Supporting Information

A case study of the MAC (Masked Acyl Cyanide) oxyhomologation of *N,N*-dibenzyl-L-phenylalaninal with *anti* diastereoselectivity: preparation of (2*S*,3*S*)-allophenylnorstatin esters

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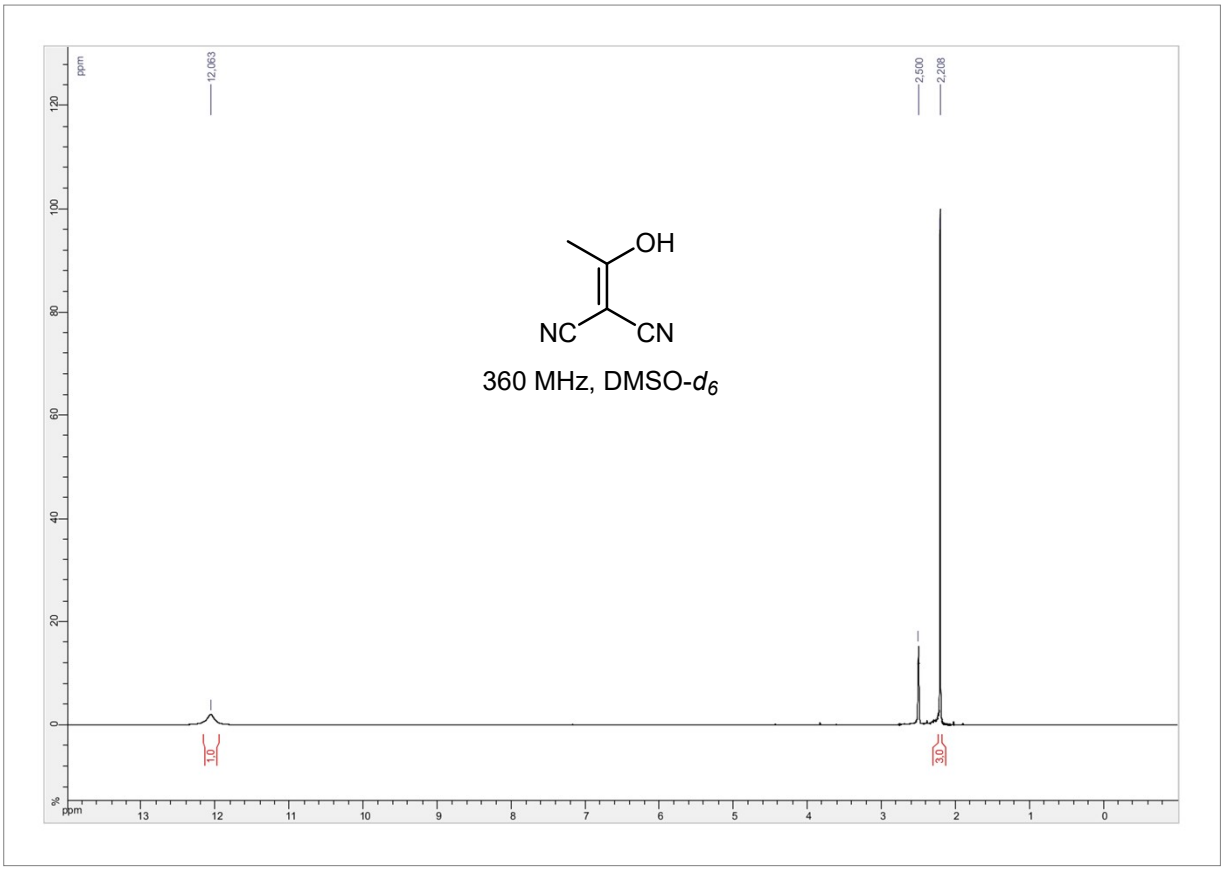
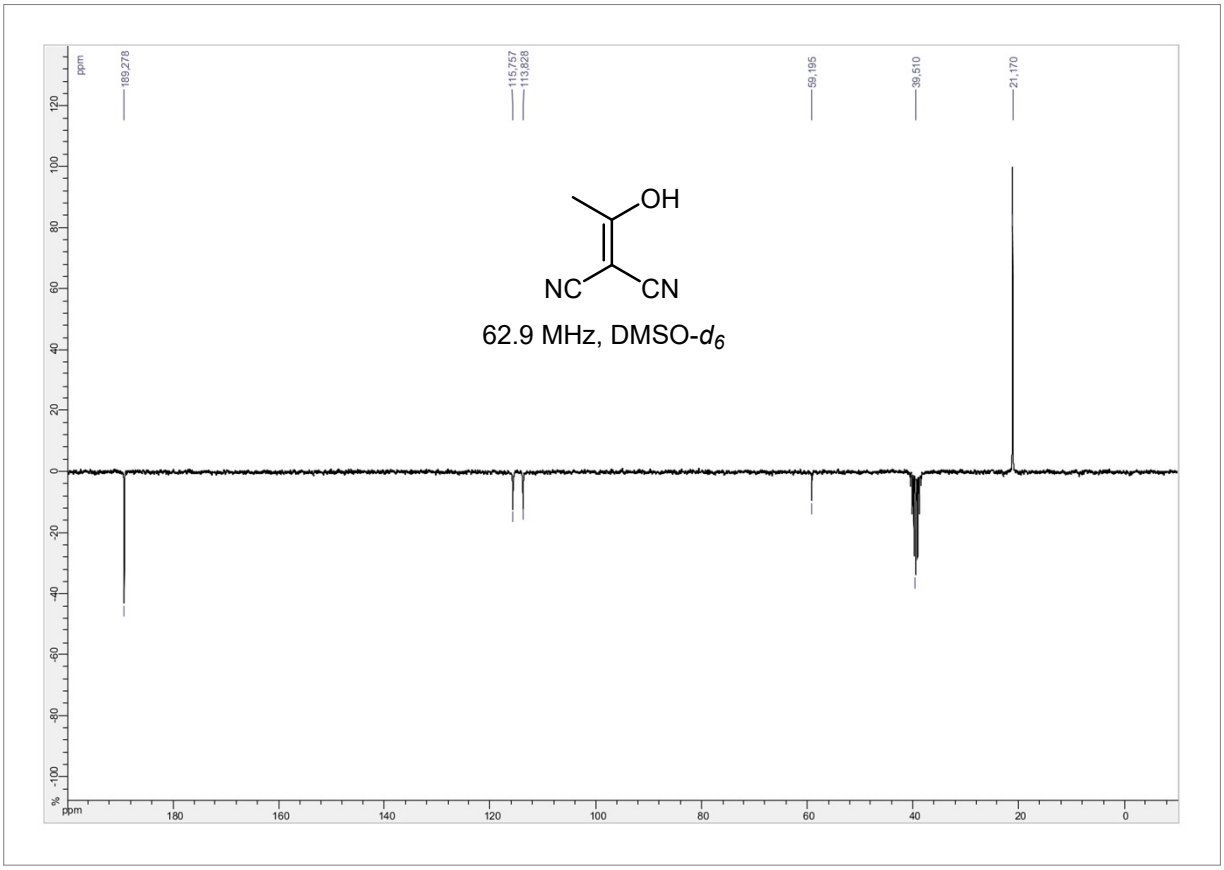
1. Copies of ^{1}H and ^{13}C NMR spectra.

2-(1-Hydroxyethylidene)malononitrile **(2)**





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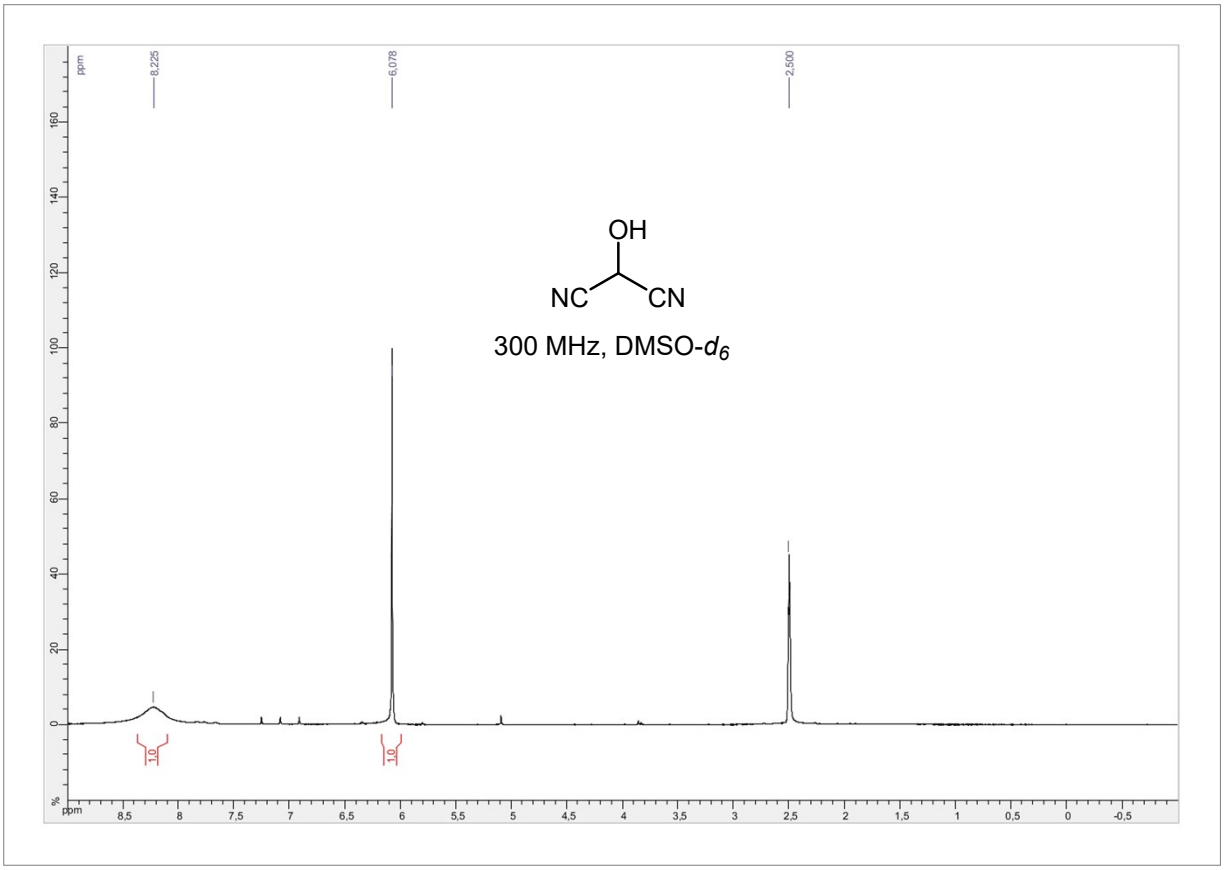
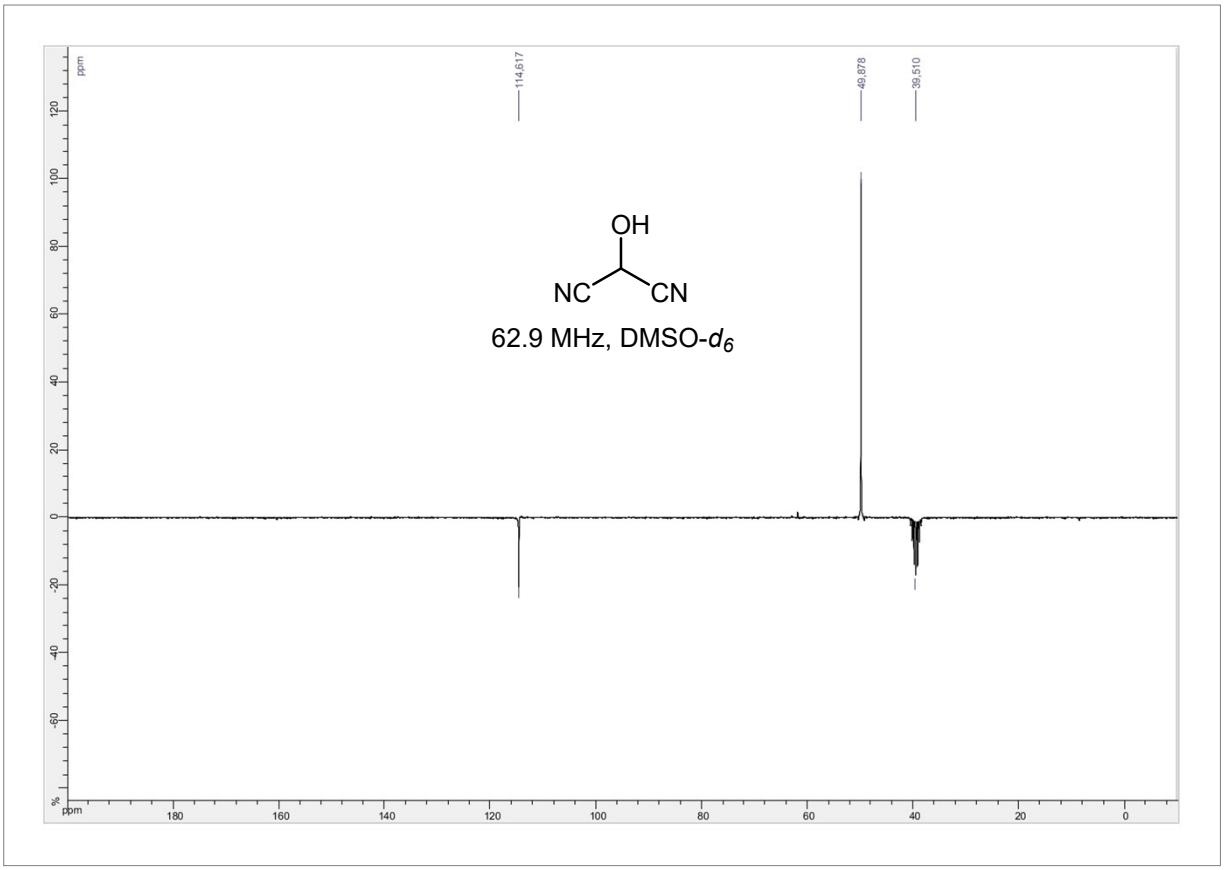
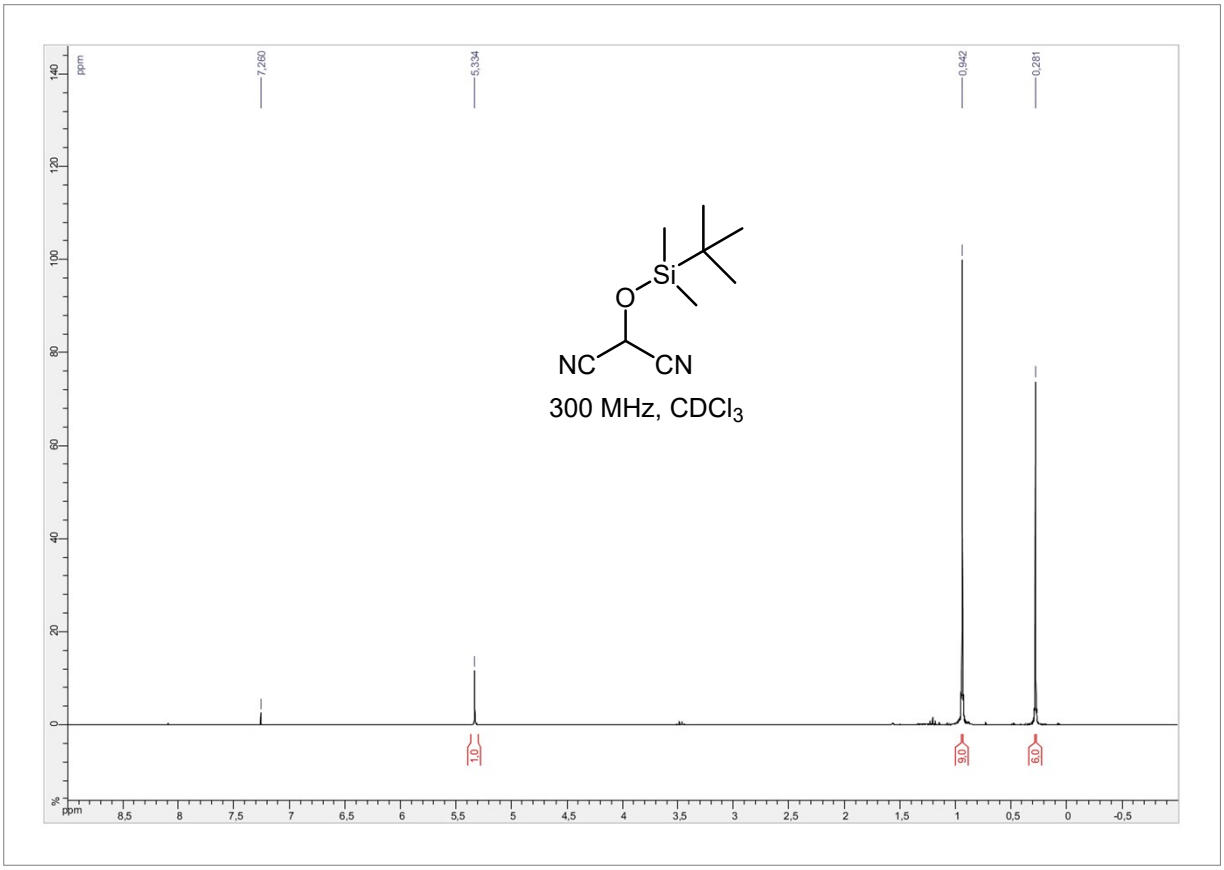
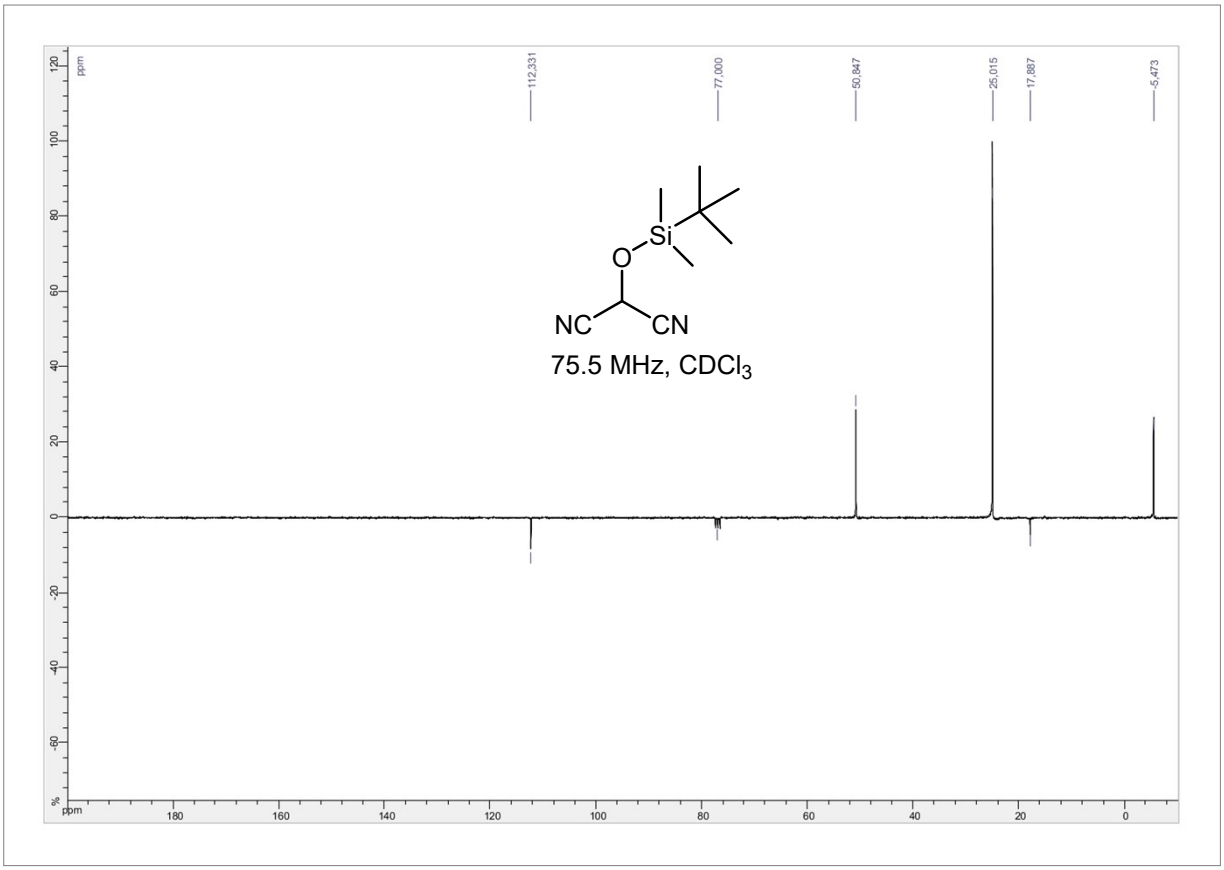


