Electronic Supplementary Material (ESI) for Chemical Communications

Highly tunable arylated cinchona alkaloids as bifunctional catalysts

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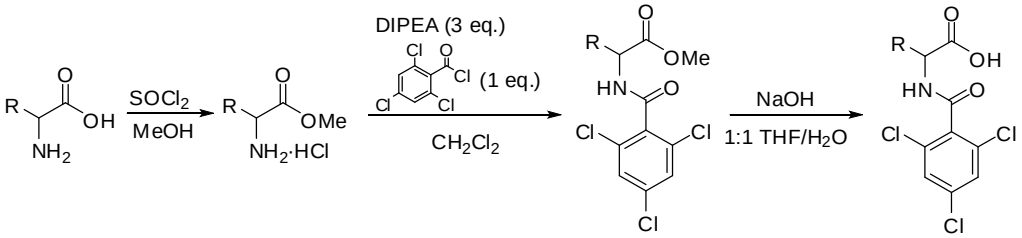
1 General

Proton Nuclear Magnetic Resonance spectra were recorded on a 400 MHz or 600MHz spectrometer in $CDCl_3$, C_6D_6 or DMSO-d_6 and referenced relative to residual $CHCl_3$ (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm). Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hertz. Carbon NMR spectra were recorded on the same instruments (100 MHz or 150 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 $60F_{254}$ slides, and visualised by UV irradiation and $KMnO_4$ staining. Infrared spectra are reported in frequency of absorption (ν cm^{-1}). Optical rotation measurements ($[\alpha]_D^{20}$) are quoted in units of 10^{-1} deg cm^2 g^{-1}. Unless otherwise stated, all compounds were sourced commercially and used without further purification. Racemic azlactones were obtained following literature procedures from the corresponding commercially available racemic aminoacids and used immediately after purification. Methylene chloride was distilled from calcium hydride and stored under argon. Tetrahydrofuran was distilled over sodiumbenzophenone ketyl radical and stored under argon. Deuterated chloroform was distilled over sodium carbonate and stored under argon. All reactions were carried out under a protective argon atmosphere unless otherwise stated. Analytical CSP-HPLC was performed on a Daicel CHIRALPAK AD-H (4.6 mm x 25 cm) column.

2 Synthesis of the *N*-Protected amino acids:

Valine, Leucine, Methionine and L-Isoleucine with D-allo were sourced commercially. Cyclohexylglycine and 2-amino-3-ethylpentanoic acid were made *via* literature procedure.[1] The aminoacids were converted into their corresponding methyl esters using standard procedures.

2.1 General procedure A for the synthesis of racemic *N*-2,4,6-trichlorobenzoyl amino acids

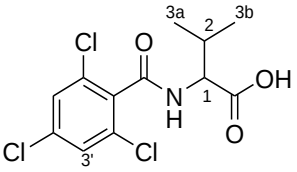


Scheme 1: General procedure for the synthesis of N-protected amino acids

A round bottomed flask containing a solution of the appropriate amino acid methyl ester in CH_2Cl_2 (0.45 M, 1.0 - 1.2 eq.) was cooled to 0 °C, triethylamine or *N,N*-diisopropylethylamine (3.0 eq.) was added followed by 2,4,6-trichlorobenzoyl chloride (1.0 eq.) which was slowly added *via* syringe. After the addition was complete, the reaction was allowed to warm to room temperature and stirred for 16 h. The solution was then diluted further with CH_2Cl_2 (*ca*. 100 mL) and washed with HCl (1 M, *ca*. 50 mL), NaOH (aq. 5% w/v, *ca*. 50 mL)) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and solvent removed *in vacuo.* The resulting material was then placed in a round bottom flask with THF (10 mL/g) and NaOH (aq. 5% w/v, 10 mL/g) and stirred for a further 16 h. The THF was then carefully removed *in vacuo* and the solution acidified by addition of HCl (6 N) and extracted using

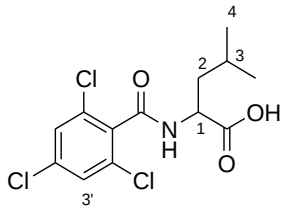
$CHCl_3$ (3 x 80 mL). The organic layers were combined, dried over $MgSO_4$, filtered and solvent removed *in vacuo* to to give the desired *N*-2,4,6-trichlorobenzoyl amino acid.

2,4,6-Trichloro-*N*-benzoyl valine (43a)



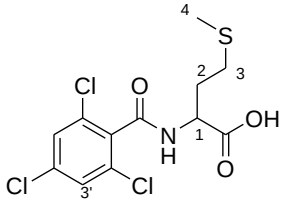
Procedure A was followed using DL-valine methyl ester (1.18 g, 9.02 mmol), 2,4,6-trichlorobenzoyl chloride, (1.28 mL, 8.20 mmol) and triethylamine, to give 2,4,6 trichloro-*N*-benzoyl valine (2.46 g, 93%) as a white solid. M.p. 162-164 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (s, 2H, H-3'), 6.32 (br d, J = 8.8, 1H, NH), 4.88 (dd, J = 4.4, 8.8, 1H, H-1), 2.47-2.37 (m, 1H, H-2), 1.15 (d, J = 6.8, 3H, H-3a), 1.05 (d, J = 6.8, 3H, H-3b). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7 (q), 163.3 (q), 135.7 (q), 133.6 (q), 132.6 (q), 127.8, 56.8, 31.0, 18.7, 17.2. IR (solid, cm^{-1}): ν 3301, 2964, 2523, 1723, 1615, 1581, 1547, 1371, 1212, 1143, 1034, 856, 820, 801, 717, 688. HRMS (ESI+): calcd. for $[C_{12}H_{12}NO_3Cl_3 + Na]^+$ requires 345.9780; found 345.9793

2,4,6-Trichloro-*N*-benzoyl leucine (44a)



Procedure A was followed using DL-leucine methyl ester (871 mg, 6.00 mmol), 2,4,6-trichlorobenzoyl chloride (0.78 mL, 5.00 mmol), and *N,N*-diisopropylethylamine (2.61 mL, 15.0 mmol), to give 2,4,6 trichloro-*N*-benzoyl leucine (1276 mg, 75%) as an off white crystalline solid. M.p. 162-164 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (s, 2H, H-3'), 6.29 (br d, J = 7.2, 1H, NH), 4.93-4.85 (m, 1H, H-1), 1.96-1.69 (m, 3H, H-2, H-3), 1.08-.99 (m, 6H, H-4). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4 (q), 163.3 (q), 135.6 (q), 133.3 (q), 132.6 (q), 127.7, 50.5, 40.8, 24.3, 22.4, 21.2. IR (solid, cm^{-1}): ν 3206, 3068, 2962, 1715, 1644, 1581, 1548, 1421, 1369, 1257, 1153, 1063, 933, 860, 820, 731. HRMS (ESI+) cald. for $[C_{16}H_{18}NO_3Cl_3 + Na]^+$ requires 400.0250; found 400.0268.

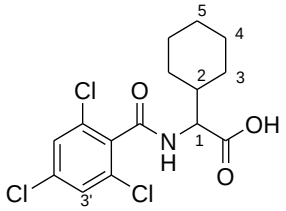
2,4,6-Trichloro-*N*-benzoyl methionine (45a)



Procedure A was followed using DL-methionine methyl ester (816 mg, 5.00 mmol), 2,4,6-trichlorobenzoyl chloride (781 µl, 5.00 mmol) and *N,N*-diisopropylethylamine (2.61 mL, 15.0 mmol) to give 2,4,6 trichloro-*N*-benzoyl methionine (1265 mg, 71%) as a white solid: M.p. 141-143 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (s, 2H, H-3'), 6.63 (br d, J = 7.6, 1H, NH), 5.05-4.98 (m, 1H, H-1), 2.70 (app. t, 2H, H-3), 2.46-2.35 (m, 1H, H-2a), 2.25-2.12 (m, 4H, H-2b, H-4). ^{13}C NMR (100 MHz, $CDCl_3$):

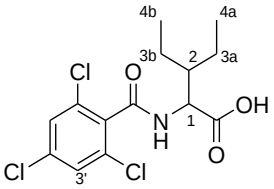
δ = 173.8 (q), 163.2 (q), 135.8 (q), 133.3 (q), 132.5 (q), 127.8, 51.3, 30.8, 29.3, 15.0. IR (solid, cm^{-1}): ν 3254, 3083, 2921, 1709, 1650, 1549, 1432, 1300, 1250, 1184, 1133, 956, 875, 851, 818, 802, 708, 679. HRMS (ESI+): calcd. for $[C_{12}H_{12}NO_3SCl_3 + Na]^+$ requires 377.9501; found 377.9499.

2,4,6-Trichloro-*N*-benzoyl cyclohexylglycine (46a)



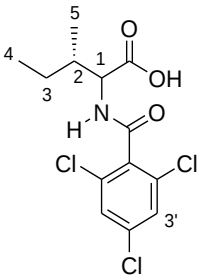
Procedure A was followed using DL-cyclohexylglycine methyl ester (1.10 g, 6.4 mmol), 2,4,6 trichlorobenzoyl chloride (1.00 mL, 6.4 mmol) and *N,N*-diisopropylethylamine (3.35 mL, 19.2 mmol) to give 2,4,6 trichloro-*N*-benzoyl cyclohexylglycine (1.91 g, 83%) as an off-white solid. M.p. 166-168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (s, 2H, H-3'), 6.46 (d, J = 8.4, 1H, NH), 4.83 (dd, 4.4, 8.4, 1H, H-1), 2.02 (m, 1H, H-2), 1.89-1.76 (m, 3H, H-3, H-5), 1.75-1.65 (m, 2H, H-4), 1.37-1.24 (m, 3H, H-3, H-5), 1.24-1.10 (m, 2H, H-4). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0 (q), 163.3 (q), 135.6 (q), 133.6 (q), 132.6 (q), 127.7, 56.6, 40.5, 29.1, 27.5, 25.6, 25.5 (2C). IR (solid, cm^{-1}): ν 3269, 3077, 2929, 2855, 1713, 1649, 1547, 1449, 1368, 1305, 1270, 1137, 908, 856, 820, 806, 729, 698. HRMS (ESI+): calcd. for $[C_{15}H_{16}NO_3Cl_3 + Na]^+$ requires 386.0093; found 386.0098.

2-(2,4,6-trichlorobenzamido)-3-ethylpentanoic acid (47b)



Procedure A was followed using DL-3-pentyl glycine methyl ester (796 mg, 5.0 mmol), 2,4,6-trichlorobenzoyl chloride (0.78 mL, 5.0 mmol) and *N,N*-diisopropylethylamine (2.61 mL, 15.0 mmol) to give 2-(2,4,6-trichlorobenzamido)-3-ethylpentanoic acid (1372 mg, 78%). M.p. 183-185 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (s, 2H, H-3'), 6.24 (d, J = 8.8, 1H, NH), 5.08 (dd, J = 3.6, 8.8, 1H, H-1), 1.98-1.87 (m, 1H, H-2), 1.56-1.29 (m, 4H, H-3a,b), 1.07 (t, J = 7.2, 3H, H-4a), 1.01 (t, J = 7.2, 3H, H-4b). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2 (q), 163.2 (q), 135.6 (q), 133.7 (q), 132.6 (q), 127.8, 53.2, 44.2, 22.5, 22.3, 11.4, 11.3. IR (solid, cm^{-1}): ν 3283, 3088, 2095, 2878, 2480, 1721, 1615, 1582, 1547, 1459, 1368, 1344, 1208, 1138, 966, 857, 820, 804, 710. HRMS (ESI+): calcd. for $C_{14}H_{16}Cl_3NO_3$ requires 374.0093; found 374.0087.

N-(2,4,6-trichlorobenzoyl)-DL-Allo-Isoleucine (48c)



Procedure A was followed using L- isoleucine with D-allo-isoleucine methyl ester (2.00 g, 11.0 mmol), 2,4,6-trichlorobenzoyl chloride (1.42 mL, 9.1 mmol) and *N,N*-diisopropylethylamine (4.79 mL, 27.5 mmol) to give **48c** (1.95 g, 64%) as a white solid. M.p. 166-169 ^{o}C. ^{1}H NMR (400 MHz, d^{6}-DMSO): Compound is a mixture of diasteromers in a ratio 1: 0.8: δ = 9.01 (d, J = 8.66, 0.8H, NH), 8.93 (d, J = 8.87, 1H, NH), 7.74 (bs, 2H +1.6H, H-3'), 4.58 (dd, J 4.65, J 8.66, 0.8H, H-1), 4.40 (t app, J = 7.39, 1H, H-1), 1.85-2.04 (1.8H, H-2), 1.49 (m, 1.8.H, 1H and 0.8 H from 3-CH_2), 1.28 (m, 1.8H, 1H and 0.8 H from 3-CH_2), 0.87-0.98 (m, 10.8H, 4-CH_3 and 5-CH_3). ^{13}C NMR (100 MHz, d^{6}-DMSO): δ = 173.6 (q), 173.3 (q), 164.1 (q), 163.9 (q), 136.7 (q), 136.6 (q), 135.1 (q), 135.1 (q), 133.2, 128.8, 57.5, 55.9, 37.7, 37.4, 26.8, 25.6, 16.7, 16.0, 12.6, 12.1. HRMS (ESI+): calcd. for $[C_{13}H_{14}NO_3NaCl_3+Na]^+$ requires 359.9937; found 359.9927. IR (solid, cm^{-1}): ν 3300, 2968, 1733, 1648, 1584, 1424, 1370, 1303, 1254, 1184, 872, 856, 821, 805, 729.

3 Conversion of *N*-2,4,6-trichlorobenzoyl amino acids to azlactones.

A round bottom flask was flushed with nitrogen, charged with a stirring bar and the appropriate *N*-2,4,6-trichlorobenzoyl amino acid (1.0 equiv.), fitted with a septum and $CHCl_3$ added *via* syringe. To this 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (1.1 equiv.) was added and stirring continued at room temperature for 1-4 h. The reaction mixture was then diluted with CH_2Cl_2 washed twice with saturated $NaHCO_3$ solution at 0 ^{o}C, followed by washing with water. The organic layer was then dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The crude product was then filtered through a pad of silica gel using CH_2Cl_2 as the eluent. The solvent was then removed *in vacuo* and the product dried as necessary under high vacuum and used inmediately without further purification.

4 Dynamic kinetic resolution of azlactones

4.1 General procedure B for the DKR of racemic azlactones. (Table 1)

A 3 mL reaction vial containing a stirring bar was charged with the appropriate catalyst (0.02 mmol). The reaction vial was flushed with argon and fitted with a stopper. CH_2Cl_2 (0.5 mL), Styrene (23 μL, 0.20 mmol) and allyl alcohol (27 μL, 0.40 mmol) were added *via* syringe followed by the appropriate azlactone (0.20 mmol). The resulting reaction was stirred at room temperature for the time indicated in Table 1. The solution was then poured directly onto a column of silica gel and the product purified by flash chromatography (2-10% EtOAc in hexane).

4.2 General procedure C for the DKR of racemic azlactones. (Table 2)

A 5 mL reaction vial containing a stirring bar was charged with the catalyst **16** (0.04 mmol). The reaction vial was flushed with argon and fitted with a stopper. The appropiate solvent (2-4 mL) and allyl alcohol (16 μL, 0.24 mmol) were added *via* syringe followed by the appropriate N-protected Valine azlactone (0.20 mmol). The resulting reaction was stirred at 19 ^{o}C for the time indicated in Table 2. The solution was filtered through a thin pad of silica gel to remove the catalyst, concentrated *in vacuo* and then purified by flash chromatography (49:1-9:1 hexane-EtOAc).

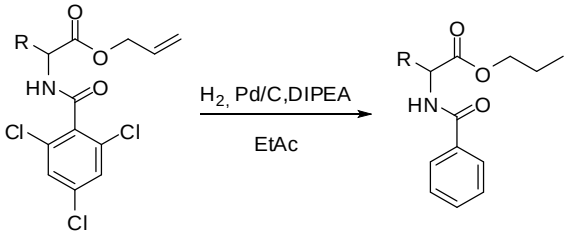
4.3 General procedure D for the DKR of racemic azlactones. (Scheme 1)

A 5 mL reaction vial containing a stirring bar was charged with the catalyst **16** (0.02-0.04 mmol). The reaction vial was flushed with argon and fitted with a stopper. $CDCl_3$ (2-4 mL) and allyl alcohol (16 μL,

0.24 mmol) were added *via* syringe followed by the appropriate N-2,4,6-trichlorobenzoyl azlactone (0.20 mmol). The resulting reaction was stirred at 19 °C for the time indicated. The solution was filtered through a thin pad of silica gel to remove the catalyst, concentrated *in vacuo* and then purified by flash chromatography (49:1-9:1 hexane-EtOAc).

