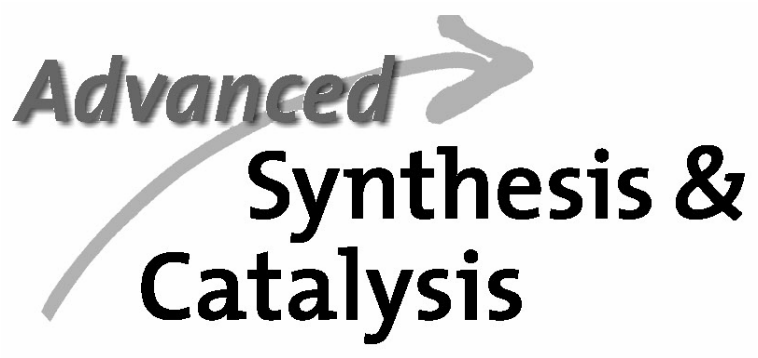

Supporting Information

Domino Hydroformylation / Enantioselective Cross-Aldol Addition

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Supporting informations

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1. General information

All reactions were carried out in a dried glassware und an argon atmosphere (Südwest-Gas, 5.0). Air and moisture sensitive liquids or solutions were transferred via syringe. All reagents were obtained commercially unless otherwise specified. DMF was dried over P_2O_5 followed by distillation according to literature procedure[1]. Hydroformylations were carried out in a steel autoclave. The reaction mixture was transferred into the autoclave under argon, which was subsequently pressurized with a 1:1 H_2:CO mixture (Hydrogen 5.0, carbonmonoxide 3.7) and in some cases with ethylene (3.0). Organic solutions were concentrated under reduced pressure by rotatory evaporation. Chromatographic purification of products was accomplished by flash chromatography on a Merck silica gel Si60® (200-400 mesh) or on neutral alumina (MP – Super I, MP Biomedicals, deactivated with 8% w/w H_2O). Thin-layer chromatography (TLC) was performed on silica gel $60F_{254}$ plates (Merck).

Nuclear magnetic resonance spectra were acquired on a Varian Mercury spectrometer (300 MHz, 75 MHz for ^1H and ^{13}C respectively), on a Bruker AMX 400 spectrometer (400 MHz, 100 MHz for ^1H and ^{13}C respectively) and on a Bruker DRX 500 spectrometer (500 MHz, 125 MHz for ^1H and ^{13}C respectively) and are referenced according to residual protio solvent signals. Data for ^1H-NMR are referenced as follows: chemical shift (d in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), integration and assignment. Data for ^{13}C-NMR are reported in terms of chemical shift (d in ppm), multiplicity (if not a singlet), coupling constant (Hz) and assignement.

GC was performed on *6890N* gas chromatograph (Agilent Technologies) using a *Supelcowax* 10 column (30.0 m × 0.25 mm, Supelco) or a Hydrodex-ß-TBDAc column (25 m × 0.25 mm, Machery-Nagel) and on a GC8000 (CE Instruments) using a G-TA column (Trifluoroacetyl-?-Cyclodextrin, 30 m × 0.25 mm, Astec) as noted.

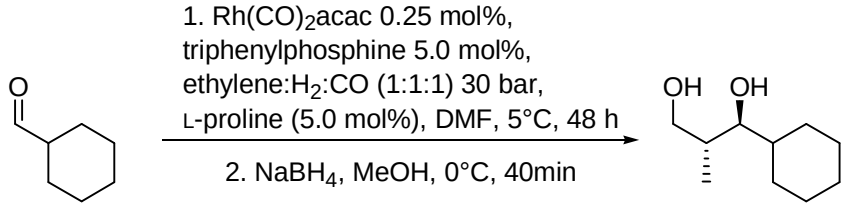
HPLC was performed on a Merck-Hitachi HPLC chromatograph using a *Chiralpak-AD-H* column (25 cm × 4.6 mm, Daicel).

Elementar analysis was performed on an Elementar vario (Elementar Analysensysteme GmbH).

2. Experimental section

General procedure for a Domino hydroformylation / proline catalyzed aldol reaction using ethylene as a substrate.

Synthesis of (2*R*, 3*S*)-1-*c*-Hexyl-2-methyl-1,3-propane diol



(112.17) (81%) (172.26)

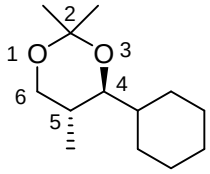
[$Rh(CO)_2acac$] (7.8 mg, 0.0302 mmol), triphenylphosphine (158.6 mg, 0.604 mmol), L-proline (69.6 mg, 0.604 mmol) and cyclohexane carbaldehyde (1.36 g, 12.4 mmol) were dissolved in DMF (2.2 ml). The solution was transferred to an autoclave, pressurized (30 bar, ethylene:H_2:CO 1:1:1), and the reaction stirred for 48 h at 5°C. The reaction mixture was then diluted with methanol (16 ml), cooled down to 0°C, and $NaBH_4$ (0.90 g, 24.0 mmol) was added portionswise. After the reduction was complete, the reaction mixture was further diluted with ethylacetate (50 mL) and hydrolyzed with water (20 mL) and sat. aqu. NH_4Cl-solution (20 mL). The phases were separated and the aqueous phase was extracted with ethylacetate (3 x 75 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography of the residue (neutral alumina, cylohexane:ethylacetate from 4:1 to 1:1) furnished (2*R*,3*S*)-3-Cyclohexyl-2-methyl-1,3-propane diol as a colourless oil (408 mg, 81% based on the conversion (24%), 99% *ee,* determined by chiral GC).

^{1}H NMR (499.87 MHz, $CDCl_3$): d= 0.87 (d, *J* = 6.9 Hz, 3H, CH_3), 1.06-1.89 (m, 12H, 2-H und *c*-hexyl), 3.31 (dd, *J* = 7.5, 4.1 Hz, 1H, 3-H), 3.61 (dd, *J* = 10.7, 6.9 Hz, 1-H), 3.75 (dd, *J* = 10.7, 3.5 Hz, 1-H). **^{13}C NMR** (125.69 MHz, $CDCl_3$): d= 14.10, 25.92, 26.26, 26.57, 26.60, 30.21, 36.39, 40.73, 67.94, 81.75.
The NMR-data is in agreement with the literature data[2].

General procedure for the conversion to the corresponding [1,3]-dioxane

A solution of the diol and *p*-TsOH.H_2O (10 mol%) in 2,2-Dimethoxypropan (1 M) was stirred by rt. After the reaction was complete (TLC), the solution was further diluted with CH_2Cl_2 and hydrolyzed with a sat. aq. $NaHCO_3$-solution. The two phases were separated, the organic phase dried over $MgSO_4$ and concentrated *in vacuo*.

(4*S*, 5*R*)-2,2,5-Dimethyl-4-cyclohexyl-[1,3]-dioxane



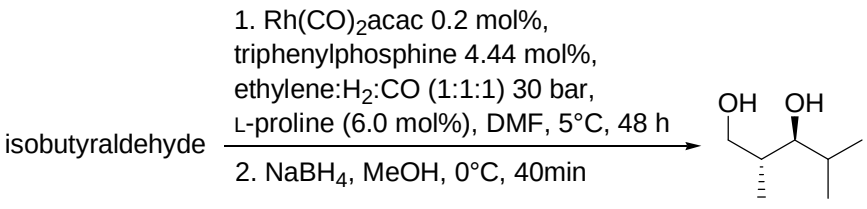
$C_{13}H_{24}O_2$
Mol. Wt.: 212,33

^{1}H NMR (400.13 MHz, C_6D_6): d= 0.42 (d, *J* = 6.7 Hz, 3H, CH_3), 1.11-1.26 (m, 3H, *c*-hexyl), 1.30 (d, *J* = 0.6 Hz 3H, 2-Me), 1.38-1.45 (m, 3H, *c*-hexyl), 1.51 (s, *J* = 0.6 Hz 3H, 2-Me), 1.55-1.66 (m, 3H, *c*-hexyl), 1.72-1.85 (m, 3H, *c*-hexyl and 5-H), 3.16 (dd, *J* = 10.1, 1.8 Hz, 4-H), 3.29 (pt, *J* = 10.6 Hz, 6-H), 3.60 (dd, *J* = 11.2, 4.9 Hz, 6-H). **^{13}C NMR** (100.61 MHz, C_6D_6): d= 12.58, 19.33, 25.59, 26.96 (2C), 27.20, 29.98, 30.50, 30.73, 39.17, 66.36, 78.97, 98.25.

The NMR-data is in agreement with the literature data[2].

The ee was estimated by chiral GC (G-TA, 1.0 mL/min, isotherm 65°C, *anti* isomer (4*S*, 5*R*) t_r = 137.3 min, *anti* isomer (4*R*, 5*S*) t_r = 140.4 min).

Synthesis of (2*R*, 3*S*)-2,4-Dimethyl-1,3-pentane diol



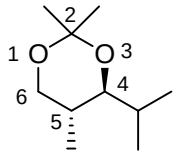
(72.11) (76%) (132.20)

From isobutyraldehyde (1.09 g, 15.1 mmol). Purified by column chromatography (neutral alumina, cyclohexane:EtOAc 8:2? 1:1) to yield the title compound as a colourless oil (437 mg, 76% based on conversion (28%)), *dr* 95:5, *ee* 98%).

^{1}H NMR (499,87 MHz, $CDCl_3$): d= 0.86 (d, *J* = 6.9 Hz, 3H, CH_3), 0.89 (d, *J* = 6.7 Hz, 3H, -*i*Pr), 0.95 (d, *J* = 6.9 Hz, 3H, -*i*Pr), 1.77-1.87 (m, 2H, 2-H, 4-H), 2.93 (br, 2H, -OH), 3.35 (dd, *J* = 8.1 Hz, 1H, 3-H), 3.63 (dd, *J* = 10.6 Hz, 7.3 Hz, 1-H), 3.75 (dd, *J* = 10.8 Hz, 3.5 Hz, 1-H). **^{13}C NMR** (125,69 MHz, $CDCl_3$): d= 13.90, 15.03, 19.89, 30.33, 37.15, 68.27, 82.21.

The NMR-data is in agreement with the literature data[3].

(4*S*, 5*R*)-2,2,5-Trimethyl-4-isopropyl-[1,3]dioxane



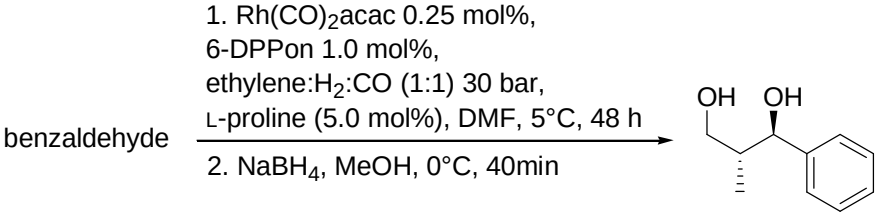
$C_{10}H_{20}O_2$
Mol. Wt.: 172,26

^{1}H NMR (499,87 MHz, $CDCl_3$): d= 0.71 (d, *J* = 6.6 Hz, 3H, CH_3), 0.86 (d, *J* = 6.9 Hz, 3H, iPr-Me), 0.93 (d, *J* = 6.9 Hz, 3H, iPr-Me), 1.35 (s, 3H, $C(CH_3)_2$), 1,38 (s, 3H $C(CH_3)_2$), 1.73-1.86 (m, 2H, iPr-CH, 5-H), 3.30 (dd, *J* = 10.1 Hz, 2.4 Hz, 1H, 4-H), 3.46 (pt, *J* = 11.2 Hz, 6-H), 3.66 (dd, *J* = 11.4 Hz, 5.0 Hz, 6-H). **^{13}C NMR** (125,69 MHz, $CDCl_3$):

d= 12.68, 14.75, 19.23, 19.80, 28.59, 29.67, 31.32, 66.40, 78.67, 98.13.

The ee was estimated by by chiral GC (Hydrodex-ß-TBDAc 25 m x 250 µm, 17.2 psi, isotherm 80°C, *anti* isomer (4*S*, 5*R*) t_r = 5.2 min, *anti* isomer (4*R*, 5*S*) t_r = 5.5 min).

Synthesis of (2*R*, 3*S*)-2-Methyl-3-Phenyl-1,3-propane diol



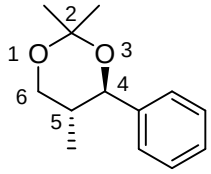
(106.12) (91%) (166.22)

From benzaldehyde (1.28 g, 12.1 mmol). Purified by column chromatography (neutral alumina, cyclohexane:EtOAc 8:2? 1:1) to yield the title compound as a colourless oil (658 mg, 91% based on conversion (36%), *dr* 3:1, *ee* 94%).

Anti:syn mixture

^{1}H NMR (400.132 MHz, $CDCl_3$): d= 0.68 (d, *J* = 7.1 Hz, 3H, *anti*-CH_3), 0.83 (d, *J* = 7.1 Hz, 3H, *syn*-CH_3), 1.98-2.08 (m, 1H, *anti/syn*-2-H), 3.16 (br, 1H, -OH), 3.25 (br, 1H, -OH), 3.64-3.76 (m, 2H, *anti/syn*-1-H), 4.51 (d, *J* = 8.4 Hz, 1H, *anti*-3-H), 4.92 (d, *J* = 3.9 Hz, *syn*-3-H), 7.24-7.40 (m, 5H, *anti/syn*-Ar-H); **^{13}C NMR** (100.613 MHz, $CDCl_3$): d= 10.84 (*syn*-CH_3), 13.87 (*anti*-CH_3), 41.48 (*syn*-2-C), 41.69 (*anti*-2-C), 66.49 (*syn*-1-C), 68.01 (*anti*-1-C), 76.20 (*syn*-3-C), 80.90 (*anti*-3-C), 126.20 (*anti*-Ar-C), 126.77 (2C, *anti*-Ar-C), 127.32 (*syn*-Ar-C), 127.91 (2C, *syn*-Ar-C), 128.38 (2C, *syn*-Ar-C), 128.50 (2C, *anti*-Ar-C), 142.75 (*syn*-Ar-C), 143.43 (*anti*-Ar-C); **CH**: calcd C: 72.26, H: 8.49, found C: 71.87, H: 8.62.

(4*S*, 5*R*)-2,2,5-Trimethyl-4-phenyl[1,3]dioxane



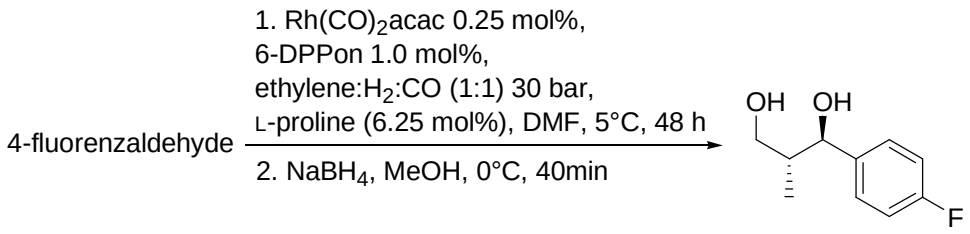
$C_{13}H_{18}O_2$
Mol. Wt.: 206,28

Anti:syn mixture

^{1}H NMR (400.132 MHz, $CDCl_3$): d= 0.33 (d, *J* = 6.8 Hz, 3H, *anti*-CH_3), 0.87 (dd, *J* = 7.1, 0.6 Hz, 3H, *syn*-CH_3), 1.31 (q, *J* = 0.6 Hz, 3H, *syn*-2-Me), 1.37 (d, *J* = 0.7 Hz, 3H, *anti*-2-Me), 1.58 (d, *J* = 0.7 Hz, 3H, *syn*-2-Me), 1.32-1.39 (m, 1H, *syn*-5-H), 1.80-1.92 (m, 2H, *anti*-5-H), 3.43 (t, *J* = 11.5 Hz, 1H, *anti*-6-H), 3.47 (dd, *J* = 11.4, 1.5 Hz, 1H, *syn*-6-H), 3.66 (dd, *J* = 11.4, 5.0 Hz, 1H, *anti*-6-H), 3.90 (ddd, *J* = 11.4, 2.8, 0.5 Hz, 1H, *syn*-6-H), 4.27 (d, *J* = 10.2 Hz, *anti*-4-H), 4.92 (d, *J* = 2.8 Hz, *syn*-4-H), 7.08-7.34 (m, 5H, *anti/syn*-Ar-H); **^{13}C NMR** (100.613 MHz, $CDCl_3$): d= 11.02 (*syn*-CH_3), 12.23 (*anti*-CH_3), 19.01 (*syn*-2-Me), 19.09 (*anti*-2-Me), 30.13 (*syn*-2-Me), 30.32 (*anti*-2-Me), 34.19 (*syn*-5-C), 36.49 (*anti*-5-C), 66.26 (*syn*-1-C), 66.41 (*syn*-1-C), 73.02 (*syn*-4-C), 79.07 (*anti*-4-C), 98.67 (*anti*-2-C), 98.98 (*syn*-2-C), 125.73 (Ar-C), 126.91 (Ar-C), 127.85 (Ar-C), 128.32 (Ar-C), 141.32 (Ar-C), 141.89 (Ar-C); **CH:** cacld. C: 75.69, H: 8.80; found C: 75.29, H: 8.91.

The ee was estimated by chiral GC (G-TA, 1.0 mL/min, isotherm 75°C, *anti* isomer (4*R*, 5*S*) t_r = 184.2 min, *anti* isomer (4*S*, 5*R*) t_r = 210.2 min, *syn* isomers t_r = 171.6 min, 183.3 min).

Synthesis of (2*R*, 3*S*)-2-Methyl-3-(4-fluorphenyl)-1,3-propane diol



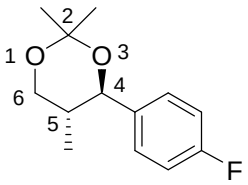
(124.11) (91%) (184.21)

From 4-fluorobenzaldehyde (1.15 g, 9.1 mmol). Purified by column chromatography (neutral alumina, cyclohexane:EtOAc 8:2? 1:1) to yield the title compound as a colorless oil (534 mg, 91% NMR-yield based on conversion (35%), dr 3:1, 94% *ee*).