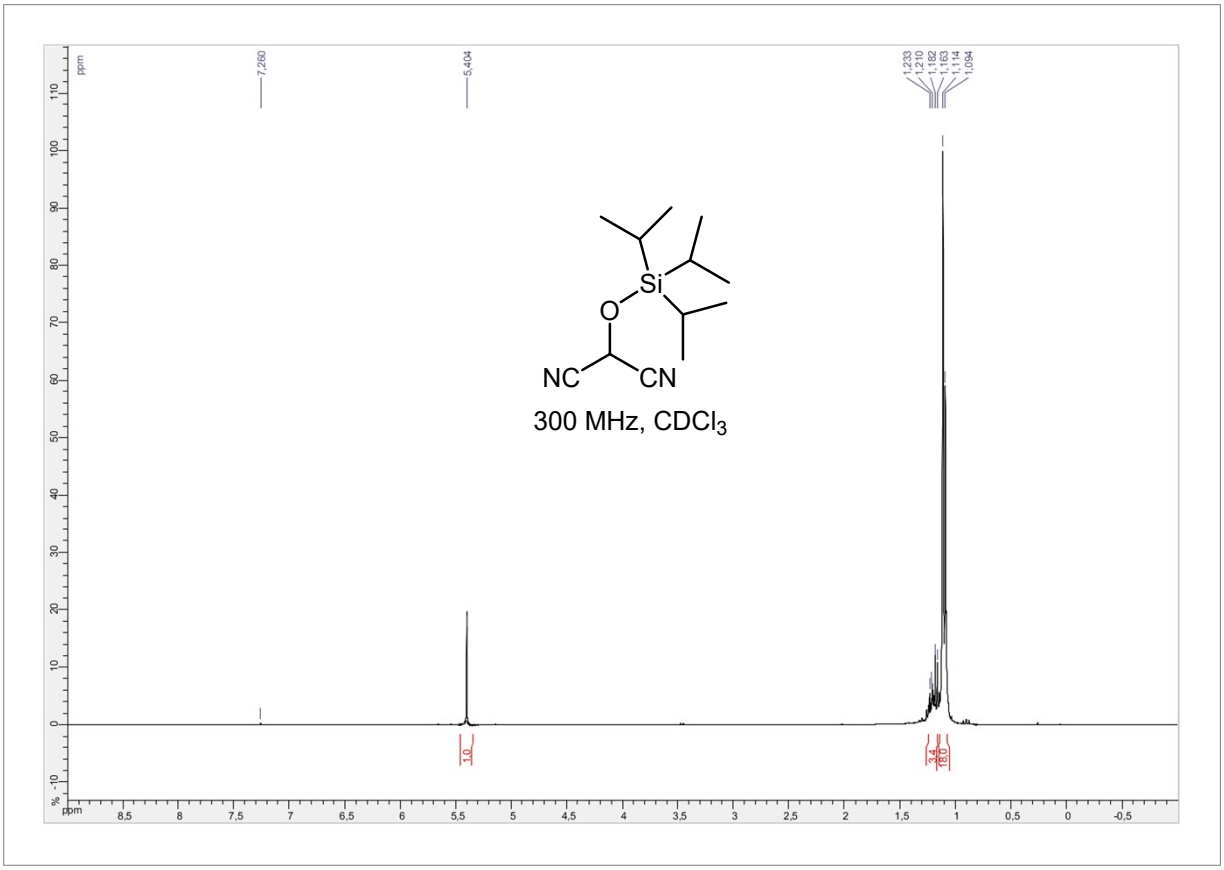


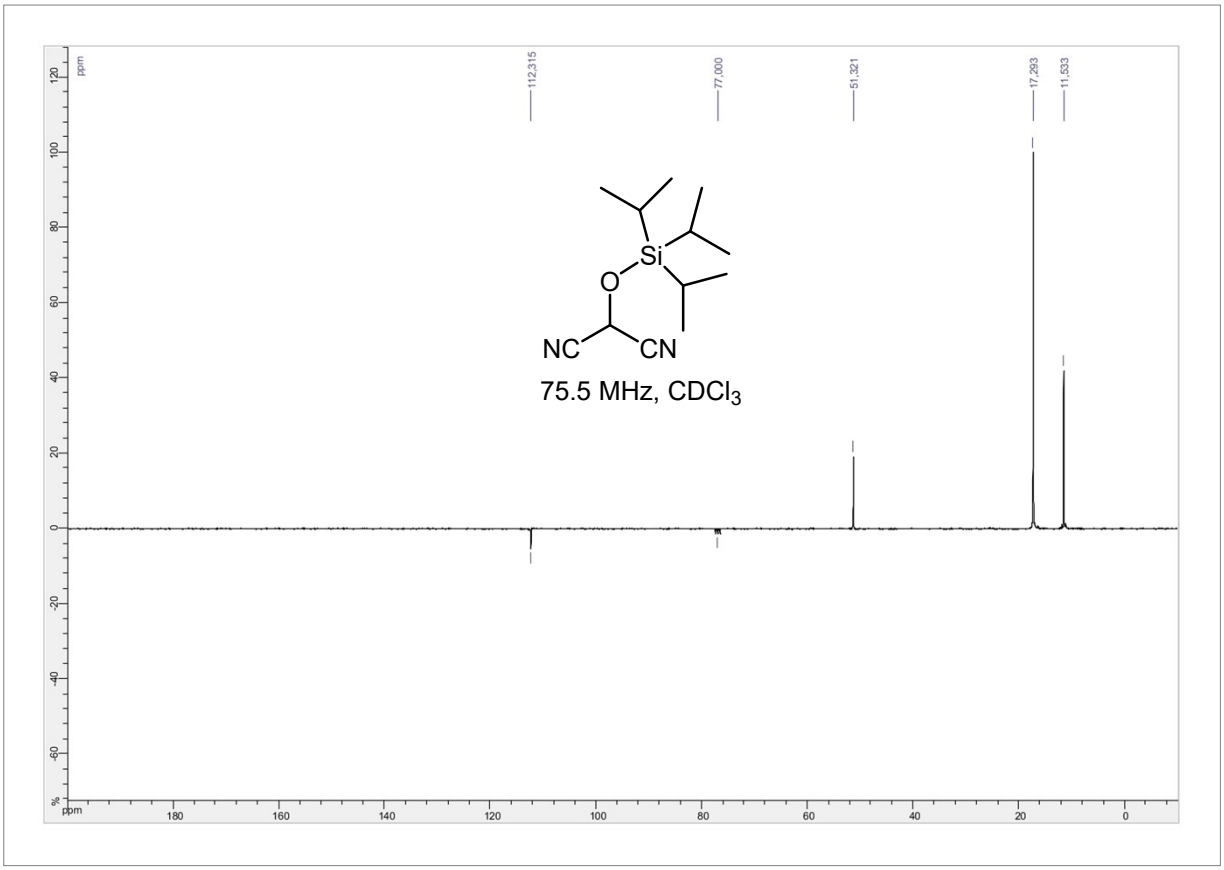
2-(*tert*-Butyldimethylsilyloxy)malononitrile : H-MAC-TBS **(1a)**



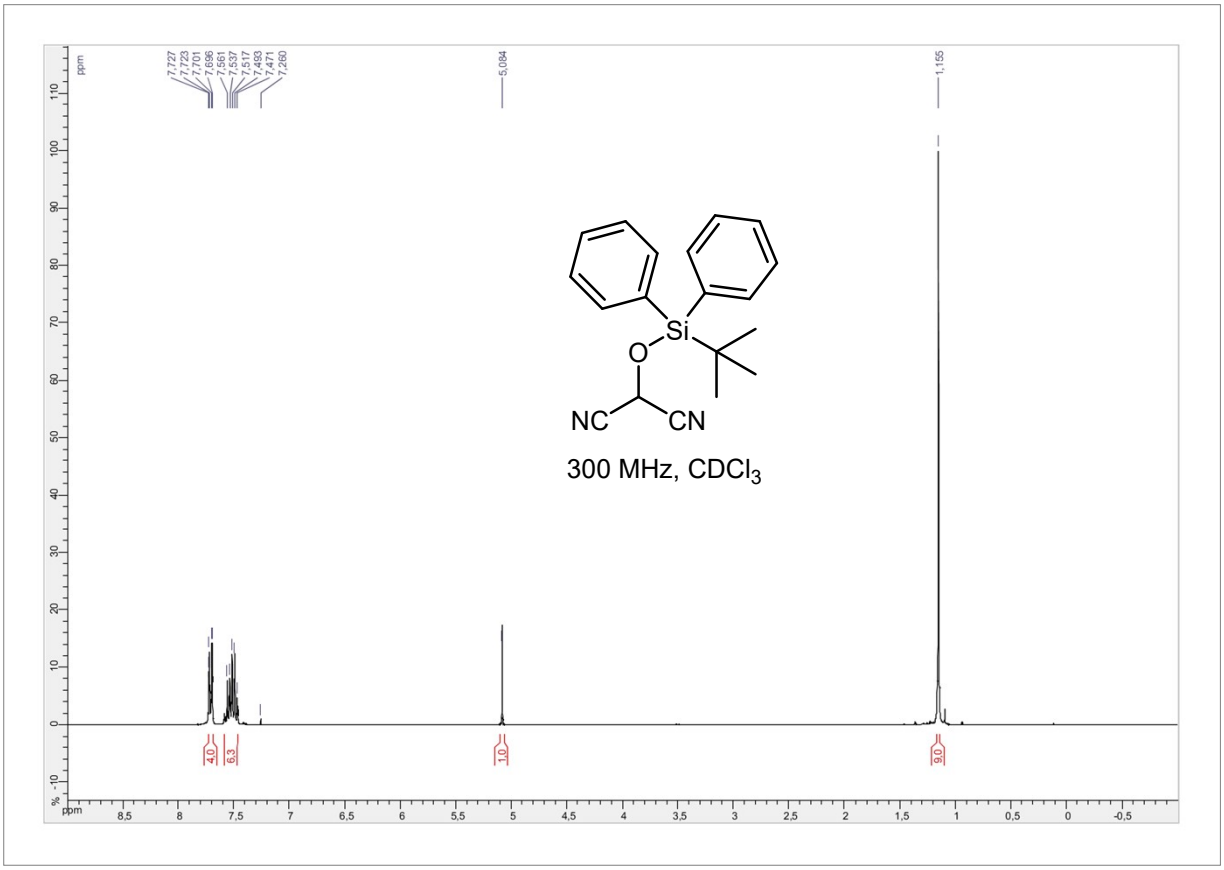


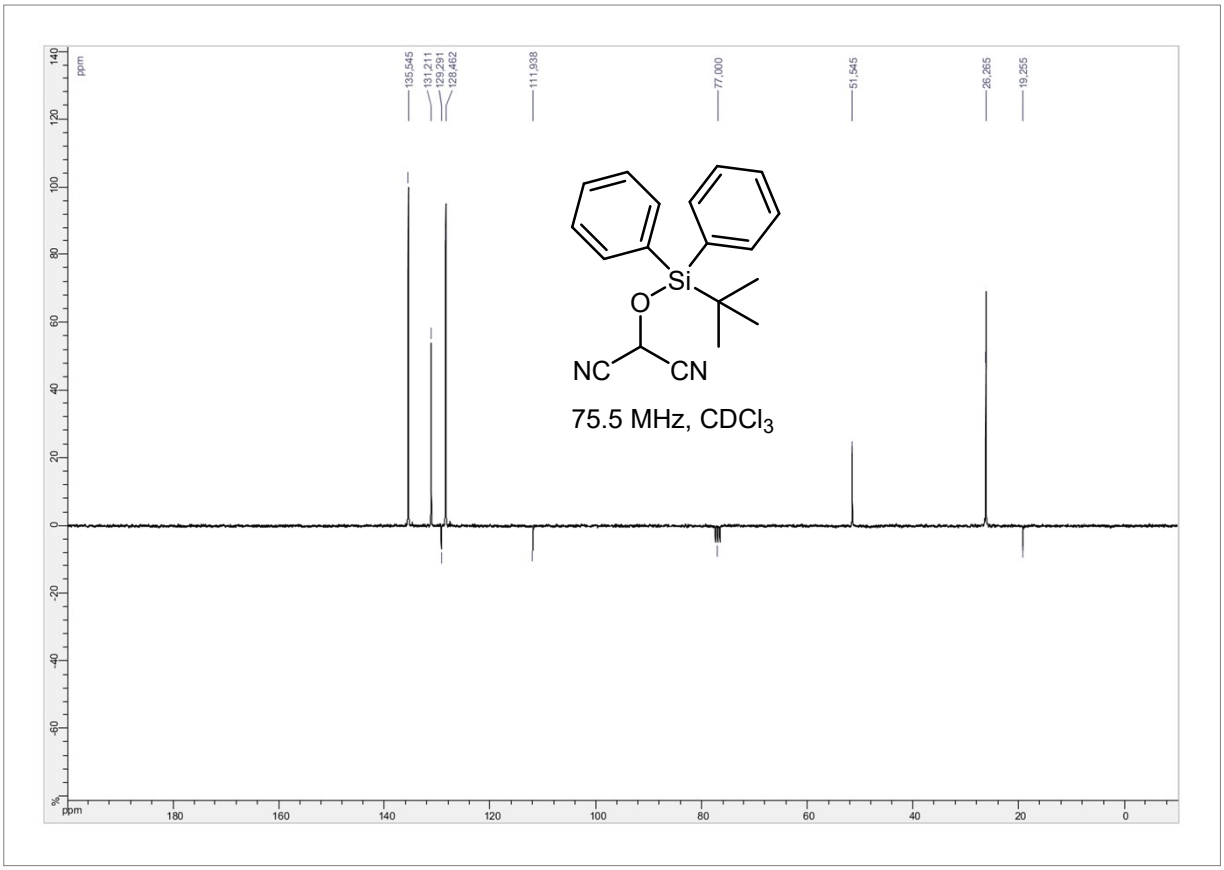
2-(Triisopropylsilyloxy)malononitrile : H-MAC-TIPS **(1b)**



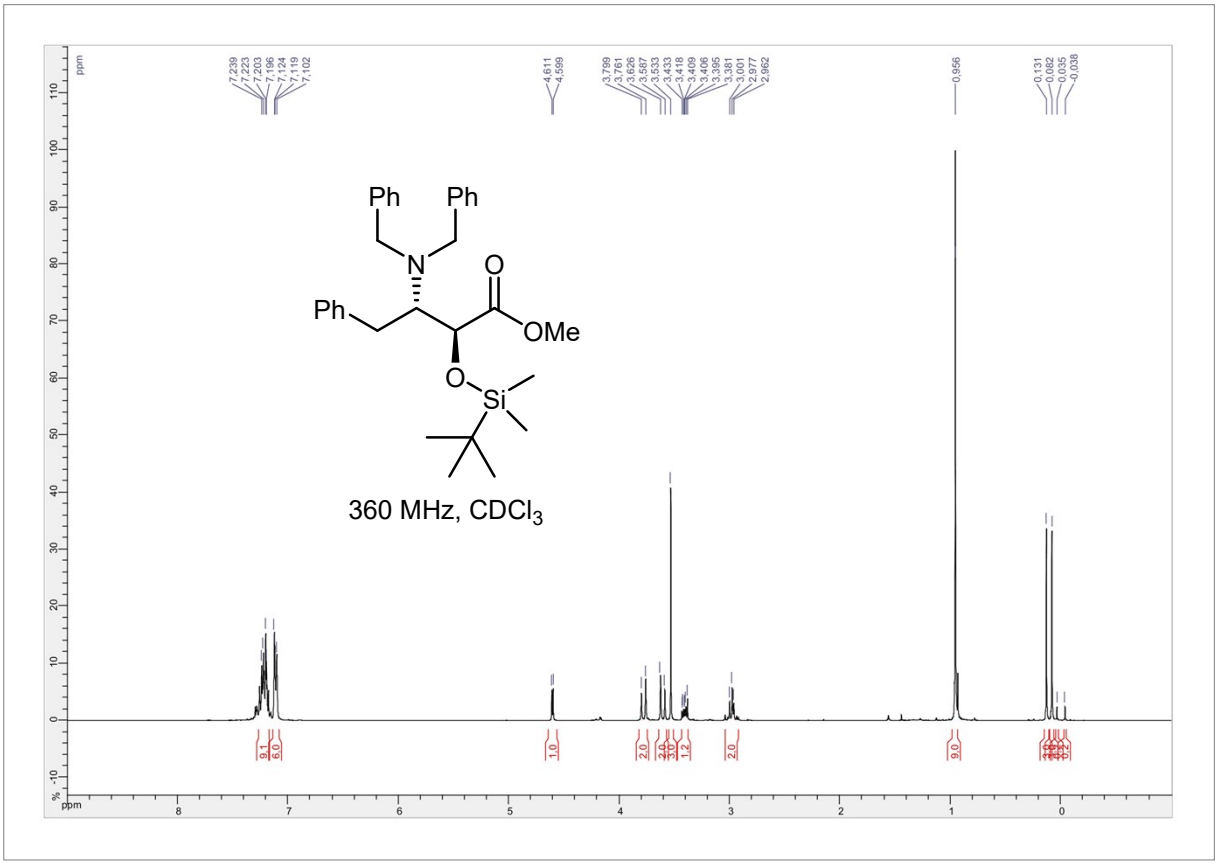


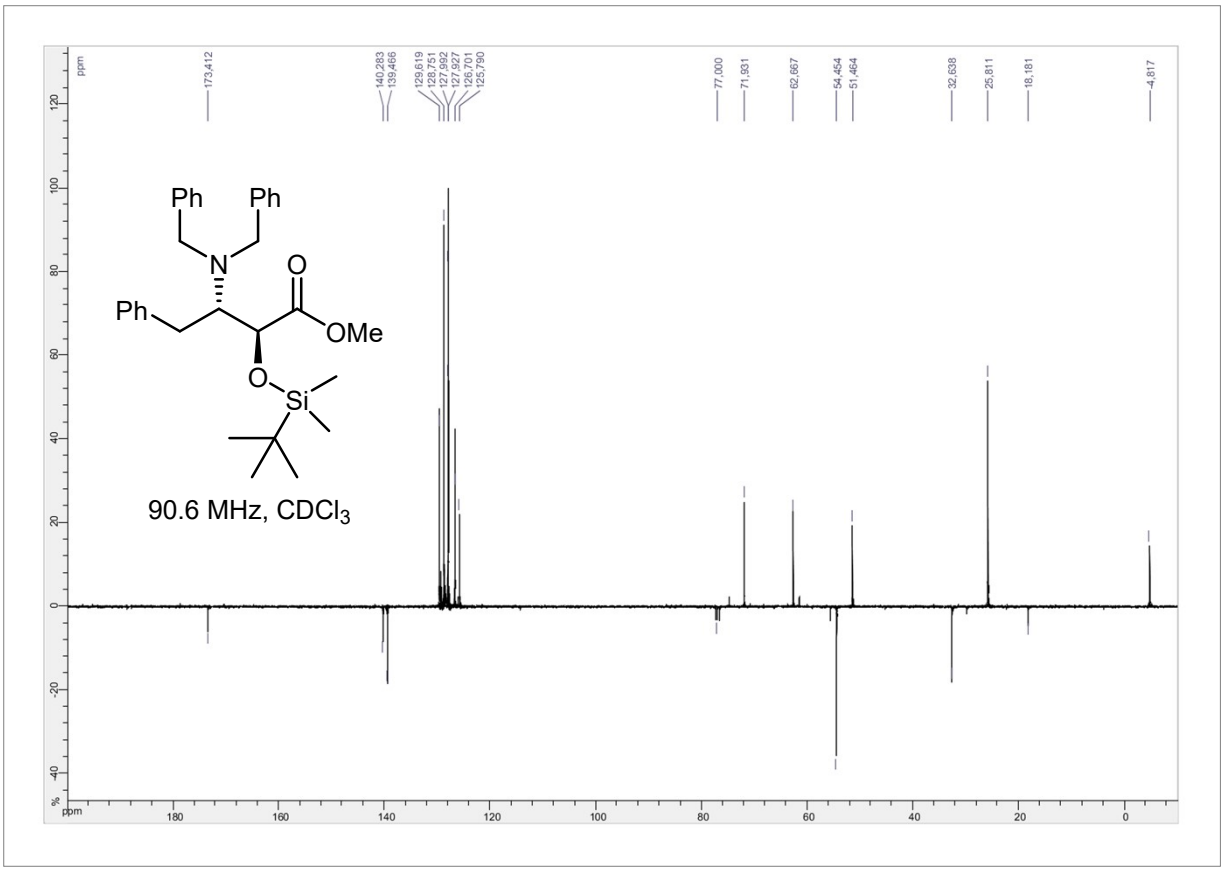
2-(*tert*-Butyldiphenylsilyloxy)malononitrile : H-MAC-TBDPS **(1c)**



