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Supporting Information

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Jesús M. García,[b] José M. Odriozola,[b] and Claudio Palomo*[a]

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Asymmetric Assembly of All-Carbon Tertiary/Quaternary Nonadjacent Stereocenters Through Organocatalytic Conjugate Addition of α-Cyanoacetates to a Methacrylate Equivalent

I. Iriarte,[a] S. Vera,[a] E. Badiola,[a] A. Mielgo,[a] M. Oiarbide,[a]* J. M. García,[b] J. M. Odriozola,[b] and C. Palomo [a]*

Electronic Supplementary Information

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1. Materials and general techniques

General experimental: All non-aqueous reactions were performed using oven-dried glassware and were magnetically stirred unless otherwise stated. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

Solvents and reagents: All reagents bought from commercial sources were used as sold. Organic solvents were evaporated under reduced pressure using a Büchi rotary evaporator. Anhydrous dichloromethane was dried over CaH_2, and diethyl ether and tetrahydrofuran were dried by filtration through activated alumina (powder ≈ 150 mesh, pore size 58 Å, basic, Sigma Aldrich) columns. $(DHQ)_2Pyr$ was purchased from Sigma Aldrich, quinine and quinidine were purchased from Alfa Aesar.

Chromatography: Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained with a dipping solution of potassium permanganate (1 g) in 100 mL of water (limited lifetime), followed by heating. Chromatographic purification was performed on ROCC 60 silica gel 40-63 μm.

Gas Chromatography: Performed using a Thermo Scientific Trace 1300 equipment with a FID. Chiral column HYDRODEX β-6TBDM, 25 m, 0.25 mm ID. Temperature gradient: 1) 100 ºC for 1 min; 2) from 100 ºC to 200 ºC at a heating rate of 10 ºC/min (11 min); 3) 200 ºC for an additional 11 min.

Mass spectra: MS spectra were recorded on an ESI-ion trap Mass spectrometer (Agilent 1100 series LC/MSD, SL model).

NMR spectra: NMR spectra were recorded using a Bruker Avance 300 MHz or 500 MHz spectrometer, chemical shifts (δ) are quoted in parts per million referenced to the residual solvent peak. In case of diastereomeric mixture, data of the major diastereomer were provided. The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet. Coupling constants (*J*) are reported in Hertz (Hz).

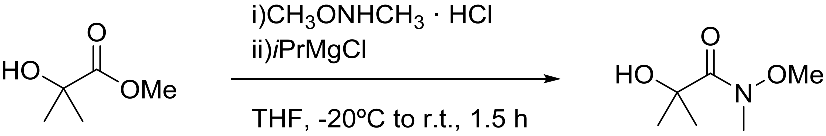
Determination of enantiomeric excesses: Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on a Waters 600 (Photodiode Array Detector Waters 2996) (column and solvent conditions are given with the compound).

Optical rotations: Optical rotations were recorded using a Jasco P-2000 polarimeter; specific rotation (SR) ($[\alpha]_D$) are reported in 10^{-1} $deg \cdot cm^2 \cdot g^{-1}$; concentrations (*c*) are quoted in g/100 mL; *D* refers to the D-line of sodium (589 nm); temperatures (*T*) are given in degree Celsius (°C).

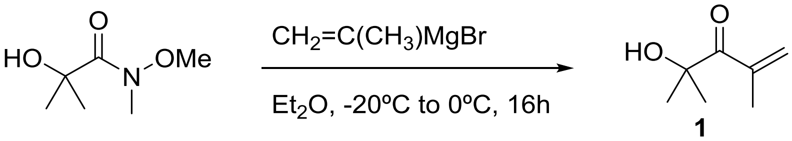
2. Full reference 2b.

2b) R. B. Woodward, E. Logusch, K. P. Nambiar, K. Sakan, D. E. Ward, B.-W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, R. B. Chtnevert, A. Fliri, K. Frobel, H.-J. Gais, D. G. Garratt, K. Hayakawa, W. Heggie, D. P. Hesson, D. Hoppe, I. Hoppe, J. A. Hyatt, D. Ikeda, P. A. Jacobi, K. S. Kim, Y. Kobuke, K. Kojima, K. Krowicki, V. J. Lee, T. Leutert, S. Malchenko, J. Martens, R. S. Matthews, B. S. Ong, J. B. Press, T. V. Rajan Babu, G. Rousseau, H. M. Sauter, M. Suzuki, K. Tatsuta, L. M. Tolbert, E. A. Truesdale, I. Uchida, Y. Ueda, T. Uyehara, A. T. Vasella, W. C. Vladuchick, P. A. Wade, R. M. Williams, H. N.-C. Wong, *J. Am. Chem. Soc.* **1981**, *103*, 3215-3217

3. Preparation of 4-hydroxy-2,4-dimethylpent-1-en-3-one 1.



2-hydroxy-N-methoxy-N,2-dimethylpropanamide: To a solution of methyl 2-hydroxy-2-methylpropanoate (15 mmol, 1.77 g, 1 equiv.) and *N*,*O*-dimethylhydroxylamine hydrochloride (22.5 mmol, 1,37 g, 1.5 equiv.) in THF (50 mL), a 2M solution of ^{i}PrMgCl in THF (60 mmol, 4 equiv.) was added at −20°C. The reaction mixture was stirred for 1.5 h at room temperature. The reaction was then quenched with an aqueous saturated solution of NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 80/20) to obtain the desired amide product as colorless oil. Yield: 1.99 g (90 %). ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[1]

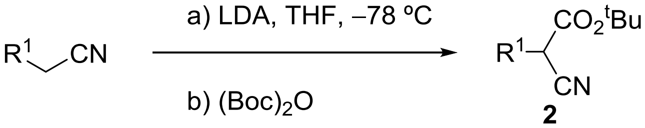


1

4-hydroxy-2,4-dimethylpent-1-en-3-one (1): To a solution of the Weinreb amide prepared as above (10 mmol, 1.85 g, 1 equiv.) in Et_2O (20 mL), a solution of isopropenyl magnesium bromide (0.5 M, 60 mL, 3 equiv.) was added at −20°C, and the resulting mixture was stirred at 0°C for 16 h. The reaction was quenched with an aqueous saturated solution of NH_4Cl (50 mL) and extracted with Et_2O (2 × 50 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (pentane/Et_2O 95/5) to obtain the desired product as a colorless oil. Yield: 833 mg (65 %). ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature[2]

4. Preparation of α-cyanoesters 2-4.

4.1. General procedure for the preparation of *tert*butyl α-cyanoesters 2.[3]



2

A solution of the corresponding nitrile (10 mmol) in THF (10 mL) was added dropwise to a solution of LDA (25 mmol, 2.5 equiv.) in THF (30 mL) cooled to –78 ºC. The reac-

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[1] F. Miege, B. M. Trost, *J. Am. Chem. Soc.* **2014**, 136, 3016-3019.

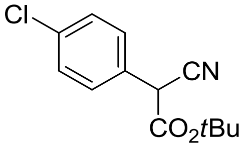
[2] A. Basheer, M. Mishima, I. Marek, *Org. Lett.*, **2011**, 13, 4076-4079.

[3] B. M. Trost, J. R. Miller, C. M. Hoffman Jr., *J. Am. Chem. Soc.* **2011**, *133*, 8165–8167.

tion mixture was allowed to stir at –78 ºC for 45 min. and then at room temperature for an additional 45 minutes. The reaction mixture was then cooled to –78 ºC and a solution of di-*tert*-butyl dicarbonate (2.62 g, 12 mmol, 1.2 equiv.) in THF (10 mL) was added *via* syringe. The reaction mixture was stirred at –78 ºC for 16 hours. The reaction mixture was quenched with saturated ammonium chloride (20 mL) and extracted with diethyl ether (3 x 50 mL). The organic layer was washed with 1N HCl (30 mL), brine (30 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the resulting crude oil was purified using silica gel chromatography (EtOAc:hexane 1:20) to yield the desired α-cyanoester **2**.

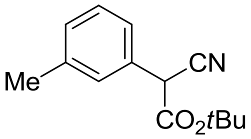
Data of **2c**, **2f**, **2g**, **2h** and **2i**:

***tert*-Butyl 2-(4-chlorophenyl)-2-cyanoacetate 2c**



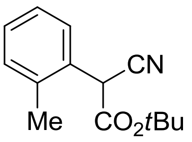
Yield: 1.701 g (6.75 mmol, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 4H), 4.58 (s, 1H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 135.3, 129.6, 129.3, 115.7, 85.0, 44.3, 27.8. UPLC-DAD-QTOF (ESI): $C_{13}H_{13}NO_2Cl$ $[M-H]^-$ calcd.: 250.0635, found: 250.0632.

***tert*-Butyl 2-cyano-2-(*m*-tolyl)acetate 2f**



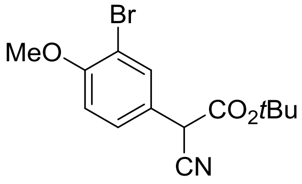
Yield: 1.693 g (7.32 mmol, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.08 (m, 4H), 4.59 (s, 1H), 2.38 (s, 3H), 1.46 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 139.2, 130.5, 129.9, 129.2, 128.5, 125.0, 116.3, 84.5, 44.8, 27.8, 21.5. HRMS (ESI): $C_{14}H_{18}NO_2$ $[M+H]^+$ calcd.: 232.1338, found: 232.1331.

***tert*-Butyl 2-cyano-2-(*o*-tolyl)acetate 2g**

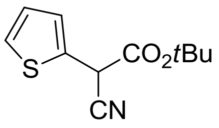


Yield: 1.274 g (5.50 mmol, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.38 (m, 1H), 7.35 – 7.17 (m, 4H), 4.79 (s, 1H), 2.40 (s, 3H), 1.46 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 136.2, 131.3, 129.6, 129.2, 128.6, 127.0, 116.3, 84.6, 42.2, 27.8, 19.5. HRMS (ESI): $C_{14}H_{18}NO_2$ $[M+H]^+$ calcd.: 232.1338, found: 232.1333.

***tert*-butyl 2-(3-bromo-4-methoxyphenyl)-2-cyanoacetate 2h**



Yield: 213 mg (31 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.60 (m, 1H), 7.41 (ddd, *J* = 8.5, 2.4, 0.5 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 4.56 (s, 1H), 3.95 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 156.4, 132.7, 128.0, 123.6, 115.7, 112.2, 112.1, 84.8, 56.3, 43.5, 27.7. $C_{14}H_{15}NO_3BrNa$ $[M]^+$ calcd.: 348.0211, found:348.0214.

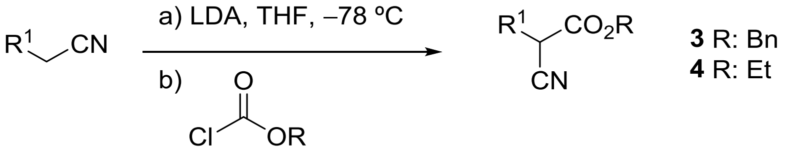


***tert*-butyl 2-cyano-2-(thiophen-2-yl)acetate 2i**

Yield: 679 mg (60 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 6.96 (m, 3H), 4.92 (s, 1H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 147.5, 131.1, 127.9, 127.1, 115.2, 85.1, 40.1, 27.6. UPLC-DAD-QTOF: $C_{11}H_{14}NO_2S$ $[M]^+$ calcd.: 224.0746, found: 224.0745.

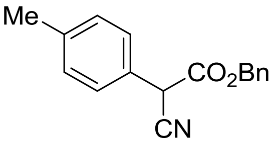
Physical and spectroscopic data of the remaining α-cyanoesters **2** were identical to those previously reported.[4]

4.2. General procedure for the preparation of α-cyanoesters 3 and 4



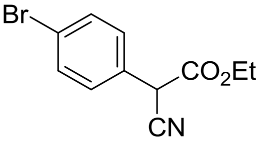
A solution of the corresponding nitrile (10 mmol) in THF (10 mL) was added dropwise to a solution of LDA (25 mmol, 2.5 equiv.) in THF (30 mL) cooled to –78 °C. The reaction mixture was allowed to stir at –78 °C for 45 min. and then at room temperature for an additional 45 minutes. The reaction mixture was then cooled to –78 °C and a solution of the corresponding chloroformate (15 mmol, 1.5 equiv.) in THF (10 mL) was added *via* syringe. The reaction mixture was stirred at –78 ºC for 16 hours. The reaction mixture was quenched with saturated ammonium chloride (20 mL) and extracted with diethyl ether (3 x 50 mL). The organic layer was washed with 1N HCl (30 mL), brine (30 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the resulting crude oil was purified using silica gel chromatography to yield the desired cyanoester.

benzyl 2-cyano-2-(p-tolyl)acetate (3e)



Yield: 886 mg (67 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.21 (m, 9H), 5.23 (s, 2H), 4.78 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 139.3, 134.6, 130.0, 128.7, 128.2, 127.9, 127.0, 115.8, 68.5, 43.4, 21.1. UPLC-DAD-QTOF: $C_{17}H_{15}NO_2Na$ $[M+Na]^+$ calcd.: 288.1000, found: 288.1000.

ethyl 2-(4-bromophenyl)-2-cyanoacetate (4b)



Yield: 1.24 g (92 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.29 (m, 4H), 4.75 (s, 1H), 4.27 – 4.18 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 132.4, 129.7, 129.2, 123.4, 115.4, 63.5, 43.1, 13.8. UPLC-DAD-QTOF: $C_{11}H_9NO_2Br$ $[M-H]^-$ calcd.: 265.9850, found: 265.9817.

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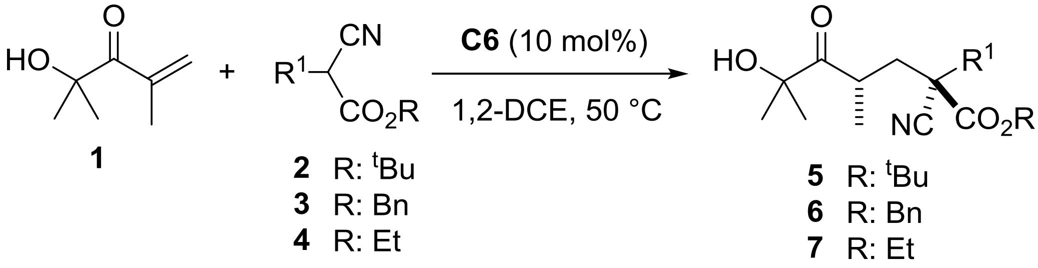
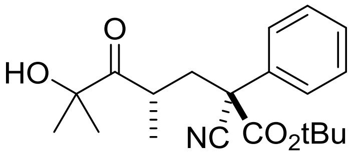
[4] E. Badiola, B. Fiser, E. Gómez-Bengoa, A. Mielgo, I. Olaizola, I. Urruzuno, J. M. García, J. M. Odriozola, J. Razkin, M. Oiarbide, C. Palomo *J. Am. Chem. Soc.* **2014**, *136*, 17869-17881

5. Catalytic conjugate addition of α-cyanoesters 2-4 to enone 1: General procedure and characterization data



General Procedure: To a mixture of the corresponding α-cyanoacetate (0.3 mmol, 1.5 equiv.) and α-hydroxy enone **1** (26 mg, 0.2 mmol, 1 equiv.) in 1,2-dichloroethane (DCE, 0.4 mL), catalyst **C6** (13 mg, 0.02 mmol) was added. The resulting mixture was stirred until consumption of the enone (monitored by ^{1}H-NMR). The reaction was treated with HCl 1N and the product was extracted with CH_2Cl_2 and the combined organic phases were dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product which was purified by flash column chromatography (eluent hexane/ethyl acetate 95/5).

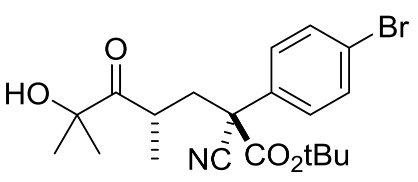
(2*S*,4*S*)-*tert*-Butyl 2-cyano-6-hydroxy-4,6-dimethyl-5-oxo-2-phenylheptanoate (5a)



Prepared according to the general procedure starting from *tert*-butyl 2-cyano-2-phenylacetate **2a** (65 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 81% (84 mg). $[\alpha]_D^{25}$ = + 27.6° (c=0.7, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.49 (m, 2H), 7.48 – 7.34 (m, 3H), 3.33 – 3.20 (m, 2H), 2.81 (dd, *J* = 14.6, 5.6 Hz, 1H), 2.17 (dd, *J* = 14.6, 5.9 Hz, 1H), 1.41 (d, *J* = 1.6 Hz, 6H), 1.39 (s, 9H), 1.08 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.8, 166.2, 135.1, 129.3, 129.1, 126.1, 118.8, 84.9, 53.8, 40.6, 36.9, 27.7, 27.2, 27.0, 19.9. UPLC-DAD-QTOF: $C_{20}H_{27}NO_4Na$ $[M+Na]^+$ calcd.: 368.1838, found: 368.1836.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 19.6 min (major.) and 24.5 min (minor.)).

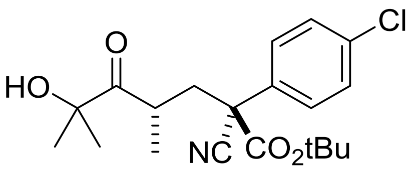
(2*S*,4*S*)-*tert*-Butyl 2-(4-bromophenyl)-2-cyano-6-hydroxy-4,6-dimethyl-5-oxoheptanoate (5b)



Prepared according to the general procedure starting from *tert*-butyl 2-cyano-2-(4-bromophenyl)acetate **2b** (88 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 69% (88 mg). $[\alpha]_D^{25}$ = + 18.5° (c=1.15, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 2H), 7.44 – 7.38 (m, 2H), 3.27 (q, *J* = 6.3, 5.9 Hz, 1H), 3.21 (s, 1H), 2.81 (dd, *J* = 14.6, 5.8 Hz, 1H), 2.10 (dd, *J* = 14.6, 5.7 Hz, 1H), 1.40 (s, 6H), 1.39 (s, 9H), 1.09 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.6, 165.8, 134.2, 132.5, 127.9, 123.5, 118.4, 85.4, 53.5, 40.6, 36.9, 27.7, 27.3, 27.1, 20.0. UPLC-DAD-QTOF: $C_{20}H_{26}NO_4BrNa$ $[M+Na]^+$ calcd.: 446.0943, found: 446.0945.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 27.1 min (minor.) and 29.3 min (major.)).

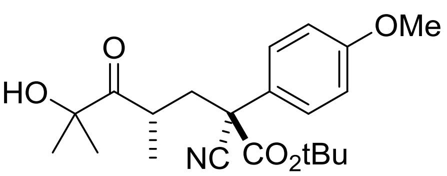
(2*S*,4*S*)-*tert*-Butyl 2-(4-chlorophenyl)-2-cyano-6-hydroxy-4,6-dimethyl-5-oxoheptanoate (5c)



Prepared according to the general procedure starting from *tert*-butyl 2-(4-chlorophenyl)-2-cyanoacetate **2c** (76 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 95% (108 mg). $[\alpha]_D^{25}$ = + 17.8° (c=4.2, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.42 (m, 2H), 7.39 – 7.33 (m, 2H), 3.34 – 3.20 (m, 2H), 2.80 (dd, *J* = 14.6, 5.9 Hz, 1H), 2.09 (dd, *J* = 14.6, 5.7 Hz, 1H), 1.39 (s, 3H), 1.37 (s, 9H), 1.08 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.6, 165.8, 135.2, 133.7, 129.5, 127.6, 118.4, 85.2, 53.4, 40.5, 36.9, 27.7, 27.2, 27.0, 19.9. UPLC-DAD-QTOF: $C_{20}H_{26}NO_4ClNa$ $[M+Na]^+$ calcd.: 402.1448, found: 02.1447.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 30.9 min (minor.) and 34.9 min (major.)).

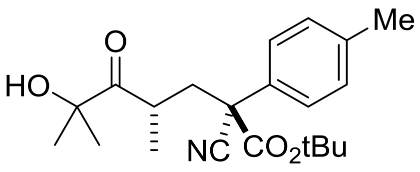
(2*S*,4*S*)-*tert*-Butyl 2-cyano-6-hydroxy-2-(4-methoxyphenyl)-4,6-dimethyl-5-oxoheptanoate (5d)



Prepared according to the general procedure starting from *tert*-butyl 2-cyano-2-(4-methoxyphenyl)acetate **2d** (74 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 70% (79 mg). $[\alpha]_D^{25}$ = + 25.4° (c=0.85, >98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.35 (m, 2H), 6.97 – 6.84 (m, 2H), 3.82 (s, 3H), 3.32 (s, 1H), 3.26 (q, *J* = 6.3, 5.8 Hz, 1H), 2.77 (dd, *J* = 14.6, 5.6 Hz, 1H), 2.19 – 2.05 (m, 1H), 1.40 (d, *J* = 2.0 Hz, 6H), 1.39 (s, 9H), 1.08 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.9, 166.3, 139.2, 135.0, 129.8, 129.2, 126.7, 123.1, 119.0, 84.8, 53.8, 40.7, 37.0, 27.7, 27.2, 27.0, 21.7, 19.9. UPLC-DAD-QTOF: $C_{21}H_{29}NO_5Na$ $[M+Na]^+$ calcd.: 398.1943, found: 398.1942.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H hexane/isopropanol 98/2, flow rate= 1 mL/min, retention time: 40.9 min).

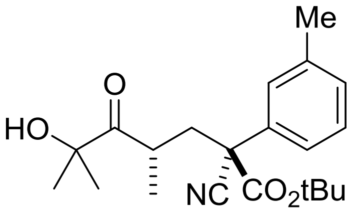
(2*S*,4*S*)-*tert*-Butyl 2-cyano-6-hydroxy-4,6-dimethyl-5-oxo-2-(*p*-tolyl)heptanoate (5e)



Prepared according to the general procedure starting from *tert*-butyl 2-cyano-2-(*p*-tolyl)acetate **2e** (69 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 67% (72 mg). $[\alpha]_D^{25}$ = + 28.7° (c=0.85, >98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 2H), 7.21 – 7.17 (m, 2H), 3.32 (s, 1H), 3.25 (q, *J* = 6.3, 5.8 Hz, 1H), 2.78 (dd, *J* = 14.6, 5.6 Hz, 1H), 2.35 (s, 3H), 2.14 (dd, *J* = 14.6, 5.9 Hz, 1H), 1.40 (d, *J* = 1.5 Hz, 6H), 1.38 (s, 9H), 1.07 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.8, 166.4, 139.0, 132.0, 130.0, 126.0, 119.0, 84.8, 53.5, 40.6, 36.9, 27.7, 27.2, 27.0, 21.2, 20.0. UPLC-DAD-QTOF: $C_{21}H_{29}NO_4Na$ $[M+Na]^+$ calcd.: 382.1994, found: 382.1998.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC hexane/isopropanol 85/15, flow rate= 1 mL/min, retention times: 10.2 min).

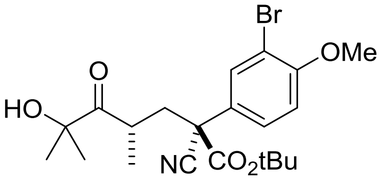
(2*S*,4*S*)-*tert*-Butyl 2-cyano-6-hydroxy-4,6-dimethyl-5-oxo-2-(*m*-tolyl)heptanoate (5f)



Prepared according to the general procedure starting from *tert*-butyl 2-cyano-2-(*m*-tolyl)acetate **2f** (69 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 83% (89 mg). [α]$_D^{25}$ = + 22.7° (c=2.35, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.24 (m, 3H), 7.19 – 7.12 (m, 1H), 3.34 (s, 1H), 3.31 – 3.22 (m, 1H), 2.78 (dd, *J* = 14.6, 5.5 Hz, 1H), 2.37 (s, 3H), 2.12 (dd, *J* = 14.6, 6.0 Hz, 1H), 1.40 (s, 6H), 1.38 (s, 9H), 1.07 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.9, 166.3, 139.2, 135.0, 129.8, 129.2, 126.7, 123.1, 119.0, 84.8, 53.8, 40.7, 37.0, 27.7, 27.2, 27.0, 21.7, 19.9. UPLC-DAD-QTOF: $C_{21}H_{29}NO_4Na$ [M+Na]$^+$ calcd.: 382.1994, found: 382.1991.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC hexane/isopropanol 99/1, flow rate= 1 mL/min, retention times: 30.4 min (major.) and 43.1 min (minor.)).

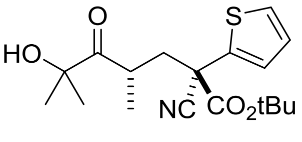
***tert*-butyl (2S,4S)-2-(3-bromo-4-methoxyphenyl)-2-cyano-6-hydroxy-4,6-dimethyl-5-oxoheptanoate (5h)**



Prepared according to the general procedure starting from cyanoacetate **2h** (98 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 57 mg (62%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 2.5 Hz, 1H), 7.48 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 3.94 (s, 3H), 3.33 – 3.27 (m, 1H), 2.81 (dd, *J* = 14.6, 5.8 Hz, 1H), 2.12 (dd, *J* = 14.6, 5.8 Hz, 1H), 1.50 – 1.40 (m, 15H), 1.14 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.4, 165.8, 156.2, 130.8, 128.1, 126.3, 118.3, 112.2, 111.9, 85.0, 56.3, 52.6, 40.4, 36.7, 27.5, 27.0, 19.8. UPLC-DAD-QTOF: $C_{21}H_{29}NO_5Br$ [M+H]$^+$ calcd.: 454.1229, found: 454.1233.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OJ-H hexane/isopropanol 98/2, flow rate= 0.5 mL/min, retention times: 54.8 min (major.) and 67.9 min (minor.). Processed Channel Descr.: PDA 210.0 nm).

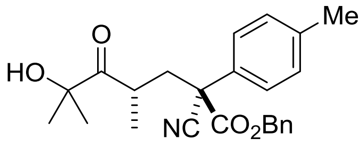
(2*S*,4*S*)-*tert*-butyl 2-cyano-6-hydroxy-4,6-dimethyl-5-oxo-2-(thiophen-2-yl)heptanoate (5i)



Prepared according to the general procedure starting from cyanoacetate **2i** (67 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 51 mg (72%). [α]$_D^{25}$ = +4.0 (c=1, 97 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 6.93 (m, 3H), 3.35 (dt, *J* = 7.0, 5.9 Hz, 1H), 2.88 (dd, *J* = 14.5, 6.1 Hz, 1H), 2.22 (dd, *J* = 14.4, 5.6 Hz, 1H), 1.49 (s, 9H), 1.44 (d, *J* = 3.1 Hz, 6H), 1.19 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.2, 165.3, 137.7, 126.8, 118.0, 85.4, 77.1, 50.8, 41.9, 36.7, 27.5, 27.1, 19.5. UPLC-DAD-QTOF: $C_{18}H_{25}NO_4SNa$ [M+Na]$^+$ calcd.: 374.1406, found: 374.1402.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H hexane/isopropanol 95/5, flow rate= 0.5 mL/min, retention times: 29.9 min (minor.) and 47.4 min (major.). Processed Channel Descr..: PDA 245.0 nm).

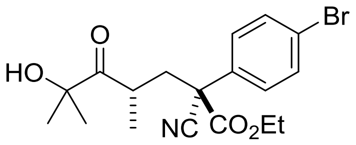
benzyl (2S,4S)-2-cyano-6-hydroxy-4,6-dimethyl-5-oxo-2-(p-tolyl)heptanoate (6e)



Prepared according to the general procedure starting from cyanoacetate **3e** (80 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 60 mg (76 %). $[\alpha]_D^{25}$ = +11.2 (c=1, 92 % *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.14 (m, 9H), 5.19 (q, *J* = 12.3 Hz, 2H), 3.40 – 3.28 (m, 1H), 2.91 (dd, *J* = 14.6, 6.1 Hz, 1H), 2.39 (s, 3H), 2.23 (dd, *J* = 14.6, 5.5 Hz, 1H), 1.39 (d, *J* = 5.9 Hz, 6H), 1.13 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.5, 167.2, 139.1, 134.5, 131.2, 129.9, 128.5, 128.5, 127.8, 125.9, 118.3, 68.6, 52.6, 40.6, 36.7, 26.9, 26.5, 21.0, 19.7. UPLC-DAD-QTOF: $C_{24}H_{28}NO_4$ $[M+H]^+$ calcd.: 394.2015, found: 394.2018.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC+AY-H hexane/isopropanol 90/10, flow rate= 0.5 mL/min, retention times: 59.0 min (major.) and 74.4 min (minor.). Processed Channel Descr.: PDA 235.0 nm).

ethyl (2S,4S)-2-(4-bromophenyl)-2-cyano-6-hydroxy-4,6-dimethyl-5-oxoheptanoate (7b)



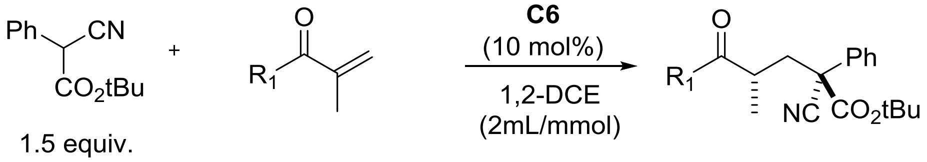
Prepared according to the general procedure starting from cyanoacetate **4b** (80 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 70 mg (88 %). $[\alpha]_D^{25}$ = +12.5 (c=1, 91 % *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.39 (m, 4H), 4.39 – 4.15 (m, 2H), 3.35 (qd, *J* = 6.8, 5.3 Hz, 1H), 2.93 (dd, *J* = 14.6, 6.4 Hz, 1H), 2.18 (dd, *J* = 14.6, 5.3 Hz, 1H), 1.43 (d, *J* = 4.7 Hz, 6H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.3, 166.9, 133.5, 132.4, 127.8, 123.4, 117.9, 77.1, 63.7, 52.6, 40.6, 36.7, 27.0, 19.9, 13.7. UPLC-DAD-QTOF: $C_{18}H_{23}NO_4Br$ $[M+H]^+$ calcd.: 396.0810, found: 396.0811.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC hexane/isopropanol 97/3, flow rate= 0.6 mL/min, retention times: 43.9 min (major.) and 51.4 min (minor.). Processed Channel Descr..: PDA 235.0 nm).

General procedure for the racemic reactions:

Racemic reactions were conducted following the above General Procedure, but using as catalyst DBU (20 mol%) and running the reaction at room temperature.

6. Results with elementary Michael acceptors other than 1

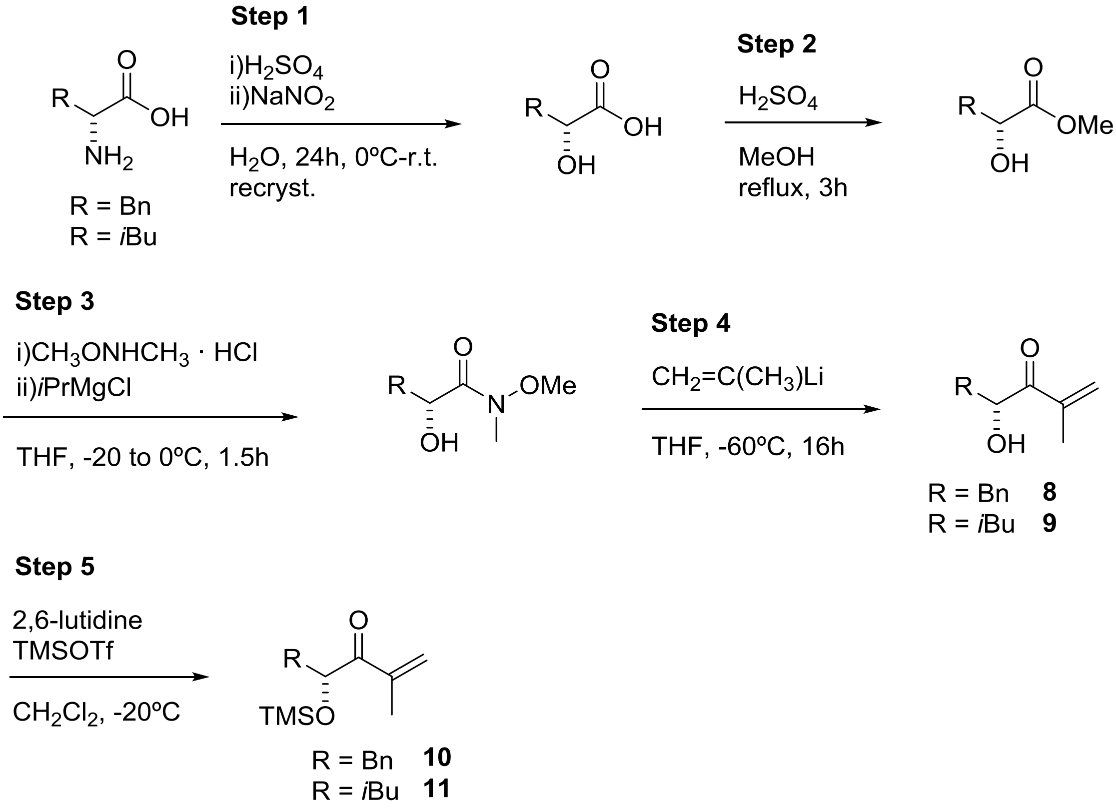


R_1	T ºC	t (h)	Conv.	Yield (%)	*dr*	*ee* (%)
Me	50	16	35			
		40	45			
		70	60			
		90	60	45	80:20	92 (major.) 42 (minor.)
OMe	50	20	0	NR	--	--
H	rt	24	100	83	60:40	14 (major.) 10 (minor.)

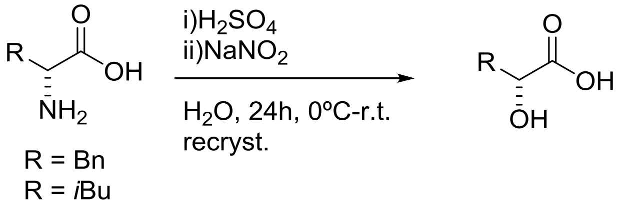
To a mixture of the cyanoacetate (0.3 mmol, 1.5 equiv.) and the corresponding Michael acceptor (0.2 mmol, 1 equiv.) in 1,2-dichloroethane (DCE, 0.4 mL), catalyst **C6** (13 mg, 0.02 mmol) was added. The resulting mixture was stirred until consumption of the electrophile (monitored by ^{1}H-NMR). The reaction was treated with HCl 1N and the product was extracted with CH_2Cl_2 and the combined organic phases were dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product. After purification by flash column chromatography (eluent hexane/ ethyl acetate) the product was isolated. NR: no reaction.

7. Catalytic conjugate addition of α-cyanoester to chiral enones 8-11 and 17.

7.1. Preparation of chiral α´-oxyenones 8, 9, 10 and 11.



Step 1: Preparation of (*R*)-2-hydroxy acids:[5]



To a suspension of the corresponding amino acid (50 mmol) in water (27.5 mL), an aqueous solution of sulfuric acid (2N, 27.5 mL) was added dropwise at 0°C. At the same temperature, an aqueous solution of sodium nitrite (2N, 27.5 mL) was also added dropwise. The reaction mixture was stirred at 0°C for 3 h. The mixture was then warmed up to r.t. and was stirred for 24 h. The mixture was extracted with Et_2O (3 × 40 mL) and the combined organic phases were dried over $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by crystallization (ethyl acetate / hexane 1:1).

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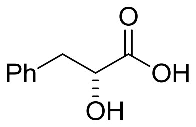
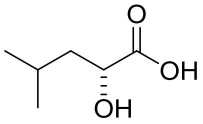
[5] A. Bodlenner, S. M. Glueck, B. M. Nestl, C. C.Gruber, N. Baudendistel, B. Hauer, W. Kroutil, K. Faber, *Tetrahedron*, **2009**, 65, 7752-7755.

(*R*)-2-hydroxy-3-phenylpropanoic acid



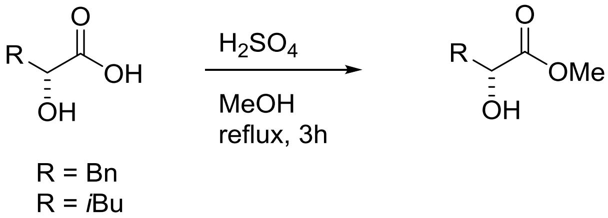
Prepared according to the general procedure starting from D-phenylalanine (50 mmol, 8.26 g). Product obtained as white crystals after recrystallization. Yield: 4.15 g (50%). ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[5]

(*R*)-2-hydroxy-4-methylpentanoic acid



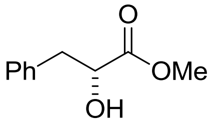
Prepared according to the general procedure starting from D-leucine (50 mmol, 6.55 g). Product obtained as white crystals after recrystallization. Yield: 3.18 g (43%). ^1H and ^{13}C NMR spectra were identical to those reported in the literature. [5]

Step 2: Preparation of methyl-(*R*)-2-hydroxy esters:[6]



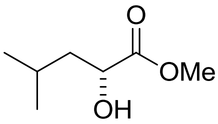
To a solution of the corresponding 2-hydroxy acid (40 mmol) in methanol (35 mL), an aqueous solution of sulfuric acid (96%, 0.93 mL) was added and the resulting mixture was heated to reflux and stirred for 3 h. The solvent was evaporated under reduced pressure and the residue was dissolved in Et_2O (50 mL) and washed successively with a saturated aqueous solution of $NaHCO_3$ (2 x 20 mL) and NaCl (20 mL). The organic phase was dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting oil was used without further purification.

(*R*)-methyl 2-hydroxy-3-phenylpropanoate



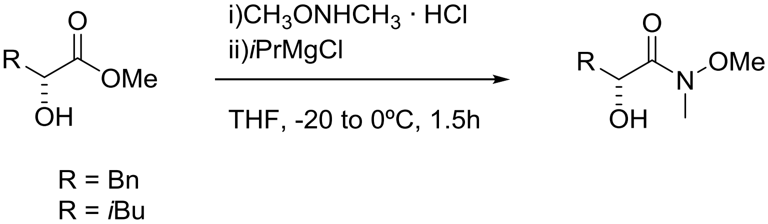
Product obtained as yellow oil. Yield: 7.28 g (100 %). ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[6]

(*R*)-methyl 2-hydroxy-4-methylpentanoate



Product obtained as colorless oil. Yield: 4.97 g (85 %). ^1H and ^{13}C NMR spectra were identical to those reported in the literature. [6]

Step 3: Preparation of (*R*)-2-hydroxy-N-methoxy-N-methylamides:[7]



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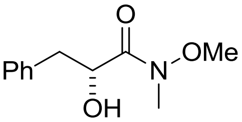
[6] M. Poterala, J. Plenkiewicz, *Tetrahedron*, **2011**, 22, 294-299.

[7] Procedure adapted from: Miege, F.; Trost, B. M. *J. Am. Chem. Soc.*, **2014**, 136, 3016-3019.

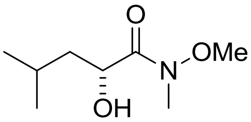
To a solution of the corresponding hydroxy ester (10 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (15 mmol, 1.5 equiv.) in THF (35 mL), a 2M solution of ^{i}PrMgCl in THF (40 mmol, 4 equiv.) was added at −20°C. The reaction mixture was stirred for 1.5 h at 0°C. The reaction was then quenched with an aqueous saturated solution of NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 80/20).

(*R*)-2-hydroxy-N-methoxy-N-methyl-3-phenylpropanamide



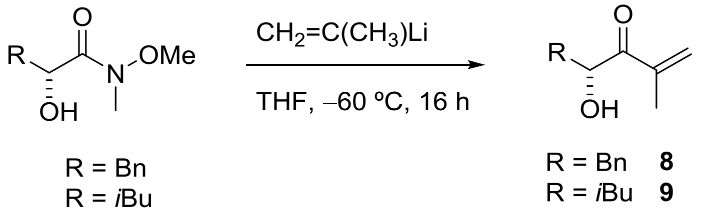
Product obtained as a white solid. Yield: 1.98 g (95 %). ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[8]

(*R*)-2-hydroxy-N-methoxy-N,4-dimethylpentanamide



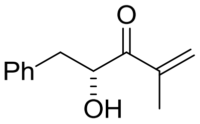
Product obtained as a colorless oil. Yield: 1.42 g (81 %). $[\alpha]_D^{23}$= +28.3 (ee >99%, c=0.6, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.44 (dd, *J* = 8.5, 3.7 Hz, 1H), 3.74 (s, 3H), 3.26 (s, 3H), 1.95 (td, *J* = 13.4, 6.7 Hz, 1H), 1.52 – 1.42 (m, 2H), 0.98 (t, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 67.3, 61.2, 44.0, 24.6, 23.6, 21.3. UPLC-DAD-QTOF: $C_8H_{17}NO_3$ $[M]^+$ calcd.: 176.1287, found: 176.1289.

Step 4: Preparation of hydroxyenones 8 and 9:



To a solution of 2-bromopropene (9 mmol, 0.79 mL, 3 equiv.) in Et_2O (5 mL), a *tert*-butyllithium solution (1.6M, 6.75 mL, 3.6 equiv.) was added at −78°C, and the resulting mixture was stirred at the same temperature for 1 h. A solution of the corresponding Weinreb amide (3 mmol) in Et_2O (10 mL) was then added at −78°C and the reaction mixture was stirred at −60°C for 16 h. The reaction was quenched with an aqueous saturated solution of NH_4Cl (50 mL) and extracted with CH_2Cl_2 (50 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 95/5).

(*R*)-4-hydroxy-2-methyl-5-phenylpent-1-en-3-one (8)



Product obtained as a yellow oil. Yield: 411 mg (72 %). $[\alpha]_D^{23}$= −49.5 (ee >99%, c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.13 (m, 5H), 6.07 – 5.95 (m, 2H), 5.11 (td, *J* = 7.0, 4.2 Hz, 1H), 3.52 (d, *J* = 7.1 Hz, 1H), 3.03 (ddd, *J* = 20.9, 14.0, 5.5 Hz, 2H), 1.96 (dd, *J* = 1.4, 0.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 142.0, 137.0, 129.8, 128.8,

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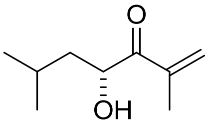
[8] M. R. Aronoff, N. A. Bourjaily, K. A. Miller, *Tetrahedron*, **2010**, 51, 6375-6377.

127.2, 126.8, 73.4, 42.9, 18.2. UPLC-DAD-QTOF: $C_{12}H_{15}O_2$ [M+Na]$^+$ calcd.: 191.1062, found: 191.1072.

The enantiomeric purity was determined by HPLC analysis (Chiralpak column AS-H, 95:5 Hexane:*i*-PrOH, 0.5 mL/min, λ=210 nm).

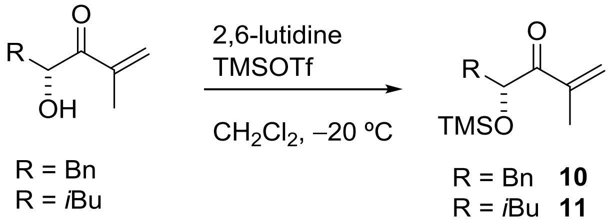
(*R*)-4-hydroxy-2,6-dimethylhept-1-en-3-one (9)



Product obtained as a yellow oil. Yield: 214 mg (46 %). $[\alpha]_D^{23}$= −32.7 (*ee* >99%, c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (d, *J* = 1.3 Hz, 2H), 4.89 – 4.77 (m, 1H), 3.41 (d, *J* = 7.0 Hz, 1H), 2.07 – 1.90 (m, 4H), 1.44 (dddd, *J* = 18.2, 14.1, 9.7, 3.5 Hz, 2H), 0.99 (dd, *J* = 25.0, 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 141.6, 126.4, 71.4, 45.9, 25.3, 24.0, 21.7, 18.3. UPLC-DAD-QTOF: $C_9H_{16}O_2$ [M+Na]$^+$ calcd.: 179.1048, found: 179.1051.

The enantiomeric purity was determined by GC analysis (Chiral column HYDRODEX β-6TBDM. Temperature gradient: 100ºC for 1 min., 10ºC/min. until minute 11, 200ºC until minute 22).

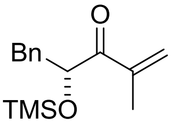
Step 5: Preparation of silyloxyenones 10 and 11:



To a solution of the corresponding hydroxyenone (2 mmol) in CH_2Cl_2 (20 mL), were added successively 2,6-lutidine (0.55 mL, 4.8 mmol, 2.4 equiv.) and TMSOTf (0.72 mL, 4 mmol, 2 equiv.) at −20°C. The mixture was stirred at -20ºC for 3 h and then EtOAc (40 mL) was added. The organic phase was washed with saturated aqueous $NaHCO_3$ (40 mL), $CuSO_4$ (3 x 40 mL), $NaHCO_3$ (2 x 40 mL) and NaCl (40 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 99/1).

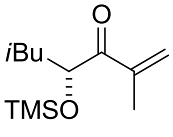
The optical purity was determined on the corresponding α′-hydroxy derivatives obtained by desilylation with H_2F_2/MeOH.

(*R*)-2-methyl-5-phenyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (10)



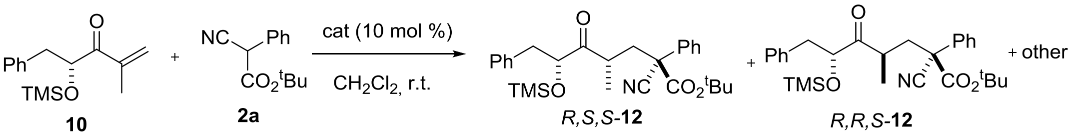
Product obtained as a yellow oil. Yield: 399 mg (72 %). $[\alpha]_D^{23}$= -1.7 (c=0.8, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.17 (m, 5H), 6.14 (s, 1H), 5.87 (dd, *J* = 1.4, 0.8 Hz, 1H), 4.84 (dd, *J* = 9.0, 4.0 Hz, 1H), 2.96 (ddd, *J* = 22.5, 13.5, 6.5 Hz, 2H), 1.93 (dd, *J* = 1.3, 0.9 Hz, 3H), -0.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 142.6, 137.9, 129.5, 128.2, 126.5, 125.5, 76.4, 42.1, 18.4, -0.4. UPLC-DAD-QTOF: $C_{15}H_{23}O_2Si$ [M]$^+$ calcd.: 263.1467, found: 263.1464.

