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Catalytic Highly Enantioselective Vinylogous Povarov Reaction

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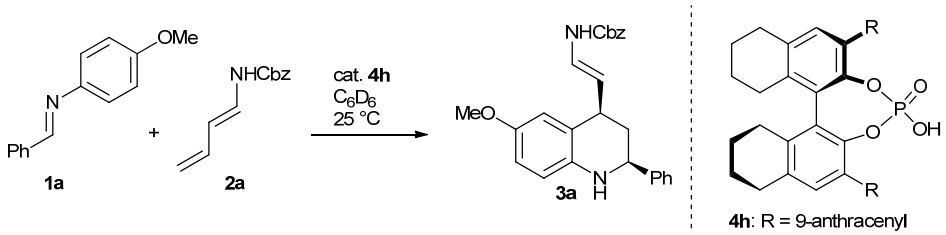
Preliminary kinetic investigation of the catalytic enantioselective vinylogous Povarov reaction

The kinetics of the reaction between imine **1a** and dienophile **2a** was preliminarily studied by ^{1}H NMR using a reaction progress analysis approach (Scheme S1).[1]



Scheme S1: Vinylogous Povarov reaction between imine **1a** and **2a** used for kinetic studies.

The kinetic experiments were set up and elaborated as follows:
A Schlenk tube equipped with a magnetic stirring bar was charged with 4 Å molecular sieves (70 mg). The molecular sieves were thermally activated under vacuum. After cooling to RT, the tube was filled with a N_2 atmosphere, then charged with the appropriate amount of imine **1a**. The appropriate amount of C_6D_6 (freshly passed through basic alumina) and of a stock 0.012 M solution of catalyst **4h** in C_6D_6 were then added. Overall, 600 μL of C_6D_6 were employed in each experiment. The solution was stirred at 25 °C for a few minutes. The appropriate amount of dienophile **2a** was then added in one portion. After few seconds stirring to homogenise the solution, the whole mixture including the molecular sieves was transferred in a pre-dried, N_2-filled NMR tube by means of a 1 mL syringe equipped with a short and large needle. The tube was placed in a Varian 400 MHz NMR instrument at 25 °C, spinned at 16-20 Hz, and after automatic lock and shimming, ^{1}H NMR spectra (nt = 1) were recorded every minute, using the automatic array pad function, until ca 70-80% conversion.

From the last ^{1}H NMR spectra recorded, it was checked that no significant decomposition of imine **1a**, dienophile **2a** or product **3a** occurred in the time frame of the analysis, nor that the reaction gave significant amounts of by-products. A preliminary control experiment carried out in the absence of catalyst **4h**, showed that background reactivity is not significant (<5% conversion after 18 h).
The spectra were collectively elaborated (phased, drift correction), and the relevant peaks integrated after baseline correction, from which the conversion at each time was determined. From the conversion, imine **2a** concentration was calculated. The resulting curve of imine vs time was plotted and fitted to a polynomial equation (ninth order) with the OriginPro 7 program. The derivative of this equation, giving the dependence of reaction rate on imine concentration, was employed for the kinetic analysis. As this curve is purely empirical, it could be used only in the range of imine concentration which was effectively employed in the experiment.

The results obtained from these experiments can be summarized as follows:

[1] D. G. Blackmond, *Angew. Chem. Int. Ed.*, 2005, **44**, 4302.

1) Reactions at different catalysts concentrations, under otherwise identical reaction conditions, to determine the order of the reaction respect to catalyst **4h**, by comparing the TOF of the experiments. TOF values were determined by dividing the reaction rate by the initial catalyst concentration used in each experiment (Figure S1).

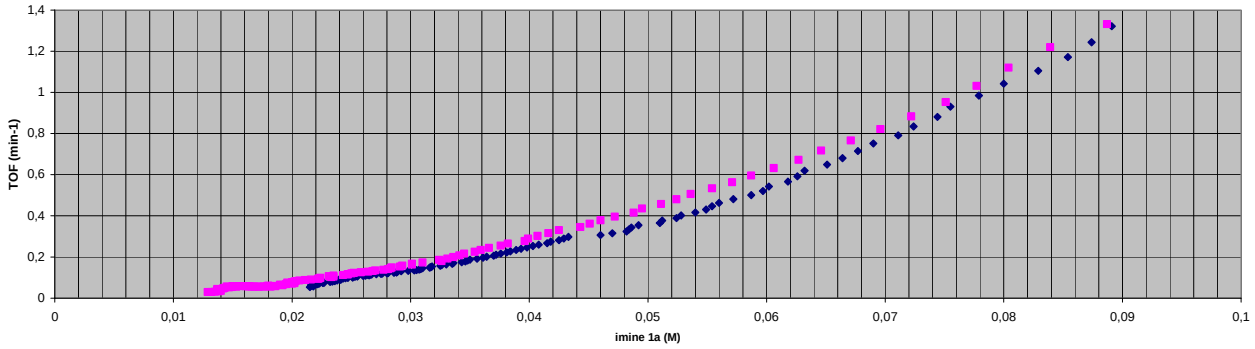


Figure S1: ♦: C_0 [imine **1a**] 0.10 M, C_0 [dienophile **2a**] 0.20 M, C_0 [catalyst **4h**] 0.0020 M. ■ C_0 [imine **1a**] 0.10 M, C_0 [dienophile **2a**] 0.20 M, C_0 [catalyst **4h**] 0.0030 M.

In the plot, the two curves are roughly superimposable. It is thus possible to conclude that the reaction is approximately first order in catalyst concentration.

2) Reactions with the "same excess". Two reactions were performed by employing the same concentration of catalyst **4h**, different starting concentration of imine **1a**, and same "excess" of dienophile **2a** in terms of concentration (Figure S2). In other words, the reaction with lower imine concentration starts exactly under the conditions (concentration of substrates and catalyst) of the other reaction at 25% conversion. This experiment shows if the activity of the catalyst is the same during the whole reaction course, or if catalyst deactivation/decomposition occurs, influencing the concentration of active catalyst which is part of the rate law.

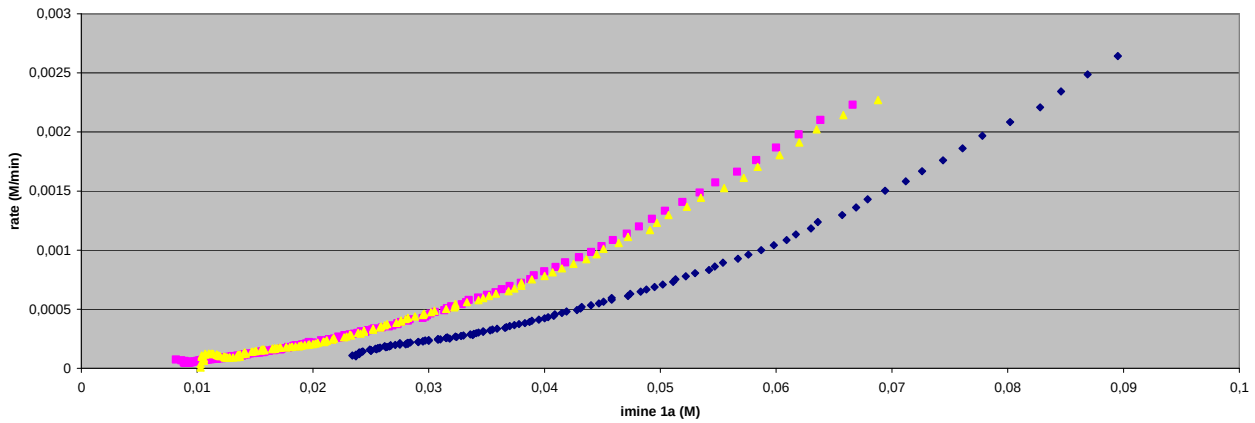


Figure S2: ♦: C_0 [imine **1a**] 0.10 M, C_0 [dienophile **2a**] 0.20 M, C_0 [catalyst **4h**] 0.0020 M. ■ C_0 [imine **1a**] 0.075 M, C_0 [dienophile **2a**] 0.175 M, C_0 [catalyst **4h**] 0.0020 M. ▲ C_0 [imine **1a**] 0.075 M, C_0 [dienophile **2a**] 0.175 M, C_0 [catalyst **4h**] 0.0020 M, C_0 [product **3a**] 0.025 M.

In Figure S2, the two curves ♦ (standard reaction) and ■ (reaction starting after 25% conversion) are not superimposable. Thus, catalyst deactivation/decomposition heavily occurs affecting (lowering) the reaction rate. To check if catalyst inhibition by the product was the reason for this behaviour, a third experiment ▲ was carried out under the same conditions of ■ but adding at the beginning the amount of product **3a** formed when the curve ♦ reaches 25% conversion. However, as this curve ▲

is roughly superimposable to ■ catalyst inhibition by the product is not the reason for this considerable decrease in catalyst activity with time.

We then performed two similar experiments, but in the absence of molecular sieves, in order to check if these drying agents were responsible for catalyst deactivation (Figure S3). Due to the much lower activity of catalyst **4h** in the absence of molecular sieves, higher catalyst/substrates initial concentrations had to be used.

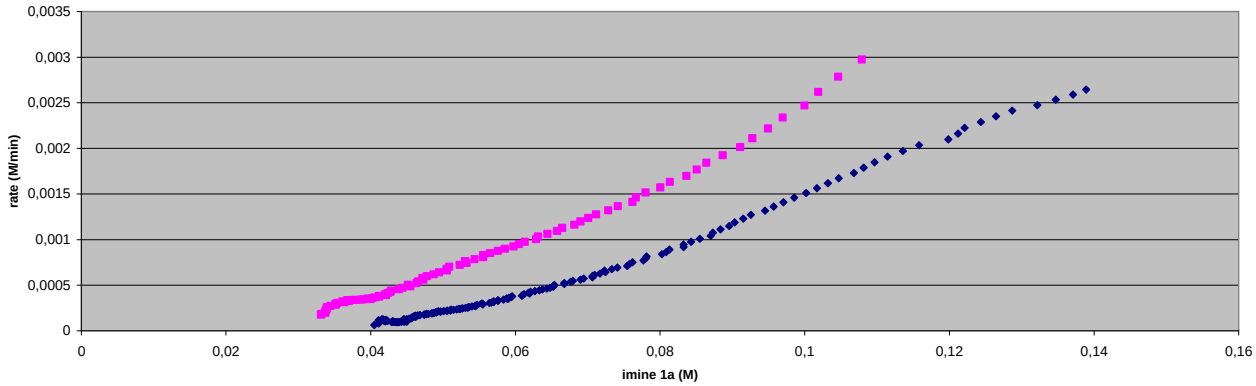


Figure S3: ♦: C_0 [imine **1a**] 0.15 M, C_0 [dienophile **2a**] 0.30 M, C_0 [catalyst **4h**] 0.015 M. ■ C_0 [imine **1a**] 0.12 M, C_0 [dienophile **2a**] 0.27 M, C_0 [catalyst **4h**] 0.015 M.

As the two curves in Figure S3 are also clearly not superimposable, catalyst deactivation is not due to the presence of molecular sieves in the reaction.

From these experiments, it can be concluded that the reaction rate is approximately first order in catalyst concentration, but that catalyst deactivation heavily occurs during the course of this reaction. This prevents the determination of a rate law using the reaction progress kinetic analysis approach, which requires the same amount of active catalyst during the whole (or most of) the reaction course. This catalyst deactivation is not due to product inhibition nor to the presence of molecular sieves.
This result suggests that the 1 mol% catalyst loading which at least has to be employed in this reaction is not due to the scarce activity of the catalyst, but rather to its decomposition, giving a crucial information on the direction to follow for decreasing the catalyst loading in this (and related) reaction.

Determination of relative and absolute configuration of the adducts 3 and 9

Conformational analysis and absolute configuration determination of 3k through chiroptical methods

In recent years, the determination of the absolute configuration (AC) of chiral molecules by spectroscopic methods other than X-ray, i.e. using chiroptical techniques like optical rotation (OR), electronic circular dichroism (ECD), and vibrational circular dichroism (VCD) has gained feasibility and reliability because of the development of methods for the prediction of these properties based on density functional theory (DFT) and on its Time-Dependent formalism (TD-DFT). It has been successfully used many times to assign the AC of chiral molecules. In fact, the assignment of the absolute configuration by chiroptical methods has been one of the main stream research field of many physical organic chemists and many theoretical chemists analysed the pitfalls and drawbacks of this approach (S. Grimme, G. Scalmani and others). Recently a whole issue of Wiley's "Chirality" (*Chirality*, Volume 20, Issue 5, Page 605-759) has been devoted to the absolute configuration assignment by spectroscopic methods. An increasing number of papers in which the AC was assigned by simulation of chiroptical spectra has appeared in the recent literature.[2] The main pitfall of this approach is the difficulty to manage flexible molecules. About this point, the adducts **3** reported herein are not really flexible, since there is a rigid core containing the two chiral centres and strong UV chromophores close to them. Thus, chirooptical methods for the assignment of the absolute configuration of adducts **3** should be reliable.

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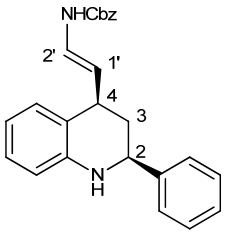
[2] Reviews: G. Bringmann, T. Bruhn, K. Maksimenka and Y. Hemberger, *Eur J Org Chem.*, 2009, 2717–2727; T. D. Crawford, M. C. Tam and M. L. Abrams, *J. Chem. Phys. A*, 2007; **111**, 12057–12068; P. L. Polavarapu, L. A. Nafie and N. Berova, Special Issue "Advances in Chiroptical Methods" *Chirality*, 2009; **29** E1–E312; G. Pescitelli, L. Di Bari and N. Berova, *Chem. Soc. Rev.*, 2011, **40**, 4603; For a review on conformational analysis for the AC determination see: A. Mazzanti and D. Casarini, D. WIREs *Comput. Mol. Sci.*, 2012, **2**, 613-641. Recent papers: J. M. Gao, J. C. Qin, G. Pescitelli, S. Di Pietro, Y. T. Ma and A. L. Zhang, *Org. Biomol. Chem.*, 2010, **8**, 3543; M. Woźnica, A. Butkiewicz, A. Grzywacz, P. Kowalska, M. Masnyk, K. Michalak, R. Luboradzki, F. Furche, H. Kruse, S. Grimme and J. Frelek, *J Org Chem.*, 2011, **76**, 3306; P. L. Polavarapu, G. Scalmani, E. K. Hawkins, C. Rizzo, N. Jeirath, I. Ibnusaud, D. Habel, D. S. Nair and S. Haleema, *J. Nat. Prod.*, 2011, **74**, 321; D. Casarini, L. Lunazzi, M. Mancinelli, A. Mazzanti and P. Scafato, *Chirality*, 2009, **21**, 16; S. Abbate, G. Longhi, E. Castiglioni, F. Lebon, P. M. Wood, L. W. L. Woo and B. V. L. Potter, *Chirality*, 2009, **21**, 802; C. Gioia, F. Fini, A. Mazzanti, L. Bernardi and A. Ricci, *J. Am. Chem. Soc.*, 2009, **131**, 9614 (here comparison between calculations and X-ray structure); M. Kwit, M. D. Rozwadowska, J. Gawroski and A. Grajewska, *J.Org. Chem.*, 2009, **74**, 8051; S. Abbate, A. Ciogli, S. Fioravanti, F. Gasparrini, G. Longhi, L. Pellacani, E. Rizzato, D. Spinelli and P. A. Tardella, *Eur. J. Org. Chem.*, 2010, 6193; G. Bencivenni, L.-Y. Wu, B. Giannichi, A. Mazzanti, F. Pesciaioli, M.-P. Song, G. Bartoli and P. Melchiorre, *Angew. Chem. Int. Ed.*, 2009, **48**, 7200 (here comparison between calculations and X-ray structure); P. L. Polavarapu, *Chirality*, 2008, **20**, 664; H. Izumi, A. Ogata, L. A. Nafie and R. K. Dukor, *J. Org. Chem.*, 2008, **73**, 2367; H. Izumi, S. Futamura, N. Tokita and Y. Hamada, *J. Org. Chem.*, 2007, **72**, 277; K. Takaishi, A. Muranaka, M. Kawamoto and M. Uchiyama, *J. Org. Chem.*, 2011, **76**, 7623; S. Lu, T. Kurtan, G. Yang, P. Sun, A. Mandi, K. Krohn, S. Draeger, B. Schulz, Y. Yi and L. Li, *Eur. J. Org. Chem.*, 2011, 5452; J. Dai, K. Krohn, U. Floerke, G. Pescitelli, G. Kerti, T. Papp, K. E. Koever, A. C. Benyei, S. Draeger and B. Schulz, *Eur. J. Org. Chem.*, 2010, 6928; C. Trindle and Z. Altun, *Theor. Chem. Acc.*, 2009, **122**, 145-155; F. J. Coughlin, K. D. Oyler, R. A. Pascal Jr. and S. Bernhard, *Inorg. Chem.*, 2008, **47**, 974; T. Mori, Y. Inoue and S. Grimme, *J. Org. Chem.*, 2006, **71**, 9797.

Accordingly, compound **3k** was selected as representative compound for the determination of the relative and absolute configuration by a combination of conformational analysis and theoretical simulations of chiro-optical spectra.



The relative stereochemistry was determined by means of NMR spectroscopy. Full assignment of the ^{1}H and ^{13}C spectra was preliminarily achieved by bi-dimensional experiments (COSY, gHSQC and gHMBC, taken in $CDCl_3$ solutions). The two diastereotopic hydrogens belonging to C-3 were found at 1.89 and 2.11 ppm. The COSY spectrum showed they are coupled with the hydrogens at 3.66 and 4.49 ppm. The hydrogen at 3.66 ppm showed additional coupling with the signal at 4.93 ppm (H-1). This allowed us to assign the signal at 3.66 ppm to H-4 and the signal at 4.49 ppm to H-2. The proton at 4.93 ppm, that is coupled with the signal at 6.64 ppm with a coupling constant of 14.1 Hz provided evidence of the *E*-geometry of the exocyclic double bond. The signals of the tetrahydroquinoline NH at 3.42 ppm and of the carbamate NH (6.45 ppm, doublet, J = 10.8 Hz) were assigned by the lack of correlation in the ^{13}C-^{1}H HSQC spectrum.

One of the signals of the two diastereotopic protons at C-3 appears as a pseudo-quartet, with a large coupling constant (J=12.4 Hz, H-3b in Figure S4). This implies that this proton is coupled with three hydrogens with similar and large coupling constants, which are consistent with the geminal coupling with H-3a and with two trans-diaxial couplings with H-2 and H-4, due to a dihedral angle close to 180°.[3] This clearly indicates that both H-2 and H-4 are in pseudo-axial position on the tetrahydroquinoline ring, whereas the phenyl and the ene-carbamate moiety occupy the pseudo-equatorial positions. As a confirm, the signal of H-3a (the second diastereotopic hydrogen of C-3) exhibits the same large geminal constant (12.4 Hz) and two small coupling constants due to the equatorial-axial coupling, where the dihedral angle is close to 90°.

[3] M. Karplus, *J. Am. Chem. Soc.*, 1963, **85**, 2870-2871

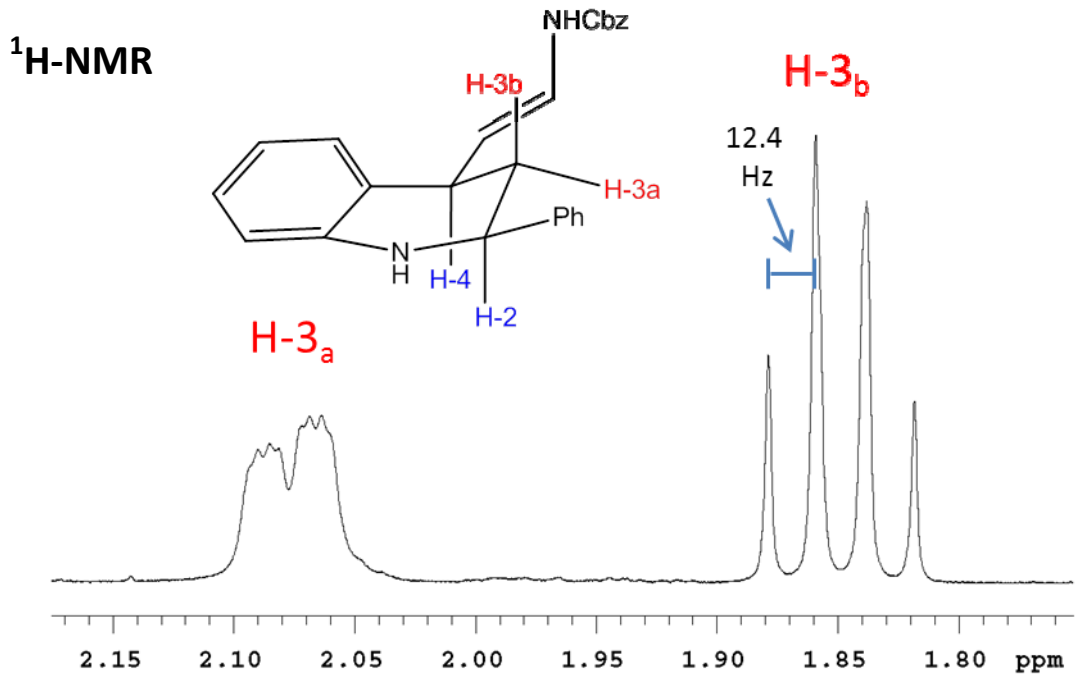


Figure S4: expansion of the ^{1}H spectrum (600 MHz in $CDCl_3$) of **3k** showing the signals of the two diastereotopic hydrogens of C-3

Mono-dimensional DPFGSE-NOE experiments[4] were acquired in order to confirm the relative stereochemistry at C-2 and C-4. On saturation of the vinylic hydrogen H-1' (trace a in Figure S5), NOE enhancement was observed for one proton at C-3 (H-3b, in pseudo-axial position) and no enhancement was observed for the other ene-carbamate proton H-2'. This confirms the *E* geometry of the double bond. The large NOE on H-3b suggests that H-1' is *anti* to H-4. On saturation of H-4, NOE are observed on H-2 (trace c in Figure S5) and on the signal of H-3a (in pseudo-equatorial position). On saturation of H-2 (trace b in Figure S5), NOE are observed for H-4 and for H-3a, thus confirming the 1-3 diaxial relationship of H-2 and H-4, already deduced from the analysis of the *J*-couplings of the ^{1}H NMR spectrum. NMR analysis thus confirms the *cis* relative configuration of the two asymmetric centres of the 1,2,3,4-tetrahydroquinoline skeleton (thus 2*R**,4*S**), and the E-geometry of the exocyclic double bond.

Having in hand the relative configuration and suitable information about the preferred conformation, the assignment of the absolute configuration was tackled by chiro-optical methods.

[4] K. Stott, J. Stonehouse, J. Keeler, T.-L. Hwang and A. J. Shaka, *J. Am. Chem. Soc.*, 1995, **117**, 4199-4200

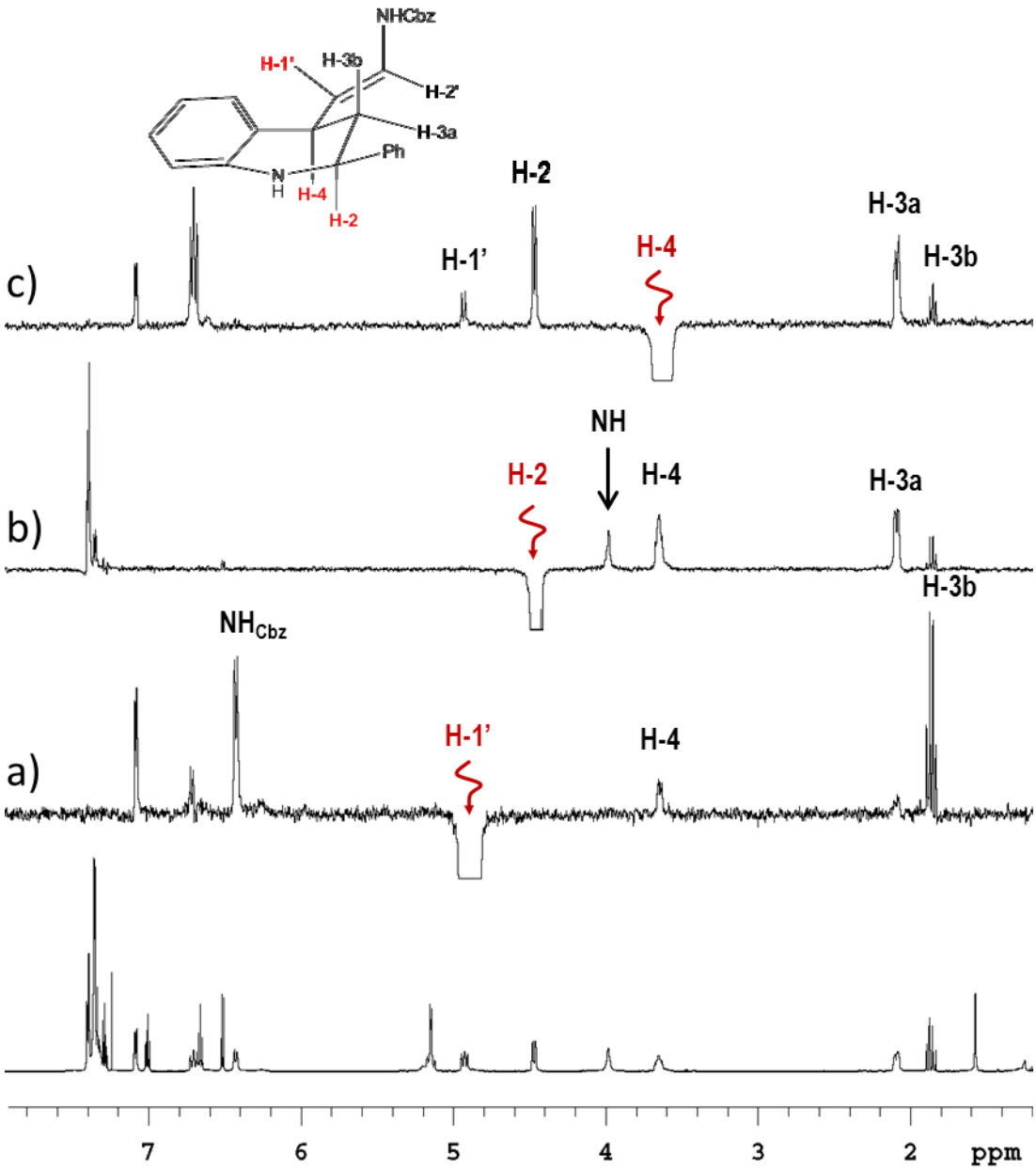


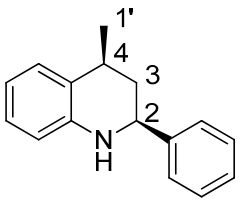
Figure S5: DPFGSE-NOE spectra of **3k** (600 MHz in $CDCl_3$). Bottom: ^{1}H-NMR control spectrum; trace a) saturation of H-1'; trace b) saturation of H-2; trace c) saturation of H-4.

The theoretical calculation of the electronic circular dichroism spectra (ECD) was selected for the absolute configuration assignment. Although the rigidity of the 1,2,3,4-tetrahydroquinoline core of compound **3k** helps in the reduction of the number of conformations to be considered,[5] the conformational freedom of the exocyclic ene-carbamate moiety represent a challenging issue for the conformational analysis step.

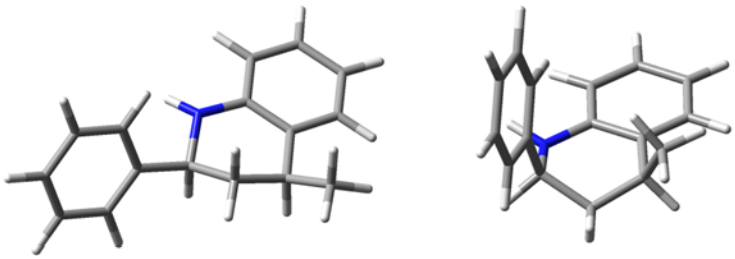
As the first stage, we performed a conformational search on a model compound where all the ene-carbamate moiety (CH=CH-NH-Cbz) was reduced to a methyl group (model compound **Me-3k**).

[5] P. L. Polavarapu, E. A. Donahue, G. Shanmugam, G. Scalmani, E. K. Hawkins, C. Rizzo, I. Ibnusaud, G. Thomas, D. Habel and D.Sebastian, *J. Phys. Chem. A*, 2011, **115**, 5665–5673

Me-3k



All the conformations found by MM search within a 10 kcal/mol window (Monte Carlo searching together with the MMFF94 molecular mechanics force field as implemented in Titan 1.0.5, Wavefunction inc.) were then optimized using DFT at the B3LYP/6-31G(d) level[6]. The harmonic vibrational frequencies of each conformation were calculated at the same level to confirm their stability (no imaginary frequencies were observed) and to evaluate the free energy of each conformation. After DFT minimization, only two conformations were found to be enclosed in the 10 kcal/mol window, and one of them (conformation **a** in figure S6) was much more stable than the other (conformation **b**). Conformation **b** differs form **a** because of the different shape of the six-membered ring, that corresponds to a pseudo-boat conformation where the phenyl ring and the methyl occupy a pseudo-axial position. The energy gain (3.25 kcal/mol as internal energy difference, 3.71 kcal/mol as ZPE-corrected free energy) suggest that **a** should be the only populated conformer in solution. (Figure S6).



Conf. a
E = 0.00
G°= 0.00

Conf. b
E = 3.25
G°=3.71

Figure S6. 3D view of the two conformations of the model compound **Me-3k** with a methyl group in position 4. Reported energies are in kcal/mol

The electronic excitation energies and rotational strengths have been calculated for the isolated

[6] Program Gaussian 09, rev A.02 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

molecule in the gas phase for the best conformation of **Me-3k** using TD-DFT with four different methods (functionals), to ascertain if different computational approaches provide different shapes of the simulated spectra.[7] Simulations were performed with the hybrid functionals BH&HLYP[8] and M06-2X,[9] the Long-range Correlated LC-ωB97XD that includes empirical dispersion,[10] and CAM-B3LYP that includes long range correction using the Coulomb Attenuating Method.[11]. The calculations employed the 6-311++G(2d,p) basis set that proved to be sufficiently accurate at a reasonable computational cost.[12] Rotational strengths were calculated in both length and velocity representation, the resulting values being very similar (RMS differences < 5%). For this reason the errors due to basis set incompleteness should be very small, or negligible.[13]

As shown in Figure S7, the simulated spectra match the Cotton effects at 190 nm and 203 when the 2*S*, 4*S* absolute configuration is assumed in the calculations. However, the lower energy Cotton effect at 229 nm is not reproduced by the calculations. This means that the contribution of the ene-carbamate moiety on the ECD spectrum cannot be ruled out, thus the simulation of the ECD spectra must be performed on the whole structure of **3k**

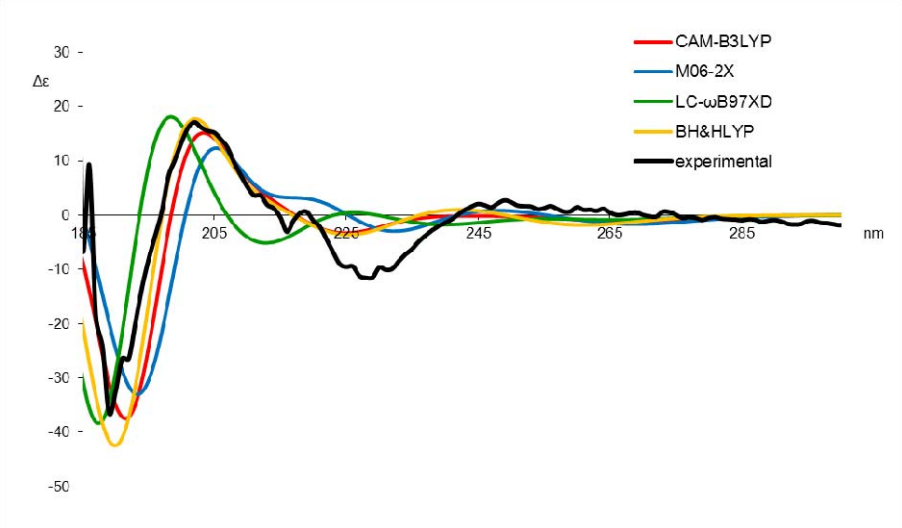


Figure S7. Black line: experimental ECD spectrum of **3k**. Colored lines: TD-DFT simulated spectra calculated for **Me-3k**.All the simulated spectra were red-shifted by 15 nm to match the experimental maximum at 203 nm.

[7] C. E.Check and T. M.Gilbert, *J. Org. Chem.*, 2005, **70**, 9828-9834
[8] In Gaussian 09 the BH&HLYP functional has the form: $0.5*E_X^{HF} + 0.5*E_X^{LSDA} + 0.5*\Delta E_X^{Becke88} + E_C^{LYP}$
[9] Y. Zhao and D.G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215-241.
[10] J-D. Chai and M. Head-Gordon, *Phys. Chem. Chem. Phys.*, 2008, **10**, 6615-6620.
[11] T. Yanai, D. Tew, and N.Handy, *Chem. Phys. Lett.* 2004, **393**, 51-57.
[12] a) G. Cera, M.Chiarucci, A. Mazzanti, M. Mancinelli and M. Bandini, *Org. Lett.*, 2012, **14**, 1350-1353; b) F. Pesciaioli, P. Righi, A. Mazzanti, G. Bartoli and G. Bencivenni, *Chem. Eur. J.*, 2011, **17**, 2482-2485; c) S. Duce, F. Pesciaioli, L. Gramigna, L. Bernardi, A. Mazzanti, A. Ricci, G. Bartoli and G. Bencivenni, *Adv. Synt. Catal.*, 2011, **353**, 860-864; d) L. Bernardi, M. Comes-Franchini, M. Fochi, V. Leo, A. Mazzanti and A. Ricci, *Adv. Synt. Catal.*, 2010, **352**, 3399-3406.
[13] P. J. Stephens, D. M. McCann, F. J. Devlin, J. R. Cheeseman and M. J. Frisch, *J. Am. Chem. Soc.*, 2004, **126**, 7514-7521.

Starting from the best conformation of **Me-3k**, a new conformational search was then performed on **3k**. After DFT optimization, two conformations were found to be very close in energy. Both exibit a pseudo-chair conformation of tetrahydroquinoline ring and they are different because of the E/Z rotational isomerism of the amidic part of the carbamate. If the internal energy is considered, the Z conformation is favoured by 1.18 kcal/mol. On the contrary, the E conformation is more stable by 0.38 kcal/mol when the free energies obtained by thermochemistry corrections are applied.

