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Supporting Information

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Biaryl Axis as a Stereochemical Relay for the Asymmetric Synthesis of Antimicrotubule Agents

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General considerations. Reagents were commercially available and used without further purification. All solvents were distilled from the appropriate drying agents immediately before use, except THF for TES deprotection which was used as received from commercial suppliers. Yields refer to chromatographically and spectroscopically homogenous materials. Reaction were monitored by thin-layer chromatography carried out on 0.25 mm SDS silica gel coated glass plates (60F254) using UV light as visualizing agent and ethanolic sulfuric molybdate and heat as staining agents. Preparative thin-layer chromatography were carried out on 1mm or 2mm SDS silica gel coated glass plates (60F254) using UV light as visualizing agent. Merck silica gel 60 (particle size 40-63 μM) was used for flash chromatography. NMR spectra were recorded on Bruker AC-300, Avance 300, DRX 400 or Avance 500 instruments and calibrated using tetramethylsilane as internal reference. The following abbreviations were used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet, br = broad. Assignments were made on the basis of COSY, NOESY or ROESY, HMQC and HMBC experiments. IR spectra were recorded on a Perkin-Elmer Spectrum BX spectrometer. Mass spectra and high resolution mass spectra (HRMS) were recorded under electrospray ionization (ESI) conditions at the Laboratoire de Spectrométrie de Masse, ICSN, Gif-sur-Yvette, France. Melting points (mp) are uncorrected and were recorded on a Büchi B-540 capillary melting point apparatus. Optical rotations were recorded on a JASCO P-1010 polarimeter. HPLC analyses were performed on a Waters system equipped with a photodiode array detector (monitoring at 200-400 nm), using a Chiracel OD or a Chiralpak AD column (25 cm x 0.46 cm) by Daicel Chemical Ind., Ltd. The enantiomeric excesses of all compounds were determined after injection of the racemic mixture. The ee's were reproducible over 2 runs (error margin ≤ 0.5%).

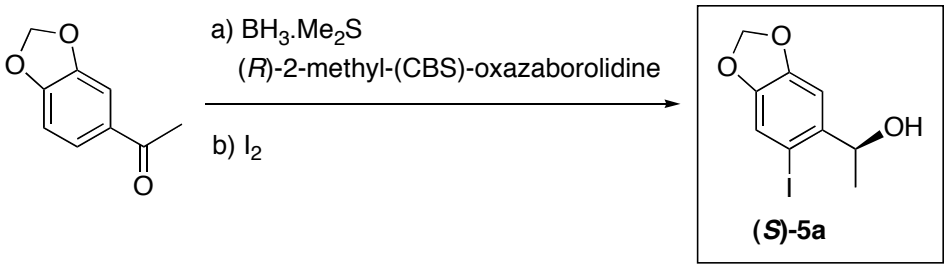
A) Synthesis of Suzuki coupling precursors

1. General iodination procedure (GP1)

To a solution of the aromatic compound (1equiv) in chloroform at 0°C were added silver trifluoroacetate (1.2 equiv) and iodine (1.05 equiv) in one portion. After stirring for 15 min at 0°C, the mixture was filtered through Celite and washed with a saturated aq. Na_2SO_3 solution. The organic layer was dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by flash chromatography on silica gel.

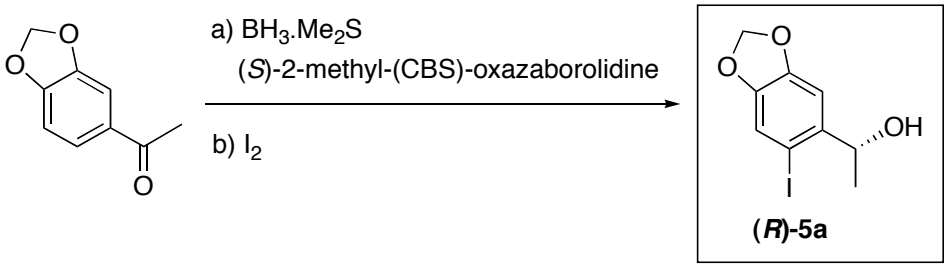
2. Synthesis of (*S*)-5a and (*R*)-5a

(*S*)-(–)-α-Methyl-2-iodo-4,5-methylenedioxybenzyl alcohol 5a



To a solution of dichloromethane (5 mL) under argon at room temperature were added (*R*)-2-methyl-CBS-oxazaborolidine (1 M in toluene, 323 μL, 0.32 mmol, 0.1 equiv) and BH_3•Me_2S (10 M in Me_2S, 323 μL, 3.23 mmol, 1 equiv). After stirring for 30 min at room temperature, a solution of methylenedioxyacetophenone (530 g, 3.23 mmol, 1 equiv) in dichloromethane (5 mL) was added dropwise over 2 h. The solution was stirred for another 3 h, methanol was then added dropwise and the solvents evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 8/2) to give the expected product as an oil (532 mg, 3.20 mmol, 99%), $[\alpha]_D^{22}$ -46 (*c* 0.99, $CHCl_3$)[1]. The general procedure GP1 using this alcohol (517 mg, 3.11 mmol) in chloroform (17 mL) gave, after purification by flash chromatography (silica gel, dichloromethane), (*S*)-**5a** as a white powder in 97% ee (669 mg, 2.29 mmol, 74%), $[\alpha]_D^{22}$ -44 (*c* 0.99, $CHCl_3$); **HPLC** (Chiracel OD, hexane/ethanol 95/5, 1.0 mL/min) t_R 10.2 min (major enantiomer), 13.6 min (minor enantiomer).

(*R*)-(+)-α-Methyl-2-iodo-4,5-methylenedioxybenzyl alcohol 5a

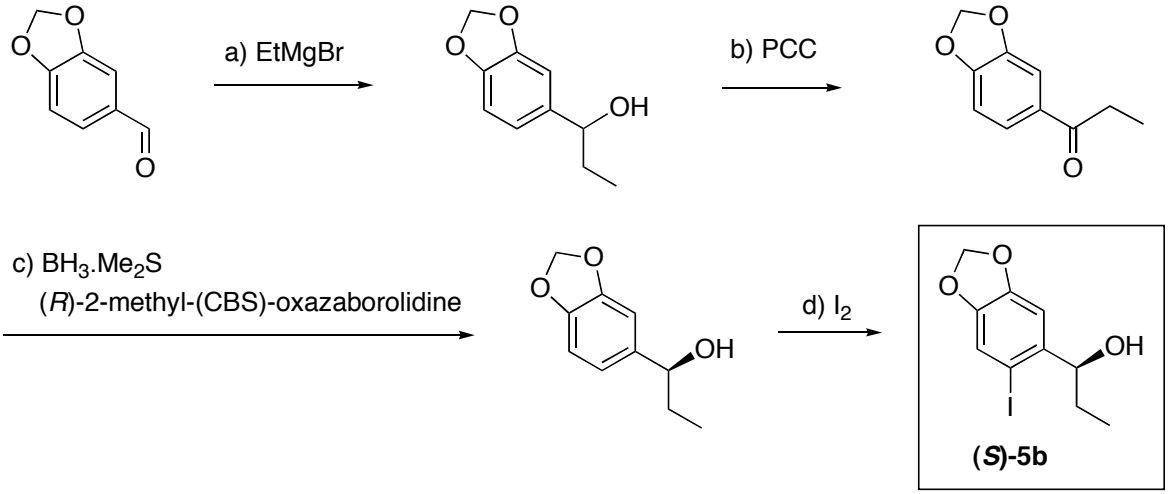


Compound (*R*)-**5a** was obtained in the same manner as above for (*S*)-**5a**, from methylenedioxyacetophenone (170 mg, 1.04 mmol) and using (*S*)-2-methyl-CBS-oxazaborolidine for the reduction, to afford iodo alcohol (*R*)-**5a** as an oil in 96% ee (227 mg, 0.78 mmol, 75% from methylenedioxyacetophenone), $[\alpha]_D^{23}$ +46 (*c* 1.00, $CHCl_3$); **HPLC**

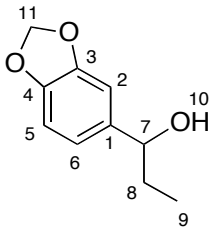
[1] S. Hashiguchi, A. Fujii, K.-J. Haack, K. Matsumura, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 288-290.

(Chiracel OD, hexane/ethanol 95/5, 1.0 mL/min) t_R 10.2 min (minor enantiomer), 13.6 min (major enantiomer).

3. Synthesis of (*S*)-5b



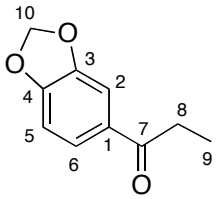
a) α-Ethyl-3,4-methylenedioxybenzyl alcohol



To a solution of 3,4-methylenedioxybenzaldehyde (2.5 g, 16.65 mmol) in THF (50mL) at -78°C was added ethylmagnesium bromide (1 M in THF, 25 mL, 24.98 mmol, 1.5 equiv) dropwise over 2 h. The mixture was stirred for 30 min at -78°C and was then allowed to warm up to room temperature. A solution of acetic acid 10% was added and the aqueous layer was extracted with diethylether. The combined organic layers were washed with water and a saturated aq $NaHCO_3$ solution until the aqueous phase reached pH 7, were dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 8/2) to give the expected alcohol as an oil (2.84 g, 15.75 mmol, 95%). The physical data were identical to those previously described in the literature.[2]

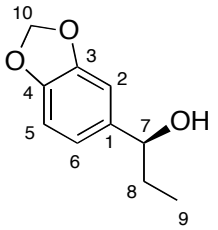
[2] E. Alesso, R. Torviso, B. Lantano, M. Erlich, L. M. Finkielsztein, G. Moltrasio, J. M. Aguirre, E. Brunet, *ARKIVOC* **2003**, *10*, 283-297.

b) 1-(3,4-methylenedioxyphenyl)propan-1-one



To a solution of the above alcohol (2.41 g, 13.35 mmol) in dichloromethane (50 mL) was added PCC (3.74 g, 17.36 mmol, 1.3 equiv) portionwise and the suspension was stirred at room temperature for 16 h before being filtered on Celite and $MgSO_4$. The filtrate was evaporated under vacuum and the residue purified by flash chromatography (silica gel, heptanes/ethyl acetate 9/1) to give the ketone as a white powder (2.11 g, 11.80 mmol, 89%). The ^{1}H NMR and IR spectra were identical to those previously described in literature.[3] **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.1(C_7), 151.7 (C_3 or C_4), 148.3 (C_3 or C_4), 132.0 (C_1), 124.2 (C_6), 108.0 (C_2 and C_5), 101.9 (C_{11}), 31.7 (C_8), 8.6 (C_9) ppm.

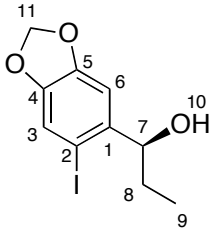
c) (*S*)-(–)-α-Ethyl-3,4-methylenedioxybenzyl alcohol



To a solution of dichloromethane (12 mL) under argon at room temperature were added (*R*)-2-methyl-CBS-oxazaborolidine (1 M in toluene, 670 μL, 0.67 mmol, 0.1 equiv) and BH_3•Me_2S (10 M in Me_2S, 670 μL, 6.70 mmol, 1 equiv). After stirring for 30 min at room temperature, a solution of the above ketone (1.19 g, 6.70 mmol, 1 equiv) in dichloromethane (12 mL) was added dropwise over 2 h. The solution was stirred for another 2 h, methanol was then added dropwise and the solvents evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 8/2) to give the expected product as an oil (1.18 g, 6.52 mmol, 97%), $[\alpha]_D^{25}$ -30 (*c* 1.05, $CHCl_3$).

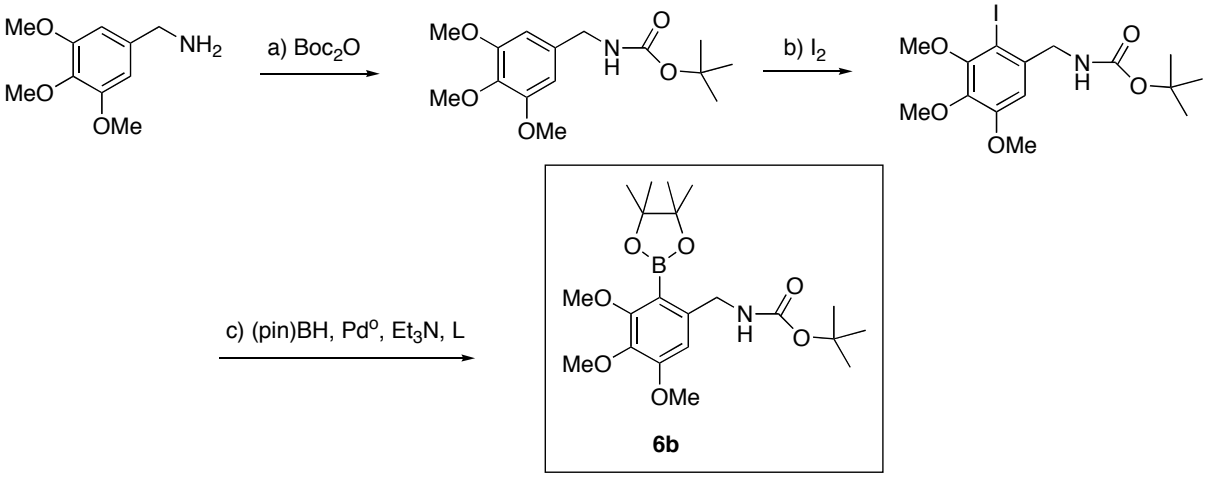
[3] E. Alesso, D. G. Tombari, I. Moltrasio, Y. Graciela, J. M. Aguirre, *Can. J. of Chem.* **1987**, *65*, 2568-2574.

d) (*S*)-(–)-α-Ethyl-2-iodo-4,5-methylenedioxybenzyl alcohol

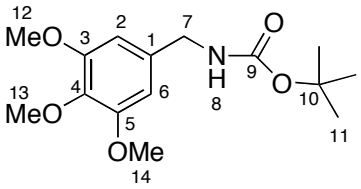


Slightly modified general procedure GP1 using the above alcohol (631 mg; 3.49 mmol), silver trifluoroacetate (925 mg, 4.19 mmol, 1.2 equiv), iodine (974 mg, 3.84 mmol, 1.1 equiv) in chloroform (35 mL) gave, after purification by flash chromatography (silica gel, dichloromethane), the expected iodo alcohol as a white solid in 98% ee (610 mg, 1.99 mmol, 57%), %), $[\alpha]_D^{25}$ -29 (*c* 1.05, $CHCl_3$); **HPLC** (Chiracel OD, hexane/ethanol 95/5, 1.0 mL/min) t_R 10.4 min (major enantiomer), 13.5 min (minor enantiomer); **mp** 117 °C ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.19 (s, 1H, H_3), 7.01 (s, 1H, H_6), 5.96 (d, J = 1.5Hz, 2H, H_{11a}), 5.95 (d, J = 1.5Hz, 2H, H_{11b}), 5.76 (dd, J = 7.5, 5.1Hz, 1H, H_7), 1.97 (s large, 1H, H_{10}), 1.79-1.56 (m, 2H, H_8), 0.98 (t, J = 7.5Hz, 3H, H_9) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.9 (C_4 or C_5), 147.9 (C_4 or C_5), 140.3 (C_1), 118.4 (C_3), 107.3 (C_6), 101.8 (C_{11}), 85.5 (C_2), 78.8 (C_7), 31.0 (C_8), 10.3 (C_9) ppm; **IR** (neat) 3307, 1470, 1231, 1036, 854 cm^{-1}.

4. Synthesis of boronate 6b

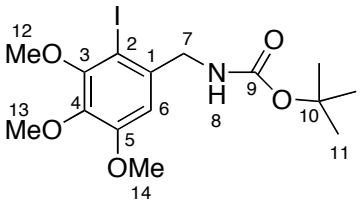


a) *N*-tert-butoxycarbonyl-3,4,5-trimethoxybenzylamine



To a solution of 3,4,5-trimethoxybenzylamine (3.00 g, 15.21 mmol) and triethylamine (3.18 mL, 22.82 mmol, 1.5 equiv) in dichloromethane (40 mL) was added Boc_2O (3.98 g, 18.25 mmol, 1.2 equiv) portionwise and the mixture was stirred at room temperature for 2 h. 5N HCl was then added dropwise and the organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated under vacuum. The oily residue was crystallized in an ethyl acetate/heptanes mixture to give the expected product as a white solid (3.99 g, 13.43 mmol, 88%). The ^{1}H NMR and IR spectra were identical to those previously described in literature.[4] **mp** 96 °C ; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.0 (C_9), 153.5 (2C, C-OCH_3), 137.3 (C-OCH_3), 134.9 (C_1), 104.6 (2C, C_2 and C_6), 79.7 (C_9), 61.0 (OCH$_3$), 56.2 (2C, OCH$_3$), 45.1 (C_7), 28.6 (3C, C_{11}) ppm; **HRMS** (ESI) calculated for $C_{15}H_{23}NO_5Na^+$ [(M+Na)$^+$] 320.1474, found 320.1472.

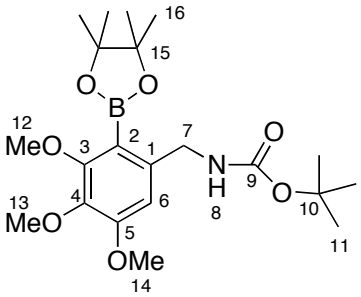
b) *N*-tert-butoxycarbonyl-2-iodo-3,4,5-trimethoxybenzylamine



The general procedure GP1 using the N-Boc protected amine (1.50 g, 5.05 mmol) in chloroform (50 mL) gave, after purification by flash chromatography (silica gel, heptanes/ethyl acetate 8/2), the product as an oil (2.09 g, 4.93 mmol, 98%): **mp** 76 °C ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.81 (s, 1H, H_6), 5.05 (br s, 1H, H_8), 4.10 (d, J = 5.7Hz, 2H, H_7), 3.87 (s, 3H, OCH_3), 3.86 (s, 6H, OCH_3), 1.46 (s, 9H, H_{11}) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ, 155.8 (C_9), 154.0 (C-OCH_3), 153.2 (C-OCH_3), 141.5 (C-OCH_3), 136.9 (C_1), 108.9 (C_6), 86.5 (C_2), 79.8 (C_{10}), 61.1 (OCH$_3$), 60.9 (OCH$_3$), 56.3 (OCH$_3$), 49.6 (C_7), 28.5 (3C, C_{11}) ppm; **IR** (neat) 3364, 1682, 1277, 1162, 1096, 1007 cm^{-1}; **HRMS** (ESI) calculated for $C_{15}H_{22}NIO_5Na^+$ [(M+Na)$^+$] 446.0440, found 446.0423.

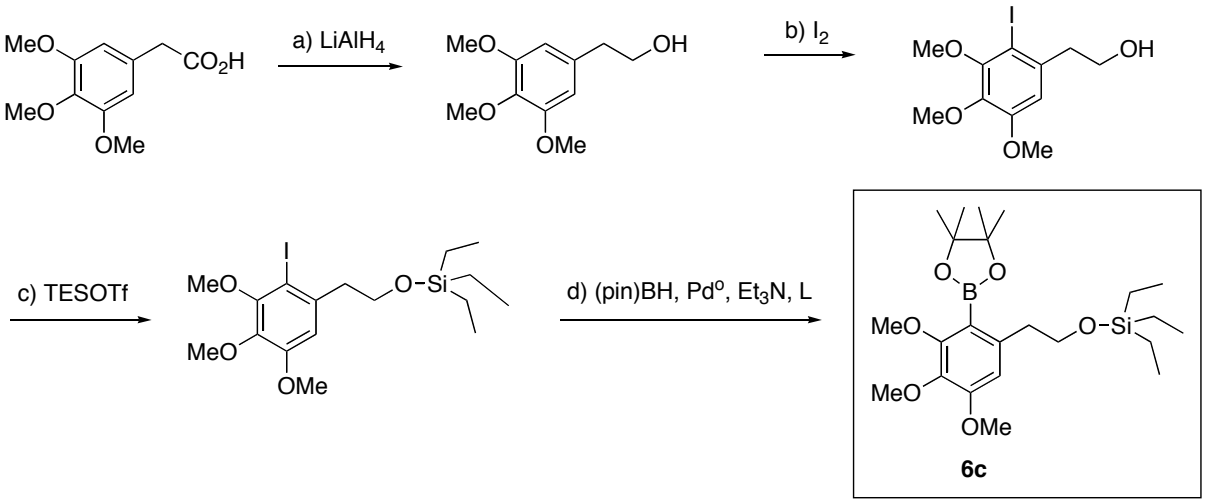
[4] S. Chandrasekhar, M. N. Reddy, L. Chandraiah, *Synlett* **2000**, *9*, 1351-1353.

c) Boronate 6b

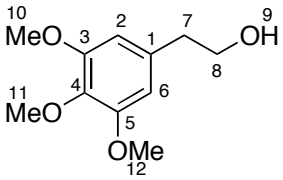


To a solution of the above iodide (2.09 g, 4.93 mmol), $Pd(OAc)_2$ (55 mg, 0.25 mmol, 0.05 equiv) and 2-(dicyclohexylphosphino)biphenyl (173 mg, 0.49 mmol, 0.1 equiv) in dioxane (20 mL) under argon at room temperature were added dropwise triethylamine (2.10 mL, 14.79 mmol, 3 equiv) and pinacolborane (1.43 mL, 9.86 mmol, 2 equiv). The mixture was heated to 80°C for 30 min, cooled to room temperature, and a saturated aq. NH_4Cl solution was added dropwise. The aqueous layer was extracted with dichloromethane, the combined organic layers were dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 9/1, 8/2, 75/25 and then 7/3) to give boronate **6b** as a brown solid (1.93 g, 4.56 mmol, 92%): **mp** 95-98 °C ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.11 (s, 1H, H_6), 5.13 (br s, 1H, H_8), 4.22 (d, J = 6.0Hz, 2H, H_7), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 1.45 (s, 9H, H_{11}), 1.38 (s, 12H, H_{16}) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.8 (C_9), 155.8 (C_3 or C_5), 155.1 (C_3 or C_5), 141.1 (C_4), 139.4 (C_1), 109.2 (C_6), 84.0 (2C, C_{15}), 79.3 (C_{10}), 61.7 (OCH$_3$), 60.9 (OCH$_3$), 56.1 (OCH$_3$), 45.3 (C_7), 28.6 (3C, C_{11}), 25.0 (4C, C_{16}) ppm; **IR** (neat) 3367, 1704, 1360, 1336, 1310, 1162, 1140, 1018 cm^{-1}; **HRMS** (ESI) calculated for $C_{15}H_{22}NIO_5Na^+$ [(M+Na)$^+$] 446.0440, found 446.0423.

