Supporting Information

Atropselective Synthesis of *N,C*-Bis(diphenylphosphanes) From Bridged 2-Arylindoles Based on Effective Point-to-Axial Asymmetric Inductions after an Unusual Dilithiation

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Table of Contens

1. General Methods

Working technique: All reactions not containing water were carried out under an N_2-atmosphere. Reaction flasks were dried in an oven (65°C) and in vacuo with a heat gun prior to use. Liquids were added with syringe and cannula through a rubber septum. Solids were added in a N_2-counterflow. Reactions containing water were carried out without inert gas atmosphere. All reactions requiring heating were heated in an oil bath.

Solvents: Tetrahydrofuran (THF) for reactions was distilled over potassium, diethyl ether (Et_2O) over sodium-potassium alloy, and dichloromethane (CH_2Cl_2) and triethyl amine (NEt_3) over CaH_2 under an N_2-atmosphere prior to use. Other solvents for that purpose were obtained commercially as "dry" or "extra dry" solvents and used without further purification. Cyclohexane (*c*-C_6H_{12}), ethyl acetate (AcOEt), methanol (MeOH), ethanol (EtOH), dichloromethane (CH_2Cl_2), and *tert*-butyl methyl ether (*t*-BuOMe) for workup and column chromatography were distilled using a rotary evaporator prior to use to remove high boiling fractions. Diethyl ether (Et_2O), pentane, and chloroform ($CHCl_3$) for that purpose were obtained as p. a. grade solvents and used without further purification.

Organo-lithium reagents were stored in a refrigerator in Schlenk flasks with PTFE screw caps and PTFE valves and were titrated using *N*-pivaloyl-*o*-toluidine[1] prior to use.

Chromatography: Thin layer chromatography (TLC) was used to monitor reactions and purification procedures. Merck silica plates with glass as supporting material (TLC Silicagel 60 F_{254}) were used. Chromatograms were, if applicable, marked in UV light at 254 nm and subsequently stained using one of the following stains: permanganate stain (0.65 g $KMnO_4$, 3.15 g K_2CO_3, 125 mL H_2O) or cerium sulfate / molybdophosphoric acid (10 g $Ce(SO_4)_2$, 25 g molybdophosphoric acid, 1 L H_2O; 80 mL conc. H_2SO_4). Flash column chromatography[2] was conducted on Macherey-Nagel & Co silica gel 60® (230-400 mesh). Chromatography conditions are documented at the respective experiment in the following manner: (d × h cm, V mL, solv1:solv2 a:b $\xrightarrow{x}$ c:d), which means: a column with the outer diameter d cm is packed with h cm silica gel. Fractions of the size V mL are collected. The product is eluted with the solvents solv1 and solv2 in the ratio a:b. The ratio was changed at fraction x to c:d.

1 J. Suffert, *J. Org. Chem.* **1989**, *54,* 509-510.
2 W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43,* 2923-2925.

Nuclear magnetic resonance spectroscopy: NMR spectra were recorded by Dr. M. Keller, F. Reinbold, and M. Schonhard on a Bruker Avance 400 spectrometer [^{1}H (400 MHz), ^{13}C (100 MHz), DQF-COSY, edHSQC, and HMBC experiments] and a Bruker DRX 500 spectrometer [^{1}H (500 MHz), ^{13}C (126 MHz), DQF-COSY, edHSQC, and HMBC experiments] or by myself on a Varian Mercury VX 300 spectrometer [^{1}H (300 MHz)] or on a Bruker Avance 300 spectrometer [^{1}H (300 MHz)]. ^{1}H NMR spectra were referenced internally to TMS or the solvent signal respectively ($CDCl_3$: 7.26 ppm, C_6D_6: 7.15 ppm, DMSO-d_6: 2.49 ppm). ^{13}C NMR spectra were referenced internally to the solvent signal ($CDCl_3$: 77.10 ppm, C_6D_6: 128.00 ppm, DMSO-d_6: 39.50 ppm). ^{1}H NMR data are reported as follows: chemical shift (δ in ppm), multiplicity (s for singlet; d for doublet; t for triplet; m for multiplet; m_c for symmetrical multiplet; br for broad signal), coupling constant(s) (Hz; ^{3}J couplings unless otherwise noted), integral, and specific assignment. ^{13}C NMR data are reported in terms of chemical shift and assignment. For AB signals the high-field part was named A and the low-field part B.

High resolution mass spectrometry: High resolution mass spectra were recorded by Dr. J. Wörth and C. Warth on a Thermo Scientific Exactive mass spectrometer equipped with an orbitrap analyzer. Ionization method: Electrospray ionization (ESI; spray voltage: 2.5-4.0 kV) or atmospheric pressure chemical ionization (APCI; spray current: 5 μA).

Elemental analysis: Elemental analyses were obtained by A. Siegel on an Elementar Vario EL CHNS analyzer.

Melting points: Melting points were determined in a Büchi melting point apparatus using open glass capillaries.

IR spectroscopy: IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer for a film of the substance on a NaCl plate unless otherwise stated.

Specific rotations: Optical rotations were measured using a 341 MC Perkin-Elmer polarimeter. The specific rotations $[\alpha]_\lambda^T$ were calculated by the formula:

$$[\alpha]_\lambda^T = \frac{\alpha\text{observed} \times 100}{c \times d}$$

with T = temperature in °C, $\alpha_{observed}$ = the experimentally observed optical rotation, c = concentration in g/100 mL, d = length of the cuvette in dm.

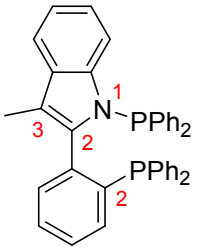
X-ray crystal structure analysis: X-ray structures of a suitable crystal were recorded by Boumahdi Benkmil of the Institute of Inorganic and Analytical Chemistry of the University of Freiburg on a Bruker SMART APEX CCD area detector diffractometer at 100 K. The structures were solved by Dr. Daniel Kratzert from the Institute of Inorganic and Analytical Chemistry of the University of Freiburg.

All crystal structures were obtained from the racemic synthesis. In fact of that some of the reported data which can be accessed via the *Cambridge Crystallographic Data Centre* show the "wrong" enantiomere. For a better understanding some of the structures shown in this supporting information were inverted into the "right" enantiomere. These structures are marked.

2. Experimental Procedures and Characterization Data

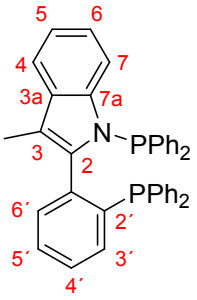
1-(Diphenylphosphino)-2-[2-(diphenylphosphino)phenyl]-3-methyl-1*H*-indole (8)

IUPAC-Numbering



$C_{39}H_{31}NP_2$
575,19

NMR-Numbering



s-BuLi (1.3 M in *c*-hexane/*n*-hexane, 0.46 ml, 0.60 mmol, 2.5 eq.) was added to a solution of 3-Methyl-2-phenyl-1*H*-indole (50 mg, 0.24 mmol) and TMEDA (0.10 ml, 70.1 mg, 0.60 mmol, 2.5 eq.) in Et_2O (3.4 ml) at room temperature. The resulting mixture was stirred for 3 h at room temperature. $ClPPh_2$ (0.41 ml, 530 mg, 2.4 mmol, 10.0 eq.) was added at –78°C. The mixture was allowed to warm slowly to room temperature and stirred for 16 h. MeOH (5 ml) was added and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica (fractions 12-20, 2.5 x 18 cm, 20 ml, *n*-hexane:Et_2O 30:1). The title compound (40.3 mg, 0.10 mmol, 40%) was obtained as a colorless solid (m.p. 162°C, Lit.[3]: 157°C).

^{1}H NMR (BlBrJl04-4120, 400.13 MHz, $CDCl_3$): δ = 1.73 (s, 3H, 3-Me), 7.46 (ddd, $^3J_{3',4'}$ = 8.5 Hz, $^4J_{3',5'}$ = 1.6 Hz, $^5J_{3',6'}$ = 0.8 Hz, 1H, 3´-H), 6.82 (ddd, $^3J_{4'3'}$ = 8.3 Hz, $^3J_{4',5'}$ = 7.1 Hz, $^4J_{4',6'}$ = 1.3 Hz, 1H, 4´-H), 7.04-7.08 (m, 3H, 5´-H and 2 x Ar-H), 7.14-7.20 (m, 4H, 4 x Ar-H), 7.22-7.26 (m, 4H, 4 xAr-H), 7.62-7.28 (m, 1H, Ar-H), 7.29-7.42 (m, 13H, 13 x Ar-H), 7.46 (ddd, $^3J_{6',5'}$ = 7.8 Hz, $^4J_{6',4'}$ = 1.3 Hz, $^5J_{6',3'}$ = 0.7 Hz, 1H, 6´-H) ppm.

^{31}P NMR (BlBrJl04-4122, 400.13 MHz, $CDCl_3$): δ = –15.58 (d, $^5J_{C\text{-}P,N\text{-}P}$ = 13.3 Hz, 1P, C-P), 35.47 (d, $^5J_{N\text{-}P,C\text{-}P}$ = 12.2 Hz, 1P, N-P) ppm.

The spectroscopic data is consistent with those reported in literature.[3]

m.p.: 162°C (Lit.[3]: 157°C)

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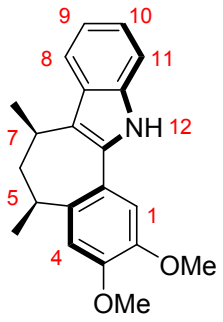
3 F. Sannicolo, T. Benincori, S. Rizzo, S. Gladiali, S. Pulacchini, G. Zotti, *Synthesis* **2001**, *15*, 2327-2336.

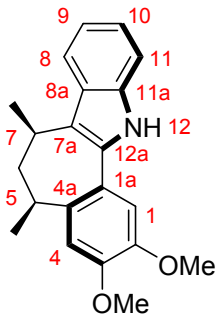
(5*S*,7*R*)-2,3-Dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*cis*-14)

IUPAC-Numbering



$C_{21}H_{23}NO_2$
321,17

NMR-Numbering



A solution of *cis*-**17** (179 mg, 0.63 mmol), $PhNHNH_2$ (0.07 ml, 74.7 mg, 0.63 mmol, 1.0 eq.) and conc. HCl (12 M in H_2O, 0.48 ml, 6.30 mmol, 10 eq.) in EtOH (1.5 ml) was heated under reflux for 24 h. H_2O (3 ml) and CH_2Cl_2 (3 ml) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica (2.0 x 18 cm, 20 ml, *n*-pentane:Et_2O 1:1). The title compound (fractions 7-20, 145 mg, 0.45 mmol, 72%) was obtained as a yellow solid.

^{1}H NMR (BlBrMz13-411000, 400.13 MHz, $CDCl_3$): δ = 1.27 (d, $^3J_{7\text{-Me},7}$ = 6.8 Hz, 3H, 7-Me), 1.44 (d, $^3J_{5\text{-Me},5}$ = 7.0 Hz, 3H, 5-Me), AB-Signal (ν_A = 1.64, $^2J_{A,B}$ = 13.6 Hz occasionally split with dd, $^3J_{A,5}$ = 10.9 Hz, $^3J_{A,7}$ = 8.9 Hz; ν_B = 2.22, $^2J_{A,B}$ = 13.6 Hz occasionally split with dd, $^3J_{B,5}$ = 10.7 Hz, $^3J_{B,7}$ =7.8 Hz, 2H, 6-H_2), 2.90-2.98 (m, 1H, 5-H), 3.60 (m_c, 1H, 7-H), 3.95 (s, 3H, 2-OMe), 3.97 (s, 3H, 3-OMe), 6.88 (s, 1H, 1-H), 7.11 (s, 1H, 4-H), 7.14 (ddd, $^3J_{9,8}$ = 8.1 Hz, $^3J_{9,10}$ = 7.2 Hz, $^4J_{9,11}$ = 1.2 Hz, 1H, 9-H), 7.21 (ddd, $^3J_{10,11}$ = 7.9 Hz, $^3J_{10,9}$ = 7.2 Hz, $^4J_{10,8}$ = 1.0 Hz, 1H, 10-H), 7.39 (ddd, $^3J_{11,10}$ = 7.9 Hz, $^4J_{11,9}$ = 1.2 Hz, $^5J_{10,8}$ = 1.0 Hz, 1H, 11-H), 7.62 (d, $^3J_{8,9}$ = 7.9 Hz, 1H, 8-H), 7.87 (br. s, 1H, 12-H) ppm.

^{13}C NMR (BlBrMz13-411005, 100.62 MHz, $CDCl_3$): δ = 20.2 (C-5-Me), 22.9 (C-7-Me), 31.9 (C-7), 34.0 (C-5), 47.8 (C-6), 56.1 (C-2-OMe), 56.4 (C-3-OMe), 108.1 (C-1), 109.8 (C-4), 110.7 (C-11), 119.2 (C-7a), 119.3 (C-8), 119.5 (C-9), 122.2 (C-10), 124.2 (C-4a), 129.6 (C-8a), 132.1 (C-12a), 136.7 (C-11a), 139.6 (C-1a), 147.2 (C-2), 148.2 (C-3) ppm.

HRMS (p. ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{23}O_2N$ 321.1723; Found 321.1715

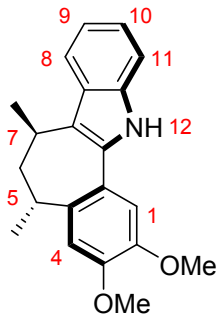
IR (film): ῡ = 749, 775, 1035, 1148, 1185, 1206, 1266, 1352, 1433, 1445, 1462, 1515, 2912, 2957, 3369 cm^{-1}.

$\boldsymbol{\alpha_D^{20}} =$ –19.59 (99% *ee*, c = 1.60 in $CHCl_3$)

m. p.: 165°C

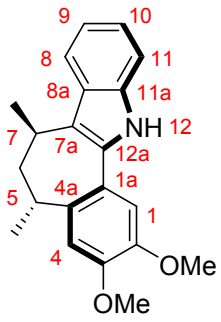
(5*R*,7*R*)-2,3-Dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*trans*-14)

IUPAC-Numbering



$C_{21}H_{23}NO_2$
321,17

NMR-Numbering



A solution of *cis*-**17** (200 mg, 0.70 mmol), $PhNHNH_2$ (0.08 ml, 91.3 mg, 0.70 mmol, 1.0 eq.) and conc. HCl (12 M in H_2O, 0.58 ml, 7.00 mmol, 10 eq.) in EtOH (2.0 ml) was heated under reflux for 24 h. H_2O (5 ml) and CH_2Cl_2 (5 ml) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica (2.5 x 19 cm, 20 ml, *n*-pentane:Et_2O 2:1). The title compound (fractions 11-21, 152 mg, 0.48 mmol, 68%, *dr* 95:5) was obtained as a yellow solid. The title compound was obtained as a single isomere after recrystallization from *n*-pentane/Et_2O.

^{1}H NMR (BlBrOk25-410100, 400.13 MHz, $CDCl_3$): δ = 1.27 (d, $^3J_{5\text{-Me},5}$ = 7.4 Hz, 3H, 5-Me), 1.50 (d, $^3J_{7\text{-Me},7}$ = 6.6 Hz, 3H, 7-Me), AB-Signal (ν_A =1.95, $^2J_{A,B}$ = 13.8 Hz occasionally split with dd, $^3J_{A,7}$ = 9.3 Hz, $^3J_{A,5}$ = 1.8 Hz; ν_B =2.19, $^2J_{A,B}$ = 13.8 Hz occasionally split with dd, $^3J_{B,5}$ = 7.6 Hz, $^3J_{B,7}$ =6.4 Hz, 2 H, 6-H_2), 3.02-3.11 (m, 1H, 5-H), 3.39 (m_c, 1H, 7-H), 3.94 (s, 3H, 2-OMe), 3.97 (s, 3H, 3-OMe), 6.81 (s, 1H, 1-H), 7.10 (s, 1H, 4-H), 7.11 (ddd, $^3J_{9,8}$ = 8.0 Hz, $^3J_{9,10}$ = 7.1 Hz, $^4J_{9,11}$ = 1.0 Hz, 1H, 9-H), 7.21 (ddd, $^3J_{10,11}$ = 8.1 Hz, $^3J_{10,9}$ = 7.0 Hz, $^4J_{10,8}$ = 1.1 Hz, 1H, 10-H), 7.39 (ddd, $^3J_{11,10}$ = 8.0 Hz, $^4J_{11,9}$ = 1.0 Hz, $^5J_{11,8}$ = 1.0 Hz, 1H, 11-H), 7.69 (d, $^3J_{4,5}$ = 7.9 Hz, 1H, 4-H), 7.91 (br. s, 1H, 12-H) ppm.

^{13}C NMR (BlBrOk25-410105, 100.62 MHz, $CDCl_3$): δ = 17.5 (C-5-Me), 22.3 (C-7-Me), 29.2 (C-7), 36.8 (C-5), 43.8 (C-6), 56.1 (C-2-OMe), 56.4 (C-3-OMe), 110.0 (C-1), 110.8 (C-11), 111.5 (C-4), 118.5 (C-7a), 119.4 (C-9), 120.1 (C-8), 122.1 (C-10), 123.7 (C-4a), 129.4 (C-8a), 132.1 (C-12a), 136.6 (C-11a), 140.2 (C-1a), 147.4 (C-3), 148.1 (C-2) ppm.

HRMS (p. ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{23}O_2N$ 322.1802; Found 322.1803

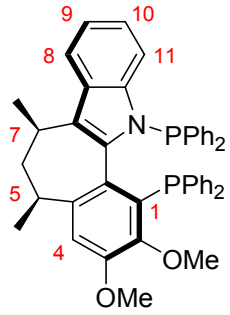
IR (film): ϋ = 740, 1037, 1146, 1183, 1201, 1259, 1432, 1445, 1462, 1470, 1517, 2910, 2929, 2956, 3373 cm^{-1}.

$\boldsymbol{\alpha_D^{20}} =$ +16.79 (99% *ee*, c = 0.81 in $CHCl_3$)

m.p.: 185°C

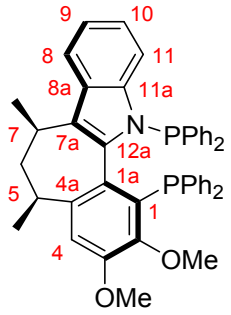
(*P*,5*S*,7*R*)-1,12-Bis(Diphenylphosphaneyl)-2,3-dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*cis*-15)

IUPAC-Numbering



$C_{45}H_{41}NO_2P_2$
689,26

NMR-Numbering



n-BuLi (1.4 M in *n*-hexane, 1.00 ml, 1.40 mmol, 2.5 eq.) was added to a suspension of *cis*-**14** (180 mg, 0.56 mmol) and TMEDA (0.21 ml, 162 mg, 1.40 mmol, 2.5 eq.) in Et_2O (10 ml) at room temperature. The resulting mixture was stirred for 3 h at room temperature. $ClPPh_2$ (0.96 ml, 1.24 g, 14.0 mmol, 10.0 eq.) was added to this mixture at –78°C. This solution was allowed to warm slowly to room temperature and was stirred at room temperature for 13 h. MeOH (3 ml) was added and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica (2.0 x 18 cm, 20 ml, *n*-pentane: Et_2O 10:1). The title compound (fractions 12-22, 272 mg, 0.40 mmol, 72%) was obtained as a colorless solid (m.p. 211°C).

^{1}H NMR (BlBrOk-5020, 500.10 MHz, $CDCl_3$, contains *t*BuOMe): δ = 0.82 (d, $^3J_{7\text{-}Me,7}$ = 7.7 Hz, 3H, 7-Me), 1.30 (d, $^3J_{5\text{-}Me,5}$ = 6.9 Hz, 3H, 5-Me), 1.56-1.61 (m, 1H, 6-H_a), 2.51 (ddd, $^2J_{6B,6A}$ = 13.6 Hz, $^3J_{6B,5}$ = 9.0 Hz, $^3J_{6B,7}$ = 4.9 Hz, 1H, 6-H_B), 2.60 (m_c, 1H, 5-H), 2.90 (s, 3H, 2-OMe), 3.42 (m_c, 1H, 7-H), 3.93 (s, 3H, 3-OMe), 6.81 (ddd, $^3J_{10,11}$= 8.2 Hz, $^3J_{10,9}$ = 7.0 Hz, $^4J_{10,8}$ = 1.3 Hz, 1H, 10-H), 6.86 (d, $^3J_{11,10}$ = 7.9 Hz, 1H, 11-H), 7.00-7.08 (m, 4H, 3 x Ar-H and 9-H), 7.09 (s, 1H, 4-H), 7.10-7.17 (m, 12H, 12 x Ar-H), 7.20-7.26 (m, 3H, 3 x Ar-H), 7.36-7.40 (m, 2H, 2 x Ar-H), 7.55 (d, $^3J_{8,9}$ = 7.8 Hz, 1H, 8-H) ppm.

^{13}C NMR (BlBrJl-5043, 125.76 MHz, $CDCl_3$, {^{31}P}-decoupled): δ = 19.1 (C-5-Me), 23.1 (C-7-Me), 26.2 (C-7), 35.4(C-5), 50.4 (C-6), 55.7 (C-3-OMe), 59.2 (C-2-OMe), 111.9 (C-4), 117.7 (C-8), 119.0 (C-11), 120.2 (C-9), 121.2 (C-10), 124.9 (C-7a), 126.4 (C-Ar), 127.0 (C-Ar), 127.4 (C-Ar), 127.4 (C-Ar), 127.6 (C-Ar), 127.8 (C-Ar), 127.8 (C-Ar), 128.0(C-Ar), 128.2 (C-Ar), 128.2 (C-Ar), 128. 6 (C-Ar), 129.0 (C-8a), 130.8 (C-Ar), 130.9 (C-11a), 130.9 (C-Ar), 131.4 (C-Ar), 131.5 (C-Ar), 131.7 (C-Ar), 132.6 (C-Ar), 132.8 (C-Ar), 133.2 (C-Ar), 133.4 (C-Ar), 135.4 (C-1a), 137.0 (2 x C-Ar), 138.6 (C-Ar), 138.8 (C-12a), 138.9 (C-Ar), 142.2 (C_4a), 150.7 (C-2), 152.6 (C-3) ppm.

^{31}P NMR (BlBrOk20-5021, 202.44 MHz, $CDCl_3$): δ = –12.20 (d, $^5J_{P,P}$ = 52.2 Hz, 1 P, *C*-P), 31.58 (d, $^5J_{P,P}$ = 52.2 Hz, 1 P, *N*-P) ppm.

IR (film): ϑ = 695, 741, 912, 1025, 1125, 1146, 1183, 1225, 1259, 1327, 1344, 1421, 1435, 1457, 2957 cm^{-1}.

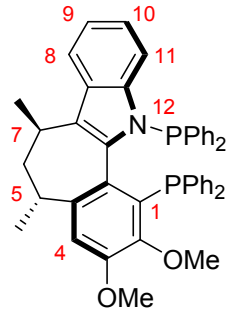
HRMS (p. ESI) m/z: $[M+H]^+$ Calcd for $C_{45}H_{42}O_2NP_2$ 690.2685; Found 690.2683

$\boldsymbol{\alpha_D^{20}}$ = –90.02 (99% *ee*, c = 0.82 in $CHCl_3$)

m.p.: 219°C

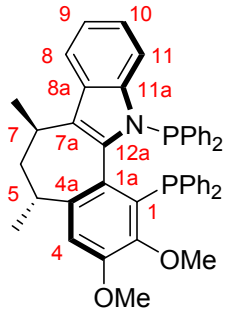
(*M*,5*R*,7*R*)-1,12-Bis(Diphenylphosphaneyl)-2,3-dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*trans*-15)

IUPAC-Numbering



$C_{45}H_{41}NO_2P_2$
689,26

NMR-Numbering



n-BuLi (1.4 M in *n*-hexane, 0.34 ml, 0.47 mmol, 2.5 eq.) was added to a suspension of *trans*-**14** (60.1 mg, 0.19 mmol) and TMEDA (0.07 ml, 53.9 mg, 0.47 mmol, 2.5 eq.) in Et_2O (4 ml) at room temperature. The resulting mixture was stirred for 3 h at room temperature. $ClPPh_2$ (0.32 ml, 412 g, 1.91 mmol, 10.0 eq.) was added to this mixture at –78°C. This solution was allowed to warm slowly to room temperature and was stirred at room temperature for 13 h. MeOH (2 ml) was added and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica (2.0 x 18 cm, 20 ml, *n*-pentane:Et_2O 10:1). The title compound (fractions 10-19, 82.1 mg, 0.12 mmol, 63%) was obtained as a colorless solid.

^{1}H NMR (BlBrJl31-500100, 500.10 MHz, $CDCl_3$): δ = 1.31 (d, $^3J_{5\text{-Me},5}$ = 7.4 Hz, 3H, 5-Me), 1.69 (d, $^3J_{7\text{-Me},7}$ = 7.2 Hz, 3H, 7-Me), AB-Signal (ν_A = 1.80, $^2J_{A,B}$ = 12.2 Hz occasionally split with dd $^3J_{A,7}$ = 12.1 Hz, $^3J_{A,5}$ = 6.4 Hz; ν_B = 2.01, $^2J_{A,B}$ = 12.2 Hz occasionally split with d, $^3J_{B,7}$ = 12.4 Hz, $^3J_{B,5}$ = 6.0 Hz, 2H, 6-H_2), 2.47 (m_c, 1H, 5-H), 2.81 (m_c, 1H, 7-H), 2.88 (s, 3H, 2-OMe), 3.92 (s, 3H, 3-OMe), 6.77 (ddd, $^3J_{10,11}$ = 8.4 Hz, $^3J_{10,9}$ = 7.1 Hz, $^4J_{10,8}$ = 1.2 Hz, 1H, 10-H), 6.86 (d, $^3J_{11,10}$ = 8.4 Hz, 1H, 11-H), 6.99-7.05 (m, 3H, 2 x Ar-H and 9-H), 7.06-7.09 (m, 1H, 1 x Ar-H), 7.08 (s, 1H, 4-H), 7.12-7.22 (m, 15H, 15 x Ar-H), 7.30-7.33 (m, 2H, 2 x Ar-H), 7.87 (d, $^3J_{8,9}$ = 8.2 Hz, 1H, 8-H) ppm.

^{13}C NMR (BlBrJl-500108, 125.76 MHz, $CDCl_3$, {^{31}P}-decoupled): δ = 18.3 (C-5-Me), 18.8 (C-7-Me), 31.4 (C-7), 35.4 (C-5), 52.9 (C-6), 55.7 (C-3-OMe), 59.2 (C-2-OMe), 111.6 (C-4), 115.6 (C-11), 120.2 (C-8), 120.2 (C-9), 120.7 (C-10), 122.0 (C-7a), 126.7 (C-Ar), 127.0 (2 x C-Ar), 127.2 (C-Ar), 127.4 (2 x C-Ar), 127.7 (C-Ar), 127.8 (2 x C-Ar), 128.2 (2 x C-Ar), 128.7 (C-Ar), 130.0 (C-8a), 131.4 (2 x C-Ar), 131.5 (C-Ar), 131.6 (C-Ar), 131.9 (2 x C-Ar), 132.8 (2 x C-Ar), 133.0 (C-6), 133.1 (C-Ar), 136.8 (C-Ar), 139.3 (C-Ar), 139.4 (C-11a), 140.0 (C-12a), 141.7 (C-4a), 150.2 (C-2), 152.6 (C-3) ppm.

^{31}P NMR (BlBrJl31-500101, 202.44 MHz, $CDCl_3$): δ = –11.61 (d, $^5J_{P,P}$ = 47.3 Hz, 1 P, *C*-P), 32.72 (d, $^5J_{P,P}$ = 47.3 Hz, 1 P, *N*-P) ppm.

IR (film): ϋ = 694, 742, 1026, 1038, 1165, 1223, 1260, 1317, 1352, 1423, 1433, 1459, 1480, 2926, 2958 cm^{-1}.

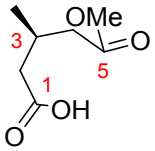
HRMS (p. ESI) m/z: $[M+H]^+$ Calcd for $C_{45}H_{42}O_2NP_2$ 690.2685; Found 690.2684

$\boldsymbol{\alpha_D^{20}}$ = +17.15 (99% *ee*, c = 0.82 in $CHCl_3$)

m.p.: 219°C

(*R*)-5-Methoxy-3-methyl-5-oxopentanoic Acid (16a)

IUPAC/NMR-Numbering



$C_7H_{12}O_4$
160,07

MeOH (4.27 ml, 3.38 g, 105 mmol, 3.0 eq.) was added to a solution of 3-Methylglutaric anhydride (**19**, 4.50 g, 35.1 mmol) and quinine (12.5 g, 38.5 mmol, 1.1 eq.) in chlorobenzene/toluene (1:1, 700 ml) at –55°C. The resulting mixture was stirred for 96 h at –55°C. The solvent was removed under reduced pressure. The residue was treated with aqueous HCl (1 M) until pH 1 was reached. Et_2O (100 ml) was added and the layers were separated. The aqueous layer was extracted with Et_2O (5 x 100 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by fractional distillation (b.p.$_{<1\ mbar}$ 119-123°C). The title compound (5.45 g, 34.0 mmol, 97%, 70% *ee*) was obtained as a colorless oil.

A Suspension of the title compound (5.45 g, 34.0 mmol) and cinchonidine (10.0 g) in acetone (98 ml) was stirred at 40°C. H_2O was added until the precipitate dissolved. The resulting mixture was stored at 4°C for 18 h. The precipitate was filtered, and the same procedure was repeated twice .The filter cake was dissolved in aqueous HCl (1 M) until pH 1 was reached. Et_2O (50 ml) was added and the layers were separated. The aqueous layer was extracted with Et_2O (5 x 50 ml) and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and the title compound (1.12 g, 7.02 mmol, 99% *ee*) was obtained as a colorless oil.

^{1}H NMR (BlBrJl13-30870, 300.13 MHz, $CDCl_3$): δ = 1.06 (d, $^3J_{3\text{-Me},3}$ = 6.4 Hz, 3 H, 3–Me), 2.23-2.34 (m, 2 H, 3-H und 4-H_A), 2.38-2.53 (m, 3 H, 2-H_2 und 4-H_B), 3.68 (s, 3 H, –OMe), 11.23 (br. s, 1 H, –COOH) ppm.

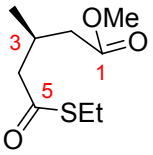
The spectroscopic data were consistent to those reported in literature.[4]

$\boldsymbol{\alpha_D^{20}}$ = +2.47 (99% *ee*, c = 1.07 in $CHCl_3$), Lit[4]: 1.10 (83% *ee*, c = 1.07 in $CHCl_3$)

[4] A. Peschiulli, Y. Gun´ko, S. J. Connon, *J. Org. Chem.* **2008**, *73*, 2454-2457.

