Electronic Supplementary Material (ESI) for ChemComm.

Enantioselective Acyl-transfer Catalysis by Fluoride ion

Ryan P. Craig, Mili Litvajova, Sarah A. Cronin and Stephen J. Connon*

Centre for Synthesis and Chemical Biology, Trinity Biomedical Sciences Institute, School of Chemistry, University of Dublin, Trinity College, Dublin 2, Ireland

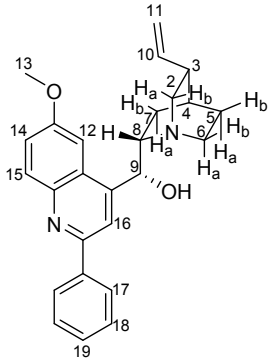
Table of Contents

General

Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400 MHz and Bruker Avance II 600MHz spectrometers, using as solvent $CDCl_3$, DMSO-d_6 or D_2O and referenced relative to residual $CHCl_3$ (δ = 7.26 ppm) DMSO (δ = 2.50 ppm) or H_2O (δ = 4.79 ppm). Chemical shifts are reported in ppm and coupling constants (*J*) in Hertz. Carbon NMR spectra were recorded on the same instruments (100.6 MHz and 150.9 MHz respectively) with total proton decoupling. Fluorine NMR spectra were recorded on the Bruker DPX400 machine (376.5 MHz). HSQC and HMBC, NMR experiments were used to aid assignment of NMR peaks when required. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. ESI mass spectra were acquired using a Waters Micromass LCT-time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC. The instrument was operated in positive or negative mode as required. EI mass spectra were acquired using a GCT Premier Micromass time of flight mass spectrometer (TOF). The instrument was operated in positive mode. Chemical Ionization (CI) mass spectra were determined using a GCT Premier Micromass mass spectrometer in CI mode utilising methane as the ionisation gas. APCI experiments were carried out on a Bruker microTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe. The instrument was operated in positive or negative mode as required. Agilent tuning mix APCI-TOF was used to calibrate the system. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualized by UV irradiation and $KMnO_4$ staining. Optical rotation measurements are quoted in units of 10^{-1} deg cm^2 g^{-1}. Anhydrous dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) and diethyl ether (Et_2O) were obtained by using Pure Solv MD-4EN Solvent Purification System. Commercially available anhydrous *t*-butyl methyl ether (MTBE) and methanol (MeOH) were used.

Catalyst Synthesis

(*R*)-(6-Methoxy-2-phenylquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methanol (SM1)

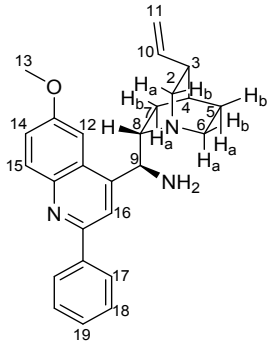


An oven dried 500 mL round-bottomed flask containing a large stirring bar was charged with quinine (6.50 g, 20.03 mmol) fitted with a septum and placed under an argon atmosphere. Anhydrous MTBE (120 mL) was added *via* syringe and the suspension was cooled to -10 °C. A solution of phenyl lithium (1.8 M in THF, 34.0 mL, 61.20 mmol) was added *via* syringe in two equal portions to the vigorously stirred suspension and the reaction mixture was stirred at -10 °C for 30 min then warmed to room temperature and stirred for 2 h. Acetic acid (15 mL) was added dropwise *via* syringe to the reaction at 0 °C, followed by H_2O (50 mL) and EtOAc (50 mL). The reaction was let warm to room temperature, then solid iodine was added in several portions to the vigorously stirred mixture until the appearance of a persistent deep brown coloration. A solution of sodium thiosulfate ($Na_2S_2O_3$, 3.00 g) in water (50 mL) was added, followed by a concentrated solution of aqueous ammonia (35%, 30 mL) and the mixture was stirred vigorously for 10 min. The organic phase was washed with brine and the aqueous phase extracted with CH_2Cl_2 (3 x 40 mL), the combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude oily residue was purified by column chromatography eluting with (8:1:0.5:0.5 Hex/EtOAc/MeOH/NEt_3), (TLC is better visualised using 7:1:1.5:0.5 Hex/EtOAc/MeOH/NEt_3) which allows for a better separation of the product from the starting alkaloid) to obtain **SM1** (4.30 g, 54%) as a white amorphous solid. M.p 146-150 °C (lit.,[1] 145-147 °C). $[\alpha]_D^{20}$ = -18.7 (*c* 0.25, $CHCl_3$).
Spectral data for this compound were consistent with those in the literature.[1]

δ_H (400 MHz, $CDCl_3$): 8.08-8.01 (3 H, m, H-15, H-17), 7.94 (1 H, s, H-16), 7.50-7.42 (3 H, m, H-14, H-18, H-19), 7.33 (1 H, dd, *J* 9.3, 2.5, H-14), 7.17 (1 H, d, *J* 2.5, H-12), 5.74 (1 H, ddd, *J* 7.7, 10.2, 17.6, H-10), 5.56 (1 H, d, *J* 3.1, H-9), 4.99-4.91 (2 H, m, H-11), 3.90 (3 H, s, H-13),

3.52-3.47 (1 H, m, H- 2b), 3.15-3.09 (2 H, m, H-6a, H-8), 2.70-2.66 (2 H, m, H-2a, H-6b), 2.32-2.19 (1 H, m, H-3), 2.11 (1H, bs, OH) 1.83-1.77 (3 H, m, H-4, H-5b, H-7b), 1.58-1.52 (2 H, m, H-5a, H-7a).

(*S*)-[6-Methoxy-2-phenylquinolin-4-yl][(2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl]methanamine (SM2)



An oven dried 250 mL round-bottomed flask containing a stirring bar was charged with **SM1** (4.05 g, 10.11 mmol), PPh_3 (3.18 g, 12.12 mmol), and placed under an argon atmosphere. Anhydrous THF (65 mL) was added *via* syringe and the resulting solution was cooled to 0 °C. Diisopropyl azodicarboxylate (DIAD) (2.4 mL, 12.19 mmol) and diphenylphosphoryl azide (DPPA) (2.6 mL, 12.11 mmol) were added dropwise *via* syringe with the resulting mixture warmed to room temperature and stirred for 16 h, then heated at reflux temperature for 2 h. The so-formed azido species was reduced *in situ via* a Staudinger reduction: the reaction mixture was cooled to room temperature, PPh_3 (3.18 g, 12.12 mmol), was added and the solution was heated at reflux temperature for 5 hours. After cooling the reaction to room temperature, H_2O (20 mL) was added and the reaction was stirred at room temperature for 20 h, followed by concentration *in vacuo* with the resulting residue dissolved in CH_2Cl_2 (30 mL). A 2.0 M aqueous solution of HCl (30 mL) was added, the aqueous phase was separated and washed with CH_2Cl_2 (3 x 20 mL). The aqueous layer was then concentrated under reduced pressure to obtain the hydrochloride salt **SM2a** (4.12 g, 80%) of the 9- *epi*-amine-derivative of the quinine-derived alkaloid as pale yellow salts.

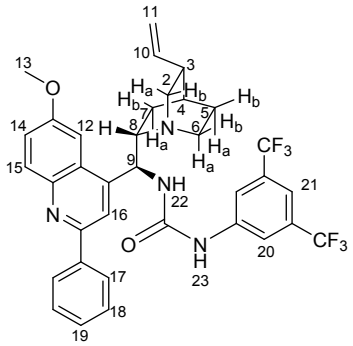
The 9-*epi*-quinine-derived alkaloids bearing an amino group at C-9 could be generated by dissolving the relative hydrochloride salt in a mixture of CH_2Cl_2 (20 mL) and a saturated aqueous solution of Na_2CO_3. The basic aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL), the organic extracts were dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to obtain the relevant

free amine base in quantitative yields. The isolated compound exhibited identical spectroscopic data to those reported in the literature.[2] $[\alpha]_D^{20}$ = + 26.4 (*c* 0.25, $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 8.17 (2 H, d, *J* 7.3, H-17), 8.12 (1 H, d, *J* 9.1, H-15), 7.98 (1 H, bs, H-16), 7.70 (1 H, bs, H-12), 7.51 (2 H, app. t, H-18), 7.47 (1 H, t, *J* 7.4 H-19), 7.42 (1 H, dd, *J* 2.7, 9.4, H-14), 5.79 (1 H, ddd, *J* 7.8, 10.1, 17.0, H-10), 5.10-4.87 (2 H, m, H-11), 4.65 (1 H, bs, H-9), 3.97 (3 H, s, H-13), 3.38-3.06 (3 H, m, H-8, H-6a, H-2b), 2.91-2.74 (2 H, m, H-2a, H-6b), 2.34-2.24 (1 H, m, H-3), 2.08 (2 H, bs, NH_2), 1.69-1.52 (3 H, m, H-4, H-5a, H-5b), 1.49- 1.34 (1 H, m, H-7b), 0.92-0.78 (1 H, m, H-7a)

HRMS (*m/z* -ESI): Found 400.2392 (M + H calculated for $C_{26}H_{30}N_3O$: 400.2389)

1-(3,5-*bis*(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxy-2-phenylquinolin-4-yl) ((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea (SM3)



A 250 mL round-bottomed flask containing a magnetic stirrer was charged with **SM2a** (2.00 g, 3.93 mmol), flushed with argon, then placed under a protective argon atmosphere. CH_2Cl_2 (35 mL) was added *via* syringe and the reaction mixture was cooled in an ice-bath. NEt_3 (2.75 mL, 19.65 mmol) was added dropwise *via* syringe and the resultant mixture was stirred at 0 °C. After 30 min 3,5-*bis*-(trifluoromethyl)phenyl isocyanate (815 µL, 4.71 mmol) was added *via* syringe and the reaction stirred at 0 °C, then warmed to room temperature. After 16 h, the reaction mixture was filtered and the liquids concentrated *in vacuo*. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 30:1), to yield **SM3** as a white solid (1.70 g, 66%). M.p. 150-152 °C. $[\alpha]_D^{22}$ = +66.9 (*c* 0.2, $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 8.79 (1H, bs, H-23), 8.19-8.14 (3H, m, H-15, H-17), 7.93 (1H, bs, H-21), 7.78-7.75 (3H, m, H-16, H-20), 7.53-7.43 (4H, m, H-14, H-18, H-19), 7.34 (1H, bs, H-12), 6.98 (1H, bs, H-9), 5.83 (1H, bs, H-22), 5.64-5.53 (1H, m, H-10), 4.99-4.96 (2H, m, H-11), 4.00 (3H, s, H-13), 3.83-3.64 (2H, m, H-8, H-6b), 3.21 (1H, app. t, H-2b), 2.81-2.72 (2H, m, H-6a, H-2a), 2.42 (1H, bs, H-3), 1.84-1.77 (4H, m, H-5a, H-5b, H-4), 1.12 (1H, bs, H-7a)

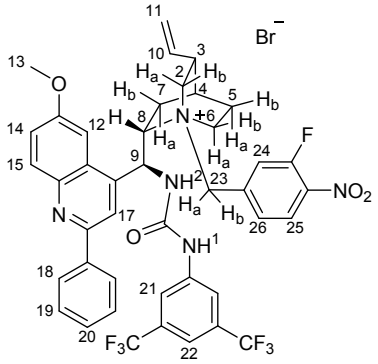
δ_C (100 MHz, $CDCl_3$): 158.5 (q), 154.7 (q), 154.6 (q), 145.0 (q), 144.0 (q), 140.7 (q), 139.3, 138.6 (q), 132.3, 131.7 (q, J_{C-F} 32.6), 129.3, 128.9, 127.3, 123.2 (q, J_{C-F} 272.9), 122.5, 118.1, 116.3, 115.4, 101.7, 60.3, 55.9, 55.0, 53.5, 50.0, 41.4, 37.8, 29.7, 26.8, 26.1, 25.8

δ_F (376 MHz, $CDCl_3$): -63.1

ν_{max} (neat)/cm^{-1}: 2988, 1670, 1632, 1550, 1473, 1386, 1348, 1272, 1223, 1172, 1129, 1009, 876, 830.

HRMS (*m/z* -ESI) : Found 653.2378 (M - H: calculated for $C_{35}H_{32}N_4O_2F_6$: 653.2356)

(1*S*,2*S*,4*S*,5*R*)-2-((*S*)-(3-(3,5-*bis*(trifluoromethyl)phenyl)ureido)(6-methoxy-2-phenylquinolin-4-yl)methyl)-1-(3-fluoro-4-nitrobenzyl)-5-vinylquinuclidin-1-ium bromide (13)



A 10 mL round-bottomed flask containing a stirring bar was charged with a bifunctional cinchona alkaloid derivative **SM3** (300.0 mg, 0.458 mmol, 1.0 equiv.), 3-fluoro-4-nitrobenzyl bromide (129.0 mg, 0.550 mmol, 1.2 equiv.) and CH_2Cl_2 (4.6 mL, 0.1 M). The reaction mixture was stirred for 3 days at room temperature. Upon completion of the reaction (TLC),

the solvent was removed *in vacuo* and the crude residue was purified by column chromatography on silica gel (eluting gradient from 100% CH_2Cl_2 to 97:3 CH_2Cl_2/MeOH, TLC is better visualised using CH_2Cl_2/MeOH 10:1, R_f = 0.4). Precipitation from Et_2O afforded **13** (228 mg, 56%) as an off-white amorphous solid. M.p. 179-182 ˚C; $[\alpha]_D^{20}$ = +121.7 (*c* = 0.2, $CHCl_3$).

δ_H (400 MHz, DMSO-d_6): 9.60 (br s, 1 H, *N*H[1]), 8.33-8.25 (m, 5 H, H-18, H-17, H-25 and H-24), 8.10 (d, 1 H, *J* 9.2, H-15), 8.04-8.01 (m, 3 H, H-21 and H-26), 7.82 (app. dd, 1 H, H-14), 7.65-7.51 (m, 6 H, H-19, H-20, H-12, H-22 and *N*H[2]), 6.31-6.26 (m, 1 H, H-9), 5.90-5.82 (m, 1 H, H-10), 5.27-5.01 (m, 5 H, H-23a, H-23b, H-11 and H-8), 4.38-4.32 (m, 1 H, H-6a), 4.04 (s, 3 H, H-13), 3.79-3.74 (m, 1 H, H-2b), 3.62-3.53 (m, 2 H, H-2a and H-6b), 2.78-2.72 (m, 1 H, H-3), 2.15-1.94 (m, 4 H, H-5a, H-5b, H-7b and H-4), 1.24-1.21 (m, 1 H, H-7a)

Note: ^{1}H NMR spectrum was recorded at 60 ˚C to yield better defined resonances.

δ_C (100 MHz, DMSO-d_6): 158.6 (C=O), 155.5 (q), 154.9 (q), 154.3 (q), 153.8 (q), 144.9 (q), 144.7 (q), 142.0 (q), 139.0, 138.4 (d, $J_{C\text{-}F}$ 7.8) (q), 137.4, 136.8 (d, $J_{C\text{-}F}$ 8.4) (q), 132.5, 131.2 (d, $J_{C\text{-}F}$ 2.3) (q), 131.1 (q, $J_{C\text{-}F}$ 32.4) (q), 130.1, 129.4, 127.6, 127.0, 126.5, 124.1 (d, $J_{C\text{-}F}$ 21.1), 123.6 (q, $J_{C\text{-}F}$ 272.6) (q), 122.8, 118.4, 117.8 (d, $J_{C\text{-}F}$ 14.4), 115.1, 102.5, 66.4, 63.8, 61.2, 56.1, 50.8, 50.3, 37.4, 27.2, 26.2, 24.7

δ_F (376 MHz, DMSO-d_6): -61.8 (CF_3), -118.7 (F)

ν_{max} (neat)/cm^{-1}: 3003, 1707, 1621, 1534, 1278, 1179, 1128, 1030, 882, 828, 651

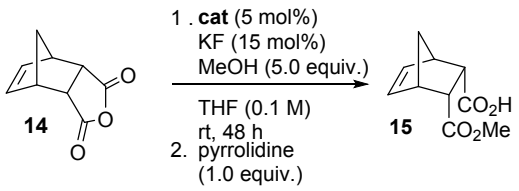
HRMS (*m/z* – APCI): Found: 808.2734 $[M]^+$ $C_{42}H_{37}N_5O_4F_7$ Requires: 808.2728

General procedure I: Desymmetrisation of *meso* anhydrides – Racemate preparation

An oven-dried 10 mL round-bottomed flask was charged with (100 mg) of the requisite anhydride and tetrabutylammonium fluoride (10 mol%, 1.0 M THF). The flask was fitted with a septum, evacuated *via* Schlenk techniques, then placed under an atmosphere of argon *via* balloon. THF (0.1 M) was added, followed by dry MeOH (3.04 mmol). The septum was

replaced with a glass stopper under a flow of argon and the reaction was left stirring at room temperature for 48 h. Conversion was determined *via* ^{1}H NMR spectroscopic analysis.

General procedure II: Desymmetrisation of *meso* anhydride 14 – catalyst evaluation (Table 2)



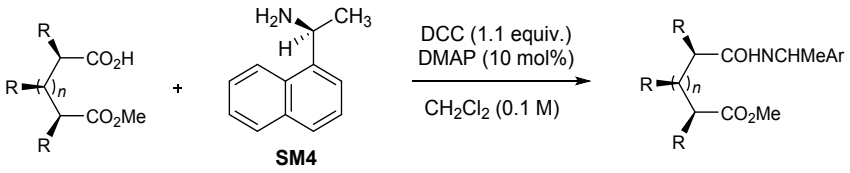
An oven-dried 5 mL round-bottomed flask was charged with *cis* norbornene-5,6-*endo*-dicarboxylic anhydride (**14**), (50 mg 0.304 mmol), the requisite catalyst (0.015 mmol – 5 mol %) and potassium fluoride (2.65 mg 0.046 mmol). The flask was fitted with a septum, evacuated *using Schlenk techniques*, and then placed under an atmosphere of argon *via* balloon. THF (0.1 M) was added to the flask followed by dry MeOH (61.5 μL, 1.52 mmol). The septum was replaced with a glass stopper under a flow of argon and the reaction was left stirring at room temperature for 48 h. Conversion was determined *via* ^{1}H NMR spectroscopic analysis. Pyrrolidine (mmol calculated on unreacted starting material) was added to quench any remaining starting material and the resulting mixture was stirred for 1 h. The solvent was removed *in vacuo* and the crude residue purified *via* column chromatography eluting from CH_2Cl_2/MeOH 19:1 to afford pure compound **15**.

General procedure III: Desymmetrisation of *meso*-anhydrides – Anhydride evaluation (Table 3)

An oven-dried 5 mL round-bottomed flask was charged with the requisite anhydride, (50 mg 0.X mmol), catalyst **13** (0.015 mmol – 5 mol %) and potassium fluoride (2.65 mg 0.046 mmol). The flask was fitted with a septum, evacuated using Schlenk techniques, and then placed under an atmosphere of argon *via* balloon. THF (3 mL, 0.1 M) was added to the flask followed by dry MeOH (61.5 μL, 1.52 mmol). The septum was replaced with a glass stopper under a flow of argon and the reaction stirred at room temperature for 72 h. Conversion was determined *via* ^{1}H NMR spectroscopic analysis. Pyrrolidine (1.0 equiv.) was added and the reaction was let stir for 1 h, then concentrated *in vacuo* to yield a crude residue purified by column chromatography eluting from CH_2Cl_2/MeOH 19:1 to furnish the desired hemiester.

The resulting hemiester was further functionalised according to general procedure IX to ascertain product *ee*.

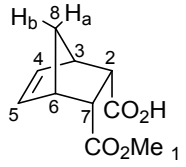
General procedure IV: Determination of the enantiomeric excess of hemiesters from Table 3 by derivatisation



The requisite hemiesters **15** and **43-49** (1.0 equiv.) were placed in a 5 mL round bottomed-flask with DCC (1.1 equiv.) and DMAP (10 mol%). The flask was fitted with a septum, evacuated using Schlenk techniques, and then placed under an atmosphere of argon *via* balloon. CH_2Cl_2 (0.1 M) was added *via* syringe followed by the chiral amine **SM4** (1.0 equiv.). The reaction was left stirring for 12 h at rt then diluted with CH_2Cl_2 (3 mL), filtered under gravity and purified *via* preparative TLC eluting from CH_2Cl_2 : EtOAc (5 : 1).

