Supporting information

Bioinspired Total Synthesis and Stereochemical Revision of the Fungal Metabolite Pestalospirane B

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Experimental Procedures

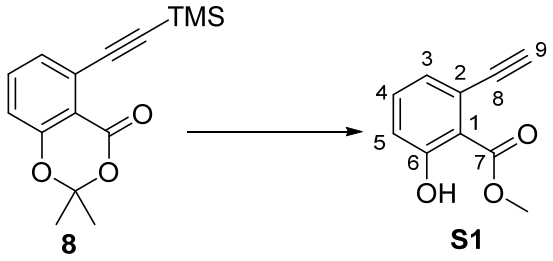
General information

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon. Tetrahydrofuran and diethyl ether were freshly distilled over sodium/benzophenone ketyl. Dichloromethane, acetonitrile, methanol and dimethylsulfoxide were freshly distilled from calcium hydride. Toluene was freshly distilled over sodium. Triethylamine and diisopropylamine were freshly distilled from calcium hydride and stored over potassium hydroxide. All other reagents were used as received unless otherwise noted.

Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions performed at low temperature were cooled either with an acetone/dry ice bath to reach −78 °C or an ice/water bath to reach 0 °C. Reactions were monitored by thin-layer chromatography (TLC) carried out on E. Merck silica gel plates using UV light as visualizing agent and an ethanolic solution of vanillin and ammonium molybdate and heat as developing agents. Kieselgel S 63-100 μm (Riedel-de-Hahn) silica gel was used for flash chromatography. Preparatory TLC was carried out on 500 μm, 20 × 20 cm UniplateTM (Analtech) silica gel thin layer chromatography plates.

NMR spectra were recorded at room temperature in $CDCl_3$, CD_3OD, $(CD_3)_3CO$, C_6D_6 or $(CD_3)SO$ solutions on either a Bruker DRX-300 spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or using a Bruker DRX-400 spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) from tetramethylsiane (δ = 0) and were measure relative to the solvent in which the sample was analysed. Coupling constants, J, are reported in hertz (Hz). Multiplicities are reported as “s” (singlet), “br s” (broad singlet), “d” (doublet), “dd” (doublet of doublets), “ddd” (doublet of doublets of doublets), “t” (triplet) and “m” (multiplets). Where distinguishable from those due to a major rotamer or diastereomer, resonances due to minor rotamers or diastereomers are denoted by an asterix. Optical rotations were measured with an Autopol® IV automatic polarimeter, using the sodium-D line (589 nm), with the concentration measured in grams per 100 mL. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using a diamond ATR sampling accessory. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. High-resolution mass spectra (HRMS) were obtained using a VG70SE spectrometer or on a micrOTOF-Q II mass spectrometer.

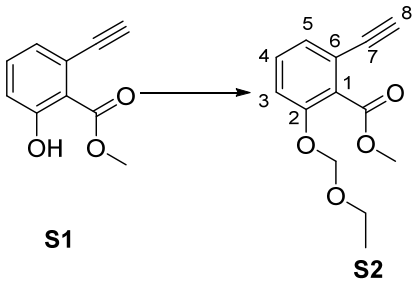
Methyl 2-ethynyl-6-hydroxybenzoate (S1)



To a stirred solution of alkyne **8**[1] (680 mg 2.50 mmol) in methanol (10 mL) was added potassium carbonate (517 mg, 2.75 mmol) at room temperature. The reaction mixture was heated to 40 ˚C and stirred for 3 h. The reaction was cooled to room temperature then quenched with sat. aq. NH_4Cl (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate\hexanes, 1:20) gave the *title compound* (0.35 mg, 0.2 mmol, 80%) as a colourless solid.

Mp: 62.9-66.1 ºC; $\mathbf{R_f}$: 0.40 (ethyl acetate\hexanes1:20); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.22 (1H, s, OH), 7.35 (1H, t, *J* = 8.2 Hz, H-4), 7.16 (1H, dd, *J* = 7.3, 1.2 Hz, H-3), 7.01 (1H, dd, *J* = 8.6, 1.5 Hz, H-5), 3.97 (3H, s, OC*H*$_3$), 3.34 (1H, s, H-9); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.5 (C=O), 162.2 (C_q, C-6), 134.0 (CH, C-4), 127.2 (CH, C-4), 123.4 (C_q, C-2), 118.8 (CH, C-5) 113.6 (C_q, C-1), 82.9 (C_q, C-8), 81.9 (CH, C-9), 52.1 (O*C*H$_3$); **IR ν_{max}** (neat): 3256, 3017, 2954, 1660, 1599, 1573, 1446, 1351, 1315, 1293, 1244, 1212, 1126, 1067, 945, 811, 742, 693, 559, 520; **HRMS**: found $[M + Na]^+$ 199.0365, $[C_{10}H_8O_3 + Na]^+$ requires 199.0366.

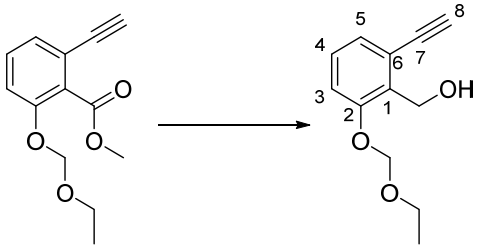
Methyl 2-(ethoxymethoxy)-6-ethynylbenzoate (S2)



To a stirred solution of phenol **S1** (1.13 g, 6.42 mmol) in dichloromethane (50 mL) was added TBAI (118 mg, 0.321 mmol) and cooled to 0 ºC. DIPEA (2.2 mL, 12.8 mmol) was added dropwise, followed by chloromethyl ethyl ether (1.2 mL, 12.8 mmol). The reaction mixture was then warmed to room temperature and stirred 16 h. The reaction was quenched with water (5 mL), washed with brine (3 x 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate\hexanes, 1:20) gave the *title compound* (1.3 g, 5.53 mmol, 90%) as a yellow oil.

$\mathbf{R_f}$: 0.20 (ethyl acetate\hexanes 1:19); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (1H, dd *J* = 8.0, 0.95, H-4), 7.20 (1H, dd, *J* = 8.4, 0.91 Hz, H-5), 7.17 (1H, dd, *J* = 7.4, 1.1 Hz, H-3), 5.23 (2H, s, OC*H*$_2$OCH$_2$CH$_3$), 3.92 (3H, s, OCH$_3$), 3.72 (2H, q, *J* = 7.3 Hz, OCH$_2$OC*H*$_2$CH$_3$), 3.18 (1H, s, H-8), 1.20 (3H, t, *J* = 6.7 Hz, OCH$_2$OCH$_2$C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.1 (C=O), 153.9 (C_q C-2), 130.5 (CH, C-4), 127.7 (C_q, C-6), 126.0 (CH, C-5), 120.9 (C_q, C-6), 115.9 (CH, C-3), 93.5 (CH$_2$, O*C*H$_2$OCH$_2$CH$_3$), 80.7 (CH, C-8), 80.5 (C_q, C-7), 64.6 (CH$_2$, OCH$_2$O*C*H$_2$CH$_3$), 52.5 (CH$_3$, OCH$_3$), 15.0 (CH$_3$, OCH$_2$OCH$_2$*C*H$_3$); **IR ν_{max}** (neat): 3288, 2977, 2936, 1750, 1736, 1573, 1509, 1467, 1419, 1328, 1299, 1255, 1212, 1134, 1116, 1029, 987, 851, 817, 766, 718, 700, 603, 558 cm^{-1}; **HRMS**: found $[M + Na]^+$ 257.0792, $[C_{13}H_{14}O_4 + Na]^+$ requires 257.0784.

[2-(Ethoxymethoxy)-6-ethynylphenyl] methanol (S3)

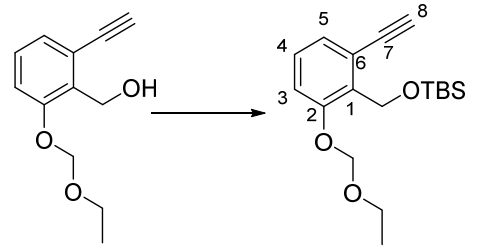


S2 **S3**

To a stirred solution of ester **S2** (2.0 g, 8.5 mmol) in THF (150 mL) at 0 ˚C was added lithium aluminium hydride (1.3 g, 34.2 mmol) was added in small portion and stirred for 3 h at this temperature. The reaction mixture was quenched with water (10 mL) and ethyl acetate (100 mL) was added. The mixture was then filtered through a pad of Celite® and the filtrate was concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate\hexanes, 1:20) gave the *title compound* (1.6 g, 7.77 mmol, 90%) as a yellow/reddish oil.

R_f: 0.20 (ethyl acetate\hexanes 1:20); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23-7.14 (3H, m, Ar-H), 5.28 (2H, s, $OCH_2OCH_2CH_3$), 4.91 (2H, br s, CH_2OH), 3.74 (2H, q, J =7.1 Hz, $OCH_2OCH_2CH_3$), 3.28 (1H, s, H-8), 2.48 (1H, br s, OH), 1.22 (3H, t, J = 7.1 Hz, $OCH_2OCH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.9 (C_q, C-6), 132.3 (C_q, C-2), 129.1 (CH, C-4), 126.7 (CH, C-3), 120.9 (C_q, C-1), 115.8 (CH, C-5), 93.8 (CH_2, C-10), 81.4 (CH, C-8), 77.5 (C_q, C-7), 64.9 (CH_2, C-11), 59.0 (CH_2, C-9), 15.2 (CH_3); **IR ν_{max}** (neat): 3555, 3283, 2984, 2895, 1733, 1575, 1463, 1393, 1249, 1191, 1149, 1112, 1088, 1036, 972, 790, 744, 641, 601, 570 cm^{-1}; **HRMS**: found $[M + H]^+$ 207.1017, $[C_{12}H_{14}O_3 + H]^+$ requires 207.1016.

***tert*-Butyl({[2-(ethoxymethoxy)-6-ethynylphenyl]methoxy})dimethylsilane (9)**



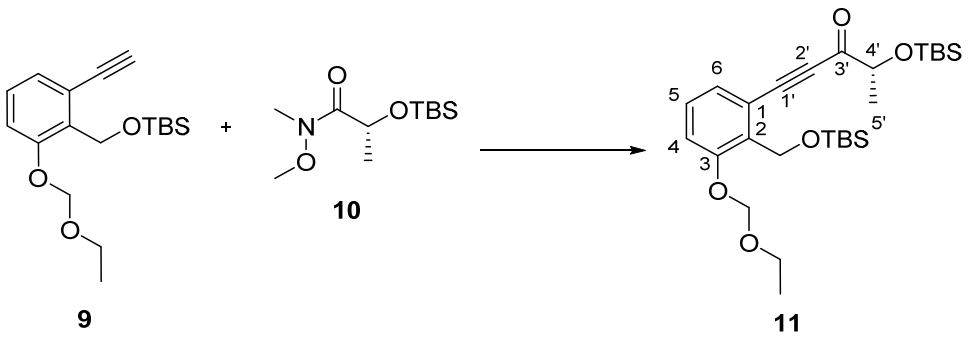
S3 **9**

To a stirred solution of alcohol **S3** (1.5 g, 7.3 mmol) in dichloromethane (100 mL) at 0 ˚C was added DMAP (45 mg, 0.36 mmol), imidazole (745 mg, 10.9 mmol) and *tert*-butyldimethylsilyl chloride (1.6 g, 10.9 mmol). The reaction mixture was then warmed to room temperature and stirred for 16 h. Sat. aq. NH_4Cl (50 mL) was then added and the aqueous layer was separated and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (3 × 80 ml), dried ($MgSO_4$), filtered and concentrated *in vacu*o. Purification by flash chromatography (ethyl acetate\hexanes, 1:19) gave the *title compound* (2.3 g, 7.3 mmol, quant) as a colourless oil.

R_f: 0.2 (ethyl acetate\hexanes 1:19); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.20-7.12 (3H, m, Ar-H), 5.25 (2H, s, $OCH_2OCH_2CH_3$), 4.90 (2H, s, CH_2OTBS), 3.75 (2H, q, J = 7.2 Hz, $OCH_2OCH_2CH_3$), 3.22 (1H, s, H-8), 1.24 (3H, t, J = 7.1 Hz, $OCH_2OCH_2CH_3$), 0.91 (9H, s, $SiMe_2{}^tBu$), 0.09 (6H, s, $SiMe_2{}^tBu$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 156.1 (C_q, C-2), 132.0 (C_q, C-6), 128.7 (CH, C-4), 126.5, (CH, C-5), 123.7 (C_q, C-1), 115.9, (CH, C-3), 93.5 (CH_2, $OCH_2OCH_2CH_3$), 81.4 (C_q, C-7), 80.5 (CH, C-8), 64.3 (CH_2, $OCH_2OCH_2CH_3$), 58.6 (CH_2, CH_2OTBS), 26.0 (3 x CH_3, $SiMe_2{}^tBu$), 18.6 (C_q, $SiMe_2{}^tBu$) 15.1 (CH_3, $OCH_2OCH_2CH_3$); **IR ν_{max}** (neat): 3675, 2952, 2929, 2856, 1757, 1576, 1462, 1390, 1248, 1195, 1149,

1113, 1046, 988, 833, 774, 722, 663, 602, 547 cm^{-1}; **HRMS**: found $[M + Na]^+$ 343.1713, $[C_{18}H_{28}O_3Si + Na]^+$ requires 343.1700.

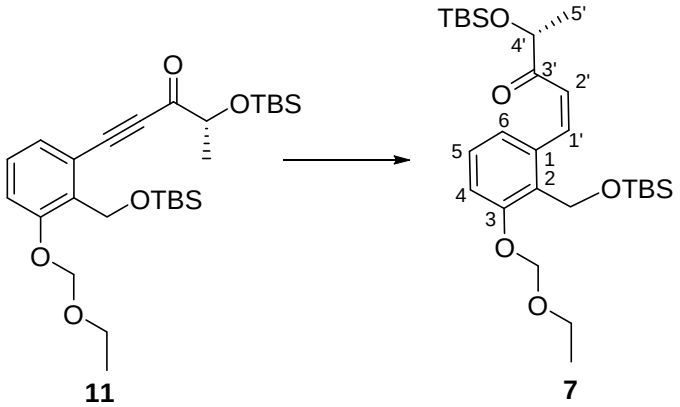
(*R*)-1-(2-{[(tert-butyldimethylsilyl)oxy]methyl}-3-(ethoxymethoxy)phenyl)-4-hydroxypent-1-yn-3-one (11)



To a stirred solution of alkyne **9** (400 mg, 0.98 mmol) in anhydrous THF (15 mL) at -78 ˚C was added LiHDMS (1.9 mL, 1 M in THF, 1.9 mmol) and stirred for 1 h. A solution of Weinreb amide **10**[2] (385.6 mg, 1.5 mmol) in anhydrous THF (3 mL) was then added dropwise and the reaction mixture was warmed to room temperature and stirred for a further 1 h. Sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with sat. aq. NH_4Cl (3 × 10 mL), brine (3 × 10 mL), dried ($NaSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate\hexanes, 1:19) gave the *title compound* (397 mg, 0.78 mmol, 80%) as a colourless oil.

$[\alpha]_D^{20}$ +14.2 (c 0.38, $CHCH_3$); $\mathbf{R_f}$: 0.20 (ethyl acetate\hexanes 1:19); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28-7.24 (3H, m, Ar-H), 5.27 (2H, s, $OCH_2OCH_2CH_3$), 4.90 (2H, d, *J* = 10.6 Hz, CH_2OTBS), 4.38 (1H, q, *J* = 6.7 Hz, H-4'), 3.71 (2H, q, *J* = 7.6 Hz, $OCH_2OCH_2CH_3$), 1.50 (3H, d, *J* = 7.0 Hz, H-5'), 1.23 (3H, t, *J* = 6.8 Hz, $OCH_2OCH_2CH_3$), 0.94 (9H, s, $SiMe_2{}^tBu$), 0.90 (9H, s, $SiMe_2{}^tBu$), 0.14 (3H, s, $SiMe_2{}^tBu$), 0.11 (9H, s, $SiMe_2{}^tBu$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 189.7 (C=O), 156.2 (C_q, C-6), 133.2 (C_q, C-2), 129.1 (CH, C-4), 127.2 (CH, C-3), 127.2 (C_q, C-1), 117.7 (CH, C-5), 93.6 (CH_2, $OCH_2OCH_2CH_3$), 92.6 (C_q, C-1'), 89.3 (C_q, C-2'), 75.5 (CH, C-4'), 64.6 (CH_2, $OCH_2OCH_2CH_3$), 58.5 (CH_2, CH_2OSi), 26.1 (3 x CH_3, $SiMe_2{}^tBu$), 25.9 (3 x CH_3, $SiMe_2{}^tBu$), 20.8 (CH_3, C-15), 18.5 (C_q, $SiMe_2{}^tBu$), 18.3 (C_q, $SiMe_2{}^tBu$), 15.2 (CH_3, $OCH_2OCH_2CH_3$), -4.7 (CH_3, $SiMe_2{}^tBu$), -5.05 (CH_3, $SiMe_2{}^tBu$), -5.21 (2 x CH_3, $SiMe_2{}^tBu$); **IR ν_{max}** (neat): 2977, 2955, 2930, 2887, 2857, 2197, 1193, 1005, 925, 902, 832, 813, 794, 775, 725, 630 cm^{-1}; **HRMS**: found $[M + Na]^+$ 529.2776, $[C_{27}H_{46}O_5Si_2 + Na]^+$ requires 529.2768.

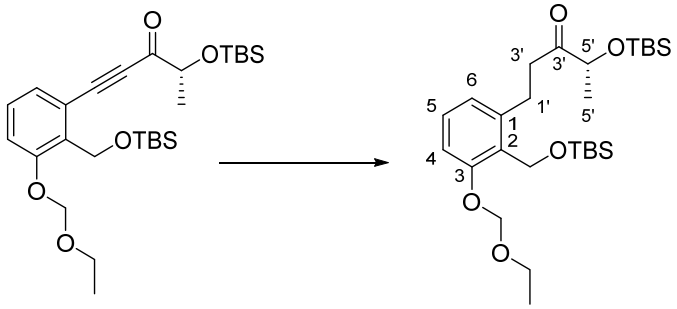
Bis((*Z*,*R*)-4-[(*tert*-butyldimethylsilyl)oxy]-1-(2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-3-(ethoxymethoxy)phenyl)pent-1-en-3-one) (7)



To a stirred solution of ynone **11** (200 mg, 0.39 mmol) in hexanes (25 mL) was added quinoline (0.3 mL, 2.3 mmol) and subjected to hydrogenation using a H-cube® flow reactor with the following settings (Lindlar catalyst, 1mL/min, 10 bar, 20 ˚C). The reaction mixture was concentrated *in vacuo* and purification by flash chromatography (ethyl acetate\hexanes, 1:19) gave the *title compound* (159 mg, 0.31 mmol, 80%) as a yellow oil;

$[\alpha]_D^{20}$ -14.4 (c 1.00, $CHCl_3$); **R_f**: 0.35 (1:19 ethyl acetate\hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 (1H, d, *J* = 12.4 Hz, H-1'), 7.14 (1H, t, *J* = 8.5 Hz, H-5'), 7.08 (1H, d, *J* = 8.5 Hz, H-6), 6.98 (1H, d, *J* = 8.5 Hz, H-4), 6.65 (1H, d, *J* = 12.4 Hz, H-2'), 5.22 (2H, s, $OCH_2OCH_2CH_3$), 4.74 (2H, s, CH_2OTBS), 4.17 (1H, q, *J* = 6.9 Hz, H-4'), 3.72 (2H, q, *J* = 7.0 Hz, $OCH_2OCH_2CH_3$), 1.29 (3H, d, *J* = 6.9 Hz, H-5'), 1.22 (3H, t, *J* = 7.2 Hz, $OCH_2OCH_2CH_3$), 0.91 (18H, d, 2 × $SiMe_2{}^tBu$), 0.07 (12H, d, $SiMe_2{}^tBu$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.0 (C=O), 155.3 (C_q, C-3), 142.4 (CH, C-1'), 138.0 (C_q, C-1), 128.3 (CH, C-5), 127.5 (C_q, C-2), 124.3 (CH, C-6), 122.7 (CH, C-2'), 114.9 (CH, C-4), 93.8 (CH_2, $OCH_2OCH_2CH_3$), 75.0 (CH, C-4'), 64.4 (CH_2, $OCH_2OCH_2CH_3$), 57.2 (CH_2, CH_2OTBS), 26.1 (3 x CH_3, $SiMe_2{}^tBu$), 25.9 (3 x CH_3, $SiMe_2{}^tBu$), 21.0 (CH_3, C-5'), 18.6 (C_q, $SiMe_2{}^tBu$), 18.3 (C_q, $SiMe_2{}^tBu$), 15.2 (CH_3, $OCH_2OCH_2CH_3$), -4.6 (CH_3, $SiMe_2{}^tBu$), -4.7 (CH_3, $SiMe_2{}^tBu$), -5.2 (2 × CH_3, $SiMe_2{}^tBu$); **IR ν_{max}** (neat): 2955, 2929, 2857, 2887, 1698, 1576, 1471, 1390, 1362, 1152, 1114, 1043, 1005, 989, 936, 883, 813, 725, 666 cm^{-1}; **HRMS**: found $[M + Na]^+$ 531.2937, $[C_{27}H_{48}O_5Si_2 + Na]^+$ requires 531.2946.

