Supplementary Material (ESI) for Chemical Communications

Supporting information

First total synthesis of moracin O and moracin P and establishment of the absolute configuration of moracin O

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II. Biological Procedures.

I. Synthesis

General: All the commercial chemicals were of reagent grade and were used without further purification. Solvent were dried with standard procedures. All reactions were carried out under an atmosphere of dried argon, in flame-dried glassware. Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined on a Varian (300 MHz) spectrometer. Chemical shifts are provided in parts per million (ppm) downfield from tetramethylsilane (internal standard) with coupling constants in hertz (Hz). Multiplicity is indicated by the following abbreviations: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), multiplet (m), broad (b). Mass spectra were recorded on a HRMS (EI-MS) was obtained on a JMS-700 (Jeol, Japan). Products from all reactions were purified by flash column chromatography using silica gel 60 (230-400 mesh Kieselgel 60) or by preparative thin layer chromatography using glass-backed silica gel plates (1mm thickness) unless otherwise indicated. Additionally, thin-layer chromatography on 0.25 mm silica plates (E. Merck, silica gel 60 F254) was used to monitor reactions. The chromatograms were visualized using ultraviolet illumination, exposure to iodine vapors, dipping in PMA or Hanessian's solution. Optical rotation was measured on a JASCO P-1020 polarimeter. The purity of the final products was checked by reversed phase high-pressure liquid chromatography (RP-HPLC), which was performed on Dionex Corp. HPLC system equipped with a UV detector set at 254 nm. The mobile phases used were A: H_2O containing 0.05% TFA, and B: CH_3CN. The HPLC employed an YMC Hydrosphere C18 (HS-302) column (5μ particle size, 12 nM pore size), 4.6 mm dia. x 150 mm with a flow rate of 1.0 mL/min. Compound purity was assessed using one of the following methods, Method A: gradient 20% B to 100% B in 30 min; Method B: gradient 25% B to 100% B in 30 min. Optical purity of the

synthesized compounds was established by chiral HPLC analysis: Chiracel OD-H (0.46 X 25 cm), 97:3 hexane: *i*-PrOH, 1.0 ml/min, λ = 210 nm.

Carbonic acid 5-*tert*-butoxycarbonyloxy-2-formyl-4-iodo-phenyl ester tert-butyl ester (5):

2,4-dihydroxybenzaldehyde (**15**) (10 g, 72.4 mmol) was dissolved in acetic acid (48 mL) before iodine monochloride (14.1 g, 86.88 mmol) dissolved in acetic acid (20 mL) was added dropwise and stirred for 6 h. The mixture was diluted with water and quenched with aqueous saturated $NaHSO_3$. The mixture was extracted rigorously with EtOAc until the extracts showed no sign of product. The combined EtOAc layers were dried over Na_2SO_4, filtered and concentrated. The crude reaction mass containing mixture of regioisomers **4** and 2,4-dihydroxy-3-iodo-benzaldehyde. These crude product were further reacted with Boc_2O (55.2 g, 0.25 mol) in the presence of anhydrous K_2CO_3 (17.5 g, 0.127 mol) in diethylether (800 mL) as solvent starring at room temperature overnight. After the completion of reaction, the reaction mixture was diluted with water and extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, and the crude residue was purified by flash column chromatography on silica g el (1:19 EtOAc/hexane) yielded **5** as low melting white solid (16.7 g, 35.97 mmol, 49 % Yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.08 (1H, s, CHO), 8.31 (1H, s, Ar-H), 7.24 (1H, s, Ar-H), 1.58 (9H, s, $C(CH_3)_3$), 1.57 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.59, 27.65, 85.20, 85.23, 86.9, 117.7, 127.1, 140.5, 149.5, 150.2, 152.9, 186.2; MS (EI) *m/z* 464 (M+); HRMS (EI+) *m/z* calculated for $C_{17}H_{21}IO_7$ 464.0332, found 464.0327.

Carbonic acid *tert*-butyl ester 5-hydroxy-2-iodo-4-(3-methyl-but-2-enyl)-phenyl ester (6):

To the stirring solution of benzaldehyde derivative **5** (15 g, 32.32 mmol) in THF/H_2O (19:1, 85.5 mL) at 0 ^oC, a pre-cooled solution of $NaBH_4$ (1.28 g, 34 mmol) in water (22.5 mL) was added. The reaction was carefully followed by TLC (7:3 hexane/EtOAc) until the disappearance of the starting material was observed. After 5 min reaction was quenched with crushed ice and acetic acid. The resulting solution was extracted with ether (2 x 100 mL), the combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to afford an oil. The oil was then dissolved in THF (180 mL), cooled to -78 ^oC and in to this reaction mixture the solution of 2-methylpropenyl magnesium bromide (0.05 M in THF, 194 mL, 97 mmol) was added. The reaction was stirred for 1 h at -78 °C, warmed to room temperature, and stirred for an additional 10 h. The reaction was quenched with 10 % HCl, extracted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (5:95 EtOAc/hexane) yielded the title compound **6** in 38% yield (5 g, 12.36 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.47 (1H, s, aromatic-H), 6.67 (1H, s, aromatic-H), 5.27 (1H, m, vinylic CH), 5.23 (1H, brs, OH), 3.29 (2H, d, CH_2, J = 6.9 Hz), 1.77 (3H, s, CH_3), 1.75 (3H, s, CH_3), 1.57 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.8, 25.7, 27.7, 28.7, 78.5, 84.2, 110.5, 120.7, 127.5, 135.4, 139.1, 150.0, 151.1, 155.3; MS (EI) *m/z* 404 (M+); HRMS (EI+) *m/z* calculated for $C_{16}H_{21}IO_4$ 404.0485, found 404.0479.

Carbonic acid *tert*-butyl ester 3-hydroxy-6-iodo-2,2-dimethyl-chroman-7-yl ester (7):

The solution of *O*-prenylated derivative **6** (1.2 g, 2.97 mmol) in $CHCl_3$ (26 mL) was added drop-wise to pre-cooled solution of *m*-chloroperbenzoic acid (615 mg, 3.56 mmol) and *p*-toluenesulphonic acid (28.3 mg, 0.15 mmol) in $CHCl_3$ (14.5 mL) at 0 ^oC. The reaction was stirred for 1 h at 0 °C, gradually warmed to room temperature, and stirred overnight. The reaction was washed with dilute aqueous $NaHCO_3$ and water,

dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was then purified by flash column chromatography on silica gel eluting with hexane/EtOAc (85:15) to afford the desired product in 61% yield (764 mg, 1.82 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (1H, s, aromatic-H), 6.69 (1H, s, aromatic-H), 3.80 (1H, t, CH, J = 5.1 Hz), 3.05 (1H, dd, CH_2, J_1 = 5.1 Hz, J_2 = 16.8 Hz), 2.77 (1H, dd, CH_2, J_1 = 5.1 Hz, J_2 = 16.8 Hz), 1.57 (9H, s, $C(CH_3)_3$), 1.34 (3H, s, CH_3), 1.30 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.0, 27.6, 30.5, 69.1, 77.4, 78.8, 84.1, 111.9, 119.3, 139.5, 150.4, 150.9, 153.9; MS (EI) *m/z* 420 (M+); HRMS (EI+) *m/z* calculated for $C_{16}H_{21}IO_5$ 420.0434, found 420.0439.

6-Iodo-2,2-dimethyl-chroman-3,7-diol (8):

To solution of benzohydropyran **7** (550 mg, 1.19 mmol) in CH_2Cl_2 (110 mL) was added $ZnBr_2$ (2.67 g, 11.9 mmol). The solution was stirred at room temperature overnight. The reaction was quenched with 1 M HCl and extracted twice with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography eluting with hexane/EtOAc (80:20) to afford the desired product in 80% yield (305 mg, 0.95 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (1H, s, aromatic-H), 6.50 (1H, s, aromatic-H), 5.07 (1H, brs, OH), 3.77 (1H, m, CH), 3.02 (1H, dd, CH_2, J_1 = 5.1 Hz, J_2 = 17.1 Hz), 2.73 (1H, dd, CH_2, J_1 = 5.1 Hz, J_2 = 17.1Hz), 1.35 (3H, s, CH_3), 1.30 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.6, 30.3, 60.4, 74.9, 77.2, 103.6, 113.8, 138.4, 154.1, 154.6; MS (EI) *m/z* 320 (M+); HRMS (EI+) *m/z* calculated for $C_{11}H_{13}IO_3$ 319.9909, found 319.9910.

2-[3,5-Bis-(*tert*-butyl-dimethyl-silanyloxy)-phenyl]-7,7-dimethyl-6,7-dihydro-5*H*-furo[3,2-g]chromen-6-ol (10):

To a well-stirred mixture of 2-iodophenol derivative **8** (300 mg, 0.94 mmol), $Pd(Ph_3P)_2Cl_2$ (65.7 mg, 0.094 mmol), CuI (35.7 mg, 0.19 mmol) and Et_3N (1 mL, 7.5

mmol) in dioxane (5 mL), a terminal alkyne **9** (680 mg, 1.9 mmol) was added under argon atmosphere. The mixture was stirred at 85 ^{o}C for 20 h. After removal of the solvent under reduced pressure the mixture was cooled, diluted with EtOAc, washed sequentially with dilute HCl, aqueous $NaHCO_3$, and water. The organic layer was then dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified through silica-gel column chromatography (50:50 CH_2Cl_2/hexane) to afford compound **10** in 37% yield (192 mg, 0.35 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21 (1H, s, aromatic-H), 6.98 (1H, s, aromatic-H), 6.91 (2H, d, J = 2.4 Hz, aromatic-H), 6.81 (1H, s, aromatic-H), 6.31 (1H, t, J = 2.4 Hz, aromatic-H), 3.84 (1H, m, CH), 3.22 (1H, dd, CH_2, J_1 = 4.2 Hz, J_2 = 16.8 Hz), 2.73 (1H, dd, CH_2, J_1 = 5.1 Hz, J_2 = 16.8 Hz), 1.39 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.00 (18H, s, 2 x $C(CH_3)_3$), 0.24 (12H, s, 2 x Si-$(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -4.3, 18.2, 22.3, 24.7, 25.7, 31.6, 53.4, 69.8, 76.9, 77.2, 99.5, 100.9, 109.8, 111.9, 114.9, 120.9, 123.1, 132.2, 150.8, 154.7, 155.1, 156.5; MS (EI) *m/z* 554 (M+); HRMS (EI+) *m/z* calculated for $C_{31}H_{46}O_5Si_2$ 554.2884, found 554.2882.

5-(6-Hydroxy-7,7-dimethyl-6,7-dihydro-5*H*-furo[3,2-g]chromen-2-yl)-benzene-1,3-diol [(±)-Moracin P, 2]:

To solution of compound **10** (17 mg, 0.031 mmol) in THF/Pyridine (4:1, 1.2 mL) in a teflon bottle was added 70% HF/Pyridine solution (0.08 mL) with a Teflon syringe at 0 ^{o}C. The reaction was gradually warmed to room temperature and stirred for 2 h. the reaction was quenched slowly with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with dil. HCl and water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was then purified by PLC (60:40 EtOAc/hexane) to afford the desired product in 75% yield (7.5 mg, 0.023 mmol). ^{1}H NMR (CD_3OD, 300 MHz) δ 7.21 (1H, s, aromatic-H), 6.87 (1H, s, aromatic-H), 6.85

(1H, s, aromatic-H), 6.75 (2H, d, J = 2.1 Hz, aromatic-H), 6.24 (1H, t, J = 2.1 Hz, aromatic-H), 3.84 (1H, dd, CH, J_1 = 5.4 Hz, J_2 = 7.5 Hz), 3.14 3.22 (1H, dd, CH_2, J_1 = 5.7 Hz, J_2 = 16.8 Hz), 2.73 (1H, dd, CH_2, J_1 = 7.5 Hz, J_2 = 16.5 Hz), 1.35 (3H, s, CH_3), 1.27 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.9, 32.4, 70.5, 78.2, 99.6, 101.8, 103.6, 104.0, 117.6, 121.7, 124.1, 133.6, 152.5, 155.9, 156.5, 159.9; MS (EI) *m/z* 326 (M+); HRMS (EI+) *m/z* calculated for $C_{19}H_{18}O_5$ 326.1154, found 326.1152; Purity >99% (as determined by RPHPLC, method A, t_R = 9.527 min).

2-(1-Hydroxy-1-methyl-ethyl)-5-iodo-2,3-dihydro-benzofuran-6-ol (12):

A solution of *m*-chloroperbenzoic acid (171 mg, 0.99 mmol) in EtOAc (10 mL) was added dropwise to a solution of **6** (200 mg, 0.49 mmol) in EtOAc (5 mL) at 0 ^{o}C. The reaction was stirred for 4 h at 0 ^{o}C and then quenched by slow addition of aqueous solution of $NaHSO_3$ (1 g in 10 mL of water). The mixture was stirred for 20 min and then the layers were separated. The organic layer was washed with $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was taken up in MeOH (9.5 mL) and LiOH (73 mg, 1.73 mmol) was added to the solution. The reaction was stirred at room temperature overnight. The MeOH was evaporated; crude residue was diluted with water, acidified with 10% HCl and extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue on silica gel (40:60 Et_2O/hexane) gave compound **12** in 57% yield (90 mg, 0.28 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (1H, s, aromotic-H), 6.50 (1H, s, aromatic-H), 5.17 (1H, bs, OH), 4.66 (1H, t, CH, J = 9 Hz), 3.10 (2H, d, CH_2, J = 9 Hz), 1.32 (3H, s, CH_3), 1.20 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.9, 29.6, 71.7, 73.3, 77.2, 90.5, 97.0, 122.0, 132.7, 154.7, 161.7; MS (EI) *m/z* 320 (M+); HRMS (EI+) *m/z* calculated for $C_{11}H_{13}IO_3$ 319.9909, found 319.9911.

2-{6-[3,5-Bis-(*tert*-butyl-dimethyl-silanyloxy)-phenyl]-2,3-dihydro-benzo[1,2-b;5,4-

b']difuran-2-yl}-propan-2-ol (13):

To a well-stirred mixture of 2-iodophenol derivative **12** (180 mg, 0.56 mmol), $Pd(Ph_3P)_2Cl_2$ (39.4 mg, 0.056 mmol), CuI (21.4 mg, 0.113 mmol) and Et_3N (0.6 mL, 4.5 mmol) in dioxane (4 mL) a terminal alkyne **9** (408 mg, 1.13 mmol) was added under argon atmosphere. The mixture was stirred at 85 ^oC for 20 h. After removal of the solvent under reduced pressure the mixture was cooled, diluted with EtOAc, washed sequentially with dilute HCl, aqueous $NaHCO_3$, and water. The organic layer was then dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified through silica-gel column chromatography (50:50 CH_2Cl_2/hexane) to afford compound **13** in 31% yield (97 mg, 0.175 mmol). ^1H NMR (DMSO-d_6, 300 MHz) δ 7.36 (1H, s, aromatic-H), 7.30 (1H, s, aromatic-H), 6.99 (1H, s, aromatic-H), 6.89 (2H, d, J = 1.5 Hz, aromatic-H), 6.26 (1H, t, J = 2.1 Hz, aromatic-H), 4.64 (1H, t, CH, J = 8.7 Hz), 3.20 (2H, dd, CH_2, J = 3.6 Hz, 8.1 Hz), 1.14 (6H, s, 2 x CH_3), 0.96 (18H, s, 2 x $C(CH_3)_3$), 0.22 (12H, s, 2 x Si-$(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -4.2, 19.1, 25.2, 25.4, 26.1, 31.1, 72.4, 91.4, 93.3, 103.0, 110.4, 112.6, 117.1, 123.9, 125.3, 133.9, 155.4, 156.5, 158.2, 160.1; MS (EI) *m/z* 554 (M+); HRMS (EI+) *m/z* calculated for $C_{31}H_{46}O_5Si_2$ 554.2884, found 554.2883.

5-[6-(1-Hydroxy-1-methyl-ethyl)-5,6-dihydro-benzo[1,2-*b*;5,4-*b'*]difuran-2-yl]-benzene-1,3-diol [(±)-Moracin O, 1]:

To solution of compound **13** (50 mg, 0.09 mmol) in THF/Pyridine (4:1, 3.5 mL) in a teflon bottle was added 70% HF/Pyridine solution (0.24 mL) with a Teflon syringe at 0 ^oC. The reaction was gradually warmed to room temperature and stirred for 2 h. the reaction was quenched slowly with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with dil. HCl and water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was then purified by PLC (60:40

EtOAc/hexane) to afford the desired product in 74.8% yield (22 mg, 0.067 mmol). ^{1}H NMR (CD_3OD, 300 MHz) δ 7.29 (1H, s, aromatic -H), 6.89 (1H, s, aromatic -H), 6.84 (1H, s, aromatic-H), 6.73 (2H, d, J = 2.1 Hz, aromatic-H), 6.22 (1H, t, J = 2.1 Hz, aromatic-H), 4.67 (1H, t, CH, J = 8.7 Hz), 3.24 (2H, m, CH_2), 1.27 (3H, s, CH_3), 1.23 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.2, 31.1, 72.5, 91.3, 93.2, 102.3, 103.4, 103.8, 116.9, 123.9, 125.1, 133.8, 156.2, 156.3, 159.9; MS (EI) *m/z* 326 (M+); HRMS (EI+) *m/z* calculated for $C_{19}H_{18}O_5$ 326.1154, found 326.1154; Purity >99% (as determined by RPHPLC, method A, t_R = 9.573 min).

***tert*-Butyl-3-(benzyloxy)-4-(3-methylbut-2-enyl)phenyl carbonate (16).** The compound prenylated phenol compound (2 g, 7.2 mmol) was dissolved in anhydrous DMF (15 mL) and added potassium carbonate (1.99 g, 14.4 mmol). To the mixture was added dropwise benzyl bromide (1.23 g, 7.2 mmol) and stirred at room temperature overnight. The solvent was evaporated under vacuo and washed with water. The mixture was extracted with ethyl acetate and separated. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc: n-Hexane= 1:9) to afford white solid 16 (1.94 g, 73%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (5H, m), 6.99 (1H, d, J=8.1 Hz), 6.45 (1H, d, J=2.4 Hz), 6.35 (1H, dd, J=2.4, 8.1 Hz), 5.29 (1H, m), 5.04 (2H, s), 4.55 (1H, br), 3.29 (2H, d, J=7.5 Hz), 1.72 (3H, s), 1.65 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.8, 152.0, 149.9, 136.9, 132.6, 129.5, 128.5, 127.9, 127.8, 127.3, 122.3, 113.1, 105.3, 83.4, 70.1, 28.2, 27.7, 25.7, 17.7; MS (EI) *m/z* 269 (M+); HRMS (EI+) *m/z* calculated for $C_{23}H_{28}O_4$ 368.1988, found 368.1994.

