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ANTI-MALARIAL ACTIVITY OF GIGANTEONE-A ISOLATED FROM FRUIT RIND OF MYRISTICA MALABARICA LAM

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ABSTRACT

M. malabarica is an evergreen belonging to family *Myristaceae* and an Indian medicinal plant used as botanical medicine to cure different types of diseases reported in traditional medicinal system, 'Ayurveda' from very antiquity. The dry fruit rinds are also used as an active ingredient for preparation of exotic spices known as 'garam masale' used in various Indian cuisine. Chemical profiling of defatted fruit rind of methanol and 20% aqueous methanol extract revealed that the presence of a diaryl nononoids a class of compounds generically known as malabaricones as major constituents along with the dimers of acyl phenol known as giganteone (dimeric form of malabaricone C). Structural characterization of these compound has been carried out by chemical, spectral and spectrometric methods by comparison with published spectroscopic data available in literature and in some cases confirmed by single crystal X ray diffraction study of crystallizable compounds where it as applicable. *In vitro* anti-malarial assay of these compounds, **1-10** has been carried out against *Plasmodium falciparum*. Experiment results revealed that a dimer of acyl phenol known as giganteone A (dimeric malabaricone C) had moderate anti-malarial activity.

KEYWORD: *M. malabarica*; fruit rinds; phenols, acyl dimer giganteone A; isolation & characterization; anti-malarial activity.

INTRODUCTION

The *Myristica* is an evergreen plant used as a folklore remedial agent to cure different kind of ailments, as botanical supplement for health care, diet supplement for health promoting purposes, as well as an active ingredient for preparation of exotic spices in various Indian cuisine.[1] *Myristica* is one of the twenty-one genera of *Myristicacae* family and includes ten accepted species.[2] Amongst, the most of them grow in the Eastern and Western Mountains of South India.[2, 3] Some of the species are also available in some part of Himalayan region.[4] The fruit rind, mace, and seeds are used as major constituents in exotic spices, condiment, and an active ingredient for formulation in herbal medicine in 'Ayurved' from immemorable time. *M. fragrans* (locally known as Jayatri) and *M malabarica* (in local dialect called as Rampatri) is the source of both nutmeg and mace.[5] Both of them are used as herbal medicine and as an active ingredient for formulation of exotic spice.[2] Earlier phytochemical investigation of *M. malabarica* rind revealed that major active ingredients are diaryl nonanoids generically known as malabaricaone A-D[6,7] while other species of *Myristica* have metabolized other class of secondary metabolites such as lignans,[8,9] resorcinol,[10] neolignans,[11-13] and isoflavonoids.[14] In an extensive study, looking for bioactive secondary metabolites from *Myristica malabarica*, a more polar extract of the rind was detailed investigated and yielded a dimer of acyl phenol known as giganteone A (**10**), which is a dimer of malabaricone C along with other substituted acyl phenols **1-9**. The structure of the known compounds was identified by comparing with their ^{1}H NMR, ^{13}C NMR, 2D NMR and HRESI-MS data published in literature.[6,7] Herein we report the isolation, structural characterization of known compounds along with giganteone A from *Myristica malabarica* reported first time. The anti-malarial activity of these compounds (**1-10**) against the parasite *Plasmodium falciparum* is reported herein.

On literature survey, it has been revealed that all plants of *Myristica* species did not biosynthesised malabaricones, as major secondary metabolites although they are belonging in same family (*Myristacae*). It has also reported in literature that some of the species of the *Myristica* plants such as *Myristica alba*,[15] *Myristica andamania*,[16] *Myristica argentea*,[8, 17] *Myristica maxima*,[18] *Myristica astrescens*,[19] *Myristica basilanica*,[17, 19] *Myristica brachipoda*,[19, 20] *Myristica brevistipes*,[20] *Myristica swamps*,[18] *Myristica fragrans*,[19-32] *Myristica maingayi*,[33] *Myristica dactyoides*,[34-35] *Myristica beddomei*,[23] *Myristica fatua*,[36-38] *Myristica magniflica*,[19,39] *Myristica phillipensis* [10, 39] *etc.* did not biosynthesised malabaricones. But malabaricone C and its dimer known as giganteone A has been reported from *M. cinnamomea*,[40-44] *Myristica gigantea*,[45] *Myristica mqaingayi*.[29] We are able to trace same secondary metabolites from *Myristica malabarica*, an evergreen tree grown in Western Ghats Mountains located along the coastal area of Arabian Sea (also known as Malabar Sea Shore). The presence of giganteone A, a dimer of acyl phenol has been reported first time from the fruit rinds of *Myristica malabarica* and its anti-malarial activity has been tested. The main credential of this medicinal plants is that the majority of Asian population relies on these plants for their primary healthcare and health promoting purposes.[46-49]

RESULTS AND DISCUSSION

Myristica malabarica is a very popular herbal spice plant, widely distributed all over India especially in Eastern and Western Ghats Mountains.[2,3] The significance of herbal spice plant has been justified as it used as a composite for botanical medicine and also use as active ingredient for preparation of exotic spices.[1] It is evergreen tree and belongs to *Myristaceae* family. It has been recognised for its ethnomedicinal uses due to its medicinal values against various kind of aliments and as an active ingredient for formulation of exotic spices in Indian cuisine.[1,3-5] In local dialect, it is also known as 'Masale phool' and used in spice due to the presence of its pleasant aroma. Dry fruit rind was used for extraction to investigate its chemical constituents. Initially, it was defatted with hexane followed by extraction with methanol at room temperature in thrice. The solvent was removed to obtain a dark brown residue. This crude residue was fractionated by column chromatography over silica gel with gradient solvent elution by using a binary mixture of n-hexane-ethyl acetate followed by methanol-chloroform to yield several fractions. Each and every fraction monitored by TLC. Fraction with similar TLC profiles were combined and, in some cases, further purified by column chromatography over silica gel, by gel permeation chromatography (GPC), by high performance liquid chromatography (HPLC) and preparative thin layer chromatography (PTLC) followed by crystallization to afford respective products. The UV absorption of these compounds very closely resembled with absorptions at 243 and 268 nm indicating presence of similar type of chromophore. Spraying with neutral $FeCl_3$ solution (in ethanol) on TLC plates showed dark green spots suggesting that these compounds bearing a phenolic hydroxyl group adjacent to an acyl carbonyl group.[50] These compounds also displayed bathochromic shift in UV spectrum of about 35-40 nm upon the addition of anhydrous $AlCl_3$ due to formation six membered complex which is stable in acidic medium.[51] This complexation with $AlCl_3$ indicated that the presence of 3-hydroxy ketone moiety in these compounds. [51] ^1H NMR spectra with mass spectral fragments arising from acyl cleavage provided a clear indication of the nature and substitution pattern of benzene rings in nonanoids and their analogues.[5]

Compounds **1**-**9** were identified as malabaricones A-D, promalabaricone B, promalabaricone C, ericanone, acyl phenol (Figure 1) by comparison of their spectroscopic data with those published for the previously identified compounds.[5, 6]

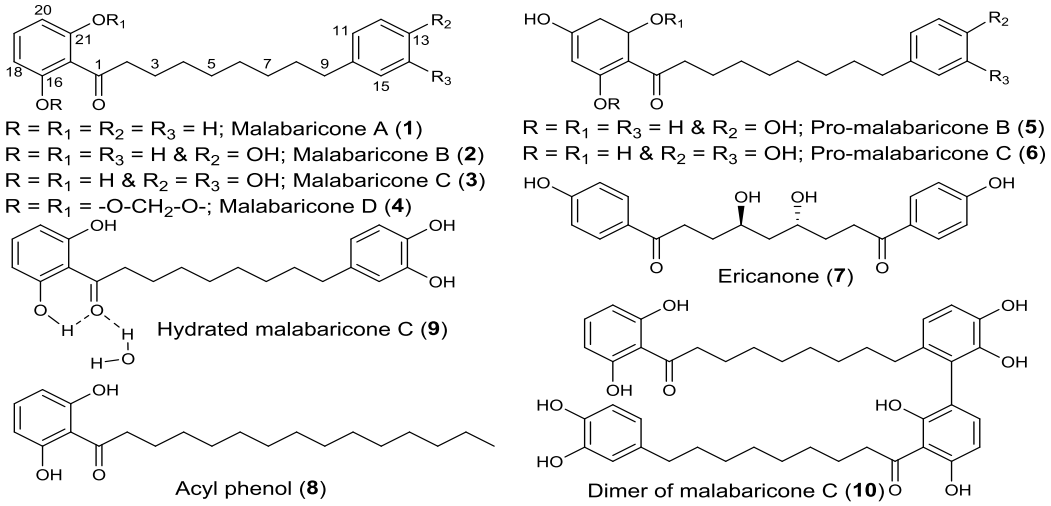


Figure 1: Chemical structure of secondary metabolites isolated from *Myristica malabarica*.

The ORTEP diagram of some of secondary metabolites isolated from Myristica malabarica are depicted below in Figure 2.

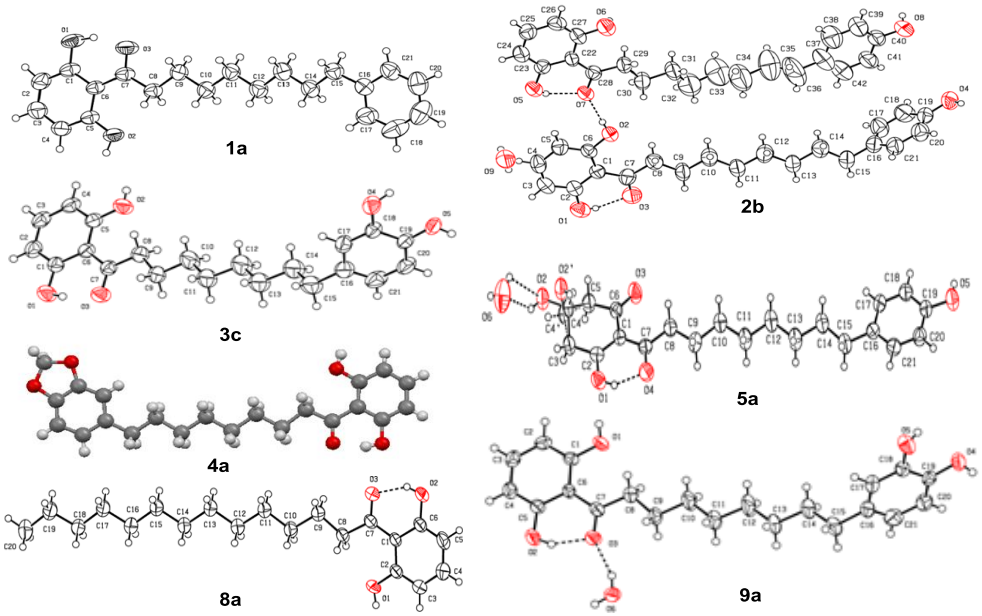


Figure 2: The ORTEP diagram of some of metabolites isolated from *Myristica malabarica.*

Compound **10** (Giganteone A, a dimer of malabaricone C) isolated as light brown coloured amorphous solid substance from aqueous methanol extract by column chromatography over silica gel followed by GPC over sephadexLH20 with gradient solvent elution. The molecular formula $C_{42}H_{50}O_{10}$ having mass 714. 340 established by HRESI. The compound **10** has been assigned as giganteone A, a dimer of acyl phenol (dimer of malabaricone C) first time reported from fruit rind of *Myristica malabarica*. Its structural characterization has been assigned in comparison of spectral data published in literature.[29, 48-58] Its structure has been assigned as dimer of acyl phenol, malabaricone C, biosynthesised by genus *Myristica*.[55-58] The structure of compound **10** is depicted below.

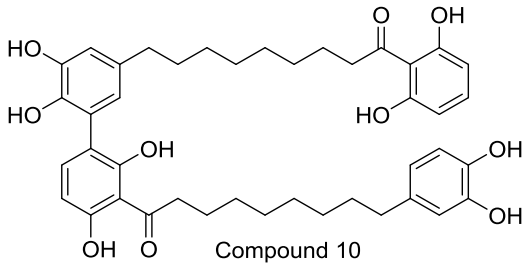


Figure 3: Chemical structure of giganteone, 10 isolated from the fruit rind of *Myristica malabarica.*

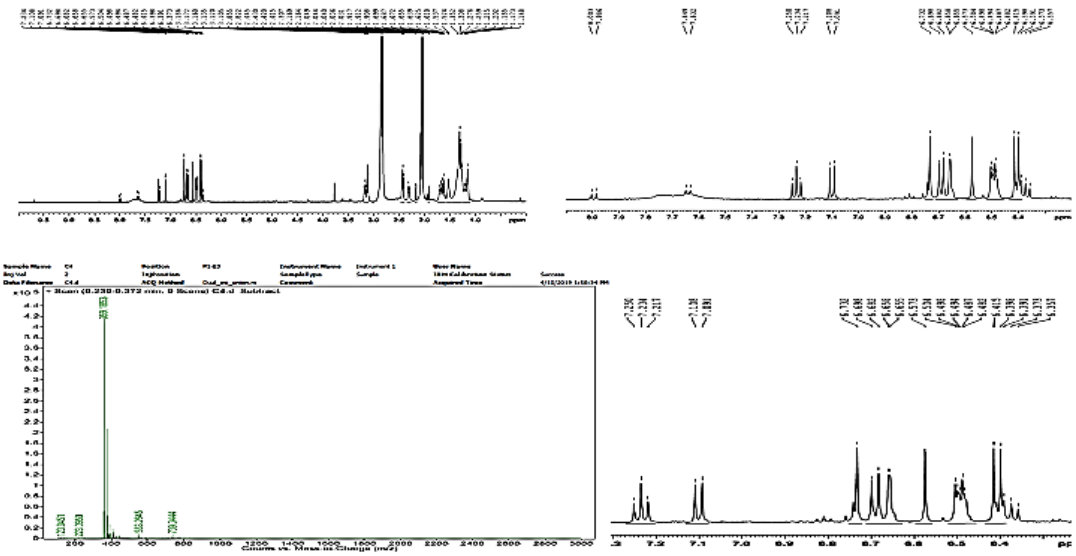


Figure 4: ^{1}H NMR spectrum (CD_3COCD_3, 200 MHz) & HR-ESI mass spectrum of giganteone A (10).

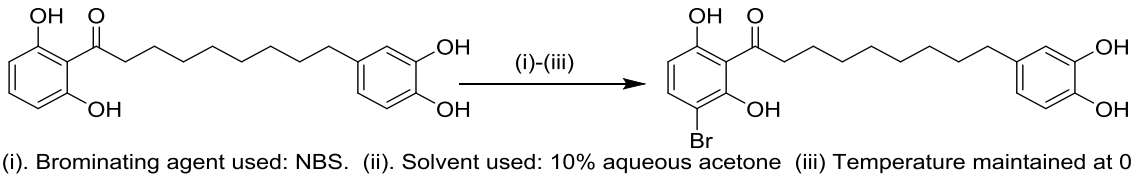
Analysis of aqueous extract of the fruit rind of *Myristica malabarica*

Major chemical constituent present in the aqueous extract of the fruit rind of *Myristica malabarica* was a carbohydrate as major ingredient. It was assigned as di-saccharide by means spectroscopic and spectrometric methods having mass 358 Da.

CONCLUSION

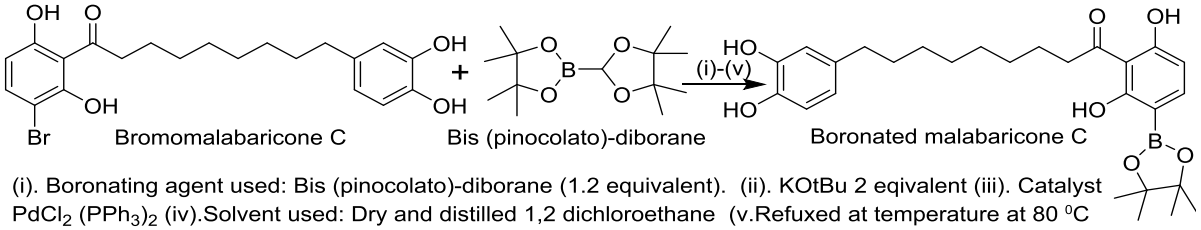
Fruit rind is an iconic spice and condiment in Indian cuisine. Ten acyl phenol (**1-10**) were isolated from defatted methanol and aqueous methanol extract of fruit rind of *M. malabarica*. The structural determination of known compounds has been secured by chemometric, spectrometric and spectroscopic methods. The identification of known compounds has been done by comparing with the spectral data available in literature. These metabolites were tested against the malaria parasite *Plasmodium falciparum* to assess the potential anti-malarial activity. Amongst the tested compounds, only the dimer of acyl phenol known as giganteone A, (dimer of malabaricone C) showed moderate anti-malarial activity with IC_{50} **3.71 ± 0.21** µM in comparison with artemisinin used as control, whereas the other products showed no activity at the highest concentration tested. To best of our knowledge, this is the first report of isolation of giganteone A from the fruit rind of *Myristica malabarica* and also its first study of anti-malarial activity.

Step1: Isolation and purification of phenol from natural resource used as substrate for bromination



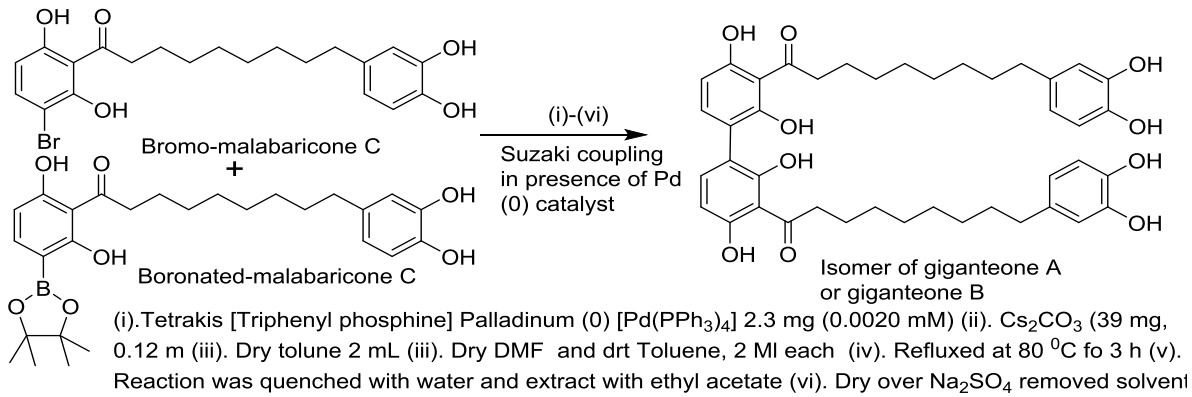
(i). Brominating agent used: NBS. (ii). Solvent used: 10% aqueous acetone (iii) Temperature maintained at 0 ^{0}C using ice bath (iv). Stirred for 12 h

Step 2: Boronation of bromo phenol using boronating agent



(i). Boronating agent used: Bis (pinocolato)-diborane (1.2 equivalent). (ii). KOtBu 2 eqivalent (iii). Catalyst $PdCl_2(PPh_3)_2$ (iv).Solvent used: Dry and distilled 1,2 dichloroethane (v.Refuxed at temperature at 80 ^{0}C using oil bath in presence of Ar gas and stirred for 3 h (vi). Quenched the reaction with KCl solution , washed with water, dried over Mg_2SO_4, remove solvent to obtain crude product

Step 3: Suzuki coupling reaction boronated phenol using using pt catalyst



(i).Tetrakis [Triphenyl phosphine] Palladinum (0) [$Pd(PPh_3)_4$] 2.3 mg (0.0020 mM) (ii). Cs_2CO_3 (39 mg, 0.12 m (iii). Dry tolune 2 mL (iii). Dry DMF and drt Toluene, 2 Ml each (iv). Refluxed at 80 ^{0}C fo 3 h (v). Reaction was quenched with water and extract with ethyl acetate (vi). Dry over Na_2SO_4 removed solvent to obtain crude product

EXPERIMENTAL SECTION

General experimental procedures

Melting points were determined using a Fischer melting point apparatus. Specific rotations were obtained using a JASCO DIP 1000 digital polarimeter. UV spectra were measured on Shimadzu UV-2100 UV-Vis spectrophotometer. NMR spectra were recorded in $CDCl_3$ or CD_3OD on a Bruker Avance 200 spectrometer using residual $CHCl_3$/HDO as an internal standard. Chemical shifts are given in ppm (δ_C & δ_H), relative to residue $CHCl_3$/HDO (7.25 & 77.00/4.78 or 3.30 & 49.00 ppm). Mass spectra were recorded using Fission 8000 (8000 series, UK) and Shimadzu QP5050A mass spectrometer, Japan. UHPLC/MS analysis of the samples was performed using a Vanquish UHPLC system coupled to a Q-Exactive quadrupole orbitrap mass

spectrometer (Thermo Fisher Scientific, USA) at the Ohio State University, College of Pharmacy Instrumentation Facility. Crystal data were collected at 293K on an Oxford Diffraction Xcalibur™ Single Crystal X-ray Diffractometer with Sapphire CCD Detector, enhance (Mo) or Cu-K\αX-ray source, and graphite monochromator using ω scans. The structures were solved by direct methods and refined using SHELXL97. Silica gel 60 (230-400 mesh, Merck) was used for analytical TLC. Silica gel 60 (70-230 mesh, Merck) was used for column chromatography. All compounds were visualized by TLC using vanillin-perchloric acid-EtOH followed by heating at 110 °C for 5 min, DNP in EtOH and neutral $FeCl_3$ in MeOH.

Plant material

The spice *M. malabarica* was purchased in a local market in Mumbai in May, 2019. The material was authenticated by Dr. Hussain Barbhuiya, Landscape and Cosmetic Maintenance Section, A & SED Division, Bhabha Atomic Research Centre, Trombay, Mumbai. A voucher specimen was deposited in the Herbarium of the Landscape & Cosmetic Maintenance Division, BARC, Mumbai-400085 having accession number HBARC00006631.

Extraction and isolation

Fresh quality fruit rind (1.250 Kg) of *M. malabarica* were dried and ground to a powder, which was extracted with methanol (2.5 L) three times at room temperature. Removal of solvent by using rota-vapour maintaining water bath temperature at 40 °C afforded a brown viscous residue (~370 g). This extract was fractionated over silica gel (5.0 kg, 230-400 mesh, Aldrich) and eluted with a step gradient of hexane, ethyl acetate in hexane, then chloroform and mixtures of methanol in chloroform to furnish one hundred fractions having volume of each aliquot was approximately 500-1000 mL. In some cases, the volume of aliquot collected is more than 1000 mL. Fractions were monitored by TLC to examine the chemical profiles. The fractions having similar chemical profiles were combined together and, in some cases, further purified by using repetitive column chromatography on open column chromatography over silica gel, gel permeation chromatography (GPC) with solvent gradual elution followed by preparative thin layer chromatography (PTLC).

Fractions 1-8 eluted with hexane to ethyl acetate (0-15%) consisted mainly of traces amount of lipids.

Fractions 9-11 eluted with chloroform-methanol (0-5%) contained fatty acids along with a phenolic compound. On evaporation yielded residue A (~150 mg), which was subjected to gel permeation chromatograph (GPC) over a sephadexLH-20 column eluted with chloroform-methanol (5-10%) in a step gradient to yield five sub-fractions A_1-A_5. Chromatography separation of sub-fractions A_3-A_4 on a silica gel open column gave compound **7** (~112 mg). Fractions 12-13 eluted by a mixture of chloroform-methanol (5%) were combined and evaporated to furnish the pale-yellow residue B (1.05 g). This was further chromatography sequentially over silica gel and then over sephadexLH-20 column eluted with 10% methanol in chloroform to yield sub-fractions B_1-B_{10}. Sub-fractions B_5-B_7 was monitored by TLC and performed chemical study with various spray reagent. It observed that sub-fractions B_5-B_7 were similar chemical profiles. They were combined (~1.2 g) and separated on a silica gel open column to afford compound **1** (~1.0 g) designated as malabaricone A.

Fractions 14-22 eluted by a mixture of chloroform-methanol (7%) were combined and evaporated to furnish a yellowish residue C (1.5 gm). This was further chromatography sequentially over silica gel and then over sephadexLH-20 column eluted with 10% methanol in chloroform to yield sub-fractions C_1-C_{15}. Sub-fractions C_5-C_{10} was monitored by TLC and performed chemical study with various spray reagents. It was observed that sub-fractions C_5-C_{10} were similar chemical profiles. They were combined (~1.2 gm) and separated on a silica gel open column to afford compound **4** (~1.1 gm), assigned as malabaricone D.

Fractions 23-33 obtained from elution with 7-10% methanol in chloroform were combined and evaporated to afford residue (2.0 gm).

Fractions 34-42 eluted with 10% methanol in chloroform were combined and evaporated to yield residue (~ 3.5 gm). These residues were monitored by TLC. Chemical profiles of these residues on TLC were similar and they were combined together. The combined residue, D (~ 5.5 gm) was chromatography on a sephadexLH-20 column eluted with chloroform-methanol (0-100%) to yield thirty-five sub-fractions D_1-D_{35}. Sub-fractions D_7-D_{25}were combined on the basis of TLC profiles to yield a residue (~ 5.0 gm) which was separated by open column chromatography over silica gel to yield compound **2** (~ 4.5 gm) compound designated as malabaricone B.

