CHEMISTRY
A EUROPEAN JOURNAL

Supporting Information

Quarternary Stereogeneric Carbons in Complex Molecules by an Asymmetric Organocatalytic Triple-Cascade Reaction

Oriol Penon,[b] Armandi Carlone,[a] Andrea Mazzanti,[a] Manuela Locatelli,[a] Letizia Sambri,[a] Guiseppe Bartoli,[a] and Paolo Melchiorre*[a]

[a] Dipartimento di Chimica Organica "A Mangini"
Alma Mater Studiorum - Universita di Bologna
viale Risorgimento, 4 - 40136 Bologna (Italy)

[b] Facultat de Farmacia
Universitat de Barcelona
Avinguda Joan XXIII s/n - 08028
Barcelona (Spain)

Contents

General Methods.

The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. ^{1}H and ^{13}C NMR spectra of compounds **4a, 7a** and **9** were recorded at 600 MHz for ^{1}H and 150.8 for ^{13}C. All the ^{1}H and ^{13}C signals were assigned by means of g-COSY, g-HSQC and g-HMBC 2D-NMR sequences. NOE spectra were recorded using the DPFGSE-NOE sequence,[1] using a mixing time of 2.00 s and "rsnob" 20 ÷ 50 Hz wide selective pulses, depending on the crowding of the spectra region. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$ and CD_3CN). Coupling constants are given in Hz. When 2D-NMR were not performed, carbon types were determined from DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh) according to the method of Still.[2] Analytically pure stereoisomers were obtained by crystallization (hexane/*i*-PrOH 9:1) for compound **7a**, and by means of semipreparative HPLC for compounds **4a** (Waters Novapak, silica 6 μm, 8x300 mm, hexane/iPrOH 97:3) and **9** (two jointed Phenomenex Luna C18(2), 10x250 mm, ACN/H_2O 90:10). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. High Resolution Mass spectra were obtained from the Department of Organic Chemistry *"A. Mangini"* Mass Spectroscopy facility. X-ray data were acquired at the Department of Physical and Inorganic Chemistry X-ray Crystallography facility, on a Bruker APEX-2 difractometer. Optical rotations are reported as follows: $[\alpha]^{rt}_{D}$ (*c* in g per 100 mL, solvent). All reactions were carried out in air and using undistilled solvent, without any precautions to exclude moisture unless otherwise noted.

[1] a) J. Stonehouse, P. Adell, J. Keeler, A. J. Shaka, *J .Am. Chem. Soc.* **1994**, *116*, 6037; b) K. Stott, J. Stonehouse, J. Keeler, T. L. Hwang, A. J. Shaka, *J. Am. Chem. Soc.* **1995**, *117*, 4199; c) K. Stott, J. Keeler, Q. N. Van, A. J. Shaka, *J. Magn. Reson.* **1997**, *125*, 302.

[2] W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

Determination of Enantiomeric Purity. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H or AS-H columns and Daicel Chiralcel OD-H column with *i*-PrOH/hexane as the eluent were used.
HPLC traces were compared to racemic samples prepared by carrying out the reactions with racemic **5** as the catalyst.

ECD spectra. UV absorption spectra were recorded at 25 °C in acetonitrile in the 200-400 nm spectral region. The cell path length was 0.1 cm, concentration was $1.43 \cdot 10^{-4}$ mol L^{-1}. CD spectra were recorded at 25°C in acetonitrile, with the same path lengths of 0.1 cm, in the range 200-400 nm; reported $\Delta\varepsilon$ values are expressed as L $mol^{-1}cm^{-1}$.

DFT Calculations. Geometry optimization were carried out at the B3LYP/6-31G(d) level by means of the Gaussian 03 series of programs[3] : the standard Berny algorithm in redundant internal coordinates and default criteria of convergence were employed. The reported energy values are not ZPE corrected. Harmonic vibrational frequencies were calculated for all the stationary points. For each optimized ground state the frequency analysis showed the absence of imaginary frequencies, whereas each transition state showed a single imaginary frequency. Visual inspection of the corresponding normal mode was used to confirm that the correct transition state had been found. NMR chemical shift calculations were obtained with the GIAO method at the B3LYP/6-311++G(2df,p)//B3LYP/6-31G(d) level. TMS, calculated at the same level of theory, was used as reference to scale the absolute shielding value. *J*-coupling calculations were obtained at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level using the program[3] option that includes the Fermi contact contribution. TD-DFT calculations

[3] Gaussian 03, Revision D.01 and E.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

were obtained at the B3LYP/6-311++G(2df,p)//B3LYP/6-31G(d) level. In order to cover the whole 190-400 nm range, 40 to 50 transition were calculated. The CD spectrum was then obtained applying a 0.3 eV Gaussian bandshape.

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[4] Aldehydes **1**, **3** and **8** were purchased from Aldrich or Alfa Aesar and used as received. Catalyst **5** was prepared according to literature procedure.[5] Ethyl *trans*-alpha-cyanocinnamate **2b** and methyl 2-chloro-alpha-cyanocinnamate **2c** were purchased from Aldrich and used as received.

CAUTION: Ethyl 2-cyanoacrylate **2a** was purchased from Aldrich; due to its high tendency to polymerization and its sensibility to light, it was diluted in toluene (1M solution) and stored in the dark at 0°C under an argon atmosphere.

[4] W. L. F. Armarengo, D. D. Perrin, In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.

Structural assignment of compounds 4a,7a and 9

NOE analysis of 7a

In the whole class of compounds **7**, the 4 stereogenic centres created during the reaction can generate up to 16 stereoisomers, but only two of them were isolated in the reaction products.

In the case of the major diastereoisomer (2° eluted from the silica column), the proton spectrum of Figure 1 shows that H-6 is coupled with H-5 with quite a large coupling constant (11.3 Hz); according to the Karplus equation, this large value should correspond to an anti-periplanar disposition of H-5 and H-6, thus the Methyl in position 5 and the phenyl ring in position 6 should be both in a pseudo-equatorial position. The coupling constant can be also calculated by DFT methods (see below), that predict a J coupling of 10.7 Hz, in fairly good agreement with the experimental value.

Owing to the crowding of the aromatic region, unambiguous identification of the proton signals of the two phenyl groups is essential to the correct interpretation of the subsequent NOE spectra. Assignment of the two pair of ortho hydrogens was obtained by saturation of the H-6 signal (3.0 ppm), yielding NOE on the ortho hydrogens of Ph(6) at 7.17 ppm, and by saturation of the H-2 signal (4.4 ppm), yielding NOE on the ortho hydrogens of Ph(2) at 7.38 ppm. (spectra not shown in Figure 1)

On selective saturation of the methyl group in position 5 (1.15 ppm), positive NOE are observed on both the o-Ph(2) and o-Ph(6) signals, being the first more intense. On the contrary, no enhancement was observed on the H-2 signal. These results imply that the phenyl group in position 2 lies on the same side of Me(5). Further data that supports this hypothesis are obtained when the H-6 signal is saturated (trace c), showing large NOE for the o-Ph(2) and for the Me(5), indicating that both these signals are very close to H-6. Using the "control" NOE on the o-Ph(6) hydrogens as a distance

[5] The catalyst **5** can be easily prepared by protection of the commercial available α,α -diphenylprolinol with TMSOTf. See: J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen *J. Am. Chem. Soc.* **200**5, *127*, 18296.

reference, a distance ratio of 1.24 between Me(5) and o-Ph(2) was derived, to be compared with the 1.22 ratio calculated on the lowest energy DFT calculated structure (see below). These data also confirm the anti relationship between H-6 and H-5, already inferred from the J-coupling analysis.

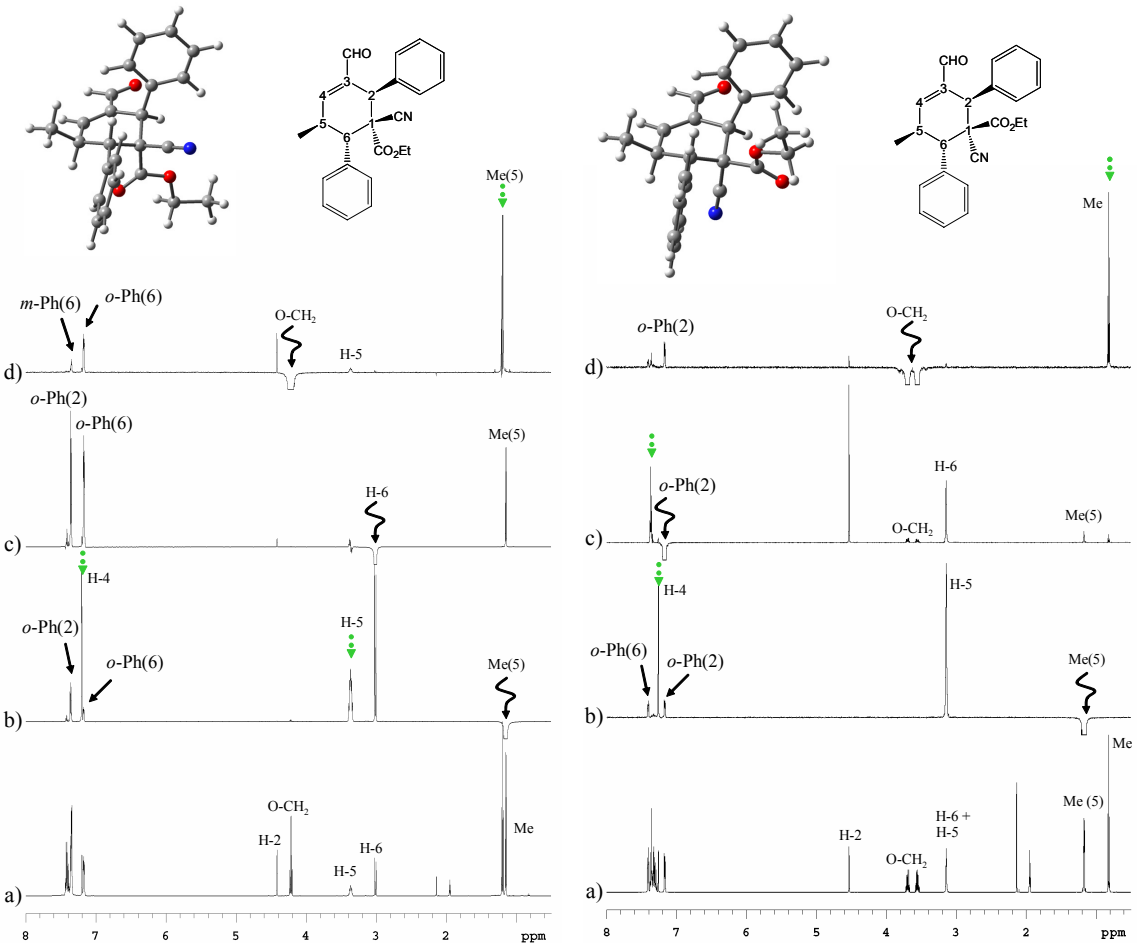


Figure 1-left. a) ^{1}H-NMR spectrum (600 MHz in CD_3CN) of the major diastereoisomer of compound **7a**. Trace b) DPFGSE-NOE spectrum obtained on saturation of the Methyl group in position 5. Trace c) DPFGSE-NOE spectrum obtained on saturation of the hydrogen in position 6. Trace d) DPFGSE-NOE spectrum obtained on saturation of the O-CH_2 signal. Green arrows indicate the "control" NOEs for each trace (i.e. enhancements that must be in any case observed due to the relative position with the saturated signal).

Figure 2-right. a) ^{1}H-NMR spectrum (600 MHz in $CDCl_3$) of the minor diastereoisomer of compound **7a**. Trace b) DPFGSE-NOE spectrum obtained on saturation of the Methyl group in position 5. Trace c) DPFGSE-NOE spectrum obtained on saturation of the ortho hydrogens of the phenyl in position 2. Trace d) DPFGSE-NOE spectrum obtained on saturation of the O-CH_2 signal. Green arrows indicate the "control" NOEs for each trace (i.e. enhancements that must be observed due to the relative position of the saturated signal).

Assignment of the relative configuration of the quaternary stereogenic centre on C(1) was deduced from selective saturation of the O-CH_2 signal: Positive NOE are observed on the o-Ph(6) signals at 7.17 ppm, on the m-Ph(6) signals (at 7.40 ppm, assigned by 2D-COSY) and on the H-5 signal; the OCH_2 group is thus syn to the phenyl in position 6, and anti to the phenyl in position 2. A small signal is visible also for H-2, due to its relatively short distance from the OCH_2. All the NOE data thus satisfactorily converge to assign the 1R*,2R*,5S*,6S* relative configuration to the major isomer of **7a**.

The NOE spectra recorded for the minor diastereoisomer of **7a** (Figure 2) show the same behaviour in the cases of the three stereogenic centres on C(2), C(5) and C(6) (trace b and c). In this isomer the signals of H5 and H6 are superimposed, thus selective saturation of the H-6 signal was unfeasible. Instead, saturation of the o-Ph(2) signal at 7.18 ppm (trace c) shows a large positive effect on H-6 (H-5 is too far to yield NOE), and a negligible enhancement of Me(5), thus confirming the same relative configuration at C(2), C(5) and C(6) already observed in the major isomer. It should be noted that the preliminary NOE spectra obtained on irradiation of H-2 and H-6 show that in the case of the minor stereoisomer of **7a**, the chemical shift of the ortho hydrogens of the two phenyl ring are reversed, thus the signal at 7.18 ppm corresponds to the pair of ortho hydrogens belonging to the phenyl in position 2, while the doublet at 7.41 ppm corresponds to the ortho hydrogens belonging to the phenyl in position 6.

On saturation of the o-Ph(2) signal (trace c), a positive NOE is also observed on the OCH_2 signal, indicating the change in the configuration of the quaternary C(1) carbon. Saturation of the OCH_2 confirms the NOE on the o-Ph(2) hydrogens, while no effect is visible on H-5 (the small effect at 3.05 ppm should be assigned to a positive NOE on the superimposed H-6), thus the 1S*,2R*,5S*,6S* relative configuration can be satisfactorily assigned. Again, a NOE effect is visible on H-2, being its intensity lower with respect to the same NOE observed in the case of the major stereoisomer.

Large variation of chemical shift is observable in the proton spectra of the two isomers of **7a**, particularly in the case of the

OCH_2 that is moved upfield by 0.6 ppm (from 4.20 to 3.62 ppm) in the minor isomer, and in the case of the H-5 signal, that is moved downfield in the case of the major isomer with respect to the minor.

The upfield shift of the OCH_2 could be explained by the effect of the aromatic ring currents, since in the minor isomer the group lies above the plane of the phenyl ring in position 2.[6]

The trend of the chemical shift can be also evaluated by computational method: DFT calculation of the chemical shifts (isolated molecule, at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) level) predicts an upfield shift of 0.35 ppm of the OCH_2 signal of the minor isomer with respect to the same signal of the major isomer, in good agreement with the observed trend. The same calculations also indicate that the H-5 signal of the major isomer is moved downfield by 0.75 ppm with respect to the same signal of the minor isomer, again in agreement with the experimental data. Finally, as a proof of the reliability of the calculation, a very small chemical shift difference (0.08 ppm) is calculated for the H-2 signal of the two isomers, to be compared with the experimental 0.06 ppm difference.

This peculiar behaviour of the chemical shift of the OCH_2 and H-5 signals can thus be used as an indicator to assign the stereochemistry of the quaternary centre at C(1) in the whole class of compounds.

X-RAY analysis

In the case of the minor diastereoisomer of compound **7a**, crystals suitable for X-ray diffraction were obtained by slow evaporation of an Hexane/iPrOH solution. The experimentally observed structure in the solid state fully confirms the relative stereochemistry already determined by NOE spectra; the crystal structure is almost identical to the one obtained by DFT calculation in the gas phase and used for the evaluation of the NOE spectra, the only difference being the orientation of the methyl group of the COOEt Moiety (Figure 3).

[6] a) L. M. Jackman, S. Sternhell, *Applications of NMR Spectroscopy in Organic Chemistry,* 2nd edition; Pergamon Press: Oxford, 1969; p 95; b) W. B. Jennings, B. M. Farrell, J. F. Malone, *Acc. Chem. Res*. **2001**, *34*, 885; c) K. Wüthrich, *Angew. Chem. Int. Ed*. **2003**, *42*, 3340.)

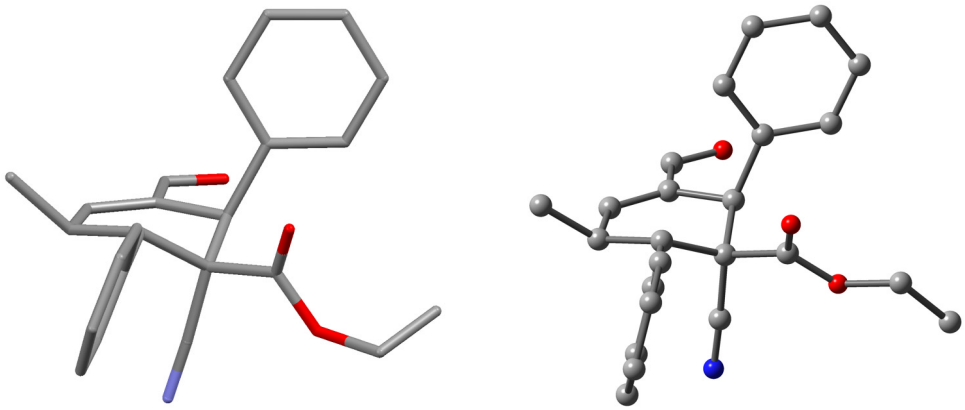
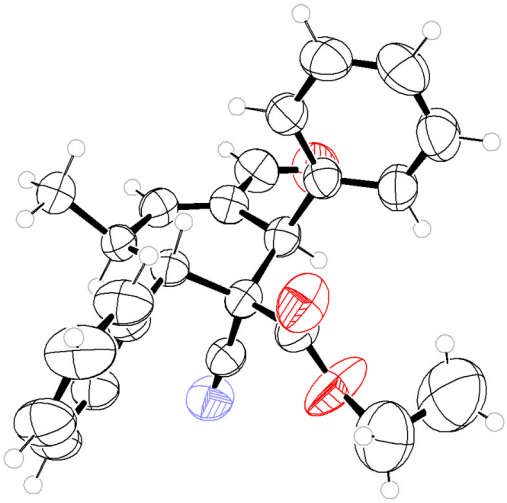


Figure 3. Left: X-ray structure of the minor isomer of **7a**
Right: Best DFT calculated structure

Crystal Data for 7a, minor isomer



Crystals obtained from hexane/iPrOH, molecular formula: $C_{26}H_{20}$, M_r = 373.43, monoclinic, space group $P2_1$ (No. 4), a = 8.4878(9), b = 9.9976(10), c = 12.5499(13) Å, β = 103.3610(10), V = 1036.13(19) Å^3, T = 298(2) K, Z = 2, ρ_c = 1.197 g cm^{-3}, F(000) = 396, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), $\mu(Mo_{K\alpha})$ = 0.079 mm^{-1}, colourless needle (0.6 × 0.2 × 0.2 mm^3), empirical absorption correction with SADABS (transmission factors: 0.9543 – 0.9844), 2400 frames, exposure time 15 s, 1.67 ≤ θ ≤ 26.00, −10≤ h ≤ 10, −12 ≤ k ≤ 12, −15 ≤ l ≤ 15, 10729 reflections collected, 4074 independent reflections (R_{int} = 0.0183), solution by direct methods (SHELXS) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2

(SHELXL), hydrogen atoms refined with a riding model, data / restraints / parameters = 4074/ 1 / 256, $S(F^2)$ = 1.079, $R(F)$ = 0.0476 and $wR(F^2)$ = 0.1150 on all data, $R(F)$ = 0.0433 and $wR(F^2)$ = 0.1112 for 3726 reflections with $I > 2\sigma(I)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0495P)^2 + 0.1949P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference peak and hole 0.228 and −0.268 e Å^{-3}. Flack Parameter 0.4 (15). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-678444. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

ECD spectra and Absolute Configuration of 7a

The lack of a suitable heavy atom precludes the use of the Bijovet method, based on anomalous X-ray dispersion, to unambiguously assign the absolute configuration (AC) of the minor diastereomer of **7a**, even if the Flack parameter[7] value obtained at the end of the structure refinement indicates the 1S,2R,5S,6S configuration as the more probable.

Using a different approach, the Electronic Circular Dichroism (ECD) spectrum could be calculated by theoretical methods and its shape (and intensity) compared with that of the experimental spectrum. If they match, the AC assumed in the calculations should then be assigned to the enantiomer whose experimental spectrum has been recorded. Theoretical calculation was carried out by means of TD-DFT method, since such a technique has been successfully employed several times[8] to predict ECD spectra and to assign the AC of organic molecules.

A preliminary conformational search, starting from the relative configuration derived from NOE spectra and X-ray data, was obtained for the minor diastereoisomers of compound **7a,** using Molecular Mechanics (MMFF force field, TITAN 1.0.4, Montecarlo algorithm).

[7] H. D. Flack *Acta Cryst.* **1983**, *A39*, 876

The analysis of the output structures revealed that, up to 2 kcal/mol with respect to the lowest energy structure, they differ only for the position of the methyl group of the COOEt moiety. The three best structures were then optimized at the B3LYP/6-31G(d) level, and for each of the optimized structures, the ECD spectrum was calculated in the 200-400 nm region at the same level (Figure 4) The three CD spectra obtained are almost super imposable, a result quite obvious when considering the very small influence of the position of the methyl group with respect to the chromophoric groups that generate the ECD spectrum.

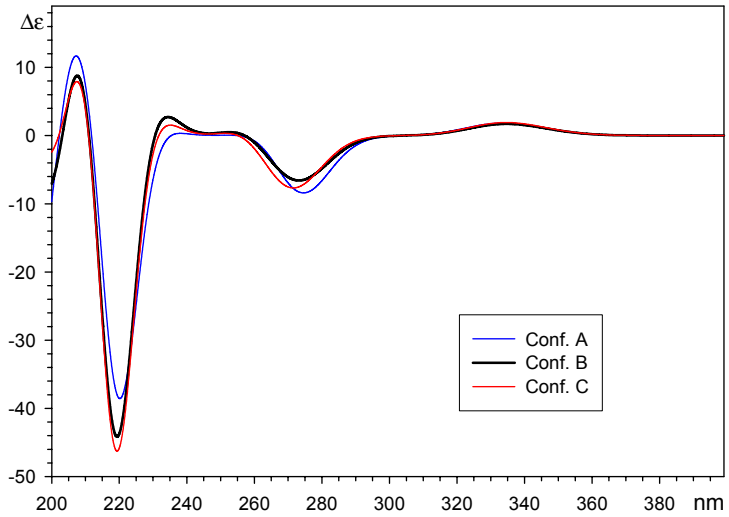


Figure 4. Calculated ECD spectra for the best three conformers of the minor isomer of **7a**

The final CD spectrum to be compared with the experimental one was then calculated only for the lowest energy structure (Figure 3, right) at the B3LYP/6-311++G(2df,p)//B3LYP/6-31G(d) level. As shown in Figure 4, the CD spectrum calculated assuming the 1S,2R,5S,6S configuration shows a shape and relative intensities analogous to that of the experimental spectrum, with a strong negative Cotton effect at lower wavelengths (≈ 220 nm), as well as a small positive effect at higher wavelengths (≈ 340 nm).

[8] See ref. 14 in the main text.

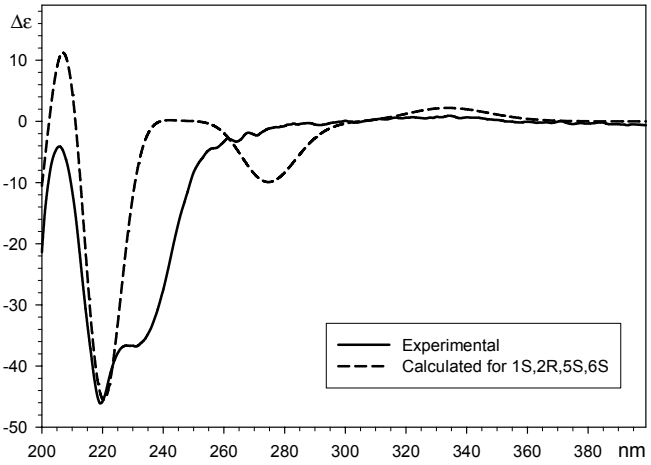


Figure 5: experimental (full trace) and calculated (dotted trace) ECD spectrum for the minor isomer of **7a**.

Accordingly, the 1S,2R,5S,6S configuration should be assigned to the minor diastereoisomer, and, as a consequence, the 1R,2R,5S,6S configuration should be assigned to the major diastereoisomer of **7a**. As a final validation, the ECD spectrum was calculated at the highest level of theory also for the major stereoisomer, following the same theoretical approach and assuming the **1R,2R,5S,6S** configuration. In this case, the calculated trace is even in a better agreement with the experimental spectrum (see Figure 1 in the main text).

Determination of the Configuration of the two diastereoisomers of 4a

In the case of the mayor isomer of **4a**, selective saturation of the Methyl signal in position 5 shows positive NOEs on the ortho hydrogens of the phenyl ring, (Figure 5, trace a), on both the diastereotopic hydrogens of the CH_2(6) and a very strong effect on the vinilic CH in position 4 of the six-membered ring. This very strong effect can be used as a distance reference to calculate the others distances. From these data the syn relationship between the Me(5) and the phenyl group can be satisfactorily assigned. Saturation of the ortho hydrogens of the phenyl group (Figure 5, trace b) confirms the relative syn relationship with the Me(5) group.

The relative stereochemistry of the quaternary centre in position 1 of the ring can be obtained from the selective saturation of the O-CH_2 signal (trace c). When this signal is irradiated, NOE effect is observed on both the ortho and meta signals of the phenyl group. These signals can be observed only if the COOEt group and the phenyl group lie on the same side of the six-membered ring. *Vice versa*, the complementary effect can be seen as NOE enhancement of the OCH_2 when the ortho hydrogens of the phenyl group are saturated (Figure 5, trace b)

It should be noted that a NOE signal is visible also for the CH in position 2. The distance of this hydrogen can be evaluated using the strong NOE effect on the ester methyl group as a distance reference, and it is consistent with the distances obtained from the DFT calculated structure.

The relative distance of the ortho hydrogens and of the H-2 from the OCH_2 can be evaluated by their NOE ratio (1.32). From the calculated structure, a very similar ratio (1.37) was obtained only in the case of a syn relationship between the COOEt and the phenyl group.

These data satisfactorily assign the 1S*,2R*,5R* relative stereochemistry to the major diastereoisomer. Further data supporting this assignment can be obtained by the NOE spectra recorded on the minor diastereoisomer (Figure 6).