Synthesis of hemiesters 15-and 43-49

Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid monomethyl ester (15)



Prepared according to general procedure III using *cis* norbornene-5 6-*endo*-dicarboxylic anhydride (**14**), (50 mg 0.304 mmol). The desired monomethyl ester **15** was obtained as a white solid after purification by flash chromatography (50 mg, 84%). M.p. 76-78 ^oC; (lit.,[3] 75-78 ^oC). $[\alpha]_D^{20}$ = +2.34 (*c* 0.13, $CHCl_3$); lit.,[3] $[\alpha]_D^{rt}$ = -7.4 (*c* 1.53, CCl_4).

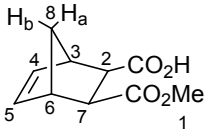
Spectral data for this compound were consistent with those in the literature.[3]

61% *ee* was determined by ^1H NMR spectroscopic analysis of the corresponding amide ester diastereoisomeric mixture prepared as in General procedure IV.

δ_H (400 MHz, $CDCl_3$): 6.36 (1H, dd, *J* 5.5, 3.0, H-4), 6.24 (1H, dd, *J* 5.5, 3.0, H-5), 3.62 (3H, s, H-1), 3.37 (1H, dd, *J* 10.0, 3.0, H-7), 3.31 (1H, dd,

J 10.0, 3.0, H-2), 3.15-3.28 (2H, m, H-3, H-6), 1.52 (1H, app. dt, H-8b), 1.36 (1H, app. br d, H-8a).

Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid monomethyl ester (43)



1

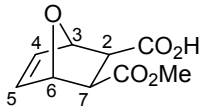
Prepared according to general procedure III using *cis* norbornene-5 6-*exo*-dicarboxylic anhydride, (50 mg 0.304 mmol). The desired monomethyl ester **43** was obtained as a white solid after purification by flash chromatography (57 mg, 95%). M.p. 73 ^{o}C; (lit.,[4] 75-78 ^{o}C). $[\alpha]_D^{20}$ = +3.25 (*c* 0.25, $CHCl_3$); lit.[4] $[\alpha]_D^{rt}$ = +7.7 (*c* 1.0, CCl_4)

Spectral data for this compound were consistent with those in the literature.[4]

44% *ee* was determined by ^{1}H NMR spectroscopic analysis of the corresponding amide ester diastereoisomeric mixture prepared as in general procedure IV.

δ_H (400 MHz, $CDCl_3$): 6.24-6.21 (2H, m, H-4, H-5), 3.66 (3H, s, H-1), 3.15-3.10 (2H, m, H-7, H-2), 2.68-2.63 (2H, m, H-3, H-6), 2.10 (1H, d, *J* 9.1, H-8b), 1.51 (1H, app. dt, H-8a)

7-oxa-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid monomethyl ester (44)



1

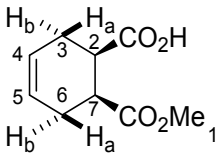
Prepared according to general procedure III using *exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride, (50 mg 0.301 mmol). The desired monomethyl ester **44** was obtained as a white solid after purification by flash chromatography (42 mg, 83%). M.p. 111-112 ^{o}C; (lit.,[3] 111 ^{o}C). $[\alpha]_D^{20}$ = -8.32 (*c* 0.30, MeOH); (opposite enantiomer formed to literature citation) lit.[3] $[\alpha]_D^{rt}$ = +8.7 (*c* 1.08, MeOH)

Spectral data for this compound were consistent with those in the literature.[3]

31% *ee* was determined by ^{1}H NMR spectroscopic analysis of the corresponding amide ester diastereoisomeric mixture prepared as in general procedure IV.

δ_H (400 MHz, $CDCl_3$): 6.49-6.45 (2H, m, H-4, H-5), 5.31-5.26 (2H, m, H-3, H-6), 3.71 (3H, s, H-1), 2.90 (1H, d, *J* 9.0, H-7), 2.84 (1H, d, *J* 9.0, H-2)

Cyclohex-4-ene-1,2-dicarboxylic acid monomethyl ester (45)



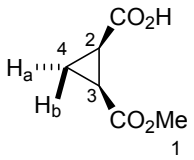
Prepared according to general procedure III using *cis*-1, 2, 3, 6-tetrahydrophthalic anhydride, (50 mg 0.328 mmol). The desired monomethyl ester **45** was obtained as a colourless oil after purification by flash chromatography (53 mg, 88%). $[\alpha]_D^{20}$ = +4.68 (*c* 0.18, $CHCl_3$); (opposite enantiomer formed to literature citation) lit.[3] $[\alpha]_D^{rt}$ = -4.9 (*c* 1.50, $CHCl_3$)

Spectral data for this compound were consistent with those in the literature.[3]

51% *ee* was determined by ^{1}H NMR spectroscopic analysis of the corresponding amide ester diastereoisomeric mixture prepared as in general procedure IV.

δ_H (400 MHz, $CDCl_3$): 5.69 (2H, s, H-4, H-5), 3.70 (3H, s, H-1), 3.10-3.04 (2H, m,H-2, H-7), 2.61-2.55 (2H, m, H-6b, H-3b), 2.41-2.33 (2H, m, H-6a, H-3a)

Cyclopropane-1, 2-dicarboxylic acid monomethyl ester (46)



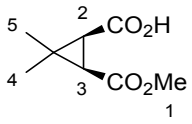
Prepared according to general procedure III using 3-oxabicyclo[3.1.0]hexane-2,4-dione, (50 mg, 0.446 mmol). The desired monomethyl ester **46** was obtained as a colourless oil after purification by flash chromatography (63 mg, 98%). $[\alpha]_D^{20}$ = +4.42 (*c* 0.13, $CHCl_3$); (opposite enantiomer formed to literature citation) lit.[3] $[\alpha]_D^{rt}$ = -10.0 (*c* 1.71, $CHCl_3$)

Spectral data for this compound were consistent with those in the literature.[3]

54% *ee* was determined by ^{1}H NMR spectroscopic analysis of the corresponding amide ester diastereoisomeric mixture prepared as in general procedure IV.

δ_H (400 MHz, $CDCl_3$): 5.65 (1H, bs, OH), 3.72 (3H, s, H-1), 2.16-2.05 (2H, m, H-2, H-3), 1.71-1.67 (1H, m, H-4a), 1.36-1.30 (1H, m, H-4b)

2,2-dimethylcyclopropane-1-dicarboxylic acid monomethyl ester (47)



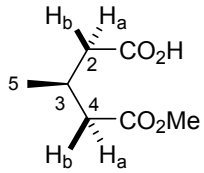
Prepared according to general procedure III using 6,6-dimethyl-3-oxabicyclo[3.1.0]hexane-2,4-dione (50 mg, 0.357 mmol). The desired monomethyl ester **47** was obtained as a colourless oil after purification by flash chromatography. (58 mg, 94%) $[\alpha]_D^{20}$ = -3.91 (*c* 0.17, $CHCl_3$); lit.[4] $[\alpha]_D^{rt}$ = -19.0 (*c* 4.08, MeOH)

Spectral data for this compound were consistent with those in the literature.[4]

39% *ee* was determined by ^{1}H NMR spectroscopic analysis of the corresponding amide ester diastereoisomeric mixture prepared as in general procedure IV.

δ_H (400 MHz, $CDCl_3$): 3.71-3.69 (3H, m, H-1), 1.96-1.91 (2H, m, H-2, H-3), 1.37 (3H, s, H-4), 1.25 (3H, s, H-5)

3-methyl-pentanedioic acid monomethyl ester (48)



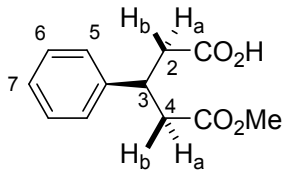
Prepared according to general procedure III using 3-methylglutaric anhydride, (50 mg, 0.390 mmol). The desired monomethyl ester **48** was obtained as a colourless oil after purification by flash chromatography. (37 mg, 88%)

Spectral data for this compound were consistent with those in the literature.[3]

6% *ee* was determined by ^{1}H NMR spectroscopic analysis of the corresponding amide ester diastereoisomeric mixture prepared as in general procedure IV.

δ_H (400 MHz, $CDCl_3$): 3.67 (3H, s, H-1), 2.51-2.38 (3H, m, H-3, H-4b, H-2b), 2.31-2.24 (2H, m, H-4a, H-2a), 1.05 (3H, d, *J* 6.5, H-5)

3-phenyl-pentanedioic acid monomethyl ester (49)



Prepared according to general procedure III using 3-phenylglutaric anhydride, (50 mg, 0.263 mmol). The desired monomethyl ester **49** was obtained and as a white solid after purification by flash chromatography. (55 mg, 94%). M.p. 93-95 ^{o}C; (lit.,[5] 93-95 ^{o}C).

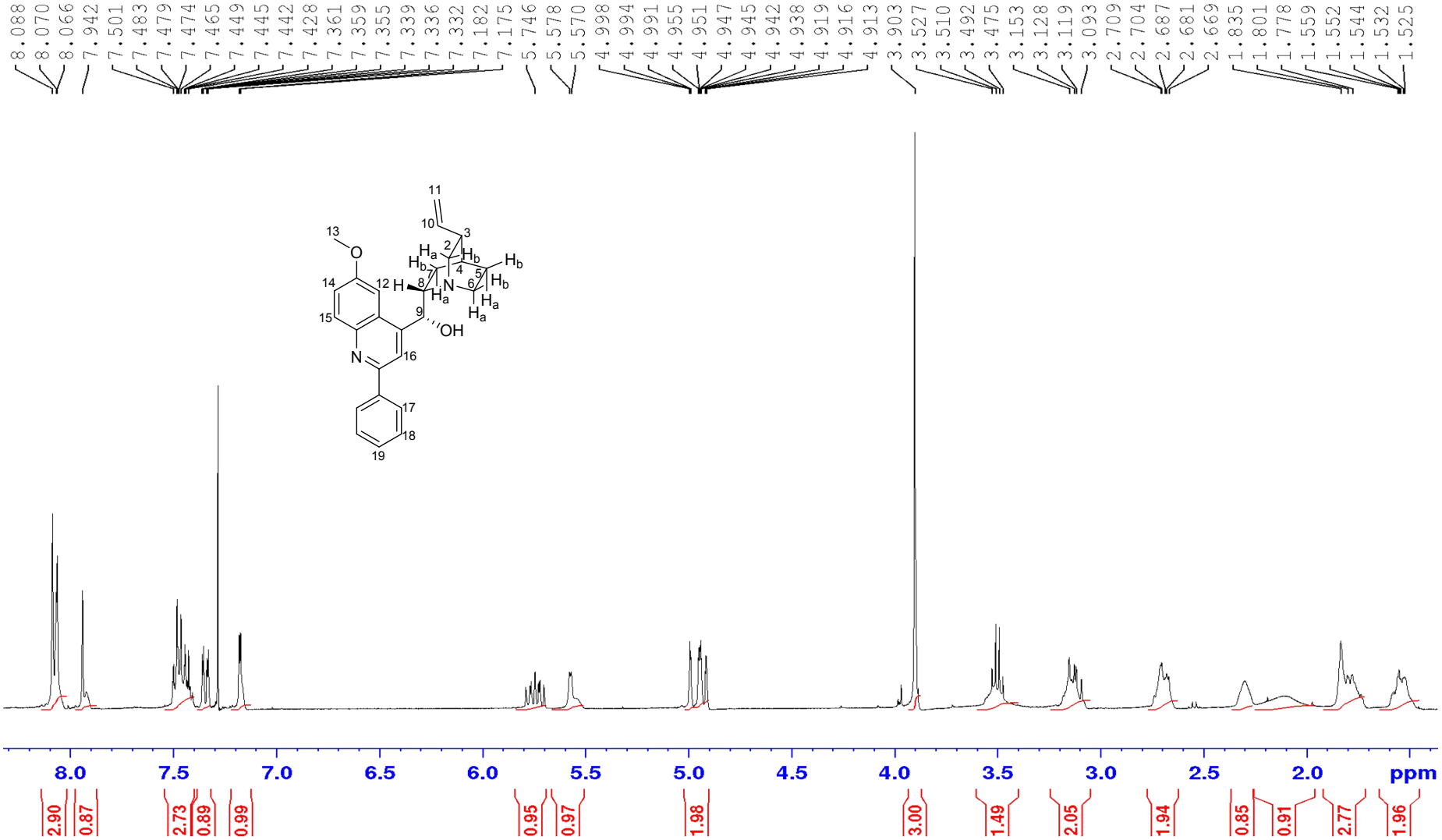
Spectral data for this compound were consistent with those in the literature.[3]

0% *ee* was determined by ^{1}H NMR spectroscopic analysis of the corresponding amide ester diastereoisomeric mixture prepared as in general procedure IV.

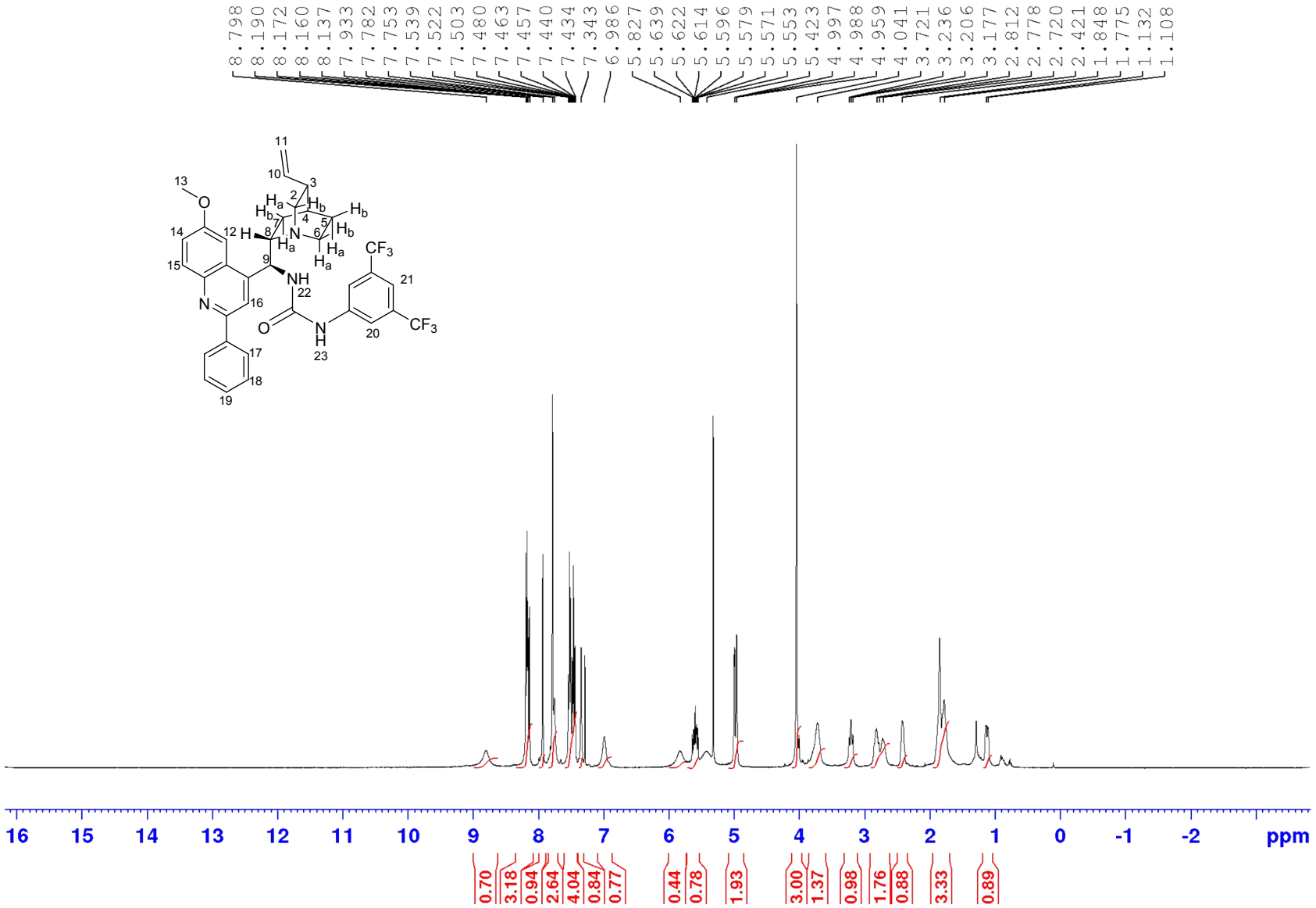
δ_H (400 MHz, $CDCl_3$): 7.32-7.21 (5H, m, H-5, H-6, H-7), 3.65-3.59 (4H, m, H-1, H-3), 2.81-2.62 (4H, m, H-2a, H-2b, H-4a, H-4b)

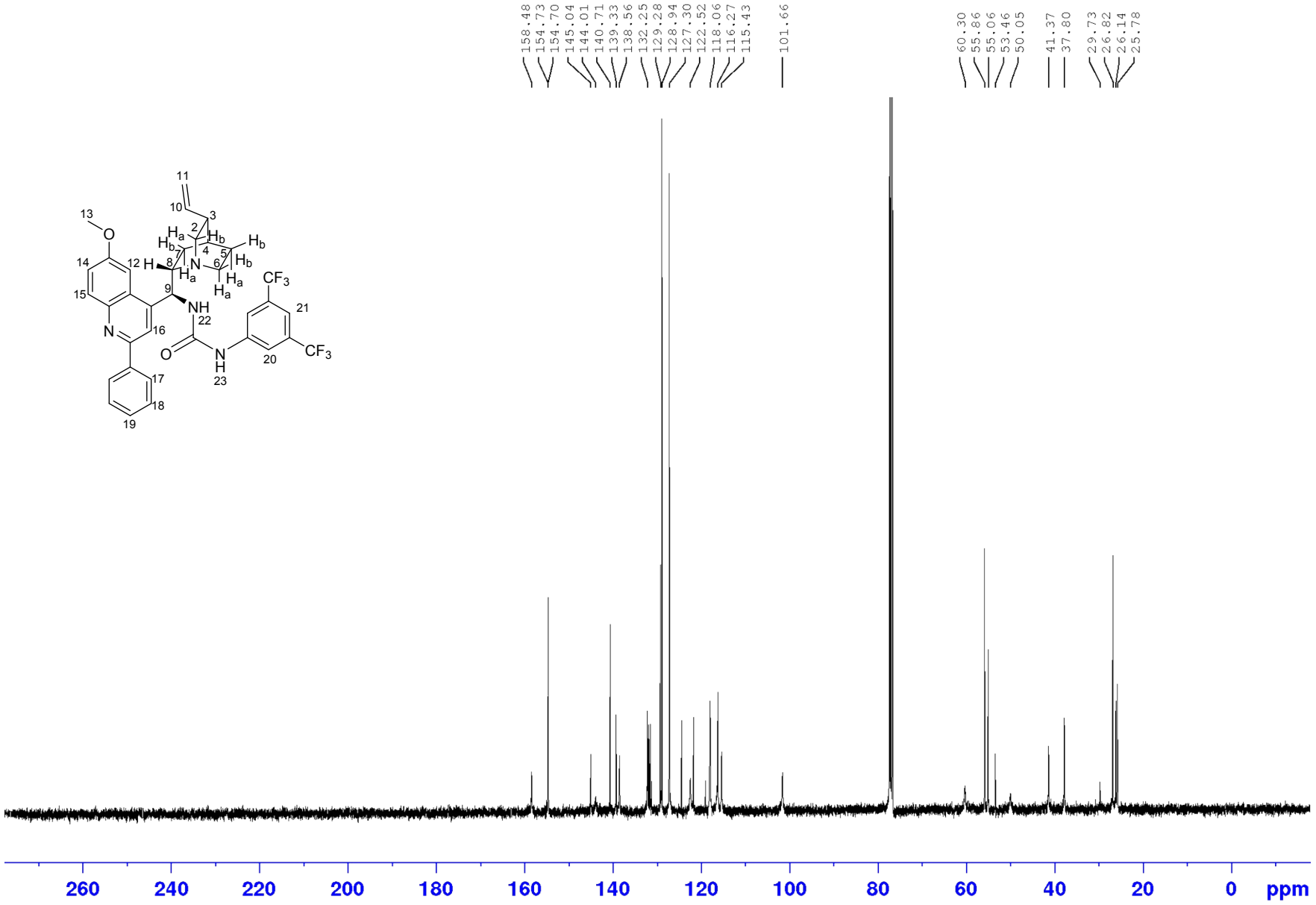
NMR Spectra

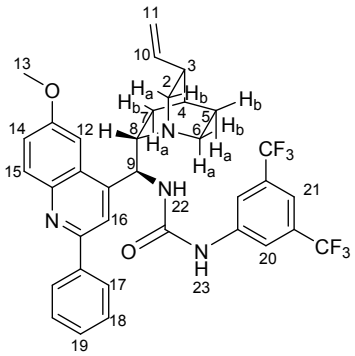
(*R*)-(6-Methoxy-2-phenylquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methanol (SM1)