Column fractions 43-59 eluted with 10-15% methanol in chloroform had similar TLC profiles and were combined an evaporate to give product, E (13.0 gm) which was purified by chromatography on a sephadexLH-20 column eluted with a gradient of chloroform to methanol (0-100%) to yield twenty-five sub-fractions E_1-E_{25}. Subtractions E_7-E_{12} (~12.5 g) had similar TLC profiles and were combined and separated on a silica gel open column eluted with a step gradient of chloroform-methanol to yield compound **3** (~11.5 g) assigned as malabaricone C, which was a major constituent in this extract.

Fractions 60-70 eluted with 15% methanol in chloroform were combined to give a residue F (300 mg), which was separated on a sephadexLH-20 column eluted with chloroform-methanol (0-100%) to give ten sub-fractions F_1-F_{10}. Sub-fractions F_4-F_5 were combined and

evaporated to furnish brown residue. This residue was repetitive chromatography over a silica gel on open column followed by preparative TLC to yield compound **8** (~150 mg) assigned as ericanone.

Fractions 71-80 eluted with 20% methanol in chloroform were combined to give a residue G (100 mg) which was separated on a sephadexLH-20 column eluted with chloroform-methanol (0-100%) to give ten sub-fractions G_1-G_{10}. Sub-fractions G_4-G_5 were combined and evaporated to furnish an off-white residue. This residue was subjected to repetitive chromatography over a silica gel on open column followed by preparative TLC to yield compounds **5** (~25 mg) assigned as promalabaricone B and **6** (14.0 mg) assigned as promalabaricone C.

Fractions 81-86 eluted with 20-25% methanol in chloroform were combined to give a residue H (150 mg) which was separated on a sephadexLH-20 column eluted with chloroform-methanol (0-100%) to give ten sub-fractions H_1-H_{10}. Sub-fractions H_5-H_7 were combined and evaporated to obtain a brown residue. This residue was repetitive chromatographed over a silica gel on open column followed by preparative TLC to yield compounds compound **5a** and **6a** (120 mg). The structural skeleton of these compounds was very similar to compounds **5** and **6** except lack of carbonyl group in aliphatic chain. Their structures are not shown here.

Fractions 87-93 eluted with 30% methanol in chloroform were combined to give a residue I (500 mg) which was separated on a sephadexLH-20 column eluted with chloroform-methanol (0-100%) to give twelve sub-fractions I_1-I_{12}. Sub-fractions I_3-I_5 were combined and evaporated to furnish a light brown residue. This residue was repetitive chromatography over a silica gel on open column followed by preparative TLC to yield a compound **(**~50 mg). The structural analysis of this compound has been carried out by means of spectrometric, spectroscopic methods and HRESI-MS. The structure of the compound has been assigned as a dimer malabaricaone C known as giganteone A (**10**).

Fractions 94-97 eluted with 35% methanol in chloroform were combined to give a residue J (~50 gm). It appeared as black sticky mass highly hygroscopic in nature. About 1.0 gm of residue J was acid hydrolysed (2N aqueous HCl) for one hour in a water bath. The hydrolysed product was worked up by usual method to afford a light brown residue JJ (~ 400 mg). This residue was monitored by TLC using 10% methanol in chloroform as solvent system and visualized on exposure in UV light. It observed that one major spot along with other three very minor spots in micro plate. This residue was purified on a sephadexLH-20 column eluted with chloroform-methanol (0-100%) to collect eight sub-fractions JJ_1-JJ_8. Sub-fractions JJ_4-JJ_5 were combined based on their TLC profiles and evaporated to furnish an off-white residue (~ 300 mg). This residue was repetitive chromatography over a silica gel on open column, preparative TLC followed by crystallization to yield a needle shaped colourless crystalline compound assigned as compound **9** (250 mg) along with trace amount compound **11** (25 mg) The major compound **9** was identified as hydrated malabaricone C by spectroscopic study and confirmed by single crystal XRD study. The structure of compound **11** has been determined as carboxy malabaricone B in comparison with ^{1}H & ^{13}C NMR data of malabaricone B.

The aqueous part contained sugars. The sugar moiety presents in the aqueous part was identified as D (+) glucose on comparison with authentic sugar D (+) glucose. So, majority of black sticky mass is glycoside of malabaricone C along with other compounds in very trace amount, but determination of number sugar moiety and attachment of sugar moiety (s) into this aglycone has been undetermined.

Fractions 98-100 eluted with 50-100% methanol in chloroform were combined to give a mug substance K (~ 100 gm). It appeared as black sticky mass, highly hygroscopic in nature. It looks like polyphenolic compounds in the form of glycosides or complex polysaccharide of the above secondary metabolites. Further investigation of this fraction has not been done.

Analysis of aqueous part of the fruit rind of Myristica malabarica

The major chemical constituent of the aqueous extract of the fruit rind of *Myristica malabarica* is carbohydrate belongs to disaccharide. The structural determination of this disaccharide has been carried out spectrometric and spectroscopic methods. The mass disaccharide has been measured as about 358 Da.

Compound **1** (malabaricone A): yellow prisms (EtOAc-Hexane); mp 82 °C; UV (MeOH), λ_{max} (log ε): 206 (1.305), 268 (0.752), 340 (0.198) nm; IR (KBr) ν_{max} : 3465, 3390, 3259, 2998 and 1625 cm^{-1}; HRESI-MS (negative mode): obs. *m/z* value 323.1898 au $[M-H]^-$; cal. *m/z* value 323.191 au $[M-H]^-$.^{1}H NMR (CD_3OD, 200 MHz) and ^{13}C NMR (CD_3OD, 50 MHz) see Table 2. CCDC reference number: 605059. https://doi.org/10.1107/S1600536806008257.

Compound **2** (malabaricone B): colourless needles (EtOAc-Hexane); mp 98 °C; UV (MeOH), λ_{max} (log ε): 224 (0.614), 270 (0.334), 346 (0.198) nm; IR (KBr) ν_{max}: 3464, 3390, 3259, 2985, 1626 cm^{-1}; HR-ESI (positive mode) *m/z*: 341.1740 Da $[M + H]^+$. ^{1}H NMR (CD_3OD, 200 MHz) and ^{13}C NMR (CD_3OD, 50 MHz) data, see Table 2. CCDC reference number: 2212418.

Compound **3** (malabaricone C): Dark yellow needles ($CHCl_3$-MeOH); mp 120 °C; UV (MeOH), λ_{max} (log ε): 206 (1.665), 270 (0.885), 342 (0.210) nm; IR (KBr) ν_{max}: 3468, 3392, 3259, 2987 and 1628 cm^{-1}; HRESI-MS (positive mode), *m/z:* 359.1844Da $[M+ H]^+$& 379.1506 Da $[M+H_2O]^+$. ^{1}H NMR (CD_3OD, 200 MHz) and ^{13}C NMR (CD_3OD, 50 MHz) see Table 2. CCDC reference number:610702. Crystal structure and crystal data of

compound **2** can be accessed using site: https://doi.org/10.1107/S1600536806015273

Compound **4** (malabaricone D): colourless rods (MeOH); mp 90 °C; UV (MeOH) λ_{max} (log ε): 228 (4.040), 268 (4.125), 342 (1.077) nm; IR (KBr) ν_{max}: 3467.50, 3387.15, 3257.05, 2898.25 and 1628.45 cm^{-1}; ^{1}H NMR (CD_3OD, 200 MHz) and ^{13}C NMR (CD_3OD, 50 MHz) data, see Table 2; HR-ESI (positive mode) *m/z*: 371.1834 Da $[M+H]^+$and 393.1662 Da $[M + Na]^+$. ^{1}H NMR (CD_3OD, 200 MHz) and ^{13}C NMR (CD_3OD, 50 MHz) see Table 2. CCDC reference number: 2212500.

Compound **5** (promalabaricone B): colourless needles; mp 141-142 °C; UV (MeOH), λ_{max} (log ε): 274 (3.2), 228 (3.8); IR (KBr) ν_{max}: 3340.1, 2918.7, 2848.4, 1737.6, 1633.4, 1585.2, 1512.8, 1447.3, 1366.2, 1245.7, 1036.5, 825.3, 781.9, 717.4 cm^{-1}; ^{1}H NMR (CD_3OD, 200 MHz) and ^{13}C NMR (CD_3OD, 50 MHz) data, see Table 2. HRESI-MS (positive mode) *m/z*: 361.1990 Da $[M+ H]^+$; ^{1}H NMR (CD_3OD, 200 MHz) and ^{13}C NMR (CD_3OD, 50 MHz) see Table 2. CCDC reference number:1501296. Crystal structure and crystal data of compound **5** can be accessed using site: https://doi.org/10.1107/S2056989016013797

Compound **6** (promalabaricone C): colourless needles (EtOAc-Hexane); mp 149-150 °C; UV (MeOH) λ_{max}: 274 (3.2), 228 (3.8); IR (KBr), ν_{max}: 3340.1, 2918.7, 2848.4, 1737.6, 1633.4, 1585.2; 1512.8, 1447.3, 1366.2, 1245.7, 1036.5, 825.3, 781.9, 717.4 cm^{-1}; HR-ESI (positive mode) *m/z*: 361.1976 Da $[M+H]^+$& 383.1813 Da $[M+Na]^+$. ^{1}H NMR (CD_3OD, 200 MHz) and ^{13}C NMR (CD_3OD, 50 MHz) see Table 3.

Compound **7** [1-(2',6'-dihydroxyphenyl)-tetradecan-1-one]: colourless needles (EtOAc-Hexane); mp 90 °C. IR (KBr), ν_{max}: 3466, 3392, 3258, 2985 and 1628 cm^{-1}; UV (MeOH), λ_{max} (log ε): 222 (0.906), 268 (0.785), 340 (0.205) nm; HRESI (negative mode) *m/z*: 319.2275 Da $[M-H]^-$ and 639.4630 $[2M-H]^-$, dimerization. ^{1}H NMR (CD_3OD, 200 MHz) and ^{13}C NMR (CD_3OD, 50 MHz) see Table 3. CCDC reference number: 1591296

Compound **8** [1-(3,7-dihydroxy-1,9-bis(4-hydroxyphenyl)-nonan-5-one]: light brown amorphous substance (EtOAc-Hexane); mp 147-150 °C. IR (KBr), ν_{max}: 3303, 2915, 2850, 1569, 1514, 1361, 12224, 1041, 851, 818 and 722 and 1628 cm^{-1}; UV (MeOH), λ_{max}: 204, 223, 237 nm; HRESI *m/z*: 359.1838 Da $[M+H]^+$ & 381.1656 Da $[M+Na]^+$. ^{1}H NMR (CD_3OD, 200 MHz) and ^{13}C NMR (CD_3OD, 50 MHz) see Table 3.

Compound **9** (hydrated malabaricone C): Colourless needles ($CHCl_3$-MeOH); mp 122 °C; UV (MeOH), λ_{max} (log ε): 206 (1.665), 270 (0.885), 342 (0.210) nm; IR (KBr), ν_{max} 3468, 3392, 3259, 2987 and 1628 cm^{-1}; ^{1}H NMR (CD_3OD, 200 MHz) and ^{13}C NMR (CD_3OD, 50 MHz) data see Table 2; HR-ESI (positive mode) *m/z* : 359.1837 Da $[M + H]^+$ & 381.1657 Da $[M + Na]^+$. ^{1}H NMR (CD_3OD, 200 MHz) and ^{13}C NMR (CD_3OD, 50 MHz) see Table 4.

Compound **10** (Giganteone A, a dimer of malabaricone C): Brown colour amorphous powder; mp 132 °C; UV (MeOH), λ_{max} (log ε): 206 (1.665), 270 (0.885), 342 (0.210) nm; IR (KBr), ν_{max} 3468, 3392, 3259, 2987 and 1628 cm^{-1}; ^{1}H NMR (CD_3OD, 200 MHz) and ^{13}C NMR (CD_3OD, 50 MHz) data see Table 2; HR-ESI (positive mode) obs. *m/z*: 739.344 Da $[M + Na]^+$; cal. *m/z*: 737.330 $[M + Na]^+$. ^{1}H NMR (CD_3OD, 200 MHz) and ^{13}C NMR (CD_3OD, 50 MHz) see Table 3.

Anti-malarial bioassay

The effect of pure compounds on parasitic growth of the *Plasmodium falciparum* Dd2 strain was measured in a 72-h growth assay in the presence of the drug as described previously with minor modifications. [59] Briefly, ring stage parasite cultures (100 µL per well, with 1% hematocrit and 1% parasitemia) were then grown for 72 h in the presence of increasing concentrations of the drug in a 5% CO_2, 5% O_2, and 90% N_2 gas mixture at 37 °C. After 72 h in culture, parasite viability was determined by DNA quantitation using SYBR Green I (25 µL of SYBR Green I in lysis buffer at 0.33 µL of SYBR Green I/mL of lysis buffer). The half-maximum inhibitory concentration (IC_{50}) calculation was performed with GraphPad Prism 10 software (GraphPad Software, Inc.) using a nonlinear regression curve fitting. The IC_{50} values are the average of three independent determinations, with each determination performed in triplicate, and results are expressed as the average ± SEM.

Table 1: Anti-malarial activity of secondary metabolites isolated from *Myristica malabarica*.

Anti-malarial activity of secondary metabolites isolated from *Myristica malabarica* against the parasite *P. falciparum* in comparison with artemisinin used as control		
Samples name	Parasite	IC_{50} in µM
1. Compound **1** (Malabaricone A)	*P. falciparum*	X > 10,000
2. Compound **2** (Malabaricone B)	*P. falciparum*	X > 10,000
3. Compound **3** (Malabaricone C)	*P. falciparum*	X > 10,000
4. Compound **4** (Malabaricone D)	*P. falciparum*	X > 10,000
5. Compound **5** (Pro-malabaricone B)	*P. falciparum*	X > 10,000
6. Compound **6** (Pro-malabaricone C)	*P. falciparum*	X > 10,000
7. Compound **7** (Ericanone)	*P. falciparum*	X > 10,000
8. Compound **8** (Acyl phenol)	*P. falciparum*	X > 10,000
9. Compound **9** (Hydrated Malabaricone C)	*P. falciparum*	X > 10,000
10. Giganteone **10** (a dimer of malabaricone C)	*P. falciparum*	**3.71±0.21**
11. Artemisinin (**control**)	*P. falciparum*	**0.012 ± 0.002**

Table 2: ^{1}H NMR (CD_3OD, 200 MHz) & ^{13}C NMR (CD_3OD, 50 MHz) data for compounds 1-5.

Position	Compound 1 (Malabaricone A)		Compound 2 (Malabaricone B)		Compound 3 (Malabaricone C)		Compound 4 (Malabaricone D)		Compound 5 (Promalabaricone B)	
	δ_H (J_{H-H}) Hz	δ_C	δ_H (J_{H-H}) Hz	δ_C	δ_H (J_{H-H}) Hz	δ_C	δ_H (J_{H-H}) Hz	δ_C	δ_H (*J* in Hz)	δ_C
1	-	209.61	-	209.64	-	209.63	-	209.59	2.97, t (7.0)	205.68
2	2.97, t (7.6)	45.67	3.19, t (7.2)	45.69	2.95, t (7.2)	45.70	2.95, t (7.4)	45.79	1.61-1.51, m	47.58
3	1.56-1.53, m	36.60	1.57-1.50, m	32.67	1.57-1.50, m	32.85	1.49-1.46, m	32.88	1.21, s	40.57
4	1.48-1.46, m	32.63	1.20, s	30.45	1.21, s	30.57	1.40-1.46, m	30.65	1.21, s	35.56
5	1.19, s	30.44	1.20, s	30.26	1.21, s	30.26	1.14, s	30.27	1.21, s	35.40
6	1.19, s	25.66	1.20, s	25.66	1.21, s	25.69	1.14, s	25.64	1.21, s	33.57
7	1.48-1.46, m	30.25	1.20, s	30.26	1.21, s	30.49	1.14, s	30.53	1.61-1.51, m	35.56
8	1.56-1.53, m	36.60	1.50-1.42, m	30.26	1.45-1.41, m	30.57	1.49-1.46, m	30.65	2.49, t (7.0)	40.57
9	2.44, t (7.0)	36.89	2.36, t (7.2)	36.89	2.32, t (7.8)	36.22	2.32, t (8.0)	36.66	-	42.13
10	-	126.51	-	126.53	-	135.74	-	137.81	7.00, dd (8.4, 2.8)	137.70
11	7.19-6.94, m	129.32	6.84, dd (8.4, 2.2)	129.33	6.47, d (2.0)	116.45	6.48, d (2.0)	109.71	6.72, dd (8.4, 2.8)	127.55
12	7.19-6.94, m	129.16	6.55, dd (8.2, 2.2)	129.18	-	145.86	-	148.91	-	113.60
13	7.19-6.94, m	143.91	-	143.92	-	143.90	-	146.75	7.00, dd (8.4, 2.8)	156.08
14	7.19-6.94, m	129.16	6.55, dd (8.2, 2.2)	129.18	6.53, d (8.0)	116.13	6.53, d (8.0)	108.86	6.72, dd (8.4, 2.8)	111.60
15	7.19- 6.94, m	129.32	6.84, dd (8.4, 2.2)	129.33	6.49, dd (8.0, 2.0)	120.61	6.47, dd (8.0,2.0)	122.06	-	129.95
16	-	111.41	-	111.34	-	111.32	-	111.37	-	113.77
17	-	163.35	-	163.35	-	163.31	-	163.40	3.08, 2.76, dd (18.0, 3.6)	193.67
18	6.21, d (8.2)	108.83	6.19, d (8.2)	108.34	6.21, d (8.2)	108.30	6.20, d (8.2)	108.38	4.38, m	42.13
19	7.05, t (8.2)	136.74	7.06, t (8.2)	136.80	7.06, t (8.2)	136.78	7.03, t (8.2)	136.79	2.67, 2.75, dd (17.8, 5.0)	63.62
20	6.21, d (8.2)	108.33	6.23, d (8.2)	108.34	6.21, d (8.2)	108.30	6.20, d (8.2)	108.38	-	40.57

21	-	163.35	-	163.35	-	163.31	-	163.40	-	198.05
22	-	-	-	-	-	-	5.69, s	101.81	-	-

Table 3: ^{1}H NMR (CD_3OD, 200 MHz) & ^{13}C NMR (CD_3OD, 50 MHz) data for reported compounds 6-8 and 10.

Position	Compound 6 (Promalabaricone C)		Compound 7 (Ericanone)		Compound 8 (Acyl phenol)		Compound 9 (Hydrated malabaricone C)	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1	-	204.21	-	208.26	-	31.27	-	209.64
2	2.91, t (7.4)	34.59	3.13, t (7.0)	44.79	2.43, t (7.0)	28.85	3.19, t (7.2)	45.70
3	1.60-1.53, m	31.29	1.67-1.66, m	31.90	1.55, m	62.07	1.57-1.50, m	32.81
4	1.22, s	28.68	1.16, brs	29.64	4.16, m	34.32	1.37, s	30.57
5	1.22, s	24.33	1.16, brs	29.54	2.91, t (7.50)	204.23	1.37, s	30.22
6	1.22, s	28.68	1.16, brs	29.54	-	31.27	1.37, s	25.65
7	1.22, s	28.86	1.16, brs	29.40	2.91, t (7.50)	62.07	1.37, s	30.46
8	1.60-1.53, m	28.86	1.16, brs	29.34	4.16, m	28.77	1.65-1.55, m	30.56
9	2.39, t (7.0)	34.37	1.16, brs	29.34	1.55, m	31.27	2.52, t (8.8)	36.19
10	-	132.41	1.16, brs	29.34	2.43, t (7.0)	132.49	-	135.75
11	6.52, d (2.0)	115.67	1.16, brs	29.34	-	118.87	6.71, d (2.0)	116.45
12	-	144.95	1.16, brs	24.48	6.94, d (8.5)	115.04	-	145.80
13	-	143.05	1.16, brs	22.66	6.64, d (8.5)	155.16	-	143.84
14	6.59 d (8.2)	115.41	0.83, t (6.0)	14.08	-	115.04	6.53, d (8.0)	116.13
15	6.37, dd (8.2, 2.0)	129.06	-	110.09	6.94, d (8.5)	112.75	6.53, dd (8.2, 2.0)	120.62
16	-	115.00	-	161.19	6.64, d (8.5)	112.75	-	111.29
17	-	155.21	6.39, d (8.2)	108.42	-	132.46	-	163.31
18	3.04 & 2.78, dd (18.2, 3.6)	28.86	7.21, t (8.2)	135.73	6.94, d (8.5)	118.87	6.45, d (8.2)	108.29
19	-	62.09	6.39, d (8.2)	108.42	6.64, d (8.5)	155.16	7.28, t (8.2)	136.78
20	2.66 & 2.75, dd (18.2, 7.4)	34.59	-	161.19	-	118.87	6.45, d (8.2)	108.30
21	-	204.21	-	-	6.64, d (8.5)	107.18	-	163.26
22	-	-	-	-	6.94, d (8.5)	-	-	-

Table 4: ^{1}H & ^{13}C NMR (CD_3COCD_3, 200 MHz & 50 MHz) of compound 10 (Giganteone A).

Compound 10 (Giganteone A, a dimer of malabaricone C)					
Moiety-I			Moiety-II		
Position	δ_H (J_{H-H}) Hz	δ_C	Position	δ_H (J_{H-H}) Hz	δ_C
1	-	209.61	1′	-	209.63
2	3.17, t (7.2)	45.67	2`	3.13, t (7.2)	45.70
3	1.69-1.67, m	36.60	3′	1.65-1.62, m	32.85
4	1.27, s	32.63	4`	1.27, s	30.57
5	1.27, s	30.44	5′	1.27, s	30.26
6	1.27, s	25.66	6′	1.27, s	25.69
7	1.27, s	30.25	7′	1.27, s	30.49
8	1.35-1.30, m	36.60	8′	1.35-1.30, m	30.57
9	2.32, t (7.8)	36.89	9′	2.42, t (7.8)	36.22
10	-	126.51	10′	-	135.74
11	6.73, d (2.0)	129.32	11′	6.65, d (2.0)	116.45
12	-	129.16	12′	-	145.86
13	-	143.91	13′	-	143.90
14	6.53, d (2.0)	129.16	14′	6.69, d (8.0)	116.13
15	-	129.32	15′	6.49, dd (8.0, 2.0)	120.61
16	-	111.41	16′	-	111.32
17	-	163.35	17′	-	163.31
18	6.40, d (8.2)	108.83	18′	-	122.30
19	7.23, t (8.2)	136.74	19′	7.10, d (8.2)	136.78
20	6.40, d (8.2)	108.33	20′	6.21, d (8.2)	108.30
21	-	163.35	21′	-	163.31

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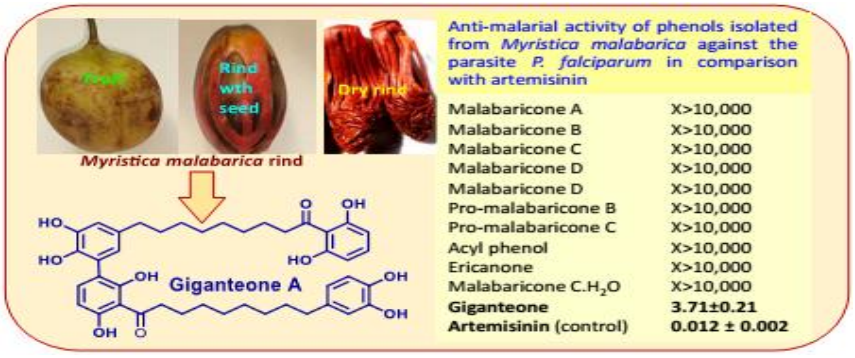
CONFLICT OF INTEREST
The authors declare that there is no conflict of interest regarding the publication of this article.

AUTHOR CONTRIBUTION STATEMENT
AKB performed isolation, structural characterization, chemical transformation and reaction, and drafted the manuscript. JHB performed and analysed *in vitro* anti-malarial assay. MBC supervised biological assays and analysis, and assisted in the final revision of the manuscript. SF confirmed the structure of the crystal by X-ray diffraction study, acquired the crystal data and analysed the crystal structure.

GRAPHICAL ABSTRACT



SUPPLEMENTARY INFORMATION

Supplementary Information is available for this paper.

Annexure 1: Supporting Information (Spectroscopic data consisting IR, UV, ^{1}H NMR,^{13}C NMR, DEFT, HMBC, EIMS, HRESI-MS of these compounds (**1-10**), single crystal structure by X-ray diffraction study of compounds) were enclosed in attached file.

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC). Copies of the data can be obtained, free of charge, on application to Director, CCDC, 12 Union Road, Cambridge CB2, 1EZ, UK (fax: +44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk

Annexure 1: Supporting Information contents.

