Electronic Supplementary Information

Spontaneous Symmetry Breaking During Interrupted Crystallization of an Axially Chiral Amino Acid Derivative

Mark A. Sephton, Christopher R. Emerson, Lev N. Zakharov and Paul R. Blakemore[*]

Department of Chemistry, Oregon State University, Corvallis, OR 97331-4003.

1. Experimental Procedures

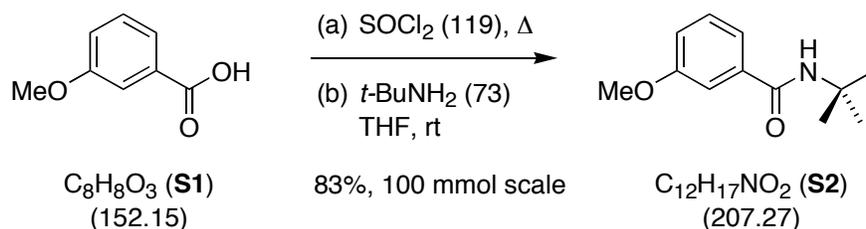### General Experimental and Analytical Techniques

All reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under an atmosphere of N_2 or Ar. THF was either freshly distilled from sodium benzophenone ketyl immediately prior to use, or else taken from a commercially available solvent purification system (SPS) employing activated Al_2O_3 drying columns.[S1] Anhydrous CH_2Cl_2 and toluene were obtained via distillation from CaH_2 or taken from a SPS using activated Al_2O_3 drying columns. Anhydrous DMF was obtained from a SPS fitted with zeolite based (4Å MS) drying columns. Preparative chromatographic separations were performed on silica gel 60 (35-75 μm) and reactions followed by TLC analysis using silica gel 60 plates (2-25 μm) with fluorescent indicator (254 nm) and visualized with UV or phosphomolybdic acid. All commercially available reagents were used as received unless otherwise noted. Melting points were determined from open capillary tubes on a

S1. A. B. Pangborn, M. A. Giardello, R. H. Grubbs and R. K. Rosen, *Organomet*., 1996, **15**, 1518-1520.
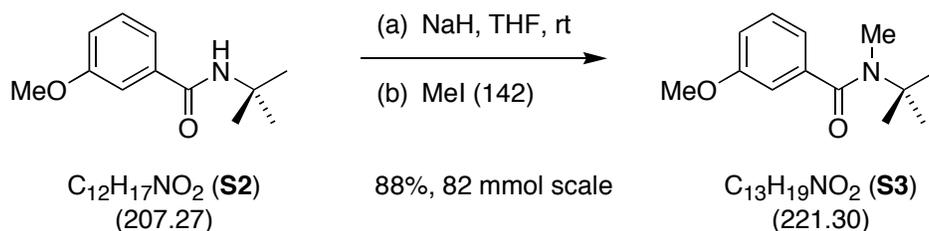
melting point apparatus and are uncorrected. Infra-red (IR) spectra were recorded in Fourier transform mode using KBr disks for solids, while oils were supported between NaCl plates ("neat"). ^{1}H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified and from the indicated deuterated solvents in standard 5 mm diameter tubes. Chemical shift in ppm is quoted relative to residual solvent signals calibrated as follows: CDCl$_3$ δ_H (CHCl$_3$) = 7.26 ppm, δ_C = 77.2 ppm; (CD$_3$)$_2$SO δ_H (CD$_3$SOCHD$_2$) = 2.50 ppm, δ_C = 39.5 ppm; CD$_3$OD δ_H (CHD$_2$OD) = 3.31 ppm, δ_C = 49.0 ppm. Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Numbers in parentheses following carbon atom chemical shifts refer to the number of attached hydrogen atoms as revealed by the DEPT spectral editing technique. Low (MS) and high resolution (HRMS) mass spectra were obtained using either electron impact (EI) or electrospray (ES) ionization techniques. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units. Optical rotation measurements were recorded on a Perkin Elmer Model 343 polarimeter from a cell with a 1.00 dm path length under the conditions indicated.

Synthesis of Bisamide 1 and Amidoamine Salt 3•TFA (Scheme 1)

(a) SOCl$_2$ (119), Δ

(b) *t*-BuNH$_2$ (73) THF, rt

83%, 100 mmol scale

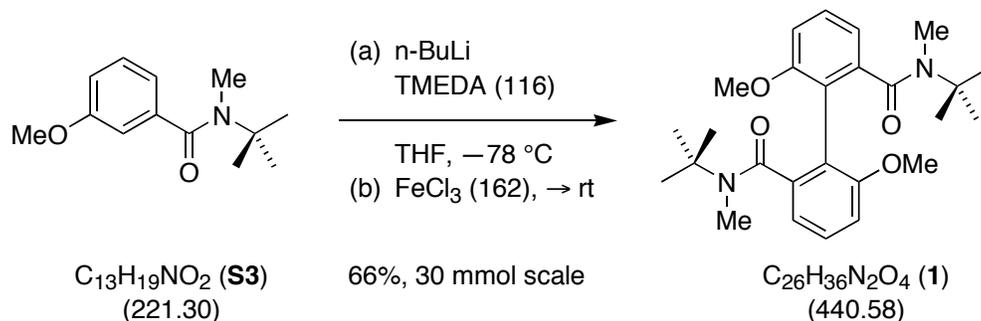C$_8$H$_8$O$_3$ (**S1**) (152.15)

C$_{12}$H$_{17}$NO$_2$ (**S2**) (207.27)

***N-tert*-Butyl-3-methoxybenzamide (S2):** A 500 mL RB flask provided with a magnetic stir bar and a reflux condenser was charged with *m*-anisic acid (**S1**, 15.2 g, 100 mmol). Neat thionyl chloride (40.0 mL, d = 1.63, 65.2 g, 0.55 mol) was cautiously added and the resulting mixture heated to a gentle reflux and stirred for 80 min. The mixture was then allowed to cool to rt and excess SOCl$_2$ removed on a rotary evaporator to afford ca. 18.2 g of the acid chloride as a brown oil. The crude acid chloride was dissolved in THF (50 mL) and added dropwise during 20 min to a stirred solution of *tert*-butylamine (26.2 mL, d = 0.696, 18.2 g, 250 mmol) in THF (150 mL) at 0 °C under Ar. The resulting viscous suspension was allowed to warm to rt and stirred for a further 3.5 h. The mixture was then diluted with EtOAc (100 mL) and washed successively with aq. 2 M HCl (2x75 mL), H$_2$O (75 mL), aq. 2 M KOH (2x75 mL) and brine (75 mL). Following this acid/ base washing treatment, the organic phase was dried (Na$_2$SO$_4$) and concentrated *in vacuo* to yield the title 2° amide (**S2**, 17.1 g, 82.6 mmol, 83%) as an essentially pure colorless solid which was used without further purification in the subsequent step: mp 102-104 °C (no recrys.); IR (KBr) 3301, 1638, 1545, 1251, 1035, 810, 762, 688 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.33 (1H, dd, *J* = 2.5, 1.7 Hz), 7.30 (1H,

tm, $J = 8.1$ Hz), 7.21 (1H, dt, $J = 7.7$, 1.4 Hz), 7.01 (1H, ddd, $J = 8.0$, 2.6, 1.0 Hz), 5.94 (1H, br s), 3.85 (3H, s), 1.47 (9H, s) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.9 (0), 160.0 (0), 137.6 (0), 129.6 (1), 118.6 (1), 117.5 (1), 112.3 (1), 55.6 (3), 51.8 (0), 29.0 (3C, 3) ppm; MS (FAB+) *m/z* 208 (M+H)$^+$ (100%), 192 (8), 180 (14), 152 (4); HRMS (FAB+) *m/z* 208.1345 (calcd. for C$_{12}$H$_{18}$NO$_2$: 208.1338).

(a) NaH, THF, rt

(b) MeI (142)

88%, 82 mmol scale

C$_{12}$H$_{17}$NO$_2$ (**S2**)
(207.27)

C$_{13}$H$_{19}$NO$_2$ (**S3**)
(221.30)

***N*-tert-Butyl-*N*-methyl-3-methoxybenzamide (S3):** A stirred suspension of NaH (4.11 g, 60 wt.% dispersion in mineral oil: supporting oil removed under Ar with hexanes wash, 103 mmol) in anhydrous THF (150 mL) at rt under Ar was treated with a solution of the 2° amide (**S2**, 17.0 g, 82.0 mmol) in anhydrous THF (100 mL) during 30 min. Effervescence was observed throughout the addition and following the completion of this operation the resulting solution of metalated amide was stirred for 1 h. Neat MeI (6.41 mL, d = 2.28, 14.6 g, 103 mmol) was then added during 5 min and the reaction mixture allowed to stir for a further 20 h at rt. After this time, the mixture was partitioned between H$_2$O (150 mL) and EtOAc (100 mL) and the layers separated. The aqueous phase was extracted with EtOAc (50 mL) and the combined organic phases washed with H$_2$O (100 mL) and brine (50 mL), then dried (Na$_2$SO$_4$), and concentrated *in vacuo* to yield the title 3° amide (**S3**, 15.9 g, 71.8 mmol, 88%) as a light yellow oil. Spectral analysis indicated that the material was of sufficient purity to be used in the next transformation without further purification. Data for **S3**: IR (neat) 2960, 1788, 1719, 1610, 1490, 1378, 1264, 1043, 798 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.27 (1H, ddd, $J = 8.1$, 7.2, 0.8 Hz), 7.00-6.94 (2H, m), 6.91 (1H, ddd, $J = 8.2$, 2.7, 1.0 Hz), 3.82 (3H, s), 2.85 (3H, s), 1.50 (9H, s) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.1 (0), 159.7 (0), 140.6 (0), 129.5 (1), 119.6 (1), 115.6 (1), 112.5 (1), 56.7 (0), 55.5 (3), 35.5 (3), 27.9 (3C, 3) ppm; MS (FAB+) *m/z* 222 (M+H)$^+$ (100%), 206 (18); HRMS (FAB+) *m/z* 222.1490 (calcd. for C$_{13}$H$_{20}$NO$_2$: 222.1494).

(a) n-BuLi
TMEDA (116)

THF, −78 °C
(b) FeCl$_3$ (162), → rt

66%, 30 mmol scale

C$_{13}$H$_{19}$NO$_2$ (**S3**)
(221.30)

C$_{26}$H$_{36}$N$_2$O$_4$ (**1**)
(440.58)

dl-1,1´-Bis[(tert-butylmethylamino)carbonyl]-3,3´-dimethoxy-2,2´-biphenyl (1): A 250 mL 3-necked RB-flask equipped with a magnetic stir bar was flushed with Ar and flame dried. The flask was allowed to cool to rt under Ar and charged with anhydrous THF (100 mL) followed by *N,N,N´,N´*-tetramethylethylenediamine (TMEDA, 5.88 mL, d = 0.77, 4.53 g, 39.0 mmol). The solution of TMEDA was cooled to 0 °C and treated with n-BuLi (18.2 mL, 2.14 M in hexanes, 39.0 mmol). The resulting n-BuLi/TMEDA complex was stirred for 15 min at 0 °C and then cooled to – 78 °C. A solution of the 3° amide (**S3**, 6.63 g, 30.0 mmol) in anhydrous THF (20 mL) was added dropwise during 15 min; a red/brown color was observed to develop. After stirring for 1 h at –78 °C, the solution/suspension of metalated amide was treated in one portion with anhydrous powdered $FeCl_3$ (5.35 g, 33.0 mmol; dried for 2 h at 110 °C under a gentle flow of Ar). In order to conveniently execute this operation, the septum protecting the central neck of the flask was momentarily removed and the dried $FeCl_3$ powder added swiftly through the open aperture while an Ar flow into the flask was maintained via one of the side-necks. The resulting purple suspension was vigorously stirred for 4 h at –78 °C and then allowed to warm to rt and stirred for a further 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl (50 mL) and filtered through a celite pad which was well washed with EtOAc (100 mL) and H_2O (100 mL). The layers of the filtrate and combined washings were shaken and separated and the aqueous phase extracted with EtOAc (2x30 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The oily brown residue (7.28 g) was further purified by column chromatography (SiO_2, eluting with 50-100% EtOAc in hexanes) to yield the desired biaryl (**1**, 4.39 g, 9.96 mmol, 66%) as a colorless solid: mp 166-170 °C (EtOAc); IR (KBr) 2958, 1642, 1570, 1465, 1365, 1257, 1046, 753 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO, T = 80 °C) δ 7.28 (2H, t, *J* = 8.1 Hz), 6.96 (2H, d, *J* = 8.1 Hz), 6.82 (2H, d, *J* = 7.5 Hz), 3.64 (6H, s), 2.68 (6H, s), 1.24 (18 H, s) ppm; ^{13}C NMR (100 MHz, d_6-DMSO, T = 80 °C) δ 169.7 (2C, 0), 157.0 (2C, 0), 139.9 (2C, 0), 127.4 (2C, 1), 122.7 (2C, 0), 118.6 (2C, 1), 110.2 (2C, 1), 54.8 (4C, 3 & 0), 33.8 (2C, 3), 26.9 (6C, 3) ppm; MS (FAB+) *m/z* 441 (M+H)$^+$ (55%), 391 (30), 307 (100), 289 (42); HRMS (FAB+) *m/z* 441.2744 (calcd. for $C_{16}H_{37}N_2O_4$: 441.2753).
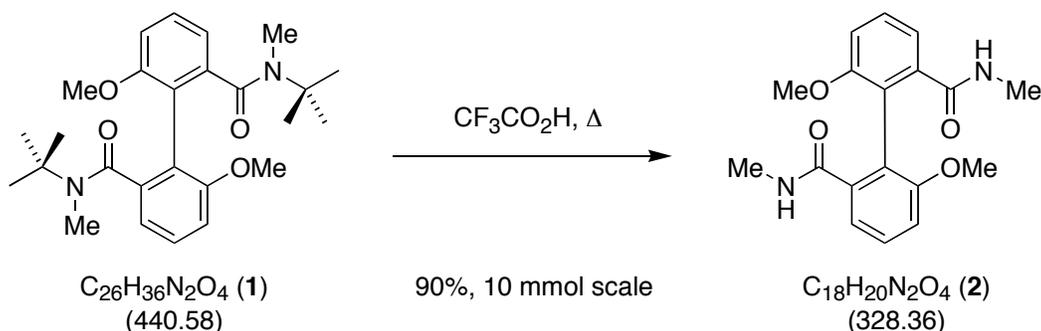
HPLC analysis of *dl*-**1** performed with a Daicel Chiralcel® OD column (4.6 mm I.D. x 250 mm), eluting with 5% *i*-PrOH in hexanes at 0.4 mL min^{-1} and monitored by UV at 210 nm, showed resolved peaks: $t_{ret.}$ (*d*-**1**) = 26.9 min, (*l*-**1**) = 29.7 min. Identical analysis of a dissolved single crystal of mass 5 mg (obtained by crystallization of *dl*-**1** from EtOAc, see Chart 1, entry 1) and exhibiting $[\alpha]_D^{25}$ = + 90.9 (c = 0.26, MeOH), indicated a 79% ee. See Figures S1 & S2.
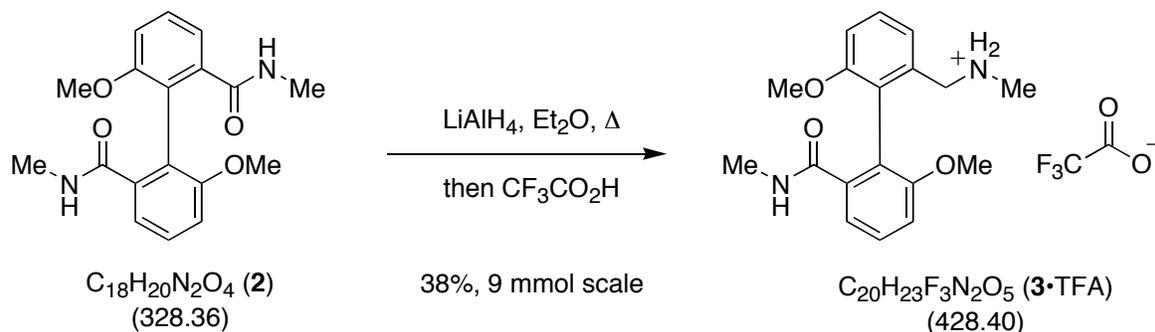