4.3.1 Sample preparation for CSP-HPLC analysis: Procedure for hydrogenolysis

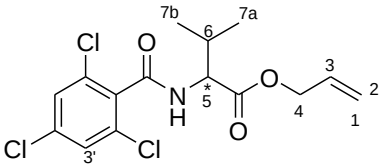
The amide products following ring-opening of trichloroaryl azlactones are difficult to resolve using CSP-HPLC due to significant peak-tailing. To circumvent this difficulty the purified ring-opened products were reduced and dechlorinated by hydrogenolysis using the following procedure.



Scheme 2:Hydrogenation of 2,4,6-Trichloro-N-benzoyl aminoacid allyl esters

The compound (0.10 mmol) was placed in a round bottomed flask with EtOAc (1 mL), *N,N*-diisopropylethylamine (70 µl, 0.40 mmol) and 10% Pd/C (10.6 mg, 10mol%). The flask was evacuated and filled with an atmosphere of H_2 (1 atm) for 4 h to afford the dechlorinated propyl ester upon purification by flash chromatography (2-10% EtOAc in hexane).

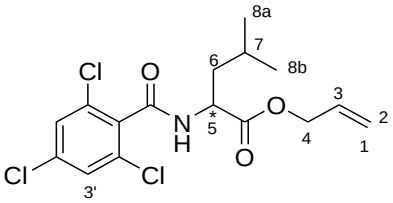
2,4,6-trichloro-*N*-Benzoyl valine allyl ester (43)



Procedure D was followed, stirring was continued for 72 h, to give the desired product (67 mg, 92%), 90% *ee*, as a white solid. M.p. 56-58 °C. CSP-HPLC analysis (using hydrogenolysis procedure): Chiralpak ADH (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 7.8 min (major enantiomer) and 11.6 min (minor enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (S, 2H, H-3'), 6.36 (d, J = 8.8, 1H, NH), 6.01-5.89 (m, 1H, H-3), 5.39 (dd, J 1.2, 17.2, 1H, H-1), 5.31 (dd, J = 1.2, 10.4, 1H, H-2), 4.85 (dd, J = 4.4, 8.8, 1H, H-5), 4.76-4.64 (m, 2H, H-4), 2.43-2.30 (m, 1H, H-6), 1.10 (d, J = 6.8, 3H, H-7a), 1.00 (d, J = 6.8, 3H, H-7b). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (q), 163.0 (q), 135.5 (q), 133.9 (q), 132.6 (q), 130.9, 127.8, 118.9, 65.7, 57.0, 31.2, 18.7, 17.3. IR (solid, cm^{-1}): ν 3283, 3077, 2963, 1731, 1651, 1569, 1536, 1246, 990, 939, 867, 736. HRMS (ESI+): calcd for $[C_{15}H_{16}NO_3Cl_3 + Na]^+$ requires 386.0093; found 386.0103.

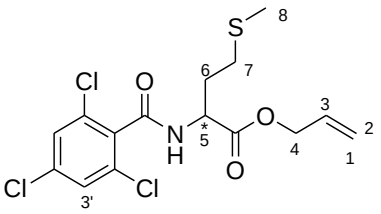
The absolute configuration of **43** was established by comparing the retention times of the reduced product with those of reduced **21** which was compared to those published in literature.[2]

2,4,6-trichloro-*N*-benzoyl leucine allyl ester (44)



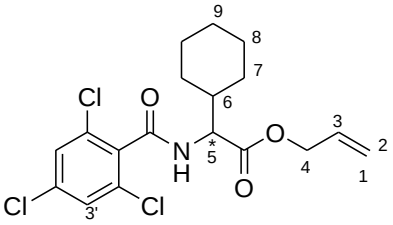
Procedure D was followed, stirring was continued for 115 h, to give the desired product (73 mg, 96%), 83% *ee*, as a colourless oil. CSP-HPLC analysis (using hydrogenolysis procedure): Chiralpak ADH (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 8.0 min (major enantiomer) and 12.2 min (minor enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$): 7.37 (s, 2H, H-3'), 6.21 (br d, J = 8.4, 1H, NH), 6.01-5.89 (s, 1H, H-3), 5.38 (dd, J = 1.2, 17.2, 1H, H-1), 5.30 (dd, J = 1.2, 10.4, 1H, H-2), 4.96-4.88 (m, 1H, H-5), 4.75-4.61 (m, 2H, H-4), 1.92-1.65 (m, 3H, H-6, H-7), 1.04 (d, J = 6.4, 3H, H-8a), 1.00 (d, J = 6.4, 3H, H-8b). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4 (q), 162.7 (q), 135.5 (q), 133.7 (q), 132.6 (q), 131.0, 127.7, 118.7, 65.7, 50.6, 41.3, 24.3, 22.4, 21.4. IR (oil, cm^{-1}): ν 3315, 2960, 1741, 1641, 1536, 1197, 1164, 693. HRMS (ESI+): calcd for $[C_{15}H_{16}NO_3Cl_3 + Na]^+$ requires 386.0093; found 386.0103.

2,4,6-trichloro *N*-Benzoyl methionine allyl ester (45)



Procedure D was followed, stirring was continued for 44h, to give the desired product (76 mg, 96%), 84 % *ee*, as a white solid. M.p. 76-78 °C. CSP-HPLC analysis: Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 10.2 min (minor enantiomer) and 12.3 min (major enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$): 7.39 (s, 2H, H-3'), 6.53 (d, J = 7.6, 1H, NH), 6.02-5.90 (m, 1H, H-3), 5.40 (dd, J = 1.2, 17.2, 1H, H-1), 5.33 (dd, J = 1.2, 10.4, 1H, H-2), 5.00 (td, J = 5.2, 7.6, 1H, H-5), 4.78-4.67 (m, 2H, H-4), 2.37-2.59 (m, 2H, H-7), 2.45-2.33 (m, 1H, H-6), 2.23-2.10 (m, 4H, H-6, H-8). ^{13}C NMR (100 MHz, $CDCl_3$): 170.4 (q), 162.8 (q), 135.6 (q), 133.5 (q), 132.5 (q), 130.7, 127.8, 119.1, 66.1, 51.5, 31.3, 29.3, 15.0. IR (solid, cm^{-1}): ν 3247, 3081, 2917, 1731, 1644, 1582, 1548, 1427, 1296, 988, 819, 690. HRMS (ESI+) calcd. for $[C_{15}H_{16}NO_3Cl_3S + H]^+$ requires 395.9995; found 395.9990.

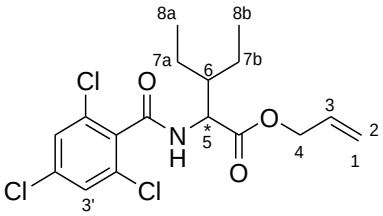
Allyl 2-(2,4,6-trichlorobenzamido)-2-cyclohexylacetate (46)



Procedure D was followed, stirring was continued for 5 d, to give the desired product (74.5 mg, 92%), 92% *ee*, as a white solid. M.p. 70-71 °C. CSP-HPLC analysis (using hydrogenolysis procedure): Chiralpak ADH (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 5.2 min (major enantiomer) and 8.4 min (minor enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$): 7.38 (s, 2H, H-3'), 6.32 (d, J = 8.8, 1H, NH), 6.00-5.89 (m, 1H, H-3), 5.39 (dd, J = 1.2, 17.2, 1H, H-1), 5.31 (dd, J = 1.2, 10.4, 1H, H-2), 4.82 (dd, J = 4.8, 8.8, 1H, H-5), 4.75-4.65 (m, 2H, H-4), 2.04-1.93 (m, 1H, H-6), 1.88-1.75

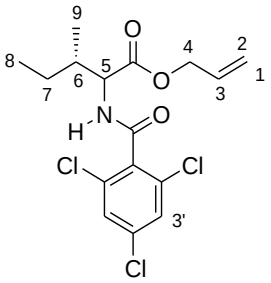
(m, 3H, H-7, H-9), 1.75-1.66 (m, 2H, H-8), 1.35-1.10 (m, 5H, H-7, H-8, H-9). ^{13}C NMR (100 MHz, $CDCl_3$): 170.4 (q), 162.9 (q), 135.5 (q), 133.9 (q), 132.6 (q), 130.97, 127.75, 118.76, 65.6, 56.7, 40.8, 29.1, 27.7, 25.6, 25.5. IR (solid, cm^{-1}): ν 3255, 3079, 2928, 2854, 1736, 1644, 1580, 1545, 1449, 1368, 1252, 1135, 991, 818, 715. HRMS (ESI+): calcd. for $[C_{18}H_{20}Cl_3NO_3 + Na]^+$ requires 426.0406; found 426.0403.

allyl 2-(2,4,6-trichlorobenzamido)-3-ethylpentanoate (47)



Procedure D was followed, stirring was continued for 5 d, to give the desired product (71 mg, 91%), 90% *ee*, as a white solid. M.p. 70-71 °C. CSP-HPLC analysis (using hydrogenolysis procedure): Chiralpak ADH (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 5.2 min (major enantiomer) and 8.5 min (minor enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$): 7.38 (s, 2H, H-3'), 6.26 (d, J = 9.2, 1H, H-NH), 6.01-5.89 (m, 1H, H-3), 5.38 (dd, J = 1.2, 17.2, 1H, H-1), 5.31 (dd, J = 1.2, 10.4, 1H, H-2), 5.05 (dd, J = 4.0, 8.8, 1H, H-5), 4.76-4.63 (m, 2H, H-4), 1.94-1.84 (m, 1H, H-6), 1.50-1.34 (m, 4H, H-7a,b), 1.06 (t, J = 7.2, 3H, H-8a), .99 (t, J = 7.2, 3H, H-8b). ^{13}C NMR (100 MHz, $CDCl_3$): 171.1 (q), 162.9 (q), 135.5 (q), 133.9 (q), 132.6, 131.0 (q), 127.7, 118.7, 65.7, 53.5, 44.4, 22.5, 22.2, 11.4, 11.3. IR (solid, cm^{-1}): ν 3262, 3083, 2956, 2876, 1740, 1651, 1583, 1549, 1339, 1203, 1139, 984, 932, 850, 814, 699. HRMS (ESI+): calcd. for $[C_{17}H_{20}Cl_3NO_3 + Na]^+$ requires 414.0406; found 414.0418.

N-(2,4,6-trichlorobenzoyl)-D-Allo-Isoleucine allyl ester (48)

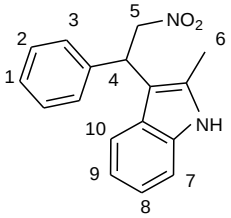


Procedure D was followed, stirring was continued for 5 d, to give the desired product (72 mg, 95%), as a colourless oil.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (s, 2H, H-3'), 6.40 (minor diastereomer, d, J = 8.4, 0.1H, NH), 7.34 (bs, 2H, H-3'), 6.33 (major diastereomer, d, J = 8.8, 1H, NH), 5.35 (d, J = 17.2, 1H, H-2), 5.91 (m, 1H, H-3), 5.27 (d, J = 10.4, 1H, H-1), 4.94 (major diasteromer, dd, J = 8.8, 3.6, 1H, H-5), 4.84 (minor diastereomer, dd, J = 4.4, 8.4, 0.10H, H-5), 4.66 (dd, J = 13.2, 5.91, 2H, H-4), 1.58 (m, 1H, H-7), 2.08 (m, 1H, H-6), 1.00 (t, J = 7.2, 3H, H-8), 1.28 (m, 1H, H-7), 0.91 (d, J = 6.8, 3H, H-9). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.2 (q), 163.4 (q), 135.8 (q), 134.3, 132.9(q), 131.4 (q), 128.1, 119.2, 66.1, 55.6, 38.1, 26.3, 14.7, 11.8. HRMS (ESI +): calcd. for $[C_{16}H_{18}NO_3NaCl_3+Na]^+$ requires 400.0250; found, 400.237. IR (oil, cm^{-1}): ν 3273, 2925, 1740, 1648, 1581, 1547, 1459, 1368, 1298, 1246, 1185, 988, 930, 854, 820.

The stereochemistry of the product was assigned by comparison with the NMR spectra recorded for the diasteromerically pure N-(2,4,6-trichlorobenzoyl)-L-Isoleucine allyl ester obtained by derivatisation of commercially available L-Isoleucine (Figure 1).

5 Addition of 2-methylindole to β-nitrostyrene

2-methyl-3-(2-nitro-1-phenylethyl)-1H-indole (51)



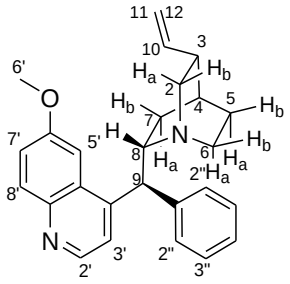
2-methylindole (32.8 mg, 0.25 mmol), styrene (28.6 µl, 0.25 mmol), CH_2Cl_2 (500 µl) and catalyst (20 mol%), were placed in a reaction vial and placed under a protective argon atmosphere. To this β-nitrostyrene (37.3 mg, 2.50 mmol), was added and stirring continued for the time indicated in table 3. The resulting solution was then purified by column chromatography (1:9 EtOAc-hexane) without prior removal of solvent to afford **51**, (34 mg, 61%), M.p. 102-104 ^{o}C (lit. m.p. 104-105 ^{o}C).[4] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83-7.97 (1H, br s, H-NH), 7.40 (1H, d, J = 8.0, H-7), 7.23-7.38 (6H, m, H-1, H-2, H-3, H-10), 7.14 (1H, app. t, H-8), 7.06 (1H, app. t, H-9), 5.09-5.33 (3H, m, H-4 and H-5), 2.43 (3H, s, H-6).

6 Synthesis of cinchona alkaloid catalysts 9-18:

6.1 General procedure E for the formation of Grignard reagents

A suspension of freshly ground magnesium turnings in dry THF (1.05 eq., 0.25 M) under argon atmosphere was placed in a round bottomed flask. Aryl bromide (1.0 equiv.) and 1,2-dibromoethane (4-5 drops) were added and the mixture was heated under reflux until all magnesium dissolved (30-240 minutes). The resulting solution was used immediately. Phenylmagnesiumbromide solution in (2.0 M in THF) was purchased from Aldrich.

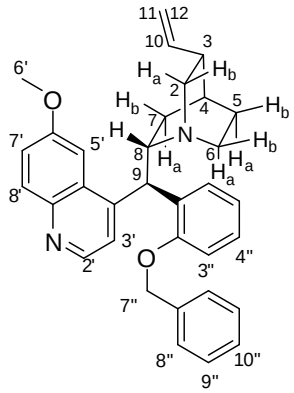
(8*S*,9*S*)-6'-methoxy-9-phenyl-cinchonan (9)[5]



Phenylmagnesiumbromide in THF (3.0 mL, 2.0 M, 6.0 mmol) was added to a solution of 9-*epi*-chloroquinine (2.0 mmol, 686 mg) in THF (10 mL) and heated under reflux for 4 h. The solution was cooled and a saturated aqueous solution of NH_4Cl (30 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (2 x 100 mL), the organic extracts were combined, dried over $MgSO_4$ and solvent was removed under reduced pressure. The resulting material was purified by column chromatography (30:20:1 hexane-EtOAc-NEt_3) to give **9** (500 mg, 65%) as an off-white solid. M.p. 147-149 ^{o}C. (Lit. m.p. 145-152°C).[6] ^{1}H NMR (600 MHz, C_6D_6): δ = 8.73 (d, J = 4.8, 1H, H-2'), 7.90 (d, J = 9.2, 1H, H-8'), 7.72-7.69 (m, 2H, H-5', H-3'), 7.47 (d, J = 7.8, 2H, H-2"), 7.37 (dd, J = 9.0, 1.8, 1H, H-7'), 7.19 (t, J = 7.2, 2H, H-3"), 7.07, (t, J = 7.2, 1H, H-4"), 6.00-6.11 (m, 1H, H-10), 5.04 (app. dd, 2H, H-11, H-12), 4.85 (d, J = 10.8, 1H, H-9), 3.97 (s, 3H, H-6'), 3.81 (s, 1H, H-8), 3.42 (s, 1H, H-6a), 3.00 (app. t, 1H, H-2b), 2.59 (br d, J = 10.2, 1H, H-2a), 2.47 (app. t, 1H, H-6b), 2.23 (s, 1H, H-3), 1.89 (s, 1H, H-7b), 1.54-1.65 (m, 2H, H-4, H-5a), 1.46 (s, 1H, H-5b), 0.70 (s, 1H, H-7a).

