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Concise Total Synthesis of Curvulone B

Debendra K Mohapatra, Shivalal Banoth, Utkal M Choudhury, Kanakaraju Marumudi, A. C Kunwar.

Affiliations below.

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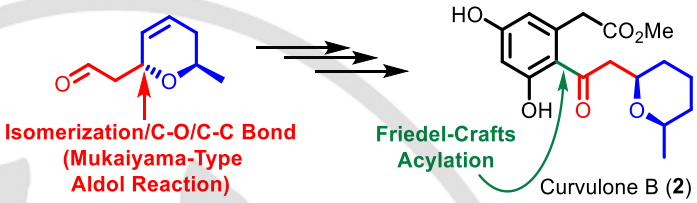
Corresponding Author:
Debendra K Mohapatra, Indian Institute of Chemical Technology CSIR, Organic Synthesis and Process Chemistry, Hyderabad, India, mohapatra@iict.res.in, dkm0077@gmail.com

Affiliations:
Debendra K Mohapatra, Indian Institute of Chemical Technology CSIR, Organic Synthesis and Process Chemistry, Hyderabad, India
Shivalal Banoth, Indian Institute of Chemical Technology CSIR, Organic Synthesis and Process Chemistry, Hyderabad, India
Utkal M Choudhury, Indian Institute of Chemical Technology CSIR, Organic Synthesis and Process Chemistry, Hyderabad, India
Kanakaraju Marumudi, Indian Institute of Chemical Technology CSIR, Centre for NMR and Structural Chemistry, Hyderabad, India
A. C Kunwar, Indian Institute of Chemical Technology CSIR, Centre for NMR and Structural Chemistry, Hyderabad, India

Concise Total Synthesis of Curvulone B

Shivalal Banoth,[a,c]
Utkal Mani Choudhury[a,c]
Kanakaraju Marumudi,[b]
Ajit C. Kunwar,[b]
Debendra K. Mohapatra*[a,c]

[a]Department of Organic Synthesis and Process Chemistry,
[b]Centre for NMR and Structural Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, INDIA.
mohapatra@iict.res.in
[c]Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201 002, INDIA.
Click here to insert a dedication.



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Abstract: A concise and convergent stereoselective synthesis of Curvulone B is described. The synthesis utilized a tandem isomerization followed by C-O and C-C bond forming reactions following Mukaiyama-type aldol conditions for the construction of the *trans*-2,6-disubstituted dihydropyran ring system as the key steps. Other important features of this synthesis are cross-metathesis, epimerization and Friedel-Crafts acylation.

Key words: Curvulone B, Mukaiyama-aldol, Friedel-Crafts acylation

Marine fungi have been long recognized as a rich source of novel secondary metabolites with biological properties such as antitumor, phytotoxic and antifungal activities, as well as cytotoxicity against human cancer cell lines.[1] In connection with the search for biologically active metabolites from fungi, Krohn and Kurtán *et al.* isolated two new curvularin-type metabolites, Curvulone A **1** and Curvulone B **2** (Figure 1) from *Curvularia sp.* obtained from the marine alga *Gracilaria folifera*.[1] Curvulone B **2** features a 2,6-disubstituted *cis*-tetrahydropyran ring and displays antitumor, antifungal, and cytotoxic activities.[2]

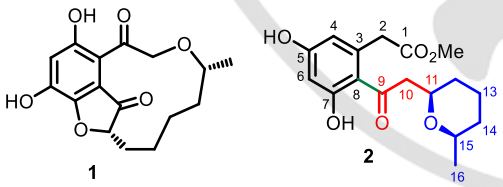
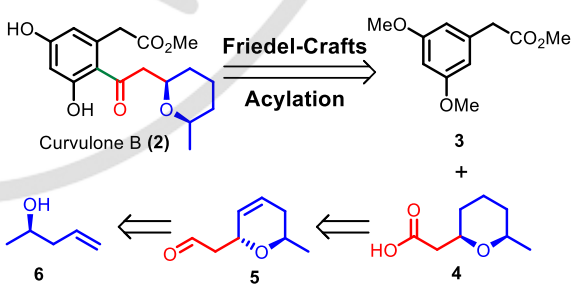


Figure 1 Structures of Curvulone A (**1**) and Curvulone B (**2**)

The structure of curvulone B was determined by 2D NMR spectroscopic and the absolute configuration was deduced by comparison of the experimental ECD spectra in acetonitrile with the Boltzman-averaged spectrum.[3] Total syntheses of curvulone B **2** have been reported by Takahashi *et al.*,[2] Bates *et al.*[4] and very recently by He *et al.*,[5] none of them involving less than a ten linear step synthesis employing an intramolecular oxa-Michael addition for the formation of THP ring. Very recently, we reported the synthesis of 2,6-*trans*-disubstituted tetrahydropyrans with a keto functionality following a Mukaiyama-type aldol reaction of 1-phenyl-1-triemthylsiloxyethylene with six membered cyclic hemiacetals in the presence of iodine.[6] To apply further the Mukaiyama-type aldol reaction and as a part of our ongoing research on the total synthesis of biologically active natural products containing pyran rings,[7] herein, we report an efficient and convergent synthesis of curvulone B in seven steps.

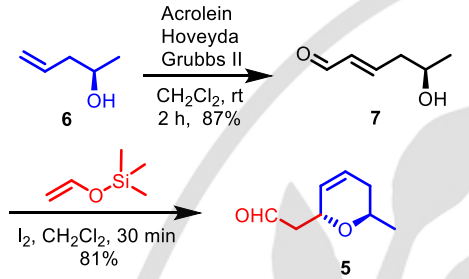
Our retrosynthetic analysis of curvulone B is outlined in Scheme 1. It was envisiged that curvulone B could be prepared via a Friedel-crafts acylation reaction between aromatic ester **3** and acid fragment **4**. Intermediate **4** was planned to be obtained from *trans*-2,6-disubstituted dihydropyran ring **5,** which in turn, could be accessible from a δ-hydroxy *α,β*-unsaturated aldehyde through tandem isomerization followed by C-O and C-C bond forming reactions of a silyl enol ether under Mukaiyama-type aldol reaction conditions. The *δ*-hydroxy *α,β*-unsaturated aldehyde would be obtained from commercially available chiral homoallyl alcohol **6** (Scheme 1).



Scheme 1 Retrosynthetic analysis of Curvulone B (**1**)

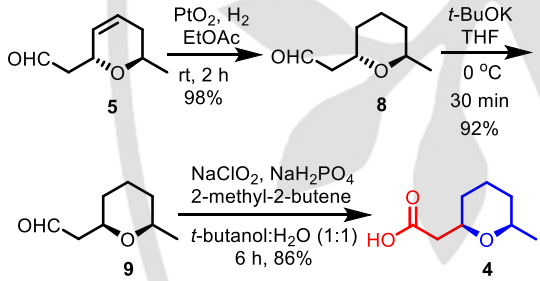
The synthesis of the key intermediate **5** began with commercially available homoallyl alcohol **6** and acrolein that, on treatment with Hoveyda-Grubbs' catalyst (10 mol%) in CH_2Cl_2,

gave cross-metathesis[8] product *δ*-hydroxy *α,β*-unsaturated aldehyde **7** in 87% yield (Scheme 2). Tandem isomerization followed by a C-O and C-C bond formation protocol under Mukaiyama-type conditions was performed by treating **7** with trimethyl(vinyloxy)silane in the presence of a catalytic amount of molecular iodine in anhydrous CH_2Cl_2 at room temperature to furnish *trans*-2,6-disubstituted-3,4-dihydro- pyran **5** as the sole product in 81% yield.[6,9,10]



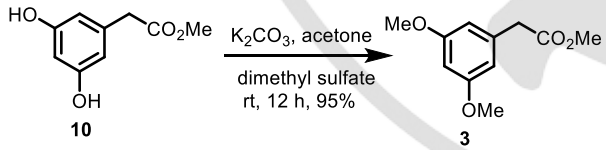
Scheme 2 Synthesis of compound **5**

The next task was to reduce the internal double bond first and then to perform the isomerization reaction. Accordingly, the double bond in compound **5** was reduced in the presence of a catalytic amount of Adam's catalyst under hydrogen in anhydrous ethyl acetate to furnish compound **8** in excellent yield. The epimerization was performed via a retro-oxa-Michael/oxa-Michael process, using potassium *tert*-butoxide in THF at 0 °C in a highly stereoselective manner, favouring the desired C-*β*-epimer **9** in 92% yield.[11]



Scheme 3 Synthesis of compound **4**

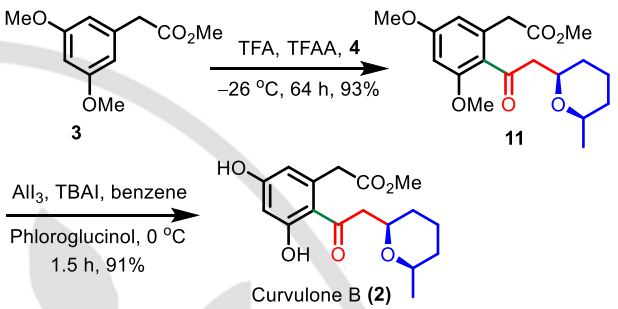
For theFriedel–Crafts acylation strategy, the key acid fragment **4** was synthesized from *cis*-pyran aldehyde **9** by Pinnick oxidation[12] using $NaClO_2$, NaH_2PO_4, *t*-BuOH:H_2O (1:1) and 2-methyl-2-butene to obtain acid **4** in 86% yield (Scheme 3).



Scheme 4 Synthesis of fragment **3**

The aromatic coupling fragment **3** was synthesized from commercially available methyl 2-(3,5-dihydroxyphenyl)acetate **10** using potassium carbonate, dimethyl sulfate in acetone to afford methyl 2-(3,5-dimethoxyphenyl)acetate (**3**) in 95% yield.[13]

Having *cis*-pyran acid **4** and methyl 2-(3,5-dimethoxyphenyl)acetate (**3**) in hand, our next objective was to combine both fragments using the key Friedel–Crafts acylation reaction. Accordingly, treatment of *cis*-pyran acid **4** with methyl 2-(3,5-dimethoxyphenyl)acetate **3** in TFA/TFAA, afforded the desired ketone **11** in 93% yield.[14]



Scheme 5 Completion of the total synthesis of Curvulone B (**2**)

The structure of compound **11** was confirmed by extensive NMR experiments including DQF-COSY, TOCSY, NOESY, HSQC and HMBC experiments. The distinctive AB spin system of double doublets at 2.97 and 3.04 ppm due to 10-H and 10-H′

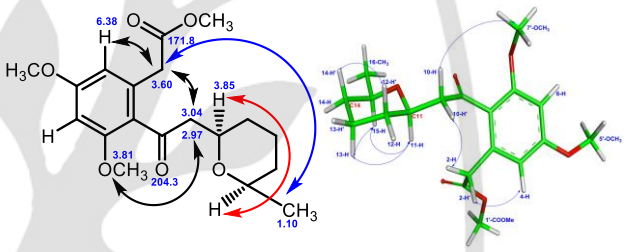


Figure 2 Energy minimized structure of **11** along with key nOe correlations (double headed arrows).

displaying HMBC correlation with the carbonyl carbon (204.3 ppm) was used to initiate the assignments. The DQF-COSY experiment helped us to assign the protons from 11-H to 15-H and the 16-CH_3 protons. The 2-CH_2 protons appear as a broad singlet at 3.60 ppm. The nOe correlations, 11-H/15-H, 11-H/13-H, 13-H/15-H, and 12-H′/14-H′ were strongly supported of the *syn* orientation of the 11-H and 15-H protons as well as $^{14}C_{11}$ chair conformation of six membered ring. Furthermore, nOe correlations between 10-H/2-CH_2, 2-CH_2/4-H and 7′-OCH_3/10-H provided strong evidence that the pyran ring occupies an *ortho*-position to methyl ester of the benzene ring, providing firm support for the proposed structure of **11** (Figure 2).

Finally, demethylation of the methoxy group of **11** was successfully achieved under Maier's conditions (AlI_3, TBAI, phloroglucinol)[15] in benzene at 0 °C to furnish curvulone B **2** in 91% yield.[16] The spectroscopic and analytical data of synthetic compound **2** were in good agreement with those reported for the natural product.[1]

In summary, a concise and stereoselective synthesis of the curvulone B **2**has been described in seven steps with 46% overall yield using iodine-catalysed tandem isomerization followed by C-O and C-C bond formation via Mukaiyama-type aldol reaction for the construction of the *trans*-2,6-disubstituted dihydropyran ring system as the key step. The other important reactions involved in the current synthetic approach are cross-metathesis, epimerization and Friedel-Crafts acylation reaction.

Acknowledgment

The authors gratefully acknowledge financial support received from the Science & Engineering Research Board (SERB), a statutory body of the Department of Science & Technology (DST), New Delhi, Government of India, through Grant No. EMR/2017/002298. We are grateful to the Director, CSIR-IICT for his kind support and providing research facilities (Manuscript communication number IICT/ Pubs/2020/106).S.B., U.M.C. and K.M. thank UGC, New Delhi, India, for financial assistance in the form of Fellowships.

