

Highly enantioselective desymmetrization of *meso* anhydrides by a bifunctional thiourea-based organocatalyst at low catalyst loadings and room temperature

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1.0 General

Proton Nuclear Magnetic Resonance spectra were recorded on a 400 MHz spectrometer in CDCl₃ (unless otherwise stated) referenced relative to residual CHCl₃ ($\delta = 7.26$ ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instrument (100 MHz) with total proton decoupling. All melting points are uncorrected. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated 60F₂₅₄ slides, and visualised by UV irradiation, KMnO₄ or anisaldehyde staining. Optical rotation measurements are quoted in units of 10⁻¹ deg cm² g⁻¹. Anhydrides **1**, **8**, **10**, **11**, and **12** were sourced commercially and used without further purification. Anhydride **7** was sourced commercially but recrystallized from toluene prior to use. Anhydride **9** was prepared from the commercially available *meso*-diacid.¹ Anhydride **13** was obtained starting from 3-phenylglutaric acid.² Catalysts **3-6** were synthesised following literature procedures.³ Toluene and methylene chloride were distilled from calcium hydride and stored under Argon. Methanol and diethyl ether were distilled over sodium-benzophenone ketyl radical and stored under argon. Commercially available anhydrous t-butyl methyl ether was used. All reactions were carried out under a protective argon atmosphere.

Racemic hemiesters were obtained by reaction of the appropriate anhydride with one equivalent of DABCO in methanol. Analytical CSP-HPLC was performed on a Daicel CHIRALPAK AD-H and OD-H (4.6 mm x 25 cm) columns.

2.0 Desymmetrization of the *meso* anhydrides into the corresponding methyl hemiesters

Room temperature procedure (Table 2, entries 1-7, 9)

A 40 mL reaction vial containing a stirring bar was charged with the appropriate anhydride (0.30 mmol) and **3** (0.003 mmol, 1.8 mg). The reaction vial was fitted with a septum and flushed with argon. MTBE (20 mL) was added followed by dry methanol (122 μ L, 3.00 mmol) in a dropwise manner *via* syringe. The solution was then stirred at room temperature for the time indicated in Table 2. When conversion was adjudged to be complete (by either TLC or $^1\text{H-NMR}$ spectroscopic analysis) the solvent was removed under reduced pressure and the crude product purified by flash-chromatography. In cases where conversion was not complete, the reaction was quenched by adding HCl (0.1 N, 10 mL) and the aqueous phase was extracted with EtOAc (2 x 10 mL). The organic phases were combined, dried over MgSO_4 , and concentrated *in vacuo* to provide the desired hemiester after purification by flash-chromatography.

Low temperature procedure (Table 2, entries 8 and 10)

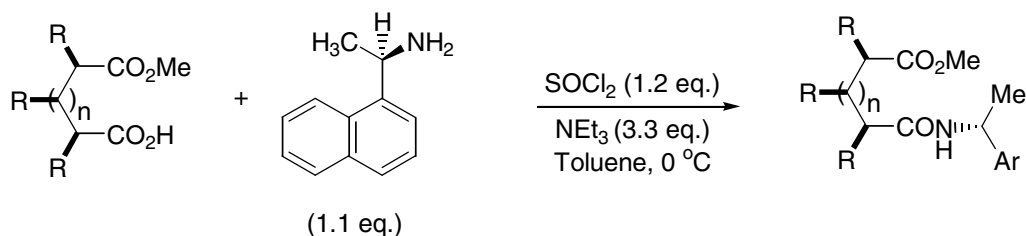
A 60 mL reaction vial containing a stirring bar was charged with the appropriate anhydride (0.30 mmol) and **3** (0.003 mmol, 1.8 mg). The reaction vial was fitted with a septum and flushed with argon. MTBE (40 mL) was added and the solution was cooled to 0 $^\circ\text{C}$. Dry methanol (122 μ L, 3.00 mmol) was added in a dropwise manner *via* syringe. The solution was then stirred at 0 $^\circ\text{C}$ for the time indicated in Table 2. When conversion was adjudged to be complete (by $^1\text{H-NMR}$ spectroscopic analysis) the solvent was removed under reduced pressure and the crude product purified by flash-chromatography to provide the desired hemiester.

Inversion of configuration: procedure

A 100 mL reaction vial equipped with a stirring bar was charged with hexahydrophthalic anhydride (0.100 g, 0.650 mmol) and **3** (0.013 mmol, 7.7 mg). The vial was fitted with a septum and flushed with argon. MTBE (43 mL) was added *via* syringe followed by allyl alcohol (444 μ L, 6.50 mmol) in a dropwise manner *via* syringe. The solution was then stirred at room temperature. After 48 h the solvent and the excess allyl alcohol were removed under reduced pressure and the residue was dissolved in dry CH_2Cl_2 (3 mL). DMAP (7.9 mg, 0.065 mmol) and dry methanol (263 μ L, 6.50 mmol) were added. DCC (134 mg, 0.650 mmol) was then added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at room temperature and under argon overnight. After removal of the white precipitate by filtration, the solution was concentrated *in vacuo* and the residue dissolved in dry THF (3 mL). Morpholine (567 μ L, 6.5 mmol) was added under an argon atmosphere followed by $\text{Pd}(\text{PPh}_3)_4$ (75 mg, 0.065 mmol) as a solution in dry THF (2 mL) and the reaction was stirred at room temperature under argon. After 2 h the solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (10 mL) and extracted with a K_2CO_3 (10% w/v) solution (3 x 10 mL). The combined aqueous layers were washed with CH_2Cl_2 (5 mL) and made acidic by addition of 1 N HCl. The acidic solution was then extracted with CH_2Cl_2 (4 x 10 mL) and the combined organic layers were dried over MgSO_4 . The solvent was concentrated *in vacuo* and the residue dissolved in a minimum amount of diethyl ether and filtered to remove residual triphenylphosphine oxide. After removing the solvent under reduced pressure, the desired pure product was obtained in 89% yield without requiring further purification and in 95% *ee* as determined by ^1H -NMR spectroscopic analysis of the corresponding amide-ester diastereoisomeric mixture prepared as in Scheme 1 (*vide infra*). $[\alpha]_{\text{D}}^{20} = -3.8$ (c 0.70, CHCl_3). The NMR spectra were consistent with those previously reported and the absolute configuration was established by comparing the optical rotation of the hemiester with the literature data.⁶

3.0 Enantiomeric excess determination of the hemiesters

The enantiomeric excess of each hemiester was determined by either $^1\text{H-NMR}$ spectroscopic or CSP-HPLC analysis after conversion of the product into a diastereoisomeric mixture of amides derived from (*R*)-1-(1-naphthyl)ethylamine (Scheme 1).⁴

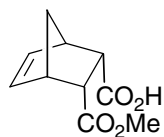


Scheme 1

A solution of thionyl chloride (0.12 mmol, 9 μL) in dry toluene (1 mL) was added to a solution of the monoester (0.1 mmol) in dry toluene (2 mL) at 0 °C. The mixture was stirred at 0 °C for 10 minutes, and dry triethylamine (0.33 mmol, 46 μL) and (*R*)-1-(1-naphthyl)ethylamine (0.11 mmol, 18 μL) were added successively. The mixture was stirred at 0 °C for 1 h and at room temperature for an additional 1 h. The residue was then dissolved in ethyl acetate (15 mL). The organic solution was washed with HCl (1 N, 10 mL), saturated aq. NaHCO₃ (10 mL) and brine (10 mL). The organic layer was then dried over magnesium sulphate and concentrated *in vacuo* to give the diastereoisomeric mixture. The enantiomeric excess was determined by comparison of either the product methyl ester resonances in the $^1\text{H-NMR}$ spectrum or by CSP-HPLC.

4.0 Characterisation data

Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid monomethyl ester (2, entry 3)



The desired monomethyl ester was obtained following the general procedure in 93% yield and as a white solid after purification by flash chromatography.

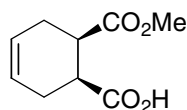
96% *ee* $[\alpha]_D^{20} = -7.4$ (c 1.53, CCl_4) as determined by $^1\text{H-NMR}$ spectroscopic and confirmed by CSP-HPLC analysis of the corresponding amide-ester diastereoisomeric mixture prepared as in Scheme 1.

Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.75 mL min^{-1} , RT, UV detection at 220 nm, retention times: 11.0 min (major diastereomer) and 16.5 (minor diastereomer).

The NMR spectra were consistent with those previously reported and the absolute configuration was established by comparing the optical rotation of the hemiester with the literature data.⁵

$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 1.36 (bd, $J = 8.5 \text{ Hz}$, 1H), 1.52 (app. dt, $J = 8.5$ and 0.3 Hz , 1H), 3.19 (m, 1H), 3.22 (m, 1H), 3.31 (dd, $J = 10$ and 3 Hz , 1H), 3.37 (dd, $J = 10$ and 3 Hz , 1H), 3.62 (s, 3H), 6.24 (dd, $J = 5.5$ and 3 Hz , 1H), 6.36 (dd, $J = 5.5$ and 3 Hz , 1H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 46.1, 46.6, 48.0, 48.2, 48.8, 51.5, 134.3, 135.6, 172.9, 178.2.

Cyclohex-4-ene-1,2-dicarboxylic acid monomethyl ester (14, entry 1)



The desired monomethyl ester was obtained following the general procedure in 99% yield and as a clear oil after purification by flash chromatography.

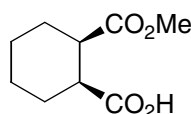
93% *ee* $[\alpha]_D^{20} = -4.9$ (c 1.50, CHCl_3) as determined by $^1\text{H-NMR}$ and confirmed by CSP-HPLC analysis of the corresponding amide-ester diastereoisomeric mixture prepared as in Scheme 1.

Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA: 93/7, 0.50 mL min⁻¹, RT, UV detection at 220 nm, retention times: 34.4 min (minor diastereomer) and 40.4 (major diastereomer).

The NMR spectra were consistent with those previously reported and the absolute configuration was established by comparing the optical rotation of the hemiester with the literature data.⁵

¹H NMR (CDCl₃) δ 2.34-2.45 (m, 2H), 2.55-2.65 (m, 2H), 3.05-3.13 (m, 2H), 3.72 (s, 3H), 5.70 (m, 2H). ¹³C NMR (CDCl₃) δ 25.1, 25.3, 39.0, 39.1, 51.5, 124.6, 124.7, 173.2, 179.0.

Cyclohexane-1,2-dicarboxylic acid monomethyl ester (15 entry 2)



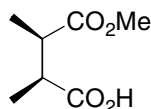
The desired monomethyl ester was obtained following the general procedure in 98% yield and as a clear oil after purification by flash chromatography.

93% *ee* [α]_D²⁰ = +3.5 (c 1.43, CHCl₃) as determined by ¹H-NMR of the corresponding amide-ester diastereoisomeric mixture prepared as in Scheme 1.

The NMR spectra were consistent with those previously reported and the absolute configuration was established by comparing the optical rotation of the hemiester with the literature data.⁶

¹H NMR (CDCl₃) δ 1.38-1.62 (m, 4H), 1.74-1.84 (m, 2H), 1.97-2.10 (m, 2H), 2.80-2.92 (m, 2H), 3.69 (s, 3H). ¹³C NMR (CDCl₃) δ 23.2, 23.3, 25.5, 25.8, 41.9, 42.1, 51.3, 173.7, 179.5.

2,3-Dimethyl-succinic acid monomethyl ester (16, entry 4)



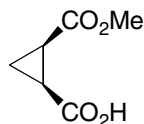
The desired monomethyl ester was obtained following the general procedure in 98% yield and as a white solid after purification by flash chromatography.

92% *ee* [α]_D²⁰ = -8.9 (c 1.12, EtOH) as determined by ¹H-NMR analysis of the corresponding amide-ester diastereoisomeric mixture prepared as in Scheme 1.

The NMR spectra were consistent with those previously reported and the absolute configuration was established by comparing the optical rotation of the hemiester with the literature data.⁶

¹H NMR (CDCl₃) δ 1.20-1.30 (m, 6H), 2.76-2.90 (m, 2H), 3.73 (s, 3H). ¹³C NMR (CDCl₃) δ 14.6, 14.8, 42.1, 42.3, 51.9, 175.0, 180.2.

Cyclopropane-1,2-dicarboxylic acid monomethyl ester (17, entry 5)



The desired monomethyl ester was obtained following the general procedure in 95% yield and as a clear oil after purification by flash chromatography.

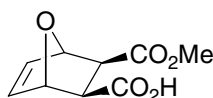
85% *ee* [α]_D²⁰ = -10.0 (c 1.71, CHCl₃) as determined by ¹H-NMR analysis of the corresponding amide-ester diastereoisomeric mixture prepared as in Scheme 1.

Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.50 mL min⁻¹, RT, UV detection at 220 nm, retention times: 70.3 min (minor diastereomer) and 81.8 (major diastereomer).

The NMR spectra were consistent with those previously reported and the absolute configuration was established by comparing the optical rotation of the hemiester with the literature data.⁵

¹H NMR (CDCl₃) δ 1.31-1.36 (m, 1H), 1.67-1.72 (m, 1H), 2.06-2.19 (m, 1H), 3.72 (s, 3H). ¹³C NMR (CDCl₃) δ 12.0, 20.8, 21.8, 52.0, 170.2, 174.6.

7-Oxa-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid monomethyl ester (18, entry 6).



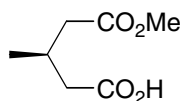
The desired monomethyl ester was obtained following the general procedure in 90% yield and as a white solid after purification by flash chromatography.

85% *ee* [α]_D²⁰ +8.7 (c 1.08, MeOH) as determined by ¹H-NMR analysis of the corresponding amide-ester diastereoisomeric mixture prepared as in Scheme 1.

The NMR spectra were consistent with those previously reported and the absolute configuration was established by comparing the optical rotation of the hemiester with the literature data.⁵

¹H NMR (CDCl₃) δ 2.85-2.88 (m, 2H), 3.72 (s, 3H), 5.29 (m, 1H), 5.33 (m, 1H), 6.45-6.50 (m, 2H). ¹³C NMR (CDCl₃) δ 46.4, 46.8, 51.9, 79.9, 80.1, 135.9, 136.3, 171.3, 176.8.

3-Methyl-pentanedioic acid monomethyl ester (19, entry 7-8).



The desired monomethyl ester was obtained following the general procedure in 98% yield and as a clear oil after purification by flash chromatography.

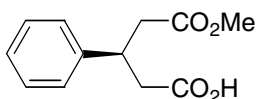
83% *ee* [α]_D²⁰ = +1.1 (c 1.36 CHCl₃) as determined by ¹H-NMR analysis of the corresponding amide-ester diastereoisomeric mixture prepared as in Scheme 1.

The hemiester could be obtained in 90% *ee* following the low temperature procedure.

The NMR spectra were consistent with those previously reported and the absolute configuration was established by comparing the optical rotation of the hemiester with the literature data.⁷

¹H NMR (CDCl₃) δ 1.06 (d, 3H, 6.0 Hz), 2.24-2.35 (m, 2H), 2.39-2.53 (m, 3H), 3.69 (s, 3H). ¹³C NMR (CDCl₃) δ 19.4, 26.7, 40.0, 40.1, 51.1, 172.4, 177.8.

3-Phenyl-pentanedioic acid monomethyl ester (20, entry 9-10)



The desired monomethyl ester was obtained following the general procedure in 98% yield and as a white solid after purification by flash chromatography.