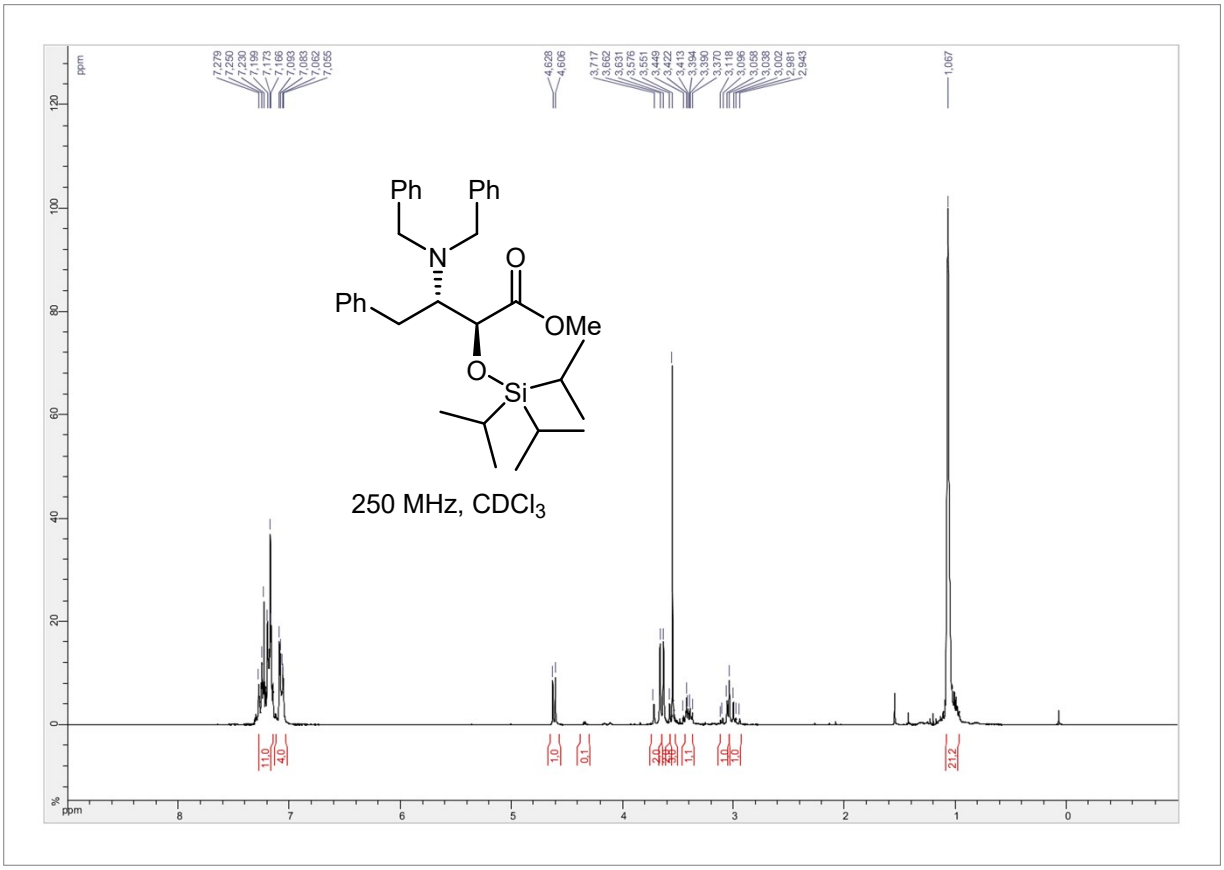


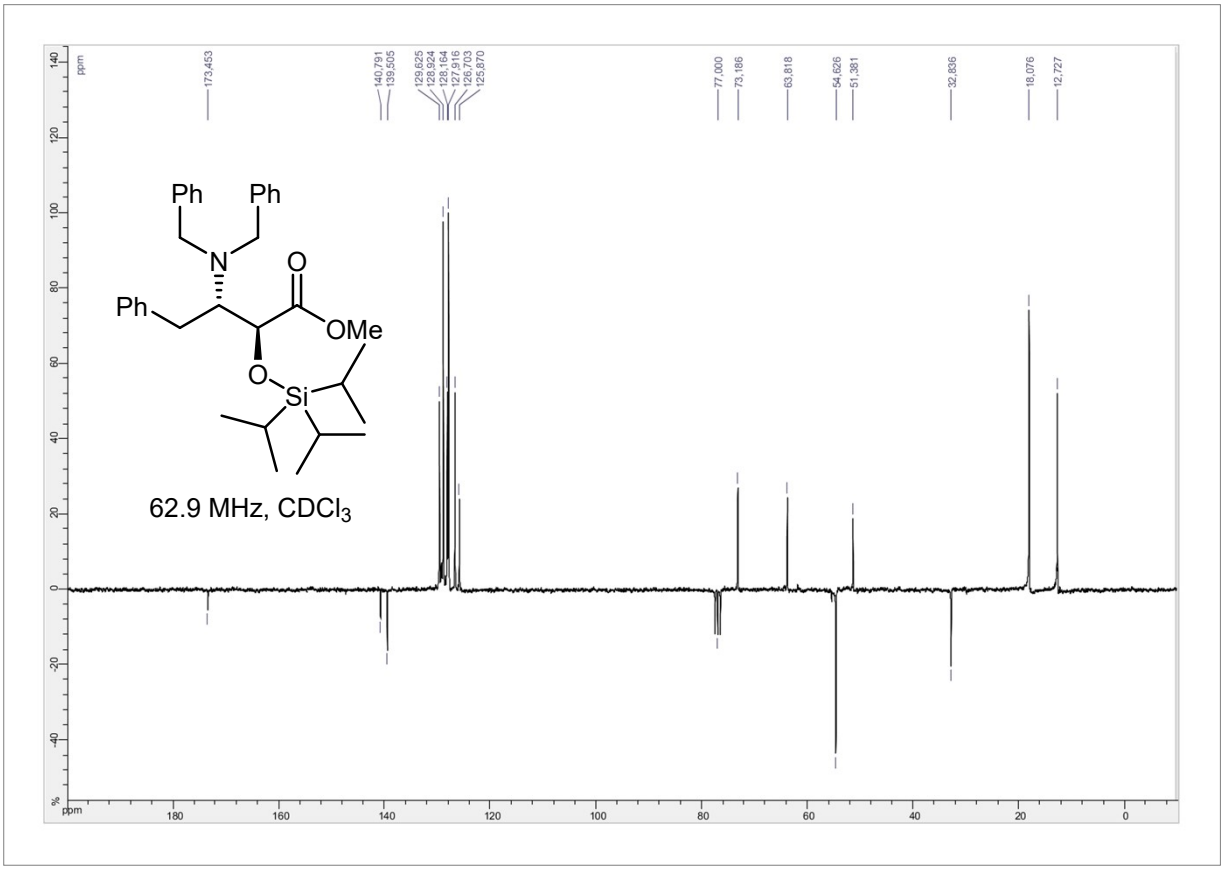
Methyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **(4a)**



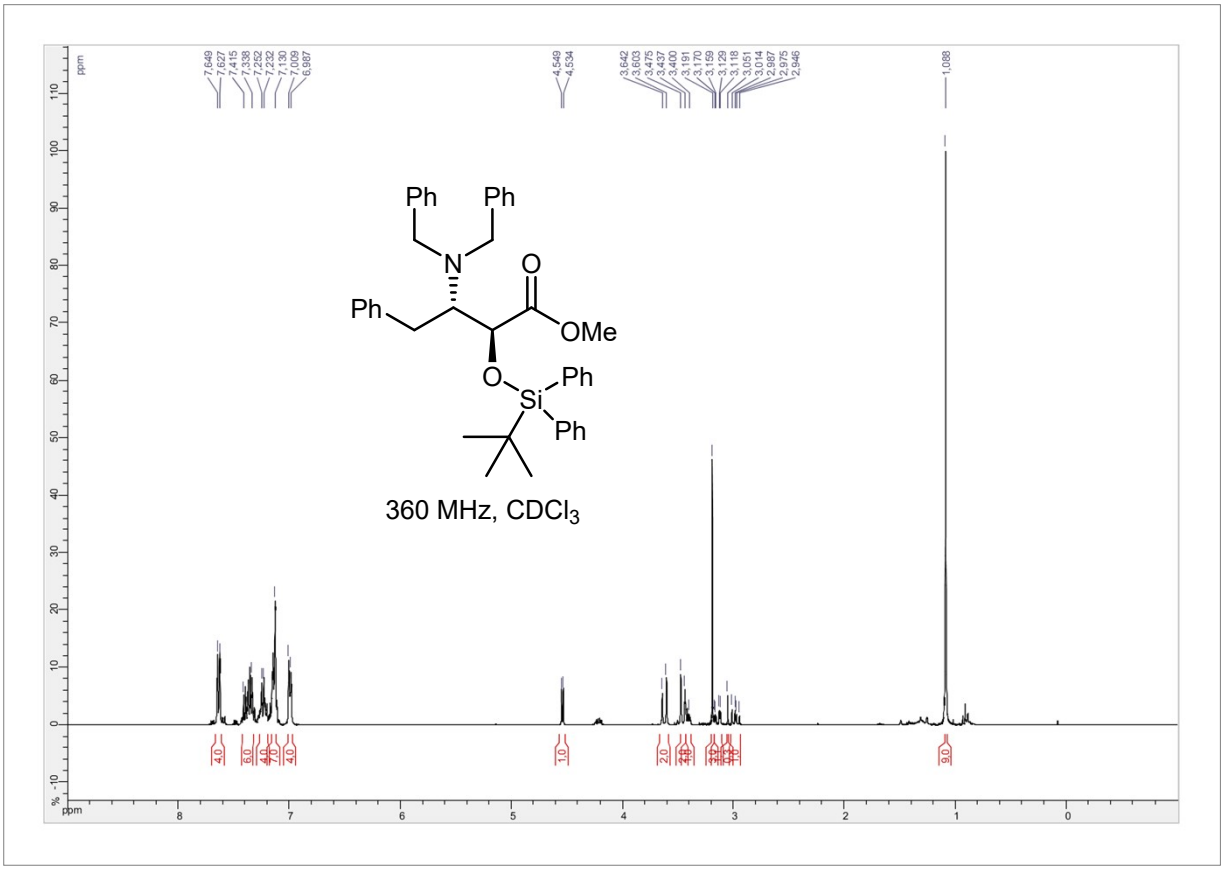


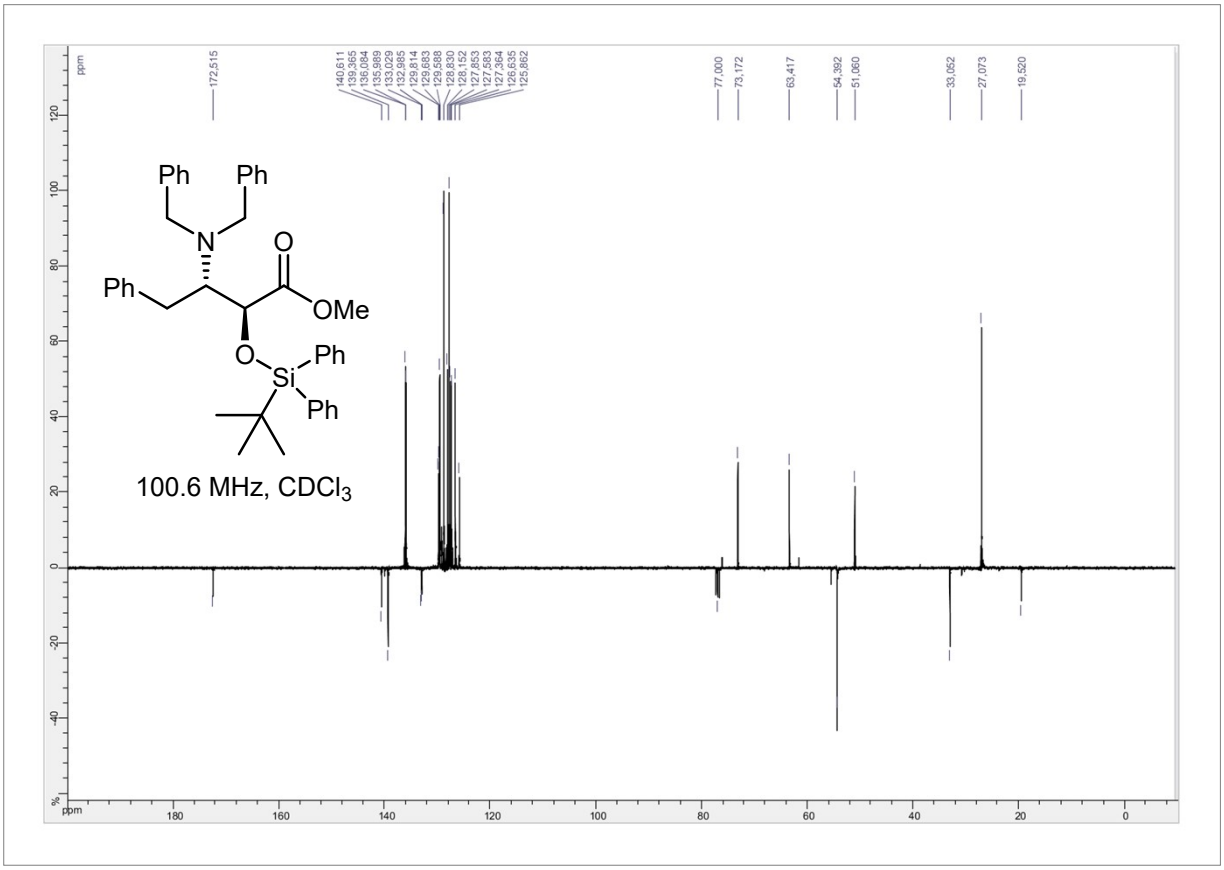
Methyl (2*S*,3*S*)-3-(dibenzylamino)-2-(triisopropylsilyloxy)-4-phenylbutanoate **(4b)**



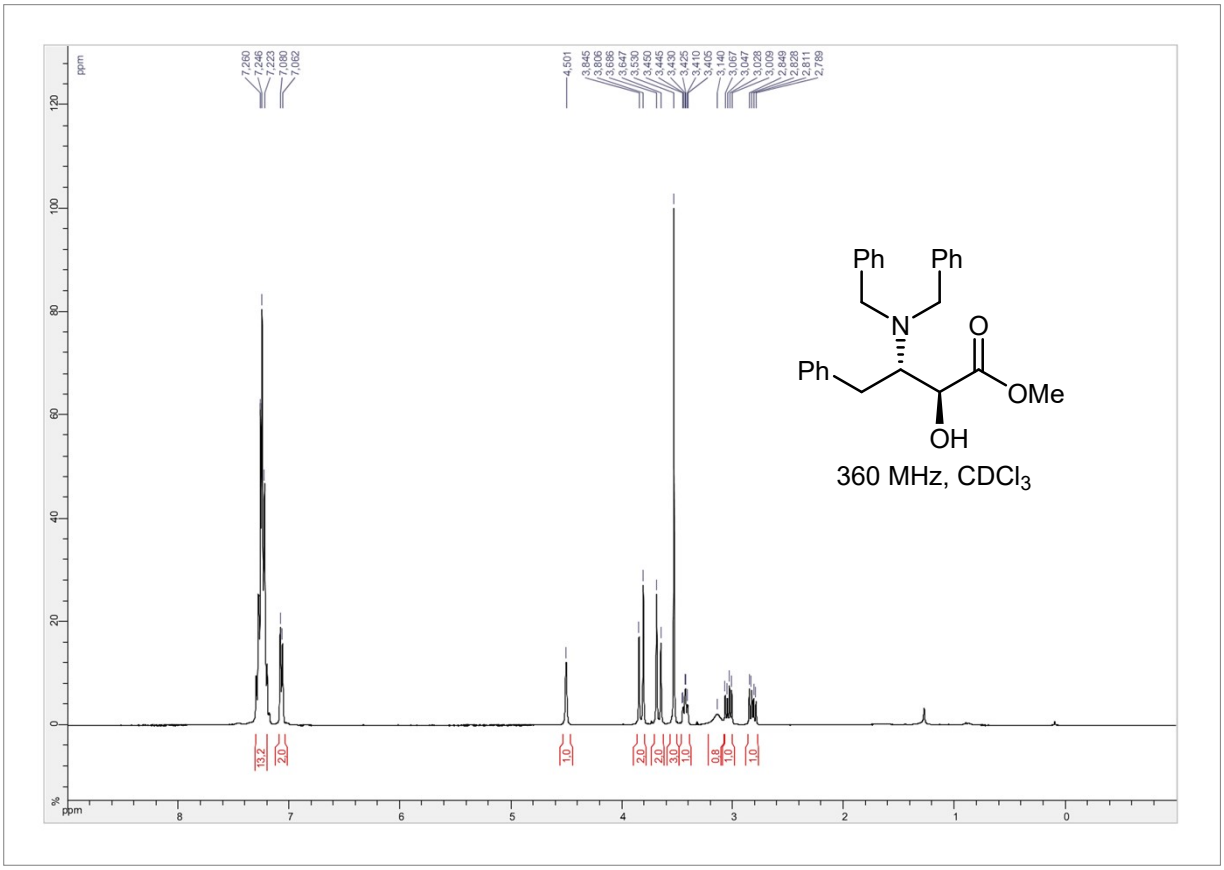


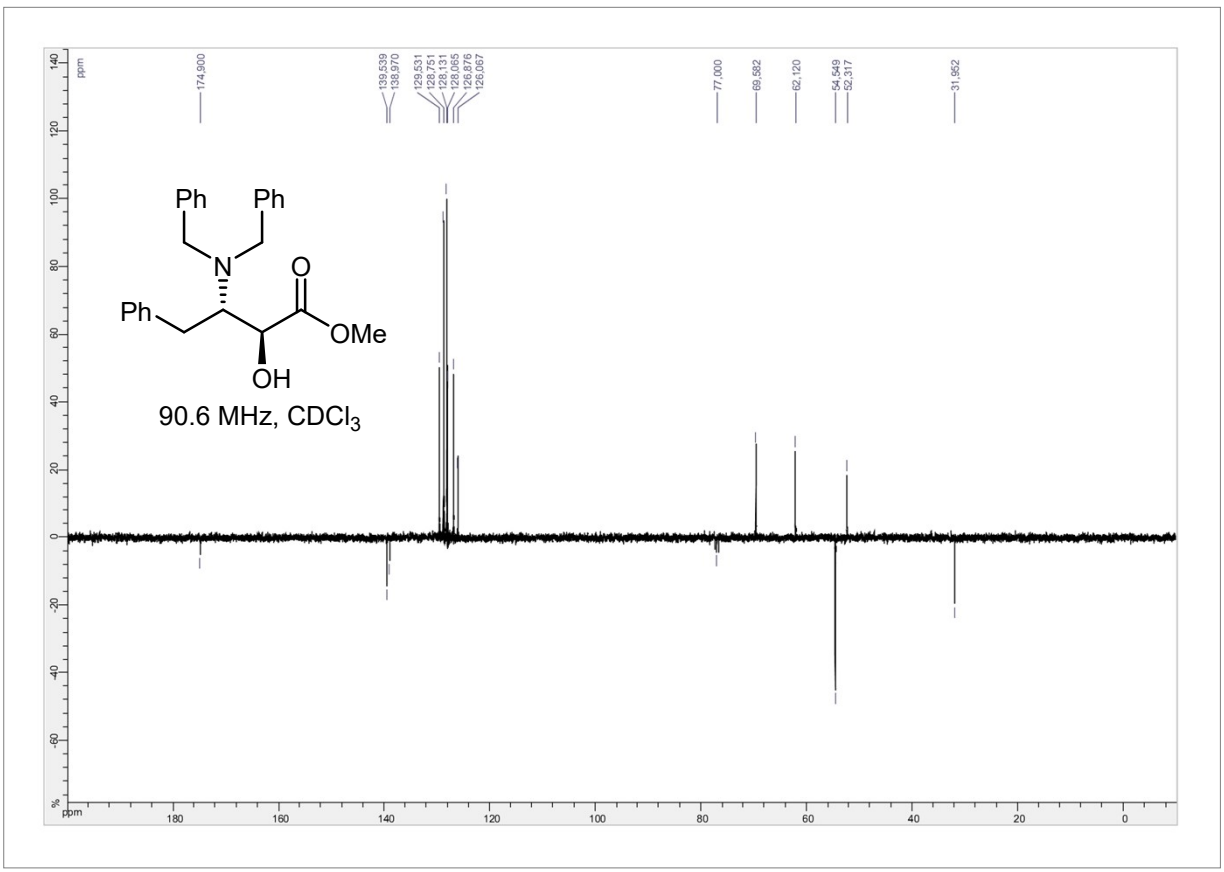
Methyl (2*S*,3*S*)-2-(*tert*-butyldiphenylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **(4c)**