5. Synthesis of boronate 6c

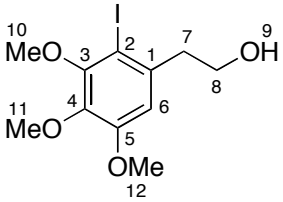


a) 2-(3,4,5-trimethoxyphenyl)ethanol



According to a modified literature procedure[5], reduction of 3,4,5-trimethoxyphenylcetic acid (1.50 g, 6.63 mmol) with $LiAlH_4$ (5.52 g, 66.3 mmol, 10 equiv) in diethylether (130 mL) gave, after flash chromatography (silica gel, heptanes/ethyl acetate 4/6), the expected product as a white solid (1.05 g, 4.95 mmol, 75%): **mp** 41 °C ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.43 (s, 2H, H_2 and H_6), 3.85-3.80 (m, 11H, OCH_3 and H_8), 2.78 (t, J = 6.6Hz, 2H, H_7) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ, 153.3 (2C, *C*-OCH_3), 136.7 (*C*-OCH_3), 134.4 (C_1), 106.0 (2C, C_2 and C_6), 63.6 (C_8), 60.9 (O*C*H_3), 56.2 (2C, O*C*H_3), 39.6 (C_7) ppm; **IR** (neat) 3393, 3331, 2940, 1588, 1421, 1235, 1122, 1005, 814 cm^{-1}; **HRMS** (ESI) calculated for $C_{11}H_{16}O_4Na^+$ [(M+Na)$^+$] 235.0946, found 235.0934.

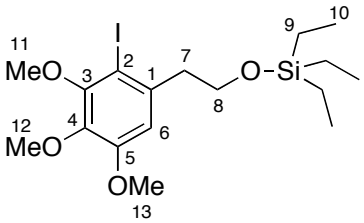
b) 2-(2-iodo-3,4,5-trimethoxyphenyl)ethanol



The general procedure GP1 using the above alcohol (1.01 g, 4.77 mmol) in chloroform (40 mL) gave, after purification by flash chromatography (silica gel, heptanes/ethyl acetate 1/1), the expected product as a white solid (1.47 g, 4.33 mmol, 91%): **mp** 68-69 °C ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.70 (s, 1H, H_6), 3.88 (s, 3H, OCH_3), 3.86-3.83 (m, 8H, 2 OCH_3 and H_8), 3.03 (t, J = 6.6Hz, 2H, H_7) ppm;**^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.7 (C_3 or C_5), 153.4 (C_3 or C_5), 140.9 (C_4), 136.9 (C_1), 109.9 (C_6), 88.5 (C_2), 62.4 (C_8), 61.1 (O*C*H_3), 60.9 (O*C*H_3), 56.3 (O*C*H_3), 44.0 (C_7) ppm;**IR** (neat) 3338, 3251, 2931, 1385, 1323, 1098, 1046, 1005 cm^{-1}; **HRMS** (ESI) calculated for $C_{11}H_{15}IO_4Na^+$ [(M+Na)$^+$] 360.9913, found 360.9943.

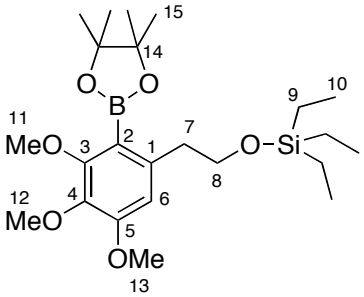
[5] F. Le Goffic, C. Galliot, A. Gouyette, *Bull. Soc. Chim. Fr.* **1975**, *5-6 (Pt 2)*, 1343-1346.

c) 2-Iodo-1-(2-triethylsilyloxy)ethyl-3,4,5-trimethoxybenzene



To a solution of the above iodo alcohol (120.7 mg, 0.357 mmol) and 2,6-lutidine (62 μL, 0.54 mmol, 1.5 equiv) in dichloromethane (2 mL) under argon at 0°C was added dropwise triethylsilyltrifluoromethane sulfonate (97 μL, 0.43 mmol, 1.2 equiv). After stirring for 20 min at 0°C and 40 min at room temperature, a saturated aq. $NaHCO_3$ solution was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 8/2) to give the title compound as a yellow oil (132.8 mg, 0.29 mmol, 82%): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.70 (s, 1H, H_6), 3.88 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.79 (t, J = 7.2Hz, 2H, H_8), 2.98 (t, J = 7.2Hz, 2H, H_7), 0.92 (t, J = 8.1Hz, 9H, H_{10}), 0.56 (q, J = 8.1Hz, 6H, H_9) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.4 (C_3 or C_5), 153.2 (C_3 or C_5), 140.8 (C_4), 137.5 (C_1), 110.3 (C_6), 88.4 (C_2), 62.5 (C_8), 61.1 (OCH$_3$), 60.8 (OCH$_3$), 56.2 (OCH$_3$), 44.3 (C_7), 6.9 (3C, C_{10}), 4.5 (3C, C_9) ppm; **IR** (neat) 2952, 2874, 1479, 1385, 1102, 1005, 725 cm^{-1}; **HRMS** (ESI) calculated for $C_{17}H_{29}IO_4Si\ Na^+$ [(M+Na)$^+$] 475.0778, found 475.0774.

d) Boronate 6c



To a solution of the above iodide (1.30 g, 2.88 mmol), $Pd(OAc)_2$ (32 mg, 0.14 mmol, 0.05 equiv) and 2-(dicyclohexylphosphino)biphenyl (101 mg, 0.29 mmol, 0.1 equiv) in dioxane (13 mL) under argon at room temperature were added dropwise triethylamine (1.20 mL, 8.64 mmol, 3 equiv) and pinacolborane (836 μL, 5.76 mmol, 2 equiv). The mixture was heated to 80°C for 30 min, cooled to room temperature, and a saturated aq. NH_4Cl solution was added dropwise. The aqueous layer was extracted with dichloromethane, the combined organic

layers were dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 9/1) to give a 95/5 inseparable mixture of boronate **6c** and the protodeiodination product as a brown oil (1.15 g, 2.45 mmol of **6c**, 85%): **^{1}H NMR** (300 MHz, $CDCl_3$) δ, 6.55 (s, 1H, H_6), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.76 (t, J = 7.2Hz, 2H, H_8), 2.83 (t, J = 7.2Hz, 2H, H_7), 1.37 (s, 12H, H_{15}), 0.92 (t, J = 7.8Hz, 9H, H_{10}), 0.55 (q, J = 7.8Hz, 6H, H_9) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.1 (C-OCH_3), 154.5 (C-OCH_3), 139.2 (2C, C-OCH_3 and C_1), 110.0 (C_6), 83.8 (2C, C_{14}), 64.8 (C_8), 61.6 (OCH$_3$), 60.9 (OCH$_3$), 56.1 (OCH$_3$), 39.9 (C_7), 25.0 (4C, C_{15}), 6.9 (3C, C_{10}), 4.5 (3C, C_9) ppm; **IR** (neat) 2953, 2936, 1338, 1142, 1105, 1021, 725 cm^{-1}; **HRMS** (ESI) calculated for $C_{23}H_{41}BO_6SiNa^+$ [(M+Na)$^+$] 475.2663, found 475.2681.

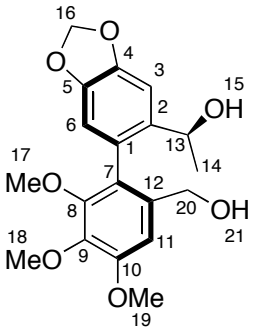
B) Synthesis of biphenyls 7a-d

1. General Suzuki-Miyaura coupling procedure (GP2)

A sealed tube was charged with the aryl halide (1 equiv), the arylboronate (1.5 equiv), $Pd(OAc)_2$ (0.05 equiv), phosphine ligand (**L1 or L2**, 0.1 equiv), $Ba(OH)_2 \bullet 8\ H_2O$ (1.1 equiv) and a 9/1 mixture of dioxane and water ([aryl halide] = 1M). The tube was sealed and placed in an oil bath heated at 100°C and stirred for 2.5 h. After cooling down to room temperature, the mixture was filtered through celite and $MgSO_4$, the filtrate was concentrated and the diastereomeric ratio of the coupling product was determined by ^{1}H NMR of the crude mixture. The residue was then purified by flash chromatography on silica gel (heptanes/ethyl acetate) to give an inseparable mixture of the expected product and a by-product of the reaction (the protodeiodination product or pinacol). The coupling product was characterized by ^{1}H and ^{13}C NMR.

For **7a**, **7b** and **7d**, the general procedure includes TES deprotection: to a solution of this mixture in THF at room temperature was added TBAF (1 equiv) and the solution was stirred for 15 min. A saturated aq. $NaHCO_3$ solution was added and the aqueous layer extracted with dichoromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (heptanes/ethyl acetate).

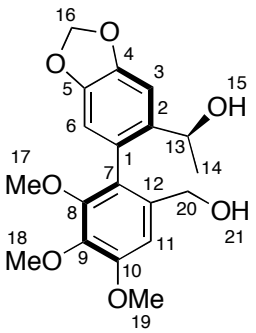
2. Synthesis of biphenyl (*S*, a*R*)-7a (Table 1, entry 1)



(*S*, a*R*)-**7a**

The general procedure GP2 using iodide (*S*)-**5a** (162 mg, 0.55 mmol), boronate **6a**[6] (372 mg, 0.83 mmol), **L1** (19.7 mg, 0.05 mmol) in dioxane (0.45 mL) and water (0.05 mL) gave, after flash chromatography (heptanes/ethyl acetate 9/1, then 7/3), a mixture of the expected biphenyl and the protodeiodination product of (*S*)-**5a** (154 mg). Treatment of this mixture (154 mg) with TBAF in THF (3 mL) gave, after flash chromatography (heptanes/ethyl acetate 1/1), biphenyl (*S*, a*R*)-**7a** as a white solid (108 mg, 0.3 mmol, 54% from (*S*)-**5a**), $[\alpha]_D^{22}$ +53 (*c* 1.15, $CHCl_3$): **mp** 179 °C; **^{1}H NMR** (300 MHz, $(CD_3)_2SO$) δ 7.08 (s, 1H, H_3), 6.97 (s, 1H, H_{11}), 6.52 (s, 1H, H_6), 6.03 (s, 2H, H_{16}), 5.03 (t, *J* = 5.1Hz, 1H, H_{21}), 4.79 (d, *J* = 4.5Hz, 1H, H_{15}), 4.30 (m, 1H, H_{13}), 4.11 (dd, *J* = 13.4, 5.3Hz, 1H, H_{20a}), 3.92 (dd, *J* = 13.4, 5.3Hz, 1H, H_{20b}), 3.83 (s, 3H, H_{17} or H_{19}), 3.75 (s, 3H, H_{18}), 3.50 (s, 3H, H_{17} or H_{19}), 0.99 (d, *J* = 6.3Hz, 3H, H_{14}) ppm; **^{13}C NMR** (75 MHz, $(CD_3)_2SO$) δ 152.4 (C_8 or C_{10}), 149.9 (C_8 or C_{10}), 146.7 (C_4 or C_5), 145.3 (C_4 or C_5), 140.1 (C_9), 139.6 (C_2), 136.3 (C_{12}), 125.8 (C_1), 124.3 (C_7), 109.8 (C_6), 106.3 (C_{11}), 105.3 (C_3), 100.8 (C_{16}), 65.2 (C_{13}), 60.6 (C_{20}), 60.5 (OCH_3), 60.4 (OCH_3), 55.6 (OCH_3), 25.2 (C_{14}) ppm; **IR** (neat) 3392, 2935, 1479, 1235, 11140, 1037, 992 cm^{-1}; **HRMS** (ESI) calculated for $C_{19}H_{22}O_7Na^+$ [(*M*+Na)$^+$] 385.1263, found 385.1260.

3. Synthesis of biphenyl (*S*, a*S*)-7e (Table 1, entry 1 – Scheme 3)

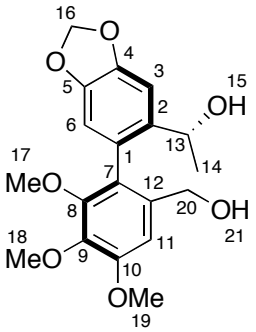


(*S*, a*S*)-**7e**

[6] O. Baudoin, A. Décor, M. Césario, F. Guéritte, *Synlett* **2003**, *13*, 2009-2012.

The above procedure allowed the isolation, after Suzuki coupling, of a small amount (30.5 mg) of a mixture of the minor diastereomer (*S*, a*S*) biphenyl and by-products of the reaction. This mixture (27.5 mg) was treated by TBAF in THF (1.5 mL) to give, after flash chromatography (heptanes/ethyl acetate 1/1), biphenyl (*S*, a*S*)-**7e** as an oil (15.8 mg, 0.044 mmol, 9% from (*S*)-**5a**): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.06 (s, 1H, H_3), 6.79 (s, 1H, H_{11}), 6.53 (s, 1H, H_6), 6.00 (s, 2H, H_{16}), 4.48 (q, 1H, J = 6.3Hz, H_{13}), 4.23 (s, 2H, H_{20}), 3.91 (s, 3H, H_{17} or H_{19}), 3.89 (s, 3H, H_{18}), 3.65 (s, 3H, H_{17} or H_{19}), 2.90 (br s, 1H, O*H*), 1.39 (d, J = 6.3Hz, 3H, H_{14}) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.3 (C_8 or C_{10}), 151.6 (C_8 or C_{10}), 147.8 (C_4 or C_5), 146.7 (C_4 or C_5), 141.9 (C_9), 137.8 (C_2), 134.8 (C_{12}), 128.1 (C_1), 127.0 (C_7), 109.8 (C_6), 108.7 (C_{11}), 105.8 (C_3), 101.3 (C_{16}), 66.2 (C_{13}), 63.1 (C_{20}), 61.0 (2C, O*C*H$_3$), 56.2 (O*C*H$_3$), 22.9 (C_{14}) ppm.

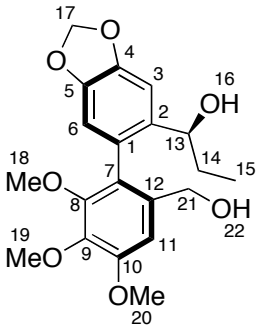
4. Synthesis of biphenyl (*R*, a*S*)-7a (Table 1, entry 2)



(*R*, a*S*)-**7a**

The general procedure GP3 using iodide (*R*)-**5a** (212 mg, 0.72 mmol), boronate **6a** (474 mg, 1.08 mmol), **L1** (32.3 mg, 0.07 mmol) in dioxane (0.64 mL) and water (0.07 mL) gave, after flash chromatography (heptanes/ethyl acetate 9/1, then 7/3), a mixture of the expected biphenyl and the protodeiodination product of (*S*)-**5a** (122 mg). Treatment of this mixture (122 mg) with TBAF in THF (2.5 mL) gave, after flash chromatography (heptanes/ethyl acetate 1/1, then 1/2), biphenyl (*R*, a*S*)-**7a** as a yellow solid (89.4 mg, 0.25 mmol, 34 % from (*R*)-**5a**), $[\alpha]_D^{25}$ -51 (*c* 1.22, $CHCl_3$).

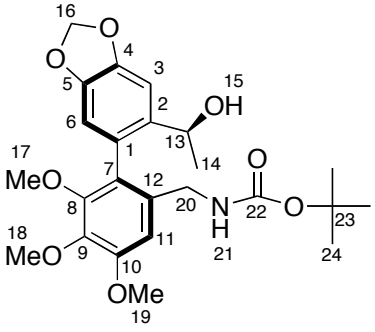
5. Synthesis of biphenyl (*S*, a*R*)-7b (Table 1, entry 3)



(*S*, a*R*)-**7b**

The general procedure GP2 using iodide (*S*)-**5b** (250 mg, 0.82 mmol), boronate **6a** (538 mg, 1.23 mmol), **L1** (32 mg, 0.08 mmol) in dioxane (0.74 mL) and water (0.08 mL) gave, after flash chromatography (heptanes/ethyl acetate 9/1, 85/15, 8/2 and then 7/3), a mixture of the expected coupling product and the protodeiodination product of (*S*)-**5b** (178 mg). Treatment of this mixture (139 mg) with TBAF in THF (3 mL) gave, after flash chromatography (heptanes/ethyl acetate 1/1), biphenyl (*S*, a*R*)-**7b** as a white solid (101 mg, 0.27 mmol, 42% from (*S*)-**5b**), $[\alpha]_D^{22}$ +67 (*c* 0.97, $CHCl_3$): **mp** 155 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.04 (s, 1H, H_3), 6.95 (s, 1H, H_{11}), 6.61 (s, 1H, H_6), 6.01 (d, *J* = 0.6Hz, 2H, H_{17}), 4.39 (d, *J* = 12.6Hz, 1H, H_{21a}), 4.31 (d, *J* = 12.6Hz, 1H, H_{21b}), 4.13 (t, *J* = 7.2Hz, 1H, H_{13}), 3.94 (s, 3H, H_{18} or H_{20}), 3.92 (s, 3H, H_{19}), 3.55 (s, 3H, H_{18} or H_{20}), 3.07 (br s, 1H, H_{16} or H_{22}), 1.84-1.61 (m, 2H, H_{14}), 0.70 (t, *J* = 7.2Hz, 3H, H_{15}) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.2 (C_8 or C_{10}), 150.8 (C_8 or C_{10}), 148.0 (C_4 or C_5), 146.8 (C_4 or C_5), 141.6 (C_9), 136.9 (C_2), 135.0 (C_{12}), 127.9 (C_1), 126.1 (C_7), 110.0 (C_6), 107.6 (C_3), 106.3 (C_{11}), 101.4 (C_{17}), 72.4 (C_{13}), 62.9 (C_{21}), 61.4 (OCH_3), 61.3 (OCH_3), 56.2 (OCH_3), 28.4 (C_{14}), 10.5 (C_{15}) ppm; **IR** (neat) 3368, 2932, 1479, 1228, 1094, 1037, 992 cm^{-1}; **HRMS** (ESI) calculated for $C_{20}H_{24}O_7Na^+$ [(*M*+Na)$^+$] 399.1420, found 399.1412.

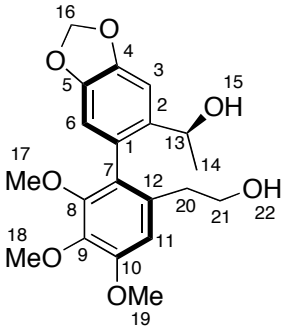
6. Synthesis of biphenyl (*S*, a*R*)-7c (Table 1, entry 4)



(*S*, a*R*)-**7c**

The general procedure GP2 using iodide (*S*)-**5a** (93 mg, 0.32 mmol), boronate **6b** (203 mg, 0.48 mmol), **L1** (12 mg, 0.03 mmol) in dioxane (0.29 mL) and water (0.03 mL) gave, after flash chromatography (heptanes/ethyl acetate 85/15, 75/25, 7/3, and then 1/1), a mixture of biphenyl (*S*, a*R*)-**7c** and pinacol (67.5 mg). Further purification by preparative TLC (heptanes/ethyl acetate 1/1) afforded pure (*S*, a*R*)-**7c** as an oil (58 mg, 0.125 mmol, 39%), $[\alpha]_D^{24}$ +30 (*c* 1.04, $CHCl_3$): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.12 (s, 1H, H_3), 6.80 (s, 1H, H_{11}), 6.57 (s, 1H, H_6), 6.00 (s, 2H, H_{16}), 4.49 (br s, 1H, H_{21}), 4.42 (q, *J* = 6.6Hz, 1H, H_{13}), 3.99 (s, 1H, H_{20}), 3.91 (s, 3H, H_{17} or H_{19}), 3.90 (s, 3H, H_{18}), 3.56 (s, 3H, H_{17} or H_{19}), 3.03 (br s, 1H, H_{15}), 1.41 (s, 9H, H_{24}), 0.70 (t, *J* = 6.6Hz, 3H, H_{14}) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.7 (C_{22}), 153.1 (C_8 or C_{10}), 151.0 (C_8 or C_{10}), 148.0 (C_4 or C_5), 147.0 (C_4 or C_5), 141.3 (C_9), 138.1 (C_2), 133.2 (C_{12} or C_1 or C_7), 127.3 (C_{12} or C_1 or C_7), 126.6 (C_{12} or C_1 or C_7), 109.7 (C_6), 108.5 (C_{11}), 106.2 (C_3), 101.4 (C_{16}), 79.7 (C_{23}), 66.6 (C_{13}), 61.5 (O*C*H$_3$), 61.3 (O*C*H$_3$), 56.2 (O*C*H$_3$), 42.8 (C_{20}), 28.5 (3C, C_{24}), 21.8 (C_{14}) ppm; **IR** (neat) 3369, 2928, 1482, 1234, 1089, 1038 cm^{-1}; **HRMS** (ESI) calculated for $C_{24}H_{31}NO_8Na^+$ [(*M*+Na)$^+$] 484.1947, found 484.1954.

7. Synthesis of biphenyl (*S*, a*R*)-7d (Table 1, entry 5)



(*S*, a*R*)-**7d**

The general procedure GP2 using iodide (*S*)-**5a** (93 mg, 0.32 mmol), boronate **6c** (275 mg of a 95/5 mixture with deboronated product, 0.48 mmol), **L2** (13 mg, 0.03 mmol) in dioxane (0.29 mL) and water (0.03 mL) gave, after flash chromatography (heptanes/ethyl acetate 9/1, then 7/3), a mixture of the expected biphenyl and the protodeiodination product of (*S*)-**5a** (91 mg). Treatment of this mixture (66 mg) with TBAF in THF (1.5 mL) gave, after flash chromatography (heptanes/ethyl acetate 1/1), biphenyl (*S*, a*R*)-**7d** as a white solid (50 mg, 0.132 mmol, 57% from (*S*)-**5a**), $[\alpha]_D^{22}$ +46 (*c* 1.00, $CHCl_3$): **mp** 153 °C ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.09 (s, 1H, H_3), 6.69 (s, 1H, H_{11}), 6.57 (s, 1H, H_6), 6.00 (s, 2H, H_{17}), 4.41 (q, *J* = 6.3Hz, 1H, H_{13}), 3.90 (s, 3H, H_{17} or H_{19}), 3.88 (s, 3H, H_{18}), 3.58 (t, *J* = 6.9Hz, 2H, H_{21}), 3.54 (s, 3H, H_{17} or H_{19}), 3.11 (br s, 1H, H_{15} or H_{22}), 2.70 (quint, *J* = 13.5, 6.9Hz, 1H, H_{20a}), 2.52

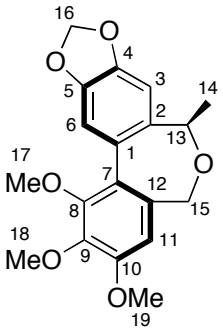
(quint, J = 13.5, 6.9Hz, 1H, H_{20b}), 1.32 (d, J = 6.3Hz, 3H, H_{14}) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.9 (C_8 or C_{10}), 151.0 (C_8 or C_{10}), 147.8 (C_4 or C_5), 146.8 (C_4 or C_5), 140.9 (C_9), 138.1 (C_2), 132.8 (C_{12}), 128.1 (C_1 or C_7), 127.5 (C_1 or C_7), 110.1 (C_6), 109.7 (C_{11}), 106.0 (C_3), 101.3 (C_{16}), 66.6 (C_{13}), 62.0 (C_{21}), 61.4 (OCH_3), 61.2 (OCH_3), 56.2 (OCH_3), 36.6 (C_{20}), 21.7 (C_{14}) ppm; **IR** (neat) 3369, 2928, 1482, 1234, 1089, 1038 cm^{-1}; **HRMS** (ESI) calculated for $C_{20}H_{24}O_7Na^+$ [(M+Na)$^+$] 399.1420, found 399.1428.