(*R*)-1-(2-{[(tert-butyldimethylsilyl)oxy]methyl}-3-(ethoxymethoxy)phenyl)-4-hydroxypentan-3-one (14)

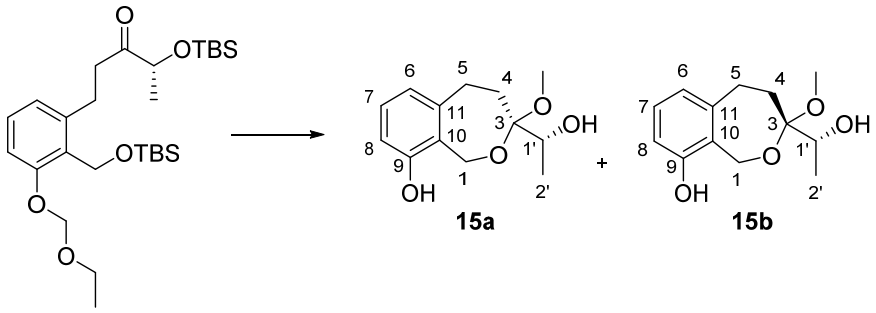


11 **14**

To a stirred solution of ynone **11** (500 mg, 0.98 mmol) in ethyl acetate (25 mL) was added Pd/C (50 mg) and the reaction mixture was placed under an atmosphere of hydrogen for 1 h. The hydrogen source was removed and the reaction mixture was filtered through a pad of Celite® and the filtrate were concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate\hexanes, 1:9) gave the *title compound* (489 mg, 0.93 mmol, 95%) as a pale yellow oil.

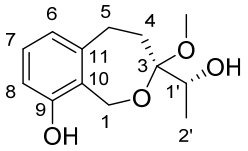
$[\alpha]_D^{20}$ +27.2 (c 1.00, $CHCl_3$); **R_f**: 0.30 (ethyl acetate\hexanes 5:95); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.15 (1H, t, *J* = 7.8 Hz, H-5), 6.98 (1H, d, *J* = 8.1 Hz, H-6), 6.83 (1H, d, *J* = 7.8 Hz, H-4), 5.22 (2H, s, $OCH_2OCH_2CH_3$), 4.79 (2H, q, *J* = 10.0 Hz, CH_2OTBS), 4.15 (1H, q, *J* = 6.6 Hz, H-4'), 3.72 (2H, q, *J* = 7.1 Hz, $OCH_2OCH_2CH_3$), 3.01-2.82 (4H, m, H-1', H-2'), 1.26-1.21 (6H, m, H-5' and $OCH_2OCH_2CH_3$), 0.88 (18H, s, 2 × $SiMe_2{}^tBu$), 0.08 (6H, s, $SiMe_2{}^tBu$), 0.05 (6H, s, $SiMe_2{}^tBu$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 213.1 (C=O), 155.8 (C_q, C-3), 143.0 (C_q, C-2), 128.8 (CH, C-5), 127.9 (C_q, C-1), 122.9 (CH, C-6), 112.6 (CH, C-4), 93.7 (CH_2, $OCH_2OCH_2CH_3$), 75.1 (CH, C-4'), 64.4 (CH_2, CH_2OTBS), 56.3 (CH_2, $OCH_2OCH_2CH_3$), 38.8 (CH_2, C-1'), 26.4 (CH_2, C-2'), 26.2 (3 x CH_3, $SiMe_2{}^tBu$), 25.9 (3 x CH_3, $SiMe_2{}^tBu$), 20.9 (CH_3, C-5'), 18.6 (C_q, $SiMe_2{}^tBu$), 18.2 (C_q, $SiMe_2{}^tBu$), 15.2 (CH_3, $OCH_2OCH_2CH_3$), -4.6 (CH_3, $SiMe_2{}^tBu$), -4.8 (CH_3, $SiMe_2{}^tBu$), -5.1 (2 × CH_3, $SiMe_2{}^tBu$); **IR ν_{max}** (neat): 2951, 2929, 2900, 2855, 1589, 1471, 1462, 1443, 1389, 1370, 1275, 1245, 1174, 1146, 1116, 1102, 1038, 1030, 1003, 941, 916, 900, 831, 812, 775, 742, 702, 681, 665 cm^{-1}; **HRMS**: found $[M + Na]^+$ 533.3097, $[C_{27}H_{50}O_5Si_2 + Na]^+$ requires 533.3089.

(*R*)-3-[(*R*)-1-hydroxyethyl]-3-methoxy-1,3,4,5-tetrahydro-2-benzoxepin-9-ol (15a) and (*S*)-3-[(*R*)-1-hydroxyethyl]-3-methoxy-1,3,4,5-tetrahydro-2-benzoxepin-9-ol (15b)



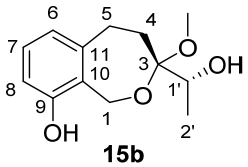
14

To a stirred solution of ketone **14** (500 mg, 0.98 mmol) in undistilled methanol (60 mL) was added trimethyl orthoformate (0.1 mL, 1.0 mmol) and camphorsulfonic acid (68 mg, 0.3 mmol) and stirred at room temperature for 24 h. A further portion of camphorsulfonic acid (23 mg, 0.099 mmol) was then added and stirred for another 5 h. Sat. aq. $NaHCO_3$ (50 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (2 × 50 mL), brine (3 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacu*o. Purification by flash chromatography (ethyl acetate\hexanes, 1:4) gave the *title compound* **15a** (79 mg, 0.33 mmol, 34%) as a colourless foam and *title compound* **15b** (82 mg, 0.34 mmol, 35%) as colourless foam.



15a

$[\alpha]_D^{24}$ -44.80 (c 1.00, $CHCl_3$); **R_f**: 0.2 (1:1 ethyl acetate\hexanes); **IR ν_{max}** (neat): 3513, 3430, 3381, 3222, 2942, 1609, 1466, 1364, 1329, 1277, 1255, 1182. 1161, 1135, 1071, 1035, 1002, 970, 935, 902, 846, 830, 784, 745, 725, 679; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.01 (1H, t, *J* = 7.6 Hz, H-7), 6.75 (1H, d, *J* = 7.7 Hz, H-6), 6.60 (1H, d, *J* = 7.7 Hz, H-8), 4.92 (1H, d, *J* = 13.8 Hz, H-1a<u>b</u>), 4.88 (1H, brs, OH), 4.76 (1H, d, *J* = 13.9 Hz, H-1a<u>b</u>), 3.99 (1H, q, *J* = 6.5 Hz, H-1'), 3.43 (3H, s, OCH_3), 3.30 (1H, td, *J* = 14.5, 2.0 Hz, H-5a<u>b</u>), 2.64 (1H, ddd, *J* = 15.1, 8.0, 2.4 Hz, H-5a<u>b</u>), 2.16 (1H, brs, OH), 1.96-1.84 (2H, m, H-4), 1.13 (3H, d, *J* = 6.7 Hz, H-2');**^{13}C NMR** (100 MHz, $CDCl_3$): δ 152.8 (C_q, C-9), 145.8 (C_q, C-11), 128.7 (CH, C-7), 125.6 (C_q, C-10), 121.5 (CH, C-6), 113.7 (CH, C-8), 103.4 (C_q, C-3), 69.3 (CH, C-1'), 55.5 (CH_2, C-1), 48.3 (CH_3, OCH_3), 29.8 (CH_2, C-4), 28.4 (CH_2, C-5), 15.8 (CH_3, C-2'); **HRMS**: found $[M + Na]^+$ 261.1098, $[C_{13}H_{18}O_4 + Na]^+$ requires 261.1097.

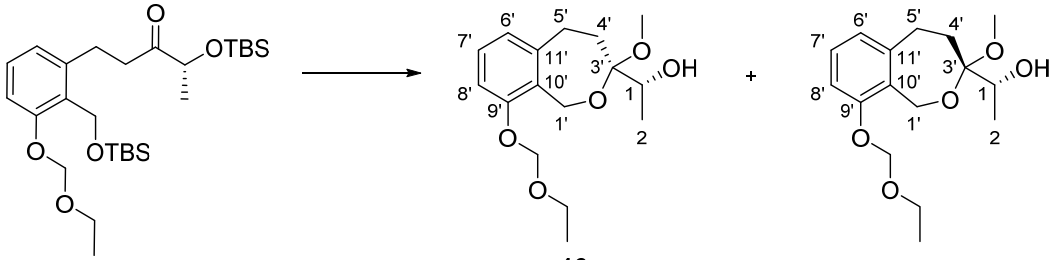


15b

$[\alpha]_D^{24}$ +46.07 (c 0.382, $CHCl_3$); **R_f**: 0.15 (1:1 ethyl acetate\hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.02 (1H, t, *J* = 8.0 Hz, H-7), 6.73 (1H, d. *J* = 7.2 Hz, H-6), 6.60 (1H, d, *J* = 8.0 Hz, H-8), 4.97 (1H, d, *J* = 13.9 Hz, H-1a<u>b</u>), 4.91 (1H, brs, OH), 4.77 (1H, d, *J* = 13.9 Hz, H-1a<u>b</u>), 3.89 (1H, q, *J* = 6.5 Hz, H-1'), 3.45 (3H, s, OCH_3), 3.25 (1H, t, *J* = 13.4 Hz, H-5a<u>b</u>), 2.64 (1H, ddd, *J* = 15.1, 8.0, 2.4 Hz, H-5a<u>b</u>), 2.42 (1H, brs, OH), 2.03 (1H, dd, *J* = 13.1, 8.0 Hz, H-4a<u>b</u>), 1.69 (1H, t, *J* = 13.5 Hz, H-4a<u>b</u>), 1.18 (3H,

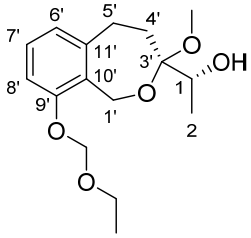
d, *J* = 6.5 Hz, H-2'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 152.9 (C_q, C-9), 145.4 (C_q, C-11), 128.5 (CH, C-7), 125.4 (C_q, C-10), 121.4 (CH, C-6), 113.6 (CH, C-8), 102.7 (C_q, C-3), 70.0 (CH, C-1'), 56.2 (CH_2, C-1), 49.2 (CH_3, OCH_3), 32.3 (CH_2, C-4), 28.8 (CH_2, C-5), 16.5 (CH_3, C-2'); **IR ν_{max}** (neat): 3513, 3430, 3381, 3222, 2942, 1609, 1466, 1364, 1329, 1277, 1255, 1182. 1161, 1135, 1071, 1035, 1002, 970, 935, 902, 846, 830, 784, 745, 725, 679 cm^{-1}; **HRMS**: found $[M + Na]^+$ 261.1098, $[C_{13}H_{18}O_4 + Na]^+$ requires 261.1097.

(*R*)-1-[(*R*)-9-(ethoxymethoxy)-3-methoxy-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (16a) and (*R*)-1-[(*S*)-9-(ethoxymethoxy)-3-methoxy-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (16b)



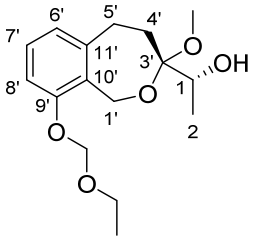
14 **16a** **16b**

To a stirred solution of ketone **14** (500 mg, 0.98 mmol) in anhydrous methanol (60 mL) was added trimethyl orthoformate (0.1 mL, 1.0 mmol) and 10-camphorsulfonic acid (68 mg, 0.3 mmol) and stirred at room temperature for 24 h. A further portion of camphorsulfonic acid (23 mg, 0.10 mmol) was added and stirred for further 30 h. Sat. aq. $NaHCO_3$ (50 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 20 mL) . The combined organic layers were washed with sat. aq. $NaHCO_3$ (2 × 50 mL), brine (3 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacu*o. Purification by flash chromatography (ethyl acetate\hexanes, 1:4) gave the *title compound* **16a** (85 mg, 0.29 mmol, 30%) as a colourless oil and *title compound* **16b** (100 mg, 0.34 mmol, 35%).



16a

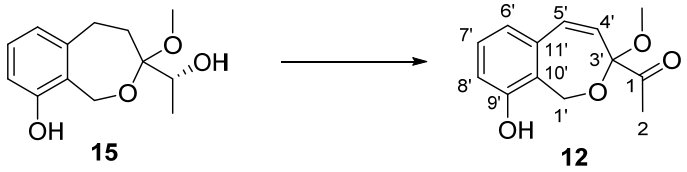
$[\alpha]_D^{24}$ -51.5 (c 1.00, $CHCl_3$); **R_f**: 0.30 (1:3 ethyl acetate\hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.12 (1H, t, *J* = 7.7 Hz, H-7'), 6.97 (1H, d, *J* = 8.0 Hz, H-6'), 6.81 (1H, d, *J* = 7.7 Hz, H-8'), 5.23 (2H, q, *J* = 6.9 Hz, $OCH_2OCH_2CH_3$), 5.01 (1H, d, *J* = 13.3 Hz, H-1'ab), 4.72 (1H, d, *J* = 13.3 Hz, H-1'ab), 3.97 (1H, q, *J* = 6.7 Hz, H-1), 3.75 (2H, q, *J* = 7.0 Hz, $OCH_2OCH_2CH_3$), 3.34 (3H, s, OCH_3), 3.32-3.27 (1H, m, H-5'ab), 2.68-2.62 (1H, m, H-5'ab), 2.06 (1H, brs, OH), 1.94-1.83 (2H, m, H-4'), 1.25 (3H, t, *J* = 7.3 Hz, $OCH_2OCH_2CH_3$), 1.12 (3H, d, *J* = 6.4 Hz, H-2'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.8 (C_q, C-9'), 145.2 (C_q, C-1'), 128.7 (CH, C-7'), 128.2 (C_q, C-10'), 122.7 (CH, C-6'), 112.7 (CH, C-8'), 103.4 (C_q, C-3'), 94.0 (CH_2, $OCH_2OCH_2CH_3$), 69.2 (CH, C-1), 64.6 (CH_2, $OCH_2OCH_2CH_3$), 55.7 (CH_2, C-1'), 48.3 (CH_3, OCH_3), 29.8 (CH_2, C-4'), 28.5 (CH_2, C-5'), 15.8 (CH, C-2), 15.3 (CH_3, $OCH_2OCH_2CH_3$); **IR ν_{max}** (neat): 3459, 2942, 1716, 1588, 1471, 1371, 1245, 1151, 1105, 1058, 1037, 997, 900, 835, 782, 745, 638, 594 cm^{-1}; **HRMS**: found $[M + Na]^+$ 319.1516, $[C_{16}H_{24}O_4 + Na]^+$ requires 319.1518.



16b

$[\alpha]_D^{24}$ +49.7 (c 1.00, $CHCl_3$); $\mathbf{R_f}$: 0.20 (1:3 ethyl acetate\hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.12 (1H, t, *J* = 7.8 Hz, H-7'), 6.98 (1H, d, *J* = 8.0 Hz, H-6'), 6.82 (1H, d, *J* = 7.5 Hz, H-8'), 5.23 (2H, s, $OCH_2OCH_2CH_3$), 5.02 (1H, d, *J* = 14.0 Hz, H-1'ab), 4.74 (1H, d, *J* = 14.0 Hz, H-1'ab), 3.87 (3H, q, *J* = 6.4 Hz, H-1), 3.74 (2H, q, *J* = 7.0 Hz, $OCH_2OCH_2CH_3$), 3.23 (1H, t, *J* = 12.4 Hz, H-5'ab), 2.69-2.63 (1H, ddd *J* = 15.4, 8.0, 1.4 Hz, H-5ab), 2.37 (1H, brs, OH), 2.03-1.97 (1H, ddd, *J* = 14.5, 8.0, 1.6 Hz, H-4'ab), 1.70 (1H, td, *J* = 12.6, 1.8 Hz, H-4'ab), 1.23 (3H, t, *J* = 7.2 Hz, $OCH_2OCH_2CH_3$), 1.17 (3H, d, *J* = 6.5 Hz, H-2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.8 (C_q, C-9'), 144.8 (C_q, C-11'), 128.5 (CH, C-1'), 127.9 (C_q, C-10'), 122.2 (CH, C-6'), 112.7 (CH, C-8'), 102.8 (C_q, C-3'), 93.9 (CH_2, $OCH_2OCH_2CH_3$), 69.9 (CH, C-1), 64.6 (CH_2, $OCH_2OCH_2CH_3$), 56.4 (CH_2, C-1'), 49.2 (CH_3, OCH_3), 32.2 (CH_2, C-4'), 28.9 (CH_2, C-5'), 16.5 (CH_3, C-2), 15.3 (CH_3, $OCH_2OCH_2CH_3$); **IR ν_{max}** (neat): 3459, 2942, 1716, 1588, 1471, 1371, 1245, 1151, 1105, 1058, 1037, 997, 900, 835, 782, 745, 638, 594 cm^{-1}; **HRMS**: found $[M + Na]^+$ 319.1516, $[C_{16}H_{24}O_4 + Na]^+$ requires 319.1515.

1-(9-hydroxy-3-methoxy-1,3-dihydro-2-benzoxepin-3-yl)ethan-1-one (12)

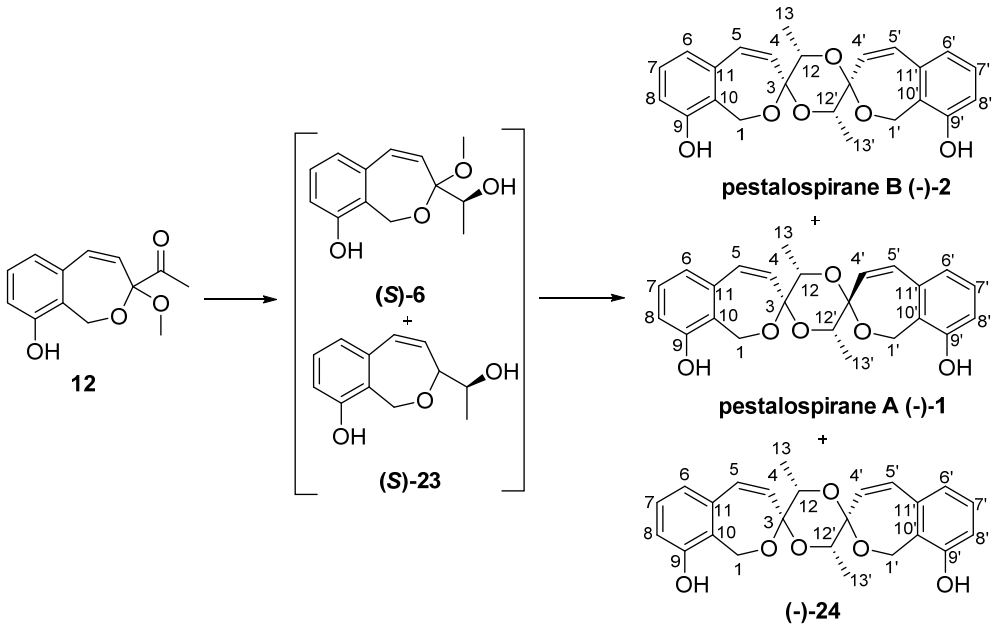


15 **12**

To a stirred solution of tetrahydrobenzo[*c*]oxepin **15** (160 mg, 0.67 mmol) in anhydrous acetonitrile (6 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (305 mg, 1.3 mmol) and the mixture was heated to 57 ˚C for 4 h. The reaction mixture was cooled to room temperature and then quenched with sat. aq. $NaHCO_3$ (5 mL) and dichloromethane (5 mL) was added and stirred for 20 min. The aqueous phase was separated and extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ until aqueous phase was colourless, brine (3 × 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacu*o. Purification by flash chromatography (ethyl acetate\hexanes, 1:4) gave the *title compound* (40 mg, 0.17 mmol, 25%) as an orange solid.

