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SUPPORTING INFORMATION

Stereodivergent access to all four stereoisomers of chiral tetrahydrobenzo[*f*][1,4]oxazepines, through highly diastereoselective multicomponent Ugi-Joullié reaction.

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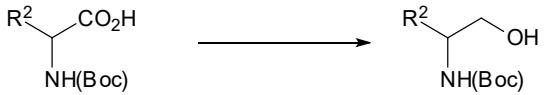
Experimental procedures

General methods

NMR spectra were taken at the indicated temperature in $CDCl_3$ or d6-DMSO at 300 MHz (^1H), and 75 MHz (^{13}C), using, as internal standard, TMS (^1H NMR: 0.000 ppm) or the central peak of $CDCl_3$ (^{13}C: 77.02 ppm), or the central peak of DMSO (^1H NMR in d_6-DMSO; 2.506 ppm), or the central peak of DMSO (^{13}C in d_6-DMSO; 39.43 ppm). Chemical shifts are reported in ppm (δ scale). Peak assignments were made with the aid of gCOSY and gHSQC experiments. HRMS: samples were analysed with a Synapt G2 QToF mass spectrometer. MS signals were acquired from 50 to 1200 m/z in ESI positive ionization mode. TLC analyses were carried out on silica gel plates and viewed at UV (254 nm) and developed with Hanessian stain (dipping into a solution of $(NH_4)_4MoO_4{\cdot}4\ H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4\ H_2O$ (1 g) in H_2SO_4 (31 ml) and H_2O (469 ml) and warming) or with ninhydrin. R_f were measured after an elution of 7-9 cm. Column chromatographies were done with the "flash" methodology using 220-400 mesh silica. Petroleum ether (40-60 °C) is abbreviated as PE. In extractive work-up, aqueous solutions were always reextracted three times with the appropriate organic solvent. Organic extracts were always dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions using dry solvents were carried out under a nitrogen atmosphere.

General procedure for the synthesis of Boc-protected amino alcohols 7a-c from the corresponding Boc-α-amino acids.

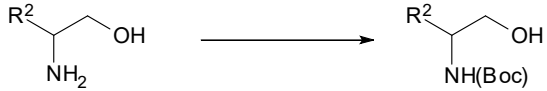


7a: R^2 = Bn
7b: R^2 = *i*Bu
7c: R^2 = *i*Pr

Boc-amino acid was dissolved in dry THF (1 mL/mmol). This solution was cooled at -10 °C, and isobutyl chloroformate (1.2 eq.) and N,N-diisopropylethylamine (1.5 eq.) were added in this order. The mixture was stirred at – 10 °C for 1h. Then it was filtered and the filtrate was cooled at -10 °C and treated with $NaBH_4$ (1.5 eq.) and H_2O (3 mL/mmol of $NaBH_4$), in this sequence. After stirring at -10 °C for 30 min and at rt for 1h, the mixture was diluted with AcOEt and with saturated aqueous NH_4Cl and 5% aqueous $(NH_4)H_2PO_4)NH_4$ (resulting pH = 5). After phase separation, the organic phases were washed with brine, and evaporated to dryness. Chromatography afforded the pure products.

7a. Chromatography: PE/AcOEt/CH_2Cl_2 2:1:2. Yield: 88%. Only (*S*)-compound was prepared and used. This compound is known.[1]
7b. Chromatography: PE/AcOEt/CH_2Cl_2 1:1:1. Yield: 87%. Only (*S*)-compound was prepared and used. This compound is known.[2]
7c. Chromatography: PE/AcOEt 3:1. Yield: 87%. Only (*S*)-compound was prepared and used. This compound is known.[2]

General procedure for the synthesis of Boc-protected amino alcohols 7d-e from the corresponding amino alcohol.



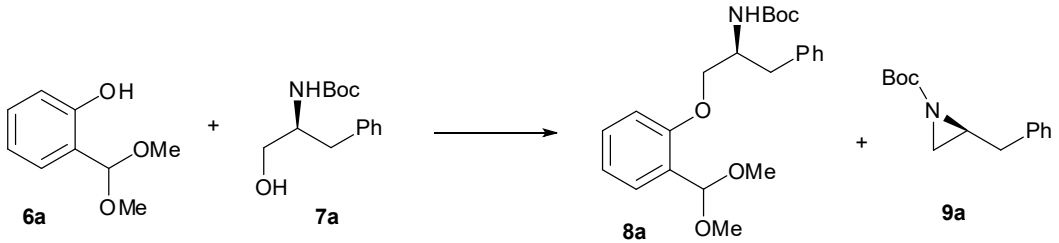
7d: R^2 = Ph
7e. R^2 = Me

1.010 g (7.36 mmol) of R-(-)-2-phenyl glycinol was dissolved in 12.3 mL of dry CH_2Cl_2. 1.13 mL (8.11 mmol, 1.1 eq.) of Et_3N and 1.771 g (8.11 mmol, 1.1 eq.) of $(Boc)_2O$ were added at this solution. The mixture was stirred overnight at room temperature, then it was diluted with CH_2Cl_2 and with 1 M HCl. After phase separation, the organic phases were washed with saturated aqueous $NaHCO_3$, and evaporated to dryness. The crude product was purified by chromatography using PE:AcOEt:CH_2Cl_2 2:1:1. The product (1.500 g, 6.32 mmol) was obtained as a white solid with a yield of 86,0%. This product is known.[3]

Using the same procedure, both (*R*)- and (*S*)-**7e** were prepared in 93% yield from the corresponding amino alcohols. They are both known.[2]

Optimization of the Mitsunobu reaction to give 8a

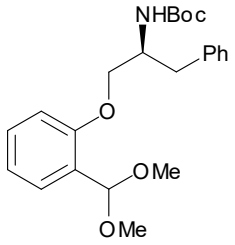
The reaction was first optimized using stoichiometric quantities of the two reagents. Thus, all the following reactions were carried out in THF at 0°C for 3 h and then at rt overnight, using 1 eq. each of **6a** and **7a** and 1.5 eq. of PPh_3 and of azodicarboxylate. A main side-product was detected, corresponding to Boc-aziridine **9a**.



Azodicarboxylate	Isolated yield of **8a** (from **1a**)	Isolated yield of 9**a** (from **1a**)
Di-*tert*-butyl azodicarboxylate (TBAD)	25%	54%
Diethyl azodicarboxylate (DEAD)	45%	31%
Diisopropyl azodicarboxylate (DIAD)	31%	44%
1,1'-(Azodicarbonyl)dipiperidine (ADDP)	72%	12%

Then, also taking into account the fact that the Boc-amino alcohol is more precious than the salicyladehyde, we decided to use a slight excess (1.2 equiv.) of salicylaldehyde. Finally, we noticed that a slight better yield was achieved by adding PPh_3 and azodicarboxylate in three portions.

Typical procedure for the Mitsunobu reaction. (*S*)-*tert*-Butyl (1-(2-(dimethoxymethyl)phenoxy)-3-phenylpropan-2-yl)carbamate 8a.

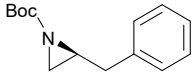


8a

A solution of salicylaldehyde (0.770 mL, 901 mg, 7.38 mmol) in dry MeOH (8.1 mL) was treated with trimethyl orthoformate (3.50 mL, 32.0 mmol) and Amberlyst 15 (100 mg). The resulting mixture was stirred at room temperature for 20 h, then diluted with CH_2Cl_2 and filtered. The filtrate was treated with solid $NaHCO_3$ (25 mg) and filtered again. The filtrate was evaporated, and the residue was taken up in CH_2Cl_2/toluene, and again evaporated to azeothropically remove all methanol. The crude acetal **6a** was obtained as a yellow oil (1.380 g). This acetal (301.7 mg, theoretical 1.61 mmol, 1.2 equiv.)

was dissolved in dry THF (2.60 mL), cooled to 0°C, and treated sequentially with Boc-amino alcohol **7a** (330.5 mg, 1.31 mmol, 1 equiv.), PPh_3 (171.8 mg, 0.655 mmol, 0.5 equiv.) and 1,1'-(Azodicarbonyl)dipiperidine (ADDP) (165.5 mg, 0.656 mmol, 0.5 equiv.). After stirring at 0°C for 60 min, further PPh_3 (171,8 mg, 0,655 mmol) and ADDP (165,5 mg, 0,656 mmol) were added. Finally, after 60 minutes, an identical amount of both reagents was added. The mixture was further stirred overnight at rt and evaporated to dryness. The crude was taken up in Et_2O and washed with 1 M NaOH, to remove excess of **6a**. The organic phase was washed with aqueous saturated NH_4Cl, evaporated and purified by chromatography (PE / AcOEt 11:1) to give pure **8a** as an oil (411.4 mg, 78% from **7a**).
R_f = 0.20 (PE / AcOEt 10:1). $[\alpha]_D = -15.1$ (c 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.54 (1 H, dd, J = 7.6, 1.6 Hz), 7.34-7.14 (6 H, m), 6.98 (1 H, t, J = 7.5 Hz), 6.76 (1 H, d, J = 8.2 Hz), 5.73 (1 H, s, C*H*$(OCH_3)_2$), 5.63 (1 H, broad d, J = 8.1 Hz, N*H*), 4.21-4.05 (1 H, broad m, C*H*N), 3.98 (1 H, dd, J = 9.3, 2.6 Hz, C*H*HO), 3.84 (1 H, dd, J = 9.3, 3.8 Hz, C*H*HO), 3.47 (3 H, s, OCH_3), 3.29 (3 H, s, OCH_3), 3.10-2.94 (2 H, m, CH_2Ph), 1.43 (9 H, s, C(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 156.5, 155.5 (*C*=O and *C*-O), 138.1, 126.1 (quat.), 129.8, 129.5 (x2), 128.5 (x2), 127.6, 126.5, 120.7, 112.3 (aromatic *C*H), 99.4 (*C*H$(OCH_3)_2$), 79.3 (*C*$(CH_3)_3$), 68.6 (*C*H_2O), 54.4 (O*C*H_3), 51.7 (O*C*H_3 and *C*HN), 38.2 (*C*H_2Ph), 28.4 (C(*C*H_3)$_3$). I.R. (ATR): ν_{max} 3346, 2978, 2930, 2897, 2827, 1700, 1606, 1590, 1522, 1494, 1455, 1442, 1388, 1365, 1337, 1284, 1244, 1203, 1164, 1125, 1096, 1047, 1033, 987, 973, 960, 921, 901, 881, 866, 850, 822, 780, 763, 742, 698, 670, 641, 623, 608 cm^{-1}. HRMS (ESI+): found 402.2287 [Calcd for $C_{23}H_{32}NO_5^+$ $(M + H)^+$ 402.2280].

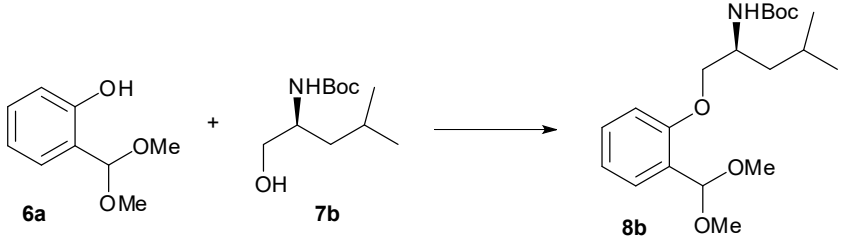
(*S*)-*tert*-Butyl 2-benzylaziridine-1-carboxylate 9a.



9a

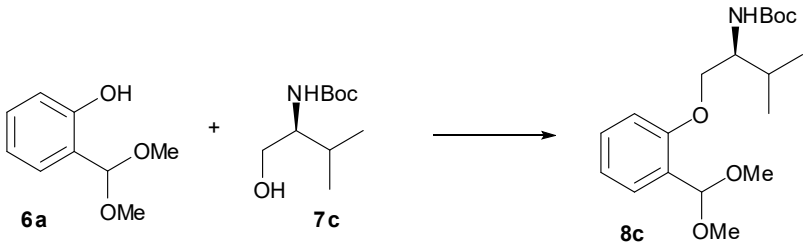
Oil. R_f = 0.49 (PE / AcOEt 10:1). ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.35-7.20 (5 H, m), 3.02-2.89 (1 H, m, C*H*N), 2.71-2.57 (2 H, m, CH_2N), 2.31 (1 H, d, J = 6.0 Hz, C*H*HPh), 2.03 (1 H, d, J = 3.6 Hz, C*H*HPh), 1.44 (9 H, s, C(CH_3)$_3$). This compound is known.[4]

(*S*)-*tert*-Butyl (1-(2-(dimethoxymethyl)phenoxy)-4-methylbutan-2-yl)carbamate 8b.



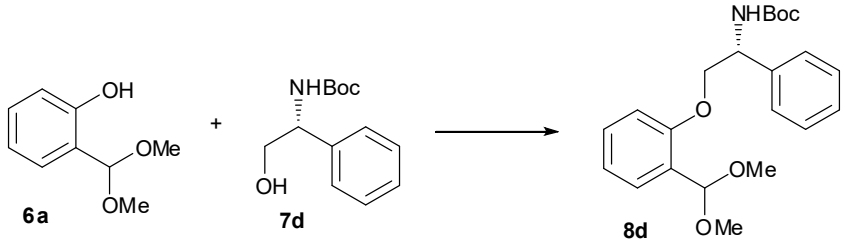
It was prepared from salicylaldehyde and Boc-amino alcohol **7b** following the same procedure described for **8a**, but using stoichiometric quantities of **6a** and Boc-amino alcohol **7b**. The isolated yield of **8b** was 65% from salicylaldehyde. Chromatography was carried out with PE: AcOEt 30:1 →10:1.
Oil. R_f = 0.34 (PE / AcOEt 30:1). $[\alpha]_D$ = + 50.3 (c 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.52 (1 H, dd, J = 7.5, 1.5 Hz), 7.29 (1 H, td, J = 7.8, 1.5 Hz), 6.97 (1 H, td, J = 7.5, 1.2 Hz), 6.85 (1 H, dd, J = 8.1, 0.6 Hz), 5.65 (1 H, s, C*H*$(OCH_3)_2$), 5.29 (1 H, broad d, J = 8.1 Hz, N*H*), 4.10-3.91 (3 H, m, C*H*N, C*H*HO), 3.43 (3 H, s, OCH_3), 3.28 (3 H, s, OCH_3), 1.80-1.45 (2 H, m, CH_2C*H*$(CH_3)_2$), 1.43 (9 H, s, C(CH_3)$_3$), 0.97 (6 H, d, J = 6.6 Hz, $(CH_3)_2$CH). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 156.6, 155.6 (*C*=O and *C*-O), 129.8, 127.5, 120.6, 112.2 (aromatic *C*H), 126.2 (quat.), 99.3 (*C*H$(OCH_3)_2$), 79.1 (*C*$(CH_3)_3$), 71.0 (*C*H_2O), 54.5 (O*C*H_3), 52.0 (O*C*H_3), 48.4 (*C*HN), 41.4 (*C*H_2*i*Pr), 28.4 (C(*C*H_3)$_3$), 24.9 (*C*H$(CH_3)_2$), 22.9, 22.5 (CH(*C*H_3)$_3$. I.R. (ATR): ν_{max} 3349, 2956, 2933, 2871, 2830, 1697, 1604, 1516, 1491, 1455, 1391, 1366, 1329, 1285, 1241, 1163, 1118, 1091, 1047, 977, 910, 872, 847, 811, 754, 731, 672, 647, 610 cm^{-1}. HRMS (ESI+): found 368.2429 [Calcd for $C_{20}H_{34}NO_5^+$ $(M + H)^+$ 368.2437].

(*S*)-*tert*-Butyl (1-(2-(dimethoxymethyl)phenoxy)-3-methylpropan-2-yl)carbamate 8c.



It was prepared from salicylaldehyde and Boc-amino alcohol **7c** following the same procedure described for **8a**, but using 1.1 equiv. of **6a** relative to Boc-amino alcohol **7c**. The isolated yield of **8c** was 55% from **7c**. Chromatography was carried out with PE: AcOEt 16:1 →10:1.
Oil. R_f = 0.25 (PE / AcOEt 16:1). $[\alpha]_D$ = –56.2 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.52 (1 H, dd, J = 7.6, 1.6 Hz), 7.29 (1 H, td, J = 7.5, 1.5 Hz), 6.98 (1 H, t, J = 7.5 Hz), 6.85 (1 H, d, J = 8.1 Hz), 5.64 (1 H, s, C*H*(OCH_3)$_2$), 5.43 (1 H, broad d, J = 9.0 Hz, N*H*), 4.21 (1 H, dd, J = 9.3, 2.8 Hz, C*H*HO), 3.92 (1 H, dd, J = 9.3, 3.8 Hz, C*H*HO), 3.73-3.60 (1 H, m, C*H*N), 3.43 (3 H, s, OC*H*$_3$), 3.26 (3 H, s, OC*H*$_3$), 2.02 (1 H, octuplet, J = 7.1 Hz, C*H*(CH_3)$_2$), 1.43 (9 H, s, C(C*H*$_3$)$_3$), 1.02 (3 H, d, J = 6.9 Hz, (C*H*$_3$)CH), 1.00 (3 H, d, J = 6.9 Hz, (C*H*$_3$)CH). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 156.7, 155.9 (*C*=O and *C*-O), 129.8, 127.5, 120.5, 112.1 (aromatic *C*H), 126.2 (quat.), 99.3 (*C*H(OCH_3)$_2$), 79.0 (*C*(CH_3)$_3$), 69.1 (*C*H_2O), 55.6 (*C*HN), 54.5 (O*C*H_3), 51.7 (O*C*H_3), 30.2 (*C*H(CH_3)$_2$), 28.4 (C(*C*H_3)$_3$), 19.6, 19.3 (CH(*C*H_3)$_3$. I.R. (ATR): ν_{max} 3348, 2962, 2934, 2829, 1711, 1604, 1591, 1516, 1491, 1456, 1390, 1365, 1286, 1240, 1170, 1121, 1092, 1073, 1045, 1028, 979, 946, 911, 883, 867, 807, 755, 737, 703, 675, 650, 620, 610 cm^{-1}. HRMS (ESI+): found 354.2284 [Calcd for $C_{19}H_{32}NO_5^+$ $(M + H)^+$ 354.2280].

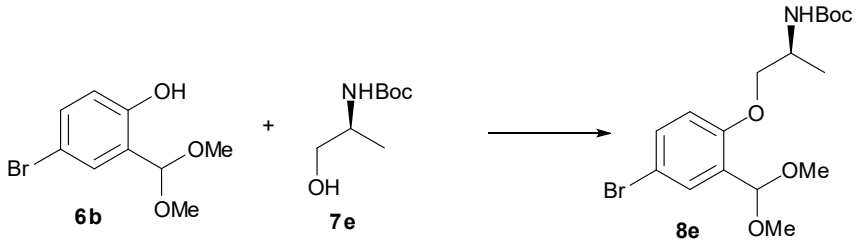
(*R*)-*tert*-Butyl (2-(2-(dimethoxymethyl)phenoxy)-1-phenylethan-1-yl)carbamate 8d.



It was prepared from salicylaldehyde and Boc-amino alcohol **7d** following the same procedure described for **8a**, but using 1.1 equiv. of **6a** relative to Boc-amino alcohol **7d**. The isolated yield of **8d** was 42% from **7c**. Chromatography was carried out with PE: AcOEt 8:1 →6:1.
Oil. R_f = 0.20 (PE / AcOEt 8:1). $[\alpha]_D$ = –33.5 (c 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.49 (1 H, dd, J = 7.6, 1.6 Hz), 7.46-7.22 (6 H, m), 6.97 (1 H, t, J = 7.5 Hz), 6.82 (1 H, d, J = 8.4 Hz), 6.12 (broad s, N*H*), 5.54 (1 H, s, C*H*(OCH_3)$_2$), 5.09 (1 H, broad s, C*H*NH), 4.32-4.15 (2 H, m, CH_2O), 3.40 (3 H, s, OC*H*$_3$), 3.28 (3 H, s, OC*H*$_3$), 1.43 (9 H, s, C(C*H*$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 156.3, 155.5 (*C*=O and *C*-O), 140.2, 126.5 (quat.), 129.8, 128.5 (x2), 127.6, 127.4, 126.8 (x2), 120.9, 112.4 (aromatic *C*H), 99.6 (*C*H(OCH_3)$_2$), 79.5 (*C*(CH_3)$_3$), 72.0 (*C*H_2O), 54.6 (O*C*H_3), 54.1 (*C*HN), 52.0 (O*C*H_3),

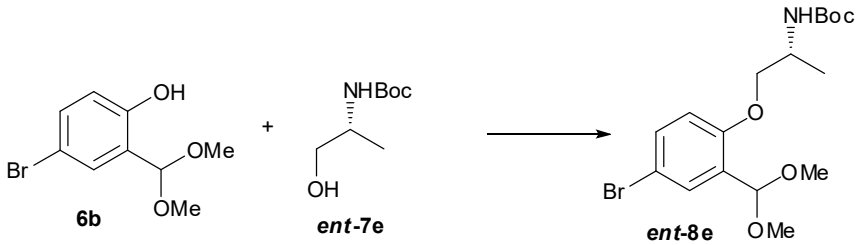
28.4 (C(CH_3)$_3$). I.R. (ATR): ν_{max} 3335, 2977, 2933, 2830, 1706, 1604, 1591, 1515, 1491, 1454, 1391, 1366, 1284, 1239, 1164, 1121, 1092, 1070, 1047, 979, 947, 902, 867, 794, 751, 699, 666, 633 cm^{-1}. HRMS (ESI+): found 388.2119 [Calcd for $C_{22}H_{30}NO_5^+$ (M + H)$^+$ 388.2124].

(*S*)-*tert*-Butyl (1-(2-(dimethoxymethyl)phenoxy)-propane-2-yl)carbamate 8e.



It was prepared from 4-bromosalicylaldehyde **1b** and Boc-amino alcohol (*S*) **7e** following the same procedure described for **8a**, but using 1.1 equiv. of **6b** relative to Boc-amino alcohol (*S*)-**7e**. The isolated yield of **8d** was 60% from **7e**. Chromatography was carried out with PE: AcOEt : CH_2Cl_2 8:1:1 →6:1:1. Oil. R_f = 0.37 (PE / AcOEt / CH_2Cl_2 8:1:1). $[\alpha]_D$ = –40.4 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.64 (1 H, d, J = 2.4 Hz), 7.38 (1 H, dd, J = 8.7, 2.7 Hz), 6.74 (1 H, d, J = 8.7 Hz), 5.61 (1 H, s, C*H*(OCH$_3$)$_2$), 5.26 (broad s, N*H*), 4.05 (1 H, broad s, C*H*NH), 4.01 (1 H, dd, J = 8.9, 2.8 Hz, C*H*HO), 3.90 (1 H, dd, J = 8.9, 4.3 Hz, C*H*HO), 3.41 (3 H, s, OC*H*$_3$), 3.28 (3 H, s, OC*H*$_3$), 1.44 (9 H, s, C(C*H*$_3$)$_3$), 1.31 (3 H, d, J = 6.6 Hz, C*H*$_3$CH). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 155.6, 155.3 (*C*=O and *C*-O), 132.4, 130.6, 114.0 (aromatic *C*H), 128.4, 113.3 (quat.), 98.5 (*C*H(OCH$_3$)$_2$), 79.3 (*C*(CH$_3$)$_3$), 72.2 (*C*H$_2$O), 54.3 (OCH$_3$), 52.0 (OCH$_3$), 45.9 (*C*HN), 28.4 (C(*C*H$_3$)$_3$), 18.2 (*C*H$_3$CH). I.R. (ATR): ν_{max} 3350, 2976, 2933, 2830, 1695, 1595, 1514, 1487, 1457, 1404, 1391, 1365, 1266, 1242, 1164, 1133, 1099, 1053, 980, 912, 875, 854, 806, 781, 752, 734, 677, 657, 645, 616 cm^{-1}. HRMS (ESI+): found 404.1075 [Calcd for $C_{17}H_{27}BrNO_5^+$ (M + H)$^+$ 404.1073].

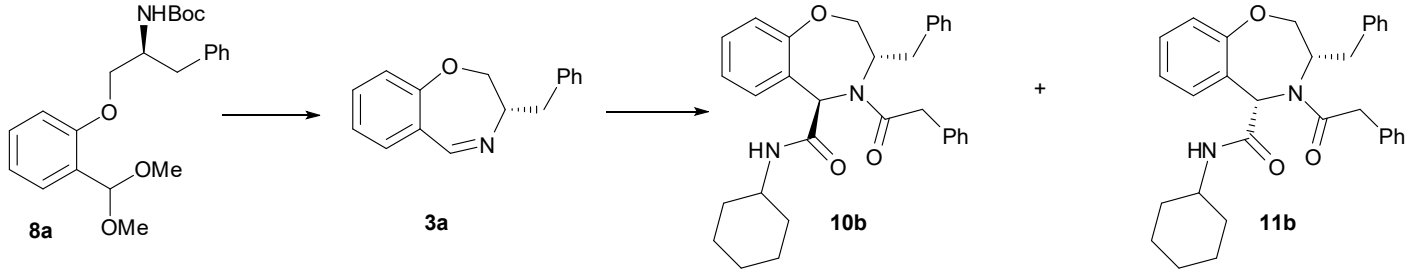
(*R*)-*tert*-Butyl (1-(2-(dimethoxymethyl)phenoxy)-propane-2-yl)carbamate *ent*-8e.



It was prepared exactly as for **8e**, but starting from ***ent*-7e**. $[\alpha]_D$ = +39.9 (c 1.0, $CHCl_3$). The other spectroscopical data were identical to those of **8e**.

Optimization of Ugi-Joulliè reaction to give 10a.

In all cases (except entries 6,9) 1.2 equivalents of acetic acid and 1.2 equivalents of *tert*-butyl isocyanide were used.



Entry	Solvent	Additive	Time	Temp.	Yield %[a]	D.r.[b]
1	MeOH	none	45 h	rt	80	96 : 4
2	CH_2Cl_2	none	38 h	rt	74	90.5 : 9.5
3	CH_2Cl_2	$ZnBr_2$ (0.5 equiv.)	45 h	rt	69	94 : 6
4	CH_2Cl_2	$ZnBr_2$ (1.0 equiv.)	48 h (incomplete)	rt	51	89:11
5	MeOH	$ZnBr_2$ (0.5 equiv.)	48 h (incomplete)	rt	49	96 : 4
6	CH_2Cl_2	$Zn(OAc)_2$ (1.2 equiv.)[c]	48 h (largely incomplete)	rt	9	95 : 5
7	THF	none	48 h (incomplete)	rt	29	88 : 12
8	THF	$ZnBr_2$ (0.5 equiv.)	48 h (incomplete)	rt	34	95 : 5
9	THF	$Zn(OAc)_2$ (1.2 equiv.)[c]	48 h (no reaction)	rt	-	-
10	EtOH	none	48 h (incomplete)	rt	62	92 : 8
11	*i*BuOH	none	48 h (incomplete)	rt	46	87 : 13

[a] Isolated yield of major diastereomer only. [b] Determined by HPLC on the crude product. [c] $Zn(OAc)_2$ was used instead of AcOH

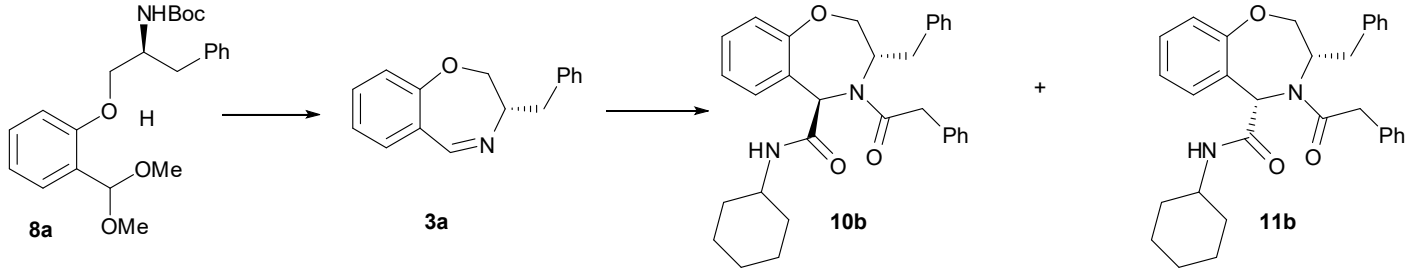
Typical procedure for the synthesis of Ugi-Joullié adducts: (*3S*,*5R*)-4-Acetyl-3-benzyl-*N*-(*tert*-butyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide 10a.

Acetal **8a** (312.4 mg, 778 µmol) was dissolved in CH_2Cl_2 (3.0 mL) and treated with 37% aqueous HCl (640 µL, 7.73 mmol). The mixture was stirred at rt for 5 h. Then it was diluted with CH_2Cl_2, and cautiously treated with 5% aqueous Na_2CO_3 (25 mL). After checking that pH > 9, the two phases were separated, washed with brine, and evaporated to dryness. The resulting crude imine **3a** (oil) was taken up in dry methanol (3.90 mL), and treated with acetic acid (53 µL, 927 µmol), and *tert*-butyl isocyanide (106 µl, 937 µmol). The mixture was stirred at rt for 45 h and evaporated to dryness. It was taken up in AcOEt, washed with saturated aqueous $NaHCO_3$ (to remove excess carboxylic acid), evaporated, and chromatographed (PE / AcOEt 2:1) to give pure **10a** (237 mg, 80%). The ratio **10a** : **11a** was determined by HPLC on the crude product and resulted = 96:4. HPLC conditions: C6-Phenyl column 150 x 3 mm, 3 µm. Flow: 0.38 ml/min. Temp: 26°C. Eluent: H_2O : CH_3CN 55:45. Detection: UV 220 nm. R_t of **10a**: 13.62. R_t of **11a**: 14.41. Minor diastereomer **11a** was recognized using a MS (ESI) detector.

White solid. R_f = 0.24 (PE / AcOEt 2:1) (R_f of **11a** = 0.31). $[\alpha]_D$ = +10.0 (c 1.06, $CHCl_3$). M.p. = 119.7-122.0 °C. ^{1}H NMR (300 MHz, d6-DMSO, 90 °C): δ = 7.57 (1 H, dd, J = 7.7, 1.6 Hz), 7.36-7.16 (6 H, m), 7.00 (2 H, t, J = 8.2 Hz), 6.47 (1 H, broad s, N*H*), 5.66 (1 H, broad s, C*H*C=O), 4.77 (1 H, broad d, J = 11.1 Hz, C*H*HO), 4.55 (1 H, broad s, C*H*N), 4.03 (1 H, dd, J = 13.2, 4.8 Hz, C*H*HO), 2.79 (1 H, dd, J = 13.4, 5.9 Hz, C*H*HPh), 2.65-2.48 (1 H, m, C*H*HPh), 2.06 (3 H, s, CH_3C=O),1.22 (9 H, s, C(CH_3)$_3$). ^{13}C NMR (75 MHz, d6-DMSO, 90 °C): δ = 169.8, 168.8 (*C*=O), 155.6 (aromatic *C*-O), 137.6, 121.4 (quat.),

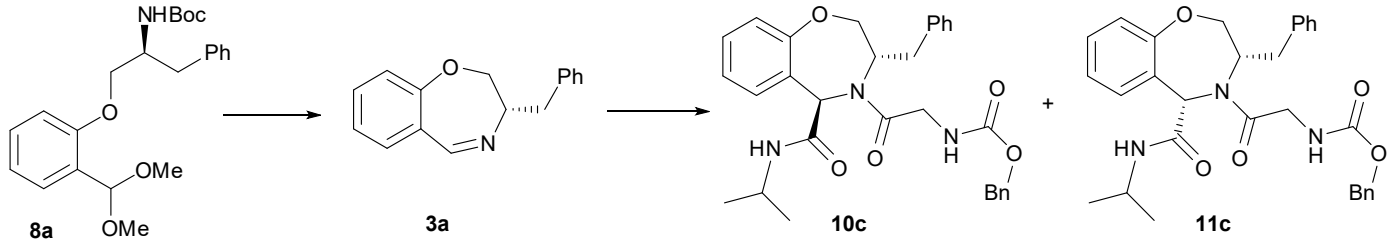
132.1, 129.6, 128.4 (x2), 127.8 (x2), 125.8, 120.9, 118.8 (aromatic *C*H), 66.6 (*C*H_2O), 62.8 (broad) (*C*HC=O), 57.5 (broad) (*C*HN), 50.2 (*C*(CH_3)$_3$), 36.4 (*C*H_2Ph), 27.8 (C(*C*H_3)$_3$), 21.2 (*C*H_3C=O). I.R. (ATR): ν_{max} 3410, 3314, 3067, 3034, 2966, 2928, 2870, 1671, 1639, 1607, 1580, 1563, 1509, 1494, 1453, 1416, 1391, 1366, 1352, 1332, 1305, 1288, 1267, 1249, 1224, 1193, 1172, 1157, 1125, 1115, 1086, 1052, 1028, 1007, 973, 937, 908, 885, 871, 862, 827, 802, 752, 731, 719, 700, 665, 644, 631, 616, 603 cm^{-1}. HRMS (ESI+): found 381.2171 [Calcd for $C_{23}H_{29}N_2O_3^+$ (M + H)$^+$ 381.2178].

(*3S*,*5R*)-3-Benzyl-*N*-(cyclohexyl)-4-phenylacetyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide 10b.



It was prepared in 65% overall yield from (*S*)-**8a**, phenylacetic acid and cyclohexyl isocyanide, following the typical procedure described for **10a**. Chromatography was carried out with PE / AcOEt / CH_2Cl_2 5 : 1 . 1. Separation of the two diastereomers was not complete. We obtained fractions with pure **10b** plus some fractions contaminated with little **11b**. The overall yield was 65%. The calculated yield of **10b** is therefore 62%. The d.r. was = 94 : 6 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O : MeOH 30:70. Detection: UV 220 nm. R_t of **10b**: 21.25. R_t of **11b**: 20.43. Minor diastereomer **11b** was recognized using a MS (ESI) detector.
White solid. R_f = 0.21 (PE / AcOEt / CH_2Cl_2 5 : 1 : 1) (R_f of **11b** = 0.24). $[\alpha]_D$ = +9.0 (c 1.0, $CHCl_3$). M.p. = 157.8-159.9 °C. ^{1}H NMR (300 MHz, d6-DMSO, 90 °C): δ = 7.42 (1 H, broad s), 7.36-7.15 (11 H, m), 7.05-6.95 (2 H, m), 6.80 (1 H, broad d, J = 6.6 Hz, N*H*), 5.72 (1 H, s, C*H*C=O), 4.75 (1 H, broad d, J = 12.3 Hz, C*H*HO), 4.61 (1 H, broad s, C*H*N), 4.02 (1 H, dd, J = 13.3, 4.6 Hz, C*H*HO), 3.84 (1 H, d, J = 15.6 Hz, C*H*HC=O), 3.67-3.50 (2 H, m, C*H*C=O, C*H*NH), 2.80 (1 H, dd, J = 13.2, 6.0 Hz, C*H*HPh), 2.65-2.48 (1 H, m, C*H*HPh), 1.80-1.45 (5 H, m, CH_2 cyclohexyl), 1.35-1.05 (5 H, m, CH_2 cyclohexyl). ^{13}C NMR (75 MHz, d6-DMSO, 90 °C): δ = 170.2 168.4 (*C*=O), 155.6 (broad) (aromatic *C*-O), 137.5, 135.1, 121.3 (quat.), 132.1, 129.6 (x2), 128.5 (x2), 128.4 (x2), 127.8 (x2), 127.6, 125.83, 125.76, 121.0, 118.7 (aromatic *C*H), 66.7 (broad) (*C*H_2O), 65.9 (broad) (*C*HC=O), 57.3 (broad) (*C*HN), 47.7 (*C*HNH), 39.4 (*C*H_2C=O, hidden by DMSO signal, visible at qHSQC), 36.3 (broad) (*C*H_2Ph), 31.2 (x2), 24.6, 23.7, 23.6 (*C*H_2 cyclohexyl). I.R. (ATR): ν_{max} 3271, 3023, 2977, 2940, 2920, 2855, 1656, 1633, 1604, 1582, 1525, 1492, 1451, 1416, 1360, 1343, 1319, 1306, 1289, 1270, 1250, 1222, 1193, 1150, 1115, 1094, 1076, 1060, 1029, 1012, 981, 968, 957, 935, 907, 893, 884, 875, 853, 826, 809, 781, 762, 749, 720, 696, 640, 619 cm^{-1}. HRMS (ESI+): found 483.2654 [Calcd for $C_{31}H_{35}N_2O_3^+$ (M + H)$^+$ 483.2648].

