Electronic Supplementary Material (ESI) for Chemical Science.

Supporting Information

Bio-inspired synthesis of xishacorenes A, B, C, and a new congener from fuscol

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1 General considerations

1.1 Solvents and reagents

Unless it is specified below, commercial reagents were purchased from Millipore Sigma, Acros, Oakwood, Strem and Alpha Aesar and used without further purification. Solvents were purchased from Fisher Scientific or Millipore Sigma. Tetrahydrofuran (THF) was sparged with N_2 and dried by passing through alumina columns using argon in a Glass Contour solvent purification system. Dichloromethane (CH_2Cl_2) was freshly distilled over CaH_2 before use. Anhydrous DMF was purchased from Millipore Sigma in Sure/Seal bottles.

1.2 Reaction setup, monitoring reaction progress, and product purification

All reactions were carried out in oven or flame-dried glassware under N_2-atmosphere using standard Schleck-techniques. Reaction temperatures above room temperature (18–21 °C) were controlled by an IKA® temperature modulator. Reaction progress was monitored using thin-layer chromatography (TLC) plates (glass backed, 60 Å, F_{254}-indicator). Analysis of the developed plates was carried out using UV-light and/or by staining with anisaldehyde or ceric ammonium molybdate (CAM) stains. Regular phase isolation and purification of products was performed using silica gel (SiO_2) by Fisher (230-400 mesh, grade 60). Silica flash column chromatography was performed either by using glass columns or with a Yamazen Smart Flash EPCLC W-Prep 2XY (dual channel) automated flash chromatography system on prefilled, premium, universal columns using ACS grade solvents. Reversed-phase chromatography was performed on an Agilent Prostar system with a Model 325 UV Detector and 440-LC Fraction Collector. For separation on semi-preparative scale, a Develosil ODS-HG-5 column was employed. Organic solvents were removed under vacuum using a Büchi temperature-controlled rotary evaporator equipped with a dry ice/isopropanol condenser.

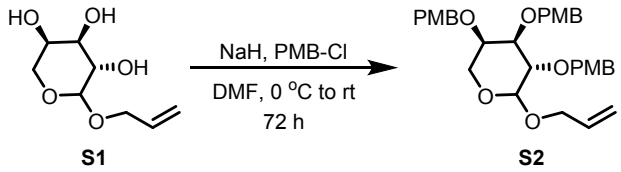
1.3 Analytical instrumentation

NMR spectra were acquired using deuterated solvents purchased from Cambridge Isotope Laboratories, Inc. ^{1}H NMR and ^{13}C NMR data were recorded on a Bruker AV-700 MHz spectrometer using $CDCl_3$ or CD_3OD solvents at 20–23 °C. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR in $CDCl_3$; δ 3.31 for ^{1}H NMR, δ 49.0 for ^{13}C NMR in CD_3OD). Data for ^{1}H NMR are reported as follows; chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, tdd = triplet of doublets of doublets, qd = quartet of doublets), coupling constant (Hz), integration. Data for ^{13}C NMR spectroscopy are reported in chemical shift (δ ppm).

High resolution mass spectrometry (HRMS) samples were analyzed on an AutoSpec Premier mass spectrometer (Waters, Manchester, UK), equipped with either an electron impact (EI) or chemical ionization ion source (CI) and MassLynx software.
IR spectroscopic data were recorded on a Bruker ALPHA FT-IR spectrophotometer using a diamond attenuated total reflectance (ATR) accessory. Samples were applied to the diamond surface as a solution in organic solvent and the data were acquired after the solvent had evaporated.
Optical rotations were acquired using a Perkin-Elmer 241 polarimeter using the Na D-line (path length 1 dm, cell volume 1 mL, c in [g / 100 mL]). UV-Vis data was acquired on a Shimadzu UV-2450 spectrophotometer using a Hellma Analytics 104-QS 10 mm quartz cuvette. Data was plotted using Kaleidagraph 4.5 software and curves were plotted as a weighted 3% fit using the Least Squares error (Lowess) method.

2 Synthetic procedures and product characterization

*2.1 Synthesis of glycoside **11***



S1 **S2**

(3S,4R,5R)-2-(allyloxy)-3,4,5-tris((4-methoxybenzyl)oxy)tetrahydro-2H-pyran (S2): **S1** was prepared according to the previously reported literature procedure.[1] **S1** (1.1 g, 5.78 mmol) was added to a flame-dried, 100 mL flask charged with a stir bar and purged with nitrogen. At room temperature, anhydrous DMF (39 mL) was added to dissolve the compound. The resulting orange solution was placed in an ice bath to stir 10 minutes before portion-wise addition of NaH (60% in oil, 1.1 g, 27.2 mmol, 4.7 equiv), stirring rapidly under nitrogen. After 30 minutes, PMB-Cl (3.5 mL, 26.0 mmol, 4.5 equiv) was added and the reaction mixture was left to stir for 72 h, warming up slowly overnight. After stirring for 72 h, the resulting mixture was placed in an ice bath for 5 minutes before anhydrous methanol (1.2 mL) was added and the reaction mixture was left to stir one more hour. The mixture was then partitioned between water (20 mL) and EtOAc (20 mL). The aqueous solution was then extracted 3 times before the organic solution was washed 5x with water (15 mL). The organic solution was dried over magnesium sulfate and concentrated by rotary evaporator. The resulting oil was subjected to column purification on silica gel via 30% EtOAc in Hexanes with an isocratic eluent (Rf of 0.6 in 50% EtOAc / Hexanes). **S2** was isolated as a mixture of diastereomers as a light-yellow oil in a 72% combined yield (2.3 g, 4.2 mmol).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.32 – 7.20 (m), 6.90 – 6.82 (m), 6.00 – 5.81 (m), 5.34 (dd, J = 17.3, 1.6 Hz), 5.29 (dd, J = 17.3, 1.6 Hz), 5.18 (dd, J = 10.4, 1.1 Hz), 4.83 – 4.52 (m),

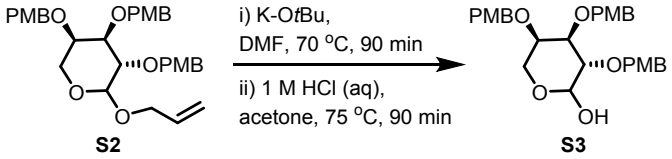
[1]Petermichl, M., Loscher, S., Schobert R. *Angew. Chem. Int. Ed.* **2016**, *55*, 10122–10125

4.42 – 4.36 (m), 4.33 (d, J = 7.0 Hz), 4.17 – 4.07 (m), 4.03 – 3.93 (m), 3.84 (dd, J = 9.0, 3.4 Hz), 3.82 – 3.78 (m), 3.71 – 3.59 (m), 3.44 (dd, J = 9.0, 3.4 Hz), 3.22 (d, J = 11.9 Hz) ppm.

^{13}C NMR (176 MHz, $CDCl_3$) δ 159.20, 159.09, 134.30, 134.12, 131.04, 130.96, 130.47, 130.32, 129.80, 129.65, 129.58, 129.55, 129.31, 129.24, 128.65, 117.77, 117.03, 113.95, 113.75, 113.71, 102.78, 96.90, 79.37, 78.84, 76.94, 76.03, 74.76, 73.58, 73.19, 72.47, 72.05, 71.75, 71.33, 70.73, 69.92, 68.32, 64.99, 62.76, 60.50, 55.31.

IR (ATR, neat) ν = 2999, 2933, 2911, 2868, 2837, 1612, 1513, 1247, 1174, 1093, 1034, 820 cm^{-1}.

HRMS (ESI+) m/z calculated for $C_{32}H_{38}O_8Na$ $[M+Na]^+$: 573.2459, found: 573.2451.



(3S,4R,5R)-2-(allyloxy)-3,4,5-tris((4-methoxybenzyl)oxy)tetrahydro-2H-pyran (S3): The following protocol was adopted from a known literature procedure.[1] A 100 mL flask containing **S2** (2.3 g, 4.2 mmol) was placed under vacuum for 1 hr, purged with nitrogen, and charged with a stir bar. Anhydrous DMF (42 mL) was added and dissolution occurred at room temperature, providing a clear orange solution. To the solution stirring at room temperature, K-O*t*Bu (0.61 g, 8.4 mmol, 2 equiv) was added and the orange solution immediately turned dark red. The flask was placed in a 70 °C oil bath and left to stir under nitrogen. The reaction mixture turned into a light orange solution once again after several minutes of stirring and slowly became darker again over the course of 45 minutes. After 90 minutes of stirring with heat, the flask was removed from the oil bath and placed into an ice bath to stir for 5 minutes. 1 M HCl (aq, 10 mL) was added dropwise, with the dark orange solution turning light yellow. EtOAc (15 mL) was then added and the solution was poured into a separatory funnel. The aqueous solution was extracted twice with EtOAc (15 mL), the organic solution was then washed 5x with H_2O (5 mL) followed by brine. The combined organic phase was then dried over magnesium sulfate and concentrated on a rotary evaporator.

The resulting orange oil was transferred into a 50 mL flask charged with a stir bar and then placed under vacuum for 2 hours. Then the flask was backfilled with nitrogen and acetone (20 mL) was added followed by 1 M HCl (aq, 3.2 mL). The resulting orange solution was then placed in an oil bath, outfitted with a reflux condenser, and stirred with heating at 75 °C. After 90 minutes, the reaction mixture was removed from heat and diluted with EtOAc (15 mL) and water (15 mL), and poured into a separatory funnel. The aqueous phase was washed 3x with EtOAc (15 mL). The combined organic phase was washed with brine, dried over magnesium sulfate, and concentrated by rotary evaporator. The resulting orange oil was subjected to flash column purification on silica gel using 50% EtOAc in hexanes as

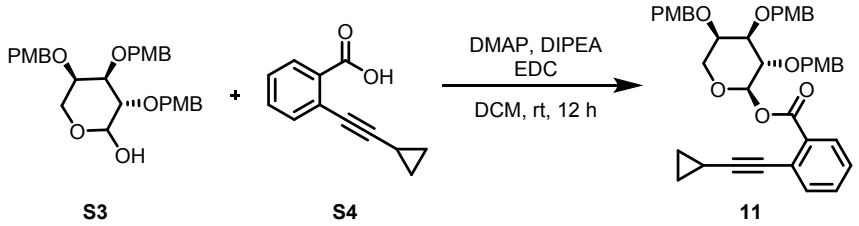
the isocratic eluent (Rf of 0.3 in 50% EtOAc / Hexanes). An inseparable mixture of **S3** diastereomers were isolated as a light-yellow oil in 80% yield (1.7 g, 3.3 mmol).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.28 – 7.15 (m), 6.90 – 6.84 (m), 5.10 (d, J = 2.3 Hz), 4.83 (s), 4.71 – 4.42 (m), 3.99 (dd, J = 11.4, 9.2 Hz), 3.87 – 3.77 (m), 3.76 – 3.71 (m), 3.61 (dd, J = 11.4, 4.8 Hz), 3.56 (dd, J = 4.8, 2.3 Hz) ppm.

^{13}C NMR (176 MHz, $CDCl_3$) δ 159.91, 159.89, 159.83, 159.75, 159.68, 159.64, 130.96, 130.70, 130.65, 130.19, 130.11, 129.91, 129.86, 129.77, 129.75, 114.33, 114.30, 114.28, 114.22, 114.18, 92.51, 76.74, 75.88, 75.33, 75.29, 73.80, 73.79, 73.62, 72.88, 72.87, 72.76, 72.00, 71.64, 71.58, 61.47, 55.72 ppm.

IR (ATR, neat) ν = 3421, 2935, 2911, 2836, 1612, 1513, 1248, 1174, 1091, 1034, 820 cm^{-1}.

HRMS (ESI+) m/z calculated for $C_{29}H_{34}O_8Na$ $[M+Na]^+$: 533.2146, found: 533.2147.



(3S,4R,5R)-3,4,5-tris((4-methoxybenzyl)oxy)tetrahydro-2H-pyran-2-yl 2-(cyclopropylethynyl)benzoate (11): Alkyne carboxylic acid **S4** was prepared according to a known literature protocol.[2] The protected arabinose **S3** (224 mg, 0.258 mmol, 1.7 equiv) was added to a 10 mL flame-dried flask that was charged with a stir bar under nitrogen. Freshly distilled anhydrous DCM (3.2 mL) was added to dissolve the substrate, and the resulting solution was then allowed to stir at room temperature. **S4** (48 mg, 0.258 mmol, 1 equiv) was added followed by DMAP (43 mg, 0.348 mmol, 1.35 equiv), DIPEA (0.113 mL, 0.644 mmol, 2.5 equiv), and EDC (chloride salt, 66 mg, 0.348 mmol, 1.35 equiv). The reaction mixture was left to stir for 12 h and was then diluted with DCM (3 mL) and the resulting mixture transferred to a separatory funnel. The organic solution was then washed with HCl (0.5 M, aq, 1 mL), followed by sodium bicarbonate and brine. The organic phase was then dried over magnesium sulfate and evaporated to dryness to yield a white foam. The resulting crude material was then subjected to silica gel chromatography with 30% EtOAc in hexanes followed by 50% EtOAc in hexanes (R_f 0.3 in 30% EtOAc in Hexanes). **11** was isolated as a clear sticky film in 53% yield (93 mg, 0.137 mmol), presumed to be a single diastereomer (as drawn).

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[2] Li, Y.; Yang, W. Z.; Ma, Y. Y.; Sun, J. S.; Shan, L.; Zhang, W. D.; Yu, B. A., Synthesis of Kaempferol 3-O-[2 ",3 "- and 2 ",4 "-Di-O-(E)-p-coumaroyl]-alpha-L-rhamnopyranosides. *Synlett* **2011**, 915–918.

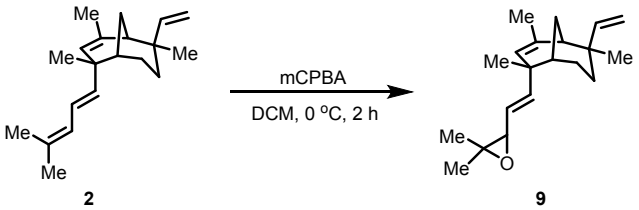
^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.35 – 7.28 (m, 3H), 7.23 (dd, *J* = 12.4, 8.5 Hz, 4H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 2H), 6.85 (dd, *J* = 8.5, 3.9 Hz, 4H), 6.02 (d, *J* = 4.6 Hz, 1H), 4.76 – 4.57 (m, 7H), 4.17 (dd, *J* = 11.7, 6.5 Hz, 1H), 3.99 – 3.96 (m, 1H), 3.90 – 3.85 (m, 2H), 3.84 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.76 (dd, *J* = 6.5, 2.9 Hz, 1H), 3.61 (dd, *J* = 11.7, 2.4 Hz, 1H), 1.59 – 1.51 (m, 1H), 0.96 – 0.89 (m, 4H) ppm.