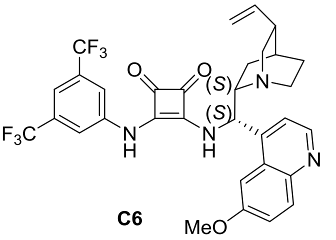
(*R*)-2,6-dimethyl-4-((trimethylsilyl)oxy)hept-1-en-3-one (11)



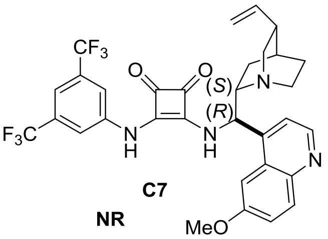
Product obtained as a yellow oil. Yield: 279 mg (61 %). $[\alpha]_D^{23}$= +0.5 (c=0.7, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (s, 1H), 5.79 (dd, *J* = 1.4, 0.8 Hz, 1H), 4.75 (dd, *J* = 9.8, 3.4 Hz, 1H), 1.93 – 1.74 (m, 4H), 1.47 (dddd, *J* = 17.2, 13.7, 9.4, 4.4 Hz, 2H), 0.92 (dd, *J* = 6.6, 2.2 Hz, 6H), 0.11 – 0.05 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 142.3, 124.9, 73.6, 44.5, 24.4, 23.3, 21.2, 18.3, -0.1. [UPLC-DAD-QTOF: $C_{12}H_{25}O_2Si$ $[M]^+$ calcd.: 229.1620, found: 229.1624.

7.2. Screening of catalysts

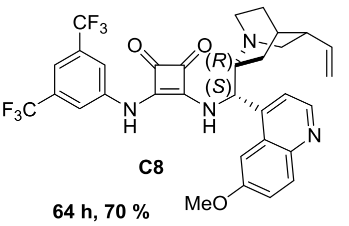



C6

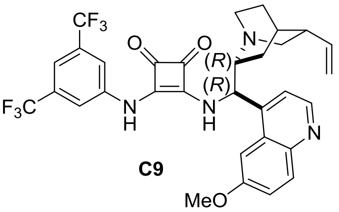
60 h, 73 %
dr: 89:11:0:0


C7

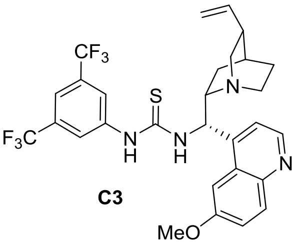
NR


C8

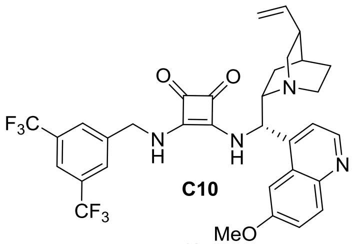
64 h, 70 %
dr: 49:41:10:0


C9

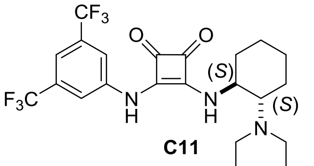
64 h, 65 %
dr: 22:21:57:0


C3

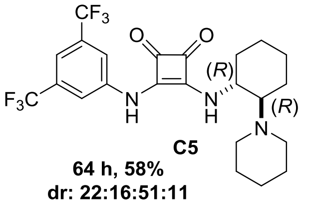
64 h, 75 %
dr: 56:35:9:0


C10

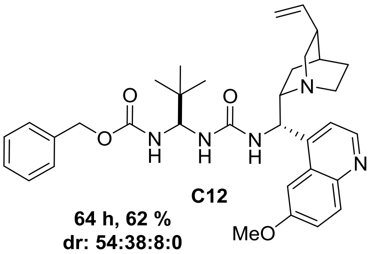
14 days, 55 %
dr: 67:30:3:0


C11

64 h, 60 %
dr: 32:23:23:22


C5

64 h, 58%
dr: 22:16:51:11


C12

64 h, 62 %
dr: 54:38:8:0

Catalysts **C1-C12** were prepared following the procedures described in the literature.[9]

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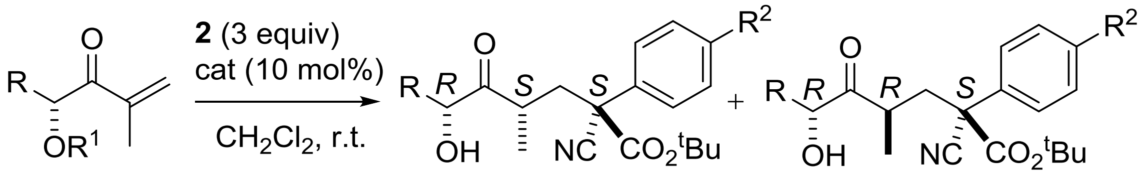
[9] **C6-C9**: W. Yang, D. M. Du, *Org. Lett.* **2010**, 12, 5450-5453. **C3**: B. Vakulya, S. Varga, A. Csampai, T. Sóos, *Org. Lett.*, **2005**, 7, 1967-1969. **C10**: J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.*, **2008**, 130, 14416-14417. **C11**, **C5**: Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem. Int. Ed.* **2010**, *49*, 153-156; W. Yang, D. M. Du, *Adv. Synth. Catal*. **2011**, 353, 1241-1246. **C12**: S. Diosdado, R. López, C. Palomo, *Chem. Eur. J.* **2014**, 20, 6526-6531.

7.3. Catalytic addition of α-cyanoacetates 2 to chiral enones 8-11.



8 R: Bn R^1: H
9 R: *i*Bu R^1: H
10 R: Bn R^1: SiMe$_3$
11 R: *i*Bu R^1: SiMe$_3$

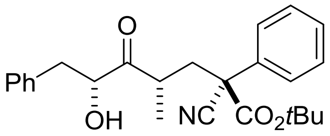
12 R: Bn R^2: H
13 R: Bn R^2: Br
14 R: *i*Bu R^2: Br
15 R: *i*Bu R^2: Cl

General Procedure: To a solution of the corresponding *tert*-butyl cyanoacetate **2** (0.6 mmol) and the corresponding α´-oxy enone **8-11** (0.2 mmol, 1 equiv.) in CH_2Cl_2 (0.4 mL), the catalyst (0.02 mmol) was added and the resulting mixture was stirred at 20 °C until consumption of the α´-oxy enone (monitored by ^{1}H-NMR; see Table 3 for reaction times). The reaction mixture was quenched with HCl 1N (5 mL) and the solution was extracted with CH_2Cl_2 (5 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure.

Reactions from α´-hydroxy enone **8/9**: The residue was submitted to purification by flash column chromatography (eluent hexane/ethyl acetate 95/5).

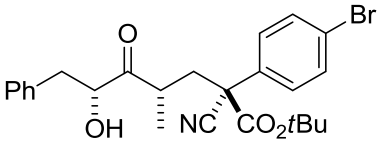
Reactions from α´-silyloxy enone **10/11**: The resulting material was dissolved in MeOH (0.5 mL) and a solution of concentrated fluorhydric acid in MeOH was added (10 mmol, 0.2 mL) and the resulting mixture was stirred at 20 °C for 2 h. Then the solvent was evaporated and the resulting residue was basified to pH 7 with sat'd solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (2 × 4 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was submitted to purification by flash column chromatography (eluent hexane/ethyl acetate 95/5).

(2*S*,4*S*,6*R*)-*tert*-butyl 2-cyano-6-hydroxy-4-methyl-5-oxo-2,7-diphenylheptanoate (12)



Prepared according to the general procedure starting from silyloxyenone **10** and cyanoacetate **2a**, and using catalyst **C6**. The title compound was isolated as an oil. Yield: 59 mg (73 %). $[\alpha]_D^{23}$ = +5.7 (c=0.3, dr: 89:11:0:0, CH_2Cl_2). ^{1}H NMR major diastereomer (300 MHz, $CDCl_3$) δ 7.71 – 7.18 (m, 10H), 4.54 (ddd, *J* = 9.3, 5.8, 3.6 Hz, 1H), 3.23 – 2.93 (m, 4H), 2.93 – 2.70 (m, 1H), 2.29 – 2.11 (m, 1H), 1.44 (s, 9H), 1.12 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR major diastereomer (75 MHz, $CDCl_3$) δ 214.1, 166.1, 136.8, 134.4, 129.3, 129.2, 128.9, 128.6, 126.8, 126.0, 118.6, 84.7, 76.0, 53.7, 39.7, 38.8, 27.5, 19.0. UPLC-DAD-QTOF: $C_{25}H_{29}NO_4Na$ $[M+Na]^+$ calcd.: 430.1993, found: 430.1994. dr: 89:11:0:0.
The ratio of diastereomers was determined by ^{1}H NMR analysis.

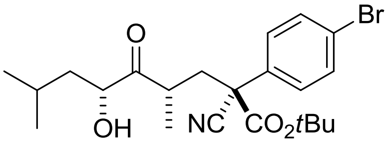
(2*S*,4*S*,6*R*)-*tert*-butyl 2-(4-bromophenyl)-2-cyano-6-hydroxy-4-methyl-5-oxo-7-phenylheptanoate (13)



Prepared according to the general procedure starting from silyloxyenone **10** and cyanoacetate **2b**, and using catalyst **C6**. The title compound was isolated as an oil. Yield: 73 mg (75 %). $[\alpha]_D^{25}$ = +4.5 (c=1, dr: 83:17:0:0, CH_2Cl_2). ^{1}H NMR major diastereomer (300 MHz, $CDCl_3$) δ 7.64 – 7.19 (m, 9H), 4.59 – 4.47 (m, 1H), 3.19 – 2.94 (m, 3H), 2.83 (dt, *J* = 14.1, 9.3 Hz, 1H), 2.17 – 2.00 (m, 1H), 1.45 (s, 9H), 1.09 (d, *J* = 13.6 Hz, 3H). ^{13}C NMR major isomer (75 MHz, $CDCl_3$) δ 212.8, 165.6, 137.0, 134.0, 132.3, 129.6, 129.3, 128.5, 127.7, 126.8, 85.1, 76.0, 54.1, 42.9, 40.6, 38.8, 27.5, 19.0. UPLC-DAD-QTOF: $C_{25}H_{29}NO_4Br$ $[M]^+$ calcd.: 486.1280, found: 486.1282. dr: 83:17:0:0.

The diastereomeric purity was determined by ^{1}H NMR analysis.

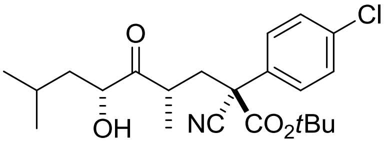
(2*S*,4*S*,6*R*)-*tert*-butyl 2-(4-bromophenyl)-2-cyano-6-hydroxy-4,8-dimethyl-5-oxononanoate (14)



Prepared according to the general procedure starting from silyloxyenone **11** and cyanoacetate **2b**, and using catalyst **C6**. The title compound was isolated as an oil. Yield: 81 mg (90 %). $[\alpha]_D^{23}$ = –1.2 (c=0.6, dr: 91:9:0:0, CH_2Cl_2). ^{1}H NMR major diastereomer (300 MHz, $CDCl_3$) δ 7.66 – 7.41 (m, 4H), 4.40 – 4.28 (m, 1H), 3.20 (d, *J* = 5.9 Hz, 1H), 3.14 – 2.84 (m, 2H), 2.14 – 1.90 (m, 2H), 1.45 (s, 9H), 1.44 – 1.24 (m, 2H), 1.19 (d, 3H), 1.08 (d, 6H). ^{13}C NMR major diastereomer (75 MHz, $CDCl_3$) δ 213.7, 165.5, 134.0, 131.7, 127.7, 123.3, 118.0, 85.1, 73.3, 42.8, 38.6, 38.5, 27.5, 24.8, 23.6, 21.0, 19.4. UPLC-DAD-QTOF: $C_{22}H_{31}NO_4Br$ $[M]^+$ calcd.: 452.1436, found: 452.1439. dr: 91:9:0:0.

The diastereomeric purity was determined by ^{1}H NMR analysis.

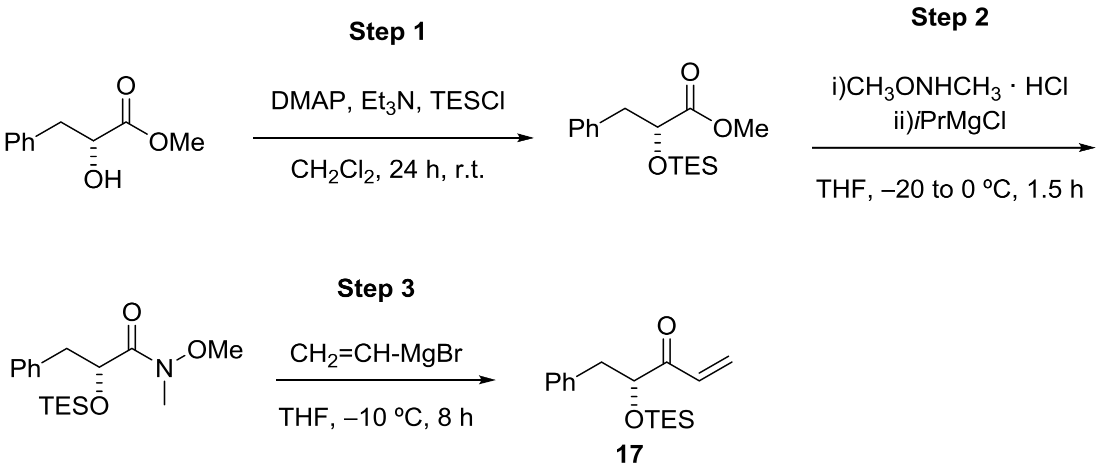
(2*S*,4*S*,6*R*)-*tert*-butyl 2-(4-chlorophenyl)-2-cyano-6-hydroxy-4,8-dimethyl-5-oxononanoate (15)



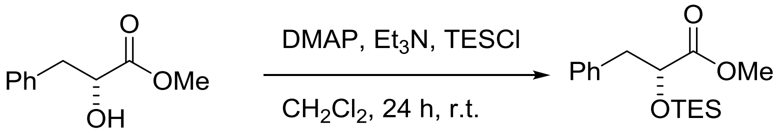
Prepared according to the general procedure starting from silyloxyenone **11** and cyanoacetate **2c**, and using catalyst **C6**. The title compound was isolated as an oil. Yield: 65 mg (80 %). $[\alpha]_D^{23}$ = –0.8 (c=0.7, dr: 90:10:0:0, CH_2Cl_2). ^{1}H NMR major diastereomer (300 MHz, $CDCl_3$) δ 7.61 – 7.35 (m, 4H), 4.43 – 4.29 (m, 1H), 3.21 (d, *J* = 5.9 Hz, 1H), 3.06 (dt, *J* = 13.4, 6.7 Hz, 1H), 3.01 – 2.90 (m, 1H), 2.06 (dt, *J* = 12.5, 4.0 Hz, 1H), 1.96 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.62 – 1.40 (m, 11H), 1.17 (d, *J* = 7.1 Hz, 3H), 1.04 – 0.98 (m, 6H). ^{13}C NMR major diastereomer (75 MHz, $CDCl_3$) δ 214.4, 165.7, 135.1, 133.5, 129.4, 127.4, 118.4, 85.1, 73.4, 53.2, 42.8, 38.6, 27.5, 24.8, 23.8, 21.1, 19.6. UPLC-DAD-QTOF: $C_{22}H_{31}NO_4Cl$ $[M]^+$ calcd.: 408.1942, found: 408.1943. dr: 90:10:0:0.

The diastereomeric purity was determined by ^{1}H NMR analysis.

7.4. Preparation of chiral α´-silyloxyenone 17.



Step 1: Preparation of methyl (*R*)-3-phenyl-2-((triethylsilyl)oxy)propanoate:[10]



To a solution of 4-dimethylamino pyridine (900 mg, 7.5 mmol), triethylamine (0.7 mL, 5 mmol), and triethylchlorosilane (1.27 mL, 7.5 mmol) in CH_2Cl_2 (7.5 mL), methyl (*R*)-2-hydroxy-3-phenylpropanoate (901 mg, 5 mmol, prepared as described on pages S12-S13) was added and the reaction was stirred at room temperature for 24 h. After filtration over celite, the filtrate was diluted with diethyl ether (50 mL) and the resulting solution was washed with brine (1 × 25 mL), HCl 3M (3 × 50 mL), and water (1 × 25 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 20/1) to give the desired compound as a colorless oil (1.21 g, 82 %). $[\alpha]_D^{23}$= + 47.4 (ee >99%, c=2.4, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.17 (m, 5H), 4.40 (dd, *J* = 8.6, 4.4 Hz, 1H), 3.74 (s, 3H), 3.19 – 2.85 (m, 2H), 0.92 – 0.79 (m, 9H), 0.57 – 0.41 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 137.3, 129.6, 128.1, 126.6, 73.5, 51.8, 41.6, 6.4, 4.3. UPLC-DAD-QTOF: $C_{16}H_{27}O_3Si$ $[M+H]^+$ cald.: 295.1729, found: 295.1733.

Step 4: Preparation of (*R*)-N-methoxy-N-methyl-3-phenyl-2-((triethylsilyl)oxy)propanamide:[11]

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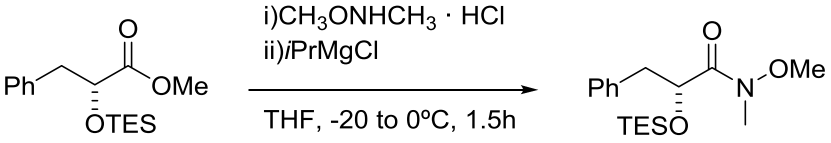
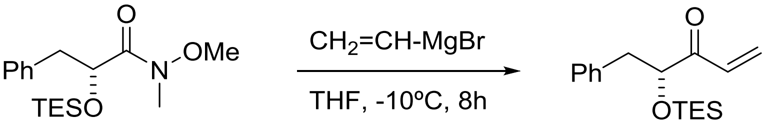
[10] Procedure adapted from: J. M. García, A. Gozalez, B. G. Kardak, J. M. Odriozola, M. Oiarbide, J. Razkin, C. Palomo, *Chem. Eur. J.*, **2008**, 14, 8768-8771.
[11] Procedure adapted from: F. Miege, B. M. Trost, *J. Am. Chem. Soc.*, **2014**, 136, 3016-3019.



To a solution of the methyl silyloxyester (1.21 g, 4.1 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (601 mg, 6.2 mmol, 1.5 equiv.) in THF (14 mL), a 2M solution of ^{i}PrMgCl in THF (8.2 mL, 16.5 mmol, 4 equiv.) was added at −20°C. The reaction mixture was stirred for 1.5 h at 0°C. The reaction was then quenched with an aqueous saturated solution of NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried over $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 80/20) to obtain the desired product as a yellow oil (1.08 g, 3.3 mmol, 81%). $[\alpha]_D^{23}$= + 3.6 (ee >99%, c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.17 (m, 5H), 4.72 (dd, *J* = 8.1, 4.9 Hz, 1H), 3.56 (s, 3H), 3.18 (s, 3H), 3.12 – 2.83 (m, 2H), 0.85 (t, *J* = 7.8 Hz, 9H), 0.60 – 0.42 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 137.7, 129.6, 128.1, 126.4, 70.8, 61.0, 41.2, 32.4, 6.4, 4.4. UPLC-DAD-QTOF: $C_{17}H_{30}NO_3Si$ $[M+H]^+$ cald.: 324.1995, found: 324.2000.

Step 5: Preparation of (*R*)-5-phenyl-4-((triethylsilyl)oxy)pent-1-en-3-one (17):

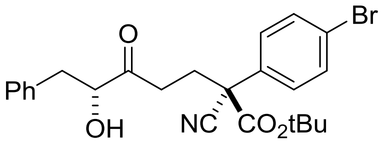


To a solution of the α-silyloxy amide (458 mg, 1.4 mmol) in dry THF (4 mL), a 0.7 M solution of vinylmagnesium bromide in THF was added at 0°C. The reaction mixture was stirred for 24 h at 0°C. The reaction was then quenched with an aqueous saturated solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 95/5) to obtain the desired product as a colorless oil (159 mg, 0.6 mmol, 43%). $[\alpha]_D^{23}$= + 15.6 (ee >99%, c=0.8, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.17 (m, 5H), 6.84 (ddd, *J* = 17.4, 10.5, 0.7 Hz, 1H), 6.42 (ddd, *J* = 17.5, 1.9, 0.7 Hz, 1H), 5.78 (dt, *J* = 10.5, 1.3 Hz, 1H), 4.38 (ddd, *J* = 8.4, 4.5, 0.7 Hz, 1H), 3.03 – 2.81 (m, 2H), 0.85 (t, *J* = 7.9 Hz, 9H), 0.52 – 0.40 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 137.4, 131.4, 130.2, 129.8, 128.6, 127.0, 79.7, 41.9, 7.0, 4.9. UPLC-DAD-QTOF: $C_{17}H_{30}NO_3Si$ $[M+H]^+$ cald.: 291.1780, found: 291.1782.

7.5. Catalytic addition of α-cyanoacetates 2b and 2c to chiral enone 17.

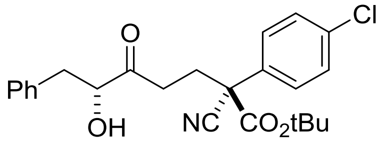
General Procedure: To a solution of *tert*-butyl cyanoacetate **2b** or **2c** (0.6 mmol) and the α´-silyloxy enone **17** (0.2 mmol, 1 equiv.) in CH_2Cl_2 (0.4 mL), catalyst **C6** (0.02 mmol) was added and the resulting mixture was stirred at 20 °C until consumption of the α´-oxy enone (monitored by ^{1}H-NMR). The reaction mixture was quenched with HCl 1N (5 mL) and the solution was extracted with CH_2Cl_2 (5 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting material was dissolved in MeOH (0.5 mL) and a solution of concentrated fluorhydric acid in MeOH was added (10 mmol, 0.2 mL) and the resulting mixture was stirred at 20 °C for 2 h. Then the solvent was evaporated and the resulting residue was basified to pH 7 with sat'd solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (2 × 4 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was submitted to purification by flash column chromatography (eluent hexane/ethyl acetate 95/5).

tert-butyl (2*S*,6*R*)-2-(4-bromophenyl)-2-cyano-6-hydroxy-5-oxo-7-phenylheptanoate (18)



Prepared according to the general procedure starting from α´-silyloxy enone **17** and cyanoacetate **2b**. The title compound was isolated as an oil. Yield: 88 mg (93 %). $[\alpha]_D^{23}$= + 11.7 (dr: > 95:5, c=2.3, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.19 (m, 9H), 4.48 – 4.34 (m, 1H), 3.13 (dd, *J* = 14.2, 4.8 Hz, 2H), 2.90 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.77 (ddd, *J* = 17.2, 12.2, 3.6 Hz, 1H), 2.62 – 2.36 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 165.0, 135.7, 132.9, 132.1, 128.9, 128.3, 127.3, 126.7, 123.0, 117.5, 84.8, 77.0, 53.1, 39.8, 34.3, 30.9, 27.2. UPLC-DAD-QTOF: $C_{24}H_{26}NO_4BrNa$ $[M+Na]^+$ cald.: 494.0943, found: 494.0950.

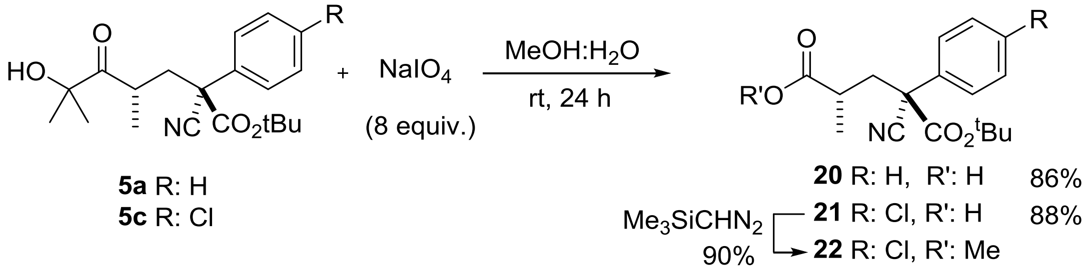
tert-butyl (2S,6R)-2-(4-chlorophenyl)-2-cyano-6-hydroxy-5-oxo-7-phenylheptanoate (19)



Prepared according to the general procedure starting from α´-silyloxy enone **17** and cyanoacetate **2c**. The title compound was isolated as an oil. Yield: 68 mg (79 %). $[\alpha]_D^{23}$= + 7.8 (dr: > 95:5, c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.20 (m, 9H), 4.48 – 4.36 (m, 1H), 3.22 – 3.08 (m, 2H), 2.96 – 2.69 (m, 2H), 2.61 – 2.36 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 165.4, 136.0, 135.2, 132.7, 129.4, 129.2, 128.6, 127.3, 127.0, 117.8, 85.1, 77.3, 53.4, 40.2, 34.6, 31.2, 27.5. UPLC-DAD-QTOF: $C_{24}H_{26}ClNO_4Na$ $[M+Na]^+$ cald.: 450.1448, found: 450.1447.

8. Chemical elaboration of adducts.

8.1. Synthesis of carboxylic acids 20, 21 and ester 22



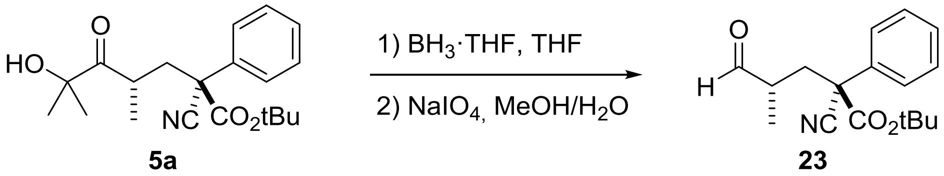
(2*S*,4*S*)-5-(*tert*-Butoxy)-4-cyano-2-methyl-5-oxo-4-phenylpentanoic acid (20)

A suspension of sodium periodate $NaIO_4$ (342 mg, 1.6 mmol) in water (0.8 mL) was added to a solution of α-hydroxy ketone **5a** (0.2 mmol) in methanol (1 mL). The mixture was stirred at room temperature until the reaction was complete (monitored by TCL, 24h). Then the solvent was removed under reduced pressure. Water (4.5 mL) was added to the crude product and the resulting mixture was extracted with Et_2O (3 x 6 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated to afford the corresponding carboxylic acid. After purifying with flash column chromatography (80:20 Hex: EtOAc) the carboxylic acid was obtained as a colorless oil (52 mg, 86% yield). $[\alpha]_D^{25}$ = + 34.9 (c=2.45, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 2H), 7.45 – 7.32 (m, 3H), 2.93 (dd, *J* = 14.4, 7.5 Hz, 1H), 2.68 (tt, *J* = 7.3, 3.5 Hz, 1H), 2.09 (dd, *J* = 14.5, 4.7 Hz, 1H), 1.40 (s, 9H), 1.21 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.3, 166.0, 135.2, 129.3, 129.0, 126.1, 118.3, 84.9, 53.9, 40.8, 37.1, 27.7, 18.8. UPLC-DAD-QTOF: $C_{17}H_{22}NO_4$ $[M+H]^+$ calcd.: 304.1549, found: 304.1553.

(2*S*,4*S*)-2-tert-butoxycarbonyl-5-methyl-2-(4-chlorophenyl)-2-cyano-4-methylpentanoic acid (21)

The same procedure as above was employed starting from α-hydroxy ketone **5c** (76 mg, 0.2 mmol). Yield 59 mg (88%). This compound was characterized as its methyl ester derivative **22**, prepared as follow: To a solution of the resulting residue (0.13 mmol, 44 mg) in MeOH (1 mL), a solution of Me_3SiCHN_2 (2M, 0.65 mmol, 0.33 mL, 5 equiv.) was added and the resulting mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 90/10). Yield 43 mg (90 %). $[\alpha]_D^{23}$ = +11.0 (c=0.5, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.34 (m, 4H), 3.74 (s, 3H), 2.90 (dd, *J* = 14.4, 8.6 Hz, 1H), 2.67 – 2.54 (m, 1H), 2.12 (dd, *J* = 14.4, 4.0 Hz, 1H), 1.45 (s, 9H), 1.21 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 166.0, 135.4, 133.8, 129.7, 127.9, 118.2, 85.3, 53.6, 52.4, 41.3, 37.1, 27.9, 19.3. UPLC-DAD-QTOF: $C_{18}H_{23}NO_4Cl$ $[M]^+$ calcd.: 352.1316, found: 352.1321.

8.2. Synthesis of aldehyde 23

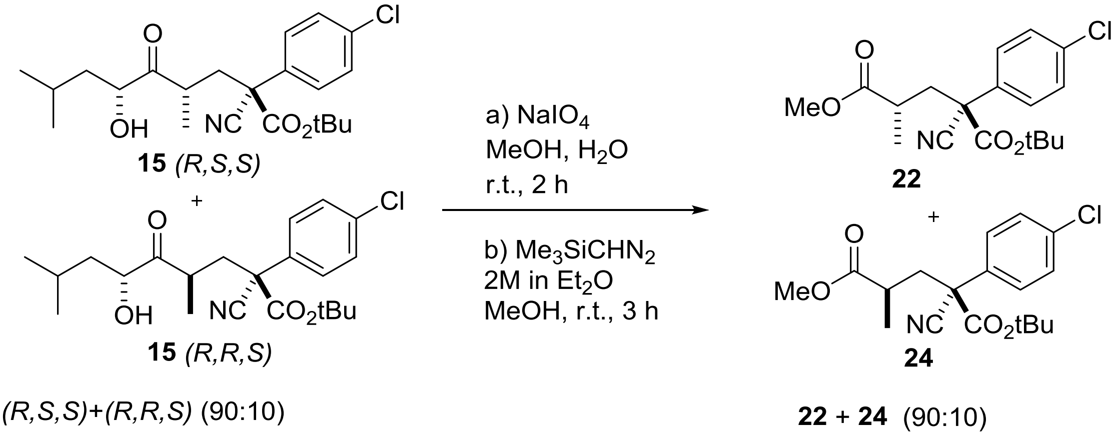


(2*S*,4*S*)-*tert*-Butyl 2-cyano-4-methyl-5-oxo-2-phenylpentanoate 23

BH_3·THF complex (1 M, 0.4 mL, 0.4 mmol) was added to a solution of α-hydroxy ketone **5a** (69 mg, 0.2 mmol) in dry THF (0.9 mL) at 0 °C and the resulting solution was stirred at the same temperature for 2 h. Then MeOH (1 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure and the residue thus obtained was subjected to oxidative scission by treatment with $NaIO_4$, under the same conditions reported above. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 95/5) to give the title compound as an oil (44 mg, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (d, J = 2.0 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.45 – 7.36 (m, 3H), 2.97 (dd, J = 14.5, 6.7 Hz, 1H), 2.67 – 2.51 (m, 1H), 1.98 (dd, J = 14.5, 5.1 Hz, 1H), 1.41 (s, 9H), 1.11 (d, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 180.6, 135.2, 129.4, 129.1, 129.0, 126.1, 85.1, 53.9, 40.8, 38.5, 27.7, 15.4.

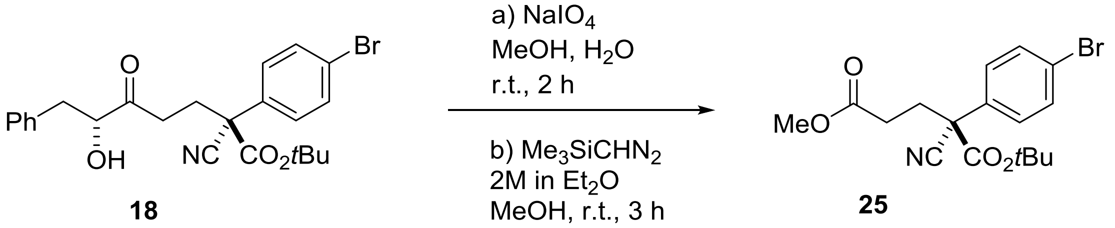
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H hexane/isopropanol 95/5, flow rate= 0.6 mL/min, retention times: 18.7 min (major.) and 22.2 min (minor.)).

8.3. Scision of 15 and 18. Synthesis of methyl esters 22, 24 and 25.

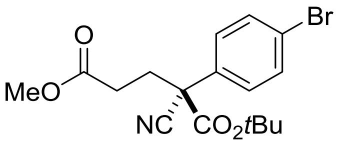


1-tert-butyl 5-methyl 2-(4-chlorophenyl)-2-cyano-4-methylpentanedioate 22/24

A suspension of $NaIO_4$ (171 mg, 0.79 mmol) in water (0.38 mL) was added to a solution of adduct **15** (90:10 mixture of diastereomers, 65 mg, 0.16 mmol) in methanol (0.79 mL). The mixture was stirred at room temperature until the starting material dissapeared (monitored by TLC) and the solvent was removed under reduced pressure. Water (2.5 mL) was added to the residue and the resulting mixture was extracted with Et_2O (3 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated. To a solution of the resulting residue (0.13 mmol, 44 mg) in MeOH (1 mL), a solution of Me_3SiCHN_2 (2M, 0.65 mmol, 0.33 mL, 5 equiv.) was added and the resulting mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 90/10). Yield (two steps): 42 mg (90:10 mixture of diastereomers, 78 %). NMR data of major isomer were identical to those of ester **22** prepared as above.

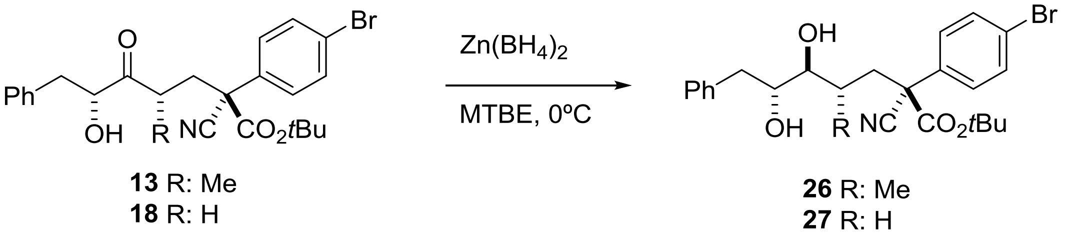


1-(*tert*-butyl) 5-methyl (*S*)-2-(4-bromophenyl)-2-cyanopentanedioate (25)



A suspension of sodium periodate $NaIO_4$ (342 mg, 1.6 mmol) in water (0.8 mL) was added to a solution of α-hydroxy ketone **18** (0.2 mmol) in methanol (1 mL) and water (0.8 mL). The mixture was stirred at room temperature until the reaction was complete (monitored by TCL, 2 h). Then the solvent was removed under reduced pressure. Water (4.5 mL) was added to the crude product and the resulting mixture was extracted with Et_2O (3 x 6 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated. To a solution of the resulting residue in MeOH (1 mL), a solution of $Me_3SiCH_2N_2$ (2M, 1 mmol, 0.5 mL, 5 equiv.) was added and the resulting mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 90/10). Yield (two steps): 65 mg (85 %). $[\alpha]_D^{23}= + 0.7$ (c=0.6, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.37 (m, 4H), 3.70 (s, 3H), 2.74 – 2.35 (m, 4H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 165.8, 133.7, 132.8, 128.1, 123.7, 118.1, 85.5, 54.0, 52.4, 33.2, 30.5, 28.0. UPLC-DAD-QTOF: $C_{17}H_{21}BrNO_4$ $[M+H]^+$ cald.: 382.0654, found: 382.0656.

8.4. Reduction of 13 and 18 to corresponding *anti*-diols 26 and 27.



Preparation of zinc borohydride[12]

A mixture of anhydrous zinc chloride (2 g, 14.5 mmol) and dry MTBE (25 mL) was refluxed until most of the solid had disolved. The mixture was allowed to stand, and the supernatant liquid was decanted from the insoluble material. The solution was added dropwise at room temperature to a stirred suspension of sodium borohydride (1.30 g, 34.5 mmol, 2.4 equiv.) in 75 mL of dry MTBE. The resulting mixture was stirred for 3

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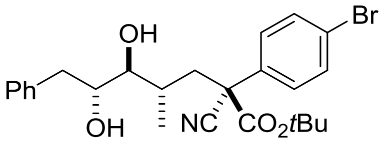
[12] W. J. Gemsler, F. Johson, A. D. B. Sloam, *J. Am. Chem. Soc.* **1960**, *82*, 6074-6081.

days at room temperature. The solids were allowed to settle, and the solution was directly used for the next reactions.

General procedure for the reduction of 13 and 18: To a solution the corresponding α′-hydroxy ketone (0.6 mmol) in dry MTBE (2 mL) a solution of zinc borohydride in MTBE was added at 0°C (25 mL) and the mixture was stirred at 0°C for 10-15 minutes. The reaction mixture was quenched with water and the layers were separated. The organic phase was dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting crude material was purified by flash column chromatography (eluent hexane / ethyl acetate 80 / 20).

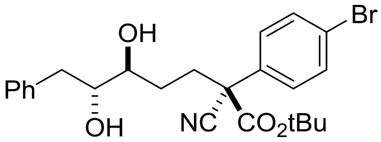
***tert*-butyl (2S,4S,6R)-2-(4-bromophenyl)-2-cyano-5,6-dihydroxy-4-methyl-7-phenylheptanoate 26**



19

Prepared according to the general procedure starting from 290 mg of ketone **13**. The title compound was isolated as a colorless oil. Yield 225 mg (76 %). $[\alpha]_D^{25}$ = +29.9 (c=1, dr >95:5, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.21 (m, 9H), 3.95 (dtd, *J* = 9.8, 4.9, 2.9 Hz, 1H), 3.55 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.00 (dd, *J* = 13.8, 2.9 Hz, 1H), 2.90 – 2.72 (m, 2H), 2.37 – 2.19 (m, 2H), 2.10 (qd, *J* = 7.3, 3.3 Hz, 1H), 1.85 (dd, *J* = 14.4, 7.8 Hz, 1H), 1.46 (s, 9H), 1.07 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 138.3, 135.3, 132.1, 129.5, 128.6, 127.6, 126.6, 122.9, 118.8, 85.5, 78.4, 72.7, 53.7, 40.9, 37.5, 33.2, 27.5, 17.7. UPLC-DAD-QTOF: $C_{25}H_{30}NO_4BrNa$ $[M+Na]^+$ calcd.: 510.1256, found: 510.1266.

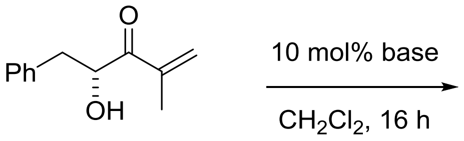
***tert*-butyl (2S,5S,6R)-2-(4-bromophenyl)-2-cyano-5,6-dihydroxy-7-phenylheptanoate 27**



Prepared according to the general procedure starting from 284 mg of ketone **18**. The title compound was isolated as a white solid. Yield: 222 mg (78 %). m. p.: 127 – 129 °C. $[\alpha]_D^{23}$= + 6.7 (dr: > 95:5, c=0.4, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.38 (m, 4H), 7.41 – 7.14 (m, 5H), 4.63 (ddd, *J* = 8.9, 7.5, 5.2 Hz, 1H), 4.32 (ddd, *J* = 10.5, 7.5, 2.9 Hz, 1H), 2.94 – 2.67 (m, 2H), 2.16 – 1.86 (m, 2H), 1.47 (s, 9H), 0.84 (d, *J* = 7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 137.6, 133.8, 132.2, 129.0, 128.5, 127.7, 126.5, 123.1, 118.1, 84.8, 79.3, 78.2, 54.3, 37.3, 34.9, 27.6, 25.2. UPLC-DAD-QTOF: $C_{24}H_{28}BrNO_4Na$ $[M+H]^+$ cald.: 496.1099, found: 496.1104.

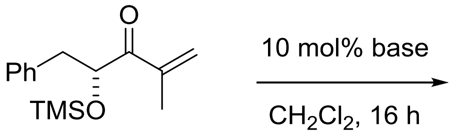
9. Configurational stability of α’-oxy ketones

9.1. Configurational stability of enones 8 and 10 against Brønsted bases[a]



8, >99% *ee*

Base	*ee*(%)
Et_3N	>99
DBU	>99
C6	>99



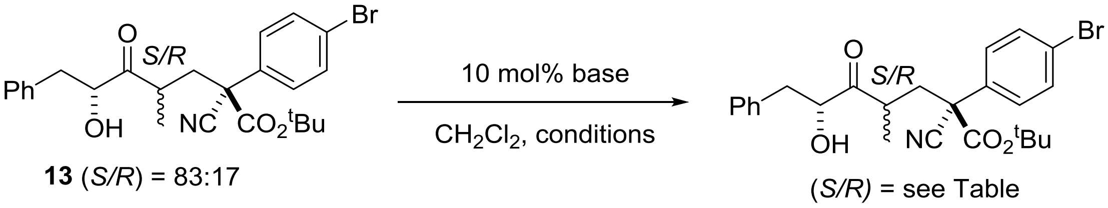
10, >99% *ee*

Base	*ee*(%)
Et_3N	>99
DBU	>99
C6	>99
C6	>99[b]

[a] Experiments carried out at room temperature. *ee*´s measured by chiral HPLC after 16 h. [b] *ee* measured by chiral HPLC after 72 h. (Conditions for HPLC: Chiralpak column AS-H, 95:5 Hexane:*i*-PrOH, 0.5 mL/min, λ=210 nm)

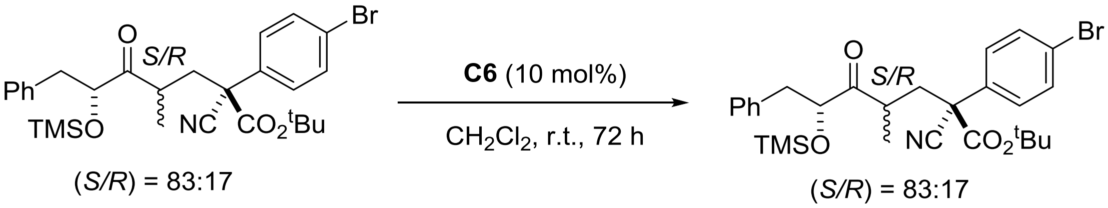
9.2. Configurational stability of Michael adduct 13 and its silyl ether

Diastereomeric ratios were determined by integration of key peaks on ^{1}H NMR.