1-(3,5-*bis*(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxy-2-phenylquinolin-4-yl) ((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea (SM3)

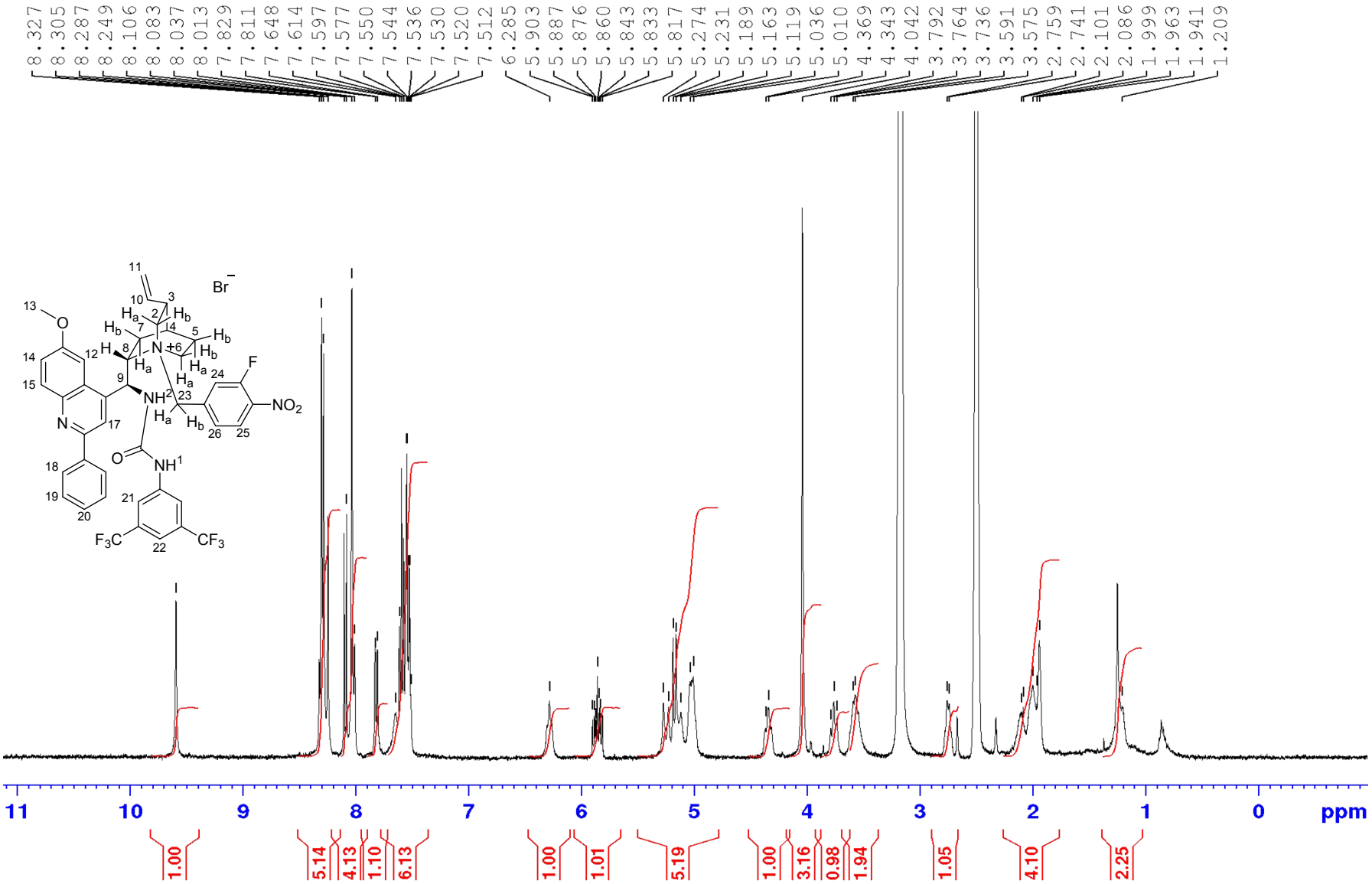


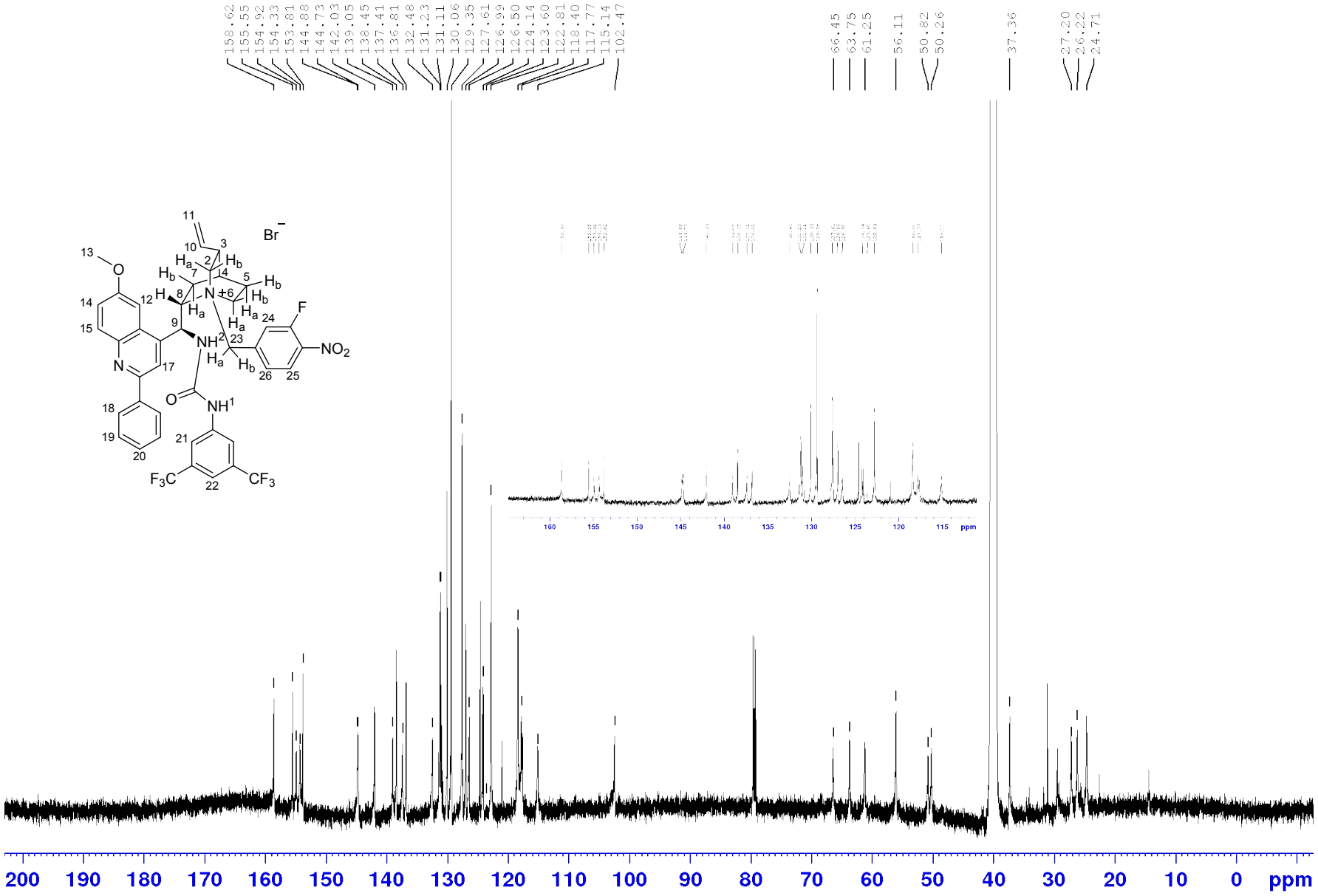

158.48
154.73
154.70
145.04
144.01
140.71
139.33
138.56
132.25
129.28
128.94
127.30
122.52
118.06
116.27
115.43
101.66
60.30
55.86
55.06
53.46
50.05
41.37
37.80
29.73
26.82
26.14
25.78
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

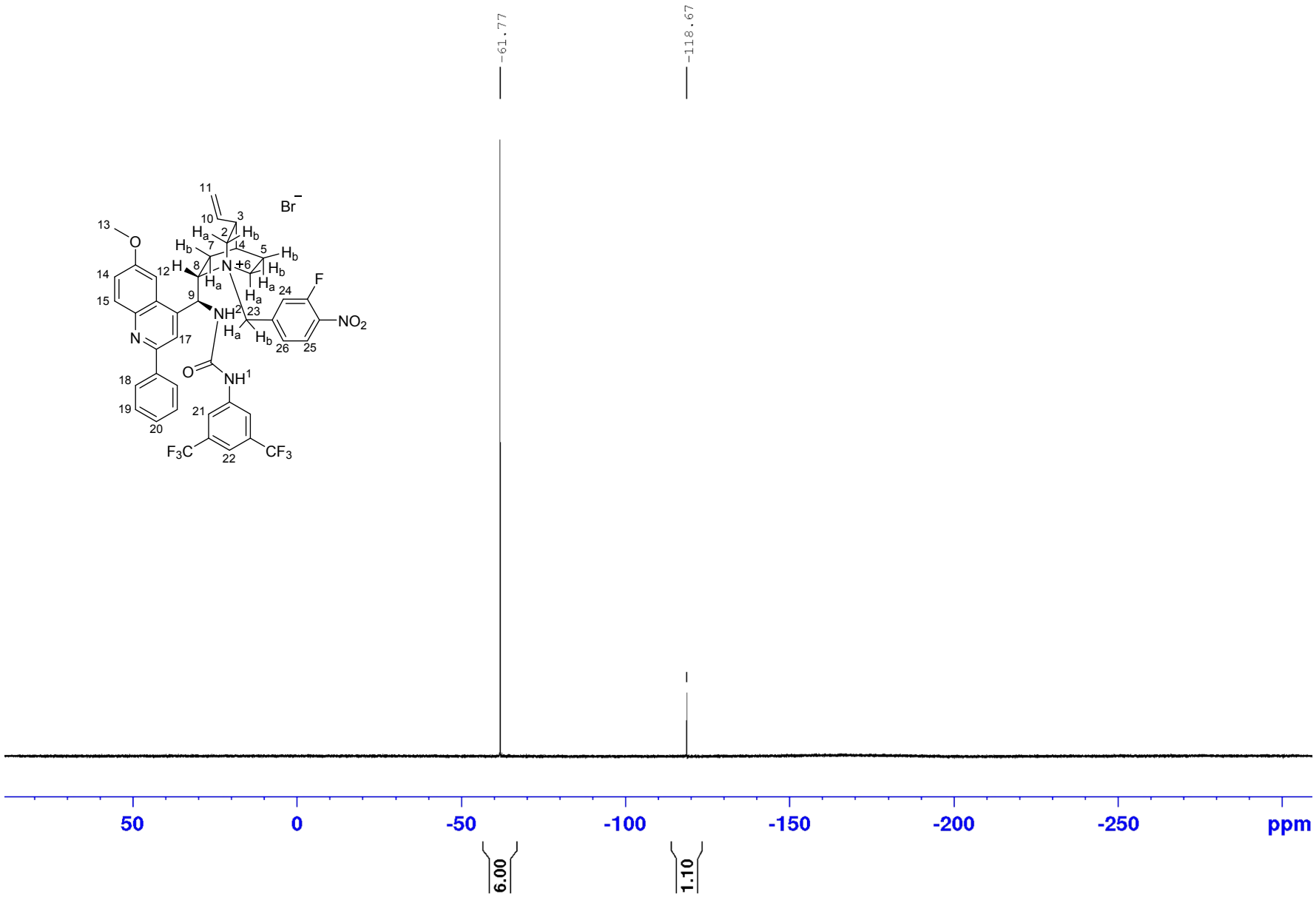

11
10
3
13
O
2
H_a
H_b
H_b
H_b
H_b
14
12
H
8
7
4
5
N
6
H_a
H_a
CF_3
15
9
NH
22
21
N
16
O
N
H
23
20
CF_3
17
18
19

-63.07
50
0
-50
-100
-150
-200
-250
ppm

(1*S*,2*S*,4*S*,5*R*)-2-((*S*)-(3-(3,5-*bis*(trifluoromethyl)phenyl)ureido)(6-methoxy-2-phenylquinolin-4-yl)methyl)-1-(3-fluoro-4-nitrobenzyl)-vinylquinuclidin-1-ium bromide (13)

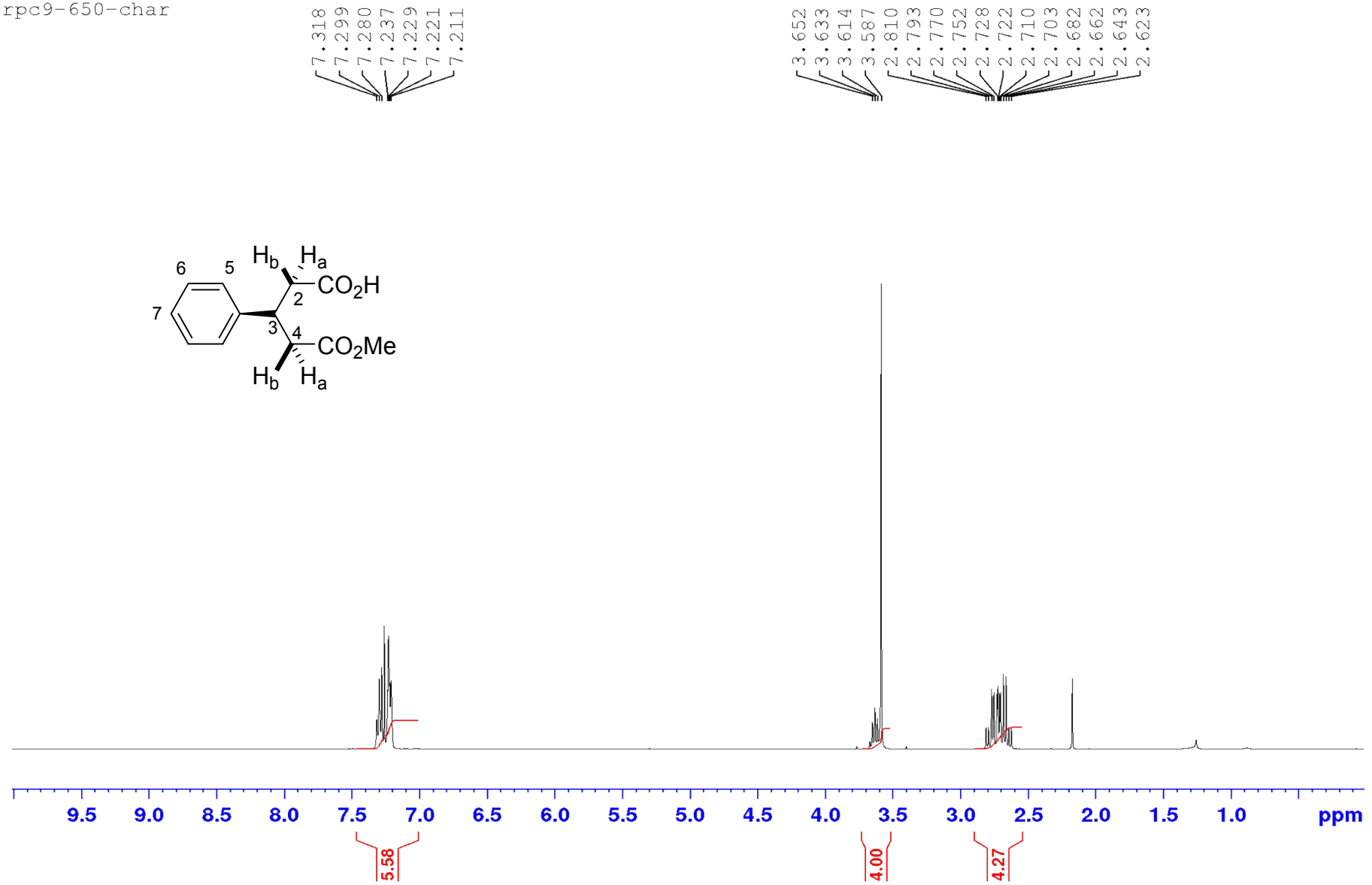



158.62
155.55
154.92
154.33
153.81
144.88
144.73
142.03
139.05
138.45
137.41
136.81
132.48
131.23
131.11
130.06
129.35
127.61
126.99
126.50
124.14
123.60
122.81
118.40
117.77
115.14
102.47
66.45
63.75
61.25
56.11
50.82
50.26
37.36
27.20
26.22
24.71
Br⁻
NO2
F
CF3
F3C
NH
NH1
O
N
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

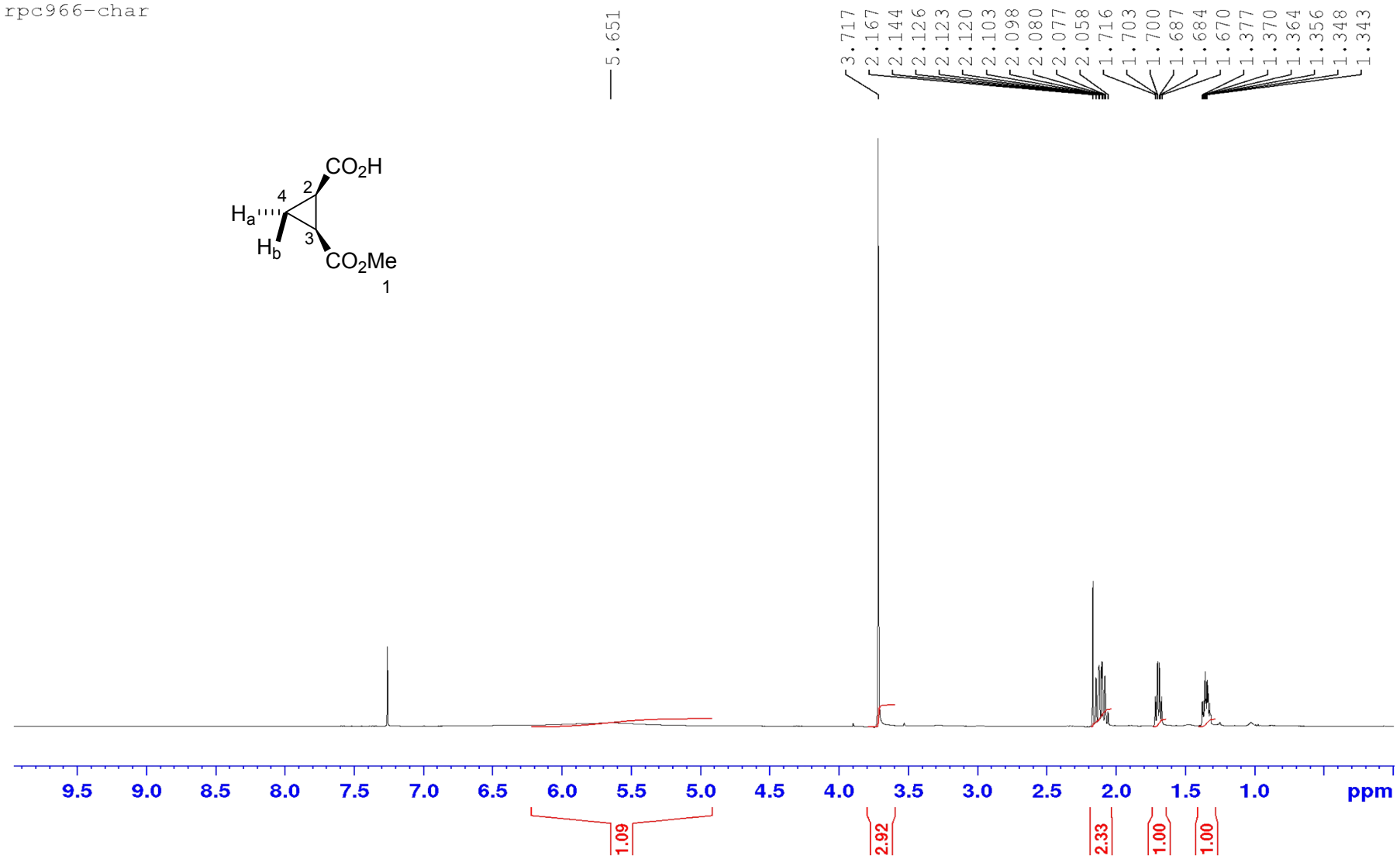

-61.77
-118.67
Br⁻
50
0
-50
-100
-150
-200
-250
ppm
6.00
1.10

3-phenyl-pentanedioic acid monomethyl ester (49)

