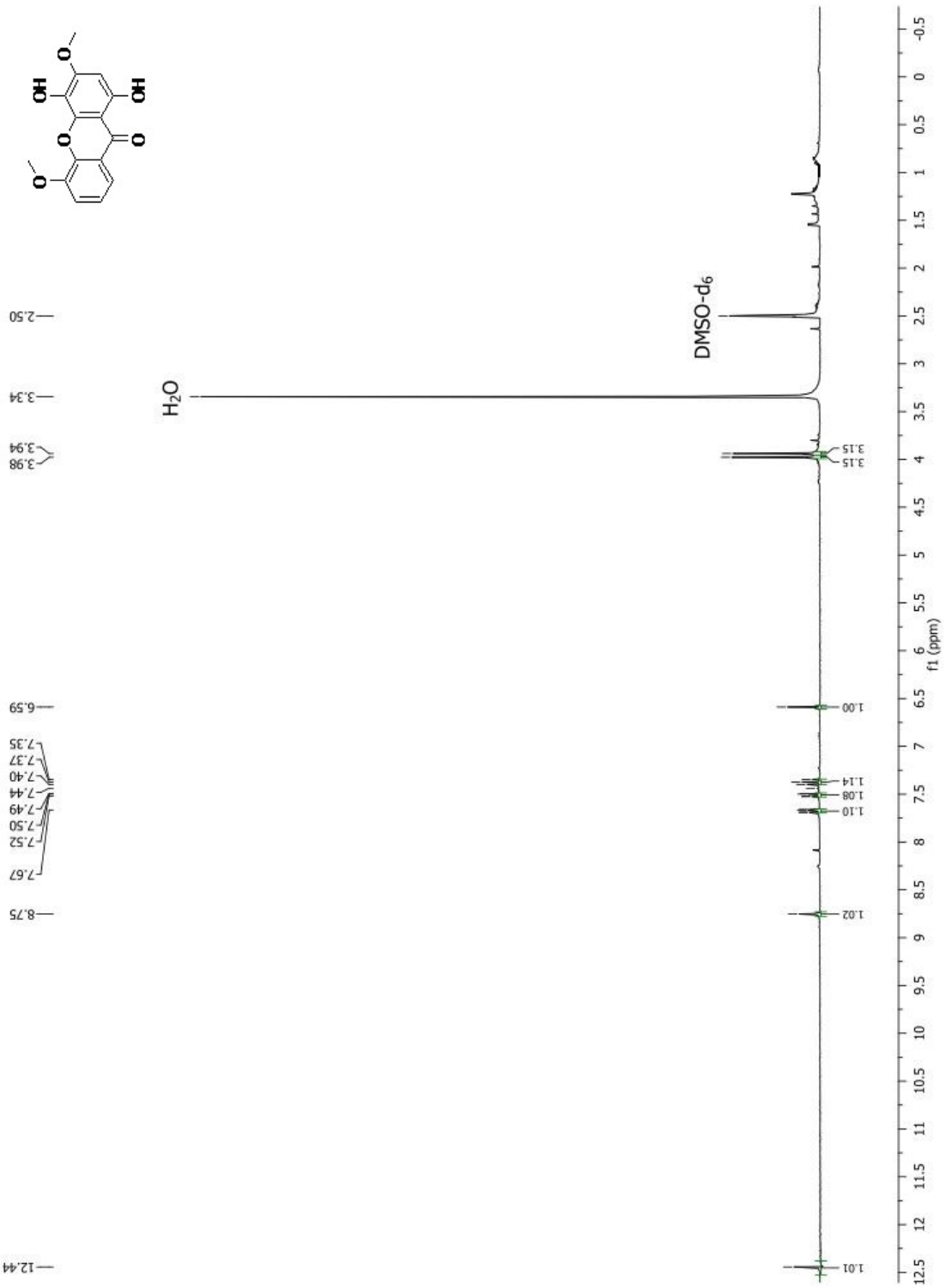


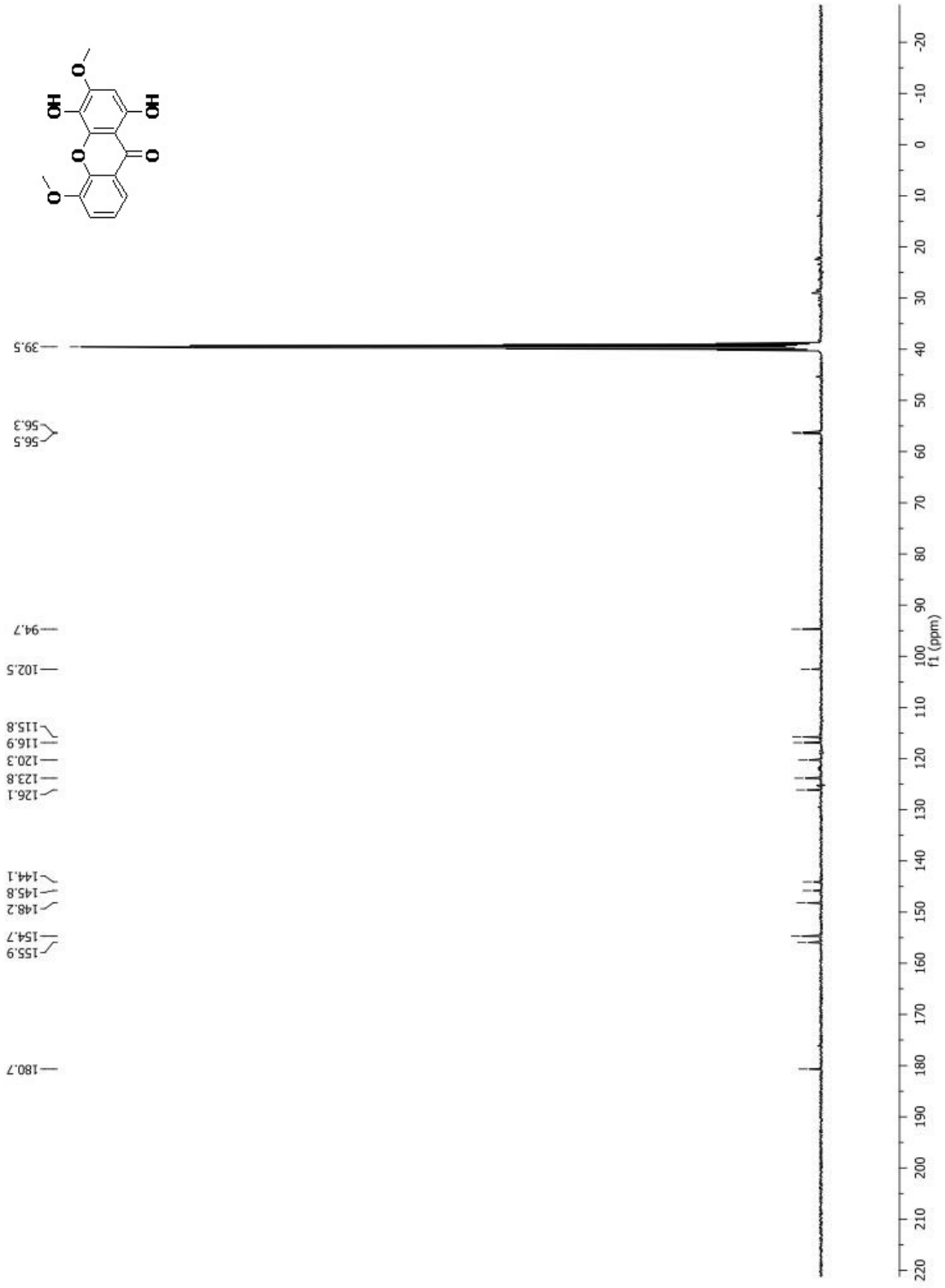


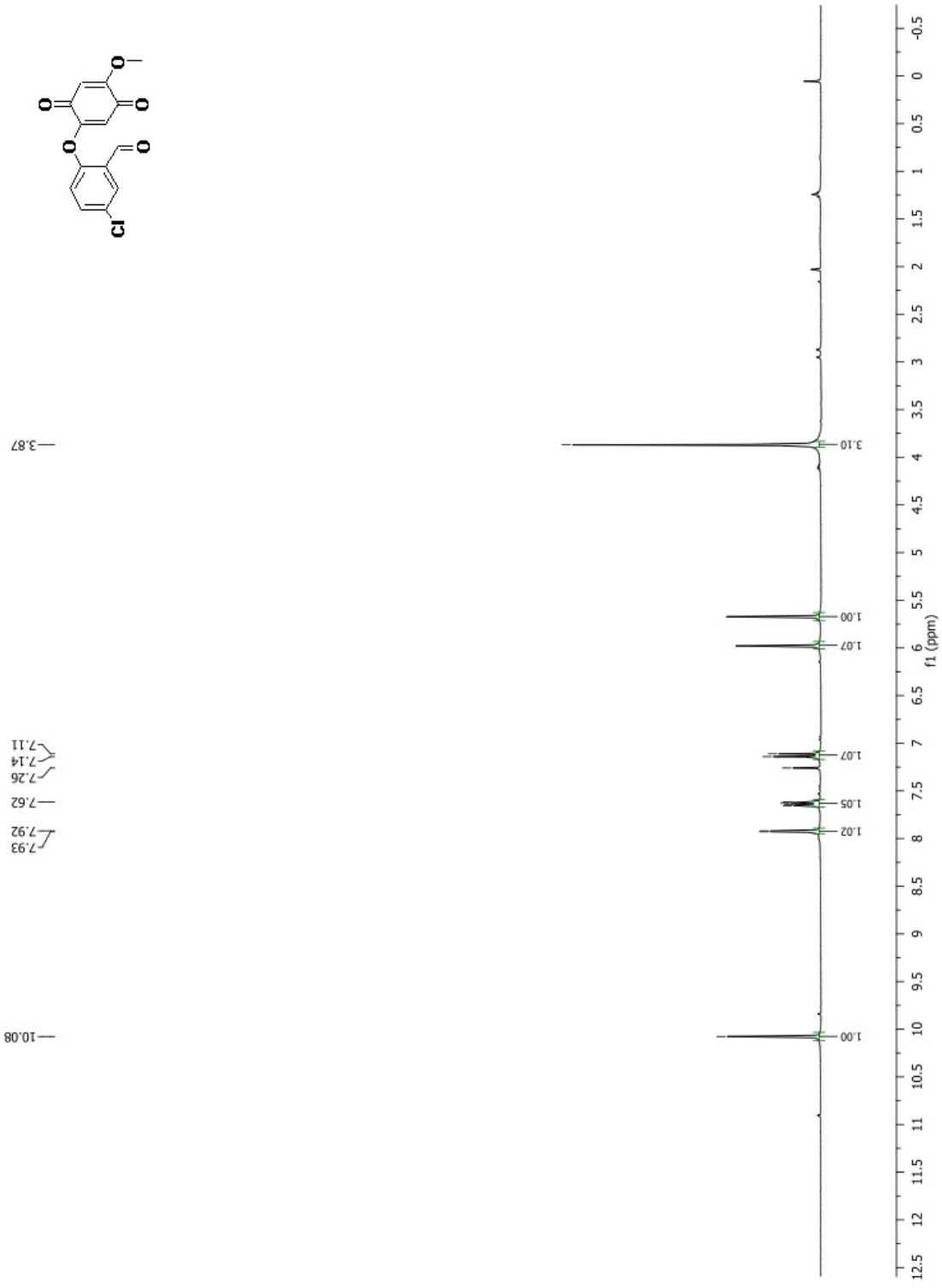


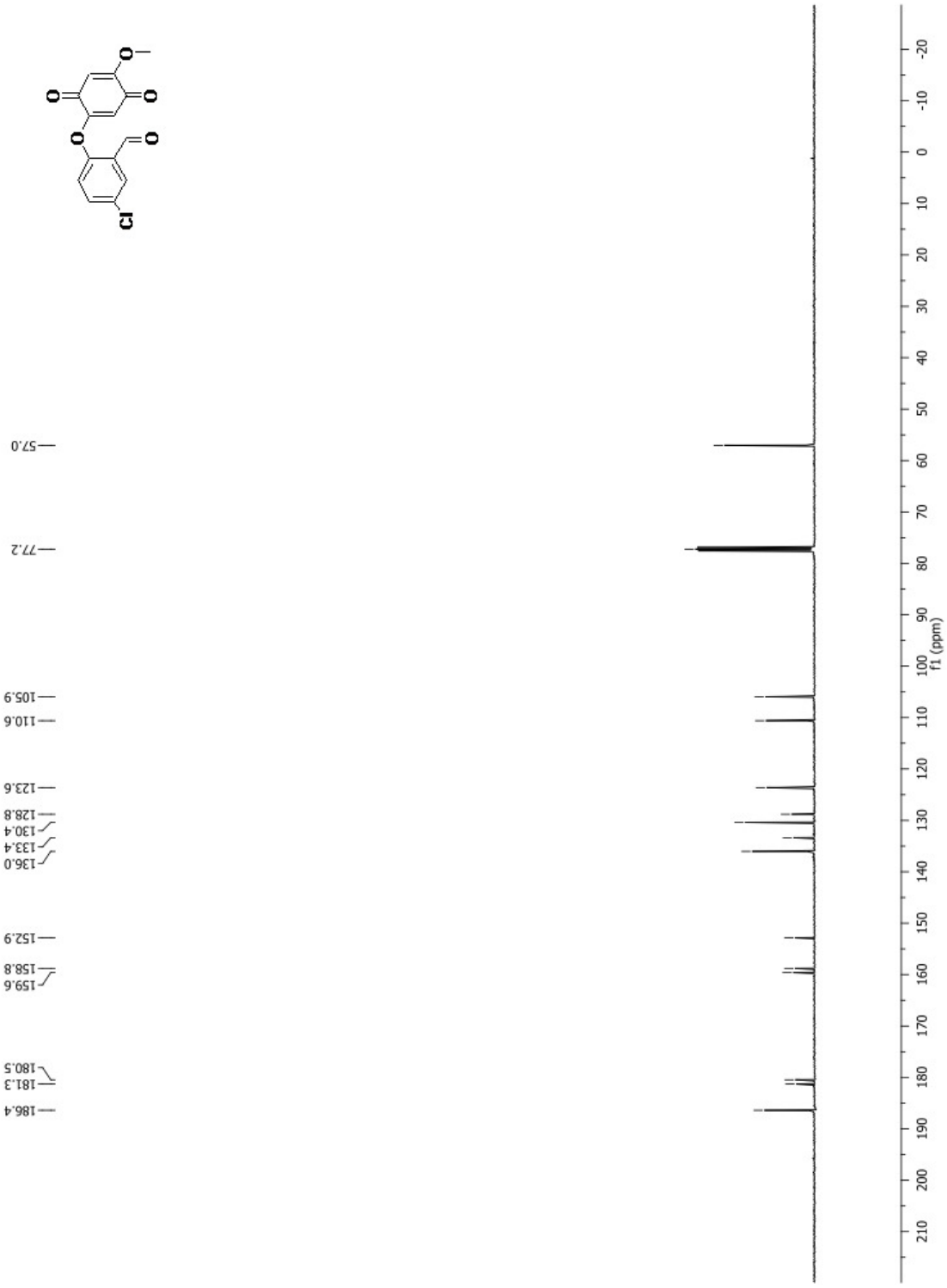


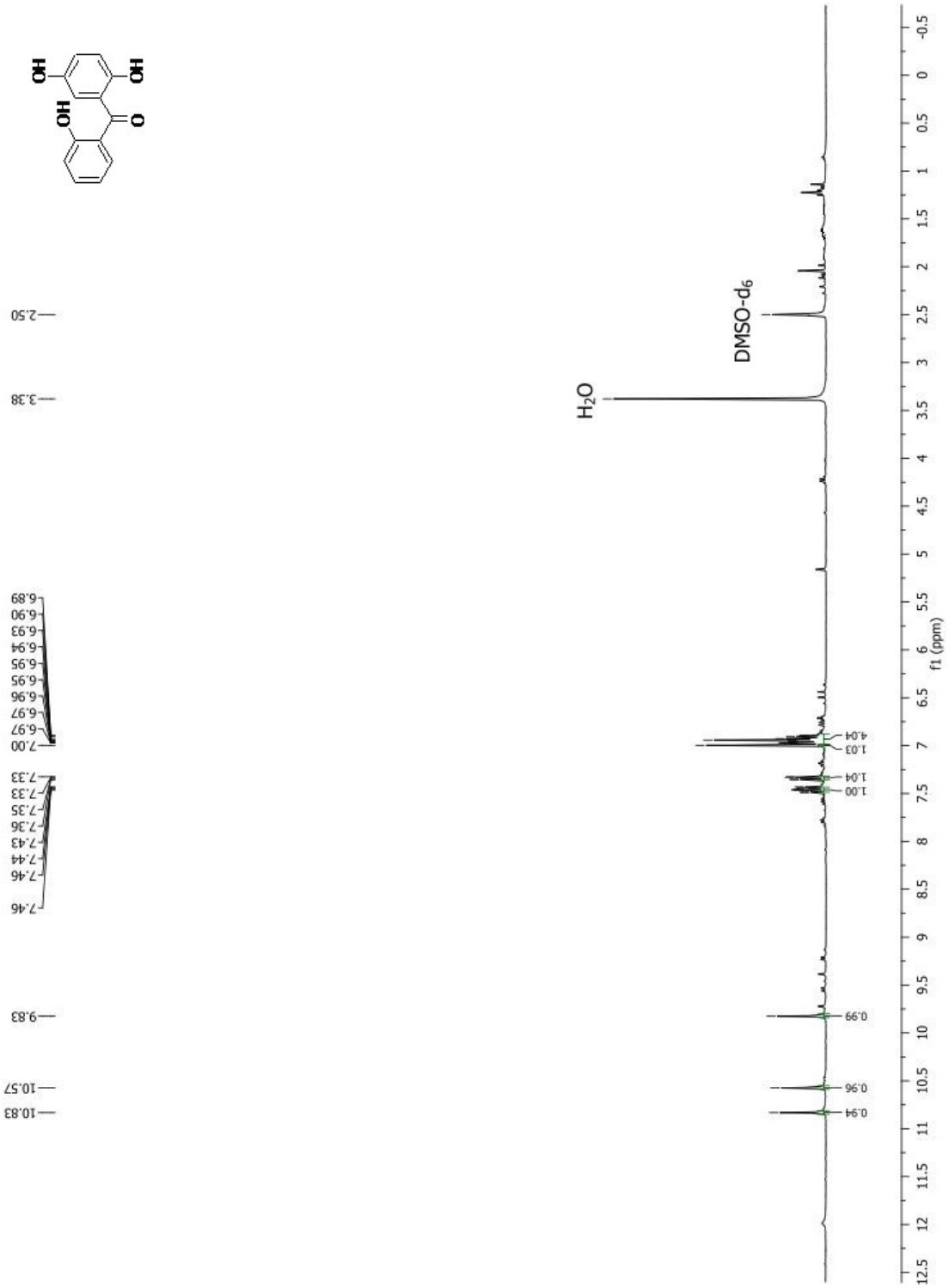


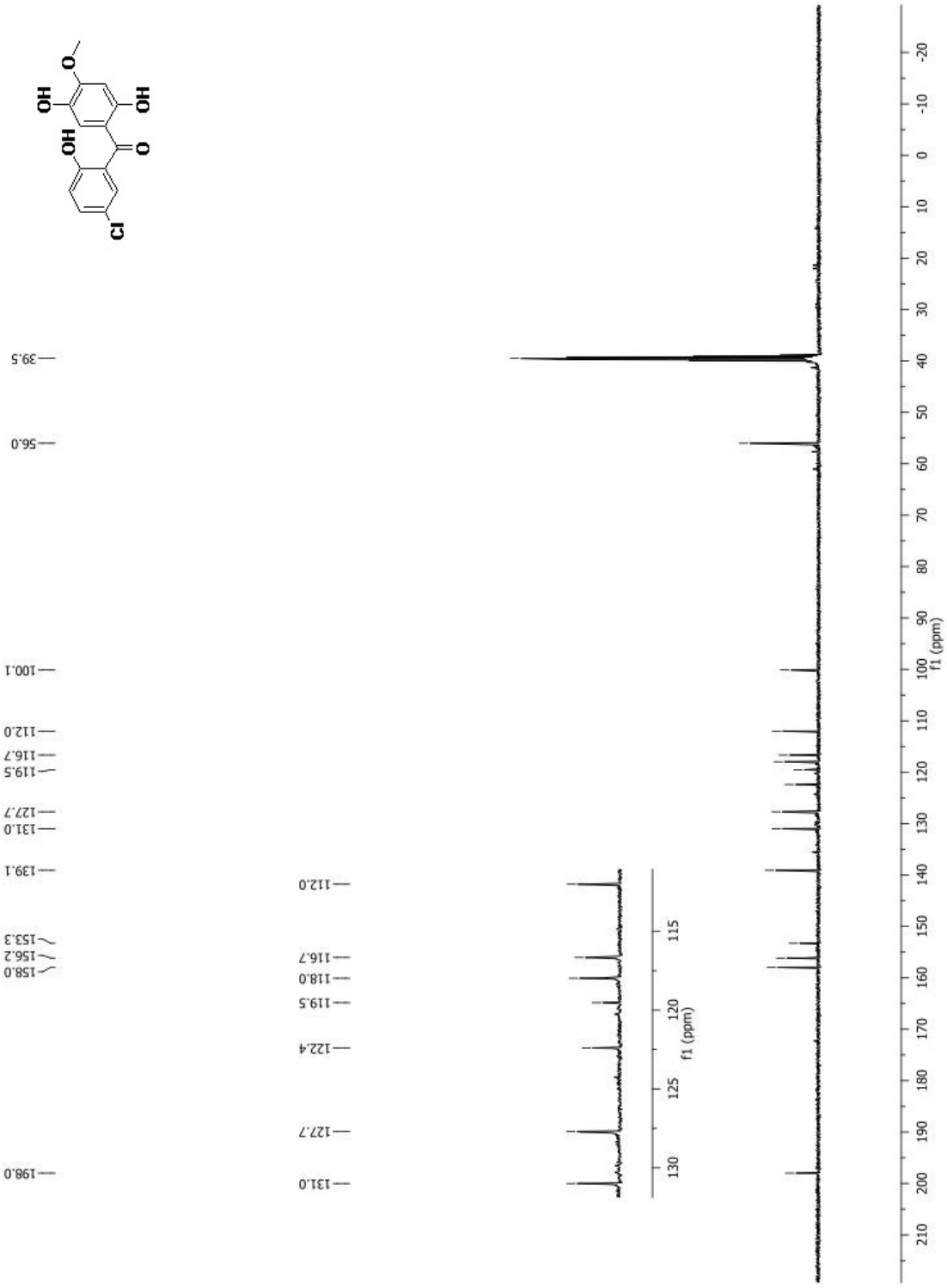