^{13}C NMR (176 MHz, $CDCl_3$) δ = 164.13, 159.32, 159.22, 134.27, 131.95, 130.94, 130.70, 130.33, 130.25, 130.11, 129.59, 129.50, 129.47, 129.24, 126.93, 125.35, 113.82, 113.80, 113.74, 100.03, 93.64, 75.76, 74.57, 73.64, 72.19, 71.61, 71.01, 61.94, 55.31, 55.29, 55.25, 8.95, 0.78 ppm.

IR (ATR, neat) ν = 2911, 2270, 1737, 1612, 1513, 1246, 1173, 1034, 820, 758 cm^{-1}.

HRMS (ESI+) m/z calculated for $C_{41}H_{42}O_9Na$ $[M+Na]^+$: 701.2721, found: 701.2728. $[\alpha]^{20}_D$ = –0.9° (c=4, $CHCl_3$).

*2.2 Fuscol Analogue **10** Synthesis*



2 9

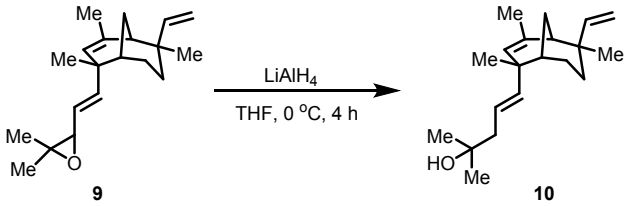
2,2-dimethyl-3-((E)-2-((1S,2R,6S)-2,4,6-trimethyl-6-vinylbicyclo[3.3.1]non-3-en-2-yl)vinyl)oxirane (9): To a flame-dried 1 dram vial purged with nitrogen and charged with a stir bar, a solution of xishacorene B (**2**, 8 mg, 0.030 mmol) dissolved in DCM (590 μL) was left to cool to 0 °C in an ice bath before the addition of mCPBA (70% by wt, 8 mg, 0.033 mmol, 1.1 equiv). The reaction mixture was left to slowly warm to rt over 1 hour. After 2 hours, the reaction mixture was quenched with sodium bicarbonate, transferred to a separatory funnel, and the aqueous solution was washed 3x with DCM (1 mL). The resulting organic solution was dried over magnesium sulfate and concentrated by rotary evaporation. The resulting residue was subjected to silica gel chromatography with an eluent of 10% EtOAc in hexanes (Rf 0.6, stained blue using anisaldehyde stain). Epoxide **9**, which was isolated as a mixture of diastereomers in 94% yield (8 mg, 0.028 mmol), was a clear oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.96 – 5.82 (m, 2H), 5.45 – 5.34 (m, 2H), 5.10 – 4.95 (m, 2H), 3.30 – 3.16 (m, 1H), 1.86 – 1.73 (m, 5H), 1.67 – 1.51 (m, 7H), 1.36 (s, 3H), 1.32 – 1.24 (m, 5H), 1.02 (d, J = 6.8 Hz, 3H), 0.88 (s, 3H) ppm.

^{13}C NMR (176 MHz, $CDCl_3$) δ 147.71, 144.24, 135.98, 131.58, 131.33, 121.96, 121.57, 111.56, 64.87, 64.67, 60.19, 44.25, 44.19, 42.45, 40.24, 36.31, 36.10, 30.23, 30.19, 29.65, 29.38, 28.65, 28.57, 27.54, 27.43, 26.42, 26.39, 25.95, 25.88, 24.73, 18.97 ppm.

IR (ATR, neat) ν = 2959, 2930, 2884, 1452, 1377, 977, 909 cm^{-1}.

HRMS (ESI+) m/z calculated for $C_{20}H_{30}ONa$ $[M+Na]^+$: 309.2188, found: 309.2188.



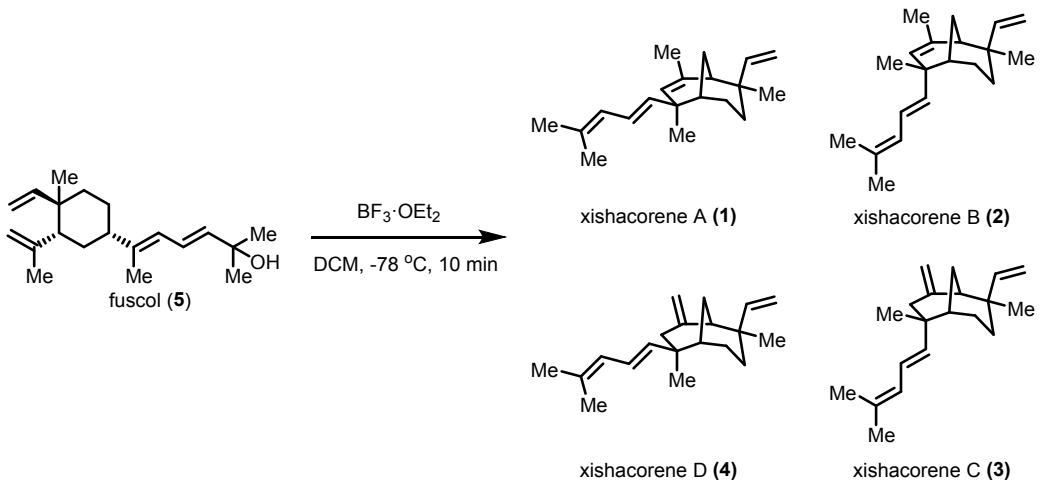
(E)-2-methyl-5-((2R,6R)-2,4,6-trimethyl-6-vinylbicyclo[3.3.1]non-3-en-2-yl)pent-4-en-2-ol (10): To a flame-dried 2 dram vial charged with a stir bar and purged with nitrogen, was added epoxide **9** (4 mg, 0.014 mmol) dissolved in anhydrous THF (0.470 mL). The solution was stirred in an ice bath for several minutes before dropwise addition of $LiAlH_4$ (2M in THF, 10 uL, 0.020 mmol, 1.44 equiv). A mild gas evolution was observed. After 1 hour, the reaction mixture was removed from the ice bath and another addition of $LiAlH_4$ (20 uL) was added. After 1 more hour of stirring, another portion of $LiAlH_4$ (20 uL) was added. After a total of 4 hours of stirring, the reaction mixture was quenched using the following Fieser and Fieser procedure: 30 μL H_2O followed by 30 μL of 15% NaOH after which 90 μL H_2O was added. The resulting suspension was dried with magnesium sulfate, filtered, and concentrated by rotary evaporation. The concentrate was then subjected to silica column chromatography with an isocratic eluent of 10% EtOAc in hexanes (stains blue using anisaldehyde stain; R_f of 0.2 in 10% EtOAc / hexanes). Tertiary alcohol **10** was isolated in 87% yield (3.5 mg, 0.012 mmol) as a clear oil.

^{1}H NMR (700 MHz, CD_3OH) δ = 5.89 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.55 – 5.45 (m, 2H), 5.39 (s, 1H), 5.03 (d, *J* = 4.7 Hz, 1H), 5.01 (d, *J* = 11.7 Hz, 1H), 2.26 – 2.16 (m, 2H), 1.81 (s, 3H), 1.75 (dt, *J* = 12.7, 2.8 Hz, 1H), 1.63 (d, *J* = 12.7 Hz, 1H), 1.56 – 1.53 (m, 3H), 1.52 – 1.50 (m, 1H), 1.41 (td, *J* = 13.3, 5.1 Hz, 1H), 1.25 (s, 2H), 1.22 (s, 3H), 1.21 (s, 3H), 1.01 (s, 3H), 0.89 (s, 3H) ppm.

^{13}C NMR (176 MHz, CD_3OH) δ = 147.68, 142.64, 135.47, 132.01, 121.39, 111.54, 70.67, 47.37, 44.27, 42.35, 40.38, 36.38, 36.09, 30.24, 29.99, 29.12, 29.08, 28.58, 27.48, 26.47, 26.11 ppm.

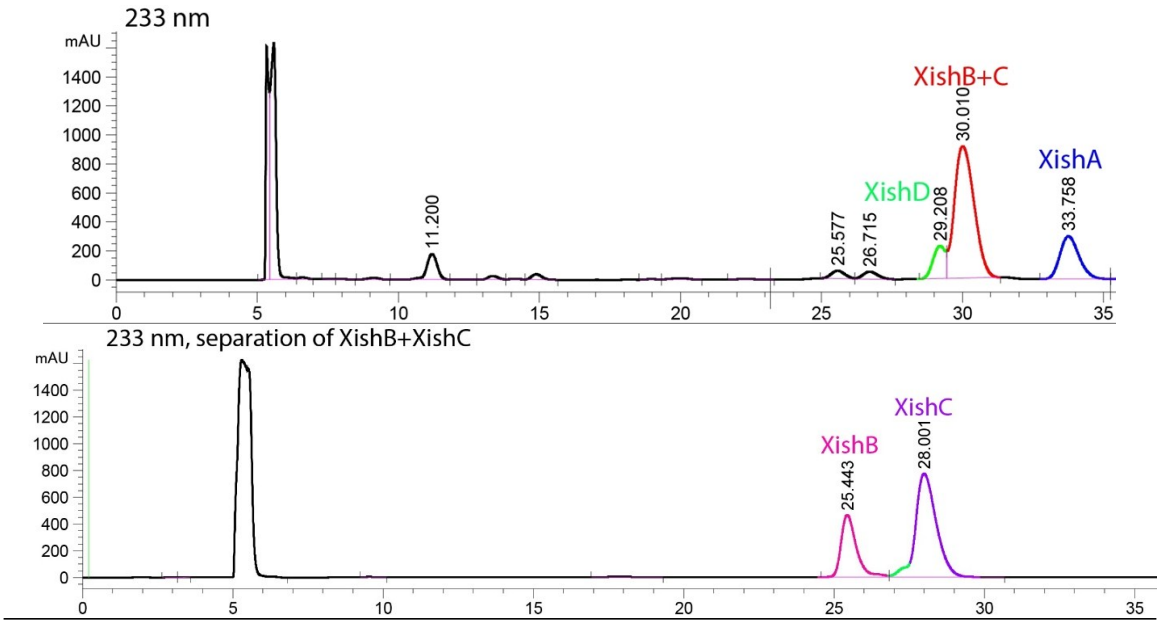
IR (ATR, neat) ν = 3352, 2965, 2930, 2884, 1452, 1377, 1148, 983, 908 cm^{-1}.

HRMS (EI+) m/z calculated for $C_{20}H_{32}O$ $[M]^+$: 288.2448, found: 288.2453. $[\alpha]^{20}_D$ = +40.0° (c=0.58, $CHCl_3$).



Optimized fuscol cyclization procedure to produce the xishacorenes: Fuscol (**5**), was prepared according to the previously reported synthesis of Kato & coworkers.[3] To a flame-dried 2-dram vial charged with a stir bar and purged with nitrogen, **5** (15 mg, 0.052 mmol) was added and dissolved in freshly distilled DCM (1.7 mL). The resulting clear solution was cooled to –78 °C and left to stir for several minutes before the careful dropwise addition of BF_3•OEt_2 (52 µL of a 1 M solution freshly prepared in anhydrous DCM, pre-cooled to –78 °C). The reaction progress was monitored with TLC (20% EtOAc in hexanes) and quenched with NH_4Cl (saturated aq. solution, 0.5 mL) as soon as the substrate (**5**) was consumed (~10 minutes). The aqueous solution was washed several times with DCM (1 mL) and the organic solution was dried over magnesium sulfate and evaporated to dryness. The resulting residue was then subjected to an initial purification using silica gel chromatography with an isocratic eluent of 5% EtOAc in hexanes to isolate a mixture with a R_f of 0.63 in 100% hexanes (absorbs in the UV; stains blue with anisaldehyde). This mixture was then evaporated and dissolved in 500 µL of HPLC grade acetone. The mixture was then subjected to semi-preparative scale, reversed-phase HPLC chromatography. In 50 µL increments, the solution was injected and subjected to a 40-minute run with an isocratic gradient of 98% MeCN with 2% H_2O to collect xishacorene D, a mixture of xishacorene B and C, and xishacorene A (See HPLC traces below). The collection was monitored at 233 nm. After several runs, the fractions were evaporated and combined accordingly. The residue containing xishacorene B, C, and trace quantities of xishacorene D was then dissolved in 250 µL of HPLC grade acetone and subjected to reversed-phase HPLC once again in a 40-minute run with an isocratic gradient of 98% MeOH with 2% H_2O. See sample HPLC traces below. The following amounts of material were isolated: **1** (1.5 mg, 0.0056 mmol, 11% yield), **2** (3 mg, 0.0110 mmol, 21% yield), **3** (1 mg, 0.0037 mmol, 7% yield), and **4** (1.5 mg, 0.0056 mmol, 11% yield).