83% *ee* [α]_D²⁰ = +8.1 (c 1.62 CHCl₃) as determined by ¹H-NMR analysis and confirmed by CSP-HPLC analysis of the corresponding amide-ester diastereoisomeric mixture prepared as in Scheme 1.

The hemiester could be obtained in 89% *ee* following the low temperature procedure.

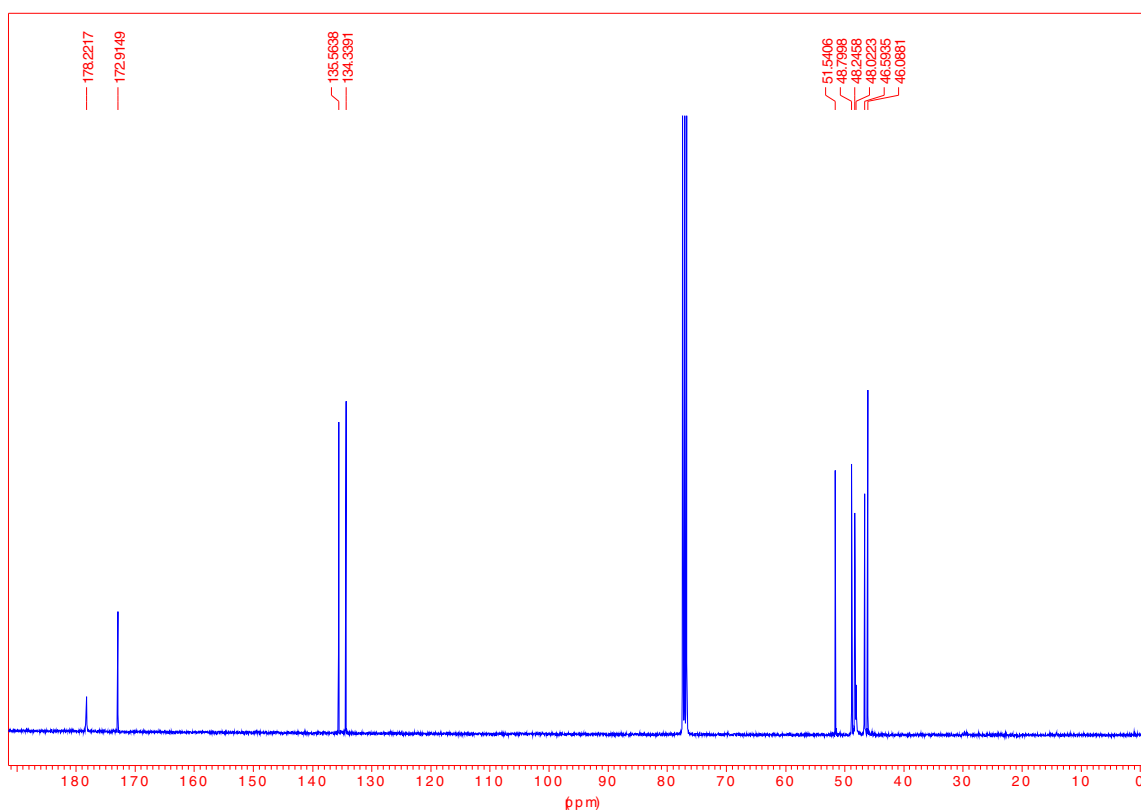
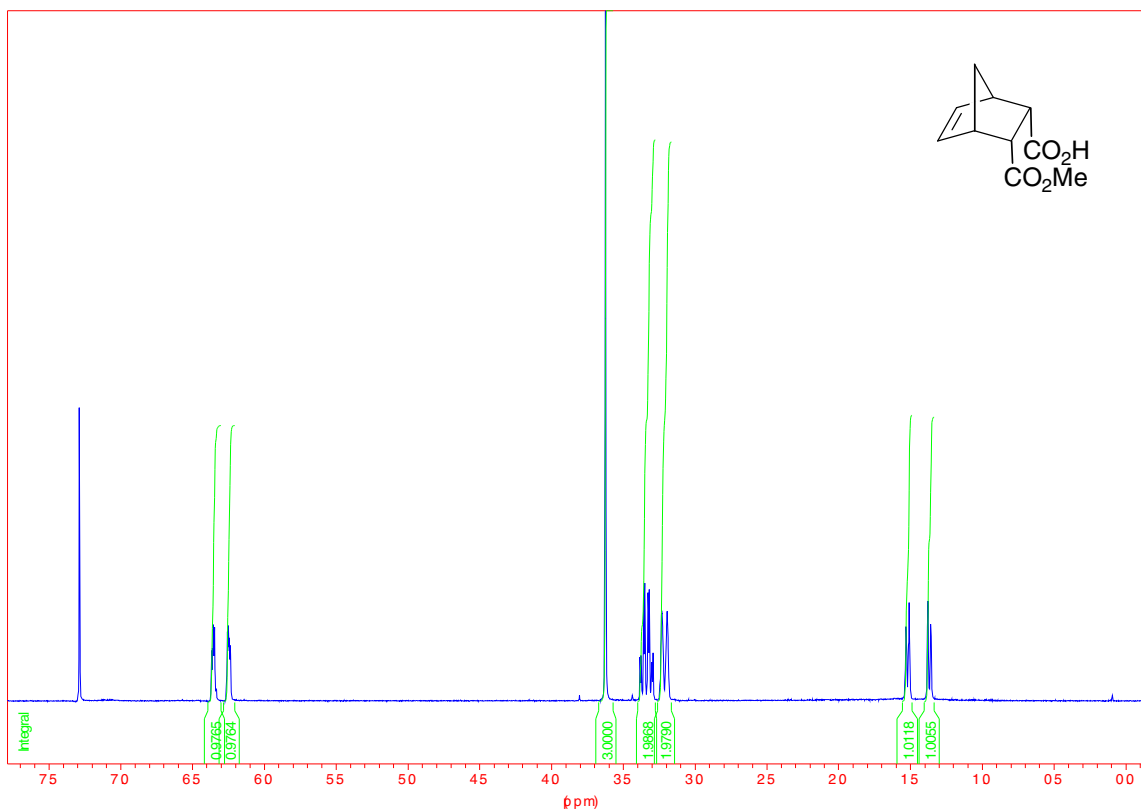
Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 23.0 min (minor diastereomer) and 35.3 (major diastereomer).

The NMR spectra were consistent with those previously reported and the absolute configuration was not determined.²

¹H NMR (CDCl₃) δ 2.65-2.85 (m, 4H), 3.55-3.70 (m, 4H), 7.20-7.35 (m, 5H). ¹³C NMR (CDCl₃) δ 37.4, 39.7, 40.0, 51.2, 126.6, 126.7, 128.2, 141.8, 171.6, 177.3.

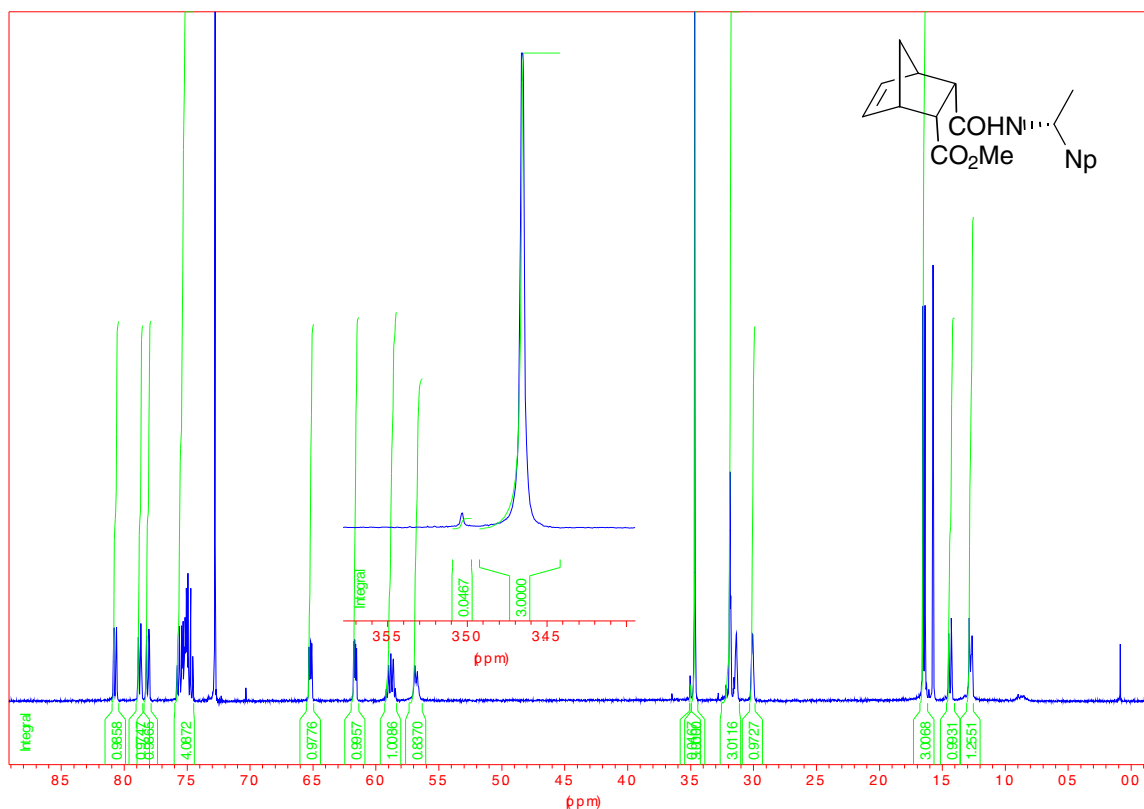
5.0 NMR Spectra

Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid monomethyl ester (2, entry 3)

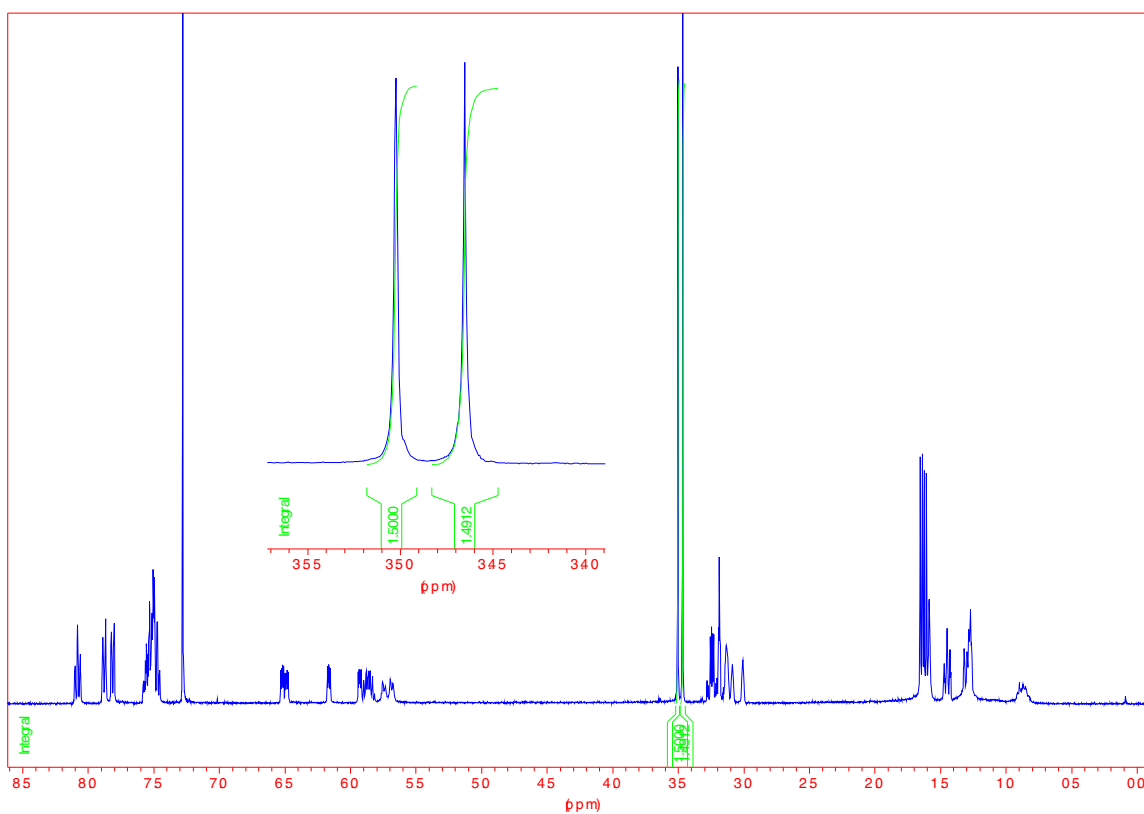


Determination of enantiomeric excess by NMR (Table 2, entry 3, 96% ee)

¹H-NMR of the diastereoisomeric mixture from hemiester product of the catalysis (CDCl₃)



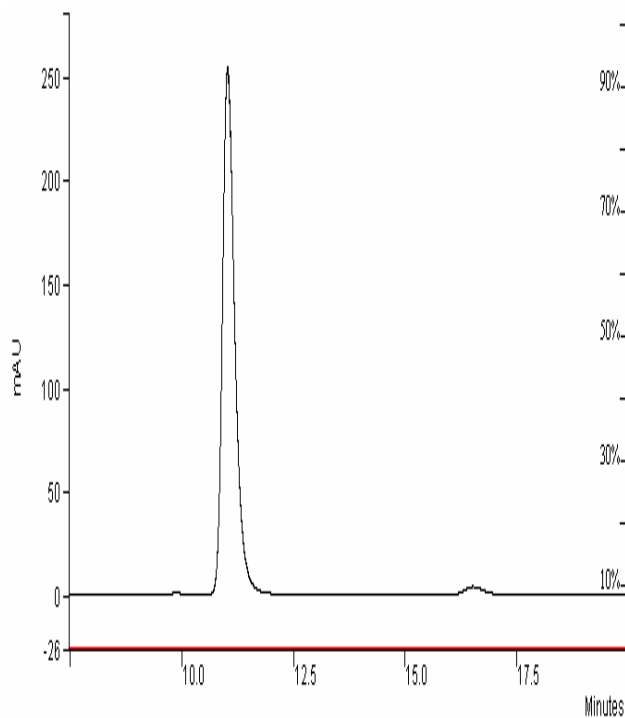
¹H-NMR of the diastereoisomeric mixture from racemic hemiester (CDCl₃)



CSP-HPLC profile of the diastereoisomeric mixture from the hemiester product of the catalysis

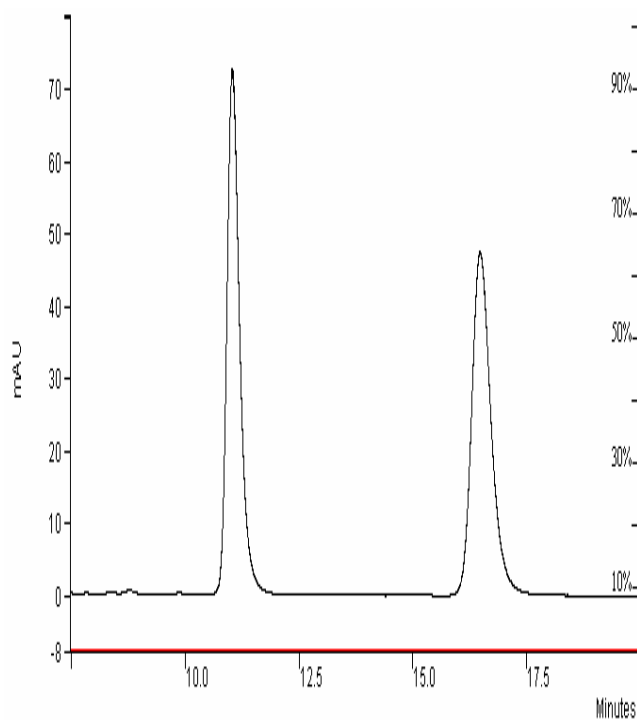
Chiralpak AD-H (4.6 mm x 25 cm),
Hexane/IPA: 90/10, 0.75 mL min⁻¹,
RT, UV detection at 220 nm