Entry No.	Legendary title
Figure S1	^{1}H NMR spectrum (CD_3OD, 200 MHz) of compound **1** (Malabaricone A)
Figure S2	^{13}C NMR spectrum (CD_3OD, 50 MHz) of compound **1** (Malabaricone A)
Figure S3	HR-ESI (negative mode) mass spectrum of compound **1** (Malabaricone A)
Figure S4	ORTEP diagram and crystal data of compound **1** (Malabaricone A)
Figure S5	^{1}H NMR spectrum (CD_3OD, 200 MHz) of compound **2** (Malabaricone B)
Figure S6	^{13}C NMR spectrum (CD_3OD, 50 MHz) of compound **2** (Malabaricone B)
Figure S7	HR-ESI (positive mode) mass spectrum of compound **2** (Malabaricone B)
Figure S8	ORTEP diagram of compound **2** crystallized as twin molecules (Malabaricone B)
Figure S9	^{1}H NMR spectrum (CD_3OD, 200 MHz) of compound **3** (Malabaricone C)
Figure S10	^{13}C NMR spectrum (CD_3OD, 50 MHz) of compound **3** (Malabaricone C)
Figure S11	HRESI-MS (positive mode) spectrum of compound **3** (Malabaricone C)
Figure S12	ORTEP diagram and crystal data of compound **3** (Malabaricone C)
Figure S13	^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of compound **4** (Malabaricone D)
Figure S14	^{13}C NMR spectrum of compound **4** (Malabaricone D)
Figure S15	HRESI-MS of compound **4** (Malabaricone D)
Figure S16	ORTEP diagram and crystal data of compound **4** (Malabaricone D)
Figure S17	^{1}H NMR (CD_3COCD_3, 200 MHz) spectrum of compound **5** (Promalabarinone B)
Figure S18	^{1}H NMR spectrum of compound **5** (Promalabarinone B)
Figure S19	^{13}C NMR (CD_3COCD_3, 50 MHz) spectrum of compound **5** (Promalabarinone B)
Figure S20	HRESI-MS of compound **5** (Promalabarinone B)
Figure S21	HRESI-MS of compound **5** (Promalabaricone B)
Figure S22	ORTEP diagram and crystal data of compound **5** (Promalabarinone B)
Figure S23	^{1}H NMR (CD_3OD, 200 MHz) spectrum of compound **6** (Promalabarinone C)
Figure S24	Expansion of ^{1}H NMR (CD_3OD, 200 MHz) spectrum of compound **6**
Figure S25	^{13}C NMR (CD_3OD, 50 MHz) spectrum of compound **6** (Promalabarinone C)
Figure S26	HREI-MS of compound **6** (Promalabaricone C)
Figure S27	^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of compound **7** (Ericanone)
Figure S28	^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of crude compound **7** (Ericanone)
Figure S29	^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound **7** (Ericanone)
Figure S30	HRESI-MS (positive mode) spectrum of compound **7** (Ericanone)
Figure S31	^{1}H NMR (CD_3OD, 200 MHz) spectrum of compound **8** (Acyl phenol)
Figure S32	Expansion of ^{1}H NMR spectrum of compound **8** (Acyl phenol)
Figure S33	^{13}C NMR spectrum of compound **8** (Acyl phenol)
Figure S34	HRESI-MS (negative mode) of compound **8** (Acyl phenol)
Figure S35	ORTEP diagram and crystal data of compound **8** (Acyl phenol)
Figure S36	^{1}H NMR spectrum (CD_3COCD_3, 200 MHz) of compound **9** (Hydrated malabaricone C)
Figure S37	Expansion of ^{1}H NMR spectrum (CD_3COCD_3, 200 MHz) of compound **9** (Hydrated malabaricone C)
Figure S38	^{13}C NMR (CD_3COCD_3, 50 MHz) spectrum of compound **9** (Hydrated malabaricone C)
Figure S39	HRESI-MS (positive mode) spectrum of compound **9** (Hydrated malabaricone C)
Figure S40	ORTEP diagram and crystal data of compound **9** (Hydrated malabaricone C)
Figure S41	^{1}H-^{1}H COSY (800 MHz, CD_3OD) of compound **3** (Malabaricone C
Figure S42	^{1}H-^{1}H COSY (800 MHz, CD_3OD) of compound **3** (Malabaricone C
Figure S43	^{1}H-^{1}H COSY (800 MHz, CD_3OD) of compound **3** (Malabaricone C
Figure S44	^{1}H-^{13}C HSQC (800 MHz, 201 MHz, CD_3OD) of compound **3** (Malabaricone C)
Figure S45	^{1}H-^{1}H COSY ($CDCl_3$, 800 MHz) of compound **8** (Acyl phenol)
Figure S46	Expansion of ^{1}H-^{1}H COSY ($CDCl_3$, 800 MHz) of compound **8** (Acyl phenol)
Figure S47	^{1}H, ^{13}C-HSQC spectrum (800 MHz, 201 MHz) of compound **8** (Acyl phenol)
Figure S48	^{1}H, ^{13}C HMBC spectrum of (800 MHz, 201 MHz) of compound **8** (Acyl phenol)

Figure S49	^{1}H NMR spectrum (CD_3OD, 200 MHz) of compound **10** (Giganteone A)
Figure S50	Expansion of ^{1}H NMR spectrum (CD_3OD, 200 MHz) of compound **10** (Giganteone A)
Figure S51	Expansion of ^{1}H NMR spectrum (CD_3OD, 200 MHz) of compound **10** (Giganteone A)
Figure S52	^{13}C NMR spectrum (CD_3OD, 50 MHz) of compound **10** (Giganteone A)
Figure S53	HRESI-MS (positive mode) of compound **10** (Giganteone A)
Figure S54	Graphical abstract
Chart C1	Flow diagram for isolation of secondary metabolites from defatted MeOH extract of the dried fruit rind of *M. malabarica*
Scheme SC1	Scheme for acid hydrolysis of glycoside
Scheme SC2	Scheme for acid hydrolysis of glycoside & separation of acid from phenol on treatment with $NaHCO_3$ solution

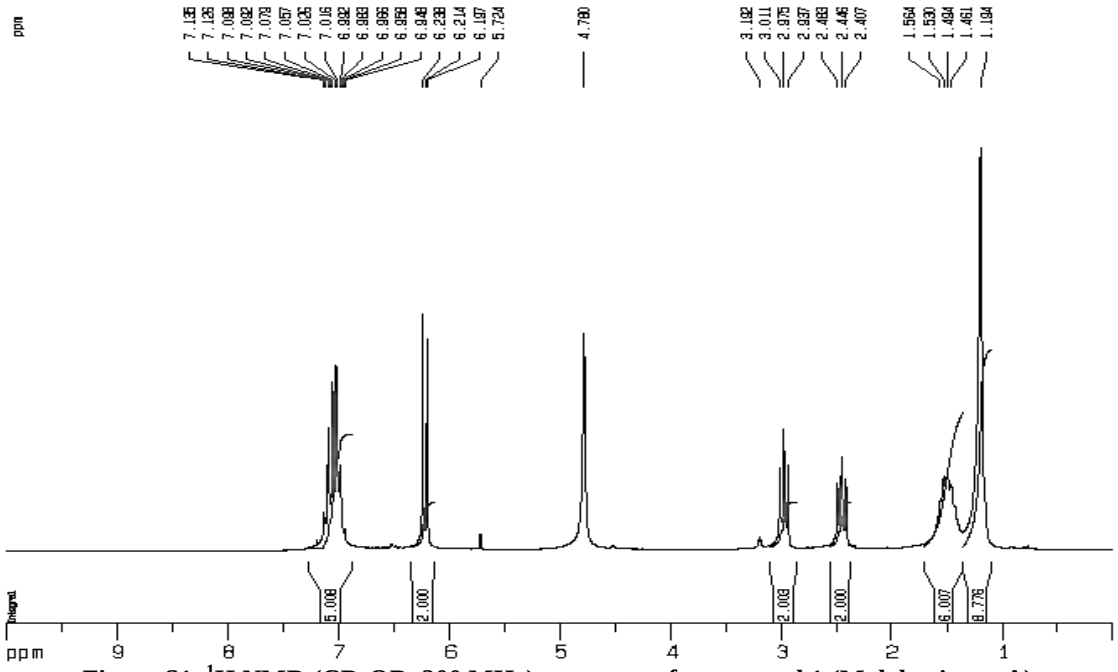


Figure S1. ^{1}H NMR (CD_3OD, 200 MHz) spectrum of compound 1 (Malabaricone A).

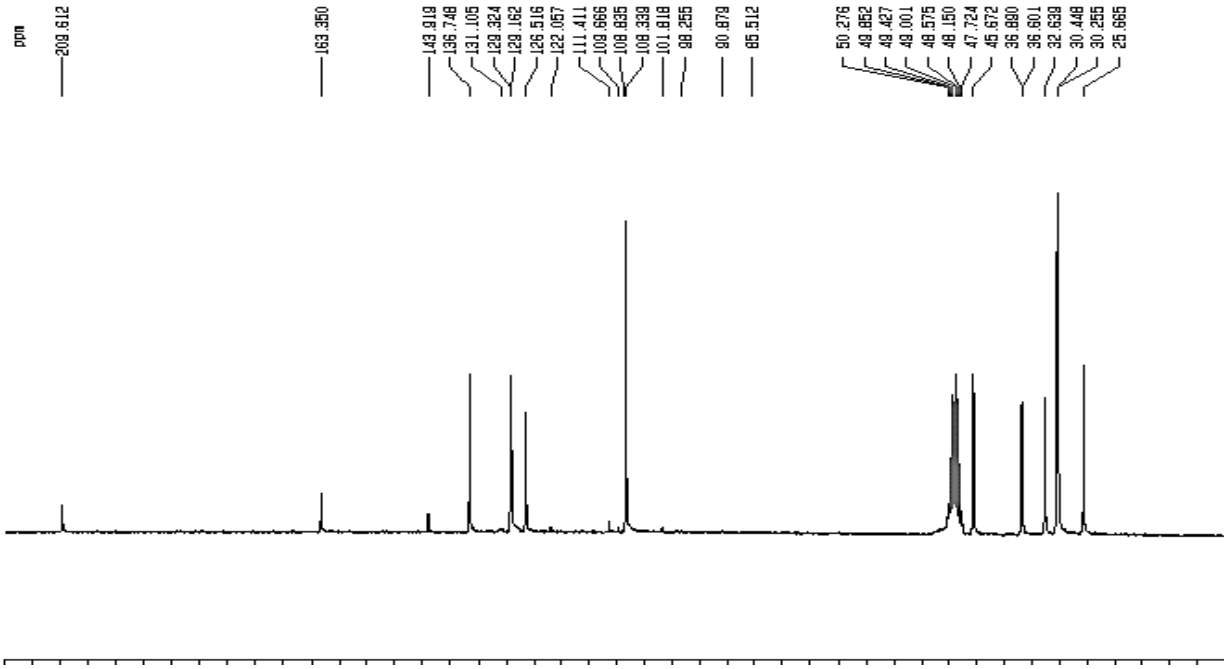


Figure S2:^{13}C NMR (CD_3OD, 50 MHz) spectrum of compound 1 (Malabaricone A).

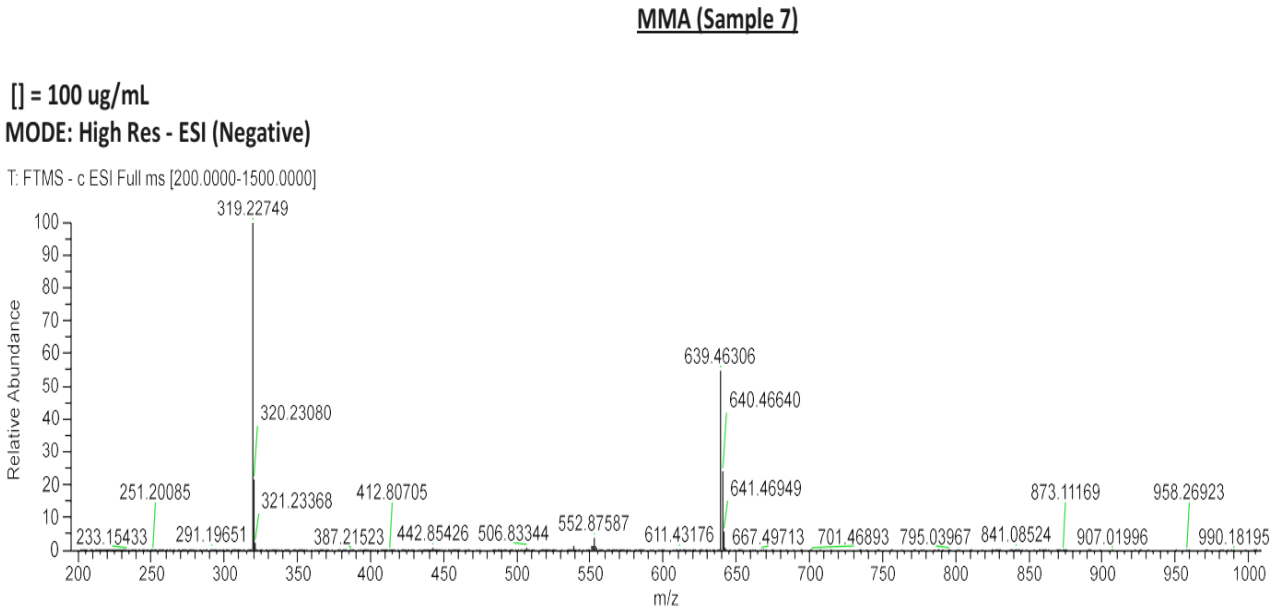


Figure S3. HRESI-MS spectrum of compound 1 (Malabaricone A)

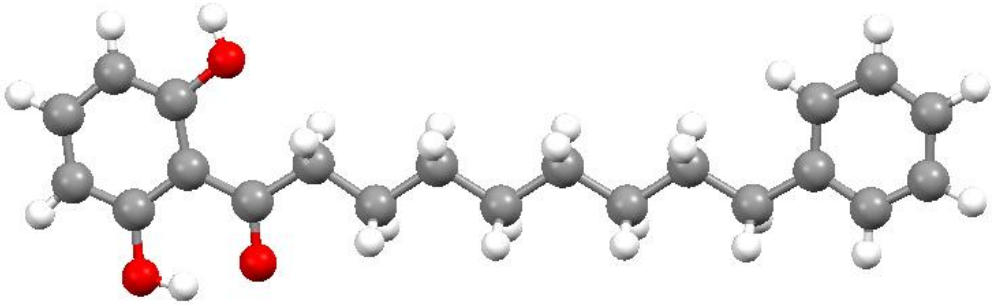


Figure S4. ORTEP diagram of compound 1 (Malabaricone A)

X-ray crystallographic analysis of compound **1** (Malabaricone A): Crystals of compound **1** were obtained from a mixture of ethyl acetate and hexane.

Crystal data of compound **1** (Malabaricone A): mono clinic crystal (0.65 x 0.18 x 0.10) mm; space group name $P2_l/n$. Unit cell dimension: a = 4.1831 (6) A, α = 90.00°; b = 32.562 (2) A; β = 98.430 (10) °; c = 13.6270 (10) A; γ = 90.00°; cell volume, V 1836.1(3); unit cell formula, Z = 4; crystal density diffraction, d_x = 1.181 Mgm^{-3}. Number of independent reflections were measured 6403, number of independent reflections 3251andnumber of independent reflections were observed [R (int.) = 0.044] 2092.Completeness of θ was 67.09, 100%; θ range for data collection 8.2 to 23.9°. Absorption correction: semi-empirical from equivalent. The structure was solved by direct methods and refined by a full matrix least squares on F^2. Final R indexes [$F^2>2\sigma(F^2)$]: R1 = 0.046, wR2 = 0.143, S = 1.04. Absorption coefficient, μ = 0.61 mm^{-1}. Cell measured angle θ_{min} 2.17 and θ_{max} 67.09. Crystal description prism; crystal colour yellow. Diffraction temperature recorded 299 (2) K, diffraction radiation used monochromator graphite. Extinction correction was done SHELXL97; extinction coefficient 0.0029 (5). Large difference peak and hole = 0.22 and -0.14 e.$Å^{-3}$.

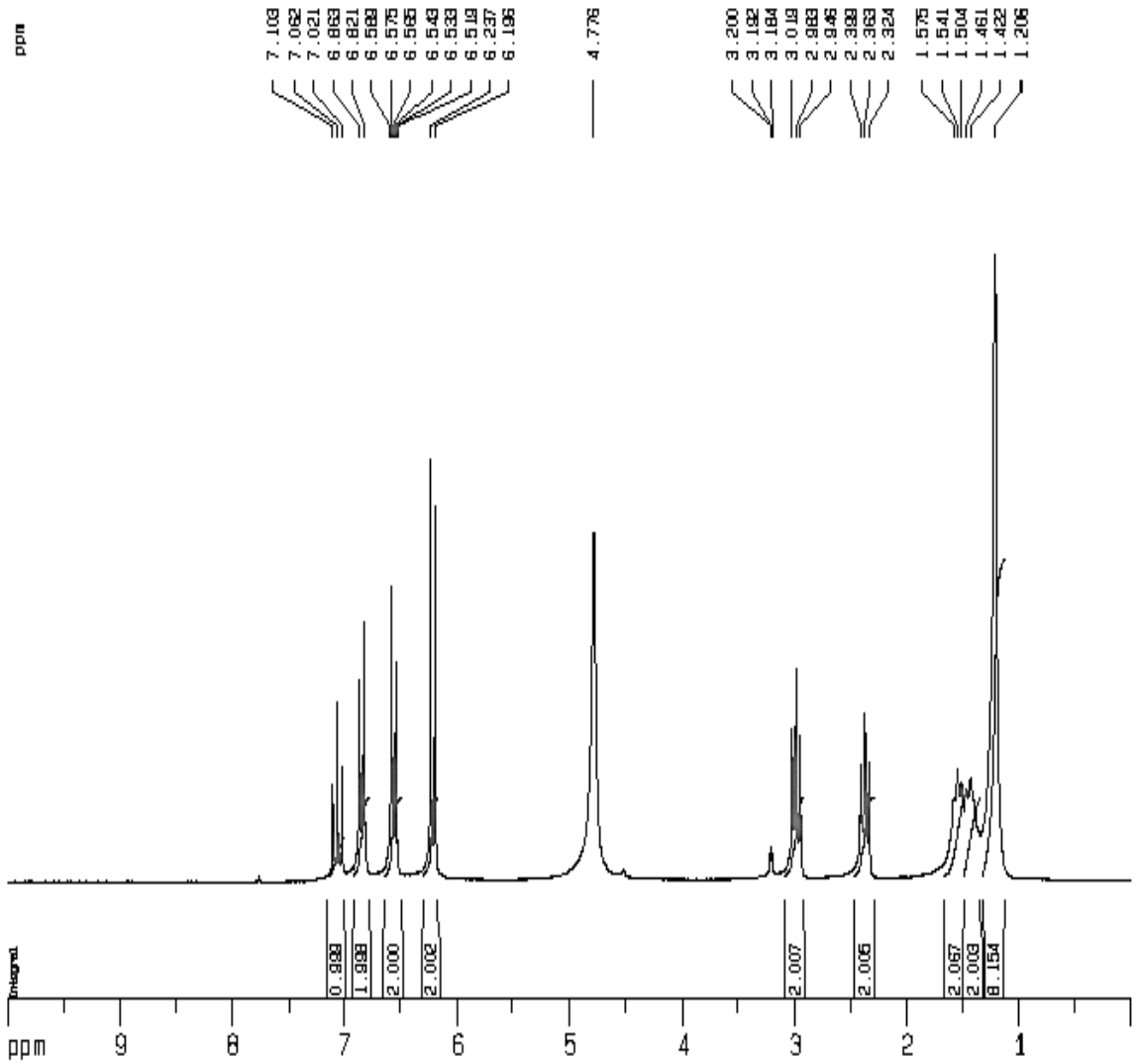


Figure S5. ^{1}H NMR (CD_3OD, 200 MHz) spectrum of compound 2 (Malabaricone B)

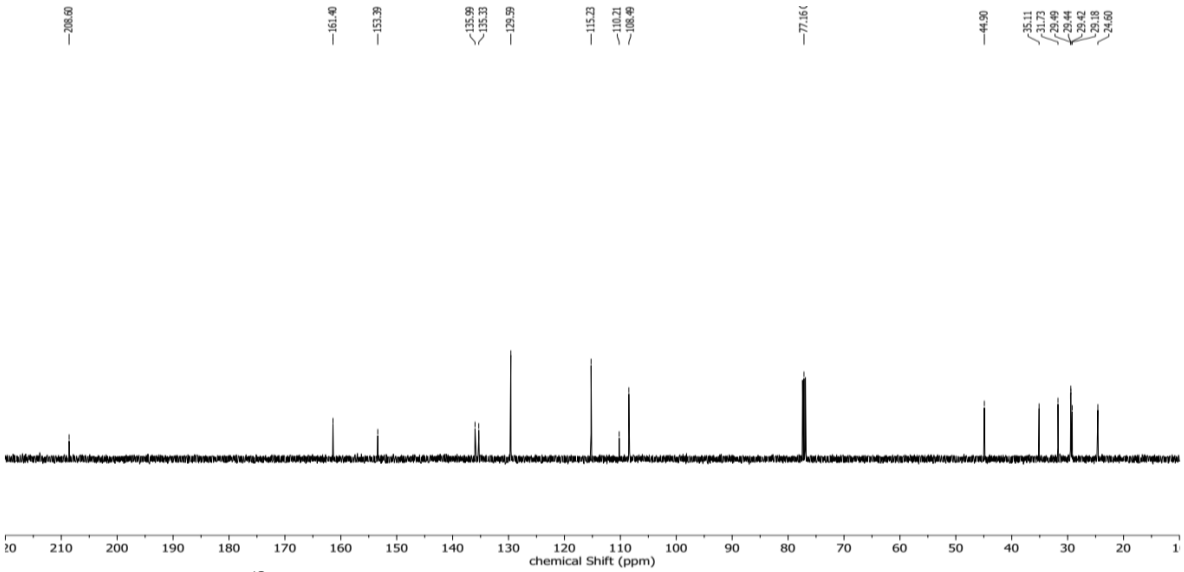


Figure S6. ^{13}C NMR (CD_3OD,50 MHz) spectrum of compound 2 (Malabaricone B)

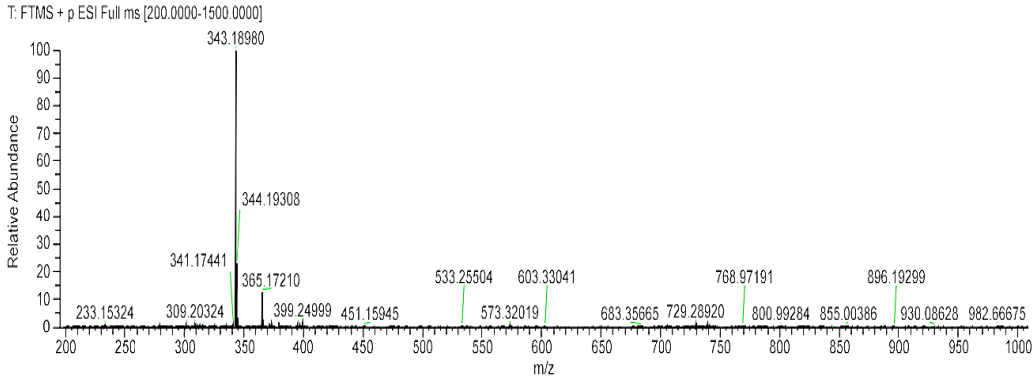


Figure S7. HRESI (positive mode) mass spectrum of compound 2 (Malabaricone B)

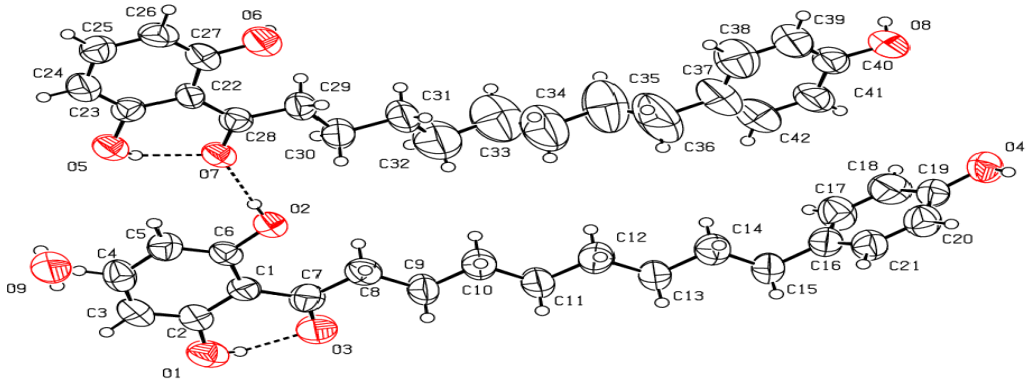


Figure S8. ORTEP diagram of compound 2 crystallized as twin molecules (Malabaricone B)

X-ray crystallographic analysis of compound **2** (Malabaricone B): Crystals of compound **2** were obtained from a mixture ethyl acetate and hexane.

