Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting Information

Enantioselective Total Synthesis of (+)-Forphenicinol via Asymmetric Organocatalysis

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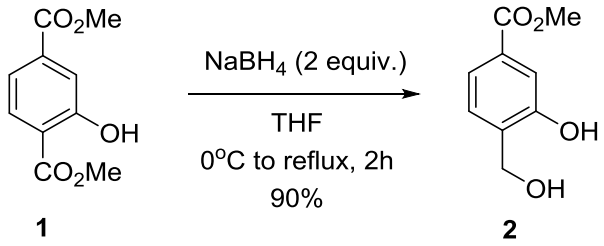
Contents

1. General information

The ^{1}H, ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. The high-resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and a time-of-flight (TOF) mass analyzer. The measurements were taken in the positive ion mode (interface capillary voltage 4500 V) in the mass range from m/z = 50 Da to m/z = 3000 Da; external and internal calibrations were done with the electrospray calibrant solution. Optical rotations were measured on a polarimeter Jasco P-2000 and calibrated with a pure solvent as a blank. HPLC analyses were performed on an HPLC system equipped with chiral stationary phase column (AD-H), detection 254 nm. Silica gel (0.060−0.200 mm) was used for column chromatography. Catalysts **I-VIII** were synthesized by reported procedures,[1] catalysts **IX-XIV** were purchased from commercial resources. The reagents and solvents were purified by standard methods.

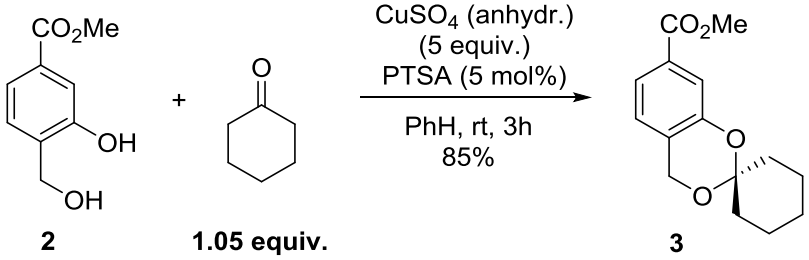
2. Experimental details and characterization data for all compounds

2.1. Synthesis of methyl 3-hydroxy-4-(hydroxymethyl)benzoate (2).



2-Hydroxydimethylterephtalate (**1**) (15.0 g, 71.4 mmol) were dissolved under nitrogen atmosphere in dry THF (100 mL). Then, $NaBH_4$ (5.4 g, 0.143 mol) was added slowly to the solution at 0 °C and the mixture was refluxed for 2 h. The solvent was removed under reduced pressure, the residue was dissolved in water (100 mL) and acidified with 2M HCl to pH 2. The organic solute was extracted from the aqueous solution with EtOAc (3 x 100 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc, 2 : 1) to afford compound **2** as light yellow solid. Yield: 11.7 g (90 %), mp 103-105 °C (104-105 °C) [2]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (brs, 2H), 7.14-7.11 (d, *J* = 7.7 Hz, 1H), 4.95 (brs, 2H), 3.90 (s, 3H) ppm. The data are in accordance with literature.[3]

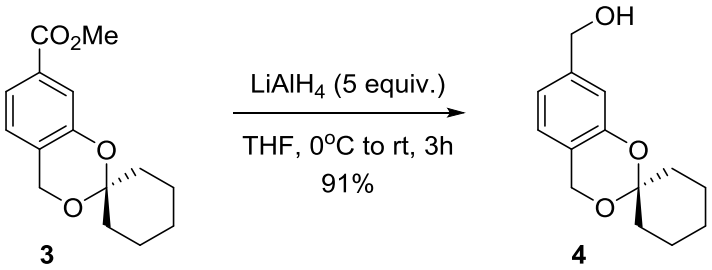
2.2. Synthesis of methyl 4H-spiro[benzo[d][1,3]dioxine-2,1'-cyclohexane]-7-carboxylate (3).



Compound **2** (11.0 g, 60.4 mmol), cyclohexanone (6.56 mL, 63.4 mmol) and PTSA (574 mg, 3.0 mmol) were successively added to a suspension of anhydrous $CuSO_4$ (48.3 g, 302 mmol) in dry benzene (50 mL). The reaction mixture was stirred at ambient temperature for 3 h, filtered and the solvent was evaporated under reduced pressure. Then, EtOAc (100 mL) was added to the residue and the solution was washed with saturated aqueous $NaHCO_3$ (3 x 100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford compound **3** as colorless viscous oil. Yield: 13.5 g (85 %).^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59-7.56 (dd, *J* = 1.6,

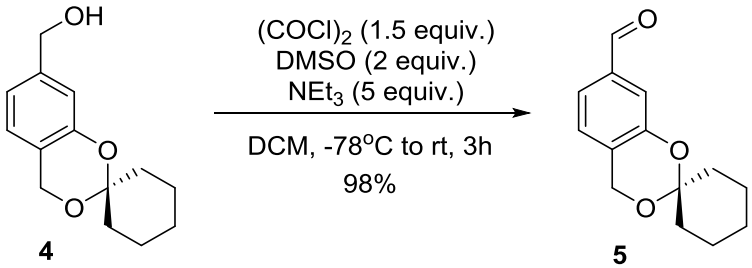
7.9 Hz, 1H), 7.55-7.54 (d, *J* = 1.6 Hz, 1H), 7.04-7.02 (d, *J* = 7.9 Hz, 1H), 4.88 (s, 2H), 3.91 (s, 3H), 1.87-1.81 (m, 4H), 1.70-1.60 (m, 4H), 1.54-1.49 (m, 2H) ppm.$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 166.7, 151.1, 130.1, 125.2, 124.7, 121.3, 118.4, 100.1, 60.2, 52.1, 33.4, 25.3, 22.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{15}H_{18}O_4[M+H]^+$: 263.1283, found 263.1286

2.3. Synthesis of (4H-spiro[benzo[d][1,3]dioxine-2,1'-cyclohexan]-7-yl)methanol (4).



Powdered $LiAlH_4$ (9.4 g, 248 mmol) was added to a solution of ester **3** (13 g, 49.6 mmol) in dry THF (100 ml) at 0 °C. The mixture was stirred for 3 h under a nitrogen atmosphere at 0 °C and heated to room temperature. Then, aqueous NaOH (10% wt, 20 ml) was added cautiously. Solid compounds were filtered off and the filtrate was concentrated under reduced pressure to afford compound **4** as colorless oil. Yield 10.6 g (91 %).^1H NMR (300 MHz, $CDCl_3$): δ 6.96-6.94 (d, *J* = 7.7 Hz, 1H), 6.91-6.87 (m, 2H), 4.83 (s, 2H), 4.62 (s, 2H), 1.84-1.80 (m, 4H), 1.69-1.60 (m, 4H), 1.53-1.49 (m, 2H) ppm.$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 151.2, 141.2, 124.8, 119.2, 118.8, 115.5, 99.8, 65.0, 60.1, 33.5, 25.3, 22.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{14}H_{18}O_3[M+H]^+$: 235.1334, found 235.1337.

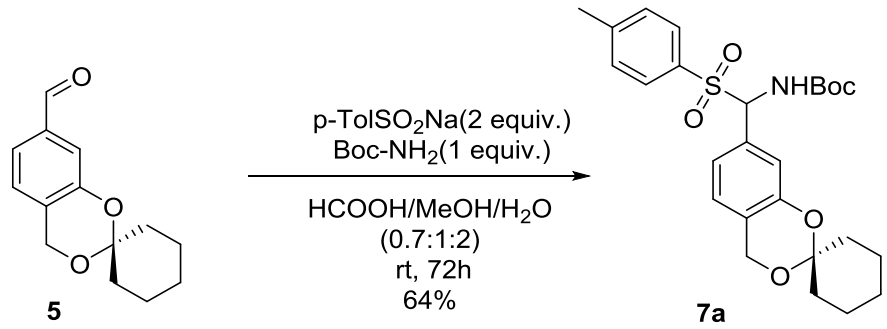
2.4. Synthesis of 4H-spiro[benzo[d][1,3]dioxine-2,1'-cyclohexane]-7-carbaldehyde (5).



A solution of DMSO (5.54 mL, 78.2 mmol) in dry DCM (30 mL) was added dropwise to a stirred solution of oxalyl chloride (5.03 mL, 58.7 mmol) in dry DCM (60 mL) under nitrogen at -78°C and the resulting mixture was stirred for 30 min. A solution of **4** (9.16 g, 39.1 mmol) in dry

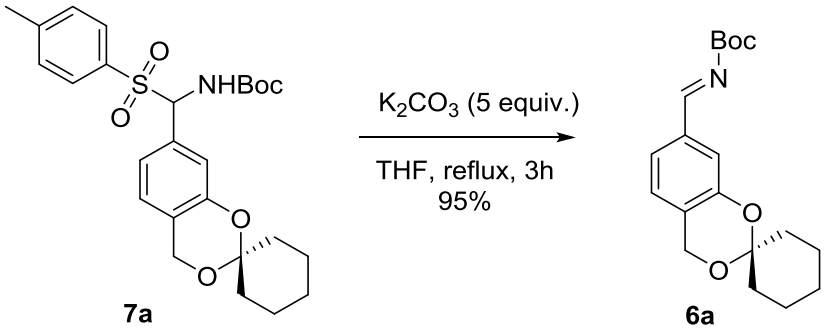
DCM (30 mL) was added slowly at the same temperature and the mixture was stirred for additional 1 h. Then, triethylamine (27.1 mL, 196 mmol) was added and the mixture was stirred for 30 min in -78 ^{o}C. Finally, water (150 mL) was added and the resulting two-phase system was stirred for 1 h. The organic layer was then separated and the aqueous layer was extracted with DCM (2 x 100 mL). Combined organic layers were dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography (Silica gel, *n*-hexane/EtOAc l3 : 1) to afford compound **5** as yellowish viscous oil. Yield 8.9 g (98 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.43-7.40 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.35-7.34 (d, *J* = 1.3 Hz, 1H), 7.13-7.10 (d, *J* = 7.8 Hz, 1H), 4.88 (s, 2H), 1.84-1.80 (m, 4H), 1.69-1.59 (m, 4H), 1.53-1.48 (m, 2H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 191.6, 151.8, 136.6, 126.9, 125.4, 121.3, 118.3, 100.4, 60.2, 33.4, 25.2, 22.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{14}H_{16}O_3[M+H]^+$: 233.1178, found 233.1181.