Time (min)	Area mAU*sec	Result %
11.027	4904	95.051
16.469	123	2.390

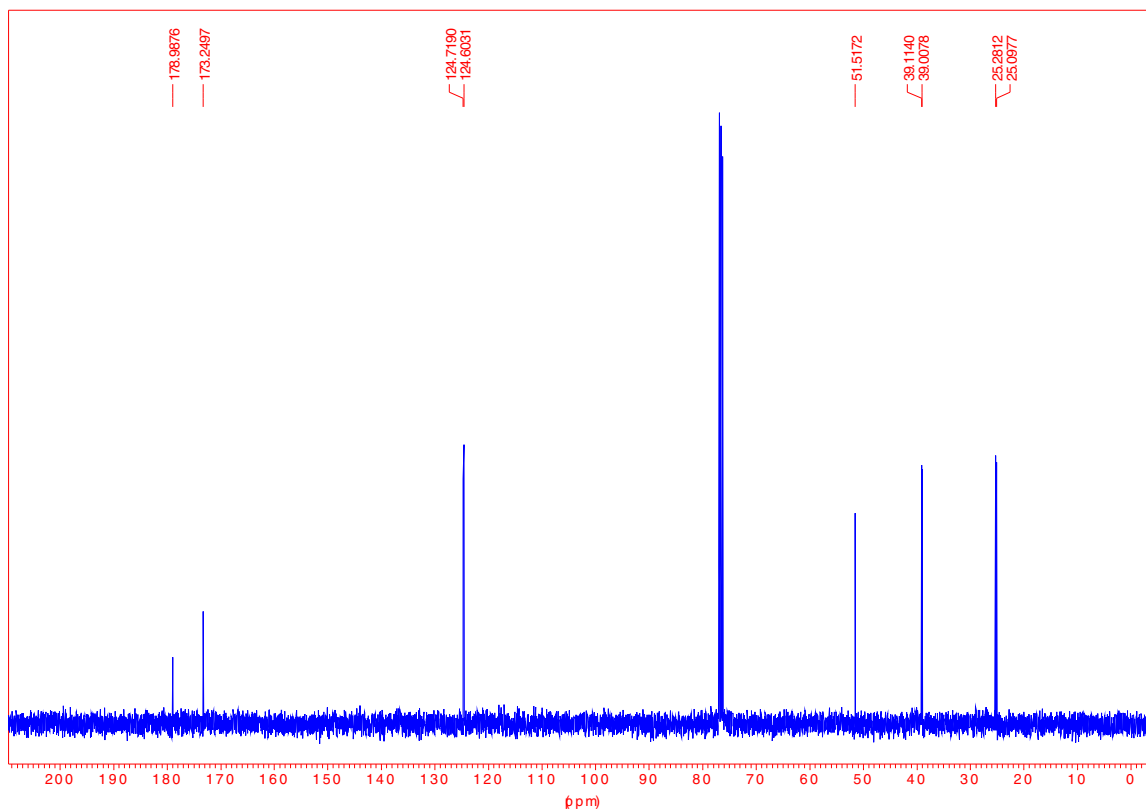
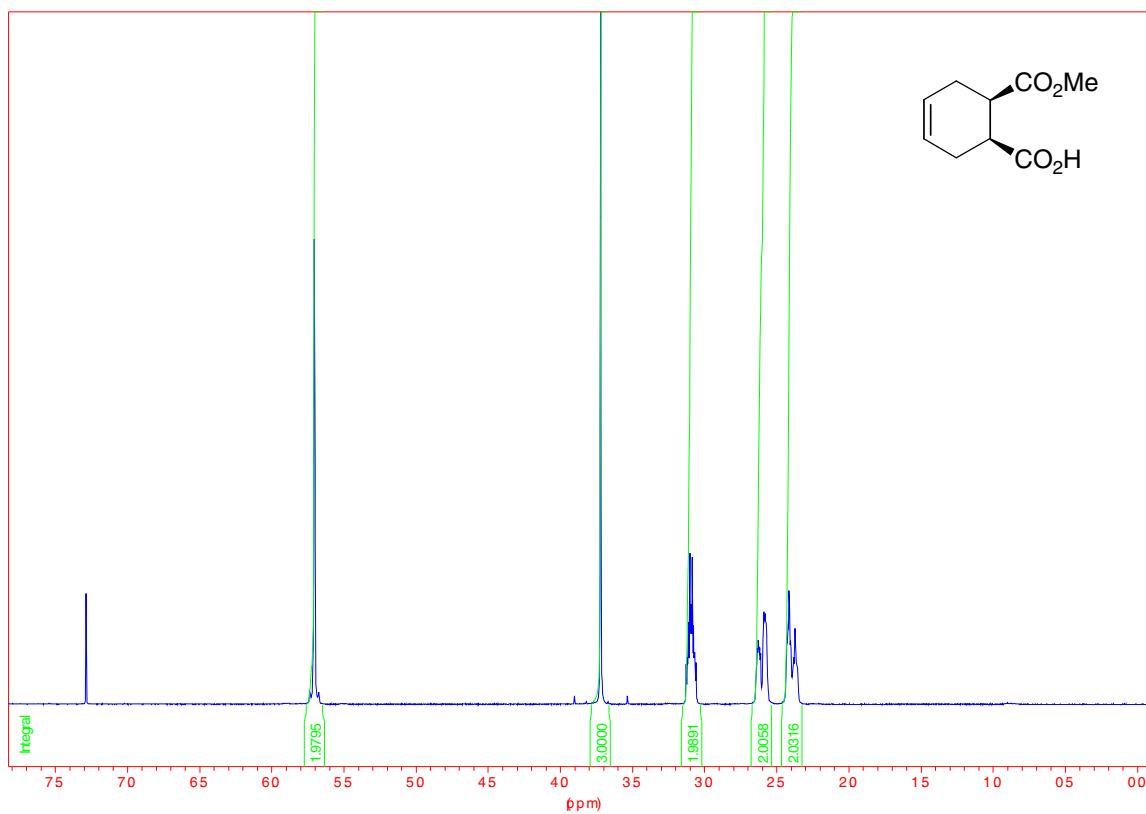


CSP-HPLC profile of the diastereoisomeric mixture from the corresponding racemic hemiester

Time (min)	Area mAU*sec	Result %
11.027	1437	48.033
16.469	1415	47.815

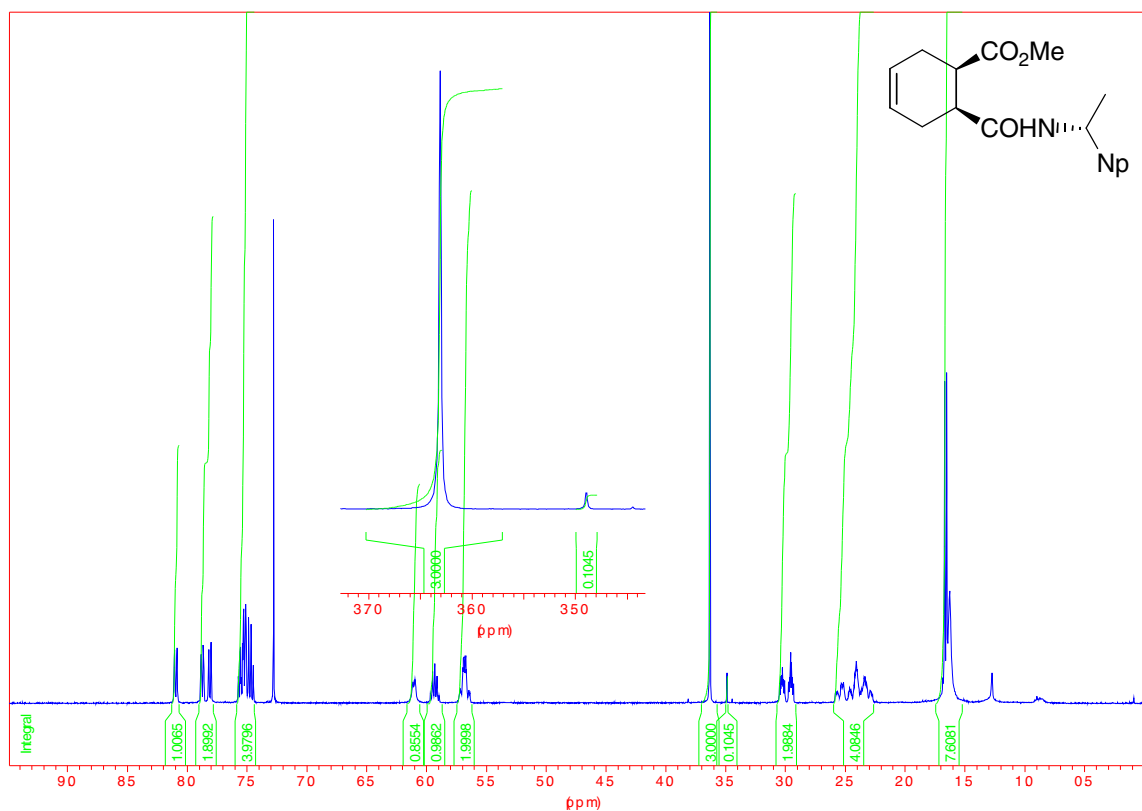


Cyclohex-4-ene-1,2-dicarboxylic acid monomethyl ester (14, entry 1)

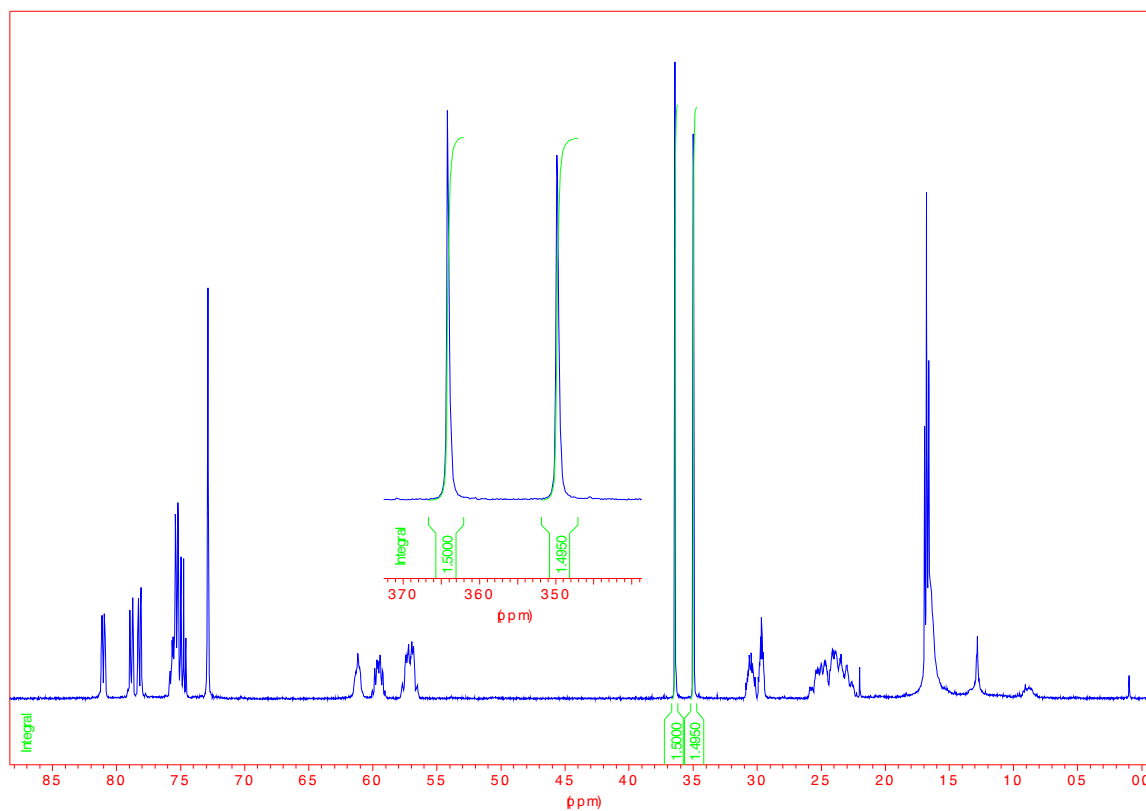


Determination of enantiomeric excess by NMR (Table 2, entry 1, 93% ee)

¹H-NMR of the diastereoisomeric mixture from hemiester product of the catalysis (CDCl₃)



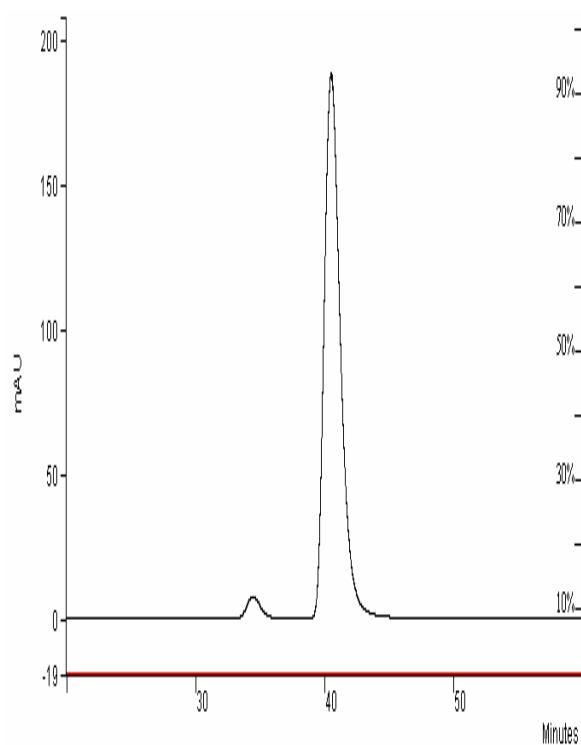
¹H-NMR of the diastereoisomeric mixture from racemic hemiester (CDCl₃)



CSP-HPLC profile of the diastereoisomeric mixture from the hemiester product of the catalysis

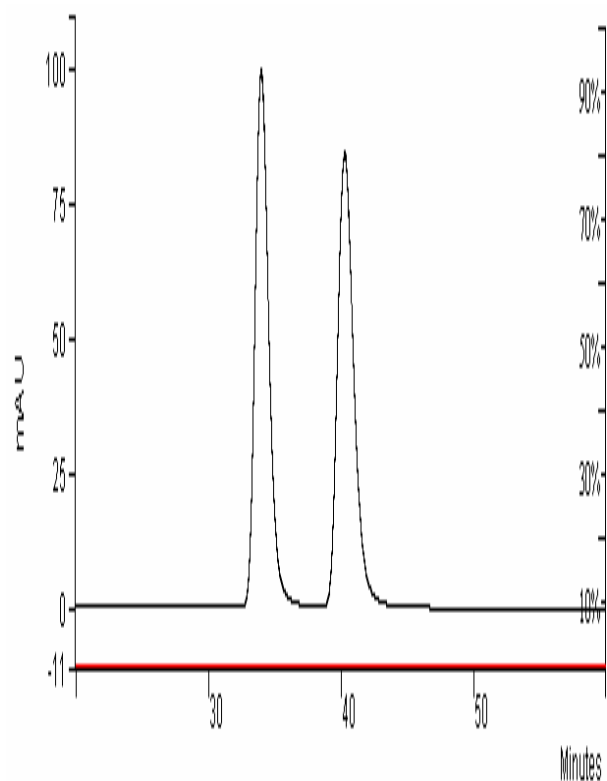
Chiralpak OD-H (4.6 mm x 25 cm),
Hexane/IPA: 93/7, 0.50 mL min⁻¹,
RT, UV detection at 220 nm