Supporting Information

Yes

Primary Data

No

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(10) **Experimental procedure for Mukaiyama-type aldol reaction: Synthesis of (2*R*,6*R*)-6-allyl-2-methyl-3,6-dihydro-2*H*-pyran, 5:**
Iodine (0.89 g, 3.51 mmol) was added at 0 °C to a stirred solution of *δ*-hydroxy *α*,*β*-unsaturated aldehyde **7** (2.0 g, 17.54 mmol) and trimethyl(vinyloxy)silane (3.85 mL, 26.31 mmol) in anhydrous CH_2Cl_2 (50 mL) and the mixture allowed to come to room temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous $Na_2S_2O_3$ (30 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography, eluting with ethyl acetate/hexane = 1:5, to furnish aldehyde **5** (1.99 g, 81%) as a pale yellow liquid.
$[\alpha]_D^{20}$ = −68.0 (*c* = 0.85, $CHCl_3$); IR (neat): *ν* = 3033, 2971, 2928, 1721, 1636, 1373, 1187, 1137, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* = 9.81 (s, 1 H), 5.87 (m, 1 H), 5.70 (d, *J* = 11.7 Hz, 1 H), 4.78 (m, 1 H), 3.83 (m, 1 H), 2.76 (ddd, *J* = 16.2, 8.8, 3.0 Hz, 1 H), 2.55 (dd, *J* = 16.2, 4.7 Hz, 1 H), 2.06–1.91 (m, 2 H), 1.21 (d, *J* = 6.2 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 201.0, 127.5, 125.2, 67.6, 64.1, 47.9, 31.5, 20.6 ppm; HRMS (ESI): *m/z* calcd. for $C_8H_{12}O_2Na$ $[M + Na]^+$ 163.0728; found 163.0724.

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(16) **Experimental procedure for the synthesis of methyl-2-(3,5-dihydroxy-2-(2-((2*R*,6*R*)-6-methyl tetrahydro-2H-pyran-2-yl)acetyl)phenyl) acetate, 2:**
A suspension of aluminium powder (192 mg, 7.37 mmol) in anhydrous benzene (5 mL), was treated with iodine (0.7 g, 2.74 mmol) under argon and the violet mixture was stirred under reflux for 30 min until the mixture became colorless. The reaction mixture was then cooled to 0 °C, and TBAI (12.7 mg, 0.034 mmol) and phloroglucinol (108 mg, 0.85 mmol) were added, before a solution of **11** (60 mg, 0.17 mmol) in anhydrous benzene (2 mL) was added in one portion. The resulting green-brown suspension was stirred for 30 min at 0 °C. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL) and diluted with ethyl acetate (15 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (25 mL), filtered, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane = 1:1, to afford curvulone B **2** (50 mg, 91%) as a colorless liquid.
$[\alpha]_D^{20}$ = −18.2 (*c* = 0.2, EtOH); IR (neat): ν = 3410, 2928, 1713, 1613, 1451, 1334, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* = 9.79 (s, 1 H), 6.28 (d, *J* = 2.3 Hz, 1 H), 6.22 (d, *J* = 2.3 Hz, 1 H), 6.08 (br s, 1 H), 4.13 (brtt, *J* = 10.5, 2.3 Hz, 1 H), 3.92 (d, *J* = 16.5 Hz, 1 H), 3.70 (s, 3 H), 3.57 (m, 1 H), 3.51 (d, *J* = 16.6 Hz, 1 H), 3.30 (dd, *J* = 14.3, 10.1 Hz, 1 H), 2.56 (dd, *J* = 14.3, 3.1 Hz, 1 H), 1.85 (m, 1 H), 1.65-1.50 (m, 3 H), 1.42 (m, 1 H), 1.25 (m, 1 H), 1.17 (d, *J* = 6.2 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 204.2, 172.4, 159.4, 135.7, 120.7, 111.7, 104.0, 77.8, 74.8, 52.0, 49.0, 39.7, 32.6, 30.7, 23.1, 21.5 ppm; HRMS (ESI): m/z calcd. for $C_{17}H_{23}O_6$ [M + H]+ 323.1489; found 323.1494.

Supporting Information

Concise Total Synthesis of Curvulone B

Shivalal Banoth,[a,c] Utkal Mani Choudhury,[a,c] Kanakaraju Marumudi,[b] Ajit C. Kunwar,[b] and Debendra K. Mohapatra,*[a,c]

Experimental

General information:

Solvents for reactions were distilled prior to use: THF and toluene were distilled from Na and benzophenone: EtOH from Mg and I_2; CH_2Cl_2 from CaH_2. All air or moisture-sensitive reactions were conducted under a nitrogen or argon atmosphere in oven or flame-dried glassware with magnetic stirring. Column chromatography was carried out by using silica gel (60–120 mesh).packed in glass columns. FTIR spectra were recorded on KBr pellets, in $CHCl_3$ or neat (as mentioned) and reported in wave numbers (cm^{-1}). High resolution mass spectra were run by the electron impact mode (ESIMS, 70 eV) or by the FAB mode (*m*-nitrobenzyl alcohol matrix), using an orbitrap mass analyzer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ as solvent on a 300 MHz or 400 MHz or 500 MHz spectrometer at ambient temperature. The coupling constant *J* is given in Hz. The chemical shifts are reported in ppm on scale downfield from TMS as internal standard and The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad.

(*R*,*E*)-5-Hydroxyhex-2-enal (7): Homoallyl alcohol **6** (2.5 g, 29.0 mmol) and acrolein (4.88 g, 87.0 mmol) were dissolved in CH_2Cl_2 (10 mL) and Argon gas was purged through it for 10 min. Hoveyda-Grubbs' 2nd generation catalyst (1.23 g, 1.45 mmol) was added to it at room temperature and again degassed for further 10 min. The reaction mixture was allowed to stir for 2 h. After completion of the reaction (monitored by TLC), solvent was removed under reduced pressure and directly purified by column chromatography on silica gel (ethyl acetate/hexane = 3:7) to afford *δ*-hydroxyl *α,β*-unsaturated aldehyde **7** (2.9 g, 87%**)** as a colorless liquid. $[\alpha]_D^{20}$ −18.0 (*c* = 1.0, $CHCl_3$); IR (neat): *ν* = 3418, 2971, 2929, 1710, 1377, 1145, 1019 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* = 9.51 (d, *J* = 7.9 Hz, 1 H), 6.94 (dt, *J* = 14.6, 7.1 Hz, 1 H), 6.19 (dd, *J* = 15.7, 7.9 Hz, 1 H), 4.04 (m, 1 H), 3.24 (br s, 1 H), 2.54–2.49

(m, 2 H), 1.27 (d, J = 6.2 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.3, 155.3, 134.5, 66.2, 41.9, 23.1 ppm; ESI-MS *m/z* 115 $[M + H]^+$.

(2*R*,6*R*)-6-Allyl-2-methyl-3,6-dihydro-2*H*-pyran (5): Iodine (0.89 g, 3.51 mmol) was added at 0 °C to a stirred solution of *δ*-hydroxy *α,β*-unsaturated aldehyde **7** (2.0 g, 17.54 mmol) and trimethyl(vinyloxy)silane (3.85 mL, 26.31 mmol) in anhydrous CH_2Cl_2 (50 mL) and allowed to come to room temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous solution of $Na_2S_2O_3$ (30 mL) and extracted with CH_2Cl_2 (2 × 50 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:5) to furnish aldehyde **5** (1.99 g, 81%) as a pale yellow liquid. $[\alpha]_D^{20} = -68.0$ (*c* = 0.85, $CHCl_3$); IR (neat): *v* = 3033, 2971, 2928, 1721, 1636, 1373, 1187, 1137, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.81 (s, 1 H), 5.87 (m, 1 H), 5.70 (d, J = 11.7 Hz, 1 H), 4.78 (m, 1 H), 3.83 (m, 1 H), 2.76 (ddd, J = 16.2, 8.8, 3.0 Hz, 1 H), 2.55 (dd, J = 16.2, 4.7 Hz, 1 H), 2.06–1.91 (m, 2 H), 1.21 (d, J = 6.2 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.0, 127.5, 125.2, 67.6, 64.1, 47.9, 31.5, 20.6 ppm; HRMS (ESI): *m/z* calcd. for $C_8H_{12}O_2Na$ $[M + Na]^+$ 163.0728; found 163.0724.

2-((2*S*,6*R*)-6-Methyltetrahydro-2*H*-pyran-2-yl)acetaldehyde (8): To a stirred solution of aldehyde **5** (1.7 g, 12.14 mmol) in anhydrous EtOAc (30 mL), was added PtO_2 (0.27 g, 1.21 mmol) under Argon atmosphere and then the reaction mixture was stirred under H_2 balloon pressure. The reaction mixture was allowed to stir at room temperature until complete consumption of the starting material (as indicated by TLC). The reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude mass was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:5) to afford aldehyde **8** (1.68 g, 98%) as a colorless liquid. $[\alpha]_D^{20} = -10.0$ (*c* = 0.75, $CHCl_3$); IR (neat): *v* = 2926, 2850, 1605, 1456, 1383, 1150, 1080 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.77 (dd, J = 3.2, 1.8 Hz, 1 H), 4.39 (m, 1 H), 3.93 (m, 1 H), 2.77 (ddd, J = 15.8, 8.4, 3.0 Hz, 1 H), 2.45 (ddd, J

= 15.8, 5.0, 1.7 Hz, 1 H), 1.80–1.58 (m, 4 H), 1.43–1.28 (m, 2 H), 1.19 (d, *J* = 6.6 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.4, 67.4, 66.3, 47.4, 31.0, 29.8, 19.3, 18.1 ppm; HRMS (ESI): *m/z* calcd. for $C_8H_{15}O_2$ $[M + H]^+$ 143.1058; found 143.1063.

2-((2*R*,6*R*)-6-Methyltetrahydro-2*H*-pyran-2-yl)acetaldehyde (9): Potassium *tert*-butoxide (0.47 g, 4.22 mmol) was added to a stirred solution of compound **8** (0.6 g, 4.22 mmol) in anhydrous THF (20 mL) at 0 °C and stirred at room temperature. After completion of reaction (monitored by TLC), it was quenched by saturated aqueous solution of ammonium chloride (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:6) to obtain compound **9** (0.55 g, 92%) as a colorless liquid. $[\alpha]_D^{20}$ = +5.0 (*c* = 1.0, $CHCl_3$); IR (neat): *v* = 2923, 2852, 1605, 1456, 1379, 1149, 1080, 1042 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.80 (t, *J* = 2.1 Hz, 1 H), 3.86 (m, 1 H), 3.48 (m, 1 H), 2.60 (ddd, *J* = 16.3, 7.7, 2.5 Hz, 1 H), 2.46 (ddd, *J* = 16.0, 4.7, 1.8 Hz, 1 H), 1.83 (m, 1 H), 1.64–1.50 (m, 3 H), 1.30-1.18 (m, 2 H), 1.15 (d, *J* = 6.1 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.7, 74.0, 72.9, 50.0, 32.8, 31.1, 23.4, 22.0 ppm; HRMS (ESI): *m/z* calcd. for $C_8H_{15}O_2$ $[M + H]^+$ 143.1050; found 143.1056.

2-((2*R*,6*R*)-6-Methyltetrahydro-2*H*-pyran-2-yl)acetic acid (4): To a stirred solution of aldehyde **9** (0.2 g, 1.4 mmol) in *tert*-butyl alcohol (5 mL), 2-methyl-2-butene (1 M solution in THF, 1.4 mL, 1.4 mmol), and sodium dihydrogen phosphate (0.5 g, 4.22 mmol), sodium chlorite (0.19 g, 2.11 mmol) dissolved in water (5 mL) were added to the reaction mixture at 0 °C. The reaction mixture was stirred for 6 h at room temperature. After completion of the reaction (monitored by TLC), it was diluted with water (10 mL) and ethyl acetate (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was

purified by silica gel column chromatography (ethyl acetate/hexane = 1:2) to afford the acid **4** (0.19 g, 86%) as a colorless liquid. $[\alpha]_D^{20}$ = +14.5 (*c* = 1.0, $CHCl_3$); IR (neat): *v* = 3451, 2932, 2859, 1712, 1292, 1209, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.78 (m, 1 H), 3.52 (m, 1 H), 2.59 (dd, *J* = 15.5, 7.5 Hz, 1 H), 2.47 (dd, *J* = 15.6, 5.2 Hz, 1 H), 1.83 (m, 1 H), 1.70–1.48 (m, 3 H), 1.31–1.20 (m, 2 H), 1.18 (d, *J* = 6.2 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8, 74.3, 73.9, 41.2, 32.7, 30.7, 23.1, 21.9 ppm; HRMS (ESI): *m/z* calcd. for $C_8H_{15}O_3$ $[M + H]^+$ 159.1015; found 159.1009.

