Direct Aldol Reactions Catalyzed by a Heterogeneous Guanidinium Salt/Proline System under Solvent-Free Conditions

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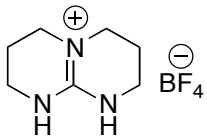
SUPPORTING INFORMATION

General

All commercially available reagents and solvents were used without further purification unless otherwise stated. Liquid aldehydes, and ketones, were in all cases distilled under reduced pressure before use. Flash chromatography of reaction products was carried out using Silica 60A, particle size 230-400 micron (Merk). Analytical thin layer chromatography (TLC) was performed on DC-Alufolien Kieselgel $60F_{254}$ 0.2 mm plates (Merk) and compounds were visualised by UV fluorescence or 5% phosphomolybdic acid in methanol. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker AC-300 or a Bruker DPX-300 spectrometer, using deuterated solvents and were referenced internally to the residual solvent peak (δ_H = 7.26 ppm, δ_C = 77.36 ppm) signal,[i] or to $CFCl_3$ (δ_F = 0.00 ppm) for ^{19}F spectra. Coupling constants (*J*-values) are given in hertzs (Hz). The DEPT 135 technique was used to assign methylene (CH_2) signals. Chemical shifts are reported as follows: value (number of protons, description of absortion, coupling constant(s) where applicable, assignment). NMR spectra assignation was aided by comparison with literature values for similar compounds. In this experimental section only clear identifiable peaks are assigned.

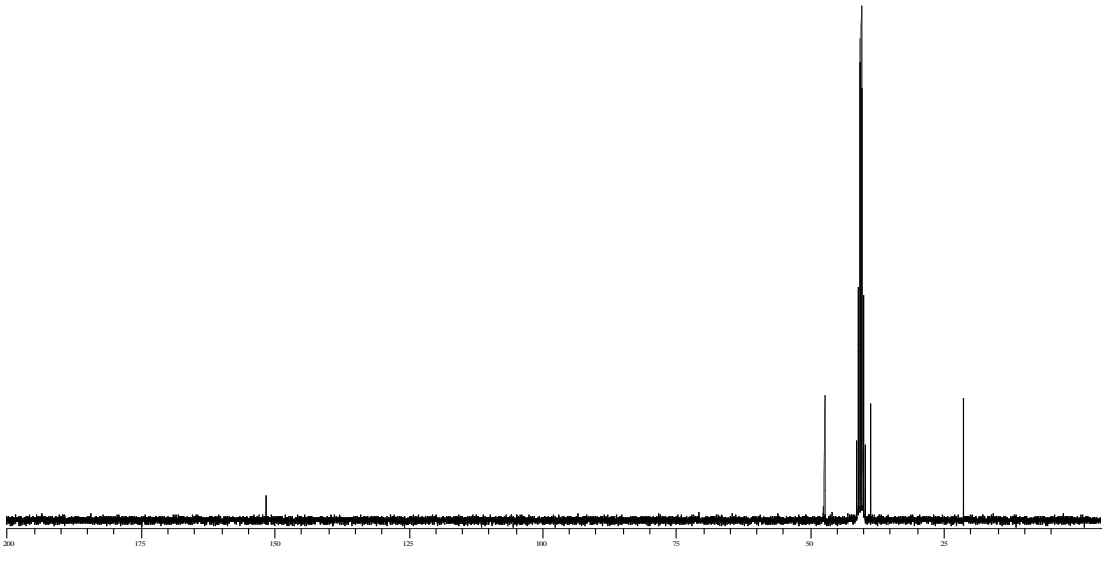
Preparation of guanidinium salts 1a-e

Tetrafluoroborate guanidinium salt (1a)

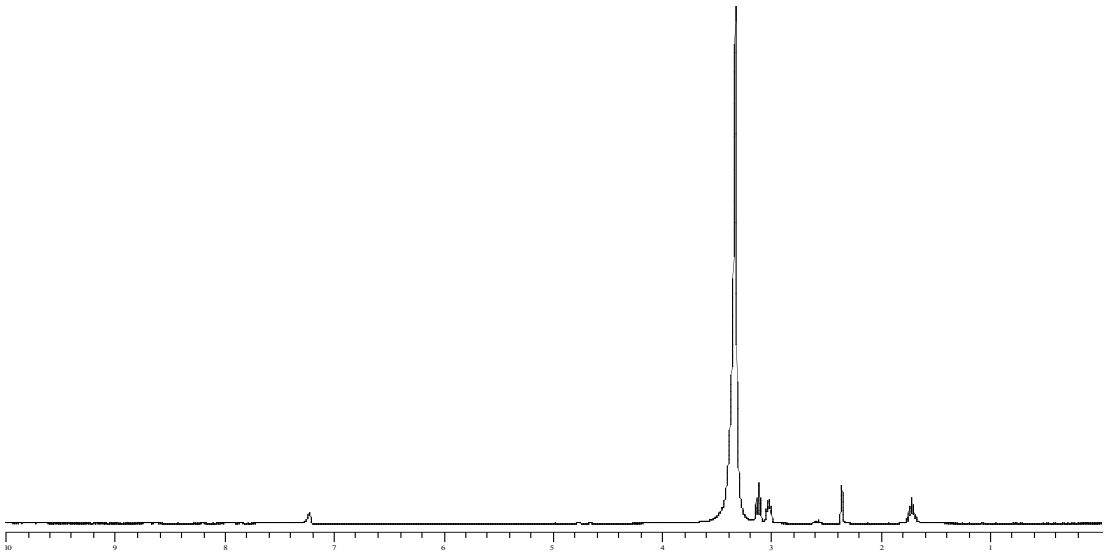


Triazabicyclo[4.4.0]dec-5-ene (300 mg, 2.16 mmol) was dissolved in methanol (5 mL) and the solution was cooled to 0 ºC before HBF_4 (48% wt. in water, 0.28 mL, 2.16 mmol) was added dropwise. The reaction mixture was vigorously stirred 30 min. before the solvent and volatiles were evacuated under reduced pressure (high vacuum pump) to render salt **1a** (490 mg, quantitative yield) as a colourless oil (ionic liquid). ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H = 7.23 (2H, s, 2 x N*H*), 3.12 (4H, t, J = 6.0 Hz, 2 x CH_2), 3.05-3.00 (4H, m, 2 x CH_2), 1.72 (4H, quint., J = 6.0 Hz, 2 x CH_2); ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C = 151.6 (CN_3), 47.3 (CH_2), 38.7 (CH_2), 21.3 (CH_2); ^{19}F NMR (DMSO-d_6, 282 MHz) δ_F = -148.31 (BF_4); MS (ESI$^+$): *m/z* (%) = 140 (100) $[TBD+H]^+$.

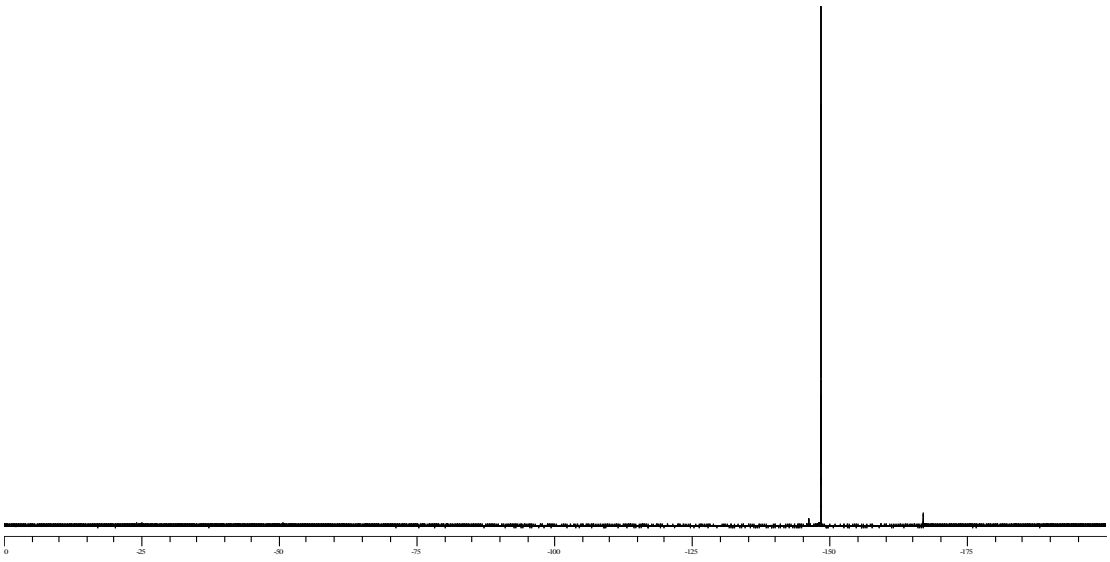
^{13}C



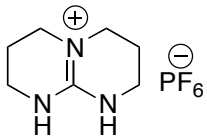
^{1}H



^{19}F

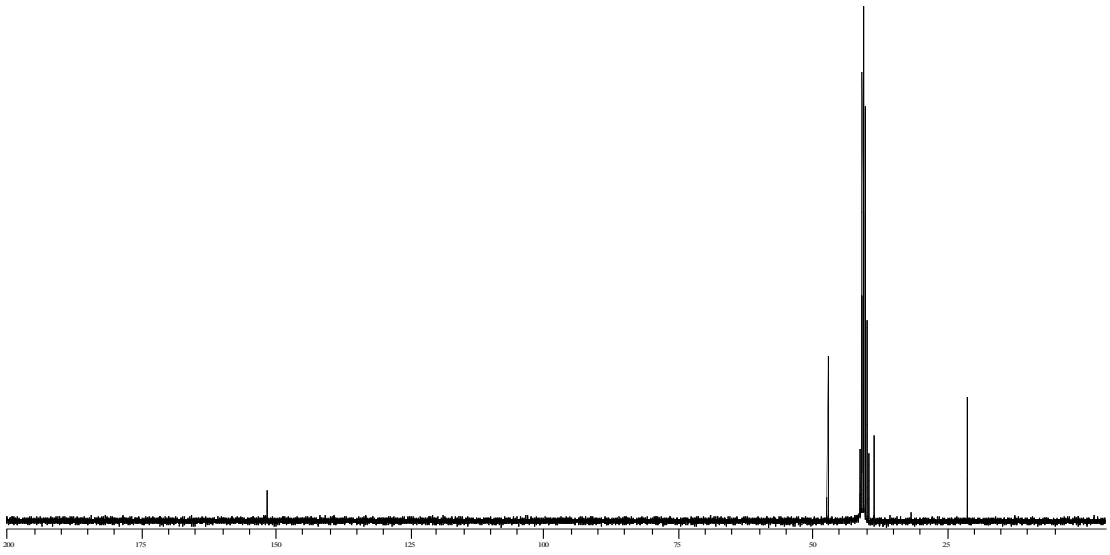


Hexafluorophosphate guanidinium salt (1c)

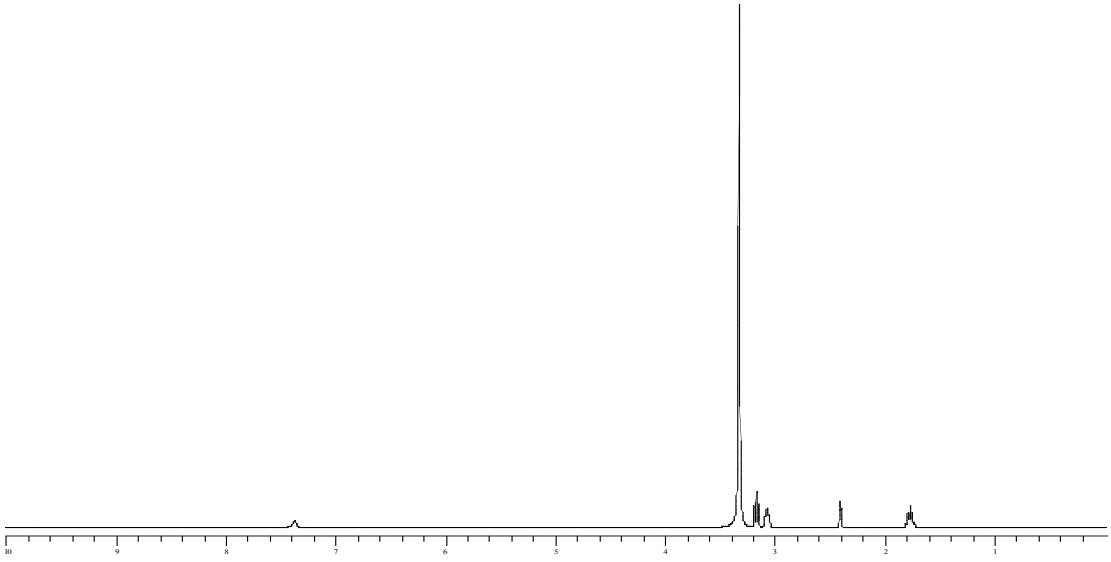


A solution of $NaPF_6$ (134 mg, 0.80 mmol) and chloride guanidinium salt **1e** (126 mg , 0.72 mmol), in deionised water (10 mL), was poured into 15 mL of CH_2Cl_2 and the resulting mixture was vigorously stirred for 1 h. The aqueous layer was carefully discarded and the organic phase was extensively dried under reduced pressure to render hexafluorophosphate **1c** (189 mg, 92%) as a white solid. Melting point = 68-69 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H = 7.37 (2H, s, 2 x N*H*), 3.17 (4H, t, J = 6.0 Hz, 2 x CH_2), 3.07 (4H, m, 2 x CH_2), 1.77 (4H, quint., J = 5.8 Hz, 2 x CH_2); ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C = 151.5 (CN$_3$), 47.3 (CH$_2$), 38.6 (CH$_2$), 21.3 (CH$_2$); ^{19}F NMR (DMSO-d_6, 282 MHz) δ_F = -65.4 (d, $^1J_{P\text{-}F}$ = 711 Hz, PF_6); MS (ESI$^+$): *m/z* (%) = 140 (100) [TBD+H]$^+$.