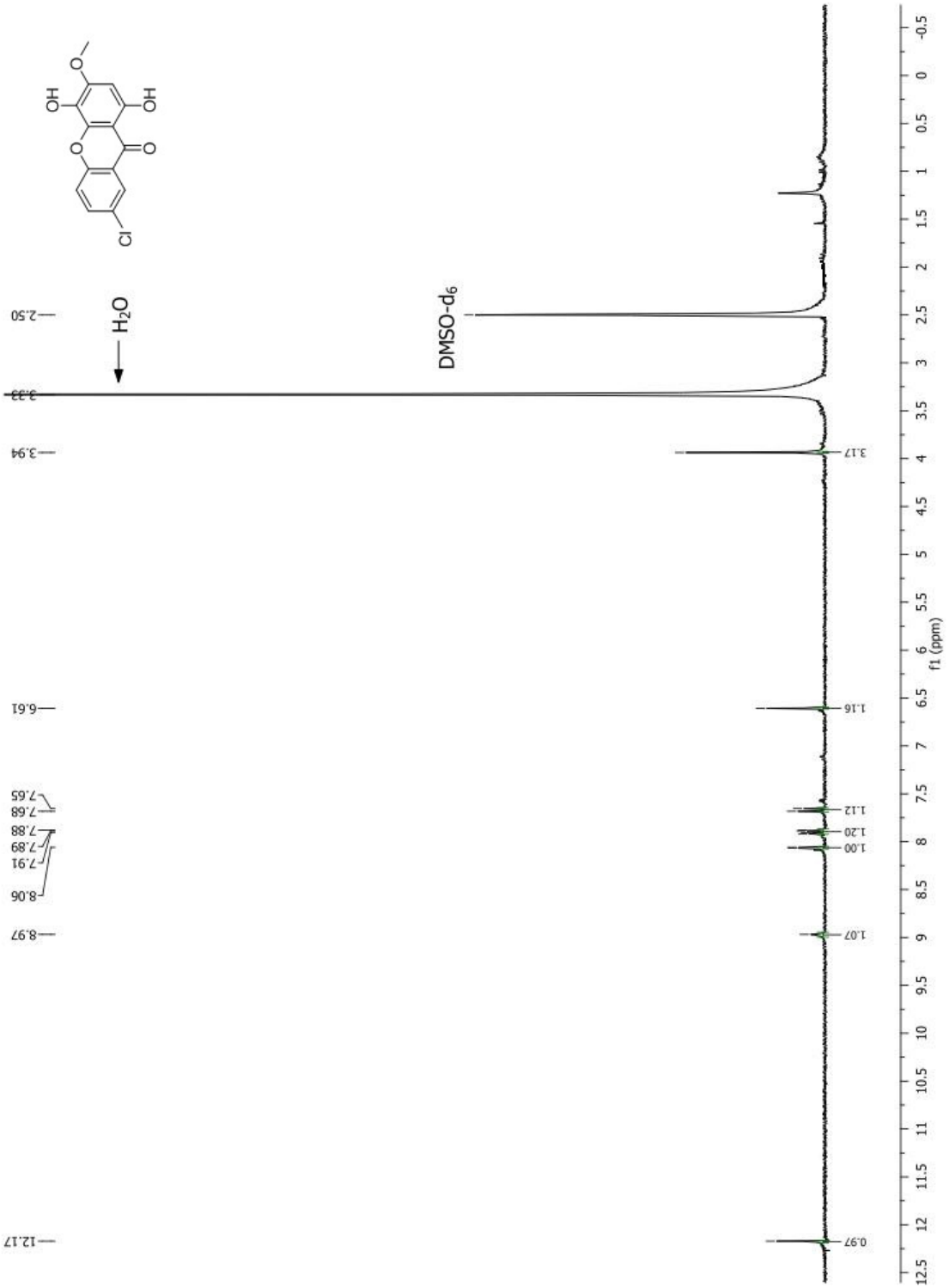


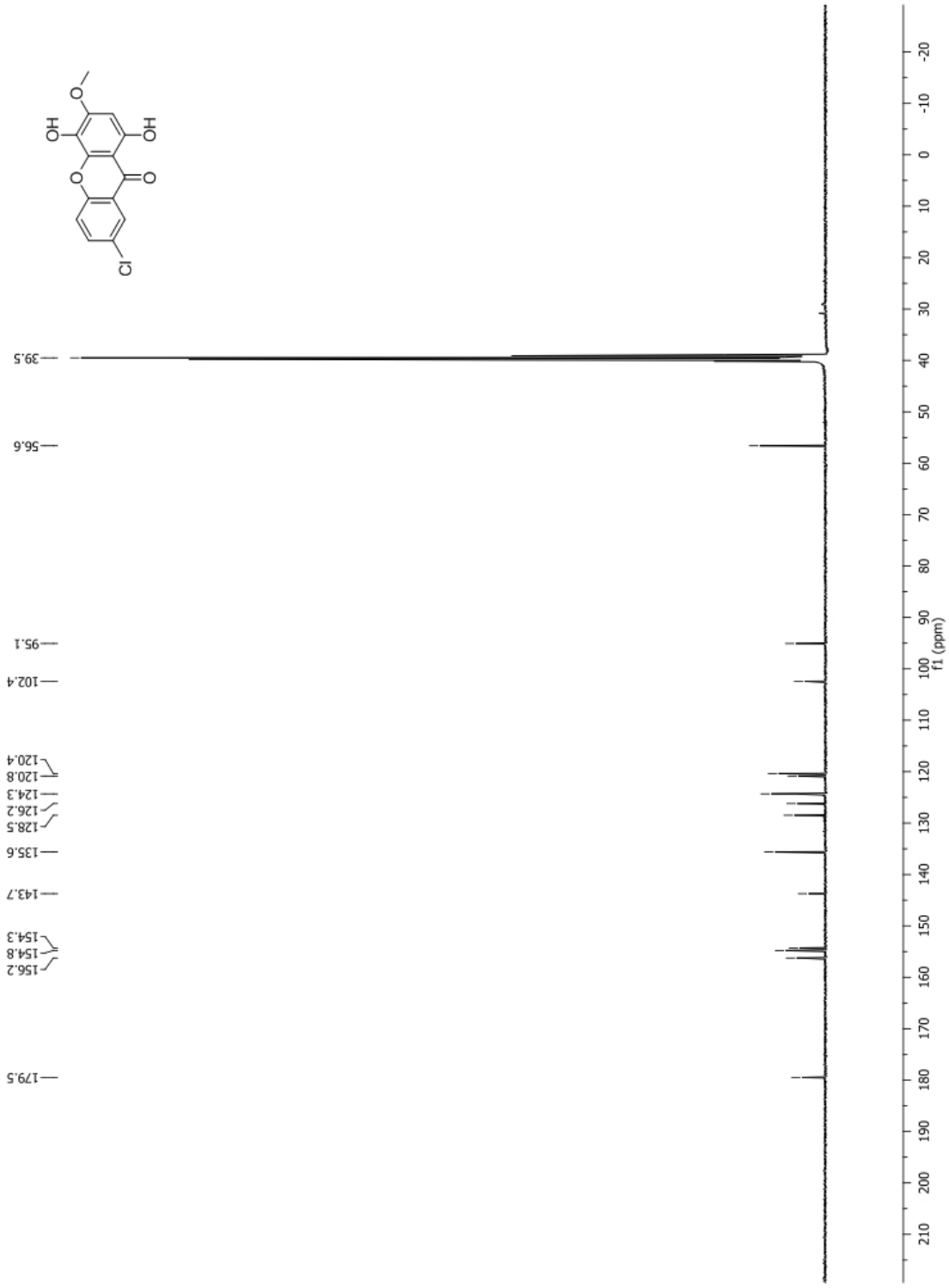


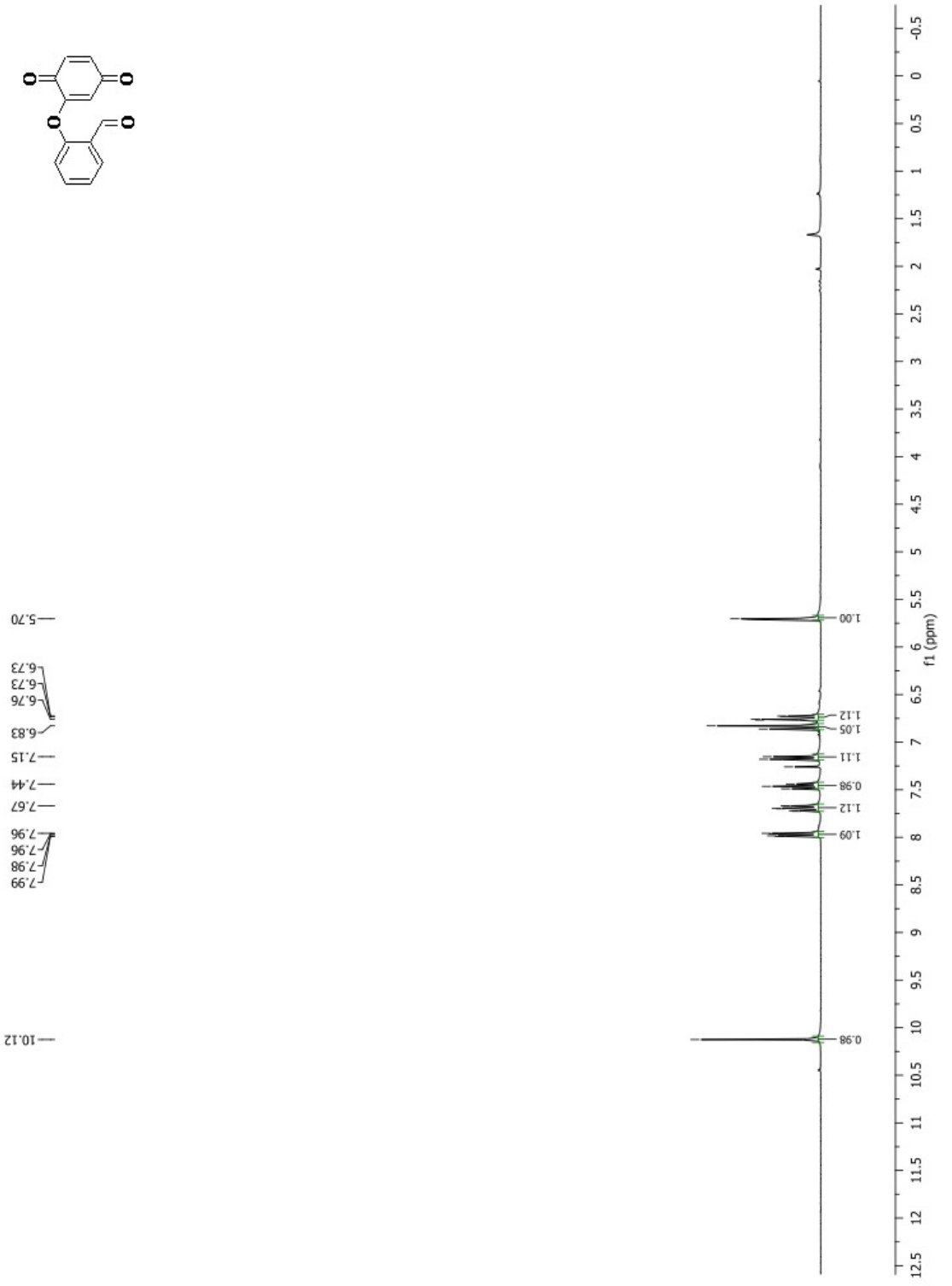


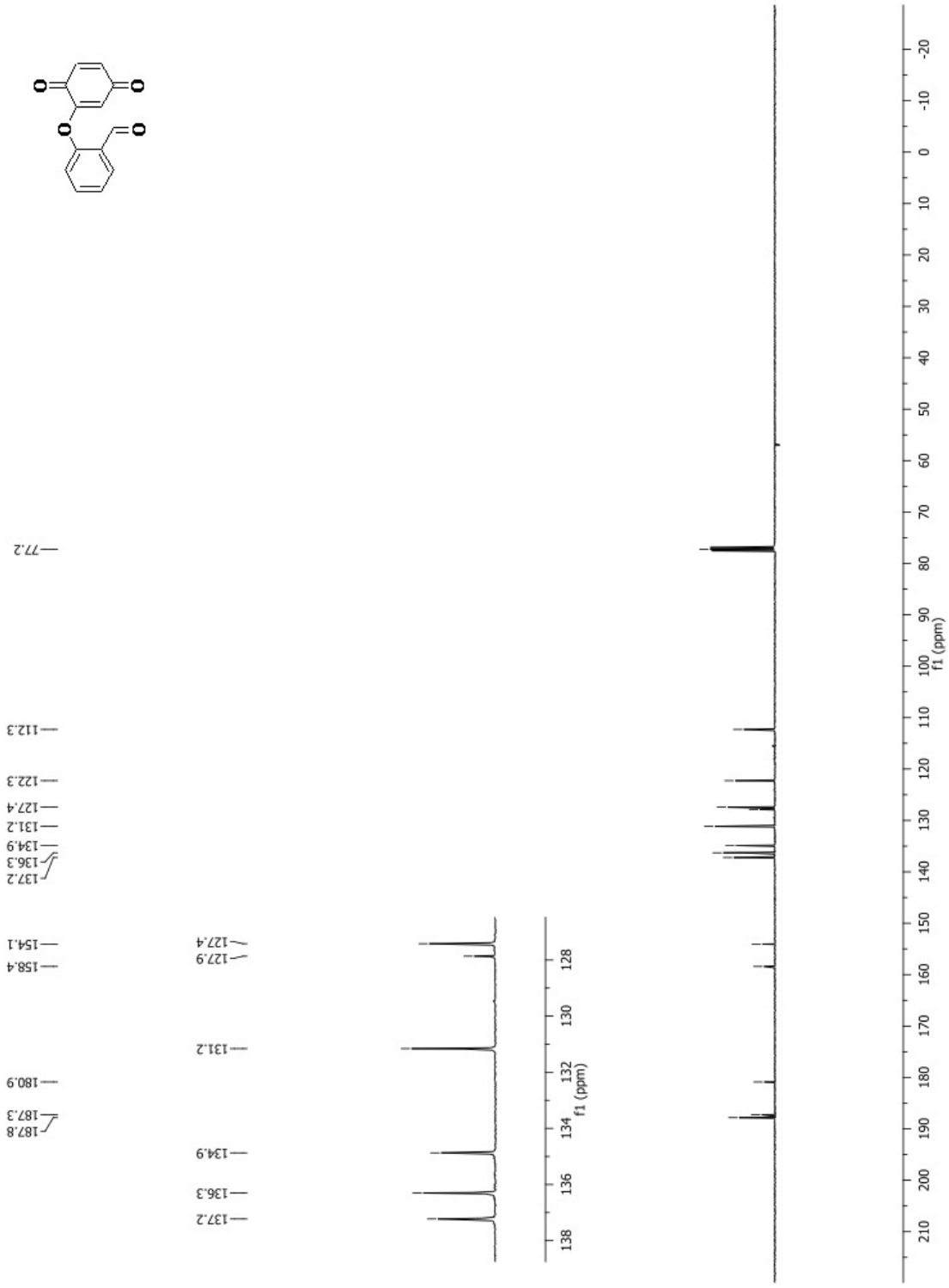


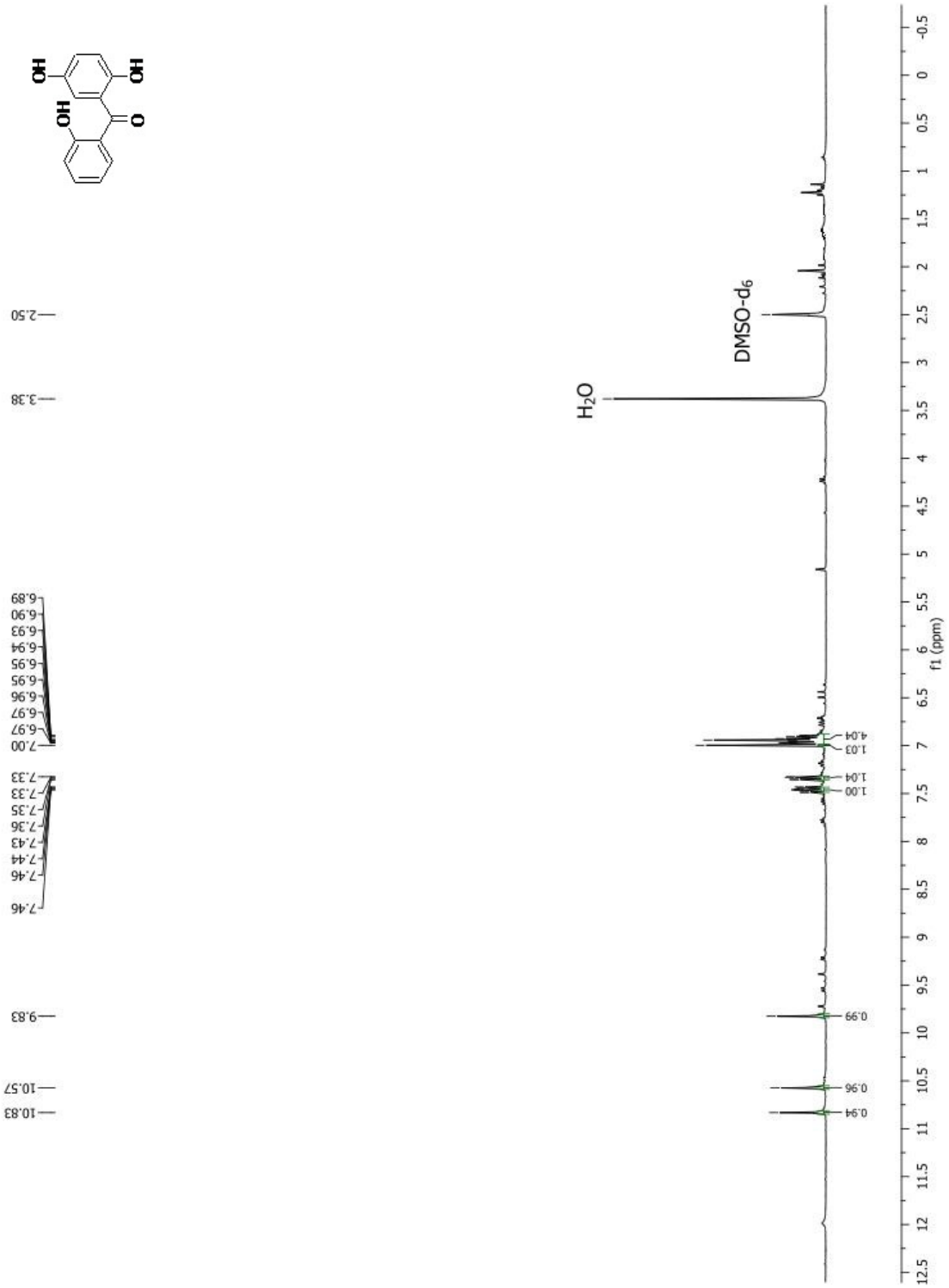


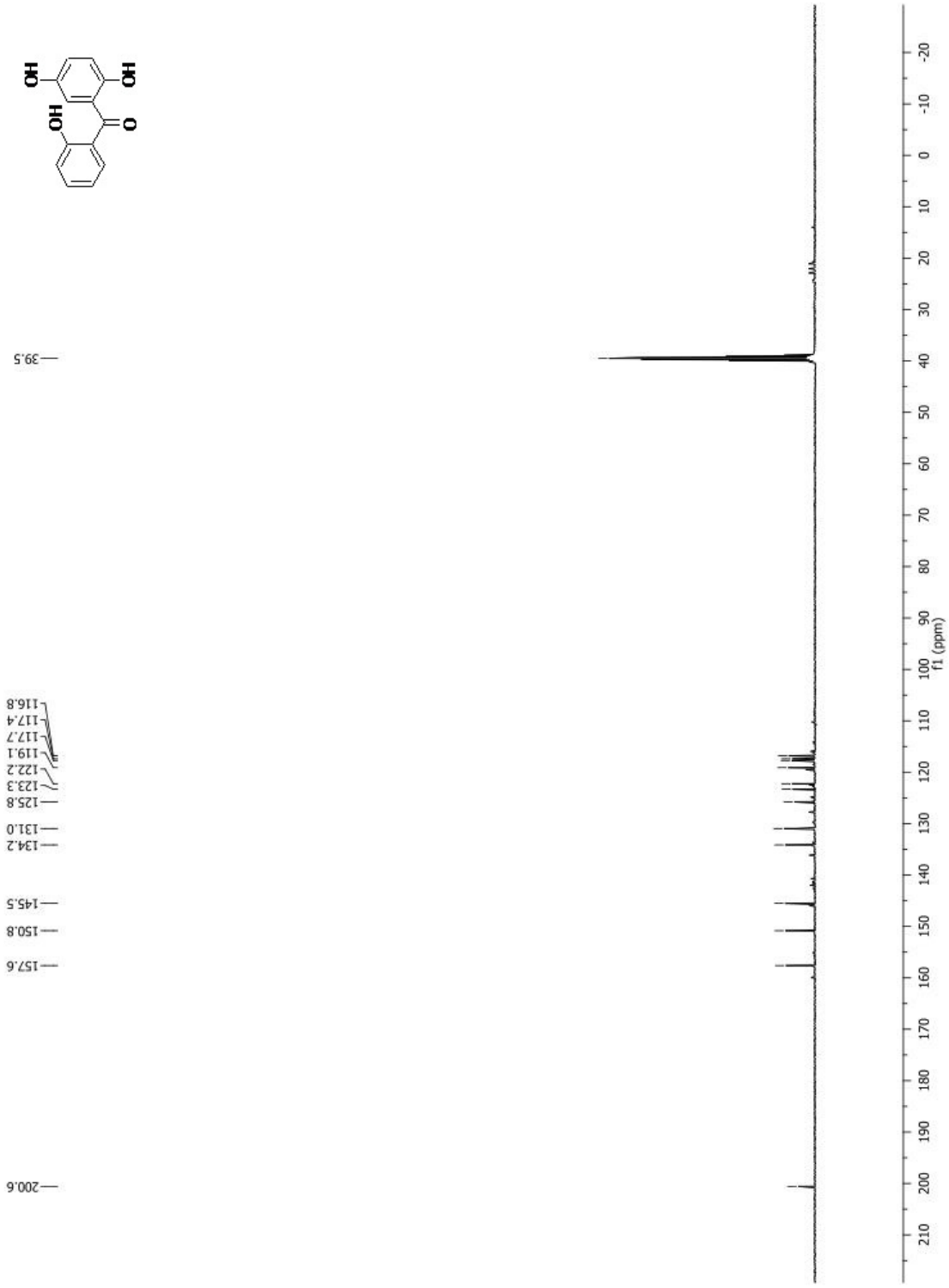