Anti:syn mixture

^{1}H NMR (400.132 MHz, $CDCl_3$): d= 0.66 (d, *J* = 7.1 Hz, 3H, *anti*-CH_3), 0.82 (d, *J* = 7.1 Hz, 3H, *syn*-CH_3), 1.94-2.06 (m, 1H, *anti/syn*-2-H), 3.04 (br, 1H, -OH), 3.38 (br, 1H, -OH), 3.60-3.78 (m, 2H, *anti/syn*-1-H), 4.51 (d, *J* = 8.5 Hz, 1H, *anti*-3-H), 4.92 (d, *J* = 3.7 Hz, *syn*-3-H), 7.00-7.05 (m, 2H, *anti/syn*-Har), 7.27-7.31 (m, 2H, *anti/syn*-Har); **^{13}C NMR** (100.613 MHz, $CDCl_3$): d= 10.70 (*syn*-CH_3), 13.79 (*anti*-CH_3), 41.43 (*syn*-2-C), 41.80 (*anti*-2-C), 66.49 (*syn*-1-C), 68.02 (*anti*-1-C), 76.20 (*syn*-3-C), 80.20 (*anti*-3-C), 115.04 (d, $J_{C,F}$ = 21.1 Hz, 2C, *syn*-Ar-C), 115.32 (d, $J_{C,F}$ = 21.4 Hz, 2C, *anti*-Ar-C), 127.75 (d, $J_{C,F}$ = 7.9 Hz, 2C, *syn*-Ar-C), 128.39 (d, $J_{C,F}$ = 8.1 Hz, 2C, *anti*-Ar-C), 138.43 (d, $J_{C,F}$ = 3.1 Hz, *syn*-Ar-C), 139.23 (d, $J_{C,F}$ = 3.2 Hz, *anti*-Ar-C), 162.08 (d, $J_{C,F}$ = 245 Hz, *syn*-Ar-C), 162.40 (d, $J_{C,F}$ = 246 Hz, *anti*-Ar-C); **CH**: calcld. C: 65.2, H: 7.11, found C: 65.45, H: 7.06.

Synthesis of (4*S*, 5*R*)-2,2,5-Trimethyl-4-(4-flurophenyl)-[1,3]-dioxane



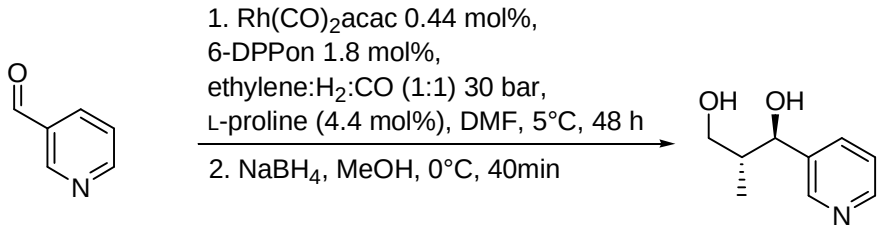
$C_{13}H_{17}FO_2$
Mol. Wt.: 224,27

Anti:syn mixture

^{1}H NMR (400.132 MHz, $CDCl_3$): d= 0.27 (d, *J* = 6.7 Hz, 3H, *anti*-CH_3), 0.79 (d, *J* = 6.9 Hz, 3H, *syn*-CH_3), 1.20-1.27 (m, 1H*, syn*-5-H), 1.30 (d, *J* = 0.5 Hz, 3H, *syn*-2-Me), 1.37 (d, *J* = 0.6 Hz, 3H, *anti*-2-Me), 1.55 (s, 3H, *syn*-2-Me), 1.56 (s, 3H, *anti*-2-Me), 1.66-1.78 (m, 1H, *anti*-5-H), 3.43 (pt, *J* = 11.4 Hz, 1H, *anti*-6-H), 3.45 (dd, *J* = 11.4, 1.6 Hz, 1H, *syn*-6-H), 3.64 (dd, *J* = 11.6, 5.0 Hz, 1H, *anti*-6-H), 3.88 (dd, *J* = 11.6, 2.9 Hz, 1H, *syn*-6-H), 4.15 (d, *J* = 10.2 Hz, *anti*-4-H), 4.92 (d, *J* = 2.5 Hz, *syn*-4-H), 6.79-6.90 (m, 2H, *anti/syn*-Ar-H), 7.05-7.12 (m, 2H, *anti/syn*-Ar-H). **^{13}C NMR** (100.613 MHz, $CDCl_3$): d= 10.87 (*syn*-CH_3), 12.31 (*anti*-CH_3), 18.97 (*syn*-2-Me), 19.04 (*anti*-2-Me), 30.07 (*syn*-2-Me), 30.26 (*anti*-2-Me), 34.16 (*syn*-5-C), 36.53 (*anti*-5-C), 66.10 (*syn*-6-C), 66.29 (*anti*-6-C), 72.48 (*syn*-4-C), 78.27 (*anti*-4-C), 98.71 (*anti*-4-C), 99.03 (*syn*-1-C), 114.98 (d, $J_{C,F}$ = 21.2 Hz, 2C, *syn*-Ar-C), 115.08 (d, $J_{C,F}$ = 21.2 Hz, 2C, *anti*-Ar-C), 127.28 (d, $J_{C,F}$ = 7.7 Hz, 2C, *syn*-Ar-C), 129.38 (d, $J_{C,F}$ = 7.9 Hz, 2C, *anti*-Ar-C), 137.11 (d, $J_{C,F}$ = 3.2 Hz, 2C, *syn*-Ar-C), 137.53 (d, $J_{C,F}$ = 3.1 Hz, *anti*-Ar-C), 162.15 (d, $J_{C,F}$ = 244 Hz, *syn*-Ar-C), 162.76 (d, $J_{C,F}$ = 245 Hz, *anti*-Ar-C). **CH**: calcd C: 69.62, H: 7.64, found C: 69.51, H: 7.75).

The ee was estimated by chiral GC (G-TA, 1.0 mL/min, isotherm 75°C, *anti* isomer (4*R*, 5*S*) t_r = 61.0 min, *anti* isomer (4*S*, 5*R*) t_r = 63.7 min, *syn* isomers t_r = 62.2 min, 66.5 min).

Synthesis of (2*R*, 3*S*)-2-Methyl-3-(3-pyridin)-(1,3)-propane diol



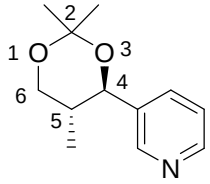
(107.11) (66%) (167.21)

From 3-pyridine carbaldehyde (728 mg, 6.8 mmol). Purified by column chromatography (silica gel, cyclohexane:EtOAc 1:1? EtOAc? EtOAc:MeOH 9:1) to yield the title compound as a pale yellow oil (578 mg, 66% NMR Yield based on conversion (77%), *dr* 5:1, 94% *ee*).

Anti:syn mixture

^{1}H NMR (400.132 MHz, $CDCl_3$): d= 1.00 (d, *J* = 7.0 Hz, 3H, *anti*-CH_3), 1.10 (d, *J* = 7.1 Hz, 3H, *syn*-CH_3), 2.26-2.38 (m, 2H, *anti/syn*-2-H), 3.97 (pt, *J* = 8.7 Hz, 1H, *anti/syn*-1-H), 4.08 (d, *J* = 10.6 Hz, 1H, *anti*-1-H), 4.90 (d, *J* = 8.8 Hz, 1H, *anti*-3-H), 5.32 (s, 1H, *syn*-3-H), 5.46 (br, 2H, -OH), 7.56-7.62 (m, 1H, *anti/syn*-Har), 8.03 (d, *J* = 7.8 Hz, 1H, *anti/syn*-Har), 8.65-8.74 (m, 2H, *anti/syn*-Har); **^{13}C NMR** (100.613 MHz, $CDCl_3$): d= 10.42 (*syn*-CH_3), 13.56 (*anti*-CH_3), 41.42 (*syn*-2-C), 41.48 (*anti*-2-C), 65.53 (*syn*-1-C), 66.06 (*anti*-1-C), 73.31 (*syn*-3-C), 77.42 (*anti*-3-C), 123.35 (*syn*-Ar-C), 123.68 (*anti*-Ar-C), 134.62 (*syn*-Ar-C), 135.01 (*anti*-Ar-C), 139.28 (*syn*-Ar-C), 139.51 (*anti*-Ar-C), 147.33 (*syn*-Ar-C), 147.52 (*syn*-Ar-C), 147.96 (*anti*-Ar-C), 148.20 (*anti*-Ar-C). **CHN**: calcd. C: 64.65, H: 7.84, N: 8.38, found C: 64.89, H: 7.58, N: 8.23).

Synthesis of (4*S*, 5*R*)-2,2,5-Trimethyl-4-[3-pyridinyl][1,3]dioxan



$C_{12}H_{17}NO_2$
Mol. Wt.: 207,27

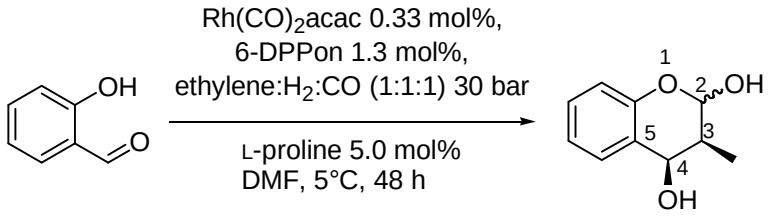
Anti:syn mixture

^{1}H NMR (400.132 MHz, $CDCl_3$): d= 0.18 (d, *J* = 6.7 Hz, 3H, *anti*-CH_3), 0.79 (d, *J* = 6.9 Hz, 3H, *syn*-CH_3), 1.20-1.27 (m, 1H, *syn*-5-H), 1.27 (d, *J* = 0.5 Hz, 3H, *syn*-2-Me), 1.27 (d, *J* = 0.6 Hz, 3H, *anti*-2-Me), 1.55 (s, 3H, *syn*-2-Me), 1.52 (d, *J* = 0.6 Hz, 3H, *anti*-2-Me), 1.61-1.72 (m, 1H, *anti*-5-H), 3.31 (pt, *J* = 11.4 Hz, 1H, *anti*-6-H), 3.56 (dd, *J* = 11.7, 5.0 Hz, 1H, *syn*-6-H), 3.64 (dd, *J* = 11.6, 5.0 Hz, 1H, *anti*-6-H), 4.13 (d, *J* = 11.6, 2.9 Hz, 1H, *syn*-6-H), 4.13 (d, *J* = 10.4 Hz, *anti*-4-H), 4.92 (d, *J* = 2.5 Hz, *syn*-4-H), 6.45 (ddd, *J* = 7.8, 4.8, 0.7 Hz, 1H, *anti*-[5-Py]), 6.78 (m, 1H, syn-[5-Py]), 7.40 (m, 1H, *syn*-[4-Py]), 7.43 (dtd, *J* = 7.8, 2.0, 0.5 Hz, 1H, *anti*-[4-Py]), 8.48 (dd, *J* = 4.8, 1.8 Hz, 1H, *anti/syn*-[6-Py]), 8.62 (d, *J* = 1.8 Hz, 1H, *syn*-[2-Py]), 8.66 (d, *J* = 2.0 Hz, 1H, *anti*-[2-Py]). **^{13}C NMR** (100.613 MHz, $CDCl_3$, *anti diastereoisomer*): d= 12.05 (CH_3), 18.97 (2-Me), 30.14 (2-Me), 36.23 (5-C), 66.09 (6-C), 76.65 (4-C), 98.75 (2-C), 123.39 (Ar-C), 127.88 (Ar-C), 134.38 (Ar-C), 149.77 (Ar-C), 149.81 (Ar-C).

The NMR-data is in agreement with the literature data[4].

The ee was estimated by chiral GC (Hydrodex-ß-TBDAc, isotherm 125°C, 8.4 psi, *anti* isomer (4*S*, 5*R*) t_r = 61.6 min, *anti* isomer (4*R*, 5*S*) t_r = 63.1 min, *syn* isomers t_r = 64.1 min, 68.6 min).

Synthesis of (3*S*, 4*R*)-4-Hydroxy-3-Methylchroman-2-ol

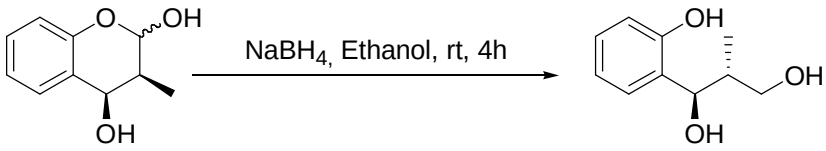


(122.12) (91%) (180.20)

From salicyladehyde (568 mg, 4.65 mmol). Purified by column chromatography (silica gel, petroleum ether:TBME 8:2? 1:1) to yield the title compound as a pale yellow oil (391 mg, 91% based on conversion (47%)).

^{1}H NMR (400.132 MHz, $CDCl_3$, 210 K): d = 1.28 (d, *J* = 5.8 Hz, 3H, -CH_3), 2.16-2.22 (m, 1H, 3-H), 4.21 (d, *J* = 6.8 Hz, 1H, -OH), 4.47 (dd, *J* = 6.6, 2.9 Hz, 1H, 4-H), 5.45 (d, *J* = 4.3 Hz, 1H, 2-H), 6.00 (d, *J* = 4.5 Hz, 1H, -OH), 6.88 (d, *J* = 6.6 Hz, 1H, Har), 6.96-7.00 (td, *J* = 5.8, 0.5 Hz, 1H, Har), 7.24-7.27 (td, *J* = 6.8, 1.2 Hz, 1H, Har), 7.28-7.30 (dd, *J* = 6.0, 1.2 Hz, 1H, Har); **^{13}C NMR** (100.612 MHz, $CDCl_3$, 210 K): d = 12.50 (CH_3), 34.87 (3-C), 67.30 (4-C), 95.85 (2-C), 117.28 (Ar-C), 121.40 (Ar-C), 123.92 (Ar-C), 130.08 (Ar-C), 130.45 (Ar-C), 149.6 (Ar-C); **CH**: calcd. C: 66.63, H: 6.71, found C: 66.89, H: 6.41.

(2*R*, 3*S*)-3-[2-hydroxyphenyl]-2-methyl-1,3-propane diol – General procedure



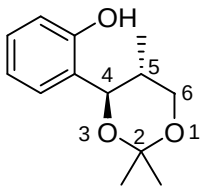
(180.20) (182.22)

To a solution of the hydroxychromanol in ethanol (0.5-1.0 M) was added $NaBH_4$ (0.5-1.0 M) portionswise ar rt and the reaction stirred a rt. After the reaction was complete (TLC), the solution was further diluted with EtOAc, hydrolyzed with a sat. aq. solution of Seignette-salts. The biphasic suspension was stirred overnight at rt and then

concentrated *in vacuo*. The residue was suspended in warm EtOAc and the remaining solid filtered off. The solution containing the triol was concentrated *in vacuo* and could be purified by column chromatography (silica gel, EtOAc).

^{1}H NMR (400.132 MHz, $CDCl_3$): d = 0.65 (d, *J* = 6.9 Hz, 3H, -CH_3), 2.24-2.33 (m, 1H, 2-H), 2.84 (br, 1H, -OH), 3.68 (pt, *J* = 10.1 Hz, 1H, 1-H), 3.89 (d, *J* = 10.2 Hz, 1H, 1-H), 4.71 (d, *J* = 8.8 Hz, 1H, 3-H), 4.80 (br, 1H, -OH), 6.80-6.84 (td, *J* = 7.3, 1.1 Hz, 1H, 8-H), 6.84-6.87 (dd, *J* = 8.1, 1.1 Hz, 1H, 6-H), 6.93-6.95 (dd, *J* = 7.6 Hz, *J* = 1.8 Hz, 1H, 9-H), 7.15-7.19 (ddd, *J* = 9.0, 7.3, 1.8 Hz, 1H, 7-H), 8.23 (br, 1H, -OH); **^{13}C NMR** (100.612 MHz, $CDCl_3$): d = 13.63 (CH_3), 39.55 (2-C), 68.76 (1-C), 81.69 (3-C), 117.26 (6-C), 119.57 (8-C), 125.89 (4-C), 128.66 (9-C), 129.16 (7-C), 155.66 (5-C); **CH**: calcd. C: 65.91, H: 7.74, found C: 65.66, H: 7.44.

(4*S*, 5*R*)-2-(2,2,5-trimethyl-[1,3]-dioxan-4-yl)phenol

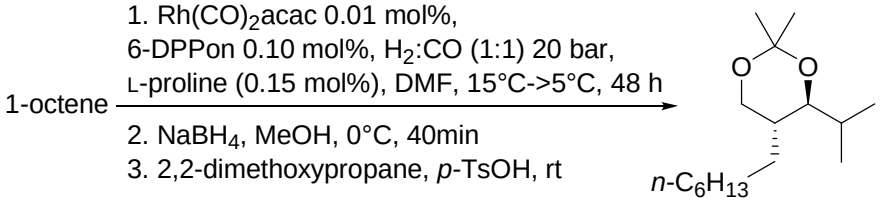


$C_{13}H_{18}O_3$
Mol. Wt.: 222,28

^{1}H NMR (400.132 MHz, $CDCl_3$): d = 0.28 (d, *J* = 6.7 Hz, 3H, -CH_3), 1.16 (s, 3H, -CH_3), 1.34 (s, 3H, -CH_3), 2.05-2.17 (m, 1H, 5-H), 3.23 (t, *J* = 11.4 Hz, 1H, 6-H), 3.47-3.51 (dd, *J* = 11.8, 5.0 Hz, 1H, 6-H), 4.32 (d, *J* = 10.6 Hz, 1H, 4-H), 6.70-6.76 (m, 2H, Har), 7.02-7.12 (m, 2H, Har), 8.54 (s, 1H, -OH); **^{13}C NMR** (100.612 MHz, $CDCl_3$): d = 12.62 (CH_3), 18.35 (CH3), 29.82 (CH3), 33.76 (5-C), 65.96 (6-C), 80.80 (4-C), 118.10 (Ar-C), 119.13 (Ar-C), 124.06 (7-Ar-C), 128.94 (Ar-C), 129.69 (Ar-C), 155.82 (8-Ar-C); **CH**: calcd. C: 70.24, H: 8.16, found C: 70.13, 8.26.

