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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses

Enantioselective Organocatalytic α-Arylation of Aldehydes

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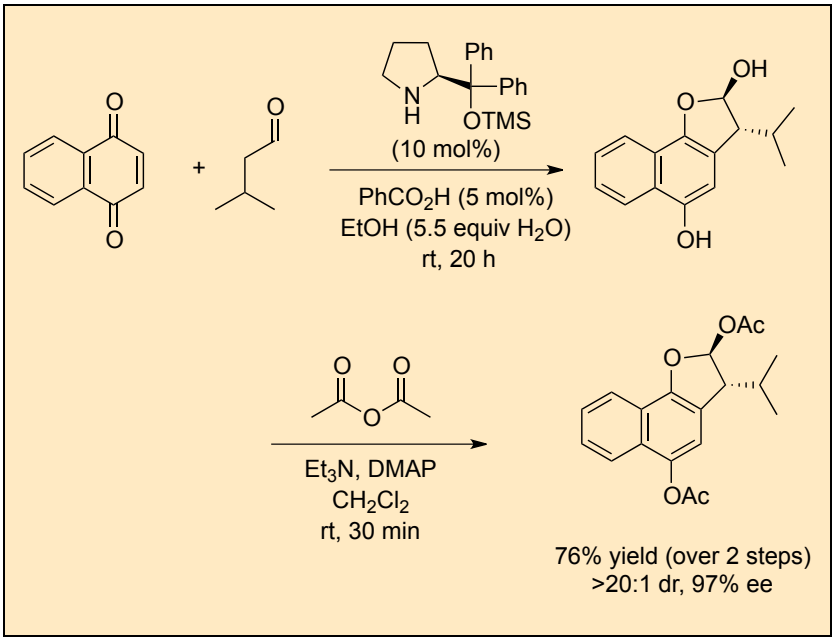
Checked by Yu-Peng He and Dawei Ma



Procedure

(2S,3R)-3-Isopropyl-2,3-dihydronaphtho[1,2-b]furan-2,5-diyl diacetate. A solution of (*S*)-2-(diphenyl-(trimethylsilyloxy)methyl)pyrrolidine (0.50 g, 1.52 mmol, 0.10 equiv) in EtOH (5 mL) is transferred to a 50-mL round-

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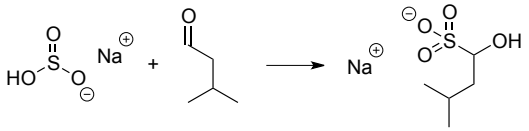
bottomed flask equipped with a 1.6-cm oval Teflon-coated magnetic stir bar (Notes 1 and 2). To the flask is added H_2O (1.5 mL, 1.5 g, 83 mmol, 5.5 equiv) using a 2 mL disposable syringe, benzoic acid (0.093 g, 0.76 mmol, 0.050 equiv) and 3-methylbutanal (8.2 mL, 6.6 g, 76 mmol, 5.0 equiv) via a 10 mL disposable syringe (Note 3). Ethanol (2 mL) is used to ensure that no reagents are left on the side of the flask. The mixture is stirred at room temperature for 15 min (Note 4) followed by addition of 1,4-naphthoquinone (2.408 g, 15.23 mmol, 1.0 equiv) and EtOH (8.2 mL) to ensure that no 1,4-naphthoquinone is left on the side of the flask (Note 5). The reaction mixture is stirred at room temperature until complete (20 h) (Note 6). The reaction is transferred to a 250 mL separatory funnel, diluted with EtOAc (60 mL) and washed with saturated aqueous $NaHSO_3$ (4 x 50 mL) and H_2O (2 x 50 mL) (Note 7). The combined aqueous layer is extracted with EtOAc (2 x 2 x 55 mL) (Note 8). The combined organic layer is dried over $MgSO_4$ (19 g) and filtered by suction through cotton wool using a glass funnel. Ethyl acetate (200 mL) is used to wash the $MgSO_4$ and the filtrate is concentrated by rotary evaporation (40 °C bath, 150-27 mmHg). The resulting oil, containing (2*R*,3*R*)-3-isopropyl-2,3-dihydronaphtho[1,2-*b*]furan-2,5-diol (Note 9), is transferred to a 250-mL round-bottomed flask using CH_2Cl_2 which is then evaporated (40 °C bath, 150-27mmHg). The flask is equipped with a 2-cm oval Teflon-coated magnetic stir bar followed by addition of DMAP (0.183 g, 1.52 mmol, 0.10 equiv). The flask is capped with a rubber septum and flushed with argon. The mixture is diluted with dry CH_2Cl_2 (76.2 mL) (Note 10), followed by addition of Et_3N (5.3 mL, 3.9 g, 38 mmol, 2.5 equiv) and acetic anhydride (3.6 mL, 3.9 g, 38 mmol, 2.5 equiv) using a 10 mL and 5 mL disposable syringe, respectively (Note 11). The reaction is stirred at room temperature for 30 min and then transferred to a 250–mL separatory funnel. The mixture is diluted with CH_2Cl_2 (50 mL) and washed with 1M aqueous HCl (2 x 100 mL), H_2O (1 x 100 mL), saturated aqueous $NaHCO_3$ (2 x 100 mL) and H_2O (1 x 100 mL). The combined aqueous layer is extracted with CH_2Cl_2 (3 x 100 mL) (Note 12) and the combined organic layer dried over $MgSO_4$ (14 g). The suspension is filtered by suction through cotton wool using a glass funnel into a 1-L round-bottomed flask using CH_2Cl_2 (200 mL) to transfer and wash the $MgSO_4$. To the filtrate is added Celite (17 g) and the solution is concentrated by rotary evaporation (40 °C bath, 550-27mmHg). The crude product is purified by flash chromatography using silica gel (Note 13) to furnish (2*S*,3*R*)-3-isopropyl-2,3-dihydronaphtho[1,2-*b*]furan-2,5-diyl diacetate (3.79 g, 76% yield, >20:1 dr (Note 14)) as a clear orange oil