Apart from the E/Z rotational isomerism, the calculated geometry of conformations **3k-a** and **3k-b** are in good agreement with the experimental NOE data, as one of the two hydrogens belonging to C-3 (H-3b) has dihedral angles close to 180° with H-2 and H-4 (179° and 168°, respectively). Also the position of H-1' corresponds to the distance constraints extracted by NOE data, with an *anti*-relationship with H-4.

Variable temperature NMR spectra, taken at -15°C in CD_3CN [14], showed that the E/Z interconversion due to rotation of the carbamate could be frozen in the NMR timescale.[15] The ratio of the two conformations due to E/Z isomerism was 90:10, corresponding to a $\Delta G°$=1.1 kcal/mol. Unfortunately, NOE spectra cannot ascertain whether the Z or the E rotamer was the more populated. DFT calculations of the chemicals shifts at the B3LYP/6-311++G(2d,p) level (GIAO approach[16]) suggested that the chemical shift of the NH-Cbz hydrogen is shielded by 0.35 ppm in the E-rotamer with respect to the NH of the Z. Since the upfield signal experimentally corresponds to the most populated conformer, this theoretical result agrees well with the calculations based on the free energies and it assigns the E-conformation (**b** in Figure S8) as the more stable rotamer in solution.

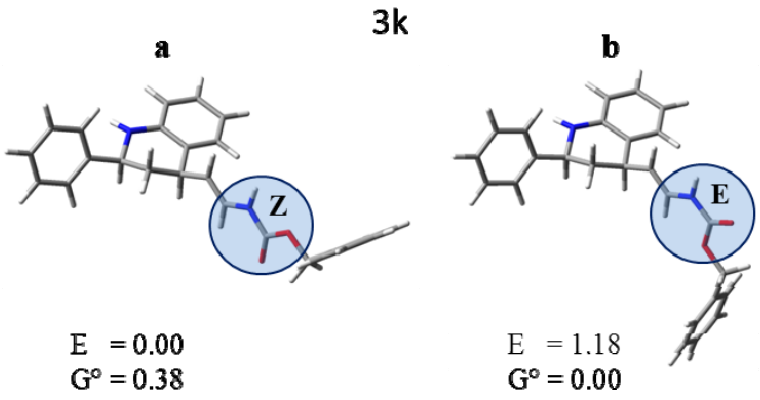


Figure S8. 3D view of the two most stable conformation of **3k**, calculated at the B3LYP/6-31G(d) level. Energy differences are in kcal/mol and represent ZPE –corrected free energy in standard conditions (G°) or uncorrected internal energies (E).

[14] These spectra were recorded in CD_3CN to avoid ambiguity in the determination of the rotamers ratio, because acetonitrile was used to record the experimental ECD spectrum.
[15] W. H. Pirkle, K. A. Simmons, and C. H. Boeder, *J. Org. Chem.* 1979, **44**, 4891-1896
[16] J. R. Cheeseman, G. W. Trucks, T. A. Keith and M. J. Frisch, *J. Chem. Phys.*, 104, **1996**, 5497-509.

The electronic excitation energies and rotational strengths were calculated in the gas phase for the two conformation of **3k** using TD-DFT with the same four different methods (functionals) and basis sets used for **Me-3k** (BH&HLYP, M06-2X, LC-ωB97XD, and CAM-B3LYP with 6-311++G(2d,p) basis set). All the calculations were performed supposing 2*S*, 4*R* Absolute Configuration,[17] with the results shown in Figure S9.

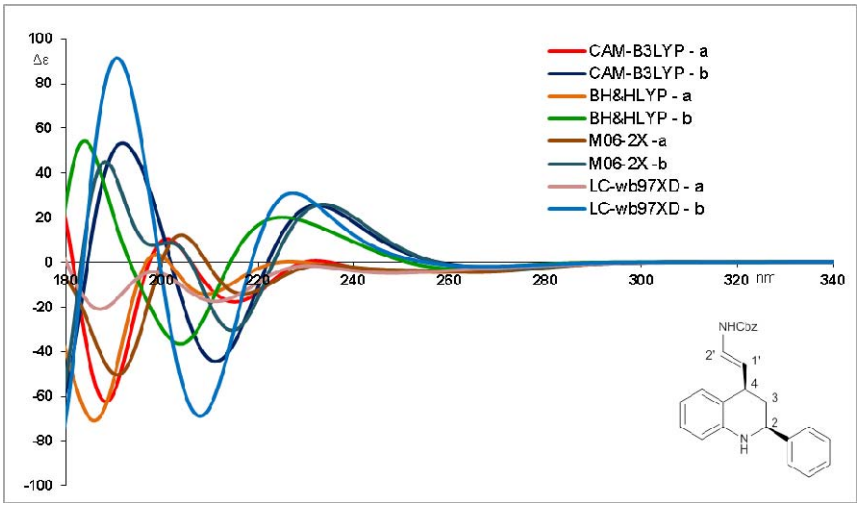


Figure S9. TD-DFT simulated spectra calculated for **3k**. The reddish set of lines corresponds to conformation **a** (Z-rotamer). The bluish set corresponds to conformation **b** (E-rotamer).

As shown in Figure S9, the simulated spectra are similar within the same conformation, but the two conformations show quite different spectra. In particular, they show opposite phase in the high energy region between 200 and 180. However, the experimental ratio to be used to get the averaged spectrum was provided by low-temperature NMR. The simulated spectra were then obtained by using a 86:14 ratio, corresponding to a $\Delta G° = 1.1$ kcal/mol at +25°C. (Figure S10). It should be stressed that if the opposite ratio of the rotamers is used the agreement is still acceptable, but the wavelength of the highest energy Cotton does not match to the experimental value. From an alternative point of view, the ECD spectrum confirms the conformational preference toward the Z-rotamer of the ene-carbamate.

[17] The 2*S*,4*R* absolute configuration of **3k** corresponds to the 2*S*,4*S* configuration of **Me-3k** because of the different priority of the substituents at C-4.

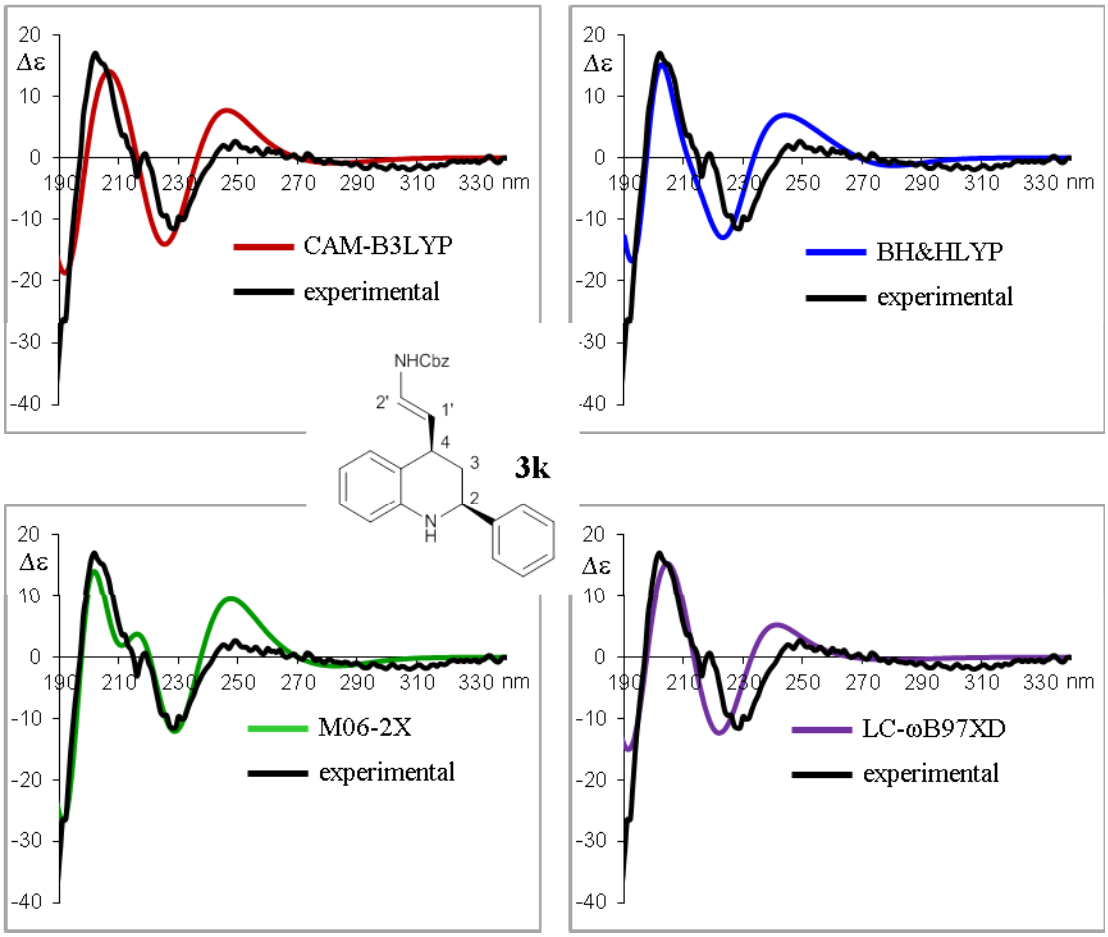


Figure S10: Simulations of the experimental ECD spectrum of **3k** (black traces). Each simulated spectrum (red, blue, green and purple lines) was obtained starting from the spectra obtained for the two conformations weighted using the experimental NMR data (86:14). The experimental spectrum of **3k** was obtained in acetonitrile solution (5.5 10^{-5} M, 0.2 cm path length). Δε are expressed in Mol L^{-1} cm^{-1}. The simulated spectra were vertically scaled to match the experimental maximum at 203 nm (0.35, 0.40, 0.43 and 0.20 for CAM-B3LYP, BH&HLYP, M06-2X and LC-ωB97XD, respectively) and red shifted (by 15, 20,15 and 15 nm, respectively)

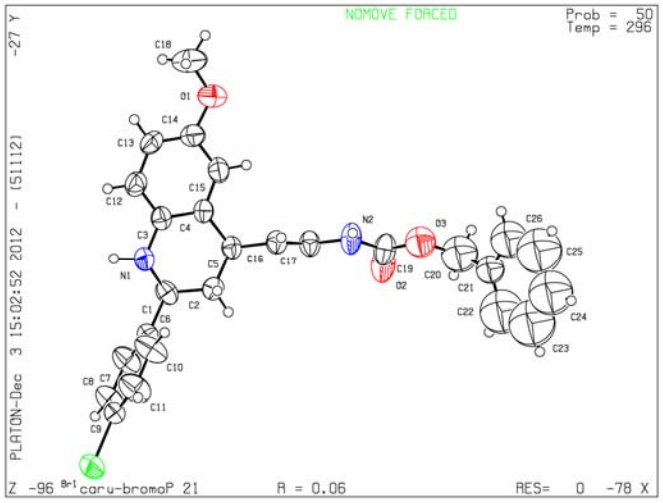
The best simulation was obtained by the M06-2X functional, but all the simulated spectra now show a good agreement with the experimental one, also in the 230 nm region. Thus the absolute configuration could be reliably assigned as 2*S*,4*R*. This result is in agreement with previously published Povarov reactions.[18]

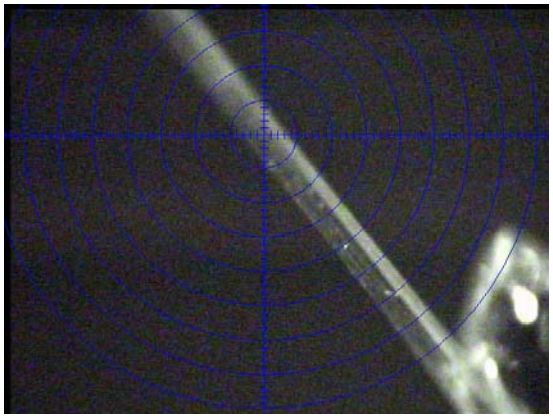
[18] *a*) H. Liu, G. Dagousset, G. Masson, P. Retailleau and J. Zhu, *J. Am. Chem. Soc.*, 2009, **131**, 4598; (*b*) G. Dagousset, J. Zhu and G. Masson, *J. Am. Chem. Soc.*, 2011, **133**, 14804; (*c*) G. Dagousset, P. Retailleau, G. Masson and J. Zhu, *Chem. Eur. J.*, 2012, **18**, 5869; (*d*) L. He, M. Bekkaye, P. Reatilleau and G. Masson, *Org. Lett.*, 2012, **14**, 3158; (*e*) C. Wang, Z.-Y. Han, H.-W. Luo and L.-Z. Gong, *Org. Lett.*, 2010, **21**, 2266; (*f*) F. Shi, G.-J. Xing, Z.-L. Tao, S.-W. Luo, S.-J. Tu and L.-Z. Gong, *J. Org. Chem.*, 2012, **77**, 6970; (*g*) J.-H. Lin, G. Zong, R.-B. Du, J.-C. Xiao and S. Liu, *Chem. Commun.*, 2012, **48**, 7738; (*h*) G. Bergonzini, L. Gramigna, A. Mazzanti, M. Fochi, L. Bernardi and A. Ricci, *Chem. Commun.*, 2010, **46**, 327.

Absolute configuration determination of 3b through X-ray diffraction

After several unsuccessful attempts, suitable crystals for the determination of the absolute configuration of the adducts by the anomalous dispersion X-ray method,[19] which requires a suitable heavy atom (Z> Si using standard Mo-Kα radiation[20]), were obtained for compound **3b** by vapour diffusion of *n*-hexane into an EtOAc ethyl acetate solution. As shown below, the determined relative and absolute configuration on compound **3b** by X-ray confirmed the stereochemistry determined on **3k** by a combination of NMR, chiro-optical and computational techniques, both for the relative configuration of the two chiral centres and the double bond, but also for the absolute configuration.

Crystal Data for compound 3b





Molecular formula: $C_{26}H_{25}N_2O_3Br$, M_r = 493.39, monoclinic, space group $P2_1$ (No. 3), a = 9.5555(17), b = 5.0614(9), c = 24.813(4) Å, β = 92.316(2), V = 1199.1(4) Å^3, T = 298(2) K, Z = 2, ρ_c = 1.367 g cm^{-3}, $F(000)$ = 508, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), $\mu(Mo_{K\alpha})$ = 1.743 mm^{-1}, colourless rods (0.40 × 0.10 × 0.05 mm^3), empirical absorption correction with SADABS (transmission factors: 0.9179 – 0.5423), 2400 frames, exposure time 90 s, $1.64 \leq \theta \leq 26.00$, $-11 \leq h \leq 11$, $-6 \leq k \leq 6$, $-30 \leq l \leq 30$, 12298 reflections collected, 4637 independent reflections (R_{int} = 0.0218), solution by direct methods (SHELXS97) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (SHELX97), hydrogen atoms refined with a riding model except for the two NH hydrogen, that were experimentally located and refined. Data / restraints / parameters ratio = 4637/ 1 / 246, $S(F^2)$ = 1.083, $R(F)$ = 0.0742 and $wR(F^2)$ = 0.1971 on all data,

[19] J. M. Bijvoet, A. F. Peerdeman and A. J. Van Bommel, *Nature*, 1951, **168**, 271.
[20] R. W. W. Hooft, L. H. Stravera and A. L. Spek, *J. Appl. Cryst.*, 2008, **41**, 96–103

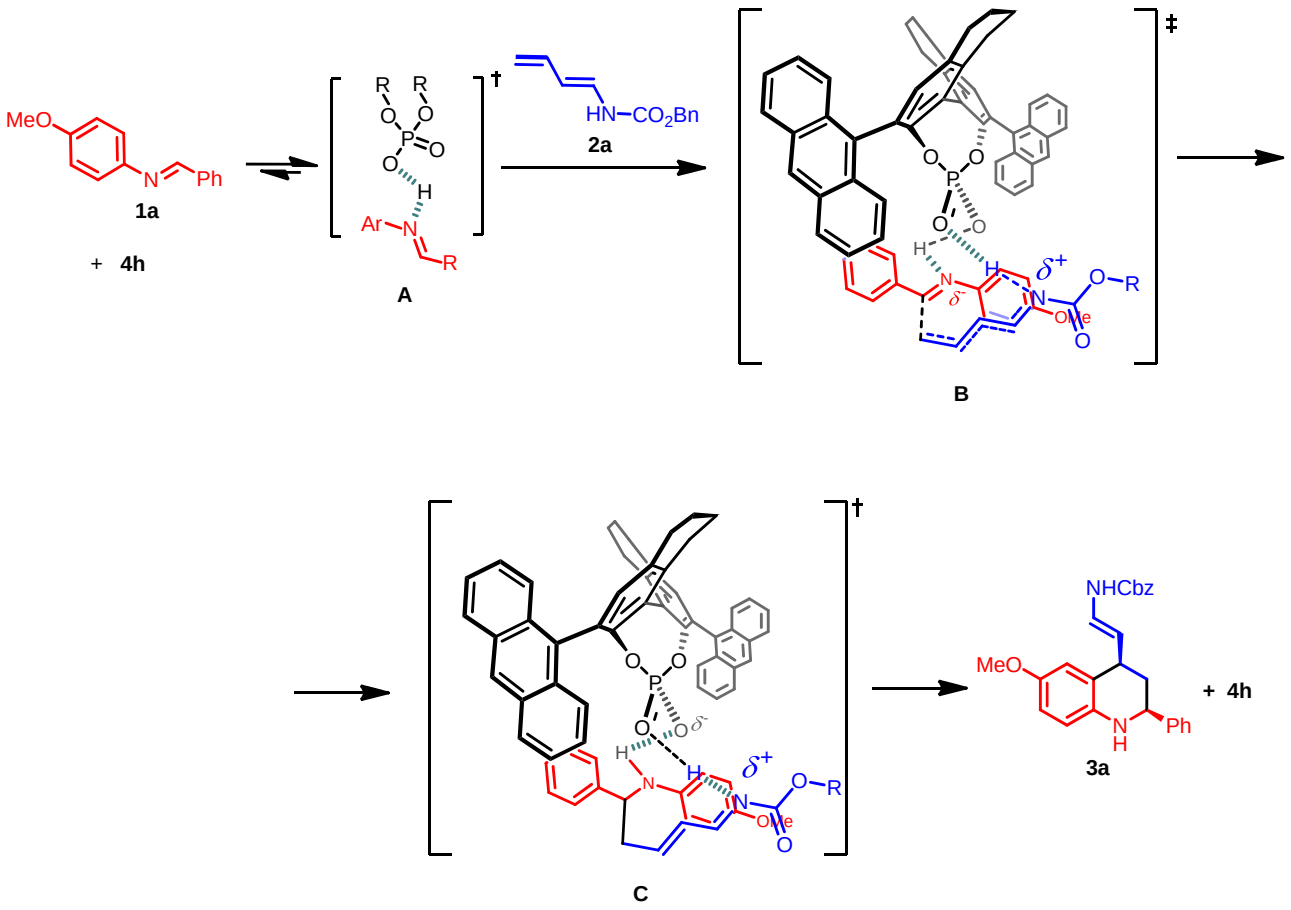
$R(F)$ = 0.0645 and $wR(F^2)$ = 0.1888 for 4637 reflections with $I > 2\sigma(I)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.1122P)^2 + 0.839P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference peak and hole 0.998 and –0.0674 e Å^{-3}. Flack Parameter for *S*,*R* absolute configuration (C1 and C5, respectively): 0.013(19). The benzyl moiety (C20-C26) was found to be disordered over two positions, and it was isotropically refined. 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-913761. 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).

Absolute and relative configuration of the remaining adducts 3

The ^{1}H NMR spectra of the other cycloadducts **3** showed, in all cases, that the signal related to H-3b appears as a pseudo-quartet. This is consistent with a *cis* relative configuration of the two asymmetric centres. Thus the relative configuration of all other cycloadducts **3** was surmised to be 2,4-*cis*, with the exception of **3o** which furnished a mixture of diastereoisomers, with the 2,4-*trans* as the major product (see below in the experimental section).

To account for the observed (2*S*,4*R*) absolute configuration, a reaction model involving double coordination of catalyst **4h** to both imine and dienophile can be considered (Scheme S2), on the basis of the generally accepted mode of action of BINOL derived phosphoric acid catalysts.[21] In particular, as shown in Scheme S2 for imine **1a** and dienophile **2a**, it can be assumed that attack of the dienophile to the imine **A**, activated by the catalyst through a hydrogen bond interaction or protonation, gives a transition state **B** wherein the phosphoryl oxygen stabilises the positive charge on the dienophile by acting as a Lewis base coordinating the carbamate proton. The large 9-anthracenyl groups guide the stereoselectivity mainly by steric interactions with the substrates, favouring attack of the dienophile at the Si-face of the activated imine. Presuming a two step cycloaddition pathway, an intermediate catalyst coordinated *N*-acyl iminium ion **C** is formed first, which then undergoes an intramolecular Friedel-Crafts reaction to give the (2*S*,4*R*)-disubstituted 1,2,3,4 tetrahydroquinoline product **3a**. We assumed a similar reaction pathway leading to the attack at the same face of the imines **1** in all other cases. This assumption is confirmed by the order of elution in the chiral stationary phase HPLC analysis (Phenomenex Lux) of cycloadducts **3**. In all cases, the reactions performed with the (*R*)-BINOL derived catalyst **4h** gave the first eluting peak as the major enantiomer.

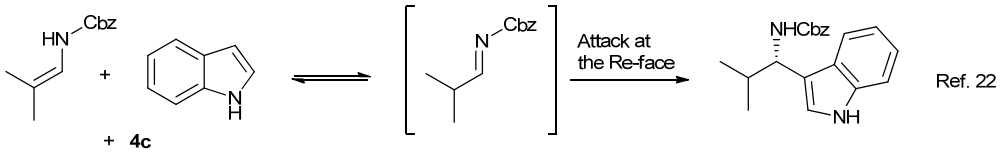
[21] L. Simón and J. M. Goodman, *J. Org. Chem.*, 2011, **76**, 1775.



Scheme S2. Proposed reaction pathway and model for enantioselectivity.

Determination of the relative configuration in compounds 9

The configuration of the chiral centre deriving from the addition of indole to the enecarbamate of cycloadduct **3a** catalysed by **4c** can be tentatively assigned on the basis of the previously reported face-selectivity of catalyst (*R*)-TRIP **4c** in the reaction of indoles with simpler enecarbamates.[22]
In particular, it is known that (*R*)-**4c** promotes a selective addition of indole at the Re-face of an intermediate N-Boc imine, generated in situ from an N-Boc enecarabamate (Scheme S3).

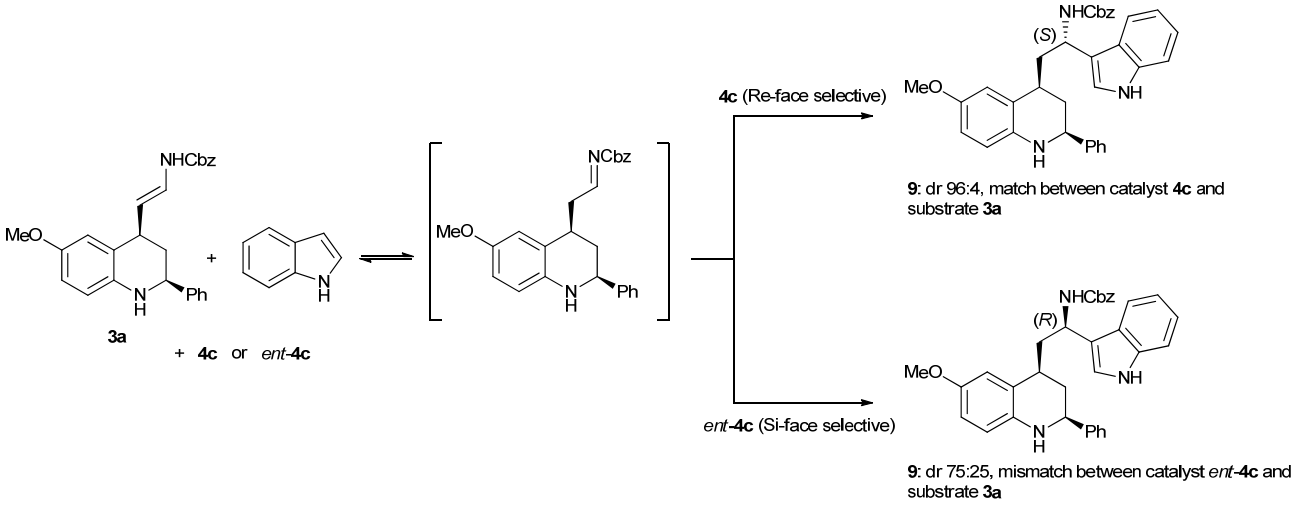


Scheme S3. Reported addition of indole to in situ generated N-carbamoyl imines catalysed by **4c**.

It can be assumed that also in our case (*R*)-**4c** promotes the attack of indole at the same prochiral face of the intermediate N-Cbz imine, derived from the enecarbamate of **3a**, giving predominantly

[22] M. Terada and K. Sorimachi, *J. Am. Chem. Soc.*, 2007, **129**, 292.

(96:4) an S configured product **9**. This hypothesis is confirmed by the reaction performed with *ent*-**4c** ((*S*)-**4c)**, which gives predominantly (75:25) the opposite diastereoisomer of **9**. Thus, the configuration of the newly formed chiral centre in the Friedel-Crafts addition is partially controlled by the catalyst employed, with (*R*)-**4c** matching the stereochemical bias given by the pre-existing chiral centres of cycloadduct **3a**, and (*S*)-**4c** mismatching this bias (see Scheme S4).



Scheme S4. Addition of indole to the enecarbamate of **3a** catalysed by **4c** and *ent*-**4c**.

Experimental Details

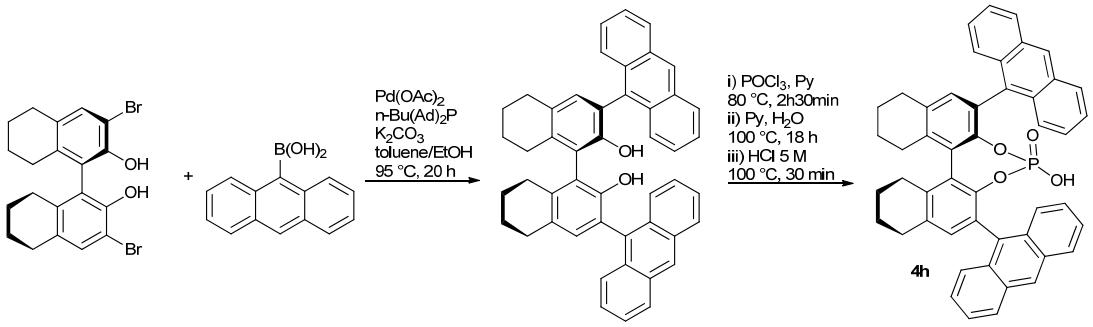
General Methods. ^{1}H, ^{13}C NMR spectra were recorded on a Varian AS 300, 400 or 600 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^{1}H and ^{13}C NMR.[23] ^{13}C NMR spectra were acquired with ^{1}H broad band decoupled mode. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES) ionisation techniques. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC, using a UV detector operating at 254 nm. Several of the ^{1}H NMR spectra show some minor, broad signals, besides the major described ones, due to the presence of a small (<10%) amount of a rotamer at the carbamate moiety (see Determination of Relative and Absolute Configuration Section).

Materials. Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. Chromatographic purifications were performed using 70-230 mesh silica. Racemic samples were prepared using diphenylphosphonic acid or $Sc(OTf)_3$ as the catalyst, in CH_2Cl_2 or toluene at room temperature for 24-60 h. Toluene was passed through neutral alumina before use. Pyridine was dried by standing on activated 4 Å molecular sieves. *N*-4-methoxyphenyl imines **1a-h** were obtained refluxing an equimolar mixture of 4-methoxyaniline and the appropriate aldehyde in EtOH for a few hours, and collected by filtration. Imines **1k-o** were obtained stirring for 48-60 h benzaldehyde and the appropriate aniline derivative in CH_2Cl_2 in the presence of activated 4 Å molecular sieves. Dienophiles **2a,c**[24] and **2b**[25] were prepared by following a literature procedure. (*R*)-3,3'-Dibromo-H8-BINOL was prepared according to the literature.[26] 9-Anthracenyl boronic acid was obtained following a reported procedure,[27] except that the crude boronic acid was employed in the Suzuki reaction.

[23] H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512.
[24] P. J. Jessup, C. B. Petty, J. Ross and L. E. Overman, *Organic Syntheses, Coll. Vol. 6*, 1988, **6**, 95.
[25] L. E. Overman, G. F. Taylor, C. B. Petty and P. J. Jessup, *J. Org. Chem.*, 1978, **43**, 2164.
[26] a) M. Rueping, B. J. Nachtsheim, R. M. Koenigs and W. Ieawsuwan, *Chem. Eur. J.*, 2010, **16**, 13116; b) M. Bartoszek, M. Beller, J. Deutsch, M. Klawonn, A. Köckritz, N. Nemati and A. Pews-Davtyan, *Tetrahedron*, 2008, **64**, 1316.
[27] US2009/286985.

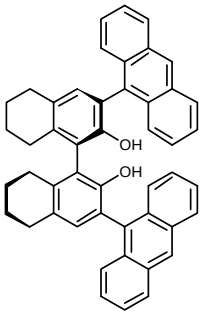
Preparation of the H8-BINOL derived phosphoric acid catalyst 4h.

The preparation of catalyst **4h** from 3,3'-dibromo-H8-BINOL reported below is based on ref.[26b] However, we have substantially modified both steps (Suzuki coupling and phosphoric acid formation, (Scheme S5). In our hands, the protocol herein described, still based on the same catalyst used in ref.[25b], proved to be more reliable than the original procedure, furnishing clean and well-characterised products.



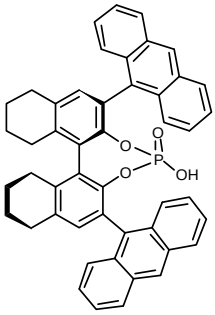
Scheme S5: Synthesis of the chiral Brønsted acid **4h**

(*R*)-3,3'-Di(anthracen-9-yl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol.



A Schlenk tube equipped with a magnetic stirring bar was charged with (*R*)-3,3'-dibromo-H8-BINOL (244 mg, 0.54 mmol), crude 9-anthracenyl boronic acid (600 mg), $Pd(OAc)_2$ (12.1 mg, 0.054 mmol), *n*-$Bu(Ad)_2P$ (21.2 mg, 0.059 mmol) and K_2CO_3 (894 mg, 0.48 mmol). The tube was evacuated, then backfilled with N_2. Toluene (6.0 mL) and EtOH (1.7 mL) were added, the Schlenk tube was closed and screw-capped and immediately placed in an oil bath pre-warmed to 95 °C. The dark mixture was stirred at this temperature for 20 h, then cooled to RT. Sat. NH_4Cl was then added and the mixture transferred to a separating funnel with the aid of a little amount of EtOAc. The phases were separated and the aqueous phase extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated. Chromatographic purification on silica gel (*n*-hexane/CH_2Cl_2 from 3:1 to 1:1) gave the title compound as a pale yellow solid in 61% yield. $[\alpha]_D^{33}$ = +34 ° (c = 0.385 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.52 (s, 2H), 8.10-8.06 (m, 2H), 8.05-8.01 (m, 2H), 7.87-7.82 (m, 2H), 7.73-7.69 (m, 2H), 7.53-7.39 (m, 6H), 7.29 (ddd, J = 8.8, 6.6, 1.5 Hz, 2H), 7.09 (s, 2H), 4.62 (s, 2H), 2.88-2.81 (m, 4H), 2.70 (dt, J_d = 18.2 Hz, J_t = 6.4 Hz, 2H), 2.64 (dt, J_d = 17.8 Hz, J_t = 6.1 Hz, 2H), 1.99-1.84 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 149.2, 137.2, 133.1, 131.8, 131.6, 131.5, 130.7, 130.6, 129.9, 128.6, 128.4, 127.1, 126.5, 126.4, 125.8, 125.7, 125.2, 125.1, 122.2, 120.9, 29.2, 27.4, 23.3, 23.1; ESIMS 669 [M + Na^+].

(*R*)-3,3'-Di(anthracen-9-yl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl hydrogen phosphate (4h)



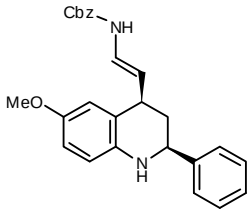
In a 100 mL round bottom flask equipped with a magnetic stirring bar, the thus obtained (*R*)-3,3'-di(anthracen-9-yl)-H8-BINOL (211 mg, 0.33 mmol) was dissolved in dry pyridine (0.6 mL). To this solution, $POCl_3$ (62 µL, 0.66 mmol) in dry pyridine (0.6 mL) was added dropwise. The mixture was then heated at 80 °C under N_2 with stirring, until TLC (*n*-hexane/CH_2Cl_2 1:1) indicated disappearance of the starting material (ca 2h30min). After cooling to RT, fresh pyridine (not dry, 6 mL) and water (10 mL) were added giving a white suspension. A condenser was applied to the flask, and the mixture was heated at 90 °C overnight (16 h) with vigorous stirring. After cooling to RT, 5 M aqueous HCl was added (ca 20 mL, until pH <1), and the resulting suspension was heated at 100 °C for 30 minutes with stirring. After cooling to RT, the mixture was transferred to a separating funnel, with

the aid of CH_2Cl_2 and water. The two phases were separated, and the aqueous phase extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure, leaving a residue which was purified by chromatography on silica gel (CH_2Cl_2/MeOH from 98:2 to 93:7). The fractions containing the phosphoric acid product were collected and evaporated, the residue dissolved in CH_2Cl_2 and transferred in a separating funnel containing an aqueous 5 M HCl solution. The phases were separated, the aqueous phase extracted with CH_2Cl_2, the organic phases combined, dried over $MgSO_4$, filtered and evaporated, affording the title compound as a pale yellow solid in 63% yield. $[\alpha]_D^{28}$ = -148 ° (c = 0.335 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) [the signal at 5.00 ppm (P(O)O***H*** integrates 3H presumably due to interactions with a water molecule] δ = 8.10 (s, 2H), 7.87 (d, J = 8.9 Hz, 2H), 7.65 (d, J = 8.9 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.42-7.29 (m, 4H), 7.20-7.10 (m, 4H), 7.07 (s, 2H), 5.00 (br s, 3H), 3.07-2.95 (m, 2H), 2.94-2.86 (m, 4H), 2.64 (dt, J_d = 17.0 Hz, J_t = 6.6 Hz, 2H), 2.09-1.80 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) [several signals are split in doublets due to J_{P-C} coupling] δ = 145.0, 144.9, 137.6, 134.92, 134.90, 133.4, 131.6, 131.2, 130.9, 130.4, 130.1, 128.5, 128.01, 127.98, 127.82, 127.78, 127.0, 126.3, 125.6, 124.70, 124.65, 29.3, 28.2, 22.8; ESIMS 731 [M + Na^+].