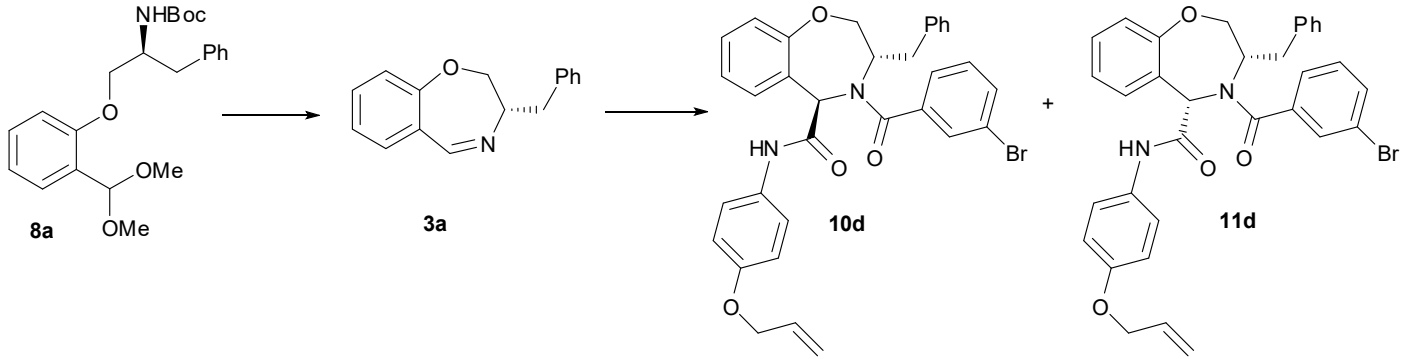
(*3S*,*5R*)-3-Benzyl-4-(2-((benzyloxycarbonyl)amino)acetyl)-*N*-(isopropyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide 10c.



It was prepared in 80% overall yield from (*S*)-**8a**, *N*-benzyloxycarbonyl glycine and isopropyl isocyanide, following the typical procedure described for **10a**. Chromatography was carried out with PE / AcOEt 2 : 1. Separation of the two diastereomers was not complete. We obtained fractions with pure **10c** plus some fractions contaminated with little **11c**. The overall yield was 80%. The calculated yield of **10c** is therefore 74.4%. The d.r. was = 94 : 6 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 1 ml/min. Temp: 26°C. Eluent: H_2O : CH_3CN 50:50. Detection: UV 220 nm. R_t of **10c**: 20.55. R_t of **11c**: 21.68. Minor diastereomer **11c** was recognized using a MS (ESI) detector.

White solid. R_f = 0.12 (PE / AcOEt 2 : 1) (R_f of **11c** = 0.17). $[\alpha]_D$ = −19.7 (c 1.0, $CHCl_3$). M.p. = 70.0-72.2 °C. ^{1}H NMR (300 MHz, d6-DMSO, 90 °C): δ = 7.56 (1 H, d, J = 7.5 Hz), 7.40-7.17 (11 H, m), 7.01 (2 H, t, J = 7.5 Hz), 7.00-6.90 (1 H, m, N*H*CH_2), 6.89 (1 H, broad d, J = 7.2 Hz, N*H*CH), 5.66 (1 H, s, C*H*C=O), 5.08 (2 H, s, PhCH_2O), 4.76 (1 H, broad d, J = 12.9 Hz, C*H*HO), 4.54 (1 H, broad s, C*H*N), 4.16 (1 H, dd, J = 16.6, 5.6 Hz, C*H*HNH), 4.01 (1 H, dd, J = 13.2, 4.5 Hz, C*H*HO), 3.93-3.77 (2 H, m, C*H*NH, C*H*HNH), 2.82 (1 H, dd, J = 13.4, 5.1 Hz, C*H*HPh), 2.62-2.48 (1 H, m, C*H*HPh), 1.08 (3 H, d, J = 6.6 Hz, CH_3), 1.00 (3 H, d, J = 6.6 Hz, CH_3). ^{13}C NMR (75 MHz, d6-DMSO, 90 °C): δ = 168.6 168.2 (*C*=O), 155.7, 155.5 (*C*=O urethane and aromatic *C*-O), 137.4, 136.6, 121.1 (quat.), 132.4, 129.6, 128.4 (x2), 127.8 (x2), 127.7 (x2), 127.1, 126.9 (x2), 125.9, 120.9, 118.7 (aromatic *C*H), 66.0 (broad) (*C*H_2O), 65.1 (Ph*C*H_2O), 61.6 (broad) (*C*HC=O), 57.2 (*C*HN), 42.3 (*C*H_2NH), 40.8 (*C*HNH), 36.3 (broad) (*C*H_2Ph), 21.3 (*C*H_3). I.R. (ATR): ν_{max} 3410, 3321, 3064, 3031, 2971, 2935, 1715, 1648, 1606, 1581, 1510, 1493, 1453, 1424, 1387, 1366, 1347, 1241, 1220, 1156, 1115, 1084, 1049, 1030, 1010, 929, 912, 892, 871, 826, 797, 749, 697, 658, 638 cm^{-1}. HRMS (ESI+): found 516.2490 [Calcd for $C_{30}H_{34}N_3O_5^+$ (M + H)$^+$ 516.2498].

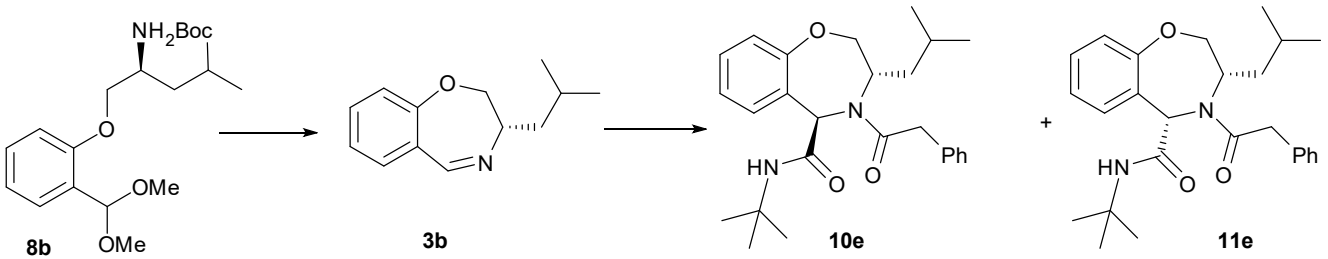
(*3S*,*5R*)-*N*-(4-Allyloxyphenyl)-3-benzyl-4-(3-bromobenzoyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide 10d.



A solution of N-(4-(allyloxy)phenyl)formamide (100 mg, 564 µmol)[5] in dry CH_2Cl_2 (0,84 mL) was cooled at 0°C and treated with 161.2, mg (676 µmol, 1.2 eq.) of Burgess reagent (Methyl *N*-(triethylammoniosulfonyl)carbamate inner salt). The mixture was stirred at 0°C for 3h, then further 66.0 mg (276 µmol)

of Burgess Reagent were added to the mixture. After 10 min. the mixture was allowed to reach room temperature and stirred for 2h. This mixture was then added to a solution of imine **3a** (400 µmol) in MeOH (1.5 mL), prepared as described above for the synthesis of **10a**. Finally, 112 mg (557 µmol mmol) of 3-bromobenzoic acid were added at this mixture. The mixture was stirred at room temperature for 48h and then 30 °C overnight. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography (PE: AcOEt 5:1) to give pure **10d** (128.8 mg, 54%). The d.r. was = 93 : 7 by HPLC of the crude product. HPLC conditions: C6-Phenyl column 150 x 3 mm, 3 µm. Flow: 0.34 ml/min. Temp: 25°C. Eluent: H_2O : CH_3CN 40:60 + 1% CF_3CO_2H. Detection: UV 220 nm. R_t of **10d**: 13.33. R_t of **11d**: 14.00. Minor diastereomer **11d** was recognized using a MS (ESI) detector. The overall yield, calculated from the d.r., was 58%.
White solid. R_f = 0.13 (PE / AcOEt 2 : 1). $[\alpha]_D$ = +57.0 (c 1.0, $CHCl_3$). M.p. = 148.6-150.7 °C. ^{1}H NMR (300 MHz, d6-DMSO, 90 °C): δ = 9.17 (1 H, s, N*H*), 7.64 (2 H, ddd, J = 8.1, 1.8, 1.0 Hz), 7.44-7.18 (9 H, m), 7.10 (1 H, td, J = 7.5, 1.2 Hz), 7.05 (1 H, dd, J = 8.1, 0.9 Hz), 7.01-6.92 (2 H, m), 6.88 (2 H, d, J = 9.0 Hz), 6.02 (1 H, ddt, J = 17.2, 10.5, 5.2 Hz, C*H*=CH_2), 5.81 (1 H, broad s, C*H*C=O), 5.37 (1 H, dq, J = 17.2, 1.6 Hz, CH=C*H*H), 5.23 (1 H, dq, J = 10.5, 1.5 Hz, CH=C*H*H), 4.95 (1 H, dd, J = 12.3, 1.8 Hz, C*H*HO), 4.53 (2 H, dt, J = 5.4, 1.5 Hz, CH_2CH=CH_2), 4.44 (1 H, broad s, C*H*N), 4.13 (1 H, dd, J = 13.0, 4.0 Hz, C*H*HO), 2.73 (1 H, dd, J = 13.2, 7.3 Hz, C*H*Ph), 2.62 (1 H, dd, J = 13.2, 8.4 Hz, C*H*HPh). ^{13}C NMR (75 MHz, d6-DMSO, 90 °C): δ = 169.1 167.4 (*C*=O), 155.6, 154.4, 138.0, 137.2, 131.2, 121.7, 121.2 (quat.), 133.3 (*C*H=CH_2), 131.9, 131.7, 130.1, 130.0, 128.5 (x2), 128.3, 127.8 (x2), 125.9, 124.6, 121.8, 121.4 (x2), 119.6, 114.4 (x2) (aromatic *C*H), 116.5 (CH=*C*H_2), 68.2 (*C*H_2CH=CH_2), 68.1 (broad) (*C*H_2O), 63.4 (broad) (*C*HC=O), 58.4 (broad) (*C*HN), 37.0 (broad) (*C*H_2Ph). I.R. (ATR): ν_{max} 3314, 3062, 2945, 2906, 2026, 1672, 1646, 1606, 1578, 1563, 1509, 1488, 1446, 1414, 1386, 1353, 1330, 1305, 1278, 1256, 1211, 1171, 1148, 1114, 1094, 1085, 1069, 1061, 1027, 1007, 967, 934, 914, 897, 887, 864, 824, 807, 752, 730, 709, 703, 682, 665, 649, 637, 605 cm^{-1}. HRMS (ESI+): found 597.1396 [Calcd for $C_{33}H_{30}BrN_2O_4^+$ $(M + H)^+$ 597.1389].

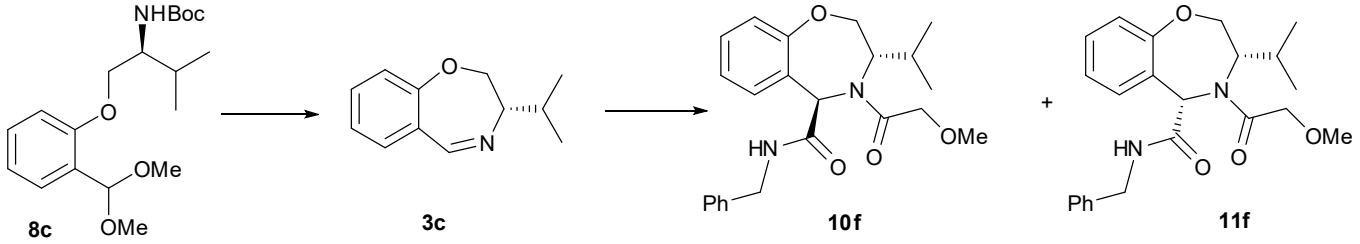
(*3S*,*5R*)-3-*iso*-Butyl-*N*-(*tert*-butyl)-4-(phenylacetyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide 10e.



It was prepared in 57% overall yield from (*S*)-**8b**, phenylacetic acid and *tert*-butyl isocyanide, following the typical procedure described for **10a**. The reaction under these conditions was not complete. Chromatography was carried out with PE / AcOEt 5 : 1. Separation of the two diastereomers was not complete. We obtained fractions with pure **10e** plus some fractions contaminated with little **1e**. The overall yield was 57%. The calculated yield of **10e** is therefore 54%. The d.r. was 96 : 4 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O : MeOH 30:70 + 1% CF_3CO_2H. Detection: UV 220 nm. R_t of **10e**: 18.25. R_t of **11e**: 16.23. Minor diastereomer **11e** was recognized using a MS (ESI) detector. Oil. R_f = 0.22 (PE / AcOEt 5 : 1) (R_f of **11e** = 0.25). $[\alpha]_D$ = +12.2 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, d6-DMSO, 90 °C): δ = 7.26-7.07 (7 H, m), 6.32 (1 H, s, N*H*), 5.52 (1 H, s, C*H*C=O), 4.59 (1 H, d, J = 12.9 Hz, C*H*HO), 4.36 (1 H, broad s, C*H*N), 4.12 (1 H, dd, J = 13.2, 5.2 Hz, C*H*HO), 3.74 (1 H, d, J = 15.6 Hz, C*H*HPh), 3.57 (1 H, d, J = 15.6 Hz, C*H*HPh), 1.51 (1 H, nonuplet, J = 6.6 Hz, C*H*(CH_3)$_2$), 1.17 (2 H, t, J = 6.9 Hz, CH_2*i*Pr), 1.11 (9 H, s, C(CH_3)$_3$), 0.74 (3 H, d, J = 6.6 Hz, CH_3CHCH$_3$), 0.67 (3 H, d, J = 6.6 Hz, CH_3CHCH$_3$). ^{13}C NMR (75 MHz, d6-DMSO, 90 °C): δ = 170.3 168.7 (*C*=O), 155.7, 135.2, 121.6 (quat.), 131.6, 129.3, 128.5 (x2), 127.6 (x2), 125.8, 120.8, 118.6 (aromatic *C*H), 67.6 (*C*H_2O), 62.3 (broad) (*C*HC=O), 54.0 (broad) (*C*HN), 50.2 (*C*H_2*i*Pr),

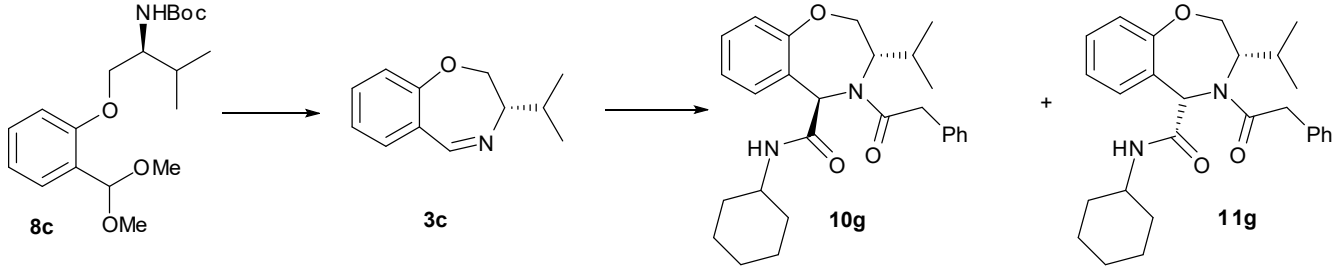
39.6 (*C*H$_2$Ph), 27.7 (C(*C*H$_3$)$_3$), 24.3 (*C*H(CH$_3$)$_2$), 22.7, 21.2 (*C*H$_3$). I.R. (ATR): ν_{max} 3413, 3331, 3063, 3030, 2959, 2930, 2870, 1683, 1644, 1604, 1580, 1508, 1492, 1452, 1411, 1393, 1365, 1348, 1309, 1264, 1248, 1219, 1168, 1144, 1115, 1096, 1076, 1057, 1030, 1004, 957, 869, 823, 804, 758, 721, 695, 634 cm^{-1}. HRMS (ESI+): found 423.2641 [Calcd for $C_{26}H_{36}N_2O_3^+$ (M + H)$^+$ 423.2648].

(*3S*,*5R*)-*N*-(Benzyl)-3-*iso*-propyl-4-(methoxyacetyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide 10f.



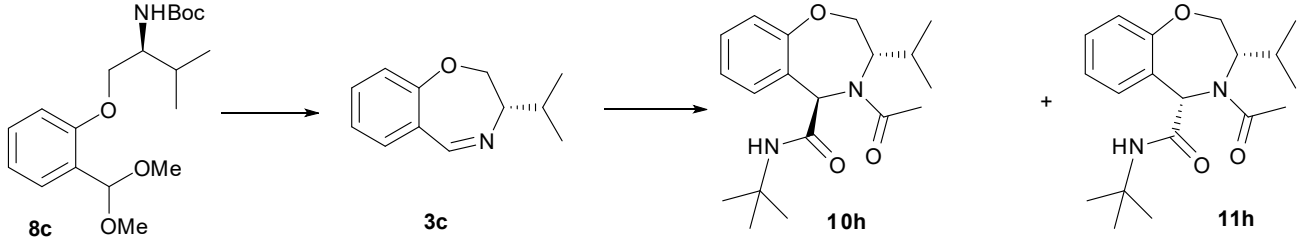
It was prepared in 53% yield from (*S*)-**8c**, methoxyacetic acid and benzyl isocyanide, following the typical procedure described for **10a**. However, in this case, the Ugi-Joullié step reaction was carred out at 40°C. Chromatography was carried out with PE / AcOEt 1 : 1, affording a complete separation of the two diastereomers. The overall yield was 56%. The d.r. was = 94 : 6 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O : MeOH 30:70 + 1% TFA. Detection: UV 220 nm. R_t of **10f**: 6.02. R_t of **11f**: 5.49. Minor diastereomer **11f** was recognized using a MS (ESI) detector.
Oil. R_f = 0.35 (PE / AcOEt 1 : 1) (R_f of **11f** = 0.46). $[\alpha]_D$ = –42.4 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, d6-DMSO, 90 °C): δ = 7.80 (1 H, s, N*H*), 7.48 (1 H, d, J = 6.6 Hz), 7.31-7.14 (6 H, m), 6.99 (1 H, td, J = 7.5, 1.2 Hz), 6.91 (1 H, dd, J = 8.1, 1.1 Hz), 5.62 (1 H, s, C*H*C=O), 4.76 (1 H, broad d, J = 12.3 Hz, C*H*HO), 4.37 (1 H, dd, J = 13.2, 4.8 Hz, C*H*HO), 4.31 (2 H, broad t, J = 5.4 Hz, CH_2NH), 4.29 (1 H, J = 14.2 Hz, C*H*HOMe), 4.11 (1 H, broad s, C*H*N), 4.01 (1 H, J = 14.2 Hz, C*H*HOMe), 3.31 (3 H, s, CH_3O), 1.59 (d of heptuplets, J = 9.9, 6.6 Hz, C*H*(CH$_3$)$_3$), 0.88 (3 H, d, J = 6.6 Hz, CH_3CHCH$_3$), 0.75 (3 H, d, J = 6.8 Hz, CH_3CHCH$_3$). ^{13}C NMR (75 MHz, d6-DMSO, 90 °C): δ = 169.3 (x2) (*C*=O), 156.0, 138.7, 122.3 (quat.), 131.6, 129.5, 127.5 (x2), 126.4 (x2), 126.0, 121.3, 119.1 (aromatic *C*H), 70.6 (*C*H$_2$OMe), 68.1 (broad) (*C*H$_2$O), 62.0 (*C*HC=O), 59.8 (broad) (*C*HN), 57.8 (O*C*H$_3$), 42.3 (*C*H$_2$NH), 28.5 (*C*H(CH$_3$)$_2$), 19.3, 18.8 (*C*H$_3$). I.R. (ATR): ν_{max} 3314, 3062, 3031, 2964, 2931, 2873, 2825, 1653, 1605, 1580, 1516, 1493, 1453, 1424, 1390, 1367, 1320, 1248, 1218, 1198, 1156, 1124, 1107, 1080, 1028, 965, 948, 860, 838, 750, 731, 698, 640, 605 cm^{-1}. HRMS (ESI+): found 397.2135 [Calcd for $C_{23}H_{29}N_2O_4^+$ (M + H)$^+$ 397.2127].

(*3S*,*5R*)-*N*-(Cyclohexyl)-3-*iso*-propyl-4-(phenylacetyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide 10g.



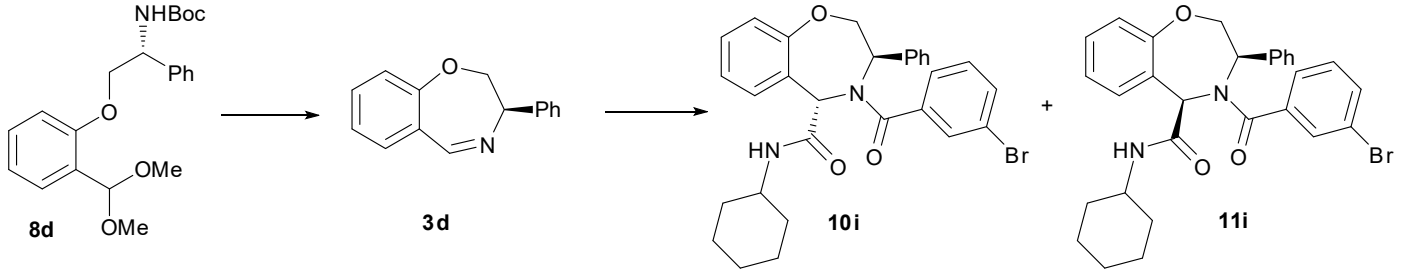
It was prepared in 79% yield from (*S*)-**8c**, phenylacetic acid and cyclohexyl isocyanide, following the typical procedure described for **10a**. However, in this case, the Ugi-Joullié step reaction was carried out at rt for 64 h. Chromatography was carried out with PE / CH_2Cl_2 / AcOEt 3 : 1 . 1, affording a complete separation of the two diastereomers. The overall yield was 82%. The d.r. was = 96 : 4 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O : MeOH 30:70. Detection: UV 220 nm. R_t of **10g**: 15.14. R_t of **11g**: 13.89. Minor diastereomer **11g** was recognized using a MS (ESI) detector.
White solid. R_f = 0.42 (PE / CH_2Cl_2 / AcOEt 3 : 1 . 1). $[\alpha]_D$ = –72.8 (c 1.0, $CHCl_3$). M.p.: 65.0-67.2 °C. ^{1}H NMR (300 MHz, d6-DMSO, 120 °C): δ = 7.39 (1 H, d, J = 7.8 Hz), 7.33-7.19 (6 H, m), 6.98 (1 H, t, J = 7.5 Hz), 6.89 (1 H, d, J = 8.1), 6.78 (1 H, broad s, N*H*), 5.61 (1 H, s, C*H*C=O), 4.63 (1 H, dd, J = 12.5, 3.0 Hz, C*H*HO), 4.35 (1 H, dd, J = 12.5, 5.5 Hz, C*H*HO), 4.20 (1 H, broad s, C*H*N), 3.86 (1 H, d, J = 15.6 Hz, C*H*HPh), 3.71 (1 H, d, J = 15.6 Hz, C*H*HPh), 3.63 (1 H, broad m, C*H*NH), 1.83-1.48 (6 H, m, C*H*$(CH_3)_2$ and CH_2 cyclohexyl), 1.38-1.10 (5 H, m, CH_2 cyclohexyl), 0.89 (3 H, d, J = 6.6 Hz, CH_3CHCH_3), 0.75 (3 H, d, J = 6.8 Hz, CH_3CHCH_3). ^{13}C NMR (75 MHz, d6-DMSO, 90 °C): δ = 171.3, 168.1 (*C*=O), 156.0, 135.4, 123.3 (quat.), 130.8, 129.3, 128.7 (x2), 127.6 (x2), 125.8, 121.4, 119.3 (aromatic *C*H), 68.6 (*C*H_2O), 62.5 (broad) (*C*HC=O), 60.4 (very broad) (*C*HN), 47.6 (*C*HNH), 39.9 (*C*H_2Ph), 31.43, 31.37, 24.6, 23.7, 23.6 (*C*H_2 cyclohexyl), 28.5 (*C*H$(CH_3)_2$), 19.3, 18.8 (*C*H_3). I.R. (ATR): ν_{max} 3418, 3320, 3064, 3031, 2930, 2854, 1647, 1604, 1581, 1510, 1493, 1450, 1408, 1387, 1367, 1348, 1319, 1248, 1217, 1153, 1113, 1080, 1031, 949, 891, 855, 810, 795, 757, 747, 719, 696, 641 cm^{-1}. HRMS (ESI+): found 435.2639 [Calcd for $C_{27}H_{35}N_2O_3^+$ $(M + H)^+$ 435.2648].

(*3S*,*5R*)-4-(Acetyl)-*N*-(*tert*-butyl)-3-*iso*-propyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide 10h.



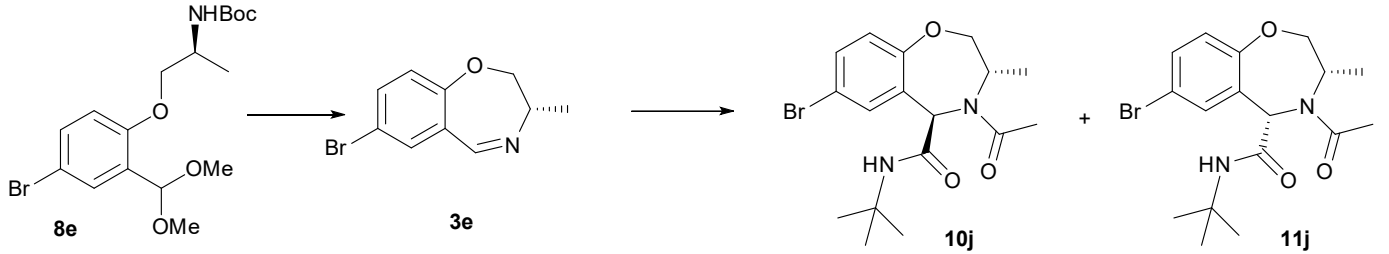
It was prepared in 52% yield from (*S*)-**8c**, acetic acid and *tert*-butyl isocyanide, following the typical procedure described for **10a**. The reaction was in this case incomplete and also 6% of starting material was recovered. Chromatography was carried out with CH_2Cl_2 / AcOEt 4 : 1, affording a complete separation of the two diastereomers. The minor diastereomer **11h** was not detected by HPLC-MS or NMR. The d.r. was thus supposed to be > 97 : 3. HPLC conditions: C6-Phenyl column 150 x 3 mm, 3 µm. Flow: 0.38 ml/min. Temp: 26°C. Eluent: H_2O : CH_3CN 60:40. Detection: UV 220 nm. R_t of **10h**: 11.66.
White solid. R_f = 0.28 (CH_2Cl_2 / AcOEt 4 : 1). $[\alpha]_D$ = –9.4 (c 0.9, $CHCl_3$). M.p.: 104.5-107.8 °C. ^{1}H NMR (300 MHz, d6-DMSO, 120 °C): δ = 7.46 (1 H, dd, J = 7.6, 1.4 Hz), 7.25 (1 H, td, J = 8.0, 1.6), 6.98 (1 H, td, J = 7.5, 1.1 Hz), 6.90 (1 H, dd, J = 8.1, 1.0), 6.62 (1 H, broad s, N*H*), 5.49 (1 H, s, C*H*C=O), 4.68 (1 H, dd, J = 12.5, 3.7 Hz, C*H*HO), 4.35 (1 H, dd, J = 12.5, 5.8 Hz, C*H*HO), 4.12 (1 H, broad s, C*H*N), 2.10 (3 H, s, CH_3C=O), 1.71 (1 H, d of heptuplets, J = 9.9, 6.6 Hz, C*H*$(CH_3)_3$), 1.26 (9 H, s, C(CH_3)$_3$), 0.90 (3 H, d, J = 6.6 Hz, CH_3CHCH_3), 0.79 (3 H, d, J = 6.8 Hz, CH_3CHCH_3). ^{13}C NMR (75 MHz, d6-DMSO, 90 °C): δ = 170.3, 168.4 (*C*=O), 155.9, 123.3 (quat.), 130.7, 129.1, 121.2, 119.2 (aromatic *C*H), 68.4 (*C*H_2O), 63.3 (broad) (*C*HC=O), 59.9 (very broad, barely visible) (*C*HN), 50.1 (*C*NH), 28.4 (*C*H$(CH_3)_2$), 27.8 (C(*C*H_3)$_3$), 21.7 (*C*H_3C=O), 19.3, 18.9 (*C*H_3). I.R. (ATR): ν_{max} 3332, 2965, 2933, 2874, 1980, 1668, 1640, 1607, 1583, 1529, 1496, 1451, 1413, 1392, 1365, 1346, 1331, 1303, 1289, 1266, 1250, 1218, 1116, 1088, 1041, 979, 945, 900, 890, 858, 841, 812, 755, 746, 689, 654, 631, 621 cm^{-1}. HRMS (ESI+): found 333.2176 [Calcd for $C_{19}H_{29}N_2O_3^+$ $(M + H)^+$ 333.2178].

(*3R*,*5S*)-4-(3-Bromobenzoyl)-*N*-(cyclohexyl)-3-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide 10i.



It was prepared in 86% yield from (*R*)-**8d**, 3-bromoacetic acid and cyclohexyl isocyanide, following the typical procedure described for **10a**. However, in this case, 1.3 equivalents of isocyanide were used. Chromatography was carried out with PE/AcOEt 3:1→AcOEt/MeOH 95:5, affording a complete separation of the two diastereomers. The minor diastereomer **11** was not isolated. An overall yield 89% was calculated on the basis of d.r. The d.r. was = 97 : 3 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O : MeOH 30:70 + 1% TFA. Detection: UV 220 nm. R_t of **10i**: 10.93. R_t of **11i**: 11.72. Minor diastereomer **11i** was recognized using a MS (ESI) detector.
White solid. R_f = 0.36 (PE/AcOEt 3 : 1). $[\alpha]_D$ = –98.5 (c 1.0, $CHCl_3$). M.p.: 229.0-231.5 °C. ^{1}H NMR (300 MHz, d6-DMSO, 90 °C): δ = 7.61 (1 H, d, J = 7.8 Hz), 7.41-7.22 (4 H, m), 7.21-7.05 (6 H, m), 6.95 (1 H, td, J = 7.4, 0.9 Hz), 6.71 (1 H, d, J = 8.1), 6.65 (1 H, broad d, J = 6.6 Hz, N*H*), 5.78 (1 H, broad s, C*H*C=O), 5.44 (1 H, broad s, C*H*Ph), 5.03 (1 H, dd, J = 13.6, 1.4 Hz, C*H*HO), 4.53 (1 H, dd, J = 13.6, 4.0 Hz, C*H*HO), 3.70-3.55 (1 H, broad m, C*H*NH), 1.82-1.47 (5 H, m, CH_2 cyclohexyl), 1.40-1.05 (5 H, m, CH_2 cyclohexyl). ^{13}C NMR (75 MHz, d6-DMSO, 90 °C): δ = 169.7, 168.5 (*C*=O), 155.3, 138.8, 138.1, 121.0, 120.3 (quat.), 132.1, 131.8, 130.0, 129.4, 128.4, 127.2 (x2), 125.9, 125.6 (x2), 124.6, 120.9, 118.9 (aromatic *C*H), 68.5 (*C*H_2O), 64.1 (broad) (*C*HC=O), 60.5 (broad) (*C*HN), 48.1 (*C*HNH), 31.1 (x2), 24.5, 23.8, 23.7 (*C*H_2 cyclohexyl). I.R. (ATR): ν_{max} 3320, 3063, 3028, 2924, 2850, 1663, 1650, 1610, 1581, 1563, 1512, 1490, 1464, 1449, 1414, 1389, 1352, 1332, 1311, 1275, 1249, 1219, 1178, 1148, 1115, 1080, 1046, 1027, 998, 977, 956, 917, 903, 894, 879, 866, 854, 823, 798, 777, 753, 741, 731, 691, 647 cm^{-1}. HRMS (ESI+): found 533.1429 [Calcd for $C_{29}H_{30}BrN_2O_3^+$ $(M + H)^+$ 533.1440].

(*3S*,*5R*)-4-(3-Acetyl)-7-bromo-*N*-(*tert*-butyl)-3-methyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide 10j.

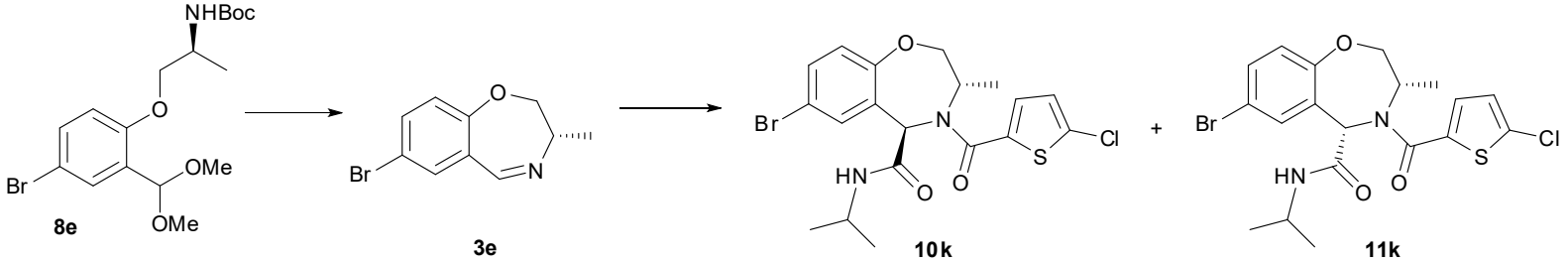


It was prepared in 68% yield from (*S*)-**8e**, acetic acid and *tert*-butyl isocyanide, following the typical procedure described for **10a**. However, in this case, during Ugi-Joullié reaction, after 24 h, additional 0.2 equivalents of isocyanide were added. Chromatography was carried out with PE/AcOEt 2:1→1:1, affording a complete separation of the two diastereomers. The minor diastereomer **11j** was not isolated. An overall yield 71% was calculated on the basis of d.r. The d.r. was = 95 : 5 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O : MeOH 50:50 + 1% CF_3CO_2H. Detection: UV 220 nm. R_t of **10j**: 13.59. R_t of **11j**: 12.51. Minor diastereomer **11j** was recognized using a MS (ESI) detector.

White solid. R_f = 0.30 (PE/AcOEt 2 : 1). R_f of **11j** = 0.42. $[\alpha]_D$ = –46.2 (c 1.0, $CHCl_3$). M.p.: 180.3-181.8 °C. ^{1}H NMR (300 MHz, d6-DMSO, 90 °C): δ = 7.74 (1 H, d, J = 2.1 Hz), 7.39 (1 H, dd, J = 8.7, 2.5 Hz), 6.85 (1 H, d, J = 8.7 Hz), 6.62 (1 H, broad s, N*H*), 5.62 (1 H, broad s, C*H*C=O), 4.85 (1 H, d, J = 13.0 Hz, C*H*HO), 4.45 (1 H, broad quintuplet, J = 5.9 Hz, C*H*CH_3), 4.18 (1 H, dd, J = 13.0, 4.9 Hz, C*H*HO), 2.12 (3 H, s, C*H*$_3$C=O), 1.25 (9 H, s, C(C*H*$_3$)$_3$), 1.10 (3 H, d, J = 6.9 Hz, C*H*$_3$CH). ^{13}C NMR (75 MHz, d6-DMSO, 90 °C): δ = 169.4, 168.6 (*C*=O), 154.9, 123.3, 111.6 (quat.), 134.3, 131.9, 120.7 (aromatic *C*H), 69.5 (*C*H_2O), 61.6 (broad) (*C*HC=O), 51.4 (broad) (*C*HN), 50.3 (*C*NH), 27.8 (C(*C*H_3)$_3$, 21.1 (*C*H_3=O), 16.2 (*C*H_3CH). I.R. (ATR): ν_{max} 3413, 3336, 2969, 2930, 1685, 1630, 1570, 1514, 1487, 1449, 1418, 1389, 1369, 1335, 1319, 1299, 1281, 1267, 1254, 1221, 1179, 1146, 1125, 1106, 1090, 1066, 1042, 1000, 962, 929, 903, 877, 823, 766, 740, 709, 689, 659, 624 cm^{-1}.HRMS (ESI+): found 383.0974 [Calcd for $C_{17}H_{24}BrN_2O_3^+$ (M + H)$^+$ 383.0970].