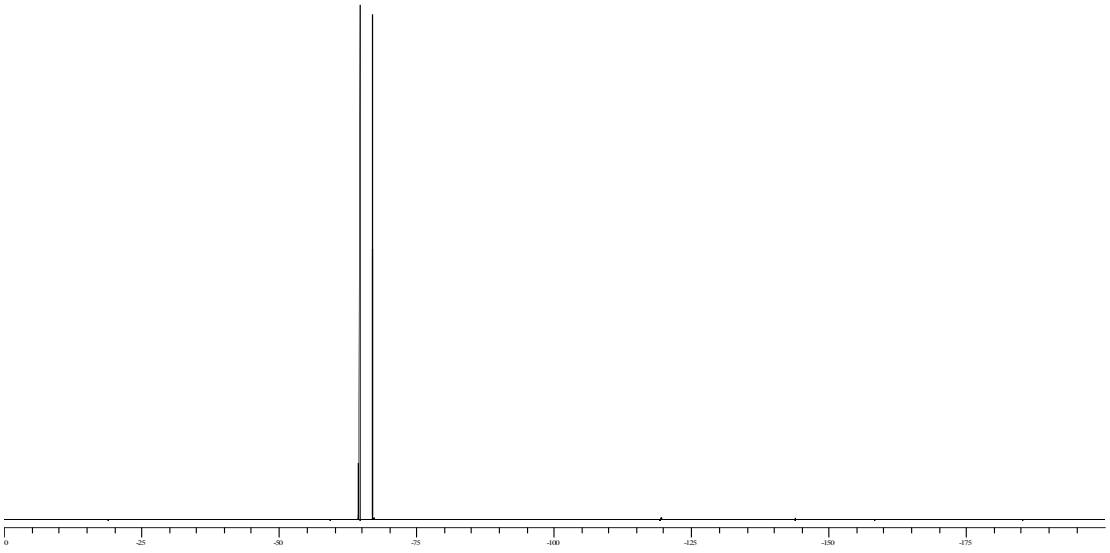
^{13}C



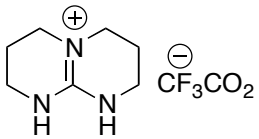
^{1}H



^{19}F

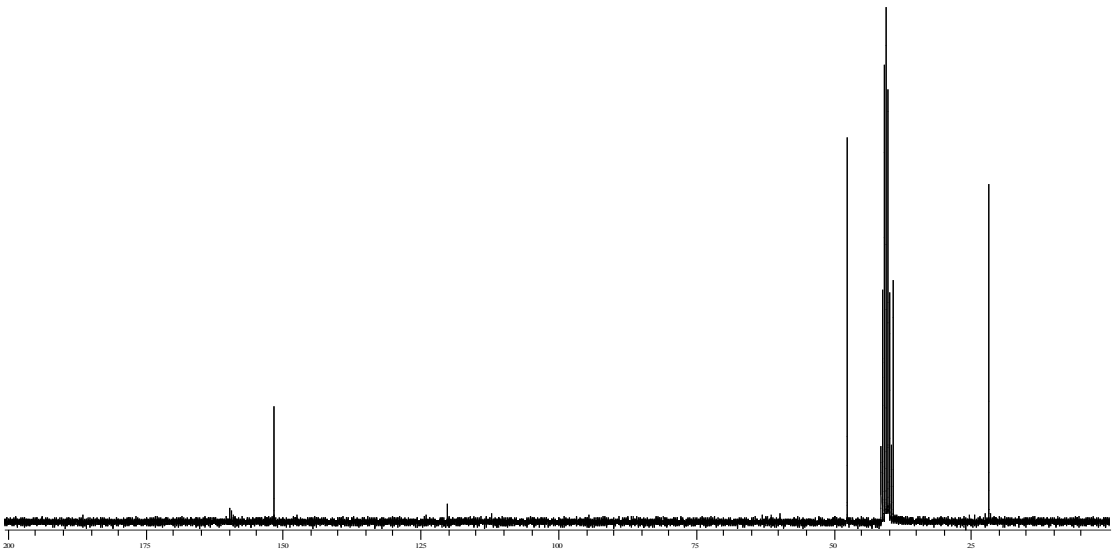


Trifluoroacetate guanidinium salt (1d)

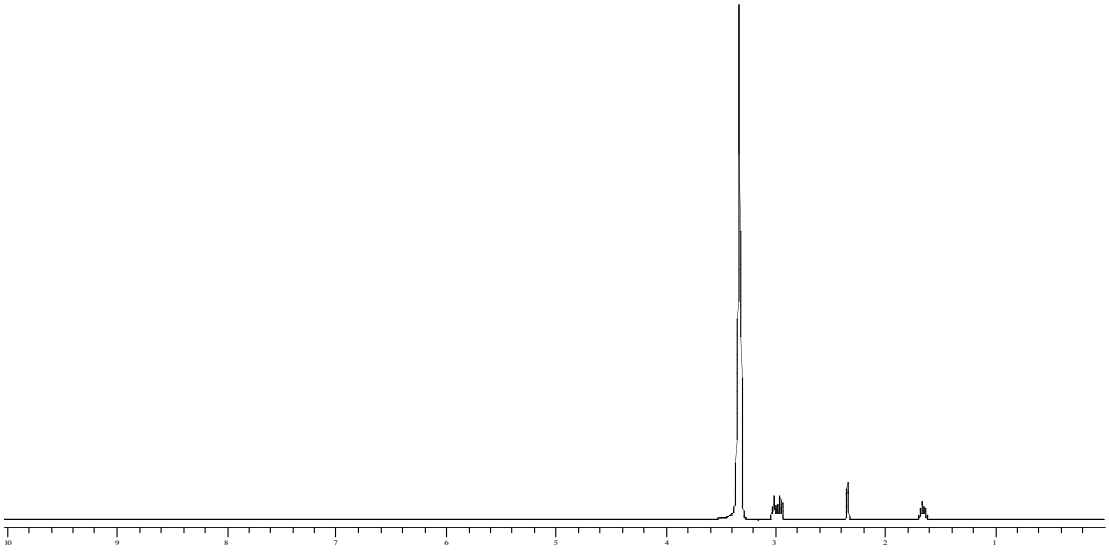


Trifluoroacetic acid (92 mg, 60 μL, 0.81 mmol) was added dropwise to a suspension of triazabicyclo[4.4.0]dec-5-ene (70 mg, 0.50 mmol) in Et_2O (5 mL) and the resulting mixture was vigorously stirred for 30 min. The solid formed was filtered off under reduced pressure and it was washed with several portions of Et_2O to give salt **1d** (193 mg, 94%) as a white solid. Melting point = 160-162 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H = 3.01 (4H, t, J = 6.0 Hz, 2 x CH_2), 2.96 (4H, t, J = 5.8 Hz, 2 x CH_2), 1.66 (4H, quintet., J = 5.9 Hz, 2 x CH_2); ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C = 159.6 (q, $^2J_{C\text{-}F}$ = 31 Hz, CF_3CO_2), 151.6 (CN_3), 118.1 (q, $^1J_{C\text{-}F}$ = 299 Hz, CF_3CO_2), 47.4 (CH_2), 39.1 (CH_2), 21.7 (CH_2); ^{19}F NMR (DMSO-d_6, 282 MHz) δ_F = -73.55 (CF_3); MS (ESI$^+$): *m/z* (%) = 140 (100) $[TBD+H]^+$.

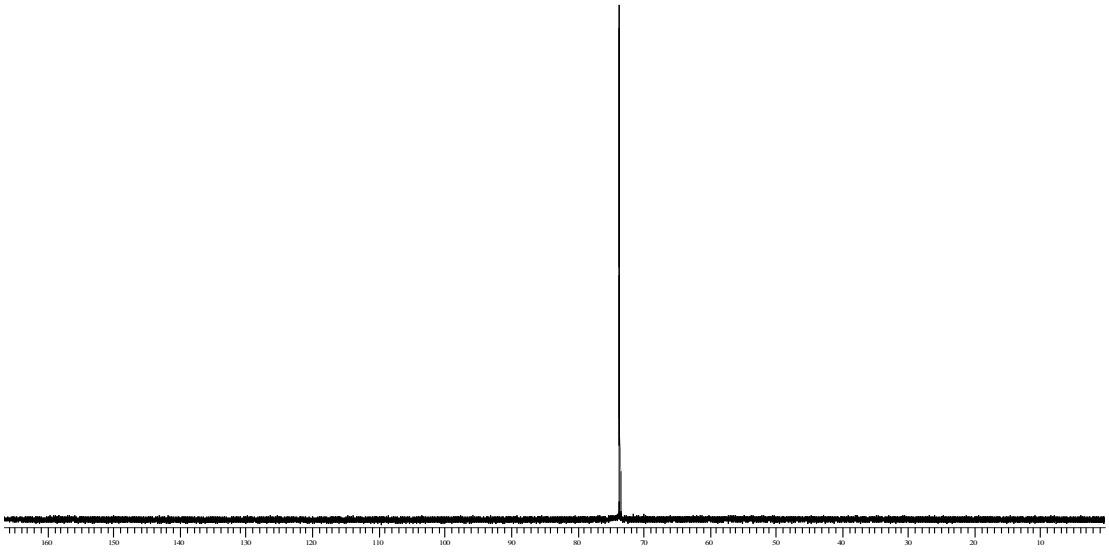
^{13}C



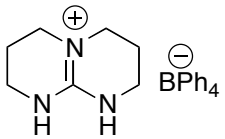
^{1}H



^{19}F

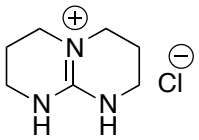


Tetraphenylborate guanidinium salt (1b)



Guanidinium salt **1b** was prepared according to a well-documented literature procedure: Linton, B.; Hamilton, A.D. *Tetrahedron* **1999**, *55*, 6027-6038.

Chloride guanidinium salt (1e)



Guanidinium salt **1e** was prepared according to a well-documented literature procedure: Linton, B.; Hamilton, A.D. *Tetrahedron* **1999**, *55*, 6027-6038.

Standard procedure for the synthesis of aldols 4a-e (SP1)

Tetrafluoroborate guanidinium salt **1a** (9.1 mg, 0.04 mmol), (*S*)-proline (6.9 mg, 0.06 mmol) and solid aldehyde **3a-e** (0.4 mmol) were weighed together inside a screw-capped test tube. Cyclohexanone **2** (393 mg, 0.41 mL, 4.0 mmol) was added to the solid mixture and the resulting suspension, placed on a test tubes grid, was allowed to stay 96 h inside a standard laboratory fridge (temperature fixed at 0-3 ºC) without agitation of mechanical stirring. The mixture was then quenched with NH_4Cl (aq. sat.), extracted with DCM (2 x 15 mL) and the organic liquors dried ($MgSO_4$). Solvents and excess of cyclohexanone were eliminated under reduced pressure. Flash chromatography of crude reaction mixtures afforded pure aldols **4a-e**.

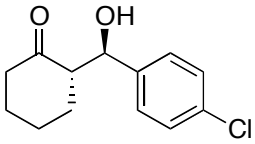
Standard procedure for the synthesis of aldols 4f-h (SP2)

Tetrafluoroborate guanidinium salt **1a** (9.1 mg, 0.04 mmol) and (*S*)-proline (6.9 mg, 0.06 mmol) were weighed together inside a screw-capped test tube. Cyclohexanone **2** (393 mg, 0.41 mL, 4.0 mmol) was added to the solid mixture and finally aldehyde **3f-h** (0.4 mmol), with the aid of a microsyringe. The resulting suspension, placed on a test tubes grid, was transferred to a standard laboratory fridge (temperature fixed at 0-3 ºC), where it stayed 96 h without agitation of mechanical stirring. The mixture was then quenched with NH_4Cl (aq. sat.), extracted with DCM (2 x 15 mL) and the organic liquors dried ($MgSO_4$). Solvents and excess of cyclohexanone were eliminated under reduced pressure. Flash chromatography of crude reaction mixtures afforded pure aldols **4f-h**.

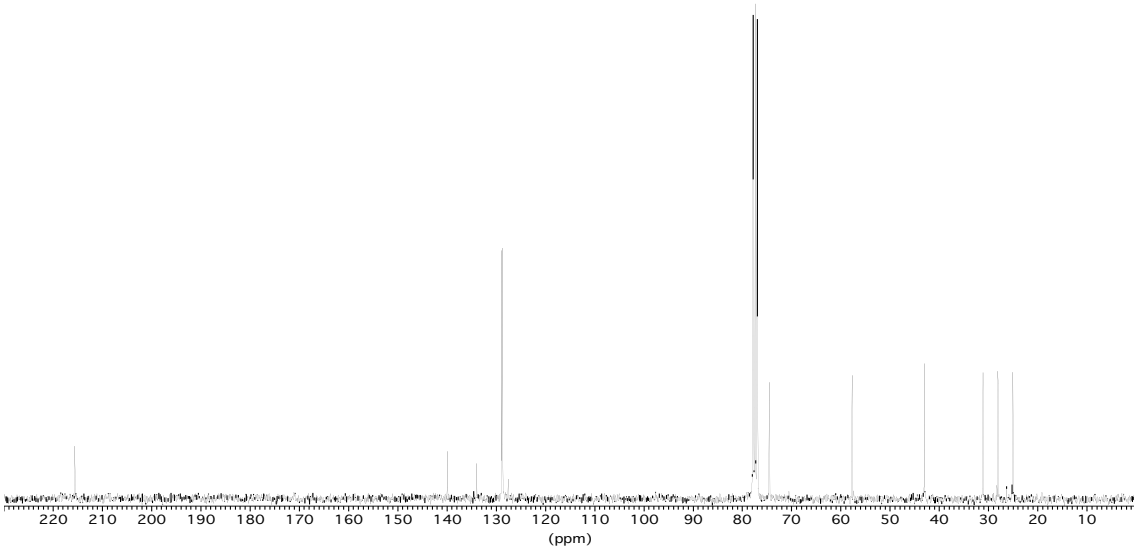
Procedure for the synthesis of aldols 5-7

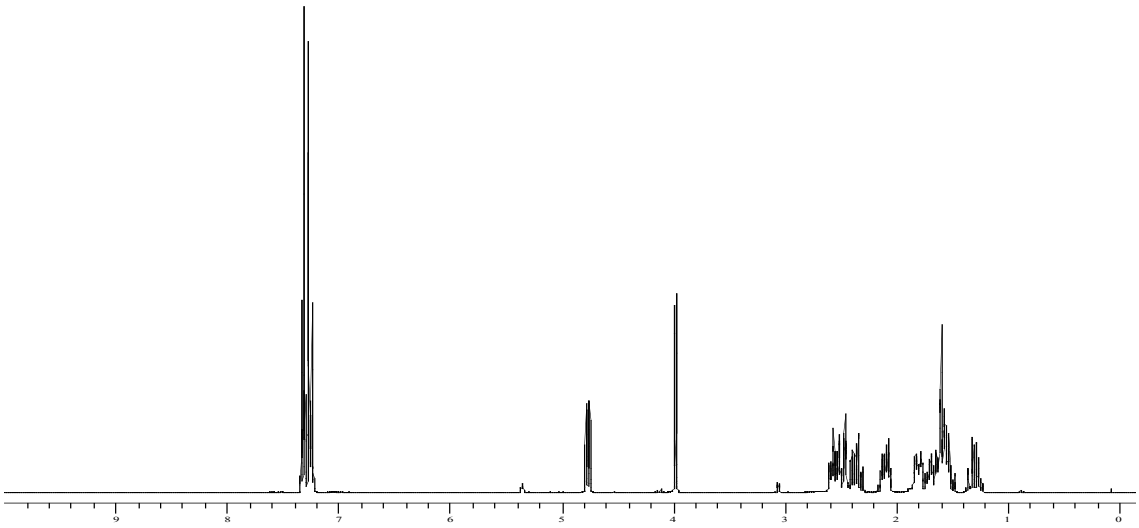
Similar to standard procedure **SP1**. 10 Equivalents of either 4-methylcyclohexanone, cyclopentanone or 2-propanone are used, respectively, for the synthesis of aldols **5**, **6**, or **7**.