C) Synthesis of target compounds 4a-d

1. General cyclization procedure (GP3)

A solution of diol (1 equiv) in dichoromethane was cooled down to the appropriate temperature, a solution of TFA (5 equiv) in dichoromethane (0.5 mL) was then added dropwise and the reaction was run until complete conversion of the starting material (followed by TLC: an aliquot of the reaction mixture was washed with a saturated aq. $NaHCO_3$ solution and extracted with ethyl acetate before being spotted on the TLC plate). A saturated aq. $NaHCO_3$ solution was added and the aqueous layer extracted with dichoromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by preparative TLC (silica gel, heptanes/ethyl acetate).

2. Biphenyl (*R*, a*R*)-4a (Table 1, entry 1)

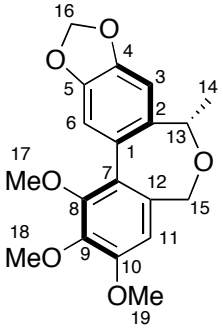


(*R*, a*R*)-**4a**

The general procedure GP3 using (*S*, a*R*)-**7a** (44.0 mg, 0.12 mmol) in 4 mL of dichoromethane at -50°C gave, after preparative TLC (heptanes/ethyl acetate 1/1), biphenyl (*R*, a*R*)-**4a** as an oil in 96% ee (35.5 mg, 0.10 mmol, 86%, 96/4 mixture of interconverting atropisomers), $[\alpha]_D^{24}$ -117 (*c* 1.09, $CHCl_3$): **HPLC** (Chiralpak AD, hexane/ethanol 99/1, 1.0

mL/min) t_R 17.4 min (major enantiomer), 29.2 min (minor enantiomer); **mp** 104 °C ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.14 (s, 1H, H_6), 7.00 (s, 1H, H_3), 6.74 (s, 1H, H_{11}), 6.04 (d, J = 1.5Hz, 1H, H_{16a}), 6.02 (d, J = 1.5Hz, 1H, H_{16b}), 4.24 (s, J = 11.3Hz, 1H, H_{15a}), 4.24 (q, J = 6.6Hz, 1H, H_{13}), 3.98 (d, J = 11.3Hz, 1H, H_{15b}), 3.94 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 1.56 (d, J = 6.6Hz, 3H, H_{14}) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.1 (C-OCH_3), 150.5 (C-OCH_3), 147.3 (C_4 or C_5), 146.9 (C_4 or C_5), 142.7 (C-OCH_3), 131.7 (C_2 or C_{12}), 131.4 (C_2 or C_{12}), 130.9 (C_1), 126.3 (C_7), 109.8 (C_6), 108.3 (C_{11}), 105.5 (C_3), 101.3 (C_{17}), 68.7 (C_{13}), 68.1 (C_{15}), 61.2 (OCH_3), 61.0 (OCH_3), 56.2 (OCH_3), 18.2 (C_{14}) ppm; **IR** (neat) 2936, 1483, 1242, 1101, 1045 cm^{-1}; **HRMS** (ESI) calculated for $C_{19}H_{20}O_6Na^+$ [(M+Na)$^+$] 367.1158, found 367.1140.

3. Biphenyl (*S*, a*S*)-4a



(*S*, a*S*)-**4a**

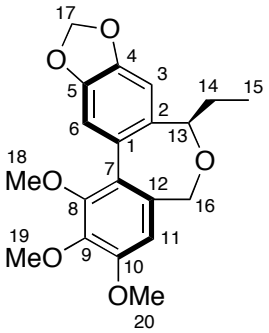
From (*R*, a*S*)-7a (Table 1, entry 2): the general procedure GP3 using (*R*, a*S*)-**7a** (76.8 mg, 0.21 mmol) in 11 mL of dichoromethane at -50°C gave, after preparative TLC (heptanes/ethyl acetate 6/4), biphenyl (*S*, a*S*)-**4b** as an oil in 94% ee (61.6 mg, 0.18 mmol, 86%), $[\alpha]_D^{23}$ +119 (*c* 1.00, $CHCl_3$); **HPLC** (Chiralpak AD, hexane/ethanol 99/1, 1.0 mL/min) t_R 14.7 min (minor enantiomer), 22.5 min (major enantiomer).

From (*S*, a*S*)-7e (Scheme 3): the general procedure GP3 using (*S*, a*S*)-**7e** (10 mg, 0.03 mmol) in 2 mL of dichoromethane at -50°C gave, after preparative TLC (heptanes/ethyl acetate 1/1), biphenyl (*S*, a*S*)-**4b** as an oil in 96% ee (7.4 mg, 0.022 mmol, 80%).

From (*S*, a*R*)-7a (Scheme 3): to a solution of diol (*S*, a*R*)-**7a** (10 mg, 0.03 mmol) in dichloromethane (1 mL) at -78°C was added DAST (7µL, 0.06 mmol, 2 equiv) in dichloromethane (50 µL). The mixture was stirred for 50 min at -78°C and a saturated aq. $NaHCO_3$ solution was added. The aqueous layer was extracted with dichoromethane, the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated

under vacuum. The residue was purified by preparative TLC (silica gel, heptanes/ethyl acetate 6/4) to give biphenyl (*S*, a*S*)-**4b** as an oil in 44% ee (5.5 mg, 0.016 mmol, 58%).

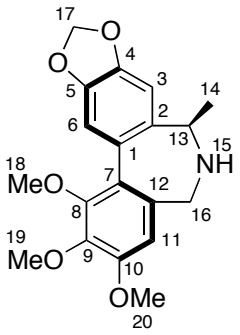
4. Biphenyl (*R*, a*R*)-4b (Table 1, entry 3)



(*R*, a*R*)-**4b**

The general procedure GP3 using (*S*, a*R*)-**7b** (23.3 mg, 0.06 mmol) in 1.5 mL of dichoromethane at -78°C gave, after preparative TLC (heptanes/ethyl acetate 6/4), biphenyl (*R*, a*R*)-**4b** as an oil in 95% ee (18 mg, 0.05 mmol, 77%, 91/9 mixture of interconverting atropisomers), $[\alpha]_D^{25}$ -80 (*c* 0.90, $CHCl_3$); **HPLC** (Chiracel OD, hexane/ethanol 99.5/0.5, 1.0 mL/min) t_R 27.6 min (major enantiomer), 55.4 min (minor enantiomer): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.06 (s, 1H, H_6), 6.88 (s, 1H, H_3), 6.64 (s, 1H, H_{11}), 5.96 (d, *J* = 1.5Hz, 1H, H_{17a}), 5.94 (d, *J* = 1.5Hz, 1H, H_{17b}), 4.29 (d, *J* = 11.1Hz, 1H, H_{16a}), 3.88-3.77 (m, 8H, 2 OCH_3, H_{13} and H_{16b}), 3.64 (s, 3H, H_{18} or H_{20}), 1.89 (m, 2H, H_{14}), 0.70 (t, *J* = 7.5Hz, 3H, H_{15}) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.1 (C_8 or C_{10}), 150.5 (C_8 or C_{10}), 147.3 (C_4 or C_5), 146.8 (C_4 or C_5), 142.7 (C_9), 131.5 (2C) and 130.9 (C_2, C_{12} and C_1), 126.5 (C_7), 109.9 (C_6), 108.4 (C_{11}), 105.7 (C_3), 101.3 (C_{17}), 74.5 (C_{13}), 67.9 (C_{16}), 61.3 (OCH$_3$), 61.0 (OCH$_3$), 56.2 (OCH$_3$), 25.2 (C_{14}), 11.1 (C_{15}) ppm; **IR** (neat) 2933, 1482, 1240, 1103, 1040 cm^{-1}; **HRMS** (ESI) calculated for $C_{20}H_{22}O_6Na^+$ [(*M*+Na)$^+$] 381.1314, found 381.1302.

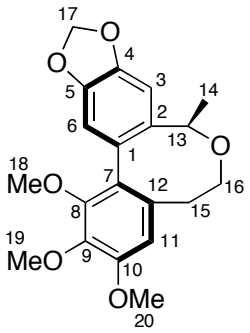
5. Biphenyl (*R*, a*R*)-4c (Table 1, entry 4)



(*R*, a*R*)-**4c**

To a solution of (*S*, a*R*)-**7c** (10.9 mg, 0.024 mmol) in dichoromethane (1 mL) cooled down to -78°C was added dropwise over 1h30 a solution of TFA (0.75 mL) in dichoromethane (1 mL). The mixture was stirred for 2h at -78°C and was then allowed to warm up to room temperature for 30 min. NaOH 1N was added dropwise until the aqueous phase reached pH 12. The aqueous layer was then extracted with dichoromethane, the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (dichoromethane/methanol 95/5, then 9/1) to give biphenyl (*R*, a*R*)-**4c** as an oil in 88% ee (7.7 mg, 0.022 mmol, 95%), $[\alpha]_D^{25}$ -47 (*c* 0.87, $CHCl_3$); **HPLC** (Chiralpak AD, hexane/*i*-PrOH 95/5 + 0.1% Et_3N, 1.0 mL/min) t_R 27.5 min (major enantiomer), 34.4 min (minor enantiomer); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.06 (s, 1H, H_6), 7.00 (s, 1H, H_3), 6.75 (s, 1H, H_{11}), 6.05 (d, J = 1.8Hz, 1H, H_{17a}), 6.02 (d, J = 1.8Hz, 1H, H_{17b}), 4.36 (br s, 1H, H_{15}), 3.92 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.85-3.77 (m, 2H, H_{13} and H_{16a}), 3.71 (s, 3H, OCH_3), 3.45 (d, J = 12.6Hz, 1H, H_{16b}), 1.63 (t, J = 6.6Hz, 3H, H_{14}) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 153.4 (C_8 or C_{10}), 150.8 (C_8 or C_{10}), 147.6 (C_4 or C_5), 147.3 (C_4 or C_5), 142.9 (C_9), 130.4 (C_{12} or C_1 or C_2), 130.0 (C_{12} or C_1 or C_2), 129.2 (C_{12} or C_1 or C_2), 125.9 (C_7), 110.3 (C_6), 108.7 (C_{11}), 105.7 (C_3), 101.5 (C_{17}), 61.2 (OCH_3), 61.1 (OCH_3), 56.2 (OCH_3), 50.2 (C_{13}), 48.0 (C_{16}), 17.2 (C_{14}) ppm; **IR** (neat) 2929, 1484, 1457, 1409, 1105, 1037 cm^{-1}; **HRMS** (ESI) calculated for $C_{19}H_{22}NO_5^+$ [(M+H)$^+$] 344.1498, found 344.1505.

6. Biphenyl (*R*, a*R*)-4d (Table 1, entry 5)

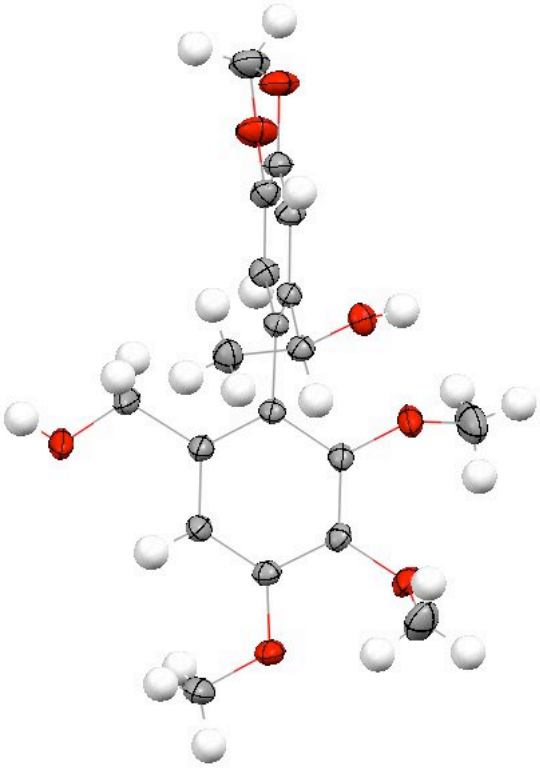


(*R*, a*R*)-**4d**

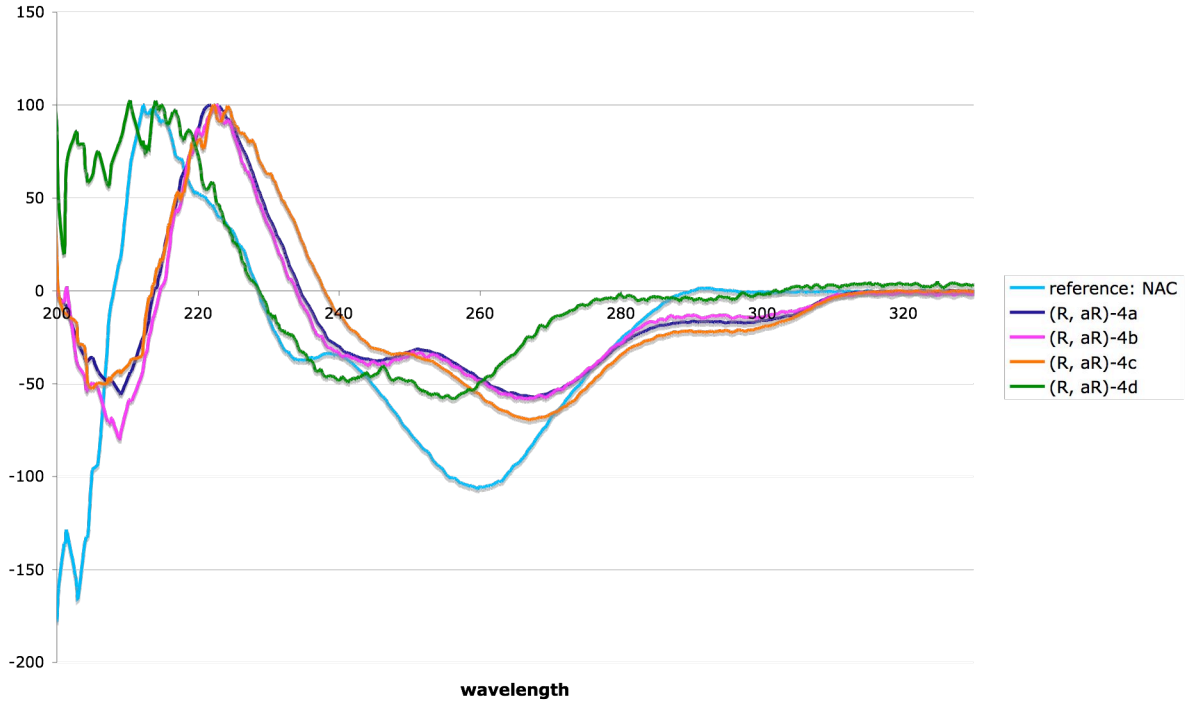
The general procedure GP3 using (*S*, a*R*)-**7d** (28.1 mg, 0.08 mmol) in 2.5 mL of dichloromethane at -45°C gave, after preparative TLC (heptanes/ethyl acetate 1/1), biphenyl (*R*, a*R*)-**4d** as a white solid in 96% ee (22.5 mg, 0.06 mmol, 84%), $[\alpha]_D^{24}$ -39 (*c* 1.00, $CHCl_3$); **HPLC** (Chiralpak AD, hexane/ethanol 95/5, 1.0 mL/min) t_R 7.5 min (major enantiomer), 20.3 min (minor enantiomer); **mp** 161-162 ° ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.07 (s, 1H, H_3), 6.79

(s, 1H, H_6), 6.52 (s, 1H, H_{11}), 6.01 (d, J = 1.5Hz, 1H, H_{17a}), 5.98 (d, J = 1.5Hz, 1H, H_{17b}), 4.08 (q, J = 6.6Hz, 1H, H_{13}), 4.12 (m, 1H, H_{16a}), 3.92 (s, 3H, H_{19}), 3.90 (s, 3H, H_{18} or H_{20}), 3.59 (s, 3H, H_{18} or H_{20}), 3.59 (t, J = 10.8Hz, 1H, H_{16b}), 2.59 (dd, J = 14.4, 5.7Hz, 1H, H_{15a}), 2.52 (ddd, J = 14.4, 10.8, 1.5Hz, 1H, H_{15b}), 1.40 (d, J = 6.6Hz, 3H, H_{14}) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.2 (C_8 or C_{10}), 151.4 (C_8 or C_{10}), 147.8 (C_4 or C_5), 146.2 (C_4 or C_5), 140.8 (C_9), 137.4 (C_{12}), 135.7 (C_2), 128.9 (C_1), 126.2 (C_7), 110.3 (C_6), 108.0 (C_{11}), 105.2 (C_3), 101.3 (C_{17}), 72.0 (C_{13}), 69.9 (C_{16}), 61.2 (O*C*H$_3$), 60.9 (O*C*H$_3$), 56.2 (O*C*H$_3$), 37.2 (C_{15}), 21.4 (C_{14}) ppm; **IR** (neat) 2921, 2842, 1454, 1236, 1101, 1031 cm^{-1}; **HRMS** (ESI) calculated for $C_{20}H_{22}O_6Na^+$ [(M+Na)$^+$] 381.1314, found 381.1322.

D) Figure S1. X-ray crystal structure of racemic biphenyl (*S*,a*R*)-**7a** (thermal ellipsoid plot at 30% probability).



E) Figure S2: Superimposition of circular dichroism spectra of N-acetylcolchinol **3** and target compounds **4a-d**

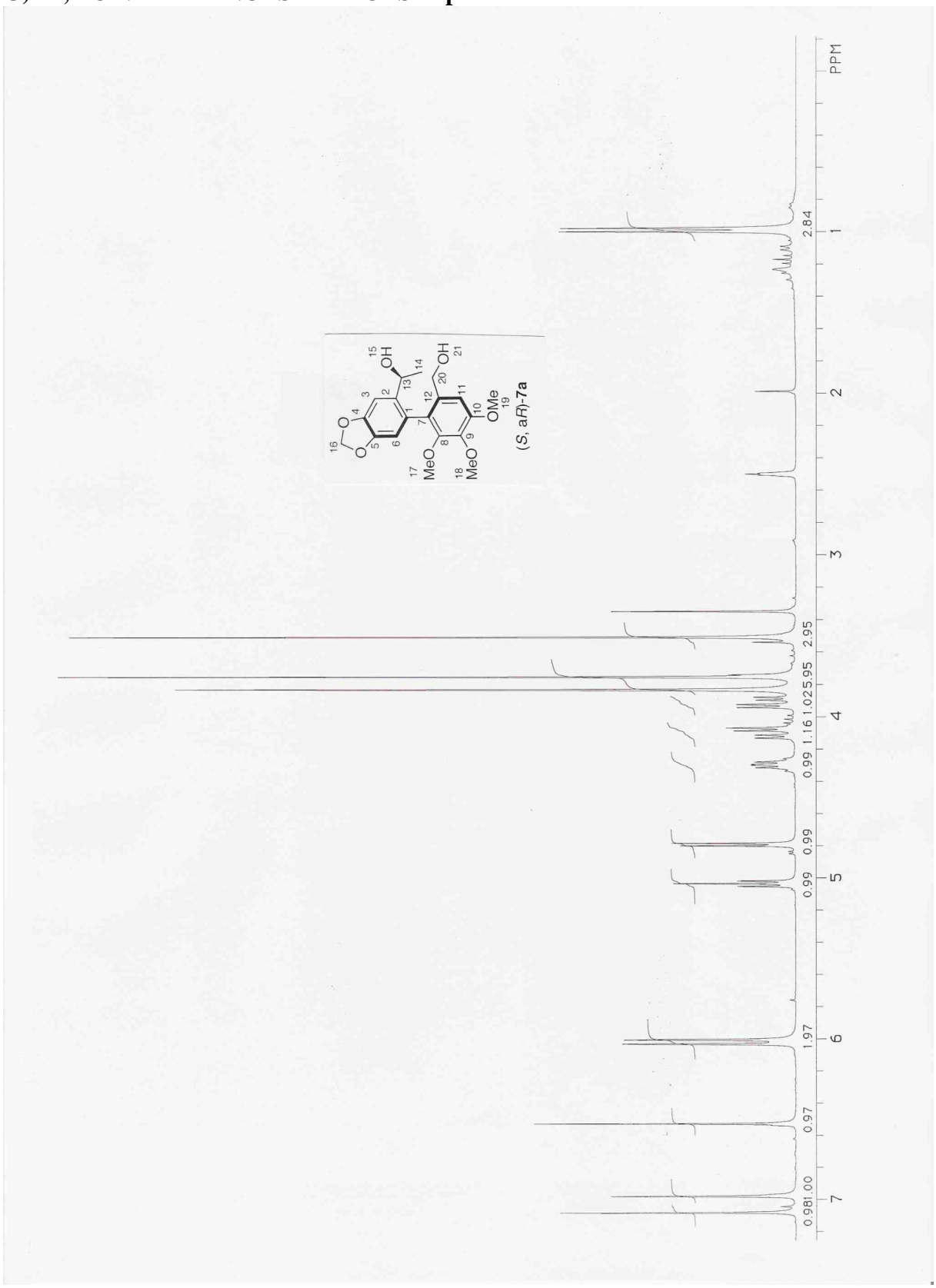


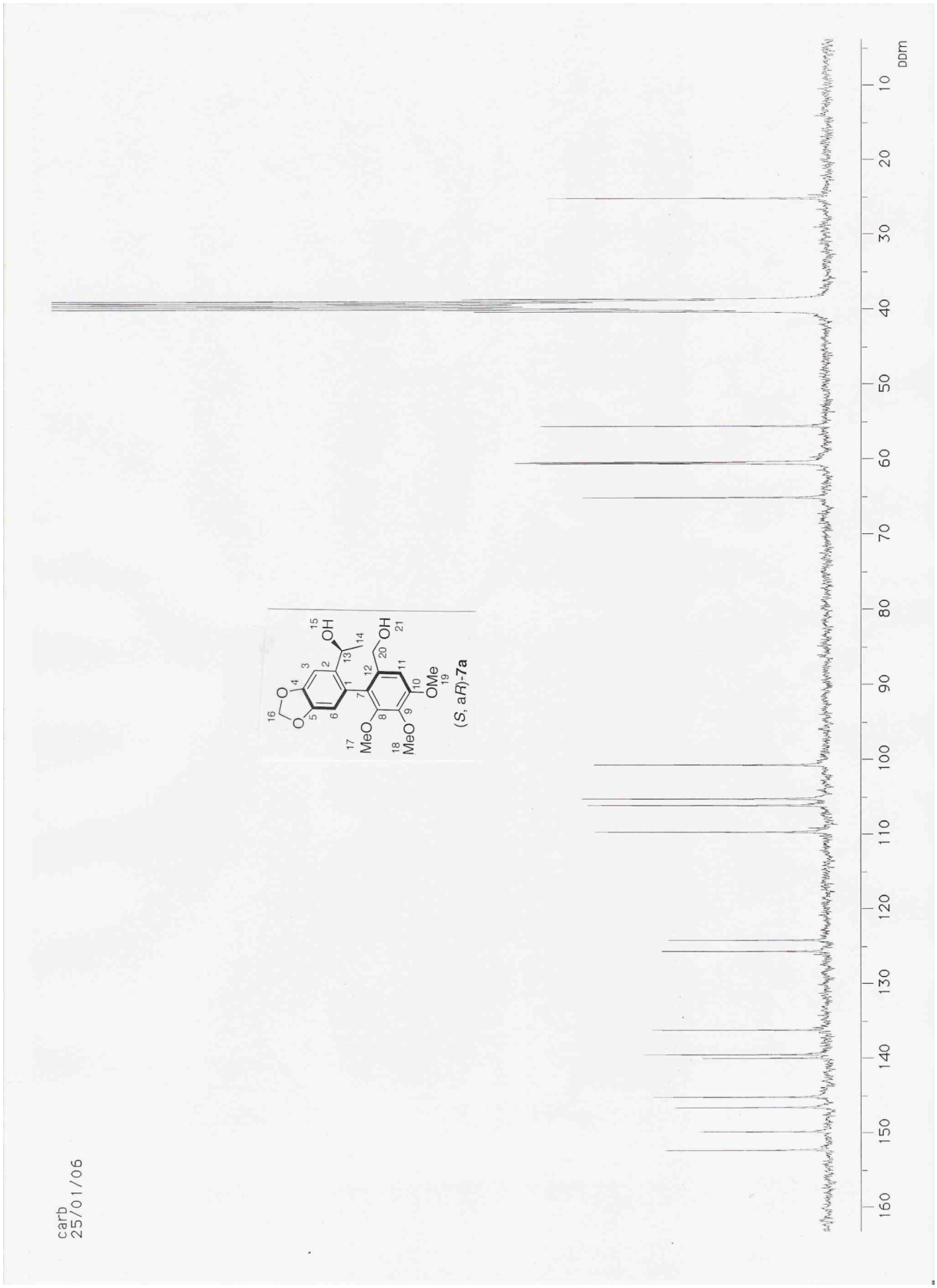
F) Inhibition of microtubule assembly[7]

The drug, dissolved in DMSO at different concentrations, was pre-incubated with a solution of tubulin at 37 °C for 10 min, then the solution was cooled to 0°C for 5 min in order to achieve complete tubulin depolymerization. The solution was then placed in a temperature-controlled cell at 37 °C (microtubule assembly) and the increase of the optical density was monitored in a UV spectrophotometer at 350 nm for 1 min. The maximum rate of assembly was recorded and compared to a sample without drug. The IC_{50} is the concentration of compound required to inhibit 50% of the rate of microtubule assembly. It was calculated from the effect of several concentrations and compared to the IC_{50} of colchicine obtained within the same day with the same tubulin preparation. Reported values are averages of three experiments.