(Note 15). Enantiomeric excess is determined to be 97% ee by chiral HPLC analysis (Notes 16 and 17).

Notes

1. The following reagents and solvents are used as received: Ethanol (VWR, Technosolv, 96% vol), pentane (Sigma-Aldrich, chromasolv, ≥99%), ethyl acetate (Sigma-Aldrich, chromasolv, ≥99.7%), dichloromethane (Sigma-Aldrich, chromasolv, ≥99.8%), (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (Sigma-Aldrich, 95%), benzoic acid (FlukaChemica, >99%), isovaleraldehyde (Sigma-Aldrich, 97%), 1,4-naphthoquinone (Sigma-Aldrich, 97%), 4-(dimethylamino)pyridine (Sigma-Aldrich, 99%), triethyl amine (Sigma-Aldrich, ≥99%), acetic anhydride (Riedel-de Haën, ACS reagent, 99%), magnesium sulfate hydrate (Sigma-Aldrich), Celite® 545 (Sigma-Aldrich), silica gel (Sigma-Aldrich, high purity grade, pore size 60 Å, 230-400 mesh particle size), chloroform-d (Sigma-Aldrich, 99.8 atom% D), hexane (Sigma-Aldrich, chromasolv, ≥97.0%), 2-propanol (Sigma-Aldrich, chromasolv, ≥99.8%). Deionized water is used throughout. The following salts are used as saturated aqueous solutions made by dissolving the salt in H_2O until saturation is reached: $NaHSO_3$ (Sigma-Aldrich, ACS reagent, mix of $NaHSO_3$ and $Na_2S_2O_5$), $NaHCO_3$ (Sigma-Aldrich, -40 +140 mesh, Na_2CO_3 2-5%). 1M HCl was prepared by mixing 459 mL H_2O and 41 mL concentrated HCl (VWR, analaR NORMAPUR. 37).
2. (*S*)-2-(Diphenyl-(trimethylsilyloxy)methyl)pyrrolidine is weighed out in a glass vial and transferred using 5 mL EtOH.
3. The composition of the solvent (H_2O to EtOH ratio) and the ratio of quinone to aldehyde are important due to the oxidation-reduction chemistry of the quinone. Previous studies have shown that 5 equiv of aldehyde and 5 equiv of H_2O are required in order to minimize reduction of the quinone to the hydroquinone.[2]
4. A slight heating of the mixture is observed upon addition of the acid. Consequently, the reaction mixture is stirred for 15 min to ensure that the mixture is cooled to room temperature, prior to addition of the quinone.
5. The EtOH is added using a 20 mL disposable syringe and the total amount of added EtOH is 15.2 mL.

6. The conversion is monitored using ^{1}H NMR spectroscopy. 1,4-Naphthoquinone shows a multiplet at 7.77 ppm, corresponding to 2 hydrogen atoms. When this signal is no longer observable, the reaction is judged complete.
7. This step is introduced in order to reduce the large amount of aldehyde present on this scale. Aldehydes are known to form water soluble bisulfite adducts with $NaHSO_3$.