2.5. Synthesis of *tert*-butyl ((4H-spiro[benzo[d][1,3]dioxine-2,1'-cyclohexan]-7-yl)(tosyl)methyl)carbamate (7a).



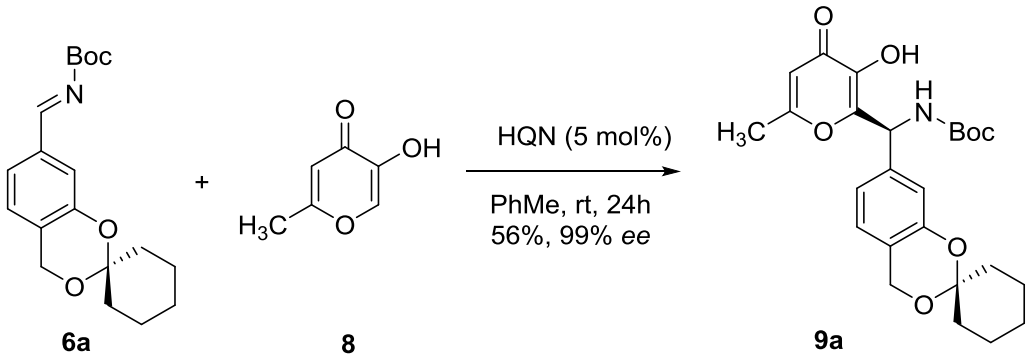
Aldehyde **5** (3.0 g, 12.9 mmol) was added to a suspension of *tert*-butylcarbamate (1.50 g, 12.9 mmol) and p-$TolSO_2Na$ (4.60 g, 25.8 mmol) in MeOH/water solvent system (1 : 2 v/v, 60 mL). Then formic acid (14 mL) was added via syringe and the reaction mixture was vigorously stirred at ambient temperature for 72 h. The precipitate was filtered off, washed successively with water (3 x 50 mL) and *n*-hexane (3 x 50 mL) and dried in air affording sulfone **7a** as colorless solid. Yield 4.0 g (64 %), mp >200 ^{o}C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81-7.78 (d, *J* = 8.0 Hz, 2H), 7.35-7.33 (d, *J* = 8.0 Hz, 2H), 7.00 (brs, 2H), 6.92 (s, 1H), 5.84-5.80 (d, *J* = 10.4 Hz, 1H), 5.72-5.68 (d, *J* = 10.4 Hz, 1H), 4.84 (s, 2H), 2.44 (s, 3H), 1.82 (brs, 4H), 1.65-1.63 (m, 4H), 1.52-1.48 (m, 2H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 151.3, 145.0, 133.9, 130.0, 129.7, 129.5, 125.0, 121.6, 120.8, 117.4, 100.1, 81.1, 59.9, 33.7, 33.4, 28.0, 25.3, 22.4, 21.6 ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{33}NO_6S$ $[M+H]^+$: 488.2107, found 488.2105.

2.6. Synthesis of *tert*-butyl ((4H-spiro[benzo[d][1,3]dioxine-2,1'-cyclohexan]-7-yl)methylene)carbamate (6a).



Sulfone **7a** (3.56 g, 7.3 mmol) was added to a suspension of anhydrous potassium carbonate (5.05 g, 36.5 mmol) in dry THF (80 mL) under argon. The reaction mixture was refluxed with stirring under argon for 3 h. Then it was cooled to ambient temperature, inorganic salts were filtered and the filtrate was concentrated under reduced pressure. The resulting solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was dried in vacuum (10 Torr) at ambient temperature for 2 h to afford *N*-Boc aldimine **6a** as colorless viscous oil. Yield 2.30 g (95 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.80 (s, 1H), 7.48-7.45 (d, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 7.07-7.05 (d, *J* = 8.0 Hz, 1H), 4.88 (s, 2H), 1.85-1.79 (m, 4H), 1.64-1.59 (m, 13H), 1.49 (m, 2H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.3, 162.6, 151.6, 134.1, 125.9, 125.2, 121.9, 121.9, 118.8, 100.2, 82.2, 60.2, 33.4, 27.9, 25.2, 22.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{19}H_{25}NO_4$ $[M+H]^+$: 332.1862, found 332.1865.

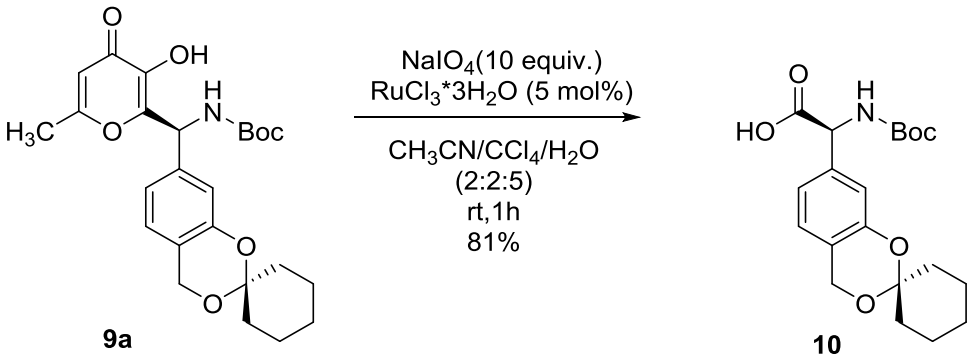
2.7. Synthesis of *tert*-butyl (*S*)-((3-hydroxy-6-methyl-4-oxo-4H-pyran-2-yl)(4H-spiro[benzo[d][1,3]dioxine-2,1'-cyclohexan]-7-yl)methyl)carbamate (9a).



Hydroquinine catalyst (HQN) (47 mg, 0.145 mmol, 5 mol%) was added to a mixture of imine **6a** (2.89 mmol, 957 mg) and allomaltol **8** (2.89 mmol, 364 mg) in PhMe (8 mL) and the obtained solution was stirred at ambient temperature for 24 h. The solvent was evaporated. The residue

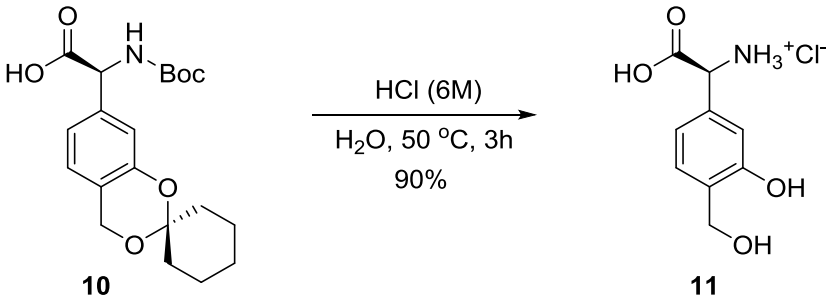
was recrystallized from PhMe/Et_2O (1 : 3, v/v) solvent system to afford compound **9a** as pink foam. Yield 740 mg (56 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96-6.93 (d, *J* = 8.0 Hz, 1H), 6.92-6.89 (d, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 6.23 (s, 1H), 6.03-6.01 (d, *J* = 8.7 Hz, 1H), 5.69-5.67 (d, *J* = 8.7 Hz, 1H), 4.81 (s, 2H), 2.31 (s, 3H), 1.83-1.79 (m, 4H), 1.66-1.61 (m, 4H), 1.47 (s, 11H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 174.1, 165.4, 154.8, 151.4, 147.9, 140.8, 138.5, 125.2, 119.8, 118.5, 115.1, 110.8, 100.0, 80.3, 59.9, 52.8, 33.5 (2C), 28.3, 25.3, 22.4, 20.1 ppm. HPLC data: 99% ee (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 70 : 30; 220 nm, flow rate: 1.0 mL/min, t_{major} = 7.9 min, t_{minor} = 9.5 min). $[\alpha]^{25}_D$ = +27.4° (c = 1.0, $CHCl_3$). HRMS (ESI): *m/z* calcd. for $C_{25}H_{31}NO_7$ $[M+H]^+$: 458.2179, found 458.2182.

2.8. Sinthesis of (*S*)-2-((*tert*-butoxycarbonyl)amino)-2-(4H-spiro[benzo[d][1,3]dioxine-2,1'-cyclohexan]-7-yl)acetic acid (10).



$NaIO_4$ (3.47 g, 16.2 mmol) and $RuCl_3$*$3H_2O$ (21 mg, 0.08 mmol) were sequentially added to a stirred solution of **9a** (740 mg, 1.62 mmol) in $CH_3CN/CCl_4/H_2O$ (2 : 2 : 5) solvent system (9 mL) and the mixture was stirred for 1 h at ambient temperature. The product was extracted with EtOAc (3 x 15 mL), the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (10 Torr) to afford *N*-protected amino acid **10** as colorless solid which can be used in the next stage without further purification. Yield 494 mg (81 %). mp = 197-199 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (brs, 2H), 6.99 (brs, 1H), 5.75 (brs, 1H), 5.08 (brs, 1H), 4.85 (s, 2H), 1.84-1.80 (m, 4H), 1.68-1.62 (m, 4H), 1.51 (s, 11H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 172.5, 151.8, 125.7, 121.3, 118.5, 117.7, 115.6, 100.3, 59.9, 45.9, 33.5, 33.4, 28.2, 25.2, 22.4 ppm. $[\alpha]^{25}_D$ = +65.3° (c = 1.0, $CHCl_3$). HRMS (ESI): *m/z* calcd. for $C_{20}H_{27}NO_6$ $[M+H]^+$: 378.1917, found 378.1920.

2.9. Synthesis of (+)-Forphenicinol hydrochloride (11).



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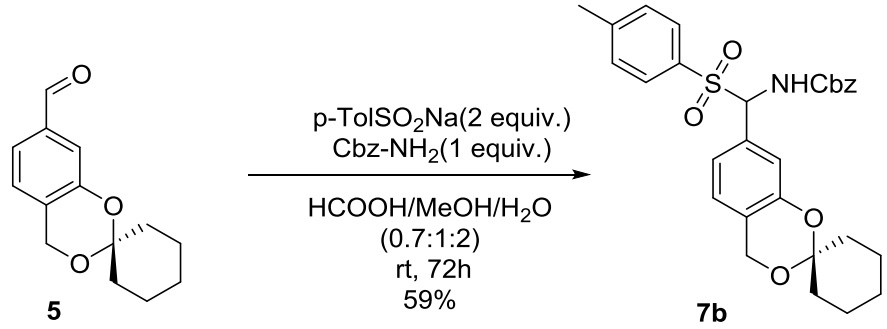
A mixture of *N*-protected amino acid **10** (494 mg, 1.31 mmol) and 6M aqueous HCl (12 mL) was heated at 50 °C for 3 h. After concentration under reduced pressure, the crude product was washed with acetone (3 x 5 mL) to give **(+)-Forphenicinol hydrochloride** (**11**) as light brown solid. Yield 275 mg (90 %), mp >200 °C (dec.). ^{1}H NMR (300 MHz, DMSO-*d6*): δ 9.71 (brs, 1H), 8.69 (brs, 3H), 6.92-6.89 (m, 2H), 6.86-6.83 (d, *J* = 7.8 Hz, 1H), 5.02 (s, 1H), 4.83 (s, 2H) ppm. ^{13}C{^{1}H} NMR (75 MHz, DMSO-*d6*): δ 170.1, 158.0, 134.6, 130.5, 119.0, 116.8, 115.5, 67.4, 55.9 ppm. $[\alpha]^{25}_{D}$ = +130.8° (c = 1.0, HCl_{aq}.(1M)), (Lit. $[\alpha]^{25}_{D}$ = +131.4° (c = 1.0, HCl_{aq}.(1M))).[4] HRMS (ESI): *m/z* calcd. for $C_9H_{11}NO_4$ $[M+H]^+$: 198.0766, found 198.0764.