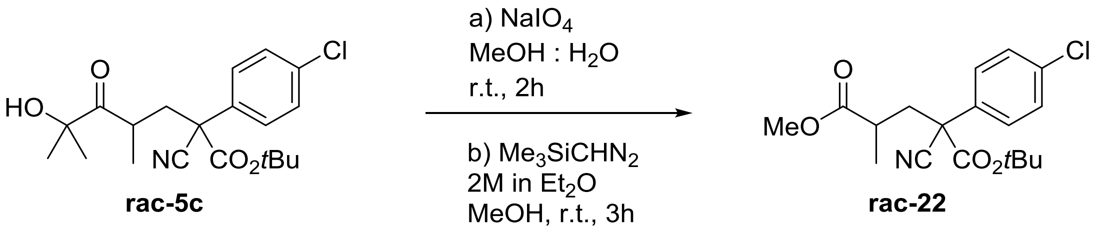
Base	t (h)	T (ºC)	*S/R*
Et$_3$N	16	r.t.	83:17
	72	r.t.	83:17
	24	40	83:17
DBU	16	r.t.	81:19
	72	r.t.	79:21
	24	40	69:31

Configurational stability of the silyl ether under the reaction conditions:



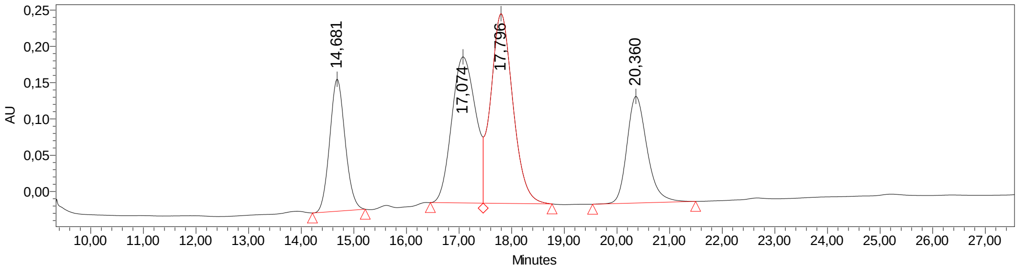
10. Asignment of configuration to adducts 15 and 18

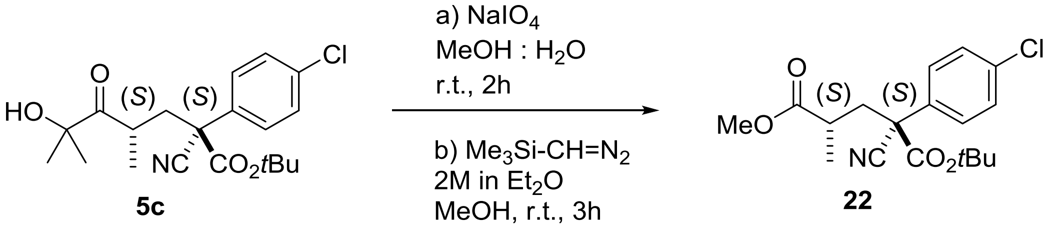
Configurational identity of each isomer of adduct **15** was established by correlation of HPLC chromatograms of the corresponding methyl ester derivatives **22** and comparison with ester products obtained from adduct **5c**, as follow:



rac-5c **rac-22**

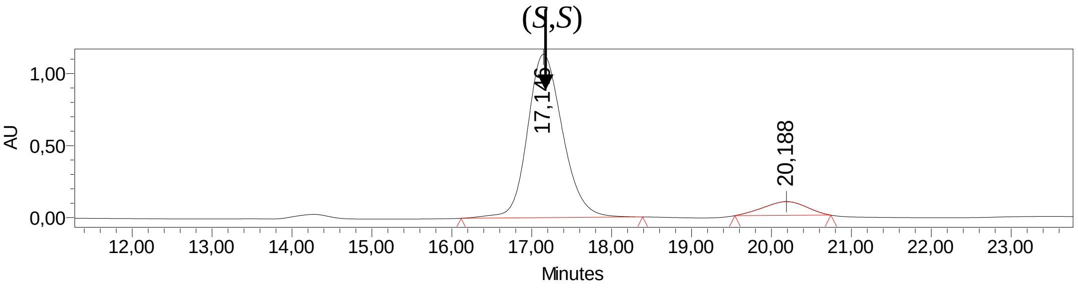
	Retention Time	% Area
1	14,681	17,14
2	17,074	29,41
3	17,796	35,45
4	20,360	18,00

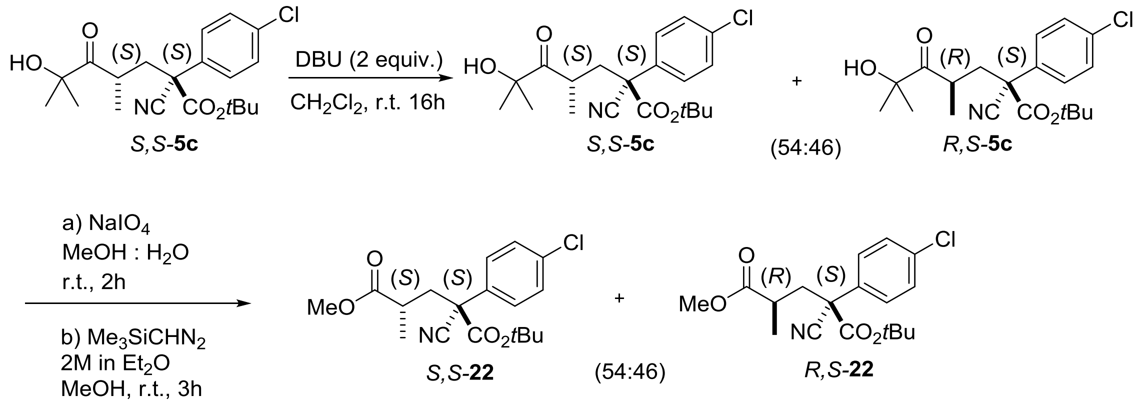




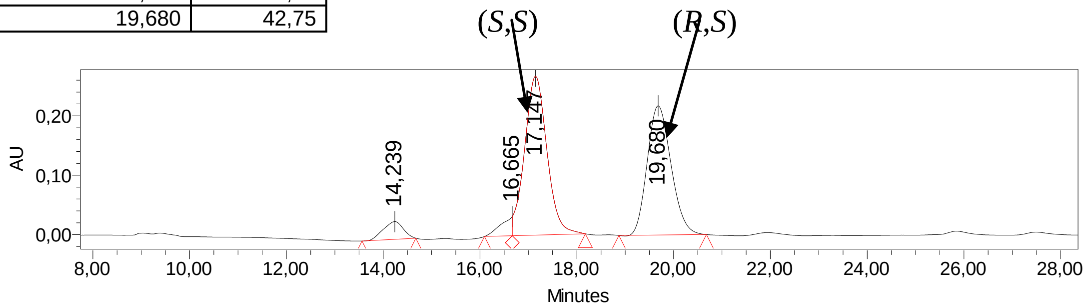
5c **22**

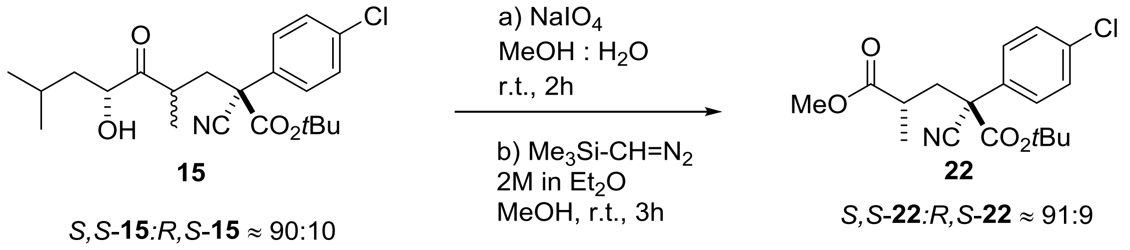
	Retention Time	% Area
1	17,146	90,63
2	20,188	9,37



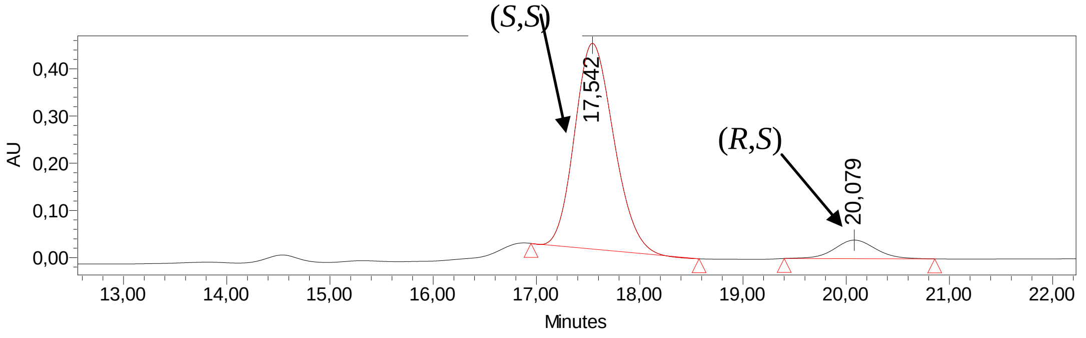


	Retention Time	% Area
1	14,239	4,93
2	16,665	3,04
3	17,147	49,27
4	19,680	42,75

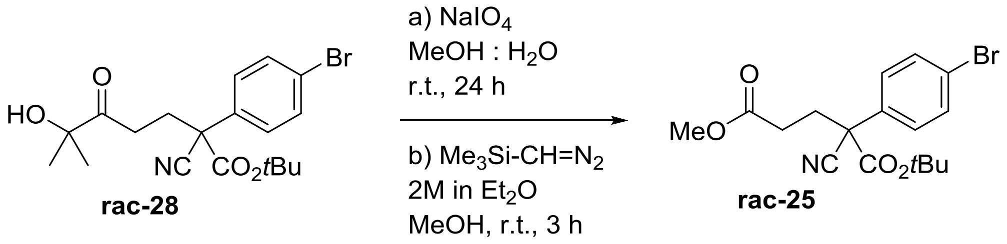




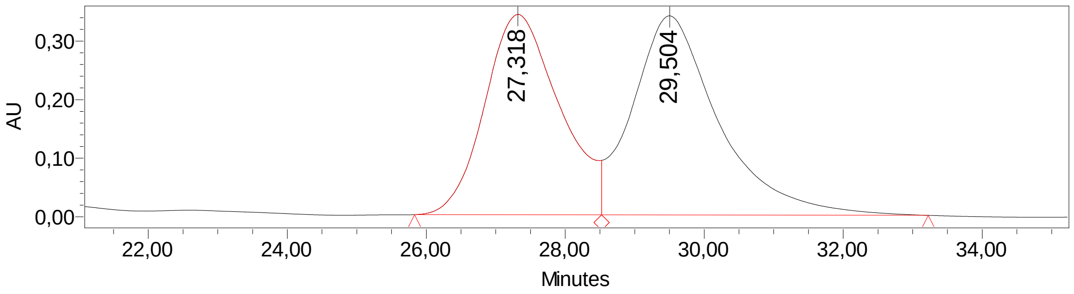
	Retention Time	% Area
1	17,542	91,35
2	20,079	8,65



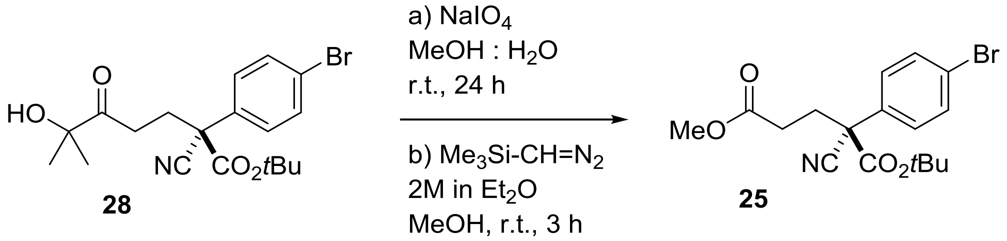
Configurational identity of adduct **18** was established by correlation of HPLC chromatograms of the corresponding methyl ester derivatives **25** and comparison with ester products obtained from previously described adducts **28** and **rac-28**,[4] as follow:



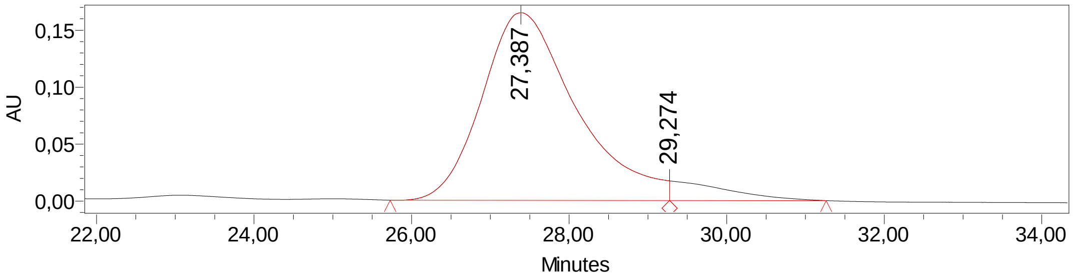
rac-28 **rac-25**



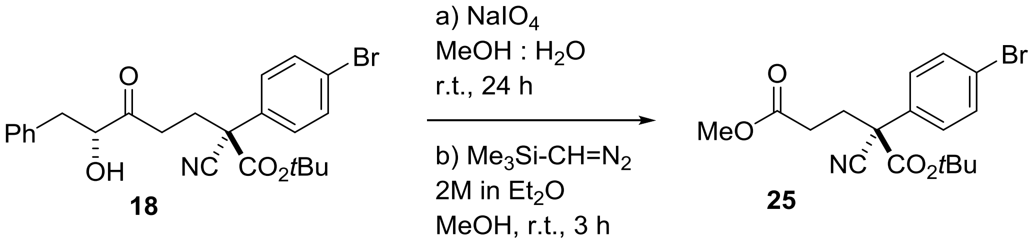
	Retention Time	% Area
1	27,318	46,71
2	29,504	53,29



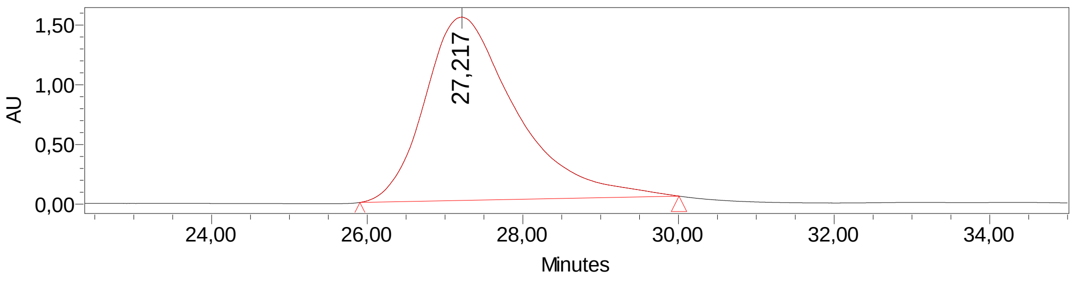
28 **25**



	Retention Time	% Area
1	27,387	94,06
2	29,274	5,94



18 **25**

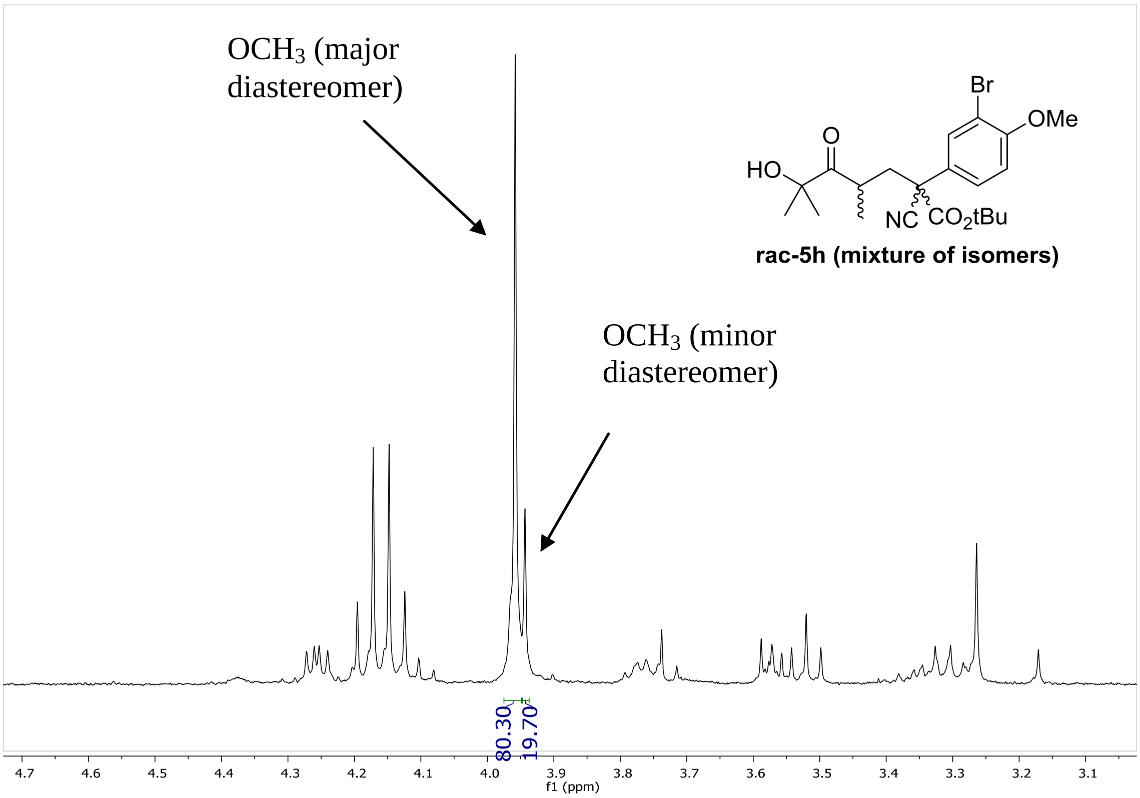


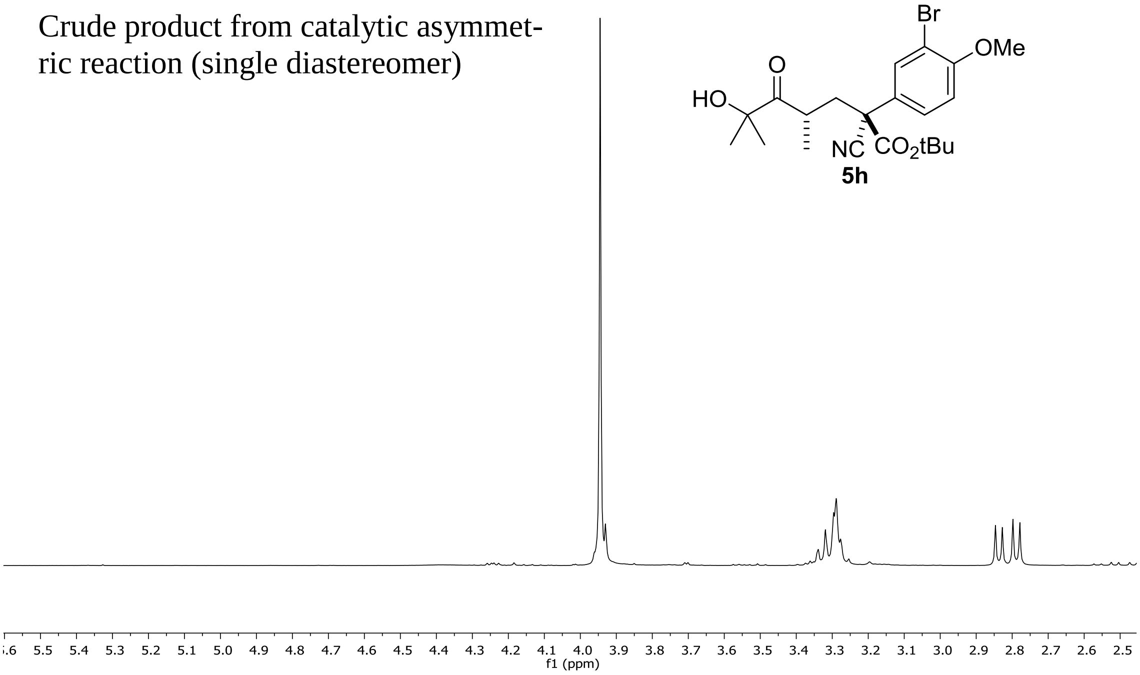
	Retention Time	% Area
1	27,217	100,00

11. Determination of the ratio of stereisomers

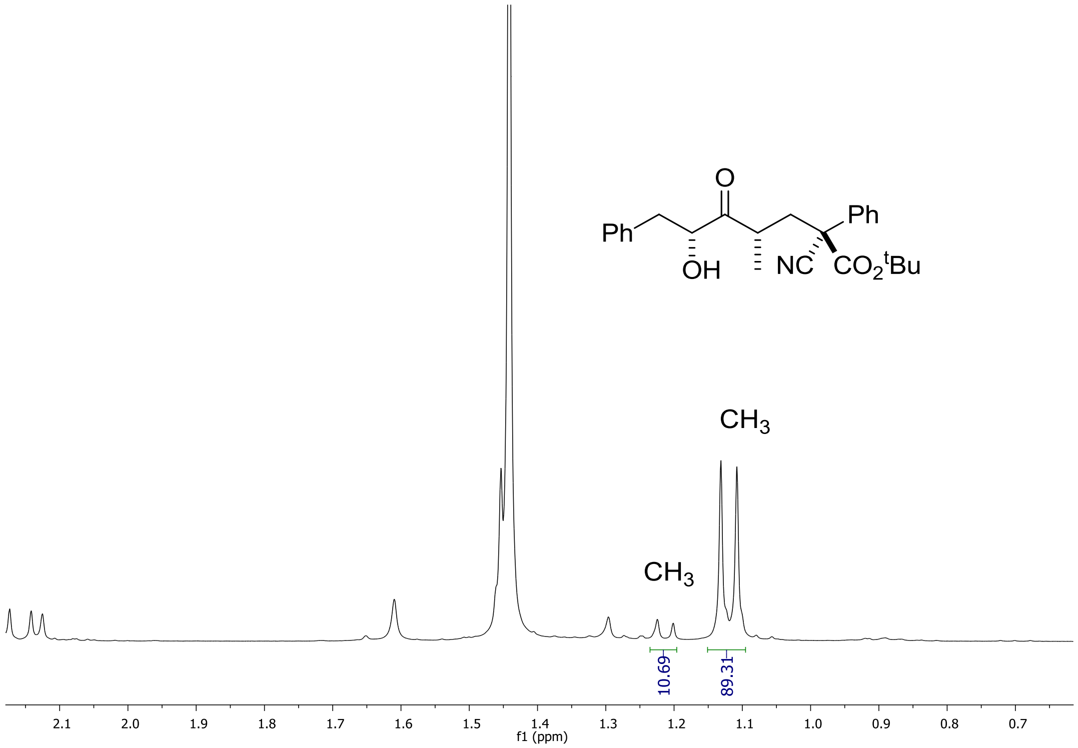
11.1 Diastereomeric ratio by NMR

(^{1}H NMR insets corresponding to reaction crudes)

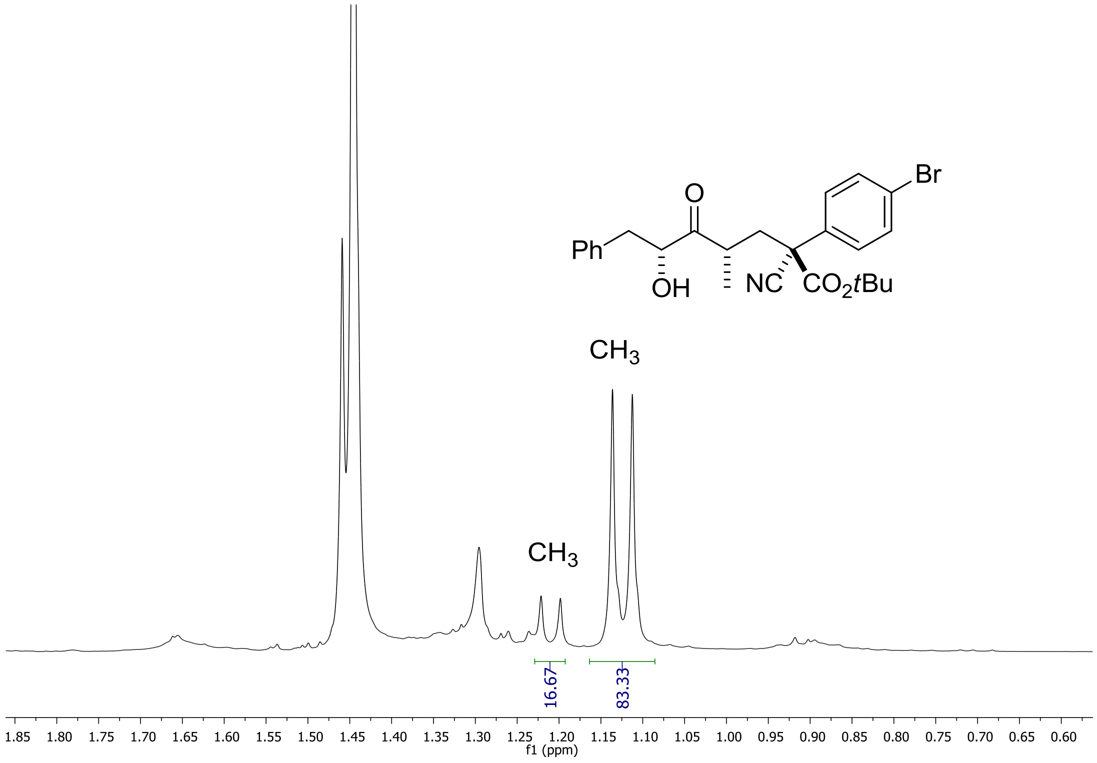




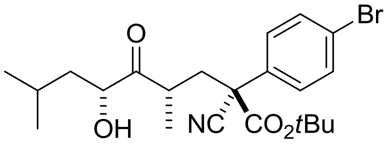
Adduct **12**:

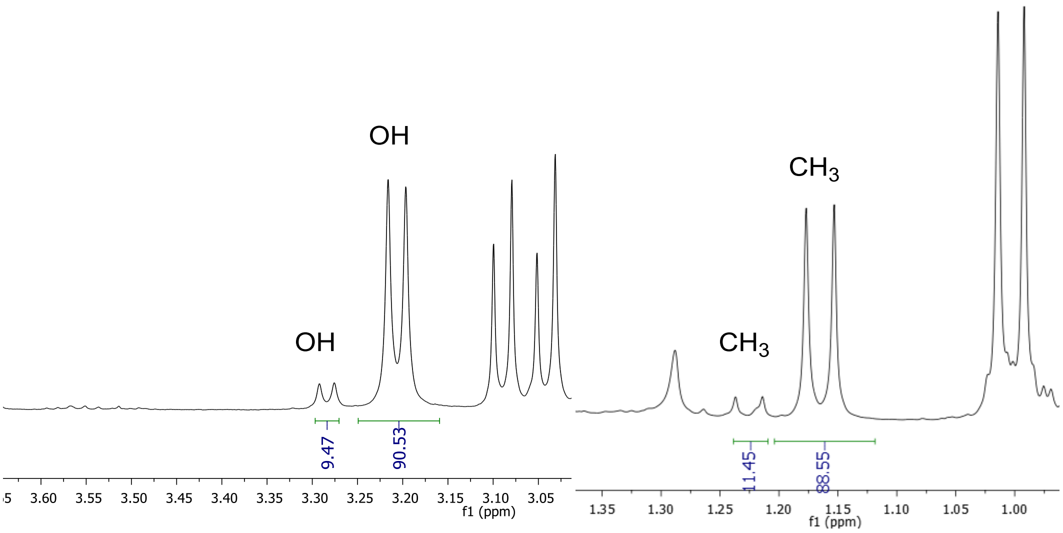


Adduct **13**:

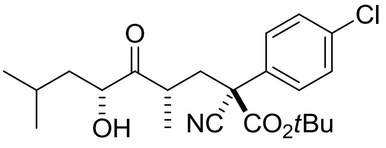


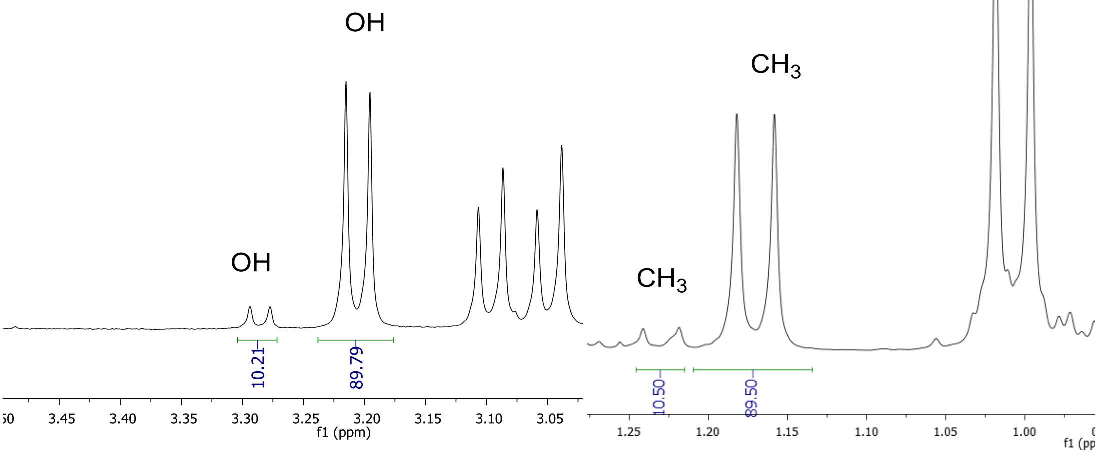
Adduct **14**:



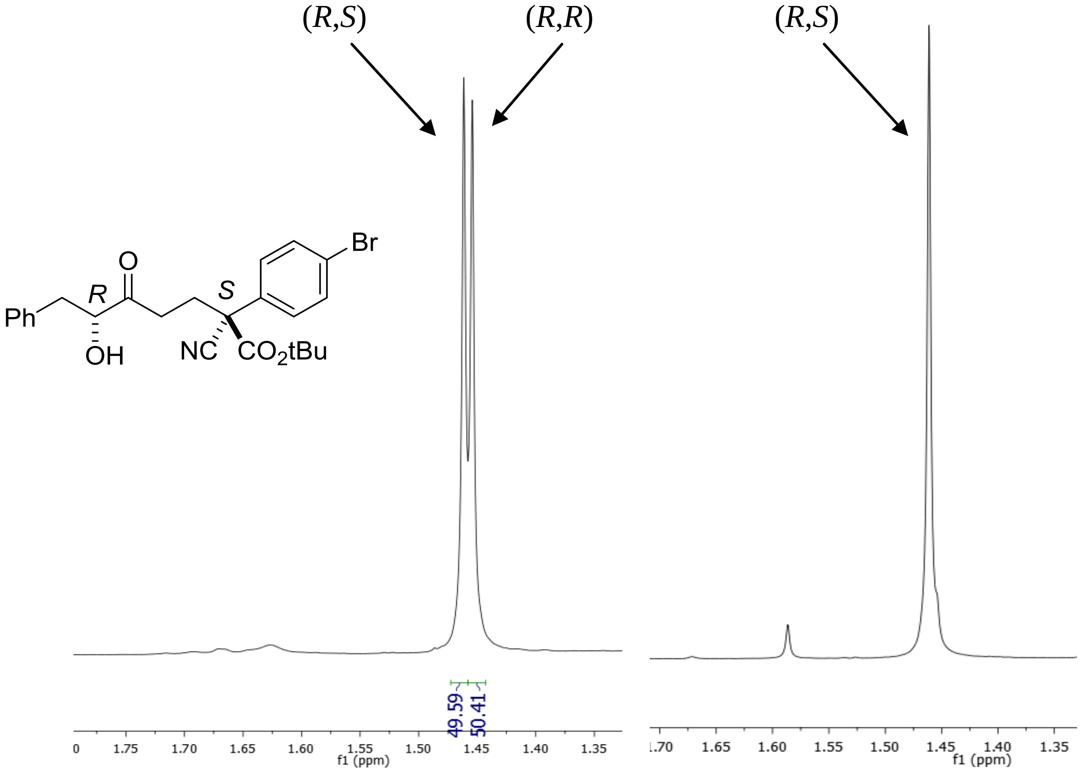


Adduct **15**:

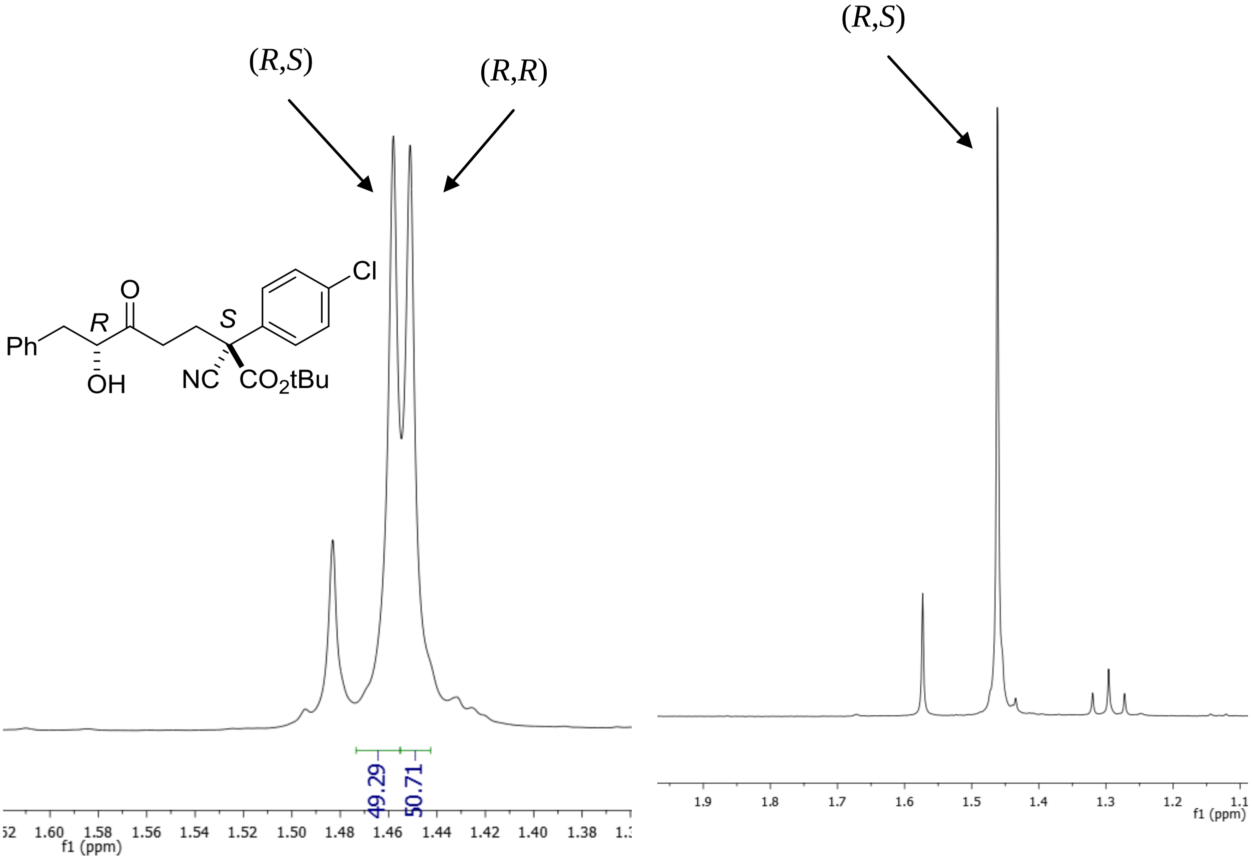




Adduct **18**:

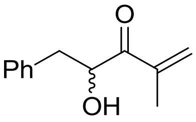


Adduct **19**:

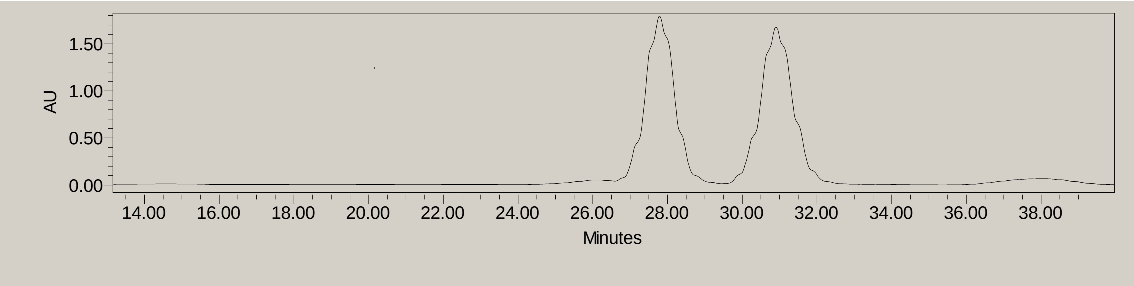


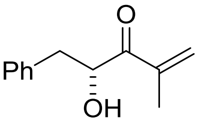
11.2. Enantiomeric ratio by HPLC/GC Chromatography

Determination of the *ee* of enones 8, 9 and 17:
Chiralpak column AS-H, 95:5 Hexane:*i*-PrOH, 0.5 mL/min, λ=210 nm.



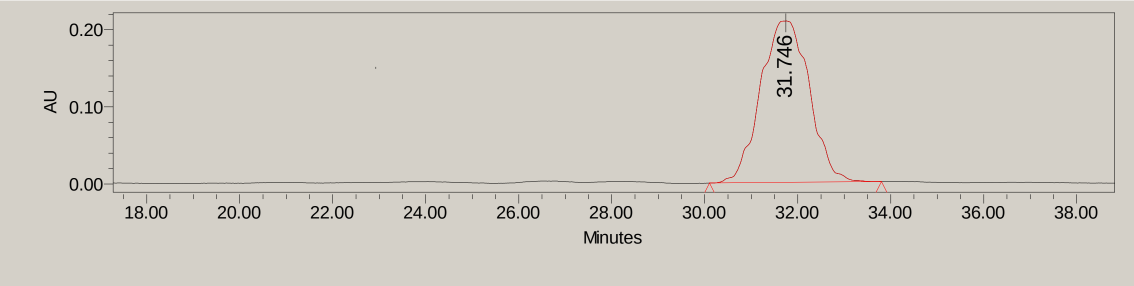
	Retention Time	% Area	Height
1	27.784	48.62	1756589
2	30.901	51.38	1657162



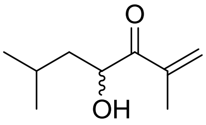


8

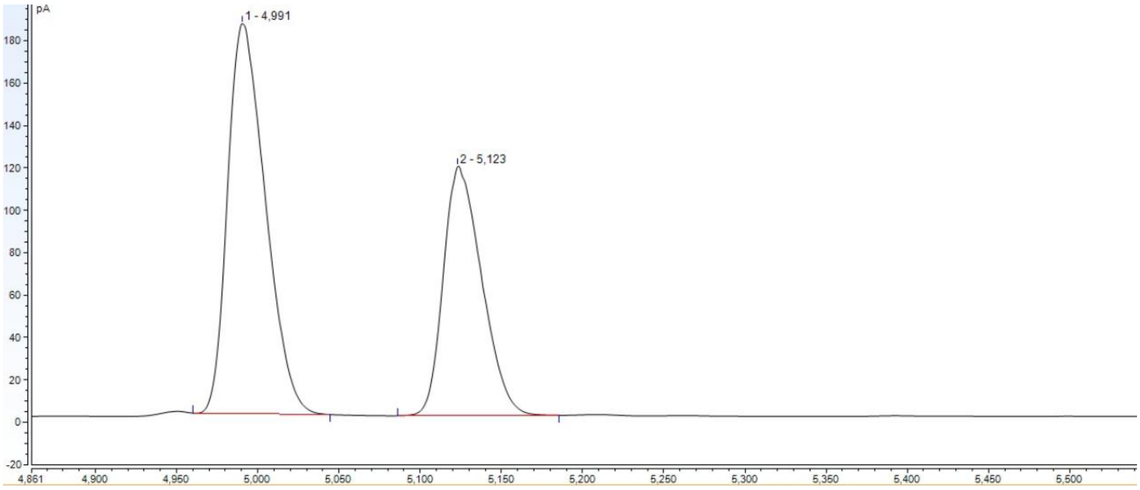
	Retention Time	% Area	Height
1	31.746	100.00	209263

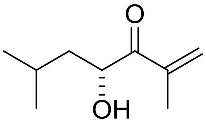


Gas Chromatography: Performed using a Thermo Scientific Trace 1300 equipment with a FID. Chiral column HYDRODEX β-6TBDM, 25 m, 0.25 mm ID. Temperature gradient: 1) 100 ºC for 1 min; 2) from 100 ºC to 200 ºC at a heating rate of 10ºC/min (11 min); 3) 200 ºC for an additional 11 min.



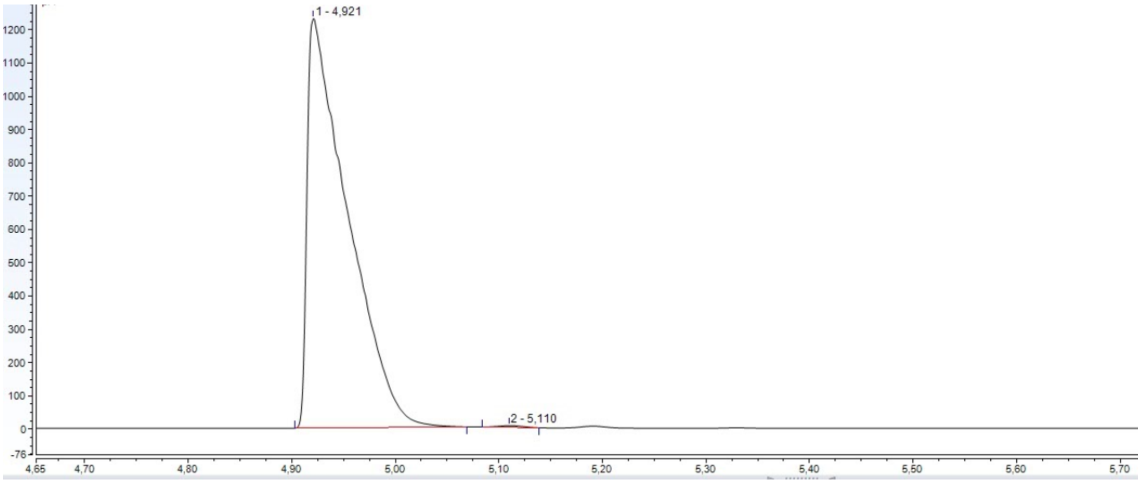
RT	Area (%)
4.99	60.5
5.12	39.5



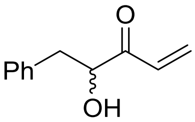


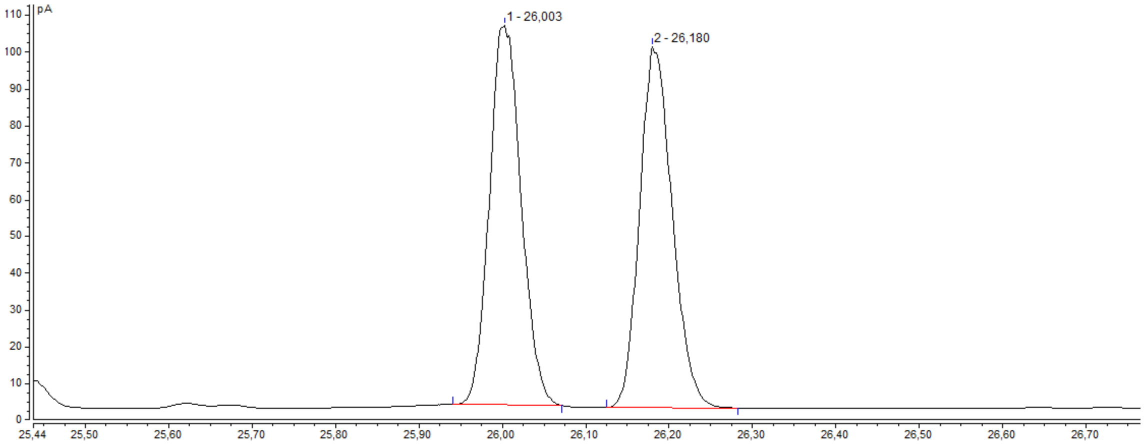
9

RT	Area (%)
4.92	99.7
5.11	0.3

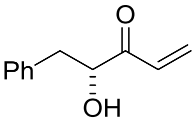


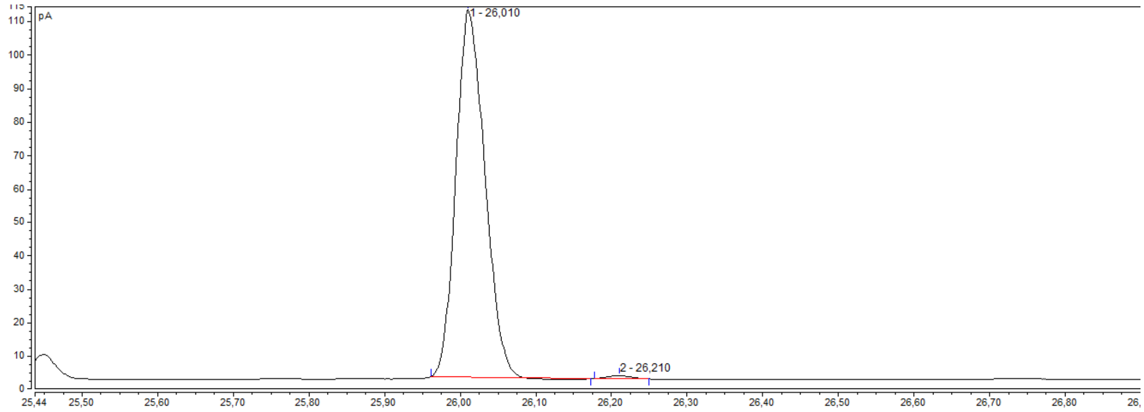
Determination of *ee* of **17** was carried out by HPLC analysis on the desilylated alcohol: To a solution of **17** (0.1 mmol) in MeOH (0.2 mL), a concentrated solution of H_2F_2 in MeOH (0.1 mL) was added at room temperature and the mixture was stirred at the same temperature for 2 h. The solvent was evaporated and a saturated solution of $NaHCO_3$ was added to the residue to adjust pH to 7. The mixture was extracted with CH_2Cl_2 (2 × 2 mL), dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude material was subjected to HPLC analysis (Chiralpak column AS-H, 95:5 Hexane:*i*-PrOH, 0.5 mL/min, λ=210 nm)





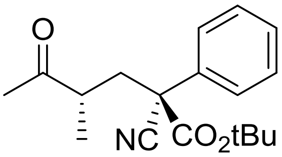
RT	Area (%)
26.003	49.22
26.180	50.78





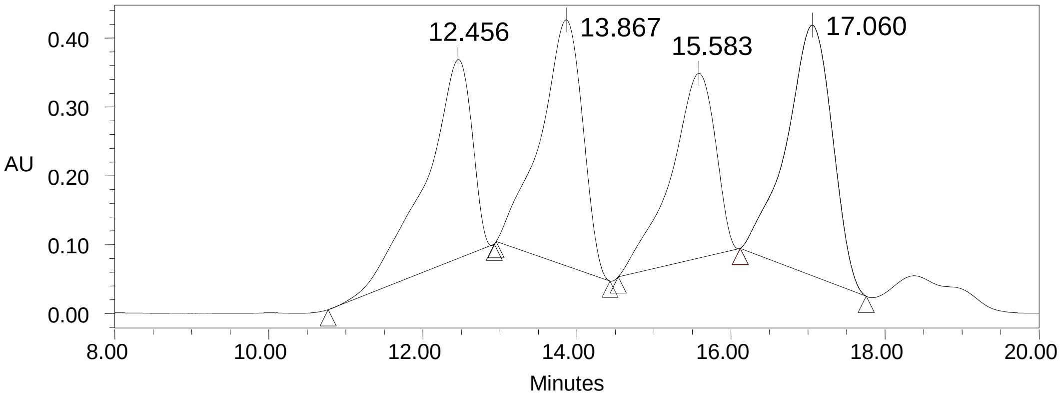
RT	Area (%)
26.010	99.53
26.210	0.47

(adduct from α-methyl 3-buten-2-one)



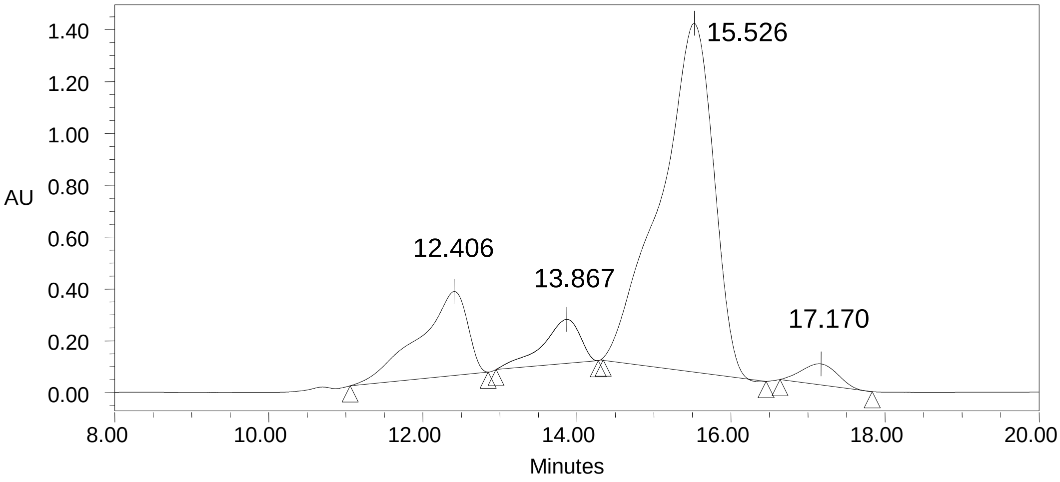
Column: AD-H
Eluent: Hex:*i*PrOH, 99:1
Flow rate = 1.0 mL/min
λ = 210 nm

racemic



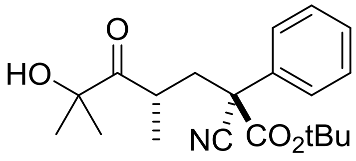
	Retention Time	Area	% Area	Height
1	12.456	12163732	23.48	288662
2	13.867	13714389	26.47	357393
3	15.583	10810537	20.86	268153
4	17.060	15126763	29.19	364032

scalemic



	Retention Time	Area	% Area	Height
2	13.867	5761668	6.61	169616
1	12.406	14165292	16.25	323895
4	17.170	2606201	2.99	80843
3	15.526	64637491	74.15	1345565

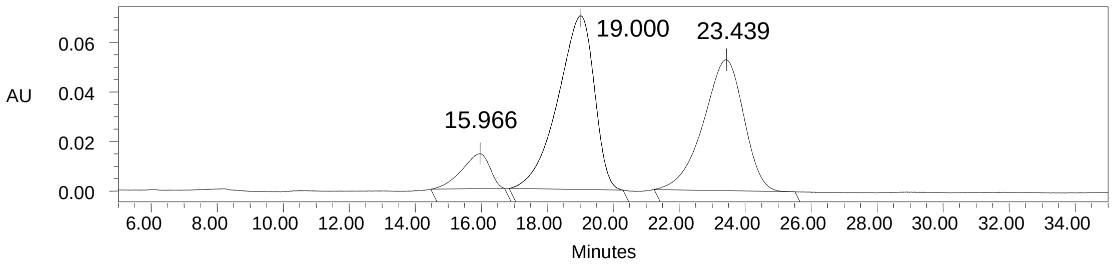
80:20 *dr* 92% *ee* (major.) 42% *ee* (minor.)