6.2 Preparation of 9-aryl-quinines

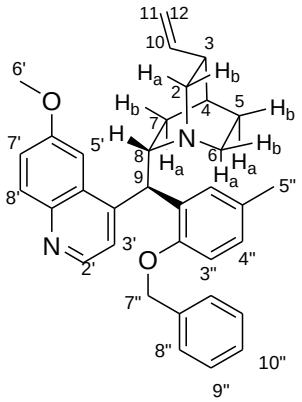
(2*S*)-2-((*R*)-(2-(benzyloxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (10a)



A solution of 9-*epi*-chloroquinine (3.13 g, 9.12 mmol) in dry THF (36.5 mL) was added to a round bottom flask containing a solution of 1-((2-bromomagnesiumphenoxy)methyl)benzene (2.62 g, 9.12 mmol) in dry THF (36.5 mL) (prepared using general procedure E), and heated under reflux overnight under a protective argon atmosphere. The resulting solution was cooled and a saturated aqueous solution of NH_4Cl (50 mL) was added. The resulting mixture was then extracted with CH_2Cl_2 (2 x 200 mL), and the organic washings were combined, dried over $MgSO_4$ and solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (25:25:1 hexane-EtOAc-NEt_3) to give **10a** (3.25 g, 88%) as an off-white solid. $[\alpha]_D^{20}$ = -44.1 (c 0.085, $CHCl_3$). M.p. 63-65 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (d, J = 4.0, 1H, H-2'), 7.97 (d, J = 9.2, 1H, H-8'), 7.59 (s, 1H, H-5') 7.10-7.46 (m, 9H, H-7', H-3', H-3", H-5", H-8", H-9", H-10"), 6.88-6.99 (m, 2H, H-6", H-4"), 5.87-5.99 (m, 1H, H-10), 5.27-5.39 (br d, 1H, H-9), 5.00-5.13 (m, 4H, H-11, H-12, H-7"), 3.78-3.66 (br s, 1H, H-8), 3.61 (s, 3H, H-6'), 3.39-3.53 (br s, 1H, H-6a), 3.16-3.32 (br s, 1H, H-2b), 2.64-2.84 (m, 2H, H-2a, H-6b), 2.24-2.33 (br s, 1H, H-3), 1.74-1.88 (br s, 1H, H-7b), 1.63-1.73 (br s, 1H, H-4), 1.47-1.64 (m, 2H, H-5a, H-5b),

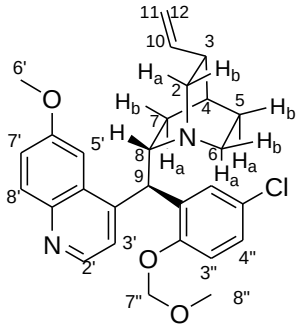
0.98-0.84 (m, 1H, H-7a). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4 (q), 157.3 (q), 147.2, 146.1 (q), 144.3 (q), 143.3 (q), 141.5, 136.5 (q), 131.5, 129.0, 128.4 (q), 128.1, 127.5, 127.2, 120.5, 120.3, 119.2, 114.9, 113.9, 111.8, 101.6, 76.8, 69.5, 59.1, 56.1, 55.1, 48.9, 40.5, 39.1, 28.3, 27.6. IR (solid, cm^{-1}): ν 2928, 2860, 1620, 1586, 1507, 1450, 1225, 1031, 916, 850, 747, 696. HRMS (ES+): calcd. for $[C_{33}H_{34}N_2O_2 + H]^+$ requires: 491.2699; found: 491.2693

(2*S*)-2-((*R*)-(5-methyl-2-(methoxymethoxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (11a)



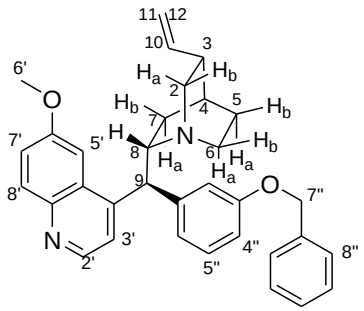
A solution of 9-*epi*-chloroquinine (2.60 g, 7.58 mmol) in dry THF (24.0 mL) was added to a round bottom flask containing a solution of 1-((2-bromomagnesium-4-methylphenoxy)methyl)benzene (2.29 g, 7.58 mmol) in dry THF (24.0 mL) (prepared using general procedure E), and heated under reflux overnight under a protective argon atmosphere. The resulting solution was cooled and a saturated aqueous solution of NH_4Cl (30 mL) was added. The resulting mixture was then extracted with CH_2Cl_2 (2 x 120 mL), and the organic washings were combined, dried over $MgSO_4$, filtered and solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (25:25:1 hexane-EtOAc-NEt_3) to give **11a** (1.54 g, 40%) as an off-white solid. M.p. 157-158 °C. $[\alpha]_D^{20}$ = -45.21 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (d, J = 4.4, 1H, H-2'), 7.97 (d, J = 9.2, 1H, H-8'), 7.63 (d, J = 2.4, 1H, H-5'), 7.44-7.33 (m, 6H, H-8", H-9", H-10", H-3'), 7.29 (dd, J = 2.4, 9.2, 1H, H-7' (partly obscured by residual $CHCl_3$ peak)), 7.15 (br s, 1H, H-6"), 6.93 (d, J = 8.4, 1H, H-4"), 6.83 (d, J = 8.4, 1H, H-3"), 6.03-5.91 (m, 1H, H-10), 5.33 (br s, 1H, H-9), 5.14-5.05 (m, 4H, H-11, H-12, H-7"), 3.72 (br s, 1H, H-8), 3.62 (s, 3H, H-6'), 3.49 (br s, H-6a), 3.24 (m, 1H, H-2b), 2.83-2.65 (m, 2H, H-6b, H-2a), 2.35-2.22 (m, 4H, H-5", H-3), 1.86 (br m, 1H, H-7b), 1.70 (br s, 1H, H-4), 1.64-1.46 (m, 2H, H-5a, H-5b), 0.89 (m, 1H, H-7a). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1 (q), 153.4 (q), 147.2 (q), 147.0, 144.16 (q), 141.8, 136.4 (q), 131.0, 129.9 (q), 129.7 (q), 129.0 (q), 128.6, 128.5, 128.1, 127.8, 127.5, 127.1, 120.8, 119.8, 113.8, 111.3, 102.0, 70.0, 59.7, 56.2, 54.8, 41.0, 39.3, 30.5, 28.2, 27.6, 20.4. IR (solid, cm^{-1}): ν 3031, 2927, 2855, 1621, 1502, 1324, 1234, 1036, 1020, 853, 797, 734, 699. HRMS (ESI+): calcd. for $[C_{34}H_{36}N_2O_2 + H]^+$ requires 505.2855; found 505.2864.

(2*S*)-2-((*R*)-(5-chloro-2-(methoxymethoxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (12a)



A solution of 9-*epi*-chloroquinine (2.06 g, 6.0 mmol) in dry THF (24.0 mL) was added to a round bottom flask containing a solution of 2-bromomagnesium-4-chloro-methoxymethylphenol (1.58 g, 6.3 mmol) in dry THF (24 mL) (prepared using general procedure E), and heated under reflux overnight under a protective argon atmosphere. The resulting solution was cooled and a saturated aqueous solution of NH_4Cl (30 mL) was added. The resulting mixture was then extracted with CH_2Cl_2 (2 x 120 mL), and the organic washings were combined, dried over $MgSO_4$, filtered and solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (25:25:1 hexane-EtOAc-NEt_3) to give **12a** (1008 mg, 35%) as an off-white solid. M.p. 136-137 °C. $[\alpha]_D^{20}$ = -151.03 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (d, J = 4.4, 1H, H-2'), 8.01 (d, J = 9.2, 1H, H-8'), 7.72 (br d, J = 2.0, 1H, H-5'), 7.39 (dd, J = 2.4, 9.2, 1H, H-7'), 7.36-7.32 (m, 2H, H-3', H-6"), 7.07 (dd, J = 2.4, 8.8, 1H, H-4"), 6.99 (d, J = 8.8, 1H, H-3"), 6.00-5.89 (m, 1H, H-10), 5.26 (br d, J = 10.8, H-9), 5. 30-5.04 (m, 4H, H-11, H-12, H-7") 4.00 (s, 3H, H-6'), 3.63 (br d, J = 8.0, H-8), 3.36 (br s, 1H, H-6a), 3.28-3.16 (m, 4H, H-8", H-2b), 2.84-2.64 (m, 2H, H-2a, H-6b), 2.30 (br s, 1H, H-3), 1.81 (br s, 1H, H-7b), 1.71 (br s, 1H, H-4), 1.68-1.50 (m, 2H, H-5a, H-5b), 0.88 (app. dd, 1H, H-7a). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3 (q), 153.0 (q), 147.2, 146.4 (q), 144.2 (q), 141.6, 132.6 (q), 131.3, 128.8 (q), 127.7, 127.0, 126.5 (q), 120.3, 119.9, 114.7, 113.9, 102.3, 94.2, 59.2, 56.1, 55.5, 55.1, 40.8, 40.7 (br), 39.2, 27.8, 27.7, 27.4. IR (solid, cm^{-1}): ν 2935, 2859, 1621, 1586, 1508, 1473, 1232, 1153, 1075, 985, 851, 813, 681. HRMS (ESI+): calcd. for $[C_{28}H_{31}N_2O_3 + H]^+$ requires: 479.2101 found: 479.2100

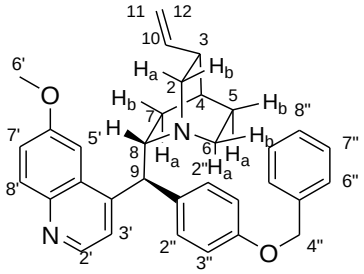
(2*S*)-2-((*S*)-(3-(benzyloxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (13a)



A solution of 9-*epi*-chloroquinine (1.71 g, 5.00 mmol) in dry THF (20 mL) was added to a round bottom flask containing a solution of 1-((3-bromomagnesiumphenoxy)methyl)benzene (1.58 g, 5.50 mmol) in dry THF (20 mL) (prepared using general procedure E), and heated under reflux for 4 h under a protective argon atmosphere. The resulting solution was cooled and a saturated aqueous solution of NH_4Cl (25 mL) was added. The resulting mixture was extracted twice with CH_2Cl_2 (2 x 150 mL), the organic extracts were combined, dried over $MgSO_4$ and solvent was removed under reduced pressure. The resulting material was purified by column chromatography (98:2 EtOAc-NH_3 (aq. 35% *w/w*)) to give **13a** (1.14 g, 48%) as an off-white solid. M.p. 122-123 °C. $[\alpha]_D^{20}$ = -10.80 (c 0.136, $CHCl_3$).

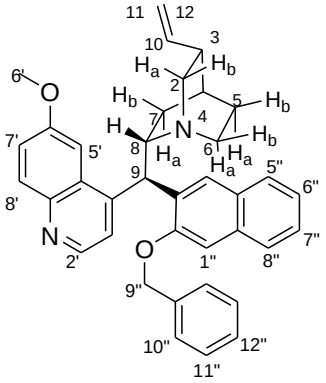
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.77 (d, J = 4.8, 1H, H-2'), 8.03 (d, J = 9.0, 1H, H-8'), 7.55 (br s, 1H, H-5'), 7.46-7.31 (m, 7H, H-8", H-9", H-10", H-3', H-7'), 7.21 (app. t, 1H, H-5"), 7.03 (d, J = 7.8, 1H, H-6"), 6.98 (s, 1H, H-2"), 6.79 (d, J = 8.4, 1H, H-4"), 6.02-5.91 (d, J = 11.2, 1H, H-10), 5.14-5.06 (m, 2H, H-11, H-12), 5.00 (s, 2H, H-7"), 4.76 (br s, 1H, H-9), 3.99 (s, 3H, H-6'), 3.71 (br s, 1H, H-8), 3.34 (br s, 1H, H-6a), 3.30-3.23 (m, 1H, H-2b), 2.86-2.73 (m, 2H, H-2a, H-6b), 2.37-2.28 (m, 1H, H-3), 1.98-1.86 (br s, 1H, H-7b), 1.76-1.71 (s, 1H, H-4), 1.67-1.55 (m, 2H, H-5a, H-5b), 0.89-0.82 (m, 1H, H-7a). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1 (q), 155.6 (q), 147.0, 144.1 (q), 141.7, 136.2 (q), 132.7, 131.1 (q), 130.1 (q), 129.0, 128.4(q), 128.1, 127.6, 127.2, 120.8, 120.7, 119.9, 119.9, 113.8, 111.4, 102.1, 76.8, 69.9, 59.5, 56.0, 54.7, 40.9, 39.2, 27.9, 27.5, 27.5. IR (solid, cm^{-1}): ν 2946, 2831, 1619, 1581, 1485, 1249, 1224, 1023, 916, 837, 771, 750, 698. HRMS (ES+): calcd. for: $[C_{33}H_{34}N_2O_2 + H]^+$ requires: 491.2699; found 491.2708

(2*S*)-2-((*S*)-(4-(benzyloxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (14a)



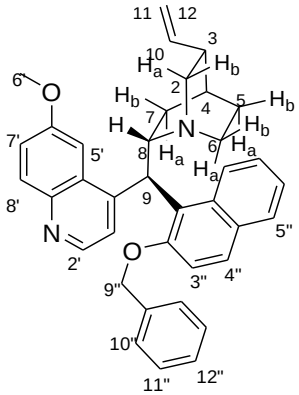
A solution of 9-*epi*-chloroquinine (5.14 g, 15.0 mmol) in dry THF (60 mL) was added to a round bottom flask containing a solution of 1-((4-bromomagnesiumphenoxy)methyl)benzene (5.62 g, 19.5 mmol) in dry THF (60 mL) (prepared using general procedure E), and heated under reflux over night under a protective argon atmosphere. The resulting solution was cooled and a saturated aqueous solution of NH_4Cl (100 mL) was added. The resulting mixture was extracted twice with CH_2Cl_2 (2 x 200 mL), the organic extracts were combined, dried over $MgSO_4$ and solvent was removed under reduced pressure. The resulting material was purified by column chromatography (40:10:1 hexane-EtOAc-NEt_3) to give **14a** (6.33 g, 86%) as an off-white solid. M.p. 50-52 ^oC. $[\alpha]_D^{20}$ = -128.5 (c 0.071, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (d, J = 4.8, 1H, H-2'), 8.04 (d, J = 9.6, 1H, H-8'), 7.54 (s, 1H, H-5'), 7.46-7.26 (m, 9H, H-3', H-7', H-2", H-6", H-7", H-8"), 6.90 (d, J = 8.4, 2H, H-3"), 6.06-5.89 (m, 1H, H-10), 5.16-5.06 (m, 2H, H-11, H-12), 4.98 (s, 2H, H-4"), 4.76 (d, J = 10, 1H, H-9), 3.99 (s, 3H, H-6'), 3.80-3.64 (br s, 1H, H-8), 3.43-3.23 (m, 2H, H-6a, H-2b), 2.88-2.73 (m, 2H, H-6b, H-2a), 2.38-2.28 (br s, 1H, H-3), 2.01-1.89 (br s, 1H, H-7b), 1.73 (br s, 1H, H-4), 1.69-1.52(br s, 2H, H-5a, H-5b), 0.93-0.81 (m, 1H, H-7a). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3 (q), 157.0 (q), 147.2, 146.6 (q), 144.4 (q), 141.5, 136.6 (q), 134.0 (q), 131.5, 128.4, 128.1, 127.5, 127.1, 120.5, 119.1, 114.4, 113.9, 101.7, 76.8 (q), 69.4, 59.2, 56.2, 55.1, 48.2, 40.5, 39.1, 28.4, 27.7, 27.6. IR (solid, cm^{-1}): ν 2936, 2202, 1620, 1586, 1507, 1471, 1228, 1027, 907, 826, 726, 696, 675. HRMS (ESI+): Calcd. for $[C_{33}H_{34}N_2O_2 + H]^+$ requires 491.2699; found 491.2682.