Time (min)	Area mAU*sec	Result %
34.414	594	3.378
40.471	16698	95.017

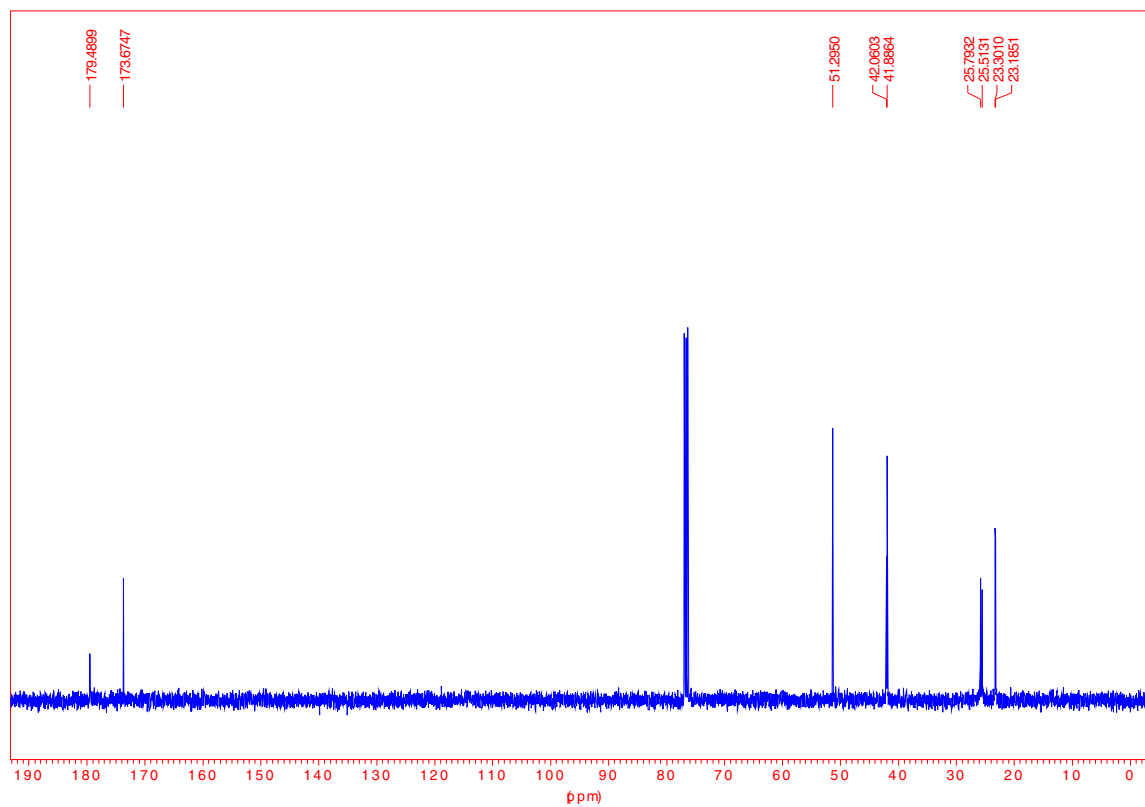
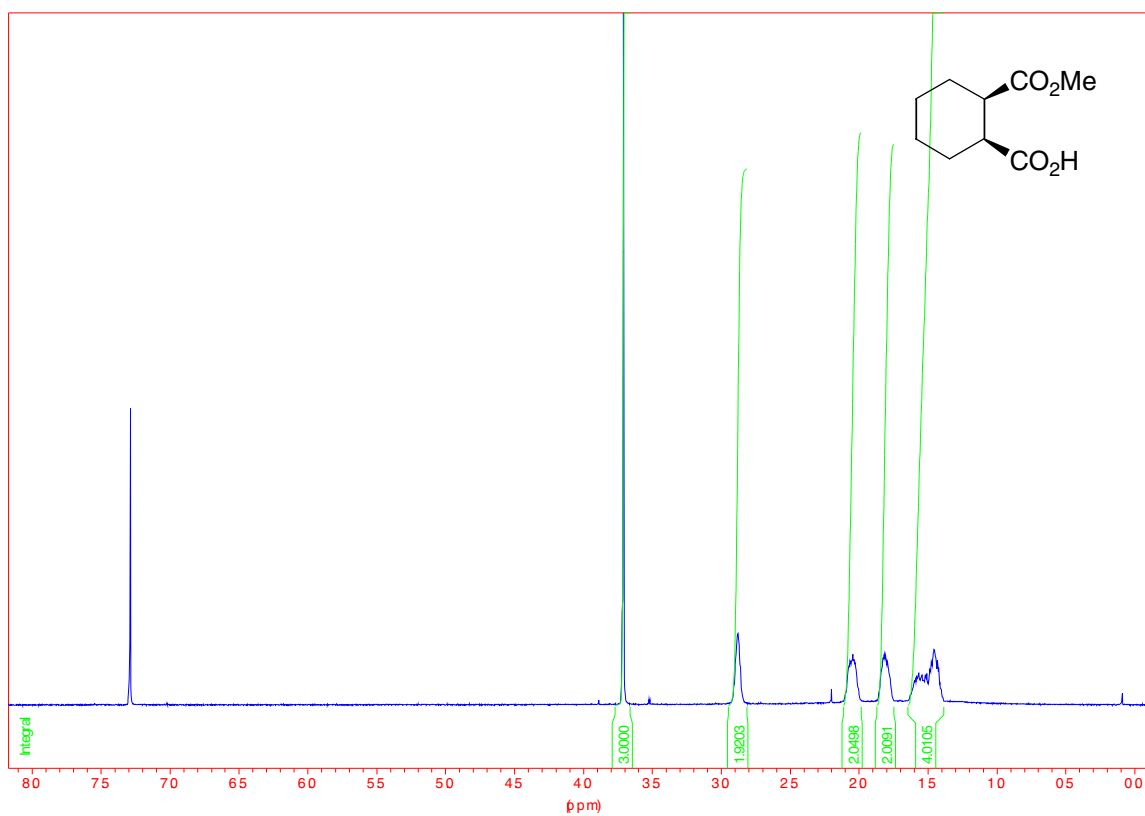


CSP-HPLC profile of the diastereoisomeric mixture from the corresponding racemic hemiester

Time (min)	Area mAU*sec	Result %
33.928	7238	49.331
40.223	7285	49.631

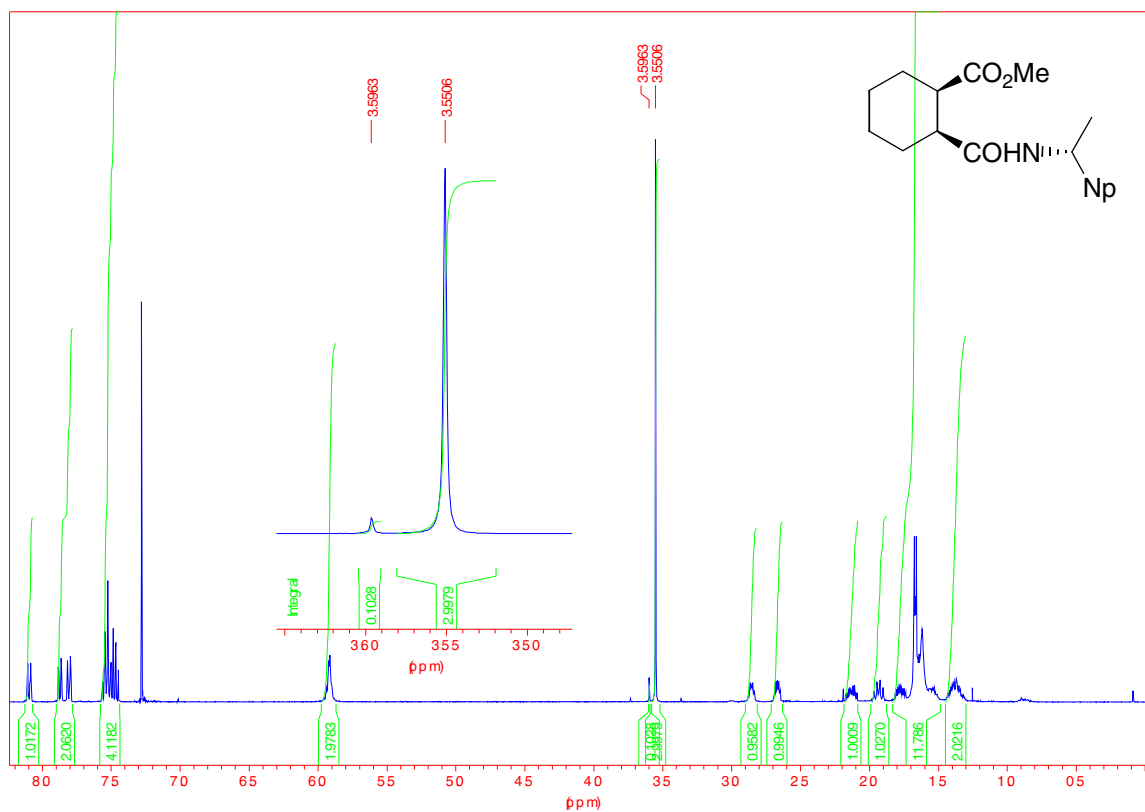


Cyclohexane-1,2-dicarboxylic acid monomethyl ester (15 entry 2)

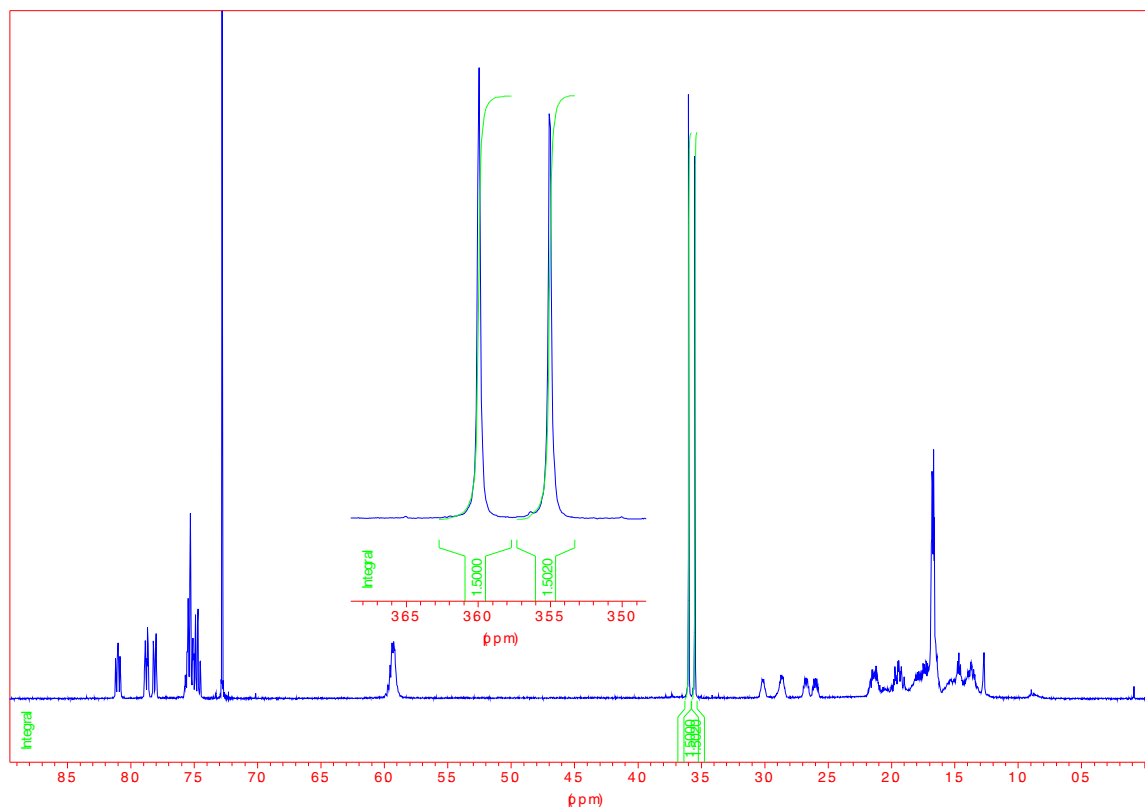


Determination of enantiomeric excess by NMR (Table 2, entry 2, 93% ee)