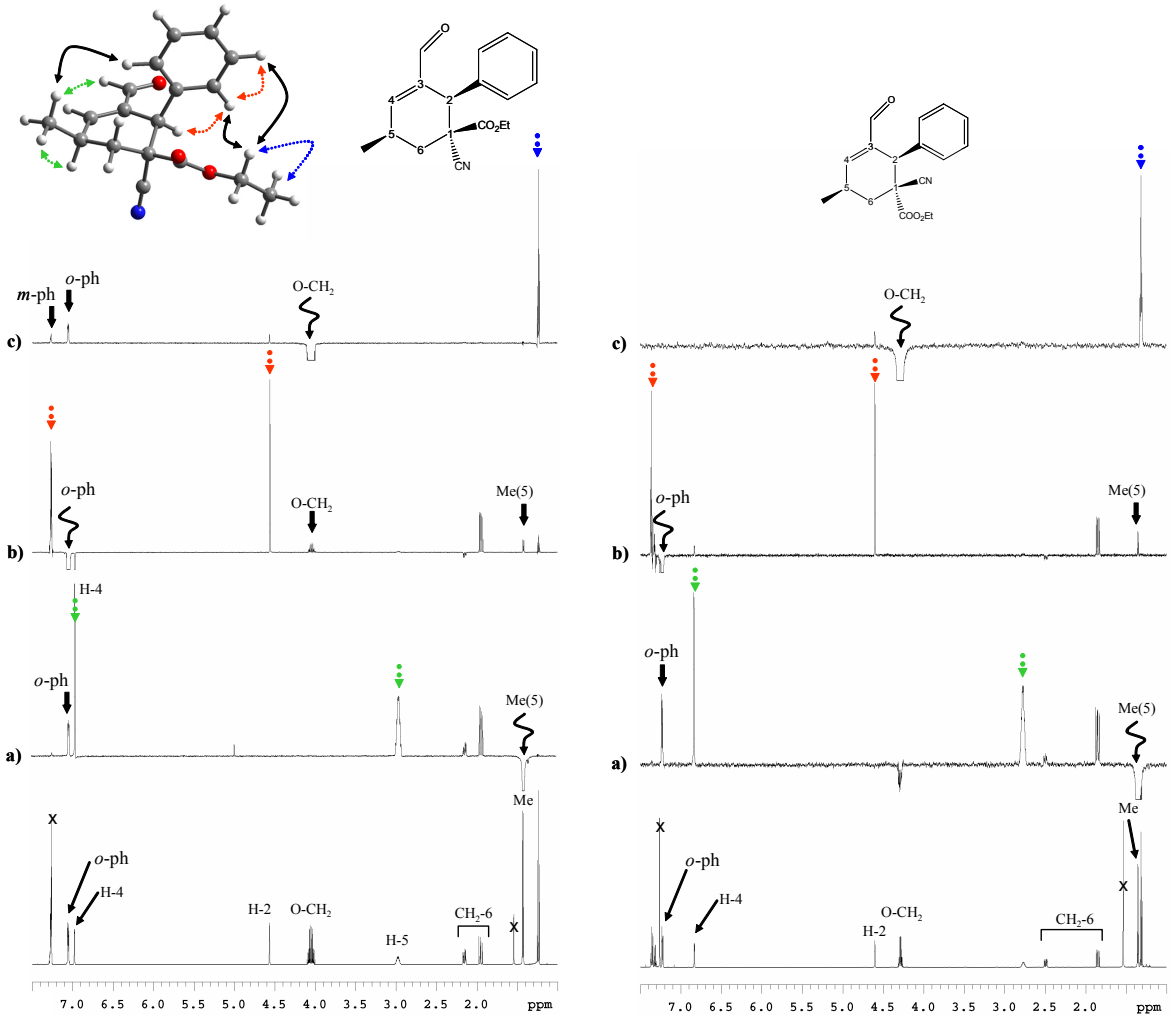


Figure 5-left. Bottom: ^{1}H-NMR spectrum (600 MHz in $CDCl_3$) of the major diastereoisomer of compound **4a**. Trace a):DPFGSE-NOE spectrum obtained on saturation of the Methyl group in position 5. Trace b) DPFGSE-NOE spectrum obtained on saturation of the ortho hydrogens of the phenyl group. Trace c) DPFGSE-NOE spectrum obtained on saturation of the O-CH_2 signal. Coloured arrows indicate the "control" NOE for each trace (i.e. enhancements that must be in any case observed due to the relative position with the saturated signal).

Figure 6-right. Bottom: ^{1}H-NMR spectrum (600 MHz in $CDCl_3$) of the minor diastereoisomer of compound **4a**. Trace a):DPFGSE-NOE spectrum obtained on saturation of the Methyl group in position 5. Trace b) DPFGSE-NOE spectrum obtained on saturation of the ortho hydrogens signal. Trace c) DPFGSE-NOE spectrum obtained on saturation of the O-CH_2 signal. Coloured arrows indicate the "control" NOEs for each trace (i.e. enhancements that must be observed due to the relative position of the saturated signal).

On saturation of the Methyl group, NOE effect is observed on the ortho phenyl hydrogens, thus confirming the same syn

relationship between phenyl and Me(5) already observed in the major diastereoisomer. Reversely, irradiation of the ortho hydrogens shows NOE effect on the Me(5) signal, but not on the OCH_2 group (Figure 6, trace b). Finally, saturation of the OCH_2 signal does not show any enhancement in the aromatic region, thus confirming the anti relationship between the phenyl and the COOEt group. As already underlined for the major isomer, a small effect is visible also in this case on the CH in position 2, that has the same distance from the OCH_2 in both the two diastereoisomers.

Absolute Configuration of the major isomer of 4a

The same TD-DFT theoretical approach already used in the case of **7a** was applied in order to assign the Absolute Configuration of the major isomer of **4a**. A preliminary conformational search, starting from the relative configuration derived from NOE spectra was obtained using Molecular Mechanics (MMFF force field, TITAN 1.0.4, Montecarlo algorithm).

Also in this case the analysis of the output structures revealed that the lowest energy structures differ only for the position of the methyl group of the COOEt moiety. Thus, the ECD spectrum to be compared with the experimental one was then calculated only for the lowest energy structure at the B3LYP/6-311++G(2df,p)//B3LYP/6-31G(d) level. As shown in Figure 1 of the main text, the CD spectrum calculated assuming the 1S,2R,5R configuration has a shape and relative intensities analogous to that of the experimental spectrum, with a strong negative Cotton effect at low wavelengths (≈ 220 nm). Consequently, the ***1R,2R,5R*** configuration has to be assigned to the minor isomer.

Relative configuration of 9 and epi-9

In the case of compounds **9** and its isomer **epi-9**, the presence of a cyclohexane motif helps in determining the relative configuration of some stereocenters, because of the stereospecific and well known J-coupling relationship generated in this kind of systems.

From the analysis of the ^{1}H-NMR spectra of the three H-2, H-3 and H-4 hydrogens (assigned by HSQC and HMBC spectra) it is evident, in both the major **9** and minor **epi-9** stereoisomer, the presence of a trans-diaxial J-coupling between H-2 and H-3 (J = 12.8 Hz), and a equatorial-axial J-coupling between H-3 and H-4 (J = 1.8 Hz for **9** and 2.0 for **epi-9**).

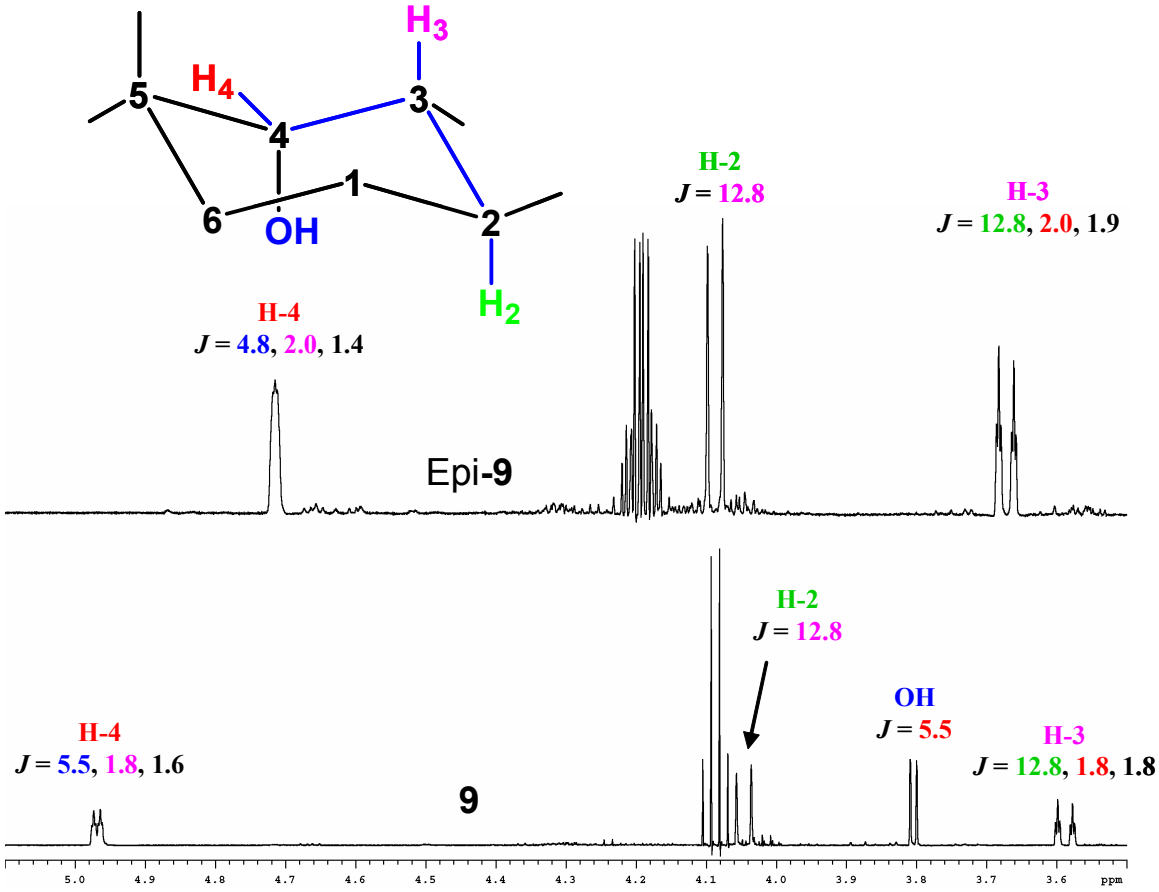


Figure 7: Part of the ^{1}H-NMR spectrum (600 MHz in CD_3CN) of compound **9** and **epi-9**. The colours indicate the relationship between the J-couplings.

These values well agree with the theoretical J-coupling obtained by DFT calculation (isolated molecule, at the B3LYP/6-31+G(d,p) //B3LYP/6-31G(d) level, and including the Fermi contact contribution), yielding values of 13.7 and 3.1 Hz for **9** (13.7 and 3.6 for epi-**9**). The relative configuration at C(2), C(3) and C(4) is thus easily assigned as shown in Figure 7.

To solve the relative configuration of the two quaternary centres, NOE spectra were acquired on saturating the Methyl group on C(5), the OCH_2, and the H-3 signal. The main difference between the NOE spectra is observed on saturation of Me(5) and of H-3: in the case of the major isomer, NOE effect on the o-Ph(5) hydrogens was observed when H-3 was saturated (figure 8, trace b), while no NOE effect was observed on the Me(5). On the contrary when the H-3 signal of the minor isomer was saturated (figure 9, trace a), a strong NOE was visible on Me(5), and no effect was observed on the o-Ph(5) hydrogens.

Thus, in the case of **9** and **epi-9,** the two isomer obtained from the reaction clearly differ in the configuration of the C(5) centre. NOE spectra obtained on saturation of the OCH_2 group show the same NOEs on the o-Ph(2) hydrogens, confirming the same configuration at the C(1) centre in both the stereoisomers. The configuration of the C(1) centre is the same already determined for the major isomer of compound **4a**. The resulting configuration is thus 1S*,2S*,3R*,4R*,5S* for the major isomer **9**, and 1S*,2S*,3R*,4R*,5R* for the minor one, **epi-9**.

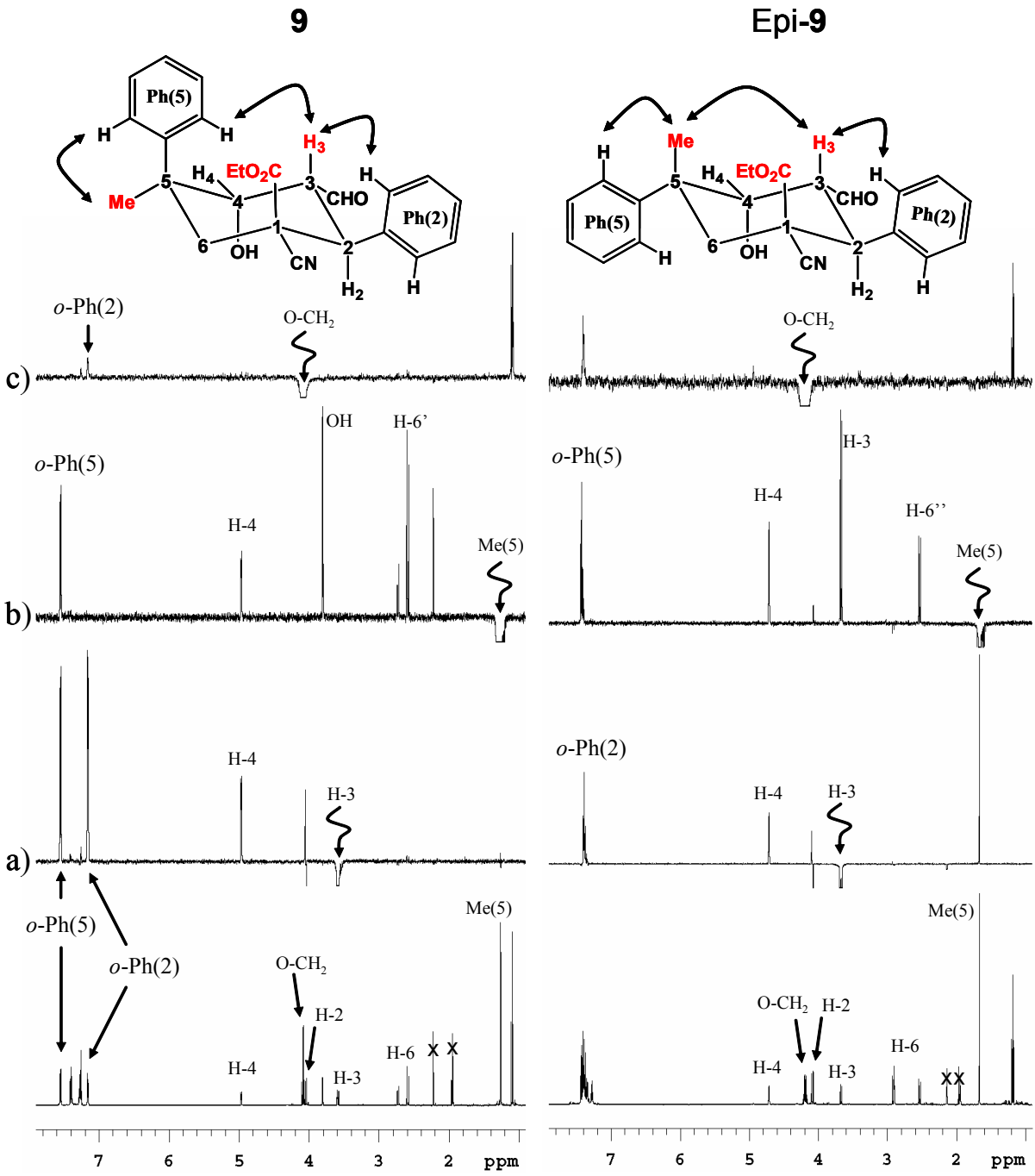
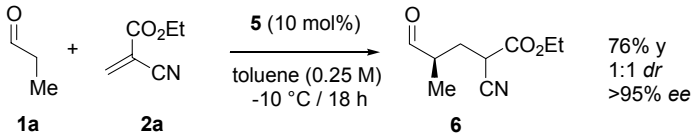


Figure 8-left. Bottom: ^{1}H-NMR spectrum (600 MHz in CD_3CN) of the major diastereoisomer of compound **9**. Trace a):DPFGSE-NOE spectrum obtained on saturation of the H-3 signal. Trace b) DPFGSE-NOE spectrum obtained on saturation of the Me(5). Trace c) DPFGSE-NOE spectrum obtained on saturation of the O-CH_2 signal.

Figure 9-right. Bottom: ^{1}H-NMR spectrum (600 MHz in CD_3CN) of the minor diastereoisomer of compound **epi-9**. Trace a):DPFGSE-NOE spectrum obtained on saturation of the H-3 signal. Trace b) DPFGSE-NOE spectrum obtained on saturation of the Me(5).. Trace c) DPFGSE-NOE spectrum obtained on saturation of the O-CH_2 signal.

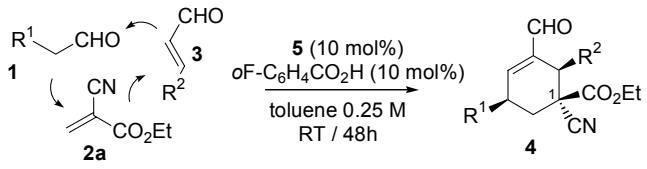
Experimental Procedures

Direct Aminocatalytic and Enantioselective Conjugate Addition of Aldehydes to Ethyl 2-cyanoacrylate.

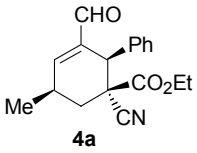


In an ordinary vial equipped with a Teflon-coated stir bar, catalyst **5** (0.03 mmol, 9.8 mg, 10 mol%) was dissolved in 0.9 mL of toluene. After addition of 0.45 mmol (1.5 equiv) of propanal **1a**, the solution was stirred for 10 minutes at -10 °C. Then ethyl 2-cyanoacrylate **2a** (1 equiv, 1M in toluene, 0.3 mL) was added and the solution was stirred for 18 hours at -10 °C. The crude reaction mixture was directly charged on silica gel and purified by flash chromatography (FC: Hexanes/AcOEt = 80/20). The compound was isolated as an inseparable 1:1 mixture of two diastereoisomers (due to the fast epimerization of one stereocenter) as a colourless oil in 76% yield and >95% ee, determined by H-NMR analysis in chiral medium (Pirkle's alcohol, R-(-)-2,2,2-trifluoroanthrylethanol). $[\alpha]^{rt}_{D}$ = + 19.1 (c = 1.0, $CHCl_3$, >95%ee, 1:1 mixture of two diastereoisomers). ^{1}H NMR (1:1 mixture of the two diastereoisomers): δ = 1.24 (d, J = 7.2, 3H), 1.26 (d, J = 7.6, 3H), 1.33 (d, J = 7.2, 6H), 1.83-1.99 (m, 2H), 2.35-2.43 (m, 2H), 2.65-2.75 (m, 2H), 3.63 (dd, J = 6.8, 1H), 3.79 (dd, J = 6.0, 1H), 4.24-4.30 (m, 4H), 9.65 (bs, 1H), 9.66 (bs, 1H); ^{13}C NMR: δ = 13.2, 13.9, 14.0, 14.1, 29.9 (2C), 35.1, 35.4, 43.4, 43.5, 63.0, 63.1, 115.9, 116.2, 165.6, 165.7, 201.9, 202.4.

General Procedure for the Organocatalytic Asymmetric Synthesis of Cyclohexene Carbaldehydes 4.



All the reactions were carried out in undistilled toluene without any precautions to exclude air. In an ordinary vial equipped with a Teflon-coated stir bar, catalyst **5** (0.04 mmol, 13.0 mg, 10 mol%) and 2-fluorobenzoic acid (0.04 mmol, 5.6 mg, 10 mol%) were dissolved in 1.12 mL of toluene. After addition of 0.8 mmol (2 equiv) of the aldehyde **1**, the solution was stirred for 10 minutes at room temperature. Then ethyl 2-cyanoacrylate **2a** (0.48 mmol, 1.2 equiv, 0.48 mL of a 1M solution in toluene) and 0.4 mmol of α,β-unsaturated aldehyde **3** (1 equiv) were sequentially added. After 48 hours stirring, the crude reaction mixture was diluted with DCM (2 mL) and flushed through a short plug of silica, using DCM/Et_2O 2/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography (FC) to yield the desired product **4**.

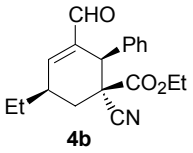


(1R,2R,5R)-1-Cyano-3-formyl-5-methyl-2-phenyl-cyclohex 3-enecarboxylic acid ethyl ester 4a (Table 1, entry 1) **–** The reaction was carried out following the general procedure to furnish the crude product [dr = 5.5:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.44 ppm, δ_{minor} 9.39 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless oil by column chromatography (hexane/AcOEt = gradient from 9/1 to 8/2 – R_F^{major}: 0.35, R_F^{minor}: 0.3 in hexane/AcOEt 7/3) in 42% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralpak AD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 7.6 min, τ_{major} = 8.7 min; $[\alpha]^{rt}_D$= - 171.3 (*c* = 1.05, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{18}H_{19}NO_3$: 297.13649; found: 297.1366. **Major isomer**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.2, 3H), 1.43 (d, *J* = 7.3, 3H, Me(5)), 1.95 (dd, *J* =

14.5 and 11.4, 1H, H6'), 2.15 (dddd, *J* = 14.5 and 6.3, 1.7 and 1.2, 1H, H6"), 2.98 (m, 1H, H-5), 4.05 (ABX_3 system, J=10.8 and 7.2, 2H, OCH_2), 4.56(s, 1H H-2), 6.98(m, 1H, H-4), 7.06(m, 2H, orto-Ph), 7.25-7.30 (m, 3H, Ph), 9.45(s, 1H, CHO); ^{13}C NMR 150.8 MHz, $CDCl_3$): δ = 12.8 (CH_3), 18.5(CH_3), 28.7 (CH), 29.6 (CH_2), 43.8 (CH),46.3 (C), 61.8 (OCH_2), 117.8 (CN), 127.5 (CH), 127.55(CH), 128.2 (CH), 134.2 (C), 137.2 (C), 153.4(CH), 165.2 (CO), 190.5(CHO).

Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.2, 3H), 1.36 (d, *J* = 7.3, 3H, Me(5)), 1.85 (dd, *J* = 14.0 and 10.8, 1H, H6'), 2.49 (dddd, *J* = 14.0 and 6.5, 1.6 and 1.1, 1H, H6"), 2.77 (m, 1H, H-5), 4.29 (ABX_3 system, 2H, OCH_2), 4.60(s, 1H H-2), 6.83(d, *J* = 2.7, 1H, H-4), 7.23(m, 2H, orto-Ph), 7.30-7.38 (m, 3H, Ph), 9.40(s, 1H, CHO); ^{13}C NMR 150.8 MHz, $CDCl_3$): δ = 13.9 (CH_3), 19.6(CH_3), 29.0 (CH), 32.8 (CH_2), 41.8 (CH),47.8 (C), 63.3 (OCH_2), 117.9 (CN), 128.3 (CH), 128.5(CH), 129.6 (CH), 136.2 (C), 138.5 (C), 153.4(CH), 166.7 (CO), 191.3(CHO).

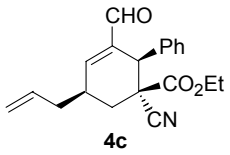
The *relative configuration* of both the major and the minor diastereomers were determined by extensive NMR NOE studies (see page S13). The minor diastereomer was determined as the 1-epimer of **4a**. The *absolute configuration* of compound **4a** (major diastereomer) was assigned by CD spectrum (see page S15).



4b

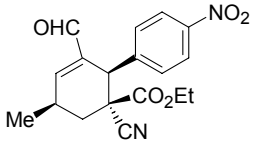
4b (Table 1, entry 3) **–** The reaction was carried out following the general procedure to furnish the crude product [dr = 3.5:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.46 ppm, δ_{minor} 9.44 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless oil by column chromatography (DCM/Et_2O = 98/2) in 35% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralcel OD-H: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 18.3 min, τ_{minor} = 19.8 min; $[\alpha]^{rt}_D$= - 329.6 (*c* = 0.76, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{19}H_{21}NO_3$: 311.15214; found: 311.1521. ^{1}H NMR (400 MHz): δ = 1.18 (t, *J* = 7.2, 3H), 1.24 (t, *J* = 7.2, 3H), 1.70-1.88 (m, 2H), 1.95 (dd, *J* = 11.2, *J* = 14.4, 1H), 2.15 (dd, *J* = 6.4, *J* = 14.4, 1H), 2.74-2.84 (m, 1H), 3.99-4.12 (m, 2H), 4.57 (s, 1H), 7.03–7.08 (m, 3H), 7.25-7.28 (m, 3H), 9.46 (s, 1H); ^{13}C NMR: δ =

11.4 (CH_3), 13.8 (CH_3), 27.3 (CH_2), 28.5 (CH_2), 36.1 (CH), 45.1 (CH), 47.3 (C), 62.8 (CH_2), 118.9 (C), 128.50 (CH), 128.53 (CH), 129.1 (CH), 135.2 (C), 138.6 (C), 153.5 (CH), 166.3 (C), 191.6 (CH).



4c

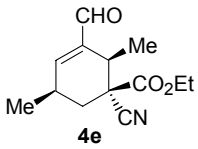
4c (Table 1, entry 4) **-** The reaction was carried out following the general procedure to furnish the crude product [dr = 3:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.44 ppm, δ_{minor} 9.45 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless oil by column chromatography (hexane/AcOEt = 9/1) in 40% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralpak AD-H: 9/1 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 10.8 min, τ_{major} = 11.6 min; $[\alpha]^{rt}_D$= - 265.9 (*c* = 0.7, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{20}H_{21}NO_3$: 323.15214; found: 323.1522. ^{1}H NMR: δ = 1.24 (t, *J* = 7.2, 3H), 1.99 (dd, *J* = 11.2, *J* = 14.4, 1H), 2.11-2.17 (m, 1H), 2.42-2.56 (m, 2H), 2.91-3.01 (m, 1H), 3.98-4.12 (m, 2H), 4.56 (s, 1H), 5.24-5.30 (m, 2H), 5.87-5.99 (m, 1H), 7.03-7.08 (m, 3H), 7.25-7.28 (m, 3H), 9.44 (s, 1H); ^{13}C NMR: δ = 13.7 (CH_3), 28.6 (CH_2), 31.6 (C), 34.5 (CH), 38.2 (CH_2), 45.0 (CH), 47.3 (C), 62.8 (CH_2), 118.8 (C), 118.9 (CH_2), 128.5 (CH), 129.1 (CH), 134.0 (CH), 135.2 (C), 139.0 (C), 152.4 (CH), 166.1 (C), 191.4 (CH).