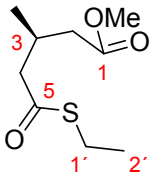
Methyl (*S*)-5-(Ethylthio)-3-methyl-5-oxopentanoate (16c)

IUPAC-Numbering



$C_9H_{16}O_3S$
204,28

NMR-Numbering



EtSH (0.02 ml, 16.8 mg, 0.27 mmol, 1.0 eq.) was added to a solution of (*R*)-**16a** (43.3 mg, 0.27 mmol), DCC (55.9 mg, 0.27 mmol, 1.0 eq.) ,and DMAP (6.60 mg, 0.05 mmol, 20 Mol-%) in CH_2Cl_2 (1.6 ml). The resulting mixture was stirred for 17 h at room temperature. The precipitate was filtered and was washed with CH_2Cl_2 (5 ml). The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica (2.0 x 14 cm, 20 ml, *c*-hexane:AcOEt 4:1). The title compound (fractions 2-5, 38.6 mg, 0.19 mmol, 70%) was obtained as a colorless oil.

^{1}H NMR (BlBrMz29-4050, 400.13 MHz, $CDCl_3$): δ = 1.01 (d, $^3J_{3\text{-Me},3}$ = 6.4 Hz, 3H, 3–Me), 1.24 (t, $^3J_{2',1'}$ = 7.5 Hz, 3H, 2´-H_3), AB-Signal (ν_A = 2.23, $^2J_{A,B}$ = 15.3 Hz occasionally split with d, $^3J_{A,3}$ = 7.3 Hz; ν_B = 2.38, $^2J_{A,B}$ = 15.5 Hz occasionally split with d, $^3J_{B,3}$ = 5.9 Hz, 2H, 2-H_2), 2.46-2.57 (m, 1H, 3-H), AB-Signal (ν_A = 2.46, $^2J_{A,B}$ = 13.4 Hz occasionally split with d, $^3J_{A,3}$ = 7.0 Hz; ν_B = 2.38, $^2J_{A,B}$ = 13.4 Hz occasionally split with d, $^3J_{B,3}$ = 5.2 Hz, 2H, 4-H_2), 2.87 (q, $^3J_{1',2'}$ = 7.5 Hz, 3H, 1´-H_3), 3.67 (s, 3H, –OMe) ppm.

^{13}C NMR (BlBrMz29-4055, 100.62 MHz, $CDCl_3$,): δ = 14.8 (C-2´), 19.7 (C-3´), 23.4 (C-1´), 28.2 (C-3), 40.6 (C-2), 50.3 (C-4), 51.6 (C-OMe), 172.7 (C-1), 198.3 (C-5) ppm.

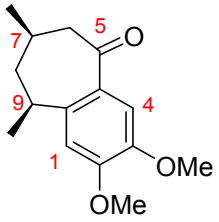
HRMS (p. ESI) m/z: $[M+Na]^+$ Calcd for $C_9H_{16}O_3NaS$ 227.0712; Found 227.0708

IR (film): ϑ = 770, 1011, 1169, 1211, 1262, 1310, 1370, 1416, 1437, 1446, 1688, 1739, 2877, 2933, 2965 cm^{-1}.

$\boldsymbol{\alpha_D^{20}}$ = +6.59 (99% *ee*, c = 0.99 in $CHCl_3$)

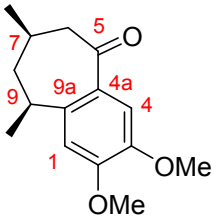
(7*R*,9*S*)-2,3-Dimethoxy-7,9-dimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (*cis*-17)

IUPAC-Numbering



$C_{15}H_{20}O_3$
248,14

NMR-Numbering



A solution of **30** (860 mg, 3.23 mmol) and polyphosphoric acid (8.60 g, 10 times the mass of **30**) in sulfolane (8 ml) was stirred at 100°C for 1 h. H_2O (10 ml) and *t*BuOMe (10 ml) were added carefully to the hot solution. The layers were separated, and the aqueous layer was extracted with *t*BuOMe (3 x 15 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica (4.5 x 20 cm, 20 ml, *c*-hexane:AcOEt 4:1). The title compound (fractions 10-17, 721 mg, 2.99 mmol, 90%, *dr* 97:3) was obtained as a pale yellow solid. The title compound was obtained as a single isomere after recrystallization from *n*-hexane (m.p.: 78°C).

^{1}H NMR (BlBrMz12-411200, 400.13 MHz, $CDCl_3$): δ = 0.98 (d, $^3J_{7\text{-Me},7}$ = 6.8 Hz, 3H, 7-Me), 1.34 (ddd, $^2J_{8\text{cis},8\text{trans}}$ = 13.8 Hz, $^3J_{8\text{cis},7}$ = 9.6 Hz, $^3J_{8\text{cis},9}$ = 7.7 Hz, 1H, 8_{cis}-H), 1.39 (d, $^3J_{9\text{-Me},9}$ = 7.2 Hz, 3H, 9-Me), 2.11 (ddd, $^2J_{8\text{trans},8\text{cis}}$ = 13.8 Hz, $^3J_{8\text{trans},7}$ = 6.5 Hz, $^3J_{8\text{trans},9}$ =4.0 Hz, 1H, 8_{trans}-H_2), 2.13-2.23 (m, 1H, 7-H), AB-Signal (ν_A = 2.63, $^2J_{A,B}$ = 15.0 Hz occasionally split with d, $^3J_{A,7}$ = 6.8 Hz; ν_B = 2.89, $^2J_{A,B}$ = 15.0 Hz occasionally split with d, $^3J_{B,7}$ = 5.1 Hz, 2H, 6-H_2), 3.12 (m_c, 1H, 9-H), 3.90 (s, 3H, 3-OMe), 3.94 (s, 3H, 2-OMe), 6.78 (s, 1H, 1-H), 7.30 (s, 1H, 4-H) ppm.

^{13}C NMR (BlBrMz12-4112005, 100.62 MHz, $CDCl_3$): δ = 21.9 (C-7-Me), 23.6 (C-9-Me), 28.9 (C-7), 36.4 (C-9), 43.6 (C-8), 49.3 (C-6), 56.0 (C-2-OMe), 56.1 (C-3-OMe), 110.1 (C-1), 111.7 (C-4), 131.6 (C-4a), 141.3 (C-9a), 147.1 (C-3), 151.6 (C-2), 203.5 (C-5) ppm.

HRMS (p. ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{21}O_3$ 249.1845; Found 249.1488

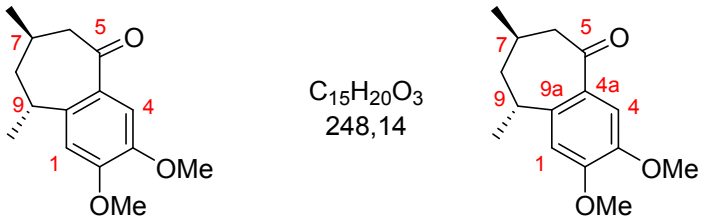
IR (film): ϑ = 745, 913, 1023, 1043, 1078, 1134, 1182, 1216, 1273, 1353, 1460, 1513, 1597, 2920, 2959 cm^{-1}.

$\boldsymbol{\alpha_D^{20}}$ = –94.40 (99% *ee*, c = 1.08 in $CHCl_3$)

Elemental analysis:	calc.	C 72.55%	H 8.12%
	found	C 72.58%	H 8.12%
	deviation	C 0.03%	H 0.00%

(7*R*,9*R*)-2,3-Dimethoxy-7,9-dimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (*trans*-17)

IUPAC-Numbering NMR-Numbering



A solution of *dia*-**30** (467 mg, 1.73 mmol) and polyphosphoric acid (4.66 g, 10 times the mass of *dia*-**30**) in sulfolane (4 ml) was stirred at 100°C for 1 h. H_2O (5 ml) and *t*BuOMe (5 ml) were added carefully to the hot solution. The layers were separated, and the aqueous layer was extracted with *t*BuOMe (3 x 10 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica (4.5 x 20 cm, 20 ml, *c*-hexane:AcOEt 4:1). The title compound (fractions 11-17, 378 mg, 1.52 mmol, 88%, *dr* 95:5) was obtained as a pale-yellow oil.

^{1}H NMR (BlBrOk14-4070, 400.13 MHz, $CDCl_3$, contains 5% of the *cis*-isomere): δ = 0.99 (d, $^3J_{7\text{-Me},7}$ = 6.7 Hz, 3H, 7-Me), 1.36 (d, $^3J_{9\text{-Me},9}$ = 6.8 Hz, 3H, 9-Me), AB-Signal (ν_A = 1.55, $^2J_{A,B}$ = 13.1 Hz occasionally split with dd, $^3J_{A,9}$ = 10.6 Hz, $^3J_{A,7}$ = 5.5 Hz; ν_B = 1.63, $^2J_{A,B}$ = 13.1 Hz occasionally split with ddd, $^3J_{B,9}$ = 10.9 Hz, $^3J_{B,7}$ = 6.3 Hz, $^4J_{B,6B}$ = 0.4 Hz, 2H, 8-H_2), 1.88 (m_c, 1H, 7-H), AB-Signal (ν_A = 2.52, $^2J_{A,B}$ = 17.4 Hz occasionally split with d, $^3J_{A,7}$ = 10.7 Hz; ν_B = 2.59, $^2J_{A,B}$ = 17.4 Hz occasionally split with dd, $^3J_{B,7}$ = 2.9 Hz, $^4J_{B,8B}$ = 0.8 Hz, 2H, 6-H_2), 3.10 (m_c, 1 H, 9-H), 3.86 (s, 3H, 3-OMe), 3.92 (s, 3H, 2-OMe), 6.73 (s, 1H, 1-H), 7.17 (s, 1H, 4-H) ppm.

^{13}C NMR (BlBrOk14-4075, 100.62 MHz, $CDCl_3$): δ = 19.5 (C-9-Me), 21.2 (C-7-Me), 27.3 (C-7), 33.4 (C-9), 43.6 (C-8), 49.7 (C-6), 56.0 (C-2-OMe), 56.0 (C-3-OMe), 108.3 (C-1), 111.3 (C-4), 131.5 (C-4a), 138.5 (C-9a), 147.2 (C-3), 152.0 (C-2), 205.1 (C-5) ppm.

HRMS (p. ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{21}O_3$ 249.1845; Found 249.1485

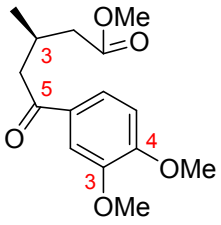
IR (film): ϑ̃ = 1039, 1132, 1173, 1212, 1274, 1293, 1325, 1364, 1400, 1511, 1575, 1599, 1666, 2914, 2957 cm^{-1}.

$\boldsymbol{\alpha_D^{20}}$ = –30.80 (99% *ee*, c = 1.02 in $CHCl_3$)

Elemental analysis:	calc.	C 72.55%	H 8.12%
	found	C 72.31%	H 7.97%
	deviation	C 0.24%	H 0.15%

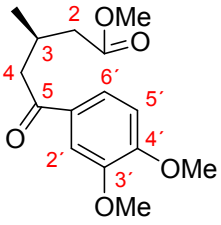
Methyl (*R*)-5-(3,4-Dimethoxyphenyl)-3-methyl-5-oxopentanoate (18)

IUPAC-Numbering



$C_{15}H_{20}O_5$
280,13

NMR-Numbering



Procedure A (resulting in a racemic mixture):

A solution of the (*R*)-monoster (**16a**, 9.99 g, 62.4 mmol) in CH_2Cl_2 (32 ml) was added to a solution of $(COCl)_2$ (7.60 ml, 8.74 g, 68.6 mmol, 1.1 eq.) and DMF (4 drops) in CH_2Cl_2 (120 ml) at room temperature. The resulting mixture was stirred for 5 h at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (30 ml). This mixture was added to a suspension of $AlCl_3$ (9.67 g, 62.4 mmol, 1.1 eq.) and veratrole (7.30 ml, 7.82 g, 56.7 mmol) in CH_2Cl_2 (300 ml) at 0°C. The resulting mixture was stirred for 20 h at room temperature. Conc. aqueous HCl (30 ml) was added carefully until the precipitate vanished. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica (6.5 x 20 cm, 100 ml, *c*-hexane: AcOEt 3:1). The title compound (fractions 23-62, 17.0 g, 60.5 mmol, 97% and 0% *ee*) was obtained as a yellow liquid.

Procedure B:

*t*BuLi (1.67 M in hexane, 0.46 ml, 0.76 mmol, 6.0 eq.) was added to a solution of 4-iodo veratrole (98.7 mg, 0.38 mmol. 3.0 eq.) in THF (0.5 ml) at –78°C. The resulting mixture was stirred for 1 h at –78°C. A solution of anhydrous $ZnCl_2$ (51.0 mg, 0.38 mmol) in THF (0.5 ml) was added to that mixture at room tempature. This solution was stirred for 1 h at room temperature. The resulting mixture was added to a solution of the thioester (**12c**, 25.1 mg, 0.13 mmol) and $PdCl_2(PPh_3)$ (8.1 mg, 0.012 mmol, 10 mol-%) in toluene (0.5 ml) at room temperature. The mixture was stirred for 16 h at room temperature. It was filtered through celite® and the filter cake was washed with *t*BuOMe (50 ml). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica (1.0 x 20 cm, 8 ml, *c*-hexane:AcOEt 5:1). The title compound (fractions 17-31, 21.9 mg, 0.08 mmol, 60% and 94%*ee*) was obtained as a yellow liquid.

Procedure C:

A solution of (2.60 g, 16.3 mmol), **21b** (3.25 g, 17.9 mmol, 1.1 eq.), $[MeOC(=O)]_2O$ (5.22 ml, 6.54 g, 48.7 mmol, 3.0 eq.), $(4\text{-}MeOPh)_3P$ (0.40 g, 1.14 mmol, 7 Mol-%) and $Pd(OAc)_2$ (0.11 g, 0.49 mmol, 3 Mol-%) in THF (61 ml) was stirred at 75°C for 24 h. The solution was filtered through celite® and the filter cake was washed with *t*BuOMe (50 ml) and H_2O (50 ml). The layers were separated, and the aqueous layer was extracted with *t*BuOMe (3 x 50 ml). The combined layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica (5.5 x 18 cm, 50 ml, *c*-hexane:AcOEt 5:1). The title compound (fractions 44-67, 3.95 g, 14.1 mmol, 79% and 98%*ee*) was obtained as a pale yellow liquid.

^{1}H NMR (BlBrJl19-4210, 400.13 MHz, $CDCl_3$): δ = 1.03 (d, $^3J_{3\text{-}Me,3}$ = 6.7 Hz, 3H, 3-Me), AB-Signal (ν_A = 2.30, $^2J_{A,B}$ = 15.3 Hz occasionally split with d, $^3J_{A,3}$ = 6.9 Hz; ν_B = 2.41, $^2J_{A,B}$ = 15.3 Hz occasionally split with d, $^3J_{B,3}$ = 6.7 Hz, 2H, 2-H_2), 2.64 (m_c, 1H, 3-H), AB-Signal (ν_A = 2.75, $^2J_{A,B}$ = 15.6 Hz occasionally split with d, $^3J_{A,3}$ = 7.7 Hz; ν_B = 3.06, $^2J_{A,B}$ = 15.6 Hz occasionally split with d, $^3J_{B,3}$ = 5.7 Hz, 2H, 4-H_2), 3.65 (s, 3H, 1-OMe), 3.92 (s, 3H, 3´–OMe)*, 3.93 (s, 3H, 4´–OMe)*, 6.87 (d, $^3J_{5',6'}$ = 8.5 Hz, 1H, 5´-H), 7.53 (d, $^4J_{2',6'}$ = 2.0 Hz, 1H, 2´-H), 7.59 (dd, $^3J_{6',5'}$ = 8.3 Hz, $^4J_{6',2'}$ = 2.1 Hz, 1H, 6´-H) ppm.

*assignments are interchangeable

^{13}C NMR (BlBrJl19-4215, 100.62 MHz, $CDCl_3$): δ = 20.15 (C-3´´), 27.3 (C-3), 41.0 (C-2), 44.5 (C-4), 51.5 (C-1´´), 56.0 (C-OMe)*, 56.1 (C-OMe)*, 110.1 (C-5´), 110.4 (C-2´), 122.9 (C-6´), 130.4 (C-1´), 149.2 (C-3´), 153.2 (C-4´), 173.0 (C-1), 197.9 (C-5) ppm.

*assignments are interchangeable

HRMS (p. ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{22}O_5$ 303.1203; Found 303.1201

IR (film): ϑ = 1023, 1152, 1170, 1268, 1294, 1417, 1417, 1439, 1462, 1515, 1587, 1594, 1673, 1734, 2957 cm^{-1}.

$\boldsymbol{\alpha_D^{20}} =$ –5.26 (98% *ee*, c = 0.59 in $CHCl_3$)

Elemental analysis:	calc.	C 64.27%	H 7.19%
	found	C 64.13%	H 7.33%
	deviation	C 0.14%	H 0.15%

Enantiomeric excess (*rac.,* 94% *ee* and 98% *ee*) was determined by HPLC on a chiral stationary phase (Kromasil 3-Amycoat, *n*-heptane:EtOH 90:10, 1 ml/min, 20°C, t_1 = 13.56 min (*R*-enantiomere), 15.16 (*S*-enantiomere).

HPLC-report of *rac.* 18

D-7000 HSM: Baeuerle Series: 0030 Report: original System: Sys No. 9

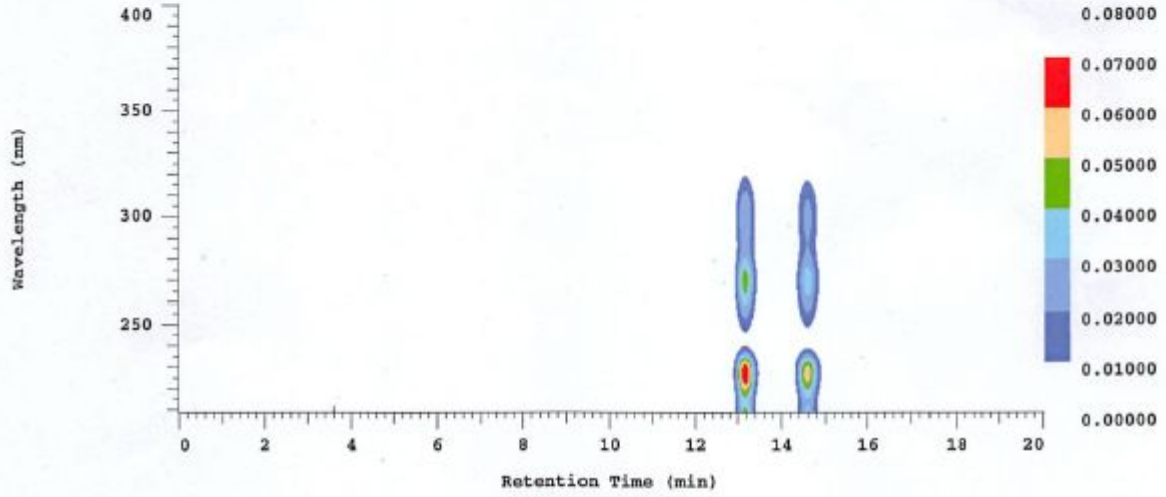
D-7000 HPLC System Manager Report

Analyzed: 07/16/18 02:46 PM
Reported: 07/16/18 03:06 PM
Processed: 07/16/18 03:06 PM

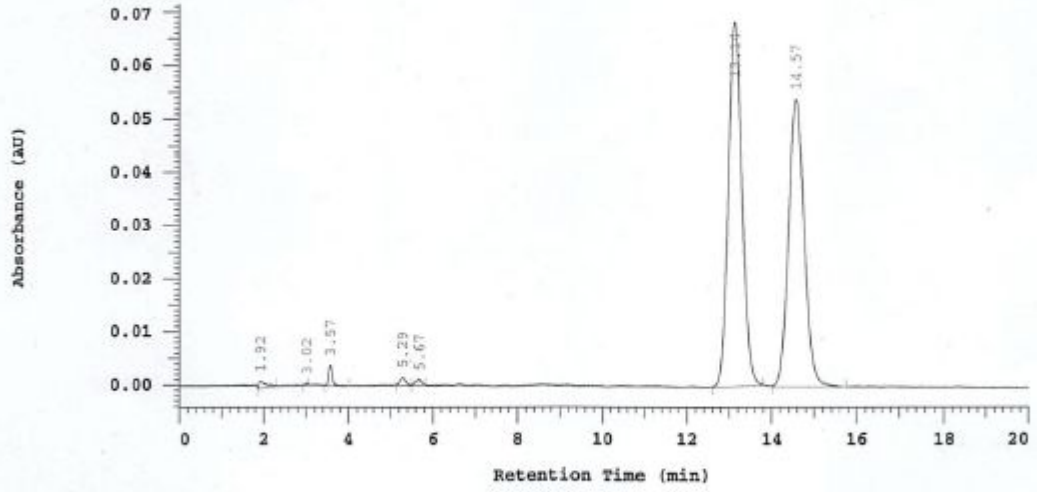
Data Path: D:\Aquisition\Baeuerle\DATA\0030\
Processing Method: Fbae-337-AmyCoat_EtOH

System(acquisition): Sys No. 9
Series:0030
Application: Baeuerle
Vial Number: 1
Sample Name: Bauerle_Fbae-600_rac
Vial Type: UNK
Injection from this vial: 1 of 1
Volume: 1.0 ul
Sample Description: nHept/EtOH 90:10,1mL, 229nm,RT

Absorbance Mode: NORMAL(2.0 AU)
Absorbance Scale: Auto
Spectral Bandwidth: AUTO
Spectral Interval: 200 ms



Chrom Type: Fixed WL Chromatogram, 229 nm



Acquisition Method: Fbae-337-AmyCoat_EtOH
Column Type: Kromasil 3-AmyCoat 4,6x150mm
Developed by: Braukmueller

Page Indicator 1

D-7000 HSM: Baeuerle Series: 0030 Report: original System: Sys No. 9

Pump A Type: L-7100
Solvent A: n-Heptan Solvent B: 2-Propanol
Solvent C: n-Heptan 0.2 DME Solvent D: EtOH
Method Description: Kromasil 3-AmyCoat 4.6x150mm mit 1 cm Vorsaeule, Ser.-Nr.: C03ACA15/A93403, n-Heptan/Ethanol 90/10, 1.0 mL/min, 229 nm, 5 µL Injektion, Raumtemp. (nicht temperiert)

Chrom Type: Fixed WL Chromatogram, 229 nm

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	1.92	7472	0.508	BB
2	3.02	522	0.036	BB
3	3.57	11842	0.805	BB
4	5.29	6347	0.431	BB
5	5.67	5050	0.343	BB
6	13.14	758933	51.584	BB
7	14.57	681099	46.293	BB
		1471265	100.000	

Peak rejection level: 0

HPLC-report of (*R*)-18 using procedure A

D-7000 HSM: Baeuerle Series: 0027 Report: original System: Sys No. 9

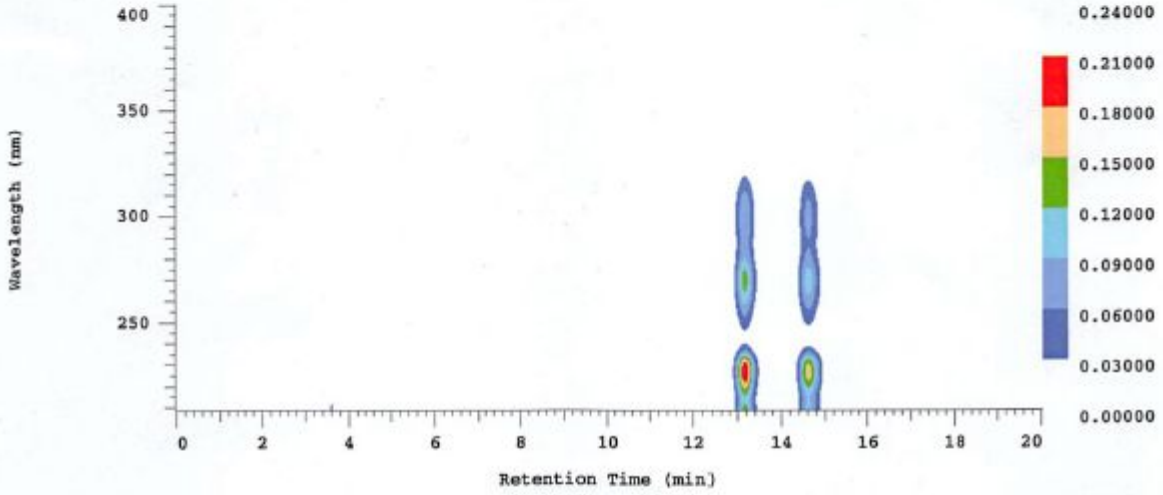
D-7000 HPLC System Manager Report

Analyzed: 07/11/18 02:17 PM
Reported: 07/11/18 02:38 PM
Processed: 07/11/18 02:38 PM

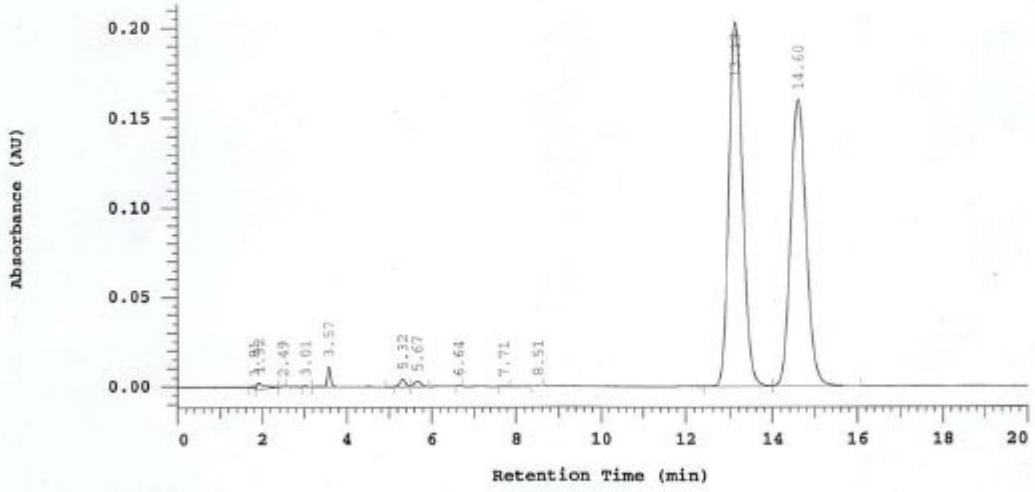
Data Path: D:\Aquisition\Baeuerle\DATA\0027\
Processing Method: Fbae-337-AmyCoat_EtOH

System(acquisition): Sys No. 9
Series:0027
Application: Baeuerle
Vial Number: 1
Sample Name: Bauerle_Fbae-600_ee
Vial Type: UNK
Injection from this vial: 1 of 1
Volume: 3.0 ul
Sample Description: nHept/EtOH 90:10,1mL, 229nm,RT

Absorbance Mode: NORMAL(2.0 AU)
Absorbance Scale: Auto
Spectral Bandwidth: AUTO
Spectral Interval: 200 ms



Chrom Type: Fixed WL Chromatogram, 229 nm



Acquisition Method: Fbae-337-AmyCoat_EtOH
Column Type: Kromasil 3-AmyCoat 4,6x150mm
Developed by: Braukmueller

D-7000 HSM: Baeuerle Series: 0027 Report: original System: Sys No. 9

Pump A Type: L-7100
Solvent A: n-Heptan Solvent B: 2-Propanol
Solvent C: n-Heptan 0.2 DME Solvent D: EtOH
Method Description: Kromasil 3-AmyCoat 4.6x150mm mit 1 cm Vorsaeule, Ser.-Nr.: C03ACA15/A93403, n-Heptan/Ethanol 90/10, 1.0 mL/min, 229 nm, 5 µL Injektion, Raumtemp. (nicht temperiert)

Chrom Type: Fixed WL Chromatogram, 229 nm

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	1.81	3784	0.086	BB
2	1.92	21667	0.492	BB
3	2.49	1312	0.030	BB
4	3.01	1870	0.042	BB
5	3.57	38102	0.866	BB
6	5.32	20102	0.457	BB
7	5.67	18039	0.410	BB
8	6.64	320	0.007	BB
9	7.71	1161	0.026	BB
10	8.51	1115	0.025	BB
11	13.13	2271088	51.590	BB
12	14.60	2023655	45.969	BB
		4402215	100.000	

Peak rejection level: 0

HPLC-report of (*R*)-18 using procedure B

D-7000 HSM: Baeuerle Series: 0028 Report: original System: Sys No. 9

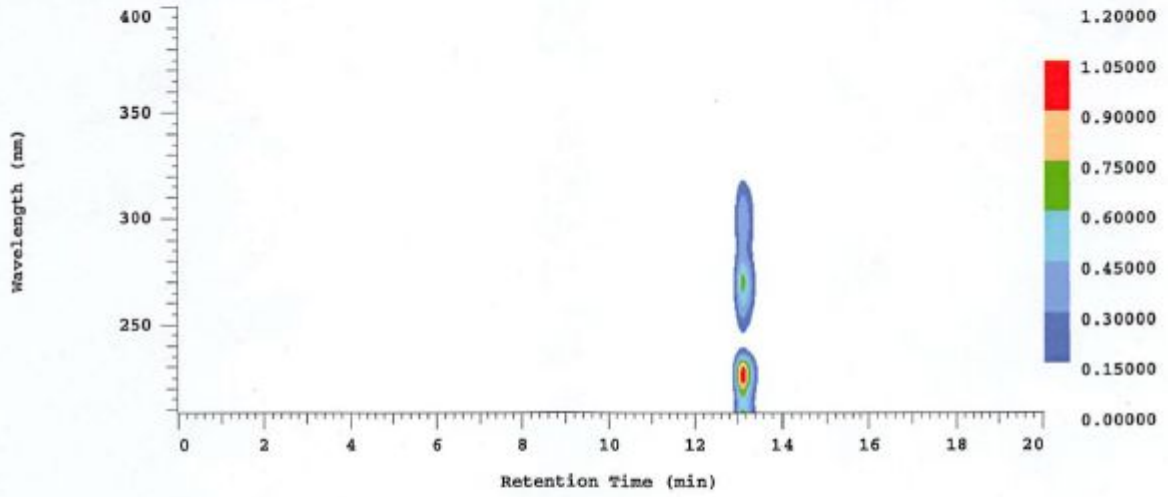
D-7000 HPLC System Manager Report

Analyzed: 07/11/18 03:41 PM
Reported: 07/11/18 04:02 PM
Processed: 07/11/18 04:02 PM