Crystal data of compound **2**: symmetry cell setting monoclinic (0.500 x 0.080 x 0.080) mm^3, space group name $P2_1/n$. Unit cell dimensions: a = 5.378 (2) Å, α = 90°; b = 17.027(4) Å, β = 90.65 (2)° ; c = 42.401 (7) Å, γ = 90°; cell volume, V = 3882.5 (18) $Å^3$; cell formula unit, Z = 4; cell measurement temperature 293(2) K; cell reflection used 14535; cell measurement θ_{min} 2.578; cell measurement θ_{max} 25.348°; crystal description colourless needle shaped crystal; crystal diffraction density, d_x =1.202 Mg/m^3; diffraction ambient temperature 293 (2) K; diffraction radiation wave length, λ = 0.71073 Å; diffraction radiation type MoK\α; diffraction radiation source fine focus sealed tube; diffraction radiation monochromator graphite. Absorption coefficient 0.083 mm^{-1}; experimental crystal F (000) = 1512; θ range for data collection 2.578 to 25.348°. Limiting index ranges: 4<=h<=6, -20<=k<=15, -40<=l<=51; independent reflections measured = 6963 [R(int.) = 0.1550]. Completeness to θ = 25.242°, 97.5%. Absorption correction: semi-empirical from equivalents. Maximum and minimum transmission = 0.993 and 0.960. The structure was solved by direct methods and refined by full-matrix least-squares on F^2. Final R indices [I>2σ(I)]: R1 = 0.0937, wR2 = 0.1844; extinction coefficient 0.0014 (4); largest difference peak and hole 0.270 and -0.259 e. $Å^{-3}$

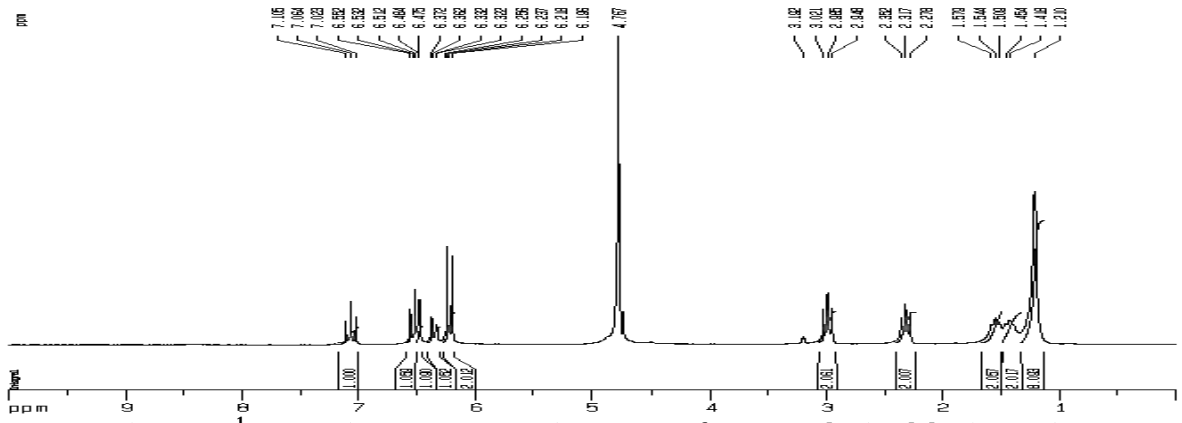


Figure S9. ^{1}H NMR (CD_3OD, 200 MHz) spectrum of compound 3 (Malabaricone C).

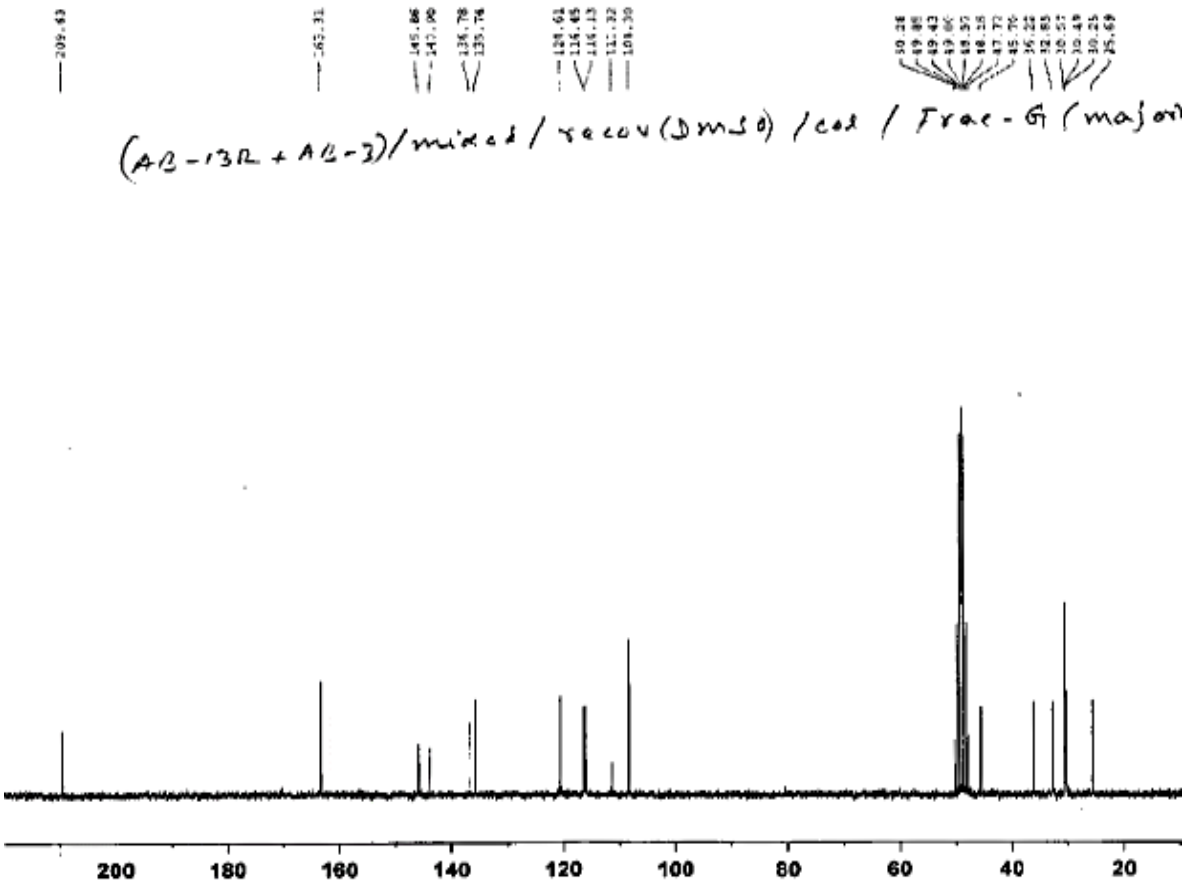


Figure S10. ^{13}C NMR (CD_3OD, 50 MHz) spectrum of compound 3 (Malabaricone C)

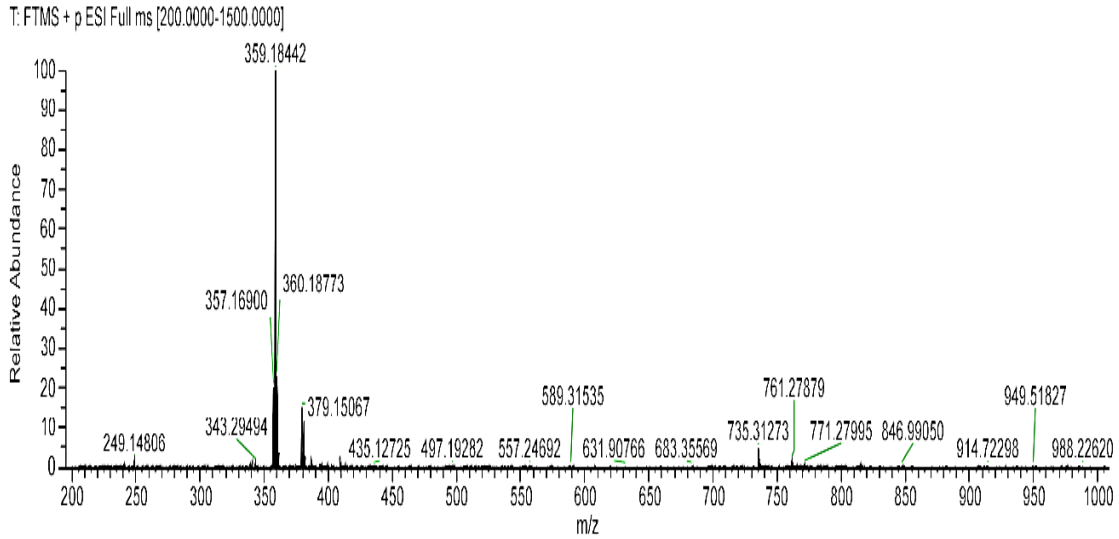


Figure S11. HRESI-MS (positive mode) spectrum of compound 3 (Malabaricone C)

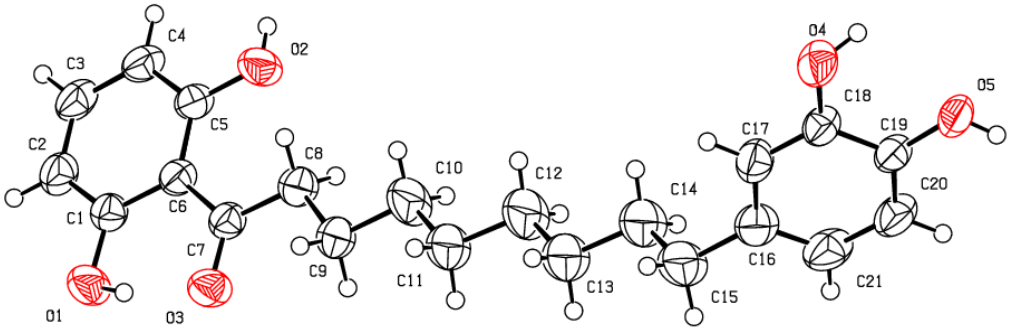


Figure S12. ORTEP diagram of compound 3 (Malabaricone C)

X-ray Crystallographic Analysis of compound **3** (Malabaricone C): Crystals of compound **3** were obtained in a mixture ethyl acetate and hexane.

Crystal data of compound **3**: symmetry cell setting orthorhombic; size of crystals used for diffraction study (0.5 5x 0.25 x 0.20 mm^3); symmetry space group $P2_12_12_1$; space group name P 2ac 2ab. Unit cell dimensions: a = 5.4549 (6), α = 90°, b = 9.176 (1), β = 90°, c = 40.718(3), γ = 90°; cell volume, V = 2038.1(3). Unit cell formula, Z = 4; cell measurement temperature, T 299 (2); cell measurement reflections used = 25; cell measurement θ_{min} = 5.81, cell measurement θ_{max} = 20.19; crystal description long needle dark yellow in color; crystal density diffraction, d = 1.227 Mgm^{-3}; diffraction ambient temperature, T 299 (2)°; diffraction radiation wave length, λ = 1.54180; diffraction radiation type CuK\α; diffraction radiation source fine focus sealed tube; diffraction radiation monochromator graphite. 3822 independent reflections were measured and 3323 reflections were observed with [R (int.) = 0.032]. Completeness to θ = 67.0, 100%. The structure was solved by direct methods and refined by a full matrix least square on F^2. Final R indices [I>2σ (I)]: R1 = 0.048, wR2 = 0.137; s = 1.04; extinction coefficient 0.0035(6), largest difference peak and hole = 0.20 and -0.21 e.$Å^{-3}$.

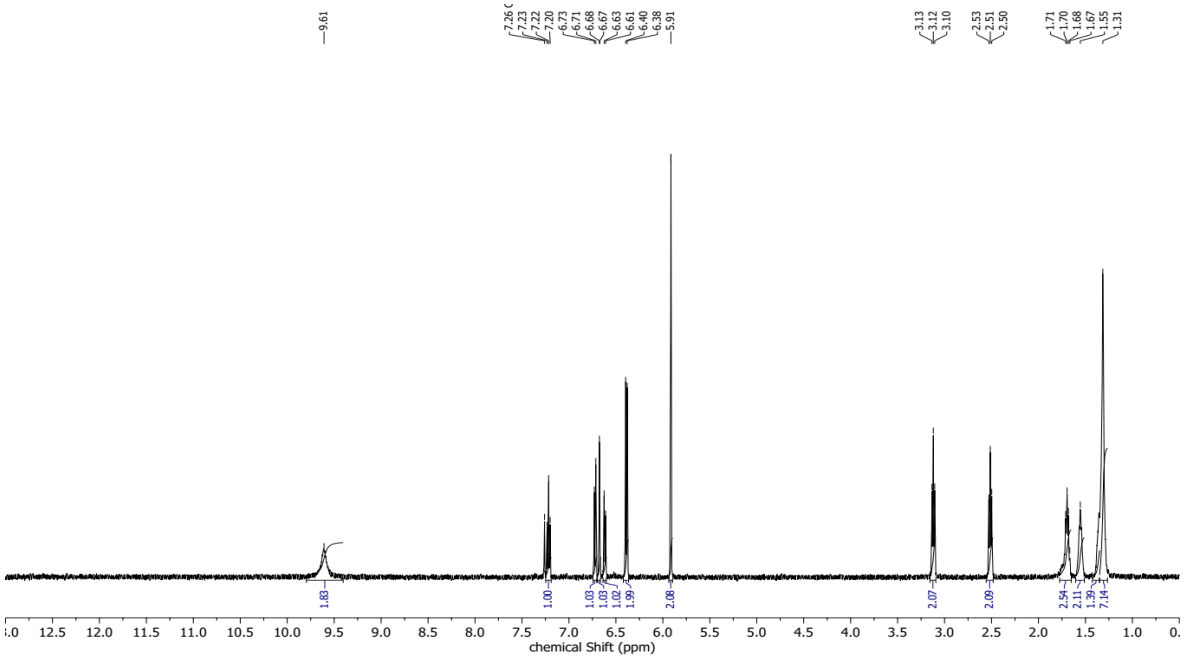


Figure S13: ^{1}H NMR (CD_3OD, 200 MHz) spectrum of compound 4 (Malabaricone D).

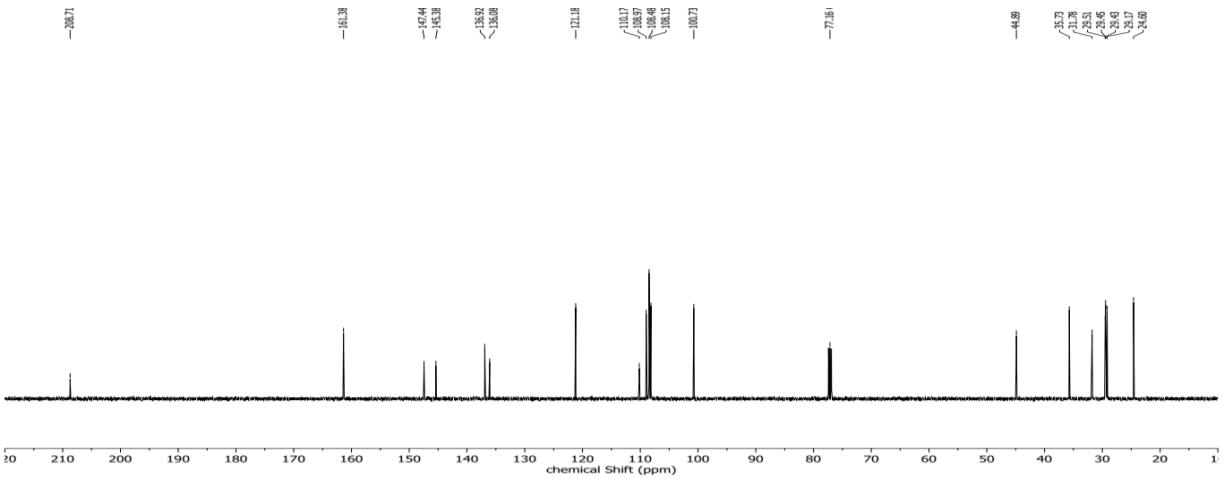


Figure S14: ^{13}C NMR (CD_3OD, 50 MHz) spectrum of compound 4 (Malabaricone D).

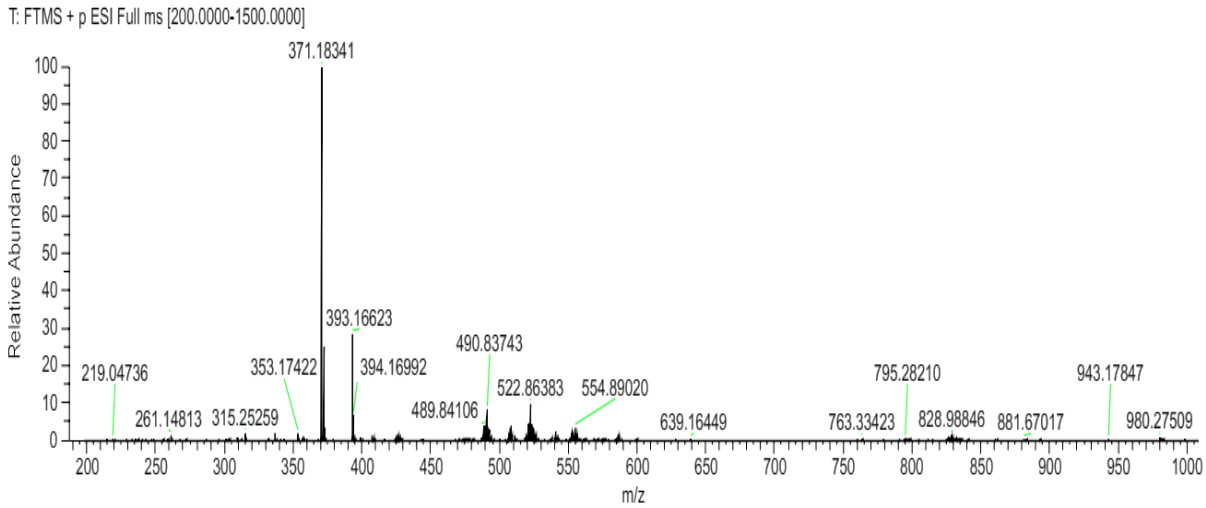


Figure S15: HRESI-MS of compound 4 [found MH^+ = 371.1834] (Malabaricone D).

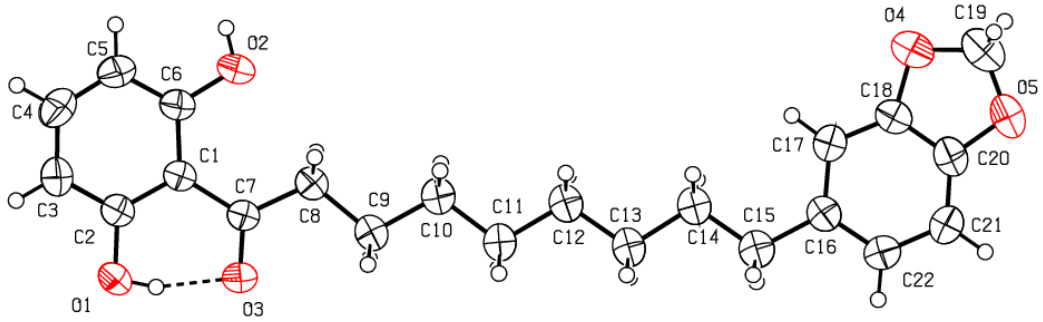


Figure S16: ORTEP diagram compound 4 (Malabaricone D.

X-ray crystallographic analysis of compound **4** (Malabaricone D): It was crystallized from a mixture of binary solvent system using ethyl acetate and hexane in ratio 20:80 v/v by slow evaporation method.

Crystal data of compound **4** (Malabaricone D): Empirical formula of molecule $C_{22}H_{26}O_5$; formula weight of it 370.43; crystal description: prism shaped yellow color; size of crystal used for diffraction study (0.480 x 0.440 x 0.240 mm^3); symmetry cell setting:monoclinic; symmetry space group name:$P2_1/c$. Unit cell dimensions: a = 12.837 (2) Å, α = 90°, b = 14.178 (2) Å, β = 98.28 (2)°, c = 10.815 (2) Å, γ = 90°; cell volume, V = 1947.8 (6) $Å^3$. Unit cell formula, Z = 4; cell measurement temperature, T 293(2) °K; cell measurement reflections collected = 7321; θ range for data collection: 2.716 to 25.347°. cell measurement θ_{min} : 2.716°, cell measurement θ_{max}: 25.347°; Index ranges-15<=h<=14, -

17<=k<=15, -12<=l<=13; crystal density diffraction, d = 1.227 Mg/m^3; diffraction ambient temperature, T 293(2)°; diffraction radiation wave length, λ = 0.71073 Å; source of diffraction radiation type MoK\α; diffraction radiation source fine focus sealed tube; diffraction radiation monochromator graphite; diffraction measurement device type: Oxford Diffraction Xcalibur (TM) Single Crystal X-ray Diffractometer with Sapphire CCD Detector. Total reflections were collected 3747 [R(int.) = 0.0515]; independent reflections were measured with 3542 [R(int.) = 0.0590]; R indices (all data): R1 = 0.1127, wR2 = 0.2302. Maximum and minimum transmission were 0.979 and 0.959; Completeness to θ = 25.242°, 99.4%. Method used for absorption correction is semi-empirical from equivalents. Structure was solved by direct methods and refined by a full matrix least square on F^2. Goodness-of-fit on $F^2$1.008Final R indices [I>2sigma(I)]: R1 = 0.0669, wR2 = 0.1773; restrain refined, s = 1.063; extinction coefficient 0.00079(17), largest difference peak and hole 0.205&-0.316 e.$Å^{-3}$.

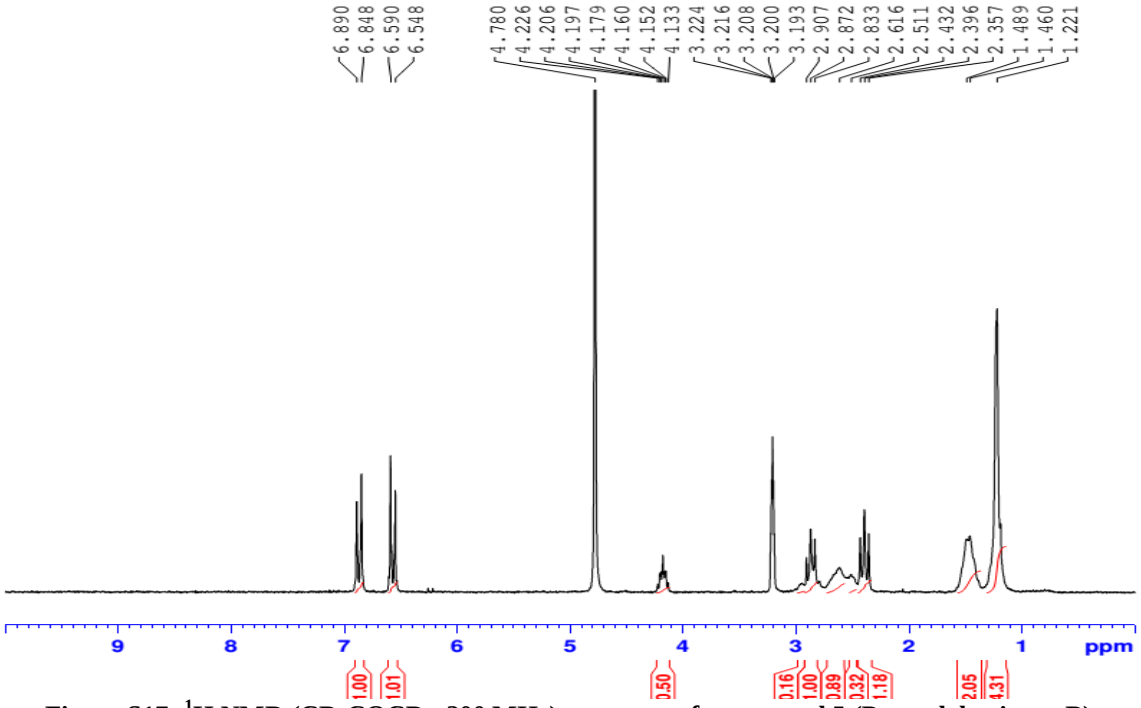


Figure S17: ^{1}H NMR (CD_3COCD_3, 200 MHz) spectrum of compound 5 (Promalabaricone B).