8. The combined aqueous layer has a total volume of approximately 400 mL, therefore 200 mL portions are extracted with EtOAc (55 mL) two times in a 250-mL separatory funnel.
9. This product is unstable on silica, and the checkers did not purify the crude reaction mixture. ^{1}H NMR and ^{13}C NMR spectra of the crude reaction mixture, as acquired by the checkers, are provided. The submitters report that the hemiacetal can be purified by flash chromatography using Iatrobeads (spherical silica gel). Purified (2*R*,3*R*)-3-isopropyl-2,3-dihydronaphtho[1,2-*b*]furan-2,5-diol (grey foam, >20:1 dr, 99% ee) has the following physical and spectroscopic data: R_f = 0.50 (50% EtOAc/50% pentane); $[\alpha]^{20}_D$ = –117.3 (c = 1.0, CH_2Cl_2); FT-IR (ATR): 3329, 2960, 1595, 1442, 1395, 1260, 1228, 1154, 1066, 1027, 1008 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 1.93 (pd, *J* = 6.9, 5.2 Hz, 1H), 3.08 (dd, *J* = 5.2, 1.7 Hz, 1H), 3.72 (s, 1H), 5.53 (s, 1H), 5.85 (d, *J* = 1.8 Hz, 1H), 6.64 (s, 1H), 7.38–7.47 (m, 2H), 7.89 (dd, *J* = 7.3, 2.0 Hz, 1H), 8.08 (dd, *J* = 7.4, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.0, 19.4, 30.5, 57.6, 104.1, 106.4, 119.8, 120.8, 121.3, 122.0, 124.5, 125.1, 126.0, 145.7, 147.2; HRMS calculated for: $[C_{15}H_{16}O_3+Na]^+$ 267.0992; found 267.0994.
10. Dichloromethane is obtained from a solvent purification system and transferred using a 20 mL disposable syringe.
11. Triethylamine and acetic anhydride are used in excess because two hydroxyl groups are acetylated.
12. CO_2 gas evolves when the acid and base solutions are combined.
13. A glass column (5.5 x 28 cm) is wet-packed (10% EtOAc/90% pentane) with silica (200 g). The Celite, with the product adsorbed, is added and the column is topped with 0.5 cm sand. The product is eluted with 10%

EtOAc/90% pentane (3 L), collecting 14 fractions of 50 mL followed by 20 mL fractions. TLC (UV visualization) is used to follow the chromatography. Fractions 33-61 are concentrated by rotary evaporation (40 °C bath, 550-27mmHg), then held under vacuum (0.08 mmHg) at room temperature overnight.

14. Diastereomeric ratio is determined by ^{1}H NMR analysis of the purified product. Only one diastereoisomer is observed.
15. When the procedure was performed on half-scale, the reaction provided 1.85 g (75%) of the product. (2*S*,3*R*)-3-Isopropyl-2,3-dihydronaphtho[1,2-*b*]furan-2,5-diyl diacetate has the following physical and spectroscopic data: R_f = 0.34 (25% EtOAc/75% pentane); FT-IR (ATR): 2962, 1762, 1599, 1459, 1435, 1368, 1205, 1160, 1063 cm^{-1}; $[\square]^{20}_D$ = –183.1 (c = 2.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.98 (d, *J* = 7.2 Hz, 6H), 2.09 (m, 4H), 2.46 (s, 3H), 3.33 (d, *J* = 5.0 Hz, 1H), 6.76 (s, 1H), 7.17 (s, 1H), 7.50 (m, 2H), 7.81 (m, 1H), 8.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.3, 19.3, 21.1, 21.3, 30.7, 55.4, 102.0, 115.4, 119.8, 120.7, 121.6, 122.1, 126.3, 126.6, 126.9, 141.0, 151.5, 169.9, 170.1; HRMS calculated for: $[C_{19}H_{20}O_5+Na]^+$ 351.1203; found 351.1201.
16. Enantiomeric excess is determined to be 96% ee by chiral HPLC using the following conditions: Chiralpak IB column (particle size: 5 μm; dimensions: 4.6 mmØ x 250 mmL) 95% hexanes/5% isopropanol, 0.5 mL/min. Retention times are: 11.3 min (minor), 12.2 min (major). A Photodiode Array Detector is used.
17. In order to determine the retention times for both enantiomers a racemic mixture of the enantiomers is prepared: In a vial (*S*)-2-(diphenyl-(trimethylsilyloxy)methyl)pyrrolidine (3.3 mg, 0.010 mmol, 0.050 equiv) and (*R*)-2-(diphenyl-(trimethylsilyloxy)methyl)pyrrolidine (3.3 mg, 0.010 mmol, 0.050 equiv) are dissolved in EtOH (0.2 mL). To the vial is added H_2O (20 μL, 20 mg, 1.1 mmol, 5.5 equiv), benzoic acid (1.4 mg, 0.010 mmol, 0.050 equiv) and 3-methylbutanal (107 μL, 86.1 mg, 1.00 mmol, 5.00 equiv). Finally, 1,4-naphthoquinone (31.6 mg, 0.20 mmol, 1.00 equiv) is added and the mixture stirred for 24 h at room temperature. The reaction mixture is diluted with EtOAc and washed with saturated aqueous $NaHSO_3$ and H_2O. The organic layer is dried over $MgSO_4$ and the filtrate concentrated by rotary evaporation. To a vial containing the crude mixture is added DMAP (2.4 mg, 0.020 mmol, 0.10 equiv), dry CH_2Cl_2 (1.0 mL), Et_3N (70 μL, 51 mg, 0.50 mmol, 2.5 equiv) and acetic anhydride (47 μL, 51 mg, 0.50 mmol, 2.5 equiv) under argon atmosphere. The reaction is stirred at room temperature

