Organocatalysis in Water at Room Temperature with *In-Flask* Catalyst Recycling

Bruce H. Lipshutz,* Subir Ghorai

Department of Chemistry & Biochemistry
University of California, Santa Barbara, California 93106

lipshutz@chem.ucsb.edu

Supporting Information

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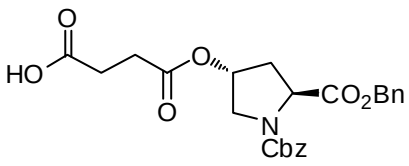
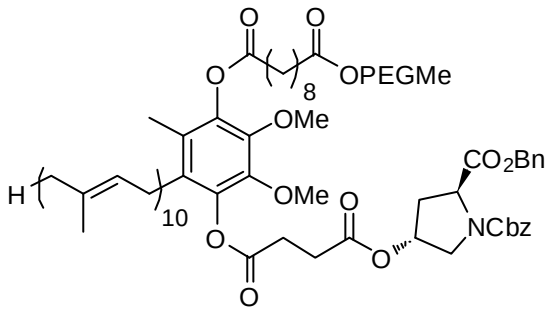
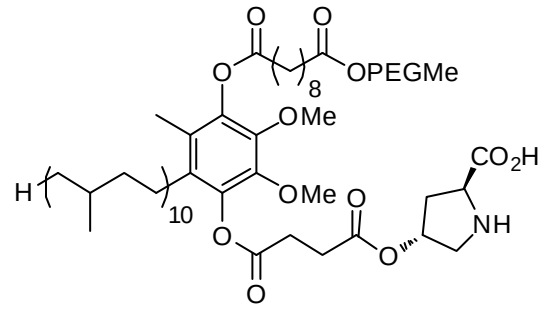
General Information: All reactions were performed either in a round bottom flask or screw cap glass vials containing a Teflon coated stir bar and septum. Column chromatography was performed using 60 Å flash silica gel. Thin-Layer-Chromatography analysis was conducted using commercially available silica gel 60 F_{254} plates. Nuclear Magnetic Resonance spectra were obtained in $CDCl_3$, with proton and carbon resonances at 400 and 100 MHz, respectively, and are referenced to the residual solvent signal at 7.27 ppm for ^1H and δ 77.23 ppm for ^{13}C. Data for ^1H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, sep = septet), coupling constant and integration. Data for ^{13}C NMR are reported in terms of chemical shift. Infrared spectra were obtained either neat or by thin-flim on NaCl plates and are reported as cm^{-1}. All commercially available reagents were used without further purification.



4-(((2*S*,4*R*)-1,2-bis((benzyloxy)carbonyl)pyrrolidin-4-yl)oxy)-4-oxobutanoic acid (4). To a solution of (2*S*,4*R*)-dibenzyl 4-hydroxypyrrolidine-1,2-dicarboxylate (**3**)[1] (1.00 g, 2.82 mmol) and succinic anhydride (0.70 g, 7.00 mmol) in pyridine (12 mL), DMAP (0.069 g, 0.56 mmol) was added and the stirring was continued at 22 °C for 12 h. The reaction mixture was added to 1(N) HCl (100 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with 1(N) HCl (3 x 50 mL), water (2 x 30 mL), dried over Na_2SO_4 and concentrated *in vacuo* affording a pale yellow liquid, which was purified by flash column chromatography on silica gel eluting with 40% EtOAC/hexane afforded the title compound **4** (1.25 g, 98%) as a colorless liquid. IR (neat): 3498, 3065, 3034, 2954, 1739, 1712, 1498, 1455, 1420, 1355, 1266, 1167, 1128, 1067, 1004, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.19 (m, 10H), 5.34-5.28 (m, 1H), 5.24 (d, *J* = 12.4 Hz, 0.5H), 5.17 (d, *J* = 12.4 Hz, 0.5H), 5.167 (s, 1H), 5.06 (s, 1H), 5.00 (s, 1H), 4.55 (t, *J* = 8.0 Hz, 0.5H), 4.48 (t, *J* = 8.0 Hz, 0.5H), 3.79-3.67 (m, 2H), 2.67-2.56 (m, 4H), 2.47-2.40 (m, 1H), 2.26-2.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 172.2, 172.0, 171.71, 171.67, 155.0, 154.4, 136.4, 136.2, 135.5, 135.3, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 73.2, 72.4, 67.6, 67.3, 67.2, 58.1, 57.9, 52.7, 52.3, 36.7, 35.6, 29.0, 28.9, 28.8; MS (ESI): *m/z* 478 (M + Na); HRMS (ESI) calcd for $C_{24}H_{25}NO_8Na$ $[M + Na]^+$ = 478.1478, found 478.1458.

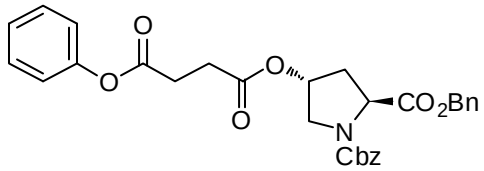


Compound 5 (precursor to catalyst 2). PQS[2] (**1**) (1.9 g, 0.63 mmol) and 4-(((2*S*,4*R*)-1,2-bis((benzyloxy)carbonyl)pyrrolidin-4-yl)oxy)-4-oxobutanoic acid (**4**) (0.43 g, 0.94 mmol) were dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDC) (0.24 g, 1.25 mmol), and DMAP (0.03 g, 0.24 mmol) were then directly added in succession to the mixture as solids. Et_3N (0.19 mL, 1.36 mmol) was added through a syringe. The resulting mixture was stirred at 22 °C for 20 h. Water was added to the reaction mixture and extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, water, brine, dried and concentrated *in vacuo* affording a colorless liquid, which was purified by flash column chromatography on silica gel, eluting with EtOAc, followed by CH_2Cl_2 to 8% MeOH/CH_2Cl_2 gradient afforded the compound **5** (1.85 g, 96%) as a white foam. IR (neat): 2954, 2858, 1740, 1714, 1644, 1455, 1417, 1350, 1325, 1291, 1250, 1100, 950, 914, 849, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.21 (m, 10H), 5.34-5.28 (m, 1H), 5.24 (d, *J* = 12.0 Hz, 0.5H), 5.18-4.96 (m, 13.5H), 4.55 (t, *J* = 8.0 Hz, 0.5H), 4.48 (t, *J* = 8.0 Hz, 0.5H), 4.24-4.22 (m, 2H), 3.85-3.69 (m, 8H), 3.68-3.46 (m, PEG), 3.39 (s, 3H), 3.20-3.16 (m, 2H), 2.94-2.89 (m, 2H), 2.74-2.69 (m, 2H), 2.63-2.55 (m, 4H), 2.45-2.41 (m, 1H), 2.34 (t, *J* = 7.6 Hz, 2H), 2.22-2.14 (m, 1H), 2.09-1.98 (m, 39H), 1.78-1.68 (m, 8H), 1.63-1.57 (m, 29H), 1.42-1.33 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 171.5, 171.3, 171.0, 169.8, 154.2, 153.6, 143.1, 143.0, 142.9, 142.8, 140.4, 140.0, 139.7, 135.9, 135.8, 135.2, 135.1, 134.9, 134.5, 134.3, 130.6, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.4, 124.5, 124.0, 123.9, 123.6, 120.9, 72.6, 71.9, 71.5, 70.2, 69.6, 68.7, 66.8, 66.5, 66.4, 62.9, 60.2, 60.1, 58.6, 57.6, 57.2, 52.1, 51.7, 39.3, 39.2, 36.1, 35.0, 33.7, 33.5, 28.7, 28.6, 28.2, 26.3, 26.2, 25.8, 25.4, 24.6, 24.4, 17.3, 15.9, 15.6, 11.7; MS (ESI): m/3z ~ 1198 $(M + 3Na)^{+3}$.

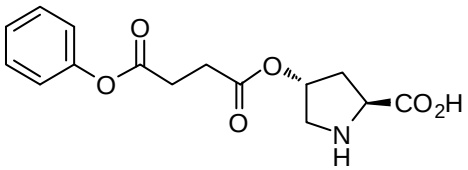


Catalyst 2. A well-stirred suspension of compound **5** (1.61 g) and Pd/C (10% w/w, 160 mg) in dry MeOH (20 mL) was fitted to a source of hydrogen (1 atm) and stirred at 22 °C for 12 h. The mixture was filtered through a pad of celite and washed with MeOH. The combined filtrates were concentrated *in vacuo* afforded the compound **2** (1.47 g, 98%) as a white waxy solid. IR (neat): 3532, 2871, 1759, 1737, 1601, 1466, 1376, 1345, 1280, 1243, 1112, 1062, 949, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.32 (br s, 1H), 4.23-4.21 (m, 2H), 3.84-3.69 (m, 8H), 3.68-3.45 (m, PEG), 3.38 (s, 3H), 2.94-2.72 (m, 4H), 2.60-2.54 (m, 2H), 2.48-2.38 (m, 2H), 2.33 (t, *J* = 7.6 Hz, 2H), 2.05 (br s, 3H),

1.79-1.72 (m, 2H), 1.65-1.59 (m, 2H), 1.55-1.49 (m, 2H), 1.38-1.04 (m, 74H), 0.96-0.83 (m, 33H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 171.15, 171.1, 170.9, 170.0, 142.7, 140.4, 139.9, 139.6, 129.2, 123.8, 71.5, 70.1, 69.7, 68.7, 62.8, 60.1, 58.5, 38.9, 37.0, 36.92, 36.89, 36.8, 36.6, 33.6, 32.3, 32.2, 28.6, 27.5, 24.6, 24.4, 24.3, 24.0, 22.3, 22.2, 19.44, 19.37, 19.31, 11.5; MS (ESI): m/3z ~ 1124 $(M + 3Na)^{+3}$.



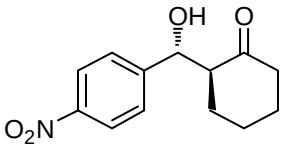
(2*S*,4*R*)-dibenzyl 4-((4-oxo-4-phenoxybutanoyl)oxy)pyrrol- idine-1,2-dicarboxylate (precursor to catalyst 6). Phenol (9.4 mg, 0.10 mmol) and 4-(((2*S*,4*R*)-1,2-bis((benzyloxy)carbonyl) pyrrolidin-4-yl)oxy)-4-oxobutanoic acid (**4**) (55 mg, 0.12 mmol) were dissolved in CH_2Cl_2 (1.5 mL) and cooled to 0 °C. 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDC) (38 mg, 0.2 mmol), and DMAP (5.5 mg, 0.045 mmol) were then directly added in succession to the mixture as solids. Et_3N (31 μL, 0.22 mmol) was added through a syringe. The resulting mixture was stirred at 22 °C for 12 h. Water was added to the reaction mixture and extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, water, brine, dried and concentrated *in vacuo* affording a colorless liquid, which was purified by flash column chromatography on silica gel, eluting with 15% EtOAC/hexane afforded the title compound (52 mg, 98%) as a colorless liquid. $[\alpha]^{20}_D$ = -38.2 (c = 1.60, $CHCl_3$); IR (neat): 3064, 3033, 2950, 2887, 1736, 1708, 1592, 1493, 1420, 1354, 1263, 1164, 1069, 1005, 918, 882, 816, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 11H), 7.23 (td, *J* = 7.6, 1.2 Hz, 2H), 7.10 (dt, *J* = 7.6, 1.2 Hz, 2H), 5.38-5.33 (m, 1H), 5.26 (d, *J* = 12.4 Hz, 0.5H), 5.18 (d, *J* = 12.4 Hz, 0.5H), 5.16 (s, 1H), 5.07 (s, 1H), 5.01 (s, 1H), 5.58 (t, *J* = 8.0 Hz, 0.5H), 4.50 (t, *J* = 8.0 Hz, 0.5H), 3.83-3.78 (m, 1.5H), 3.71 (d, *J* = 12.4 Hz, 0.5H), 2.94-2.86 (m, 2H), 2.75-2.70 (m, 2H), 2.50-2.42 (m, 1H), 2.28-2.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 171.6, 171.5, 170.8, 154.9, 154.3, 150.7, 136.5, 136.4, 135.6, 135.4, 129.6, 128.7, 128.65, 128.6, 128.5, 128.3, 128.25, 128.2, 128.0, 126.0, 121.5, 73.2, 72.5, 67.5, 67.2, 67.1, 58.2, 57.9, 52.7, 52.3, 36.8, 35.7, 29.3, 29.26; MS (ESI): *m/z* 554 (M + Na), 570 (M + K); HRMS (ESI) calcd for $C_{30}H_{29}NO_8Na$ $[M + Na]^+$ = 554.1791, found 554.1778.



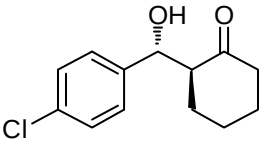
Catalyst 6. A well-stirred suspension of (2*S*,4*R*)-dibenzyl 4-((4-oxo-4-phenoxybutanoyl)oxy)pyrrol- idine-1,2-dicarboxylate (45 mg) and Pd/C (10% w/w, 5 mg) in dry MeOH (1 mL) was fitted to a source of hydrogen (1 atm) and stirred at 22 °C for 12 h. The mixture was filtered through a pad of celite and washed with MeOH. The combined filtrates were concentrated *in vacuo* afforded the compound **6** (26 mg, 99%) as a colorless liquid. IR (neat): 3536, 2852, 1758, 1739, 1600, 1458, 1353, 1300, 1256, 1104, 954, 849 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (t, *J*

= 7.2 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 5.29 (br s, 1H), 4.02 (br s, 1H), 3.60 (br s, 1H), 3.15 (br s, 1H), 2.82 (br s, 2H), 2.67 (br s, 2H), 2.28 (br s, 2H); MS (ESI): *m/z* 330 (M + Na); HRMS (ESI) calcd for $C_{15}H_{17}NO_6Na$ $[M + Na]^+$ = 330.0954, found 330.0952.

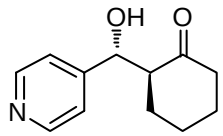
General procedure for the asymmetric direct aldol reaction using the catalyst 2 in water. Aromatic aldehyde **7** (0.10 mmol), ketone **8** (0.50 mmol) and catalyst **2** (33 mg, 0.01 mmol) were sequentially added into a Teflon-coated-stir-bar-containing glass vial at room temperature. H_2O (0.25 mL) was added and the resulting solution was allowed to stir at room temperature for 18-48 hours. The homogeneous reaction mixture was then diluted with EtOAc (1 mL), filtered through a bed of silica gel layered over Celite, and the bed further washed (3 x 4 mL) with EtOAc to collect all of the aldol product material. The volatiles were removed *in vacuo* to afford the crude product which was subsequently purified by flash chromatography on silica gel (sovent noted) to afford the title compounds.



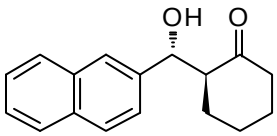
(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(4-nitrophenyl)methyl]cyclohexanone [(2*S*,1′*R*)-].[3] The representative procedure was followed using 4-nitrobenzaldehyde (15 mg, 0.10 mmol), cyclohexanone (52 μL, 0.50 mmol) and catalyst **2** (33 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 20% EtOAc/hexanes) afforded the product as a white solid (23 mg, 93%). Enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak AD, *i*PrOH/hexane = 20:80), λ = 254 nm, flow rate 0.5 mL/min, t_{Rminor} = 24.172 min, t_{Rmajor} = 31.140 min; Data for the *anti* isomer (2*S*,1′*R*): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 4.90 (dd, *J* = 8.4, 3.2 Hz, 1H), 4.09 (d, *J* = 3.2 Hz, 1H), 2.63-2.56 (m, 1H), 2.54-2.48 (m, 1H), 2.42-2.33 (m, 1H), 2.16-2.10 (m, 1H), 1.86-1.82 (m, 1H), 1.73-1.66 (m, 1H), 1.64-1.52 (m, 2H), 1.44-1.37 (m, 1H).



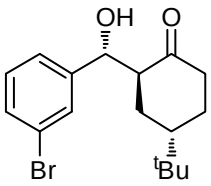
(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(4-chlorophenyl)methyl]cyclohexanone [(2*S*,1′*R*)-9a].[3] The representative procedure was followed using 4-chlorobenzaldehyde (14 mg, 0.10 mmol), cyclohexanone (52 μL, 0.50 mmol) and catalyst **2** (33 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 20% EtOAc/hexanes) afforded the product as a colorless oil (21 mg, 88%). Enantiomeric excess: 90%, determined by HPLC (Daicel Chiralpak AD, *i*PrOH/hexane = 10:90), λ = 254 nm, flow rate 0.5 mL/min, t_{Rminor} = 27.468 min, t_{Rmajor} = 32.012 min; Data for the *anti* isomer (2*S*,1′*R*)-**9a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.74 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.97 (d, *J* = 2.4 Hz, 1H), 2.58-2.44 (m, 2H), 2.38-2.28 (m, 1H), 2.09-2.05 (m, 1H), 1.80-1.76 (m, 1H), 1.66-1.50 (m, 3H), 1.29-1.25 (m, 1H).