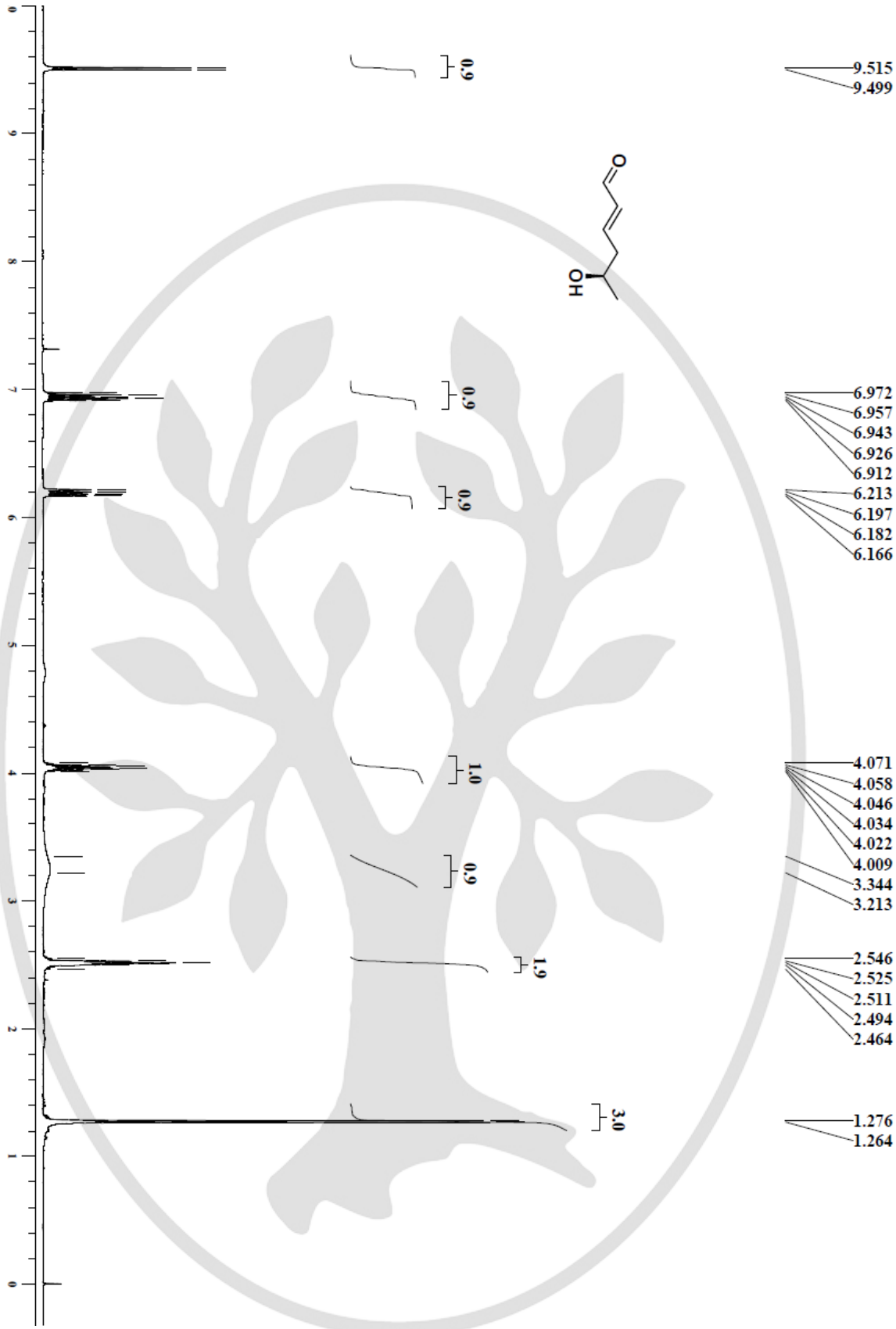
Methyl 2-(3,5-dimethoxyphenyl)acetate (3): Anhydrous potassium carbonate (0.56 g, 4.12 mmol) was added to the solution of methyl-3,5-dihydroxyphenylacetate (**10**) (0.5 g, 2.74 mmol) in acetone (15 mL) at room temperature followed by dimethyl sulphate (0.32 mL, 3.3 mmol). The solution was reflux for 12 h, cooled to room temperature and filtered. The organic layer was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:4) to afford methyl-3,5-dimethoxyphenylacetate (**3**) (0.54 g, 95%) as a pale yellow liquid. IR (neat): *v* = 3387, 2926, 1716, 1603, 1423, 1203, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.43 (d, *J* = 2.2 Hz, 2 H), 6.37 (t, *J* = 2.2 Hz, 1 H), 3.78 (s, 6 H), 3.69 (s, 3 H), 3.56 (s, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 160.7, 135.9, 107.2, 99.1, 55.2, 52.0, 41.3 ppm; HRMS (ESI): *m/z* calcd. for $C_{11}H_{14}NaO_4$ $[M + Na]^+$ 233.0784; found 233.0780.

Methyl 2-(3,5-dimethoxy-2-(2-((2*R*,6*R*)-6-methyltetrahydro-2*H*-pyran-2-yl)acetyl)phenyl)acetate (11): Trifluoroacetic acid (5 mL) and trifluoroacetic anhydride (2.5 mL) were added to methyl 2-(3,5-dimethoxyphenyl)acetate (**3**) (90 mg, 0.43 mmol) at –26 °C. Then acid **4** (0.17 g, 1.1 mmol) was added and the resulting reaction mixture was stirred for 64 h at –26 °C. After completion of the reaction (monitored by TLC), the reaction mixture was poured into ice (5 g). Saturated aqueous solution of $NaHCO_3$ (10 mL), and ethyl acetate (15 mL) were added followed by solid sodium hydrogen carbonate to neutralize. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine (30 mL), dried

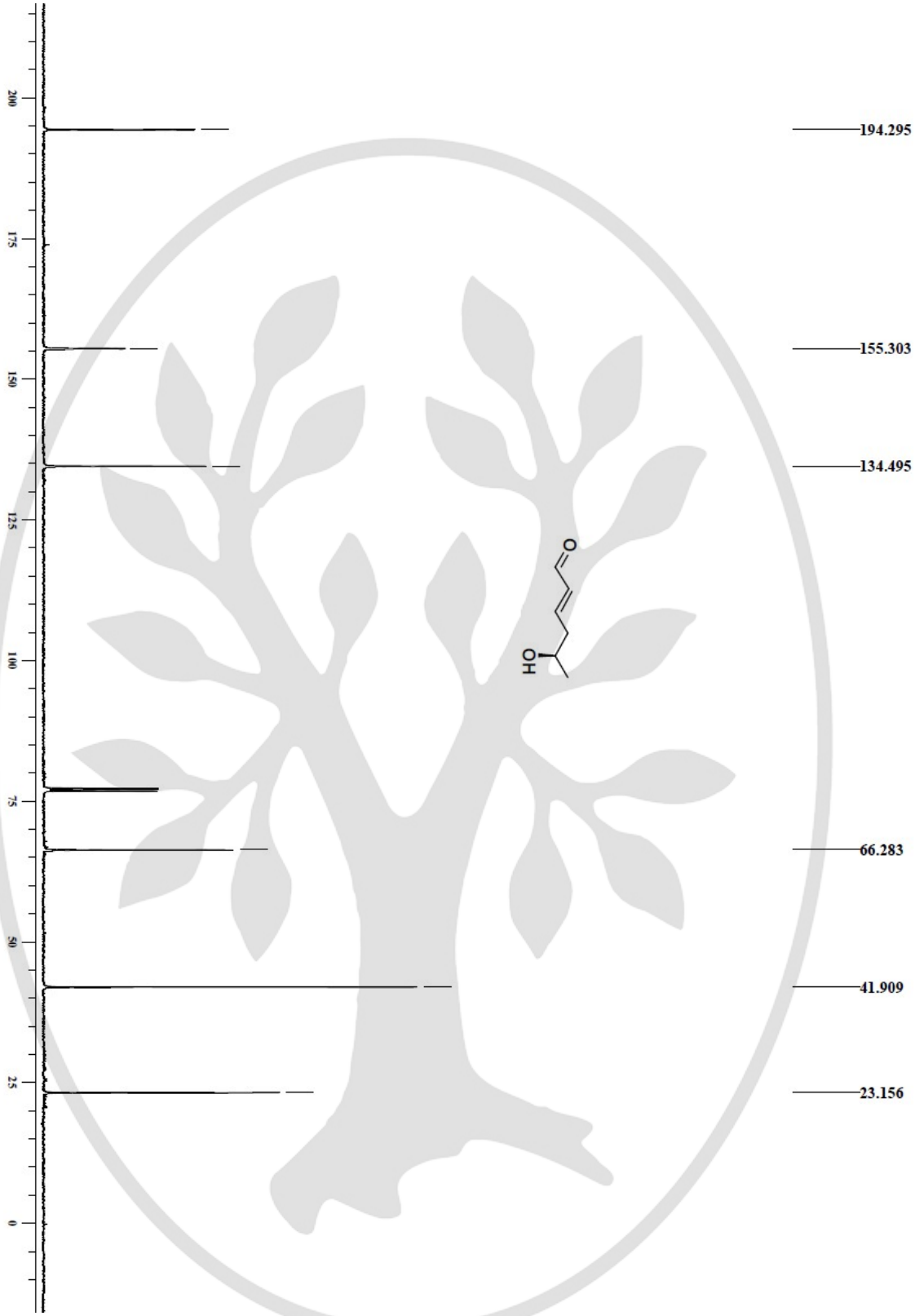
over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:4) to afford **11** (140 mg, 93%) as a colorless liquid. $[\alpha]_D^{20}$ = –5.3 (*c* = 0.28, $CHCl_3$); IR (neat): *v* = 3450, 2937, 2843, 1737, 1679, 1319, 1157 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.38 (s, 2 H), 3.87 (m, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.70 (s, 3 H), 3.61 (s, 2 H), 3.42 (m, 1 H), 3.05 (dd, *J* = 16.0, 7.0 Hz, 1 H), 2.97 (dd, *J* = 16.0, 5.9 Hz, 1 H), 1.78 (m, 1 H), 1.69-1.64 (m, 2 H), 1.57-1.49 (m, 2 H), 1.17 (dd, *J* = 10.9, 3.9 Hz, 1 H), 1.11 (d, *J* = 6.1 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.3, 171.8, 161.4, 158.8, 134.9, 123.9, 107.9, 97.3, 74.7, 73.8, 55.5, 55.3, 51.9, 51.3, 38.8, 33.0, 31.2, 23.5, 22.0 ppm; HRMS (ESI): *m/z* calcd. for $C_{19}H_{26}NaO_6$ $[M + Na]^+$ 373.1622; found 373.1606.

Methyl-2-(3,5-dihydroxy-2-(2-((2*R*,6*R*)-6-methyltetrahydro-2*H*-pyran-2-yl)acetyl)phenyl)acetate (2); A suspension of Al powder (192 mg, 7.37 mmol) in anhydrous benzene (5 mL), was treated with I_2 (0.7 g, 2.74 mmol) under Argon and the violet mixture was stirred under reflux for 30 min until the color changed to a colorless mixture. After the reaction mixture was cooled to 0 °C, a few crystal of TBAI (12.7 mg, 0.034 mmol) and phloroglucinol (108 mg, 0.85 mmol) were added before a solution of methoxy compound **11** (60 mg, 0.17 mmol) in anhydrous benzene (2 mL) was added in one portion. The resulting green-brown suspension was stirred for 30 min at 0 °C. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous solution of $Na_2S_2O_3$ (10 mL) and diluted with ethyl acetate (15 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:1) to afford Curvulone B (**2**) (50 mg, 91%) as a colorless liquid. $[\alpha]_D^{20}$ = –18.2 (*c* = 0.2, EtOH); IR (neat): *v* = 3410, 2928, 1713, 1613, 1451, 1334, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1 H), 6.28 (d, *J* = 2.3 Hz, 1 H), 6.22 (d, *J* = 2.3 Hz, 1 H), 6.08 (br s, 1 H), 4.13 (brtt, *J* = 10.5, 2.3 Hz, 1 H), 3.92 (d, *J* = 16.5 Hz, 1 H),

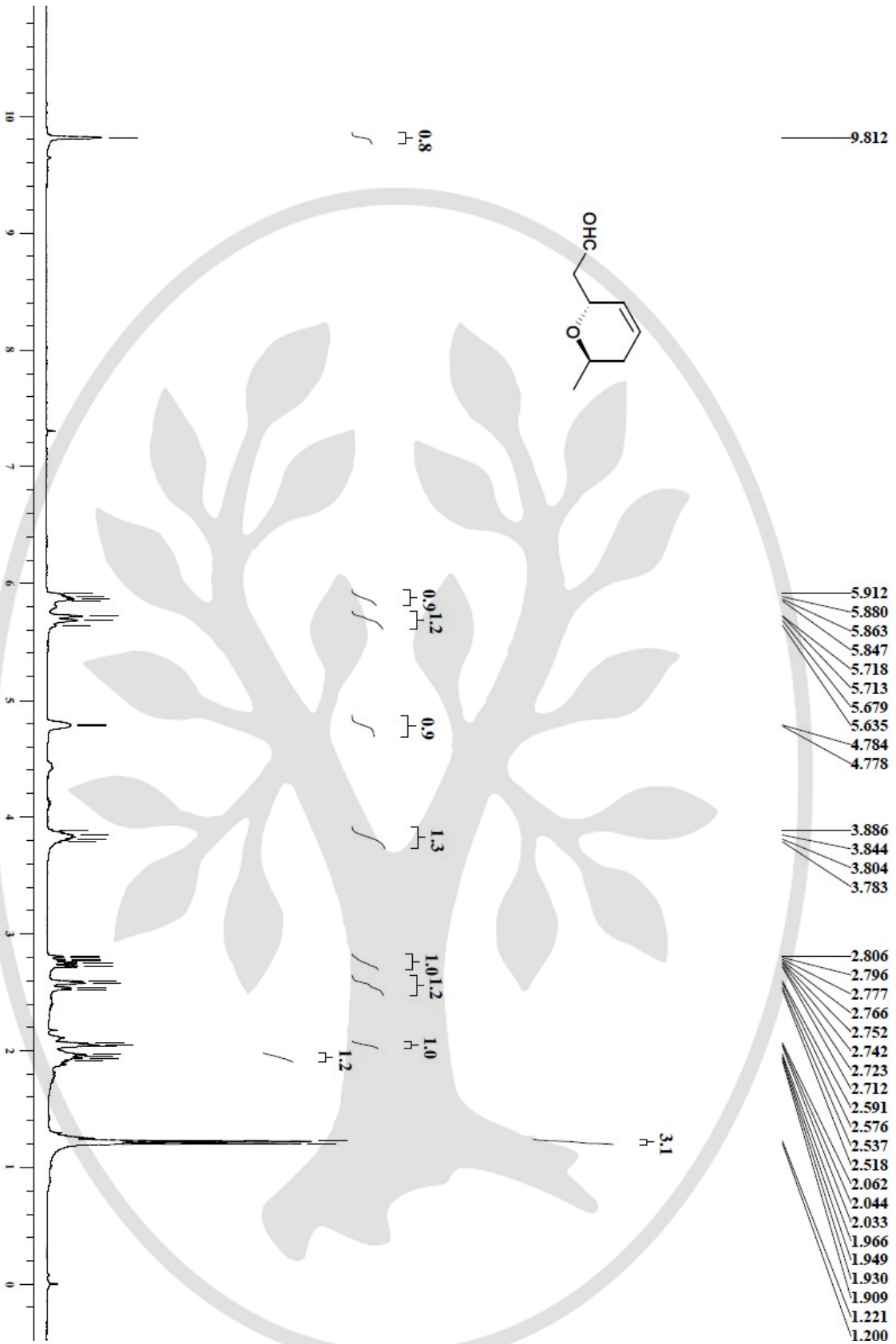
3.70 (s, 3 H), 3.57 (m, 1 H), 3.51 (d, *J* = 16.6 Hz, 1 H), 3.30 (dd, *J* = 14.3, 10.1 Hz, 1 H), 2.56 (dd, *J* = 14.3, 3.1 Hz, 1 H), 1.85 (m, 1 H), 1.65-1.50 (m, 3 H), 1.42 (m, 1 H), 1.25 (m, 1 H), 1.17 (d, *J* = 6.2 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 172.4, 159.4, 135.7, 120.7, 111.7, 104.0, 77.8, 74.8, 52.0, 49.0, 39.7, 32.6, 30.7, 23.1, 21.5 ppm; HRMS (ESI): *m/z* calcd. for $C_{17}H_{23}O_6$ $[M + H]^+$ 323.1489; found 323.1494.