The ee was estimated by chiral HPLC (AD-H, *n*-heptane/isopropanol 300/1, 1mL/min, *anti* isomer (4*R*, 5*S*) t_r = 12.2 min, *anti* isomer (4*S*, 5*R*) t_r = 16.2 min, *syn* isomers t_r = 14.6 min, 19.0 min).

Synthesis of (4*S*, 5*R*)-4-Isopropyl-5-(*n*-heptyl)-2,2-dimethyl[1,3]dioxane



(112.21) (86%) (256.42)

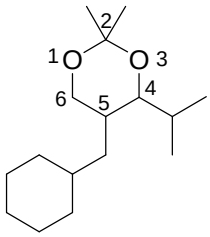
$Rh(CO)_2(acac)$ (5.2 mg, 0.0201 mmol, 0.01 eq) and 6-DPPon were solubilized in DMF (1.5 mL). The solution was transferred to an autoclave, pressurized (8 bar H_2:CO) and stirred at 60°C for 30 min (catalyst´s preforming). After cooling down a solution of L-proline (34.8 mg, 0.302 mmol, 0.15 eq), 1-octene (316 µL, 2.01 mmol, 1 eq.), isobutyraldehyde (0.92 mL, 10.07 mmol, 5 eq) und 1,3,5-trimethoxybenzol as an internal standard in DMF (1.0 mL) was added to the preformed catalyst, the autoclave was pressurized (20 bar H_2:CO) and the reaction stirred at 15°C for 44h. The autoclave was then depressurized, the reaction mixture was cooled down to 0°C, diluted with methanol (14 mL) and $NaBH_4$ (756 mg, 20.0 mmol, 10 eq) was added portionswise. After the reduction was complete (40 min), the reaction mixture was further diluted with EtOAc (50 mL) and hydrolyzed with H_2O (20 mL) and a sat. aq. NH_4Cl-solution. The phases were separated and the aqueous phase extracted with EtOAc (3 x 75 mL). The combined organic phases were washed with brine, dried ovwer $MgSO_4$, and concentrated *in vacuo*. The residue was solubilized in 2,2-dimethoxypropane and crystals of *p*-TsOH (10 mol%) were added at rt. After the reaction was complete (TLC), the reaction mixture was further diluted with CH_2Cl_2 and hydrolyzed with a sat. aq. $NaHCO_3$-solution. The two phases were separated, the organic phase dried over $MgSO_4$ and concentrated *in vacuo*. The crude [1,3]-dioxane mixture was analyzed by GC. The title compound can be purified by a colum chromatography (neutral alumina, petroleum ether:diethylether 95:5) to yield the title compound as a colorless liquid (*dr* 19:1, 97% *ee*).

^{1}H NMR (400.132 MHz, $CDCl_3$): d = 0.74-0.85 (m, 2H, $-CH_2$), 0.90 (t, *J* = 7.2 Hz, 3H, $-CH_3$), 1.00 (d, *J* = 6.8 Hz, 3H, *i*Pr), 1.05 (d, *J* = 6.9 Hz, 3H, *i*Pr), 1.00-1.32 (m, 10H, $-CH_2$), 1.33 (s, *J* = 0.6 Hz, 3H, 2-CH_3), 1.51 (s, *J* = 0.6 Hz, 3H, 2-CH_3), 1.67-1.79 (m, 1H, 5-H), 1.79 (heptd, *J* = 6.8, 2.4 Hz, 1H, *i*Pr), 3.30 (dd, *J* = 10.0, 2.4 Hz, 1H, 4-H), 3.39 (dd, *J* = 11.4, 10.0 Hz, 1H, 6-H), 3.80 (dd, *J* = 11.4, 4.9 Hz, 1H, 6-H); **^{13}C NMR**

(100.612 MHz, $CDCl_3$): d = 14.29 (-CH_3), 14.94 (*i*Pr), 19.62 (2-Me), 20.22 (*i*Pr), 23.04 (-CH_2), 26.70 (-CH_2), 28.30 (-CH_2), 28.75 (*i*Pr), 29.54 (-CH_2), 29.68 (2-Me), 30.22 (-CH_2), 32.20 (-CH_2), 36.45 (5-C), 64.35 (6-C), 77.52 (4-C), 98.08 (2-C); **CH**: calcd. C: 74.94, H: 12.58, found C: 74.62, H: 12.39.

The ee was estimated by chiral GC (G-TA, isotherm 110°C, 1mL/min, *anti* isomer (4*S*, 5*R*) t_r = 39.2 min, *anti* isomer (4*R*, 5*S*) t_r = 40.2 min).

Synthesis of (4*S*, 5*R*)-4-Isopropyl-5-methylcyclohexyl-[1,3]dioxane

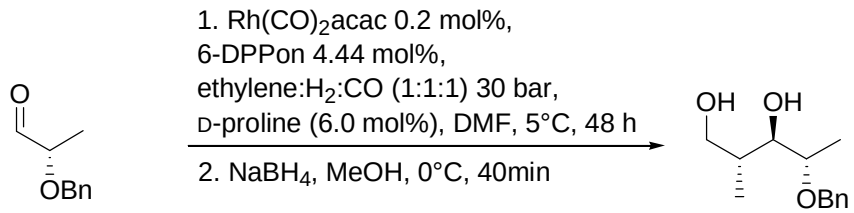


$C_{16}H_{30}O_2$
Mol. Wt.: 254,41

^{1}H NMR (400.132 MHz, $CDCl_3$): d = 0.57-0.71 (m, 2H, -CH_2), 090-1.02 (m, 2H, -CH_2), 1.00 (d, *J* = 6.8 Hz, 3H, -*i*Pr), 1.00-1.10 (m, 3H, -CH und -CH_2), 1.10 (d, *J* = 6.9 Hz, 3H, -*i*Pr), 1.33 (d, *J* = 0.6 Hz, 3H, 2-CH_3), 1.52 (s, *J* = 0.6 Hz, 3H, 2-CH_3), 1.56-1.67 (m, 6H, -CH_2), 1.74-1.88 (m, 2H, -*i*Pr und 5-H), 3.26 (dd, *J* = 10.0, 2.4 Hz, 1H, 4-H), 3.38 (dd, *J* = 11.4, 10.2 Hz, 1H, 6-H), 3.82 (dd, *J* = 11.5, 5.0 Hz, 1H, 6-H); **^{13}C NMR** (100.612 MHz, $CDCl_3$): d = 14.83 (*i*Pr), 19.53 (2-Me), 20.24 (*i*Pr), 26.40 (-CH_2), 26.64 (-CH_2), 26.88 (-CH_2), 28.51 (-*i*Pr), 29.78 (2-Me), 32.67 (-CH_2), 33.53 (-CH), 34.60 (-CH), 35.02 (-CH_2), 36.03 (-CH_2), 64.62 (6-C), 77.76 (4-C), 98.02 (2-C); **CH**: calcd C: 75.54, H: 11.89, found C: 75.57, H: 11.75

The ee was estimated by chiral GC (G-TA, isotherm 95°C, 1 mL/min, *anti* isomer (4*R*, 5*S*) t_r = 118.2 min, *anti* isomer (4*S*, 5*R*) t_r = 120.5 min,).

Synthesis of (2*R*, 3*S*, 4*S*)-4-benzyloxy-2-methyl-(1,3)-pentane diol

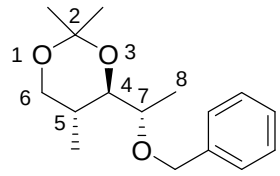


(72.11) (73%) (132.20)

From (*S*)-2-Benzyloxypropionaldehyde (764 mg, 4.65 mmol). Purified by column chromatography (neutral alumina, cyclohexane:EtOAc 8:2? 1:1) to yield the title compound as a colourless oil (541 mg, 73% based on conversion (71%), *dr* 85:5:5:5).

^{1}H NMR (400.13 MHz, $CDCl_3$): d = 0.93 (d, *J* = 7.0 Hz, 3H, CH_3), 1.29 (d, *J* = 6.2 Hz, 3H, CH_3), 1.87-1.97 (m, 1H, 2-H), 2.84 (s, 2H, -OH), 3.38 (dd, *J* = 6.4, 4.6 Hz, 1H, 3-H), 3.64 (dd, *J* = 11.0, 6.5 Hz, 1H, 1-H), 3.68 (qd, *J* = 6.3, 4.5 Hz, 1H, 4-H), 3.73 (dd, *J* = 11.0, 3.8 Hz, 1H, 1-H), 4.45 (d, *J* = 11.5 Hz, 1H, -CH_2Ph), 4.70 (d, *J* = 11.5 Hz, 1H, -CH_2Ph), 7.28-7.40 (m, 5H, Ph); **^{13}C NMR** (100.61 MHz, $CDCl_3$): d = 14.6 (CH_3), 15.9 (CH_3), 36.7 (2-C), 66.6 (1-C), 70.9 (-CH_2Ph), 75.2 (4-C), 80.3 (3-C), 127.9 (1C, Ar-C), 127.9 (2C, C, Ar-C), 128.5 (2C, Ar-C), 138.2 (1C, Ar-C), **CH**: calcd C: 69.61, H: 8.99, found C: 69.31, H: 9.07.

(4*S*, 5*R*, 7*S*)-4-[1-benzyloxyethyl]-2,2,-5-trimethyl-[1,3]dioxane

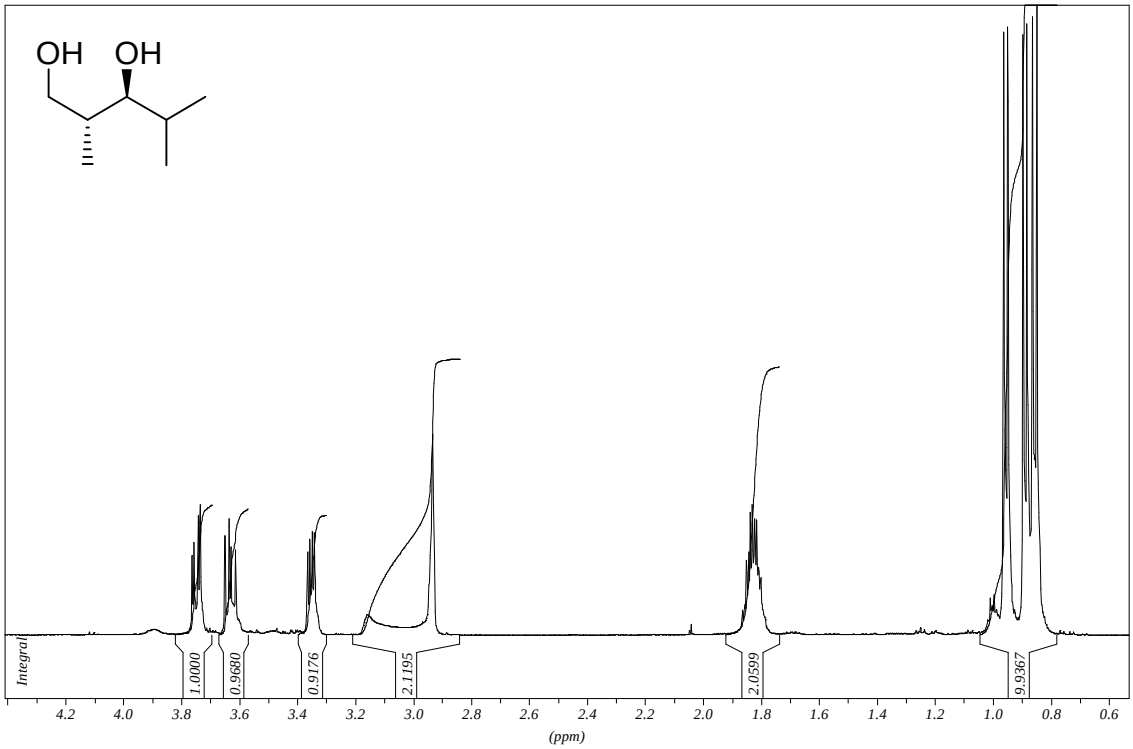


$C_{16}H_{24}O_3$
Mol. Wt.: 264,36

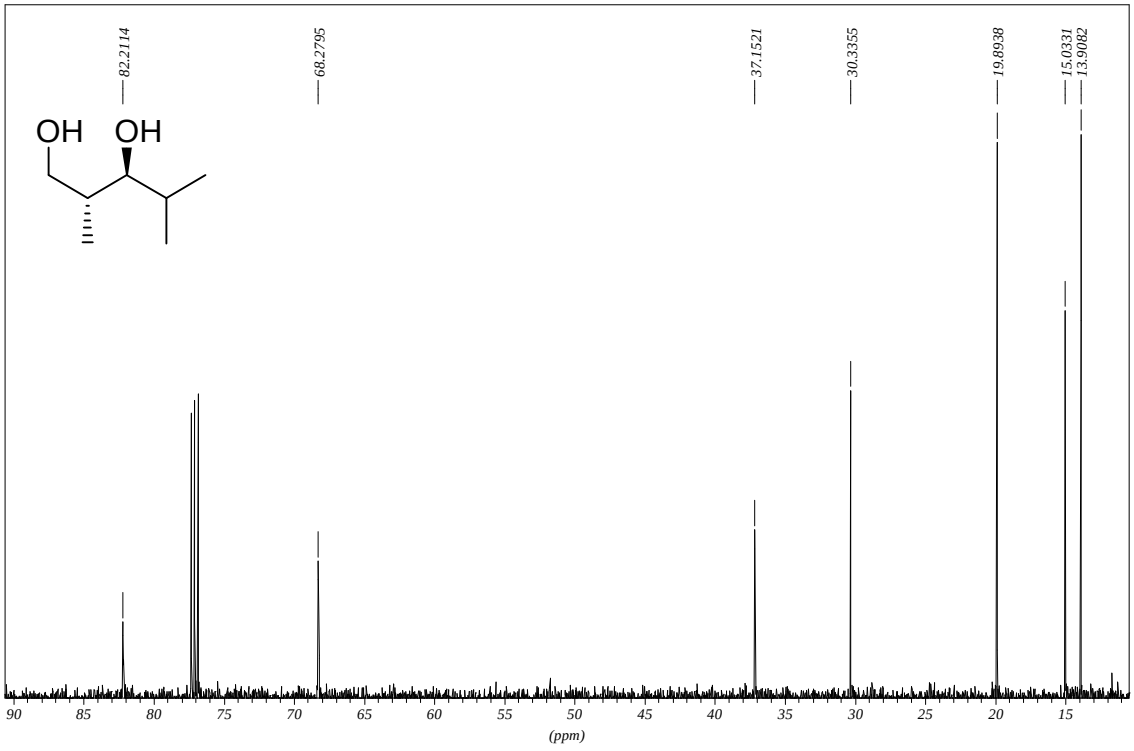
^{1}H NMR (499.87 MHz, C_6D_6): d= 0.55 (d, *J* = 6.6 Hz, 3H, 5-Me), 1.22 (d, *J* = 6.6 Hz, 3H, 8-H), 1.27 (s, 3H, 2-Me), 1.50 (s, 3H, 2-Me), 2.08-2.18 (m, 1H, 5-H), 3.30 (pt, *J* = 11.3 Hz, 1H, 6-H), 3.39 (dd, *J* = 10.1, 2.8 Hz, 1H, 4-H), 3.54 (qd, *J* = 6.3, 2.5 Hz, 1H, 7-H), 3.60 (dd, *J* = 11.3, 5.1 Hz, 1H, H-6), 4.23 (d, *J* = 11.9 Hz, 1H, -CH_2Ph), 4.57 (d, *J* = 11.9 Hz, 1H, -CH_2Ph), 7.07-7.28 (m, 5H, Ph); **^{13}C NMR** (125.69 MHz, C_6D_6): d= 12.6 (-CH_3), 14.8 (-CH_3), 19.1 (2-Me), 29.9 (2-Me or 5-C), 30.0 (2-Me or 5-

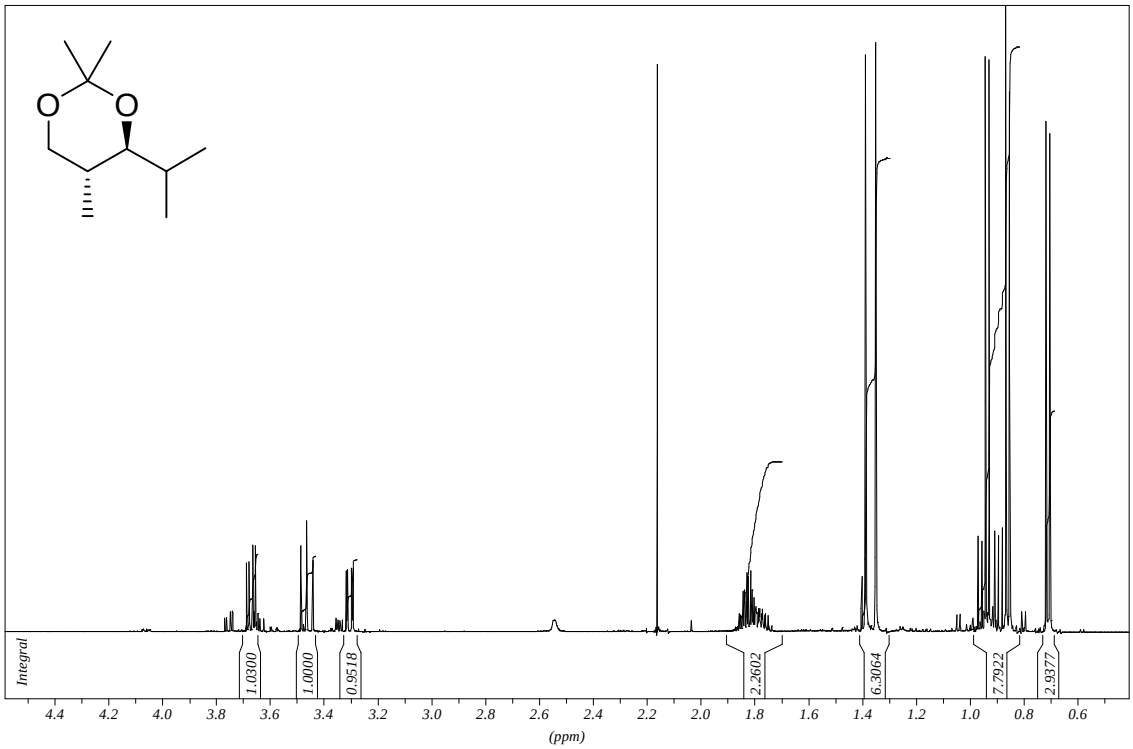
C), 66.2, 70.8, 75.1, 77.1, 98.3 (2-C), 127.5 (C-Ar), 127.8 (2C, C-Ar), 128.4 (2C, C-Ar), 138.9 (C-Ar); **CH**: calcd C: 72.69, H: 9.15, found C: 72.45, H: 9.12.