(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(4-pyridyl)methyl]cyclohexanone [(2*S*,1′*R*)-9b].[4] The representative procedure was followed using 4-pyridinecarboxaldehyde (9.4 μL, 0.10 mmol), cyclohexanone (52 μL, 0.50 mmol) and catalyst **2** (33 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 75% EtOAc/hexanes) afforded the product as a white solid (18 mg, 90%). Enantiomeric excess: 90%, determined by HPLC (Daicel Chiralpak AD, *i*PrOH/hexane = 10:90), λ = 254 nm, flow rate 0.5 mL/min, t_{Rminor} = 52.096 min, t_{Rmajor} = 54.132 min; Data for the *anti* isomer (2*S*,1′*R*)-**9b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, *J* = 6.0 Hz, 2H), 7.26 (d, *J* = 6.0 Hz, 2H), 4.78 (dd, *J* = 8.4, 3.2 Hz, 1H), 4.02 (d, *J* = 3.2 Hz, 1H), 2.63-2.56 (m, 1H), 2.52-2.47 (m, 1H), 2.37 (tdd, *J* = 13.2, 6.0, 1.2 Hz, 1H), 2.16-2.09 (m,1H), 1.87-1.82 (m, 1H), 1.74-1.52 (m, 3H), 1.46-1.35 (m, 1H).

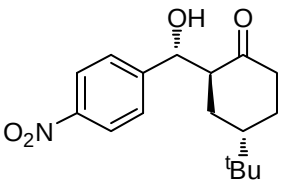


(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(2-naphthyl)methyl]cyclohexanone [(2*S*,1′*R*)-9c].[4] The representative procedure was followed using 2-naphthaldehyde (15.6 mg, 0.10 mmol), cyclohexanone (52 μL, 0.50 mmol) and catalyst **2** (33 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 20% EtOAc/hexanes) afforded the product as a white solid (19 mg, 74%). Enantiomeric excess: 92%, determined by HPLC (Daicel Chiralpak AD, *i*PrOH/hexane = 5:95), λ = 254 nm, flow rate 0.5 mL/min, t_{Rminor} = 93.228 min, t_{Rmajor} = 96.688 min; Data for the *anti* isomer (2*S*,1′*R*)-**9c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.83 (m, 3H), 7.76 (s, 1H), 7.50-7.47 (m, 3H), 4.98 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.07 (d, *J* = 2.4 Hz, 1H), 2.76-2.69 (m, 1H), 2.55-2.49 (m, 1H), 2.40 (tdd, *J* = 13.2, 6.0, 1.2 Hz, 1H), 2.14-2.06 (m, 1H), 1.80-1.73 (m, 1H), 1.71-1.48 (m, 3H), 1.40-1.30 (m, 1H).

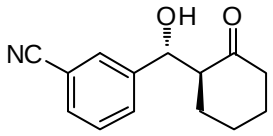


(2*S*,4*S*,1′*R*)-4-*tert*-Butyl-2-[1′-Hydroxy-1′-(3-bromophenyl)methyl]cyclohexanone [(2*S*,4*S*,1′*R*)-9d]. The representative procedure was followed using 3-bromobenzaldehyde (18.5 mg, 0.10 mmol), 4-*tert*-butylcyclohexanone (77 mg, 0.50 mmol) and catalyst **2** (33 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 20% EtOAc/hexanes) afforded the product as a white solid (27 mg, 80%). Enantiomeric excess: 91%, determined by HPLC (Daicel Chiralpak AD, *i*PrOH/hexane = 10:90), λ = 254 nm, flow rate 0.5 mL/min, t_{Rminor} = 15.520 min, t_{Rmajor} = 71.464 min; Data for the *anti* isomer (2*S*,4*S*,1′*R*)-**9d**: $[\alpha]^{20}_D$ = -61.6 (c = 1.00, $CHCl_3$); m.p.: 119-123 °C; IR (thin film): 3375, 2955, 2868, 1694, 1595, 1571, 1469, 1434, 1365, 1334, 1226, 1155,1097, 1071, 1052, 793 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (t, *J* = 1.6 Hz, 1H), 7.46 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.29 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 4.86 (d, *J* = 9.6 Hz, 1H), 2.63 (dt, *J* = 9.2, 6.8 Hz, 1H), 2.54-2.42 (m, 2H), 2.03-1.99 (m, 1H), 1.63-1.50 (m, 2H), 1.49-1.36 (m, 2H), 0.80 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.9, 143.9, 131.5, 130.3, 130.2, 125.7,

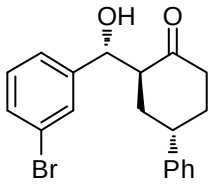
122.9, 74.4, 55.4, 42.4, 39.4, 33.0, 27.8, 27.3, 25.4; MS (ESI): *m/z* 361 (M + Na), 363 (M + 2 + Na); HRMS (ESI) calcd for $C_{17}H_{23}O_2BrNa$ $[M + Na]^+$ = 361.0779, found 361.0776.



(2*S*,4*S*,1′*R*)-4-*tert*-Butyl-2-[1′-Hydroxy-1′-(4-nitrophenyl)methyl]cyclohexanone [(2*S*,4*S*,1′*R*)-9e].[5] The representative procedure was followed using 4-nitrobenzaldehyde (15 mg, 0.10 mmol), 4-*tert*-butylcyclohexanone (77 mg, 0.50 mmol) and catalyst **2** (33 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 30% EtOAc/hexanes) afforded the product as a white solid (26 mg, 85%). Enantiomeric excess: 79%, determined by HPLC (Daicel Chiralpak AD, *i*PrOH/hexane = 20:80), λ = 254 nm, flow rate 0.5 mL/min, t_{Rminor} = 16.896 min, t_{Rmajor} = 30.708 min; Data for the *anti* isomer (2*S*,4*S*,1′*R*)-**9e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 4.97 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.63 (d, *J* = 2.8 Hz, 1H), 2.67 (dt, *J* = 8.8, 7.2 Hz, 1H), 2.57-2.51 (m, 1H), 2.47-2.38 (m, 1H), 1.99-1.96 (m, 1H), 1.62-1.38 (m, 4H), 0.79 (s, 9H).

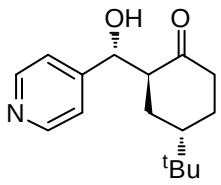


(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(3-cyanophenyl)methyl]cyclohexanone [(2*S*,1′*R*)-9f]. The representative procedure was followed using 3-cyanobenzaldehyde (13 mg, 0.10 mmol), cyclohexanone (52 μL, 0.50 mmol) and catalyst **2** (33 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 20% EtOAc/hexanes) afforded the product as a white solid (18 mg, 80%). Enantiomeric excess: 97%, determined by HPLC (Daicel Chiralpak AD, *i*PrOH/hexane = 10:90), λ = 273 nm, flow rate 0.5 mL/min, t_{Rmajor} = 46.924 min, t_{Rminor} = 60.276 min; Data for the *anti* isomer (2*S*,1′*R*)-**9f**: $[\alpha]^{20}_D$ = +28.0 (c = 0.30, $CHCl_3$); m.p.: 69-72 °C; IR (thin film): 3498, 2941, 2864, 2229, 1704, 1483, 1449, 1434, 1311, 1229, 1130, 1042, 805 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (t, *J* = 1.2 Hz, 1H), 7.60 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.57 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 4.82 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.08 (d, *J* = 2.8 Hz, 1H), 2.61-2.54 (m, 1H), 2.53-2.48 (m, 1H), 2.41-2.33 (m, 1H), 2.15-2.09 (m, 1H), 1.85-1.80 (m, 1H), 1.67 (qt, *J* = 12.8, 4.0 Hz, 1H), 1.59-1.51 (m, 2H), 1.35 (qd, *J* = 12.8, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.1, 142.8, 131.7, 130.9, 129.4, 118.9, 112.7, 74.2, 57.3, 42.8, 30.9, 27.8, 24.9; MS (ESI): *m/z* 252 (M + Na); HRMS (ESI) calcd for $C_{14}H_{15}NO_2Na$ $[M + Na]^+$ = 252.1000, found 252.0993.

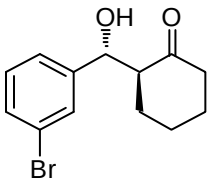


(2*S*,4*S*,1′*R*)-4-Phenyl-2-[1′-Hydroxy-1′-(3-bromophenyl)methyl]cyclohexanone [(2*S*,4*S*,1′*R*)-9g]. The representative procedure was followed using 3-bromobenzaldehyde (18.5 mg, 0.10 mmol), 4-phenylcyclohexanone (87 mg, 0.50 mmol) and catalyst **2** (33 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 20% EtOAc/hexanes) afforded the product as a white solid (29.5 mg, 82%). Enantiomeric excess: 86%, determined by HPLC (Daicel Chiralpak AD, *i*PrOH/hexane = 20:80), λ = 218 nm, flow rate

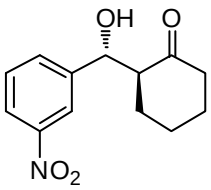
1.0 mL/min, t_{Rminor} = 16.316 min, t_{Rmajor} = 86.196 min; Data for the *anti* isomer (2*S*,4*S*,1′*R*)-**9g**: $[\alpha]^{20}_{D}$ = -6.0 (c = 0.85, $CHCl_3$); m.p.: 109-112 °C; IR (thin film): 3417, 3060, 3028, 2931, 1710, 1596, 1571, 1496, 1456, 1429, 1326, 1197, 1155, 1071, 1040, 908, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (t, *J* = 1.6 Hz, 1H), 7.47 (dt, *J* = 7.2, 1.6 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.29 -7.22 (m, 3H), 7.47 (d, *J* = 7.2 Hz, 2H), 4.93 (d, *J* = 9.6 Hz, 1H), 3.38 (br s, 1H), 3.19-3.13 (m, 1H), 2.78 (dt, *J* = 9.6, 6.0 Hz, 1H), 2.63-2.50 (m, 2H), 2.41-2.33 (m, 1H), 2.23-2.15 (m, 1H), 2.01-1.94 (m, 1H), 1.79-1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.1, 143.6, 142.9, 131.6, 130.4, 130.3, 129.0, 126.8, 126.7, 125.9, 123.0, 74.3, 54.9, 39.2, 37.2, 34.6, 31.8; MS (ESI): *m/z* 381 (M + Na), 383 (M + 2 + Na); HRMS (ESI) calcd for $C_{19}H_{19}O_2BrNa$ $[M + Na]^+$ = 381.0466, found 381.0467.



(2*S*,4*S*,1′*R*)-4-*tert*-Butyl-2-[1′-Hydroxy-1′-(4-pyridyl)methyl]cyclohexanone [(2*S*, 4*S*,1′*R*)-9h]. The representative procedure was followed using 4-pyridinecarboxaldehyde (9.4 μL, 0.10 mmol), 4-*tert*-butylcyclohexanone (77 mg, 0.50 mmol) and catalyst **2** (33 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 75% EtOAc/hexanes) afforded the product as a white solid (22 mg, 85%). Enantiomeric excess: 75%, determined by HPLC (Daicel Chiralpak AD, *i*PrOH/hexane = 10:90), λ = 254 nm, flow rate 1.0 mL/min, t_{Rminor} = 14.548 min, t_{Rmajor} = 19.412 min; Data for the *anti* isomer (2*S*,4*S*,1′*R*)-**9h**: $[\alpha]^{20}_{D}$ = -68.0 (c = 0.47, $CHCl_3$); m.p.: 129-132 °C; IR (thin film): 3432, 2960, 2870, 1713, 1604, 1564, 1478, 1415, 1366, 1331, 1226, 1152, 1099, 1049, 1005, 829, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 6.0 Hz, 2H), 7.29 (d, *J* = 6.0 Hz, 2H), 4.85 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.55 (d, *J* = 3.2 Hz, 1H), 2.65 (dt, *J* = 9.2, 6.4 Hz, 1H), 2.53 (ddd, *J* = 16.8, 4.8, 2.8 Hz, 1H), 2.47-2.38 (m, 1H), 2.00-1.95 (m, 1H), 1.65-1.41 (m, 4H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.9, 151.3, 149.7, 122.1, 73.3, 55.3, 42.3, 39.3, 32.9, 27.9, 27.3, 25.7; MS (ESI): *m/z* 284 (M + Na), 262 (M + H); HRMS (ESI) calcd for $C_{16}H_{24}NO_2Na$ $[M + Na]^+$ = 284.1626, found 284.1625.



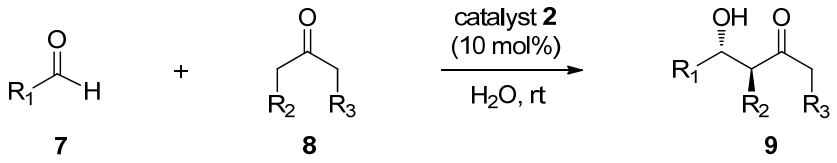
(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(3-bromophenyl)methyl]cyclohexanone [(2*S*,1′*R*)-9i].[6] The representative procedure was followed using 3-bromobenzaldehyde (18.5 mg, 0.10 mmol), cyclohexanone (52 μL, 0.50 mmol) and catalyst **2** (33 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 20% EtOAc/hexanes) afforded the product as a colorless oil (23 mg, 82%). Enantiomeric excess: 86%, determined by HPLC (Daicel Chiralpak AD, *i*PrOH/hexane = 10:90), λ = 254 nm, flow rate 0.5 mL/min, t_{Rmajor} = 25.464 min, t_{Rminor} = 27.408 min; Data for the *anti* isomer (2*S*,1′*R*)-**9i**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (t, *J* = 2.0 Hz, 1H), 7.43 (dt, *J* = 7.2, 2.0 Hz, 1H), 7.24-7.20 (m, 2H), 4.75 (d, *J* = 8.8 Hz, 1H), 2.58-2.51 (m, 1H), 2.49-2.46 (m, 1H), 2.41-2.33 (m, 1H), 2.13-2.08 (m, 1H), 1.84-1.79 (m, 1H), 1.69-1.55 (m, 3H), 1.38-1.27 (m, 1H).



(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(3-nitrophenyl)methyl]cyclohexanone [(2*S*,1′*R*)-9j].[3] The representative procedure was followed using 3-nitrobenzaldehyde (15 mg, 0.10 mmol), cyclohexanone (52 μL, 0.50 mmol) and catalyst **2** (33 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 20% EtOAc/hexanes) afforded the product as a white solid (22 mg, 91%). Enantiomeric excess: 91%, determined by HPLC (Daicel Chiralpak AD, *i*PrOH/hexane = 10:90), λ = 254 nm, flow rate 0.5 mL/min, t_{Rmajor} = 44.864 min, t_{Rminor} = 58.564 min; Data for the *anti* isomer (2*S*,1′*R*)-**9j**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (t, *J* = 1.2 Hz, 1H), 8.17 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.68 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 4.90 (dd, *J* = 8.4, 3.2 Hz, 1H), 4.13 (d, *J* = 3.2 Hz, 1H), 2.65-2.60 (m, 1H), 2.54-2.49 (m, 1H), 2.42-2.33 (m, 1H), 2.15-2.11 (m, 1H), 1.86-1.80 (m, 1H), 1.70-1.55 (m, 3H), 1.42-1.38 (m, 1H).

General procedure for catalyst recycling (Table 3). 4-nitrobenzaldehyde (60 mg, 0.40 mmol), cyclohexanone (208 μL, 2.00 mmol) and catalyst **2** (132 mg, 0.04 mmol) were sequentially added into a Teflon-coated-stir-bar-containing glass vial at room temperature. H_2O (1.0 mL) was added and the resulting solution was allowed to stir at room temperature for 24 hours. Then EtOAc (3 mL) was added to the reaction mixture and stirred for 10 sec. The reaction mixture was then allowed to separate and the upper (EtOAc) layer was removed by pippet. The aqueous layer was successively washed with EtOAc (3 x 3 mL). The combined EtOAc extracts layers were evaporated to afford the crude product, which was purified by flash column chromatography on silica gel eluting with 20% EtOAC/hexane afforded the aldol product. Then for the second run, above 4-nitrobenzaldehyde (60 mg, 0.40 mmol), cyclohexanone (208 μL, 2.00 mmol) were added again to the same reaction vessel and stirred at room temperature for another 24 hours. The work up was conducted in exactly the same way as described for the first cycle. This reaction was repeated two more times, each using the above substrates.