Figure S1. Morphology of crystals obtained from crystallization of *dl*-**1** from EtOAc solution. Scale in cm.
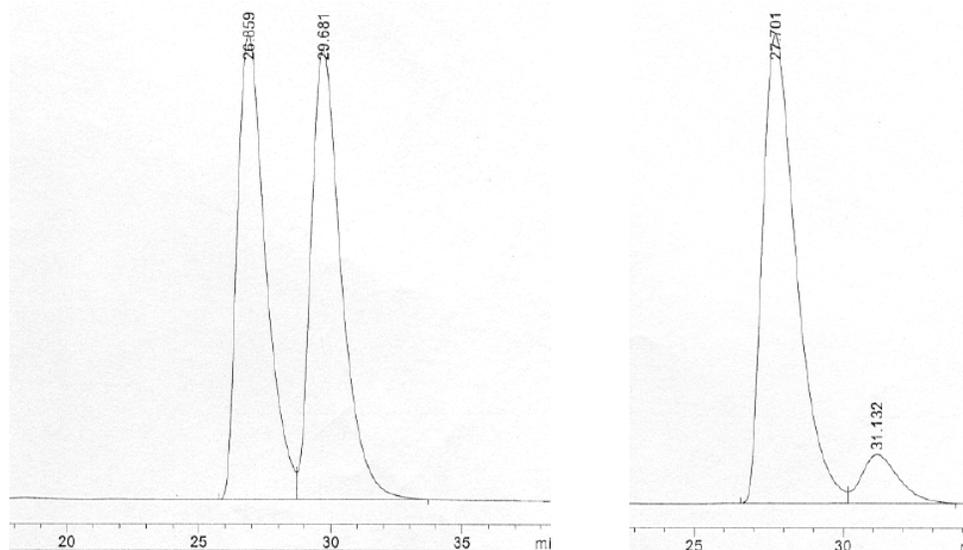
Figure S2. HPLC analysis of **1** with Daicel Chiralcel® OD column
[left trace: racemic sample, right trace: sample with $[\alpha]_D^{25} = +90.9$ (c = 0.26, MeOH)]

$C_{26}H_{36}N_2O_4$ (**1**)
(440.58)

CF$_3$CO$_2$H, Δ

90%, 10 mmol scale

$C_{18}H_{20}N_2O_4$ (**2**)
(328.36)

dl-**1,1´-Bis[(methylamino)carbonyl]-3,3´-dimethoxy-2,2´-biphenyl (2):** A solution of the bis-*tert*-butyl amide (**1**, 4.39 g, 9.96 mmol) in trifluoroacetic acid (30 mL) was heated to a gentle reflux and stirred for 14 h. The resulting dark brown solution was allowed to cool and concentrated *in vacuo*. The oily residue was treated with *t*-butyl methyl ether (TBME, 10 mL) and a brief period of trituration resulted in the formation of a thick colorless precipitate of the desired product. The suspension was vacuum filtered on a Buchner funnel and the filter cake washed with TBME (3x2 mL) then sucked dry to afford the desired 2° bisamide (**2**, 2.94 g, 8.95 mmol, 90%) in a very pure state as a colorless powder: mp 259-261 °C (MeOH); IR (KBr) 3453, 3304, 1629, 1557, 1466, 1329, 1261 cm^{-1}; ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 8.34 (2H, q, *J* = 4.6 Hz), 7.34 (2H, t, *J* = 8.0 Hz), 7.07 (2H, dm, *J* = 7.7 Hz), 7.00 (2H, dd, *J* = 7.5, 0.8 Hz), 3.57 (6H, s), 2.46 (6H, d, *J* = 4.7 Hz) ppm; ^{13}C NMR (100 MHz, d$_4$-MeOH) δ 169.5 (2C, 0), 156.3 (2C, 0), 138.9 (2C, 0), 128.4 (2C, 1), 123.0 (2C, 0), 118.8 (2C, 1), 112.5 (2C, 1), 55.7 (2C, 3), 25.5 (2C, 3) ppm; MS (EI+) *m/z* 328 (100%), 270 (100), 241 (85), 226 (31); HRMS (EI+) *m/z* 328.1423 (calcd. for $C_{18}H_{20}N_2O_4$: 328.1423).

$C_{18}H_{20}N_2O_4$ (**2**)
(328.36)

LiAlH$_4$, Et$_2$O, Δ

then CF$_3$CO$_2$H

38%, 9 mmol scale

$C_{20}H_{23}F_3N_2O_5$ (**3•TFA**)
(428.40)

***dl*-3,3′-Dimethoxy-1-[(methylamino)carbonyl]-1′-[(methylamino)methyl]-2,2′-biphenyl trifluoroacetic acid salt (3•TFA):** A stirred solution of the 2° amide (**2**, 2.94 g, 8.95 mmol) in anhydrous Et$_2$O (300 mL) at rt under Ar was treated portionwise with LiAlH$_4$ (2.72 g, 71.6 mmol, 8.0 eq). The resulting suspension was heated at a gentle reflux for 73 h, then allowed to cool to rt and carefully quenched by the addition of wetted Na$_2$SO$_4$ (30 g of a sample generated by adding 15 mL H$_2$O to 50 g of anhydrous crystalline Na$_2$SO$_4$ solid). The quenched reaction mixture was vigorously stirred at rt for 16 h then solids removed by filtration through a shallow celite pad. The solid residues were well washed with Et$_2$O (150 mL) and the filtrate and combined washings concentrated *in vacuo* to afford 2.60 g of a colorless oil. The residual oil ($\leq$ 8.28 mmol free base of **3**) was dissolved in THF (15 mL) and TFA (0.61 mL, d = 1.54, 944 mg, 8.28 mmol) added. After stirred for 25 min at rt, a milky precipitate of the desired TFA salt formed and hexanes (20 mL) was added to encourage further product deposition. The precipitate was isolated by filtration to afford 1.47 g of **3•TFA** (1.47 g, 3.43 mmol, 38%) as a fine colorless powder which was of high purity as determined by ^{1}H NMR analysis: mp 204 °C dec. (EtOH); IR (KBr) 3448, 3299, 1676, 1623, 1472, 1266, 1202, 1136, 1083 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 10.05 (1H, br s), 9.76 (1H, br s), 7.46 (1H, t, J = 7.6 Hz), 7.40 (1H, t, J = 7.7 Hz), 7.16 (1H, dm, J = 7.6 Hz), 7.10 (1H, dm, J = 8.5 Hz), 7.05 (1H, dm, J = 7.6 Hz), 7.00 (1H, dm, J = 8.4 Hz), 6.05 (1H, br q, J = 4.5 Hz), 3.99 (1H, br d, J = 12.5 Hz), 3.72 (3H, s), 3.69-3.65 (1H, obscured), 3.66 (3H, s), 2.75 (3H, d, J = 4.9 Hz), 2.50 (3H, br s) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.0 (0), 162.4 (CO$_2$CF$_3$, q, J_{CCF} = 34.4 Hz), 157.0 (0), 156.9 (0), 138.9 (0), 132.2 (0), 130.5 (1), 130.0 (1), 125.4 (0), 123.8 (1), 121.9 (0), 118.6 (1), 121.3 (CF$_3$, q, J_{CF} = 276 Hz), 113.3 (1), 112.6 (1), 56.1 (2C, 3), 51.2 (2), 32.6 (3), 27.0 (3) ppm; ^{19}F (282 MHz, CDCl$_3$) δ –75.5 (3F, s) ppm; MS (EI+, free base) *m/z* 314 (10%, M$^{+\bullet}$), 283 (100), 254 (45), 224 (59), 178 (24), 122 (49), 105 (52), 77 (34), 69 (57); HRMS (EI+, free base) *m/z* 314.1638 (calcd. for $C_{18}H_{22}N_2O_3$: 314.1631).

Figure S3. Morphology of crystals obtained from crystallization of *dl*-**3•TFA** from unstirred EtOH solution. Scale in cm.

Crystallization of 3•TFA and %Ee Determination by HPLC Analysis of its p-Anisoyl Amide Derivative (Chart 2)

Crystallization of 3•TFA without stirring: A 50 mL Erlenmeyer flask was charged with a powder sample of *dl*-**3**•TFA (200 mg, 467 μmol) and absolute EtOH (2.00 mL) added. The contents of the flask were briefly heated (ca 20 sec.) to a gentle boil using a hot air gun resulting in complete dissolution of the racemic salt. To remove any particulates, the hot ethanolic solution was then filtered through a short glass wool plug (contained within a Pasteur pipette) into a 10 mL RB flask (14/24 joint). The RB flask was provided with a loose fitting Al-foil cap and left to stand undisturbed as its contents slowly cooled to ambient temperature. Once the formation of a significant quantity of needles was noticed (>100 individuals sited across multiple colonies), the crystals (see Figure S3 above) were isolated by vacuum filtration (using a Hirsch funnel) and a little more EtOH (ca. 1 mL) used to fully transport and wash the collected material. After being allowed to air dry, the crystalline material was assayed for mass and then an optical rotation measurement taken in MeOH. Data for 10 individual crystallization experiments conducted as described above are shown in Table S1 (Entries 1-10) and are represented graphically in Chart 2.
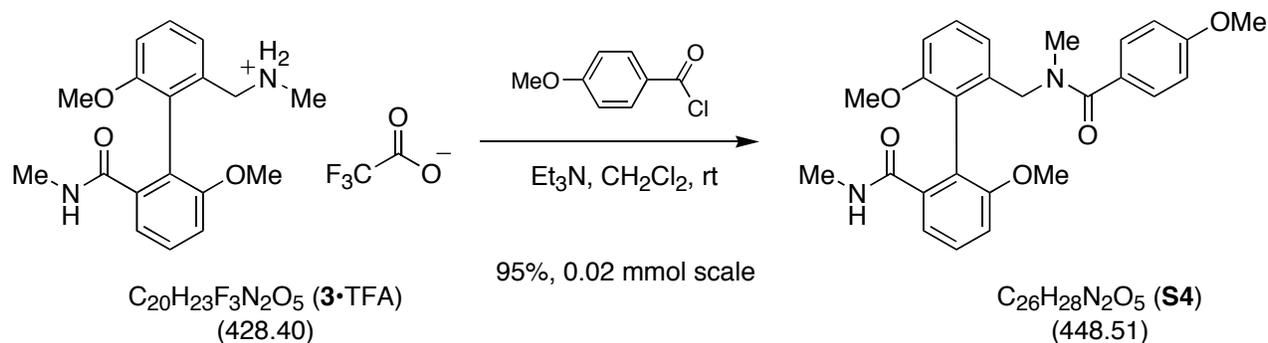
Crystallization of 3•TFA with stirring: A 25 mL Erlenmeyer flask was charged with a powder sample of *dl*-**3**•TFA (150 mg, 350 μmol) and absolute EtOH (1.50 mL) added. The contents of the flask were briefly heated (ca 10 sec.) to a gentle boil using a hot air gun resulting in complete dissolution of the racemic salt. To remove any particulates, the hot ethanolic solution was then filtered through a short glass wool plug (contained within a Pasteur pipette) into a 10 mL RB flask (14/24 joint) that was provided with a small teflon coated magnetic stir bar (8 mm x 1 mm x 1 mm). The RB flask was provided with a loose fitting Al-foil cap and the mother liquor stirred at ca. 400 rpm (Troemner-Mag® stirrer unit on setting #2) as it was allowed to cool to ambient temperature. The solution would become cloudy with tiny particles of suspended solid within 5-10 minutes. The fine powdery solid was isolated by vacuum filtration (using a Hirsch funnel) and a little more EtOH (ca. 1 mL) used to fully transport and wash the collected material. The solid was further washed with Et$_2$O (2x2 mL) to facilitate removal of EtOH and then sucked dry. As before, the collected material was assayed for mass and then an optical rotation measurement taken in MeOH. Data for 10 individual crystallization experiments conducted as described above are shown in Table S1 (Entries 11-20) and are represented graphically in Chart 2.