5a

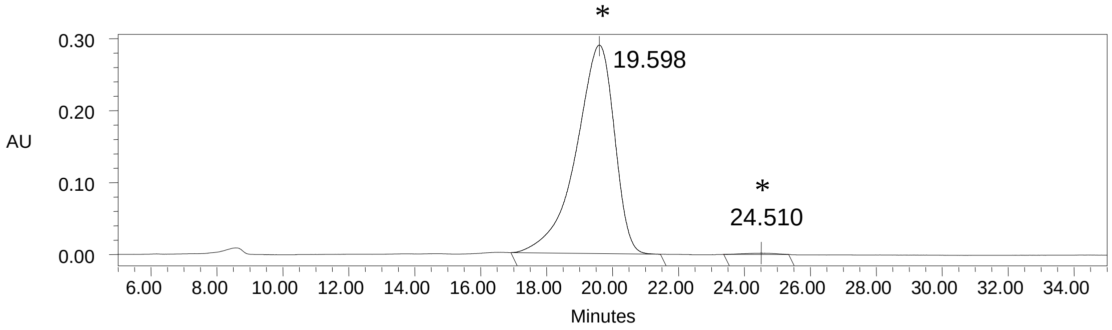
Column: IC
Eluent: Hex:*i*PrOH, 98:2
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**5a** (mixture of diastereomers)



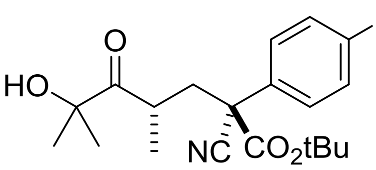
	Retention Time	Area	% Area	Height
1	15.966	837575	7.81	14122
2	19.000	5381088	50.18	70135
3	23.439	4504790	42.01	52851

Scalemic-**5a**



	Retention Time	Area	% Area	Height
1	19.598	23362803	99.45	289755
2	24.510	128192	0.55	1887

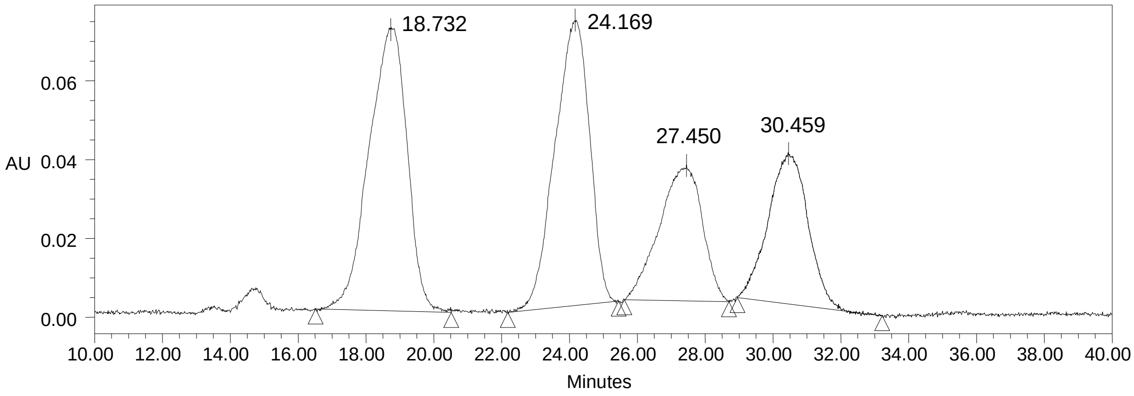
>99:1 *dr*, 99% *ee* ((*) single diastereomer)



5b

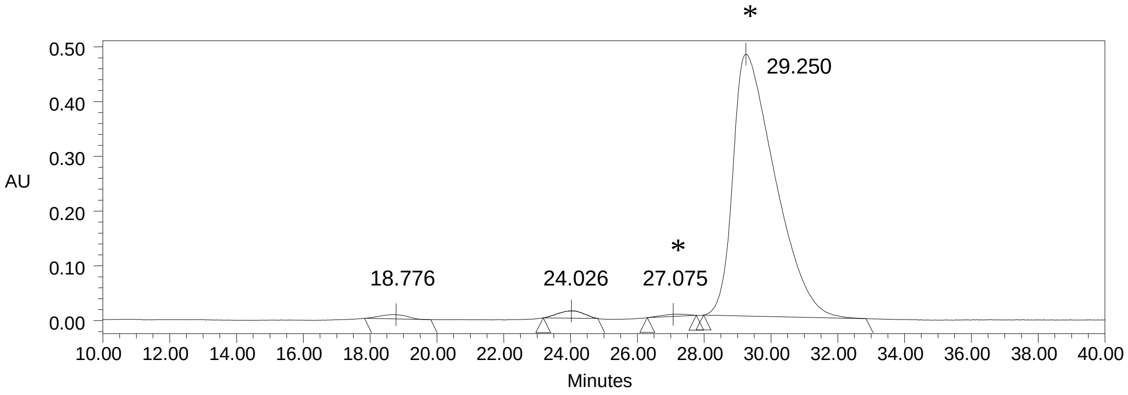
rac-**5b** (mixture of diastereomers)

Column: IA
Eluent: Hex:*i*PrOH, 98:2
Flow rate = 1.0 mL/min
λ = 210 nm



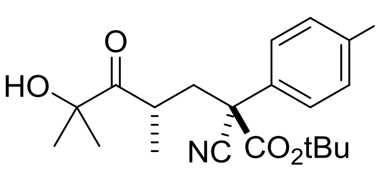
	Retention Time	Area	% Area	Height
4	30.459	3124822	18.47	38178
3	27.450	3005918	17.77	33990
2	24.169	5160114	30.50	72419
1	18.732	5625158	33.25	71581

Scalemic-**5b**



	Retention Time	Area	% Area	Height
1	18.776	303672	0.70	6358
2	24.026	728872	1.69	13463
3	27.075	271135	0.63	4586
4	29.250	41913775	96.98	478108

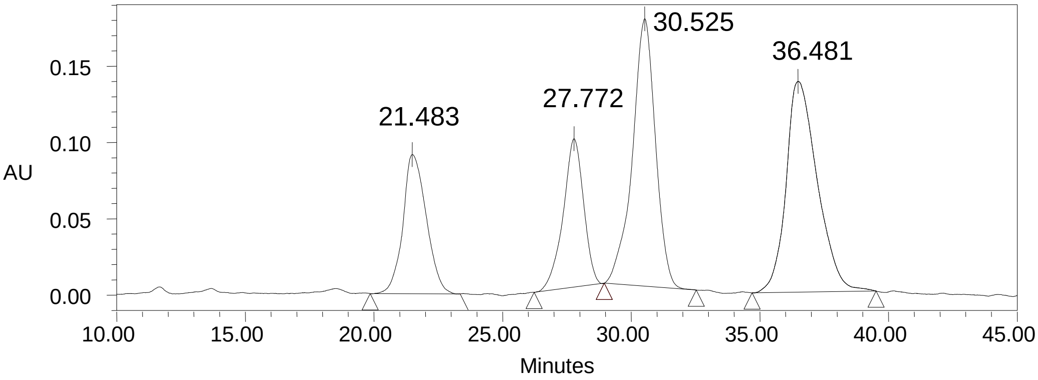
98:2 *dr* , 98% *ee* ((*) major diastereomer)



5c

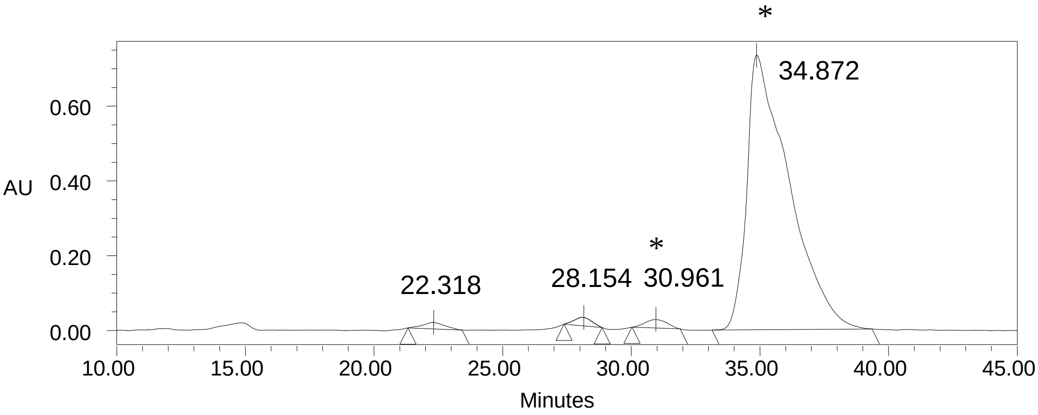
Column: IA
Eluent: Hex:*i*PrOH, 98:2
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**5c** (mixture of diastereomers)



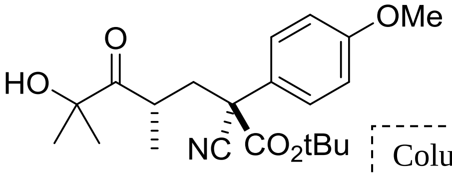
	Retention Time	Area	% Area	Height
1	21.483	5762780	17.07	91140
2	27.772	5378653	15.93	97241
3	30.525	10944371	32.42	175296
4	36.481	11675291	34.58	138092

Scalemic-**5c**



	Retention Time	Area	% Area	Height
1	22.318	1019460	1.17	17217
2	28.154	1095755	1.25	22859
3	30.961	1346425	1.54	22596
4	34.872	84031295	96.04	734174

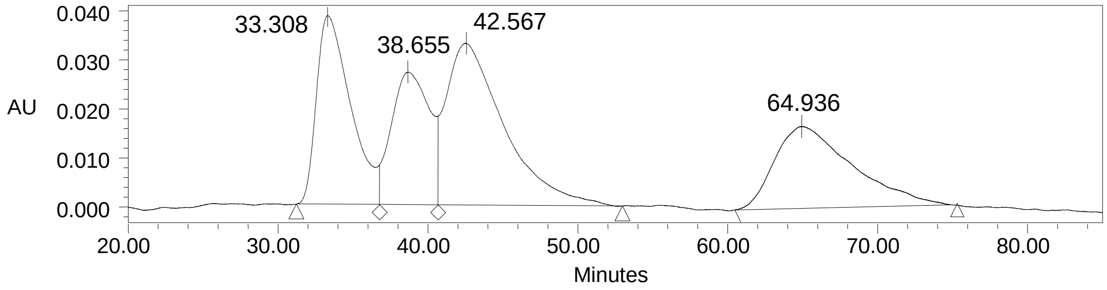
98:2 *dr* , 96% *ee* ((*) major diastereomer)



5d

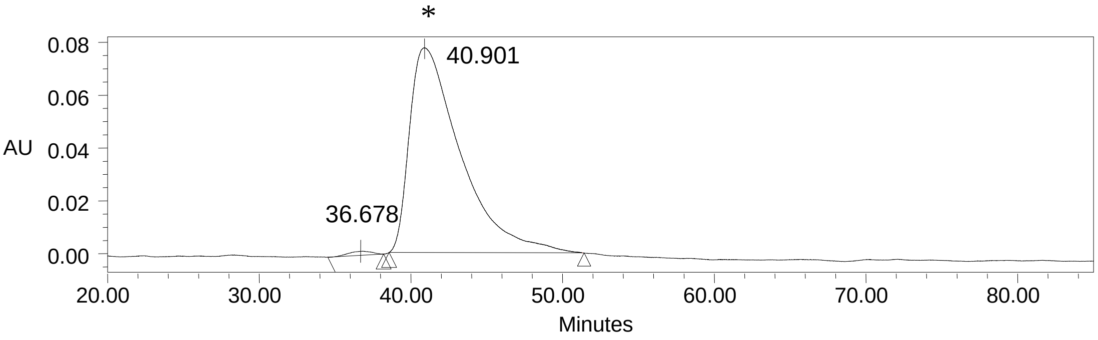
Column: AY-H
Eluent: Hex:*i*PrOH, 98:2
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**5d** (mixture of diastereomers)



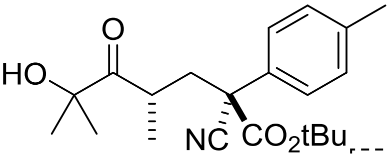
	Retention Time	Area	% Area	Height
4	64.936	6017265	23.38	16754
3	42.567	8833842	34.32	32995
2	38.655	4775763	18.55	27054
1	33.308	6113472	23.75	38484

Scalemic-**5d**



	Retention Time	Area	% Area	Height
2	40.901	18121094	99.10	77559
1	36.678	164964	0.90	1578

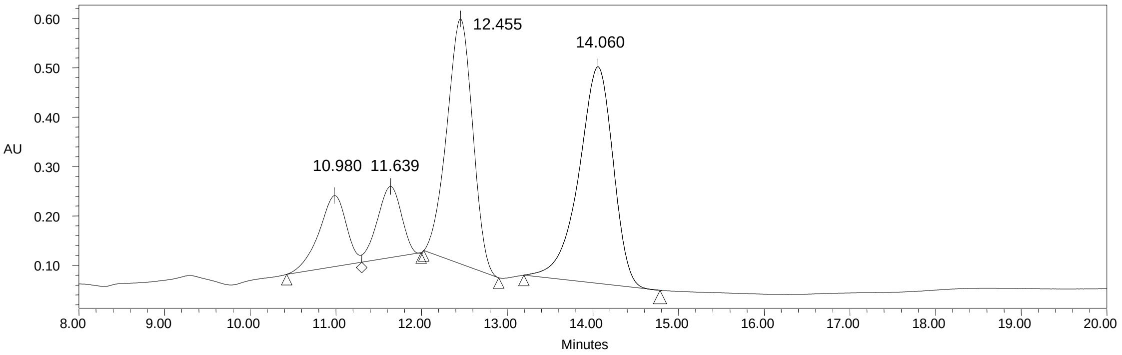
99:1 *dr*, 99% *ee* ((*) major diastereomer)



5e

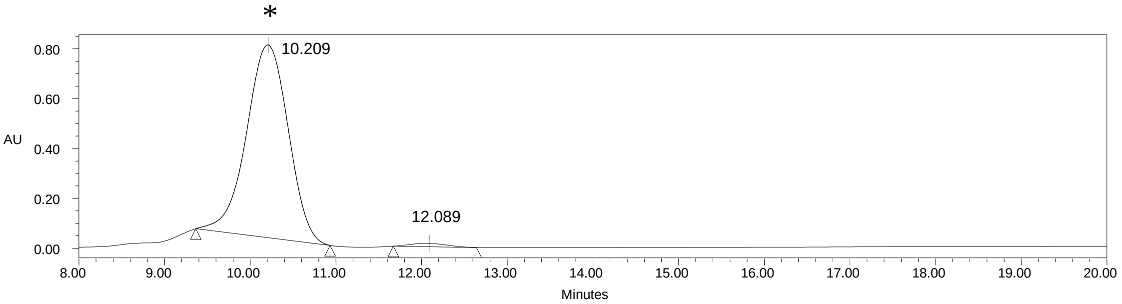
Column: IC
Eluent: Hex:*i*PrOH, 85:15
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**5e** (mixture of diastereomers)



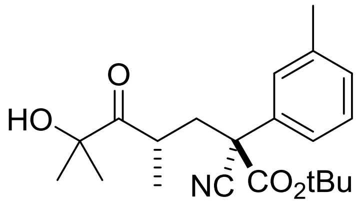
	Retention Time	Area	% Area	Height
4	14.060	12213367	42.68	438711
3	12.455	10395302	36.32	495986
2	11.639	2812315	9.83	144101
1	10.980	3197850	11.17	143683

Scalemic-**5e**



	Retention Time	Area	% Area	Height
2	12.089	395670	1.49	13281
1	10.209	26248711	98.51	772819

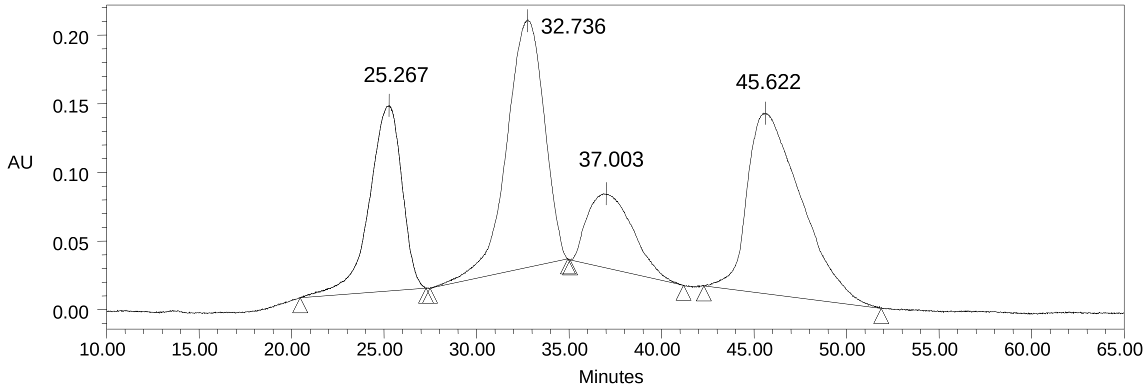
98:2 *dr*, 99% *ee* ((*) major diastereomer)



5f

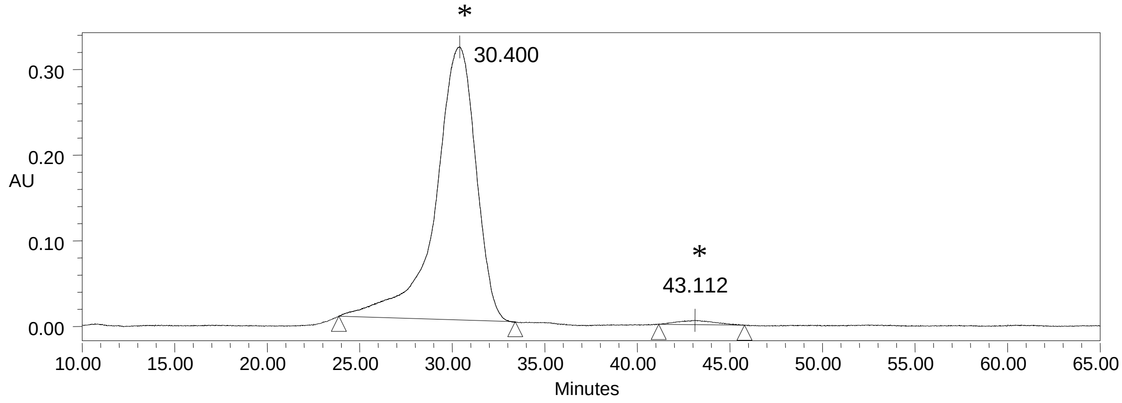
Column: IC
Eluent: Hex:*i*PrOH, 99:1
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**5f** (mixture of diastereomers)



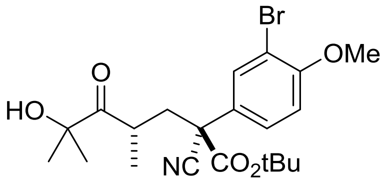
	Retention Time	Area	% Area	Height
4	45.622	26889132	34.34	131594
3	37.003	9316343	11.90	53895
2	32.736	25504192	32.57	180199
1	25.267	16586096	21.18	134673

Scalemic-**5f**



	Retention Time	Area	% Area	Height
1	30.400	48766610	98.61	318693
2	43.112	686201	1.39	5069

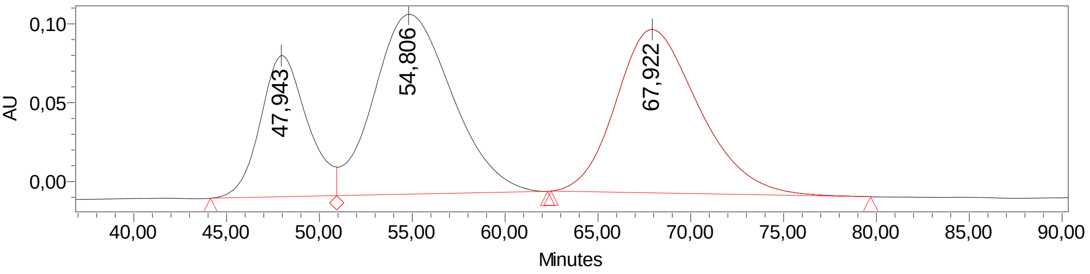
>99:1 *dr*, 97% *ee* ((*) single diastereomer)



5h

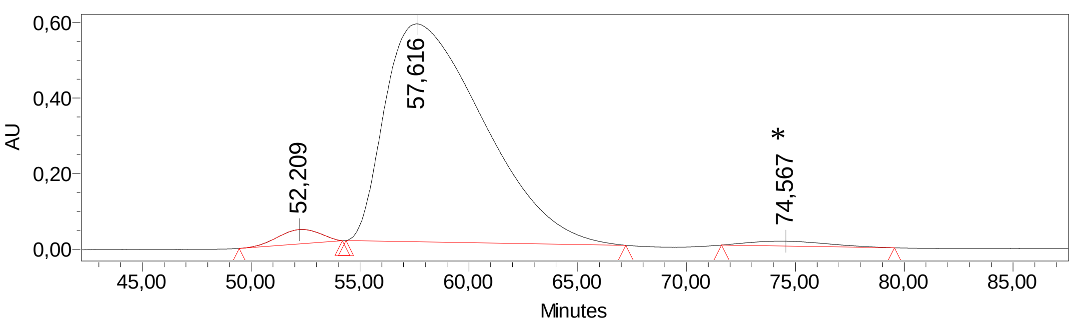
Daicel Chiralpak AY-H hexane/isopropanol 95/5, flow rate= 0.5 mL/min, retention times: 54.8 min (major.) and 67.9 min (minor.). Processed Channel Descr.: PDA 245.0 nm.

Rac-**5h** (mixture of diastereomers)



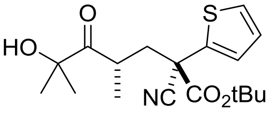
	Retention Time	% Area
1	47,943	19,36
2	54,806	41,05
3	67,922	39,60

Scalemic **5h**



	Retention Time	% Area
1	52,209	2,69
2	57,616	95,62
3	74,567	1,69

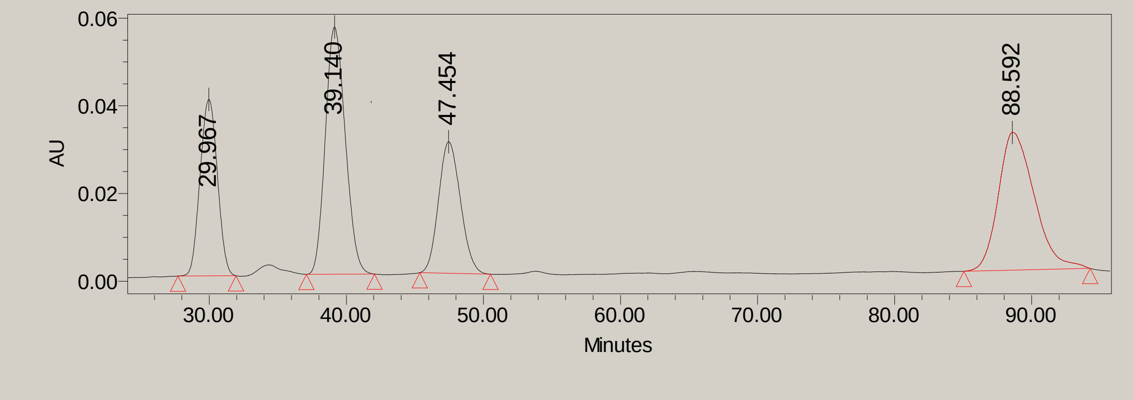
97:3 *dr*, 96% *ee* ((*) major diastereomer)



5i

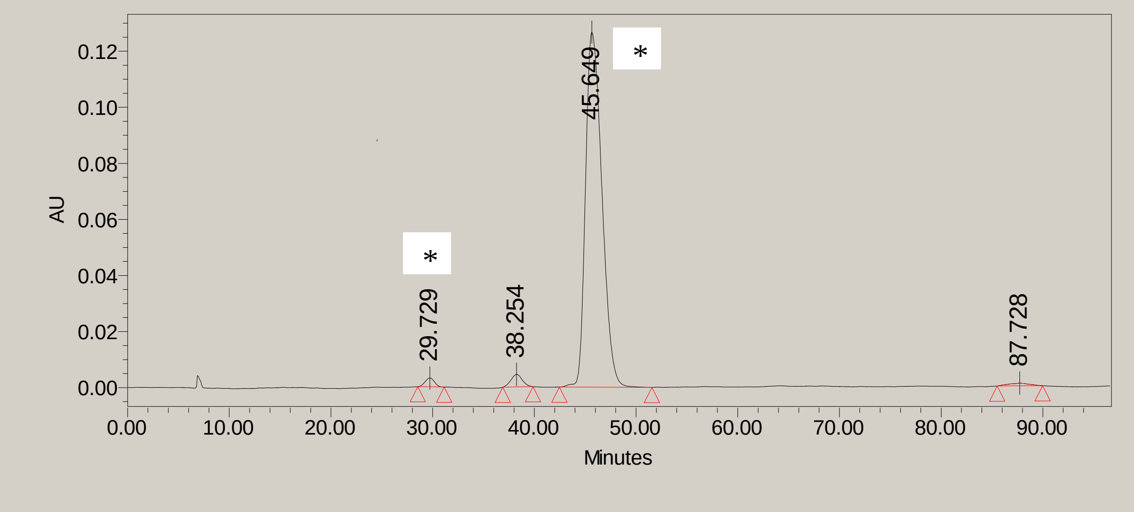
Daicel Chiralpak AY-H hexane/isopropanol 95/5, flow rate= 0.5 mL/min, retention times: 29.9 min (minor.) and 47.4 min (major.). Processed Channel Descr.: PDA 245.0 nm.

Rac-**5i** (mixture of diastereomers)



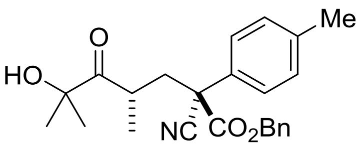
	Retention Time	% Area
1	29.967	19.33
2	39.140	31.20
3	47.454	18.19
4	88.592	31.28

scalemic **5i**



	Retention Time	% Area
1	29.729	1.35
2	38.254	2.34
3	45.649	95.37
4	87.728	0.94

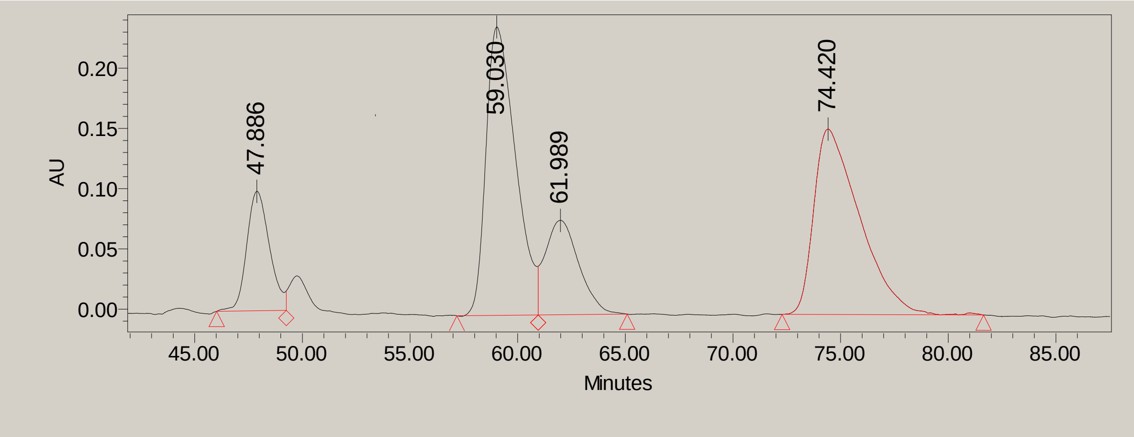
96:4 *dr*, 97% *ee* ((*) major diastereomer)



6e

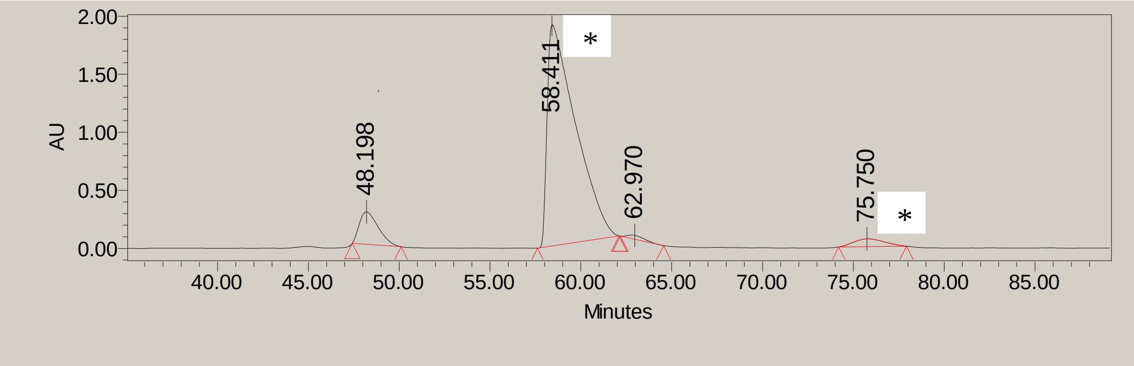
Daicel Chiralpak IC+AY-H hexane/isopropanol 90/10, flow rate= 0.5 mL/min, retention times: 59.0 min (major.) and 74.4 min (minor.). Processed Channel Descr.: PDA 235.0 nm.

Rac-**6e** (mixture of diastereomers)



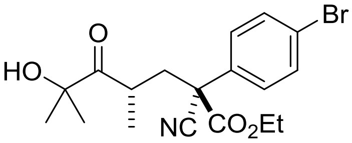
	Retention Time	% Area
1	47.886	11.89
2	59.030	37.23
3	61.989	13.86
4	74.420	37.01

Scalemic **6e**



	Retention Time	% Area
1	48.198	8.57
2	58.411	87.19
3	62.970	0.90
4	75.750	3.34

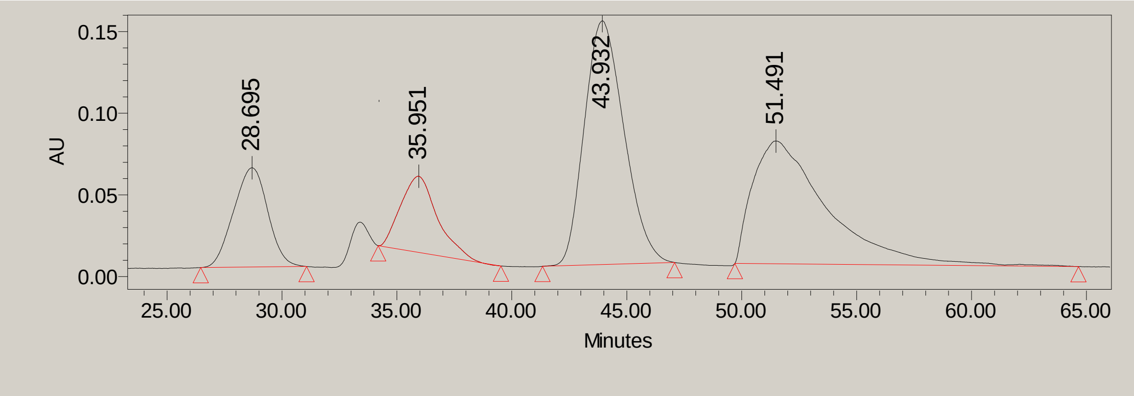
90:10 *dr*, 92% *ee* ((*) major diastereomer)



7b

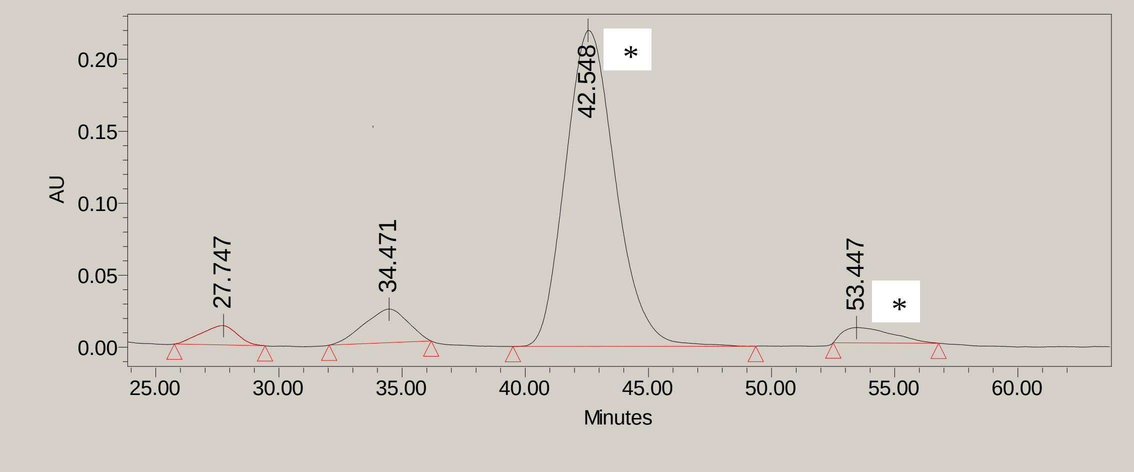
Daicel Chiralpak IC hexane/isopropanol 97/3, flow rate= 0.6 mL/min, retention times: 43.9 min (major.) and 51.4 min (minor.). Processed Channel Descr.: PDA 235.0 nm.

Rac-**7b** (mixture of diastereomers)



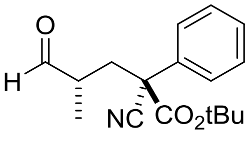
	Retention Time	% Area
1	28.695	13.57
2	35.951	11.20
3	43.932	38.67
4	51.491	36.56

Scalemic **7b**



	Retention Time	% Area
1	27.747	3.72
2	34.471	7.84
3	42.548	84.42
4	53.447	4.02

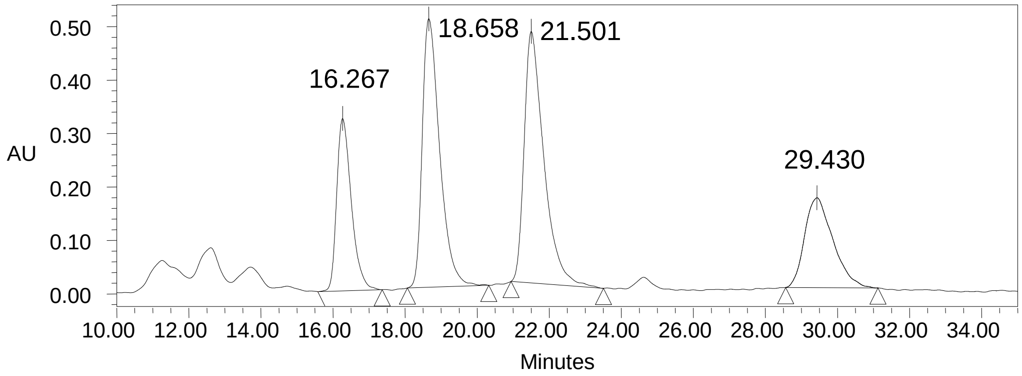
88:12 *dr*, 91% *ee* ((*) major diastereomer)



23

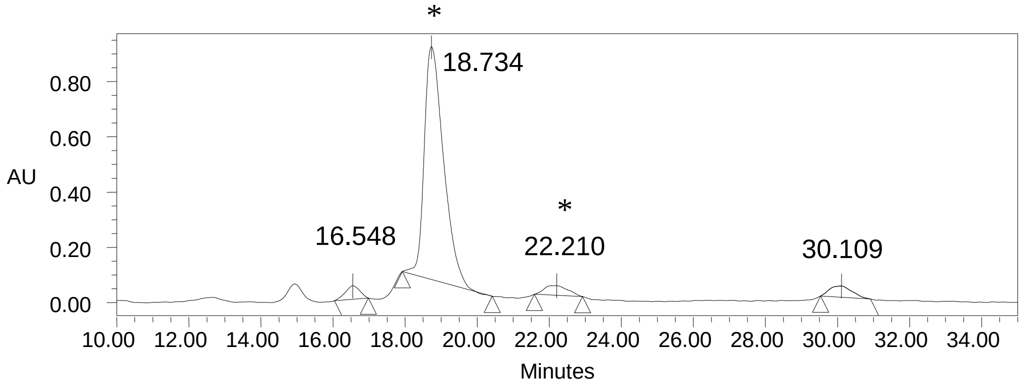
Column: AY-H
Eluent: Hex:*i*PrOH, 95:5
Flow rate = 0.6 mL/min
λ = 210 nm

Rac-**23** (mixture of diastereomers)



	Retention Time	Area	% Area	Height
1	16.267	9103329	17.17	322348
2	18.658	16850925	31.79	502337
3	21.501	17846964	33.67	470486
4	29.430	9206326	17.37	168054

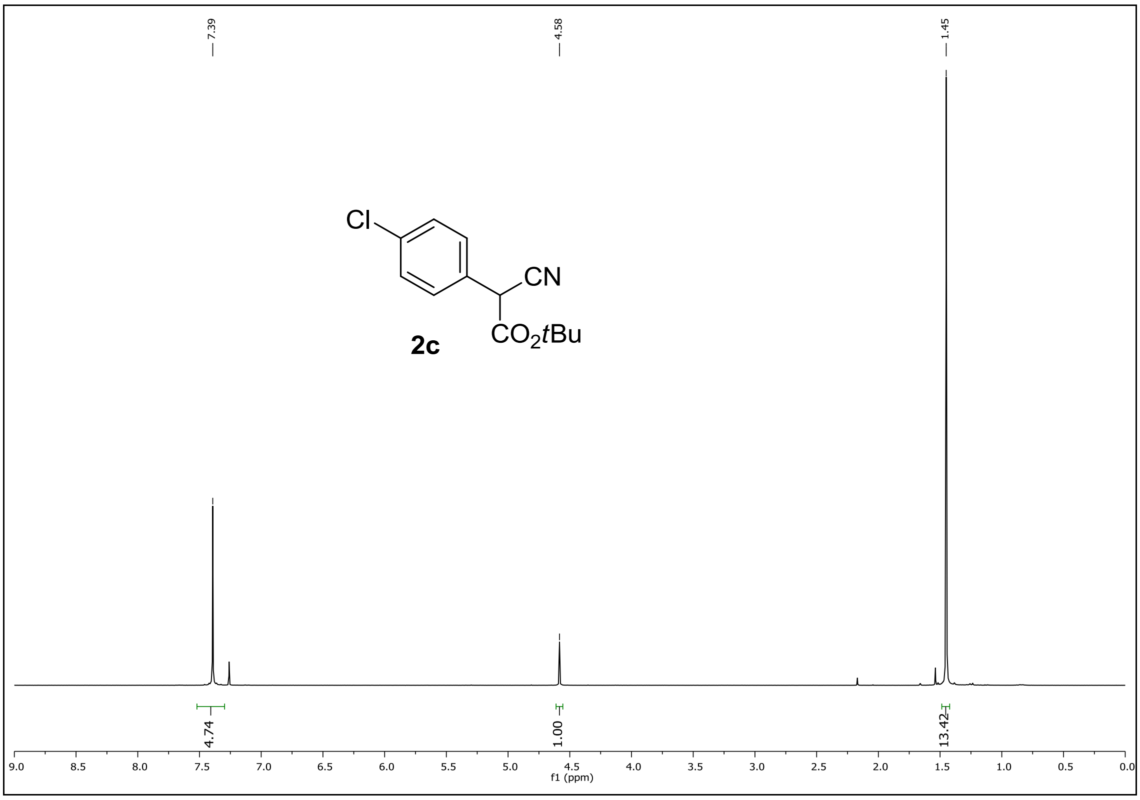
scalemic-**23**

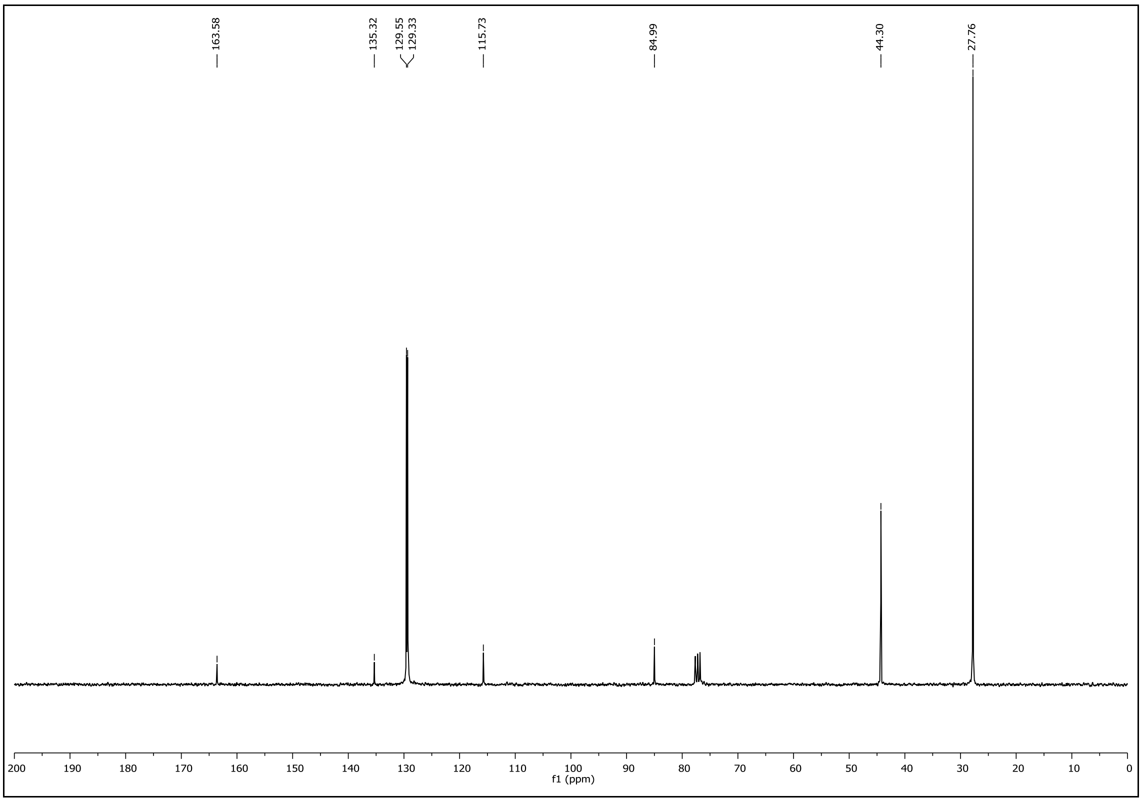


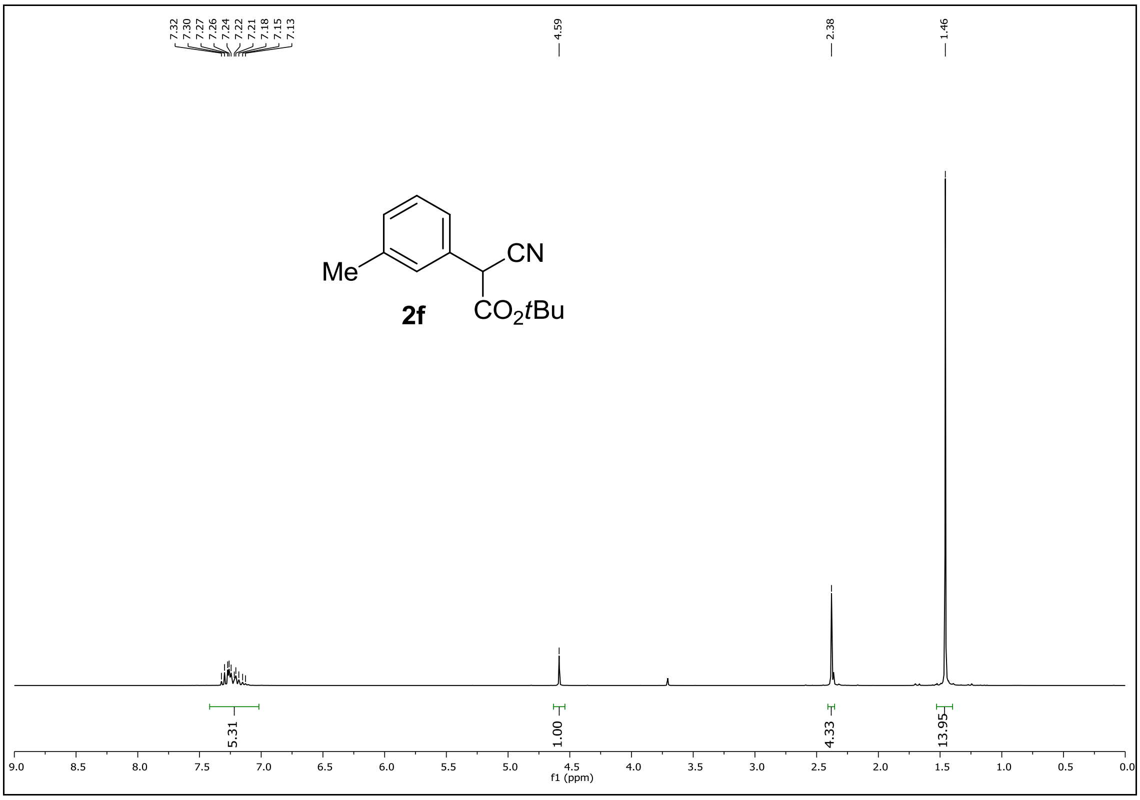
	Retention Time	Area	% Area	Height
1	16.548	1376800	3.31	48689
2	18.731	38142958	91.73	894624
3	22.231	1191685	2.87	28830
4	30.123	869363	2.09	26716