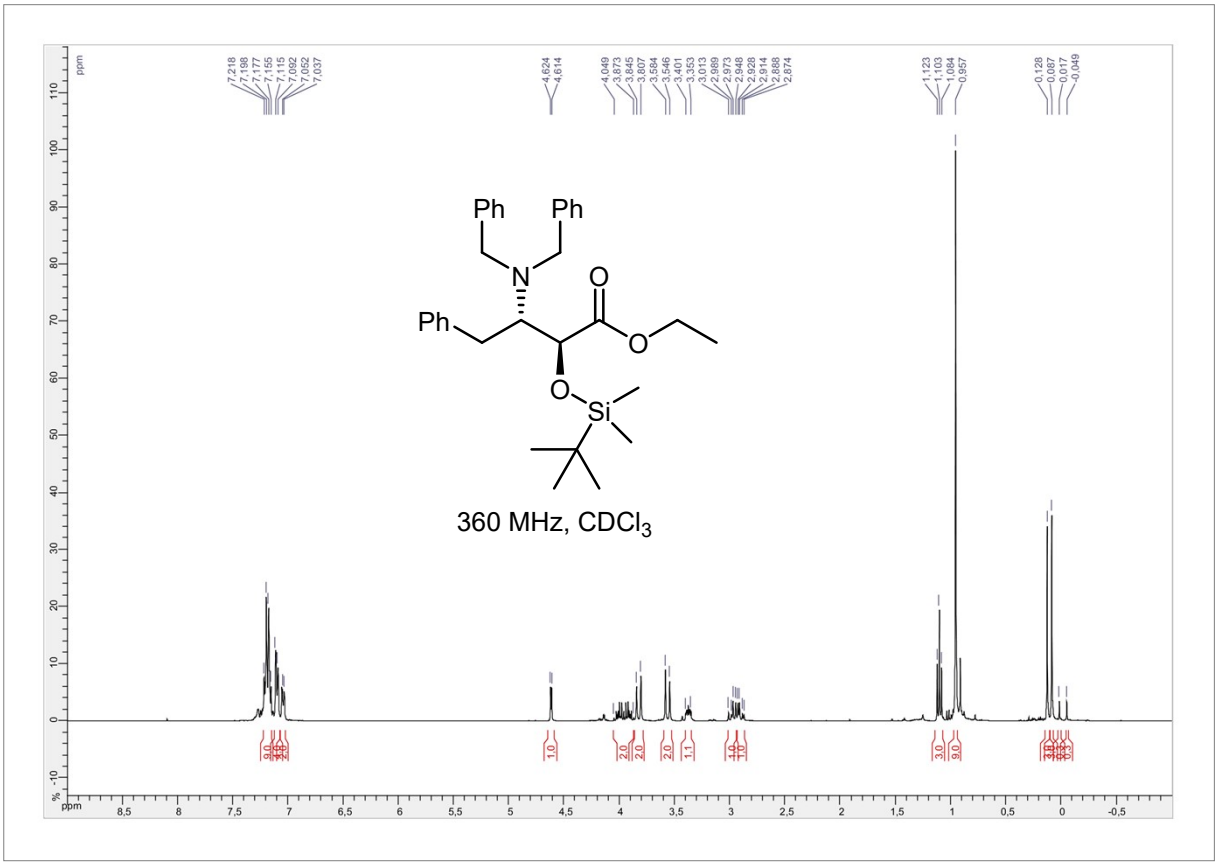


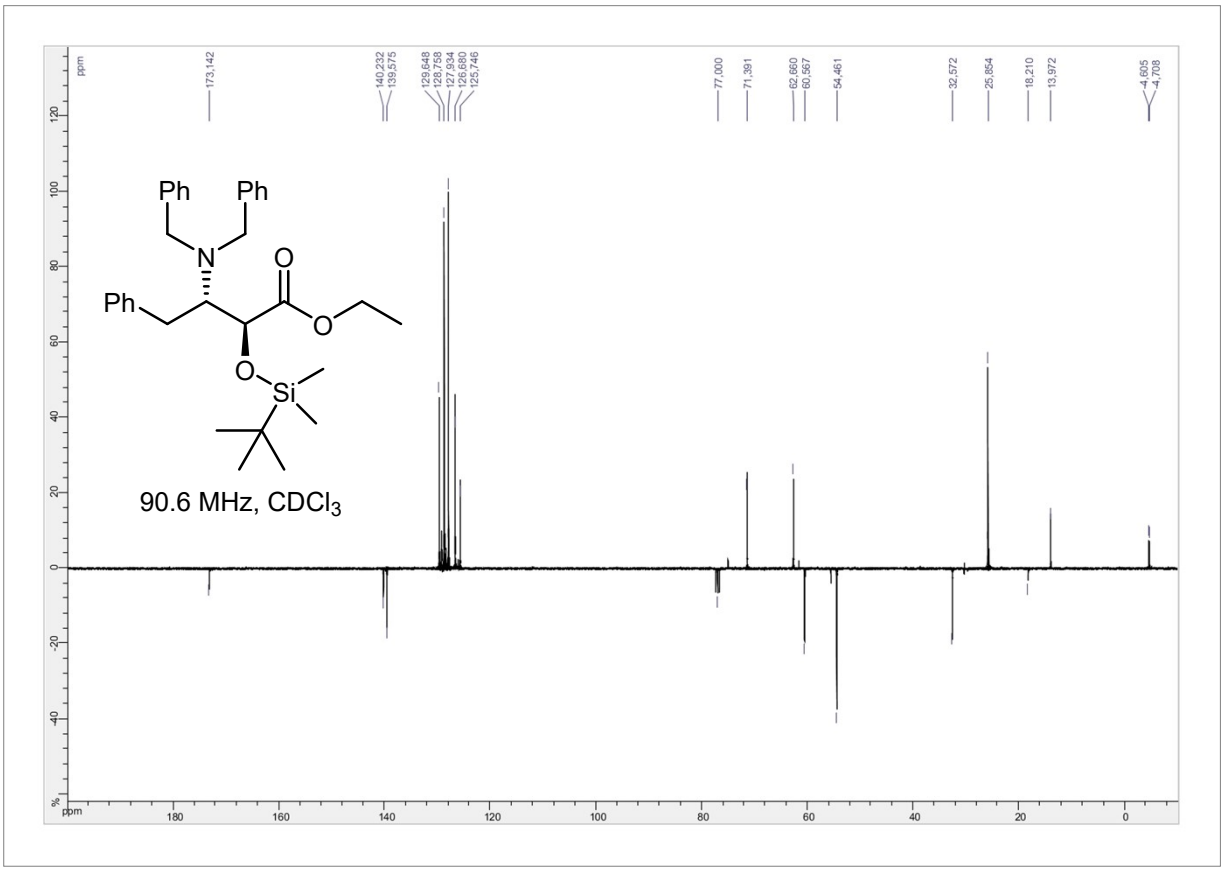
Methyl (2*S*,3*S*)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate **(5)**



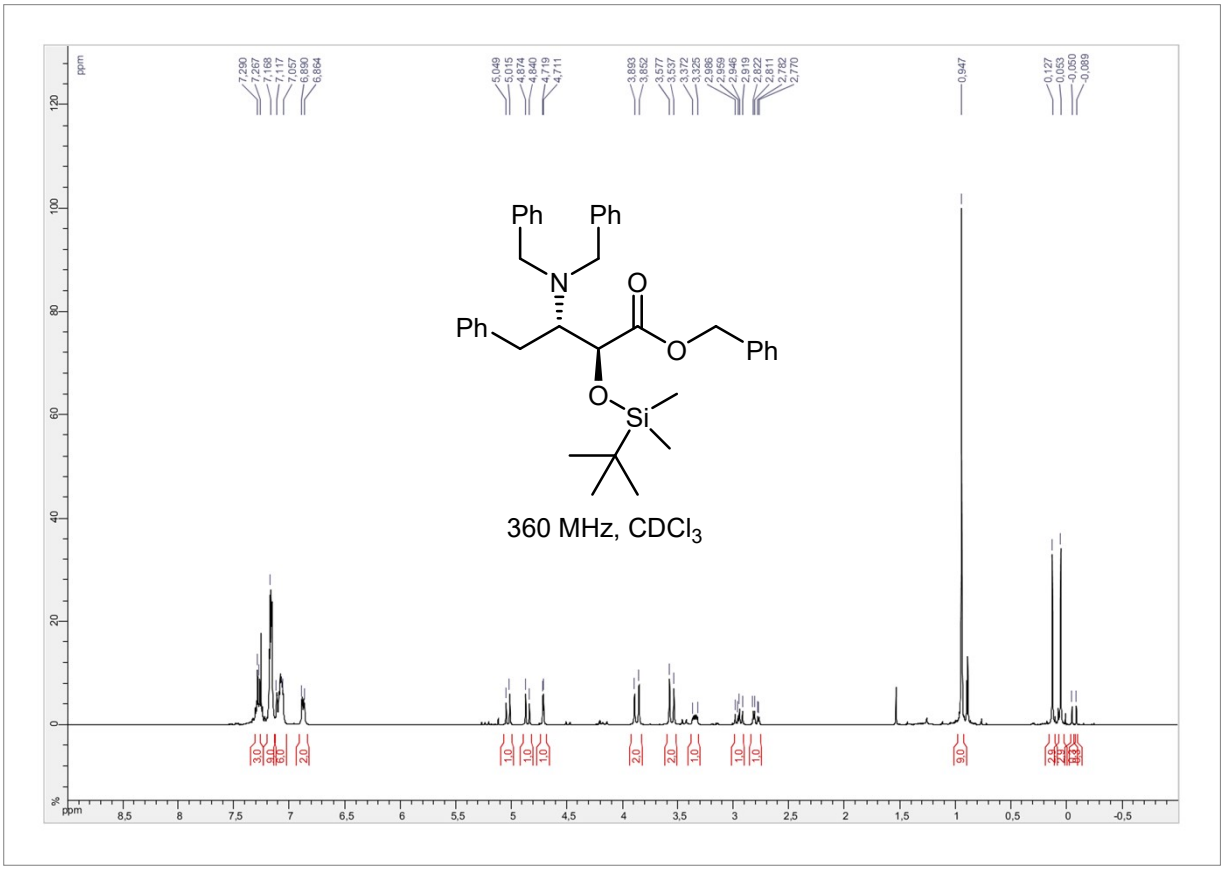


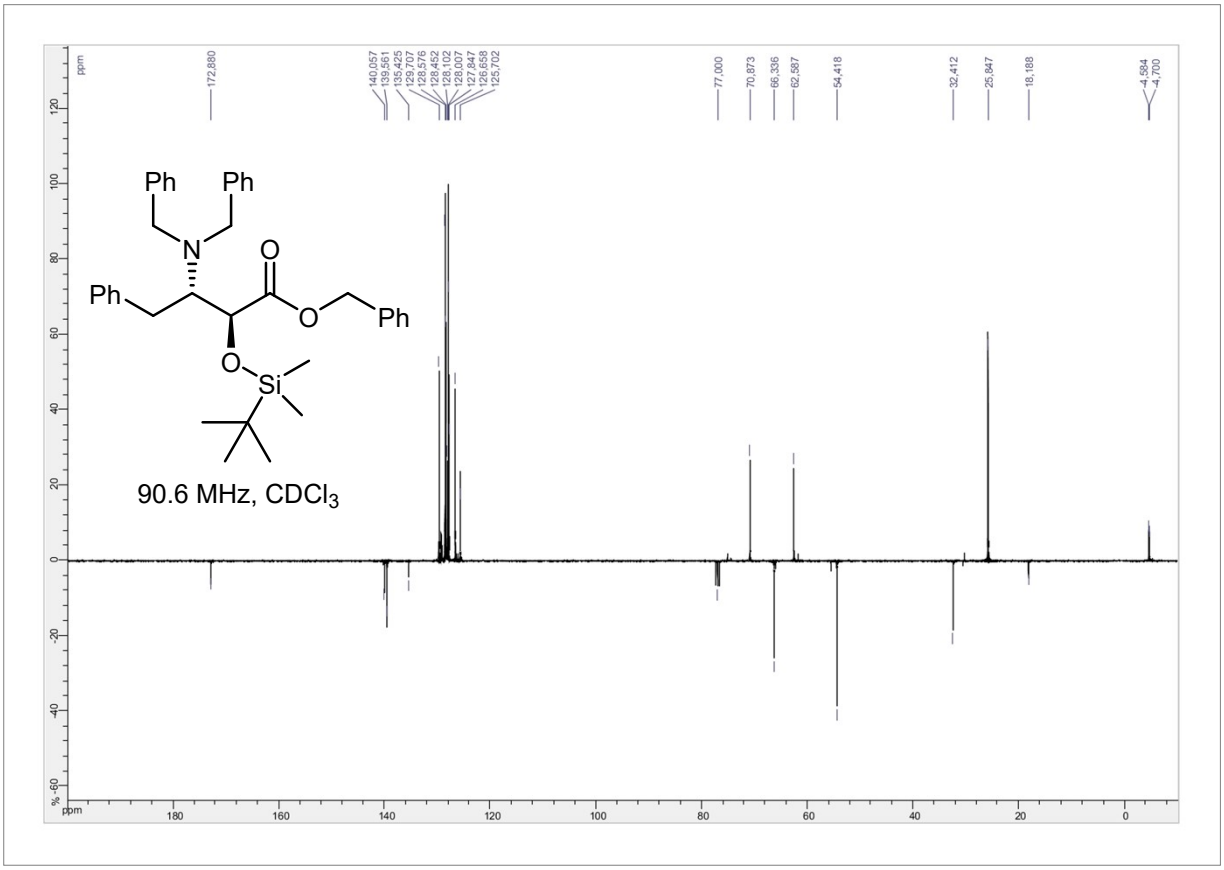
Ethyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **(6)**



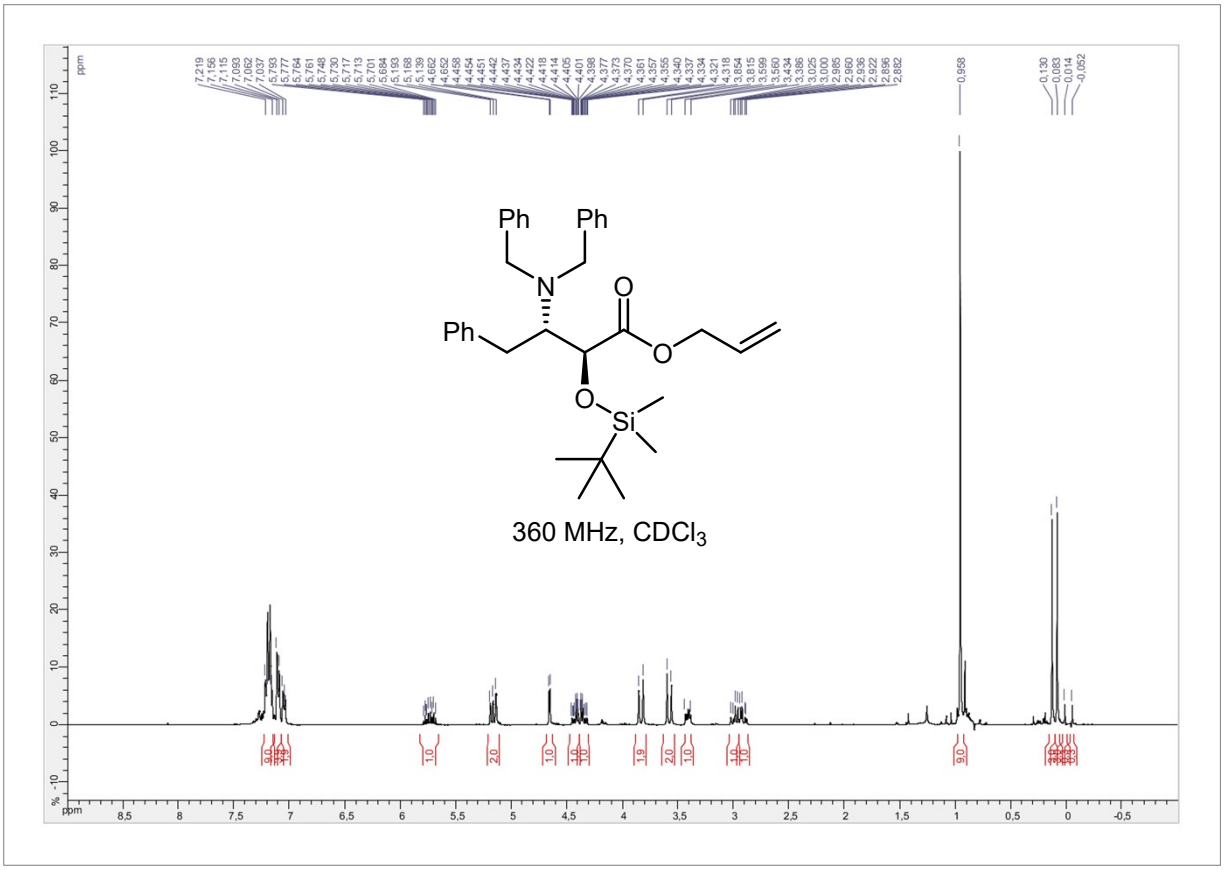


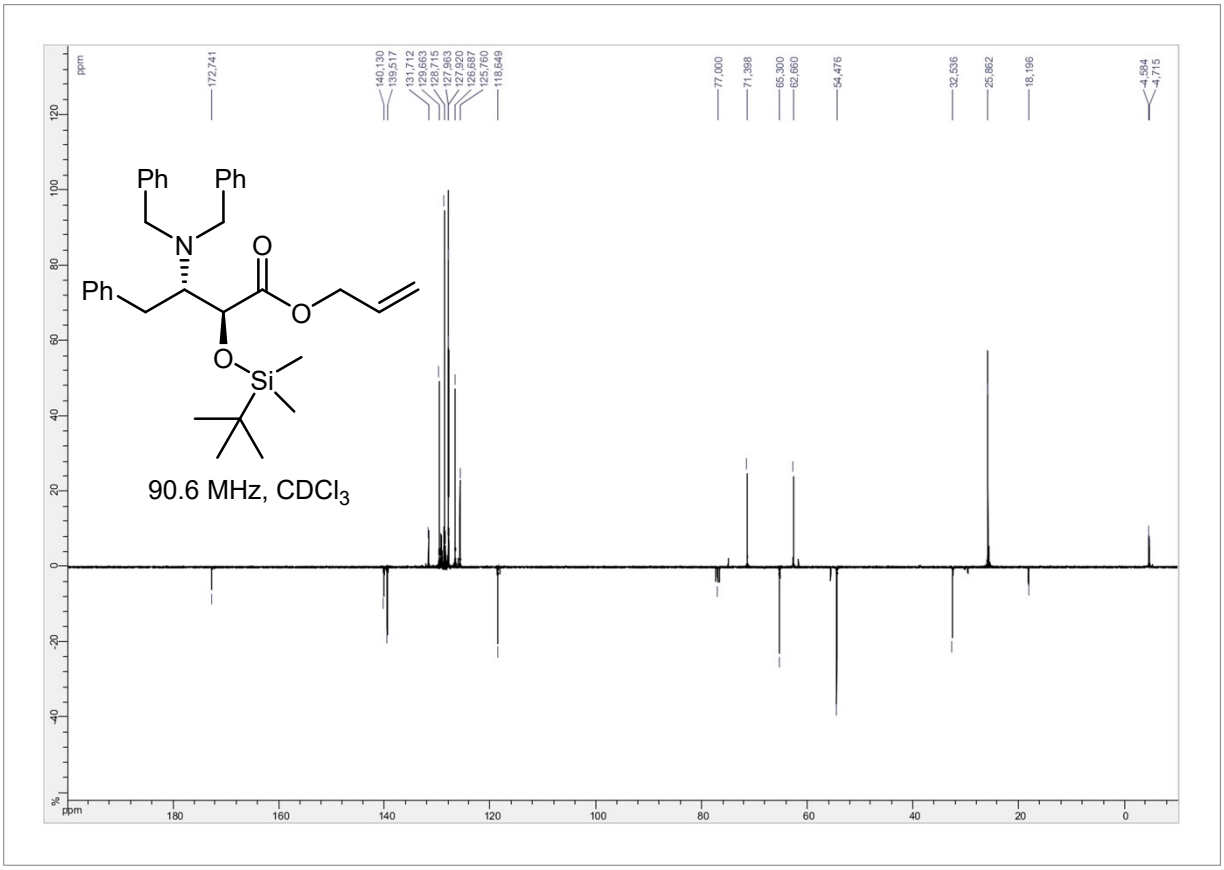
Benzyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **(7)**