NOTE: Interruption of the crystallization before too great a yield was realized was critical for the obtainment of non-racemic material. On rare occassions, solid material collected above a 15% yield would not be racemic (e.g., experiment #1 in Table S1); however, more commonly, crystal crops recovered in higher yield would exhibit insignificant optical rotations indicating an ee below 5%.

Table S1. Spontaneous resolution of *dl*-**3**•TFA by crystallization from EtOH (and see Chart 2). Experiments 1-10 conducted without stirring, experiments 11-20 conducted with stirring.

expt. #	ambient temp.	time allowed for crystal growth	mass recovery	optical rotation	
1	25 °C	16.8 h	25.0%	$[\alpha]_D^{22} = +16.4$	(c = 0.72, MeOH)
2	25 °C	2.3 h	10.4%	$[\alpha]_D^{25} = -36.6$	(c = 0.58, MeOH)
3†	23 °C	3.5 h	7.0%	$[\alpha]_D^{23} = +104.4$	(c = 0.51, MeOH)
4	22 °C	2.5 h	8.5%	$[\alpha]_D^{22} = -3.4$	(c = 0.72, MeOH)
5	24 °C	5.0 h	5.6%	$[\alpha]_D^{22} = +15.3$	(c = 0.56, MeOH)
6	22 °C	24.0 h	5.9%	$[\alpha]_D^{22} = -92.5$	(c = 0.59, MeOH)
7	23 °C	5.3 h	4.7%	$[\alpha]_D^{24} = +9.3$	(c = 0.59, MeOH)
8	23 °C	3.8 h	9.6%	$[\alpha]_D^{24} = -14.6$	(c = 0.67, MeOH)
9	24 °C	6.0 h	7.0%	$[\alpha]_D^{23} = -11.1$	(c = 0.70, MeOH)
10	22 °C	4.6 h	3.2%	$[\alpha]_D^{21} = +110.5$	(c = 0.32, MeOH)
11	24 °C	45 min	12.9%	$[\alpha]_D^{23} = +54.1$	(c = 1.27, MeOH)
12	24 °C	50 min	11.6%	$[\alpha]_D^{23} = -104.2$	(c = 1.16, MeOH)
13	21 °C	35 min	12.0%	$[\alpha]_D^{22} = -25.3$	(c = 0.45, MeOH)
14	21 °C	12 min	8.5%	$[\alpha]_D^{21} = +52.9$	(c = 0.64, MeOH)
15	21 °C	15 min	15.7%	$[\alpha]_D^{21} = -59.2$	(c = 1.18, MeOH)
16	23 °C	8 min	3.6%	$[\alpha]_D^{22} = +72.6$	(c = 0.27, MeOH)
17	23 °C	11 min	10.5%	$[\alpha]_D^{22} = +25.0$	(c = 0.79, MeOH)
18	23 °C	14 min	5.1%	$[\alpha]_D^{22} = -24.2$	(c = 0.45, MeOH)
19	22 °C	7 min	7.6%	$[\alpha]_D^{22} = -43.6$	(c = 0.61, MeOH)
20	22 °C	14 min	12.6%	$[\alpha]_D^{22} = -33.5$	(c = 1.01, MeOH)

† HPLC analysis of derived p-anisoyl amide **S4** revealed 97% ee (see below).

C$_{20}$H$_{23}$F$_3$N$_2$O$_5$ (**3•TFA**)
(428.40)

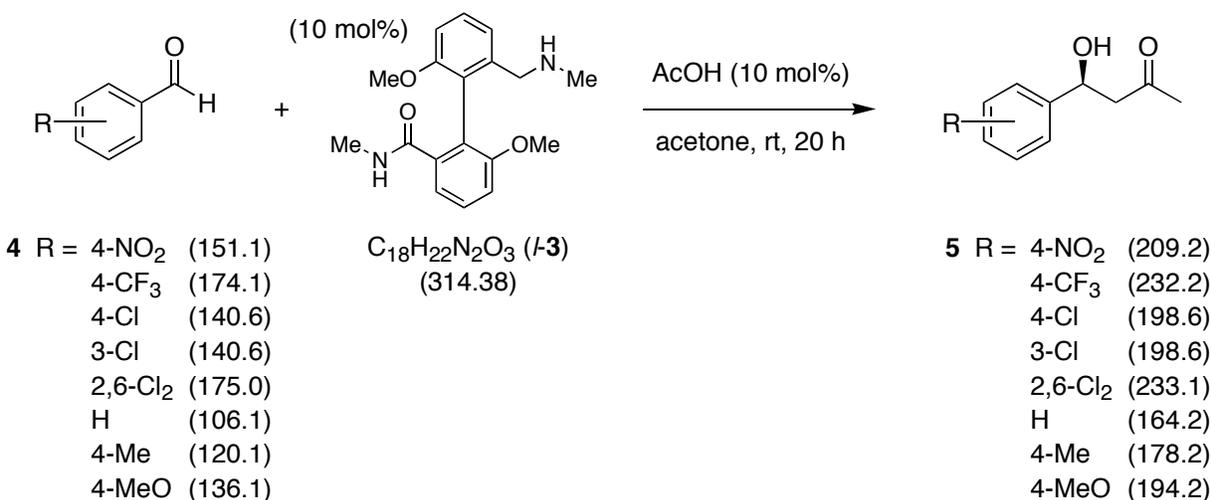95%, 0.02 mmol scale

C$_{26}$H$_{28}$N$_2$O$_5$ (**S4**)
(448.51)

p-Anisoyl amide derivative of amidoamine 3 (S4): A stirred solution of optically active *d*-**3•TFA** obtained from experiment #3 above [8.0 mg, 18.7 μmol, $[\alpha]_D^{23}$ = +104.4 (c = 0.51, MeOH)] in CH$_2$Cl$_2$ (1 mL) was treated with Et$_3$N (50 μL, d = 0.722, 36 mg, 0.36 mmol) followed by neat molten p-anisoyl chloride (25 μL, d = 1.24, 31 mg, 0.18 mmol). The reaction mixture was allowed to stir for 18 h at rt and then diluted with CH$_2$Cl$_2$ (5 mL) and shaken with 2.0 M aq. HCl (10 mL). The layers were separated and the aqueous phase extracted with CH$_2$Cl$_2$ (5 mL). The combined organic phases were washed successively with 2.0 M aq. NaOH (2x10 mL) and brine (10 mL), then dried (Na$_2$SO$_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO$_2$, eluting with 5% MeOH in CH$_2$Cl$_2$) to afford the title amide derivative (+)-**S4** (8.0 mg, 17.8 μmol, 95%) as a colorless waxy solid (mp 44-55 °C, no recrys.). HPLC analysis of this sample and comparison to a chromatogram similarly obtained from a racemic sample revealed a 97% ee (see below). Data for (+)-**S4**: $[\alpha]_D^{24}$ = + 71.8 (c= 0.45, CHCl$_3$, 97% ee); IR (neat) 3319, 2924, 2853, 1616, 1464, 1254, 1070, 754 cm^{-1}; ^{1}H NMR (300 MHz, d$_6$-DMSO, T = 80 °C) δ 7.37 (1H, t, *J* = 7.9 Hz), 7.32 (2H, d, *J* = 8.9 Hz), 7.32 (1H, br t, *J* = 8.2 Hz), 7.10 (2H, d, *J* = 8.0 Hz), 6.96-6.87 (5H, m), 4.23 (2H, br s), 3.80 (3H, s), 3.63 (3H, s), 3.60 (3H, s), 2.82 (3H, s), 2.50 (3H, d, *J* = 6.8 Hz) ppm; ^{13}C NMR (100 MHz, d$_6$-DMSO, T = 80 °C) δ 170.1 (0), 167.9 (0), 159.8 (0), 156.6 (0), 156.4 (0), 138.6 (0), 137.1 (0), 128.2 (0), 128.1 (3C, 1), 127.9 (1), 124.3 (0), 122.4 (0), 119.0 (1), 117.4 (1), 113.2 (2C, 1), 112.0 (1), 109.7 (1), 55.3 (3), 55.2 (3), 54.9 (3), 28.5 (2), 28.1 (3), 25.3 (3) ppm; MS (EI+) *m/z* 448 (12%, M$^{+\bullet}$), 313 (100), 282 (24), 241 (16), 135 (20); HRMS (EI+) *m/z* 448.2018 (calcd. for C$_{26}$H$_{28}$N$_2$O$_5$: 448.1998).

HPLC analysis of *dl*-**S4** performed with a Daicel Chiralcel® OD column (4.6 mm I.D. x 250 mm), eluting with 10% *i*-PrOH in hexanes at 1.5 mL min^{-1} and monitored by UV at 254 nm, showed resolved peaks: t$_{ret.}$ (*d*-**S4**) = 48.5 min, (*l*-**S4**) = 66.9 min. Identical analysis of the enantioenriched sample of *d*-**S4** prepared as described above from *d*-**3•TFA** (with provenance from crystallization experiment #3, Table S1) indicated a 97% ee. See Figure S4.
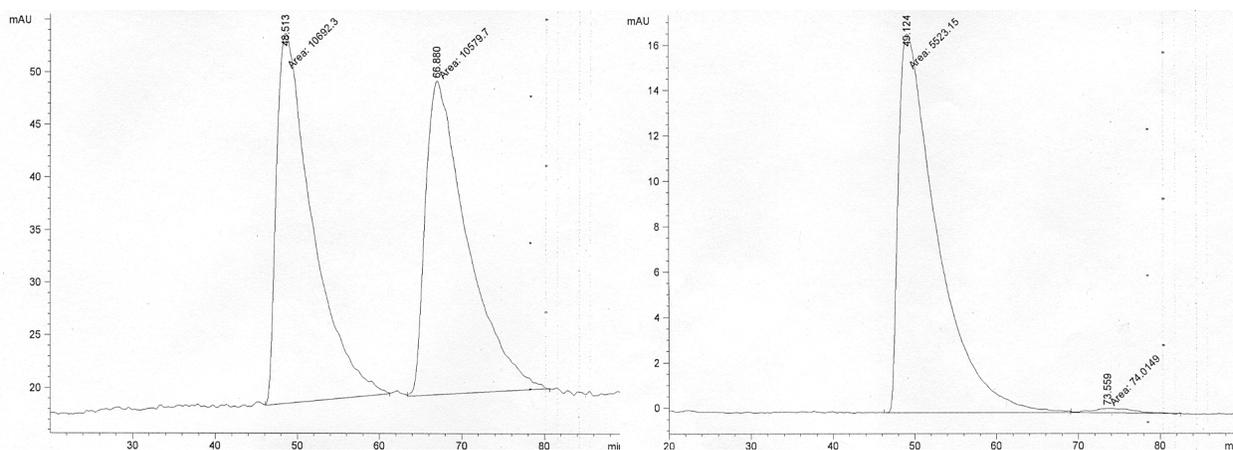
Figure S4. HPLC analysis of **S4** with Daicel Chiralcel® OD column
[left trace: *dl*-**S4**, right trace: *d*-**S4** of 97% ee]

Acetone Aldol Reactions with Benzaldehydes (Table 1)

4 R =	4-NO$_2$	(151.1)
	4-CF$_3$	(174.1)
	4-Cl	(140.6)
	3-Cl	(140.6)
	2,6-Cl$_2$	(175.0)
	H	(106.1)
	4-Me	(120.1)
	4-MeO	(136.1)

C$_{18}$H$_{22}$N$_2$O$_3$ (*l*-**3**)
(314.38)

5 R =	4-NO$_2$	(209.2)
	4-CF$_3$	(232.2)
	4-Cl	(198.6)
	3-Cl	(198.6)
	2,6-Cl$_2$	(233.1)
	H	(164.2)
	4-Me	(178.2)
	4-MeO	(194.2)

Generation of free-base of amidoamine 3: An enantioenriched sample of *l*-**3**•TFA (243 mg, 0.568 mmol, 82% ee) was dissolved in CH$_2$Cl$_2$ (10 mL) and shaken with 2M aq. KOH (10 mL). The layers were separated and the aqueous phase extracted with CH$_2$Cl$_2$ (2x5 mL). The combined organic phases were dried (Na$_2$SO$_4$) and concentrated *in vacuo* to give the free-base *l*-**3** (178 mg, 0.566 mmol, 99%) as a colorless oil: $[\alpha]_D^{21}$ = −114.6 (c = 1.12, CHCl$_3$, 82% ee).