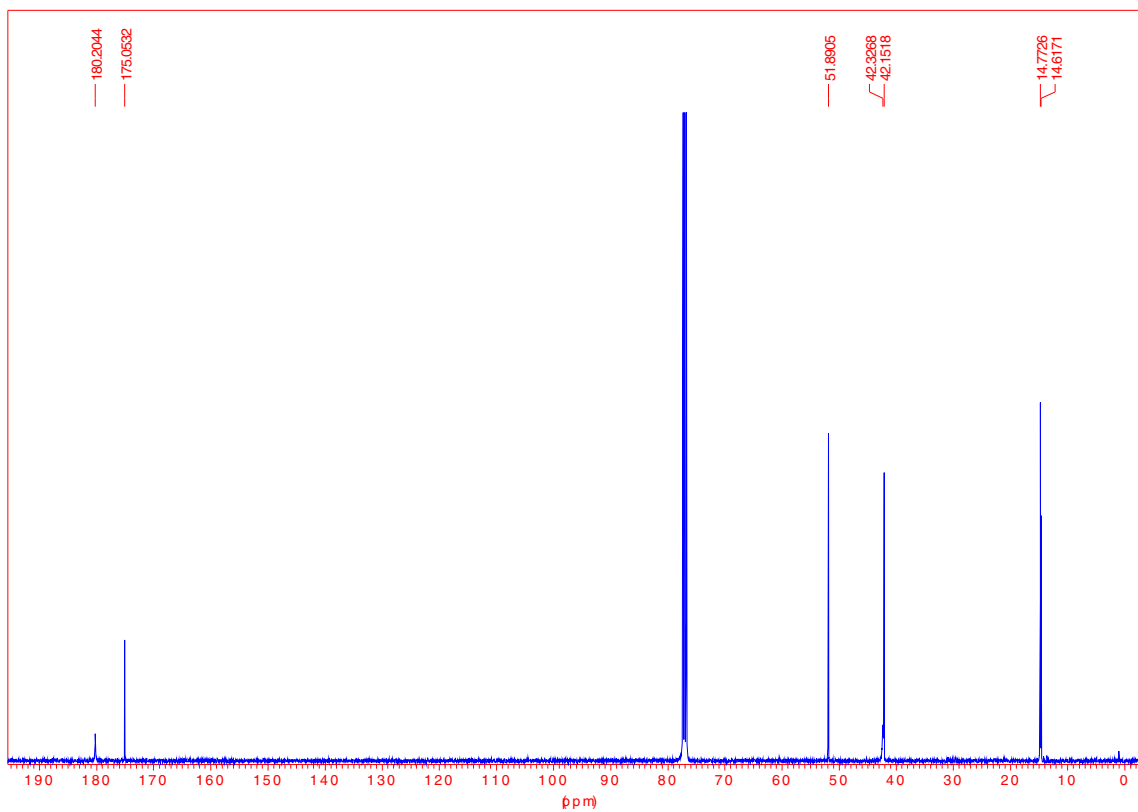
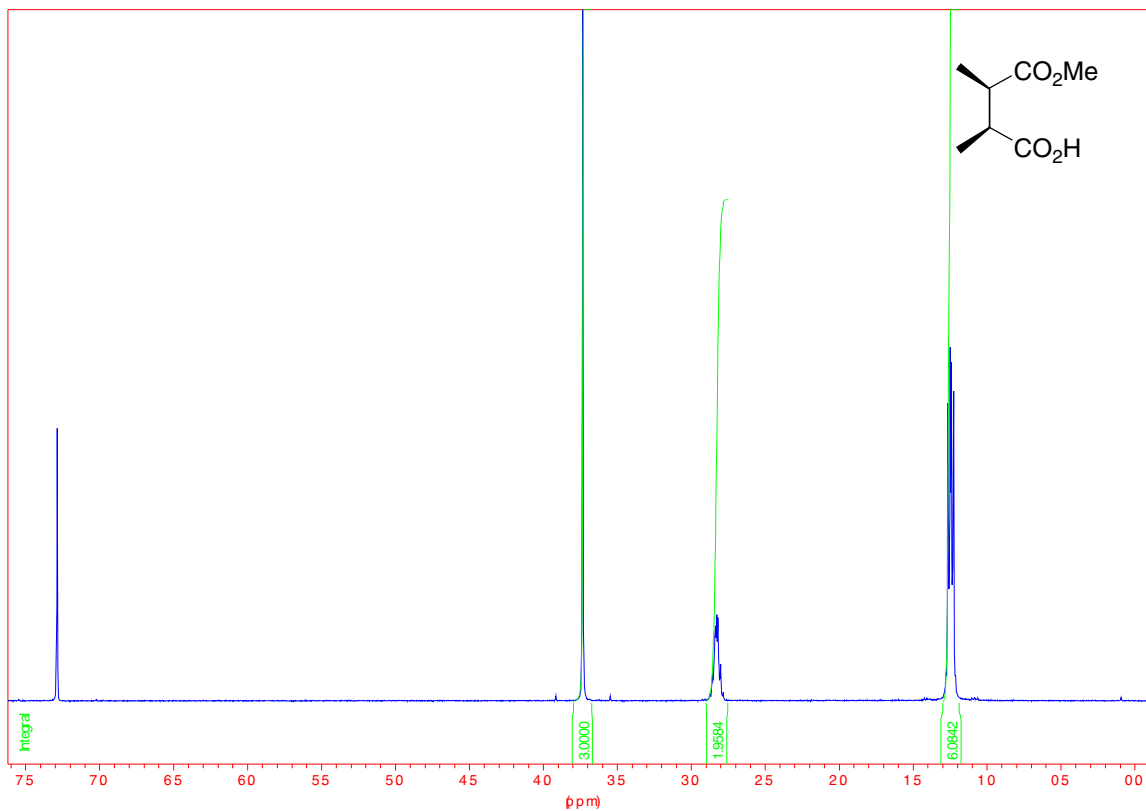
¹H-NMR of the diastereoisomeric mixture from hemiester product of the catalysis (CDCl₃)



¹H-NMR of the diastereoisomeric mixture from racemic hemiester (CDCl₃)



2,3-Dimethyl-succinic acid monomethyl ester (16, entry 4)

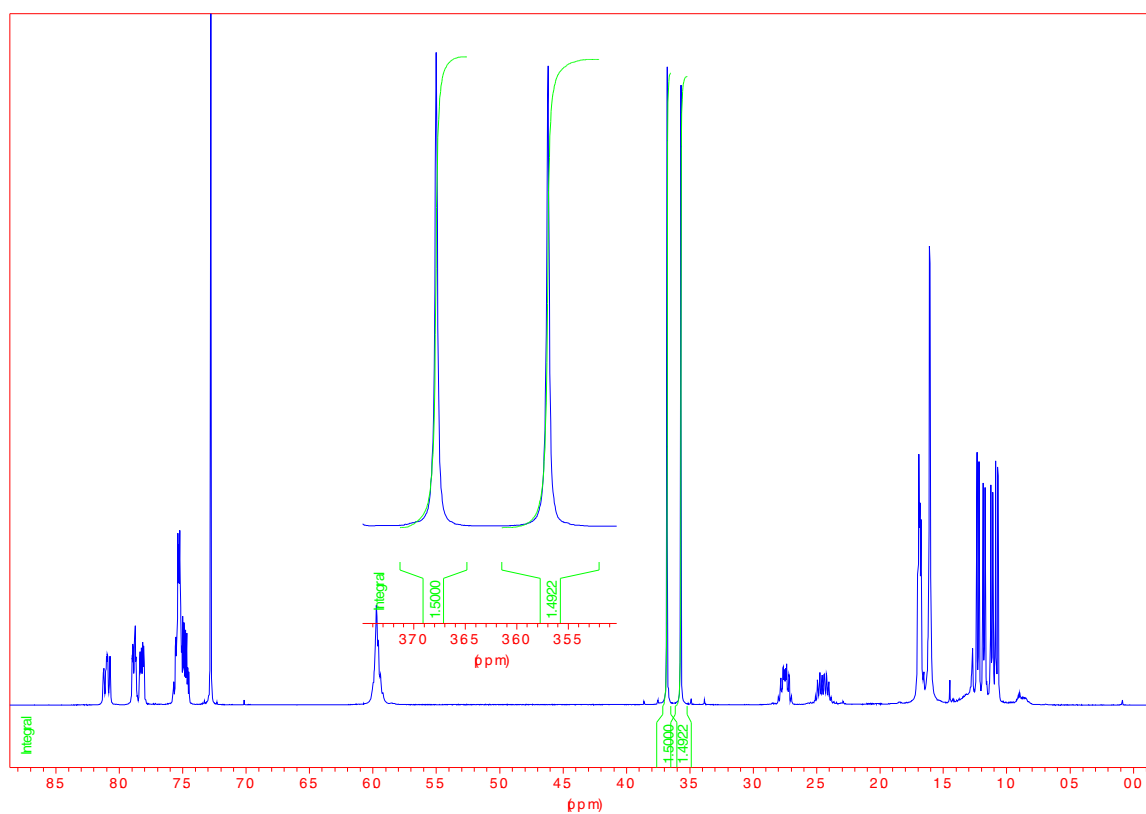


Determination of enantiomeric excess by NMR (Table 2, entry 4, 92% ee)

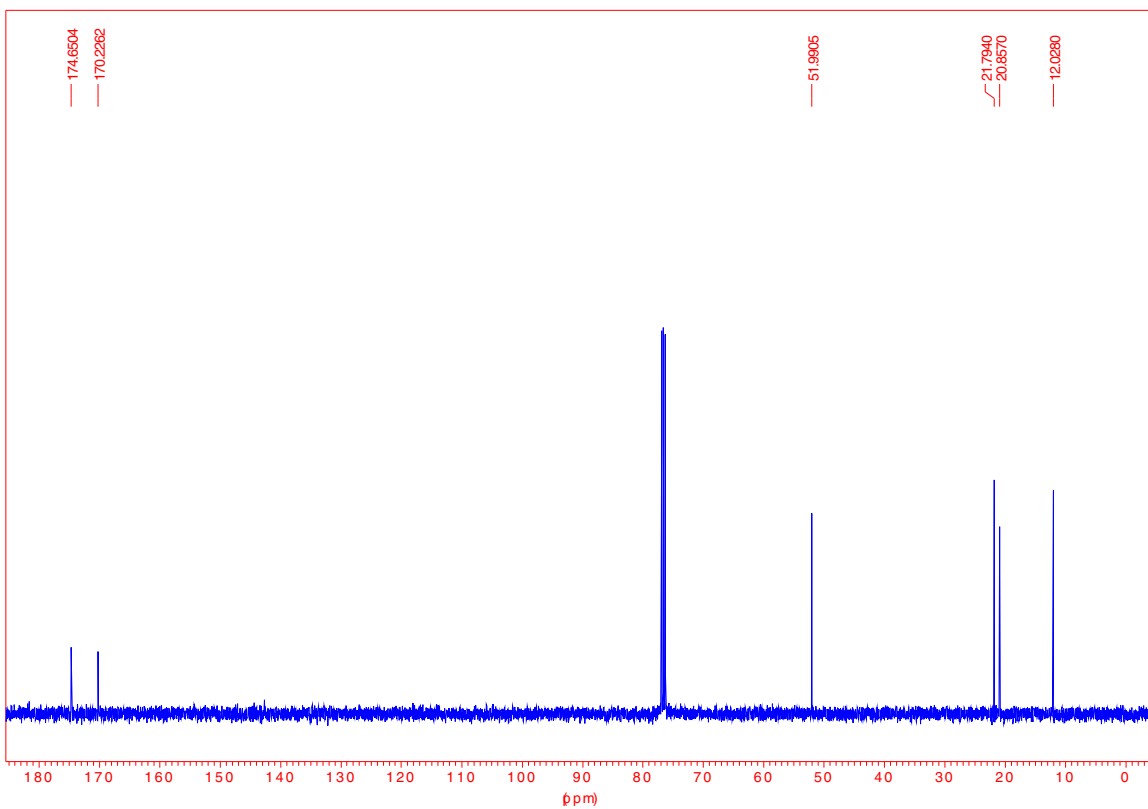
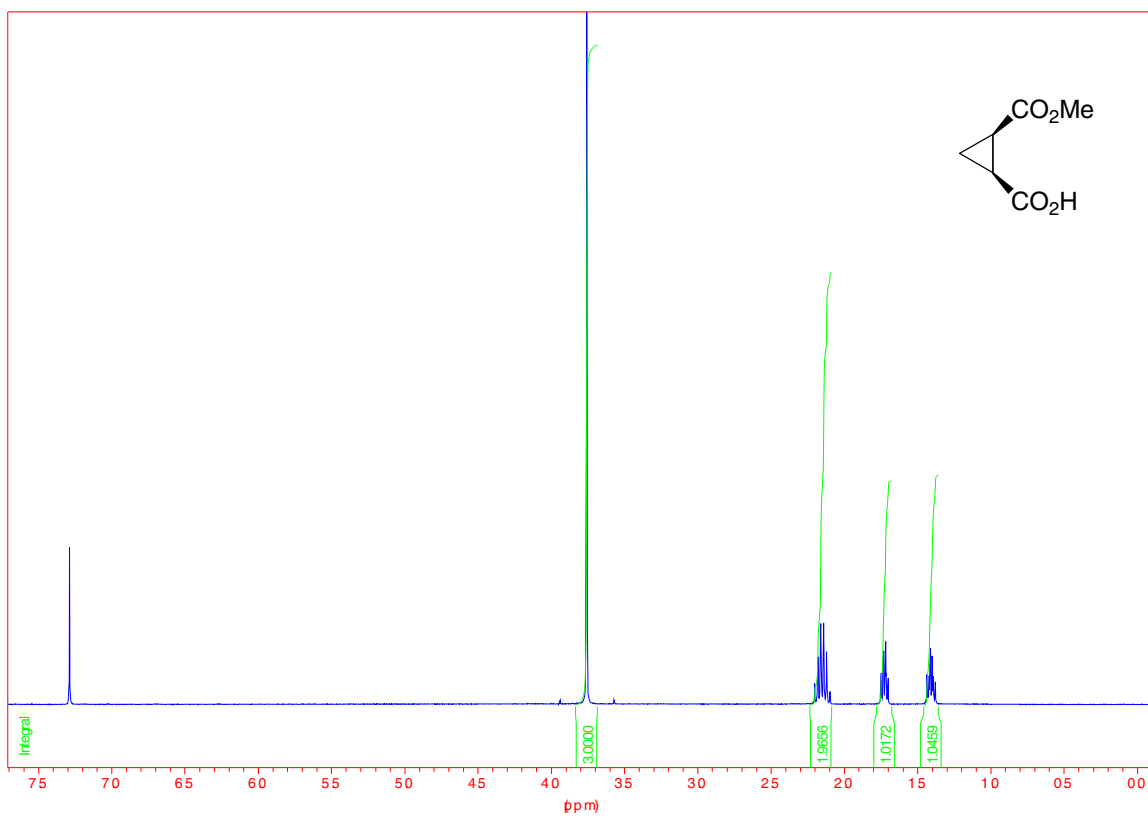
¹H-NMR of the diastereoisomeric mixture from hemiester product of the catalysis (CDCl₃)



¹H-NMR of the diastereoisomeric mixture from racemic hemiester (CDCl₃)

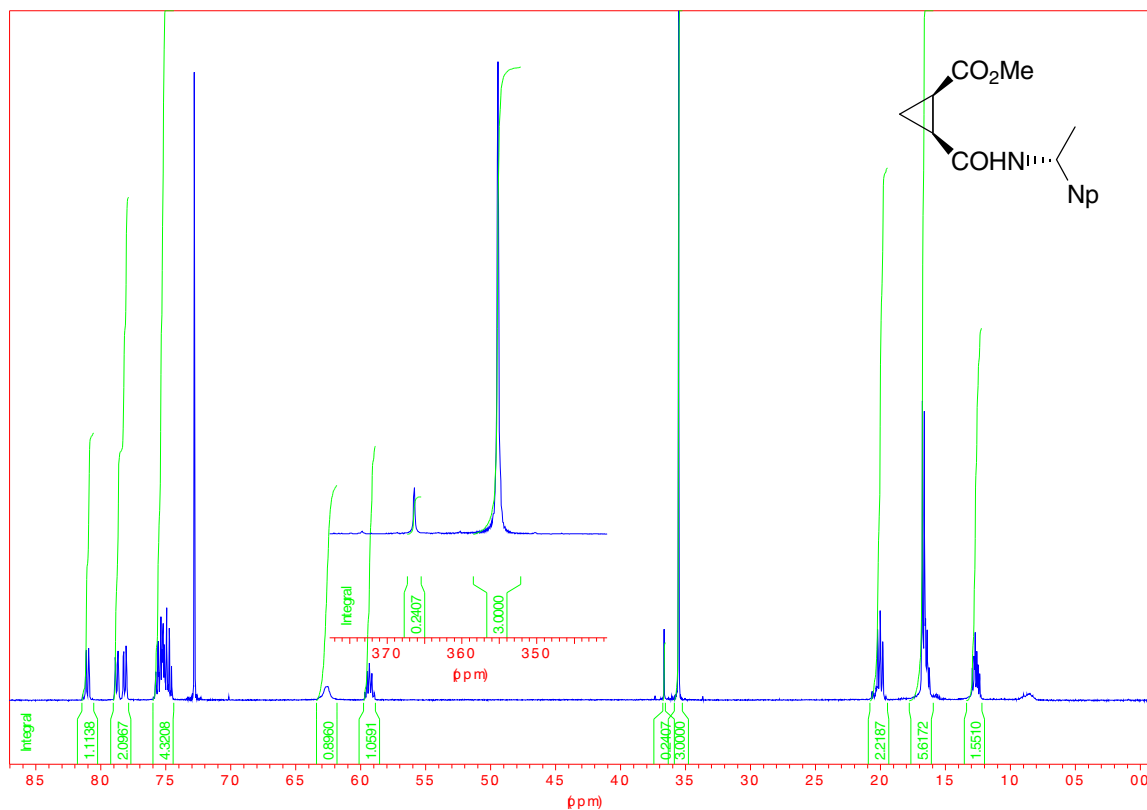


Cyclopropane-1,2-dicarboxylic acid monomethyl ester (17, entry 5)