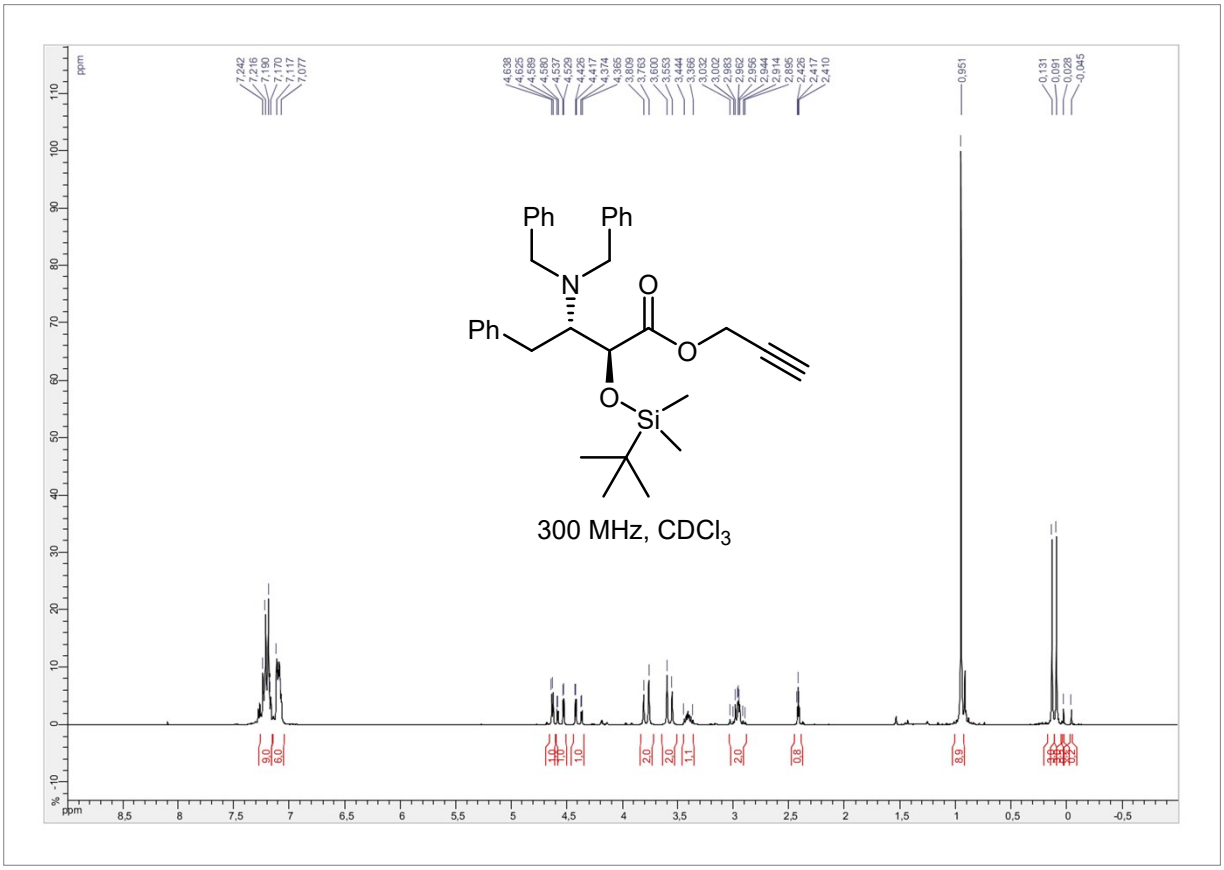


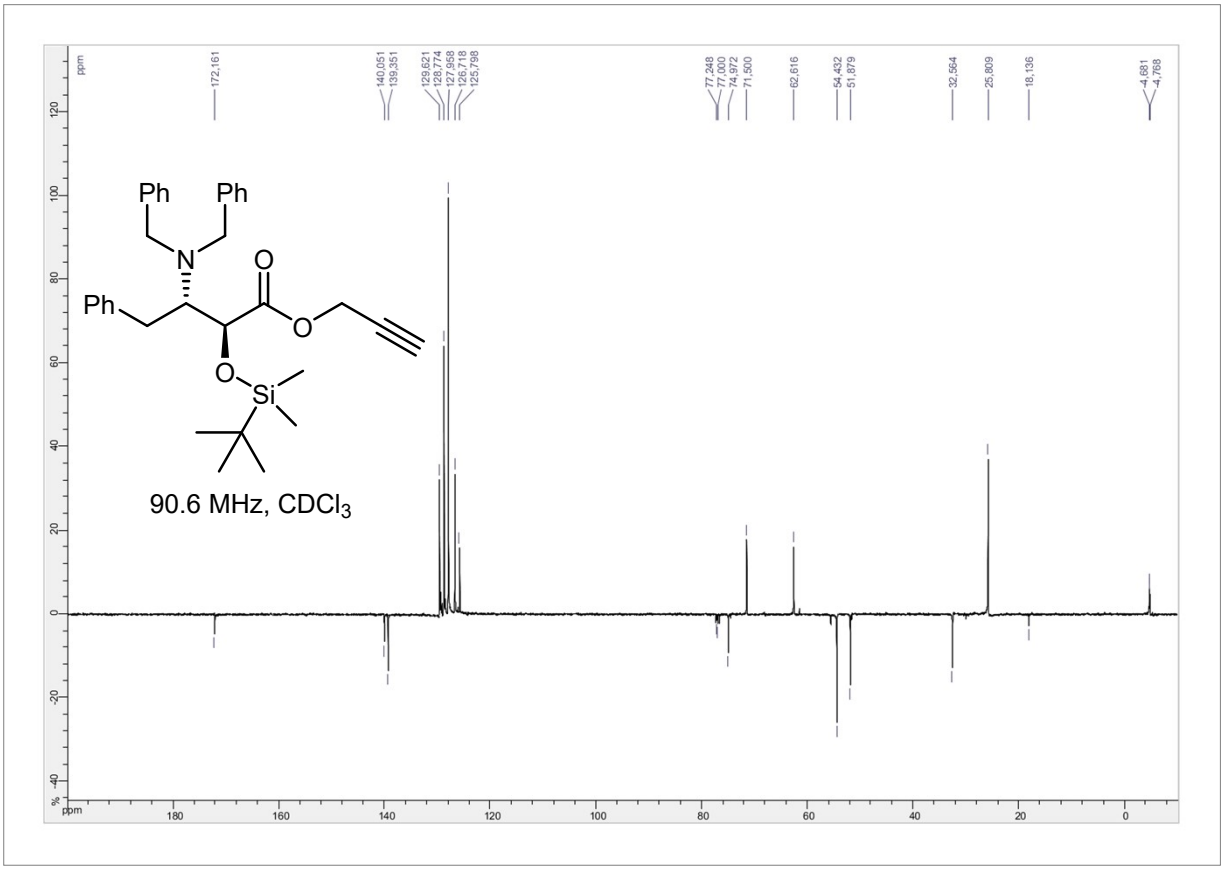
Allyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **(8)**



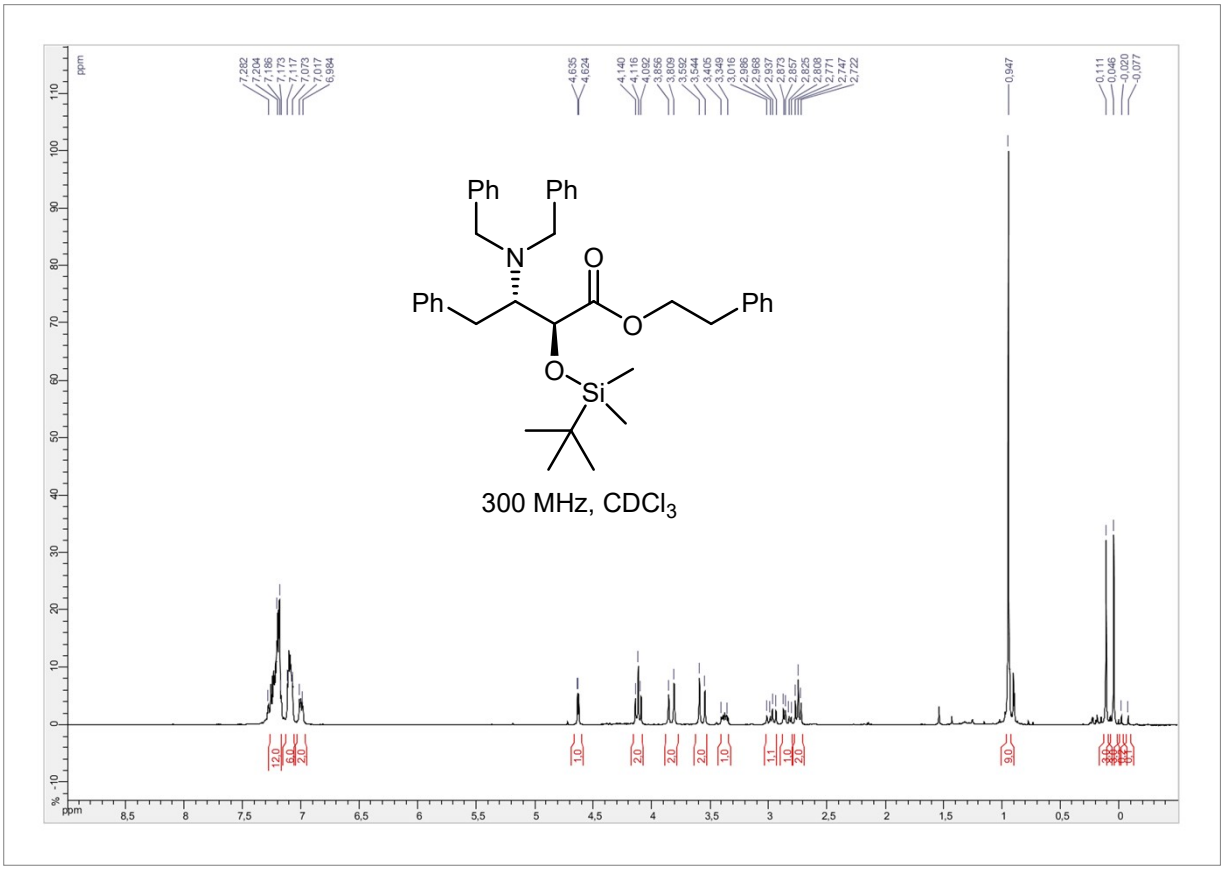


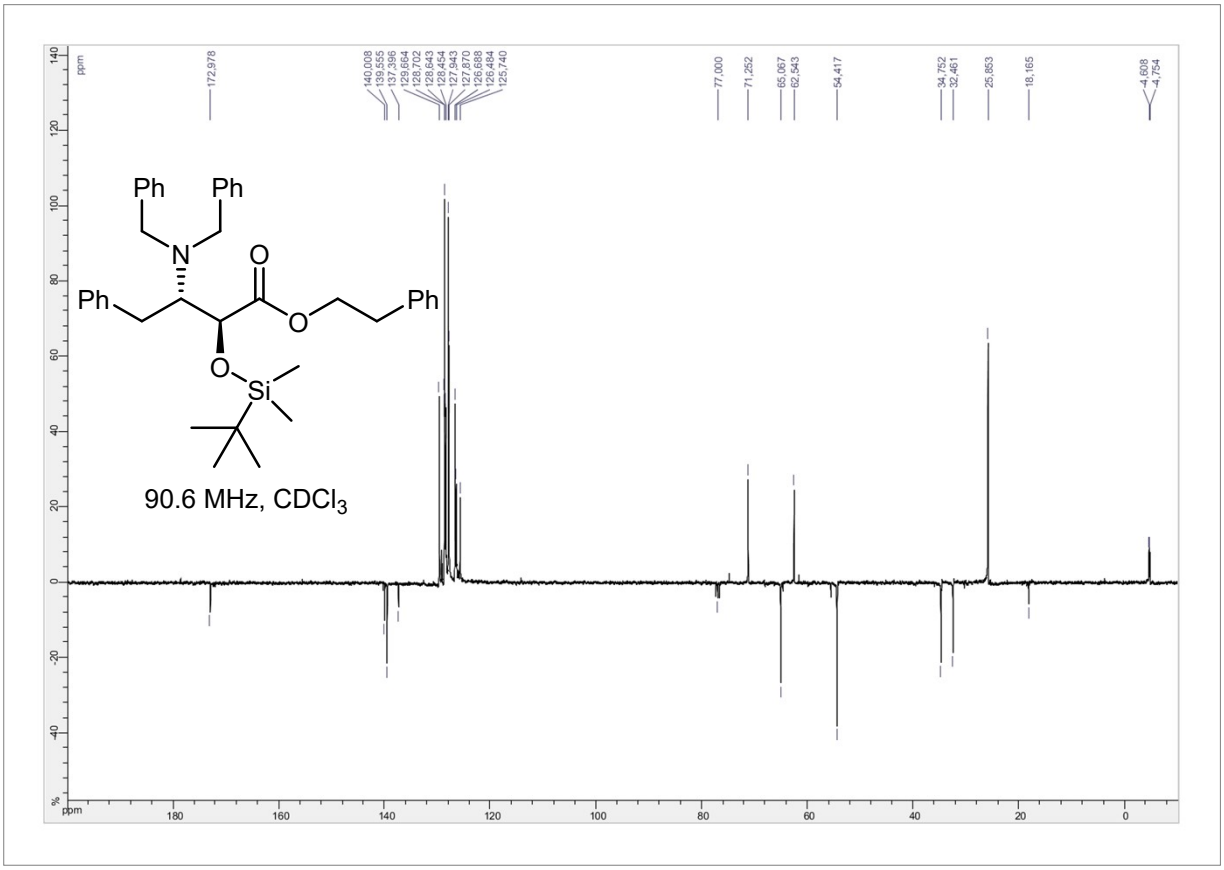
Propargyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **(9)**



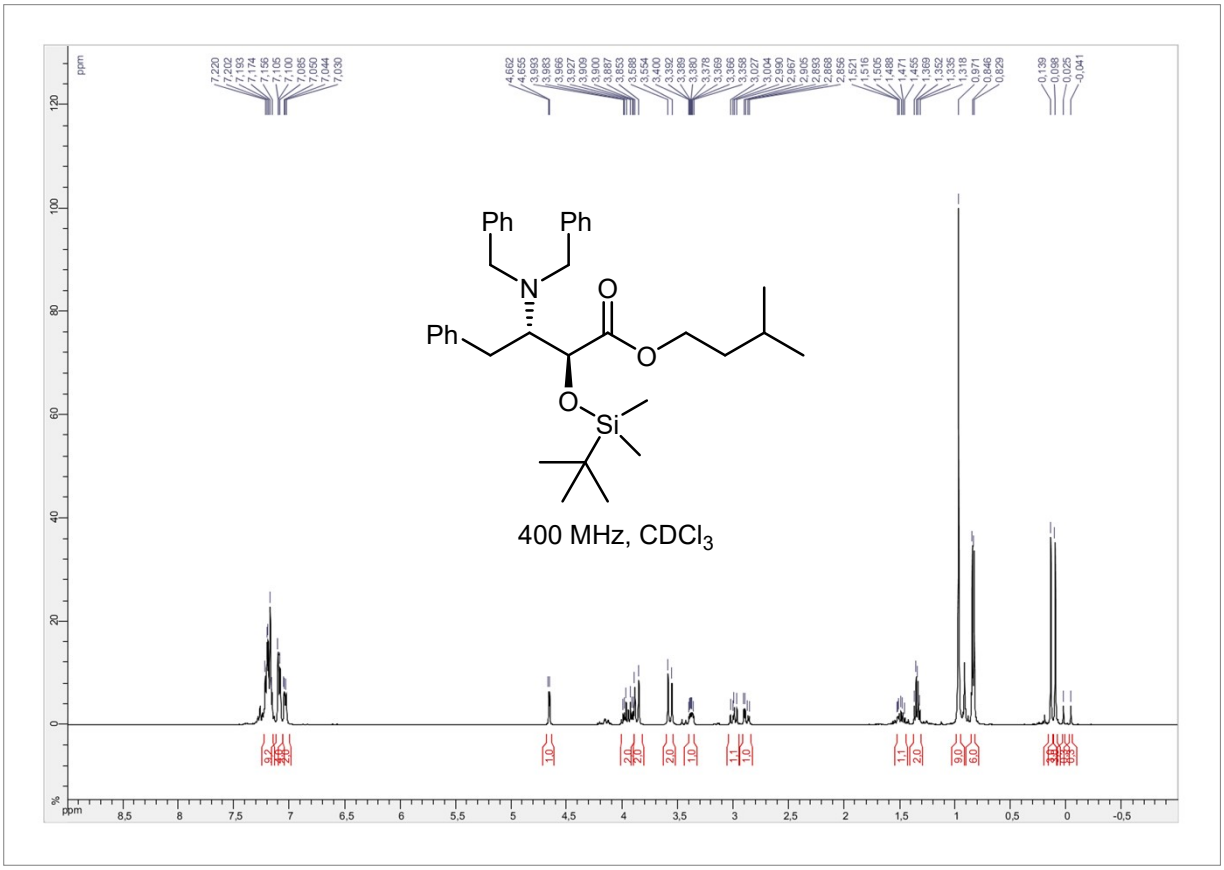


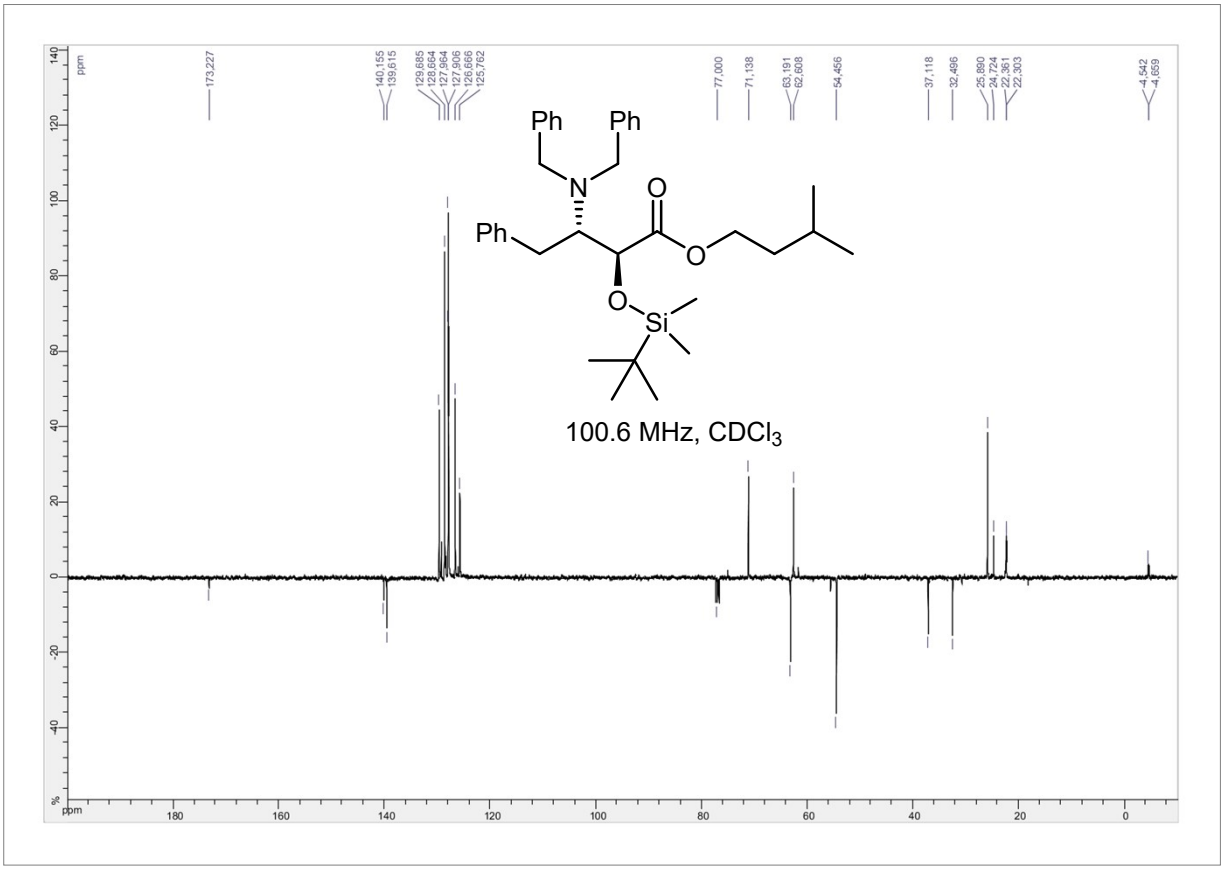
2-Phenylethyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **(10)**



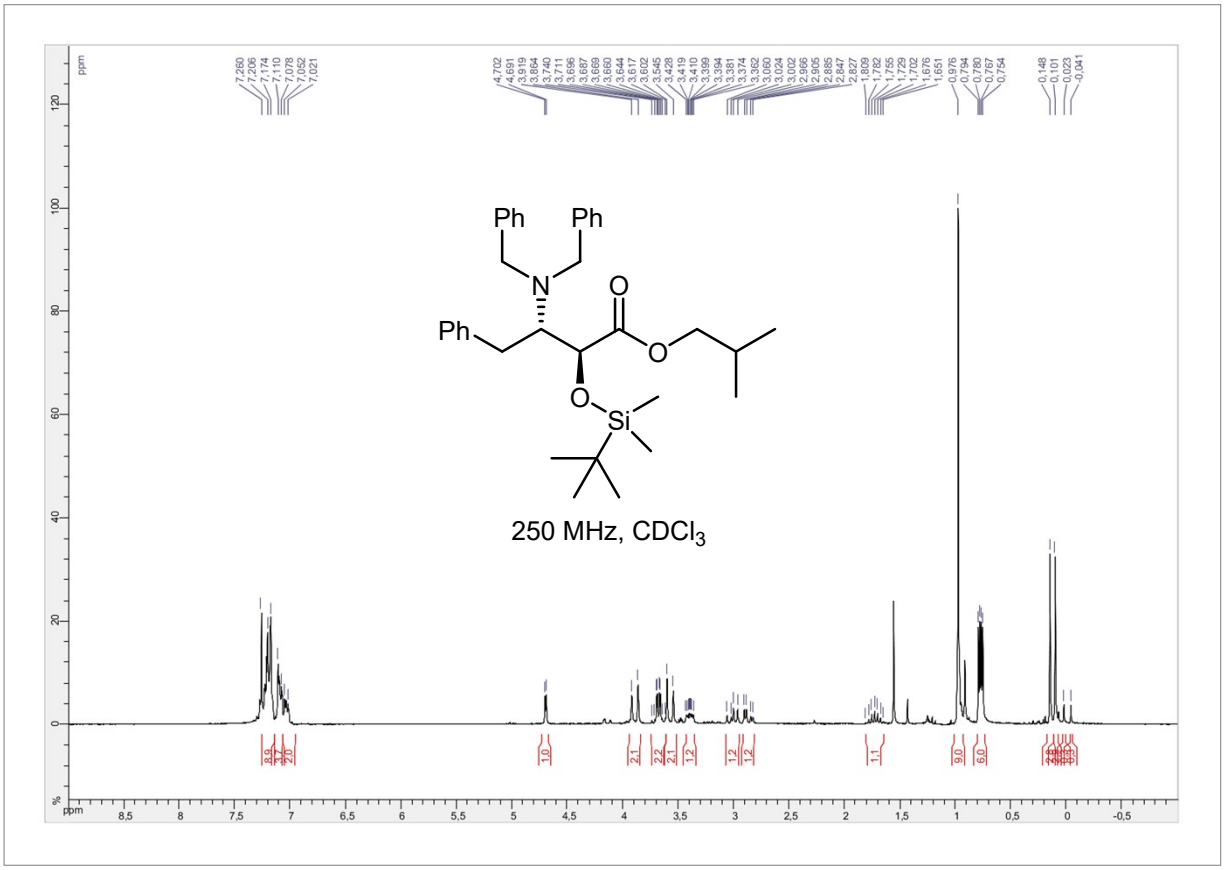


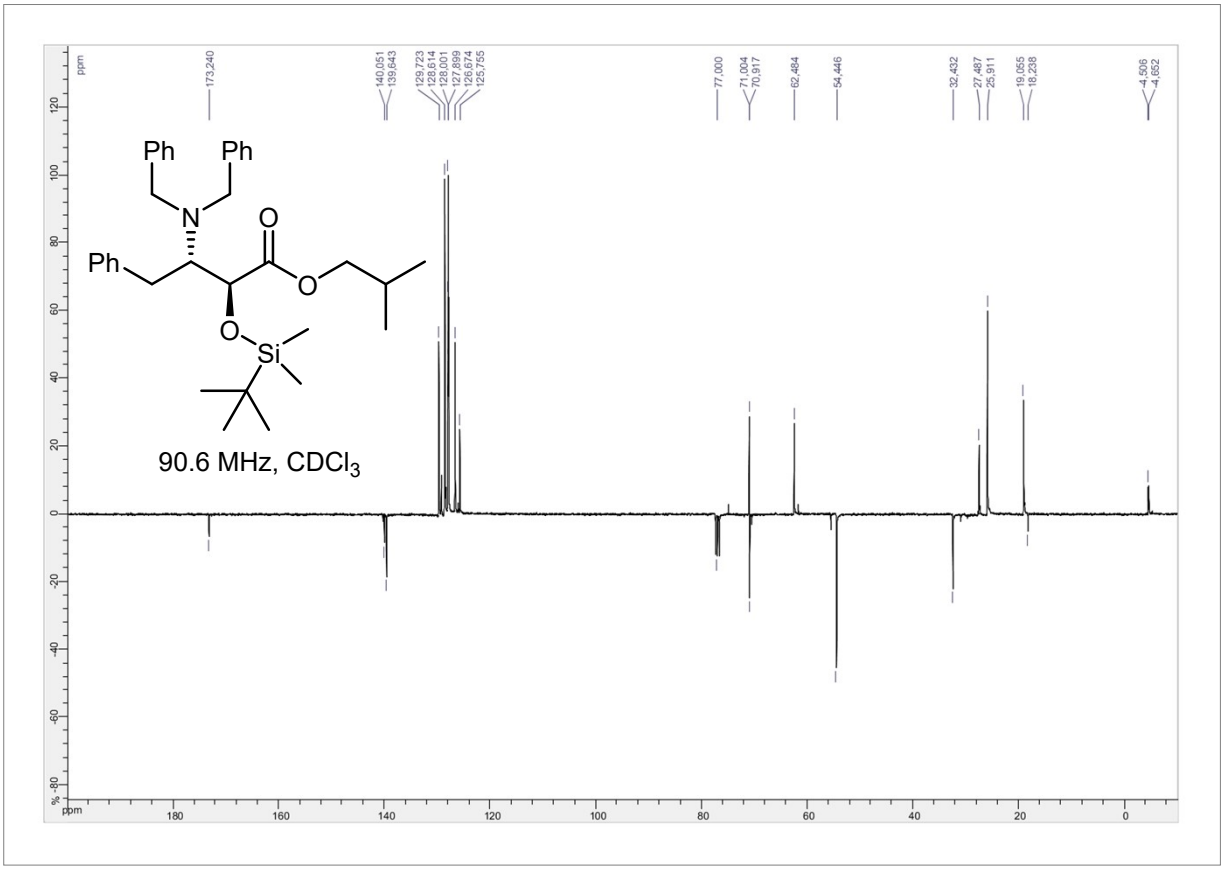
3-Methylbutyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **(11)**