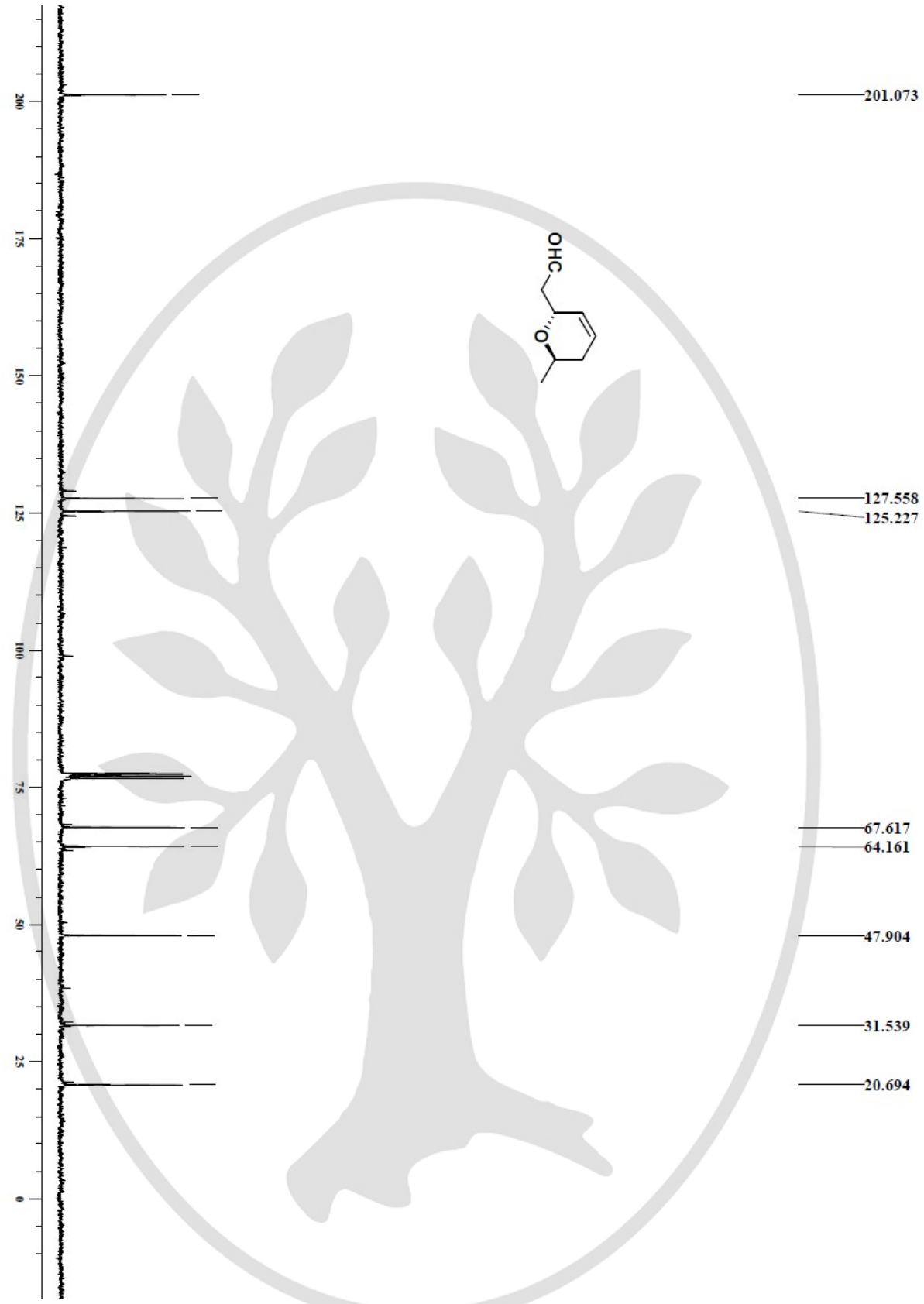
^{1}H NMR of Compound **7** (500 MHz, $CDCl_3$)



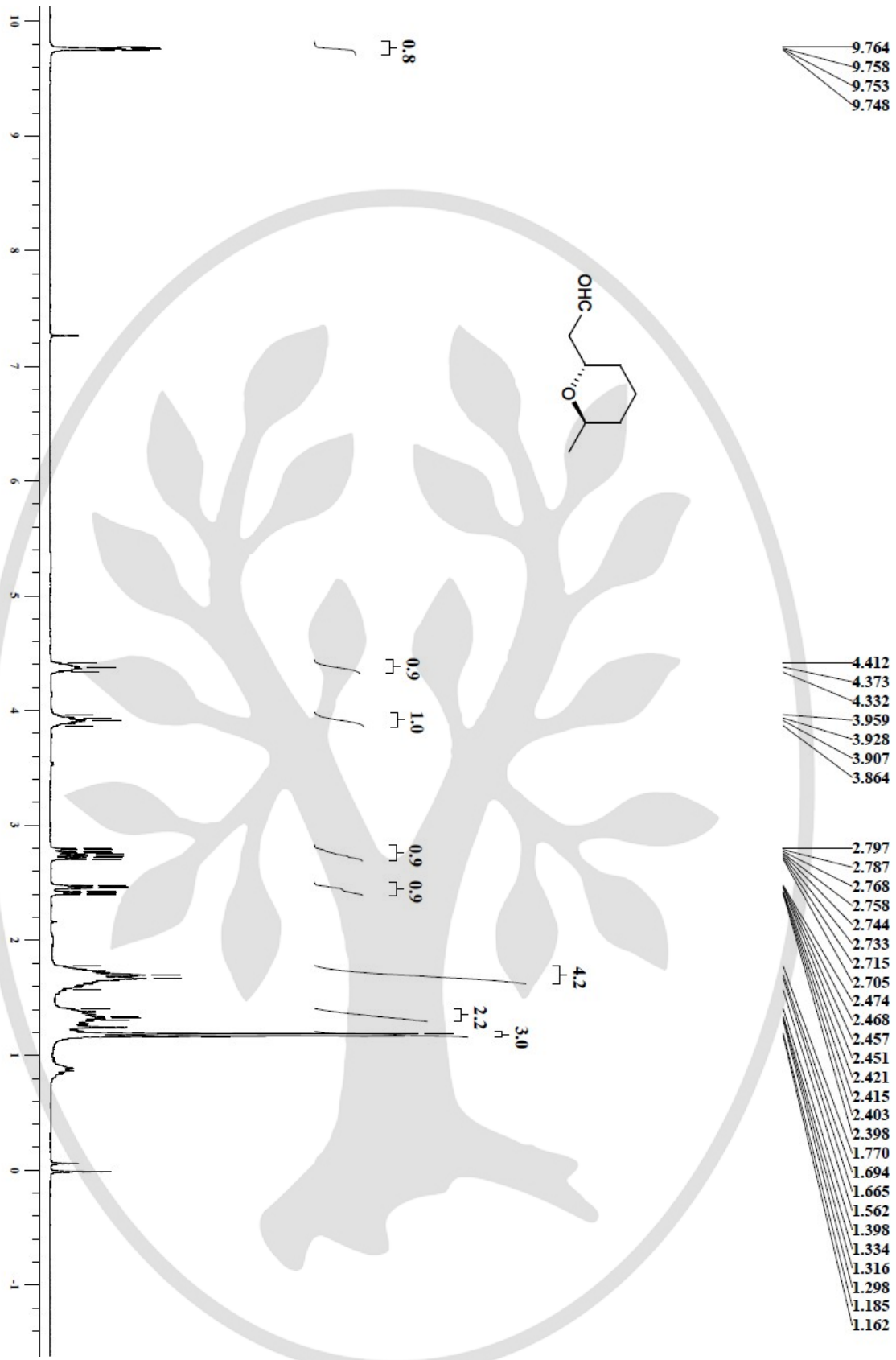
^{13}C NMR of Compound **7** (125 MHz, $CDCl_3$)



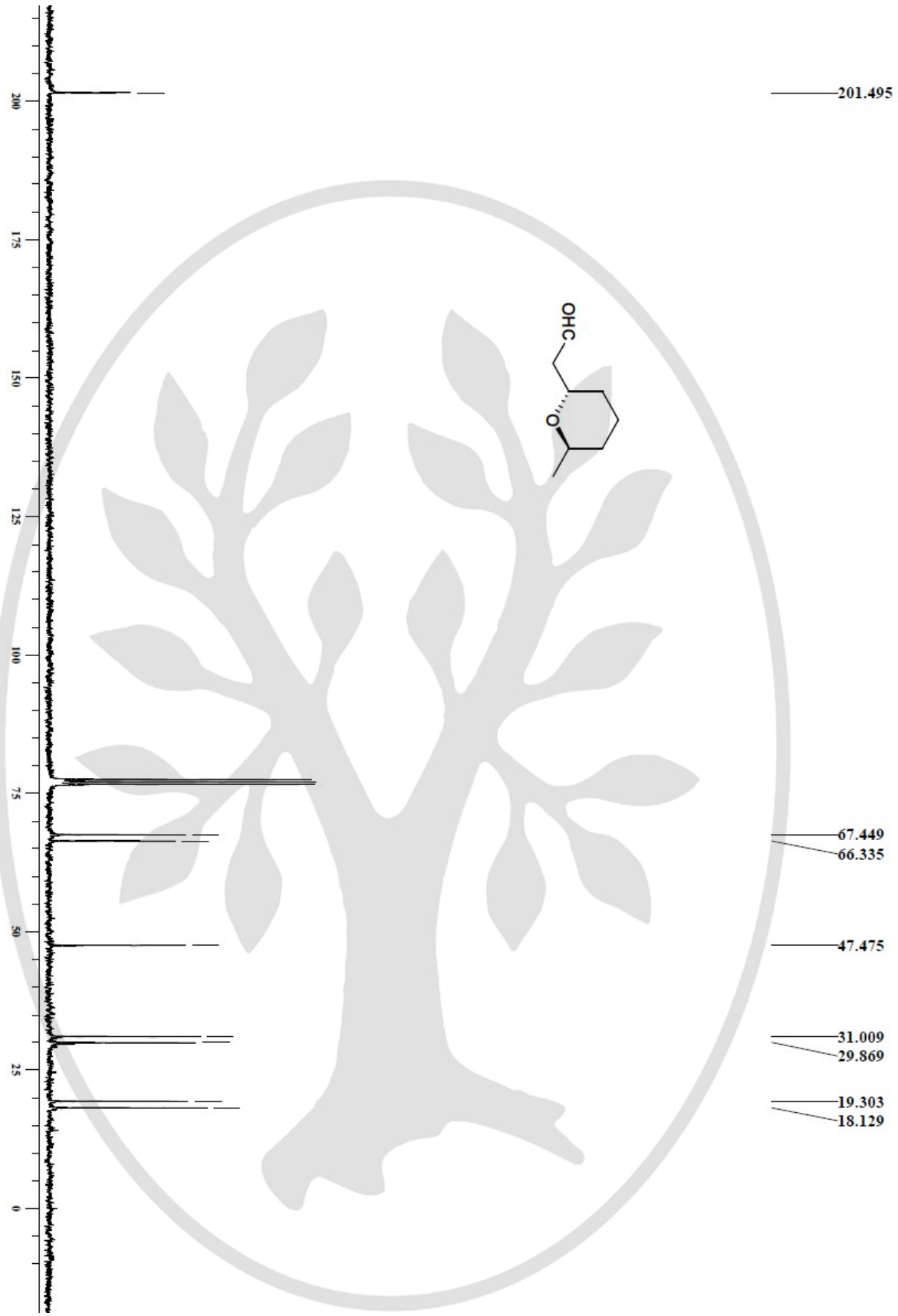
^{1}H NMR of Compound **5** (300 MHz, $CDCl_3$)