for 30 min and then diluted with CH_2Cl_2 and washed with 1M aqueous HCl, H_2O, saturated aqueous $NaHCO_3$ and H_2O. The organic layer is dried over $MgSO_4$. To the filtrate is added Celite and the suspension concentrated by rotary evaporation. The crude product is purified by flash chromatography using silica gel (10% EtOAc/90% pentane) to furnish the product *rac*-**5a**.

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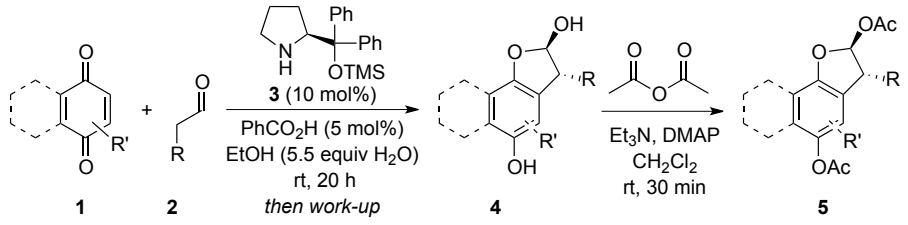
Discussion

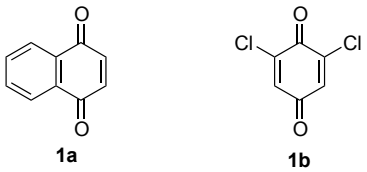
In organocatalysis, two different mechanistic approaches are commonly considered: covalent and non-covalent catalysis. For the covalent approach, chiral secondary amines are very powerful catalysts for the enantioselective functionalization of carbonyl compounds. Over the last decade a large number of α-, β- and γ-functionalizations, involving enamine, iminium-ion and dienamine intermediates, respectively, have been reported.[3] The development of enantioselective α-arylation reactions of carbonyl compounds is very important in contemporary organic synthesis as this reaction introduces a $C(sp^3)$-$C(sp^2)$ bond. This reaction has been a challenge and prior to the present study, this reaction has mostly relied on transition-metal catalyzed approaches.[4]

The present procedure describes an organocatalytic, enantioselective α-arylation of aldehydes, in which quinones are applied as the aromatic partner, to afford optically active α-arylated aldehydes. Following the addition/aromatization sequence, subsequent hemiacetal formation affords the 2,3-dihydrobenzofuran products.

In order to make the previously reported α-arylation protocol[2] suitable for a larger scale synthesis, some modifications have been developed. The present procedure is improved by lowering the catalyst loading from 20 mol% to 10 mol%, using 5 mol% benzoic acid. Furthermore, to simplify the purification process, an acetylation with acetic anhydride has been applied as it stabilizes the products without loss of enantiopurity.

Table 1. Scope of the organocatalytic, enantioselective α–arylation of aldehydes[a]





Entry	Quinone	R	T [°C]	Product	Yield[a] [%]	ee[a] [%]	dr
1	**1a**	*i*-Pr (**2a**)	rt	**5a**	74-77	97-98	>20:1
2	**1a**	*n*-Hex (**2b**)	–11	**5b**	57-58	97-99	>20:1
3	**1a**	Et (**2c**)	0	**5c**	50-56	93-94	>20:1
4	**1b**	*i*-Pr (**2a**)	0	**5d**	66-70	98-99	>20:1

[a]The presented intervals represent two runs.