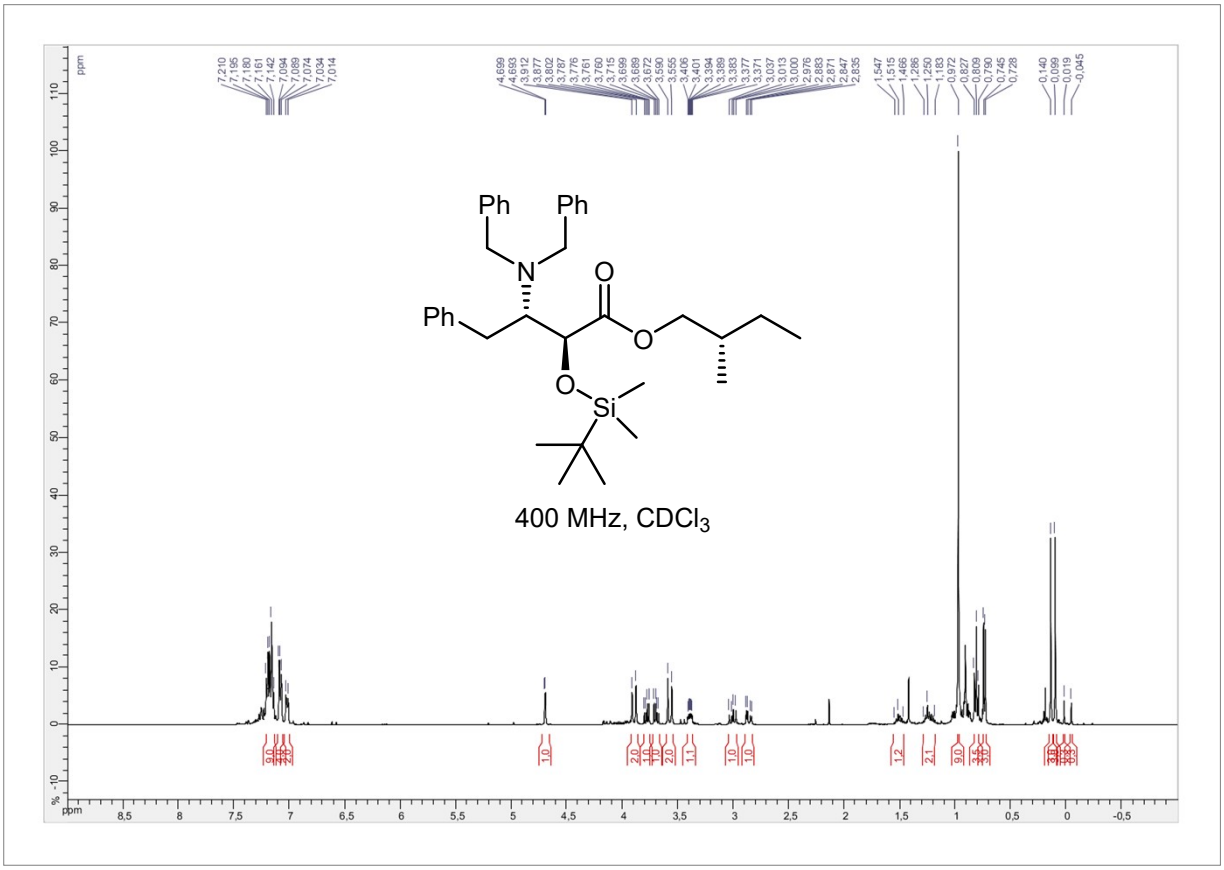


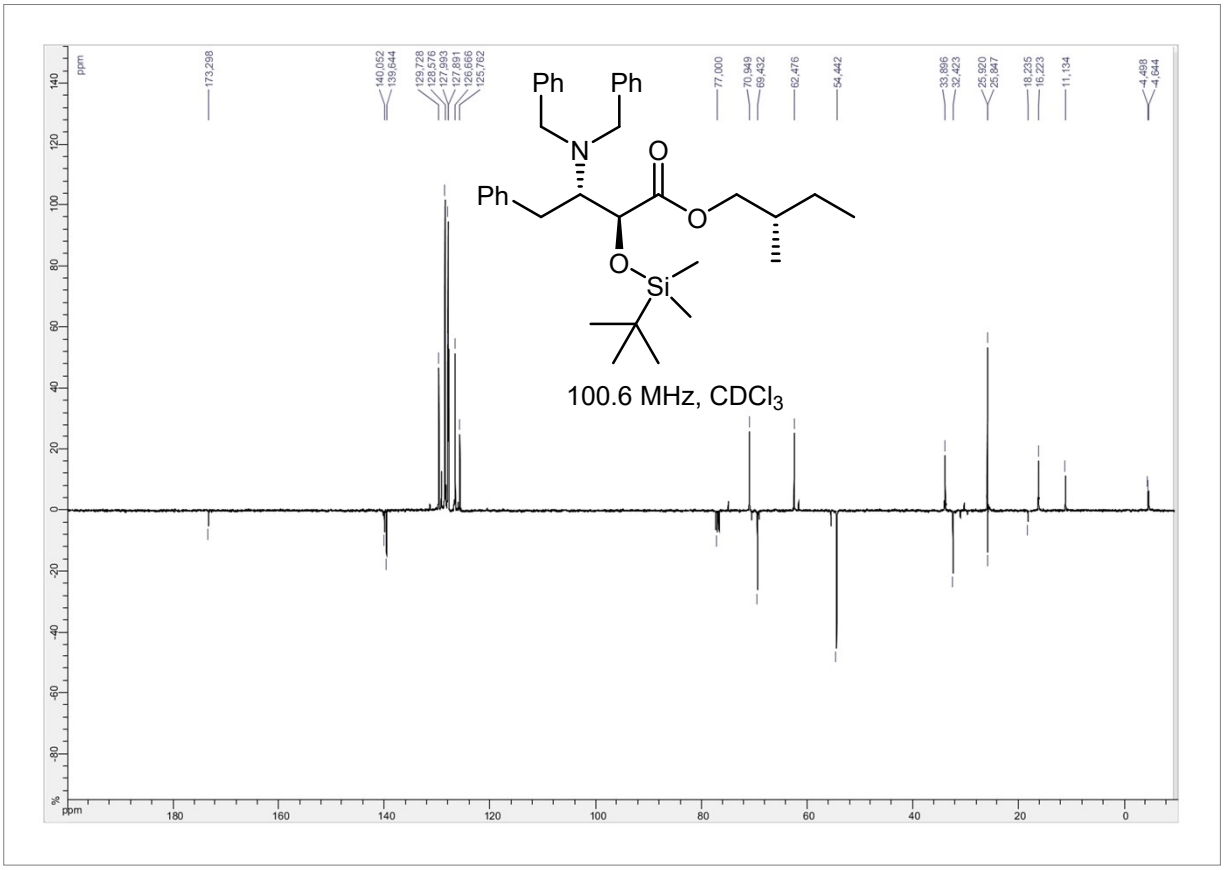
Isobutyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **(12)**



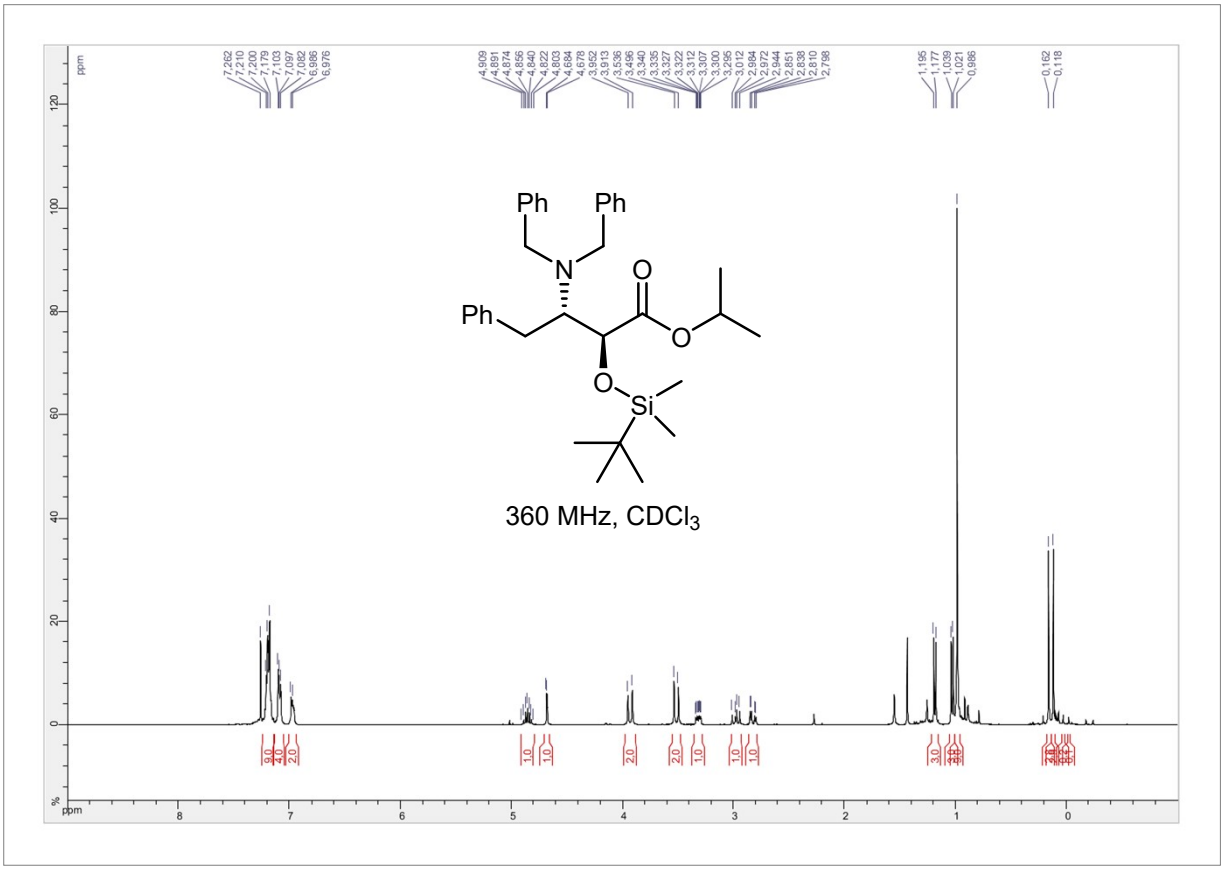


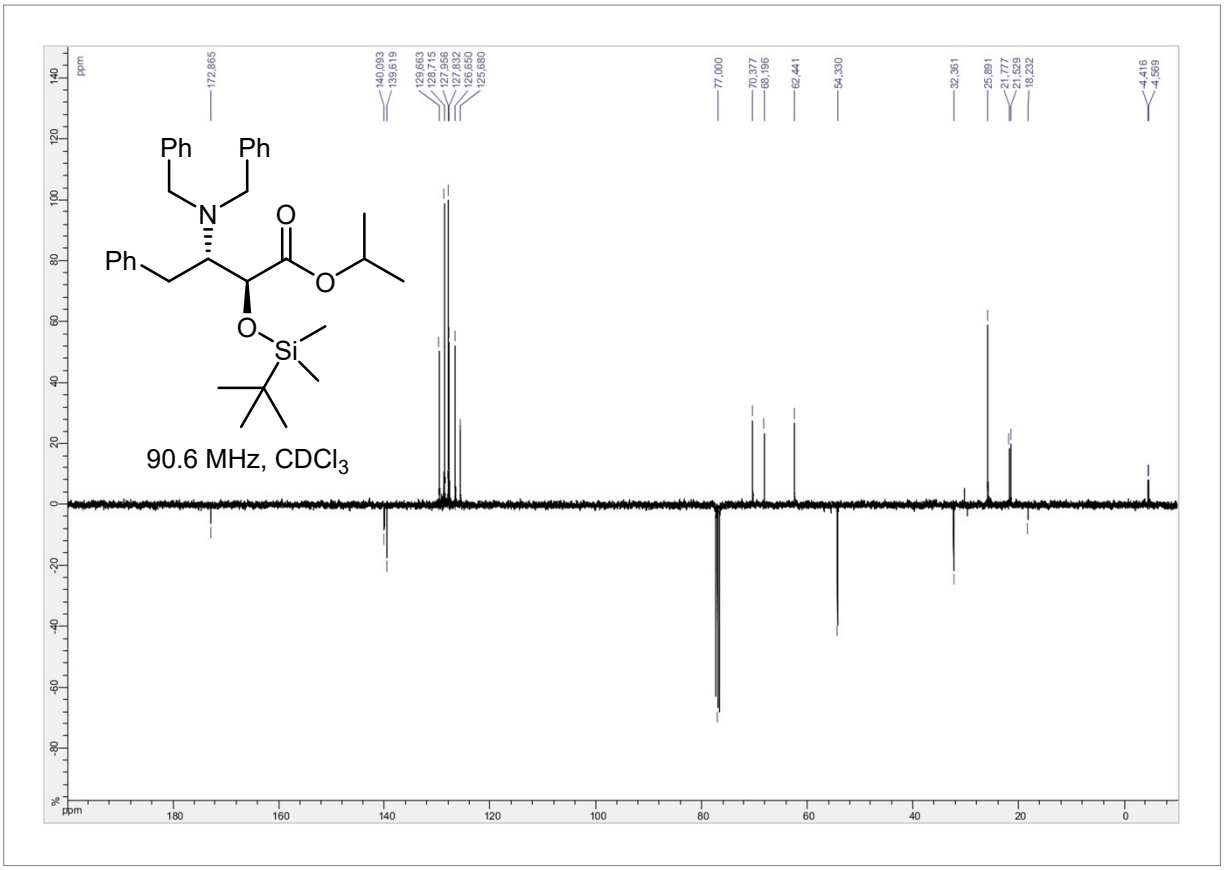
(*S*)-2-Methylbutyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **(13)**



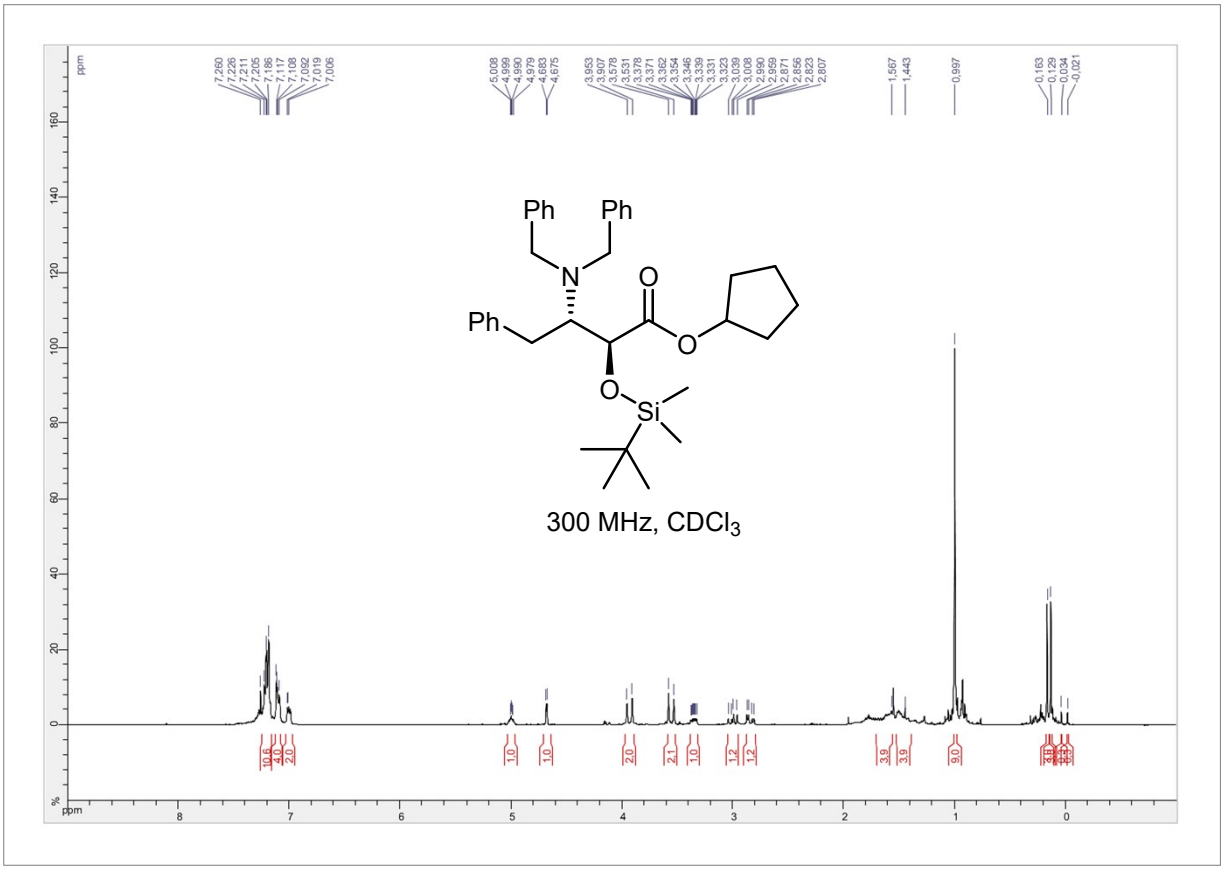


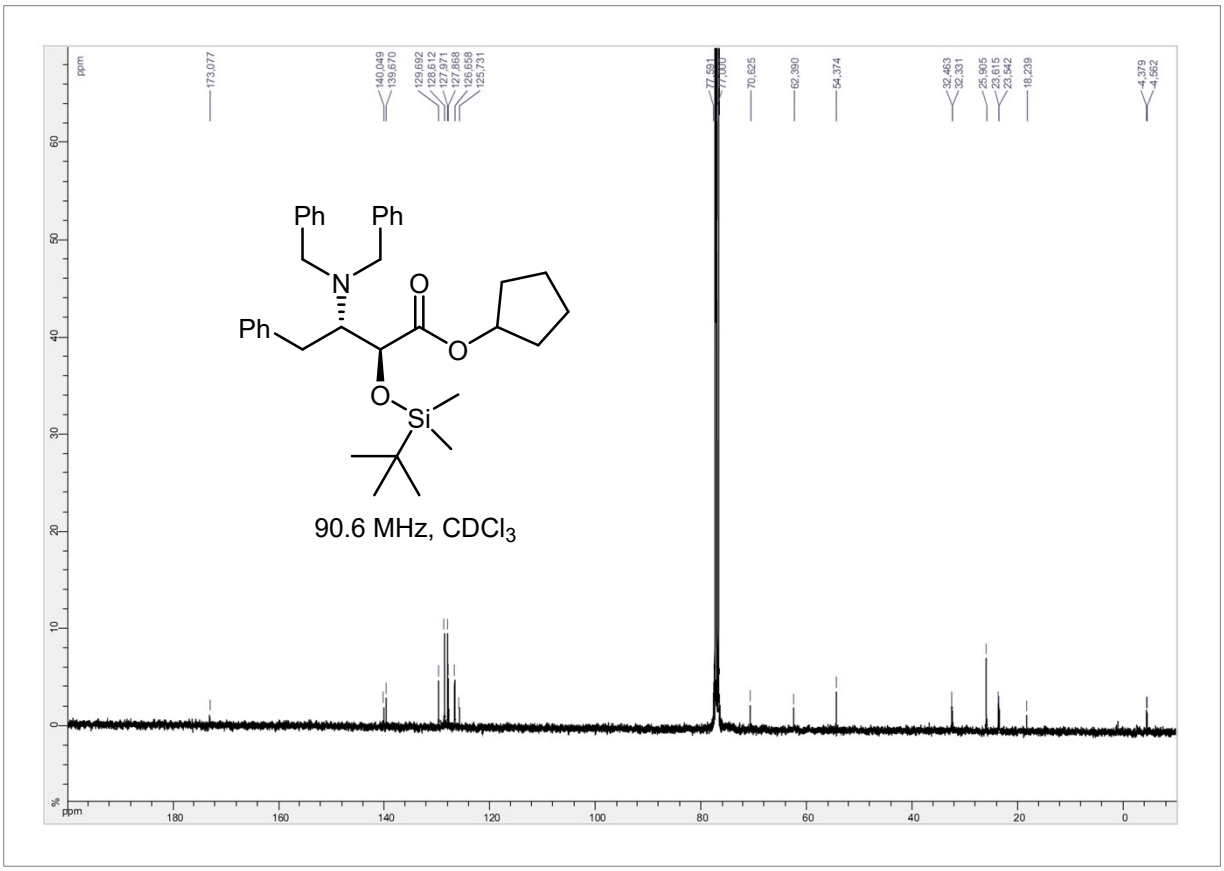
Isopropyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **(14)**



