Electronic Supplementary Material (ESI) for Catalysis Science & Technology

Access to enantiopure 3-methyl-3,4-dihydroisocoumarins and 3-methyl-1,2,3,4-tetrahydroisoquinolines via chemoenzymatic asymmetric transformations

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SUPPORTING INFORMATION (page 1 of 38 pages)

Table of Contents

General Procedures

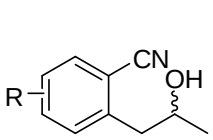
Chemical reagents were purchased from different commercial sources and used without further purification. Solvents were distilled over an adequate desiccant under nitrogen. Alcohol dehydrogenases from *Lactobacillus brevis* (LB-ADH, 300 U/mL), *Candida parapsilosis* (ADH CP, 30 U/mL), and *Rhodococcus ruber* (ADH A, 18 U/mg) were obtained from Codexis Inc. *Lactobacillus Kefir* (LK-ADH, 0.42 U/mg) was purchased from Fluka. We especially thank Prof. Wolfgang Kroutil for the generous gift of ADH-A over expressed in *E. coli* BL21 cells: Cells were grown in LB-amp medium (1 L, 100 mg/L) at 30 ºC and 250 r.p.m. for 24 h. Then, an additional amount of ampicillin (50 mg/L), $ZnCl_2$ (100 mg/L) and isopropyl thiogalactoside (IPTG, 450 mg/L) were added and shaked for 24 h at 20 ºC. The cells were centrifuged afterwards and the pellet was washed and suspended in phosphate buffer (pH 7.5, 50 mM), frozed with liquid nitrogen and lyophilized. The obtained cells were stored at 4 ºC.

Candida antarctica lipase type B (CAL-B, Novozyme 435, 7300 PLU/g) was a gift from Novozymes. *Pseudomonas cepacia* lipase currently known as *Burkhloderia cepacia* lipase (PSL-C I, 1638 U/g solid) and *Pseudomonas fluorescens* lipase (AK, 22100 U/g) were acquired from Sigma-Aldrich. *Candida antarctica* lipase A (CAL-A, 2.6 U/mg solid) was purchased from Codexis. Pancreas porcine lipase (PPL, 46 U/mg solid), *Candida rugosa* lipase (CRL, 1.41 U/g) and *Candida cylindracea* lipase (CCL, 1.41 U/mg solid) were obtained from Sigma. *Rhizomuccor miehei* lipase (RM, 150 IUN/g) and *Thermomyces lanuginosus* lipase (TLL, 250 IUN/g) were purchased from Novozymes, and Alcalase (476 U/g) was obtained from CLEA technologies. Solvents were distilled over an adequate desiccant under nitrogen.

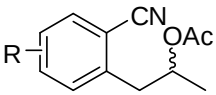
Flash chromatographies were performed using silica gel 60 (230-240 mesh). Melting points were taken on samples in open capillary tubes and are uncorrected. IR spectra were recorded on using NaCl plates or KBr pellets in a Perkin-Elmer 1720-X F7. ^{1}H, ^{13}C NMR, DEPT were obtained using AV-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz), AV-400 (^{1}H, 400.13 MHz and ^{13}C, 100.6 MHz) spectrometers. The chemical shifts are given in delta (δ) values and the coupling constants (J) in Hertz (Hz). High resolution mass spectra (HRMS) experiments were carried out by ESI^{+} using a BrukerMicroTofQ spectrometer. Measurement of the optical rotation was done in a Perkin-Elmer 241 polarimeter.

High performance liquid chromatography (HPLC) analyses were carried out in a Hewlett Packard 1100 chromatograph UV detector at 210 nm using a Chiralpak AS column (25 cm $\times$ 4.6 mm I.D.), Chiralpak IC (25 cm $\times$ 4.0 mm I.D.) and Chiralcel OB-H column (25 cm $\times$ 4.6 mm I.D.).

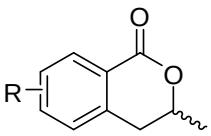
Table S1. Analytical separation by HPLC of different substrates.



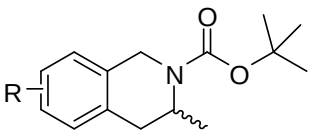
(±)-**2a**-**f**



(±)-**3a**-**f**



(±)-**5a**-**d**,**f**



(±)-**8a**-**d**

a: R= H; **b**: R= 4-Me; **c**: R= 5-OMe; **d**: R= 5-Me; **e**: R= 3-Me; **f**: R= 4-F

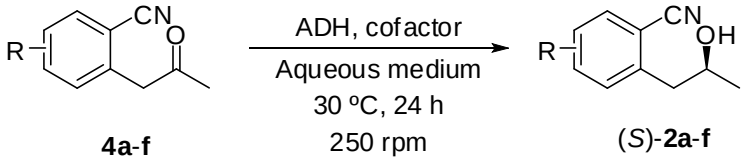
Compound	Column	T (°C)	Eluent (n-hexane/2-propanol)[a]	Time (min)	Rs[b]
(±)-**2a**	OB-H	30	97:3	21.6 (*S*) and 25.1 (*R*)	1.6
(±)-**2b**	OB-H	30	97:3	22.6 (*S*) and 25.9 (*R*)	1.3
(±)-**2c**	AS	30	95:5	16.1 (*S*) and 19.1 (*R*)	1.2
(±)-**2d**	AS	30	95:5	14.0 (*S*) and 16.7 (*R*)	1.7
(±)-**2e**	AS	30	95:5	13.0 (*S*) and 15.5 (*R*)	1.8
(±)-**2f**	AS	30	95:5	16.4 (*S*) and 18.8 (*R*)	1.5
(±)-**3a**	OB-H	30	97:3	16.8 (*R*) and 18.5 (*S*)	0.9
(±)-**3b**	AS	30	95:5	12.5 (*R*) and 14.4 (*S*)	1.5
(±)-**3c**	IC	30	90:10	15.8 (*R*) and 17.9 (*S*)	2.0
(±)-**3d**	IC	30	90:10	13.3 (*R*) and 14.2 (*S*)	1.1
(±)-**3e**	IC	30	95:5	28.9 (*R*) and 31.4 (*S*)	2.2
(±)-**3f**	IC	30	93:7	16.4 (*R*) and 17.5 (*S*)	1.7
(±)-**5a**	AS	30	95:5	24.5 (*S*) and 33.4 (*R*)	3.3
(±)-**5b**	AS	30	85:15	10.7 (*S*) and 18.1 (*R*)	6.6
(±)-**5c**	AS	30	85:15	10.4 (*S*) and 18.1 (*R*)	5.7
(±)-**5d**	AS	30	85:15	13.9 (*S*) and 17.8 (*R*)	2.2
(±)-**5f**	AS	30	85:15	16.6 (*S*) and 19.0 (*R*)	1.6
(±)-**8a**	IC	15	98:2	8.8 (*S*) and 10.2 (*R*)	1.7
(±)-**8b**	IC	30	95:5	9.1 (*S*) and 9.8 (*R*)	1.0
(±)-**8c**	IC	30	90:10	5.5 (*S*) and 6.0 (*R*)	1.5
(±)-**8d**	IC	30	98:2	8.8 (*S*) and 11.5 (*R*)	3.3

[a] A 0.8 mL/min flow was used in all cases; [b] $R_s = 2x[t_R(S) - t_R(R)]/ w_{b1}(S) + w_{b2}(R)$.

Gas chromatography analyses (GC) were carried out in a Hewlett-Packard 6890 series flame detector (FID) using: Rt-β-dexe column (30 m × 0.25 mm I.D.) for the determination of the enantiomeric excess and HP-1 column (30 m × 0.32 mm × 0.25 μm) for the conversion. GC conditions and retention times are given in:

- Table S2 for determination of conversion values in bioreduction processes
- Table S3 for the measurement of the enantiomeric excess.

Table S2. Analytical separation by GC of different ketones **2a**-**f** and alcohols **4a**-**f** for conversion measurement. (Method: HP-1 column, temperature program: 80 ºC (5 min) then 5 ºC/min until 200 ºC then 200 ºC (5 min), inlet 225 ºC and detector 250 ºC).

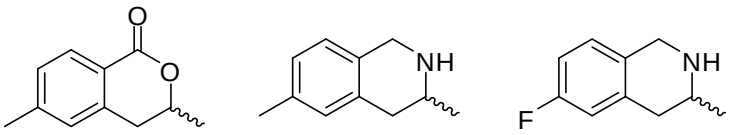


4a-**f** (*S*)-**2a**-**f**

a: R= H; **b**: R= 4-Me; **c**: R= 5-OMe; **d**: R= 5-Me; **e**: R= 3-Me; **f**: R= 4-F

Product	Time (min)
2a	13.3
2b	18.5
2c	15.4
2d	15.2
2e	15.6
2f	11.9
4a	11.3
4b	17.4
4c	14.2
4d	13.7
4e	14.1
4f	10.4

Table S3. Analytical separation by GC of different substrates for the enantiomeric excess measurement. (Rt-β-dexe column, inlet 225 ºC and detector 250 ºC).

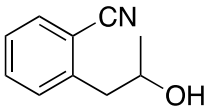


(±)-**5e** (±)-**9e** (±)-**9f**

Product	Temperature program	Time (min)	Rs[a]
5e	80 ºC (2 min) then 2 ºC/min until 150 ºC then 150 ºC (2 min) then 3 ºC/min until 180 ºC	34.2 (*S*) and 34.6 (*R*)	1.1
9e	80 ºC (2 min) then 2 ºC/min until 150 ºC then 150 ºC (2 min) then 3 ºC/min until 180 ºC	50.8 (*S*) and 53.8 (*R*)	1.2
9f	105 ºC (70 min) then 0.5 ºC/min until 120 ºC then 10 ºC/min until 200 ºC	77.8 (*S*) and 79.4 (*R*)	1.0

[a] $R_s = 2x[t_R(S) - t_R(R)]/ w_{b1}(S) + w_{b2}(R)$.

Spectroscopical and analytical data of 2-(2-Hydroxypropyl)benzonitrile (2a)



Spectroscopical data for (±)-alcohol 2a

Colourless oil. Isolated yield (71%). R_f (50% Et_2O/Hexane): 0.14. IR (NaCl): 3432, 3051, 2971, 2224, 1610, 1456, 1121 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.29 (d, $^3J_{HH}$= 6.2 Hz, 3H), 1.83 (br s, 1H), 2.74-3.20 (m, 2H), 4.13 (ddd, $^3J_{HH}$= 7.7, 6.2, 4.9 Hz, 1H), 7.28-7.42 (m, 2H), 7.53 (td, $^3J_{HH}$= 7.6 Hz; $^4J_{HH}$= 1.4 Hz, 1H), 7.63 (dd, $^3J_{HH}$= 7.7 Hz; $^4J_{HH}$= 1.4 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.7 (CH_3), 43.6 (CH_2), 67.7 (CH), 112.5 (C), 118.0 (C), 126.5 (CH), 130.5 (CH), 132.4 (CH+CH), 142.5 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{11}NNaO)^+$ $(M+Na)^+$: 184.0733 found: 184.0728.

Analytical separation for alcohol (±)-2a (HPLC)

Column: Chiralcel OB-H

Eluent: *n*-hexane/2-propanol 97:3

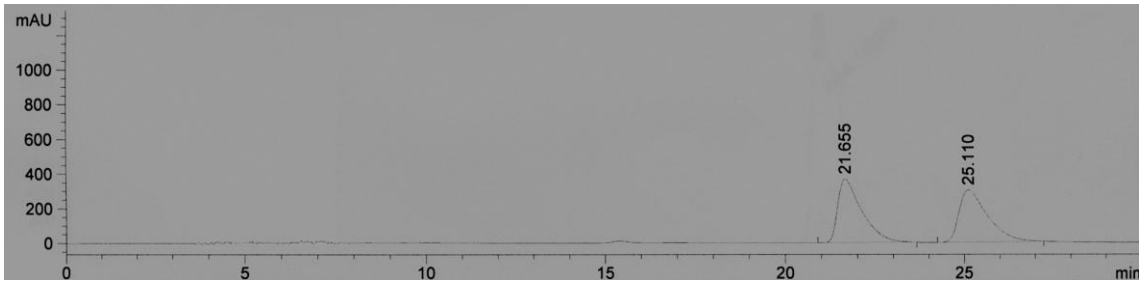
Flow: 0.8 mL/min

Temperature: 30 ºC

Retention times: t_R (*S*) = 21.6 min, t_R (*R*) = 25.1 min

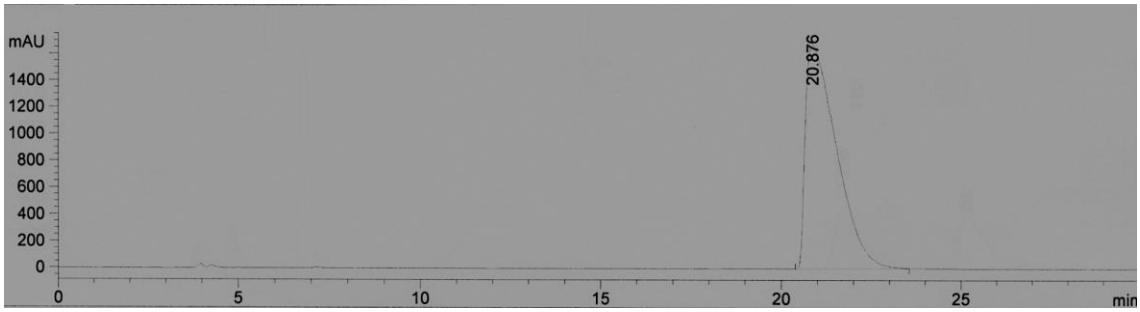
Rs: 1.6

HPLC separation for both enantiomers of alcohol (±)-2a

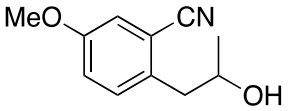


Alcohol (*S*)-2a in >99% *ee* from the bioreduction process of 4a (>97% isolated yield)

(*S*)-**2a**: $[\alpha]^{20}_D$ +39.5 (*c* 1, $CHCl_3$) (>99% *ee*).



Spectroscopical and analytical data of 2-(2-Hydroxypropyl)-5-methoxybenzonitrile (2b)



Spectroscopical data for alcohol (±)-2b

White solid. Isolated yield (72%). R_f (50% Et_2O/Hexane): 0.10. Mp: 43-45 ºC. IR (KBr): 3459, 3039, 2980, 2225, 1630, 1456 and 1111 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.27 (d, $^3J_{HH}$= 6.2 Hz, 3H), 1.58 (br s, 1H), 2.78-3.01 (m, 2H), 3.81 (s, 3H), 4.08 (dtd, $^3J_{HH}$= 7.7, 6.2, 5.6 Hz; $^4J_{HH}$= 1.5 Hz, 1H), 7.06 (d, $^4J_{HH}$= 2.8 Hz, 1H), 7.07-7.14 (m, 1H), 7.28 (d, $^3J_{HH}$= 8.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.0 (CH_3), 43.0 (CH_2), 55.5 (CH_3), 68.4 (CH), 113.5 (C), 116.9 (CH), 118.1 (C), 119.4 (CH), 131.8 (CH), 134.6 (C), 158.0 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{13}NNaO_2)^+$ $(M+Na)^+$: 214.0838 found: 214.0831.