(*S*)-*tert*-butyl-3-(benzyloxy)-4-(2, 3 - dihydroxy-3-methylbutyl)phenyl carbonate (17a). The long neck flask was equipped with AD-mix-α (1.9 g), tert-BuOH (10 mL) and water (10 mL). The mixture was stirred at room temperature for 10 min and

methansulfonamide (155 mg, 1.63 mmol) was added at 0 ℃. The mixture was stirred at 0 ℃ for 30 min and olefin 16 (500 mg, 1.36 mmol) was added at once. The reaction mixture was stirred at 0 ℃ for 48 h. When the reaction was stirred at 0 ℃, solid sodium sulfite was added and allowed to warm at room temperature for 30 min. Then the mixture was extracted with ethyl acetate and separated. The organic layer was washed with aqueous of potassium hydroxide. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure to obtain crude product, which was purified by column chromatography on silica gel (EtOAc: n-Hexane= 1:9) to afford 17a as white crystal (430 mg, 79%, 90% ee); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41~7.34 (5H, m), 7.19 (1H, s, *J*=8.1 Hz), 6.80 (1H, s), 6.77 (1H, d, *J*=2.1 Hz), 5.05 (2H, s), 3.61 (1H, d, *J*=10.2 Hz), 2.99 (1H, d, *J*=13.2 Hz), 2.55 (1H, dd, *J*=10.2, 13.2 Hz), 1.56 (9H, s), 1.19 (6H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.1, 151.9, 150.7, 136.2, 131.5, 128.6, 128.2, 127.5, 125.2, 113.5, 105.6, 83.6, 78.0, 72.7, 70.5, 33.1, 27.7, 26.1, 23.5; MS (EI) *m/z* 402 (M+); HRMS (EI+) *m/z* calculated for $C_{23}H_{30}O_6$ 402.2042, found 402.2039; Optical Rotation: $[\alpha]^{31}_D$ = -69.2 (*c* 0.03, MeOH).

The enantiomeric excess was determined by HPLC analysis using a CHIRALCEL OD column (Dicel Chemical, 0.46 x 250mm; 2-propanol/hexane, 3:97; flow rate 0.7mL/min; UV detection at 210nm). Major and minor constituents of **10** were found at t_R 30.1 and 24.9 min, respectively.

(*R*)-3-(benzyloxy)-4-(2,3-oxy-3-methylbutyl)phenol (18a). To a solution of compound **17a** (176 mg, 0.43 mmol) in pyridine (4 mL) was added TsCl (500 mg, 2.6 mmol) at 0 ℃ and stirred at 0 ℃ for 1 h. Then the reaction solution was stirred at room temperature overnight and the solvent was evaporated under vacuo. The residue was dissolved in 3 mL of methanol followed by addition of potassium carbonate (483 mg,

3.49 mmol). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with solution of citric acid and extracted with diethyl ether. The organic layer was dried and concentrated under reduced pressure. The crude product was purified by preparative TLC to obtain **18a** as a colorless oil (60 mg, 47%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42~7.32 (5H, m), 7.01 (1H, d, *J*=8.1 Hz), 6.46 (1H, d, *J*=2.4 Hz), 6.35 (1H, dd, *J*=2.4, 8.1 Hz), 5.40 (1H, s), 5.02 (2H, s), 3.04 (1H, t, *J*=6 Hz), 2.84 (1H, d, *J*=6 Hz), 1.32 (6H, s); MS (EI) *m/z* 284 (M+); HRMS (EI+) *m/z* calculated for $C_{18}H_{20}O_3$ 284.1412, found 284.1415.

(*R*)-2-(1-hydroxy-1-methylethyl)-2,3-dihydro-benzofuran-6-ol (19a). The compound **18a** (60 mg, 0.21 mmol) was dissolved in 1 mL of ethanol and added palladium black (60 mg) under argon atmosphere. To the mixture was added dropwise (169 mg, 0.2 mL) of 1, 4-cyclohexadiene and stirred at room temperature for 4 h. The reaction mixture was filtered through a Celite pad and concentrated under reduced pressure. The resulting residue was purified by preparative TLC to yield **19a** as white solid (30 mg, 73%); ^{1}H NMR (CD_3OD, 300 MHz) δ 6.89 (1H, d, *J*=7.2 Hz), 6.22 (1H, q, *J*=2.1, 7.2 Hz), 6.18 (1H, d, *J*=2.1 Hz), 4.53 (1H, t, *J*=9 Hz), 3.02 (1H, d, *J*=9 Hz), 1.20 (6H, s); MS (EI) *m/z* 194 (M+); HRMS (EI+) *m/z* calculated for $C_{11}H_{14}O_3$ 194.0943, found 194.0940; Optical Rotation: $[\alpha]^{31}_D$ = +24.4 (*c* 0.02, MeOH).

(*R*)-2-(1-hydroxy-1-methylethyl)-5-iodo-2,3-dihydro-benzofuran-6-ol (20a). The compound **19a** (70 mg, 0.36 mmol) was dissolved in 5 mL of acetic acid and added solution of iodine chloride (70 mg, 0.43 mmol) in acetic acid. Then the reaction solution was stirred at room temperature for 3 h and quenched with aqueous of sodium bisulfite. The mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by preparative TLC to obtain **20a** as white solid (75 mg, 65%); ^{1}H NMR

(CD_3OD, 300 MHz) δ 7.36 (1H, s), 6.30 (1H, s), 4.56 (1H, t, *J*=8.7 Hz), 3.05 (2H, d, *J*=8.7 Hz), 1.12 (6H, s); ^{13}C NMR (CD_3OD, 75 MHz) δ 163.0, 157.6, 134.9, 122.1, 97.7, 91.6, 72.5, 72.0, 30.6, 25.3, 25.1; MS (EI) *m/z* 320 (M+); HRMS (EI+) *m/z* calculated for $C_{11}H_{13}IO_3$ 319.9909, found 319.9907; Optical Rotation: $[\alpha]^{31}_D$ = +13.6 (*c* 0.02, MeOH).

(*R*)-2-{6-[3,5-bis-(tert-butyl-dimethylsilanyloxy)-phenyl]-2,3,5,6-tetrahydrobenzo[1,2-b;5,4-b']difuran-2-yl}-propa-2-ol (21a). To a well-stirred mixture of 2-iodophenol derivative 20a (160 mg, 0.50 mmol), $Pd(PPh_3)_2Cl_2$ (36 mg, 0.04 mmol), CuI (20 mg, 0.10 mmol) and Et_3N (404 mg, 4.0 mmol) in dioxane (5 mL) a terminal alkyne (362 mg, 1.0 mmol) was added under argon atmosphere. The mixture was stirred at 85 ℃ for 20 h. After removed of the solvent under reduced pressure the mixture was cooled, diluted with ethyl acetate, washed sequentially with dilute HCl, aqueous $NaHCO_3$, and water. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The residue was purified by PTLC (n-hexane: EA= 9:1) to afford compound **21a** (52 mg, 19%); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36 (1H, s), 7.30 (1H, s), 6.99 (1H, s), 6.89 (2H, d, *J*=1.5 Hz), 6.26 (1H, t, *J*=2.1 Hz), 4.64 (1H, t, *J*=8.7 Hz), 3.20 (2H, dd, *J*=3.6, 8.1 Hz), 1.14 (6H, s), 0.96 (18H, s), 0.22 (12H, s); MS (EI) *m/z* 554 (M+); HRMS (EI+) *m/z* calculated for $C_{31}H_{46}O_5Si_2$ 554.2884, found 554.2888; Optical Rotation: $[\alpha]^{31}_D$ = +9.50 (*c* 0.06, MeOH).

(*R*)-5-[6-(1-hydroxy-1-methylethyl)-2,3,5,6-tetrahydro-benzo[1,2-b;5,4-b']difuran-2-yl]-benzene-1,3-diol (*R*)-1. To solution of compound **21a** (52 mg, 0.09 mmol) in THF/pyridine (4:1, 3.5 mL) in a Teflon bottle was added 70% HF/pyridine solution (0.25 mL) with a Teflon syringe at 0 ℃. The reaction was gradually warmed to room temperature and stirred for 2 h. The reaction was quenched slowly with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with

dilute HCl and water, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was then purified by PTLC (n-hexane: EA=6:4) to obtain (*R*)-Moracin O in 53% yield (16 mg); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.29 (1H, s, Ar-H), 6.89 (1H, s, Ar-H), 6.84 (1H, s, Ar-H), 6.73 (1H, d, *J*=2.1Hz), 6.74 (1H, d, *J*=2.1Hz), 6.22~6.20 (1H, m), 4.67 (1H, t, CH, *J*=8.7Hz), 3.24 (2H, m, CH_2), 1.27 (3H, s, CH_3), 1.23 (3H, s, CH_3); ^{13}C NMR (CD_3OD, 75 MHz) δ 159.97, 156.26, 133.85, 125.14, 124.01, 116.99, 103.81, 103.44, 102.37, 93,24, 91.40, 72.52, 31.19, 25.40, 25.24; FT-IR (solid, neat) ν_{max} 3242, 2923, 1261, 1139 cm^{-1}; MS (EI) *m/z* 326 (M+); HRMS (EI+) *m/z* calculated for $C_{19}H_{18}O_5$ 326.1154, found 326.1159; Purity 100% (as determined by NR-HPLC, method 25%~100%, 40min , t_R =10.33min); Optical Rotation: $[\alpha]^{28}_D$ = -4.45 (*c* 0.05, MeOH); natural Moracin O: $[\alpha]^{25}_D$ = -4.02 (*c* 0.04, MeOH).

(*R*)-tert-butyl-3-(benzyloxy)-4-(2, 3 - dihydroxy-3-methylbutyl)phenyl carbonate (17b). The long neck flask was equipped with AD-mix-β (1.9 g), tert-BuOH (10 mL) and water (10 mL). The mixture was stirred at room temperature for 10min and methansulfonamide (155 mg, 1.63 mmol) was added at 0 ℃. The mixture was stirred at 0 ℃ for 30 min and olefin 16 (500 mg, 1.36 mmol) was added at once. The reaction mixture was stirred at 0 ℃ for 48 h. When the reaction was stirred at 0 ℃, solid sodium sulfite was added and allowed to warm at room temperature for 30 min. Then the mixture was extracted with ethyl acetate and separated. The organic layer was washed with aqueous of potassium hydroxide. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure to obtain crude product, which was purified by column chromatography on silica gel (EtOAc: n-Hexane= 1:9) to afford 17b as white crystal (440 mg, 80.6%, 95% e.e.); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43~7.35 (5H, m), 7.19 (1H, s, *J*=7.2 Hz), 6.80 (1H, s), 6.77 (1H, d, *J*=2.1 Hz), 5.05 (2H, s), 3.61 (1H, dd, *J*=1.5, 10.8 Hz), 2.98 (1H, dd, *J*=1.5,

13.2 Hz), 2.55 (1H, dd, *J*=10.8, 13.2 Hz), 1.56 (9H, s), 1.19 (6H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.1, 151.9, 150.7, 136.2, 131.5, 128.6, 128.2, 127.5, 125.2, 113.5, 105.6, 83.6, 78.0, 72.7, 70.5, 33.1, 27.7, 26.1, 23.5; MS (EI) *m/z* 402 (M+); HRMS (EI+) *m/z* calculated for $C_{23}H_{30}O_6$ 402.2042, found 402.2037; Optical Rotation: $[\alpha]^{31}_D$ = +71.8 (*c* 0.03, MeOH).

The enantiomeric excess was determined by the same method as described above. Major and minor constituents of **10** were found at t_R 25.4 and 31.9 min, respectively.

(S)-3-(benzyloxy)-4-(2,3-oxy-3-methylbutyl)phenol (18b). To a solution of compound **17b** (228 mg, 0.57 mmol) in pyridine (6 mL) was added TsCl (648 mg, 3.40 mmol) at 0 ℃ and stirred at 0 ℃ for 1 h. Then solution was stirred at room temperature overnight and the solvent was evaporated in vacuo. The residue was dissolved in 8 mL of methanol followed by addition of potassium carbonate (627 mg, 4.54 mmol). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with solution of citric acid and extracted with diethyl ether. The organic layer was dried and concentrated under reduced pressure. The crude product was purified by preparative TLC to obtain **18b** as a colorless oil (70 mg, 43.5%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42~7.32 (5H, m), 7.01 (1H, d, *J*=8.1 Hz), 6.46 (1H, d, *J*=2.4 Hz), 6.34 (1H, dd, *J*=2.4, 8.1 Hz), 5.61 (1H, s), 5.01 (2H, s), 3.05 (1H, t, *J*=6 Hz), 2.85 (1H, d, *J*=6 Hz), 1.32 (6H, s); MS (EI) *m/z* 284 (M+); HRMS (EI+) *m/z* calculated for $C_{18}H_{20}O_3$ 284.1412, found 284.1407.

(S)-2-(1-hydroxy-1-methylethyl)-2,3-dihydro-benzofuran-6-ol (19b). The compound **18b** (269 mg, 0.95 mmol) was dissolved in 5 mL of ethanol and added palladium black (269 mg) under argon atmosphere. To the mixture was added dropwise (758 mg, 0.88 mL) of 1, 4-cyclohexadiene and stirred at room temperature for 4 h. The reaction mixture was filtered through a Celite pad and concentrated under reduced pressure. The

resulting residue was purified by preparative TLC to yield **19b** as white solid (160 mg, 87%); ^{1}H NMR (CD_3OD, 300 MHz) δ 6.90 (1H, d, *J*=8.0 Hz), 6.22 (1H, dd, *J*=2.1, 8.0 Hz), 6.19 (1H, d, *J*=2.1 Hz), 4.54 (1H, t, *J*=9 Hz), 3.02 (1H, d, *J*=9 Hz), 1.20 (6H, s); MS (EI) *m/z* 194 (M+); HRMS (EI+) *m/z* calculated for $C_{11}H_{14}O_3$ 194.0943, found 194.0940; Optical Rotation: $[\alpha]^{31}_{D}$ = -25.6 (*c* 0.02, MeOH).

(S)-2-(1-hydroxy-1-methylethyl)-5-iodo-2,3-dihydro-benzofuran-6-ol (20b). The compound **19b** (160 mg, 0.82 mmol) was dissolved in 10 mL of acetic acid and added solution of iodine chloride (160 mg, 0.99 mmol) in acetic acid. Then the reaction solution was stirred at room temperature for 3 h and quenched with aqueous of sodium bisulfite. The mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by preparative TLC to obtain **20b** as white solid (167 mg, 63%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (1H, s), 6.50 (1H, s), 4.63 (1H, t, *J*=9.6 Hz), 3.14 (2H, d, *J*=9.0 Hz), 1.26 (6H, s); ^{13}C NMR (CD_3OD, 75 MHz) δ 163.0, 157.6, 134.9, 122.1, 97.7, 91.6, 72.5, 72.0, 30.6, 25.3, 25.1; MS (EI) *m/z* 320 (M+); HRMS (EI+) *m/z* calculated for $C_{11}H_{13}IO_3$ 319.9909, found 319.9912; Optical Rotation: $[\alpha]^{31}_{D}$ = -15.06 (*c* 0.02, MeOH).

(S)-2-{6-[3,5-bis-(tert-butyl-dimethylsilanyloxy)-phenyl]-2,3,5,6-tetrahydrobenzo[1, 2-b;5,4-b']difuran-2-yl}-propa-2-ol (21b). To a well-stirred mixture of 2-iodophenol derivative **20b** (170 mg, 0.53 mmol), $Pd(pph_3)_2Cl_2$ (37 mg, 0.05 mmol), CuI (20 mg, 0.11 mmol) and Et_3N (430 mg, 4.25 mmol) in dioxane (10 mL) a terminal alkyne (385 mg, 1.06 mmol) was added under argon atmosphere. The mixture was stirred at 85 ℃ for 20 h. After removed of the solvent under reduced pressure the mixture was cooled, diluted with ethyl acetate, washed sequentially with dilute HCl, aqueous $NaHCO_3$, and water. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to

dryness. The residue was purified by PTLC (n-hexane: EA= 9:1) to afford compound **21b** (45 mg, 15%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.36 (1H, s), 7.30 (1H, s), 6.99 (1H, s), 6.90 (2H, d, *J*=1.5 Hz), 6.25 (1H, t, *J*=2.1 Hz), 4.61 (1H, t, *J*=8.7 Hz), 3.18 (2H, dd, *J*=2.1, 8.1 Hz), 1.14 (6H, s), 0.97 (18H, s), 0.22 (12H, s); MS (EI) *m/z* 554 (M+); HRMS (EI+) *m/z* calculated for $C_{31}H_{46}O_5Si_2$ 554.2884, found 554.2887; Optical Rotation: $[\alpha]^{31}_{D}$ = -9.87 (*c* 0.1, MeOH).

(S)-5-[6-(1-hydroxy-1-methylethyl)-2,3,5,6-tetrahydro-benzo[1,2-b;5,4-b']difuran-2-yl]-benzene-1,3-diol (S)-1. To solution of compound **21b** (45 mg, 0.08 mmol) in THF/pyridine (4:1, 3.2 mL) in a Teflon bottle was added 70% HF/pyridine solution (0.22 mL) with a Teflon syringe at 0 ℃. The reaction was gradually warmed to room temperature and stirred for 2 h. The reaction was quenched slowly with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with dilute HCl and water, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was then purified by PTLC (n-hexane: EA=6:4) to obtain (*S*)-Moracin O in 54% yield (14 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (1H, s, Ar-H), 6.88 (1H, s, Ar-H), 6.85 (1H, s, Ar-H), 6.74 (1H, d, *J*=2.4Hz), 6.73 (1H, d, *J*=2.4Hz), 6.23~6.21 (1H, m), 4.64 (1H, t, CH, *J*=8.7Hz), 3.24 (2H, m, CH_2), 1.28 (3H, s, CH_3), 1.24 (3H, s, CH_3); ^{13}C NMR (CD_3OD, 75 MHz) δ 159.99, 156.40, 133.84, 125.12, 124.00, 116.98, 103.81, 103.46, 102.36, 93.23, 91.40, 72.52, 31.19, 25.37, 25.25; FT-IR (solid, neat) ν_{max} 3237, 2914, 1262, 1132 cm^{-1}; MS (EI) *m/z* 326 (M+); HRMS (EI+) *m/z* calculated for $C_{19}H_{18}O_5$ 326.1154, found 326.1149; Purity 100% (as determined by NR-HPLC, method 25%~75%, 40min, t_R = 10.29min); Optical Rotation: $[\alpha]^{31}_{D}$ = +3.60 (*c* 0.08, MeOH).