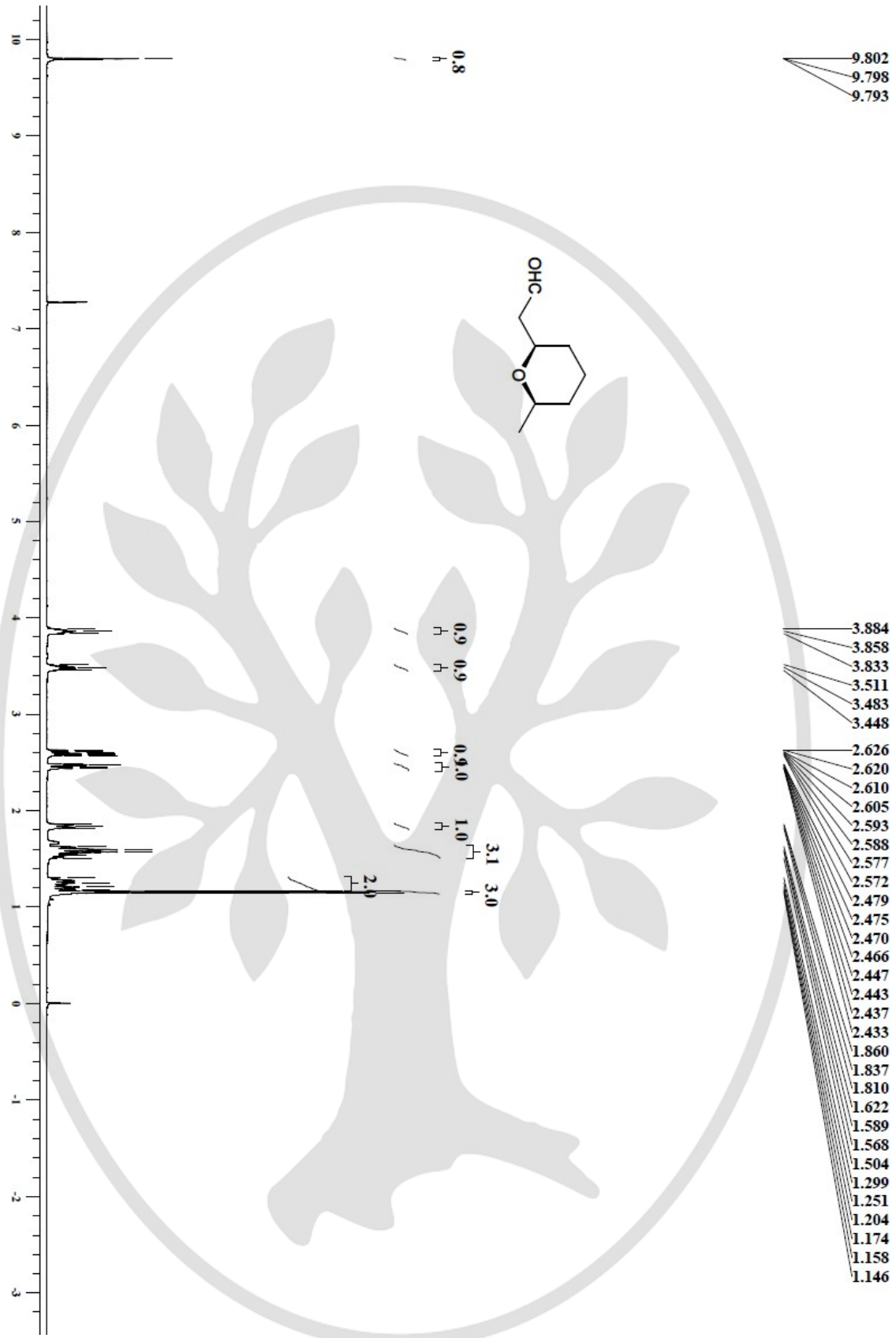
^{13}C NMR of Compound **5** (75 MHz, $CDCl_3$)



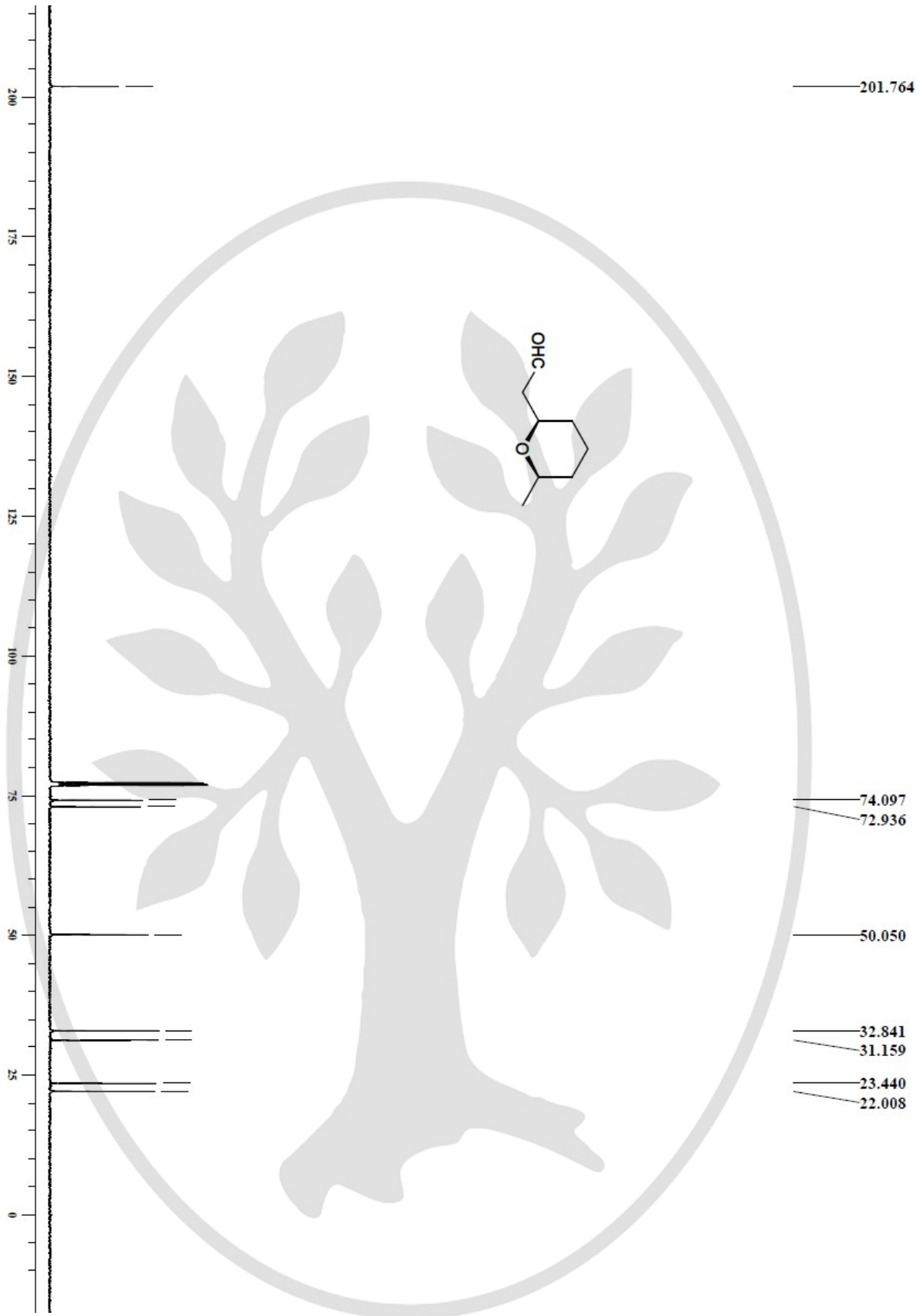
^{1}H NMR of Compound **8** (300 MHz, $CDCl_3$)



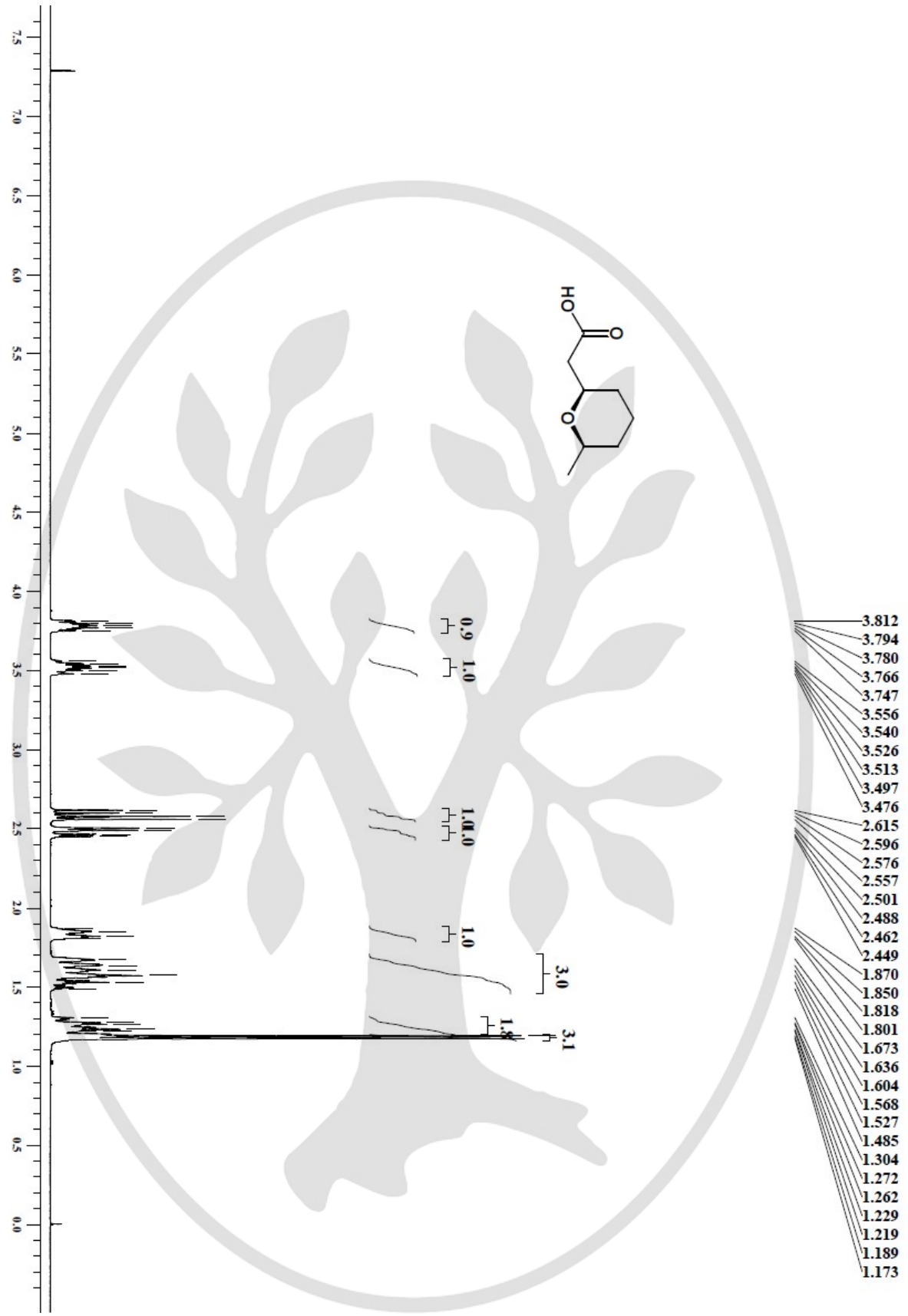
^{13}C NMR of Compound **8** (75 MHz, $CDCl_3$)