[3] Kosugi, H.; Yamabe, O.; Kato, M., Synthetic study of marine lobane diterpenes: efficient synthesis of (+)-fuscol. *J. Chem. Soc. Perkin Trans 1* **1998**, 217–221.



xishacorene A (**1**): IR (ATR, neat) ν = 2954, 2925, 2856, 1637, 1553, 1451, 1376, 1102, 908 cm^{-1}. HRMS (EI+) m/z calculated for $C_{20}H_{30}$ $[M]^+$: 270.2342, found: 270.2349. $[\alpha]^{20}_D$ = +54.7° (c=0.075, MeOH), $[\alpha]^{20}_D$ = +30.8° (c=0.13, $CHCl_3$). UV (Cyclohexane): λ_{max} = 239 cm^{-1}, ε = 9,448 M^{-1} cm^{-1}.

xishacorene B (**2**): IR spectrum found to match previously synthesized compound. HRMS (EI+) was taken once again for confirmation, m/z calculated for $C_{20}H_{30}$ $[M]^+$: 270.2342, found: 270.2347. UV (Cyclohexane): λ_{max} = 240 cm^{-1}, ε = 11,145 M^{-1} cm^{-1}.

xishacorene C (**3**): IR (ATR, neat) ν = 2961, 2922, 2875, 1640, 1553, 1450, 1374, 1107, 1034, 986, 909, 889 cm^{-1}. HRMS (EI+) m/z calculated for $C_{20}H_{30}$ $[M]^+$: 270.2342, found: 270.2344. $[\alpha]^{20}_D$ = +31.3° (c=0.1, MeOH), $[\alpha]^{20}_D$ = +41.2° (c=0.17, $CHCl_3$). UV (Cyclohexane): λ_{max} = 239 cm^{-1}, ε = 18,594 M^{-1} cm^{-1}.

xishacorene D (**4**): IR (ATR, neat) ν = 2956, 2924, 2857, 1728, 1639, 1554, 1450, 1375, 1257, 1170, 1099, 908, 889 cm^{-1}. HRMS (EI+) m/z calculated for $C_{20}H_{30}$ $[M]^+$: 270.2342, found: 270.2352. $[\alpha]^{20}_D$ = –8.6° (c=0.07, $CHCl_3$). UV (Cyclohexane): λ_{max} = 240 cm^{-1}, ε = 9,721 M^{-1} cm^{-1}.

xishacorene A

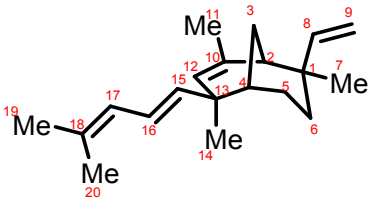


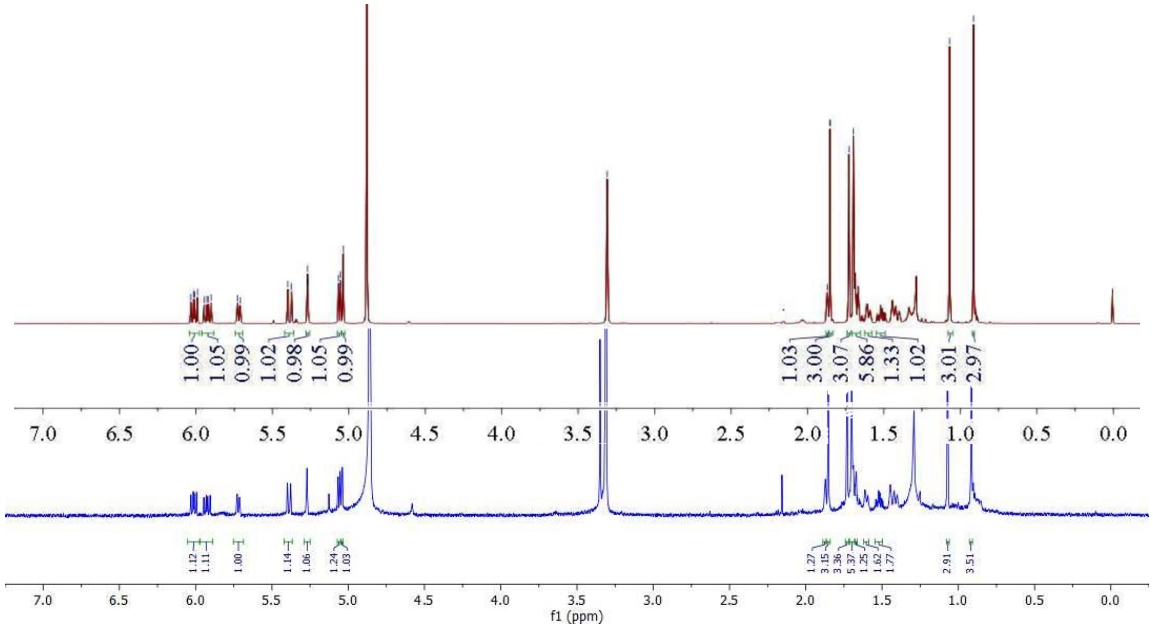
Table S1: Comparison of NMR-data of natural and synthetic xishacorene A (1)

position	natural δ_H lit.[4] (500 MHz, CD_3OD)	synthetic δ_H (700 MHz, CD_3OD)	natural δ_C lit.[4] (125 MHz, CD_3OD)	synthetic δ_H (176 MHz, CD_3OD)
1			41.8	41.8
2	1.87 t (J = 2.9 Hz)	1.87 m	45.7	45.8
3ax	1.67 dt (J = 12.5, 2.9 Hz)	1.67 m	27.9	27.9
3eq	1.60 ddd (J = 12.5, 3.2, 2.9 Hz)	1.60 m		
4	1.44 t (J = 2.9 Hz)	1.44 m	36.5	36.5
5ax	1.67 m	1.67 m	25.6	25.6
5eq	1.69 m	1.69 m		
6ax	1.51 ddd (J = 13.6, 13.5, 5.6 Hz)	1.51 td (J = 13.4, 5.6 Hz)	30.7	30.7
6eq	1.41 dt (J = 13.5, 2.8 Hz)	1.41 m		
7	0.91 s	1.07 s	31.1	31.1
8	5.92 dd (J = 17.7, 11.0 Hz)	5.93 dd (J = 17.7, 11.0 Hz)	148.8	148.9
9a	5.05 dd (J = 17.7,11.0 Hz)	5.05 dd (J = 7.9, 1.3 Hz)	112.1	112.1
9b	5.04 dd (J = 11.0, 1.3 Hz)	5.04 m		
10			136.8	136.5
11	1.85 d (J = 1.3 Hz)	1.85 d (J = 0.8 Hz)	26.4	26.4
12	5.27 t (J = 1.3 Hz)	5.27 t (J = 1.3 Hz)	133.8	133.8
13			42.0	42.0
14	1.07 s	1.07 s	24.3	24.2
15	5.39 d (J = 15.2 Hz)	5.39 d (J = 15.2 Hz)	143.2	143.2
16	6.01 dd (J = 15.2, 10.7 Hz)	6.01 dd (J = 15.2, 10.7 Hz)	124.5	124.8
17	5.72 brd (10.7 Hz)	5.72 brd (10.7 Hz)	126.6	126.6
18			133.4	133.4
19	1.73 s	1.73 s	26.0	26.0
20	1.70 s	1.70 s	18.2	18.2

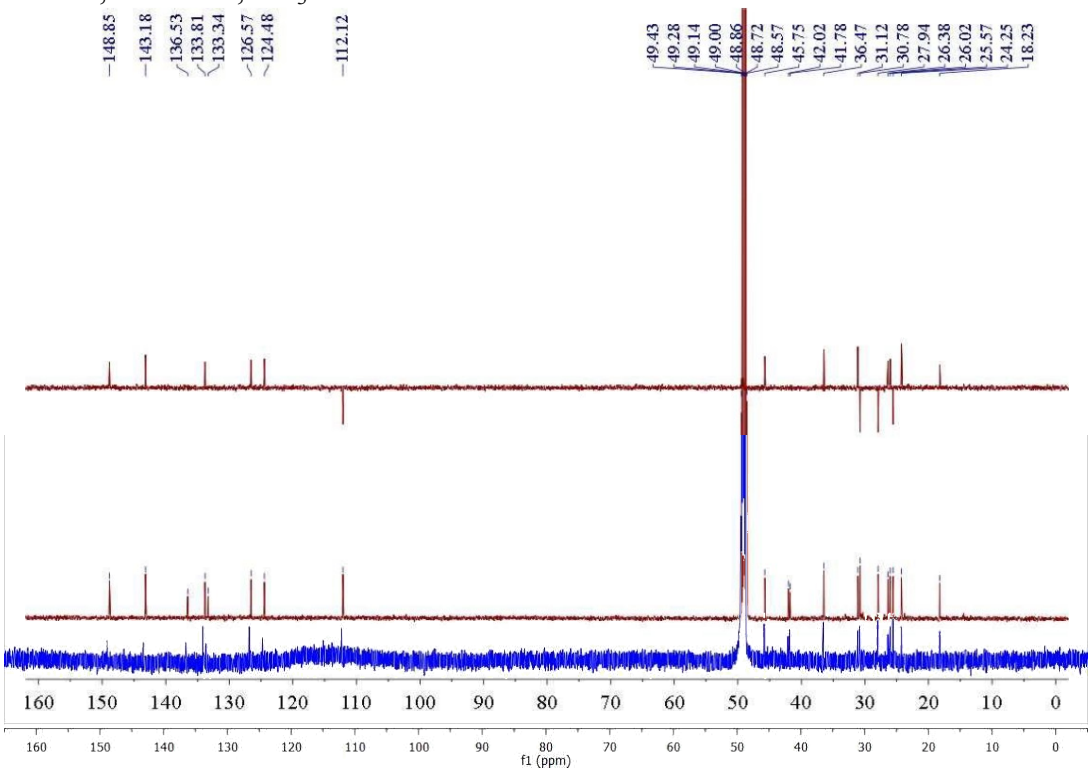
Overlay of material prepared through cyclization of fuscol (blue) with naturally isolated (red) xishacorene A (**1**)[4]

^{1}H-NMR, 700 MHz, CD_3OD

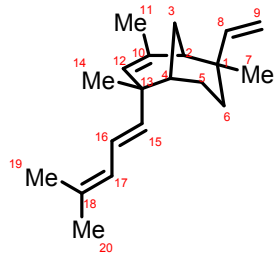
[4] F. Ye, Z.-D. Zhu, J.-S. Chen, J. Li, Y.-C. Gu, W.-L. Zhu, X.-W. Li, Y.-W. Guo, *Org. Lett.* **2017**, *19*, 4183–4186.



^{13}C-NMR, 176 MHz, CD_3OD



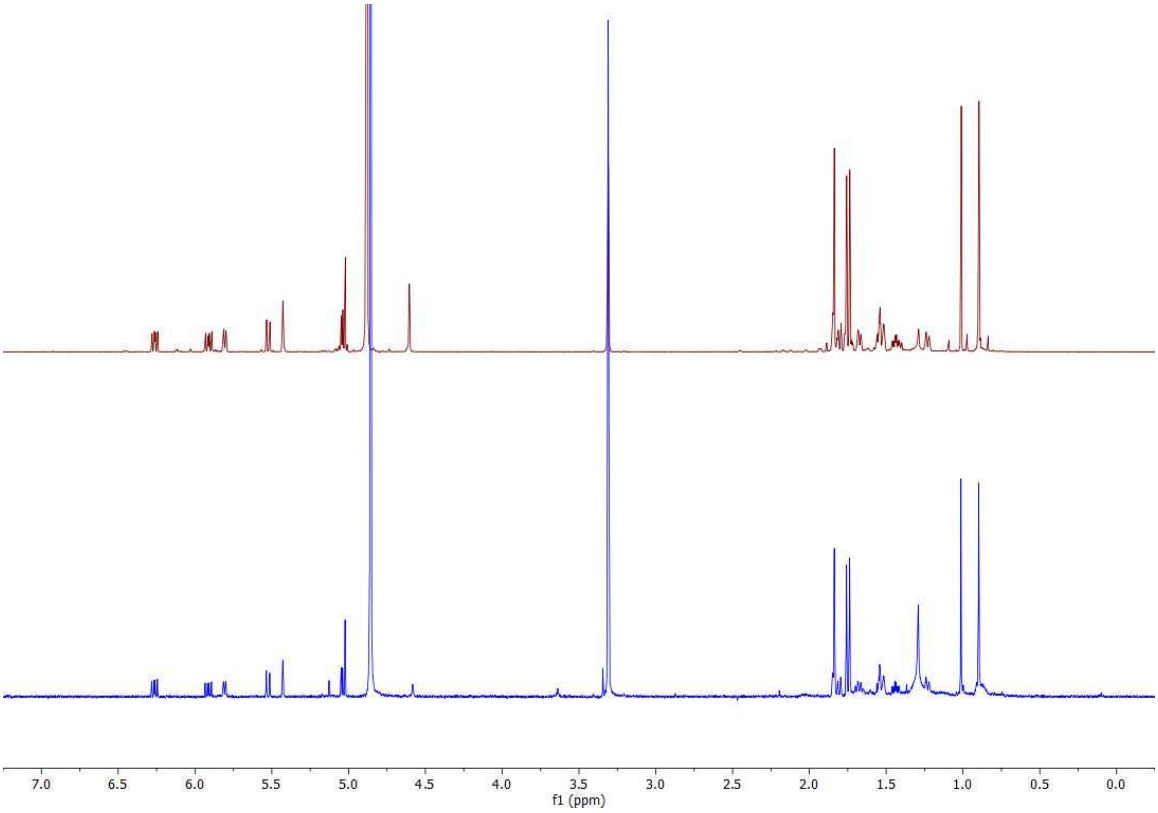
xishacorene B (2)



For xishacorene B (**2**), the compound isolated from the cyclization was found to be identical to that prepared previously in our laboratory. We have also included overlay spectra below.

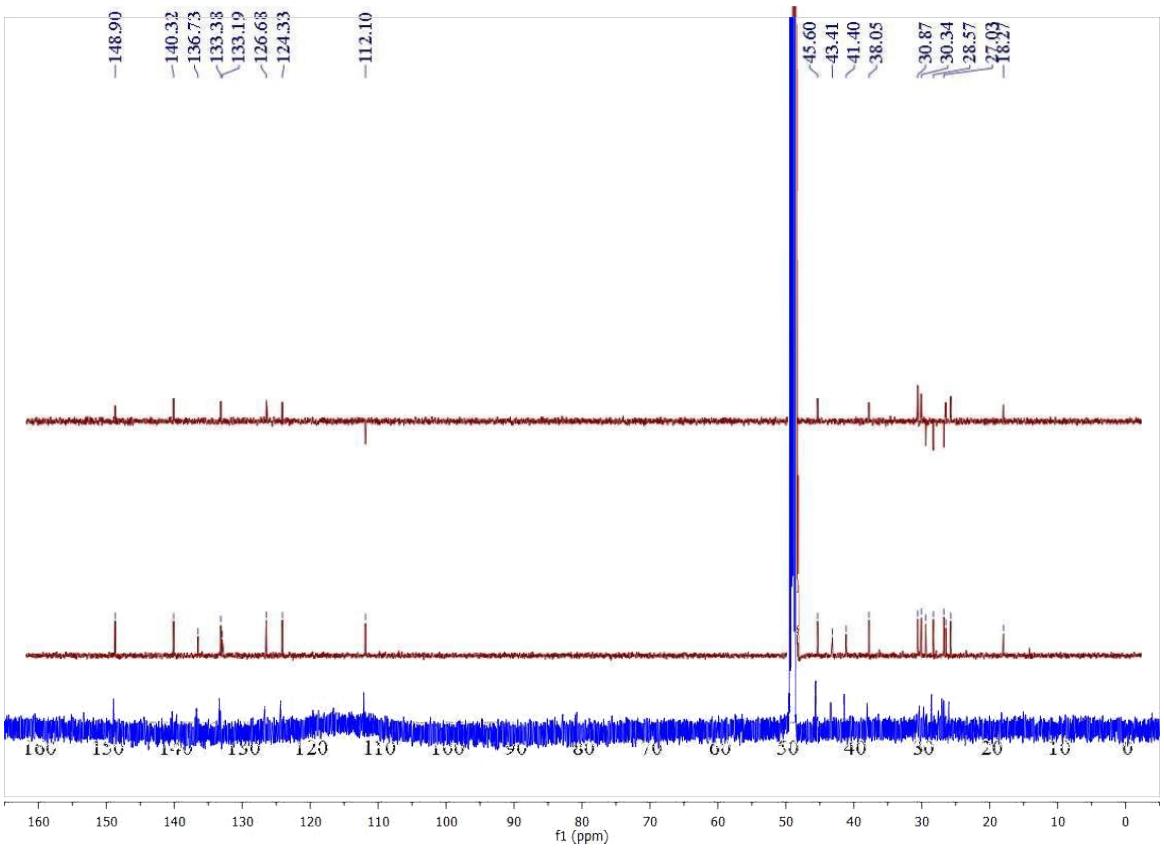
Overlay of material prepared through cyclization of fuscol (blue) with previously synthesized (red) xishacorene B (**2**).[5]

^{1}H-NMR, 700 MHz, CD_3OD



^{13}C-NMR, 176 MHz, CD_3OD

[5] Kerschgens, I.; Rovira, A. R.; Sarpong, R. *J. Am. Chem. Soc.* **2018**, *140*, 9810–9813.