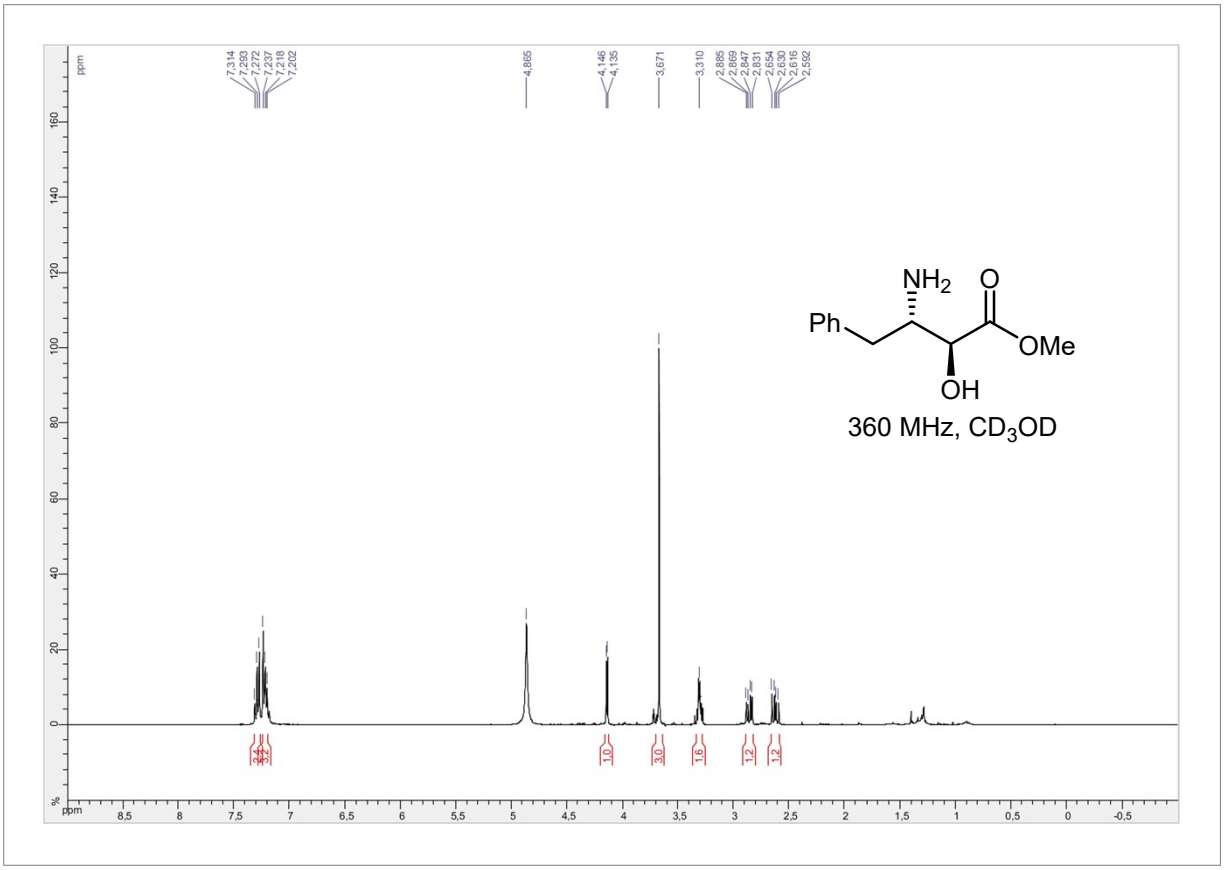


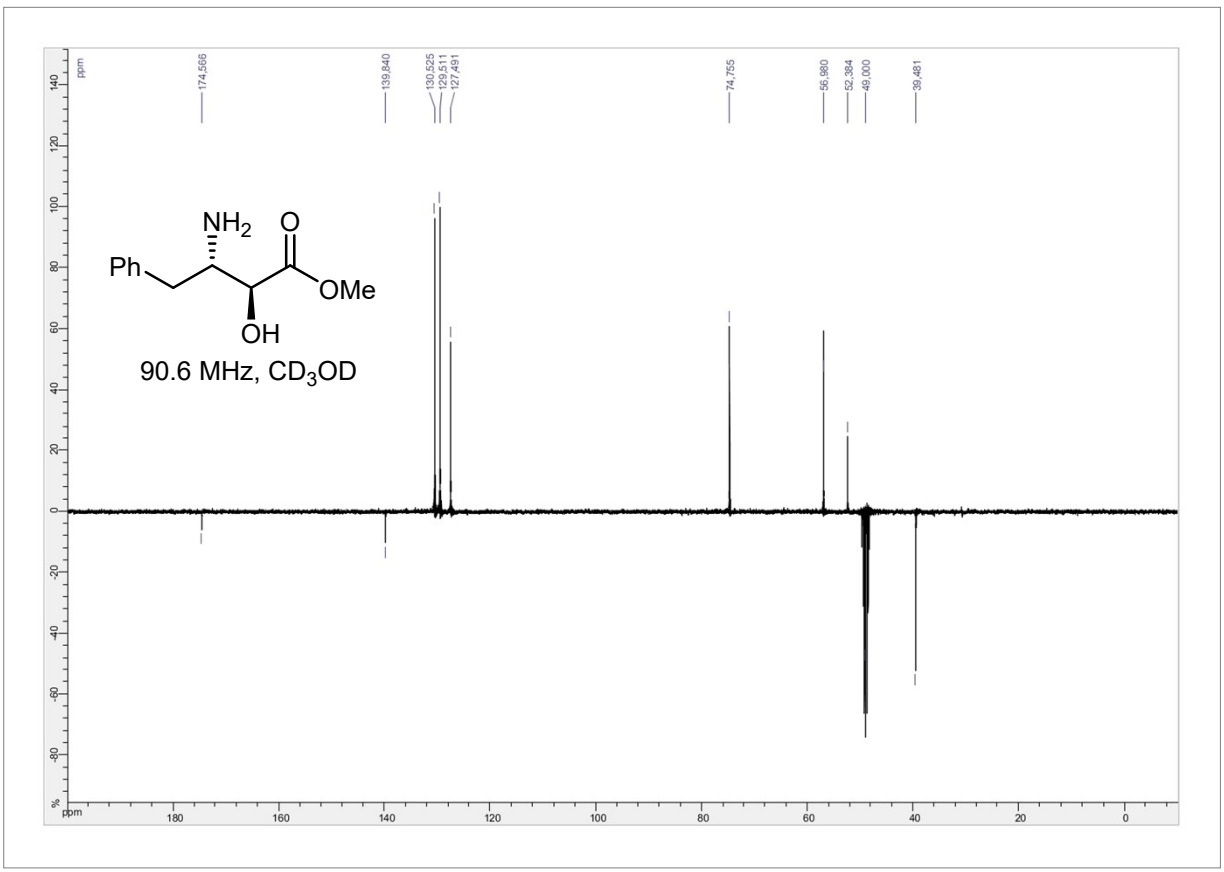
Cyclopentyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **(15)**



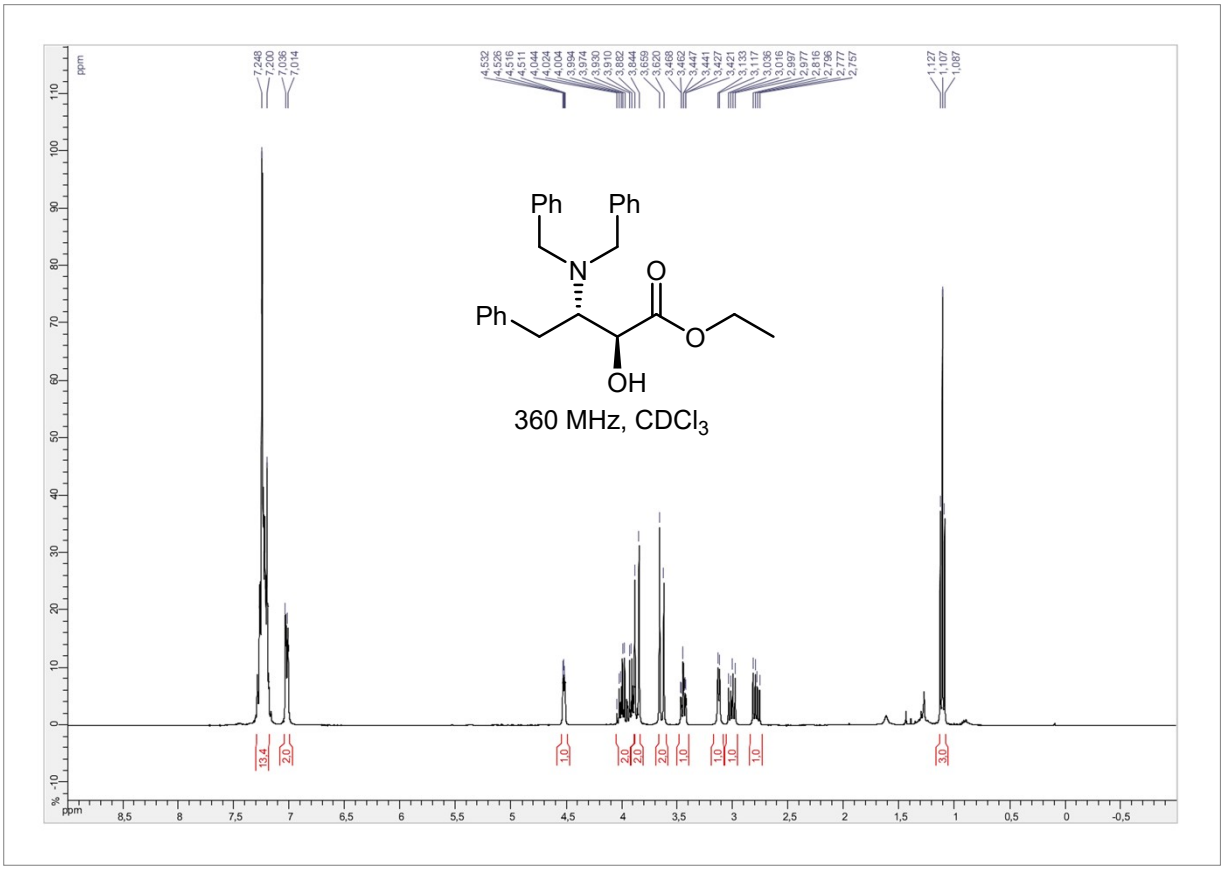


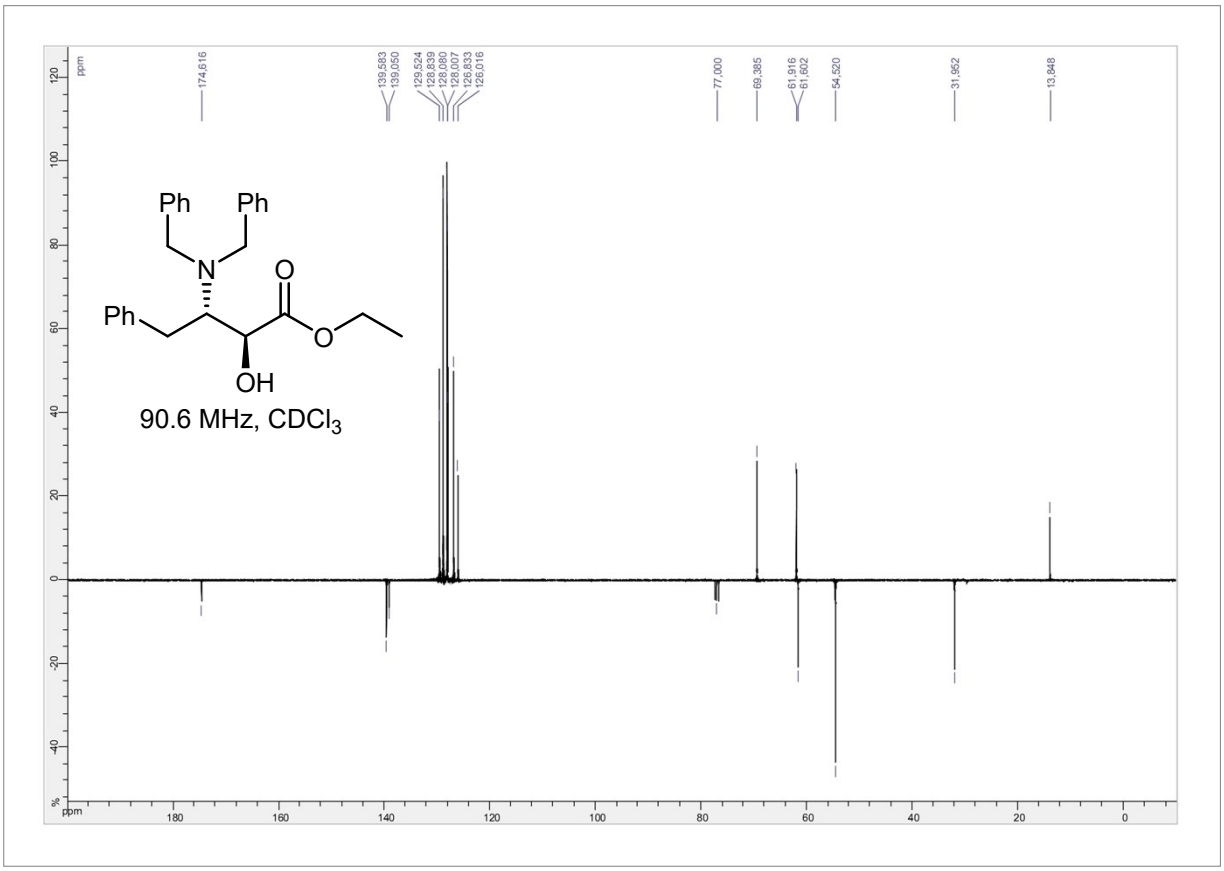
Methyl (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoate **(16)**



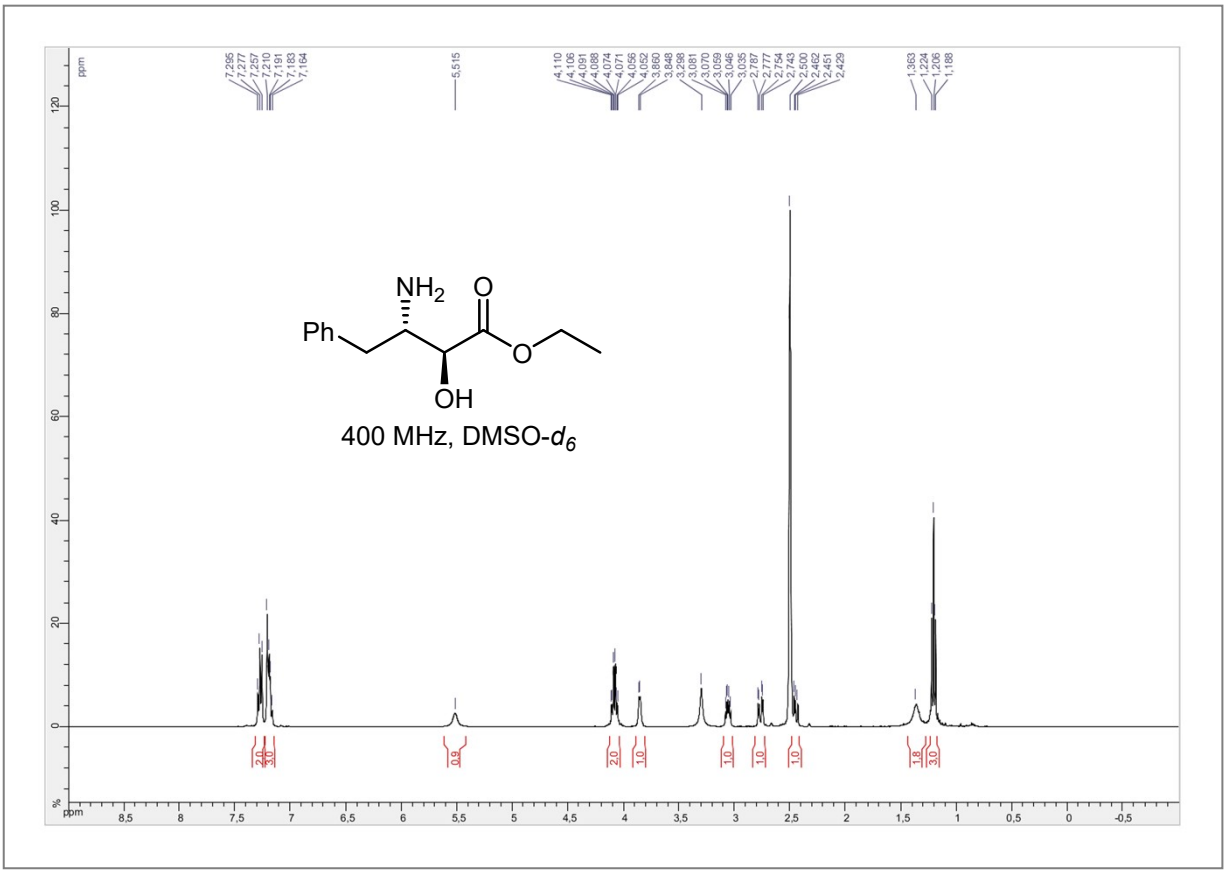


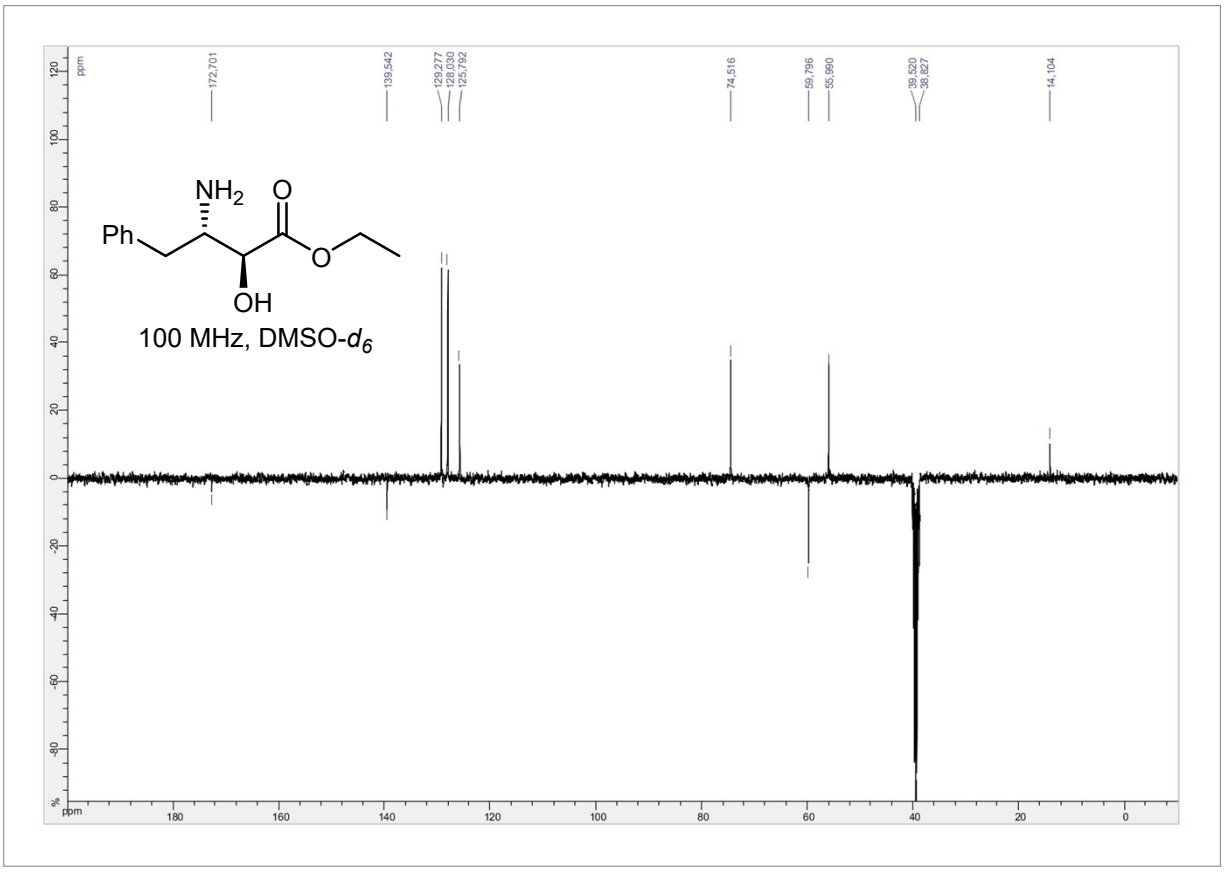
Ethyl (2*S*,3*S*)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate **(17)**