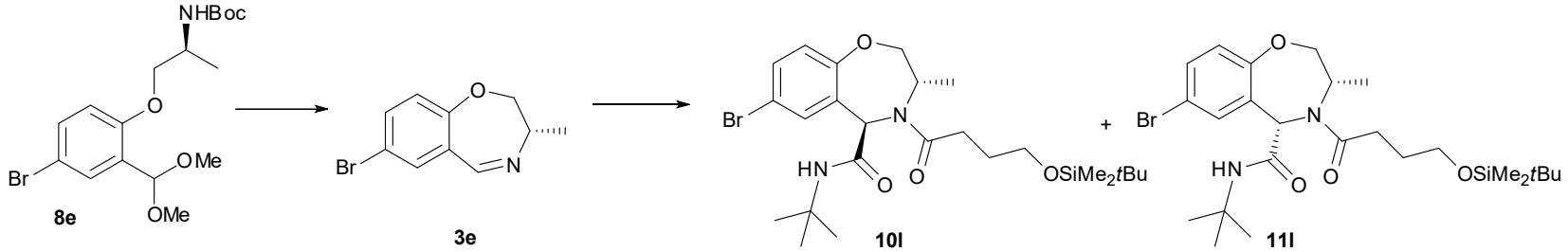
(*3R*,*5S*)-4-(3-Acetyl)-7-bromo-*N*-(*tert*-butyl)-3-methyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide *ent*-10j.
It was prepared exactly as for the enantiomer **10j**. $[\alpha]_D$ = +44.9 (c 1.0, $CHCl_3$). All the other data were identical to those of the enantiomer.

(*3S*,*5R*)-7-Bromo-4-(5-chlorothiophene-2-carbonyl)-*N*-isopropyl-3-methyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide 10k.



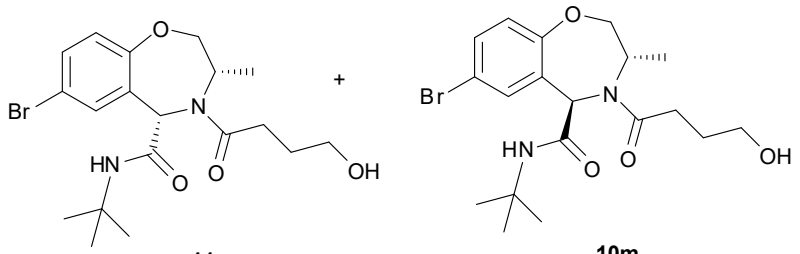
It was prepared in 60% yield from (*S*)-**8e**, 5-chloro-2-thienoic acid and isopropyl isocyanide, following the typical procedure described for **10a**. However, in this case, for the Ugi-Joullié reaction, 1.4 equivalents of isocyanide were used. Chromatography was carried out with PE/AcOEt 4:1→3:1. The minor diastereomer **11k** was not isolated. The overall yield was calculated to be 63% on the basis of d.r. The d.r. was = 95 : 5 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O : MeOH 50:50. Detection: UV 220 nm. R_t of **10k**: 16.27. R_t of **11k**: 15.68. Minor diastereomer **11k** was recognized using a MS (ESI) detector.
White solid. R_f = 0.33 (PE/AcOEt 4 : 1). $[\alpha]_D$ = –71.3 (c 1.0, $CHCl_3$). M.p.: 166.8-169.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.41 (1 H, dd, J = 8.7, 2.4 Hz), 7.22 (1 H, d, J = 2.3 Hz), 7.17 (1 H, d, J = 3.9 Hz), 6.90-6.85 (2 H, m), 5.63 (1 H, broad s, C*H*C=O), 5.49 (1 H, broad s, N*H*), 4.63 (1 H, d, J = 13.5 Hz, C*H*HO), 4.70-4.58 (1 H, m, C*H*CH_3), 1.31 (3 H, d, J = 6.8 Hz, C*H*$_3$CH), 1.12 (3 H, d, J = 6.6 Hz, C*H*$_3$CHCH_3), 1.10 (3 H, d, J = 6.6 Hz, C*H*$_3$CHCH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 168.8, 164.6 (*C*=O), 155.5, 135.7, 134.6, 122.1, 113.7 (quat.), 134.1, 133.8, 128.6, 126.2, 121.9 (aromatic *C*H), 70.2 (*C*H_2O), 64.4 (*C*HC=O), 53.9 (*C*HN), 42.5 (*C*HNH), 22.4, 22.3 (*C*H_3)$_2$CH, 16.8 (*C*H_3CH). I.R. (ATR): ν_{max} 3283, 3094, 2977, 2933, 2876, 1657, 1623, 1514, 1486, 1434, 1386, 1344, 1316, 1277, 1251, 1220, 1186, 1145, 1129, 1107, 1059, 998, 951, 933, 874, 859, 840, 771, 743, 688 cm^{-1}.HRMS (ESI+): found 471.0156 [Calcd for $C_{19}H_{21}BrClN_2O_3S^+$ (M + H)$^+$ 471.0145].

(*3S*,*5R*)-7-Bromo-4-(5-chlorothiophene-2-carbonyl)-*N*-isopropyl-3-methyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide 10l.



Acetal **8e** (395.4 mg, 976 µmol) was dissolved in CH_2Cl_2 (3.7 mL) and treated with 37% aqueous HCl (808 µL, 9.67 mmol). The mixture was stirred at rt for 5 h. Then it was diluted with CH_2Cl_2, and cautiously treated with a solution of Na_2CO_3 (765 mg, 7.21 mmol) in water (16.0 mL). After checking that pH > 9, the two phases were separated, washed with brine, and evaporated to dryness. The resulting crude imine **3e** (yellow oil)(197.5 mg) was taken up in dry methanol (4.75 mL), and treated with *tert*-butyl isocyanide (131 µl, 1.15 mmol) and with 3-((tert-butyldimethylsilyl)oxy)propanoic acid (252 mg, 1.15 mmol). The mixture was stirred at rt for 24 h. Then further *tert*-butyl isocyanide (21 µL, 0.25 mmol) were added. After strring for 24 h more, the mixture was evaporated to dryness and chromatographed (PE / AcOEt 5:1) to give pure **10l** (284 mg, 54%). The minor diastereome **11l** was not isolated. The ratio **10l** : **11l** was determined by HPLC on the crude product and resulted = 95:5. HPLC conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O : MeOH 50:50 + 1% CF_3CO_2H up to 20 minutes. Then 100% MeOH + 1% CF_3CO_2H. Detection: UV 220 nm. R_t of **10l**: 20.82. R_t of **11l**: 20.45. Minor diastereomer **11l** was recognized using a MS (ESI) detector. The overall yield was calculated to be 57% on the basis of d.r.
Oil. R_f = 0.33 (PE/AcOEt 5 : 1). $[\alpha]_D$ = –23.0 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, d6-DMSO, 90 °C): δ = 7.72 (1 H, d, J = 2.5 Hz), 7.39 (1 H, dd, J = 8.7, 2.5 Hz), 6.85 (1 H, d, J = 8.7 Hz), 6.57 (1 H, broad s, N*H*), 5.64 (1 H, broad s, C*H*C=O), 4.82 (1 H, d, J = 13.1 Hz, C*H*HO), 4.47 (1 H, broad quintuplet, J = 6.1 Hz, C*H*CH_3), 4.18 (1 H, dd, J = 13.1, 4.9 Hz, C*H*HO), 3.64 (2 H, t, J = 6.4 Hz, CH_2OSi), 2.55 (1 H, dt, J = 15.6, 7.2 Hz, C*H*HC=O), 2.37 (1 H, dt, J = 15.6, 7.2 Hz, C*H*HC=O), 1.77 (2 H, quintuplet, J = 6.9 Hz, C$H_2$$CH_2$OSi), 1.25 (9 H, s, C(C$H_3$)$_3$), 1.11 (3 H, d, J = 6.8 Hz, CH_3CH), 0.89 (9 H, s, SiC(CH_3)$_3$), 0.05 (6 H, s, (CH_3)$_2$Si). ^{13}C NMR (75 MHz, d6-DMSO, 90 °C): δ = 171.7, 168.6 (*C*=O), 155.0, 123.4, 111.6 (quat.), 134.2, 131.9, 120.6 (aromatic *C*H), 69.4 (*C*H_2O), 61.4 (*C*H_2OSi), 61.2 (broad) (*C*HC=O), 51.1 (*C*HN), 50.2 (*C*NH), 28.4 (*C*H_2C=O), 27.8 (C(*C*H_3)$_3$, *C*$H_2$$CH_2$OSi), 25.3 (SiC(*C*$H_3$)$_3$), 17.3 (Si*C*$(CH_3)_3$)), 16.2 (*C*$H_3$CH), –5.9 ((*C*$H_3$)$_2$Si). I.R. (ATR): ν_{max} 3418, 3344, 2956, 2929, 2857, 1686, 1625, 1538, 1507, 1486, 1472, 1462, 1454, 1412, 1393, 1365, 1323, 1273, 1250, 1235, 1181, 1124, 1100, 1060, 1005, 968, 939, 834, 775, 752, 679, 664, 626, 612 cm^{-1}.HRMS (ESI+): found 541.2103 [Calcd for $C_{25}H_{42}BrN_2O_4Si^+$ (M + H)$^+$ 541.2097].

HPLC conditions for analysis of the diastereomeric ratio of 10m and 11m.



11m **10m**

Column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O : MeOH 90:10 + 1% CF_3CO_2H up to 20 minutes. Then 100% MeOH + 1% CF_3CO_2H. Detection: UV 220 nm. R_t of **10m**: 17.93. R_t of **11m**: 18.58. The ratio was 90 : 10 (**11m** . **10m**).

HPLC conditions for analysis of the enantiomeric composition of 10j, 11j, *ent*-10j, and *ent*-11j.
Column: Chiral Pak AD 250 x 4, 6 µm. Flow: 0.8 ml/min. Temp: 25°C. Eluent: hexane : isopropanol 97:3. Detection: DAD (chromatograms are reported at 220 nm). R_t of **10j**: 28.24. R_t of **11j**: 24.31. R_t of *ent*-**10j**: 32.27 R_t of *ent*-**11j**: 29.43.

4-((*tert*-Butyldimethylsilyl)oxy)butanoic acid 12
γ-Butyrolactone (0.763 mL, 10.0 mmol) was dissolved in a solution of NaOH (451 mg, 11.3 mmol) in MeOH (10.0 mL). The mixture was stirred at room temperature for 2 h. It was then evaporated and the crude product (1.2043 g) was taken up in dry DMF (20.0 mL). The mixture was cooled to 0°C and then *tert*-butyldimethylchlorosilane (3.299 g, 21.9 mmol) and imidazole (2.257 g, 33.1 mmol) were added. The mixture was stirred overnight at room temperature. It was diluted with PE / Et_2O 1:1 and washed with water. The organic phases were dried over Na_2SO_4, filtered and evaporated under reduced pressure at low temperature (the rotavapor bath was kept near 0°C). The resulting colourless oil (4.206 g) was taken up with a mixture of water (30.0 mL), MeOH (10.0 mL), THF (10.0 mL), and treated with K_2CO_3 (2.767g, 20.0 mmol). The resulting mixture was stirred at room temperature overnight. It was then concentrated to remove most MeOH and THF, diluted with Et_2O and extracted with water. The aqueous phase was acidified to pH = 4 with HCl 1M and extracted with Et_2O. The organic phases were dries over Na_2SO_4, filtered and evaporated under reduced pressure. The desired product (1.4773 g, 68%) was obtained as a colourless oil and used as such without any purification.

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2. S. K. Reddy Guduru, S. Chamakuri, I. O. Raji, K. R. MacKenzie, C. Santini and D. W. Young, *J. Org. Chem.*, 2018, **83**, 11777-11793.
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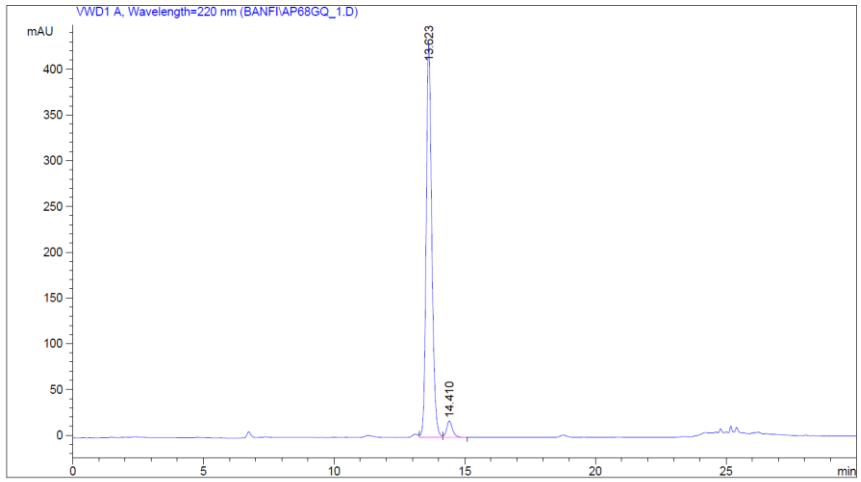
HPLC and NMR determination of enantiomeric excesses and diastereomeric ratios

HPLC of crude 10a + 11a after Ugi-Joullié reaction

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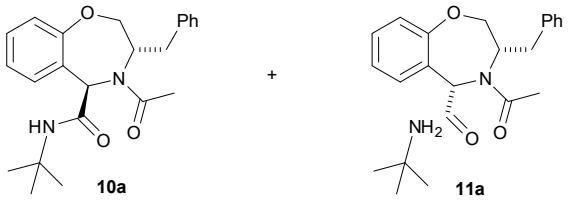
================================================================
                    Area Percent Report
================================================================

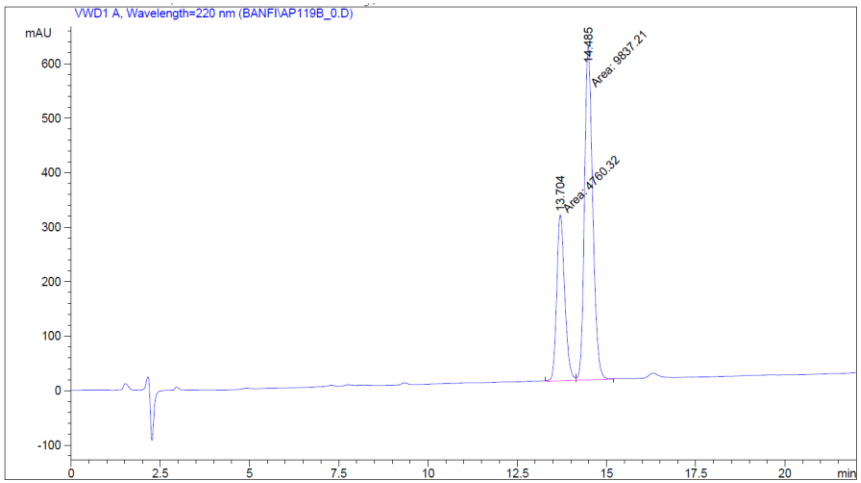
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|---------|----------|-------|
   1  13.623 VV    0.2297 6410.38281  428.97720  95.7331
   2  14.410 VB    0.2373  285.71570   18.03100   4.2669
```



HPLC of crude 10a + 11a after epimerization promoted by KOH

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================================================================
                    Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|---------|----------|-------|
   1  13.704 MF    0.2605 4760.31543  304.53952  32.6104
   2  14.485 FM    0.2677 9837.21387  612.36823  67.3896
```
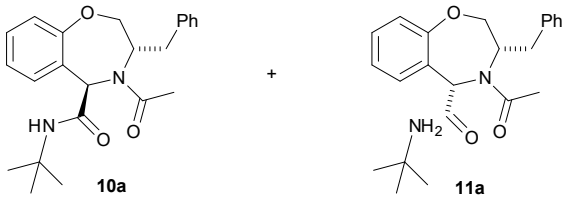
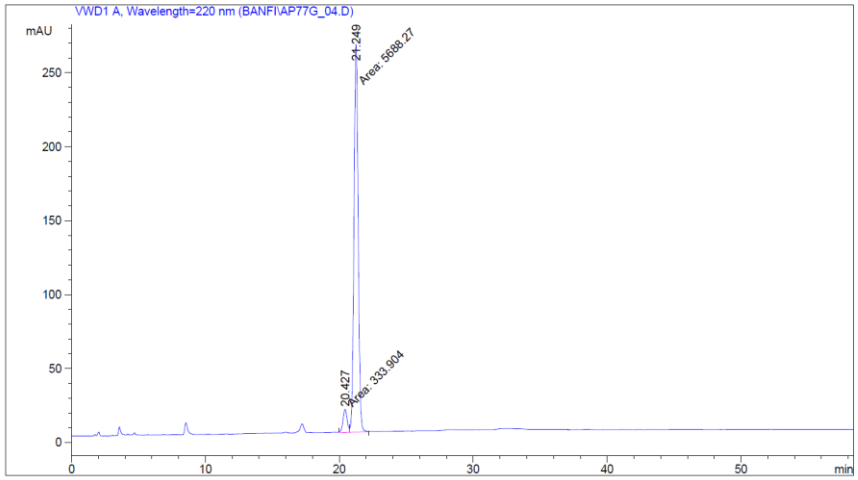



HPLC of crude 10b + 11b

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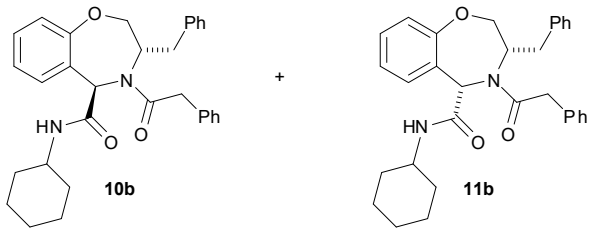
================================================================================
                            Area Percent Report
================================================================================

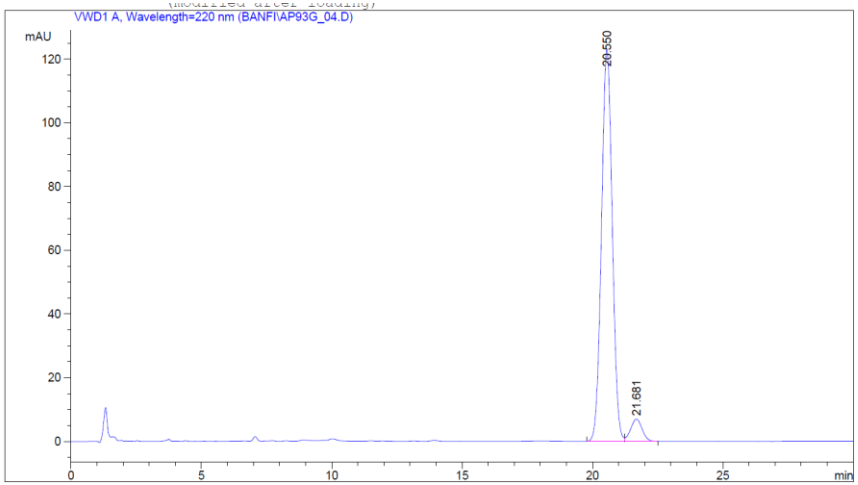
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  20.427 MF    0.3592  333.90381   15.49456   5.5446
   2  21.249 FM    0.3614 5688.26855  262.29486  94.4554
```



HPLC of crude 10c + 11c

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

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  20.550 BV    0.4486 3527.66724  122.85065  94.3224
   2  21.681 VB    0.4790  212.34320    6.94468   5.6776

Totals :                  3740.01044  129.79533
```
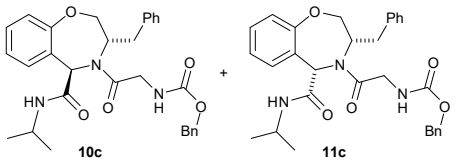
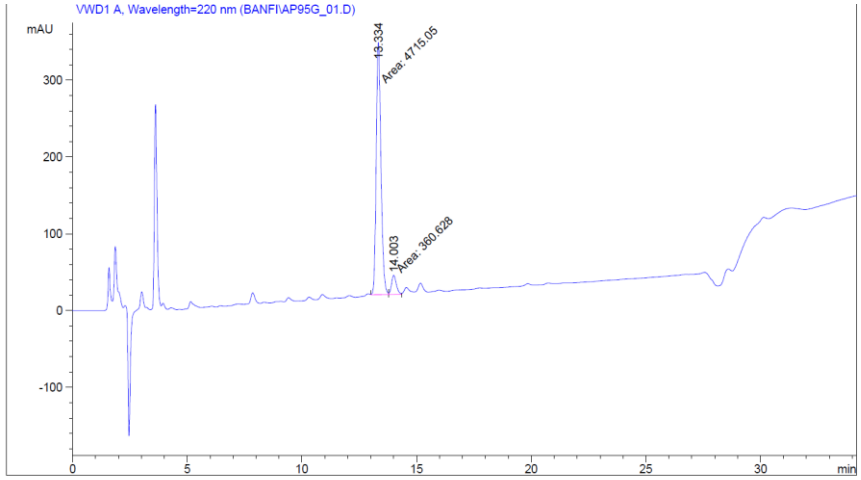



HPLC of crude 10d + 11d

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

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|---------|---------|--------|
   1  13.334 MF    0.2392 4715.04932  328.57242  92.8950
   2  14.003 FM    0.2420  360.62830   24.84063   7.1050
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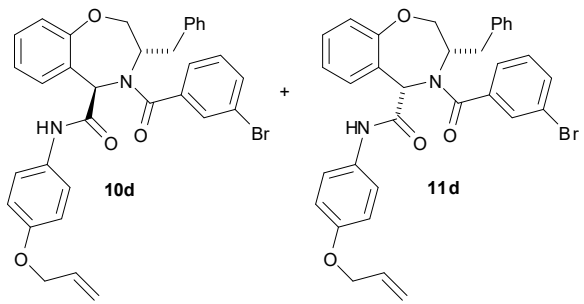
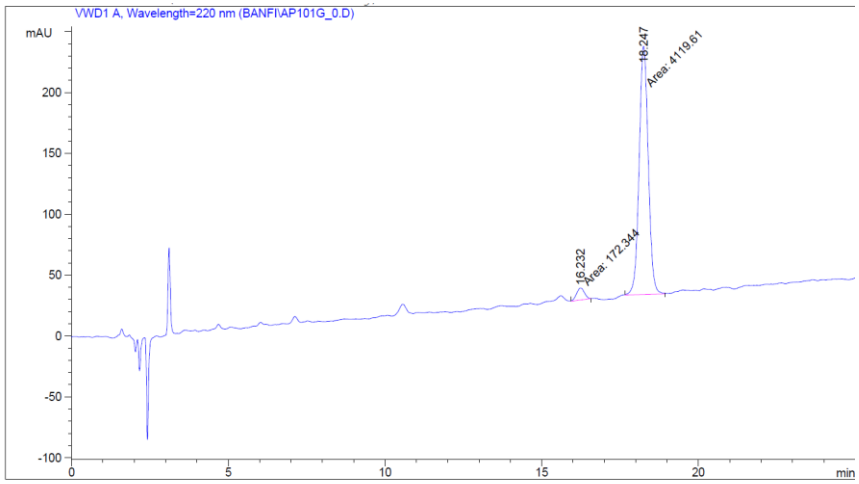


HPLC of crude 10e + 11e

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

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|---------|---------|--------|
   1  16.232 MM    0.2911  172.34360    9.86690   4.0155
   2  18.247 MM    0.3363 4119.61475  204.16066  95.9845
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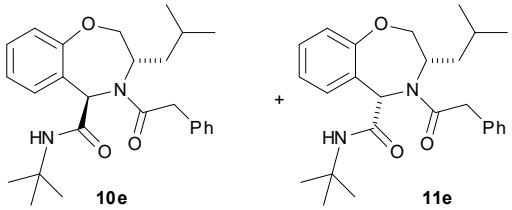
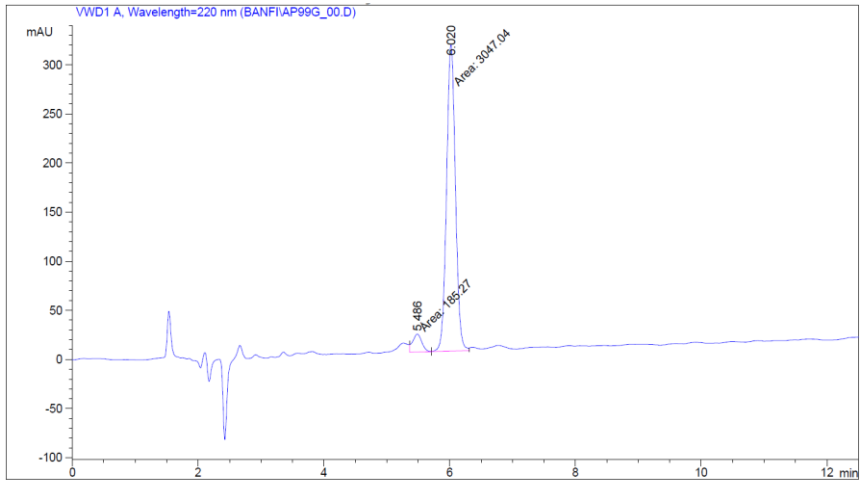


HPLC of crude 10f + 11f

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

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|---------|---------|--------|
   1   5.486 FM    0.1689  185.27025   18.28515   5.7318
   2   6.020 MF    0.1627 3047.03931  312.05853  94.2682
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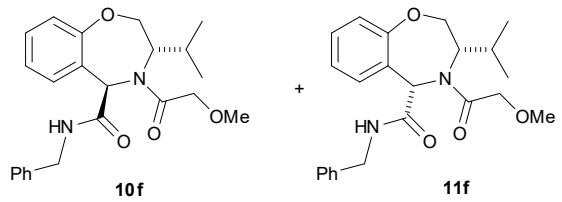
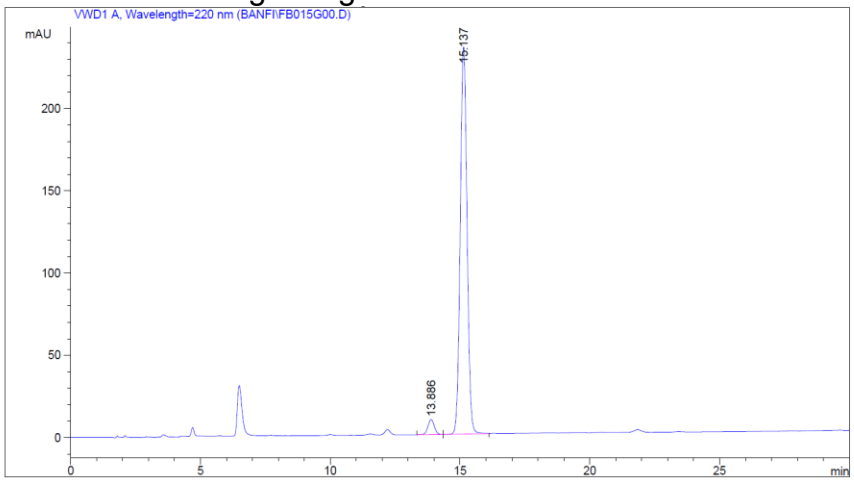


HPLC of crude 10g + 11g

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================================================================================
                            Area Percent Report
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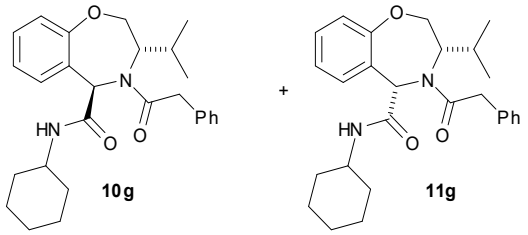
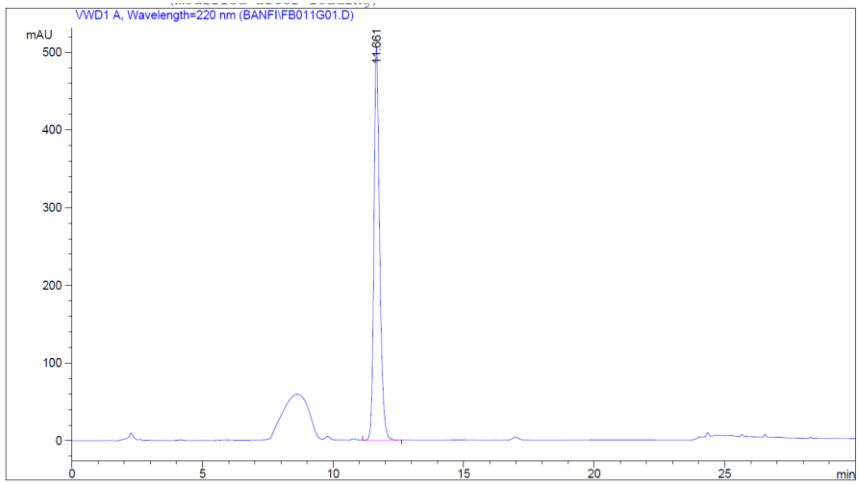
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|---------|---------|--------|
   1  13.886 PP    0.2689  159.05804    9.19113   3.5708
   2  15.137 VB    0.2858 4295.31494  235.29900  96.4292
```



HPLC of crude 10h

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

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  11.661 VV    0.2277 7715.28467  505.11163 100.0000
```
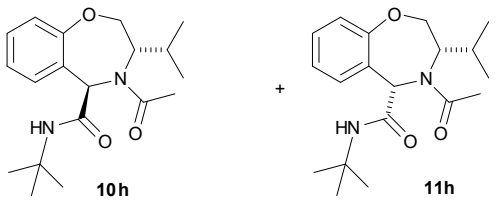
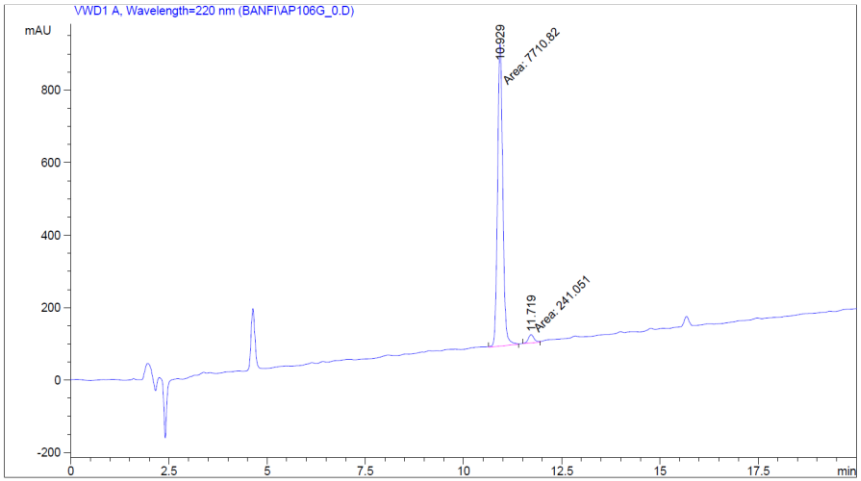
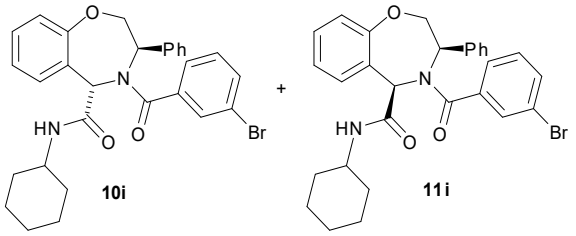



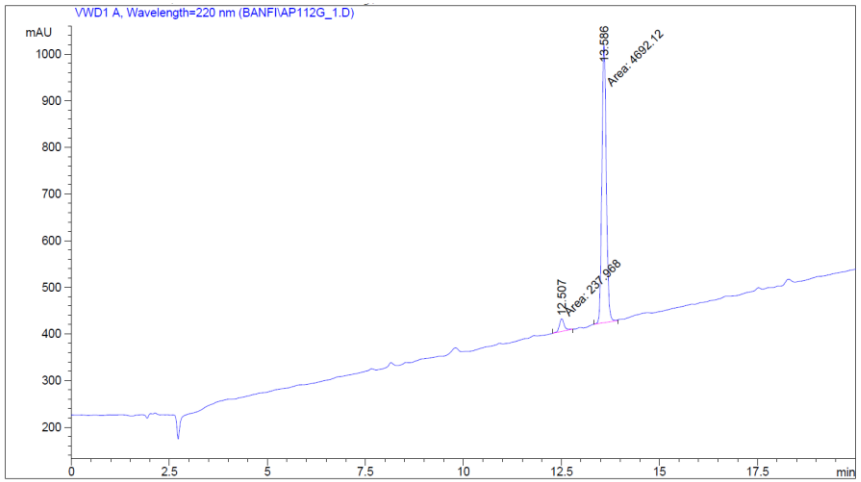
HPLC of crude 10i + 11i



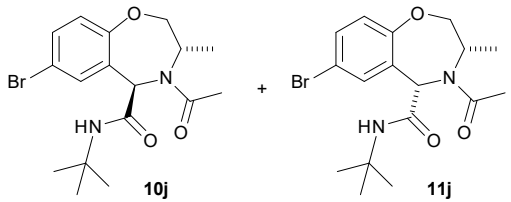

```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  10.929 MM    0.1538 7710.82275  835.43097  96.9686
   2  11.719 MM    0.1742  241.05122   23.06897   3.0314
```



HPLC of crude 10j + 11j

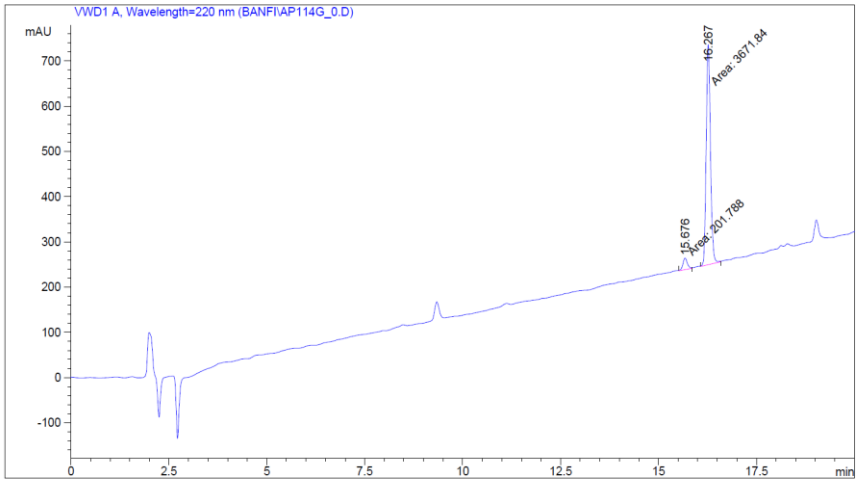



```
================================================================
                    Area Percent Report
================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.507 MM    0.1441  237.96765   27.53019   4.8268
   2  13.586 MM    0.1313 4692.12158  595.68738  95.1732
```

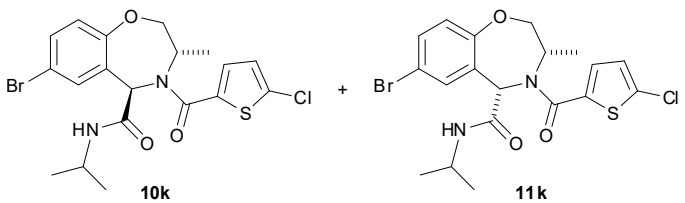


10j + **11j**

HPLC of crude 10k + 11k

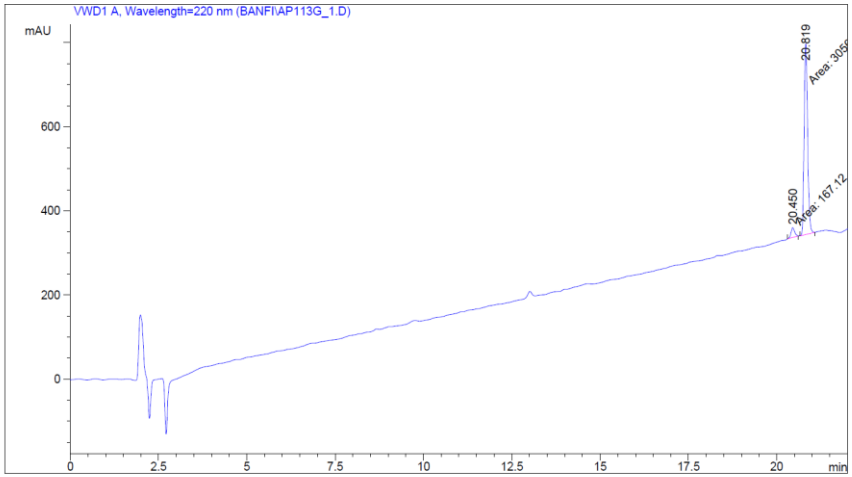



```
================================================================
                    Area Percent Report
================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  15.676 MM    0.1331  201.78844   25.26794   5.2093
   2  16.267 MM    0.1256 3671.84375  487.42706  94.7907
```