M.p.: 119.3-125.4 ˚C; $\mathbf{R_f}$: 0.20 (1:4 ethyl acetate\hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.18 (1H, d, *J* = 7.6 Hz, H-7'), 6.95 (1H, d, *J* = 8.0 Hz, H-6'), 6.76 (1H, d, *J* = 8.0 Hz, H-8'), 6.74 (1H, d, *J* = 12.4 Hz, H-4'), 5.82 (1H, d, *J* = 12.3 Hz, H-5'), 5.25 (1H, d, *J* = 13.4 Hz, H-1'ab), 4.83 (1H, brs, OH), 4.45 (1H, d, *J* = 13.3 Hz, H-1'ab), 3.30 (3H, s, OCH_3), 2.04 (3H, s, H-2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 205.3 (C=O), 152.3 (C_q, C-9'), 136.5 (C_q, C-11'), 133.8 (CH, C-5'), 129.8 (CH, C-7'), 128.5 (CH, C-4'), 127.4 (C_q, C-10'), 123.6 (CH, C-6'), 115.3 (CH, C-8'), 105.5 (C_q, C-3'), 57.8 (CH_2, C-1'), 50.0 (CH_3, OCH_3), 25.9 (CH_3, C-2); **IR ν_{max}** (neat): 3381, 2924, 2854, 1715, 1642, 1581, 1465, 1455, 1348, 1333, 1299, 1268, 1224, 1204, 1186, 1158, 1087, 1026, 982, 949, 935, 840, 805, 730, 694; **HRMS**: found $[M + Na]^+$ 257.0784, $[C_{13}H_{14}O_4 + Na]^+$ 257.0784 requires.

(-)-Pestalospirane B (-)-2, (-)-pestalospirane A (-)-1 and unnatural pestalospirane (-)-24

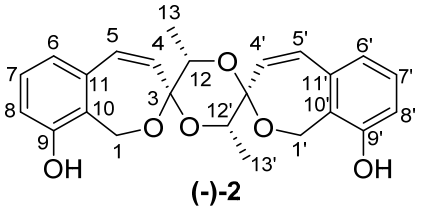


To a stirred solution of (*R*)-(-)-2-methyl-CBS-oxazaborolidine (70 µL, 1.0 M in THF, 0.07 mmol) was added borane *N*,*N*-diethylaniline complex (50 µL, 0.25 mmol) in THF (1.5 mL) and the mixture was stirred for 20 min at -10 ˚C. A solution of benzo[*c*]oxepin **12** (58 mg, 0.25 mmol) in THF (6 mL) was then added drop wise over 30 min. The reaction mixture was stirred for 30 mins at -10 ºC then methanol (2 mL) was added and the mixture was concentrated *in vacuo*. The crude residue was filtered through a pad of silica to afford alcohols (-)-**6** and (-)-**23** which were used immediately in the next step.

To a stirred solution of (*S*)-**6** and (-)-**23** (55 mg) in dichloromethane (5 mL) at -78 ˚C was added trifluoroacetic acid (25 µL) and stirred at this temperature for 1 h. The reaction was quenched with trimethylamine (0.03 mL) and warmed to room temperature. Water (5 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) dried ($MgSO_4$), filtered and concentrated *in vacu*o. Purification by flash chromatography (ethyl acetate/hexanes, 2:3) gave an inseparable mixture of the *title compounds* (30 mg, 0.07 mmol, 60% over two steps) as a colourless solid in a 9:1:1 ratio.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{27.5}}$ -5.7 (c 0.25, $CHCl_3$); $\mathbf{R_f}$: 0.20 (3:10 ethyl acetate\hexanes); **HRMS**: found $[M + Na]^+$ 431.1476, $[C_{24}H_{24}O_6 + Na]^+$ requires 431.1479.

(-)-Pestalospirane B

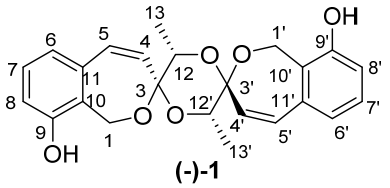


(-)-2

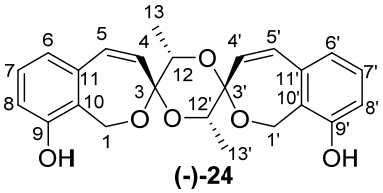
δH/ C	^{1}H NMR (CD_3CN) Lit.[3] m (*J* [Hz])	^{1}H NMR (CD_3CN) Synthetic m (*J* [Hz])	^{13}C NMR (CD_3CN) Lit.[3]	^{13}C NMR (CD_3CN) Synthetic
1	α 4.52, d (13.8) β 4.97, d, (13.8)	α 4.51, d (13.8) β 4.97, d, (13.8)	57.3, CH_2 -	57.3, CH_2 -
3	-	-	104.9, C_q	104.8, C_q
4	5.92, d (12.5)	5.92, d (12.5)	132.0, CH	132.0, CH
5	6.67, d (12.5)	6.67, d (12.5)	131.4, CH	131.6, CH
6	6.89, d (7.6)	6.89, d (7.9)	123.5, CH	123.4, CH
7	7.13, dd (7.6, 8.1)	7.13, t (7.4)	129.2, CH	129.1, CH
8	6.78, d (8.1)	6.78, d (8.1)	115.5, CH	115.4, CH
9	-	-	154.1, C_q	154.0, C_q
10	-	-	127.7, C_q	127.6, C_q
11	-	-	137.8, C_q	137.8, C_q
12	4.03, q (6.5)	4.03, q (6.5)	67.8, CH	67.6, CH
13	0.94, d (6.5)	0.94, d (6.5)	16.4, CH_3	16.4, CH_3
OH	7.08, br	7.07, br		

(-)-Pestalospirane A (-)-1 and unnatural pestalospirane (-)-24

(-)-Pestalospirane A



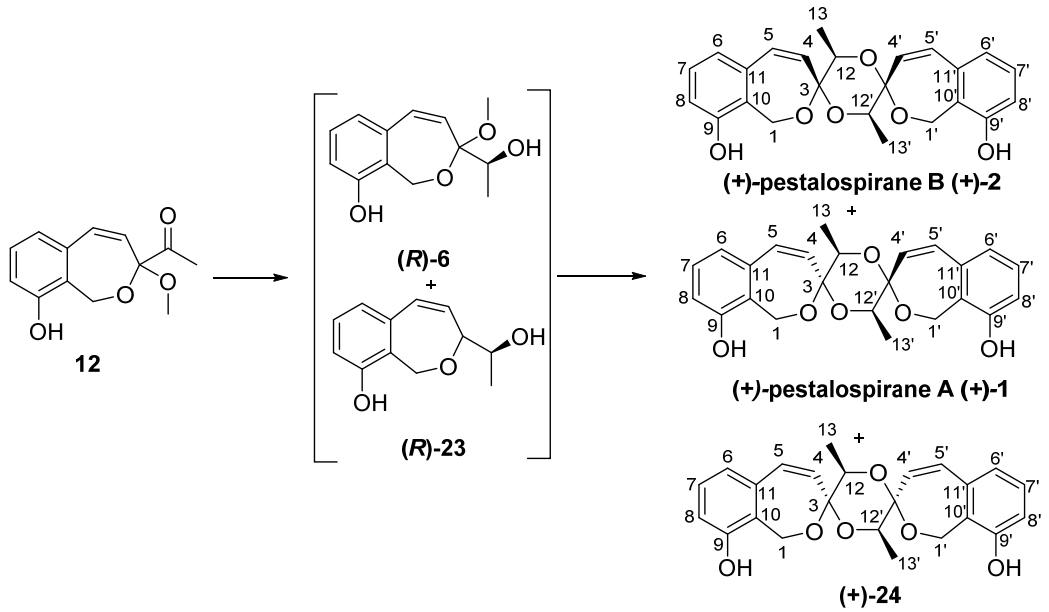
(-)-1



(-)-24

δH/C	^{1}H NMR (CD_3CN) Lit.[3] m (*J* [Hz])	^{1}H NMR (CD_3CN) Synthetic m (*J* [Hz])	^{1}H NMR (CD_3CN) Synthetic
1	α 4.49, d (13.8)	α 4.49, d (13.8)	α 4.47, d (13.8)
	β 5.02, d, (13.8)	β 5.03, d, (13.8)	β 5.06, d, (13.8)
3	-	-	-
4	5.93, d (12.5)	5.92, d (12.5)	5.75, d (12.5)
5	6.65, d (12.5)	6.67, d (12.5)	6.62, d (12.5)
6	6.90, d (7.6)	6.89, d (7.9)	6.89, d (7.9)
7	7.13, dd (7.6, 8.1)	7.13, t (7.4)	7.13, t (7.4)
8	6.78, d (8.1)	6.78, d (8.1)	6.78, d (8.1)
9	-	-	-
10	-	-	-
11	-	-	-
12	3.71, q (6.7)	4.71, q (6.5)	4.18, q (6.5)
13	1.37, d (6.6)	1.37, d, (6.6)	0.90, d, (6.6)
OH	7.25, br	-	
1’	α 4.45, d (13.8)	α 4.45, d (13.8)	
	β 5.05, d, (13.8)	β 5.06, d, (13.8)	
3’	-	-	
4’	5.78, d (12.5)	5.92, d (12.5)	
5’	6.63, d (12.5)	6.67, d (12.5)	
6’	6.89, d (7.6)	6.89, d (7.9)	
7’	7.13, dd (7.6, 8.1)	7.13, dt (7.4)	
8’	6.78, d (8.1)	6.78, d (8.1)	
9’	-	-	
10’	-	-	
11’	-	-	
12’	4.27, q (6.5)	4.27, q (6.5)	
13’	0.92, d (6.5)	0.92, d (6.5)	
OH’	7.25, br	-	

(+)-Pestalospirane B (+)-2, (+)-pestalospirane A (+)-1 and unnatural pestalospirane (+)-24



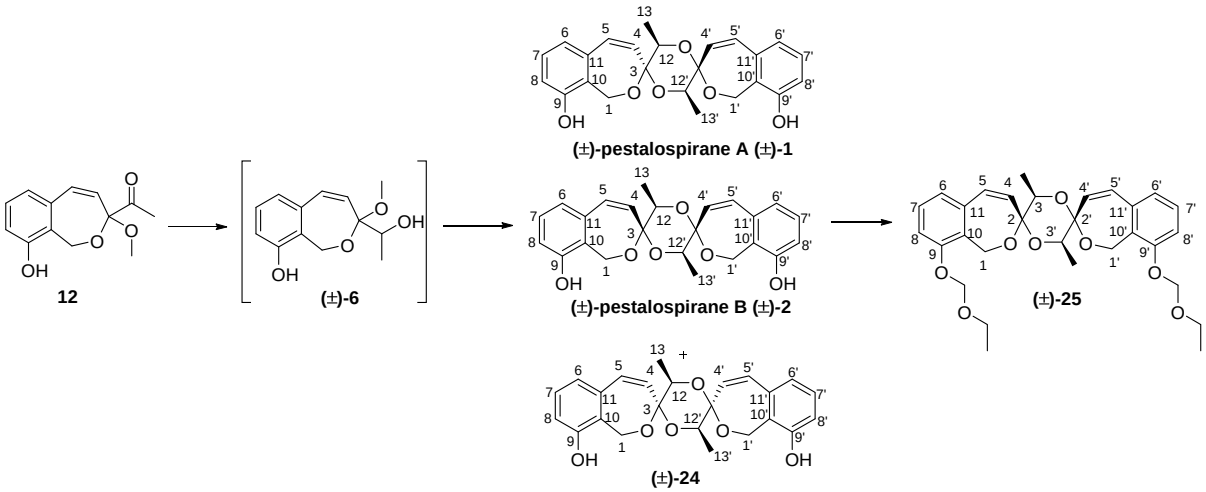
To a stirred solution of (*S*)-(-)-2-methyl-CBS-oxazaborolidine (70 µL, 1.0 M in THF, 0.07 mmol) was added borane *N*,*N*-diethylaniline complex (50 µL, 0.25 mmol) in THF (1.5 mL) and the mixture was stirred for 20 min at -10 ˚C. A solution of benzo[c]oxepin **12** (58 mg, 0.25 mmol) in THF (6 mL) was then added drop wise over 30 min. The reaction mixture was stirred for 30 mins at -10 ºC then methanol (2 mL) was added and the mixture was concentrated *in vacuo*. The crude residue was filtered through a pad of silica to afford alcohols (*R*)-**6** and (*R*)-**23** which were used immediately in the next step.

To a stirred solution of the mixture of (*R*)-**6** and (*R*)-**23** (55 mg) in dichloromethane (5 mL) at -78 ˚C was added trifluoroacetic acid (25 µL) and the mixture was stirred at this temperature for 1 h. The reaction was quenched with trimethylamine (0.03 mL) and warmed to room temperature. Water (5 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) dried ($MgSO_4$), filtered and concentrated *in vacu*o. Purification by flash chromatography (ethyl acetate\hexanes, 2:3) gave a mixture of *title compounds* (30 mg, 60% over two steps) as a colourless solid in a 9:1:1 ratio.

$[\alpha]_D^{27.5}$ +6.3 (c 0.27, $CHCl_3$); **R**$_f$: 0.20 (3:10 ethyl acetate\hexanes); **IR** ν_{max} (neat): 3361, 2924, 2854, 1738, 1661, 1584, 1466, 1352, 1260, 1081, 1058, 1015, 802, 760, 733, 692; **HRMS**: found $[M + Na]^+$ 431.1476, $[C_{24}H_{24}O_6 + Na]^+$ requires 431.1479. NMR data as described for (-)-**1**, (-)-**2** and (-)-**24**.

Calculating the enantiomeric excess of (-)-pestalospirane B and (+)-pestalospirane B

Preparation of racemic pestalospirane B diEOM ether (±)-25



To a stirred solution of benzo[*c*]oxepin **12** (20 mg, 0.08 mmol) in methanol (5 mL) at 0 ˚C was added cerium (III) chloride heptahydrate (63.5 mg, 0.17 mmol) and sodium borohydride (7 mg, 0.17 mmol) and stirred for 10 min. The reaction was quenched with water (2 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* affording alcohol (±)-**6** which was used immediately in the next step.

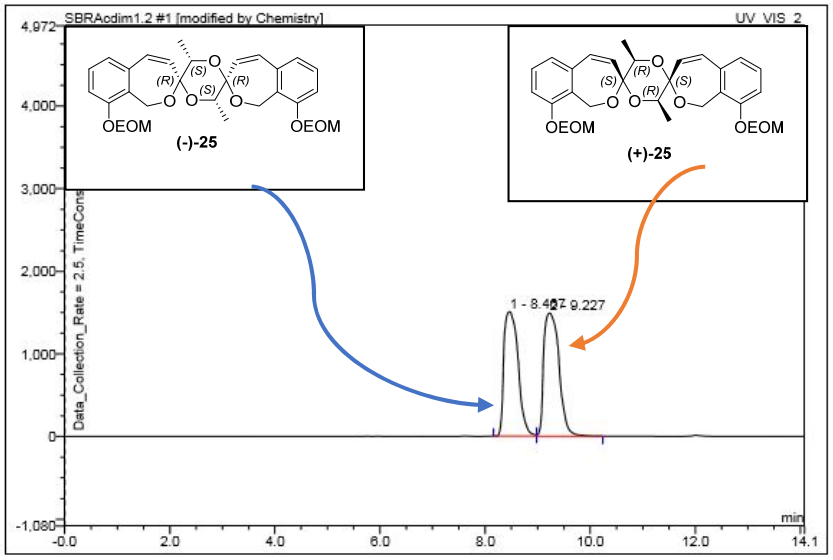
To a stirred solution of crude alcohol (±)-**6** (20 mg, 0.08 mmol) in dichloromethane (5 mL) at -78 ˚C and was added trifluoroacetic acid (1 drop) and stirred at this temperature for 1 h. The reaction was quenched with trimethylamine (0.03 mL) and warmed to room temperature. Water (5 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) dried ($MgSO_4$), filtered and concentrated *in vacu*o. Purification by flash chromatography (ethyl acetate\hexanes, 2:3) gave a mixture of *title compound* (±)-**2** (13 mg, 0.03 mmol, 75% over two steps) as a colourless solid and along with trace quantities of (±)-**1** and (±)-**24**, NMR data described for the enantioenriched mixture.

To a mixture of (±)-**2**, (±)-**1** and (±)-**24** (3 mg, 7 μmol) in dichloromethane (2 mL) at 0 ˚C was added DIPEA (0.15 mL, 8 μmol) dropwise, followed by chloromethyl ethyl ether (55 μL, 7 μmol). The reaction mixture was then warmed to room temperature and stirred for 16 h. The reaction was quenched with water (1 mL), washed with brine (3 x 2 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by preparatory TLC (ethyl acetate/hexanes, 2:3) gave the *title compound* (2.3 mg, 4 μmol, 40%) as a colourless solid.

R_f: 0.35 (2:3 ethyl acetate\hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.22 (2H, t, *J* = 8.0 Hz, H-7 and H-7'), 7.07 (2H, d, *J* = 8.4 Hz, H-6 and H-6'), 6.98 (2H, d, *J* = 7.7 Hz, H-8 and H-8'), 6.68 (2H, d, *J* = 12.7 Hz, H-5 and H-5'), 5.98 (2H, d, *J* = 12.5 Hz, H-4 and H-4'), 5.25 (4H, q, *J* = 6.8 Hz, 2 × $OCH_2OCH_2CH_3$), 5.17 (2H, d, *J* = 13.7 Hz, H-1ab and H-1'ab), 4.62 (2H, d, *J* = 13.7 Hz, H-1ab and H-1'ab), 4.14 (2H, q, *J* = 6.5 Hz, H-2 and H-2'), 3.73 (4H, q, *J* = 7.5 Hz, 2 × $OCH_2OCH_2CH_3$), 1.23 (6H, t, *J* = 6.8 Hz, 2 × $OCH_2OCH_2CH_3$), 1.06 (6H, d, *J* = 6.4 Hz, 2 × $CHCH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.1 (2 × C_q, C-9 and C-9'), 136.8 (2 × C_q, C-11 and C-11'), 131.3 (2 × CH_2, C-5 and C-5'), 131.1 (2 × CH_2, C-4 and C-4'), 129.5 (2 × C_q, C-10 and C-10') 128.2 (2 × CH, C-7 and C-7'), 124.2 (2 × CH, C-6 and C-6'), 113.9 (2 × CH, C-8 and C-8'), 104.1 (2 × C_q, C-2 and C-2'), 94.1 (2 × CH_2, $OCH_2OCH_2CH_3$), 67.0 (2 × CH, C-3 and C-3'), 64.6 (2 × CH_2, $OCH_2OCH_2CH_3$), 57.0 (2 × CH_2, C-1 and C-1'), 16.3 (2 × CH_3, $CH(CH_3)$), 15.2 (2 × CH_3, $OCH_2OCH_2CH_3$); **IR ν_{max}** (neat): 2924, 2854, 2166,

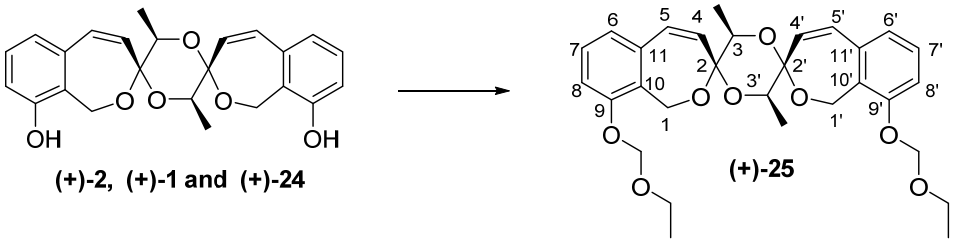
1978, 1737, 1670, 1460, 1377, 1259, 1216, 1017, 797, 740 cm^{-1}; **HRMS**: found $[M + Na]^+$ 547.2299, $[C_{30}H_{36}O_8 + Na]^+$ requires 547.2302.