Analytical separation for alcohol (±)-2b (HPLC)

Column: Chiralcel OB-H

Eluent: *n*-hexane/2-propanol 97:3

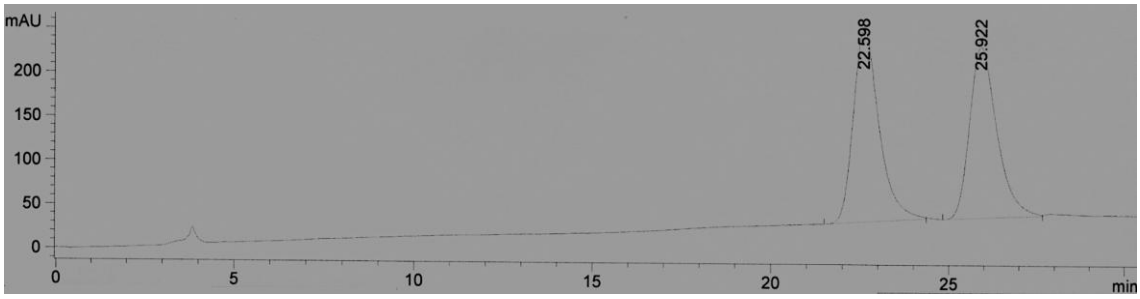
Flow: 0.8 mL/min

Temperature: 30 ºC

Retention times: t_R (*S*) = 22.6 min, t_R (*R*) = 25.9 min

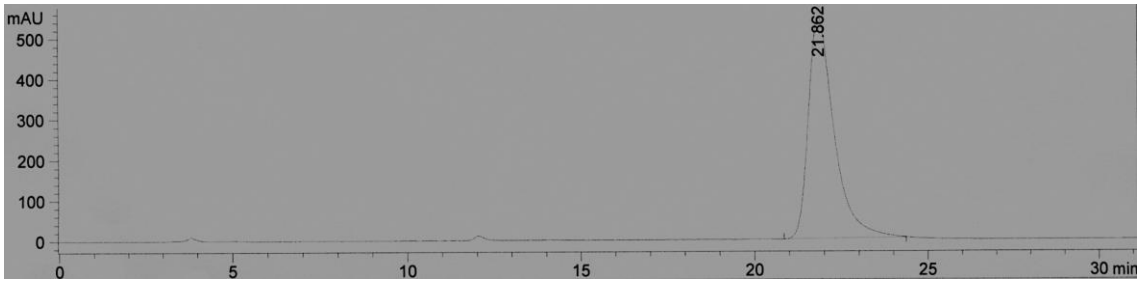
Rs: 1.3

HPLC separation for both enantiomers of alcohol (±)-2b

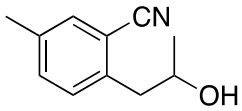


Alcohol (*S*)-2b in >99% *ee* from the bioreduction process of 4b (93% isolated yield)

(*S*)-**2b**: $[\alpha]^{20}_D$ +34.3 (*c* 1, $CHCl_3$) (>99% *ee*)



Spectroscopical and analytical data of 2-(2-Hydroxypropyl)-5-methylbenzonitrile (2c)



Spectroscopical data for alcohol (±)-2c

Colourless oil. Isolated yield (72%). R_f (50% Et_2O/Hexane): 0.12. IR (NaCl): 3430, 3067, 2979, 2224, 1609, 1350 and 1196 cm^{-1}.^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.26 (d, $^3J_{HH}$= 6.2 Hz, 3H), 1.81 (br s, 1H), 2.34 (s, 3H), 2.92 (qd, $^2J_{HH}$= 13.7 Hz; $^3J_{HH}$= 6.3 Hz, 2H), 4.09 (ddd, $^3J_{HH}$= 7.7, 6.2, 4.9 Hz, 1H), 7.25 (d, $^3J_{HH}$= 8.0 Hz, 1H), 7.29-7.37 (m, 2H), 7.42 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.3 (CH_3), 22.6 (CH_3), 43.2 (CH_2), 67.8 (CH), 112.3 (C), 118.1 (C), 130.4 (CH), 132.6 (CH), 133.4 (CH), 136.5 (C), 139.5 (C). HRMS (ESI$^+$, *m/z*): calcd for $(C_{11}H_{13}NNaO)^+$ $(M+Na)^+$: 198.0889 found: 198.0880.

Analytical separation for alcohol (±)-2c (HPLC)

Column: Chiralpak AS

Eluent: *n*-hexane/2-propanol 95:5

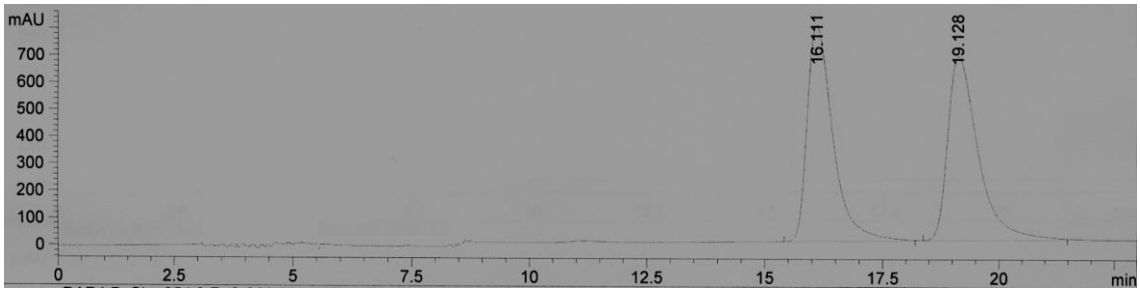
Flow: 0.8 mL/min

Temperature: 30 ºC

Retention times: t_R (*S*) = 16.1 min, t_R (*R*) = 19.1 min

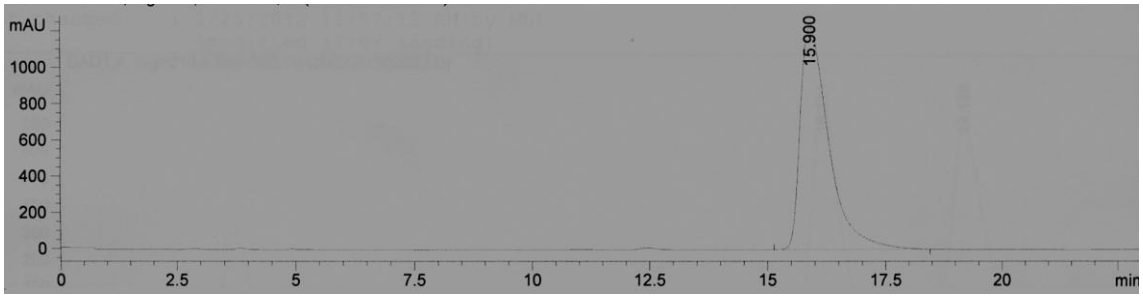
Rs: 1.2

HPLC separation for both enantiomers of alcohol (±)-2c

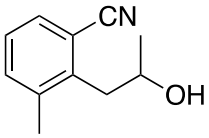


Alcohol (*S*)-2c in >99% *ee* from the bioreduction process of 4c (>97% isolated yield)

(*S*)-**2c**: $[\alpha]^{20}_D$ +34.7 (*c* 1, $CHCl_3$) (>99% *ee*)



Spectroscopical and analytical data of 2-(2-Hydroxypropyl)-3-methylbenzonitrile (2d)



Spectroscopical data for alcohol (±)-2d

Colourless oil. Isolated yield (84%). R_f (50% Et_2O/Hexane): 0.13. IR (NaCl): 3420, 3044, 2967, 2223, 1615, 1466 and 986 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.23 (d, $^3J_{HH}$= 6.2 Hz, 3H), 2.34 (s, 3H), 2.68 (br s, 1H), 2.83-3.07 (m, 1H), 3.91-4.25 (m, 2H), 7.13 (t, $^3J_{HH}$= 7.7 Hz, 1H), 7.31 (d, $^3J_{HH}$= 7.6 Hz, 1H), 7.39 (d, $^3J_{HH}$= 7.6 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.6 (CH_3), 23.0 (CH_3), 40.8 (CH_2), 67.8 (CH), 113.2 (C), 118.6 (C), 126.4 (CH), 130.3 (CH), 134.5 (CH), 138.1 (C), 140.9 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{13}NNaO)^+$ $(M+Na)^+$: 198.0889 found: 198.0889.

Analytical separation for alcohol (±)-2d (HPLC)

Column: Chiralpak AS

Eluent: *n*-hexane/2-propanol 95:5

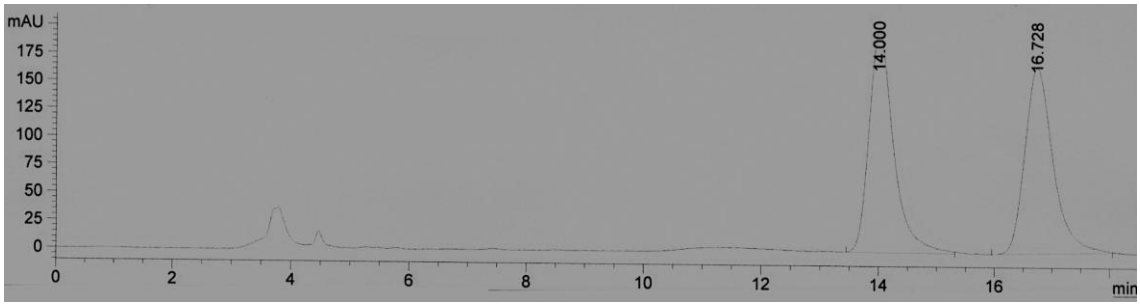
Flow: 0.8 mL/min

Temperature: 30 ºC

Retention times: t_R (*S*) = 14.0 min, t_R (*R*) = 16.7 min

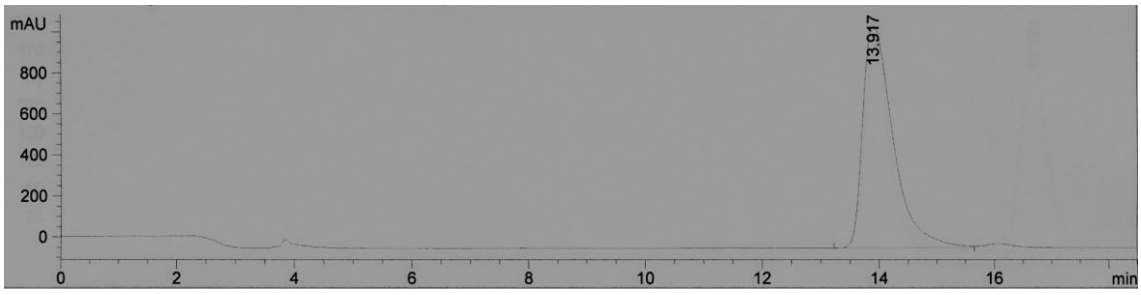
Rs: 1.7

HPLC separation for both enantiomers of alcohol (±)-2d

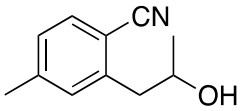


Alcohol (*S*)-2d in >99% *ee* from the bioreduction process of 4d (82% isolated yield)

(*S*)-**2d**: $[\alpha]^{20}_D$ +53.3 (*c* 1, $CHCl_3$) (>99% *ee*)



Spectroscopical and analytical data of 2-(2-Hydroxypropyl)-4-methylbenzonitrile (2e)



Spectroscopical data for alcohol (±)-2e

White solid. Isolated yield (69%). R_f (50% Et_2O/Hexane): 0.14. Mp: 45-47 ºC. IR (KBr): 3410, 3033, 2980, 2225, 1620, 1456 and 1100 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.11 (d, $^3J_{HH}$= 6.2 Hz, 3H), 2.25 (s, 3H), 2.78 (d, $^3J_{HH}$= 6.3 Hz, 2H), 3.18 (br s, 1H), 3.95 (q, $^3J_{HH}$= 6.3 Hz, 1H), 6.98 (d, $^3J_{HH}$= 7.9 Hz, 1H), 7.08 (s, 1H), 7.34 (d, $^3J_{HH}$= 7.9 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.2 (CH_3), 22.4 (CH_3), 43.3 (CH_2), 67.4 (CH), 109.1 (C), 118.0 (C), 127.1 (CH), 131.0 (CH), 132.0 (CH), 142.2 (C), 143.0 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{13}NNaO)^+$ $(M+Na)^+$: 198.0889 found: 198.0883.

Analytical separation for alcohol (±)-2e (HPLC)

Column: Chiralpak AS

Eluent: *n*-hexane/2-propanol 95:5

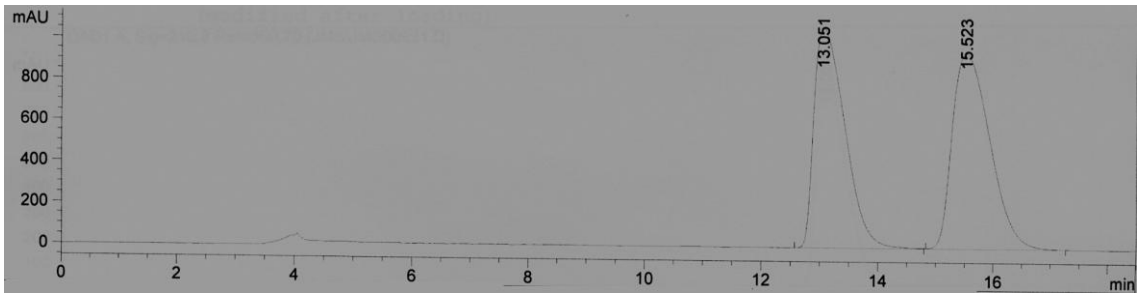
Flow: 0.8 mL/min

Temperature: 30 ºC

Retention times: t_R (*S*) = 13.0 min, t_R (*R*) = 15.5 min

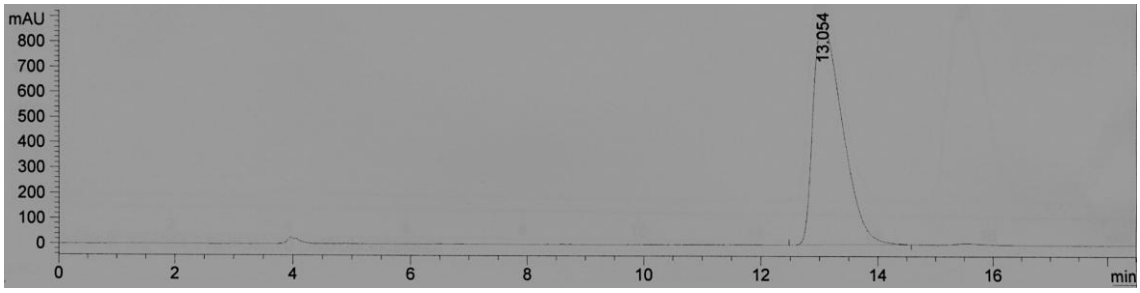
Rs: 1.8

HPLC separation for both enantiomers of alcohol (±)-2e

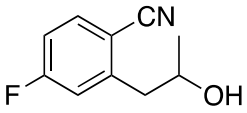


Alcohol (*S*)-2e in >99% *ee* from the bioreduction process of 4e (62% isolated yield)

(*S*)-**2e**: $[\alpha]^{20}_D$ +29.7 (*c* 1, $CHCl_3$) (>99% *ee*)



Spectroscopical and analytical data of 4-fluoro-2-(2-Hydroxypropyl)benzonitrile (2f)



Spectroscopical data for alcohol (±)-2f

Hygroscopic solid. Isolated yield (73%). R_f (50% Et_2O/Hexane): 0.14. IR (NaCl): 3402, 3015, 2990, 2224, 1605, 1356 and 1067 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.26 (d, $^3J_{HH}$= 6.2 Hz, 3H), 2.19 (br s, 1H), 2.94 (qd, $^2J_{HH}$= 13.8 Hz; $^3J_{HH}$= 6.2 Hz, 2H), 4.09 (ddd, $^3J_{HH}$= 7.9, 6.3, 4.8 Hz, 1H), 6.95-7.08 (m, 1H), 7.11 (dd, $^3J_{HH}$= 9.3 Hz; $^4J_{HH}$= 2.7 Hz, 1H), 7.53-7.81 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.9 (CH_3), 43.5 (CH_2), 67.6 (CH), 108.8 (C), 114.4 (d, $^2J_{CF}$= 22.7 Hz, CH), 117.5 (C), 118.0 (d, $^2J_{CF}$= 22.5 Hz, CH), 134.8 (d, $^3J_{CF}$= 9.7 Hz, CH), 146.2 (d, $^3J_{CF}$= 9.2 Hz, C), 164.6 (d, $^1J_{CF}$= 256.1 Hz, C). HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{10}FNNaO)^+$ $(M+Na)^+$: 202.0639 found: 202.0629.