List of obvious difference between ***syn*-9** and ***anti*-9** on ^{1}H NMR



7 **8** **9**

entry	R_1	R_2 R_3	product	^{1}H NMR (-CHOH)	
				syn	***anti***
–	4-$O_2NC_6H_4$-	—$(CH_2)_3$—	---	5.48 (d, *J* = 1.6 Hz)	4.90 (dd, *J* = 8.4, 3.2 Hz)
1	4-ClC_6H_4-	—$(CH_2)_3$—	**9a**	5.34 (d, *J* = 2.0 Hz)	4.74 (dd, *J* = 8.8, 2.4 Hz)
2	4-pyridinyl-	—$(CH_2)_3$—	**9b**	5.39 (br s)	4.78 (dd, *J* = 8.4, 3.2 Hz)
3	2-naphthyl-	—$(CH_2)_3$—	**9c**	5.58 (d, *J* = 2.8 Hz)	4.98 (dd, *J* = 8.8, 2.4 Hz)
4	3-BrC_6H_4-	—$(CH_2CH^tBuCH_2)$—	**9d**	5.34 (d, *J* = 1.6 Hz)	4.86 (d, *J* = 8.6 Hz)
5	4-$O_2NC_6H_4$-	—$(CH_2CH^tBuCH_2)$—	**9e**	5.48 (d, *J* = 1.6 Hz)	4.97 (dd, *J* = 8.8, 2.8 Hz)
6	3-CNC_6H_4-	—$(CH_2)_3$—	**9f**	5.42 (br s)	4.82 (dd, *J* = 8.4, 2.8 Hz)
7	3-BrC_6H_4-	—$(CH_2CHPhCH_2)$ —	**9g**	5.41 (d, *J* = 1.6 Hz)	4.93 (d, *J* = 9.6 Hz)
8	4-pyridinyl-	—$(CH_2CH^tBuCH_2)$—	**9h**	5.33 (d, *J* = 1.6 Hz)	4.85 (dd, *J* = 9.2, 3.2 Hz)
9	3-BrC_6H_4-	—$(CH_2)_3$—	**9i**	5.36 (d, *J* = 1.6 Hz)	4.75 (d, *J* = 8.8 Hz)
10	3-$O_2NC_6H_4$-	—$(CH_2)_3$—	**9j**	5.48 (d, *J* = 2.0 Hz)	4.90 (dd, *J* = 8.4, 3.2 Hz)

References

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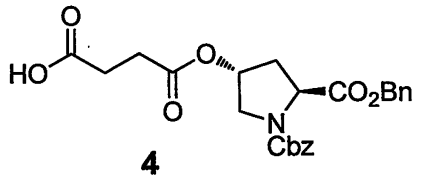

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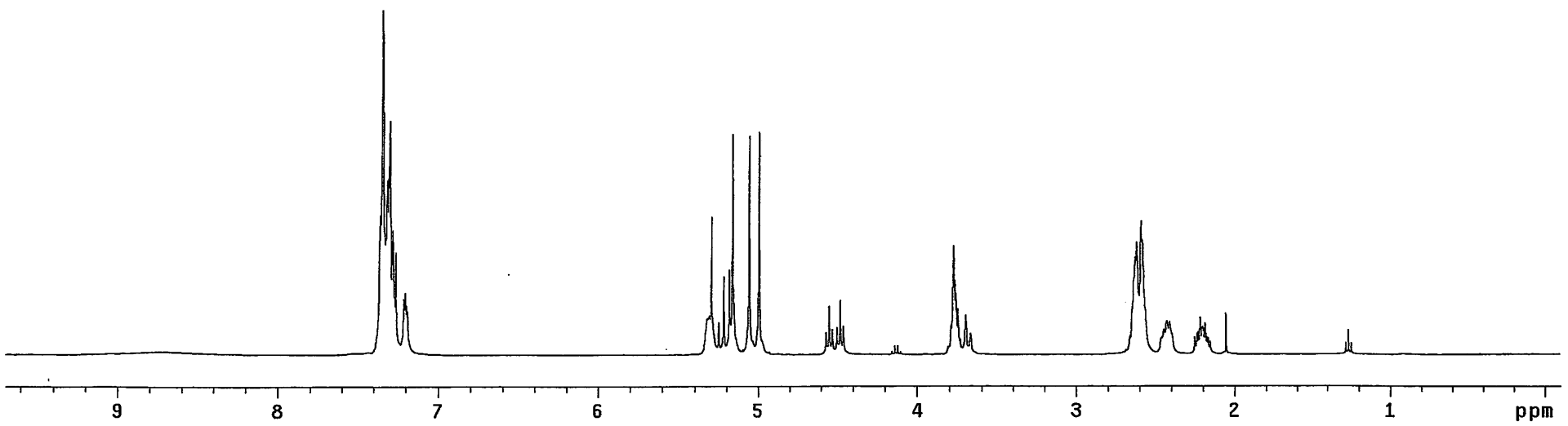

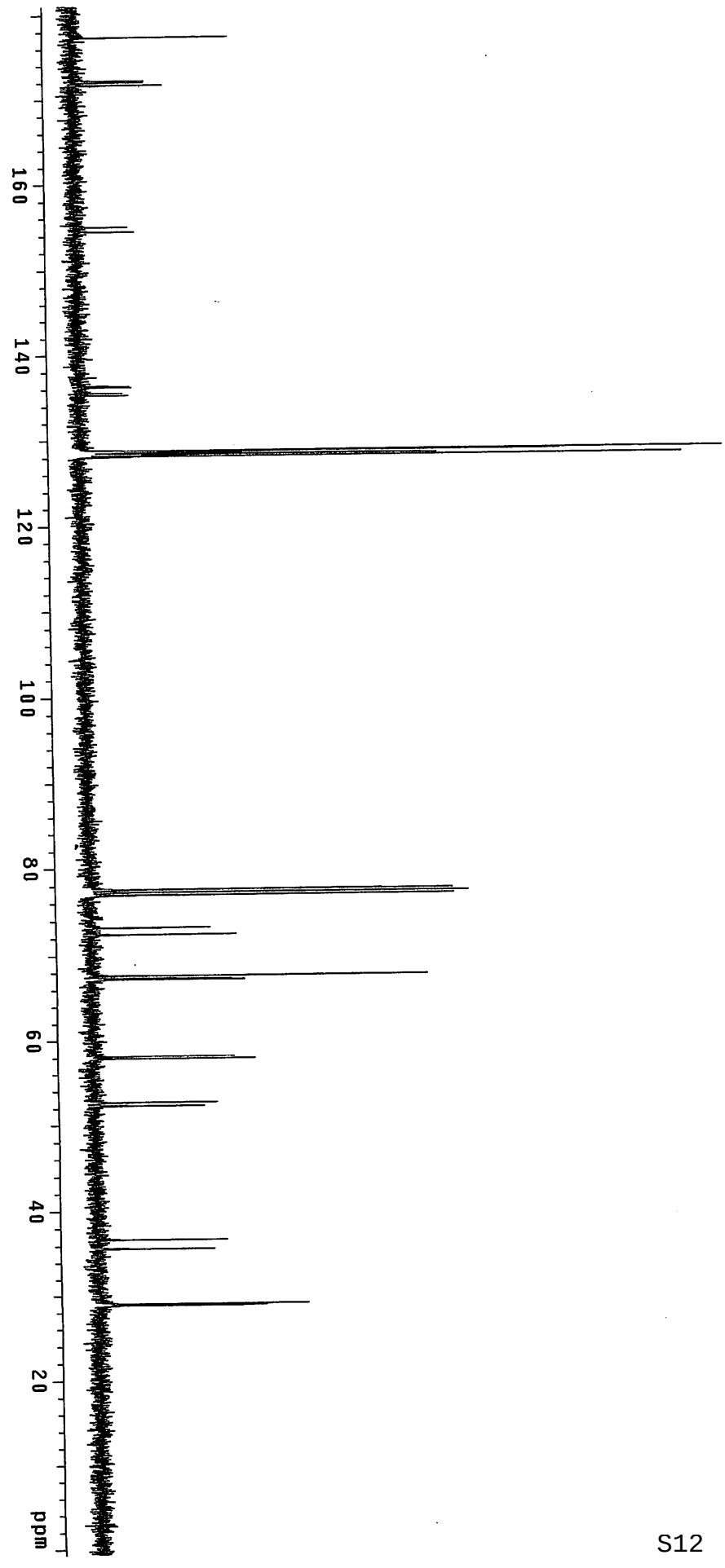

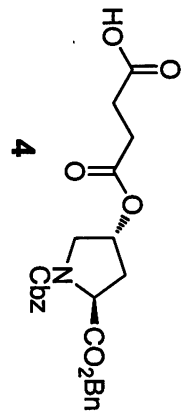

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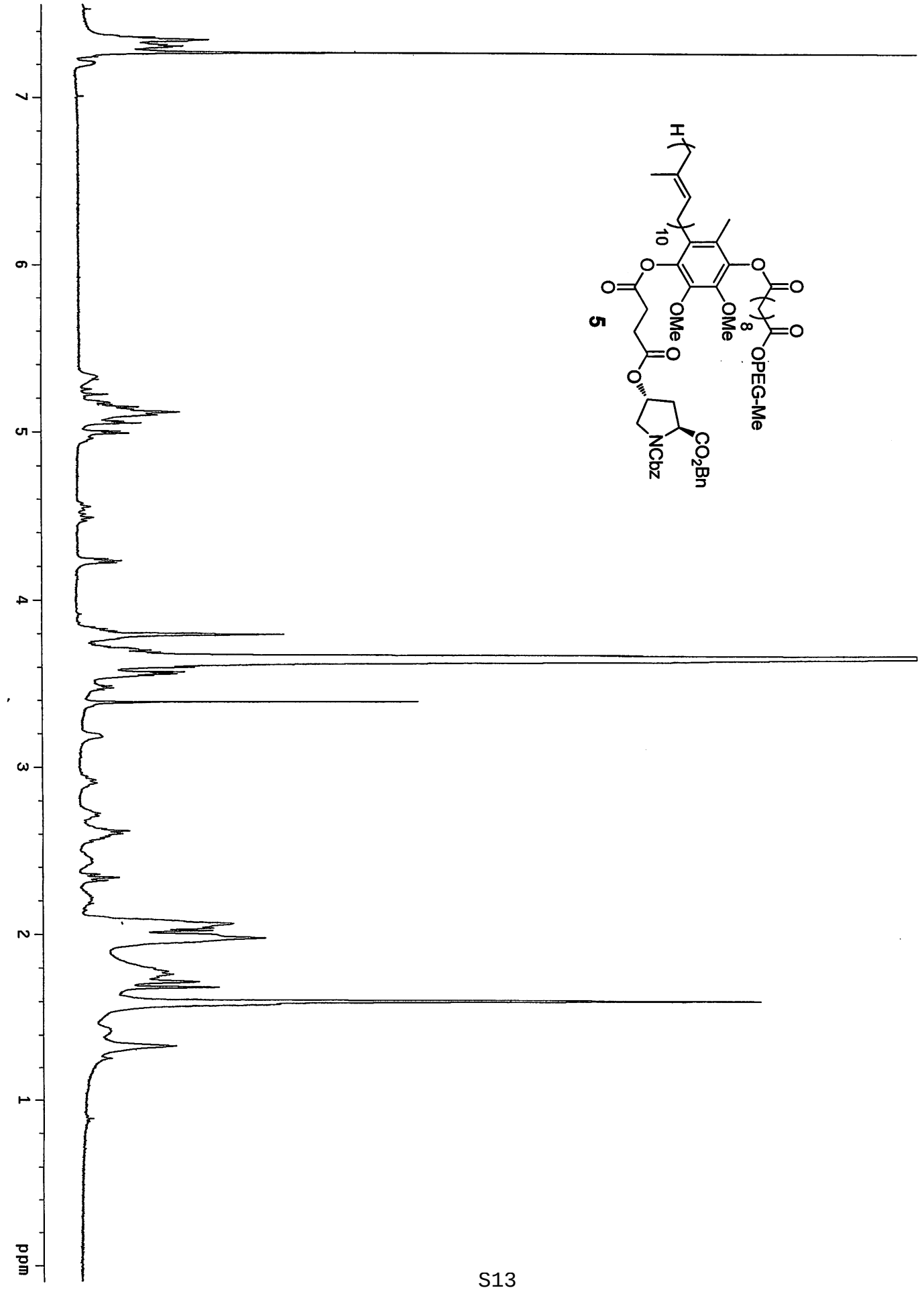
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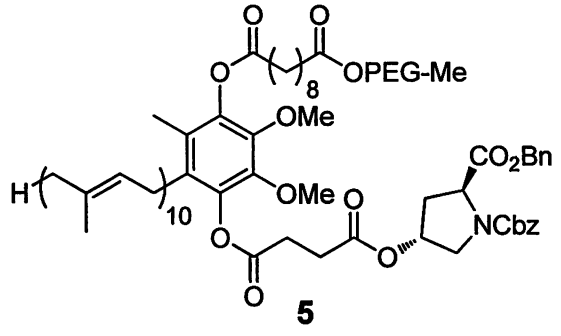