4d

4d (Table 1, entry 5) **-** The reaction was carried out following the general procedure to furnish the crude product [dr = 3.8:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.46 ppm, δ_{minor} 9.42 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a white solid by column chromatography (hexane/AcOEt = gradient from 9/1 to 8/2) in 34% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and 98% ee). HPLC analysis on a Chiralpak AD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 12.9 min, τ_{major} = 17.5 min; $[\alpha]^{rt}_D$= - 249.6 (*c* = 0.575, $CHCl_3$, 98% ee). HRMS: *m/z* calcd

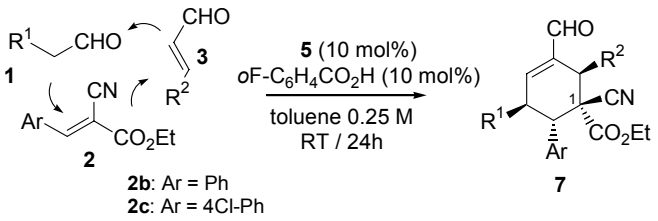
for $C_{18}H_{18}N_2O_5$: 342.12157; found: 342.1212. ^{1}H NMR (400 MHz): δ = 1.27 (t, J = 7.2, 3H), 1.45 (d, J = 7.2, 3H), 1.86 (dd, J = 11.2, J = 14.4, 1H), 2.22 (dd, J = 6.4, J = 14.4, 1H), 2.98-3.07 (m, 1H), 4.02-4.16 (m, 2H), 4.62 (s, 1H), 7.07 (s, 1H), 7.24 (d, J = 8.8, 2H), 8.14 (d, J = 8.8, 2H), 9.46 (s, 1H); ^{13}C NMR: δ = 13.8 (CH_3), 19.4 (CH_3), 29.7 (CH), 30.7 (CH_2), 44.3 (CH), 47.1 (C), 63.3 (CH_2), 118.1 (C), 123.7 (CH), 130.1 (CH), 137.5 (C), 142.7 (C), 147.9 (C), 155.3 (CH), 165.7 (C), 191.2 (CH).



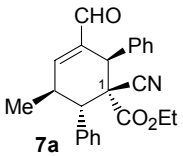
4e

4e (Table 1, entry 6) **-** The reaction was carried out following the general procedure to furnish the crude product [dr = 2.5:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.44 ppm, δ_{minor} 9.38 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless oil by column chromatography (hexane/AcOEt = gradient from 95/5 to 85/15 – R_F^{minor}: 0.35, R_F^{major}: 0.3 in hexane/AcOEt 8/2) in 42% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralpak AD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 13.3 min, τ_{minor} = 13.7 min; $[\alpha]^{rt}_D$= - 25.8 (c = 0.875, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{13}H_{17}NO_3$: 235.12084; found: 235.1206. ^{1}H NMR: δ = 1.21 (d, J = 7.2, 3H), 1.27 (t, J = 7.2, 3H), 1.30 (d, J = 7.2, 3H), 1.83 (dd, J = 10.4, J = 13.6, 1H), 2.51-2.68 (m, 2H), 3.36-3.46 (m, 1H), 4.21 (q, J = 7.2, 2H), 6.50 (d, J = 2.4, 1H), 9.38 (s, 1H); ^{13}C NMR: δ = 13.8 (CH_3), 17.7 (CH_3), 19.7 (CH_3), 29.1 (CH), 30.6 (CH), 33.1 (CH_2), 46.7 (C), 63.0 (CH_2), 118.5 (C), 141.7 (C), 152.8 (CH), 166.8 (C), 192.2 (CH).

General Procedure for the Organocatalytic Asymmetric Synthesis of Cyclohexene Carbaldehydes 7 Having Four Stereogenic Centers.



All the reactions were carried out in undistilled toluene without any precautions to exclude air. In an ordinary vial equipped with a Teflon-coated stir bar, catalyst **5** (0.04 mmol, 13.0 mg, 10 mol%) and 2-fluorobenzoic acid (0.04 mmol, 5.6 mg, 10 mol%) were dissolved in 1.6 mL of toluene. After addition of 0.8 mmol (2 equiv) of the aldehyde **1**, the solution was stirred for 10 minutes at room temperature. Then cyanoacrylate **2b** or **2c** (0.48 mmol, 1.2 equiv) and 0.4 mmol of α,β-unsaturated aldehyde **3** (1 equiv) were sequentially added. After *24* hours stirring, the crude reaction mixture was diluted with DCM (2 mL) and flushed through a short plug of silica, using DCM/Et_2O 2/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography (FC) to yield the desired product **7**.



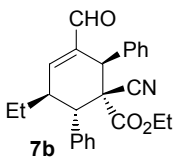
7a

(1R,2R,5S,6S)-1-Cyano-3-formyl-5-methyl-2,6-diphenyl-cyclohex-3-enecarboxylic acid ethyl ester 7a (Table 2, entry 1) **–** The reaction was carried out following the general procedure to furnish the crude product [dr = 2.6:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.48 ppm, δ_{minor} 9.52 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a white solid by column chromatography (hexane/AcOEt = gradient from 9/1 to 8/2 – R_F^{minor}: 0.35, R_F^{major}: 0.3 in hexane/AcOEt 7/3) in 52% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralpak AD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 8.1 min, τ_{major} = 9.1 min; $[\alpha]^{rt}_D$= - 15.2 (*c* = 0.87, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for

$C_{24}H_{23}NO_3$: 373.16779; found: 373.1678. ^{1}H NMR (600 MHz, CD_3CN): δ = 1.15 (d, J = 7.0, 3H, Me(5)),1.20 (t, J = 7.2, 3H), 3.01 (d, J = 10.8, 1H, H6), 3.36 (m, 1H, H-5), 4.22 (q, J = 7.2, 2H, OCH_2), 4.41 (s, 1H, H-2), 7.17(dd, J = 7.2 and 3.7, 2H, orto-Ph), 7.20(m, 1H, H-4), 7.33-7.45 (m, 8H, Ph), 9.45(s, 1H, CHO); ^{13}C NMR 150.8 MHz, CD_3CN): δ = 13.2 (CH_3), 17.6(CH_3), 34.4 (CH), 44.7 (CH), 49.0 (CH), 54.8 (C), 63.0 (OCH_2), 117.6 (CN), 128.3 (CH), 128.4(CH), 128.5 (CH), 128.6(CH), 129.6 (CH), 130.3 (CH), 137.1 (C), 137.4 (C), 137.8 (C), 155.7(CH), 166.8 (CO), 192.4(CHO).

The minor diastereomer was also isolated as a single stereoisomer and as a white solid by column chromatography in 20% yield. (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralcel OD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 19.8 min, τ_{minor} = 23.9 min. $[\alpha]^{rt}_D$= - 152.4 (*c* = 0.79, $CHCl_3$, 99% ee). Crystal suitable for X-ray diffraction studies were obtained by slow evaporation of a hexane/iPrOH 9:1 v/v solution. ^{1}H NMR (600 MHz, CD_3CN): δ = 0.82 (t, J = 7.0, 3H), 1.15 (m, 3H, Me(5)), 3.14 (m, 2H, H6+H5), 3.56 (dq, J=10.7, 7.0, 1H, OCH_2), 3.69 (dq, J=10.7, 7.0, 1H, OCH_2), 4.53 (s, 1H, H-2), 7.17(m, 2H, orto-Ph), 7.26(bs, 1H, H-4), 7.28-7.39 (m, 6H, Ph), 7.40-7.47 (m, 2H, Ph), 9.51(s, 1H, CHO); ^{13}C NMR 150.8 MHz, CD_3CN): δ = 12.7 (CH_3), 17.0(CH_3), 36.9 (CH), 45.9 (CH), 48.0 (CH), 54.5 (C), 62.3 (OCH_2), 119.2 (CN), 128.0 (CH), 128.4(CH), 128.45 (CH), 128.7(CH), 129.3 (CH), 129.5 (CH), 133.3 (C), 137.4 (C), 138.4 (C), 155.6(CH), 165.6 (CO), 192.3(CHO).

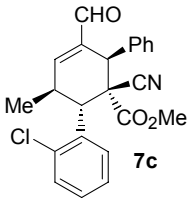
The *relative configuration* of both the major and the minor diastereomers were determined by extensive NMR NOE studies (see page S5) and X-ray analysis (minor isomer, see page S8). The minor diastereomer was determined as the 1-epimer of **7a**. *The absolute configuration* of compound **7a** (major diastereomer) was assigned by CD spectrum (see page S10).



7b

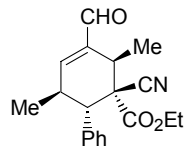
7b (Table 2, entry 3) **-** The reaction was carried out following the general procedure to furnish the crude product [dr = 2.3:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.50 ppm, δ_{minor} 9.53 ppm - s)]. The title compound (major diastereomer) was isolated as a

single stereoisomer and as a white solid by column chromatography (hexane/AcOEt = gradient from 9/1 to 85/15 – R_F^{minor}: 0.35, R_F^{major}: 0.3 in hexane/AcOEt 7/3) in 40% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralcel OD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 16.2 min, τ_{minor} = 25.4 min; $[\alpha]^{rt}_D$= - 77.3 (*c* = 0.97, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{25}H_{25}NO_3$: 387.18344; found: 387.1832. ^{1}H NMR: δ = 1.07 (t, *J* = 7.2, 3H), 1.23 (t, *J* = 7.2, 3H), 1.39-1.50 (m, 1H), 1.66-1.76 (m, 1H), 3.08 (d, *J* = 10.8, 1H), 3.36-3.44 (m, 1H), 4.16-4.24 (m, 2H), 4.41 (s, 1H), 7.16-7.21 (m, 2H), 7.25-7.33 (m, 6H), 7.36-7.42 (m, 3H), 9.50 (s, 1H); ^{13}C NMR: δ = 11.1 (CH_3), 13.8 (CH_3), 25.3 (CH_2), 40.5 (CH), 45.3 (CH), 46.7 (CH), 54.6 (C), 62.9 (CH_2), 117.0 (C), 128.4 (CH), 128.56 (CH), 128.61 (CH), 129.47 (CH), 129.85 (CH), 136.5 (C), 137.9 (C), 153.5 (CH), 166.8 (C), 191.6 (CH).



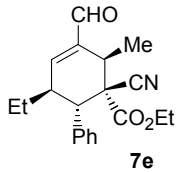
7c

7c (Table 2, entry 4) **–** The reaction was carried out following the general procedure to furnish the crude product [dr = 2.0:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.54 ppm, δ_{minor} 9.50 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a white solid by column chromatography (hexane/AcOEt = gradient from 9/1 to 85/15 – R_F^{major}: 0.3, R_F^{minor}: 0.25 in hexane/AcOEt 7/3) in 32% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralcel OD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 10.5 min, τ_{major} = 11.7 min; $[\alpha]^{rt}_D$= - 84.1 (*c* = 0.875, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{23}H_{20}NO_3Cl$: 393.11317; found: 393.1133. ^{1}H NMR: δ = 1.23 (d, *J* = 7.2, 3H), 3.01-3.11 (m, 1H), 3.29 (s, 3H), 4.08 (d, *J* = 10.8, 1H), 4.66 (s, 1H), 7.10-7.20 (m, 4H), 7.25-7.30 (m, 1H), 7.37-7.41 (m, 4H), 7.86 (dd, *J* = 1.6, *J* = 8.0, 1H), 9.54 (s, 1H); ^{13}C NMR: δ = 17.1 (CH_3), 38.3 (CH), 39.7 (CH), 48.7 (CH), 52.7 (C), 53.8 (CH_3), 118.9 (C), 126.7 (CH), 127.6 (CH), 128.68 (CH), 128.71 (CH), 128.81 (CH), 128.96 (CH), 129.5 (CH), 135.0 (C), 136.5 (C), 136.8 (C), 137.9 (C), 154.4 (CH), 165.5 (C), 191.2 (CH).



7d

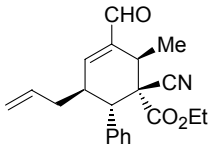
7d (Table 2, entry 5) **-** The reaction was carried out following the general procedure to furnish the crude product [dr = >20:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.48 ppm, δ_{minor} 9.52 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless liquid by column chromatography (hexane/AcOEt = gradient from 9/1 to 8/2) in 48% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and 98% ee). HPLC analysis on a Chiralcel OD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 7.7 min, τ_{minor} = 11.4 min; $[\alpha]^{rt}_D$= + 116.6 (*c* = 1.14, $CHCl_3$, 98% ee). HRMS: *m/z* calcd for $C_{19}H_{21}NO_3$: 311.15214; found: 311.1522. ^{1}H NMR: δ = 1.06 (d, *J* = 7.2, 3H), 1.17 (t, *J* = 7.2, 3H), 1.46 (d, *J* = 7.2, 3H), 2.89 (d, *J* = 10.4, 1H), 3.23-3.30 (m, 1H), 3.36-3.44 (m, 1H), 4.10-4.16 (m, 2H), 6.79 (d, *J* = 2.8, 1H), 7.29-7.37 (m, 5H), 9.48 (s, 1H); ^{13}C NMR: δ = 13.7 (CH_3), 18.67 (CH_3), 18.71 (CH_3), 38.1 (CH), 34.7 (CH), 49.2 (CH), 53.6 (C), 62.6 (CH_2), 117.6 (C), 128.4 (CH), 128.7 (CH), 129.3 (CH), 136.8 (C), 140.1 (C), 154.8 (CH), 166.8 (C), 192.4 (CH).



7e

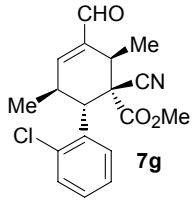
7e (Table 2, entry 6) **-** The reaction was carried out following the general procedure to furnish the crude product [dr = >20:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.49 ppm, δ_{minor} 9.53 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless liquid by column chromatography (hexane/Et_2O = gradient from 85/15 to 75/25) in 39% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and 98% ee). HPLC analysis on a Chiralcel OD-H column: 9/1 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 8.0 min, τ_{minor} = 12.9 min; $[\alpha]^{rt}_D$= + 187.4 (*c* = 0.975, $CHCl_3$, 98% ee). HRMS: *m/z* calcd for $C_{24}H_{23}NO_3$: 373.16779; found: 373.1678. ^{1}H NMR: δ = 0.92 (t, *J* = 6.8, 3H), 1.17 (t, *J* = 6.8, 3H), 1.25-1.35 (m, 1H), 1.45 (d, *J* = 6.8, 3H), 1.56-1.66 (m, 1H), 3.05 (d, *J* = 10.4, 1H), 3.24-3.34 (m, 2H), 4.08-4.15 (m, 2H), 6.90 (d, *J* = 2.4, 1H), 7.29-7.37 (m, 5H),

9.49 (s, 1H); ^{13}C NMR: δ = 10.3 (CH_3), 13.7 (CH_3), 18.6 (CH_3), 24.8 (CH_2), 33.9 (CH), 40.6 (CH), 46.3 (CH), 53.6 (C), 62.6 (CH_2), 117.7 (C), 128.4 (CH), 128.7 (CH), 129.3 (CH), 136.8 (C), 141.0 (C), 153.1 (CH), 166.9 (C), 192.3 (CH).



7f

7f (Table 2, entry 7) **-** The reaction was carried out following the general procedure to furnish the crude product [dr = >20:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.48 ppm, δ_{minor} 9.52 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless liquid by column chromatography (hexane/Et_2O = gradient from 85/15 to 75/25) in 40% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralpak AD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 5.9 min, τ_{major} = 6.4 min; $[\alpha]^{rt}_D$= + 166.2 (*c* = 1.04, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{21}H_{23}NO_3$: 337.16779; found: 337.1679. ^{1}H NMR: δ = 1.17 (t, *J* = 7.2, 3H), 1.44 (d, *J* = 7.2, 3H), 1.91-2.01 (m, 1H), 2.33-2.40 (m, 1H), 3.07 (d, *J* = 10.8, 1H), 3.23-3.28 (m, 1H), 3.42-3.49 (m, 1H), 4.09-4.15 (m, 2H), 4.99-5.07 (m, 1H), 5.12-5.16 (m, 1H), 5.59-5.71 (m, 1H), 6.89 (d, *J* = 2.8, 1H), 7.29-7.38 (m, 5H), 9.48 (s, 1H); ^{13}C NMR: δ = 13.7 (CH_3), 18.6 (CH_3), 34.0 (CH), 35.9 (CH_2), 39.2 (CH), 45.9 (CH), 53.5 (C), 62.6 (CH_2), 117.6 (C), 119.1 (CH_2), 128.5 (CH), 128.8 (CH), 129.4 (CH), 133.6 (CH), 136.5 (C), 144.1 (CH), 152.6 (CH), 166.9 (C), 192.2 (CH).

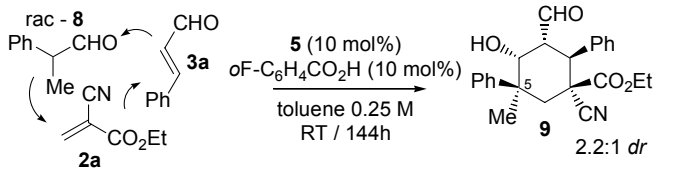


7g

7g (Table 2, entry 8) **-** The reaction was carried out following the general procedure to furnish the crude product [dr = 7.6:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.48 ppm, δ_{minor} 9.53 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless liquid by column chromatography (hexane/Et_2O = 8/2) in 38% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and 99% ee). HPLC

analysis on a Chiralcel OD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 9.6 min, τ_{minor} = 15.0 min; $[\alpha]^{rt}_{D}$= + 272.1 (*c* = 0.92, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{18}H_{18}NO_3Cl$: 331.09752; found: 331.0976. ^{1}H NMR: δ = 1.04 (d, *J* = 7.2, 3H), 1.52 (d, *J* = 7.2, 3H), 3.25-3.37 (m, 2H), 3.72 (s, 3H), 3.95 (d, *J* = 10.8, 1H), 6.79 (d, *J* = 2.8, 1H), 7.26-7.34 (m, 3H), 7.47-7.50 (m, 1H), 9.48 (s, 1H); ^{13}C NMR: δ = 18.1 (CH_3), 18.4 (CH_3), 34.8 (CH), 35.5 (CH), 43.3 (CH), 52.3 (C), 53.3 (CH), 116.8 (C), 127.4 (CH), 127.9 (CH), 129.4 (CH), 130.2 (CH), 135.1 (C), 136.5 (C), 140.1 (C), 154.6 (CH), 167.5 (C), 192.3 (CH).

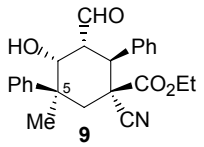
Organocatalytic Asymmetric Synthesis of Cyclohexane 9 Having Five Stereocenters - Two of which Quaternary by all-Carbon Substitution.



9: 36% isolated yield, 96% *ee*
epi-**9**: 19% isolated yield, 91% *ee*

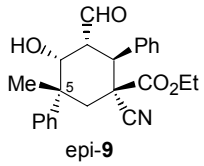
In an ordinary vial equipped with a Teflon-coated stir bar, catalyst **5** (0.04 mmol, 13.0 mg, 10 mol%) and 2-fluorobenzoic acid (0.04 mmol, 5.6 mg, 10 mol%) were dissolved in 1.12 mL of toluene. After addition of 0.8 mmol (2 equiv, 106 μL) of rac-2-phenyl propanal **8**, the solution was stirred for 10 minutes at room temperature. Then ethyl 2-cyanoacrylate **2a** (0.48 mmol, 1.2 equiv, 0.48 mL of a 1M solution in toluene) and 0.4 mmol cinnamaldehyde **3a** (1 equiv, 50.2 μL) were sequentially added. After 48 hours stirring, the crude reaction mixture was diluted with DCM (2 mL) and flushed through a short plug of silica, using DCM/Et_2O 2/1 as the eluent. Solvent was removed *in vacuo* to furnish the crude product [dr = 2.2:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.47 ppm, δ_{minor} 9.44 ppm – d, in $CDCl_3$)]. Both the diastereomers were isolated as white solids by column chromatography (hexane/Et_2O = gradient from 85/15 to 6/4 – R_F^{minor}: 0.3, R_F^{major}: 0.2 in hexane/Et_2O 1/1) and subsequently further purified by semipreparative HPLC using

a Luna C18(2) column (5 μm, 10x250 mm, 5 ml/min, ACN/H_2O 90:10 v/v, UV detector at 220 nm). *The relative configuration of both the diastereomers **9** was determined by extensive NMR NOE studies* (see page S16), whereas the absolute configuration was assumed in analogy with compounds **4a** and **7a**, considering an uniform reaction mechanism. In particular, the C(2) stereocenter should have the same absolute configuration as it is directly forged by the efficient shielding of the chiral fragment of the catalyst, which determines a selective engagement with the *Re* face of the iminium intermediate formed with cinnamaldehyde.



9

9 – The major diastereomer **9** was isolated in 36% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and 96% ee). HPLC analysis on a Chiralpak AD-H: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 7.9 min, τ_{minor} = 11.4 min; $[\alpha]^{rt}_D$= - 7.9 (*c* = 0.9, $CHCl_3$, 96% ee). HRMS: *m/z* calcd for $C_{24}H_{25}NO_4$: 391.17835; found: 391.1786. ^{1}H NMR (600 MHz, CD_3CN): δ = 1.10 (t, *J* = 7.2, 3H), 1.26 (s, 3H, Me(5)), 2.59 (d, *J* = 14.4, 1H, H-6'), 2.73 (dd, *J* = 14.4 and 1.4, 1H, H-6"), 3.59 (ddd, J= 12.8, 1.8 and 1.8, 1H, H-3), 3.80 (d, J = 5.5, 1H, OH), 4.05 (d, J=12.8, 1H, H-2), 4.09 (q, *J* = 7.2, 2H, OCH_2), 4.97 (ddd, J= 5.5, 1.8 and 1.6, 1H, H-4), 7.16(m, 2H, orto-Ph-2), 7.24-7.29 (m, 4H, Ph), 7.55 (m, 2H, Ph), 7.55 (m, 2H, ortho-Ph-5), 9.50(d, J = 1.8, 1H, CHO); ^{13}C NMR 150.8 MHz, CD_3CN): δ = 13.4 (CH_3), 30.8(CH_3), 37.5 (CH), 41.9 (CH), 42.2 (C), 51.2 (CH), 51.7 (C), 63.1 (OCH_2), 69.0 (CH), 116.6 (CN), 126.6 (CH), 126.8(CH), 128.2 (CH), 128.6 (CH), 128.8 (CH), 129.2 (CH), 136.9 (C), 144.1 (C), 168.7 7(CO), 202.5(CHO).



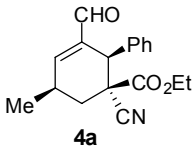
epi-**9**

epi-9 (5 epimer) – The minor diastereomer epi-**9** was isolated in 19% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and 91% ee). HPLC analysis on a Chiralcel OD-H: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 17.1 min, τ_{major} = 27.4 min; $[\alpha]^{rt}_D$= + 2.1 (*c* = 0.83, $CHCl_3$, 91% ee). ^{1}H NMR (600 MHz, CD_3CN): δ = 1.18 (t, *J* = 7.3, 3H), 1.67 (s, 3H, Me(5)), 2.53 (dd, *J* = 13.7 and 1.5, 1H, H-6"), 2.90 (d, J = 4.4, 1H, OH), 2.92 (d, *J* = 13.7, 1H, H-

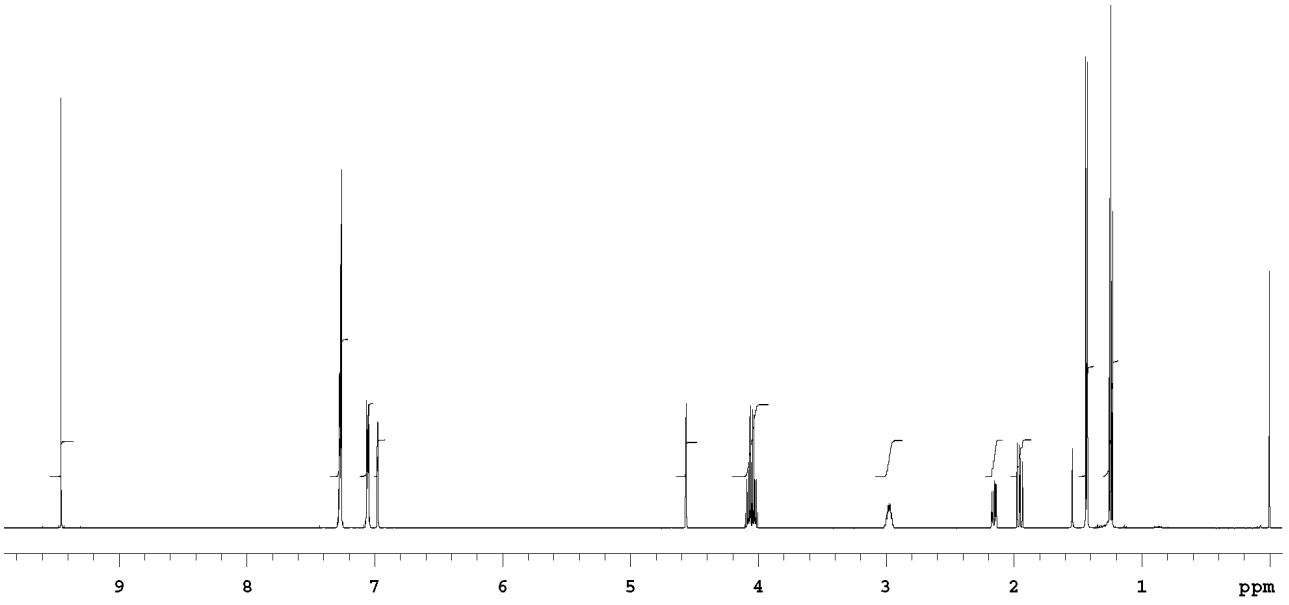
6'), 3.67 (ddd, J= 12.8, 2.0 and 1.9, 1H, H-3), 4.09 (d, J=12.8, 1H, H-2), 4.19 (m, 2H, OCH_2), 4.71 (ddd, J = 4.8, 2.0 and 1.4, 1H, H-4), 7.28(m, 2H, Ph), 7.33-7.45 (m, 8H, Ph), 9.45(d, J = 1.9, 1H, CHO); ^{13}C NMR 150.8 MHz, CD_3CN): δ = 13.4 (CH_3), 26.1(CH_3), 36.8 (CH), 41.0 (CH), 42.7 (C), 50.9 (CH), 51.6 (C), 63.4 (OCH_2), 72.0 (CH), 119.5 (CN), 125.7 (CH), 126.7(CH), 128.4 (CH), 128.7 (CH), 128.9 (CH), 129.4 (CH), 137.3 (C), 147.0 (C), 169.0 (CO), 202.1(CHO).