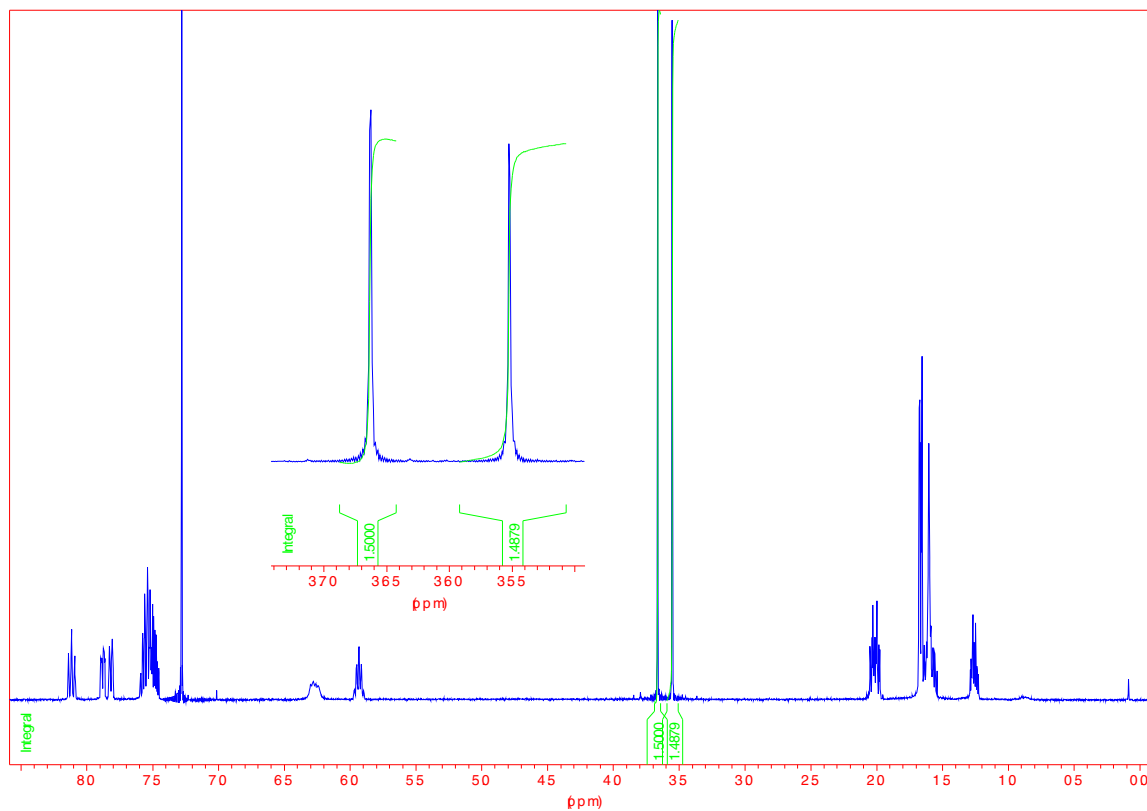


Determination of enantiomeric excess by NMR (Table 2, entry 5, 85% ee)

¹H-NMR of the diastereoisomeric mixture from hemiester product of the catalysis (CDCl₃)



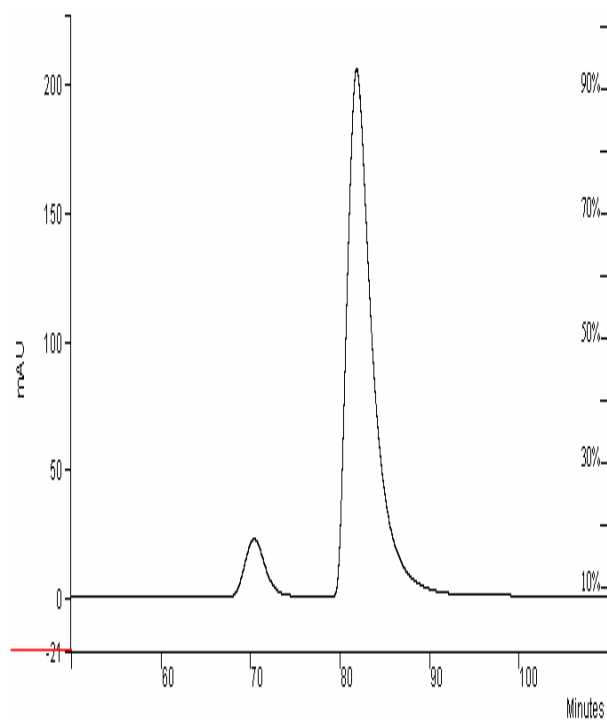
¹H-NMR of the diastereoisomeric mixture from racemic hemiester (CDCl₃)



CSP-HPLC profile of the diastereoisomeric mixture from the hemiester product of the catalysis

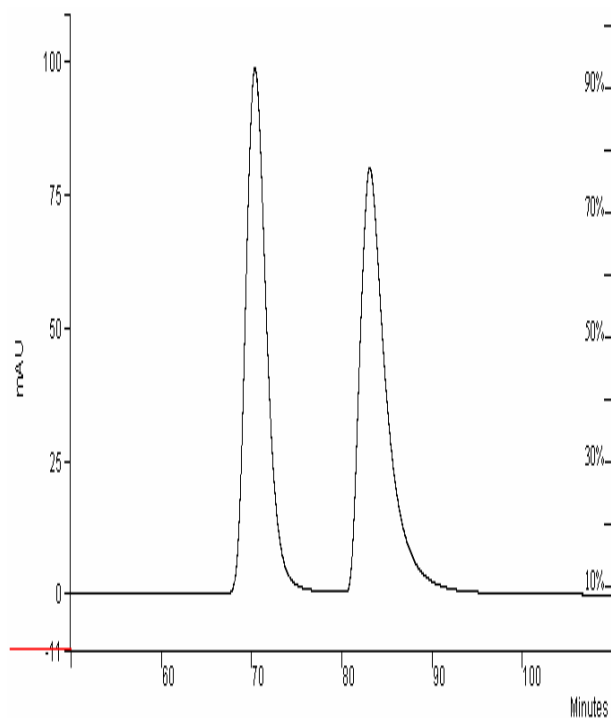
Chiralpak OD-H (4.6 mm x 25 cm),
Hexane/IPA: 95/5, 0.50 mL min⁻¹,
RT, UV detection at 220 nm

Time (min)	Area mAU*sec	Result %
70.346	3553	7.838
81.812	40942	90.318

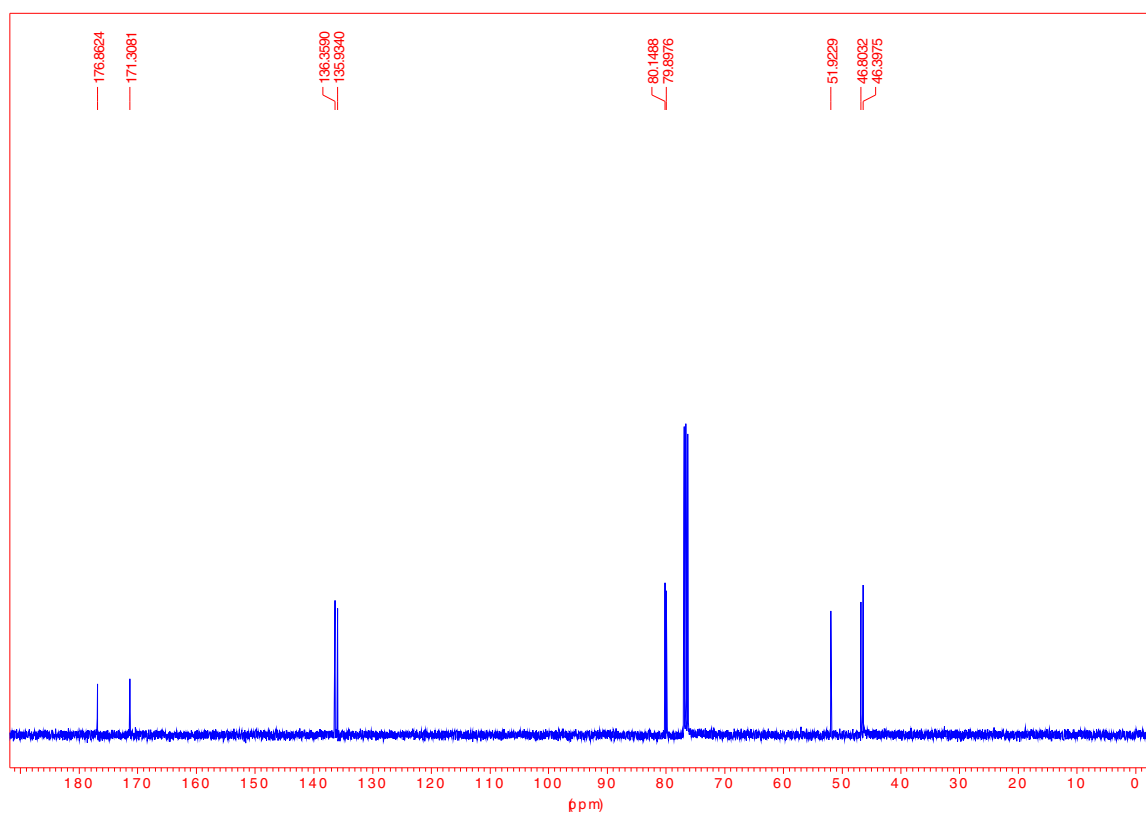
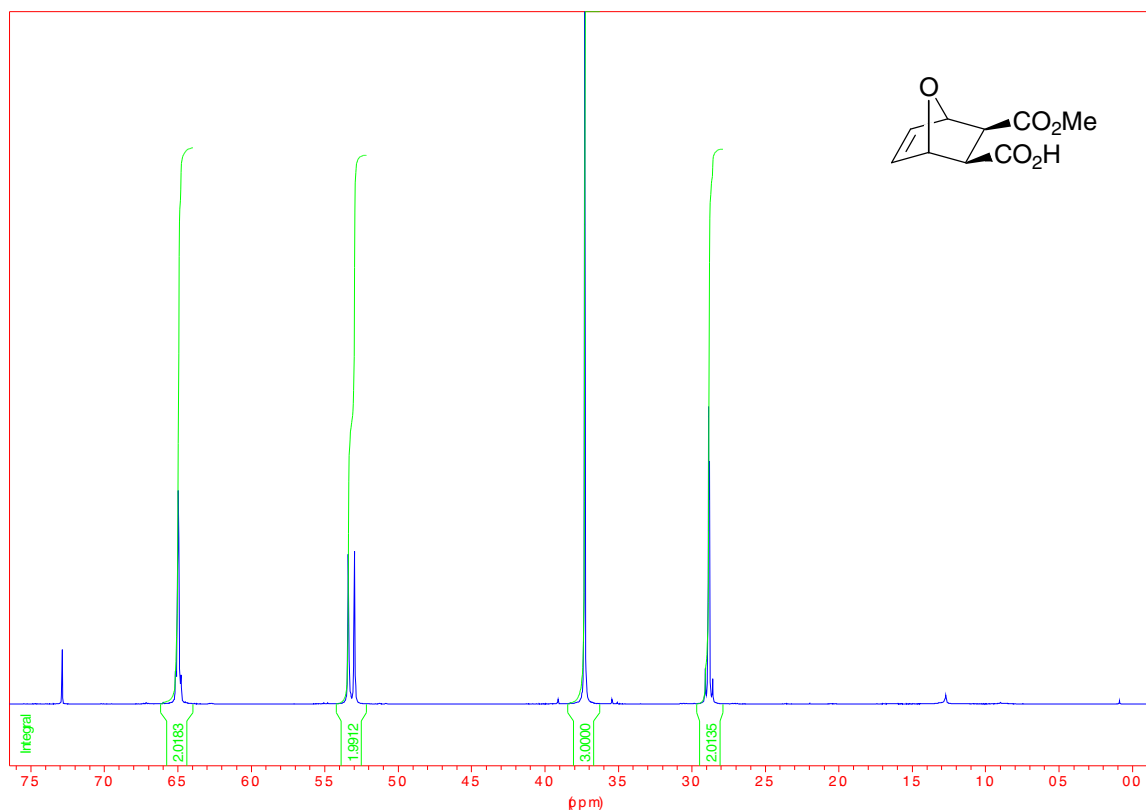


CSP-HPLC profile of the diastereoisomeric mixture from the corresponding racemic hemiester

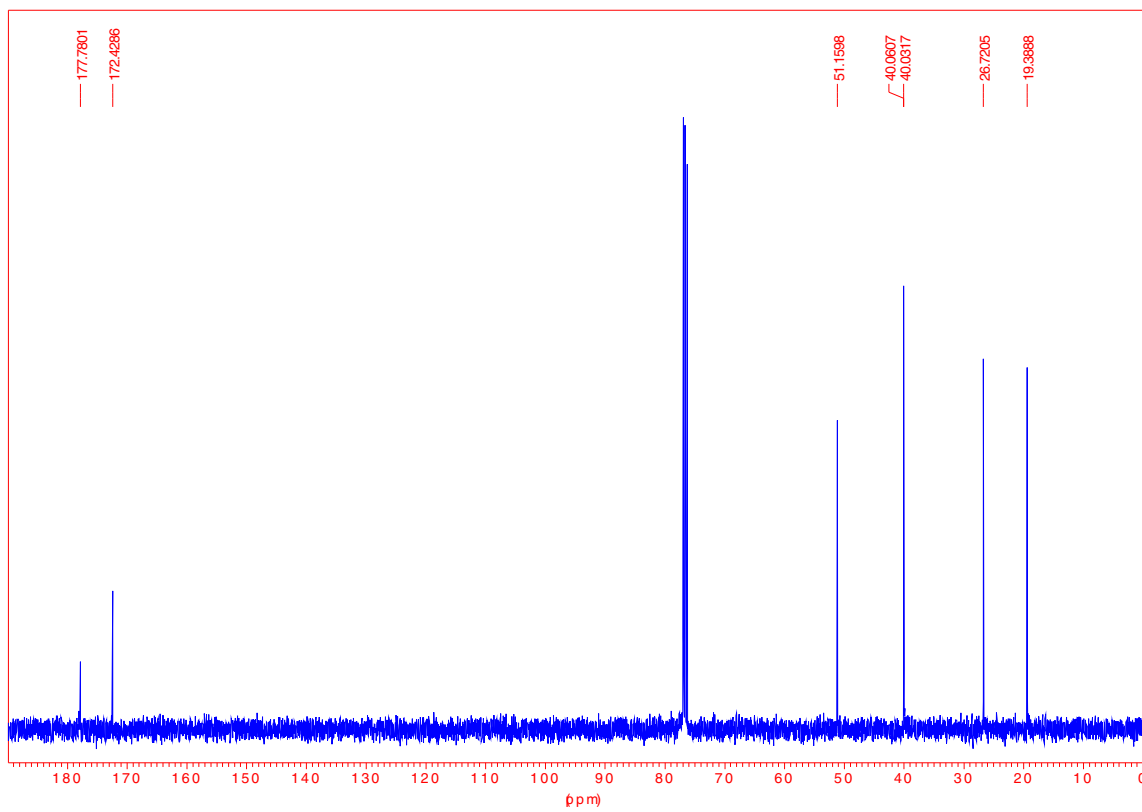
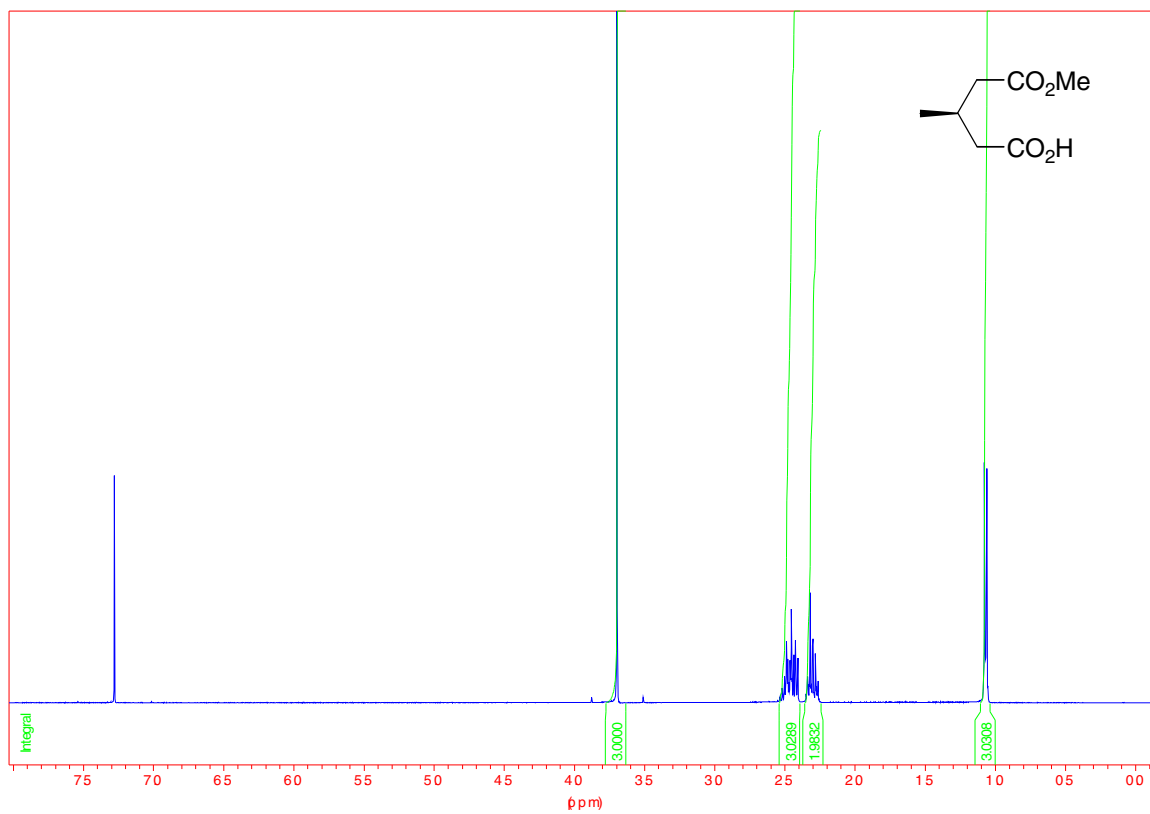
Time (min)	Area mAU*sec	Result %
70.337	15716	48.679
83.056	16282	50.431