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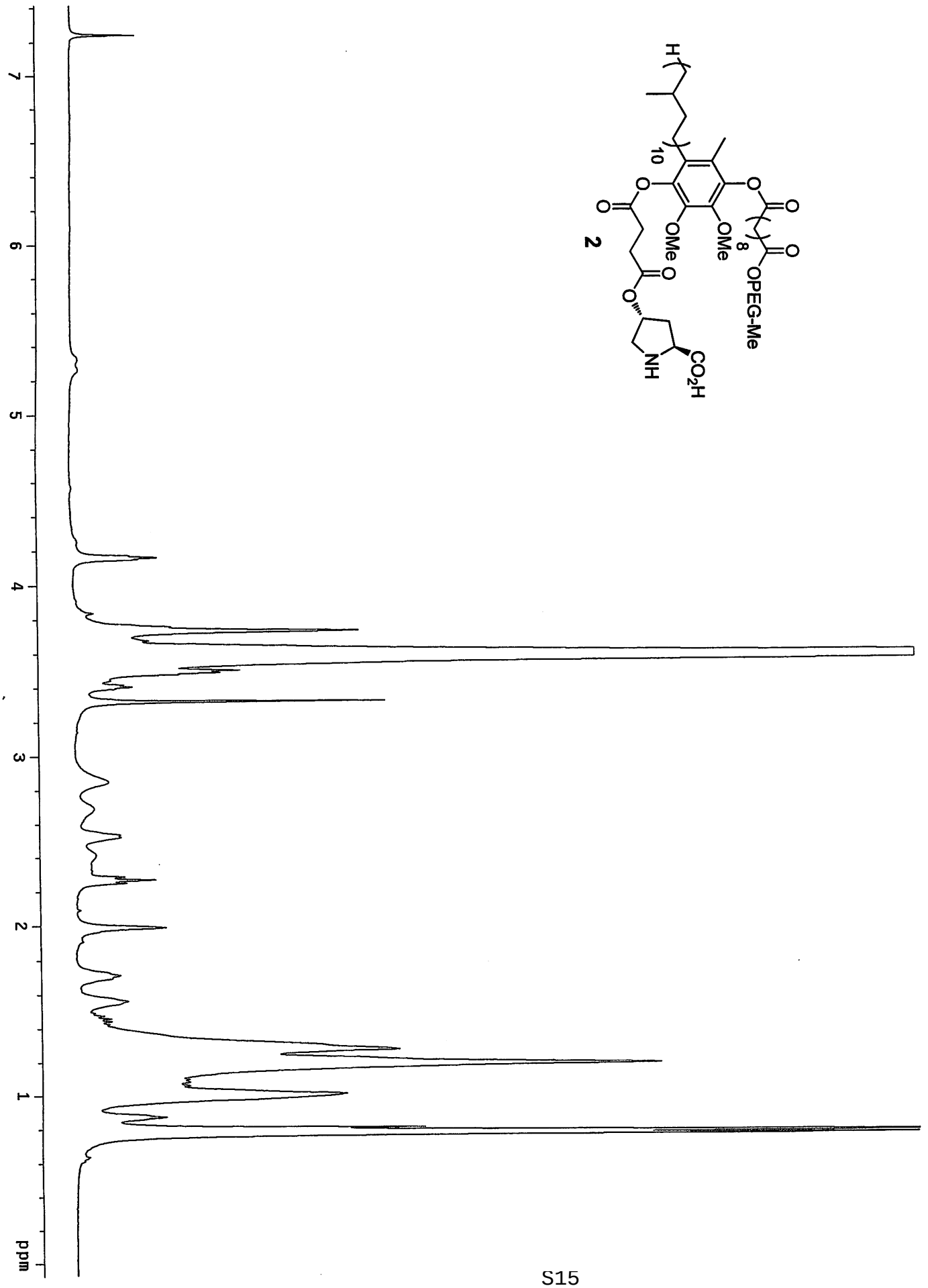
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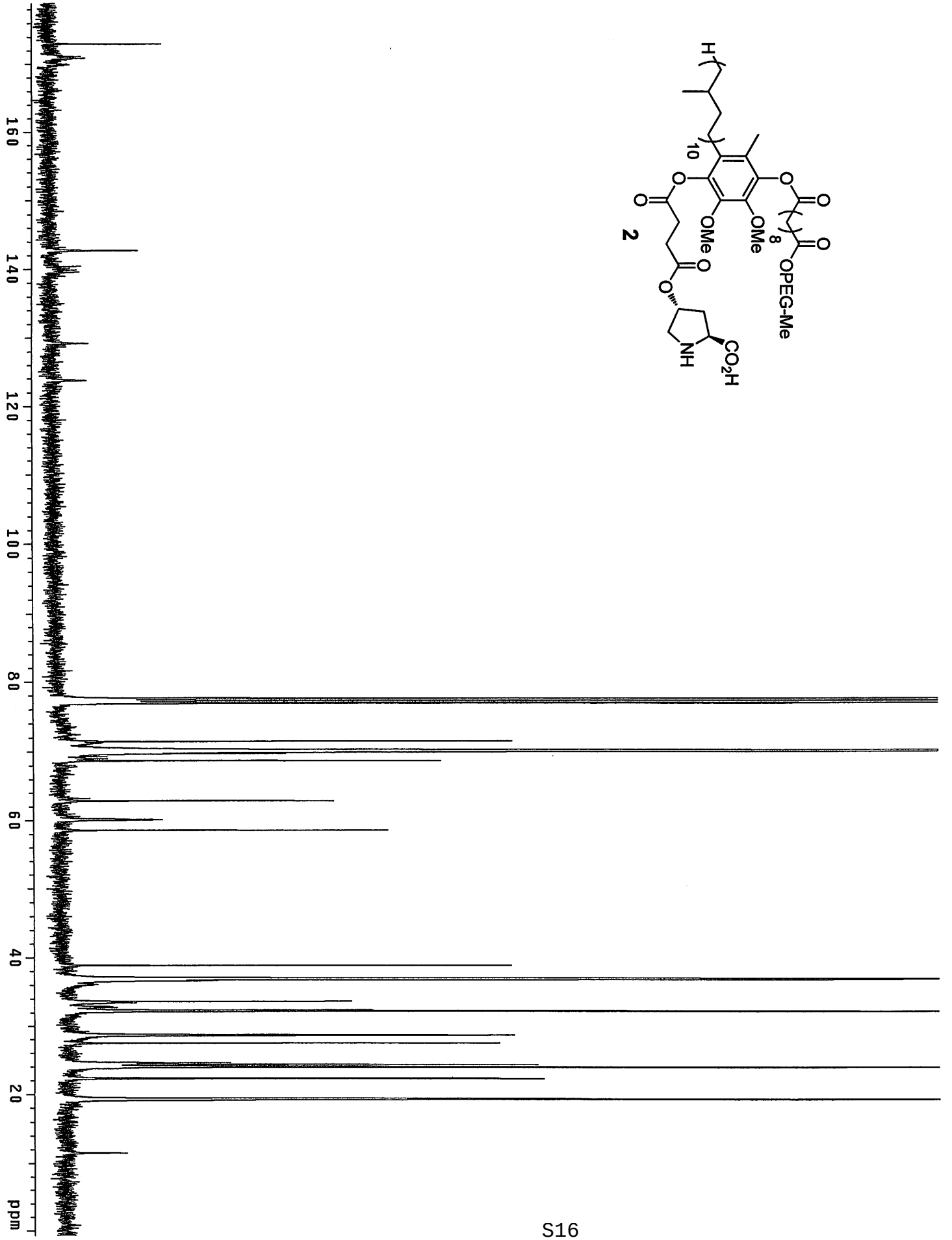
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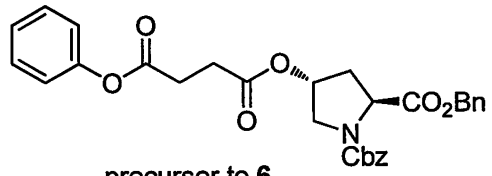
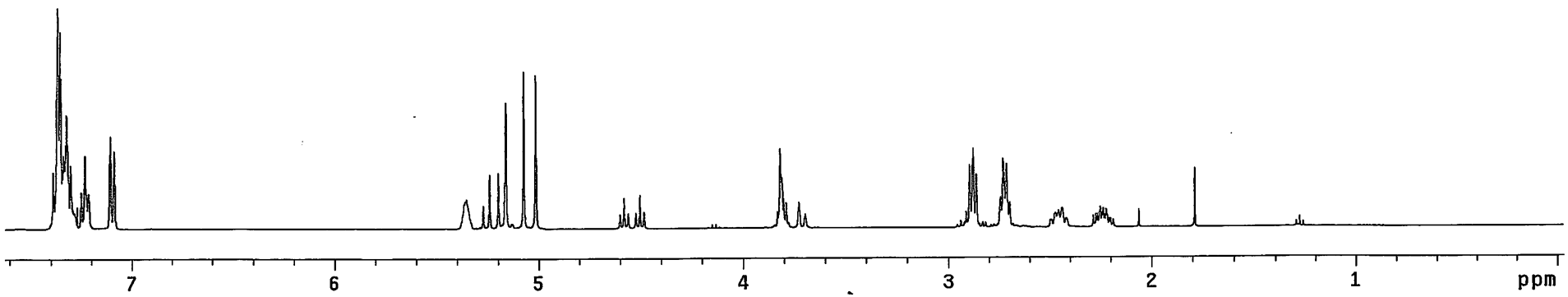
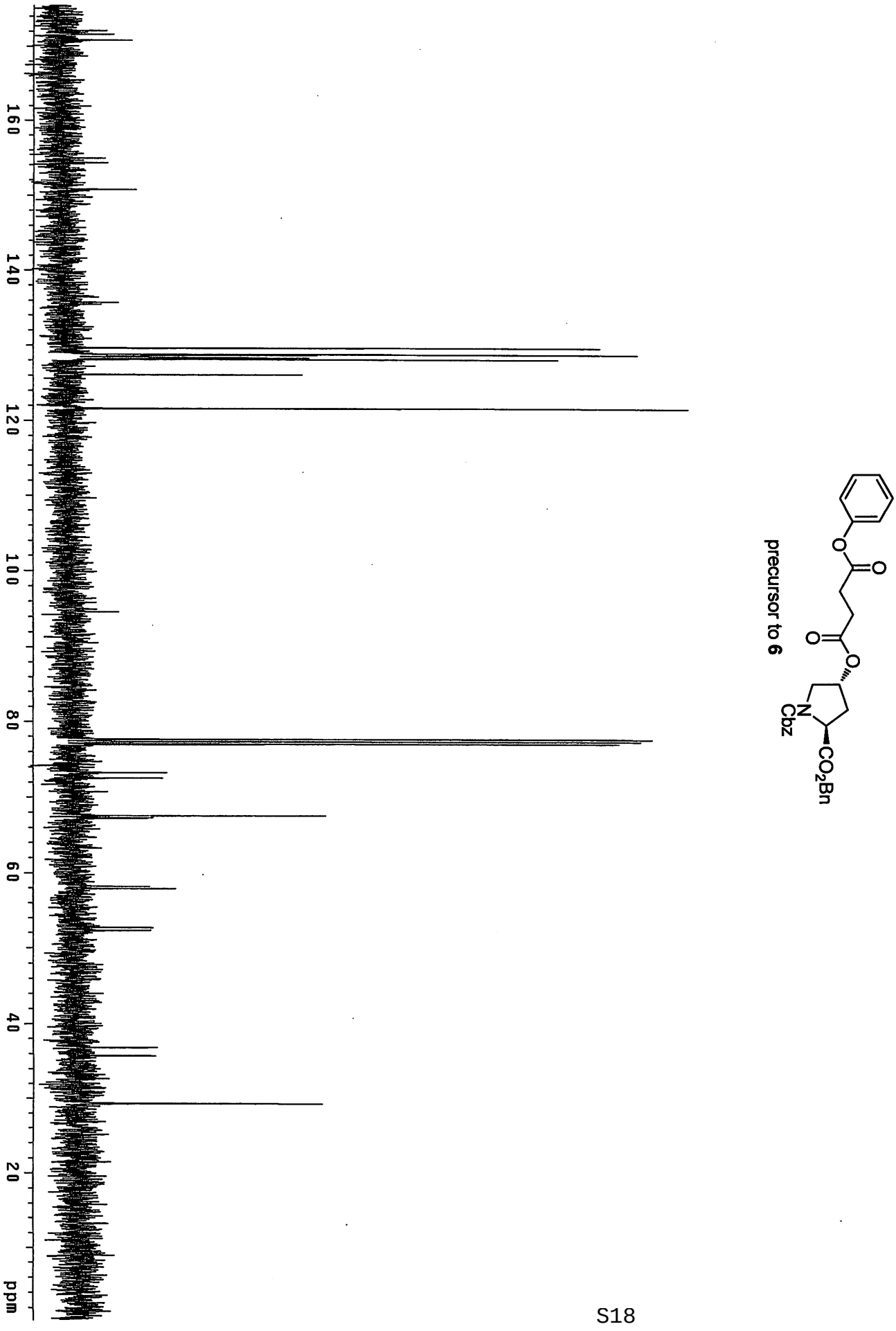


precursor to **6**





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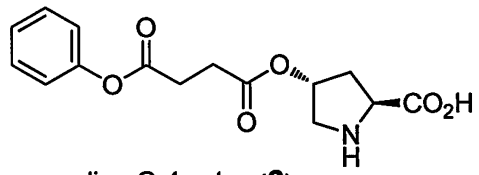
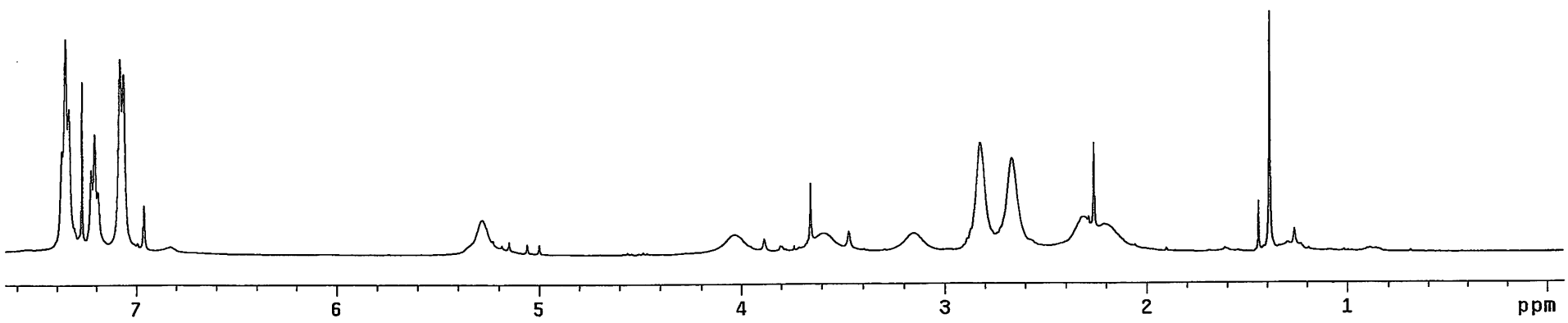
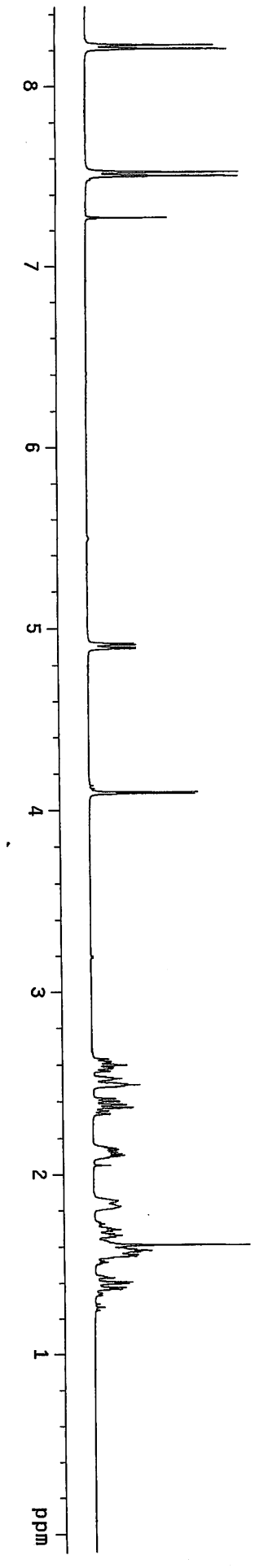


proline C-4 ester (**6**)

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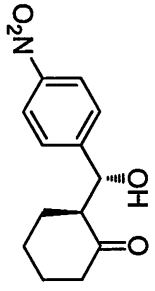
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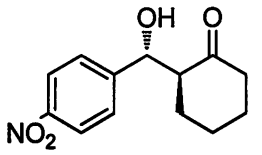
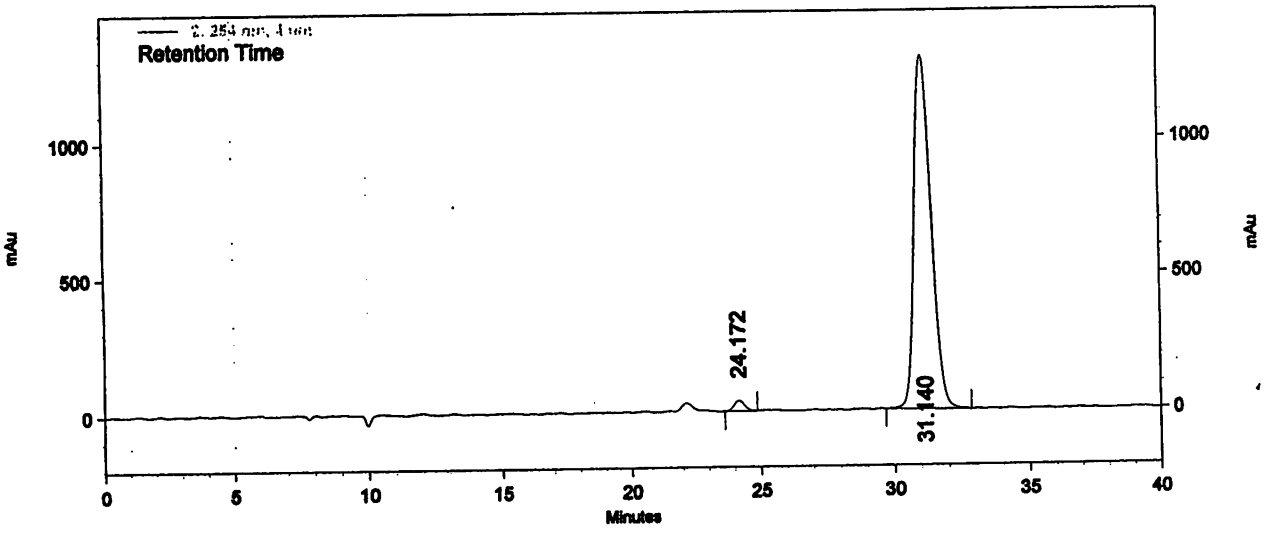
O

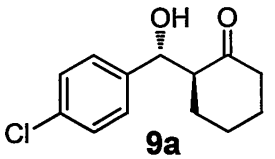


Daicel Chiralpak AD Column
iPrOH/hexane = 20:80, λ = 254 nm, flow rate = 0.5 mL/min.