Figure 1. Chiral HPLC trace (±)-25



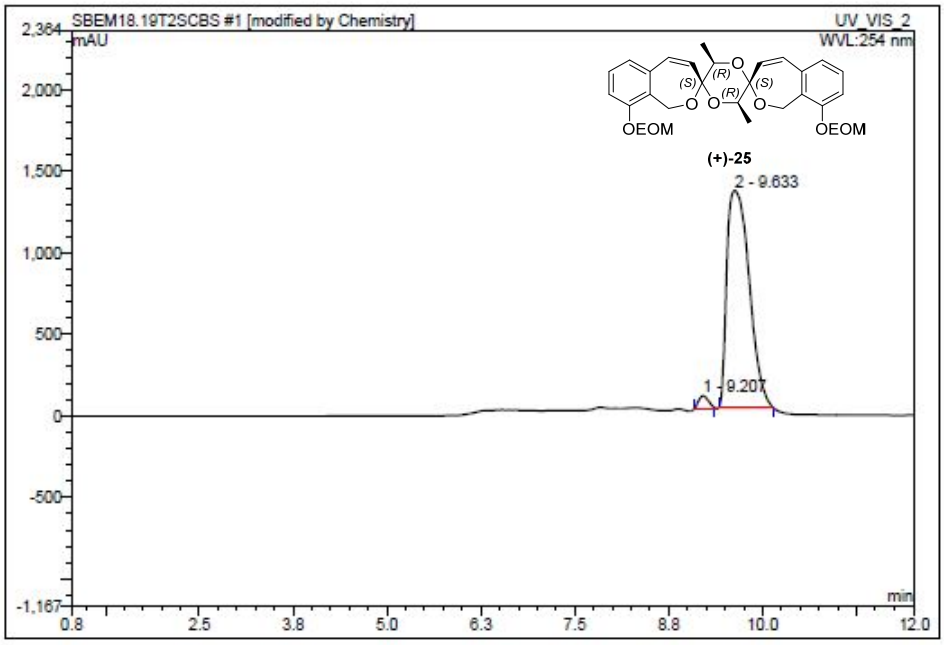
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.47	n.a.	1504.513	472.098	48.55	n.a.	BM *
2	9.23	n.a.	1487.304	500.229	51.45	n.a.	MB*
Total:			2991.817	972.327	100.00	0.000	

(+)-Pestalospirane B diEOM ether (+)-25



To a mixture of (+)-**2**, (+)-**1** and (+)-**24** (3 mg, 7 µmol) in dichloromethane (2 mL) at 0 ˚C was added DIPEA (0.15 mL, 8 µmol) dropwise, followed by chloromethyl ethyl ether (55 µL, 7 µmol). The reaction mixture was then warmed to room temperature and stirred for 16 h. The reaction was quenched with water (1 mL), washed with brine (3 x 2 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by preparatory TLC (ethyl acetate/hexanes, 2:3) gave the *title compound* (2.3 mg, 4 µmol, 40%) as a colourless solid **e.e = 97%** (HPLC, Chiralpak® AD-H, hexanes/isopropanol (1:10), t_1 (R) = 9.21 min, t_2 (S) = 9.63 min; $[\alpha]_D^{27.5}$ +25.2 (c 0.25, $CHCl_3$); NMR data as described for previously (±)-**25**.

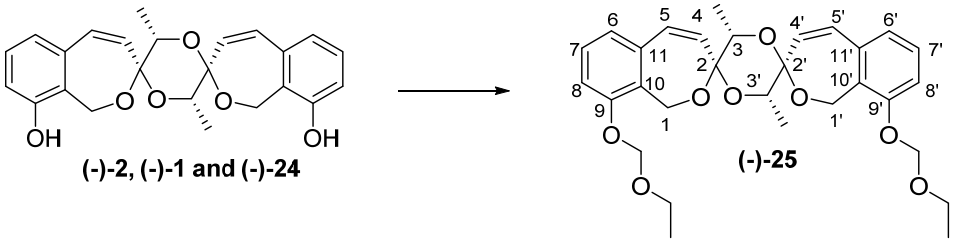
Figure 2. Chiral HPLC trace (+)-25



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.21	n.a.	77.827	11.943	2.54	n.a.	BM *
2	9.63	n.a.	1330.253	457.952	97.46	n.a.	BMB*
Total:			1408.081	469.895	100.00	0.000	

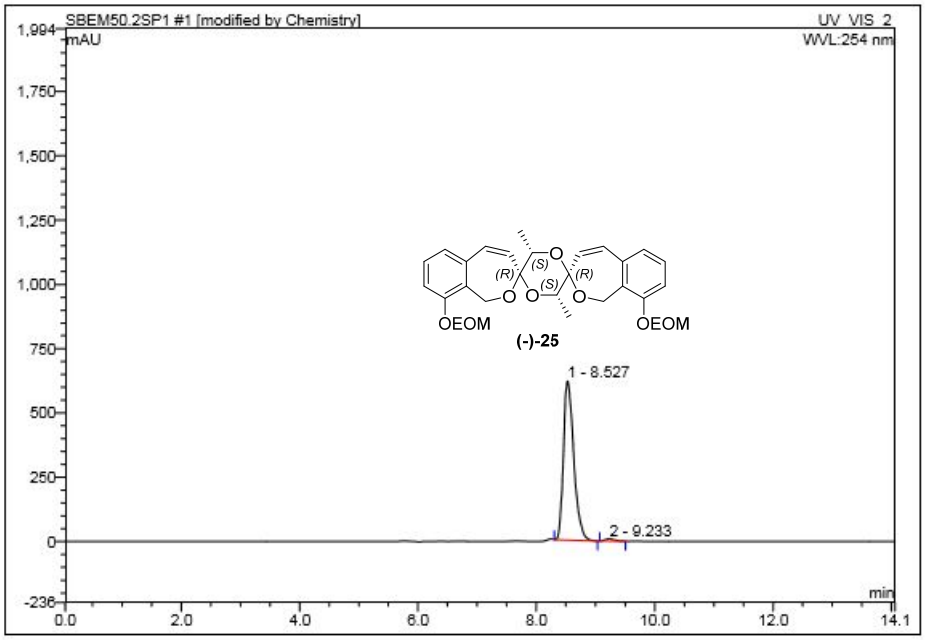
HPLC conditions: Chiralpak® AD-H, hexanes\isopropanol (1:10), flow rate: 0.5 min/mL: t_1 (*R,S,S,R*) = 9.21 min, t_2 (*S,R,R,S*) = 9.63 min

(-)-Pestalospirane B diEOM ether (-)-25



To a mixture of (-)-**2**, (-)-**1** and (-)-**24** (3 mg, 7 µmol) in dichloromethane (2 mL) at 0 ˚C was added DIPEA (0.15 mL, 8 µmol) dropwise, followed by chloromethyl ethyl ether (55 µL, 7 µmol). The reaction mixture was then warmed to room temperature and stirred for 16 h. The reaction was quenched with water (1 mL), washed with brine (3 x 2 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by preparatory TLC (ethyl acetate\hexanes, 2:3) gave the *title compound* (2.3 mg, 4 µmol, 40%) as a colourless solid **e.e = 98%** (HPLC, Chiralpak® AD-H, hexanes/isopropanol (4:40), t_1 (R) = 8.53 min, t_2 (S) = 9.23 min; $[\alpha]_D^{27.5}$ -24.0 (c 0.25, $CHCl_3$); NMR data as described for (±)-**25**.

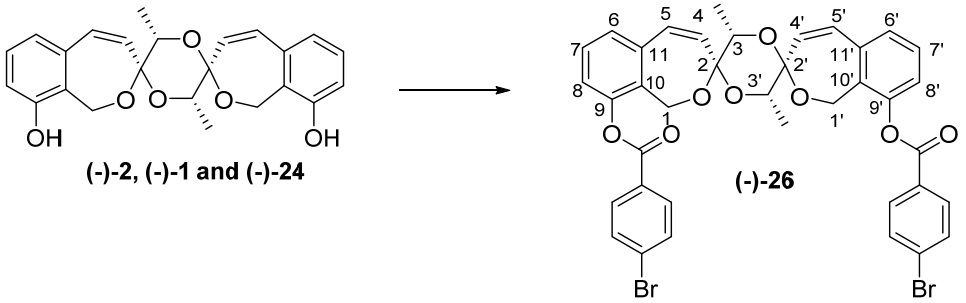
Figure 3. Chiral HPLC trace of (-)-25



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.53	n.a.	617.157	124.629	98.64	n.a.	BMB*
2	9.23	n.a.	8.822	1.718	1.36	n.a.	BMB*
Total:			625.979	126.346	100.00	0.000	

HPLC conditions: Chiralpak® AD-H, hexanes\isopropanol (1:10), flow rate: 0.5 min/mL: t_1 (*R,S,S,R*) = 8.53 min, t_2 (*S,R,R,S*) = 9.23 min

(3*R*,3'*S*,5'*R*,6'*S*)-9''-(4-bromobenzoyloxy)-3',6'-dimethyl-1*H*,1''*H*-dispiro[2-benzoxepine-3,2'-[1,4]dioxane-5',3''-[2]benzoxepine]-9-yl 4-bromobenzoate (-)-26



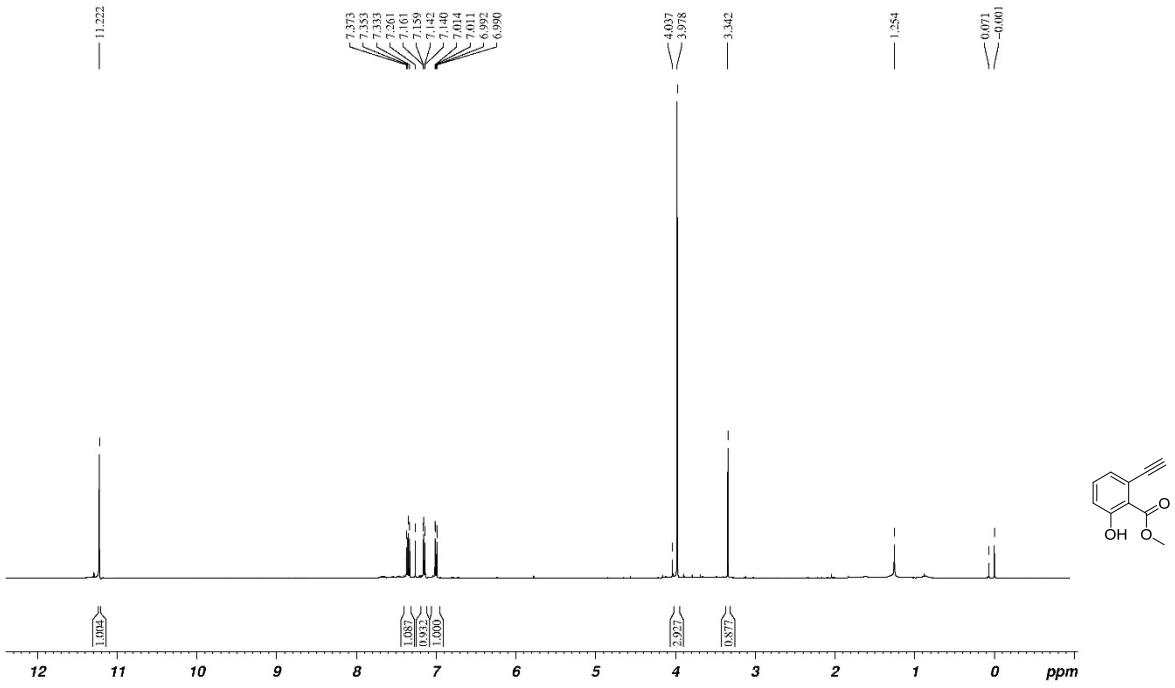
To a mixture of (-)-**2**, (+)-**1** and (+)-**24** (15 mg, 0.04 mmol) in dichloromethane (5 mL) at 0 ˚C was added DMAP (1 mg, 8 µmmol), triethylamine (22 µL, 0.16 mmol) and *p*-bromobenzoyl chloride (35 mg, 0.16 mmol) and stirred for 1.5 h. The reaction mixture was then quenched with water (2 mL) and the aqueous layer was separated and extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate\hexanes, 1:9) gave *title compound* which was recrystallized from methanol\dichloromethane\hexanes (1:1:1) at -4 ˚C to give the *title compound* (24 mg, 0.03 mmol, 80%) as a colourless crystal.

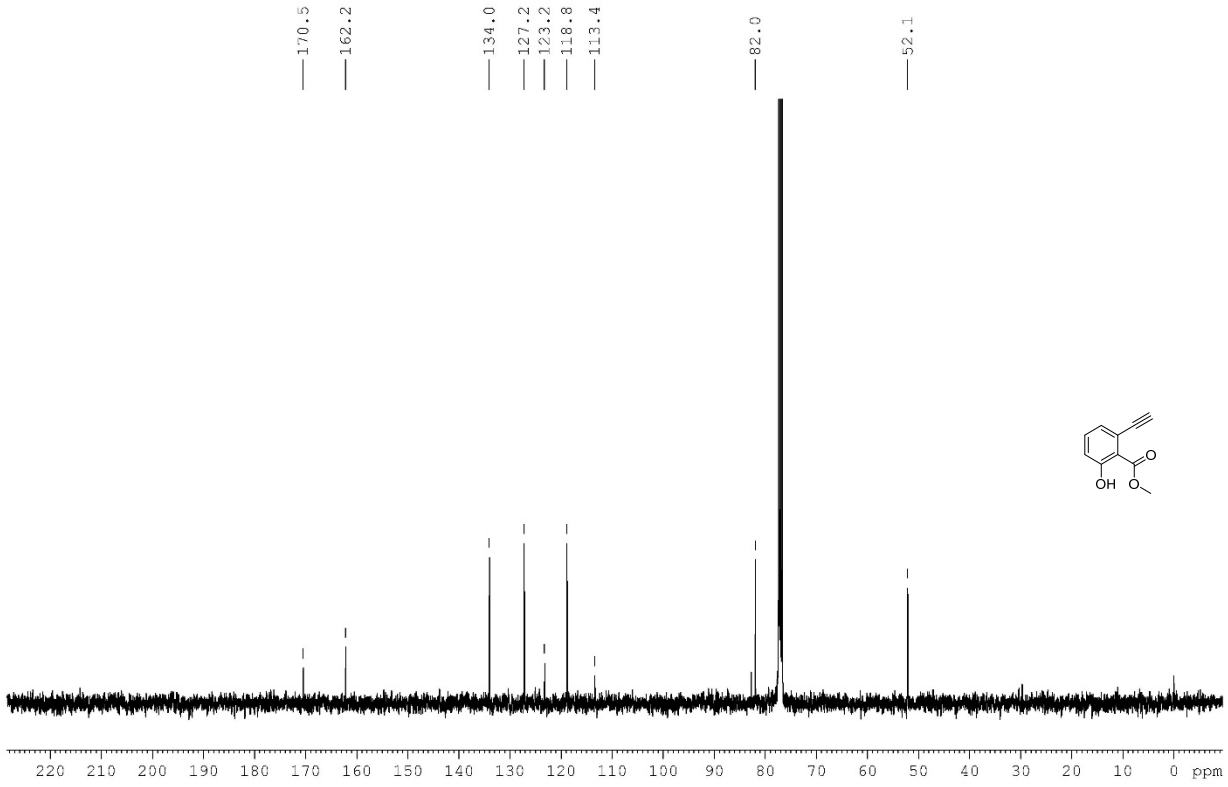
$[\alpha]_D^{27.5}$ -39.0 (c 0.30, $CHCl_3$); **M.p:** 252-255 ˚C; $\mathbf{R_f}$: 0.40 (1:4 ethyl acetate\hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09 (4H, d, *J* = 8.5 Hz, Ar-H), 7.68 (4H, d, *J* = 8.5 Hz, Ar-H), 7.35 (2H, t, *J* = 7.7 Hz,

H-7 and H-7'), 7.28 (2H, m, H-6 and H-6'), 7.01 (2H, d, J = 7.7 Hz, H-8 and H-8'), 6.76 (2H, d, J = 12.5 Hz, H-5 and H-5'), 6.00 (2H, d, J = 12.5 H-4 and H-4'), 4.67 (2H, s, H-1 and H-1'), 4.06 (2H, q, J = 6.6 Hz, H-3 and H-3'), 1.03 (6H, d, J = 6.8 Hz, CH(CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.6 (2 × C_q, C=O), 147.4 (2 × C_q, C-9 and C-9'), 137.1 (2 × C_q, C-11 and C-11'), 132.3 (2 × CH, Ar-C), 131.9 (4 × CH, Ar-C), 131.5 (2 × CH, C-4 and C-4'), 130.7 (2 × CH, C-5 and C-5'), 129.3 (2 × C_q, Ar-C), 128.8 (2 × CH, C-7), 128.3 (2 × CH, C-6 and C-6'), 128.1 (2 × C_q, Ar-C) , 121.3 (2 × CH, C-8 and C-8'), 104.1 (2 × C_q, C-2 and C-2'), 67.1 (2 × CH, C-3 and C-3'), 57.5 (2 × CH_2, C-1 and C-1'), 16.1 (2 × CH_3, CH(*C*H_3); **IR ν_{max}** (neat): 2923, 2853, 2157, 2034, 1704, 1416, 1263, 1226, 1071, 1049, 1009, 804, 751 cm^{-1}; **HRMS**: found $[M + Na]^+$ 795.0210, $[C_{38}H_{30}Br_2O_8 + Na]^+$ requires 795.0200.