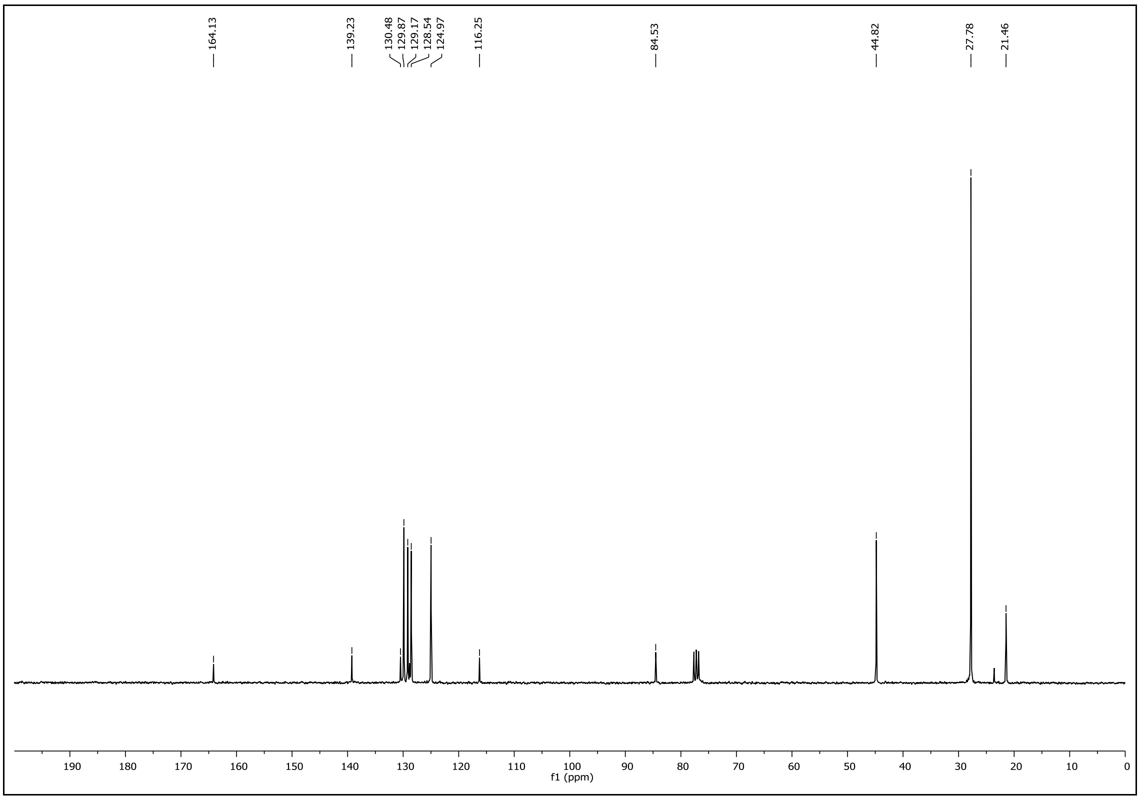
95:5 *dr*   94% *ee* ((*) major diastereomer)

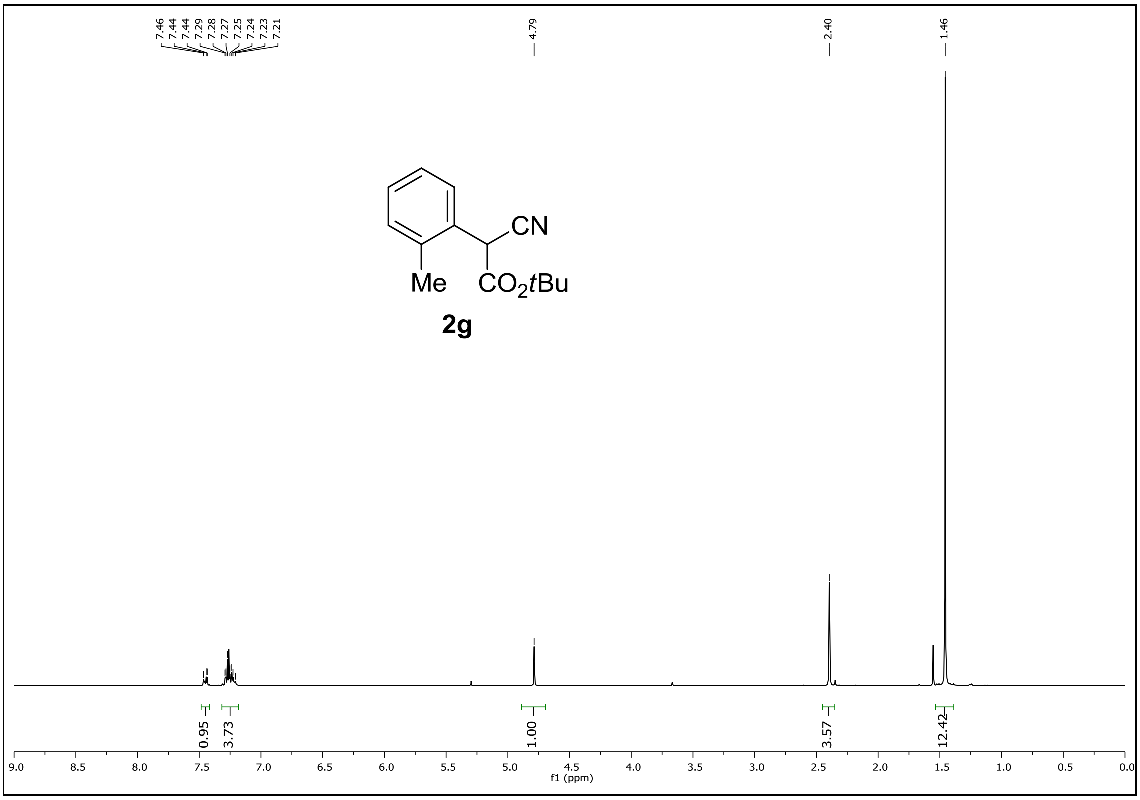
12. NMR spectra



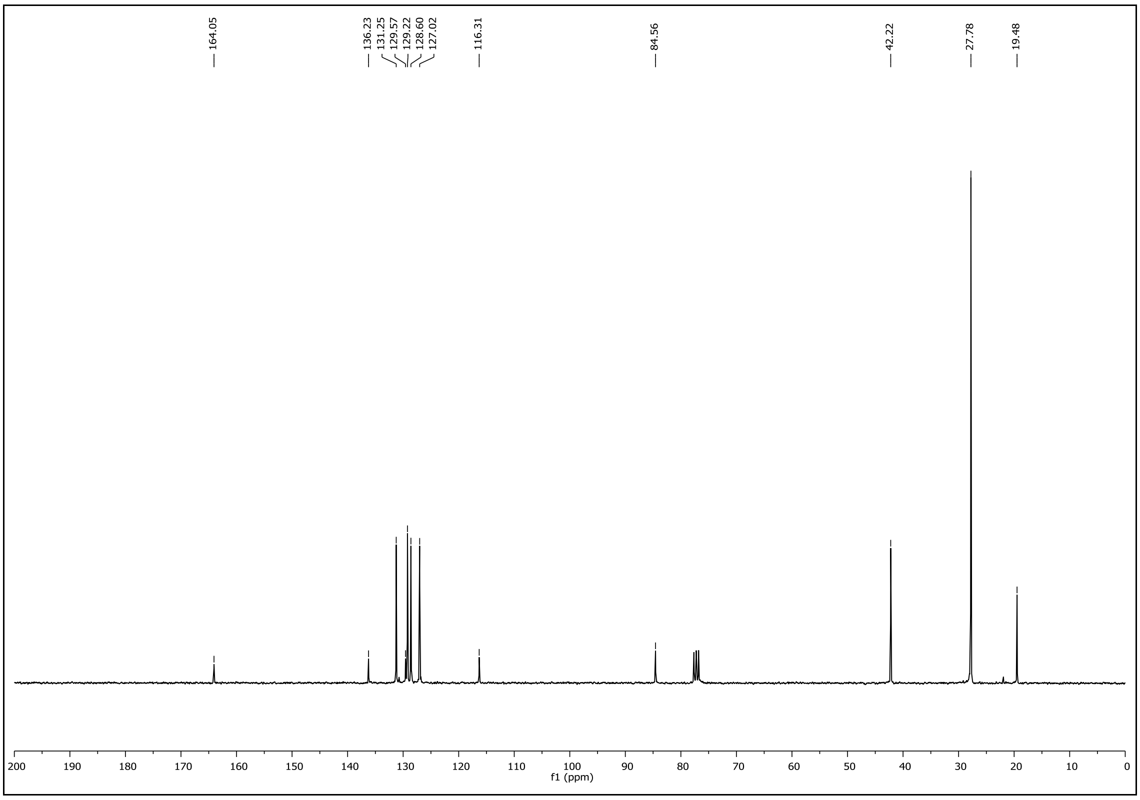



7.32
7.30
7.27
7.26
7.24
7.22
7.21
7.18
7.15
7.13
4.59
2.38
1.46
Me
CN
CO2tBu
2f
5.31
1.00
4.33
13.95
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


164.13
139.23
130.48
129.87
129.17
128.54
124.97
116.25
84.53
44.82
27.78
21.46
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

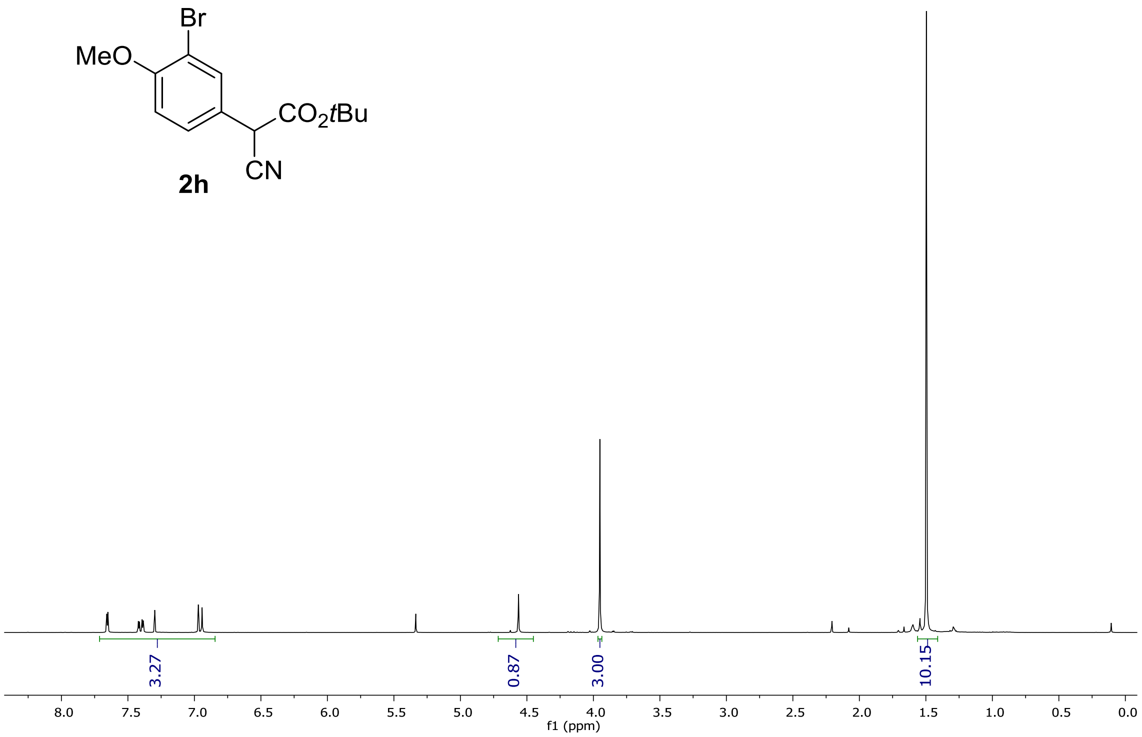

2g

7.46
7.44
7.44
7.29
7.28
7.27
7.25
7.24
7.23
7.21
4.79
2.40
1.46
CN
Me
CO2tBu
0.95
3.73
1.00
3.57
12.42
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


164.05
136.23
131.25
129.57
129.22
128.60
127.02
116.31
84.56
42.22
27.78
19.48
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Br
MeO
CO2tBu
CN

2h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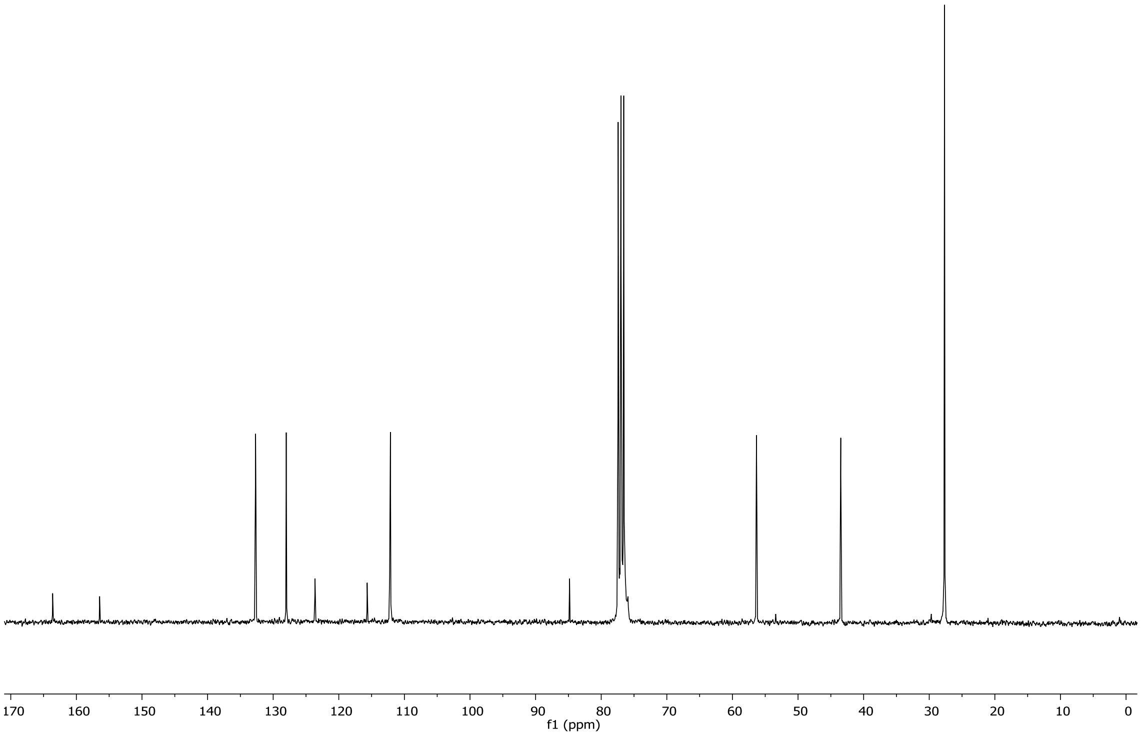
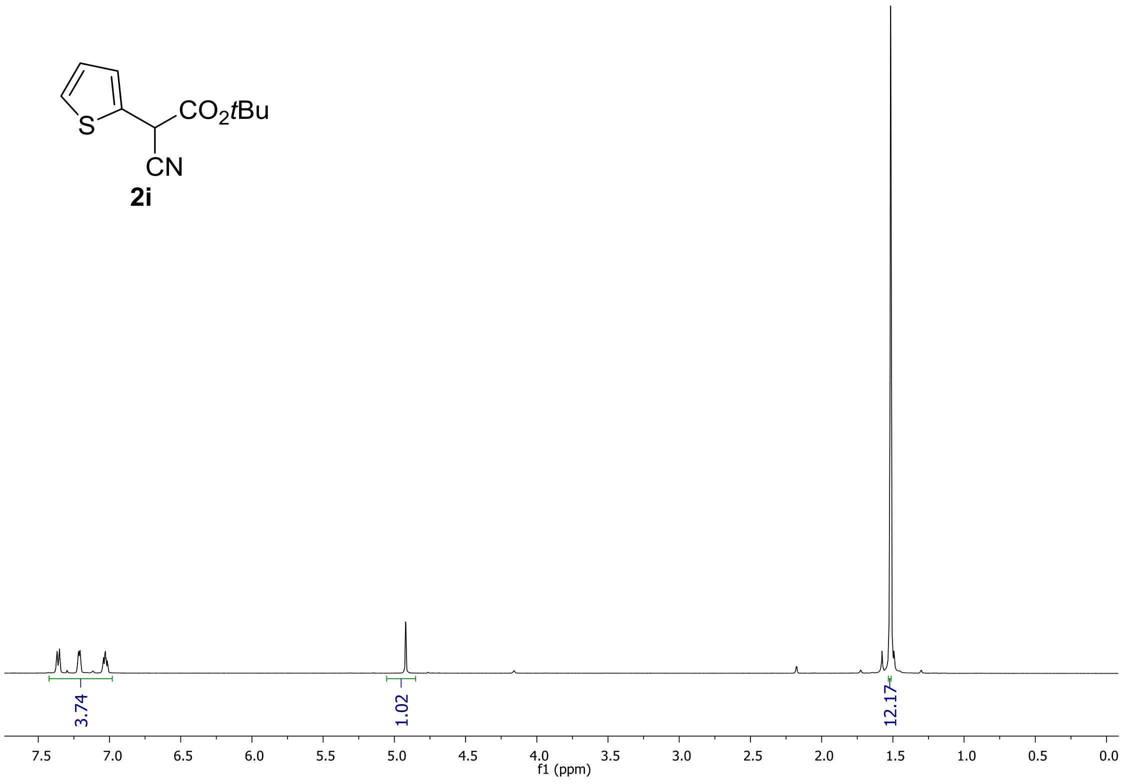
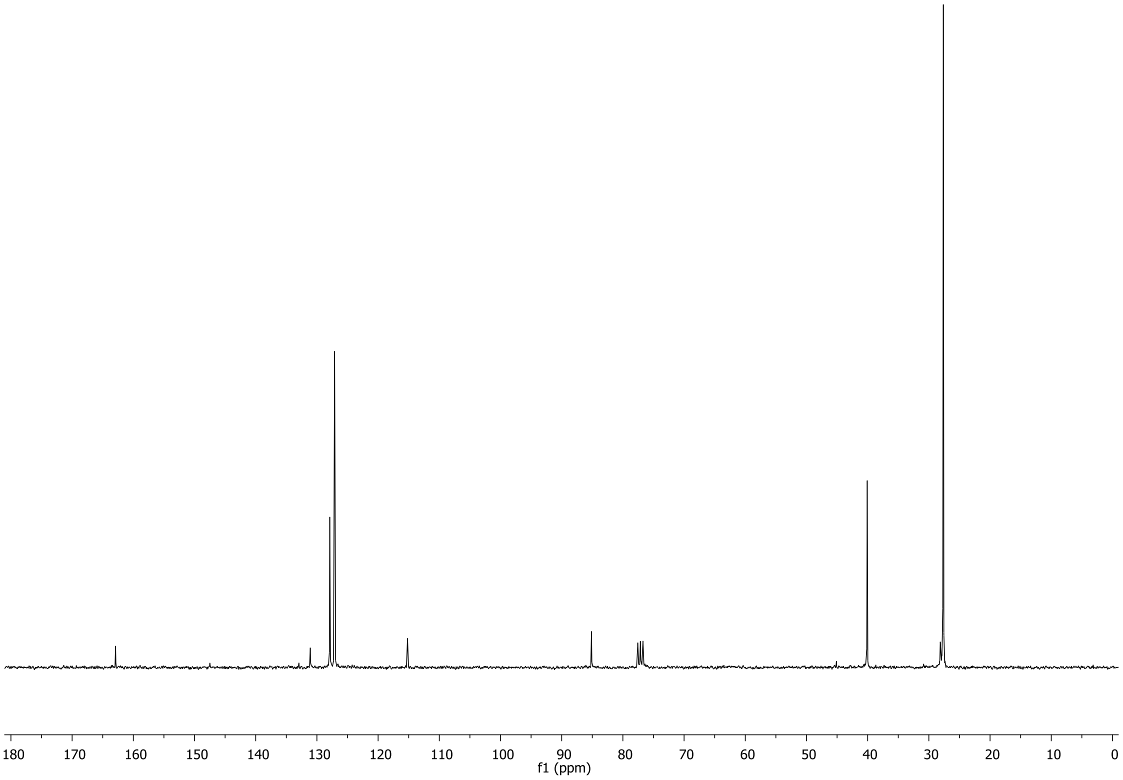
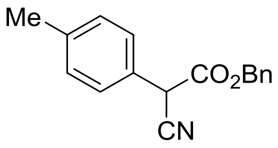
0.87
3.00
10.15
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

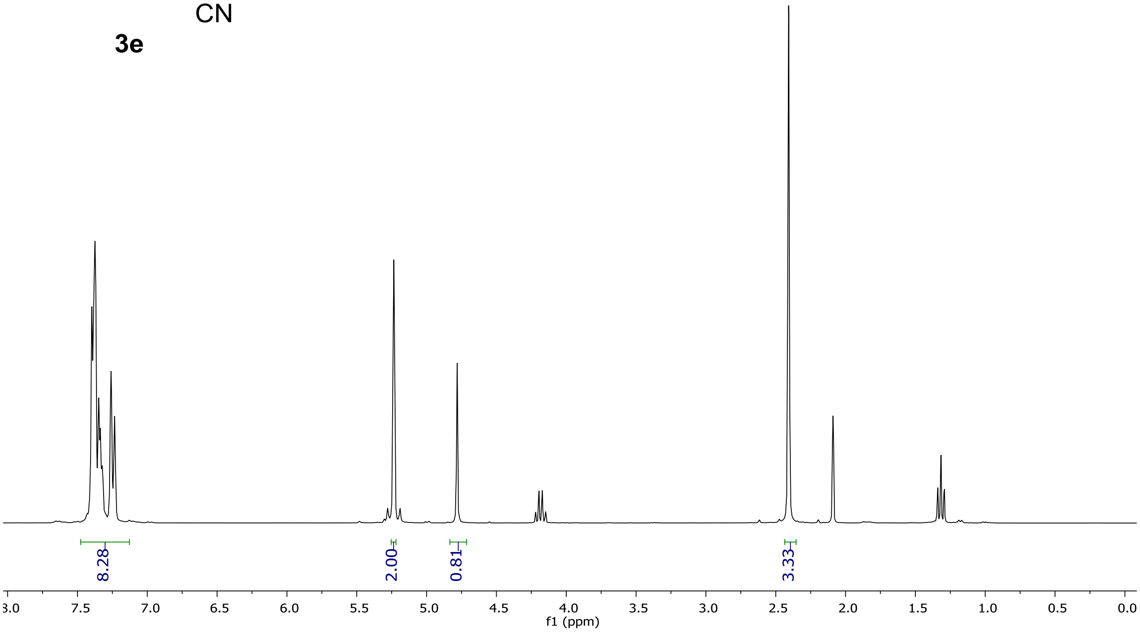

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

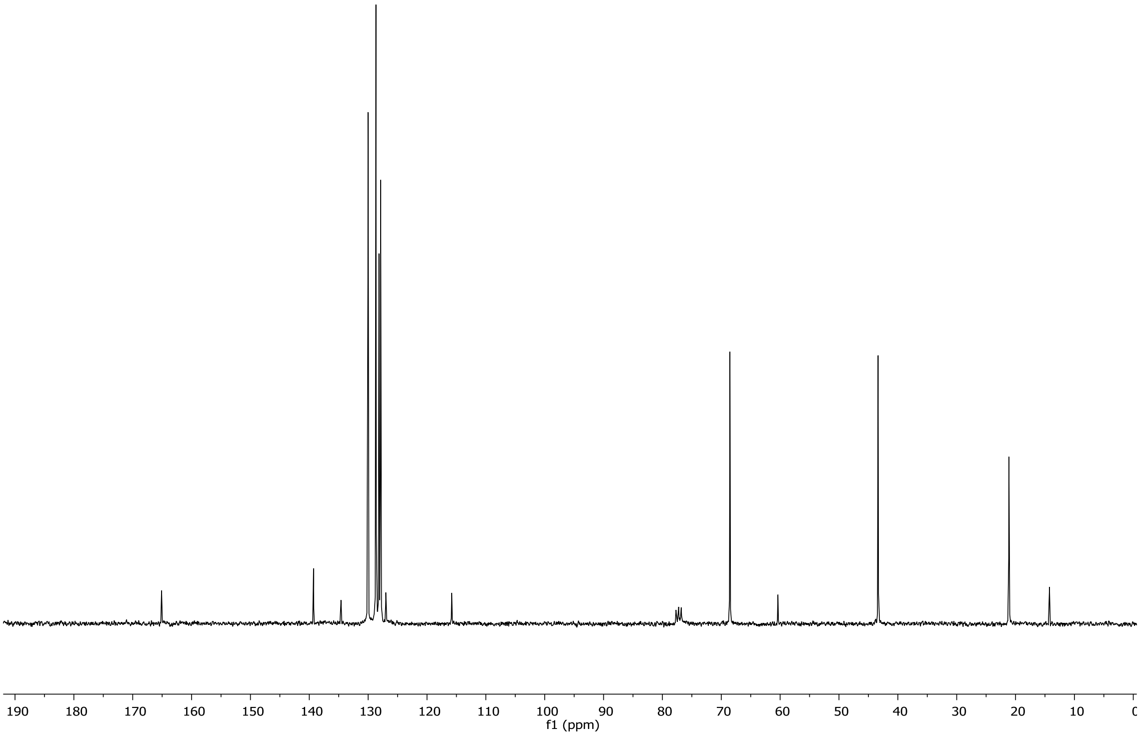

CO2tBu
S
CN
2i
3.74
1.02
12.17
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