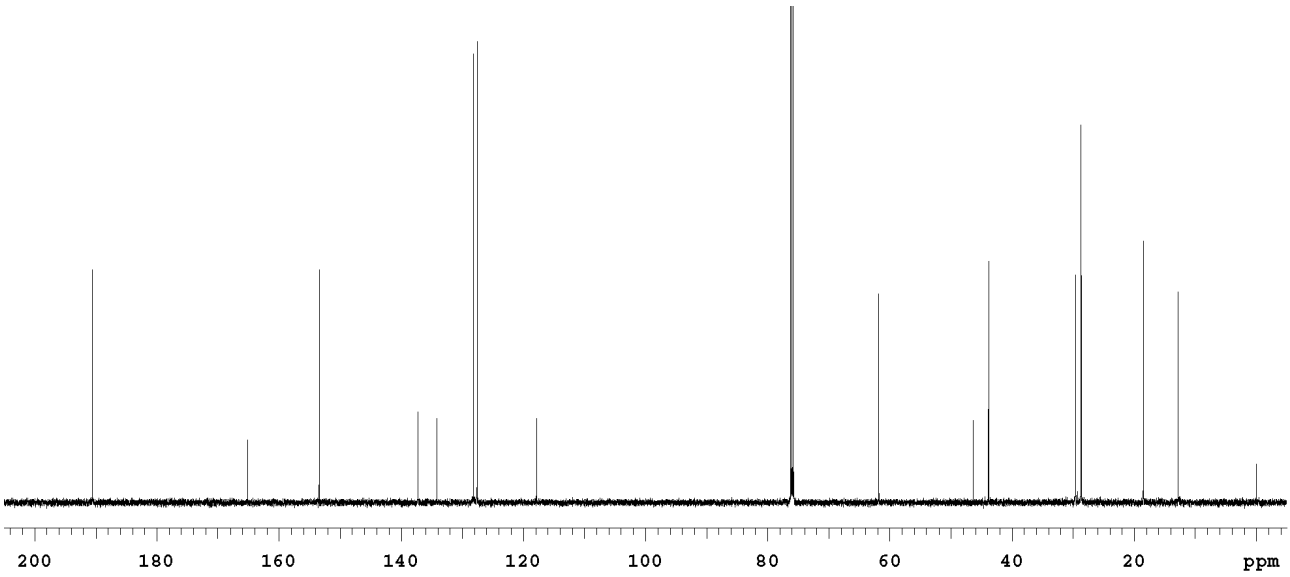
Representative NMR Spectra

Compound **4a**, major isomer

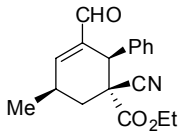


4a

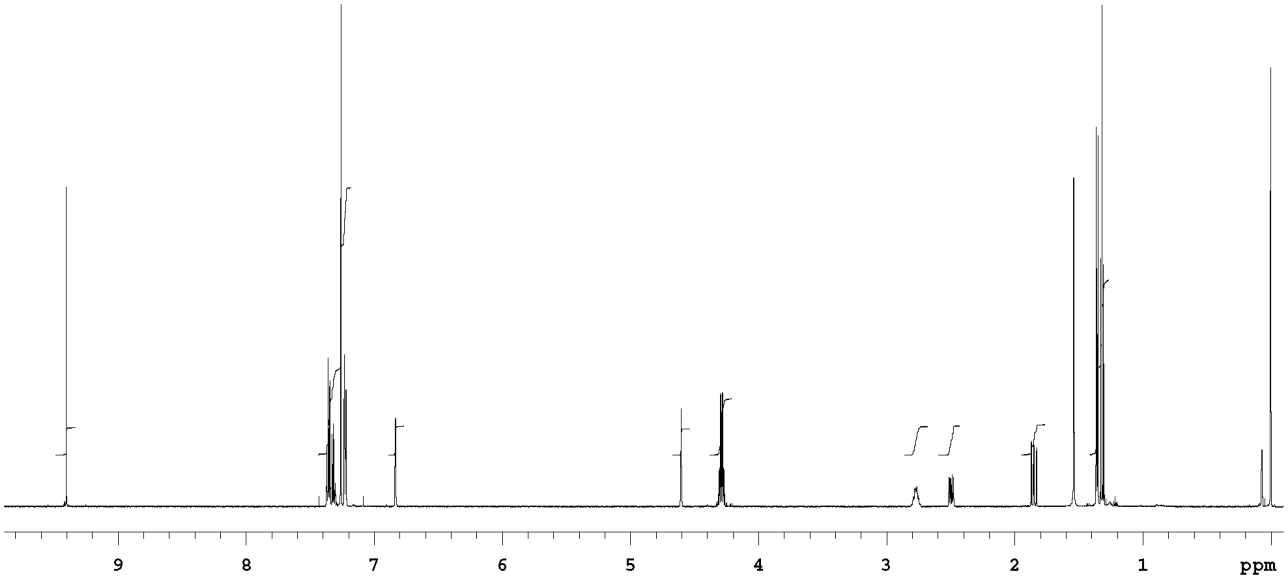


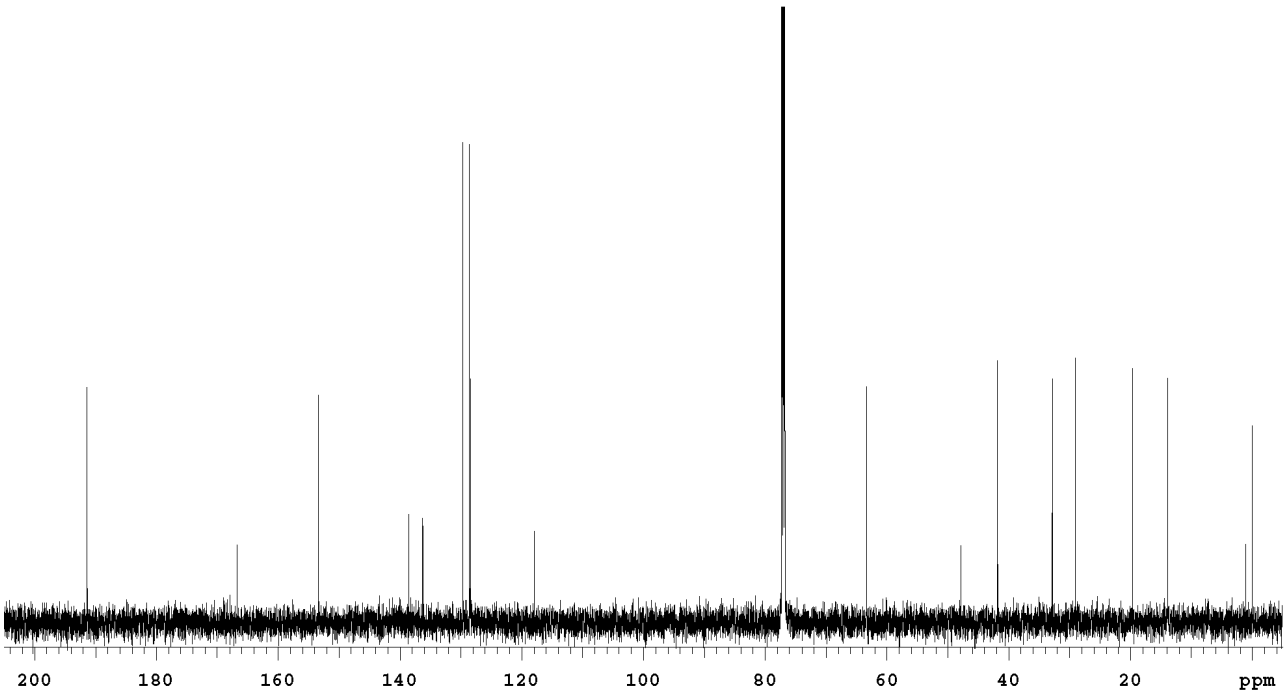


Compound **4a**, minor isomer

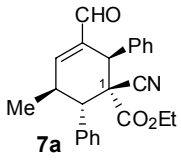


4a-minor

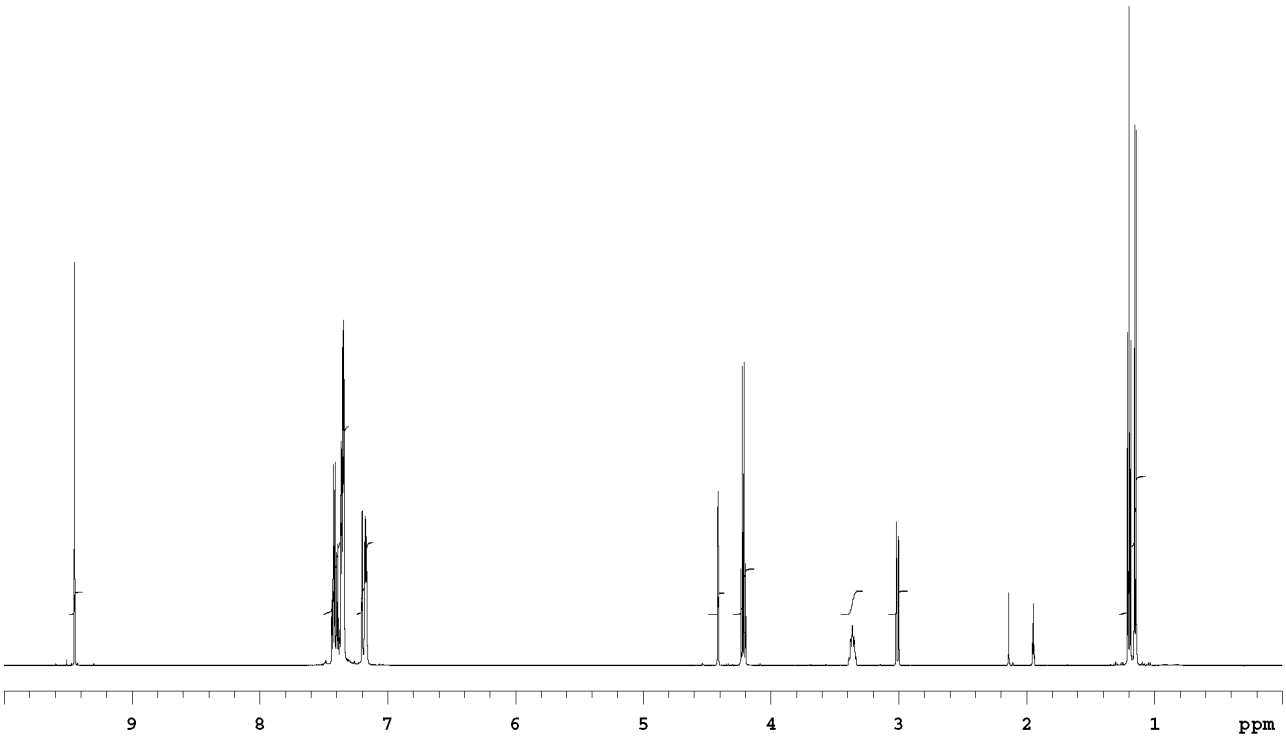


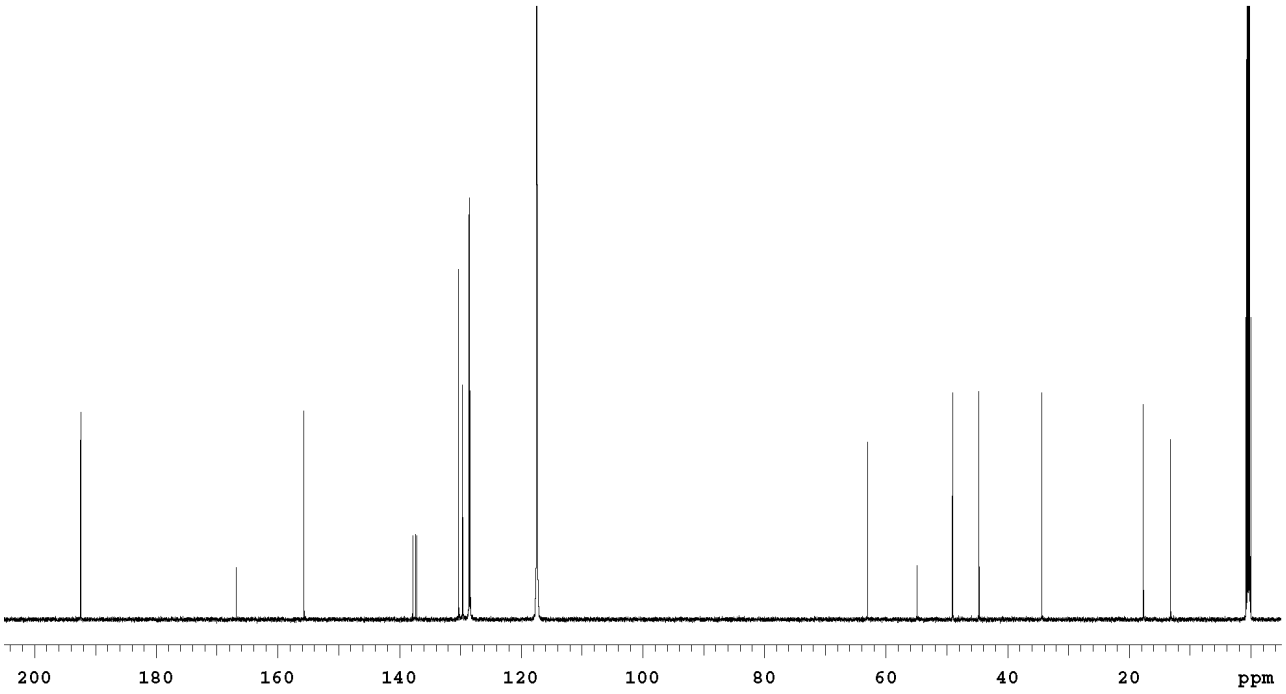


Compound **7a**, major isomer

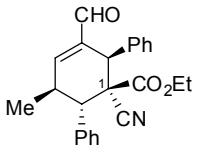


7a

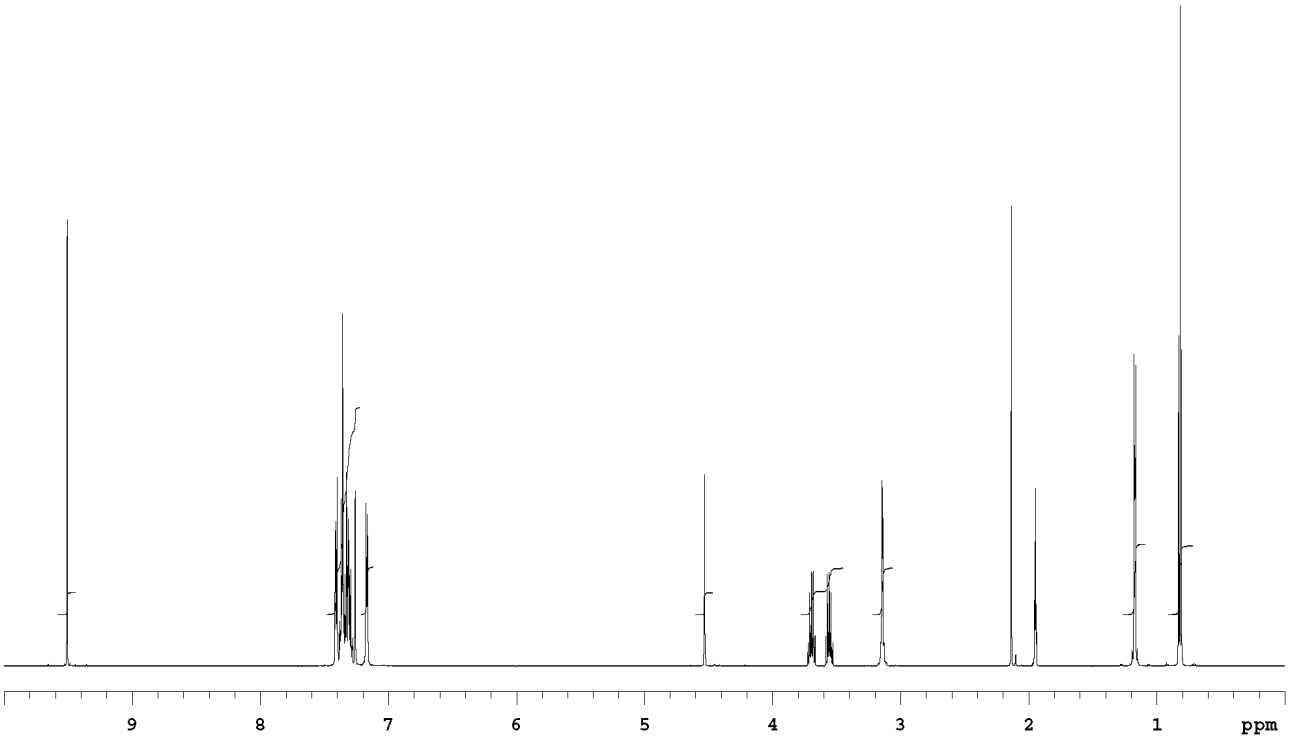


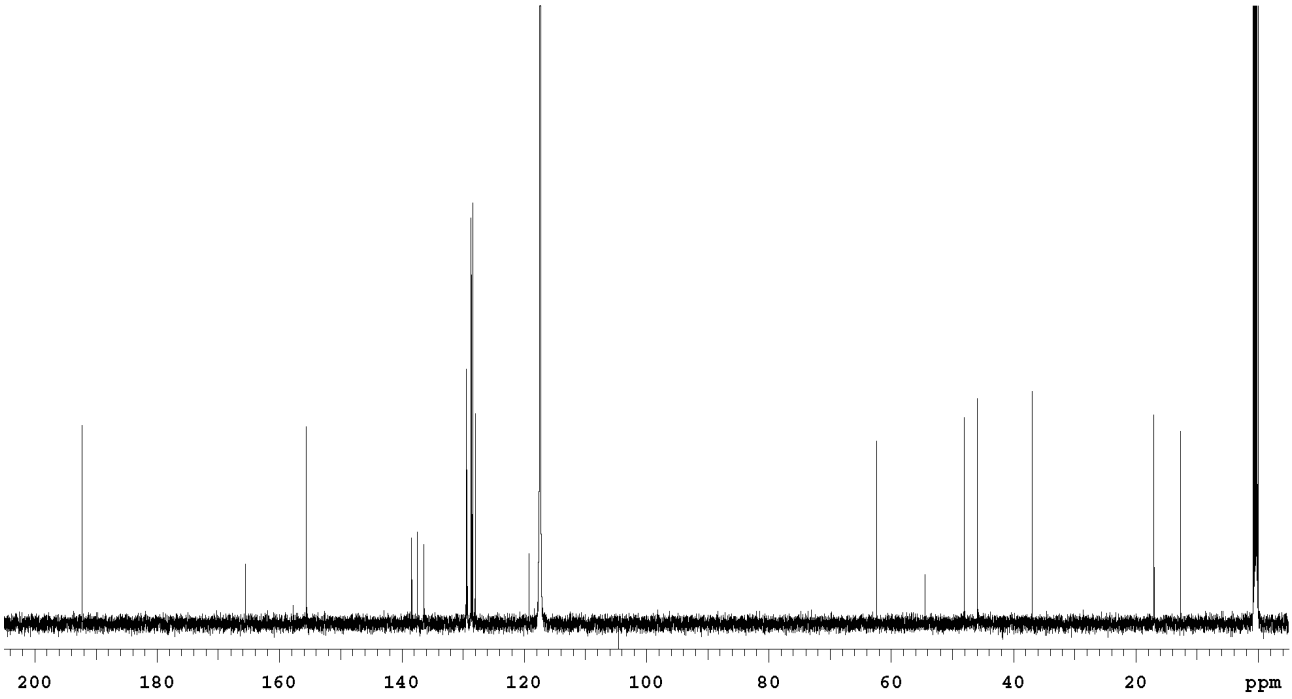


Compound **7a**, minor isomer

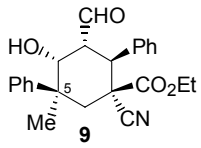


7a-minor

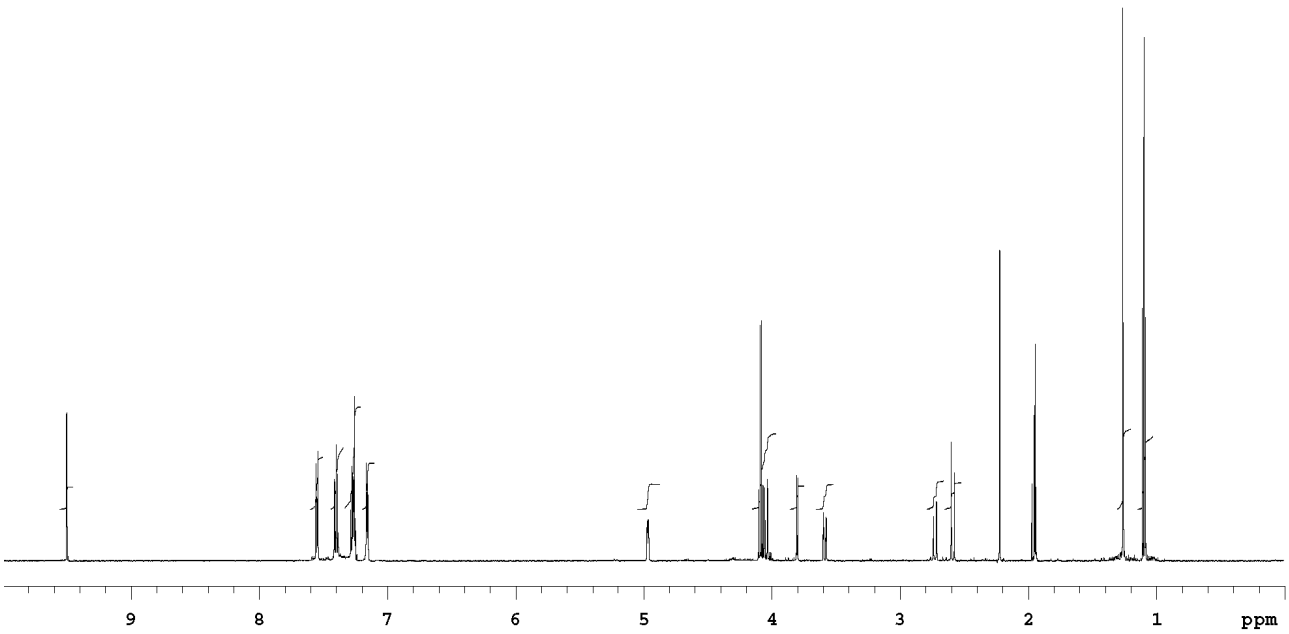