(2*S*)-2-((*R*)-(2-(benzyloxy)naphthalen-3-yl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (15a)



Procedure as for **10a** using a solution of 2-(benzyloxy)-3-bromomagnesiumnaphthalene (739 mg, 2.19 mmol) in THF (6.0 mL) and 9-*epi*-chloroquinine (500 mg, 1.46 mmol) in THF (6.0 mL) to give **15a** (310 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, J = 3.6, 1H, H-2'), 7.98 (d, J = 8.8, 1H, H-8'), 7.79-7.85 (br s, 1H, H-5'), 7.66 (d, J = 8.0, 1H, H-5"), 7.73 (d, J = 8.0, 1H, H-8"), 7.57 (d, J = 2.4, 1H, H-4"), 7.27-7.41 (m, 9H, H-3', H-7', H-6", H-7", H-10", H-11", H-12"), 7.23 (s, 1H, H- 1"), 5.89-6.01 (m, 1H, H-10), 5.37-5.50 (br s, 1H, H-9), 5.05-5.27 (m, 4H, H-11, H-12, H-9"), 3.80-3.95 (br s, 1H, H-8), 3.66 (s, 3H, H-6'), 3.42-3.56 (br s, 1H, H-6a), 3.21-3.36 (br s, 1H, H-2b), 2.69-2.93 (m, 2H, H-6b, H-2a), 2.27-2.41 (br s, 1H, H-3), 1.81-1.96 (br s, 1H, H-7b), 1.49-1.79 (m, 3H, H-4, H-5a, H-5b), 0.96-1.10 (br s, 1H, H-7a). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1 (q), 154.5 (q), 147.0, 144.2 (q), 141.8, 135.8 (q), 132.9 (q), 132.0 (q), 131.1, 129.0 (q), 128.6 (q), 128.4 (q), 128.1, 127.8, 127.7, 127.5, 127.2, 125.9, 125.5, 123.3, 120.8, 120.1, 113.8, 106.14, 102.0, 76.8, 70.0, 59.7, 56.2, 54.7, 41.0, 39.3, 27.8, 27.6, 27.5. IR (solid, cm^{-1}): ν 2934, 2863, 1617, 1505, 1359, 1240, 1183, 1080, 1035, 915, 851, 739, 712. HRMS (ESI+): Calcd. for $[C_{37}H_{36}N_2O_2 + H]^+$ requires 541.2855; found 541.2858.

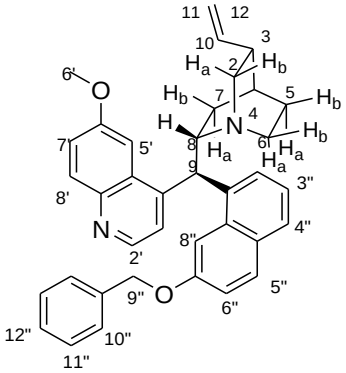
(2*S*)-2-((*R*)-(2-(benzyloxy)naphthalen-1-yl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (16a)



Procedure as for **10a** using a solution of 2-(benzyloxy)-1-bromomagnesiumnaphthalene (1.68 g, 5.00 mmol) in THF (9.0 mL) and 9-*epi*-chloroquinine (686 mg, 2.00 mmol) in THF (9 mL) to give **16a** (895 mg, 82%). M.p. 103-104 °C. $[\alpha]_D^{20}$ = +198.5 (c 0.125, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.83-8.90 (br s, 0.24H, H-8"), 8.72 (d, J = 7.8, 0.76H, H-8"), 8.42 (d, J = 4.8, 0.76H, H-2'), 8.32 (d, J = 8.4, 0.24H, H-2'), 7.91 (d, J = 9.0, 1H, H-8'), 7.80-7.87 (m, 1H, H-5"), 7.69-7.79 (m, 1H, H-4"), 7.61-7.68 (m, 1H, H-7"), 7.35-7.55(m, 6H, H-6", H-10", H-11", H-12"), 7.28-7.34 (m, 1H, H-5'), 7.15-7.26 (m, 3H, H-3', H-3", H-7'), 6.06-6.17 (m, 0.24H, H-10), 5.85-6.01 (m, 0.76H, H-10), 5.54-5.63 (m, 0.24H, H-9), 5.37 (d, J = 11.4, 0.76H, H-9), 5.04-5.22 (m, 3H, H-9", H-12), 4.76-4.89 (m, 1H, H-11), 4.36-4.59 (m, 1H, H-8), 3.72 (s, 0.76H, H-6'), 3.29-3.57 (m, 3.28H, H-6a, H-6'), 3.03-3.23 (m, 1H, H-2b), 2.78-2.88 (m, 0.76H, H-3), 2.56-2.74 (m, 1H, H-3, H-6b), 2.41-2.52 (m, 0.24H, H-6b), 2.23-2.34 (m, 1H, H-2a), 2.08-2.16 (m, 1H, H-7a), 1.65-1.88 (m, 2H, H-4, H-5a), 1.47-1.60 (m, 0.76H, H-5b), 1.34-1.46 (m, 0.24H, H-5b), 1.13-1.22 (m, 0.24H, H-7b), 0.91-1.02 (m, 0.76H, H-7b).^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3 (q), 155.1 (q), 146.8, 144.6 (q), 144.4 (q), 142.5, 136.6 (q), 133.3 (q), 131.6, 130.0, 129.6 (q), 129.5, 128.7, 128.6,

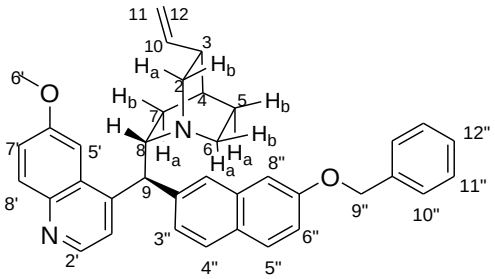
128.5, 127.3, 126.9, 123.5, 123.0, 122.8, 121.2, 114.6, 114.3, 102.2, 77.3, 70.6 (q), 56.8 (q), 56.4, 55.7, 44.6, 42.3, 40.1, 30.5, 28.3, 28.0. (^{13}C resonances associated with the major rotamer only) IR (solid, cm^{-1}): ν 2924, 2860, 1620, 1508, 1453, 1430, 1237, 1088, 1024, 907, 803, 729, 696. HRMS (ESI+): Calcd. for $[C_{37}H_{36}N_2O_2 + H]^+$ requires 541.2855; found 541.2855.

(2*S*)-2-((*S*)-(2-(benzyloxy)naphthalen-8-yl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (17a)



Procedure as for **10a** using a solution of 2-(benzyloxy)-8-bromomagnesiumnaphthalene (739 mg, 2.19 mmol) in THF (6.0 mL), 9-*epi*-chloroquinine (500 mg, 1.46 mmol) and THF (6.0 mL) to give **17a** (895 mg, 39%). M.p. 62-64 °C. $[\alpha]_D^{20}$ = -124.5 (c 0.068, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, J = 4.4, 1H, H-2'), 8.09 (d, J = 9.6, 1H, H-8'), 7.95-8.02 (br s, 1H, H-5'), 7.80 (d, J = 6.8, 1H, H-2"), 7.70 (app. t, 2H, H-11"), 7.23-7.52 (m, 9H, H-3', H-7', H-3", H-4", H-5", H-8", H-10", H-12"), 7.11 (d, J = 8.4, 1H, H-6"), 5.89-6.04 (m, 1H, H-10), 5.56 (d, J = 9.6, 1H, H-9), 4.91-5.18 (m, 4H, H-9", H-11, H-12), 4.33 (app. d, 1H, H-8), 3.84-3.99 (m, 4H, H-6', H-6a), 3.18-3.36 (m, 3H, H-2a, H-2b, H-6b), 2.90-3.02 (m, 1H, H-3), 2.69-2.82 (m, 1H, H-6b), 2.28-2.41(m, 1H, H-7b), 1.53-1.83 (m, 3H, H-4, H-5a, H-5b), 1.24-1.37 (m, 1H, H-7a). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9 (q), 151.6 (q), 142.7, 139.3 (q), 136.7, 131.4 (q), 128.1 (q), 127.4, 125.5, 124.5 (q), 123.8 (q), 123.4, 123.3 (q), 122.8, 122.3, 122.1 (q), 122.0, 120.6, 118.3, 116.1, 115.3, 112.9, 109.3, 98.3, 97.2, 64.6, 54.4, 50.9, 50.5, 50.4, 36.3, 34.4, 23.1, 22.7, 21.8. IR (solid, cm^{-1}): ν 2937, 2862, 1621, 1508, 1449, 1361, 1245, 1214, 1027, 908, 827, 727, 695. HRMS (ESI+): Calcd. for $[C_{37}H_{36}N_2O_2 + H]^+$ requires 541.2855; found 541.2848.

(2*S*)-2-((*S*)-(2-(benzyloxy)naphthalen-7-yl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (18a)



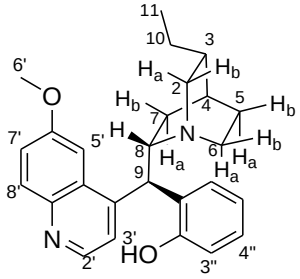
Procedure as for **10a** using a solution of 2-(benzyloxy)-7-bromomagnesiumnaphthalene (1.01 g, 3.00 mmol) in THF (9.0 mL) and 9-*epi*-chloroquinine (686 mg, 2.00 mmol) in THF (9.0 mL) to give **18a** (460 mg, 43%). M.p. 162-163 °C. $[\alpha]_D^{20}$ = -168.8 (c 0.201, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (d, J = 4.4, 1H, H-2'), 8.02 (d, J = 9.2, 1H, H-8'), 7.63-7.71 (m, 3H, H-3", H-4", H-8"), 7.56-7.62 (br s, 1H, H-5'), 7.46-7.51 (m, 3H, H-3', H-10"), 7.31-7.45 (m, 5H, H-7', H-5", H-11", H-12"), 7.09-7.18 (m, 2H, H-1", H-6"), 5.93-6.05 (m, 1H, H-10), 5.07-5.22 (m, 4H, H-9", H-11, H-12), 4.93 (d, J = 10.8, 1H, H-9), 3.80-4.08 (m, 4H, H-6', H-8), 3.36-3.51 (br s, 1H, H-6a), 3.21-3.33 (m, 1H, H-2b), 2.74-2.90 (m, 2H, H-2a, H-6b), 2.29-2.41 (br s, 1H, H-3), 1.89-2.07 (br s, 1H, H-7b), 1.74-1.82 (br s, 1H, H-4), 1.56-1.73 (m, 2H, H-5a, H-5b), 0.89-1.03 (m, 1H, H-7a). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3 (q), 156.5 (q), 147.2, 146.0 (q), 144.4 (q), 141.4, 139.7 (q), 136.5 (q), 134.1 (q), 131.5, 128.7, 128.4 (q), 128.1, 127.6 (q),

127.5, 127.0, 125.3, 123.6, 120.5, 118.3, 114.0, 106.7, 101.8, 85.0, 76.8, 69.5, 59.2, 56.1, 55.1, 49.3, 40.6, 39.0, 28.4, 27.6, 27.5. IR (solid, cm^{-1}): ν 2944, 2859, 1628, 1508, 1452, 1377, 1256, 1184, 1025, 1008, 827, 728. HRMS (ESI+): Calcd. for $[C_{37}H_{36}N_2O_2 + H]^+$ requires 541.2855; found 541.2859.

6.3 General procedure F for the debenzylation of protected catalysts by hydrogenation

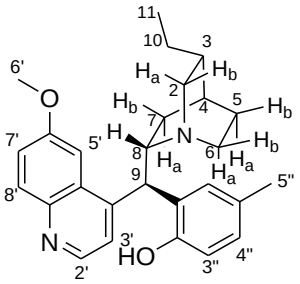
The benzylated catalyst precursors were placed in a round bottom flask with solvent and the flask was flushed with argon. 10% Pd/C (10 mol%) was added, the flask was evacuated, placed under an atmosphere of hydrogen gas at atmospheric pressure and stirred for 2-5 d. The flask was then evacuated and filled with an inert atmosphere. The mixture was filtered through a layer of celite with CH_2Cl_2 and/or MeOH or EtOH as the eluens. The solvent was removed *in vacuo* to afford the product.

(8*S*,9*R*)-9-(2-hydroxyphenyl)-6'-methoxy-10,11-dihydro-cinchonan (10)



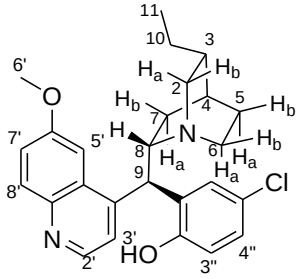
Procedure F was followed using **10a** (3.20 g, 6.71 mmol), 10% Pd/C (752 mg, 10 mol%), and EtOH (160 mL) to give **10** (2.66 g, 99%). M.p. 121-122 °C. $[\alpha]_D^{20}$ = -43.0 (c 0.123, $CHCl_3$). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.92 (br s, 1H, OH), 8.70 (d, J = 4.8, 1H, H-2'), 7.96 (br s, 1H, H-5'), 7.87 (d, J = 9.6, 1H, H-8'), 7.69 (d, J = 4.8, 1H, H-3'), 7.34 (dd, J = 2.4, 9.0, 1H, H-7'), 7.13 (d, J = 7.2, 1H, H-6"), 6.87 (t, J = 7.2, 1H, H-4"), 6.76 (d, J = 8.4, 1H, H-3"), 6.60 (t, J = 7.2, 1H, H-5"), 5.17 (d, J = 11.2, 1H, H-9), 3.93 (s, 3H, H-6'), 3.71 (d, J = 7.8, 1H, H-8), 3.46 (br s, 1H, H-6a), 2.96 (app. t, 1H, H-2b), 2.47 (br s, 1H, H-6b), 2.29 (app. d, 1H, H-2a), 1.89 (br s, 1H, H-7b), 1.49-1.54 (m, 2H, H-5b, H-4), 1.3-1.48 (m, 4H, H-3, H-5a, H-10), 0.86 (t, J = 7.2, 3H, H-11), 0.65 (1H, br s, H-7a). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 157.5 (q), 154.7 (q), 148.1 (q), 147.9, 144.3 (q), 131.4, 129.7 (q), 129.4 (q), 128.6, 126.8, 121.3, 120.3, 119.3, 115.2, 103.3, 59.3, 58.0, 55.8, 41.9, 41.1, 37.1, 29.2, 28.6, 27.3, 26.0, 12.4. IR (solid, cm^{-1}): ν 2928, 2969, 1621, 1586, 1508, 1454, 1237, 1029, 844, 827, 750, 711, 678. HRMS (ESI+): Calcd. for $[C_{26}H_{30}N_2O_2 + H]^+$ requires 403.2386; found 403.2378.

(8*S*,9*R*)-9-(5-2-methylhydroxyphenyl)-6'-methoxy-10,11-dihydro-cinchonan (11)



Procedure F was followed using **11a** (1.50 g, 2.97 mmol), 10% Pd/C (316 mg, 10 mol%), and EtOH (50 mL) to give **11** (1.23 g, 99%). M.p. 217-218 °C. $[\alpha]_D^{20}$ = -38.8 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.70 (br s, 1H, OH), 8.71 (d, J = 4.4, 1H, H-2'), 7.94 (br s, 1H, H-5'), 7.87 (d, J = 9.2, 1H, H-8'), 7.69 (d, J = 4.4, 1H, H-3'), 7.33 (dd, J = 2.4, 9.2, 1H, H-7'), 6.89 (br s, 1H, H-4"), 6.66 (br m, 2H, H-3", H-6"), 5.13 (d, J = 11.2, 1H, H-9), 3.91 (s, 3H, H-6'), 3.70 (br m, 1H, H-8), 3.50 (br m, 1H, H-6a), 2.96 (br m, 1H, H-2b), 2.45 (br m, 1H, H-6b), 2.28 (br m, 1H, H-2a), 2.03 (s, 3H, H-5"), 1.91 (m, 1H, H-7b), 1.60-1.27 (m, 6H, H-3, H-4, H-5a, H-5b and H-10), 0.85 (t, J = 7.2, 3H, H-11), 0.63 (m, 1H, H-7a). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.2 (q), 152.1 (q), 147.8 (q), 147.7, 143.9 (q), 131.0, 129.1 (q), 128.8 (q), 128.5, 127.2 (q), 127.1, 121.0, 119.9, 114.8, 103.0, 59.0, 57.2, 55.5, 41.7, 40.8, 36.8, 29.0, 28.2, 27.0, 25.6, 20.3, 12.1. IR (solid, cm^{-1}): ν 2957, 2937, 2859, 2599, 1623, 1586, 1505, 1436, 1319, 1242, 1017, 853, 813, 641. HRMS (ESI+): calcd. for $[C_{27}H_{32}N_2O_2 + H]^+$ requires 417.2542; found 417.2540.