(*S*)-2-((*R*)-hydroxy(4-chlorophenyl)methyl)cyclohexan-1-one (4a)[ii]

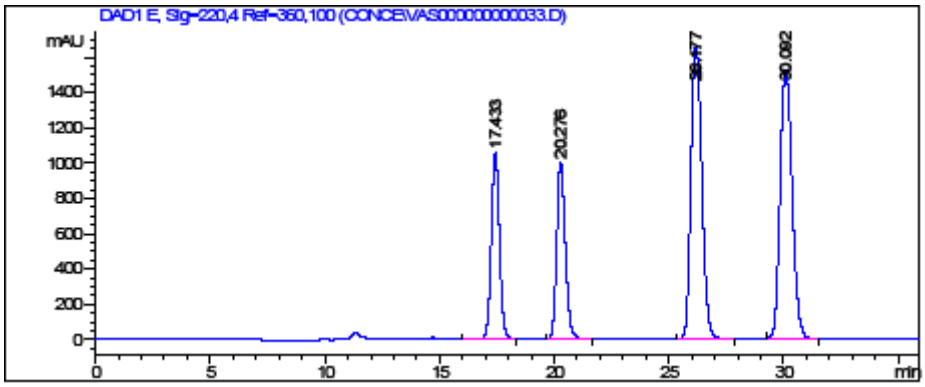


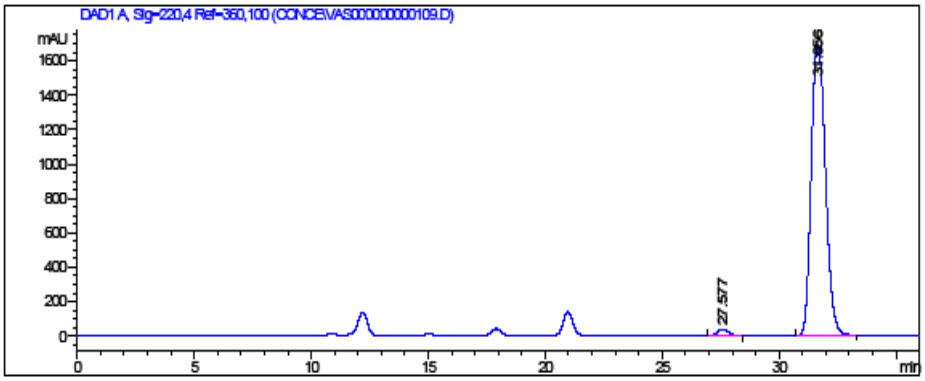
Prepared according to **SP1**. Yellow solid. Purified by flash chromatography (Hex/EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34-7.29 (2H, m, Ar*H*), 7.27-7.24 (2H, m, Ar*H*), 4.76 (1H, dd, *J* = 8.7, 2.8 Hz, C*H*OH), 3.98 (1H, d, *J* = 2.8 Hz, O*H*), 2.60-2.29 (3H, m, C*H* + CH_2), 2.14-2.04 (1H, m, C*H*), 1.82-1.50 (4H, m, 2 x CH_2), 1.36-1.21 (1H, m, C*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.6 (*C*=O), 139. (Ar*C*), 133.9 (Ar*C*), 128.9 (2 x Ar*C*H), 128.7 (2 x Ar*C*H), 74.5 (*C*HOH), 57.7 (*C*H), 43.0 (CH_2), 31.1 (CH_2), 28.1 (CH_2), 25.1 (CH_2).





It was obtained in a maximum of 98% *ee*. The optical purity was determined by HPLC on chiralpak AD-H column (hexane/2-propanol 90:10), flow rate 0.5 mL/min, λ 220 nm.





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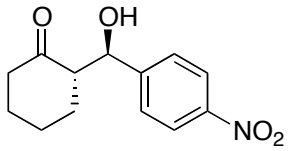
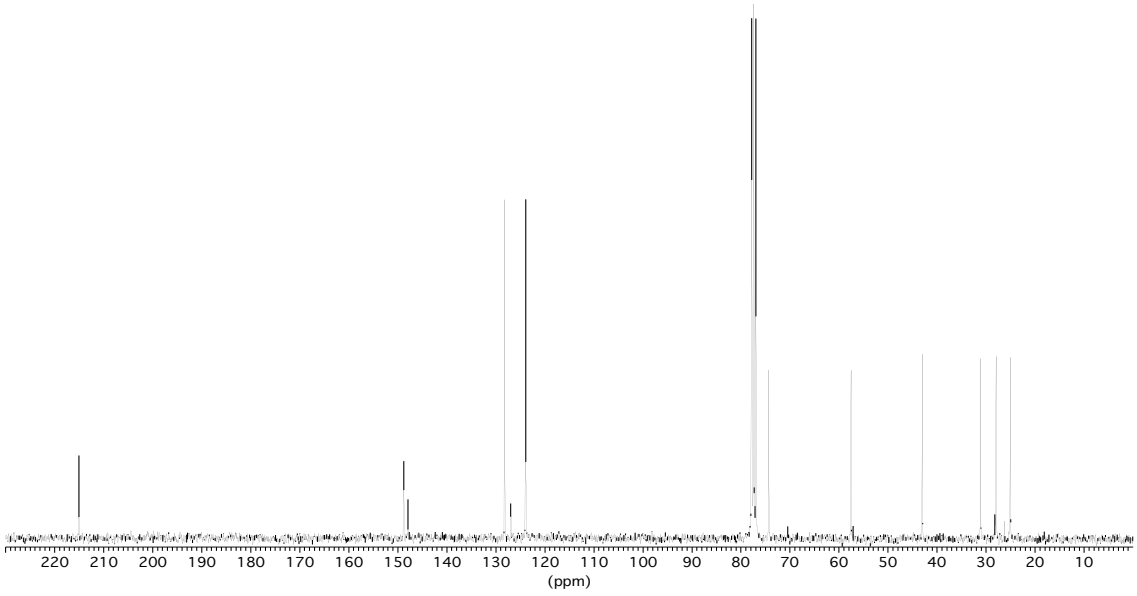
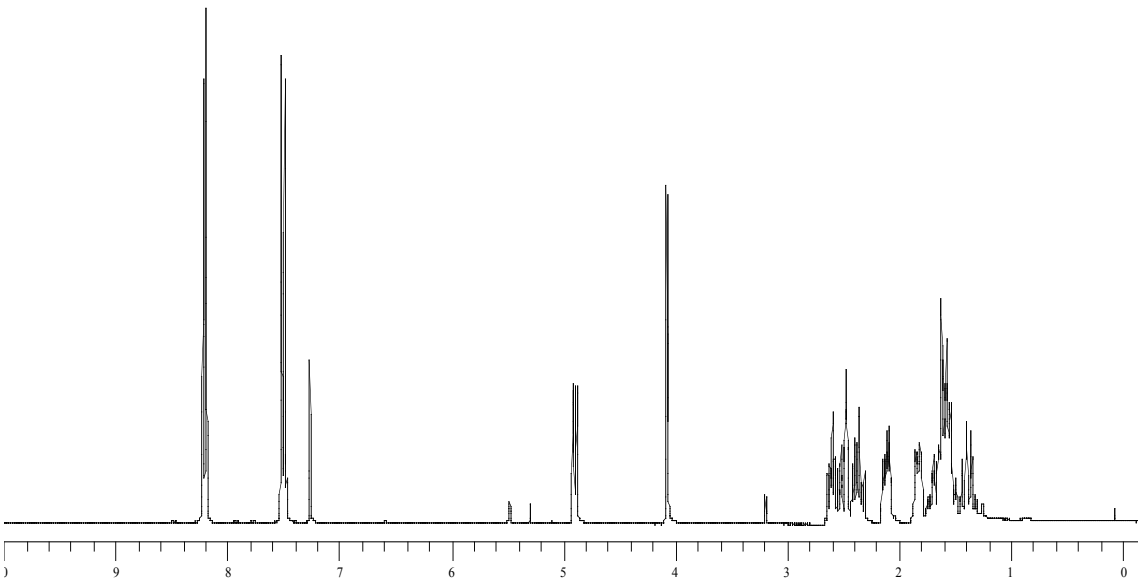
(*S*)-2-((*R*)-hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (4b)[2]

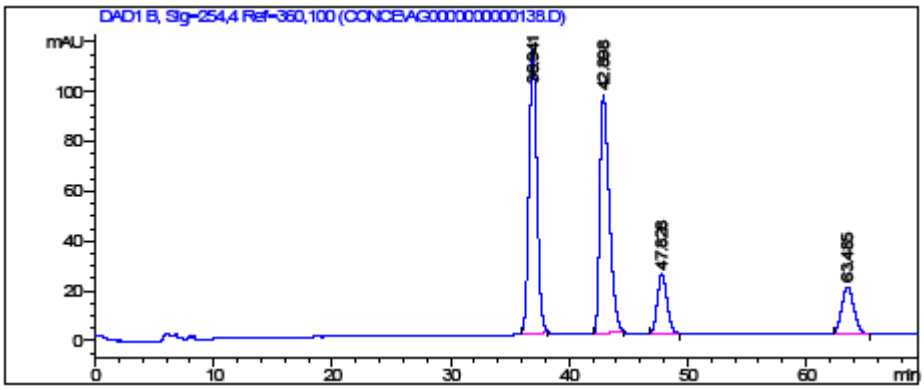


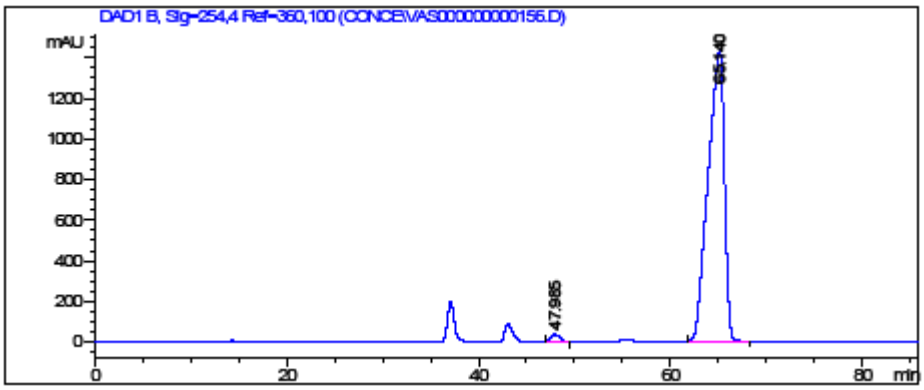
Prepared according to **SP1**. Orangish solid. Purified by flash chromatography (Hex/EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21-8.18 (2H, m, Ar*H*), 7.52-7.47 (2H, m, Ar*H*), 4.89 (1H, dd, *J* = 8.4, 3.1 Hz, C*H*OH), 4.07 (1H, d, *J* = 3.1 Hz, O*H*), 2.63-2.30 (3H, m, C*H* + CH_2), 2.15-2.07 (1H, m, C*H*), 1.85-1.52 (4H, m, 2 x CH_2), 1.45-1.30 (1H, m, C*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.0 (*C*=O), 148.7 (Ar*C*), 147.9 (Ar*C*), 128.2 (2 x Ar*C*H), 123.9 (2 x Ar*C*H), 74.3 (*C*HOH), 57.5 (*C*H), 43.0 (*C*H_2), 31.1 (*C*H_2), 28.0 (*C*H_2), 25.0 (*C*H_2).





It was obtained in a maximum of 99% *ee*. The optical purity was determined by HPLC on a chiralpak AD-H column (hexane/2-propanol 90:10), flow rate 0.5 mL/min, λ 254 nm.