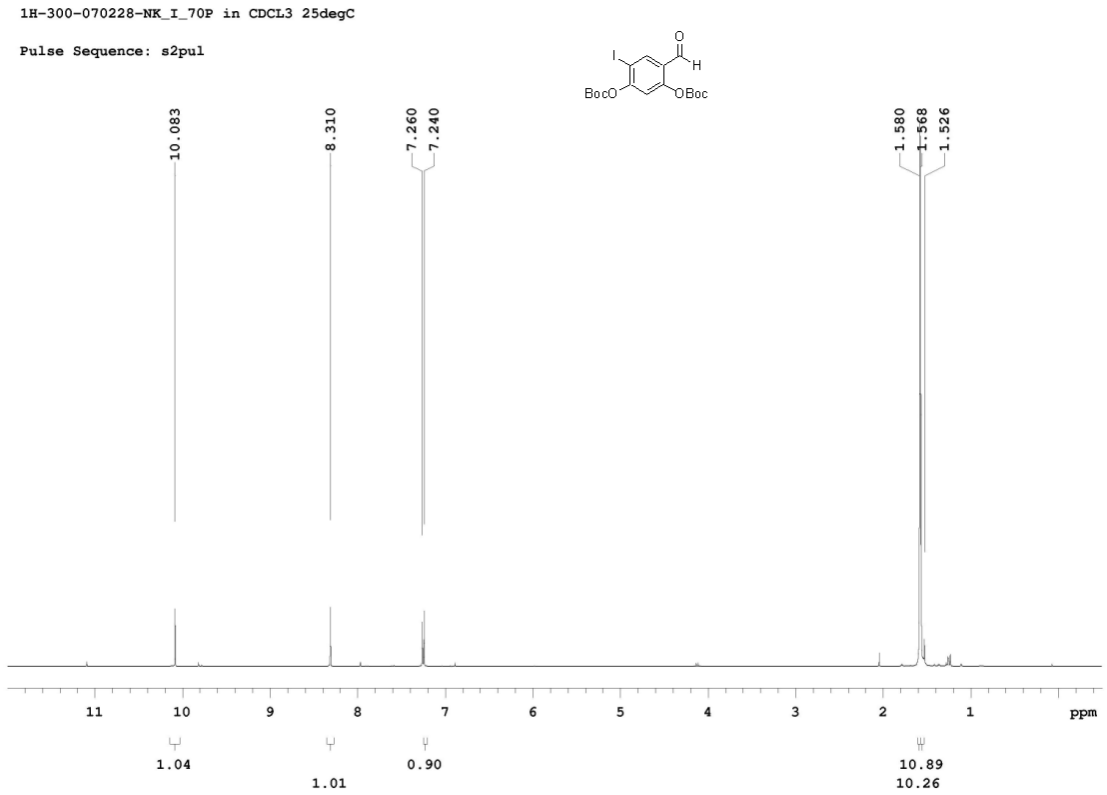


Fig S1: ^{1}H NMR spectrum of compound **5**.

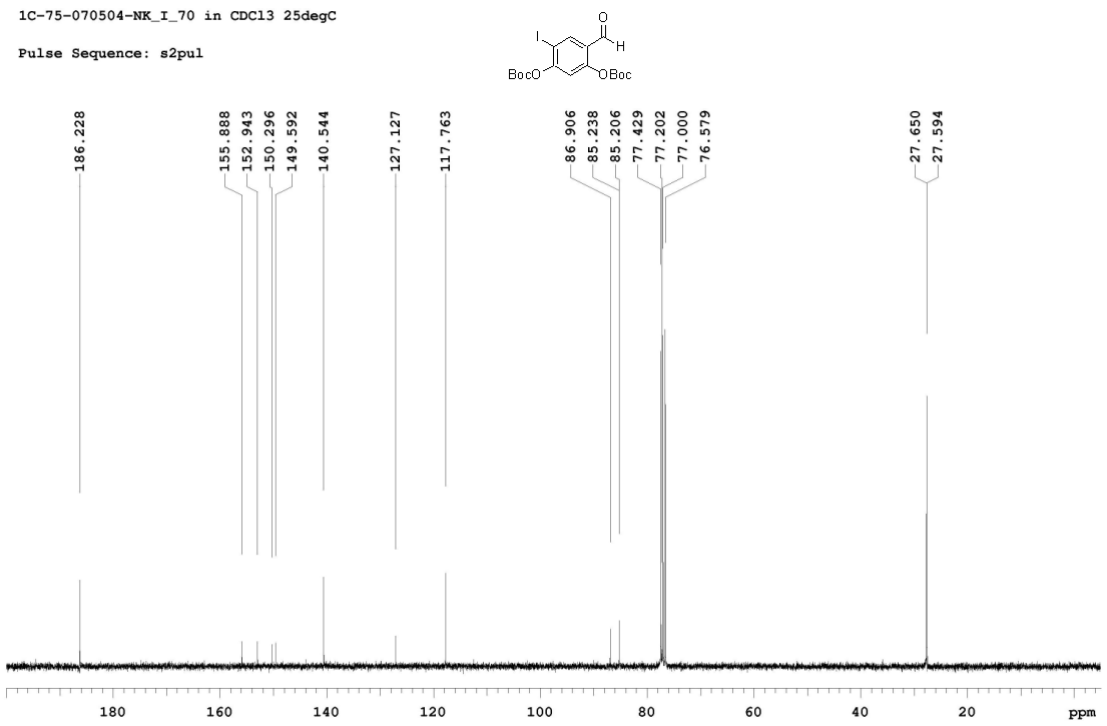


Fig S2: ^{13}C NMR spectrum of compound **5**.

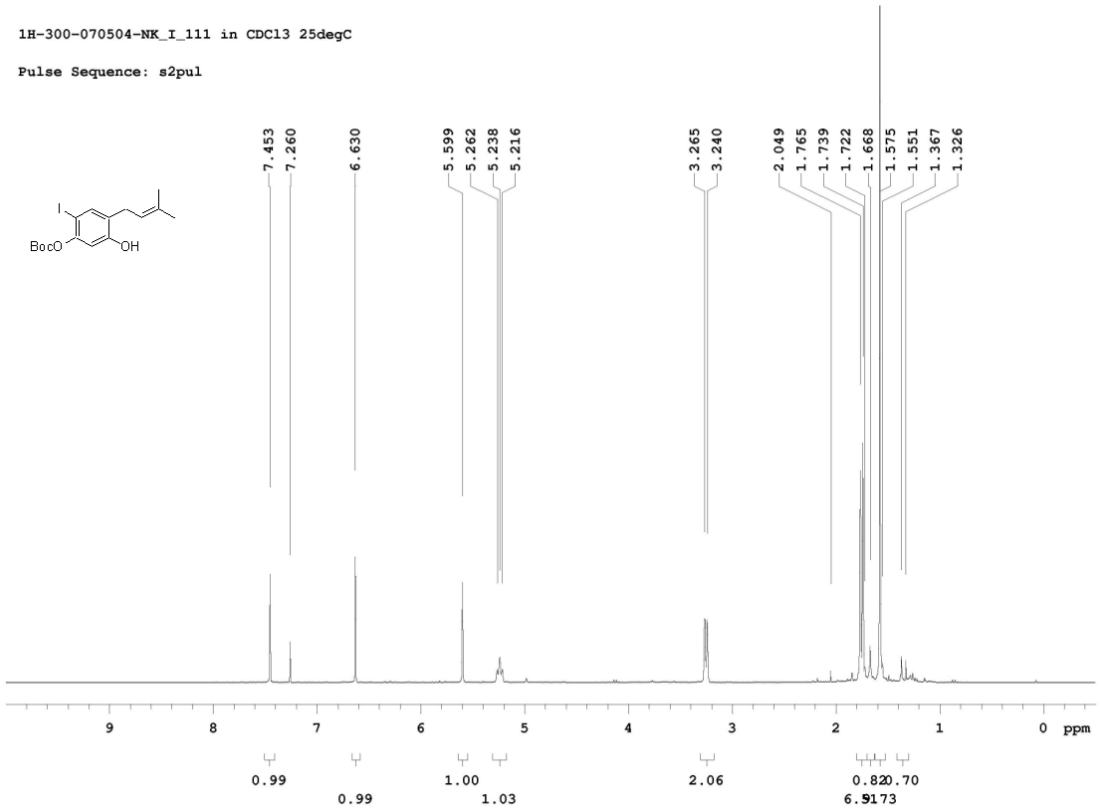


Fig S3: ^{1}H NMR spectrum of compound **6**.

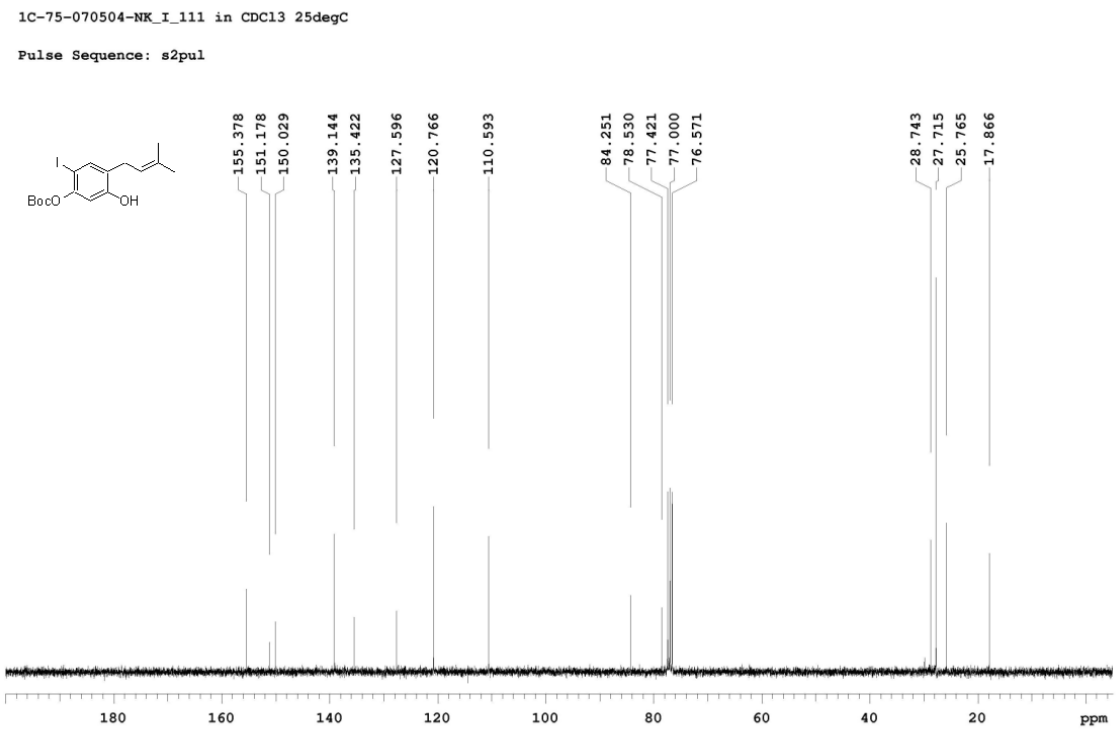


Fig S4: ^{13}C NMR spectrum of compound **6**.

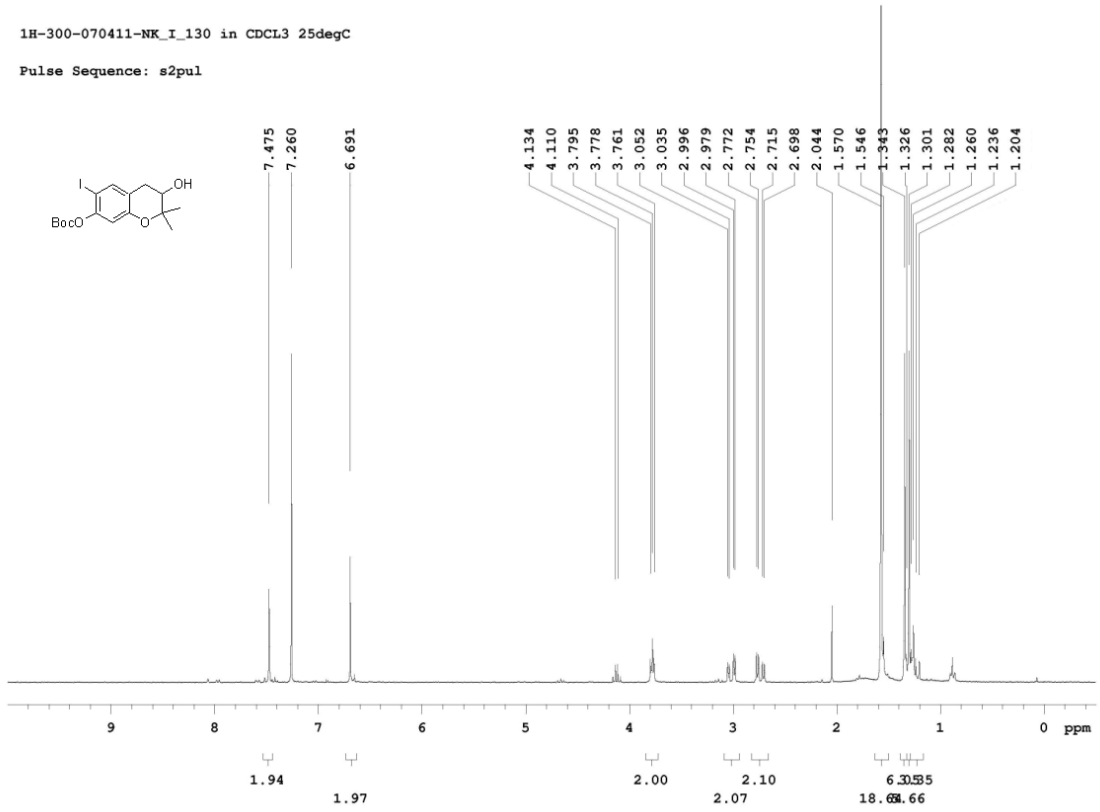


Fig S5: ^{1}H NMR spectrum of compound **7**.

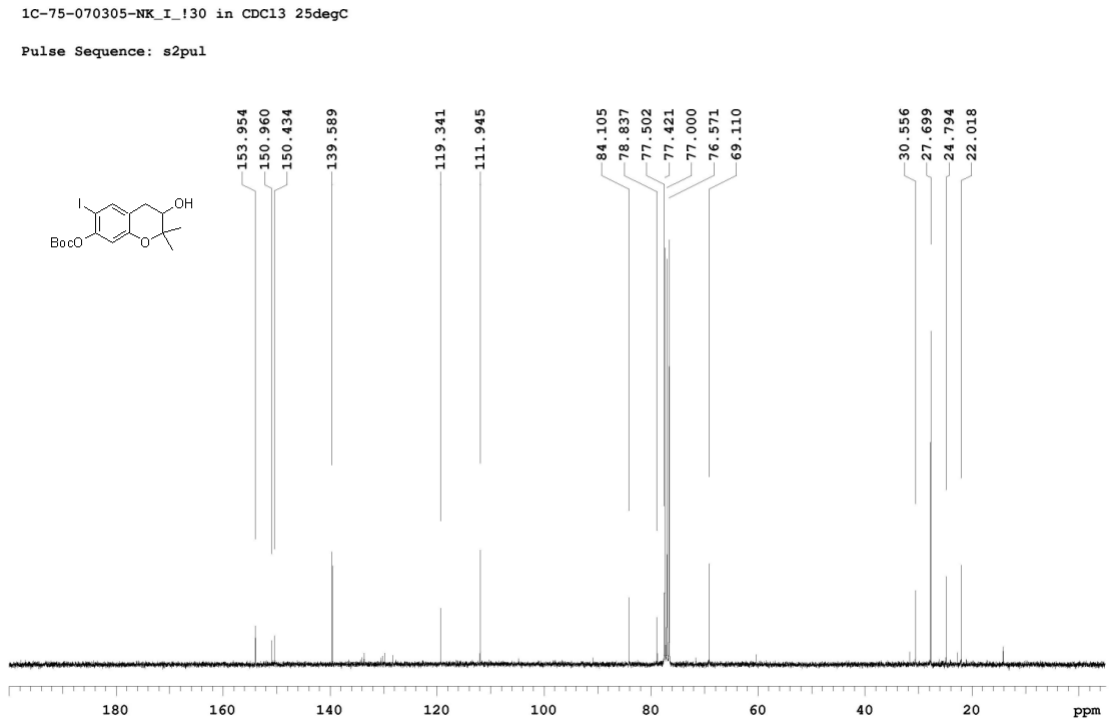


Fig S6: ^{13}C NMR spectrum of compound **7**.