Analytical separation for alcohol (±)-2f (HPLC)

Column: Chiralpak AS

Eluent: *n*-hexane/2-propanol 95:5

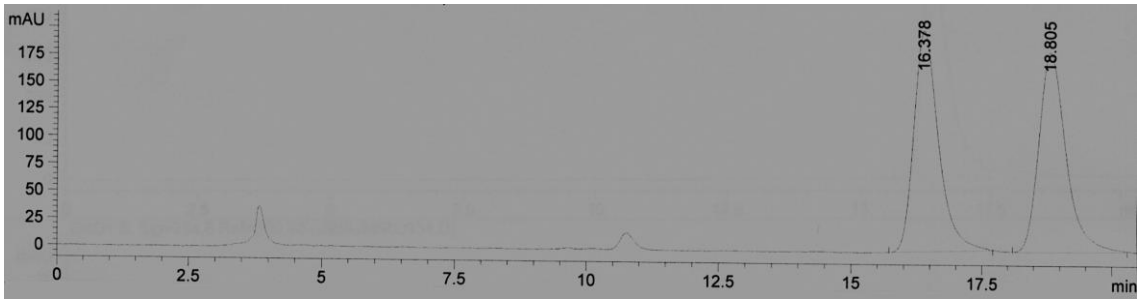
Flow: 0.8 mL/min

Temperature: 30 ºC

Retention times: t_R (*S*) = 16.4 min, t_R (*R*) = 18.8 min

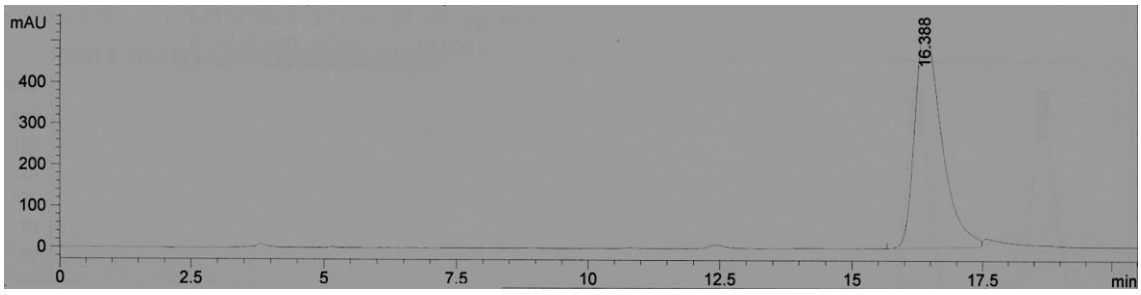
Rs: 1.5

HPLC separation for both enantiomers of alcohol (±)-2f

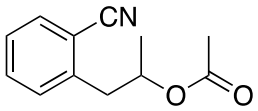


Alcohol (*S*)-2f in >99% *ee* from the bioreduction process of 4f (77% isolated yield)

(*S*)-**2f**: $[\alpha]^{20}_D$ +40.3 (*c* 1, $CHCl_3$) (>99% *ee*)



Spectroscopical and analytical data of 1-(2-Cyanophenyl)propan-2-yl acetate (3a)



Spectroscopical data for acetate (±)-3a

Colourless oil. Isolated yield (97%). R_f (50% Et_2O/Hexane): 0.32. IR (NaCl): 3090, 2963, 2228, 1737, 1608 and 1204 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.27 (d, $^3J_{HH}$= 6.3 Hz, 3H), 1.95 (s, 3H), 3.06 (d, $^3J_{HH}$= 6.3 Hz, 2H), 5.16 (q, $^3J_{HH}$= 6.3 Hz, 1H), 7.29-7.37 (m, 2H), 7.45-7.55 (m, 1H), 7.60 (d, $^3J_{HH}$= 7.7 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.0 (CH_3), 21.4 (CH_3), 40.7 (CH_2), 70.8 (CH), 113.6 (C), 118.3 (C), 127.5 (CH), 130.8 (CH), 132.9 (CH), 133.1 (CH), 141.8 (C), 170.5 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{12}H_{13}NNaO_2)^+$ $(M+Na)^+$: 226.0838 found: 226.0844.

Analytical separation for acetate (±)-3a (HPLC)

Column: Chiralcel OB-H

Eluent: *n*-hexane/2-propanol 97:3

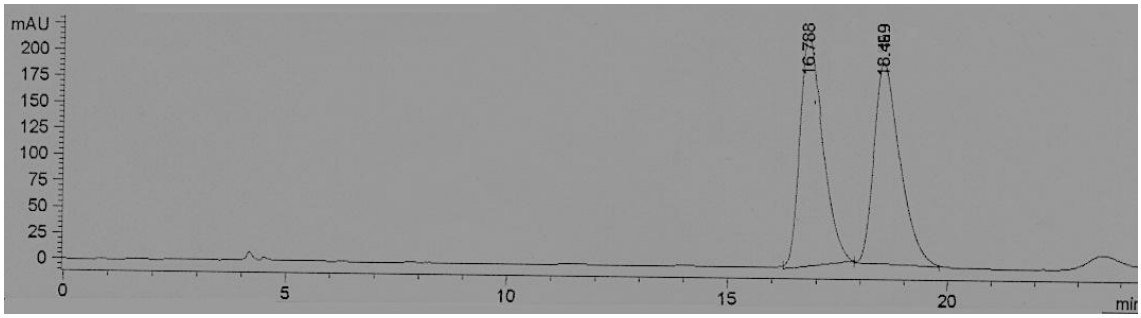
Flow: 0.8 mL/min

Temperature: 30 ºC

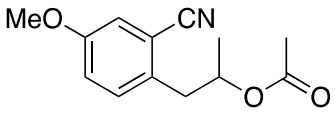
Retention times: t_R (*R*) = 16.8 min, t_R (*S*) = 18.5 min

Rs: 0.9

HPLC separation for both enantiomers of acetate (±)-3a



Spectroscopical and analytical data of 1-(2-Cyano-4-methoxyphenyl)propan-2-yl acetate (3b)



Spectroscopical data for acetate (±)-3b

Brown oil. Isolated yield (87%). R_f (50% Et_2O/Hexane): 0.27. IR (NaCl): 3035, 2989, 2227, 1738, 1590 and 1260 cm^{-1}.^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.27 (d, $^3J_{HH}$= 6.3 Hz, 3H), 1.98 (s, 3H), 3.00 (d, $^3J_{HH}$= 6.4 Hz, 2H), 3.80 (s, 3H), 5.13 (q, $^3J_{HH}$= 6.3 Hz, 1H), 6.98-7.15 (m, 2H), 7.23 (d, $^3J_{HH}$= 8.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.5 (CH_3), 21.1 (CH_3), 39.4 (CH_2), 55.5 (CH_3), 70.6 (CH), 113.8 (C), 116.7 (CH), 117.9 (C), 119.4 (CH), 131.6 (CH), 133.4 (C), 158.0 (C), 170.3 (C). HRMS (ESI$^+$, *m/z*): calcd for $(C_{13}H_{15}NNaO_3)^+$ $(M+Na)^+$: 256.0944 found: 296.0952.

Analytical separation for acetate (±)-3b (HPLC)

Column: Chiralpak AS

Eluent: *n*-hexane/2-propanol 95:5

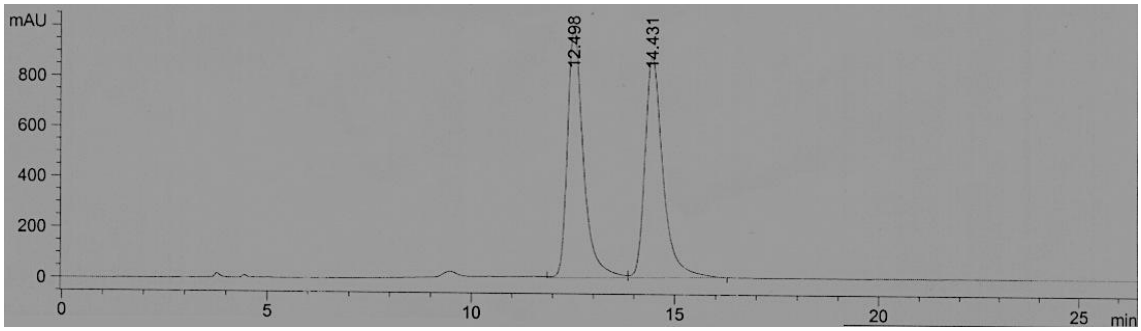
Flow: 0.8 mL/min

Temperature: 30 ºC

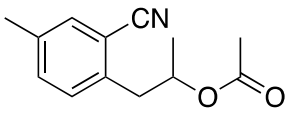
Retention times: t_R (*R*) = 12.5 min, t_R (*S*) = 14.4 min

Rs: 1.5

HPLC separation for both enantiomers of acetate (±)-3b



Spectroscopical and analytical data of 1-(2-Cyano-4-methylphenyl)propan-2-yl acetate (3c)



Spectroscopical data for acetate (±)-3c

Pale brown oil. Isolated yield (82%). R_f (50% Et_2O/Hexane): 0.31. IR (NaCl): 3088, 2993, 2228, 1743, 1619 and 1174 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.28 (d, $^3J_{HH}$= 6.3 Hz, 3H), 1.98 (s, 3H), 2.34 (s, 3H), 3.03 (d, $^3J_{HH}$= 6.4 Hz, 2H), 5.15 (q, $^3J_{HH}$= 6.3 Hz, 1H), 7.22 (d, $^3J_{HH}$= 8.0 Hz, 1H), 7.30 (d, $^4J_{HH}$= 2.4 Hz, 1H), 7.42 (d, $^4J_{HH}$= 1.8 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.8 (CH_3), 20.6 (CH_3), 21.1 (CH_3), 39.9 (CH_2), 70.6 (CH), 113.0 (C), 118.2 (C), 130.3 (CH), 132.9 (CH), 133.5 (CH), 137.1 (C), 138.4 (C), 170.3 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{13}H_{15}NNaO_2)^+$ $(M+Na)^+$: 240.0995 found: 240.0989.

Analytical separation for acetate (±)-3c (HPLC)

Column: Chiralpak IC

Eluent: *n*-hexane/2-propanol 90:10

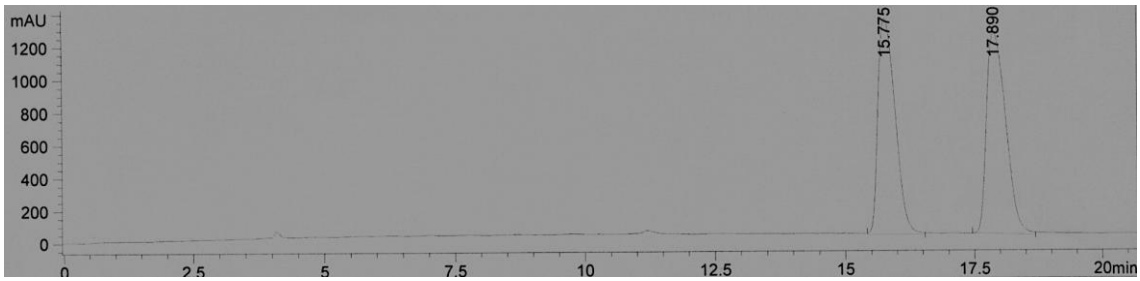
Flow: 0.8 mL/min

Temperature: 30 ºC

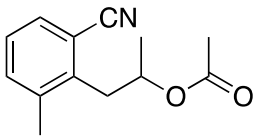
Retention times: t_R (*R*) = 15.8 min, t_R (*S*) = 17.9 min

Rs: 2.0

HPLC separation for both enantiomers of acetate (±)-3c



Spectroscopical and analytical data of 1-(2-Cyano-6-methylphenyl)propan-2-yl acetate (3d)



Spectroscopical data for acetate (±)-3d

White solid. Isolated yield (84%). Mp: 42-44 ºC. R_f (50% Et_2O/Hexane): 0.32. IR (KBr): 3056, 2960, 2226, 1738, 1603 and 1316 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.35 (d, $^3J_{HH}$= 6.2 Hz, 3H), 1.96 (s, 3H), 2.41 (s, 3H), 2.99-3.30 (m, 2H), 5.08-5.24 (m, 1H), 7.21 (t, $^3J_{HH}$= 7.7 Hz, 1H), 7.32-7.40 (m, 1H), 7.47 (dd, $^3J_{HH}$= 7.6 Hz; $^4J_{HH}$= 1.6 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.6 (CH_3), 20.1 (CH_3), 21.1 (CH_3), 38.0 (CH_2), 70.0 (CH), 114.0 (C), 118.6 (C), 127.1 (CH), 130.6 (CH), 134.7 (CH), 138.3 (C), 139.6 (C), 170.3 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{13}H_{15}NNaO_2)^+$ $(M+Na)^+$: 240.0995 found: 240.0998.

Analytical separation for acetate (±)-3d (HPLC)

Column: Chiralpak IC

Eluent: *n*-hexane/2-propanol 90:10

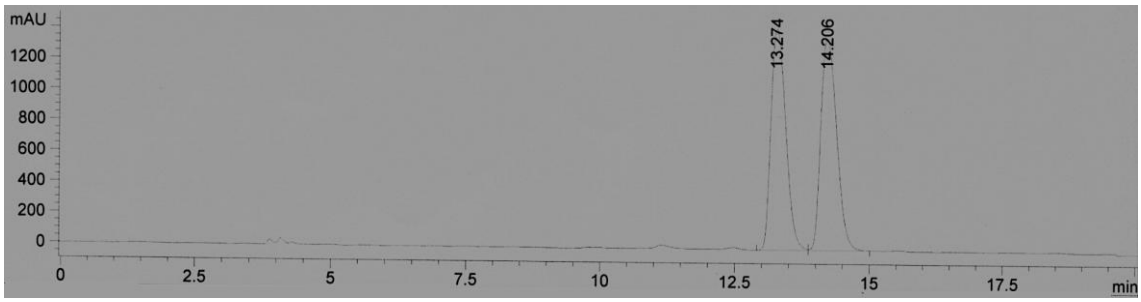
Flow: 0.8 mL/min

Temperature: 30 ºC

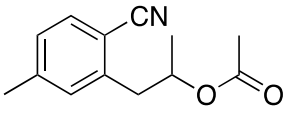
Retention times: t_R (*R*) = 13.3 min, t_R (*S*) = 14.2 min

Rs: 1.1

HPLC separation for both enantiomers of acetate (±)-3d



Spectroscopical and analytical data of 1-(2-Cyano-5-methylphenyl)propan-2-yl acetate (3e)



Spectroscopical data for acetate (±)-3e

Brown oil. Isolated yield (82%). R_f (50% Et_2O/Hexane): 0.30. IR (NaCl): 3044, 2980, 2225, 1748, 1656 and 1200 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.27 (d, $^3J_{HH}$= 6.3 Hz, 3H), 1.98 (s, 3H), 2.37 (s, 3H), 3.02 (d, $^3J_{HH}$= 6.4 Hz, 2H), 5.14 (dt, $^3J_{HH}$= 6.8, 6.1 Hz, 1H), 7.02-7.19 (m, 2H), 7.49 (d, $^3J_{HH}$= 7.8 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.5 (CH_3), 21.1 (CH_3), 21.6 (CH_3), 40.1 (CH_2), 70.6 (CH), 110.2 (C), 118.2 (C), 127.9 (CH), 131.2 (CH), 132.5 (CH), 141.2 (C), 143.4 (C), 170.3 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{13}H_{15}NNaO_2)^+$ $(M+Na)^+$: 240.0995 found: 240.0991.