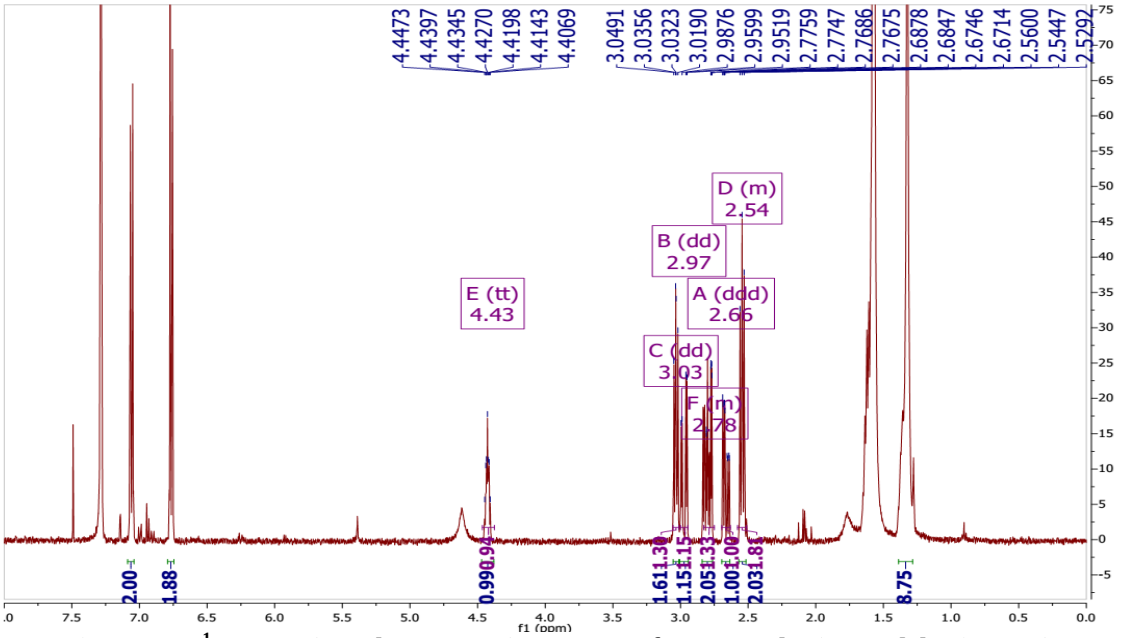


Figure S18: ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound 5 (Promalabaricone B)

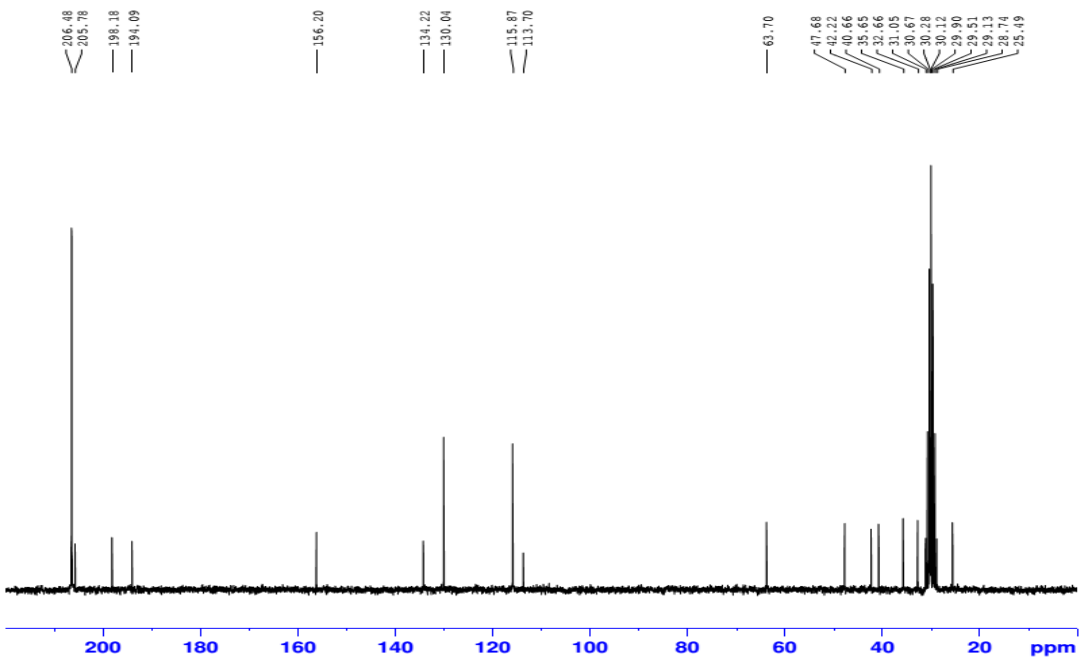


Figure S19: ^{13}C NMR (CD_3COCD_3,50 MHz) spectrum of compound 5 (Promalabaricone B)

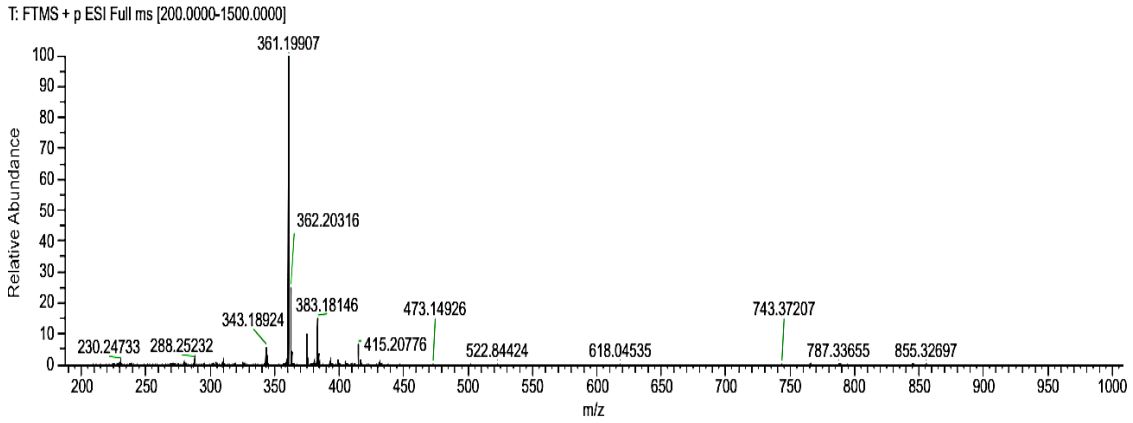


Figure S20: HR-ESI mass spectrum of compound 5 (Promalabaricone B)

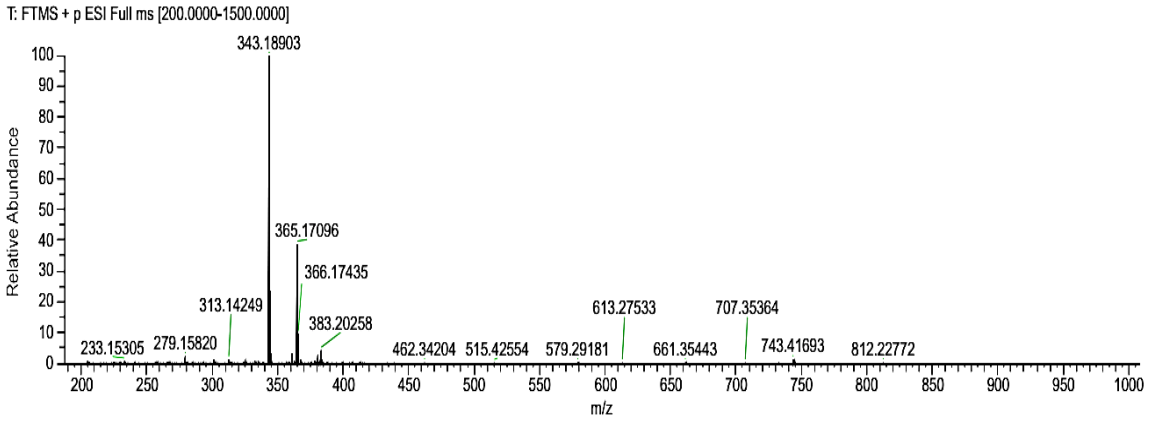


Figure S21: HR-ESI Mass Spectrum of compound 5 [M-H_2O] (Promalabaricone B) recorded from OSU, USA.

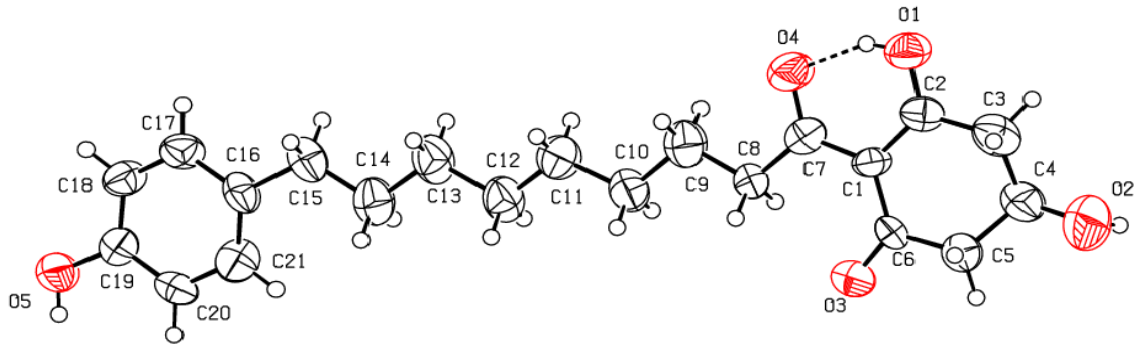


Figure S22: ORTEP diagram of compound 5 (Promalabaricone B)

X-ray crystallographic analysis of compound **5** (promalabaricone B): It was from a mixture of ethyl acetate and hexane by slow evaporation technique at room temperature.

Crystal data of compound **5** (Promalabaricone B): orthorhombic crystal (0.28 x 0.12 x 0.20 mm^3); space group name Pbca. Unit cell dimension measured: a = 15.690 (2) A, α = 90°; b = 5.382 (1) A, β = 90°; c = 48.546 (5) A, γ = 90°; cell volume, V = 4099 (10) A^3. Unit cell formula, Z = 8; absorption coefficient, μ = 0.09 mm^{-1}. Experimental crystal F (000) = 1632. Number of independent reflections were measured = 8537 and number of independent reflections observed 3753 [R(int.) = 0.1072]. Completeness to θ = 25.24, 98.8%. Crystal density diffraction, d_x =1.226 Mg/m^3. Absorption correction: semi-empirical equivalents; crystal description orthorhombic, crystal colour -colourless. Diffraction radiation ambient temperature 293(2) K; diffraction radiation wavelength, λ = 0.71073 A; diffraction radiation type MoK\α; diffraction radiation source fine focuses sealed tube; diffraction radiation monochromator graphite; θ range for data collection 2.596 to 25.346°. Limiting indices -18<=h<=14, -4<=k<=6, -23<=l<=58; Maximum and minimum transmission: 0.998 and 0.976; Structure was solved by direct methods refined by full-matrix least-squares on F^2. Final R indices [I >2σ (I)]: R1 = 0.1406, wR2 = 0.3301; R indices (all data) R1 = 0.3407, wR2 = 0.4505; largest difference peak and hole 0.656 and -0.268 e. A^{-3}.

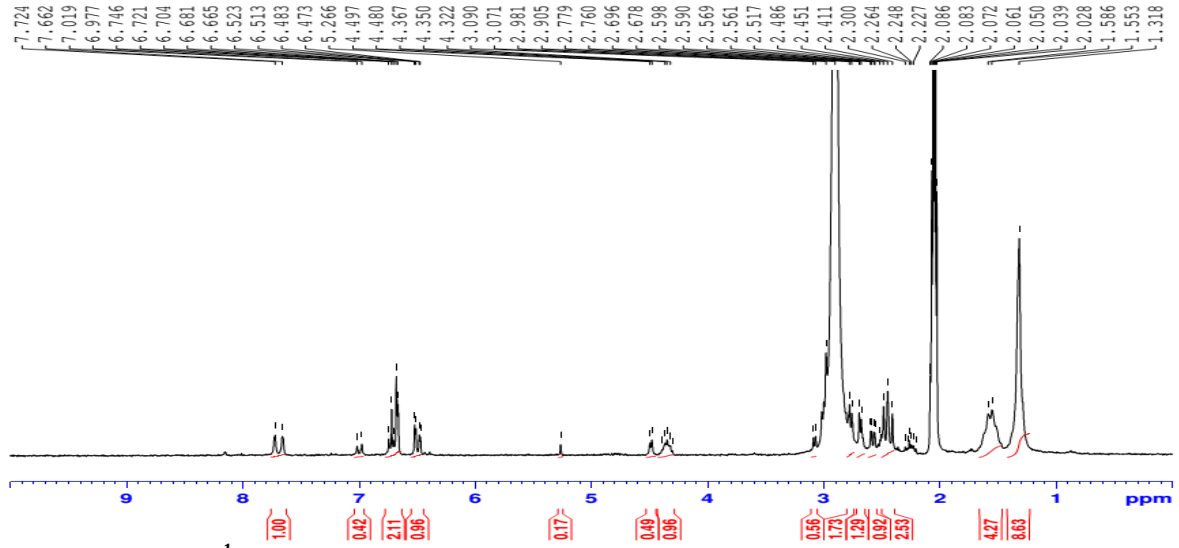


Figure S23.^{1}H NMR (CD_3OD, 200 MHz) spectrum of compound 6 (Promalabaricone C)

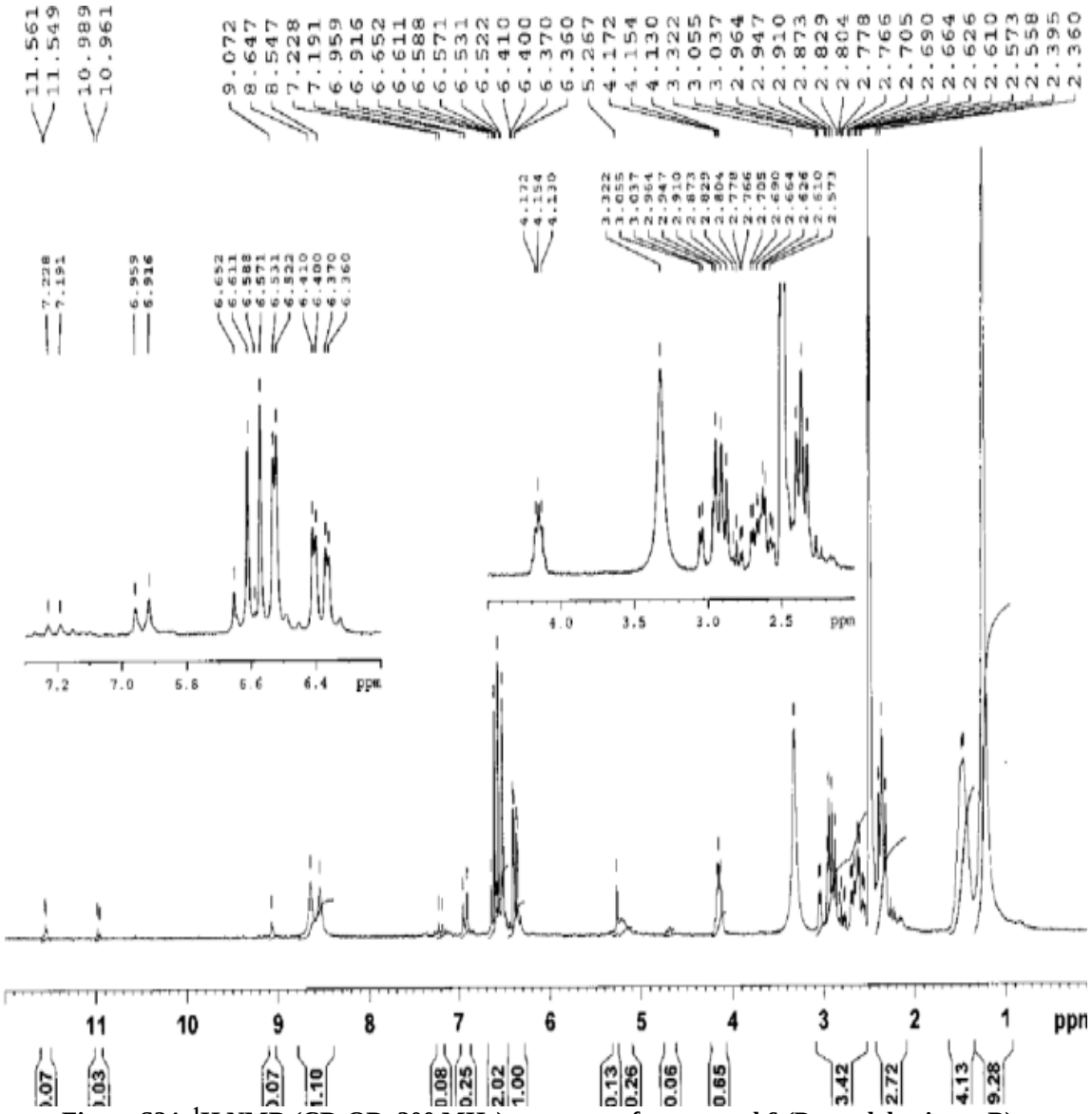


Figure S24. ^{1}H NMR (CD_3OD, 200 MHz) spectrum of compound 6 (Promalabaricone B).

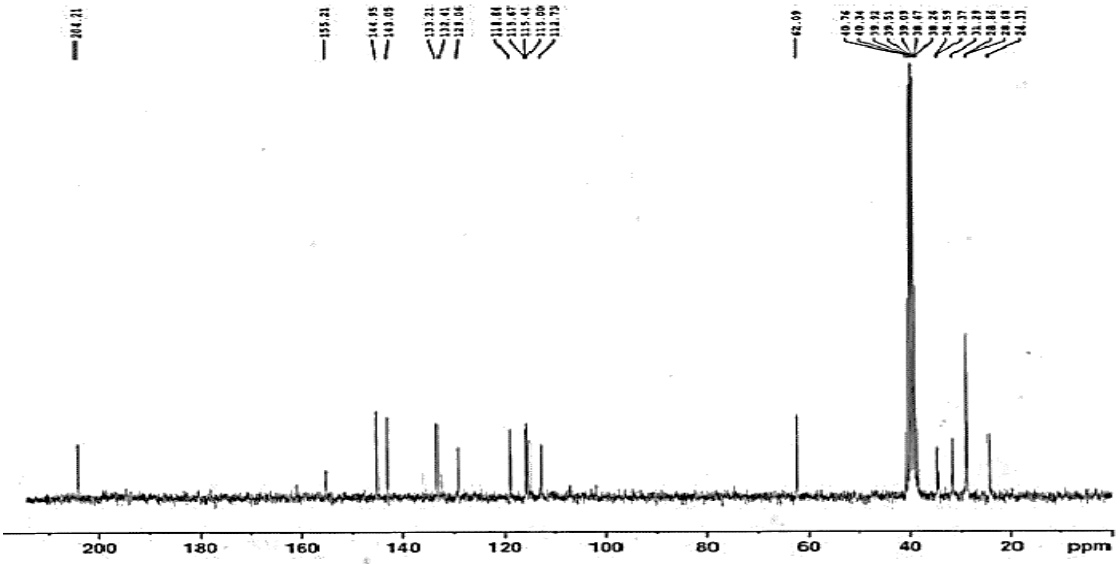


Figure S25. ^{13}C NMR (CD_3OD, 50 MHz) spectrum of compound 6 (Promalabaricone B).

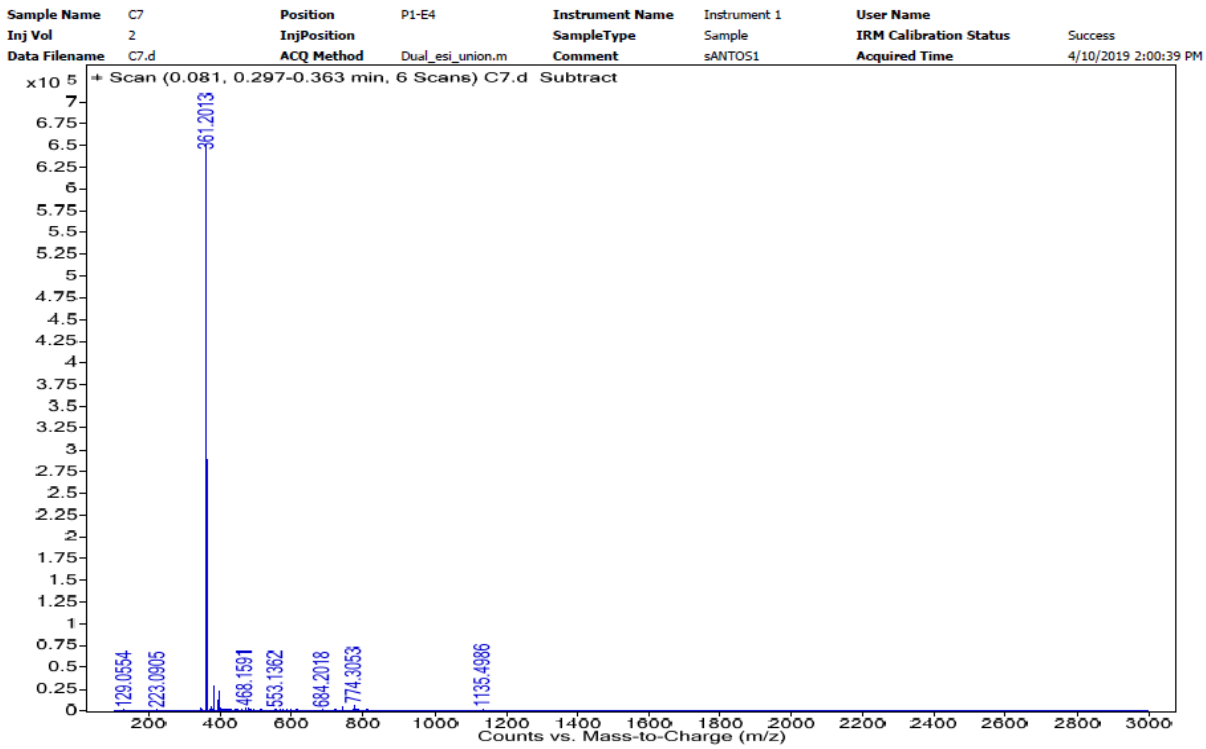


Figure S26. HRESI-MS spectrum of compound 6 [one water molecule eliminated (M^+-H_2O)] (Promalabaricone B).

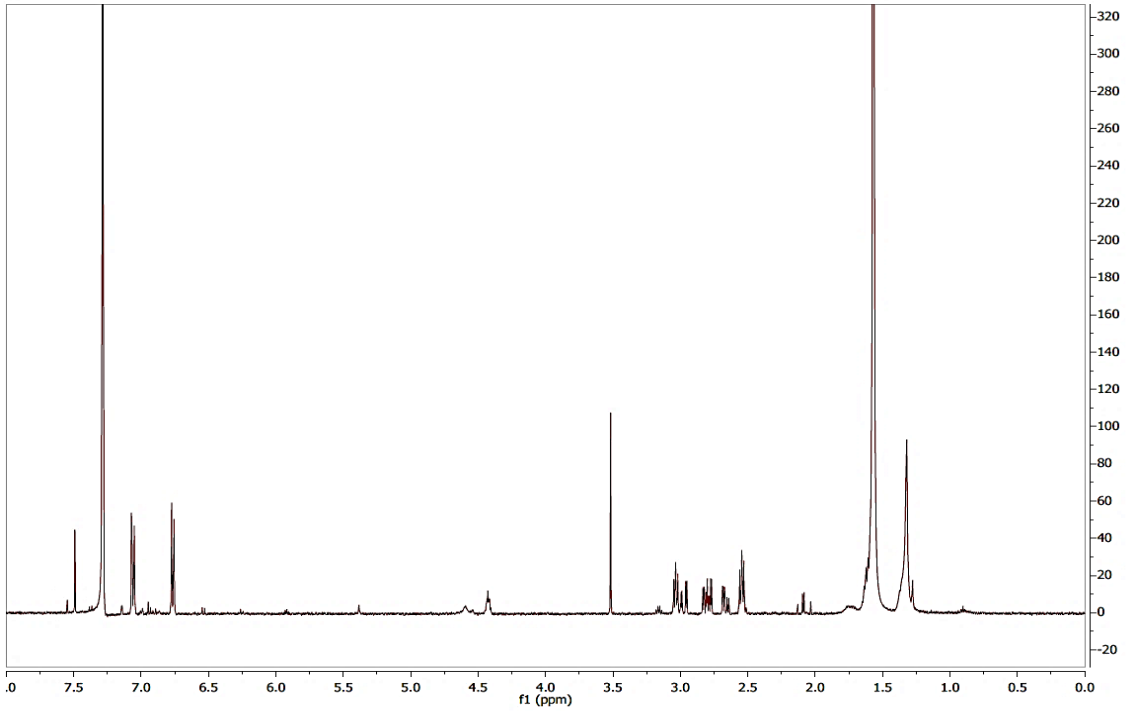


Figure S27. ^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of compound 7 (Ericanone).

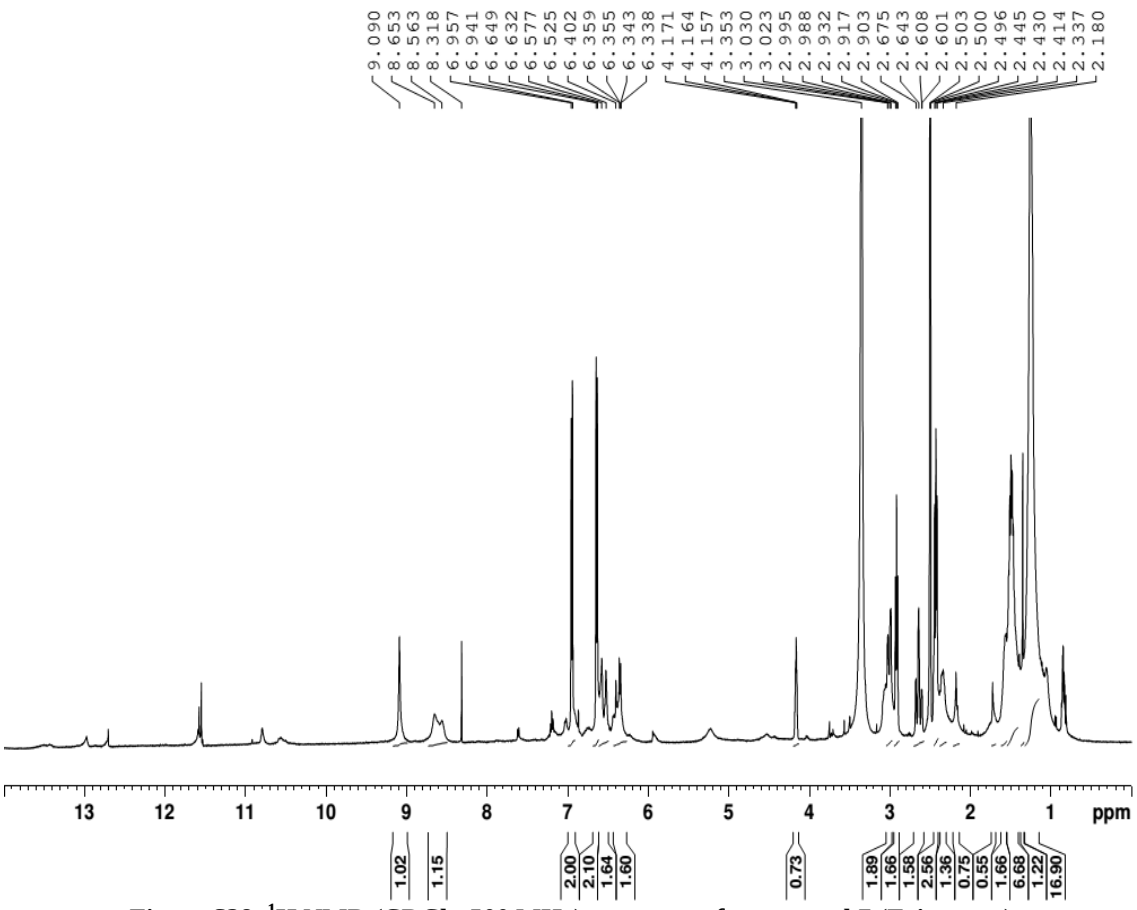


Figure S28. ^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of compound 7 (Ericanone).