3. Spectra

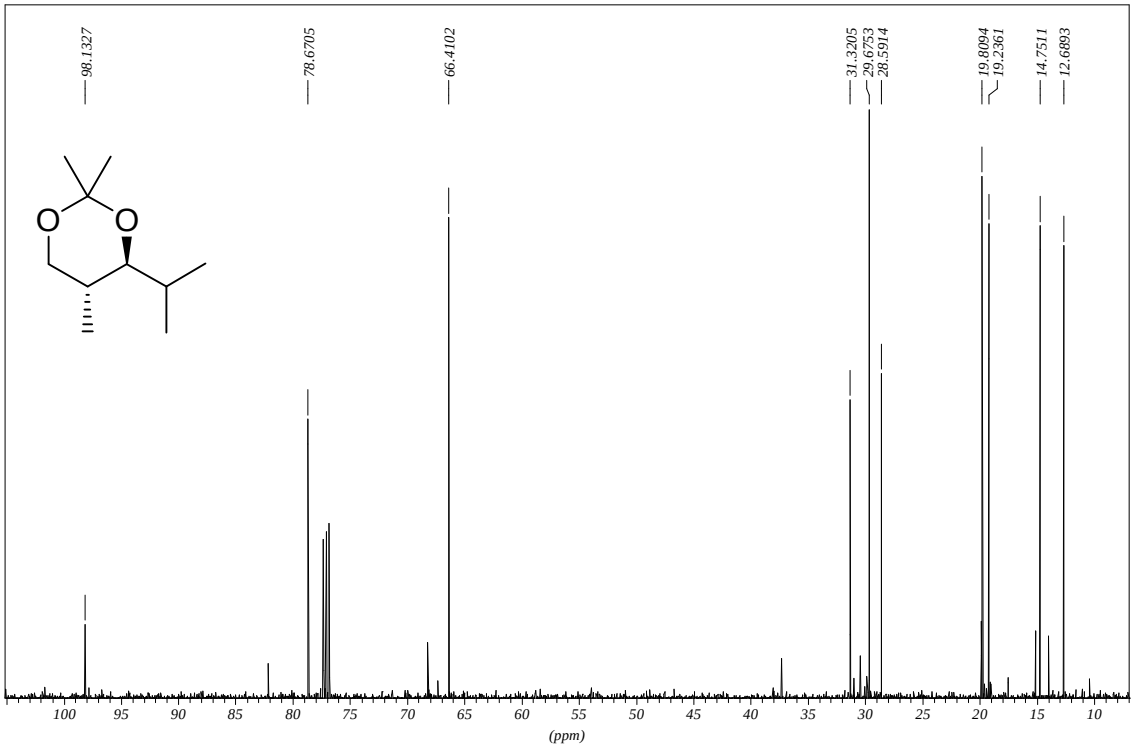


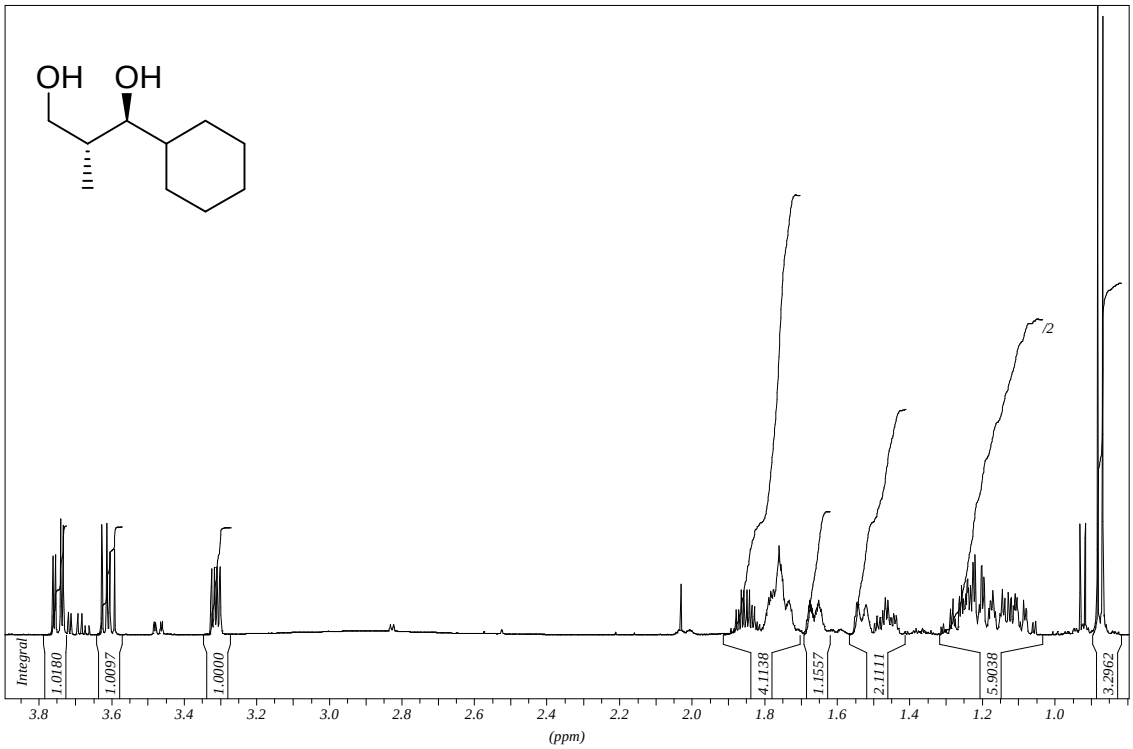
abbtmz03-505,abillard,oa-416-b-2f-1,cdcl3=77,1



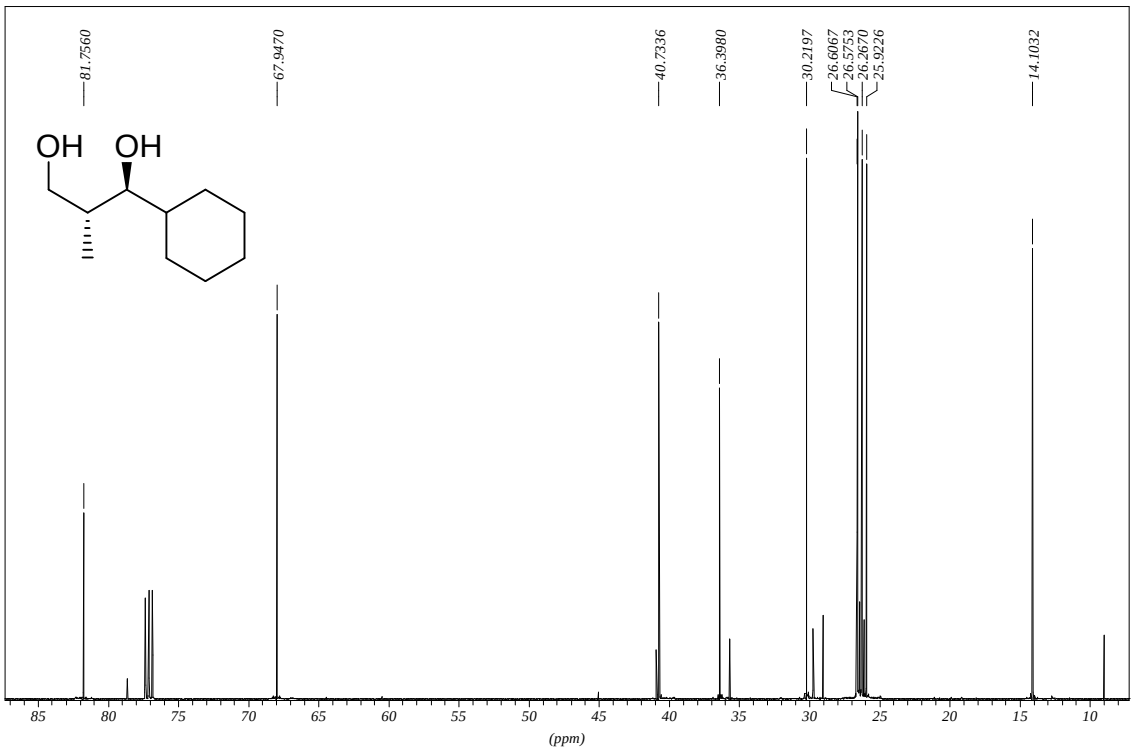


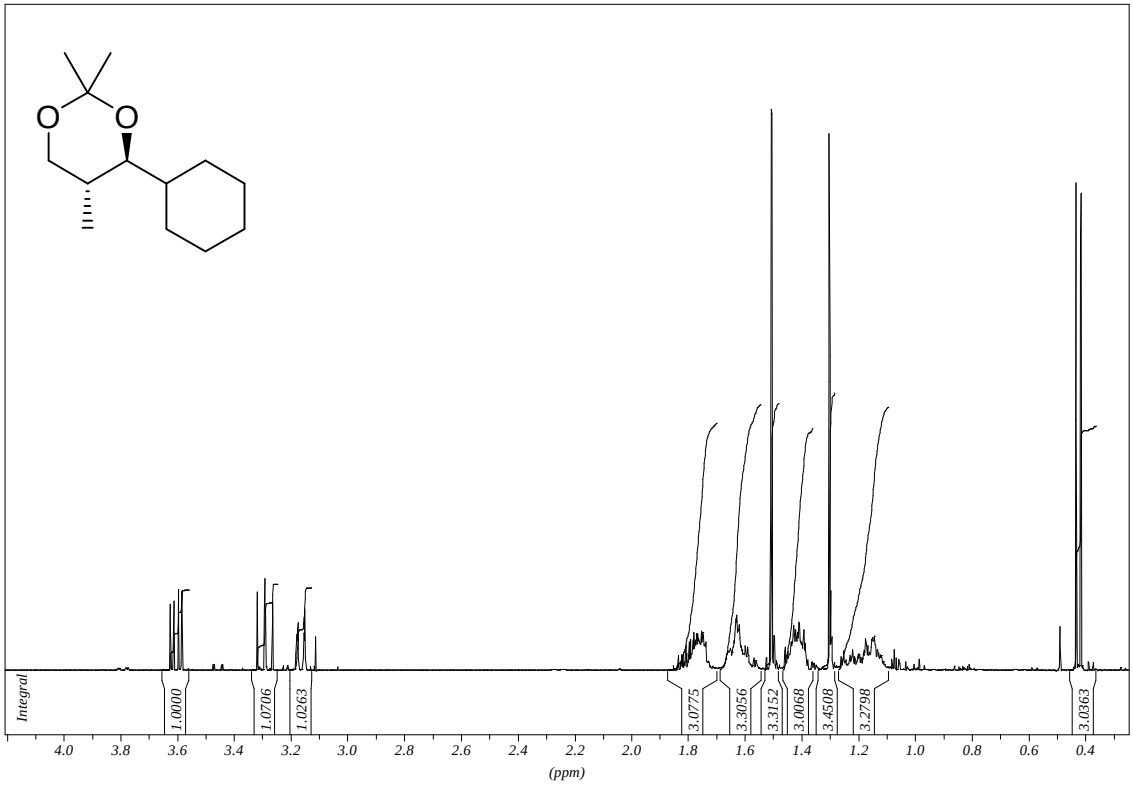
ABBTAP06-510,ABILLARD,OA-416-MIX,CDCL3=77,1





ABBTMZ18-515,ABILLARD,OA-419-P,CDCL3=77,1




Integral
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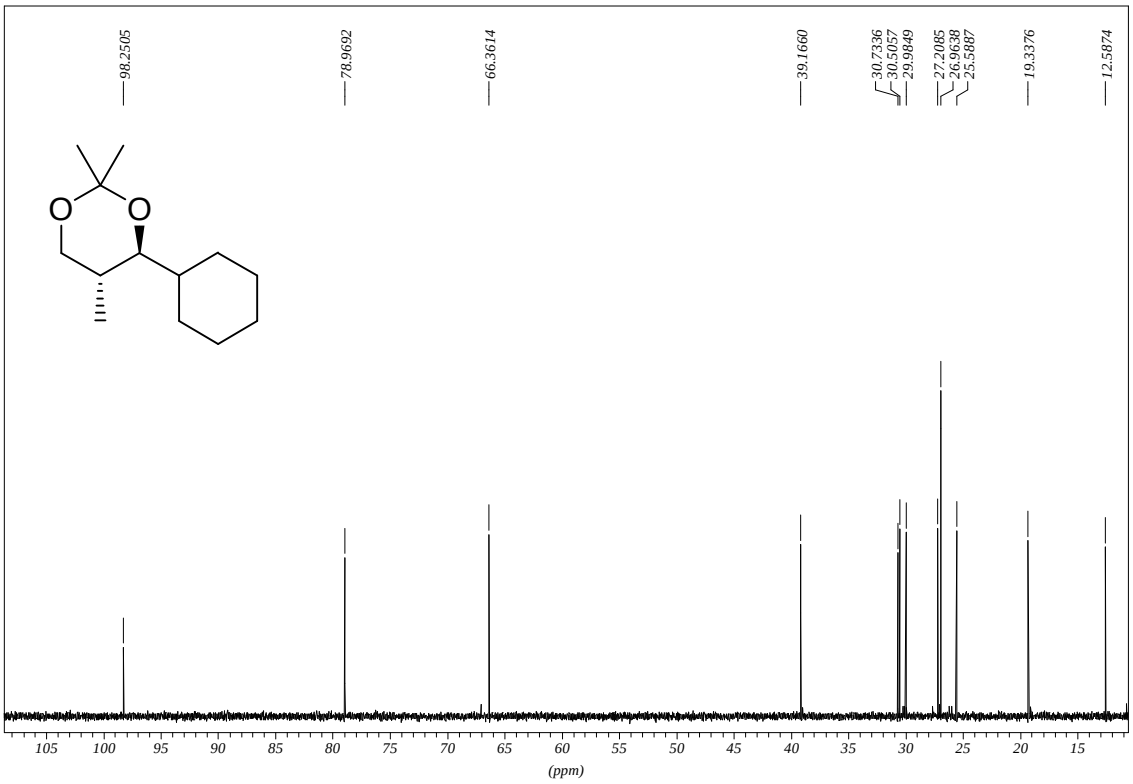
3.0775
3.3056
3.3152
3.0068
3.4508
3.2798
3.0363
4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4
(ppm)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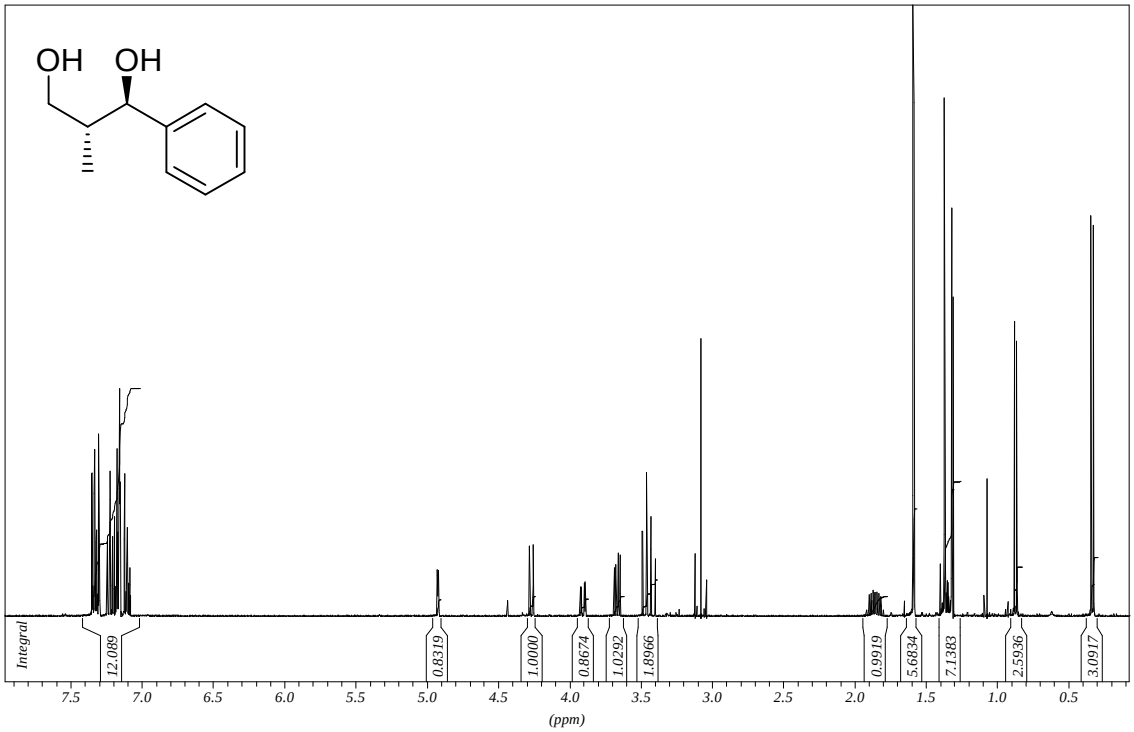
39.1660
30.7336
30.5057
29.9849
27.2085
26.9638
25.5887
19.3376
12.5874
105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15
(ppm)