Analytical separation for acetate (±)-3e (HPLC)

Column: Chiralpak IC

Eluent: *n*-hexane/2-propanol 95:5

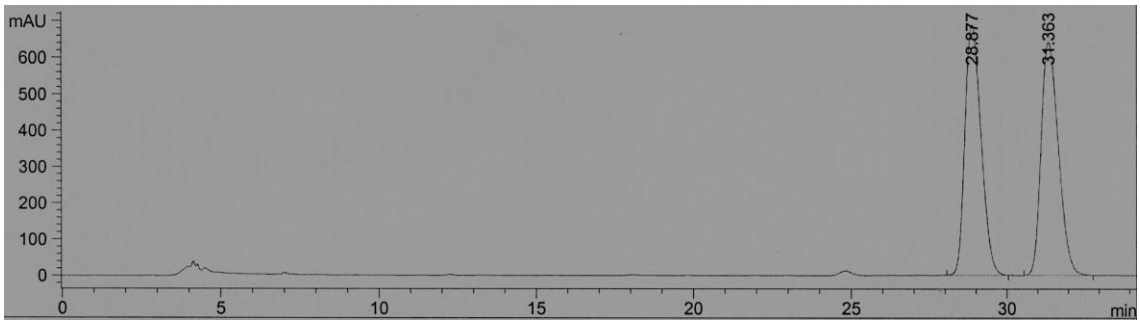
Flow: 0.8 mL/min

Temperature:30 ºC

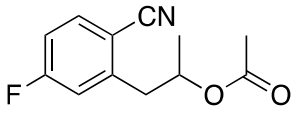
Retention times: t_R (*R*) = 28.9 min, t_R (*S*) = 31.4 min

Rs: 2.2

HPLC separation for both enantiomers of acetate (±)-3e



Spectroscopical and analytical data of 1-(2-Cyano-5-fluorophenyl)propan-2-yl acetate (3f)



Spectroscopical data for acetate (±)-3f

Colourless oil. Isolated yield (98%). R_f (50% Et_2O/Hexane): 0.29. IR (NaCl): 3054, 2965, 2226, 1734, 1638 and 1188 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.31 (d, $^3J_{HH}$= 6.3 Hz, 3H), 1.99 (s, 3H), 2.77-3.14 (m, 2H), 5.07-5.31 (m, 1H), 6.88-7.15 (m, 2H), 7.63-7.69 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.7 (CH_3), 21.1 (CH_3), 40.3 (CH_2), 70.1 (CH). 109.6 (C), 115.1 (d, $^2J_{CF}$= 22.8 Hz, CH), 117.4 (C), 118.0 (d, $^2J_{CF}$= 22.6 Hz, CH), 135.1 (d, $^3J_{CF}$= 9.8 Hz, CH), 145.0 (d, $^3J_{CF}$= 9.0 Hz, C), 164.8 (d, $^1J_{CF}$= 256.1 Hz, C), 170.4 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{12}H_{12}FNNaO_2)^+$ $(M+Na)^+$: 244.0744 found: 244.0749.

Analytical separation for acetate (±)-3f (HPLC)

Column: Chiralpak IC

Eluent: *n*-hexane/2-propanol 93:7

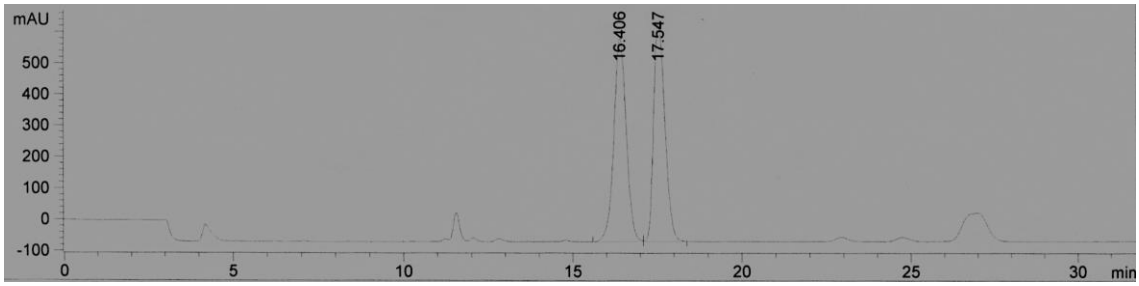
Flow: 0.8 mL/min

Temperature: 30 ºC

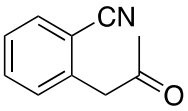
Retention times: t_R (*R*) = 16.4 min, t_R (*S*) = 17.5 min

Rs: 1.7

HPLC separation for both enantiomers of acetate (±)-3f



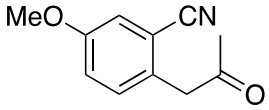
Spectroscopical data of 2-(2-Oxopropyl)benzonitrile (4a)



Spectroscopical data for ketone 4a

White solid. Isolated yield (72%). R_f (50% Et_2O/Hexane): 0.20. Mp: 29-31 ºC. IR (KBr): 3048, 2984, 2225, 1719, 1613, 1554 and 1287 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.28 (s, 3H), 3.97 (s, 2H), 7.16-7.46 (m, 1H), 7.46-7.74 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 30.0 (CH_3), 48.5 (CH_2), 113.2 (C), 117.7 (C), 127.6 (CH), 130.8 (CH), 132.7 (CH), 132.8 (CH), 138.0 (C), 203.4 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_9NNaO)^+$ $(M+Na)^+$: 182.0576 found: 182.0579.

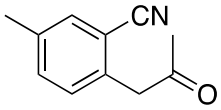
Spectroscopical data of 5-Methoxy-2-(2-oxopropyl)benzonitrile (4b)



Spectroscopical data for ketone 4b

White solid. Isolated yield (75%). R_f (50% Et_2O/Hexane): 0.16. Mp: 71-73 ºC. IR (KBr): 3069, 2979, 2227, 1719, 1607, 1503 and 1290 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.21 (s, 3H), 3.75 (s, 3H), 3.85 (s, 2H), 7.00-7.10 (m, 2H), 7.15 (d, $^3J_{HH}$= 8.2 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 29.6 (CH_3), 47.4 (CH_2), 55.3 (CH_3), 113.6 (C), 116.8 (CH), 117.4 (C), 119.2 (CH), 129.9 (C), 131.7 (CH), 158.2 (C), 203.8 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{11}NNaO_2)^+$ $(M+Na)^+$: 212.0682 found: 212.0685.

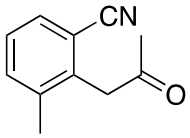
Spectroscopical data of 5-Methyl-2-(2-oxopropyl)benzonitrile (4c)



Spectroscopical data for ketone 4c

White solid. Isolated yield (72%). R_f (50% Et_2O/Hexane): 0.19. Mp: 41-43 ºC. IR (KBr): 3055, 2976, 2226, 1713, 1624, 1498 and 1299 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.22 (s, 3H), 2.31 (s, 3H), 3.89 (s, 2H), 7.14 (d, $^3J_{HH}$= 8.0 Hz, 1H), 7.28-7.36 (m, 1H), 7.40 (d, $^4J_{HH}$= 2.2 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.4 (CH_3), 29.6 (CH_3), 47.9 (CH_2), 112.7 (C), 117.6 (C), 130.4 (CH), 132.6 (CH), 133.5 (CH), 134.9 (C), 137.5 (C), 203.6 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{11}NNaO)^+$ $(M+Na)^+$: 196.0733 found: 196.0734.

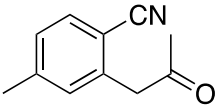
Spectroscopical data of 3-Methyl-2-(2-oxopropyl)benzonitrile (4d)



Spectroscopical data for ketone 4d

White solid. Isolated yield (73%). R_f (50% Et_2O/Hexane): 0.20. Mp: 97-99 ºC. IR (KBr): 3033, 2980, 2227, 1710, 1643, 1512 and 1303 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.21 (s, 3H), 2.24 (s, 3H), 3.99 (s, 2H), 7.22 (t, $^3J_{HH}$= 7.7 Hz, 1H), 7.36 (m, $^3J_{HH}$= 7.7 Hz, 1H), 7.41-7.58 (d, $^3J_{HH}$= 7.7 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.5 (CH_3), 29.7 (CH_3), 46.2 (CH_2), 113.5 (C), 118.0 (C), 127.4 (CH), 130.1 (CH), 134.5 (CH), 136.7 (C), 138.4 (C), 203.2 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{11}NNaO)^+$ $(M+Na)^+$: 196.0733 found: 196.0737.

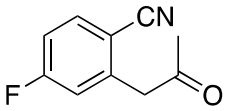
Spectroscopical data of 4-Methyl-2-(2-oxopropyl)benzonitrile (4e)



Spectroscopical data for ketone 4e

White solid. Isolated yield (81%). R_f (50% Et_2O/Hexane): 0.21. Mp: 55-57ºC. IR (KBr): 3076, 2954, 2225, 1716, 1627, 1545 and 1327 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.27 (s, 3H), 2.37 (s, 3H), 3.92 (s, 2H), 7.10 (s, 1H), 7.14-7.19 (m, 1H), 7.52 (d, $^3J_{HH}$= 7.8 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.6 (CH_3), 29.9 (CH_3), 48.4 (CH_2), 110.1 (C), 117.9 (C), 128.4 (CH), 131.4 (CH), 132.5 (CH), 137.8 (C), 143.7 (C), 203.6 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{11}NNaO)^+$ $(M+Na)^+$: 196.0733 found: 196.0733.

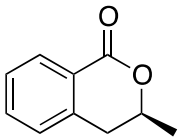
Spectroscopical data of 4-Fluoro-2-(2-oxopropyl)benzonitrile (4f)



Spectroscopical data for ketone 4f

White solid. Isolated yield (70%). R_f (50% Et_2O/Hexane): 0.20. Mp: 37-39 ºC. IR (KBr): 3045, 2979, 2226, 1722, 1623, 1453 and 1320 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.95 (s, 2H), 6.78-7.14 (m, 2H), 7.53-7.68 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 29.9 (CH_3), 48.0 (CH_2), 109.2 (d, $^4J_{CF}$= 3.4 Hz, C), 115.1 (d, $^2J_{CF}$= 22.7 Hz, CH), 116.9 (C), 118.3 (d, $^2J_{CF}$= 22.9 Hz, CH), 134.7 (d, $^3J_{CF}$= 9.6 Hz, CH), 141.2 (d, $^3J_{CF}$= 9.2 Hz, C), 164.5 (C, d, $^1J_{CF}$= 256.1 Hz), 202.5 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_8FNNaO)^+$ $(M+Na)^+$: 200.0482: found 200.0485.

Spectroscopical and analytical data of (*S*)-3-Methylisochroman-1-one (5a)



Spectroscopical data for isochromanone 5a

White solid. Isolated Yield (85%). R_f (30% EtOAc/Hexane): 0.47. Mp: 54-56 ºC. IR (KBr): 3096, 2980, 1720, 1606, 1276 and 1141 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.48 (d, $^3J_{HH}$= 6.2 Hz, 3H), 2.80-3.04 (m, 2H), 4.50-4.81 (m, 1H), 7.20 (d, $^3J_{HH}$= 7.7 Hz, 1H), 7.34 (t, $^3J_{HH}$= 7.6 Hz, 1H), 7.49 (t, $^3J_{HH}$= 7.4 Hz, 1H), 8.04 (t, $^3J_{HH}$= 7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.7 (CH_3), 34.6 (CH_2), 74.9 (CH), 124.7 (C), 127.2 (CH), 127.4 (CH), 130.0 (CH), 133.5 (CH), 138.9 (C), 165.4 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{10}NaO_2)^+$ $(M+Na)^+$: 185.0573 found: 185.0581. (*S*)-**5a**: $[\alpha]^{20}_D$ +116.1 (*c* 1, $CHCl_3$) (>99% *ee*). Described in reference 4 $[\alpha]^{20}_D$ +90.2 (*c* 0.55, CH_2Cl_2).

Analytical separation for isochromanone (±)-5a (HPLC)

Column: Chiralpak AS

Eluent: *n*-hexane/2-propanol 95:5

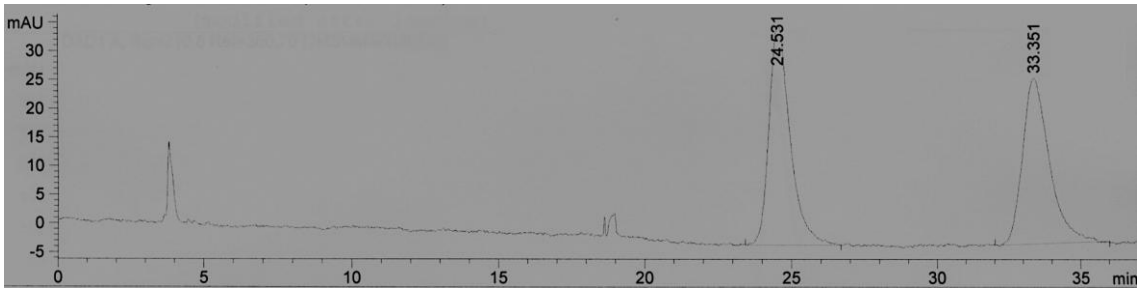
Flow: 0.8 mL/min

Temperature: 30 ºC

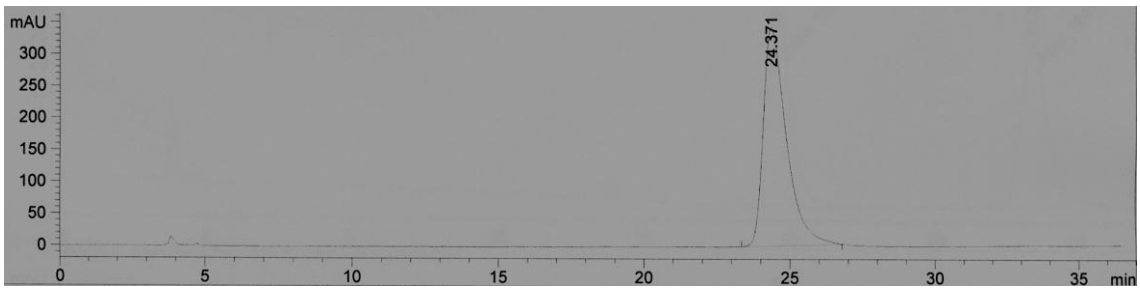
Retention times: t_R (*S*) = 24.5 min, t_R (*R*) = 33.4 min

Rs: 3.3

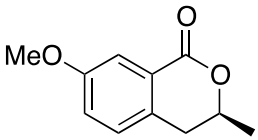
HPLC separation for both enantiomers of isochromanone (±)-5a



Isochromanone (*S*)-5a in >99% *ee*



Spectroscopical and analytical data of (*S*)-7-Methoxy-3-methylisochroman-1-one (5b)



Spectroscopical data for isochromanone 5b

White solid. Isolated yield (79%). R_f (30% EtOAc/Hexane): 0.40. Mp: 94-96 ºC. IR (KBr): 3080, 2989, 1719, 1655, 1244 and 1198 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.48 (d, $^3J_{HH}$= 6.3 Hz, 3H), 2.74-2.95 (m, 2H), 3.81 (s, 3H), 4.43-4.47 (m, 1H), 6.91-7.17 (m, 2H), 7.54 (d, $^4J_{HH}$= 2.7 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.7 (CH_3), 33.9 (CH_2), 55.4 (CH_3), 75.3 (CH), 112.7 (CH), 121.4 (CH), 125.5 (C), 128.3 (CH), 131.2 (C), 158.8 (C), 165.6 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{12}NaO_3)^+$ $(M+Na)^+$: 215.0679 found: 215.0687. (*S*)-**5b**: $[\alpha]^{20}_D$ +119.8 (*c* 1, $CHCl_3$) (>99% *ee*).