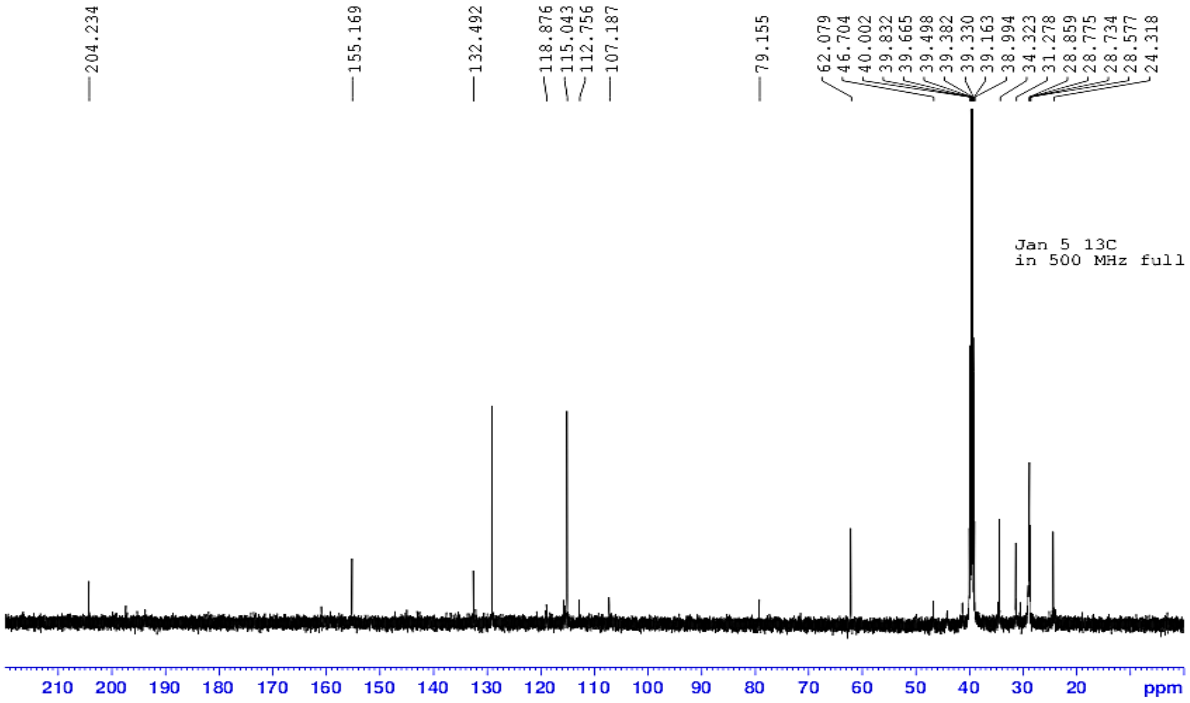


Figure S29.^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of compound 7 (Ericanone).

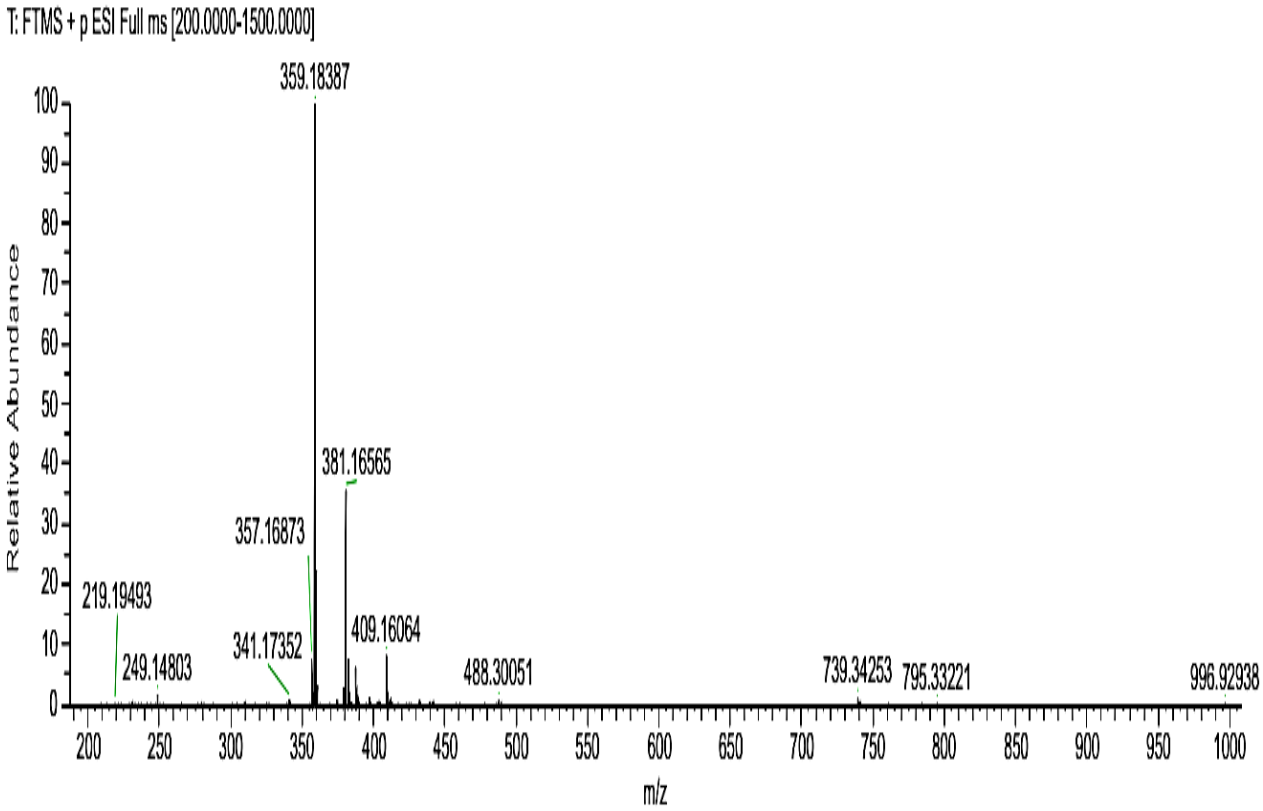


Figure S30. HRESI-MS spectrum (in positive mode) of compound 7 (Ericanone), recorded from OSU, USA.

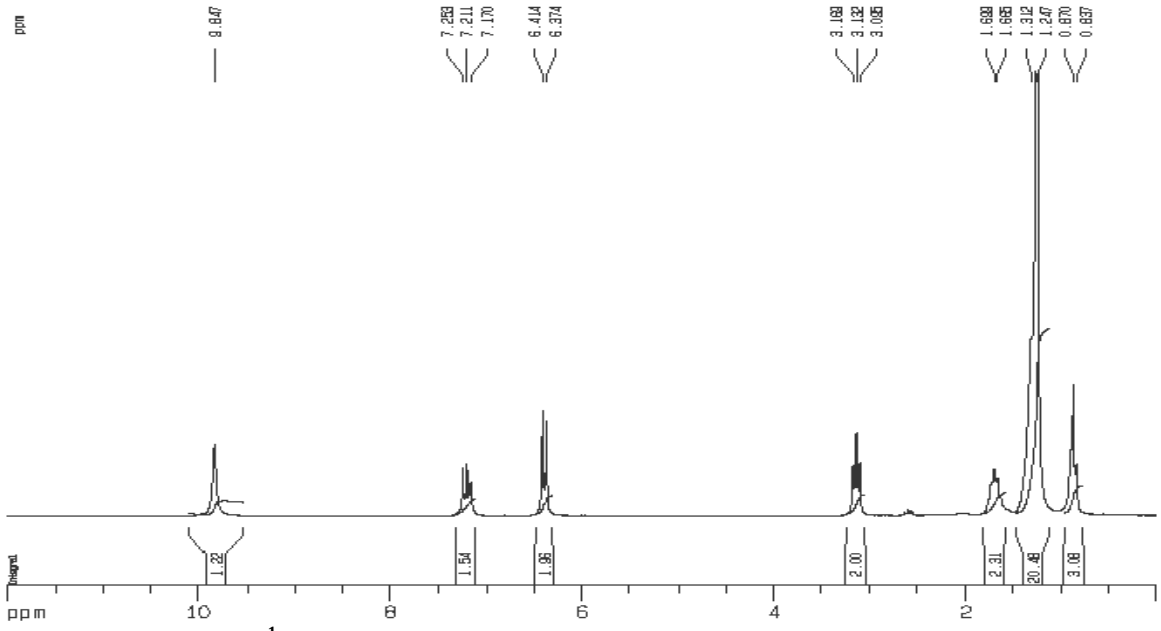


Figure S31. ^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of compound 8 (Acyl phenol).

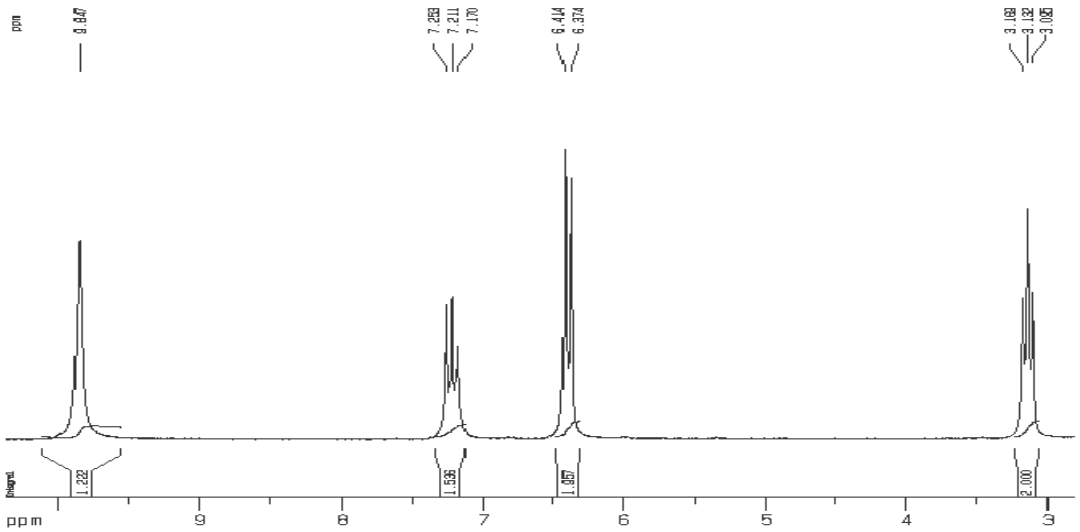


Figure S32. ^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of compound 8 (Acyl phenol).

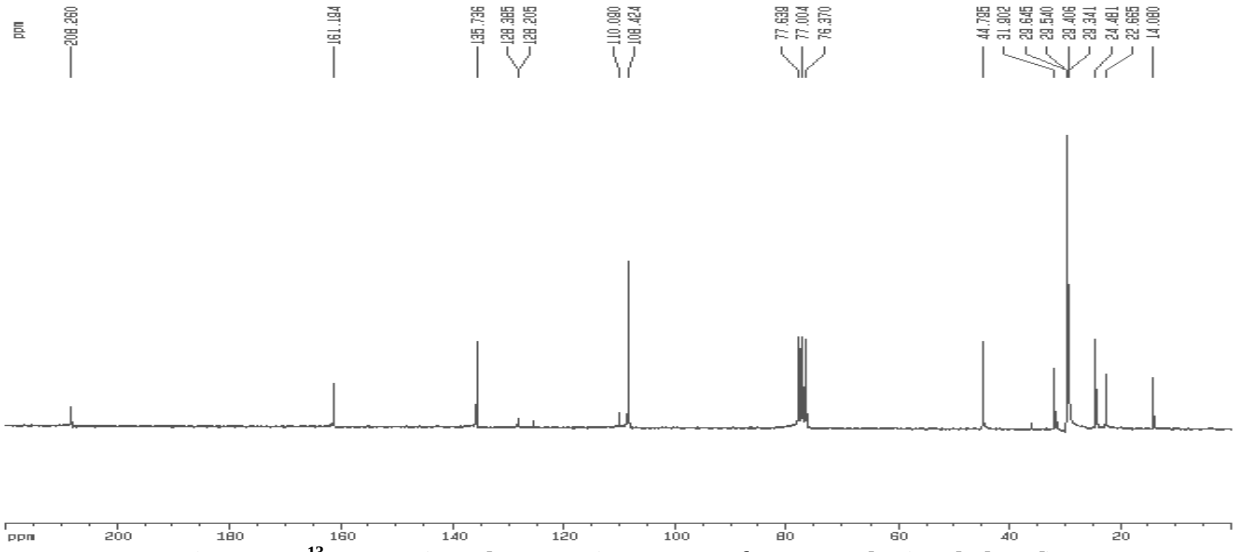


Figure S33.^{13}C NMR ($CDCl_3$,50 MHz) spectrum of compound 8 (Acyl phenol)

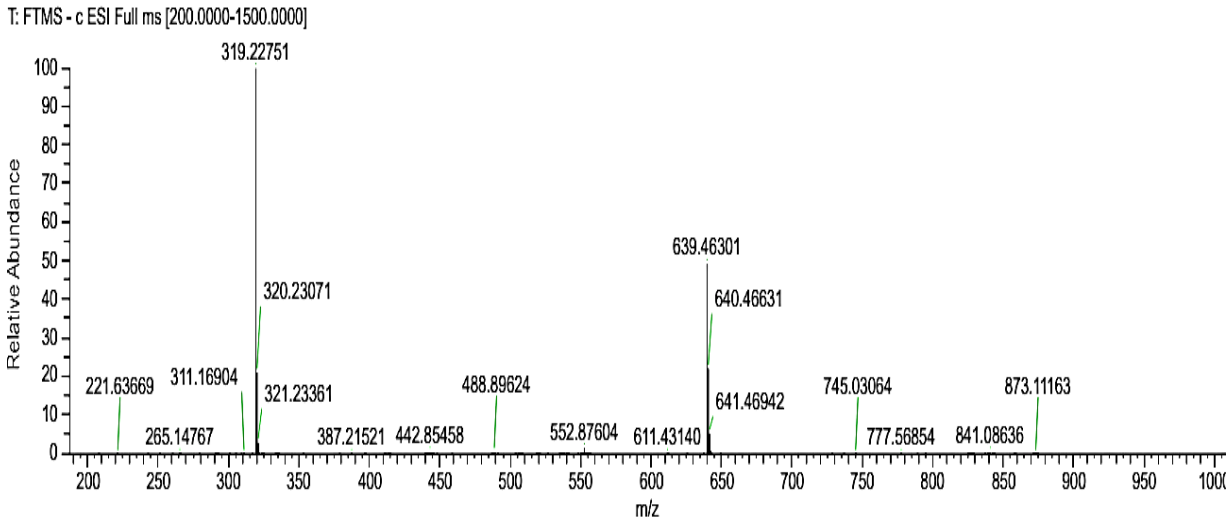


Figure S34. HRESI-MS (negative mode) of compound 8 (Acyl phenol).

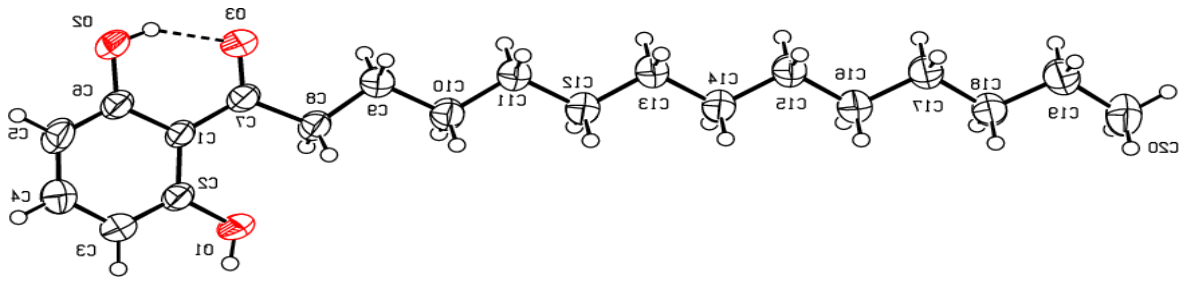


Figure S35. ORTEP diagram of compound 8 (Acyl phenol).

X-ray Crystallographic Analysis of compound **8** (Acyl phenol): It was crystallized from a mixture of ethyl acetate and hexane in ratio 10:90 v/v by slow evaporation method at room temperature.

Crystal data of compound **7** (Acyl, phenol): monoclinic crystal (0.50 x 0.12 x 0.08 mm); space group name P 21/c; crystal description long needle; crystal colour pale yellow. Unit cell dimensions: a = 4.2047 (6) A, α = 90°; b = 34.146 (4) A, β = 97.67 (1) °; c = 13.347 (3) A, γ = 90°; cell volume, V = 1899.1 (6) A^3. Unit cell formula, Z = 4; cell measurement temperature 293 (2) K; cell measurement θ_{min} = 2.84 deg. Cell measurement θ_{max} = 25.34 deg. Crystal density diffraction, d_x =1.121 Mg/m^3. Diffraction temperature 293K; diffraction radiation wave length, λ = 0.71073 A; diffraction radiation type MoK\α. Diffraction radiation source fine focus sealed tube. Absorption coefficient, μ = 0.07 mm^{-1}. Total number of independent reflections were measured 6324, number of independent reflections 3396 and number of independent reflections were observed [R (int.) = 0.0252] = 2217. Completeness to theta = 25.34; 98.3%. Absorption correction: semi-empirical from equivalents. Maximum and minimum transmission = 0.9942 and 0.9643. The structure was solved by direct methods and refined by full-matrix least-squares on F^2. Final R indices [$F^2>2\sigma(F^2)$], R1 = 0.0857, wR (F^2) = 0.160; R indices (all data) R1 = 0.1364, wR2 = 0.1604. Largest difference peak and hole 0.19 and -0.16 e. A^{-3}.

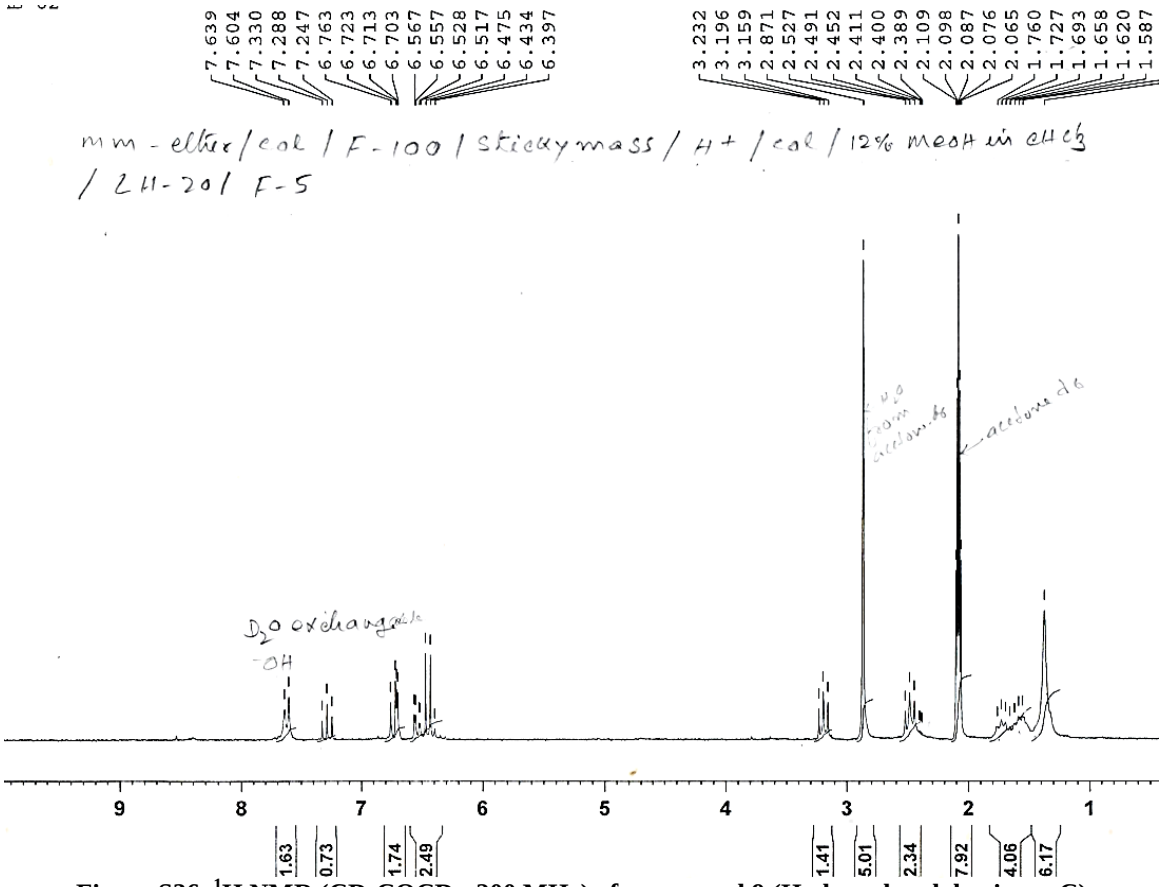


Figure S36. ^1H NMR (CD_3COCD_3, 200 MHz) of compound 9 (Hydrated malabaricone C)

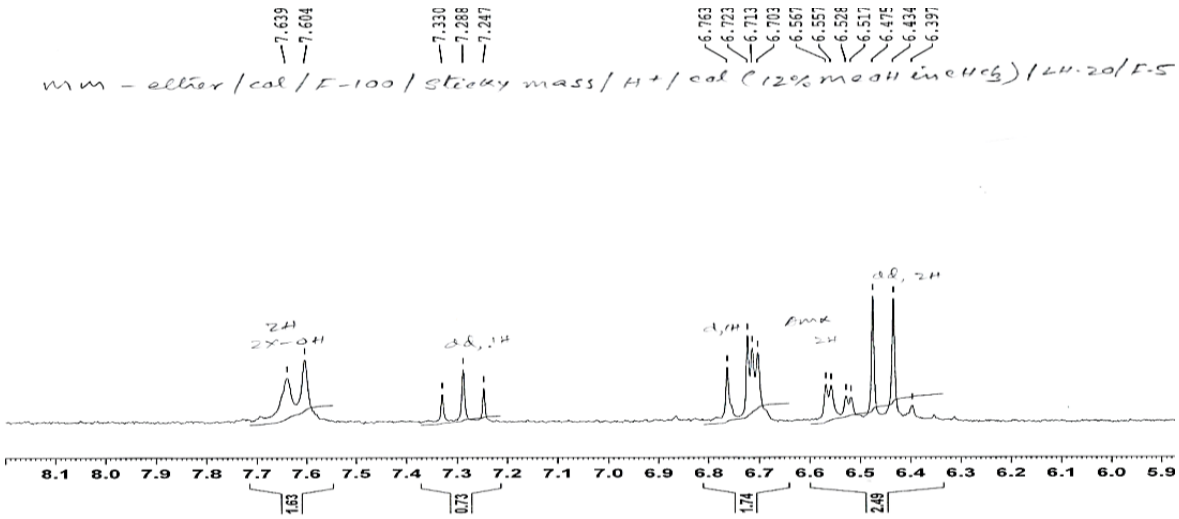


Figure S37. Expansion of ^{1}H NMR (CD_3COCD_3, 200 MHz) of compound 9 (Hydrated malabaricone C)

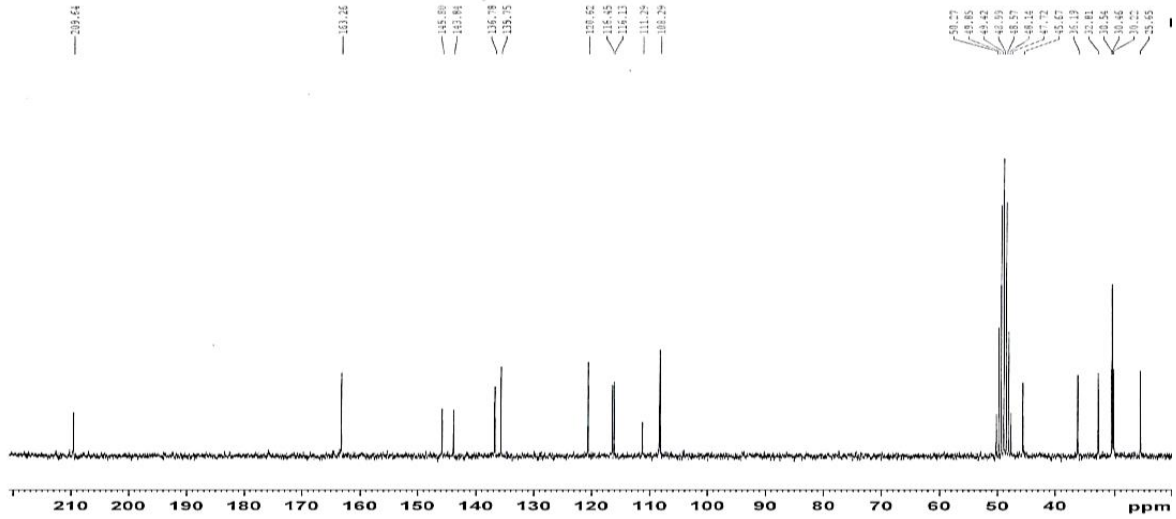


Figure S38. ^{13}C NMR (CD_3COCD_3, 50 MHz) of compound 9 (Hydrated malabaricone C)