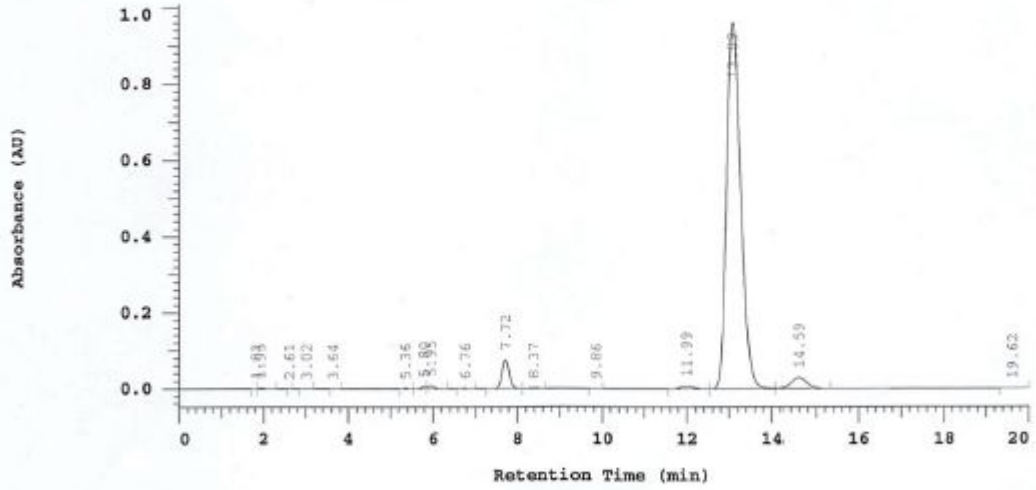
Data Path: D:\Aquisition\Baeuerle\DATA\0028\
Processing Method: Fbae-337-AmyCoat_EtOH

System(acquisition): Sys No. 9
Series:0028
Application: Baeuerle
Vial Number: 1
Sample Name: Bauerle_Fbae-644-1_ee
Vial Type: UNK
Injection from this vial: 1 of 1
Volume: 1.5 ul
Sample Description: nHept/EtOH 90:10,1mL, 229nm,RT

Absorbance Mode: NORMAL(2.0 AU)
Absorbance Scale: Auto
Spectral Bandwidth: AUTO
Spectral Interval: 200 ms



Chrom Type: Fixed WL Chromatogram, 229 nm



Acquisition Method: Fbae-337-AmyCoat_EtOH
Column Type: Kromasil 3-AmyCoat 4,6x150mm
Developed by: Braukmueller

D-7000 HSM: Baeuerle Series: 0028 Report: original System: Sys No. 9

Pump A Type: L-7100
Solvent A: n-Heptan Solvent B: 2-Propanol
Solvent C: n-Heptan 0.2 DME Solvent D: EtOH
Method Description: Kromasil 3-AmyCoat 4.6x150mm mit 1 cm Vorsaeule, Ser.-Nr.: C03ACA15/A93403, n-Heptan/Ethanol 90/10, 1.0 mL/min, 229 nm, 5 µL Injektion, Raumtemp. (nicht temperiert)

Chrom Type: Fixed WL Chromatogram, 229 nm

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	1.82	1621	0.013	BB
2	1.93	11382	0.095	BB
3	2.61	438	0.004	BB
4	3.02	2461	0.020	BB
5	3.64	380	0.003	BB
6	5.36	5558	0.046	BB
7	5.80	22185	0.185	BV
8	5.95	48089	0.400	VB
9	6.76	3594	0.030	BB
10	7.72	445825	3.711	BB
11	8.37	13343	0.111	TBB
12	9.86	1445	0.012	BB
13	11.99	82177	0.684	BB
14	13.09	11002756	91.595	BV
15	14.59	366942	3.055	TBB
16	19.62	4217	0.035	BB
		12012413	100.000	

Peak rejection level: 0

HPLC-report of (*R*)-18 using procedure C

D-7000 HSM: Baeuerle Series: 0031 Report: original System: Sys No. 9

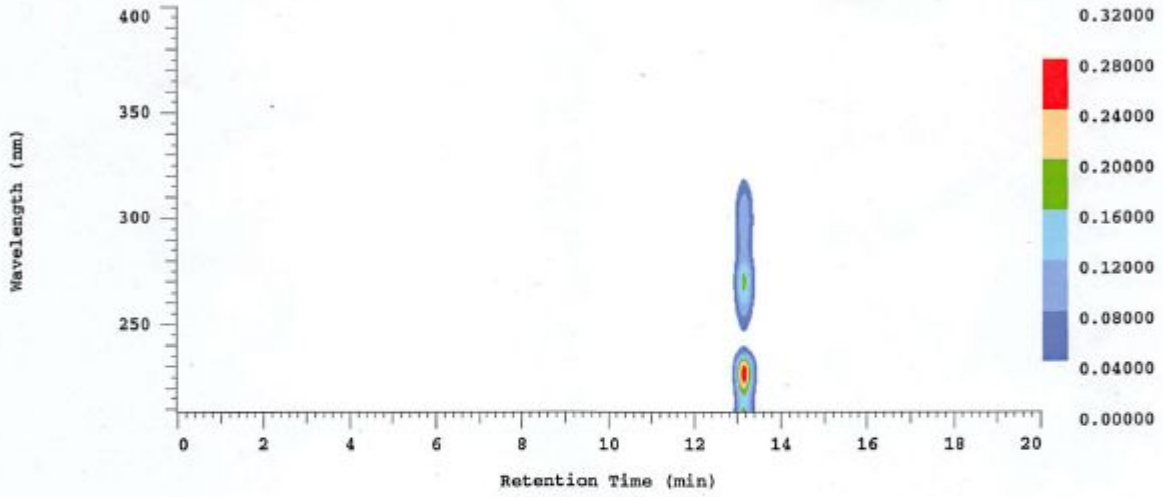
D-7000 HPLC System Manager Report

Analyzed: 07/16/18 03:52 PM
Reported: 07/16/18 04:12 PM
Processed: 07/16/18 04:12 PM

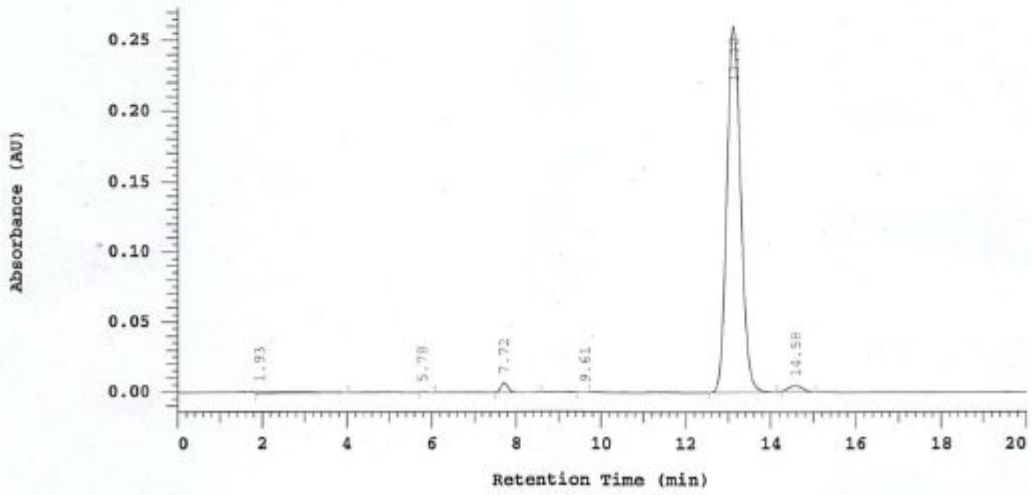
Data Path: D:\Aquisition\Baeuerle\DATA\0031\
Processing Method: Fbae-337-AmyCoat_EtOH

System(acquisition): Sys No. 9
Series:0031
Application: Baeuerle
Vial Number: 1
Sample Name: Bauerle_Fbae-645_ee
Vial Type: UNK
Injection from this vial: 1 of 1
Volume: 1.0 ul
Sample Description: nHept/EtOH 90:10,1mL, 229nm,RT

Absorbance Mode: NORMAL(2.0 AU)
Absorbance Scale: Auto
Spectral Bandwidth: AUTO
Spectral Interval: 200 ms



Chrom Type: Fixed WL Chromatogram, 229 nm



Acquisition Method: Fbae-337-AmyCoat_EtOH
Column Type: Kromasil 3-AmyCoat 4,6x150mm
Developed by: Braukmueller

D-7000 HSM: Baeuerle Series: 0031 Report: original System: Sys No. 9

Pump A Type: L-7100
Solvent A: n-Heptan Solvent B: 2-Propanol
Solvent C: n-Heptan 0.2 DME Solvent D: EtOH
Method Description: Kromasil 3-AmyCoat 4.6x150mm mit 1 cm Vorsaeule, Ser.-Nr.: C03ACA15/A93403, n-Heptan/Ethanol 90/10, 1.0 mL/min, 229 nm, 5 µL Injektion, Raumtemp. (nicht temperiert)

Chrom Type: Fixed WL Chromatogram, 229 nm

Peak Quantitation: AREA
Calculation Method: AREA%

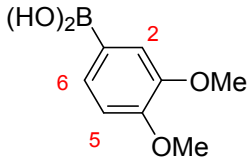
No.	RT	Area	Area %	BC
1	1.93	42609	1.403	BB
2	5.78	940	0.031	BB
3	7.72	35907	1.182	BB
4	9.61	1030	0.034	BB
5	13.12	2914283	95.928	BB
6	14.58	43210	1.422	BB
		3037979	100.000	

Peak rejection level: 0

98 !

(3,4-Dimethoxyphenyl)boronic Acid (21b)

IUPAC/NMR-Numbering



$C_8H_{11}BO_4$
182,08

n-BuLi (2.2 M in hexane, 30.3 ml, 66.7 mmol, 1.1 eq.) was added to a solution of 4-bromo veratrole (9.02 ml, 13.6 g, 60.6 mmol) in THF (123 ml) at –78°C. The resulting mixture was stirred for 1 h at –78°C. $B(OMe)_3$ (11.0 ml, 10.2 g, 90.9 mmol, 1.5 eq.) was added slowly at –78°C. The resulting mixture was allowed to warm up to room temperature and was stirred for 17 h. Aqueous HCl (1 M) was added until pH 1 was obtained and the mixture was stirred for 2 h at room temperature. The layers were separated, and the aqueous layer was extracted with AcOEt (3 x 150 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was diluted in AcOEt (20 ml) and hexane (150 ml). The precipitate was filtered and washed with AcOEt (3 ml) and hexane (30 ml). The title compound (6.62 g, 64%, Lit[5]: 60%) was obtained was a colorless solid.

^{1}H NMR (BlBrJl17-31050, 300.13 MHz, $CDCl_3$): δ = 3.98 (s, 3H, 3–OMe)*, 4.02 (s, 3 H, 4-OMe)*, 7.03 (d, $^3J_{5,6}$ = 8.3 Hz, 1H, 5-H), 7.69 (d, $^4J_{2,6}$ = 1.3 Hz, 1H, 2-H), 7.21 (dd, $^3J_{6,5}$ = 8.9 Hz, $^4J_{6,2}$ = 1.4 Hz, 1H, 6-H) ppm.

*assignments are interchangeable

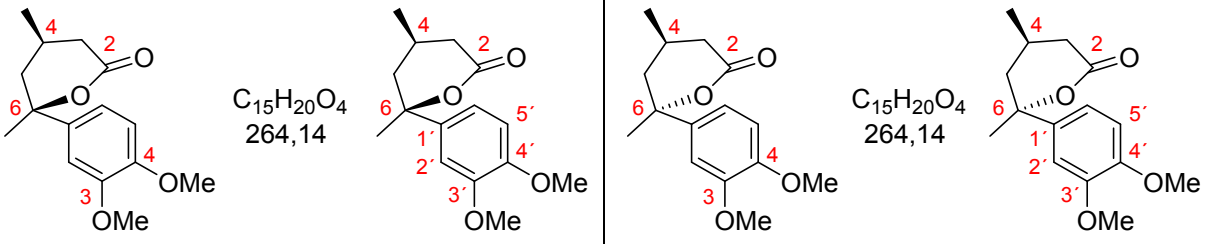
The spectroscopic data were consistent to those reported in literature.[5]

m.p.: >220°C (Lit[5]: 245-248°C)

[5] Q.-Q. Zhang, J.-H. Xie, X.-H. Yang, J.-B. Xie, Q.-L. Zhou, *Org. Lett.* **2012**, *14*, 6158-6161

(4*R*,6*S*)-6-(3,4-Dimethoxyphenyl)-4,6-dimethyltetrahydro-2H-pyran-2-one (29) and (4*R*,6*R*)-6-(3,4-Dimethoxyphenyl)-4,6-dimethyltetrahydro-2H-pyran-2-one (*dia*-29)

IUPAC-Numbering NMR-Numbering IUPAC-Numbering NMR-Numbering



A solution of **14** (2.47 g, 8.83 mmol) in THF (8.8 ml) was slowly added to a solution of MeMgCl (3.0 M in THF, 4.41 ml, 13.2 mmol, 1.5 eq.) in THF (44 ml) at 0°C. The resulting mixture was stirred at room temperature for 17 h. A sat. aqueous Na_2CO_3 solution (30 ml) was added and the layers were separated. The aqueous layer was extracted with *t*BuOMe (3 x 50 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica (6.0 x 17 cm, 50 ml, *c*-hexane: AcOEt 6:1). **29** (fractions 63-97, 903 mg, 3.41 mmol, 39%, single isomer) was obtained as colorless solid (m. p. 94°C). *dia*-**29** (fractions 113-139, 581 mg, 2.23 mmol, 25%, single isomer) was obtained as a colorless solid (m. p. 92°C). Both isomers can be recrystallized from *n*-hexane if necessary.

Analytical data of **29**:

^{1}H NMR (BlBrJn07-4260, 400.13 MHz, C_6D_6): δ = 0.44 (d, $^3J_{4\text{-Me},4}$ = 6.6 Hz, 3H, 4-Me), AB-Signal (ν_A = 1.06, $^2J_{A,B}$ = 13.8 Hz occasionally split with d, $^3J_{A,4}$ = 12.2 Hz; ν_B = 1.81, $^2J_{A,B}$ = 13.8 Hz occasionally split with dd, $^3J_{B,4}$ = 3.5 Hz, $^4J_{B,3B}$ = 2.9 Hz, 2H, 5-H_2), 1.38-1.46 (m, 1H, 4-H), 1.45 (s, 3H, 6-Me), H_A), AB-Signal (ν_A = 1.60, $^2J_{A,B}$ = 17.5 Hz occasionally split with d, $^3J_{A,4}$ = 11.2 Hz; ν_B = 2.25, $^2J_{A,B}$ = 17.5 Hz occasionally split with dd, $^3J_{B,4}$ = 5.9 Hz, $^4J_{B,5B}$ = 2.0 Hz, 2H, 3-H_2), 3.39 (s, 3H, 4´-OMe), 3.43 (s, 3H, 3´-OMe), 6.53 (d, $^3J_{5',6'}$ = 8.3 Hz, 1H, 5´-H), 6.73 (dd, $^3J_{6',5'}$ = 8.4 Hz, $^4J_{6',2'}$ = 2.3 Hz, 1H, 6´-H), 6.86 (d, $^4J_{2',6'}$ = 2.3 Hz, 1H, 2-H) ppm.

^{13}C NMR (BlBrJn07-4265, 100.62 MHz, C_6D_6): δ = 21.1 (C-4-Me), 23.9 (C-4), 32.3 (C-6-Me), 37.9 (C-3), 43.1 (C-5), 55.6 (C-4´-OMe), 55.6 (C-3´-OMe), 84.2 (C-6), 109.4 (C-2´), 112.4 (C-5´), 116.7 (C-6´), 138.4 (C-1´), 149.2 (C-4´), 150.3 (C-3´), 169.9 (C-2) ppm.

HRMS (p. ESI): $[M+Na]^+$ Calcd for $C_{15}H_{20}O_4Na$ 287.1251; Found 287.1251

IR (film): ϋ = 767, 867, 988, 1026, 1093, 1141, 1183, 1224, 1256, 1409, 1455, 1513, 1733, 2932, 2956 cm^{-1}.

$\boldsymbol{\alpha_D^{20}} =$ +13.82 (99% *ee*, c = 0.94 in $CHCl_3$)

Elemental analysis:	calc.	C 68.16%	H 7.63%
	found	C 67.86%	H 7.53%
	deviation	C 0.30%	H 0.10%

Analytical data of *dia*-**29**:

^{1}H NMR (BlBrMz01-500700, 500.32 MHz, C_6D_6): δ = 0.49 (d, $^3J_{4\text{-Me},4}$ = 6.3 Hz, 3H, 4-Me), 1.19-1.25 (m, 1H, 5-H_A), 1.35 (d, $^4J_{6\text{-Me},5}$ = 0.7 Hz, 3H, 6-Me), 1.51-1.57 (m, 1 H, 3-H_A), 1.54-1.57 (m, 1H, 4-H), 1.58-1.60 (m, 1H, 5-H_B), 2.31-2.36 (m, 1H, 3-H_B), 3.41 (s, 3H, 4′-OMe), 3.45 (s, 3H, 3′-OMe), 6.61 (d, $^3J_{5',6'}$ = 8.4 Hz, 1H, 5′-H), 6.82 (dd, $^3J_{6',5'}$ = 8.4 Hz, $^4J_{6',2'}$ = 2.3 Hz, 1H, 6′-H), 7.03 (d, $^4J_{2',6'}$ = 2.3 Hz, 1H, 2′-H) ppm.

^{13}C NMR (BlBrMz01-500705, 125.82 MHz, C_6D_6): δ = 21.2 (C-4-Me), 24.3 (C-4), 29.4 (C-6-Me), 38.1 (C-3), 43.5 (C-5), 55.7 (C-4′-OMe), 55.7 (C-3′-OMe), 83.2 (C-6), 109.1 (C-2′), 112.2 (C-5′), 116.4 (C-6′), 140.1 (C-1′), 149.4 (C-4′), 150.2 (C-3′), 169.2 (C-2) ppm.

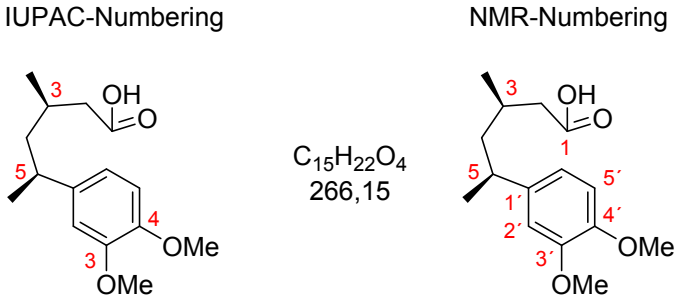
HRMS (p. ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{20}O_4Na$ 287.1254; Found 287.1252

IR (film): ϋ = 812, 982, 1026, 1088, 1108, 1143, 1174, 1216, 1252, 1412, 1463, 1520, 1730, 2934, 2957 cm^{-1}.

$\boldsymbol{\alpha_D^{20}} =$ +27.54 (99% *ee*, c = 0.94 in $CHCl_3$)

Elemental analysis:	calc.	C 68.16%	H 7.63%
	found	C 68.12%	H 7.76%
	deviation	C 0.04%	H 0.13%

(3*R*,5*S*)-5-(3,4-dimethoxyphenyl)-3-methylhexanoic Acid (30)



A suspension of **29** (903 mg, 3.42 mmol) and Pd on Carbon (10 wt-%, 545 mg, 0.51 mmol, 15 Mol-%) in EtOH (6 ml) was degassed with the freeze, pump and thaw method and rinsed with H_2 (3 times). This mixture was stirred at room temperature under a H_2-atmosphere (1 bar) for 24 h. The mixture was filtered through celite® and the filter cake was washed with AcOEt (3 x 15 ml). Saturated aqueous Na_2CO_3 solution (10 ml) was added and the layers were separated. The organic layer was extracted with sat. aqueous Na_2CO_3 solution (3 x 20 ml). The combined aqueous layers were treated with conc. HCl until pH 1 was reached. This mixture was diluted with AcOEt (60 ml) and the layers were separated. The aqueous layer was extracted with AcOEt (3 x 60 ml) and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure. The title compound (860 mg, 3.26 mmol, 95%, *dr* 97:3) was obtained as a colorless oil without further purification.

^{1}H NMR (BlBrOk31-4070, 400.13 MHz, $CDCl_3$, contains 3% of the *anti*-isomere): δ = 0.96 (d, $^3J_{3\text{-Me},3}$ = 6.7 Hz, 3H, 3-Me), 1.21 (d, $^3J_{6,5}$ = 6.7Hz, 3 H, 6-H_3), AB-Signal (ν_A = 1.40, $^2J_{A,B}$ = 13.7 Hz occasionally split with dd, $^3J_{A,3}$ = 8.7 Hz, $^3J_{A,5}$ = 5.4 Hz; ν_B = 1.70, $^2J_{A,B}$ = 13.7 Hz occasionally split with dd, $^3J_{B,3}$ = 9.4 Hz, $^3J_{B,5}$ =4.8 Hz, 2H, 4-H_2), 1.77-1.85 (m, 1H, 3-H), AB-Signal (ν_A = 2.14, $^2J_{A,B}$ = 15.1 Hz occasionally split with d, $^3J_{A,3}$ = 7.4 Hz; ν_B = 2.28, $^2J_{A,B}$ = 15.1 Hz occasionally split with d, $^3J_{B,3}$ = 6.4 Hz, 2H, 2-H_2), 2.75 (m_c, 1H, 5-H), 3.85 (s, 3H, 4′-OMe), 3.87 (s, 3H, 3′-OMe), 6.71 (d, $^4J_{2',6'}$ = 2.1 Hz, 1H, 2′-H), 6.71 (dd, $^3J_{6',5'}$ = 8.7 Hz, $^4J_{6',2'}$ = 2.1 Hz, 1H, 6′-H), 6.80 (d, $^3J_{5',6'}$ = 8.7 Hz, 1H, 5′-H), 10.90 (br. s, 1H, –COOH) ppm.

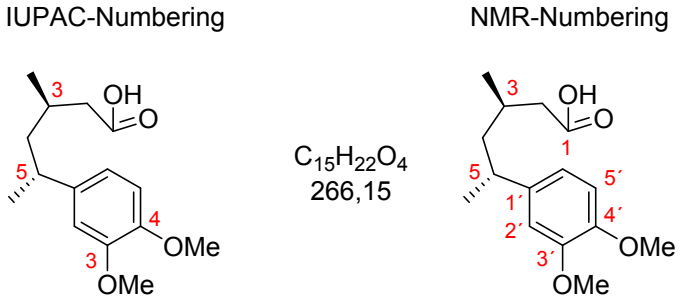
^{13}C NMR (BlBrOk31-4075, 100.62 MHz, $CDCl_3$): δ = 19.6 (C-3-Me), 23.8 (C-6), 28.0 (C-3), 37.1 (C-5), 41.8 (C-2), 45.0 (C-4), 55.9 (C-3′-OMe), 56.0 (C-4′-OMe), 110.3 (C-2′), 111.4 (C-5′), 119.7 (C-6′), 139.6 (C-1′), 147.4 (C-4′), 149.1 (C-3′), 178.7 (C-1) ppm.

HRMS (+p. ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{22}O_4Na$ 289.1410; Found 287.1411

IR (film): ϋ = 764, 807, 854, 1028, 1143, 1234, 1261, 1419, 1463, 1518, 1592, 1706, 2836, 2958 cm^{-1}.

$\boldsymbol{\alpha_D^{20}} =$ +4.70 (99% *ee*, c = 1.00 in $CHCl_3$)

(3*R*,5*R*)-5-(3,4-Dimethoxyphenyl)-3-methylhexanoic Acid (*dia*-30)



A suspension of *dia*-**29** (581 mg, 2.20 mmol) and Pd on Carbon (10 wt-%, 351 mg, 0.33 mmol, 15 Mol-%) in EtOH (4 ml) was degassed with the freeze, pump and thaw method and rinsed with H_2 (3 times). This mixture was stirred at room temperature under a H_2-atmosphere (1 bar) for 24 h. The mixture was filtered through celite® and the filter cake was washed with AcOEt (3 x 10 ml). Saturated aqueous Na_2CO_3 solution (10 ml) was added and the layers were separated. The organic layer was extracted with a sat. aqueous Na_2CO_3 solution (3 x 20 ml). The combined aqueous layers were treated with conc. HCl until pH 1 was reached. This mixture was diluted with AcOEt (60 ml) and the layers were separated. The aqueous layer was extracted with AcOEt (3 x 60 ml) and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure. The title compound (534 mg, 2.02 mmol, 92%, *dr* 95:5) was obtained as a colorless oil without further purification.

^{1}H NMR (BlBrOk31-4070, 400.13 MHz, $CDCl_3$, contains 5% of the *anti*-isomere): δ = 0.96 (d, $^3J_{3\text{-Me},3}$ = 6.7 Hz, 3H, 3-Me), 1.22 (d, $^3J_{6,5}$ = 6.7 Hz, 3H, 6-H_2), AB-Signal (ν_A = 1.49, $^2J_{A,B}$ = 13.7 Hz occasionally split with dd, $^3J_{A,3}$ = 7.5 Hz, $^3J_{A,5}$ = 7.5 Hz; ν_B = 1.55, $^2J_{A,B}$ = 13.7 Hz occasionally split with dd, $^3J_{B,3}$ = 7.0 Hz, $^3J_{B,5}$ =7.0 Hz, 2H, 4-H_2), 1.95 (m_c, 1H, 3-H), AB-Signal (ν_A = 2.15, $^2J_{A,B}$ = 15.0 Hz occasionally split with d, $^3J_{A,3}$ = 8.3 Hz; ν_B = 2.38, $^2J_{A,B}$ = 15.0 Hz occasionally split with d, $^3J_{B,3}$ = 5.4 Hz, 2H, 3-H_2), 2.78 (m_c, 1H, 5-H), 3.86 (s, 3H, 4′-OMe), 3.88 (s, 3H, 3′-OMe), 6.70 (d, $^4J_{2',6'}$ = 2.0 Hz, 1H, 2′-H), 6.73 (dd, $^3J_{6',5'}$ = 8.2 Hz, $^4J_{6',2'}$ = 2.1 Hz, 1H, 6′-H), 6.80 (d, $^3J_{5',6'}$ = 8.1 Hz, 1H, 5′-H), 10.51 (br. s, 1H, –COOH) ppm.

^{13}C NMR (BlBrOk31-4075, 100.62 MHz, $CDCl_3$): δ = 19.9 (C-3-Me), 22.2 (C-6), 28.2 (C 3), 37.1 (C-5), 41.3 (C-2), 45.7 (C-4), 56.0 (C-3′-OMe), 56.0 (C-4′-OMe), 110.3 (C 2′), 111.4 (C-5′), 118.7 (C-6′), 140.3 (C-1′), 147.5 (C-4′), 149.0 (C-3′), 178.6 (C-1) ppm.

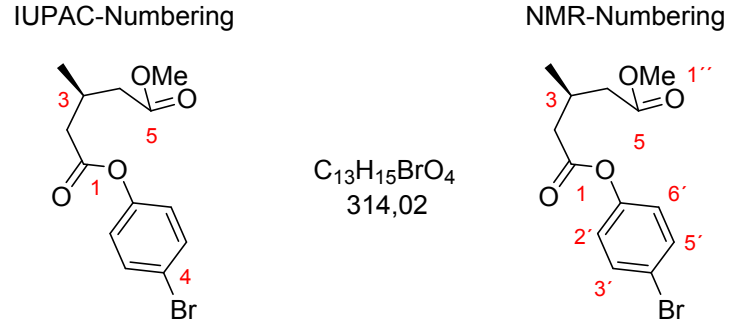
HRMS (+p. ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{26}O_4Na$ 284.1856; Found 284.1857

IR (film): ϋ = 772, 1029, 1141, 1165, 1236, 1260, 1419, 1463, 1518, 1706, 1733, 2837, 2873, 2930, 2959 cm^{-1}.

$\boldsymbol{\alpha_D^{20}} =$ +10.01 (99% *ee*, c = 1.01 in $CHCl_3$)

Elemental analysis:	calc.	C 67.65%	H 8.33%
	found	C 67.72%	H 8.41%
	deviation	C 0.07%	H 0.08%

1-(4-Bromophenyl) 5-methyl (*S*)-3-methylpentanedioate (31)



4-bromo phenol (22.7 mg, 0.16 mmol, 1.0 eq.) was added to a solution of (*R*)-**16a** (25 mg, 0.16 mmol), DCC (33.1 mg, 0.16 mmol, 1.0 eq.) and DMAP (5.0 mg, 0.16 mmol, 20 Mol-%) in CH_2Cl_2 (1.0 ml). The resulting mixture was stirred for 15 h at room temperature. The precipitate was filtered and was washed with CH_2Cl_2 (4 ml). The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica (1.0 x 20 cm, 8 ml, *c*-hexane:AcOEt 21:1). The title compound (fractions 14-26, 40.2 mg, 0.13 mmol, 80%) was obtained as a colorless oil.

^{1}H NMR (BlBrJa19-31030, 300.13 MHz, $CDCl_3$): δ = 1.14 (d, $^3J_{3\text{-Me},3}$ = 6.6 Hz, 3H, 3-Me), 2.33-2.41 (m, 1H, 2-H), 2,45-2.71 (m, 3H, 2-H und 4-H_2), 3.71 (s, 3H, 1´´-H_3), 7.01 (m_c, 2H, 2´-H and 6´-H), 7.51 (m_c, 2H, 3´-H and 5´-H) ppm.

The spectroscopic data were consistent to those reported in literature.[6]

$\boldsymbol{\alpha_D^{20}}$ = 4.12 (99% *ee*, c = 0.93 in $CHCl_3$)

Enantiomeric excess (99% *ee*) was determined by HPLC on a chiral stationary phase (Kromasil 3-AmyCoat, *n*-heptane:*i*PrOH 95:5, 1 ml/min, 10°C, t_1 = 10.49 min (*R*-Enantiomere), 13.02 (*S*-Enantiomere).

[6] R. Manzano, J. M. Andres, M.-D. Muruzabal, R. Pedrosa, *J. Org. Chem.* **2010**, *75*, 5417-5420.