rpc9-650-char

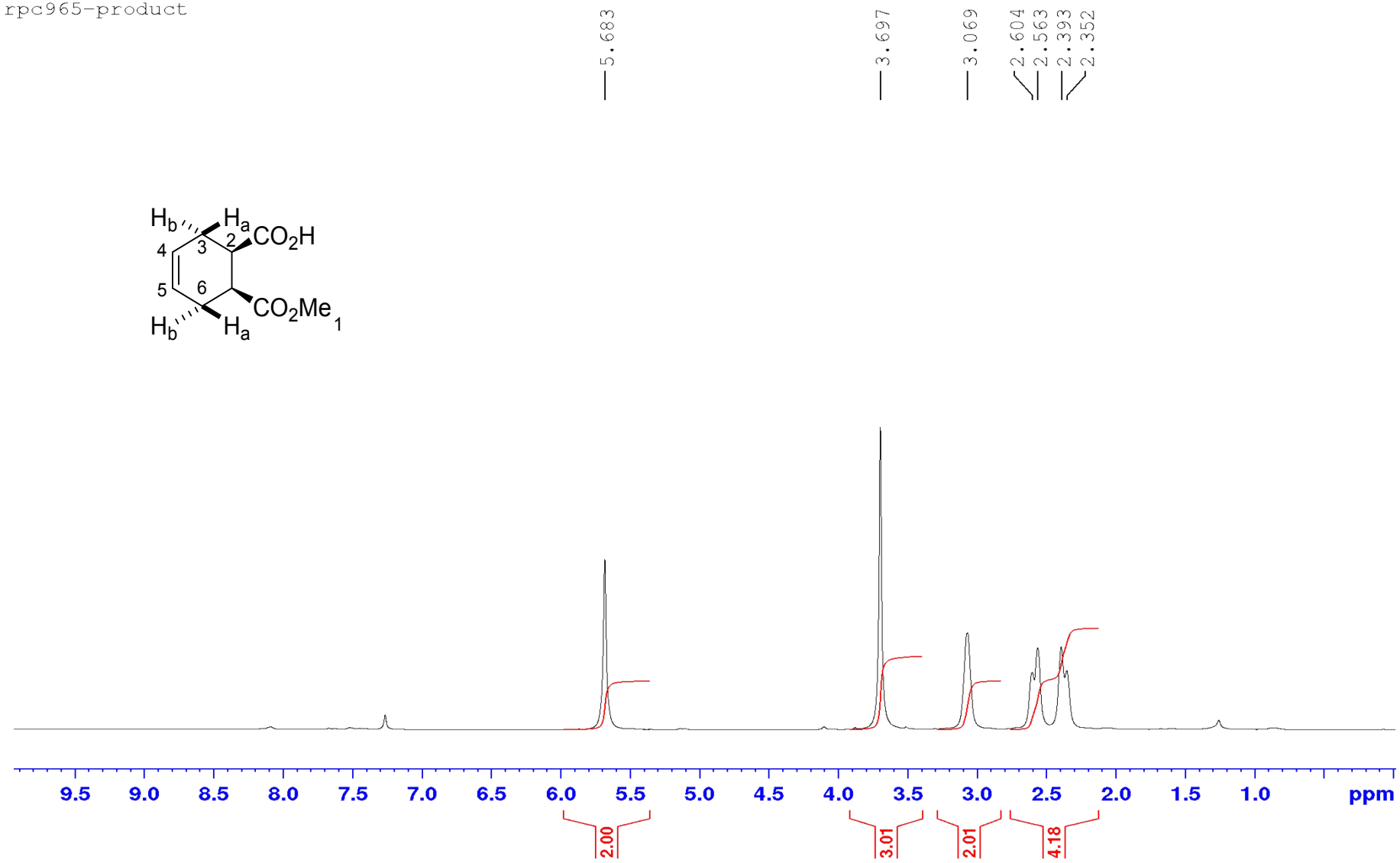


Cyclopropane-1, 2-dicarboxylic acid monomethyl ester (46)

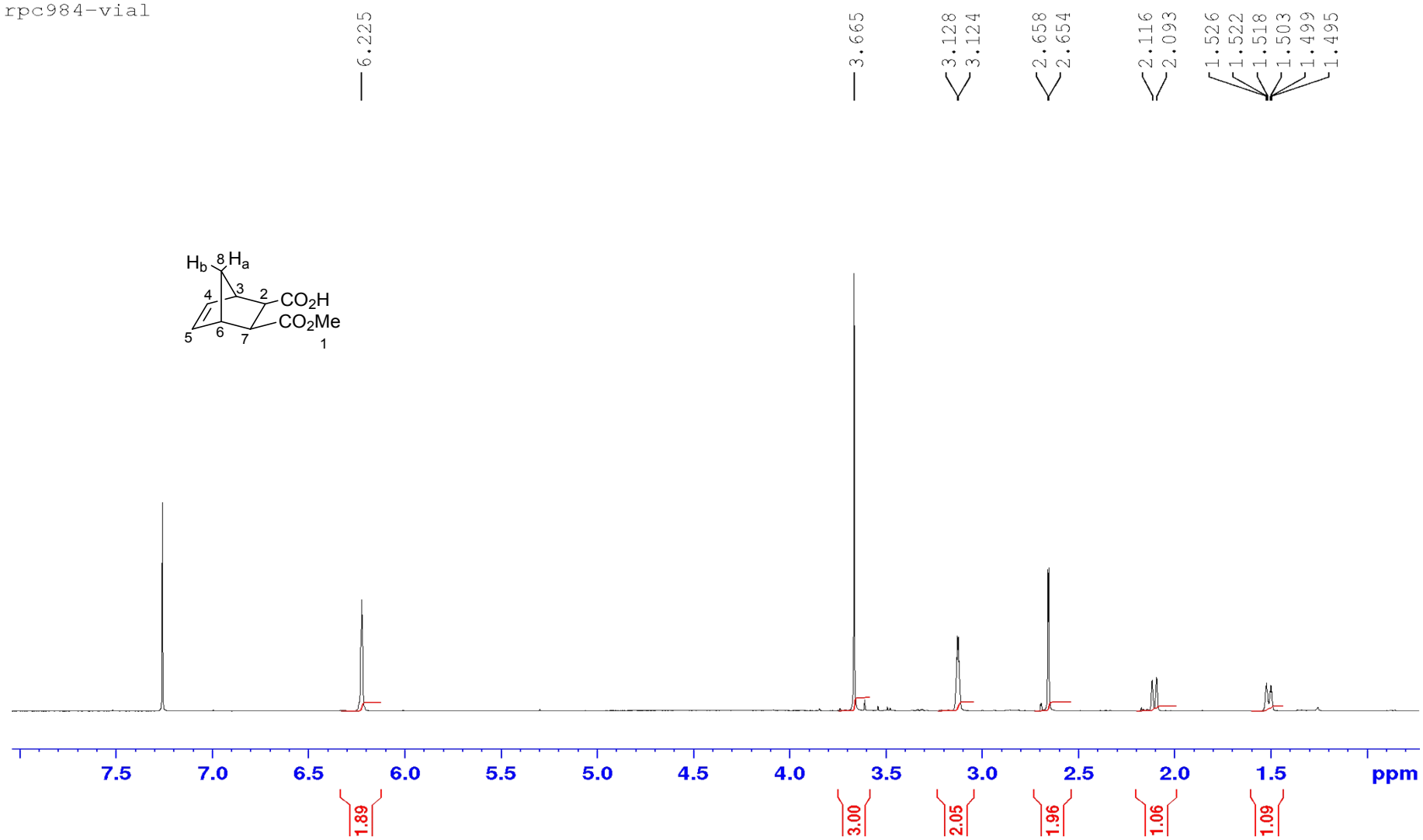


Cyclohex-4-ene-1,2-dicarboxylic acid monomethyl ester (45)

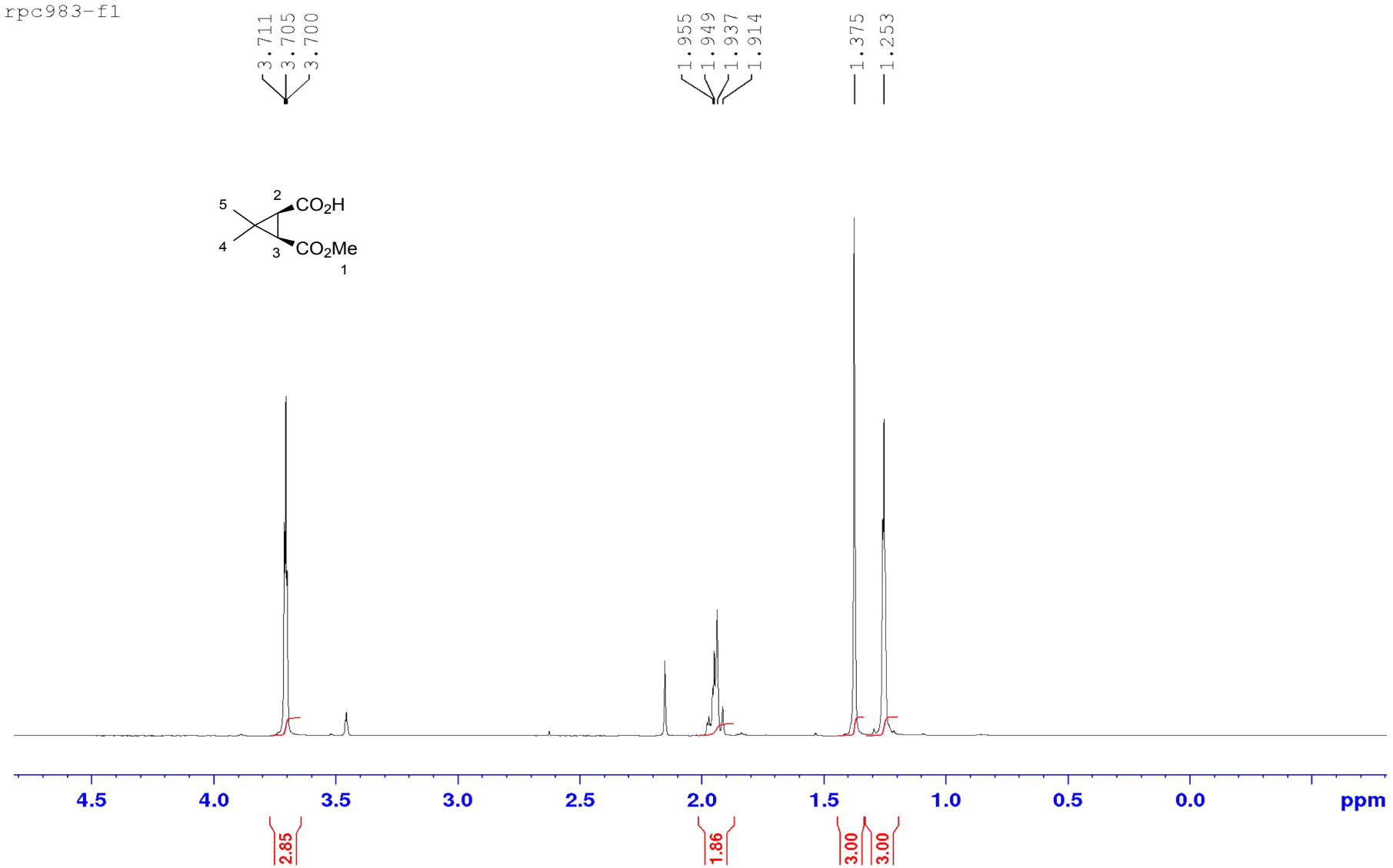
rpc965-product



Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid monomethyl ester (43)

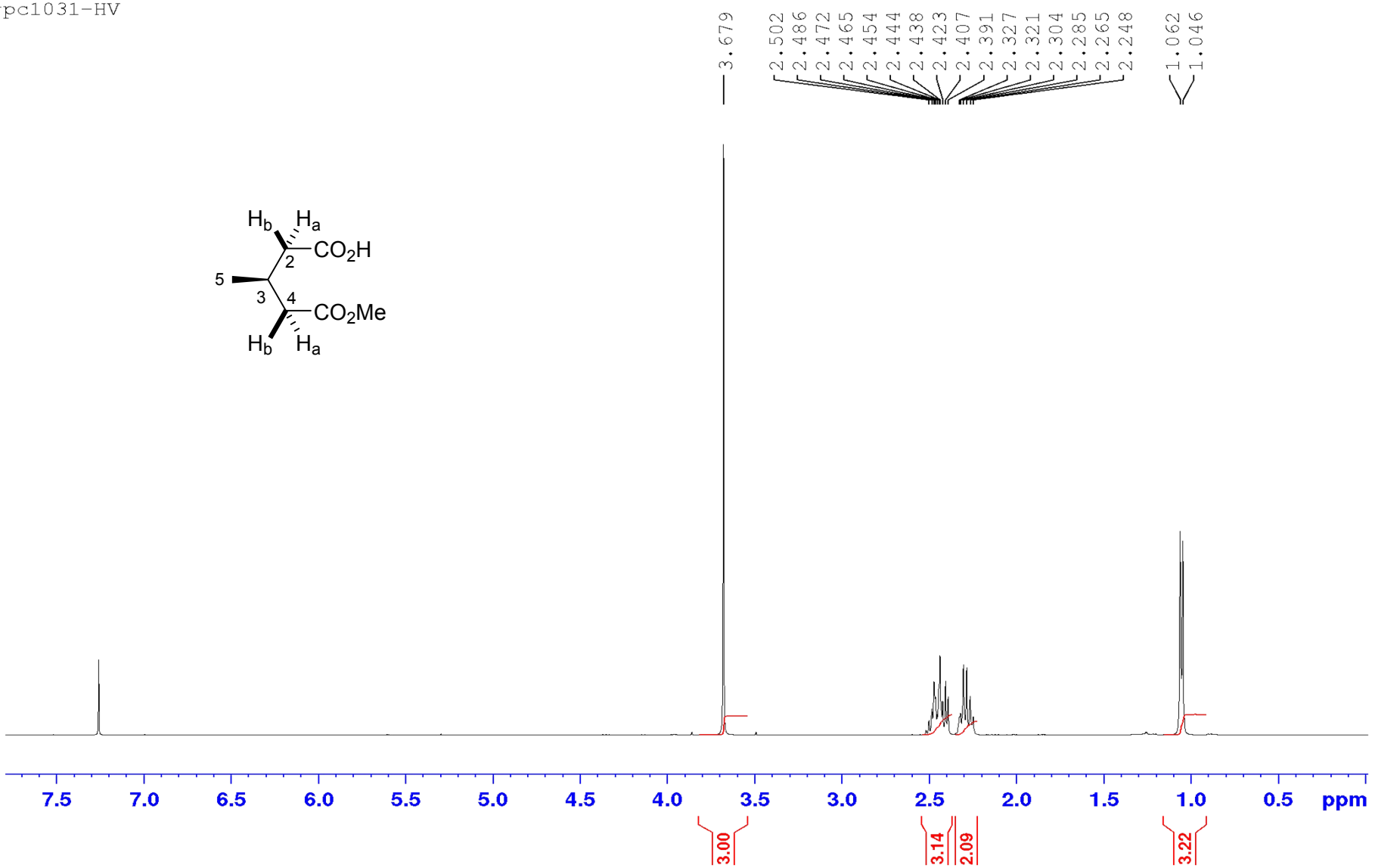


2,2-dimethylcyclopropane-1-dicarboxylic acid monomethyl ester (47)

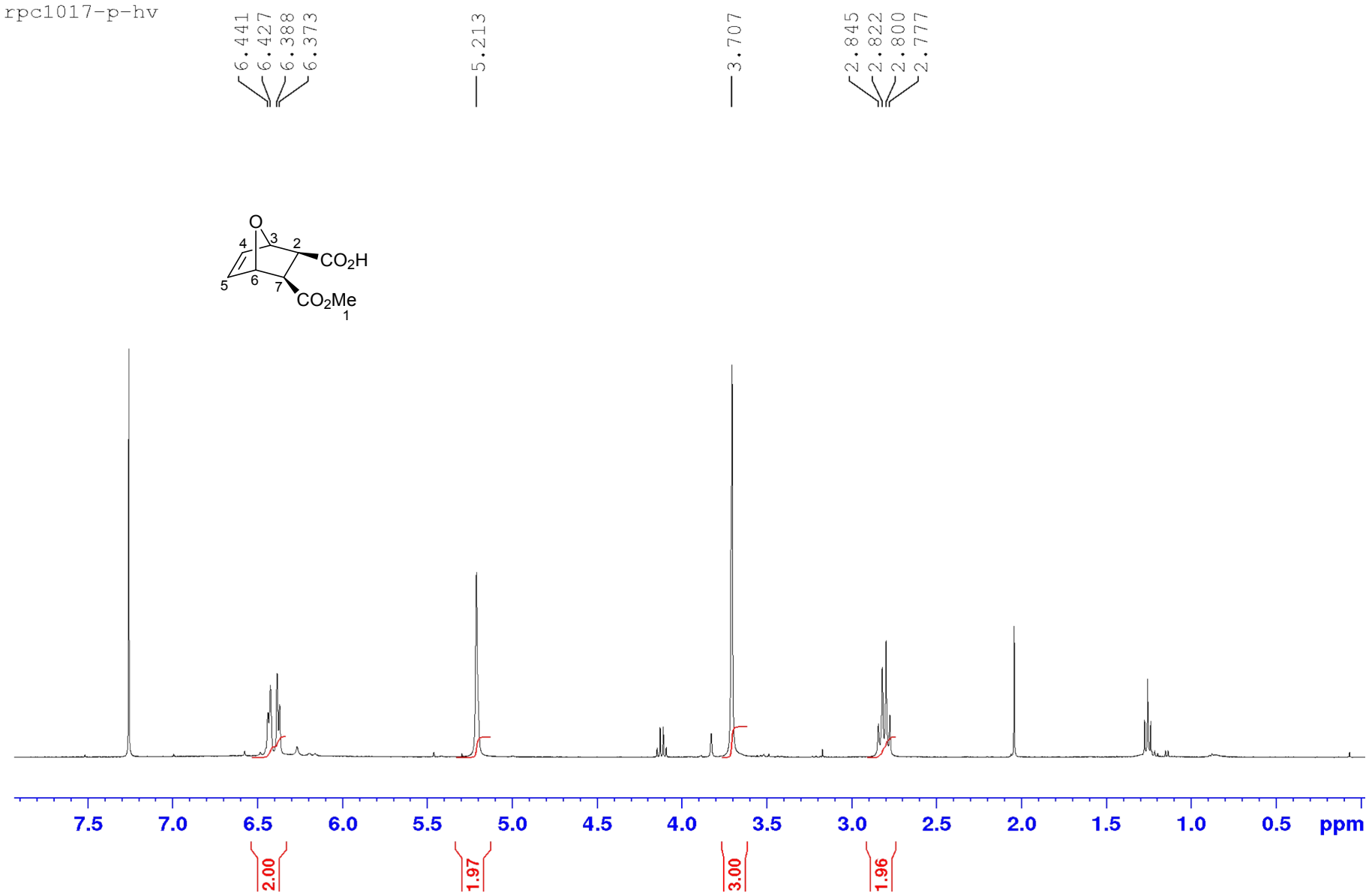


3-methyl-pentanedioic acid monomethyl ester (48)