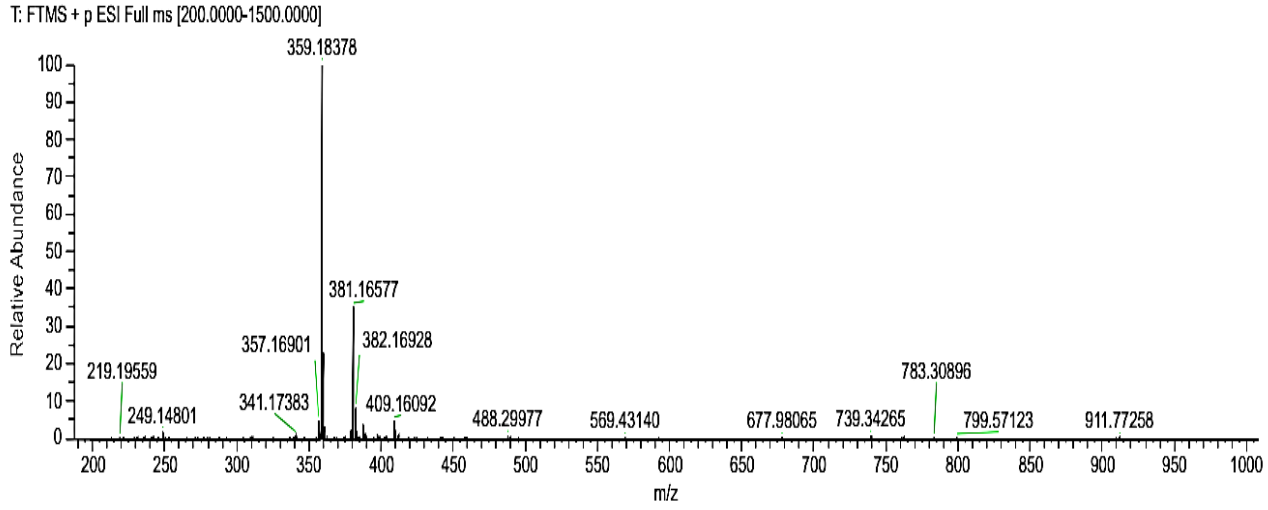


Figure S39. HR-ESIMS spectrum (positive mode) of compound 9 (Hydrated malabaricone C)

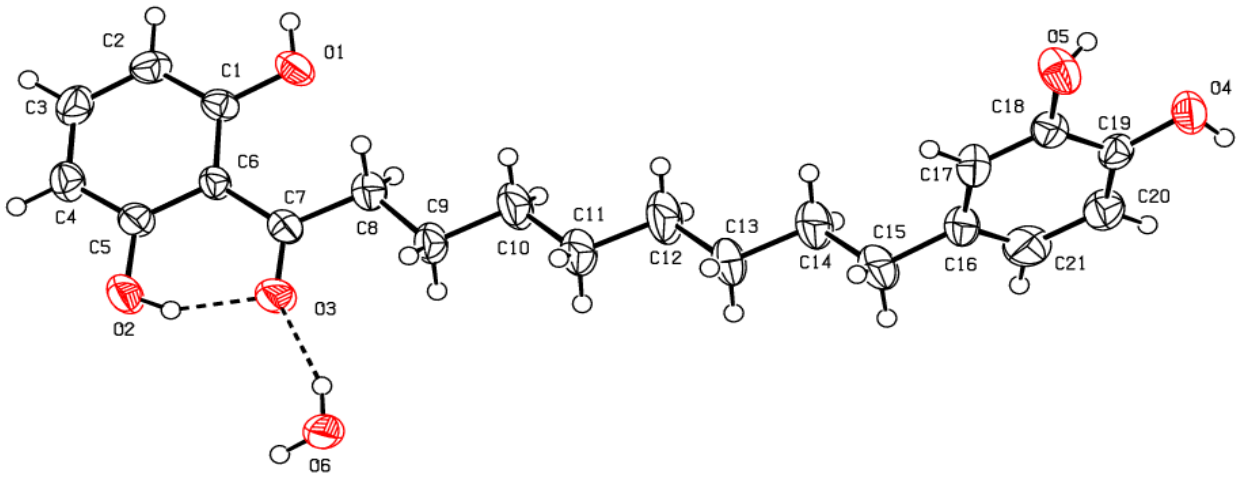


Figure S40. ORTEP diagram of compound 9 (Hydrated malabaricone C)

Crystal data of compound **9** (Hydrated malabaricone C): symmetry cell setting orthorhombic; size of crystals used for diffraction study (0.55 x 0.25 x 0.20 mm^3); symmetry space group $P2_12_12_1$; space group name P 2ac 2ab. Unit cell dimensions: a = 5.4549 (6), α = 90°, b = 9.176 (1), β = 90°, c = 40.718 (3), γ = 90°; cell volume, V = 2038.1 (3). Unit cell formula, Z = 4; cell measurement temperature, T 299 (2); cell measurement reflections used = 25; cell measurement θ_{min} = 5.81, cell measurement θ_{max} = 20.19; crystal description long needle dark yellow in color; crystal density diffraction, d = 1.227 Mgm^{-3}; diffraction ambient temperature, T 299 (2)°; diffraction radiation wave length, λ = 1.54180; diffraction radiation type CuK\α; diffraction radiation source fine focus sealed tube; diffraction radiation monochromator graphite. 3822 independent reflections were measured and 3323 reflections were observed with [R (int.) = 0.032]. Completeness to θ = 67.0, 100%. The structure was solved by direct methods and refined by a full matrix least square on F^2. Final R indices [I>2σ (I)]: R1 = 0.048, wR2 = 0.137; s = 1.04; extinction coefficient 0.0035(6), largest difference peak and hole = 0.20 and -0.21 e.$Å^{-3}$.

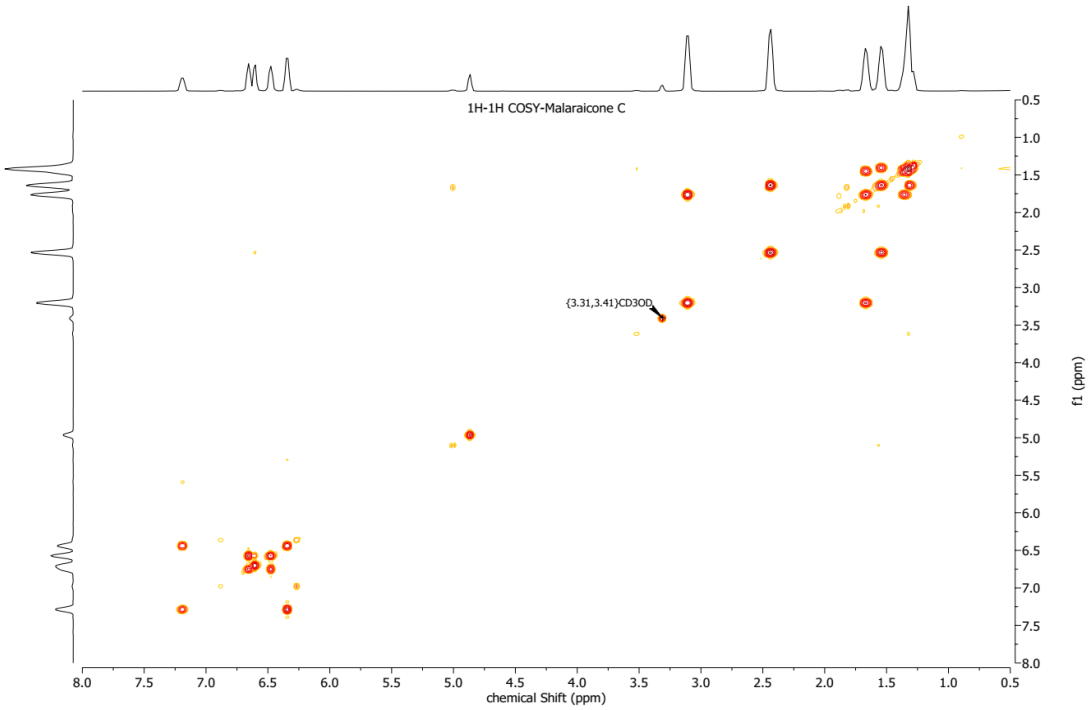


Figure S41: ^1H-^1H COSY (800 MHz, CD_3OD) of compound 3 (Malabaricone C)

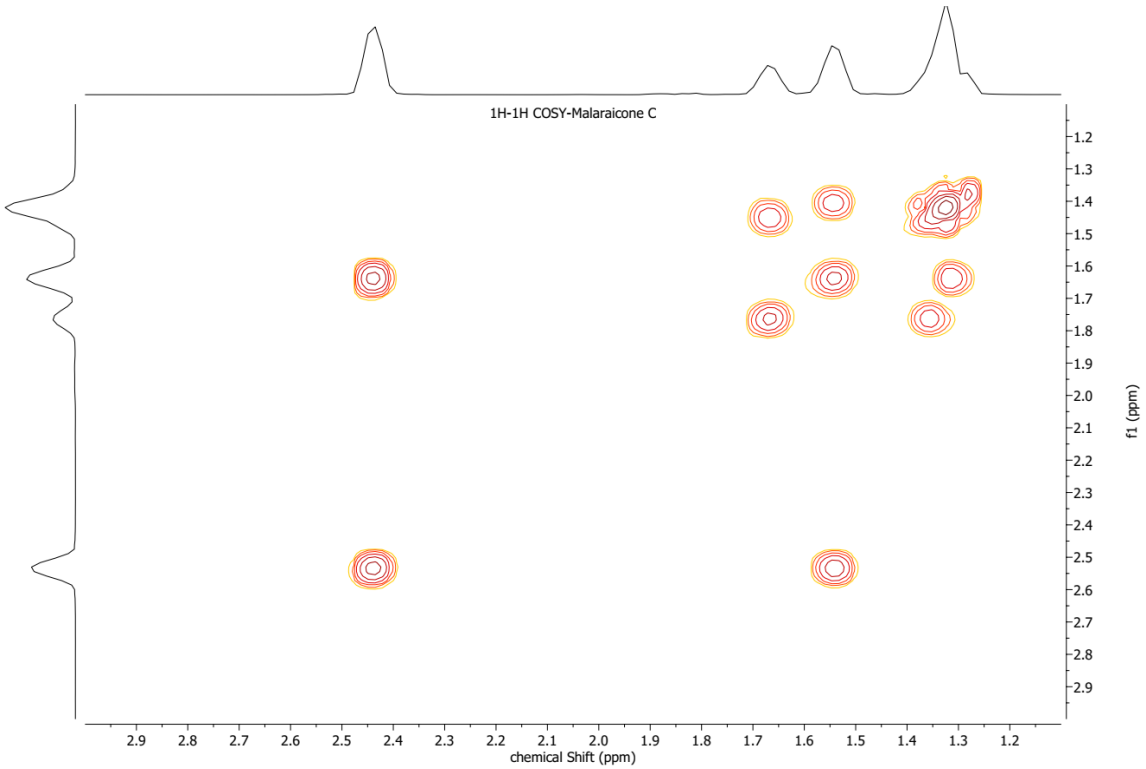


Figure S42: Expansion of ^{1}H-^{1}H COSY (800 MHz, CD_3OD) of compound 3 (Malabaricone C)

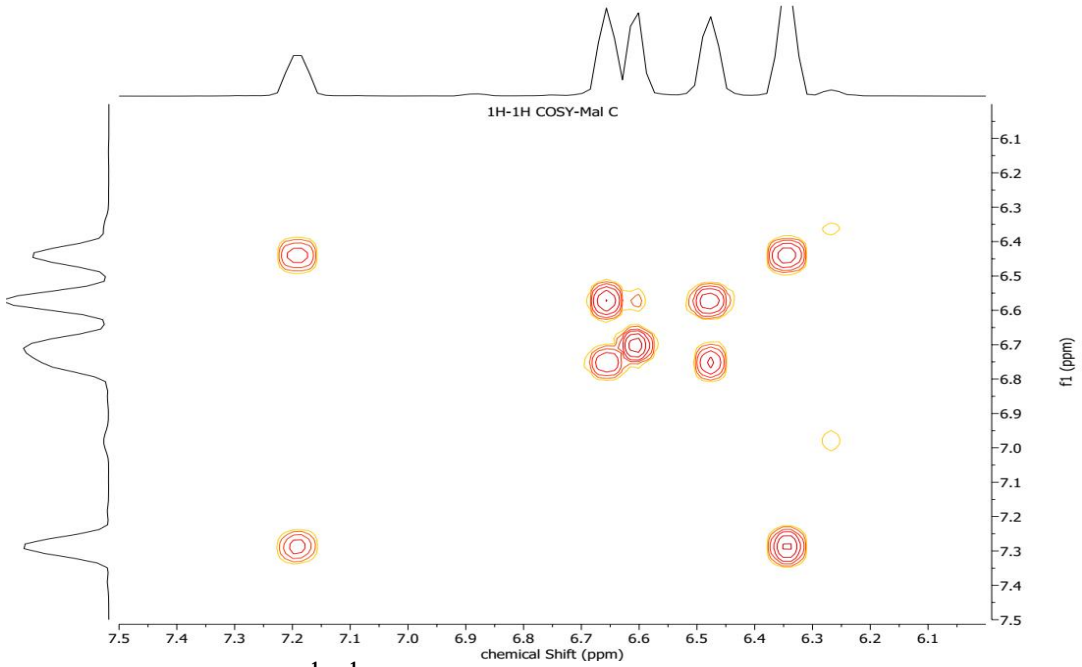


Figure S43: Expansion of ^{1}H-^{1}H COSY (800 MHz, CD_3OD) of compound 3 (Malabaricone C)

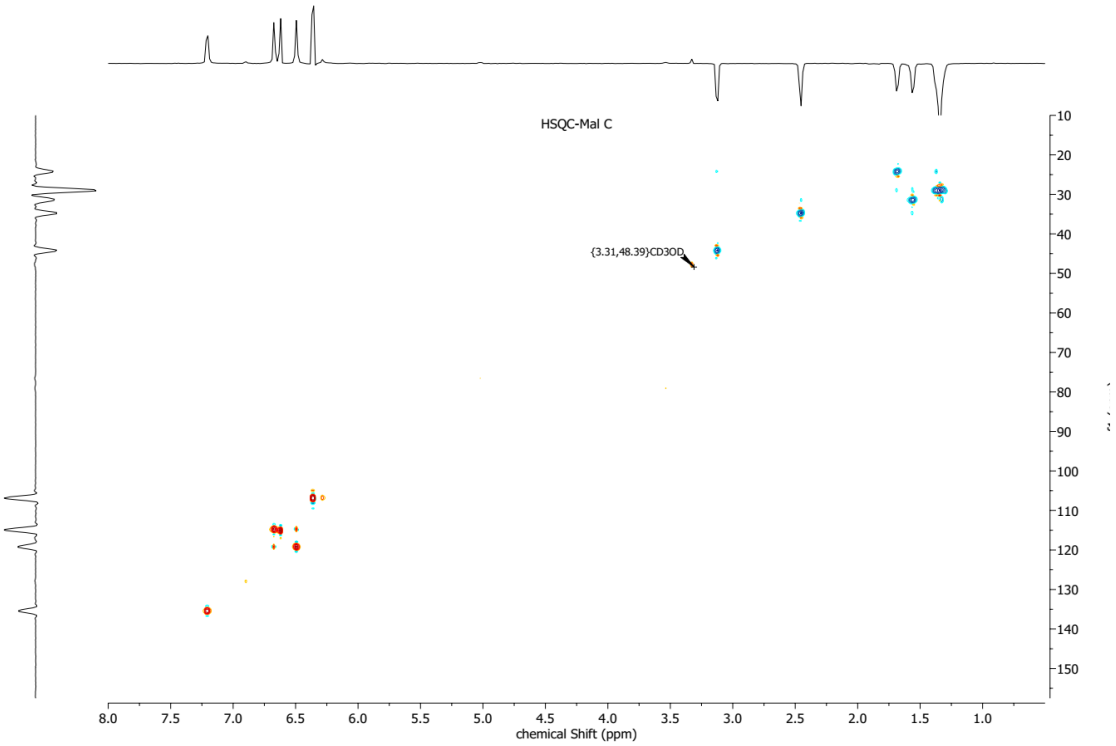


Figure S44: ^{1}H-^{13}C HSQC (800 MHz, 201 MHz, CD_3OD) of compound 3 (Malabaricone C)

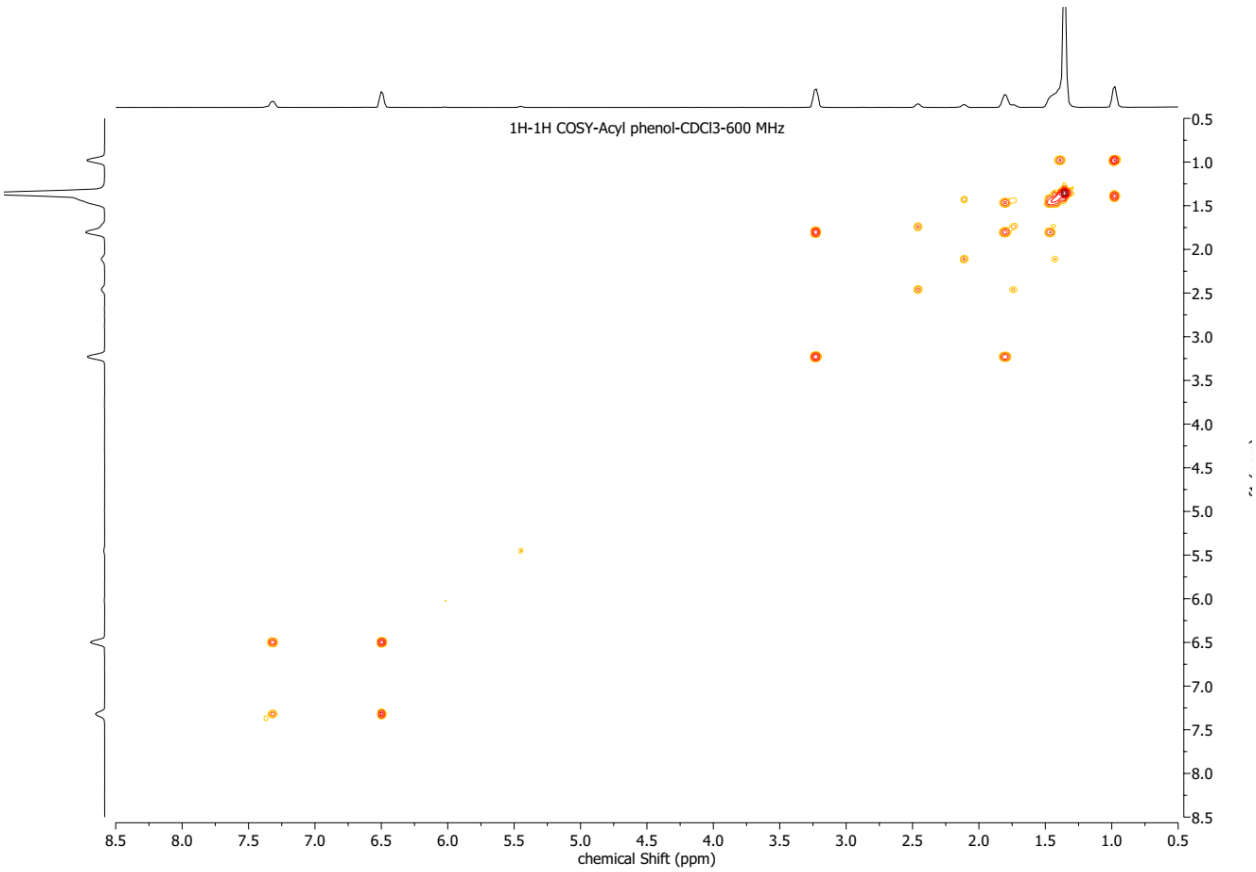


Figure S45: ^{1}H-^{1}H COSY ($CDCl_3$, 800 MHz) of compound 8 (Acyl phenol)

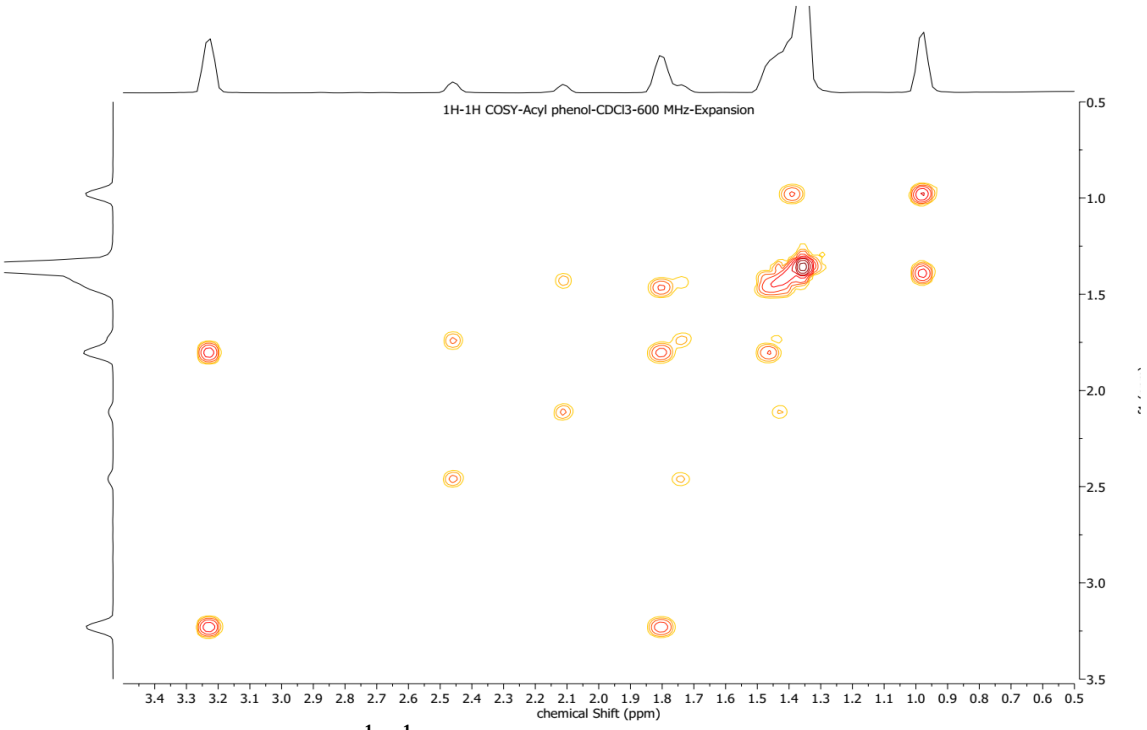


Figure S46: Expansion of ^{1}H-^{1}H COSY (800 MHz, $CDCl_3$) of compound 8 (Acyl phenol)

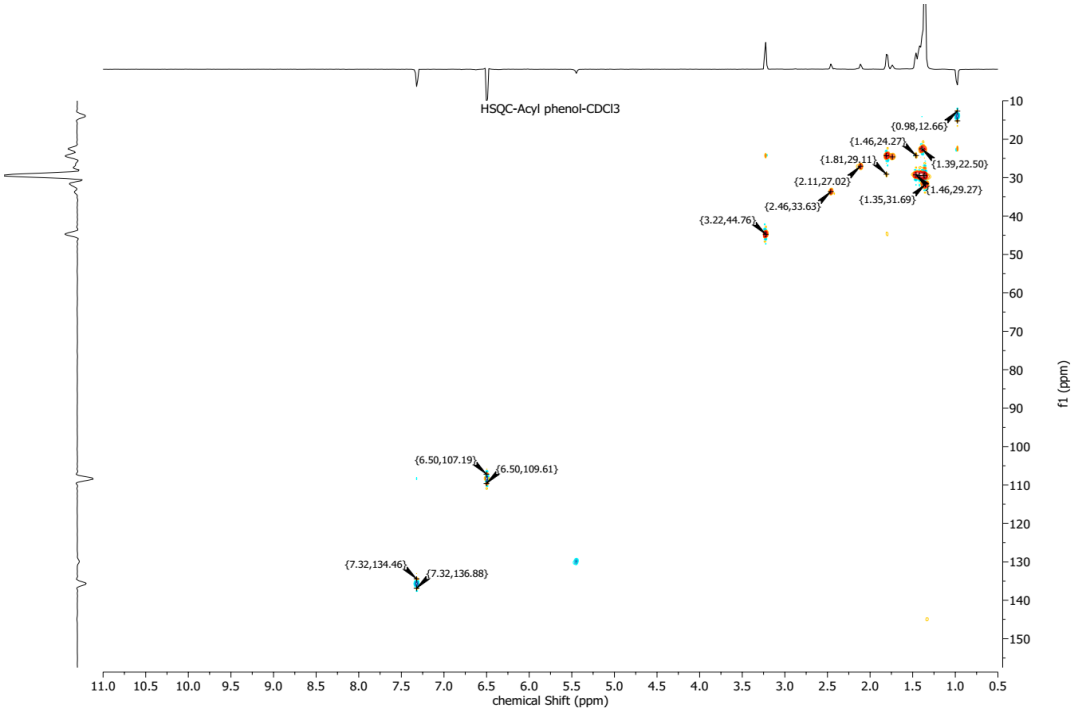


Figure S47: ^{1}H, ^{13}C-HSQC spectrum (800 MHz, 201 MHz) of compound 8 (Acyl phenol)