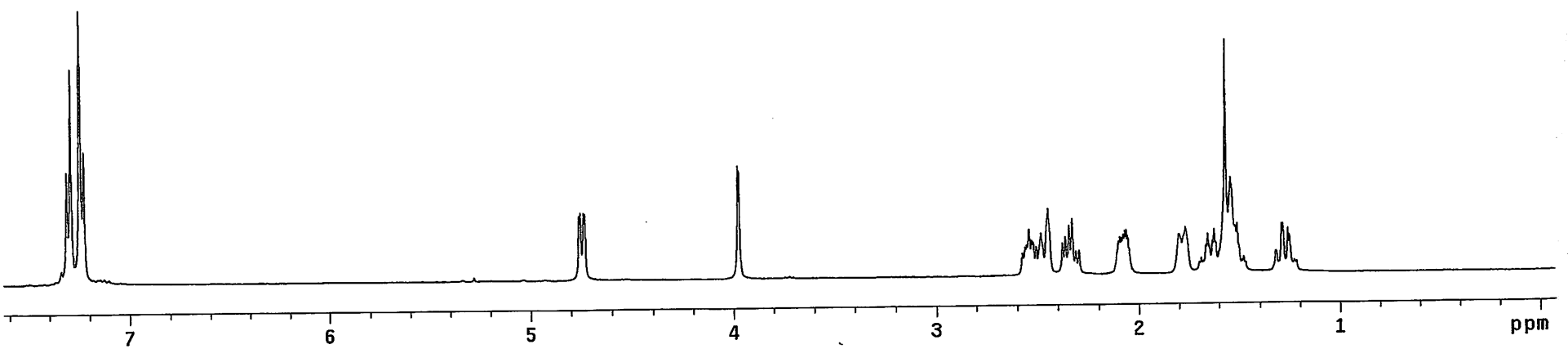


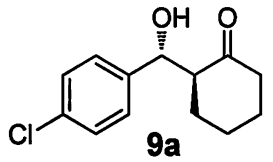
2: 254 nm, 4 nm Results

Retention Time	Area	Area %
24.172	1085525	1.88
31.140	56629040	98.12
Totals	57714565	100.00



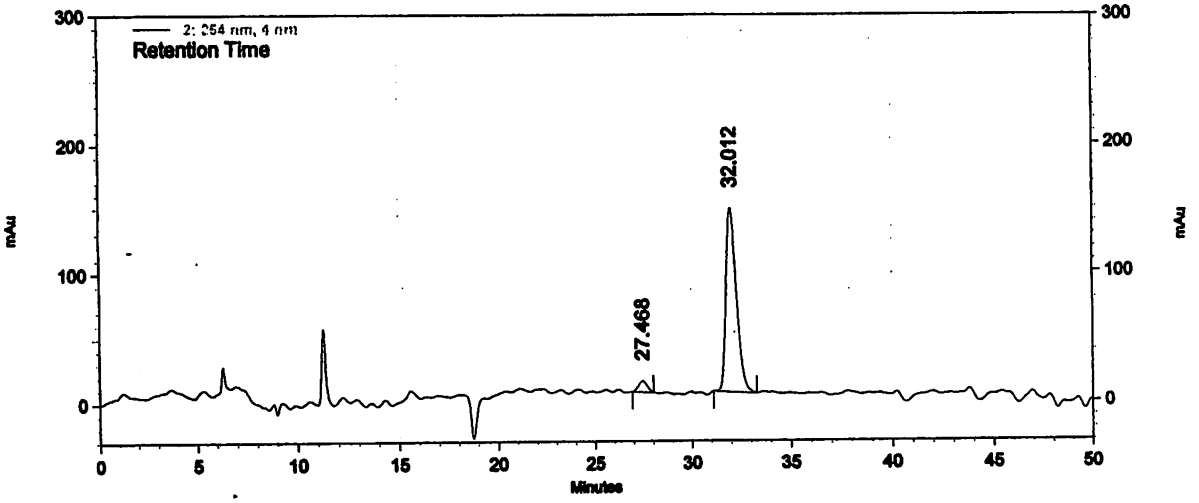
9a





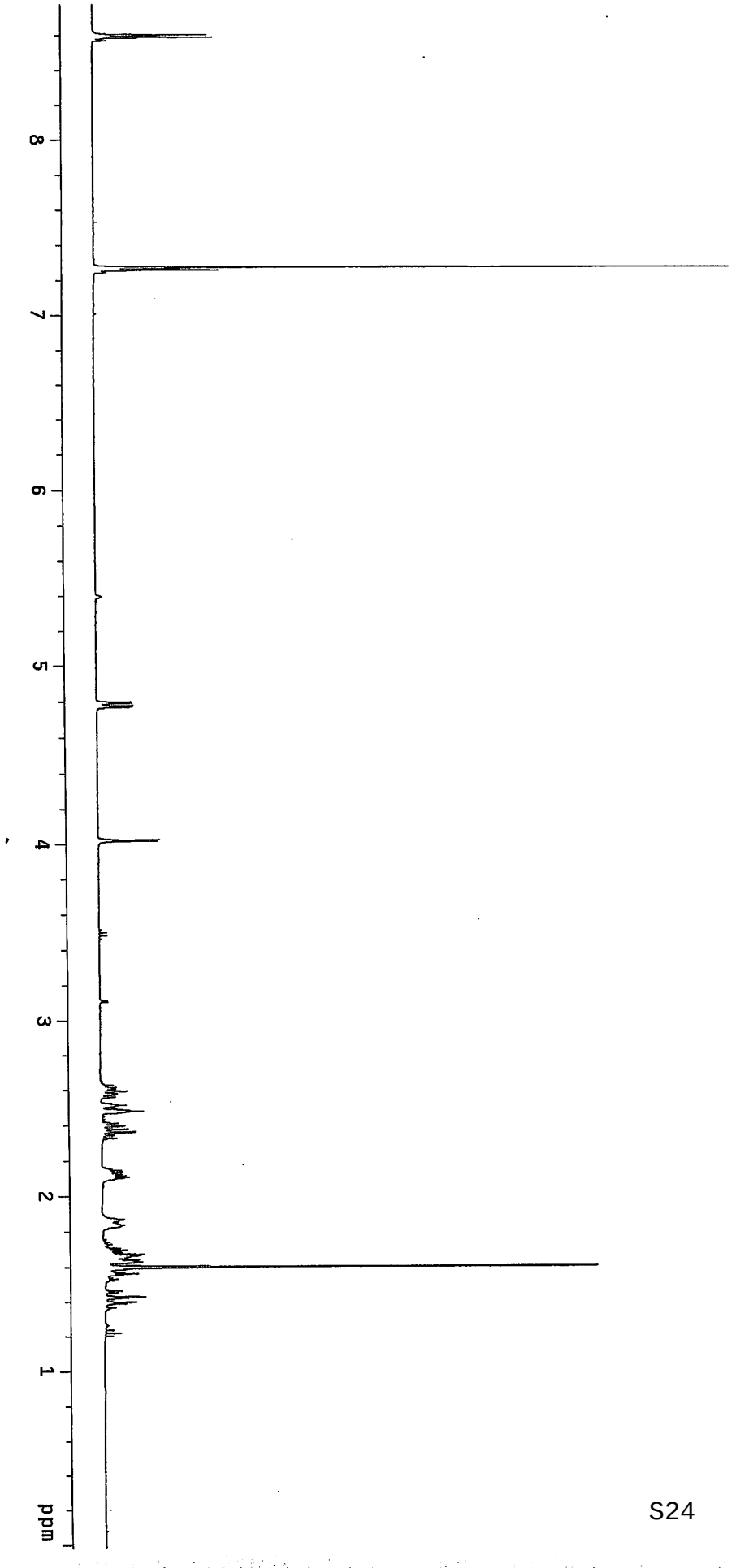
9a

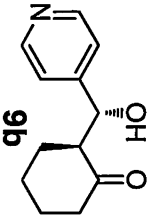
Daicel Chiralpak AD Column
iPrOH/hexane = 10:90, λ = 254 nm, flow rate = 0.5 mL/min.



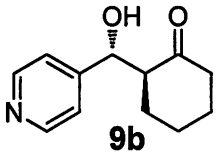
2: 254 nm, 4 nm Results

Retention Time	Area	Area %
27.468	262725	4.81
32.012	5199420	95.19
Totals	5462145	100.00





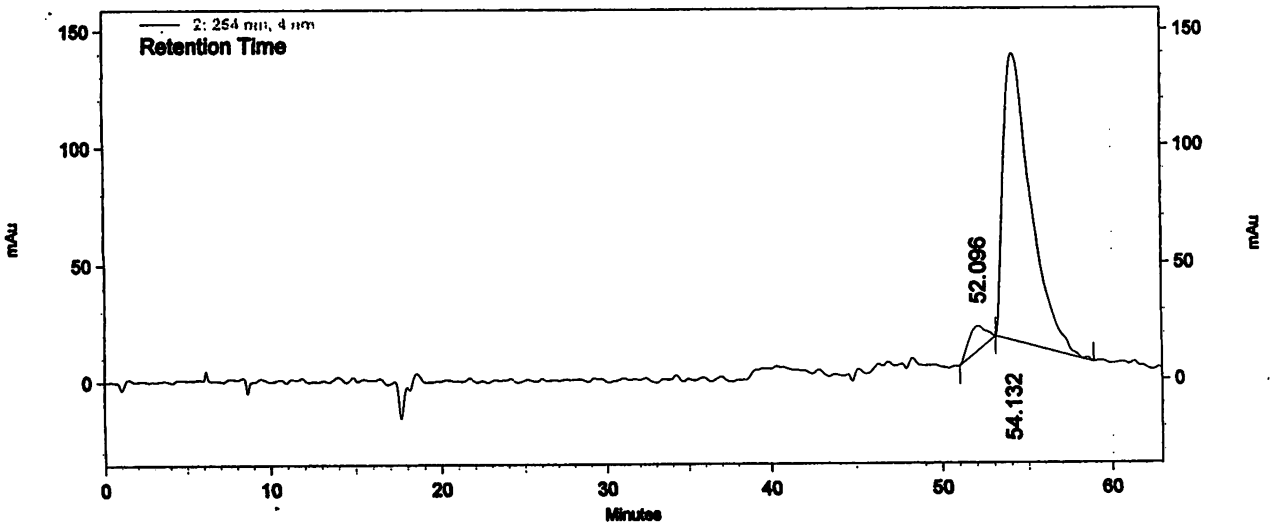
9b



9b

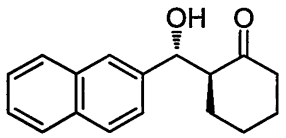
Daicel Chiralpak AD Column

iPrOH/hexane = 10:90, λ = 254 nm, flow rate = 0.5 mL/min.

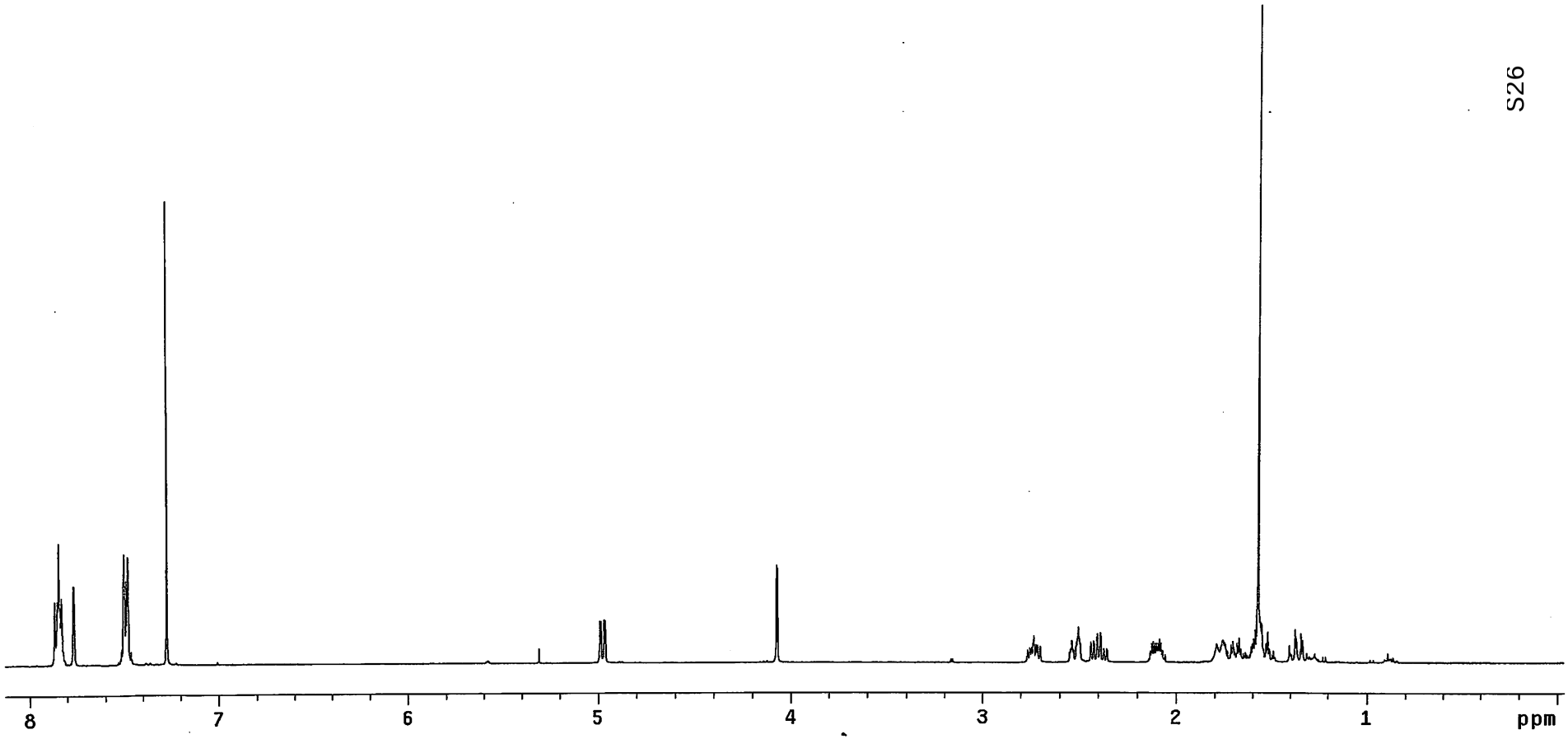


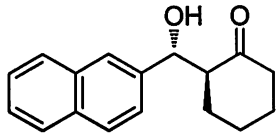
2: 254 nm, 4 nm Results

Retention Time	Area	Area %
52.096	747289	5.18
54.132	13685708	94.82
Totals	14432997	100.00



9c

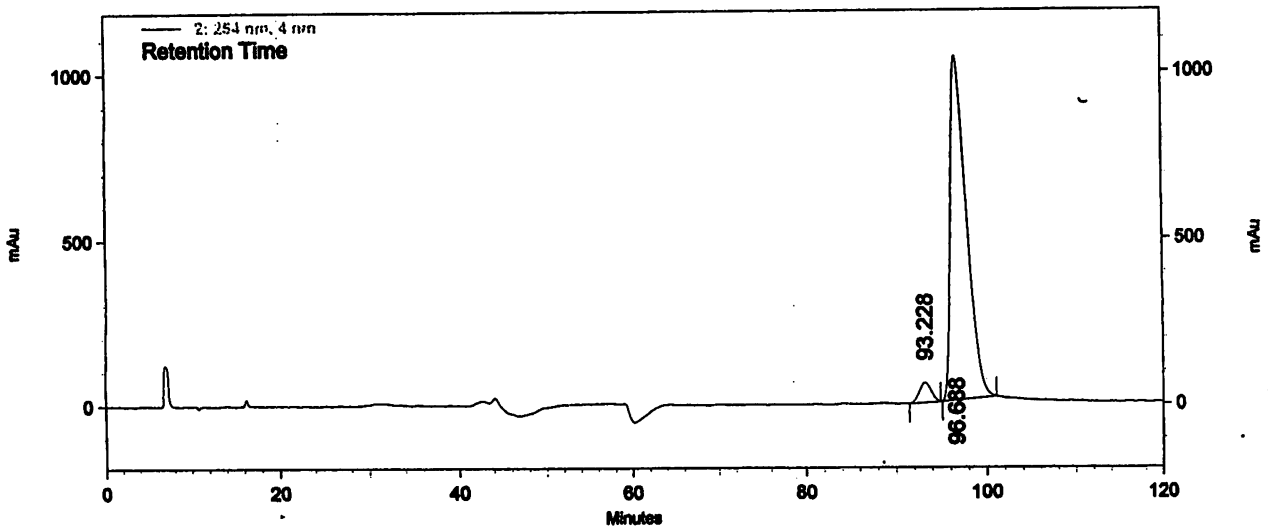




9c

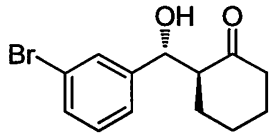
Daicel Chiralpak AD Column

iPrOH/hexane = 5:95, λ = 254 nm, flow rate = 0.5 mL/min.