[7] F. Zavala, D. Guénard, J.-P. Robin, E. Brown, *J. Med. Chem*. **1980**, *23*, 546-549.

G) ^{1}H, ^{13}C NMR and NOESY or ROESY spectra for 7a-d and 4a-d

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25/01/06
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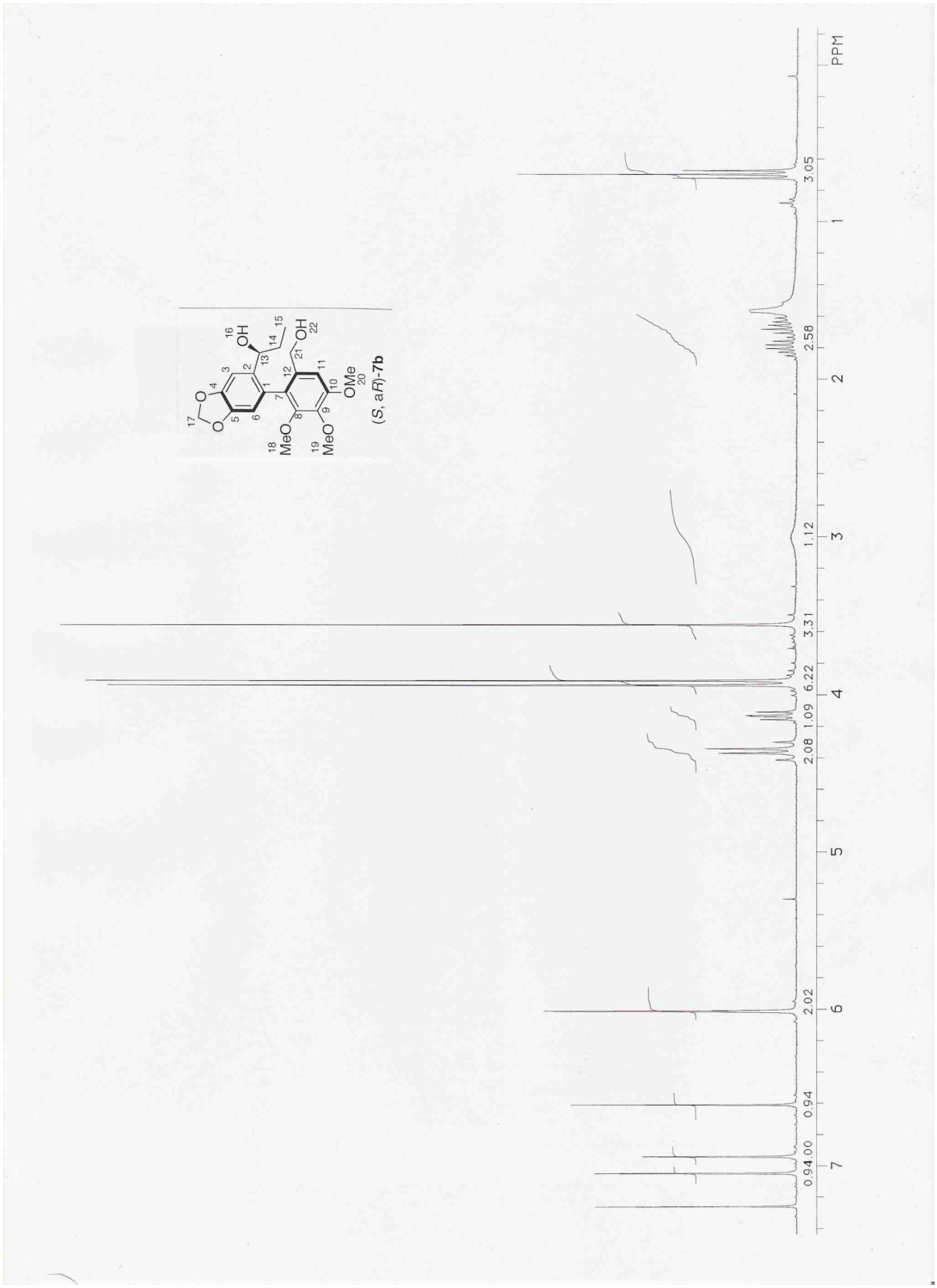
ppm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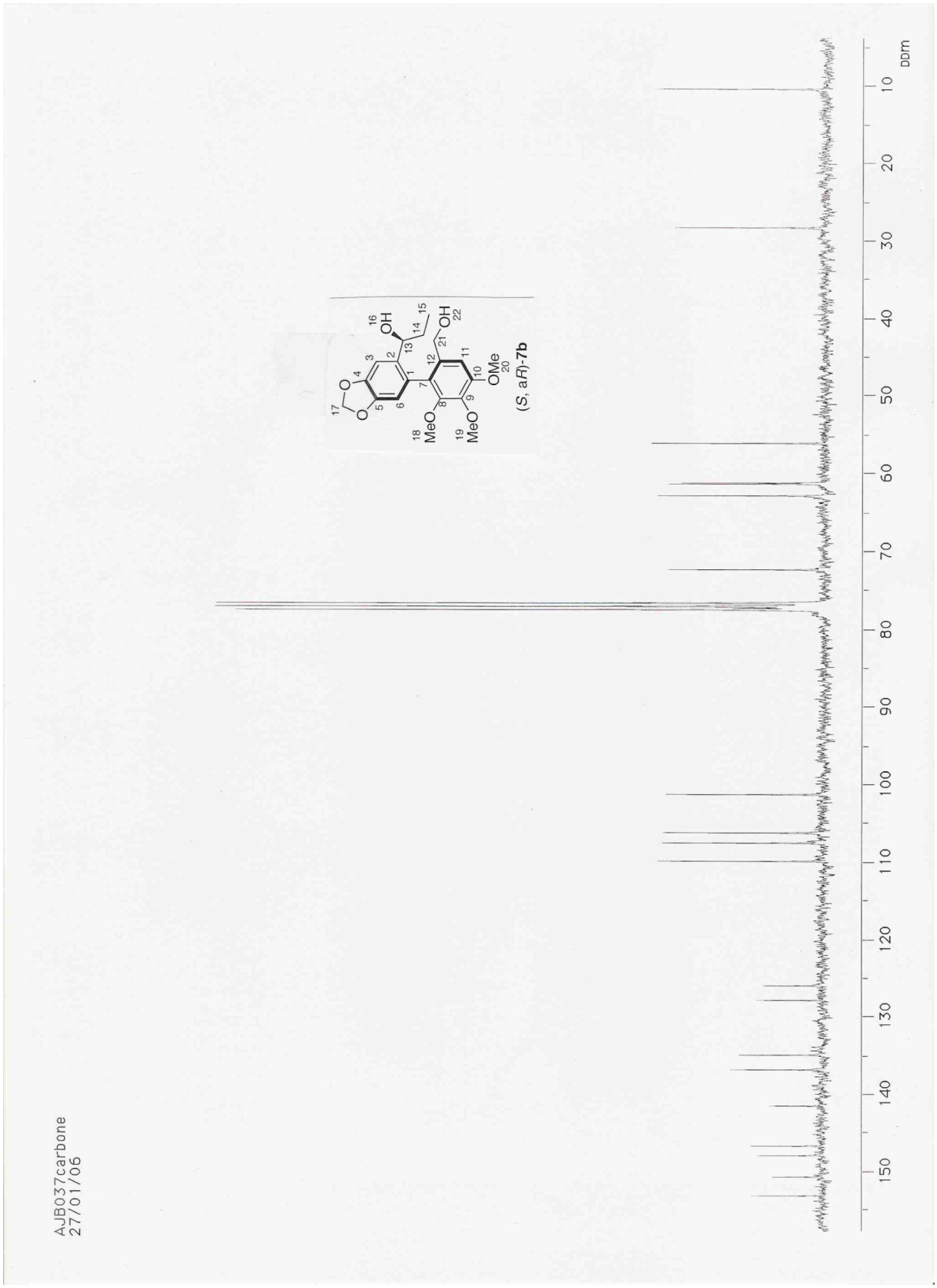
1.09
6.22
3.31
1.12
2.58
3.05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27/01/06
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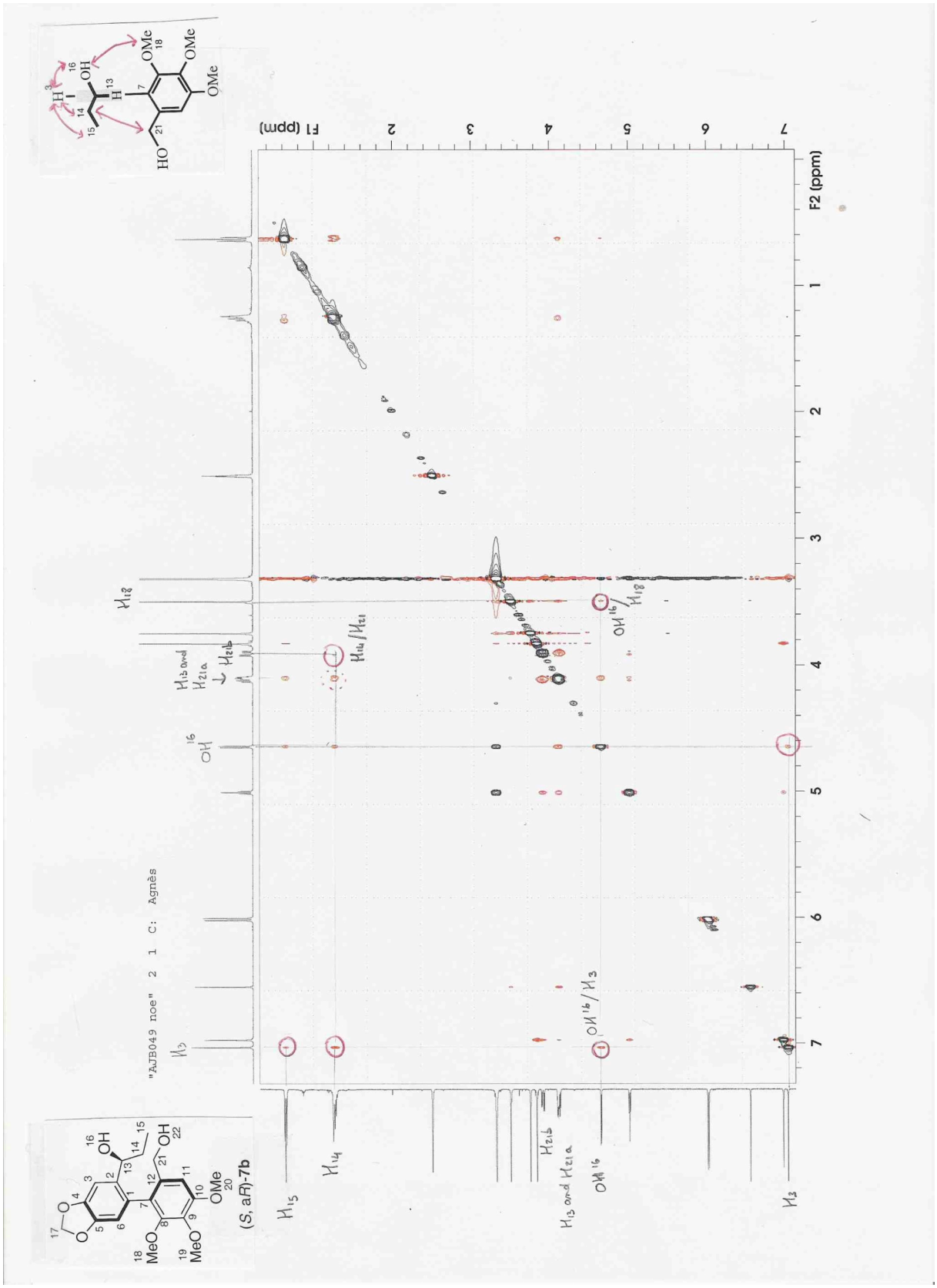
ppm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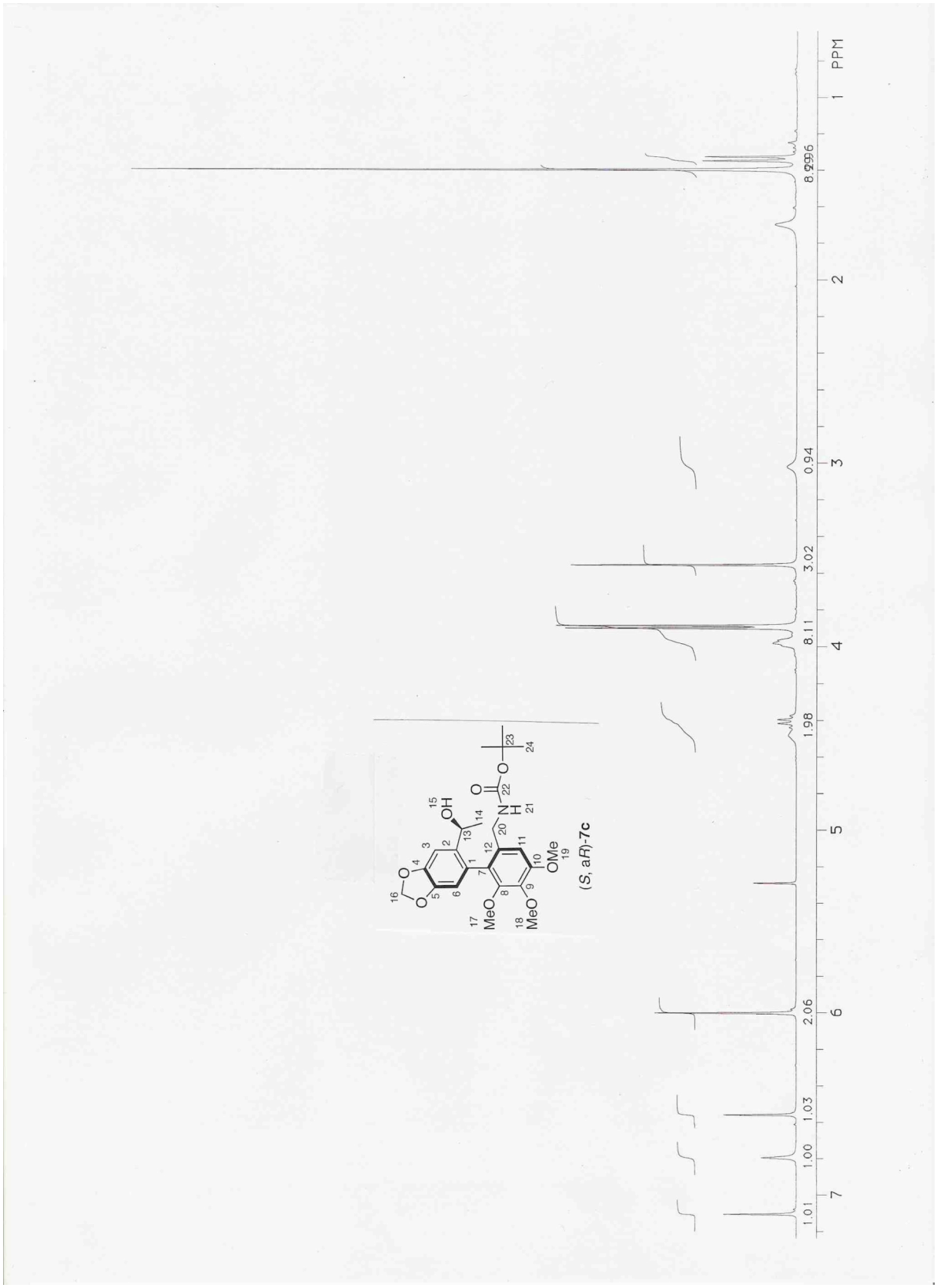
F1 (ppm)
F2 (ppm)
(S, aR)-7b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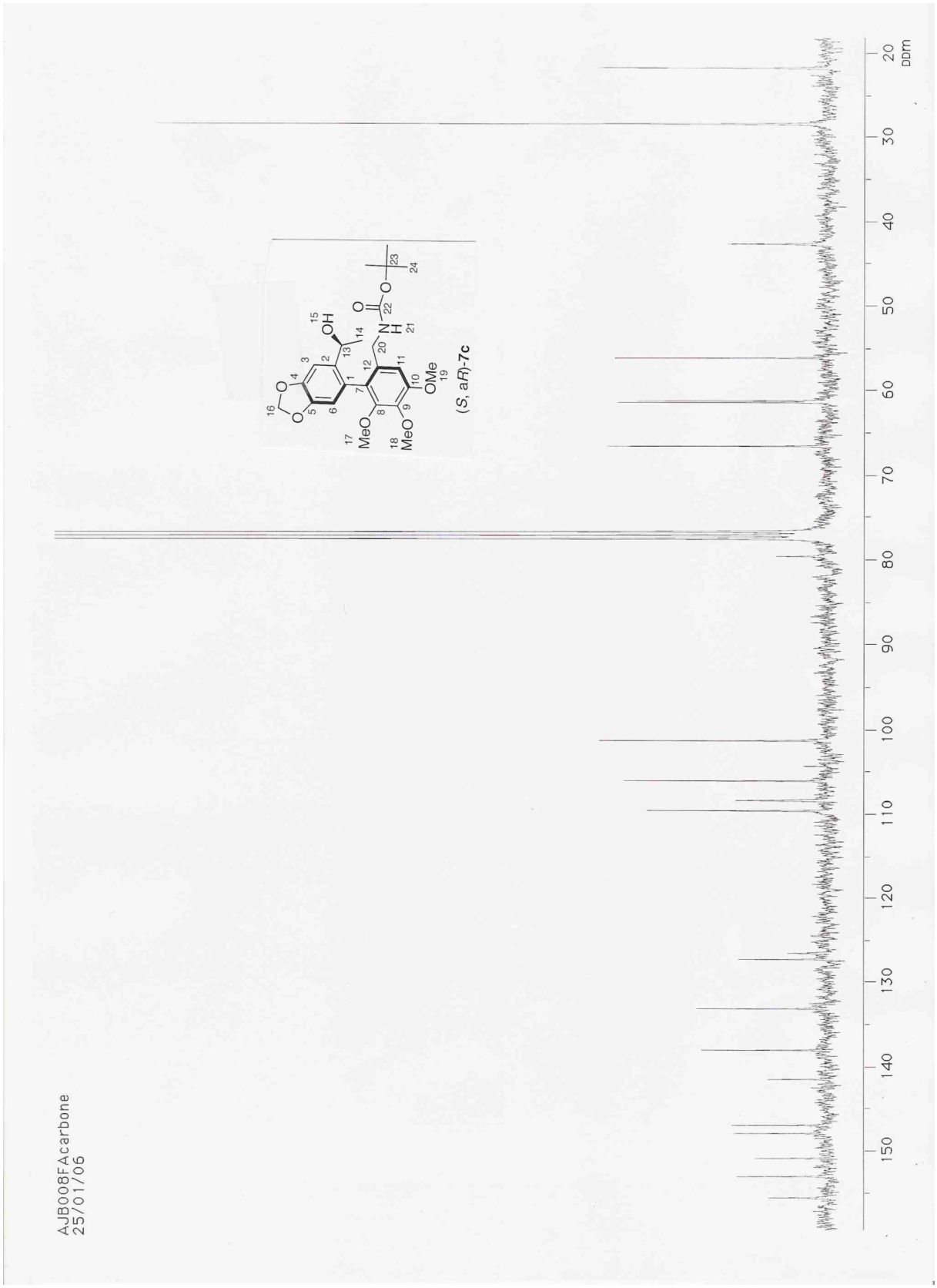
2.06
1.98
8.11
3.02
0.94
8.996
PPM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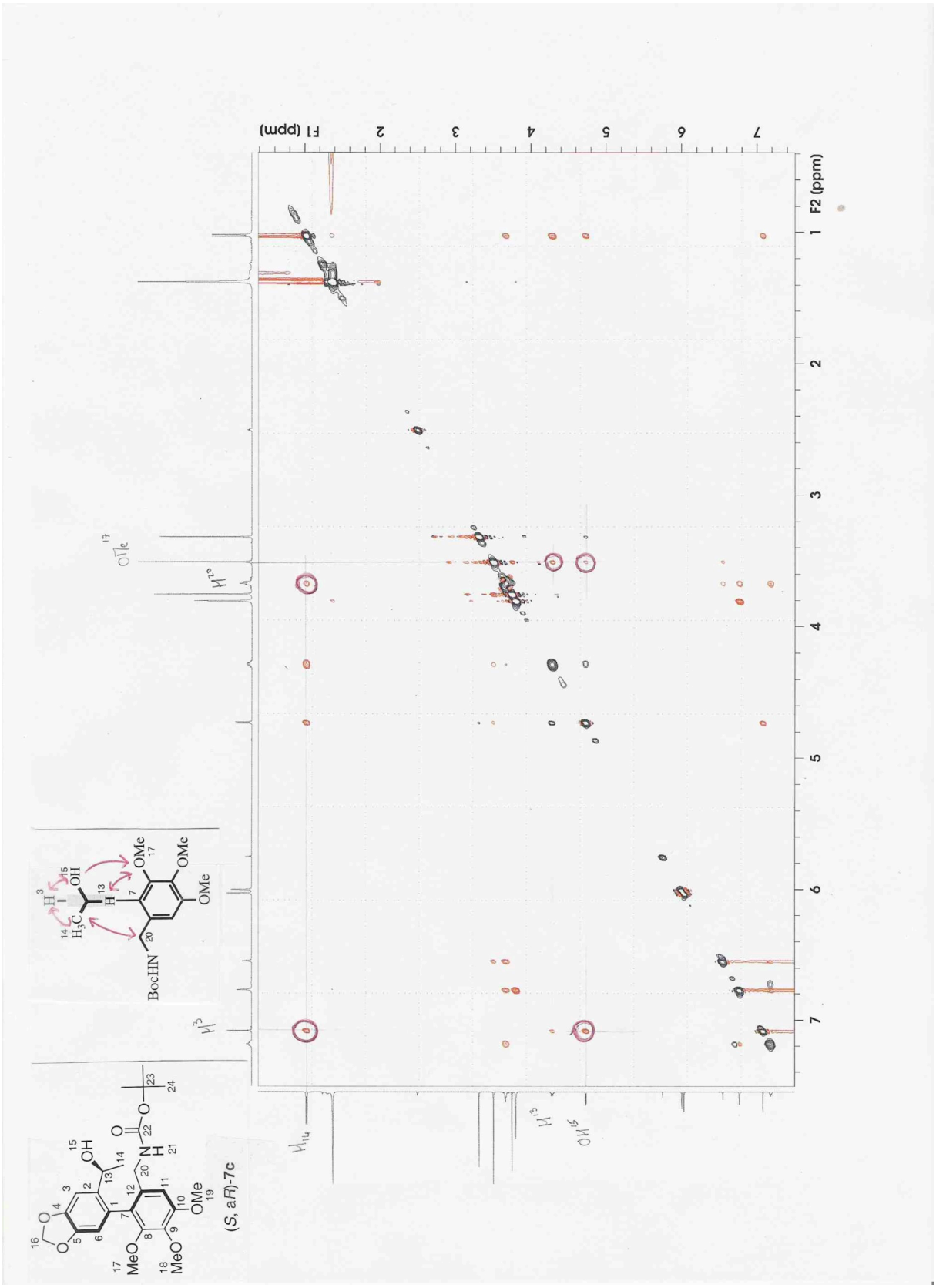
NH
O