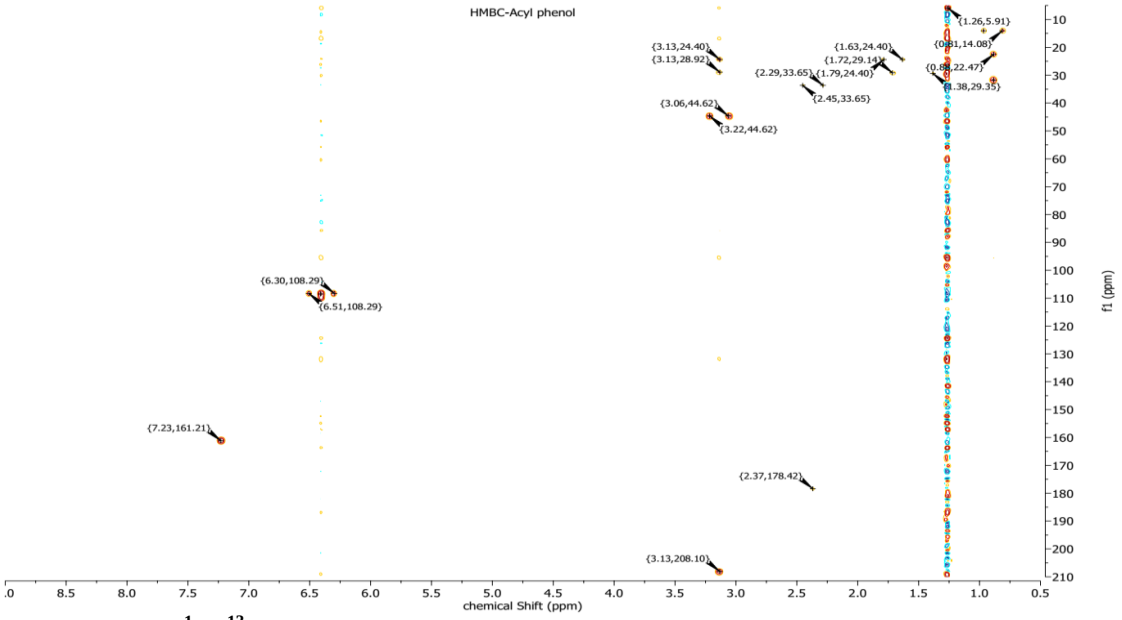


Figure S48: ^{1}H, ^{13}C HMBC spectrum of (800 MHz, 201 MHz) of compound 8 (Acyl phenol)

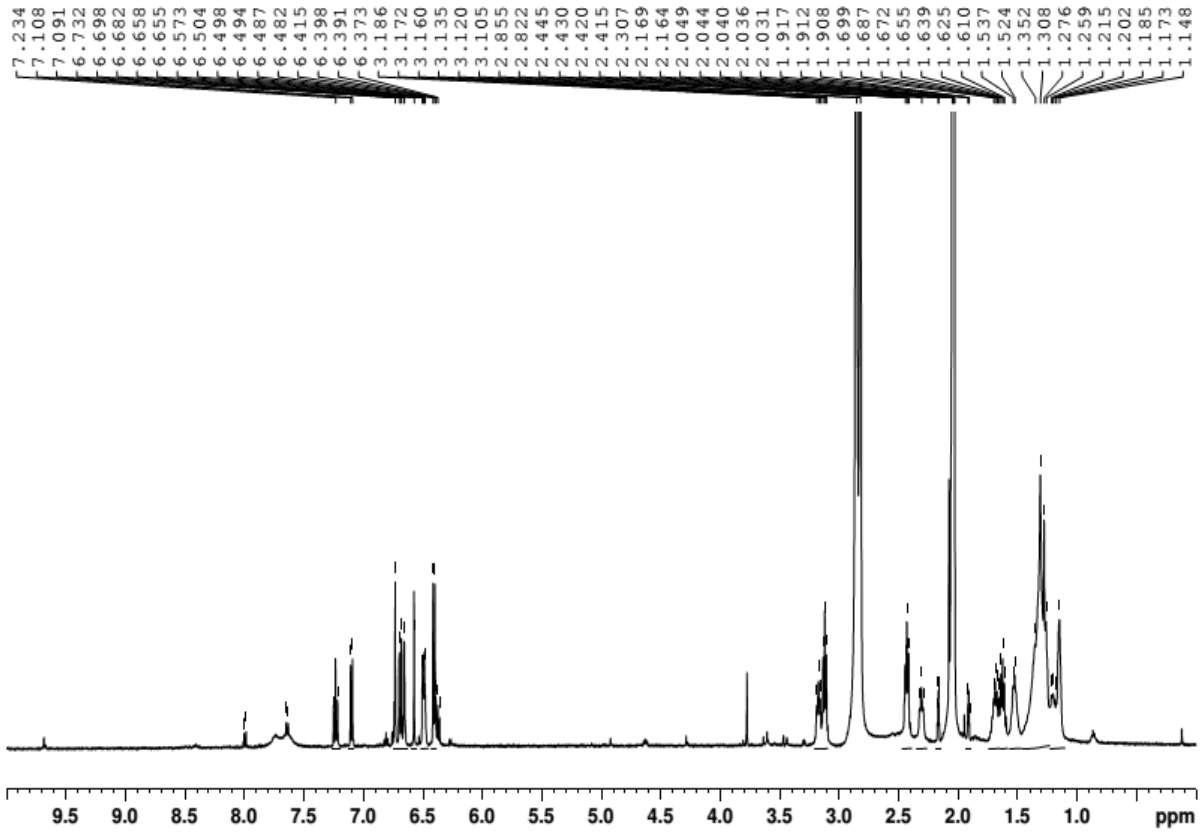


Figure S49.^{1}H NMR (CD_3COCD_3, 500 MHz) spectrum of compound 9 (Giganteone A, dimer of malabaricone C)

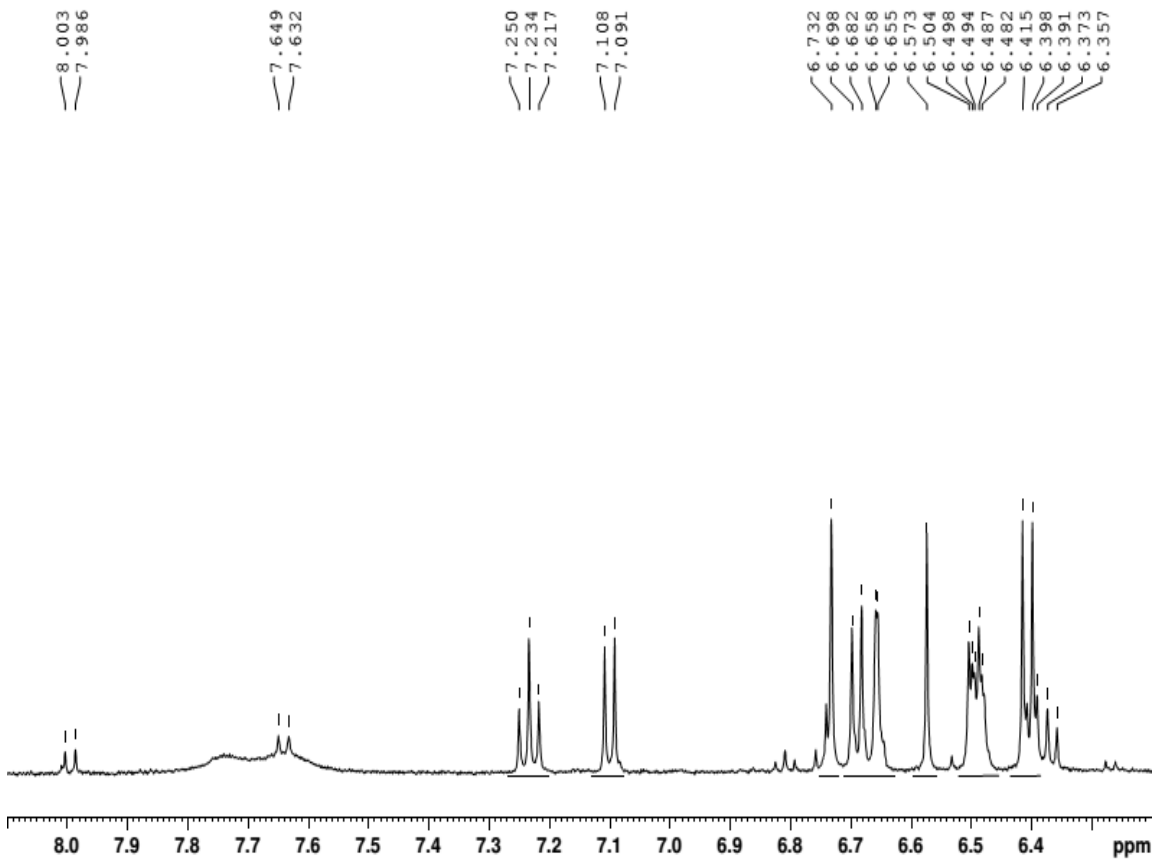


Figure S50. Expansion of ^{1}H NMR (CD_3COCD_3, 500 MHz) spectrum of compound 9 (Giganteone A, dimer of malabaricone C).

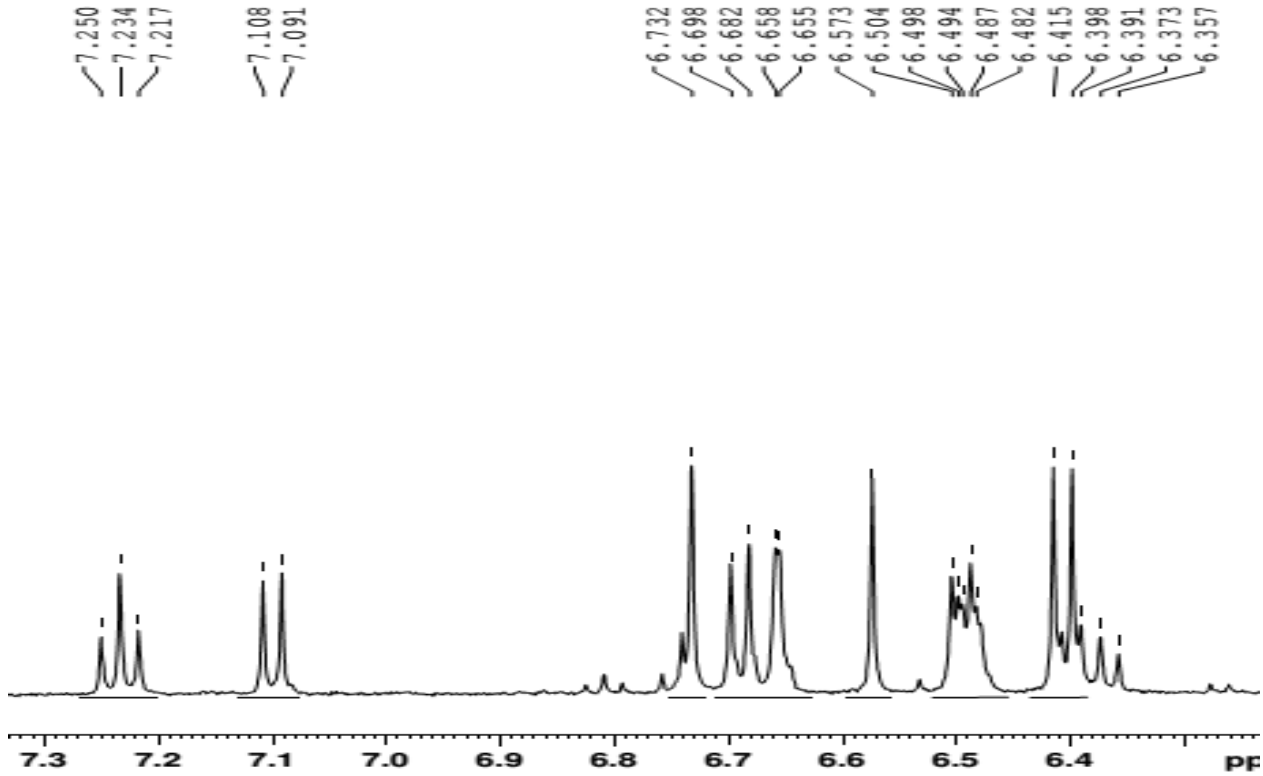


Figure S51. Expansion of ^{1}H NMR (CD_3COCD_3, 500 MHz) spectrum of compound 9 (Giganteone A, dimer of malabaricone C)

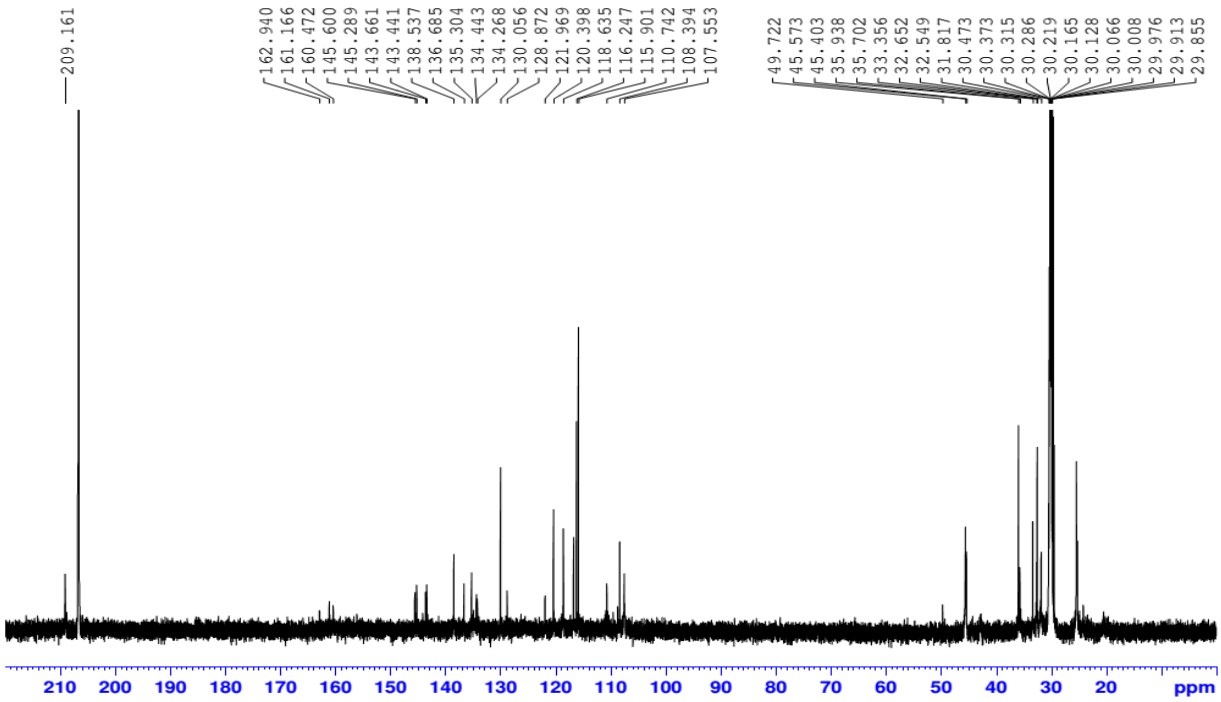


Figure S52. ^{13}**C NMR (CD_3COCD_3, 125 MHz) spectrum of compound 9 (Giganteone A, dimer of malabaricone C).**

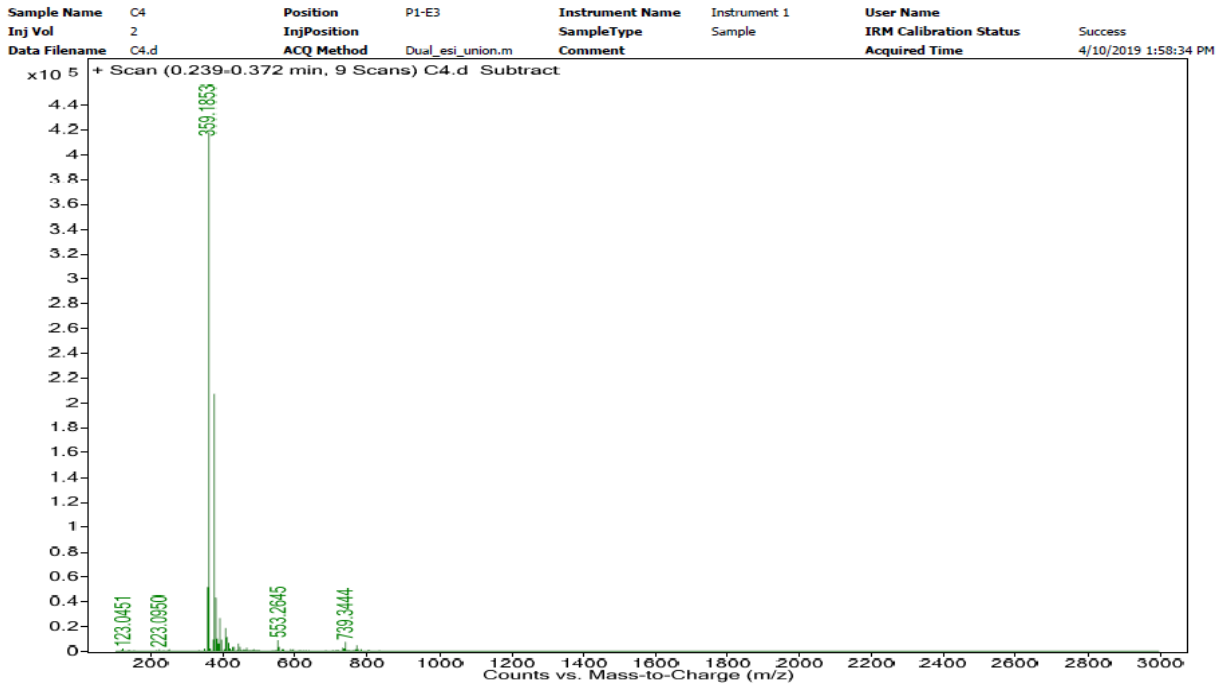
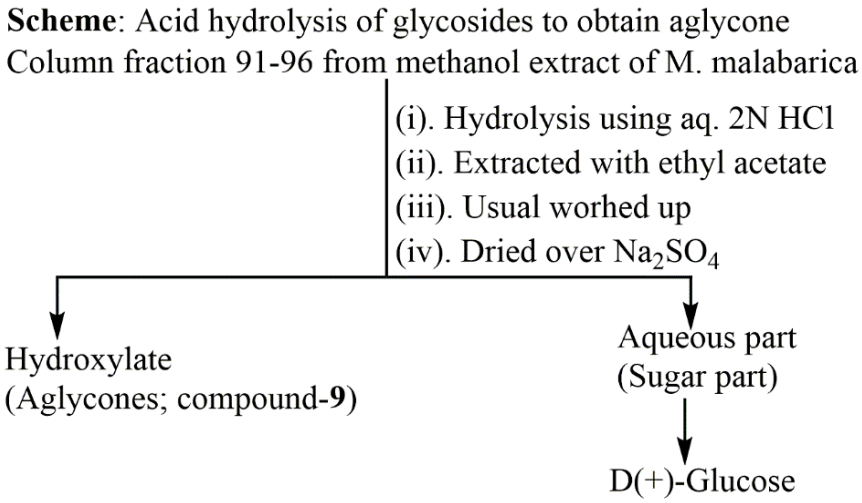


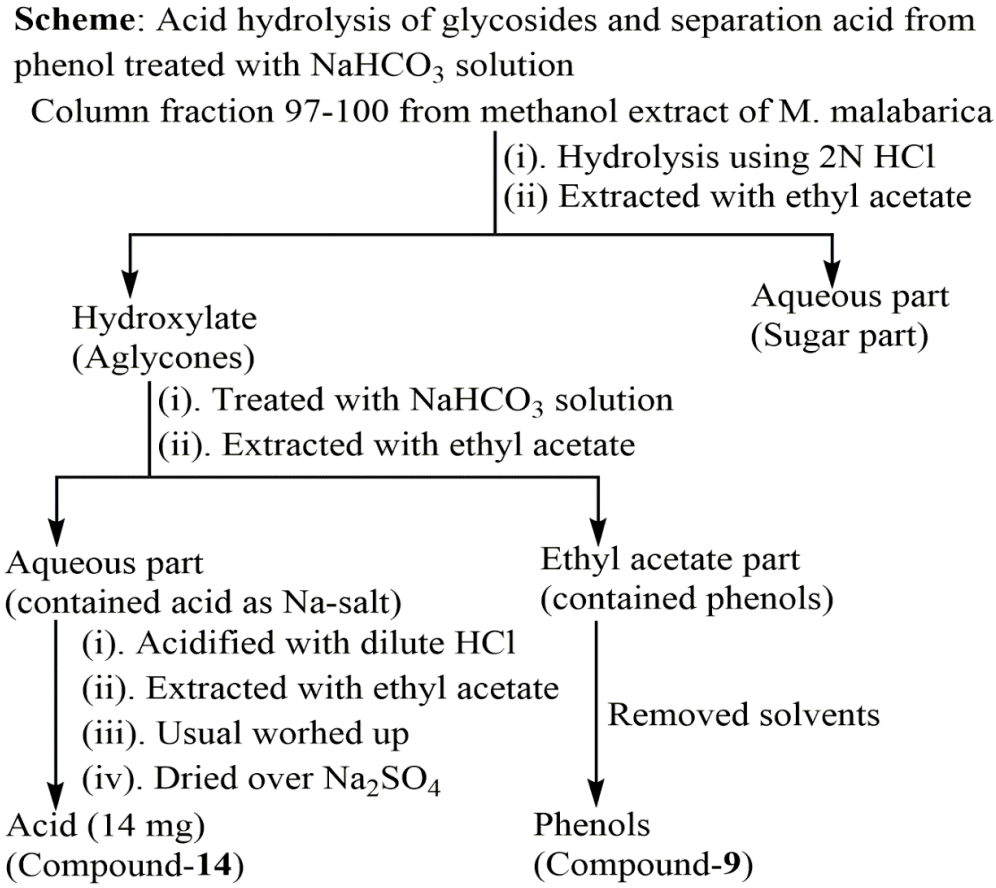
Figure S53. HR-ESI MS spectrum of compound 9 (Giganteone A, dimer of malabaricone C)

Chart 1: Flow chart for isolation of secondary metabolites from MeOH extract of *Myristica malabarica*

Solvent extraction: Freshly dried fruit rind of *M. malabarica* (amt used 1.250 Kg) collected from local market, Mumbai. Percolation of these powdered material carried out with distilled MeOH (2.5 L x 24 hrs x 3). Solvent was removed by using rota-vapor at maintaining temperature of water bath at about 40 °C.					
Column chromatography separation: Viscous brown residue (370 gm); subjected to column chromatography over silica gel (SiO_2 used 5.0 kg; particle size 230-400 mesh, Aldrich, USA); eluted with a binary mixture EtOAc in hexane followed MeOH in $CHCl_3$ as solvent system with gradient elution by changing the polarity. Fractions were collected with volume of each aliquot least 500-1000 ml or more volume of aliquots.					
S. no	**Column Fractions**	**Solvent system used**	**Yield/Residue**	**Purification CC/ SiO_2/ sephadexLH 20**	**Name of the isolated secondary metabolites**
1	Fraction 1-8	0-15% EtOAc in hexane	Sticky mass	Not done	lipids
2	Fraction 9-11	0-5% MeOH in $CHCl_3$	Crude residue, A (~150 mg)	Sub-fractionated	Acyl phenol (**7**)
3	Fraction 12-14	5-10% MeOH in $CHCl_3$	Residue B (1.25 gm)	Sub-fractionatedB_5-B_7	Malabaricone A (**1**), substantial amt. 1.00 gm
4	Fraction 27-30	10% MeOH in $CHCl_3$	Crude residue, C (1.5 gm)	Sub-fractionatedC_7-C_{11}	Malabaricone D (**4**), substantial amt. 1.25 gm
5	Fraction 34-42	10% MeOH in $CHCl_3$	Light brown residue, D (1.25 gm)	Sub-fractionated D_7-D_{12}	Malabaricone B (**2**), substantial amt. 2.05 gm
6	Fraction 44-56	10% MeOH in $CHCl_3$	Pale yellow residue E (13.0 gm)	Sub-fractionated E_7-E_{20}	Malabaricone C (**3**), major amount 11.5 gm
7	Fraction 60-70	15-20% MeOH in $CHCl_3$	Brown sticky mass F (300 mg)	Sub-fractionated F_4-F_5	Compound **8**, minor amount 100 mg
9	Fraction 71-80	15-20% MeOH in $CHCl_3$	Light brown sticky mass G (100 mg)	Sub-fractionated G_5-G_7	Pro-malabaricone B (**5**), amt. 25 mg & pro-malabaricone C, amt. 14 mg
10	Fraction 81-86	20-25% MeOH in $CHCl_3$	Colourless solid, H (150mg)	Sub-fractionated H_3-H_5 (120 mg)	Product similar to compound **5** & **6** without carbonyl group
11	Fraction 87-90	30-35 % MeOH in $CHCl_3$	Sticky brown mass, I (500 mg)	Sub-fractionated I_3-I_5	Dimers of malabaricones, identified as Giganteone A (a dimer of malabaricone C)
12	Fraction 91-96	50-70% MeOH in $CHCl_3$	Sticky mass, J (50 gm)	Glycosides	Hydrolysis, aglycone, hydrated malabaricone C
13	Fraction 97-100	80-100% MeOH in $CHCl_3$	Polyphenolic compounds in the form of glycosides	Sub-fractionated Not done	Analysis not carried out



Scheme 1: Scheme for acid hydrolysis of glycoside.



Scheme 2: Scheme for acid hydrolysis of glycoside & separation of acid from phenol on treatment with $NaHCO_3$ solution.

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