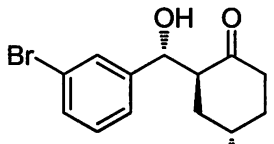


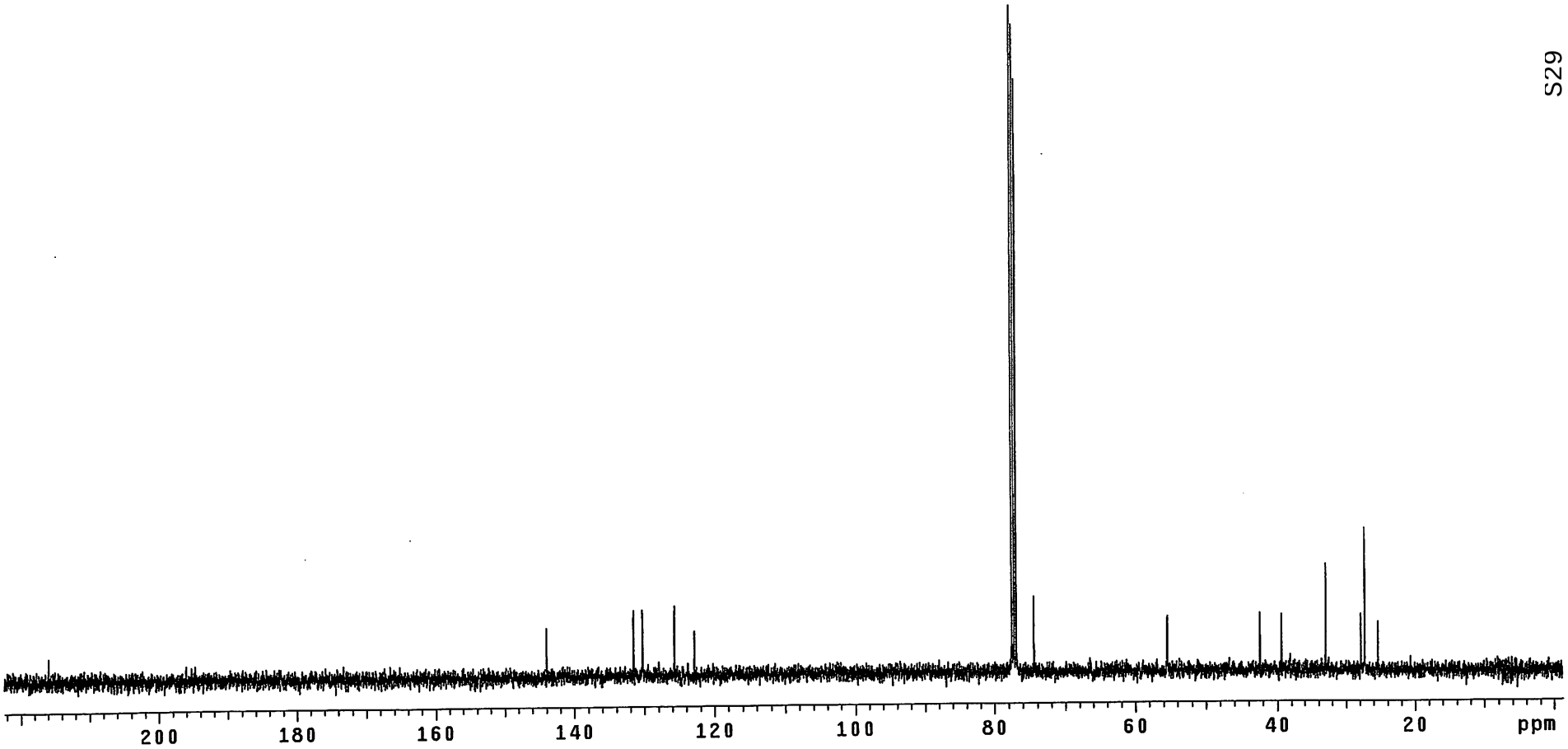
2: 254 nm, 4 nm Results

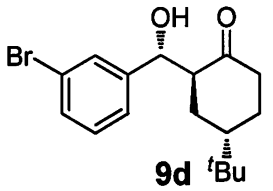
Retention Time	Area	Area %
93.228	5412304	4.10
96.688	126657472	95.90
Totals	132069776	100.00



9d

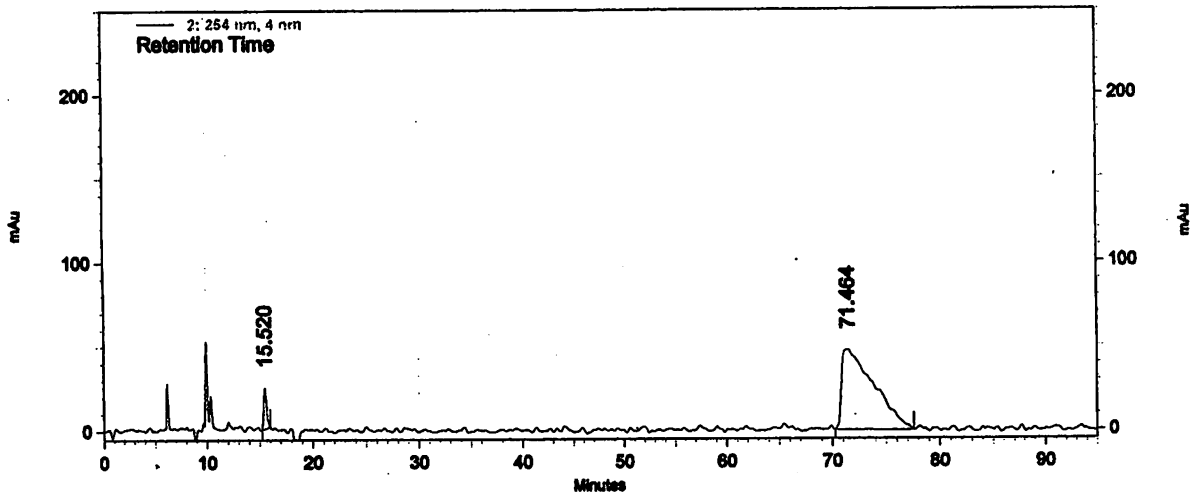

OH
O
Br
9d
tBu


200
180
160
140
120
100
80
60
40
20
ppm



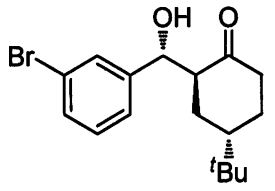
9d ^{t}Bu

Daicel Chiralpak AD Column
iPrOH/hexane = 10:90, λ = 254 nm, flow rate = 0.5 mL/min.



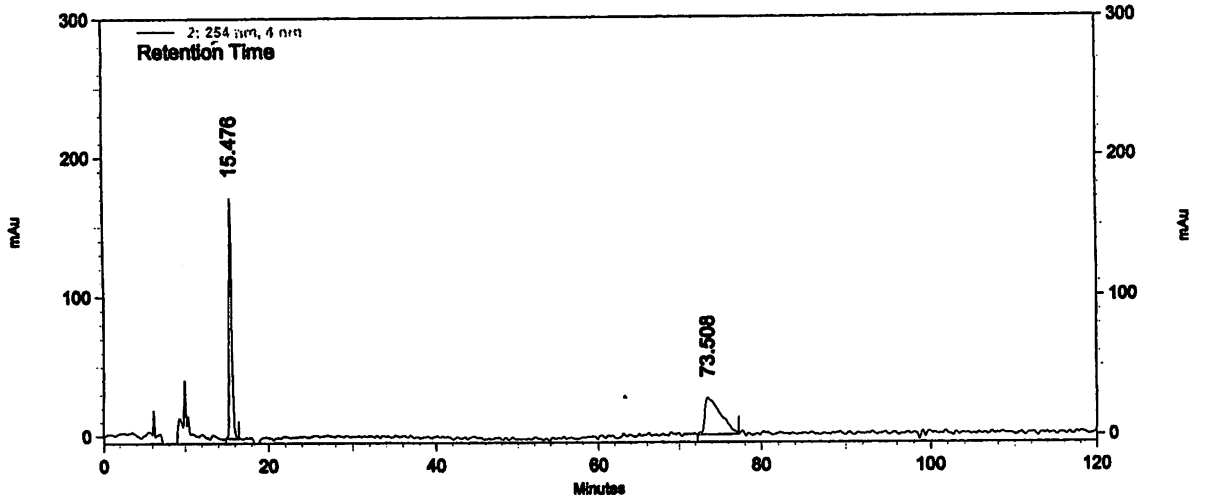
2: 254 nm, 4 nm Results

Retention Time	Area	Area %
15.520	452150	4.39
71.464	9858024	95.61
Totals	10310174	100.00



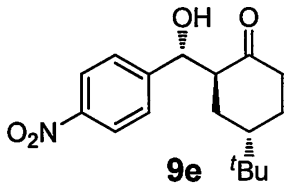
9d (racemic)

Daicel Chiralpak AD Column
iPrOH/hexane = 10:90, λ = 254 nm, flow rate = 0.5 mL/min.

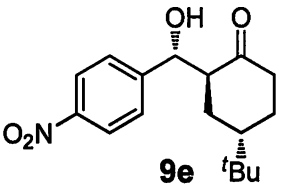


2: 254 nm, 4 nm Results

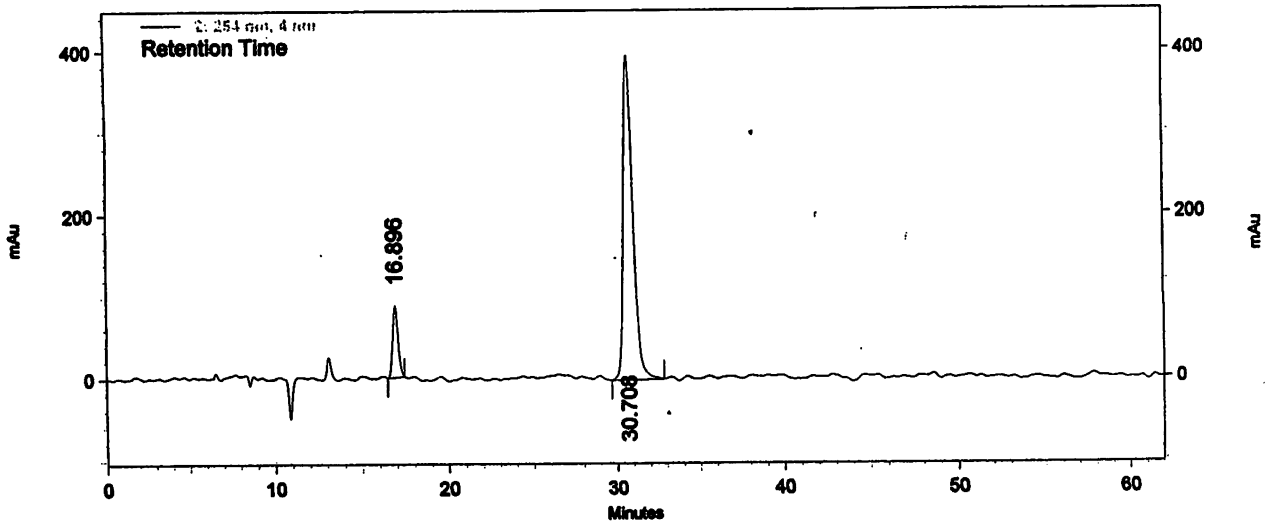
Retention Time	Area	Area %
15.476	3653099	50.93
73.508	3519557	49.07
Totals	7172656	100.00


OH
O
O_2N
9e
^{t}Bu

8
7
6
5
4
3
2
1
ppm

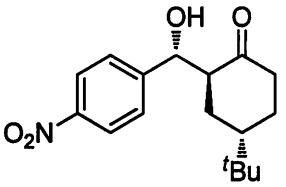


Daicel Chiralpak AD Column
iPrOH/hexane = 20:80, λ = 254 nm, flow rate = 0.5 mL/min.



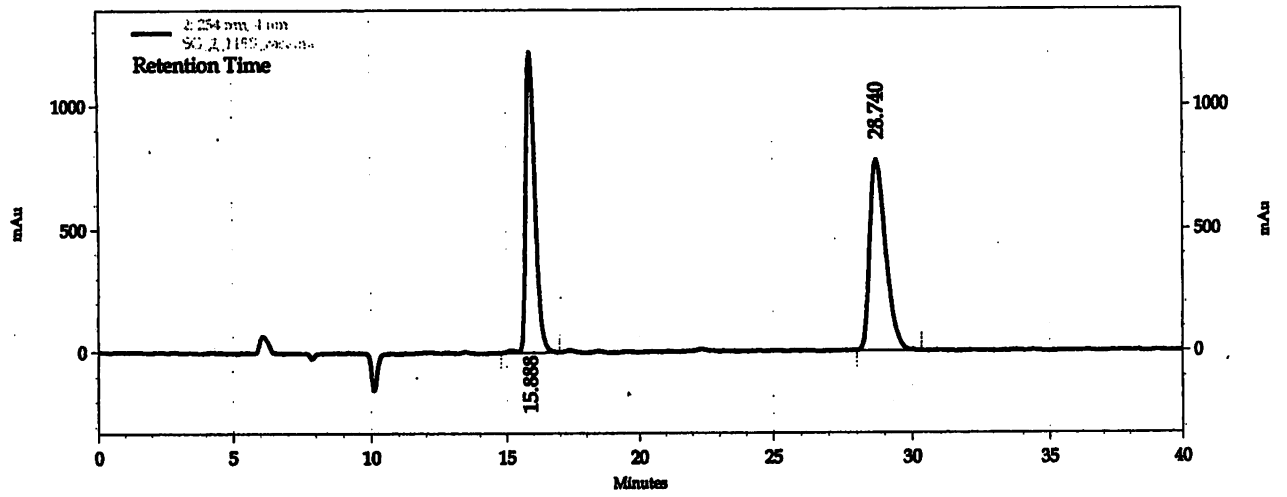
2: 254 nm, 4 nm Results

Retention Time	Area	Area %
16.896	1905920	10.61
30.708	16062137	89.39
Totals	17968057	100.00



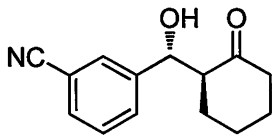
9e (racemic)

Daicel Chiralpak AD Column
iPrOH/hexane = 20:80, λ = 254 nm, flow rate = 0.5 mL/min.

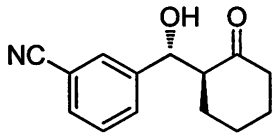


2: 254 nm, 4 nm
Results

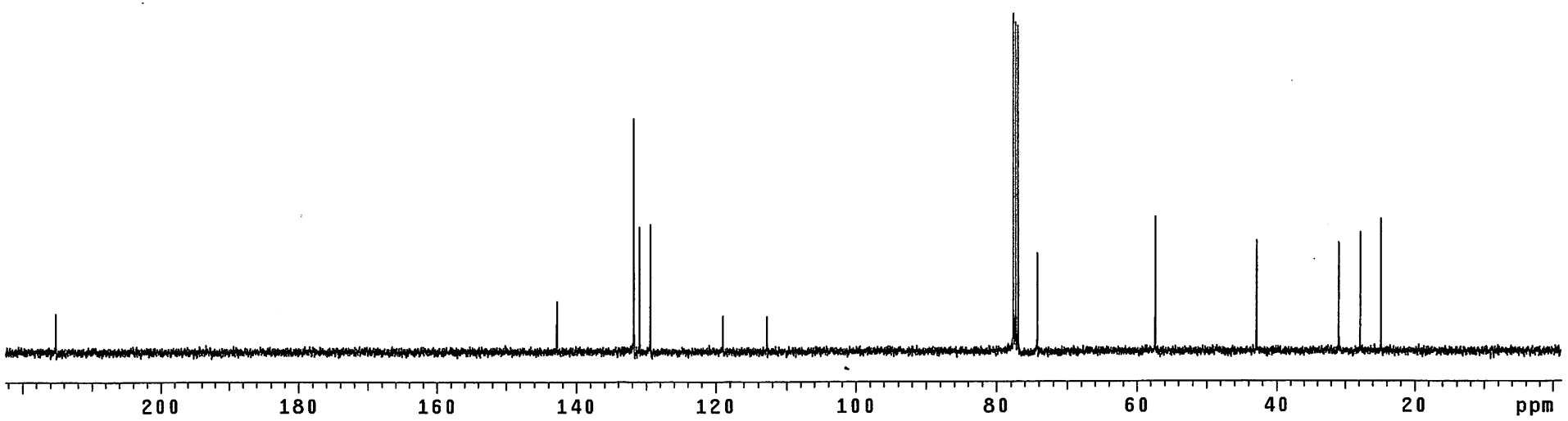
Retention Time	Area	Area %	Height	Height %
15.888	29630477	49.00	1218420	61.09
28.740	30833762	51.00	775981	38.91
Totals	60464239	100.00	1994401	100.00

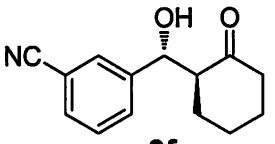


9f



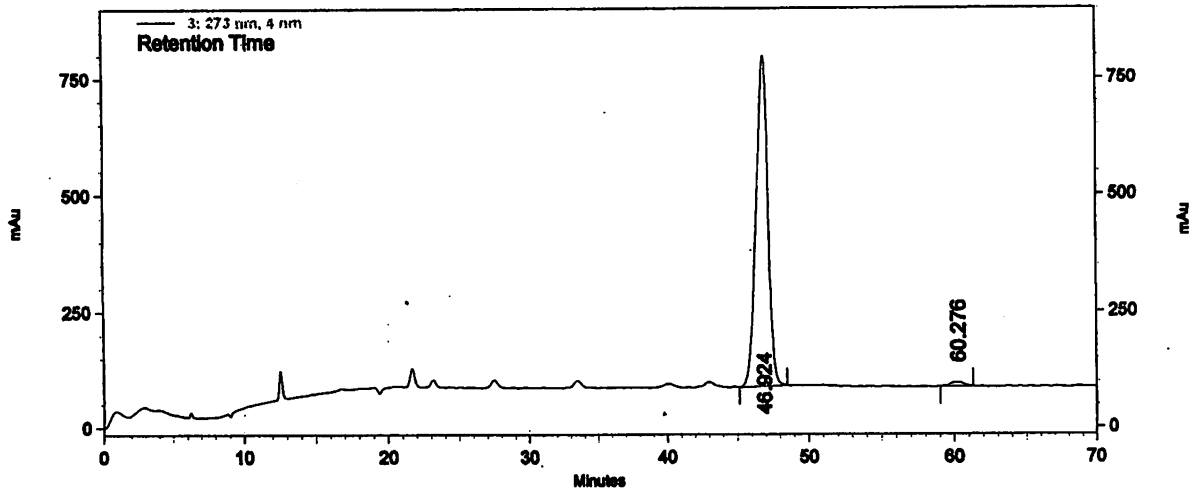
9f





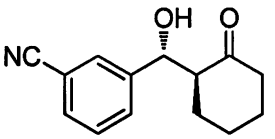
9f

Daicel Chiralpak AD Column
iPrOH/hexane = 10:90, λ = 273 nm, flow rate = 0.5 mL/min.