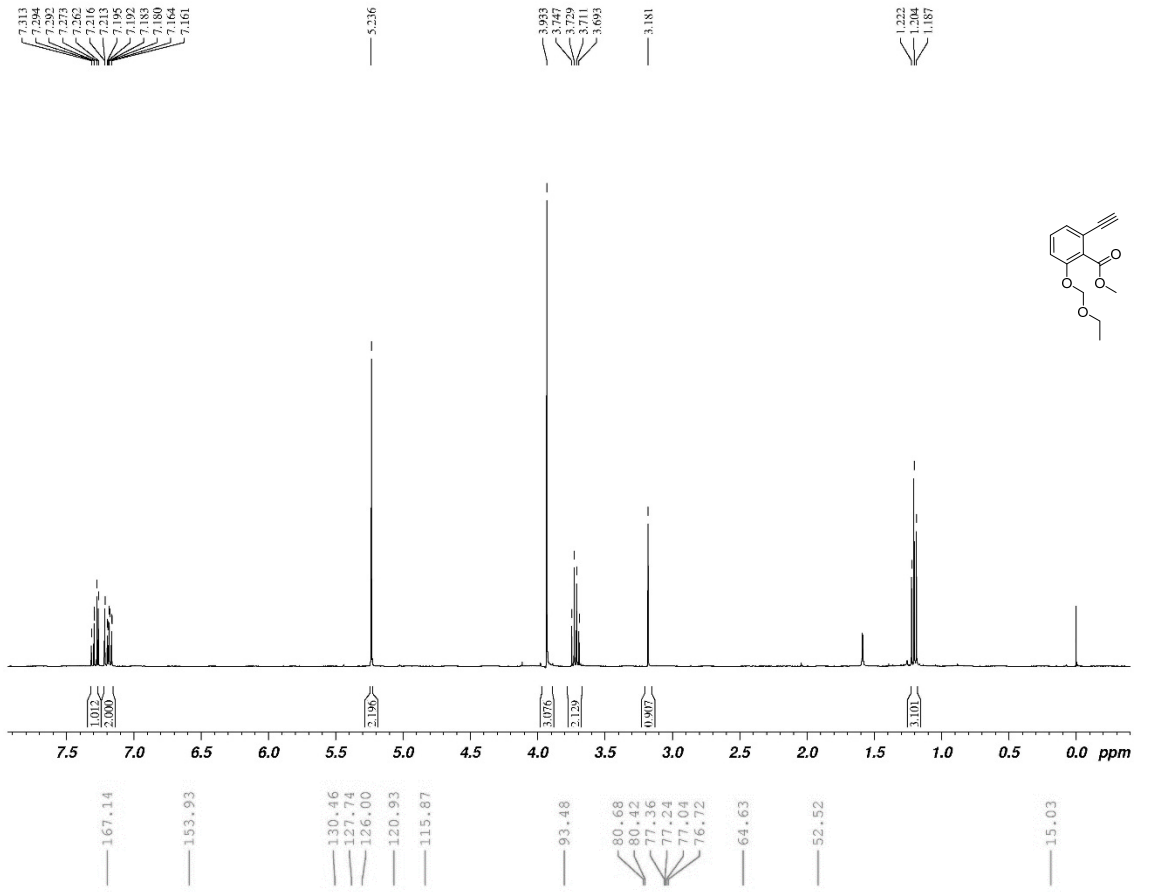
NMR Spectra

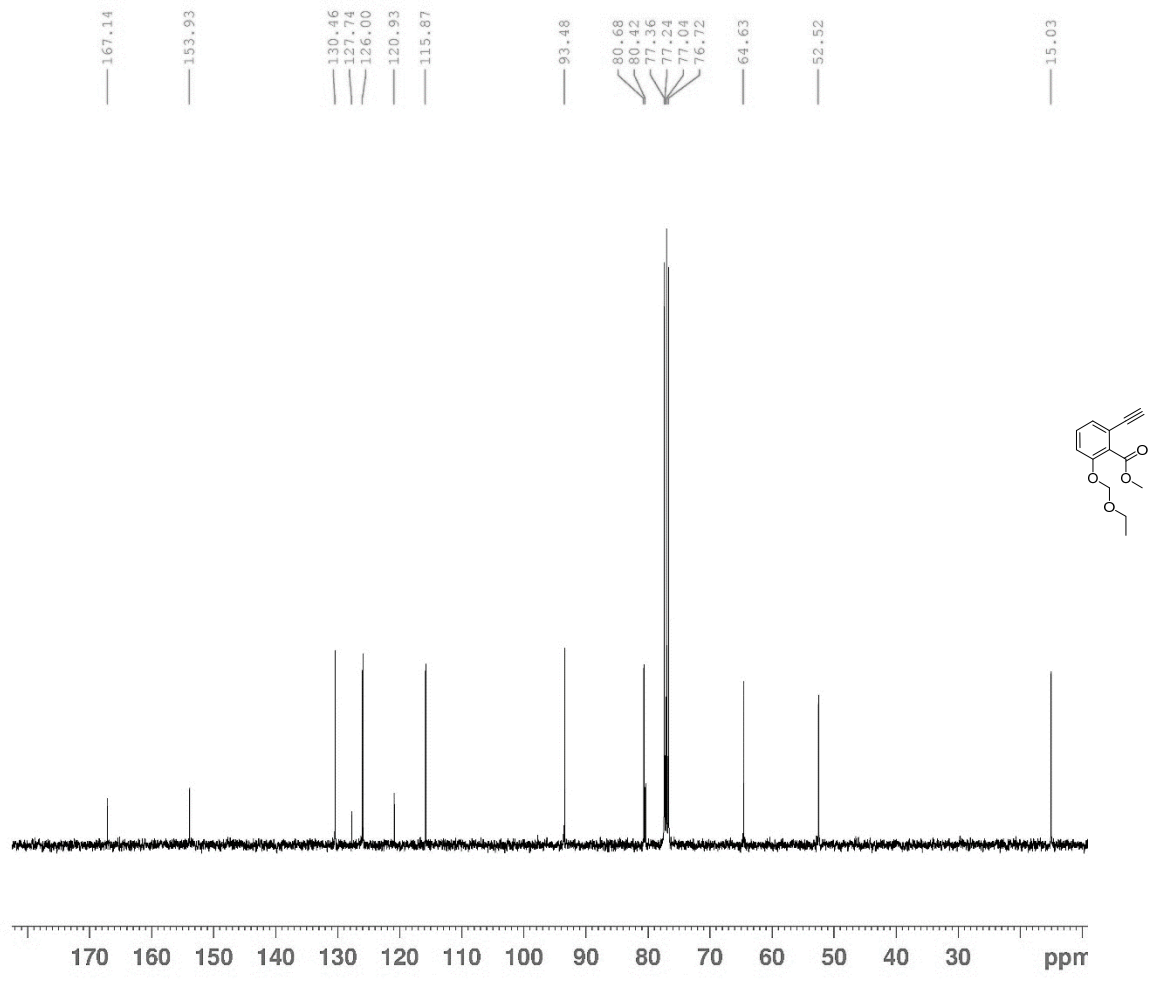
Methyl 2-ethynyl-6-hydroxybenzoate (S1)



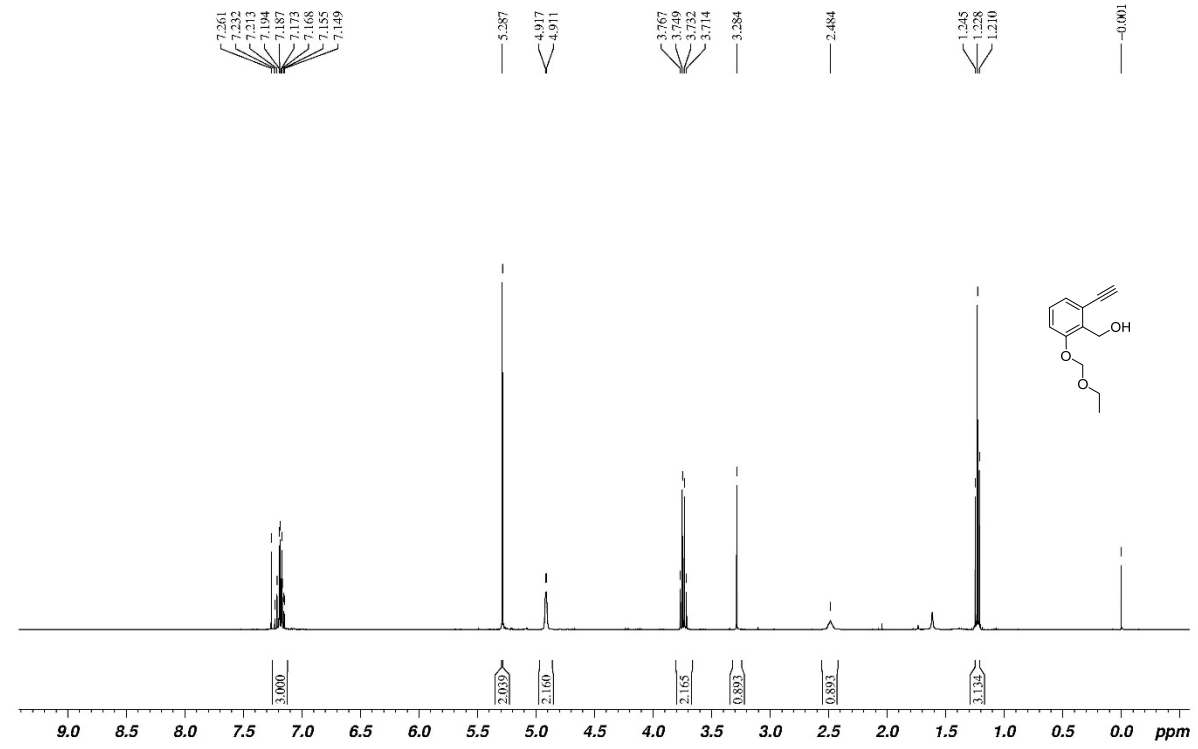


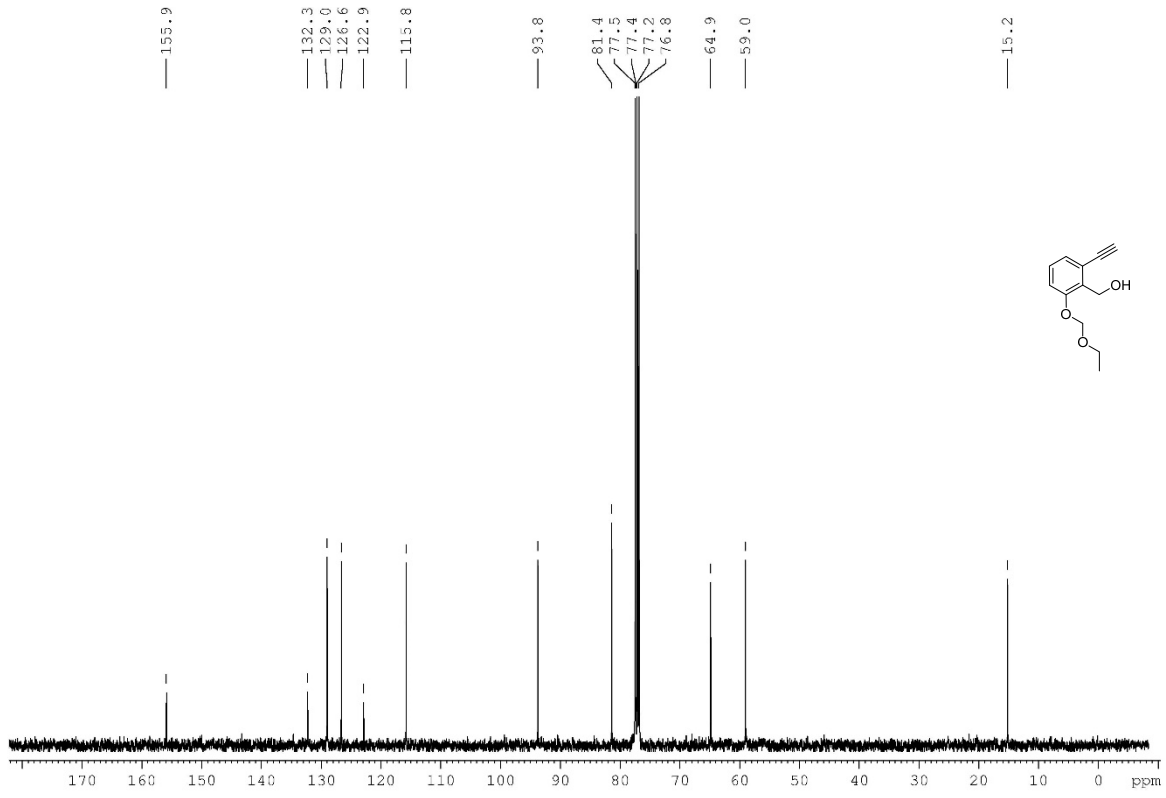
Methyl 2-(ethoxymethoxy)-6-ethynylbenzoate (S2)



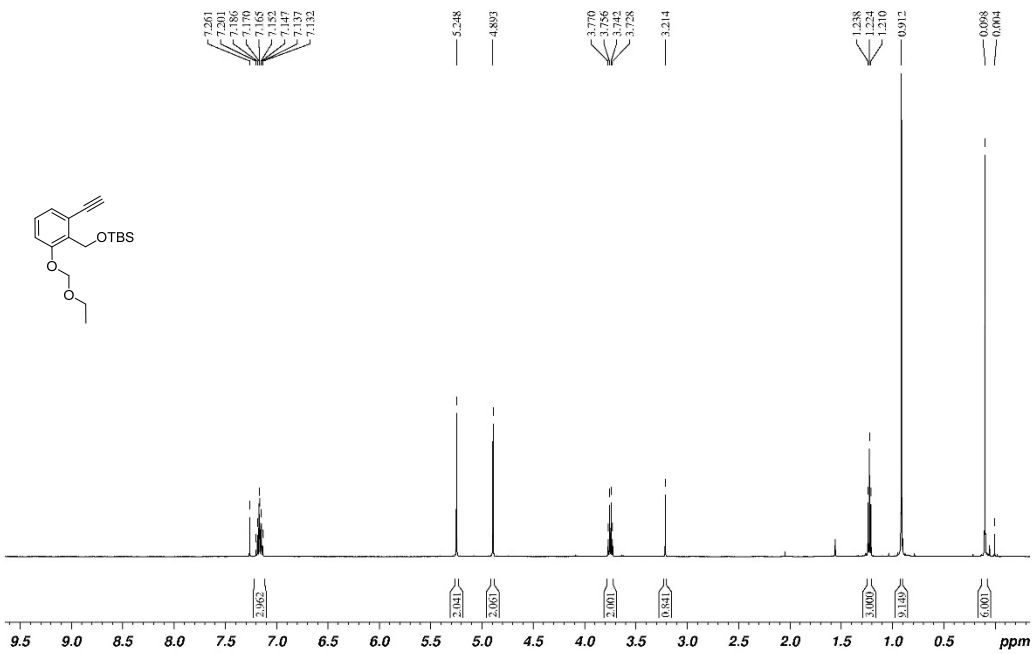


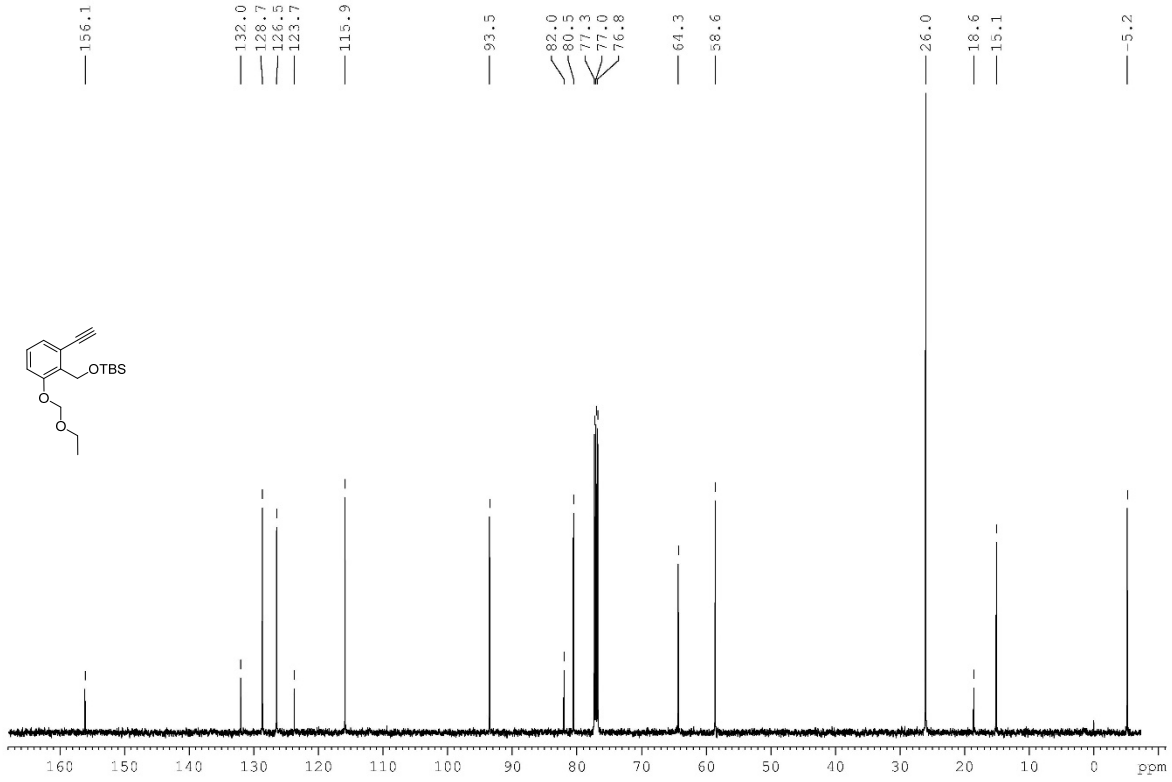
[2-(Ethoxymethoxy)-6-ethynylphenyl] methanol (S3)



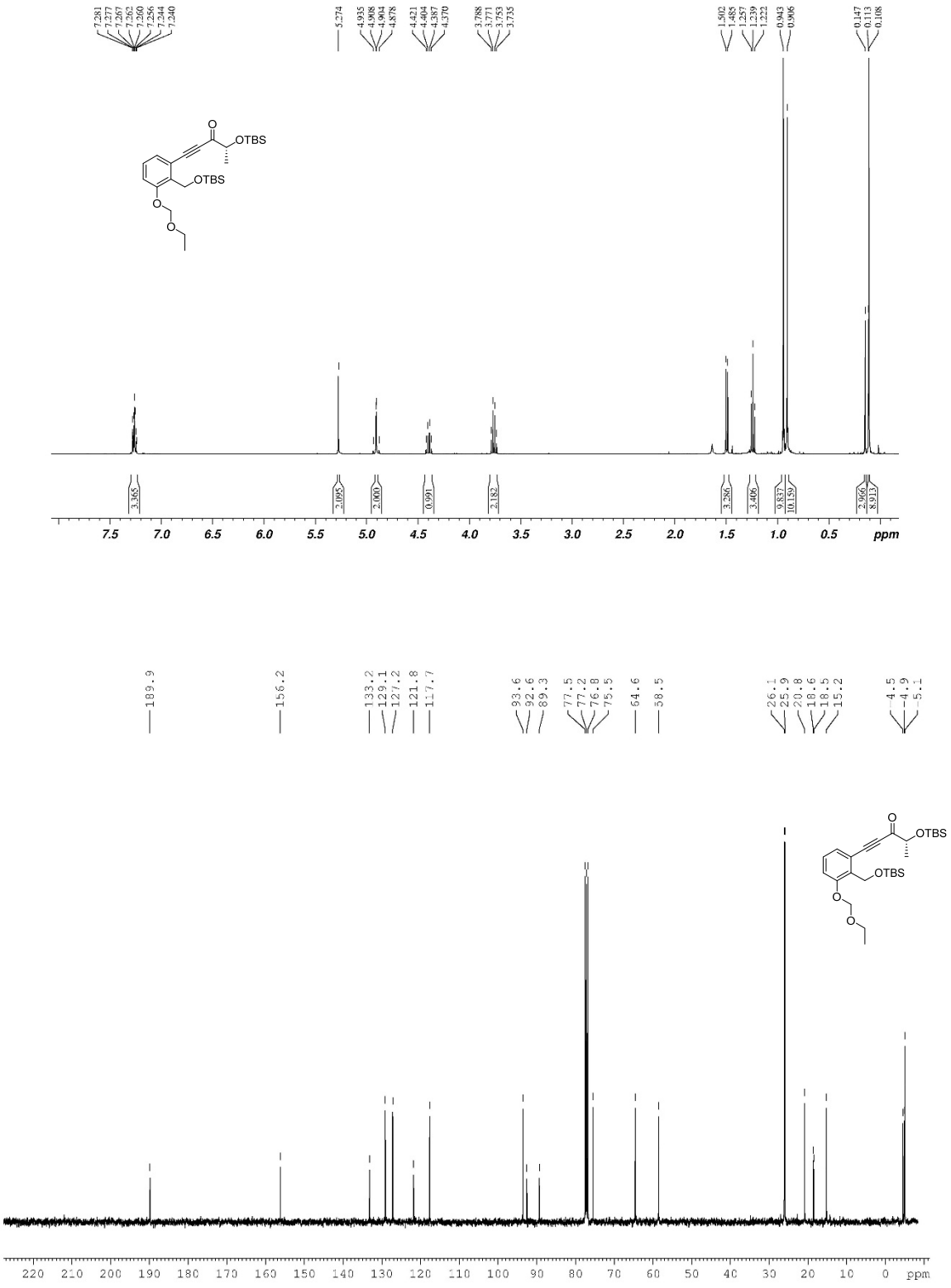


***tert*-Butyl({[2-(ethoxymethoxy)-6-ethynylphenyl]methoxy})dimethylsilane (9)**

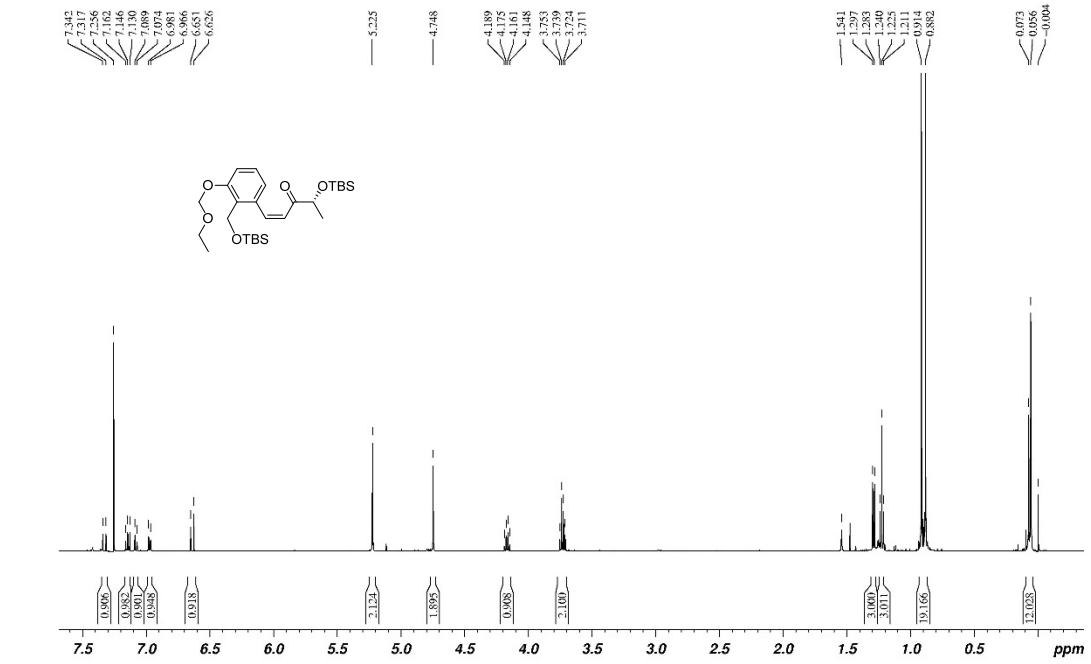


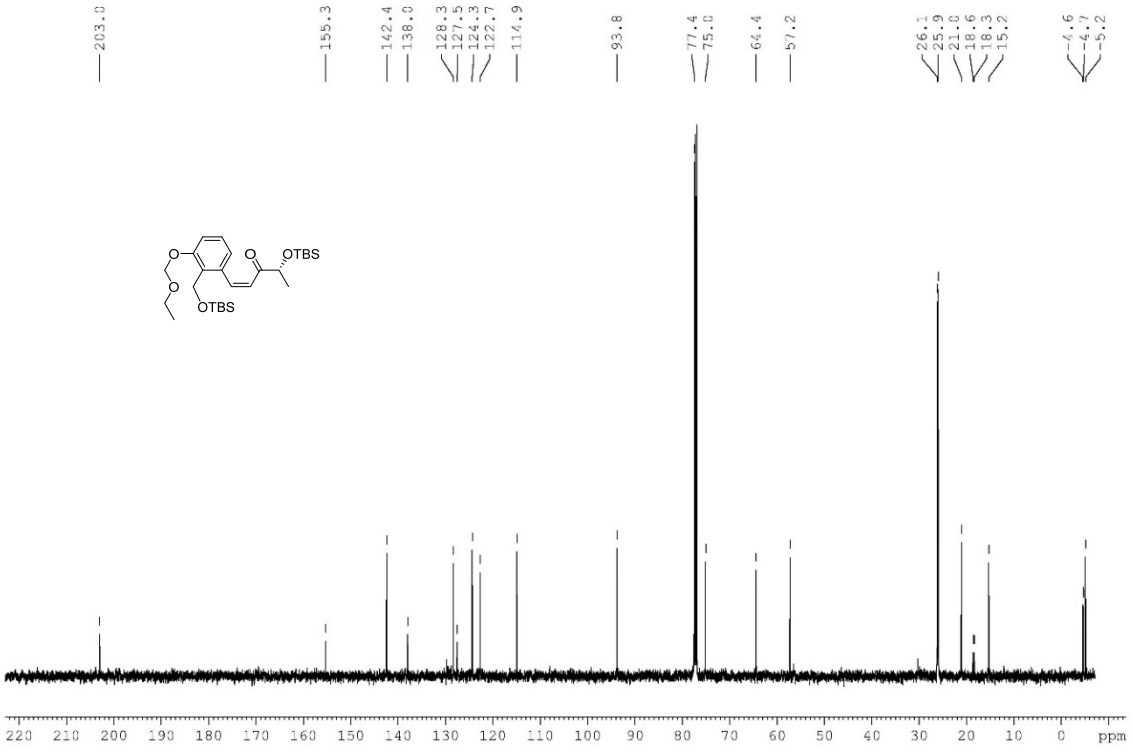


(*R*)-1-(2-{[(tert-butyldimethylsilyl)oxy]methyl}-3-(ethoxymethoxy)phenyl)-4-hydroxypent-1-yn-3-one (11)