General procedure for the catalytic enantioselective vinylogous Povarov reaction.
To a Schlenk tube equipped with a magnetic stirring bar, 4 Å powdered molecular sieves (20 mg) were added. The molecular sieves were thermally activated under vacuum for 5 minutes and then allowed to cool to r.t. After backfilling the Schlenk tube with nitrogen, the aldimine **1a-h**, **1k-o** (0.15 mmol) was added, followed by catalyst **4h** (2.7 mg, 0.0038 mmol, 2.5 mol%), and toluene (0.60 mL). The mixture was allowed to stir for 5 minutes and then the dienophile **2a-c** (0.18 mmol or 0.30 mmol) was added in one portion. The mixture was then stirred at room temperature under a nitrogen atmosphere. After 16 h, the reaction mixture was filtered through a plug of silica gel, and the plug was washed with Et_2O (4x). After concentration of solvents, the residue was analyzed by ^1H NMR spectroscopy to determine the diastereomeric ratio of the cycloadducts **3**. Finally, the residue was purified by chromatography on silica gel. In some cases, the residue was instead purified by dissolving it in a minimal amount of CH_2Cl_2, followed by precipitation with *n*-hexane, and final removal of the supernatant with a Pasteur pipette after few minutes of decantation. The enantiomeric excess of the adducts purified by precipitation was determined on their crude mixture.

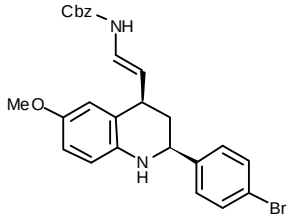
Three-component procedure.
To a Schlenk tube equipped with a magnetic stirring bar, 4 Å powdered molecular sieves (110 mg) were added. The molecular sieves were then thermally activated under vacuum for 10 minutes and then allowed to cool to r.t. After backfilling the Schlenk tube with nitrogen, *p*-anisidine (0.15 mmol), the catalyst **4h** (5.4 mg, 0.0076 mmol, 5.0 mol%), and toluene (0.30 mL) were added, followed by the dienophile **2** (0.30 mmol). A solution of the aldehyde in toluene (0.30 mL, 0.15 mmol) was finally added, and the resulting mixture was stirred at room temperature under a nitrogen atmosphere. After 16 h, the reaction mixture was worked up and purified as in the above procedure.

Benzyl ((*E*)-2-((2*S*,4*R*)-6-methoxy-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3a)



Following the general procedure using 0.18 mmol of dienophile **2a**, the title compound was obtained as a white solid in 85% yield, after chromatography on silica gel (*n*-hexane/EtOAc 8:2). A single diastereoisomer was observed by ^1H NMR in the crude mixture. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 19.4 min, t_{min} = 45.1 min, 98% ee). $[\alpha]_D^{27}$ = -45 ° (c = 0.62, CH_2Cl_2); ^1H NMR ($CDCl_3$, 600 MHz) δ = 7.44-7.28 (m, 10H), 6.76-6.68 (m, 2H), 6.65 (dd, J = 8.4, 2.9 Hz, 1H), 6.54 (d, J = 10.1 Hz, 1H), 6.50 (d, J = 9.1 Hz, 1H), 5.18 (d, J = 12.9 Hz, 1H), 5.15 (d, J = 12.8 Hz, 1H), 4.90 (dd, J = 14.6, 10.3 Hz 1H), 4.41 (d, J = 11.4 Hz, 1H), 3.80 (br s, 1H), 3.73 (s, 3H), 3.68-3.59 (m, 1H), 2.14-2.04 (m, 1H), 1.86 (q, J = 14.1Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 153.5, 152.2, 144.0, 139.0, 136.0, 128.6, 128.6, 128.3, 128.2, 127.6, 126.6, 125.2, 124.9, 115.4, 114.6, 113.6, 113.5, 67.2, 56.8, 55.9, 40.3, 39.6; ESIMS 437 [M + Na^+].
Using the three component procedure, the title compound was obtained in 70% yield and in 98% ee.

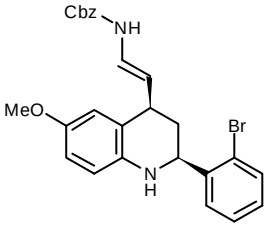
Benzyl ((*E*)-2-((2*S*,4*R*)-2-(4-bromophenyl)-6-methoxy-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3b)



Following the general procedure using 0.18 mmol of dienophile **2a**, the title compound was obtained in 83% yield as a pale yellow solid, after chromatography on silica gel (CH_2Cl_2). A single diastereoisomer was observed by ^1H NMR in the crude mixture. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm,

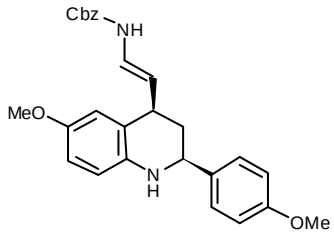
t_{maj} = 23.4 min, t_{min} = 36.4 min, 99% ee). $[\alpha]_D^{28}$ = -29 ° (c = 0.51 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.49-7.45 (m, 2H), 7.42-7.32 (m, 5H), 7.31-7.27 (m, 2H), 6.76-6.66 (m, 2H), 6.65 (dd, J = 8.6, 3.0 Hz, 1H), 6.51 (br d, J = 9.8 Hz, 1H), 6.49 (d, J = 8.6 Hz, 1H), 5.17 (d, J = 11.2 Hz, 1H), 5.15 (d, J = 11.2 Hz, 1H), 4.88 (dd, J = 14.2, 9.2 Hz, 1H), 4.37 (dd, J = 11.0, 2.0 Hz, 1H), 3.74 (br s, 1H), 3.72 (s, 3H), 3.68-3.57 (m, 1H), 2.05 (ddd, J = 13.2, 5.9, 2.3 Hz, 1H), 1.80 (q, J = 11.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ = 153.5, 152.3, 143.1, 138.6, 135.9, 131.7, 128.6, 128.33, 128.30, 128.2, 125.3, 124.8, 121.2, 115.5, 114.5, 113.5, 113.2, 67.2, 56.3, 55.9, 40.3, 39.4. ESIMS: 515/517 [M + Na^+].

Benzyl ((*E*)-2-((2*S*,4*R*)-2-(2-bromophenyl)-6-methoxy-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3c)



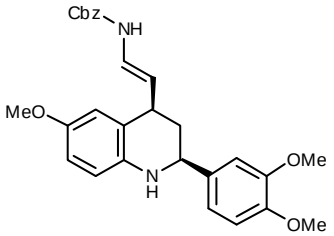
Following the general procedure using 0.30 mmol of dienophile **2a**, the title compound was obtained as a pale yellow solid in 90% yield, after chromatography on silica gel (CH_2Cl_2). A single diastereoisomer was observed by ^{1}H NMR in the crude mixture. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 18.4 min, t_{min} = 27.2 min, 92% ee). $[\alpha]_D^{27}$ = -99 ° (c = 0.62, CH_2Cl_2), ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.64 (d, J = 7.9 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.41-7.30 (m, 6H), 7.17-7.11 (m, 1H), 6.80-6.70 (m, 2H), 6.66 (dd, J = 8.4, 2.9 Hz, 1H), 6.54 (d, J = 8.5 Hz, 1H), 6.44 (br d, J = 10.4 Hz, 1H), 5.17 (br s, 2H), 4.96-4.86 (m, 1H), 4.83 (d, J = 10.5 Hz, 1H), 3.74 (br s, 4H), 3.72-3.64 (m, 1H), 2.27-2.19 (m, 1H), 1.69 (q, J = 11.8 Hz, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 153.5, 152.4, 142.5, 138.9, 135.9, 133.0, 128.9, 128.6, 128.4, 128.3, 127.9, 127.7, 125.3, 125.1, 123.1, 115.8, 114.5, 113.6, 113.3, 67.2, 55.9, 55.2, 39.4, 38.2; ESIMS 515/517 [M + Na^+].

Benzyl ((*E*)-2-((2*S*,4*R*)-6-methoxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3d)



Following the general procedure using 0.18 mmol of dienophile **2a**, the title compound was obtained as a pale yellow solid in 78% yield, after precipitation. A single diastereoisomer was observed by ^{1}H NMR in the crude mixture. The enantiomeric excess of the product was determined by chiral stationary phase HPLC on the crude product (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 18.6 min, t_{min} = 31.2 min, 99% ee). $[\alpha]_D^{27}$ = -30 ° (c = 0.46, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.48-7.28 (m, 7H), 6.89 (d, J = 8.7 Hz, 2H), 6.70 (dd, J = 17.9, 15.1 Hz, 2H), 6.63 (dd, J = 8.6, 3.0, 1H), 6.48 (d, J = 8.7 Hz, 2H), 5.16 (br s, 2H), 4.91 (dd, J = 14.0, 9.6 Hz, 1H), 4.36 (d, J = 11.4 Hz, 1H), 3.94-3.83 (m, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.69-3.59 (m, 1H), 2.09-2.01 (m, 1H), 1,86 (q, J = 11.4 Hz, 1H); ^{3}C NMR ($CDCl_3$, 100 MHz) δ = 159.1, 153.5, 152.1, 139.1, 136.2, 136.0, 128.6, 128.3, 128.2 127.7, 125.1, 124.8, 115.3, 114.6, 114.0, 113.6, 113.4, 67.2, 56.2, 55.9, 55.3, 40.3, 39.6; ESIMS 467 [M + Na^+].

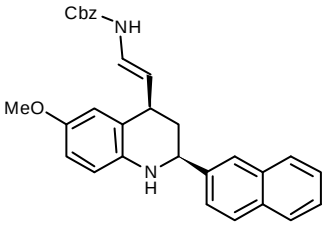
Benzyl ((*E*)-2-((2*S*,4*R*)-2-(3,4-dimethoxyphenyl)-6-methoxy-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3e)



Following the general procedure using 0.18 mmol of dienophile **2a**, the title compound was obtained as a pale yellow solid in 63% yield, after chromatography on silica gel (*n*-hexane/EtOAc 2:1). A single diastereoisomer was observed by ^{1}H NMR in the crude mixture. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 34.5 min, t_{min} = 39.7 min, 99% ee). $[\alpha]_D^{27}$ = -33 ° (c = 0.92, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.41-7.29 (m, 5H), 6.98-6.90 (m, 2H), 6.84 (d, J =

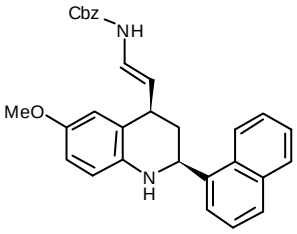
8.1 Hz, 1H), 6.76-6.67 (m, 2H) 6.64 (dd, J = 8.4, 2.9 Hz, 1H), 6.52 (br d, J = 11.9 Hz, 1H), 6.49 (d, J = 8.6 Hz, 1H), 5.18 (br d, J =12.5 Hz, 1H), 5.14 (br d, J =12.5 Hz, 1H), 4.92 (dd, J = 14.1, 9.5 Hz, 1H), 4.35 (dd, J = 11.4, 2.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.80 (br s, 1H), 3.72 (s, 3H), 3.68-3.59 (m, 1H), 2.10-2.02 (m, 1H), 1.84 (q, J = 12.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 153.5, 152.2, 149.1, 148.4, 139.0, 136.7, 136.0, 128.6, 128.3, 128.2, 125.1, 124.9, 118.7, 115.4, 114.6, 113.55, 113.5, 111.1, 109.5, 67.2, 56.6, 55.95, 55.93, 55.88, 40.5, 39.6; ESIMS 497 [M + Na^+].

Benzyl ((*E*)-2-((2*S*,4*R*)-6-methoxy-2-(naphthalen-2-yl)-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3f)



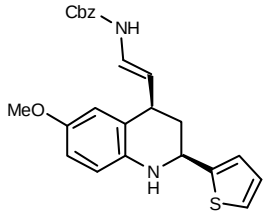
Following the general procedure using 0.30 mmol of dienophile **2a**, the title compound was obtained as a pale yellow solid in 91% yield, after chromatography on silica gel (CH_2Cl_2/EtOAc 100:0 to 95:5). A single diastereoisomer was observed by ^{1}H NMR in the crude mixture. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 32.8 min, t_{min} = 44.4 min, 98% ee). $[\alpha]_D^{27}$ = -31 ° (c = 0.360, CH_2Cl_2), ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.89-7.81 (m, 4H), 7.57-7.44 (m, 3H), 7.42-7.30 (m, 5H), 6.80-6.65 (m, 3H), 6.61-6.52 (m, 2H), 5.17 (br s, 2H), 4.91 (dd, J = 9.7, 14.1 Hz, 1H), 4.56 (d, J = 11.7 Hz, 1H), 3.63 (s, 3H), 3.60-3.51 (m, 1H), 2.21-2.11 (m, 1H), 1.94 (q, J = 11.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 153.6, 152.2, 141.5, 139.0, 136.0, 133.5, 133.1, 128.61, 128.57, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 126.2, 125.8, 125.2, 125.0, 124.9, 115.5, 114.7, 113.5, 67.2, 56.9, 55.9, 40.2, 39.6; ESIMS 464 [M + Na^+].
Using the three-component procedure, the title compound was obtained in 70% yield and >99% ee.

Benzyl ((*E*)-2-((2*S*,4*R*)-6-methoxy-2-(naphthalen-1-yl)-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3g)



Following the general procedure using 0.30 mmol of dienophile **2a**, the title compound was obtained as a pale yellow solid in 79% yield, after chromatography on silica gel (CH_2Cl_2). A single diastereoisomer was observed by ^{1}H NMR in the crude mixture. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 27.6 min, t_{min} = 62.9 min, 89% ee). $[\alpha]_D^{22}$ = -126 (c = 0.30, CH_2Cl_2), ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 8.14 (br d, J =7.9 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.56-7.45 (m, 3H), 7.42-7.30 (m, 5H), 6.80-6.73 (m, 2H), 6.68 (dd, J = 8.5, 2.8 Hz, 1H), 6.56 (d, J = 8.7 Hz, 1H), 6.51 (br d, J = 10.5 Hz, 1H), 5.22 (br d, J = 10.6 Hz, 1H), 5.16 (d, J = 12.2 Hz, 1H), 5.14 (d, J = 12.2 Hz, 1H), 4.92 (dd, J = 13.7, 9.6 Hz, 1H), 3.98 (br s, 1H), 3.82-3.75 (m, 1H), 3.75 (s, 3H), 2.35-2.29 (m, 1H), 1.98 (br q, J = 12.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 153.5, 152.3, 139.2, 139.1, 136.0, 133.9, 130.8, 129.0, 128.6, 128.4, 128.2, 128.0, 126.2, 125.7, 125.6, 125.2, 125.1, 115.8, 114.7, 113.6, 113.5, 67.2, 65.9, 56.0, 39.8, 39.0; ESIMS 464 [M + Na^+].

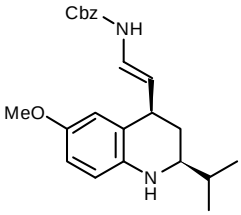
Benzyl ((*E*)-2-((2*S*,4*R*)-6-methoxy-2-(thiophen-2-yl)-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3h)



Following the general procedure using 0.30 mmol of dienophile **2a**, the title compound was obtained as a pale yellow solid in 53% yield, after chromatography on silica gel (CH_2Cl_2/EtOAc 98:2). A single diastereoisomer was observed by ^{1}H NMR in the crude mixture. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 20.1 min, t_{min} = 38.5 min, 87% ee). $[\alpha]_D^{27}$ = -51 ° (c = 0.980, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.42-7.28 (m, 5H), 7.22 (dd, J = 5.0, 1.2 Hz, 1H), 7.05-7.00 (m, 1H), 6.98-6.94 (m,

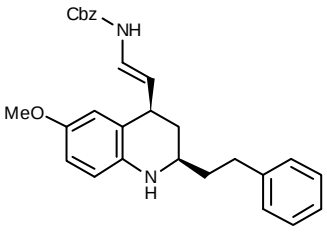
1H), 6.76-6.66 (m, 2H), 6.63 (dd, J = 8.6, 2.9 Hz, 1H), 6.52-6.43 (m, 2H), 5.16 (br s, 2H), 4.89 (dd, J = 13.9, 9.7 Hz, 1H), 4.73 (d, J = 11.0 Hz, 1H), 3.92 (br s, 1H), 3.71 (s, 3H), 3.68-3.59 (m, 1H), 2.24-2.15 (m, 1H), 1.93 (q, J = 11.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 153.4, 152.4, 148.0, 138.2, 135.9, 128.5, 128.3, 128.2, 126.5, 125.1, 124.9, 124.1, 123.5, 115.6, 114.4, 113.4, 113.2, 67.1, 55.8, 52.4, 41.1, 39.2; ESIMS 443 [M + Na^+].

Benzyl ((*E*)-2-((2*S*,4*R*)-2-isopropyl-6-methoxy-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3i)



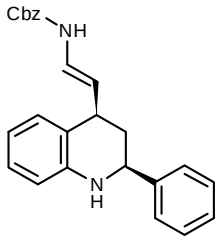
Following the three-component procedure, the title compound was obtained as a pale yellow solid in 80% yield, after chromatography on silica gel (CH_2Cl_2).The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 80:20, 0.75 mL/min, λ = 254 nm, t_{maj} = 13.4 min, t_{min} = 19.8 min, 99% ee). $[\alpha]_D^{27}$ = -22 ° (c = 0.80, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.45-7.32 (m, 5H), 6.76-6.57 (m, 3H), 6.49-6.40 (m, 2H), 5.17 (br s, 2H), 4.92 (dd, J = 13.9, 9.6 Hz, 1H), 3.70 (s, 3H), 3.52-3.38 (m, 2H), 3.13-3.03 (m, 1H), 1.96-1.87 (m, 1H), 1.76-1.70 (m, 1H), 1.46 (q, J = 12.1 Hz, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 153.5, 151.9, 139.1, 136.0, 128.6, 128.4, 128.2, 125.3, 124.8, 115.3, 114.5, 114.2, 113.4, 67.2, 57.2, 55.9, 39.2, 33.9, 32.7, 18.3, 18.1; ESIMS 403 [M + Na^+].

Benzyl ((*E*)-2-((2*R*,4*R*)-6-methoxy-2-phenethyl-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3j)[28]



Following the three-component procedure, the title compound was obtained as a pale yellow solid in 76% yield, after chromatography on silica gel (CH_2Cl_2/*n*-hexane from 2:1 to 100:0). The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 24.7 min, t_{min} = 34.1 min, 84% ee). $[\alpha]_D^{27}$ = -32 ° (c = 0.81, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.41-7.19 (m, 10H), 6.75-6.45 (m, 5H), 5.18 (br s, 2H), 4.91 (dd, J = 14.1, 9.6 Hz, 1H), 3.70 (s, 3H), 3.51-3.42 (m, 1H), 3.35-3.26 (m, 1H), 2.78-2.69 (m, 2H), 2.05-1.98 (m, 1H), 1.85 (dd, J = 7.5, 14.0 Hz, 2H), 1.55 (q, J = 11.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 153.5, 152.5, 141.6, 137.8, 135.9, 128.6, 128.5, 128.4, 128.3, 126.0, 124.9, 115.9, 114.5, 113.8, 67.2, 55.8, 51.6, 38.9, 38.1, 37.2, 31.9; ESIMS 465 [M + Na^+].

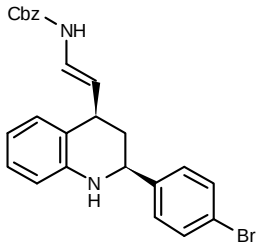
Benzyl ((*E*)-2-((2*S*,4*R*)-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3k)



Following the general procedure using 0.30 mmol of dienophile **2a**, the title compound was obtained as a pale yellow solid in 94% yield as a pale yellow solid, after chromatography on silica gel (CH_2Cl_2). A single diastereoisomer was observed by ^{1}H NMR in the crude mixture. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 22.4 min, t_{min} = 47.3 min, 99% ee). $[\alpha]_D^{28}$ = -58 ° (c = 0.515, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.45-7.28 (m, 10H), 7.11 (br d, J = 7.8 Hz, 1H), 7.03 (br t, J = 7.6 Hz, 1H), 6.77-6.69 (m, 1H), 6.68 (dt, J_t = 7.8 Hz, J_d = 1.2 Hz, 1H), 6.53 (dd, J = 7.9, 1.1 Hz, 1H), 6.48 (br d, J = 10.8 Hz, 1H), 5.20 (d, J = 12.2 Hz, 1H), 5.16 (d, J = 12.2 Hz, 1H), 4.94 (dd, J = 14.3, 9.8 Hz, 1H), 4.49 (dd, J = 11.1, 2.3 Hz, 1H), 4.00 (br s, 1H), 3.72-3.61 (m, 1H), 2.11 (ddd, J = 12.9, 5.4, 2.4 Hz, 1H), 1.89 (br q, J = 11.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 153.5, 144.7, 143.9, 135.9, 128.8, 128.6, 128.5, 128.3, 128.2, 127.7, 127.5, 126.6, 125.0, 123.4, 117.5, 114.2, 113.6, 67.1, 56.5, 40.1, 39.1; ESIMS 407 [M + Na^+].

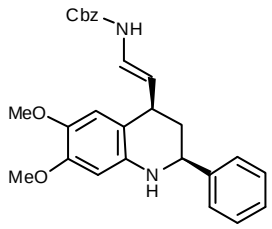
[28] The descriptors of the absolute configuration of compound **3j** is different from the other of compounds **3** because of the different priority of substituents at C-2.

Benzyl ((*E*)-2-((2*S*,4*R*)-2-(4-bromophenyl)-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3l)



Following the general procedure using 0.18 mmol of dienophile **2a**, the title compound was obtained as a pale orange solid in 74% yield, after precipitation. A single diastereoisomer was observed by ^{1}H NMR in the crude mixture. The enantiomeric excess of the product was determined by chiral stationary phase HPLC on the crude product (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj}= 23.0 min, t_{min} = 32.7 min, 99% ee). $[\alpha]_D^{27}$ = -19 ° (c = 0.360, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.52-7.46 (m, 2H), 7.42-7.27 (m, 6H), 7.09 (d, J = 7.4 Hz, 1H), 7.06-6.98 (m, 1H), 6.72-6.64 (m, 2H), 6.52 (d, J = 7.9 Hz, 1H), 6.42 (d, J = 10.7 Hz, 1H), 5.22-5.10 (br s, 2H), 4.92 (dd, J = 14.1, 9.5 Hz, 1H), 4.45 (d, J = 11.6 Hz, 1H), 3.95 (br s, 1H), 3.70-3.58 (m, 1H), 2.09-2.03 (m, 1H), 1.82 (q, J = 11.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 153.5, 144.5, 143.0, 135.9, 131.8, 128.8, 128.6, 128.4, 128.3, 128.2, 127.5, 125.2, 123.4, 121.3, 117.8, 114.4, 113.4, 67.2, 56.0, 40.2, 39.1; ESIMS 487/489 [M + Na^+].

Benzyl ((*E*)-2-((2*S*,4*R*)-6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3m)



Following the general procedure using 0.18 mmol of dienophile **2a**, the title compound was obtained as a pale yellow solid in 98% yield, after chromatography on silica gel (CH_2Cl_2/EtOAc 98:2). A single regio- and diastereo-isomer was observed by ^{1}H NMR in the crude mixture. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 28.1 min, t_{min} = 38.3 min, 97% ee). $[\alpha]_D^{27}$ = -27 ° (c = 0.87, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.44-7.27 (m, 10H), 6.72 (dd, J = 13.7, 11.2, 1H), 6.65 (s, 1H), 6.57 (br s, 1H), 6.14 (s, 1H), 5.19 (br d, J = 12.6, 1H), 5.15 (br d, J = 12.6, 1H), 4.89 (dd, J = 13.9, 9.8, 1H), 4.40 (d, J = 11.1, 1H), 3.83-3.78 (m, 1H), 3.787 (s, 3H), 3.778 (s, 3H), 3.66-3.57 (m, 1H), 2.09 (ddd, J = 13.0, 5.4, 1.7, 1H), 1.84 (q, J = 12.2, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 153.6, 148.9, 143.9, 141.7, 139.0, 136.0, 128.64, 128.60, 128.4, 128.3, 127.7, 126.6, 124.9, 114.9, 114.0, 113.5, 99.4, 67.2, 57.0, 56.9, 55.8, 40.5, 39.0; ESIMS 467 [M + Na^+].

The reaction can in principle give two regioisomeric cycloadducts **3m** and **3m'**(Figure S7). From the ^{1}H NMR spectrum, it is possible to determine that the only cycloadduct formed is the 6,7-dimethoxy regioisomer **3m**, as the signals related to the aromatic protons of the 1,2,3,4-tetrahydroquinoline moiety, at 6.65 and 6.14 ppm, appear as two singlets, and are thus indicative of a *para* relationship between these protons as **3m**.

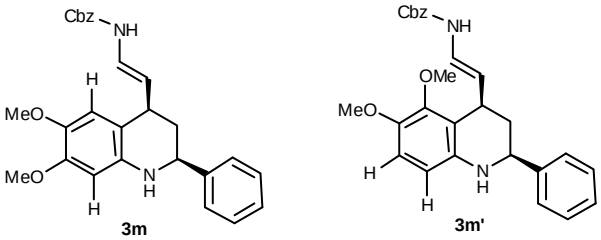
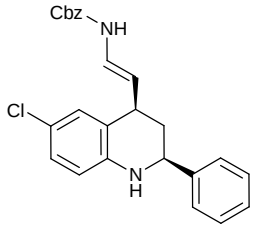


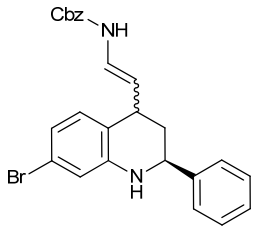
Figure S11: Compounds **3m** and **3m'**

Benzyl ((*E*)-2-((2*S*,4*R*)-6-chloro-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3n)



Following the general procedure using 0.30 mmol of dienophile **2a**, the title compound was obtained as a pale yellow solid in 25% yield, after chromatography on silica gel (CH_2Cl_2/*n*-hexane 2:1). A single diastereoisomer was observed by ^{1}H NMR in the crude mixture. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 23.8 min, t_{min} = 53.5 min, 98% ee). $[\alpha]_D^{27}$ = -41 ° (c = 0.63, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.41-7.30 (m, 11H), 7.05 (br d, J = 2.4 Hz, 1H), 6.96 (dd, J =8.5, 2.4 Hz, 1H), 6.72 (dd, J =14.0, 11.4 Hz, 1H), 6.44 (d, J = 8.5 Hz, 1H), 5.17 (br s, 2H), 4.90 (dd, J =14.1, 9.6 Hz,1H), 4.46 (dd, J = 11.4, 2.3 Hz, 1H), 4.00 (br s, 1H), 3.66-3.56 (m, 1H), 2.13-2.06 (m, 1H), 1.84 (q, J = 11.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 153.5, 152.0, 143.5, 143.3, 135.9, 128.7, 128.6, 128.4, 128.3, 127.8, 127.3, 126.5, 125.6, 125.1, 122.0, 115.25, 112.6, 67.2, 56.5, 39.6, 39.2; ESIMS 418 [M + Na^+]

Benzyl ((*E*)-2-((2*S*,4*R*)-7-bromo-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate and ((*E*)-2-((2*S*,4*S*)-7-bromo-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3o)



Following the general procedure using 0.30 mmol of dienophile **2a**, the two diastereoisomers of the title compound were obtained in 60% combined yield, after chromatography on silica gel. ^{1}H NMR analysis of the crude mixture indicated a 2.8:1 ratio, in favour of the 2,4-*trans* diastereosiomer. The two diastereoisomers were separated by chromatography on silica gel (CH_2Cl_2/*n*-hexane 2:1): the minor 2,4-*cis* diastereoisomer as the first R_f fraction and the major 2,4-*trans* diastereoisomer as the second R_f fraction. The enantiomeric excesses of the two diastereoisomers were determined by chiral stationary phase HPLC (minor diastereoisomer: Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 34.0 min, t_{min} = 59.6 min, 99% ee; major diastereoisomer: Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 30.8 min, t_{min} = 69.0 min, 99% ee).
The reaction can in principle give two regioisomeric cycloadducts **3o** and **3o'**(Figure S12). From the ^{1}H NMR spectrum, it is possible to determine that the only cycloadducts formed are the minor and the major diastereoisomers of the 7-bromo regioisomer **3o**: the signals related to the aromatic protons of the 1,2,3,4-tetrahydroquinoline moiety of the minor diastereoisomer, at 6.93 (br d, J = 8.1 Hz, 1H), 6.76 (dd, J = 8.2, 1.9 Hz, 1H) and 6.56 (d, J = 1.9 Hz, 1H) are indicative of the *ortho*/*meta* relationship and not compatible with the *ortho*/*ortho* one. Also the signals related to the aromatic proton of the 1,2,3,4-tetrahydroquinoline moiety of the major diastereoisomer (H_6) at 6.58 is critical for the attribution of the regiochemistry, since it appear as a doublet of doublets (dd, J = 7.3, 2.0 Hz, 1H) and is thus indicative of a *ortho*/*meta* relationship with the other aromatic protons.

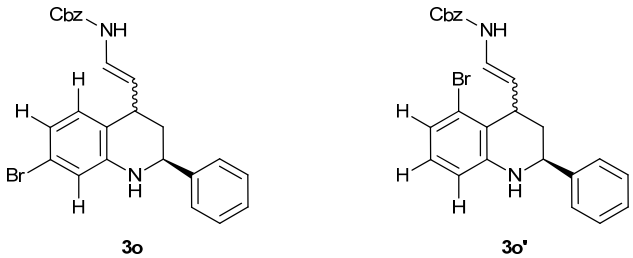


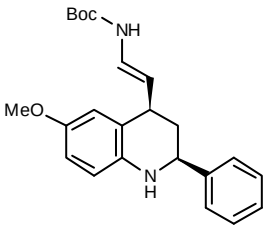
Figure S12: Compounds **3o** and **3o'**.

Minor 2,4-*cis* diastereoisomer:
$[\alpha]_D^{27}$ = -69 ° (c = 0.28, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.41-7.28 (m, 10H), 6.93 (br d, J = 8.1 Hz, 1H) 6.76 (dd, J = 8.2, 1.9 Hz, 1H), 6.67-6.63 (m, 1H), 6.56 (d, J = 1.9 Hz, 1H), 6.42 (br d,

J = 11.0 Hz, 1H), 5.16 (br s, 2H), 4.89 (dd, J = 14.0, 9.7 Hz, 1H), 4.48 (dd, J = 11.5, 2.6 Hz, 1H), 3.61-3.51 (m, 1H), 2.13-2.06 (m, 1H), 1.82 (q, J = 11.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 153.4, 145.9, 143.2, 135.8, 130.1, 128.7, 128.5, 128.3, 128.2, 127.8, 126.4, 125.4, 120.8, 120.0, 116.3, 112.7, 67.15, 56.4, 39.6, 38.7; ESIMS 462, 464 [M + Na^+].
The relative configuration of this diastereoisomer was tentatively assigned as 2,4-*cis* on the basis of the ^{1}H NMR signals relative to the H_3 protons: as in all other cycloadducts **3**, one of these two protons (at 1.82 ppm) gives a pseudo-quartet, with a large J = 11.8 Hz, which can be accounted for two large axial-axial coupling constants with H_2 and H_4 (besides the large geminal coupling with its geminal proton), deriving from a 2,4-*cis* relative configuration.

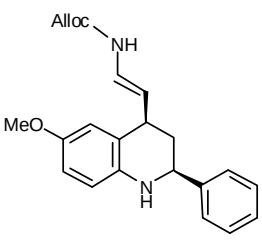
Major 2,4-*trans* diastereoisomer:
$[\alpha]_D^{27}$ = -42° (c = 0.67, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.39-7.24 (m, 10H), 7.21-7.15 (m, 1H), 6.94-6.87 (m, 2H), 6.58 (dd, J = 7.3, 2.0 Hz, 1H), 6.29 (dd, J = 13.9, 11.0 Hz, 1H), 5.9 (br d, J = 10.8 Hz, 1H), 5.07 (br s, 2H), 4.58-4.53 (m, 1H), 4.50 (dd, J = 14.1, 7.6 Hz, 1H), 4.28 (br s, 1H), 3.84-3.75 (m, 1H), 2.40 (ddd, J = 13.5, 6.6, 5.0 Hz, 1H), 2.22 (ddd, J = 13.5, 5.8, 5.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 153.2, 146.3, 144.4, 136.1, 128.5, 128.4, 128.35, 128.3, 128.25, 126.9, 126.4, 126.15, 124.5, 122.1, 122.0, 113.6, 113.45, 67.00, 54.0, 38.2, 37.1. ESIMS 462/464 [M + Na^+].
The relative configuration of this diastereoisomer was tentatively assigned as 2,4-*trans* on the basis of the ^{1}H NMR signals relative to the H_3 protons: in contrast with all other cycloadducts **3**, both signals given by these protons appear as ddd, with a large J = 13.5 Hz geminal coupling constant between themselves, and two J ca = 5.5 Hz with the vicinal H_2 and H_4 protons. This pattern is expected for a 2,4-*trans* configuration, wherein two chair conformations are energetically viable and give rise to undefined equatorial and axial coupling constants between H_3 protons and the vicinal H_2 and H_4.

tert-Butyl ((*E*)-2-((2*S*,4*R*)-6-methoxy-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3p)



Following the general procedure using 0.30 mmol of dienophile **2b**, the title compound was obtained as a white solid in 89% yield, after precipitation. A single diastereoisomer was observed by ^{1}H NMR in the crude mixture. The enantiomeric excess of the product was determined by chiral stationary phase HPLC on the crude mixture (Phenomenex Lux, *n*-hexane/*i*-PrOH 80:20, 0.75 mL/min, λ = 254 nm, t_{maj} = 12.6 min, t_{min} = 19.9 min, 99% ee). $[\alpha]_D^{27}$ = -18 ° (c = 0.360, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.44-7.27 (m, 5H), 6.76-6.62 (m, 3H), 6.49 (d, J = 8.6 Hz, 1H), 6.29 (br d, J = 10.3 Hz, 1H), 4.84 (dd, J = 13.6, 9.4 Hz, 1H), 4.42 (dd, J = 11.3, 2.4 Hz, 1H), 3.78 (br s, 1H), 3.74 (s, 3H), 3.70-3.58 (m, 1H), 2.14-2.05 (m, 1H), 1.86 (q, J = 11.9, 1H), 1.48 (br s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 152.7, 152.1, 144.0, 138.9, 128.5, 127.5, 126.5, 125.3, 125.0, 115.2, 114.6 113.3, 112.1, 80.3, 56.8. 55.9, 40.3, 39.5, 28.2; ESIMS 404 [M + Na^+].