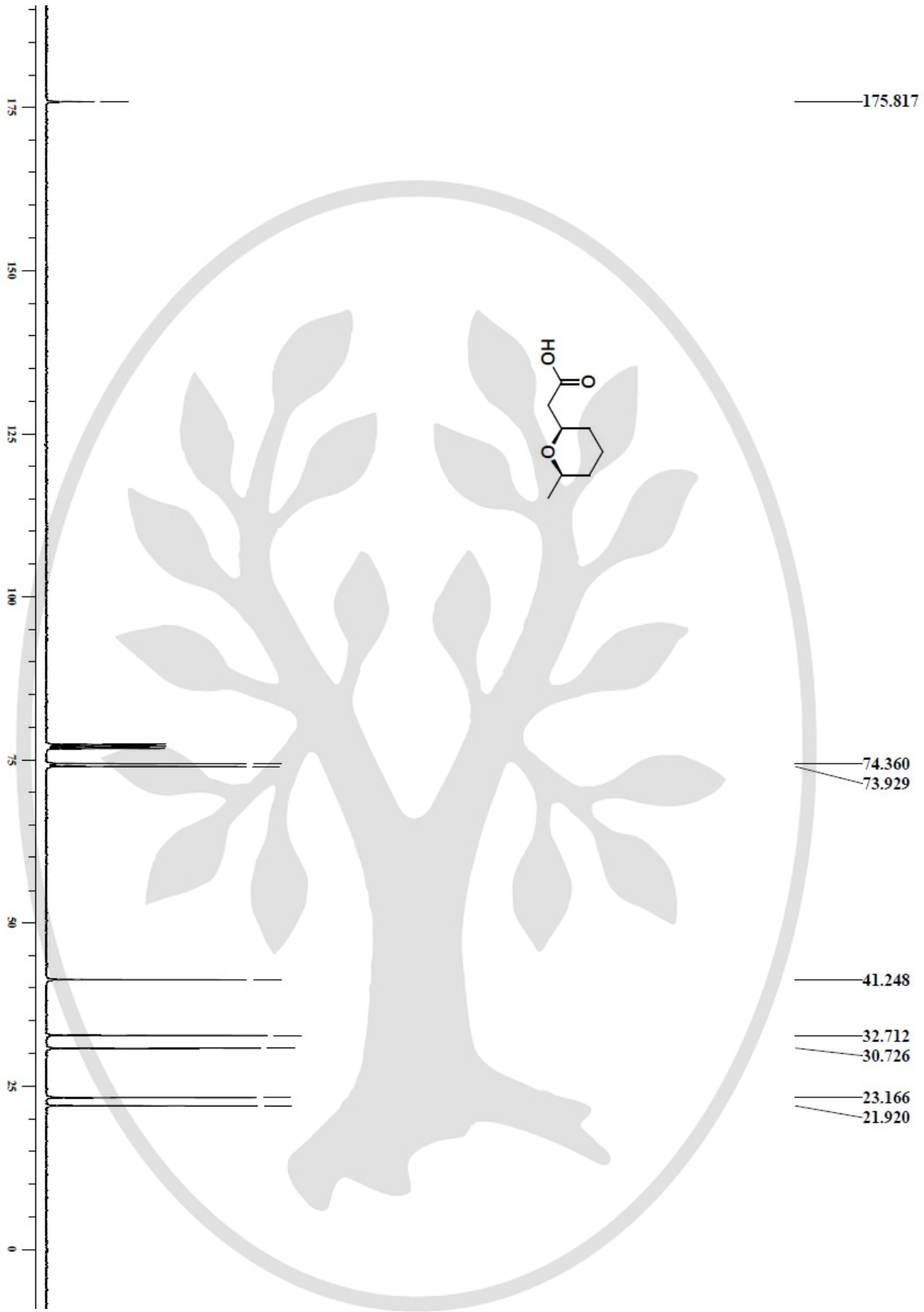
^{1}H NMR of Compound ***9*** (500 MHz, $CDCl_3$)



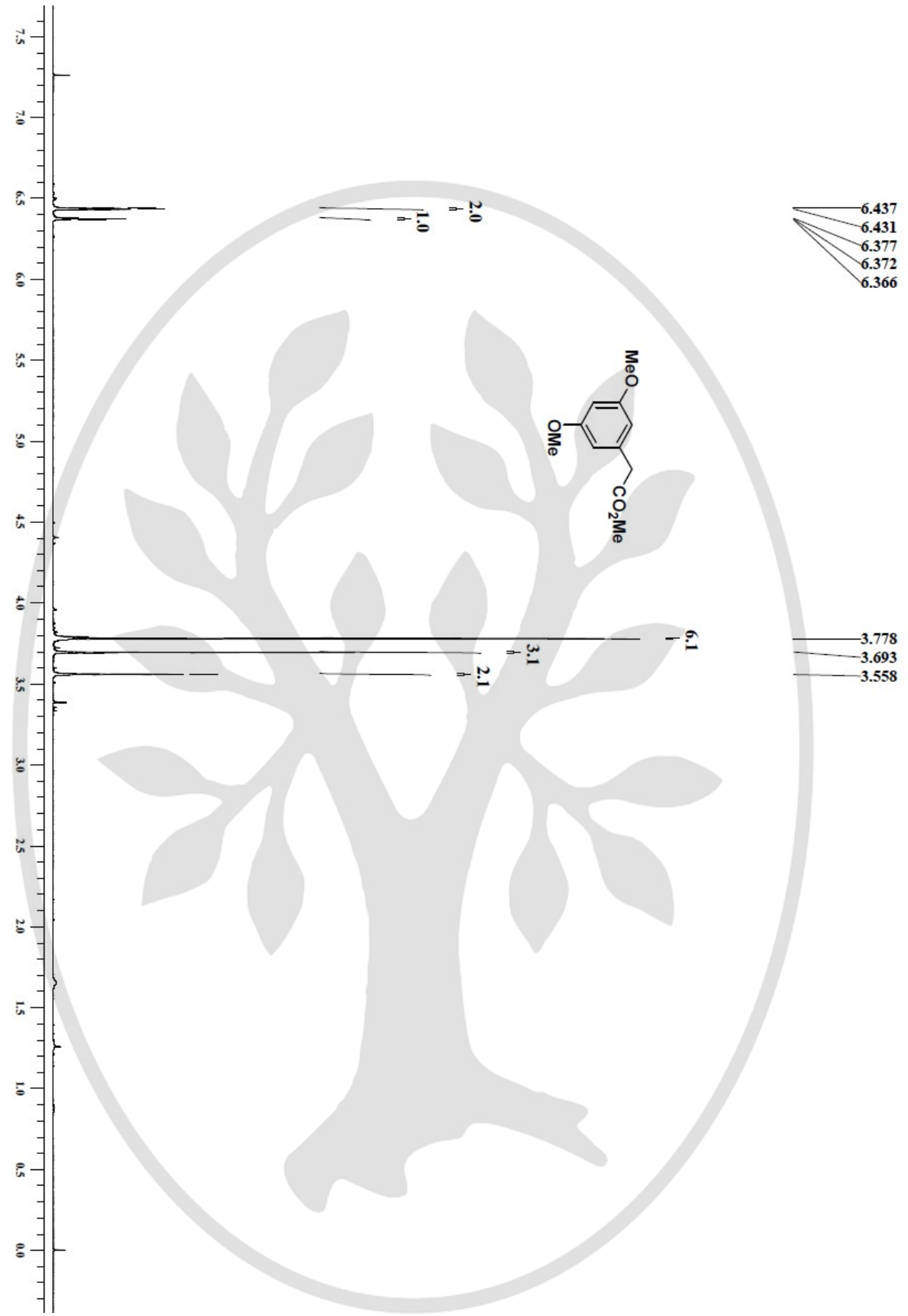
^{13}C NMR of Compound **9** (125 MHz, $CDCl_3$)



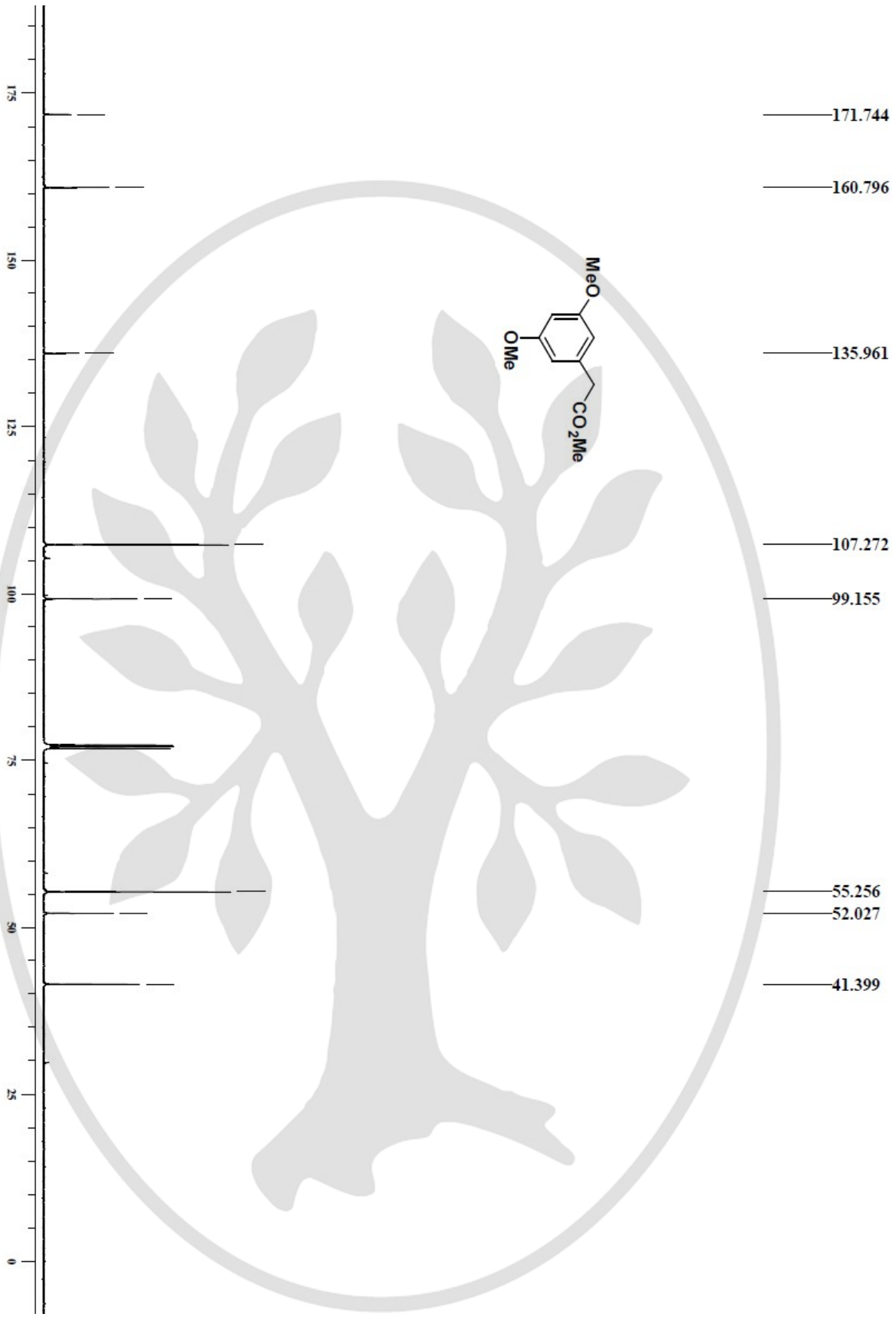
^{1}H NMR of Compound **4** (400 MHz, $CDCl_3$)



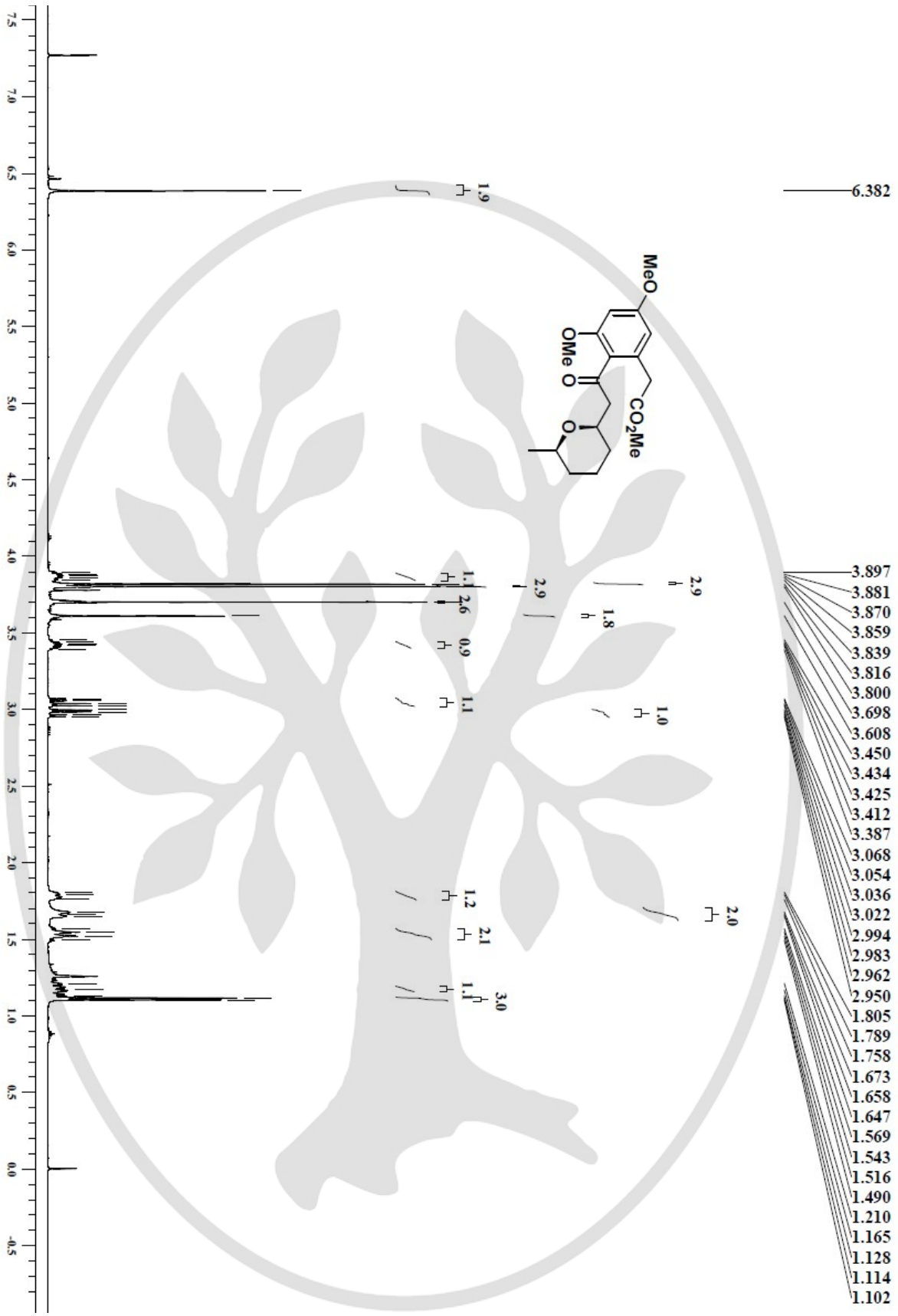
^{13}C NMR of Compound **4** (100 MHz, $CDCl_3$)