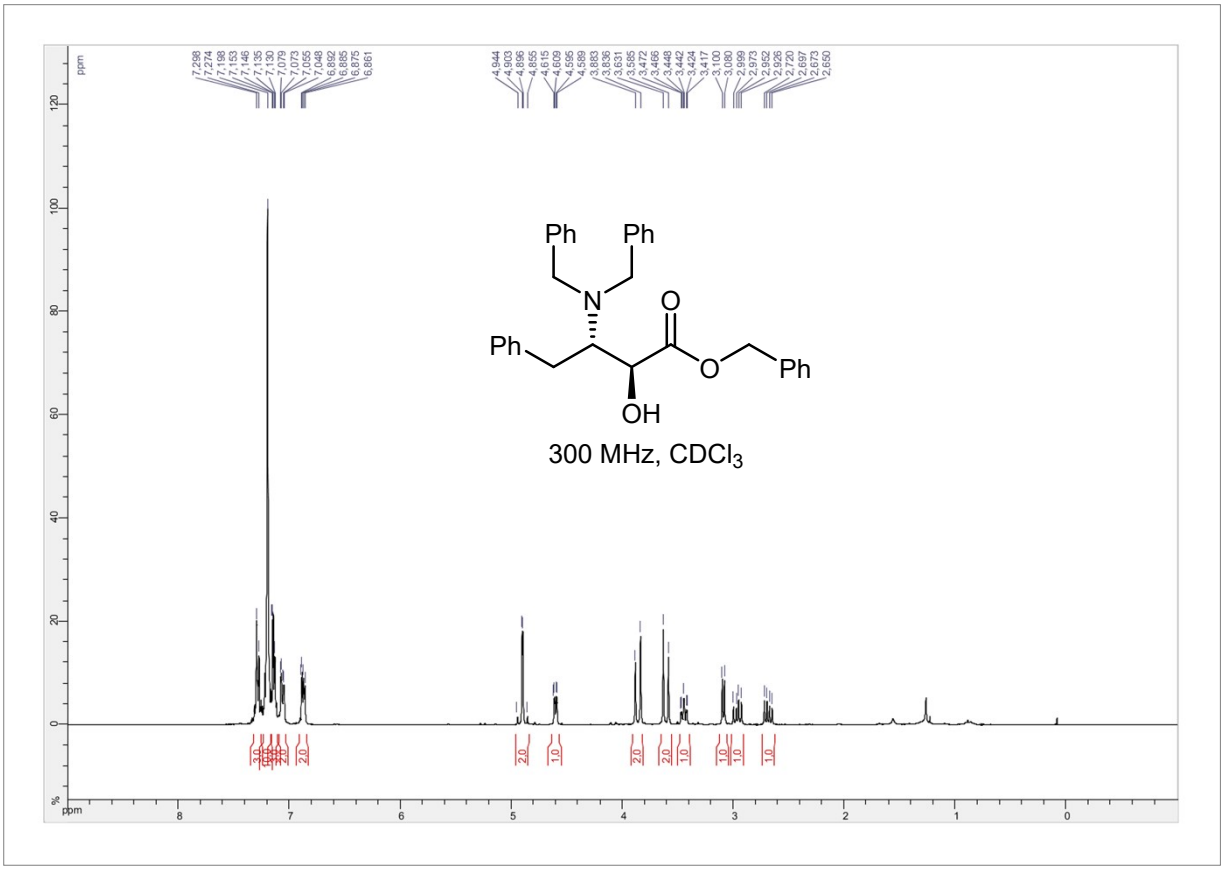


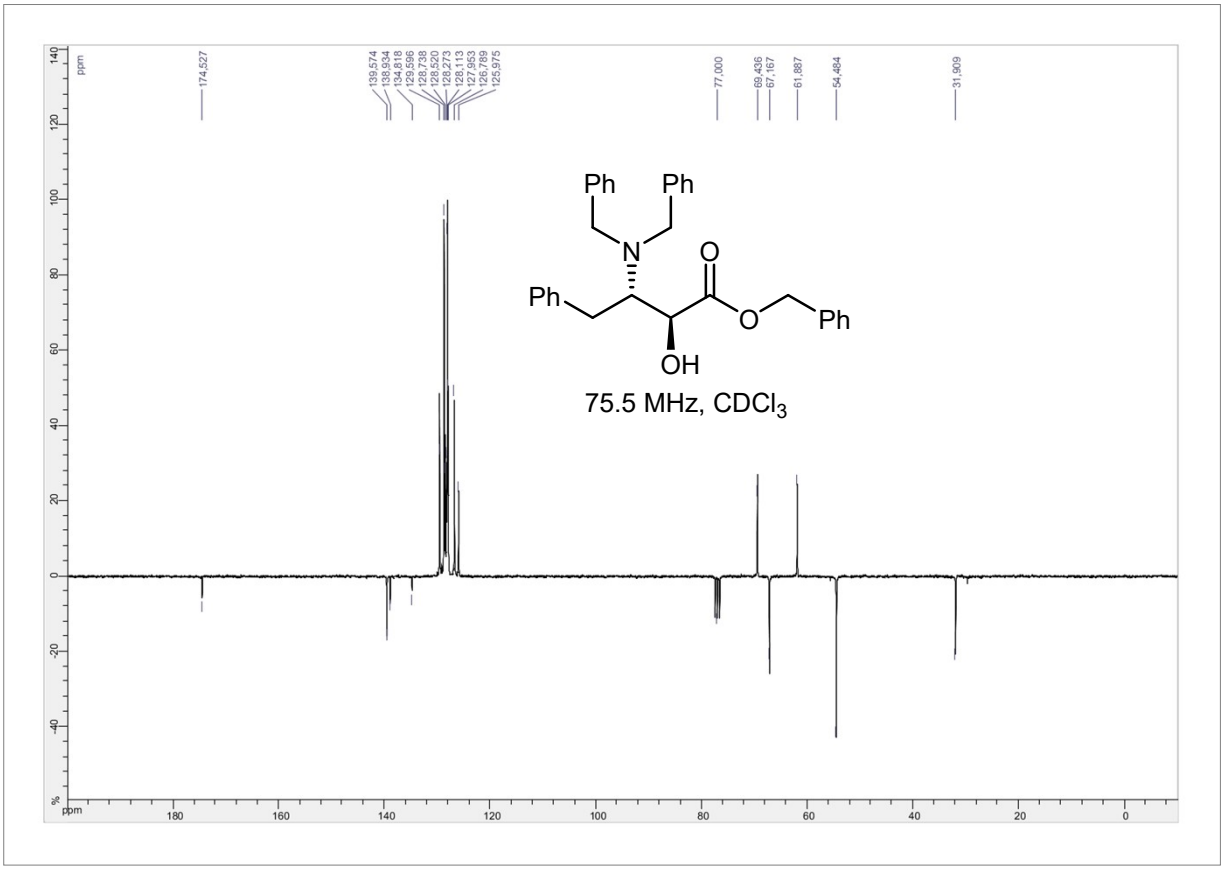
Ethyl (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoate **(18)**



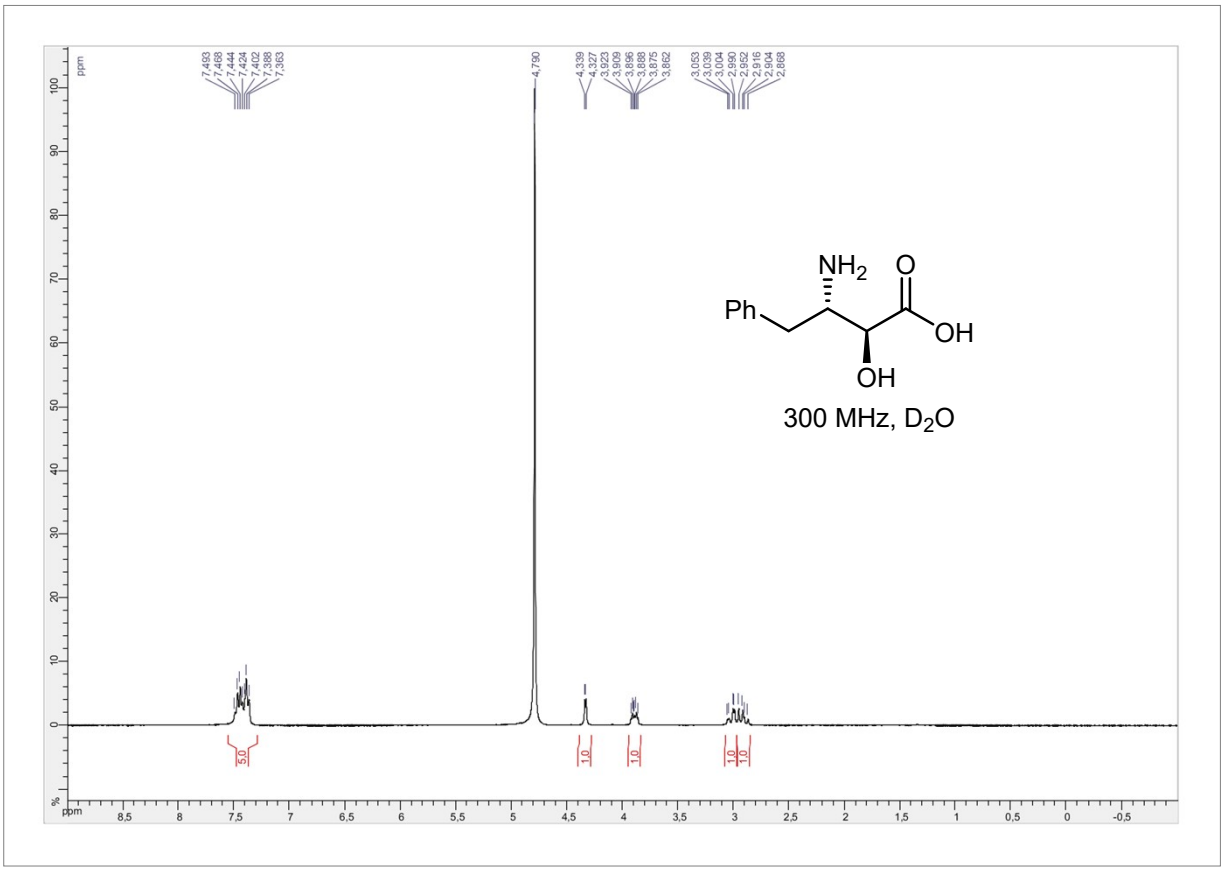


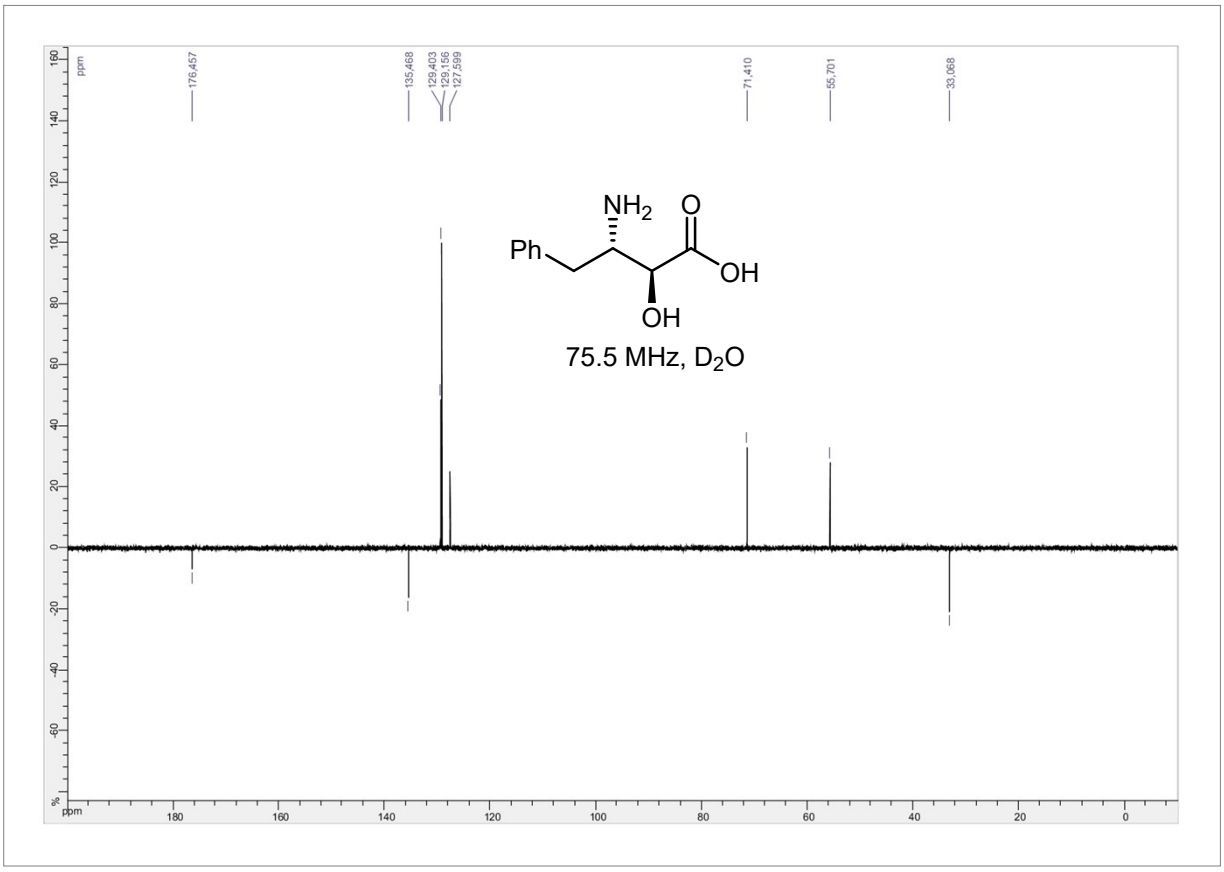
Benzyl (2*S*,3*S*)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate **(19)**





(2*S*,3*S*)-3-Amino-2-hydroxy-4-phenylbutanoic acid: (−)-Allophenylnorstatin **(20)**





2. Crystallographic data for compound 4c.

A single crystal suitable for X-ray diffraction was obtained by slow diffusion of pentane into a Et_2O solution of **4c** at ambient temperature. X-ray diffraction data were collected by using a VENTURE PHOTON100 CMOS Bruker diffractometer with Micro-focus IμS source CuKα radiation. The crystal was mounted on a CryoLoop (Hampton Research) with Paratone-N (Hampton Research) as cryoprotectant and then flash-frozen in a nitrogen gas stream at 100 K. The temperature of the crystal was maintained by means of a 700 series Cryostream cooling device to within an accuracy of ± 1 K. The data were corrected for Lorentz polarization and absorption effects. The structure was solved by direct methods using SHELXS-97[1] and refined against F^2 by full-matrix least-squares techniques using SHELXL-2018[2] with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with isotropic thermal parameters. Calculations were performed by using the Crystal Structure crystallographic software package WINGX.[3] The absolute configuration was determined by refining the Flack parameters[4] using a large number of Friedel's pairs.

An ORTEPO drawing of the molecule is shown in Figure S1. The crystal data collection and refinement parameters are given in Table S1.

CCDC 2088378 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/Community/Requestastructure.

[1] Sheldrick, G. M. SHELXS-97, Program for Crystal Structure Solution, University of Göttingen, Göttingen, Germany, **1997**.
[2] Sheldrick, G. M. *Acta Crystallogr. A* **2008**, *64*, 112–122.
[3] Farrugia, L. J. *J. Appl. Cryst*. **1999**, *32*, 837–838.
[4] Parsons, S.; Flack, H. D.; Wagner, T. *Acta Crystallogr. B* **2013**, *69*, 249–259.

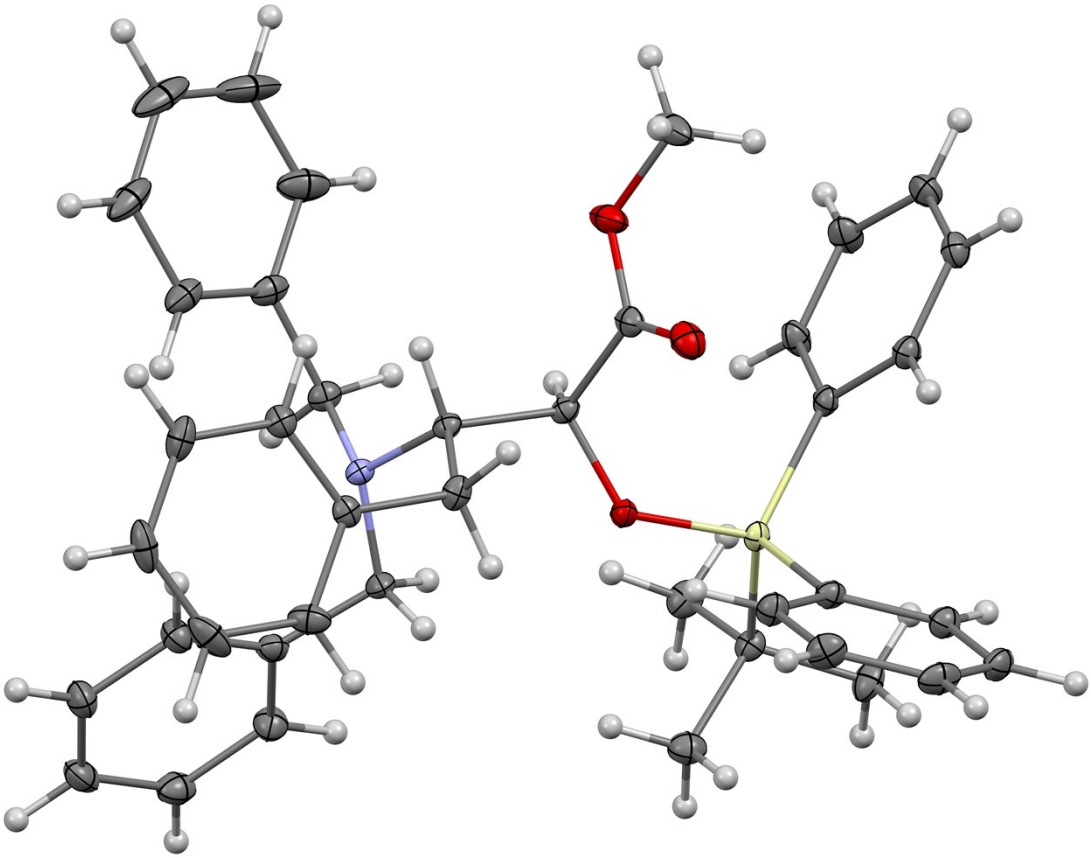
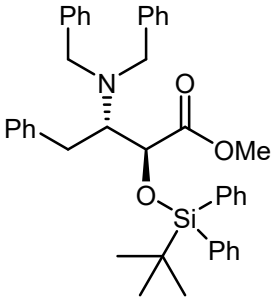


Figure S1. An ORTEP drawing of compound **4c**. Thermal ellipsoids are shown at the 30% level. For the sake of clarity, only one molecule of the asymmetric unit is shown.



4c

Table S1. Crystallographic data and structure refinement details.

Compound	**4c**
CCDC	2088378
Empirical Formula	$C_{41}\,H_{45}\,N\,O_3\,Si$
M_r	627.87
Crystal size, mm^3	0.17 × 0.15 × 0.10
Crystal system	monoclinic
Space group	$P\,2_1$
a, Å	10.8331(4)
b, Å	24.5894(10)
c, Å	13.8643(5)
α, °	90
β, °	107.0600(10)
γ, °	90
Cell volume, Å^3	3530.7(2)
Z ; Z’	4 ; 2
T, K	100(1)
Radiation type ; wavelength Å	CuKα ; 1.54178
F_{000}	1344
μ, mm^{-1}	0.880
θ range, °	3.334 - 66.836
Reflection collected	53 535
Reflections unique	12 440
R_{int}	0.0379
GOF	1.024
Refl. obs. (I>2σ(I))	12 132
Parameters	837
Flack parameter	0.052(7)
wR_2 (all data)	0.0793
R value (I>2σ(I))	0.0308
Largest diff. peak and hole (e$^-$.Å^{-3})	0.477 ; –0.282