148.90
140.32
136.73
133.38
133.19
126.68
124.33
112.10
45.60
43.41
41.40
38.05
30.87
30.34
28.57
27.03
18.27
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

xishacorene C (3)

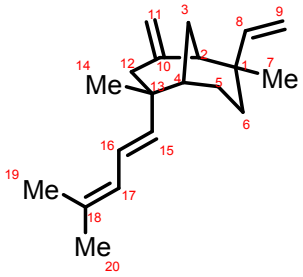


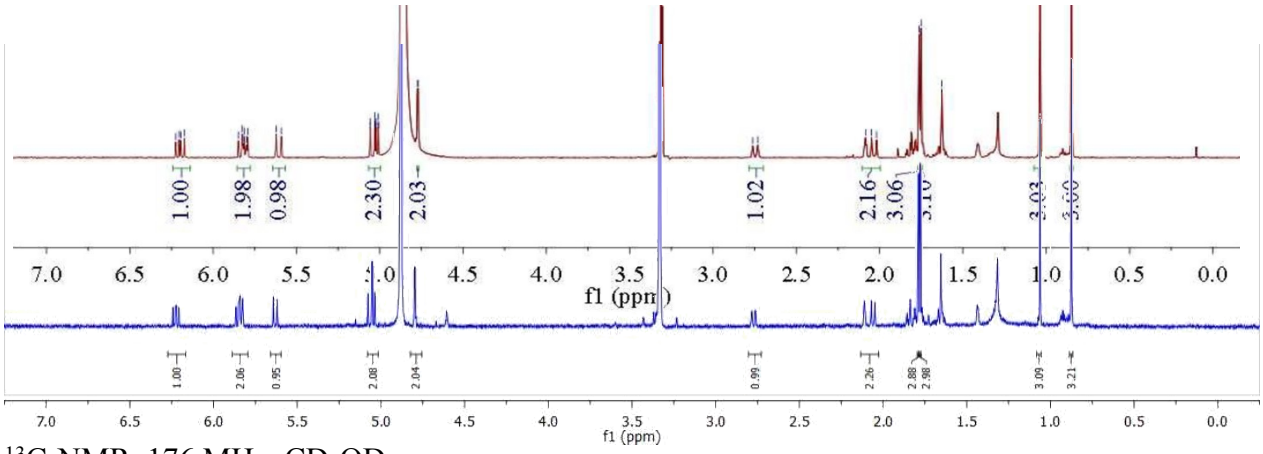
Table S2: Comparison of NMR-data of natural and synthetic xishacorene C (3)

position	natural δ_H lit.[6] (500 MHz, CD_3OD)	synthetic δ_H (700 MHz, CD_3OD)	natural δ_C lit.[4] (125 MHz, CD_3OD)	synthetic δ_H (176 MHz, CD_3OD)
1			39.8	39.8
2	2.08 t (J = 2.9 Hz)	2.08 t (J = 2.7 Hz)	50.1	50.1
3ax	1.81 m	1.81 m	29.3	29.3
3eq	1.78 m	1.78 m		
4	1.41 brs	1.41 brs	39.7	39.7
5ax	1.74 m	1.74 m	26.5	26.5
5eq	1.63 m	1.63 m		
6ax	1.60−1.65 m	1.60−1.65 m	31.7	31.7
6eq	1.60−1.65 m	1.60−1.65 m		
7	0.85 s	0.85 s	29.4	29.4
8	5.82 dd (J = 17.6, 11.0 Hz)	5.82 dd (J = 17.6, 11.0 Hz)	149.4	149.4
9a	5.04 dd (J = 17.6, 1.2 Hz)	5.04 dd (J = 14.1, 1.1 Hz)	111.8	111.8
9b	5.02 dd (J = 11.0, 1.2 Hz)	5.02 dd (J = 7.3, 1.1 Hz)		
10			149.7	149.7
11	4.77 d (J = 2.4 Hz)	4.77 d (J = 2.3 Hz)	112.3	112.3
12ax	2.75 d (J = 14.8 Hz)	2.75 d (J = 14.6 Hz)	43.8	43.8
12eq	2.03 d (J = 14.8 Hz)	2.03 d (J = 14.6 Hz)		
13			41.5	41.5
14	1.04 s	1.04 s	28.1	28.1
15	5.61 d (J = 15.5 Hz)	5.61 d (J = 15.5 Hz)	143.2	143.2
16	6.20 dd (J = 15.5, 10.6 Hz)	6.20 dd (J = 15.5, 10.6 Hz)	123.7	123.7
17	5.81 brd (J = 10.6 Hz)	5.81 (d, J = 10.3 Hz)	126.8	126.8
18			133.4	133.4
19	1.76 s	1.76 (s)	26.0	26.1
20	1.75 s	1.75 (s)	18.3	18.3

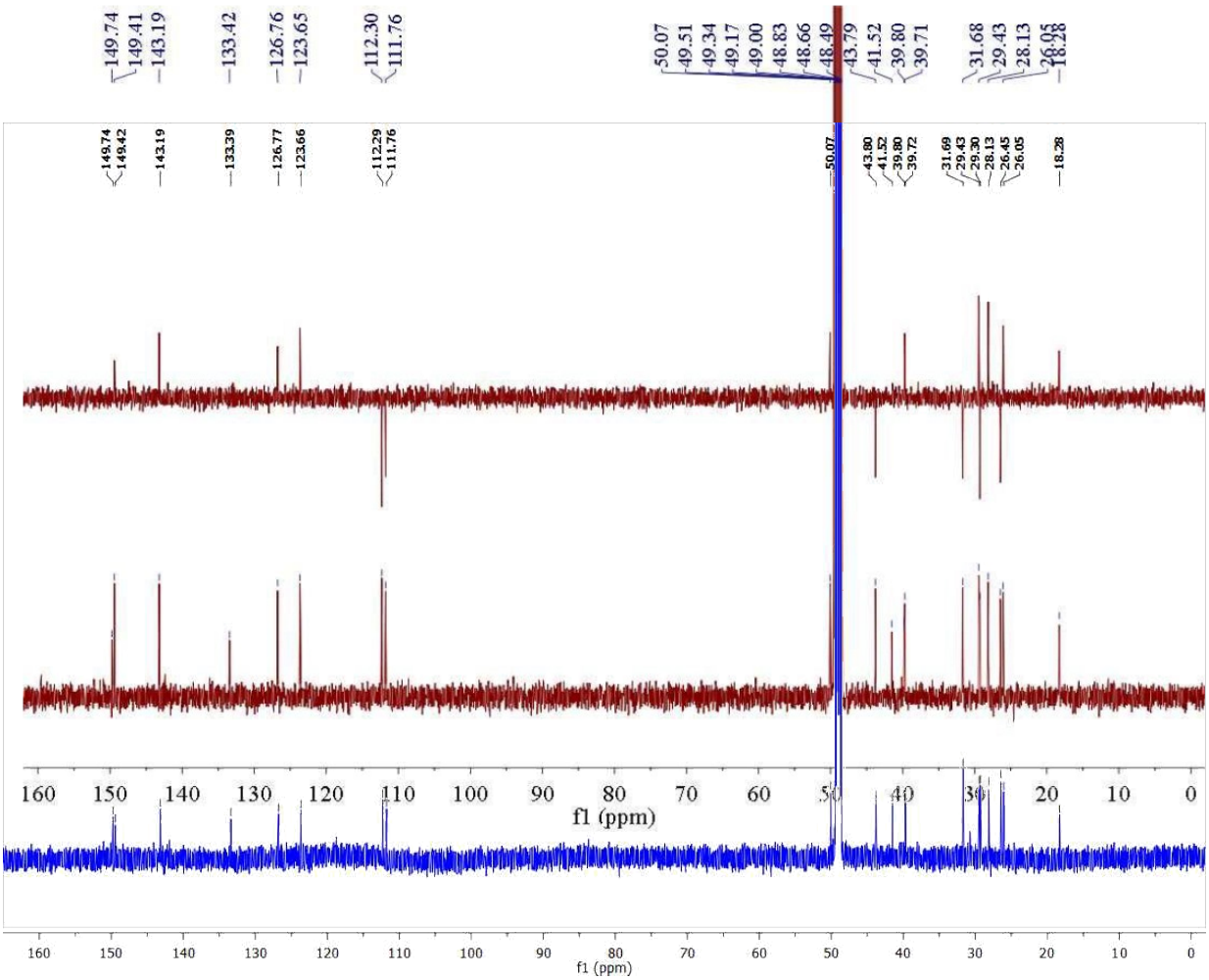
[6] F. Ye, Z.-D. Zhu, J.-S. Chen, J. Li, Y.-C. Gu, W.-L. Zhu, X.-W. Li, Y.-W. Guo, *Org. Lett.* **2017**, *19*, 4183–4186.

Overlay of material prepared through cyclization of fuscol (blue) with naturally isolated (red) xishacorene C (**3**).

^{1}H-NMR, 700 MHz, CD_3OD

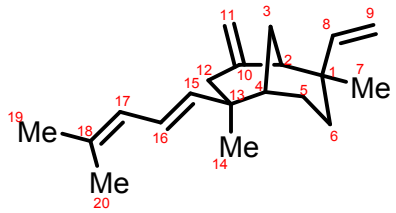


^{13}C-NMR, 176 MHz, CD_3OD

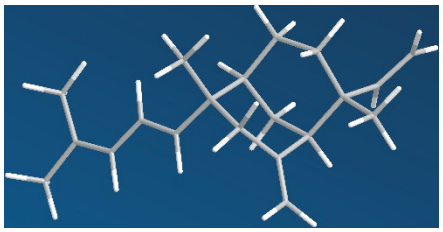


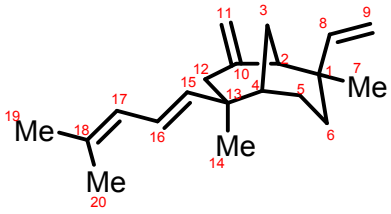
xishacorene D (4)

The following are tables of interpreted 1D and 2D experimental data used to assign the structure of compound **4**, which we have named xishacorene D:

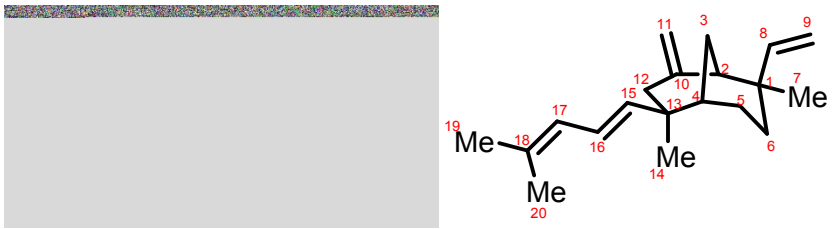


Number	δ_H	δ_C
1	-	38.81
2	2.08 (t, *J* = 3.7 Hz)	48.68
3a	1.68 m	28.82
3b	1.68 m	-
4	1.43 m	37.48
5a	1.86 m	24.20
5b	1.725 m	-
6a	1.65 m	31.20
6b	1.72 m	-
7	0.85 s	29.39
8	5.83 (dd, *J* = 17.6, 10.9 Hz)	148.33
9a	5.04 (d, *J* = 11.5 Hz)	111.47
9b	5.02 (d, *J* = 4.7 Hz)	-
10	-	148.69
11a	4.81 (t, *J* = 2.0 Hz)	111.2
11b	4.74 (d, *J* = 2.0 Hz)	-
12a	2.38 (d, *J* = 15.9 Hz)	43.66
12b	2.43 (d, *J* = 15.9 Hz)	-
13	-	40.41
14	1.07 s	27.72
15	5.53 (d, *J* = 15.5 Hz)	142.41
16	6.3 (dd, *J* = 15.5, 10.9 Hz)	123.59
17	5.78 (brd, *J* = 10.2 Hz)	125.82
18	-	142
19	1.76 s	26
20	1.74 s	18.5