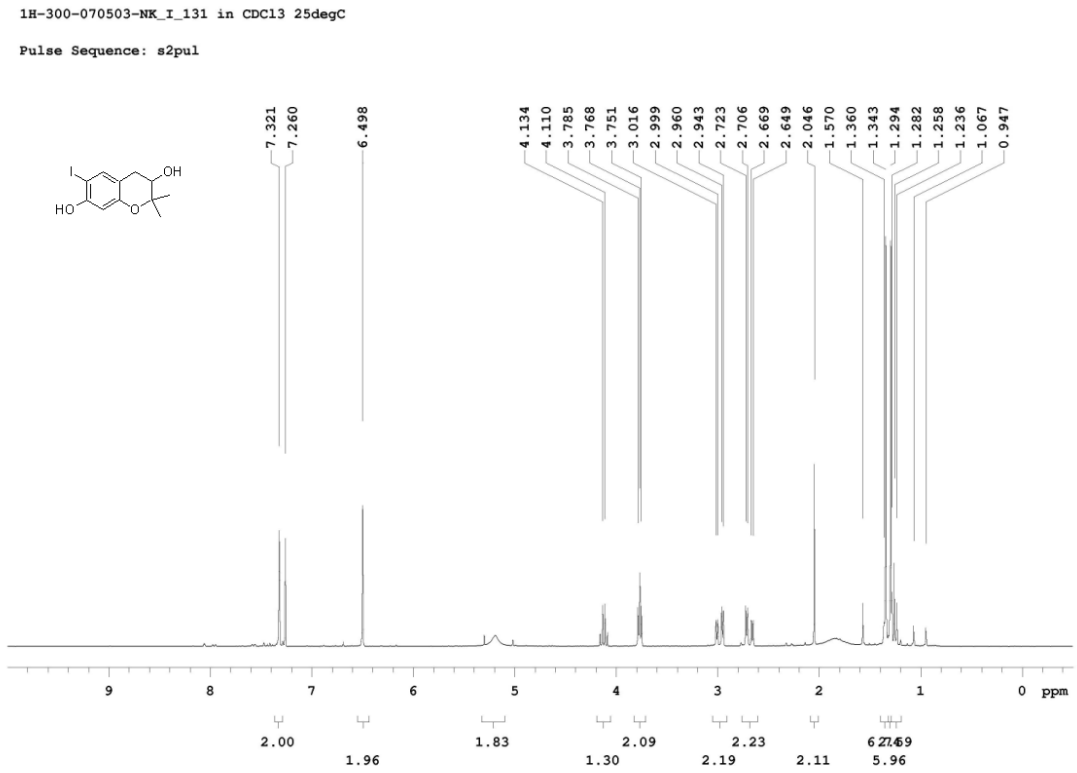


Fig S7: ^{1}H NMR spectrum of compound **8**.

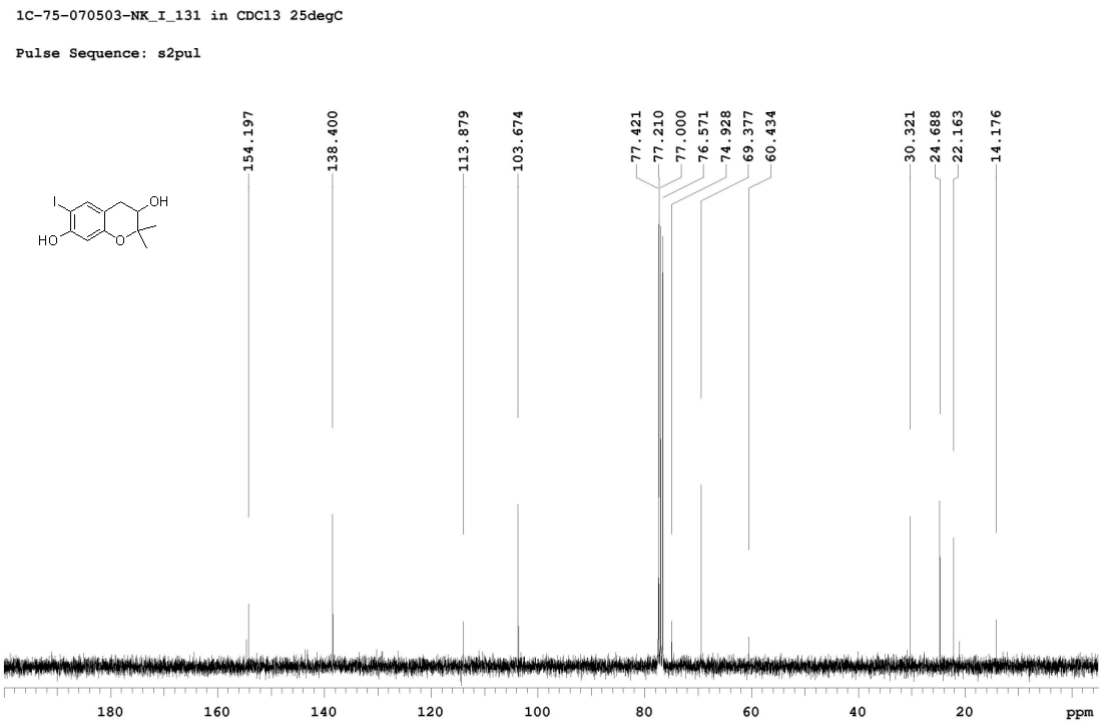


Fig S8: ^{13}C NMR spectrum of compound **8**.

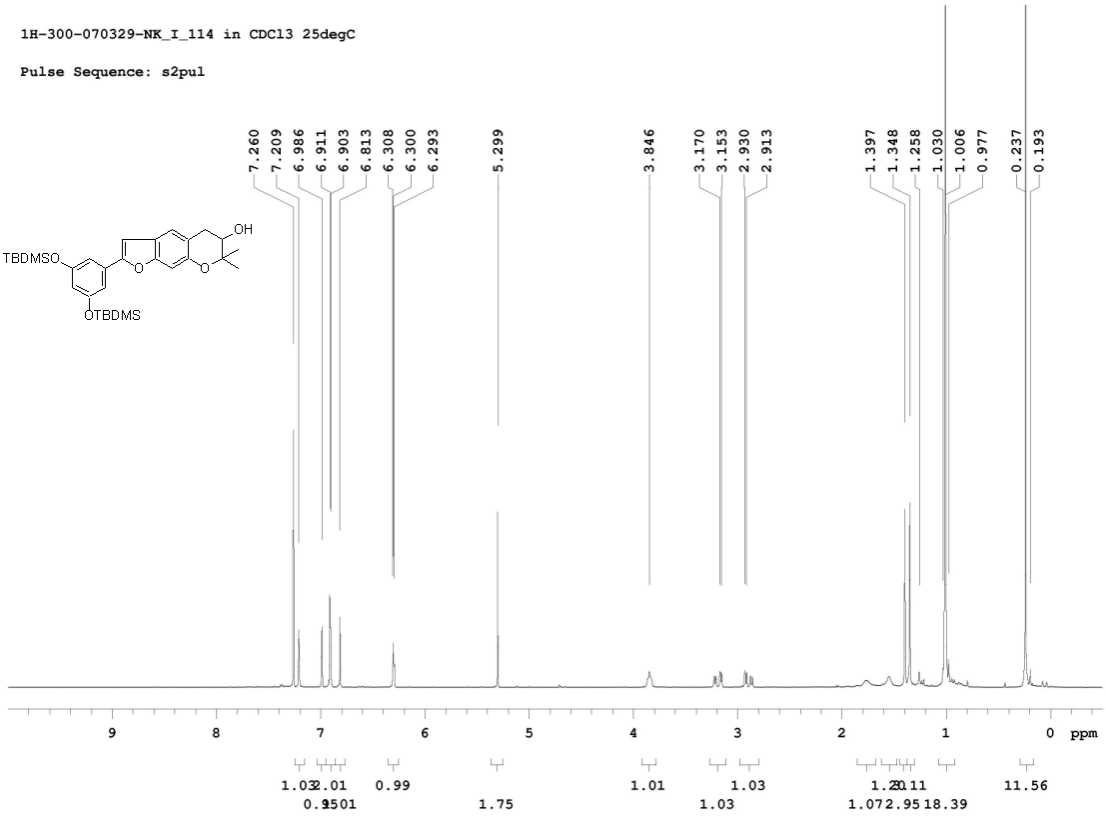


Fig S9: ^{1}H NMR spectrum of compound **10**.

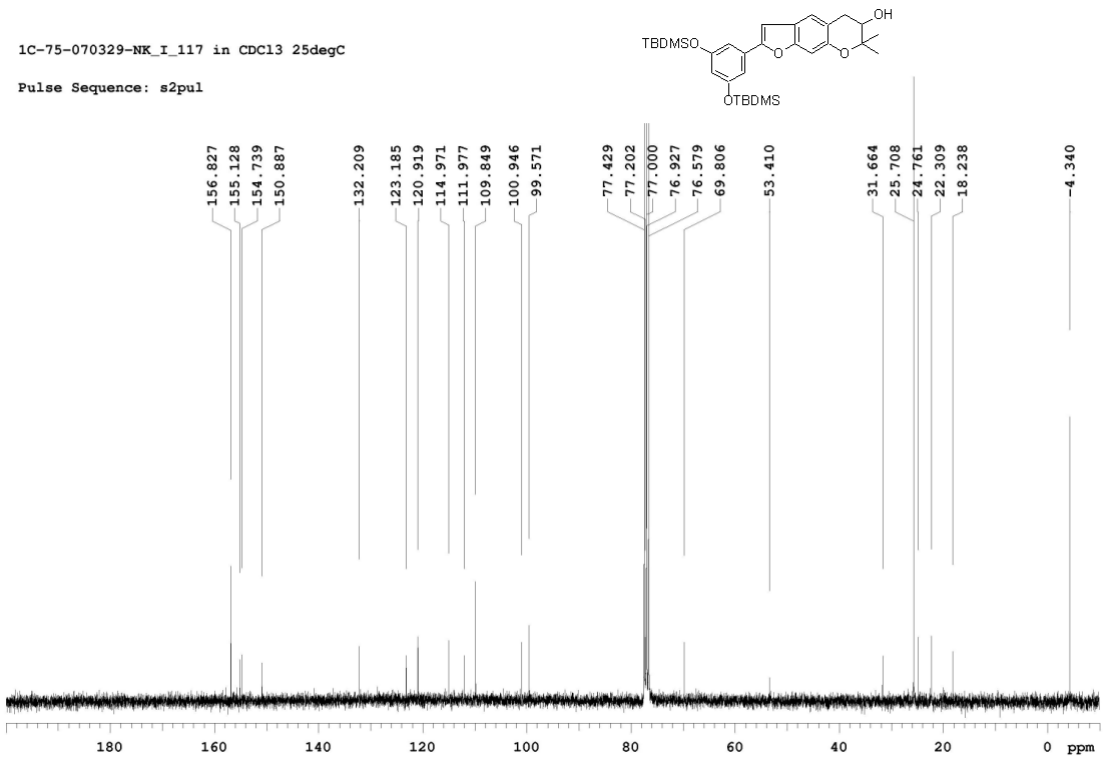


Fig S10: ^{13}C NMR spectrum of compound **10**.

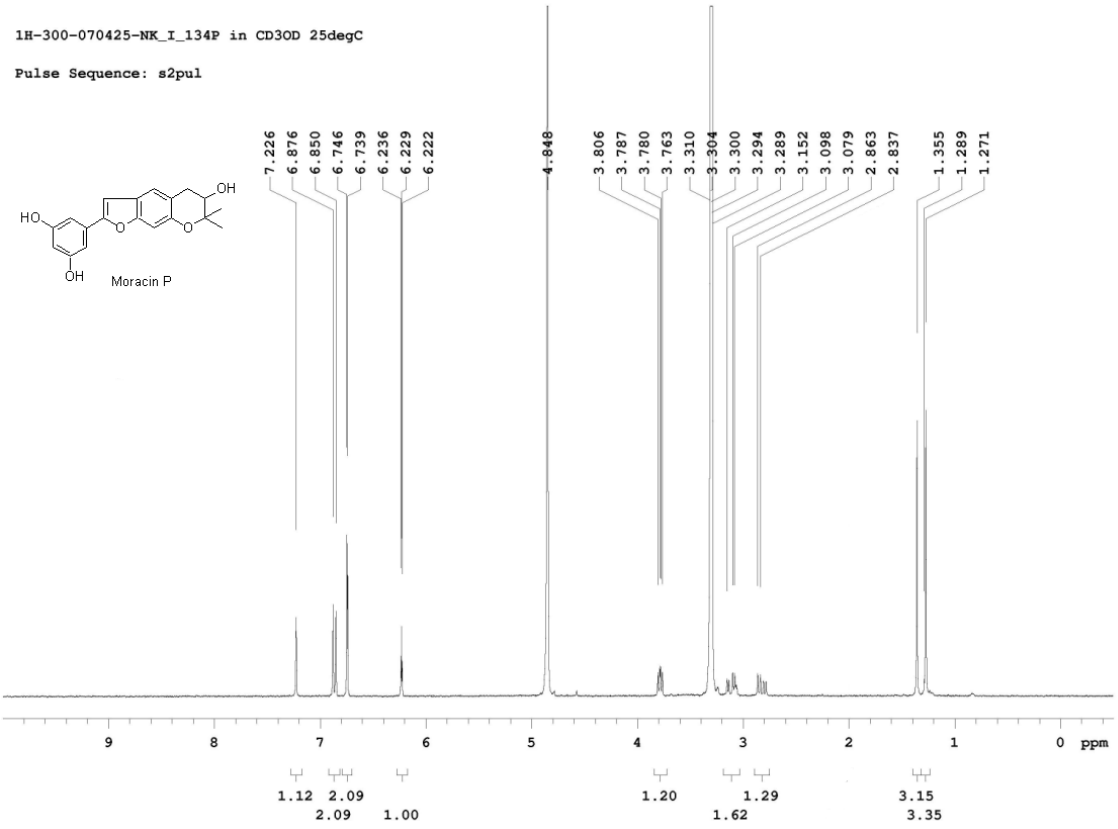


Fig S11: ^{1}H NMR spectrum of compound **2**.

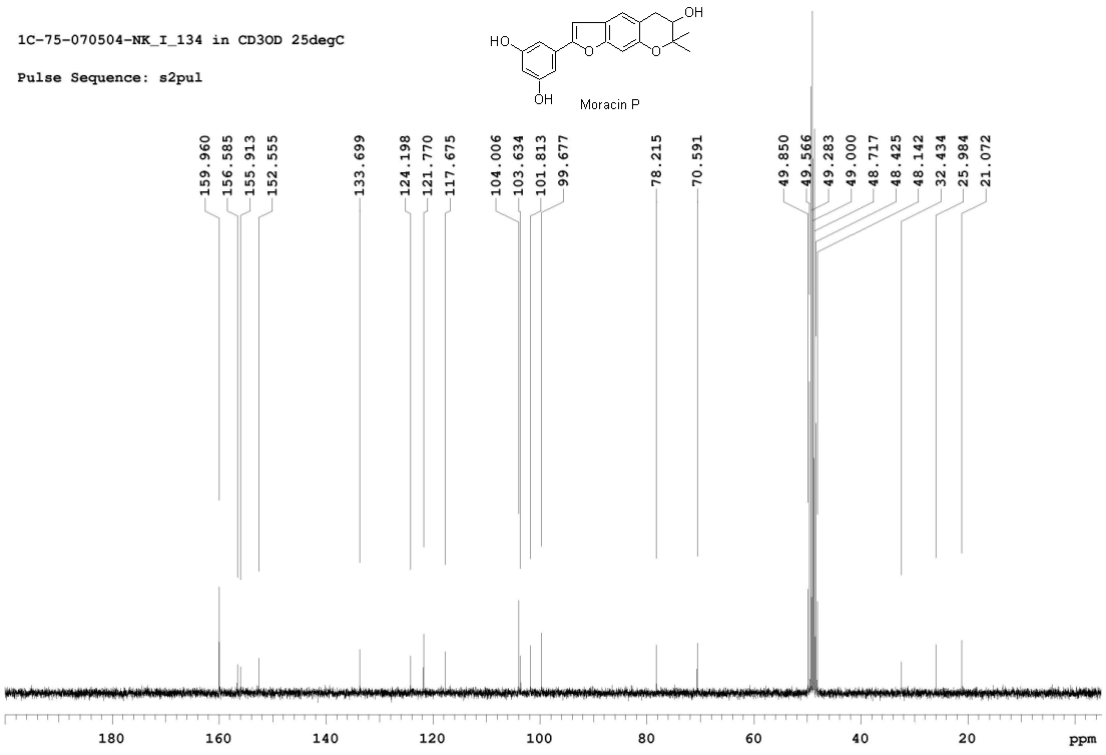


Fig S12: ^{13}C NMR spectrum of compound **2**.

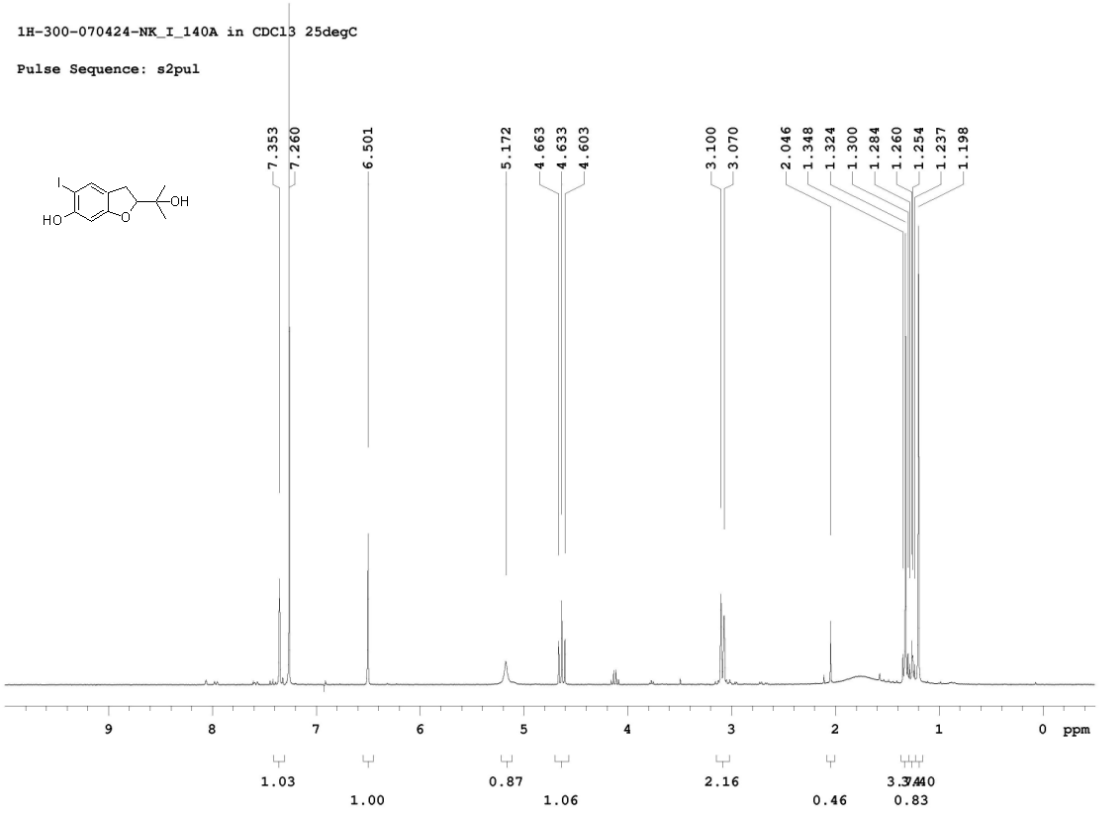


Fig S13: ^{1}H NMR spectrum of compound **12**.