ppm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OMe
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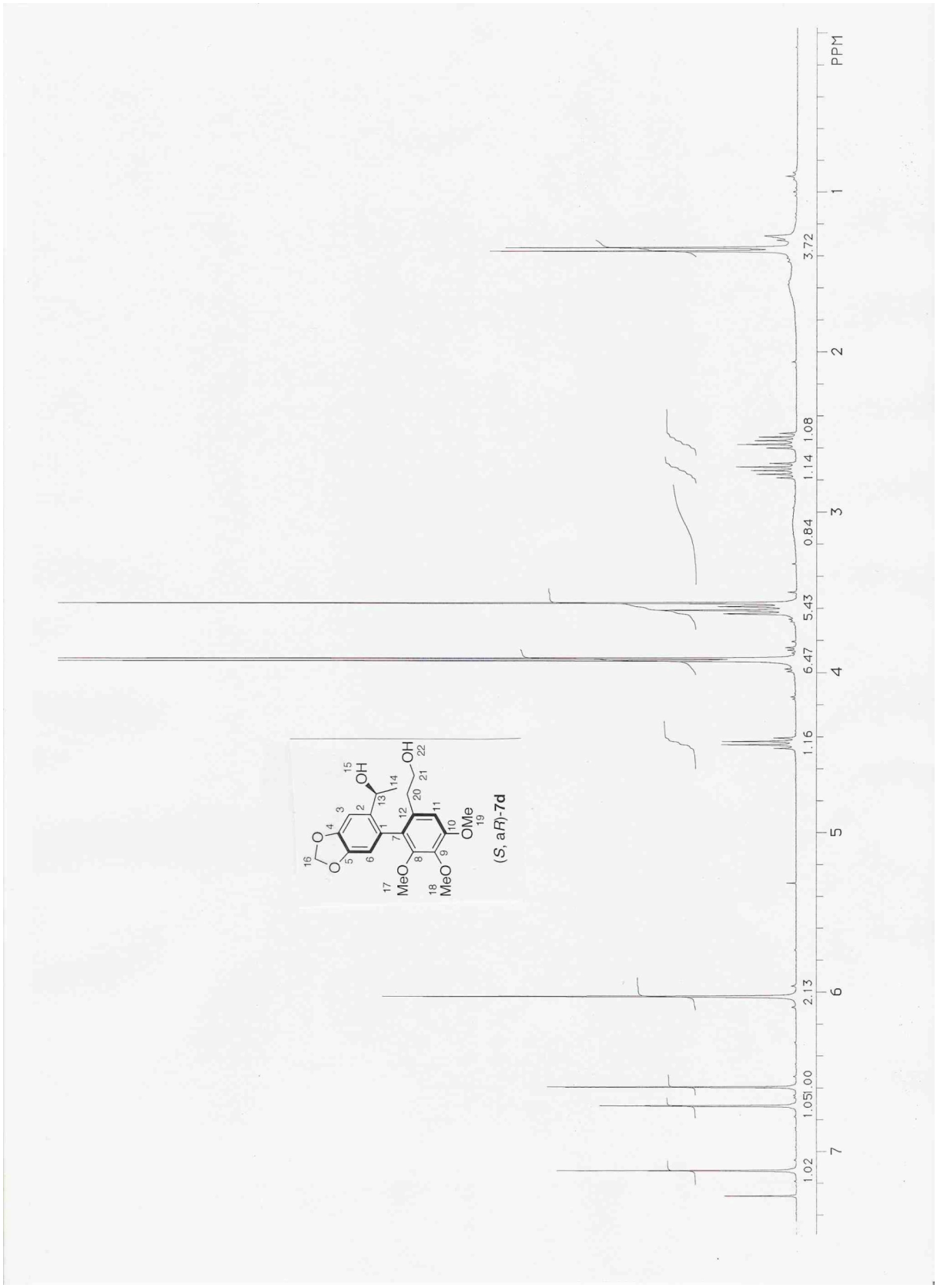
NH
OH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2.13
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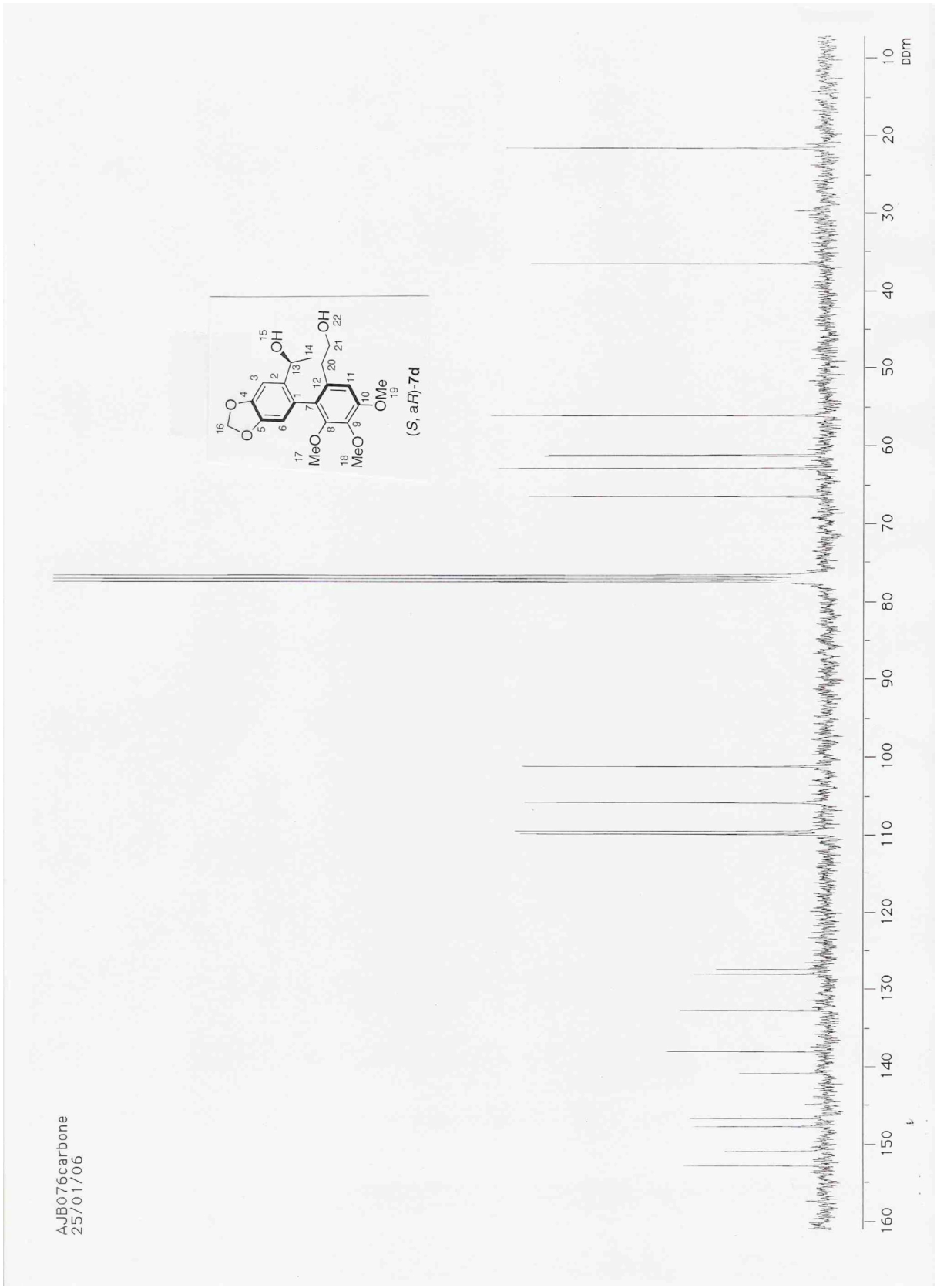
6.47
5.43
0.84
1.14
1.08
3.72
PPM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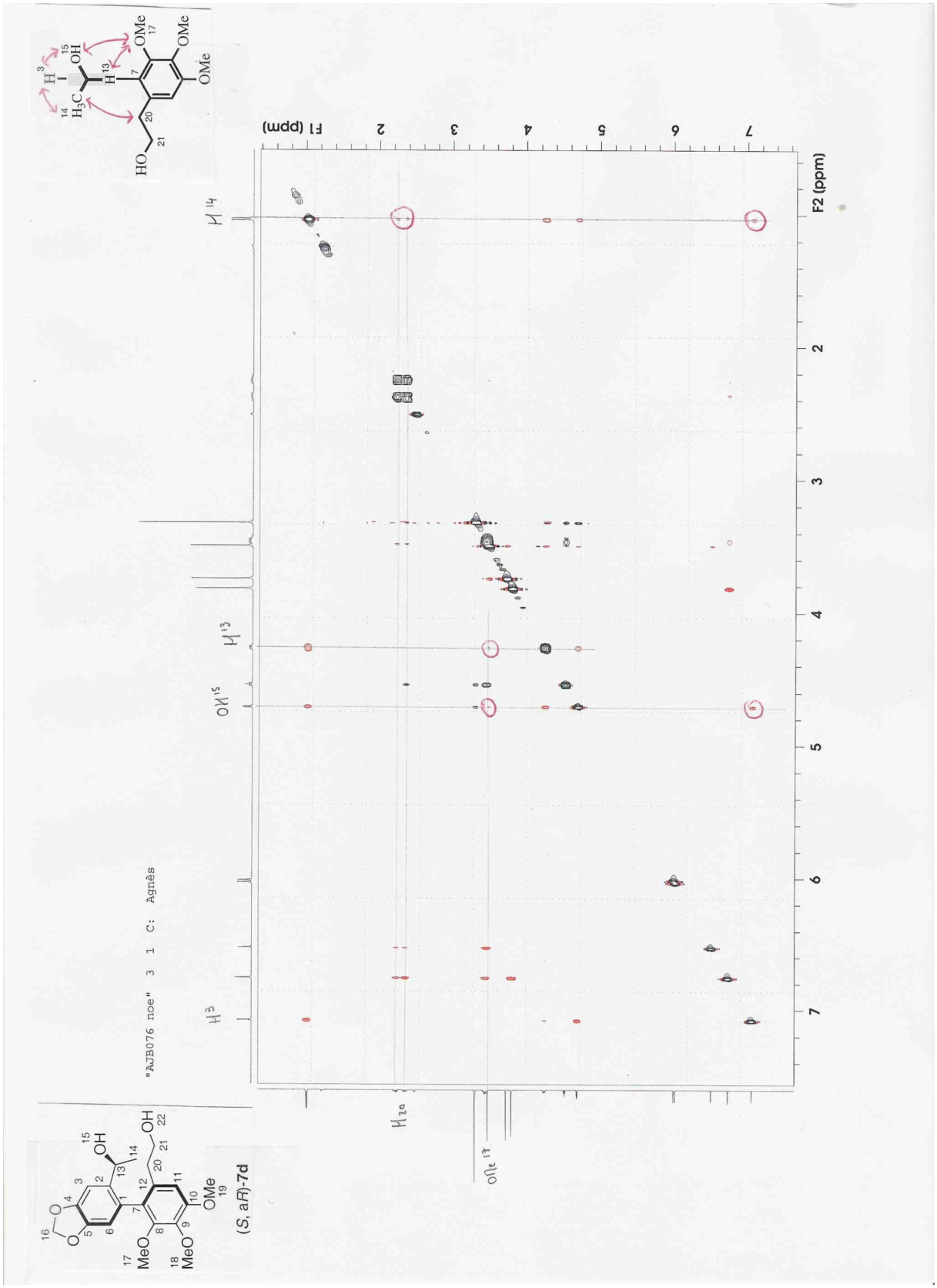
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F1 (ppm)
F2 (ppm)
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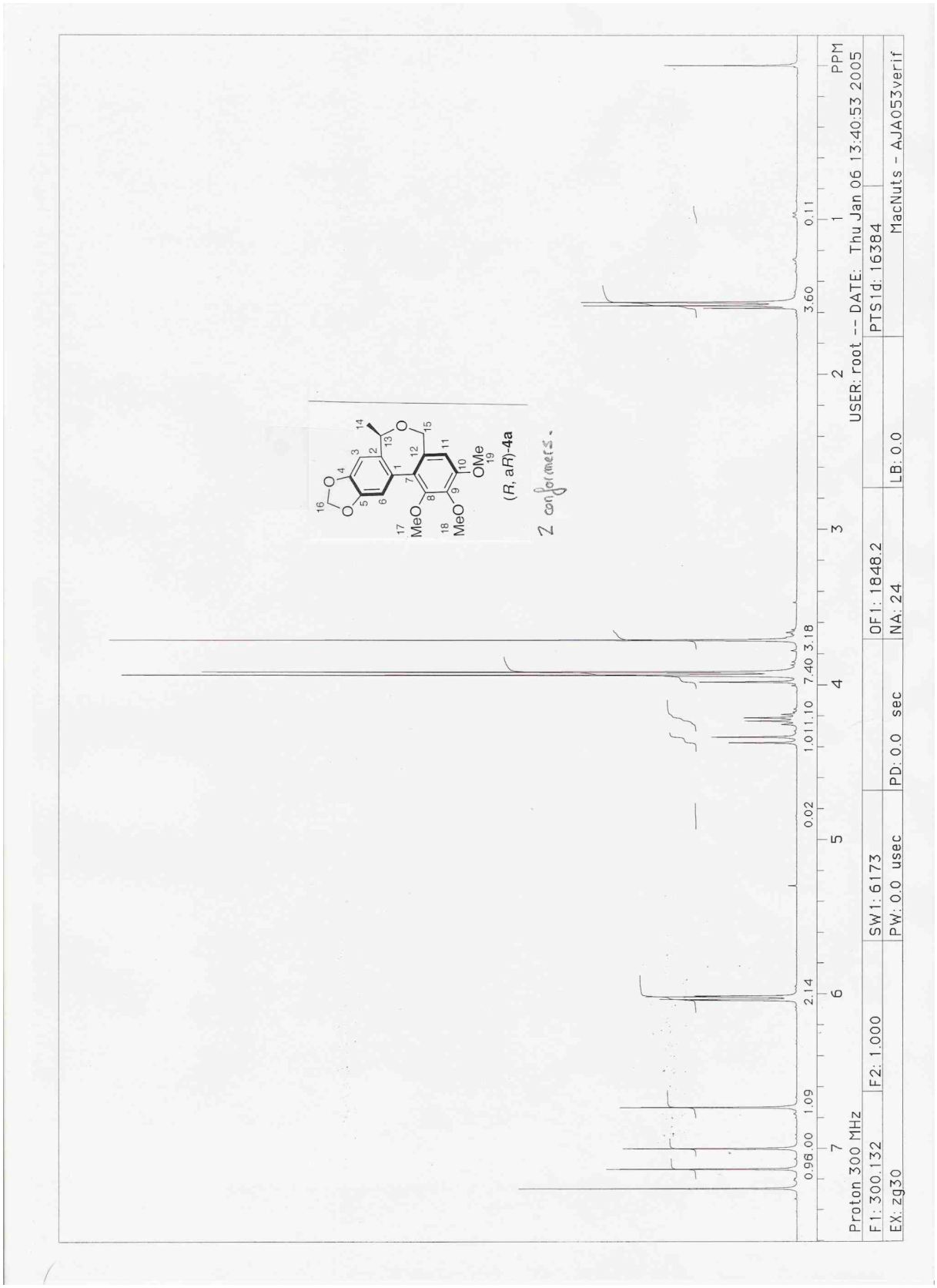
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2 conformers.
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PTS1d: 16384
EX: zg30
PW: 0.0 usec
PD: 0.0 sec
NA: 24
LB: 0.0
MacNuts - AJA053verif
USER: root -- DATE: Thu Jan 06 13:40:53 2005
PPM
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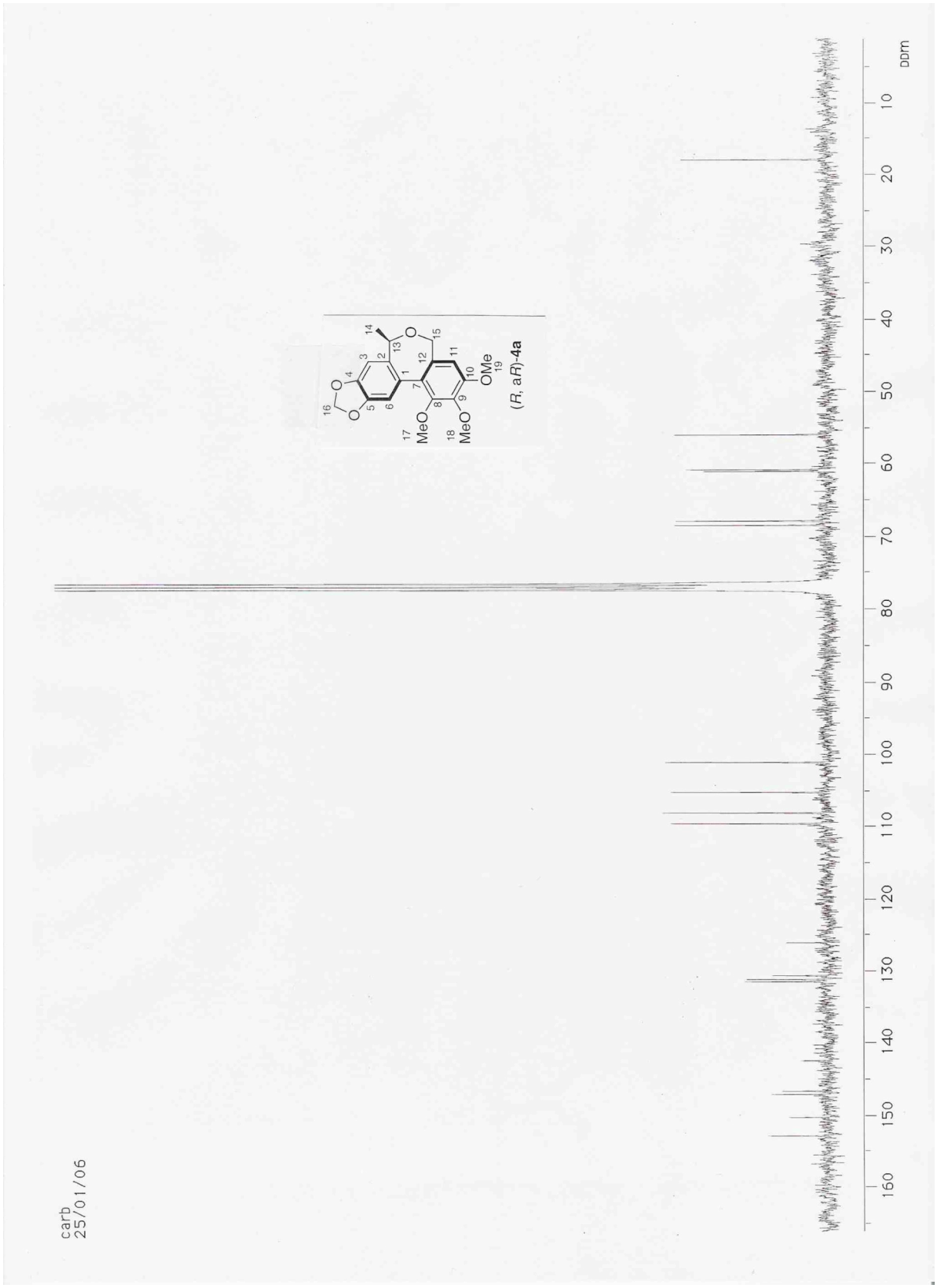
carb
25/01/06
ppm
(R, aR)-4a