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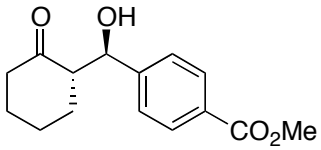
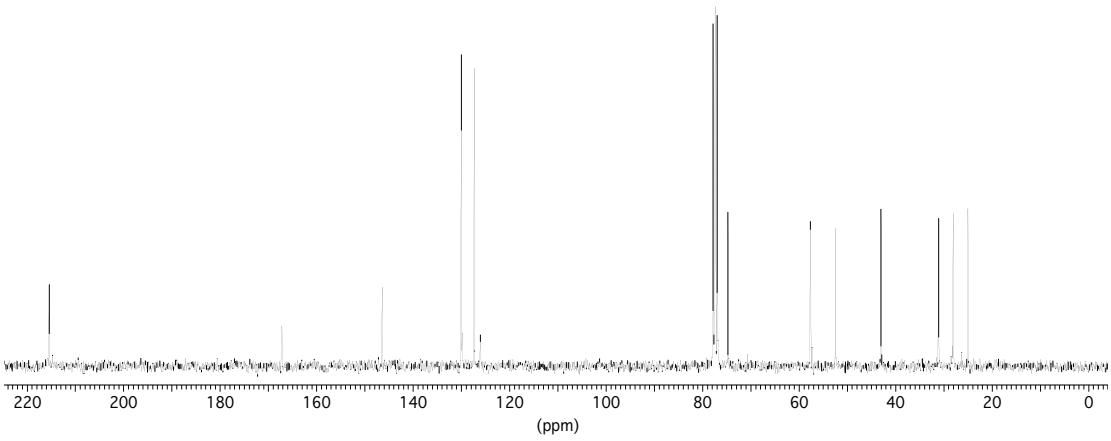
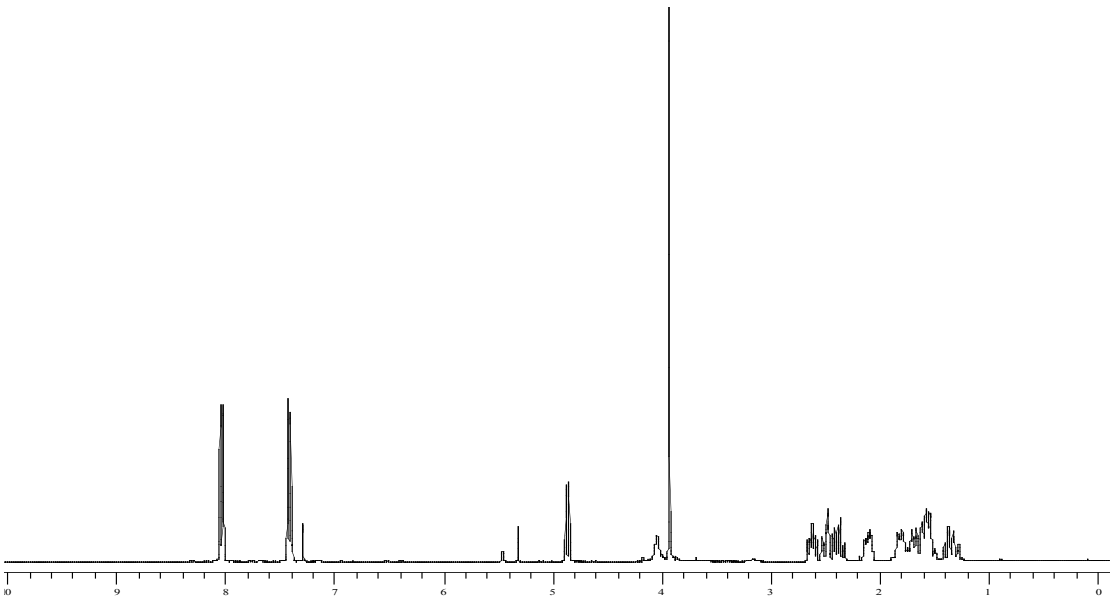
(*S*)-2-((*R*)-hydroxy(4-methoxycarbonylphenyl)methyl)cyclohexan-1-one (4c)[2]

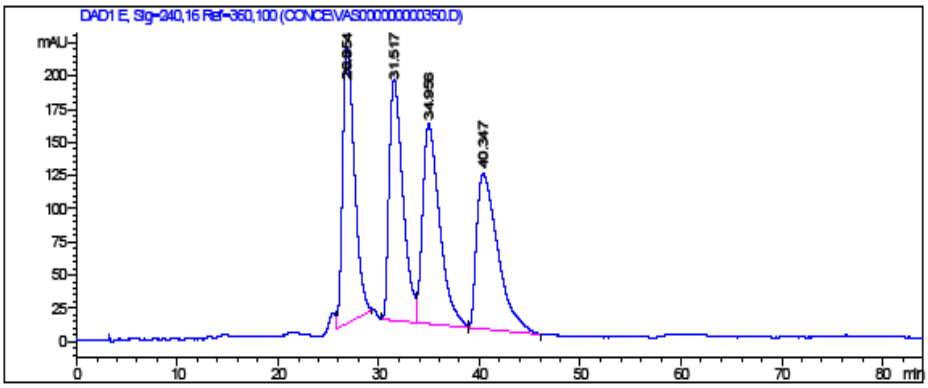


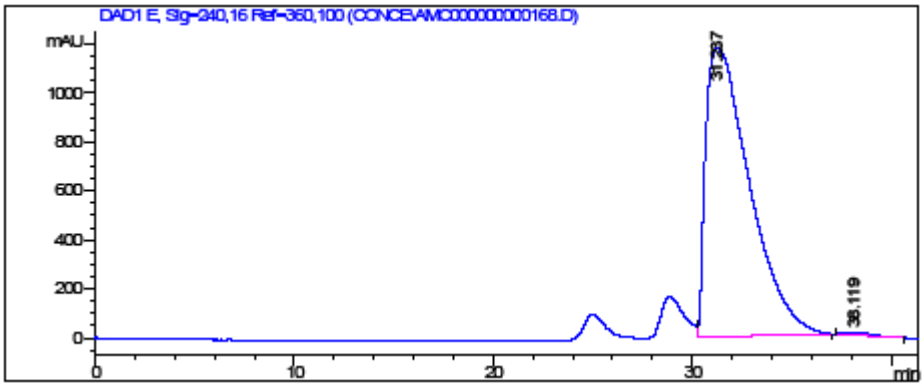
Prepared according to **SP1**. Yellow solid. Purified by flash chromatography (Hex/EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02-7.99 (2H, m, Ar*H*), 7.40-7.37 (2H, m, Ar*H*), 4.84 (1H, d, *J* = 8.5 Hz, C*H*OH), 4.01 (1H, s, CHO*H*), 3.90 (3H, t, *J* = 0.6 Hz, CO_2CH_3), 2.64-2.29 (3H, m, C*H* + CH_2), 2.12-2.03 (1H, m, C*H*H), 1.81-1.51 (4H, m, 2 x CH_2), 1.37-1.24 (1H, m, CH*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.4 (*C*=O), 167.2 (CO_2), 146.4 (Ar*C*), 130.0 (2 x Ar*C*H), 127.4 (2 x Ar*C*H), 126.1 (Ar*C*), 74.7 (*C*HOH), 57.6 (*C*H), 52.4 (CO_2CH_3), 43.0 (CH_2), 31.1 (CH_2), 28.0 (CH_2), 25.0 (CH_2).





It was obtained in a maximum of 99% *ee*. The optical purity was determined by HPLC on a chiralpak OD-H column (hexane/2-propanol 98:2), flow rate 1.0 mL/min, λ 240 nm.





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2	38.119	0.5249

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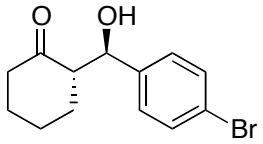
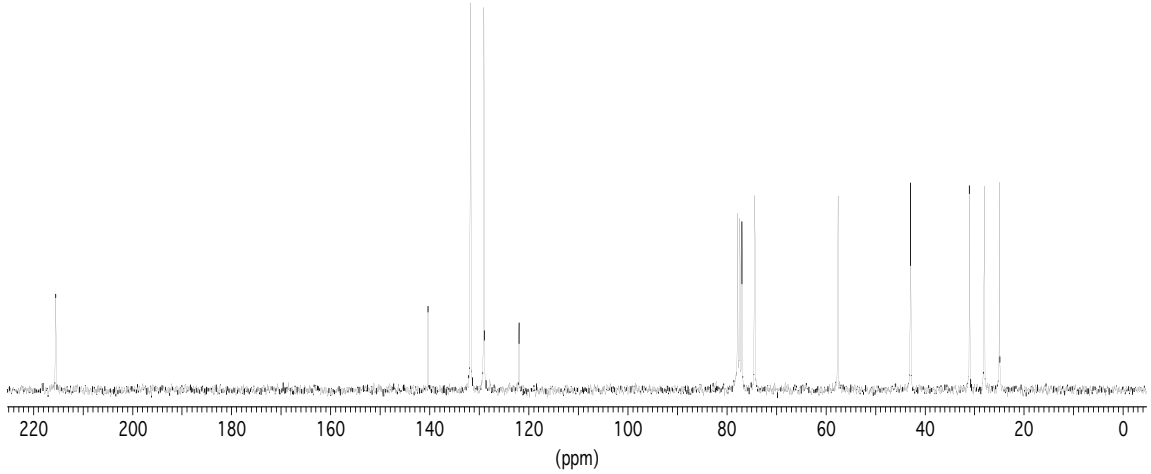
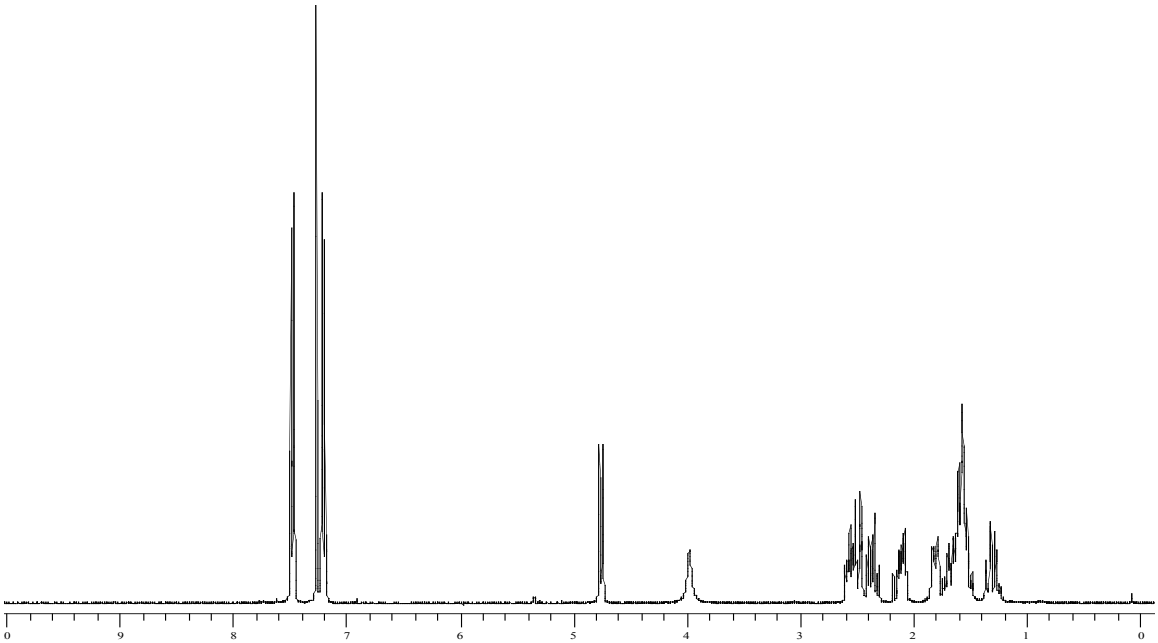
(*S*)-2-((*R*)-hydroxy(4-bromophenyl)methyl)cyclohexan-1-one (4d)[2]

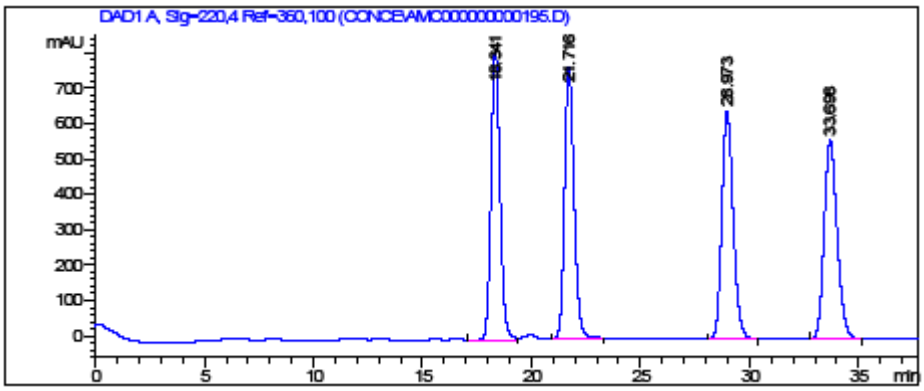


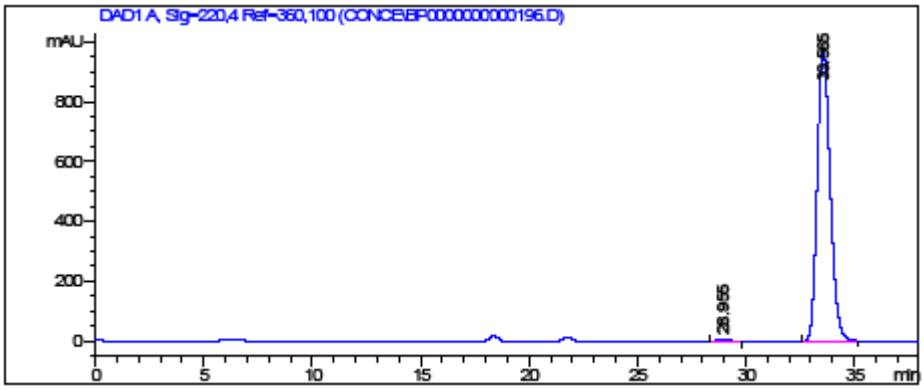
Prepared according to **SP1**. Yellow solid. Purified by flash chromatography (Hex/EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49-7.45 (2H, m, Ar*H*), 7.21-7.18 (2H, m, Ar*H*), 4.75 (1H, d, *J* = 8.7 Hz, C*H*OH), 3.97 (1H, s, O*H*), 2.59-2.29 (3H, m, C*H* + CH_2), 2.13-2.05 (1H, m, C*H*H), 1.83-1.47 (4H, m, 2 x CH_2), 1.36-1.22 (1H, m, CH*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.4 (*C*=O), 140.3 (Ar*C*), 131.7 (2 x Ar*C*H), 129.0 (2 x Ar*C*H), 122.0 (Ar*C*), 74.4 (*C*HOH), 57.6 (*C*H), 43.0 (CH_2), 31.0 (CH_2), 28.0 (CH_2), 25.0 (CH_2).