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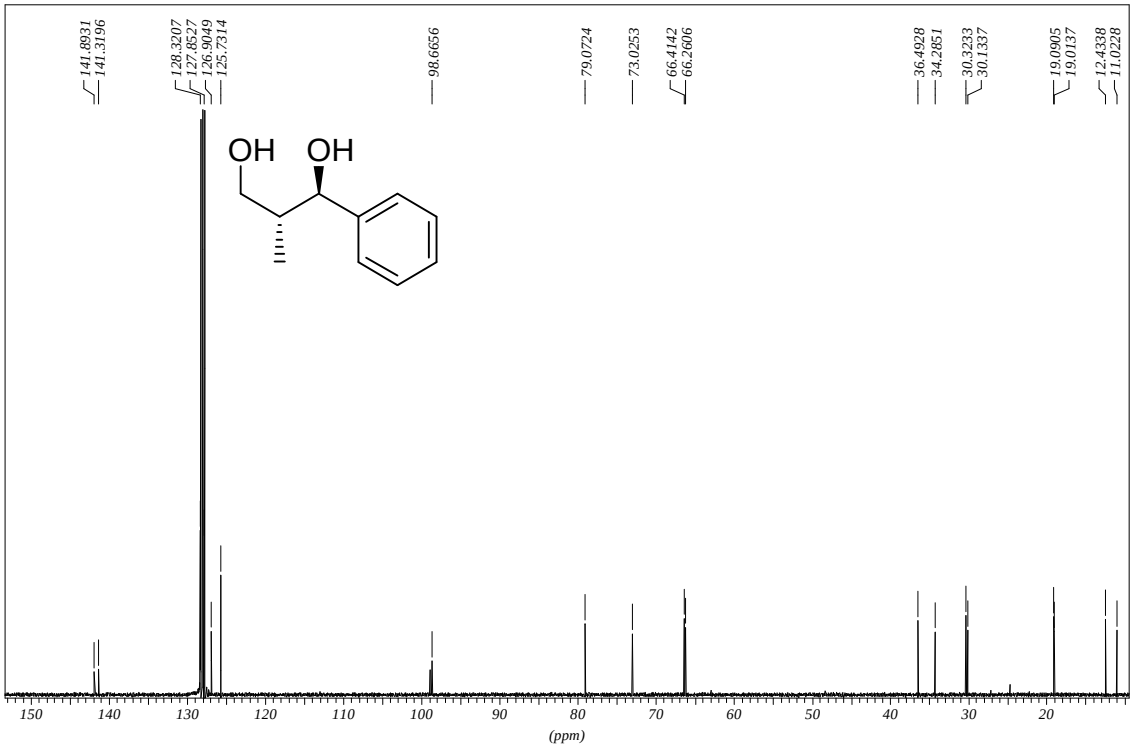
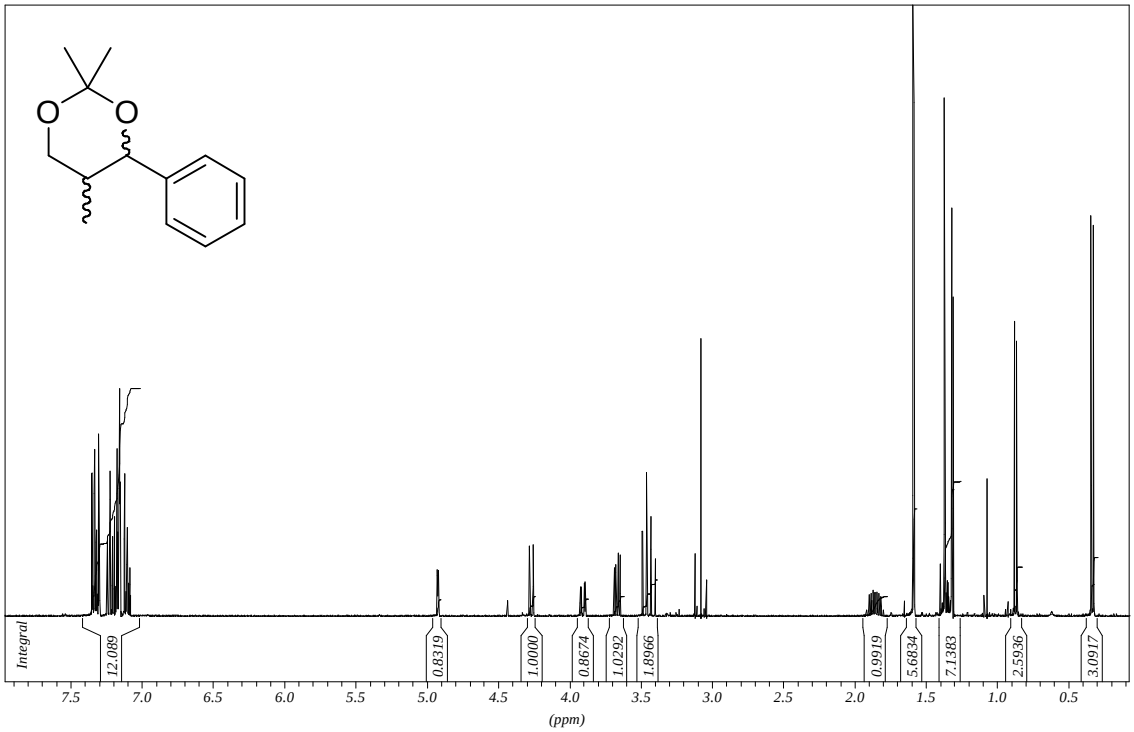
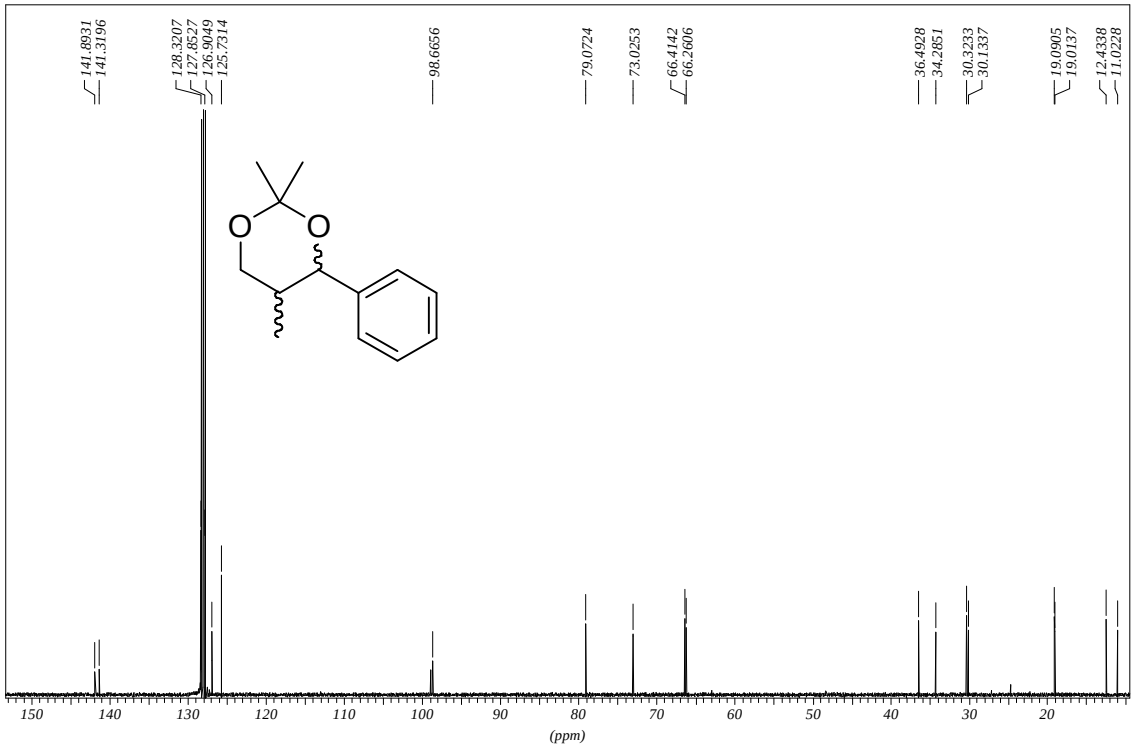
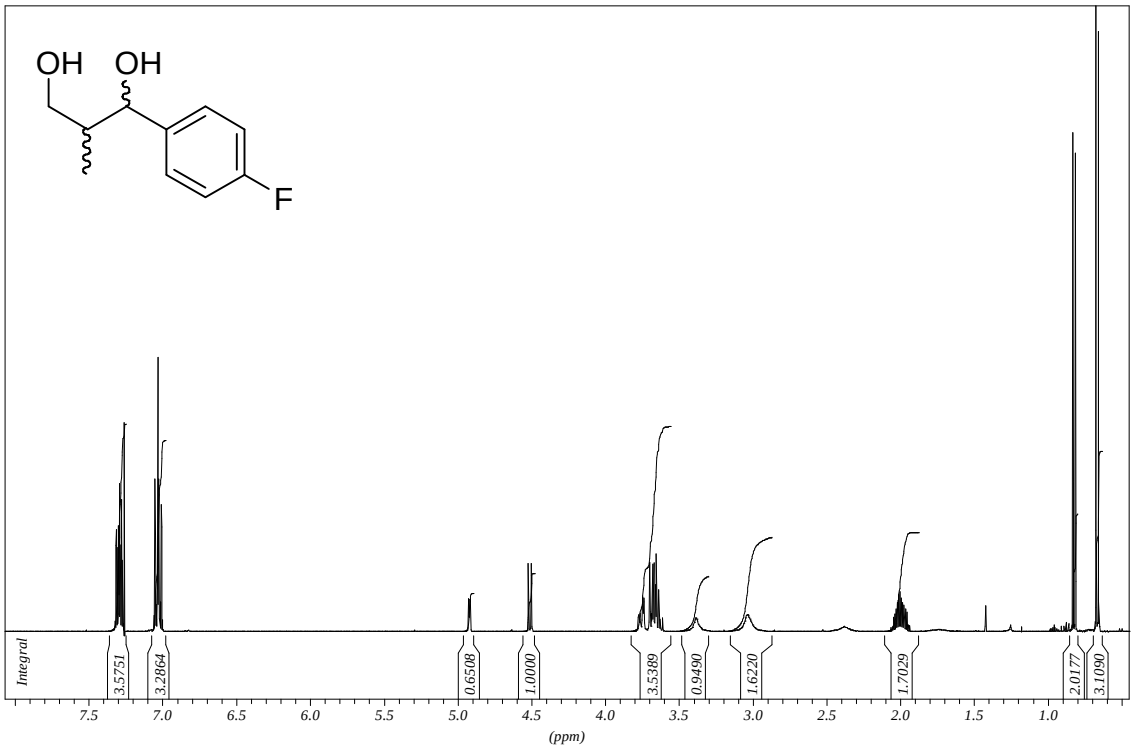


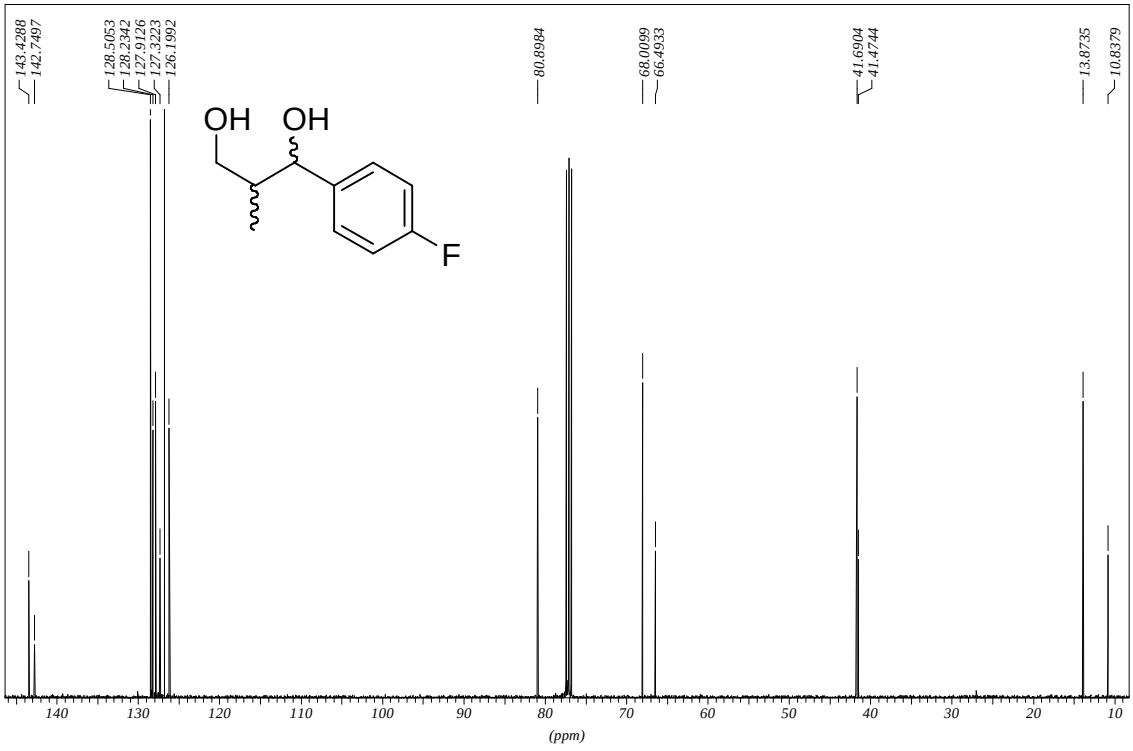


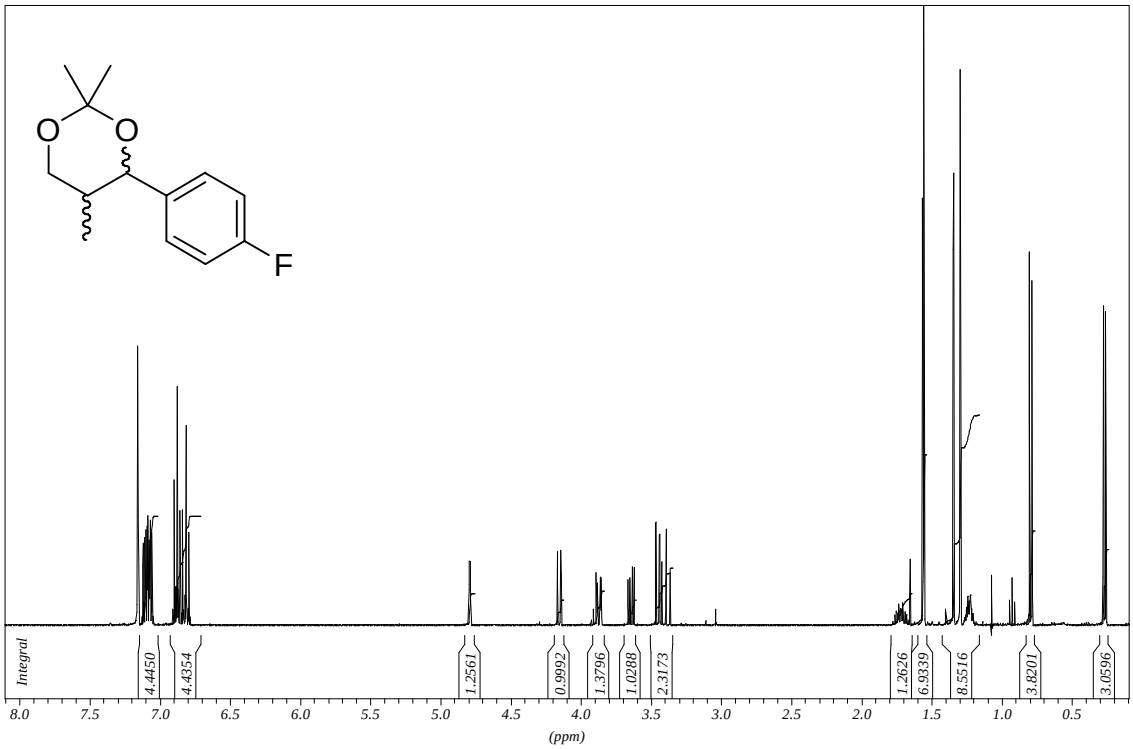
ABBTOK26-4032,ABILLARD,OA-540-C-F,C6D6=128,00