Allyl ((*E*)-2-((2*S*,4*R*)-6-methoxy-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)carbamate (3q)



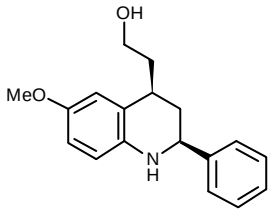
Following the general procedure using 0.18 mmol of dienophile **2c**, the title compound was obtained as a pale yellow solid in 73% yield, after chromatography on silica gel (*n*-hexane/EtOAc 8:2). A single diastereoisomer was observed by ^{1}H NMR in the crude mixture. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 11.0 min, t_{min} = 21.4 min, 99% ee). $[\alpha]_D^{27}$ = -52° (c = 0.66 , CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ

= 7.45-7.27 (m, 5H), 6.76-6.67 (m, 2H), 6.65 (dd, J = 8.6, 3.0 Hz, 1H), 6.50 (d, J = 9.1 Hz, 1H), 6.45 (d, J = 11.2 Hz, 1H), 6.01-5.84 (m, 1H), 5.33 (d, J = 17.0 Hz, 1H), 5.25 (d, J = 10.4 Hz, 1H), 4.92 (dd, J = 14.2, 9.8 Hz, 1H), 4.72-4.52 (m, 2H), 4.42 (dd, J = 11.4, 2.3 Hz, 1H), 3.79 (br s, 1H), 3.73 (s, 3H), 3.70-3.60 (m, 1H), 2.14-2.06 (m, 1H), 1.87 (q, J = 11.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 153.4, 152.2, 144.0, 139.0, 132.3, 128.7, 128.6, 127.6, 126.6, 125.2, 124.8, 118.2, 115.4, 114.6, 113.5, 66.0, 56.8, 55.9, 40.3, 39.5; ESIMS 387 [$M + Na^+$].

Product elaboration

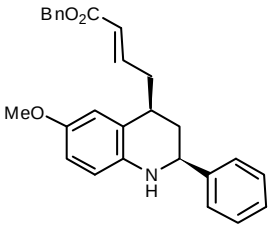
Hydrolysis of the enecarbamate to the aldehyde followed by reduction/olefination:

2-((2*S*,4*R*)-6-Methoxy-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)ethanol (6)



In a round bottomed flask, product **3a** (30 mg, 0.072 mmol) was dissolved in acetone (0.900 mL) and cooled to 0 °C. Aq. 1 M HCl (0.700 mL, 0.700 mmol) was then added in 2 min, while stirring. The resulting solution was allowed to warm to rt, and, after 4 h, quenched with saturated aqueous $NaHCO_3$, and extracted three times with CH_2Cl_2; the organic layers were combined and dried over a short celite pad and the solvents were evaporated. The thus obtained crude aldehyde was dissolved in methanol (1.0 mL) and the mixture was cooled at -35 °C with a liquid nitrogen/acetone bath. Excess $NaBH_4$ (ca 15 mg) was added and the mixture was allowed to warm to -20 °C with stirring. After 15 min, the reaction was monitored by TLC (CH_2Cl_2/EtOAc 94:6). Since the aldehyde was still detected, additional $NaBH_4$ (ca 5 mg) was added. After additional 20 minutes the reaction was complete (TLC), and the mixture was quenched with saturated aqueous NH_4Cl and extracted three times with CH_2Cl_2. The organic layers were combined and dried over a celite pad. After evaporation of the solvents, the crude product was purified by column chromatography (CH_2Cl_2/Et_2O 9:1) to give the title compound as a pale yellow solid in 62% overall yield (over two steps). A single diastereoisomer was observed by ^{1}H NMR in the crude mixture, thus showing that epimerisation did not occur. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 11.4 min, t_{min} = 18.8 min, 96% ee), thus showing that racemisation did not occur to a considerable extent. $[\alpha]_D^{27}$ = -9° (c = 0.77 CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.44-7.28 (m, 5H), 6.82 (d, J = 2.8 Hz, 1H), 6.64 (dd, J = 8.4, 2.8 Hz, 1H), 6.51 (d, J = 8.6 Hz, 1H), 4.32 (dd, J = 11.3, 2.6 Hz, 1H), 3.86-3.69 (m, 6H), 3.29-3.19 (m, 1H), 2.35-2.19 (m, 2H), 1.81-1.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 152.4, 144.4, 139.6, 128.6, 127.6, 126.6, 126.0, 115.6, 113.0, 112.7, 60.5, 57.1, 55.9, 38.5, 37.9, 33.3; ESIMS 306 [M + Na^+].

(*E*)-Benzyl 4-((2*R*,4*S*)-6-methoxy-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)but-2-enoate (7)

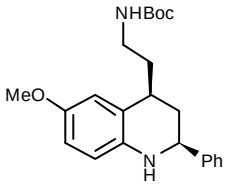


In a round bottomed flask, product **3a** (30 mg, 0.072 mmol) was dissolved in acetone (0.900 mL) and cooled to 0 °C. Aq. 1 M HCl (0.700 mL, 0.700 mmol) was then added in 2 min, while stirring. The resulting solution was allowed to warm to rt, and, after 4 h, quenched with saturated aqueous $NaHCO_3$, and extracted three times with CH_2Cl_2; the organic layers were combined and dried over a short celite pad and the solvents were evaporated. The crude aldehyde was dissolved in CH_2Cl_2 (1.0 mL) and the mixture was cooled at 0 °C with a water/ice bath. Benzyl (triphenyl-phosphoranylidene)-acetate (41 mg, 0.100 mmol) was added under stirring. Progress of the reaction was monitored by TLC (CH_2Cl_2). After 1 h, the reaction was complete, and the mixture was passed over a celite pad. The crude product was purified by column chromatography (CH_2Cl_2/EtOAc 99:1) to give the title compound as a pale yellow solid in 86% overall yield (over two steps). A single diastereoisomer was observed by ^{1}H NMR in the crude mixture, thus showing that epimerisation did not occur, and that olefination proceeded with full *E*-selectivity. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm, t_{maj} = 20.8min, t_{min} = 29.5min, >99% ee), thus showing that racemisation did not occur. $[\alpha]_D^{27}$ = -34° (c = 0.11 CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.49-7.27 (m, 10H), 7.08-6.95 (m, 1H), 6.77 (d, J = 2.7 Hz, 1H), 6.65 (dd, J = 8.5, 2.7 Hz, 1H), 6.53 (d, J = 8.5 Hz, 1H), 5.93 (d, J = 15.8 Hz, 1H), 5.15 (br s, 2H), 4.35 (dd, J = 11.0, 2.7 Hz, 1H), 3.75 (br s, 3H), 3.31-3.19 (m, 1H), 2.94-2.82 (m, 1H), 2.48-2.35 (m, 1H), 2.17-2.08 (m, 1H), 1.72 (q, J = 11.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 165.7, 146.4,

135.0, 127.5, 127.2, 127.1, 126.7, 125.7, 122.1, 112.1, 112.0, 65.1, 55.9, 54.9, 37.5, 36.8, 34.7; ESIMS 436 [M + Na^+].

Reduction of the enecarbamate to a protected amine:

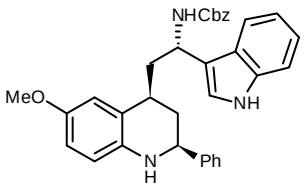
***tert*-Butyl (3-((2*S*,4*S*)-6-methoxy-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)ethyl)carbamate (8)**



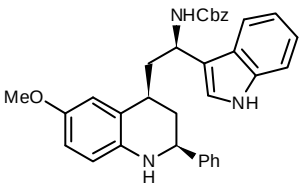
A Schlenk tube was equipped with a magnetic stirring bar and saturated with a nitrogen atmosphere. Ammonium formate (43 mg, 0.66 mmol) was added in one portion, followed by 1 mL of MeOH, activated Pd/C (10 wt %, 12 mg) and finally the product **3p** (21 mg, 0.055 mmol). The mixture was stirred at room temperature for five minutes and then warmed to 35 °C. Progress of the reaction was monitored by TLC (CH_2Cl_2). After 1 h, the reaction was complete and the mixture was passed over a celite pad, diluted with CH_2Cl_2, and washed with water. The organic phase was dried over a short celite pad, the solvents were evaporated and the crude product was purified by column chromatography (CH_2Cl_2) to give the title compound as a colourless oil in 87% overall yield. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Phenomenex Lux, *n*-hexane/*i*-PrOH 80:20, 0.75 mL/min, λ = 254 nm, t_{maj} = 18.2 min, t_{min} = 25.4 min, 94% ee) thus showing that racemisation did not occur to a considerable extent. $[\alpha]_D^{27\,°C}$ =; -13° (c = 0.60, CH_2Cl_2);^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.45-7.27 (m, 5H), 6.78 (d, J = 2.4 Hz, 1H), 6.64 (dd, J = 2.4, 8.6 Hz, 1H), 6.51 (d, J = 8.6 Hz, 1H), 4.54 (br s, 1H), 4.31 (dd, J = 2.7, 11.4 Hz, 1H), 3.76 (s, 3H), 3.27-3.05 (m, 3H), 2.27-2.08 (m, 2H), 1.82-1.60 (m, 2H), 1.43 (br s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 155.9, 152.4, 144.3, 139.6, 128.6, 127.6, 126.6, 125.7, 115.7, 113.1, 112.8, 79.2, 57.1, 55.9, 38.4, 38.2, 35.4, 34.2, 28.4; ESIMS 405 [M + Na^+].

Addition of indole to the enecarbamate (for a tentative assignment of the relative configuration of the adducts, see the section "Determination of the relative and absolute configuration of adducts 3 and 9", on page S16):

Benzyl ((*S*)-1-(1*H*-indol-3-yl)-2-((2*S*,4*R*)-6-methoxy-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)ethyl)carbamate and benzyl ((*R*)-1-(1*H*-indol-3-yl)-2-((2*S*,4*R*)-6-methoxy-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)ethyl)carbamate (9)



from catalyst **4c**



from catalyst *ent*-**4c**

A vial equipped with a magnetic stirring bar was sequentially charged with compound **3a** (29 mg, 0.076 mmol), CH_2Cl_2 (0.50 mL), indole (27 mg, 0.228 mmol, 3 equiv.) and catalyst **4c** (5.7 mg, 10 mol%). The vial was carefully capped, and warmed to 55 °C with stirring. After 16 h, the solution was passed through a short pad of silica, the pad washed with CH_2Cl_2 and Et_2O and the solvent evaporated, leaving a residue which was analysed by ^{1}H NMR showing a 94:6 diasteremoeric ratio, favouring the S configured diastereoisomer at the α-indol-3-yl chiral centre. Chromatographic purification on silica gel (CH_2Cl_2/Et_2O from 100:0 to 95:5) gave the title compound as a diastereomeric mixture and as a white solid in 91% yield. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chralpak ADH, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm; major diastereoisomer: t_{maj} = 46.8 min, t_{min} = 75.9 min, >99% ee), thus showing that racemisation did not occur.

The same reaction, performed with *ent*-**4c** as the catalyst, afforded the title compound in 88% yield and as a diastereomeric mixture. The diastereomeric ratio, determined by ^{1}H NMR on the crude mixture, was found to be 75:25, favouring the R configured diastereoisomer at the α-indol-3-yl chiral centre, in contrast with the reaction performed with **4c**. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chralpak ADH, *n*-hexane/*i*-PrOH 70:30,

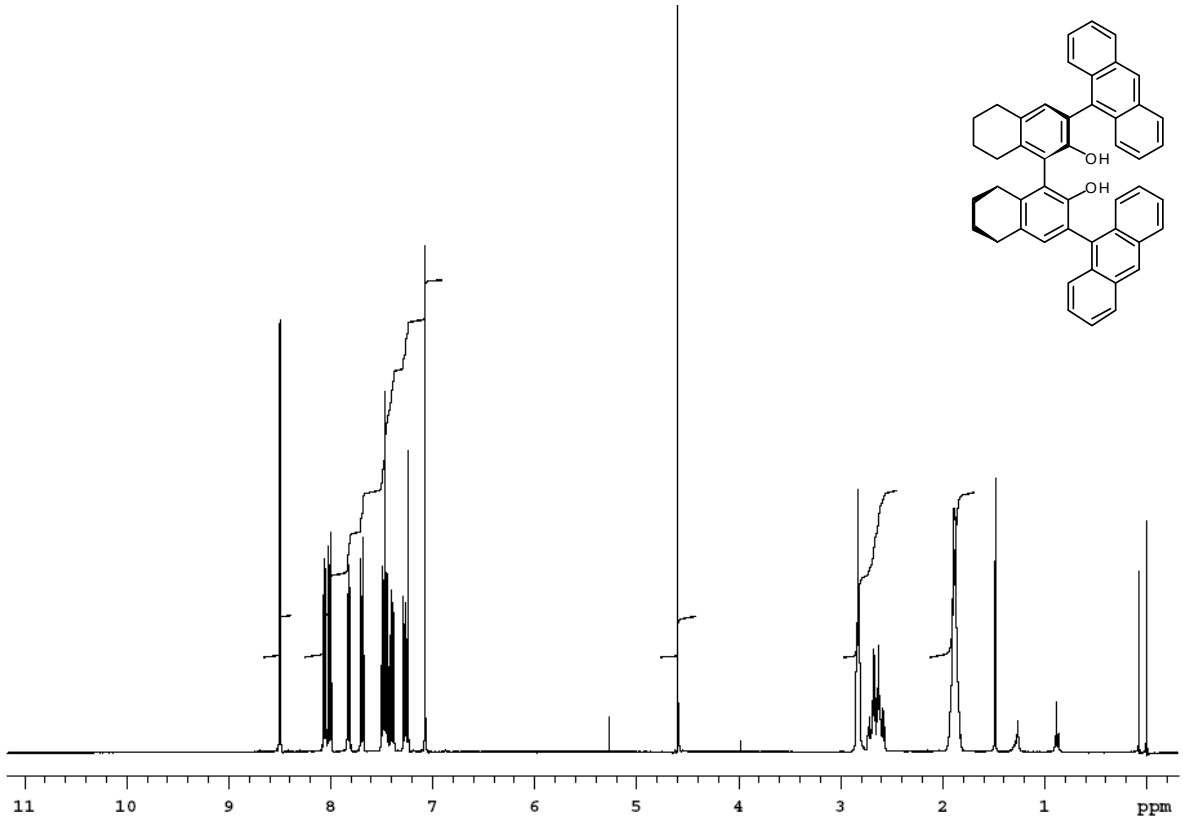
0.75 mL/min, λ = 254 nm; minor diastereoisomer: t_{maj} = 46.8 min, t_{min} = 75.9 min, 90% ee, major diastereoisomer: t_{maj} = 66.3 min, t_{min} = 35.2 min, 98% ee), thus showing that racemisation did not occur.

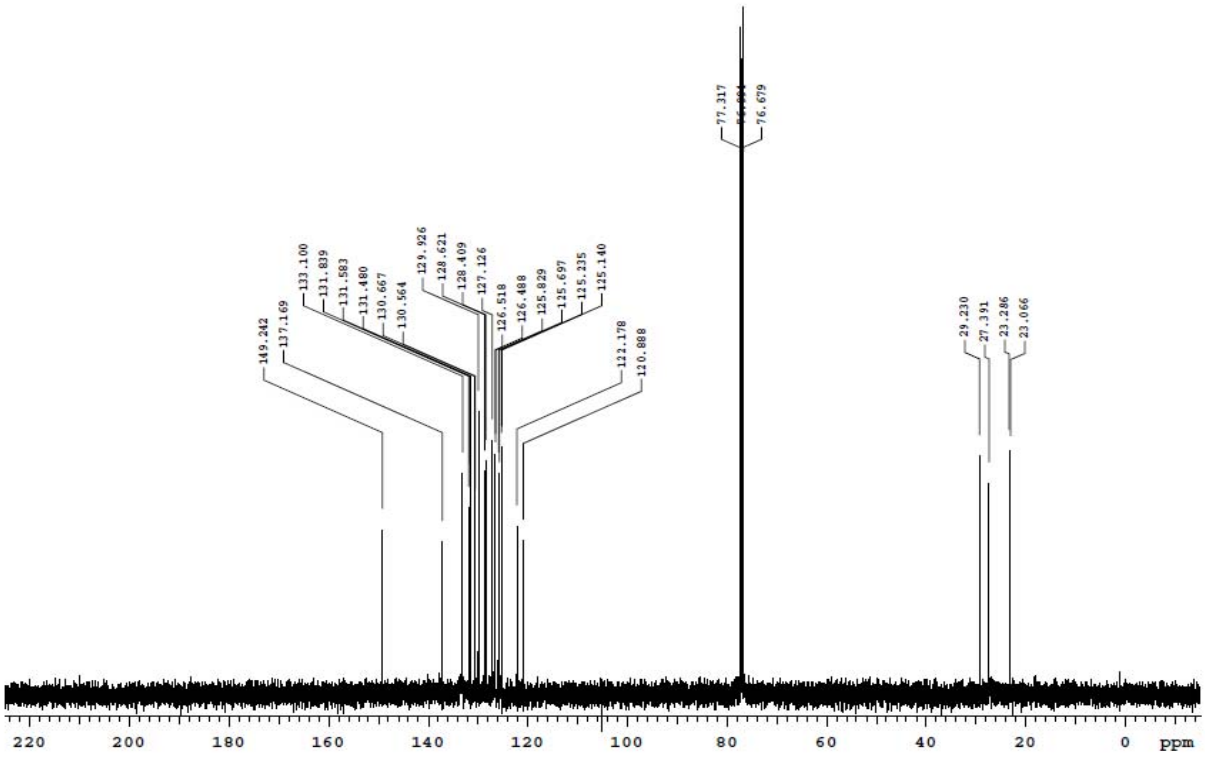
The same title compound was also obtained in a one-pot procedure: to the catalytic reaction for obtaining **3a** (after 18 h), indole (88 mg, 0.75 mmol) and catalyst **4c** (11.3 mg, 10 mol%) were sequentially added, and the resulting mixture was heated at 80 °C for 4 h with stirring. The mixture was then filtered on a short plug of silica, the plug washed several times with Et_2O, and the solvents evaporated, leaving a residue which was analysed by ^{1}H NMR showing a 94:6 diastereomeric ratio, presumably at the α-NHCbz chiral centre. Chromatographic purification on silica gel (CH_2Cl_2/Et_2O from 100:0 to 95:5) gave the title compound as a diastereomeric mixture and as a pale yellow solid in 61% yield. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chralpak ADH, *n*-hexane/*i*-PrOH 70:30, 0.75 mL/min, λ = 254 nm; major diastereoisomer: t_{maj} = 46.8 min, t_{min} = 75.9 min, 99% ee).

Spectral data for the major diastereoisomer (S-configured at the α-indol-3-yl chiral centre) deriving from the reaction with catalyst **4c**:
^{1}H NMR ($CDCl_3$, 600 MHz) δ = 8.11 (br s, 1H), 7.61 (br d, J = 8.3 Hz, 1H), 7.44-7.39 (m, 2H), 7.38-7.26 (m, 9H), 7.18 (t, J = 7.7 Hz, 1H), 7.08 (br t, J = 7.7 Hz, 1H), 7.00 (br s, 1H), 6.86 (br s, 1H), 6.65 (dd, J = 8.6, 2.6 Hz, 1H), 6.54 (br d, J = 8.6 Hz, 1H), 5.31 (br t, J = 8.6 Hz, 1H), 5.15 (d, J = 12.2 Hz, 1H), 5.13 (d, J = 12.3 Hz, 1H), 5.00 (d, J = 9.1 Hz, 1H), 4.32 (br d, J = 11.1 Hz, 1H), 3.75 (s, 3H), 3.31-3.21 (m, 1H), 2.66-2.53 (m, 2H), 2.10-2.01 (m, 1H), 1.79 (q, J = 10.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 156.1, 152.3, 144.3, 137.9, 136.6, 136.5, 128.6, 128.5, 128.1, 128.0, 127.5, 126.7, 125.8, 122.4, 120.9, 119.8, 119.4, 118.1, 115.6, 113.5, 112.5, 111.3, 66.7, 57.0, 55.9, 46.0, 42.2, 38.6, 33.4; ESIMS 554 [M + Na^+].

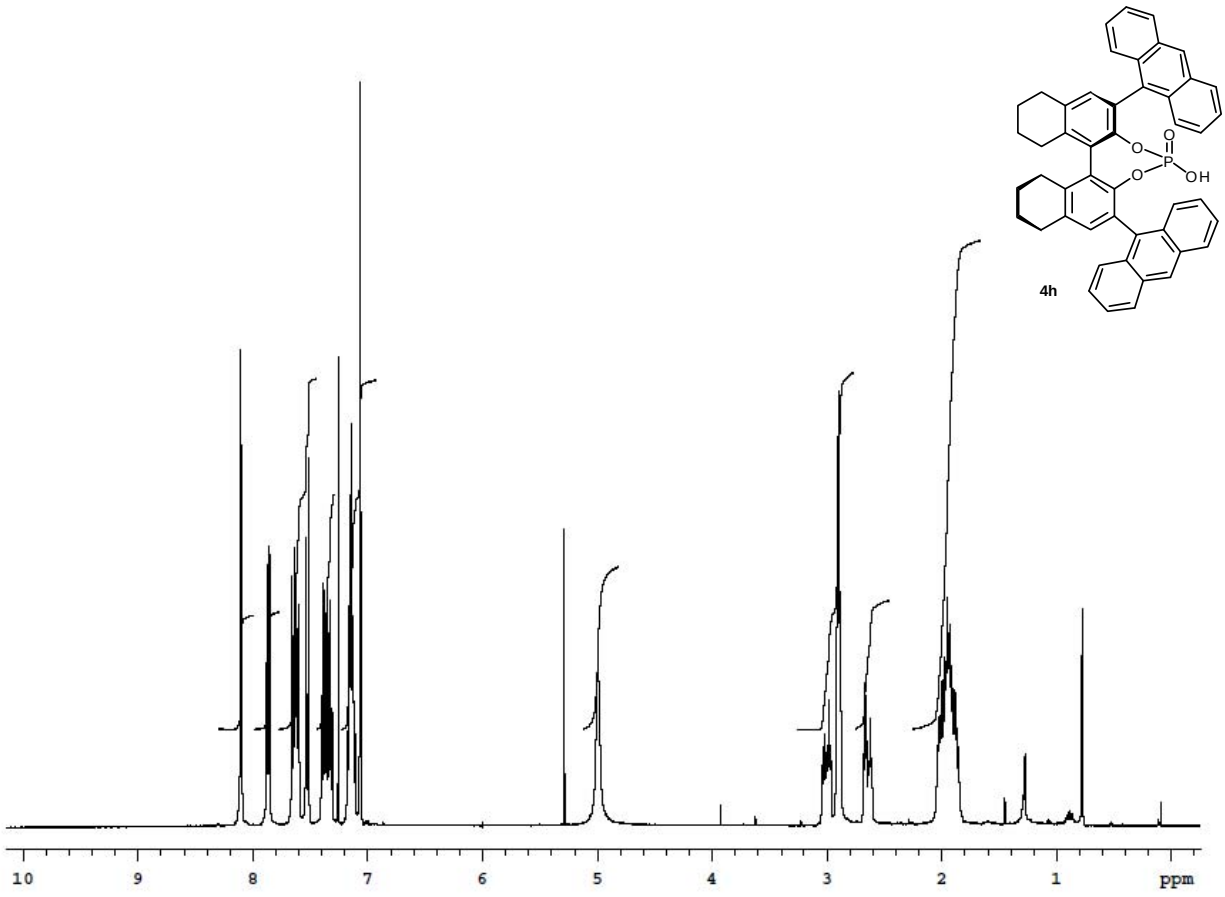
Spectral data for the diastereomeric mixture (favouring the R-configured product at the α-indol-3-yl chiral centre) deriving from the reaction with catalyst *ent*-**4c**:
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.20 (br s, $1H_{maj}$), 8.11 (br s, $1H_{min}$), 7.73 (br d, J = 8.3 Hz, $1H_{maj}$), 7.61 (br d, J = 8.61 Hz, $1H_{min}$), 7.40-7.00 (m, $16H_{maj}$, $16H_{min}$), 6.86 (br s, $1H_{min}$), 6.76 (br s, $1H_{maj}$), 6.65 (dd, J = 8.4, 2.6 Hz, $1H_{min}$), 6.61 (dd, J = 8.6, 2.9 Hz, $1H_{maj}$), 6.54 (br d, J = 8.7 Hz, $1H_{min}$), 6.49 (br d, J = 8.5 Hz, $1H_{maj}$), 5.38-5.28 (m, $1H_{min}$), 5.23-4.98 (m, $3H_{maj}$, $3H_{min}$), 4.32 (br d, J = 10.8 Hz, $1H_{min}$), 4.10 (dd, J = 11.1, 2.0 Hz, $1H_{maj}$), 3.75 (s, $3H_{min}$), 3.72 (s, $3H_{maj}$), 3.32-3.20 (m, $1H_{min}$), 2.97-2.83 (m, $1H_{maj}$), 2.86-2.70 (m, $1H_{maj}$), 2.67-2.53 (m, $2H_{min}$), 2.35-2.23 (m, $1H_{maj}$), 2.19-2.03 (m, $1H_{maj}$, $1H_{min}$), 1.97-1.74 (m, $1H_{maj}$, $1H_{min}$). ^{13}C NMR ($CDCl_3$, 100 MHz) [signals of both diastereoisomers] δ = 155.1, 154.5, 151.3, 143.0, 138.4, 135.6, 135.5, 127.6, 127.5, 127.4, 127.2, 127.1, 127.0, 126.9, 126.6, 126.5, 125.8, 125.7, 125.3, 124.8, 124.7, 124.5, 121.5, 121.4, 121.1, 119.0, 118.8, 118.4, 118.2, 117.7, 114.8, 114.6, 112.4, 112.3, 111.5, 111.4, 110.5, 110.3, 65.7, 65.6, 56.0, 55.9, 54.9, 54.8, 46.0, 45.0, 41.1, 40.4, 37.6, 37.3, 33.0, 32.4. ESIMS 554 [M + Na^+].

Copies of the ^{1}H and ^{13}C NMR spectra of synthesized compounds[29]