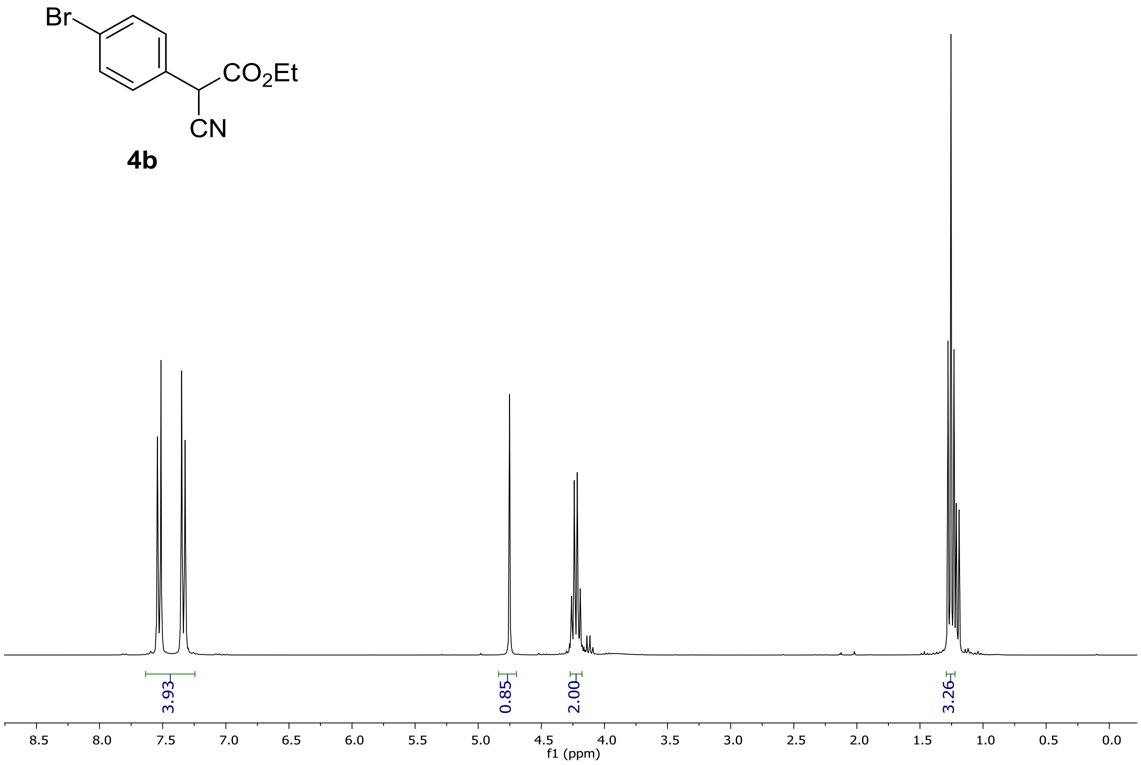

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

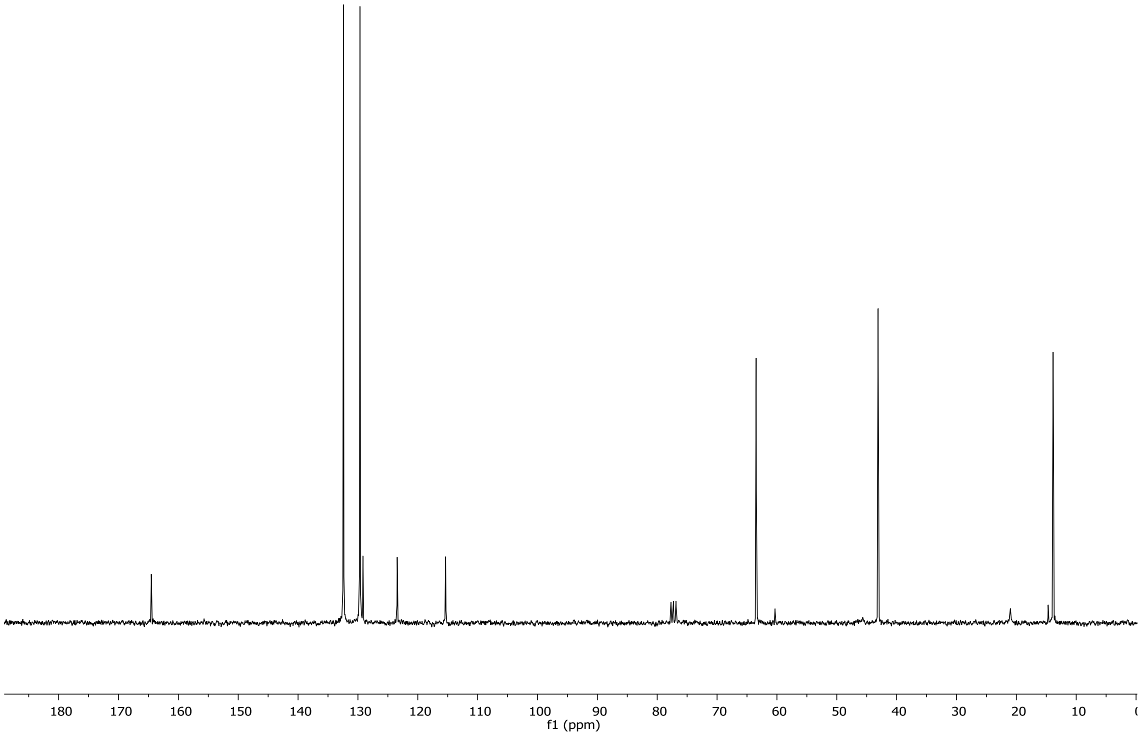

Me
CO2Bn
CN

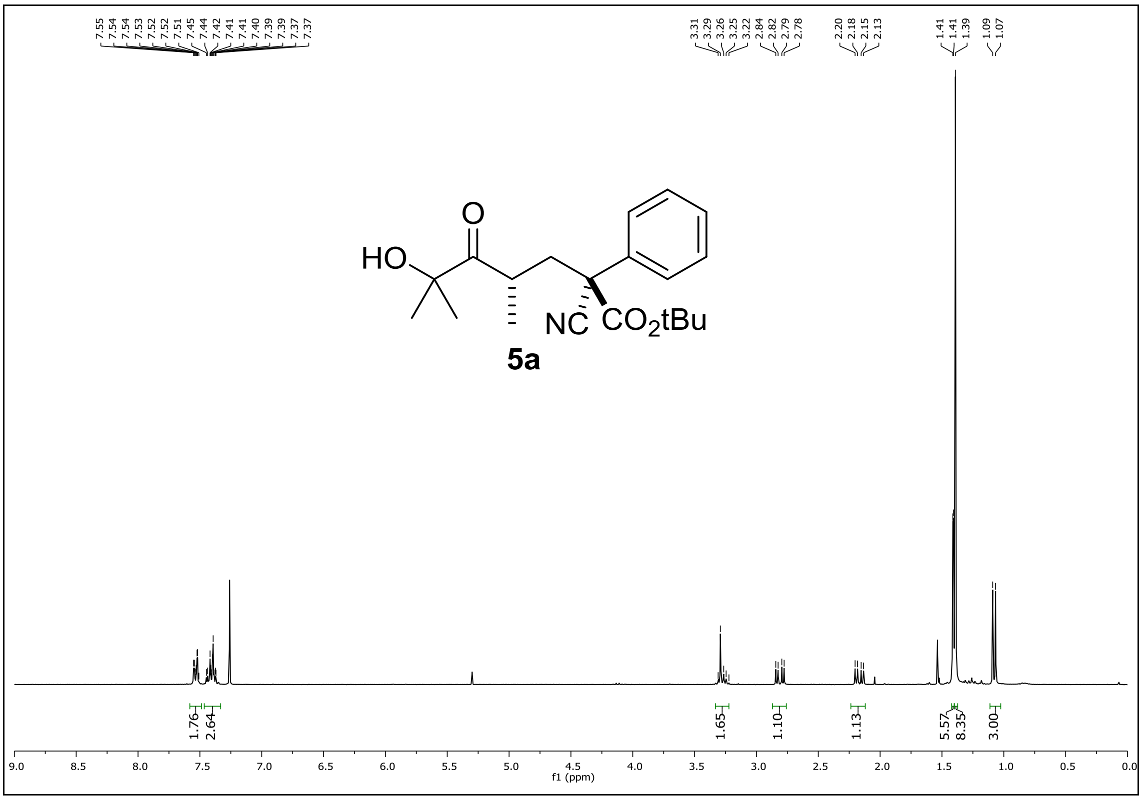
3e


8.28
2.00
0.81
3.33
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Br
CO2Et
CN
4b
3.93
0.85
2.00
3.26
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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7.51
7.45
7.44
7.42
7.41
7.41
7.40
7.39
7.37
7.37
3.31
3.29
3.26
3.25
3.22
2.84
2.82
2.79
2.78
2.20
2.18
2.15
2.13
1.41
1.41
1.39
1.09
1.07
HO
O
NC
CO2tBu
5a
1.76
2.64
1.65
1.10
1.13
5.57
8.35
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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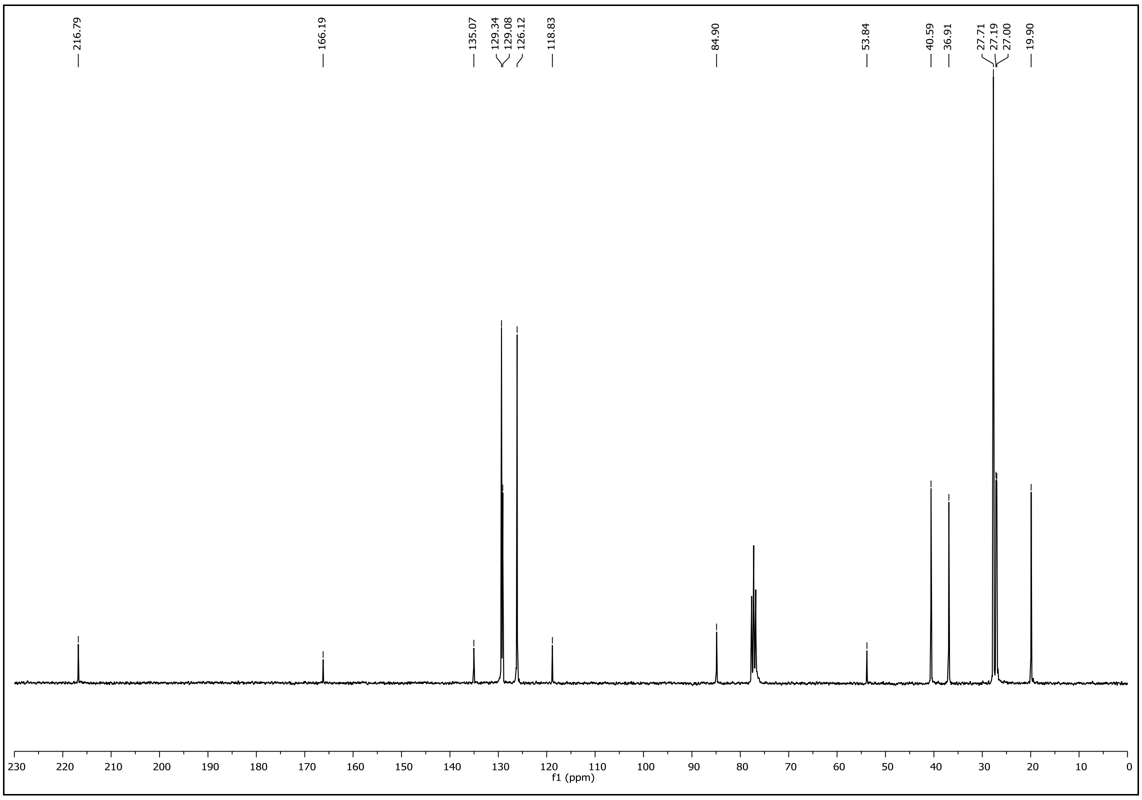
0.0
f1 (ppm)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166.19
135.07
129.34
129.08
126.12
118.83
84.90
53.84
40.59
36.91
27.71
27.19
27.00
19.90
230
220
210
200
190
180
170
160
150
140
130
120
110
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90
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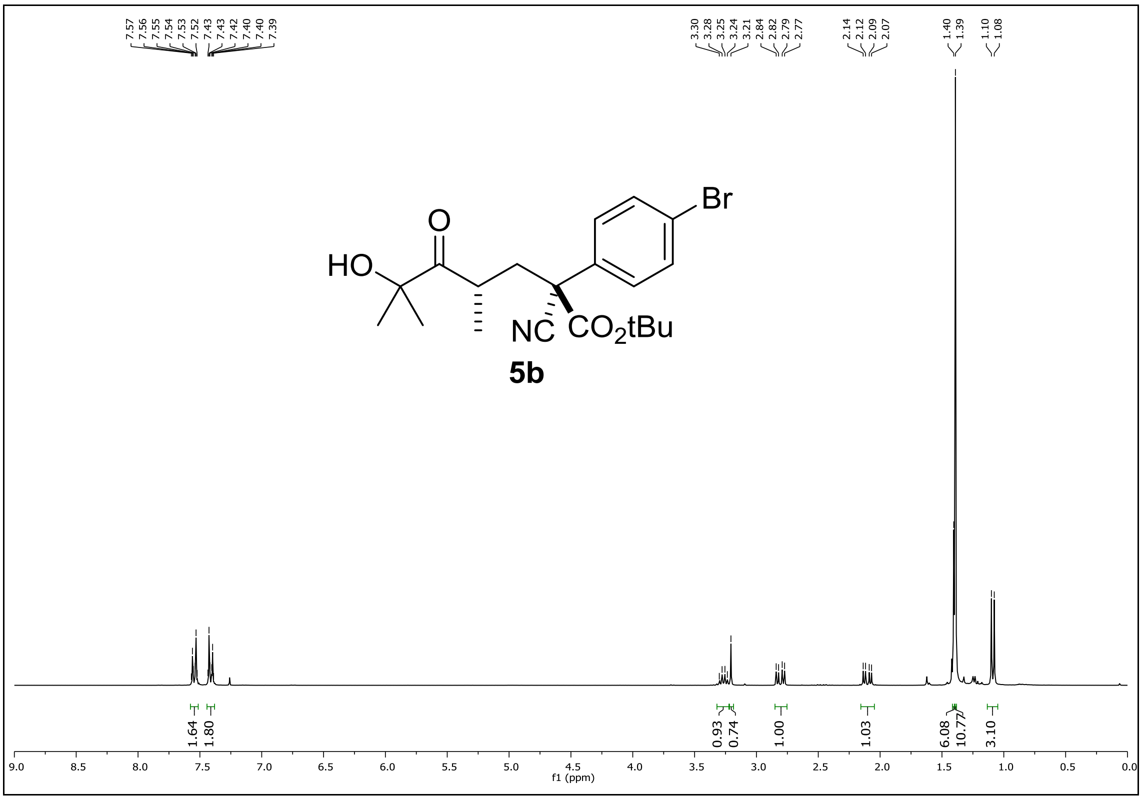
50
40
30
20
10
0
f1 (ppm)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7.40
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3.30
3.28
3.25
3.24
3.21
2.84
2.82
2.79
2.77
2.14
2.12
2.09
2.07
1.40
1.39
1.10
1.08
Br
O
HO
NC
CO2tBu
5b
1.64
1.80
0.93
0.74
1.00
1.03
6.08
10.77
3.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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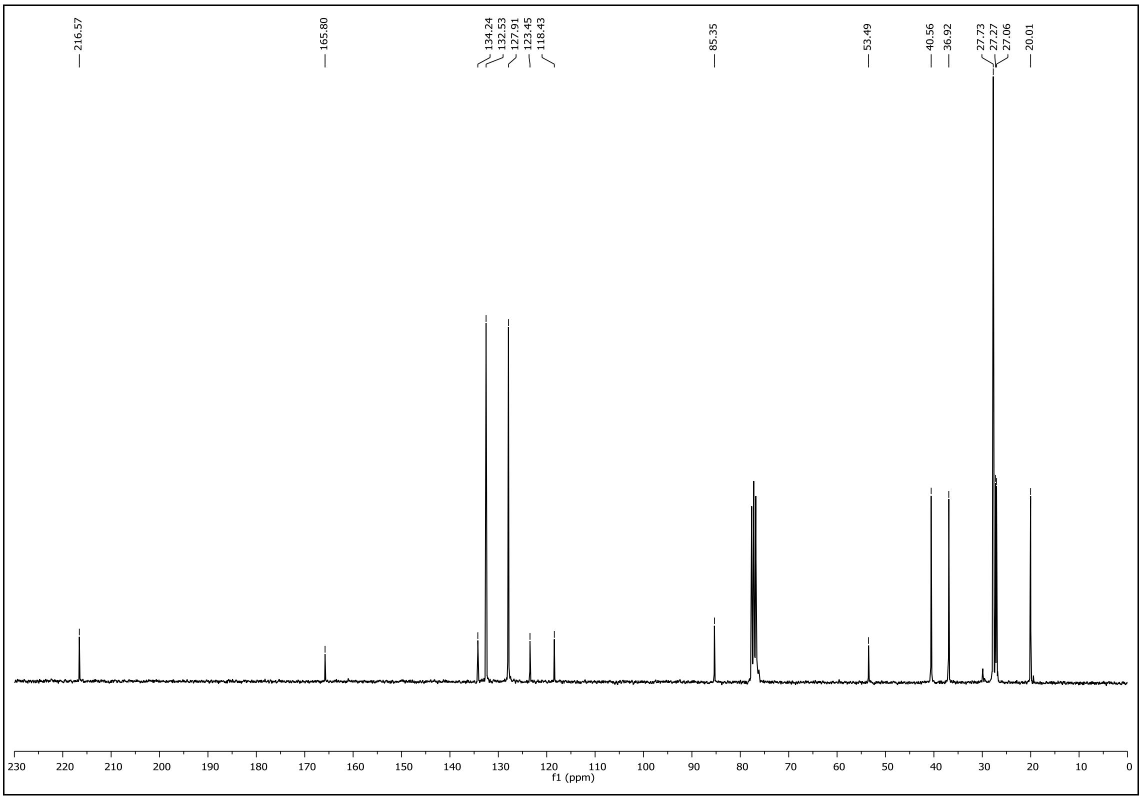
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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27.27
27.06
20.01
230
220
210
200
190
180
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120
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50
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30
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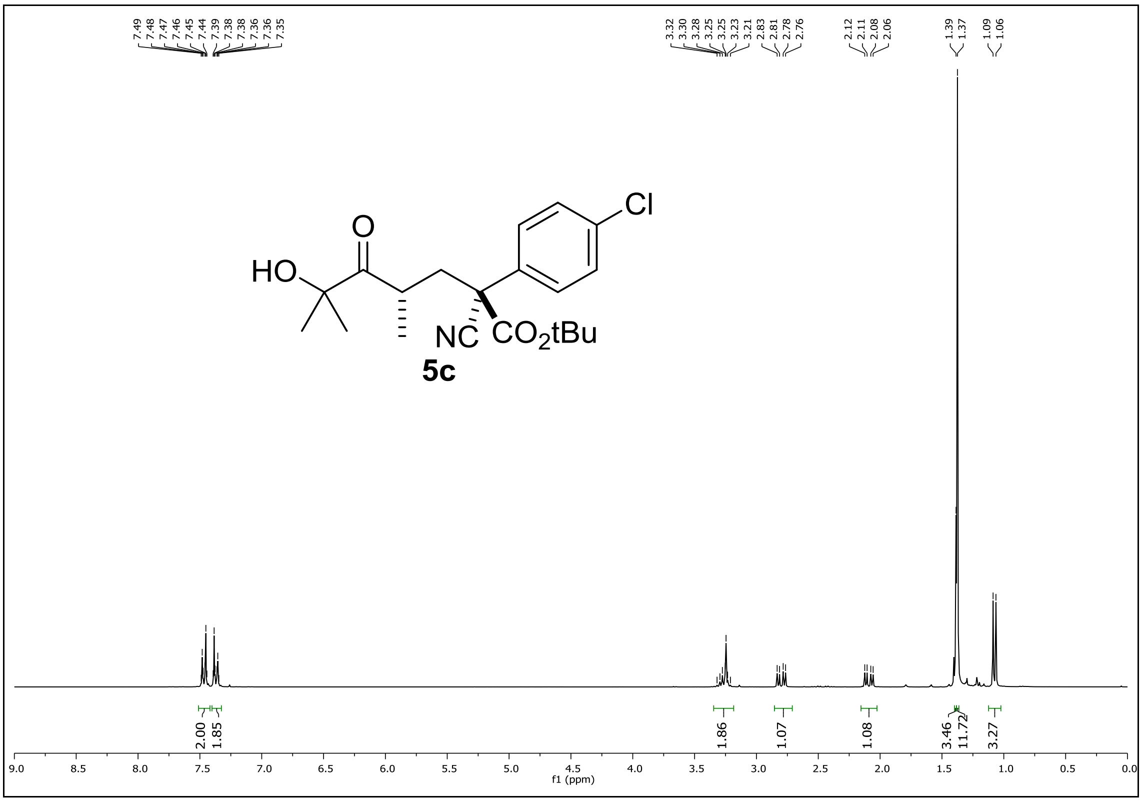
f1 (ppm)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7.44
7.39
7.38
7.38
7.36
7.36
7.35
3.32
3.30
3.28
3.25
3.25
3.23
3.21
2.83
2.81
2.78
2.76
2.12
2.11
2.08
2.06
1.39
1.37
1.09
1.06
HO
O
Cl
NC
CO2tBu
5c
2.00
1.85
1.86
1.07
1.08
3.46
11.72
3.27
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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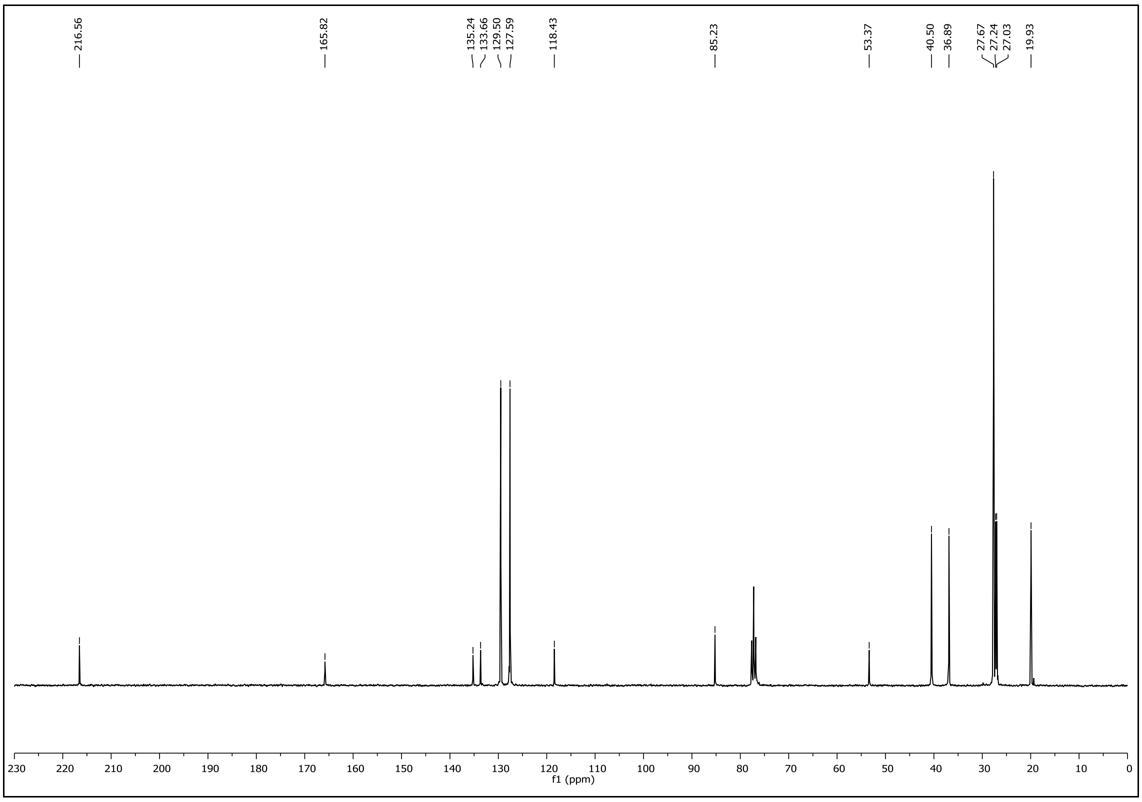
0.0
f1 (ppm)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85.23
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27.24
27.03
19.93
230
220
210
200
190
180
170
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150
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120
110
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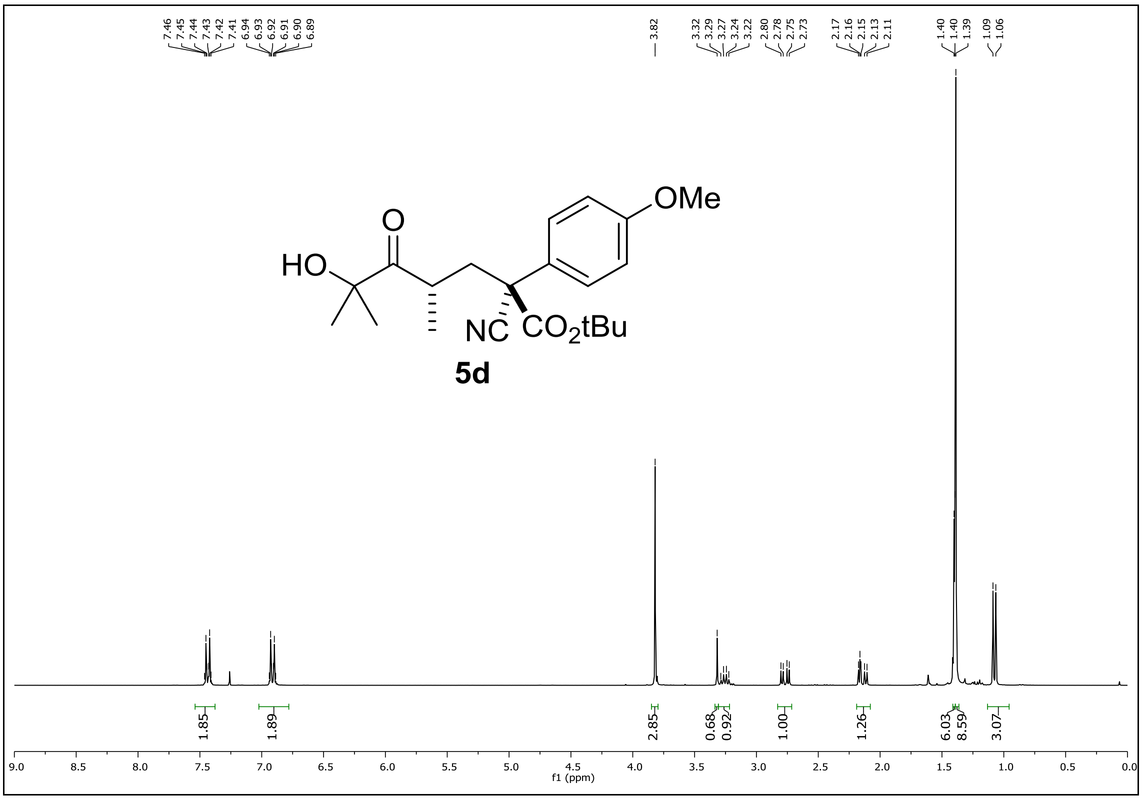
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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3.32
3.29
3.27
3.24
3.22
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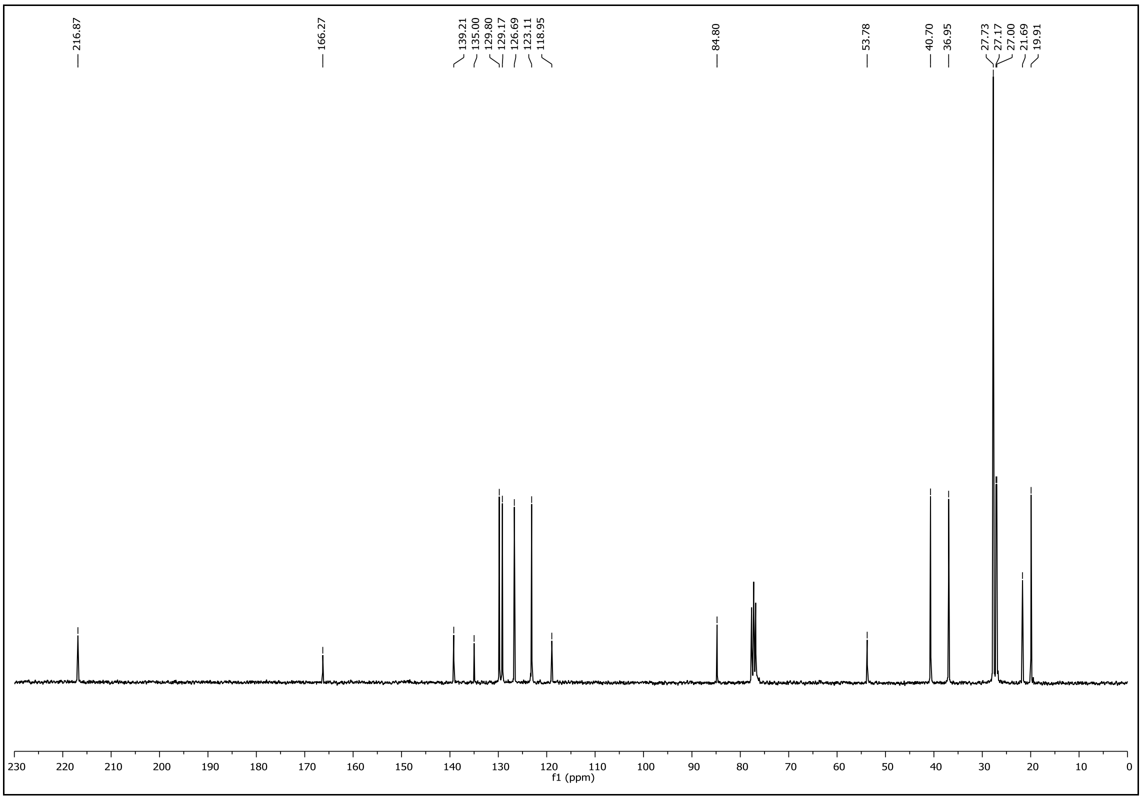
2.78
2.75
2.73
2.17
2.16
2.15
2.13
2.11
1.40
1.40
1.39
1.09
1.06
OMe
O
HO
NC
CO2tBu
5d
1.85
1.89
2.85
0.68
0.92
1.00
1.26
6.03
8.59
3.07
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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129.17
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123.11
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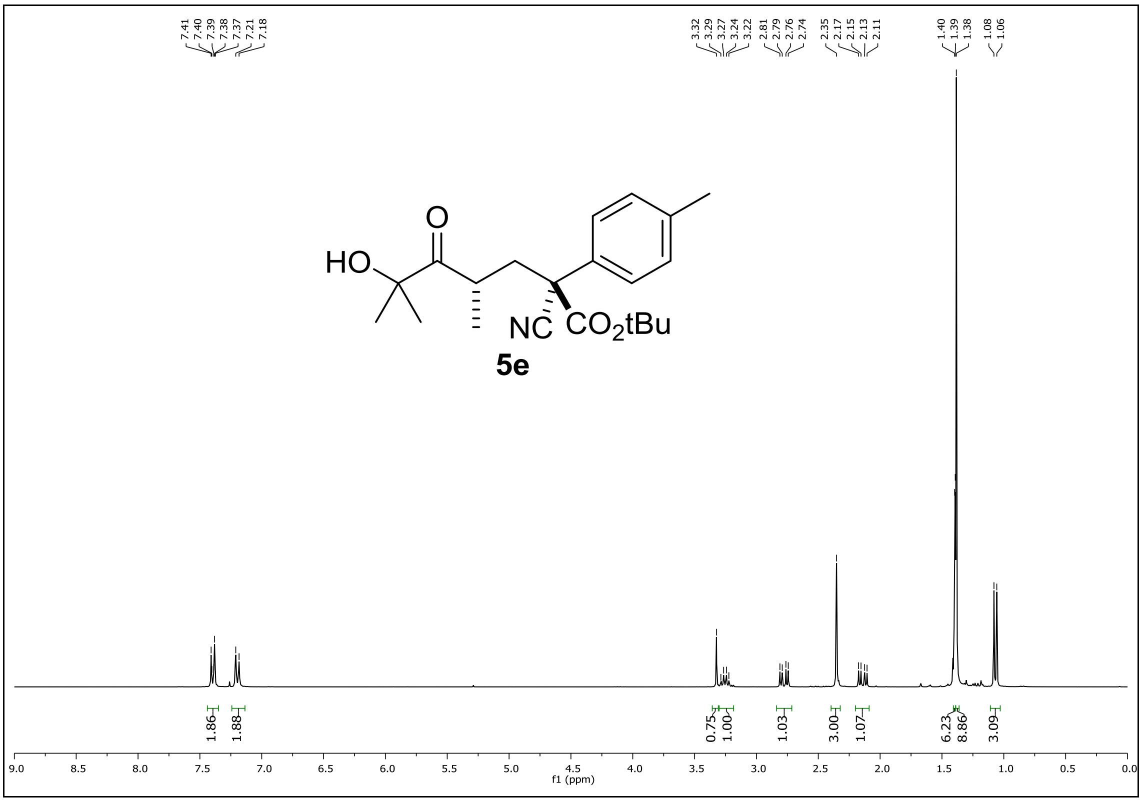
84.80
53.78
40.70
36.95
27.73
27.17
27.00
21.69
19.91
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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3.27
3.24
3.22
2.81
2.79
2.76
2.74
2.35
2.17
2.15
2.13
2.11
1.40
1.39
1.38
1.08
1.06
HO
O
NC
CO2tBu
5e
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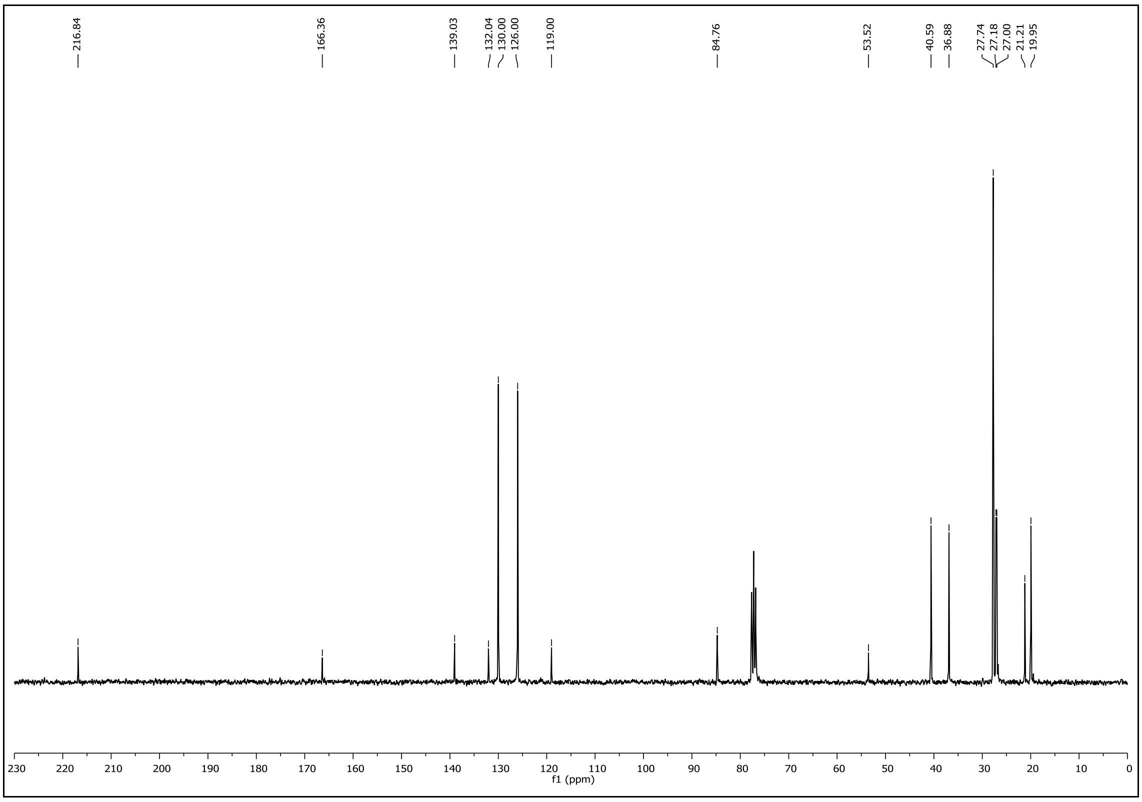
0.75
1.00
1.03
3.00
1.07
6.23
8.86
3.09
f1 (ppm)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132.04
130.00
126.00
119.00
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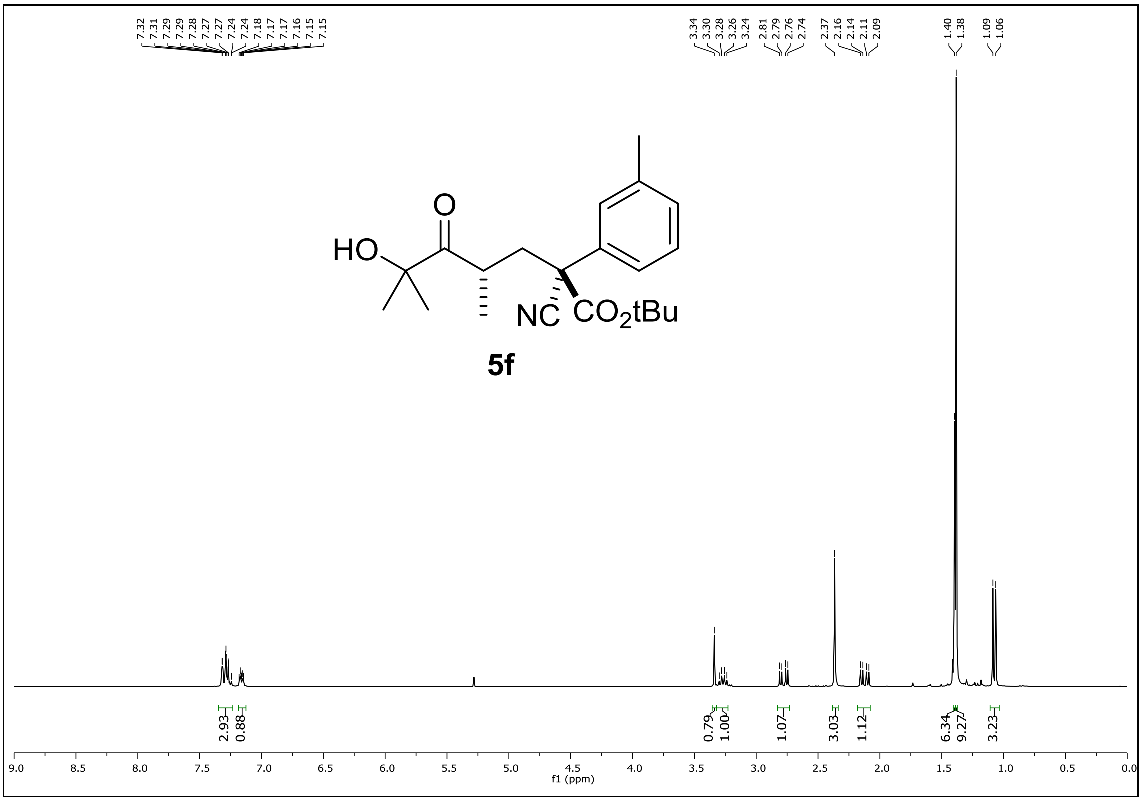
53.52
40.59
36.88
27.74
27.18
27.00
21.21
19.95
f1 (ppm)


7.32
7.31
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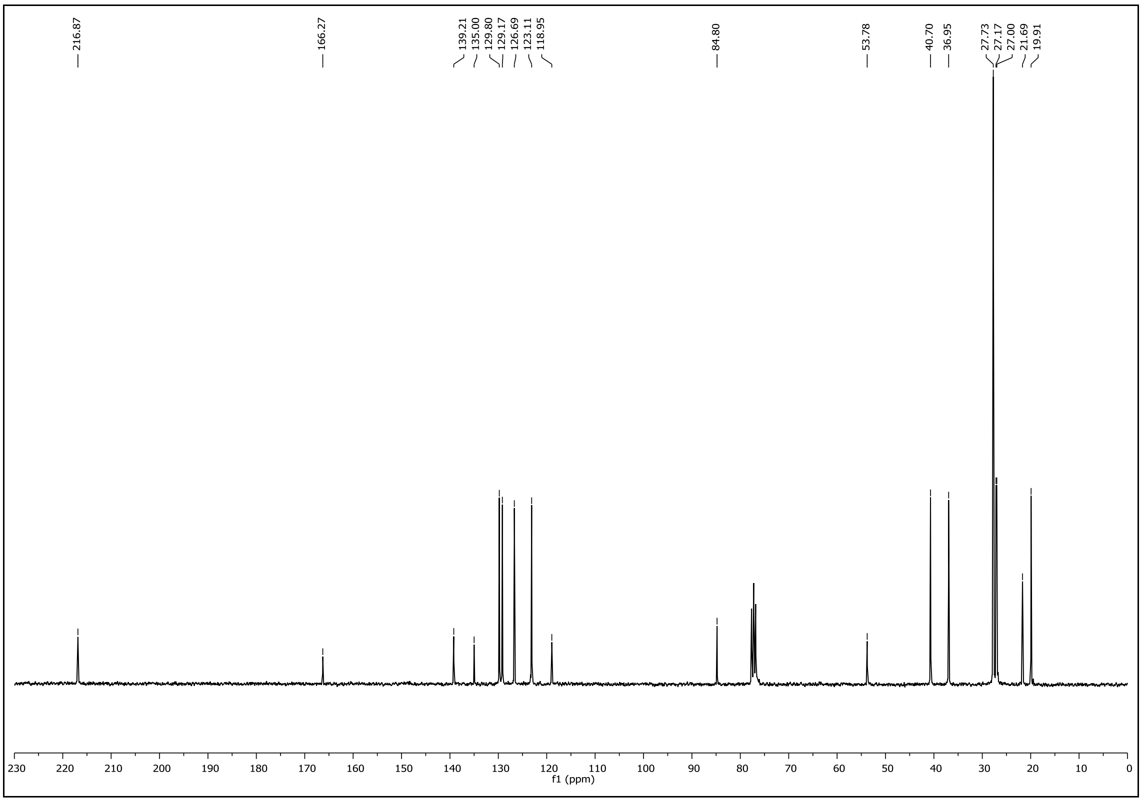
7.29
7.28
7.27
7.27
7.24
7.24
7.18
7.17
7.17
7.16
7.15
7.15
3.34
3.30
3.28
3.26
3.24
2.81
2.79
2.76
2.74
2.37
2.16
2.14
2.11
2.09
1.40
1.38
1.09
1.06
HO
O
NC
CO2tBu
5f
2.93
0.88
0.79
1.00
1.07
3.03
1.12
6.34
9.27
3.23
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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166.27
139.21
135.00
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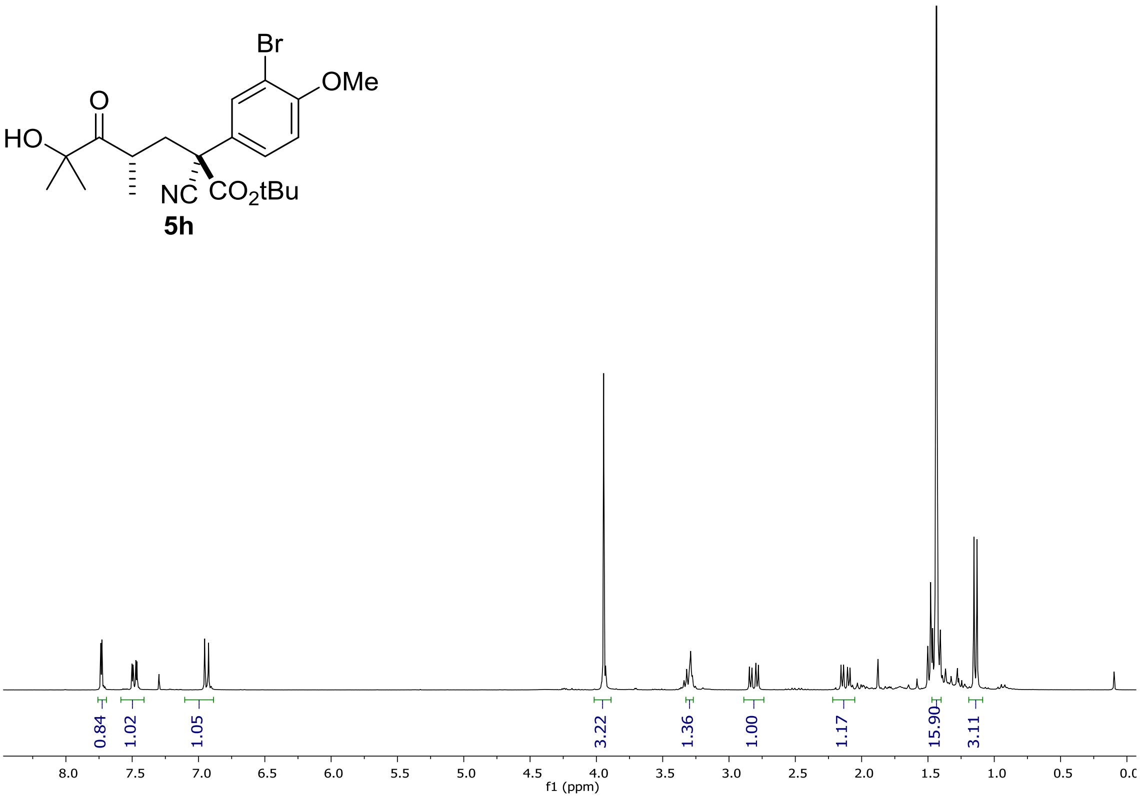
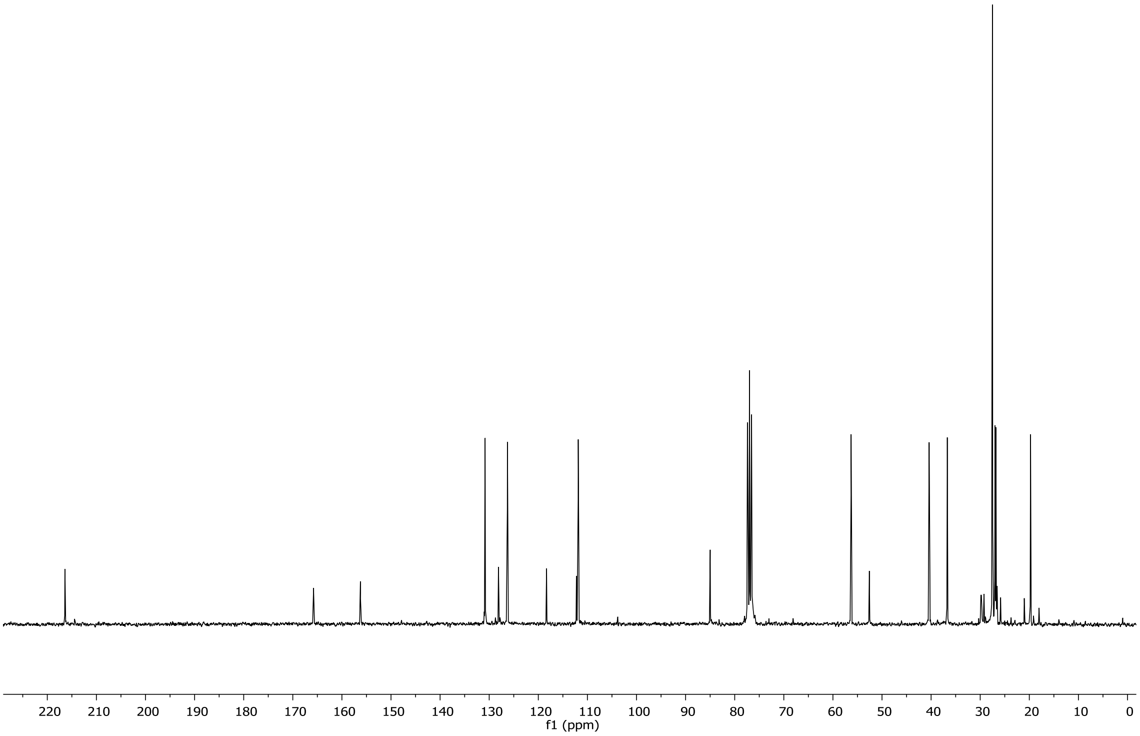
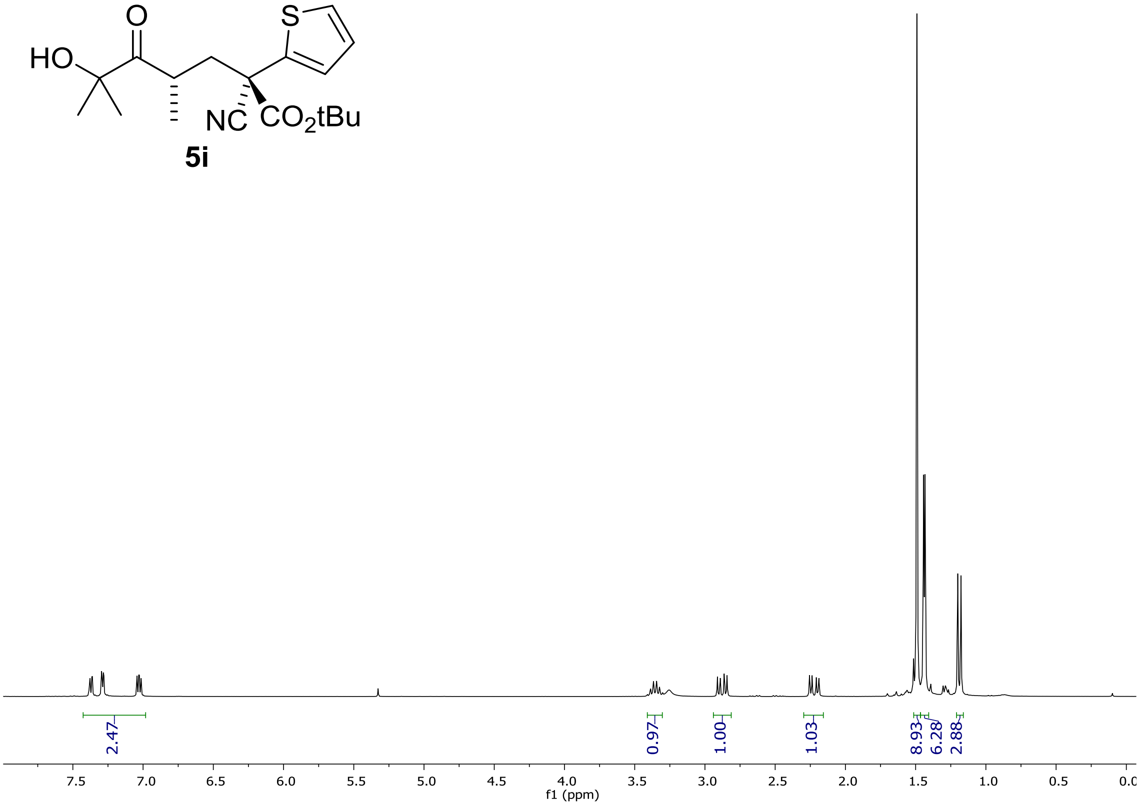
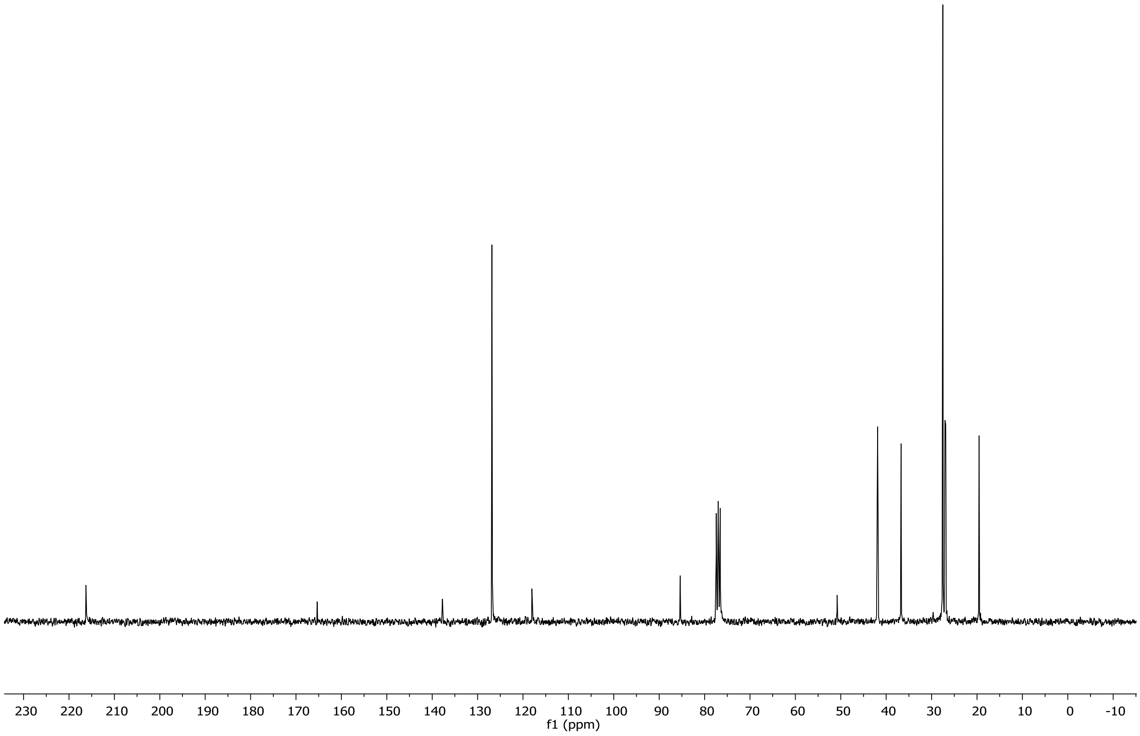
129.17
126.69
123.11
118.95
84.80
53.78
40.70
36.95
27.73
27.17
27.00
21.69
19.91
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

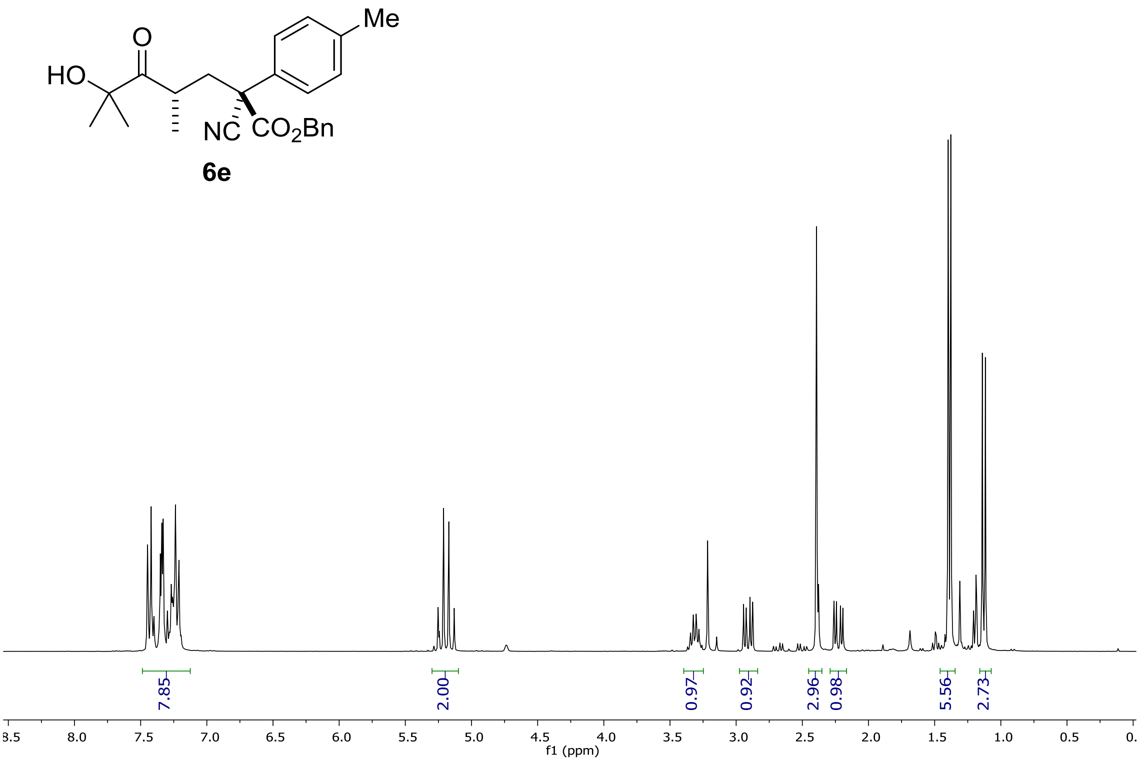

Br
OMe
O
HO
NC
CO2tBu
0.84
1.02
1.05
3.22
1.36
1.00
1.17
15.90
3.11
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.C
f1 (ppm)

5h

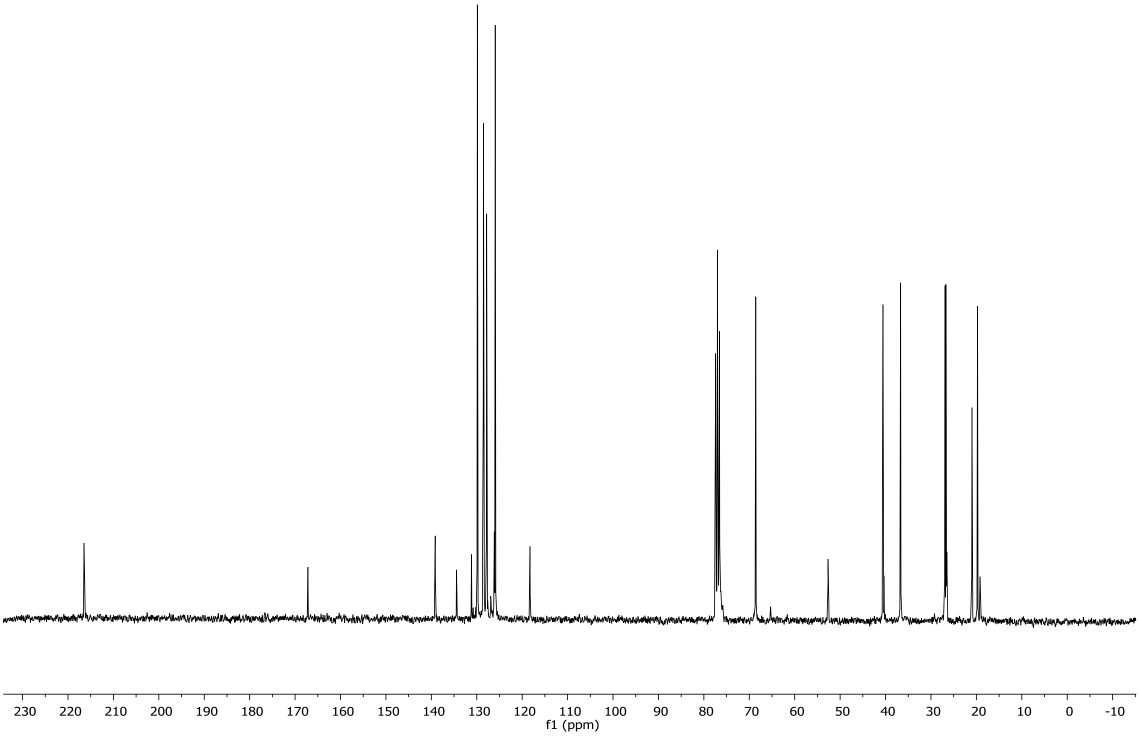

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

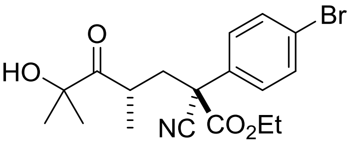

HO
O
S
NC
CO2tBu
5i
2.47
0.97
1.00
1.03
8.93
6.28
2.88
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

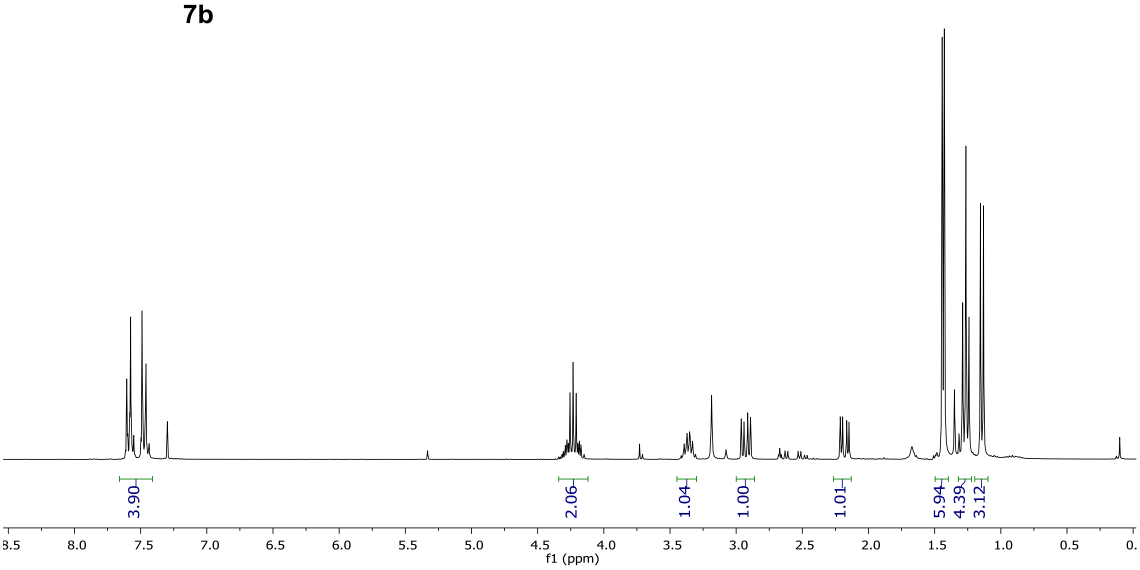

Me
HO
O
NC
CO2Bn
7.85
2.00
0.97
0.92
2.96
0.98
5.56
2.73
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)

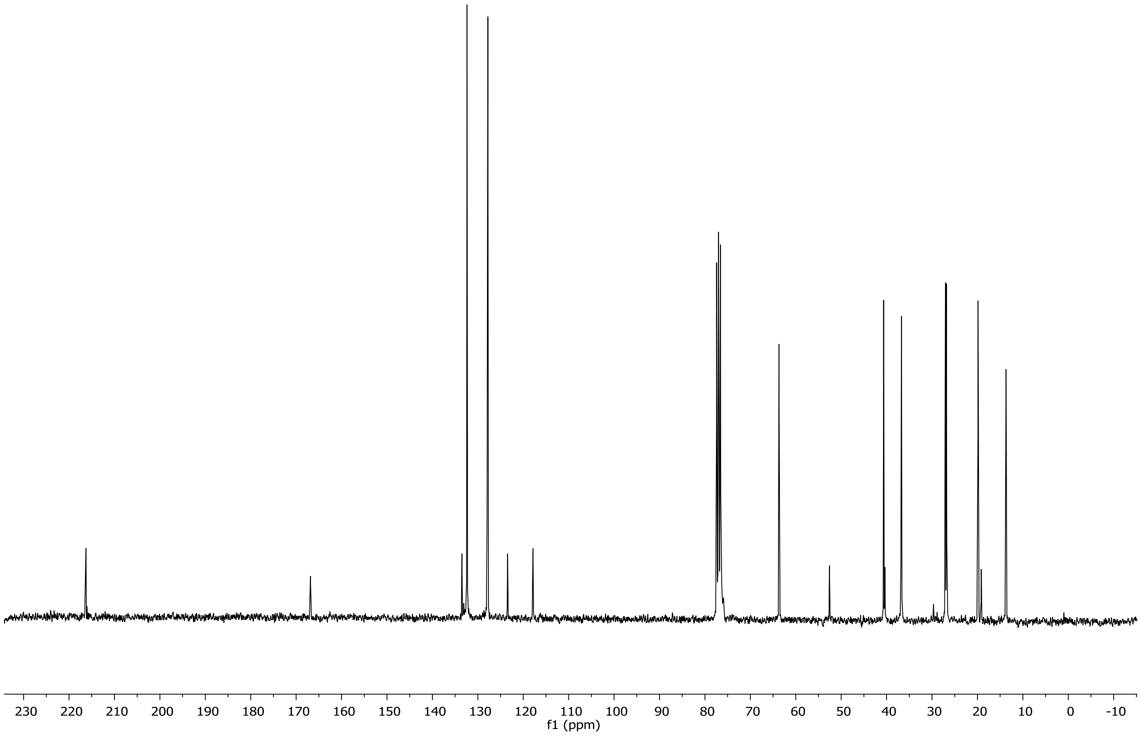
6e

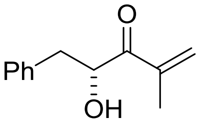

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Br
O
HO
NC
CO2Et

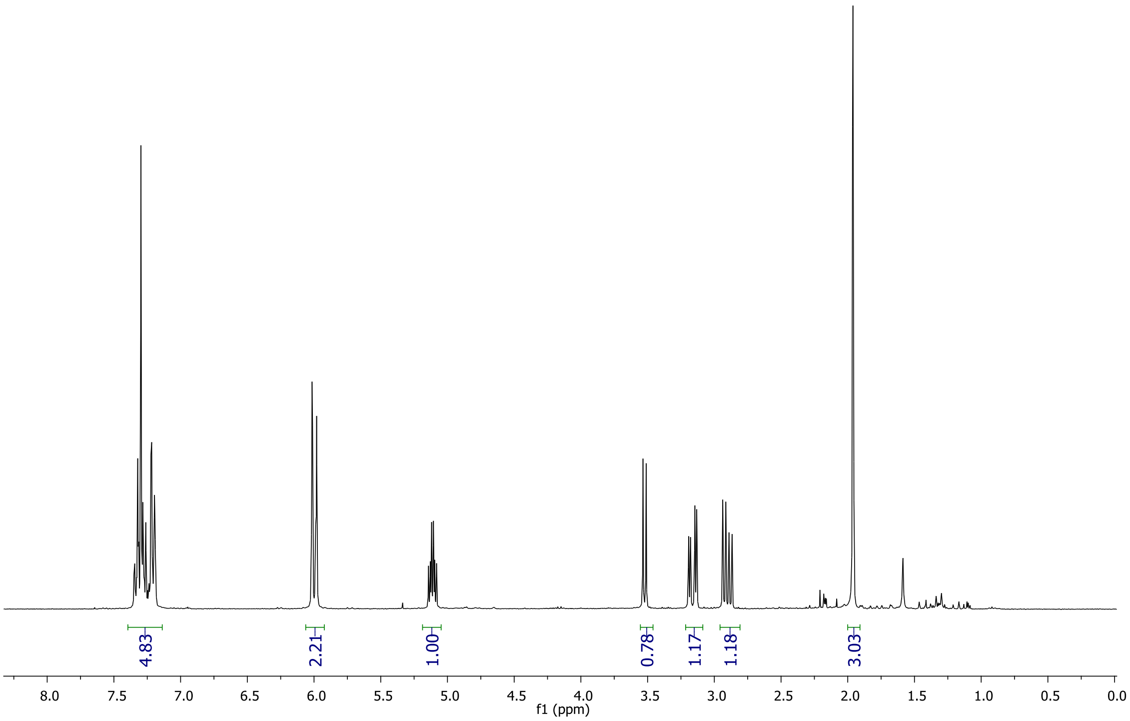
7b


3.90
2.06
1.04
1.00
1.01
5.94
4.39
3.12
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)