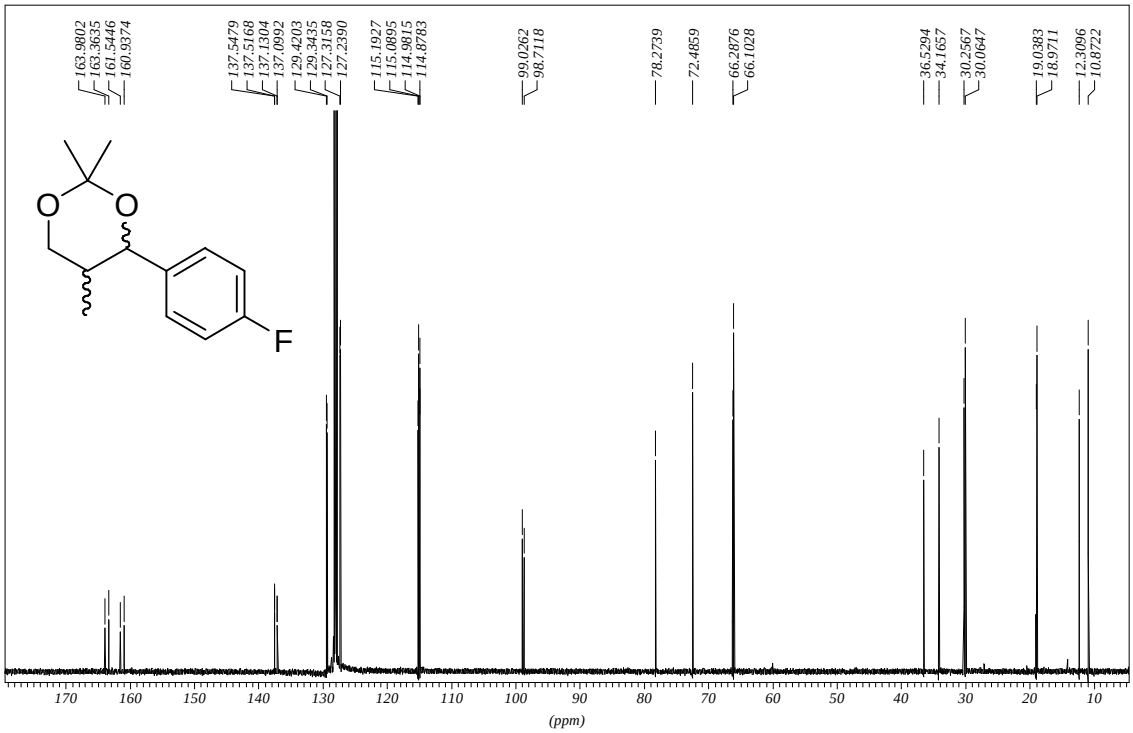


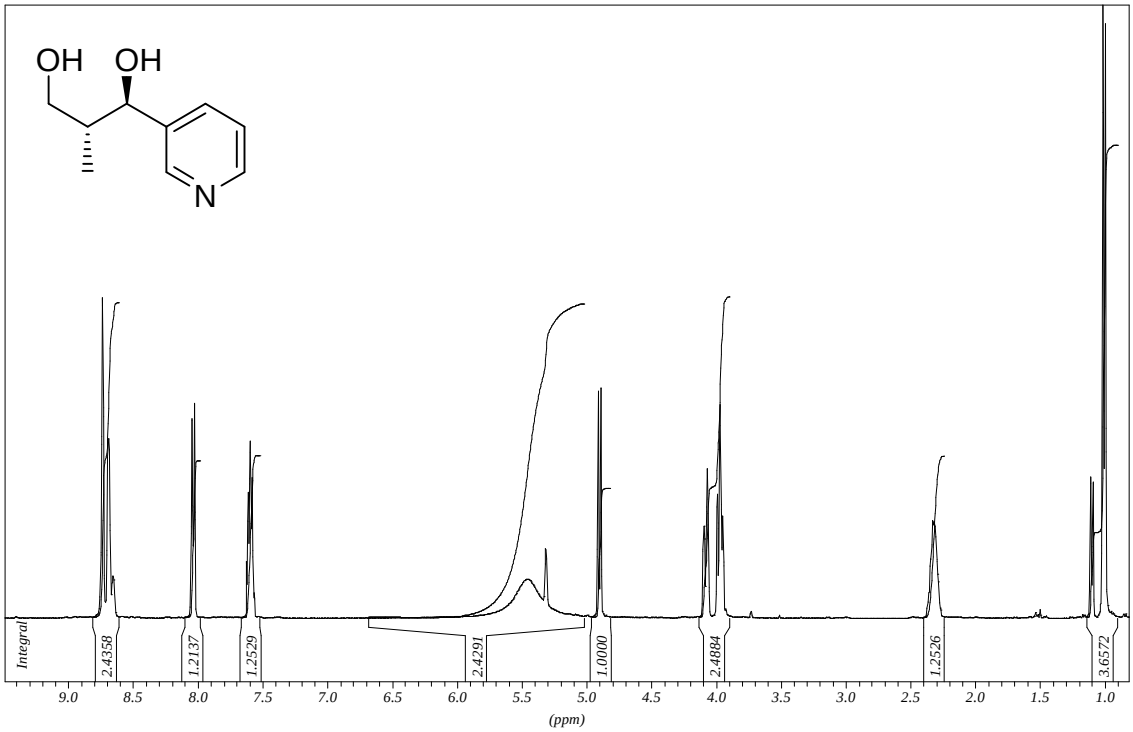
ABBTNO10-4032,ABILLARD,OA-550-B-KG,CDCL3=77,1



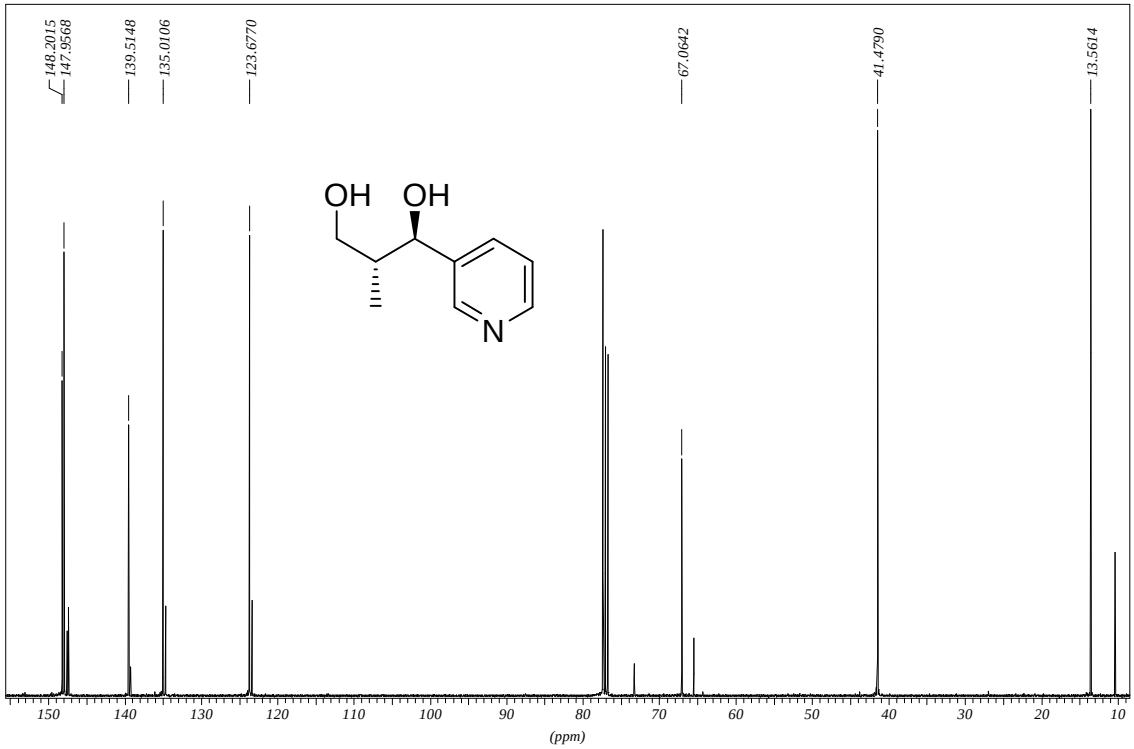


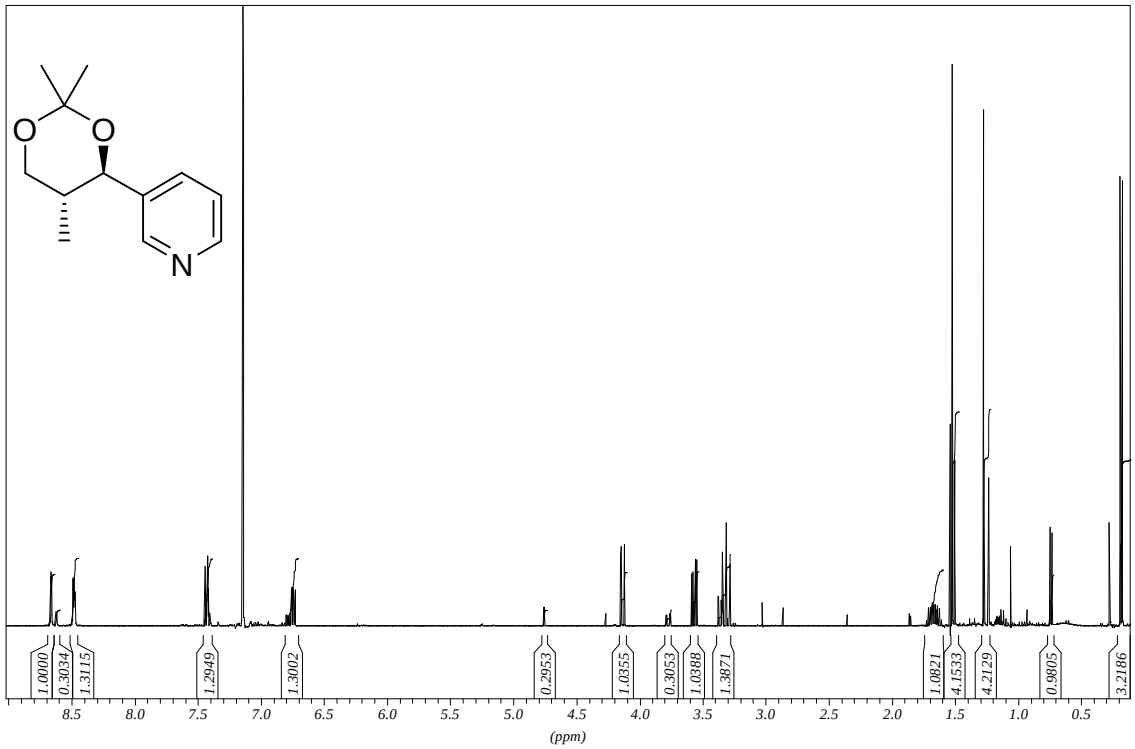
ABBTOK26-4042,ABILLARD,OA-531-C-F.C6D6=128,00



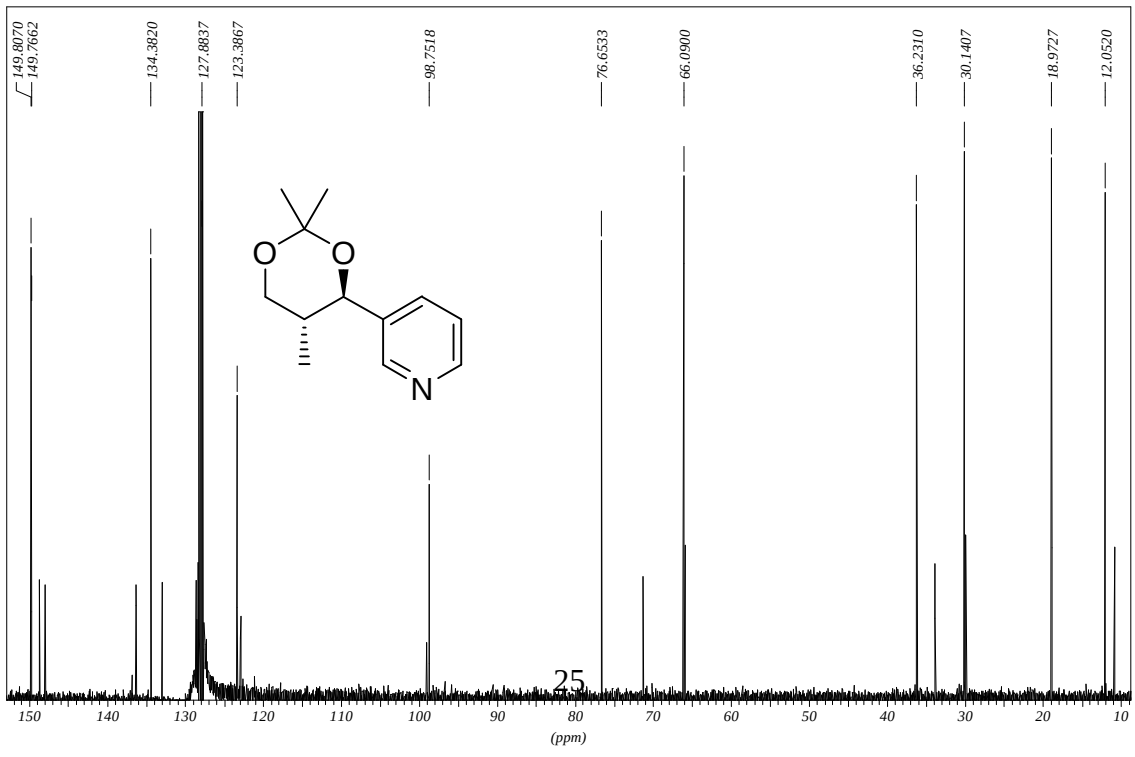


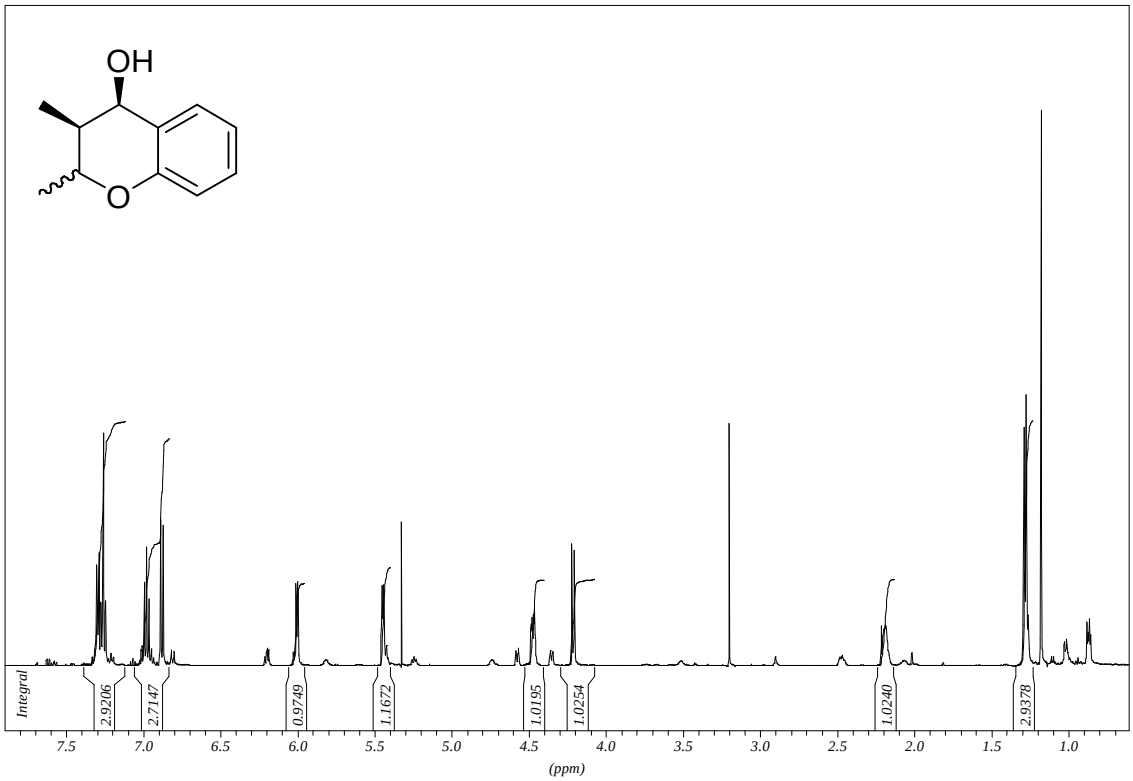
AbBtJa17-4062,Abillard,OA-749-b-diol,CDCl3=77,1