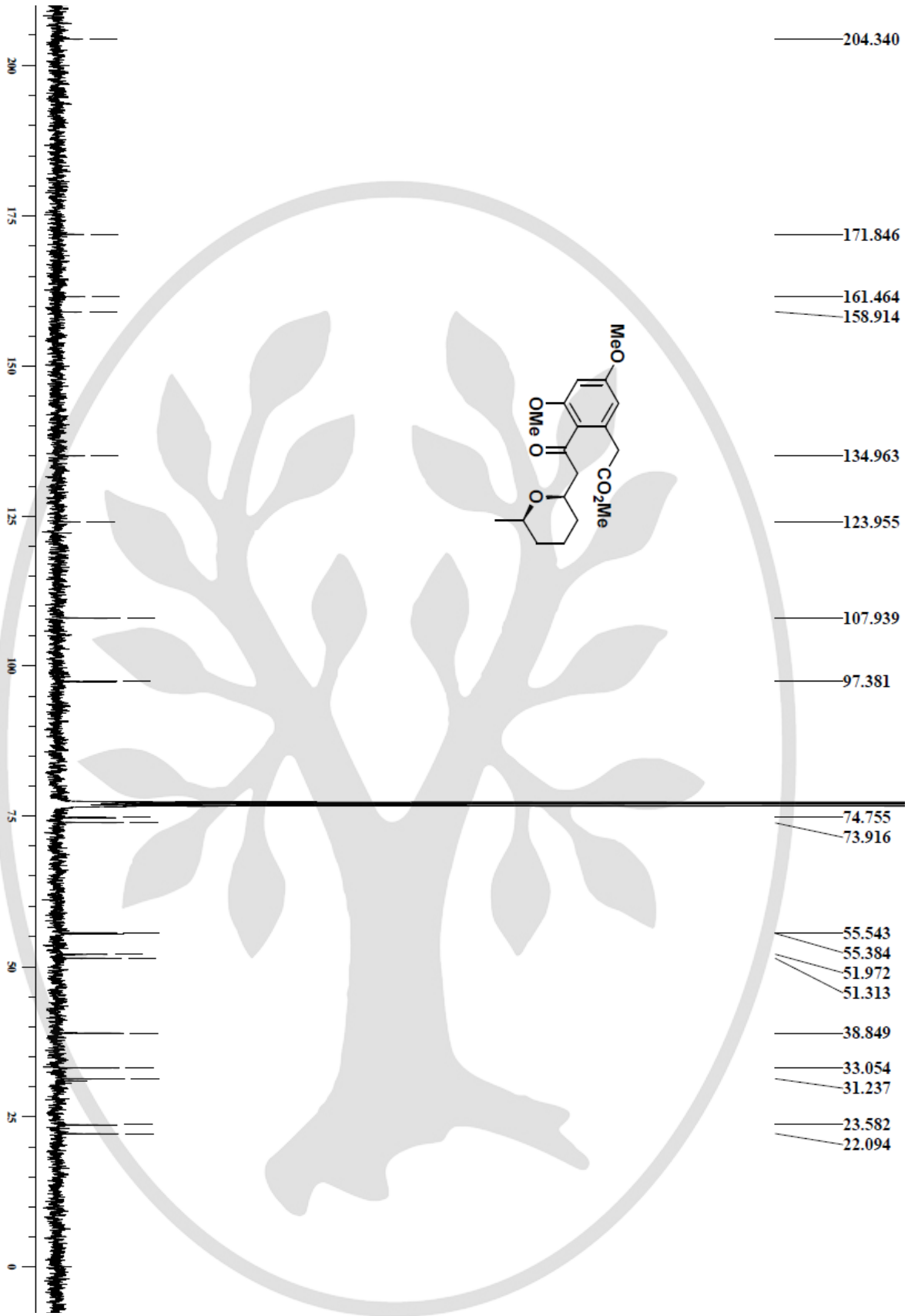
^{1}H NMR of Compound **3** (400 MHz, $CDCl_3$)



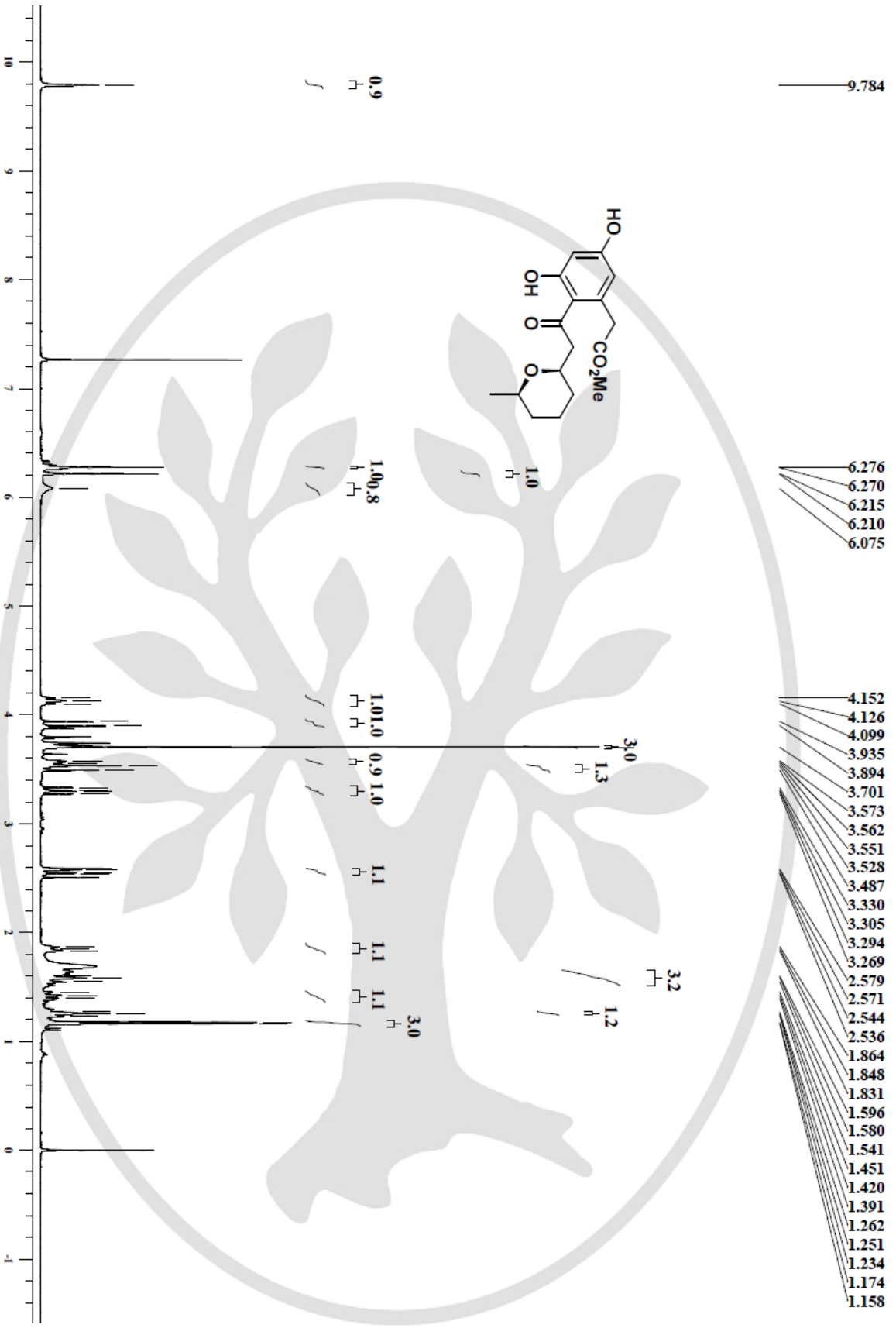
^{13}C NMR of Compound **3** (125 MHz, $CDCl_3$)



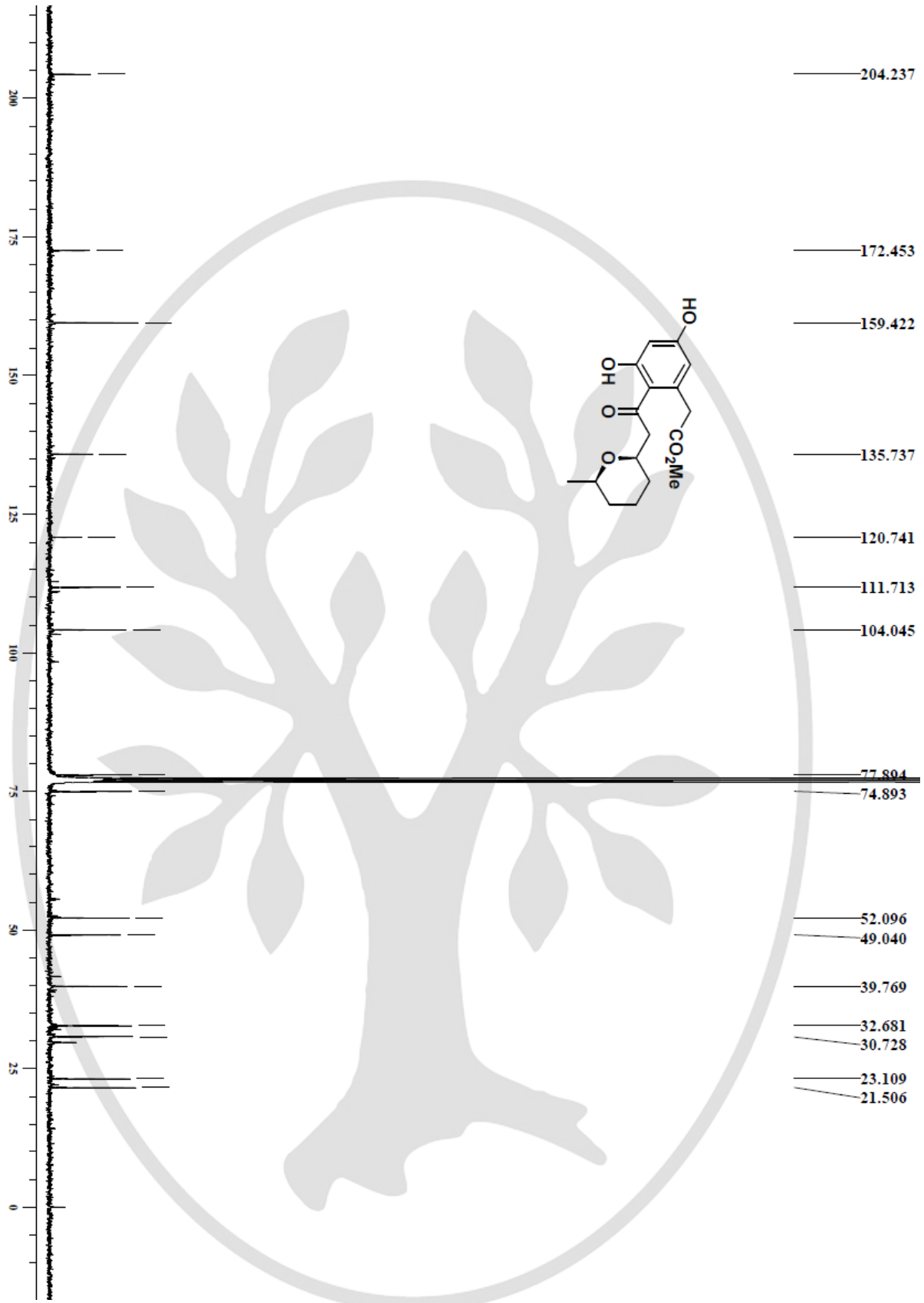
^{1}H NMR of Compound **11** (500 MHz, $CDCl_3$)