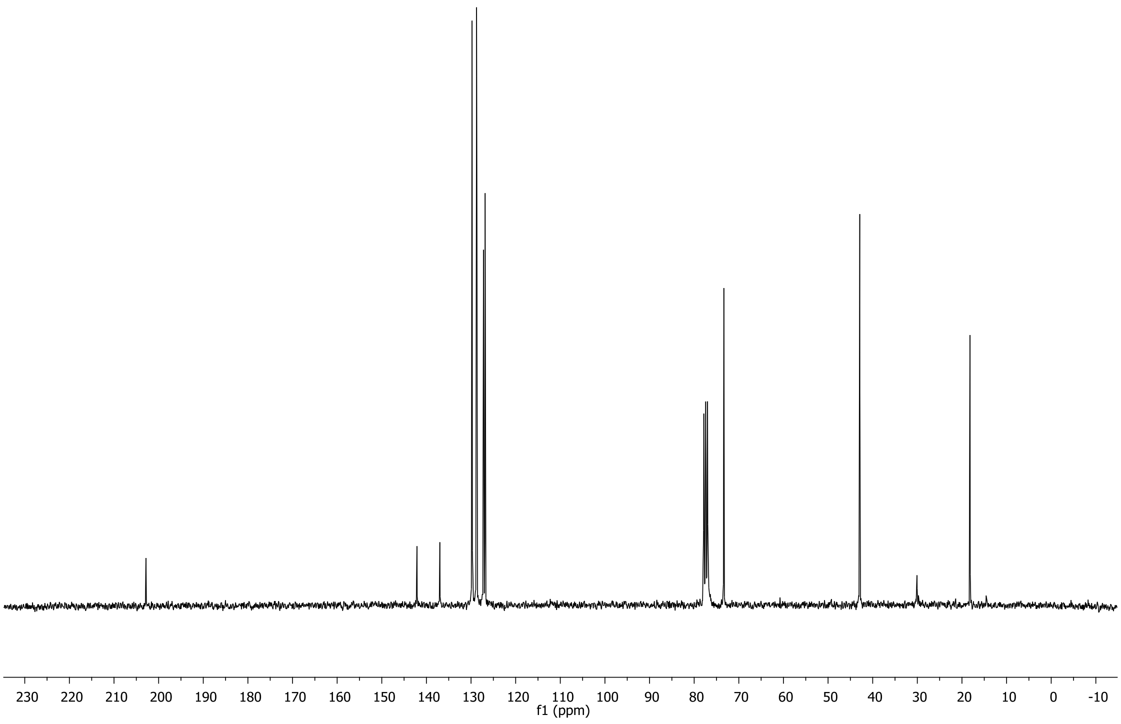

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



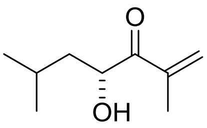
8



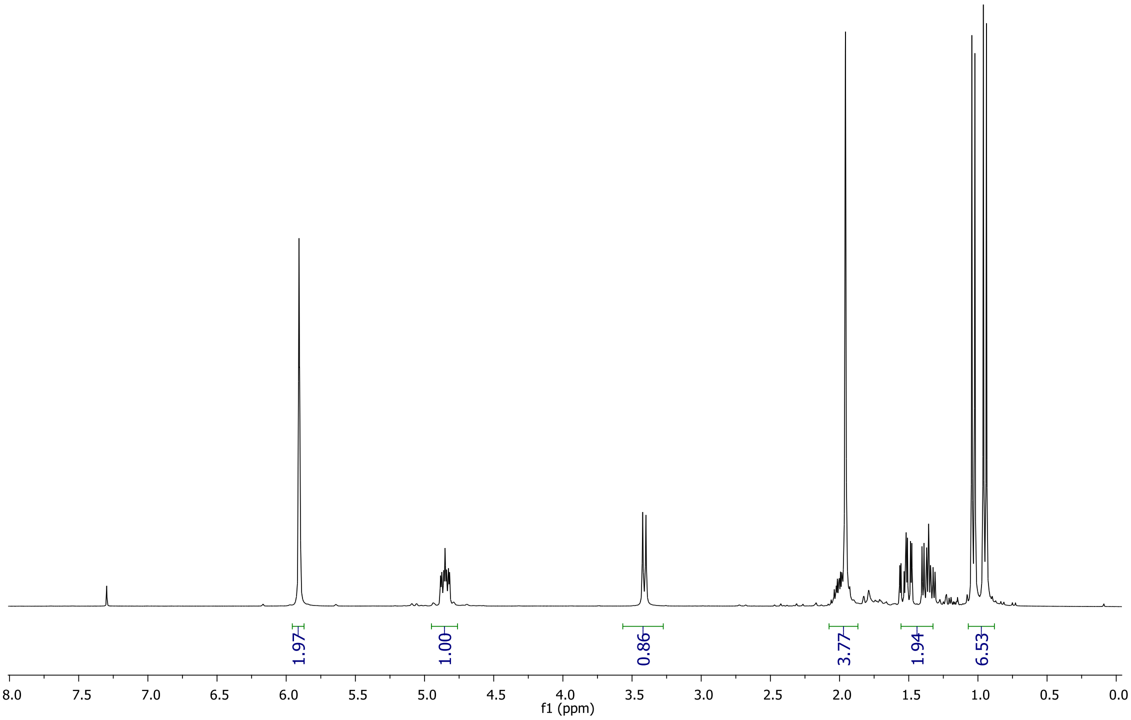
4.83
2.21
1.00
0.78
1.17
1.18
3.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

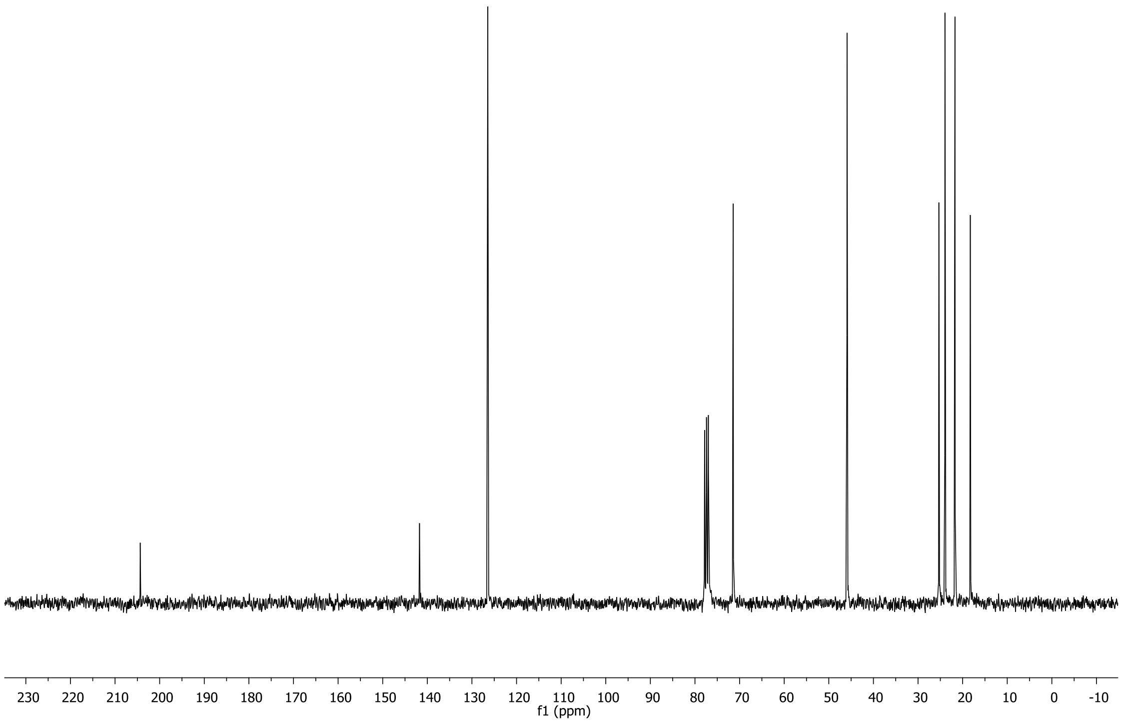


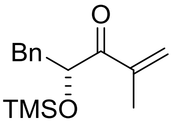
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
OH

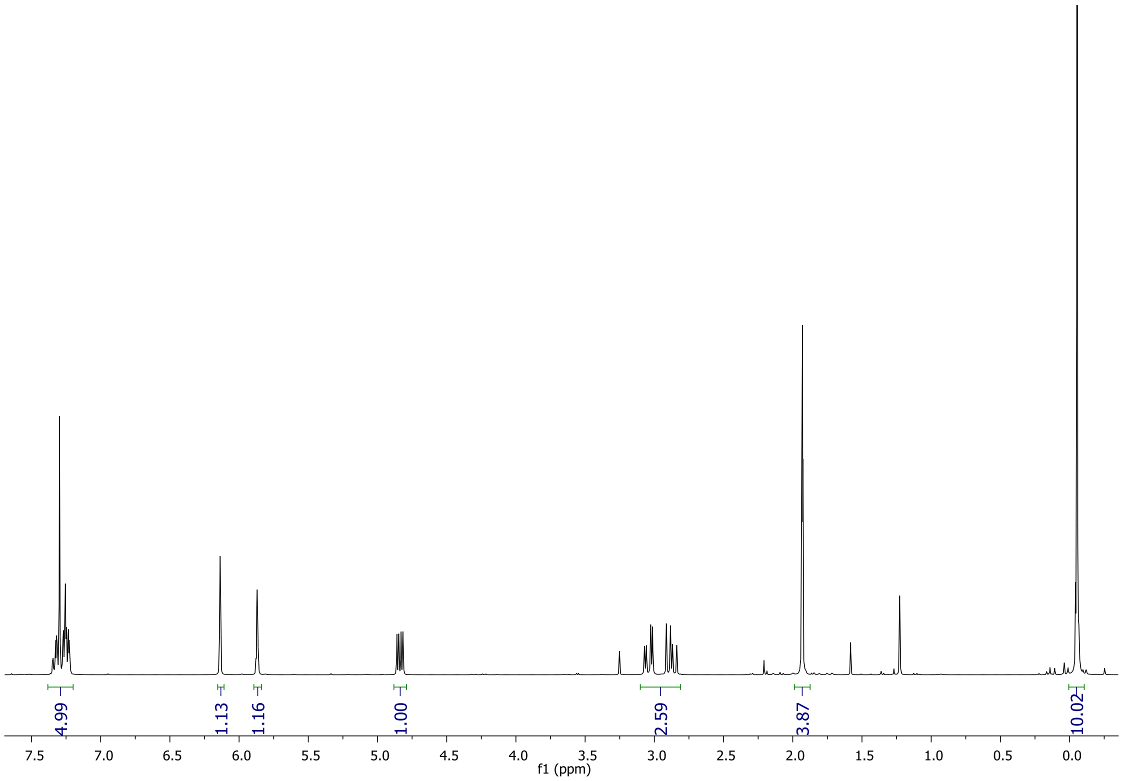
9

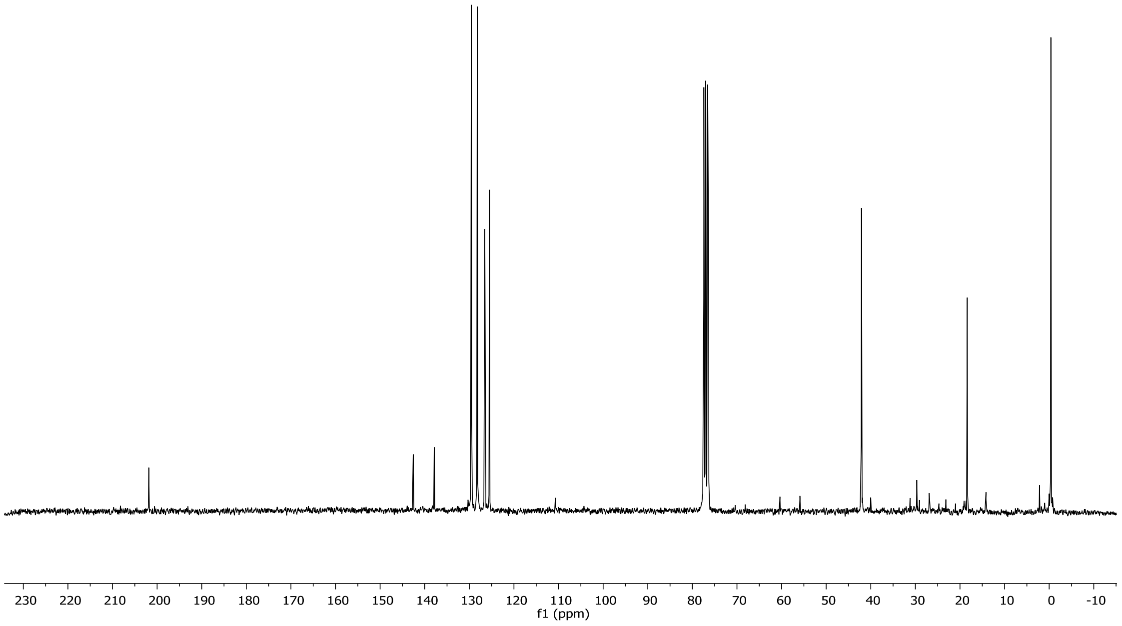

1.97
1.00
0.86
3.77
1.94
6.53
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

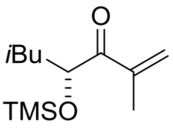

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
Bn
TMSO

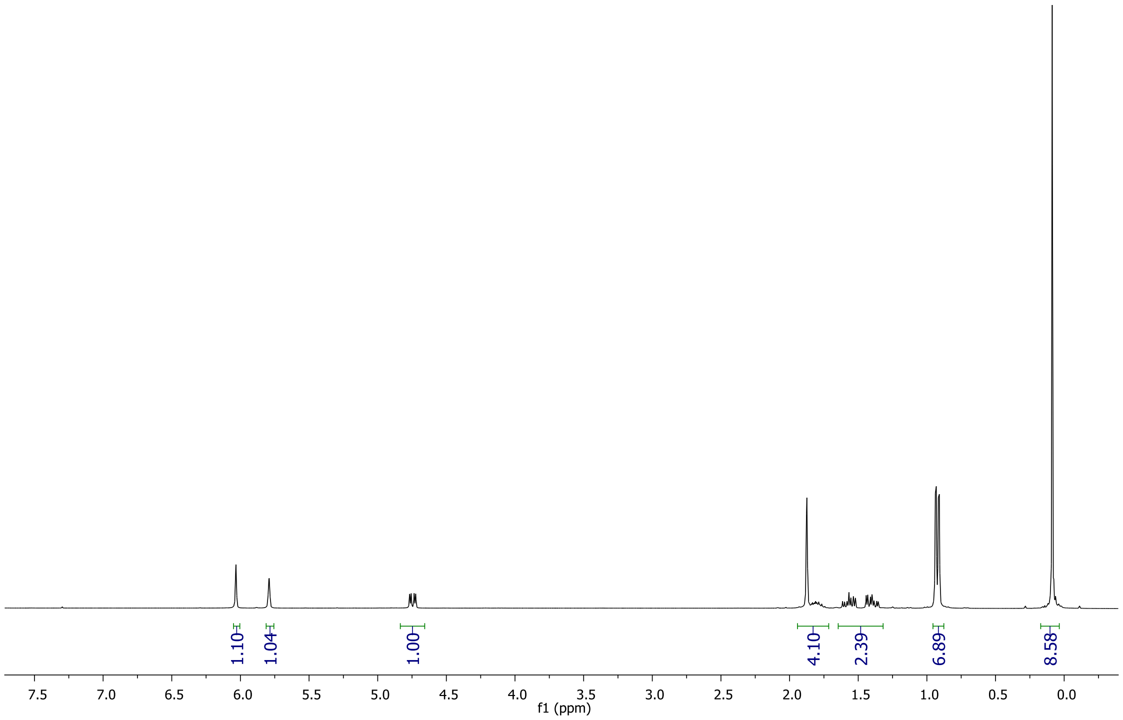
10

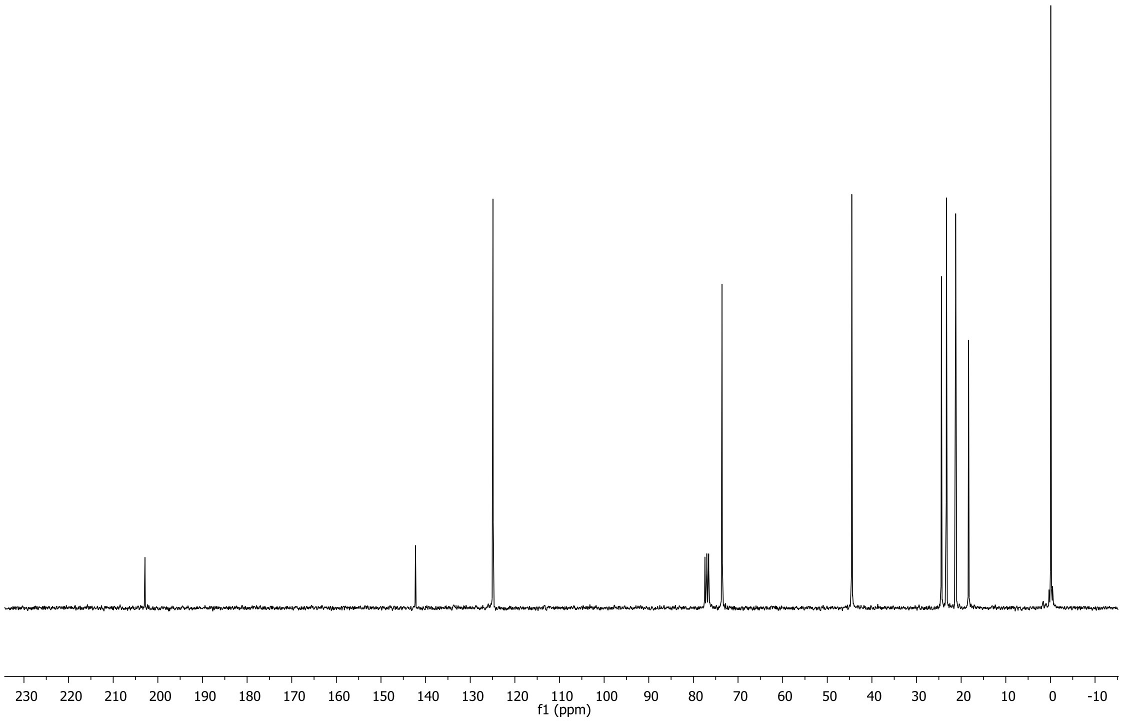

4.99
1.13
1.16
1.00
2.59
3.87
10.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

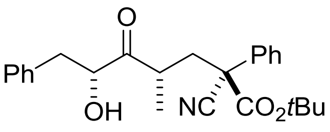

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
iBu
TMSO

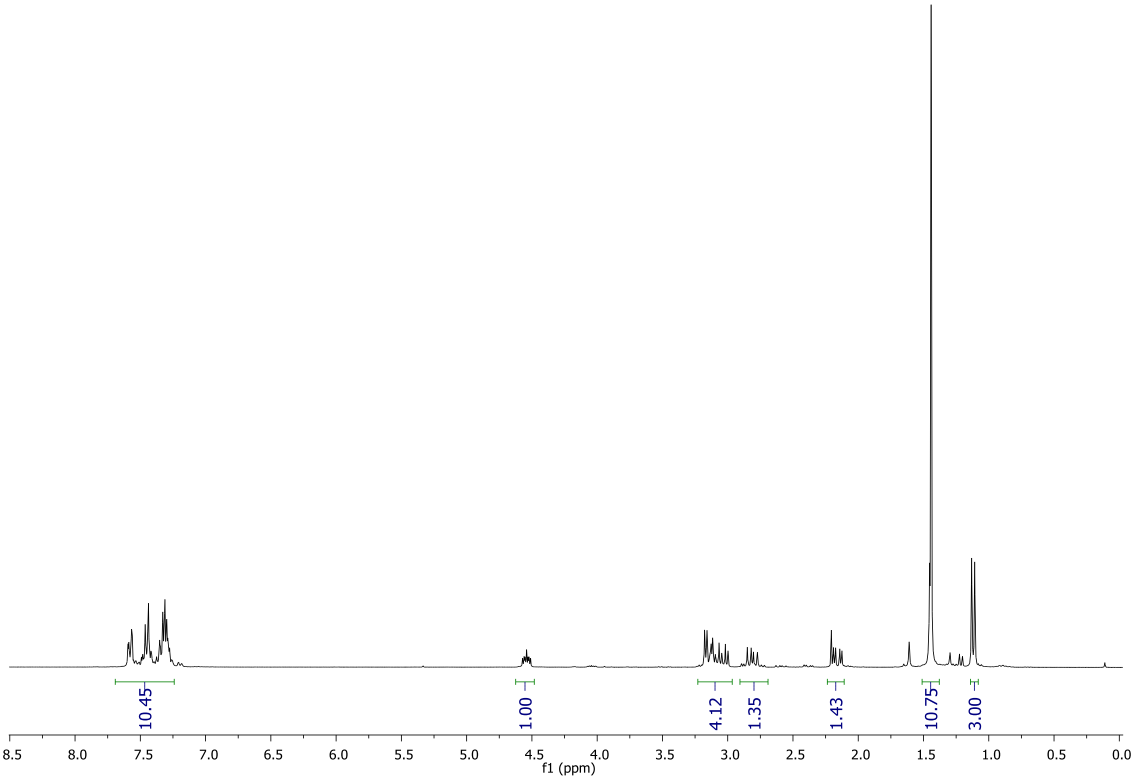
11

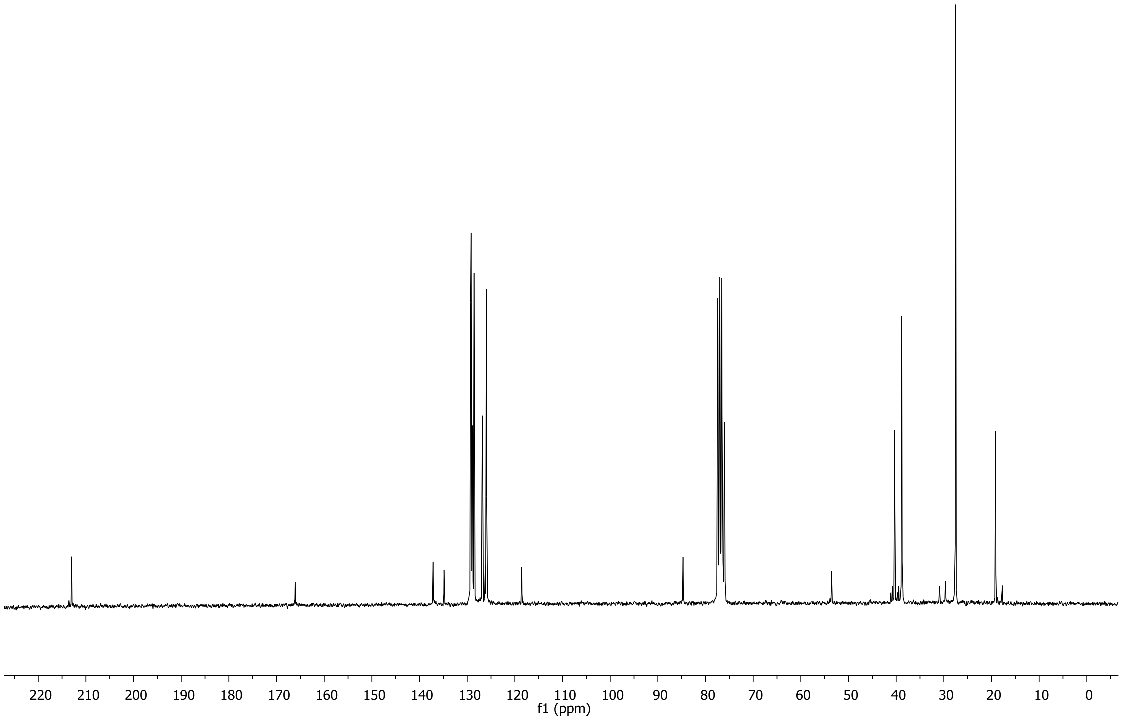

1.10
1.04
1.00
4.10
2.39
6.89
8.58
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

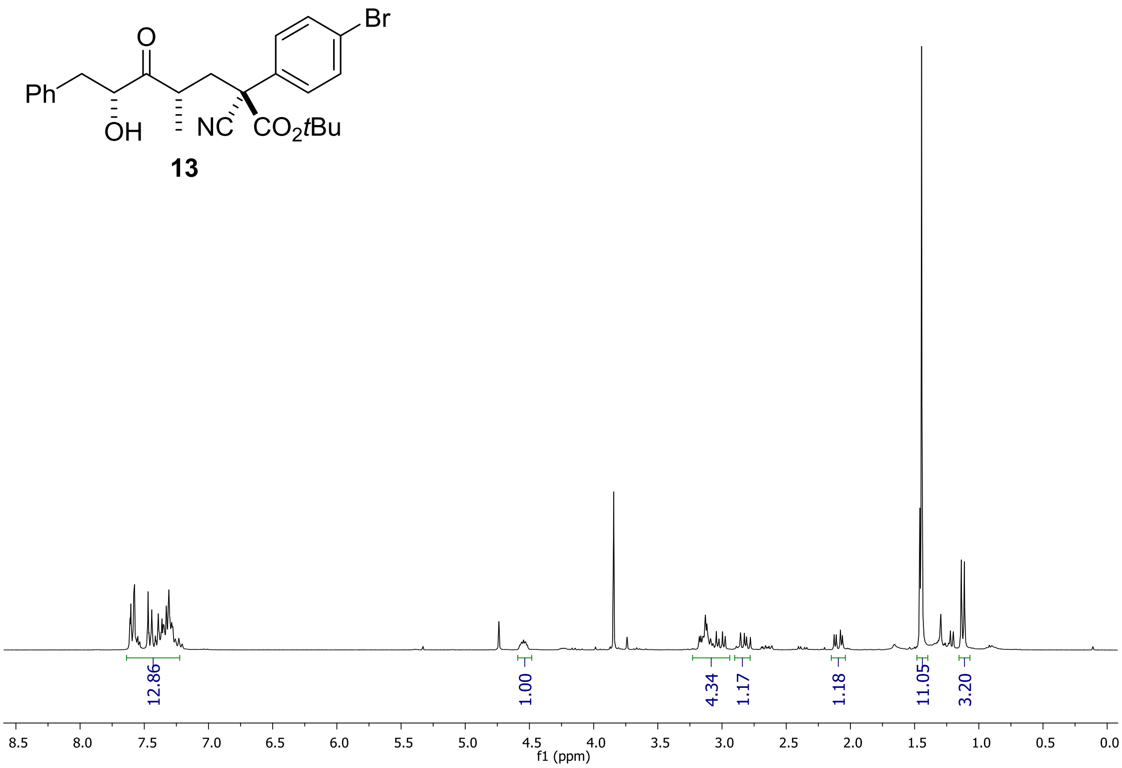

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
Ph
Ph
OH
NC
CO2tBu

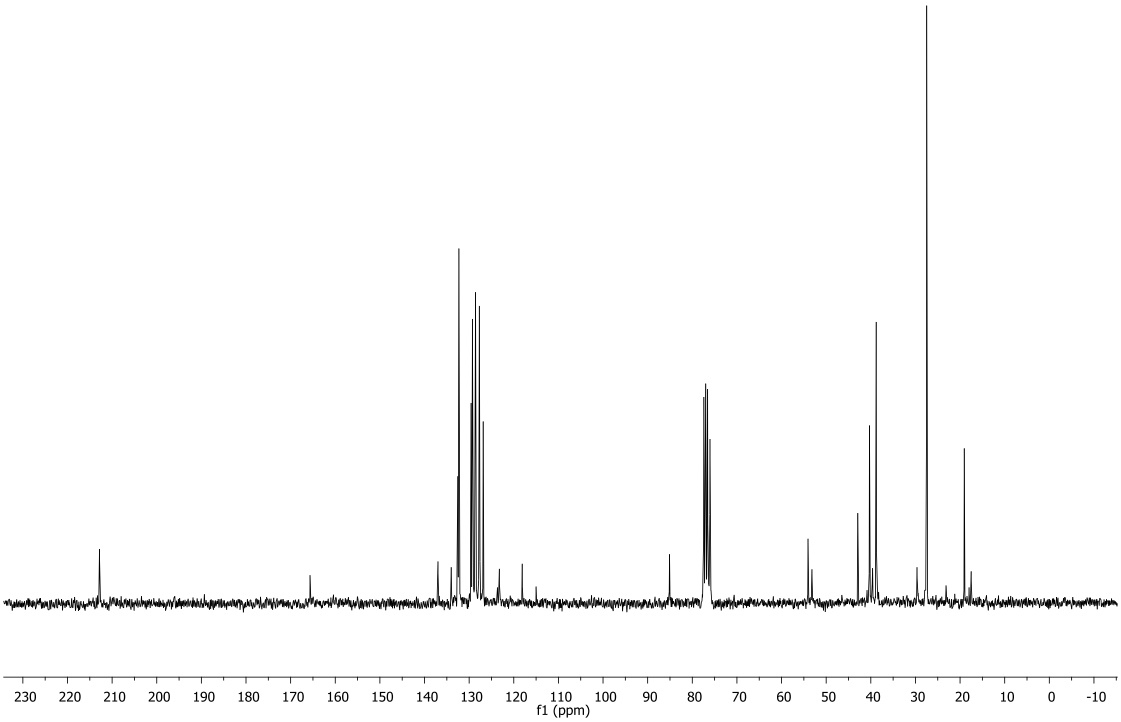
12


10.45
1.00
4.12
1.35
1.43
10.75
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

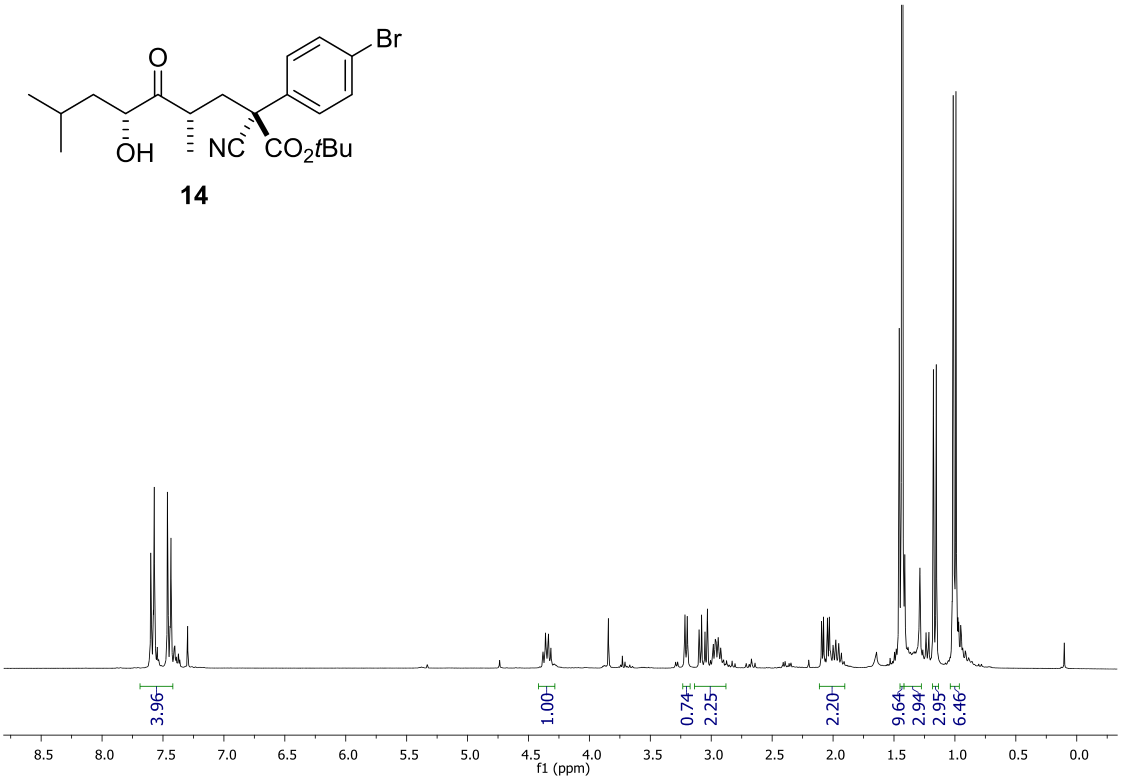

Br
O
Ph
OH
NC
CO2tBu
12.86
1.00
4.34
1.17
1.18
11.05
3.20
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

13

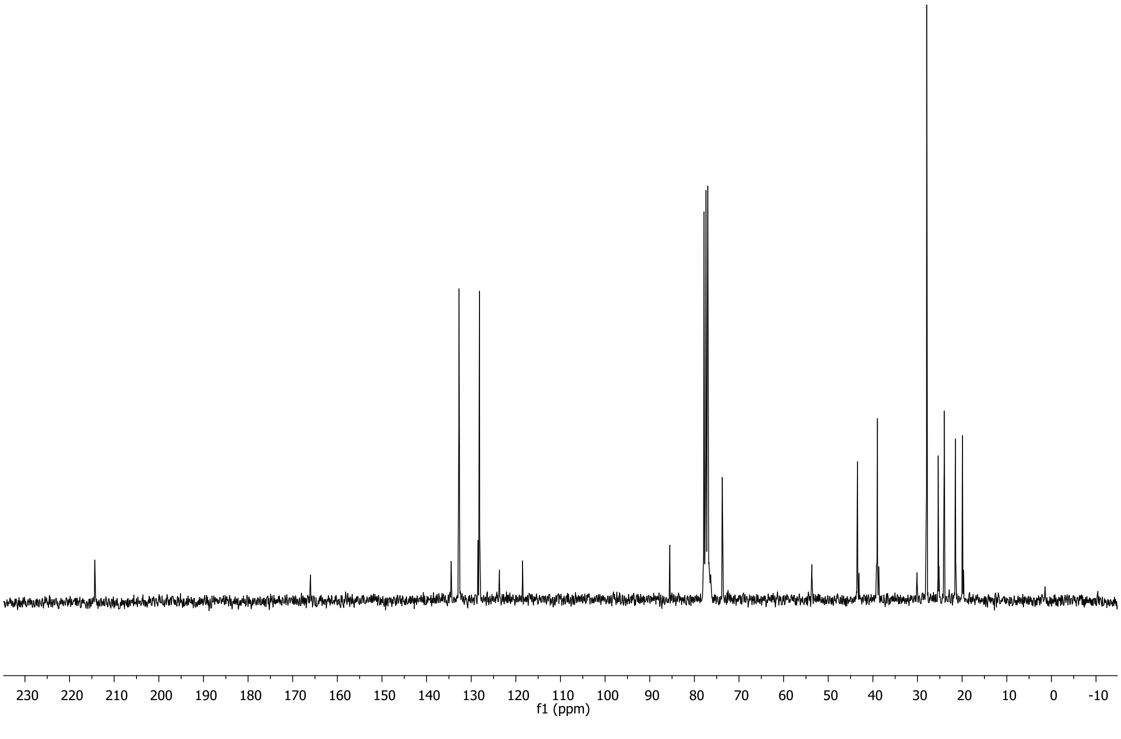

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Br
O
OH
NC
CO2tBu

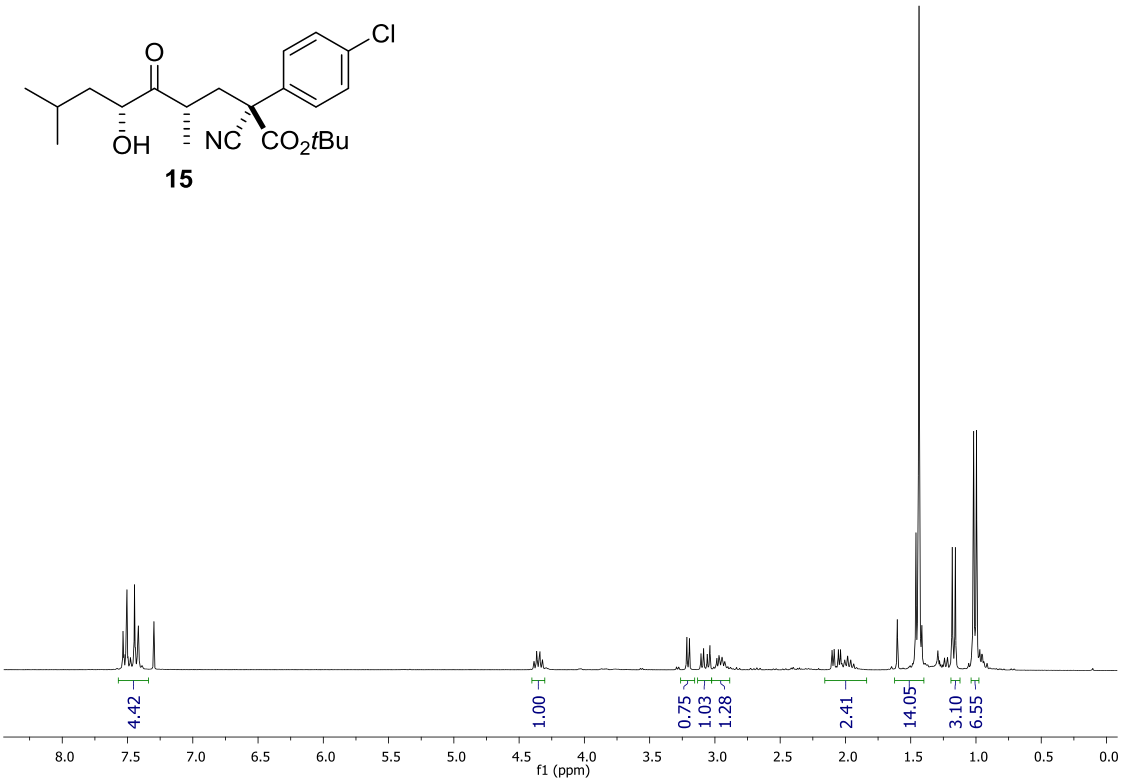
14



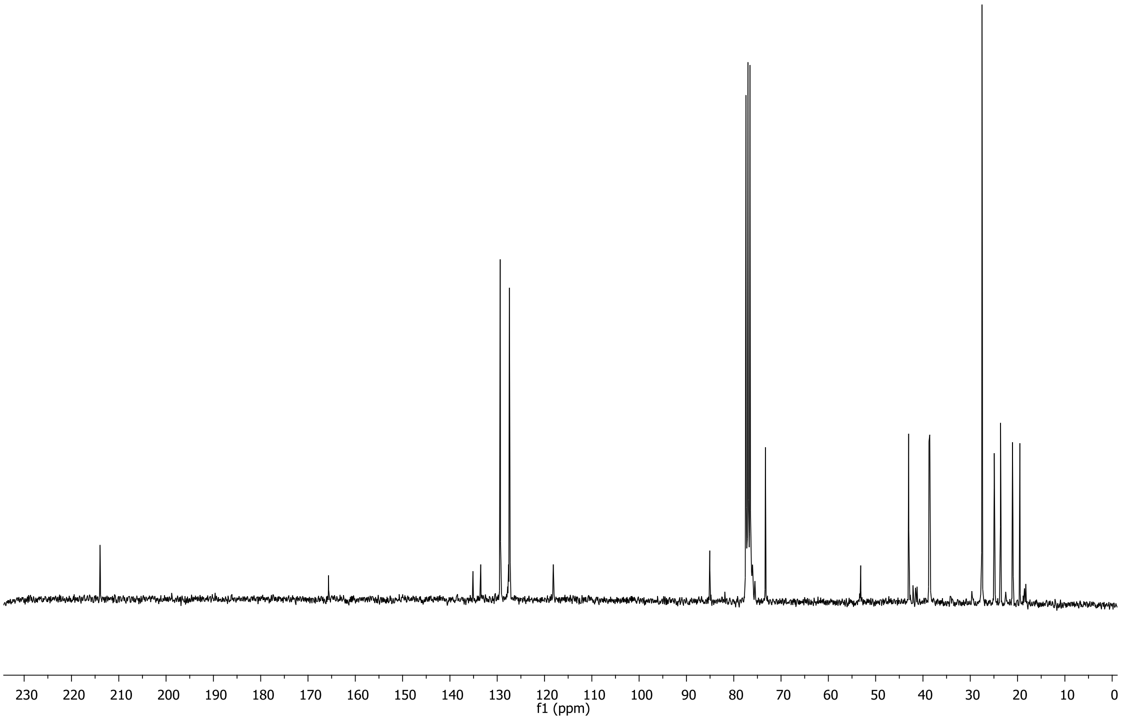
3.96
1.00
0.74
2.25
2.20
9.64
2.94
2.95
6.46
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

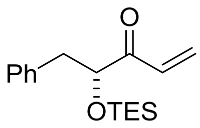


230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

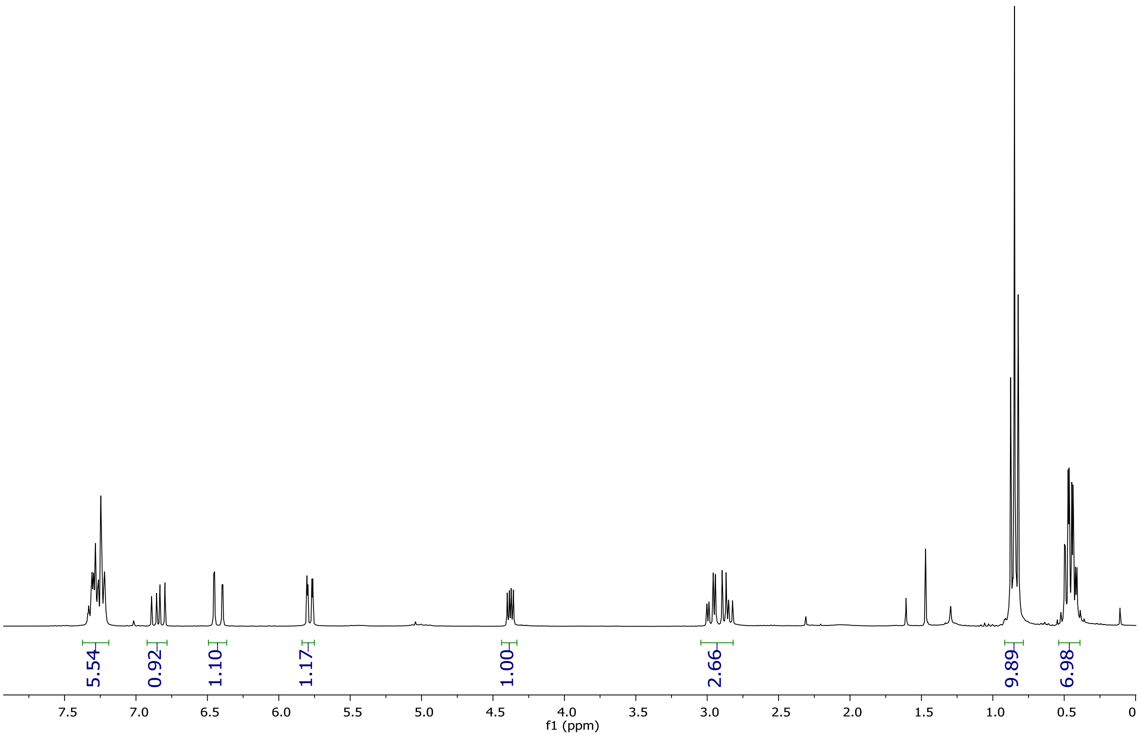

O
Cl
OH
NC
CO2tBu
4.42
1.00
0.75
1.03
1.28
2.41
14.05
3.10
6.55
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

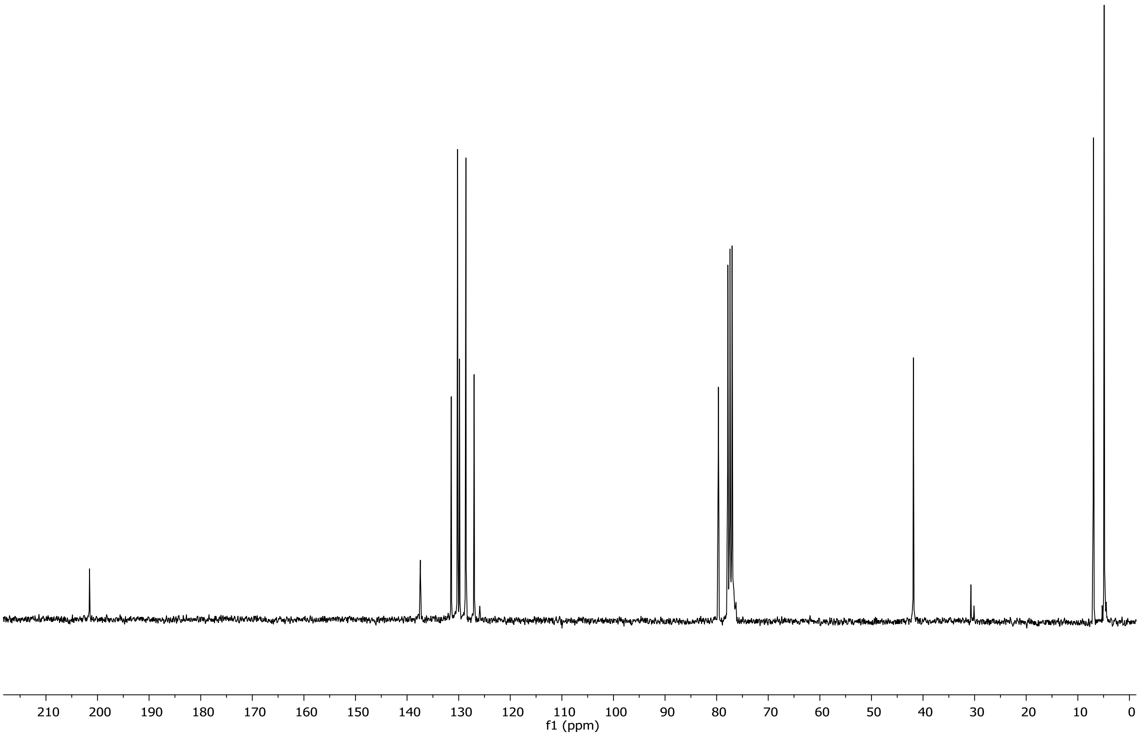
15

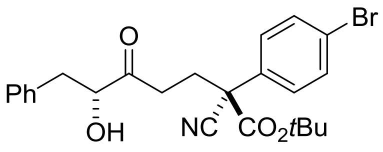

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
Ph
OTES

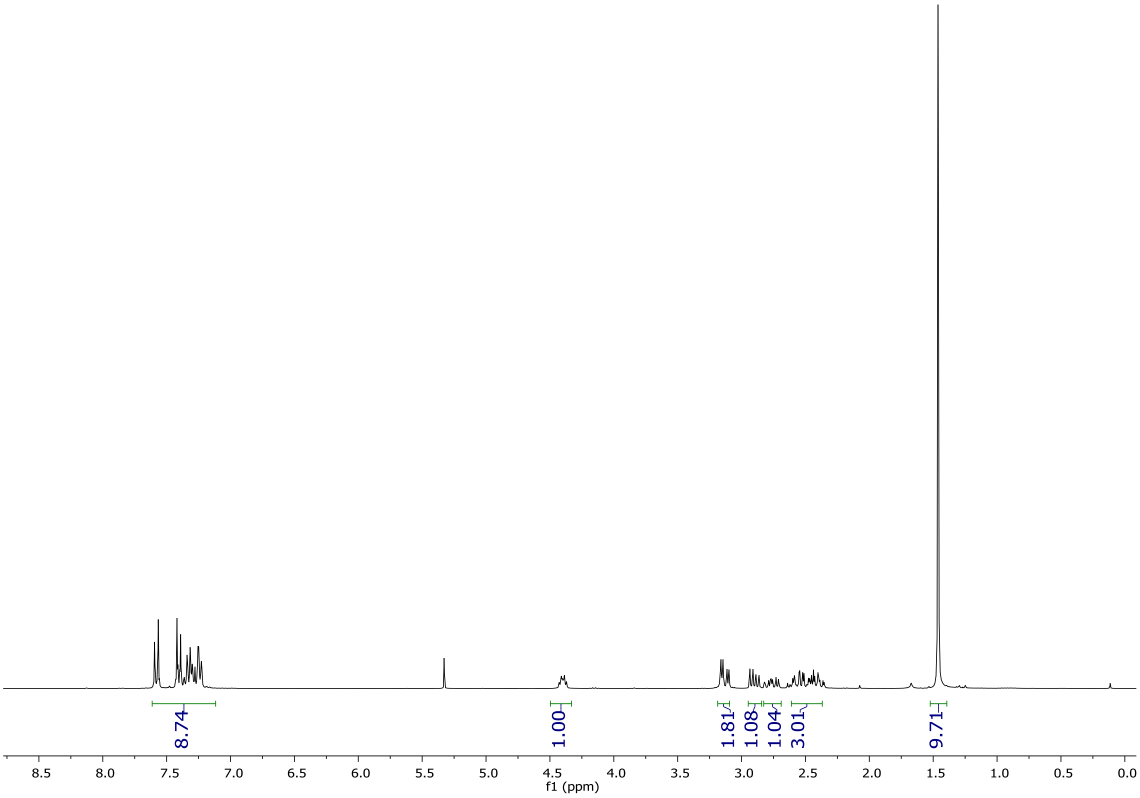
17

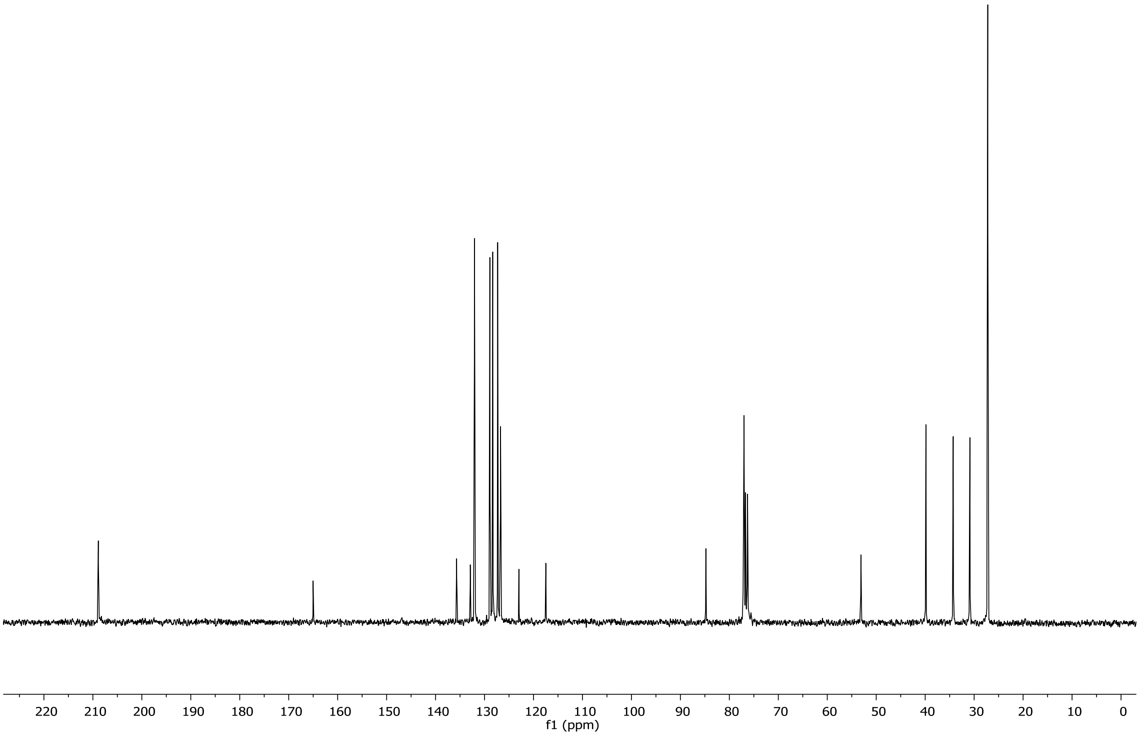

5.54
0.92
1.10
1.17
1.00
2.66
9.89
6.98
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