[29] Several of the ^{1}H NMR spectra of compounds **3** and **9** show some minor, broad signals, besides the major described ones, due to the presence of a small (<10%) amount of a rotamer at the carbamate moiety (see the section "Determination of Relative and Absolute Configuration of Compounds 3 and 9", page S11).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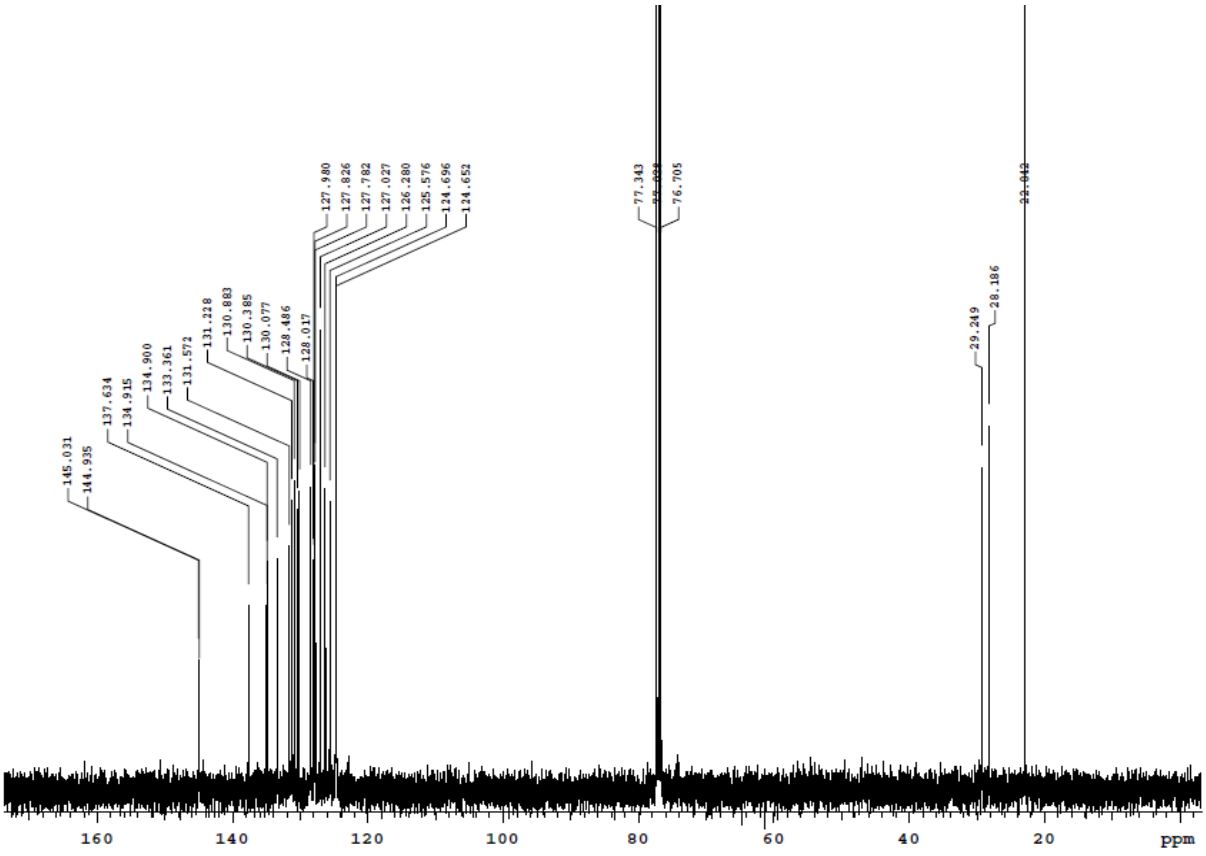
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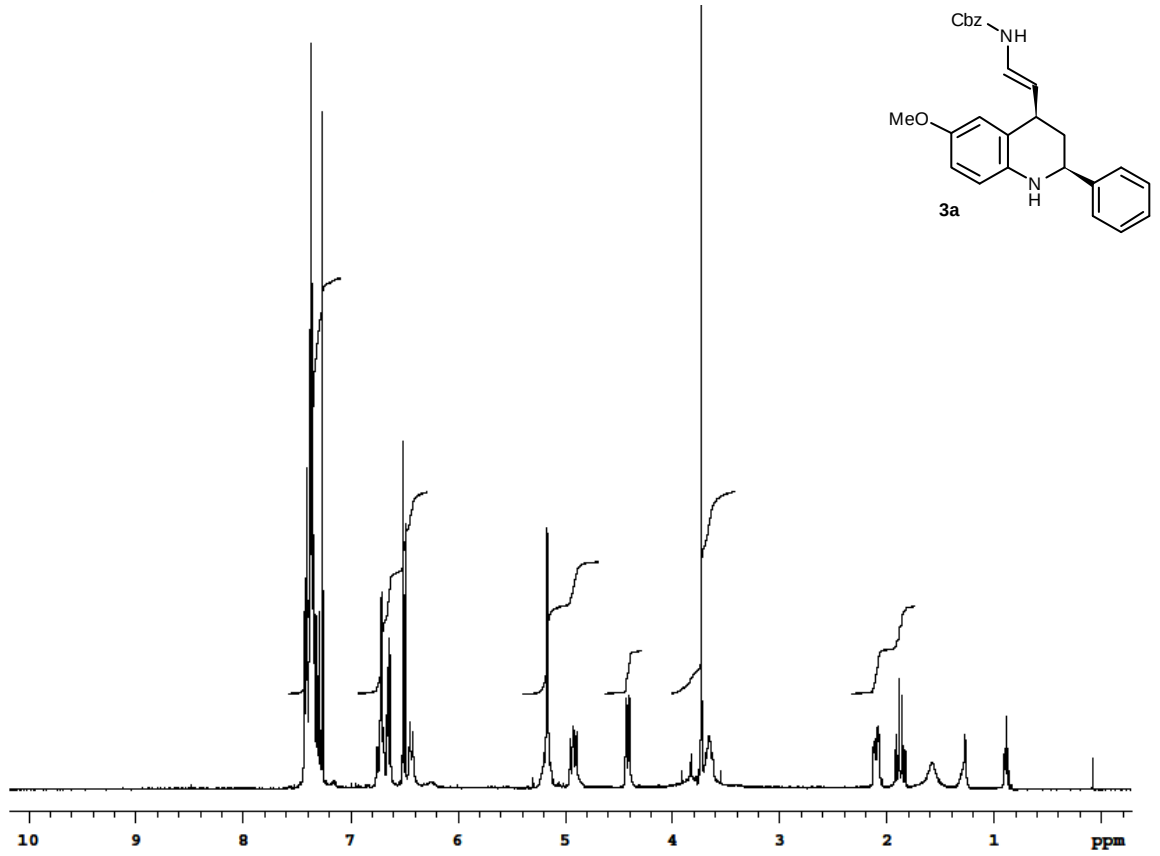
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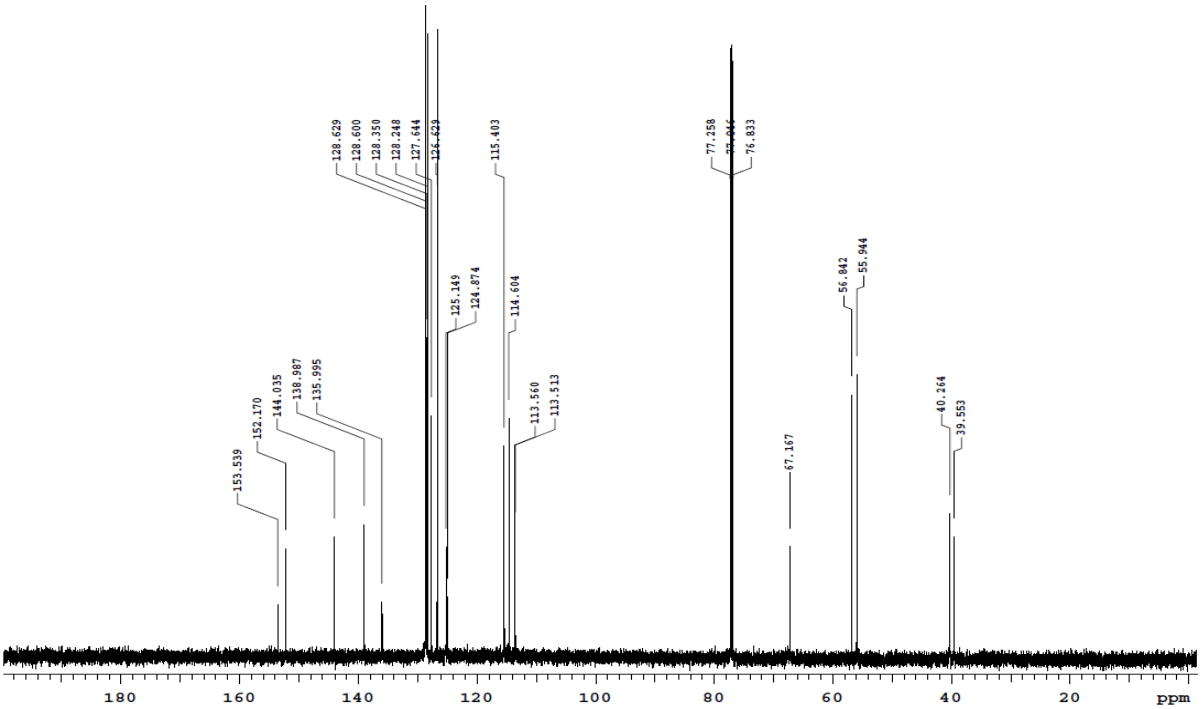
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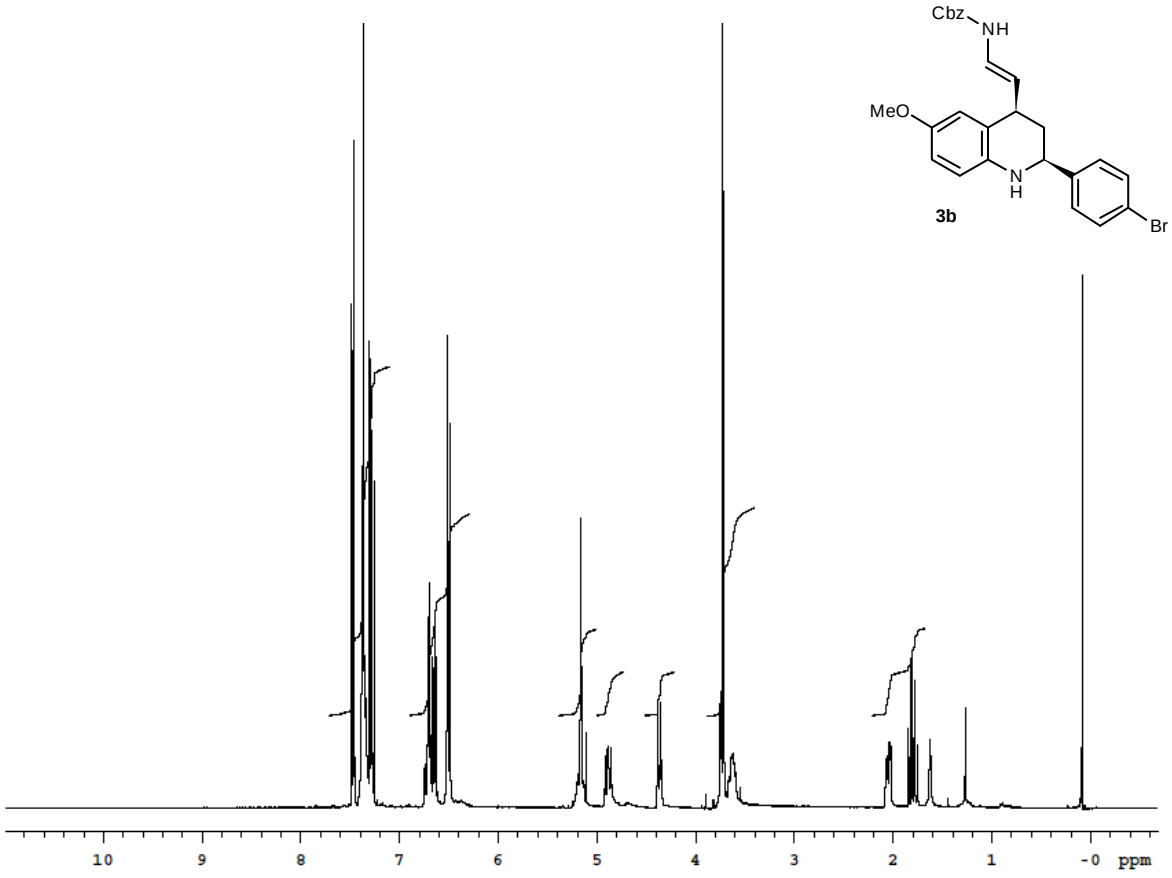
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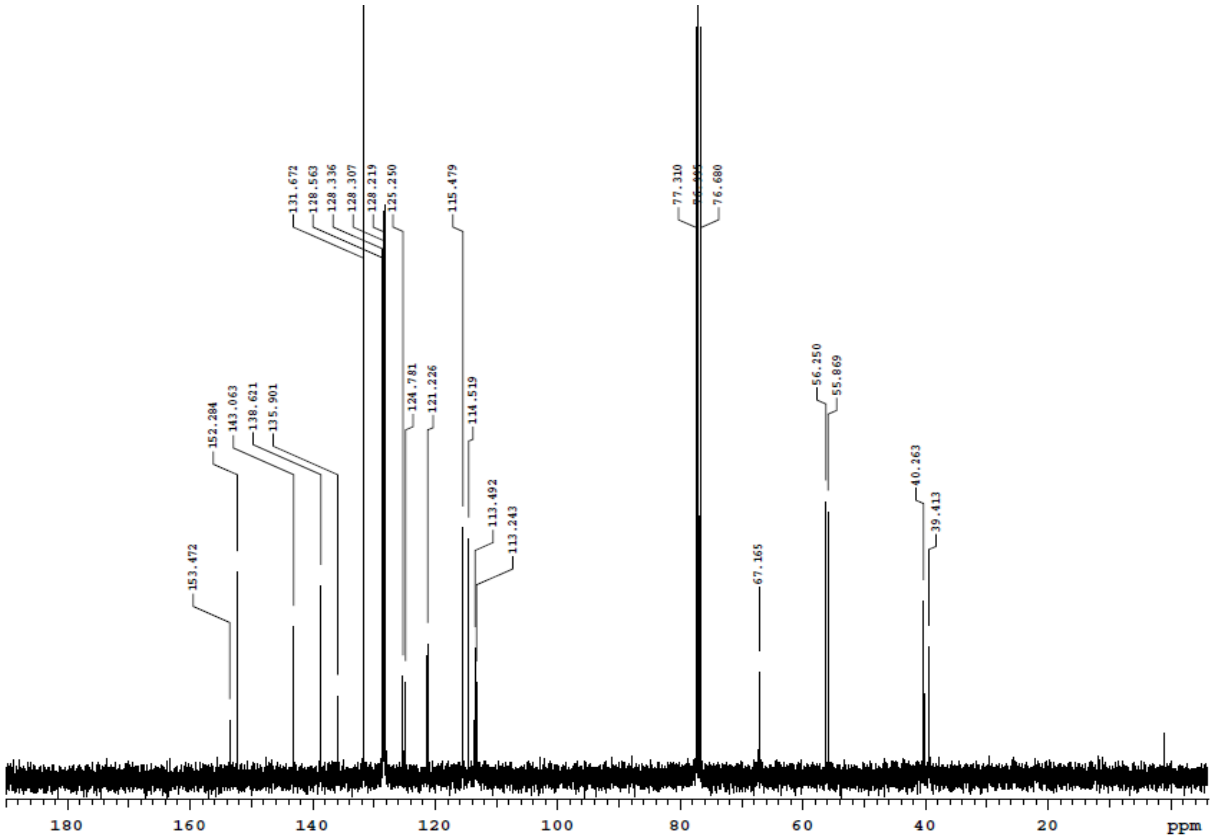
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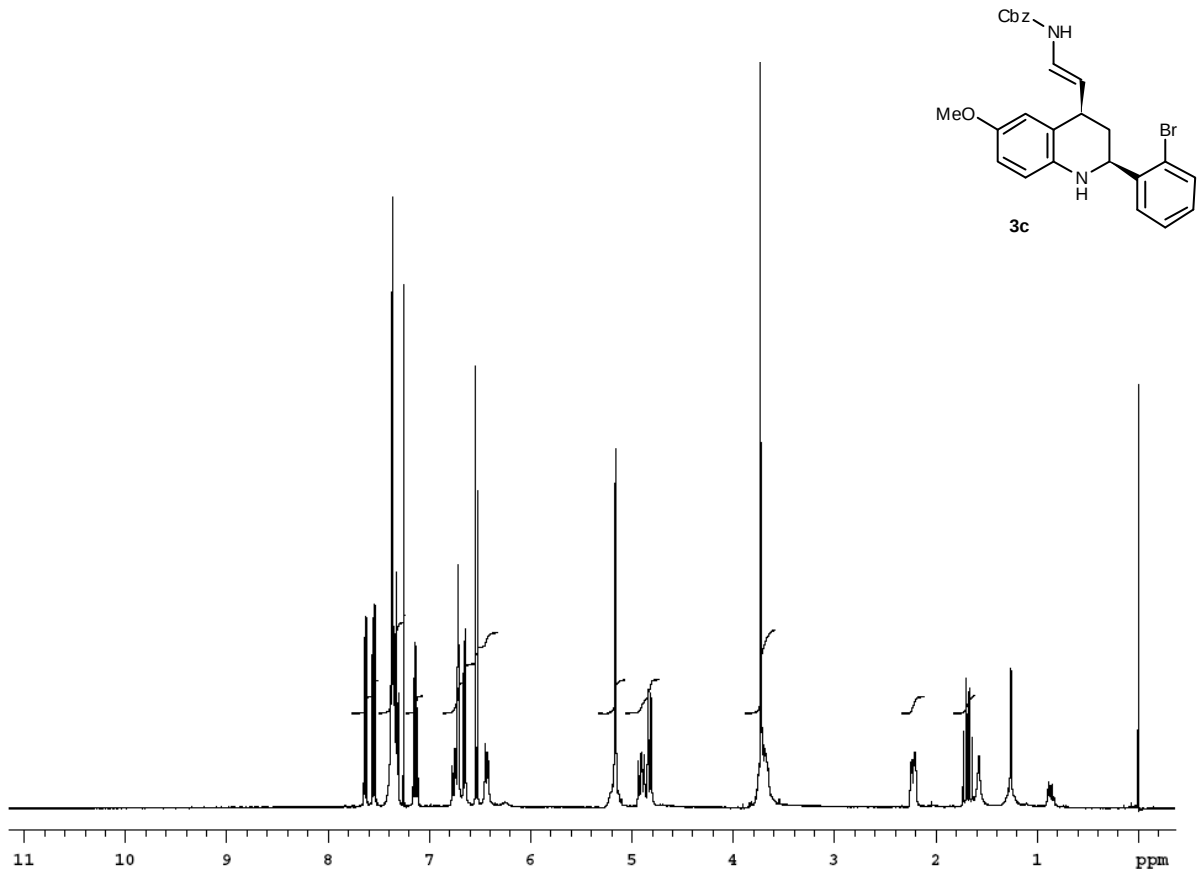

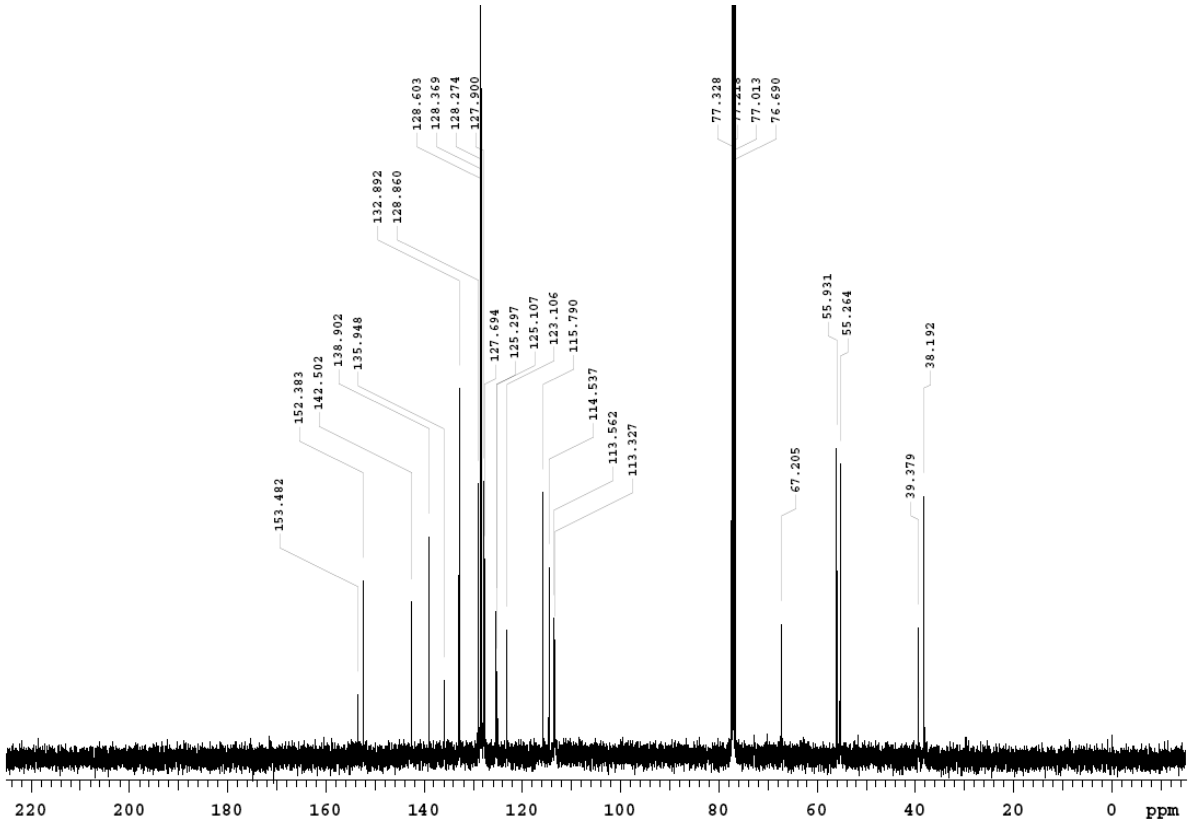

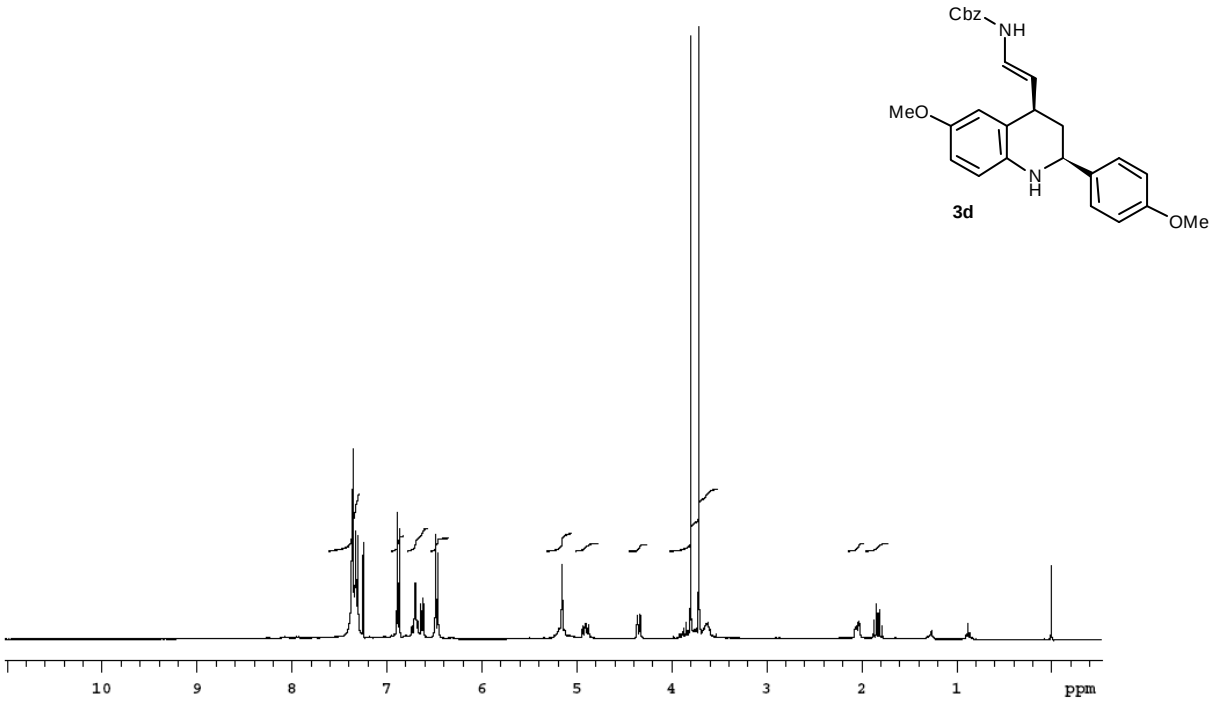
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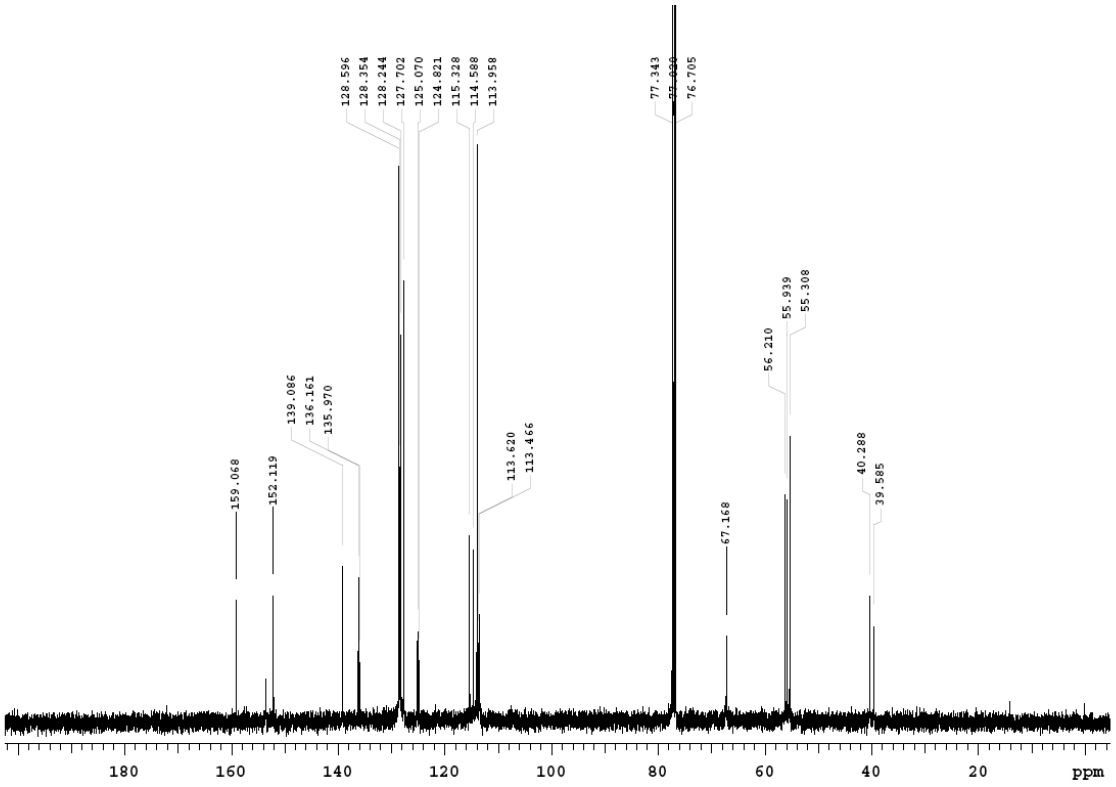
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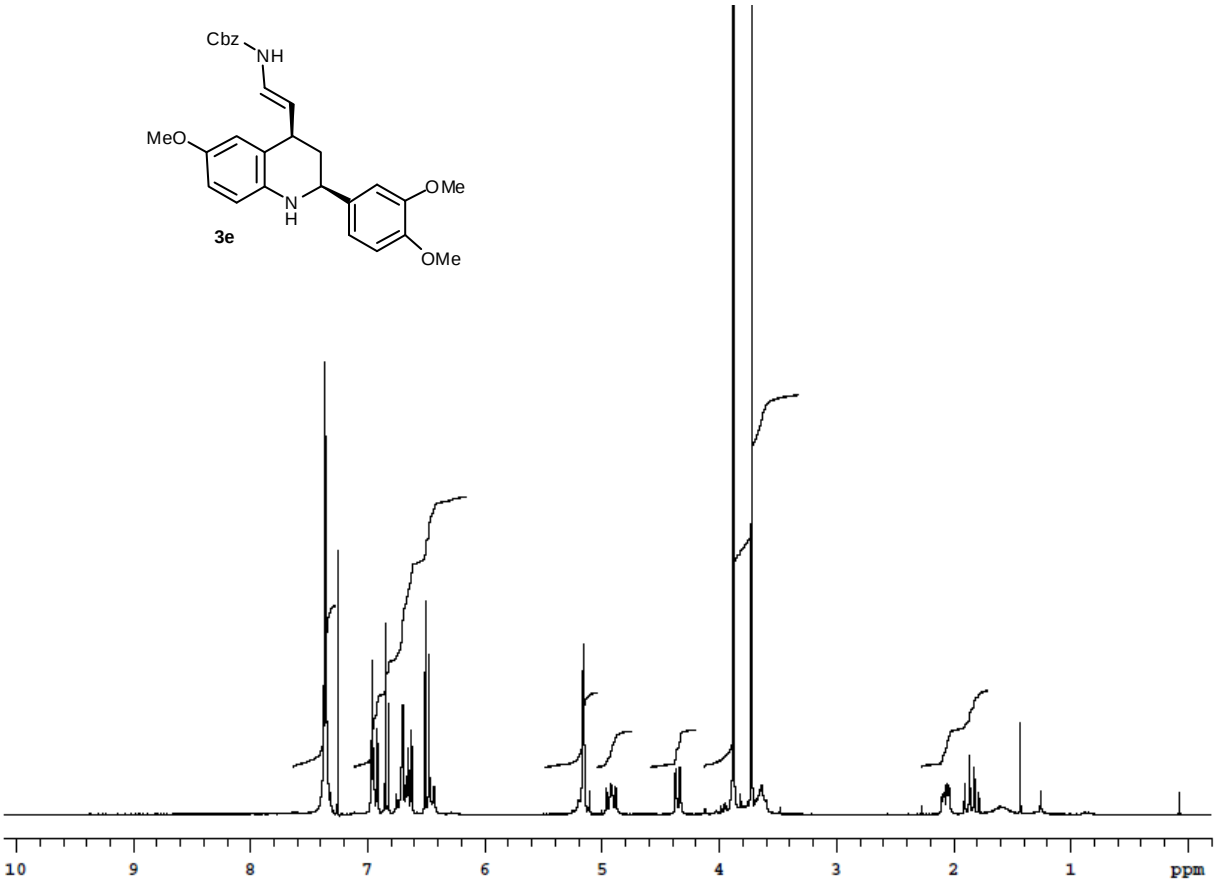
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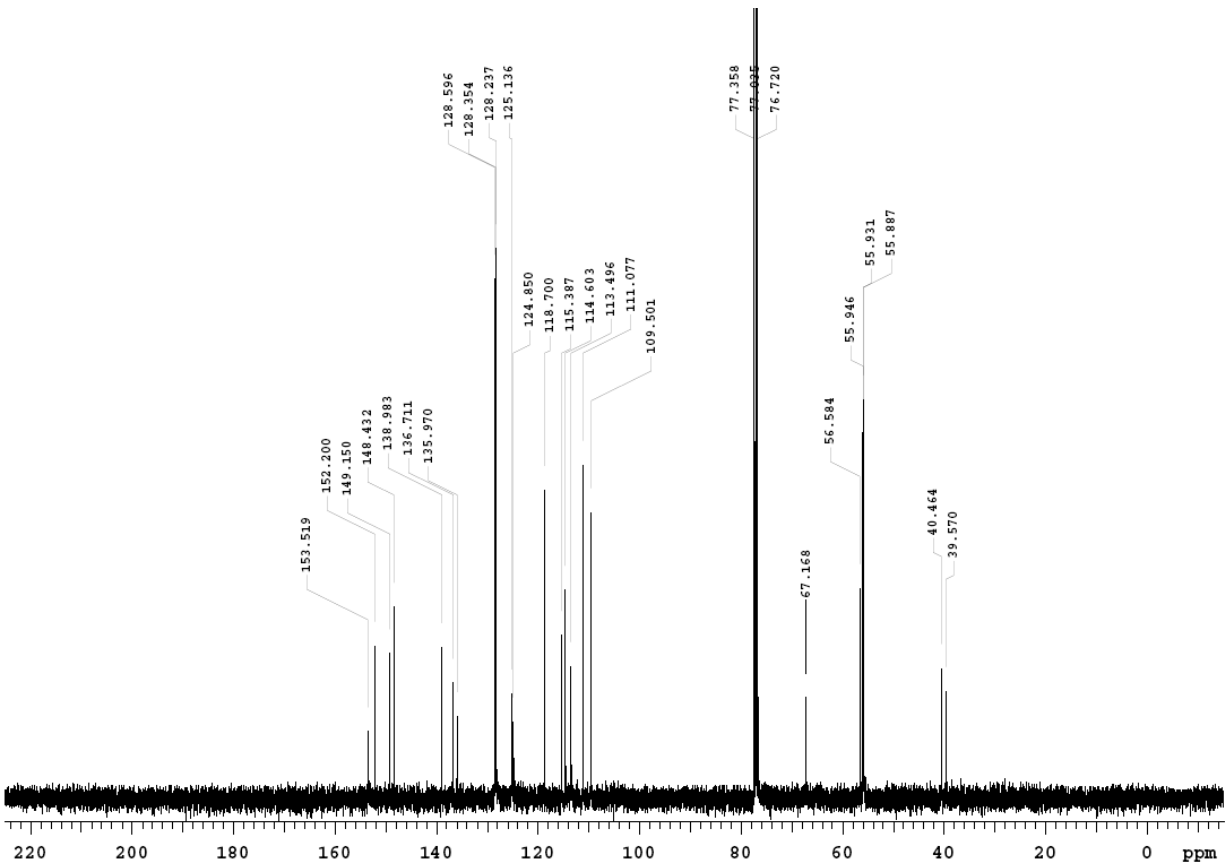
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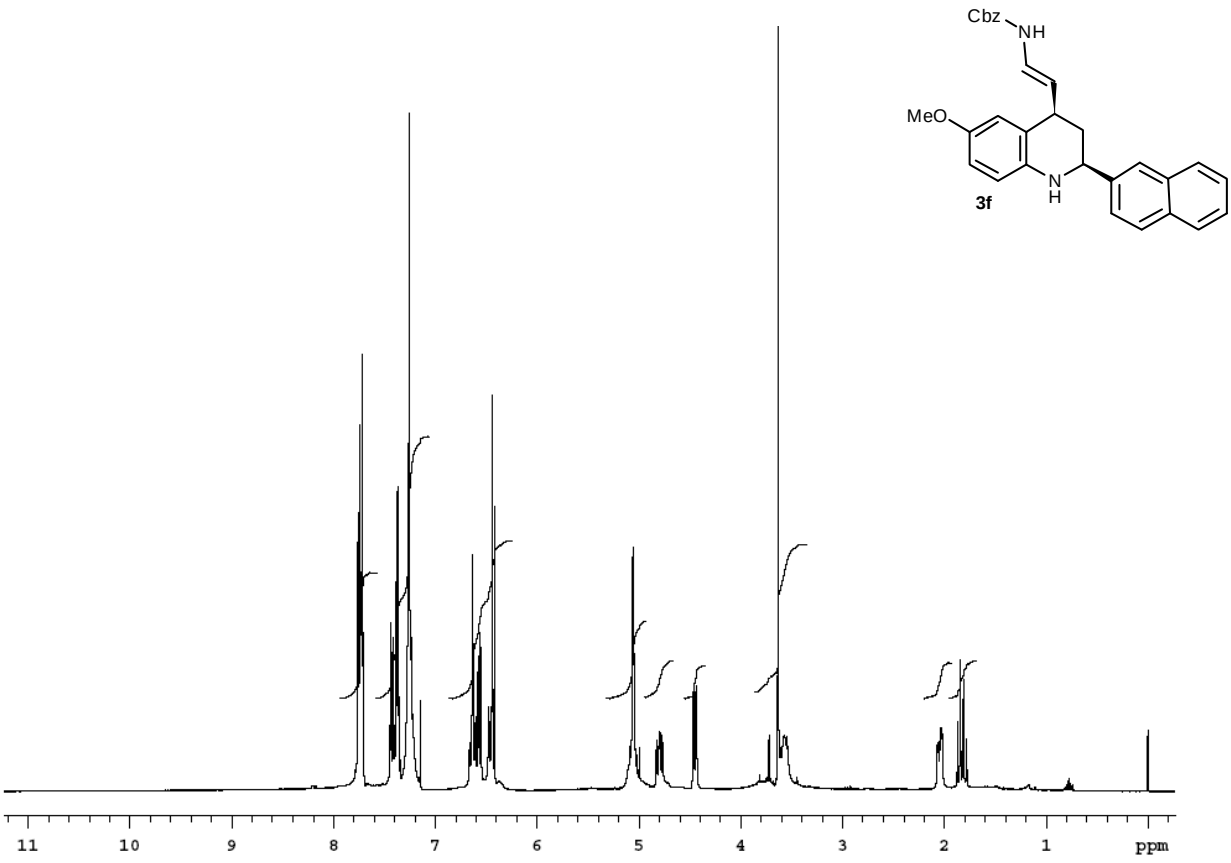
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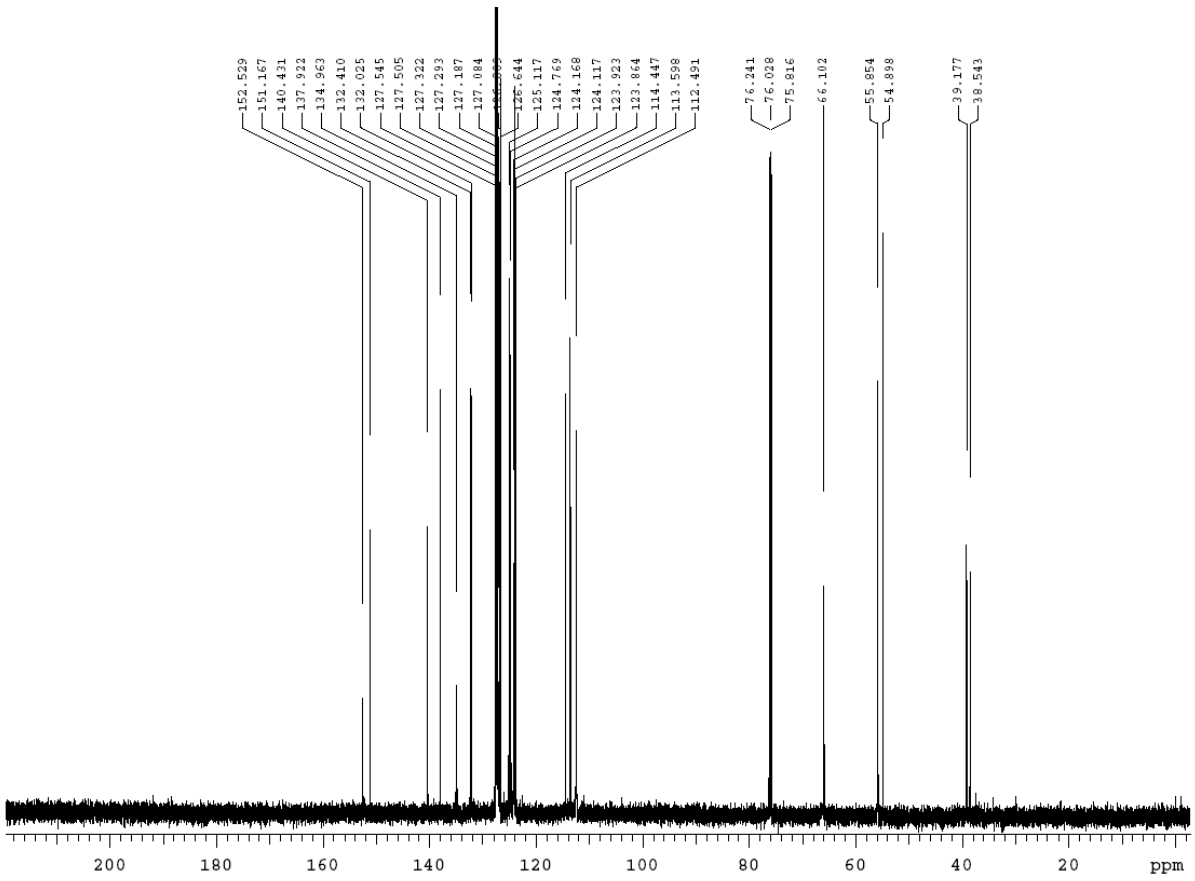
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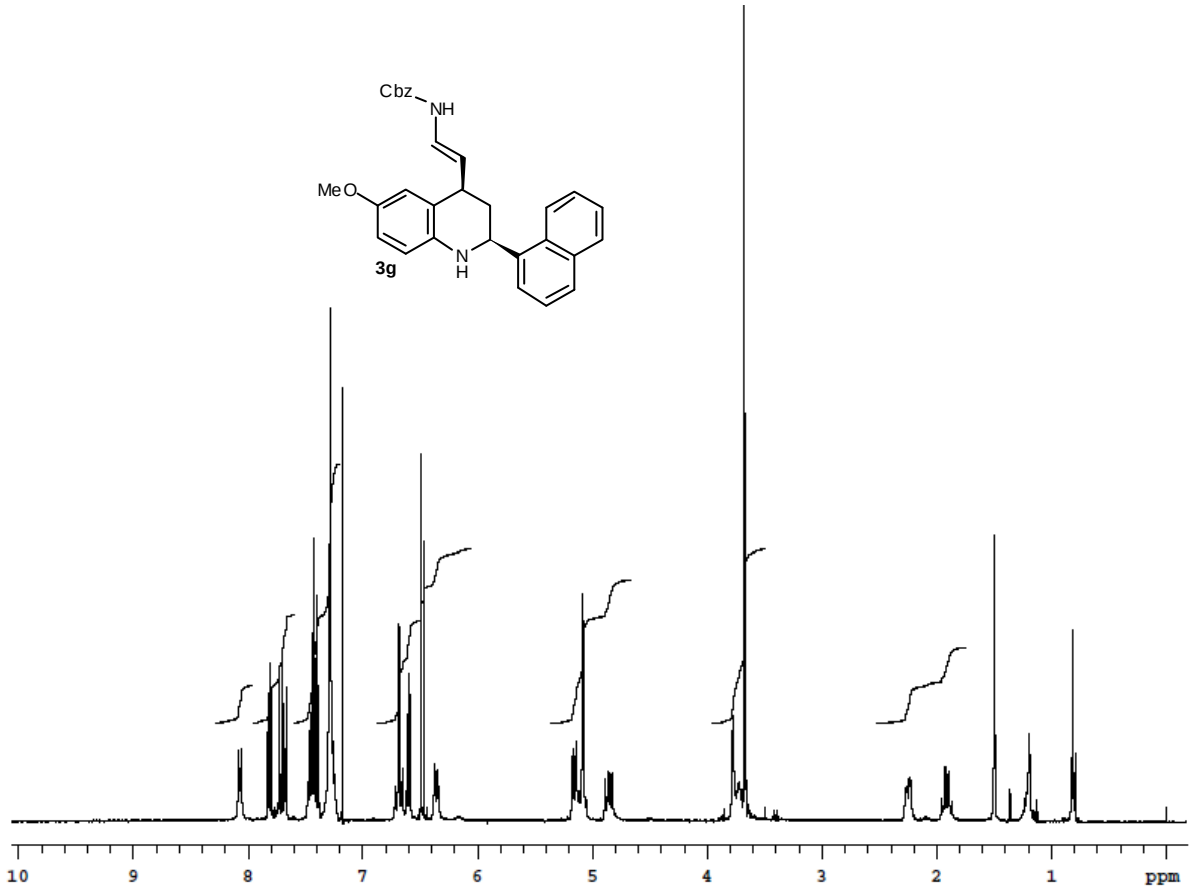
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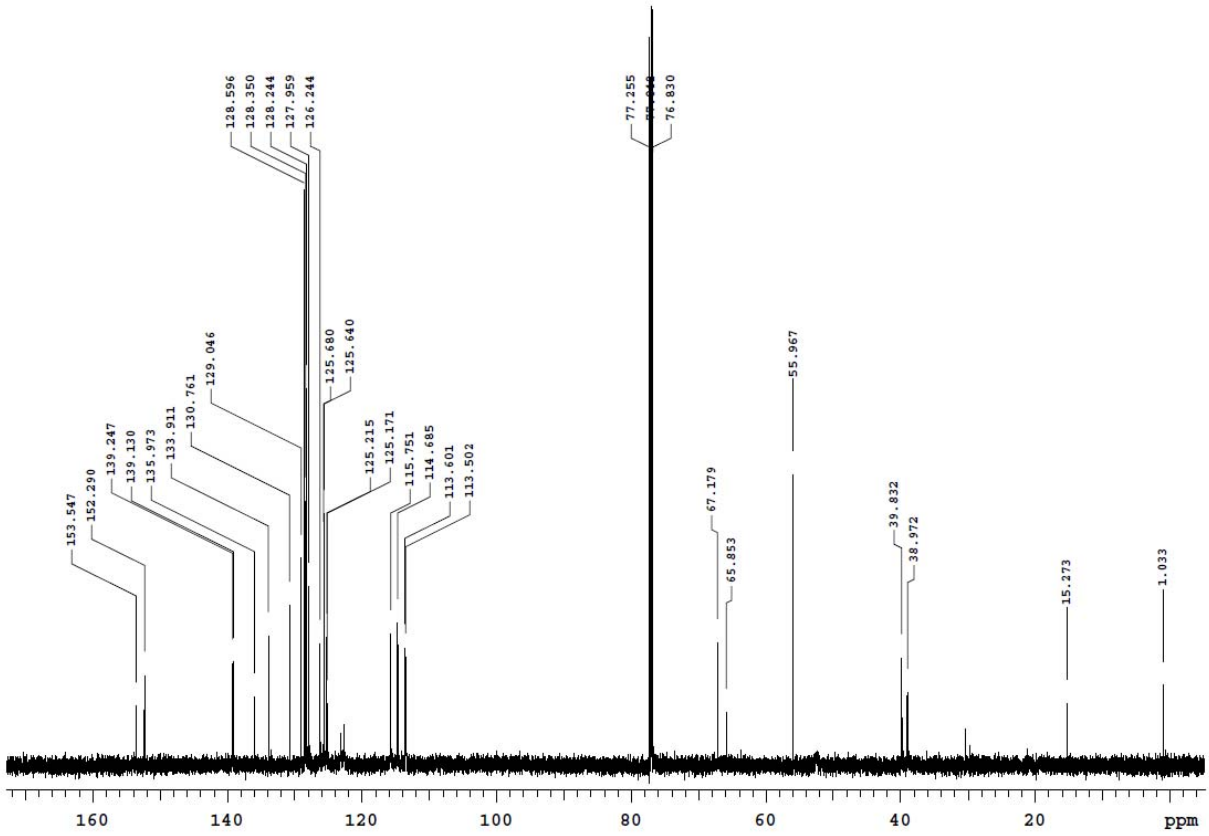
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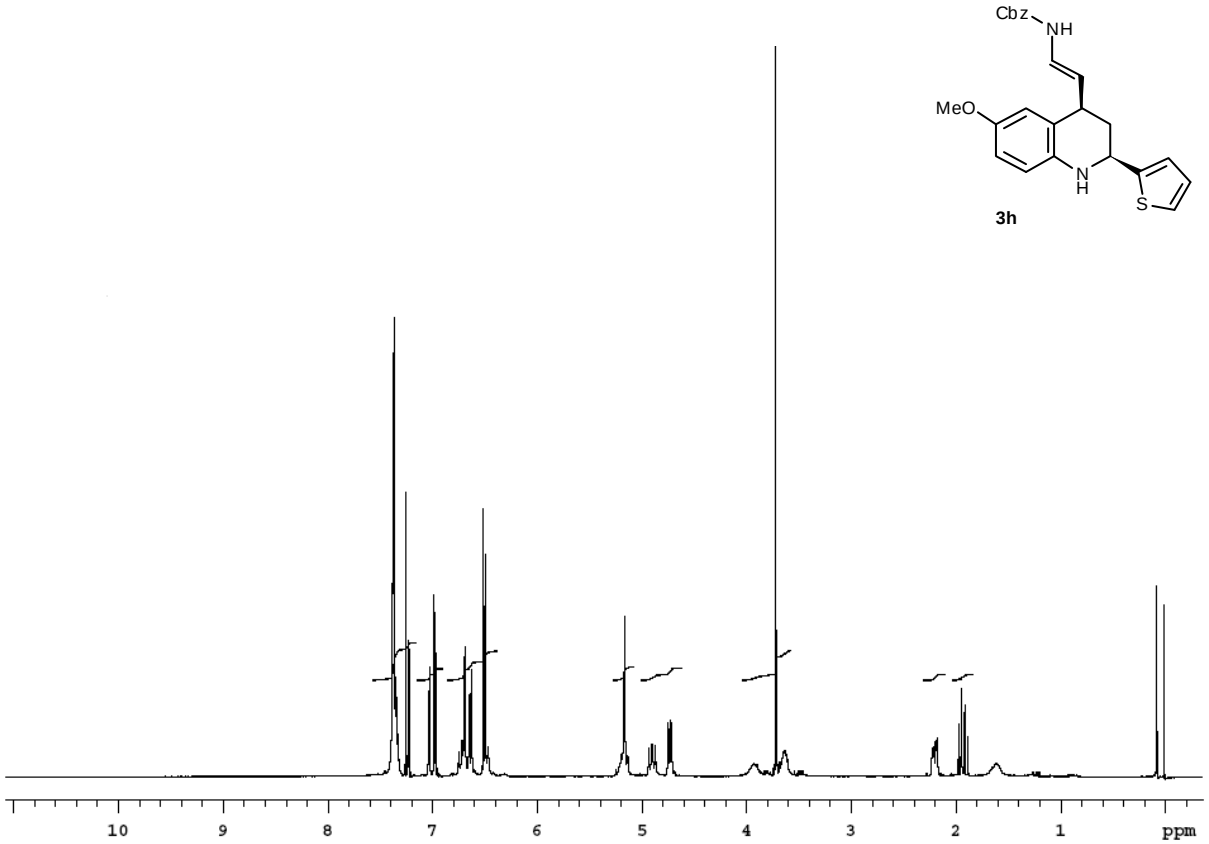
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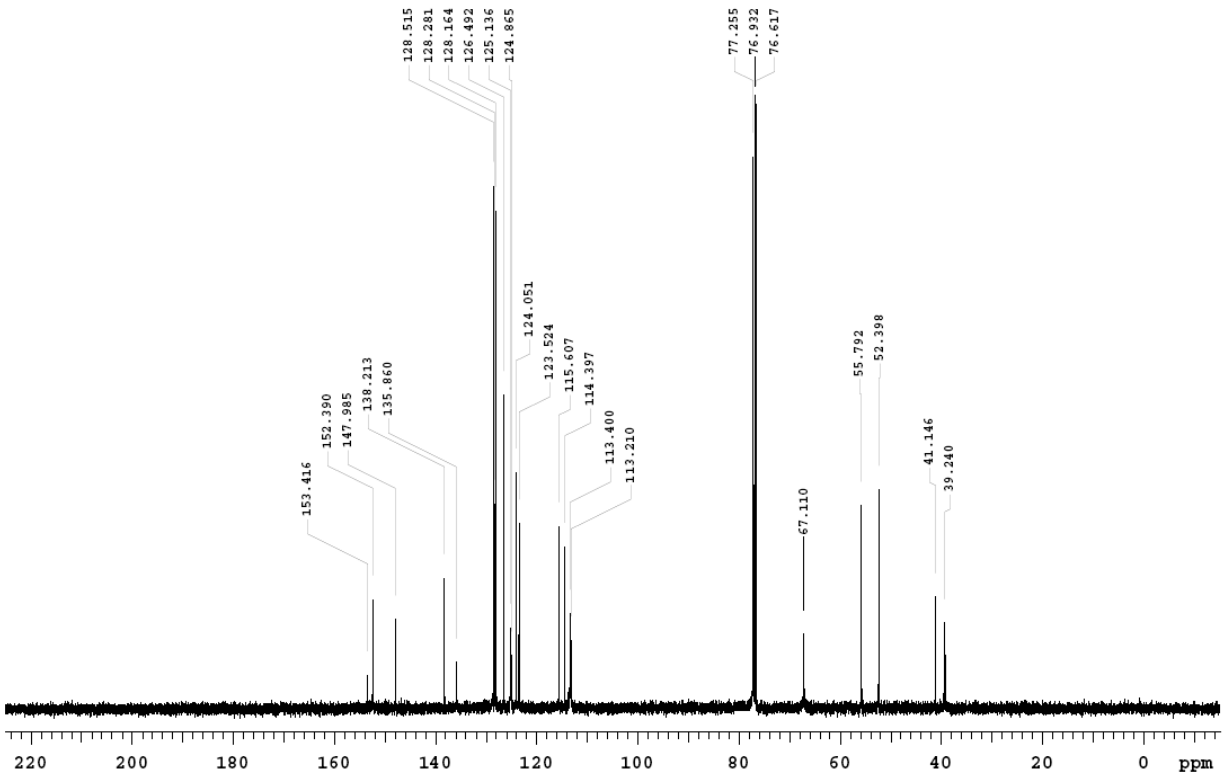
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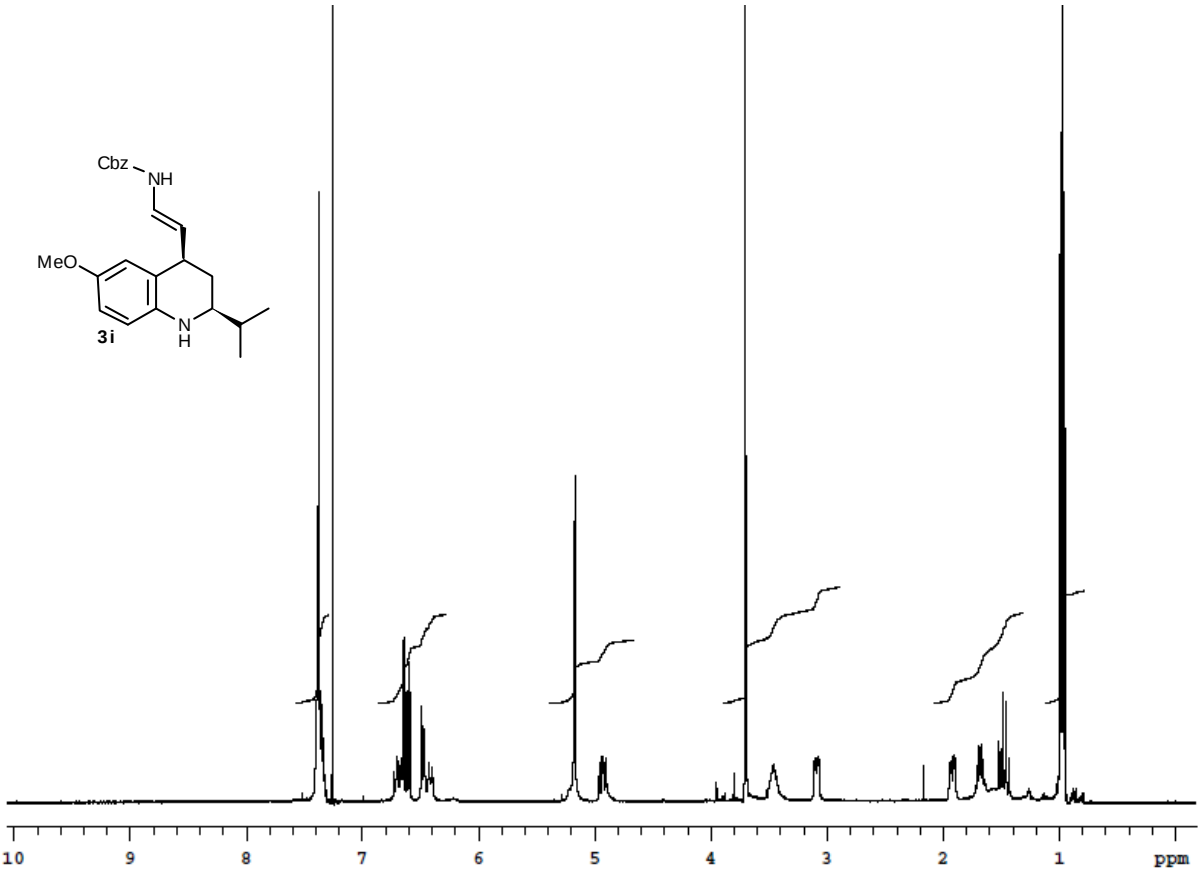
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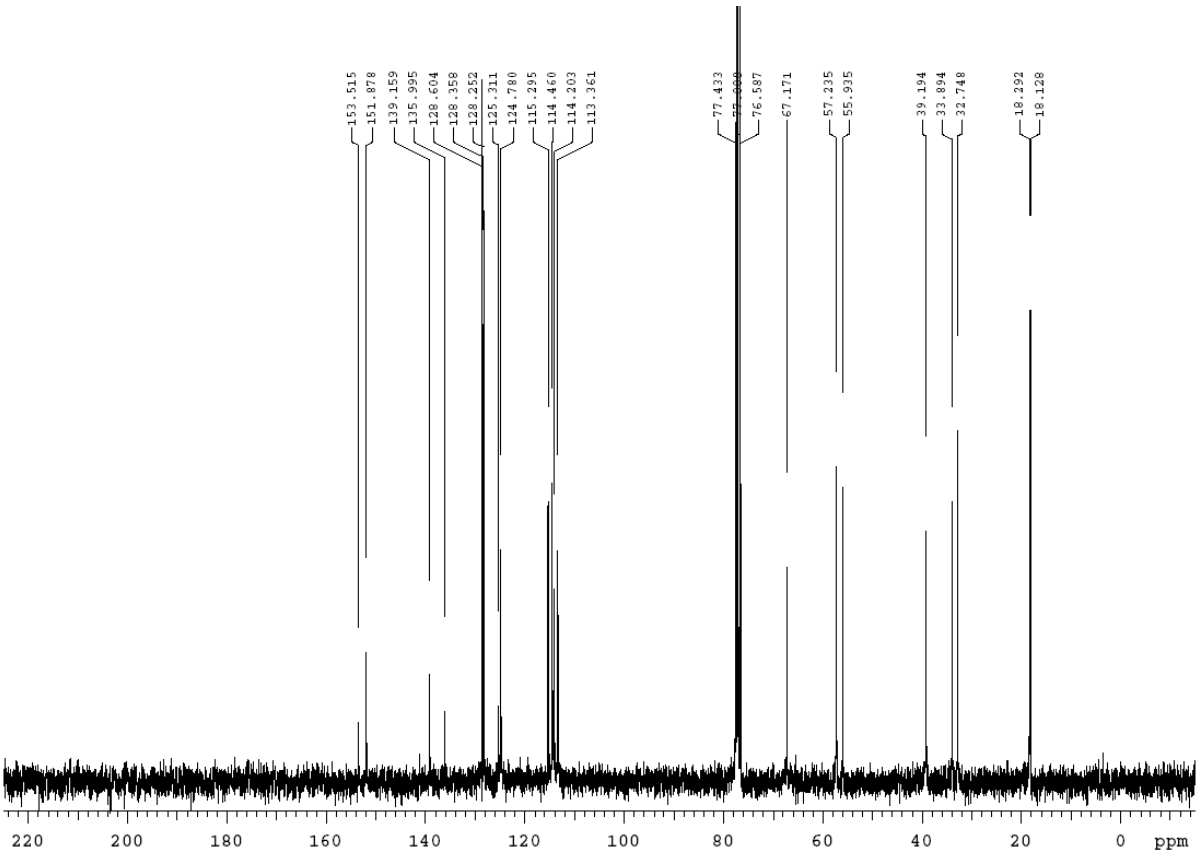
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114.460
114.203
113.361
77.433
76.587
67.171
57.235
55.935
39.194
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18.128
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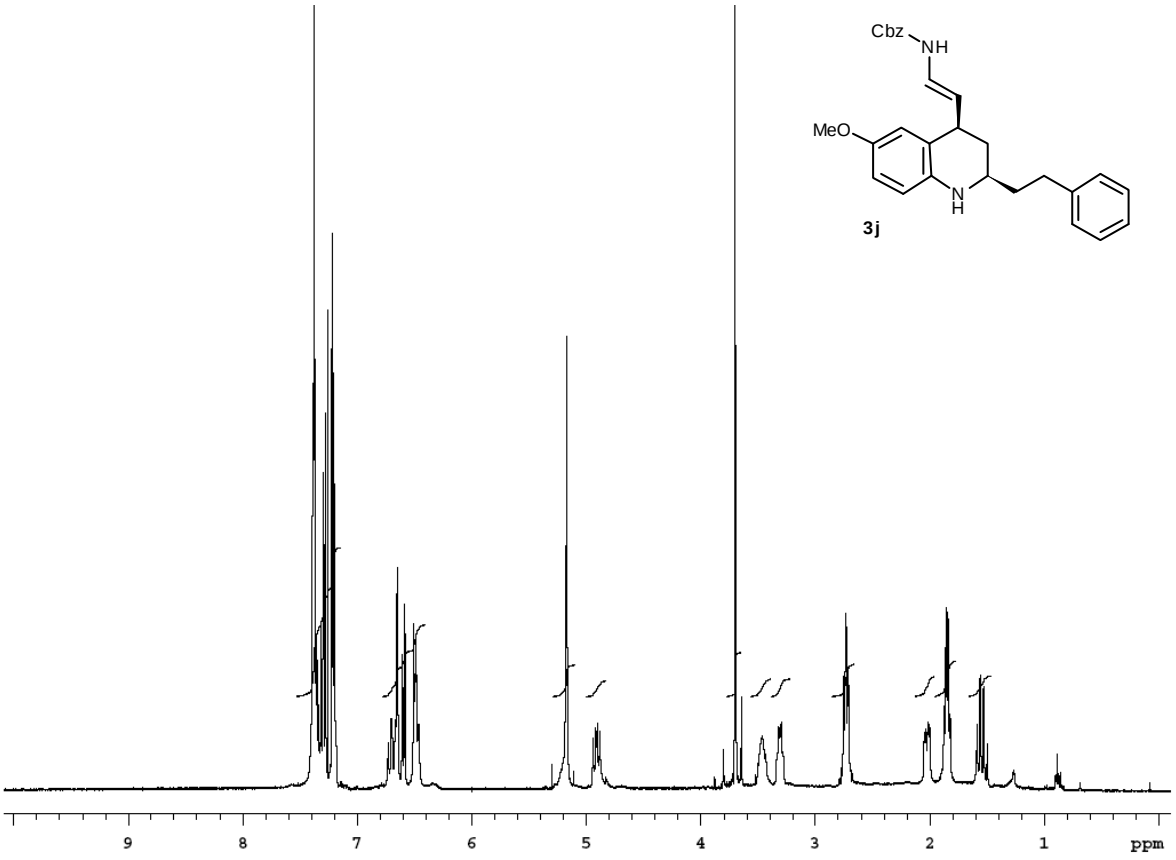