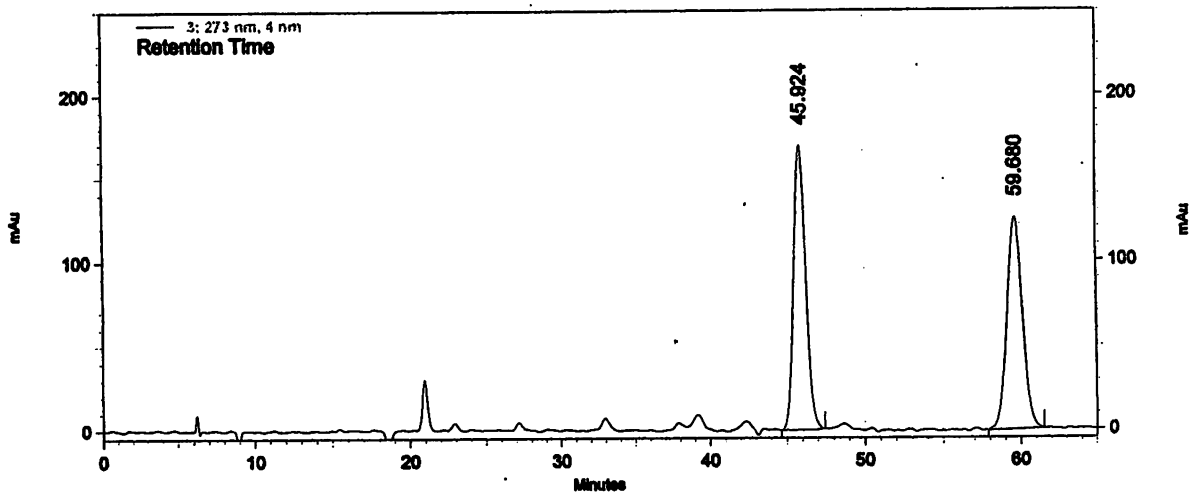
3: 273 nm, 4 nm Results

Retention Time	Area	Area %
46.924	40893966	98.66
60.276	555135	1.34
Totals	41449101	100.00



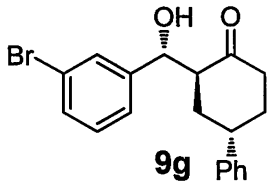
9f (racemic)

Daicel Chiralpak AD Column
iPrOH/hexane = 10:90, λ = 273 nm, flow rate = 0.5 mL/min.

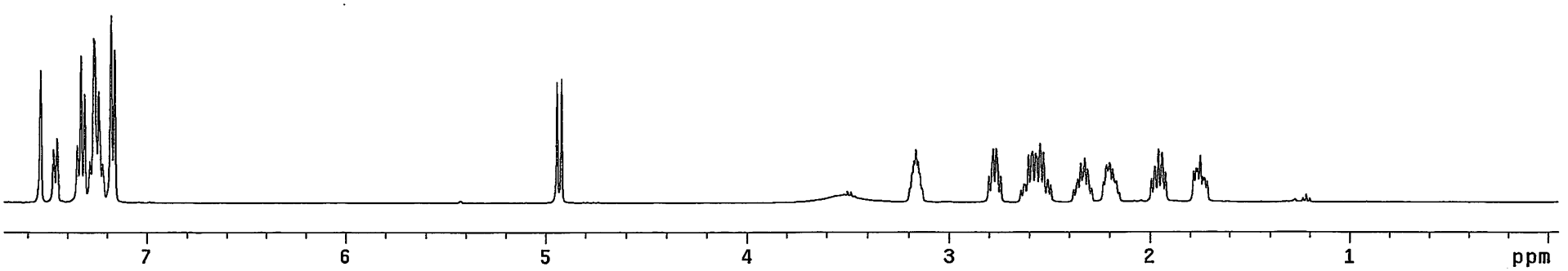


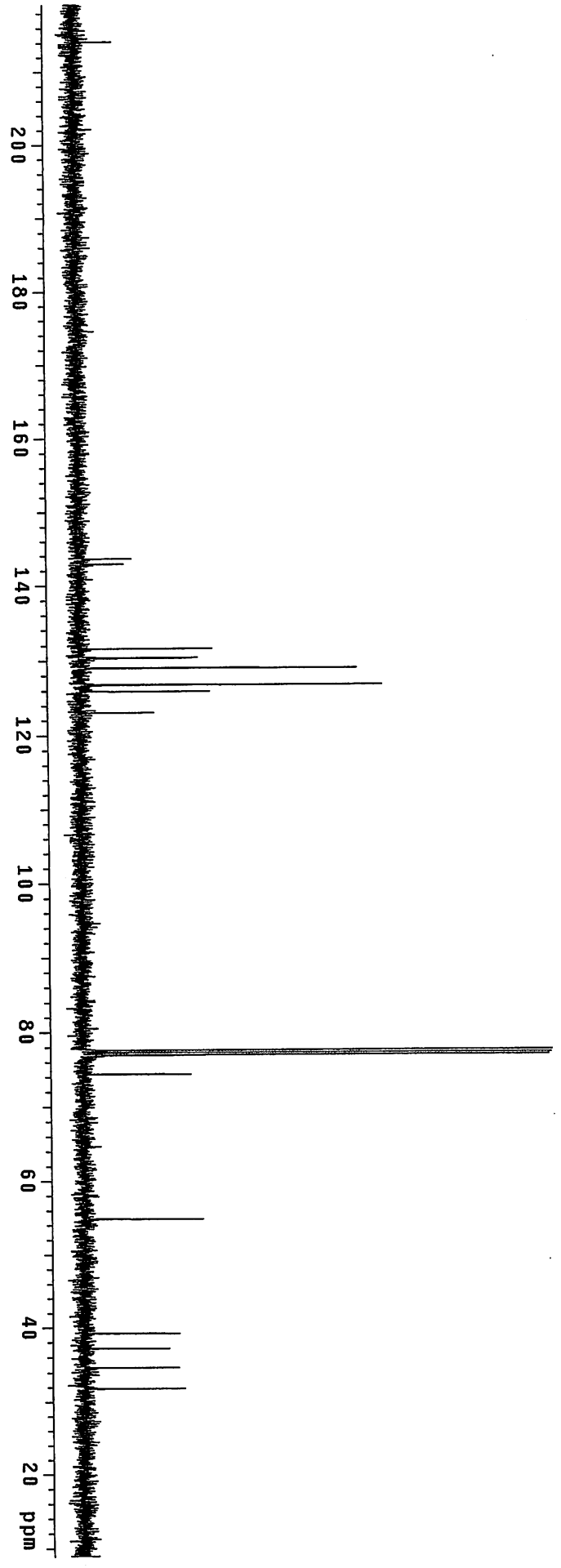
3: 273 nm, 4 nm Results

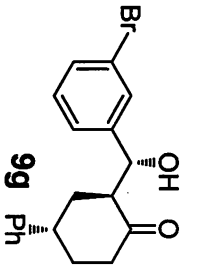
Retention Time	Area	Area %
45.924	9138351	50.93
59.680	8805542	49.07
Totals	17943893	100.00



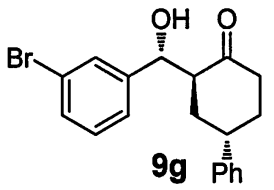
9g





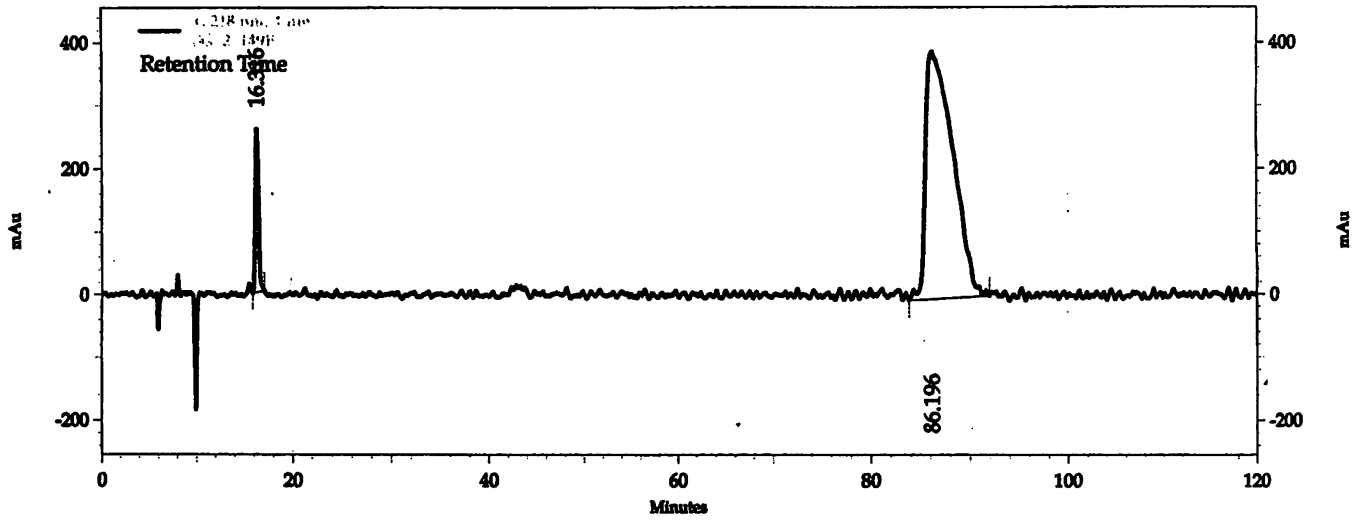


9g



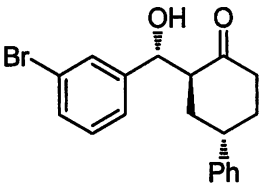
9g

Daicel Chiralpak AD Column
iPrOH/hexane = 20:80, λ = 218 nm, flow rate = 1.0 mL/min.



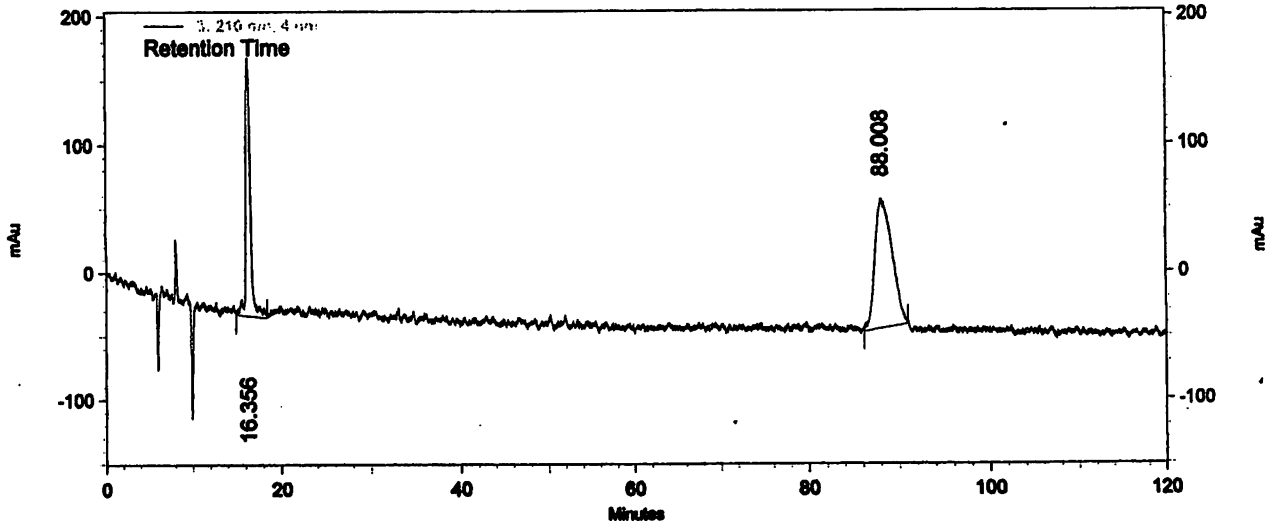
1: 218 nm, 4 nm
Results

Retention Time	Area	Area %	Height	Height %
16.316	5831736	7.21	260107	39.83
86.196	75052341	92.79	392871	60.17
Totals	80884077	100.00	652978	100.00



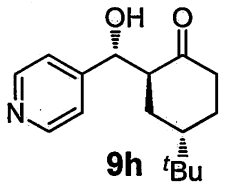
9g (racemic)

Daicel Chiralpak AD Column
iPrOH/hexane = 20:80, λ = 218 nm, flow rate = 1.0 mL/min.