It was obtained in a maximum of 99% *ee*. The optical purity was determined by HPLC on a chiralpak AD-H column (hexane/2-propanol 90:10), flow rate 0.5 mL/min, λ 220 nm.





Area Percent Report

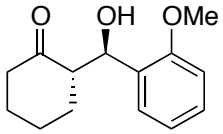
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

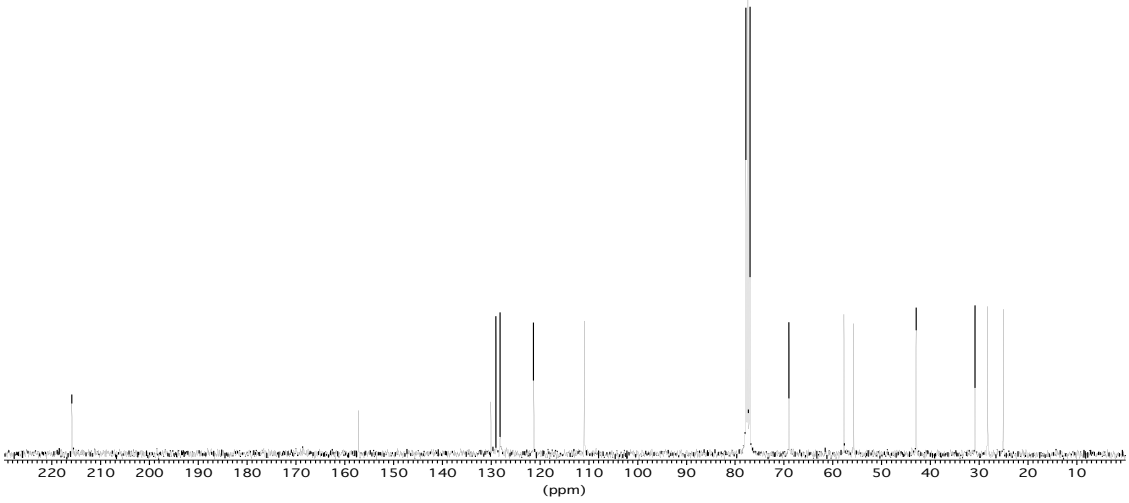
Peak #	RetTime [min]	Area %
1	28.955	0.7077
2	33.565	99.2923

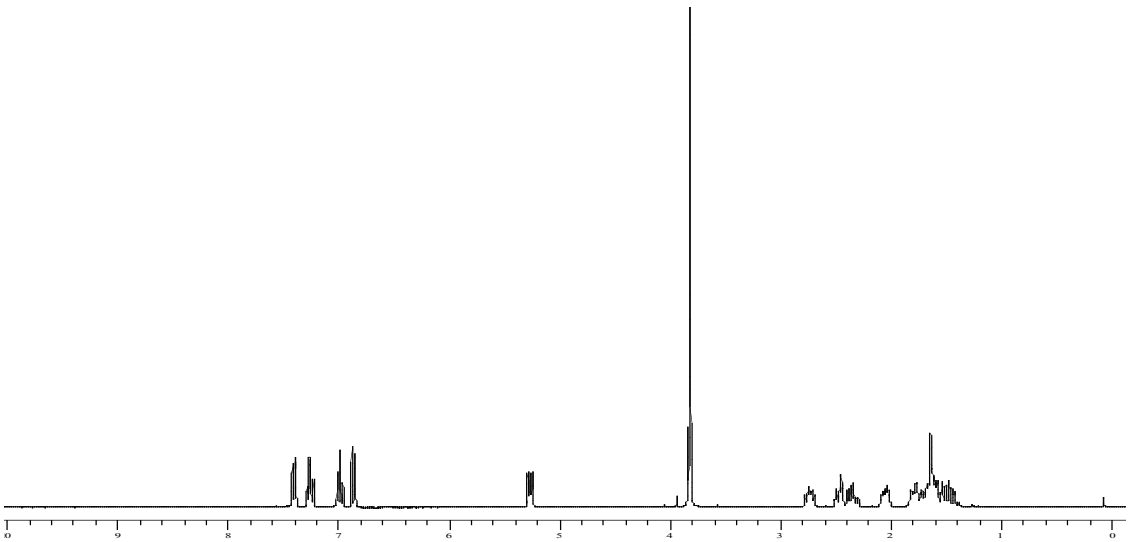
*** End of Report ***

(*S*)-2-((*R*)-hydroxy(2-methoxyphenyl)methyl)cyclohexan-1-one (4e)[iii]

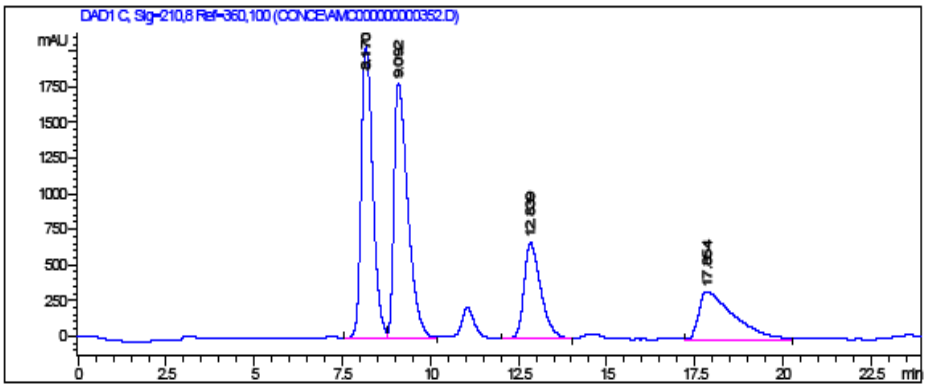


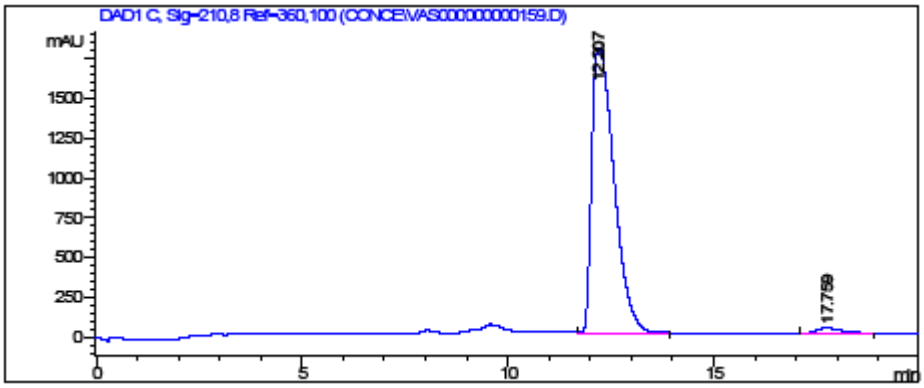
Prepared according to **SP1**. Yellow solid. Purified by flash chromatography (Hex/EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41-7.38 (1H, m, Ar*H*), 7.28-7.22 (1H, m, Ar*H*), 7.00-6.95 (1H, m, Ar*H*), 6.88-6.85 (1H, m, Ar*H*), 5.26 (1H, dd, *J* = 8.5, 4.6 Hz, C*H*OH), 3.83 (1 H, s, O*H*), 3.81 (3 H, s, OCH_3), 2.77-2.69 (1 H, m, C*H*), 2.49-2.29 (2 H, m, CH_2), 2.08-2.01 (1 H, m, C*H*), 1.81-1.42 (5 H, m, C*H* + (2 x CH_2)); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.9 (*C*=O), 157.1 (Ar*C*), 130.0 (Ar*C*), 128.9 (Ar*C*H), 128.1 (Ar*C*H), 121.2 (Ar*C*H), 110.8 (Ar*C*H), 68.9 (*C*HOH), 57.6 (*C*H), 55.7 (O*C*H_3), 42.9 (*C*H_2), 30.8 (*C*H_2), 28.3 (*C*H_2), 25.0 (*C*H_2).





It was obtained in a maximum of 98% *ee*. The optical purity was determined by HPLC on a chiralcel OD column (hexane/2-propanol 95:5), flow rate 1.0 mL/min, λ 210 nm.





Area Percent Report

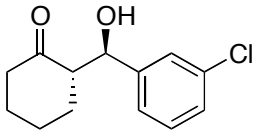
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

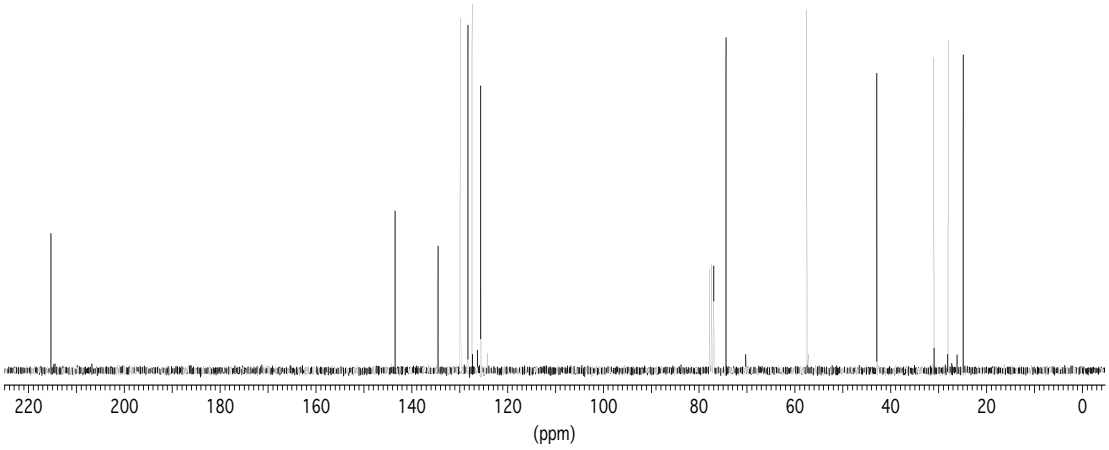
Peak #	RetTime [min]	Area %
1	12.207	98.9537
2	17.759	1.0463

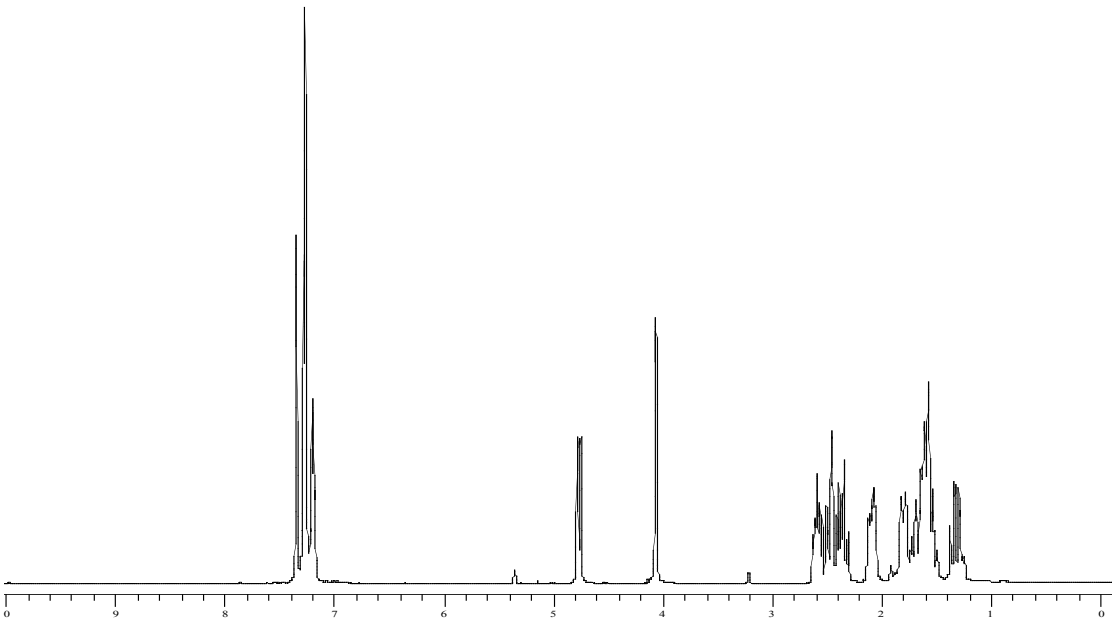
*** End of Report ***

(*S*)-2-((*R*)-hydroxy(3-chlorophenyl)methyl)cyclohexan-1-one (4f)[3]

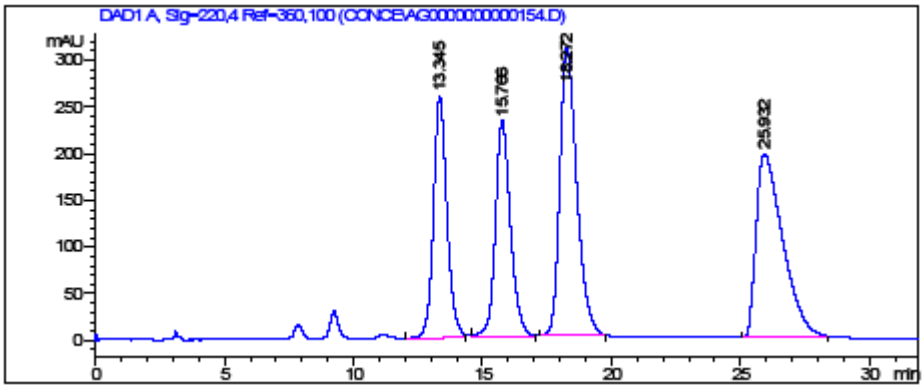


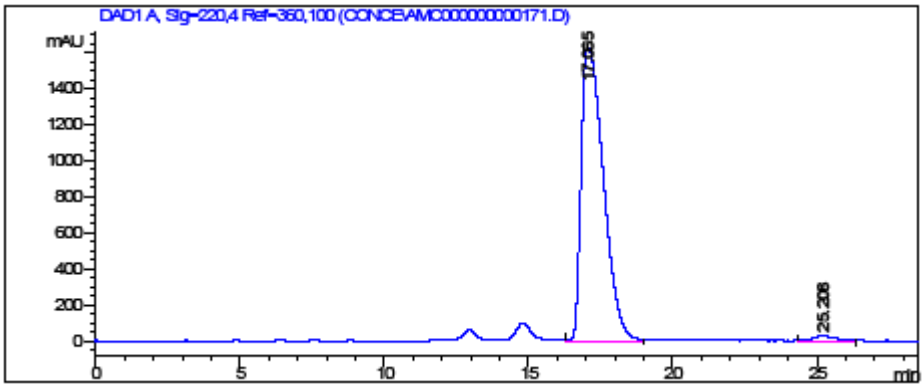
Prepared according to **SP2**. White solid. Purified by flash chromatography (Hex/EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34-7.17 (4H, m, Ar*H*), 4.76 (1H, dd, *J* = 1.89, 8.7 Hz, C*H*OH), 4.06 (1H, d, J = 1.74 Hz, CHO*H*), 2.63-2.30 (3H, m, C*H* + CH_2), 2.11-2.04 (1H, m, C*H*H), 1.82-1.52 (4H, m, 2 x CH_2), 1.37-1.23 (1H, m, CH*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.3 (*C*=O), 143.4 (Ar*C*), 134.5 (Ar*C*), 129.8 (Ar*C*H), 128.2 (Ar*C*H), 127.4 (Ar*C*H), 125.5 (Ar*C*H), 74.4 (*C*HOH), 57.5 (*C*H), 42.8 (*C*H_2), 31.0 (*C*H_2), 27.9 (*C*H_2), 24.9 (*C*H_2).