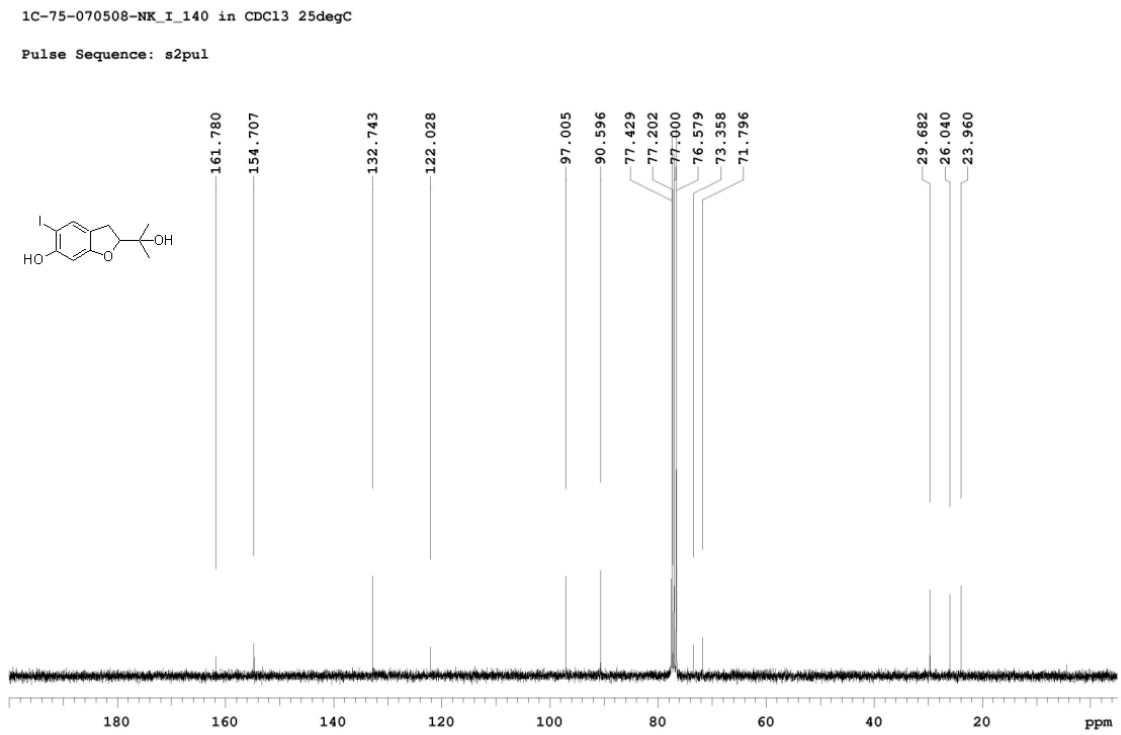


Fig S14: ^{13}C NMR spectrum of compound **12**.

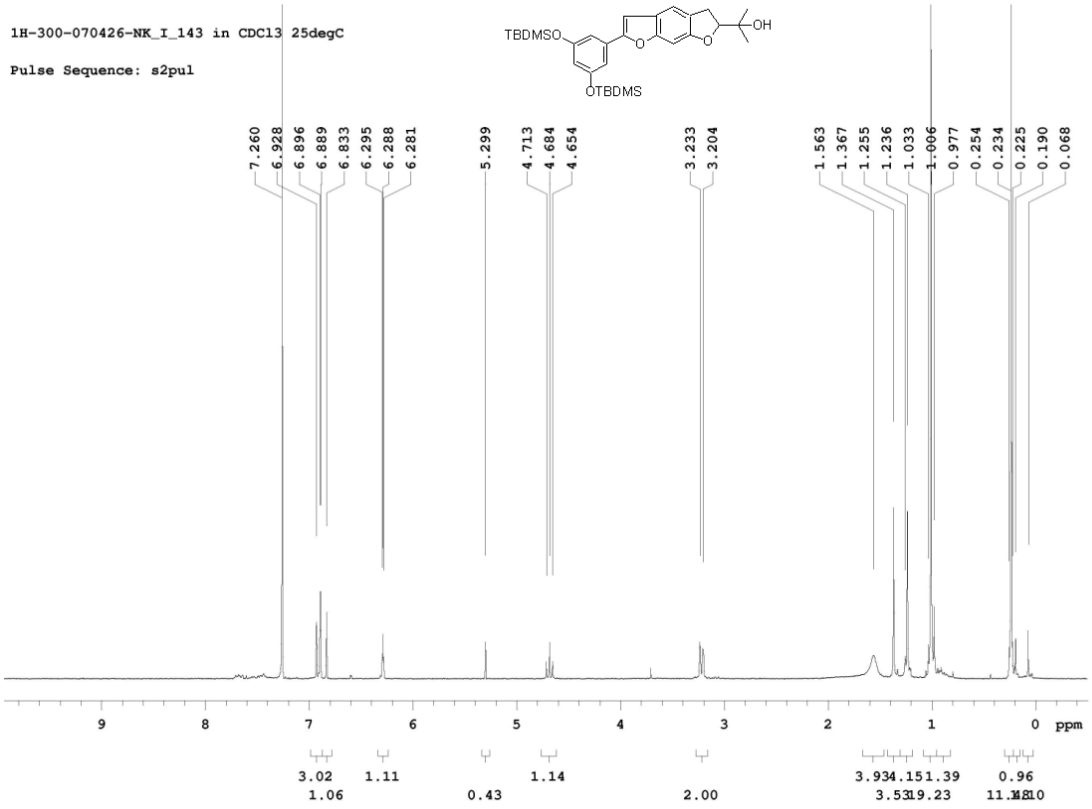


Fig S15: ^{1}H NMR spectrum of compound **13**.

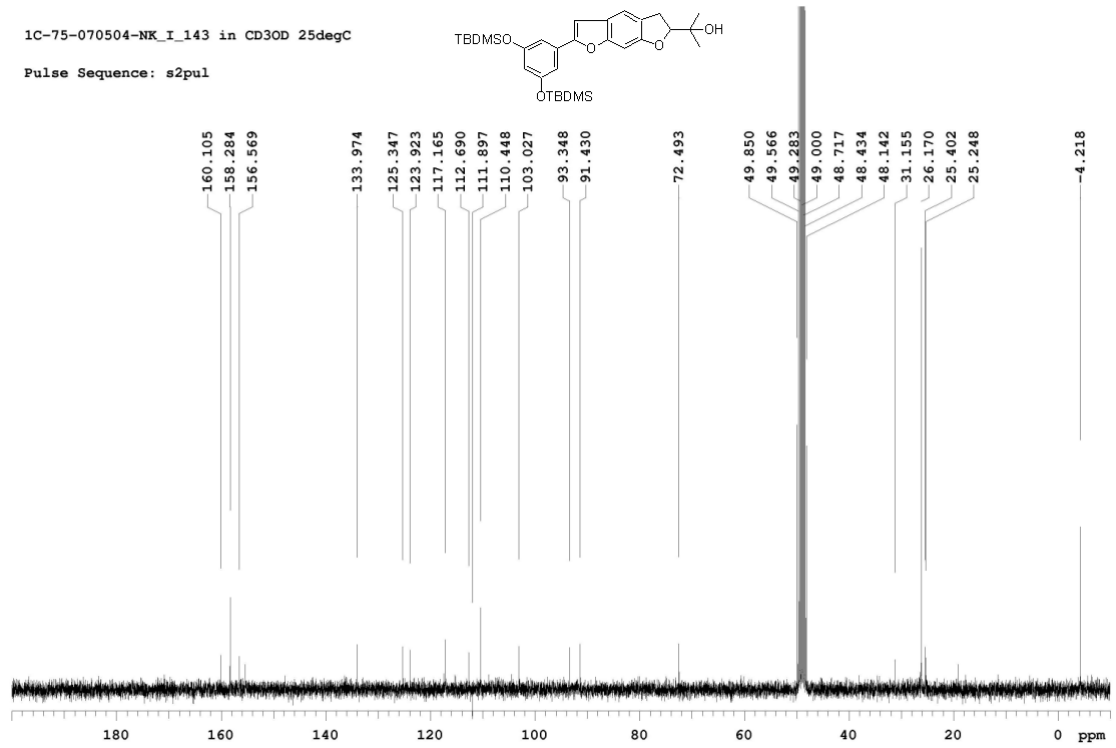


Fig S16: ^{13}C NMR spectrum of compound **13**.

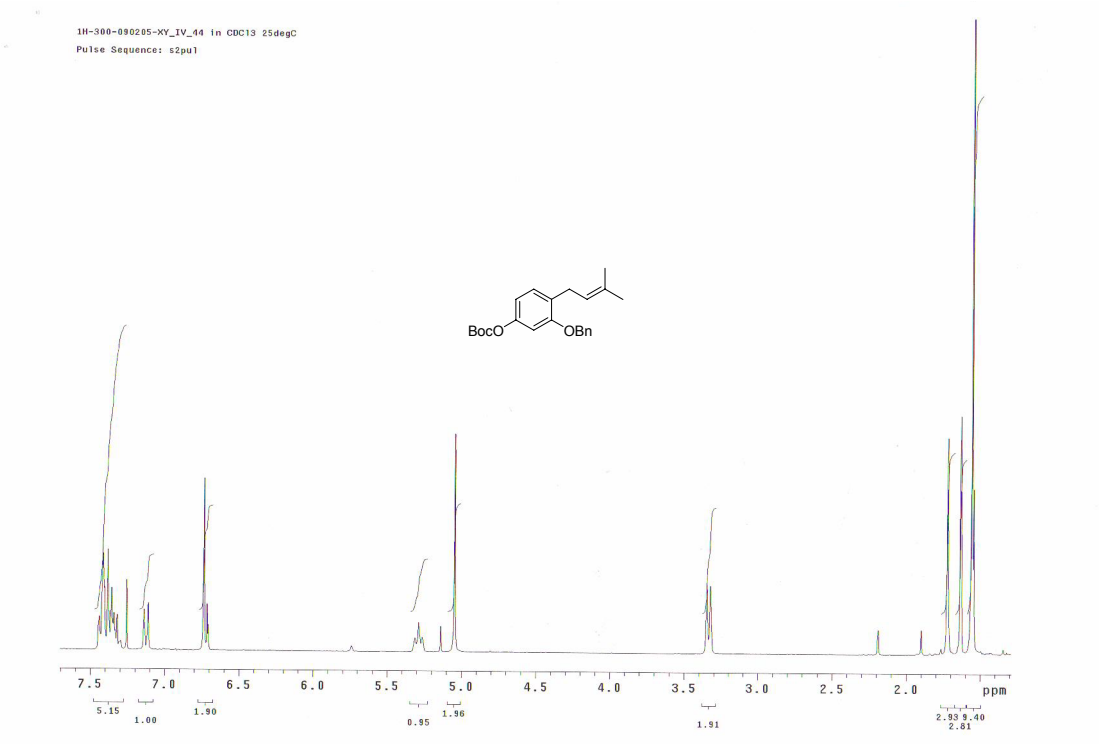


Fig S17: ^{1}H NMR spectrum of compound **16**.

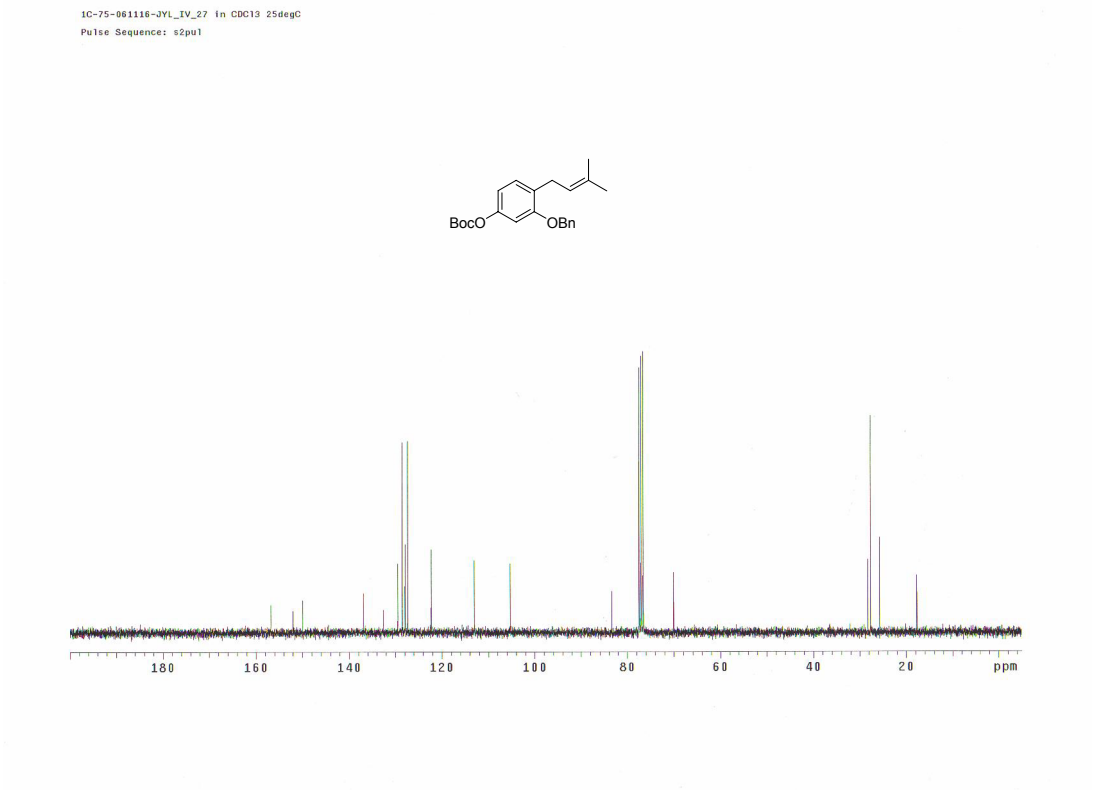


Fig S18: ^{13}C NMR spectrum of compound **16**.

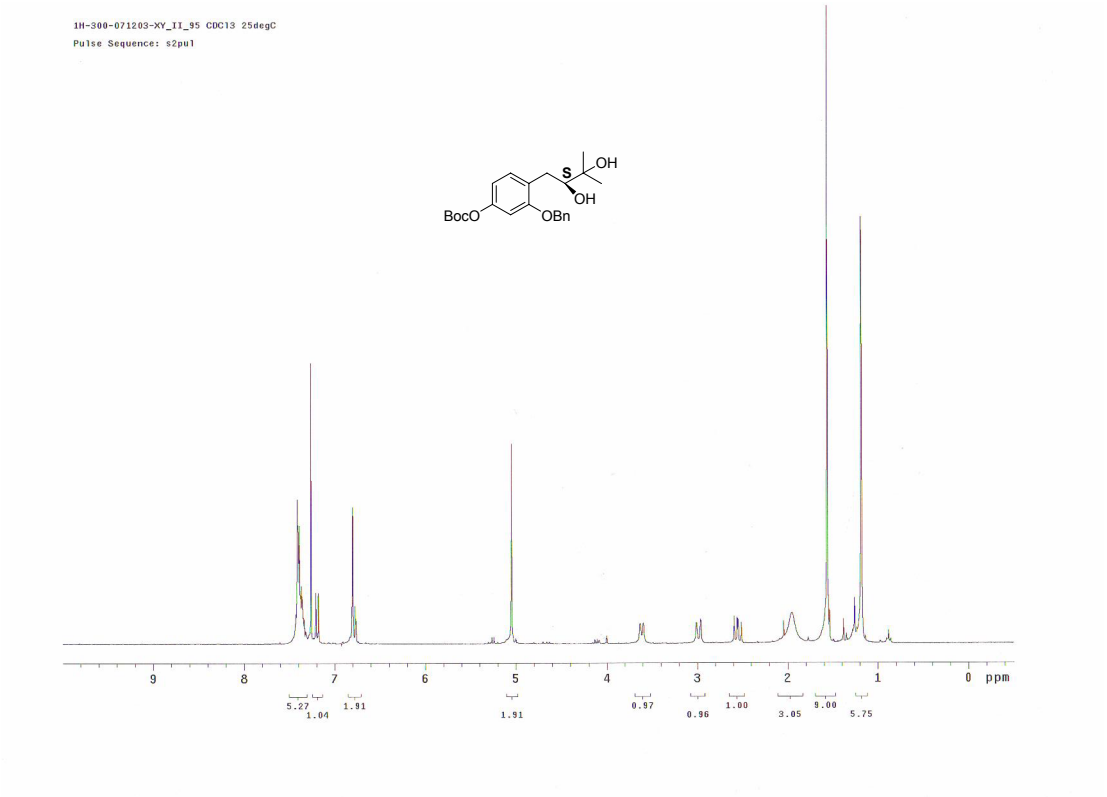


Fig S19: ^{1}H NMR spectrum of compound **17a**.