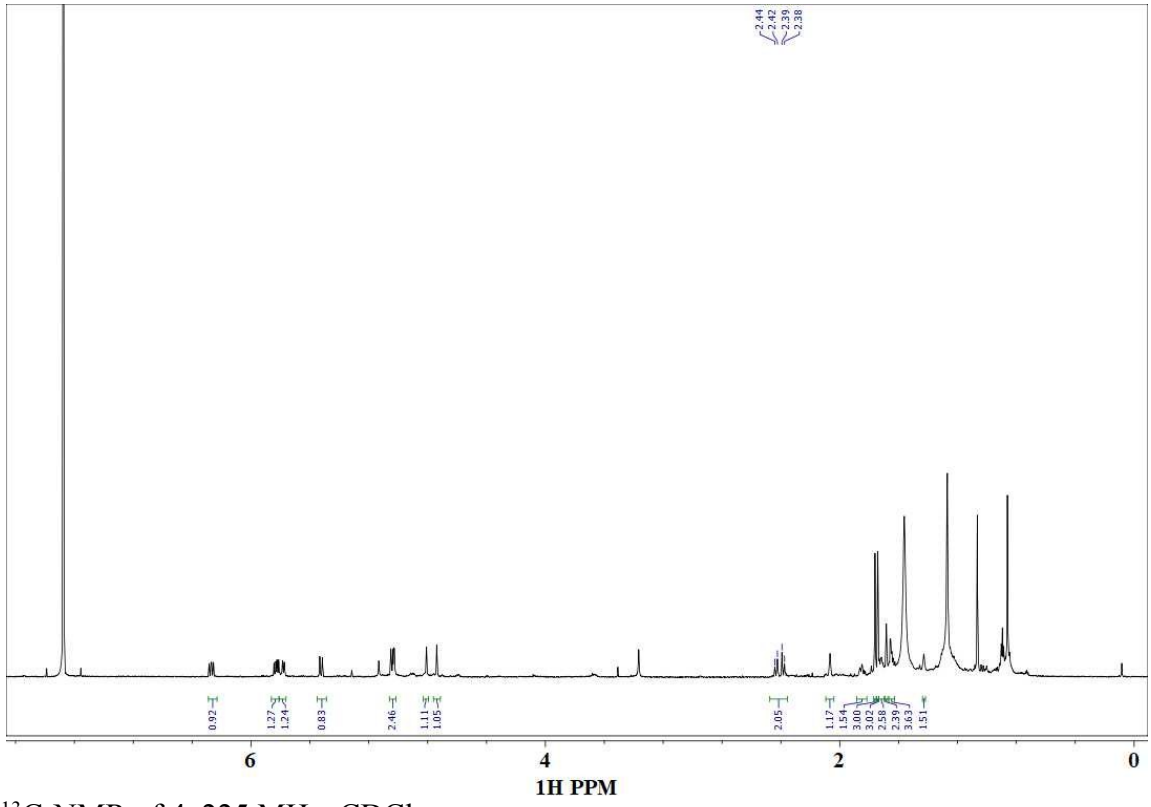


Number	δ_H	δ_C	**gCOSY Value**	**gCOSY Protons**	**HMBC Value**	**HMBC Correlation**
1	-	38.81	-	-	-	-
2	2.08	48.68	2.08: 1.68	H2: H3	2.08: 31, 37, 43, 111.22, 148.67	H2: C6, C4, C12, C11, (C8 or C12)
3a	1.68	28.82	1.68: 2.07,1.43	H3: H2, H4	1.68: 24.19, 40.56, 48.68, 148.72	H3: C5, C13, C2, C10
3b	1.68	'	"	"	"	"
4	1.43	37.48	1.43: 1.69, 1.85	H4: H3, H5	-	-
5a	1.86	24.20	1.86: 1.73	H5a: H5b	-	-
5b	1.73	"	1.73: 1.86, 1.43	H5b: H5a, H4	-	-
6a	1.65	31.20	-	-	1.65: 148.29	H6a: H8
6b	1.71	"	-	-	1.71: 148.29	H6b: H8
7	0.85	29.39	-	-	0.85: 31.31, 38.82, 48.55, 148.30	H7: C6, C1, C2, C8
8	5.83	148.33	5.83: 5.04/2	H8: H9a/b	5.83: 29.15, 31.16, 38.88, 49.00	H8: C7, C6, C1, C2
9a	5.04	111.47	5.04: 5.83	H9a: H8	5.05, 5.04: 38.79, 148.44	H9: C1, C8
9b	5.02	"	5.02: 5.83	H9b: H8	"	"
10	-	148.69	-	-	-	-
11a	4.81	111.2	4.81: 2.4	H11a: H12	4.81, 4.74: 43.58, 48.58, 148.69	H11: C12, C2, C10
11b	4.74	"	4.74: 2.4	H11b: H12		
12	2.4	43.66	2.4: 4.82	H12: H11	2.4: 27.59, 37.42, 40.37, 48.69, 111.14, 142.42, 148.69	H12: C14, C4, C13, C2, C11, C15, C10
13	-	40.41	-	-	-	-
14	1.07	27.72	-	-	1.07: 37.53, 40.41, 43.64, 142.43	H14: C4, C13, C12, C15
15	5.53	142.41	5.53: 6.33	H15: H16	5.53: 27.72, 37.5, 40.38, 43.67, 125.86	H15: H14, H4, H13, H12, H17
16	6.3	123.59	6.3: 5.53, 5.80	H16: H15, H17	6.3: 40.4, 125.53, 133.23	H16: H13, H17, H18
17	5.78	125.82	5.78: 6.31.76	H17: H16, H19	5.78: 18.58, 26.19, 142.6	H17: C19, C20, C15
18	-	133.27	-	-	-	-
19	1.76	26	1.76: 5.78	H19: H17	1.76: 18.5, 125.65, 133.35	H5: C20, C17, C18
20	1.74	18.5	1.74: 5.78	H20: H17	1.74: 26.11, 125.65, 133.35	H5: C19, C17, C18

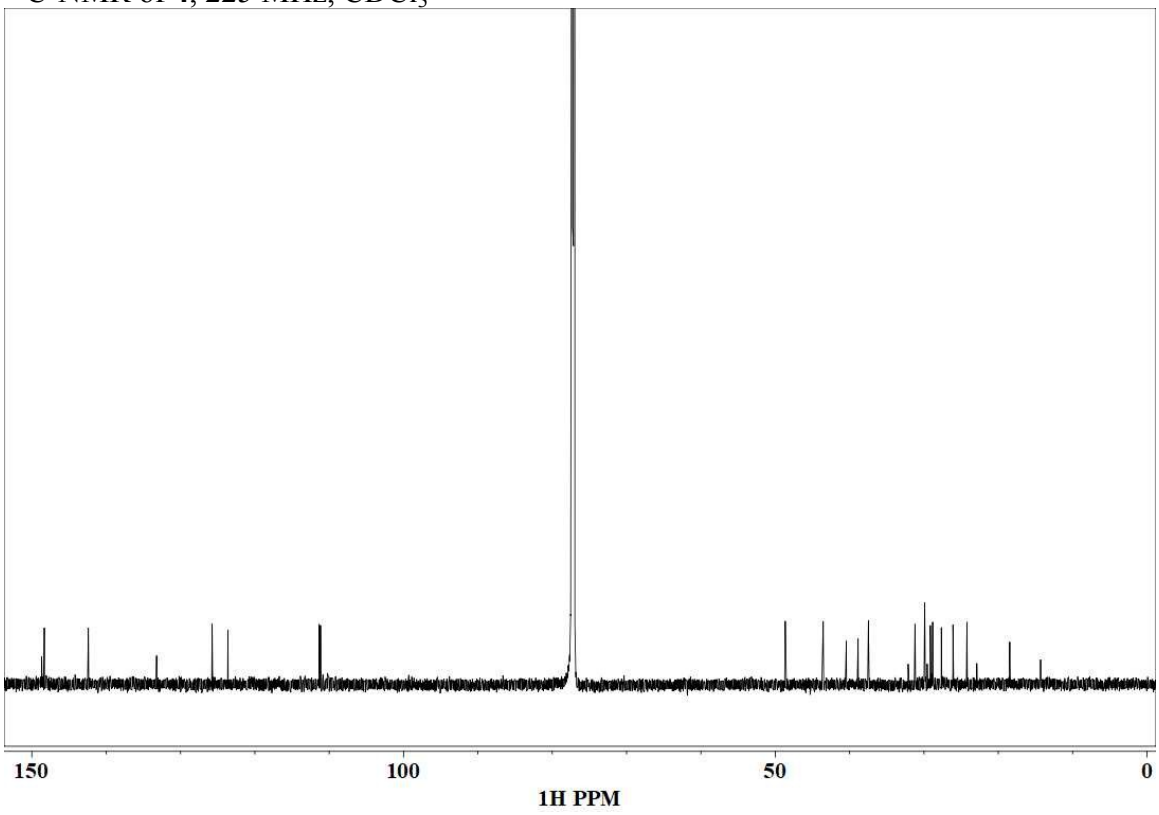


Number	δ_H	δ_C	**NOE Correlation**	**NOE Protons**
1	-	38.81	-	-
2	2.08	48.68	2.08: 0.86, 1.68, 4.75, 5.04, 5.83	H2: H7, H3, H11b, H9a, H8
3a	1.68	28.82	1.68: 1.43, 2.07, 5.05, 5.52, 5.82	H3: H4, H2, H9a, H15, H8
3b	1.68	-	"	"
4	1.43	37.48	1.43: 1.05, 1.71, 1.88, 5.51	H4: H14, H6b, H5a, H15
5a	1.86	24.20	1.86: 1.07, 1.44, 1.70	H5a: H14, H4, H6b
5b	1.725	-	1.73: 1.86	H5b: H5a
6a	1.65	31.20	1.65: 0.86, 1.85, 2.43, 5.02	H6a: H7, H5a, H12, H9b
6b	1.72	-	1.72: 1.43	H6b: H4
7	0.85	29.39	0.85: 1.66, 2.05, 2.43, 4.75, 5.03, 5.79	H7: H2, H6, H9, H11, H8, H12
8	5.83	148.33	5.83: 0.86, 1.68, 2.07, 5.04	H8: H7, H3, H2, H9a
9a	5.04	111.47	5.02: 0.88, 1.68, 2.08	H9a: H7, H3, H2
9b	5.02	-	5.02: 0.88, 1.68, 2.08, 5.84	H9b: H7, H3, H2, H8
10	-	148.69	-	-
11a	4.81	111.2	4.81: 0.9, 2.38, 5.06, 6.30	H11a: H7, H12, 9a, H16
11b	4.74	-	4.74: 0.9, 2.05	H11b: H7, H2
12	2.4	43.66	2.4: 1.66, 1.07, 4.80, 5.53, 6.30	H12: H3a, H14, H11a, H15, H16
13	-	40.41	-	-
14	1.07	27.72	1.07: 1.44, 1.65, 1.85, 2.42, 5.53, 6.27	H14: H4, H6a, H5a, H12, H15, H16
15	5.53	142.41	5.53: 1.08, 1.43, 1.69, 2.4, 5.76	H15: H14, H4, H12, H17
16	6.3	123.59	6.3: 1.07, 1.43, 1.74, 2.4, 4.8	H16: H14, H4, H20, H12, H11a
17	5.78	125.82	5.78: 1.76, 5.53	H17: H19, H15
18	-	142	-	-
19	1.76	26	1.76: 5.78	H19: H17
20	1.74	18.5	1.74: 6.25	H20: H16