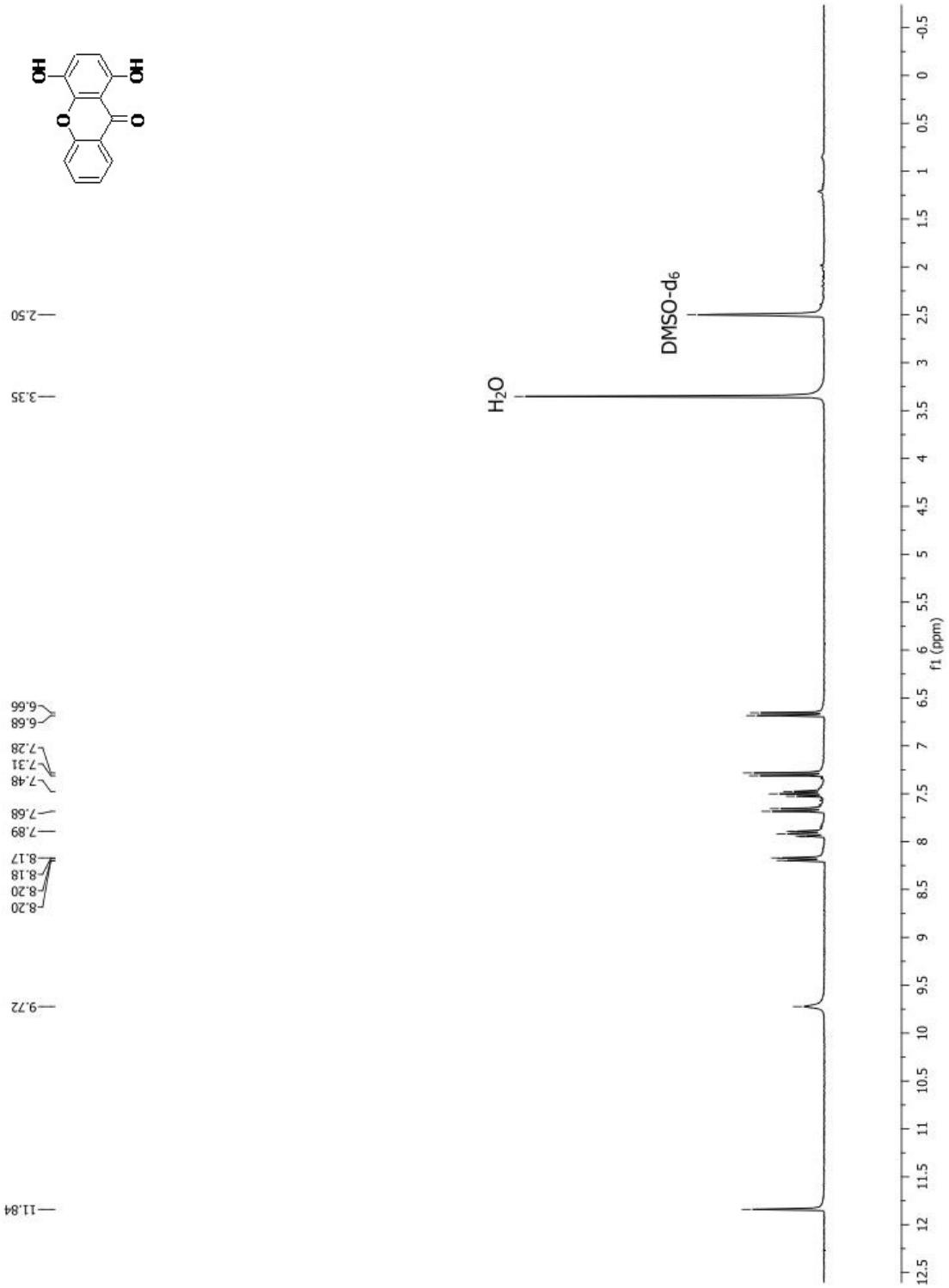


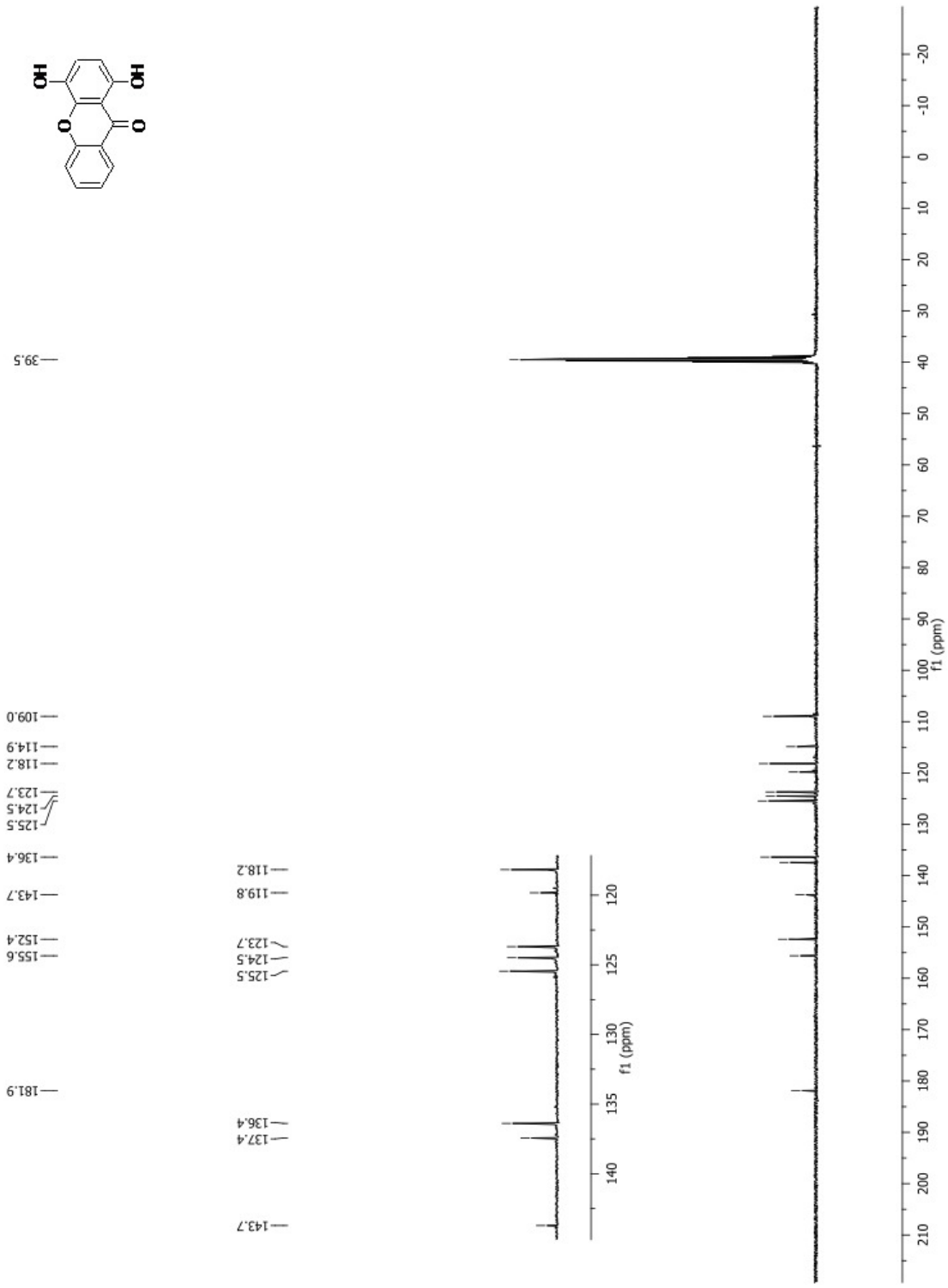


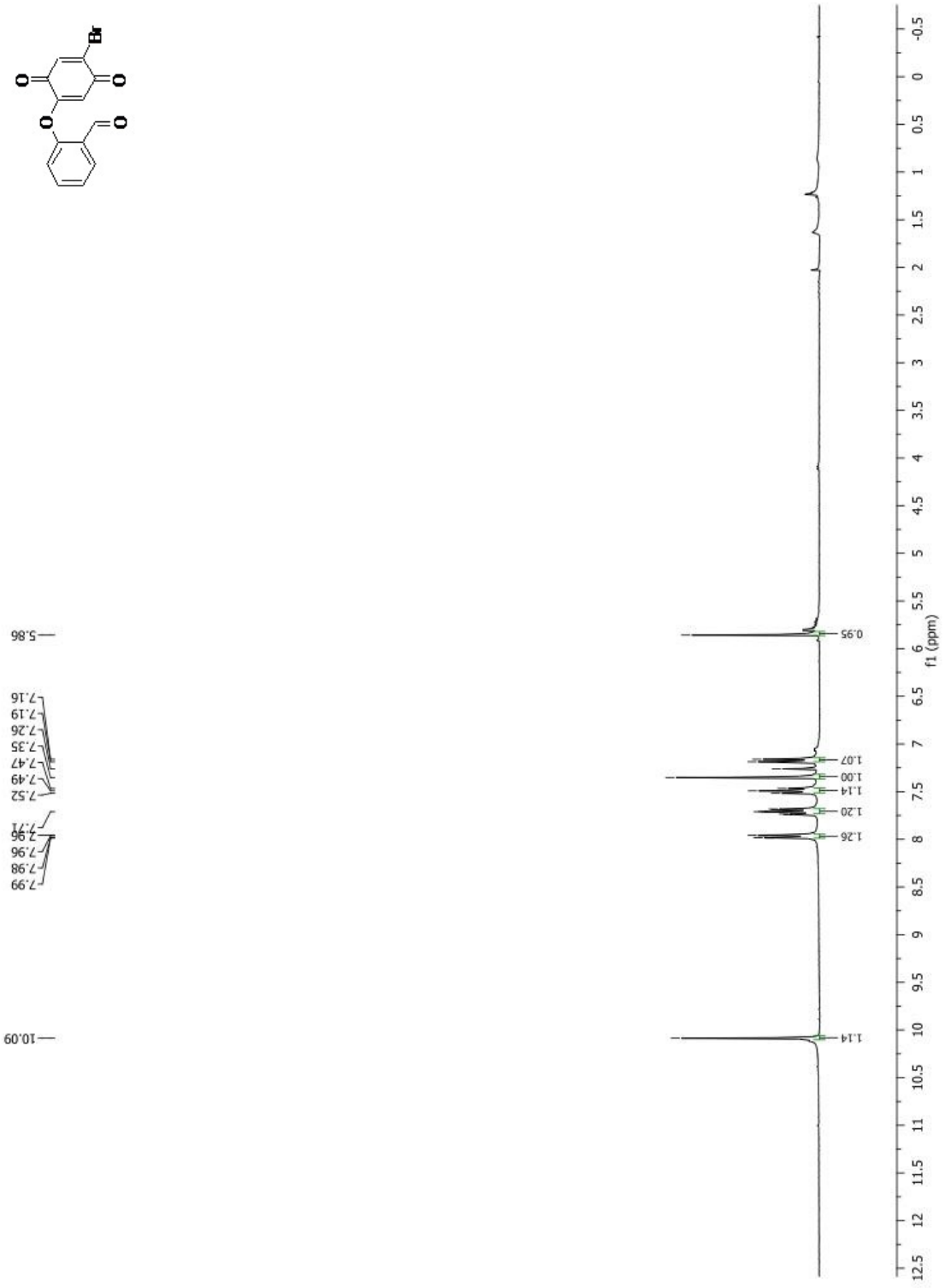


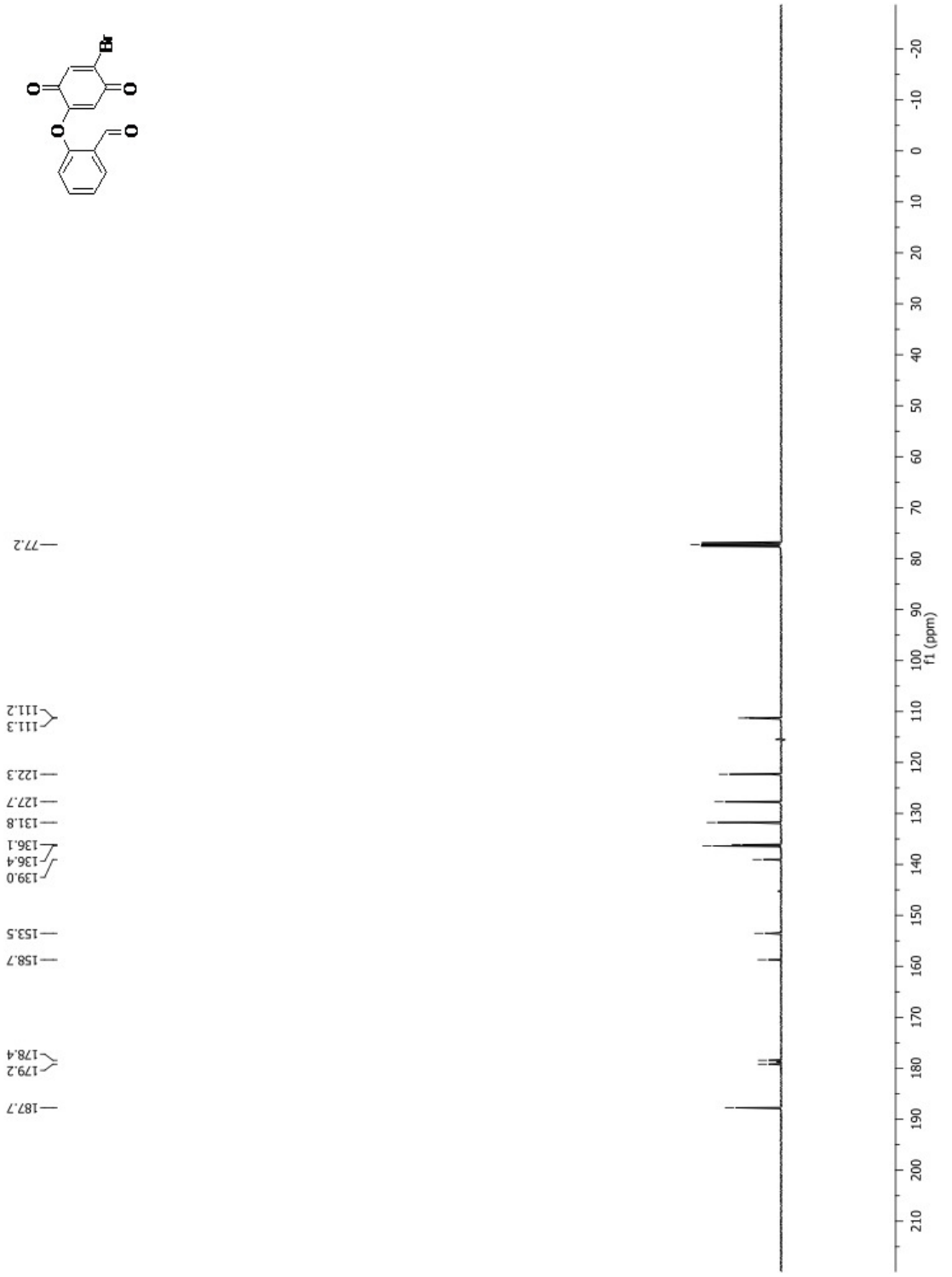


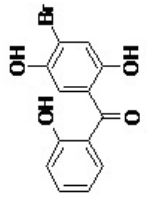


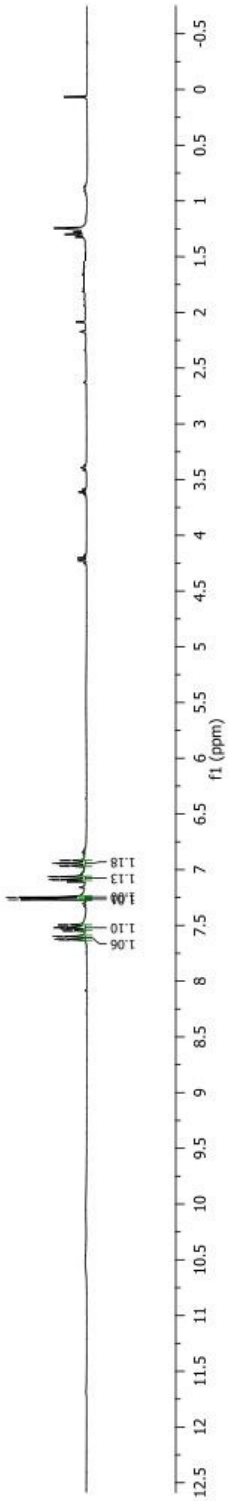