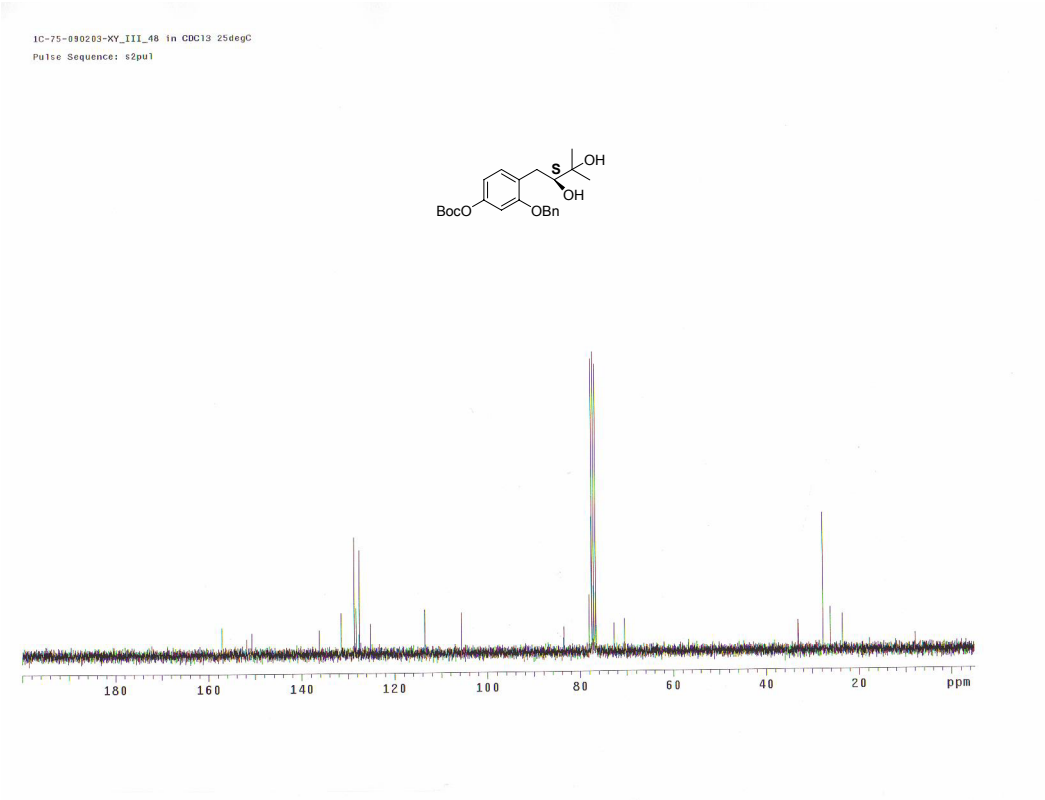


Fig S20: ^{13}C NMR spectrum of compound **17a**.

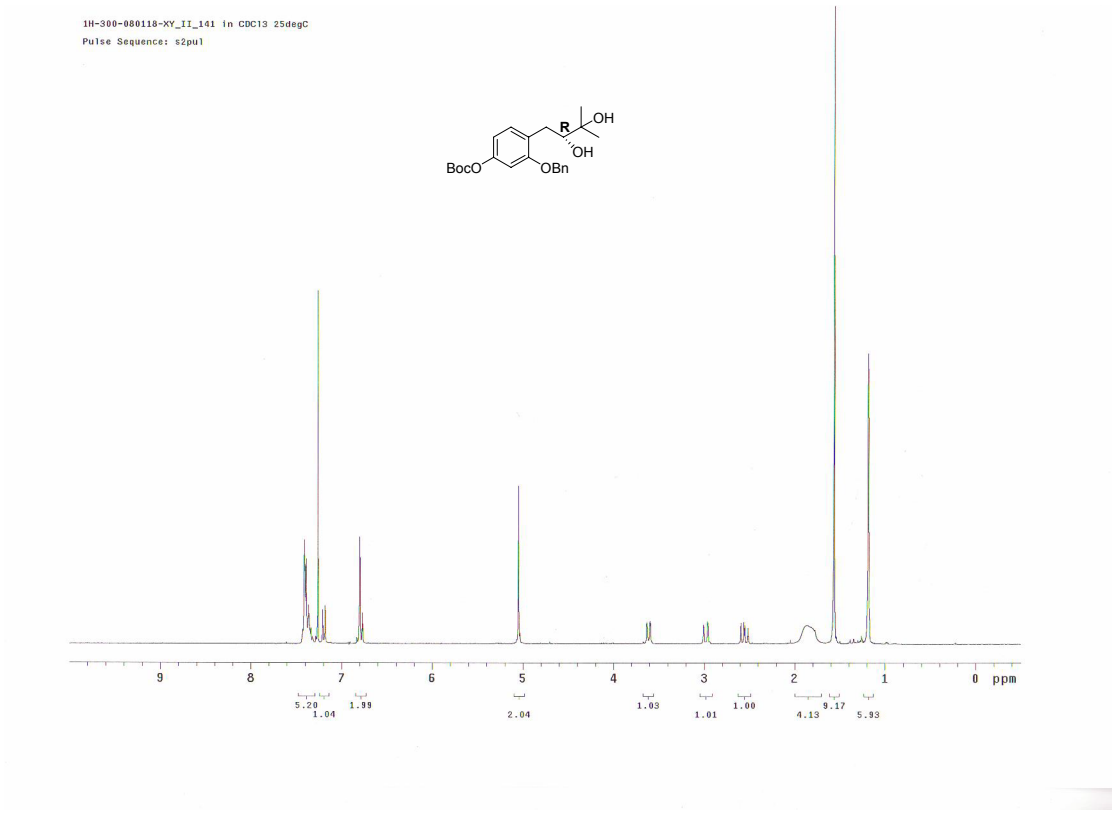


Fig S21: ^{1}H NMR spectrum of compound **17b**.

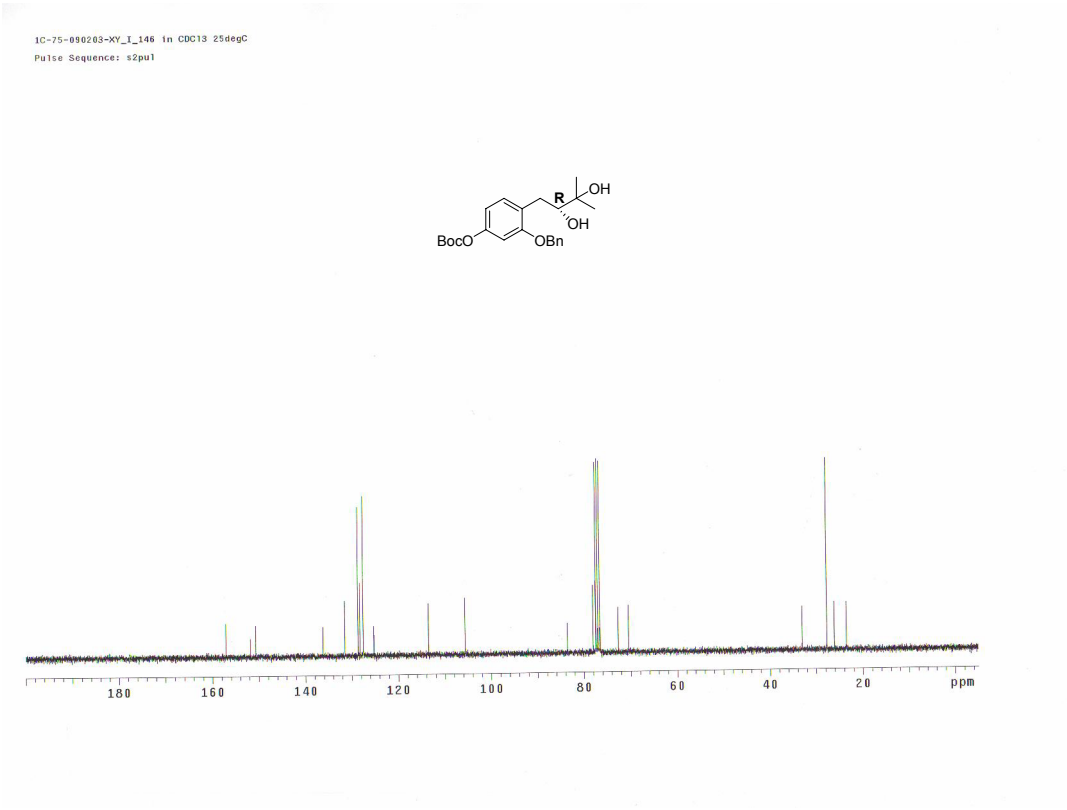


Fig S22: ^{13}C NMR spectrum of compound **17b**.

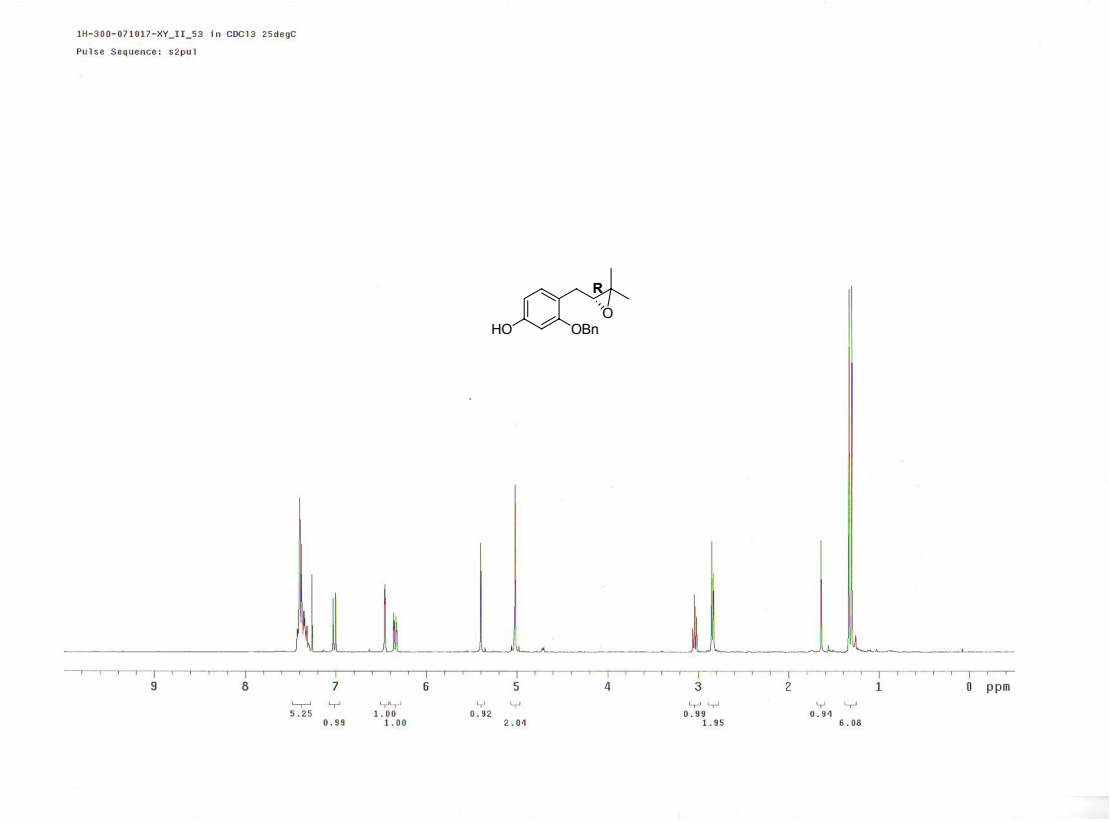


Fig S23: ^{1}H NMR spectrum of compound **18a**.

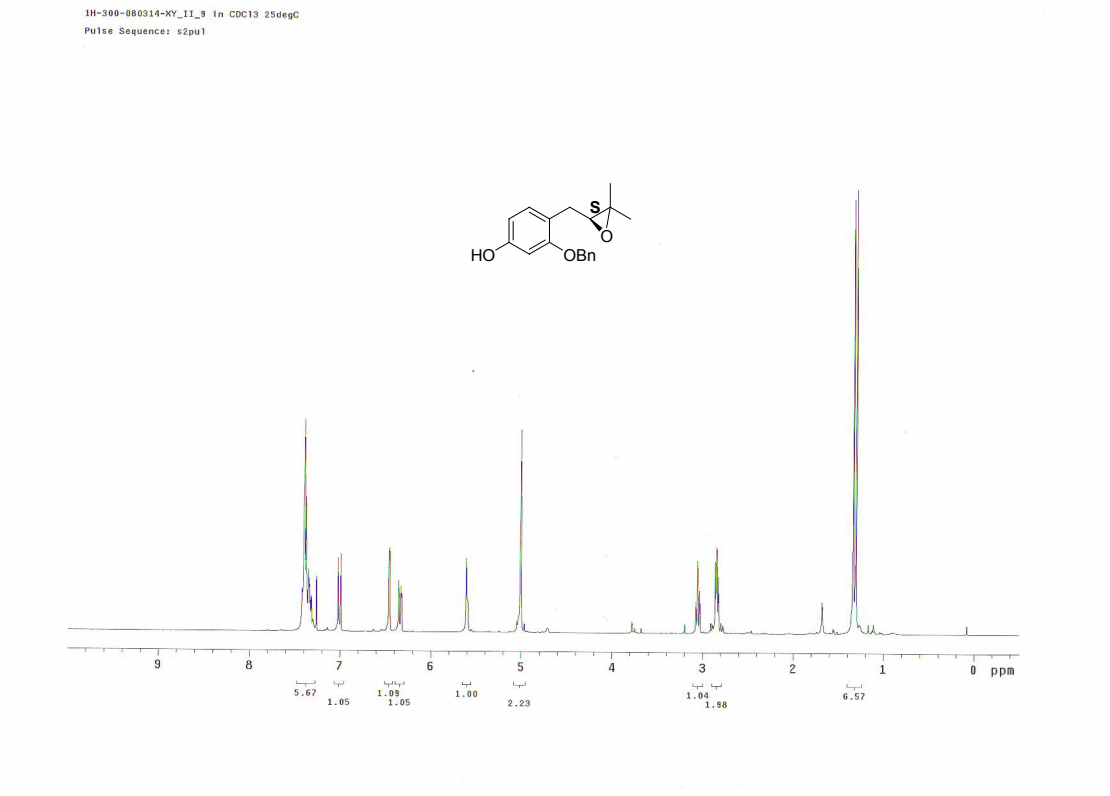


Fig S24: ^{1}H NMR spectrum of compound **18b**.

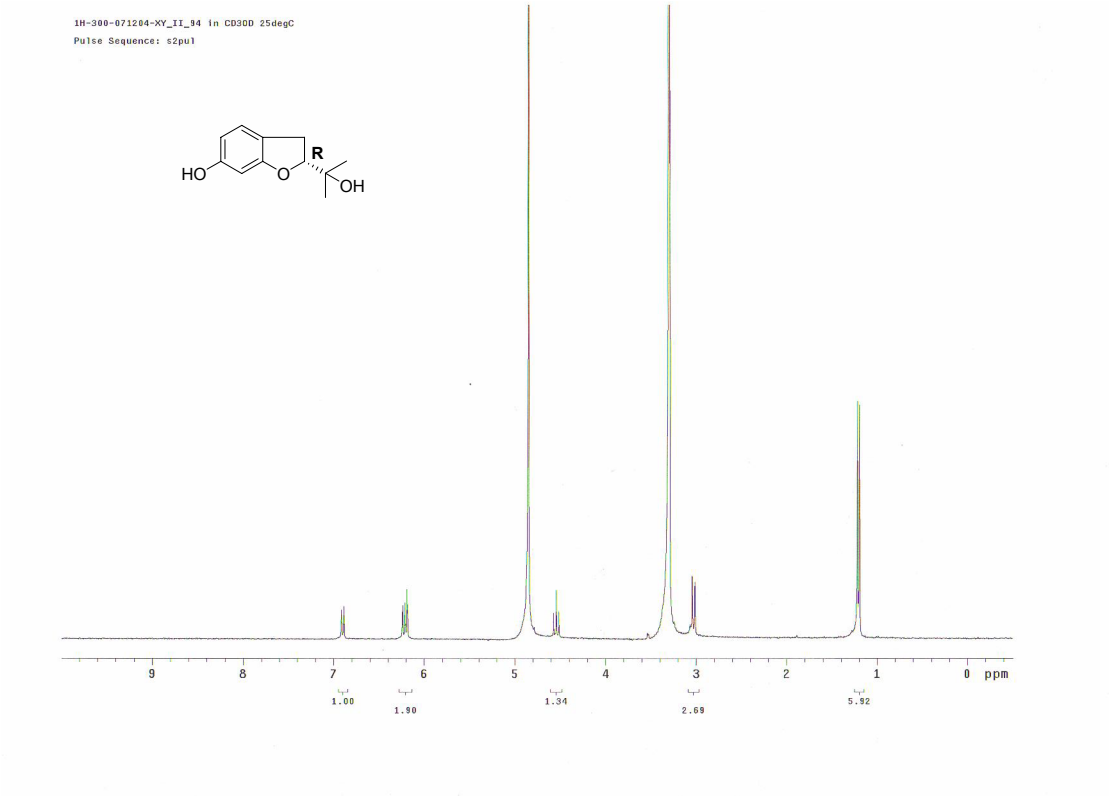


Fig S25: ^{1}H NMR spectrum of compound **19a**.

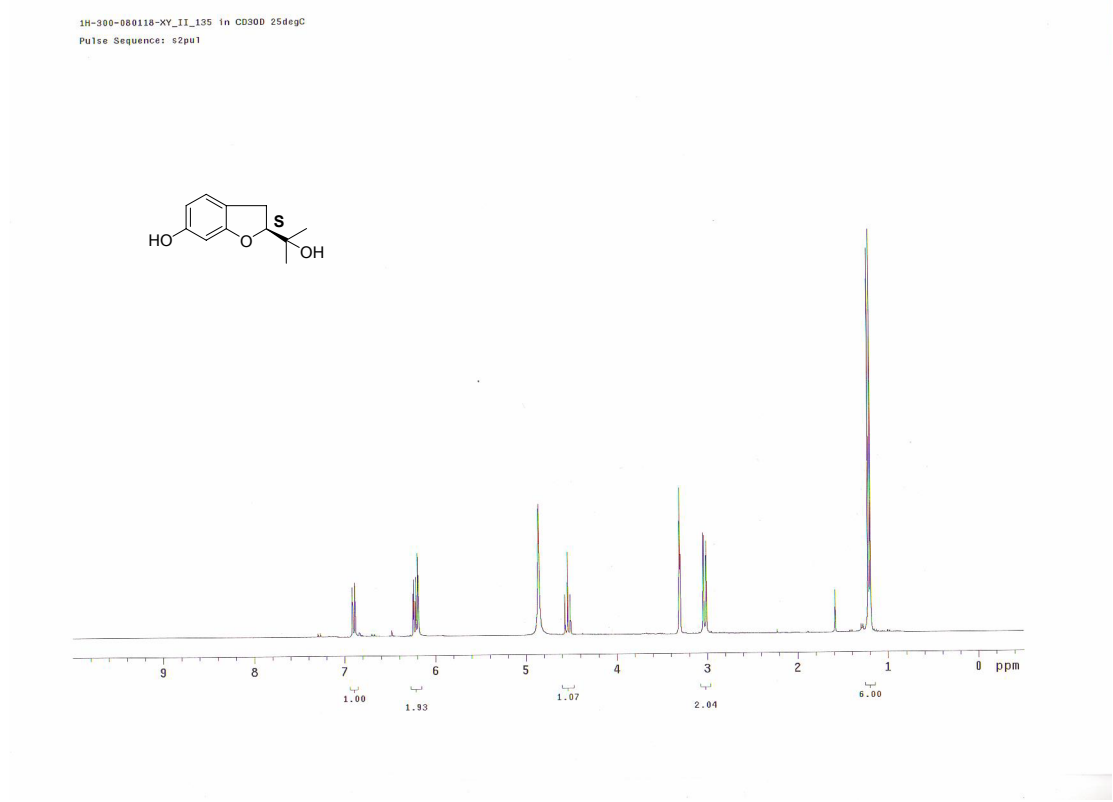


Fig S26: ^{1}H NMR spectrum of compound **19b**.