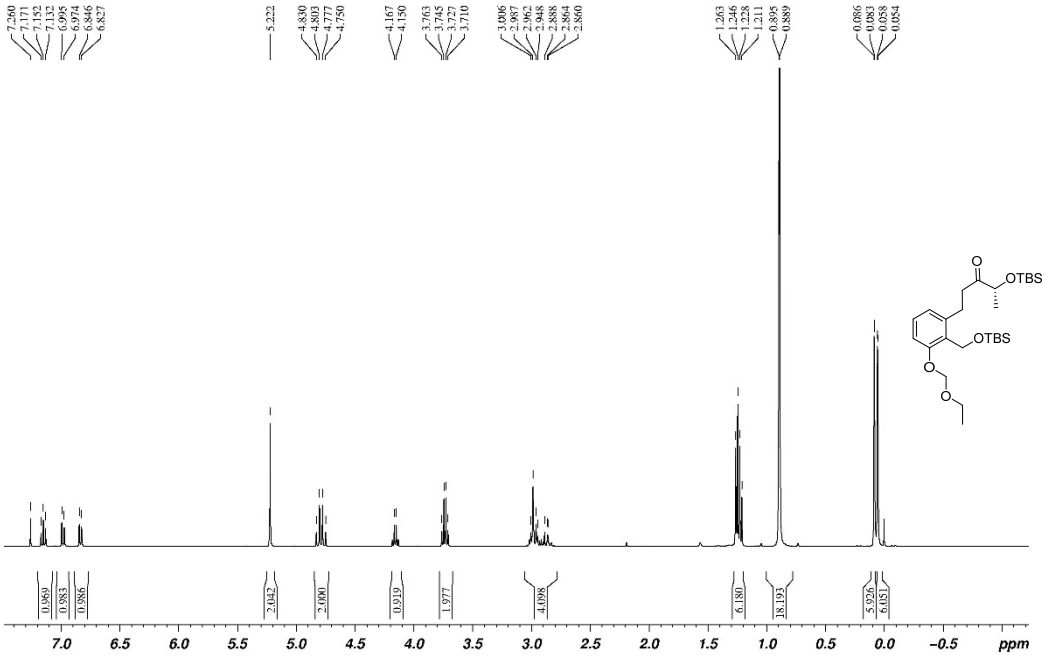


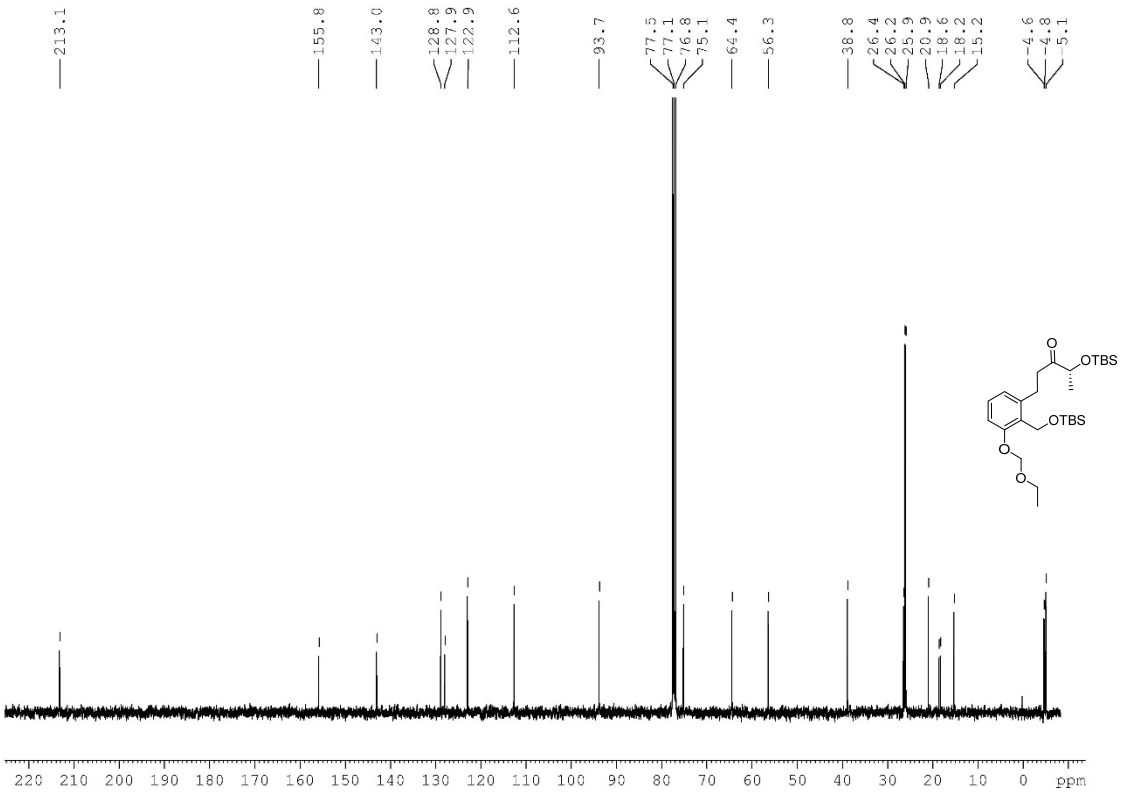
Bis((*Z*,*R*)-4-[(*tert*-butyldimethylsilyl)oxy]-1-(2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-3-(ethoxymethoxy)phenyl)pent-1-en-3-one) (7)



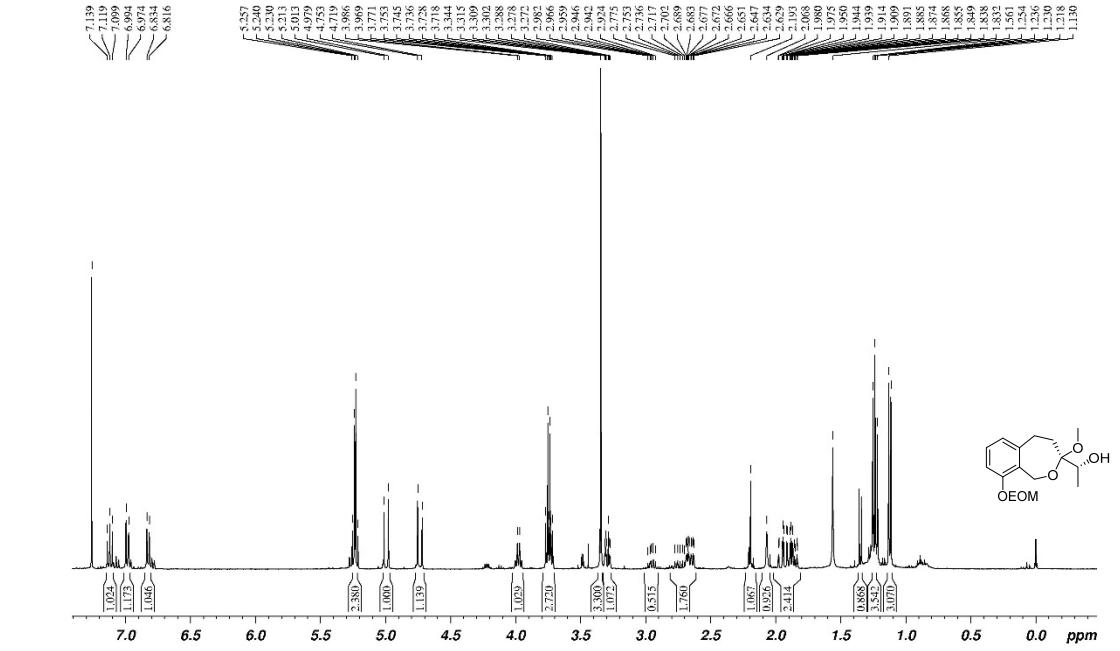


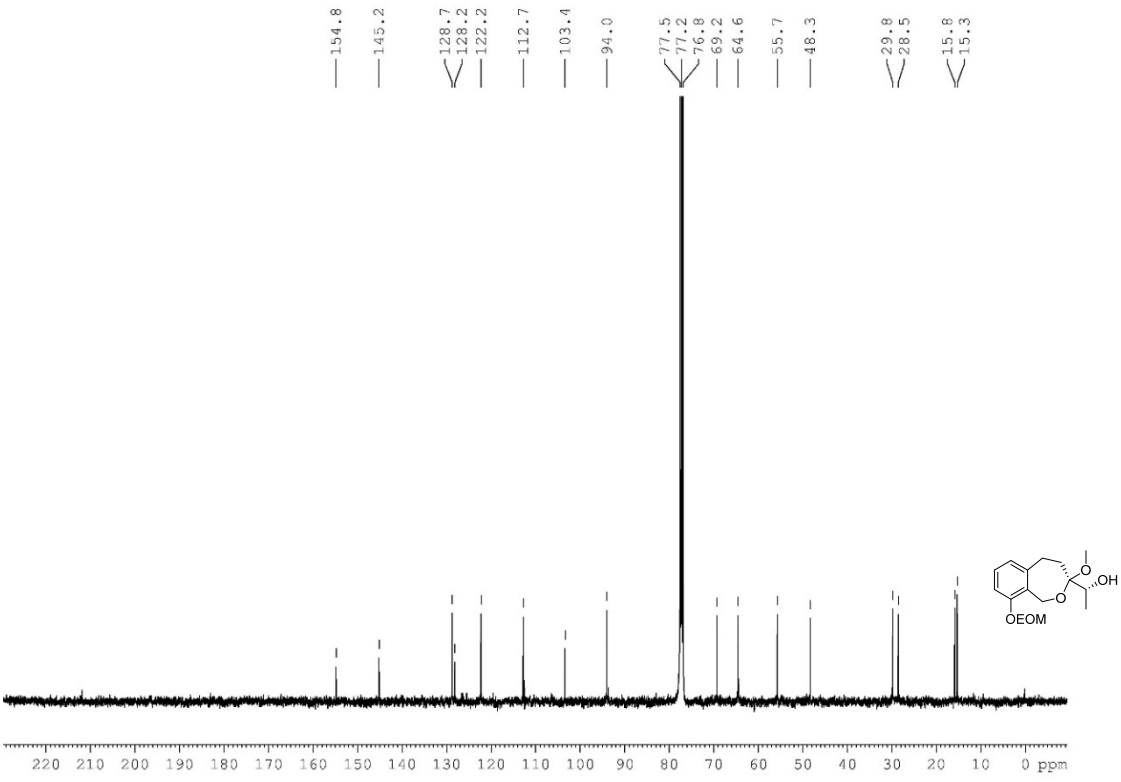
(*R*)-1-(2-{[(tert-butyldimethylsilyl)oxy]methyl}-3-(ethoxymethoxy)phenyl)-4-hydroxypentan-3-one **(14)**



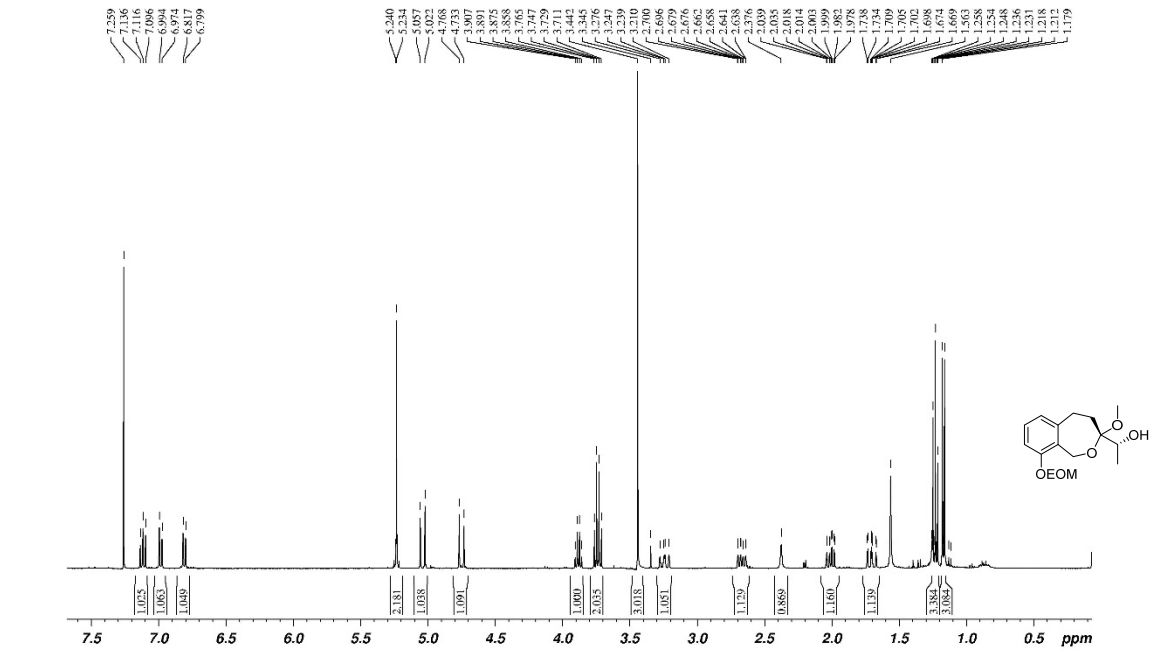


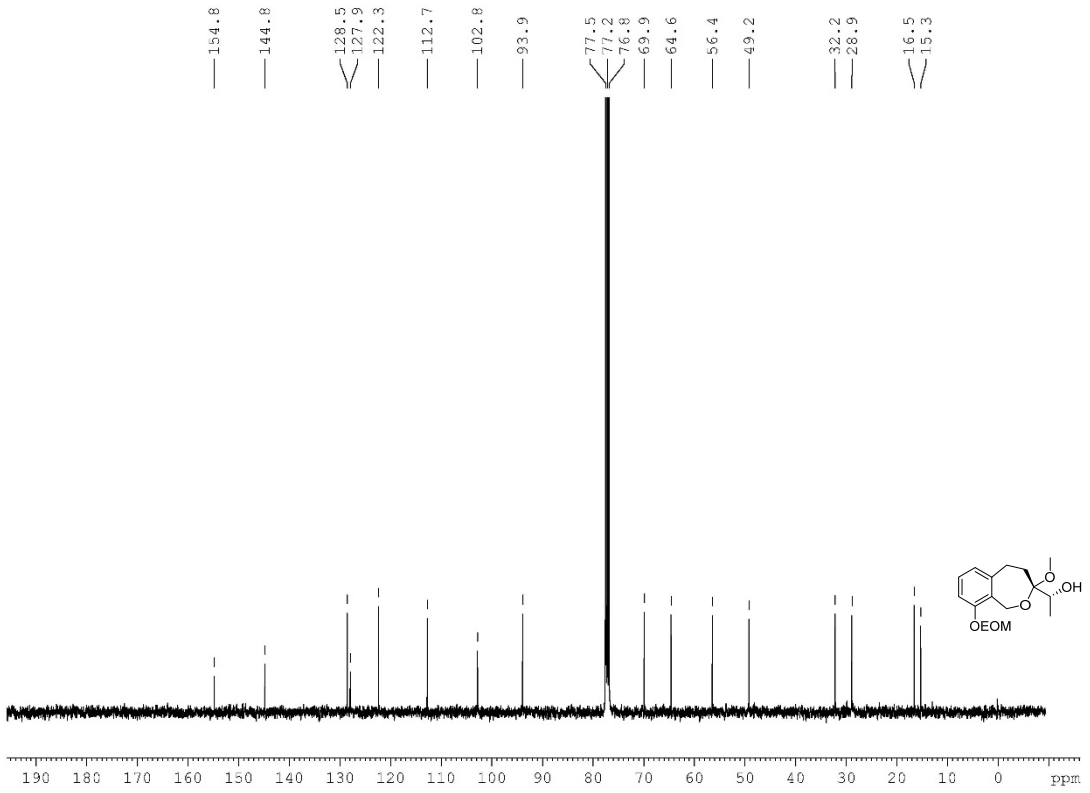
(*R*)-1-[(*R*)-9-(ethoxymethoxy)-3-methoxy-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (16a)