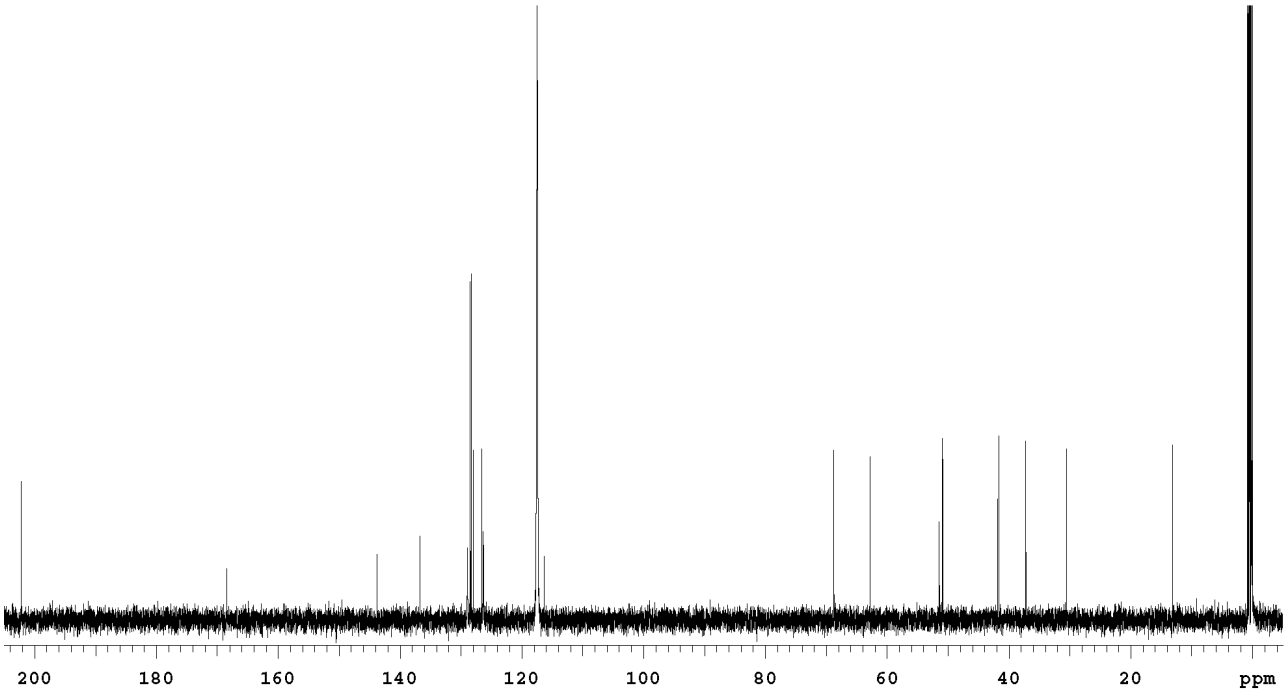


Compound **9**

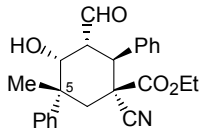

CHO
HO
Ph
Ph
5
CO2Et
Me
CN

9

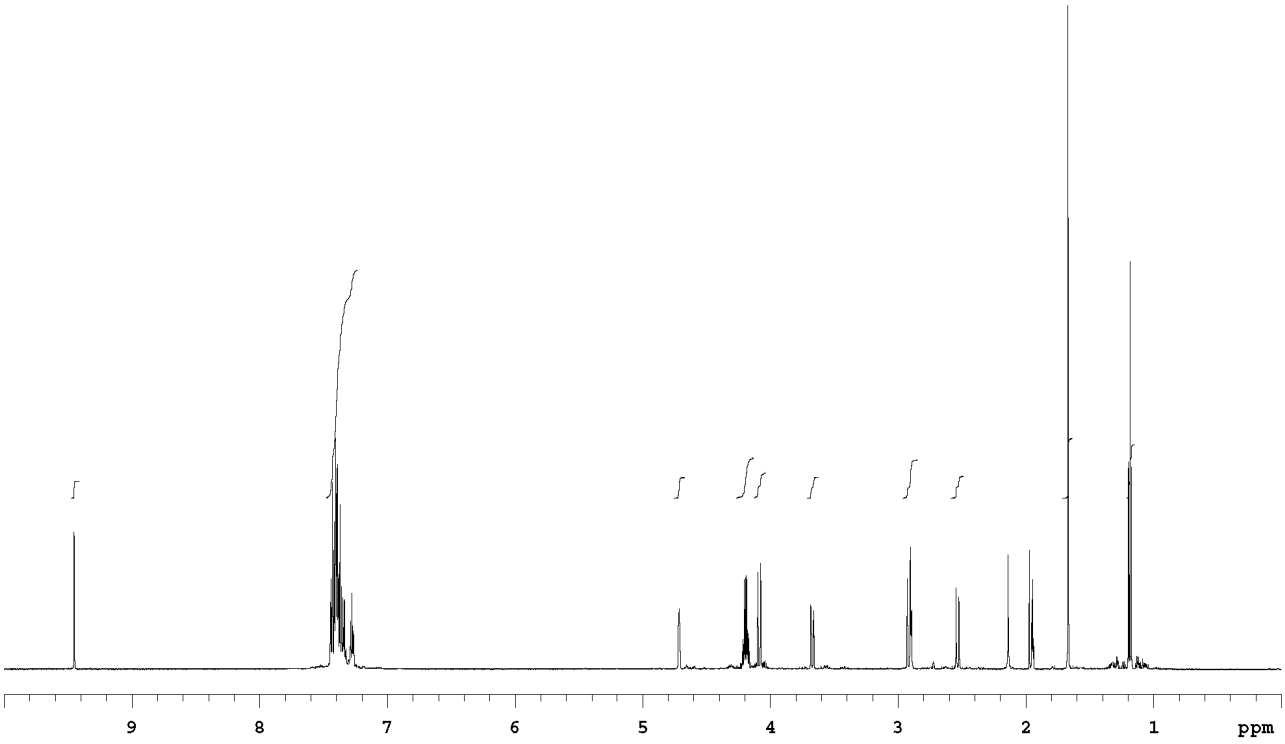

9
8
7
6
5
4
3
2
1
ppm

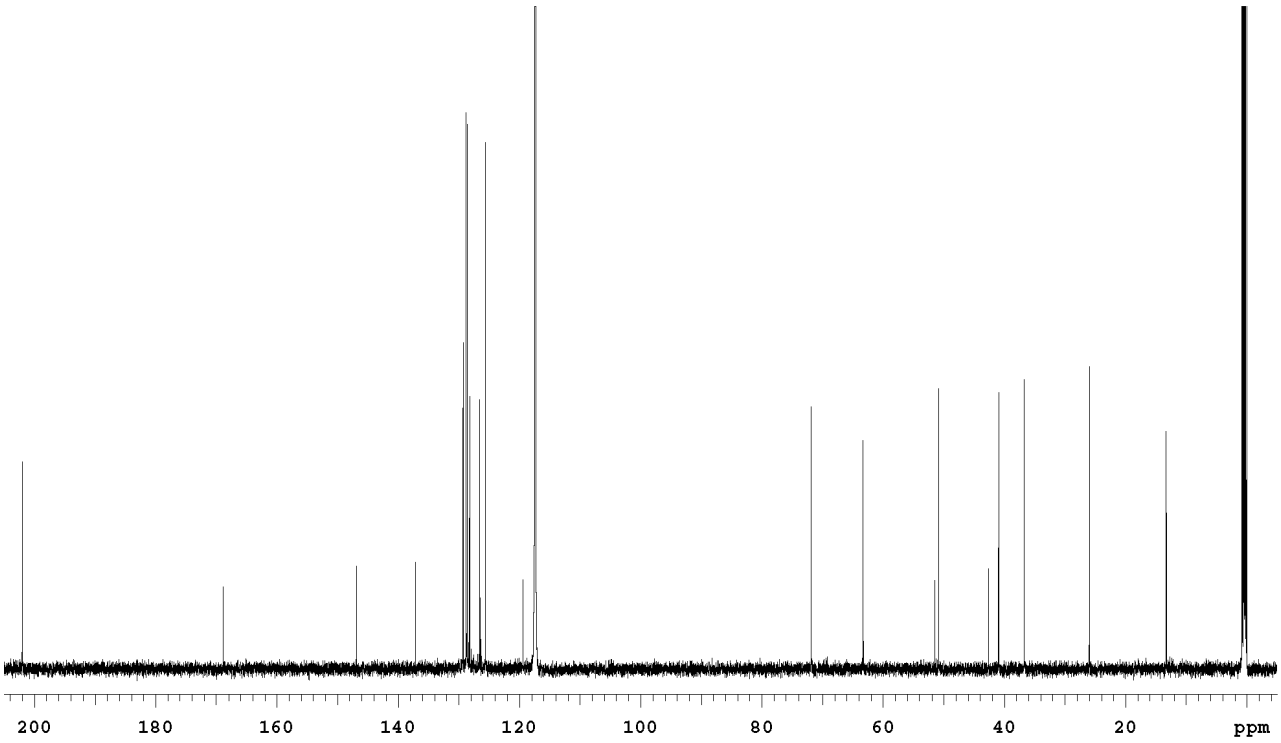

200
180
160
140
120
100
80
60
40
20
ppm

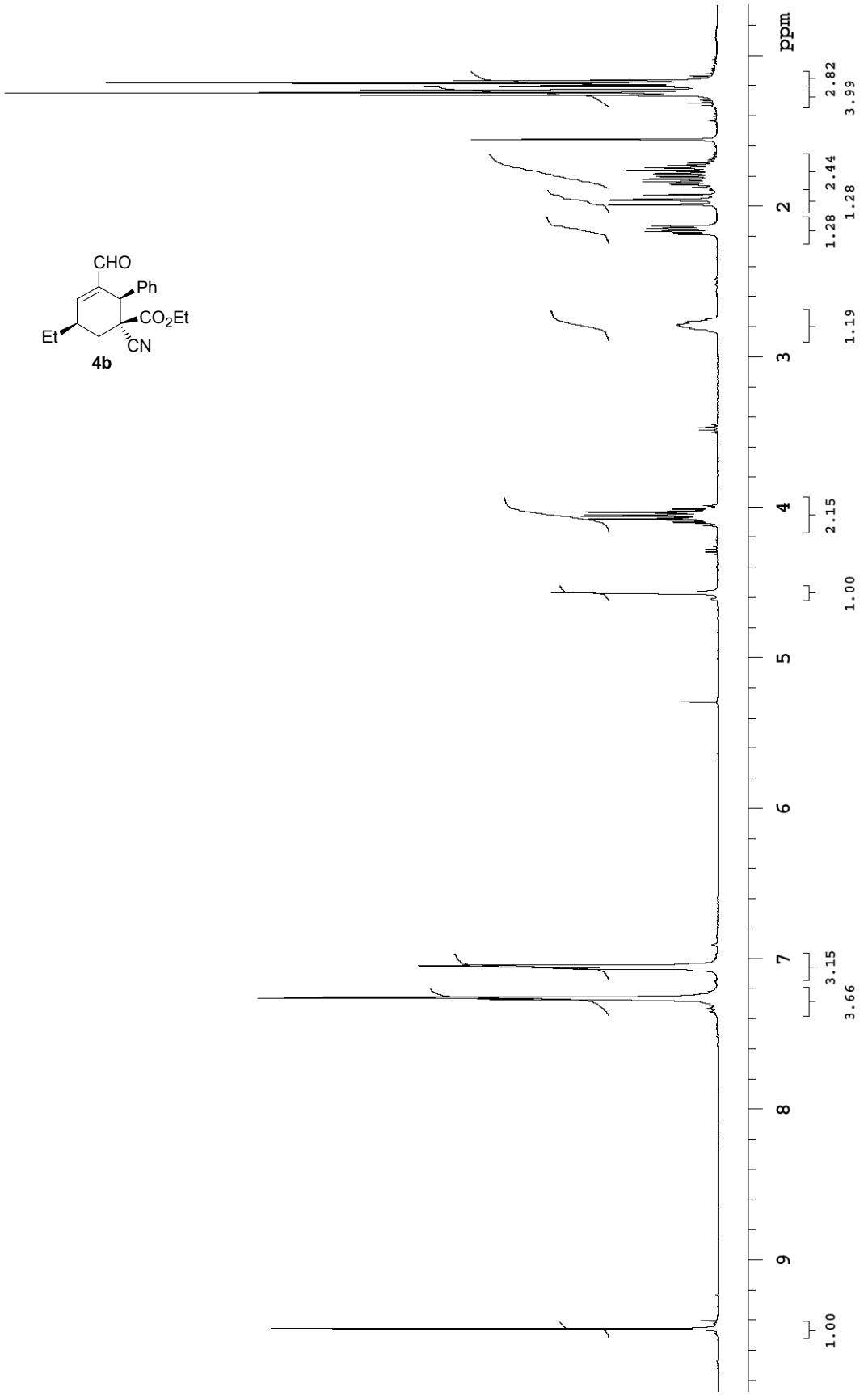
Compound **epi-9**

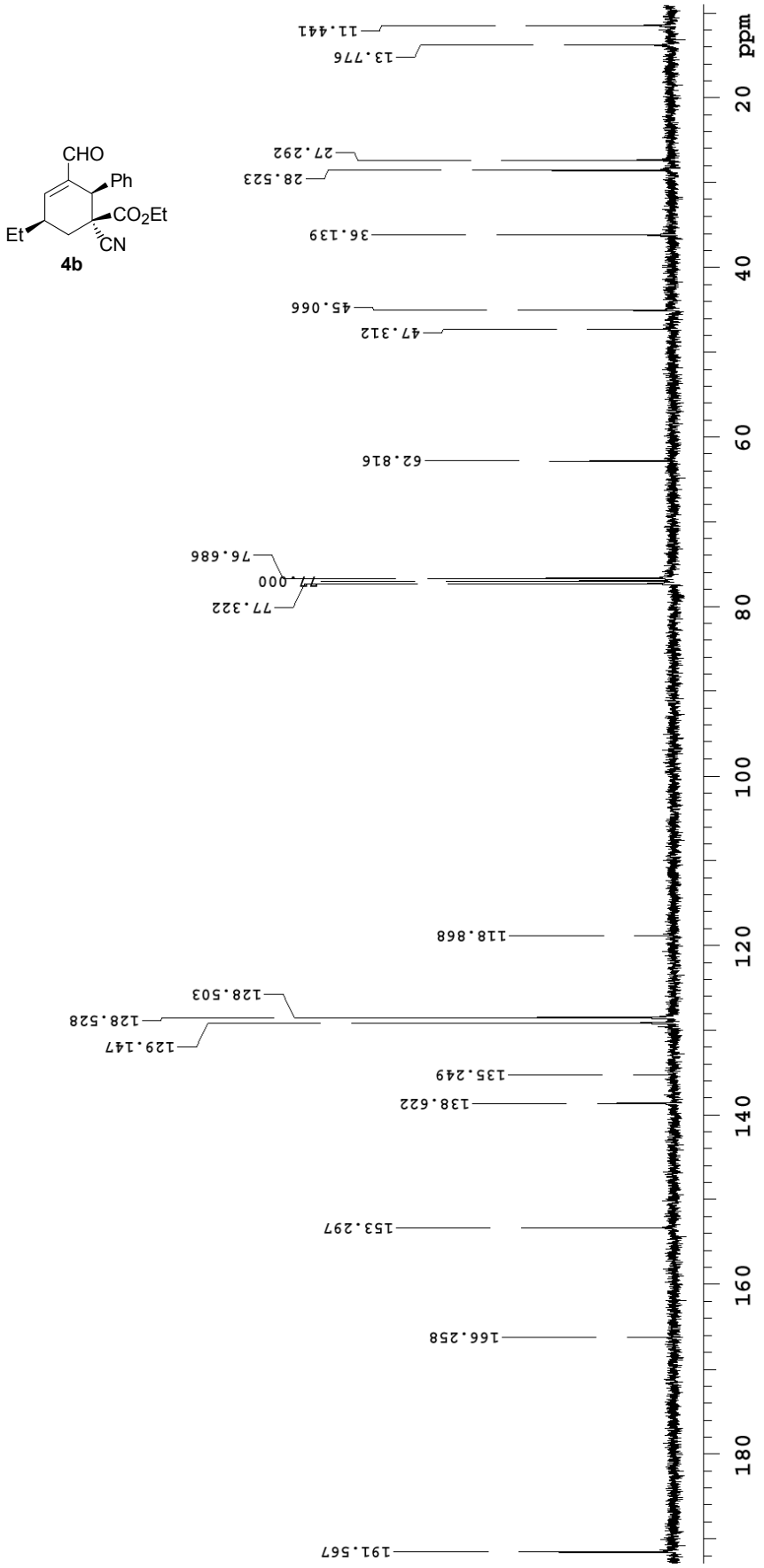


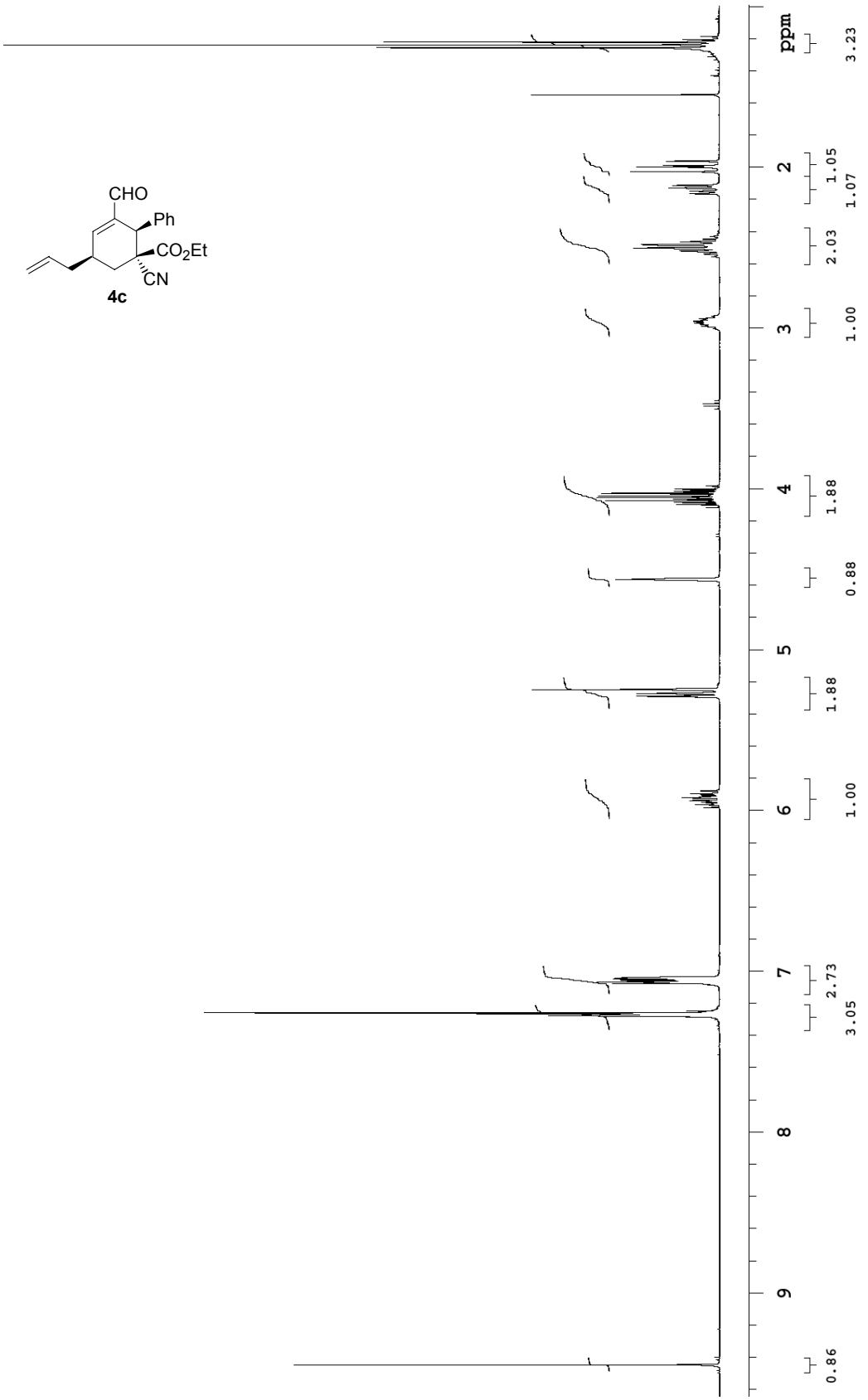
epi-9

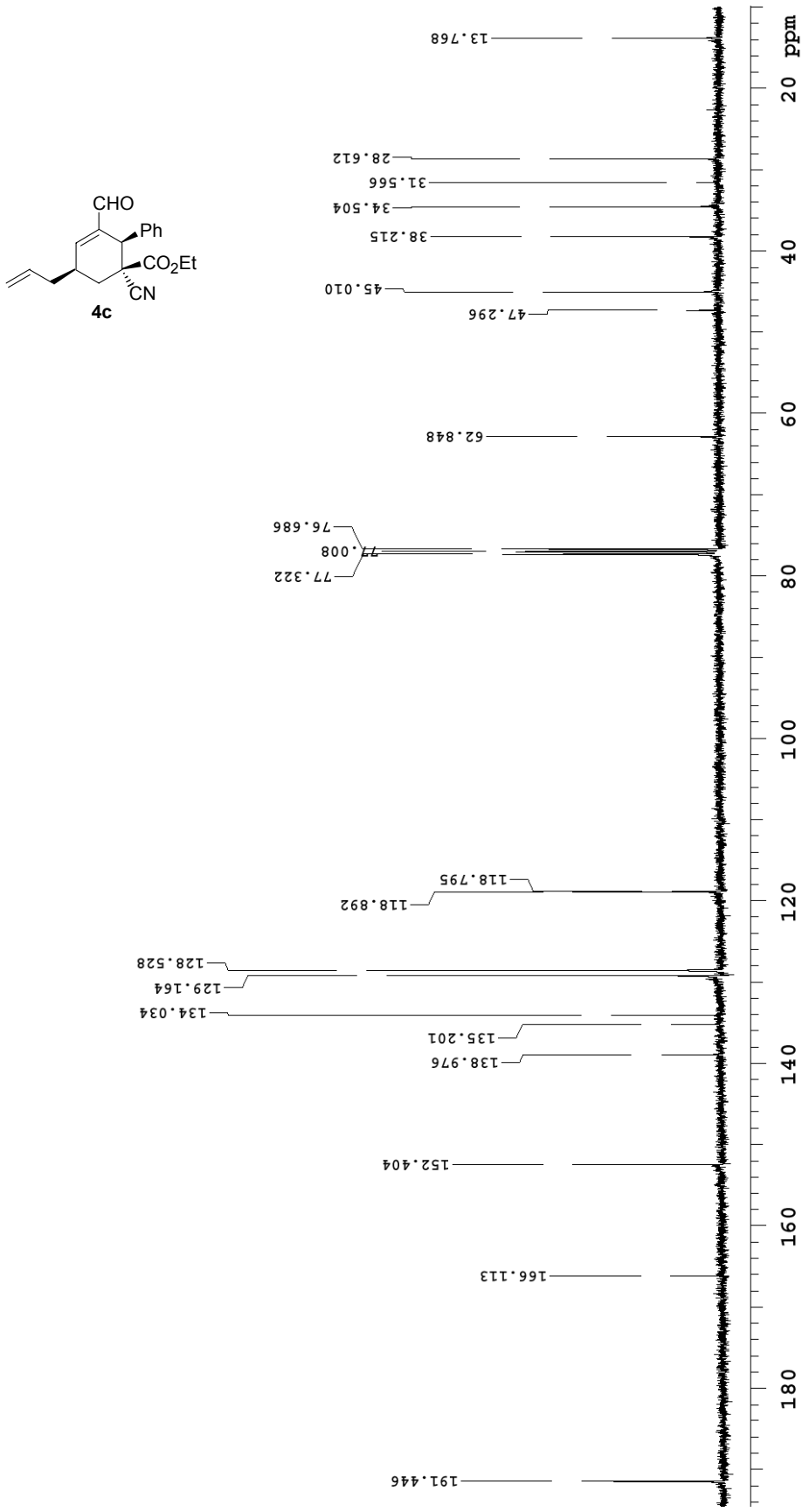


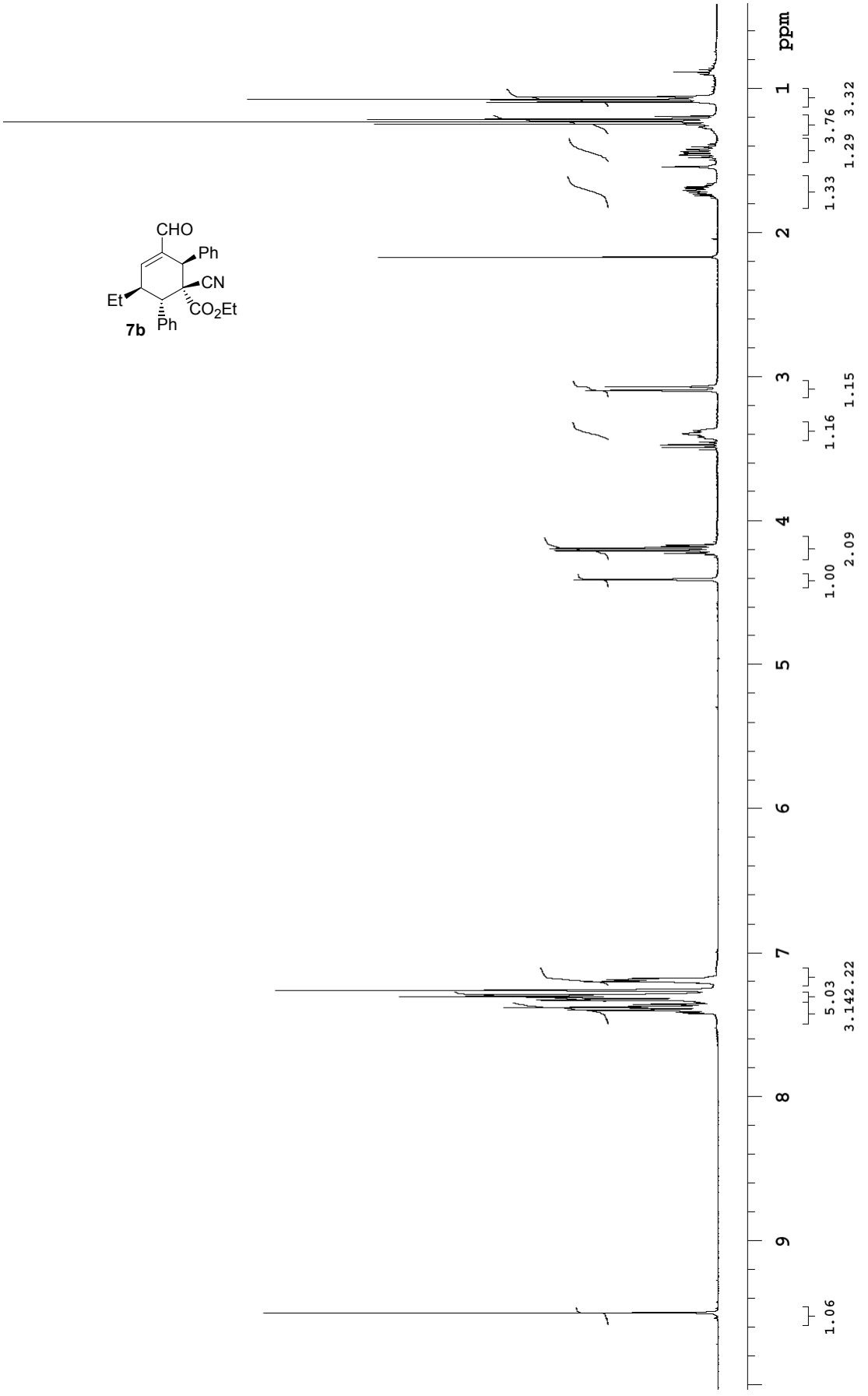


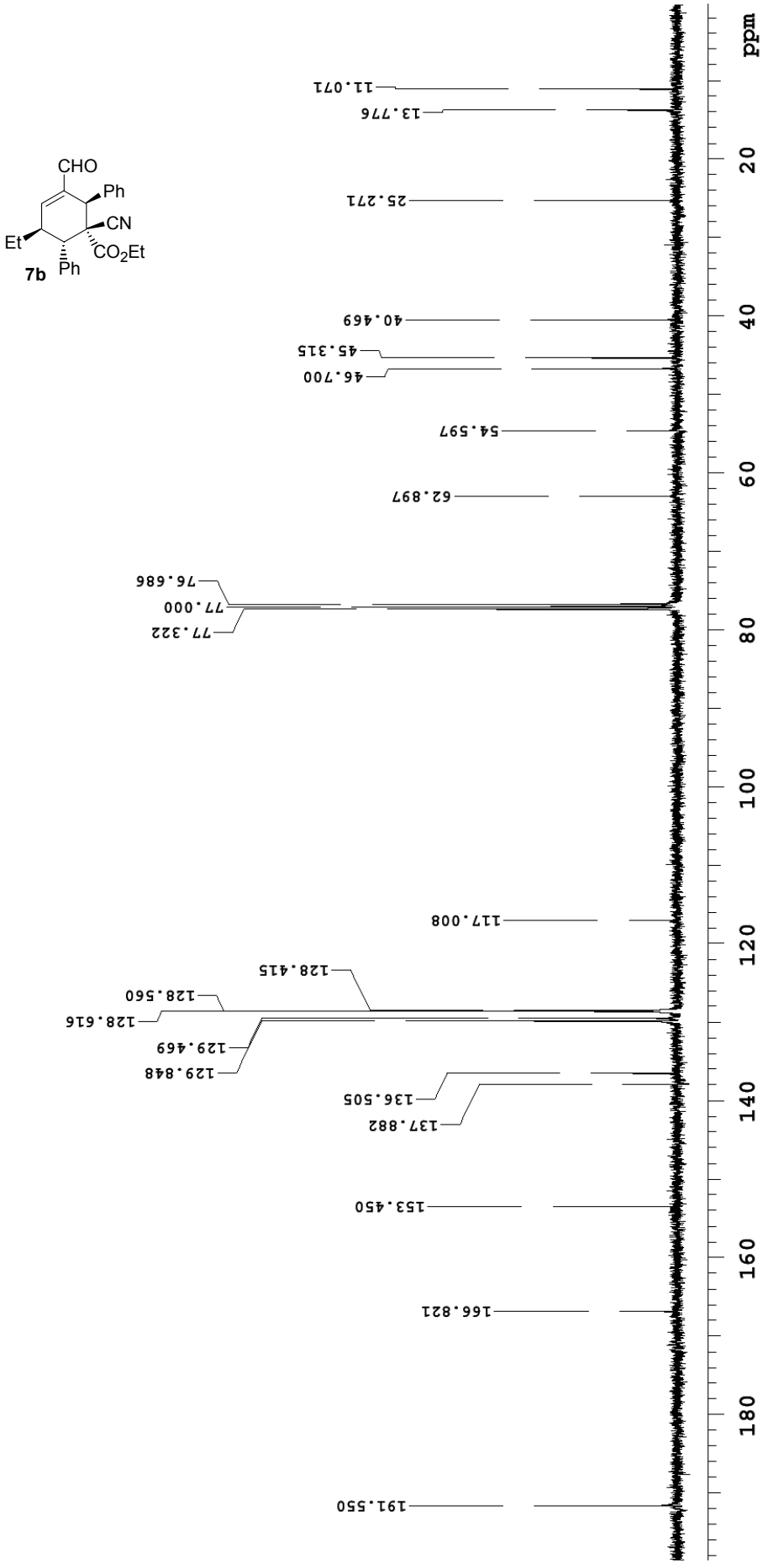

CHO
Ph
CO2Et
Et
CN
4b
ppm
1 2 3 4 5 6 7 8 9
1.00
3.15
3.66
2.15
1.00
1.28
2.44
1.28
1.19
2.82
3.99
1.00