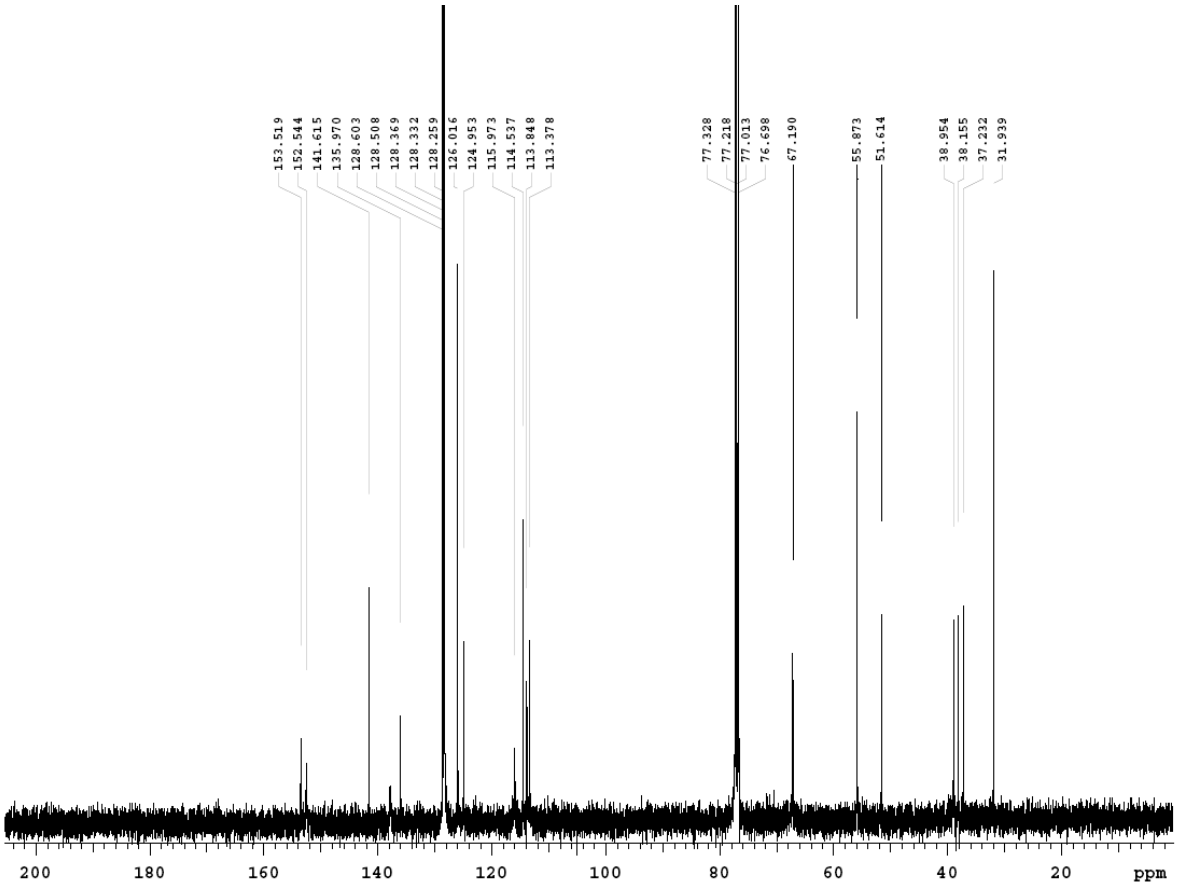

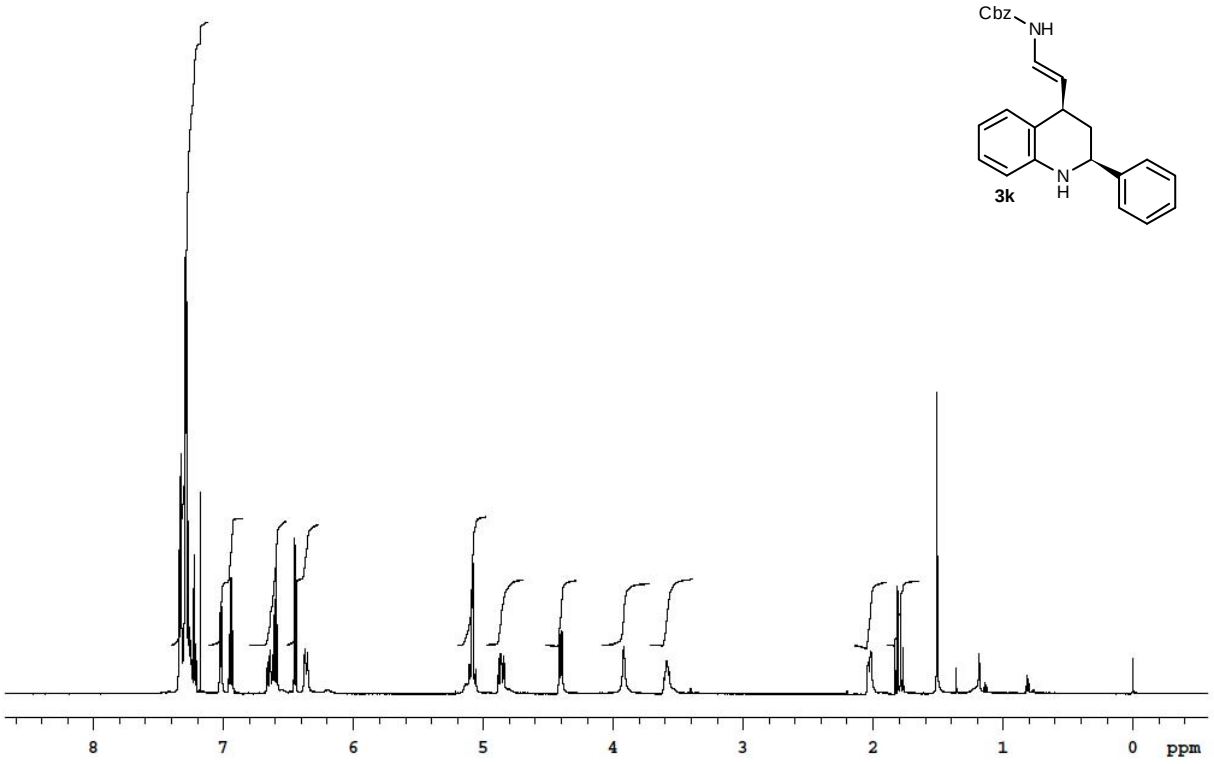
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N
H
3k
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7
6
5
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3
2
1
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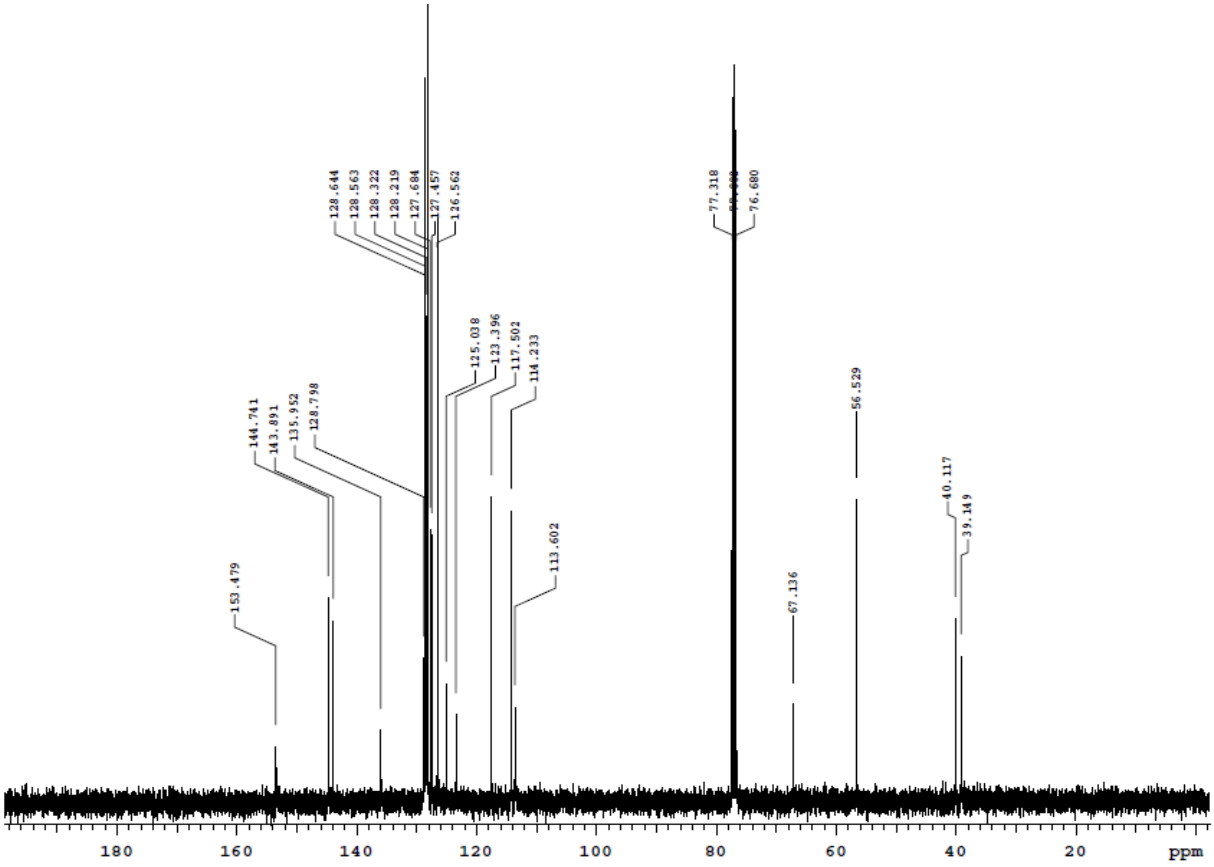
ppm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125.038
123.396
117.502
114.233
113.602
153.479
144.741
143.891
135.952
128.798
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67.136
56.529
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39.149
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140
120
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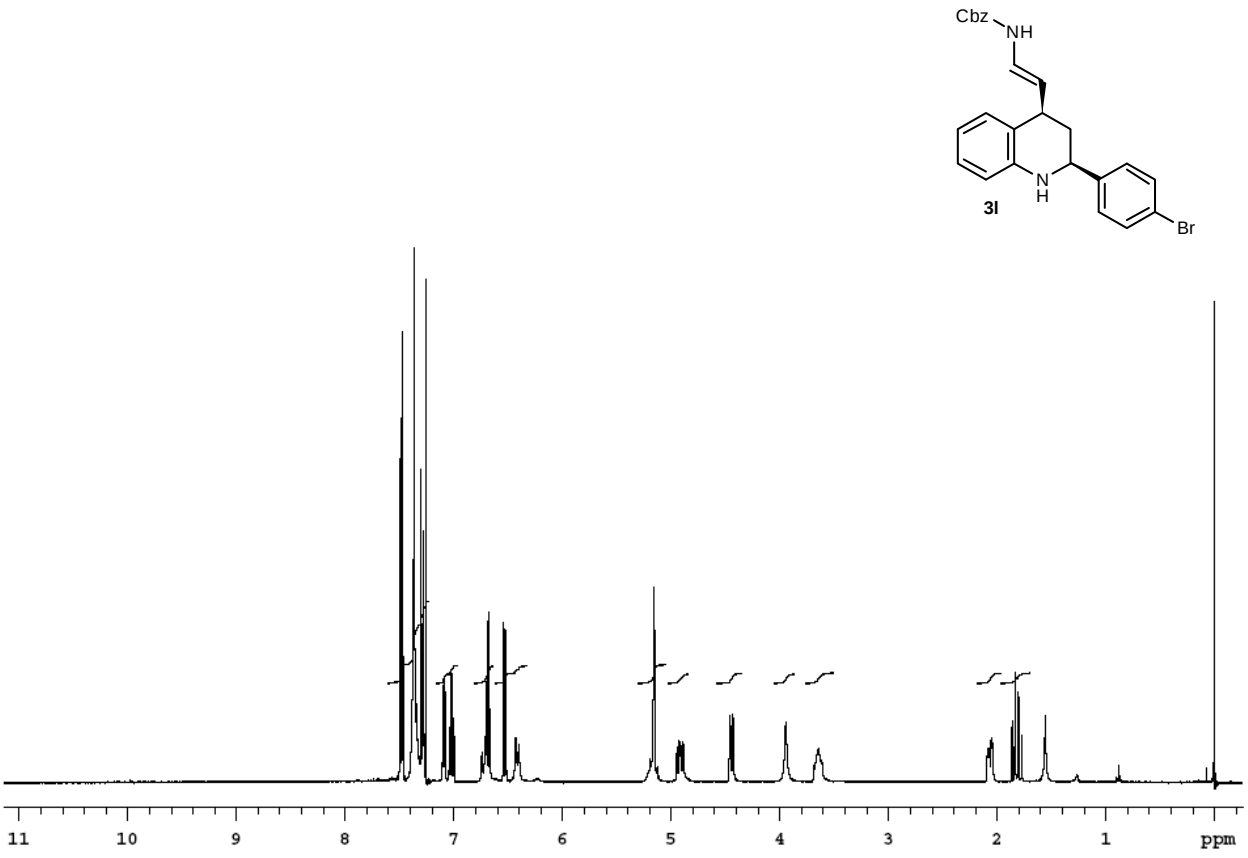
60
40
20
ppm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N
H
Br
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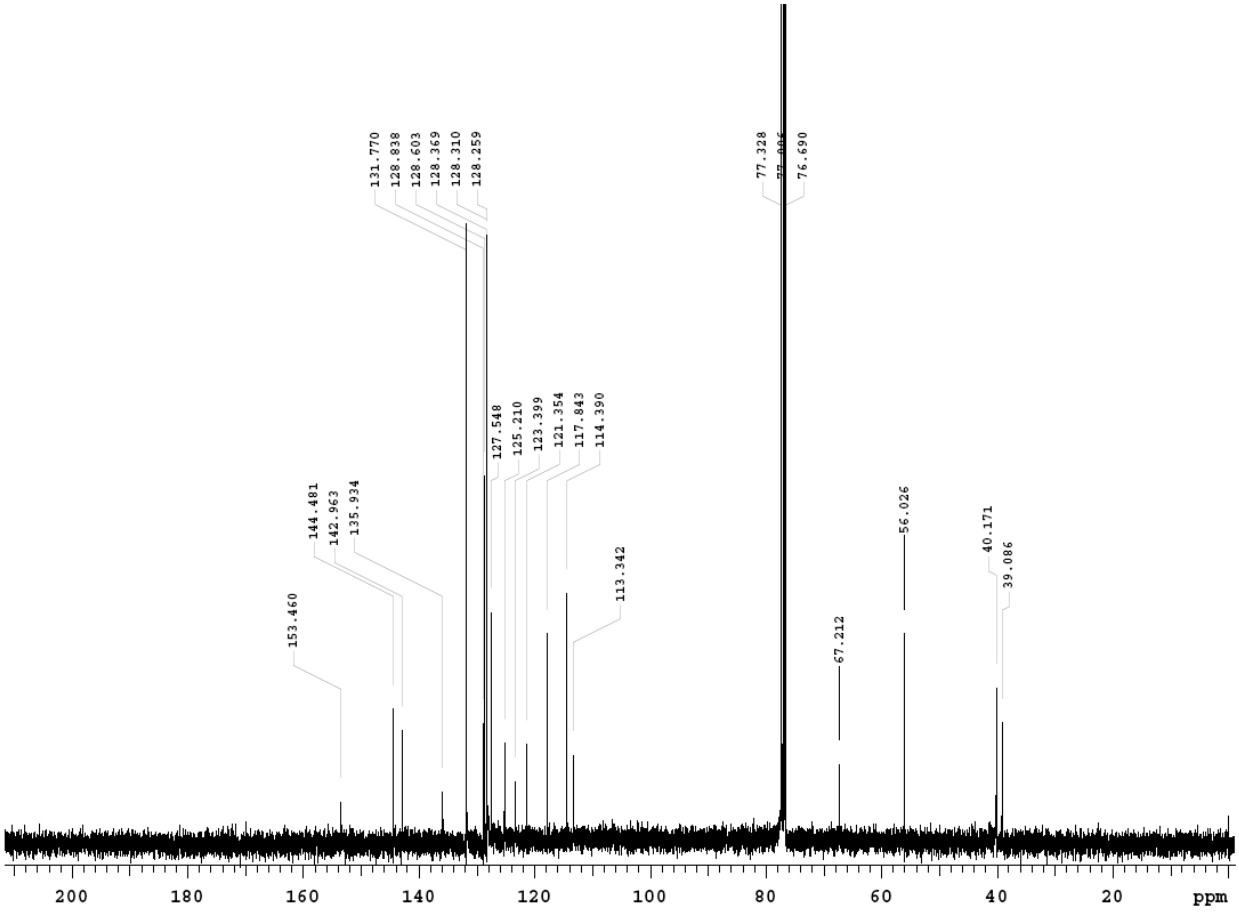
10
9
8
7
6
5
4
3
2
1
ppm