It was obtained in a maximum of 98% *ee*. The optical purity was determined by HPLC on a chiralcel OD column (hexane/2-propanol 98:2), flow rate 1.0 mL/min, λ 220 nm.





Area Percent Report

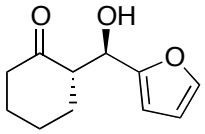
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

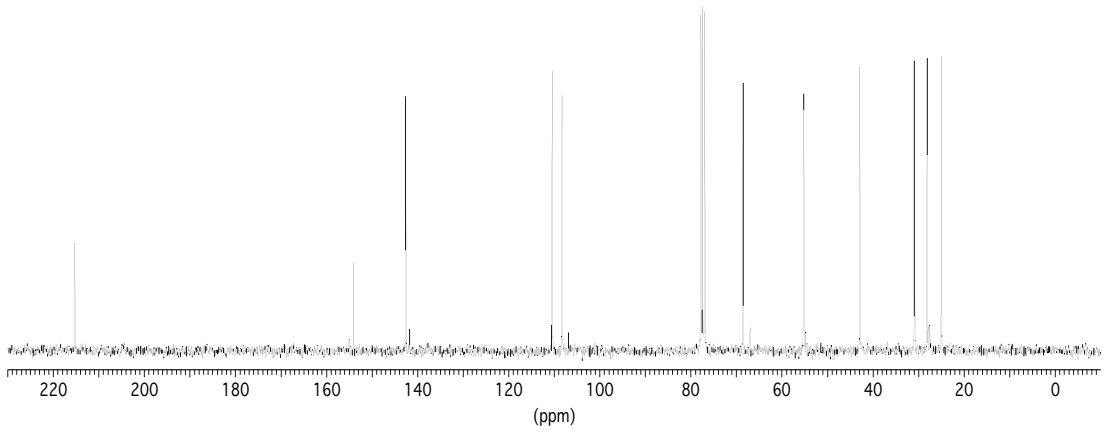
Peak #	RetTime [min]	Area %
1	17.065	99.1506
2	25.208	0.8494

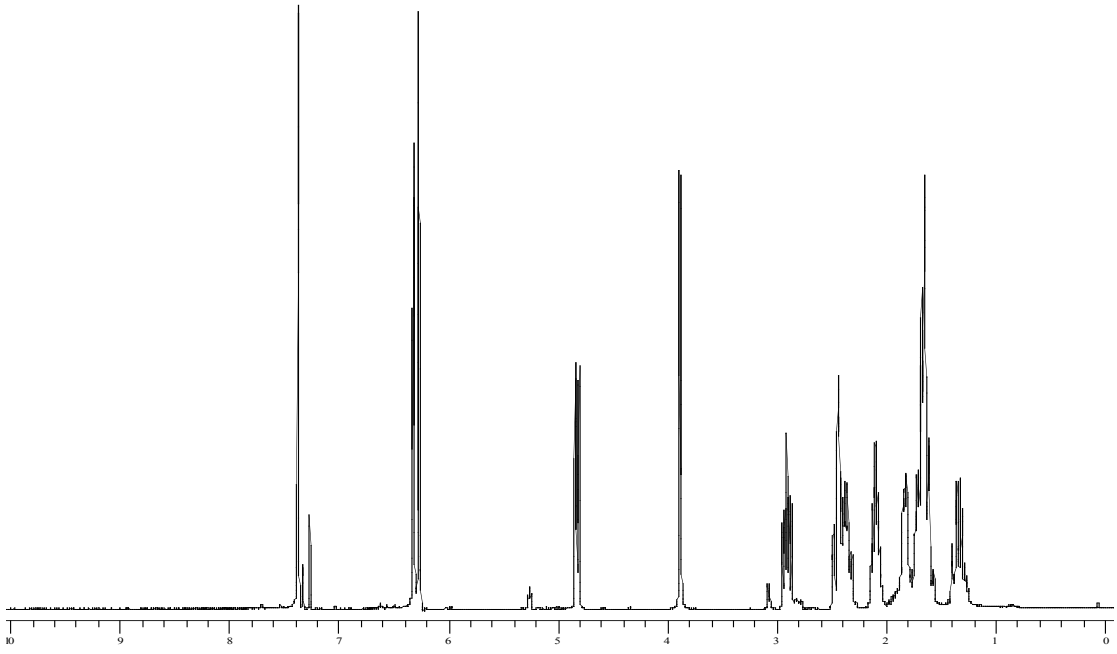
*** End of Report ***

(*S*)-2-((*R*)-hydroxy(2-furyl)methyl)cyclohexan-1-one (4g)[iv]

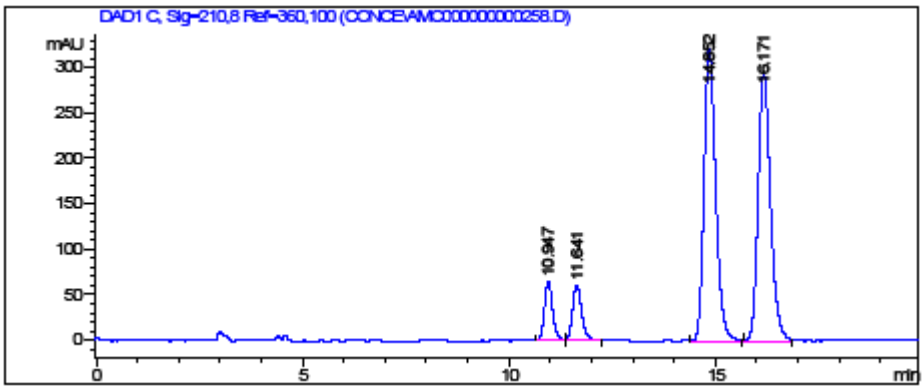


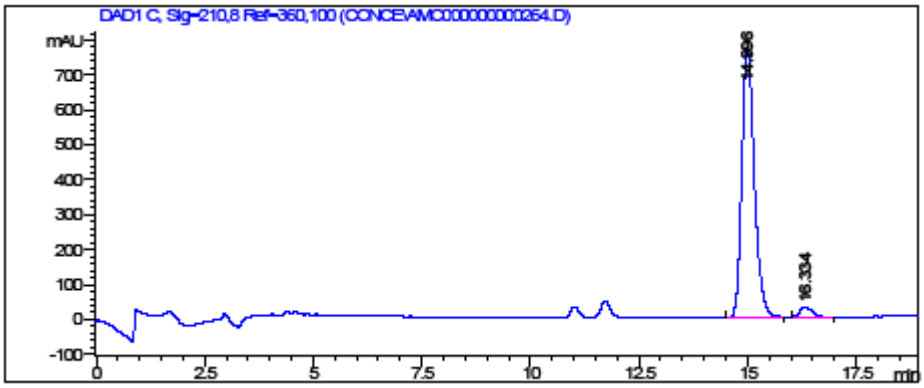
Prepared according to **SP2**. Yellow solid. Purified by flash chromatography (Hex/EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37-7.32 (1H, m, Ar*H*), 6.32-6.25 (2H, m, Ar*H*), 4.82 (1H, dd, *J* = 8.3, 3.6 Hz, C*H*OH), 3.88 (1H, d, *J* = 3.8 Hz, O*H*), 2.95-2.77 (1H, m, C*H*), 2.49-2.30 (2H, m, CH_2), 2.13-2.05 (1H, m, C*H*H), 1.86-1.56 (4H, m, 2 x CH_2), 1.42-1.24 (1H, m, CH*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.2 (*C*=O), 154.0 (Ar*C*), 142.6 (Ar*C*H), 110.4 (Ar*C*H), 108.2 (Ar*C*H), 68.5 (*C*HOH), 55.2 (*C*H), 42.9 (*C*H_2), 30.9 (*C*H_2), 28.1 (*C*H_2), 25.0 (*C*H_2).





It was obtained in a maximum of 91% ee. The optical purity was determined by HPLC on a chiralpak AD-H column (hexane/2-propanol 90:10), flow rate 1.0 mL/min, λ 210 nm.





Area Percent Report

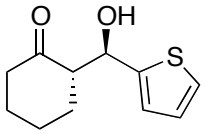
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

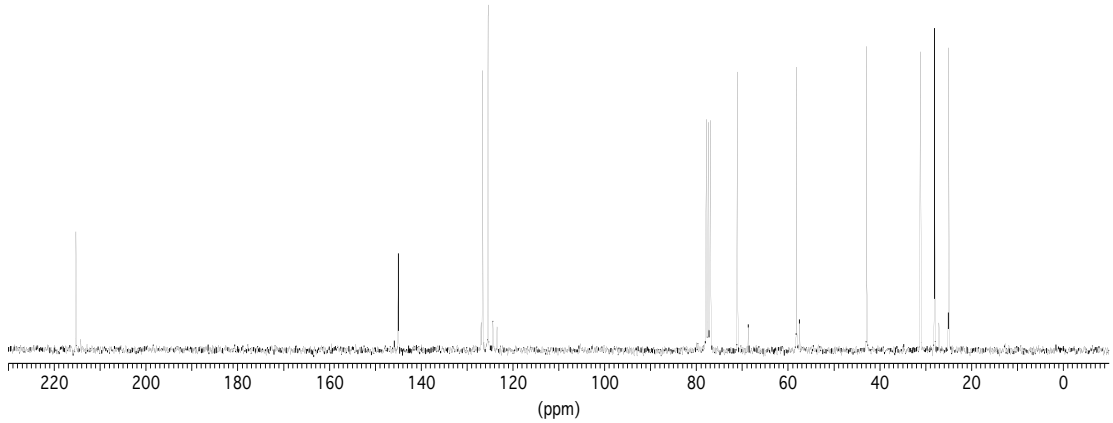
Peak #	RetTime [min]	Area %
1	14.996	95.4712
2	16.334	4.5288

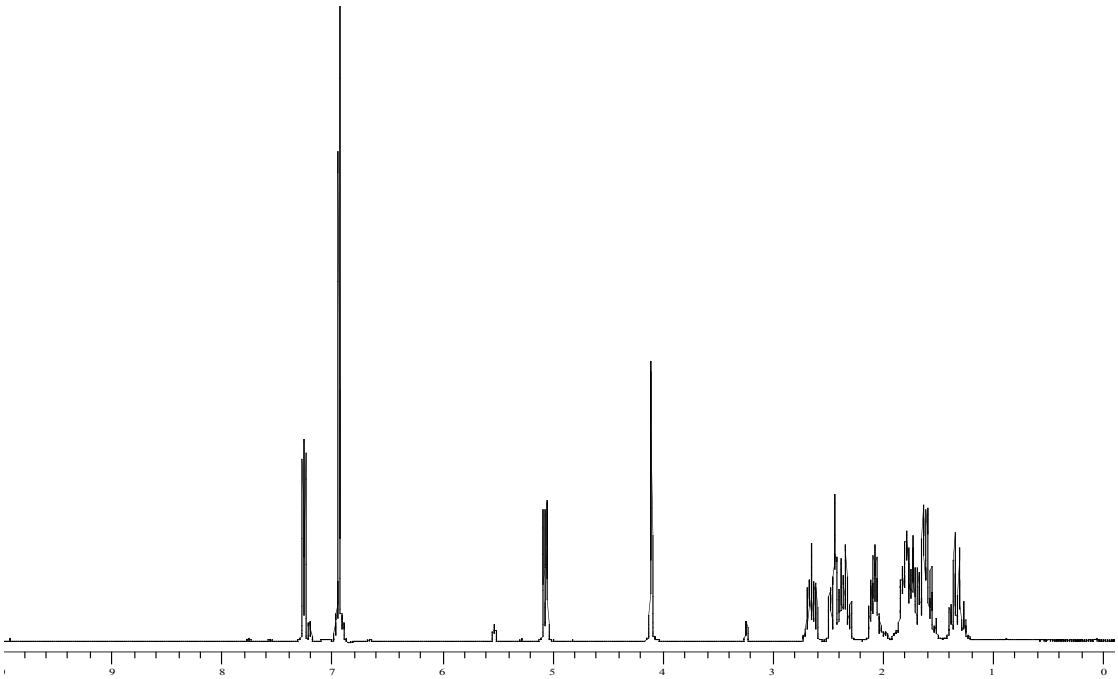
*** End of Report ***

(*S*)-2-((*R*)-hydroxy(2-thiophenyl)methyl)cyclohexan-1-one (4h)[4]