Acetone aldol reactions. General procedure: A 2.5 mL screw-capped glass vial was charged with the aldehyde (0.50 mmol) followed by a freshly prepared solution of the enantioenriched free-base **3** in acetone (1.00 mL, 0.05 M, 0.050 mmol, 10 mol%). Neat acetic acid (2.9 *m*L, d = 1.05, 3.0 mg, 0.051 mmol) was then added, the screw-cap was applied, and the vial contents briefly shaken and then allowed to stand at ambient temperature for 20 h. After this time the mixture was diluted with

EtOAc (5 mL) and washed successively with 2 M aq. HCl (5 mL) and H_2O (5 mL). The organic phase was then dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was analyzed by ^{1}H NMR spectroscopy to ascertain the relative distribution of desired aldol product (AL), α,α'-acetone double aldol adduct (DAL), aldol condensation adduct (AC), and unreacted starting aldehyde (SM) (see data in Table 1). The aldol adduct **5** was isolated by column chromatography (SiO_2, eluting with 30-50% EtOAc in hexanes); purity and identity confirmed by ^{1}H NMR analysis, and ee assayed by a combination of optical rotation and HPLC experiments. (Note: slight traces of benzoic acids were evident in some of the aldol products after chromatography, presumably the result of aerial oxidation of the aldehyde; aqueous base washing of the aldol during work-up to remove this minor contaminant results in decomposition and should be avoided). ^{1}H NMR spectral data for aldol adducts were in agreement with those previously reported.[S2] The sign of optical rotation obtained for products indicated that (*S*)-configurated aldol adducts **5** were generated preferentially from *l*-**3**, albeit in very low enantiomeric excess in all cases. The absolute configurational assignment was further confirmed by HPLC chromatograms run under previously validated conditions.[S2]

(*S*)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one (5, R = 4-NO$_2$; Table 1, entry 1): Subjection of 4-nitrobenzaldehyde (76 mg, 0.50 mmol) to the protocol described above using catalyst *l*-**3** (10 mol%, 82% ee) afforded the aldol (*S*)-**5** (R = 4-NO$_2$, 36 mg, 0.172 mmol, 34%) as a colorless oil: $[\alpha]_D^{21} = -3.20$ (c = 1.00, CHCl$_3$) {lit.[S2a] for (*R*)-isomer at 99% ee, $[\alpha]_D^{21} = + 66.2$ (c = 0.50, CHCl$_3$)}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.20 (2H, d, *J* = 8.5 Hz), 7.54 (2H, d, *J* = 8.5 Hz), 5.28-5.23 (1H, m), 3.64 (1H, br s), 2.90-2.83 (2H, m), 2.22 (3H, s) ppm. ^{1}H NMR data in agreement with those previously reported.[S2a]

HPLC analysis conducted according to conditions previously validated.[S2a] Thus, injection of the sample into a Daicel Chiralpak AS-H column (4.6 mm I.D. x 250 mm), eluting with 30% *i*-PrOH in hexanes at 1.0 mL min^{-1} and monitored by UV at 210 nm, afforded resolved peaks: $t_{ret.}$ [(*R*)-**5** R = 4-NO$_2$] = 12.4 min (48.7%), $t_{ret.}$ [(*S*)-**5** R = 4-NO$_2$] = 16.0 min (51.3%), revealing a 2.6% ee in favor of the (*S*)-isomer.

Note: The above synthesis of **5** (R = 4-NO$_2$) was repeated using catalyst *d*-**3** (10 mol%, 63% ee) and product purified and analyzed as before. An isolated yield of 33% was obtained and a 2.3% ee was now determined by HPLC analysis that was in favor of the opposite (*R*)-isomer, as expected.

S2. (a) Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang and L.-Z. Gong, *J. Am. Chem. Soc.*, 2005, **127**, 9285-9289. (b) A. Russo, G. Botta and A. Lattanzi, *Tetrahedon*, 2007, **63**, 11886-11892. (c) M. R. Vishnumaya and V. K. Singh, *J. Org. Chem.*, 2009, **74**, 4289-4297. (d) Y. Zhou and Z. Shan, *Tetrahedron Asymmetry*, 2006, **17**, 1671-1677. Note: ^{1}H NMR data for **8** (R = 2,6-Cl$_2$) provided in ref. S2a are erroneous, correct spectral data for this compound (and agreeing with those we obtained) appear in ref. S2b.

(*S*)-4-Hydroxy-4-[4-(trifluoromethyl)phenyl]butan-2-one (5, R = 4-CF₃; Table 1, entry 2):

Subjection of 4-(trifluoromethyl)benzaldehyde (87 mg, 0.50 mmol) to the protocol described above using catalyst *l*-**3** (10 mol%, 82% ee) afforded the aldol (*S*)-**5** (R = 4-CF₃, 48 mg, 0.207 mmol, 41%) as a colorless oil: $[\alpha]_D^{21} = -2.69$ (c = 1.04, CHCl₃) {lit.[S2a] for (*R*)-isomer at 98% ee, $[\alpha]_D^{21} = +57.6$ (c = 0.51, CHCl₃)}; ¹H NMR (400 MHz, CDCl₃) δ 7.60 (2H, d, *J* = 8.0 Hz), 7.47 (2H, d, *J* = 8.0 Hz), 5.21 (1H, t, *J* = 5.7 Hz), 3.53 (1H, br s), 2.89-2.79 (2H, m), 2.20 (3H, s) ppm. ¹H NMR data in agreement with those previously reported.[S2a]

HPLC analysis conducted according to conditions previously validated.[S2a] Thus, injection of the sample into a Daicel Chiralpak AS-H column (4.6 mm I.D. x 250 mm), eluting with 10% *i*-PrOH in hexanes at 0.50 mL min⁻¹ and monitored by UV at 210 nm, afforded resolved peaks: t_ret. [(*R*)-**5** R = 4-CF₃] = 19.7 min (49.3%), t_ret. [(*S*)-**5** R = 4-CF₃] = 24.0 min (50.7%), revealing a 1.4% ee.

(*S*)-4-Hydroxy-4-(4-chlorophenyl)butan-2-one (5, R = 4-Cl; Table 1, entry 3): Subjection of 4-chlorobenzaldehyde (70 mg, 0.50 mmol) to the protocol described above using catalyst *l*-**3** (10 mol%, 82% ee) afforded the aldol (*S*)-**5** (R = 4-Cl, 13 mg, 0.065 mmol, 13%) as a colorless oil: $[\alpha]_D^{21} = -2.25$ (c = 0.80, CHCl₃) {lit.[S2a] for (*R*)-isomer at 99% ee, $[\alpha]_D^{21} = +70.5$ (c = 0.50, CHCl₃)}; ¹H NMR (400 MHz, CDCl₃) δ 7.32 (2H, d, *J* = 8.6 Hz), 7.29 (2H, d, *J* = 8.7 Hz), 5.13 (1H, dd, *J* = 8.1, 4.2 Hz), 3.40 (1H, br s), 2.88-2.80 (2H, m), 2.20 (3H, s) ppm. ¹H NMR data in agreement with those previously reported.[S2a]

HPLC analysis conducted according to conditions previously validated.[S2a] Thus, injection of the sample into a Daicel Chiralpak AS-H column (4.6 mm I.D. x 250 mm), eluting with 10% *i*-PrOH in hexanes at 1.0 mL min⁻¹ and monitored by UV at 210 nm, afforded resolved peaks: t_ret. [(*R*)-**5** R = 4-Cl] = 14.0 min (49.6%), t_ret. [(*S*)-**5** R = 4-Cl] = 17.3 min (50.5%), revealing a 0.9% ee.

(*S*)-4-Hydroxy-4-(3-chlorophenyl)butan-2-one (5, R = 3-Cl; Table 1, entry 4): Subjection of 3-chlorobenzaldehyde (70 mg, 0.50 mmol) to the protocol described above using catalyst *l*-**3** (10 mol%, 82% ee) afforded the aldol (*S*)-**5** (R = 3-Cl, 24 mg, 0.121 mmol, 24%) as a colorless oil: $[\alpha]_D^{21} = -1.50$ (c = 1.40, CHCl₃) {lit.[S2c] for (*R*)-isomer at 96% ee, $[\alpha]_D^{21} = +33.2$ (c = 2.10, CHCl₃)}; ¹H NMR (400 MHz, CDCl₃) δ 7.38 (1H, br s), 7.31-7.21 (3H, m), 5.14 (1H, dd, *J* = 7.6, 4.6 Hz), 3.35 (1H, br s), 2.90-2.80 (2H, m), 2.21 (3H, s) ppm. ¹H NMR data in agreement with those previously reported.[S2d]

HPLC analysis conducted similarly to related compound **5** (R = 4-Cl). Thus, injection of the sample into a Daicel Chiralpak AS-H column (4.6 mm I.D. x 250 mm), eluting with 7.5% *i*-PrOH in hexanes at 0.5 mL min⁻¹ and monitored by UV at 210 nm, afforded resolved peaks: t_ret. [(*R*)-**5** R = 3-Cl] = 30.6 min (49.70%), t_ret. [(*S*)-**5** R = 3-Cl] = 33.6 min (50.30%), revealing a 0.6% ee.

(*S*)-4-Hydroxy-4-(2,6-dichlorophenyl)butan-2-one (5, R = 2,6-Cl$_2$; Table 1, entry 5): Subjection of 2,6-dichlorobenzaldehyde (88 mg, 0.50 mmol) to the protocol described above using catalyst *l*-**3** (10 mol%, 82% ee) afforded the aldol (*S*)-**5** (R = 2,6-Cl$_2$, 67 mg, 0.287 mmol, 58%) as a colorless oil: $[\alpha]_D^{21}$ = + 0.52 (c = 2.12, CHCl$_3$) {lit.[S2a] for (*R*)-isomer at 96% ee, $[\alpha]_D^{22}$ = − 47.4 (c = 0.58, CHCl$_3$)}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30 (2H, d, *J* = 8.0 Hz), 7.15 (1H, t, *J* = 8.0 Hz), 5.98 (1H, dm, *J* = 9.8 Hz), 3.47 (1H, dd, *J* = 17.1, 10.2 Hz), 3.24 (1H, br s), 2.75 (1H, dm, *J* = 17.0 Hz), 2.25 (3H, s) ppm. ^{1}H NMR data in agreement with those previously reported.[S2b]

HPLC analysis conducted under similar conditions to those previously validated.[S2a] Injection of the sample into a Daicel Chiralpak AS-H column (4.6 mm I.D. x 250 mm), eluting with 10% *i*-PrOH in hexanes at 1.0 mL min^{-1} and monitored by UV at 210 nm, afforded resolved peaks: $t_{ret.}$ [(*R*)-**5** R = 2,6-Cl$_2$] = 10.9 min (49.6%), $t_{ret.}$ [(*S*)-**5** R = 2,6-Cl$_2$] = 12.5 min (50.4%), revealing a 0.8% ee.

(*S*)-4-Hydroxy-4(phenylbutan-2-one (5, R = H; Table 1, entry 6): Subjection of benzaldehyde (53 mg, 0.50 mmol) to the protocol described above using catalyst *l*-**3** (10 mol%, 82% ee) afforded the aldol (*S*)-**5** (R = H, 5 mg, 0.030 mmol, 6%) as a colorless oil: $[\alpha]_D^{21}$ = − 3.75 (c = 0.13, CHCl$_3$) {lit.[S2a] for (*R*)-isomer at 98% ee, $[\alpha]_D^{20}$ = + 74.8 (c = 0.61, CHCl$_3$)}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37-7.26 (5H, m), 5.17 (1H, dd, *J* = 9.2, 2.6 Hz), 3.45 (1H, br s), 2.90 (1H, dd, *J* = 17.2, 8.4 Hz), 2.82 (1H, dd, *J* = 17.5, 3.1 Hz), 2.20 (3H, s) ppm. ^{1}H NMR data in agreement with literature data.[S2a]

HPLC analysis conducted under similar conditions to those previously validated.[S2a] Thus, injection of the sample into a Daicel Chiralpak AS-H column (4.6 mm I.D. x 250 mm), eluting with 7.5% *i*-PrOH in hexanes at 1.0 mL min^{-1} and monitored by UV at 210 nm, afforded resolved peaks: $t_{ret.}$ [(*R*)-**5** R = H] = 15.9 min (49.2%), $t_{ret.}$ [(*S*)-**5** R = H] = 18.9 min (50.9%), revealing a 1.7% ee.

(*S*)-4-Hydroxy-4-(4-methylphenyl)butan-2-one (5, R = 4-Me; Table 1, entry 7): Subjection of 4-methylbenzaldehyde (60 mg, 0.50 mmol) to the protocol described above using catalyst *l*-**3** (10 mol%, 82% ee) afforded the aldol (*S*)-**5** (R = 4-Me, 2 mg, 0.011 mmol, 2%) as a colorless oil: $[\alpha]_D^{21}$ = − 4.50 (c = 0.20, CHCl$_3$) {lit.[S2a] for (*R*)-isomer at 97% ee, $[\alpha]_D^{20}$ = + 60.3 (c = 0.25, CHCl$_3$)};^{1}H NMR (400 MHz, CDCl$_3$) δ 7.25 (2H, d, *J* = 8.0 Hz), 7.16 (2H, d, *J* = 8.1 Hz), 5.13 (1H, dd, *J* = 9.0, 3.3 Hz), 3.15 (1H, br s), 2.89 (1H, dd, *J* = 17.5, 9.1 Hz), 2.80 (1H, dd, *J* = 17.5, 3.3 Hz), 2.34 (3H, s), 2.19 (3H, s) ppm. ^{1}H NMR data in agreement with those previously reported.[S2a] Limited purity of the small sample obtained prevented a reliable determination of ee by HPLC in this case.

(*S*)-4-Hydroxy-4-(4-methoxyphenyl)butan-2-one (5, R = 4-OMe; Table 1, entry 8): Subjection of 4-methoxybenzaldehyde (68 mg, 0.50 mmol) to the protocol described above using catalyst *l*-**3** (10 mol%, 82% ee) afforded nothing but a slight trace of the targeted aldol adduct **5** (R = 4-MeO) which was not isolated (<1% by ^{1}H NMR analysis of the crude reaction mixture).