10k + **11k**

HPLC of crude 10l + 11l

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

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]     %
----|------|----|-------|----------|---------|-------|
   1  20.450 MM    0.1180  167.12010   23.60336   5.1841
   2  20.819 MM    0.1119 3056.55444  455.33575  94.8159
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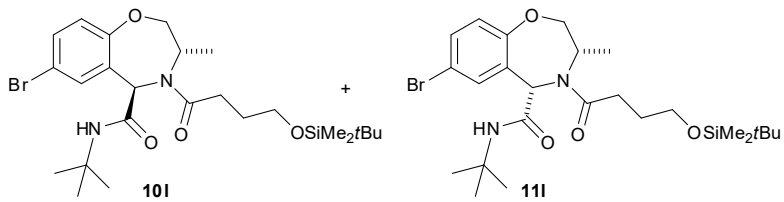
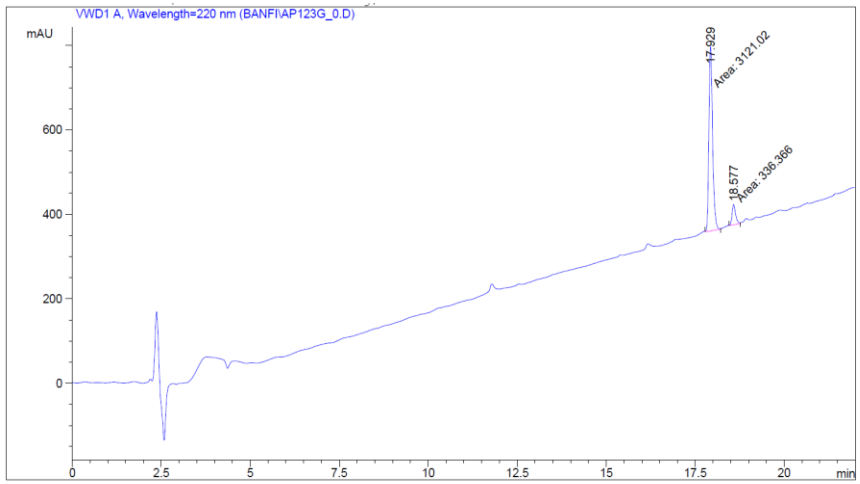


10l **11l**

HPLC of crude 11m + 10m (after reaction of 10l with TBAF)

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

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]     %
----|------|----|-------|----------|---------|-------|
   1  17.929 MM    0.1190 3121.02319  437.27203  90.2711
   2  18.577 MM    0.1171  336.36569   47.86787   9.7289
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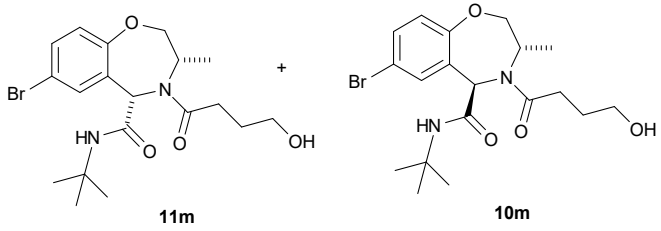
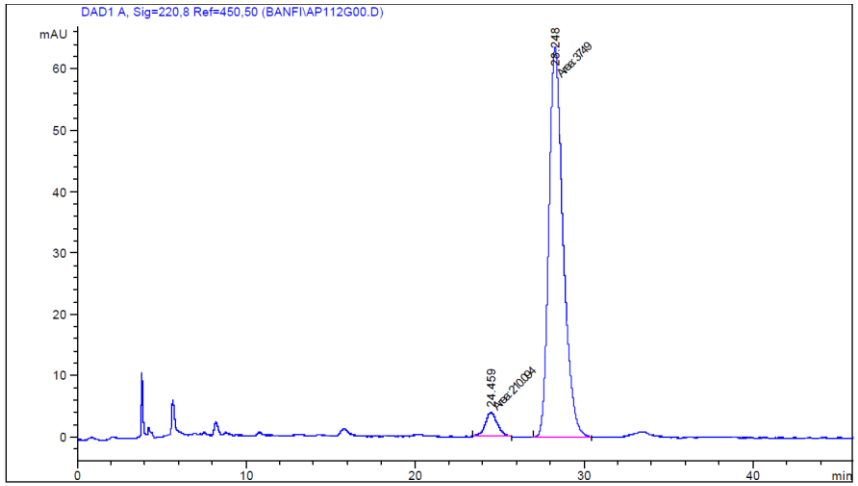


11m **10m**

HPLC of chiral stationary phase of crude **11j** + **10j** after Ugi-Joullié reaction

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                    Area Percent Report
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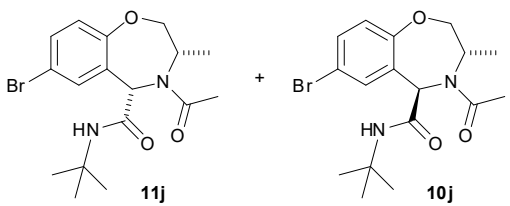
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