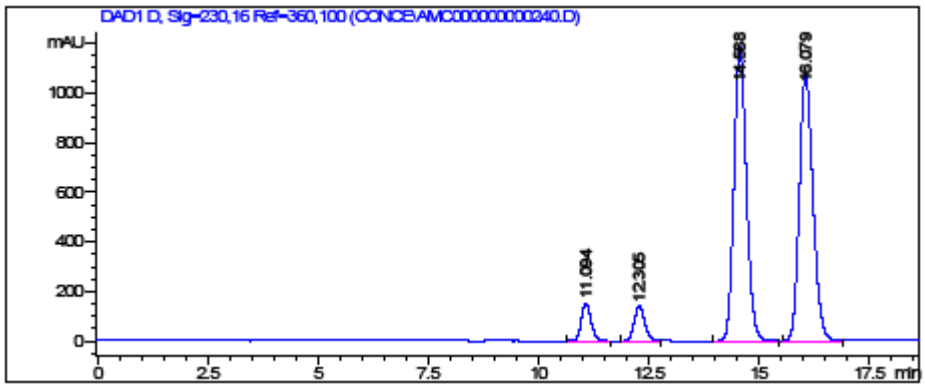


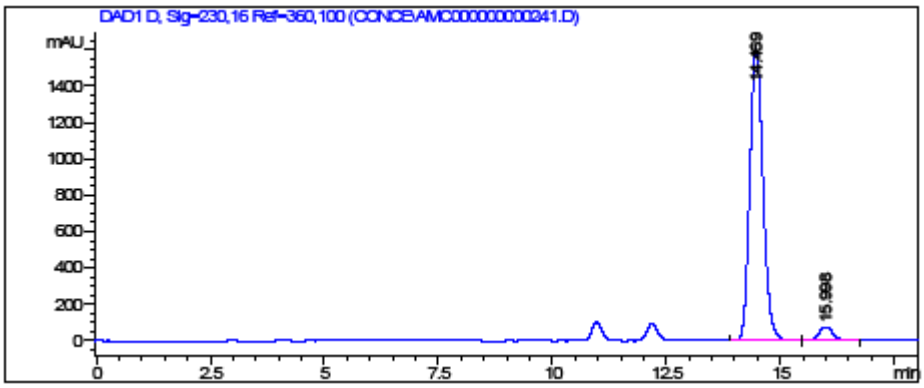
Prepared according to **SP2**. Yellow oil. Purified by flash chromatography (Hex/EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28-7.21 (1H, m, Ar*H*), 6.99-6.91 (2H, m, Ar*H*), 5.08 (1H, dd, *J* = 8.4, 3.0 Hz, C*H*OH), 4.12 (1H, d, *J* = 3.2 Hz, O*H*), 2.70-2.61 (1H, m, C*H*), 2.50-2.30 (2H, m, CH_2), 2.15-2.06 (1H, m, C*H*H), 1.86-1.54 (4H, m, 2 x CH_2), 1.41-1.26 (1H, m, CH*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.2 (*C*=O), 145.0 (Ar*C*-S), 126.6 (Ar*C*H-S), 125.4 (Ar*C*H), 125.3 (Ar*C*H), 71.0 (*C*HOH), 58.1 (*C*H), 42.9 (*C*H_2), 31.1 (*C*H_2), 28.0 (*C*H_2), 25.0 (*C*H_2).





It was obtained in a maximum of 90% *ee*. The optical purity was determined by HPLC on a chiralpak AD-H column (hexane/2-propanol 90:10), flow rate 1.0 mL/min, λ 230 nm.





Area Percent Report

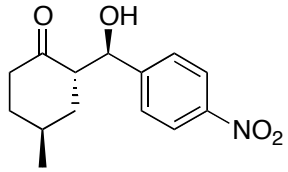
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

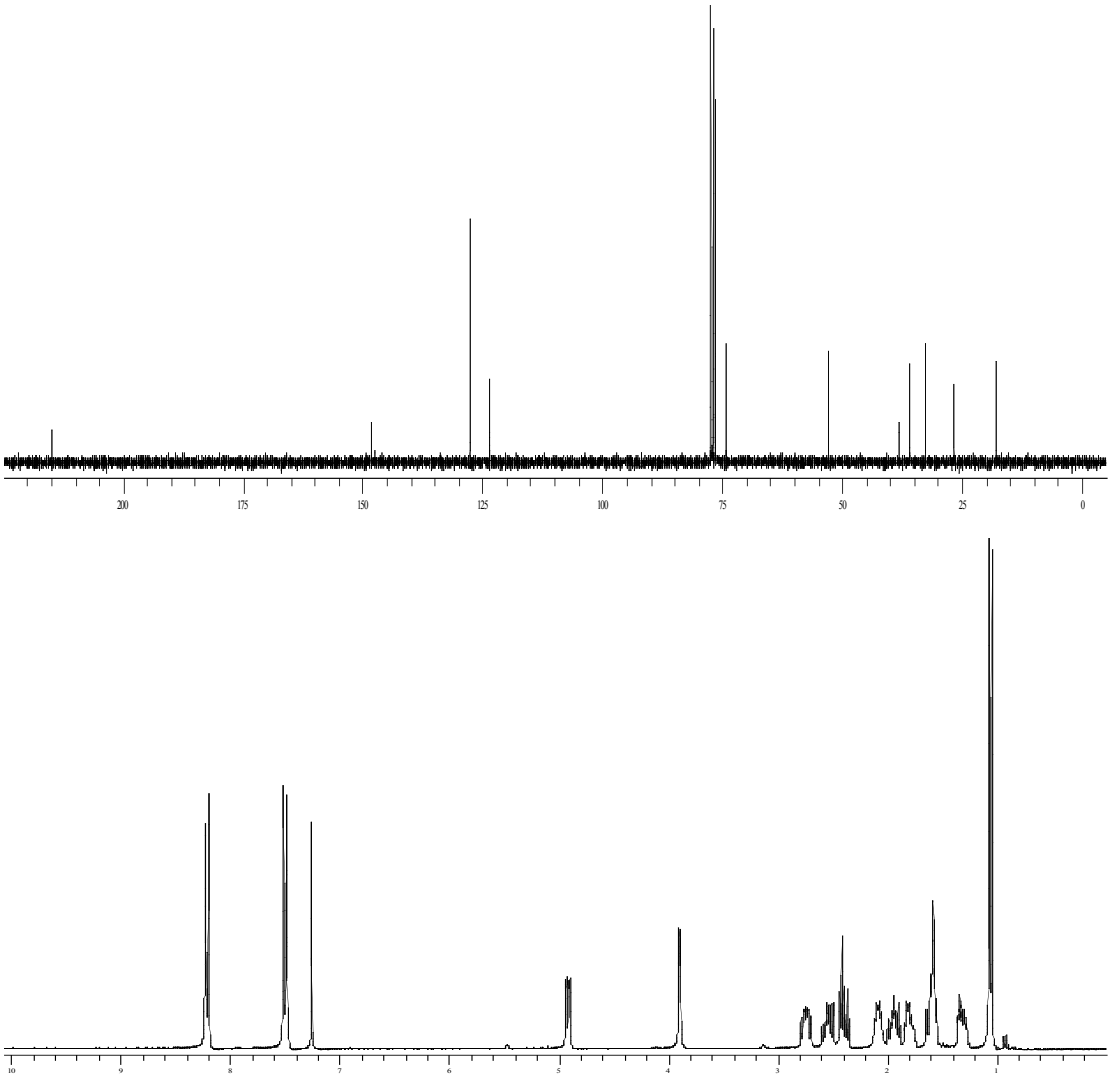
Peak #	RetTime [min]	Area %
1	14.469	94.9704
2	15.998	5.0296

*** End of Report ***

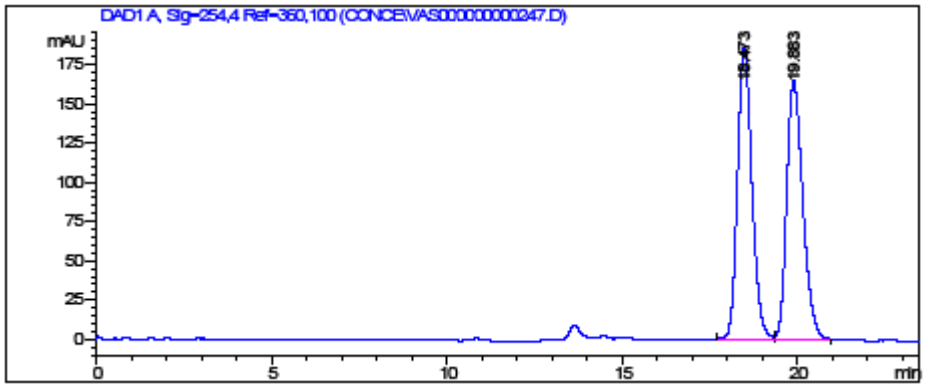
((2*S*,4*S*)-2-((*R*)-hydroxy(4-nitrophenyl)methyl)-4-methylcyclohexanone (5)[v]

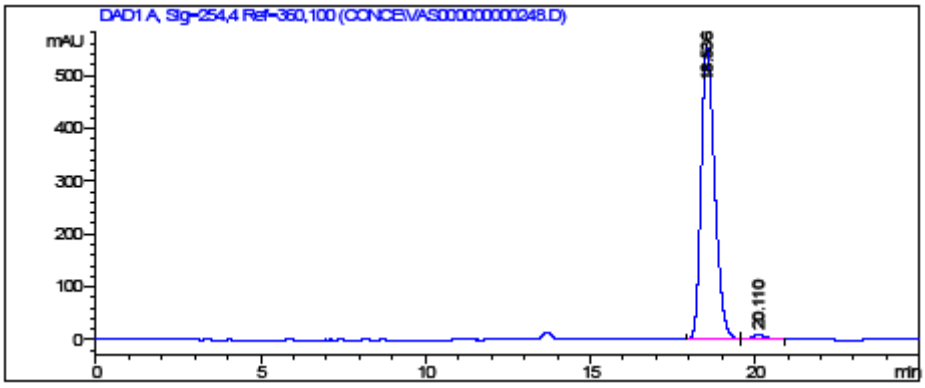


Yellow solid. Purified by flash chromatography (Hex/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.22 (2H, d, *J* = 8.7 Hz, ArC*H*), 7.51 (2H, d, *J* = 8.7 Hz, ArC*H*), 4.92 (1H, dd, *J* = 8.5, 2.5 Hz, C*H*OH), 3.90 (1H, d, *J* = 2.5 Hz, O*H*), 2.78-2.70 (1H, m, C*H*), 2.60-2.49 (1H, m, C*H*), 2.43-2.35 (1H, m, C*H*), 2.11-2.04 (1H, m, C*H*), 2.00-1.88 (1H, m, C*H*), 1.88-1.74 (1H, m, C*H*), 1.65-1.55 (1H, m, C*H*), 1.36-1.25 (1H, m, C*H*), 1.06 (3H, d, *J* = 7.0 Hz, CH_3); ^{13} C NMR ($CDCl_3$, 75 MHz) δ = 215.3 (*C*=O), 148.7 (Ar*C*), 148.0 (Ar*C*), 128.2 (Ar*C*H), 124.0 (Ar*C*H), 74.5 (*C*HOH), 53.2 (*C*H), 38.5 (*C*H_2), 36.4 (*C*H), 33.2 (*C*H_2), 27.0 (*C*H_2), 18.5 (*C*H_3).



It was obtained in a maximum of 97% *ee*. The optical purity was determined by HPLC on a chiralpak AD-H column (hexane/2-propanol 85:15), flow rate 1.0 mL/min, λ 254 nm.





Area Percent Report

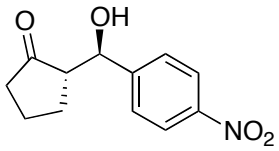
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

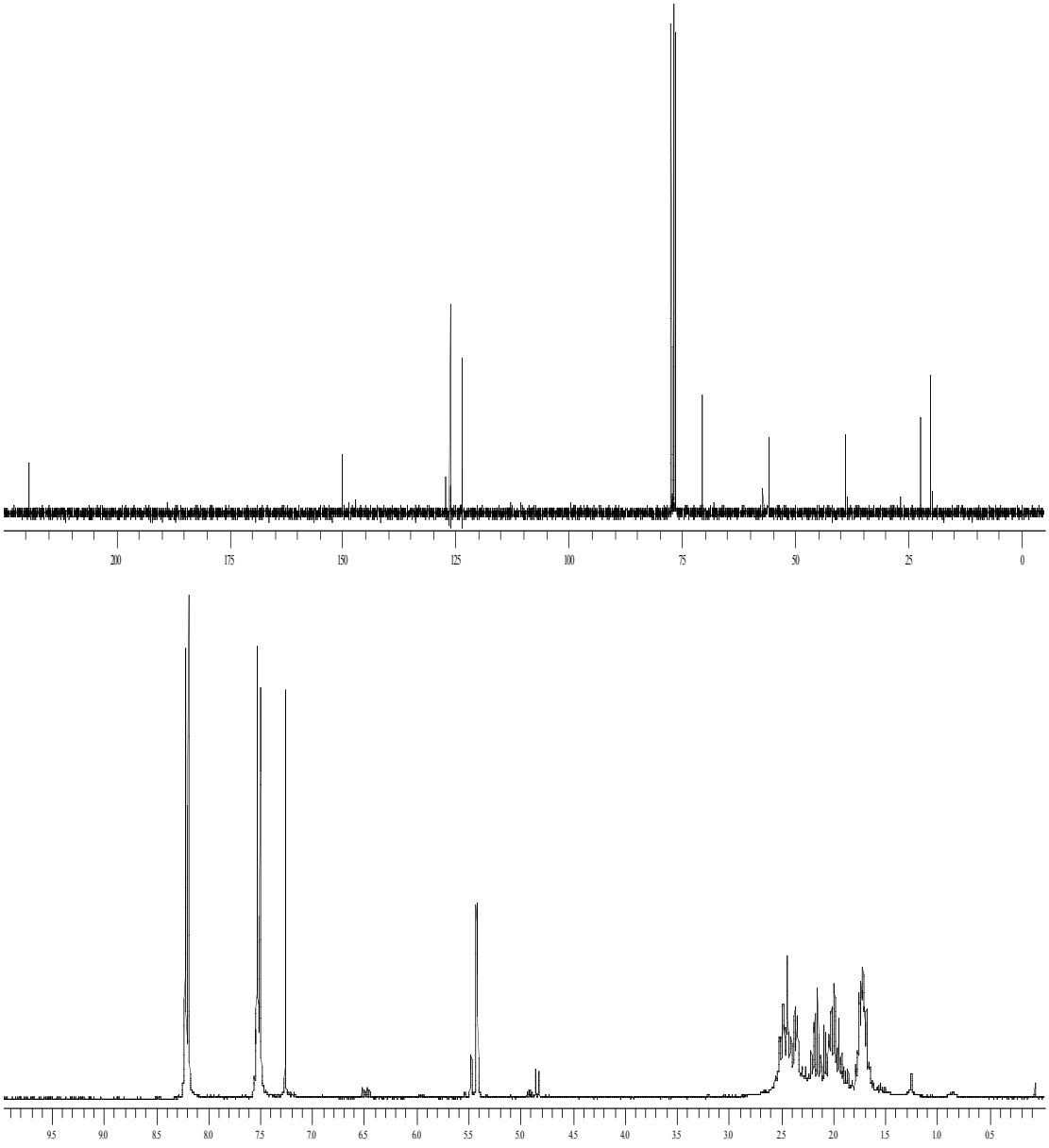
Peak #	RetTime [min]	Area %
1	18.536	98.5206
2	20.110	1.4794