Details for X-ray Diffraction Analyses and ORTEP Diagrams for 1 and 3•TFA

Diffraction intensities for **1** and **3•TFA** (TFA = CF_3CO_2H) were collected at 173 K on a Bruker Apex diffractometer using MoKα radiation (λ = 0.71073 Å). Space groups were determined based on systematic absences. Absorption corrections were applied by SADABS.[S3] Structures were solved by direct methods and standard Fourier techniques and refined on F^2 using full matrix least-squares procedures. Non-H atoms were refined with anisotropic thermal parameters. H atoms were found on the F-map and refined with isotropic thermal parameters except those in two terminal Me groups in **3•TFA** which were placed in calculated positions and refined in a rigid group model. The CF_3 group in **3•TFA** is disordered over two positions in the ratio 74/26. Final refinements were made without merging of Friedel opposites and Flack parameters were determined as 0.0(12) (for **1**) and 0.2(7) (for **3•TFA**); however, anomalous scattering data were not used to assign absolute configurations to optical isomers (absolute structures in the X-ray data are arbitrary). All calculations were performed using the Bruker SHELXTL package.[S4] CIF files are also available as ESI as a separate download and X-ray data for **1** and **3•TFA** were deposited to the Cambridge Crystallographic Data Centre with call numbers CCDC 748439 and CCDC 748440, respectively (see Figures S5-S7).
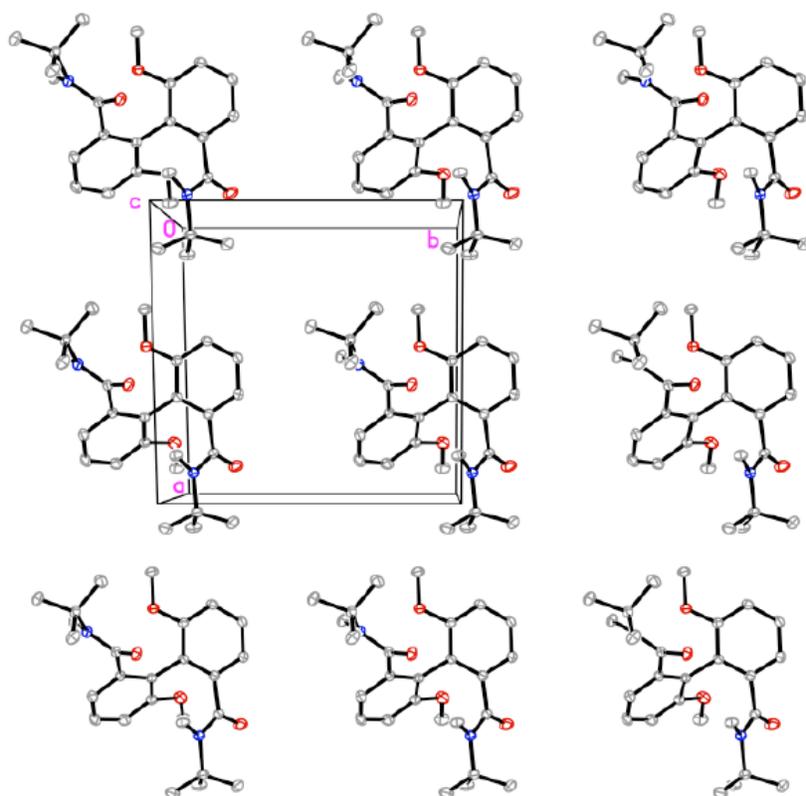
Figure S5. Extended ORTEP diagram for bisamide **1** conglomerate illustrating packing of homochiral units within the crystal. 50% probability ellipsoids are plotted for non-hydrogen atoms.

S3. G. M. Sheldrick, SADABS: University of Göttingen, Germany, 1995.
S4. Bruker; SHELXTL 6.10; Bruker AXS Inc.: Madison, Wisconsin, USA, 2000.
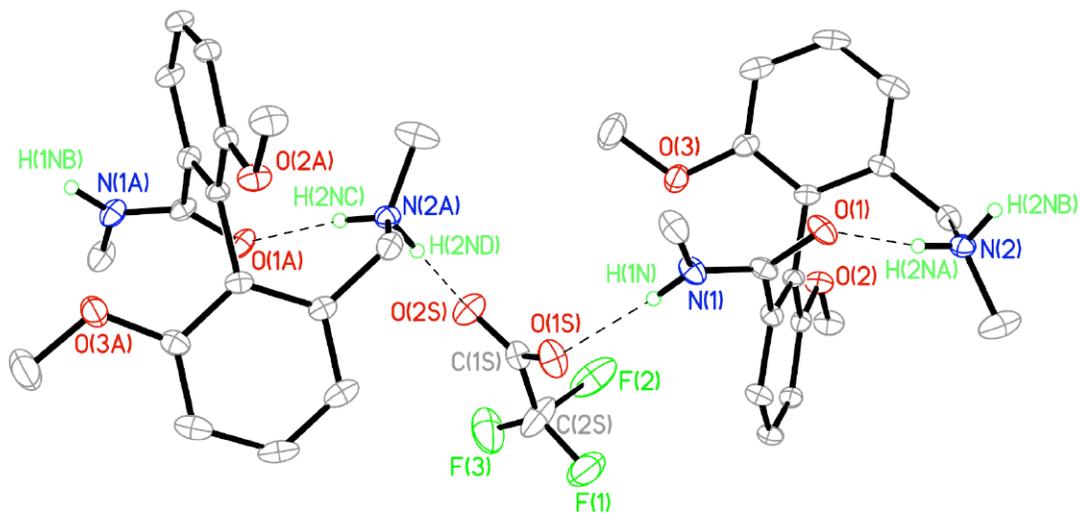
Figure S6. ORTEP diagram for amidoamine salt **3**•TFA.
50% probability ellipsoids are plotted for non-hydrogen atoms.
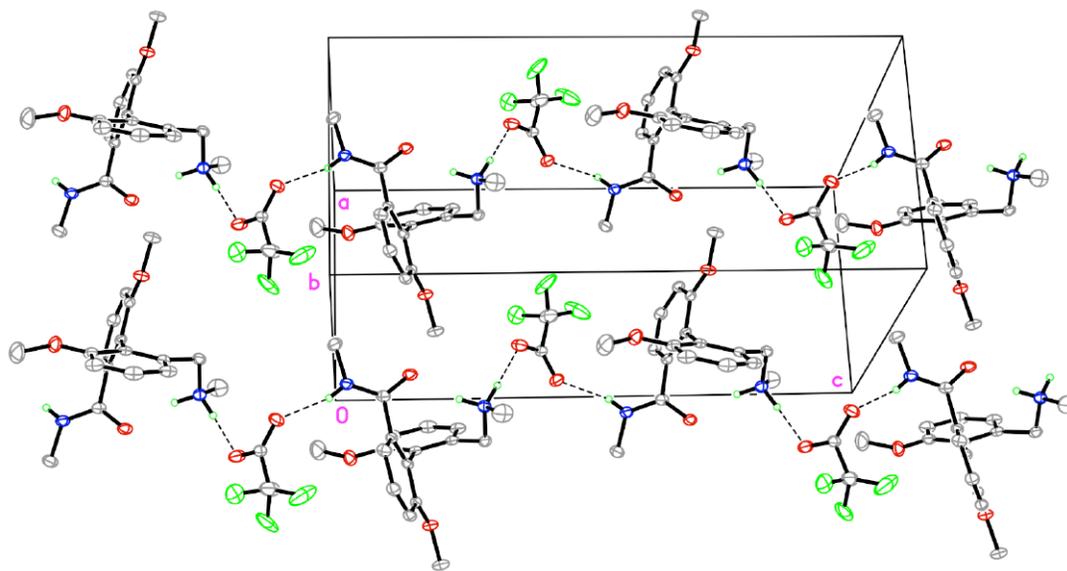
Figure S7. Extended ORTEP diagram for amidoamine salt **3**•TFA conglomerate
illustrating packing of homochiral biphenyls and bridging TFA units within the crystal.
50% probability ellipsoids are plotted for non-hydrogen atoms.

Electronic Supplementary Information: ^{1}H & ^{13}C NMR Spectra

Spontaneous Symmetry Breaking During Interrupted Crystallization of an Axially Chiral Amino Acid Derivative

Mark A. Sephton, Christopher R. Emerson, Lev N. Zakharov and Paul R. Blakemore[*]

Department of Chemistry, Oregon State University, Corvallis, OR 97331-4003.

^{1}H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified using standard 5 mm diameter tubes. Chemical shift in ppm is quoted relative to residual solvent signals calibrated as follows:

CDCl$_3$ δ_H (CHCl$_3$) = 7.26 ppm, δ_C (CDCl$_3$) = 77.2 ppm; d$_6$-DMSO δ_H (CHD$_2$SOCD$_3$) = 2.50 ppm, δ_C [(CD$_3$)$_2$SO] = 39.50 ppm

^{1}H NMR: 300 MHz, CDCl$_3$

S2: C$_{12}$H$_{17}$NO$_2$ (207.27)

^{13}C NMR: 75 MHz, CDCl$_3$

S2: C$_{12}$H$_{17}$NO$_2$ (207.27)

166.889
160.004
137.609
129.595
118.558
117.546
112.312
77.520
77.203
76.885
55.622
51.816
29.040

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 p

S18

^{1}H NMR: 300 MHz, CDCl$_3$

S3: C$_{13}$H$_{19}$NO$_2$ (221.30)

S19
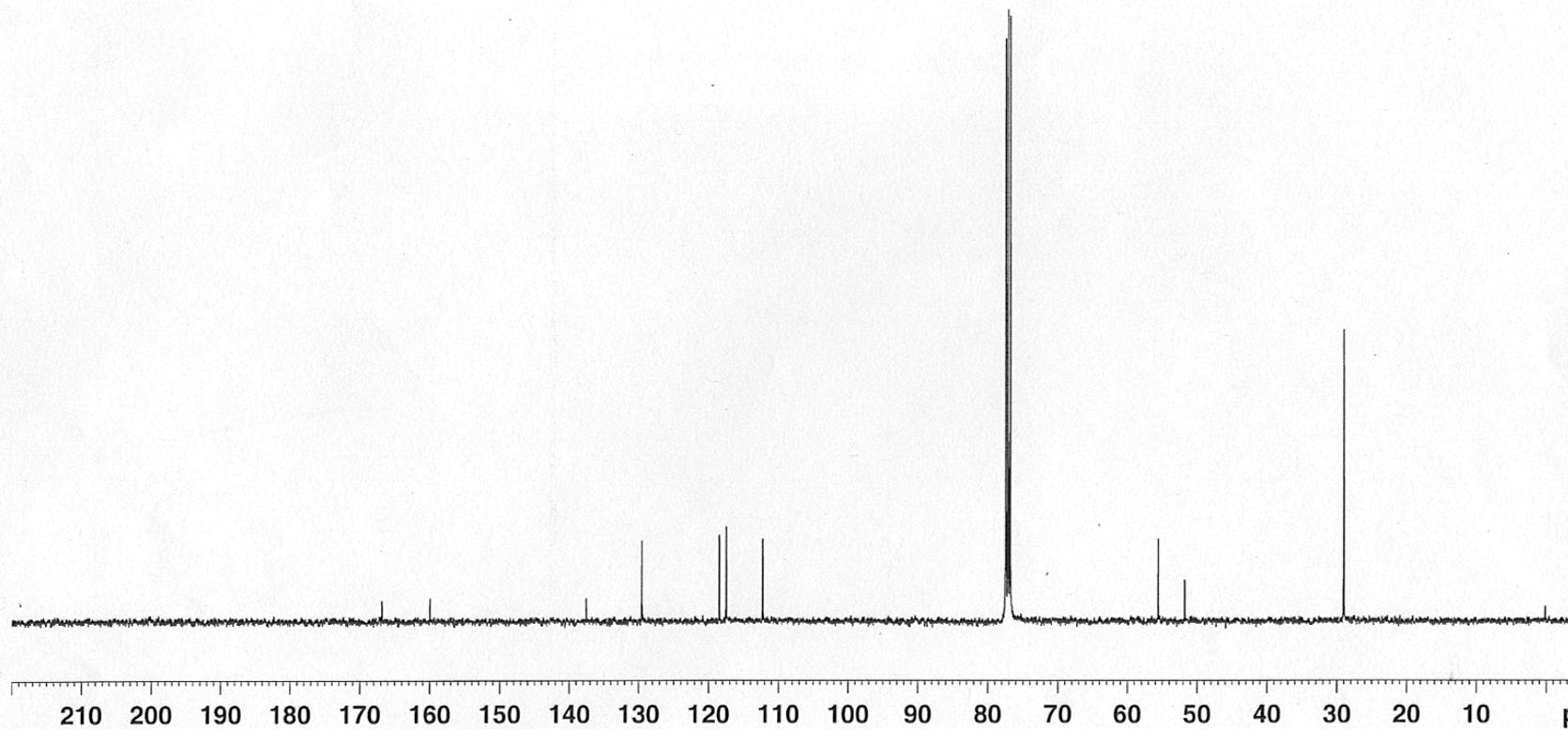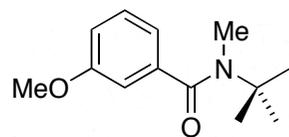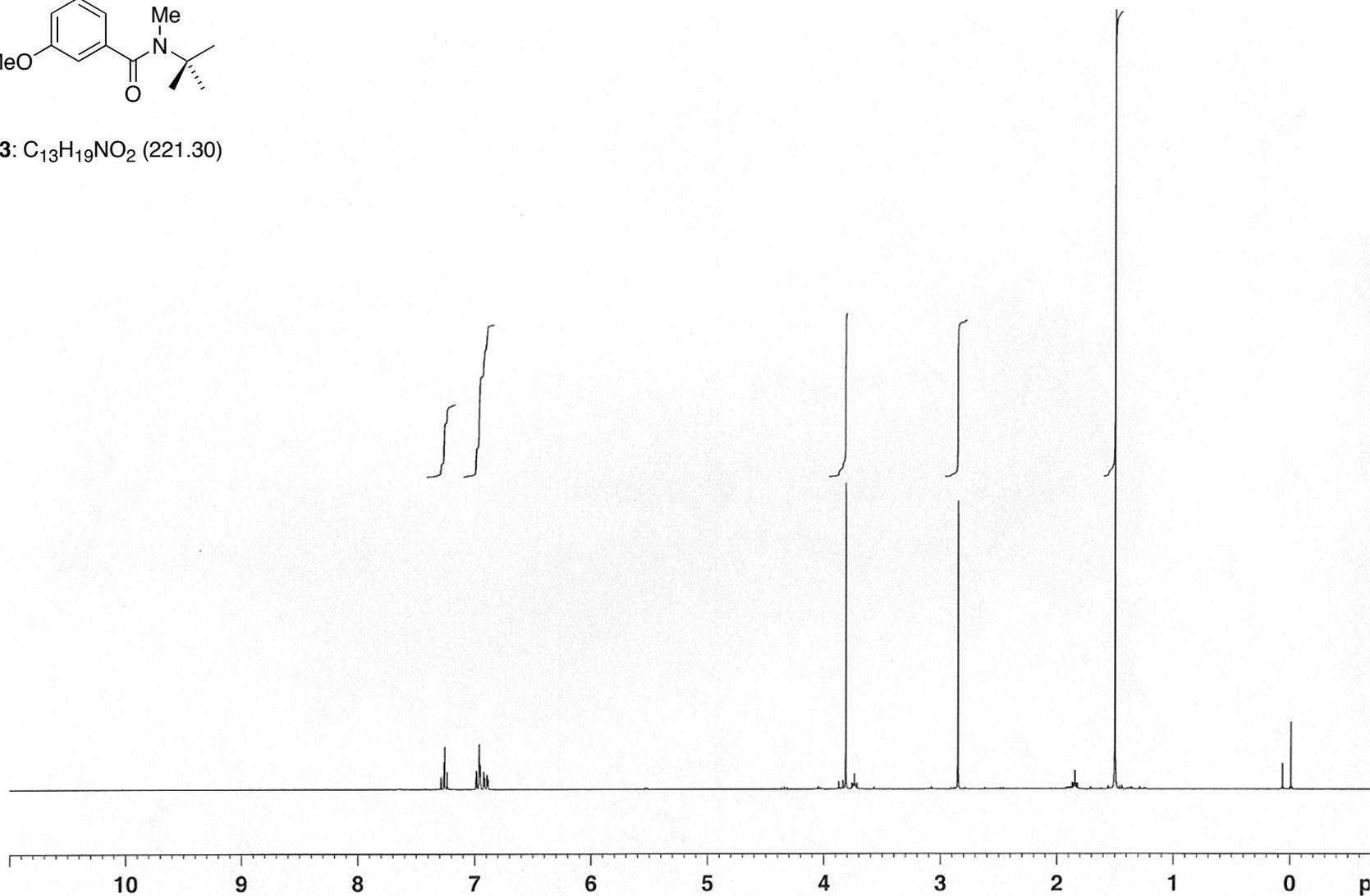
^{13}C NMR: 75 MHz, CDCl$_3$