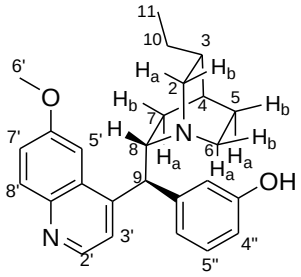
(8*S*,9*R*)-9-(5-2-chlorohydroxyphenyl)-6'-methoxy-10,11-dihydro-cinchonan (12)



A round bottom flask was charged with **12a** (500 mg, 1.04 mmol) and HCl (aq. 5 M, 10 mL), and stirred for 16 h. The resulting solution was neutralised using a saturated aqueous solution of $NaHCO_3$ and extracted three times with CH_2Cl_2 (3 x 35 mL). The organic extracts were combined, dried over $MgSO_4$ and solvent removed under reduced pressure. The resulting material was then placed in a round bottom flask, dissolved in EtOAc (10 mL) and methanol (5 mL) and placed under a protective argon atmosphere. % Pd/C (70 mg) was added, and the flask was evacuated and filled with an atmosphere of H_2 at 1 atm. This was stirred for 30 minutes before the flask was evacuated and refilled with argon. The resulting mixture was filtered through a pad of celite with EtOAc as the eluens. The solvent was removed under reduced pressure and the resulting material was purified by flash chromatography (30:20:1 hexane-EtOAc-NEt_3) to give **12** (377 mg, 83%) as a white solid. M.p. 204-205 °C. $[\alpha]_D^{20}$ = -24.8 (c 0.165, $CHCl_3$). ^{1}H NMR (400 MHz, MeOD-d_4): δ = 8.70 (d, J = 4.8, 1H, H-2'), 7.97 (br s, 1H, H-5'), 7.90 (d, J = 9.2, 1H, H-8'), 7.74 (d, J = 4.8, 1H, H-3'), 7.37 (dd, J = 2.8, 9.2, 1H, H-7'), 7.17 (br s, 1H, H-6"), 6.95 (dd, J = 2.4, 8.4, 1H, H-4"), 6.78 (d, J = 8.4, 1H, H-3"), 5.35 (d, J = 10.4, 1H, H-9), 3.99 (s, 3H, H-6'), 3.90 (m, 1H, H-8), 3.71 (m, 1H, H-6a), 3.15 (m, 1H, H-2b), 2.65 (m, 1H, H-2a), 2.49 (m, 1H, H-6b), 2.09 (m,

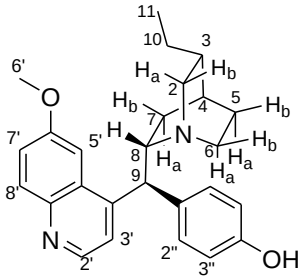
1H, H-7b), 1.75-1.64 (m, 2H, H-3, H-5b), 1.62-1.47 (m, 4H, H-4, H-5a, H-10), 0.95 (t, J = 6.8, 3H, H-11), 0.84 (m, 1H, H-7a). ^{13}C NMR (100 MHz, MeOD-d_4): δ = 159.3 (q), 154.3 (q), 148.8 (q), 146.8, 144.0 (q), 130.3 (q), 129.8, 128.4 (q), 128.1, 127.2, 124.6 (q), 122.3, 119.8, 116.6, 102.2, 60.1, 57.6, 55.0, 42.2, 40.9, 36.9, 28.7, 27.6, 27.1, 25.7, 11.0. IR (solid, cm^{-1}): ν 2926, 2860, 2581, 1622, 1584, 1513, 1477, 1432, 1264, 1242, 1018, 813, 727, 653. HRMS (ESI+): Calcd. for $[C_{26}H_{29}N_2O_2Cl + H]^+$ requires 437.1996; found 437.2106.

(8*S*,9*S*)-9-(3-hydroxyphenyl)-6'-methoxy-10,11-dihydro-cinchonan (13)



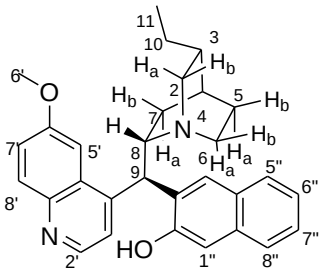
Procedure F was followed using **13a** (800 mg, 1.68 mmol), 10% Pd/C (188 mg, 10 mol%), and EtOH (40 mL) to give **13** (673 mg, 99%). M.p. 111-112 °C $[\alpha]_D^{20}$ = -148.8 (c 0.088, $CHCl_3$). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.11 (s, 1H, OH), 8.72 (d, J = 4.8, 1H, H-2'), 7.90 (d, J = 9.6, 1H, H-8'), 7.68 (s, 1H, H-5'), 7.64 (d, J = 4.2, 1H, H-3'), 7.37 (d, J = 9.0, 1H, H- 7'), 6.97 (t, J = 7.2, 1H, H-5"), 6.88 (d, J = 7.2, 1H, H-6"), 6.78 (s, 1H, H-2"), 6.47 (d, J = 7.2, 1H, H-4"), 4.73 (d, J = 10.8, 1H, H-9), 3.96 (s, 3H, H-6'), 3.68 (br s, 1H, H-8), 3.38 (br s, 1H, H-6a), 2.98 (app. t, 1H, H-2b), 2.48 (br s, 1H, H-6b), 2.33 (app. d, 1H, H-2a), 1.82 (br s, 1H, H-7b), 1.58 (br s, 2H, H-4, H-5a), 1.3-1.5 (m, 4H, H-3, H-5b, H-10), 0.86 (t, J = 7.2, 3H, H-11), 0.64 (br s, 1H, H-7a). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.1 (q), 156.9 (q), 147.7, 146.8 (q), 144.6 (q), 144.1 (q), 131.3, 128.7, 120.8, 119.8, 119.1, 115.2, 112.8, 102.9, 79.2 (q), 58.4, 57.6, 55.6, 49.0, 40.4, 36.9, 28.6, 28.4, 27.1, 25.7, 12.1. IR (solid, cm^{-1}): ν 2929, 2862, 1621, 1586, 1509, 1454, 1364, 1230, 1030, 828, 756, 714, 697. HRMS (ESI+): Calcd. for $[C_{26}H_{30}N_2O_2 + H]^+$ requires 403.2386; found 403.2394.

(8*S*,9*S*)-9-(4-hydroxyphenyl)-6'-methoxy-10,11-dihydro-cinchonan (14)



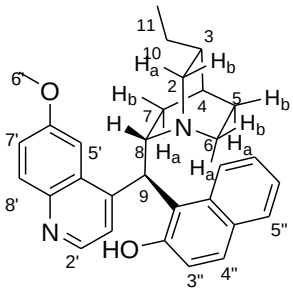
Procedure F was followed using **14a** (100 mg, 0.21 mmol), 10% Pd/C (23.5 mg, 10 mol%), and EtOH (5 mL) to give **14** (81 mg, 99%). M.p. 177-178 °C. $[\alpha]_D^{20}$ = -187.7 (c 0.089, $CHCl_3$). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.07 (s, 1H, OH), 8.70 (d, J = 4.2, 1H, H-2'), 7.89 (d, J = 9.0, 1H, H-8'), 7.67 (br s, 1H, H-5'), 7.63 (d, J = 4.8, 1H, H-3'), 7.37 (dd, J = 2.4, 9.0, 1H, H-7'), 7.21 (d, J = 8.4, 2H, H-2"), 6.57 (d, J = 8.4, 2H, H-3"), 4.71 (d, J = 10.8, 1H, H-9), 3.95(s, 3H, H-6'), 3.65 (br s, 1H, H-8), 3.35 (H-6a under DMSO residual peak), 2.98 (app. t, 1H, H-2b), 2.46 (br s, 1H, H-6b), 2.34 (br s, 1H, H-2a), 1.80 (br s, 1H, H-7b), 1.58 (app. br s, 2H, H-4, H-5a), 1.32-1.49 (m, 4H, H-10, H-3, H-5b), 0.85 (t, J = 7.2, 3H, H-11), 0.63 (br s, 1H, H-7a). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 157.5 (q), 155.7 (q), 148.0, 147.7 (q), 144.4 (q), 131.6, 129.3, 129.3 (q), 128.7, 121.0, 120.0, 115.0, 103.2, 58.8, 57.9, 55.9, 48.9, 48.5, 37.2, 31.0 (q), 28.9, 27.3, 26.1, 12.4. IR (solid, cm^{-1}): ν 2928, 2864, 1619, 1588, 1508, 1455, 1431, 1364, 1235, 1172, 1030, 824. HRMS (ESI+): Calcd. for $[C_{26}H_{30}N_2O_2 + H]^+$ requires 403.2386; found 403.2367.

(8*S*,9*R*)-6'-methoxy-9-(2-hydroxynaphtalen-3-yl)-cinchonan (15)



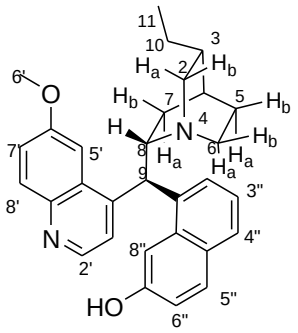
Procedure F was followed using **15a** (210 mg, 0.39 mmol), 10% Pd/C (42 mg, 10 mol%), and toluene (11.0 mL) to give **15** which was purified by column chromatography (49:1 CH_2Cl_2-NEt_3) to give 43 (165 mg, 95%) as a white solid. 1H NMR (400 MHz, $CDCl_3$): δ = 8.79-8.90 (br s, 1H, H-2'), 8.05 (d, J = 9.2, 1H, H-8'), 7.61 (d, J = 8.0, 1H, H-5"), 7.25-7.44 (m, 6H, H-3', H-5', H-7', H-4", H-7", H8"), 7.06-7.22 (m, 2H, H-1", H-6"), 4.57-5.58 (br m, 2H, H-OH, H-9), 3.83 (app. br s, 4H, H-6', H-8), 3.34-3.60 (br s, 1H, H-6a), 3.18-3.33 (m, 1H, H-2b), 2.87-3.01 (m, 1H, H-6b), 2.62-2.74 (app. d, 1H, H-2a), 1.66-1.81 (m, 3H, H-3, H-4, H-7b), 1.50-1.64 (m, 2H, H-5a, H-5b), 1.33-1.46 (m, 2H, H-10), 0.94-1.06 (br s, 1H, H-7a), 0.81-0.93 (m, 3H, H-11). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5 (q), 155.1 (q), 146.7, 144.8 (q), 133.8 (q), 131.5, 131.1 (q), 128.1 (q), 127.2 (q), 127.1, 125.5, 125.0, 122.7 (q), 122.2, 121.5, 112.9, 102.1, 76.8, 59.9, 55.3, 55.2, 40.1, 36.6, 28.4, 27.2, 27.1, 25.1, 20.6, 13.7, 11.6. IR (solid, cm^{-1}): ν 2934, 2873, 1618, 1580, 1506, 1463, 1241, 1225, 1183, 1085, 1035, 1016, 999, 979, 853, 827, 757, 741, 713, 702. HRMS (ESI+): Calcd. for $[C_{30}H_{32}N_2O_2 + H]^+$ requires 453.2542; found 453.2540.

(8*S*,9*R*)-6'-methoxy-9-(1-hydroxynaphtalen-2-yl)-cinchonan (16)



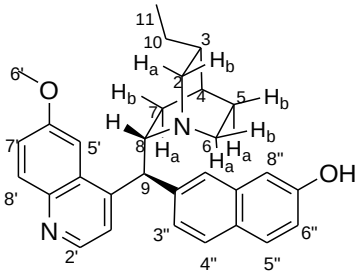
Procedure F was followed using **16a** (420 mg, 0.78 mmol), 10% Pd/C (83 mg, 10 mol%), and EtOH (20 mL) to give **16** (352 mg, 99%). M.p. 121-122 °C. $[\alpha]_D^{20}$ = -203.8 (c 0.067, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (d, J = 4.0, 1H, H-2'), 8.03 (d, J = 8.8, 1H, H-5"), 7.94-7.99 (br s, 1H, H-5'), 7.91 (d, J = 8.8, 1H, H-8"), 7.58-7.69 (m, 3H, H-3', H-7", H-6"), 7.21-7.32 (m, 2H, H-3", H-7'), 7.12-7.20 (m, 2H, H-4", H-8'), 4.97-5.25 (br s, 1H, H-9), 3.85-4.04 (m, 4H, H-6', H-8), 3.31-3.42 (m, 1H, H-6a), 3.18-3.30 (m, 1H, H-2b), 2.79-2.92 (m, 1H, H-2a), 2.56-2.67 (m, 1H, H-6b), 1.87-2.00 (m, 2H, H-4, H-7b), 1.52-1.76 (m, 4H, H-3, H-5a, H-5b, H-7a), 1.22-1.38 (m, 2H, H-10), 0.86 (t, J = 7.6, 3H, H-11). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1 (q), 154.9 (q), 146.3, 144.9 (q), 133.5 (q), 131.3, 129.4, 129.0 (q), 128.4, 127.5 (q), 125.5, 123.8 (q), 122.9, 122.3, 121.7, 121.3, 117.2 (q), 102.3, 76.8, 57.7, 55.4, 55.1, 41.0, 35.8, 29.2, 27.4, 26.4, 25.6, 25.4, 11.3. IR (solid, cm^{-1}): ν 2829, 2870, 1619, 1507, 1455, 1314, 1236, 1029, 1006, 857, 818, 740. HRMS (ESI+): Calcd. for $[C_{30}H_{32}N_2O_2 + H]^+$ requires 453.2542; found 453.2535.

(8*S*,9*S*)-6'-methoxy-9-(7-hydroxynaphtalen-1-yl)-cinchonan (17)



Procedure F was followed using **17a** (1800 mg, 3.32 mmol), 10% Pd/C (360 mg, 10 mol%), and EtOAc (90 mL). The resulting product was purified by column chromatography (2:5:93 NEt_3:MeOH:EtOAc) to give **17** (986 mg, 66%). M.p. 256 °C (dec.). $[\alpha]_D^{20}$ = +103.1 (c 0.012, $CHCl_3$). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.90 (s, 1H, OH), 8.71 (d, J = 4.8, 1H, H-2'), 7.91-7.98 (br s, 1H, H-5'), 7.86 (d, J = 8.4, 1H, H-8'), 7.80-7.43 (m, 5H, H-3', H-2", H-3", H-4" and H-5"), 7.30 (d, J = 8.4, 1H, H-7'), 7.00-7.20 (m, 2H, H-6", H-8"), 5.33-5.53 (br s, 1H, H-9), 4.08-4.26 (br s, 1H, H-8), 3.80 (s, 3H, 6'), 3.59-3.31 (br m, 1H, H-2b) (partly obscured by residual H_2O peak), 2.82-3.01 (br s, 1H, H-6a), 2.20-2.58 (partly obscured by residual solvent peak), (m, 2H, H-6b, H-2a), 1.84-2.04 (br s, 1H, H-7b), 1.56-1.80 (m, 2H, H-4, H-5a), 1.21-1.55 (m, 4H, H-10, H-3, H-5b), 0.93-1.09 (br s, 1H, H-7a), 0.76-0.91 (t, J = 7.2, 3H, H-11). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.2 (q), 155.8 (q), 147.7, 144.0 (q), 133.1 (q), 131.4, 130.6, 128.6 (q), 128.5 (q), 128.2 (q), 126.5, 126.1, 122.2, 121.4, 120.5, 117.7, 105.4, 102.4, 60.8 (q), 57.2, 55.6, 54.9, 48.6, 43.1, 41.3, 36.7, 28.1, 27.0, 25.3, 12.1. IR (solid, cm^{-1}): ν 2948, 2868, 1619, 1585, 1508, 1452, 1359, 1221, 1026, 836, 748, 712. HRMS (ESI+): Calcd. for $[C_{30}H_{32}N_2O_2 + H]^+$ requires 453.2542; found 453.2541.