7-Oxa-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid monomethyl ester (18, entry 6)

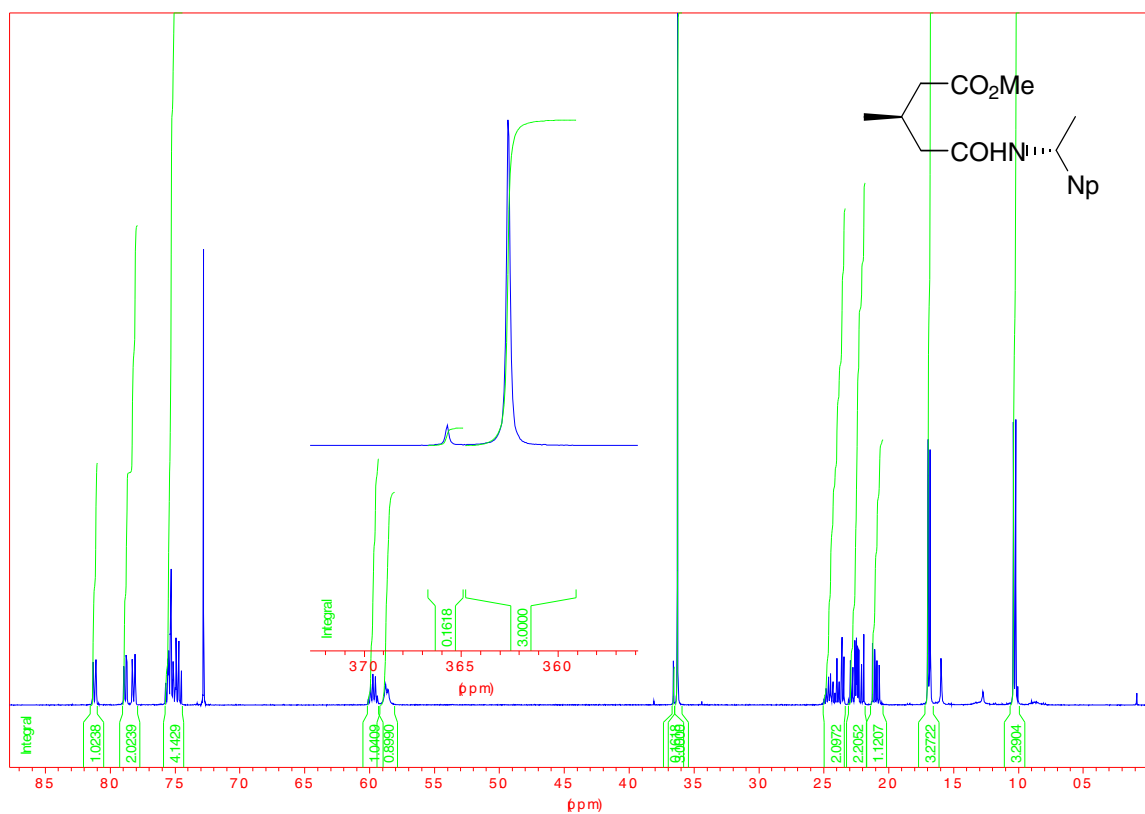


3-Methyl-pentanedioic acid monomethyl ester (19, entry 7-8)

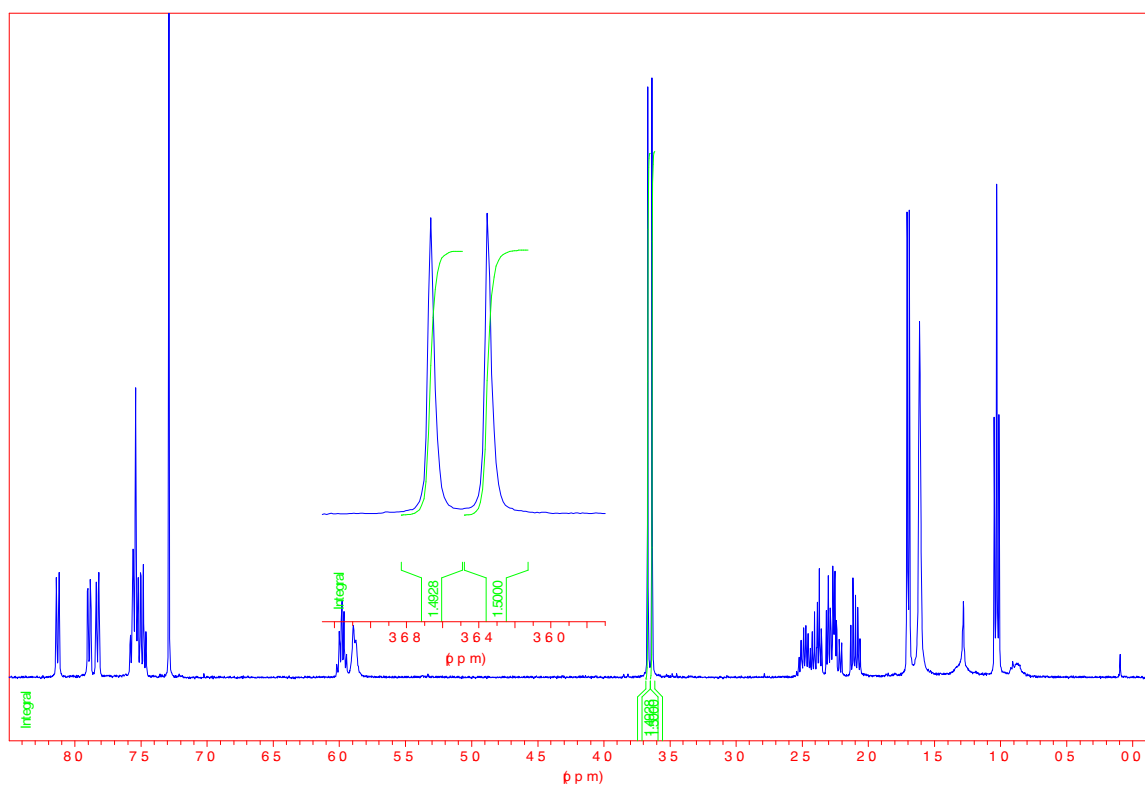


Determination of enantiomeric excess by NMR (Table 2, entry 8, 90% ee)

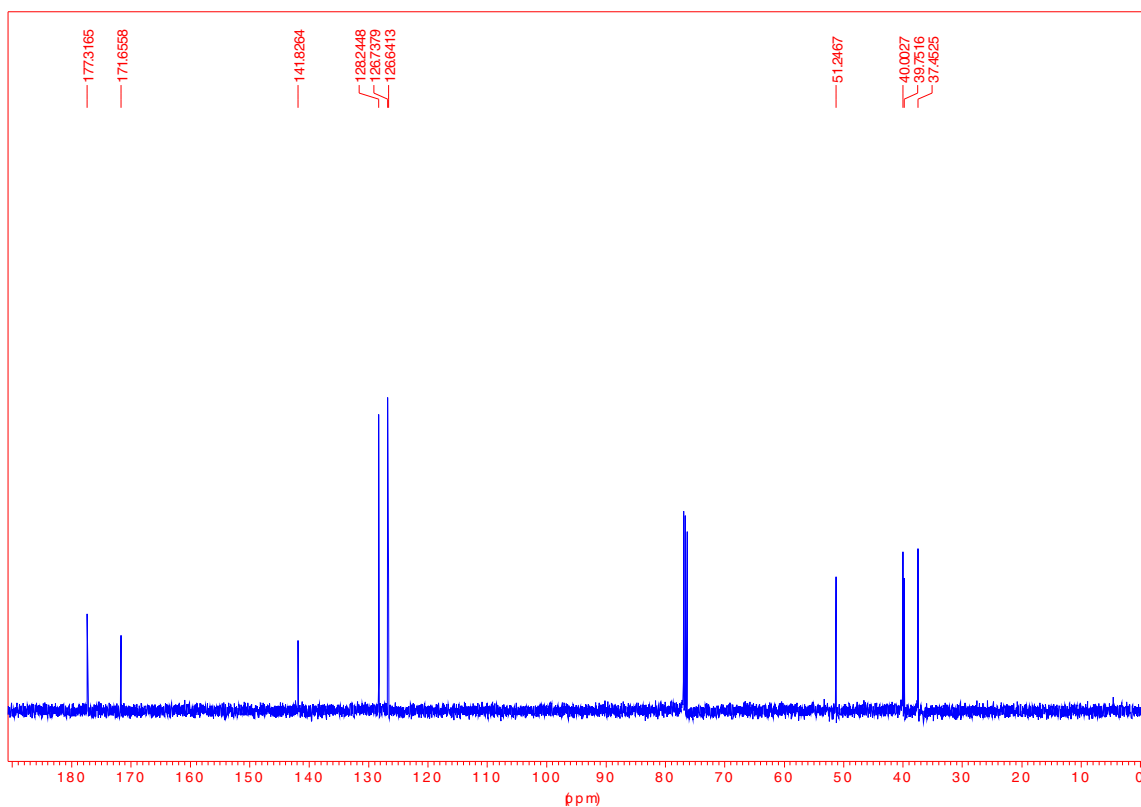
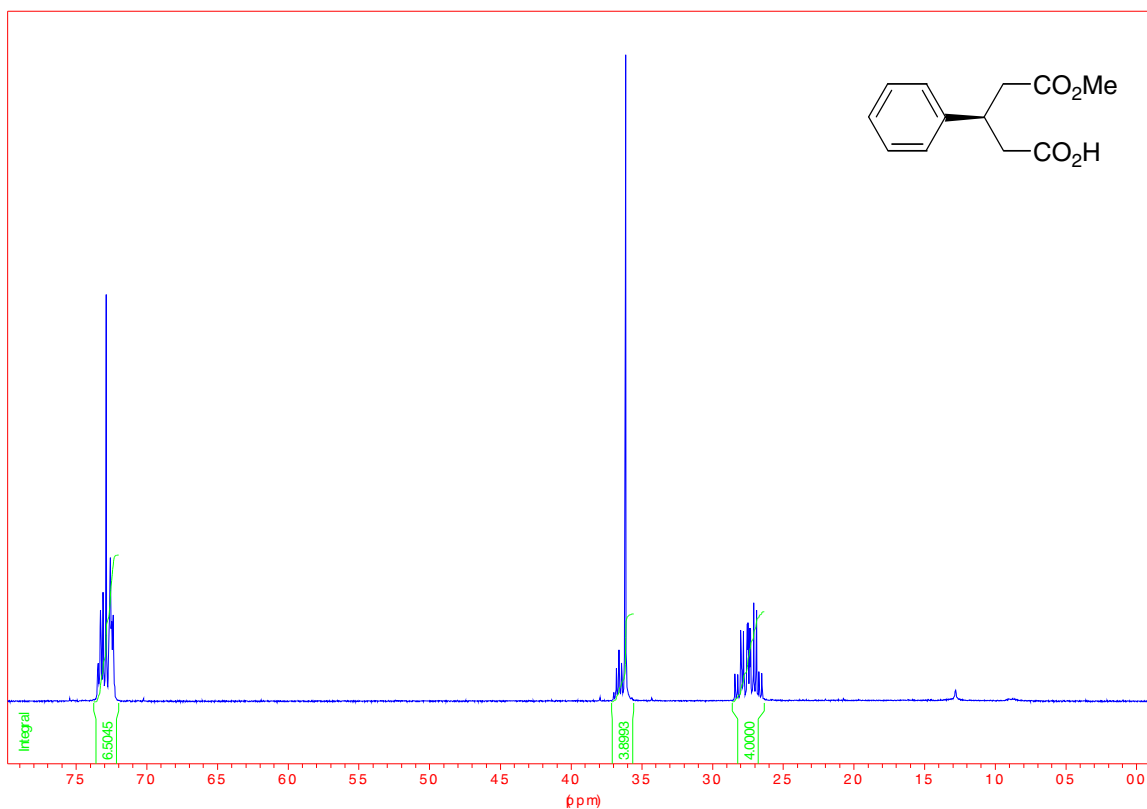
¹H-NMR of the diastereoisomeric mixture from hemiester product of the catalysis (CDCl₃)



¹H-NMR of the diastereoisomeric mixture from racemic hemiester (CDCl₃)