HPLC-report of *rac.* 31

```
Data File D:\LC_DATA\BAEUERLE\DATA\BAEUERLE_FBAE-335_RAC_ 2019-09-07 15-43-52.D
Sample Name: Baeuerle_Fbae-335_rac_

=====================================================================
Acq. Operator   : SYSTEM
Sample Operator : SYSTEM
Acq. Instrument : HPLC5                          Location : Vial 1
Injection Date  : 07.09.2019 15:45:05
                                                 Inj Volume : 5.000 µl
Method          : D:\LC_DATA\BAEUERLE\METHODS\BAEUERLE_PBRPH_ME-3-METHYLGLUTARAT_98_LC.M
Last changed    : 21.05.2019 13:36:07 by SYSTEM
Method Info     : Kromasil 3-AmyCoat 4.6 x 150 mm mit 1 cm Vorsaeule, n-Heptan/2-Propanol 98
                  /2, 1.0 mL/min, 5 µL Injektion, 220 nm, 10°C  temperiert
                  ee-Bestimmung von Methyl-3-methylglutarat als para-Brom-Phenolester

Sample Info     : Kromasil 3-AmyCoat 4.6 x 150 mm
                  mit 4.0 x 10 mm Vorsaeule
                  Ser.-Nr.: A87897
                  n-Heptan / 2-PrOH 98:2
                  Flussrate: 1.0 mL/min
                  Injektionvolumen: 5 µL
                  Detektor: 220 nm
                  Temperatur: 10°C temperiert
                  Druck: 97 bar
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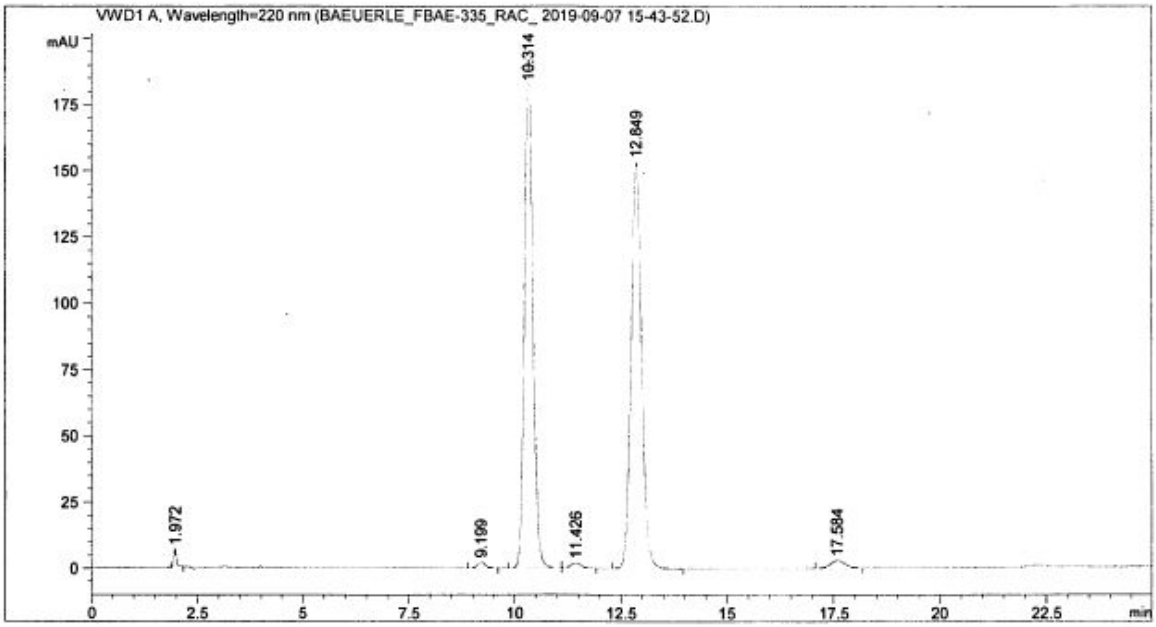


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=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs
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Data File D:\LC_DATA\BAEUERLE\DATA\BAEUERLE_FBAE-335_RAC_ 2019-09-07 15-43-52.D
Sample Name: Baeuerle_Fbae-335_rac_

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.972	VV	0.0684	34.28526	7.23372	0.6277
2	9.199	BB	0.1968	28.37401	2.24776	0.5195
3	10.314	BB	0.2119	2651.41821	192.24007	48.5413
4	11.426	BB	0.2358	27.74407	1.76511	0.5079
5	12.849	BB	0.2661	2653.92798	153.29080	48.5872
6	17.584	BB	0.3456	66.44324	2.90386	1.2164
Totals :				5462.19277	359.68132	

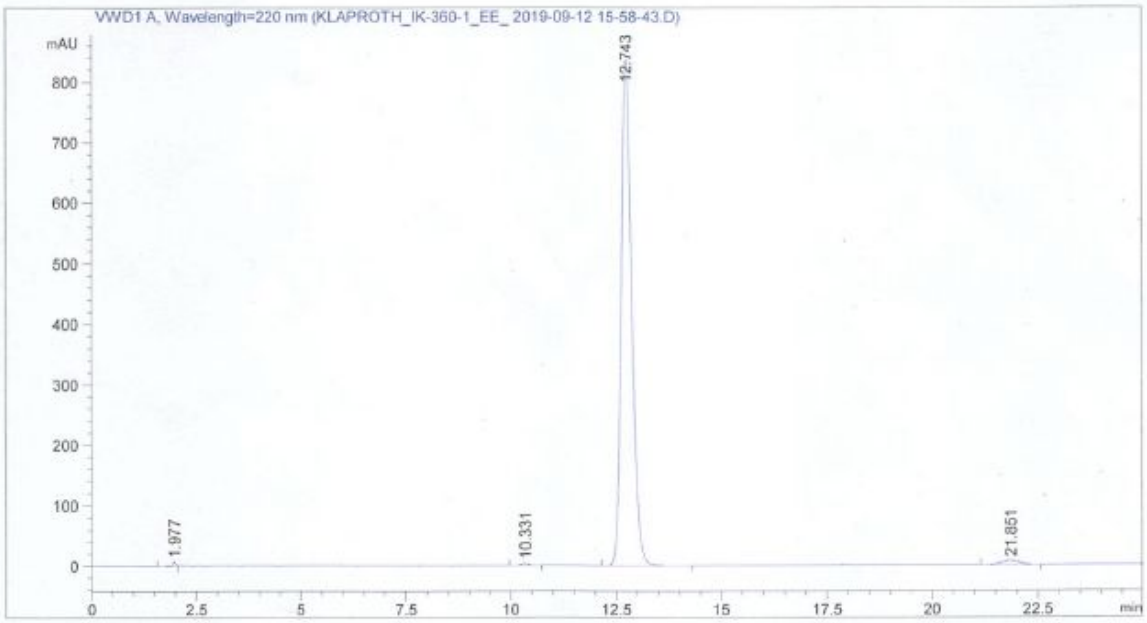
*** End of Report ***

HPLC-report of (*S*)-31

```
Data File D:\LC_DATA\BAEUERLE\DATA\KLAPROTH_IK-360-1_EE_ 2019-09-12 15-58-43.D
Sample Name: Klaproth_IK-360-1_ee_

=====================================================================
Acq. Operator   : SYSTEM
Sample Operator : SYSTEM
Acq. Instrument : HPLC5                          Location : Vial 1
Injection Date  : 12.09.2019 15:59:55
                                                 Inj Volume : 5.000 µl
Method          : D:\LC_DATA\BAEUERLE\METHODS\BAEUERLE_PBRPH_ME-3-METHYLGLUTARAT_98_LC.M
Last changed    : 21.05.2019 13:36:07 by SYSTEM
Method Info     : Kromasil 3-AmyCoat 4.6 x 150 mm mit 1 cm Vorsaeule, n-Heptan/2-Propanol 98
                  /2, 1.0 mL/min, 5 µL Injektion, 220 nm, 10°C  temperiert
                  ee-Bestimmung von Methyl-3-methylglutarat als para-Brom-Phenolester