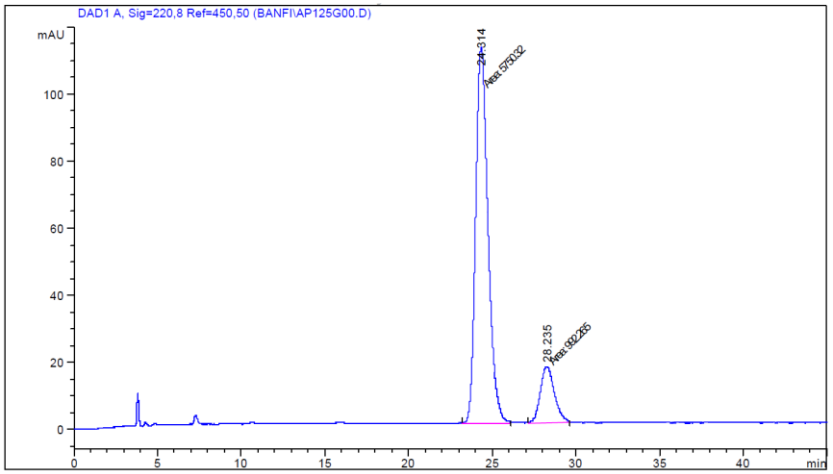

Signal 1: DAD1 A, Sig=220,8 Ref=450,50

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  24.459 MM    0.8556  210.09351    4.09243   5.3066
   2  28.248 MM    0.9804 3749.00391   63.73133  94.6934
```



11j **10j**

HPLC of chiral stationary phase of **11j** + **10j** after epimerization (partially enriched in **11j** by chromatography).




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

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,8 Ref=450,50

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
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   2  28.235 MM    0.9750  992.26495   16.96245  14.7164
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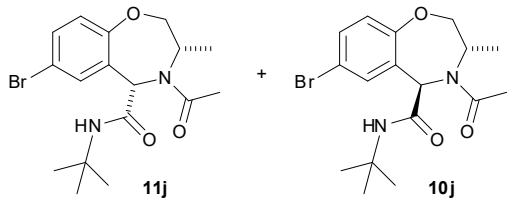
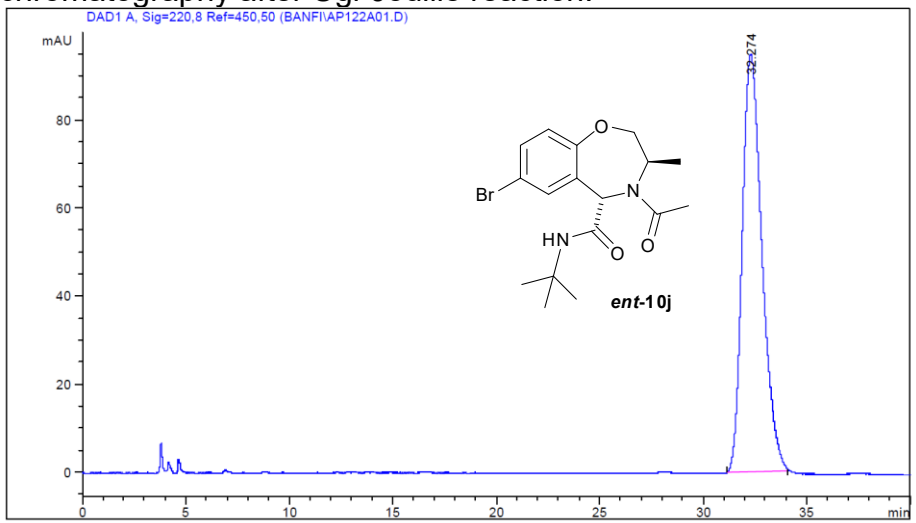
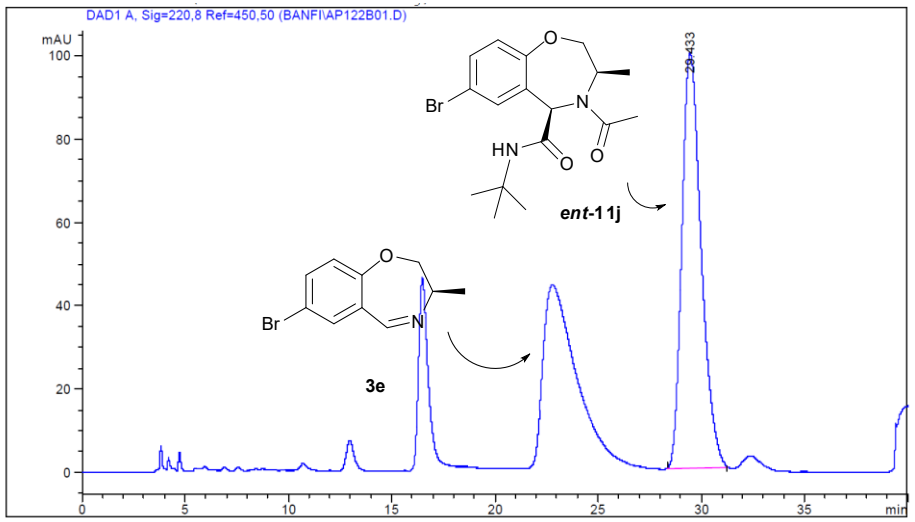


11j **10j**

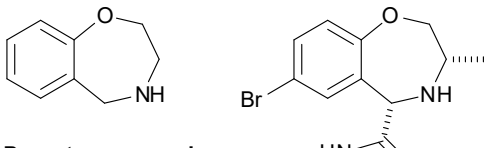
HPLC of chiral stationary phase of pure ***ent*-10j** isolated by chromatography after Ugi-Joullié reaction.



HPLC of chiral stationary phase of ***ent*-11j** isolated by prep TLC after Ugi-Joullié reaction (impure of some starting imine **3e**).

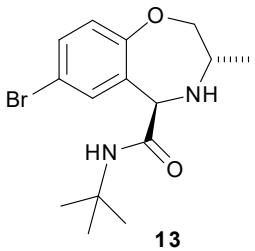


Conformational analysis of compounds 13 and 14



Parent compound

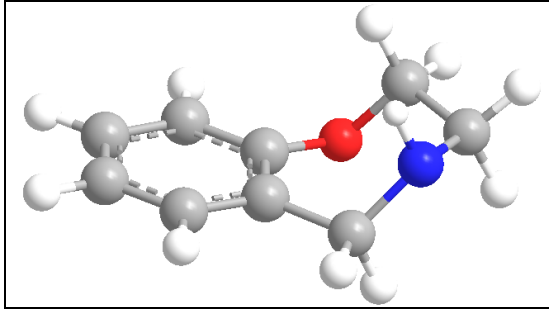
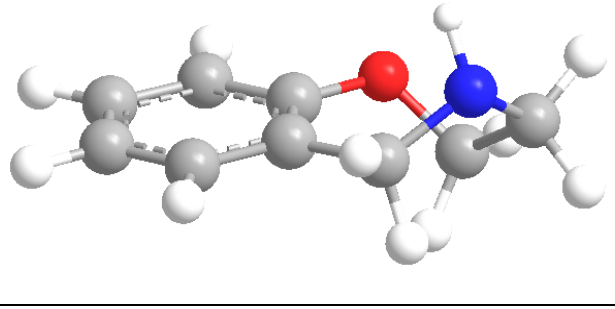
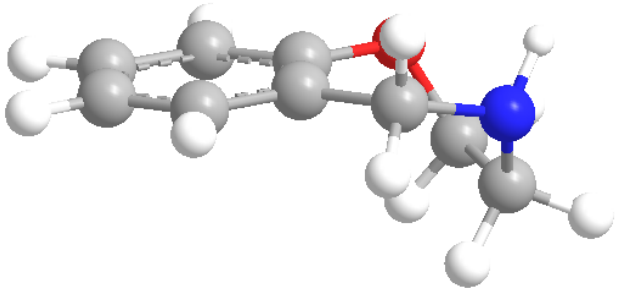
14



13

This study was carried out Using the commercial software ChemBio3D Ultra and the MOPAC (PM3) interface.
First of all we have searched for all the local minima of the parent compound

This parent compound gives rise to three conformations with similar energy. One of them resembles a chair, while the second one resembles a twist and the third one a boat. Thus, here we conventionally adopt these three terms. Obviously, each of these three conformations exist in two possible enantiomeric forms, which are in equilibrium.
A notable difference between them is that in the chair and twist conformations the axial hydrogen at *C*-5 is located on the same side of the median plane than *C*-2 and *C*-3. On the contrary, in the boat, they are opposite.

Chair	Twist	Boat
		

When passing to the real compound, the two conformations of each type become diastereomeric. Thus, we must consider 6 different conformations for each diastereomer. We have searched for the absolute minimum for each of them. According to the heat of formation found, the ones evidenced in yellow are more likely

Conformations of cis compound (14)						
Number	**Type**	**Heat of formation (Kcal/mol)**	**Position of H-5**	**Position of H-3**	**Distance between H-5 and H-3 (Å)**	**Dihedral angles between H-2 and H-3**
1	Chair	-60.49	axial	axial	2.31	178, 61
2	Twist	-59.48	axial	axial	2.45	91, 29

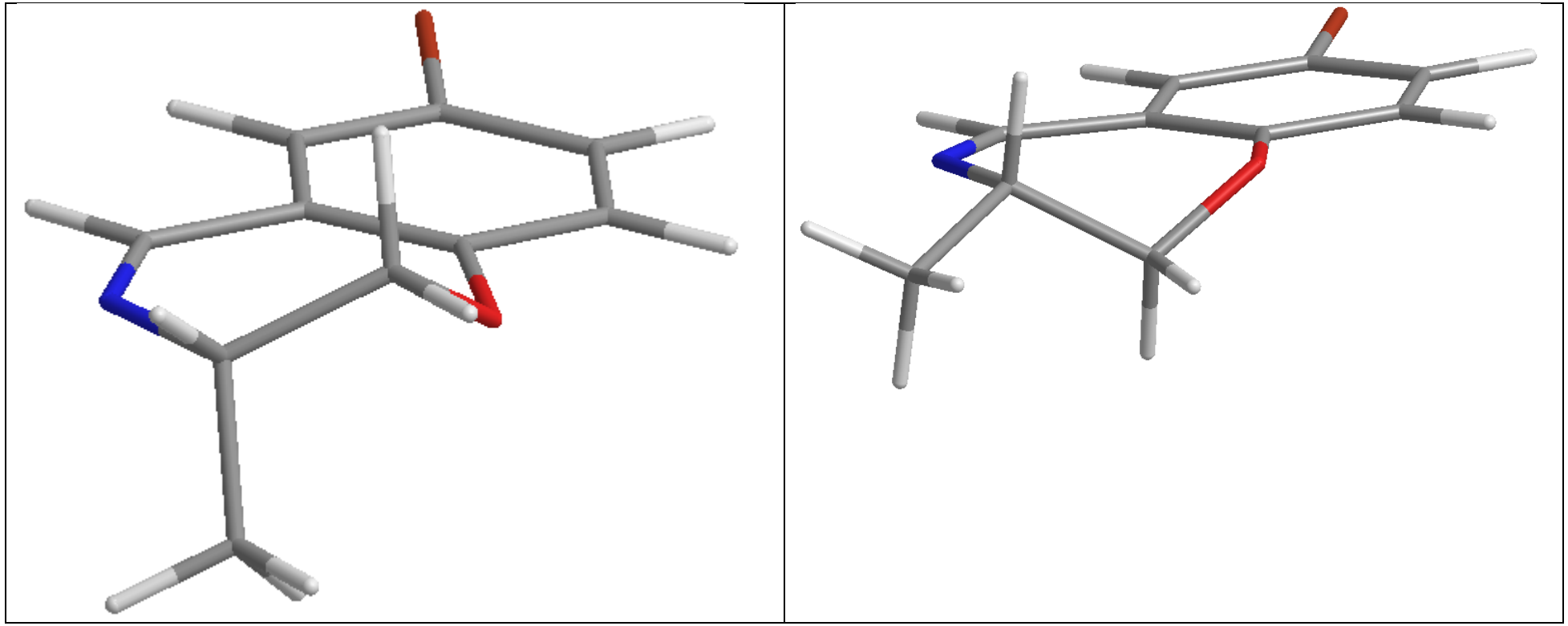
3	Boat	-59.39	equatorial	axial	2.50	153, 32
4	Chair	-57.76	equatorial	equatorial	4.09	68, 52
5	Twist	-57.15	equatorial	equatorial	4.11	175, 55
6	Boat	is converted to other conformations	axial	equatorial	-	-

Conformations of trans compound (13)						
Number	**Type**	**Heat of formation (Kcal/mol)**	**Position of H-5**	**Position of H-3**	**Distance between H-5 and H-3 (Å)**	**Dihedral angles between H-2 and H-3**
1	Chair	-60.06	equatorial	axial	3.61	67, 53
2	Chair	-59.79	axial	equatorial	3.68	174, 65
3	Twist	-59.55	axial	equatorial	3.61	149, 28
4	Twist	-58.73	equatorial	axial	3.73	97, 24
5	Boat	is converted to other conformations	axial	axial	-	-
6	Boat	is converted to other conformations	equatorial	equatorial	-	-

From these results, it is clear that in general, as expected, conformations that place H-3 and/or H-5 in axial position are favoured. Obviously this meas that the substituents at C-5 and/or at C-3 are equatorial. Therefore, the lower energy is obtained for the chair conformation of the *cis* compound, where both hydrogens are axial.
In any case, the differences in heat of formation among the best three conformations of both isomers is too scarce to allow us to draw conclusion on the preferred one.
However, from the data in the tables, it is evident that no conformation of *trans* isomer may be able to give a nOe between H-3 and H-5. On the contrary, the best three conformations of *cis* compound can. NOESY experiments have shown that only the amine derived from the minor (kinetically unfavoured) diastereomer of the Ugi-Joullié reaction gives this nOe. We thus think that this is a proof of the onfigurational assignment.
Unfortunately, we are not able to measure precisely both J between H-3 and H-2, because one of the diastereotopic H-2 falls very near to H-3 in both isomers. These coupling constants could have given an useful information reagrding the stereochemical equilibria, because, as can be seen fro the tables, the dihedral angles are quite different among them.

Conformational analysis of imine 3e