With the improved reactions conditions, the generality of the procedure has been illustrated by varying both the quinone and aldehyde components (Table 1). Reactions with 1,4-naphthoquinone were performed using three different aliphatic aldehydes, all resulting in the desired products (**5a**-**c**) in good yields ranging from 50–77% over two steps and high enantio- and diastereoselectivities (93–99% and >20:1 dr). Furthermore, 2,6-dichlorobenzoquinone was reacted with 3-methylbutanal affording product **5d** in 66–70% yield, 98–99% ee and >20:1 dr.

The suggested mechanism for the direct α-arylation consists of two catalytic cycles. The stereogenic center is formed in the first cycle - the reaction of the enamine intermediate with the quinone. In the second cycle a series of proton-transfer reactions leads to the optically active α-arylated aldehyde (obtained as a hemiacetal). H_2O is suggested to be crucial for the proton-transfer reactions.[2]

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

(*S*)-2-(Diphenyl-(trimethylsilyloxy)methyl)pyrrolidine; (848821-58-9)
Benzoic acid; (65-85-0)
3-Methylbutanal; (590-86-3)
1,4-Naphthoquinone; (130-15-4)
N,*N*-Dimethylaminopyridine; (1122-58-3)
Triethylamine; (121-44-8)
Acetic anhydride; (108-24-7)

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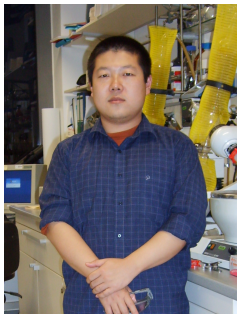
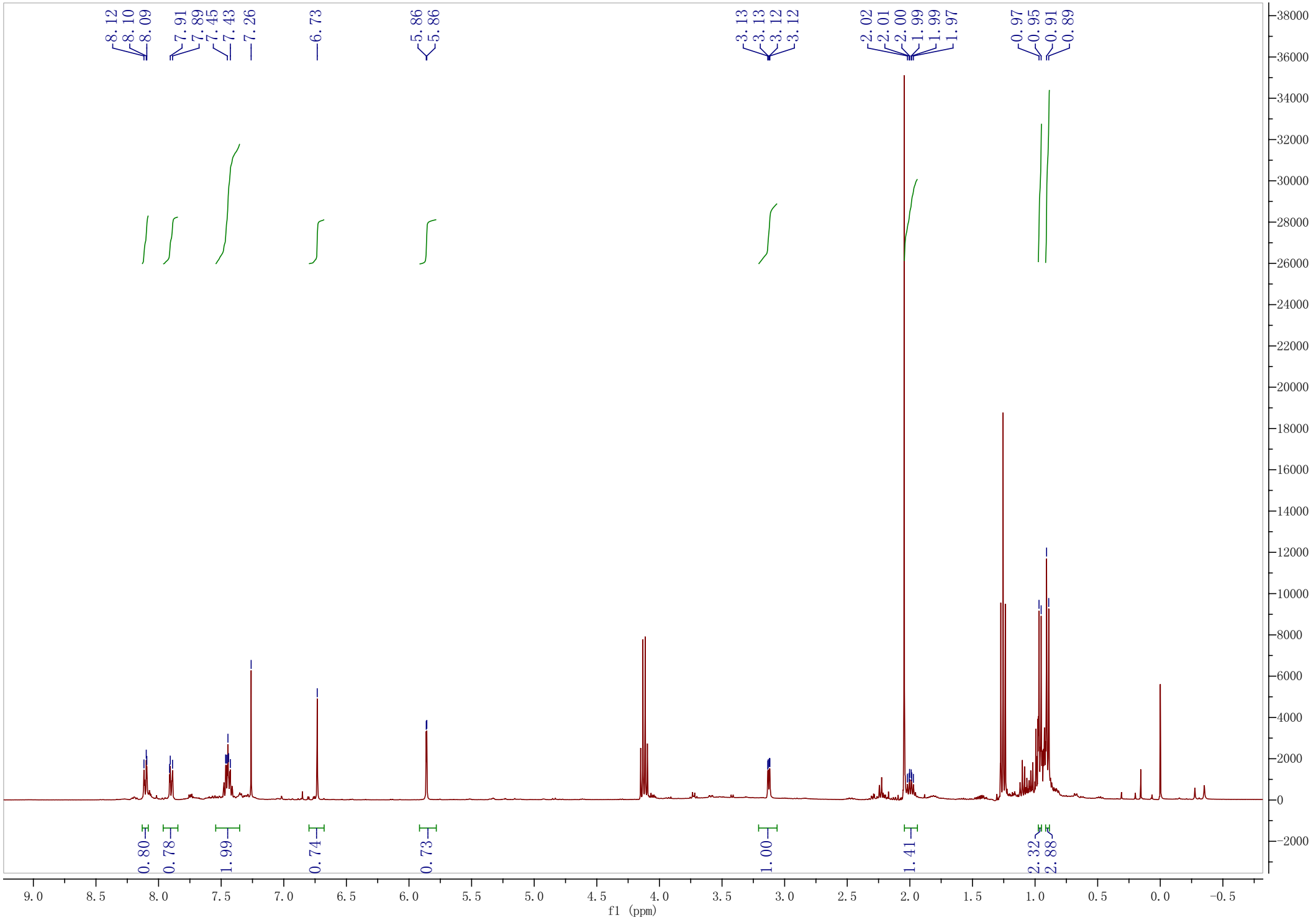
Kim L. Jensen was born in Svendborg, Denmark, in 1985. In 2012, he earned his Ph. D. with Prof. Karl Anker Jørgensen at the Center for Catalysis, Aarhus University. He is currently pursuing postdoctoral research with Prof. Timothy F. Jamison at Massachusetts Institute of Technology (MIT).