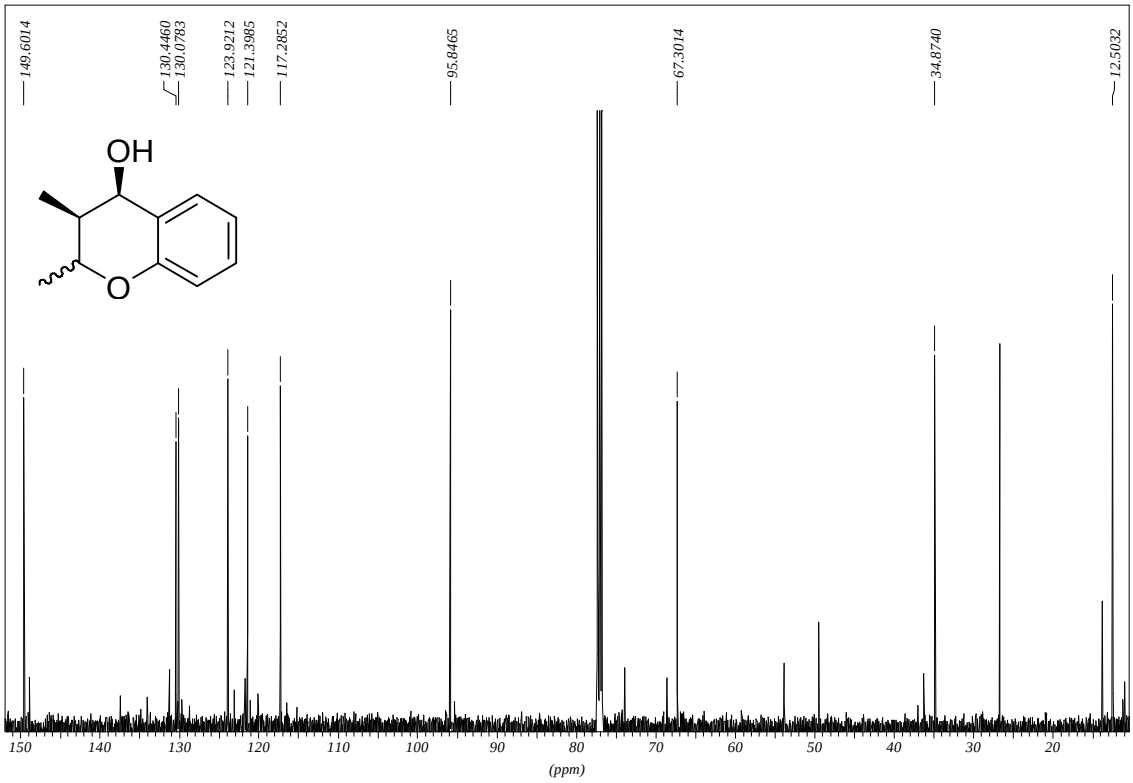


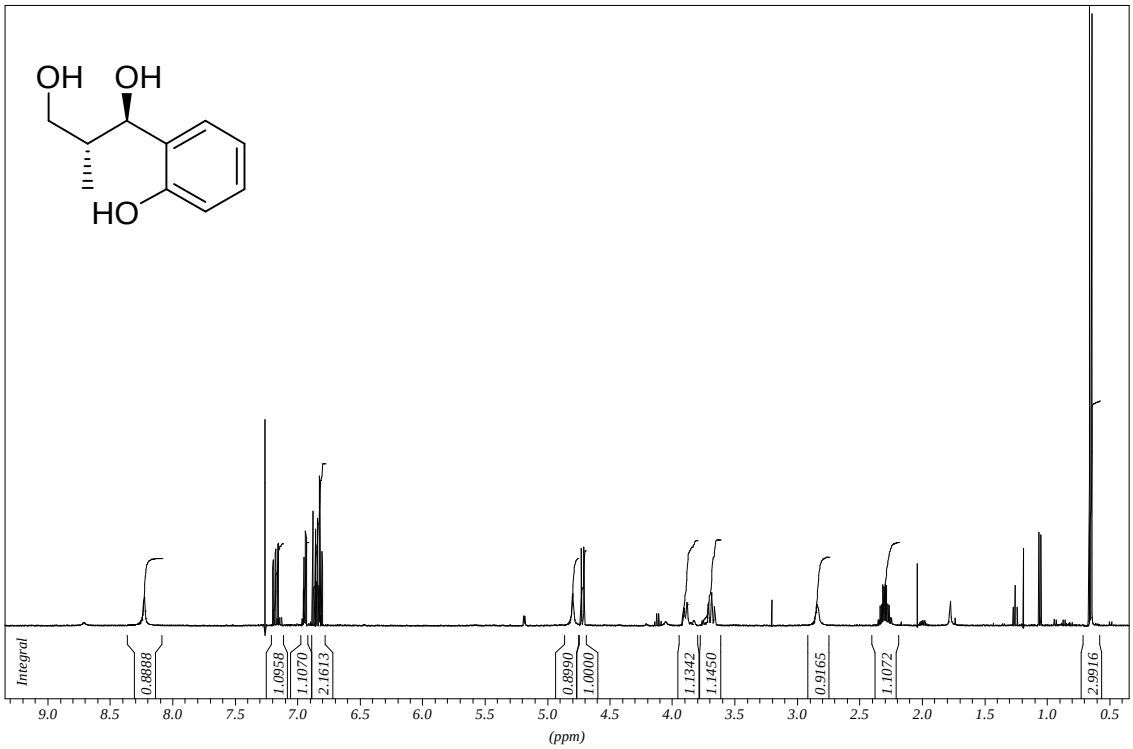


AbBtJn09-4061,Abillard,OA-749-2-c-Ac,C6D6=128

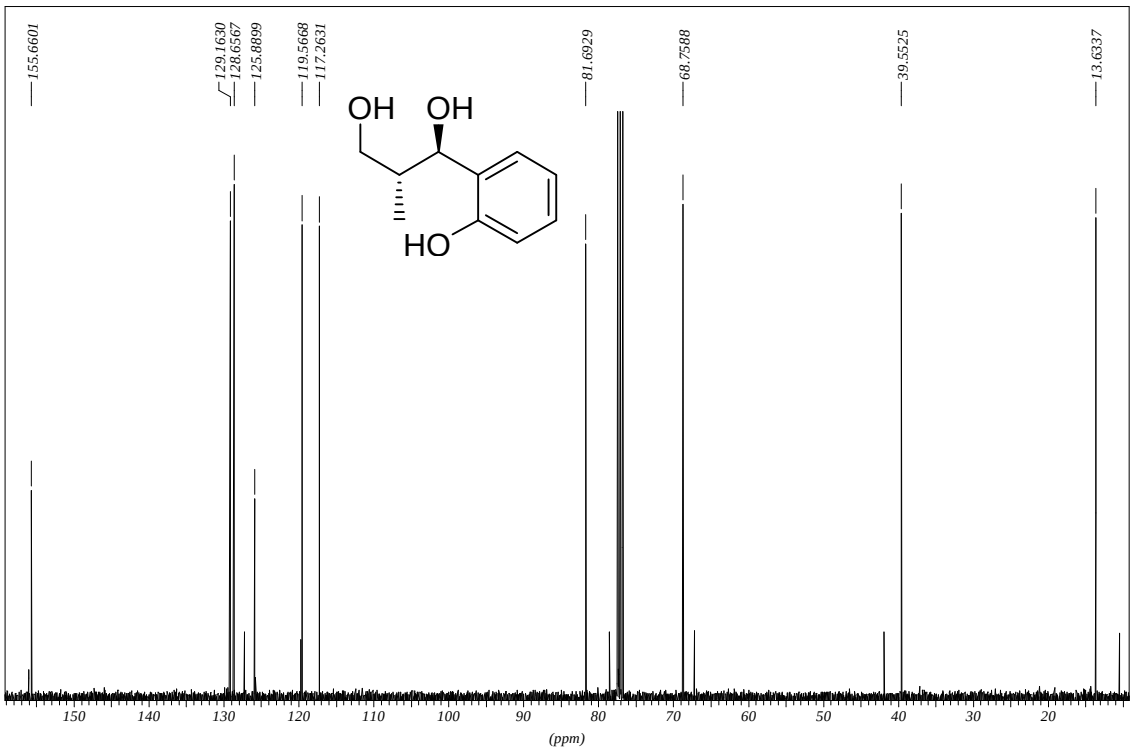


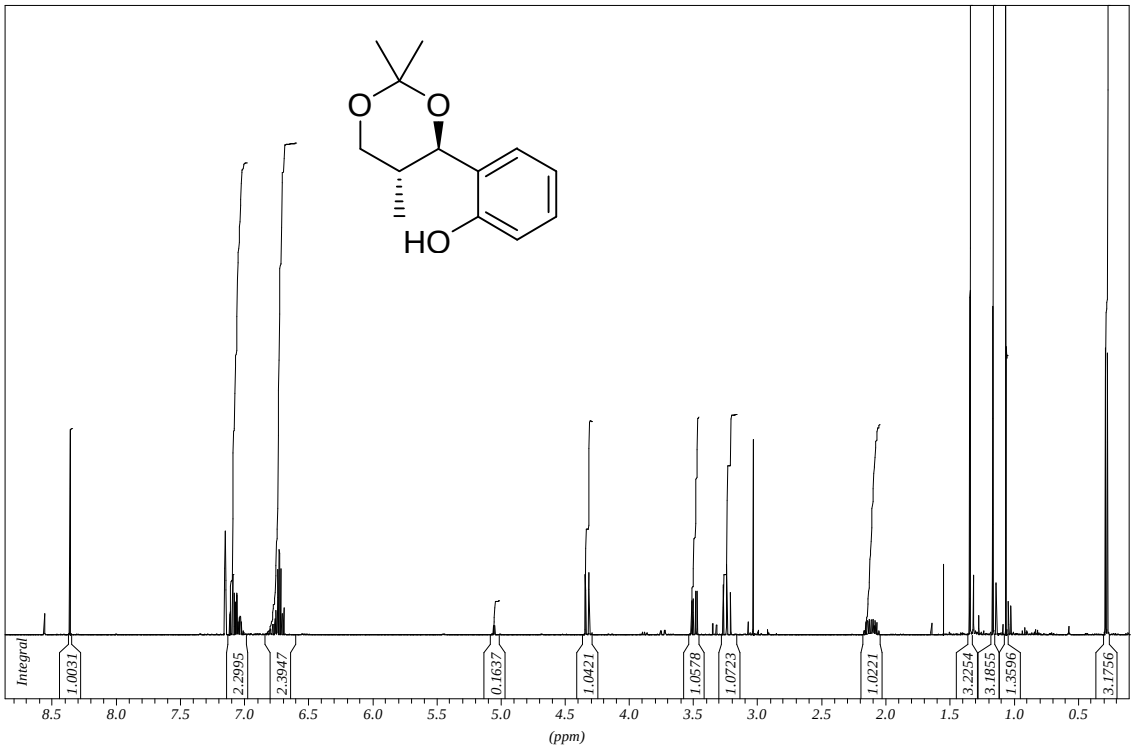

OH
O
Integral
2.9206
2.7147
0.9749
1.1672
1.0195
1.0254
1.0240
2.9378
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)


149.6014
130.4460
130.0783
123.9212
121.3985
117.2852
95.8465
67.3014
34.8740
12.5032
OH
O
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)

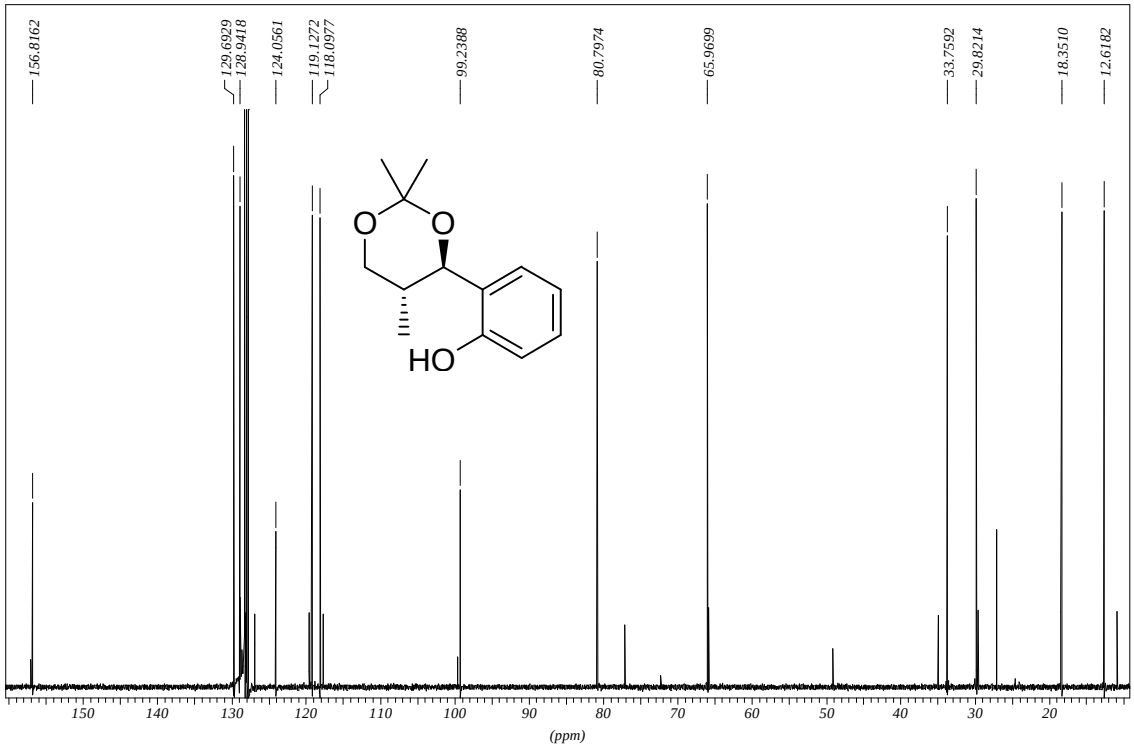


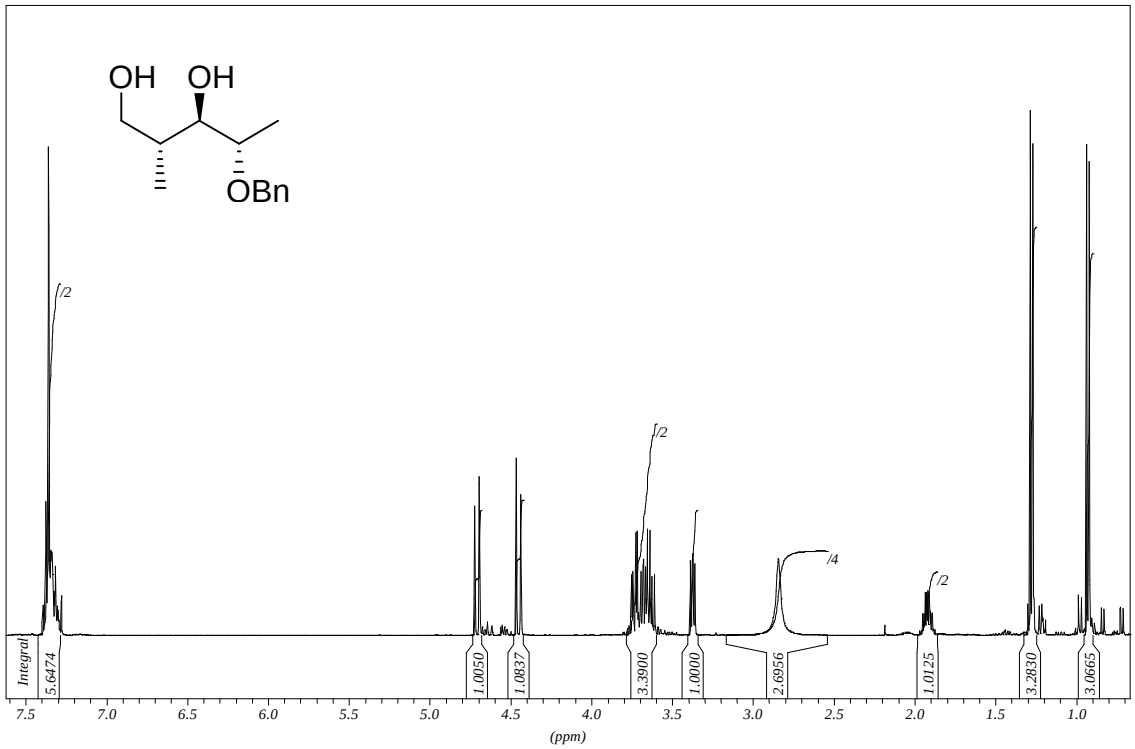
AbBtNo15-4012,Abillard,OA-Triol-F,CDCl3=77,1



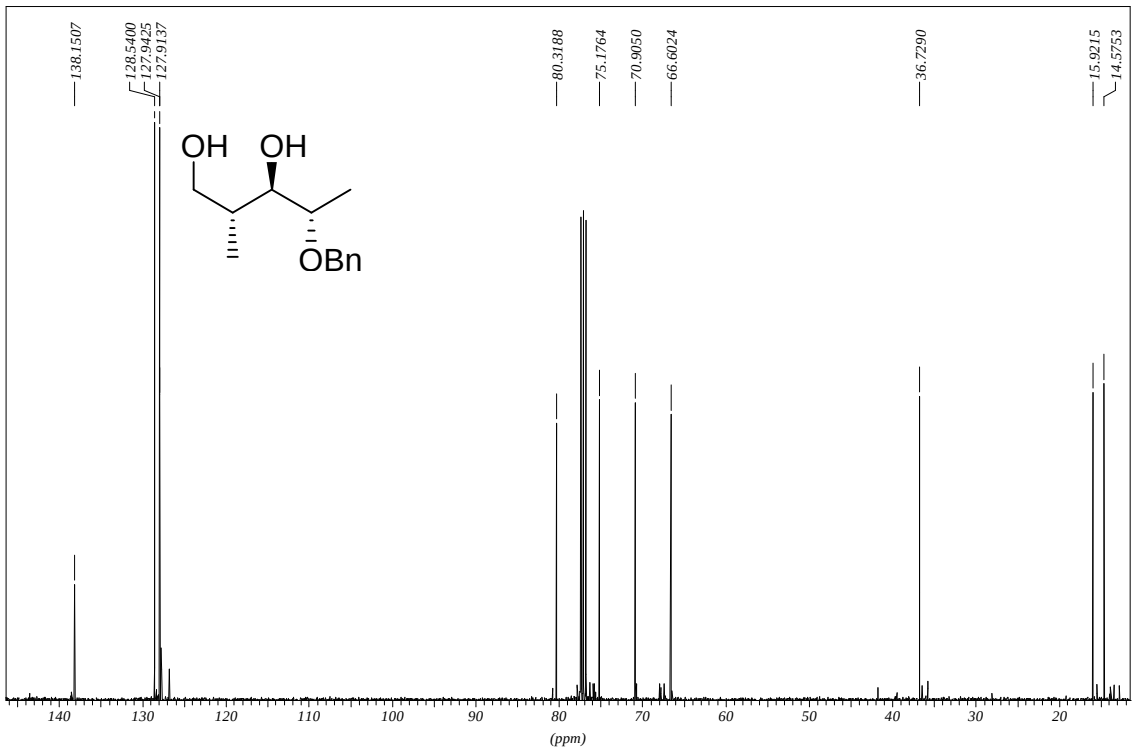


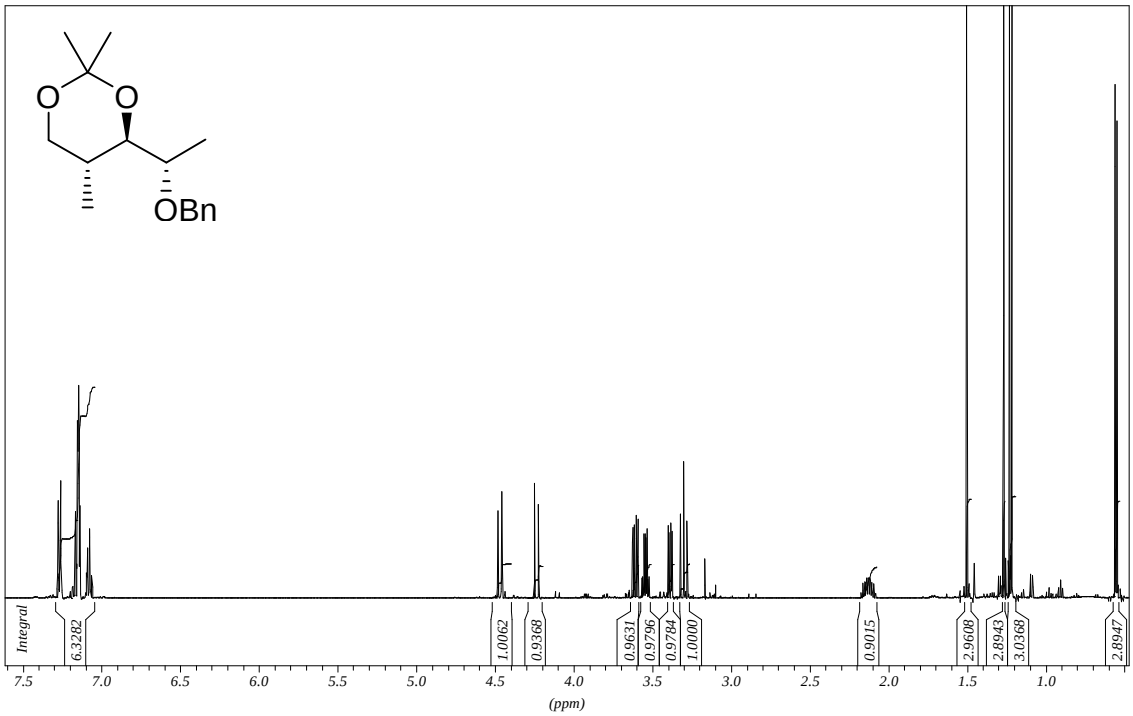
AbBtNo02-4022,Abillard,OA-866-c-f,C6D6=128