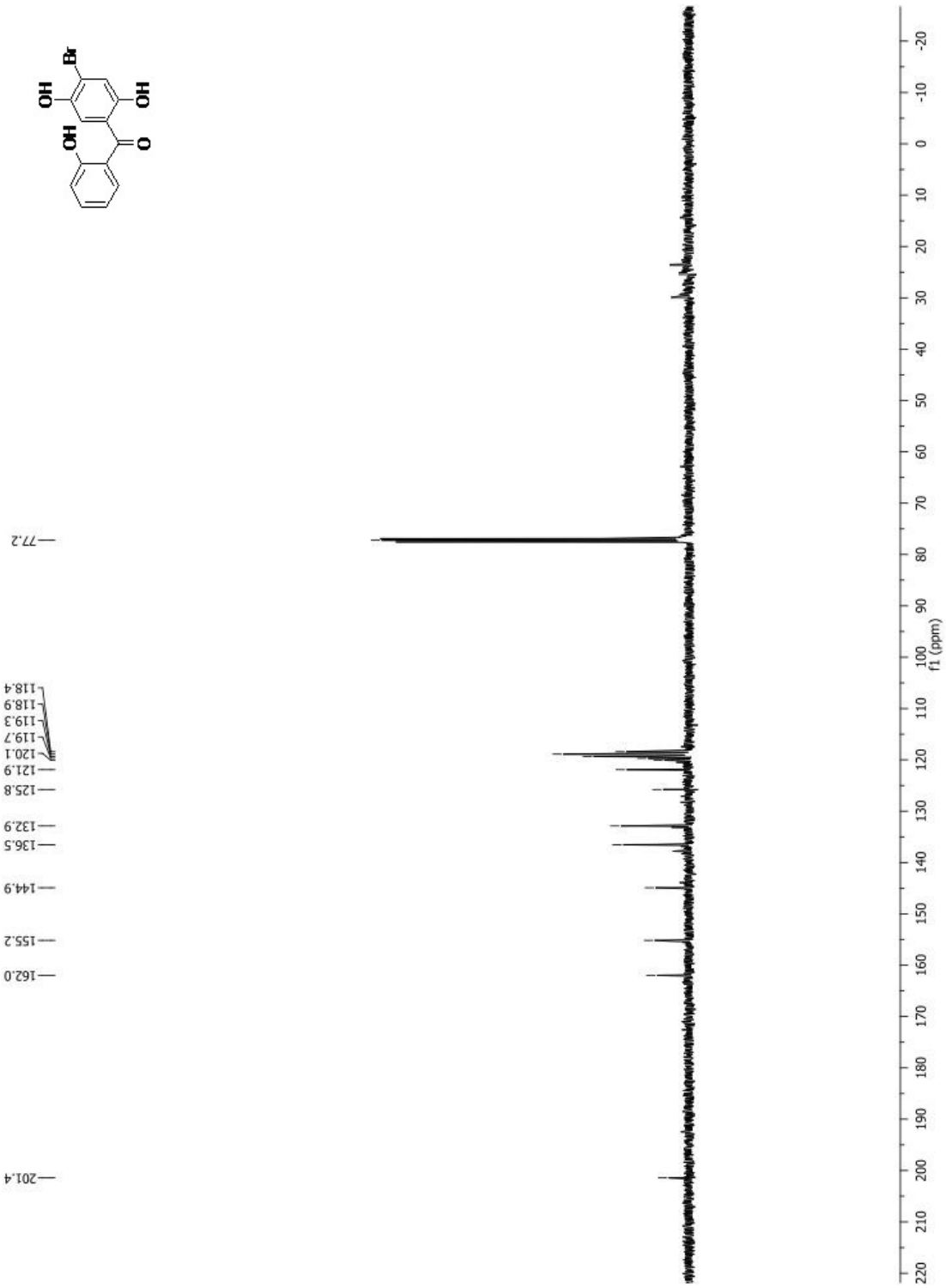


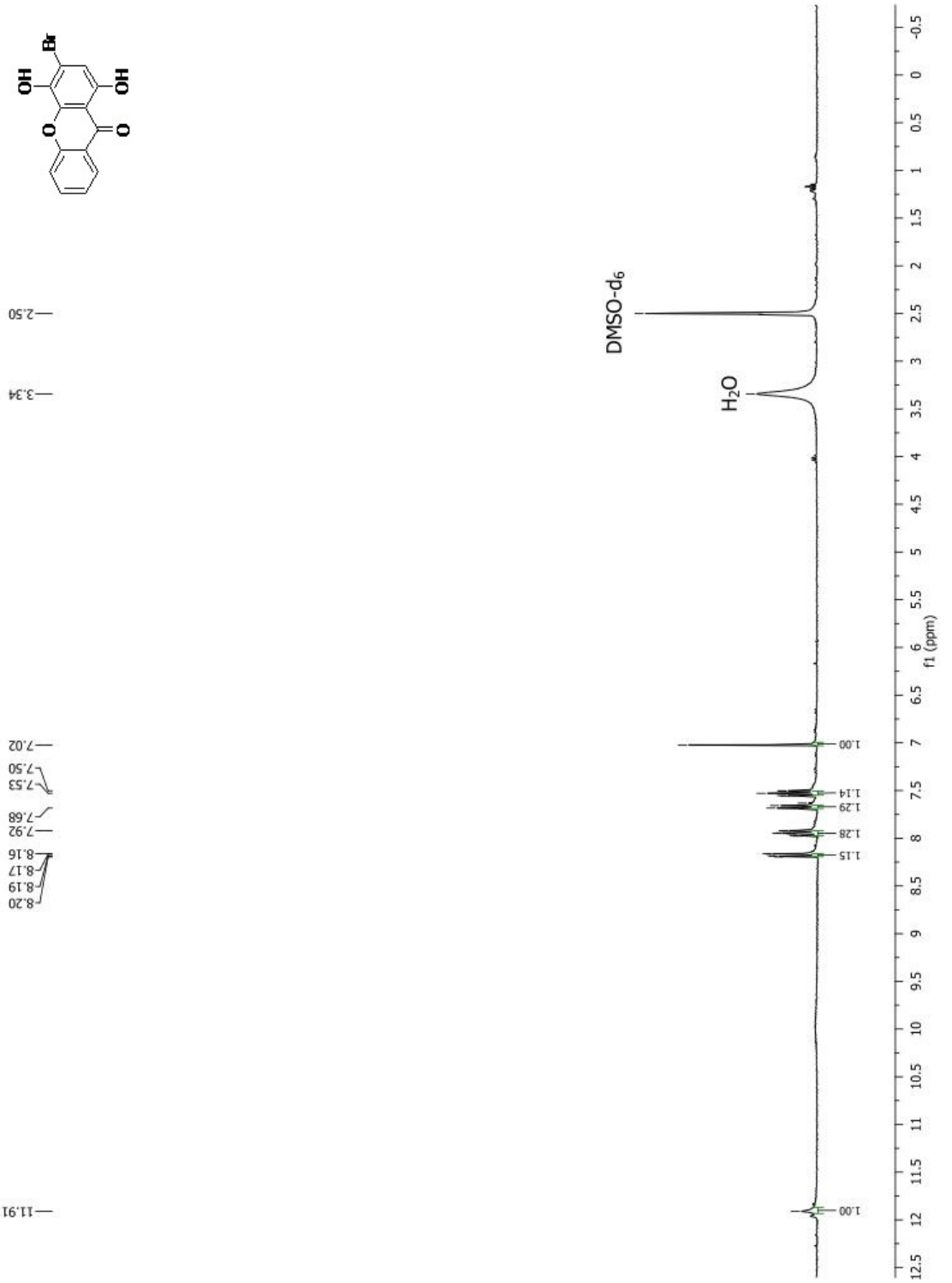


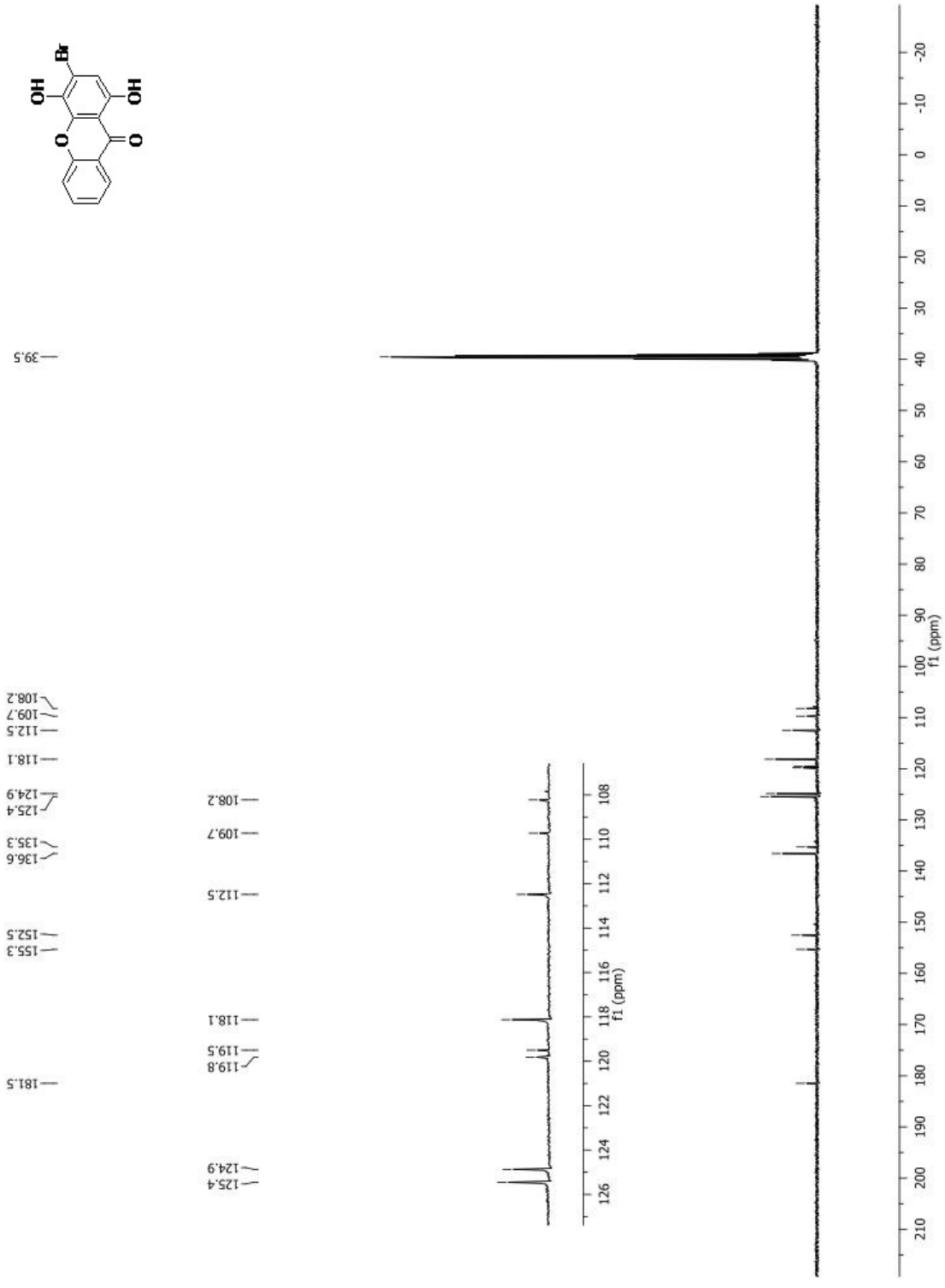












ACKNOWLEDGEMENTS

First of all, I express my greatest appreciation to my major professor, Dr. George A. Kraus, who lead me through my research for a Ph.D degree. His mentoring in research, experimental expertise, clean thinking and strict work rules benefited my work a lot. Without his help, I won't be able to get my Ph.D degree.

I would like to thank my graduate committee members, Dr. Robert S.Houk, Dr. Patricia A. Murphy, Dr. Arthur Winter and Dr. Yan Zhao, for their help on my research.

I would like to thank all of the group members of the Kraus' group for providing a friendly home that always made me feel not alone.

I would like to thank my parents and brother for their love, support and sacrifices. My mother, father and brother have supported my studies all the time and helped take care of my life to finish this degree.

I would like to leave my last acknowledgement for my family. I would like to thank Xiaowen, my beautiful wife, for her deep love, and her encouragement throughout some stressful times. I would like to thank Lexi, my lovely daughter, for making me smile all the time.