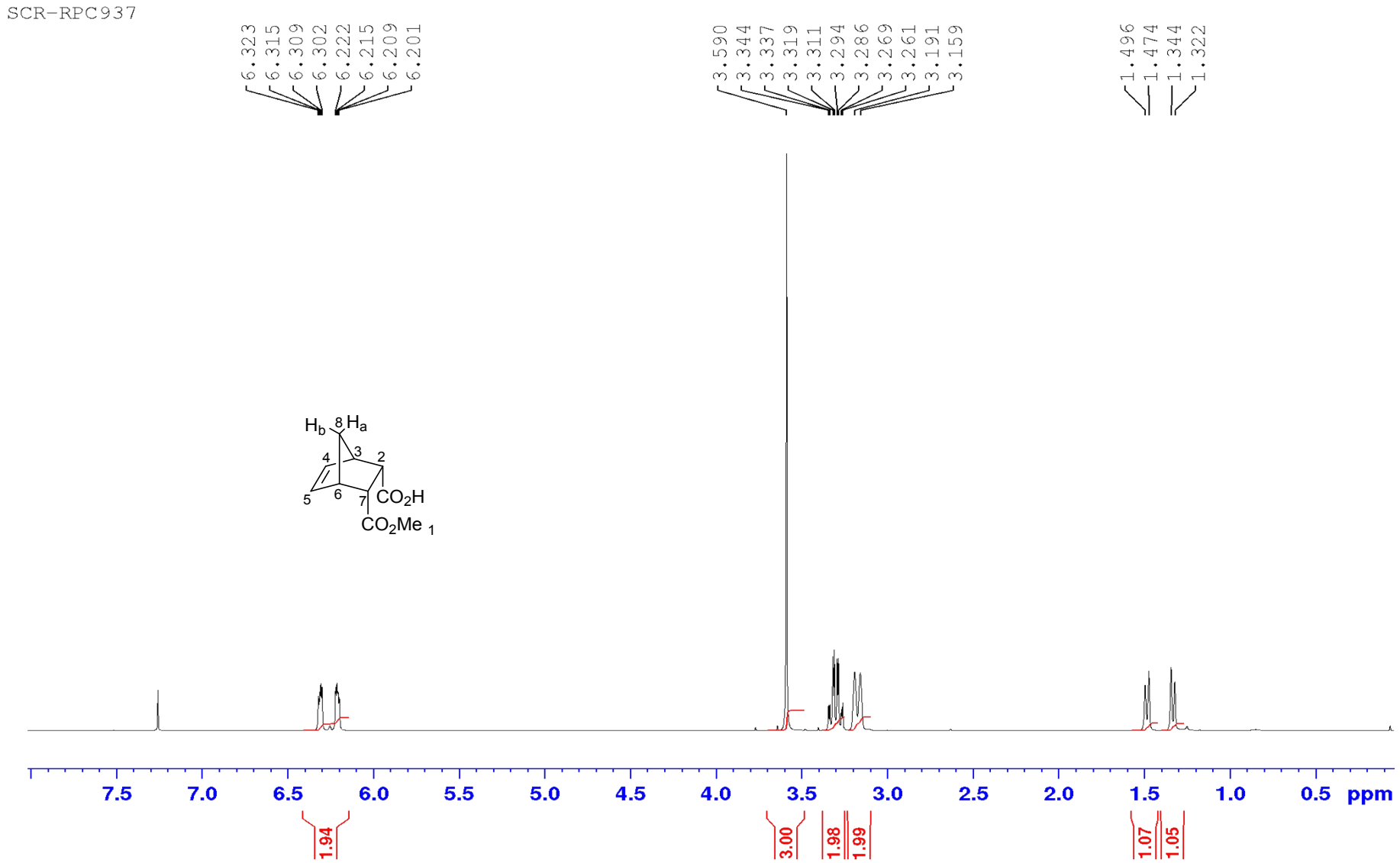
rpc1031-HV



7-oxa-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid monomethyl ester (44)

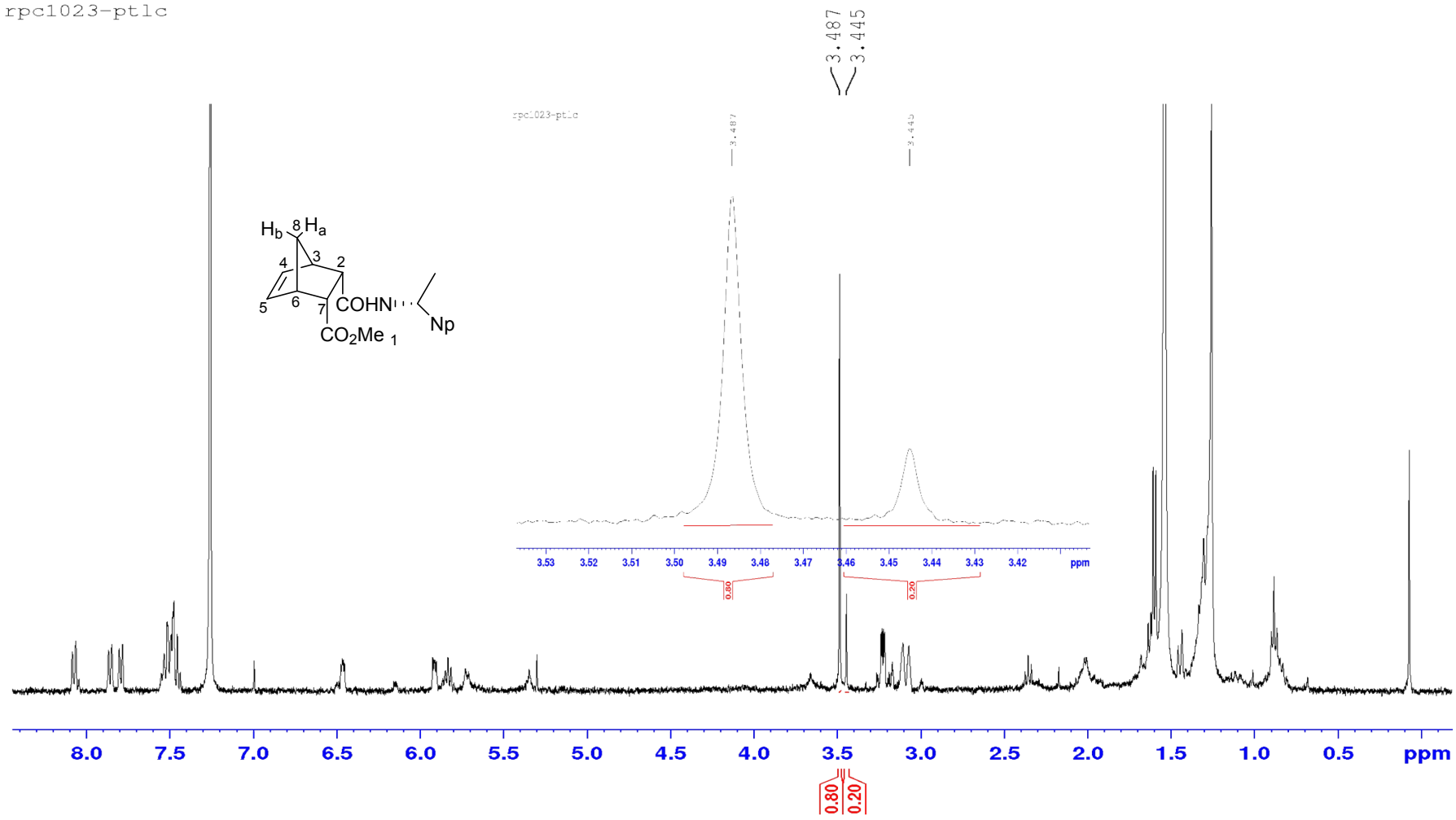


Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid monomethyl ester (15)

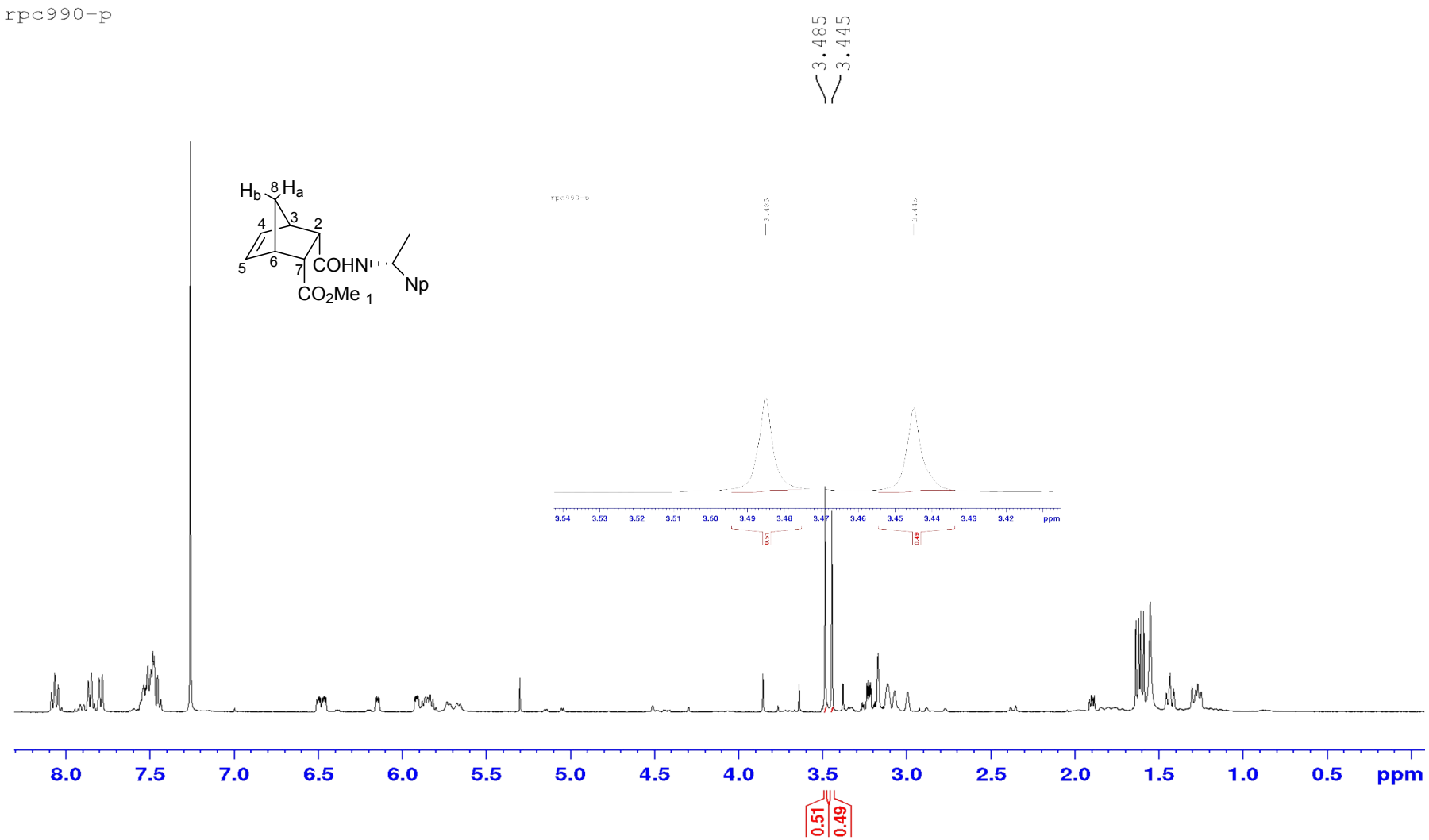


Determination of enantiomeric excess by NMR spectroscopy

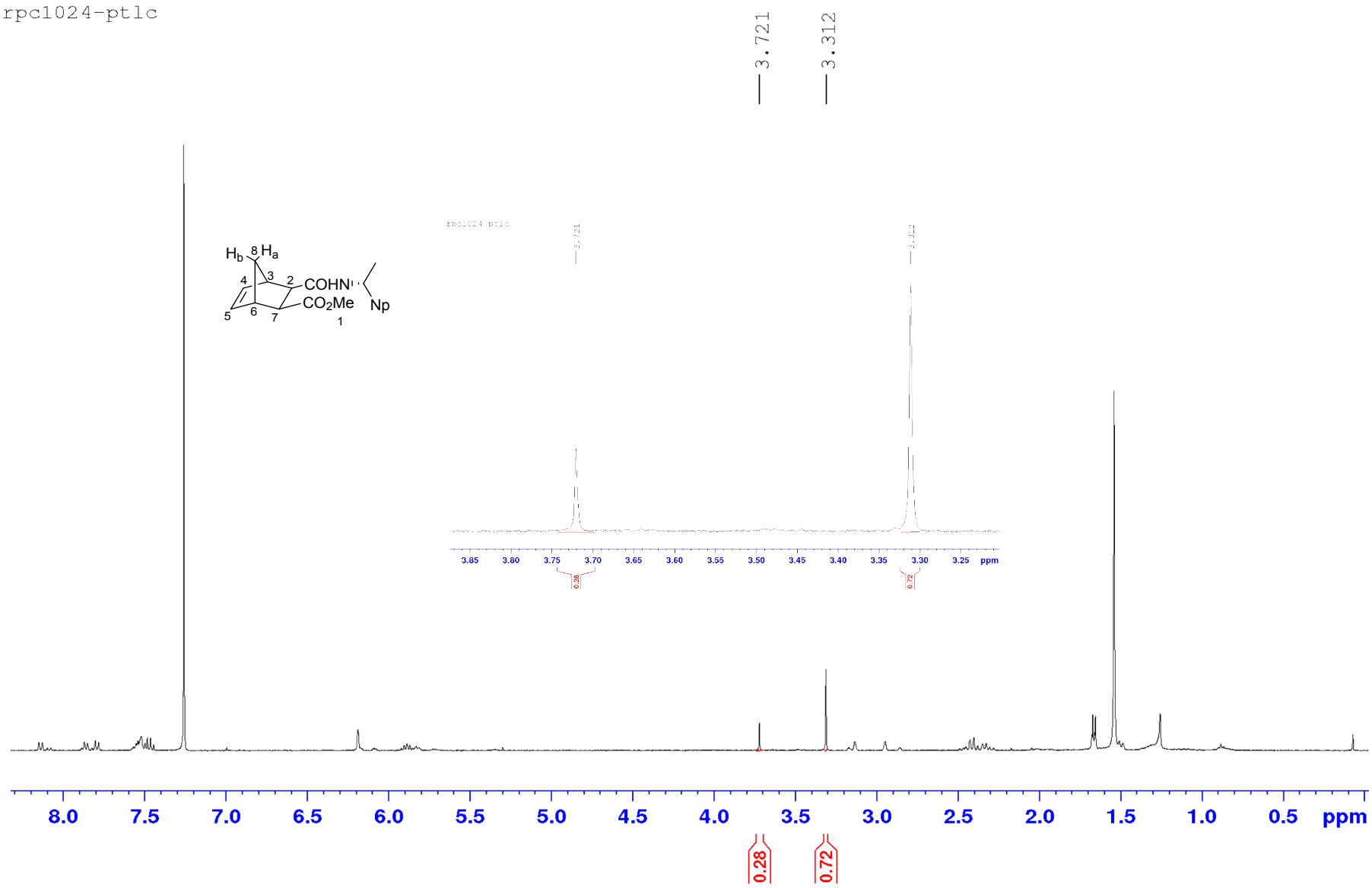
^{1}H NMR of the diastereoisomeric mixture after hemiester derivatisation ($CDCl_3$). (Table 3, entry 1, 61% *ee*)



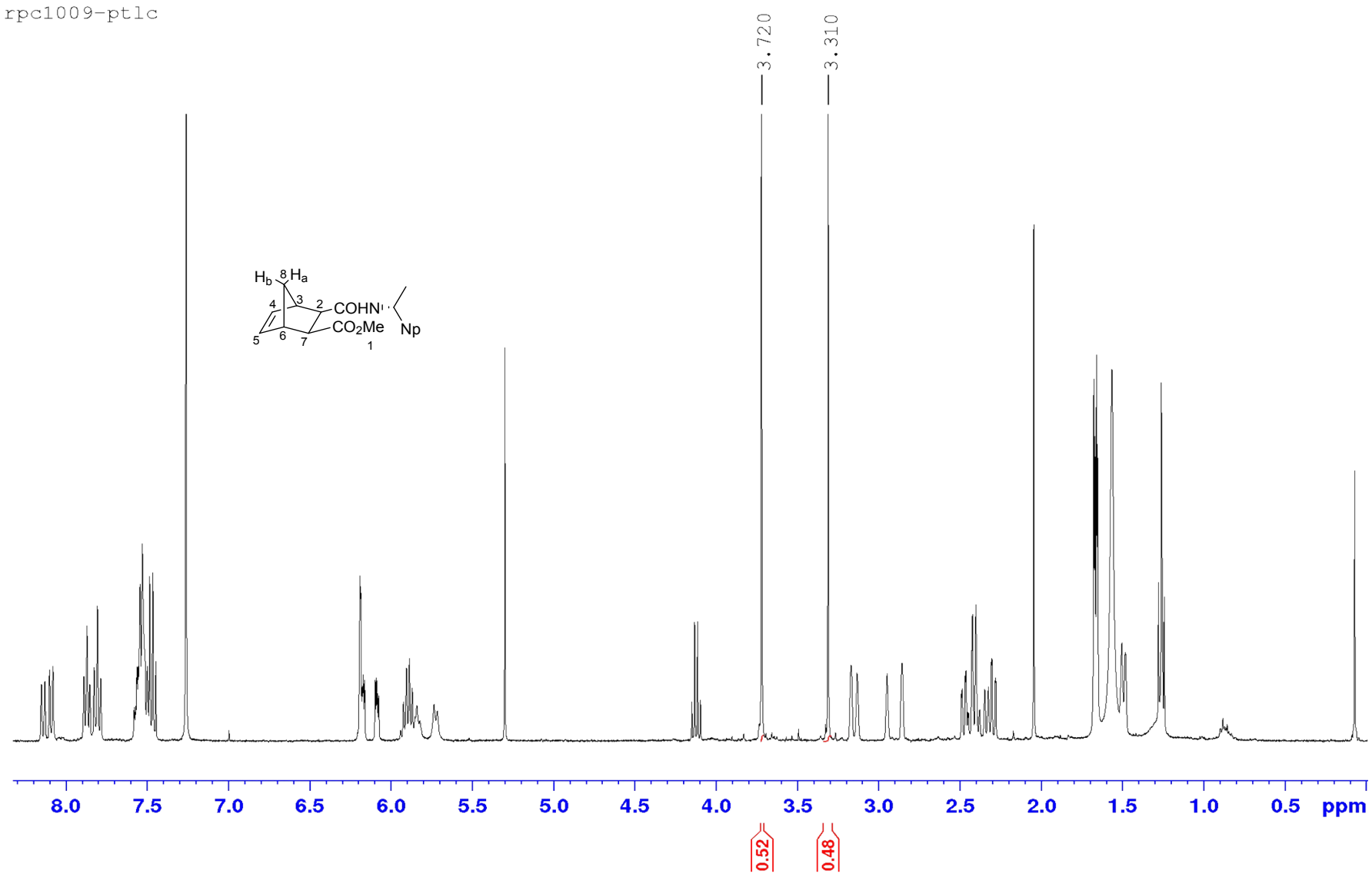
^{1}H NMR of the diastereoisomeric mixture after derivatisation of the racemic hemiester ($CDCl_3$)



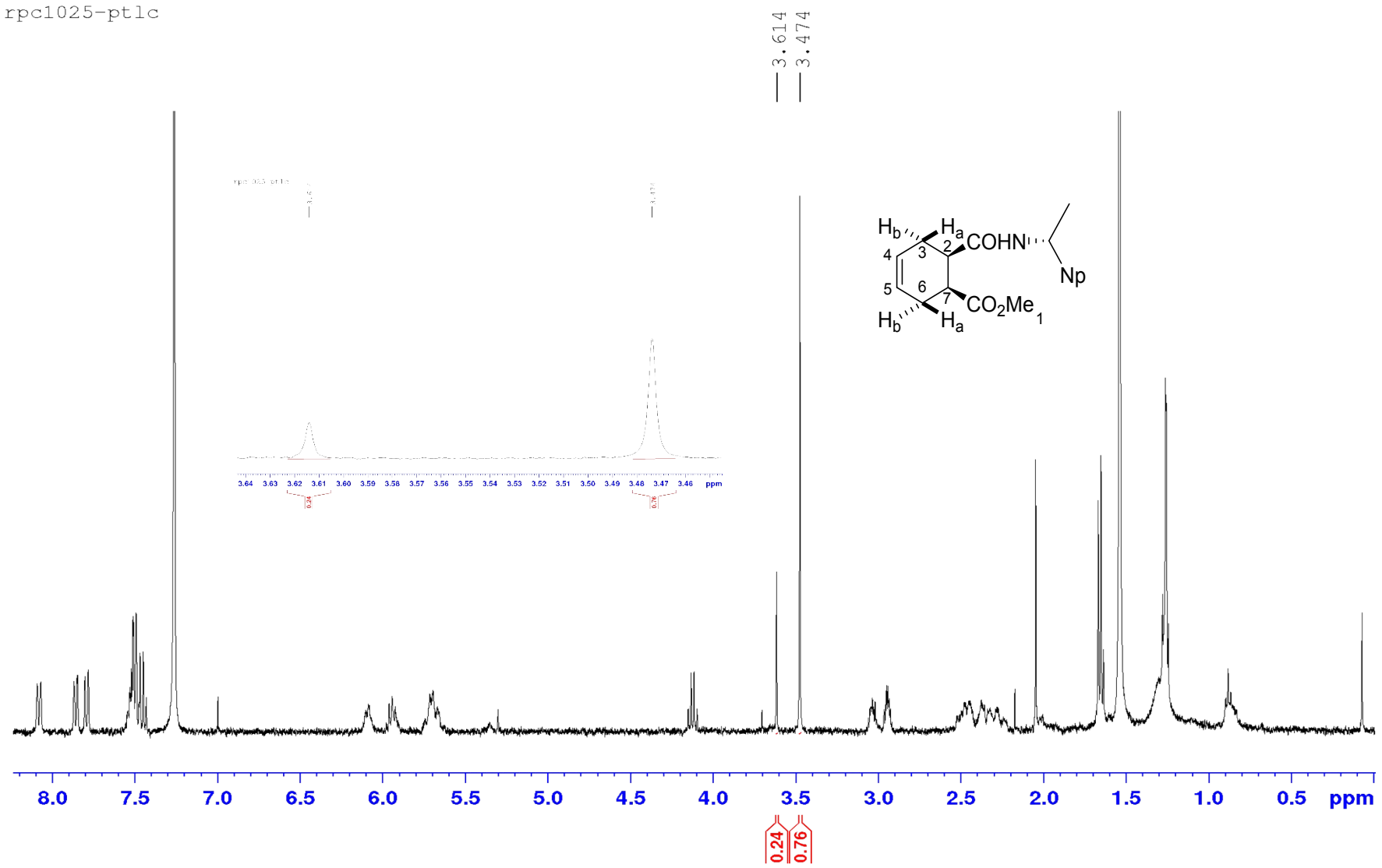
^{1}H NMR of the diastereoisomeric mixture after hemiester derivatisation ($CDCl_3$). (Table 3, entry 2, 44% *ee*)