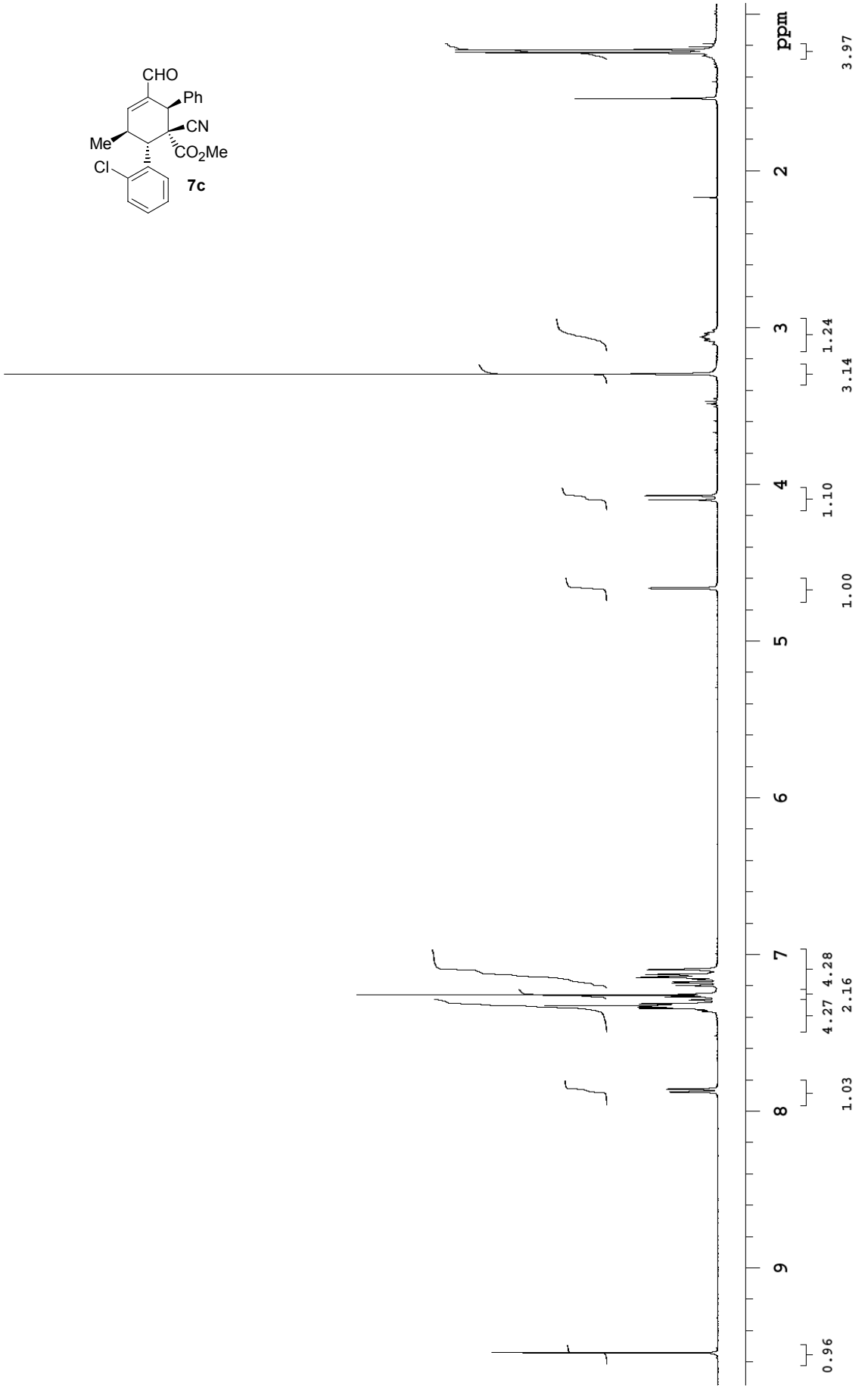

CHO
Ph
CO2Et
Et
CN
4b
11.441
13.776
27.292
28.523
36.139
45.066
47.312
62.816
76.686
77.000
77.322
118.868
128.503
128.528
129.147
135.249
138.622
153.297
166.258
191.567
ppm
20
40
60
80
100
120
140
160
180

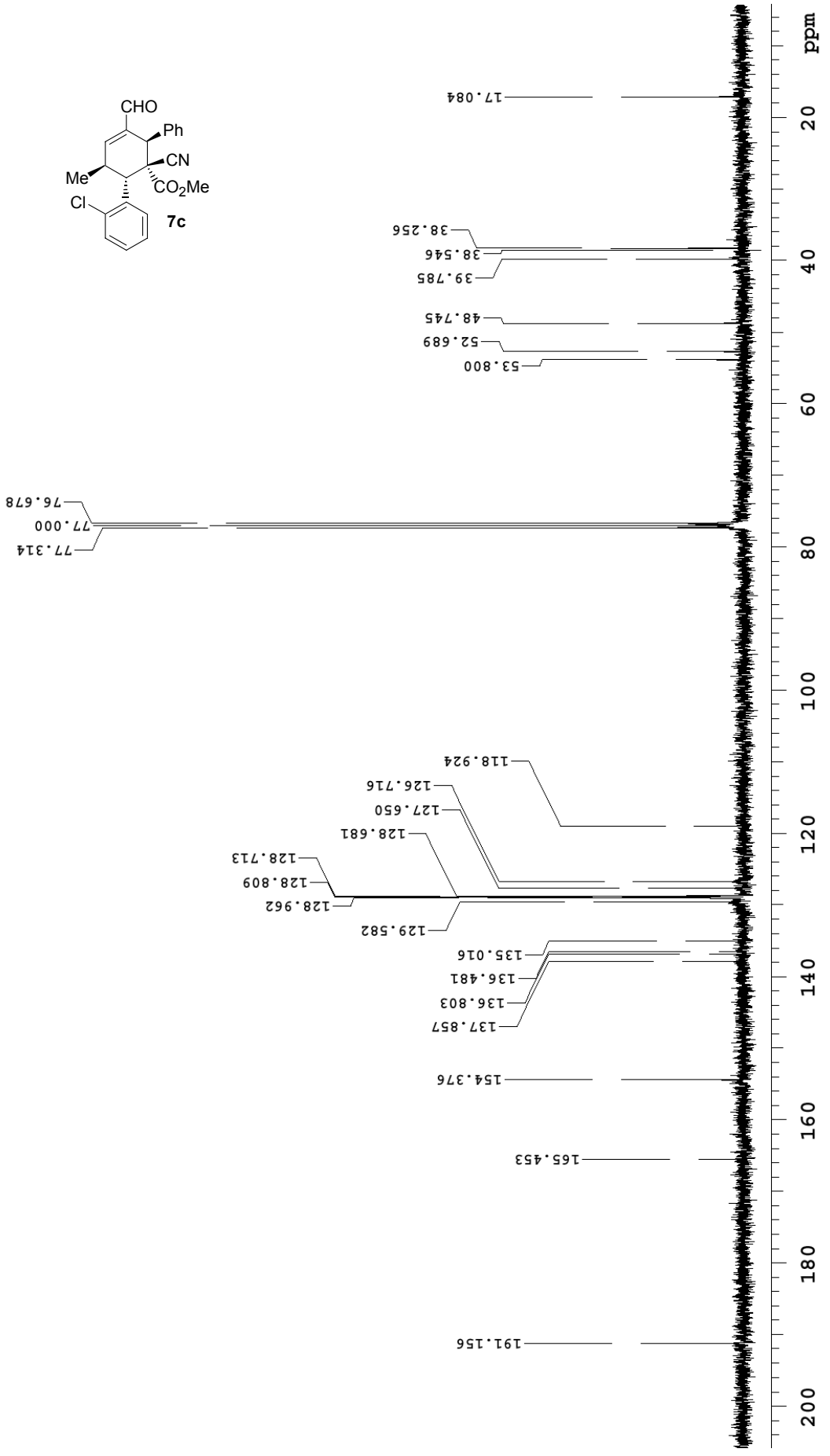

CHO
Ph
CO2Et
CN
4c
ppm
0.86
2.73
3.05
1.88
1.00
1.88
0.88
1.00
2.03
1.07
1.05
3.23

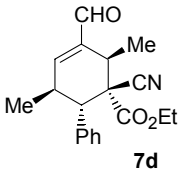

CHO
Ph
CO2Et
CN
4c
13.768
28.612
31.566
34.504
38.215
45.010
47.296
62.848
76.686
77.008
77.322
118.795
118.892
128.528
129.164
134.034
135.201
138.976
152.404
166.113
191.446
20
40
60
80
100
120
140
160
180
ppm


CHO
Ph
CN
Et
CO2Et
Ph
7b
ppm
1
2
3
4
5
6
7
8
9
1.06
5.03
3.142.22
1.00
2.09
1.16
1.15
1.33
3.76
1.29
3.32

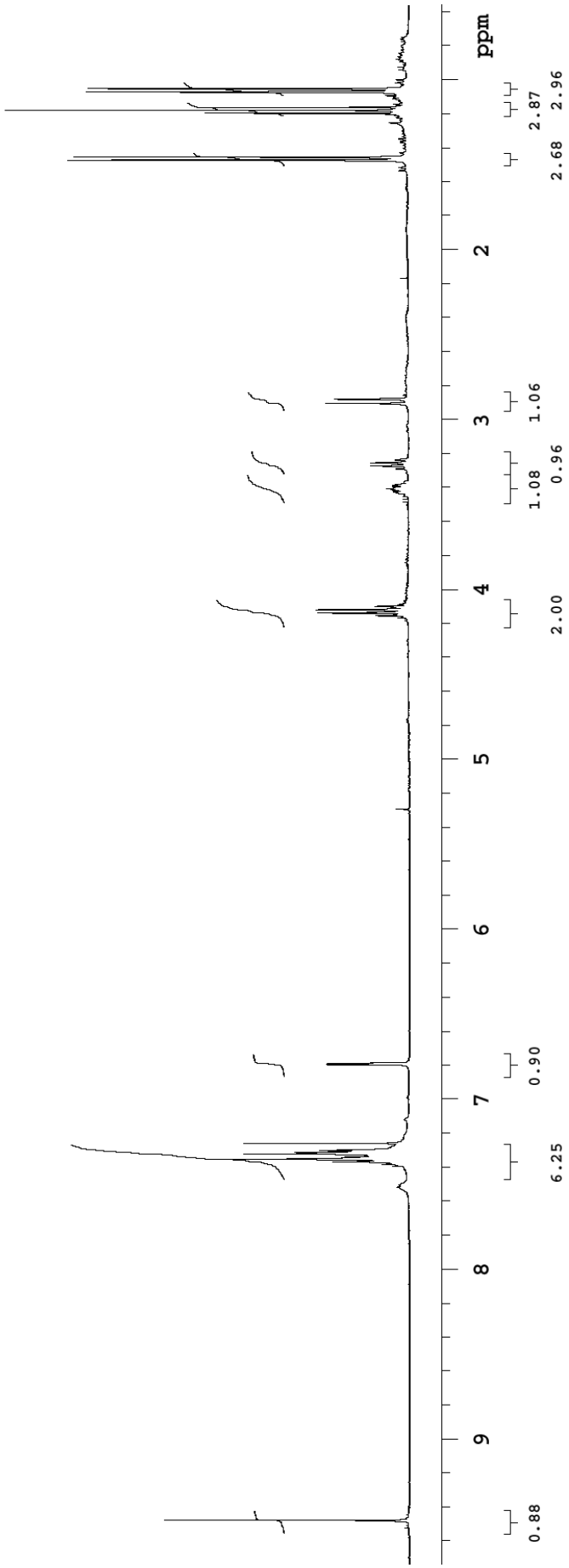

CHO
Ph
CN
Et
CO2Et
Ph
7b
11.071
13.776
25.271
40.469
45.315
46.700
54.597
62.897
76.686
77.000
77.322
117.008
128.415
128.560
128.616
129.469
129.848
136.505
137.882
153.450
166.821
191.550
ppm
20
40
60
80
100
120
140
160
180

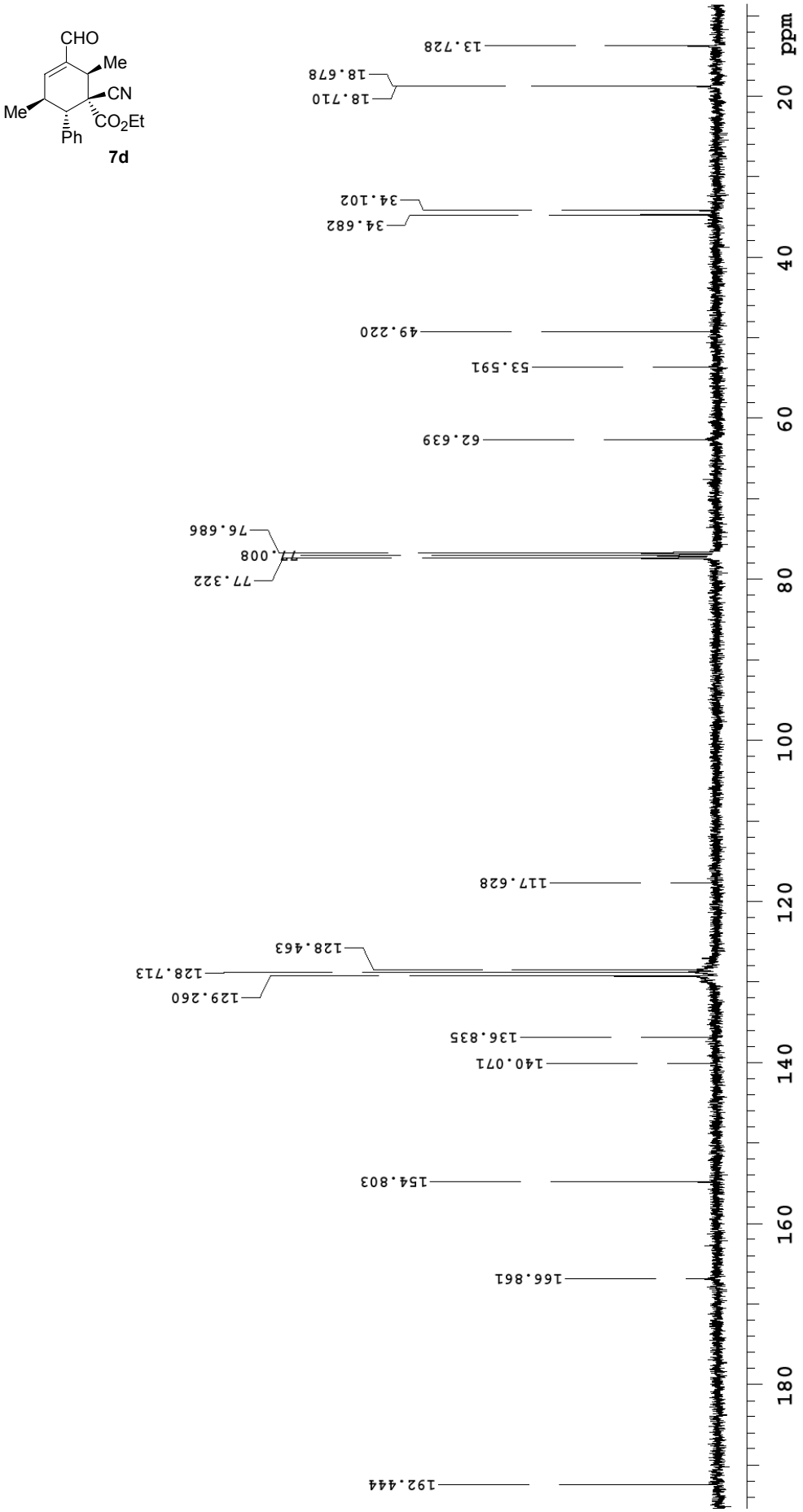

CHO
Ph
CN
Me
CO2Me
Cl
7c
ppm
1
2
3
4
5
6
7
8
9
3.97
1.24
3.14
1.10
1.00
4.27
4.28
2.16
1.03
0.96

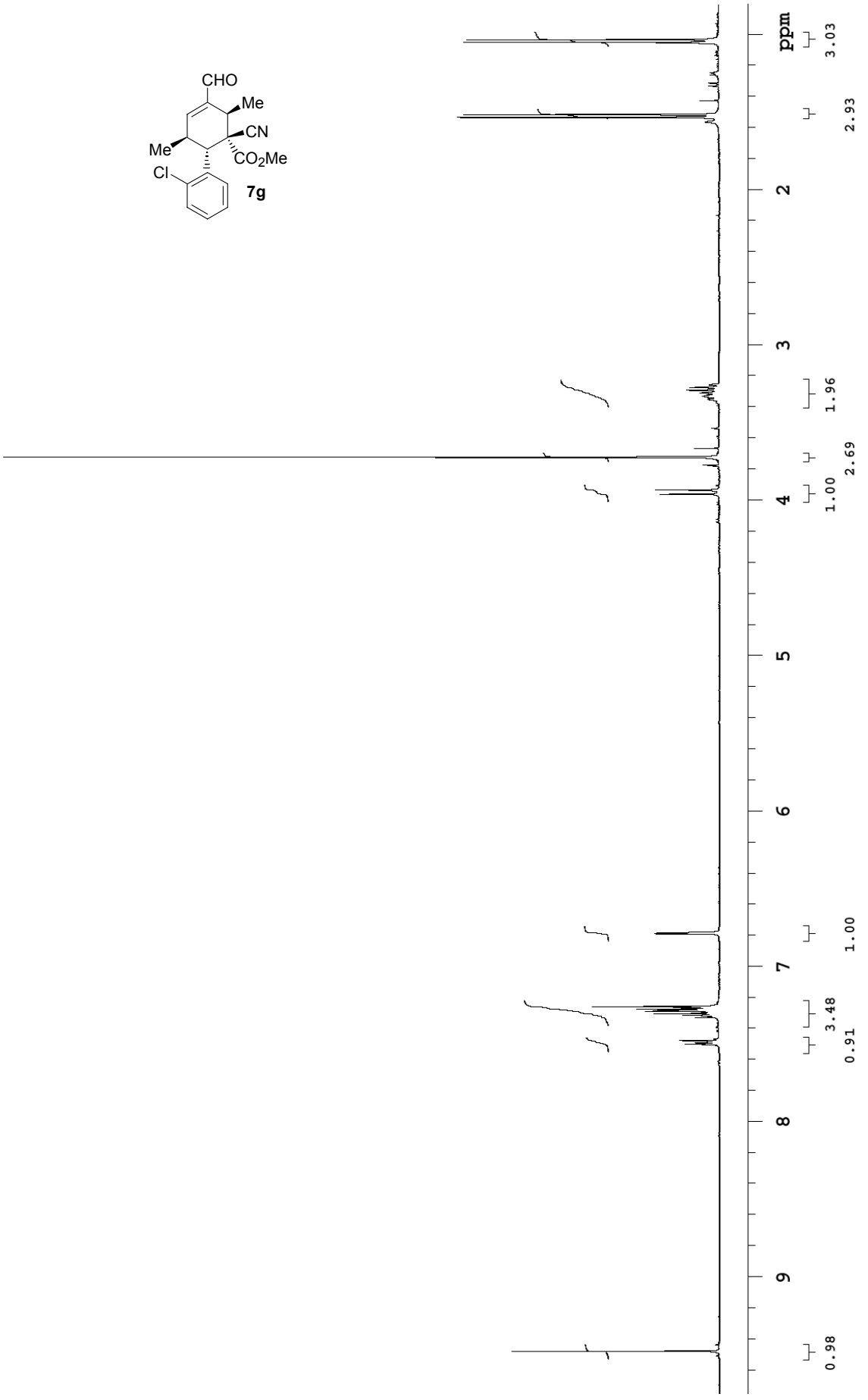

CHO
Ph
CN
Me
CO2Me
Cl
7c
17.084
38.256
38.546
39.785
48.745
52.689
53.800
76.678
77.000
77.314
118.924
126.716
127.650
128.681
128.713
128.809
128.962
129.582
135.016
136.481
136.803
137.857
154.376
165.453
191.156
ppm
20
40
60
80
100
120
140
160
180
200

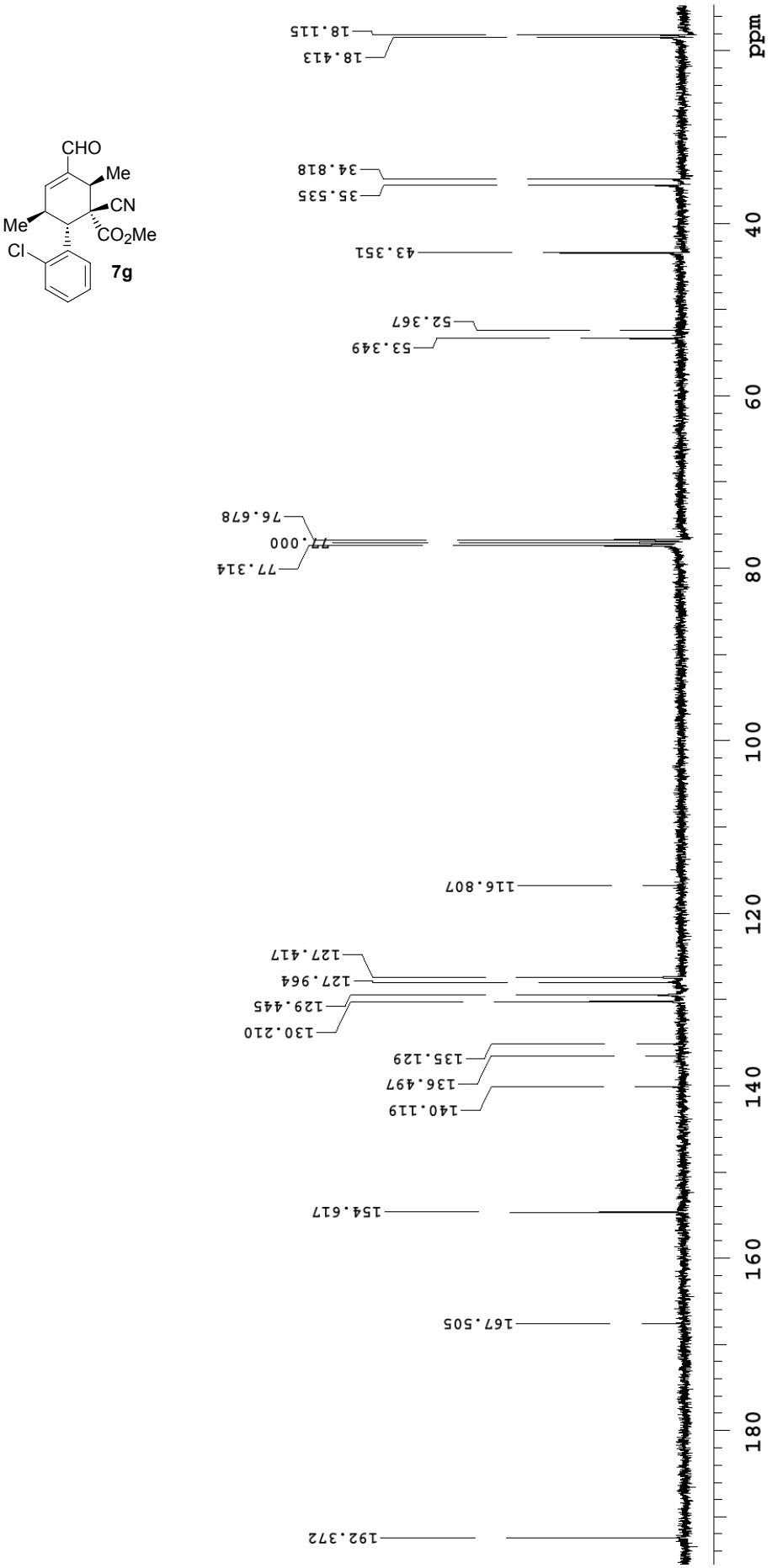

CHO
Me
CN
Me
CO2Et
Ph

7d

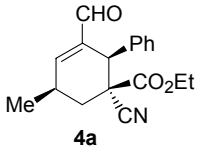

ppm
1
2
3
4
5
6
7
8
9
2.87
2.96
2.68
1.06
1.08
0.96
2.00
0.90
6.25
0.88


CHO
Me
CN
Me
CO2Et
Ph
7d
13.728
18.678
18.710
34.102
34.682
49.220
53.591
62.639
76.686
77.008
77.322
117.628
128.463
128.713
129.260
136.835
140.071
154.803
166.861
192.444
ppm
20
40
60
80
100
120
140
160
180


CHO
Me
CN
Me
CO2Me
Cl
7g
ppm
0.98
3.48
0.91
1.00
1.00
2.69
1.96
3.03
2.93

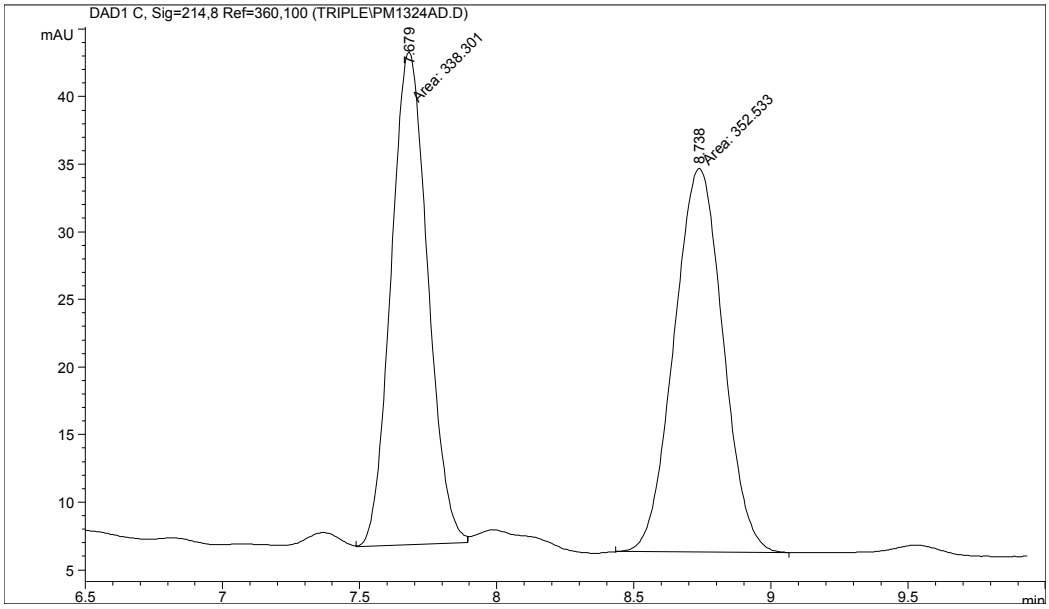

CHO
Me
CN
Me
CO2Me
Cl
7g
18.115
18.413
34.818
35.535
43.351
52.367
53.349
76.678
77.000
77.314
116.807
127.417
127.964
129.445
130.210
135.129
136.497
140.119
154.617
167.505
192.372
ppm
40
60
80
100
120
140
160
180