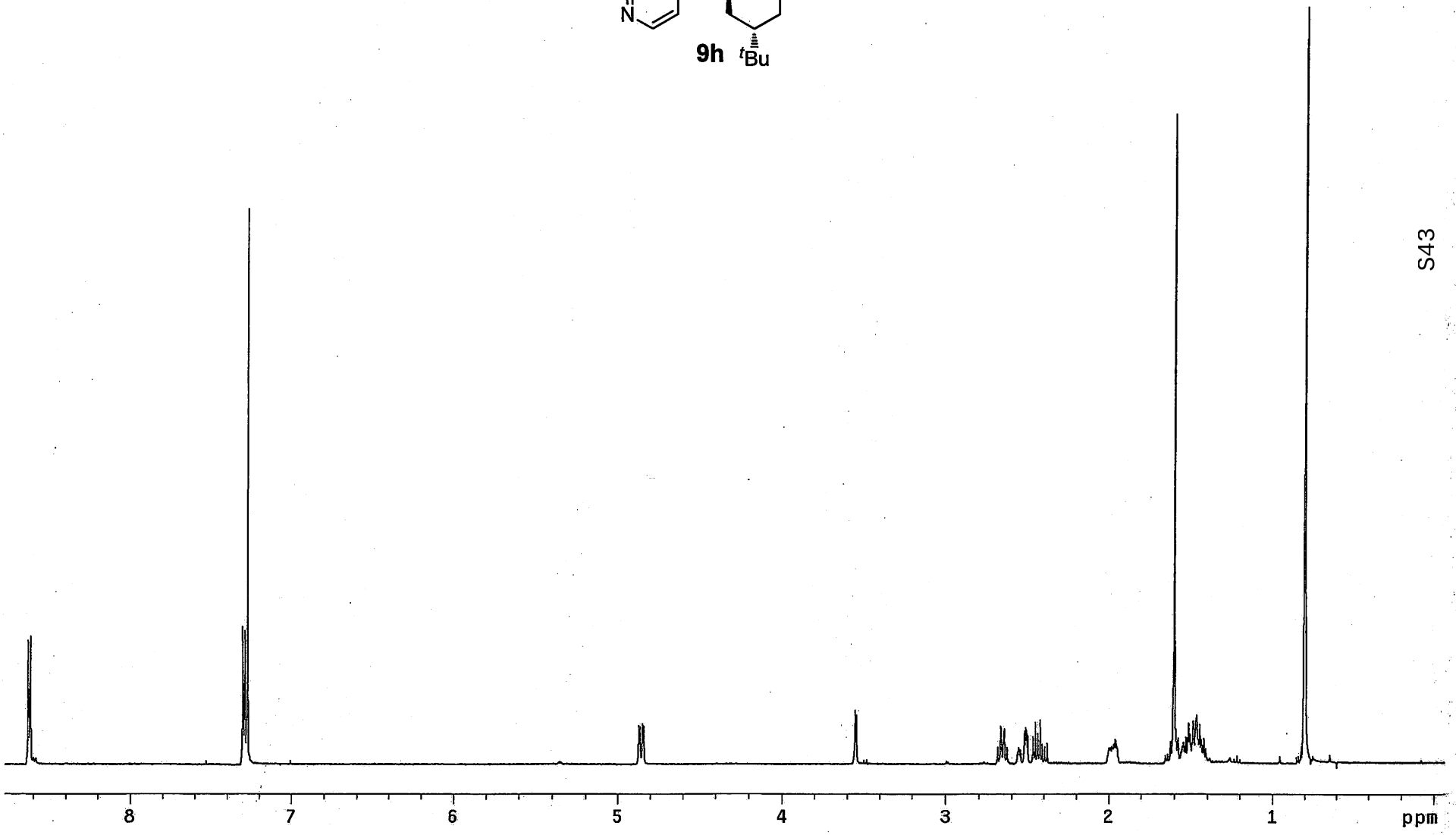


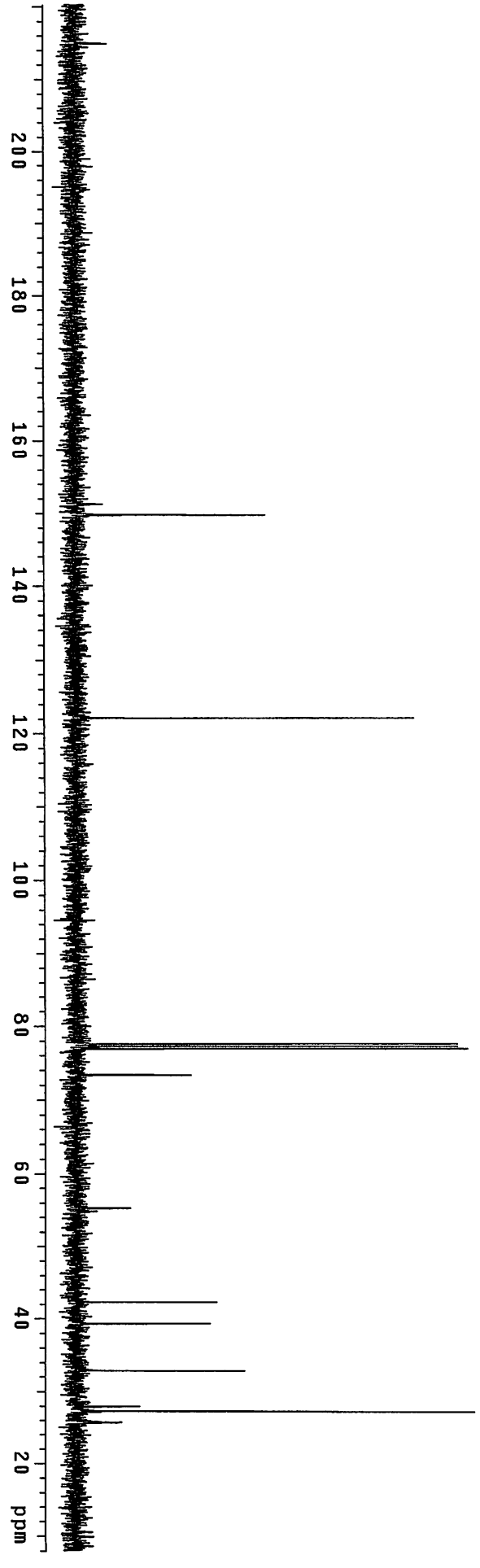
3: 210 nm, 4 nm Results

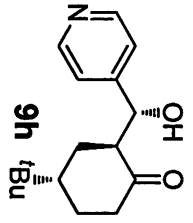
Retention Time	Area	Area %
16.356	7378329	35.69
88.008	13294555	64.31
Totals	20672884	100.00



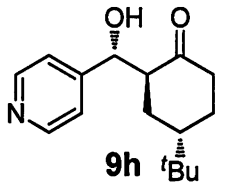
9h ^{t}Bu





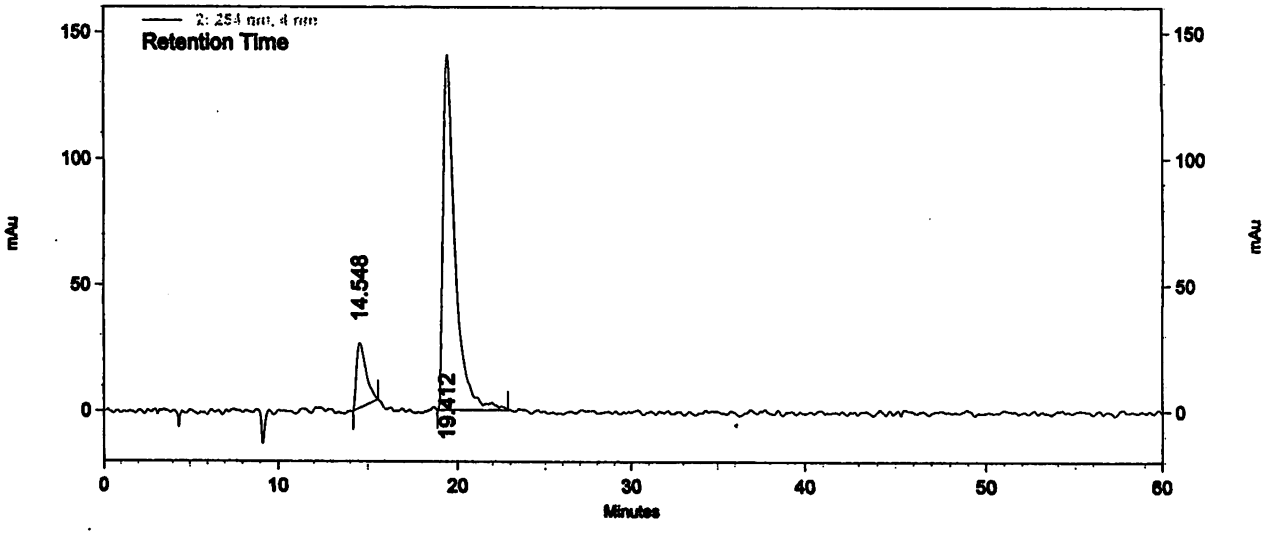


9h



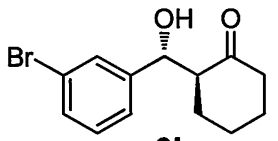
9h ^{t}Bu

Daicel Chiralpak AD Column
iPrOH/hexane = 10:90, λ = 254 nm, flow rate = 1.0 mL/min.

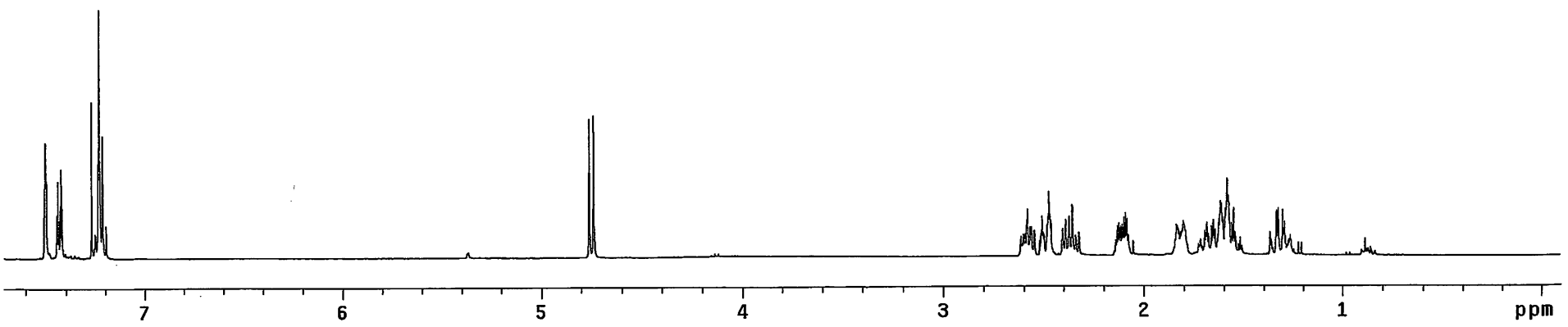


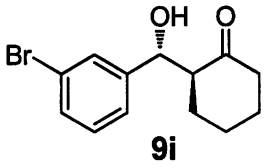
2: 254 nm, 4 nm Results

Retention Time	Area	Area %
14.548	943187	12.53
19.412	6582252	87.47
Totals	7525439	100.00



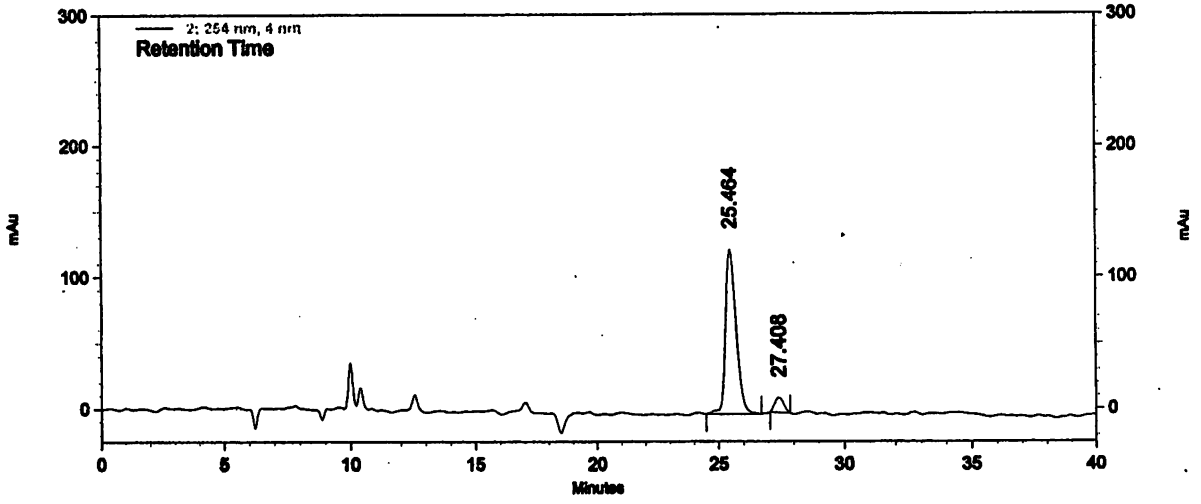
9i





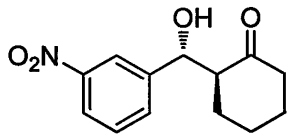
9i

Daicel Chiralpak AD Column
iPrOH/hexane = 10:90, λ = 254 nm, flow rate = 0.5 mL/min.

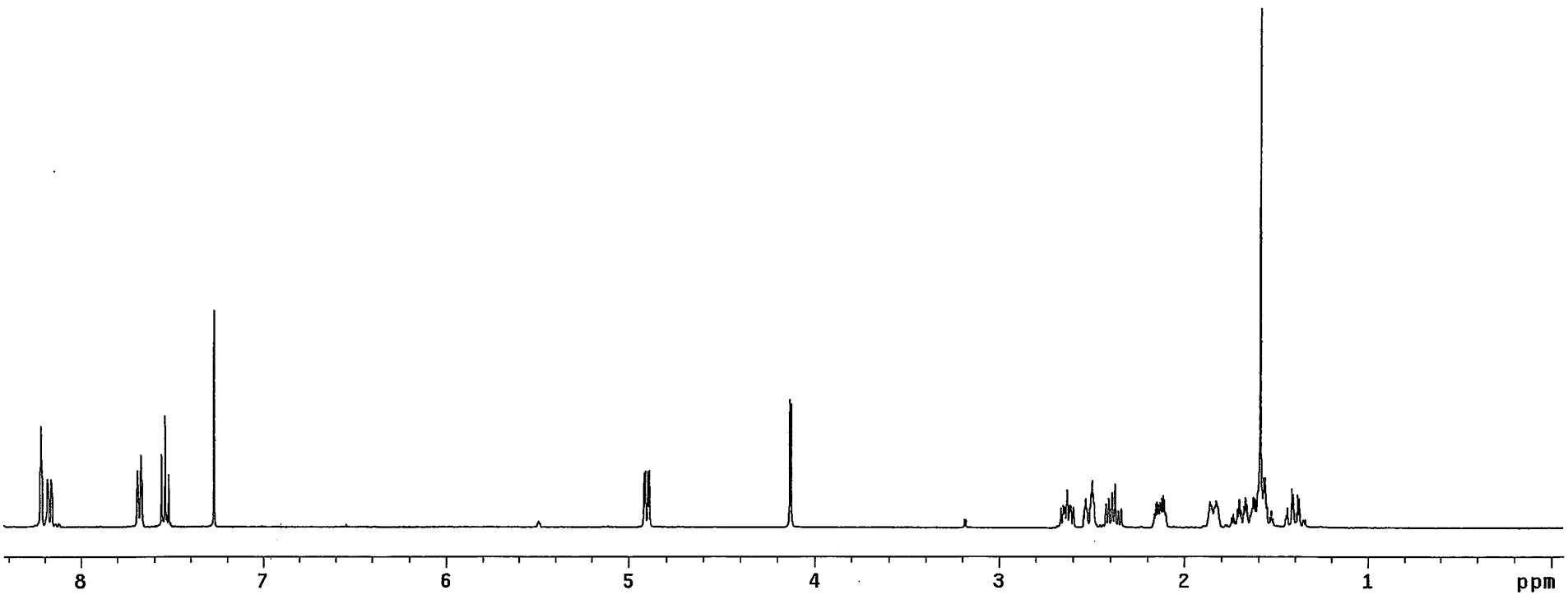


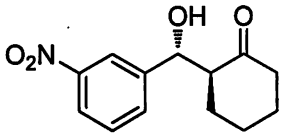
2: 254 nm, 4 nm Results

Retention Time	Area	Area %
25.464	3715377	92.92
27.408	282973	7.08
Totals	3998350	100.00



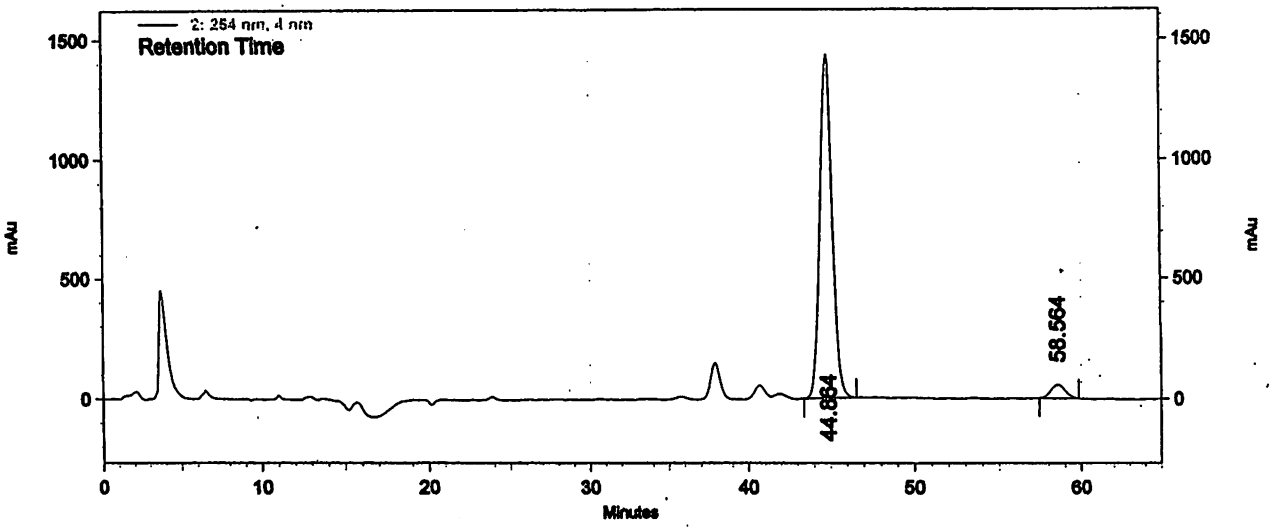
9j





9j

Daicel Chiralpak AD Column
iPrOH/hexane = 10:90, λ = 254 nm, flow rate = 0.5 mL/min.



2: 254 nm, 4 nm Results

Retention Time	Area	Area %
44.864	72903283	95.55
58.564	3392696	4.45
Totals	76295979	100.00