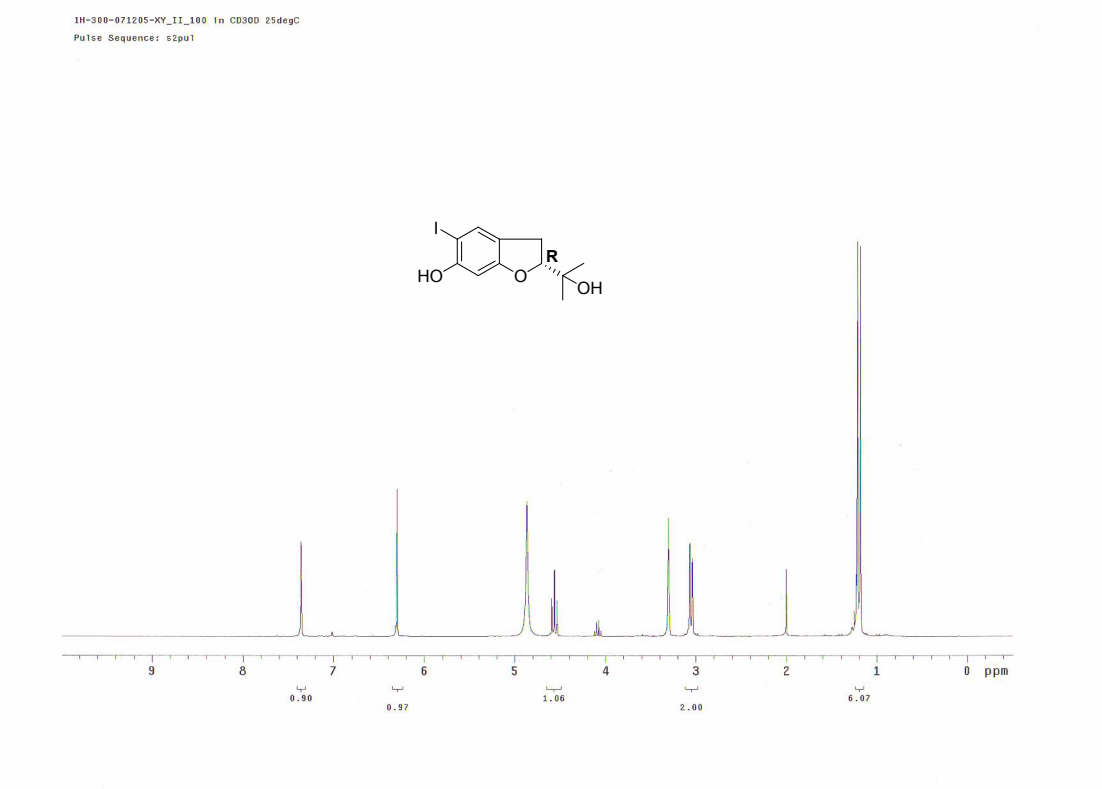


Fig S27: ^{1}H NMR spectrum of compound **20a**.

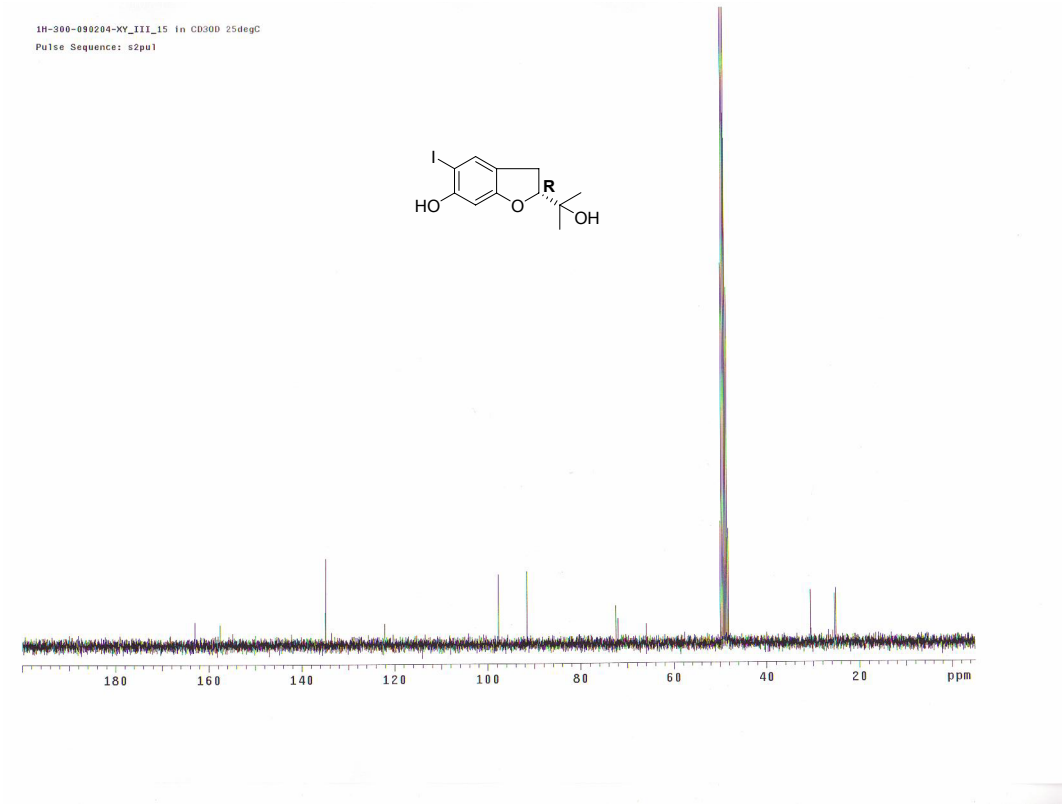


Fig S28: ^{13}C NMR spectrum of compound **20a**.

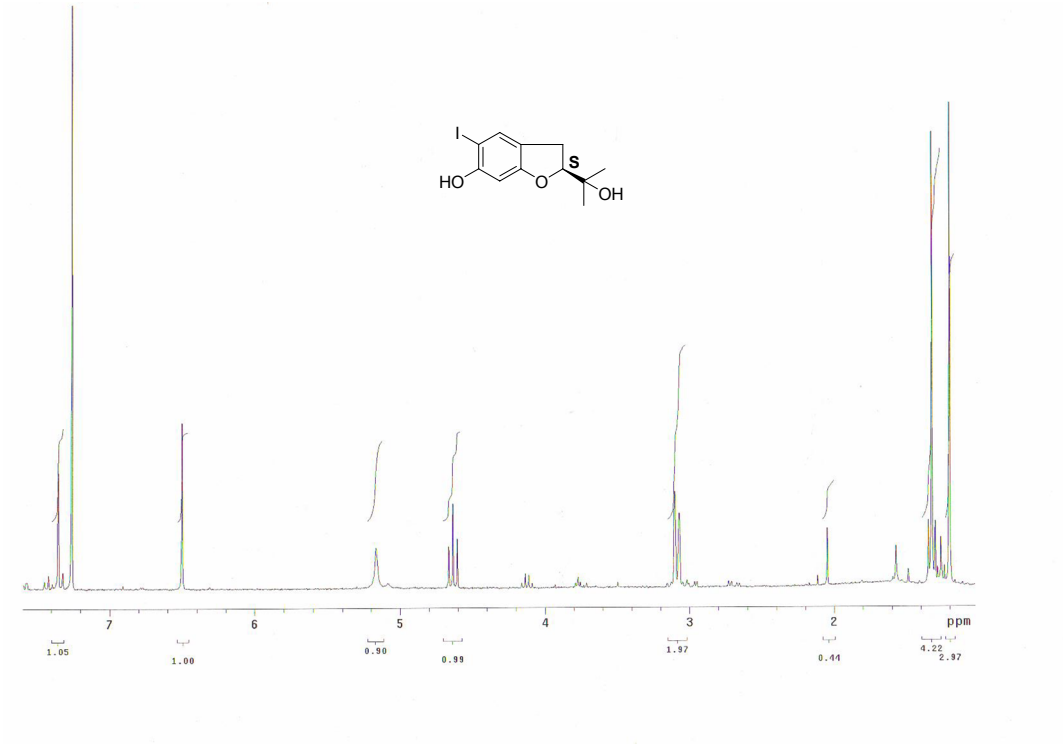


Fig S29: ^{1}H NMR spectrum of compound **20b**.

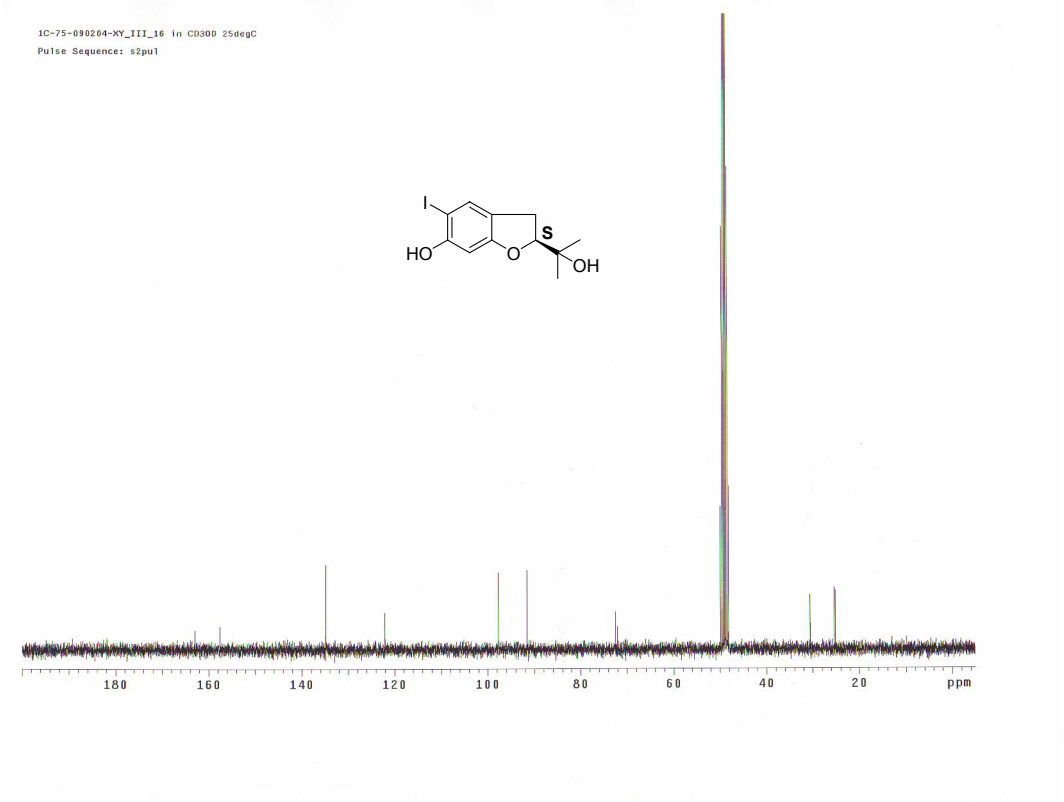


Fig S30: ^{13}C NMR spectrum of compound **20b**.

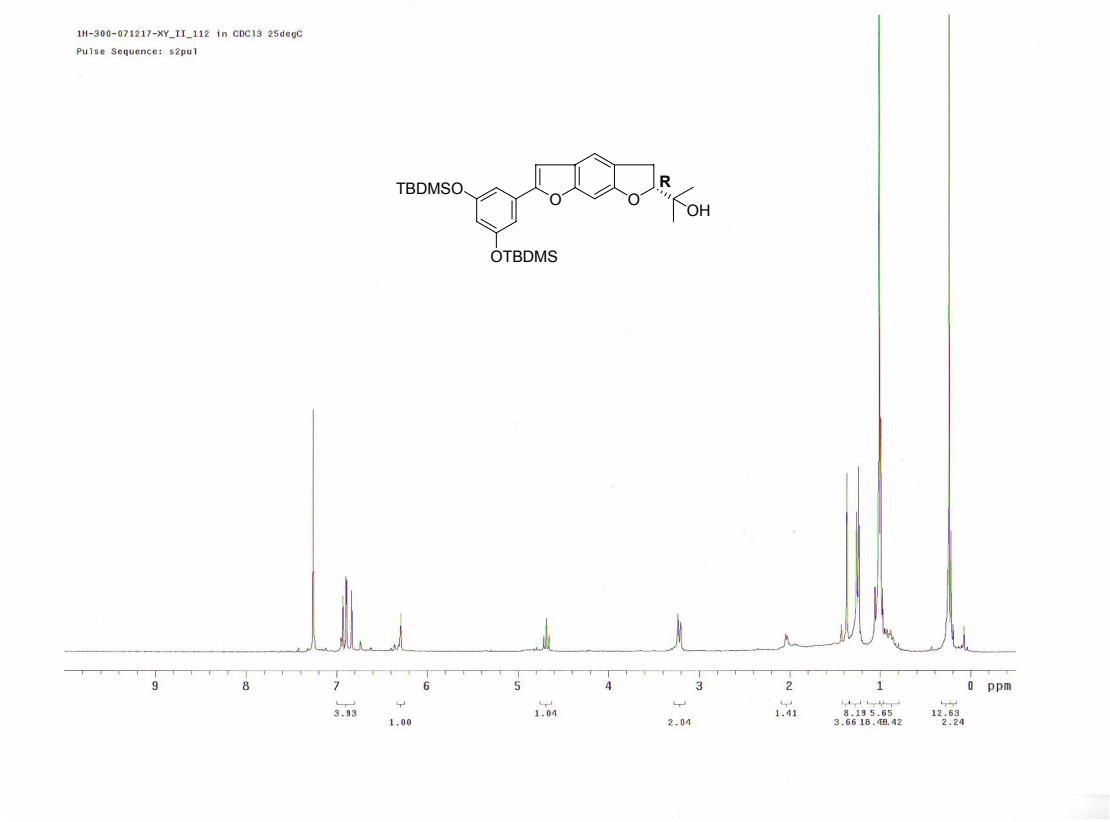


Fig S31: ^{1}H NMR spectrum of compound **21a**.

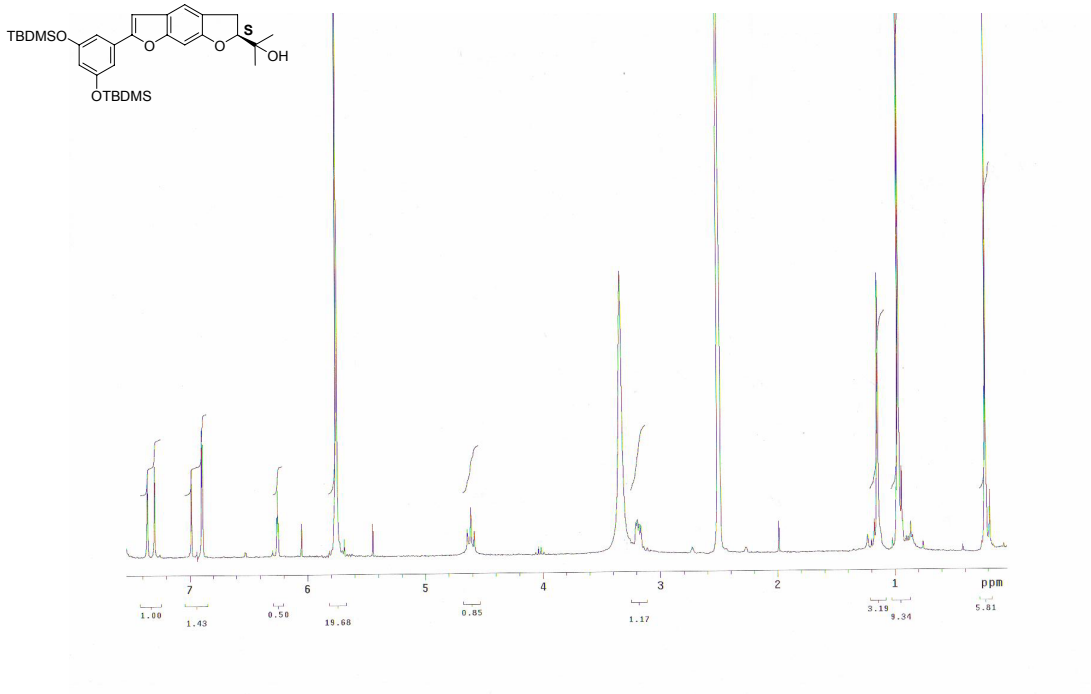


Fig S32: ^{1}H NMR spectrum of compound **21b**.

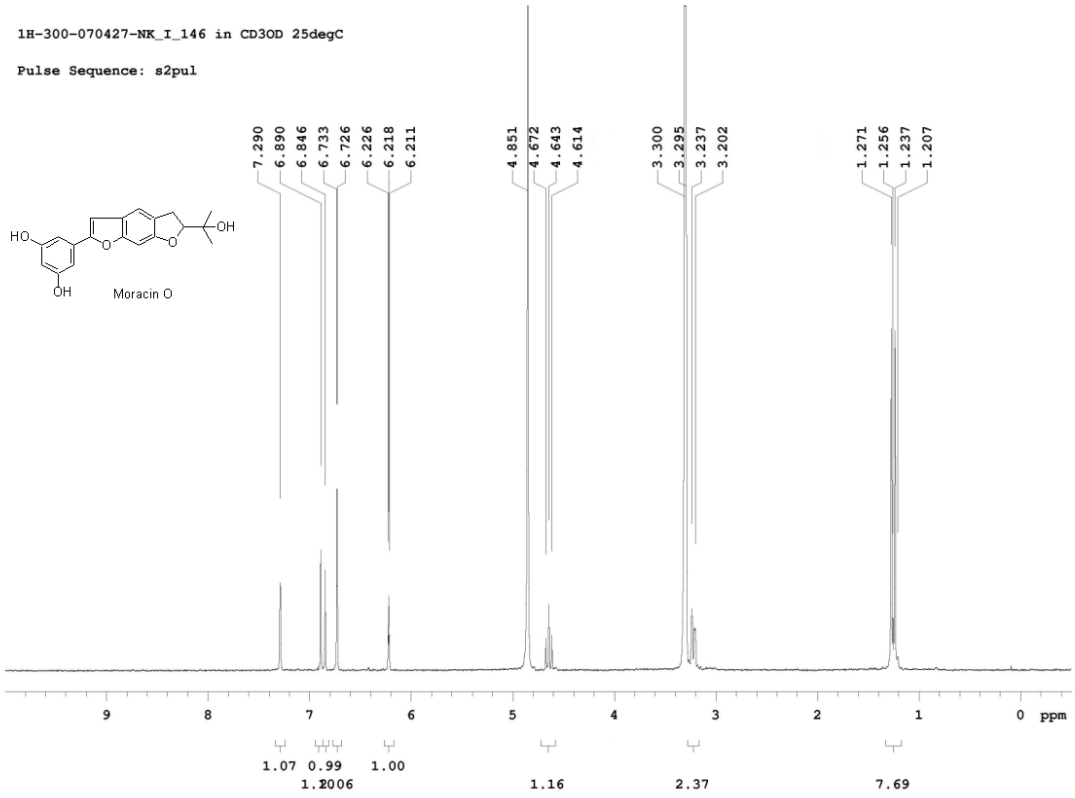


Fig S33: ^{1}H NMR spectrum of compound **1**.