Karl Anker Jørgensen received his Ph. D. from Aarhus University in 1984. He was a post-doc. with Prof. Roald Hoffmann, Cornell University, 1985. In 1985, he became an Assistant Professor at Aarhus University and in 1992 he moved up the ranks to Professor. His research interests are the development, understanding and application of asymmetric catalysis.



Yu-Peng received his Ph. D. from Max-Planck-Institute of Molecular Physiology in Germany with Prof. Herbert Waldmann in 2010. He became an Associate Professor at Liaoning Shihua University in 2011. Currently, he is as visiting scholar with Prof. Dawei Ma in SIOC.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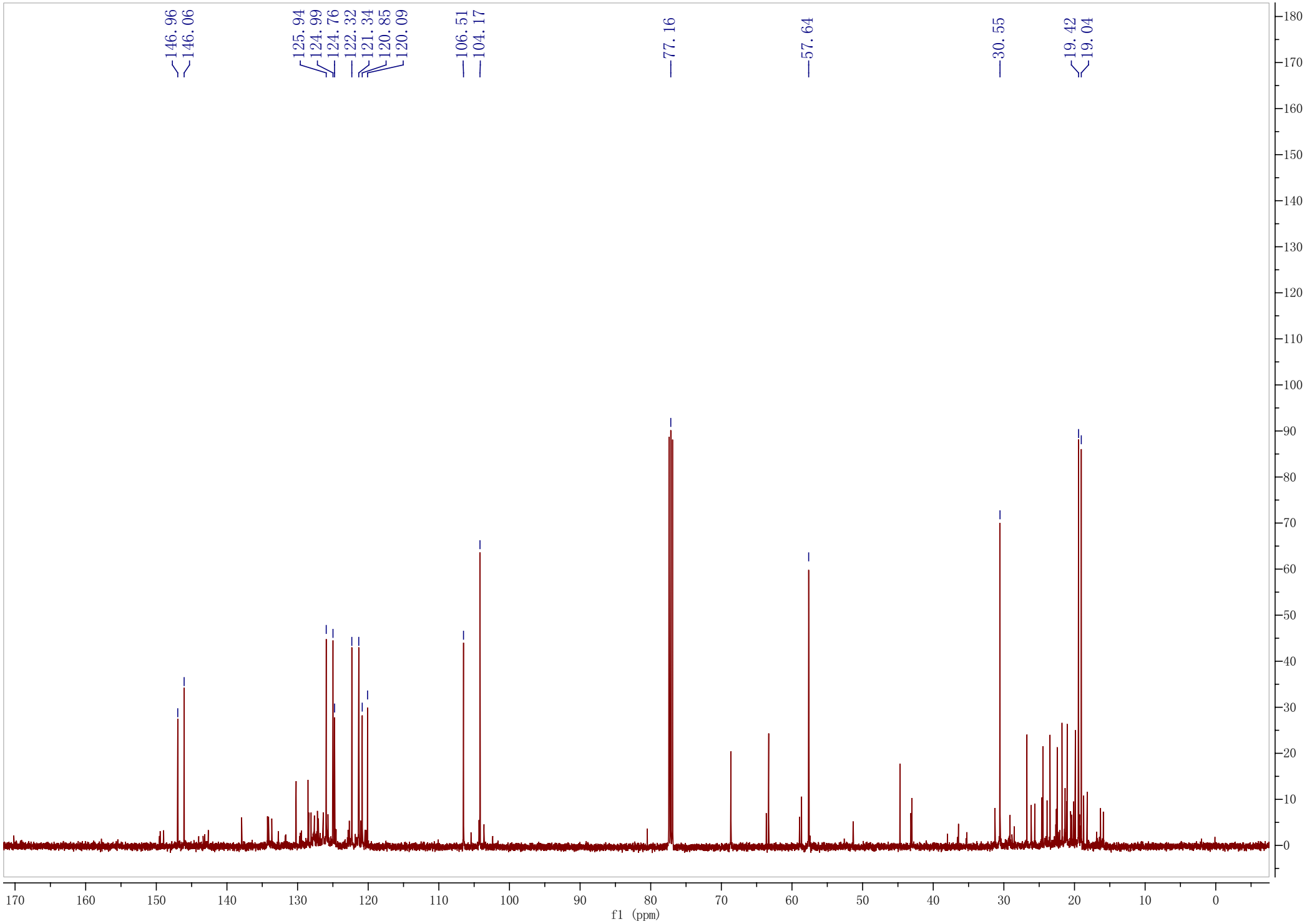
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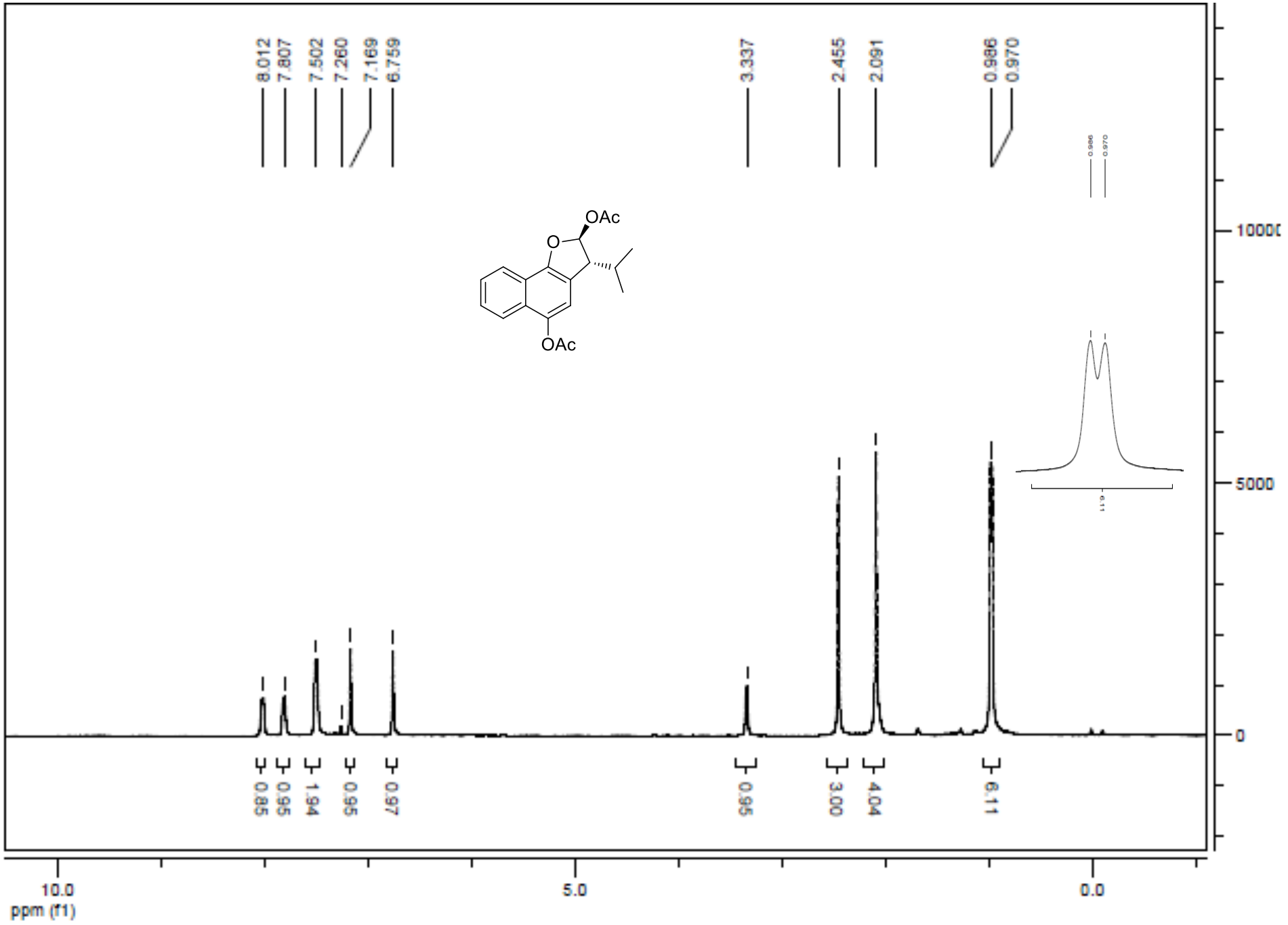
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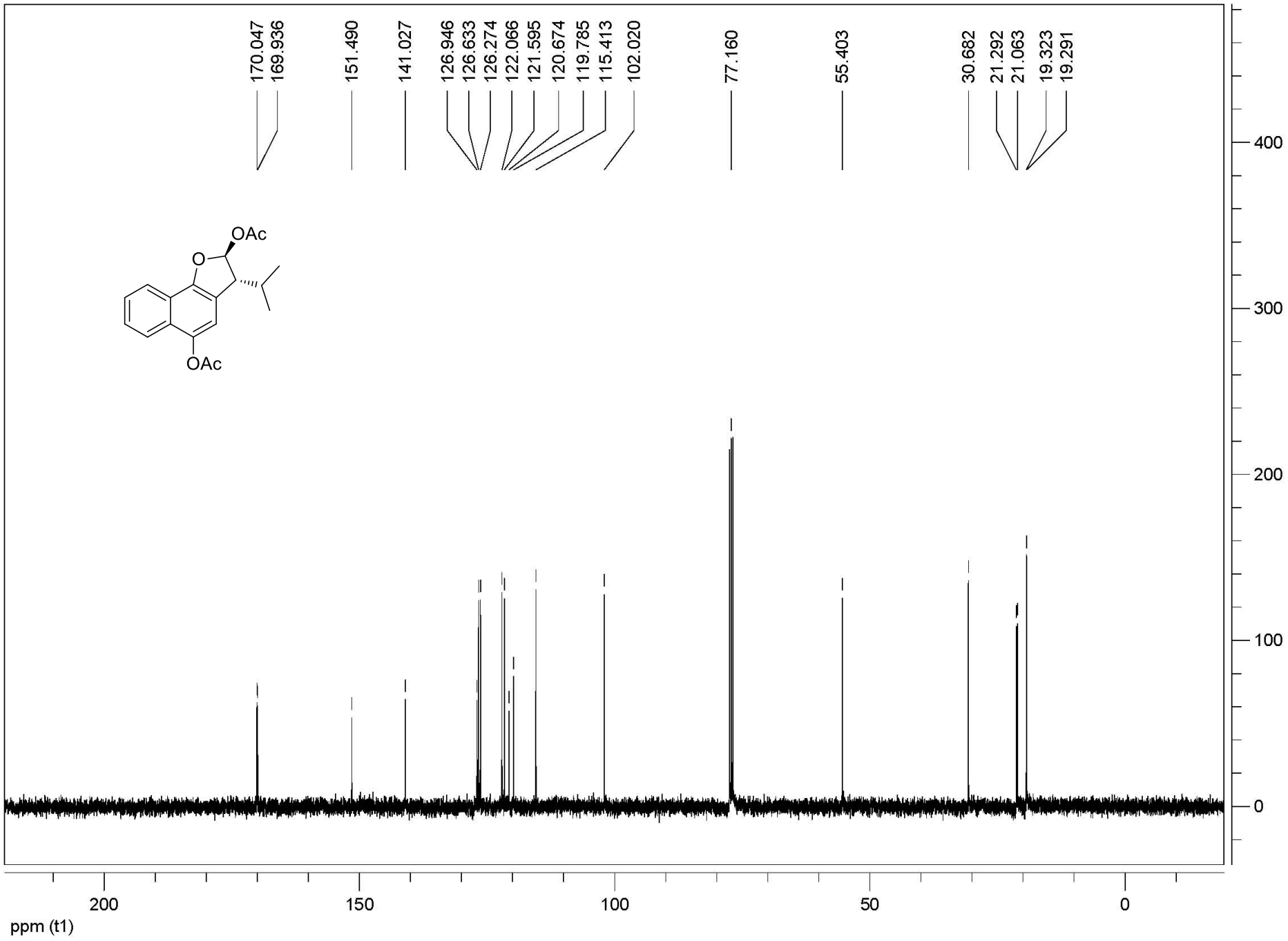
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