S3: C$_{13}$H$_{19}$NO$_2$ (221.30)

173.06
159.73
140.62
129.50
119.59
115.61
112.54
77.52
77.20
76.89
56.69
55.53
35.45
27.91

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

S20

^{1}H NMR: 400 MHz, d_6-DMSO, T = 80 °C

1: $C_{26}H_{36}N_2O_4$ (440.58)

^{13}C NMR: 100 MHz, d$_6$-DMSO, T = 80 °C

1: C$_{26}$H$_{36}$N$_2$O$_4$ (440.58)

169.69
156.97
139.89
127.36
122.73
118.59
110.18
54.82
40.12
39.92
39.71
39.50
39.29
39.08
38.87
33.75
26.94

CHCl$_3$

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
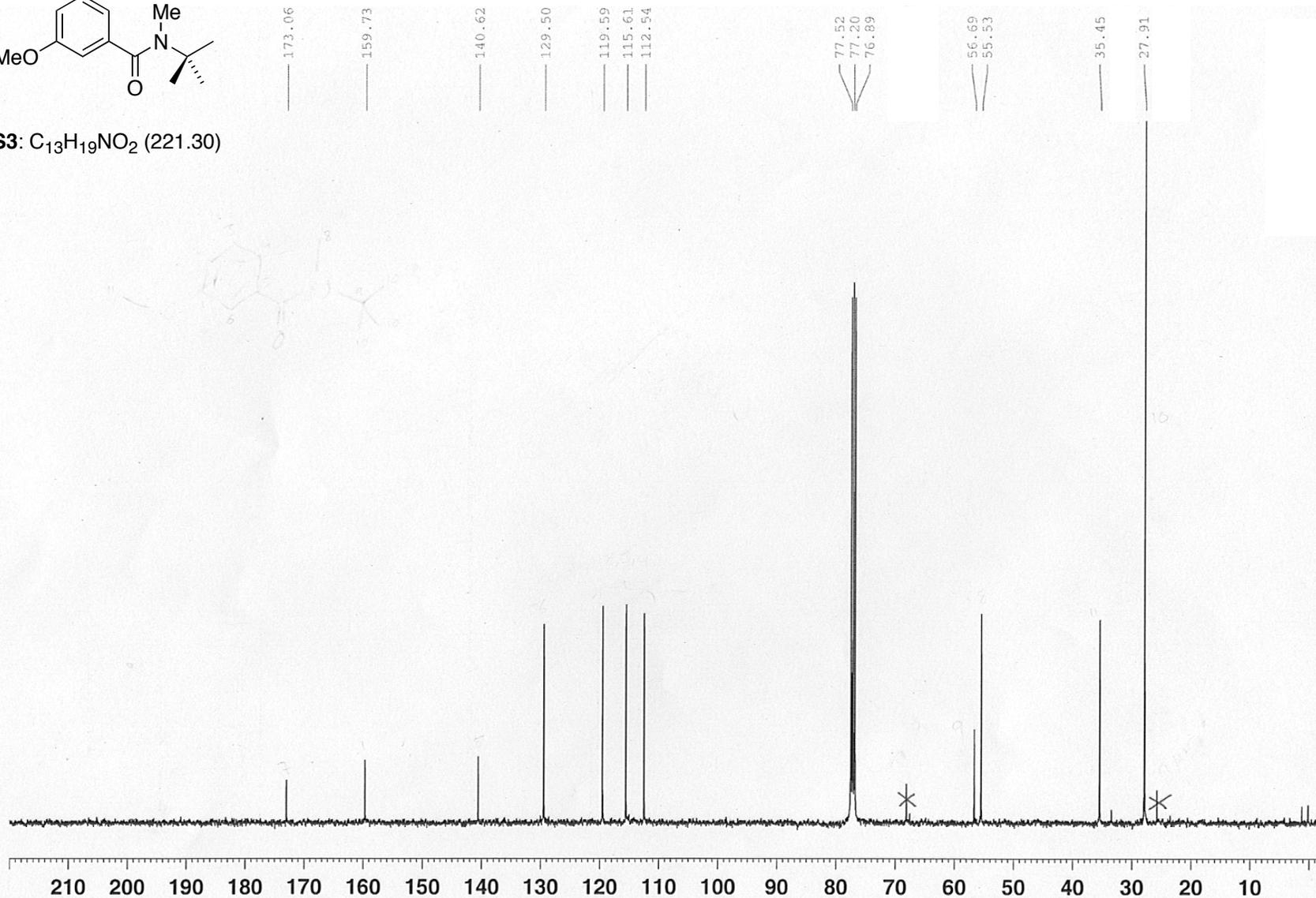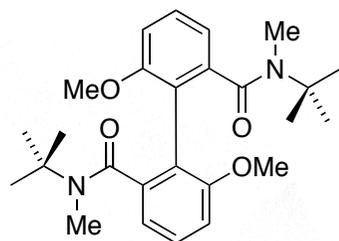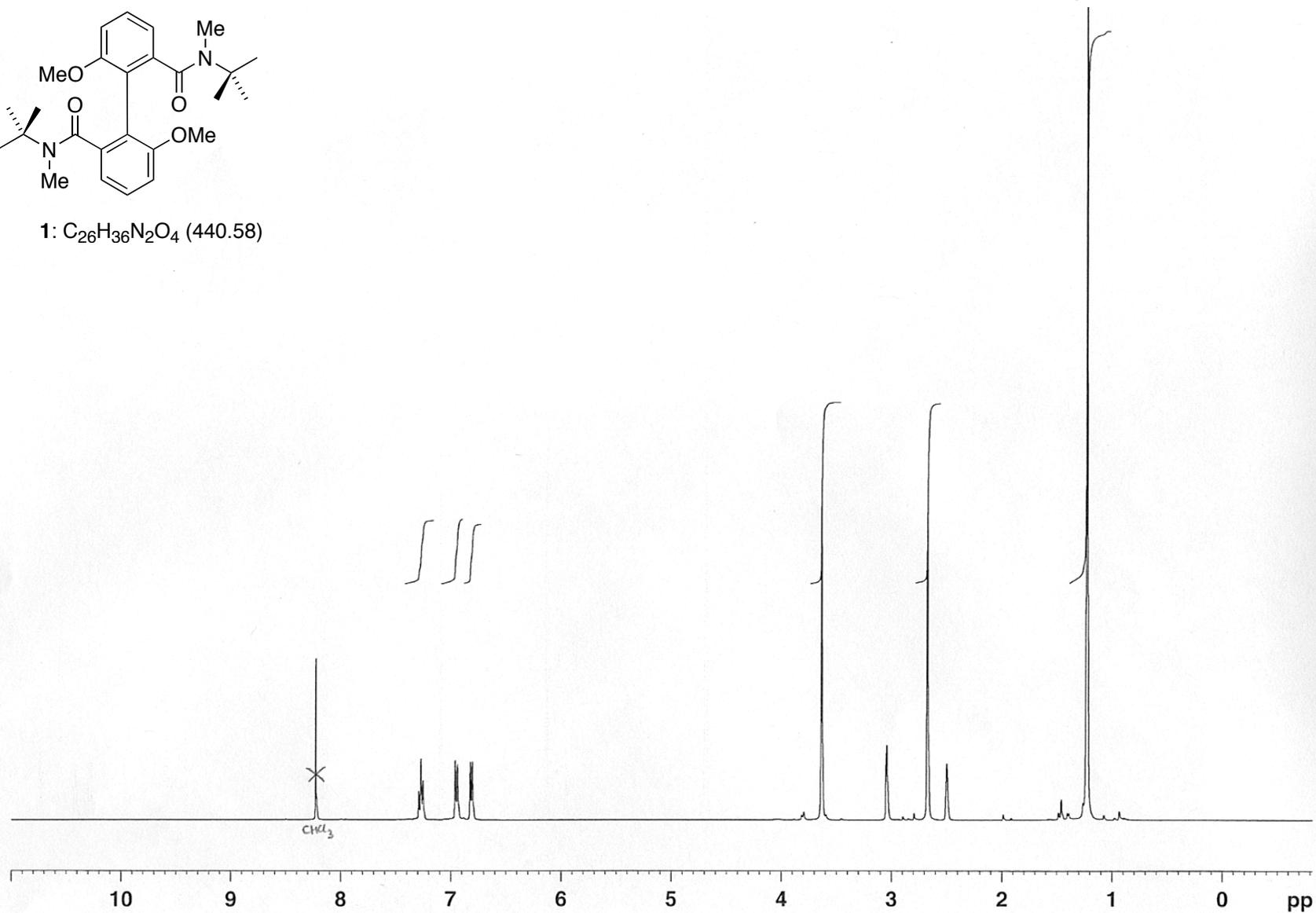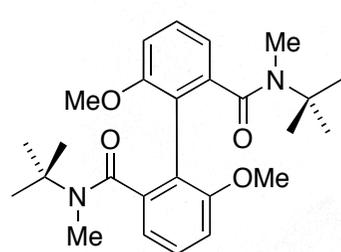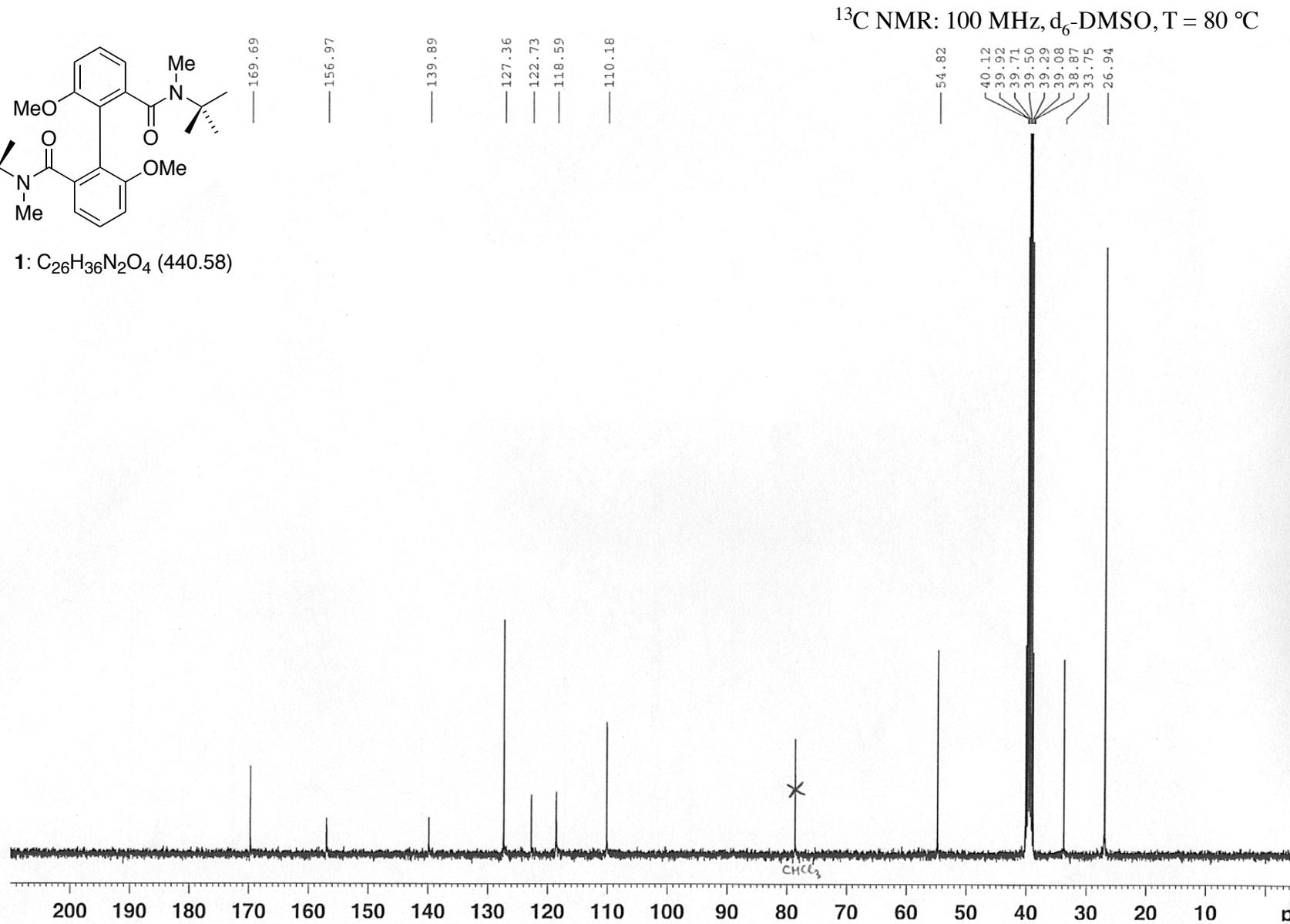
^{1}H NMR: 400 MHz, d$_6$-DMSO
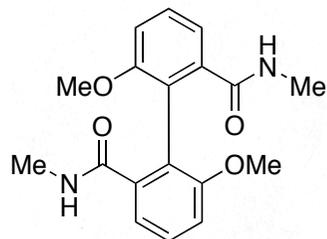
2: $C_{18}H_{20}N_2O_4$ (328.36)