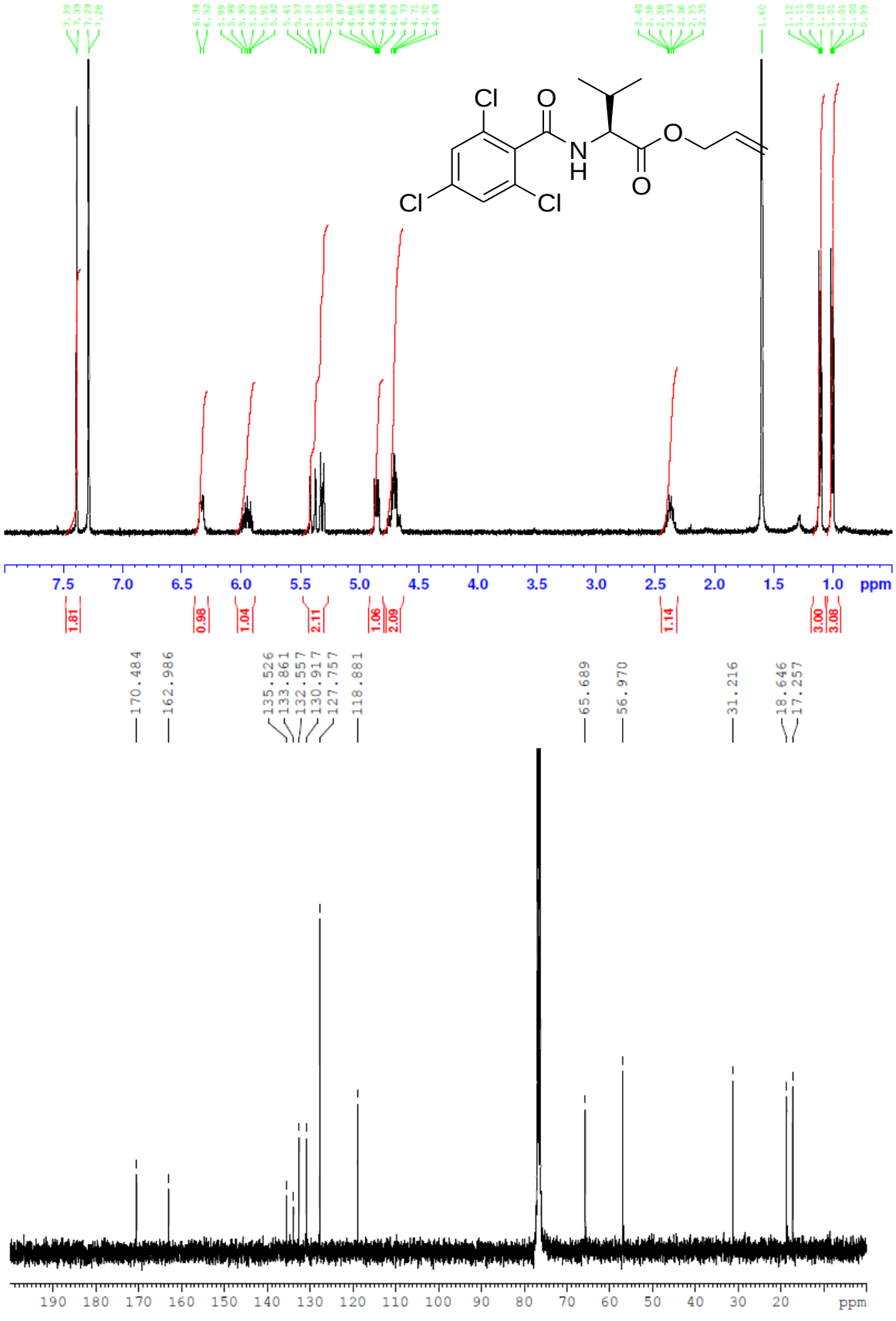
(8*S*,9*S*)-6'-methoxy-9-(7-hydroxynaphtalen-2-yl)-cinchonan (18)



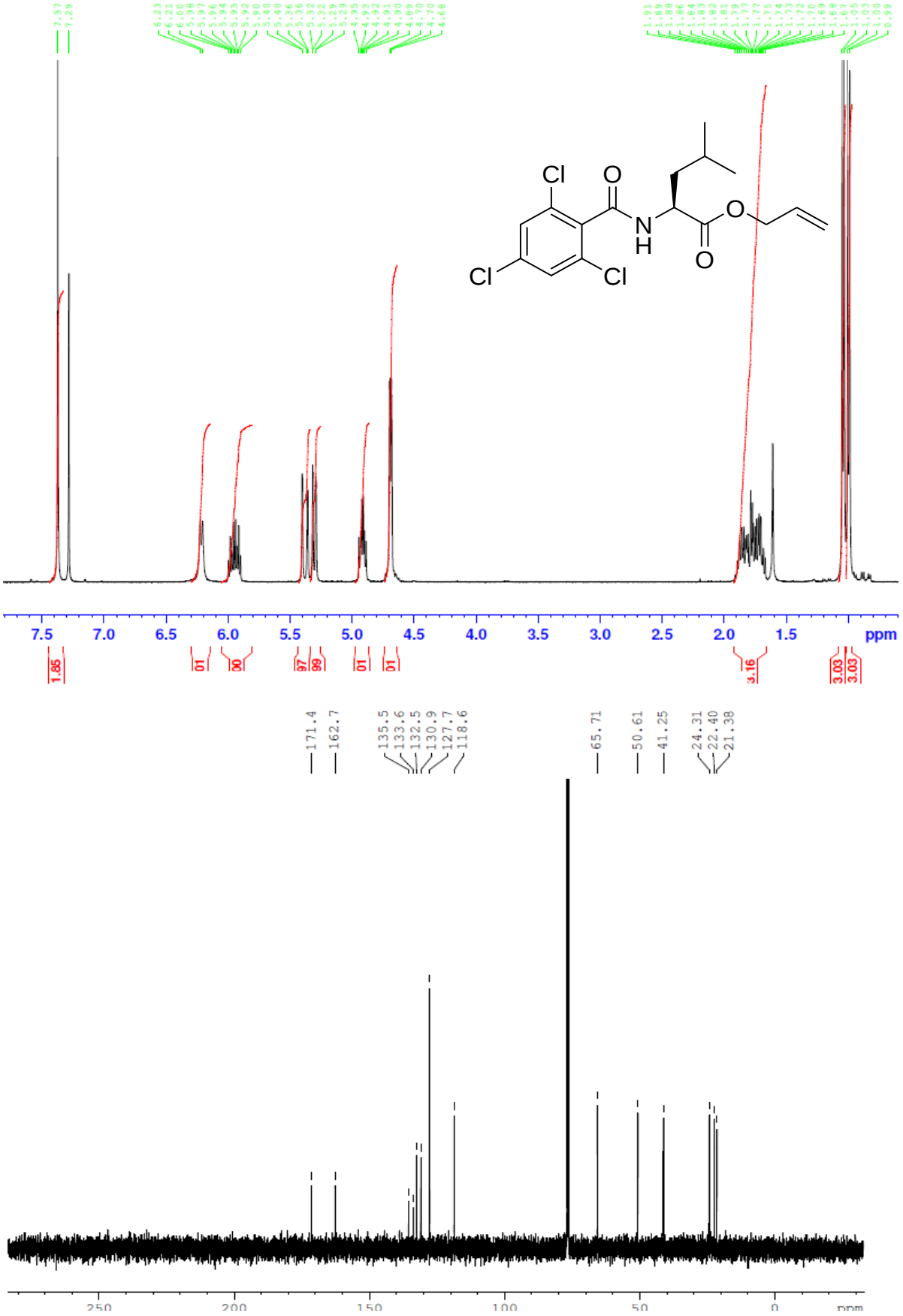
Procedure F was followed using **18a** (360 mg, 0.66 mmol), 10% Pd/C (71 mg, 10 mol%), and EtOH (17.5 mL) to give **18** (295 mg, 99%). M.p. 99-101 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.59 (s, 1H, H-OH), 8.74 (d, J = 4.2, 1H, H-2'), 7.88 (d, J = 9.6, 1H, H-8'), 7.79 (br s, 1H, H-5'), 7.77 (d, J = 4.2, 1H, H-3'), 7.59 (d, J = 9.0, 1H, H-5"), 7.56 (d, J = 8.4, 1H, H-3"), 7.31-7.37 (m, 2H, H-4", H-7'), 7.00 (s, 1H, H-8"), 6.96 (d, J = 8.4, 1H, H-6"), 4.95 (d, J = 9.6, 1H, H-9), 3.98 (s, 3H, H-6'), 3.85 (br s, 1H, H-8), 3.48 (br s, 1H, H-6a), 2.94 (br s, 1H, H-2b), 2.39 (br s, 1H, H-6b), 2.35 (br s, 1H, H-2a), 1.89 (br s, 1H, H-7b), 1.62 (br s, 2H, H-4, H-5a), 1.31-1.50 (m, 4H, H-3, H-5b, H-10), 0.97 (br s, 3H, H-11), 0.74 (br s, 1H, H-7a). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 157.1 (q), 155.2 (q), 147.7, 144.1 (q), 134.4 (q), 131.3, 128.7, 127.0, 126.3 (q), 125.0, 123.2, 120.8, 119.8, 117.9, 108.3, 102.8, 67.0 (q), 59.7, 58.3, 57.5, 55.6, 49.4, 45.7 (q), 36.8, 30.6, 28.3, 27.0, 25.7, 25.1 (q), 12.0. IR (solid, cm^{-1}): ν 2928, 2862, 1621, 1586, 1509, 1454, 1364, 1216, 1174, 1028, 830, 712. HRMS (ESI+): Calcd. for $[C_{30}H_{32}N_2O_2 + H]^+$ requires 453.2542; found 453.2540.

7 NMR spectra for 10 and 43-48

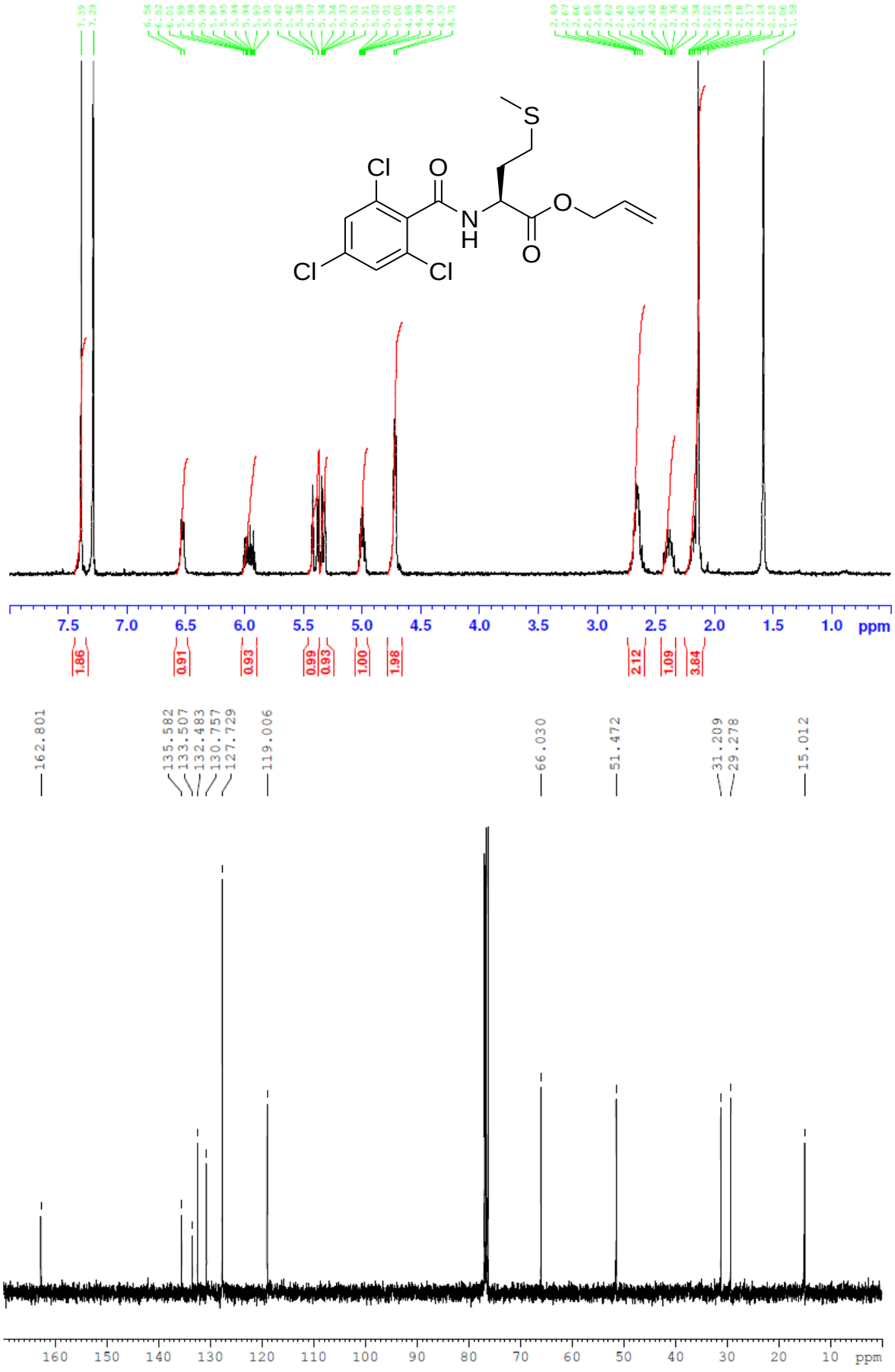
2,4,6-trichloro-*N*-Benzoyl valine allyl ester (43)



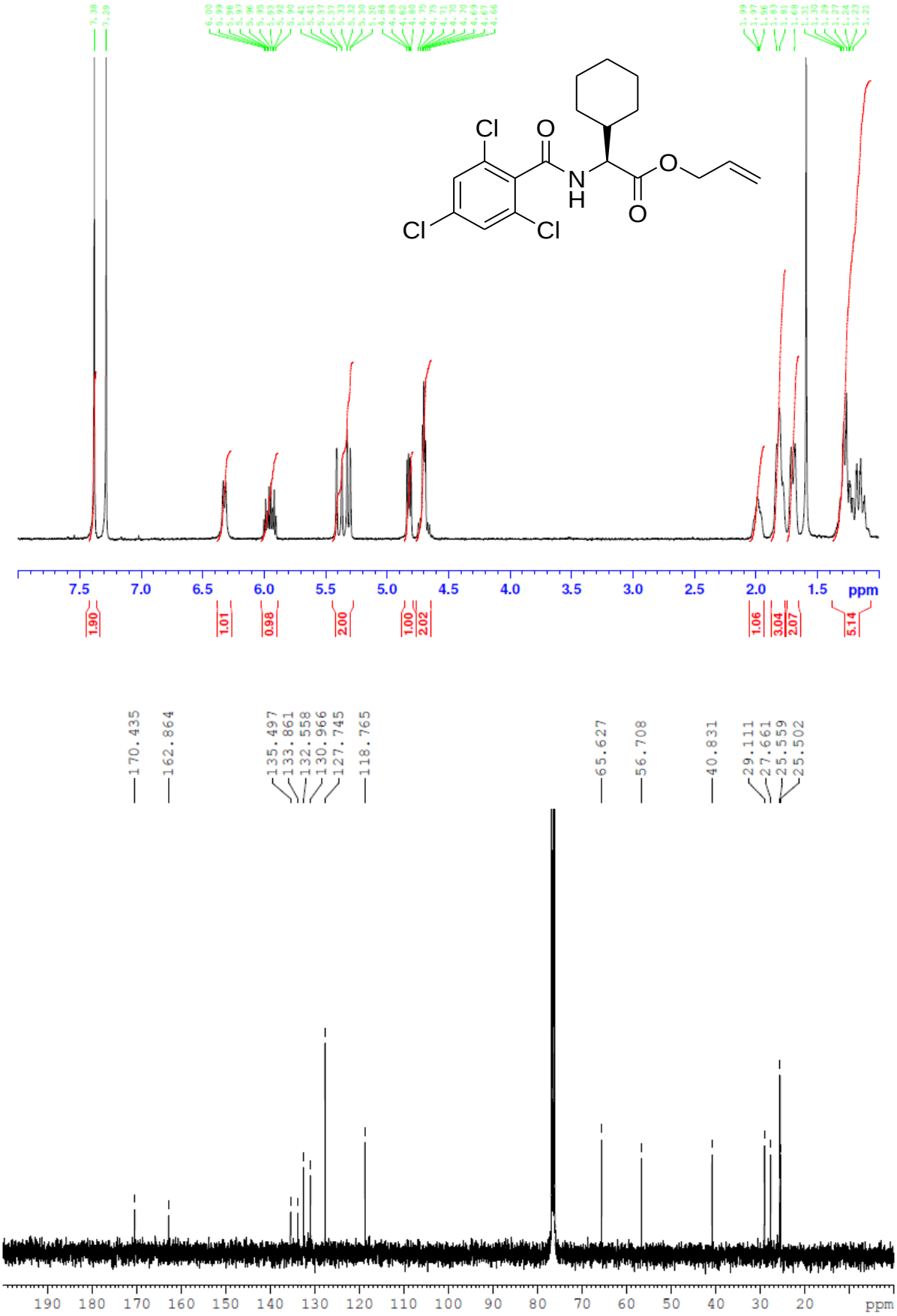
2,4,6-trichloro-*N*-benzoyl leucine allyl ester (44)