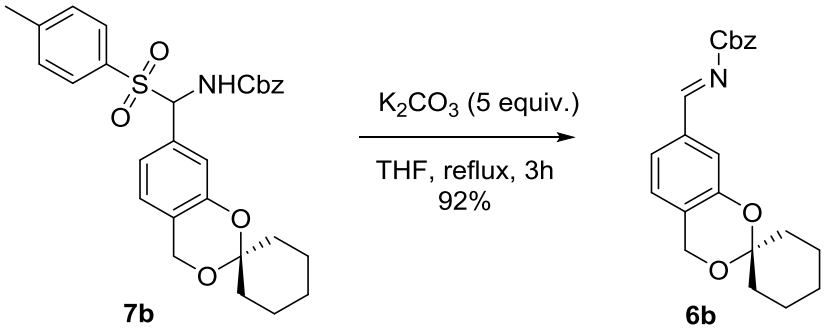
3. Additional experiments and characterization data

3.1. Synthesis of benzyl ((4H-spiro[benzo[d][1,3]dioxine-2,1'-cyclohexan]-7-yl)(tosyl)methyl)carbamate 7b



Aldehyde **5** (3.0 g, 12.9 mmol) was added to a suspension of Cbz-NH_2 (1.95 g, 12.9 mmol) and p-TolSO_2Na (4.6 g, 25.8 mmol) in MeOH/water solvent system (1 : 2 v/v, 60 mL). Then formic acid (14 mL) was added via syringe and the reaction mixture was vigorously stirred for 72 h. The precipitate was filtered off, washed successively with water (3 x 50 mL) and *n*-hexane (3 x 50 mL) and dried in air affording sulfone carbamate **7b** as colorless solid. Yield 3.97 g (59 %), mp >200 ºC (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.72 (d, *J* = 8.0 Hz, 2H), 7.36-7.27 (m, 7H), 6.98 (brs, 2H), 6.89 (brs, 1H), 5.96-5.92 (m, 1H), 5.88-5.84 (m, 1H), 4.97 (s, 2H), 4.84 (s, 2H), 2.44 (s, 3H), 1.81 (brs, 4H), 1.64 (brs, 4H), 1.51 (brs, 2H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 151.4, 145.1, 139.4, 135.9, 135.6, 133.6, 129.7, 128.5, 128.2, 125.1, 121.8, 120.5, 117.4, 67.9, 59.9, 33.6, 33.4, 25.3, 22.4, 21.7 ppm. HRMS (ESI): *m/z* calcd. for $C_{29}H_{31}NO_6S$ $[M+H]^+$: 522.1950, found 522.1947.

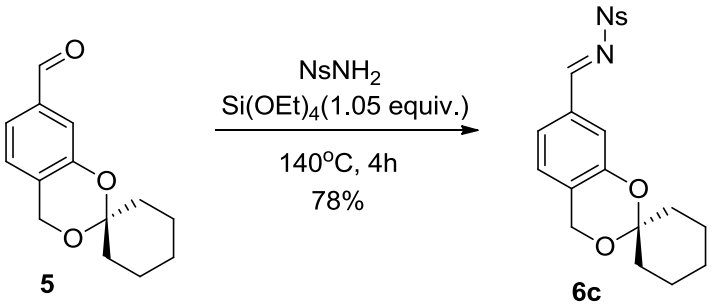
3.2. Synthesis of benzyl ((4H-spiro[benzo[d][1,3]dioxine-2,1'-cyclohexan]-7-yl)methylene)carbamate (6b).



A mixture of sulfone carbamate **7b** (3.53 g, 6.8 mmol), anhydrous potassium carbonate (4.67 g, 33.8 mmol) and dry THF (75 mL) was refluxed with stirring under argon for 3 h. Then it was

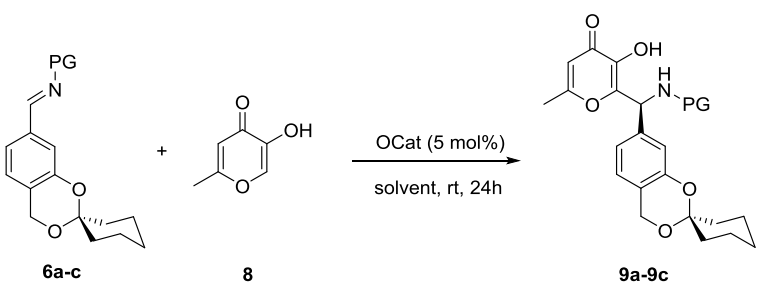
cooled to ambient temperature, inorganic salts were filtered off and the filtrate was concentrated under reduced pressure. The resulting solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was dried in vacuum (10 Torr) at ambient temperature for 2 h to afford imine **6b** as colorless viscous oil. Yield 2.26 g (92 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.43-7.40 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.35-7.34 (d, *J* = 1.3 Hz, 1H), 7.13-7.10 (d, *J* = 7.8 Hz, 1H), 4.88 (s, 2H), 1.84-1.80 (m, 4H), 1.69-1.59 (m, 4H), 1.53-1.48 (m, 2H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 191.6, 151.8, 136.6, 126.9, 125.4, 121.3, 118.3, 100.4, 60.2, 33.4, 25.2, 22.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{22}H_{23}NO_4$ $[M+H]^+$: 366.1705, found 366.1701.

3.3. Synthesis of *N*-((4H-spiro[benzo[d][1,3]dioxine-2,1'-cyclohexan]-7-yl)methylene)-2-nitrobenzenesulfon amide (6c).



Tetraethoxysilane (1.27 mL, 5.76 mmol) was added to a suspension of aldehyde **5** (1.27 g, 5.49 mmol) and 2-nitrophenylsulfonamide (1.10 g, 5.49 mmol) and the mixture was stirred at 140 °C with Dean-Stark trap under argon for 4 h. The raw product was recrystallized from EtOAc and dried under reduced pressure (10 torr) affording imine **6c**. Yield 1.78 g (78 %), mp = 115-117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.80 (s, 1H), 7.48-7.45 (d, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 7.07-7.05 (d, *J* = 8.0 Hz, 1H), 4.88 (s, 2H), 1.85-1.79 (m, 4H), 1.64-1.59 (m, 13H), 1.49 (m, 2H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.3, 162.6, 151.6, 134.1, 125.9, 125.2, 121.9, 121.9, 118.8, 100.2, 82.2, 60.2, 33.4, 27.9, 25.2, 22.4 ppm.HRMS (ESI): *m/z* calcd. for $C_{20}H_{20}N_2O_6S$ $[M+H]^+$: 417.1120, found 417.1123.

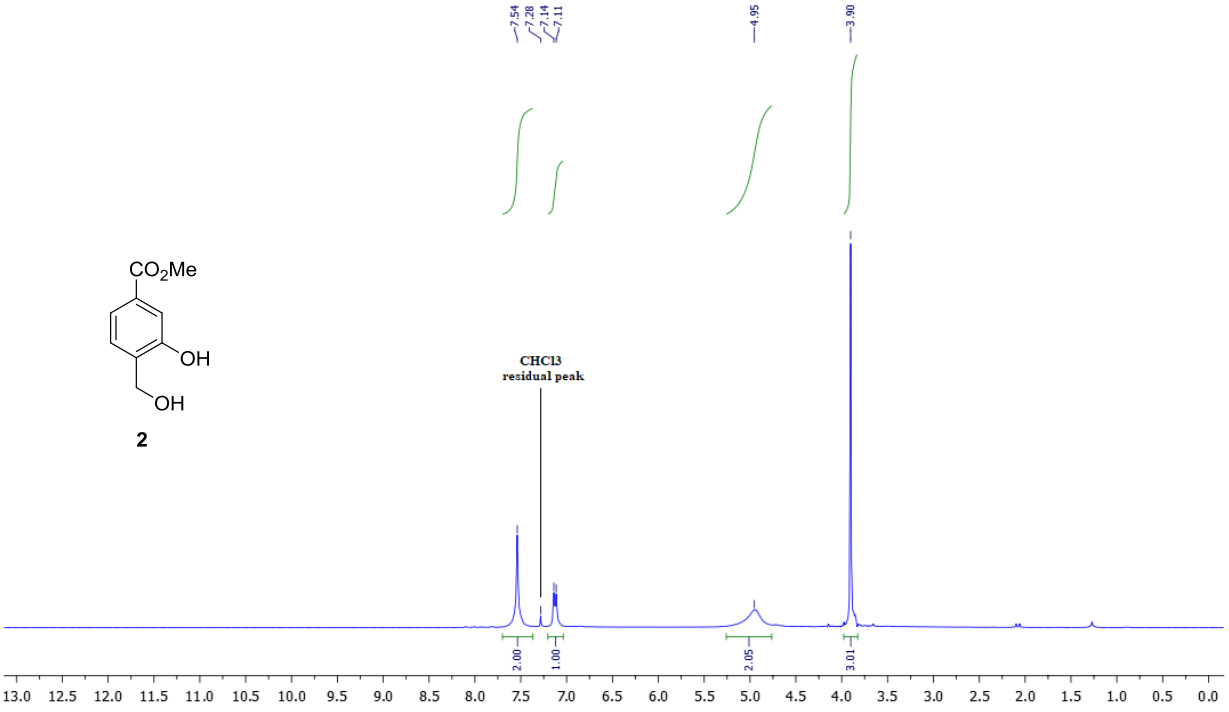
3.4. Optimization of model reactions between 6a-c and allomaltol 8