Sample Info     : Kromasil 3-AmyCoat 4.6 x 150 mm
                  mit 4.0 x 10 mm Vorsaeule
                  Ser.-Nr.: A87897
                  n-Heptan / 2-PrOH 98:2
                  Flussrate: 1.0 mL/min
                  Injektionvolumen: 5 µL
                  Detektor: 220 nm
                  Temperatur: 10°C temperiert
                  Druck: 97 bar
```

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=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs
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Data File D:\LC_DATA\BAEUERLE\DATA\KLAPROTH_IK-360-1_EE_ 2019-09-12 15-58-43.D
Sample Name: Klaproth_IK-360-1_ee_

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.977	BV	0.0627	30.06430	7.07491	0.2030
2	10.331	BB	0.2101	41.66473	3.05384	0.2813
3	12.743	BB	0.2672	1.45472e4	835.50305	98.2163
4	21.851	BB	0.4722	192.46243	6.18639	1.2994
Totals :				1.48114e4	851.81819	

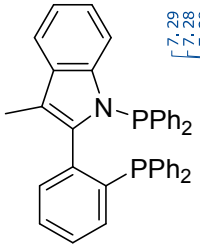
*** End of Report ***

99.4 % ee

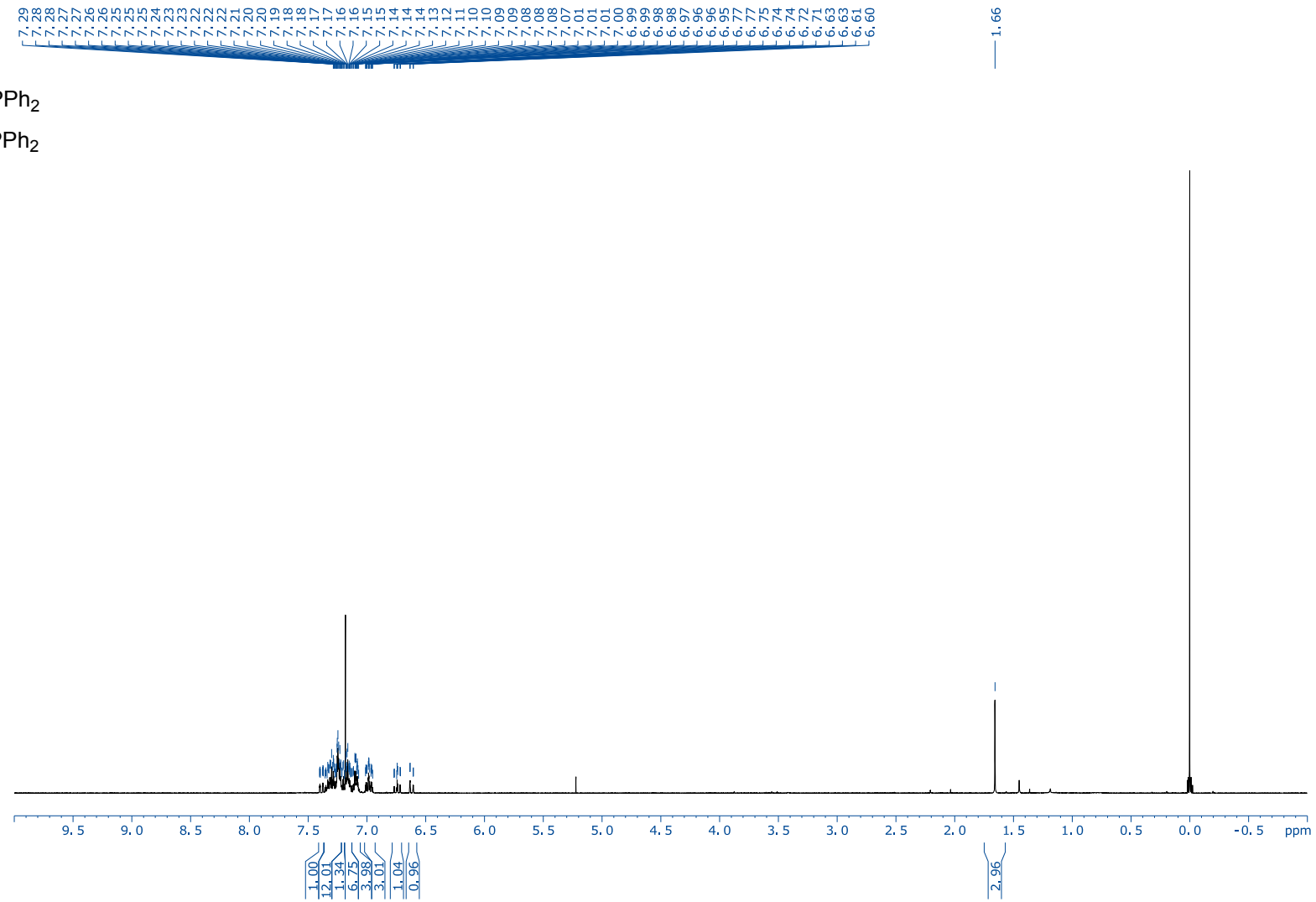
3. ^{1}H, ^{13}C, and ^{31}P NMR Spectra in Numerical Order

1-(Diphenylphosphino)-2-[2-(diphenylphosphino)phenyl]-3-methyl-1*H*-indole (8)

^{1}H NMR (300.13 MHz, $CDCl_3$):

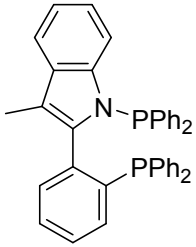


iso-**8**

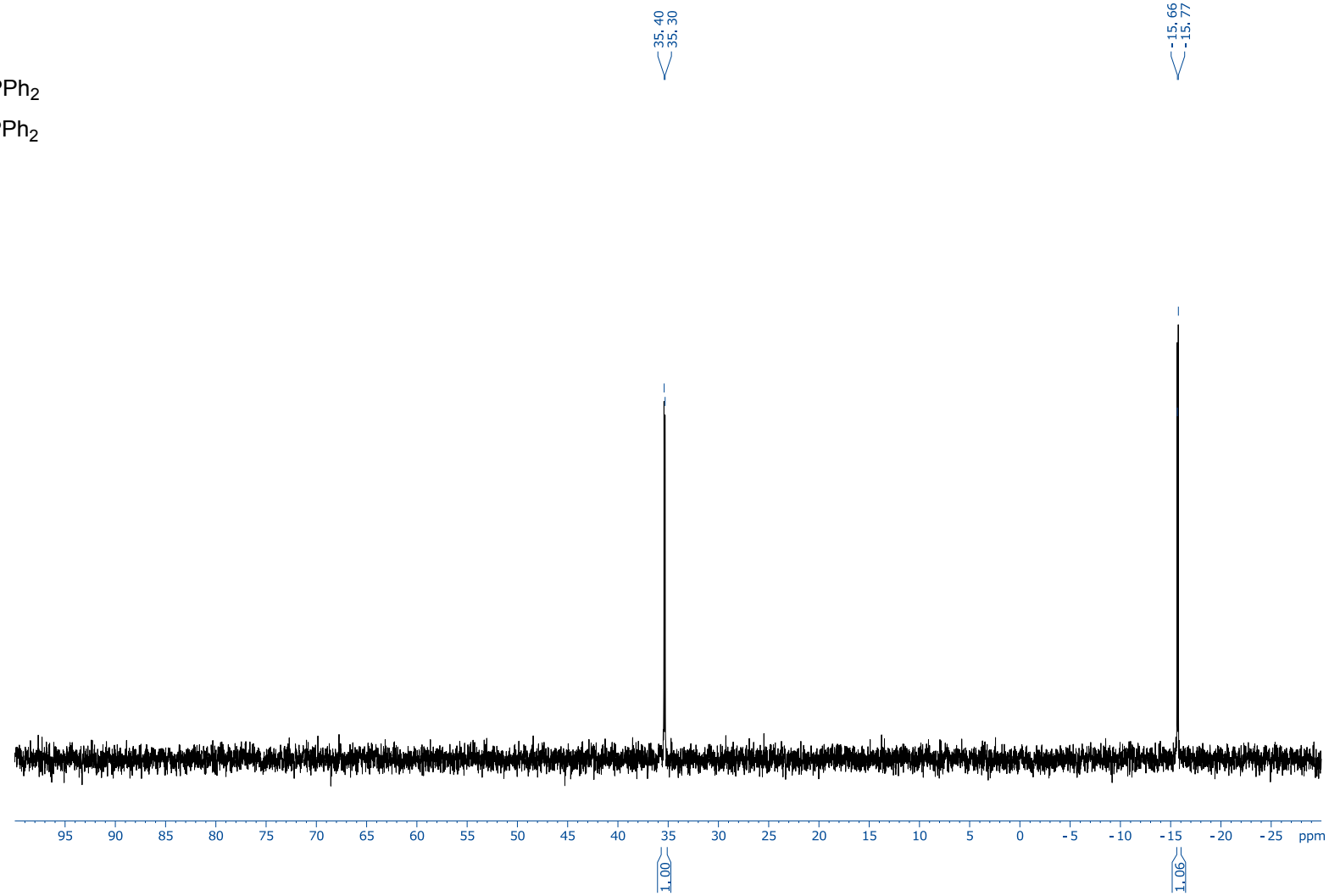


1-(Diphenylphosphino)-2-[2-(diphenylphosphino)phenyl]-3-methyl-1*H*-indole (8)

^{31}P NMR (121.49 MHz, $CDCl_3$):

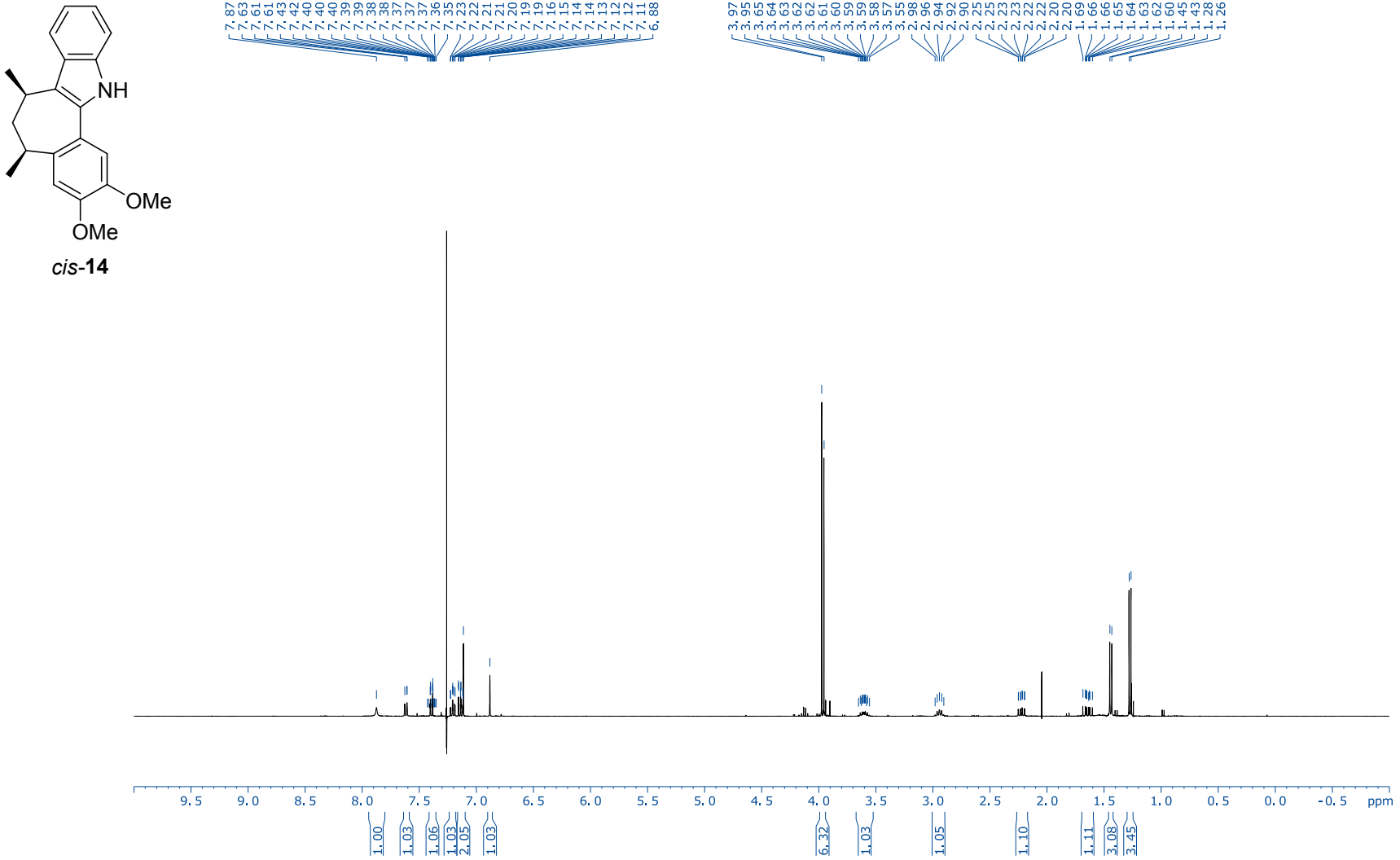


iso-**8**



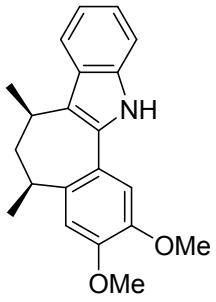
(5*S*,7*R*)-2,3-Dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*cis*-**14**)

^{1}H NMR (400.13 MHz, $CDCl_3$):

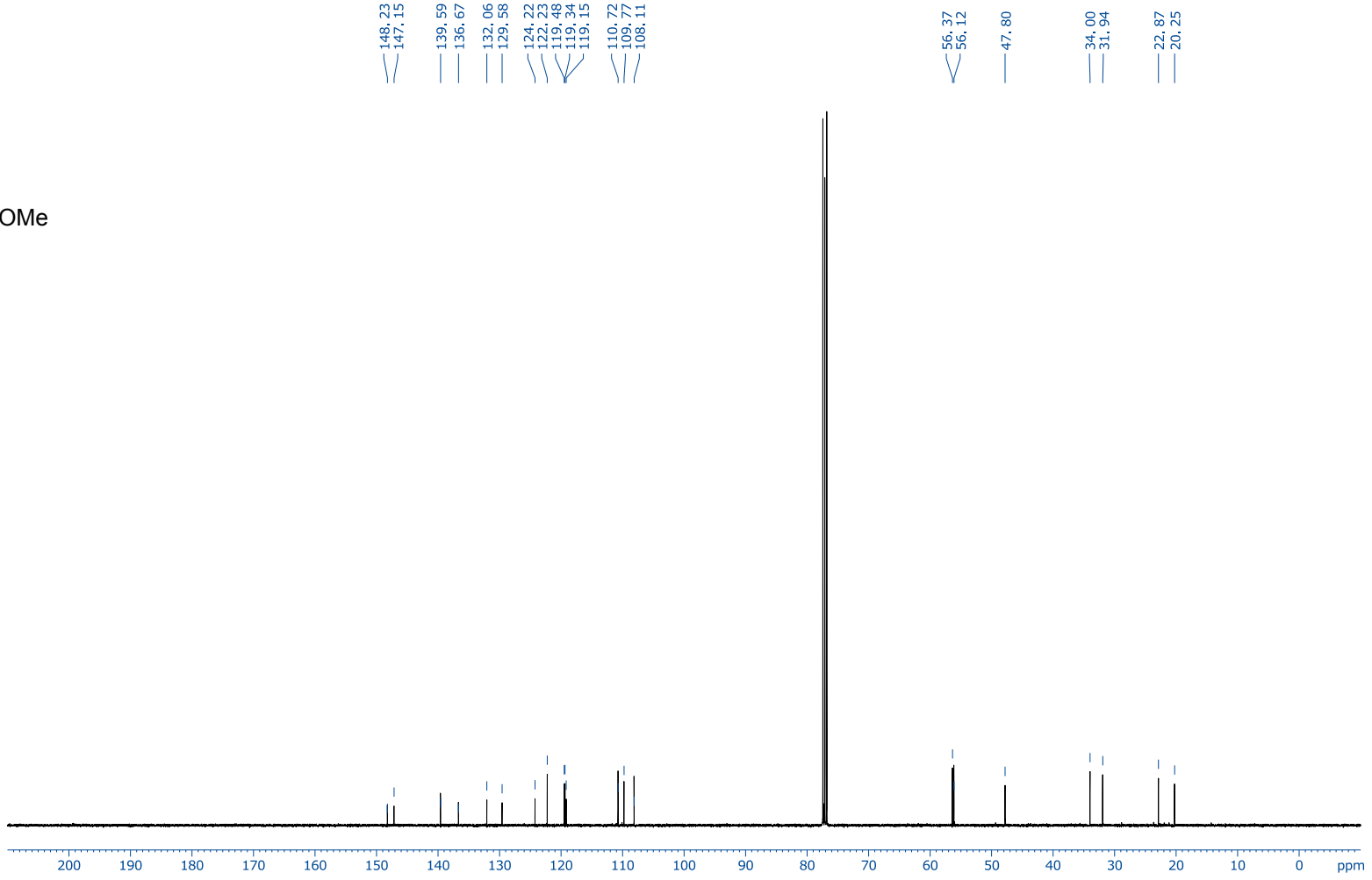


(5*S*,7*R*)-2,3-Dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*cis*-**14**)

^{13}C NMR (100.61 MHz, $CDCl_3$):

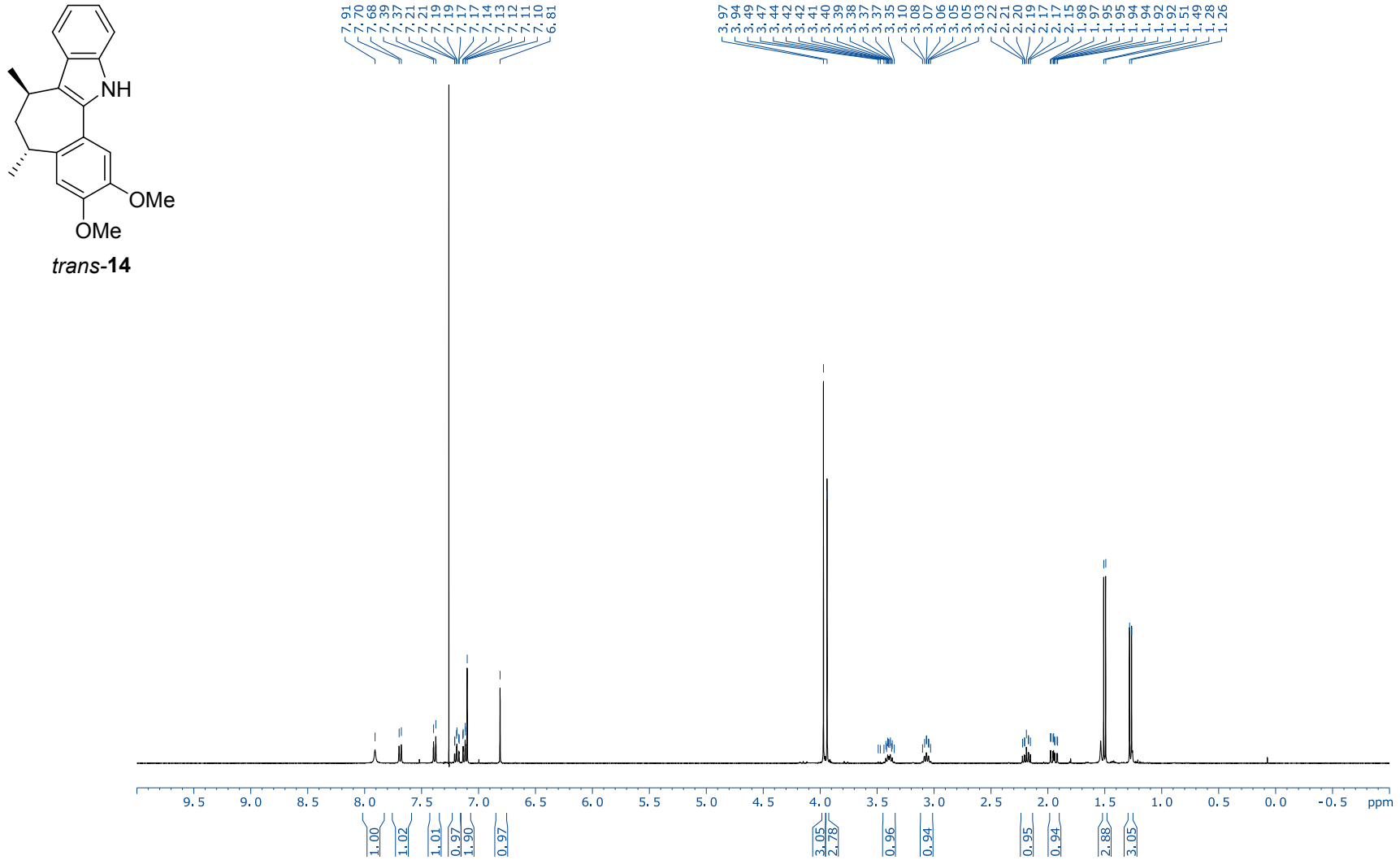


cis-**14**



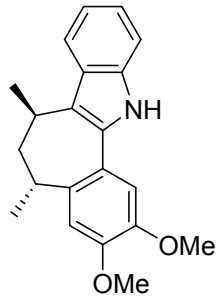
(5*R*,7*R*)-2,3-Dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*trans*-**14**)

^{1}H NMR (400.13 MHz, $CDCl_3$):

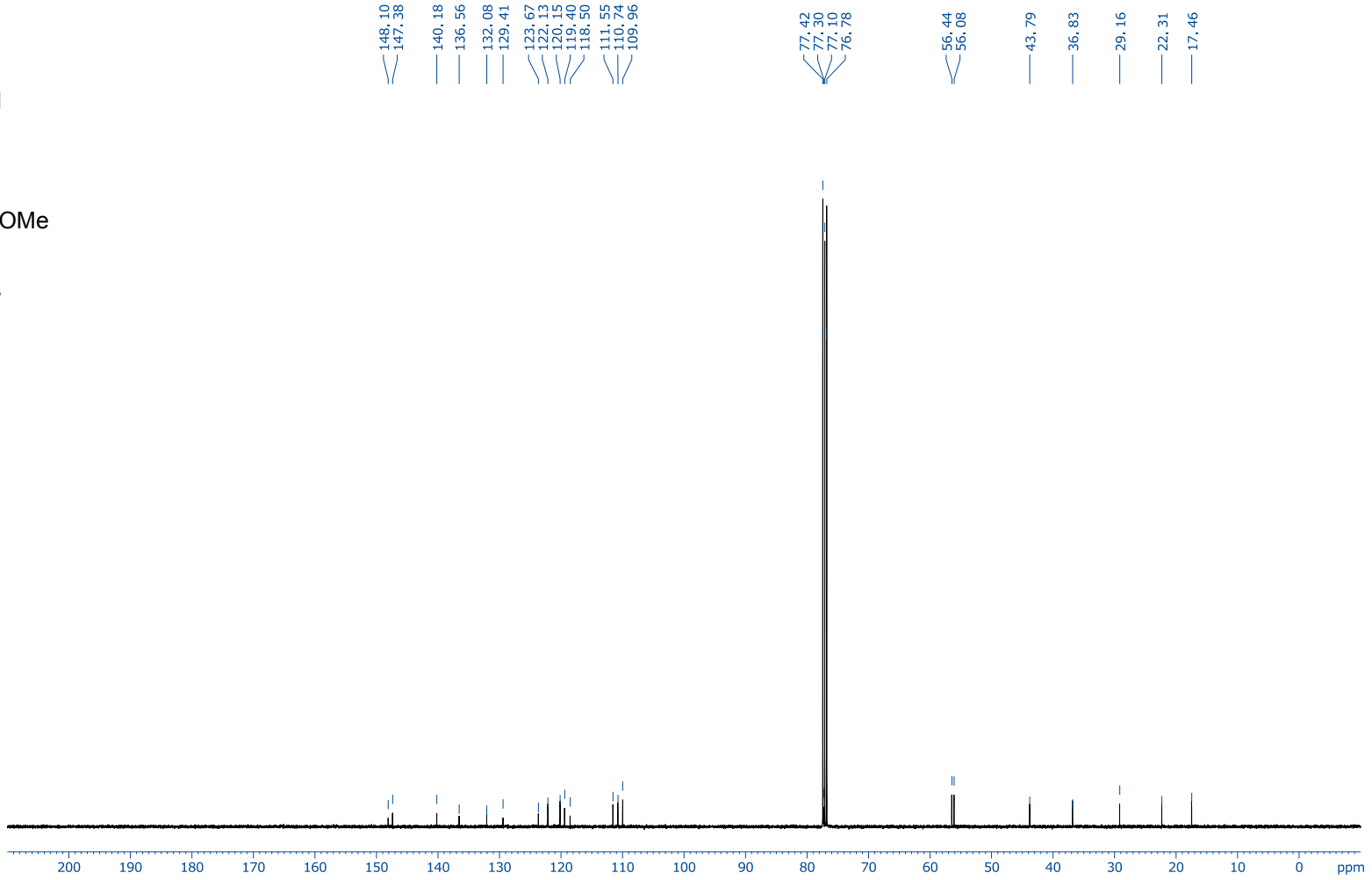


(5*R*,7*R*)-2,3-Dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*trans*-**14**)

^{13}C NMR (100.61 MHz, $CDCl_3$):

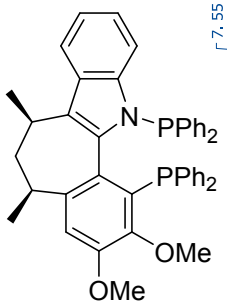


trans-**14**

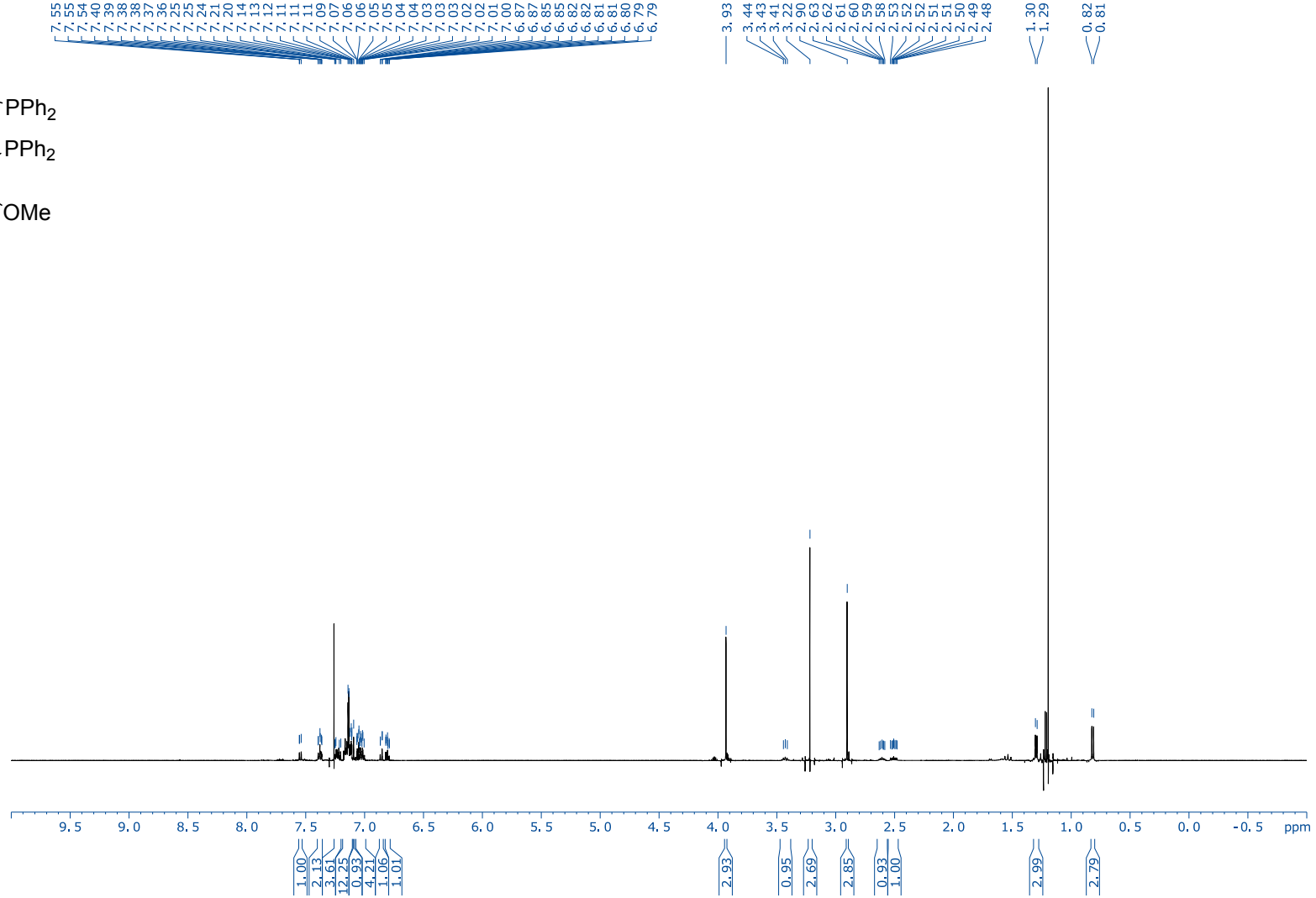


(*P*,5*S*,7*R*)-1,12-Bis(Diphenylphosphaneyl)-2,3-dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*cis*-**15**)

^{1}H NMR (500.10 MHz, $CDCl_3$):

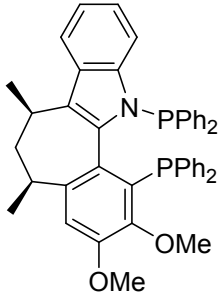


cis-**15**

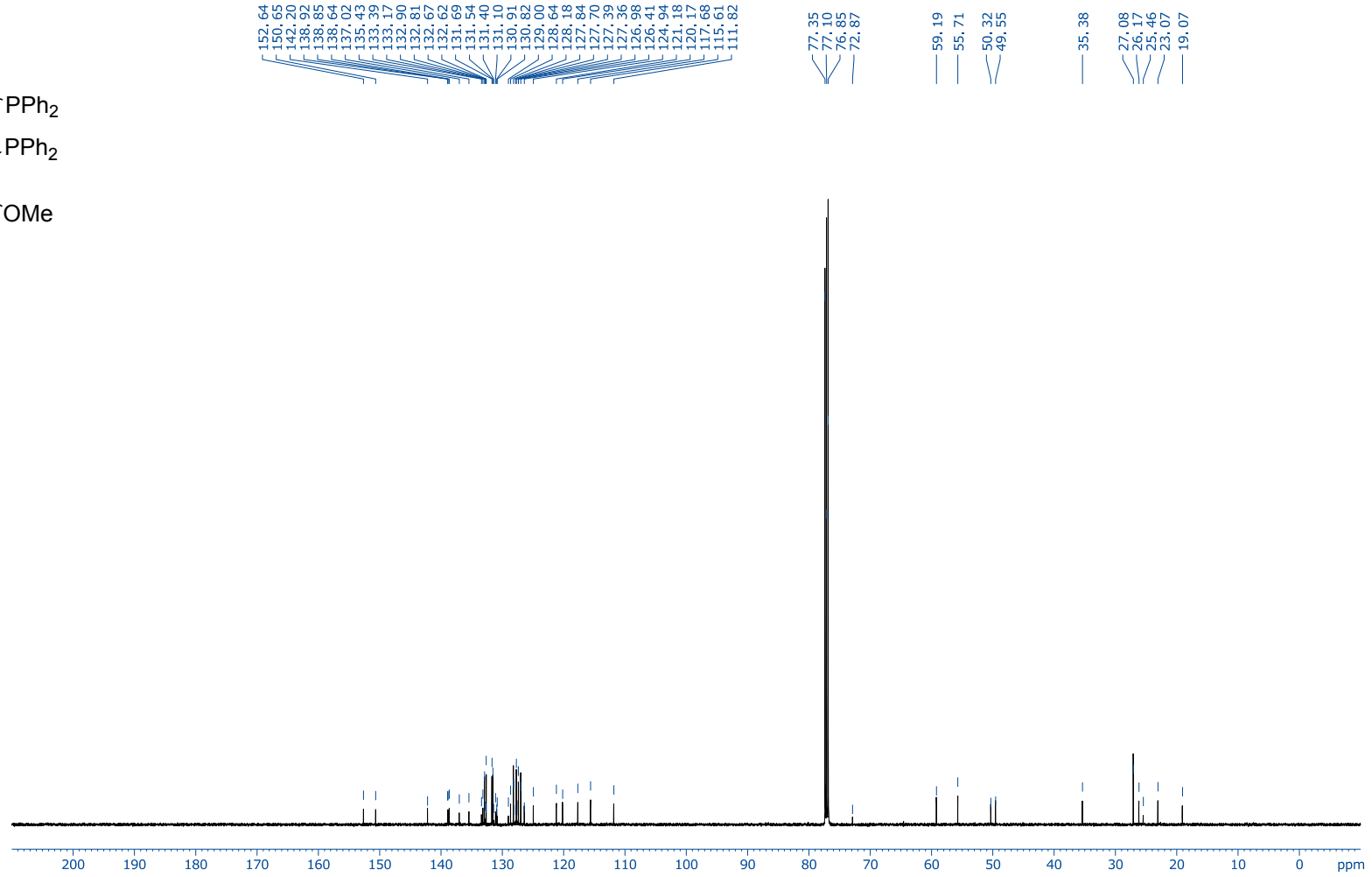


(*P*,5*S*,7*R*)-1,12-Bis(Diphenylphosphaneyl)-2,3-dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*cis*-**15**)

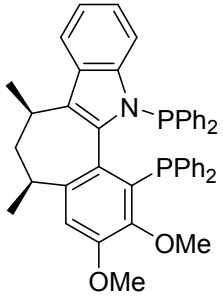
^{13}C NMR (125.75 MHz, {^{31}P}-decoupled, $CDCl_3$):



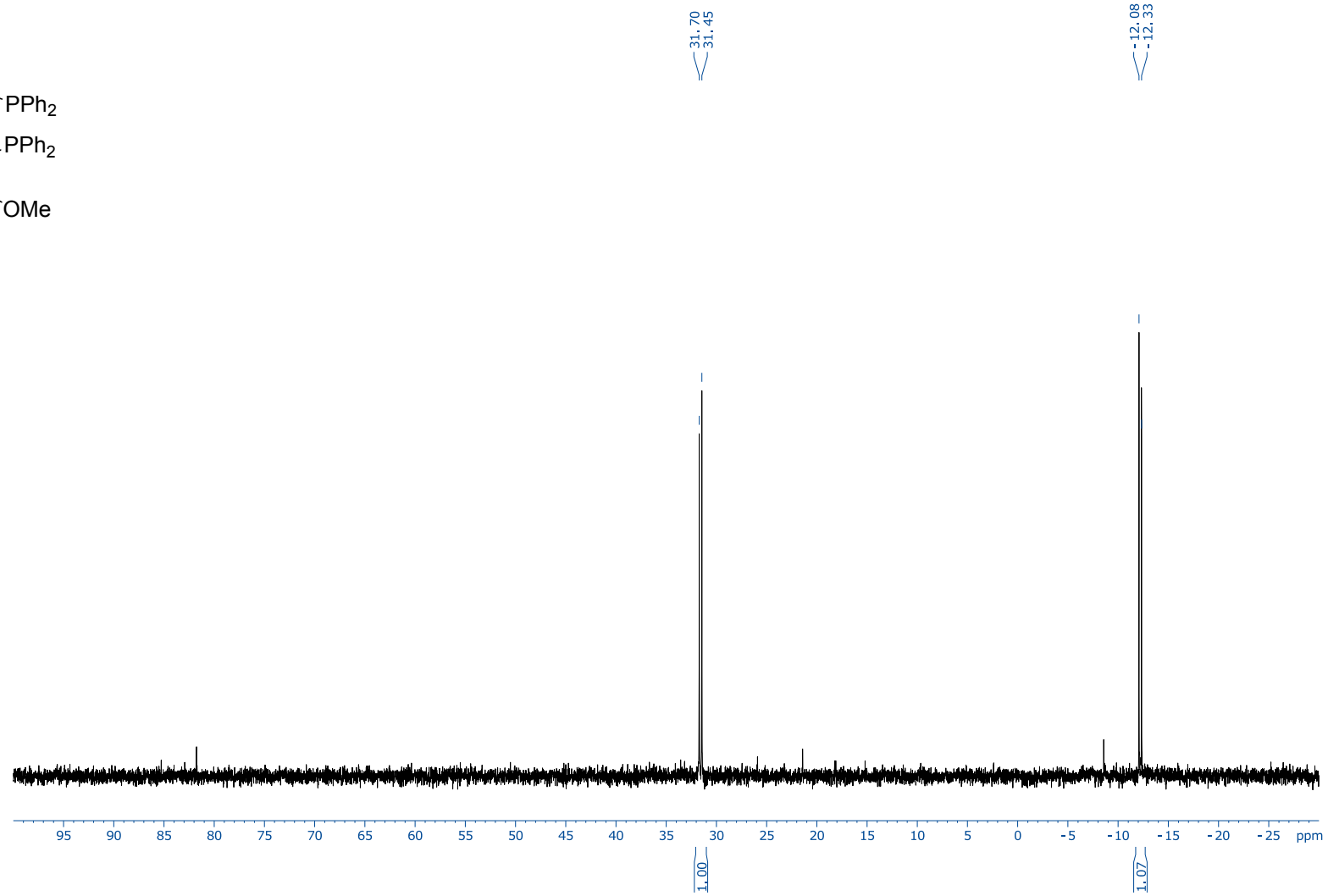
cis-**15**



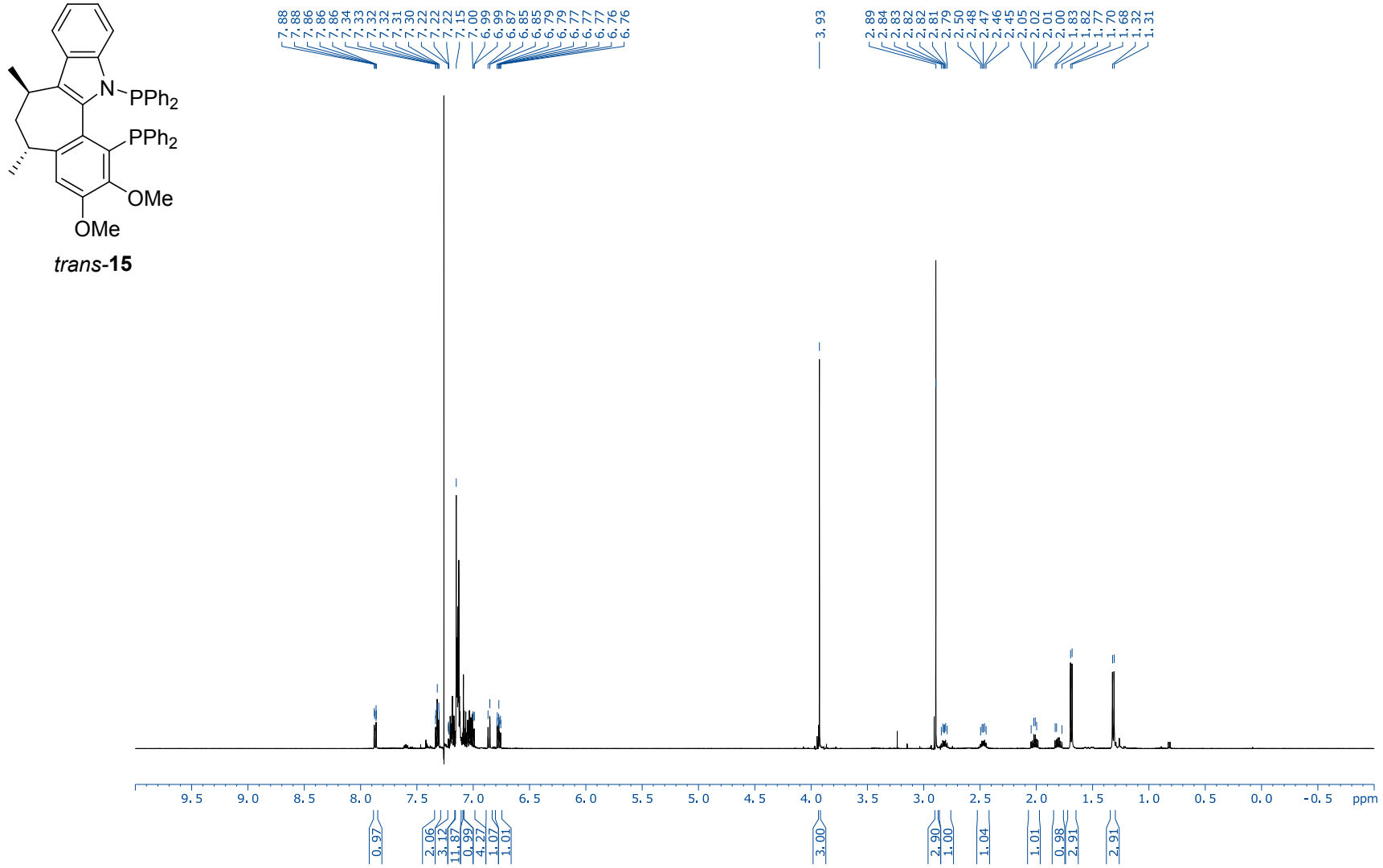
(*P*,5*S*,7*R*)-1,12-Bis(Diphenylphosphaneyl)-2,3-dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*cis*-**15**)
^{31}P NMR (202.44 MHz, $CDCl_3$):



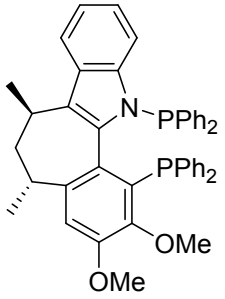
cis-**15**



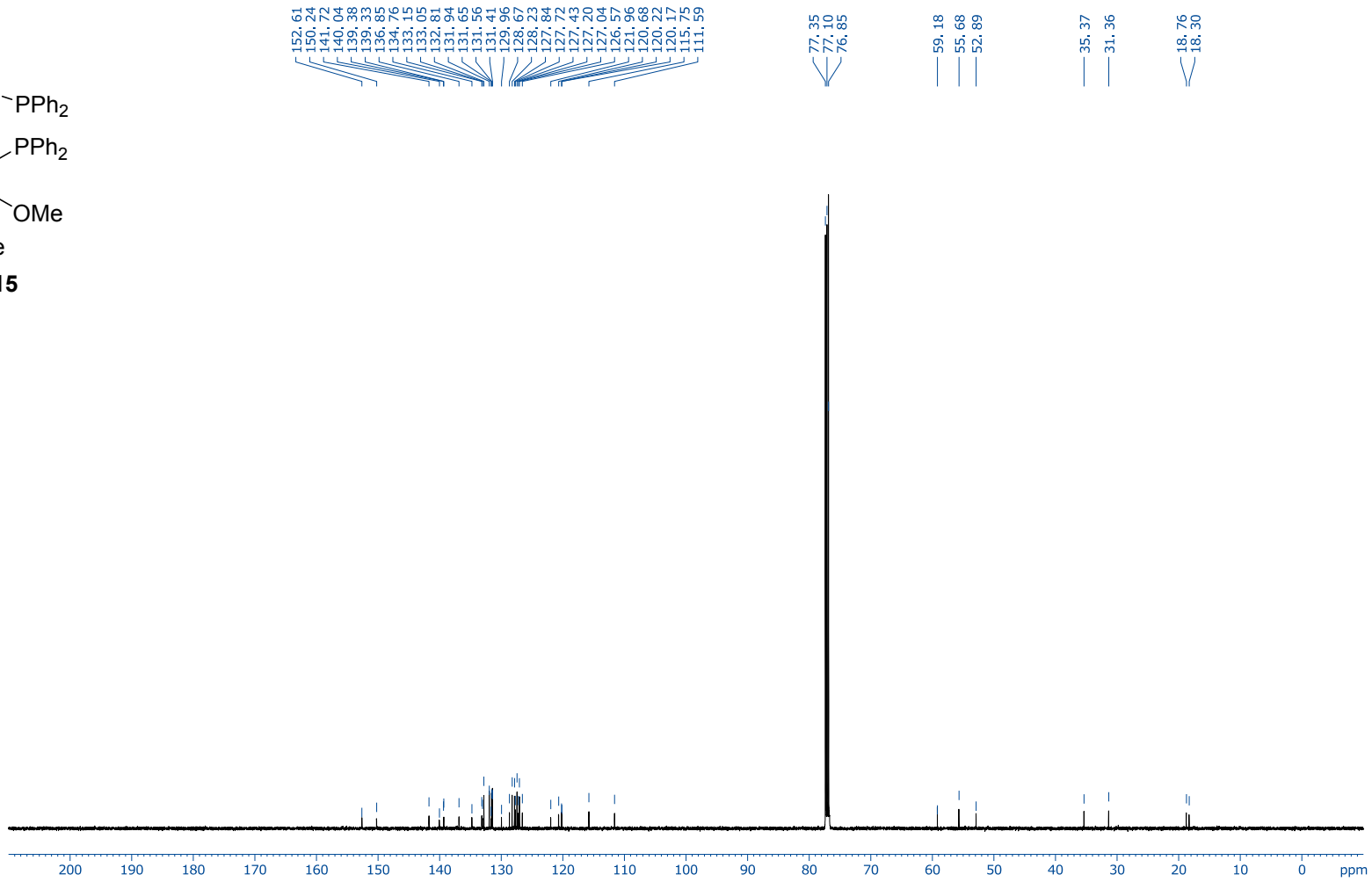
(*M*,5*R*,7*R*)-1,12-Bis(Diphenylphosphaneyl)-2,3-dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*trans*-**15**)
^{1}H NMR (500.10 MHz, $CDCl_3$):



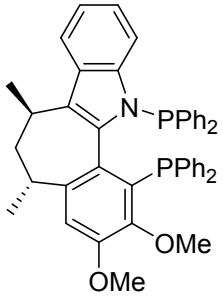
(*M*,5*R*,7*R*)-1,12-Bis(Diphenylphosphaneyl)-2,3-dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*trans*-**15**)