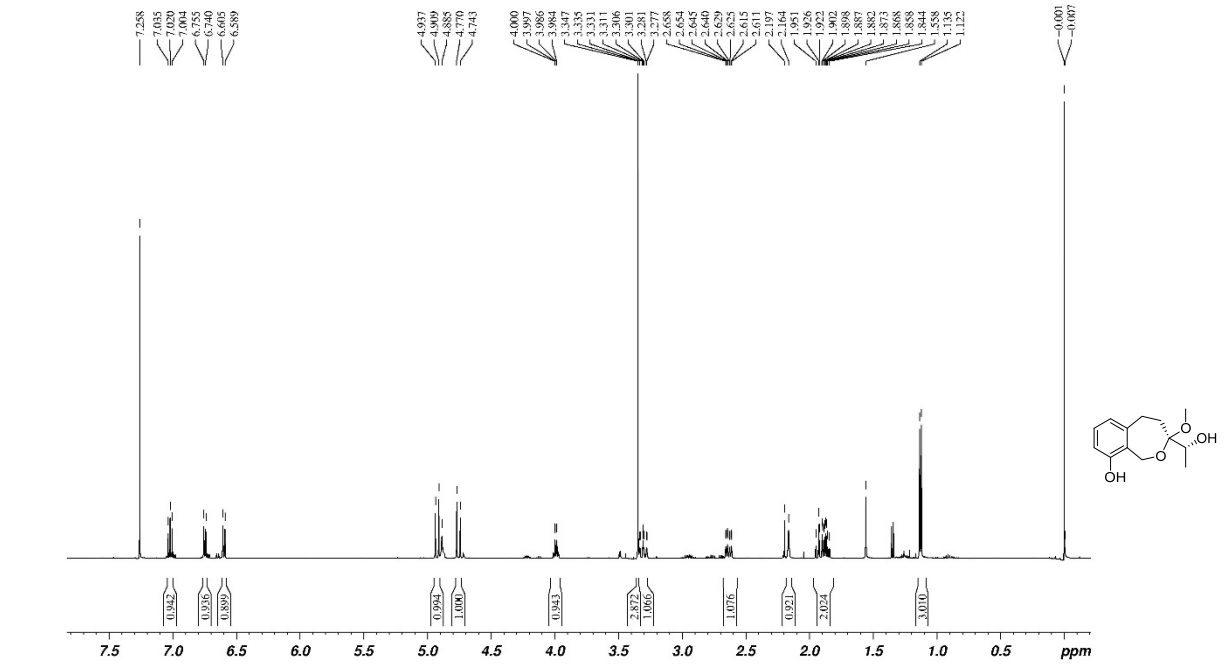


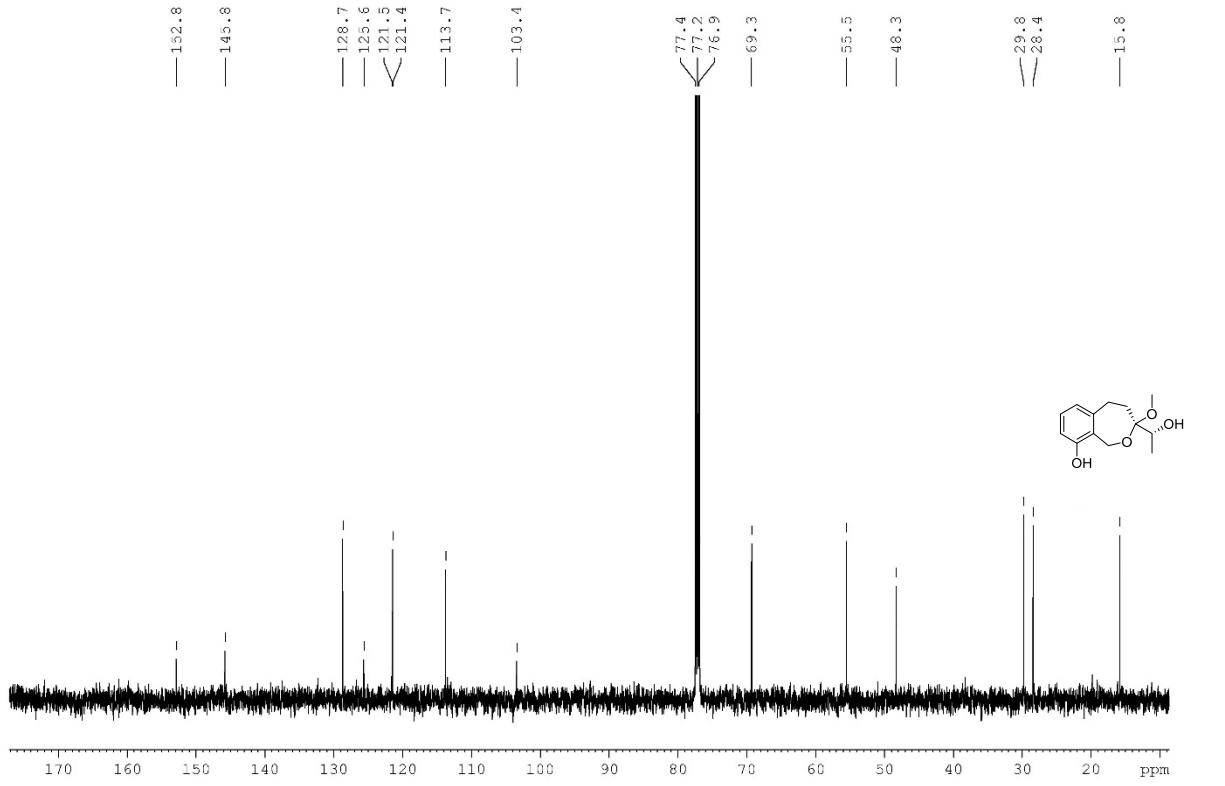
(*S*)-3-[(*R*)-1-hydroxyethyl]-3-methoxy-1,3,4,5-tetrahydro-2-benzoxepin-9-ol (16b)



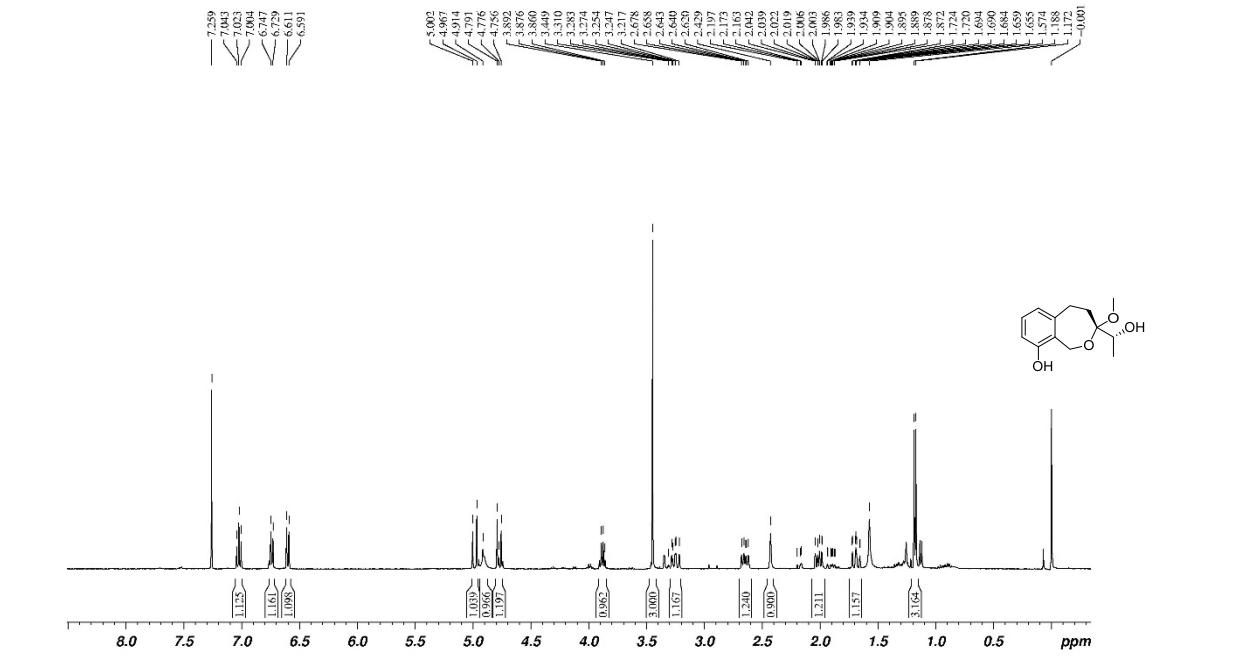


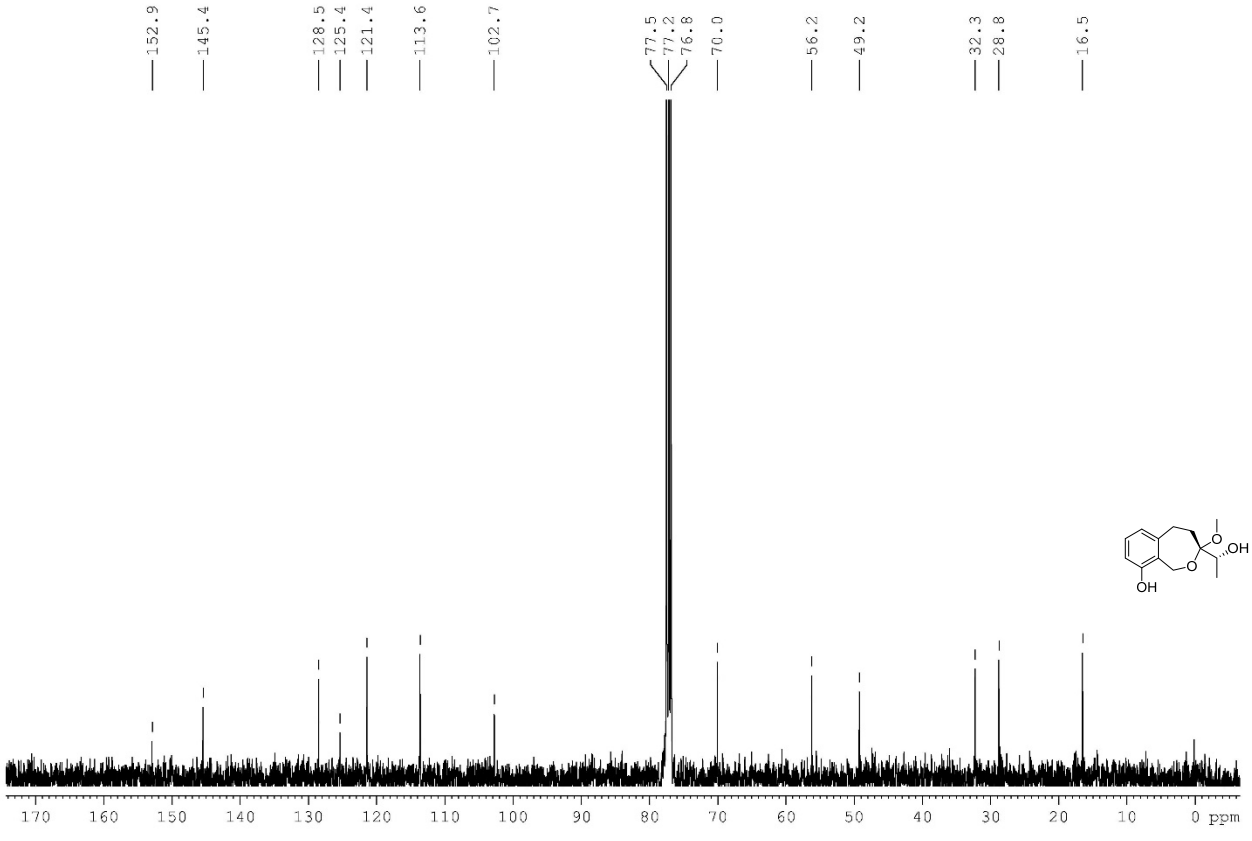
(*R*)-3-[(*R*)-1-hydroxyethyl]-3-methoxy-1,3,4,5-tetrahydro-2-benzoxepin-9-ol (15a)



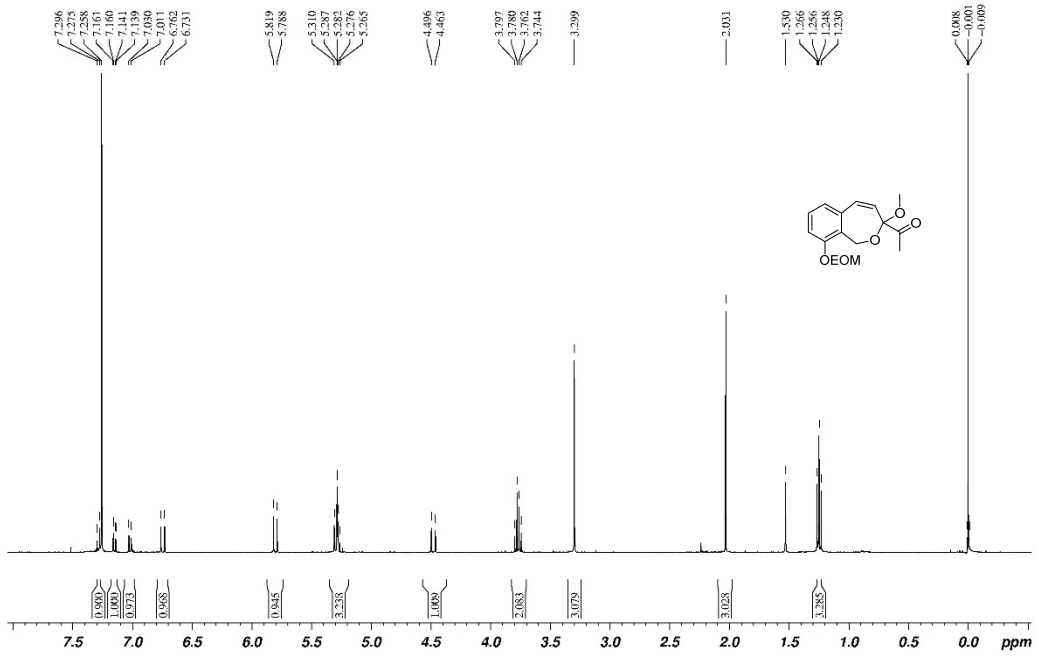


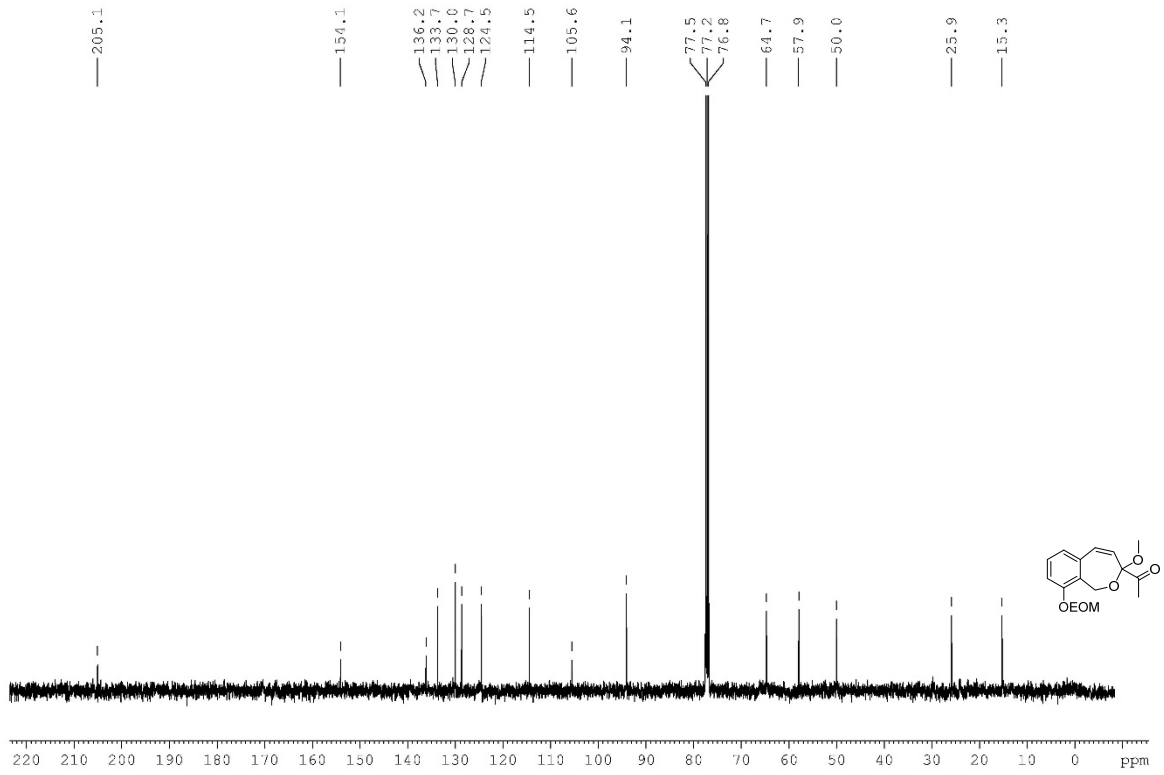
(*S*)-3-[(*R*)-1-hydroxyethyl]-3-methoxy-1,3,4,5-tetrahydro-2-benzoxepin-9-ol (15b)



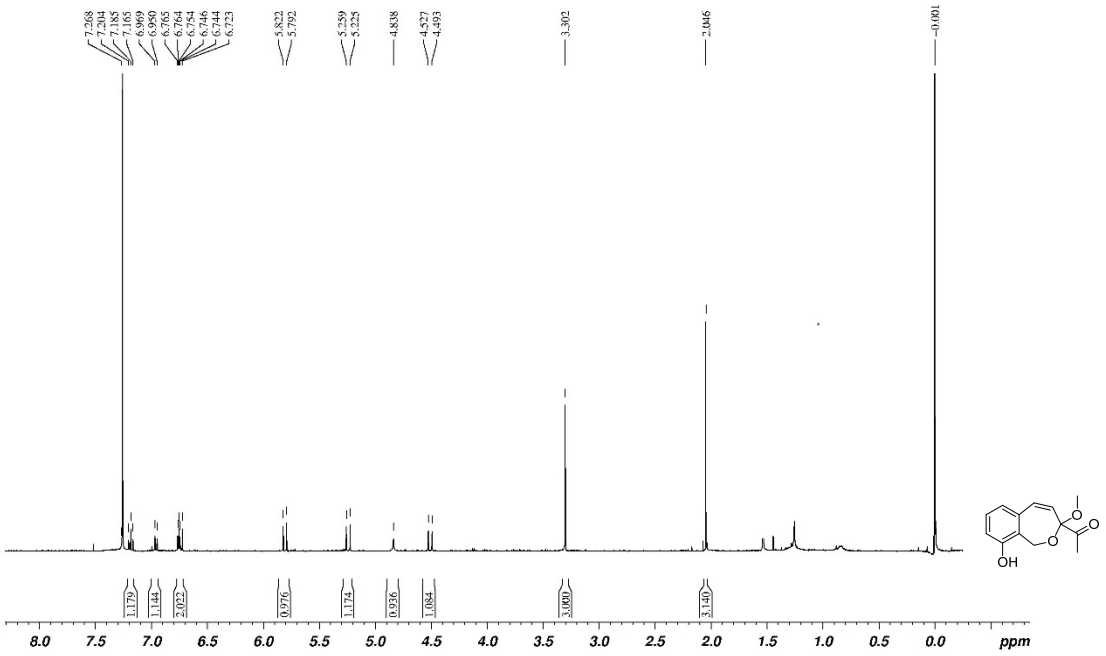


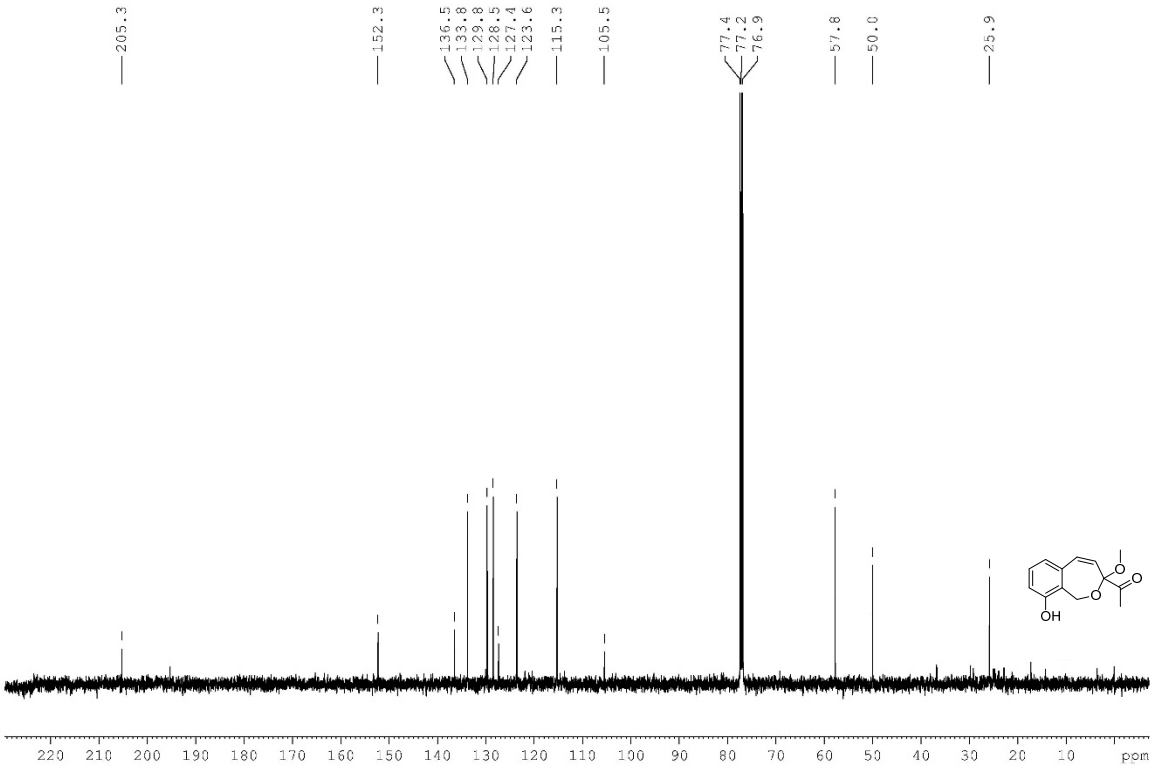
1-[9-(ethoxymethoxy)-3-methoxy-1,3-dihydro-2-benzoxepin-3-yl]ethan-1-one (13)