INTERCONVERTING ATROPISOMERS.
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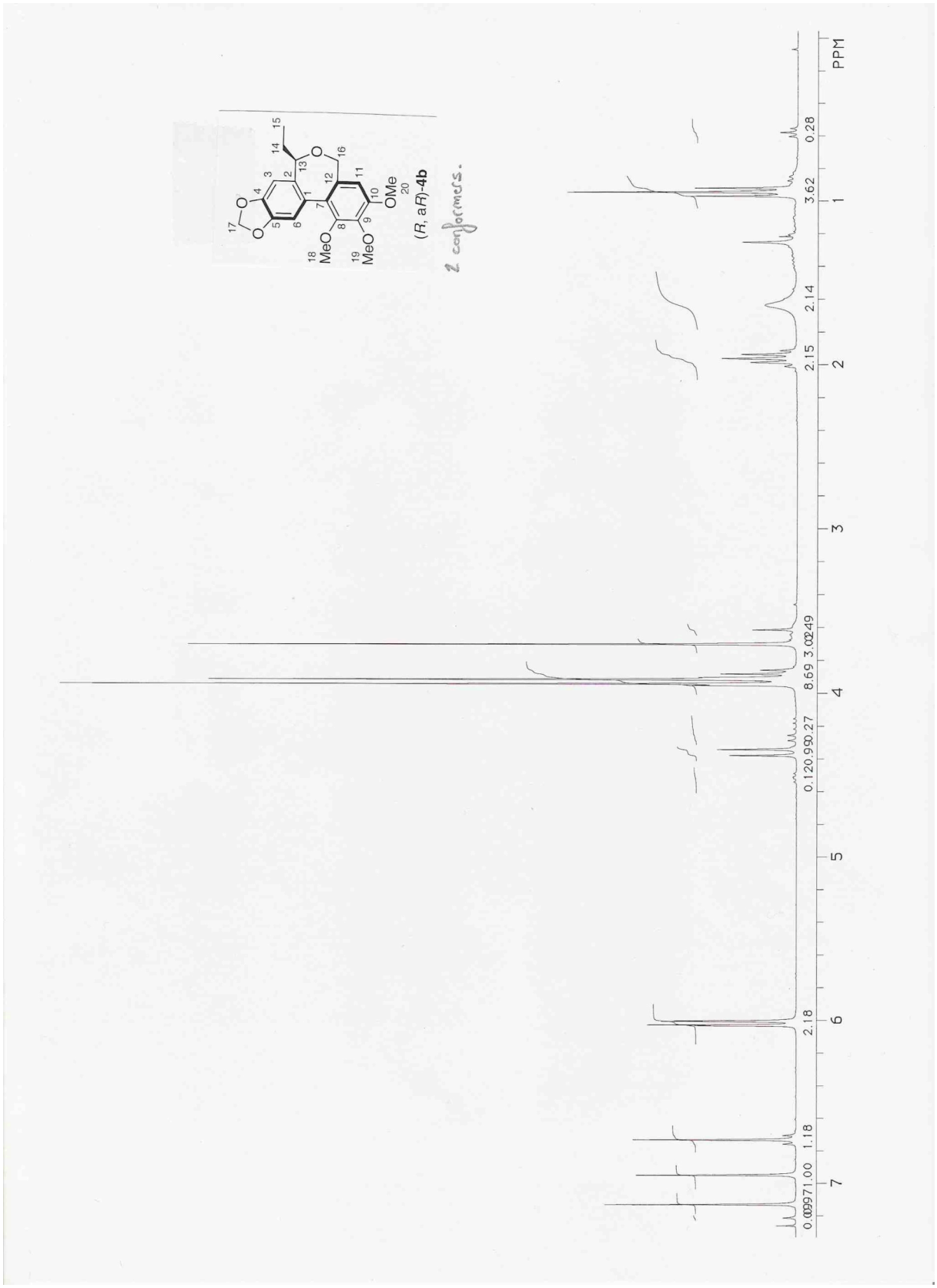
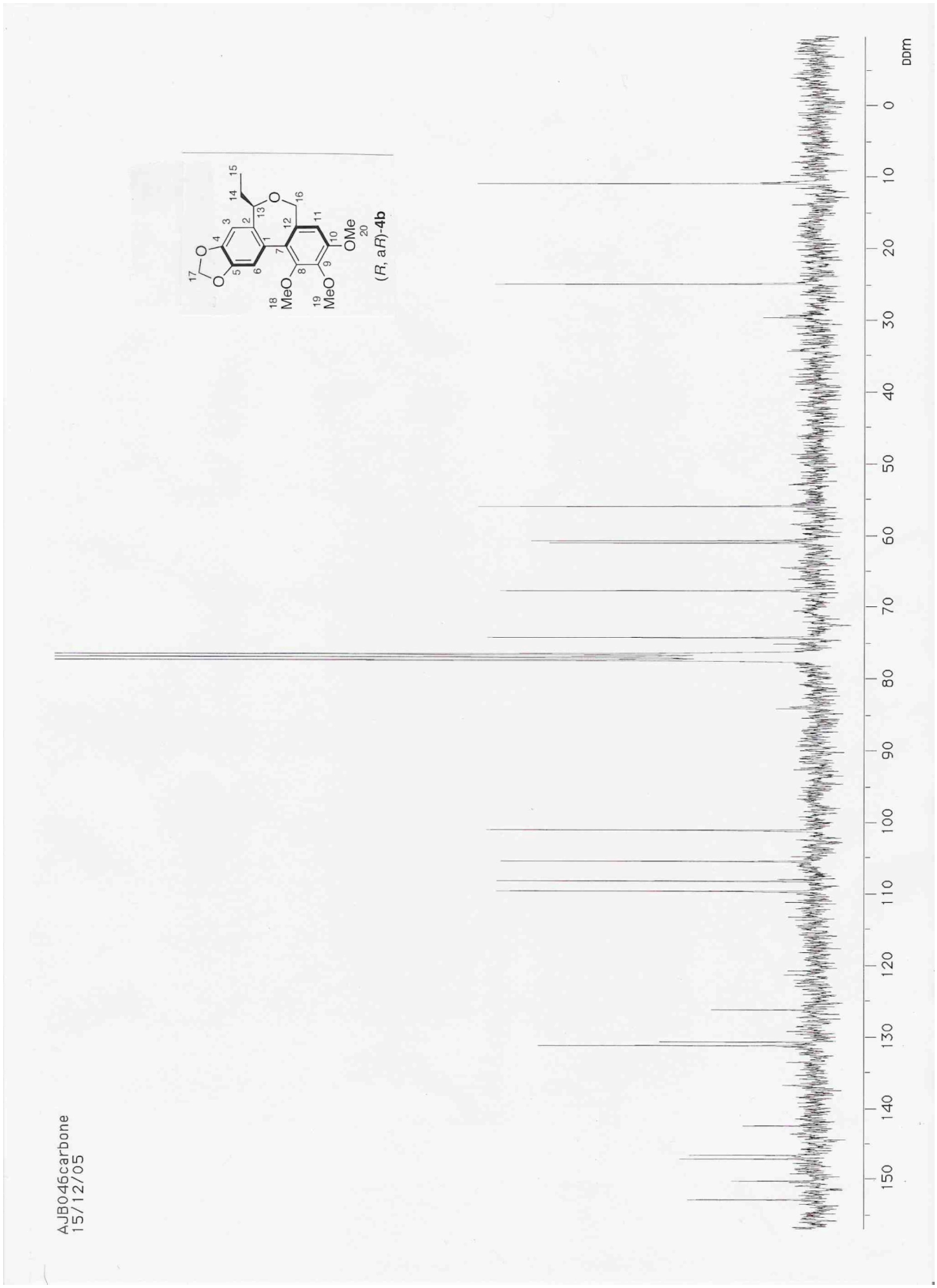
F2 (ppm)
(R, aR)-4a


(R, aR)-4b
2 conformers.
PPM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15/12/05
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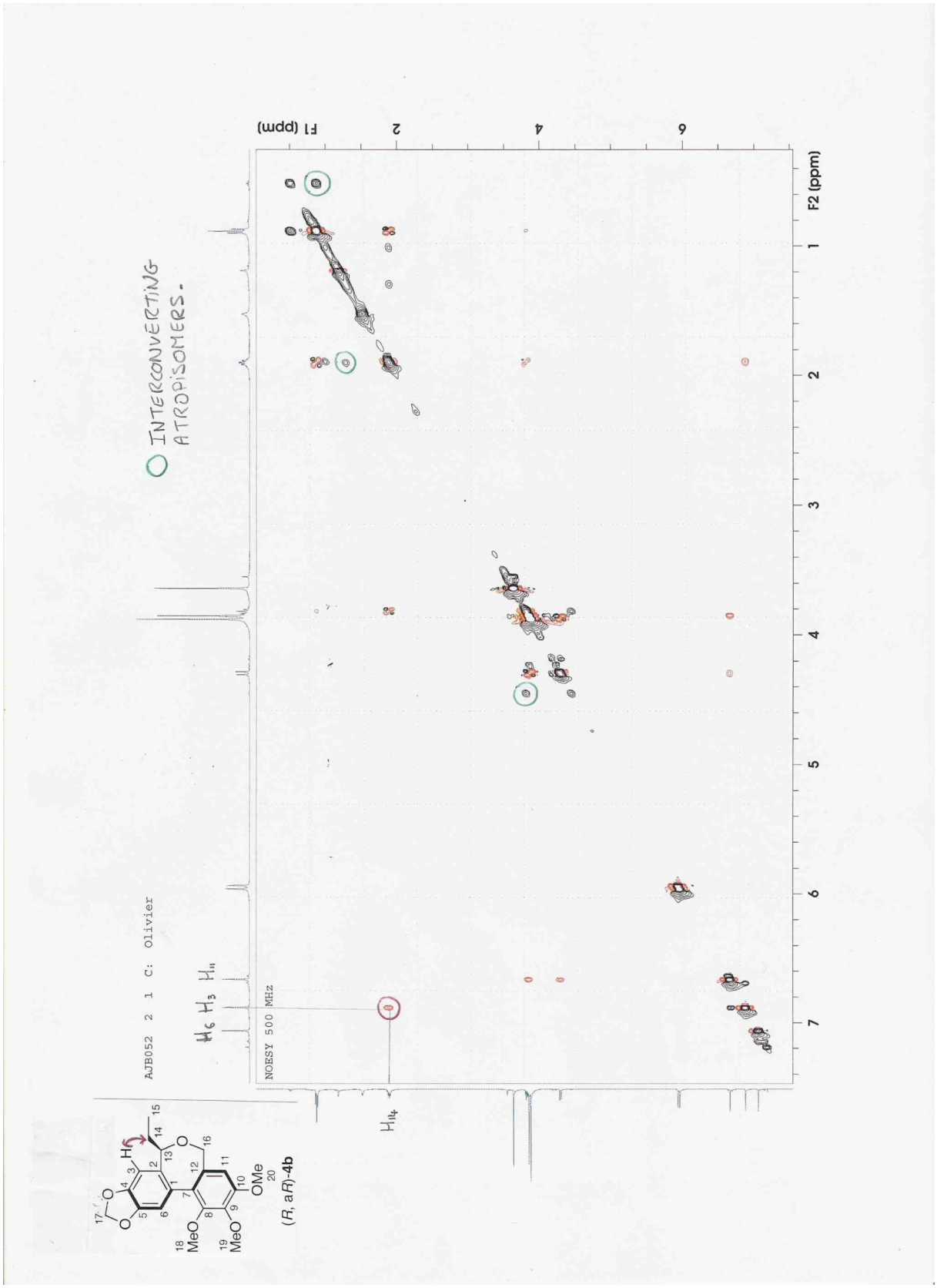
OMe
ppm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NOESY 500 MHz
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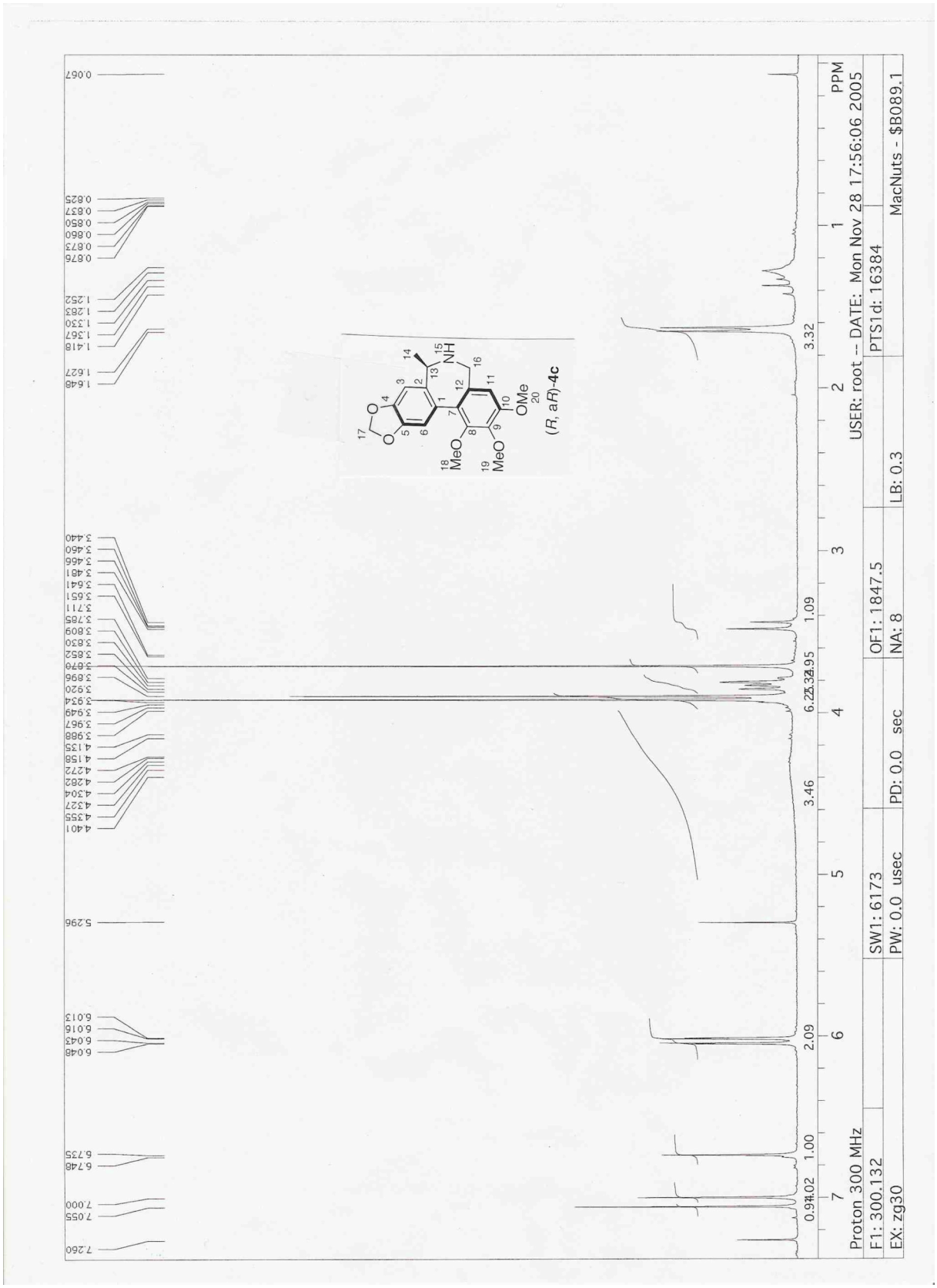
F2 (ppm)
(R, aR)-4b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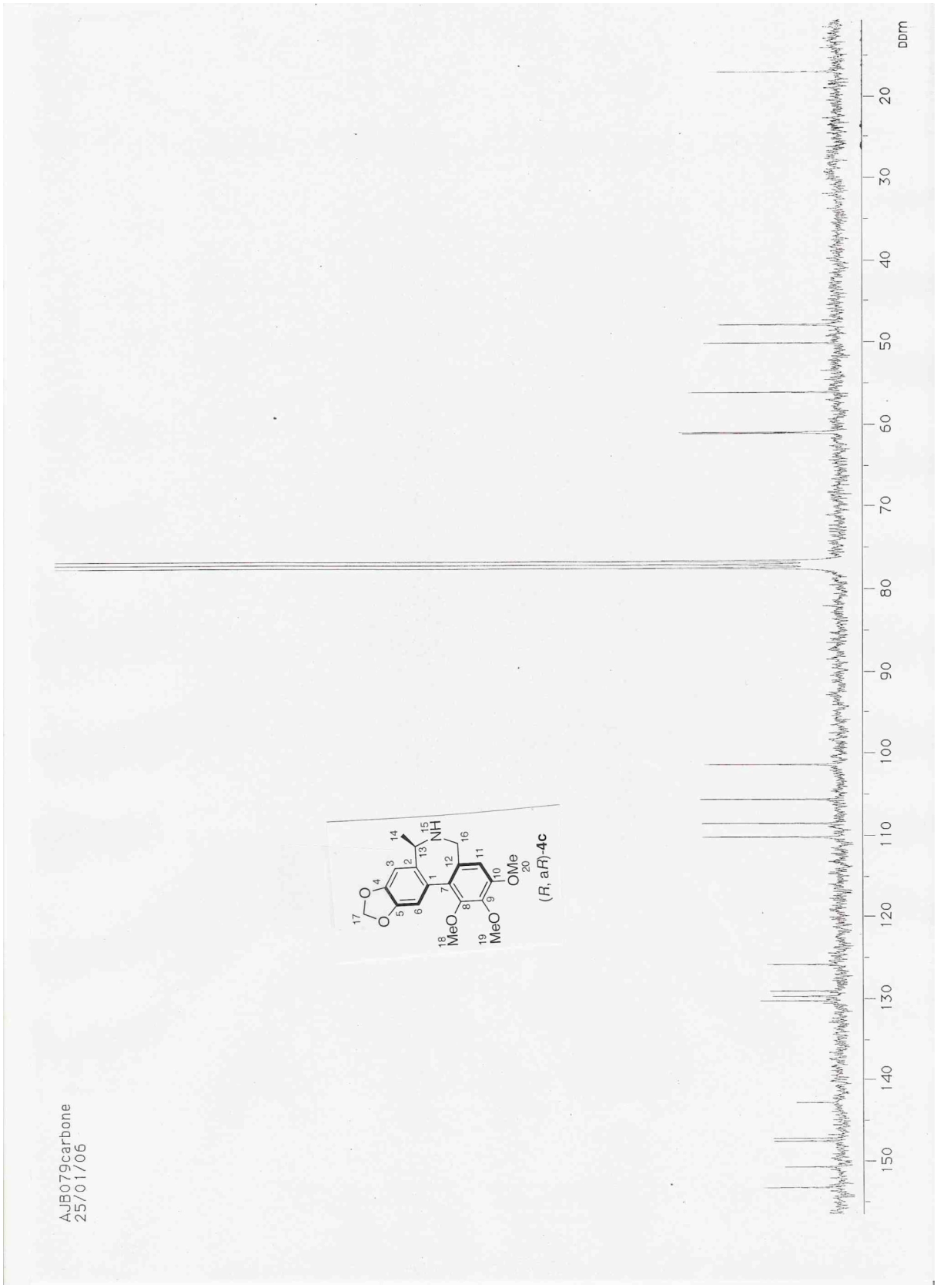
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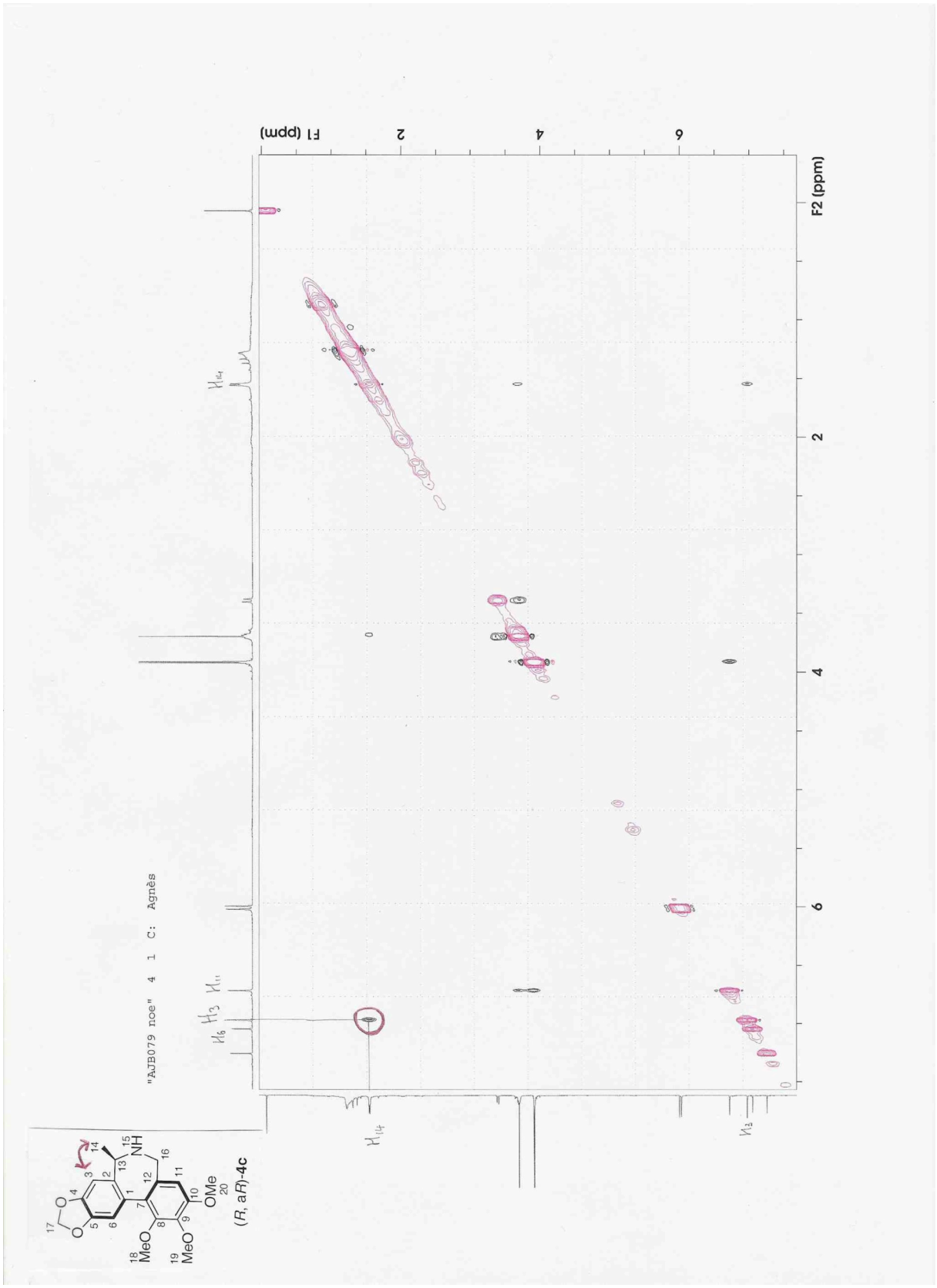
25/01/06
(R, aR)-4c
ppm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F2 (ppm)
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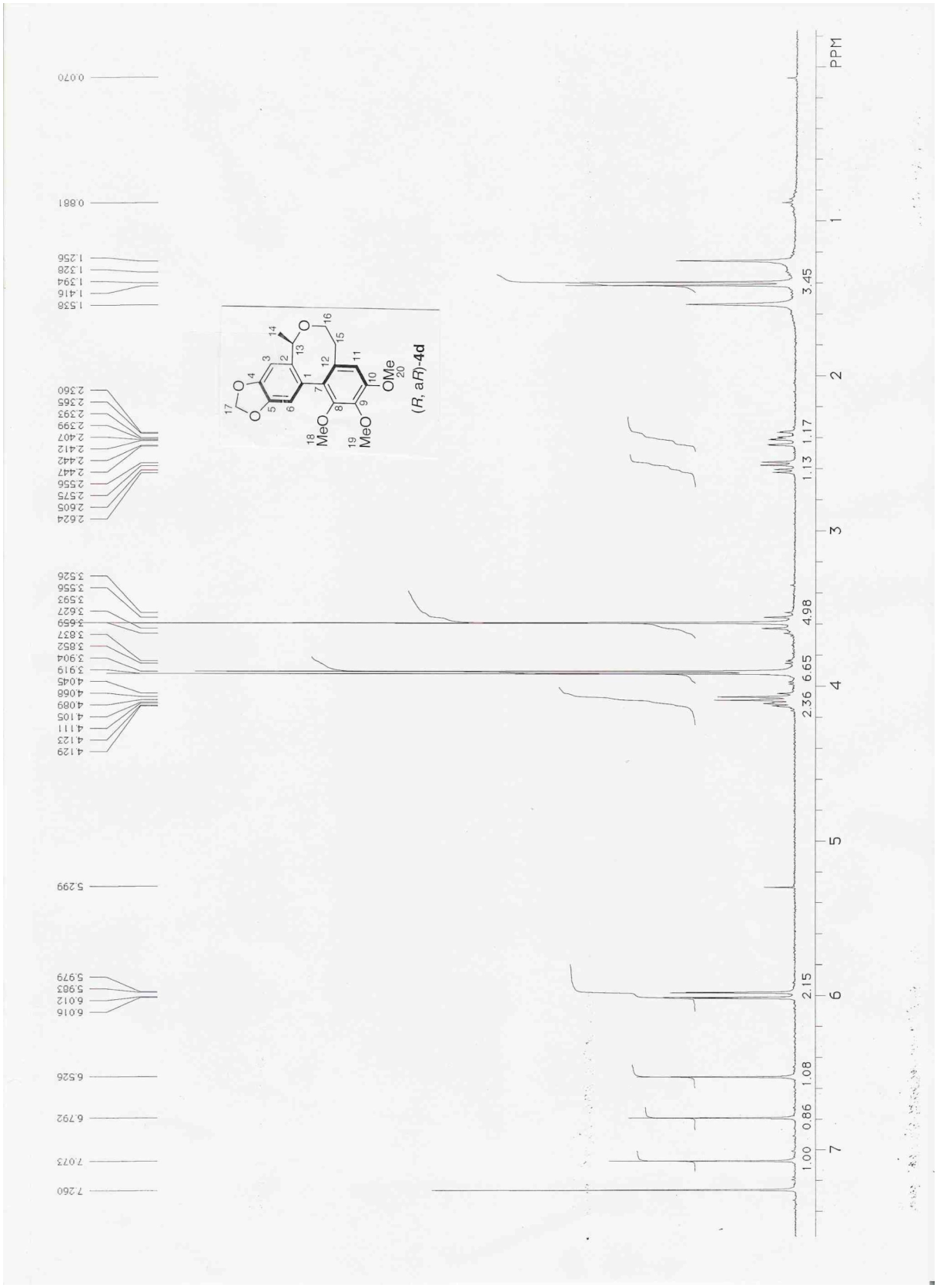
(R, aR)-4c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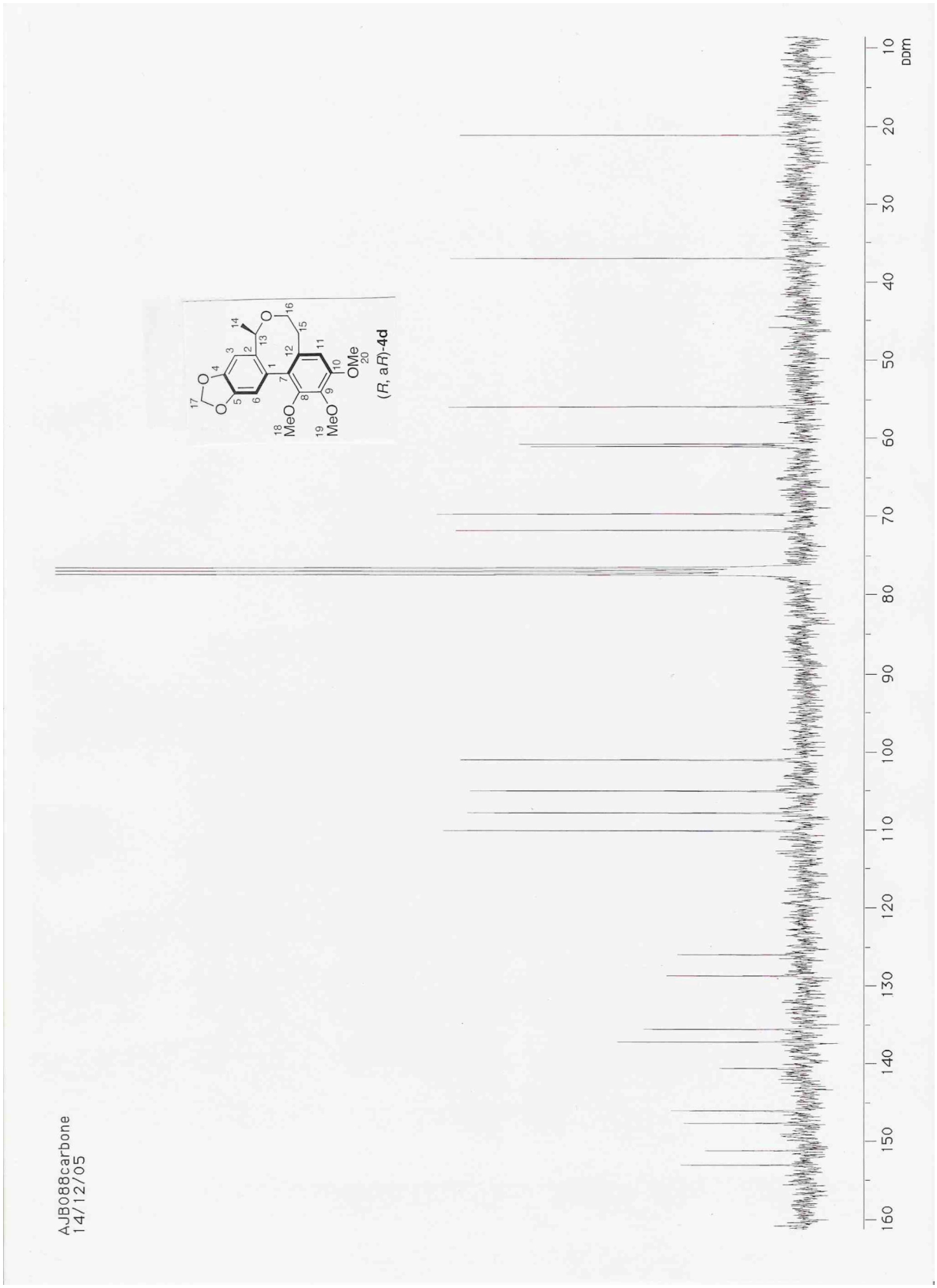
MeO
OMe
PPM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14/12/05
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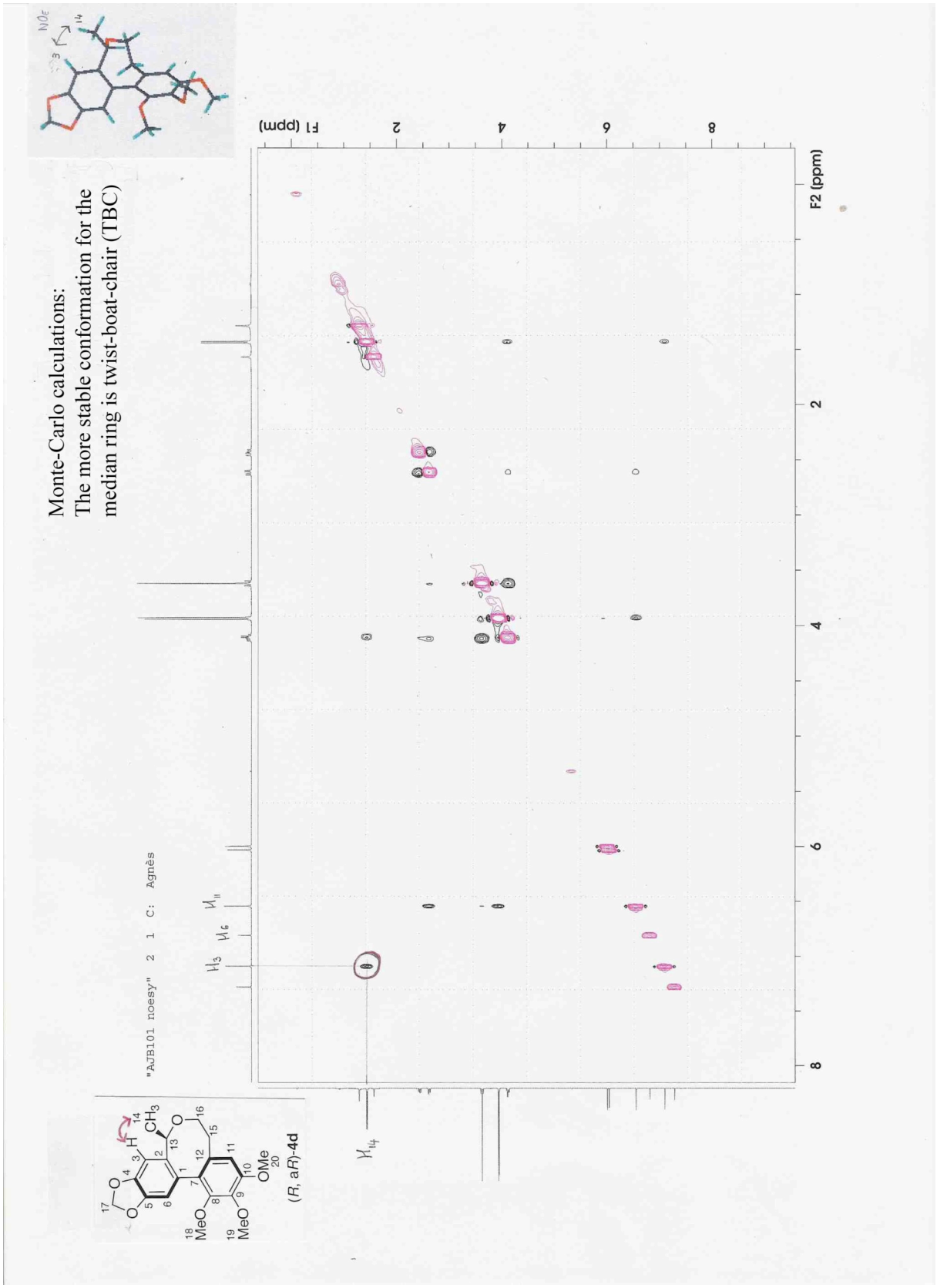
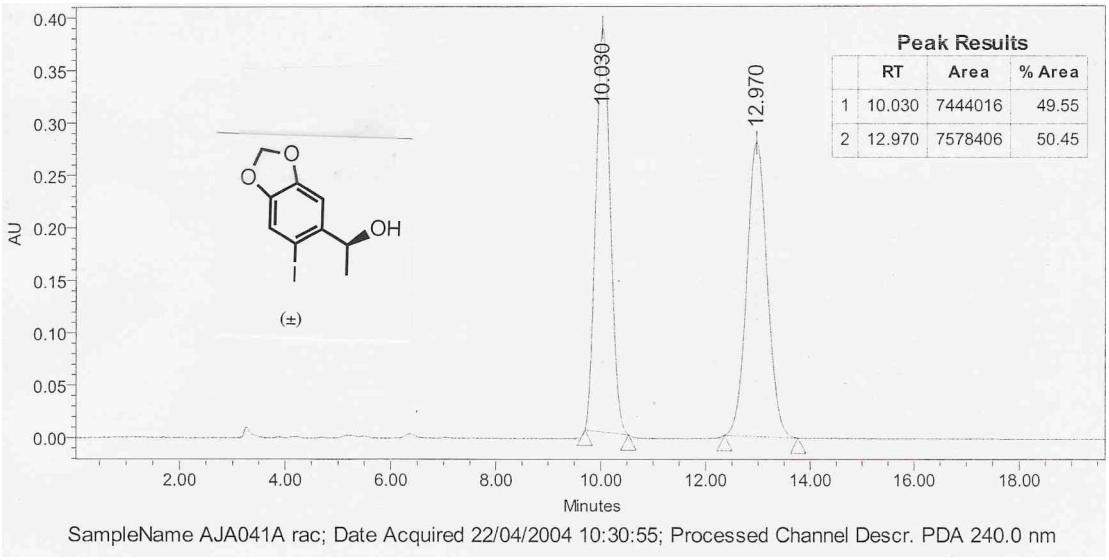
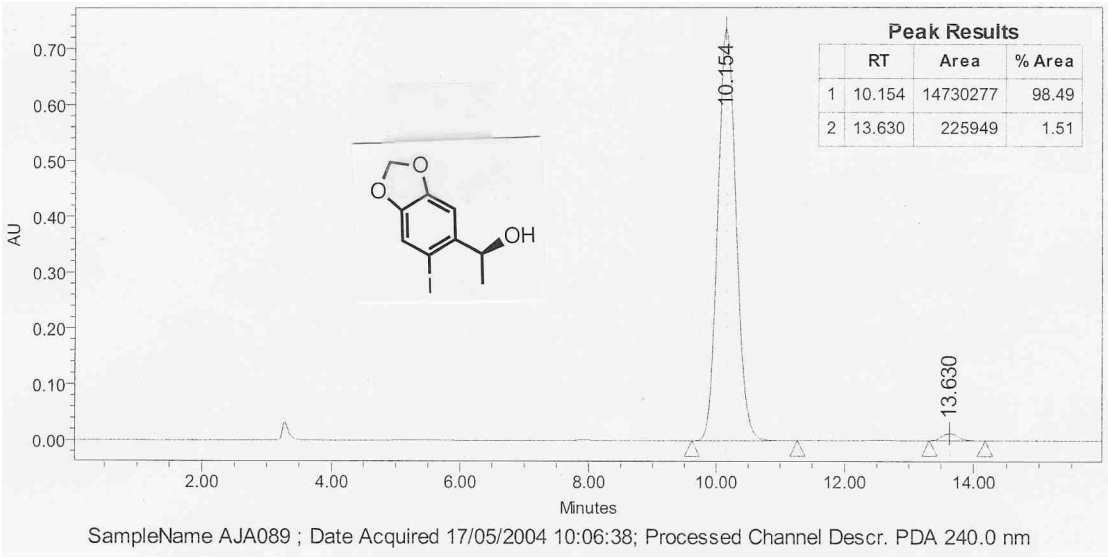
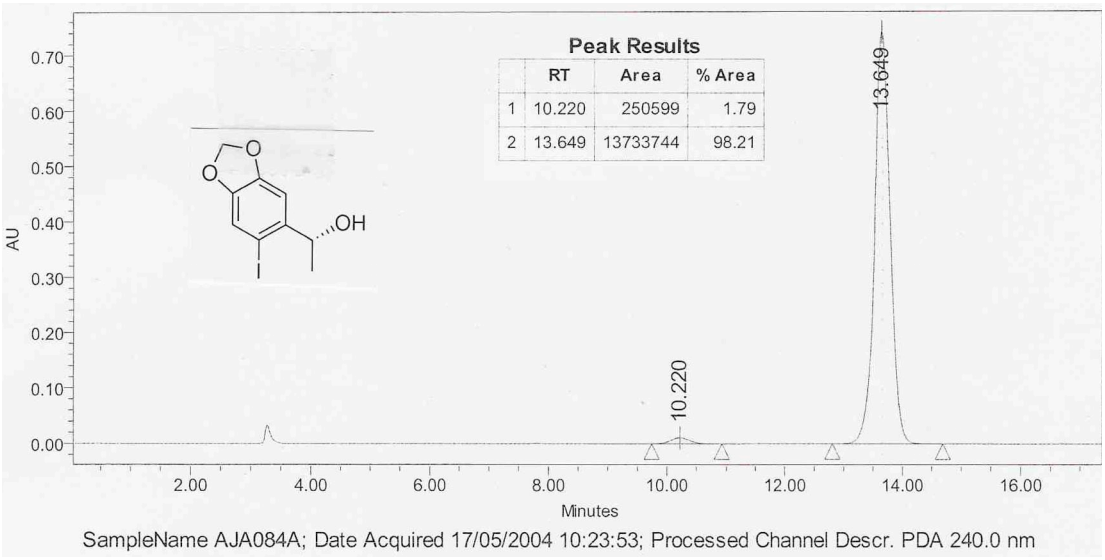
ppm