^{13}C NMR (125.75 MHz, {^{31}P}-decoupled, $CDCl_3$):



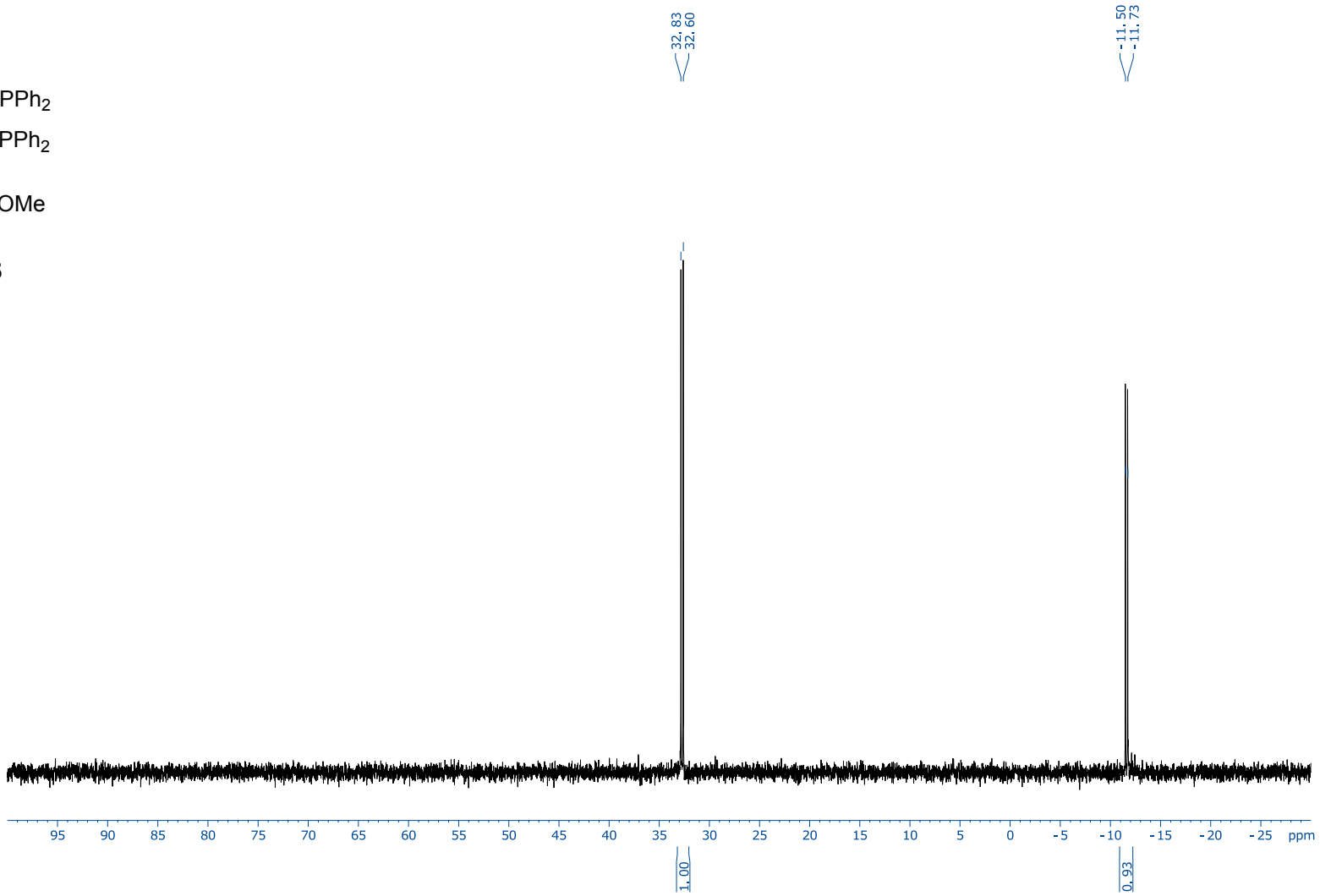
trans-**15**



(*M*,5*R*,7*R*)-1,12-Bis(Diphenylphosphaneyl)-2,3-dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*trans*-**15**)
^{31}P NMR (202.44 MHz, $CDCl_3$):

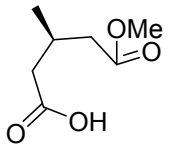


trans-**15**

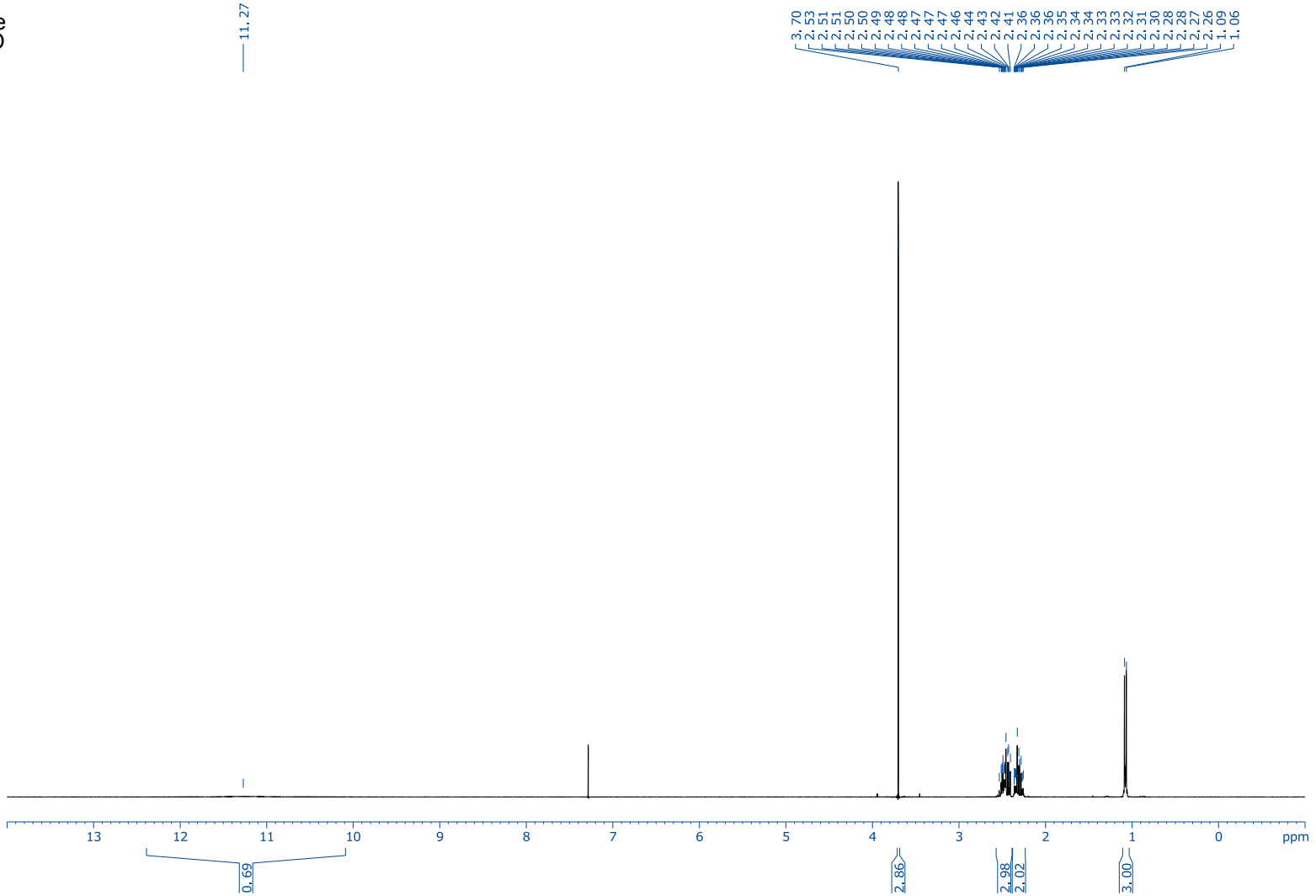


(*R*)-5-Methoxy-3-methyl-5-oxopentanoic acid (16a)

^{1}H NMR (300.13 MHz, $CDCl_3$):

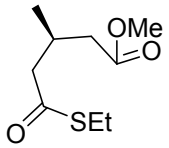


16a

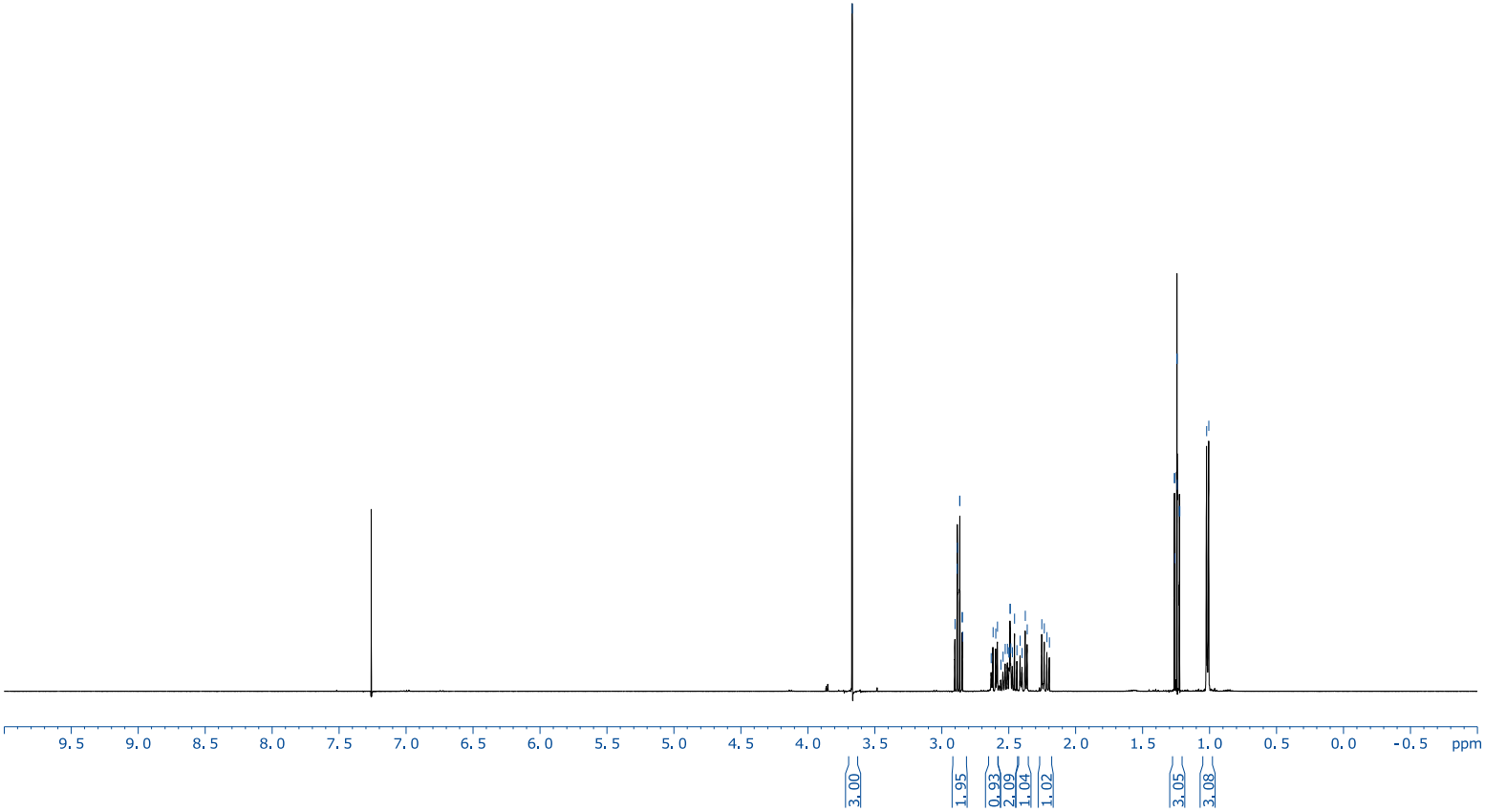


Methyl (*S*)-5-(Ethylthio)-3-methyl-5-oxopentanoate (16c)

^{1}H NMR (400.13 MHz, $CDCl_3$):

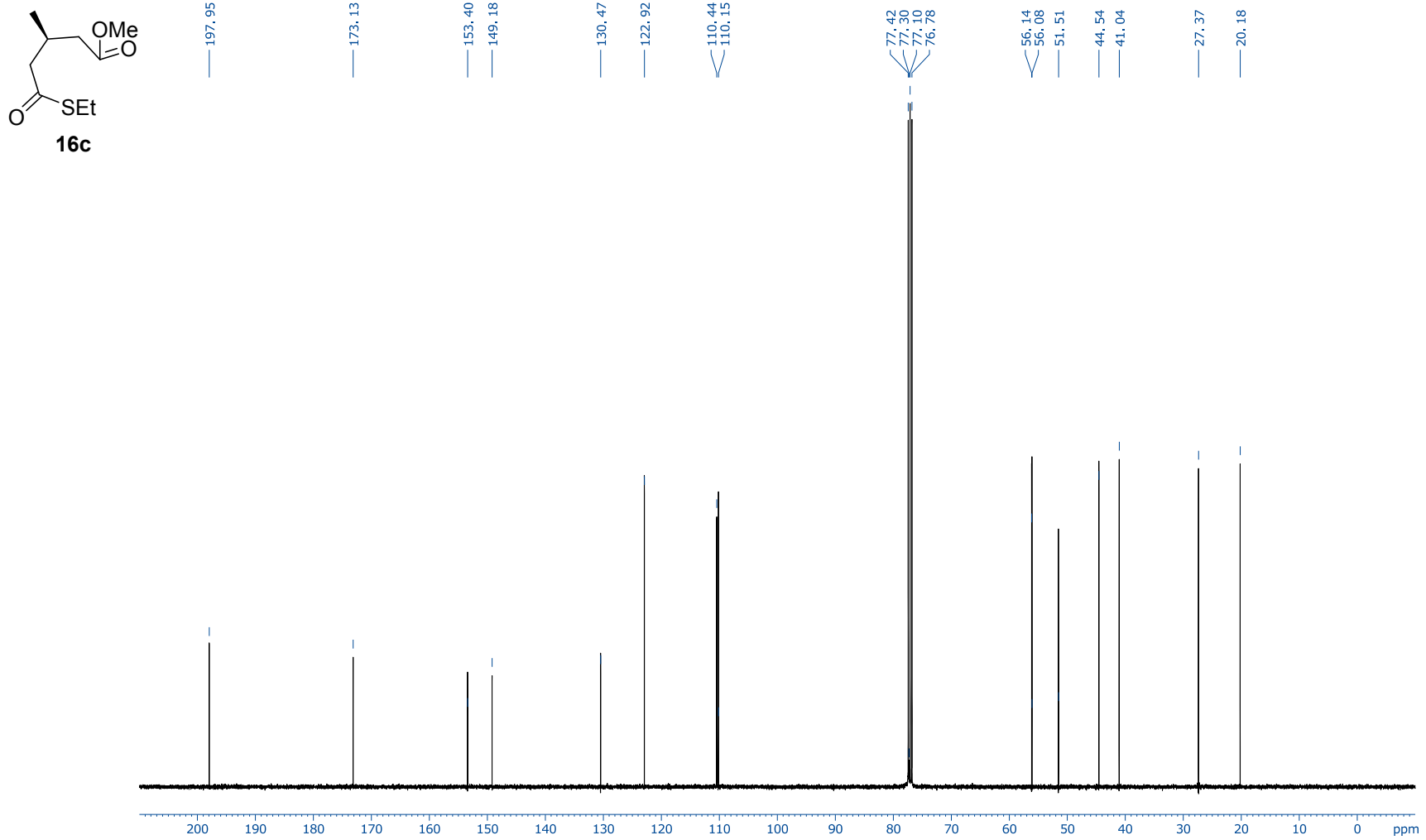


16c



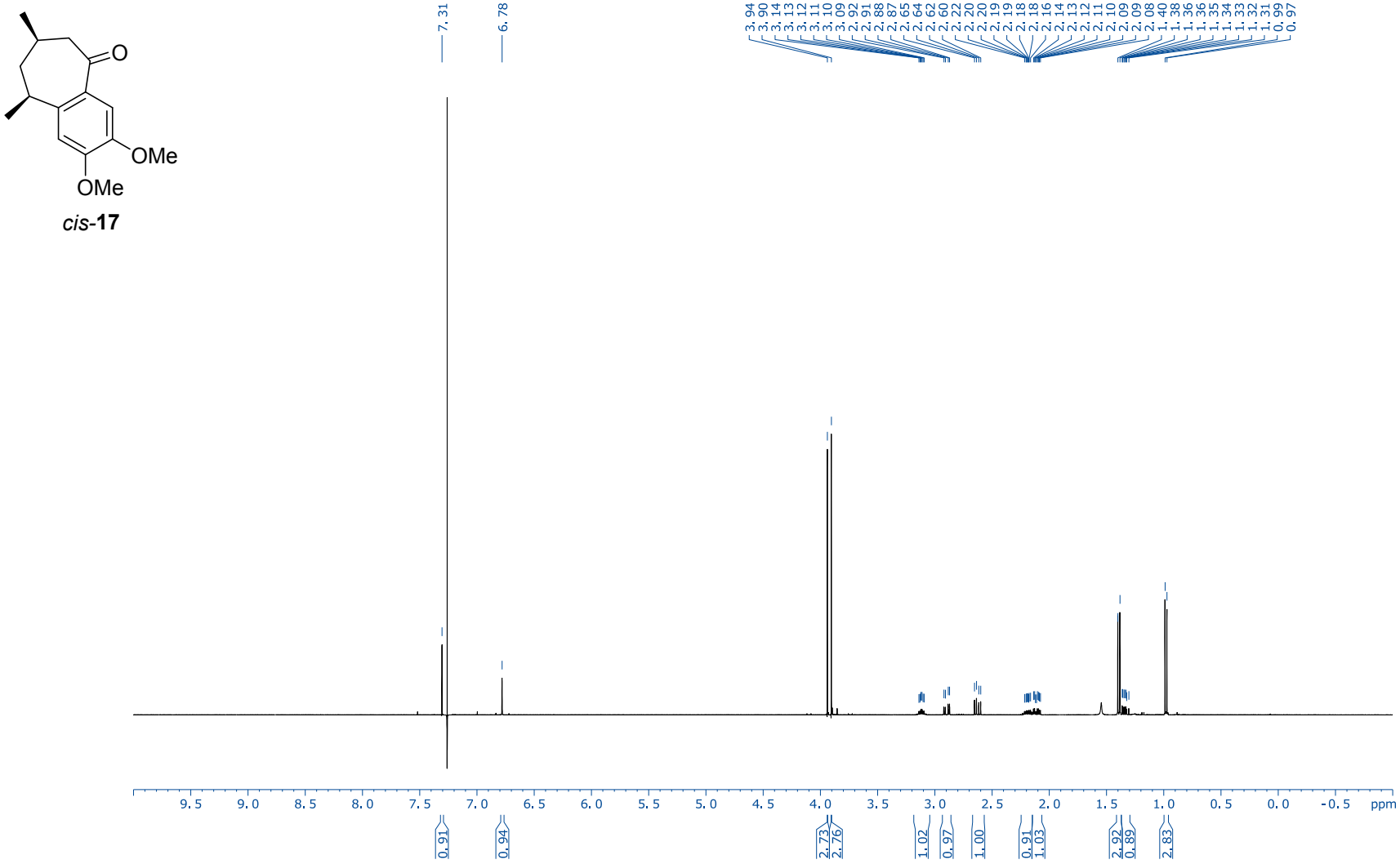
Methyl (*S*)-5-(Ethylthio)-3-methyl-5-oxopentanoate (16c)

^{13}C NMR (100.61 MHz, $CDCl_3$):



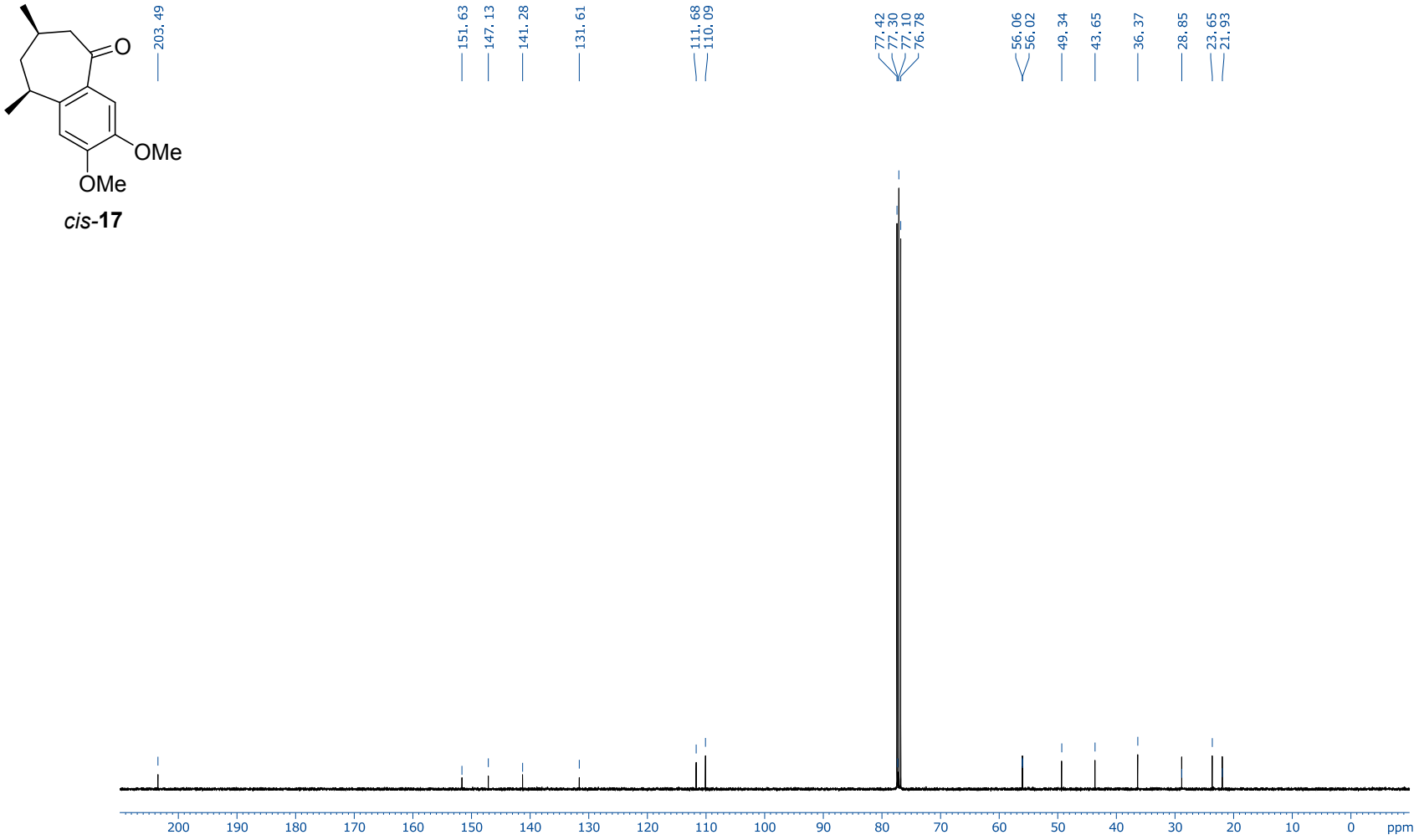
(7*R*,9*R*)-2,3-Dimethoxy-7,9-dimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (*cis*-**17**)

^{1}H NMR (400.13 MHz, $CDCl_3$):



(7*R*,9*R*)-2,3-Dimethoxy-7,9-dimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (*cis*-**17**)

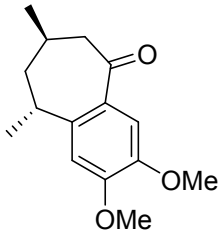
^{13}C NMR (100.61 MHz, $CDCl_3$):



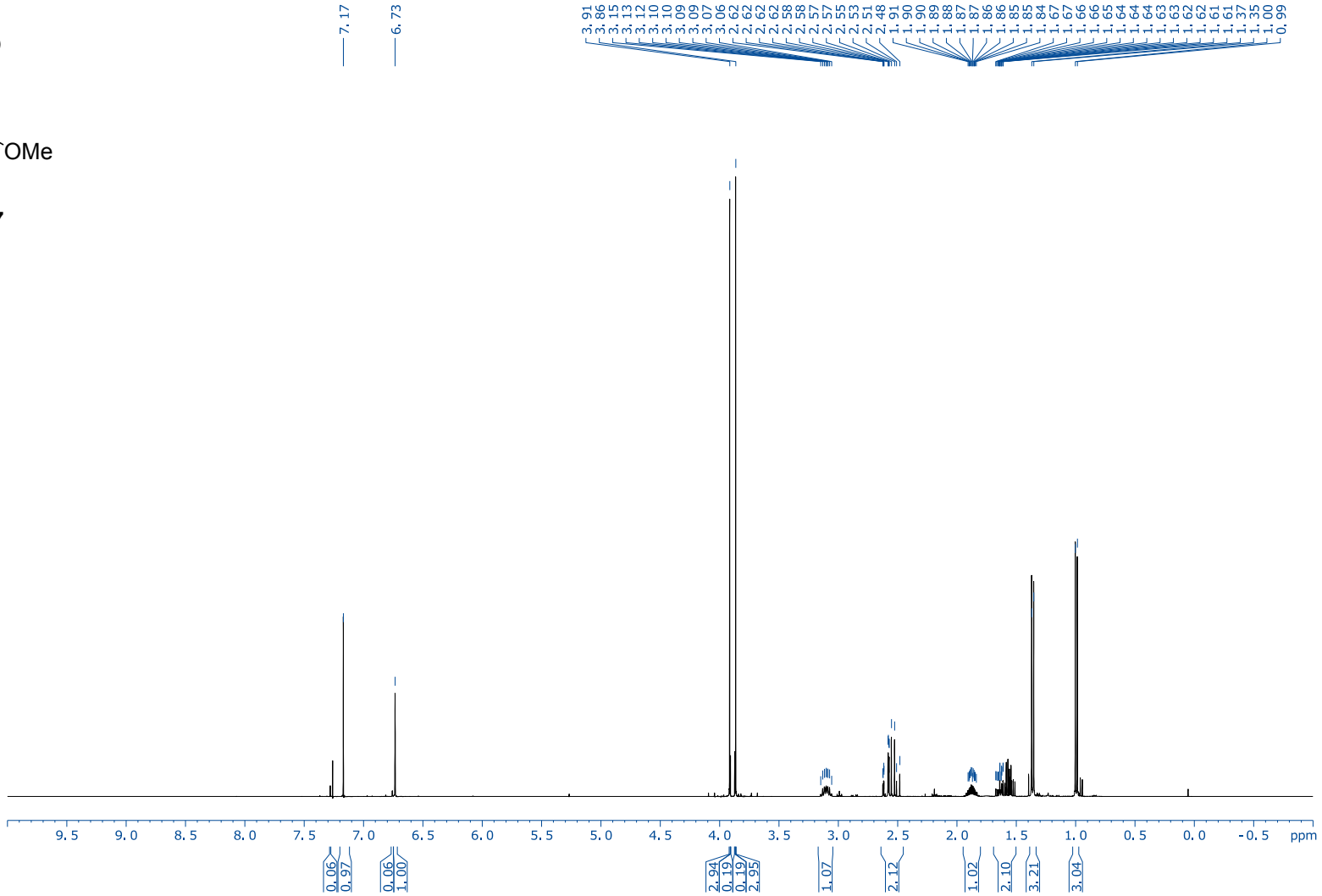
cis-**17**

(7*R*,9*R*)-2,3-Dimethoxy-7,9-dimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (*trans*-**17**)

^{1}H NMR (400.13 MHz, $CDCl_3$):

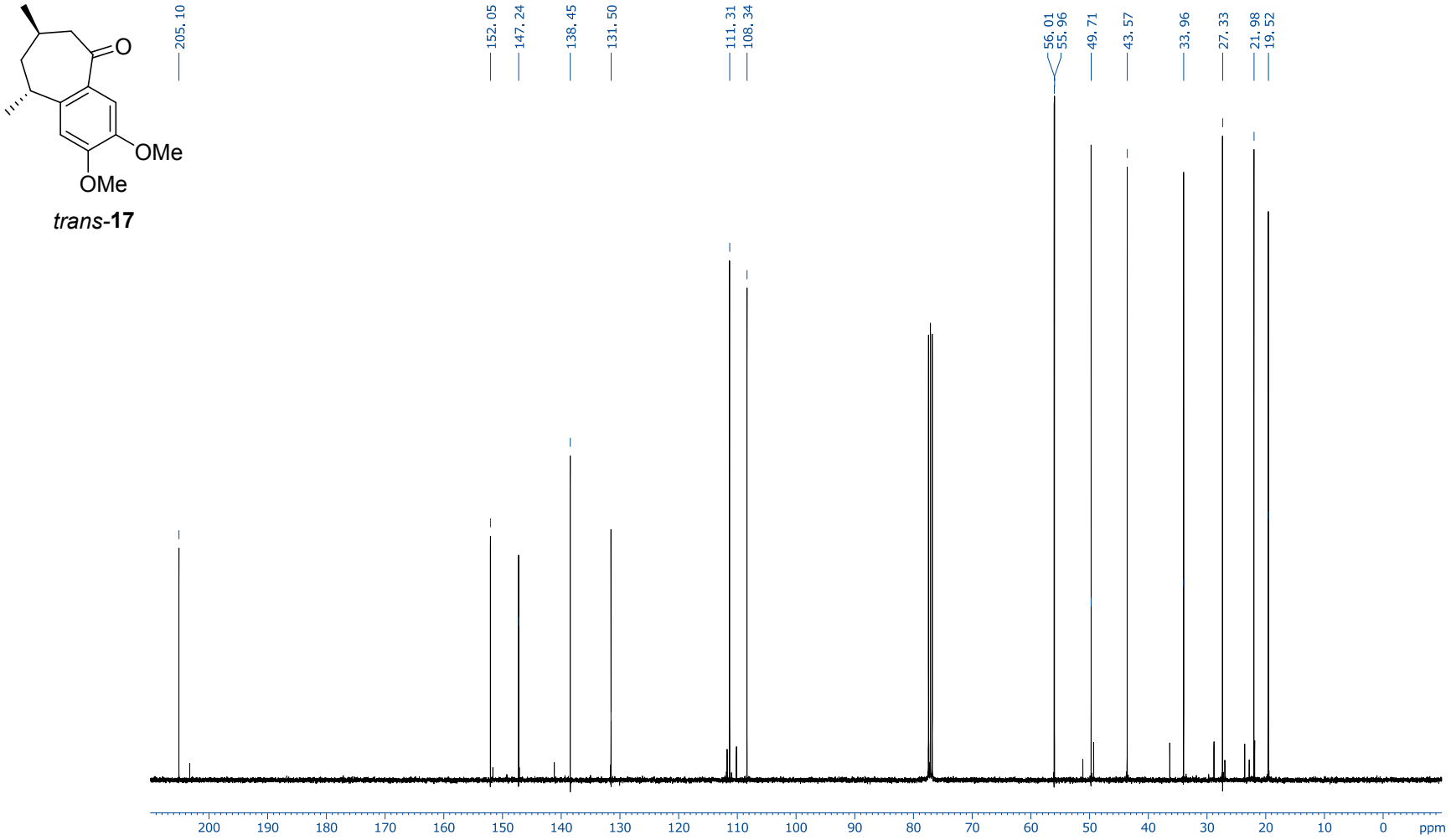


trans-**17**



(7*R*,9*R*)-2,3-Dimethoxy-7,9-dimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (*trans*-**17**)

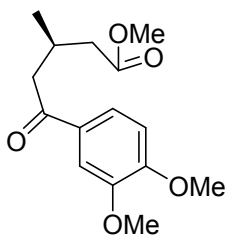
^{13}C NMR (100.61 MHz, $CDCl_3$):



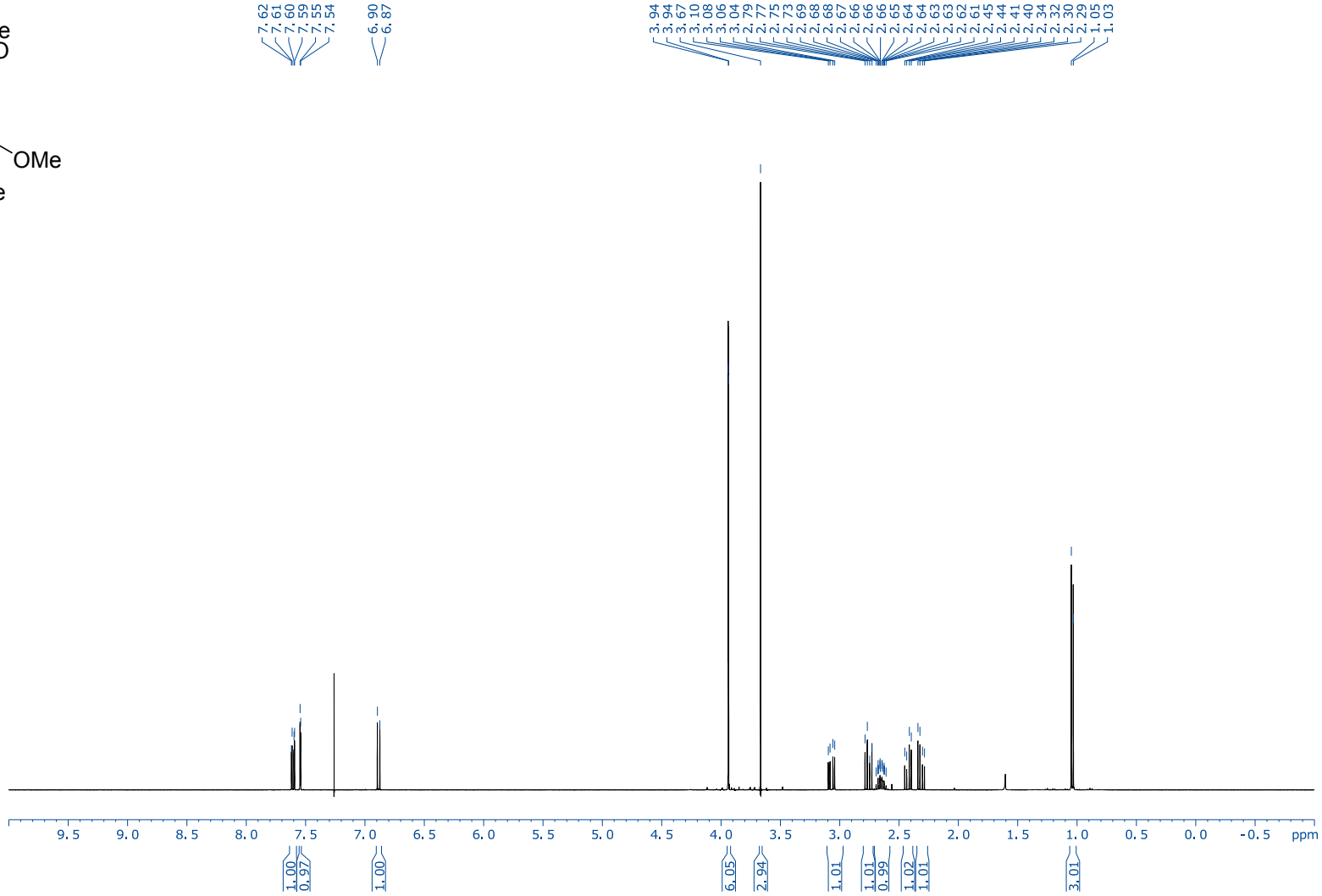
trans-**17**

Methyl (*R*)-5-(3,4-Dimethoxyphenyl)-3-methyl-5-oxopentanoate (18)

^{1}H NMR (400.13 MHz, $CDCl_3$):

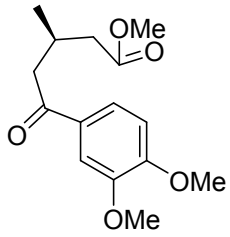


18

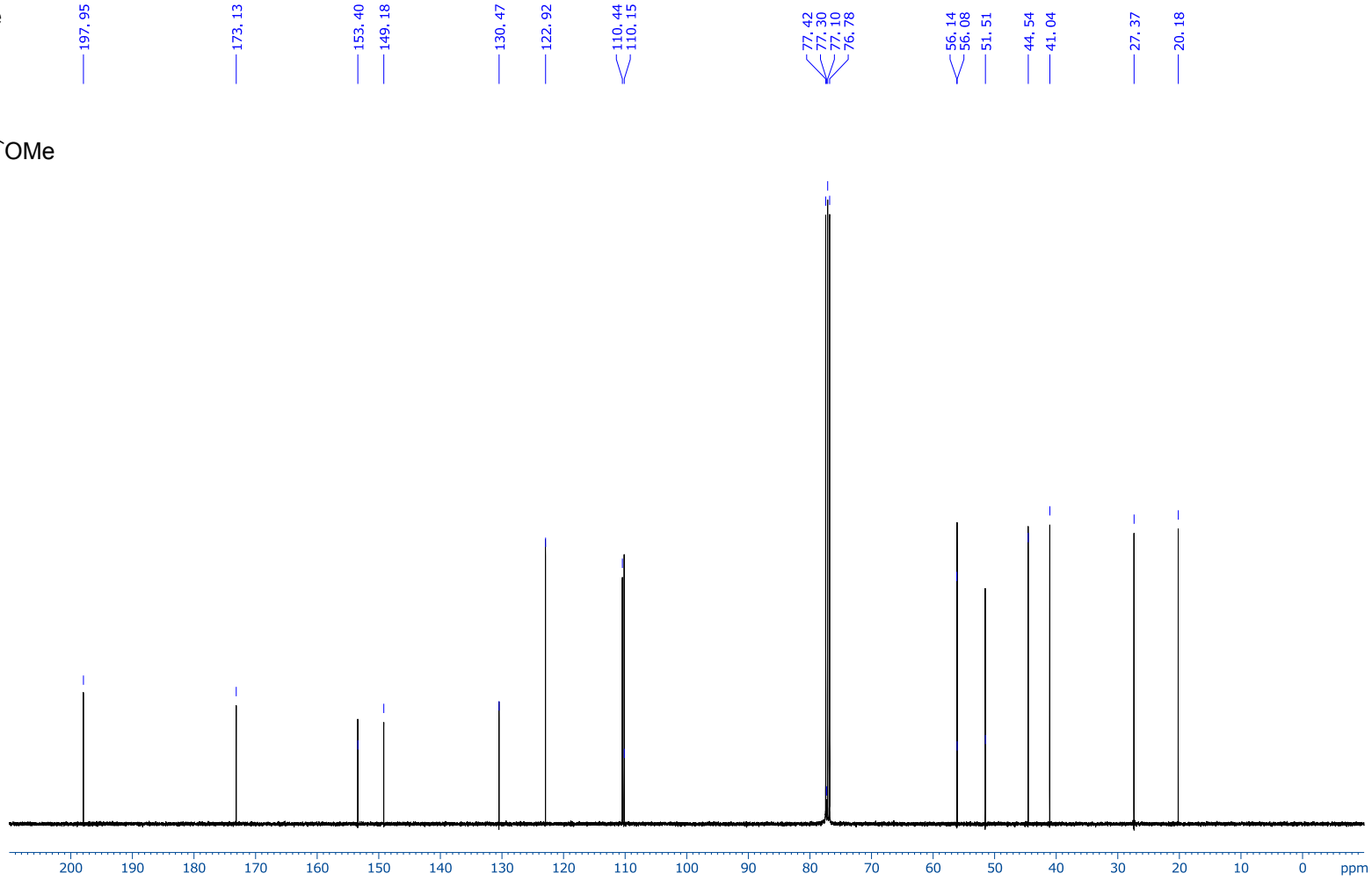


Methyl (*R*)-5-(3,4-Dimethoxyphenyl)-3-methyl-5-oxopentanoate (18)

^{13}C NMR (100.61 MHz, $CDCl_3$):

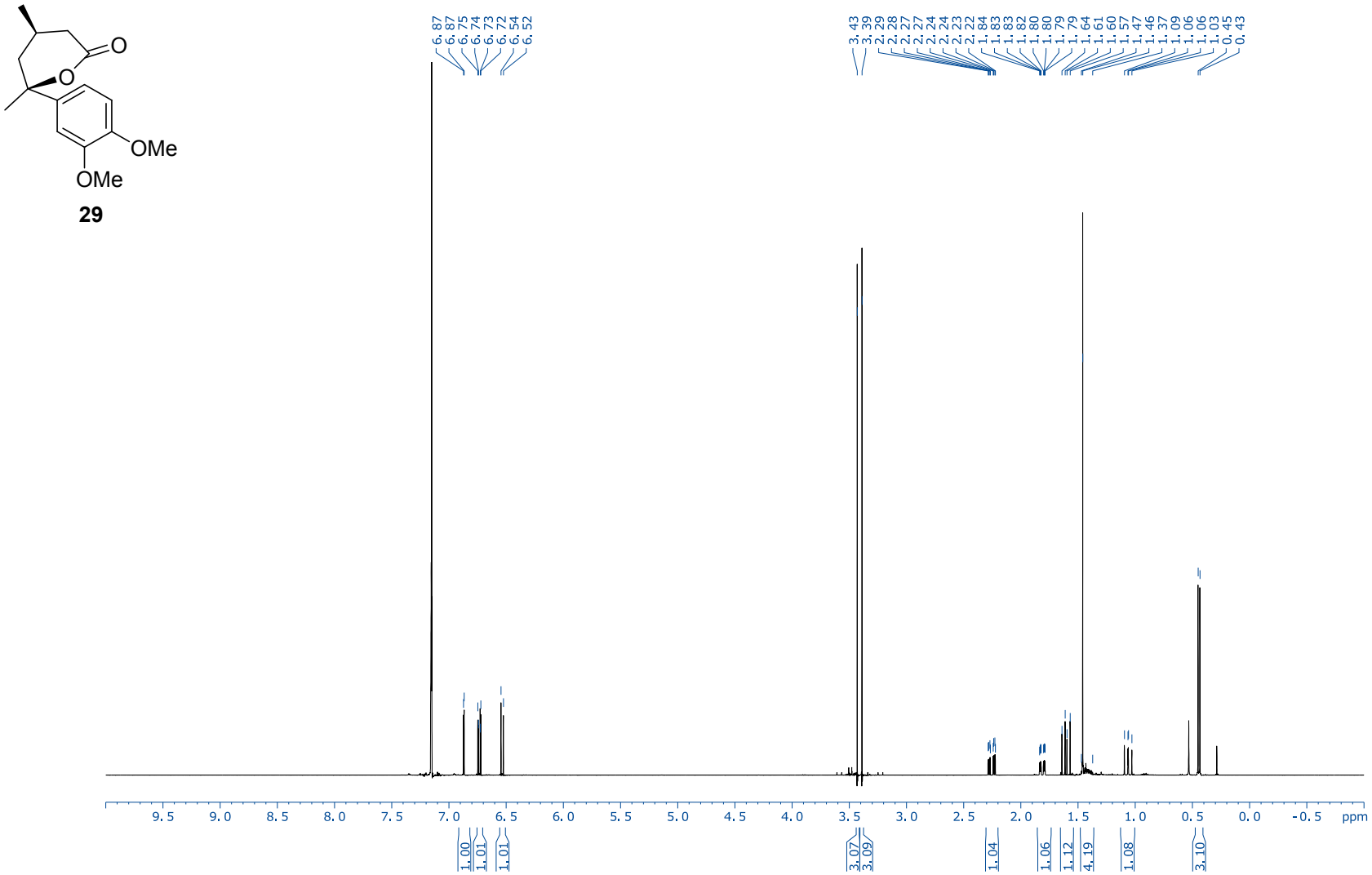


18



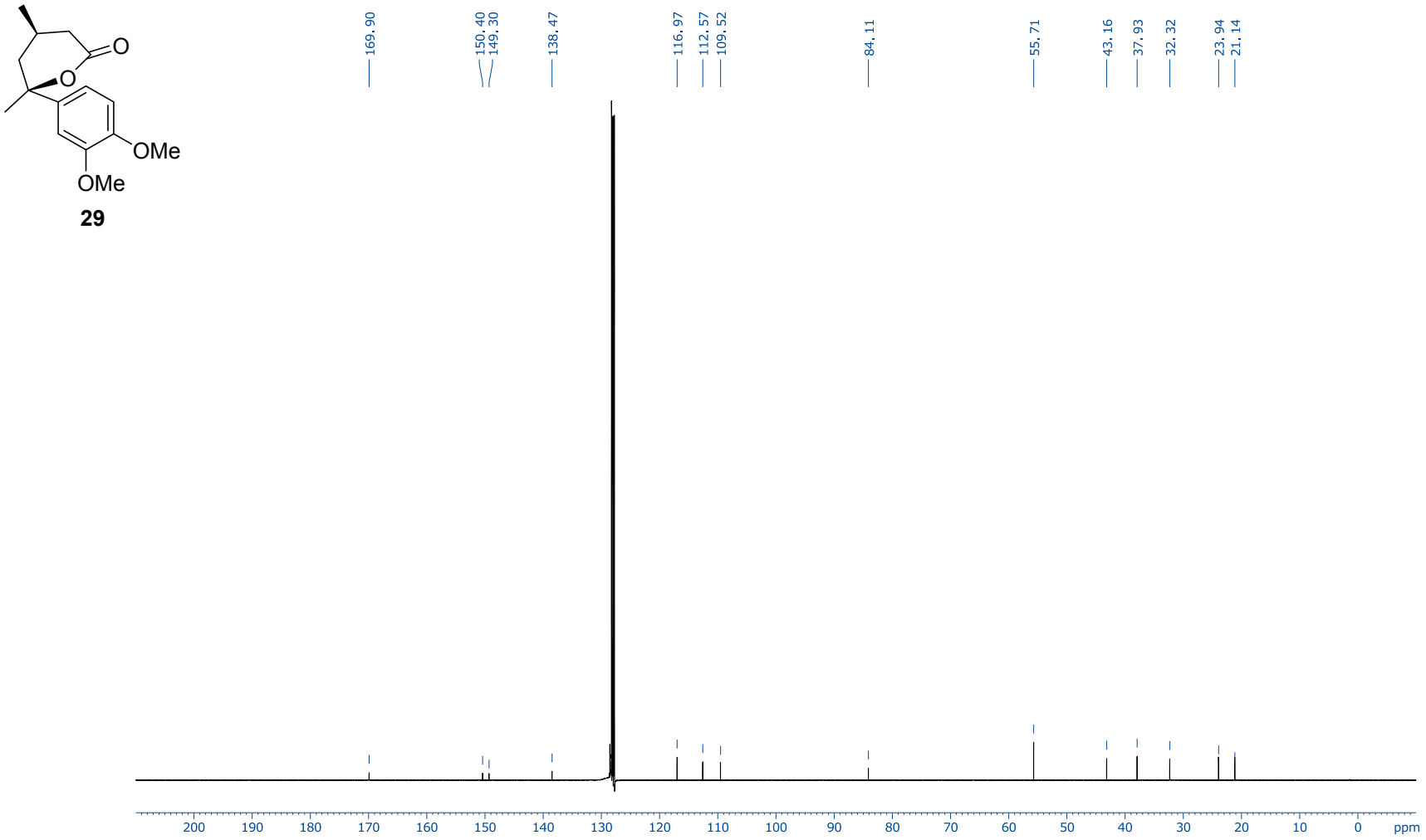
(4*R*,6*S*)-6-(3,4-Dimethoxyphenyl)-4,6-dimethyltetrahydro-2H-pyran-2-one (29)

^{1}H NMR (400.13 MHz, C_6D_6):



(4*R*,6*S*)-6-(3,4-Dimethoxyphenyl)-4,6-dimethyltetrahydro-2H-pyran-2-one (29)

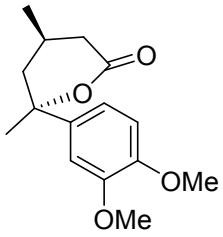
^{13}C NMR (100.61 MHz, C_6D_6):



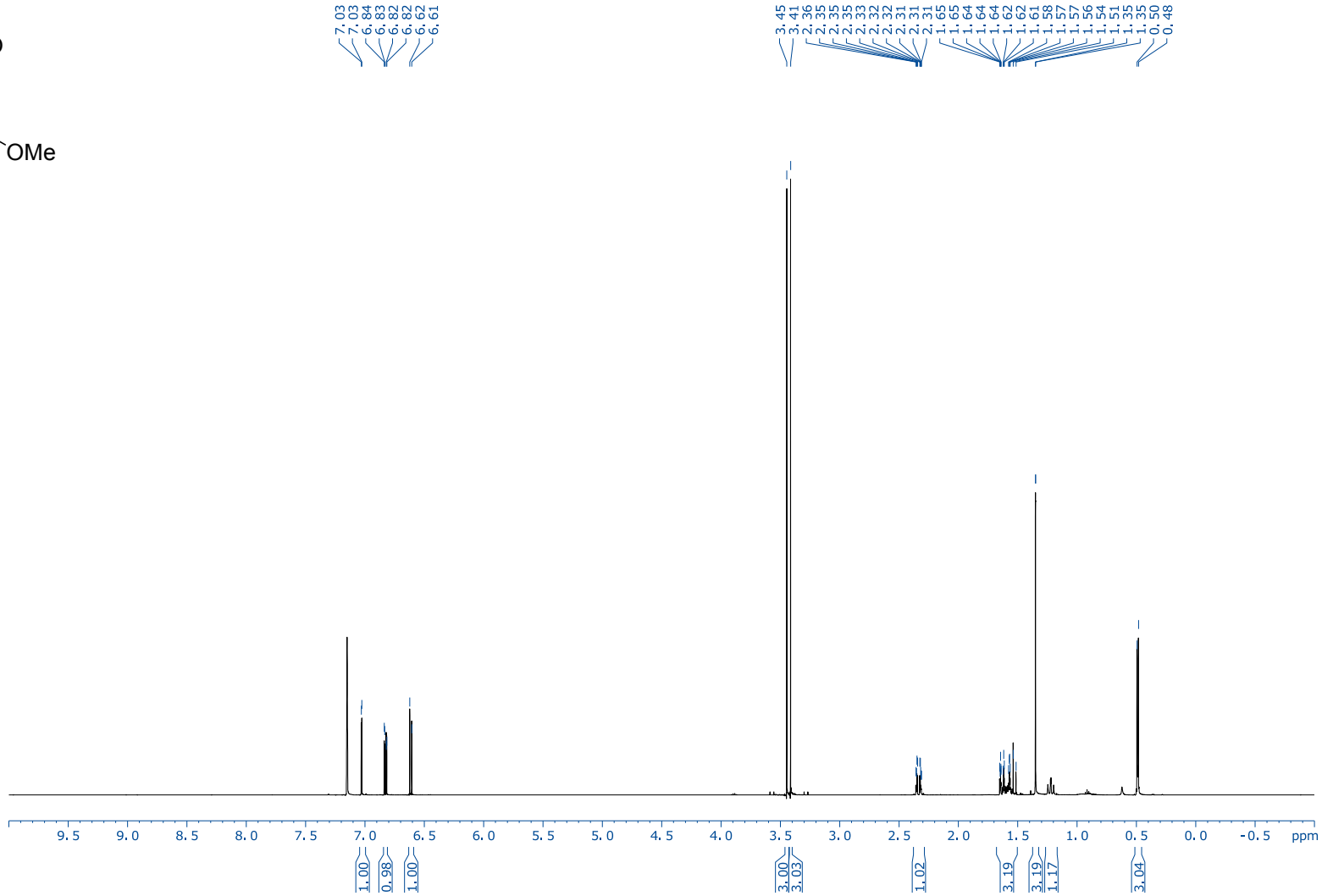
29

(4*R*,6*R*)-6-(3,4-Dimethoxyphenyl)-4,6-dimethyltetrahydro-2H-pyran-2-one (*dia*-**29**)

^{1}H NMR (500.22 MHz, C_6D_6):

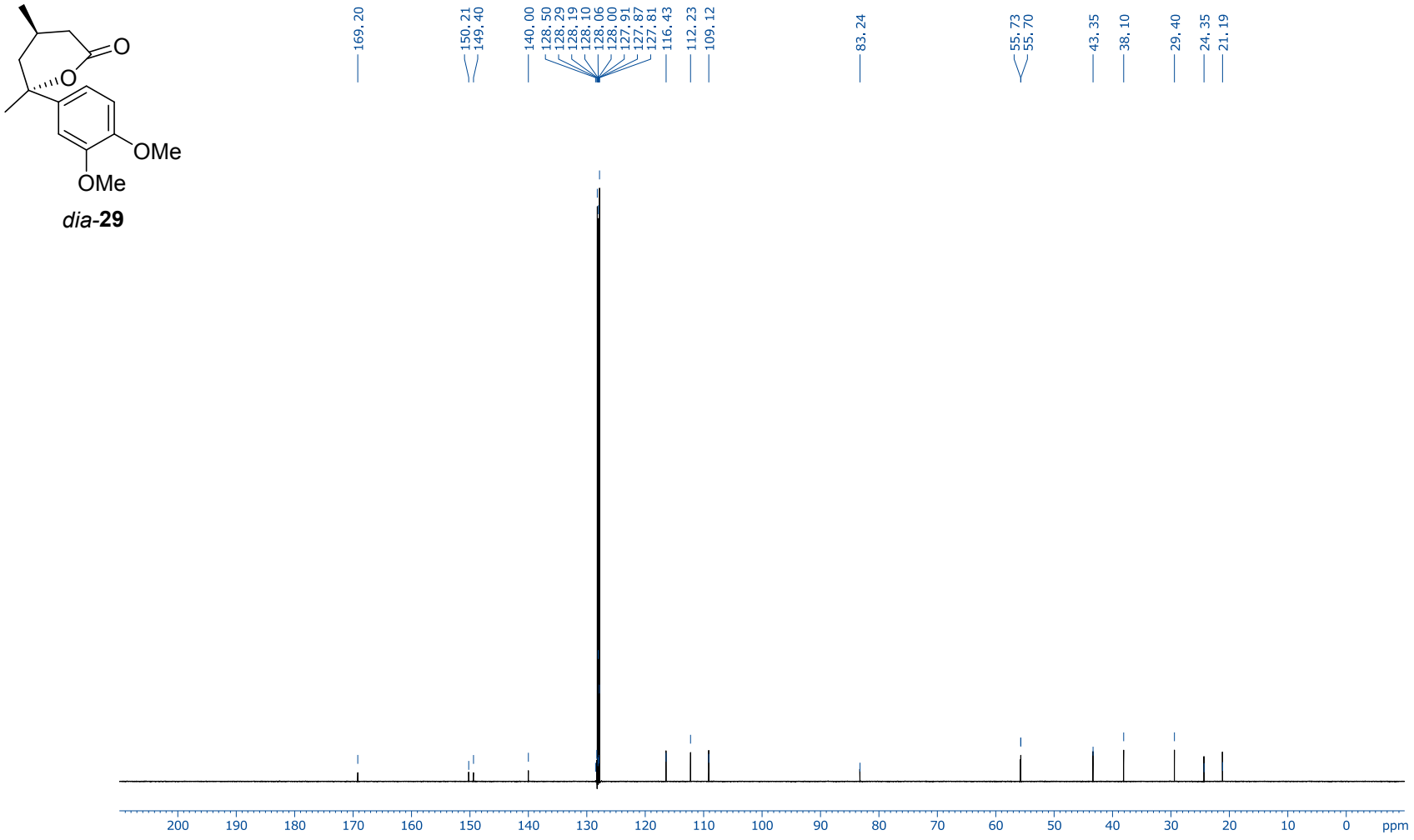


dia-**29**



(4*R*,6*R*)-6-(3,4-Dimethoxyphenyl)-4,6-dimethyltetrahydro-2H-pyran-2-one (*dia*-**29**)

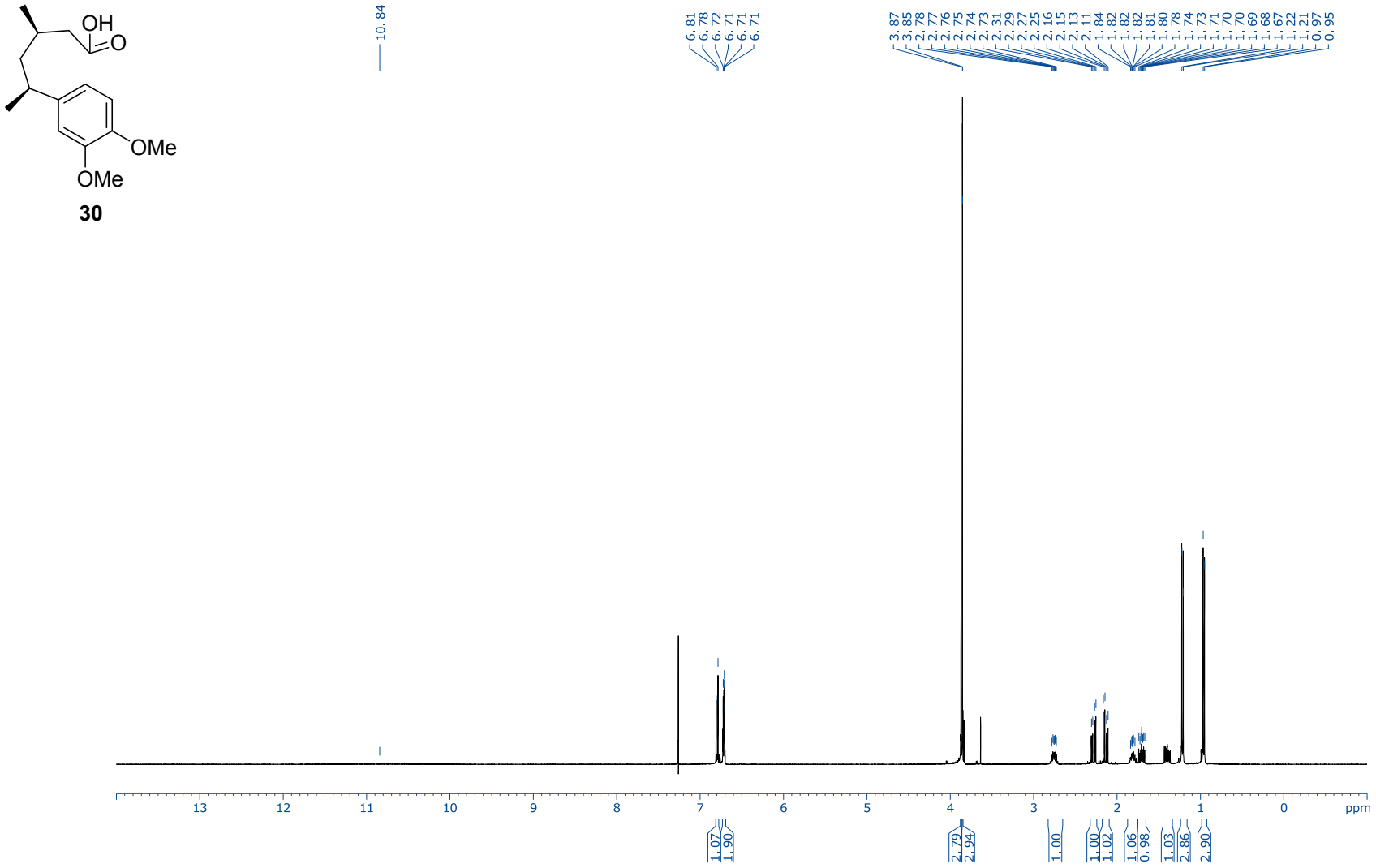
^{13}C NMR (125.75 MHz, C_6D_6):



dia-**29**

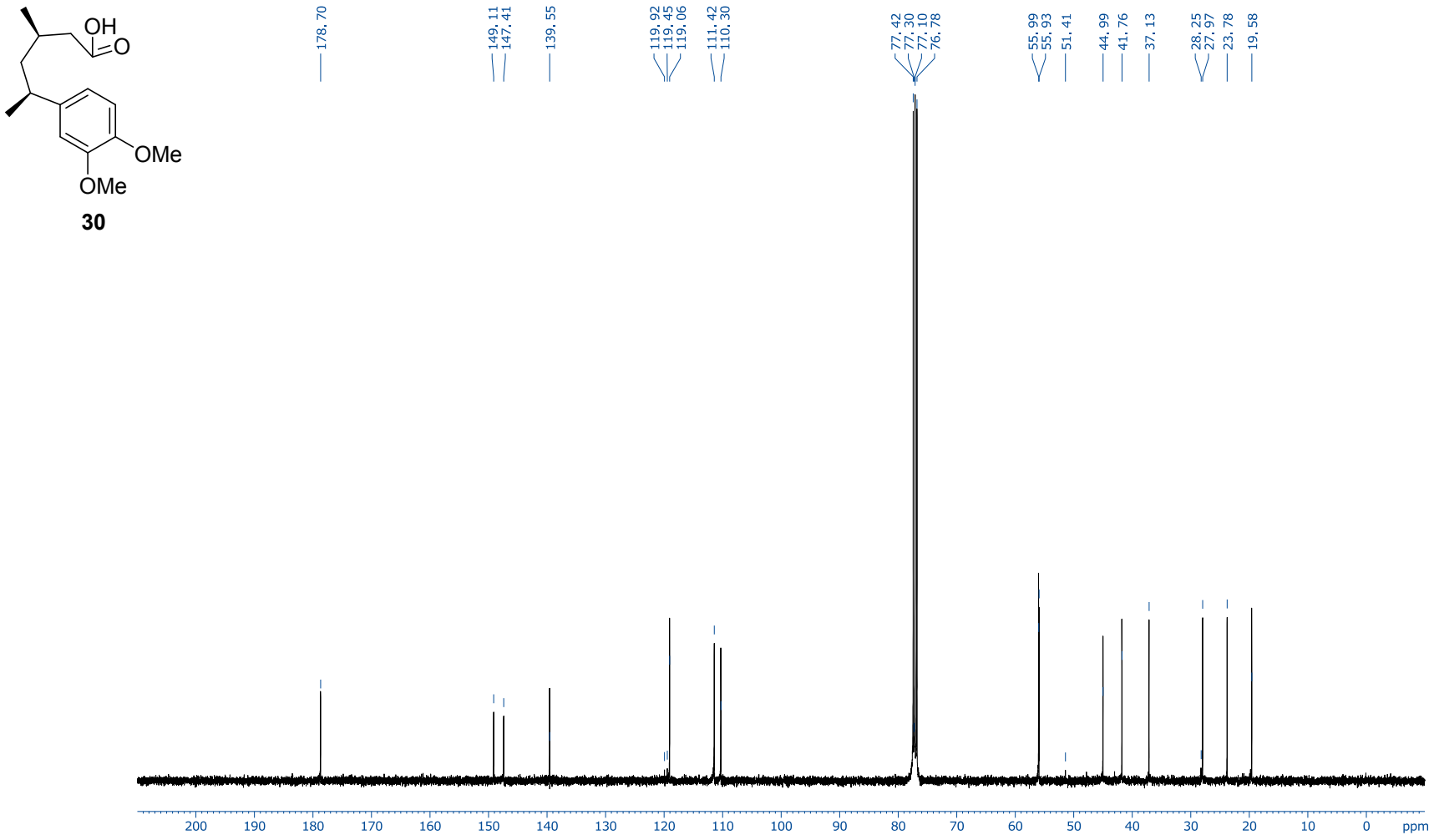
(3*R*,5*S*)-5-(3,4-Dimethoxyphenyl)-3-methylhexanoic acid (30)

^{1}H NMR (400.13 MHz, $CDCl_3$):



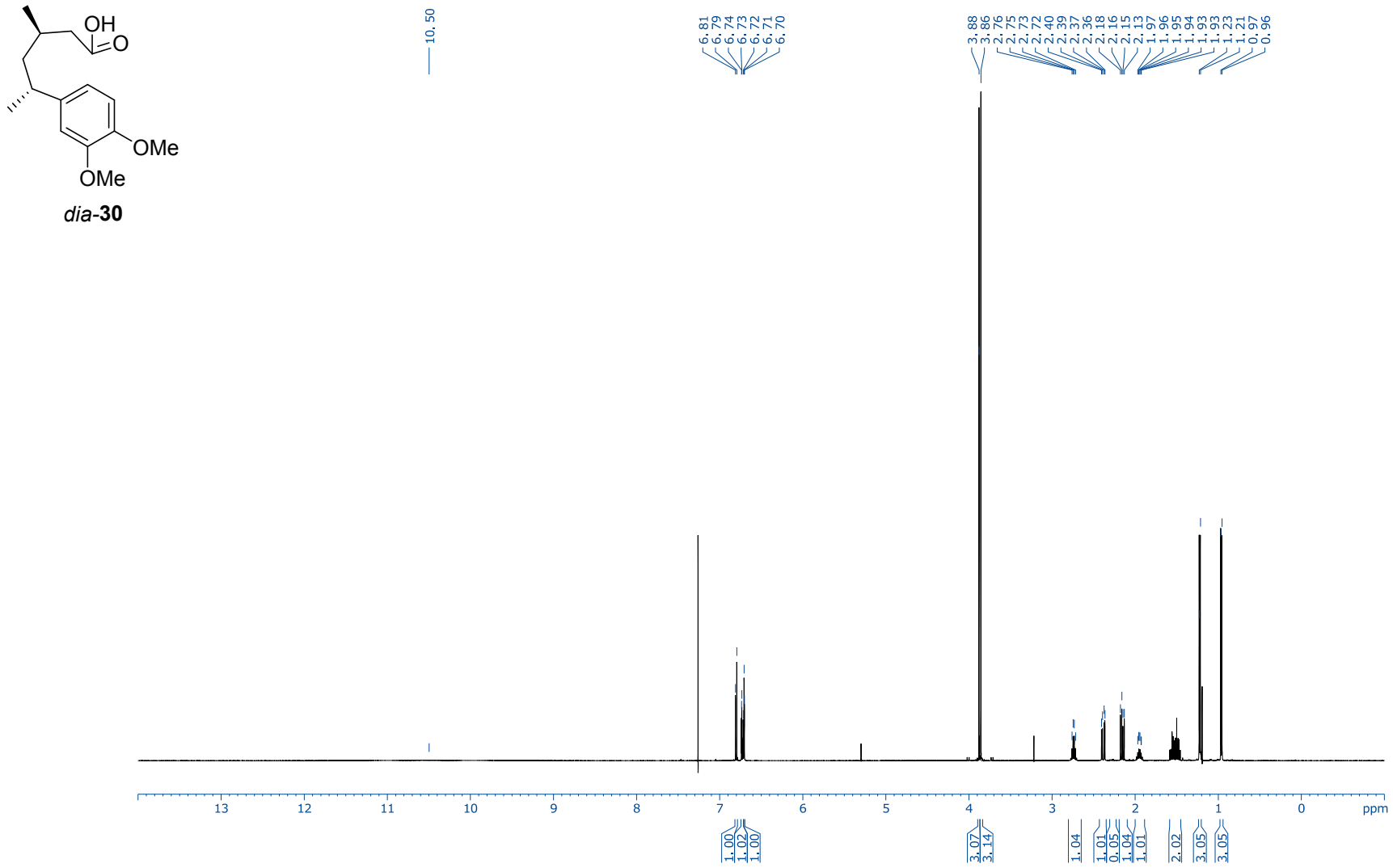
(3*R*,5*S*)-5-(3,4-Dimethoxyphenyl)-3-methylhexanoic acid (30)

^{13}C NMR (100.61 MHz, $CDCl_3$):



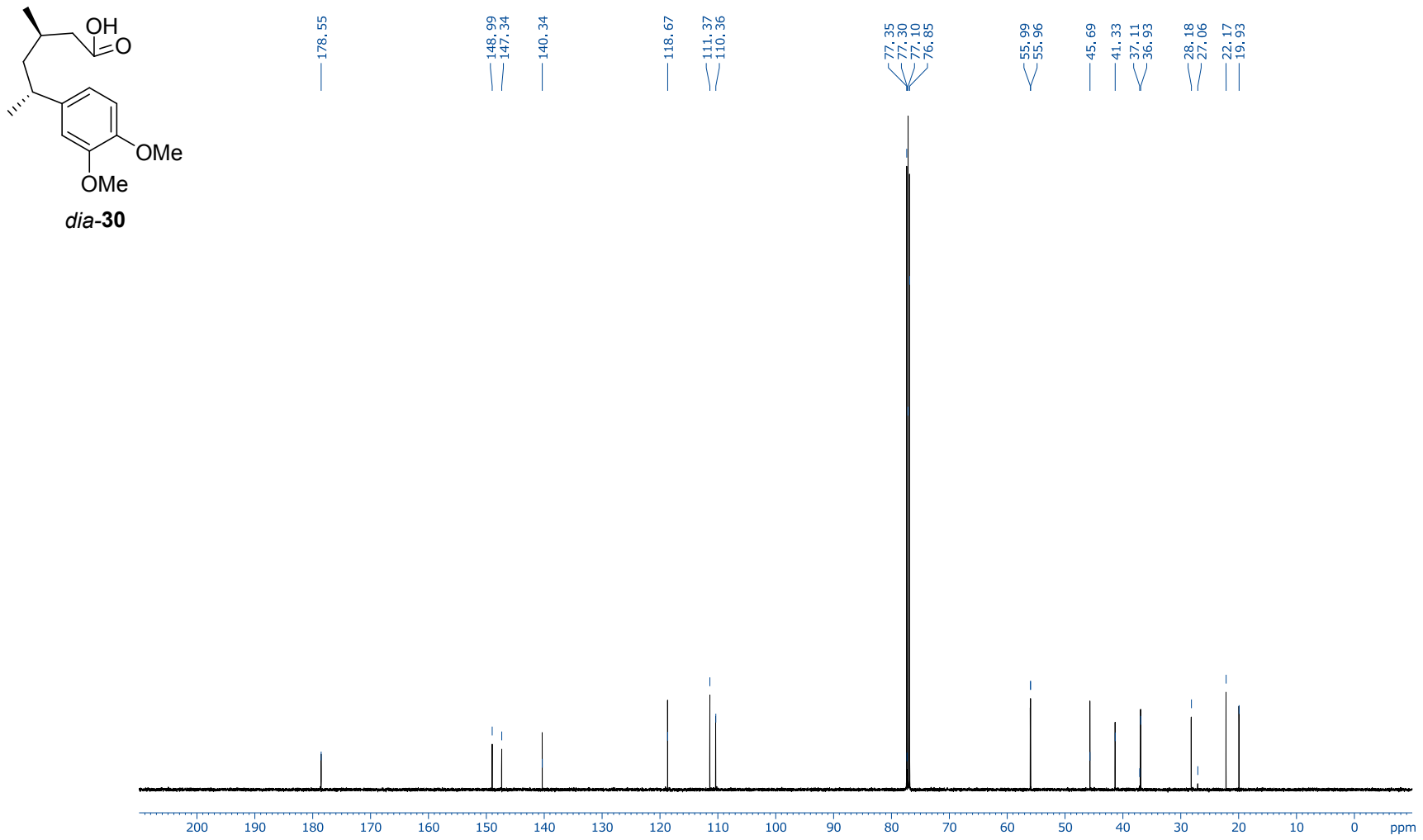
(3*R*,5*R*)-5-(3,4-Dimethoxyphenyl)-3-methylhexanoic acid (*dia*-**30**)

^{1}H NMR (400.13 MHz, $CDCl_3$):



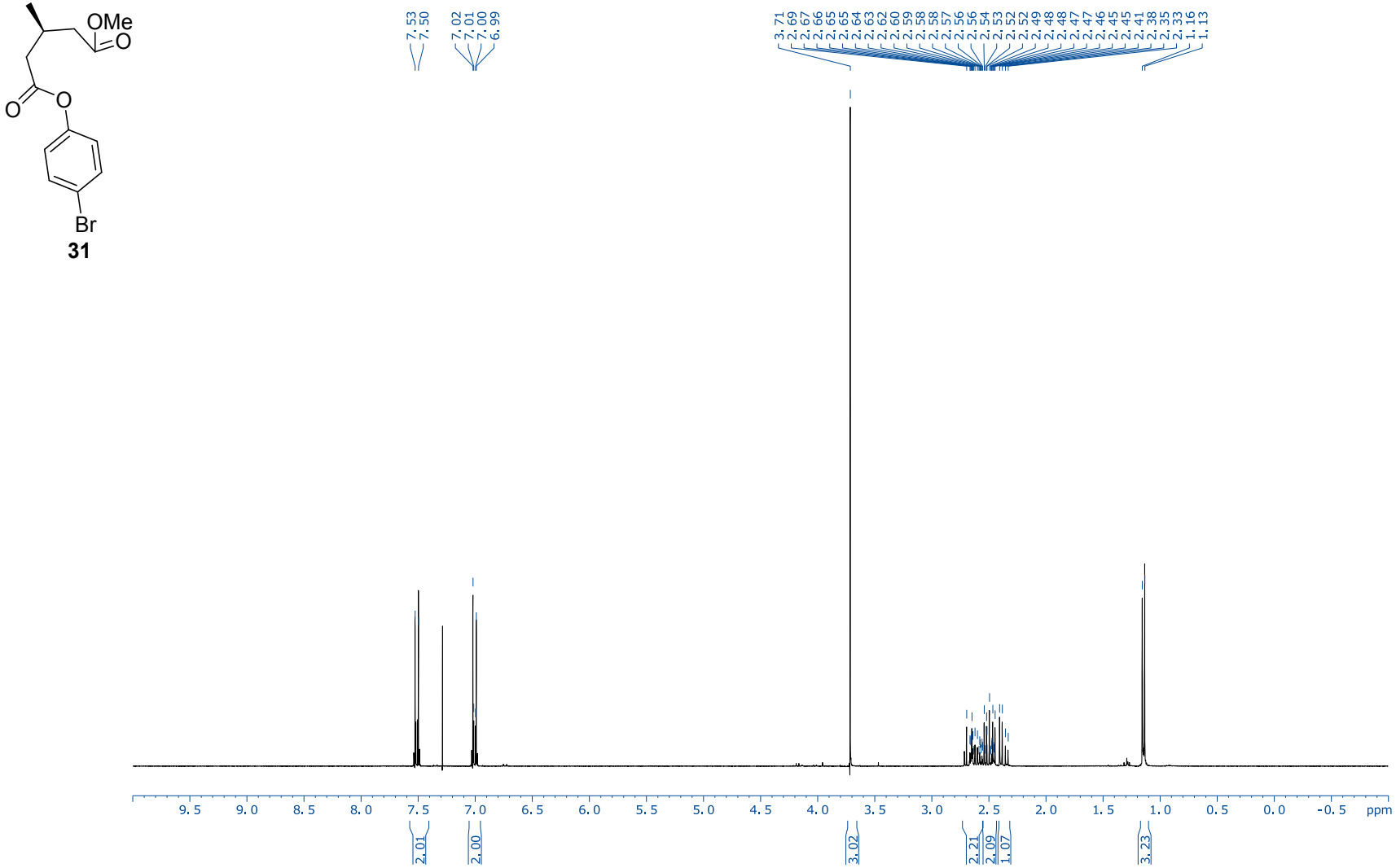
(3*R*,5*R*)-5-(3,4-Dimethoxyphenyl)-3-methylhexanoic acid (*dia*-**30**)

^{13}C NMR (100.61 MHz, $CDCl_3$):



1-(4-Bromophenyl) 5-methyl (*S*)-3-methylpentanedioate (31)

^{1}H NMR (300.13 MHz, $CDCl_3$):