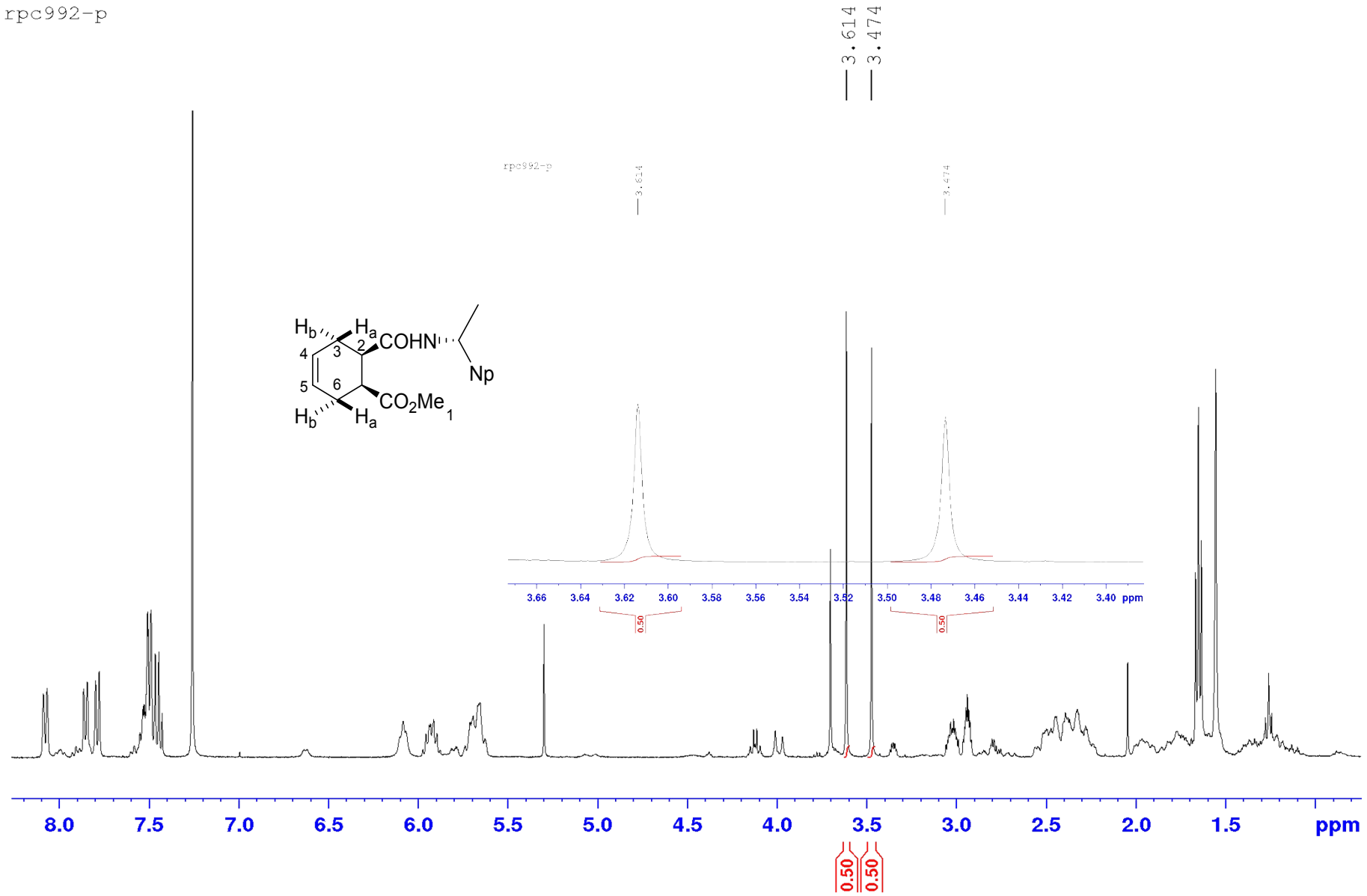
^{1}H NMR of the diastereoisomeric mixture after derivatisation of the racemic hemiester ($CDCl_3$)



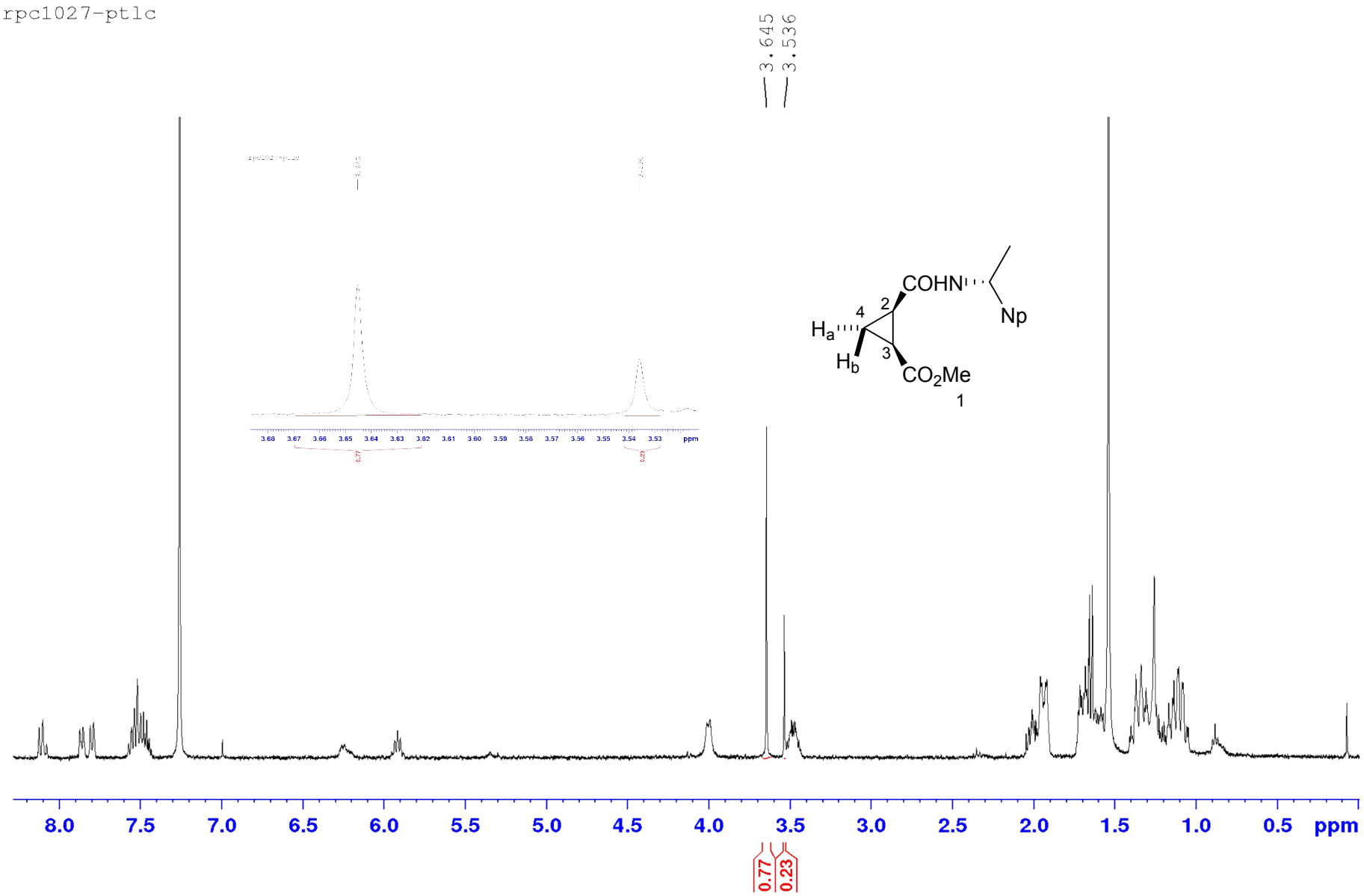
^{1}H NMR of the diastereoisomeric mixture after hemiester derivatisation ($CDCl_3$). (Table 3, entry 4, 51% *ee*)



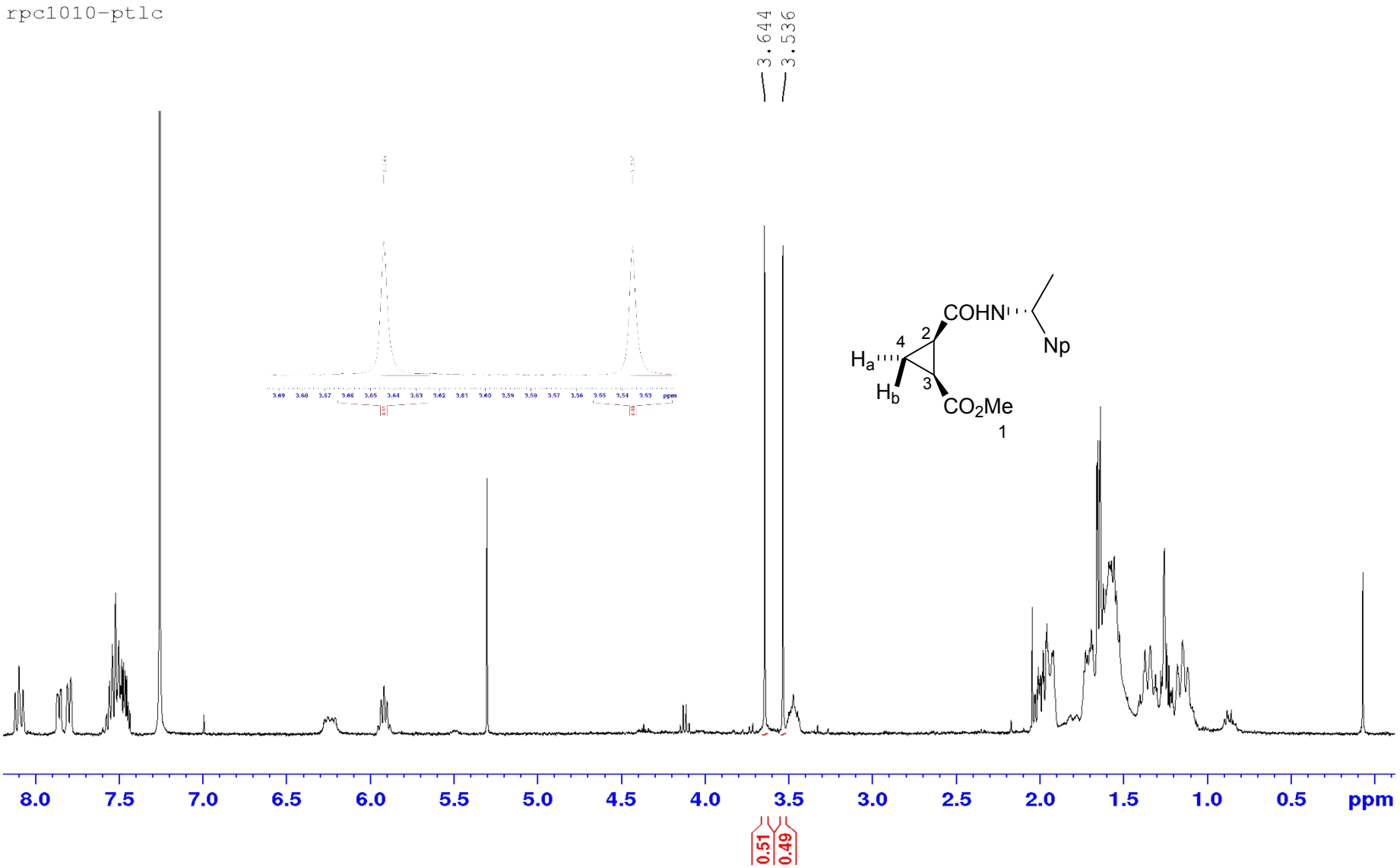
^{1}H NMR of the diastereoisomeric mixture after derivatisation of the racemic hemiester ($CDCl_3$)



^{1}H NMR of the diastereoisomeric mixture after hemiester derivatisation ($CDCl_3$). (Table 3, entry 5, 54% *ee*)

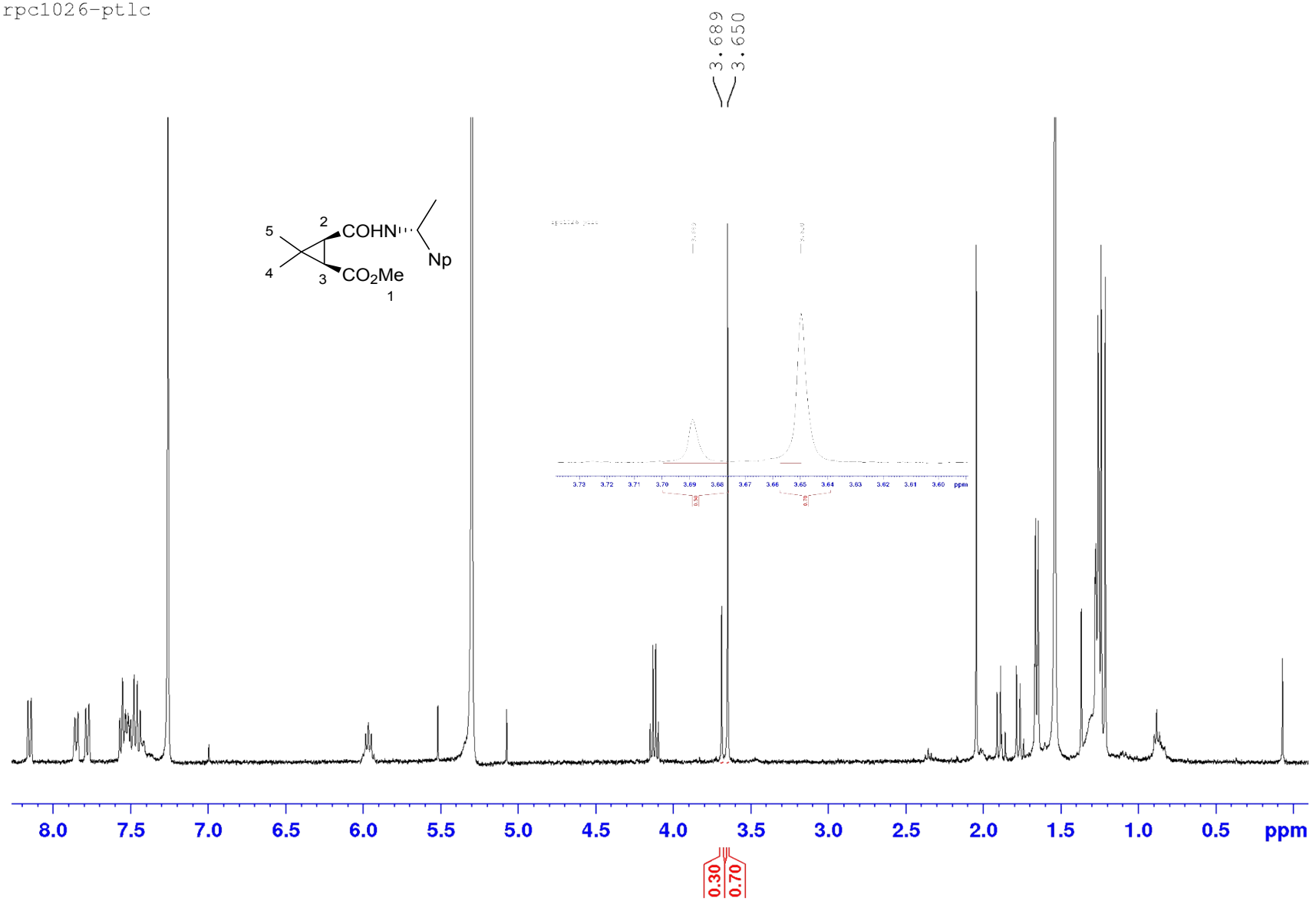


^{1}H NMR of the diastereoisomeric mixture after derivatisation of the racemic hemiester ($CDCl_3$)

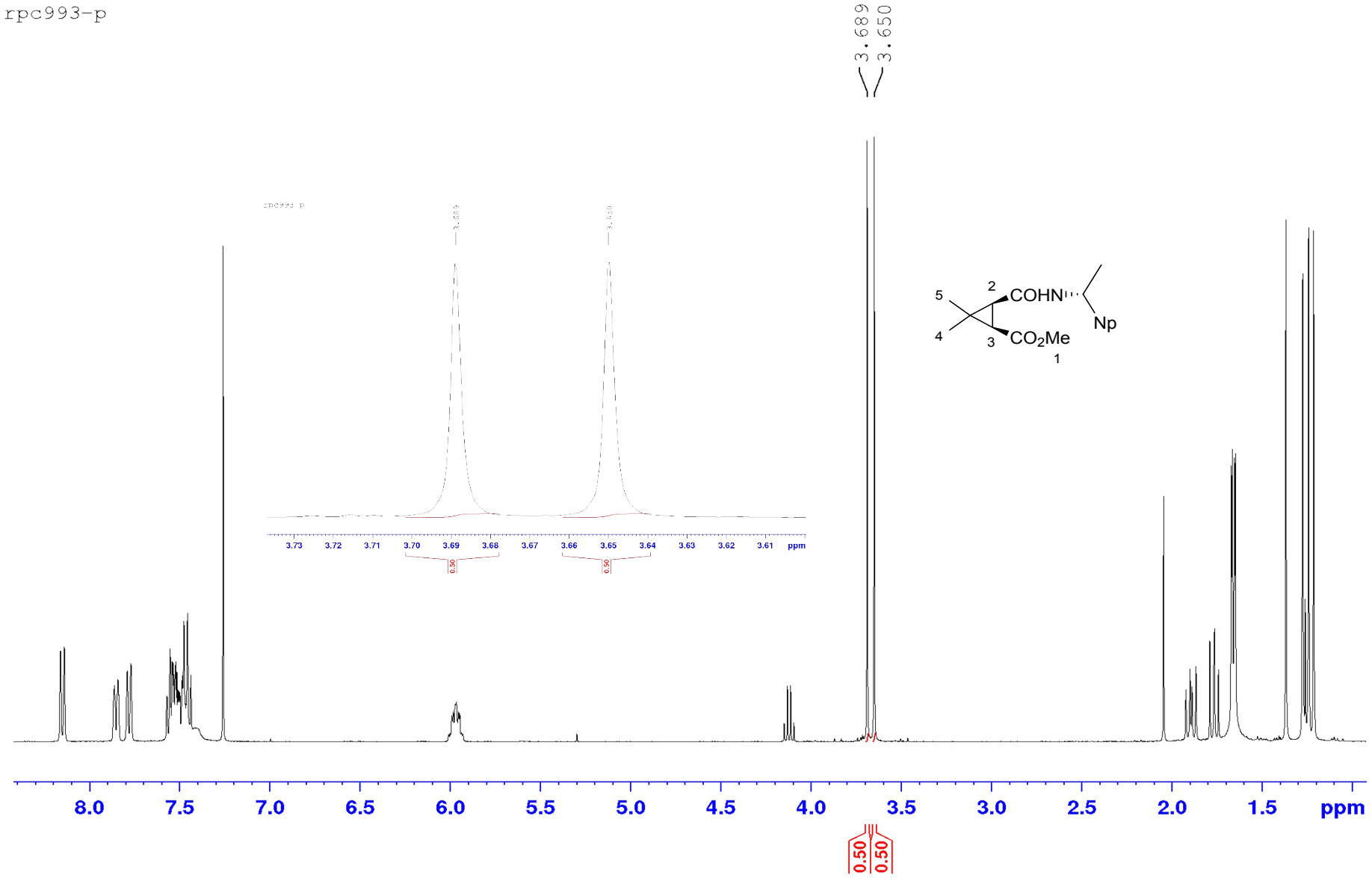


^{1}H NMR of the diastereoisomeric mixture after hemiester derivatisation ($CDCl_3$). (Table 3, entry 6, 39% *ee*)