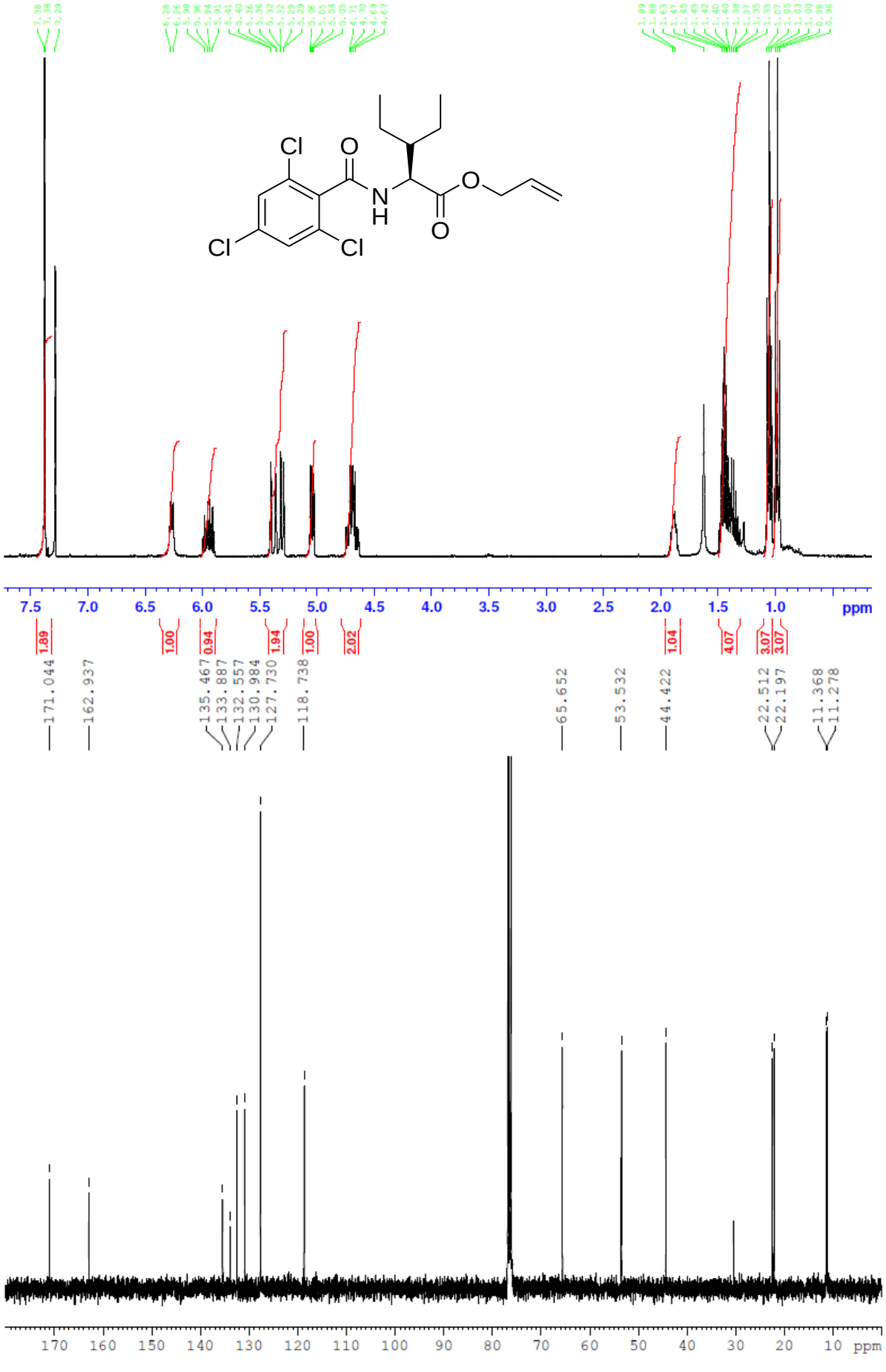
2,4,6-trichloro *N*-Benzoyl methionine allyl ester (45)



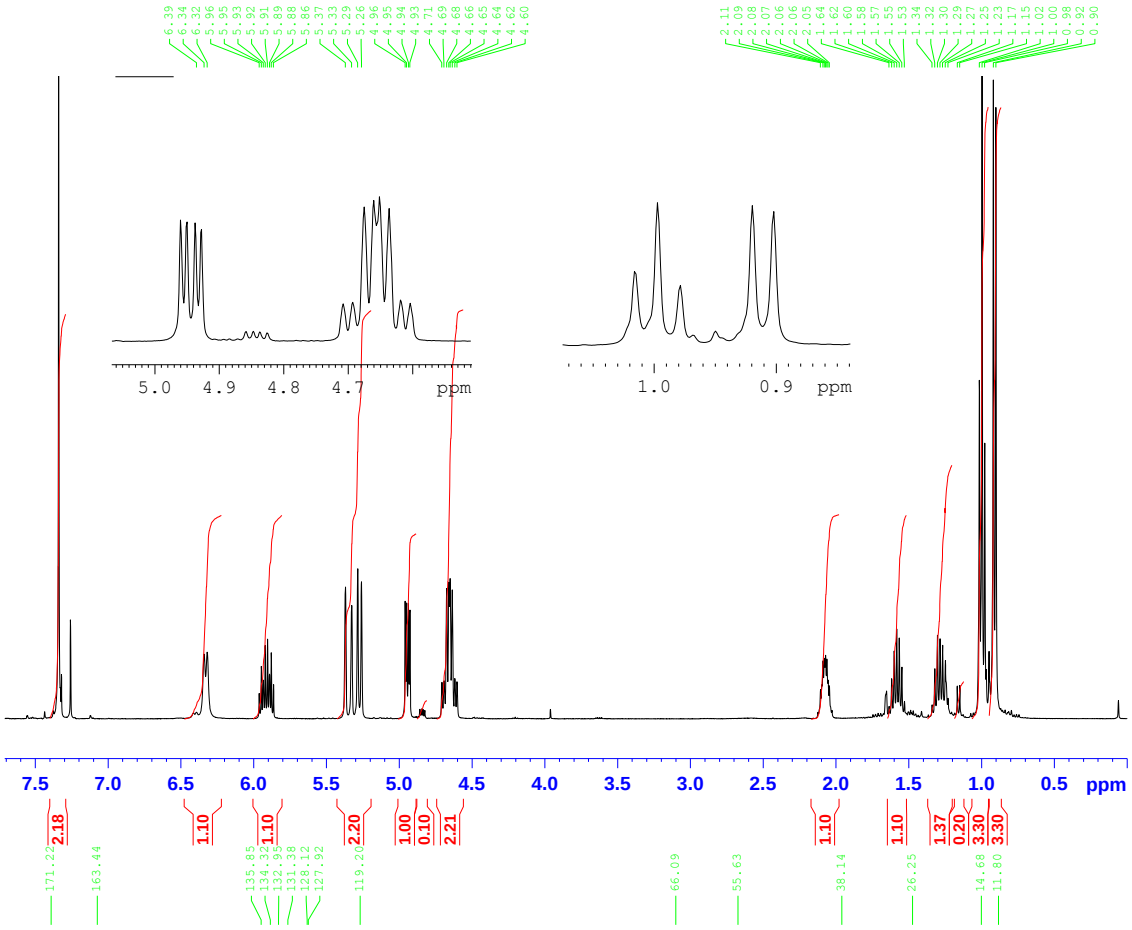
Allyl 2-(2,4,6-trichlorobenzamido)-2-cyclohexylacetate (46)

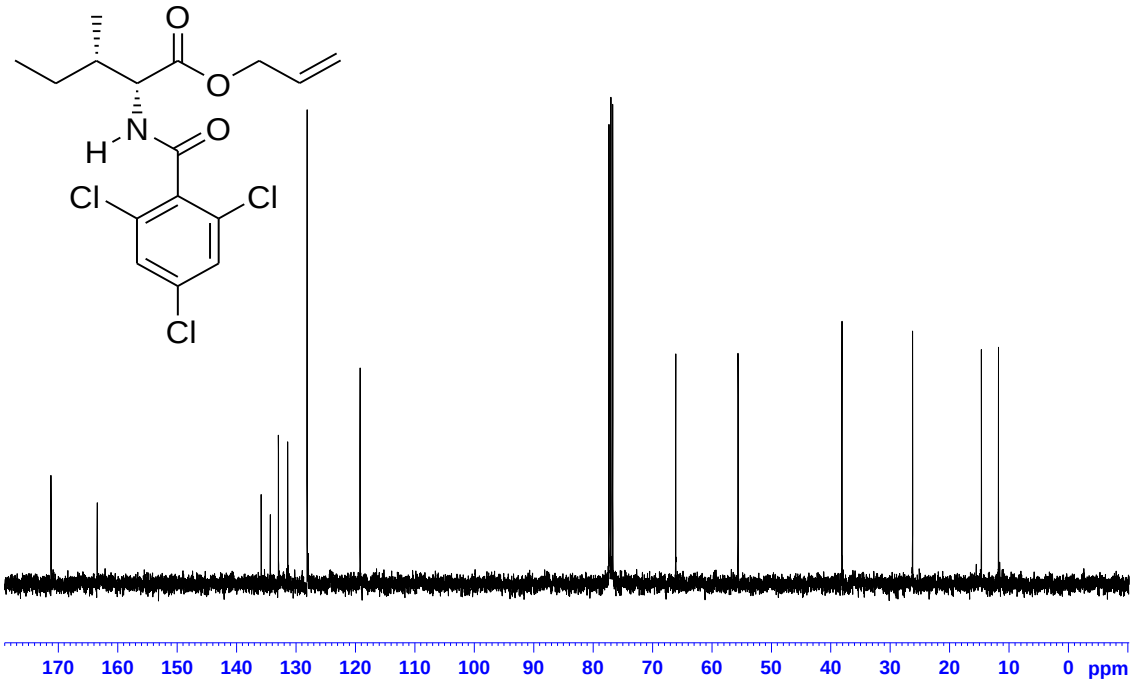


allyl 2-(2,4,6-trichlorobenzamido)-3-ethylpentanoate (47)



N-(2,4,6-trichlorobenzoyl)-D-Allo-Isoleucine allyl ester (48)