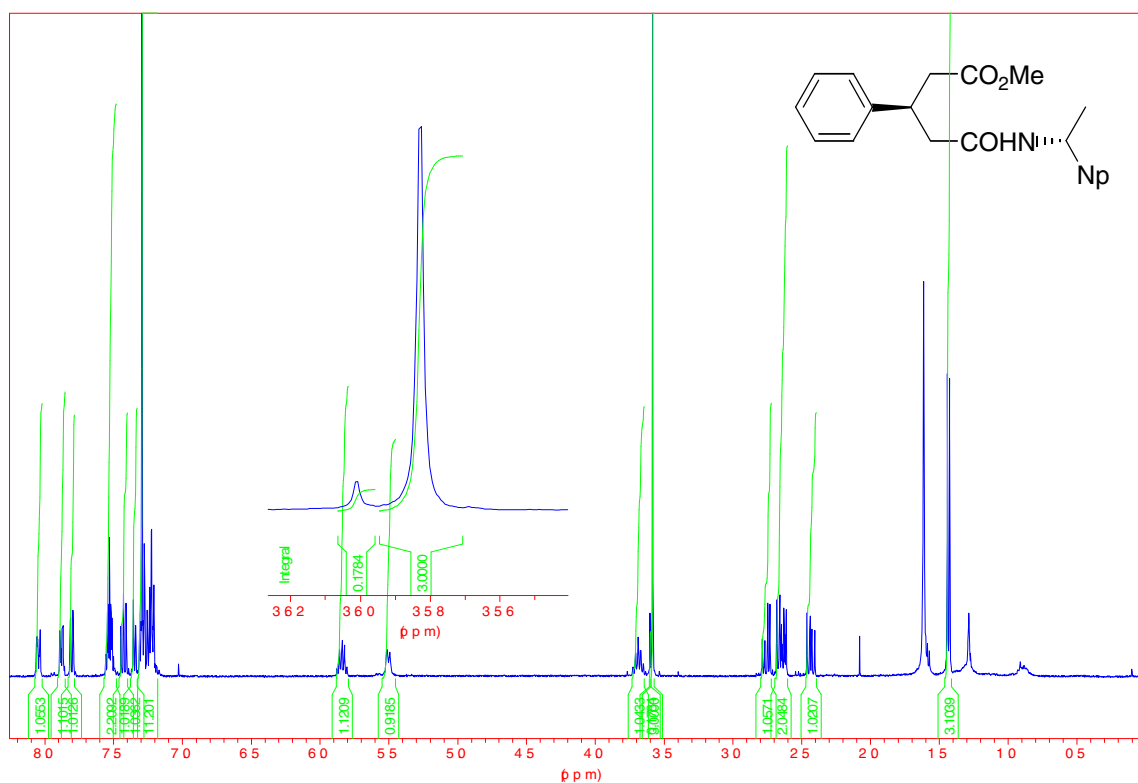


3-Phenyl-pentanedioic acid monomethyl ester (20, entry 9-10)

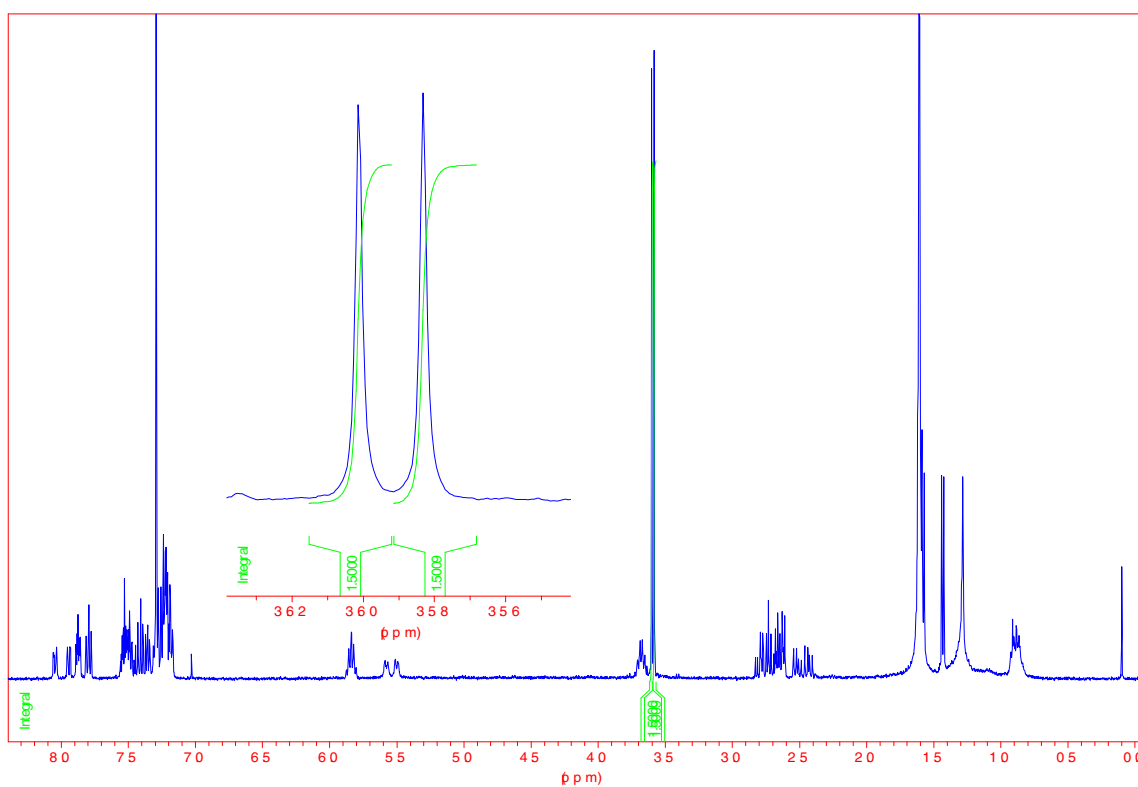


Determination of enantiomeric excess by NMR (Table 2, entry 10, 89% ee)

¹H-NMR of the diastereoisomeric mixture from hemiester product of the catalysis (CDCl₃)



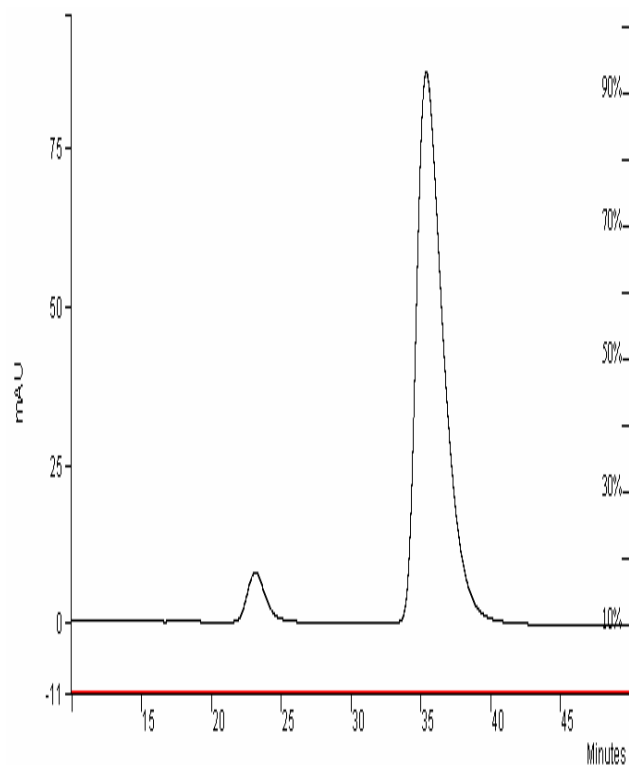
¹H-NMR of the diastereoisomeric mixture from racemic hemiester (CDCl₃)



CSP-HPLC profile of the diastereoisomeric mixture from the hemiester product of the catalysis

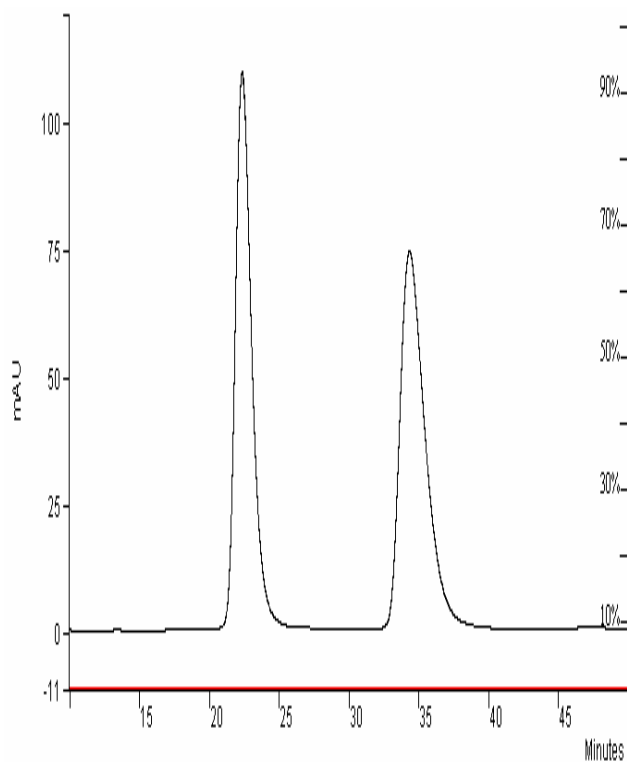
Chiralpak OD-H (4.6 mm x 25 cm),
Hexane/IPA: 90/10, 1.0 mL min⁻¹,
RT, UV detection at 220 nm

Time (min)	Area mAU*sec	Result %
23.092	725	5.680
35.345	11720	91.848

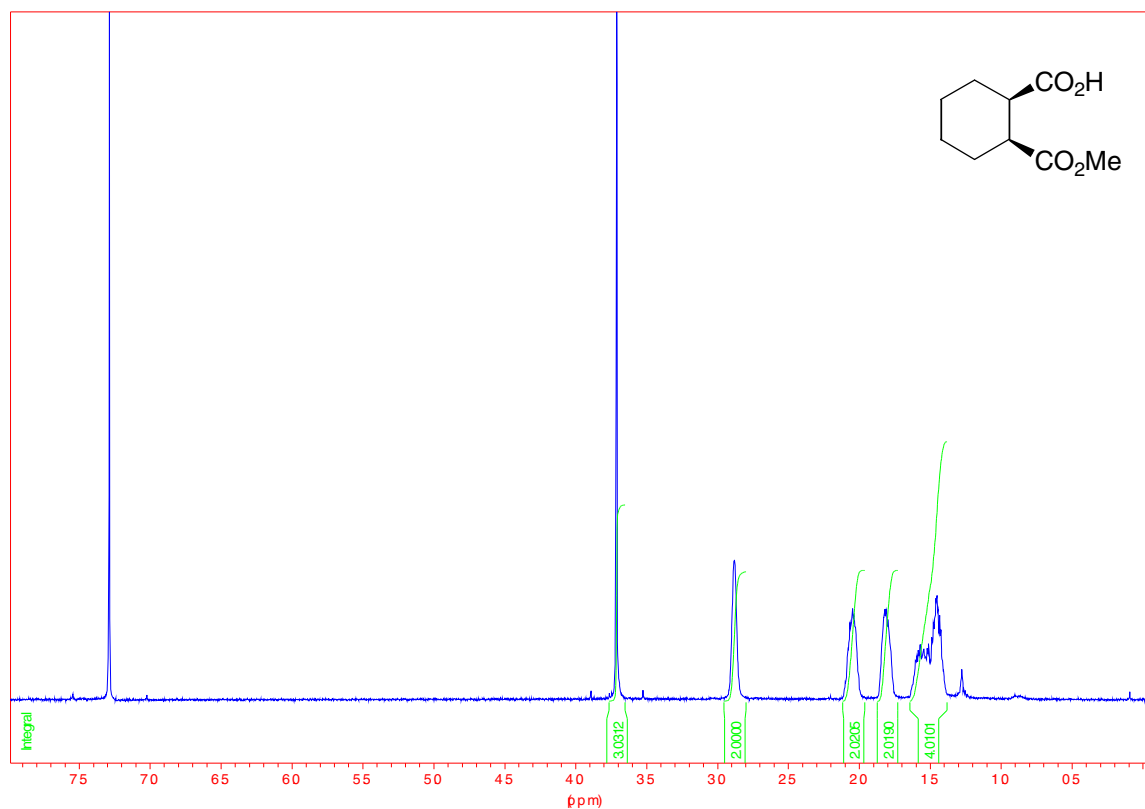


CSP-HPLC profile of the diastereoisomeric mixture from the corresponding racemic hemiester

Time (min)	Area mAU*sec	Result %
22.305	8934	48.113
34.288	9290	50.030

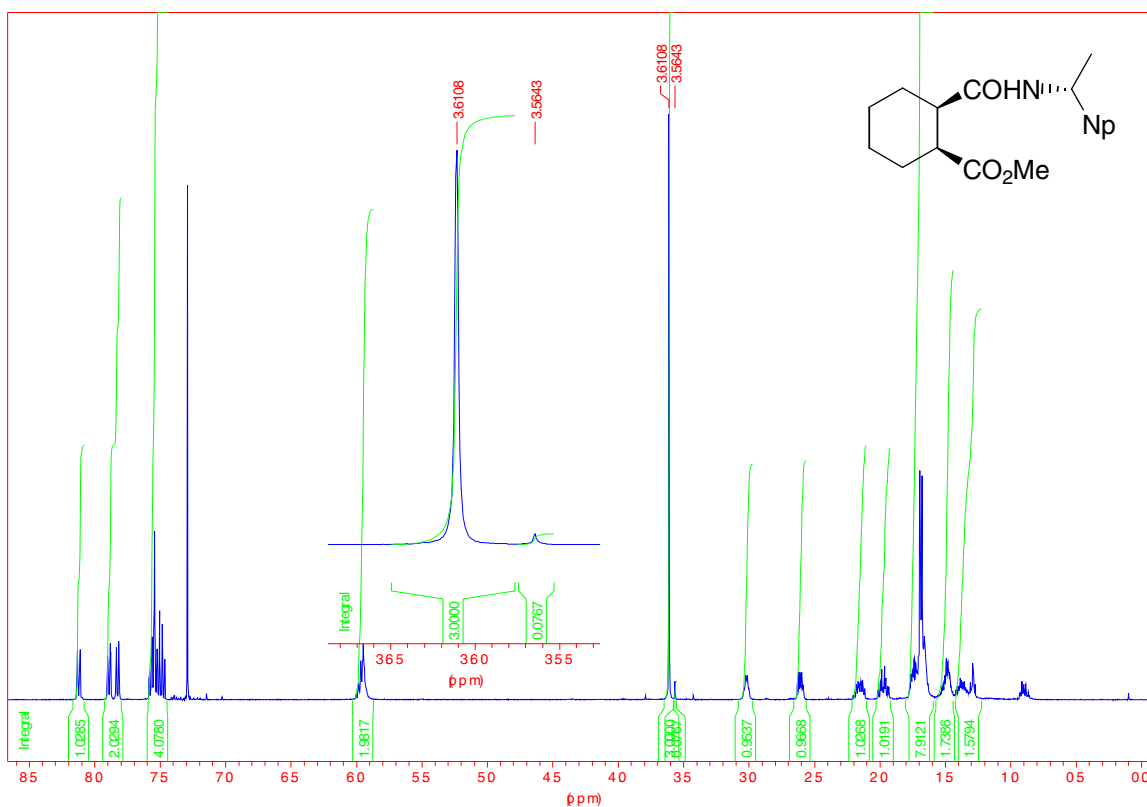


Cyclohexane-1,2-dicarboxylic acid monomethyl ester (22)



Determination of enantiomeric excess by NMR (95% ee)

$^1\text{H-NMR}$ of the diastereoisomeric mixture from hemiester with inverted configuration (CDCl_3)



6.0 References

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