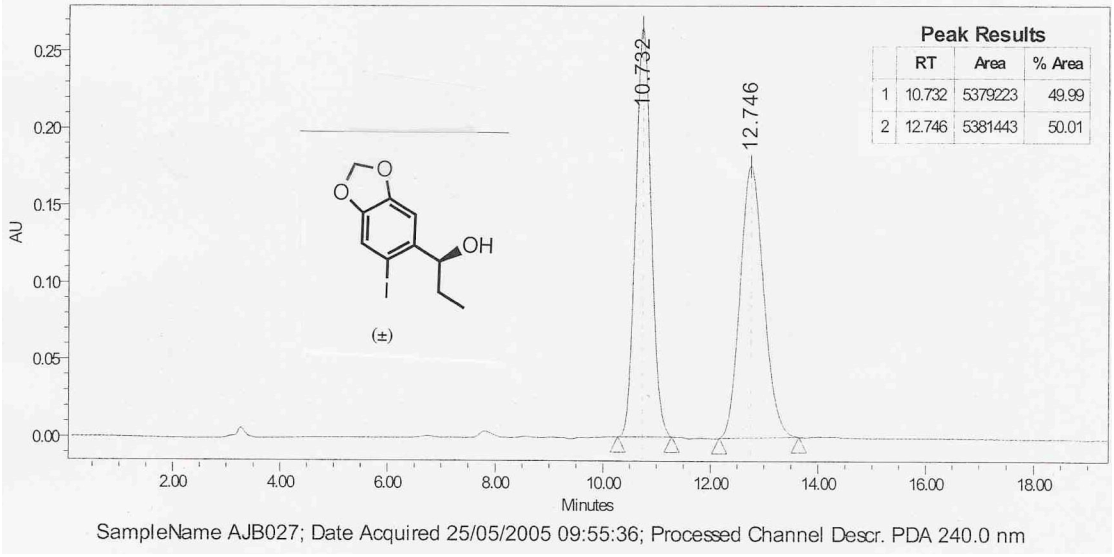

Monte-Carlo calculations:
The more stable conformation for the median ring is twist-boat-chair (TBC)
"AJB101 noesy" 2 1 C: Agnès
F1 (ppm)
F2 (ppm)
(R, aR)-4d

HPLC spectra for (*S*)-5a, (*R*)-5a, (*S*)-5b and cyclic compounds








Peak Results
RT Area % Area
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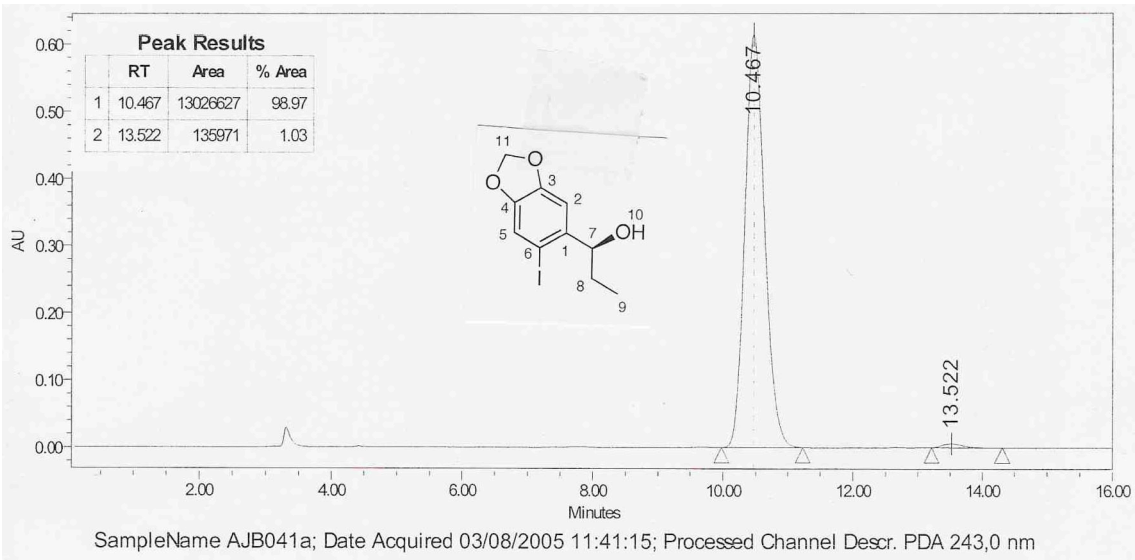
2 12.746 5381443 50.01
10.732
12.746
OH
(±)
AU
Minutes
SampleName AJB027; Date Acquired 25/05/2005 09:55:36; Processed Channel Descr. PDA 240.0 nm