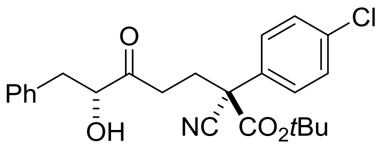

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Br
O
Ph
OH
NC
CO2tBu

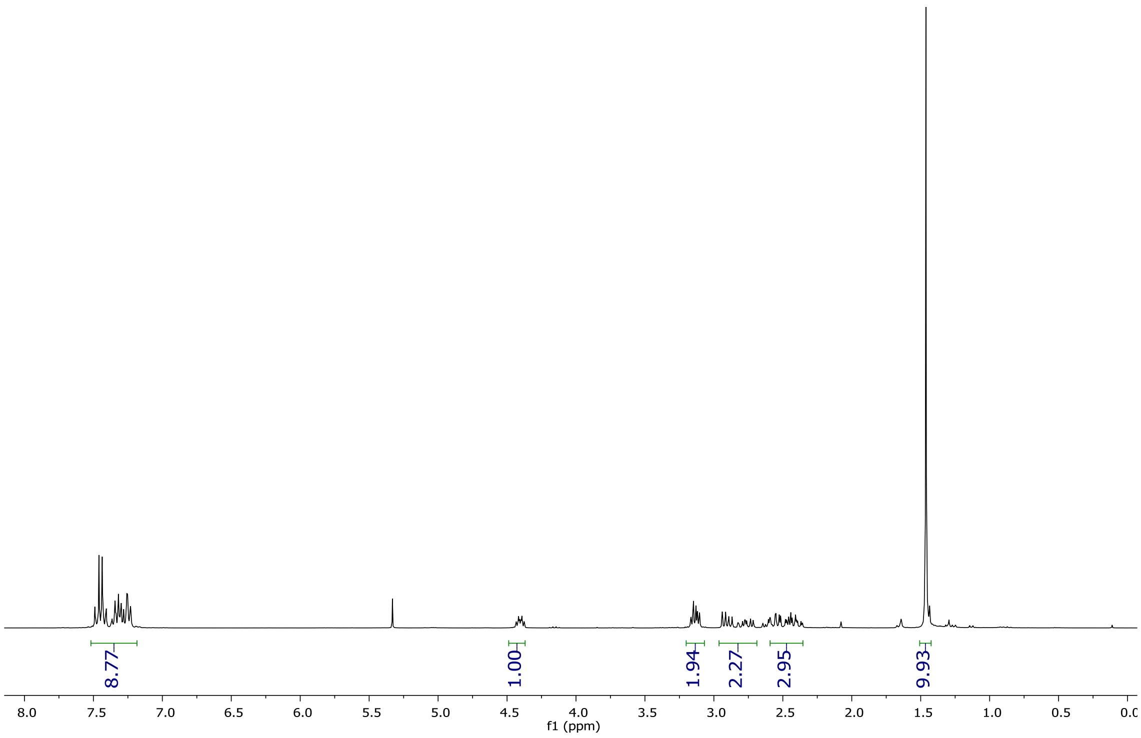
18

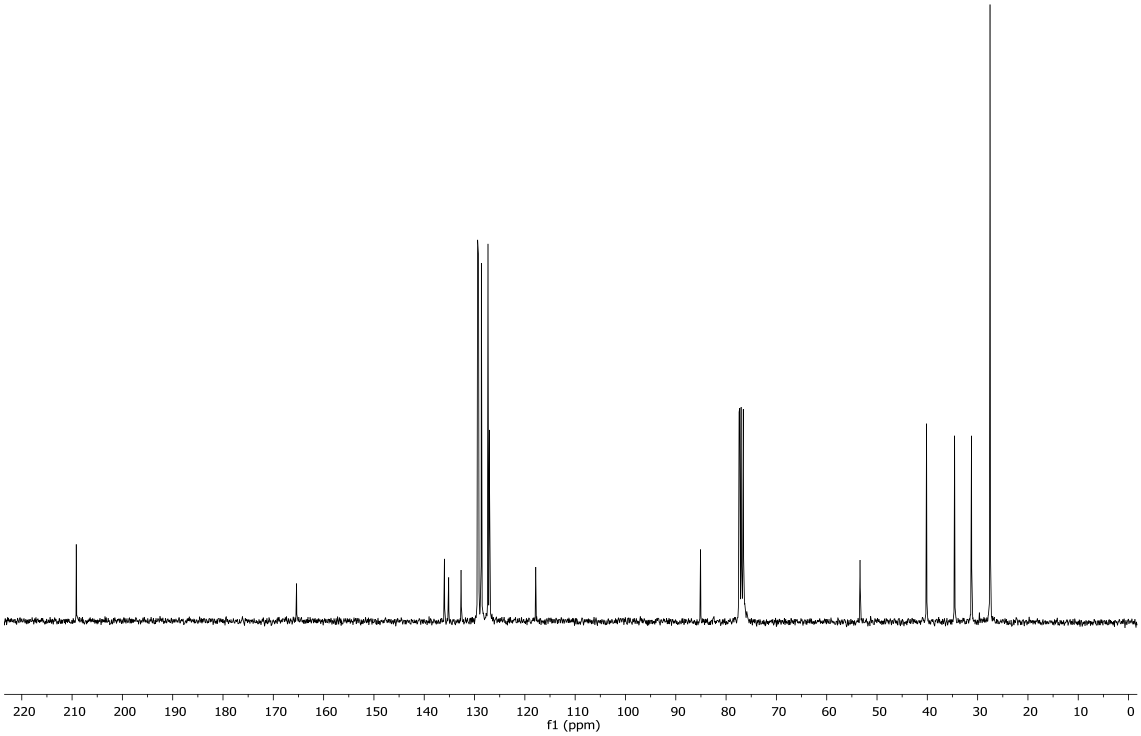

8.74
1.00
1.81
1.08
1.04
3.01
9.71
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

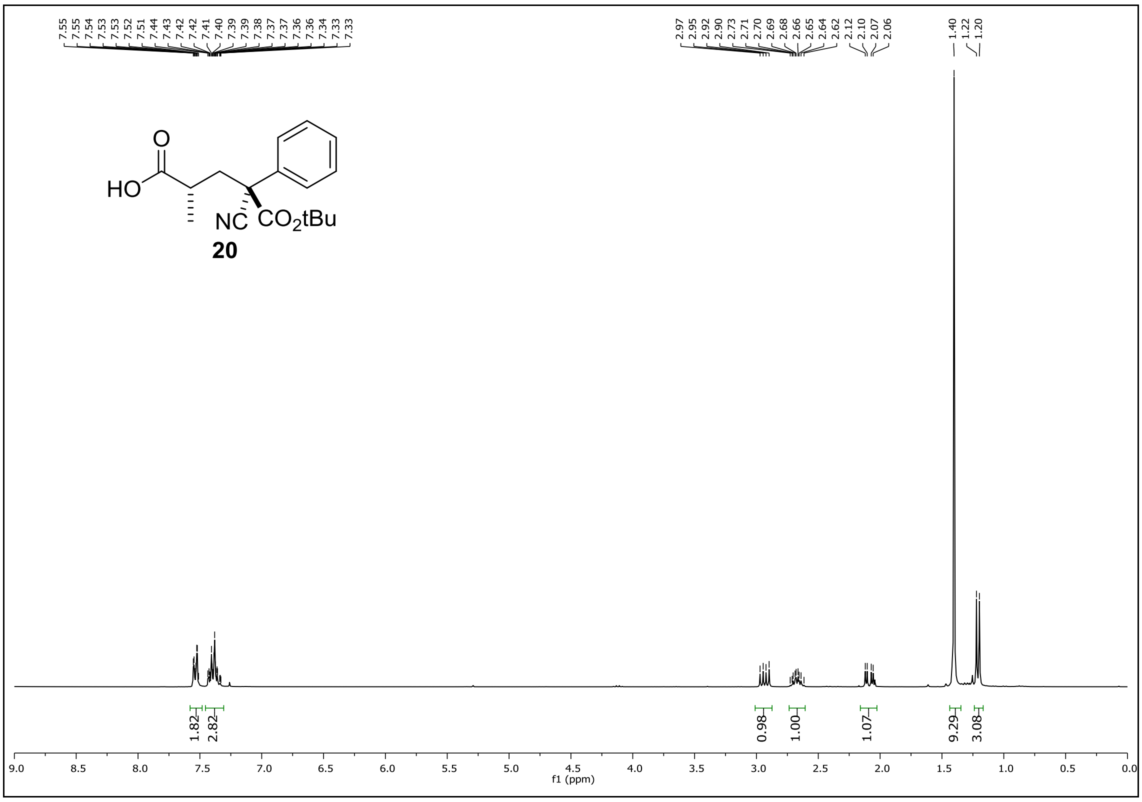

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

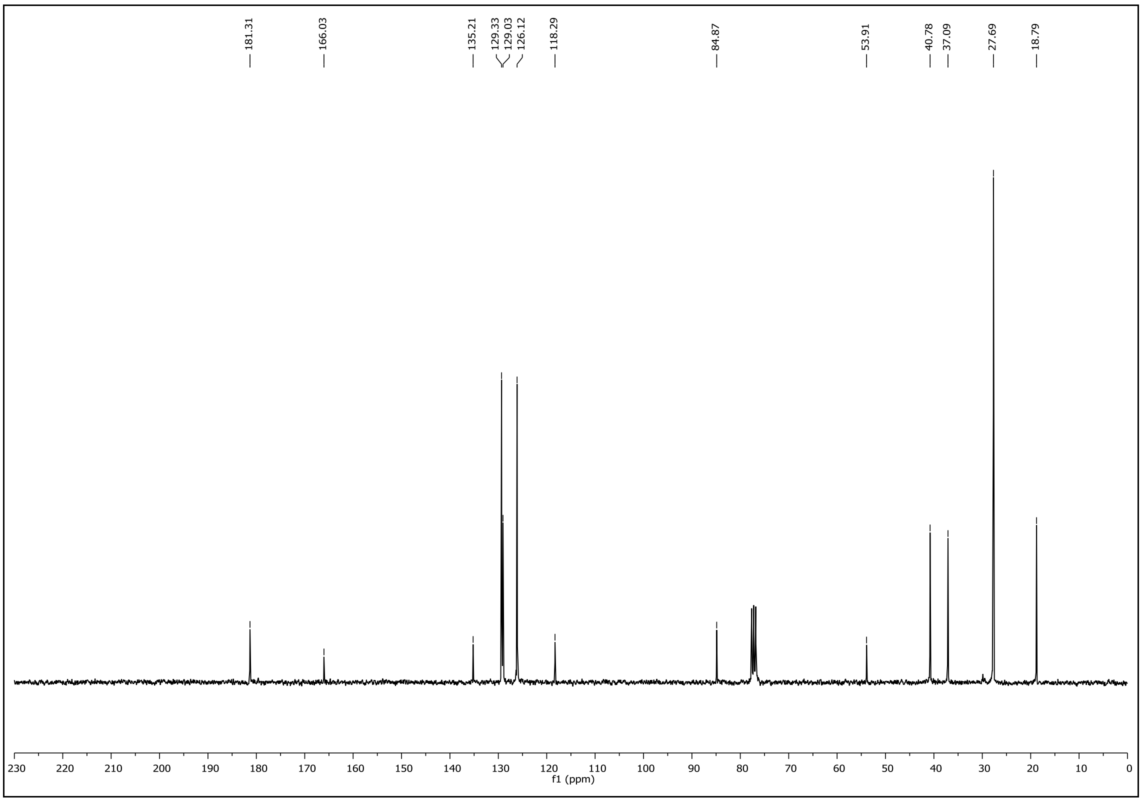

O
Cl
Ph
OH
NC
CO2tBu

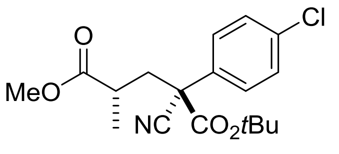
19


8.77
1.00
1.94
2.27
2.95
9.93
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

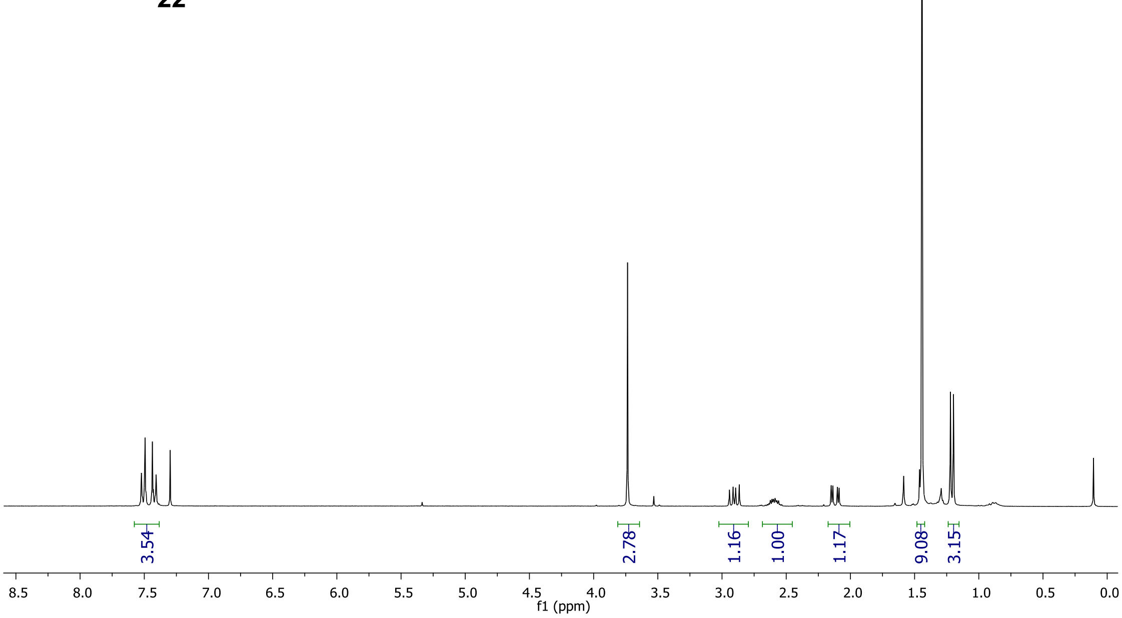

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.55
7.55
7.54
7.53
7.53
7.52
7.51
7.44
7.43
7.42
7.42
7.41
7.40
7.39
7.39
7.38
7.37
7.37
7.36
7.34
7.33
7.33
2.97
2.95
2.92
2.90
2.73
2.71
2.70
2.69
2.68
2.66
2.65
2.64
2.62
2.12
2.10
2.07
2.06
1.40
1.22
1.20
HO
O
NC
CO2tBu
20
1.82
2.82
0.98
1.00
1.07
9.29
3.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


181.31
166.03
135.21
129.33
129.03
126.12
118.29
84.87
53.91
40.78
37.09
27.69
18.79
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MeO
O
NC
CO2tBu
Cl

22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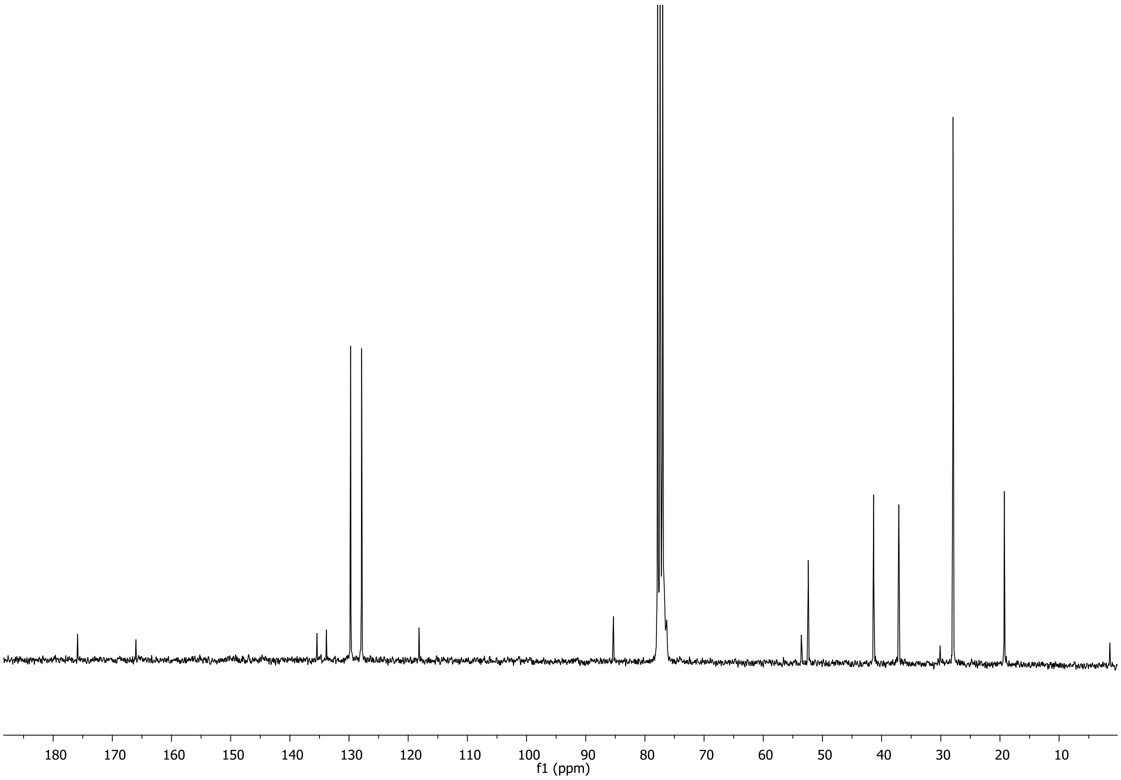
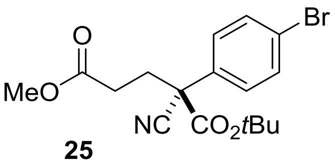
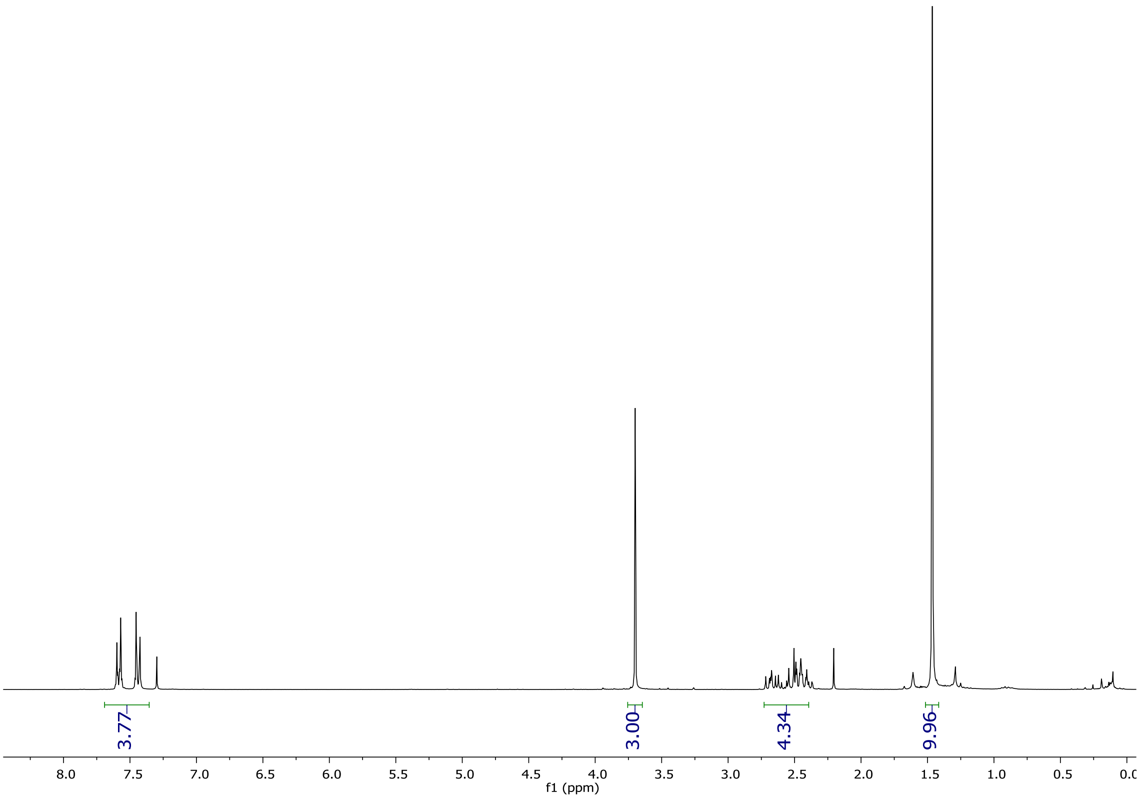
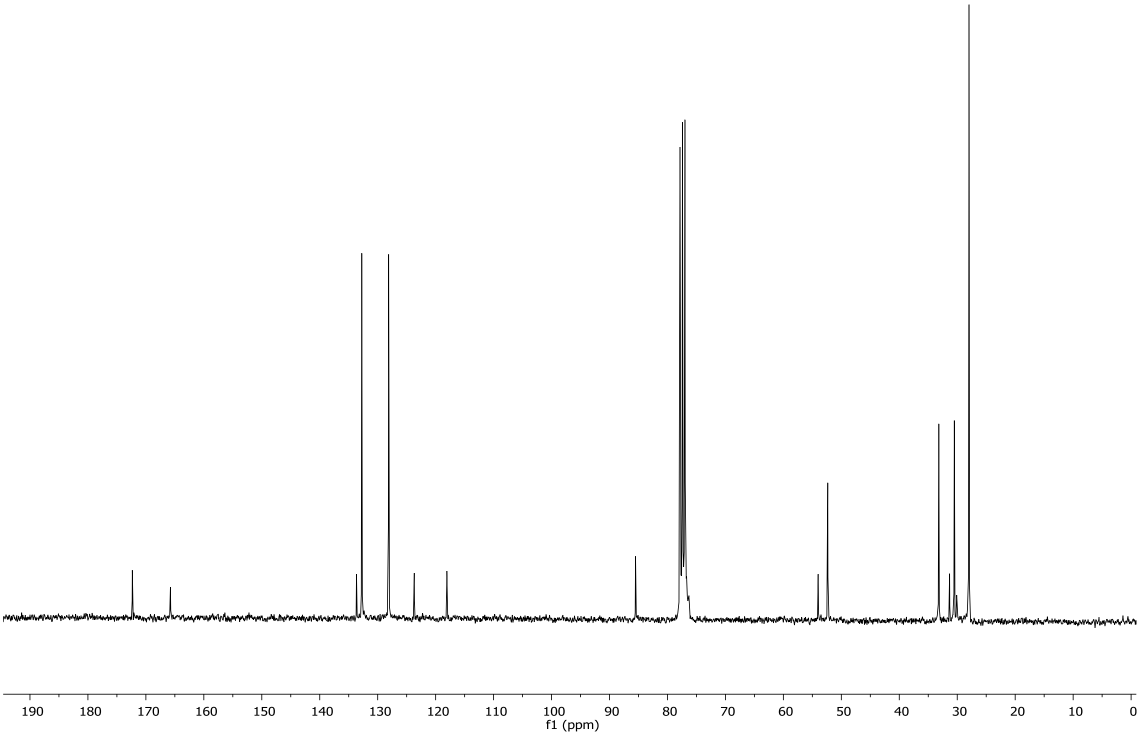
2.78
1.16
1.00
1.17
9.08
3.15
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

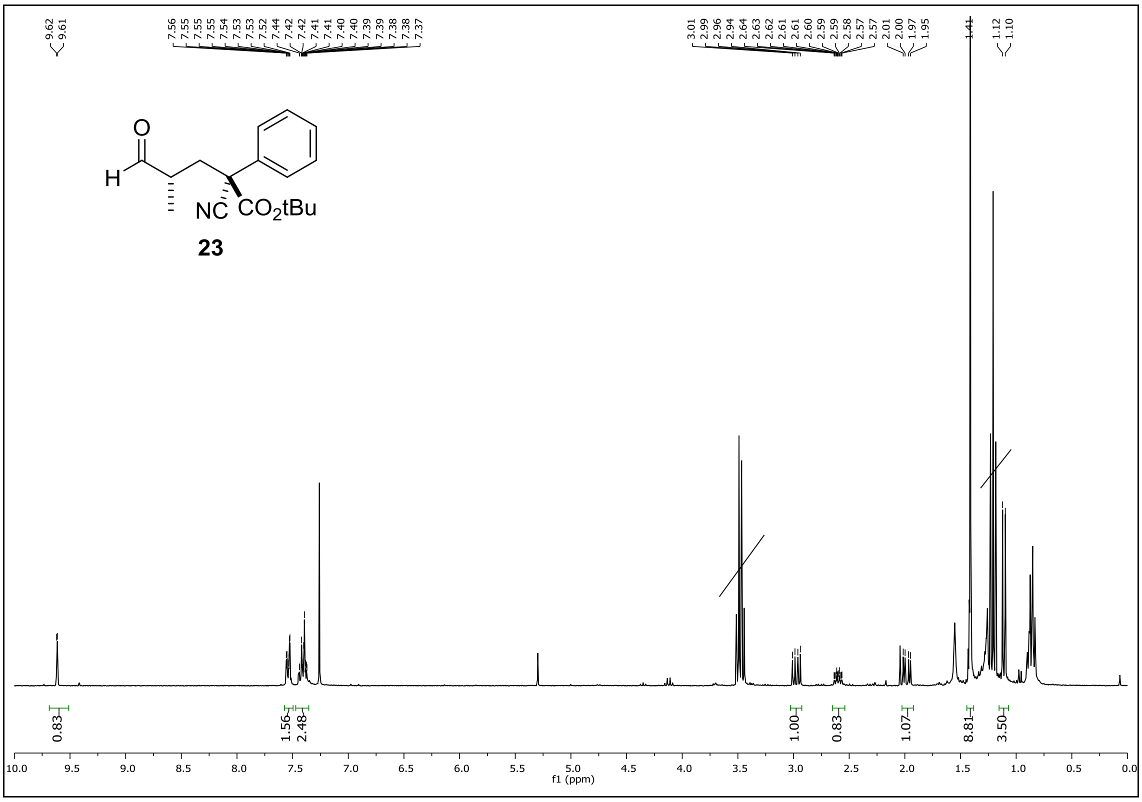

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

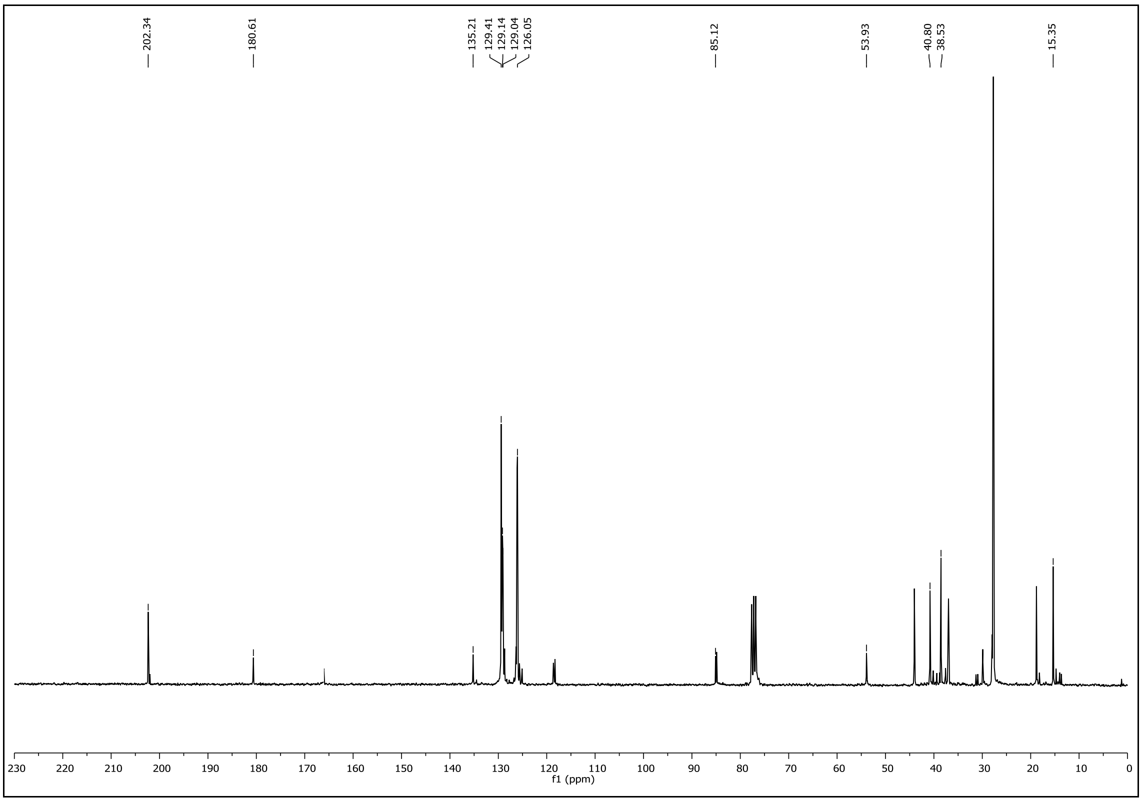

Br
O
MeO
NC
CO2tBu

25


3.77
3.00
4.34
9.96
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


9.62
9.61
7.56
7.55
7.55
7.54
7.53
7.53
7.52
7.44
7.42
7.42
7.41
7.41
7.40
7.39
7.39
7.38
7.38
7.37
3.01
2.99
2.96
2.94
2.64
2.63
2.62
2.61
2.61
2.60
2.59
2.59
2.58
2.57
2.57
2.01
2.00
1.97
1.95
1.41
1.12
1.10
O
H
NC
CO2tBu
23
0.83
1.56
2.48
1.00
0.83
1.07
8.81
3.50
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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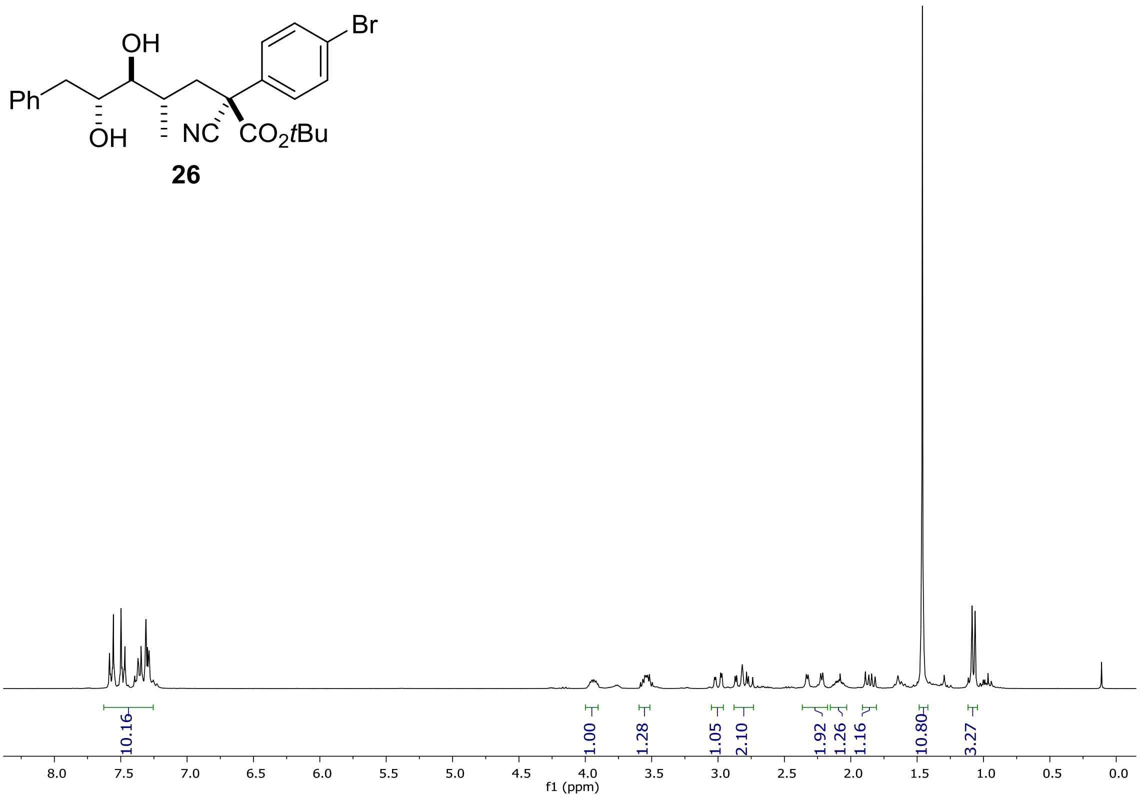
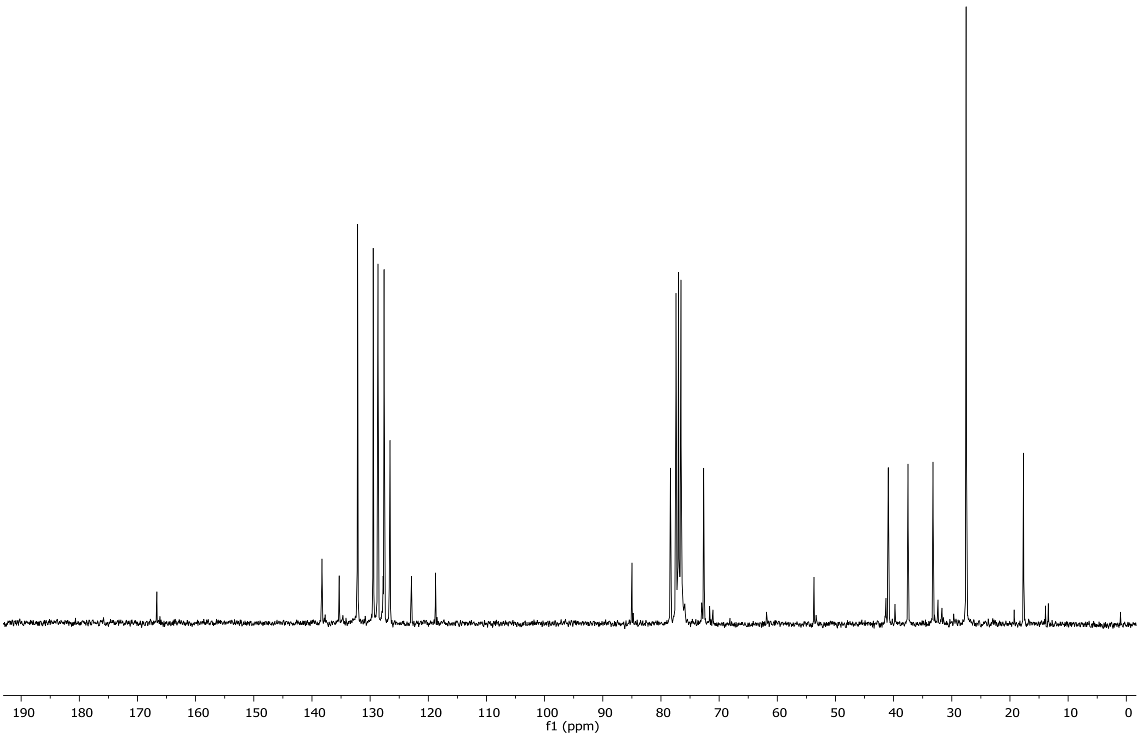
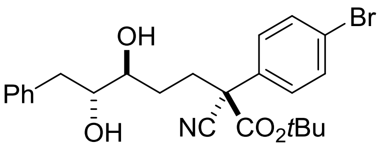
180.61
135.21
129.41
129.14
129.04
126.05
85.12
53.93
40.80
38.53
15.35
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

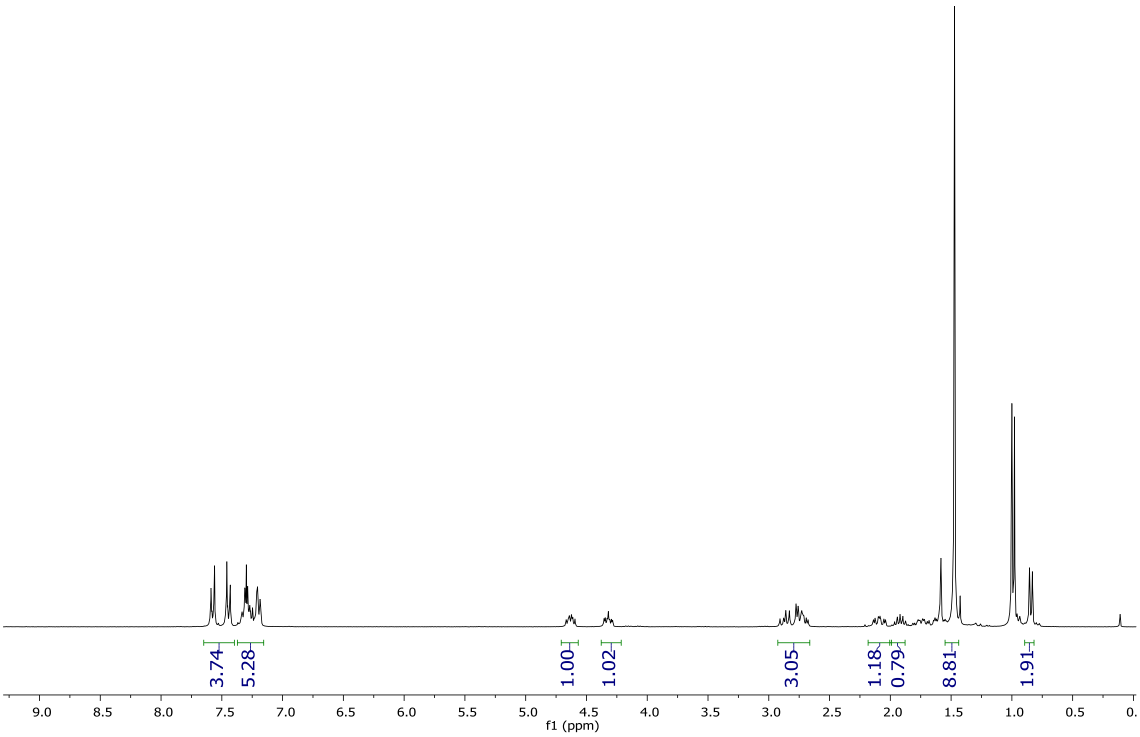

Br
OH
Ph
OH
NC
CO2tBu
10.16
1.00
1.28
1.05
2.10
1.92
1.26
1.16
10.80
3.27
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

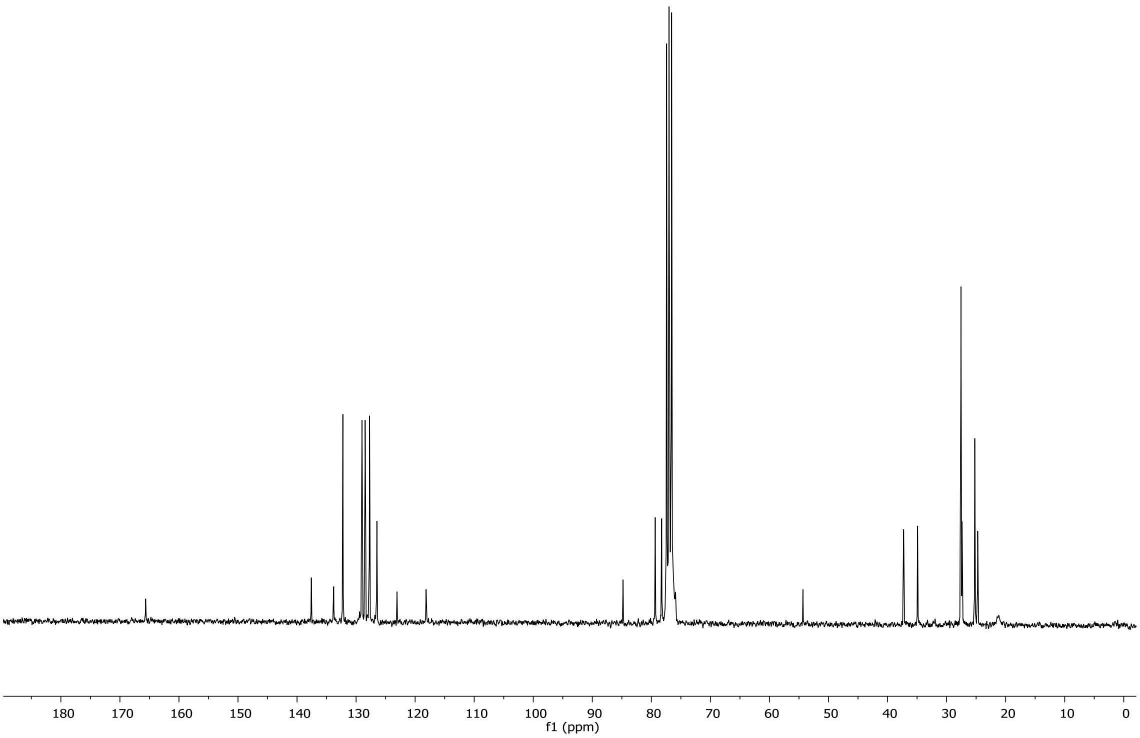
26


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OH
Br
Ph
OH
NC
CO2tBu

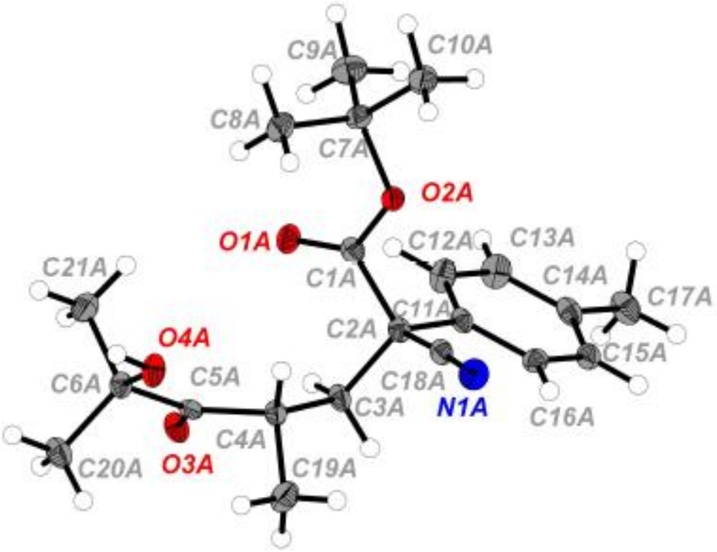
27

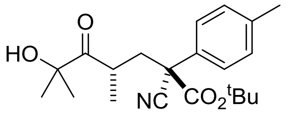

3.74
5.28
1.00
1.02
3.05
1.18
0.79
8.81
1.91
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

13. X-Ray Analysis: ORTEP diagram of compounds 5e.

CCDC-1470018 contains the supplementary crystallographic data for the structural analysis of **5e**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.





5e