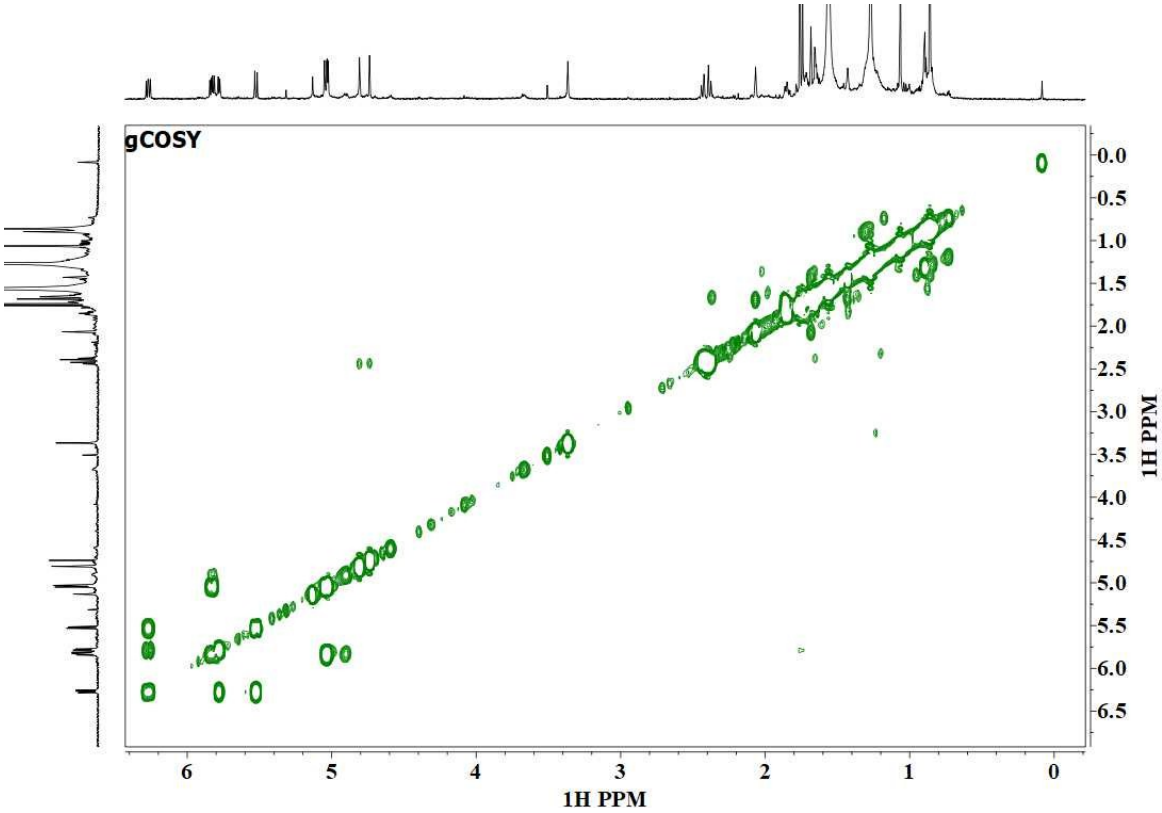
^{1}H-NMR of **4**, 900 MHz, $CDCl_3$



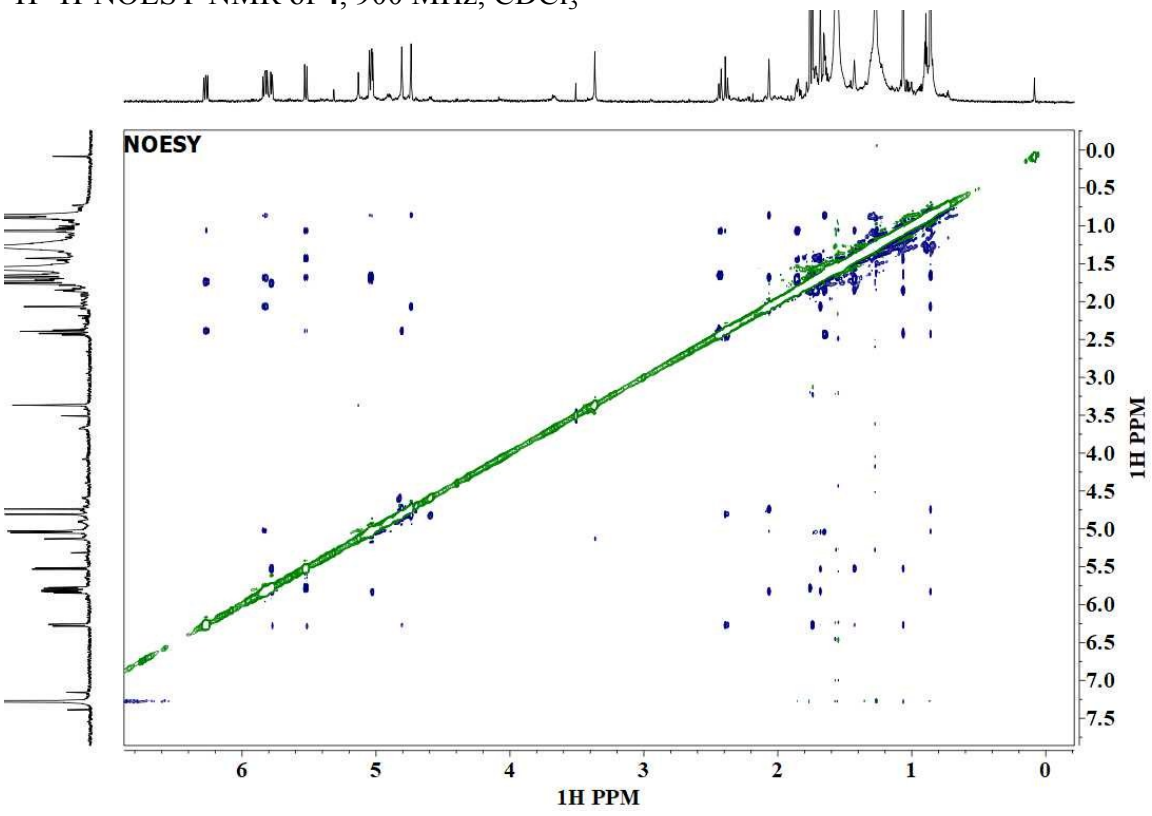
^{13}C-NMR of **4**, 225 MHz, $CDCl_3$



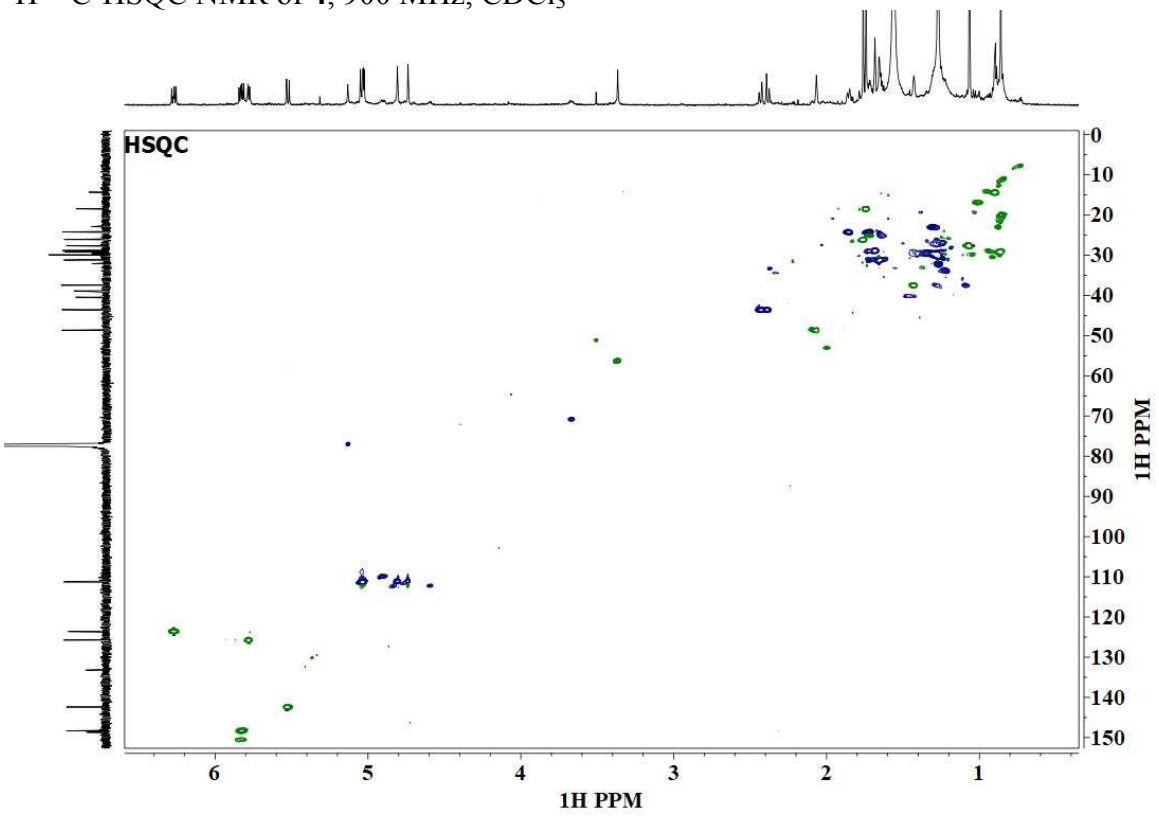
^{1}H-^{1}H-COSY NMR of **4**, 900 MHz, $CDCl_3$



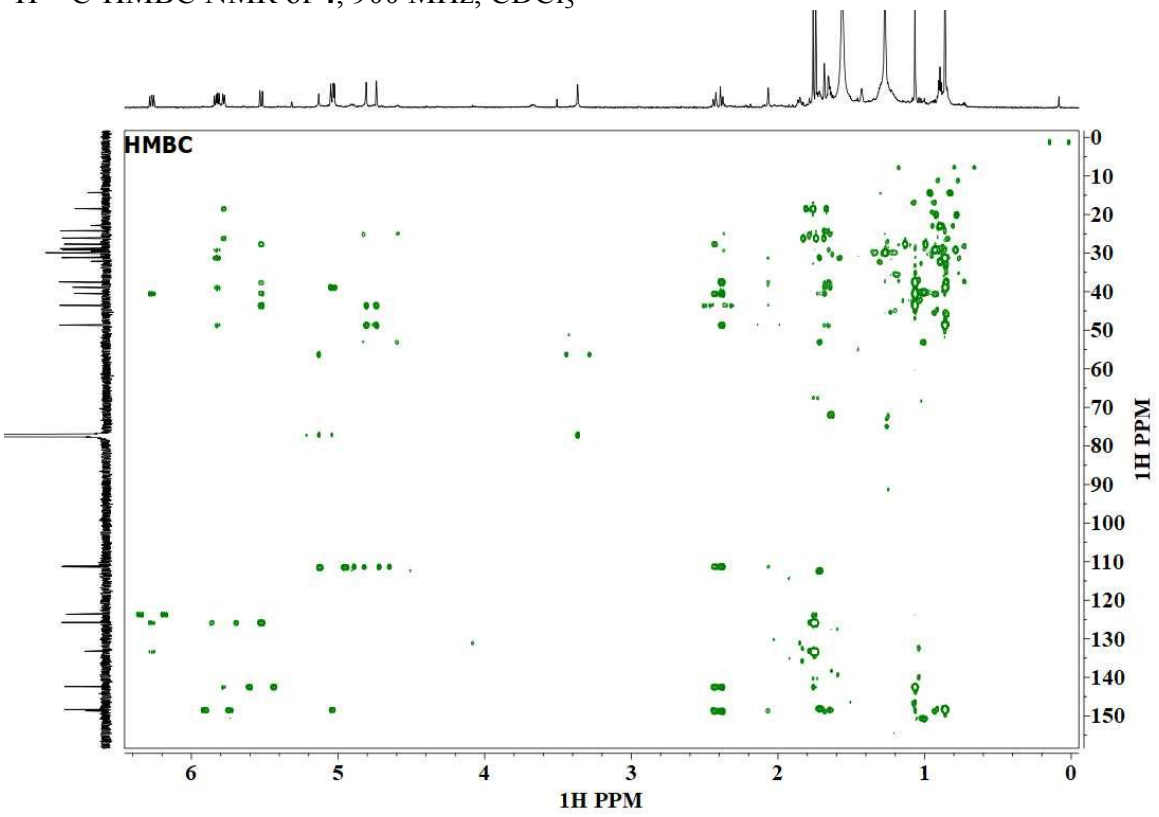
^{1}H-^{1}H-NOESY NMR of **4**, 900 MHz, $CDCl_3$