Analytical separation for isochromanone (±)-5b (HPLC)

Column: Chiralpak AS

Eluent: *n*-hexane/2-propanol 85:15

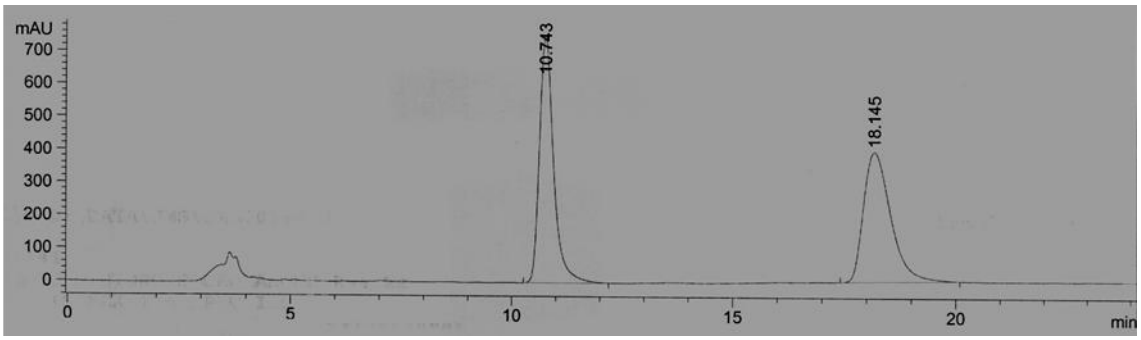
Flow: 0.8 mL/min

Temperature: 30 ºC

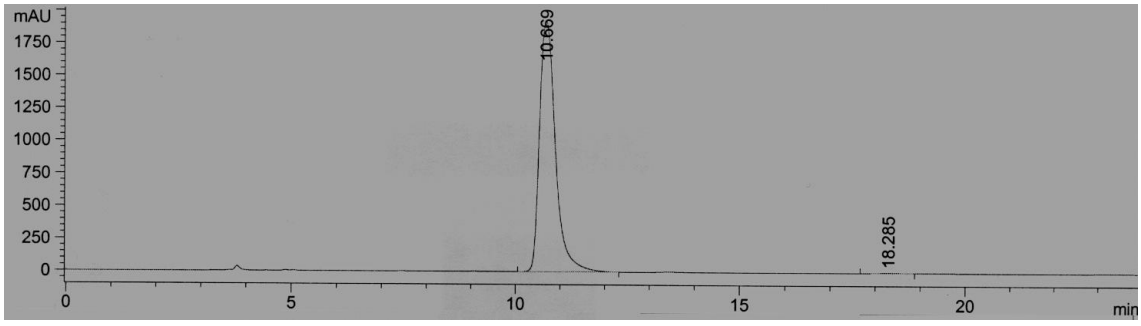
Retention times: t_R (*S*) = 10.7 min, t_R (*R*) = 18.1 min

Rs: 6.6

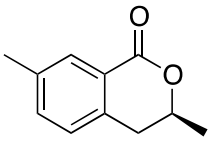
HPLC separation for both enantiomers of isochromanone (±)-5b



Isochromanone (*S*)-5b in >99% *ee*



Spectroscopical and analytical data of (*S*)-3,7-Dimethylisochroman-1-one (5c)



Spectroscopical data for isochromanone 5c

White solid. Isolated yield (79%). R_f (30% EtOAc/Hexane): 0.44. Mp: 48-50 ºC. IR (KBr): 3065, 2975, 1722, 1610 and 1213 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.49 (d, $^3J_{HH}$= 6.3 Hz, 3H), 2.36 (s, 3H), 2.80-2.99 (m, 1H), 4.46-4.76 (m, 1H), 7.11 (d, $^3J_{HH}$= 7.7 Hz, 1H), 7.32 (dd, $^3J_{HH}$= 7.7 Hz; $^4J_{HH}$= 1.8 Hz, 1H), 7.88 (d, $^4J_{HH}$= 2.2 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.8 (CH_3), 20.9 (CH_3), 34.4 (CH_2), 75.1 (CH), 118.8 (C), 124.6 (C), 127.1 (CH), 130.4 (CH), 134.4 (CH), 136.0 (C), 137.3 (C), 165.8 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{12}NaO_2)^+$ $(M+Na)^+$: 199.0730 found: 199.0737. (*S*)-**5c**: $[\alpha]^{20}_D$ +163.3 (*c* 1, $CHCl_3$) (>99% *ee*).

Analytical separation for isochromanone (±)-5c (HPLC)

Column: Chiralpak AS

Eluent: *n*-hexane/2-propanol 85:15

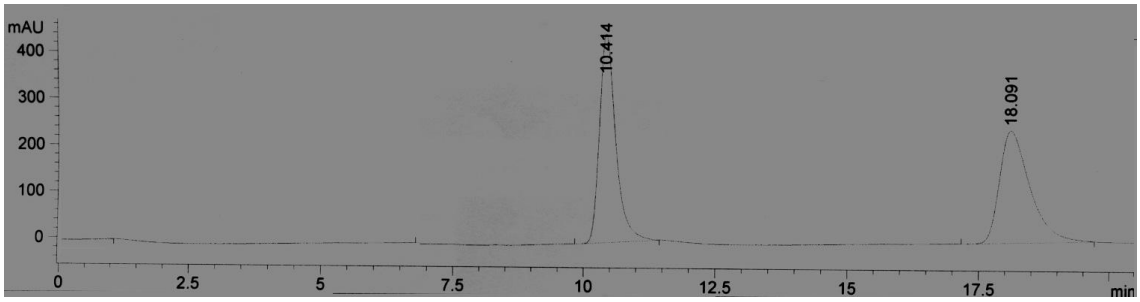
Flow: 0.8 mL/min

Temperature: 30 ºC

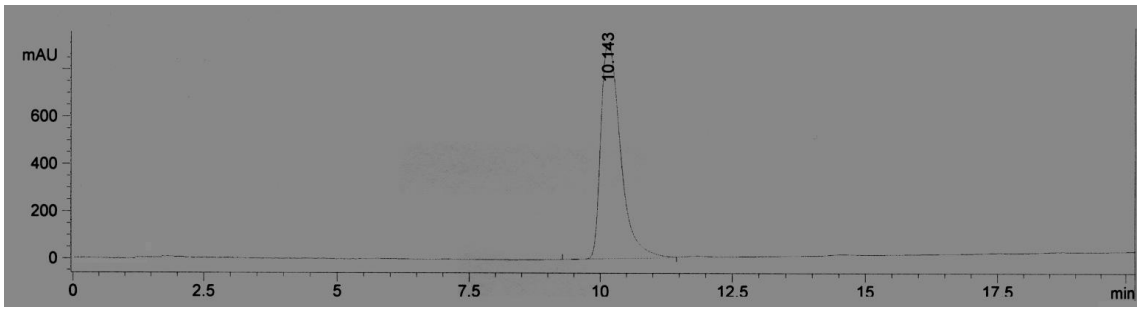
Retention times: t_R (*S*) = 10.4 min, t_R (*R*) = 18.1 min

Rs: 5.7

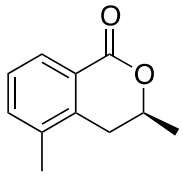
HPLC separation for both enantiomers of isochromanone (±)-5c



Isochromanone (*S*)-5c in >99% *ee*



Spectroscopical and analytical data of (*S*)-3,5-Dimethylisochroman-1-one (5d)



Spectroscopical data for isochromanone 5d

White solid. Isolated yield (71%). R_f (30% EtOAc/Hexane): 0.44. Mp: 61-63 ºC. IR (KBr): 3089, 2976, 1720, 1630, 1254 and 1110 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.54 (d, $^3J_{HH}$= 6.2 Hz, 3H), 2.32 (s, 3H), 2.59-3.22 (m, 2H), 4.52-4.75 (m, 1H), 7.28 (t, $^3J_{HH}$= 7.6 Hz, 1H), 7.40 (d, $^3J_{HH}$= 7.5 Hz, 1H), 7.78-8.12 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.8 (CH_3), 21.0 (CH_3), 31.9 (CH_2), 74.2 (CH), 124.8 (C), 126.9 (CH), 128.0 (CH), 134.9 (CH+C), 137.6 (C), 165.9 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{12}NaO_2)^+$ $(M+Na)^+$: 199.0730 found: 199.0731. (*S*)-**5d**: $[\alpha]^{20}_D$ +91.3 (*c* 1, $CHCl_3$) (>99% *ee*).

Analytical separation for isochromanone (±)-5d (HPLC)

Column: Chiralpak AS

Eluent: *n*-hexane/2-propanol 85:15

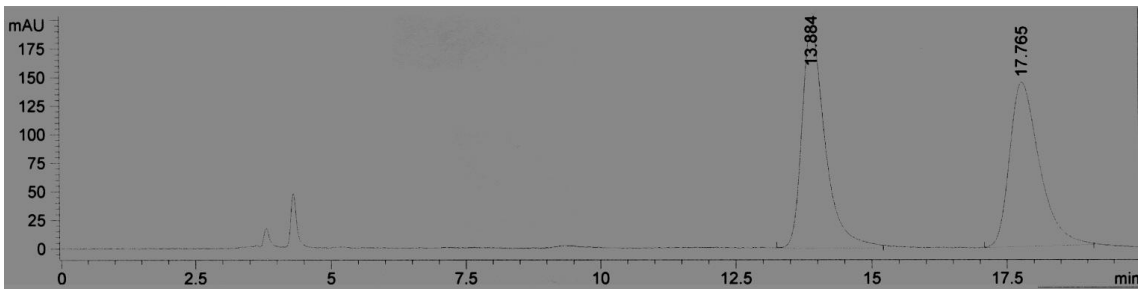
Flow: 0.8 mL/min

Temperature: 30 ºC

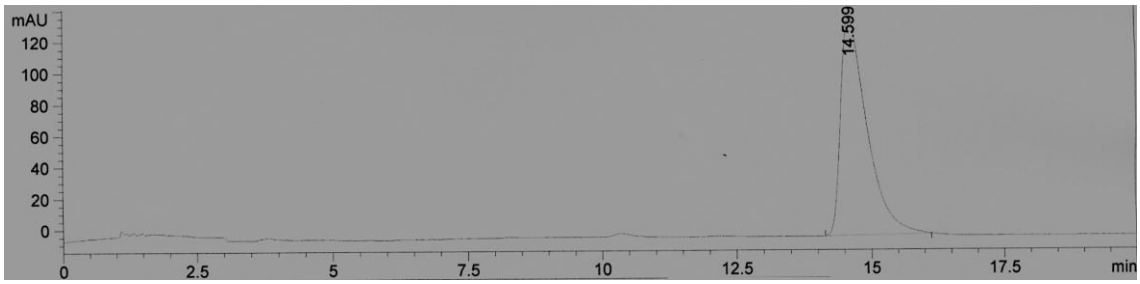
Retention times: t_R (*S*) = 13.9 min, t_R (*R*) = 17.8 min

Rs: 2.2

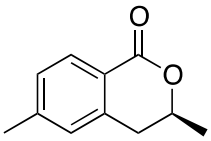
HPLC separation for both enantiomers of isochromanone (±)-5d



Isochromanone (*S*)-5d in >99% *ee*



Spectroscopical and analytical data of (*S*)-3,6-Dimethylisochroman-1-one (5e)



Spectroscopical data for isochromanone 5e

White solid. Isolated yield (90%). R_f (30% EtOAc/Hexane): 0.44. Mp: 63-65 ºC. IR (KBr): 3073, 2988, 1721, 1599, 1265 and 1191 cm^{-1}.^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.49 (d, $^3J_{HH}$= 6.3 Hz 3H), 2.39 (s, 3H), 2.71-3.04 (m, 2H), 4.47-4.80 (m, 1H), 7.02 (s, 1H), 7.17 (dd, $^3J_{HH}$= 8.1; $^4J_{HH}$= 1.9 Hz, 1H), 7.96 (d, $^3J_{HH}$= 7.9 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.8 (CH_3), 21.6 (CH_3), 34.8 (CH_2), 74.9 (CH), 122.2 (C), 127.8 (CH), 128.4 (CH), 130.2 (CH), 139.0 (C), 144.5 (C), 165.7 (C). HRMS (ESI$^+$, *m/z*): calcd for $(C_{11}H_{12}NaO_2)^+$ $(M+Na)^+$: 199.0730 found: 199.0733. (*S*)-**5e**: $[\alpha]^{20}_D$ +122.6 (*c* 1, $CHCl_3$) (>99% *ee*).

Analytical separation for isochromanone (±)-5e (GC)

Column: RT-β-dexe

Inyector temperature: 225 ºC

Carrier gas flow: 1.1 mL/min

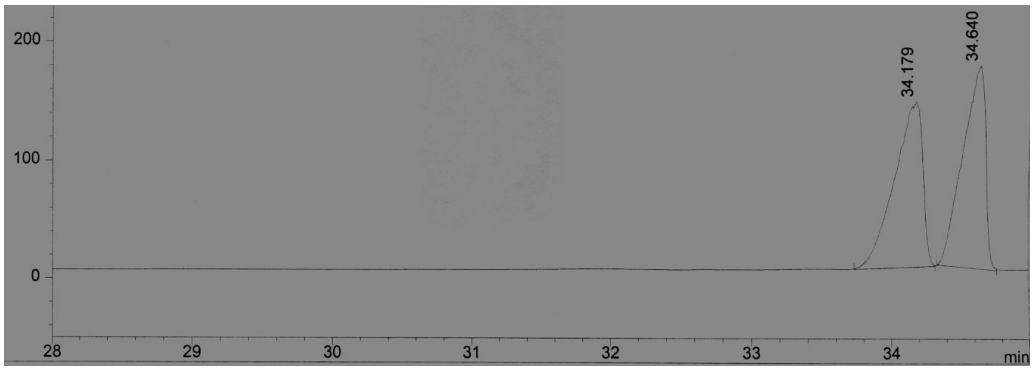
Detector temperature: 250 ºC

Retention times: t_R (*S*) = 34.2 min, t_R (*R*) = 34.6 min

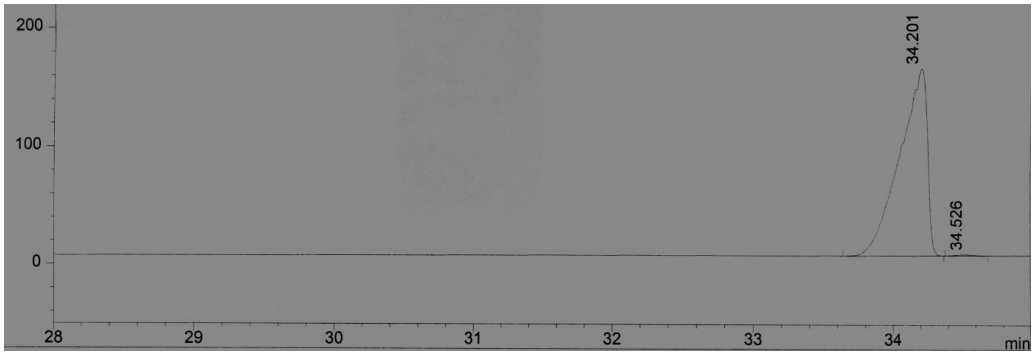
Rs: 1.1

Temperature program: 80 ºC (2 min) then 2 ºC/min until 150 ºC then 150 ºC (2 min) then 3 ºC/min until 180 ºC

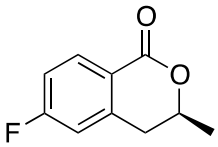
GC separation for both enantiomers of isochromanone (±)-5e



Isochromanone (*S*)-5d in >99% *ee*



Spectroscopical and analytical data of (*S*)-6-Fluoro-3-methylisochroman-1-one (5f)



Spectroscopical data for isochromanone 5f

White solid. Isolated yield (85%). R_f (30% EtOAc/Hexane): 0.45. Mp: 45-47 ºC. IR (KBr): 3080, 2985, 1720, 1632, 1290 and 1020 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.51 (d, $^3J_{HH}$= 6.3 Hz, 3H), 2.84-3.06 (m, 2H), 4.54-4.76 (m, 1H), 6.80-6.97 (m, 1H), 6.99-7.11 (m, 1H), 7.74-8.38 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.7 (CH_3), 34.8 (CH_2), 74.8 (CH), 114.1 (d, $^2J_{CF}$= 21.9 Hz, CH), 115.1 (d, $^2J_{CF}$= 22.3 Hz, CH), 121.2 (C), 133.2 (d, $^3J_{CF}$= 9.9 Hz, CH), 142.0 (d, $^3J_{CF}$= 9.8 Hz, C), 164.0 (C), 166.0 (d, $^1J_{CF}$= 210.1 Hz, C). HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_9FNaO_2)^+$ $(M+Na)^+$: 203.0479 found: 203.0473. (*S*)-**5f**: $[\alpha]^{20}_D$ +153.0 (*c* 1, $CHCl_3$) (>99% *ee*).