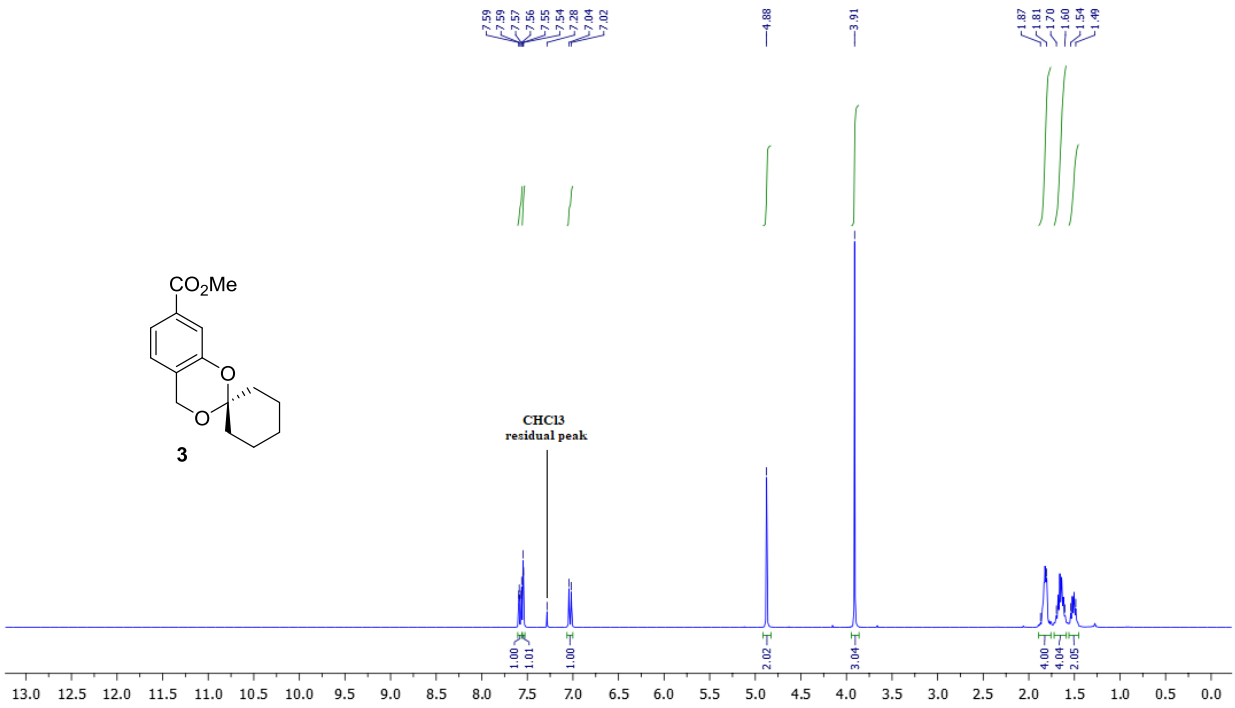


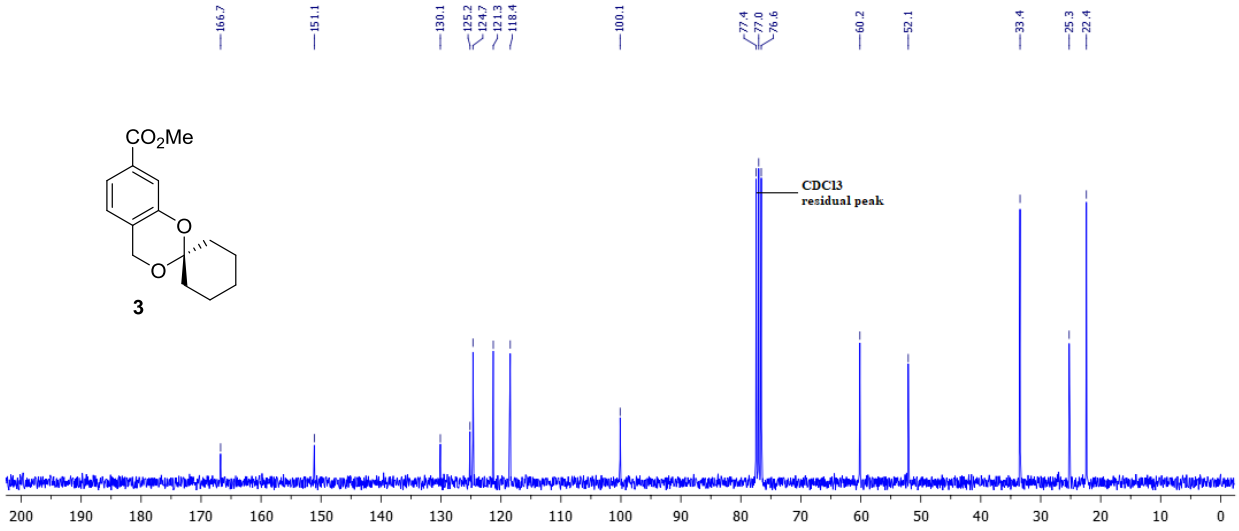
Entry	PG	OCat	Solvent	Yield[b], 9 (%)	*ee*[c] (%)
1	Boc	**I**	DCM	89	5
2	Cbz	**I**	DCM	80	2
3	Ns	**I**	DCM	91	0
4	Boc	**II**	DCM	85	3
5	Cbz	**II**	DCM	82	7
6	Ns	**II**	DCM	89	0
7	Boc	**III**	DCM	79	6
8	Cbz	**III**	DCM	80	5
9	Ns	**III**	DCM	90	0
10	Boc	**IV**	DCM	80	5
11	Cbz	**IV**	DCM	76	5
12	Ns	**IV**	DCM	81	0
13	Boc	**V**	DCM	71	10
14	Cbz	**V**	DCM	65	7
15	Ns	**V**	DCM	75	7
16	Boc	**VI**	DCM	83	8
17	Cbz	**VI**	DCM	82	13
18	Ns	**VI**	DCM	91	2
19	Boc	**VII**	DCM	60	-32 [c]
20	Cbz	**VII**	DCM	80	-21 [c]
21	Ns	**VII**	DCM	79	-30 [c]
22	Boc	**VIII**	DCM	69	10
23	Cbz	**VIII**	DCM	72	21
24	Ns	**VIII**	DCM	71	19
25	Boc	**IX**	DCM	81	49
26	Cbz	**IX**	DCM	88	34
27	Ns	**IX**	DCM	81	42
28	Boc	**X**	DCM	86	54
29	Cbz	**X**	DCM	83	38
30	Ns	**X**	DCM	85	43
31	Boc	**XI**	DCM	78	-35 [c]
32	Cbz	**XI**	DCM	74	-42 [c]
33	Ns	**XI**	DCM	78	-31 [c]
34	Boc	**XII**	DCM	70	-36 [c]
35	Cbz	**XII**	DCM	73	-40 [c]
36	Ns	**XII**	DCM	78	-35 [c]
37	Boc	**XIII**	DCM	79	12
38	Cbz	**XIII**	DCM	62	34
39	Ns	**XIII**	DCM	64	42
40	Boc	**XIV**	DCM	81	-9 [c]
41	Cbz	**XIV**	DCM	65	-29 [c]
42	Ns	**XIV**	DCM	74	-39 [c]
43	Boc	**X**	THF	86	43
44	Boc	**X**	EtOH	n.r.	n.d.
45	Boc	**X**	MTBE	64	61
46	Boc	**X**	PhMe	95(59)[d]	80(99)[d]
47[e]	Boc	**X**	PhMe	45	81
48[f]	Boc	**X**	PhMe	50	75
49	Cbz	**X**	PhMe	75	14
50	Ns	**X**	PhMe	81	23 [c]

[a)] Unless otherwise specified, the reactions were carried out with catalyst **I**-**XIV** (5 mol%), **6a-c** (0.1 mmol) and **8** (12.6 mg, 0.1 mmol) in the corresponding solvent (0.25 mL) for 24 h at ambient temperature. [b)] Yield obtained after evaporation of solvent and filtration through SG. [c)] HPLC data were obtained on the chiral phase (CHIRALPAK AD-H column, *n*-hexane/*i*-PrOH 70:30, flow rate 1.00 mL/min, 220 nm). [d)] Data for **9a** recrystallized from PhMe-Et_2O (3:1) are given in parentheses. [e)] The reaction was carried out at 0 ^oC. [f)] The reaction was carried with 2 mol% of **X.**

4. NMR pictures of all compounds



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125.2
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118.4
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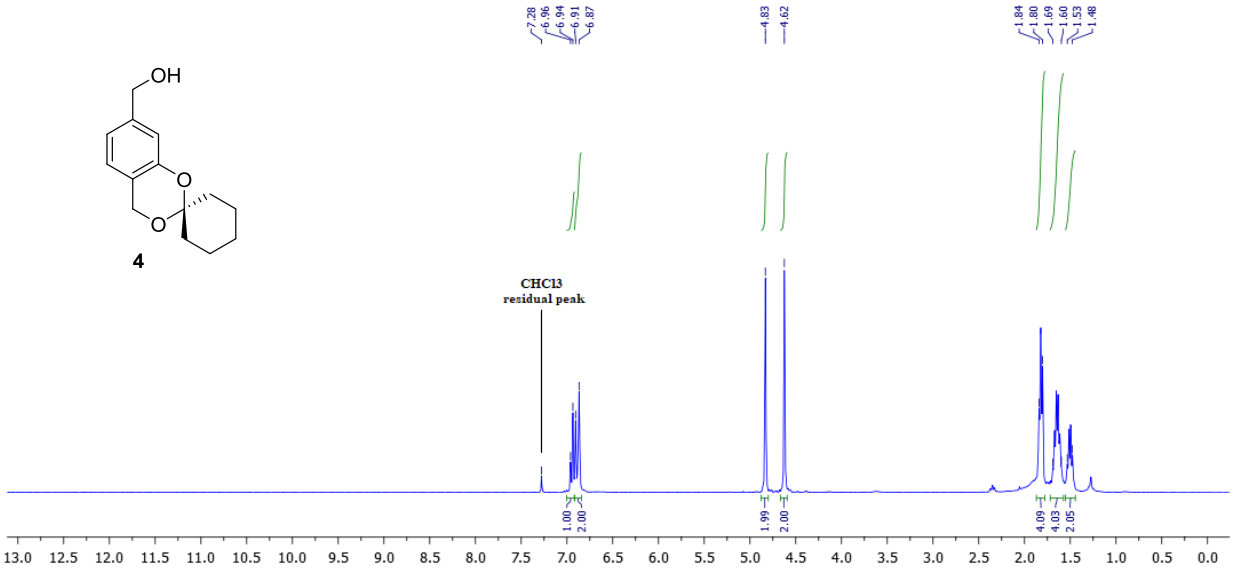
52.1
33.4
25.3
22.4
CO2Me
O
O
3
CDCl3
residual peak
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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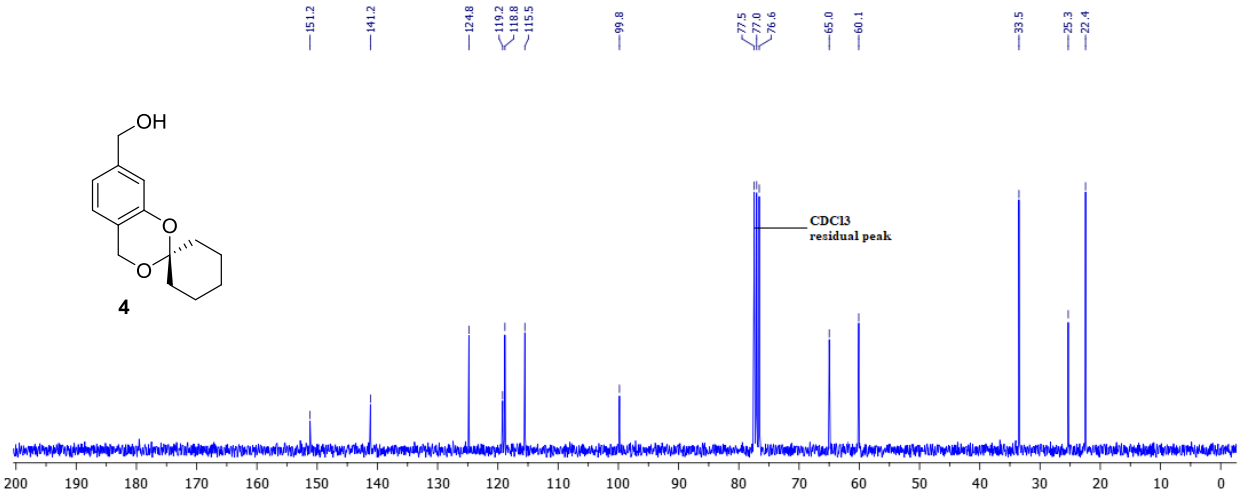
6.96
6.94
6.91
6.87
4.83
4.62
1.84
1.80
1.69
1.60
1.53
1.48
OH
O
O
4
CHCl3
residual peak
1.00
2.00
1.99
2.00
4.09
4.03
2.05
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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141.2
124.8
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118.8
115.5
99.8
77.5
77.0
76.6
65.0
60.1
33.5
25.3
22.4
OH
O
O
4
CDCl3
residual peak
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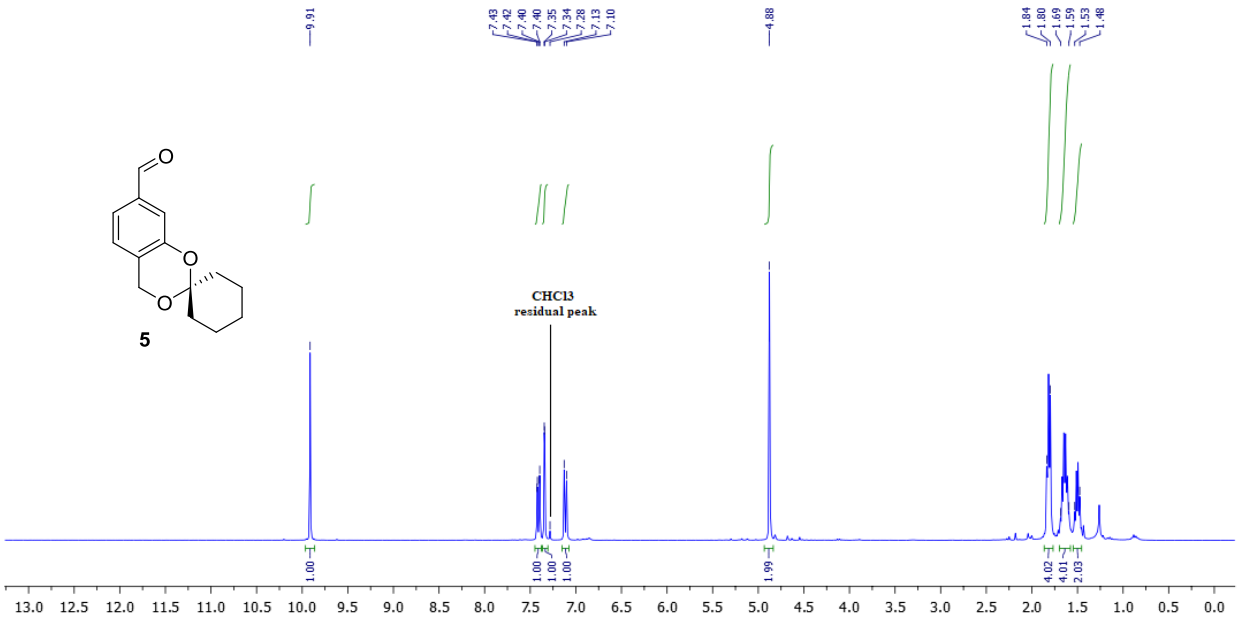
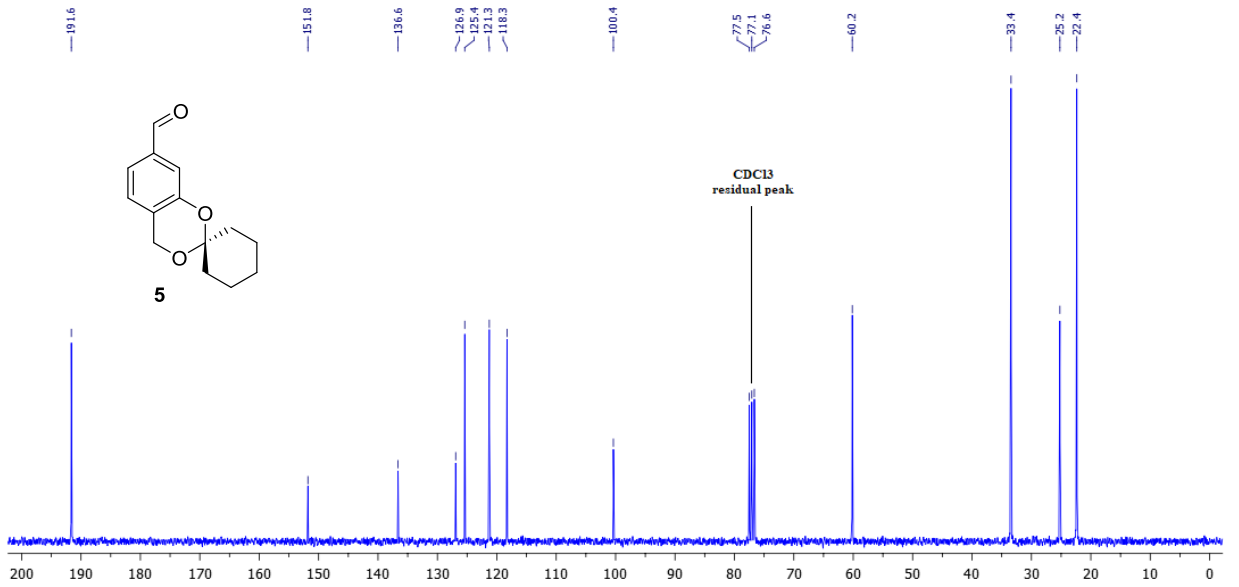