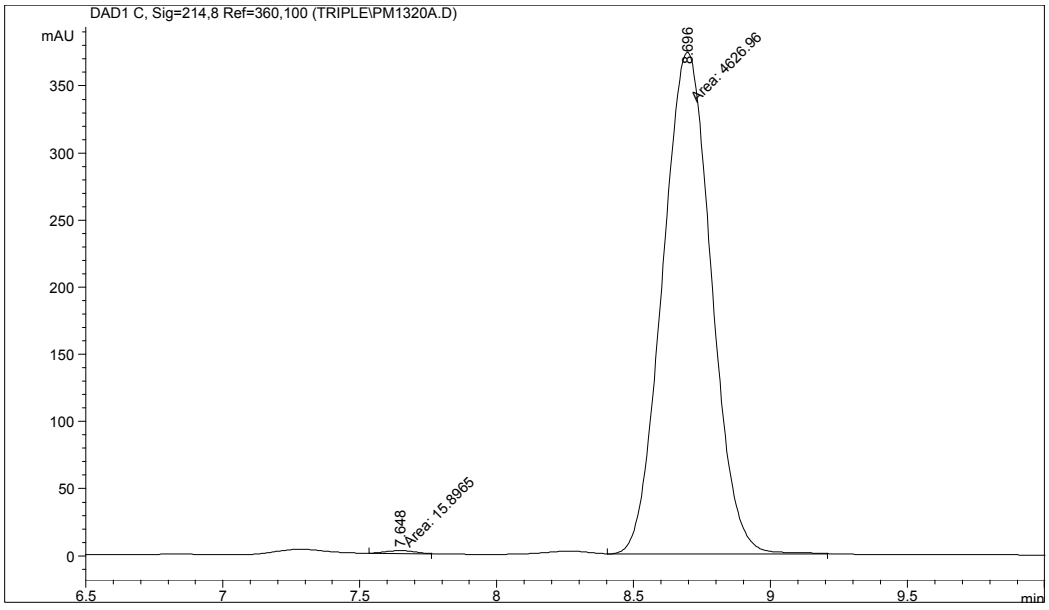
Representative HPLC Traces



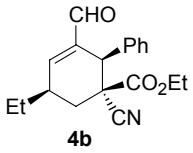
4a

Chiralpak AD-H column (8/2 hexane/*i*PrOH – flow rate: 0.75 mL/min)



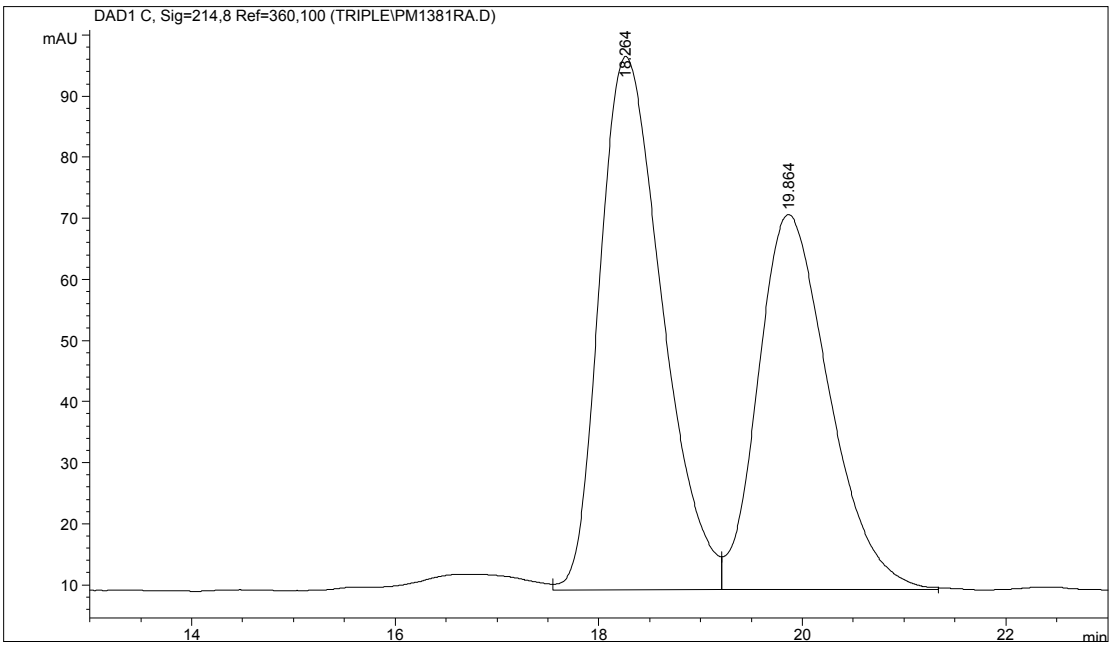


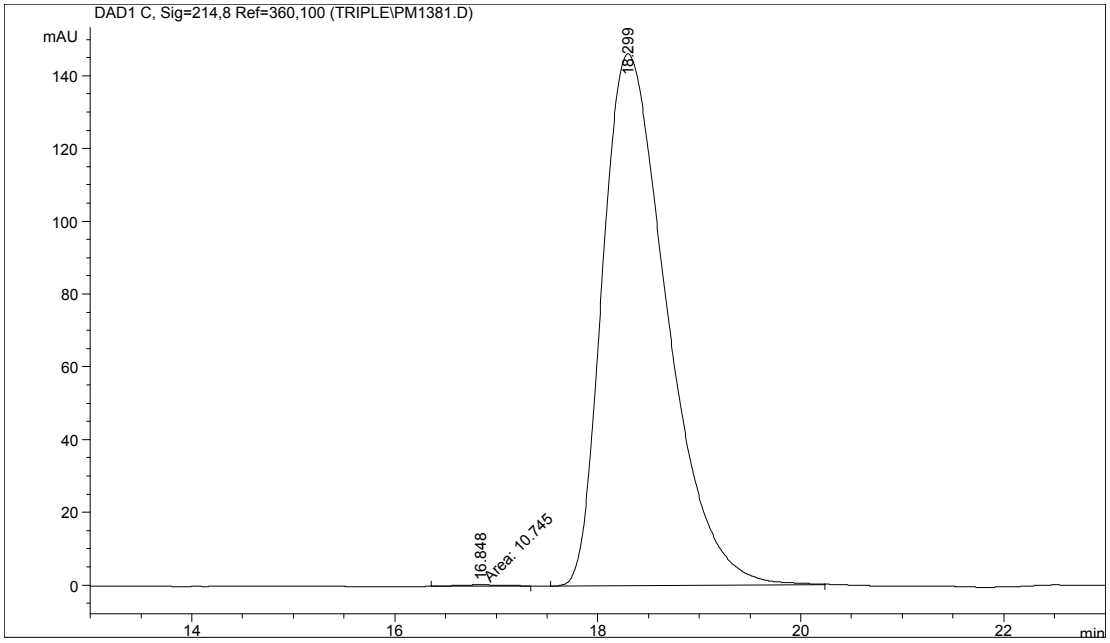
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.648	MM	0.1252	15.89653	2.11676	0.3424
2	8.696	MM	0.2062	4626.96094	374.04504	99.6576
Totals :				4642.85746	376.16180	

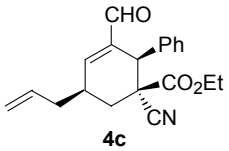


4b

Chiralcel OD-H column (95/5 hexane/*i*PrOH - flow rate: 0.75 mL/min)

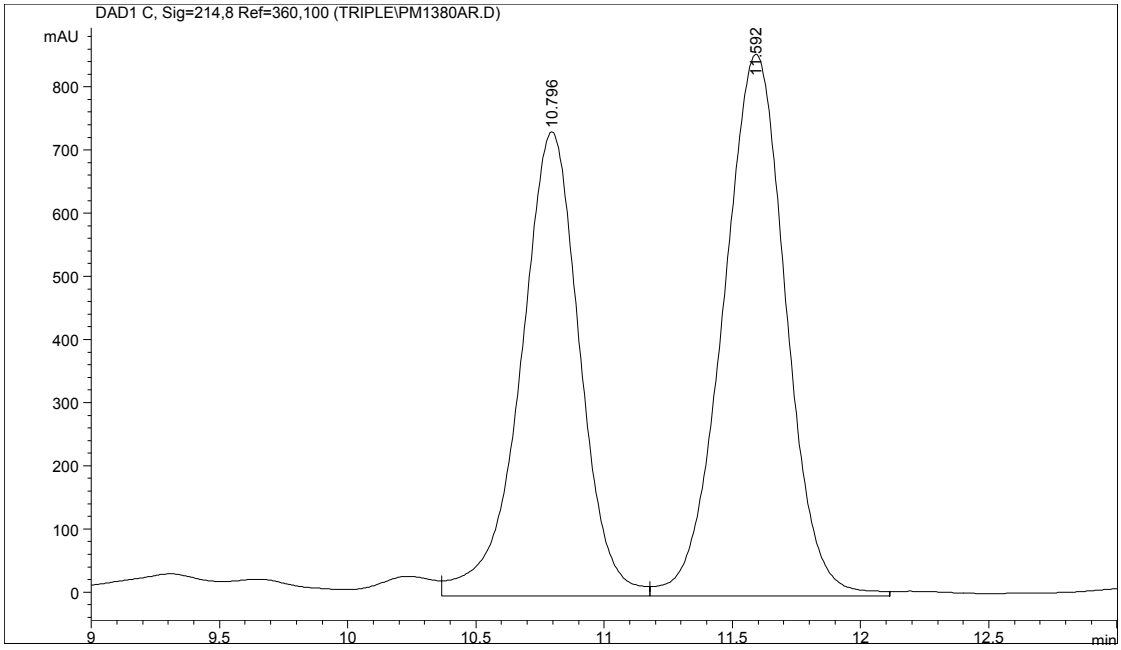


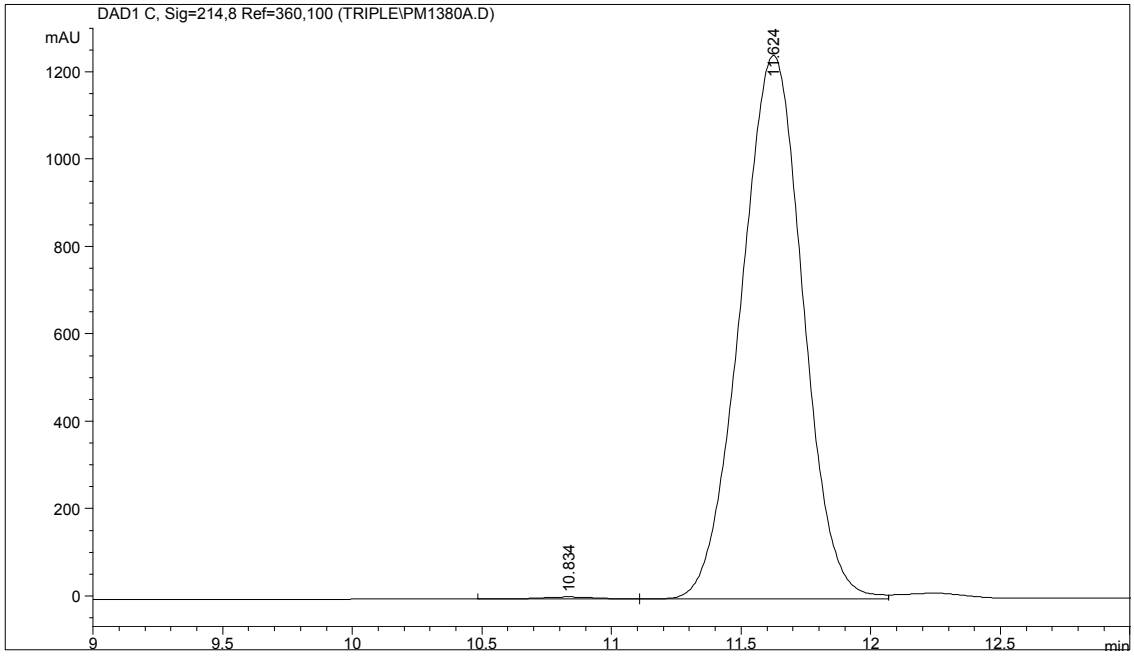




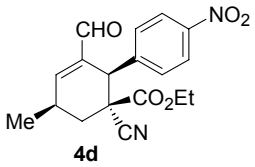
4c

Chiralpak AD-H column (9/1 hexane/*i*PrOH – flow rate: 0.75 mL/min)



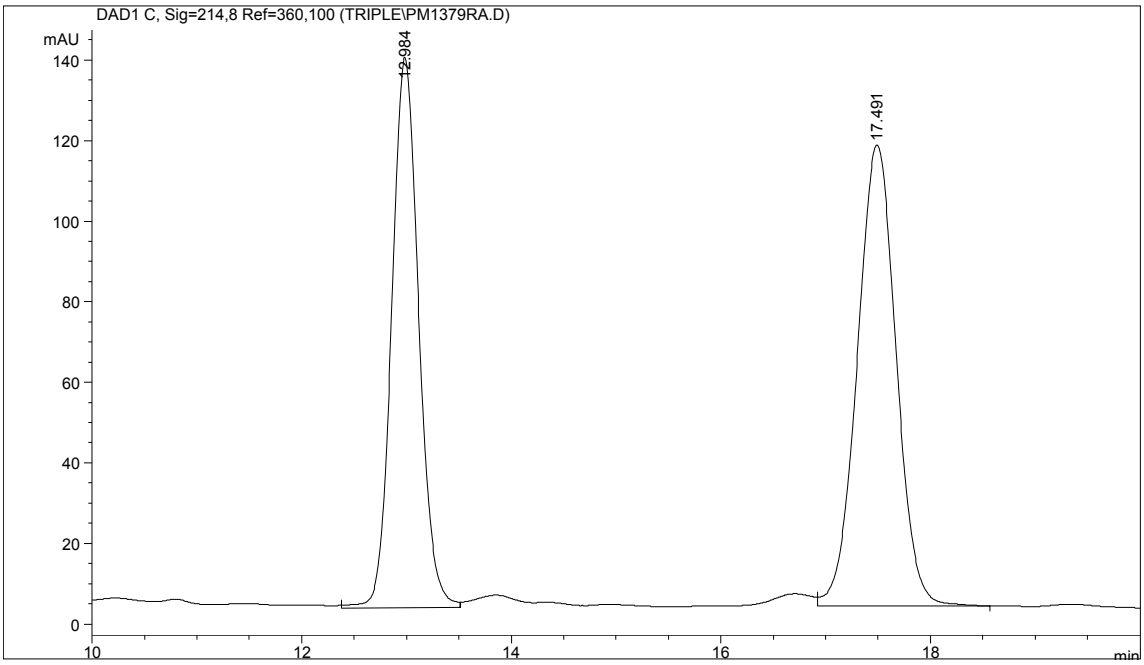


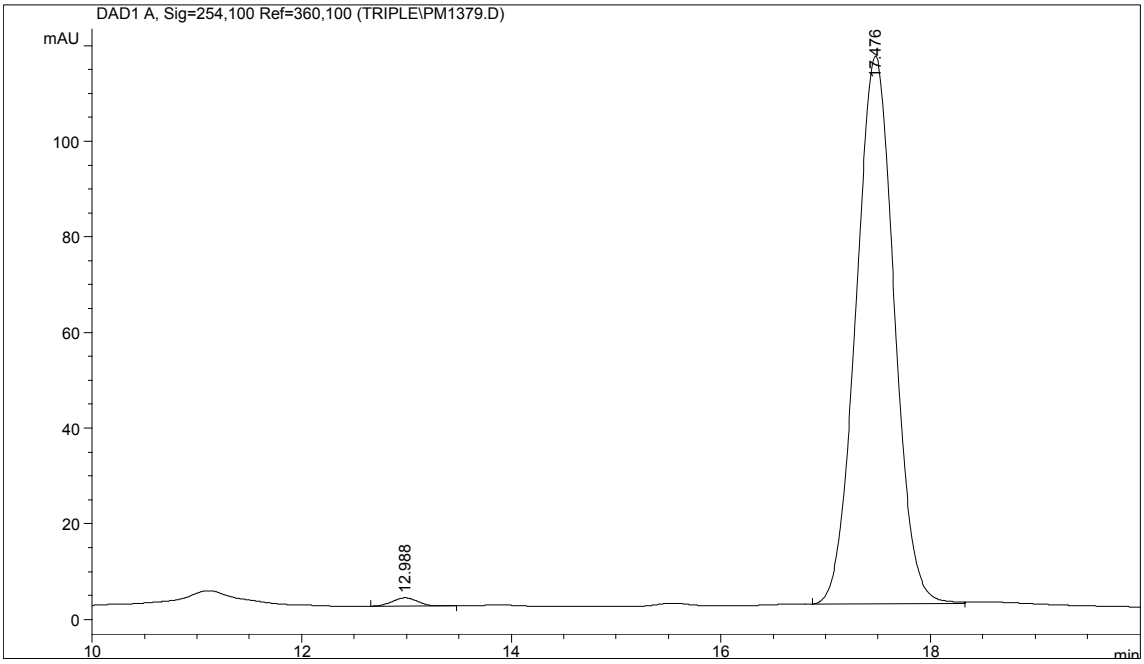
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.834	VV	0.2396	77.93015	4.95210	0.3732
2	11.624	VV	0.2589	2.08033e4	1245.46448	99.6268
	Totals :			2.08812e4	1250.41658	



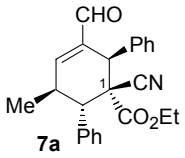
4d

Chiralpak AD-H column (8/2 hexane/*i*PrOH – flow rate: 0.75 mL/min)





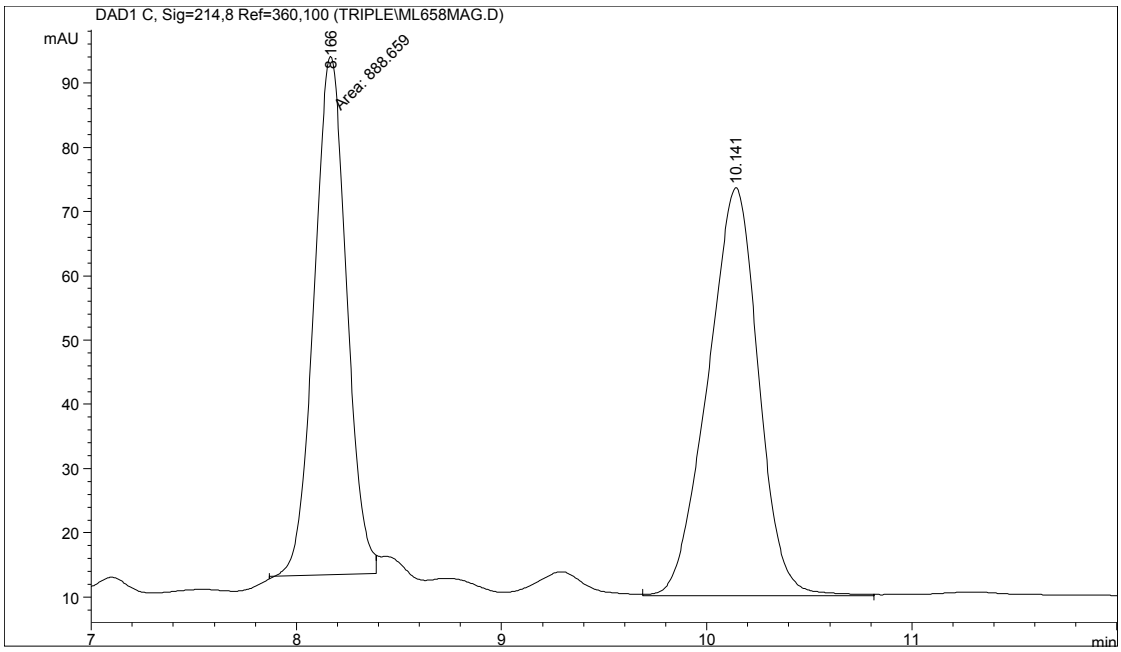
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.988	PP	0.2624	27.87572	1.70785	0.9514
2	17.476	BB	0.3956	2901.96582	114.52723	99.0486
	Totals :			2929.84154	116.23508	

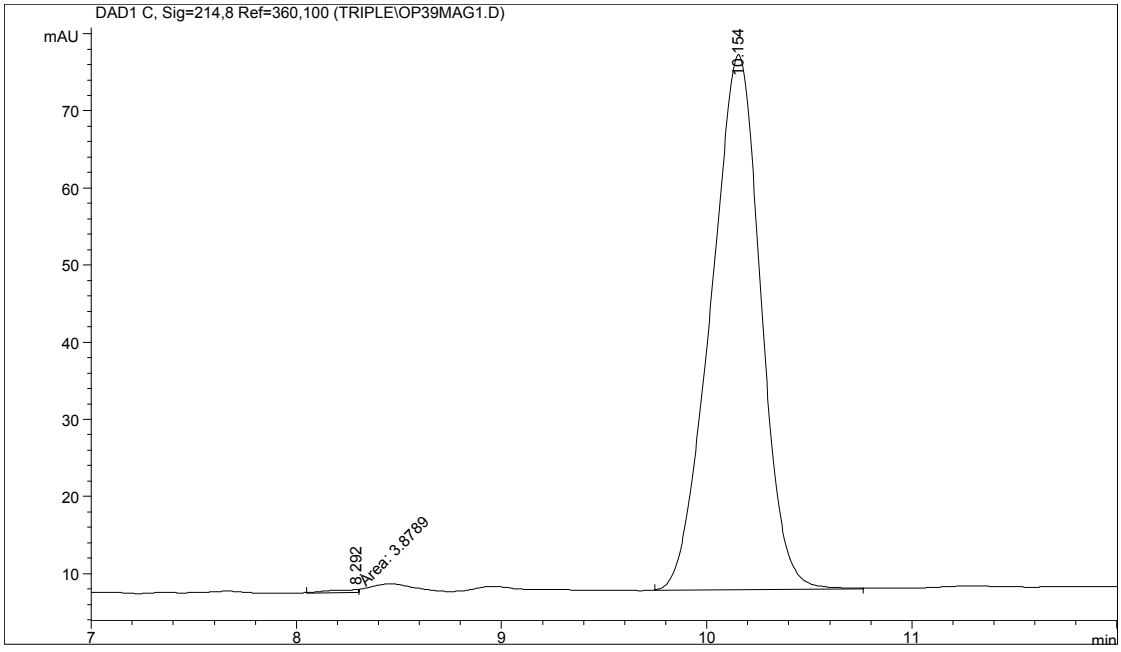


7a

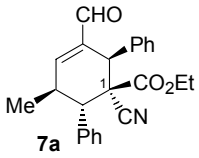
Major

Chiralpak AD-H column (8/2 hexane/*i*PrOH – flow rate: 0.75 mL/min)





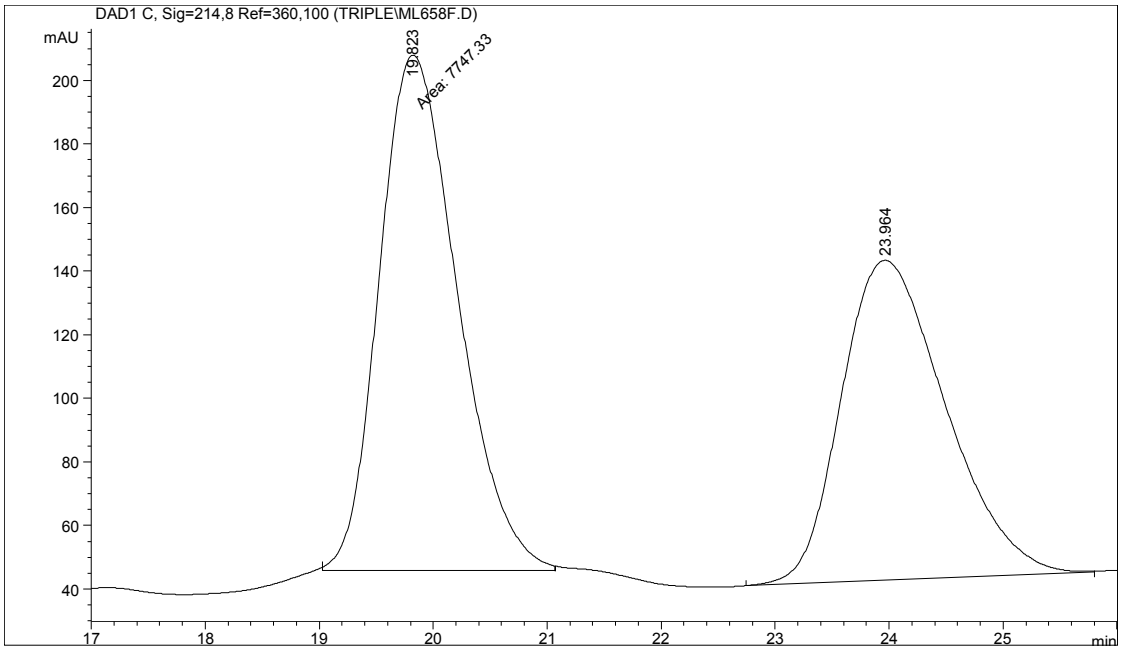
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.292	MM	0.1932	3.87890	3.34606e-1	0.3307
2	10.154	BB	0.2527	1169.13831	69.33710	99.6693
Totals :				1173.01721	69.67170	

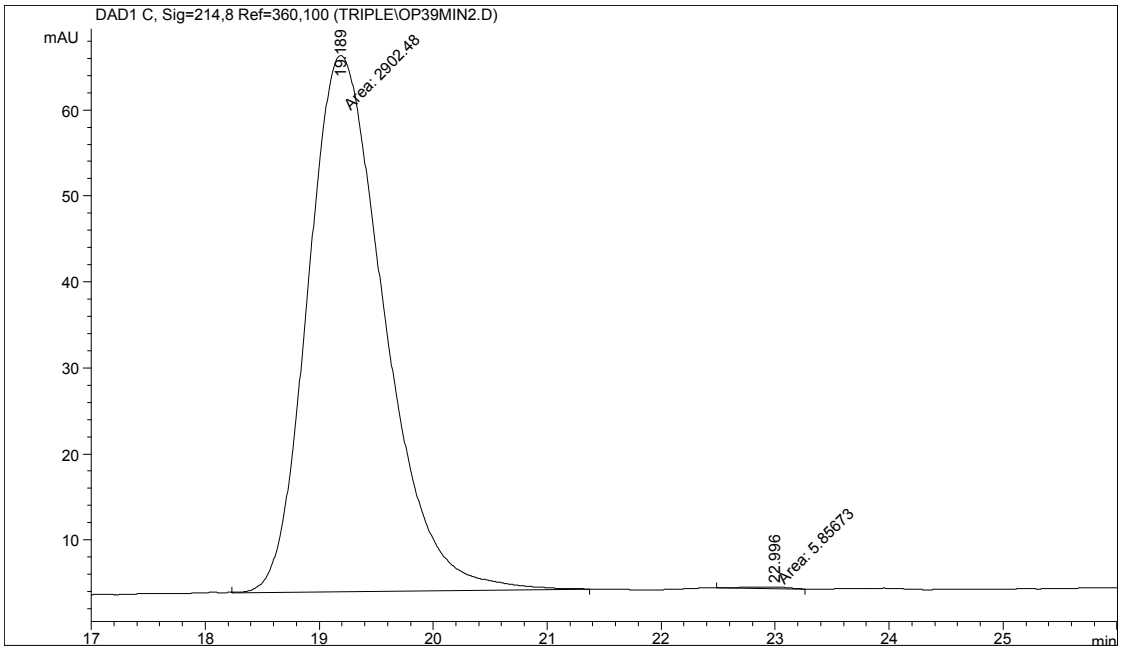


7a

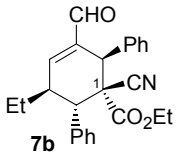
Minor

Chiralcel OD-H column (95/5 hexane/*i*PrOH - flow rate: 0.75 mL/min)