Analytical separation for isochromanone (±)-5f (HPLC)

Column: Chiralpak AS

Eluent: *n*-hexane/2-propanol 85:15

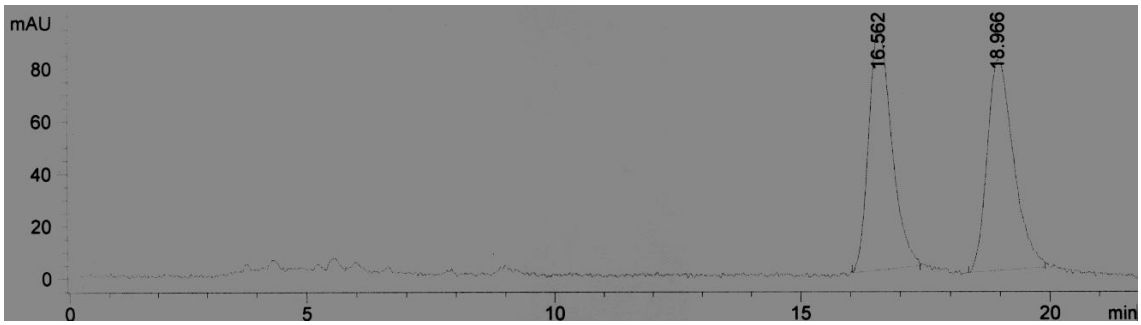
Flow: 0.8 mL/min

Temperature: 30 ºC

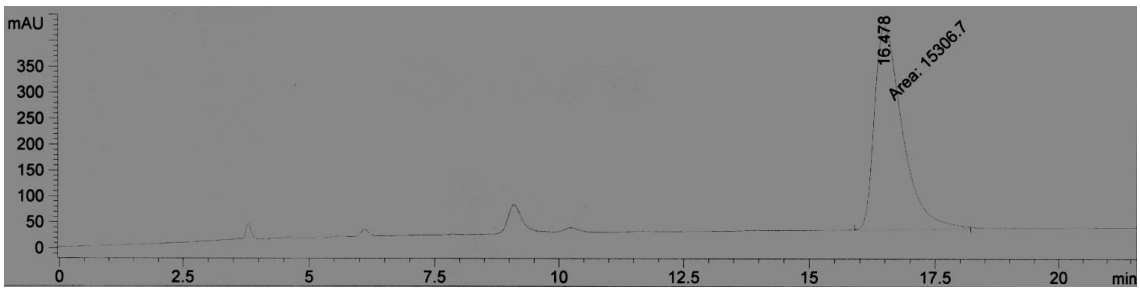
Retention times: t_R (*S*) = 16.6 min, t_R (*R*) = 19.0 min

Rs: 1.6

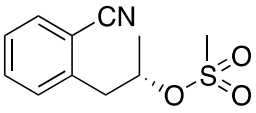
HPLC separation for both enantiomers of isochromanone (±)-5f



Isochromanone (*S*)-5d in >99% *ee*



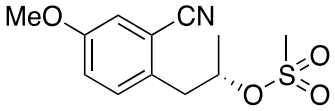
Spectroscopical data of (*S*)-1-(2-Cyanophenyl)propan-2-yl methanesulfonate (6a)



Spectroscopical data for methanesulfonate 6a

White solid. Isolated yield (88%). R_f (50% Et_2O/Hexane): 0.15. Mp: 52-54 ºC. IR (KBr): 3054, 2980, 2226, 1360 and 1194 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.42 (d, $^3J_{HH}$= 6.3 Hz, 3H), 2.69 (s, 3H), 3.12 (d, $^3J_{HH}$= 6.4 Hz, 2H), 4.94 (q, $^3J_{HH}$= 6.3 Hz, 1H), 7.28-7.39 (m, 2H), 7.52 (td, $^3J_{HH}$= 7.6 Hz; $^4J_{HH}$= 1.3 Hz, 1H), 7.59 (d, $^3J_{HH}$= 6.3 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.8 (CH_3), 37.6 (CH_3), 40.6 (CH_2), 78.7 (CH), 112.7 (C), 117.5 (C), 127.4 (CH), 130.7 (CH), 132.5 (CH), 132.6 (CH), 139.8 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{13}NNaO_3S)^+$ $(M+Na)^+$: 262.0508 found: 262.0497. (*S*)-**6a**: $[\alpha]^{20}_D$ +21.9 (*c* 1, $CHCl_3$) (>99% *ee*).

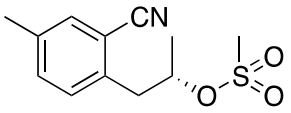
Spectroscopical data of (*S*)-1-(2-Cyano-4-methoxyphenyl)propan-2-yl methanesulfonate (6b)



Spectroscopical data for methanesulfonate 6b

White solid. Isolated yield (89%). R_f (50% Et_2O/Hexane): 0.11. Mp: 68-70 ºC. IR (KBr): 3045, 2977, 2226, 1352 and 1143 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.42 (d, $^3J_{HH}$= 6.3 Hz, 3H), 2.74 (s, 3H), 3.06 (d, $^3J_{HH}$= 6.3 Hz, 2H), 3.76 (s, 3H), 4.91 (q, $^3J_{HH}$= 6.3 Hz, 1H), 6.95-7.17 (m, 2H), 7.26 (dd, $^3J_{HH}$= 8.3 Hz; $^4J_{HH}$= 0.8 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.7 (CH_3), 37.8 (CH_3), 39.9 (CH_2), 55.3 (CH_3), 79.0 (CH), 113.5 (C), 116.9 (CH), 117.5 (C), 119.3 (CH), 131.8 (C), 132.0 (CH), 158.3 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{12}H_{15}NNaO_4S)^+$ $(M+Na)^+$: 292.0614 found: 292.0629. (*S*)-**6b**: $[\alpha]^{20}_D$ +18.7 (*c* 1, $CHCl_3$) (>99% *ee*).

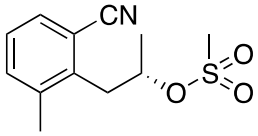
Spectroscopical data of (*S*)-1-(2-Cyano-4-methylphenyl)propan-2-yl methanesulfonate (6c)



Spectroscopical data for methanesulfonate 6c

White solid. Isolated yield (82%). R_f (50% Et_2O/Hexane): 0.14. Mp: 44-46 ºC. IR (KBr): 3043, 2982, 2225, 1366 and 1090 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.44 (d, $^3J_{HH}$= 6.2 Hz, 3H), 2.32 (s, 3H), 2.74 (s, 3H), 3.10 (d, $^3J_{HH}$= 6.8 Hz, 2H), 4.85-5.04 (m, 1H), 7.19-7.29 (m, 1H), 7.34 (d, $^3J_{HH}$= 8.2 Hz, 1H), 7.42 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.4 (CH_3), 20.8 (CH_3), 37.8 (CH_3), 40.4 (CH_2), 78.9 (CH), 112.6 (C), 117.7 (C), 130.7 (CH), 132.8 (CH), 133.6 (CH), 136.9 (C), 137.6 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{12}H_{15}NNaO_3S)^+$ $(M+Na)^+$: 276.0665 found: 276.0670. (*S*)-**6c**: $[\alpha]^{20}_D$ +23.8 (*c* 1, $CHCl_3$) (>99% *ee*).

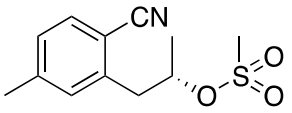
Spectroscopical data of (*S*)-1-(2-Cyano-6-methylphenyl)propan-2-yl methanesulfonate (6d)



Spectroscopical data for methanesulfonate 6d

White solid. Isolated yield (84%). R_f (50% Et_2O/Hexane): 0.15. Mp: 101-103 ºC. IR (KBr): 3060, 2990, 2226, 1356 and 1175 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.51 (d, $^3J_{HH}$= 6.2 Hz, 3H), 2.39 (s, 3H), 2.65 (s, 3H), 3.09-3.31 (m, 2H), 4.86-5.04 (m, 1H), 7.25 (t, $^3J_{HH}$= 7.7 Hz, 1H), 7.41 (d, $^3J_{HH}$= 7.6 Hz, 1H), 7.48 (dd, $^3J_{HH}$= 7.7 Hz, $^4J_{HH}$= 1.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.5 (CH_3), 21.3 (CH_3), 37.5 (CH_3), 38.0 (CH_2), 78.6 (CH), 113.4 (C), 118.1 (C), 127.4 (CH), 130.5 (CH), 134.8 (CH), 138.3 (C), 138.4 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{12}H_{15}NNaO_3S)^+$ $(M+Na)^+$: 276.0665 found: 276.0679. (*S*)-**6d**: $[\alpha]^{20}_D$ +27.2 (*c* 1, $CHCl_3$) (>99% *ee*).

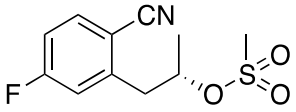
Spectroscopical data of (*S*)-1-(2-Cyano-5-methylphenyl)propan-2-yl methanesulfonate (6e)



Spectroscopical data for methanesulfonate 6e

White solid. Isolated yield (96%). R_f (50% Et_2O/Hexane): 0.15. Mp: 66-68 ºC. IR (KBr): 3081, 2993, 2225, 1350 and 985 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (d, $^3J_{HH}$= 6.2 Hz, 3H), 2.35 (s, 3H), 2.71 (s, 3H), 3.08 (d, $^3J_{HH}$= 6.4 Hz, 2H), 4.93 (q, $^3J_{HH}$= 6.9 Hz, 1H), 7.03-7.21 (m, 2H), 7.47 (d, $^3J_{HH}$= 7.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2 (CH_3), 21.7 (CH_3), 38.1 (CH_3), 41.0 (CH_2), 79.2 (CH), 110.1 (C), 118.2 (C), 128.6 (CH), 131.8 (CH), 132.8 (CH), 140.0 (C), 144.0 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{12}H_{15}NNaO_3S)^+$ $(M+Na)^+$: 276.0665 found: 276.0666. (*S*)-**6e**: $[\alpha]^{20}_D$ +17.1 (*c* 1, $CHCl_3$) (>99% *ee*).

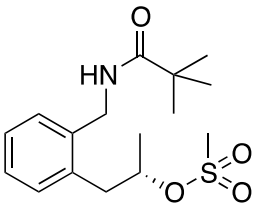
Spectroscopical data of (*S*)-1-(2-Cyano-5-fluorophenyl)propan-2-yl methanesulfonate (6f)



Spectroscopical data for methanesulfonate 6f

White solid. Isolated yield (86%). R_f (50% Et_2O/Hexane): 0.16. Mp: 99-101 ºC. IR (KBr): 3045, 2976, 2224, 1362 and 1200 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.45 (d, $^3J_{HH}$= 6.2 Hz, 3H), 2.82 (s, 3H), 3.15 (d, $^3J_{HH}$= 6.3 Hz, 2H), 4.78-5.16 (m, 1H), 6.85-7.19 (m, 2H), 7.64 (dd, $^3J_{HH}$= 8.5, 5.6 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.8 (CH_3), 38.1 (CH_3), 40.8 (CH_2), 78.1 (CH), 109.2 (d, $^4J_{CF}$= 3.5 Hz, C), 115.3 (d, $^2J_{CF}$= 22.6 Hz, CH), 117.0 (C), 118.3 (d, $^2J_{CF}$= 22.8 Hz, CH), 135.0 (d, $^3J_{CF}$= 9.8 Hz, CH), 143.3 (d, $^3J_{CF}$= 9.2 Hz, C), 164.5 (d, $^1J_{CF}$= 257.2 Hz, C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{12}FNNaO_3S)^+$ $(M+Na)^+$: 280.0414 found: 280.0418. (*S*)-**6f**: $[\alpha]^{20}_D$ +25.5 (*c* 1, $CHCl_3$) (>99% *ee*).

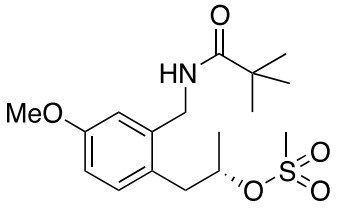
Spectroscopical data of (*S*)-1-(2-(Pivalamidomethyl)phenyl)propan-2-yl methanesulfonate (7a)



Spectroscopical data for carbamate 7a

White solid. Isolated yield (73%). R_f (50% Et_2O/Hexane): 0.13. Mp: 64-66 ºC. IR (KBr): 3438, 3059, 2981, 1707, 1350 and 1174 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.44 (s, 9H), 1.50 (d, $^3J_{HH}$= 6.2 Hz, 3H), 2.49 (s, 3H), 2.78-3.19 (m, 2H), 4.20-4.50 (m, 2H), 4.72-5.05 (m, 2H), 7.03-7.41 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.0 (CH_3), 28.5 ($3CH_3$), 37.7 (CH_3), 39.5 (CH_2), 42.3 (CH_2), 79.8 (C), 81.1 (CH), 127.7 (CH), 127.9 (CH), 129.2 (CH), 131.3 (CH), 135.2 (C), 137.5 (C), 155.8 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{16}H_{25}NNaO_5S)^+$ $(M+Na)^+$: 366.1346 found 366.1349. HRMS (ESI^+, *m/z*): calcd for $(C_{16}H_{25}NNaO_5S)^+$ $(M+Na)^+$: 366.1346 found: 366.1349. (*S*)-**7a**: $[\alpha]^{20}_D$ +22.7 (*c* 1, $CHCl_3$) (>99% *ee*).

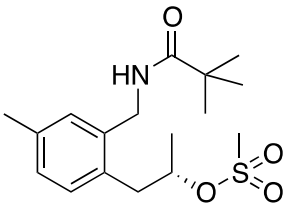
Spectroscopical data of (*S*)-1-(4-Methoxy-2-(pivalamidomethyl)phenyl)propan-2-yl methanesulfonate (7b)



Spectroscopical data for carbamate 7b

White solid. Isolated yield (82%). R_f (50% Et_2O/Hexane): 0.12. Mp: 82-84 ºC. IR (KBr): 3420, 3083, 2991, 1709, 1364 and 990 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.41 (s, 9H), 1.44 (d, $^3J_{HH}$= 6.1 Hz, 3H), 2.48 (s, 3H), 2.76-3.02 (m, 2H), 3.73 (s, 3H), 4.14-4.39 (m, 2H), 4.54-4.92 (m, 1H), 5.08 (br s, 1H), 6.73 (dd, $^3J_{HH}$= 8.4 Hz; $^4J_{HH}$= 2.7 Hz, 1H), 6.81 (d, $^4J_{HH}$= 2.7 Hz, 1H), 7.08 (d, $^3J_{HH}$= 8.4 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.4 (CH_3), 28.1 ($3CH_3$), 37.3 (CH_3), 38.3 (CH_2), 41.9 (CH_2), 55.0 (CH_3), 79.3 (C), 81.0 (CH), 112.6 (CH), 114.0 (CH), 126.5 (C), 131.9 (CH), 138.5 (C), 155.6 (C), 158.6 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{17}H_{27}NNaO_6S)^+$ $(M+Na)^+$: 396.1451 found: 396.1472. (*S*)-**7b**: $[\alpha]^{20}_D$ +26.9 (*c* 1, $CHCl_3$) (>99% *ee*).