3l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128.259
127.548
125.210
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121.354
117.843
114.390
113.342
153.460
144.481
142.963
135.934
77.328
76.690
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56.026
40.171
39.086
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140
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60
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20
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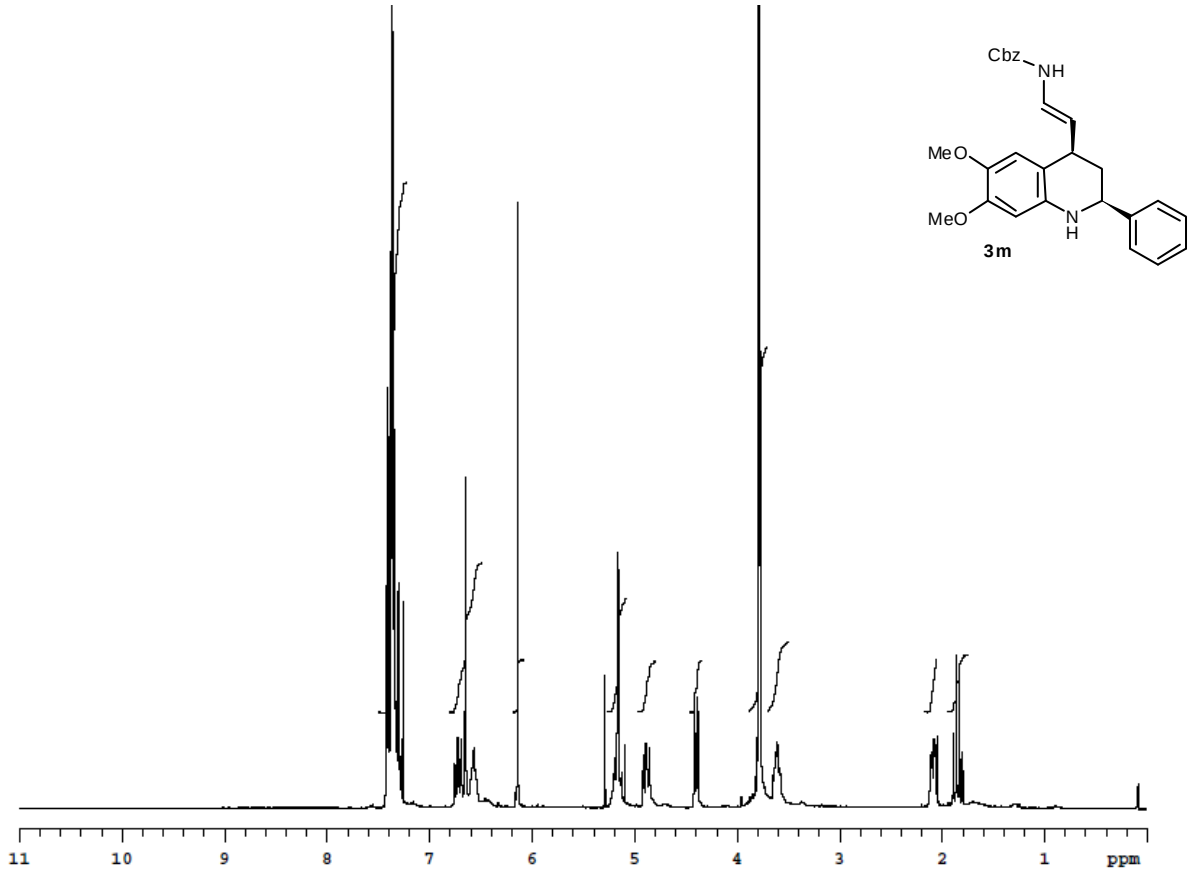
Cbz
NH
MeO
MeO
N
H
3m
11
10
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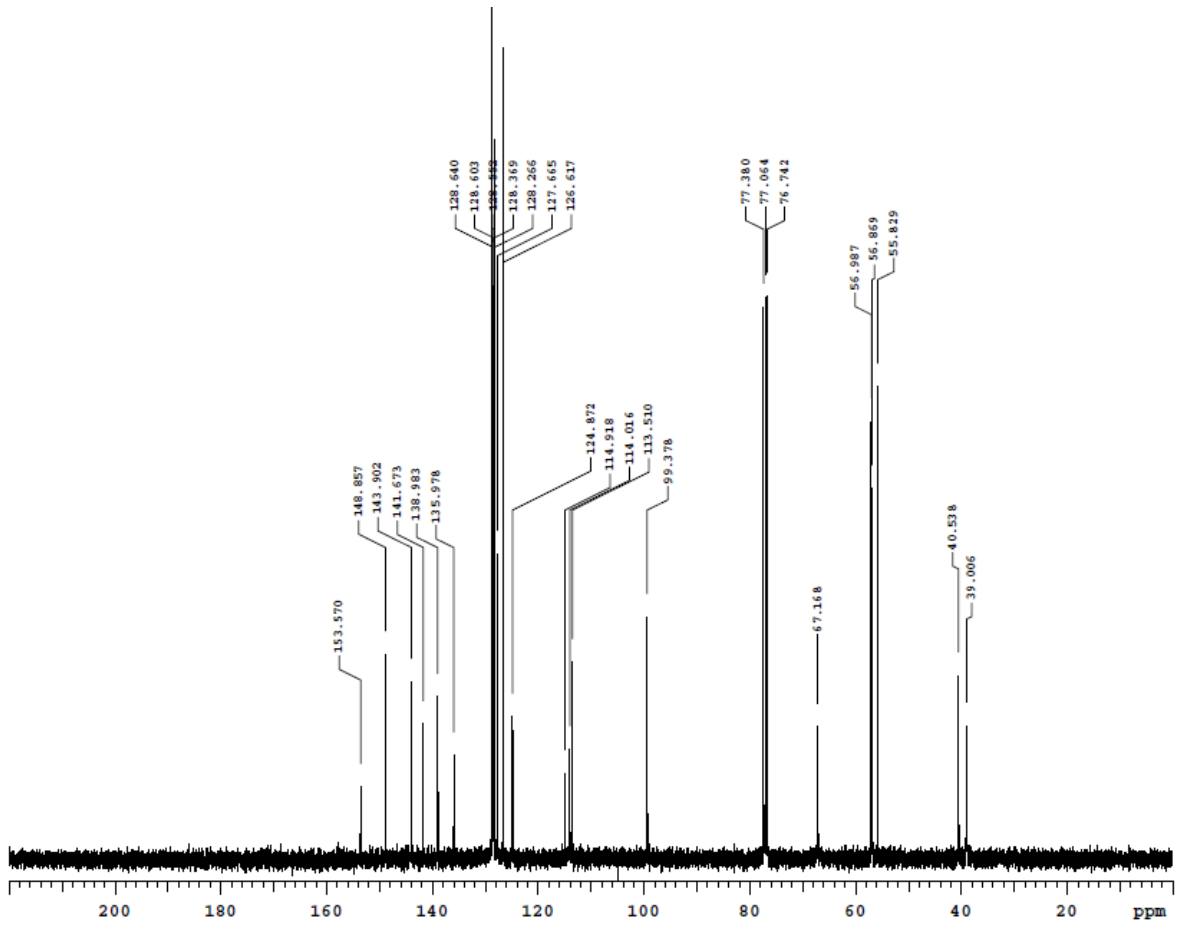
8
7
6
5
4
3
2
1
ppm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128.369
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127.665
126.617
124.872
114.918
114.016
113.510
99.378
153.570
148.857
143.902
141.673
138.983
135.978
77.380
77.064
76.742
67.168
56.987
56.869
55.829
40.538
39.006
200
180
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140
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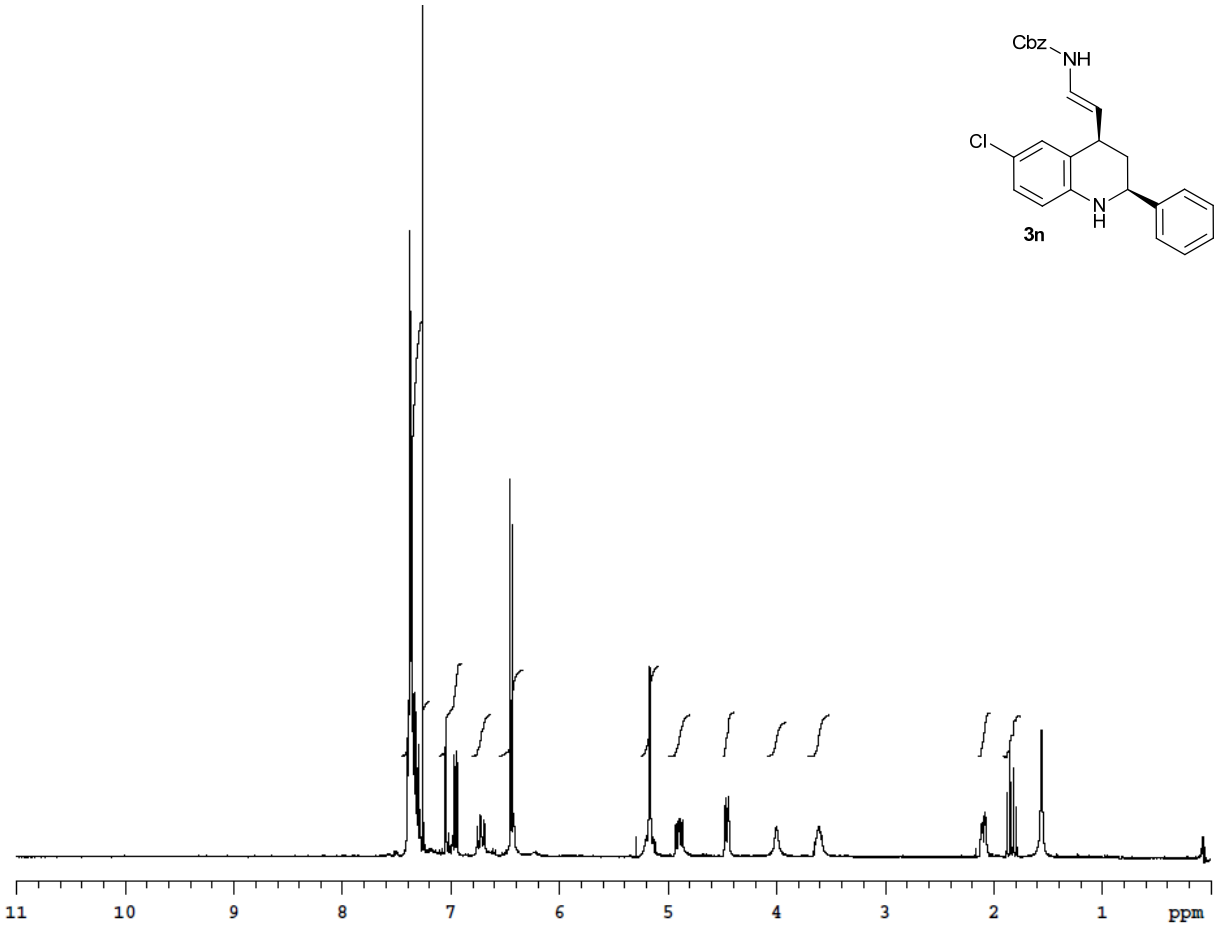
60
40
20
ppm


Cbz
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Cl
N
H
3n
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10
9
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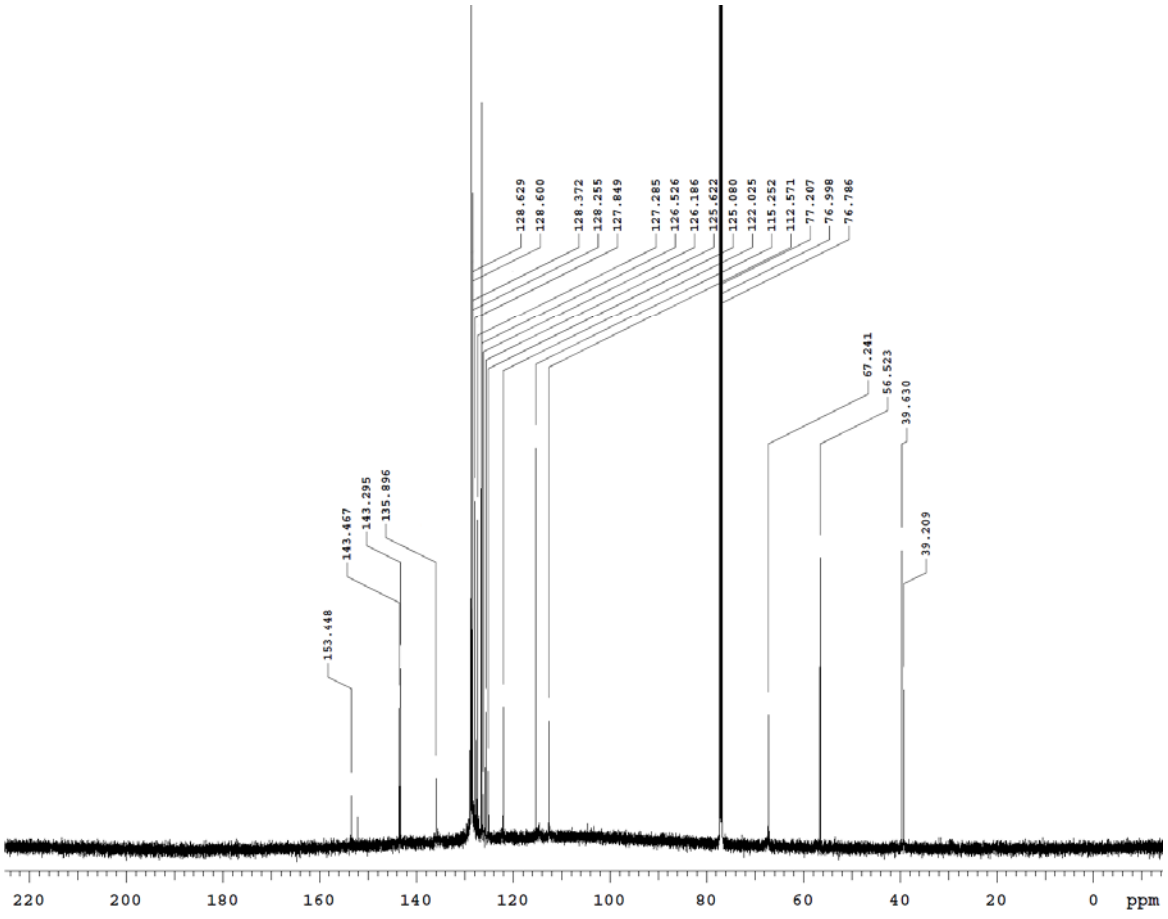
7
6
5
4
3
2
1
ppm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128.372
128.255
127.849
127.285
126.526
126.186
125.622
125.080
122.025
115.252
112.571
77.207
76.998
76.786
67.241
56.523
39.630
39.209
143.467
143.295
135.896
153.448
220
200
180
160
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120
100
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40
20
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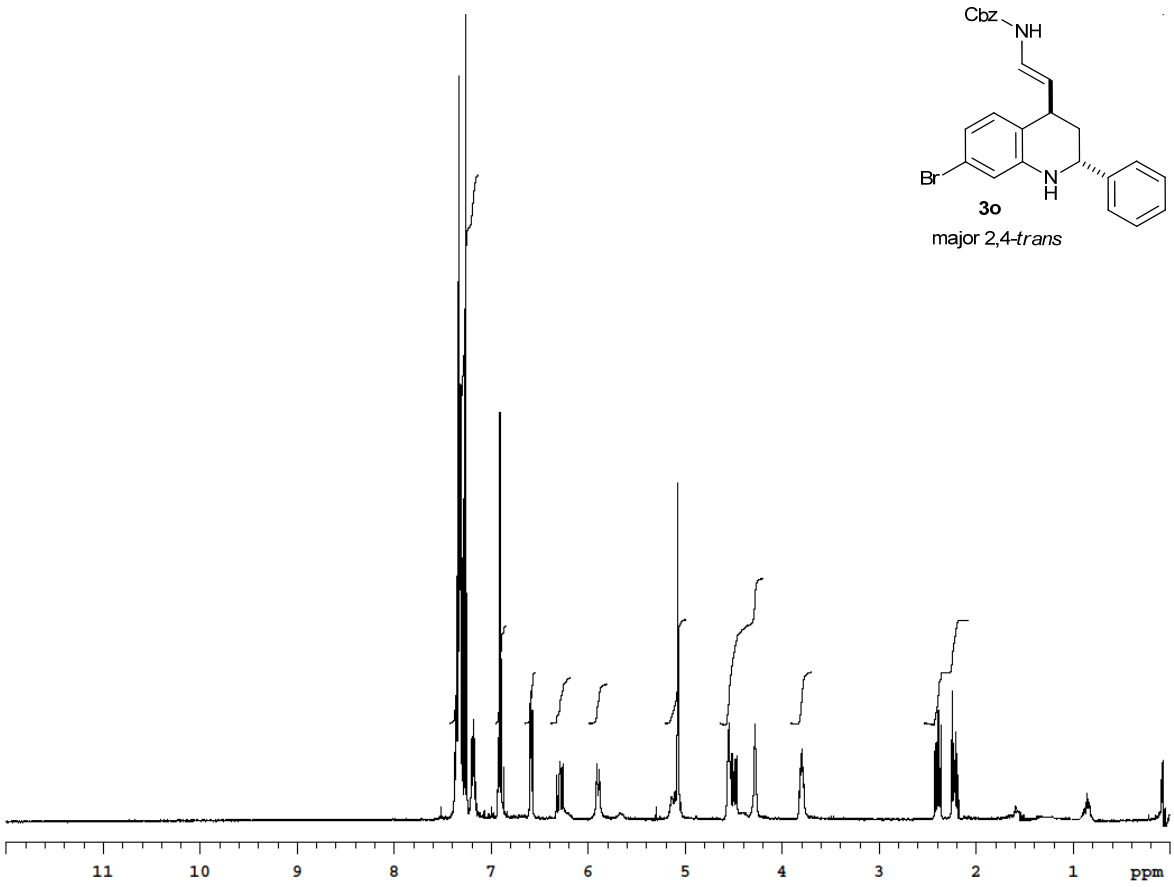
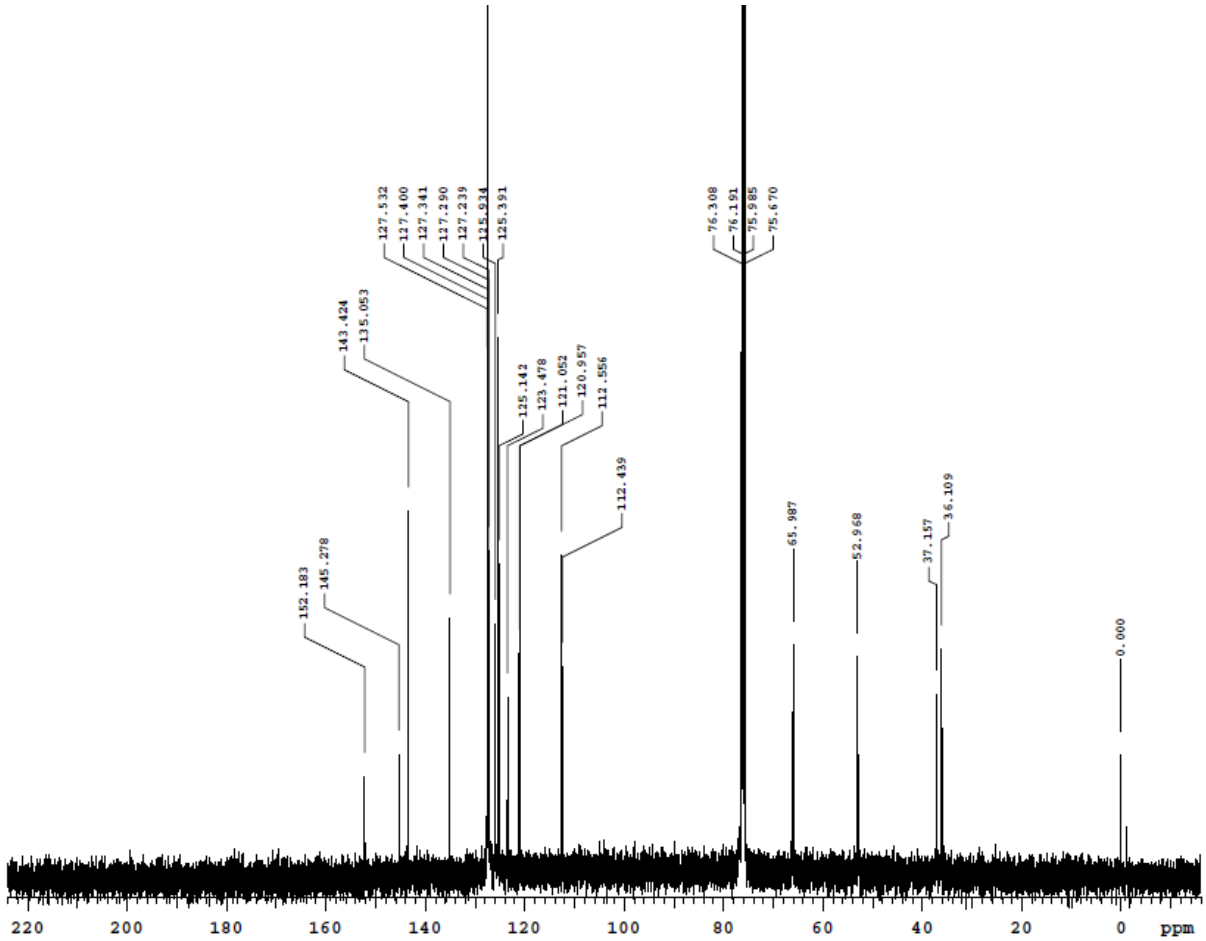
ppm


Cbz
NH
Br
N
H
3o
major 2,4-trans
11
10
9
8
7
6
5
4
3
2
1
ppm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127.341
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127.239
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143.424
135.053
125.142
123.478
121.052
120.957
112.556
112.439
152.183
145.278
76.308
76.191
75.985
75.670
65.987
52.968
37.157
36.109
0.000
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200
180
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140
120
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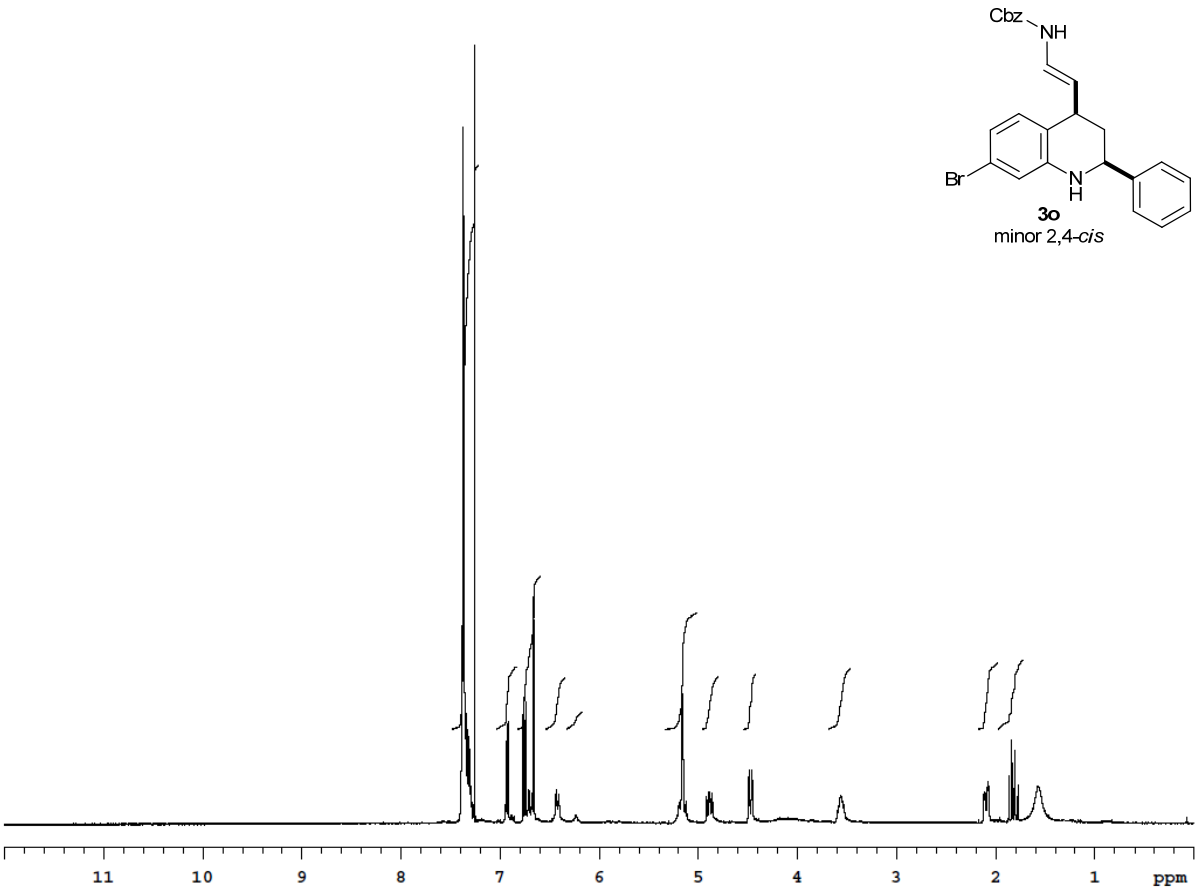
80
60
40
20
0
ppm


Cbz
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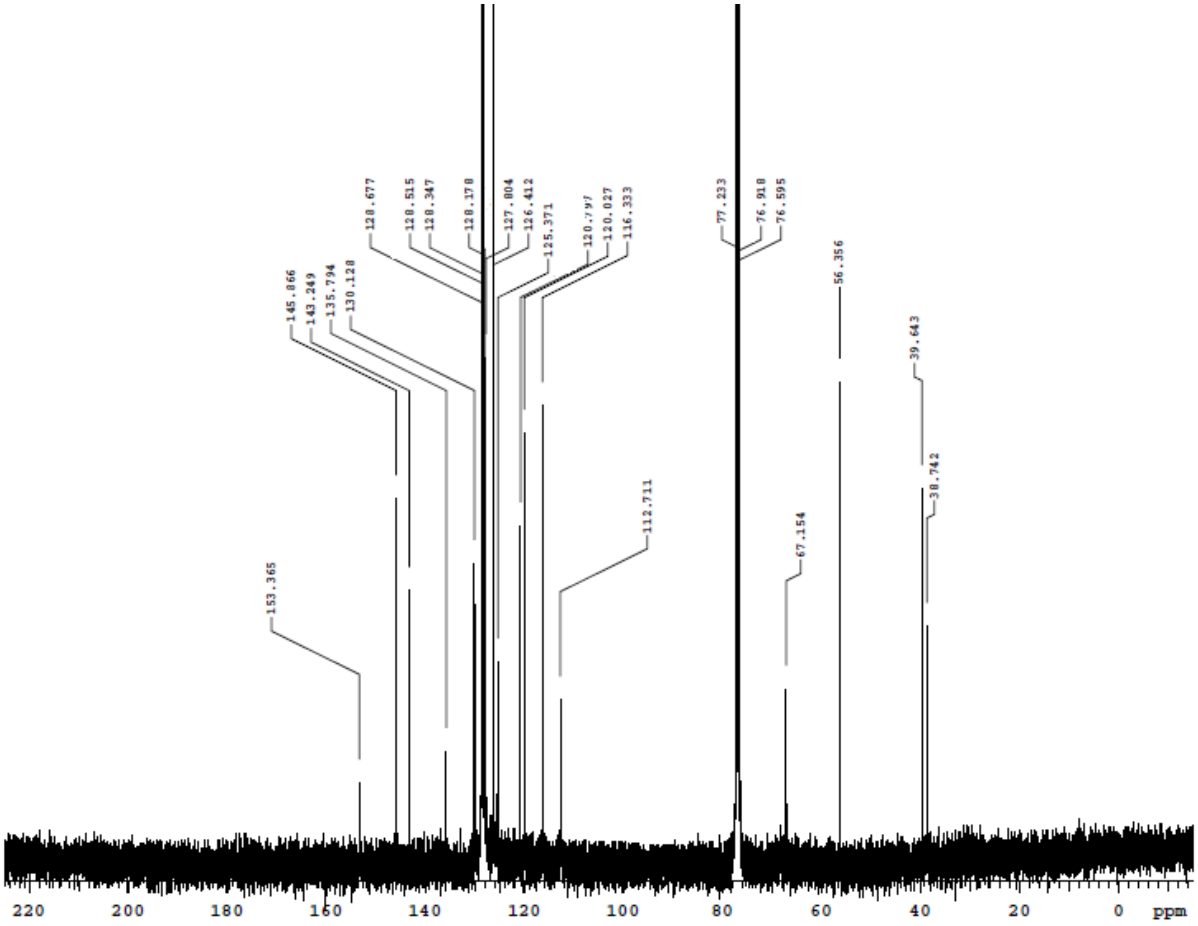
Br
N
H
3o
minor 2,4-cis
11
10
9
8
7
6
5
4
3
2
1
ppm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120.515
120.347
120.178
127.804
126.412
125.371
120.797
120.027
116.333
77.233
76.918
76.595
56.356
39.643
38.742
67.154
112.711
153.365
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200
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140
120
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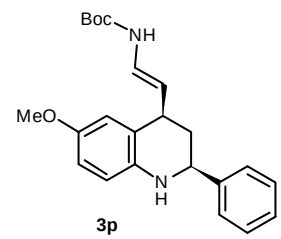
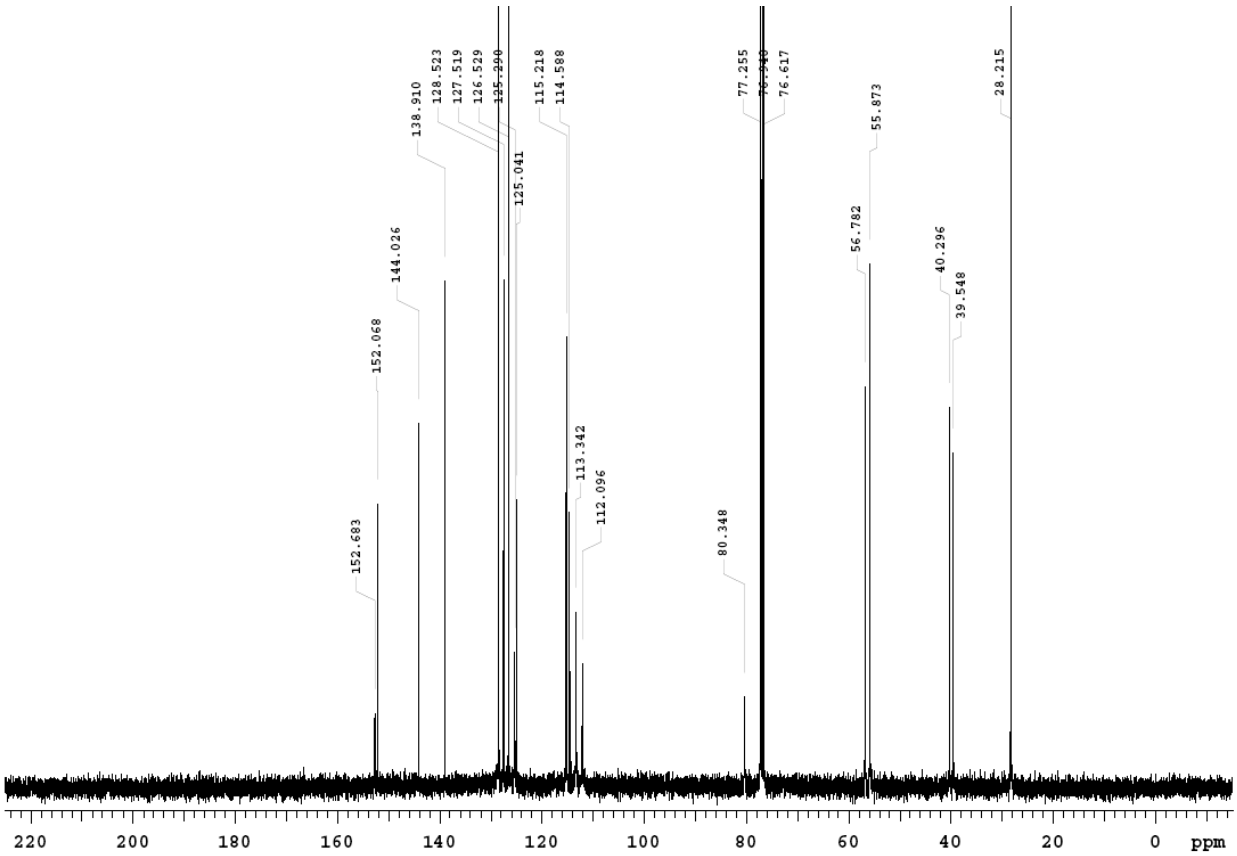
ppm