^{1}H-^{13}C-HSQC NMR of **4**, 900 MHz, $CDCl_3$

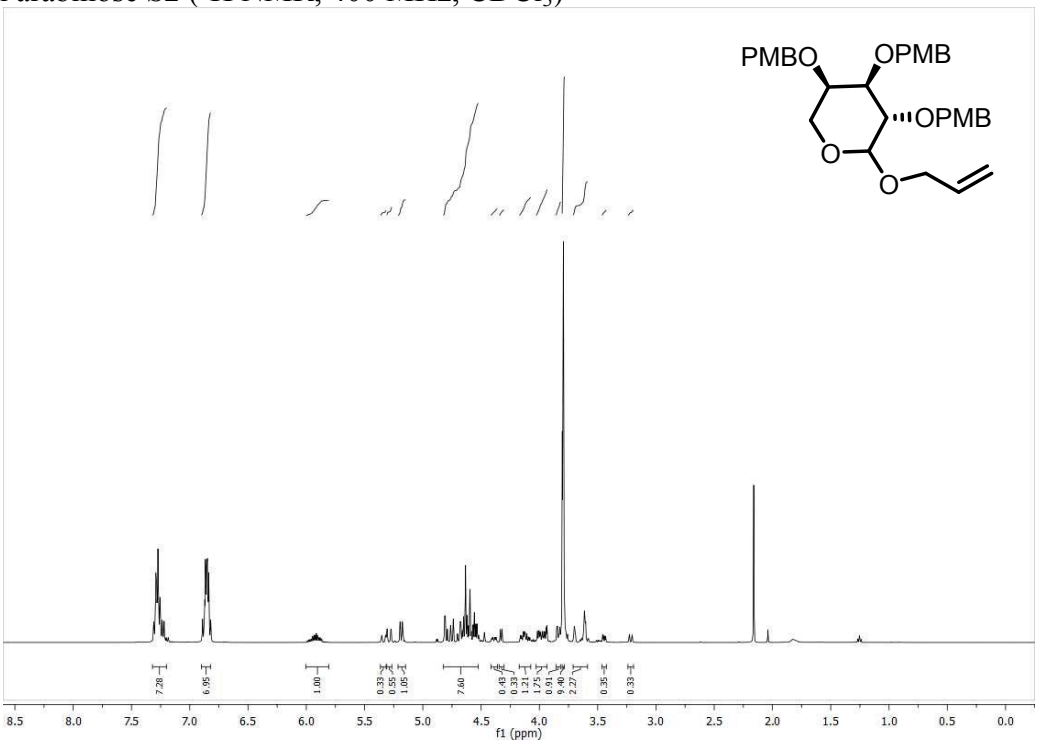


^{1}H-^{13}C-HMBC NMR of **4**, 900 MHz, $CDCl_3$

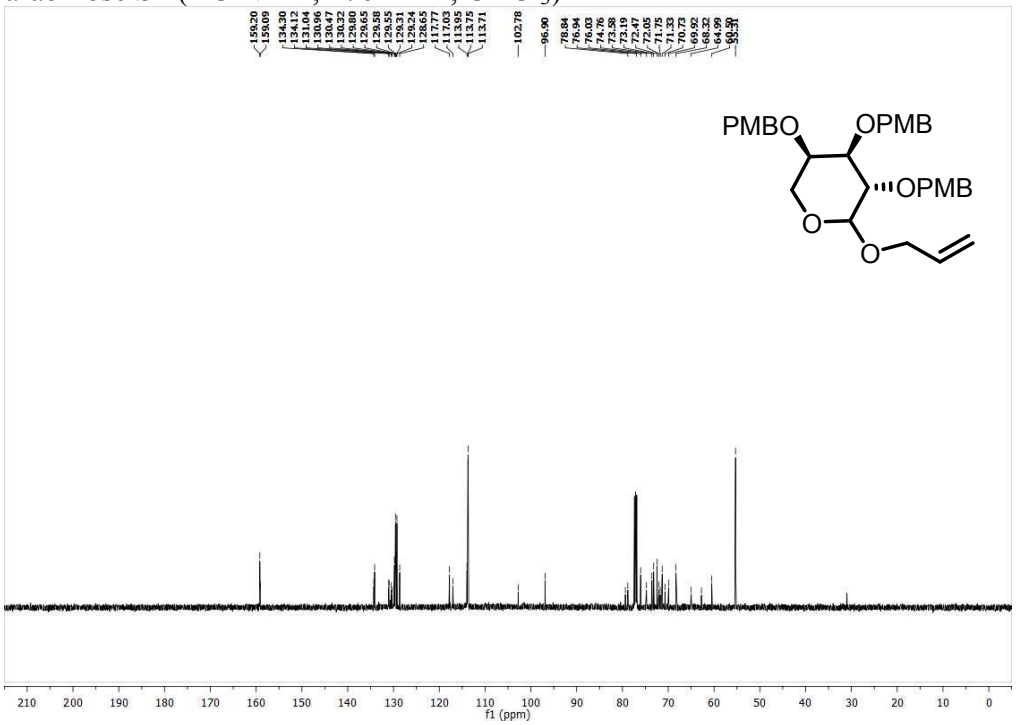


3 NMR Spectra

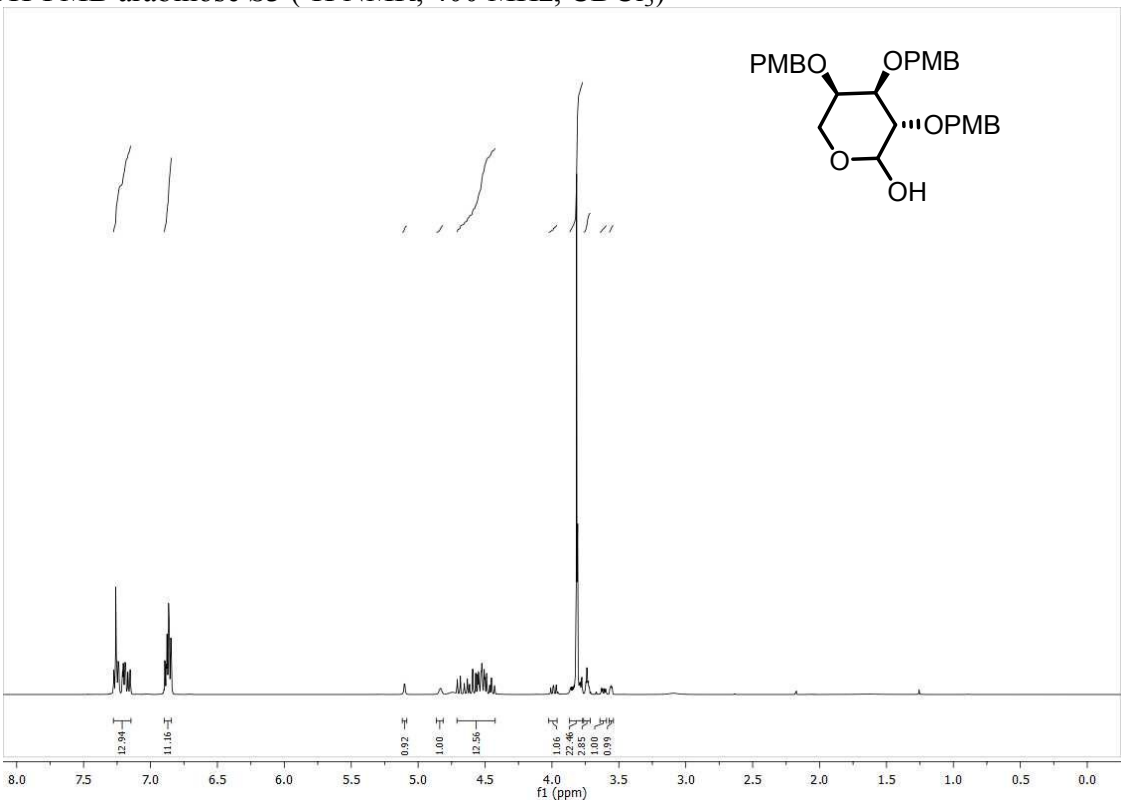
Allyl arabinose **S2** (^{1}H NMR, 400 MHz, $CDCl_3$)



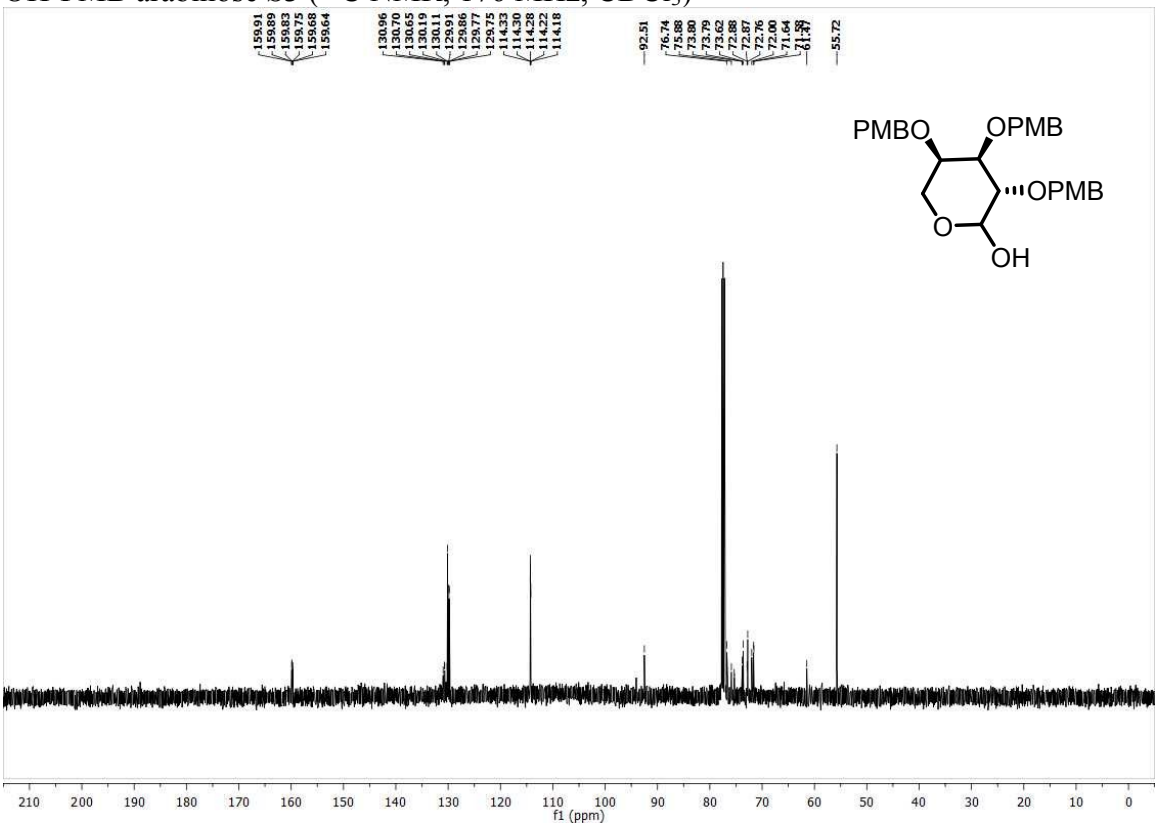
Allyl arabinose **S2** (^{13}C NMR, 176 MHz, $CDCl_3$)



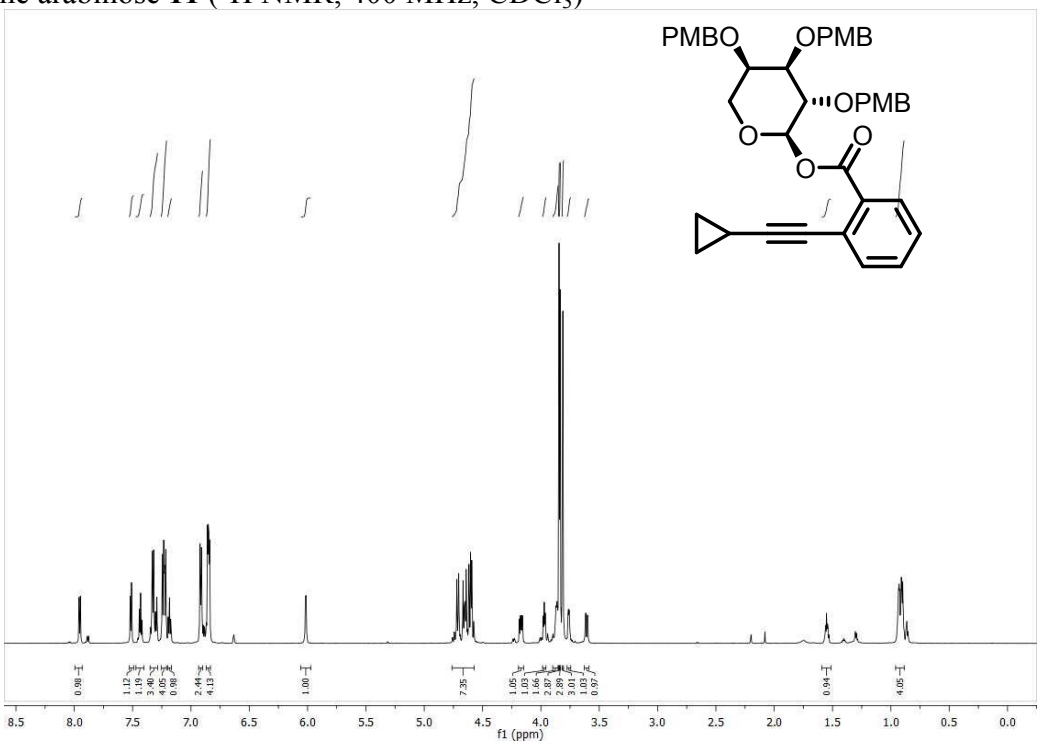
OH-PMB arabinose **S3** (^{1}H NMR, 400 MHz, $CDCl_3$)



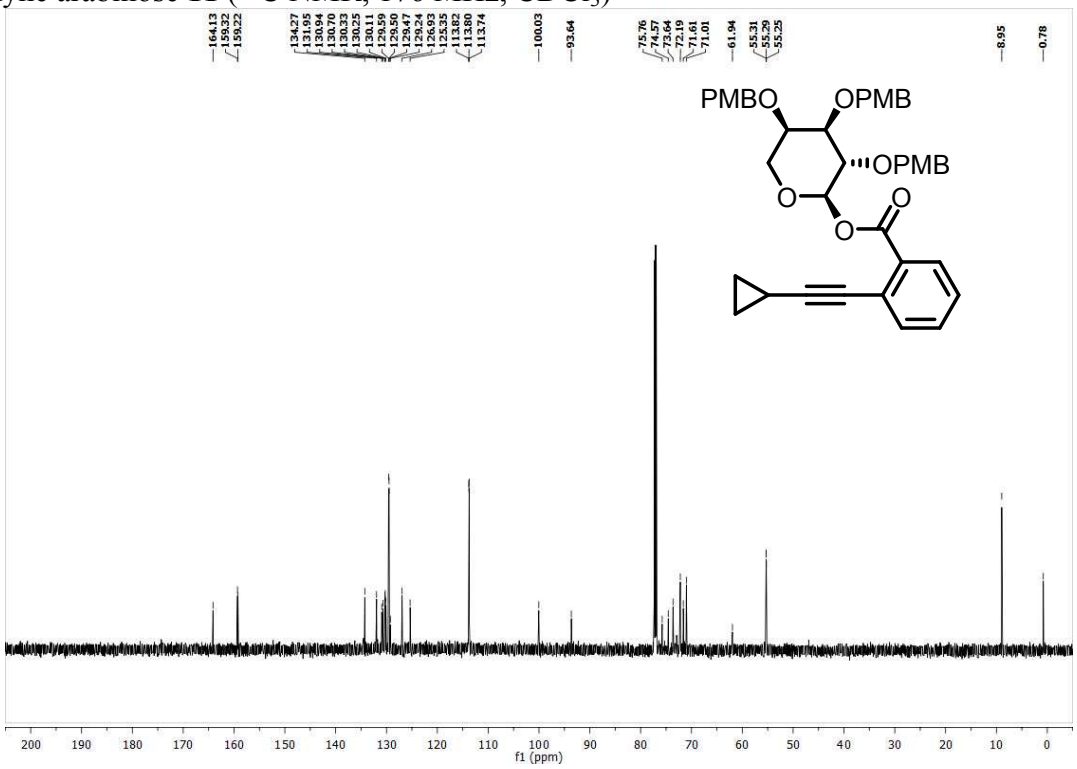
OH-PMB arabinose **S3** (^{13}C NMR, 176 MHz, $CDCl_3$)



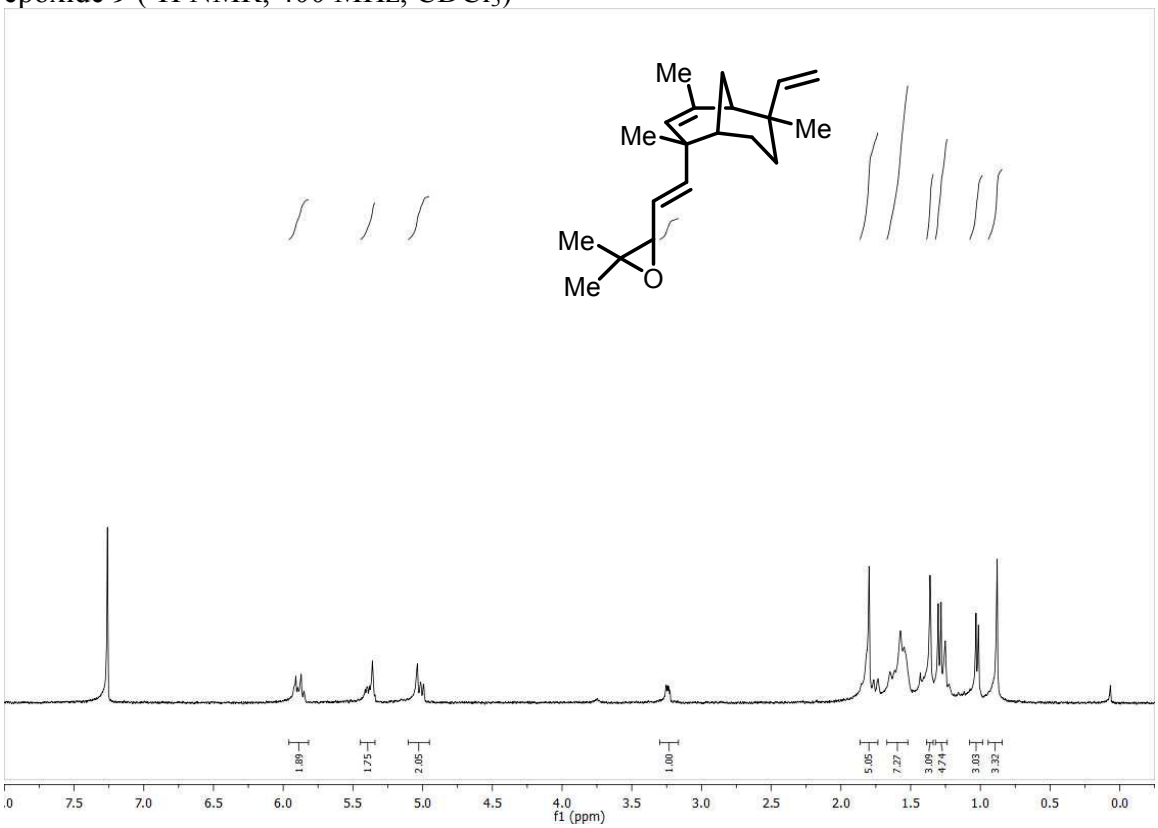
alkyne arabinose **11** (^{1}H NMR, 400 MHz, $CDCl_3$)