Imine **3e** exists in just two half-chair conformations depicted below, The one on the left has the methyl substituent in axial position. The conformation on the right is more stable by about 0.80 Kcol/mol, according to MOPAC - PM3. In both conformations the C=N bond is coplanar to the benzene ring, and the face *trans* to the substituent is less encoumbered.



Conformational analysis of amides 10j-11j

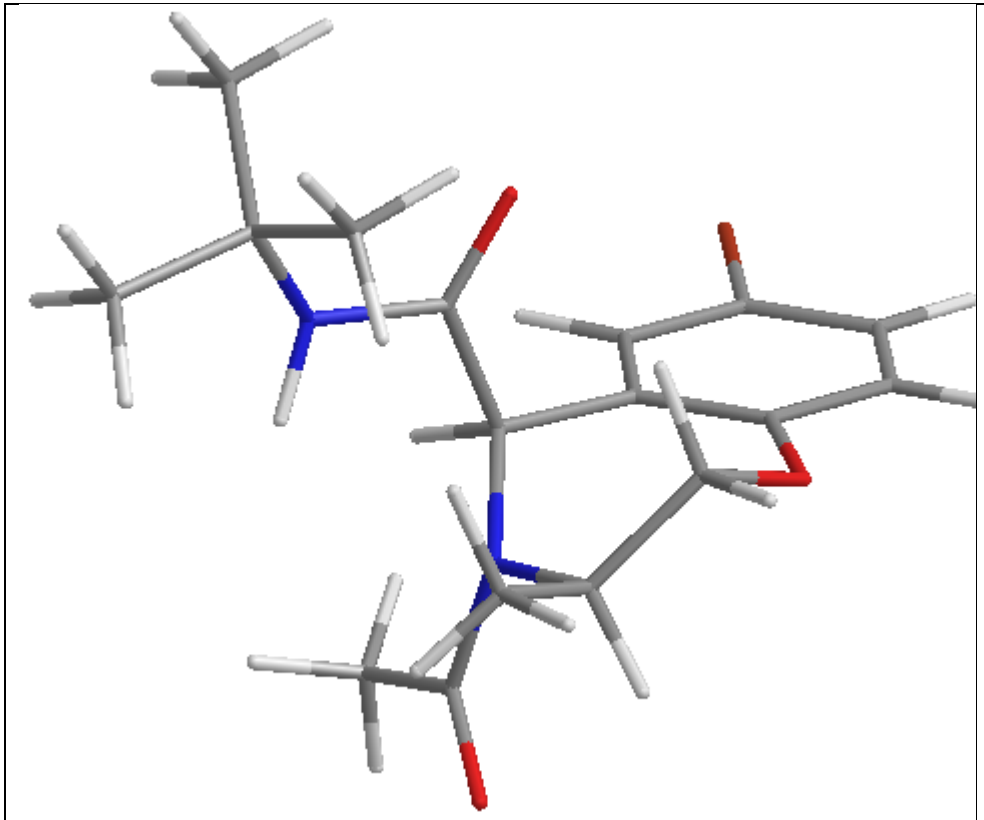
This study was carried out Using the commercial software ChemBio3D Ultra and the MOPAC (PM3) interface.

As for the amines **13** and **14**, there are three types of conformations. One of them resembles a chair, while the second one resembles a twist and the third one a boat. Thus, here we conventionally adopt these three terms. Obviously, each of these three conformations exist in two possible diastereomeric forms, which are in equilibrium.

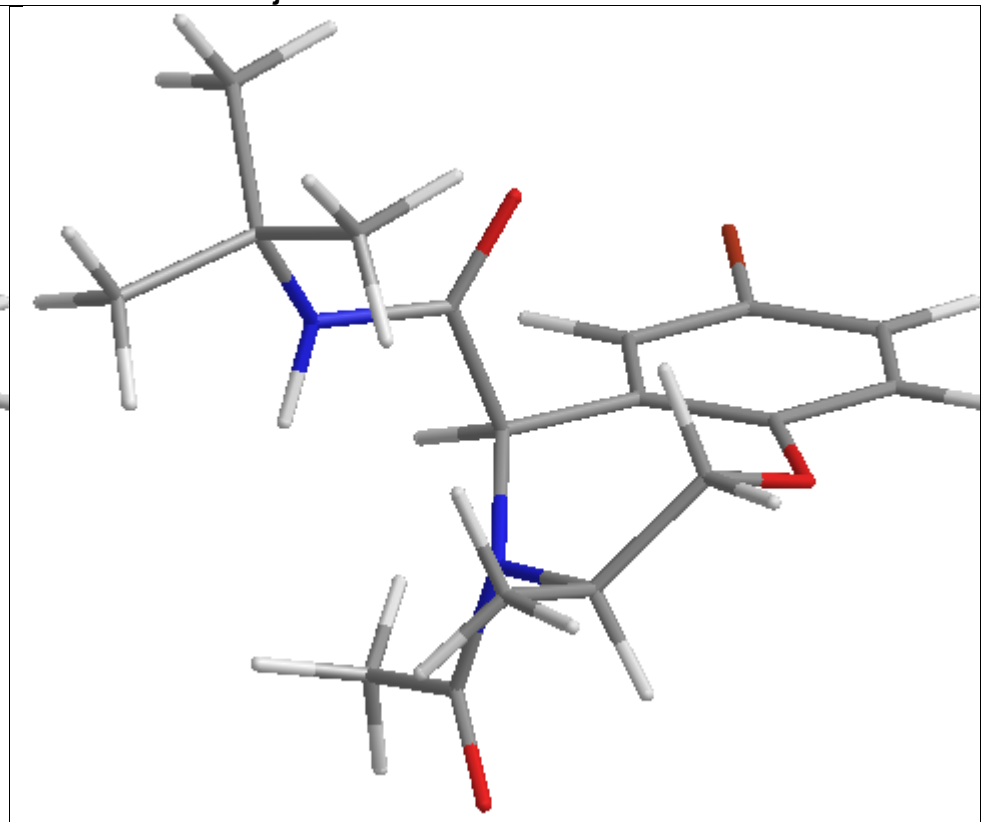
For the *cis* compound **11j**, two conformations clearly emerge as the most stable ones:

- Conformation **A** is a twist where the CONH*t*Bu group is axial and the methyl equatorial. Heat of formation = –99.50 Kcal/mol
- Conformation **B** is a half-chair with the two substituents in axial position. Heat of formation = –98.86 Kcal/mol

CONFORMATIONS OF *CIS* COMPOUND 11j



CONFORMATION A

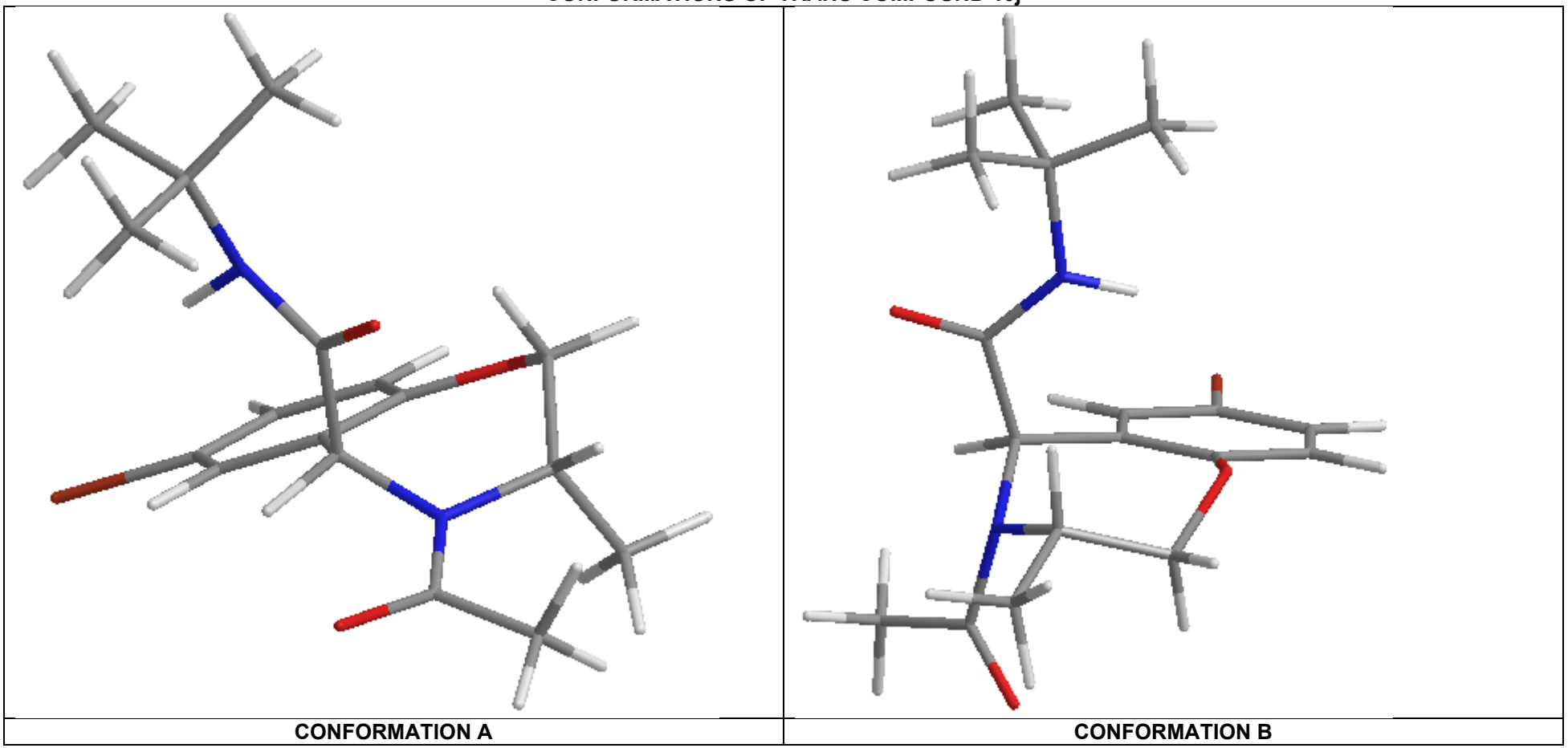


CONFORMATION B

For the *trans* compound **10j**, two conformations clearly emerge as the most stable ones:

- Conformation **A** is a twist where the CONH*t*Bu group is axial and the methyl axial. Heat of formation = –98.45 Kcal/mol
- Conformation **B** is a half-chair where the CONH*t*Bu group is axial and the methyl equatorial. Heat of formation = –98.29 Kcal/mol

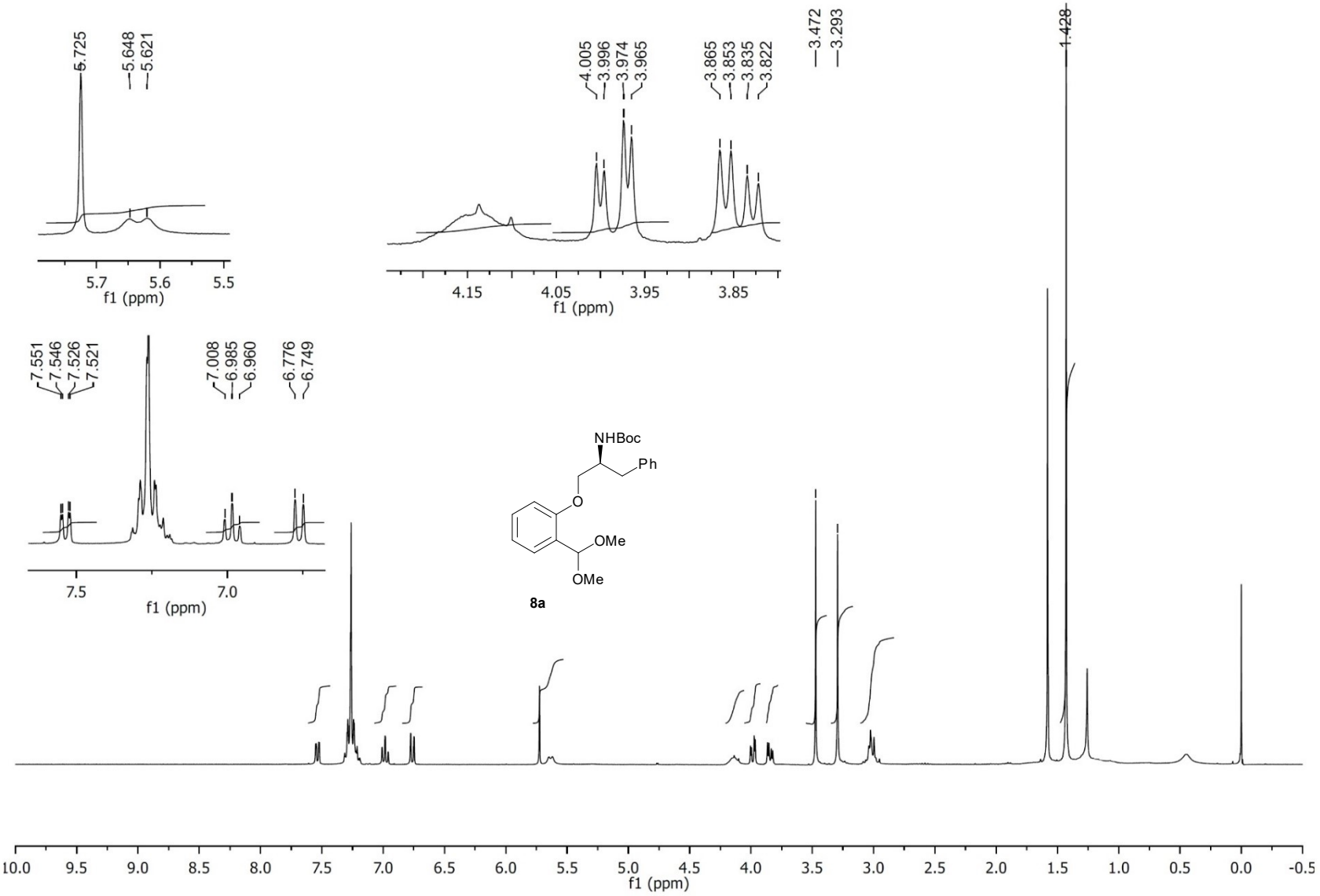
CONFORMATIONS OF *TRANS* COMPOUND 10j

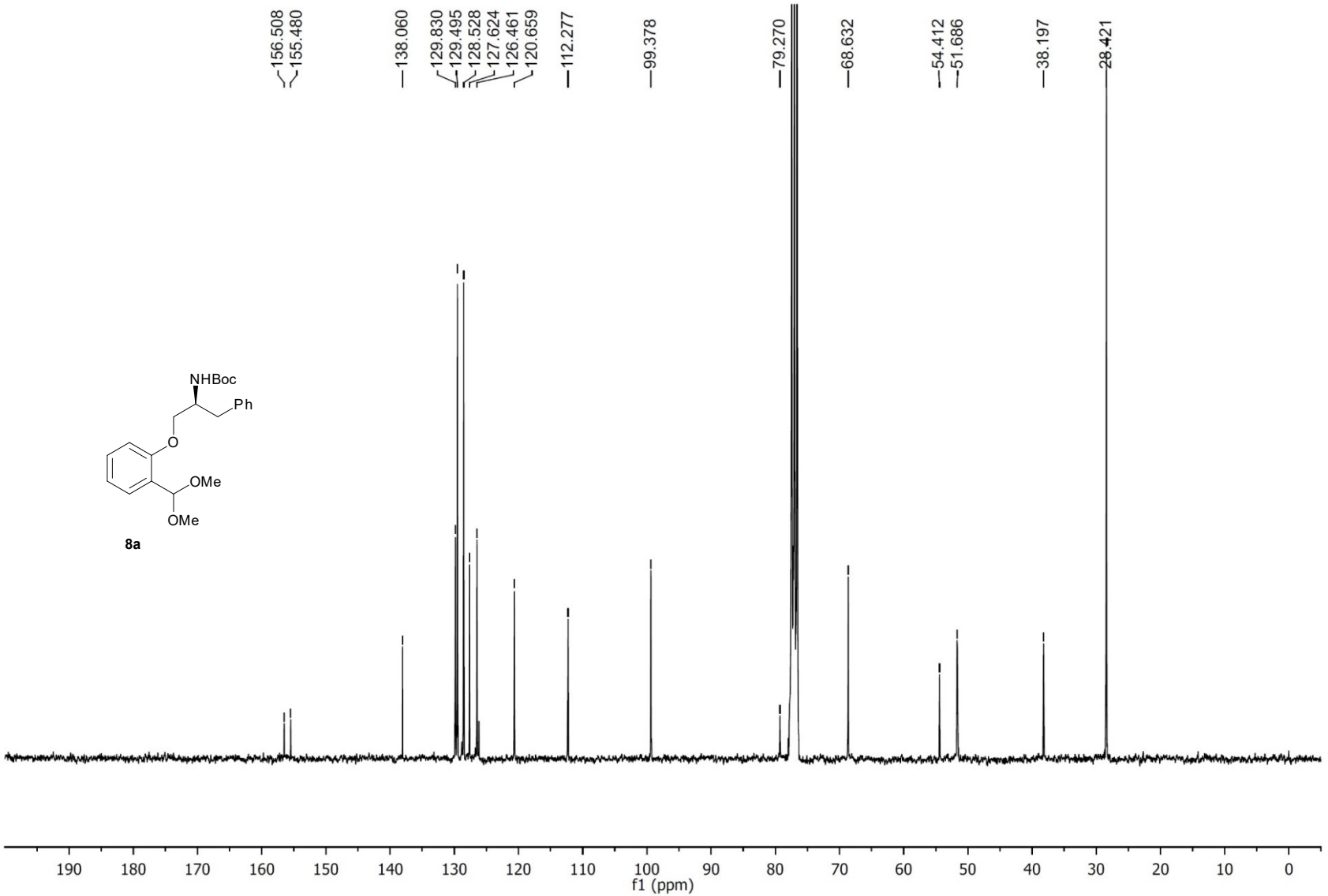


CONFORMATION A	**CONFORMATION B**

From these calculations, it is clear that the CONH*t*Bu group prefers an axial position. The *cis* compound seem to be more stable, as demonstrated experimentally by the equilibration under base catalysis.

^{1}H and ^{13}C NMR spectra of all new compounds

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129.830
129.495
128.528
127.624
126.461
120.659
112.277
99.378
79.270
68.632
54.412
51.686
38.197
28.421
NHBoc
Ph
O
OMe
OMe
8a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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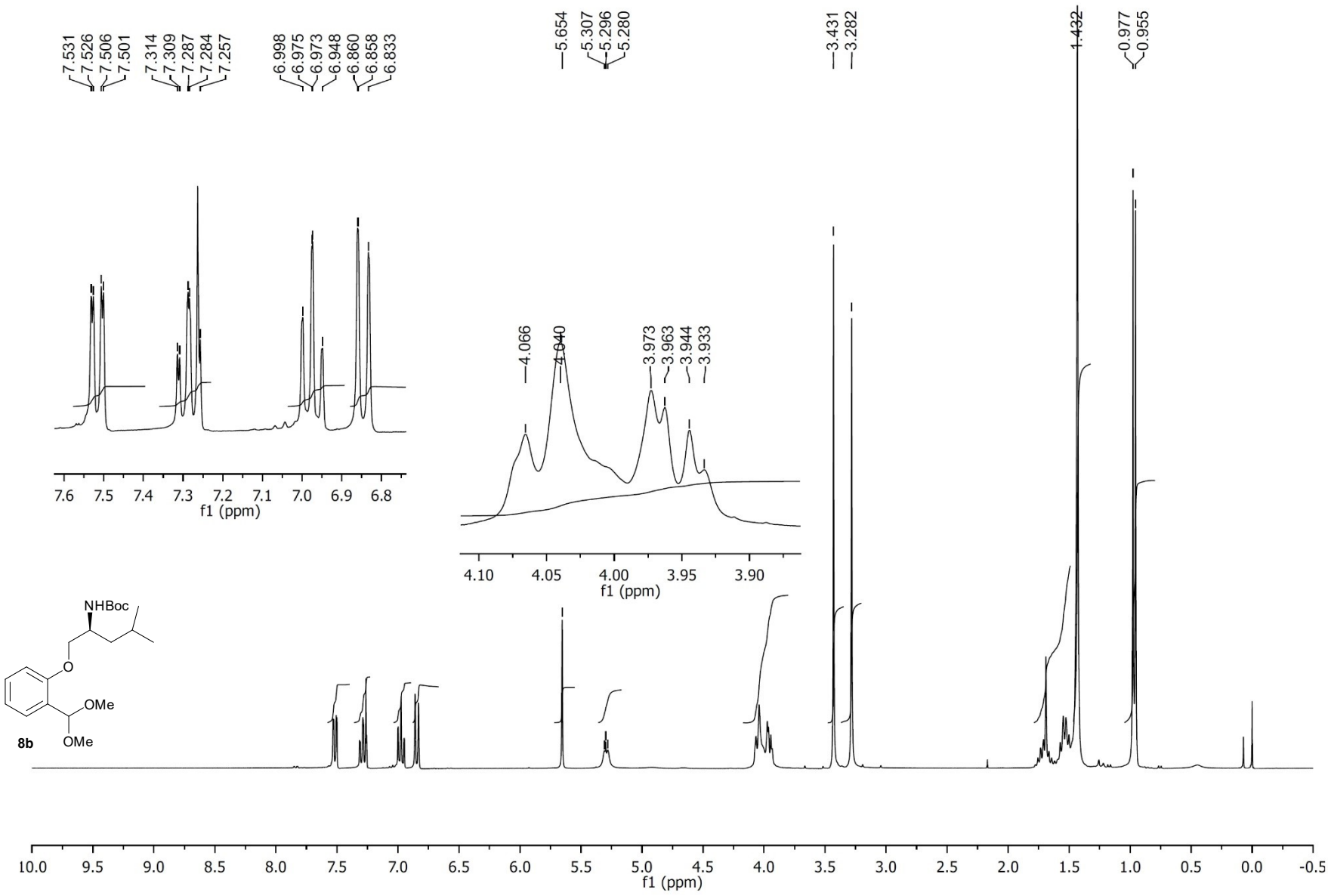
f1 (ppm)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6.860
6.858
6.833
5.654
5.307
5.296
5.280
3.431
3.282
1.432
0.977
0.955
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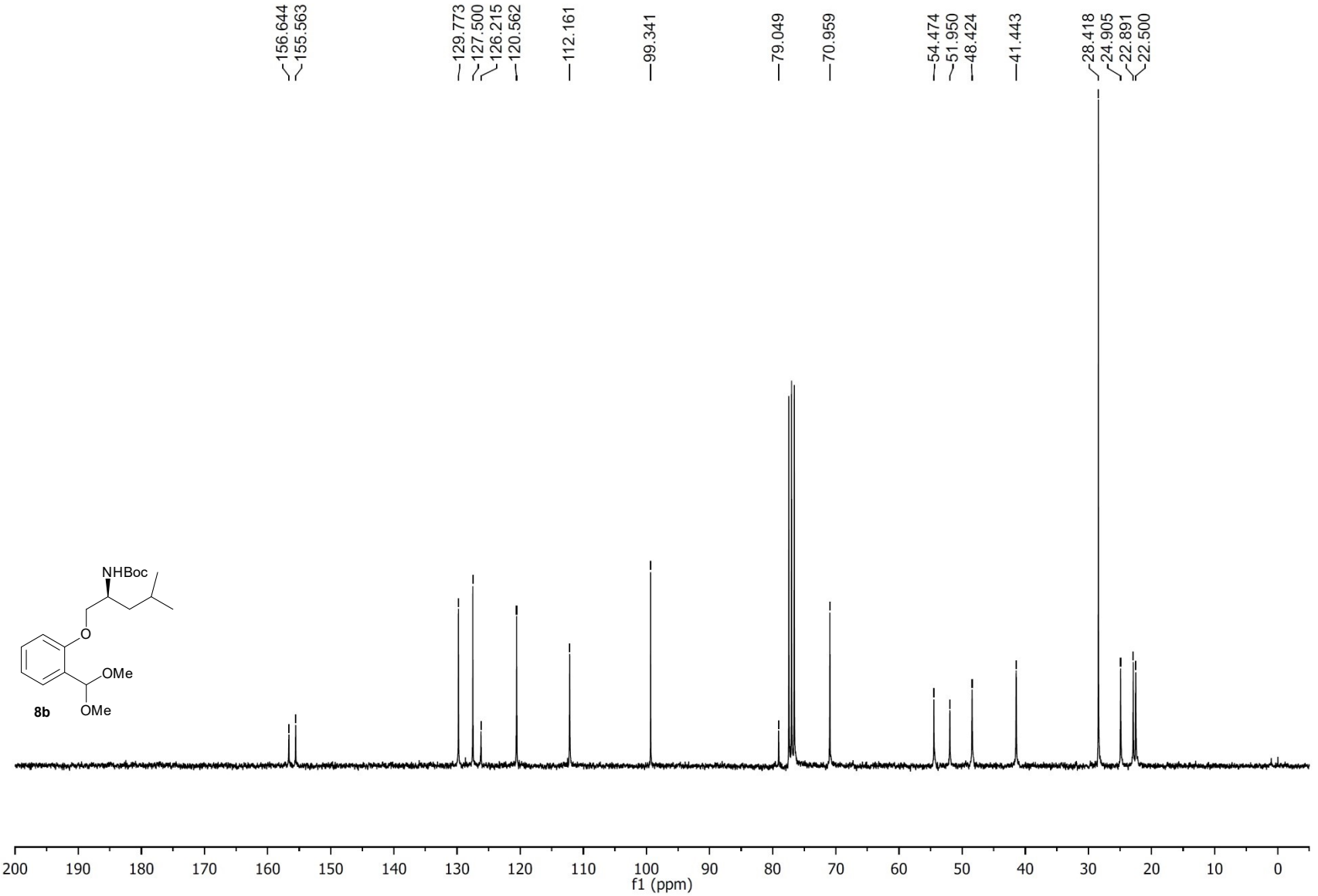
3.973
3.963
3.944
3.933
f1 (ppm)
NHBoc
O
OMe
OMe
8b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28.418
24.905
22.891
22.500
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O
OMe
OMe
8b
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190
180
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130
120
110
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70
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50
40
30
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10
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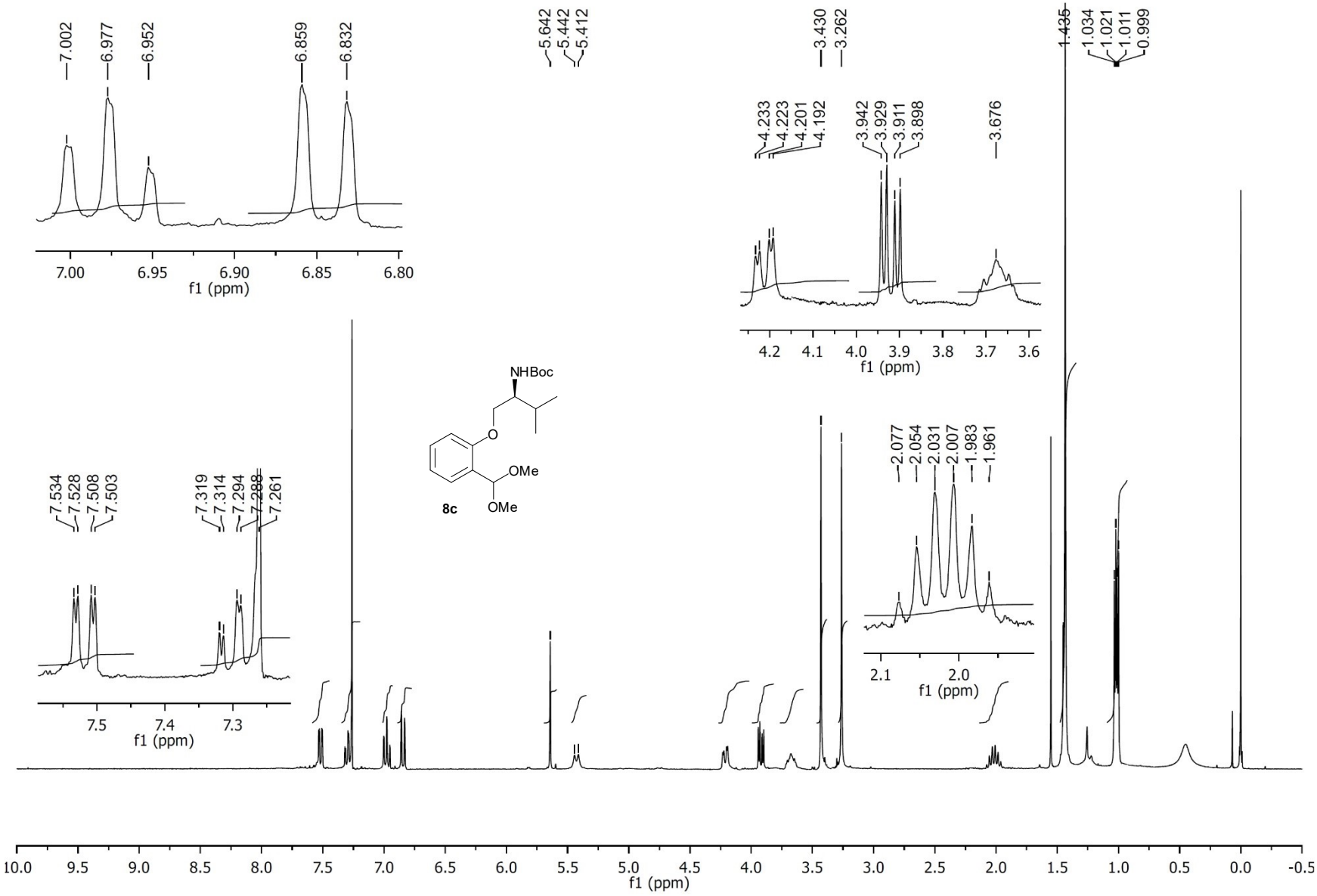
f1 (ppm)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7.00
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6.80
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5.442
5.412
3.430
3.262
1.435
1.034
1.021
1.011
0.999
4.233
4.223
4.201
4.192
3.942
3.929
3.911
3.898
3.676
4.2
4.1
4.0
3.9
3.8
3.7
3.6
f1 (ppm)
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O
OMe
OMe
8c
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7.528
7.508
7.503
7.319
7.314
7.294
7.288
7.261
7.5
7.4
7.3
f1 (ppm)
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2.054
2.031
2.007
1.983
1.961
2.1
2.0
f1 (ppm)
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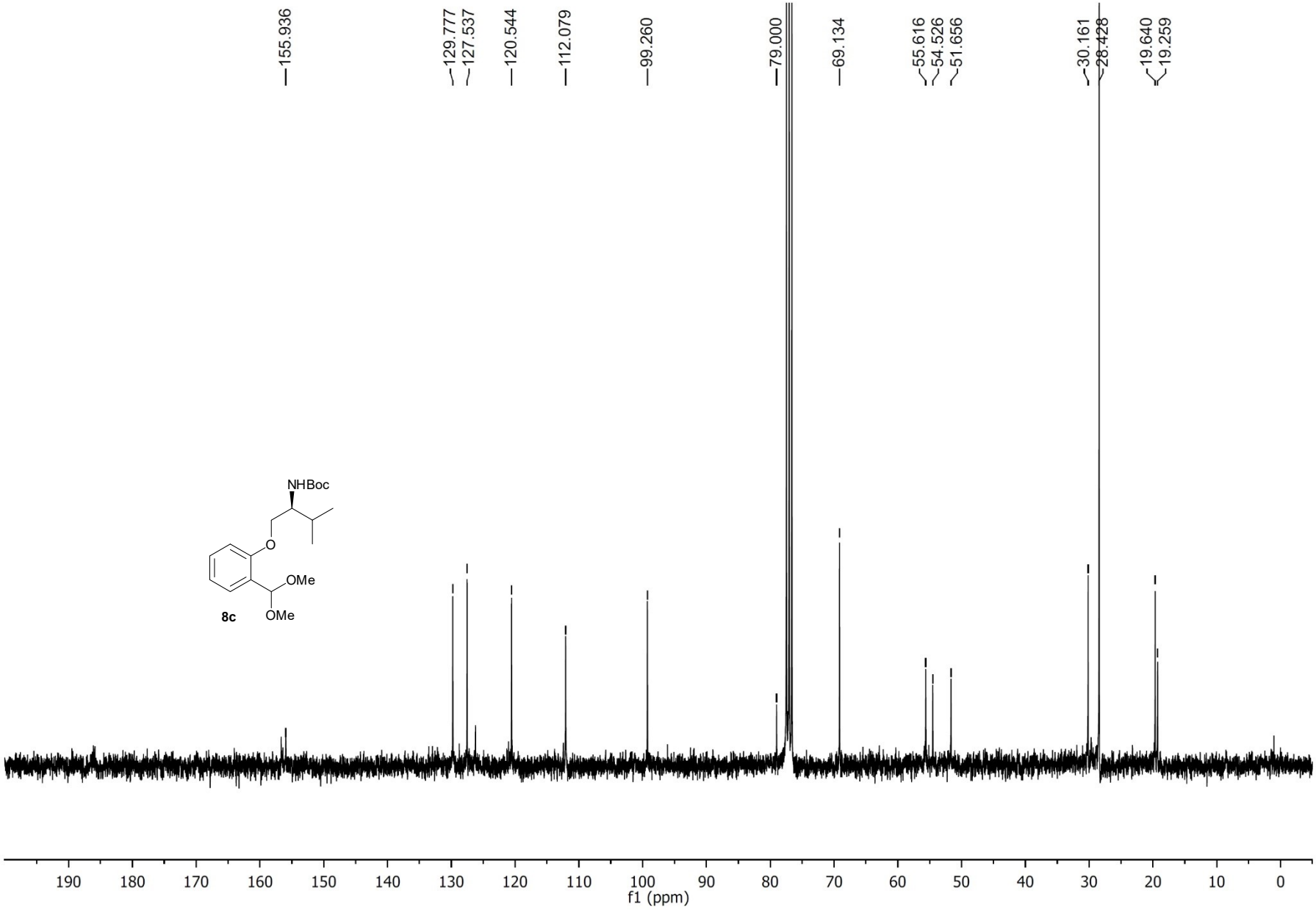
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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112.079
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54.526
51.656
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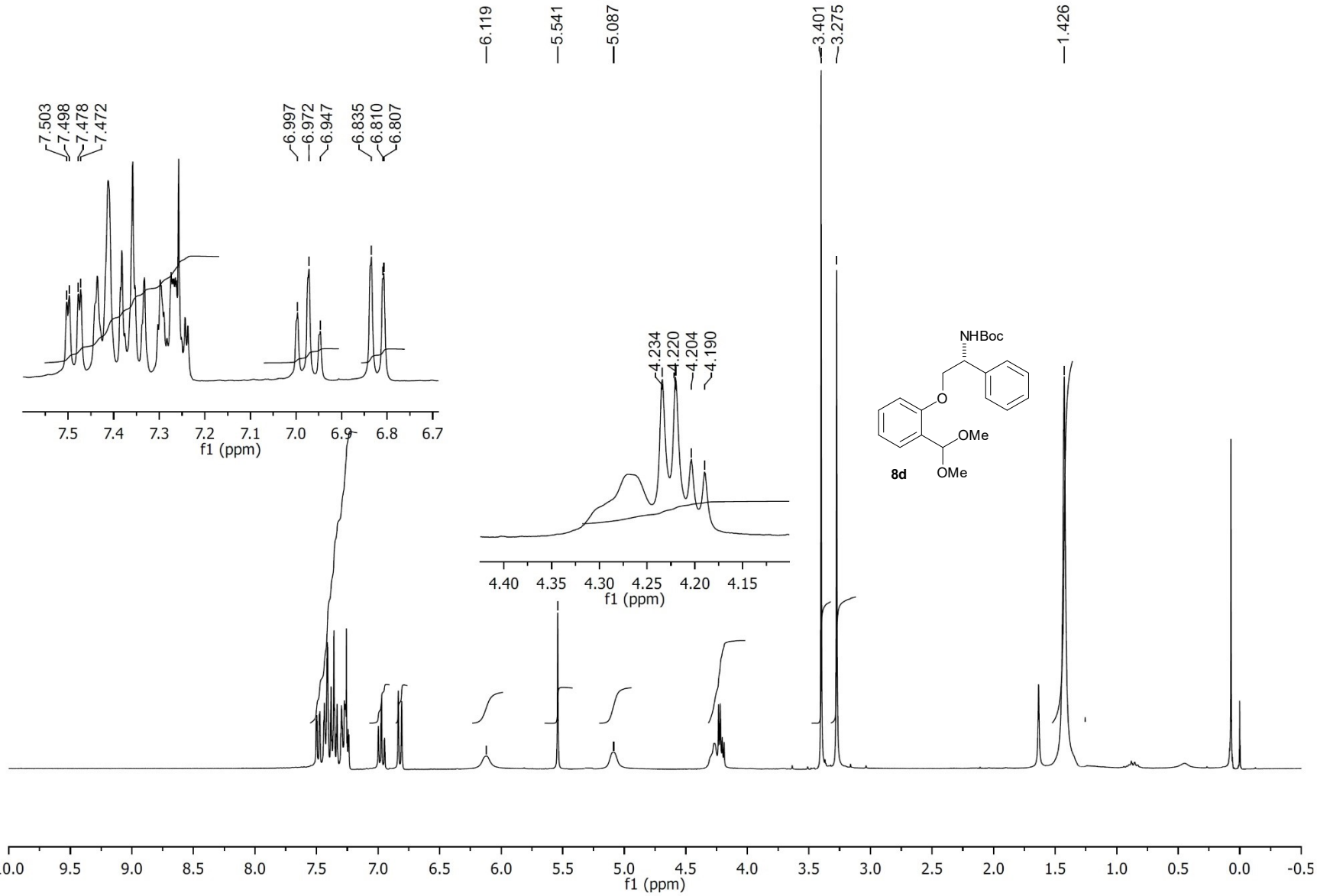
28.428
19.640
19.259
NHBoc
O
OMe
OMe
8c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

S36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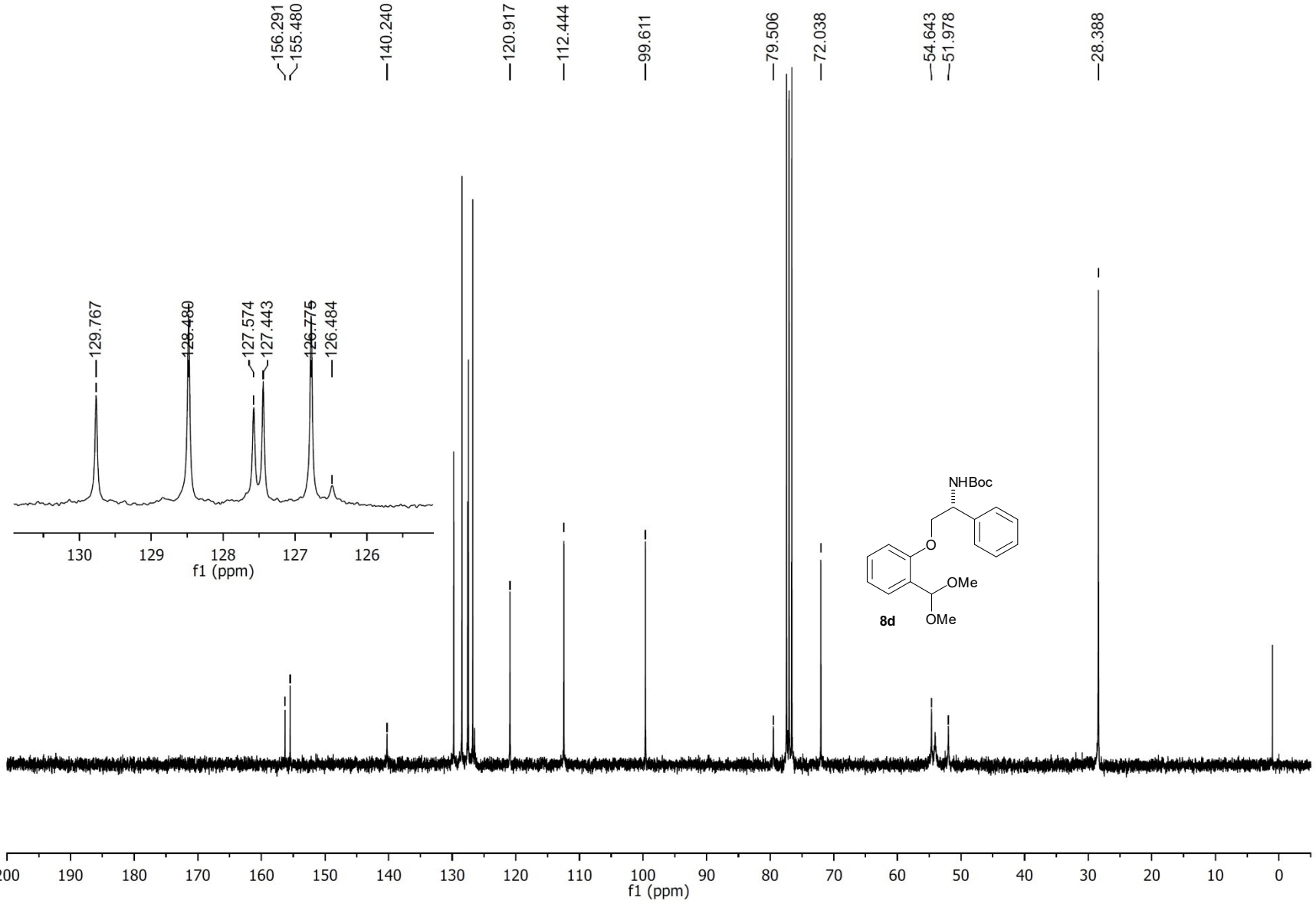
6.997
6.972
6.947
6.835
6.810
6.807
6.119
5.541
5.087
4.234
4.220
4.204
4.190
3.401
3.275
1.426
NHBoc
O
OMe
OMe
8d
f1 (ppm)
f1 (ppm)
f1 (ppm)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72.038
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128.480
127.574
127.443
126.775
126.484
130
129
128
127
126
f1 (ppm)
NHBoc
O
OMe
OMe
8d
200
190
180
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150
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130
120
110
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90