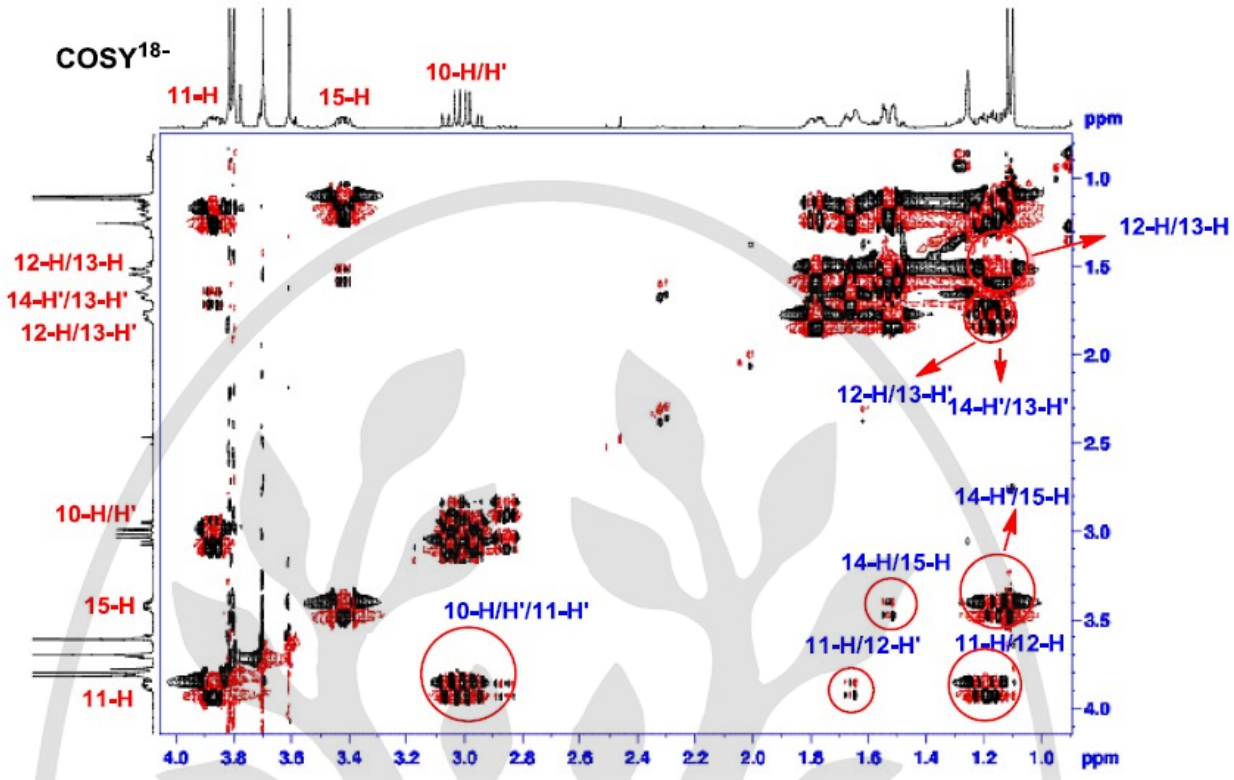
^{13}C NMR of Compound **11** (100 MHz, $CDCl_3$)



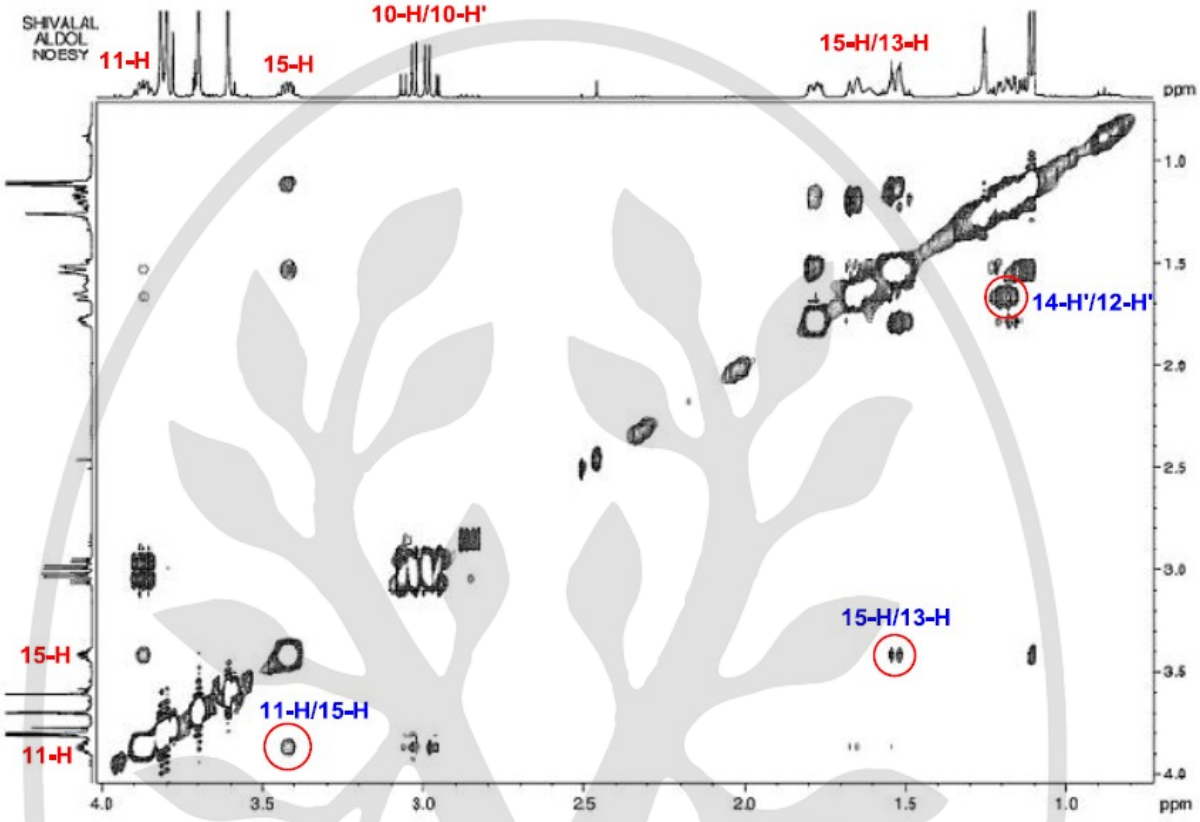
^{1}H NMR of Compound **2** (400 MHz, $CDCl_3$)



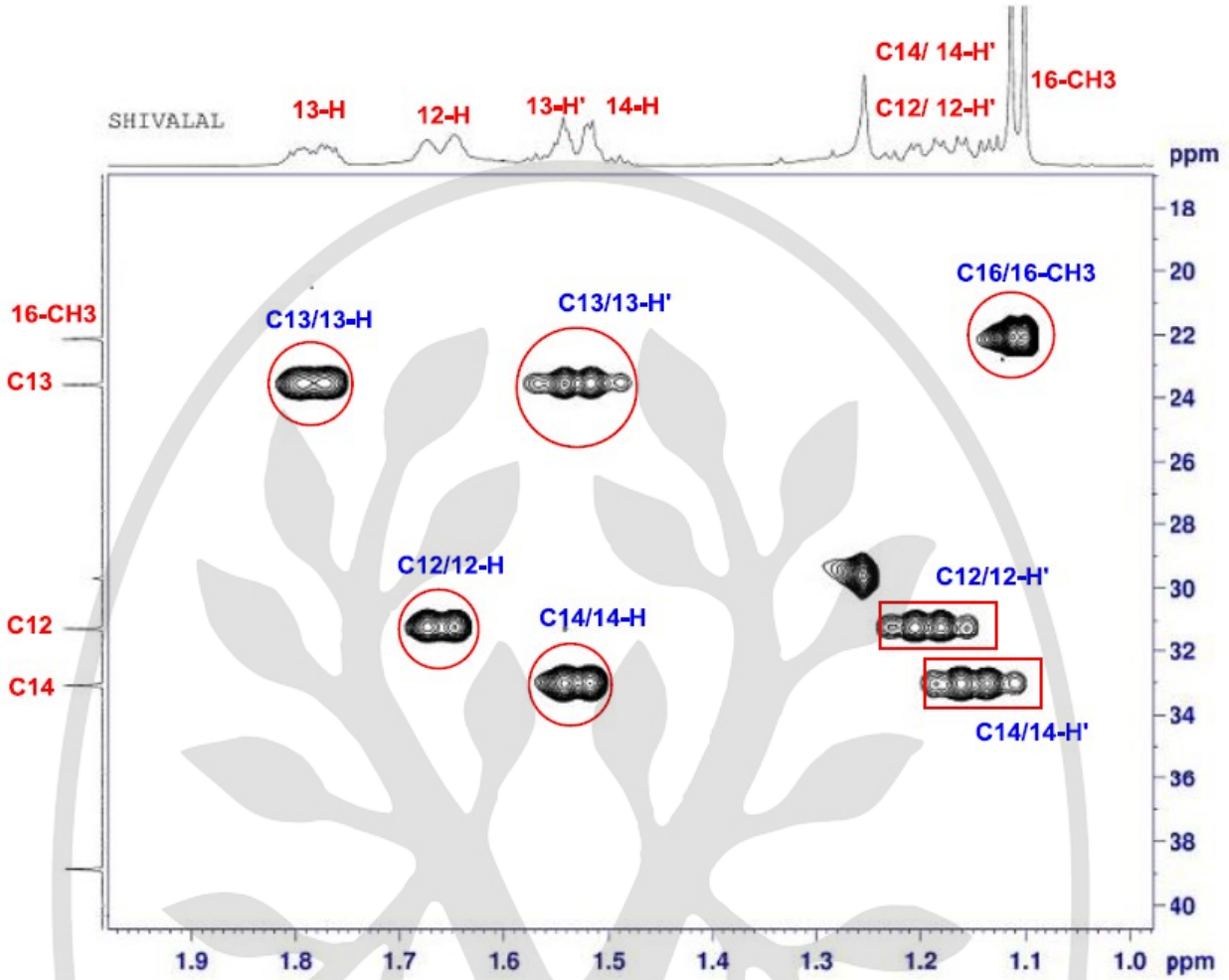
^{13}C NMR of Compound **2** (100 MHz, $CDCl_3$)



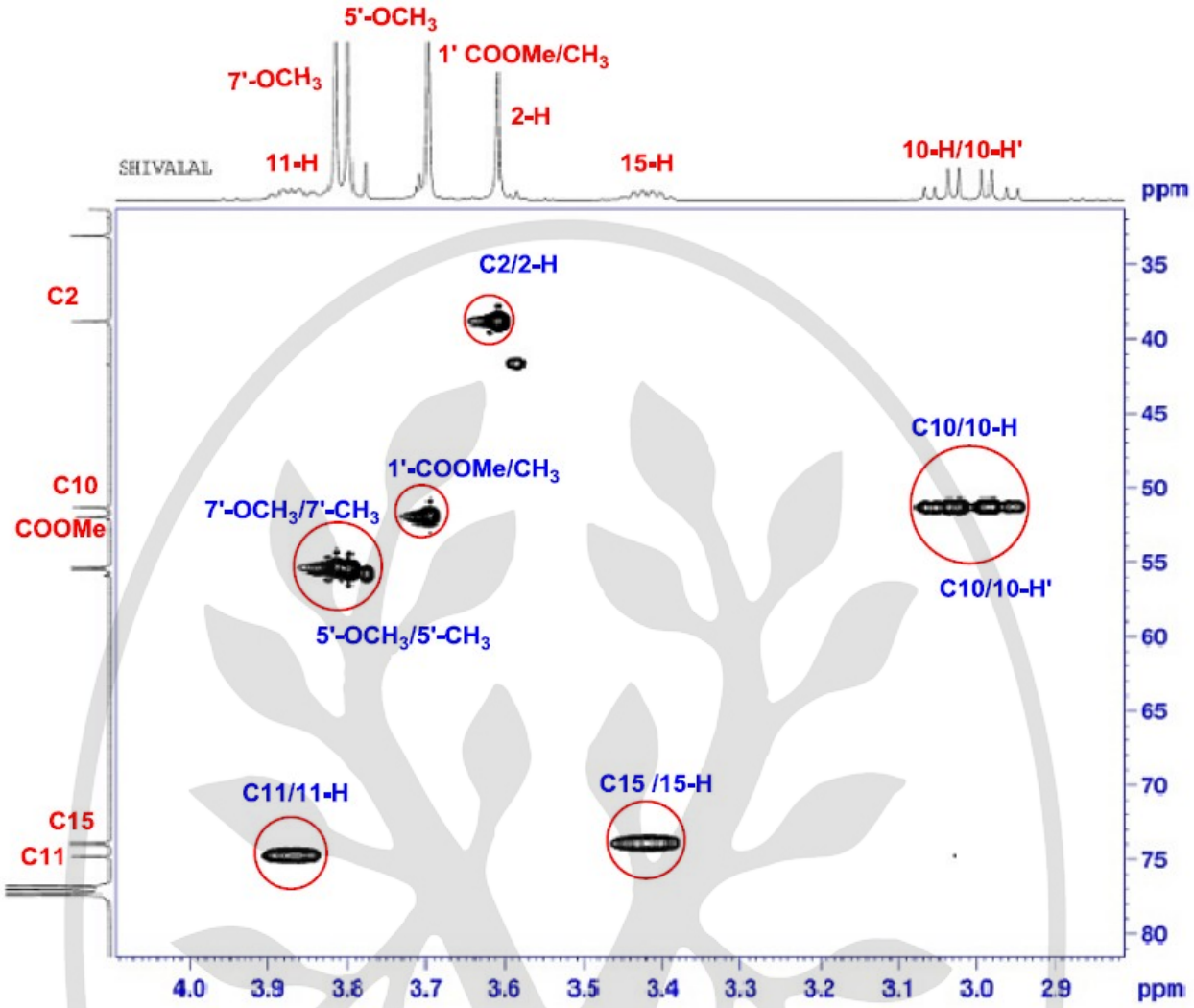
DQF-COSY Spectrum with ^{1}H-^{1}H correlation of 11 (500 MHz, $CDCl_3$, 298 K)



NOESY (Nuclear Overhauser Effect Spectroscopy) Spectrum with characteristic NOE (^{1}H-^{1}H) correlation of 11 (500 MHz, $CDCl_3$, 298 K)



HSQC (Hetero-nuclear single quantum correlation) spectrum with ^{13}C-^{1}H correlation of 11 (500 MHz, $CDCl_3$, 298 K)



HSQC (Hetero-nuclear single quantum correlation) spectrum with ^{13}C-^{1}H correlation of 11 (500 MHz, $CDCl_3$, 298 K)