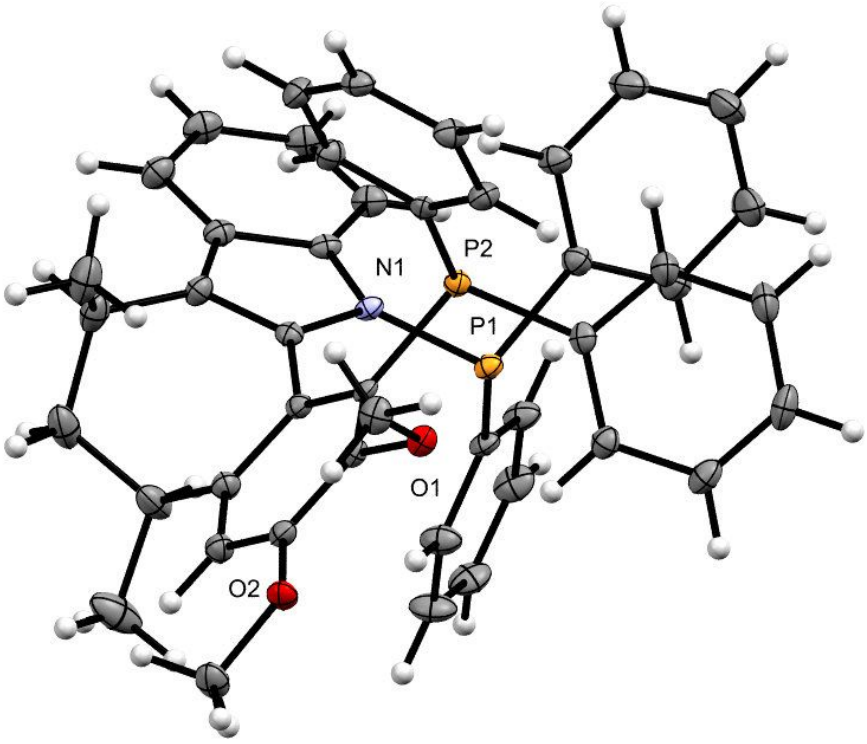


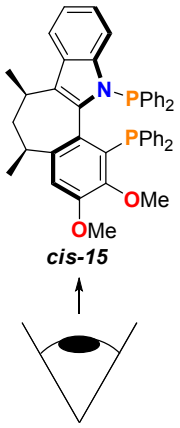
4. Crystallographic Data of the Shown Compounds in Numerical Order

(*P*,5*R*,7*S*)-1,12-Bis(Diphenylphosphaneyl)-2,3-dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*cis*-15)

The supplementary crystallographic data for this compound are contained in CCDC 1549686. These data are provided free of charge by the *Cambridge Crystallographic Data Centre* and can be obtained via the link www.ccdc.cam.ac.uk/data_request/cif

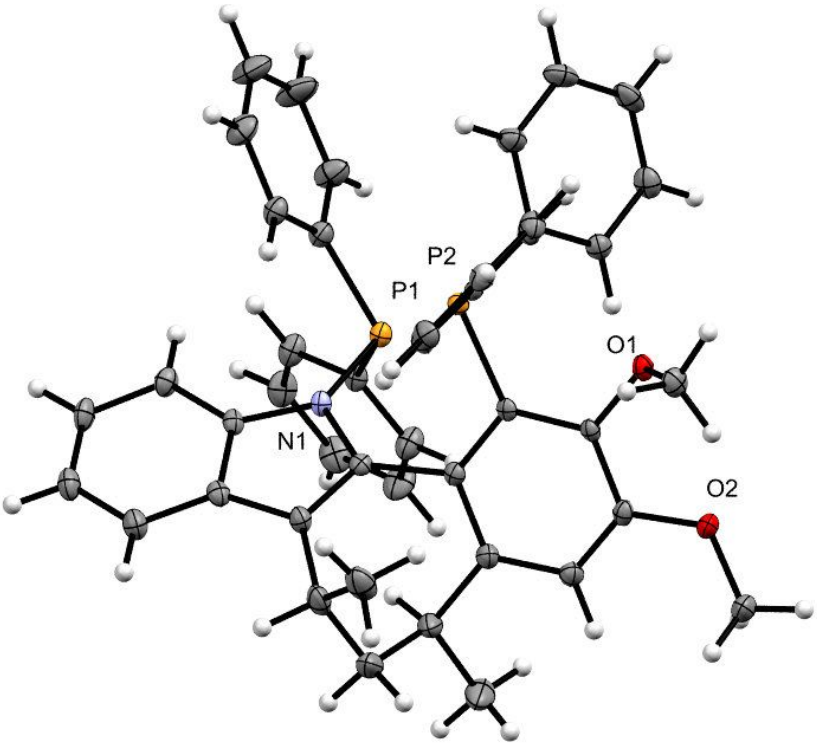
Figure 1: *ORTEP-Plot of cis*-**15** showing the view along the biaryl axis[7]

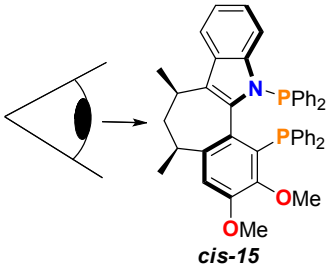




[7] This structure was inverted. The other enantiomere is shown in the CCDC data. Also the solvents molecule is removed in this picture.

Figure 2: *ORTEP-Plot of cis*-**15** showing the view on the 7-membered bridge





cis-15

***Table 1**: Crystal data and structure refinement for Fbae_331_0m_a/cis*-**15**

Compound	**Brueckner_FBac_331_0m_a**
CCDC	1549686
Formula	$C_{50}H_{52}NO_3P_2$
$D_{calc.}$/ g cm^{-3}	1.234
μ/mm^{-1}	0.148
Formula Weight	776.86
Colour	colourless
Shape	needle
Size/mm^3	0.20×0.06×0.05
T/K	100(2)
Crystal System	monoclinic
Space Group	$P2_1/c$
a/Å	9.0323(3)
b/Å	18.1198(6)
c/Å	25.5714(9)
α/°	90
β/°	92.805(2)
γ/°	90
V/Å^3	4180.1(2)
Z	4
Z'	1
Wavelength/Å	0.710730
Radiation type	MoK□
Θ_{min}/°	1.378
Θ_{max}/°	25.401
Measured Refl.	49439
Independent Refl.	7666
Reflections Used	5011
R_{int}	0.0724
Parameters	570
Restraints	147
Largest Peak	0.486
Deepest Hole	-0.313
GooF	1.026
wR_2 (all data)	0.1632
wR_2	0.1426
R_1 (all data)	0.1116
R_1	0.0642

(*M*,5*R*,7*R*)-1,12-Bis(Diphenylphosphaneyl)-2,3-dimethoxy-5,7-dimethyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole (*trans*-15)

The supplementary crystallographic data for this compound are contained in CCDC 1561798. These data are provided free of charge by the *Cambridge Crystallographic Data Centre* and can be obtained via the link www.ccdc.cam.ac.uk/data_request/cif

Figure 3: *ORTEP-Plot of trans*-**15** showing the view along the biaryl axis

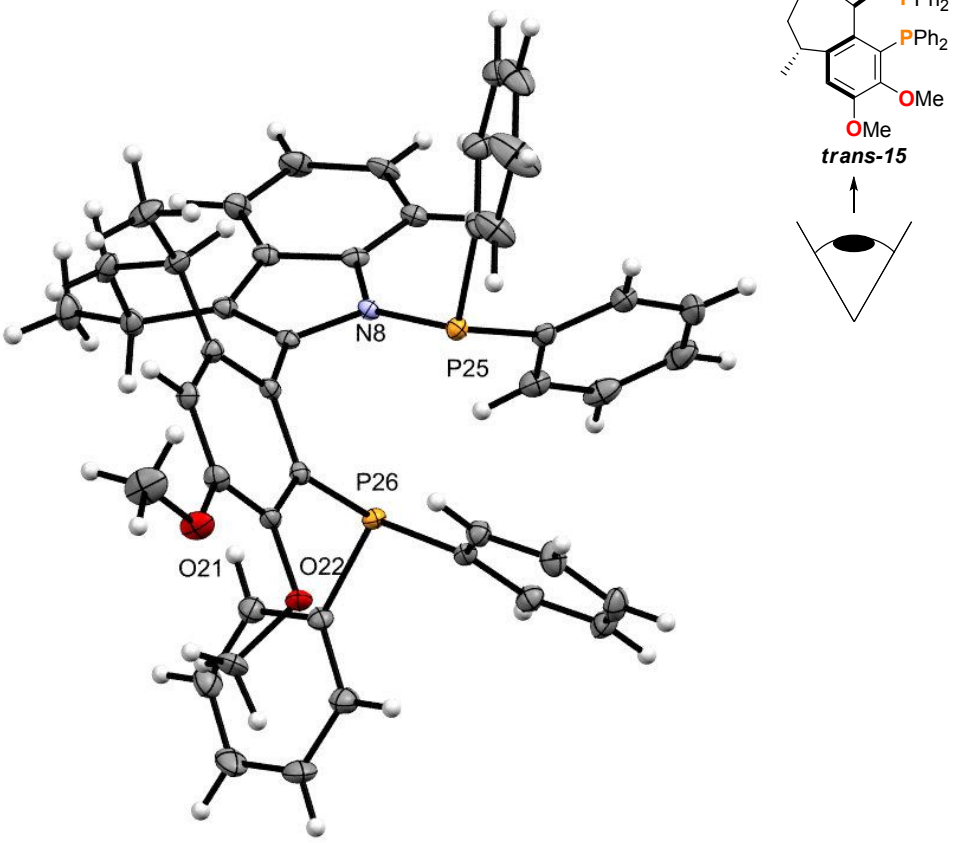


Figure 4: *ORTEP-Plot of trans*-**15** showing the view on the 7-membered bridge

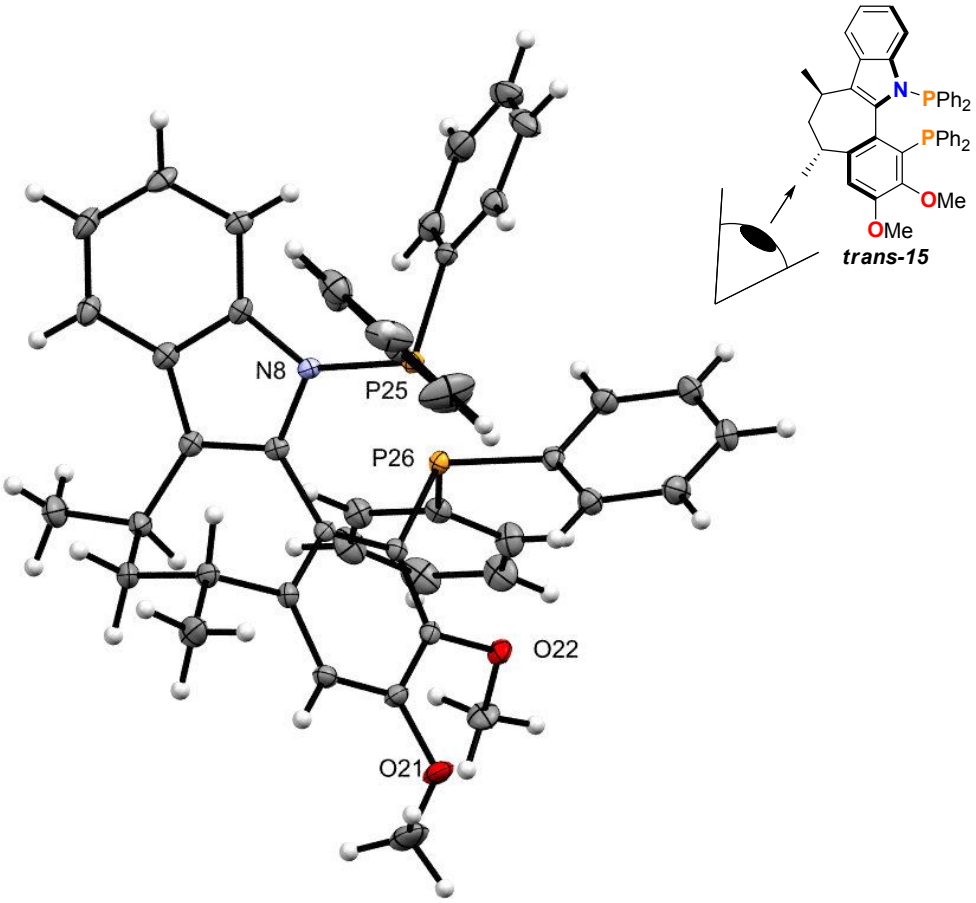


Table 2: *Crystal data and structure refinement for Fbae_446_0m_a/trans-***17**

Compound	**Brueckner_FBae_446_0m_a**
Formula	$C_{45}H_{41}NO_2P_2$
$D_{calc.}$/ g cm^{-3}	1.236
μ/mm^{-1}	0.156
Formula Weight	689.73
Colour	colourless
Shape	block
Size/mm^3	0.24×0.12×0.10
T/K	100
Crystal System	monoclinic
Flack Parameter	-0.008(15)
Hooft Parameter	0.011(15)
Space Group	$P2_1$
a/Å	9.2032(2)
b/Å	16.5837(4)
c/Å	12.6680(3)
α/°	90
β/°	106.5570(10)
γ/°	90
V/Å^3	1853.26(8)
Z	2
Z'	1
Wavelength/Å	0.710730
Radiation type	MoK□
Θ_{min}/°	1.677
Θ_{max}/°	27.536
Measured Refl.	31954
Independent Refl.	8479
Reflections Used	8230
R_{int}	0.0217
Parameters	455
Restraints	1
Largest Peak	0.238
Deepest Hole	-0.191
GooF	1.026
wR_2 (all data)	0.0707
wR_2	0.0697
R_1 (all data)	0.0293
R_1	0.0279

(7*R*,9*S*)-2,3-Dimethoxy-7,9-dimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (*cis*-17)

The supplementary crystallographic data for this compound are contained in CCDC 1533414. These data are provided free of charge by the *Cambridge Crystallographic Data Centre* and can be obtained via the link www.ccdc.cam.ac.uk/data_request/cif.