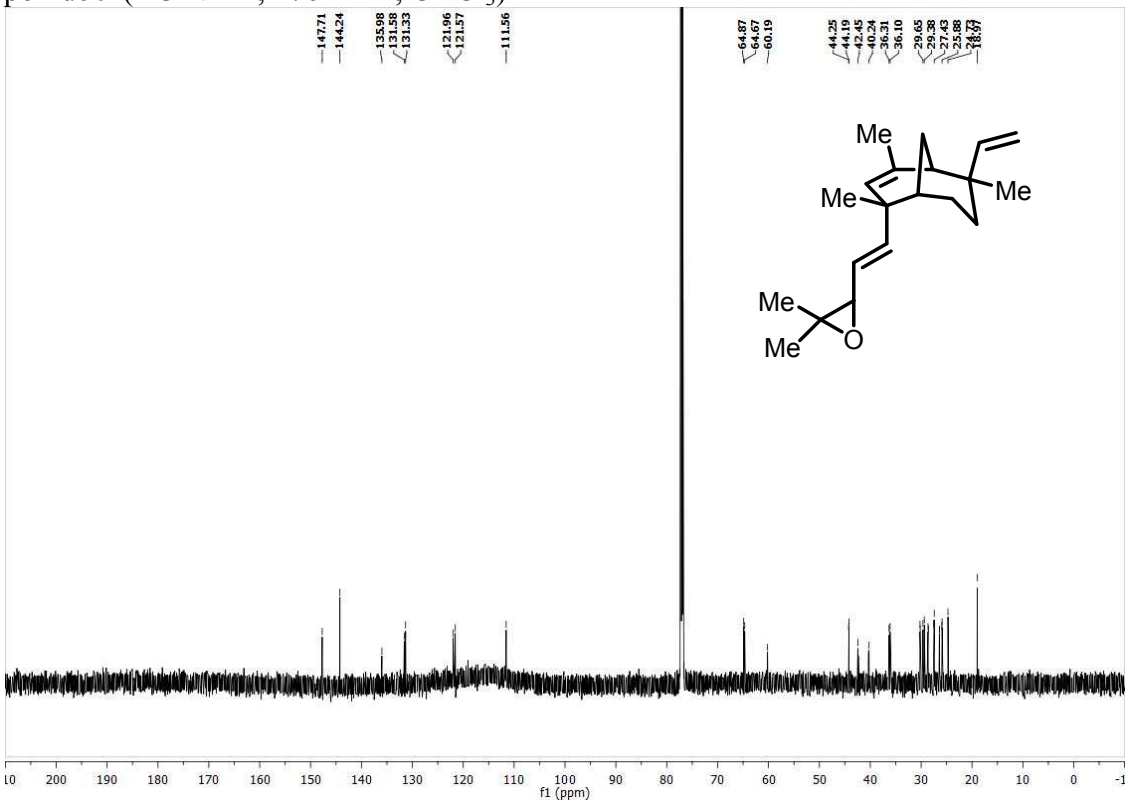
alkyne arabinose **11** (^{13}C NMR, 176 MHz, $CDCl_3$)



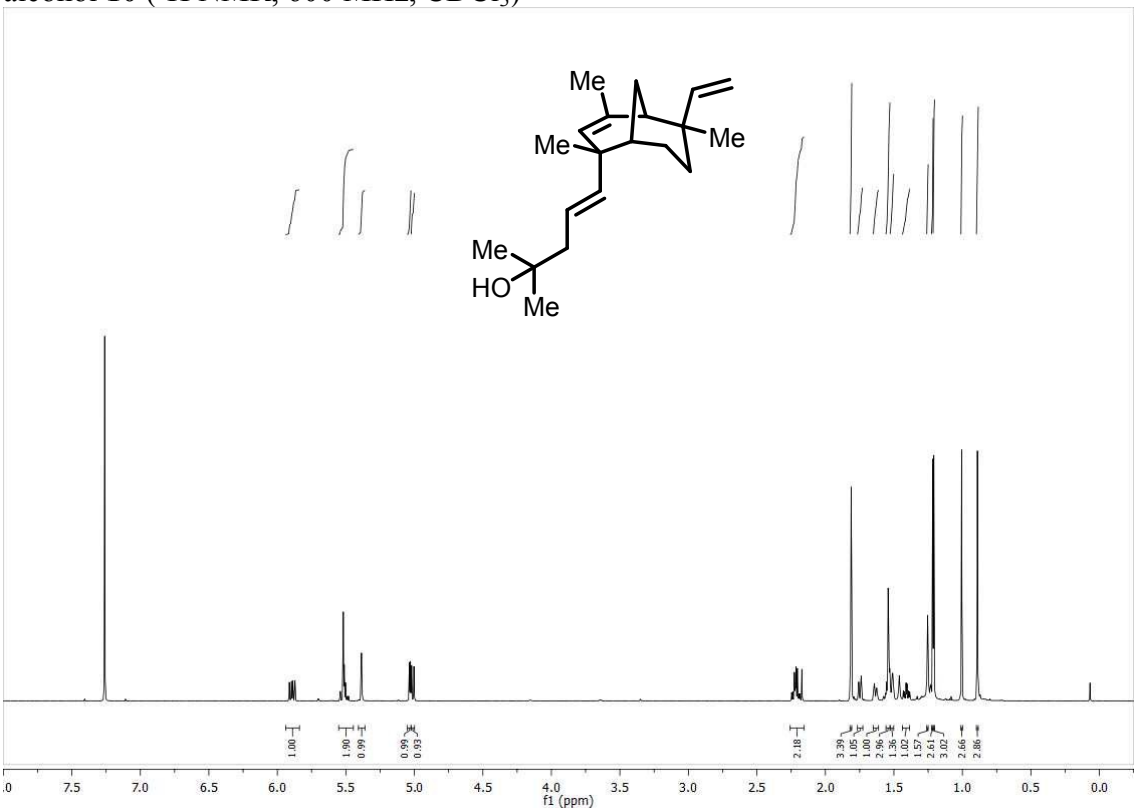
epoxide **9** (^{1}H NMR, 400 MHz, $CDCl_3$)



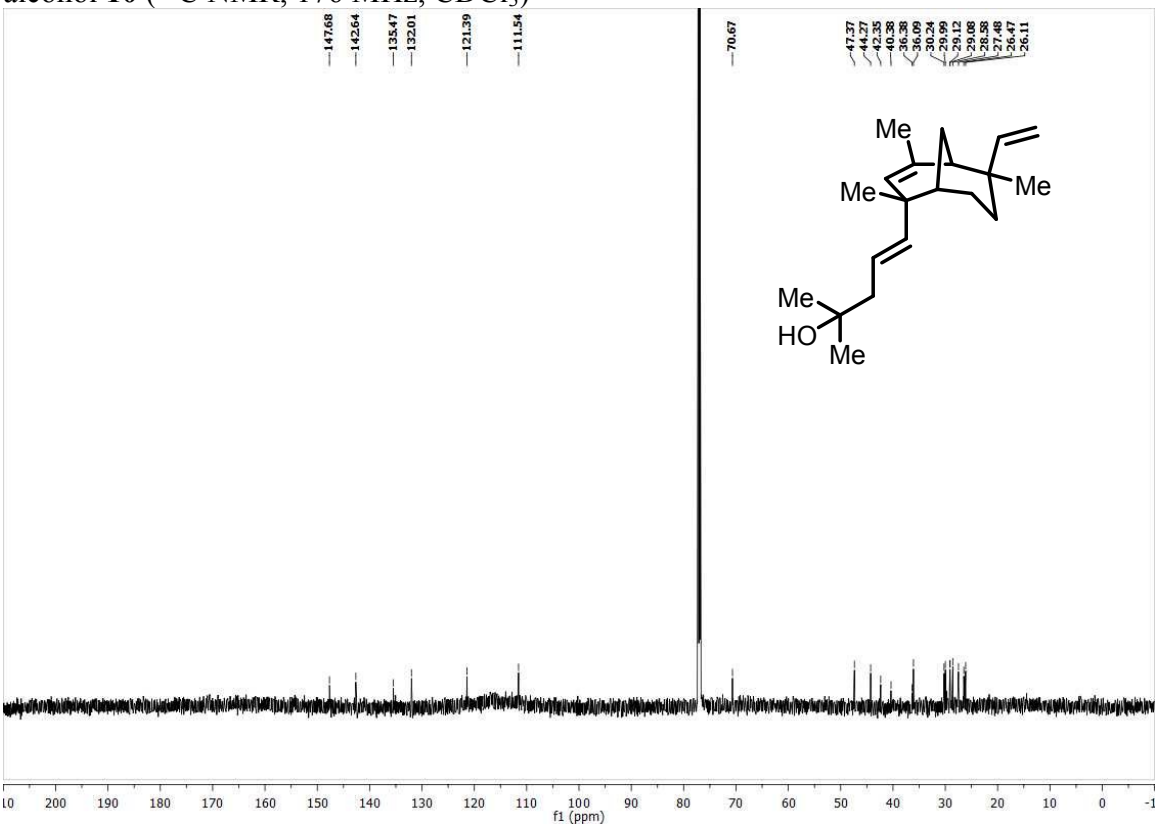
epoxide **9** (^{13}C NMR, 176 MHz, $CDCl_3$)



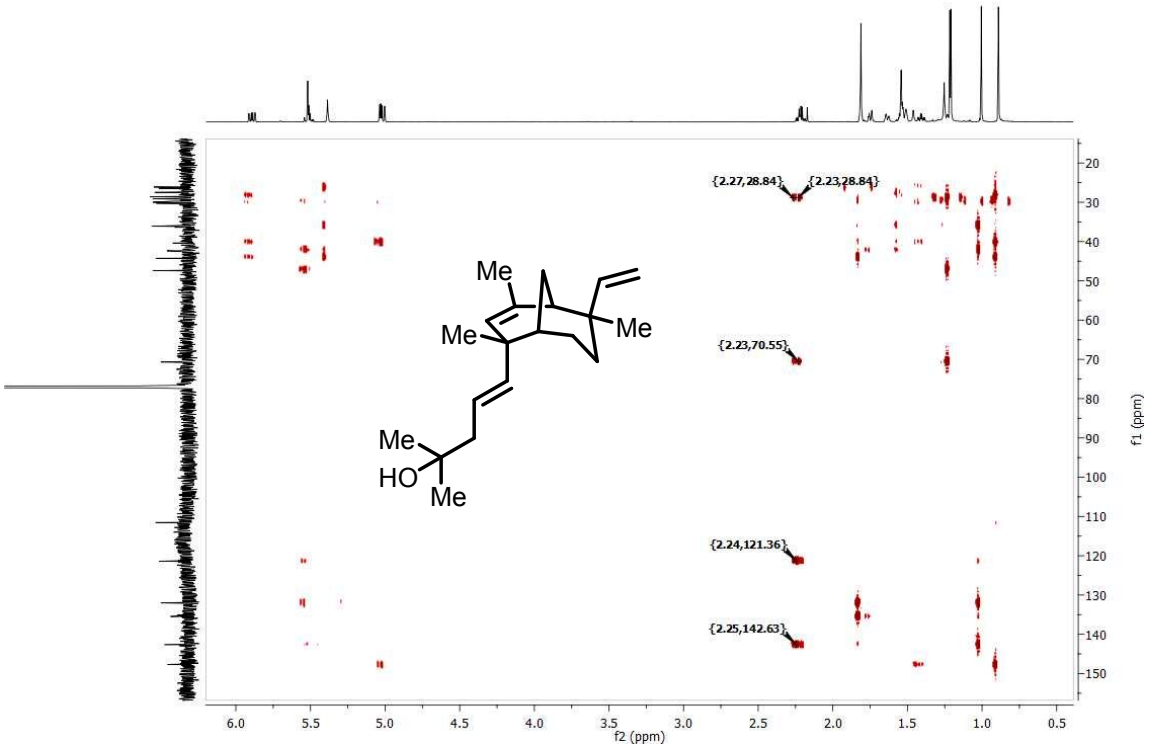
alcohol **10** (^{1}H NMR, 600 MHz, $CDCl_3$)



alcohol **10** (^{13}C NMR, 176 MHz, $CDCl_3$)

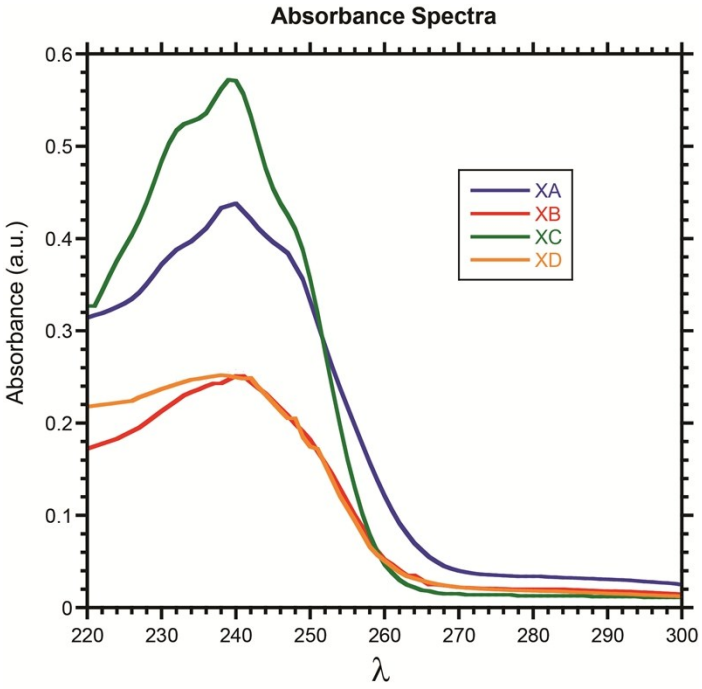


alcohol **10** (^{1}H-^{13}C HMBC, 600 MHz, $CDCl_3$)



4 Biological Assay Studies

Selected absorbance spectra for xishacorene A (XA), B (XB), C (XC), D (XD) in cyclohexane



Biological Methods

THP1-Dual™ reporter cells were originally purchased from InvivoGen. Cell culture was performed at 37°C in a humidified atmosphere containing 5% CO_2. THP1-Dual™ cells were cultured in RPMI 1640 medium containing 10% fetal bovine serum (FBS) supplemented with 100 U/mL penicillin, 100 µg/ml streptomycin, 100 µg/ml normocin (InvivoGen).

For the luciferase reporter experiment, THP1-Dual™ cells were incubated with different compounds at different concentrations as indicated in the graph for 1 hours, followed by stimulation with 10 µM ML RR-S2 cGAMP for 24 hours. Cell supernatant was collected to measure reporter activity using QUANTI-Luc (InvivoGen) in SpectraMax M5. Cell viability was measured by the CellTiter-Glo Luminescent cell viability assay (Promega) following the manufacturer's instructions.

IRF Luciferase Reporter Assay (No treatment with ML RR-S2 cGAMP)