9.91
7.43
7.42
7.40
7.40
7.35
7.34
7.28
7.13
7.10
4.88
1.84
1.80
1.69
1.59
1.53
1.48
CHCl3
residual peak
5
1.00
1.00
1.00
1.00
1.99
4.02
4.01
2.03
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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151.8
136.6
126.9
125.4
121.3
118.3
100.4
77.5
77.1
76.6
60.2
33.4
25.2
22.4
CDCl3
residual peak
5
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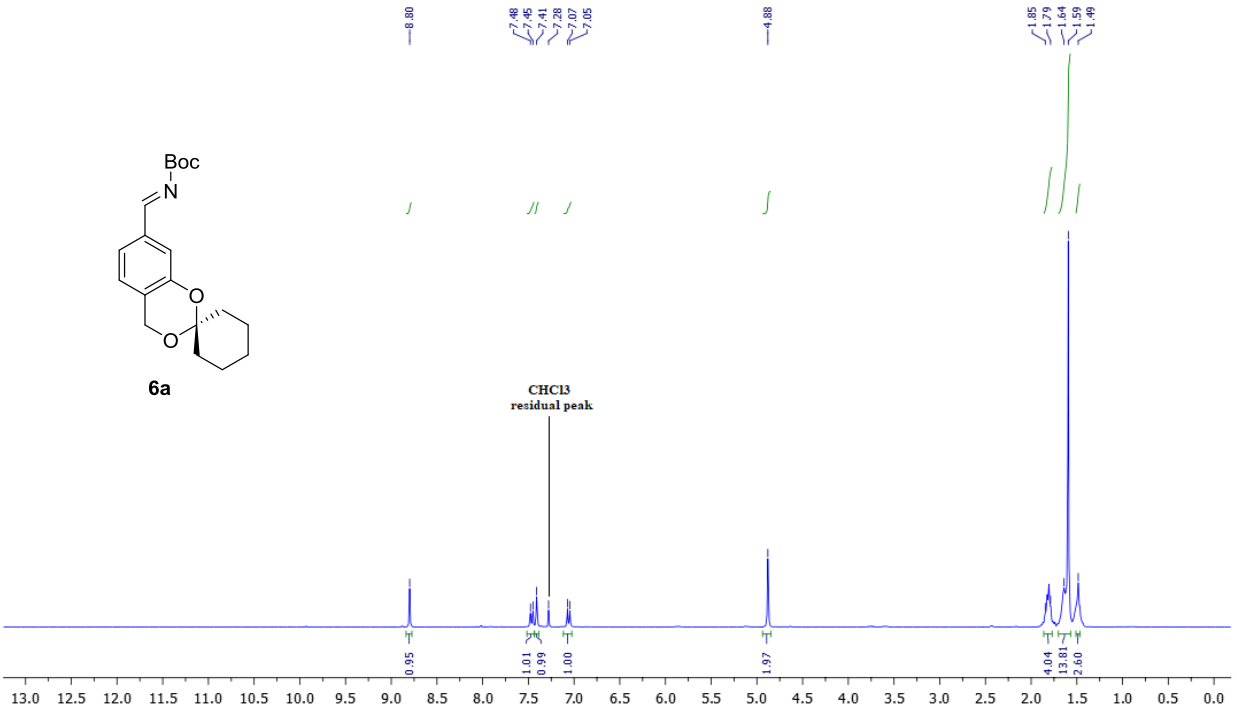
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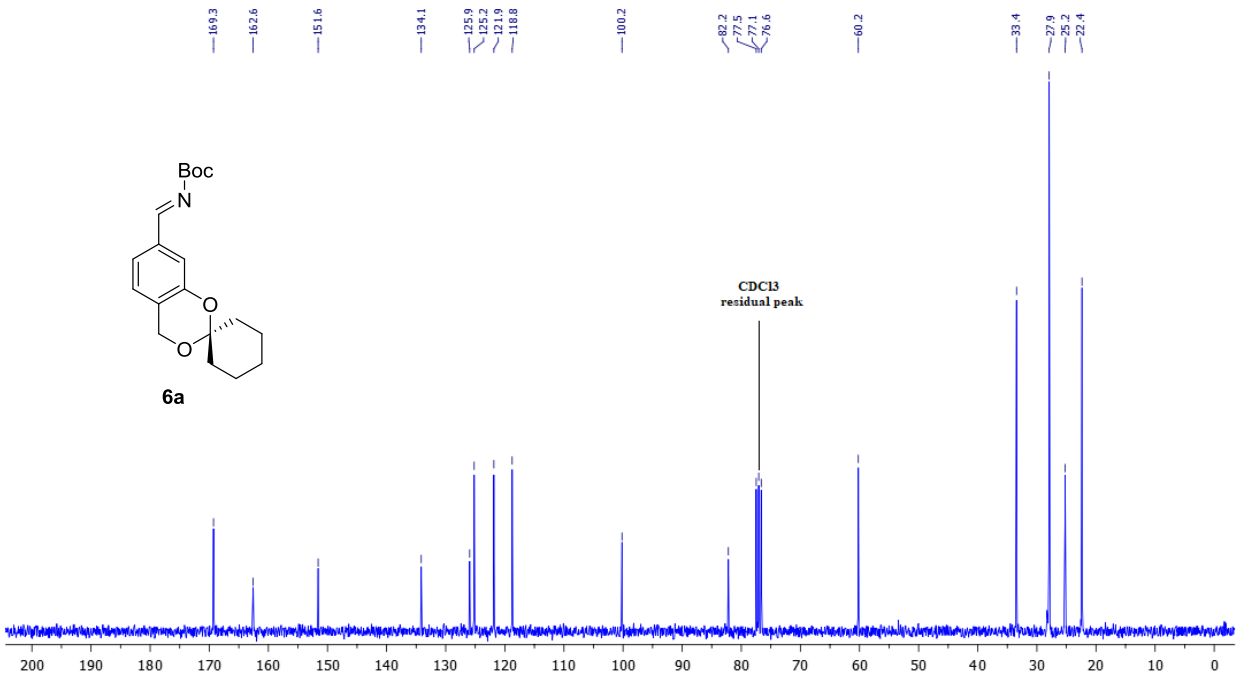
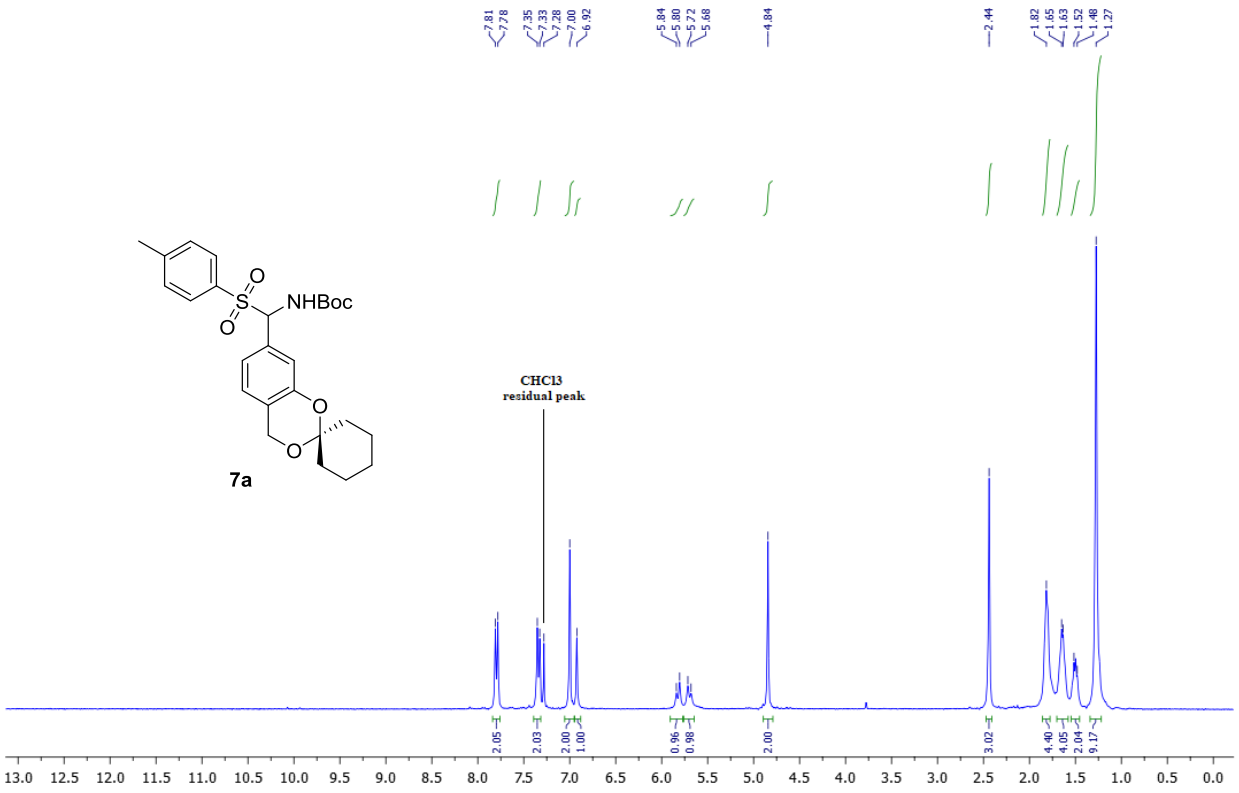
7.48
7.45
7.41
7.28
7.07
7.05
4.88
1.85
1.79
1.64
1.59
1.49
Boc
N
O
O
6a
CHCl3
residual peak
0.95
1.01
0.99
1.00
1.97
4.04
13.81
2.60
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