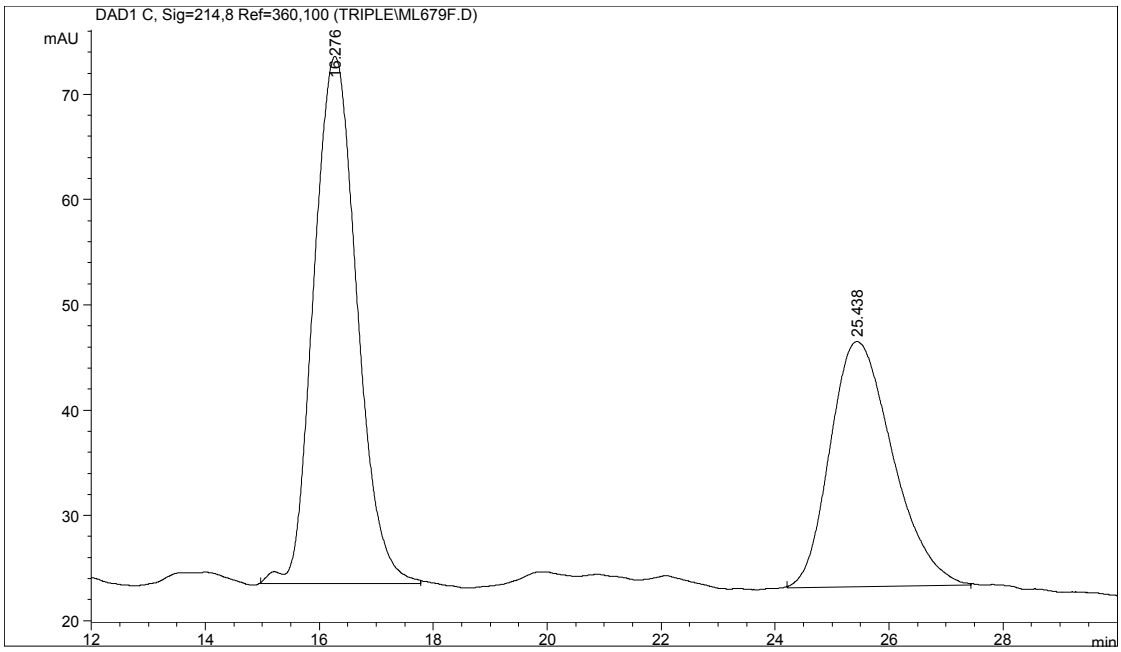


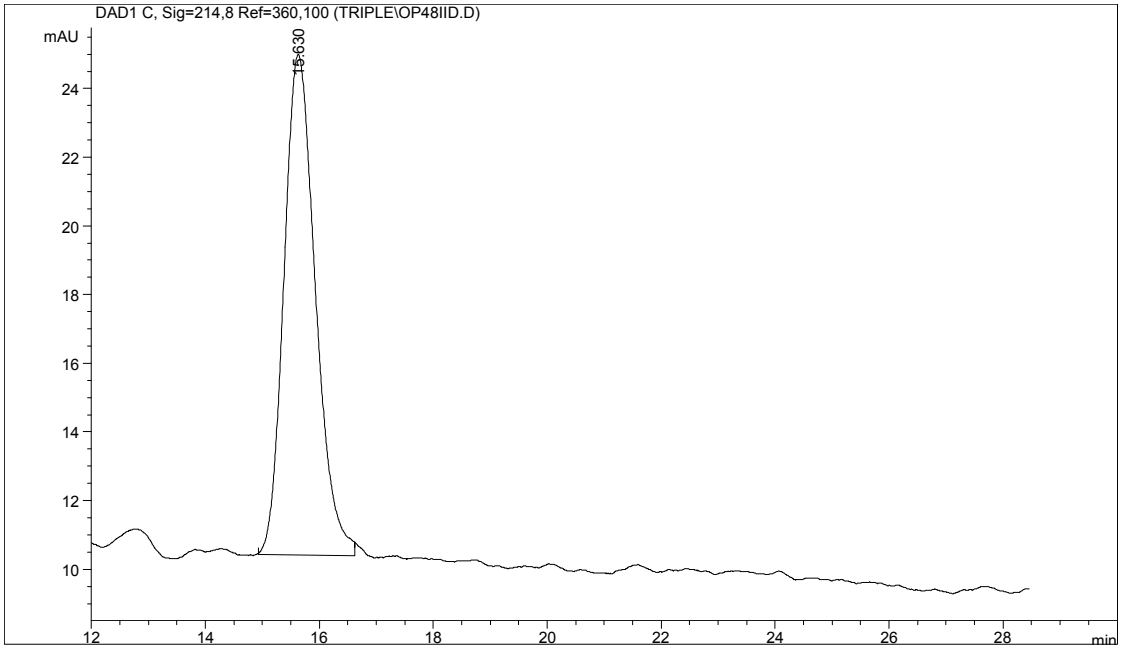
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.189	MM	0.7761	2902.48193	62.32906	99.7986
2	22.996	MM	0.4233	5.85673	2.30572e-1	0.2014
Totals :				2908.33867	62.55963	

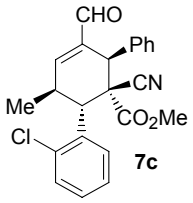


7b

Chiralcel OD-H column (95/5 hexane/*i*PrOH - flow rate: 0.75 mL/min)

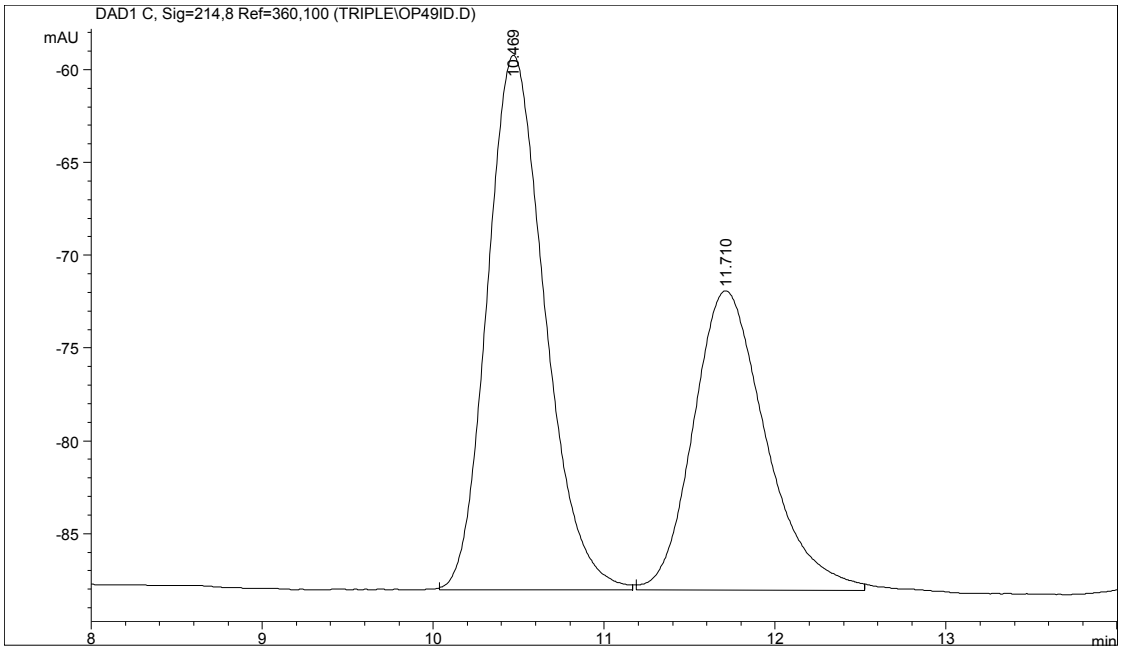


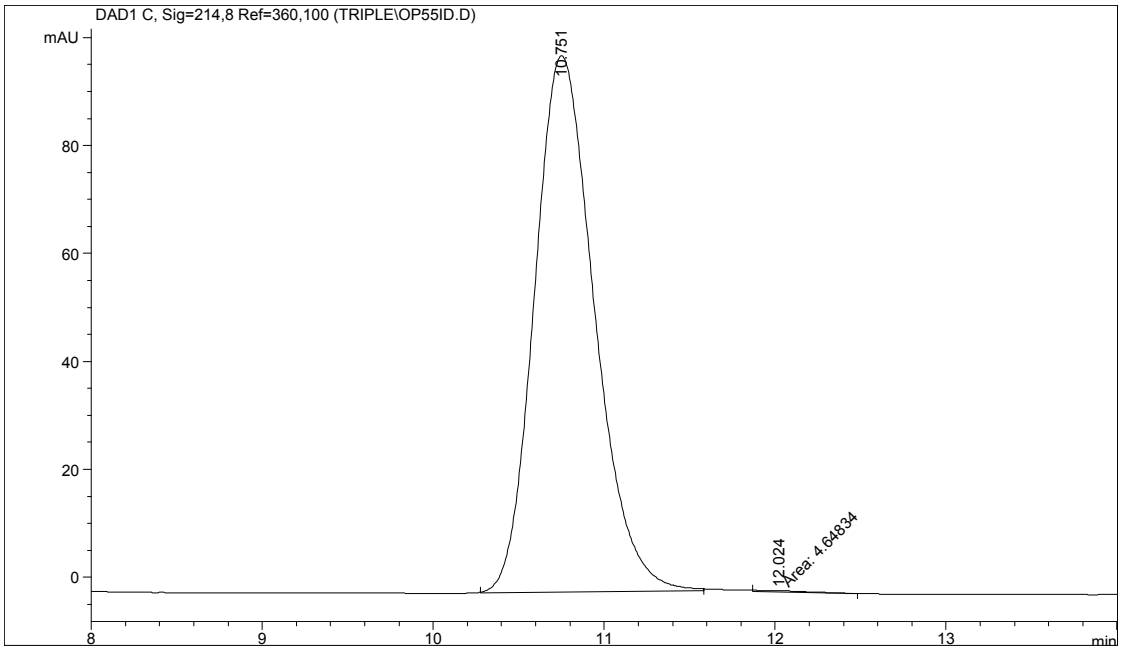




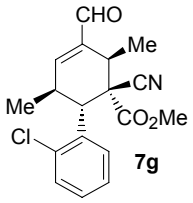
7c

Chiralcel OD-H column (8/2 hexane/*i*PrOH – flow rate: 0.75 mL/min)



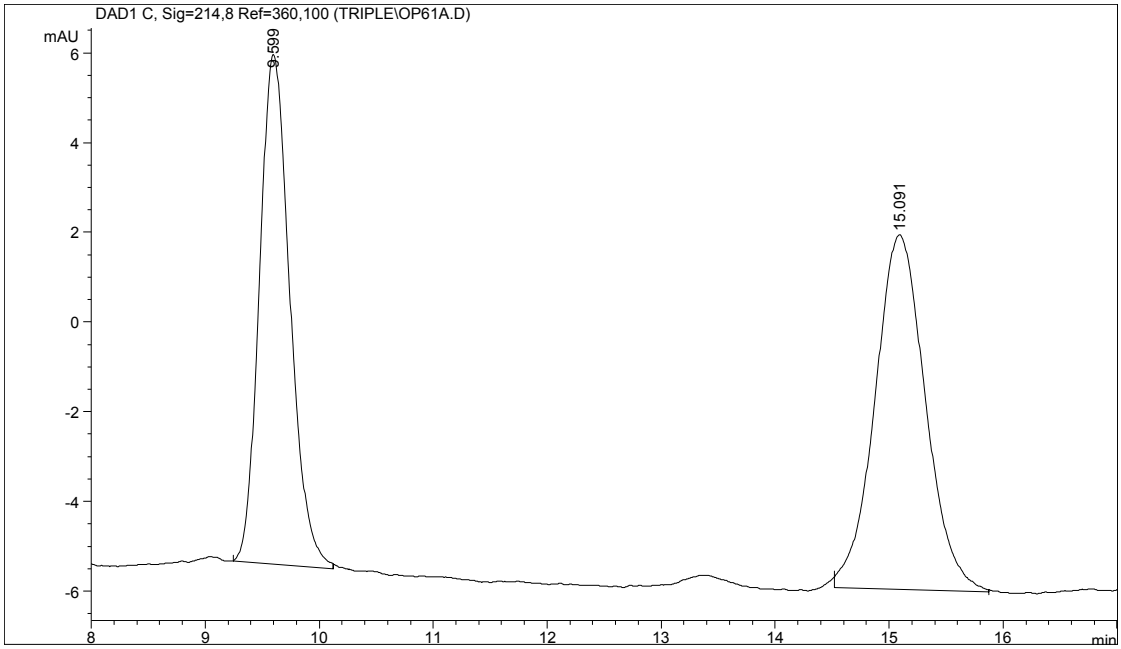


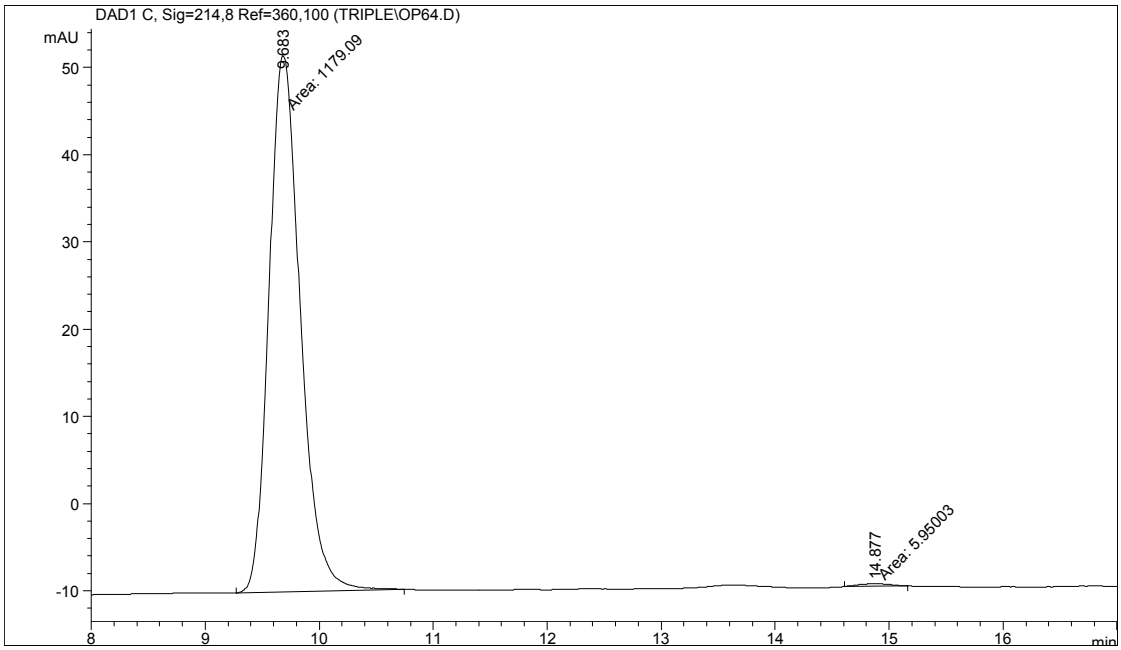
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.751	BB	0.3782	2422.19946	99.43402	99.8085
2	12.024	MM	0.3875	4.64834	1.99905e-1	0.1915
Totals :				2426.84780	99.63393	



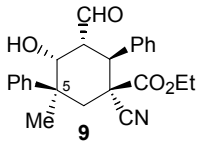
7g

Chiralcel OD-H column (8/2 hexane/*i*PrOH – flow rate: 0.75 mL/min)



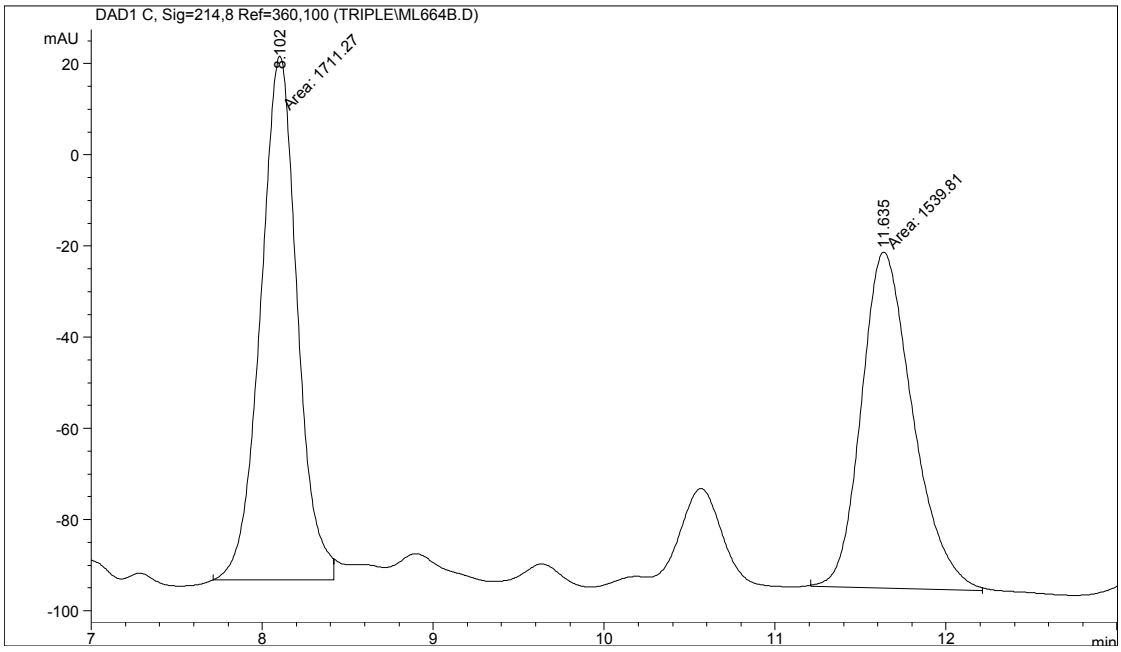


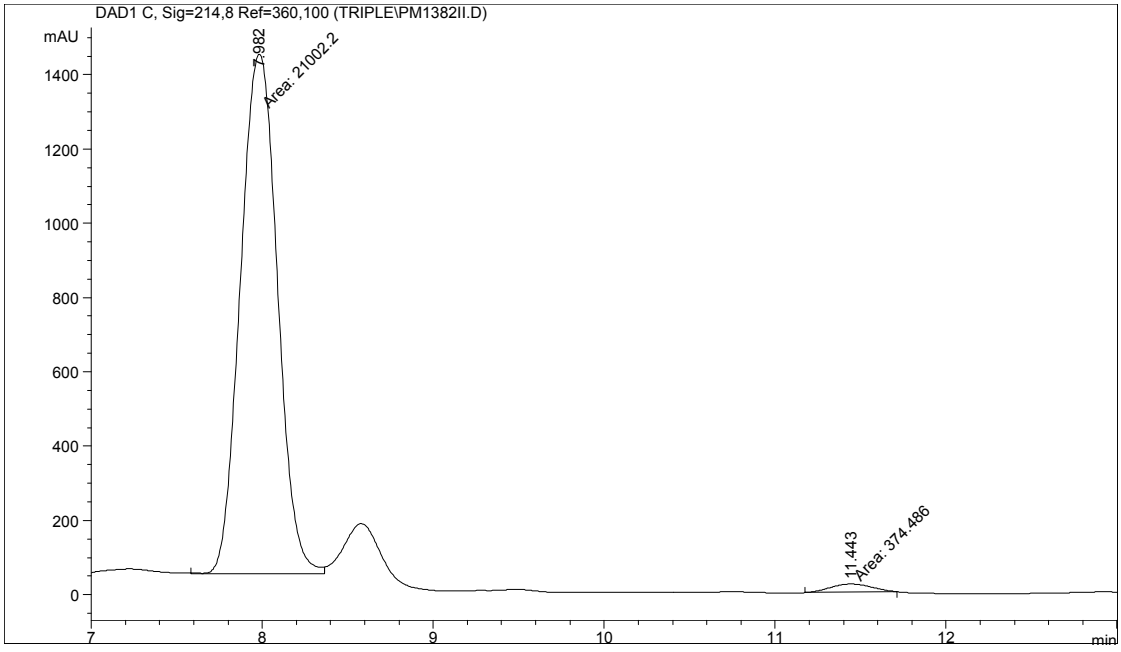
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.683	MM	0.3194	1179.09314	61.52499	99.4979
2	14.877	MM	0.3277	5.95003	3.02572e-1	0.5021
Totals :				1185.04317	61.82757	



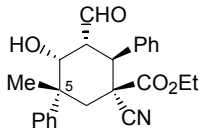
9

Chiralpak AD-H column (8/2 hexane/*i*PrOH – flow rate: 0.75 mL/min)



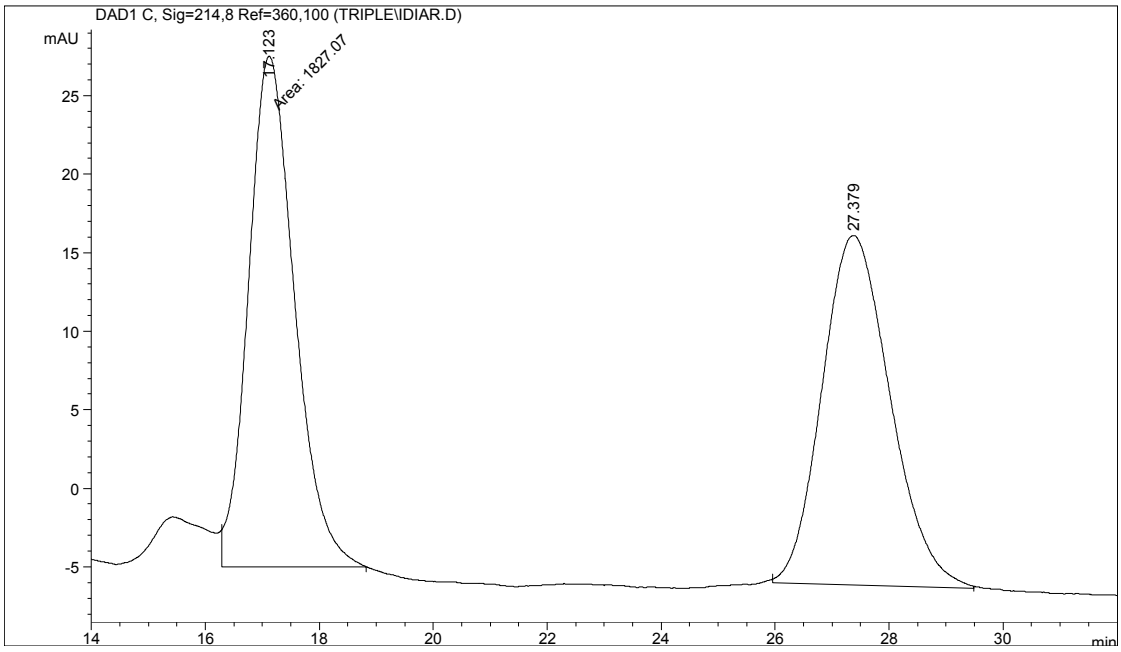


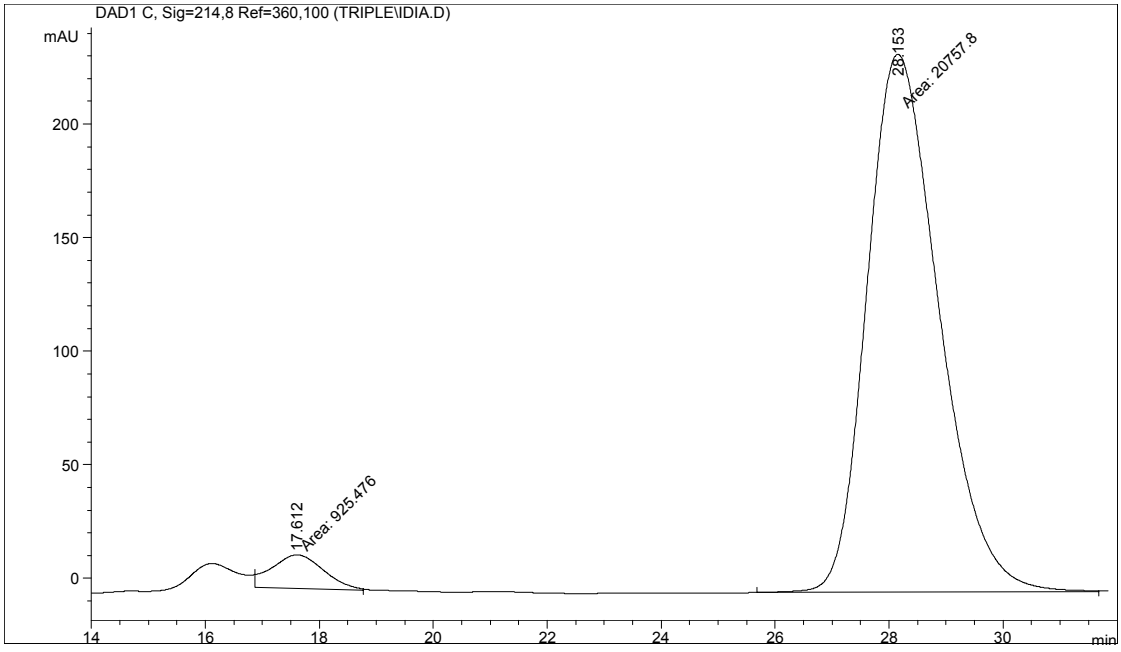
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.982	MM	0.2503	2.10022e4	1398.61401	98.2482
2	11.443	MM	0.2791	374.48642	22.35911	1.7518
Totals :				2.13767e4	1420.97312	



epi-**9**

Chiralcel OD-H column (8/2 hexane/*i*PrOH – flow rate: 0.75 mL/min)





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.612	MM	1.0473	925.47620	14.72834	4.2682
2	28.153	MM	1.4613	2.07578e4	236.75639	95.7318
Totals :				2.16832e4	251.48474	