Peak Results
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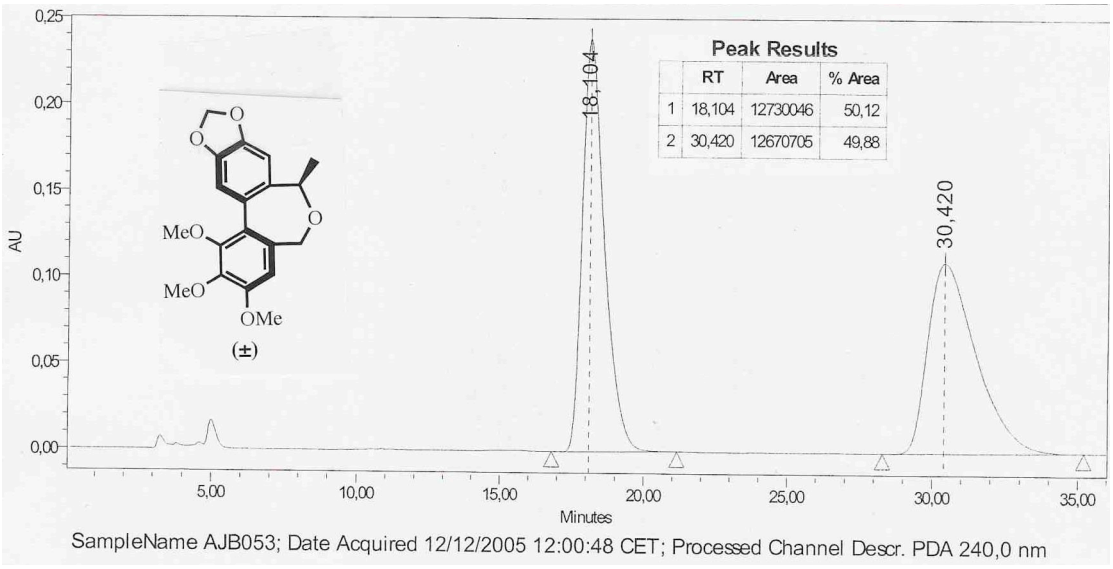
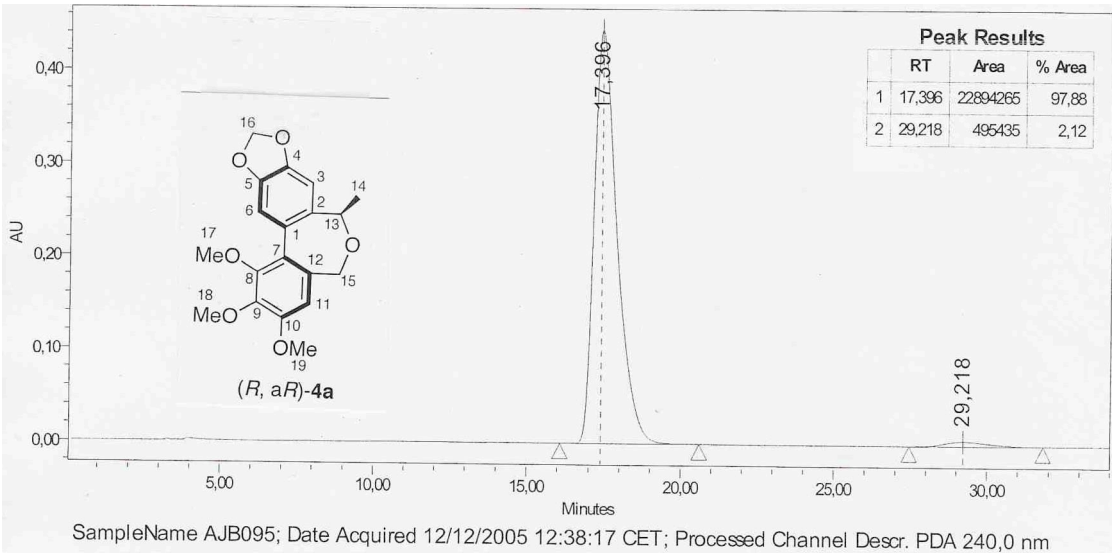
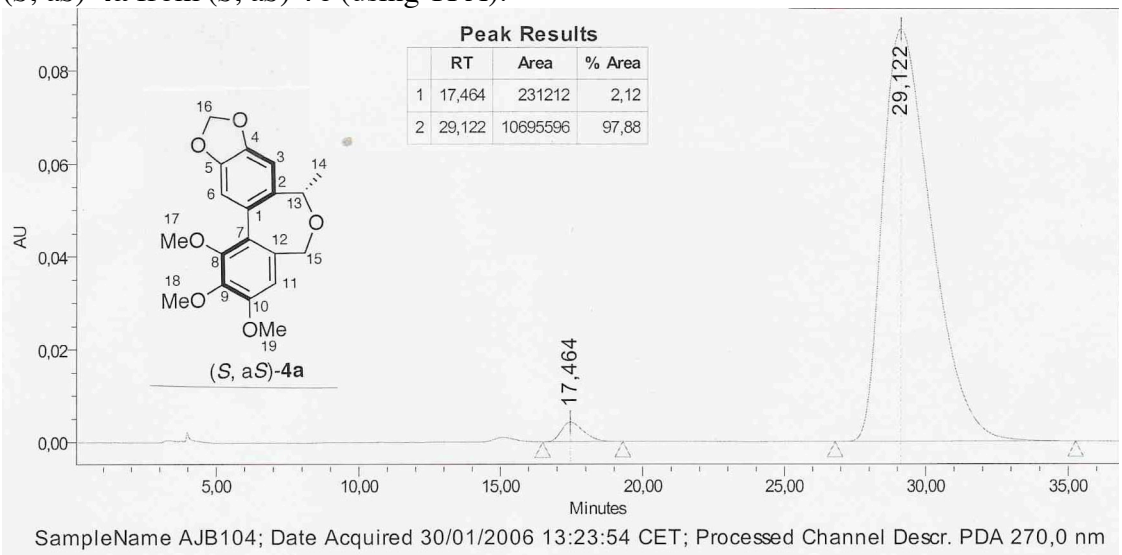
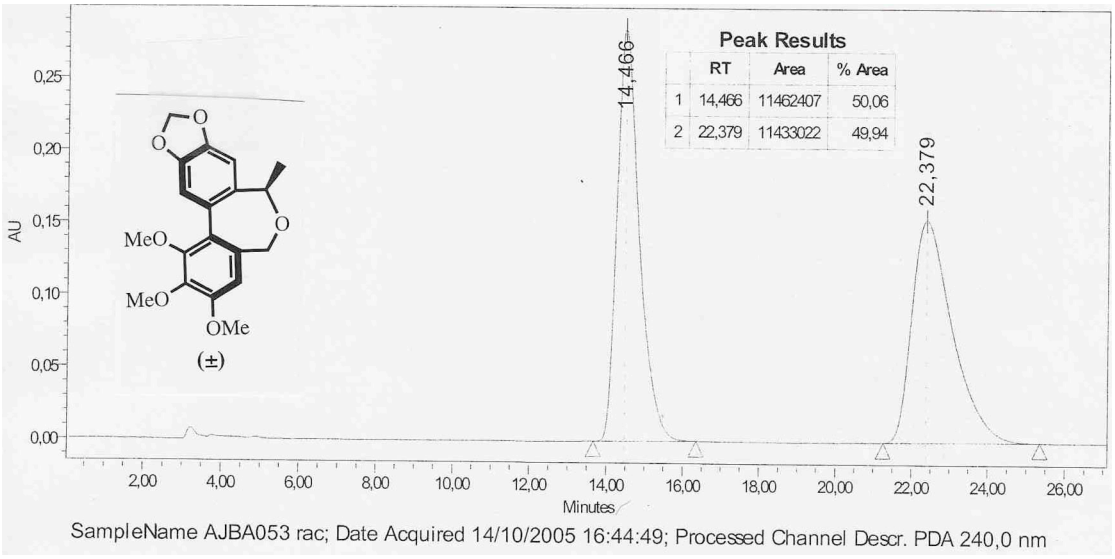
2 13.522 135971 1.03
10.467
13.522
OH
AU
Minutes
SampleName AJB041a; Date Acquired 03/08/2005 11:41:15; Processed Channel Descr. PDA 243,0 nm



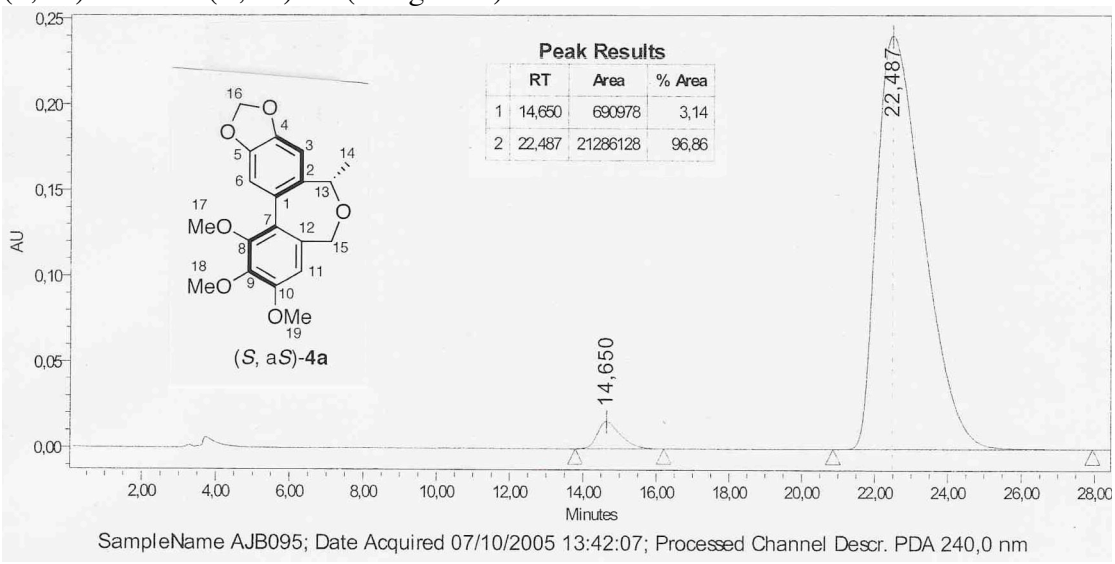


(*S*, a*S*)-**4a** from (*S*, a*S*)-**7e** (using TFA):

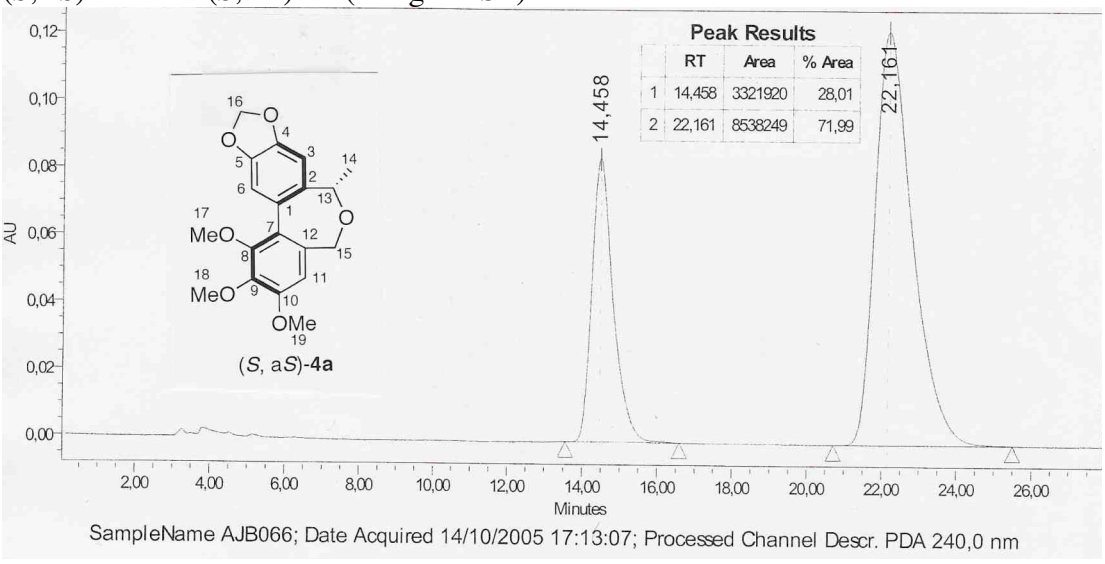


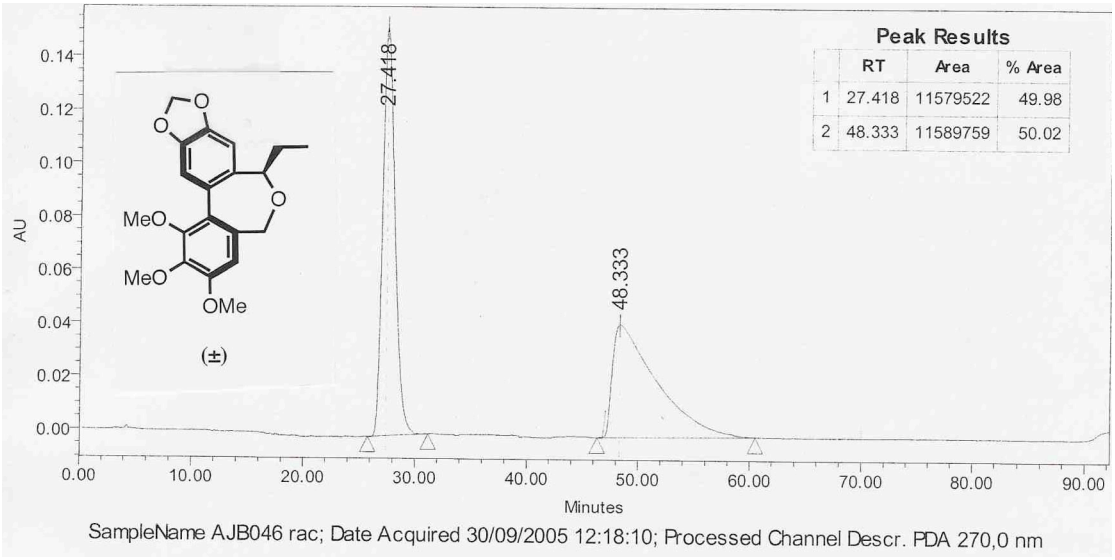


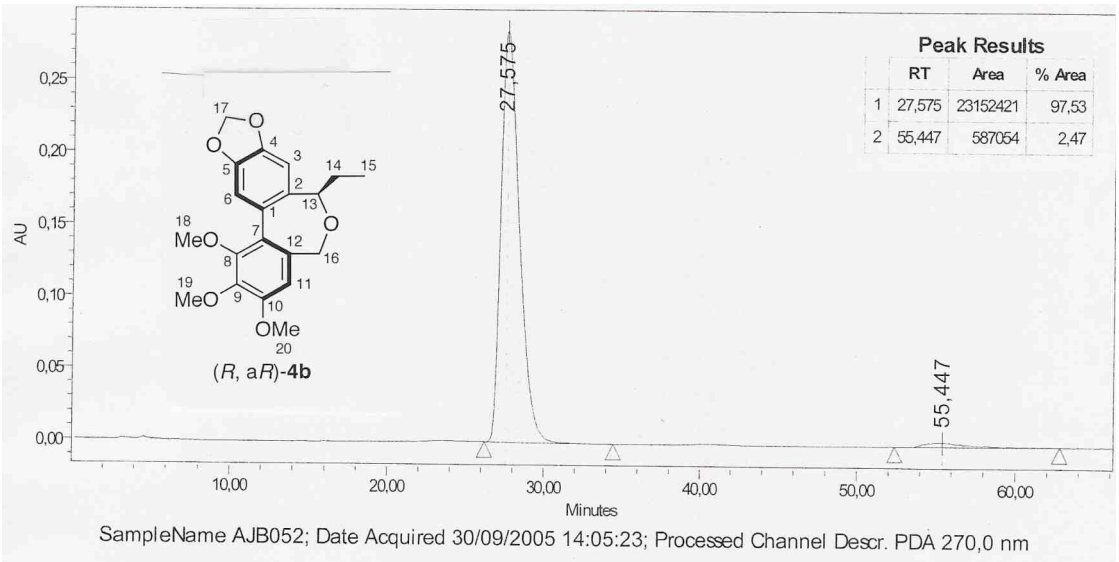
(*S*, a*S*)-**4a** from (*R*, a*S*)-**7a** (using TFA):

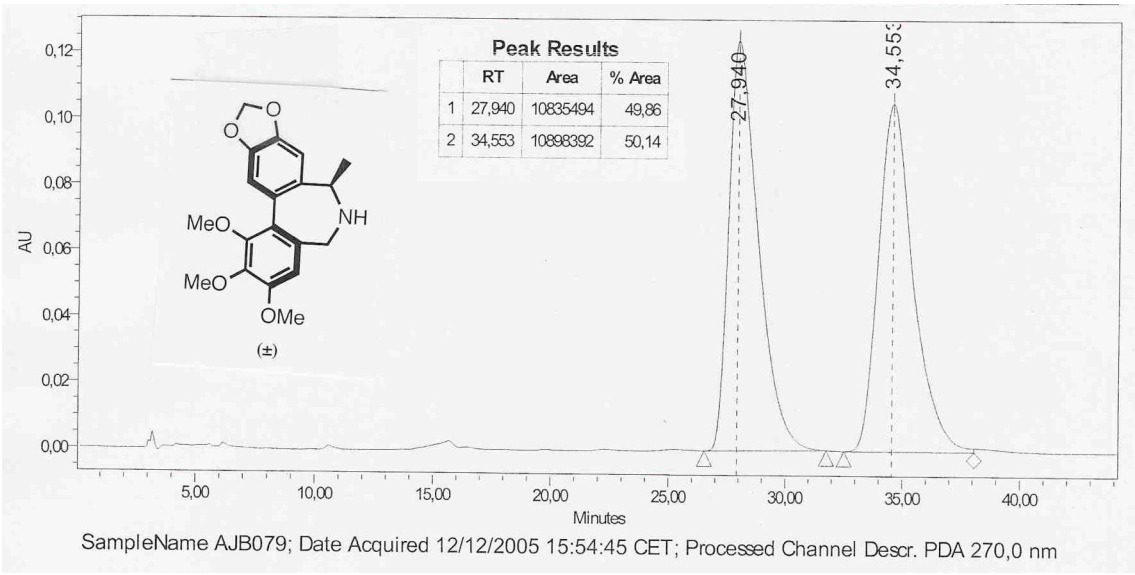


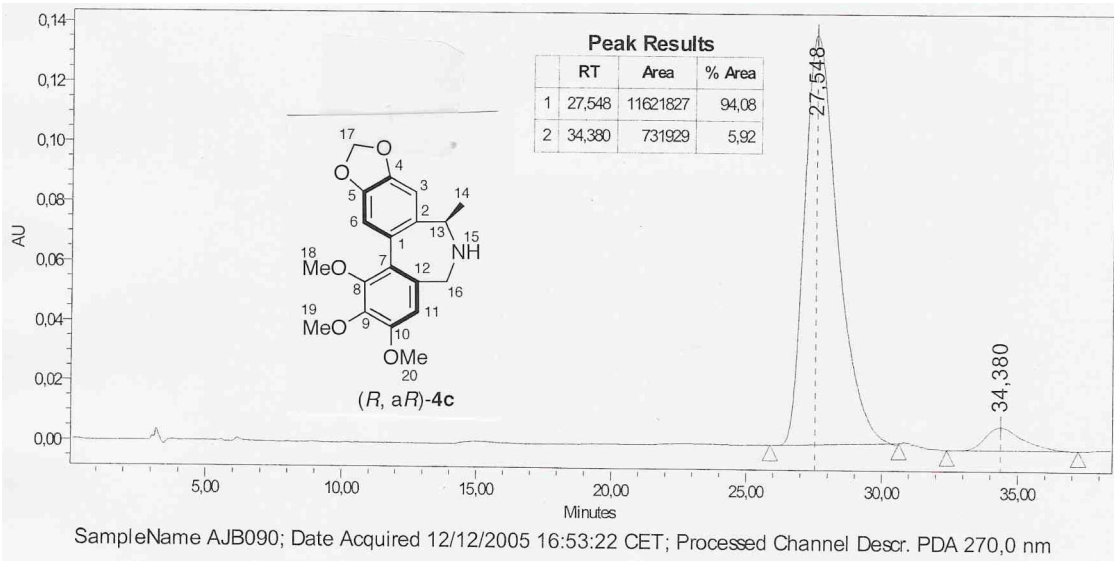
(*S*, a*S*)-**4a** from (*S*, a*R*)-**7a** (using DAST):

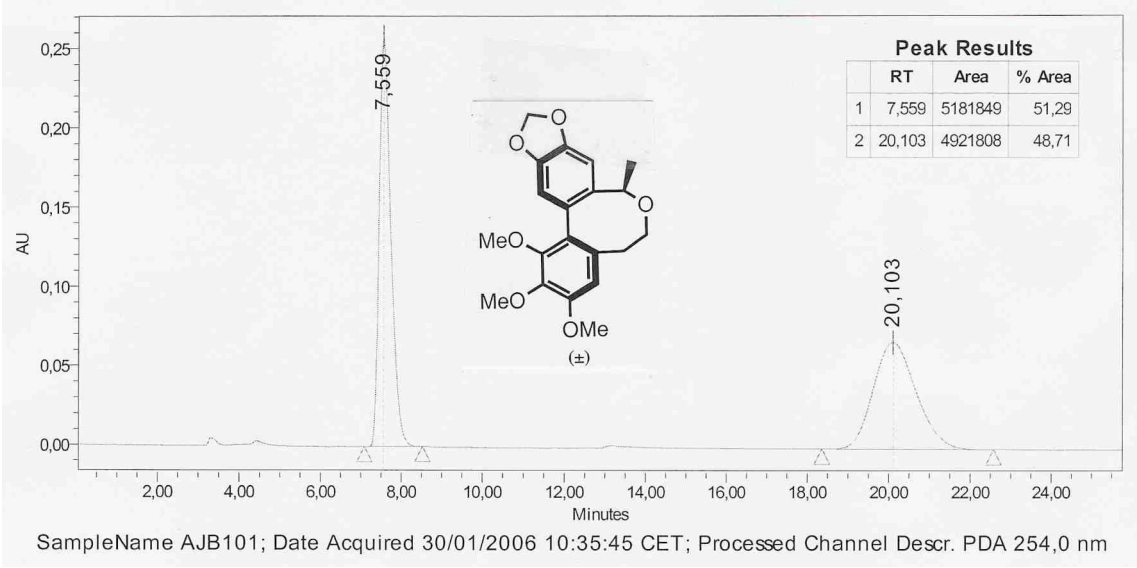


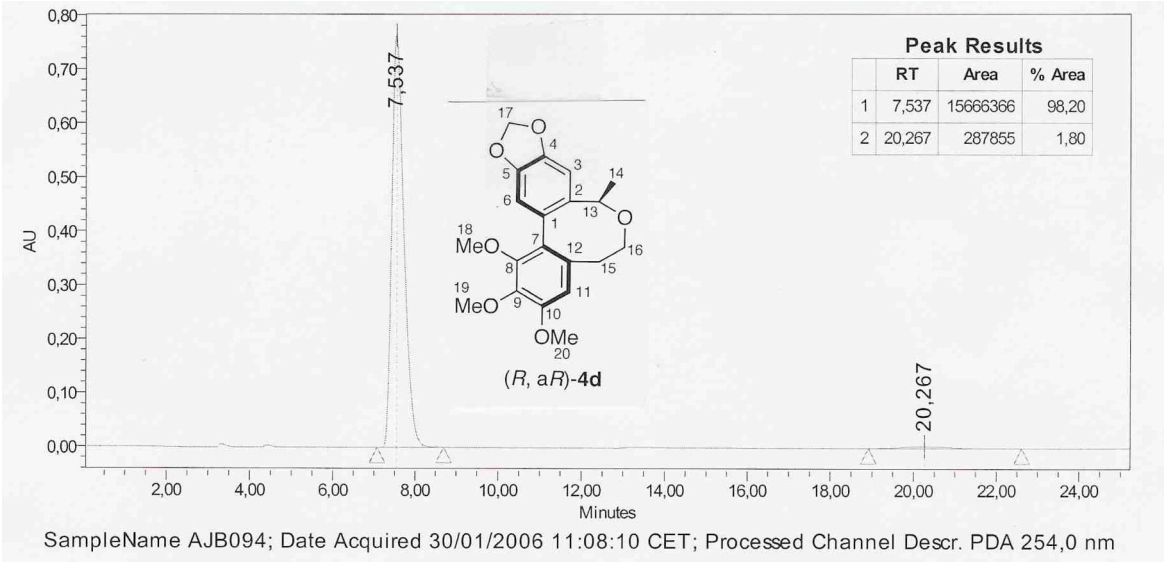

Peak Results
RT Area % Area
1 27.418 11579522 49.98
2 48.333 11589759 50.02
27.418
48.333
MeO
MeO
OMe
(±)
AU
Minutes
SampleName AJB046 rac; Date Acquired 30/09/2005 12:18:10; Processed Channel Descr. PDA 270,0 nm


Peak Results
RT Area % Area
1 27,575 23152421 97,53
2 55,447 587054 2,47
27,575
55,447
(R, aR)-4b
AU
Minutes
SampleName AJB052; Date Acquired 30/09/2005 14:05:23; Processed Channel Descr. PDA 270,0 nm


Peak Results
RT Area % Area
1 27,940 10835494 49,86
2 34,553 10898392 50,14
27,940
34,553
AU
Minutes
MeO
MeO
OMe
NH
(±)
SampleName AJB079; Date Acquired 12/12/2005 15:54:45 CET; Processed Channel Descr. PDA 270,0 nm


Peak Results
RT Area % Area
1 27,548 11621827 94,08
2 34,380 731929 5,92
27,548
34,380
AU
Minutes
(R, aR)-4c
SampleName AJB090; Date Acquired 12/12/2005 16:53:22 CET; Processed Channel Descr. PDA 270,0 nm


Peak Results
RT Area % Area
1 7,559 5181849 51,29
2 20,103 4921808 48,71
7,559
20,103
MeO
MeO
OMe
(±)
AU
Minutes
SampleName AJB101; Date Acquired 30/01/2006 10:35:45 CET; Processed Channel Descr. PDA 254,0 nm


Peak Results
RT Area % Area
1 7,537 15666366 98,20
2 20,267 287855 1,80
7,537
20,267
MeO
MeO
OMe
(R, aR)-4d
AU
Minutes
SampleName AJB094; Date Acquired 30/01/2006 11:08:10 CET; Processed Channel Descr. PDA 254,0 nm