169.3
162.6
151.6
134.1
125.9
125.2
121.9
118.8
100.2
82.2
77.5
77.1
76.6
60.2
33.4
27.9
25.2
22.4
Boc
N
O
O
6a
CDCl3
residual peak
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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7.78
7.35
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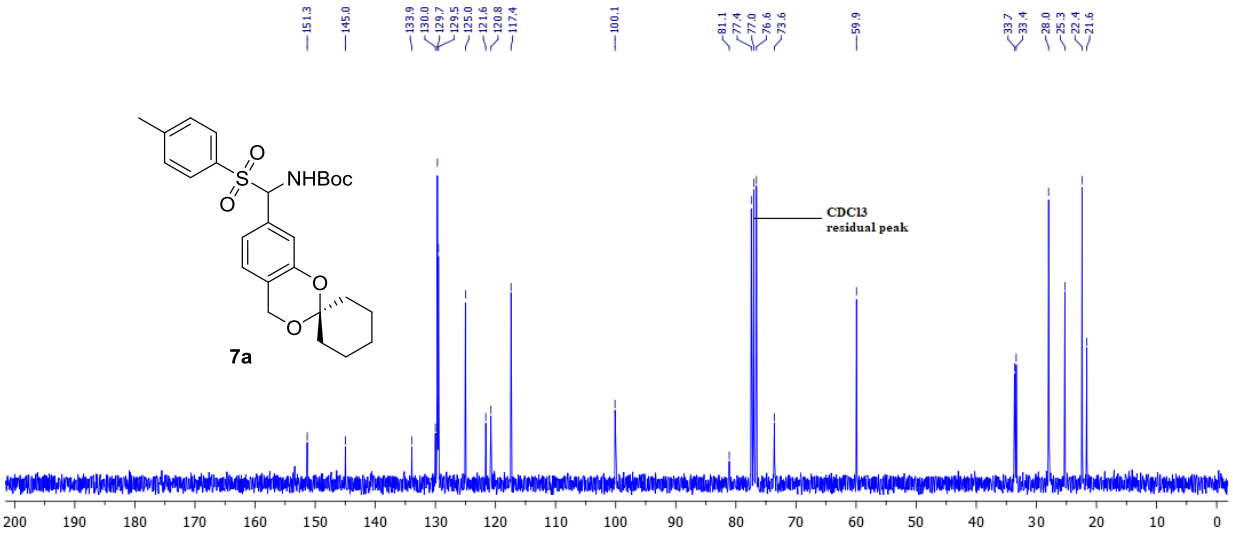
7.00
6.92
5.84
5.80
5.72
5.68
4.84
2.44
1.82
1.65
1.63
1.52
1.48
1.27
NHBoc
O
O
O
O
O
7a
CHCl3
residual peak
2.05
2.03
2.00
1.00
0.96
0.98
2.00
3.02
4.40
4.05
2.04
9.17
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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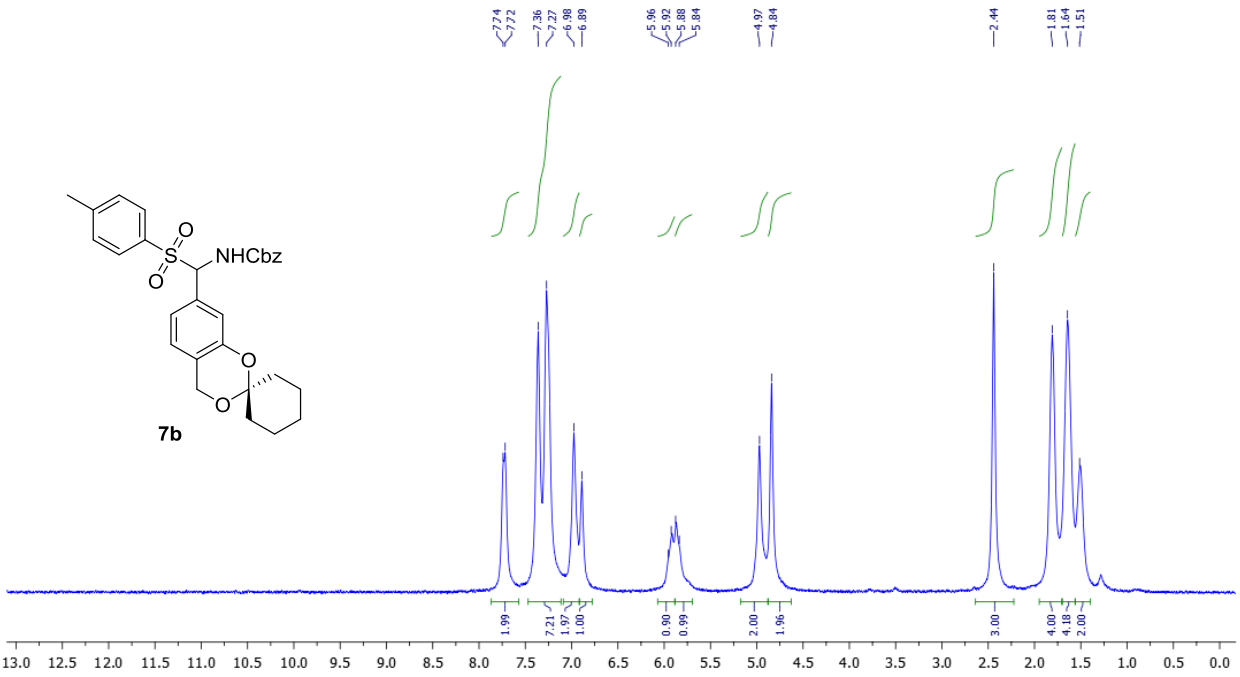
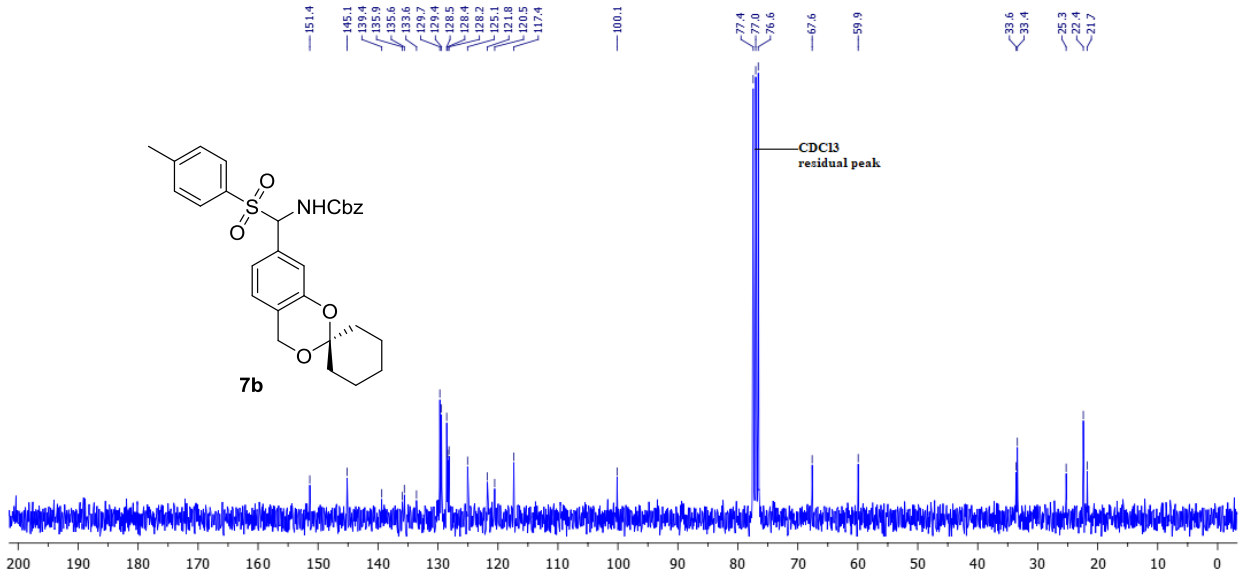
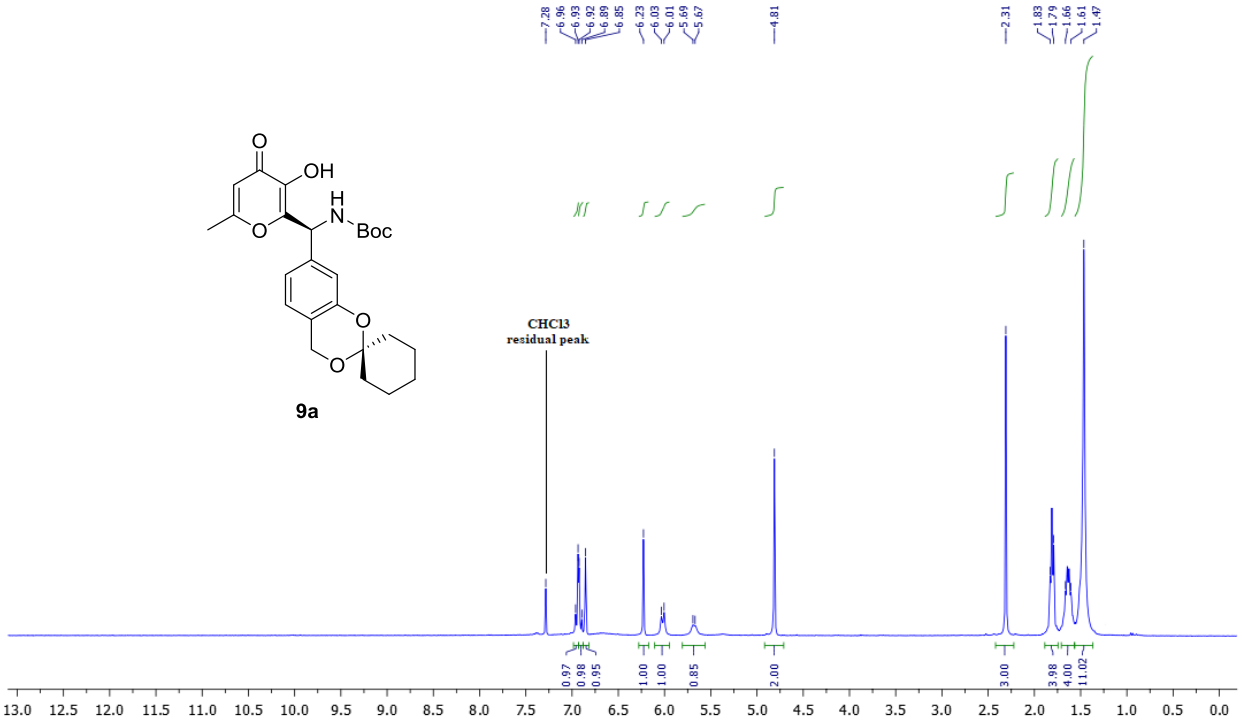
129.5
125.0
121.6
120.8
117.4
100.1
81.1
77.4
77.0
76.6
73.6
59.9
33.7
33.4
28.0
25.3
22.4
21.6
NHBoc
O
O
O
O
O
7a
CDCl3
residual peak
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