Boc
NH
MeO
N
H

3p

11
10
9
8
7
6
5
4
3
2
1
ppm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127.519
126.529
125.290
125.041
115.218
114.588
113.342
112.096
80.348
77.255
76.617
56.782
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39.548
28.215
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200
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120
100
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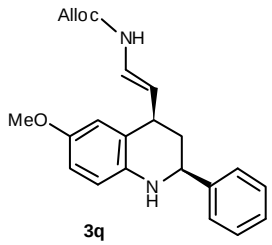
60
40
20
0
ppm


Alloc
NH
MeO
N
H

3q

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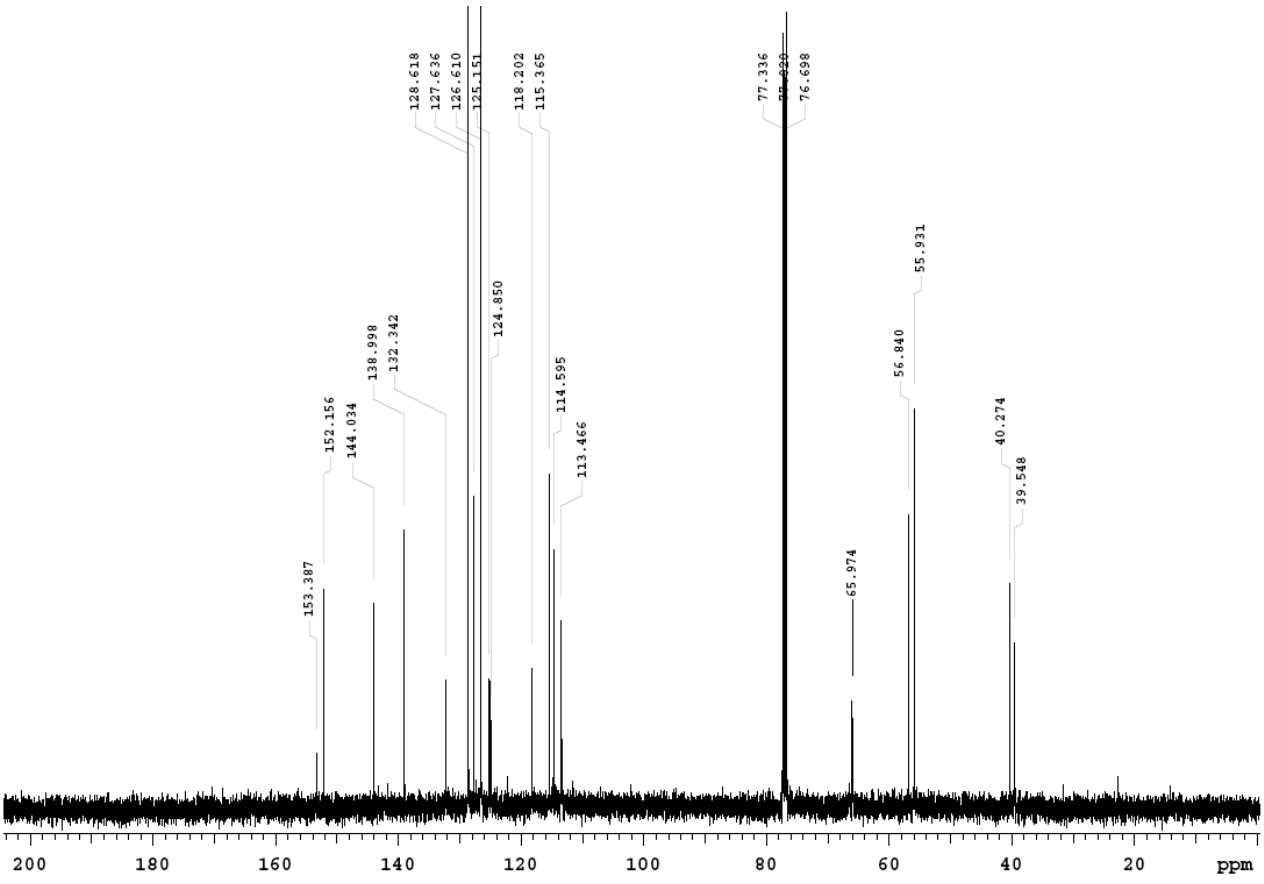
10
9
8
7
6
5
4
3
2
1
ppm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77.336
76.698
124.850
114.595
113.466
152.156
144.034
138.998
132.342
153.387
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55.931
40.274
39.548
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140
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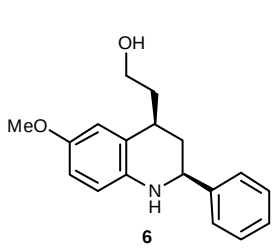
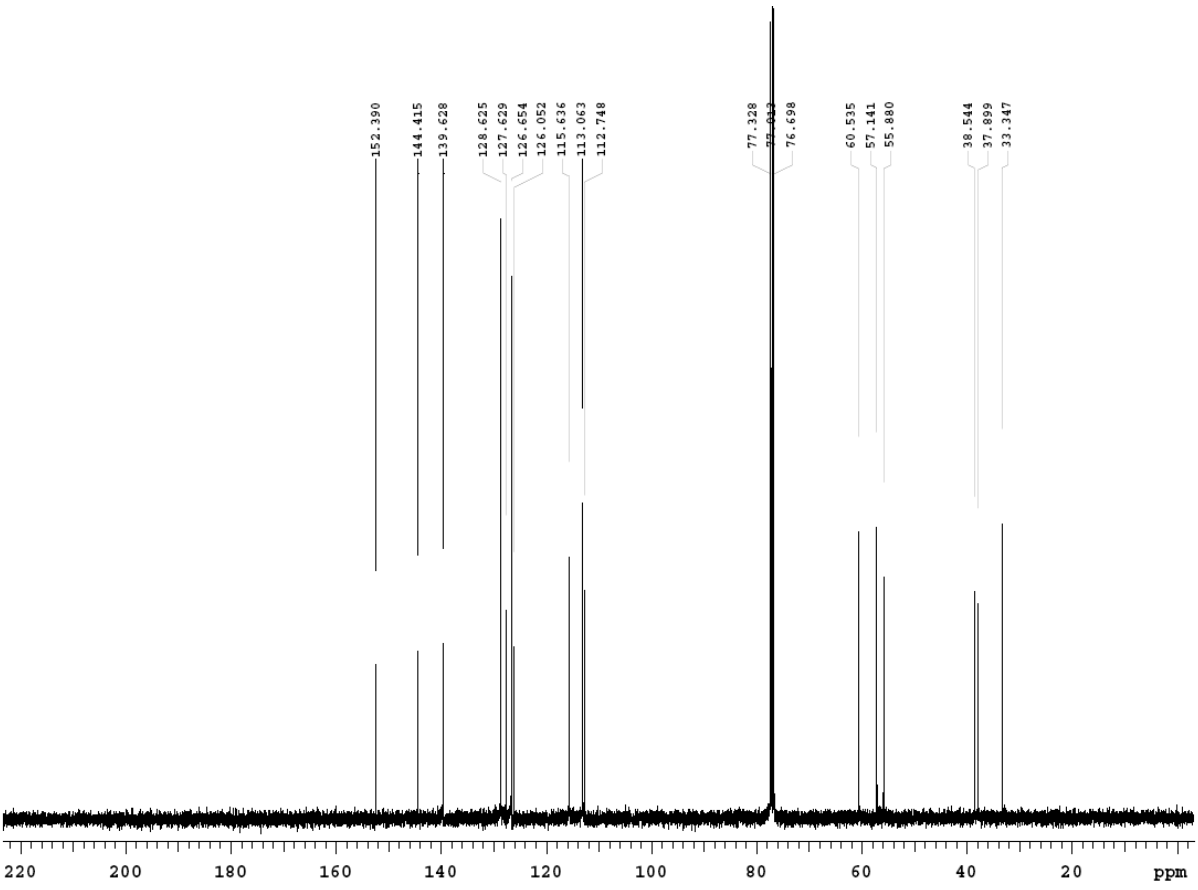
80
60
40
20
ppm


OH
MeO
N
H

6

10
9
8
7
6
5
4
3
2
1
ppm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139.628
128.625
127.629
126.654
126.052
115.636
113.063
112.748
77.328
76.698
60.535
57.141
55.880
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37.899
33.347
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200
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140
120
100
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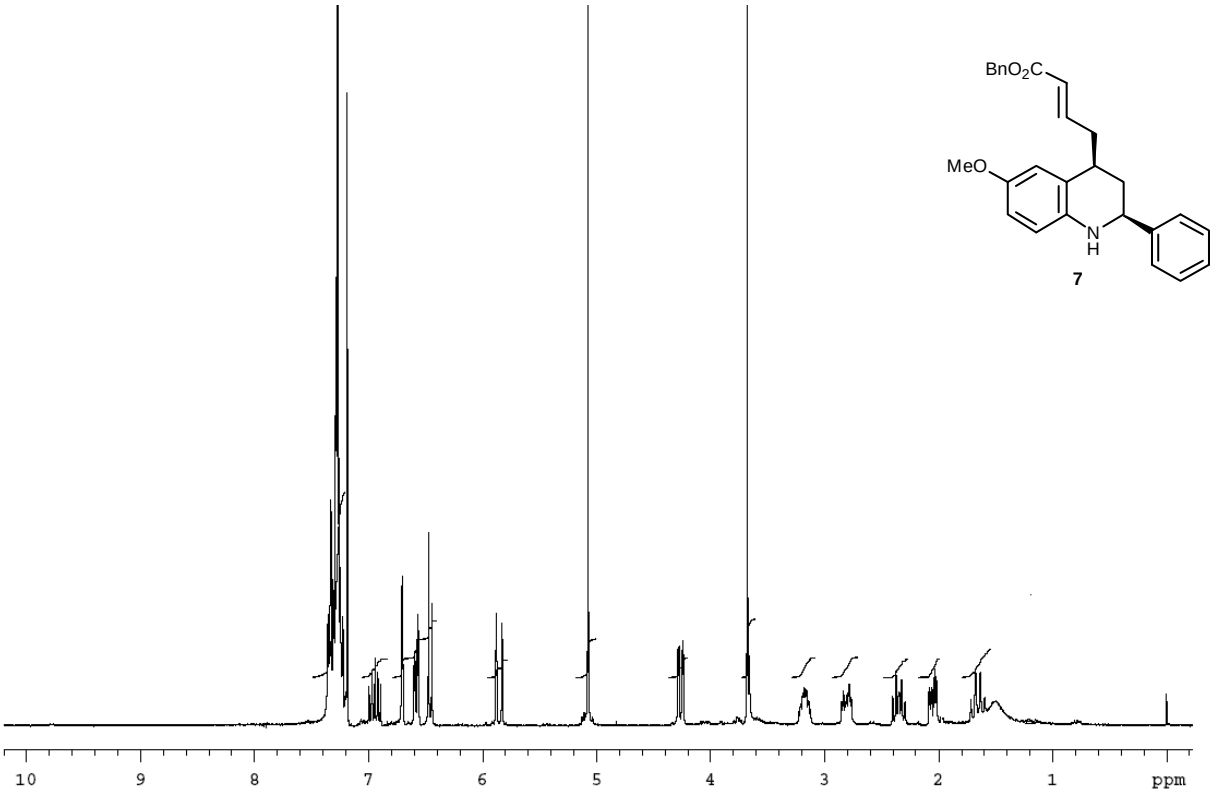
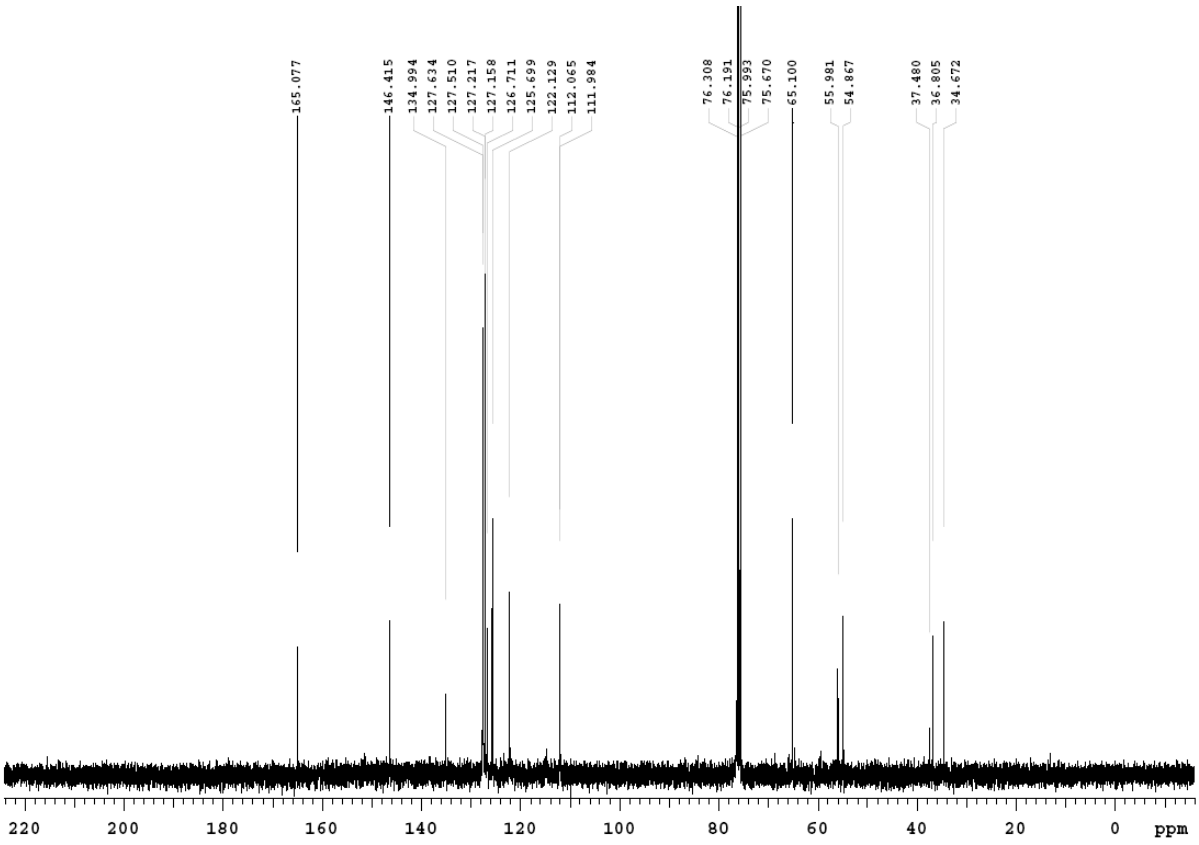
60
40
20
ppm


BnO2C
MeO
N
H
7
10
9
8
7
6
5
4
3
2
1
ppm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126.711
125.699
122.129
112.065
111.984
76.308
76.191
75.993
75.670
65.100
55.981
54.867
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36.805
34.672
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120
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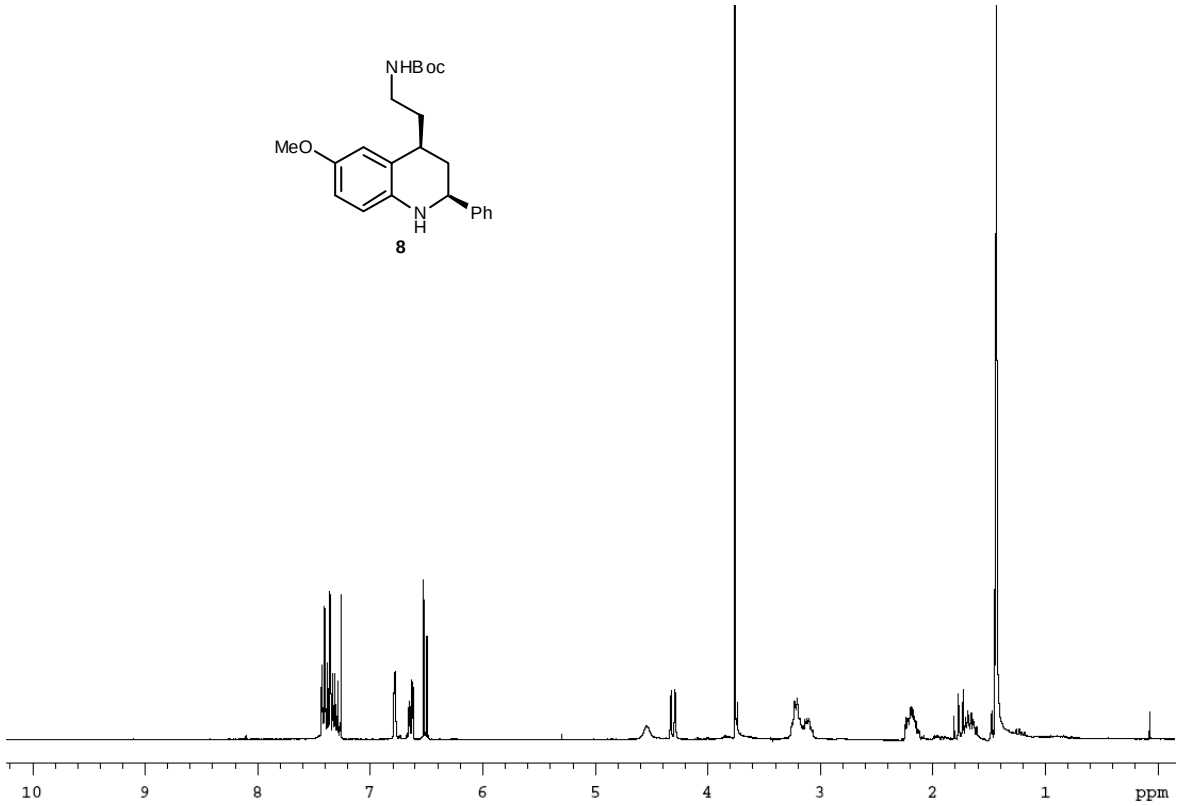
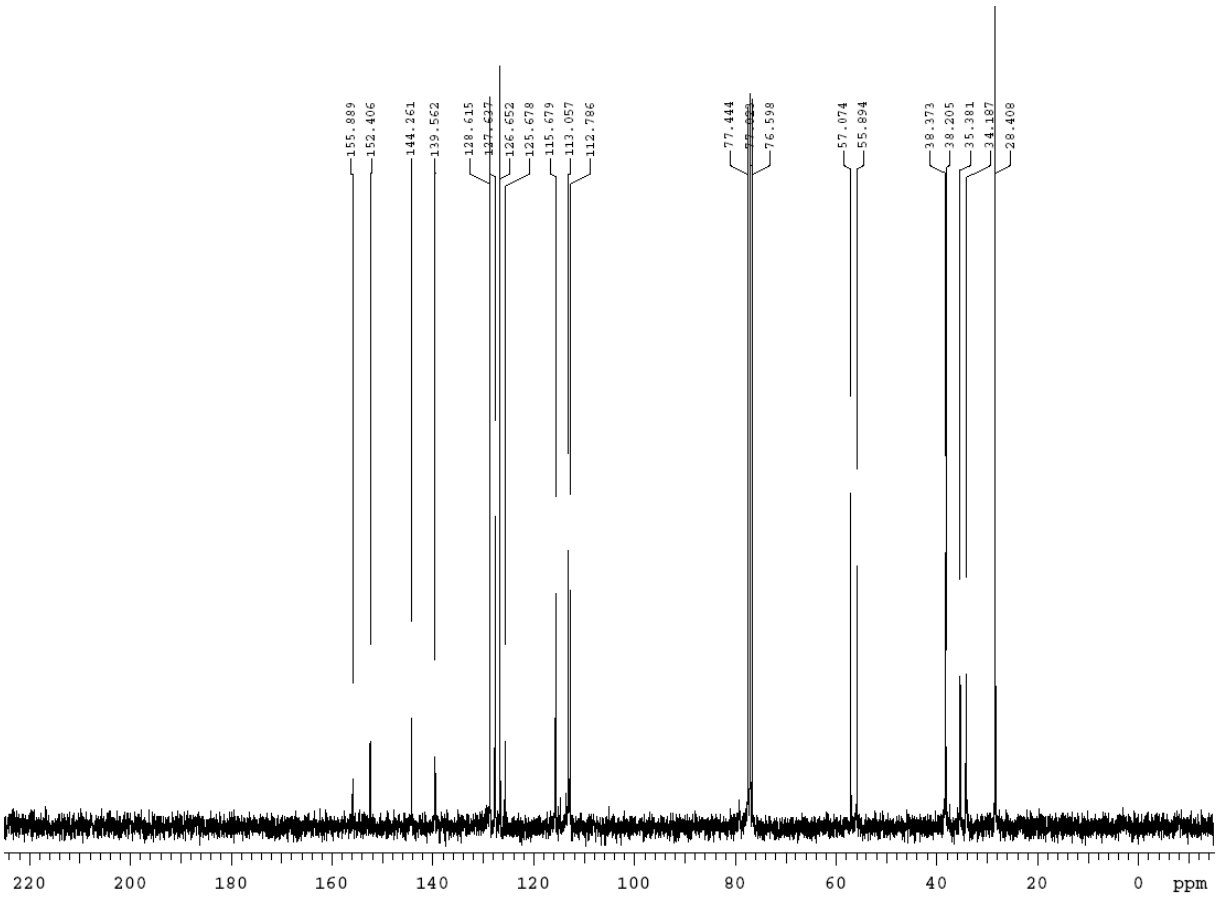

NHBoc
MeO
N
H
Ph
8
10
9
8
7
6
5
4
3
2
1
ppm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127.627
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125.678
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113.057
112.786
77.444
76.598
57.074
55.894
38.373
38.205
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34.187
28.408
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200
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120
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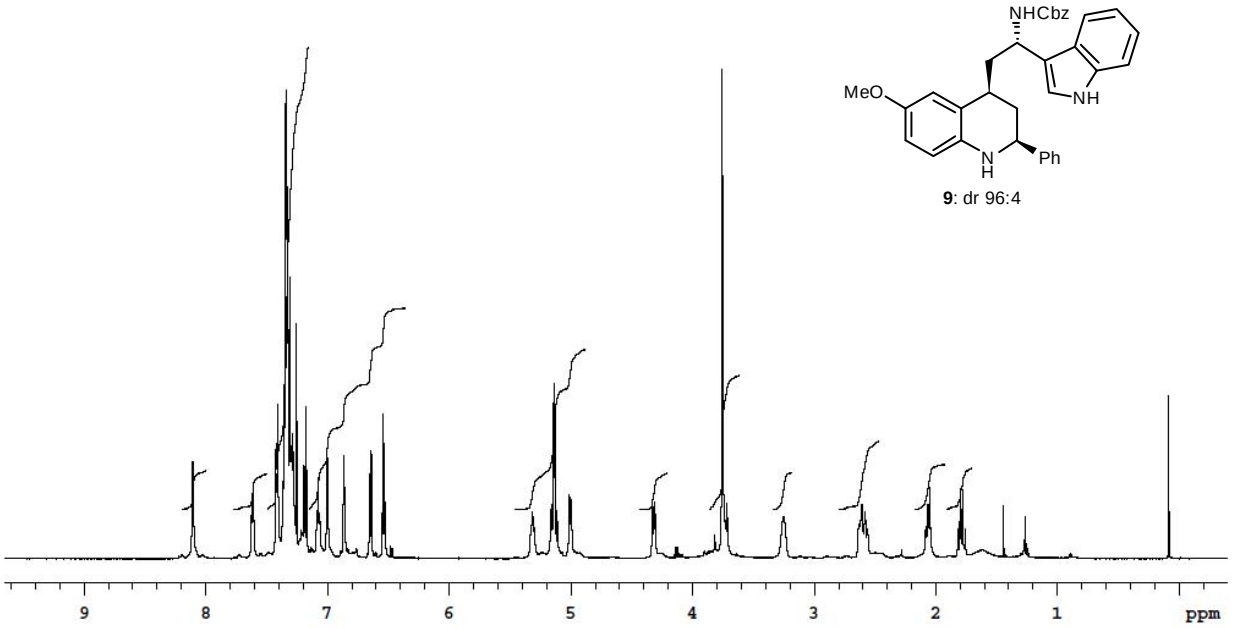
0
ppm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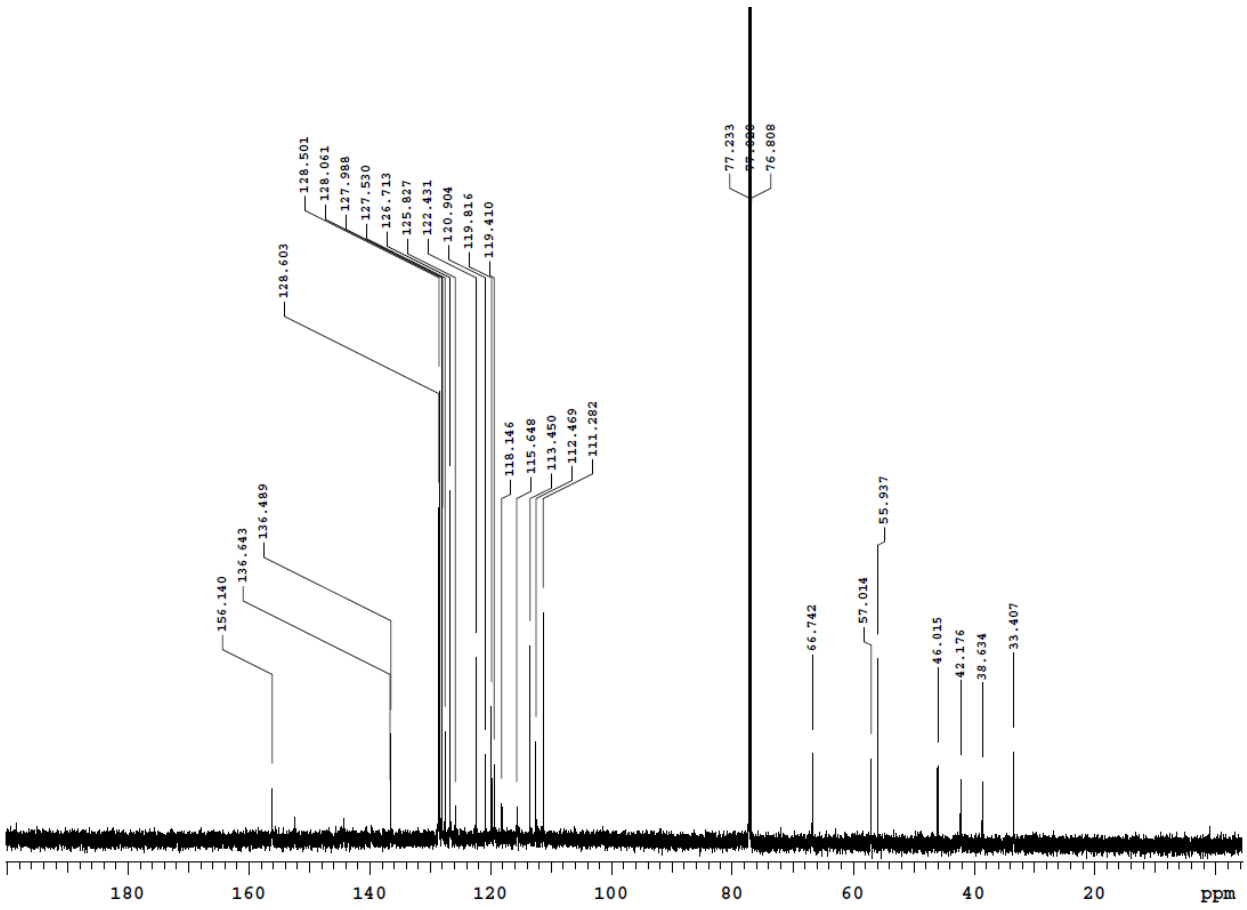
MeO
NH
N
H
Ph
9
8
7
6
5
4
3
2
1
ppm

9: dr 96:4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127.530
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125.827
122.431
120.904
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119.410
128.603
118.146
115.648
113.450
112.469
111.282
77.233
76.808
156.140
136.643
136.489
66.742
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46.015
42.176
38.634
33.407
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140
120
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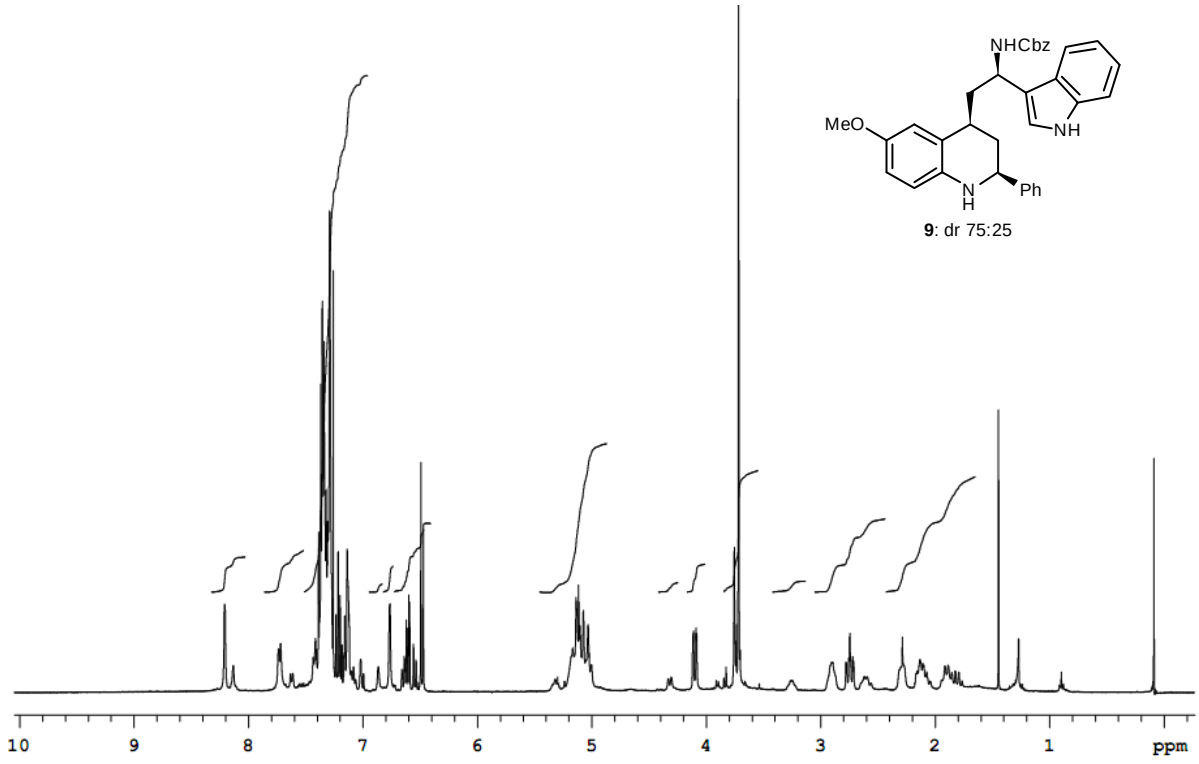
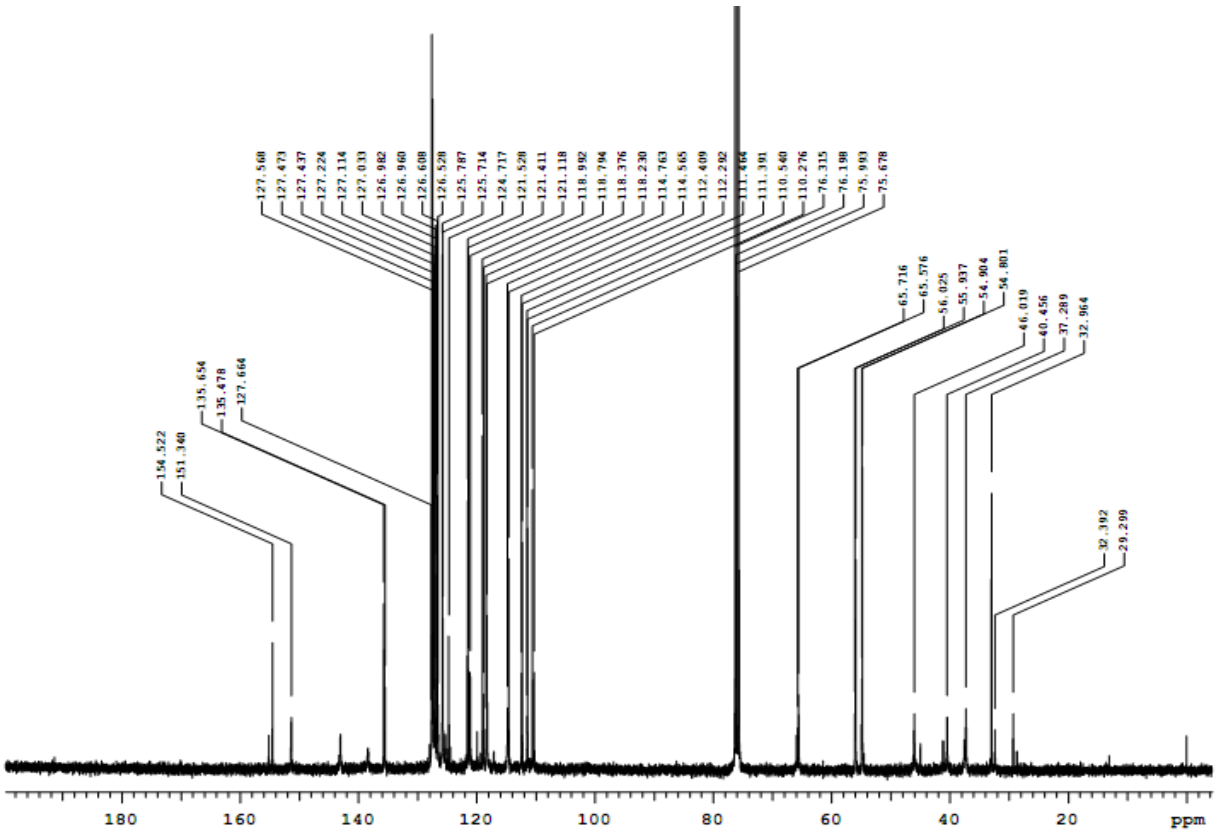
60
40
20
ppm


NHCbz
MeO
NH
N
H
Ph
10
9
8
7
6
5
4
3
2
1
ppm

9: dr 75:25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126.528
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124.717
121.528
121.411
121.118
118.982
118.794
118.376
118.230
114.763
114.565
112.409
112.292
111.484
111.391
110.540
110.276
76.315
76.198
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75.678
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65.576
56.025
55.937
54.904
54.801
46.019
40.456
37.289
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29.299
154.522
151.340
135.654
135.478
127.664
180
160
140
120
100
80
60
40
20
ppm