2: $C_{18}H_{20}N_2O_4$ (328.36)

^{13}C NMR: 100 MHz, d_6-DMSO

156.33
138.89
128.43
122.97
118.78
112.52
55.74
40.13
39.92
39.71
39.50
39.29
39.08
38.87
25.54

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

^{1}H NMR: 400 MHz, CDCl$_3$

3·TFA: C$_{20}$H$_{23}$F$_3$N$_2$O$_5$ (428.40)

S25

^{13}C NMR: 100 MHz, CDCl$_3$

3•TFA: C$_{20}$H$_{23}$F$_3$N$_2$O$_5$ (428.40)

171.964

156.985
156.943

138.886
132.223
130.479
130.021
125.431
123.829
121.891
118.551
113.263
112.600

77.521
77.204
76.886

56.140
51.155

32.627
26.997

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 p

S26

^{1}H NMR: 300 MHz, d$_6$-DMSO, T = 80 °C

S4: C$_{26}$H$_{28}$N$_2$O$_5$ (448.51)

S27

^{13}C NMR: 100 MHz, d$_6$-DMSO, T = 80 °C

S4: C$_{26}$H$_{28}$N$_2$O$_5$ (448.51)

Peak labels (left cluster):
170.097, 167.949, 159.775, 156.571, 156.357, 138.624, 137.052, 128.219, 128.172, 128.119, 127.927, 124.328, 122.426, 118.980, 117.350, 113.176, 112.037, 109.665

Peak labels (right cluster):
55.340, 55.248, 54.881, 40.130, 39.921, 39.712, 39.503, 39.294, 39.086, 38.877, 28.467, 28.092, 25.331

x-axis: 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 p

S28

^{1}H NMR: 400 MHz, CDCl$_3$

5 R = 4-NO$_2$

C$_{10}$H$_{11}$NO$_4$ (209.2)
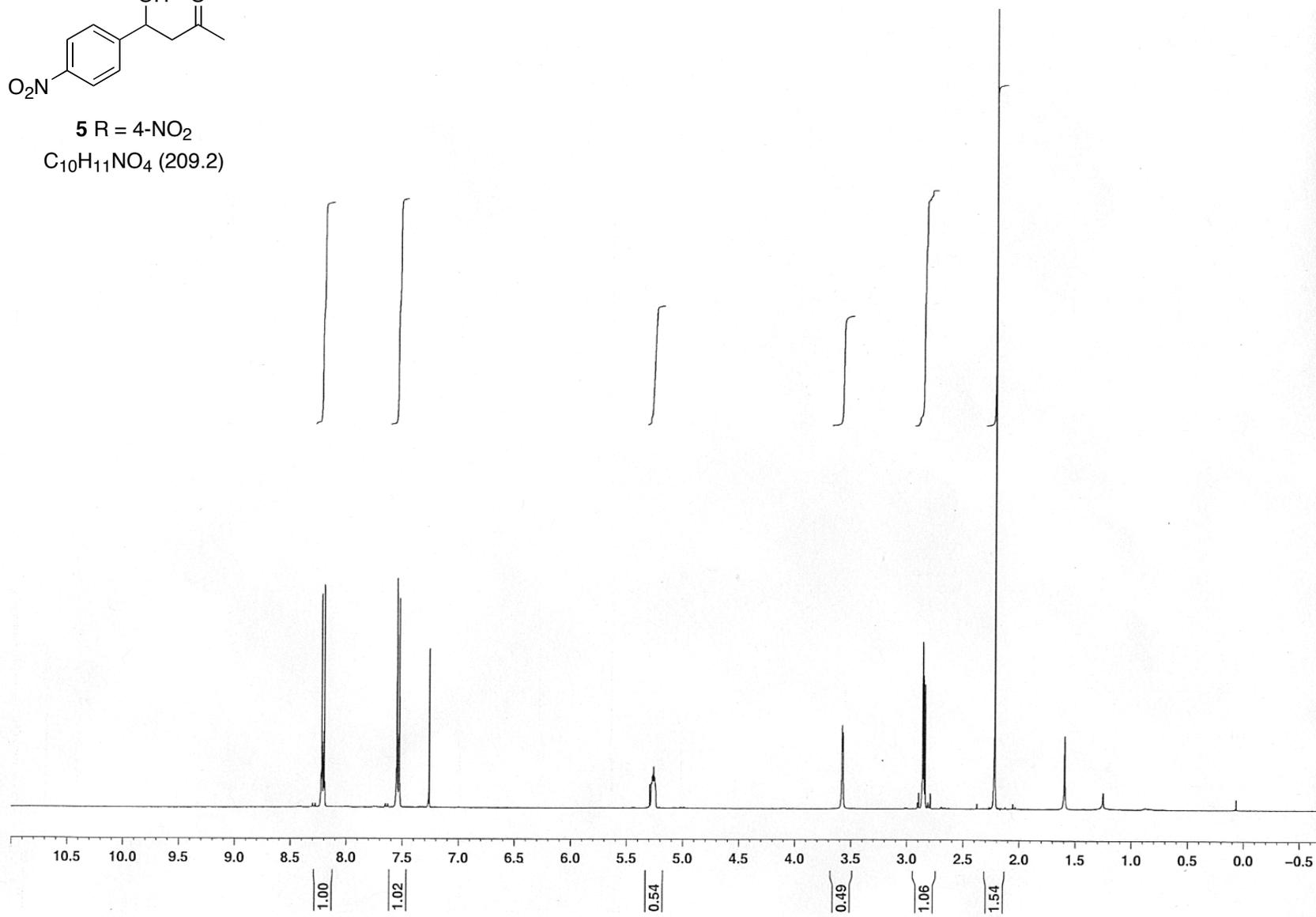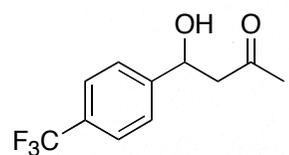
^{1}H NMR: 400 MHz, CDCl$_3$

5 R = 4-CF$_3$

C$_{11}$H$_{11}$F$_3$O$_3$ (232.2)

^{1}H NMR: 400 MHz, CDCl$_3$
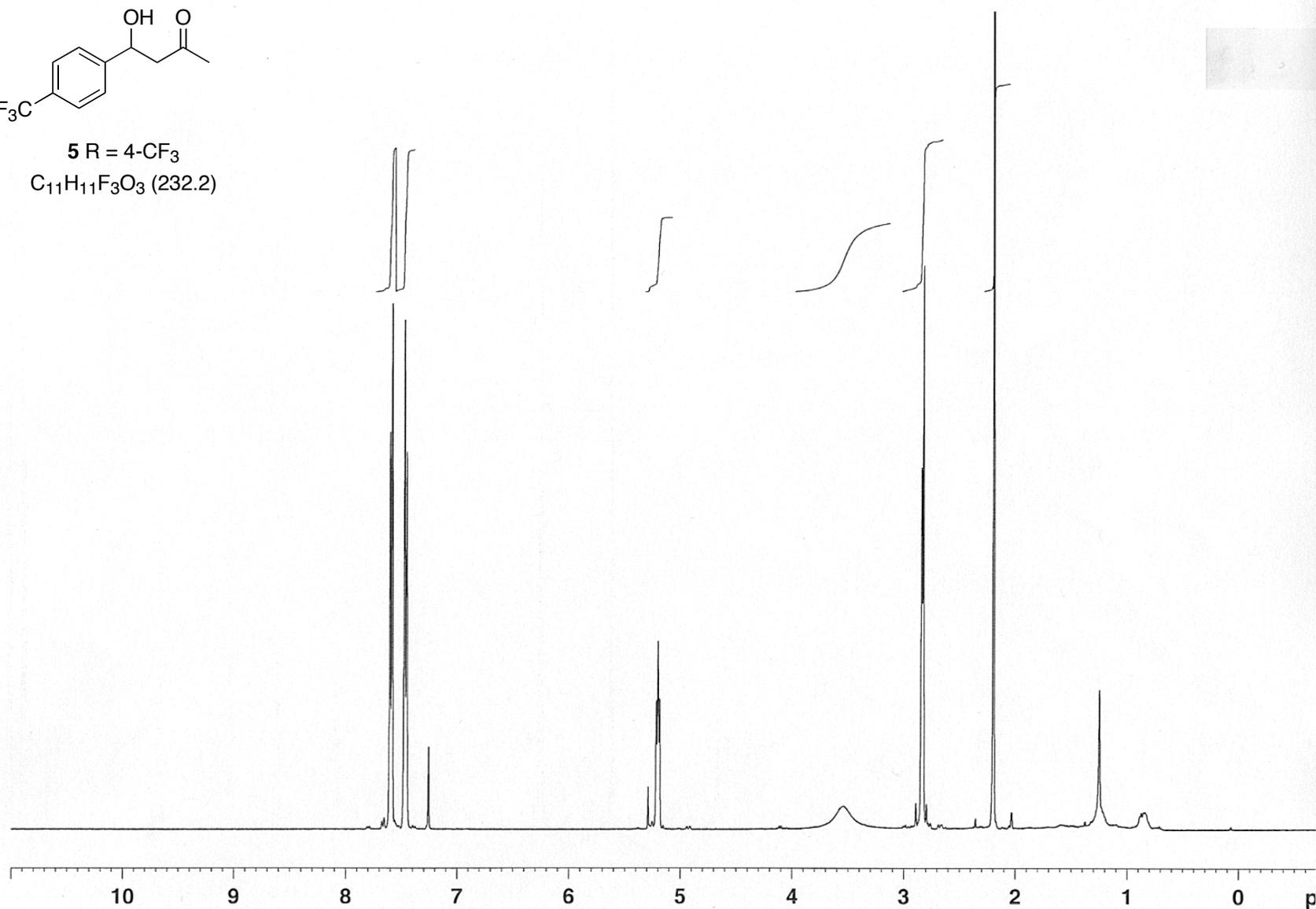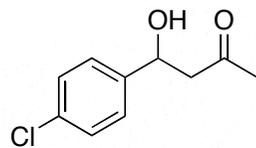
5 R = 4-Cl

C$_{10}$H$_{11}$ClO$_2$ (198.6)

S31
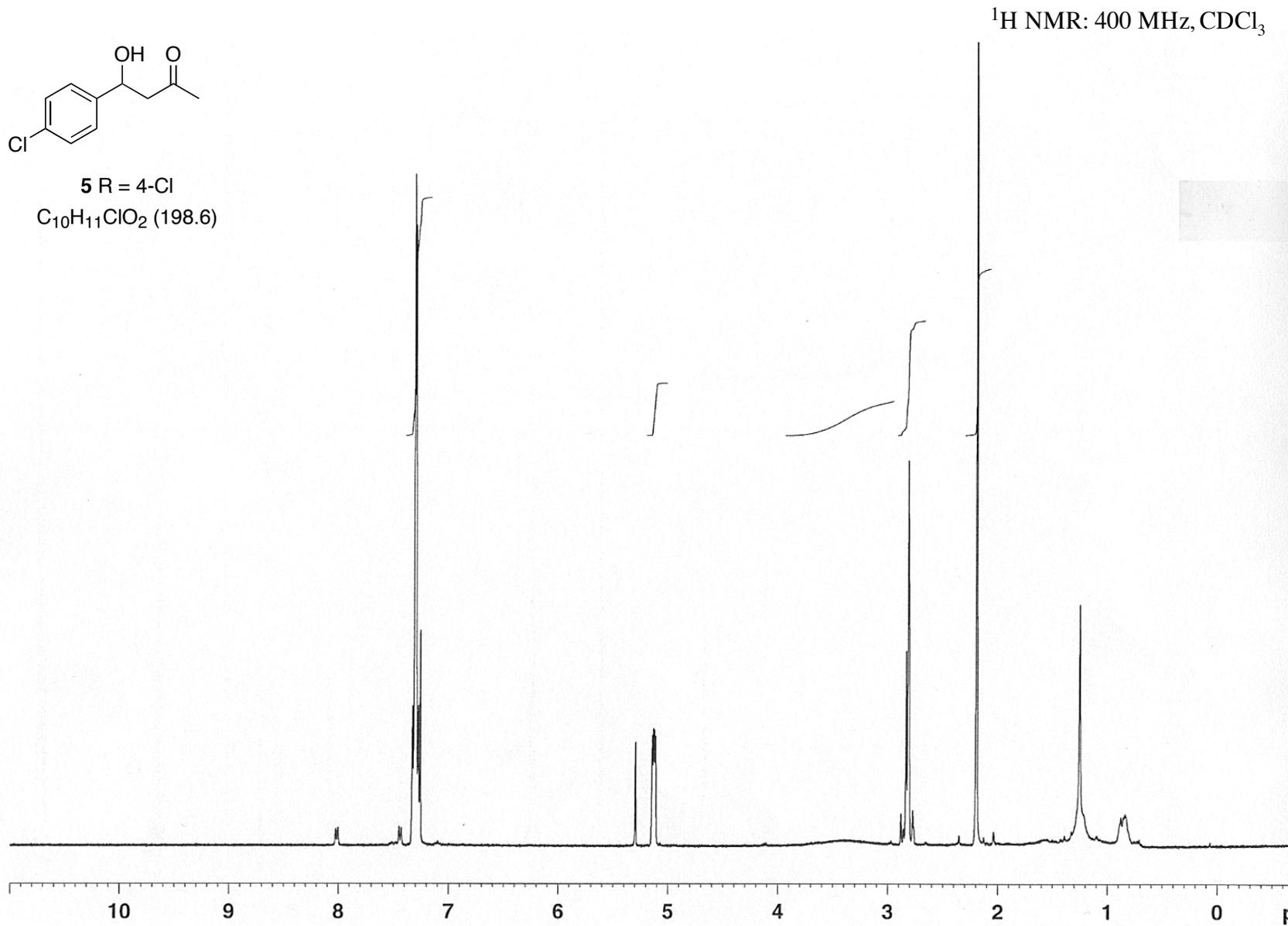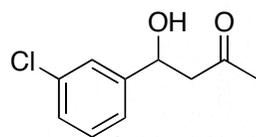
^{1}H NMR: 400 MHz, CDCl$_3$