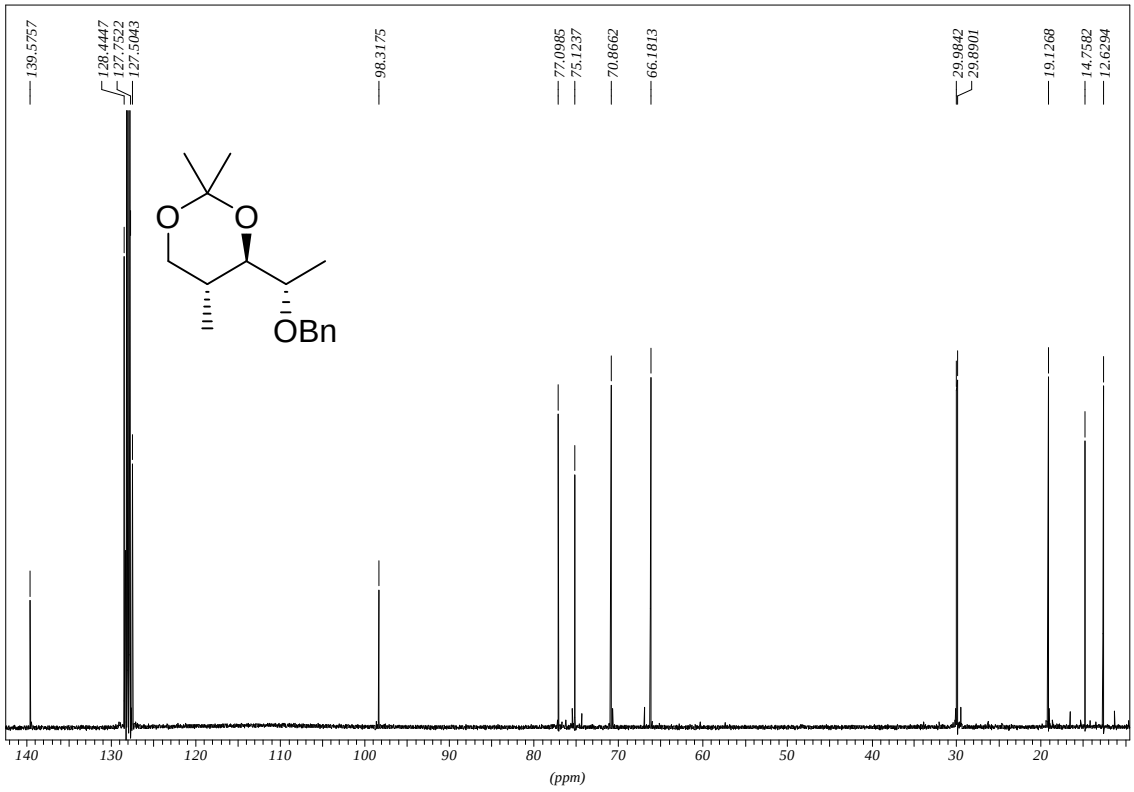


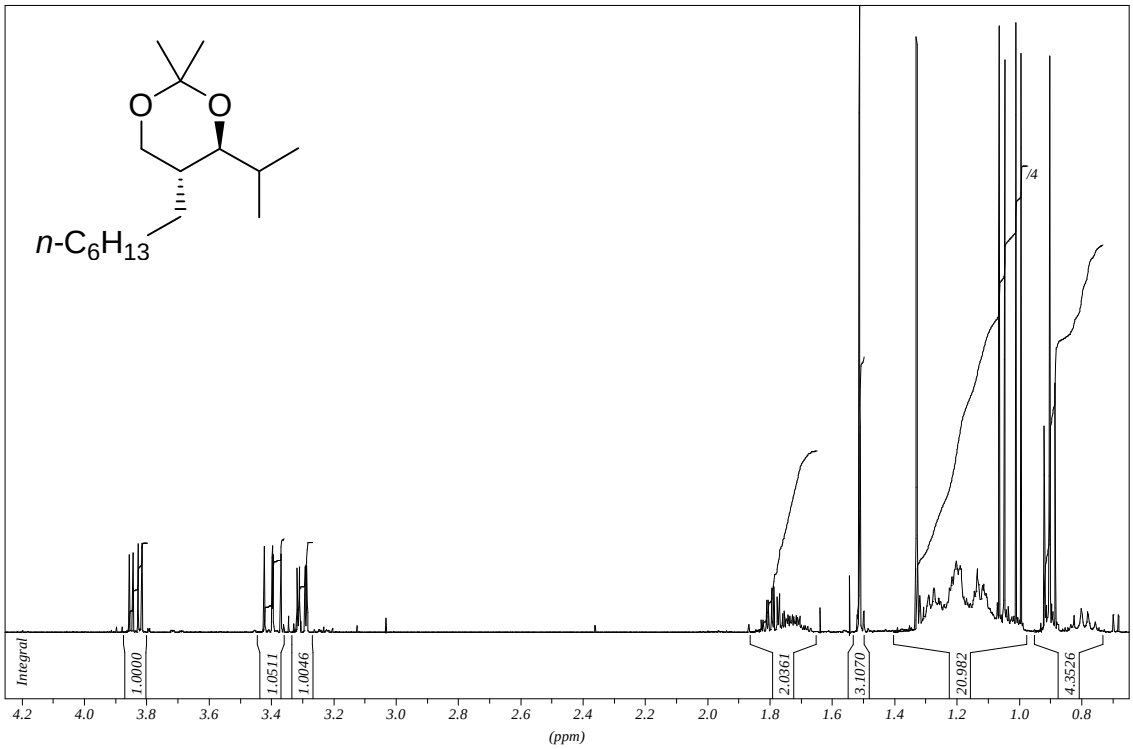


AbBtAp10-4022,Abillard,OA-EB-74-Diol,CDCl3=77,1

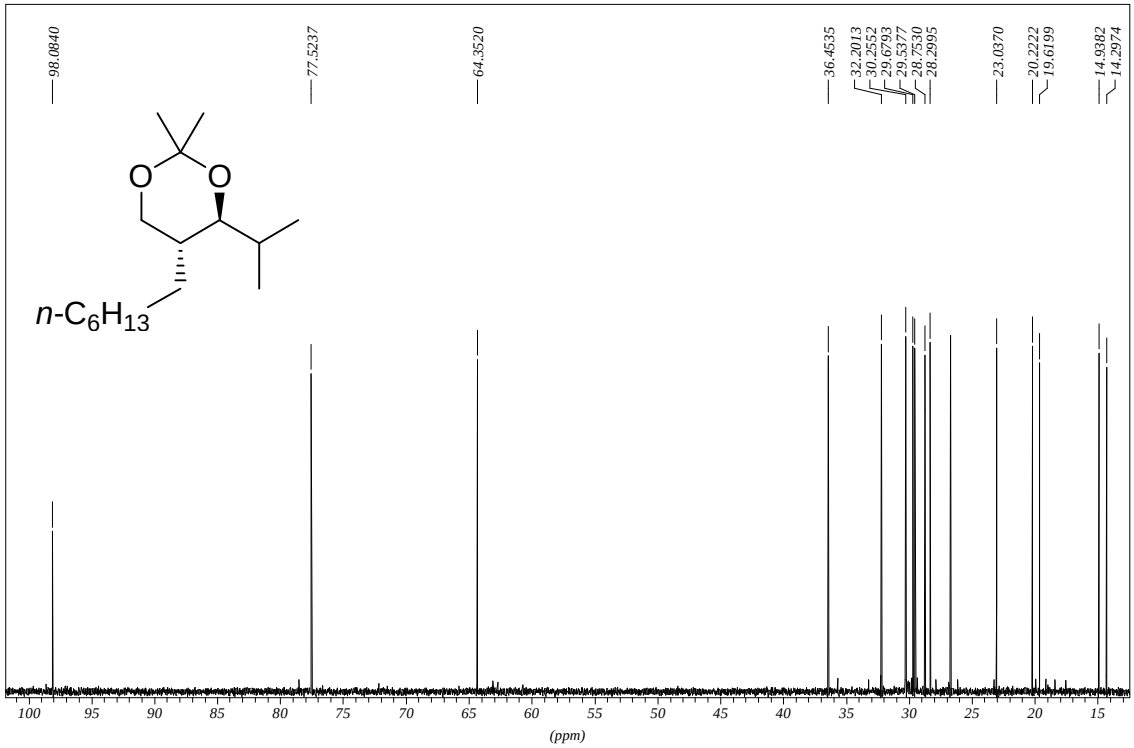


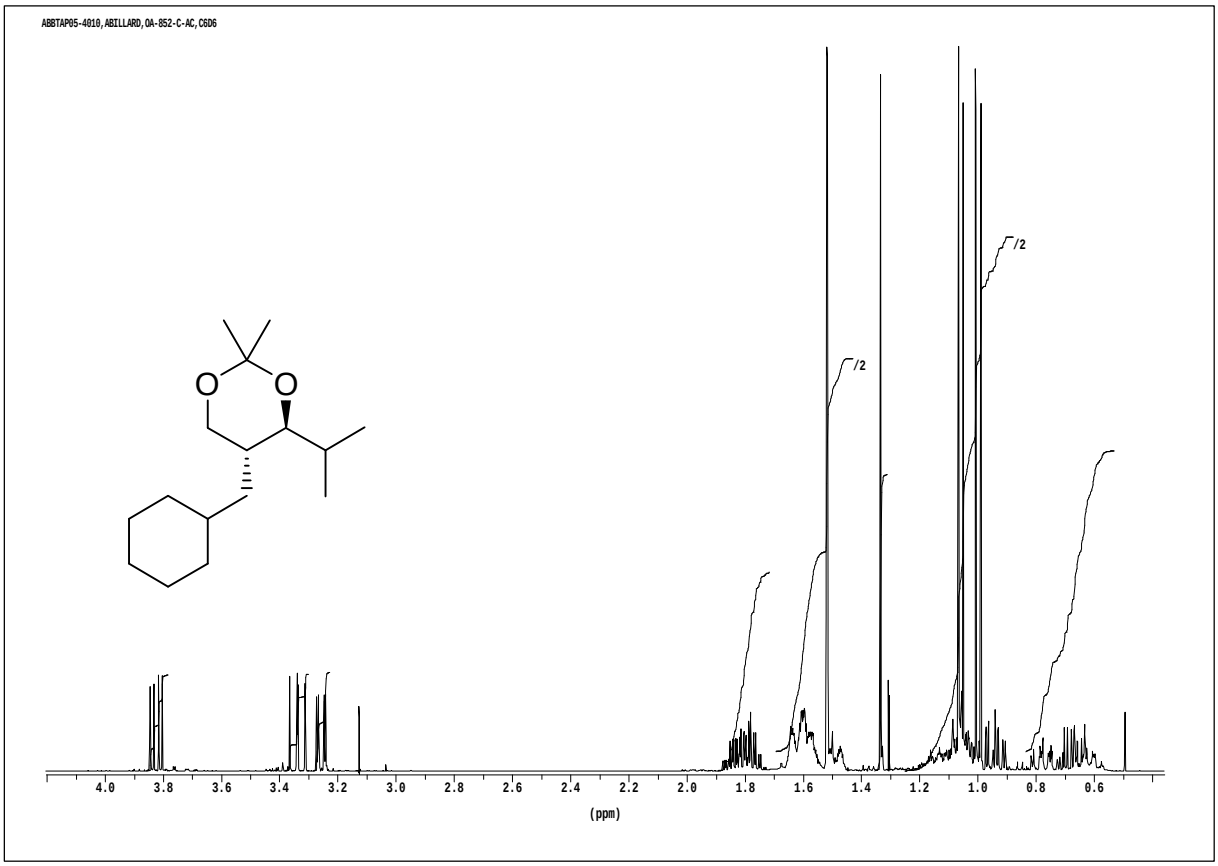

O
O
OBn
Integral
6.3282
1.0062
0.9368
0.9631
0.9796
0.9784
1.0000
0.9015
2.9608
2.8943
3.0368
2.8947
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

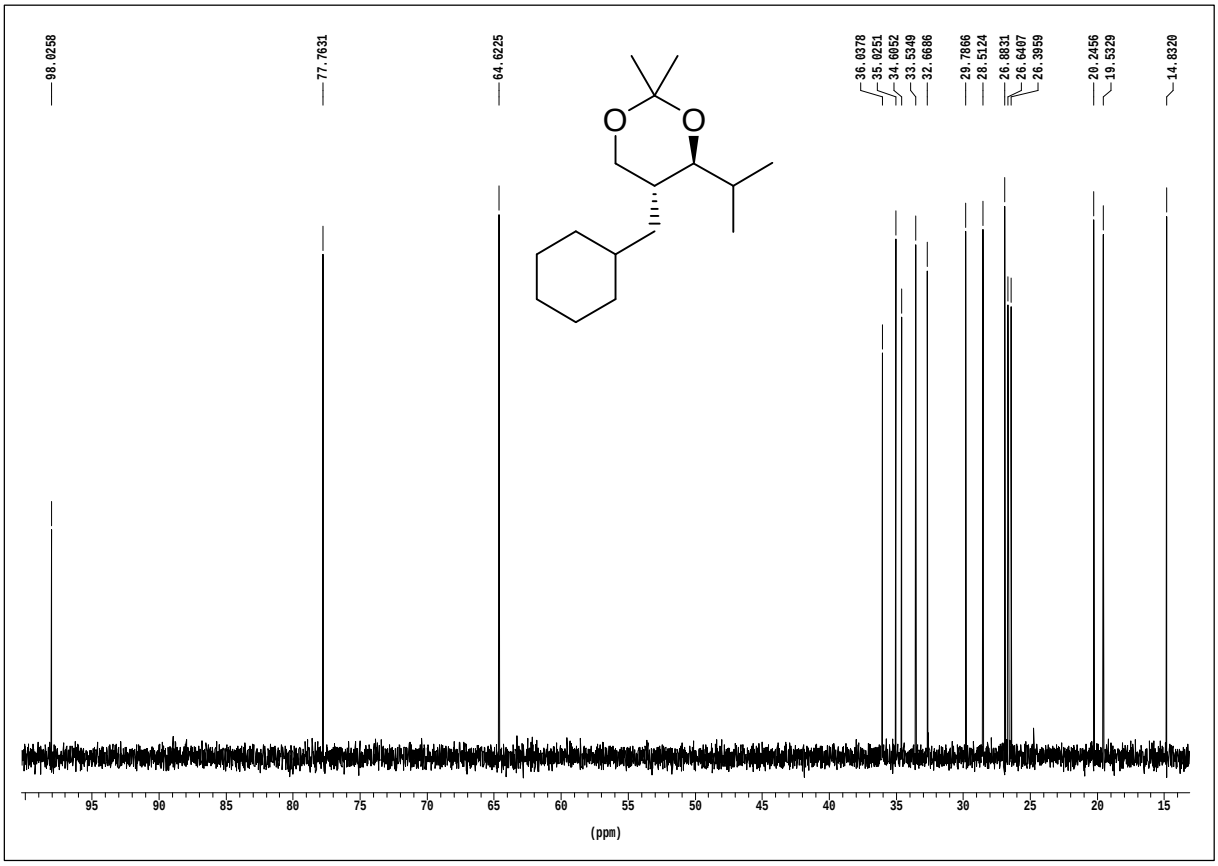

139.5757
128.4447
127.7522
127.5043
98.3175
77.0985
75.1237
70.8662
66.1813
29.9842
29.8901
19.1268
14.7582
12.6294
O
O
OBn
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)



AbBtJn09-4054,Abillard,OA-459-c-Ac,C6D6




ABBTAP05-4010,ABILLARD,OA-852-C-AC,C6D6
/2
/2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
(ppm)


98.0258
77.7631
64.6225
36.0378
35.0251
34.6052
33.5349
32.6686
29.7866
28.5124
26.8831
26.6407
26.3959
20.2456
19.5329
14.8320
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
(ppm)

4. Literature

(1) D. R. Burfield, R. H. Smithers, *J. Org. Chem.* **1978**, *43, 20*, 3966-3968.

(2) Ghosh, A. K.; Kim, J. *Org. Lett.* **2003**, *5*, *7*, 1063-1065.

(3) R. O. Duthaler, P. Herold, S. Wyler-Helfer, M. Riediker *Helv. Chim. Acta* **1990**, *73*, *3*, 659-673.

(4) Fujimoto, Katsuhiko; Sakai, Hirokazu; Nakai, Takeshi; *Chem.Lett.* **1993**, *8*, 1397-1400.