Figure 5: *ORTEP-Plot of cis*-**17**

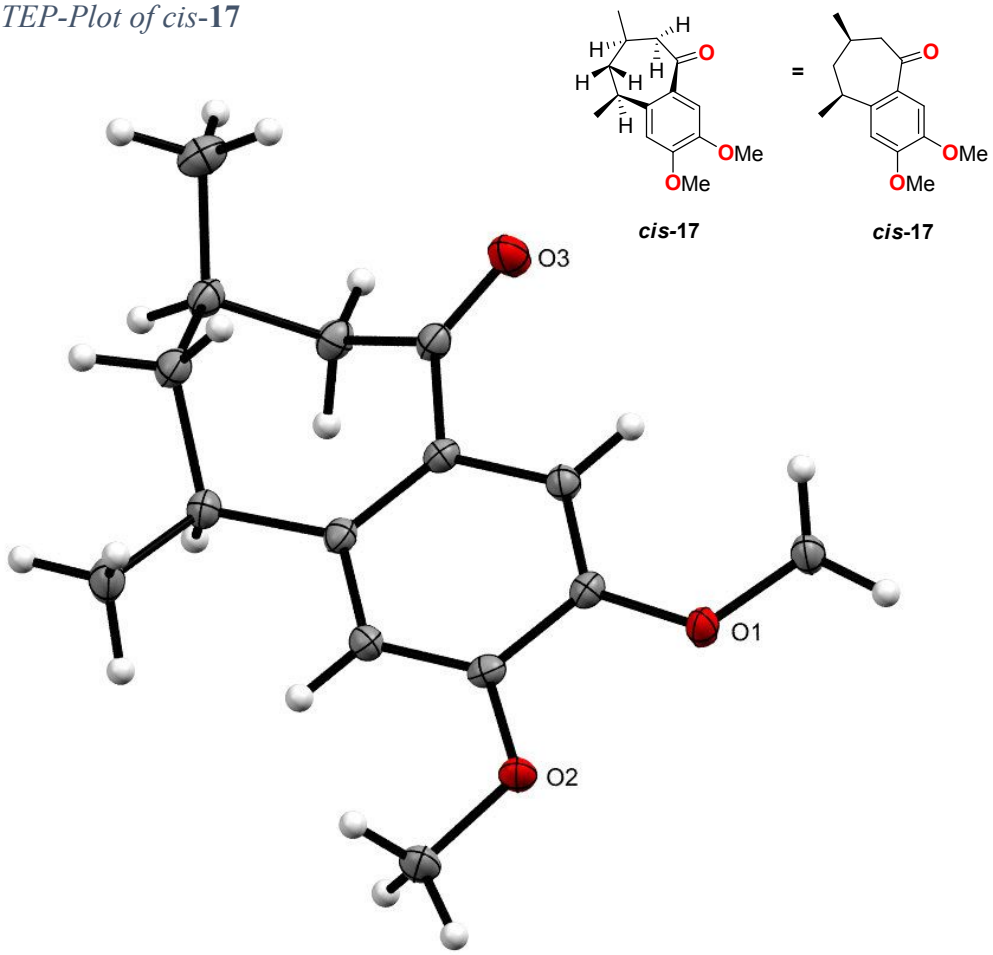


Table 3: *Crystal data and structure refinement for Fbae_318/cis-***17**

Compound	**Brueckner_FBae_318**
Formula	$C_{15}H_{20}O_3$
$D_{calc.}$/ g cm^{-3}	1.276
μ/mm^{-1}	0.087
Formula Weight	248.31
Colour	colourless
Shape	plate
Size/mm^3	0.16×0.12×0.07
T/K	100(2)
Crystal System	triclinic
Space Group	P-1
a/Å	8.452(5)
b/Å	8.809(8)
c/Å	9.260(6)
α/°	93.89(3)
β/°	107.309(11)
γ/°	98.597(14)
V/Å^3	646.2(8)
Z	2
Z'	1
Wavelength/Å	0.710730
Radiation type	MoK□
Θ_{min}/°	2.320
Θ_{max}/°	28.679
Measured Refl.	14748
Independent Refl.	3322
Reflections Used	2766
R_{int}	0.0184
Parameters	167
Restraints	0
Largest Peak	0.380
Deepest Hole	-0.198
GooF	1.047
wR_2 (all data)	0.1247
wR_2	0.1191
R_1 (all data)	0.0568
R_1	0.0464

(4*R*,6*S*)-6-(3,4-Dimethoxyphenyl)-4,6-dimethyltetrahydro-2H-pyran-2-one (29)

The supplementary crystallographic data for this compound are contained in CCDC 1578270. These data are provided free of charge by the *Cambridge Crystallographic Data Centre* and can be obtained via the link www.ccdc.cam.ac.uk/data_request/cif.

***Figure 6**: ORTEP-Plot of* **29**

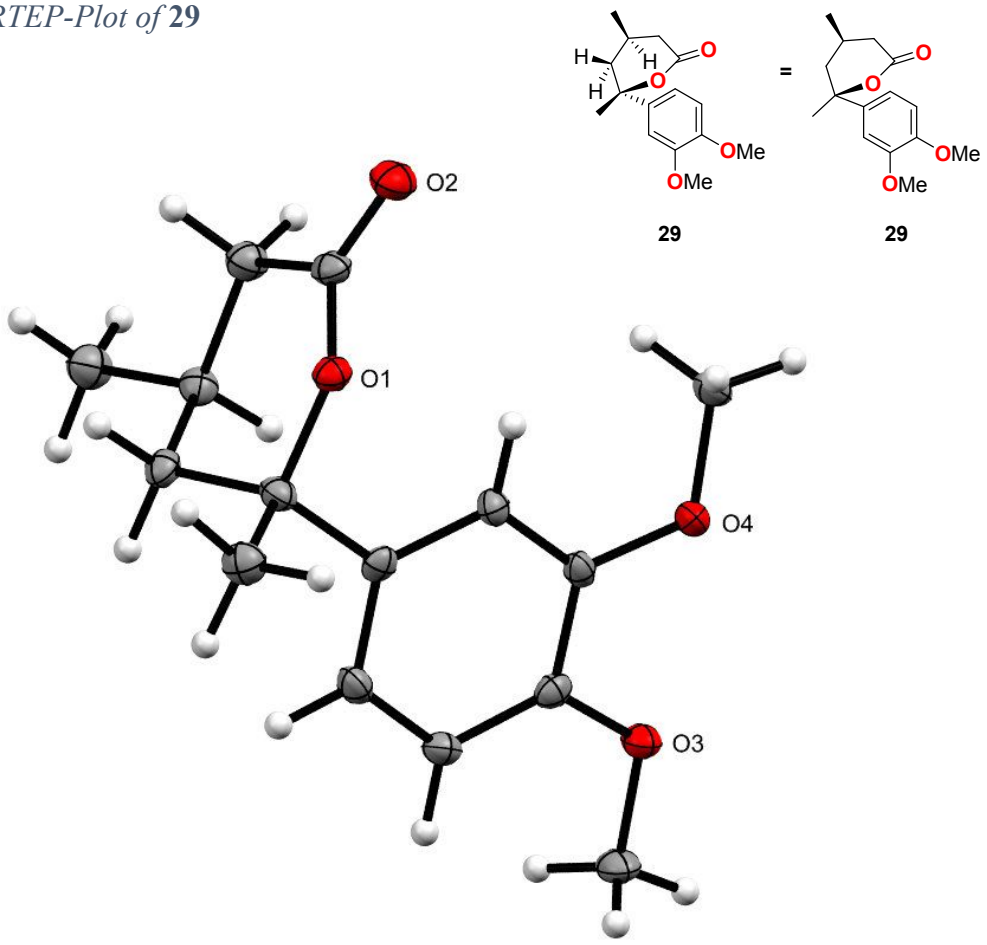


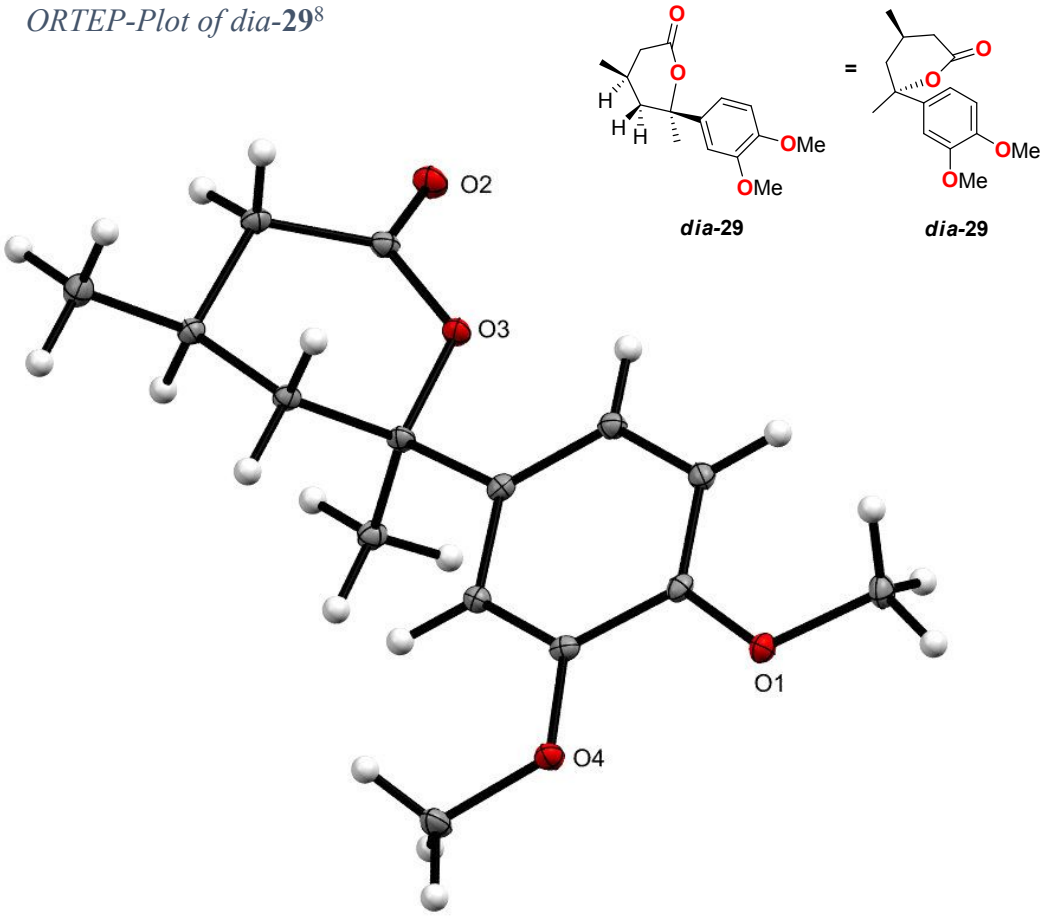
Table 4**: Crystal data and structure refinement for IK113_1_a/**29

Compound	**Brueckner_IK113_1_a**
Formula	$C_{15}H_{20}O_4$
$D_{calc.}$/ g cm^{-3}	1.280
μ/mm^{-1}	0.092
Formula Weight	264.31
Colour	colourless
Shape	block
Size/mm^3	0.23×0.22×0.18
T/K	100
Crystal System	monoclinic
Space Group	$P2_1/c$
a/Å	14.2048(6)
b/Å	8.2660(3)
c/Å	12.5190(5)
α/°	90
β/°	111.073(2)
γ/°	90
V/Å^3	1371.64(10)
Z	4
Z'	1
Wavelength/Å	0.710730
Radiation type	MoK□
Θ_{min}/°	1.536
Θ_{max}/°	26.459
Measured Refl.	2826
Independent Refl.	2826
Reflections Used	2601
R_{int}	0.0299
Parameters	177
Restraints	0
Largest Peak	0.382
Deepest Hole	-0.416
GooF	1.165
wR_2 (all data)	0.1891
wR_2	0.1878
R_1 (all data)	0.0792
R_1	0.0748

(4*R*,6R)-6-(3,4-Dimethoxyphenyl)-4,6-dimethyltetrahydro-2H-pyran-2-one (*dia*-29)

The supplementary crystallographic data for this compound are contained in CCDC 1533413. These data are provided free of charge by the *Cambridge Crystallographic Data Centre* and can be obtained via the link www.ccdc.cam.ac.uk/data_request/cif.

Figure 7: *ORTEP-Plot of dia-***29**[8]



[8] This structure was inverted. The other enantiomere is shown in the CCDC data.

Table 5: *Crystal data and structure refinement for Fbae314_2m/dia-***29**

Compound	**Brueckner_FBae314_2m**
Formula	$C_{15}H_{20}O_4$
$D_{calc.}$/ g cm^{-3}	1.263
μ/mm^{-1}	0.091
Formula Weight	264.31
Colour	yellow
Shape	plate
Size/mm^3	0.19×0.15×0.08
T/K	100(2)
Crystal System	monoclinic
Space Group	$P2_1/n$
a/Å	8.642(6)
b/Å	13.994(10)
c/Å	11.560(7)
α/°	90
β/°	96.197(14)
γ/°	90
V/Å^3	1390.0(16)
Z	4
Z'	1
Wavelength/Å	0.710730
Radiation type	MoK□
Θ_{min}/°	2.293
Θ_{max}/°	28.305
Measured Refl.	17577
Independent Refl.	3438
Reflections Used	2573
R_{int}	0.0345
Parameters	176
Restraints	0
Largest Peak	0.352
Deepest Hole	-0.254
GooF	1.058
wR_2 (all data)	0.1396
wR_2	0.1278
R_1 (all data)	0.0679
R_1	0.0495

5. Additional Literature References for Asymmetric Methanolyses of 3-Methylglutaric Anhydride

Excerpted from the hits of a Sci-Finder® search of asymmetric methanolyses of 3-Methylglutaric anhydride (October 2, 2019):

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