NHCbz
7b


NHCbz
7b
CDCl3
residual peak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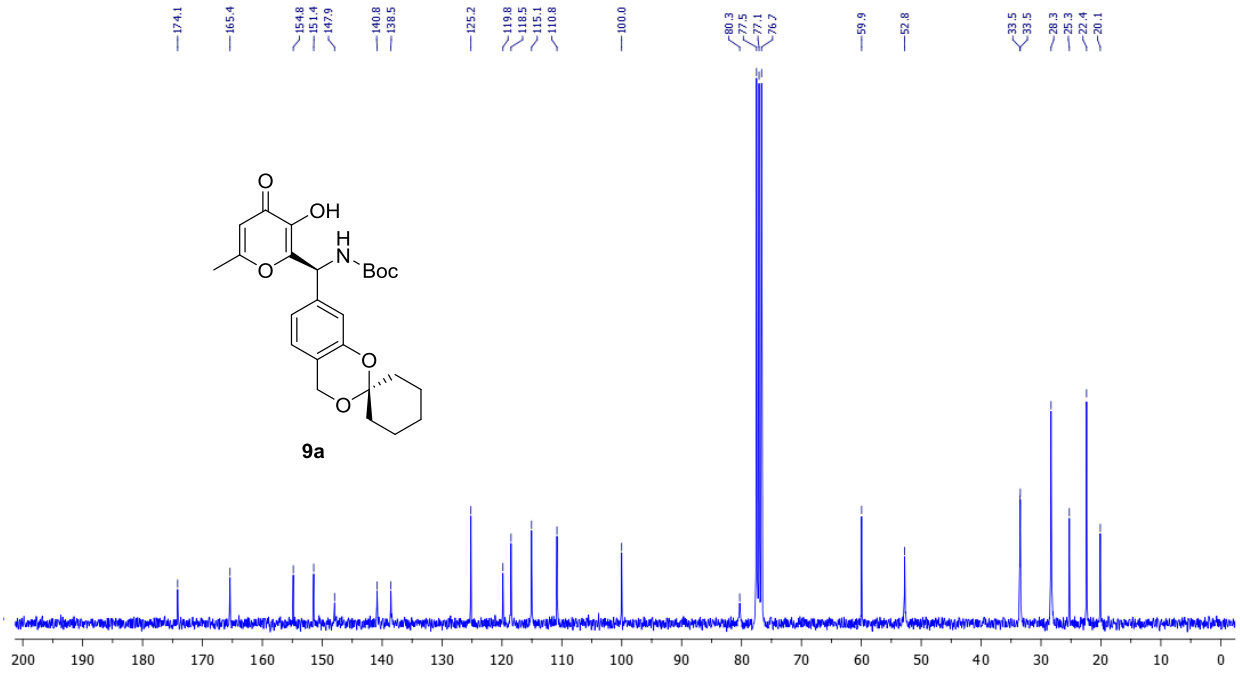
6.96
6.93
6.92
6.89
6.85
6.23
6.03
6.01
5.69
5.67
4.81
2.31
1.83
1.79
1.66
1.61
1.47
O
OH
H
N
Boc
O
O
O
9a
CHCl3
residual peak
0.97
0.98
0.95
1.00
1.00
0.85
2.00
3.00
3.98
4.00
11.02
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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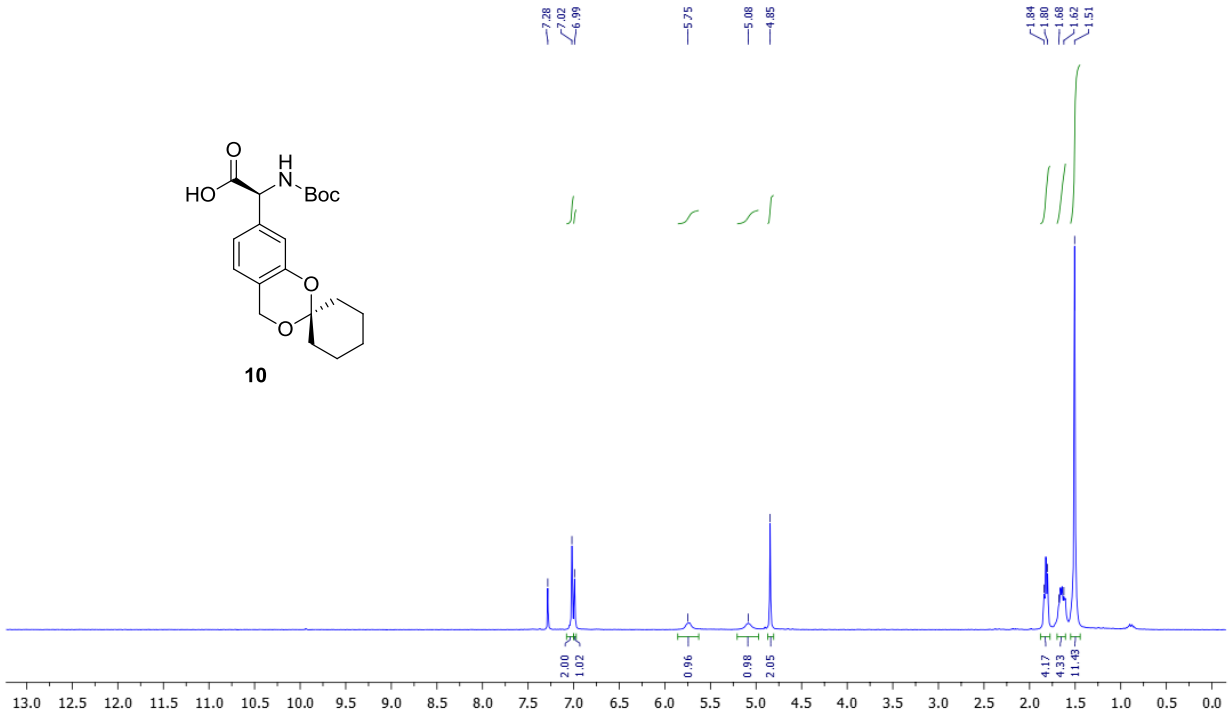
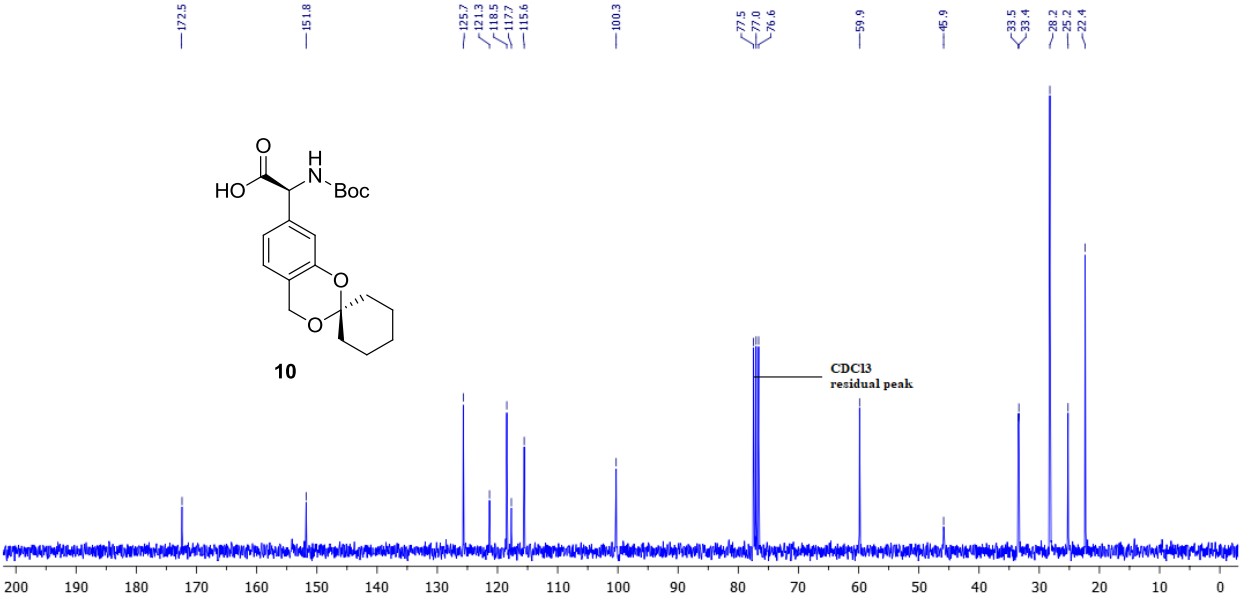
154.8
151.4
147.9
140.8
138.5
125.2
119.8
118.5
115.1
110.8
100.0
80.3
77.5
77.1
76.7
59.9
52.8
33.5
33.5
28.3
25.3
22.4
20.1
O
OH
H
N
Boc
O
O
O
9a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


HO
O
H
N
Boc
O
O
10
7.28
7.02
6.99
5.75
5.08
4.85
1.84
1.80
1.68
1.62
1.51
2.00
1.02
0.96
0.98
2.05
4.17
4.33
11.43
13.0 12.5 12.0 11.5 11.0 10.5 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