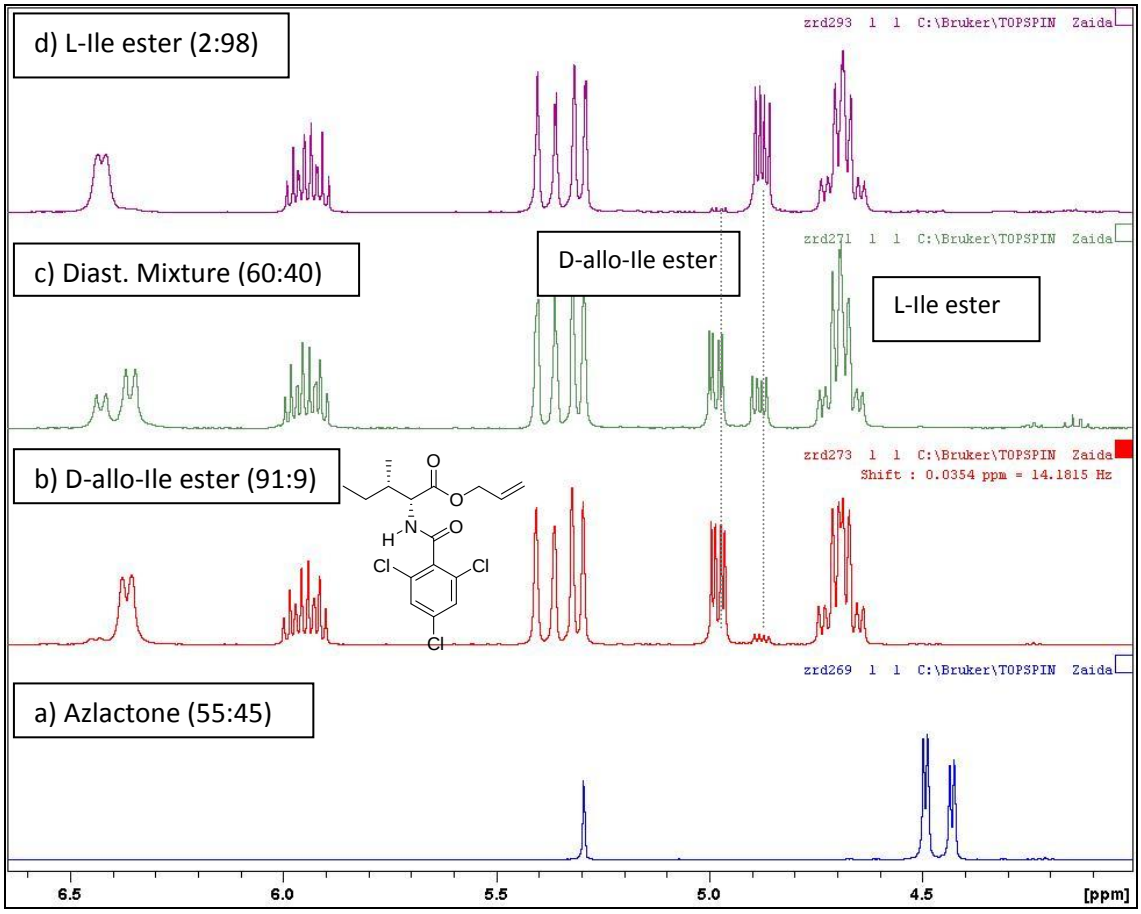
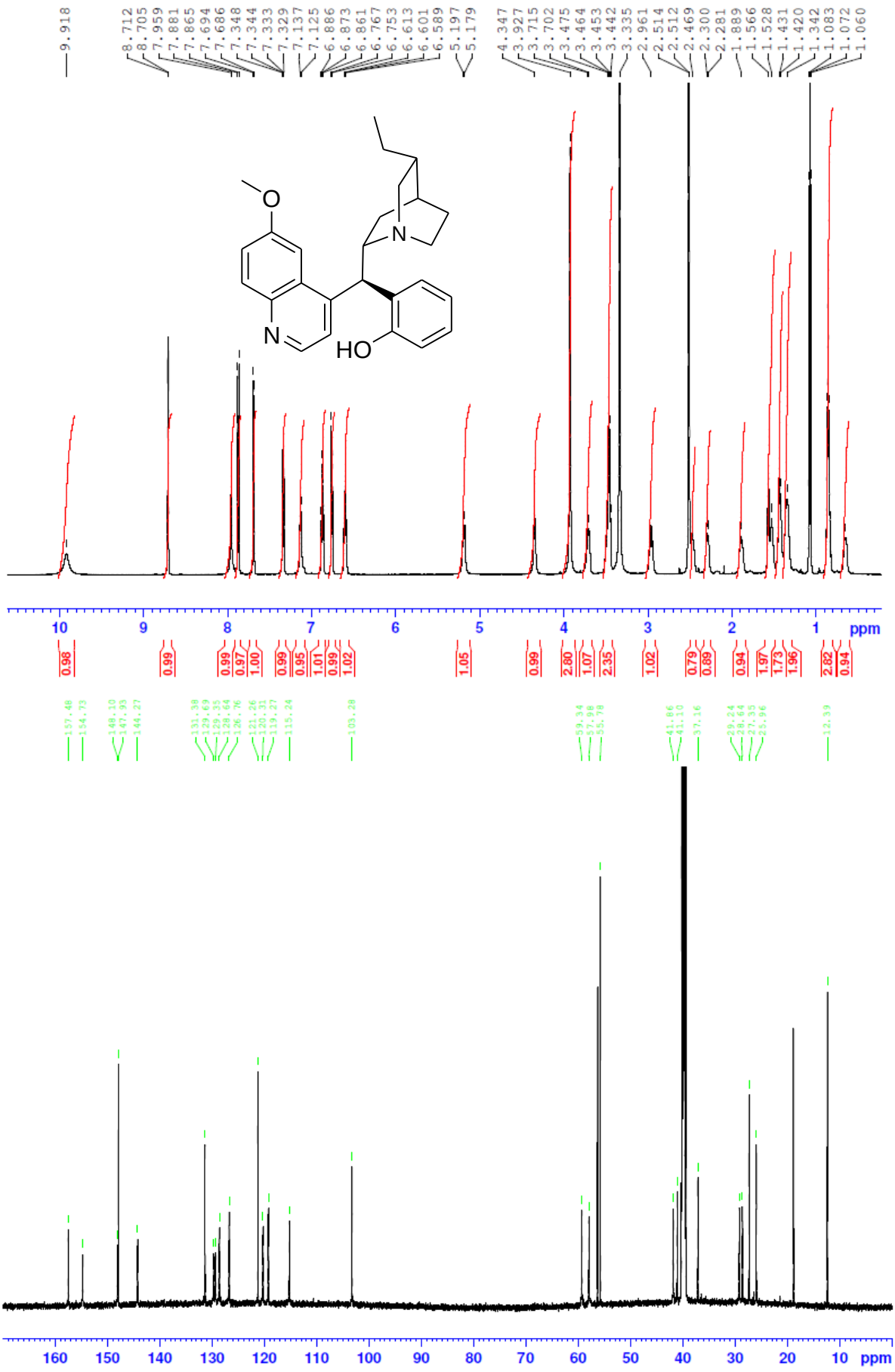
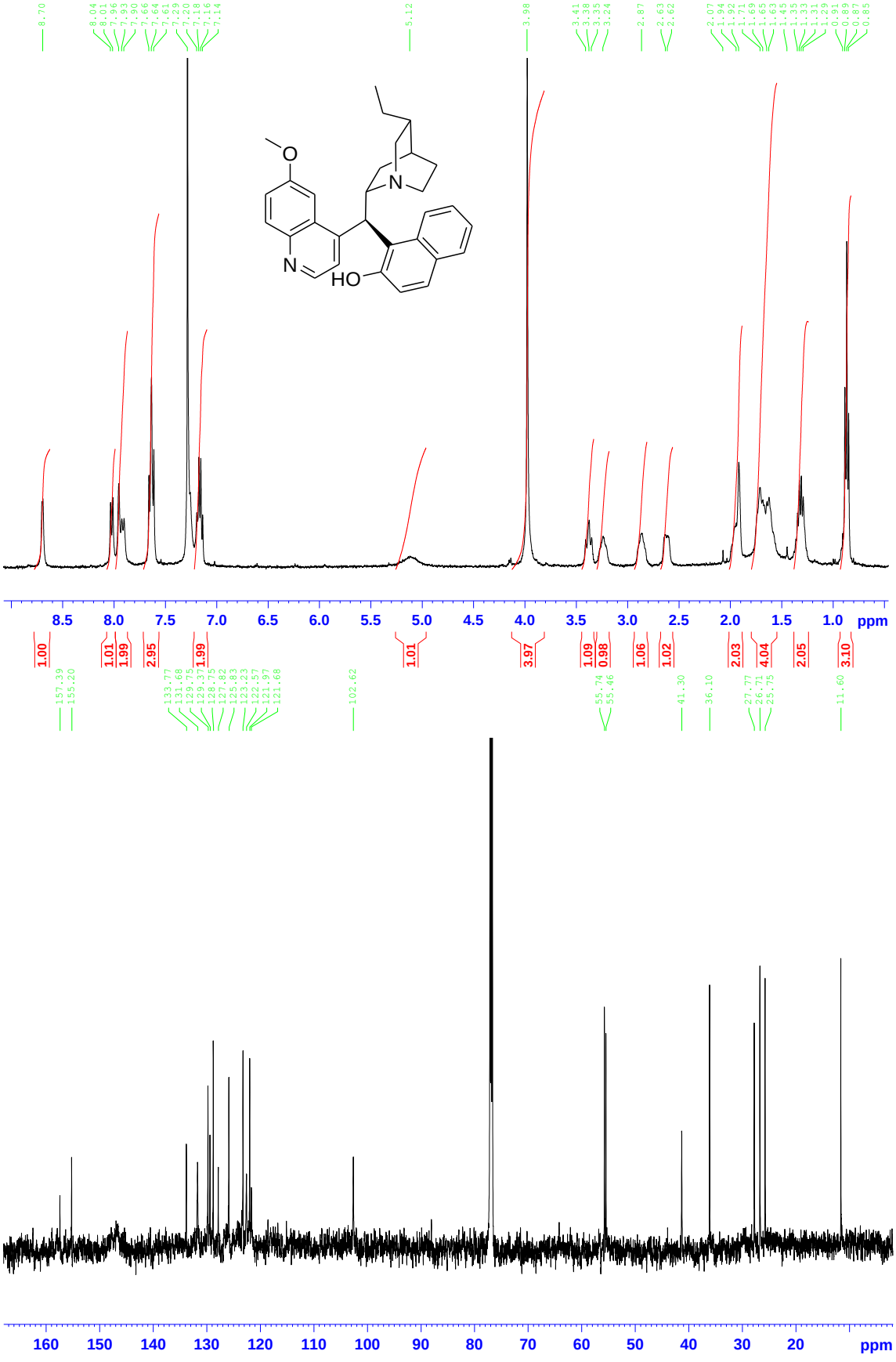


Figure 1: ^{1}NMR spectra corresponding to: a) the azlactone starting material, b) D-allo-isoleucine allyl ester obtained using catalyst **16**, c) the mixture of diastereomers of D-allo-isoleucine and L-Isoleucine allyl ester obtained using Et_3N as the catalyst and d) L-Isoleucine allyl ester obtained as a single diasteromer starting from commercially available L-Isoleucine. The arrows highlight the diagnostic resonances associated with the α-protons of the isoleucine side chain of the two diasteromers.

(8*S*,9*S*)-9-(2-hydroxyphenyl)-6'-methoxy-10,11-dihydro-cinchonan (10)



(8*S*,9*R*)-6'-methoxy-9-(1-hydroxynaphtalen-2-yl)-cinchonan (16)

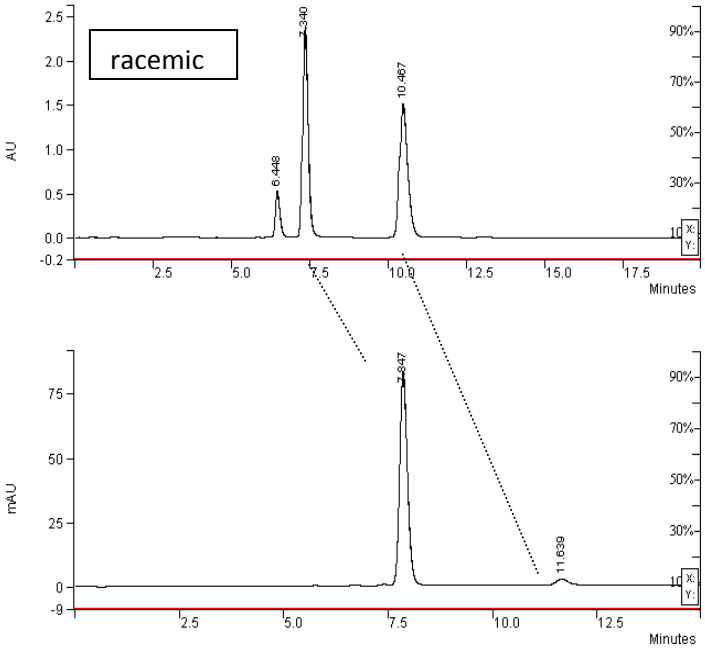


8 HPLC data

2,4,6-trichloro-*N*-Benzoyl valine allyl ester (43)

CSP-HPLC conditions after hydrogenolysis of **43**: Chiralpak ADH (4.6 mm × 250mm), eluent 9:1 hexane/isopropanol, flow 1mL/min., UV detection at λ 220nm.

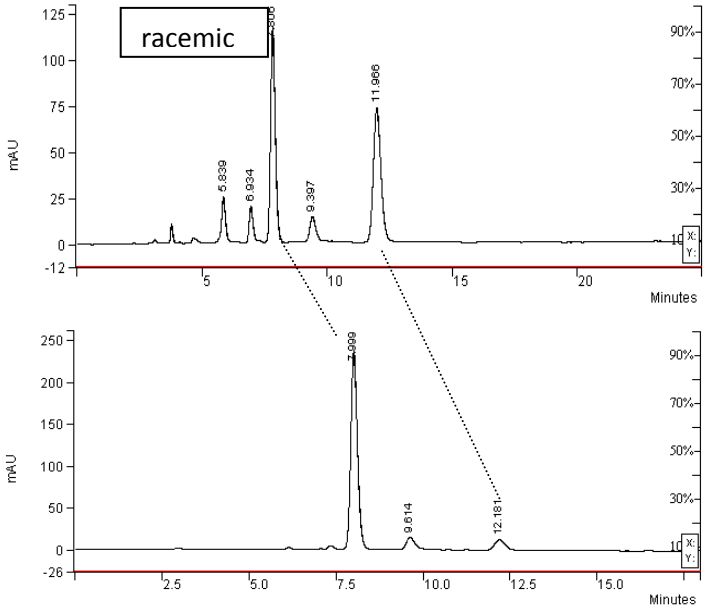
Peak	Retention time (min.)	Area (%)
1	7.8	95.24
2	11.6	4.76



2,4,6-trichloro-*N*-benzoyl leucine allyl ester (44)

CSP-HPLC conditions after hydrogenolysis of **44**: Chiralpak ADH (4.6 mm × 250mm), eluent 9:1 hexane/isopropanol, flow 1mL/min., UV detection at λ 220nm.

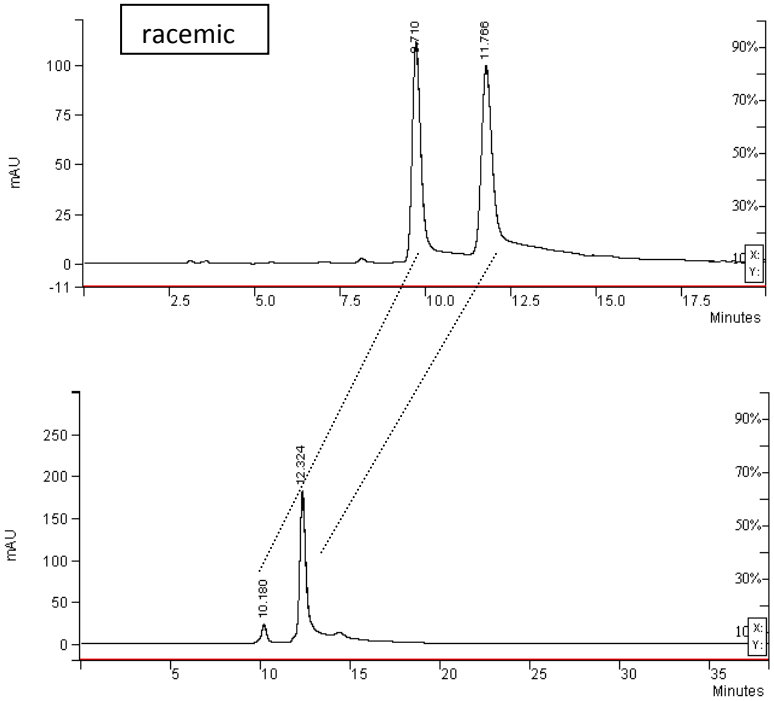
Peak	Retention time (min.)	Area (%)
1	8.0	85.44
3	12.2	7.22



2,4,6-trichloro *N*-Benzoyl methionine allyl ester (45)

CSP-HPLC conditions: Chiralpak ADH (4.6 mm × 250mm), eluent 9:1 hexane/isopropanol, flow 1mL/min., UV detection at λ 220nm.

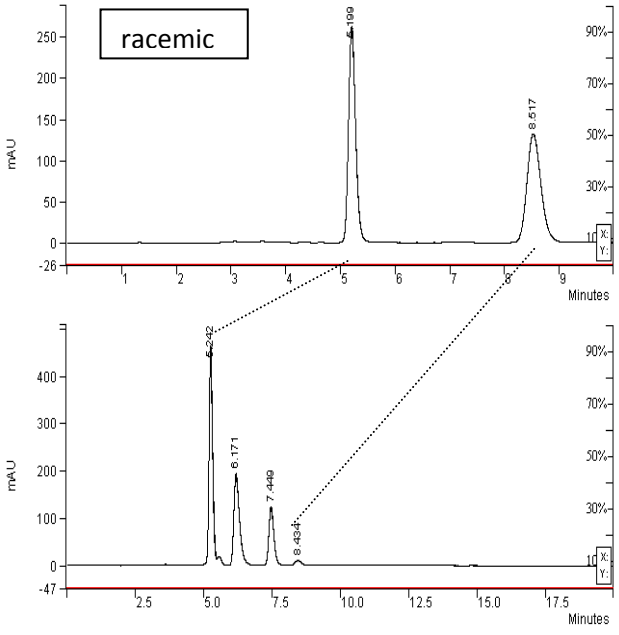
Peak	Retention time (min.)	Area (%)
1	10.2	7.66
2	12.3	92.34



Allyl 2-(2,4,6-trichlorobenzamido)-2-cyclohexylacetate (46)

CSP-HPLC conditions after hydrogenolysis of **46**: Chiralpak ADH (4.6 mm × 250mm), eluent 9:1 hexane/isopropanol, flow 1mL/min., UV detection at λ 220nm.

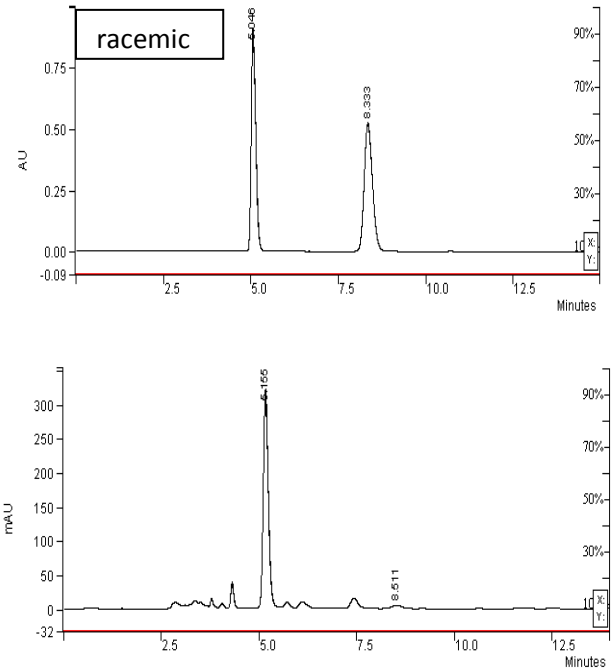
Peak	Retention time (min.)	Area (%)
1	5.2	48.47
4	8.4	1.91



allyl 2-(2,4,6-trichlorobenzamido)-3-ethylpentanoate (47)

CSP-HPLC conditions after hydrogenolysis of **47**: Chiralpak ADH (4.6 mm × 250mm), eluent 9:1 hexane/isopropanol, flow 1mL/min., UV detection at λ 220nm.

Peak	Retention time (min.)	Area (%)
1	5.2	97.1
2	8.5	2.9



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