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70
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50
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30
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10
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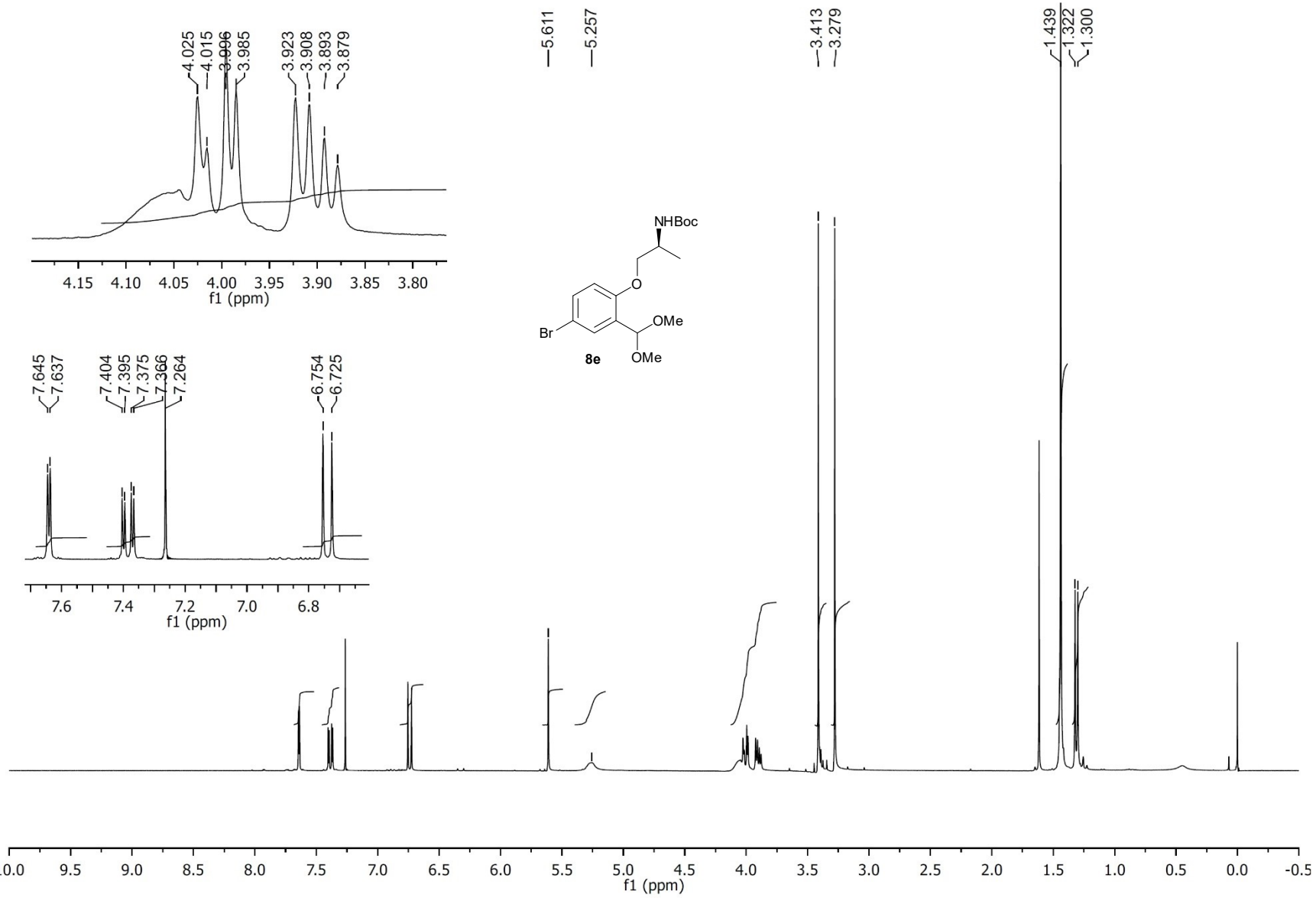
f1 (ppm)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3.923
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3.879
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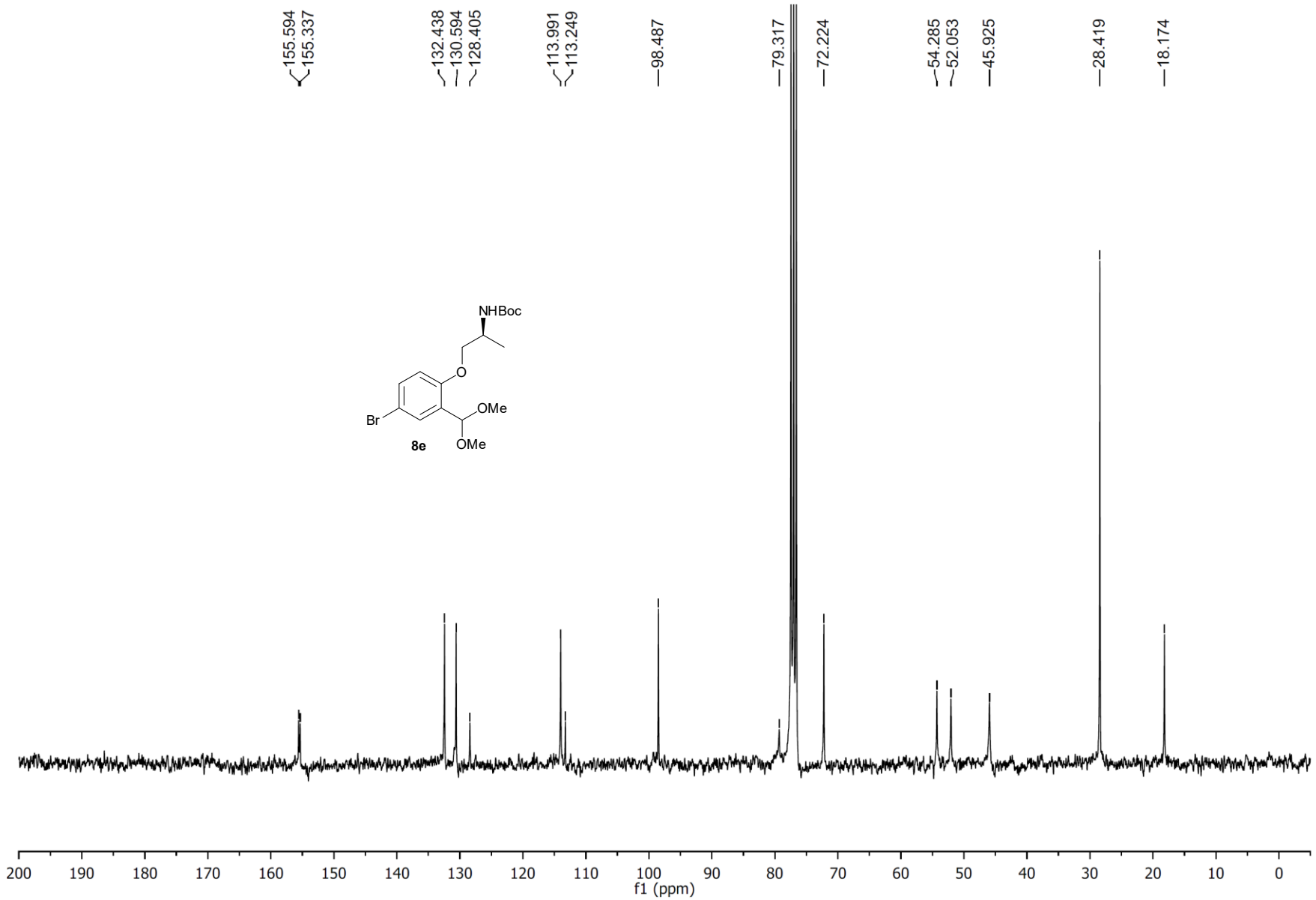
f1 (ppm)
5.611
5.257
3.413
3.279
1.439
1.322
1.300
NHBoc
O
OMe
Br
OMe
8e
7.645
7.637
7.404
7.395
7.375
7.366
7.264
6.754
6.725
7.6 7.4 7.2 7.0 6.8
f1 (ppm)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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54.285
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45.925
28.419
18.174
NHBoc
O
OMe
Br
OMe
8e
200
190
180
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120
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50
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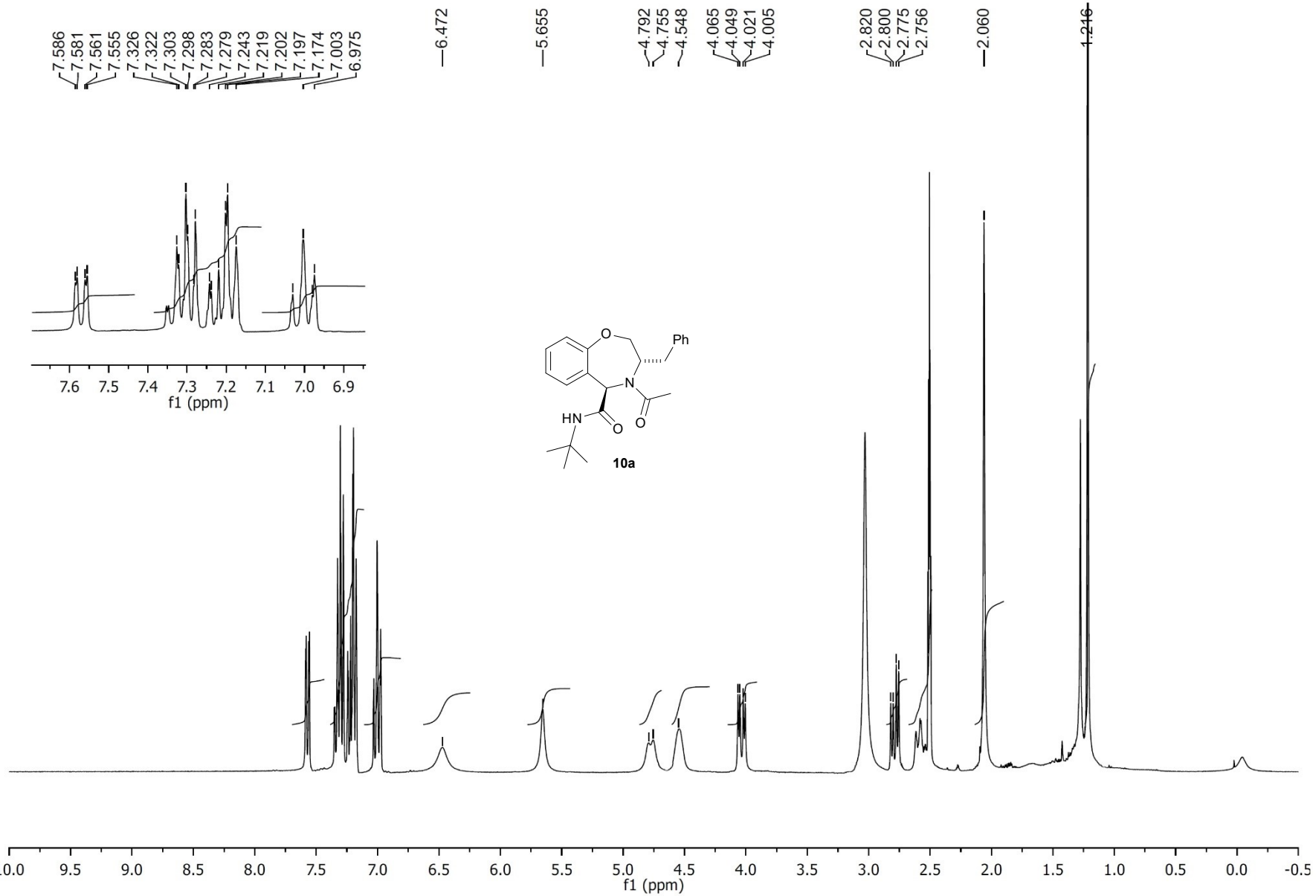
20
10
0
f1 (ppm)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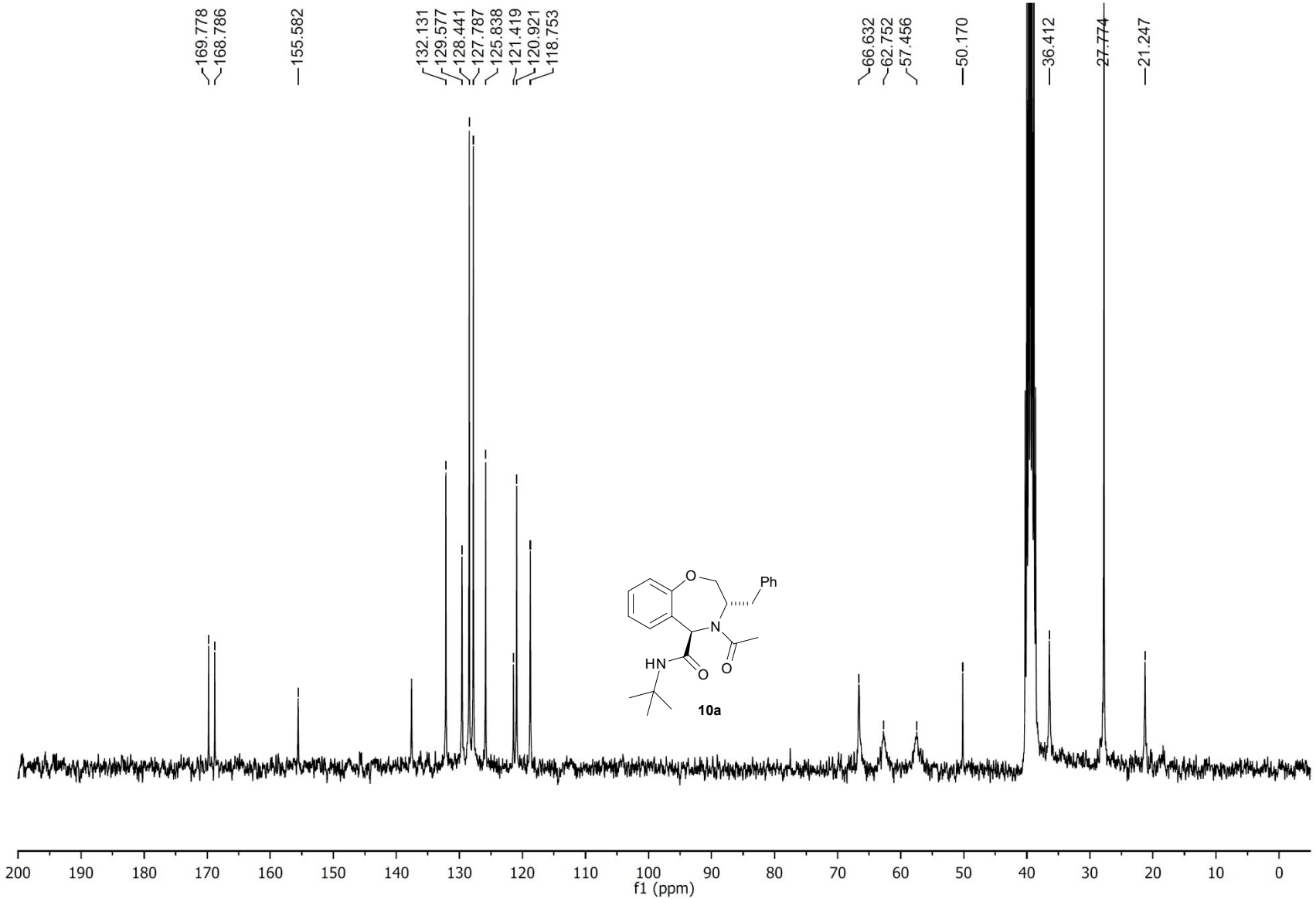
7.202
7.197
7.174
7.003
6.975
6.472
5.655
4.792
4.755
4.548
4.065
4.049
4.021
4.005
2.820
2.800
2.775
2.756
2.060
1.216
7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
O
Ph
N
HN
O
O
10a
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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62.752
57.456
50.170
36.412
27.774
21.247
Ph
N
O
HN
O
O
10a
200
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180
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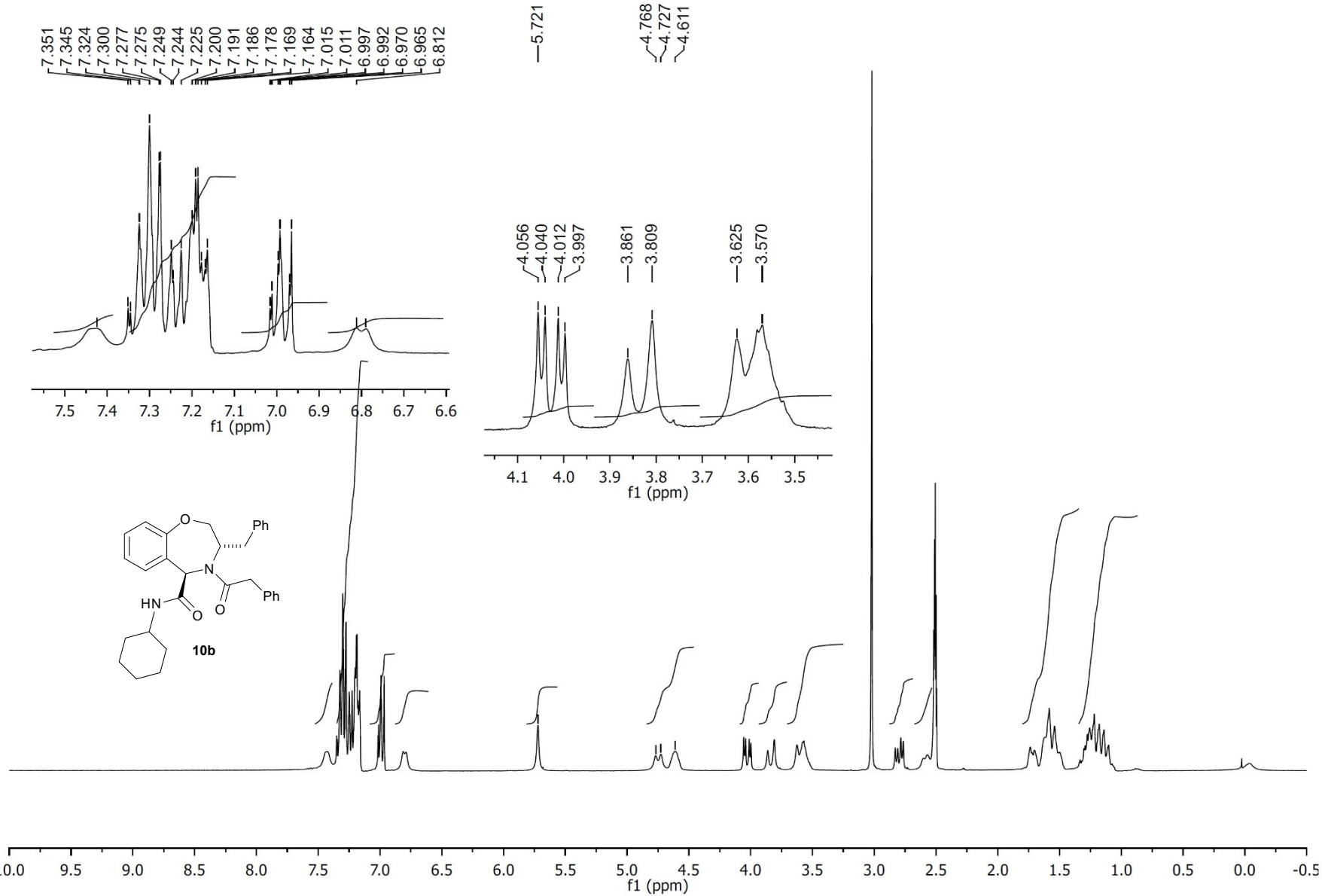
0
f1 (ppm)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7.277
7.275
7.249
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7.200
7.191
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7.178
7.169
7.164
7.015
7.011
6.997
6.992
6.970
6.965
6.812
5.721
4.768
4.727
4.611
4.056
4.040
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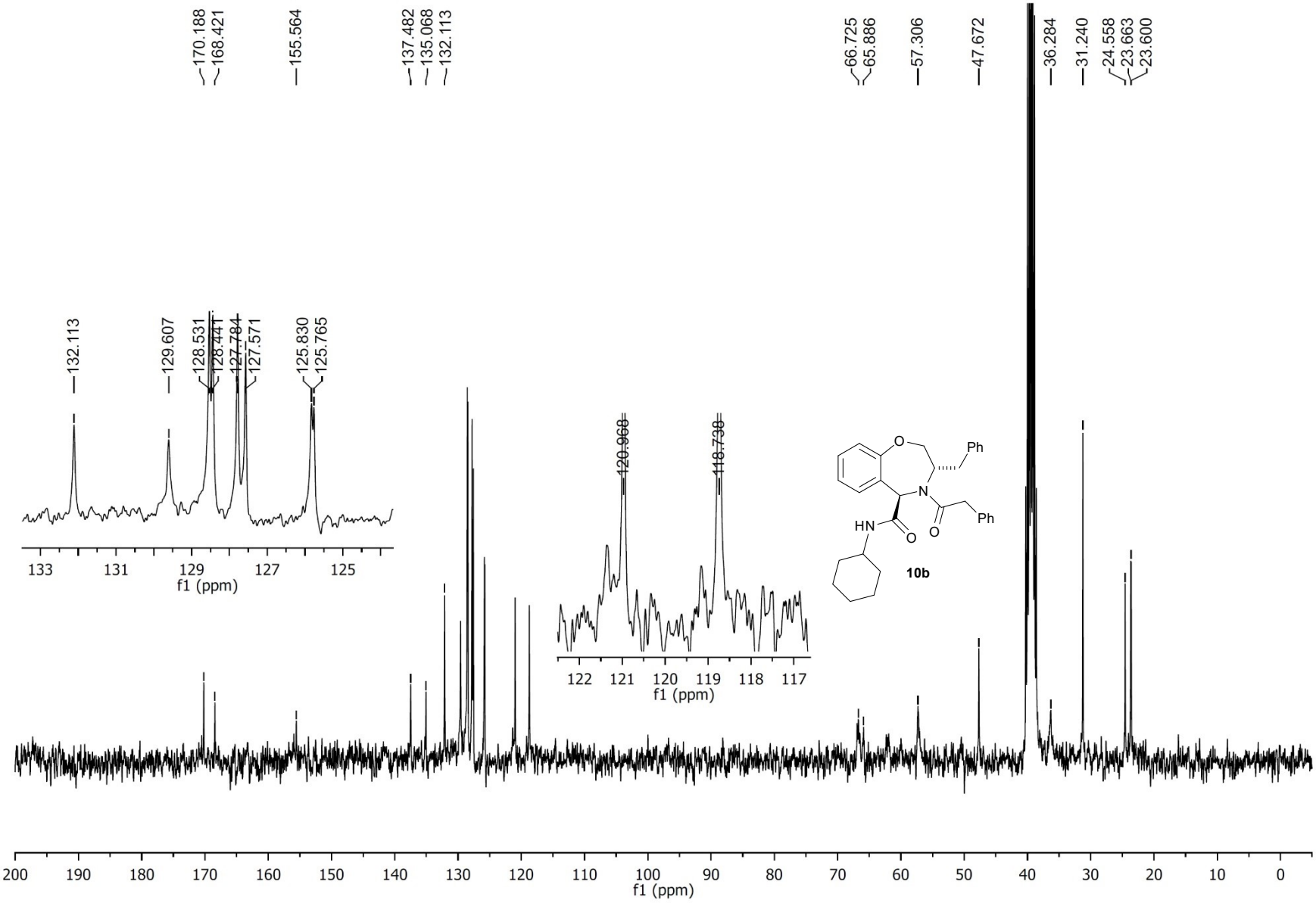
f1 (ppm)
Ph
Ph
HN
O
O
O
N
10b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135.068
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65.886
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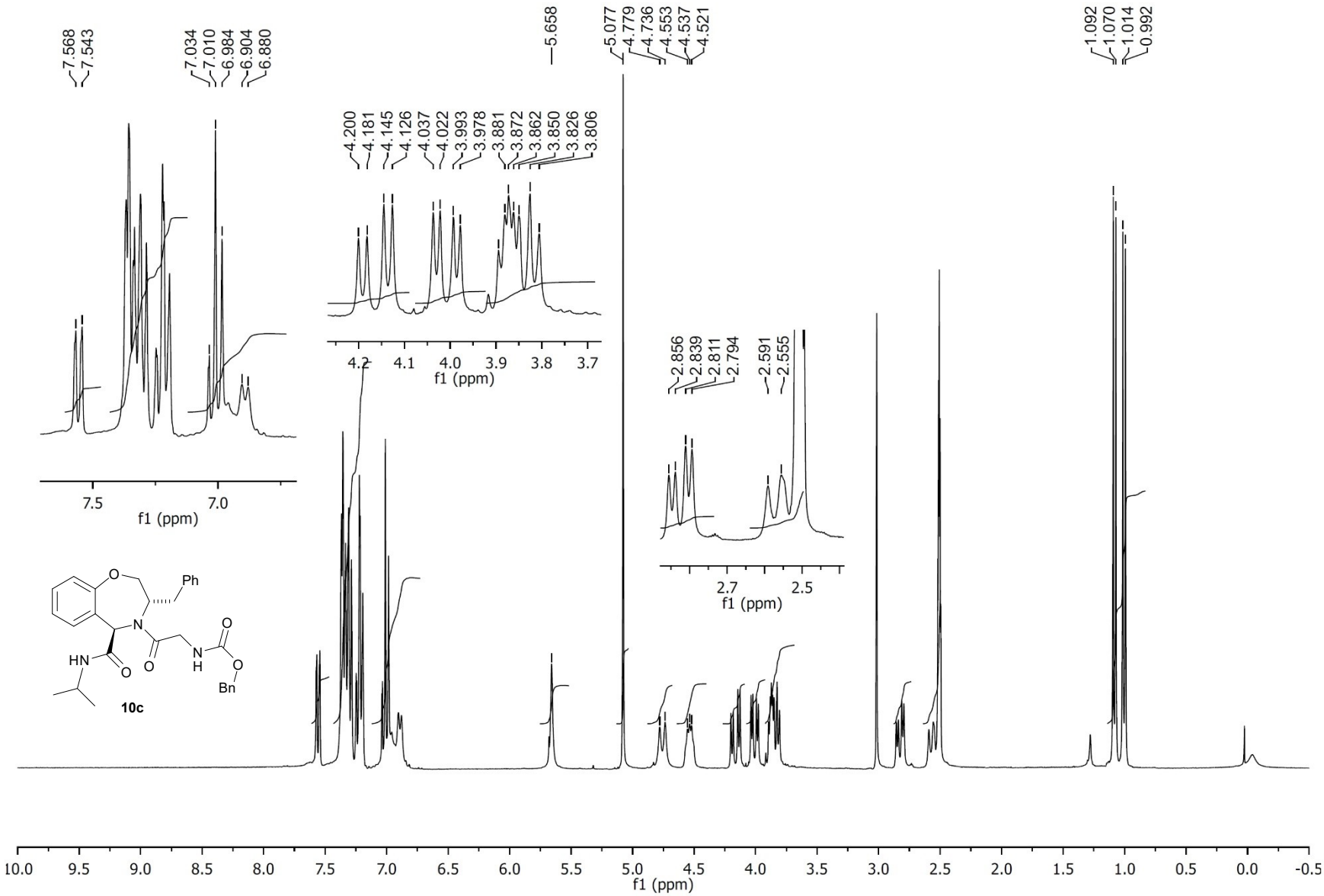
47.672
36.284
31.240
24.558
23.663
23.600
132.113
129.607
128.531
128.441
127.784
127.571
125.830
125.765
133
131
129
127
125
f1 (ppm)
120.968
118.738
122
121
120
119
118
117
f1 (ppm)
O
Ph
N
HN
O
O
Ph
10b
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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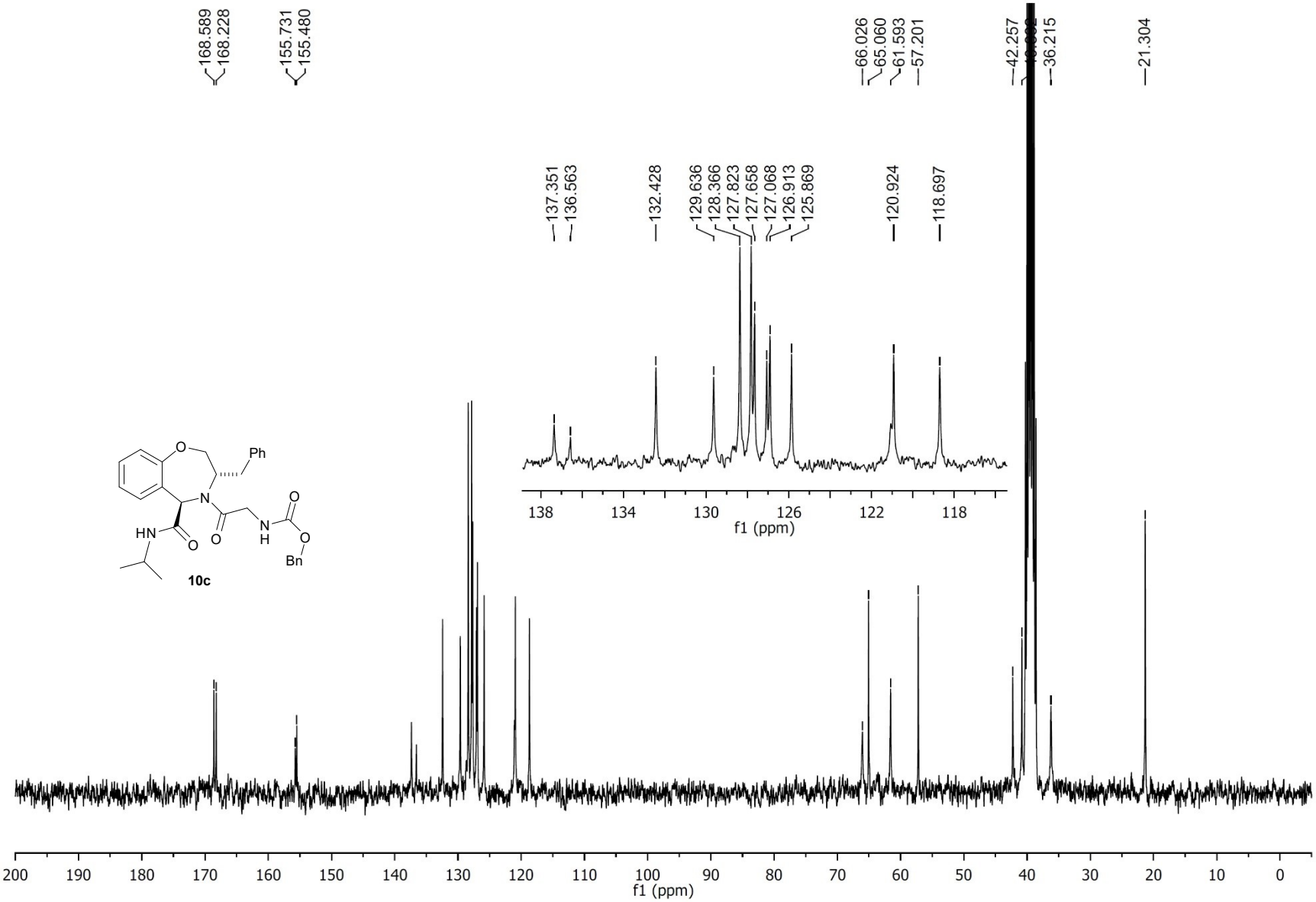
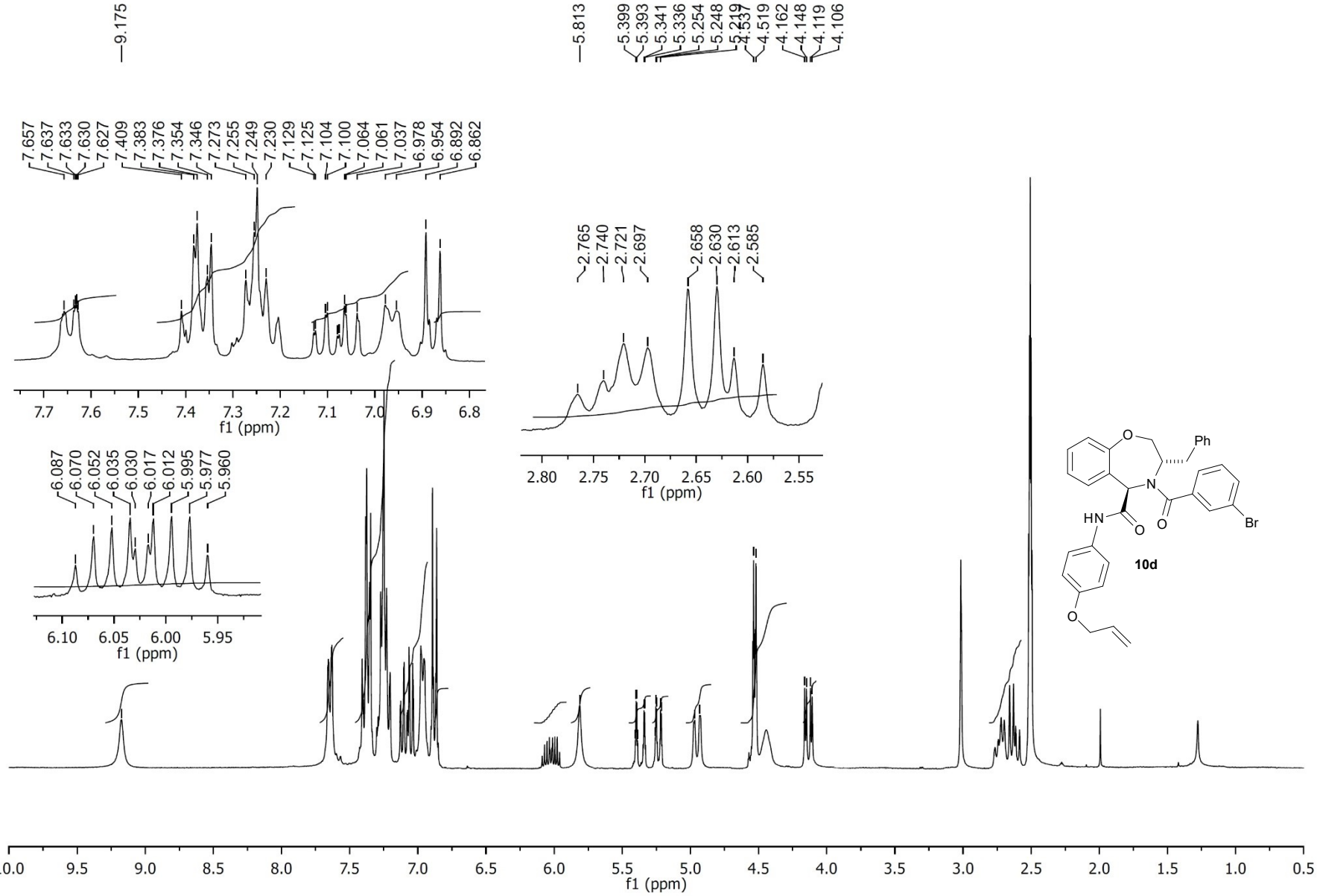
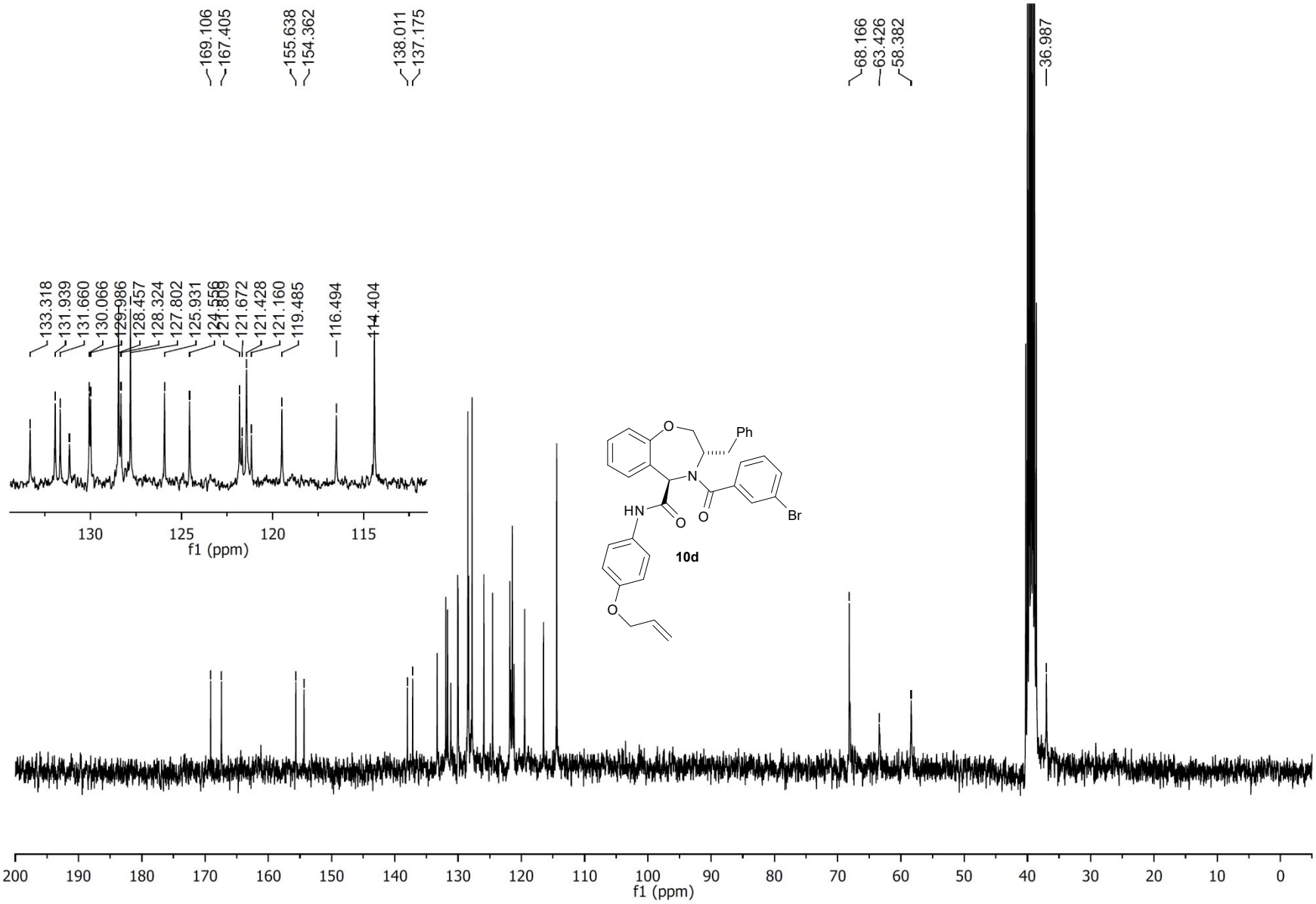
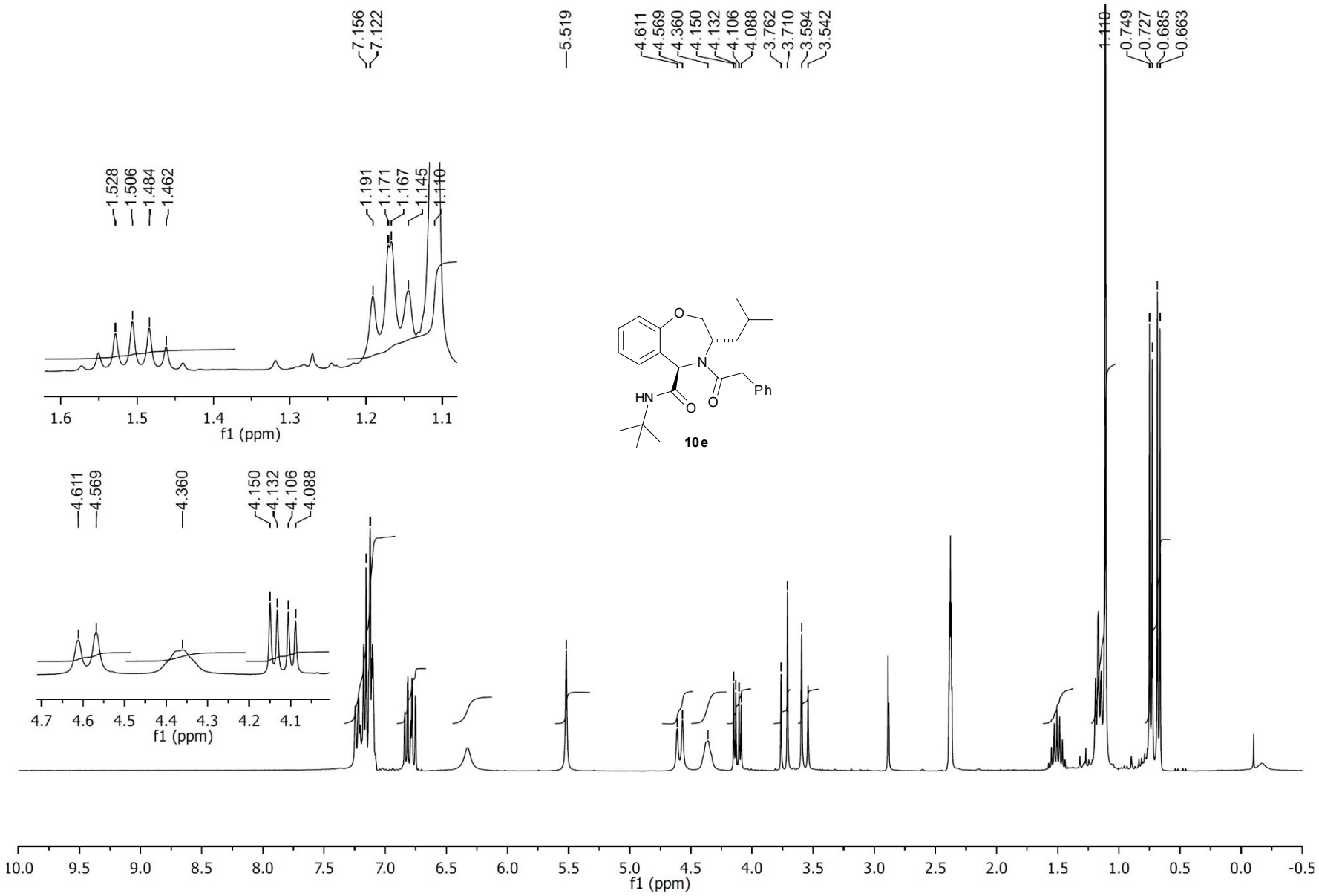
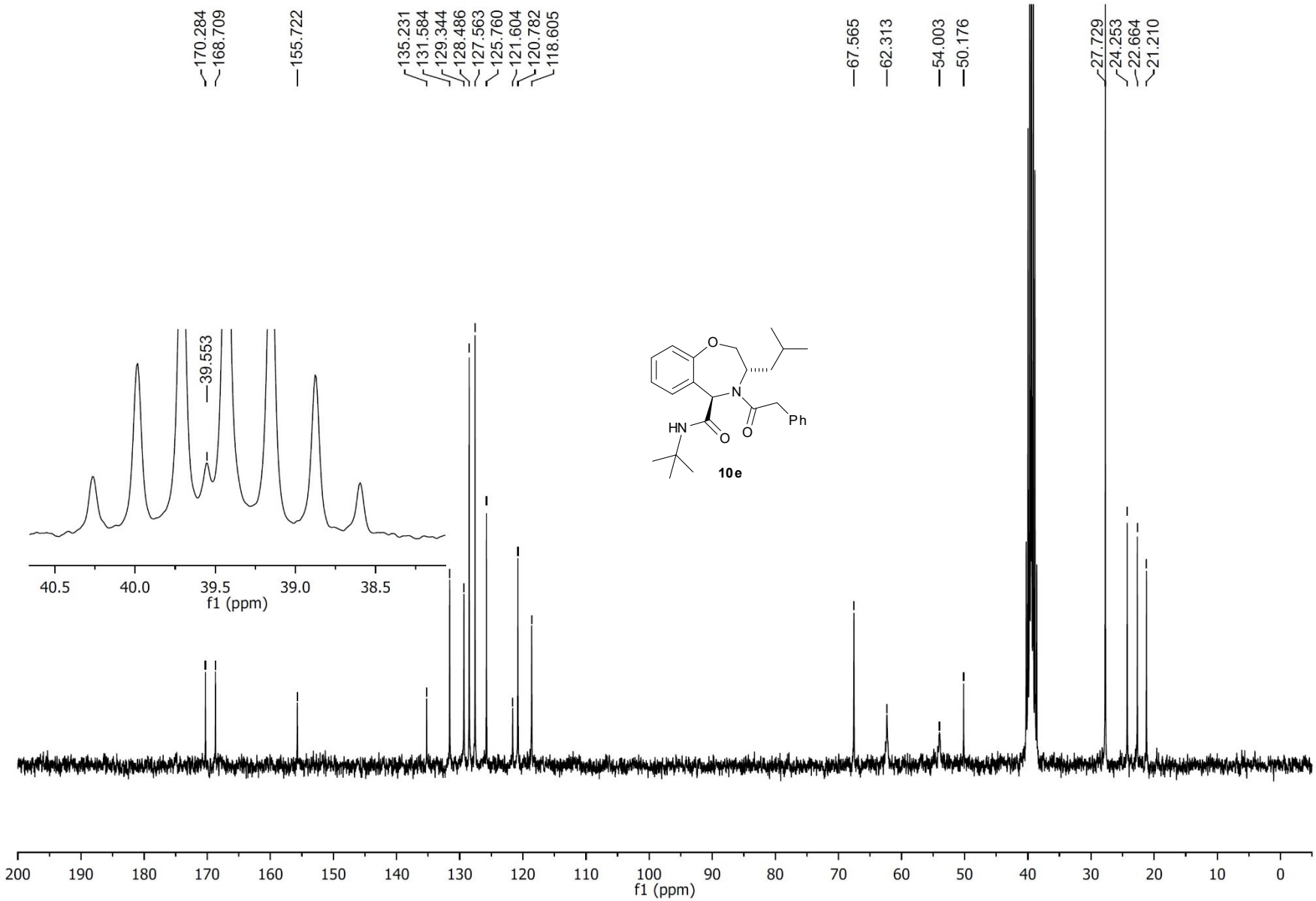
7.543
7.034
7.010
6.984
6.904
6.880
5.658
5.077
4.779
4.736
4.553
4.537
4.521
1.092
1.070
1.014
0.992
4.200
4.181
4.145
4.126
4.037
4.022
3.993
3.978
3.881
3.872
3.862
3.850
3.826
3.806
2.856
2.839
2.811
2.794
2.591
2.555
f1 (ppm)
10c

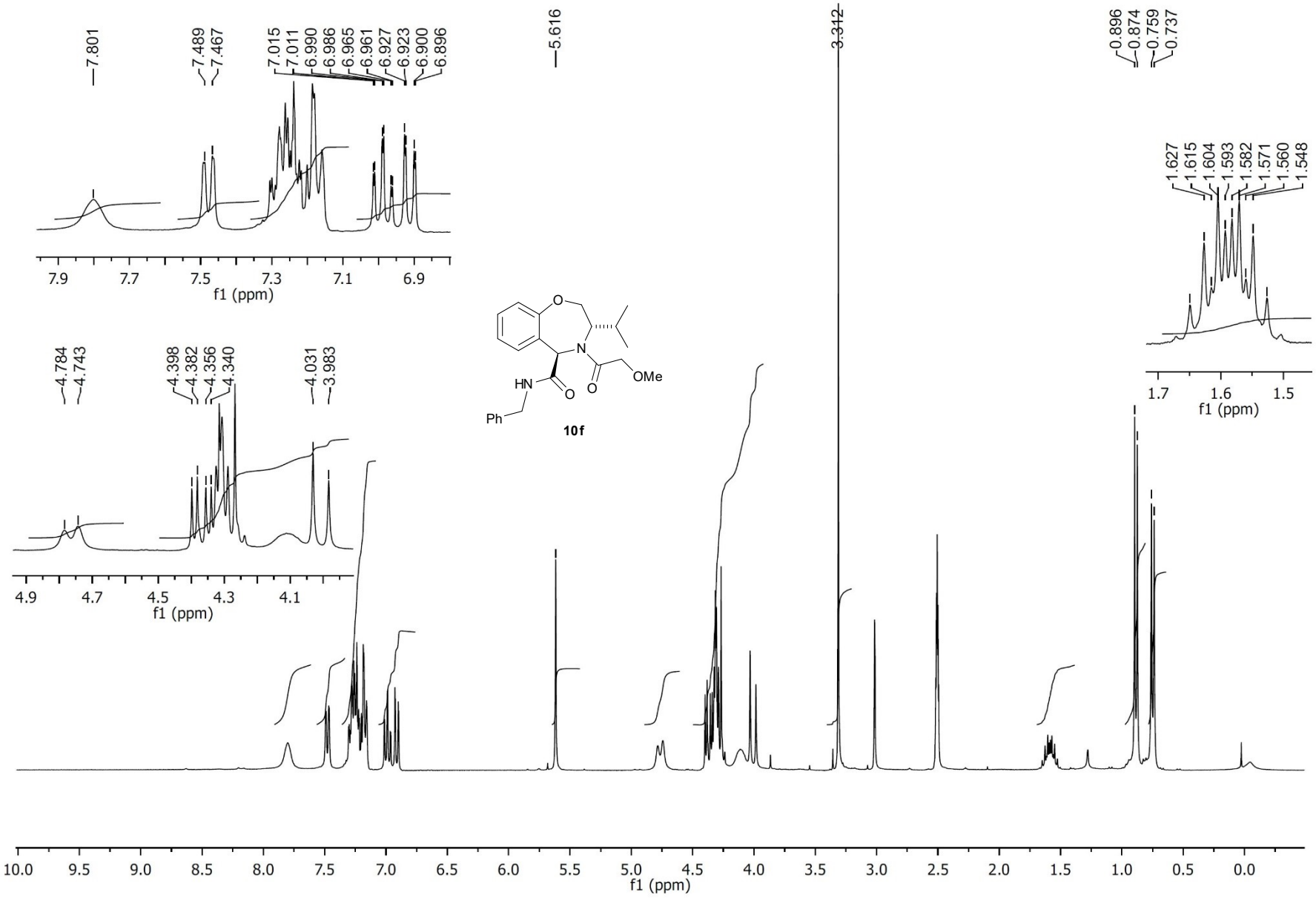

168.589
168.228
155.731
155.480
66.026
65.060
61.593
57.201
42.257
36.215
21.304
137.351
136.563
132.428
129.636
128.366
127.823
127.658
127.068
126.913
125.869
120.924
118.697
Ph
N
O
HN
O
N
H
O
O
Bn
10c
138
134
130
126
122
118
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

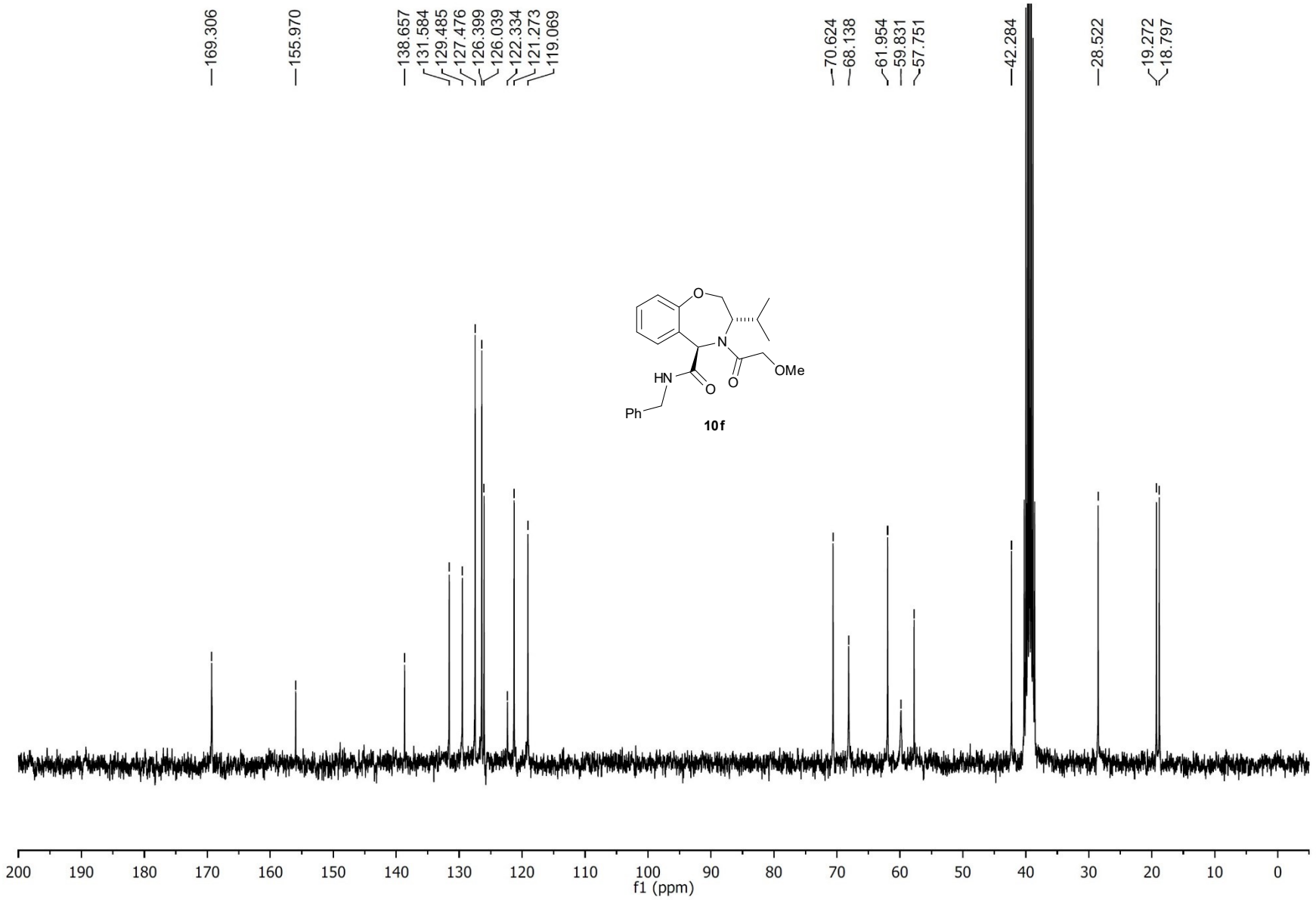

9.175
5.813
5.399
5.393
5.341
5.336
5.254
5.248
5.219
5.137
4.519
4.162
4.148
4.119
4.106
7.657
7.637
7.633
7.630
7.627
7.409
7.383
7.376
7.354
7.346
7.273
7.255
7.249
7.230
7.129
7.125
7.104
7.100
7.064
7.061
7.037
6.978
6.954
6.892
6.862
2.765
2.740
2.721
2.697
2.658
2.630
2.613
2.585
6.087
6.070
6.052
6.035
6.030
6.017
6.012
5.995
5.977
5.960
f1 (ppm)
10d

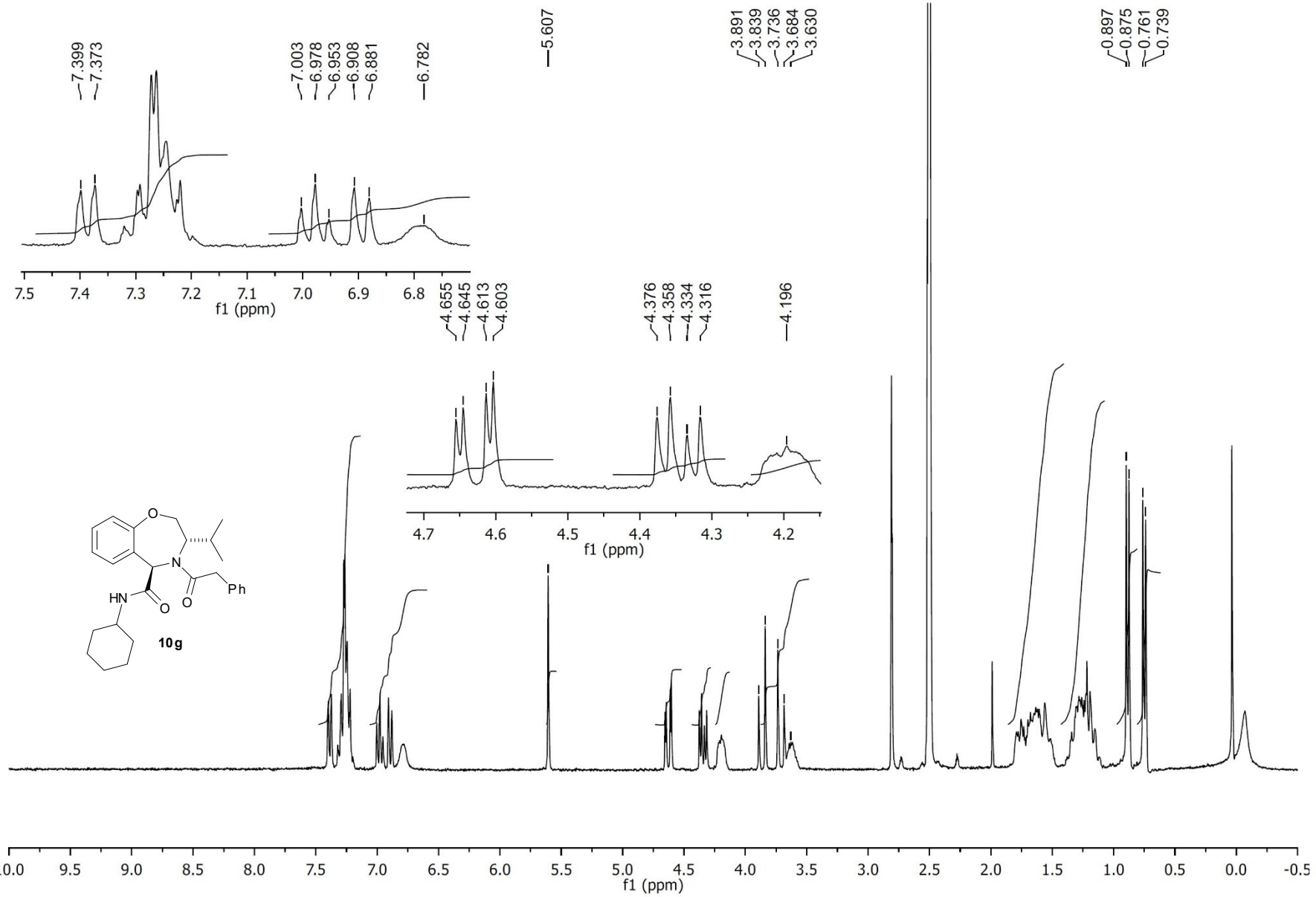

169.106
167.405
155.638
154.362
138.011
137.175
68.166
63.426
58.382
36.987
133.318
131.939
131.660
130.066
129.986
128.457
128.324
127.802
125.931
121.672
121.428
121.160
119.485
116.494
114.404
130
125
120
115
f1 (ppm)
O
Ph
N
HN
O
O
Br
10d
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

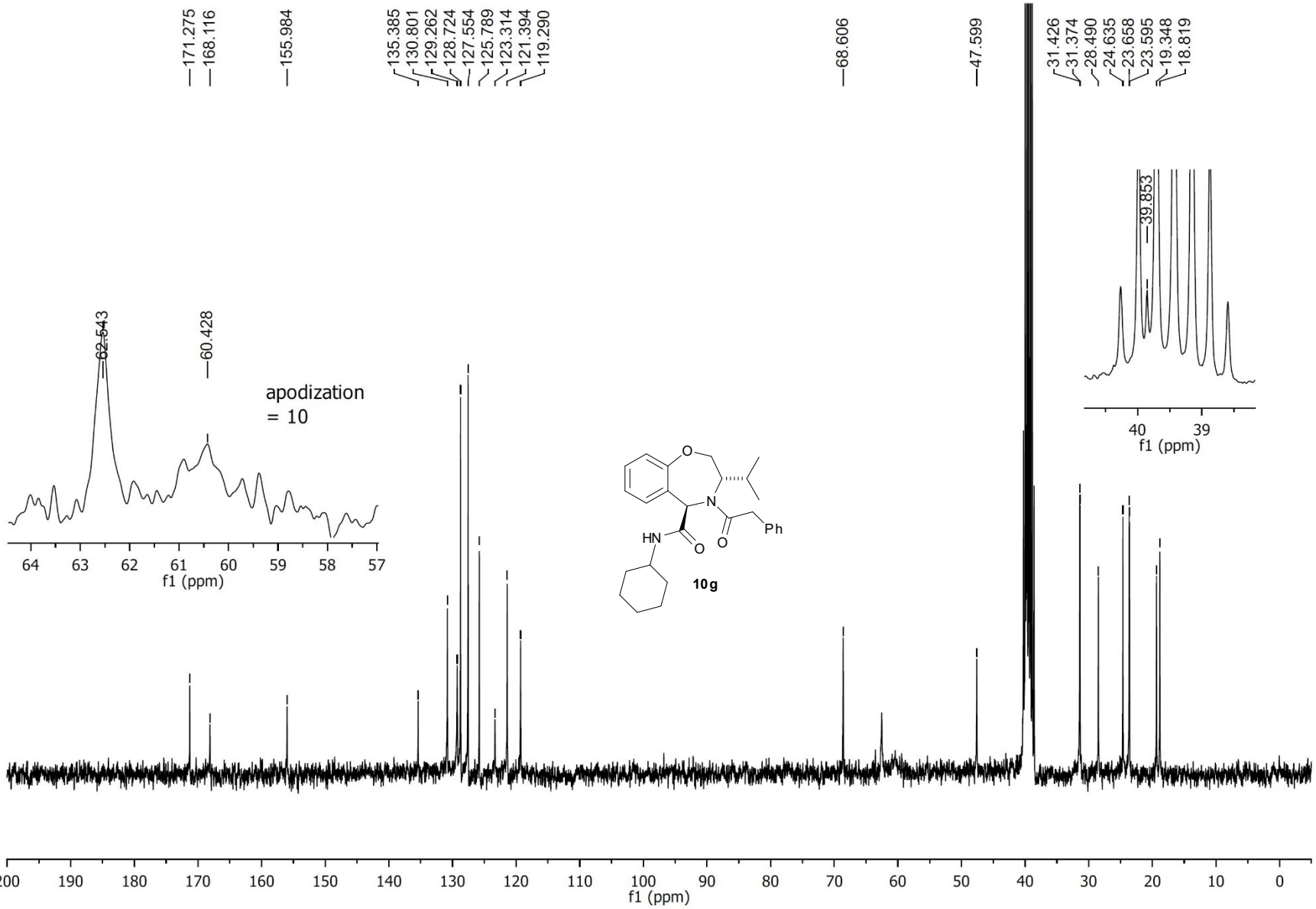

7.156
7.122
5.519
4.611
4.569
4.360
4.150
4.132
4.106
4.088
3.762
3.710
3.594
3.542
1.110
0.749
0.727
0.685
0.663
1.528
1.506
1.484
1.462
1.191
1.171
1.167
1.145
1.110
f1 (ppm)
4.611
4.569
4.360
4.150
4.132
4.106
4.088
f1 (ppm)
O
N
HN
O
O
Ph
10e
f1 (ppm)

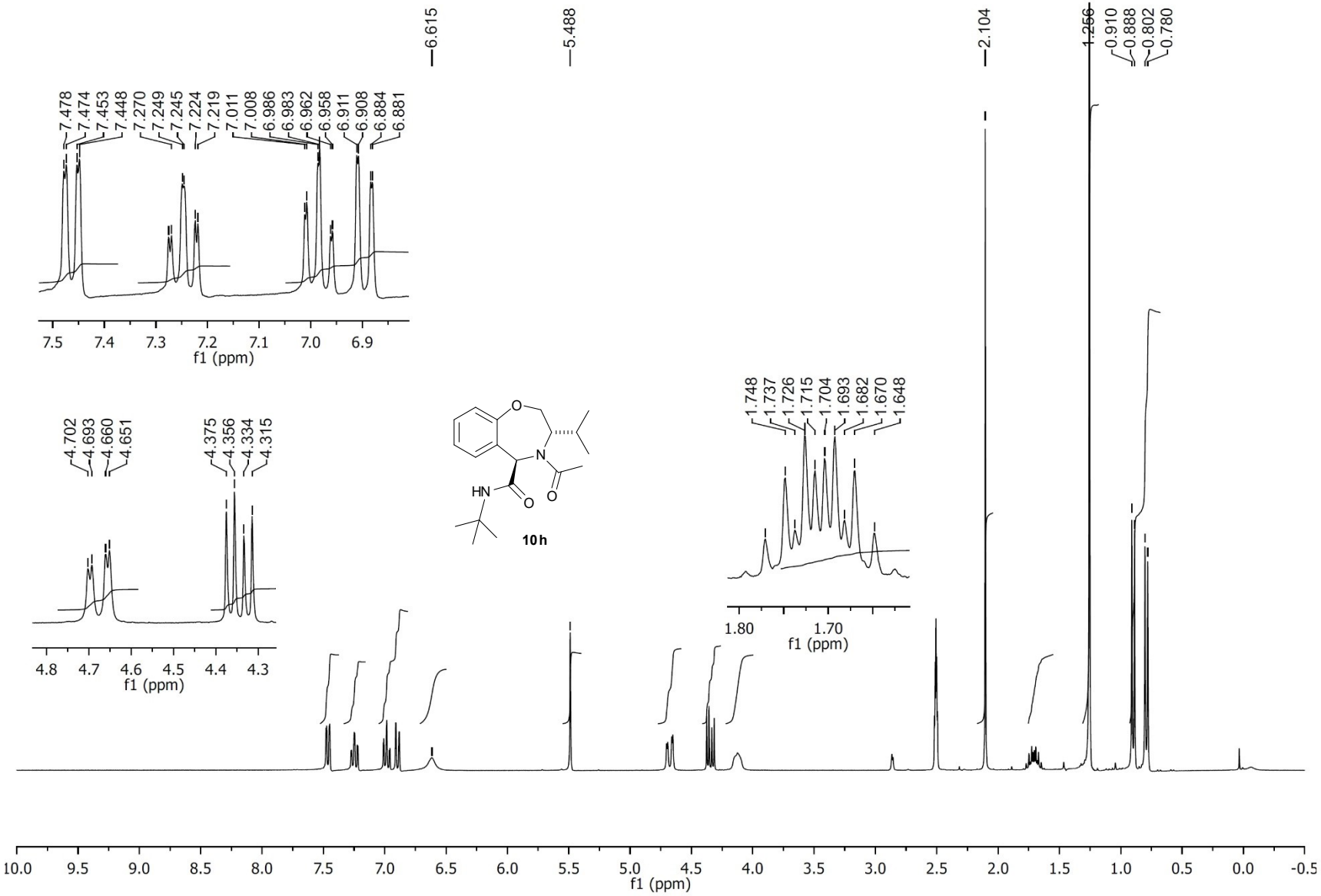

170.284
168.709
155.722
135.231
131.584
129.344
128.486
127.563
125.760
121.604
120.782
118.605
67.565
62.313
54.003
50.176
27.729
24.253
22.664
21.210
39.553
40.5
40.0
39.5
39.0
38.5
f1 (ppm)
O
N
HN
O
O
Ph
10e
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

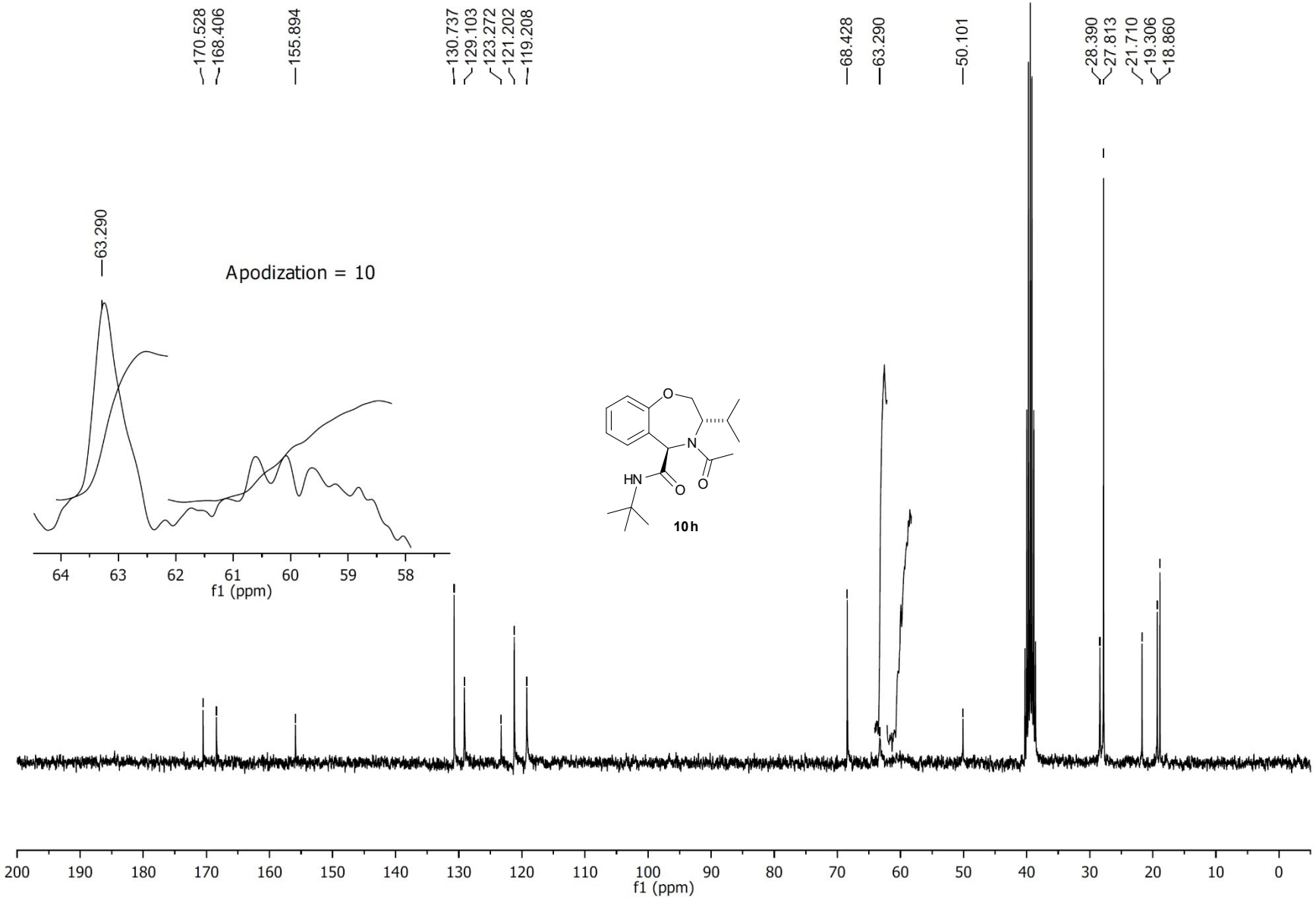

7.801
7.489
7.467
7.015
7.011
6.990
6.986
6.965
6.961
6.927
6.923
6.900