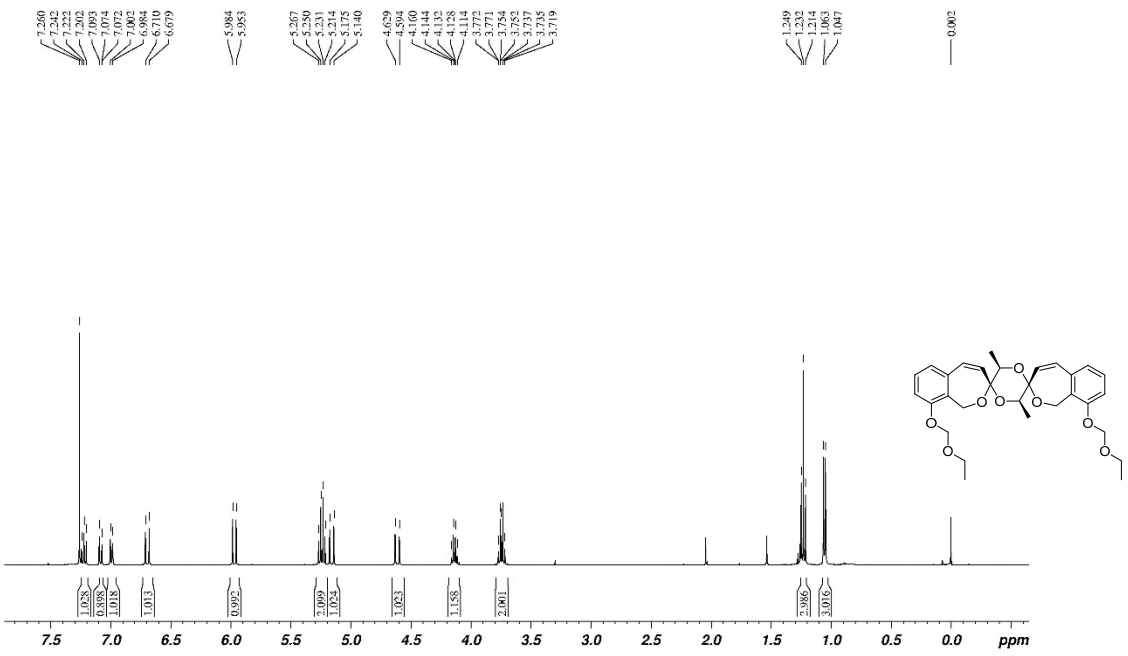


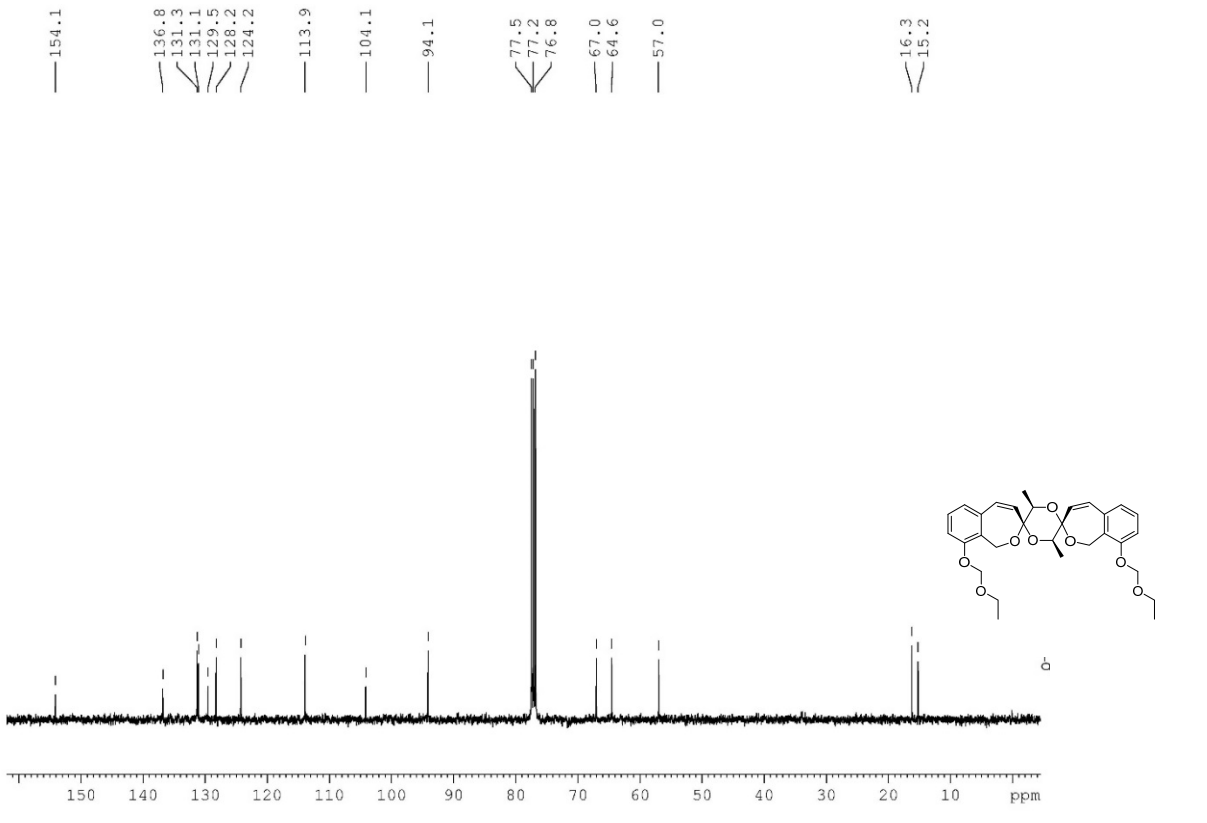
1-(9-hydroxy-3-methoxy-1,3-dihydro-2-benzoxepin-3-yl)ethan-1-one (12)



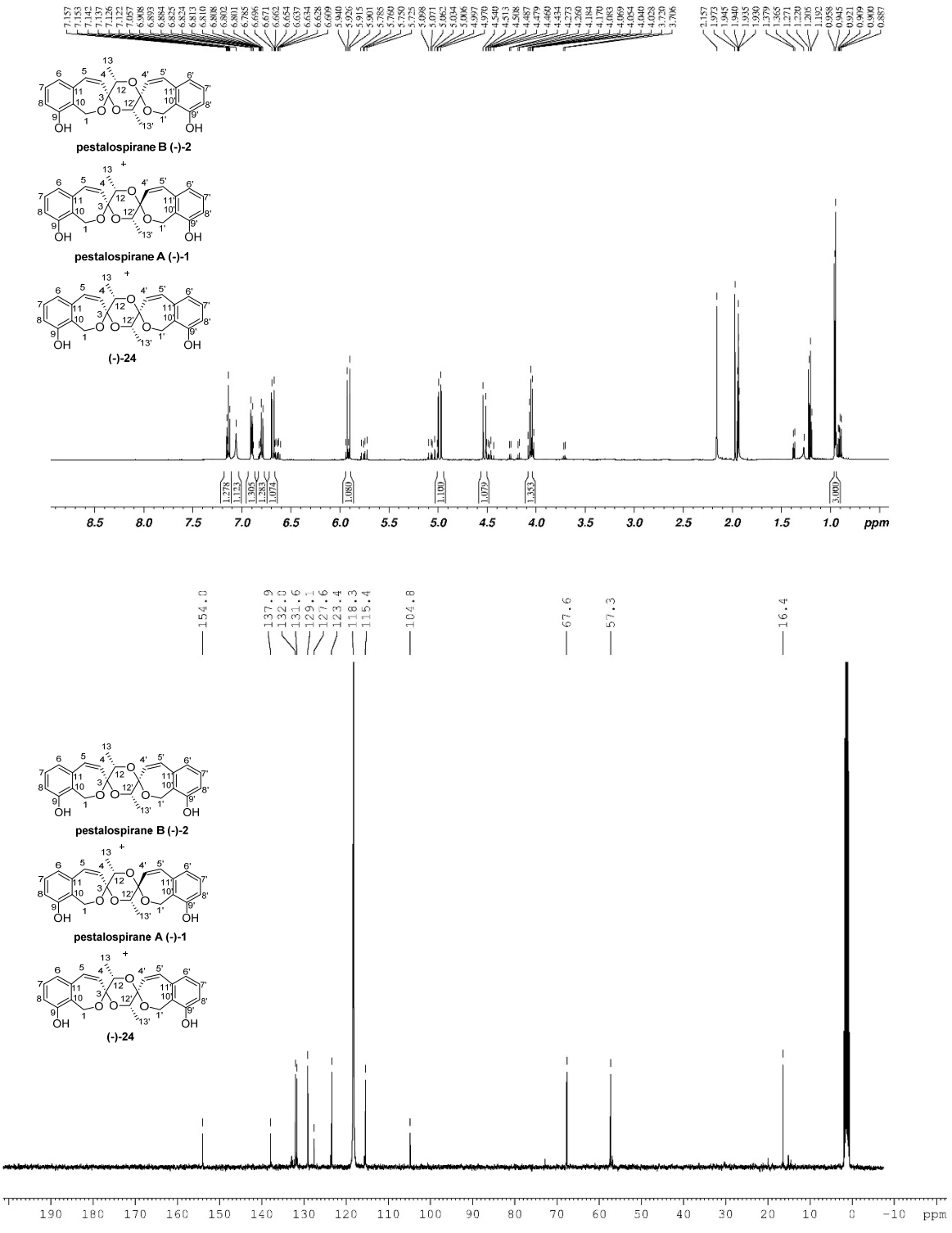


(±)-9,9''-bis(Ethoxymethoxy)-3',6'-dimethyl-1*H*,1''*H*-dispiro[2-benzoxepine-3,5'-[1,4]dioxane-2',3''-[2]benzoxepine] (±-25)

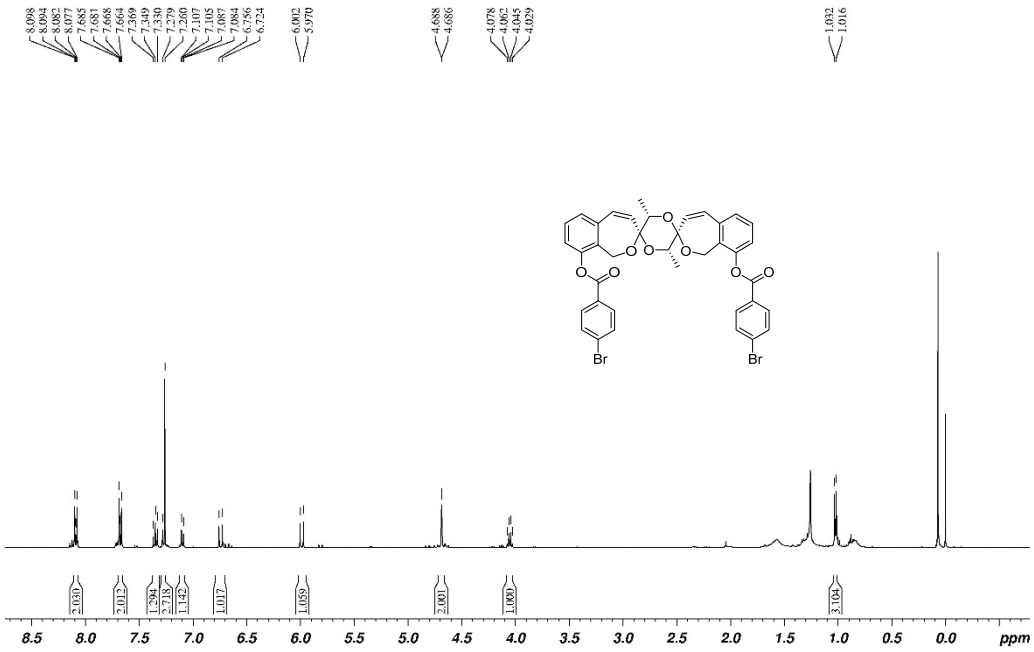


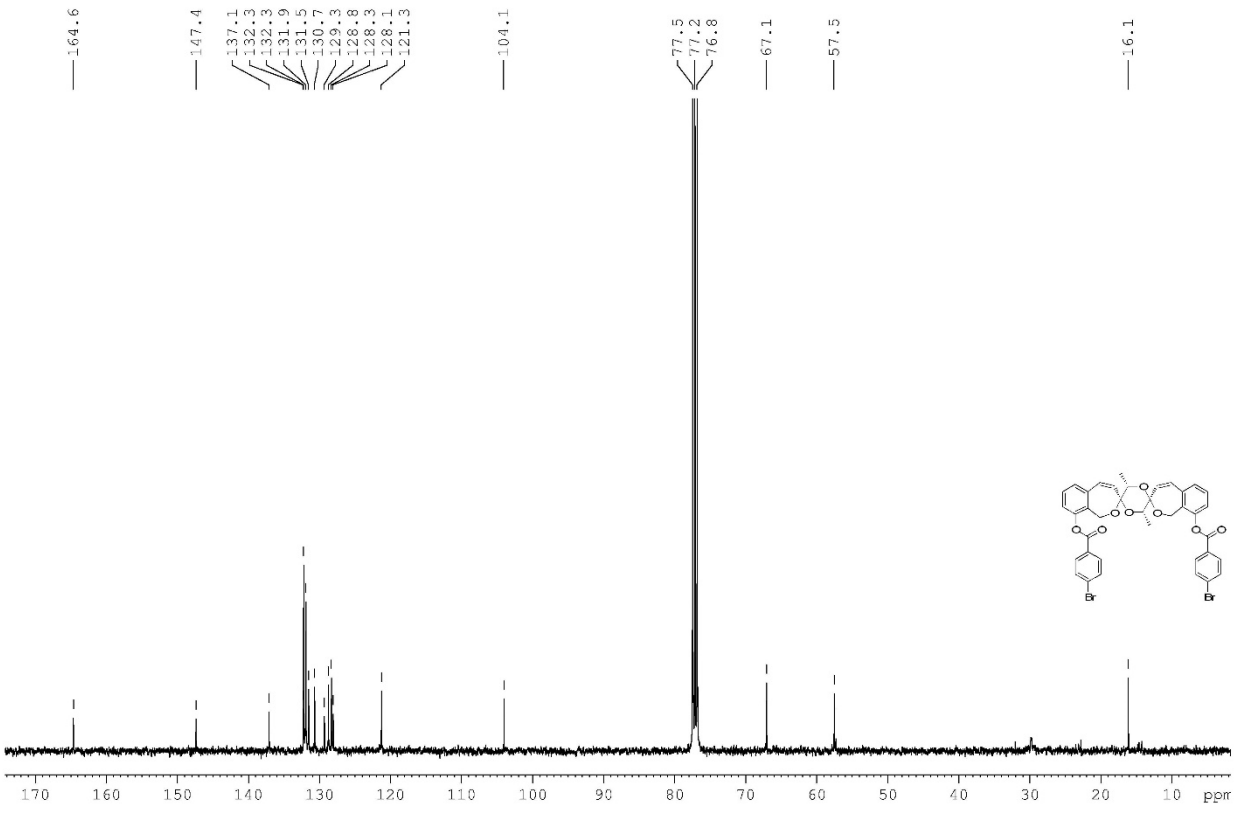


(-)-Pestalospirane B (-)-2, (-)-pestalospirane A (-)-1 and unnatural pestalospirane (-)-24

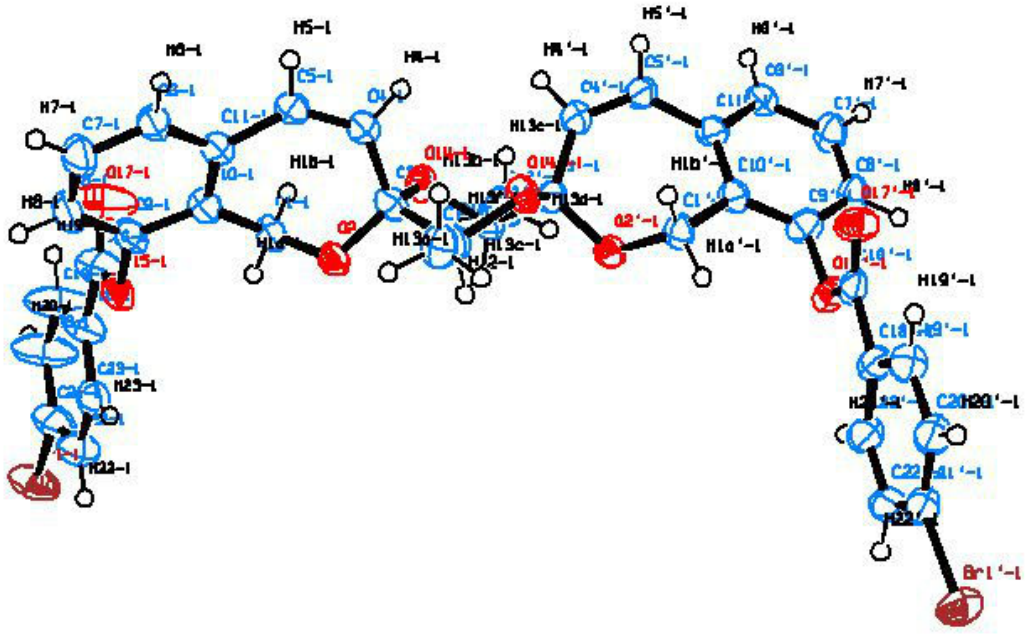


(-)-(3*R*,3'*S*,5'*R*,6'*S*)-9''-(4-bromobenzoyloxy)-3',6'-dimethyl-1*H*,1''*H*-dispiro[2-benzoxepine-3,2'-[1,4]dioxane-5',3''-[2]benzoxepine]-9-yl 4-bromobenzoate (-)-26





Crystal Structural Data for (-)-26



General Information

Thin needles of compound (-)-**26** were passed through Paratone-*N* oil and were mounted in nylon loops for flash cooling in liquid nitrogen. Crystals were transported frozen to the Australian Synchrotron where data were collected on the MX1 beamline at 100K and at a wavelength of 0.71073 Å using the Blu-Ice software package. Oscillation data were processed using XDS to a theta max value of 27.16˚. Unmerged intensity data from XDS were converted to SHEXL hkl format using XDSCONV. The structure was solved using SHELXT and atoms visualised using shelXle. One molecule of compound (-)-**356** was located in the structure. Additionally, an extended chain of *N*-hexane molecules fills a channel in the crystal the *N*-hexane is modelled as three carbon atoms with crystal symmetry producing the remainder of the molecule. The C-C distance of the N-hexane was restrained to 1.50 Å for stable refinement in SHELXL. Heavy atoms were fully refined by least squares refinement in SHELXL before anisotropic refinement and the subsequent additional of hydrogen atoms in idealised positions.

Audit creation method	SHELXL-97	
Identification code	data 15712	
Empirical formula	$C_{41}H_{36}Br_2O_8$	
Formula weight	816.5	
Temperature	100 (2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 14.5480 (15) Å	alpha = 90.00(3)˚
	b = 7.384 (3) Å	beta = 93.28 (3)˚
	c = 16.613 Å	gamma = 90.00 (3)˚
Volume	1781.7 (8) $Å^3$	
Z	2	
Density (calculated)	1.281 Mg/m^3	
Absorption coefficient	2.330 mm^{-1}	
F(000)	832	
Crystal size	0.15 mm	
Theta range for data collection	1.40 - 27.16˚	
Limiting incides	18 <=h<= 18, -9 <=k<= 9, -21 <=l<= 21	
Reflection collected	28036/ 7780 [R(int) = 0.0561]	
Completeness to theta = 27.16˚	98.60%	
Refinement method	Full-matric least squares on F^2	
Data/ restraints/ parameters	7780/ 3/ 459	
Goodness of fit on F^2	1.341	
Final R indices [I>2sigma(I)]	R1 = 0.0661, wR2 = 0.1788	
R indices (all data)	R1 = 0.0809, wR2 = 0.1877	
Absolute structure parameters	0.035(11)	
Largest diff. peak and hole	1.545 and -1.036 $e.Å^{-3}$	

References

(1) Bajwa, N.; Jennings, M. P. *J. Org. Chem.* **2006**, *71*, 3646-3649.
(2) Iosub, A. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2015**, *137*, 3454-3457.
(3) Kesting, J. R.; Olsen, L.; Staerk, D.; Tejesvi, M. V.; Kini, K. R.; Prakash, H. S.; Jaroszewski, J. W. *J. Nat. Prod*. **2011**, *74*, 2206-2215.