5 R = 3-Cl

C$_{10}$H$_{11}$ClO$_2$ (198.6)

S32
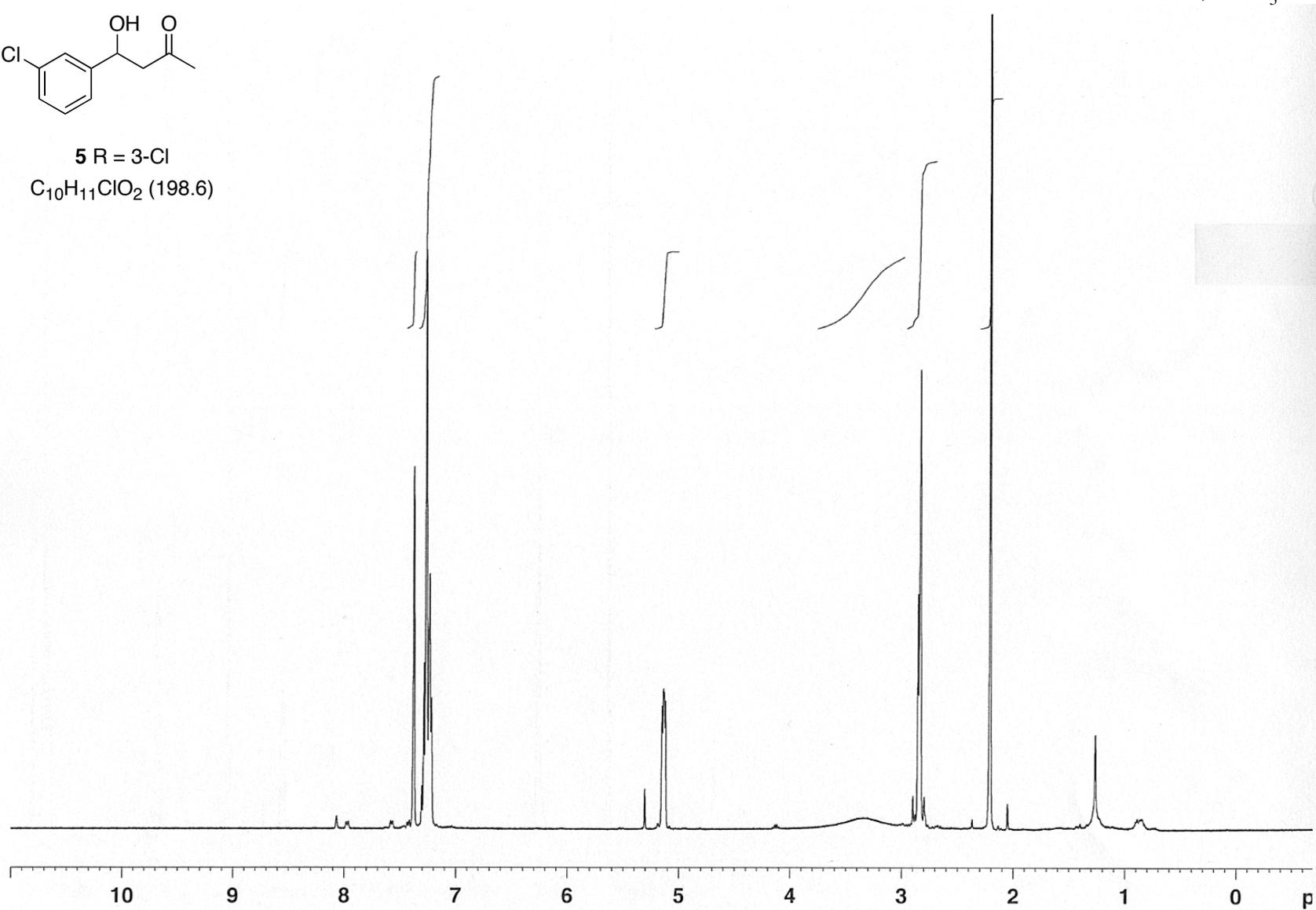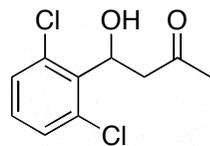
^{1}H NMR: 400 MHz, CDCl$_3$

5 R = 2,6-Cl$_2$

C$_{10}$H$_{10}$Cl$_2$O$_2$ (233.1)

S33
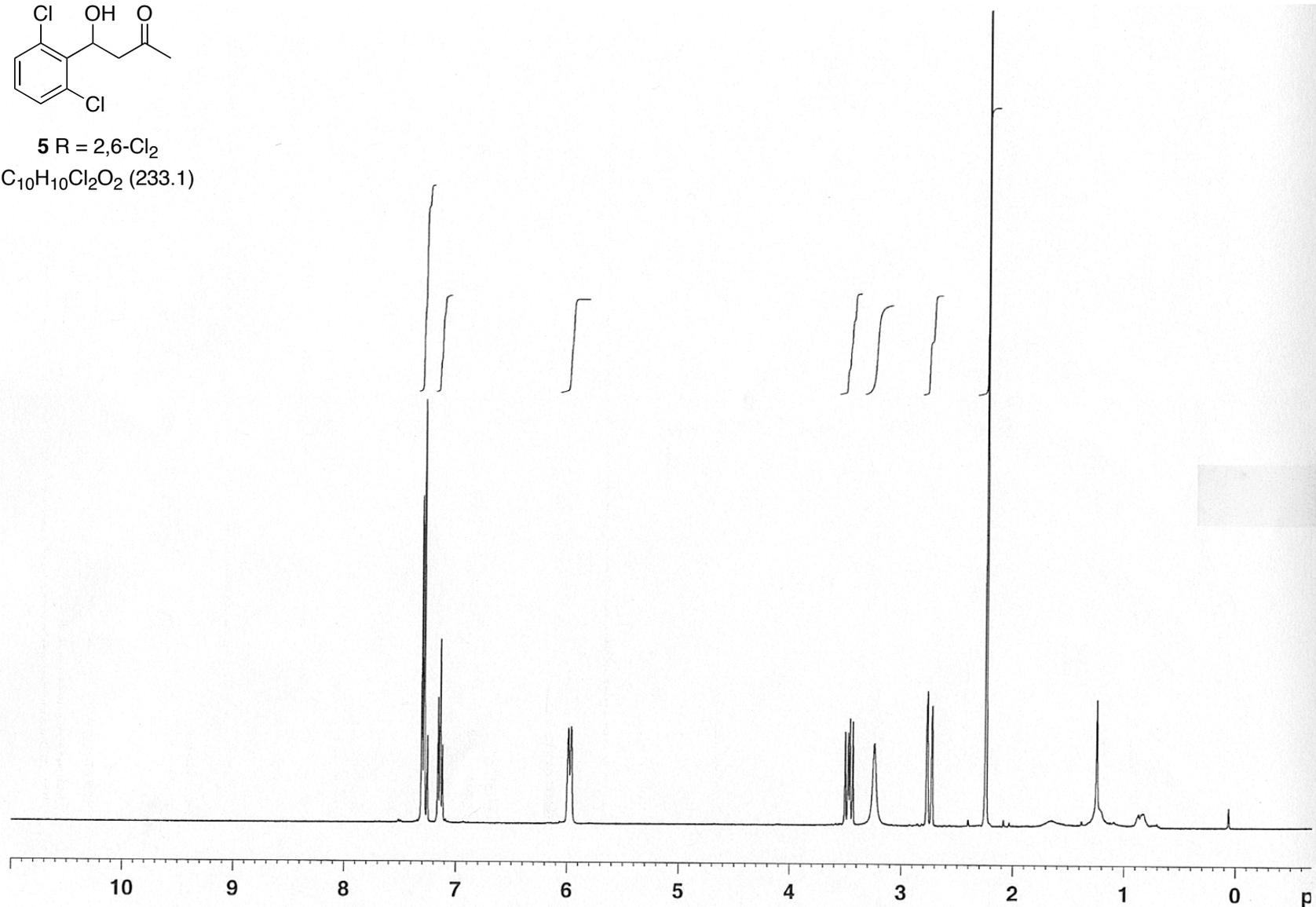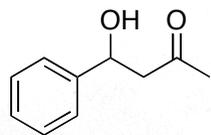
^{1}H NMR: 400 MHz, CDCl$_3$

5 R = H

C$_{10}$H$_{12}$O$_2$ (164.2)
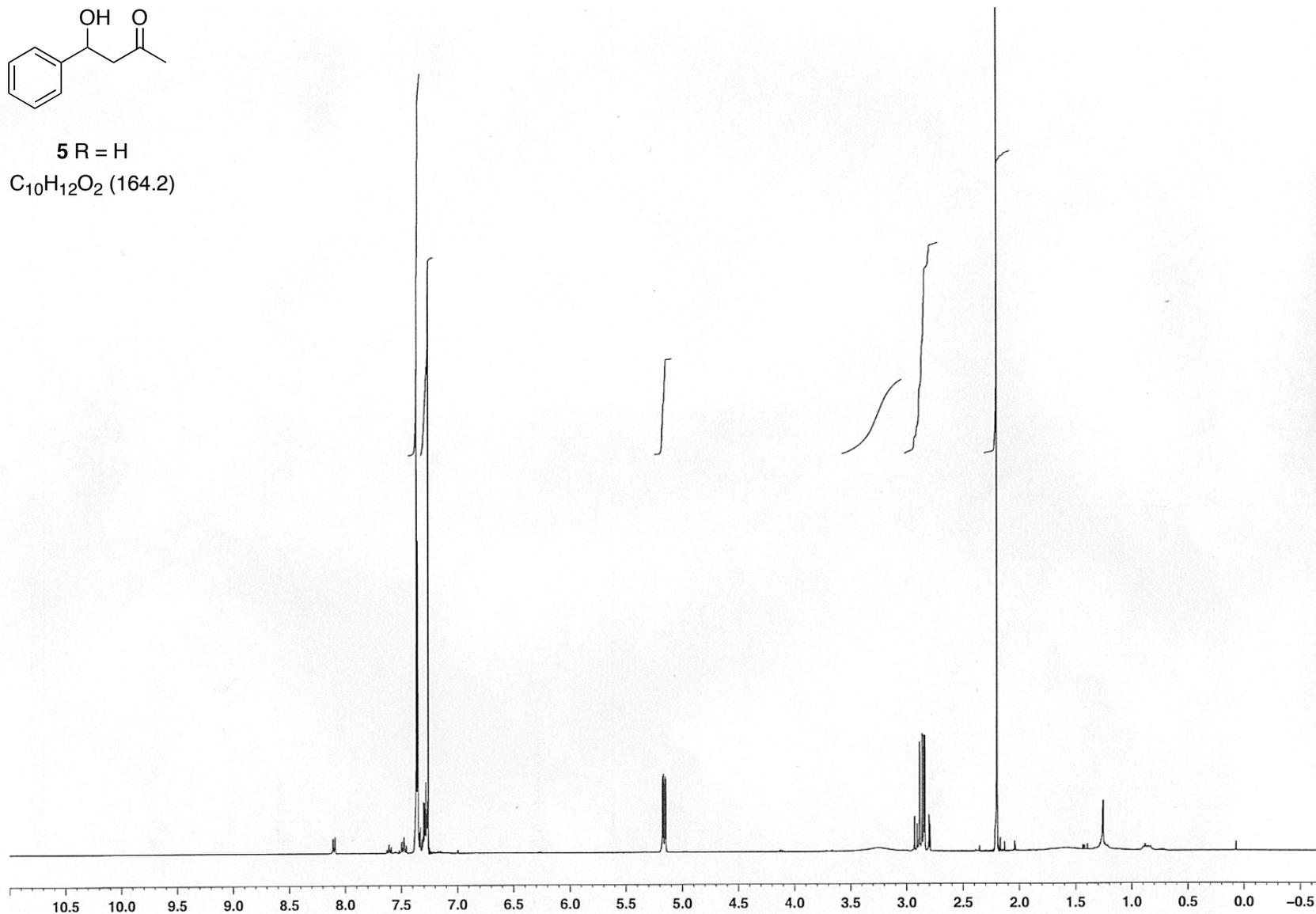
^{1}H NMR: 400 MHz, CDCl$_3$

5 R = 4-Me

C$_{11}$H$_{14}$O$_2$ (178.2)