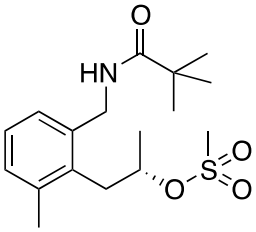
Spectroscopical data of (*S*)-1-(4-Methyl-2-(pivalamidomethyl)phenyl)propan-2-yl methanesulfonate (7c)



Spectroscopical data for carbamate 7c

White solid. Isolated yield (81%). R_f (50% Et_2O/Hexane): 0.15. Mp: 77-79 ºC. IR (KBr): 3455, 3062, 2988, 1704, 1327 and 1020 cm^{-1} .^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.47 (d, $^3J_{HH}$= 6.2 Hz, 3H), 2.28 (s, 3H), 2.49 (s, 3H), 2.78-3.12 (m, 2H), 4.08-4.43 (m, 2H), 4.74-4.89 (m, 1H), 4.97 (br s, 1H), 6.90-7.22 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.8 (CH_3), 21.6 (CH_3), 28.2 ($3CH_3$), 37.4 (CH_3), 38.8 (CH_2), 42.0 (CH_2), 79.4 (C), 81.0 (CH), 128.2 (CH), 129.6 (CH), 130.9 (CH), 131.7 (C), 136.8 (C), 137.0 (C), 155.6 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{17}H_{27}NNaO_5S)^+$ $(M+Na)^+$: 380.1502 found: 380.1491. (*S*)-**7c**: $[\alpha]^{20}_D$ +24.9 (*c* 1, $CHCl_3$) (>99% *ee*).

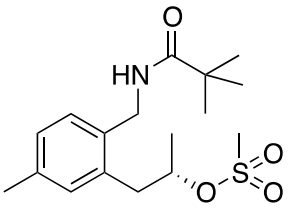
Spectroscopical data of (*S*)-1-(2-Methyl-6-(pivalamidomethyl)phenyl)propan-2-yl methanesulfonate (7d)



Spectroscopical data for carbamate 7d

White solid. Isolated yield (74%). R_f (50% Et_2O/Hexane): 0.15. Mp: 87-89 ºC. IR (KBr): 3403, 3055, 2990, 1710, 1379 and 1112 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.52 (d, $^3J_{HH}$= 6.2 Hz, 1H), 2.31 (s, 3H), 2.34 (s, 3H), 2.66-3.24 (m, 2H), 4.20-4.51 (dd, $^3J_{HH}$= 11.6, 5.9 Hz, 2H), 4.66-4.96 (m, 1H), 5.02 (br s, 1H), 6.44-7.27 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1 (CH_3), 22.0 (CH_3), 28.2 ($3CH_3$), 35.1 (CH_2), 36.9 (CH_3), 42.3 (CH_2), 79.3 (C), 80.4 (CH), 126.5 (CH), 127.1 (CH), 129.8 (CH), 133.4 (C), 137.4 (C), 137.6 (C), 155.6 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{17}H_{27}NNaO_5S)^+$ $(M+Na)^+$: 380.1502 found: 380.1494. (*S*)-**7d**: $[\alpha]^{20}_D$ +22.9 (*c* 1, $CHCl_3$) (>99% *ee*).

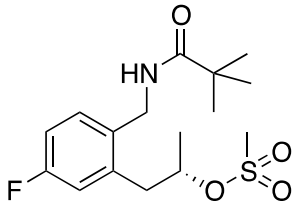
Spectroscopical data of (*S*)-1-(5-Methyl-2-(pivalamidomethyl)phenyl)propan-2-yl methanesulfonate (7e)



Spectroscopical data for carbamate 7e

White solid. Isolated yield (70%). R_f (50% Et_2O/Hexane): 0.16. Mp: 91-93 ºC. IR (KBr): 3455, 3072, 2974, 1709, 1344 and 1213 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.39 (s, 9H), 1.44 (d, $^3J_{HH}$= 6.2 Hz, 3H), 2.25 (s, 3H), 2.43 (s, 3H), 2.76-3.06 (m, 2H), 4.12-4.37 (m, 2H), 4.75-4.87 (m, 1H), 5.10 (brs, 1H), 6.86-7.04 (m, 2H), 7.13 (d, $^3J_{HH}$= 8.2 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.6 (CH_3), 21.5 (CH_3), 28.1 ($3CH_3$), 37.1 (CH_3), 38.9 (CH_2), 41.5 (CH_2), 79.1 (C), 80.9 (CH), 127.8 (CH), 128.8 (CH), 131.4 (CH), 134.1 (C), 134.5 (C), 136.9 (C), 155.4 (C). HRMS (ESI$^+$, *m/z*): calcd for $(C_{17}H_{27}NNaO_5S)^+$ $(M+Na)^+$: 380.1502 found: 380.1489. (*S*)-**7e**: $[\alpha]^{20}_D$ +17.7 (*c* 1, $CHCl_3$) (>99% *ee*).

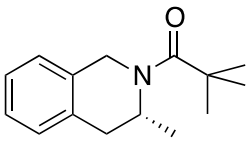
Spectroscopical data of (*S*)-1-(5-Fluoro-2-(pivalamidomethyl)phenyl)propan-2-yl methanesulfonate (7f)



Spectroscopical data for carbamate 7f

White solid. Isolated yield (73%). R_f (50% Et_2O/Hexane): 0.16. Mp: 54-56 ºC. IR (KBr): 3445, 3088, 2976, 1711, 1234 and 959 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.40 (s, 9H), 1.45 (d, $^3J_{HH}$= 6.2 Hz, 3H), 2.58 (s, 3H), 2.72-3.22 (m, 2H), 4.10-4.38 (m, 2H), 4.77-4.94 (m, 1H), 5.07 (brs, 1H), 6.35-7.02 (m, 2H), 7.24 (dd, $^3J_{HH}$= 9.2, 5.9 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.3 (CH_3), 28.1 ($3CH_3$), 37.5 (CH_3), 39.0 (CH_2), 41.2 (CH_2), 79.3 (C), 80.0 (CH), 113.9 (d, $^2J_{CF}$= 21.0 Hz, CH), 117.3 (d, $^2J_{CF}$= 21.4 Hz, CH), 130.5 (d, $^3J_{CF}$= 8.6 Hz, CH), 133.0 (d, $^4J_{CF}$= 3.2 Hz, C), 137.0 (C), 155.4 (C), 161.5 (d, $^1J_{CF}$= 246.3 Hz, C). HRMS (ESI$^+$, *m/z*): calcd for $(C_{16}H_{24}FNNaO_5S)^+$ $(M+Na)^+$: 384.1251 found: 384.1240. (*S*)-**7f**: $[\alpha]^{20}_D$ +23.8 (*c* 1, $CHCl_3$) (>99% *ee*).

Spectroscopical and analytical data of (*R*)-2,2-Dimethyl-1-(3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl)propan-1-one (8a)



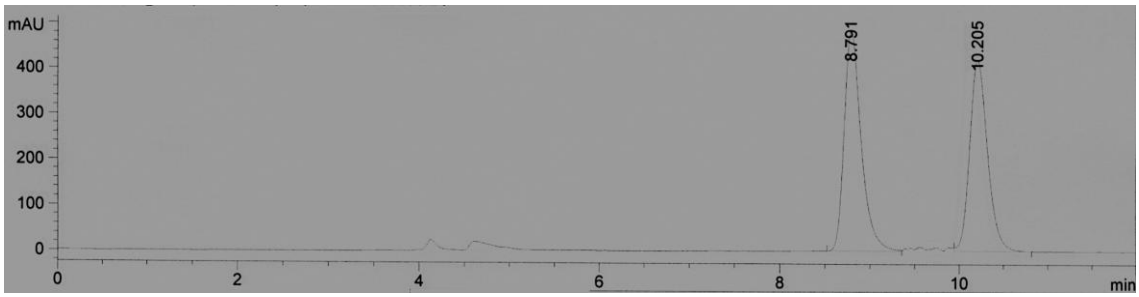
Spectroscopical data for *N*-Boc isoquinoline 8a

Hygroscopic solid. Isolated yield (61%). R_f (5% EtOAc/Hexane): 0.21. IR (NaCl): 3055, 2987, 1690 and 1266 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.07 (d, $^3J_{HH}$= 6.7 Hz, 3H), 1.50 (s, 9H), 2.43-2.67 (m, 1H), 2.95-3.20 (m, 1H), AB system (δ_A= 4.28, δ_B= 4.75, J_{HH}= 16.9 Hz), 4.58 (br s, 1H), 7.05-7.22 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.1 (CH_3), 28.5 ($3CH_3$), 34.9 (CH_2), 42.6 (CH_2), 44.9 (CH), 79.6 (C), 126.0 (CH), 126.0 (CH), 126.5 (CH), 129.1 (CH), 133.1 (2C), 154.8 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{15}H_{21}NNaO_2)^+$ $(M+Na)^+$: 270.1465 found: 270.1459. (*R*)-**8a**: $[\alpha]^{20}_D$ +64.2 (*c* 1, $CHCl_3$) (>99% *ee*).

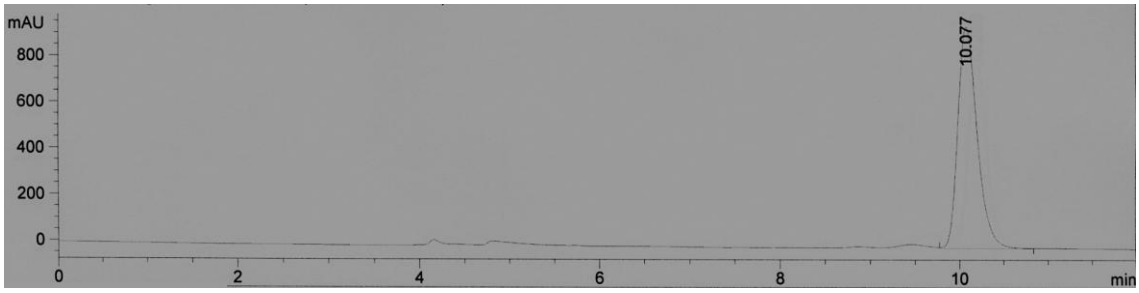
Analytical separation for *N*-Boc isoquinoline (±)-8a (HPLC)

Column: Chiralpak IC	Eluent: *n*-hexane/2-propanol 98:2
Flow: 0.8 mL/min	Temperature: 15 ºC
Retention times: t_R (*S*) = 8.8 min, t_R (*R*) = 10.2 min	Rs: 1.7

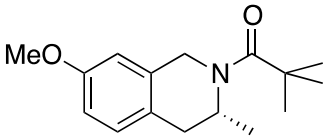
HPLC separation for both enantiomers of *N*-Boc isoquinoline (±)-8a



N*-Boc isoquinoline (*R*)-8a in >99% *ee



Spectroscopical and analytical data of (*R*)-1-(7-Methoxy-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2-dimethylpropan-1-one (8b)



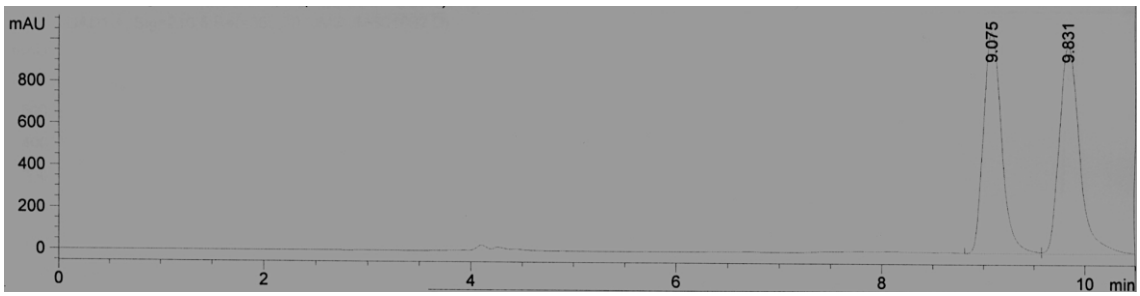
Spectroscopical data for *N*-Boc isoquinoline 8b

Hygroscopic solid. Isolated yield (55%). R_f (5% EtOAc/Hexane): 0.17. IR (KBr): 3043, 2990, 1685 and 1289 cm^{-1}. ^1H NMR (400.13 MHz, CD_3CN, 60 ºC): δ 1.07 (d, $^3J_{HH}$= 6.7 Hz, 3H), 1.50 (s, 9H), 2.42-2.62 (m, 1H), 2.87-3.05 (m, 1H), 3.79 (s, 3H), AB system (δ_A= 4.24, δ_B= 4.71, J_{HH}= 16.9 Hz), 4.45-4.53 (m, 1H), 6.61-6.90 (m, 2H), 7.08 (d, $^3J_{HH}$= 8.2 Hz, 1H). ^{13}C NMR (100.6 MHz, CD_3CN): δ 17.7 (CH_3), 28.0 ($3CH_3$), 34.0 (CH_2), 42.9 (CH_2), 46.1 (CH), 55.3 (CH_3), 79.3 (C), 111.4 (CH), 113.0 (CH), 125.8 (C), 130.1 (CH), 135.0 (C), 154.9 (C), 158.6 (C). HRMS (ESI$^+$, *m/z*): calcd for $(C_{16}H_{23}NNaO_3)^+$ $(M+Na)^+$: 300.1570 found: 300.1556. (*R*)-**8b**: $[\alpha]^{20}_D$ +67.5 (*c* 1, $CHCl_3$) (>99% *ee*).

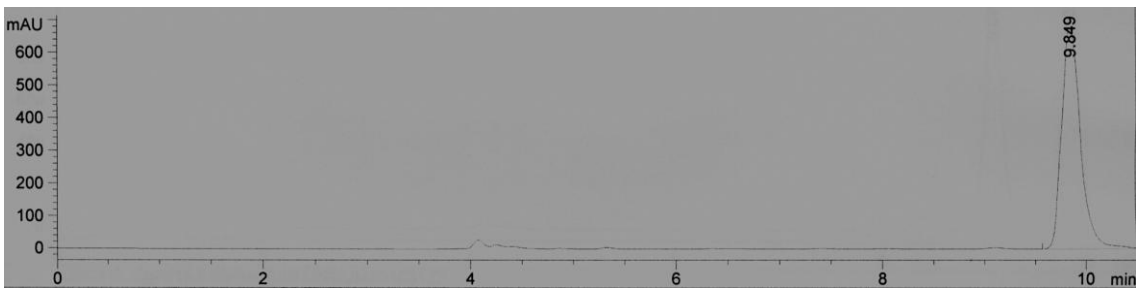
Analytical separation for *N*-Boc isoquinoline (±)-8b (HPLC)

Column: Chiralpak IC	Eluent: *n*-hexane/2-propanol 98:2
Flow: 0.8 mL/min	Temperature: 15 ºC
Retention times: t_R (*S*) = 9.1 min, t_R (*R*) = 9.8 min	Rs: 1.0

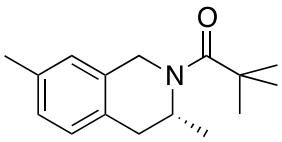
HPLC separation for both enantiomers of *N*-Boc isoquinoline (±)-8b



N-Boc isoquinoline (*R*)-8b in >99% *ee*



Spectroscopical and analytical data of (*R*)-1-(3,7-Dimethyl-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2-dimethylpropan-1-one (8c)



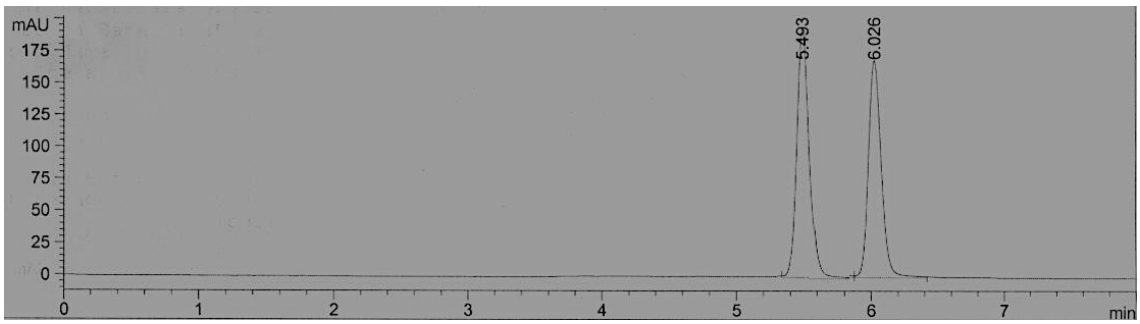
Spectroscopical data for *N*-Boc isoquinoline 8c

White solid. Isolated yield (62%). R_f (5% EtOAc/Hexane): 0.20. Mp: 52-54 ºC. IR (KBr): 3064, 2992, 1688 and 1245 cm^{-1}. ^1H NMR (400.13 MHz, CD_3CN, 60 ºC): δ 1.10 (d, $^3J_{HH}$= 6.7 Hz, 3H), 1.53 (s, 9H), 2.36 (s, 3H), 2.58-2.70 (m, 1H), 2.94-3.23 (m, 1H), AB system (δ_A= 4.24, δ_B= 4.72, J_{HH}= 16.9 Hz), 4.48-4.62 (m, 1H), 6.92-7.23 (m, 3H). ^{13}C NMR (100.6 MHz, CD_3CN, 60 ºC): δ 17.7 (CH3), 20.3 (CH3), 28.0 (3CH3), 34.4 (CH2), 42.7 (CH2), 46.0 (CH), 79.2 (C), 126.6 (CH), 127.6 (CH), 129.1 (CH), 130.7 (C), 133.7 (C), 135.9 (C), 154.9 (C) . HRMS (ESI^+, *m/z*): calcd for $(C_{16}H_{23}NNaO_2)^+$ $(M+Na)^+$: 284.1621 found: 284.1609. (*R*)-**8c**: $[\alpha]^{20}_D$ +77.6 (*c* 1, $CHCl_3$) (>99% *ee*).