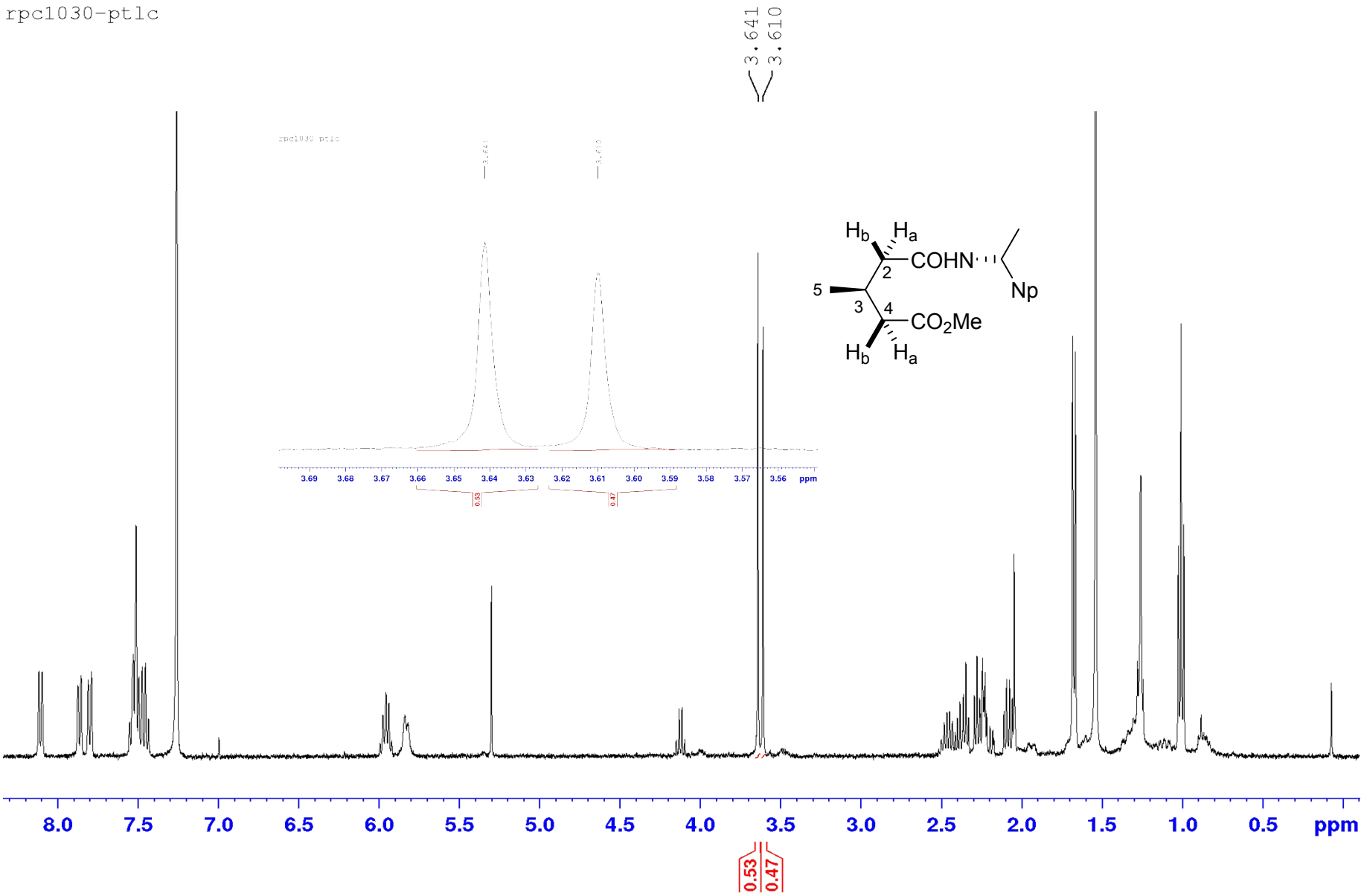
rpc1026-ptlc



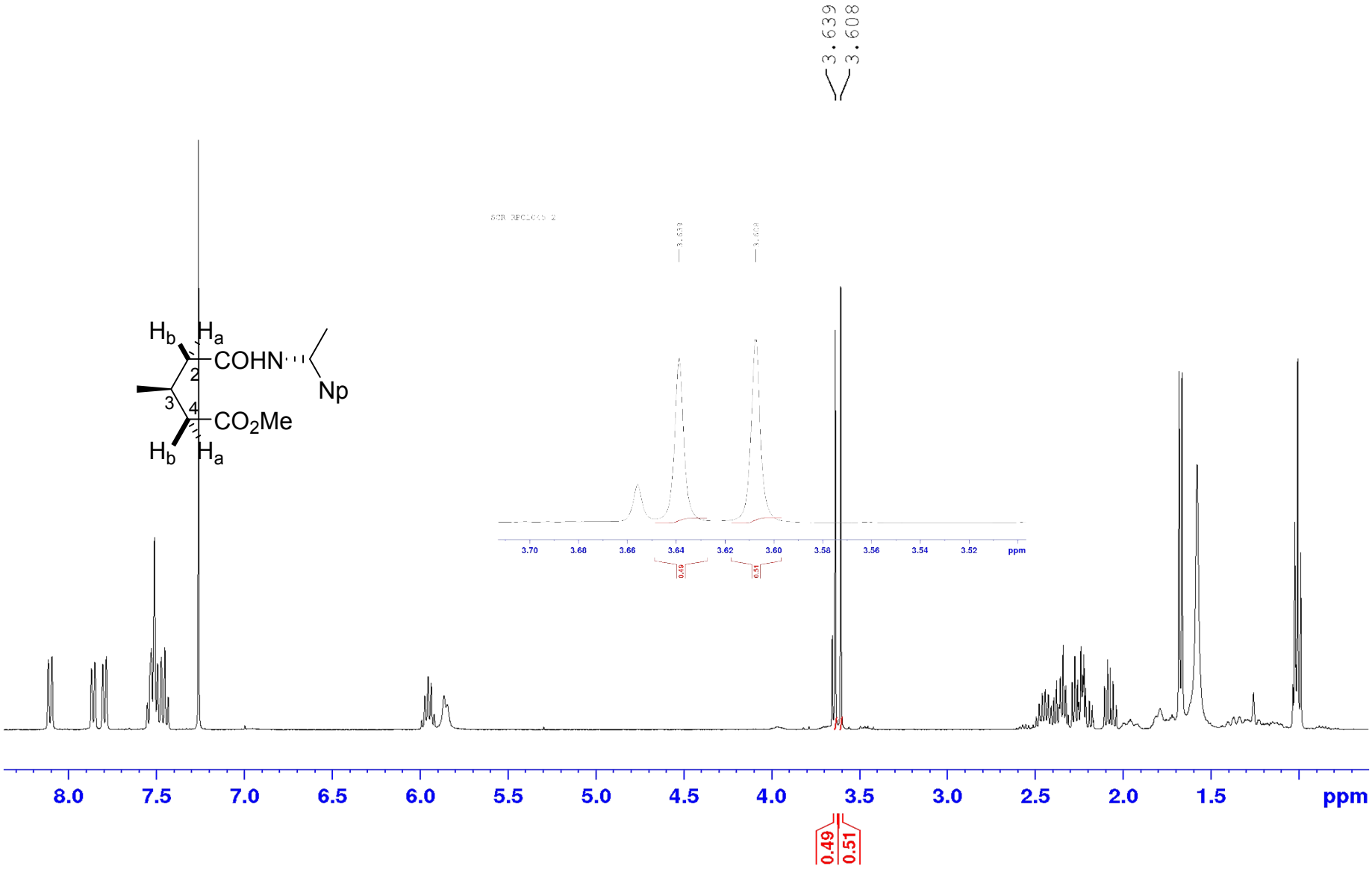
^{1}H NMR of the diastereoisomeric mixture after derivatisation of the racemic hemiester ($CDCl_3$)



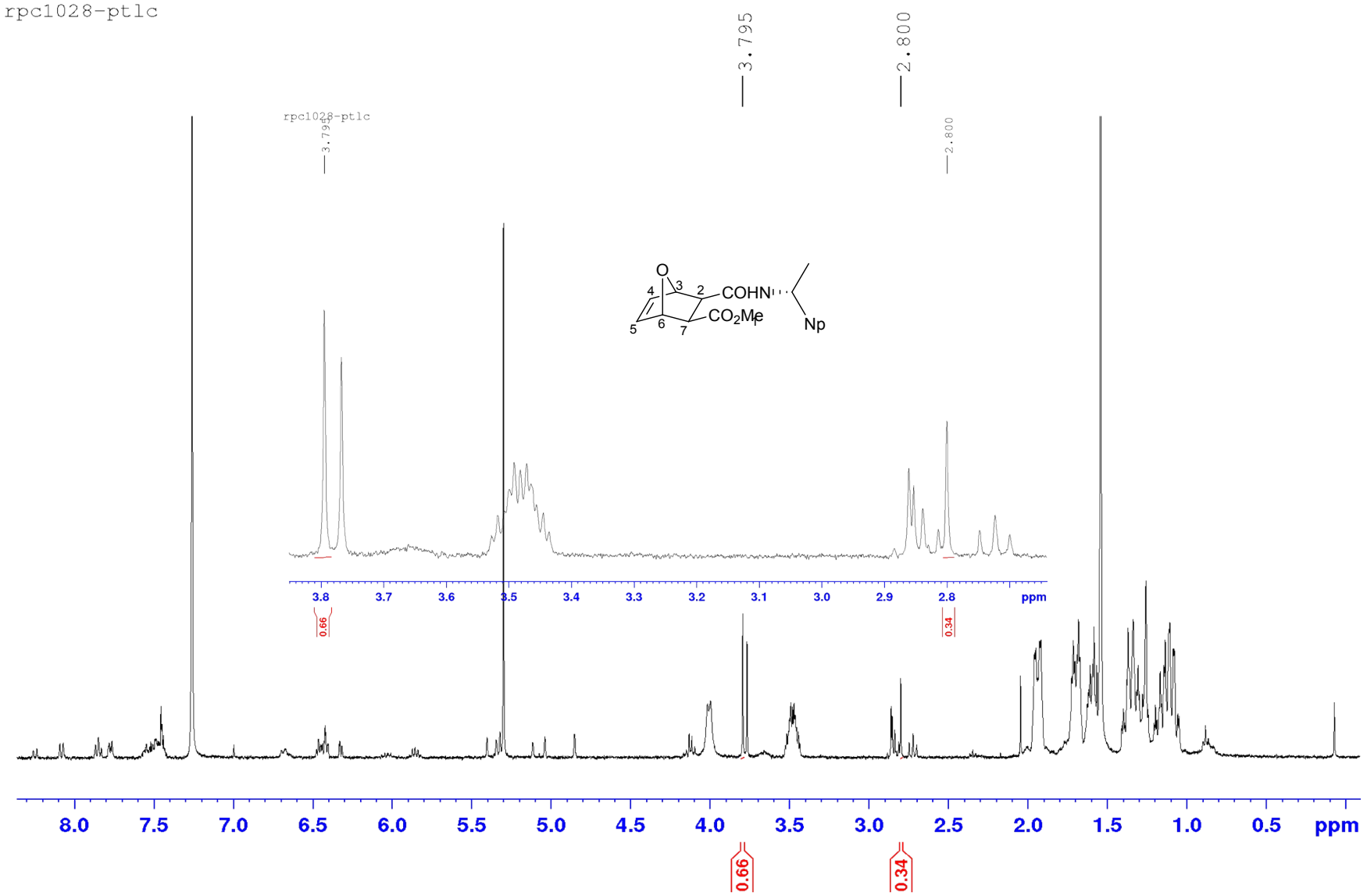
^{1}H NMR of the diastereoisomeric mixture after hemiester derivatisation ($CDCl_3$). (Table 3, entry 7, 6% *ee*)



^{1}H NMR of the diastereoisomeric mixture after derivatisation of the racemic hemiester ($CDCl_3$)

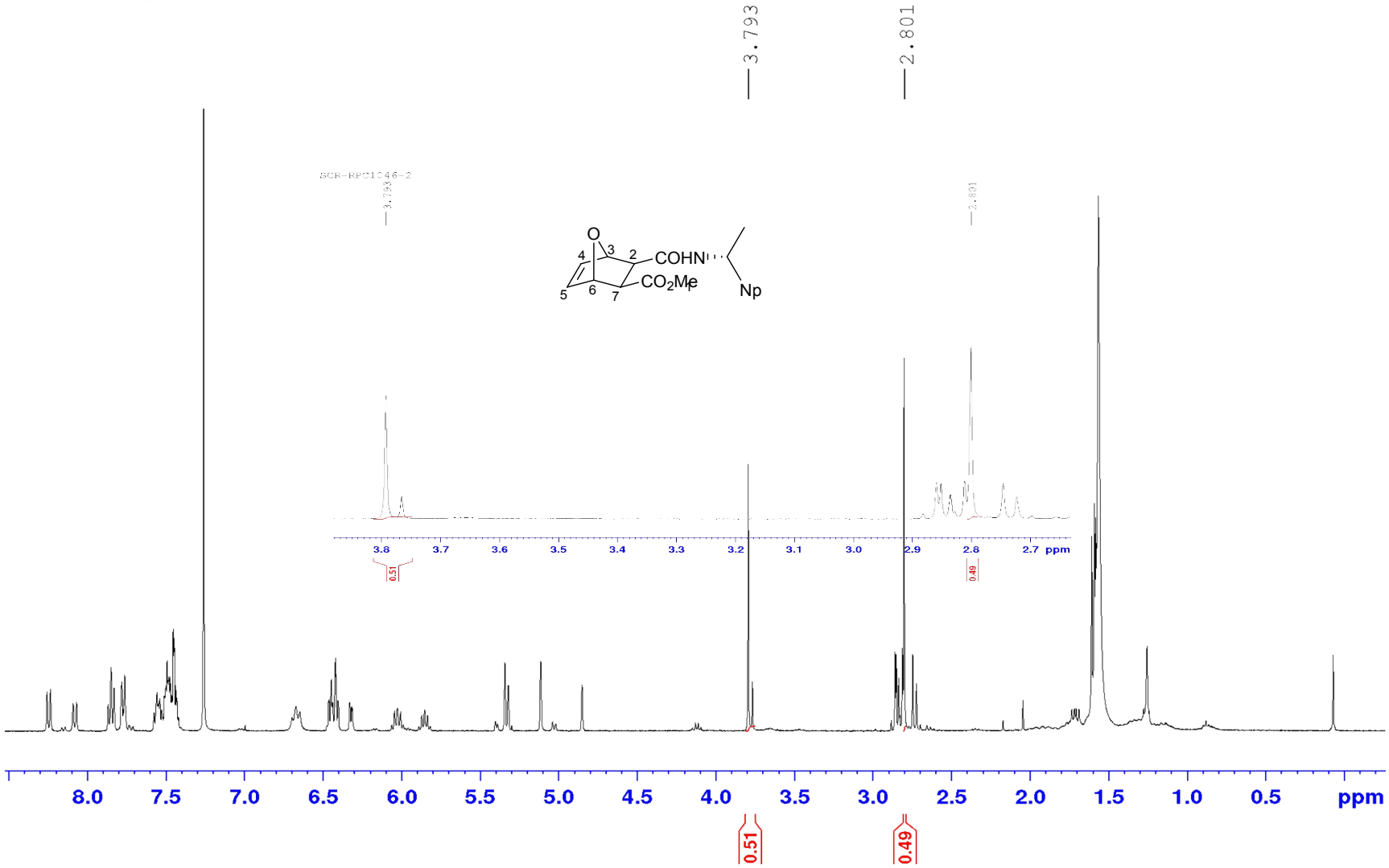


^{1}H NMR of the diastereoisomeric mixture after hemiester derivatisation ($CDCl_3$). (Table 3, entry 3, 33% *ee*)

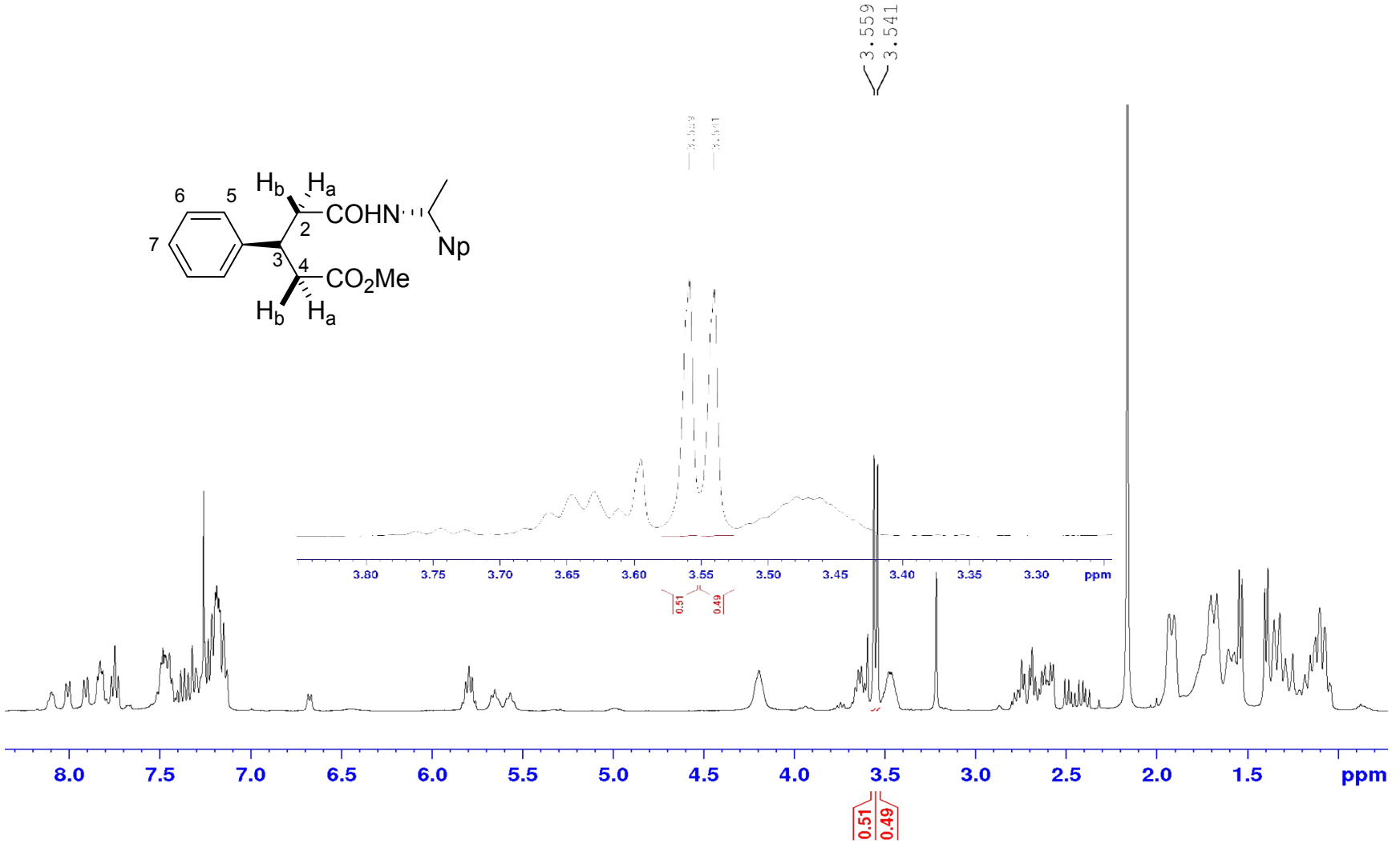


^{1}H NMR of the diastereoisomeric mixture after derivatisation of the racemic hemiester ($CDCl_3$)