172.5
151.8
125.7
121.3
118.5
117.7
115.6
100.3
77.5
77.0
76.6
59.9
45.9
33.5
33.4
28.2
25.2
22.4
HO
O
H
N
Boc
O
O
10
CDCl3
residual peak
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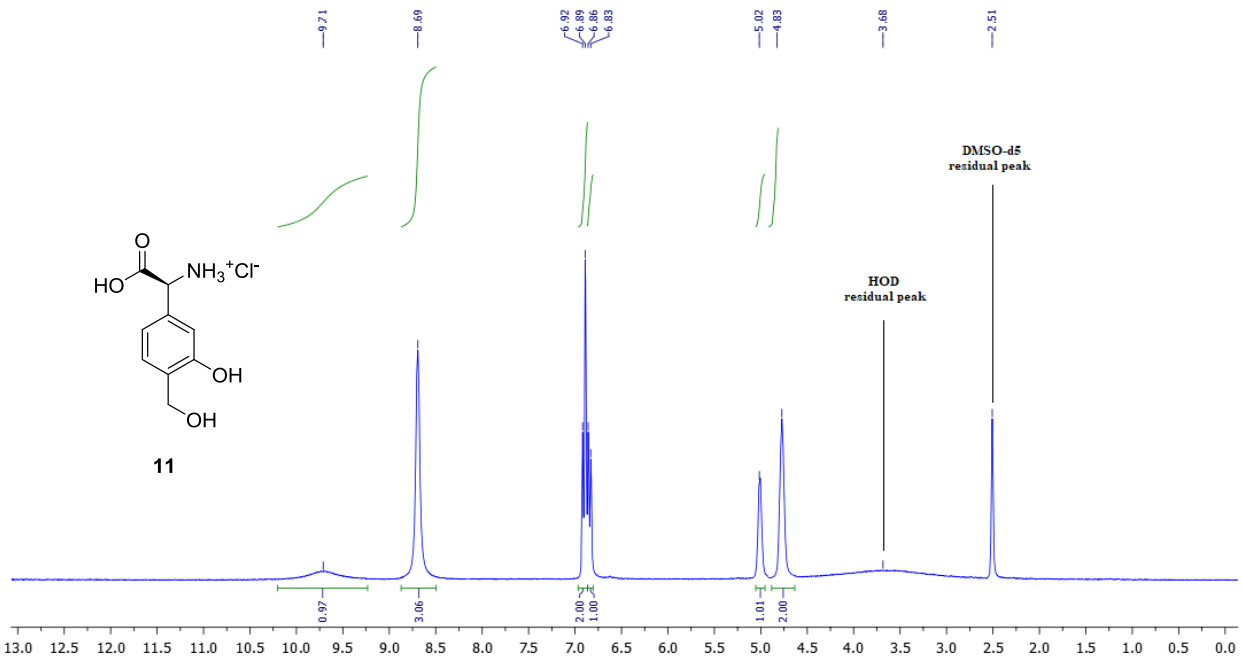
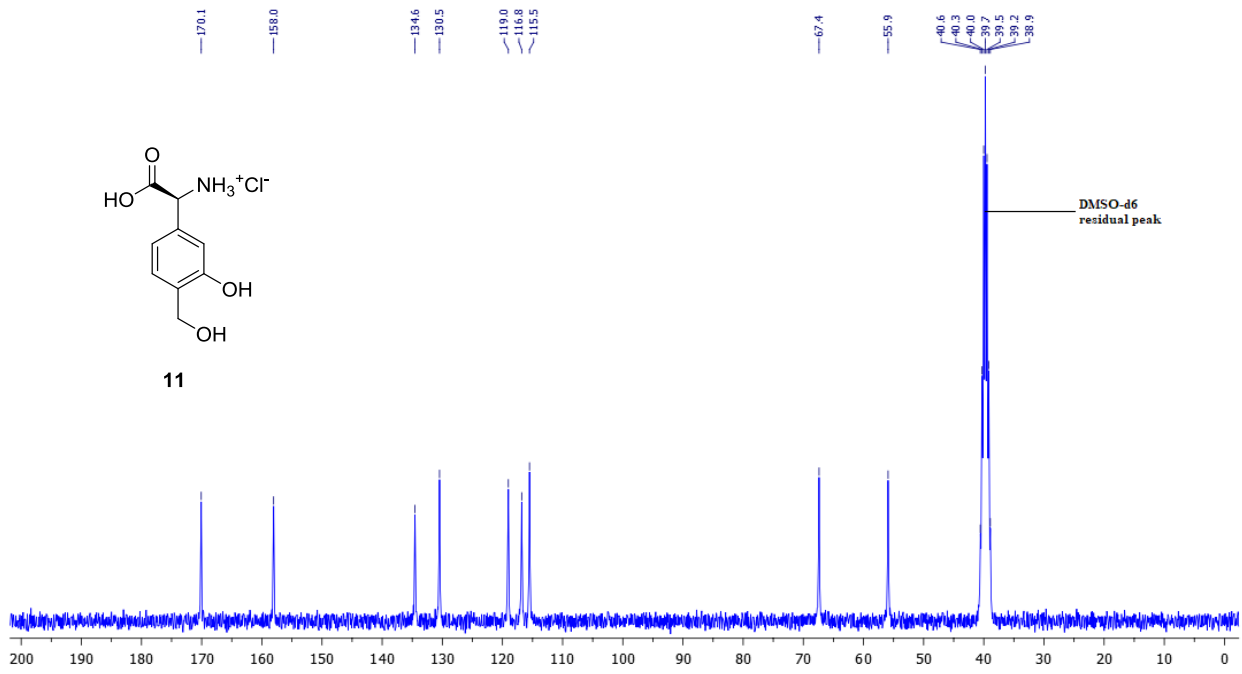

9.71
8.69
6.92
6.89
6.86
6.83
5.02
4.83
3.68
2.51
DMSO-d5
residual peak
HOD
residual peak
HO
O
NH3+Cl-
OH
OH
11
0.97
3.06
2.00
1.00
1.01
2.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


170.1
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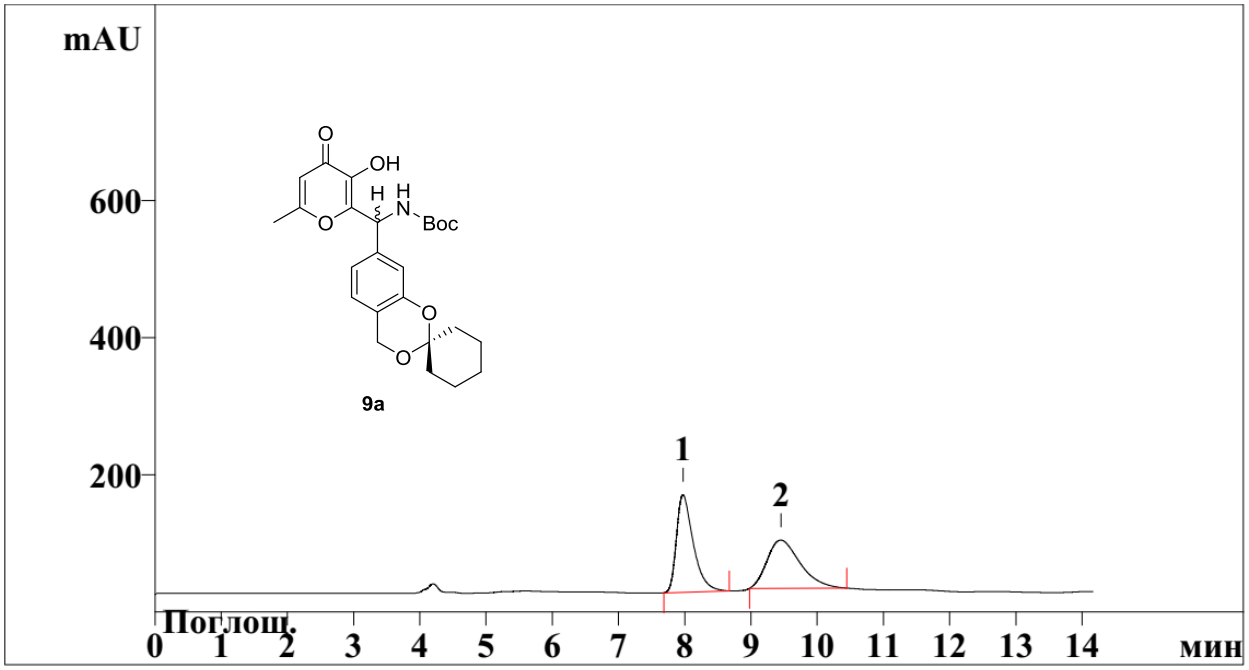
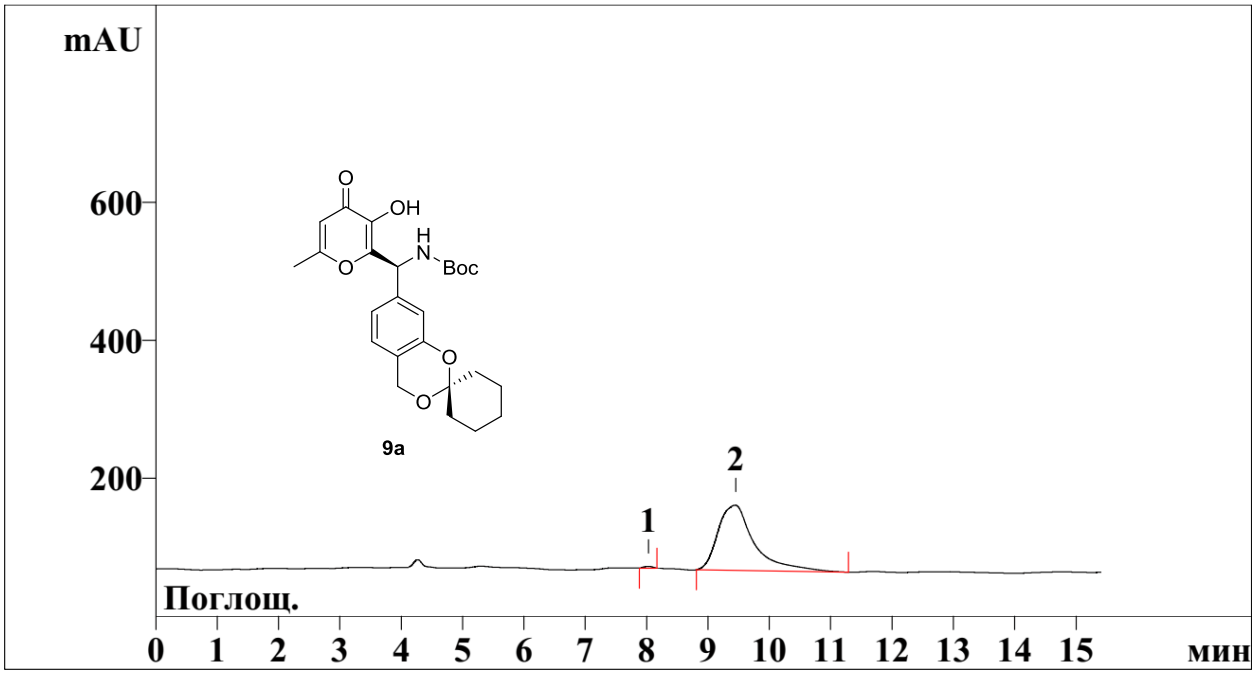
130.5
119.0
116.8
115.5
67.4
55.9
40.6
40.3
40.0
39.7
39.5
39.2
38.9
DMSO-d6
residual peak
HO
O
NH3+Cl-
OH
OH
11
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

5. HPLC data for catalytic adduct 9a.



Пик	Время мин	Высота mAU	Площадь mAU*сек	Конц.	Площадь пика
1	7.975	142.24	2515.13	2515	50.698
2	9.453	70.45	2445.92	2446	49.302
2	14.17	212.70	4961.05	4961	



Пик	Время мин	Высота mAU	Площадь mAU*сек	Конц.	Площадь пика
1	8.025	2.83	29.68	29.68	0.75513
2	9.446	94.65	3900.84	3901	99.245
2	30.79	97.48	3930.52	3931	

References

[1] (a) Y. Qian, G. Ma, A. Lv, H. L. Zhu, J. Zhao, V. H. Rawal, *Chem. Commun.* **2010**, *46*, 3004-3006; (b) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416-14417; (c) A. S. Kucherenko, A. A. Kostenko, A. N. Komogortsev, B. V. Lichitsky, M. Y. Fedotov, S. G. Zlotin, *J. Org. Chem.* **2019**, 84, 4304-4311; (d) B.-Y. Li, Y. Lin, D.-M. Du, *J. Org. Chem.* **2019**, *84*, 11752-11762; (e) S. P. Pósa, G. Dargó, S. Nagy, P. Kisszékelyi, Z. Garádi, L. Hámori, G. Szakács, J. Kupai, S. Tóth, *Bioorg. Med. Chem.* **2022**, *67*, 116855; (f) B. L. Zhao, D.-M. Du, *Adv. Synth. Catal.* **2016**, *358*, 3992-3998; (g) X. Gu, H. Yuan, J. Jiang, Y. Wu, W.-J. Bai, *Org. Lett.* **2018**, *20*, 7229-7233; (h) A. A. Kostenko, A. S. Kucherenko, A. N. Komogortsev, B. V. Lichitsky, S. G. Zlotin, *Org. Biomol. Chem.* **2018**, *16*, 9314-9318.

[2] (a) MERCK & CO INC - US4335250, 1982, A)

[3] (a) M. Lehmann, M. Dechant, M. Holzapfel, A. Schmiedel, C. Lambert, *Angew. Chem. Int. Ed.* **2019**, *58*, 3610-3615.

[4] (a) H. Morishima, J. Yoshizawa, R. Ushijima, T. Takeuchi, H. Umezawa, *J. Antibiot.* **1982**, *35*, 1500-1506.