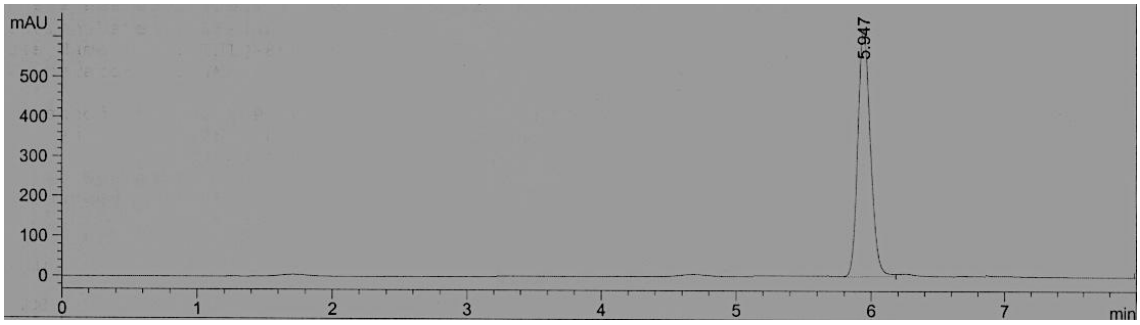
Analytical separation for *N*-Boc isoquinoline (±)-8c (HPLC)

Column: Chiralpak IC	Eluent: *n*-hexane/2-propanol 98:2
Flow: 0.8 mL/min	Temperature: 30 ºC
Retention times: t_R (*S*) = 5.5 min, t_R (*R*) = 6.0 min	Rs: 1.5

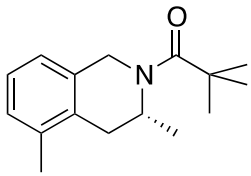
HPLC separation for both enantiomers of *N*-Boc isoquinoline (±)-8c



N*-Boc isoquinoline (*R*)-8c in >99% *ee



Spectroscopical and analytical data of (*R*)-1-(3,5-Dimethyl-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2-dimethylpropan-1-one (8d)



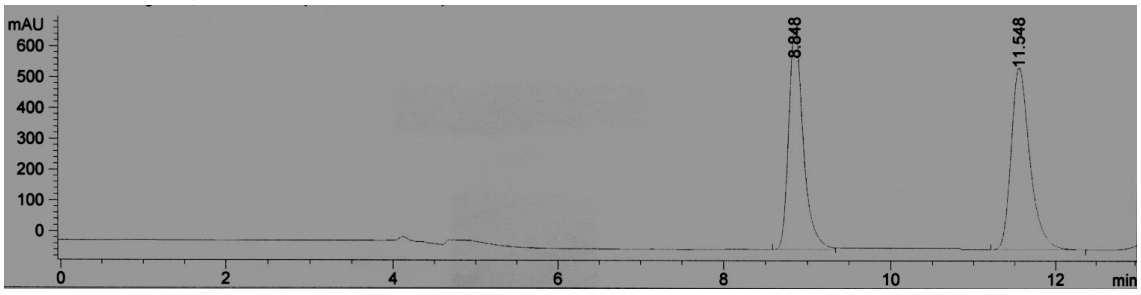
Spectroscopical data for *N*-Boc isoquinoline 8d

Hygroscopic solid. Isolated yield: 61%. R_f (5%EtOAc/Hexane): 0.20. IR (KBr): 3090, 2983, 1690 and 1294 cm^{-1}. ^1H NMR (400.13 MHz, MeCN, 60 ºC): δ 0.99 (d, $^3J_{HH}$= 6.8 Hz, 3H), 1.40 (s, 9H), 2.18 (s, 3H), 2.47-2.61 (m, 1H), 2.73-2.87 (m, 1H), AB system (δ_A= 4.18, δ_B= 4.62, J_{HH}= 16.6 Hz), 4.40-4.52 (m, 1H), 6.81-6.94 (m, 1H), 6.95-7.14 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 17.9 (CH_3), 18.4 (CH_3), 28.0 ($3CH_3$), 31.6 (CH_2), 42.7 (CH_2), 45.8 (CH), 79.3 (C), 123.9 (CH), 125.9 (CH), 128.2 (CH), 132.3 (C), 133.8 (C), 136.8 (C), 154.9 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{16}H_{23}NNaO_2)^+$ $(M+Na)^+$: 284.1621 found 284.1615. (*R*)-**8d**: $[\alpha]^{20}_D$ +47.8 (*c* 1, $CHCl_3$) (>99% *ee*).

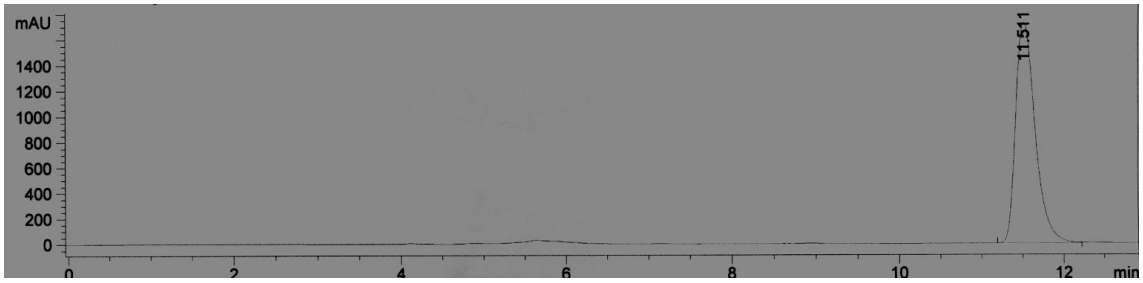
Analytical separation for *N*-Boc isoquinoline (±)-8d (HPLC)

Column: Chiralapak IC	Eluent: *n*-hexane/2-propanol 98:2
Flow: 0.8 mL/min	Temperature: 30 ºC
Retention times: t_R (*S*) = 8.8 min, t_R (*R*) = 11.5 min	Rs: 3.3

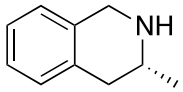
HPLC separation for both enantiomers of *N*-Boc isoquinoline (±)-8d



N-Boc isoquinoline (*R*)-8d in >99% *ee*



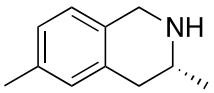
Spectroscopical of (*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline (9a)



Spectroscopical data for tetrahydroisoquinoline 8a

White solid. Isolated yield (54%). R_f (10% CH_2Cl_2/MeOH): 0.11. Mp: 270 ºC (dec). IR (KBr): 3242, 2959, 2918, 1614, 1504. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.31 (d, $^3J_{HH}$= 6.3 Hz, 3H), 2.48-2.66 (m, 1H), 2.73-2.90 (m, 1H), 3.12 (brs, 2H), 4.12 (d, $^3J_{HH}$= 3.9 Hz, 2H), 6.94-7.19 (m, 4H).^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.9 (CH_3), 36.6 (CH_2), 47.8 (CH_2), 49.2 (CH), 125.8 (CH), 126.0 (CH), 126.2 (CH), 129.0 (CH), 134.2 (C), 134.3 (C). HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{14}N)^+$ $(M+H)^+$: 148.1121 found 148.1130. (*R*)-**9a**: $[\alpha]^{20}_D$ -110.0 (*c* 0.6, $CHCl_3$) (>99% *ee*). Described in reference 19a $[\alpha]^{20}_D$ -113.6 (*c* 1, $CHCl_3$).

Spectroscopical and analytical data of (*R*)-3,6-Dimethyl-1,2,3,4-tetrahydroisoquinoline (9e)



Spectroscopical data for tetrahydroisoquinoline 9e

White solid. Isolated yield (47%). R_f (10% CH_2Cl_2/MeOH): 0.11. Mp: 262-264 ºC (dec). IR (KBr): 3250, 2957, 2920, 1625, 1505. ^{1}H NMR (300.13 MHz, CD_3OD): δ 1.44 (d, $^3J_{HH}$= 6.3 Hz, 3H), 2.44 (s, 3H), 2.60-2.82 (m, 1H), 2.73-2.86 (m, 1H), 2.98-3.15 (m, 1H), 4.18 (s, 2H), 6.78-7.14 (m, 3H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 21.4 (CH_3), 21.8 (CH_3), 37.4 (CH_2), 48.5 (CH_2), 50.8 (CH), 127.4 (CH), 128.2 (CH), 130.7 (CH), 131.8 (C), 135.3 (C), 137.4 (C). HRMS (ESI$^+$, *m/z*): calcdfor $(C_{11}H_{16}N)^+$ $(M+H)^+$: 162.1277 found: 162.1275. (*R*)-**9e**: $[\alpha]^{20}_D$ -107.2 (*c* 0.5, $CHCl_3$) (>99% *ee*).

Analytical separation for tetrahydroisoquinoline (±)-5e (GC)

Column: RT-β-dexe

Inyector temperature: 225 ºC

Carrier gas flow: 1.1 mL/min

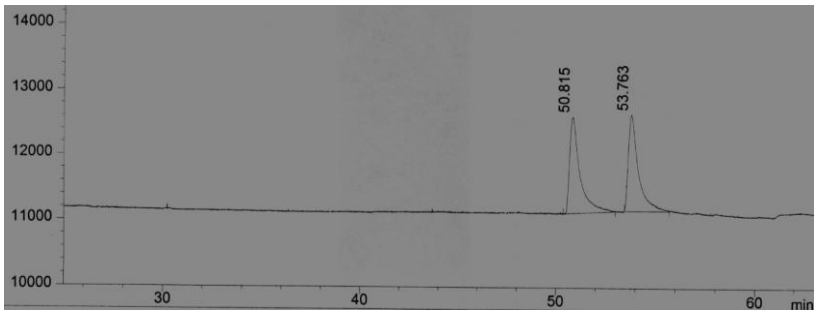
Detector temperature: 250 ºC

Retention times: t_R (*S*) = 50.8 min, t_R (*R*) = 53.8 min

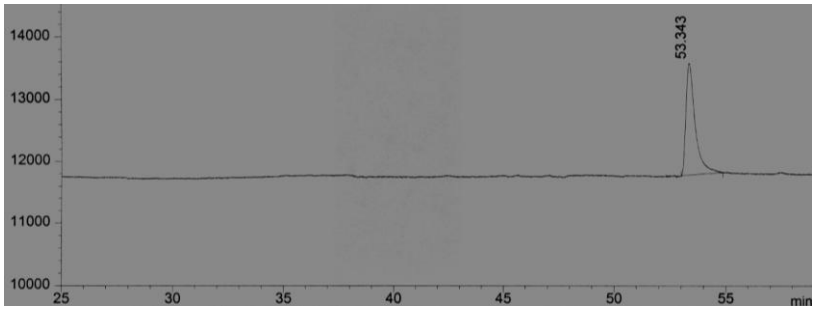
Rs: 1.2

Temperature program: 80 ºC (2 min) then 2 ºC/min until 150 ºC then 150 ºC (2 min) then 3 ºC/min until 180 ºC

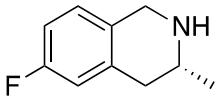
GC separation for both enantiomers of tetrahydroisoquinoline (±)-9e



Tetrahydroisoquinoline (*R*)-9e in >99% *ee*



Spectroscopical and analytical data of (*R*)-6-Fluoro-3-methyl-1,2,3,4-tetrahydroisoquinoline (9f)



Spectroscopical data for tetrahydroisoquinoline 9f

White solid. Isolated yield (25%). R_f (10% CH_2Cl_2): 0.13. Mp: 246-248 ºC (dec). IR (KBr): 3243, 2961, 1615, 1504. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.23 (d, $^3J_{HH}$= 6.4 Hz, 3H), 1.54 (br s, 1H), 2.28-2.58 (m, 1H), 2.68-2.81 (m, 1H), 2.95-3.05 (m, 1H), 3.75-4.20 (m, 2H), 6.65-6.88 (m, 2H), 6.97 (dd, $^3J_{HH}$= 8.3, 5.8 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.3 (CH_3), 37.3 (CH_2), 48.0 (CH_2), 48.9 (CH), 112.7 (d, $^2J_{CF}$= 21.5 Hz, CH), 115.1 (d, $^2J_{CF}$= 20.4 Hz, CH), 127.3 (d, $^3J_{CF}$= 8.0 Hz, CH), 130.9 (C), 136.9 (d, $^3J_{CF}$= 7.4 Hz, C), 161.1 (d, $^1J_{CF}$= 243.4 Hz, C). HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{13}FN)^+$ $(M+H)^+$: 166.1027 found: 166.1049. (*R*)-**9f**: $[\alpha]^{20}_D$ -120.0 (*c* 0.5, $CHCl_3$) (>99% *ee*).

Analytical separation for tetrahydroisoquinoline (±)-9f (GC)

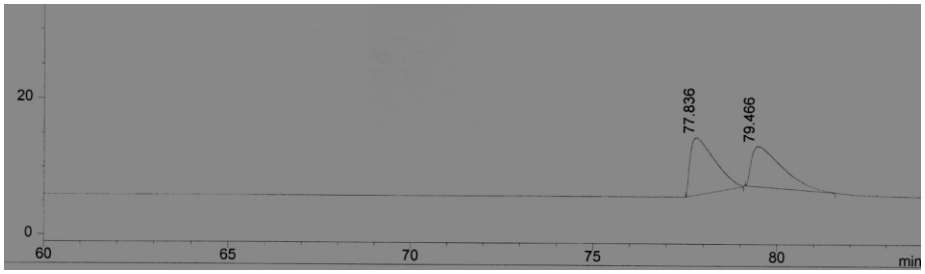
Column: RT-β-dexe — Inyector temperature: 225 ºC

Carrier gas flow: 1.1 mL/min — Detector temperature: 250 ºC

Retention times: t_R (*S*) = 77.8 min, t_R (*R*) = 79.4 min — Rs: 1.0

Temperature program: 105 ºC (70 min) then 0.5 ºC/min until 120 ºC then 10 ºC/min until 200ºC

GC separation for both enantiomers of tetrahydroisoquinoline (±)-9f



Tetrahydroisoquinoline (*R*)-9f in >99% *ee*