6.896
5.616
3.312
0.896
0.874
0.759
0.737
1.627
1.615
1.604
1.593
1.582
1.571
1.560
1.548
4.784
4.743
4.398
4.382
4.356
4.340
4.031
3.983
f1 (ppm)
10f

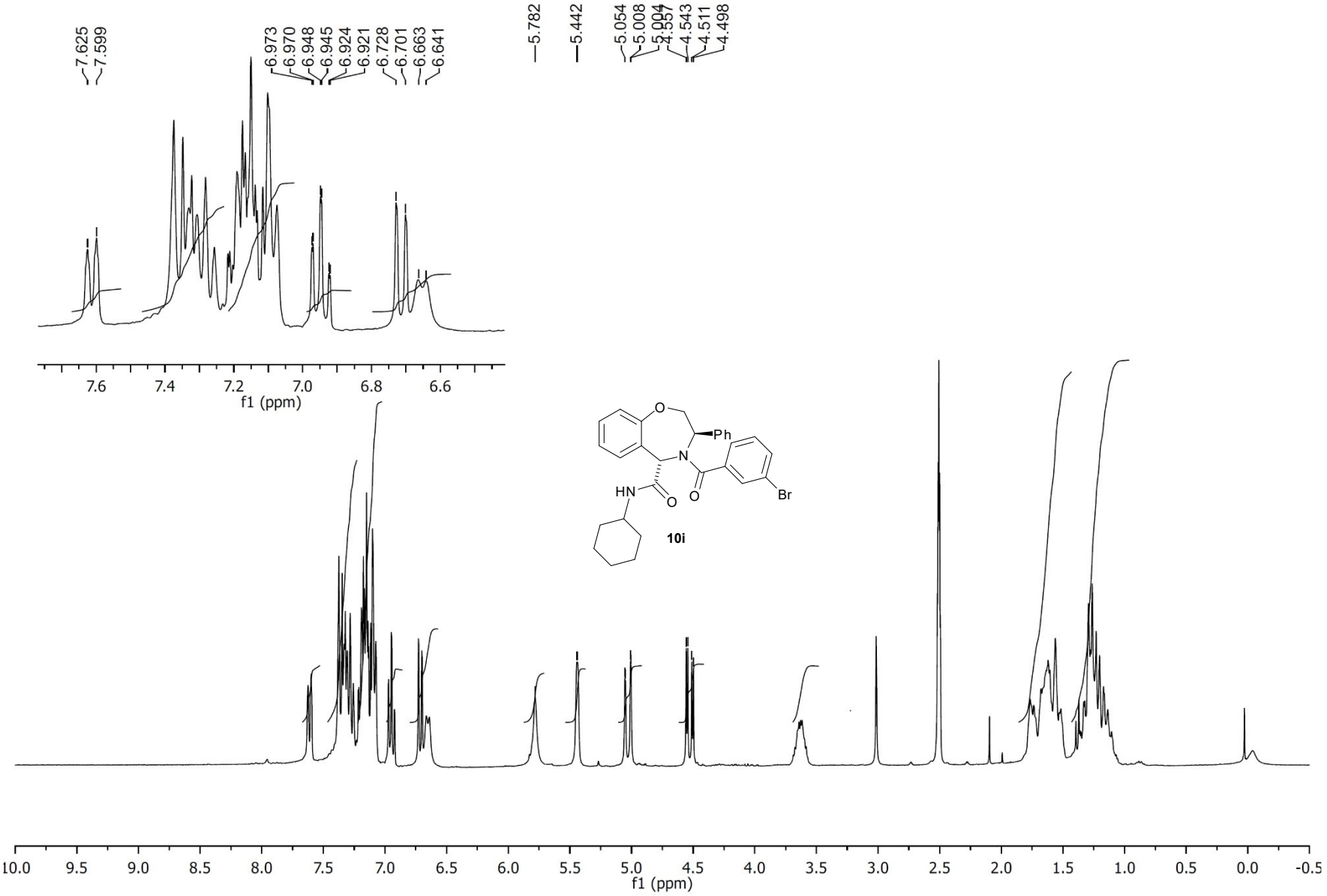

169.306
155.970
138.657
131.584
129.485
127.476
126.399
126.039
122.334
121.273
119.069
70.624
68.138
61.954
59.831
57.751
42.284
28.522
19.272
18.797
O
N
HN
O
O
OMe
Ph
10f
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

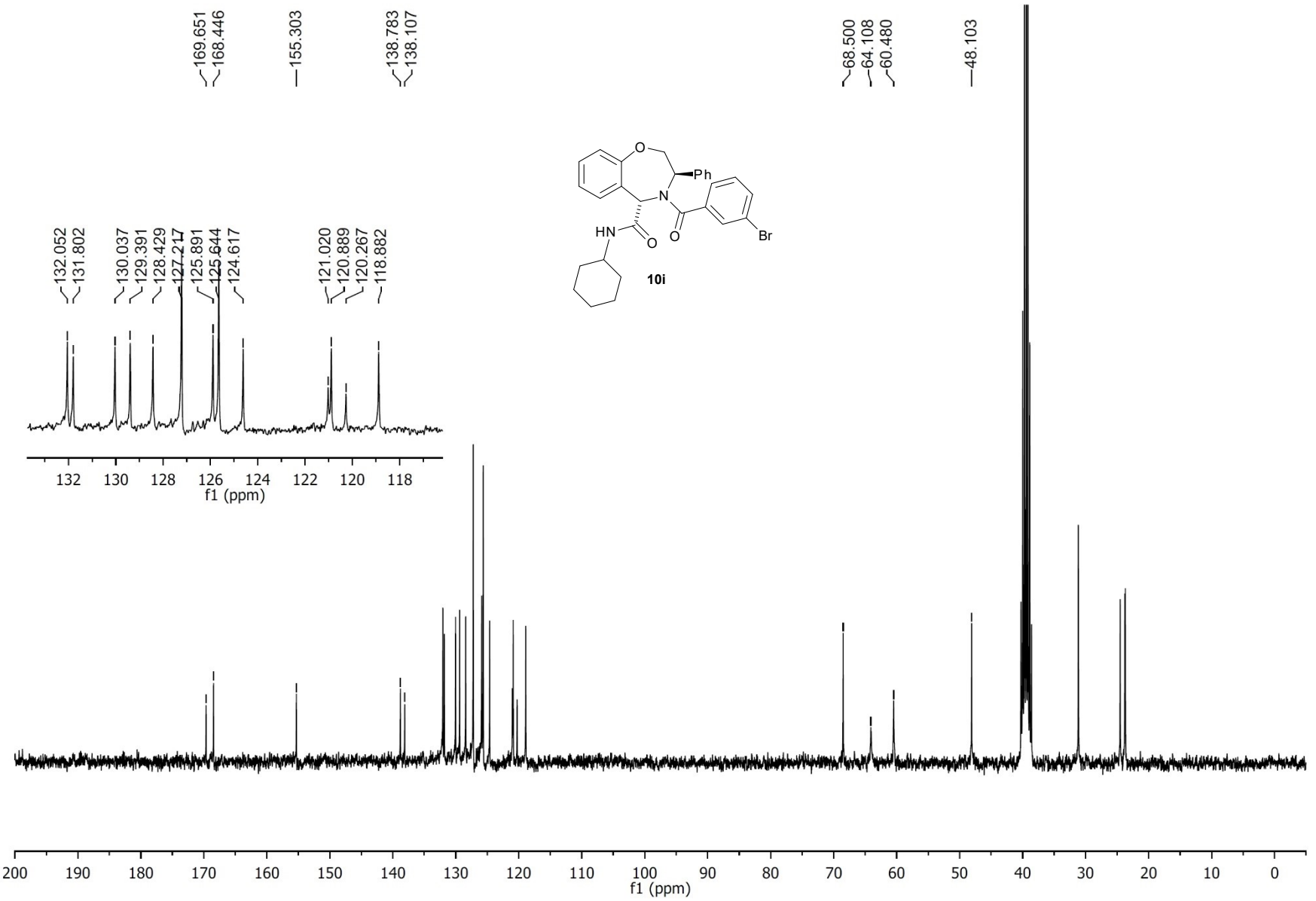

7.399
7.373
7.003
6.978
6.953
6.908
6.881
6.782
5.607
3.891
3.839
3.736
3.684
3.630
0.897
0.875
0.761
0.739
4.655
4.645
4.613
4.603
4.376
4.358
4.334
4.316
4.196
f1 (ppm)
HN
O
N
O
Ph
10g


171.275
168.116
155.984
135.385
130.801
129.262
128.724
127.554
125.789
123.314
121.394
119.290
68.606
47.599
31.426
31.374
28.490
24.635
23.658
23.595
19.348
18.819
62.543
60.428
apodization
= 10
64 63 62 61 60 59 58 57
f1 (ppm)
39.853
40 39
f1 (ppm)
O
N
HN
O
O
Ph
10g
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


6.615
5.488
2.104
1.256
0.910
0.888
0.802
0.780
7.478
7.474
7.453
7.448
7.270
7.249
7.245
7.224
7.219
7.011
7.008
6.986
6.983
6.962
6.958
6.911
6.908
6.884
6.881
7.5 7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
4.702
4.693
4.660
4.651
4.375
4.356
4.334
4.315
4.8 4.7 4.6 4.5 4.4 4.3
f1 (ppm)
1.748
1.737
1.726
1.715
1.704
1.693
1.682
1.670
1.648
1.80 1.70
f1 (ppm)
O
N
HN
O
O
10h
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


170.528
168.406
155.894
130.737
129.103
123.272
121.202
119.208
68.428
63.290
50.101
28.390
27.813
21.710
19.306
18.860
63.290
Apodization = 10
64
63
62
61
60
59
58
f1 (ppm)
HN
O
N
O
O
10h
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.625
7.599
6.973
6.970
6.948
6.945
6.924
6.921
6.728
6.701
6.663
6.641
5.782
5.442
5.054
5.008
5.004
4.557
4.543
4.511
4.498
7.6
7.4
7.2
7.0
6.8
6.6
f1 (ppm)
O
Ph
N
HN
O
O
Br
10i
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


169.651
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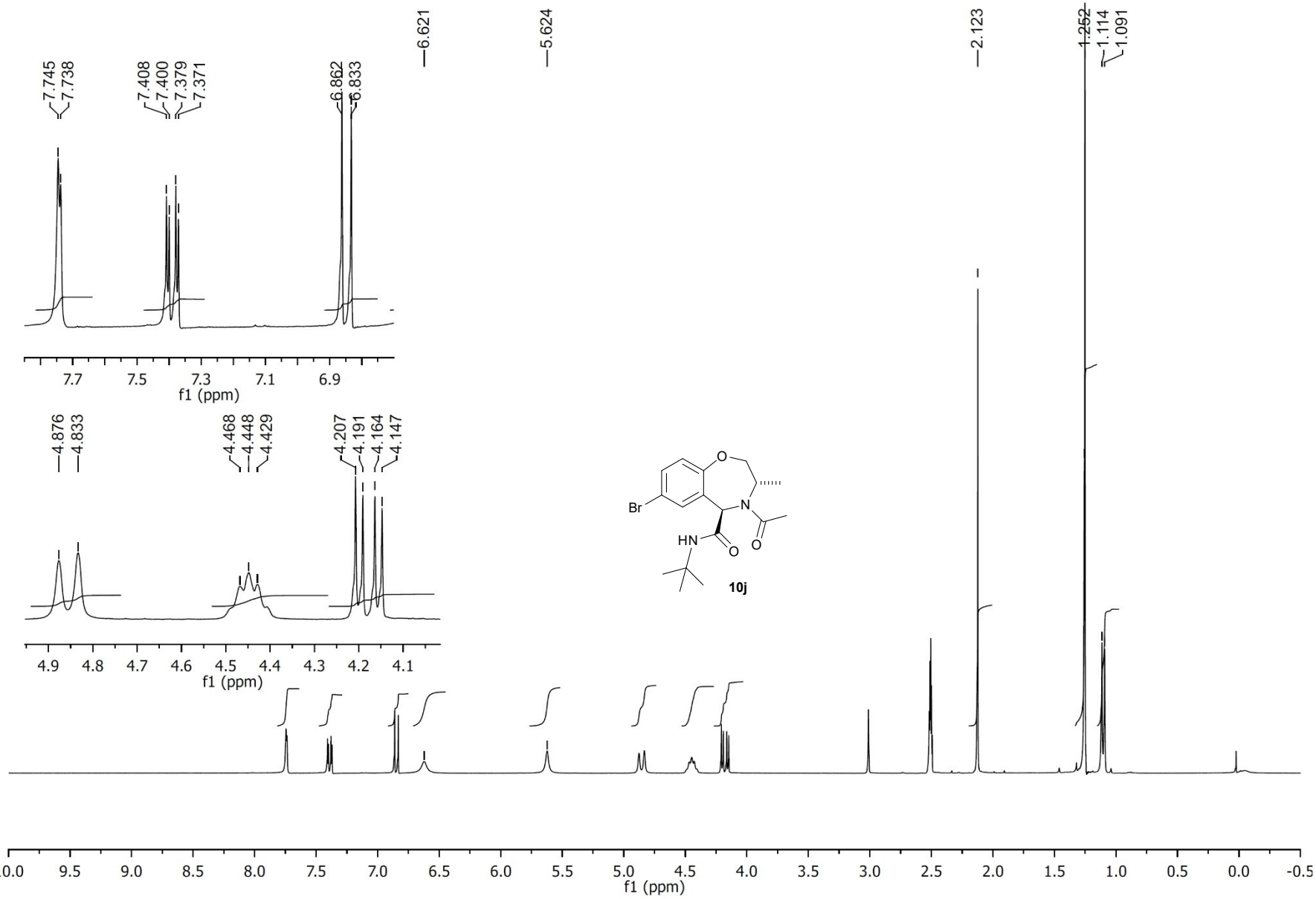
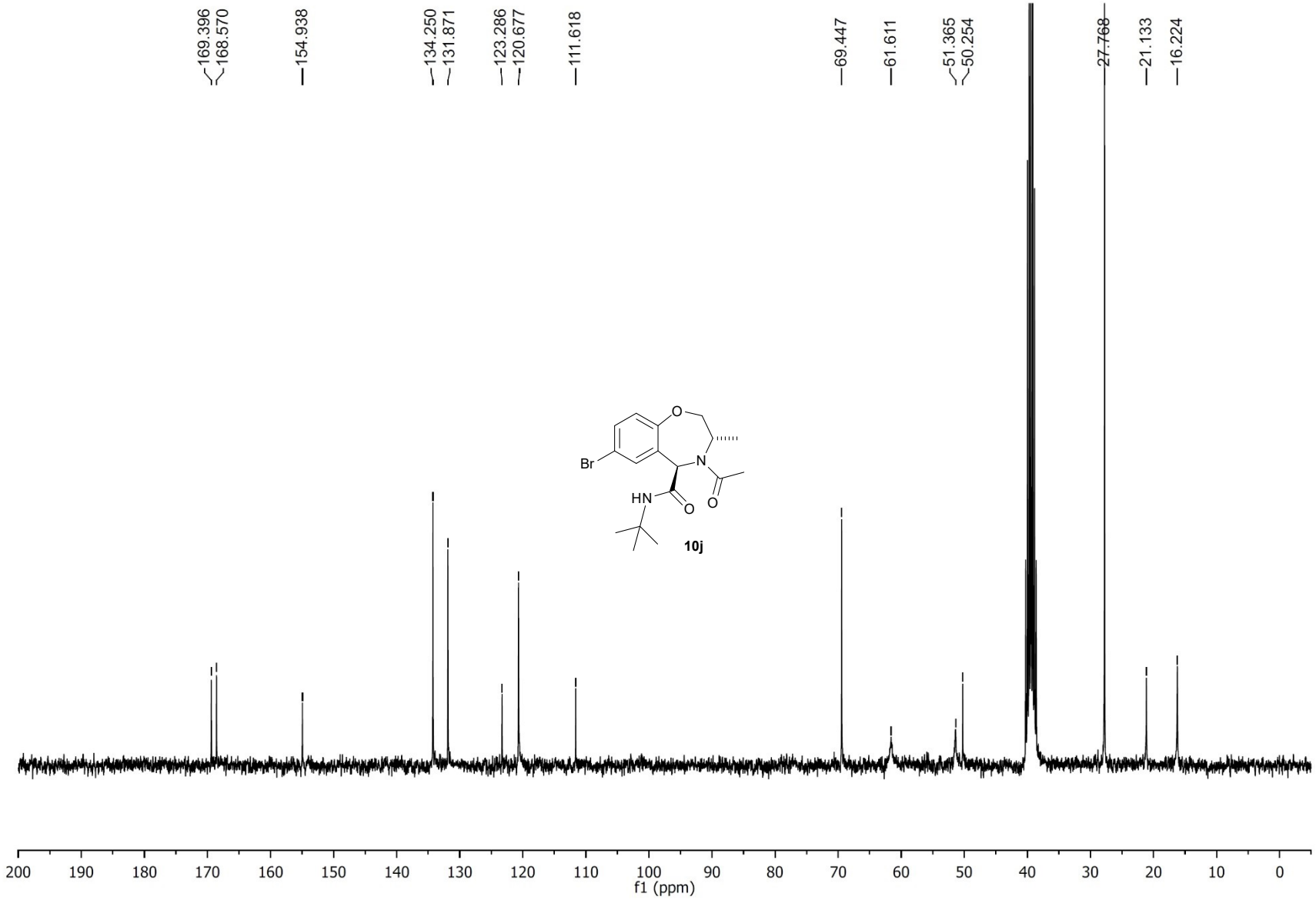
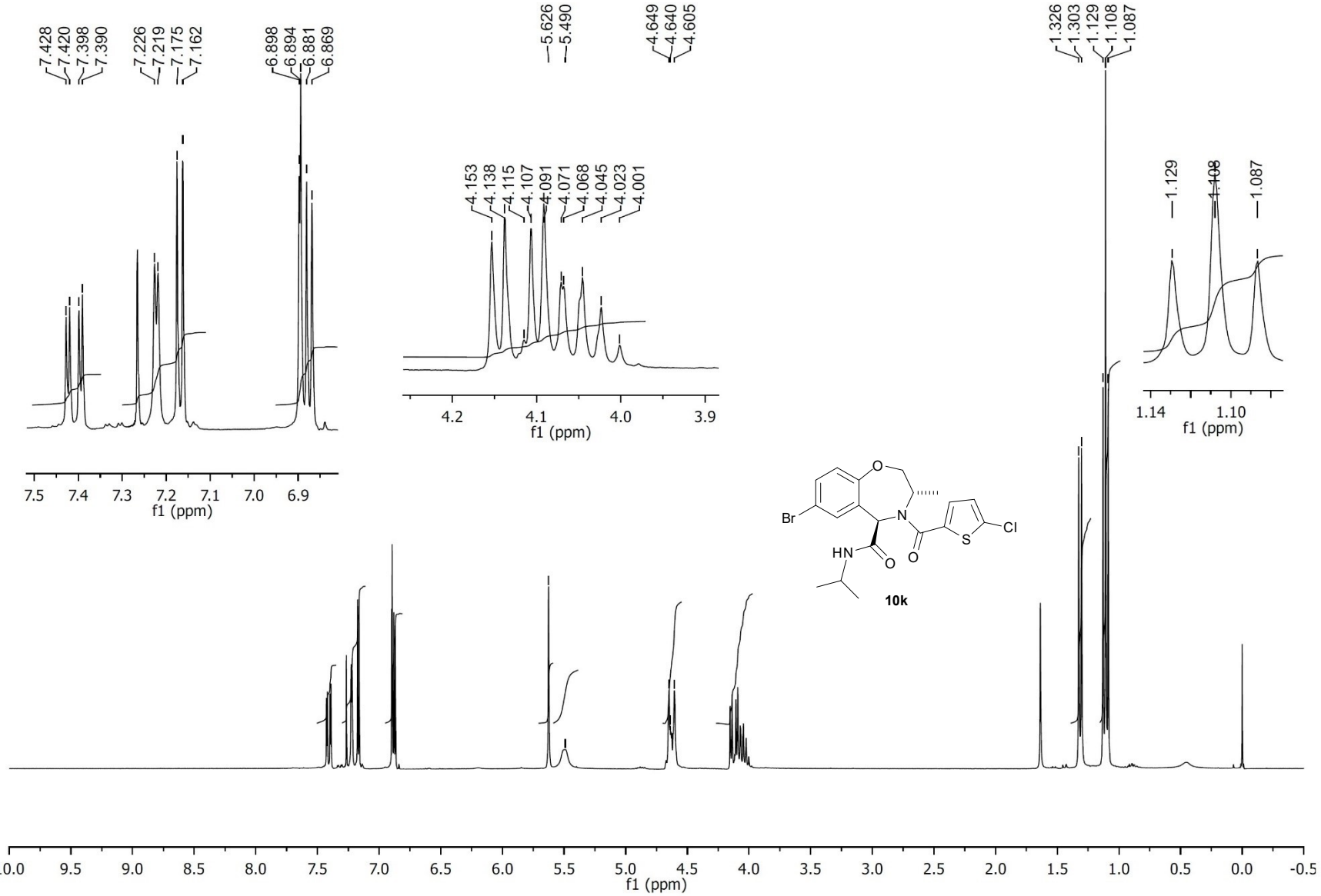
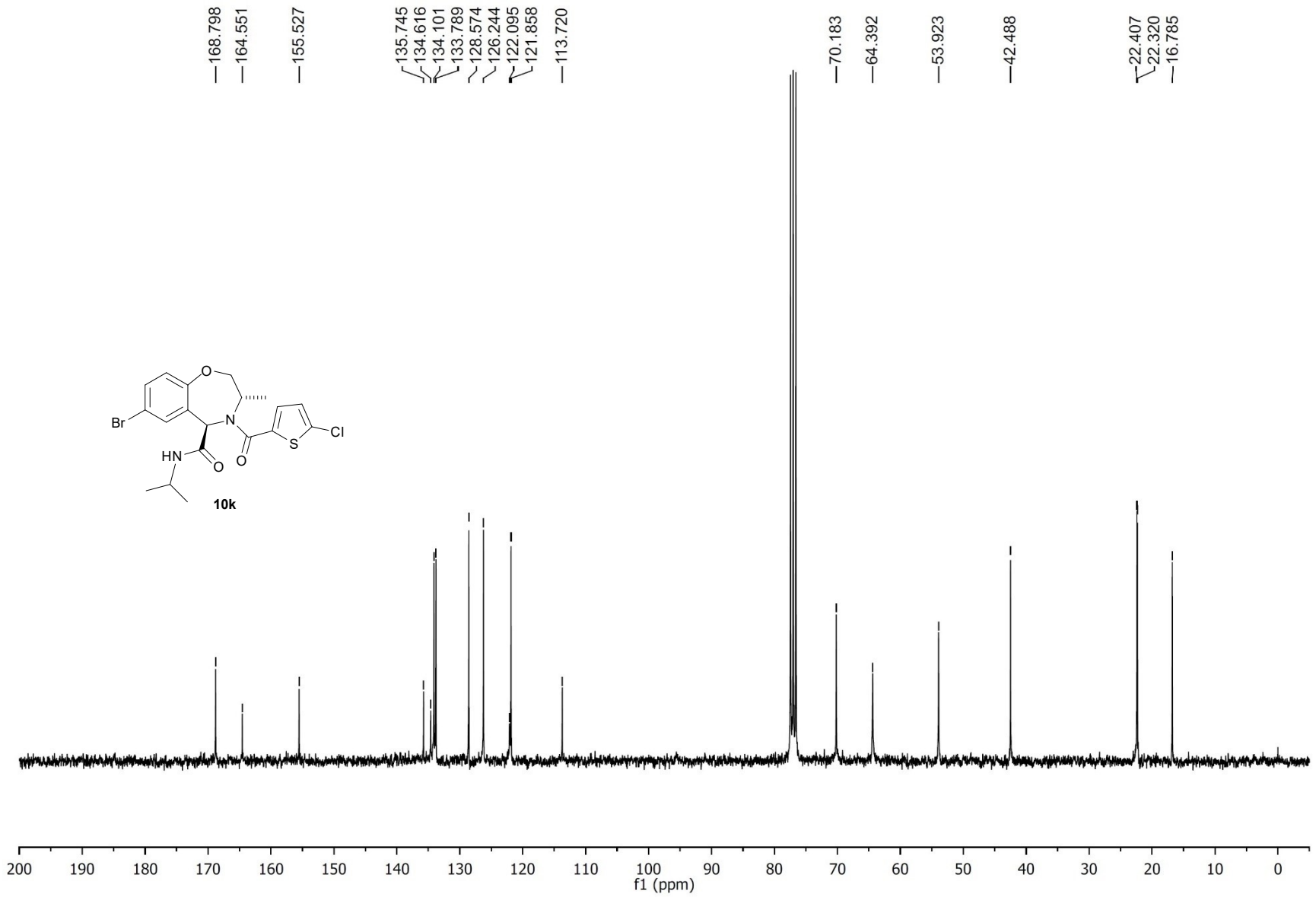
155.303
138.783
138.107
68.500
64.108
60.480
48.103
132.052
131.802
130.037
129.391
128.429
127.217
125.891
125.644
124.617
121.020
120.889
120.267
118.882
O
Ph
N
HN
O
O
Br
10i
132 130 128 126 124 122 120 118
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.745
7.738
7.408
7.400
7.379
7.371
6.862
6.833
6.621
5.624
2.123
1.252
1.114
1.091
4.876
4.833
4.468
4.448
4.429
4.207
4.191
4.164
4.147
Br
O
N
HN
O
O
10j
f1 (ppm)


169.396
168.570
154.938
134.250
131.871
123.286
120.677
111.618
69.447
61.611
51.365
50.254
27.768
21.133
16.224
Br
O
N
HN
O
O
10j
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.428
7.420
7.398
7.390
7.226
7.219
7.175
7.162
6.898
6.894
6.881
6.869
5.626
5.490
4.649
4.640
4.605
4.153
4.138
4.115
4.107
4.091
4.071
4.068
4.045
4.023
4.001
1.326
1.303
1.129
1.108
1.087
Br
O
N
HN
O
O
S
Cl
10k
f1 (ppm)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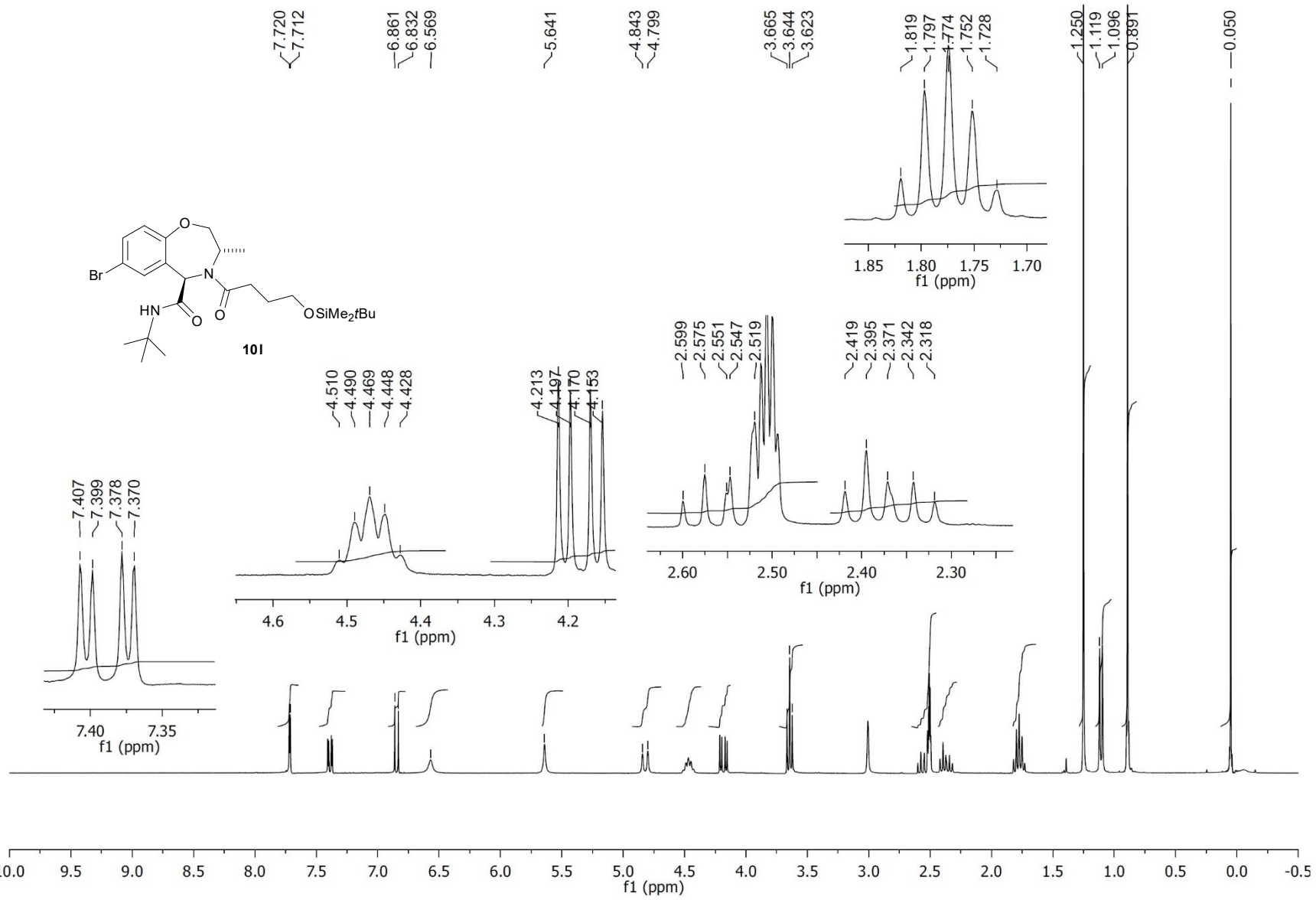
164.551
155.527
135.745
134.616
134.101
133.789
128.574
126.244
122.095
121.858
113.720
70.183
64.392
53.923
42.488
22.407
22.320
16.785
Br
Cl
S
N
O
HN
O
O
10k
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.712
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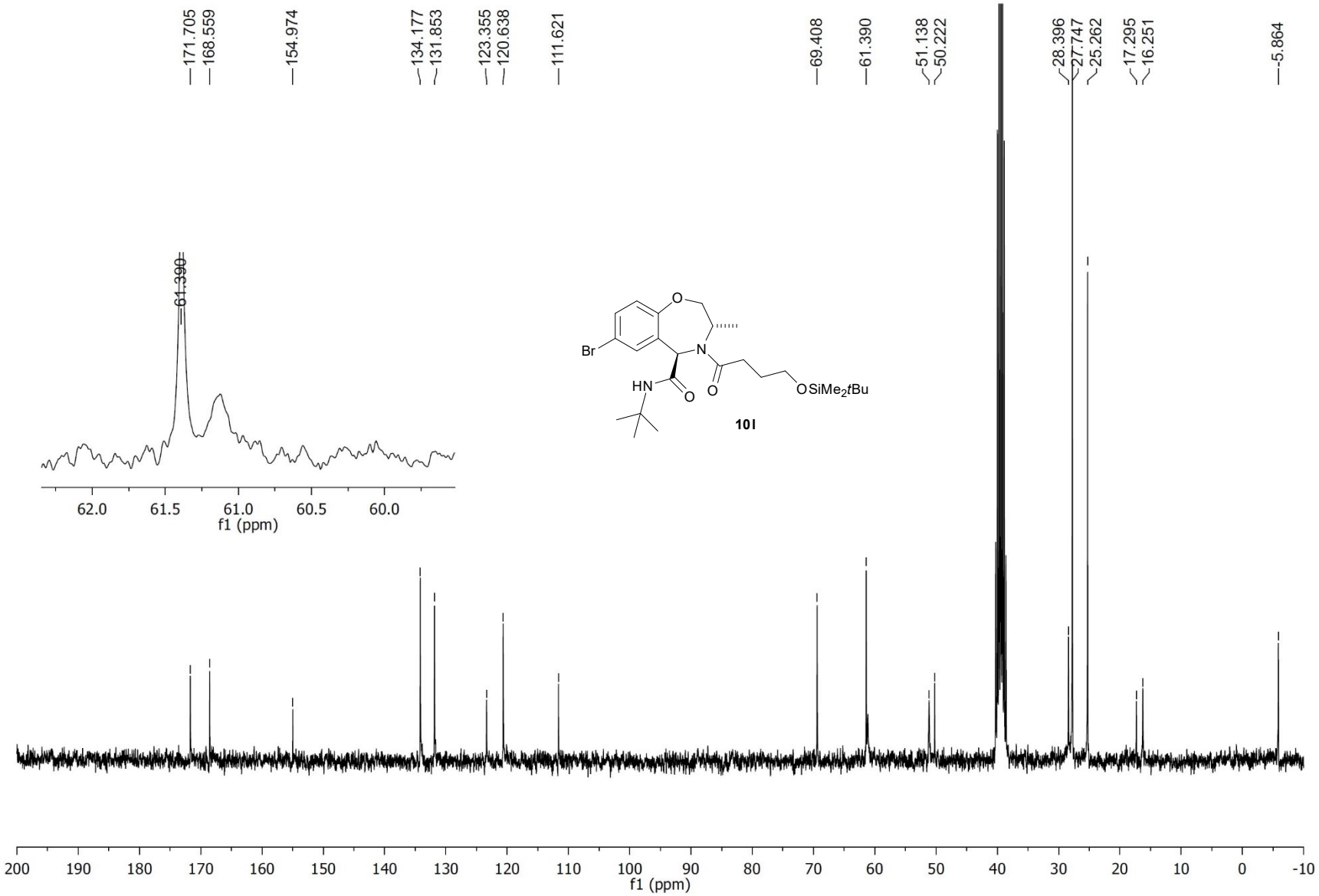
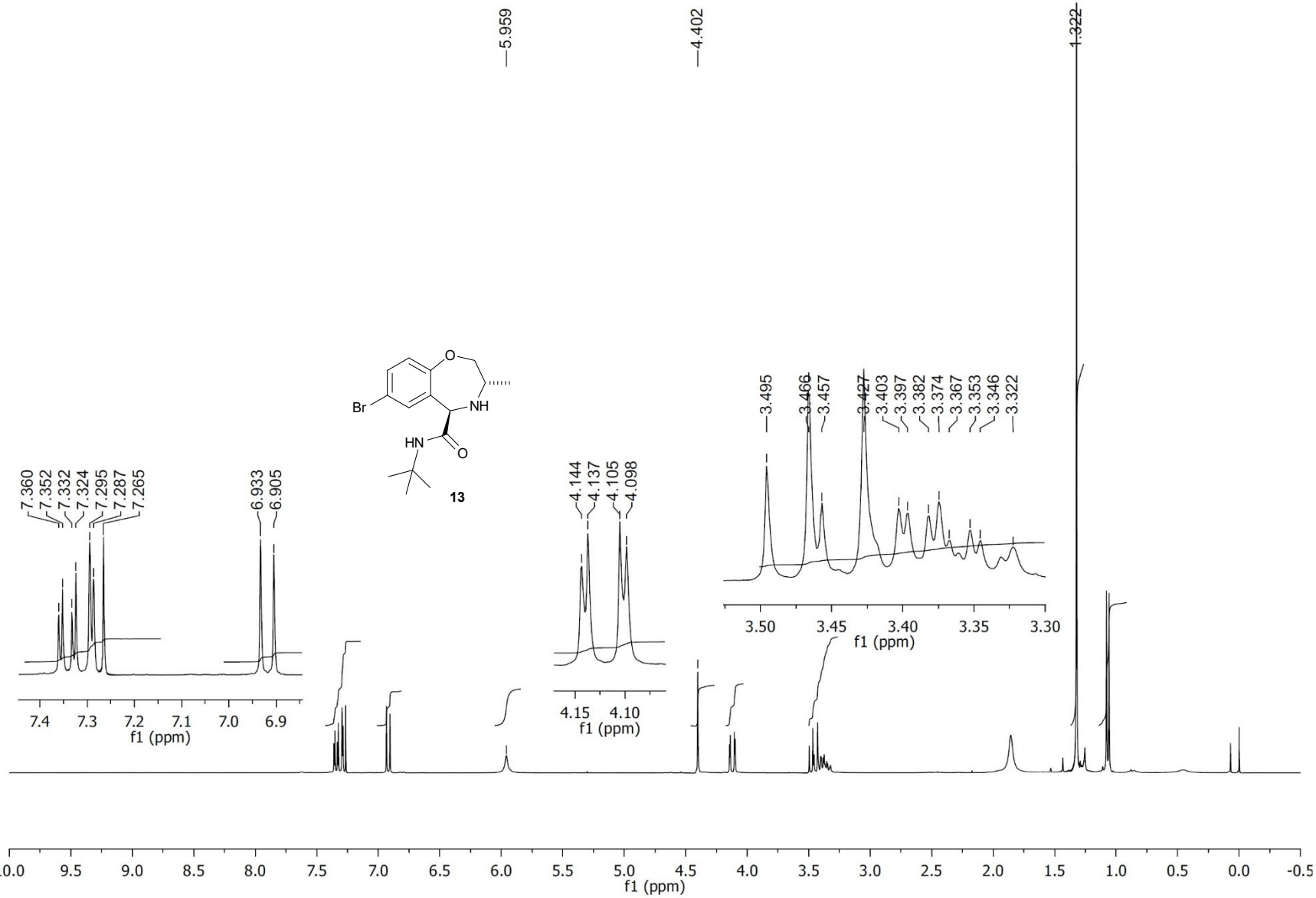
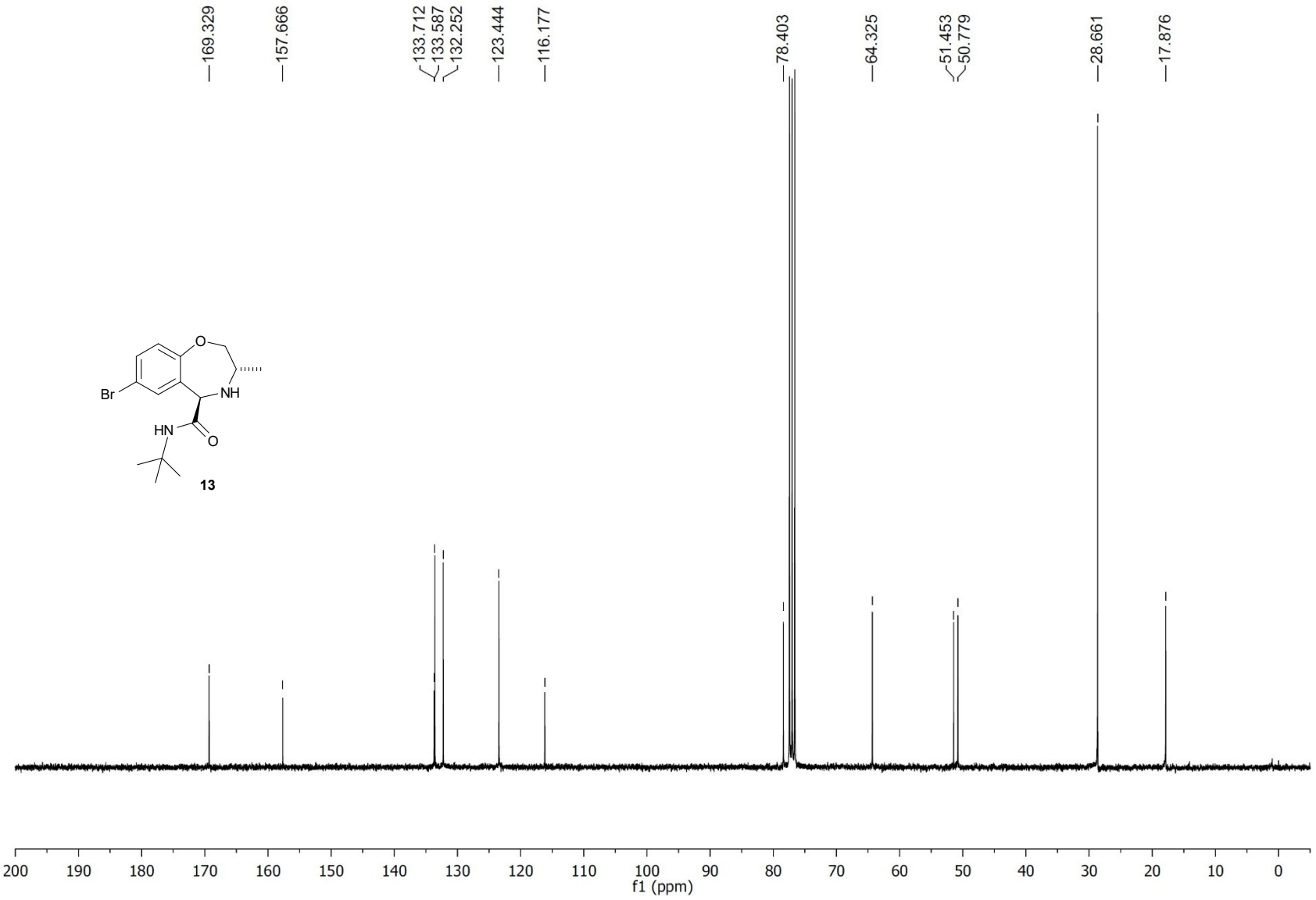
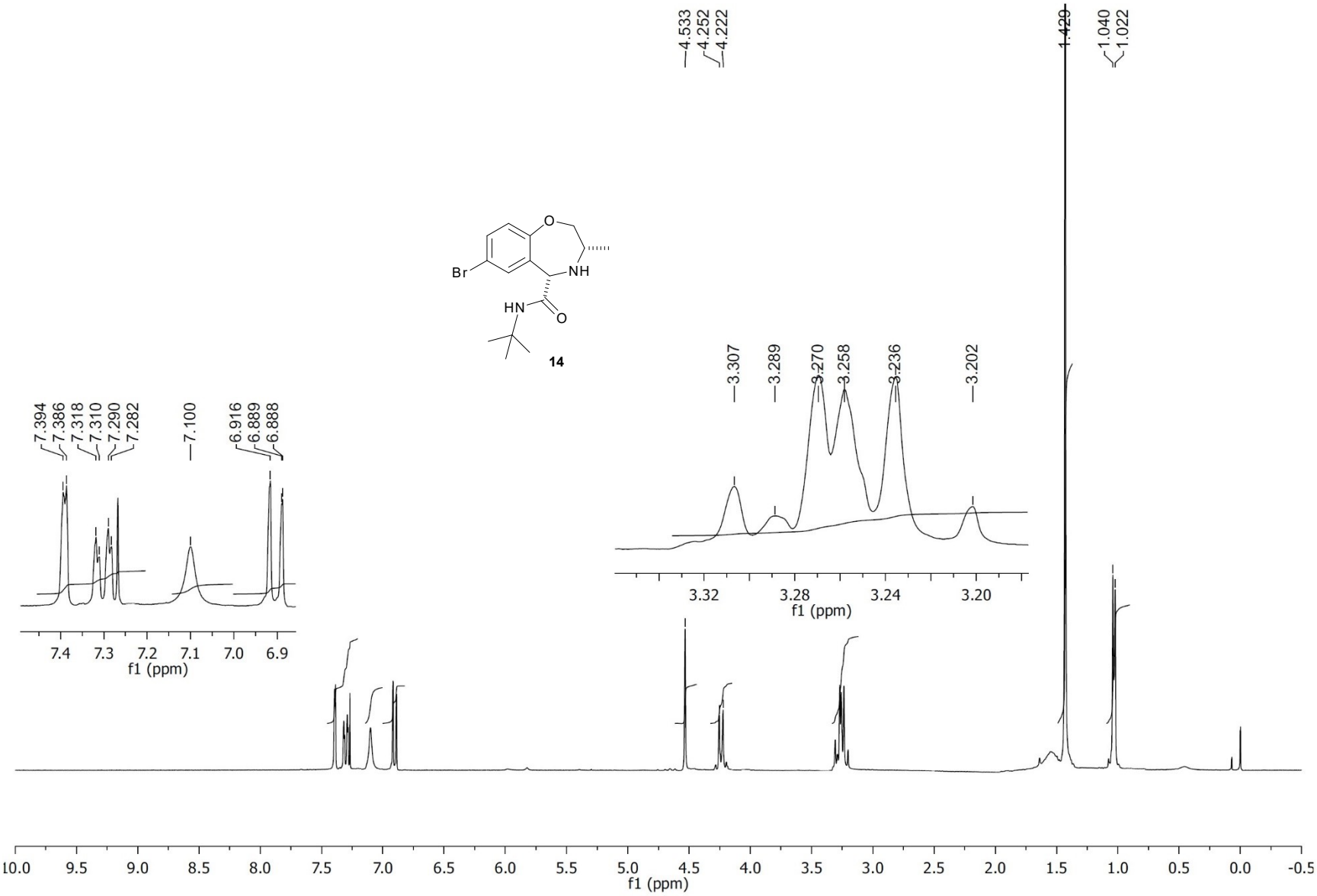
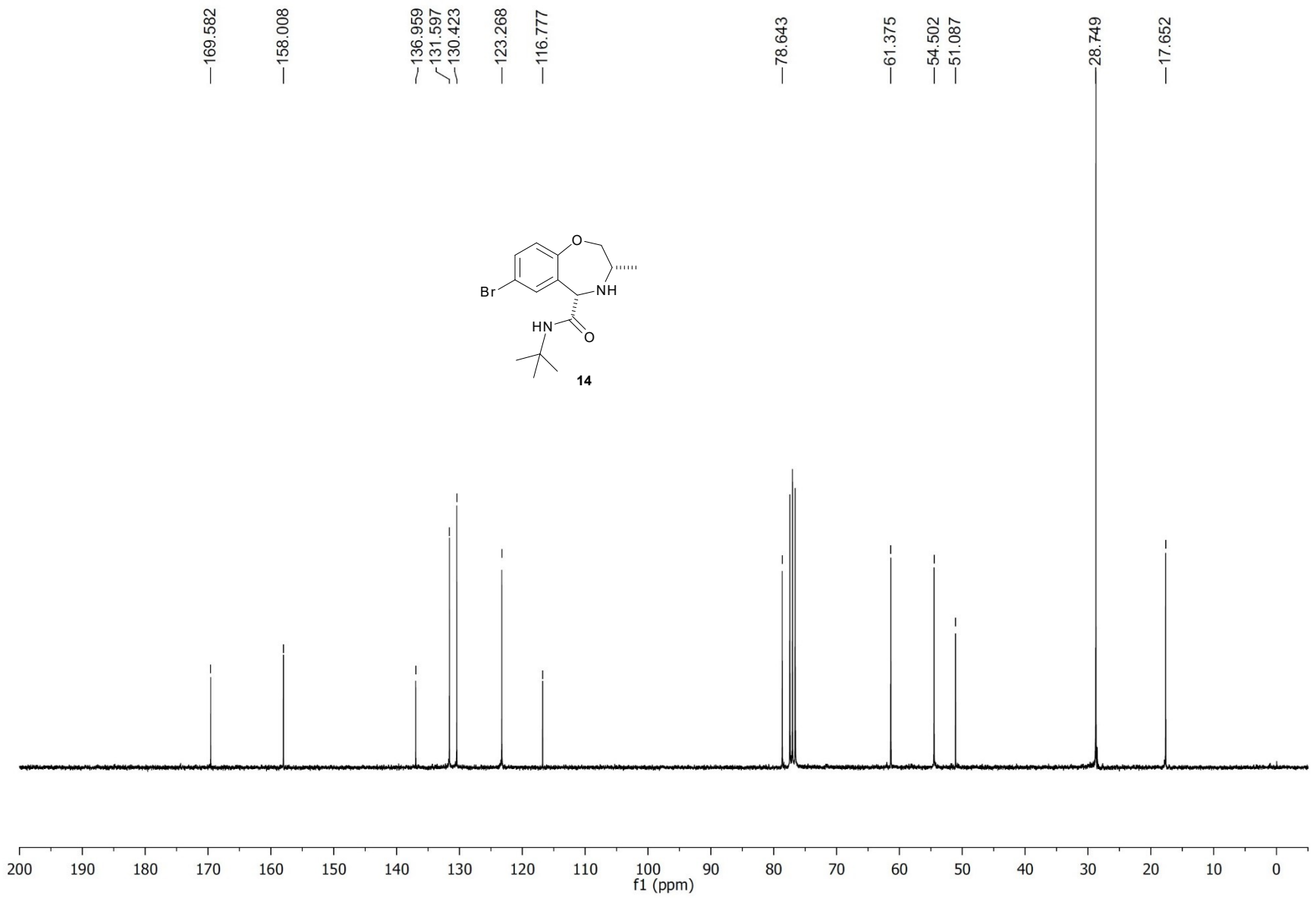
6.832
6.569
5.641
4.843
4.799
3.665
3.644
3.623
1.819
1.797
1.774
1.752
1.728
1.250
1.119
1.096
0.891
0.050
Br
HN
O
N
O
OSiMe2tBu
10l
4.510
4.490
4.469
4.448
4.428
4.213
4.197
4.170
4.153
2.599
2.575
2.551
2.547
2.519
2.419
2.395
2.371
2.342
2.318
7.407
7.399
7.378
7.370
f1 (ppm)


171.705
168.559
154.974
134.177
131.853
123.355
120.638
111.621
69.408
61.390
51.138
50.222
28.396
27.747
25.262
17.295
16.251
-5.864
61.390
62.0
61.5
61.0
60.5
60.0
f1 (ppm)
Br
N
O
HN
O
O
OSiMe2tBu
10l
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


5.959
4.402
1.322
7.360
7.352
7.332
7.324
7.295
7.287
7.265
6.933
6.905
4.144
4.137
4.105
4.098
3.495
3.466
3.457
3.427
3.403
3.397
3.382
3.374
3.367
3.353
3.346
3.322
Br
O
NH
HN
O
13
7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
4.15 4.10
f1 (ppm)
3.50 3.45 3.40 3.35 3.30
f1 (ppm)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


169.329
157.666
133.712
133.587
132.252
123.444
116.177
78.403
64.325
51.453
50.779
28.661
17.876
Br
NH
HN
O
O
13
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


4.533
4.252
4.222
1.429
1.040
1.022
7.394
7.386
7.318
7.310
7.290
7.282
7.100
6.916
6.889
6.888
3.307
3.289
3.270
3.258
3.236
3.202
Br
O
NH
HN
O
14
f1 (ppm)
f1 (ppm)
f1 (ppm)


169.582
158.008
136.959
131.597
130.423
123.268
116.777
78.643
61.375
54.502
51.087
28.749
17.652
Br
NH
HN
O
O
14
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)