*** End of Report ***

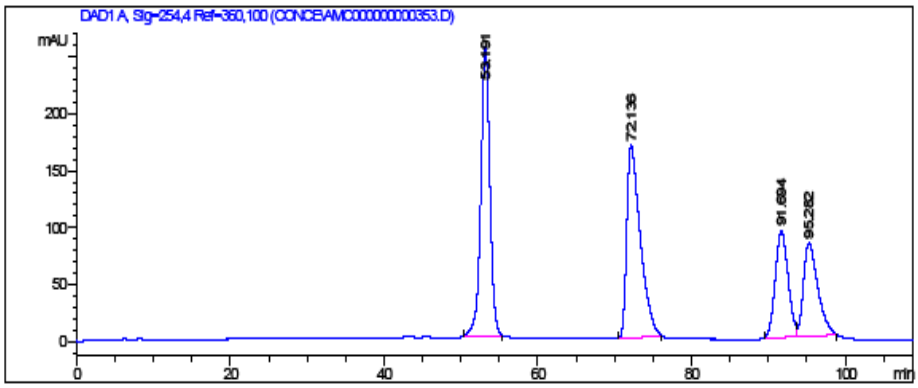
(*S*)-2-((*R*)-hydroxy(4-nitrophenyl)methyl)cyclopentan-1-one (6)[2]

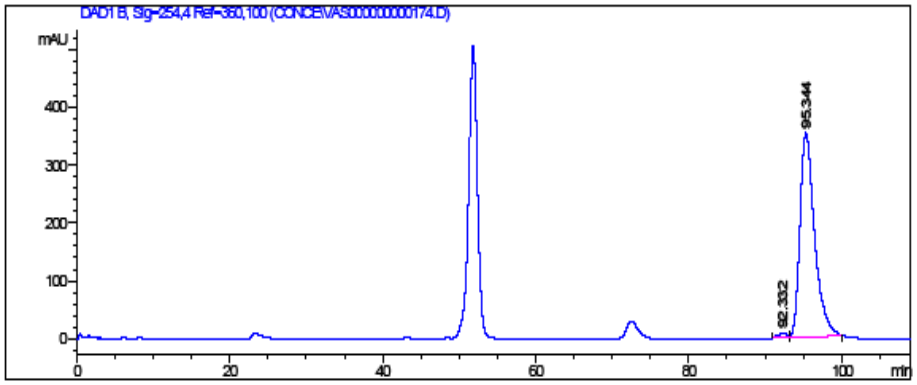


Yellow solid. Purified by flash chromatography (Hex/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.21 (2H, d, *J* = 8.7 Hz, ArC*H*), 7.52 (2H, d, *J* = 8.7 Hz, ArC*H*), 5.43 (1H, d, *J* = 2.9 Hz, C*H*OH), 2.55-1.63 (7H, m, C*H* + 3 x CH_2); ^{13} C NMR ($CDCl_3$, 75 MHz) δ = 219.8 (*C*=O), 150.4 (Ar*C*), 127.7 (Ar*C*), 126.7 (Ar*C*H), 124.0 (Ar*C*H), 70.9 (*C*HOH), 56.4 (*C*H), 39.3 (CH_2), 22.8 (CH_2), 20.7 (CH_2).



It was obtained in a maximum of 98% *ee*. The optical purity was determined by HPLC on a chiralpak AD-H column (hexane/2-propanol 95:5), flow rate 0.5 mL/min, λ 254 nm.





Area Percent Report

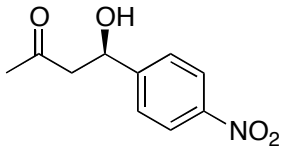
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254,4 Ref=360,100

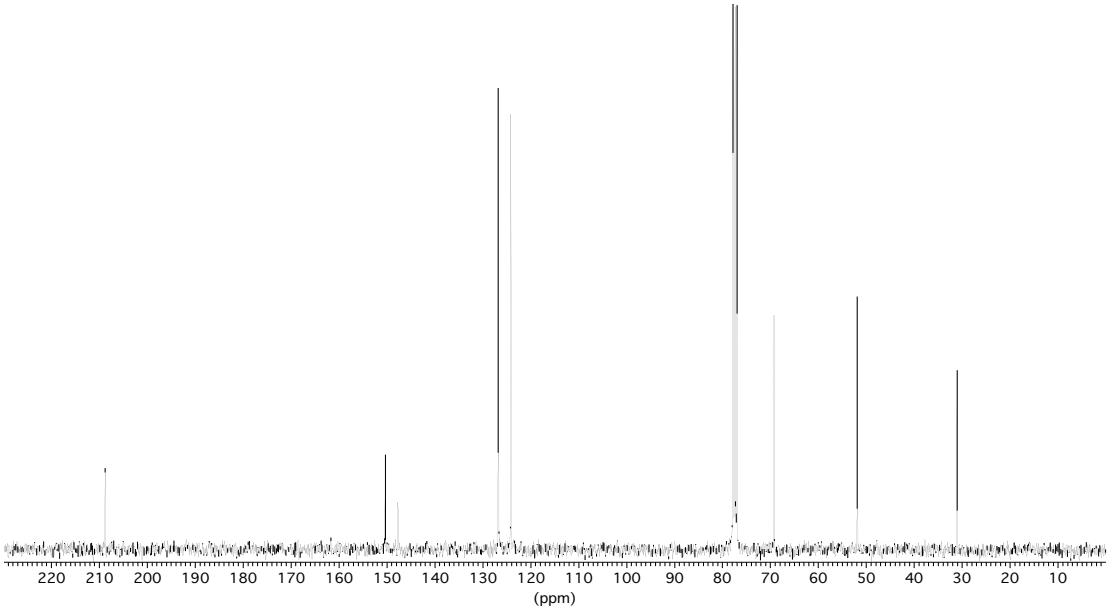
Peak #	RetTime [min]	Area %
1	92.332	1.1297
2	95.344	98.8703

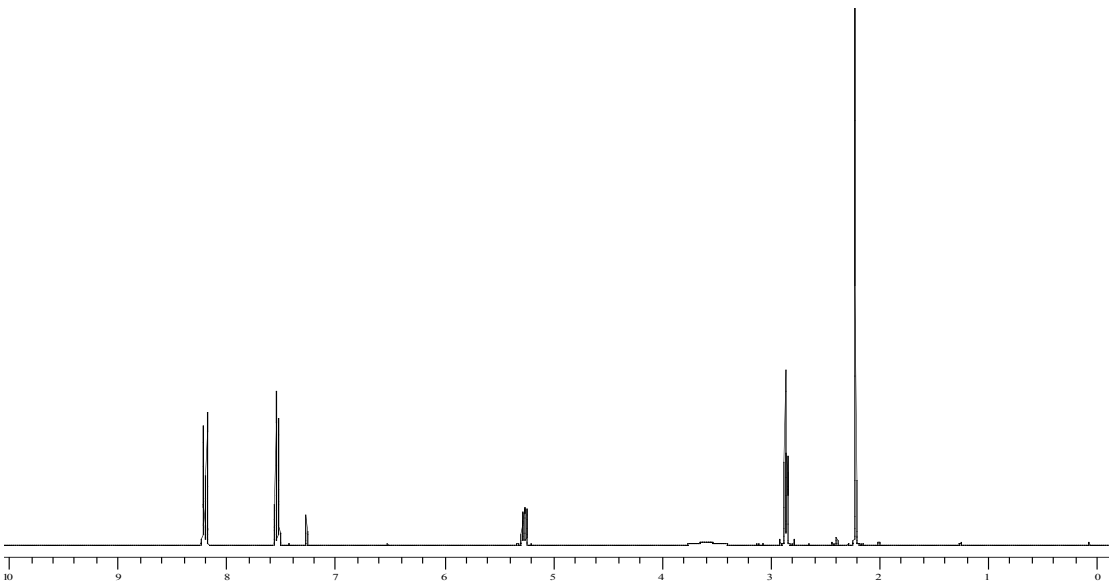
*** End of Report ***

(*R*)-4-hydroxy-4-(4-nitrophenyl)butan-2-one (7)[2]

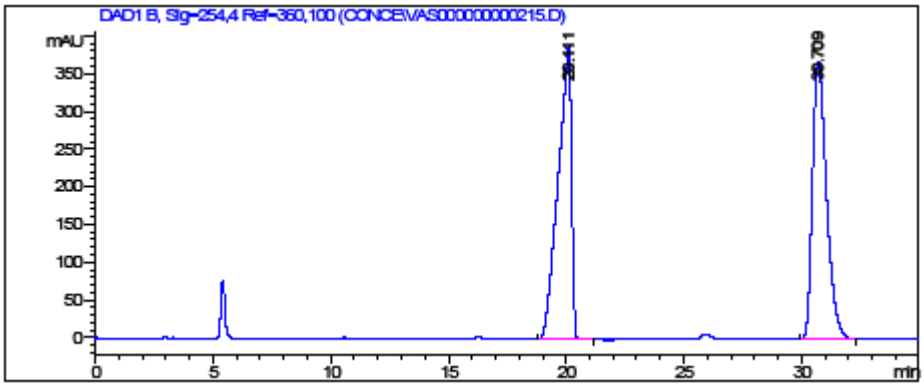


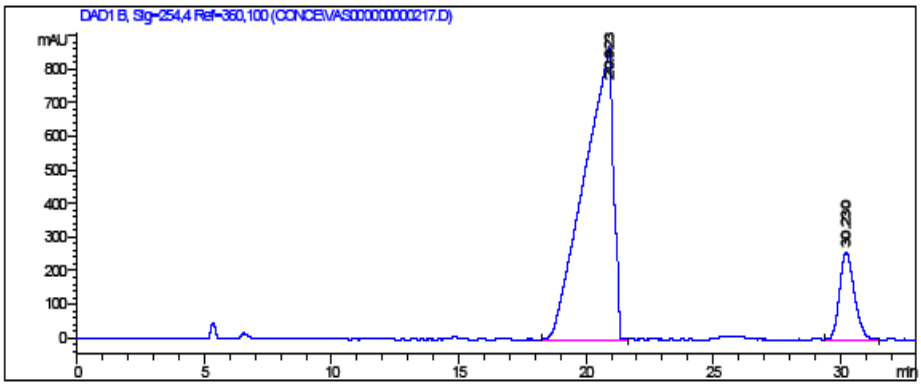
Orangish solid. Purified by flash chromatography (Hex/EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21-8.17 (2H, m, Ar*H*), 7.55-7.51 (2H, m, Ar*H*), 5.26 (1H, dd, *J* = 7.3, 5.2 Hz, C*H*OH), 3.54 (1H, s, CHO*H*), 2.86-2.83 (2H, m, CH_2), 2.21 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.8 (*C*=O), 150.3 (Ar*C*), 147.7 (Ar*C*), 126.7 (2 x Ar*C*H), 124.1 (2 x Ar*C*H), 69.2 (*C*HOH), 51.8 (*C*H_2), 31.0 (*C*H_3).





It was obtained in a maximum of 74% *ee*. The optical purity was determined by HPLC on a chiralpak AD-H column (hexane/2-propanol 90:10), flow rate 1.0 mL/min, λ 254 nm, on the corresponding *O*-acetyl product derivative.





Area Percent Report

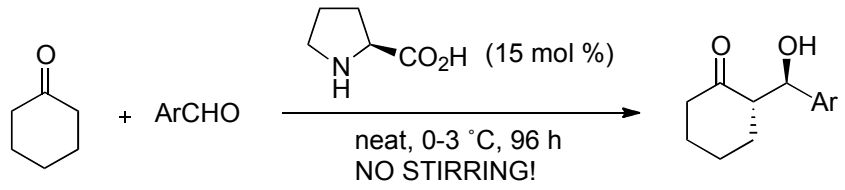
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Area %
1	20.923	86.7976
2	30.230	13.2024

*** End of Report ***

Overview of the results obtained in the **direct aldol reaction without the addition of guanidinium salt 1a**:



entry	ArCHO	product	conv %[a]	anti/syn[a]	ee %[b]
1	**3a** 4-ClPh	**4a**	81	69:31	54
2	**3b** 4-NO_2Ph	**4b**	>99	85:15	n.d.[c]
3	**3c** 4-CO_2MePh	**4c**	56	76:24	95
4	**3d** 4-BrPh	**4d**	26	69:31	94
5[d]	**3b** 4-NO_2Ph	**6**	93	38:62	92

General conditions: ketone (4.0 mmol), ArCHO (0.4 mmol), (*S*)-proline (15 mol %), no solvent, reaction mixture was left to stand 96 h inside a standard laboratory fridge (0-3 ºC) with no stirring. [a] Determined by ^{1}H NMR spectroscopy from crude reaction mixtures. [b] Enantiomeric excess of anti diastereoisomer, as determined by chiral HPLC on crude reaction mixtures. [c] Enantiomeric excess not described. Impurity hampered appropriate HPLC measure. [d] Cyclopentatone was used as ketone.

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[ii] Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas III, C.F. *J. Am. Chem. Soc.* **2006**, *128*, 734.
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[v] Companyó, X.; Valero, G.; Crovetto, L.; Moyano, A.; Rios, R. *Chem. Eur. J.* **2009**, *15*, 6564.