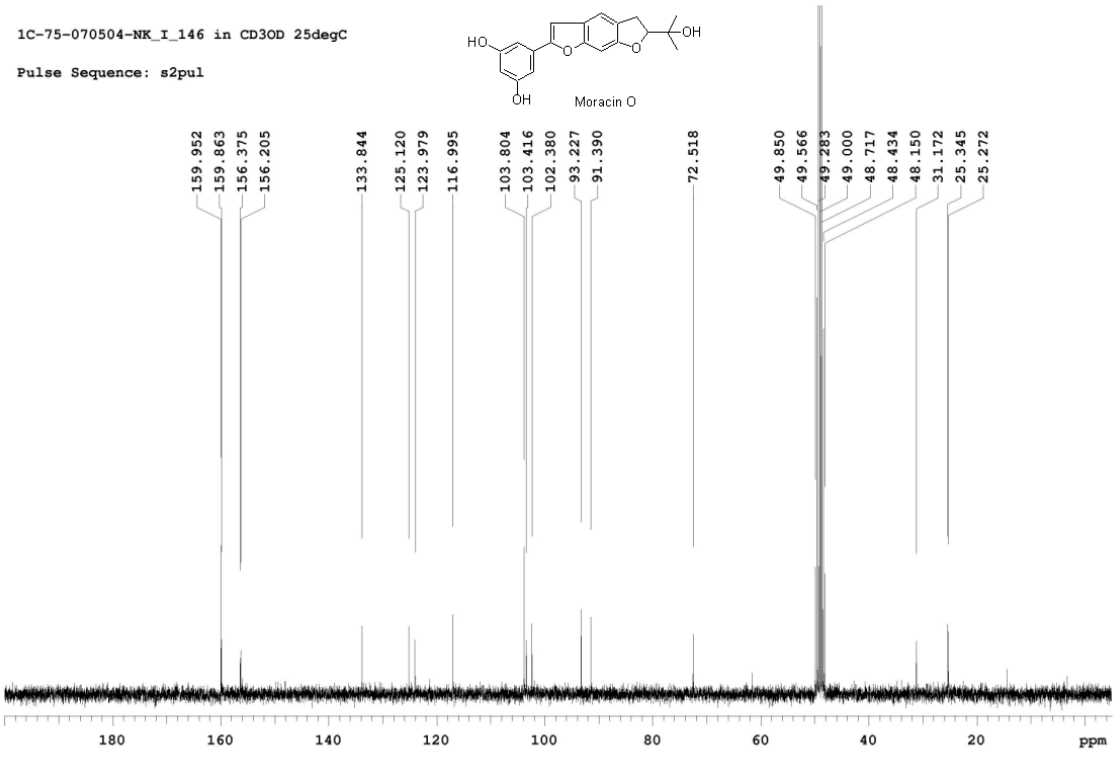


Fig S34: ^{13}C NMR spectrum of compound **1**.

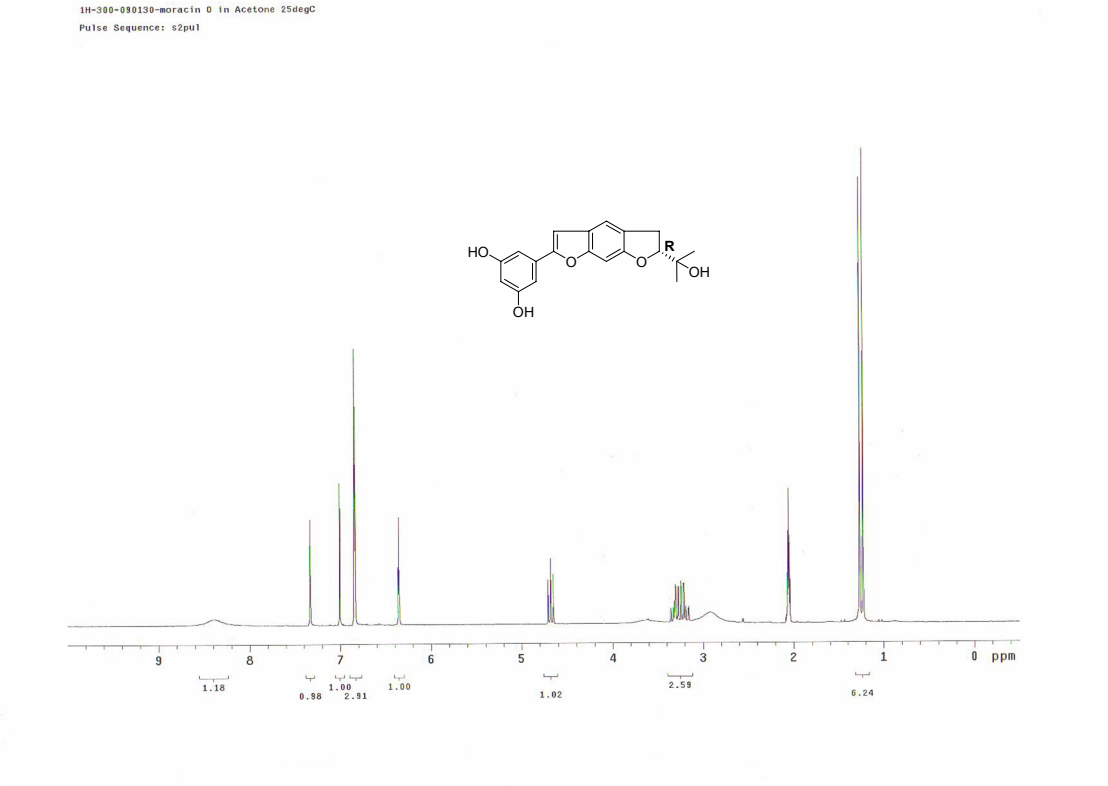


Fig S35: ^{1}H NMR spectrum of compound **(R)-1**.

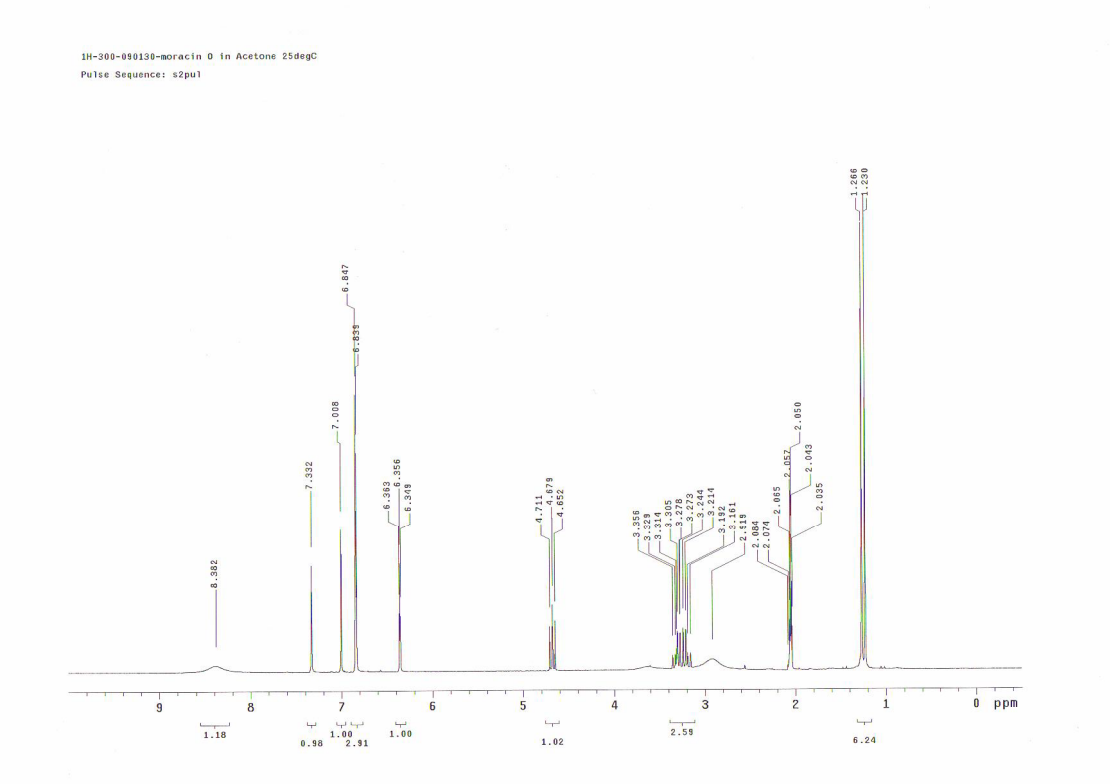
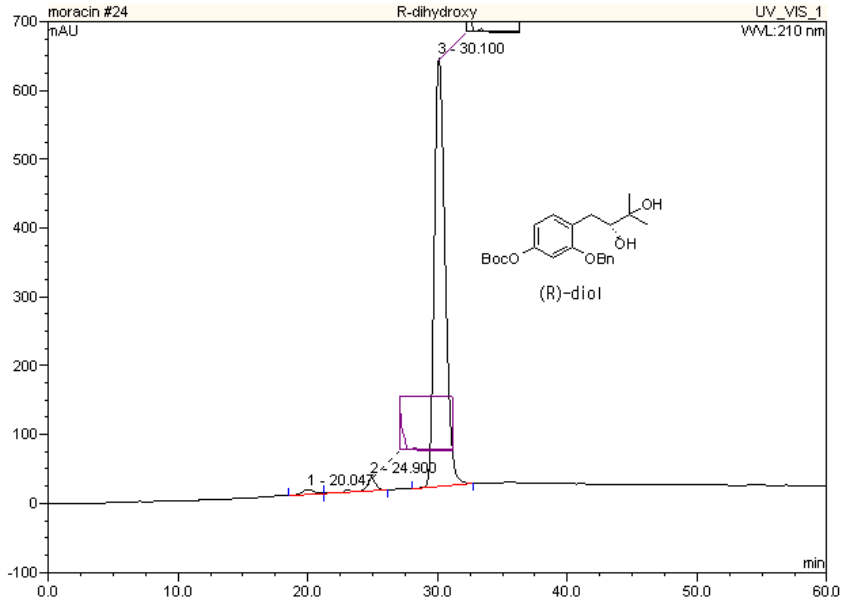


Fig S36: ^{1}H NMR spectrum of natural moracin O.

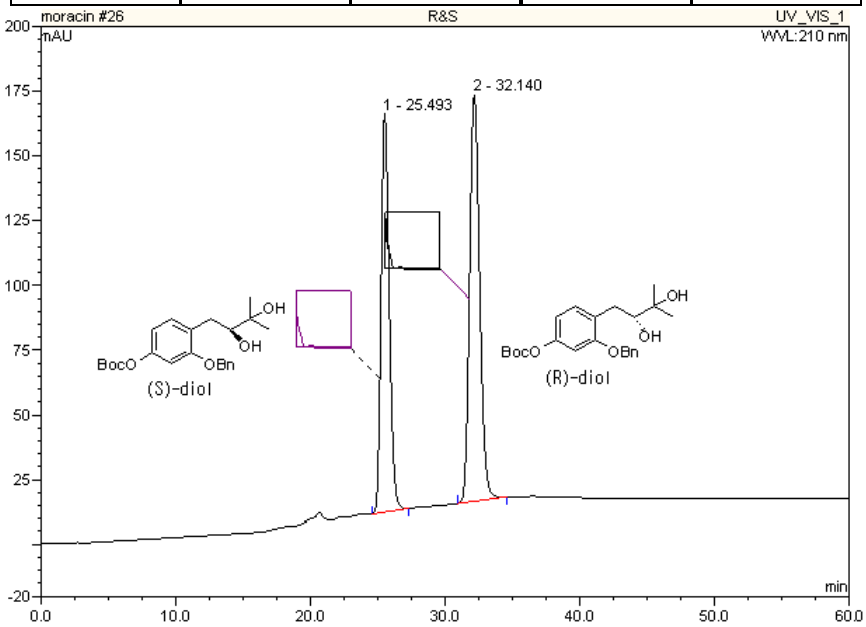
(*R*)-diol-*95% ee*.

	min	mAU*min	mAU	%
1	20.047	7.4785	6.976	1.2
2	24.9	15.1032	19.292	2.43
3	30.1	599.634	621.634	96.37



A mixture of *(R)* and *(S)*-diol

	min	mAU*min	mAU	%
1	25.493	105.7216	149.804	44.43
2	32.14	132.2369	152.95	55.57



(S)*-diol-*90% ee.

	min	mAU*min	mAU	%
1	20.647	6.1027	2.671	4.56
2	25.373	121.2917	173.473	90.53
3	31.993	6.5814	7.435	4.91

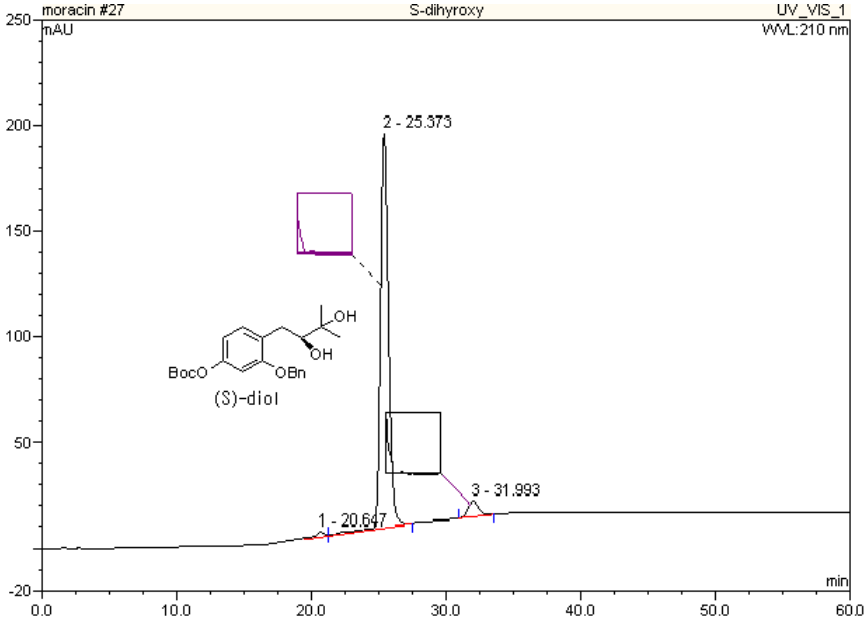


Figure S37: Chiral HPLC of compound **17a** and **17b**.

II. Biological Procedures

The newly synthesized compounds were evaluated for their potential to inhibit HIF-1 activation induced by hypoxia (1% O_2, 94% N_2, and 5% CO_2) using a HIF-1-mediated cell-based reporter assay in human hepatocellular carcinoma Hep3B cells. All the assays were performed under standard assay conditions by employing hypoxic condition and following the previously described assay protocol.[1]

Cell Culture. Human hepatocellular carcinoma Hep3B cells were obtained from ATCC (American Type Culture Collection, Manassas, VA) were maintained in RPMI 1640

(Invitrogen, Grand Island, NY) supplemented with 10% (V/V) fetal bovine serum (Hyclone, Logan, UT), penicillin, and streptomycin in a humidified 5% CO_2 atmosphere at 37 °C. Hypoxic culture was kept in a gas-controlled chamber (Thermo Electron Corp., Marietta OH) maintained at 1% O_2, 94% N_2, and 5% CO_2 at 37 °C.

Cell based HRE reporter Assay. The ability of the compounds to inhibit hypoxia-inducible factor-1 was determined by a reporter assay. At 75–90% confluence, cells were transiently co-transfected with the vectors for pGL3-HRE-Luciferase plasmid,[2] which contains six copies of HREs derived from the human VEGF gene, and pRL-CMV (Promega, Madison, WI) using Lipofectamine plus reagent according to the instructions of manufacturer (Invitrogen). Following 48 h incubation, the cells were treated with various concentrations of the tested compounds and incubated for 16 h in hypoxia. The luciferase assay was performed using a Dual-luciferase reporter assay system according to the instructions of the manufacturer (Promega). Luciferase activity was determined in Microlumat Plus luminometer (EG&G Berthold, Bad Wildbad, Germany) by injecting 100 μL of assay buffer containing luciferin and measuring light emission for 10 sec. The results were normalized to the activity of renilla luciferase expressed by cotransfected *Rluc* gene under the control of a constitutive promoter.

Statistical Analysis. Each experiment was performed at least three times, and

representative data are shown. Data in the table are given as mean values ± standard deviation from separate experiments. Means were checked for statistical differences by using the Student's *t*-test with error probabilities of $p < 0.05$.

Reference

1. Cai, X. F.; Jin, X.; Lee, D.; Yang T. Y.; Lee, K.; Hong, Y.-S., Lee, J.-H., Lee, J. J. *J. Nat. Prod*. **2006**, 69, 1095-1097.

2. Maxwell, P. H.; Wiesener, M. S.; Chang, G.-W.; Clifford, S. C.; Vaux, E. C.; Cockman, M. E.; Wykoff, C. C.; Pugh, C. W.; Mather, E. R.; Ratcliffe, P. J. *Nature* 1999, 399, 271-275.