SCR-RPC1046-2

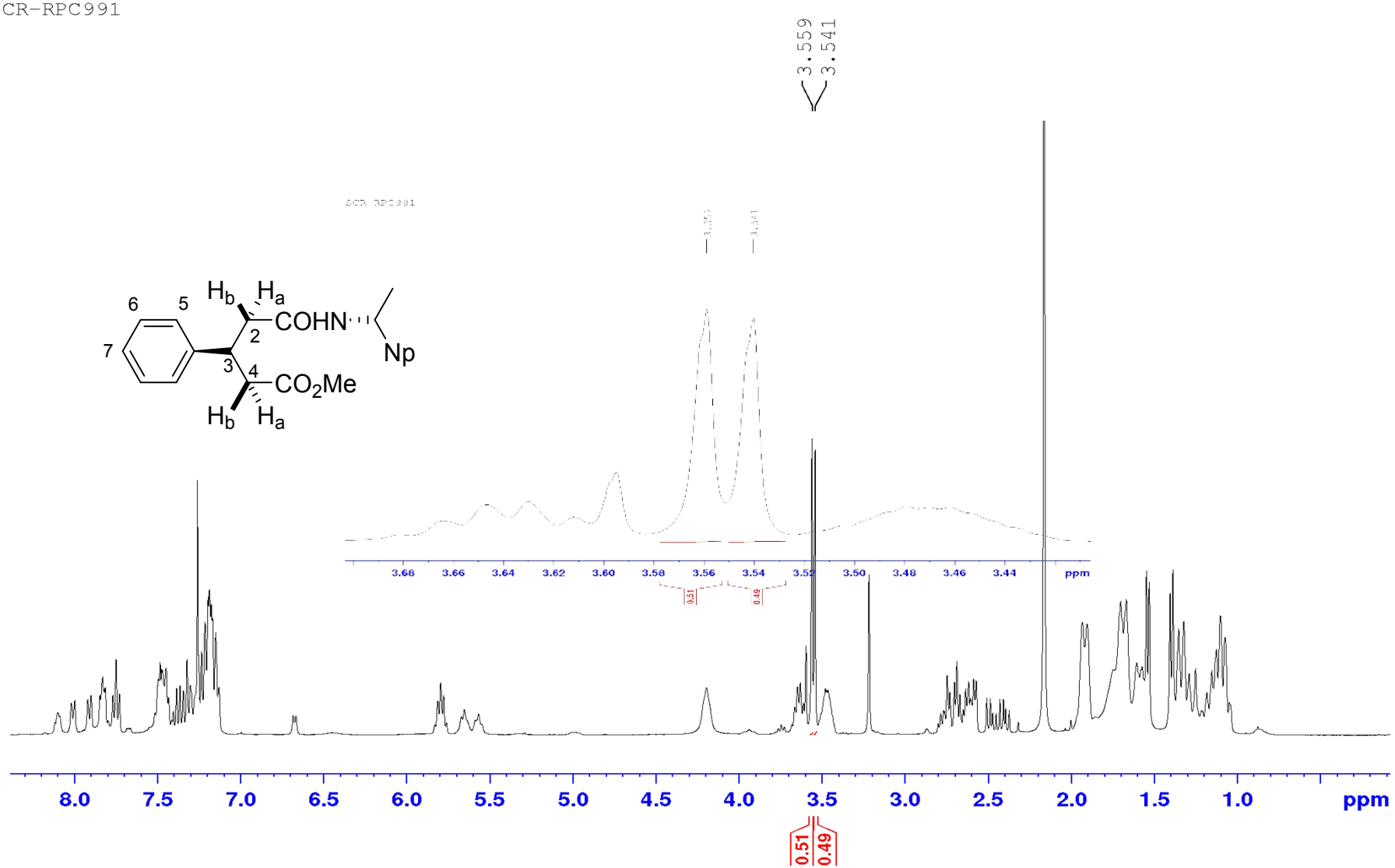


^{1}H NMR of the diastereoisomeric mixture after hemiester derivatisation ($CDCl_3$). (Table 3, entry 8, 0% *ee*)



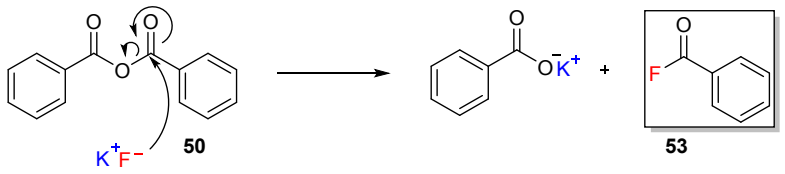
^{1}H NMR of the diastereoisomeric mixture after derivatisation of the racemic hemiester ($CDCl_3$)

SCR-RPC991



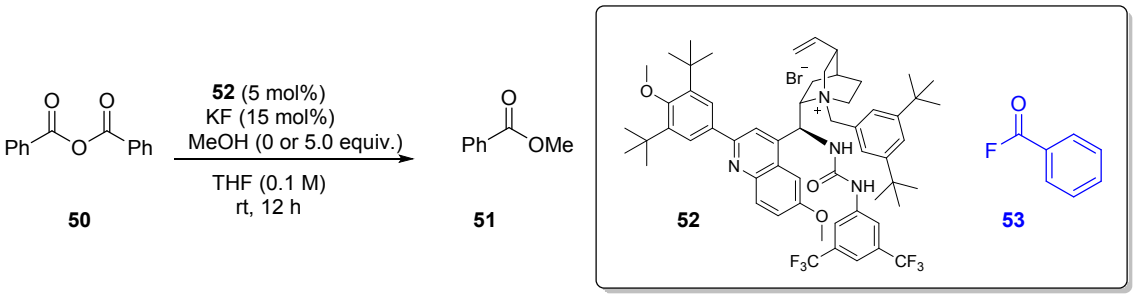
Nucleophilic catalysis: proof of concept

We elected to use benzoic anhydride (**50**) as a model compound. Attack on its acyl centre by fluoride would generate benzoyl fluoride (**53**, Scheme 1); a known compound, the existence of which *in situ* could be identified by spectroscopic methods.



Scheme 1 Generation of benzoyl fluoride by nucleophilic attack of fluoride on benzoic anhydride.

To mimic the reaction conditions utilised in Table 2, a catalytic amount of KF would be required in the presence of a chiral bifunctional phase-transfer catalyst (Scheme 2).



Scheme 2 Experiment designed to detect the acyl fluoride intermediate under catalytically relevant conditions.

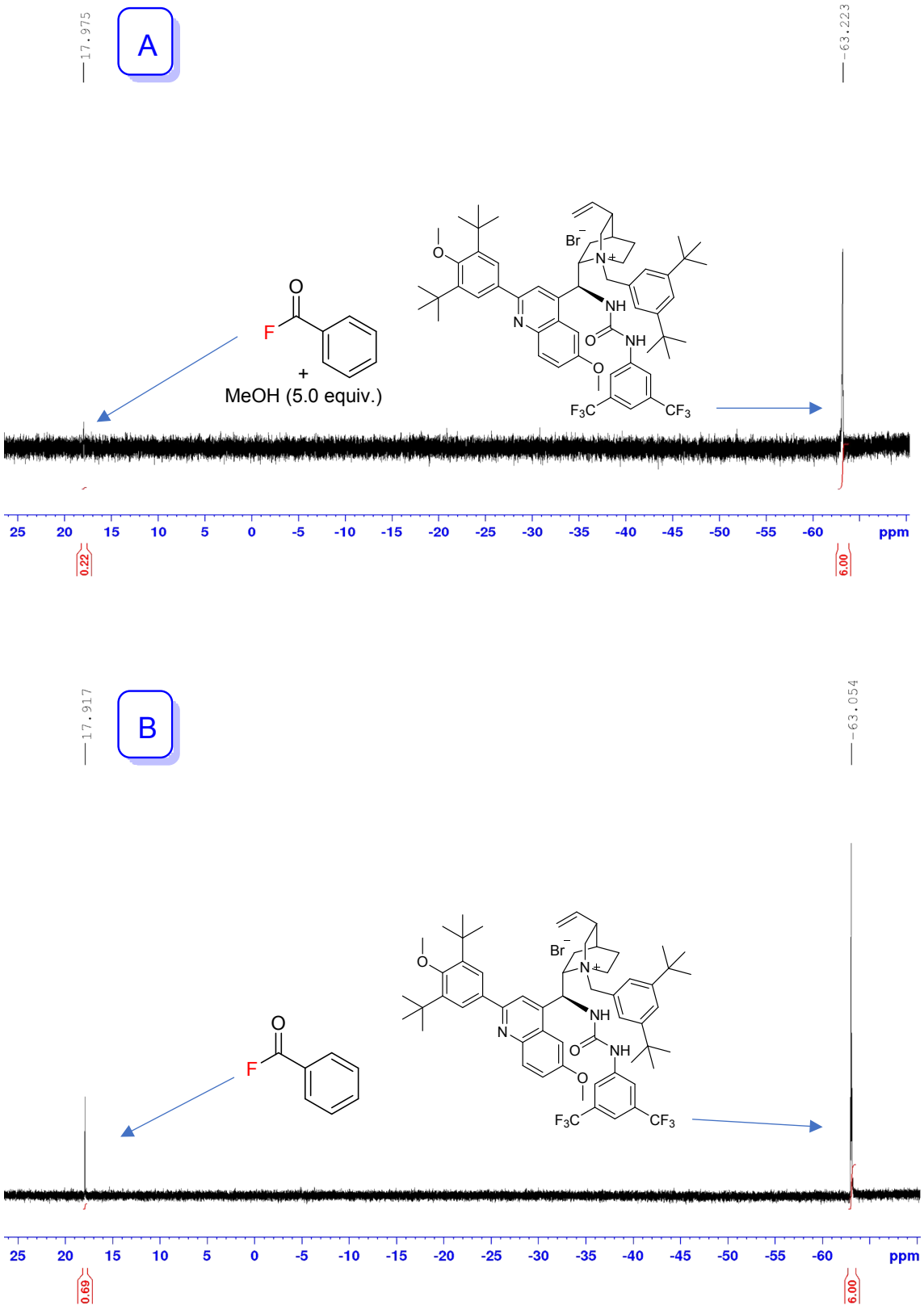


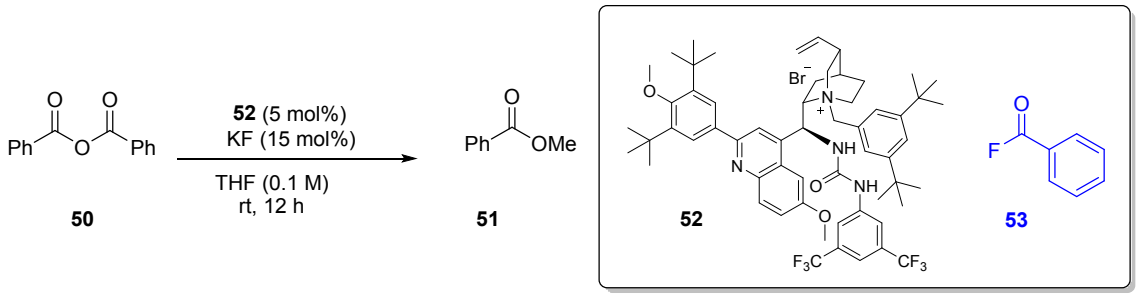
Figure 1 Observation of benzoyl fluoride in the ^{19}F NMR spectrum of reactions both with (**A**) and without (**B**) methanol.

The reaction was carried out with and without MeOH, and in both instances the characteristic fluorine resonance at ~17.9 ppm was observed albeit at lower levels using five equivalents of

MeOH. This was to be expected as methanol solvates the fluoride anion, thereby decreasing its nucleophilicity (Figure 1) and also destroys the acyl fluoride by methanolysis.

The same reaction, devoid of both phase-transfer catalyst and methanol, failed to produce any acyl fluoride. The reaction was also attempted using TBAB, to ascertain the importance of the hydrogen bond-donating subunit in catalysts such as **13**. Acyl fluoride formation was detected, albeit in very small amounts (<2%), which suggested that the catalyst's hydrogen bond donating moieties may assist in the phase transfer of fluoride ion.

Theoretically, the maximum amount of benzoyl fluoride capable of forming in solution was 15% (as 15 mol% of KF was employed). The reaction below was carried out and samples were taken periodically and analysed by ^{19}F NMR spectroscopic techniques (using one equivalent of fluorobenzene as the internal standard). The results were conclusive: with 15% of benzoyl fluoride formed after 265 min, with no further change after 12 h reaction (**Figure**).



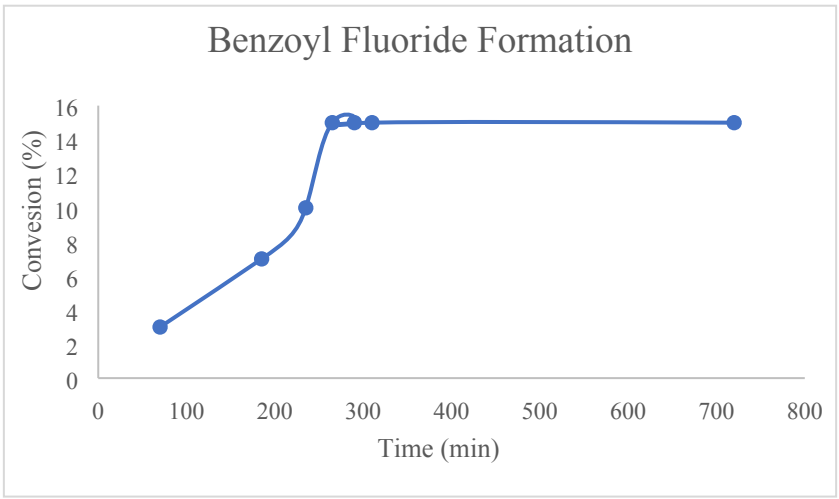
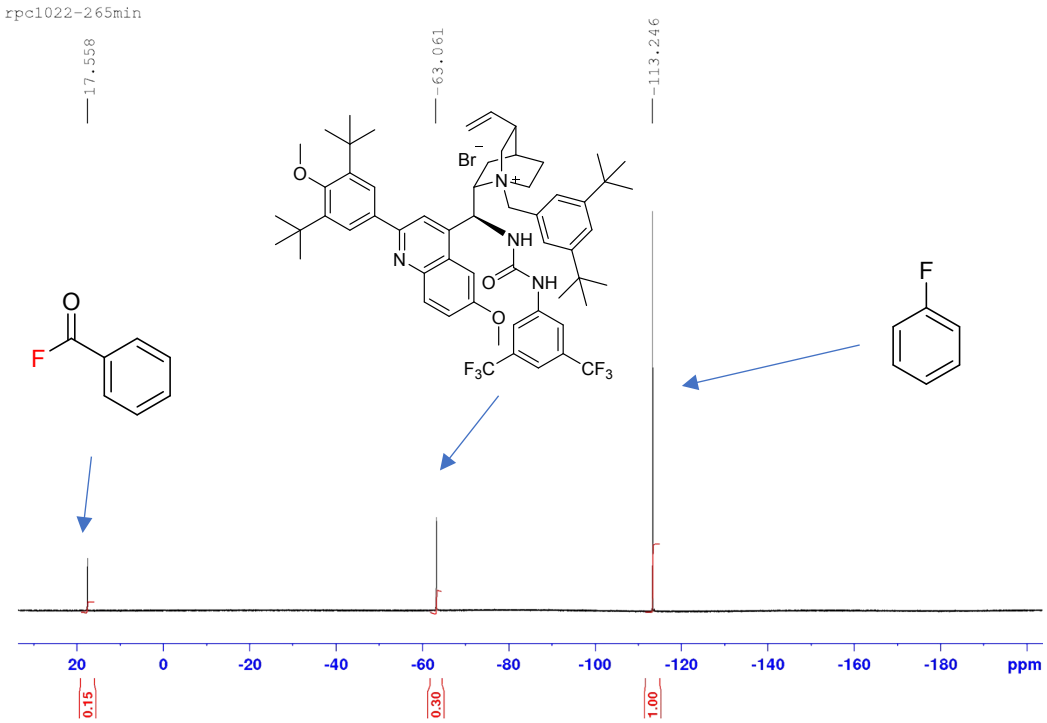
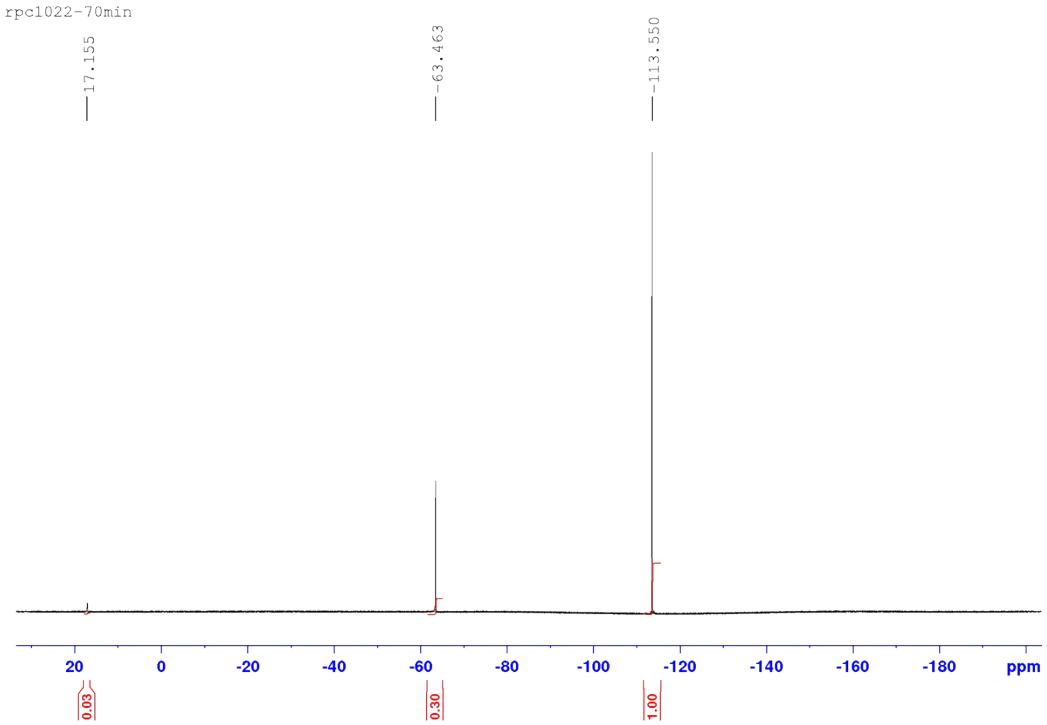


Figure 2 Formation of benzoyl fluoride over a 12 h period.

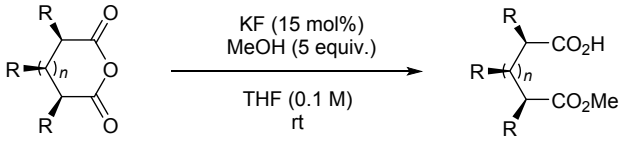
Benzoyl fluoride formation: ^{19}F NMR spectroscopic analysis (t = 265 min)

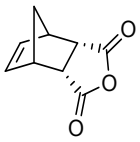
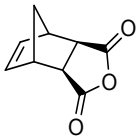
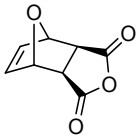
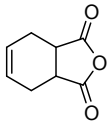
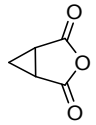
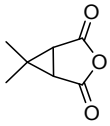
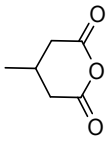
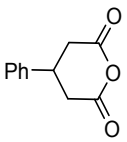


^{19}F NMR spectroscopic analysis (t = 70 min)



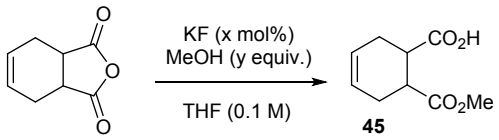
Control reactions of different *meso*-anhydrides in the absence of PTC



entry	anhydride	time (h)	temp (°C)	conv. (%)[a]
1		48	25	0
2		48	25	98
3		48	25	0
4		48	25	100
5		48	25	0
6		48	25	0
7		a) 24 b) 24 c) 48	a) 25 b) 0 c) -10	72[b] 15 22
8		48	25	100

[a]Conversion determined by ^{1}H NMR spectroscopy. [b]5 mol% of KF used

Varying amounts of KF and MeOH in an attempt to obviate the background reaction.



45

entry	time (h)	loading (x)	MeOH (y)	conv. (%)[a]
1	24	15	1	30
2	24	5	5	71
3	24	5	1	48
4	18	1	1	42
5	18	0	5	24

[a]Conversion determined by ^{1}H NMR spectroscopy.

References

1. C. Cornaggia, F. Manoni, E. Torrente, S. Tallon and S. J. Connon, *Org. Lett.*, 2012, **14**, 1850–1853.
2. A. Lee, C. M. Reisinger and B. List, *Adv. Synth. Catal.*, 2012, **354**, 1701–1706
3. A. Peschiulli, Y. Gunko and S. J. Connon, *J. Org. Chem.*, 2008, **73**, 2454–2457
4. C. Bolm, I. Schiffers, C. L. Dinter and A. Gerlach, *J. Org. Chem.,* 2000, **65**, 6984–6991.
5. J. A. K. Peter E. Reed, *J. Med. Chem.*, 1991, **34**, 1162–1176.