Supporting Information

Enantioselective Synthesis of Oseltamivir Phosphate (Tamiflu) via the Iron-Catalyzed Stereoselective Olefin Diazidation

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A. General Information

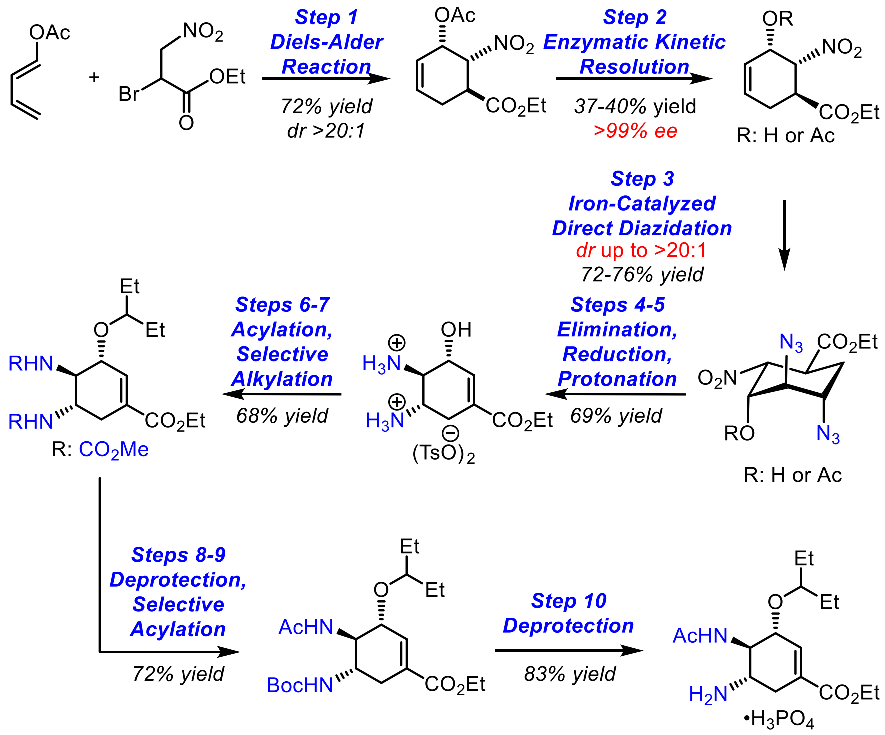
General Procedures. All reactions were performed in oven-dried or flame-dried round-bottom flasks and vials. Stainless steel syringes and cannula were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230−400 mesh) from Sigma−Aldrich.

Materials. Commercial reagents were purchased from Sigma−Aldrich, Fluka, EM Science, and Lancaster and used as received. All solvents were used after being freshly distilled unless otherwise noted.

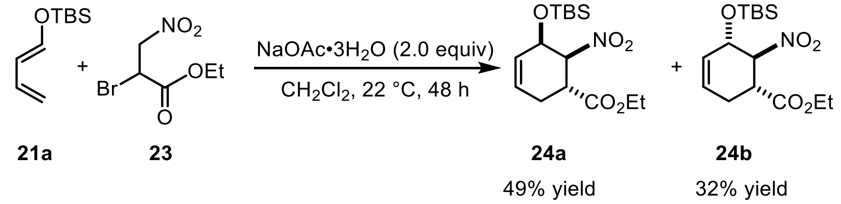
Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker UltraShield−400 (400 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak ($CHCl_3$ δ 7.26). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$ δ 77.0). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet), coupling constants in Hertz (Hz), and integration. The mass spectroscopic data were obtained at the Georgia State University mass spectrometry facility using a Micromass Platform II single quadrupole instrument. Infrared (IR) spectra were obtained using a Perkin Elmer Spectrum 100 FT-IR spectrometer. Data are represented as follows: frequency of absorption (cm^{-1}) and absorption strength (s = strong, m = medium, w = weak).

Abbreviations Used: THF–tetrahydrofuran, EtOAc–ethyl acetate, EtOH–ethanol, Et_2O–diethyl ether, CH_2Cl_2–dichloromethane, MeCN–acetonitrile, $TMSN_3$–trimethylsilyl azide, TEA–triethylamine, TFA–trifluoroacetic acid, TLC–thin layer chromatography, Boc_2O–di-*tert*-butyl dicarbonate, DMAP–4-dimethylaminopyridine, MsOH–methanesulfonic acid, TfOH–trifluoromethanesulfonic acid, Ph_3P–triphenylphosphine, $TsOH{\cdot}H_2O$–*p*-toluenesulfonic acid monohydrate.

B. Summary of the Overall Synthetic Scheme

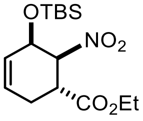


C. Enantioselective Synthesis of Highly Cyclic Allylic Alcohols for the Iron-Catalyzed Stereoselective Diazidation



(*E*)-(Buta-1,3-dien-1-yloxy)(*ter*t-butyl)dimethylsilane **21a** and ethyl 2-bromo-3-nitropropanoate **23** are prepared with known literature procedures.[1,2]

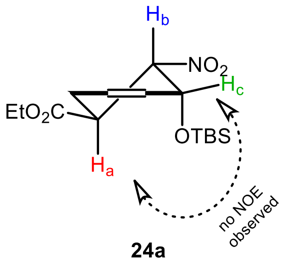
To an oven-dried 25 mL round bottom flask equipped with a stir bar was added finely ground NaOAc·3H$_2$O (1.81 g, 13.3 mmol, 2.0 equiv). The flask was evacuated and backfilled with N$_2$. Subsequently, anhydrous CH$_2$Cl$_2$ (10 mL), (*E*)-(buta-1,3-dien-1-yloxy)(*tert*-butyl)dimethylsilane **21a** (1.84 g, 10.0 mmol, 1.5 equiv) and ethyl 2-bromo-3-nitropropanoate **23** (1.5 g, 6.6 mmol, 1.0 equiv) were added. The reaction mixture was stirred at room temperature for 48 h until **23** was fully consumed (monitored by TLC). The reaction mixture was filtered and the solid was washed with CH$_2$Cl$_2$ (15 mL). The combined CH$_2$Cl$_2$ filtrate was washed with brine (15 mL) and dried over Na$_2$SO$_4$. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 100:1 to 10:1) to afford the **24a** as colorless oil (1.07 g, 49% yield) along with **24b** as colorless oil (0.7 g, 32% yield).



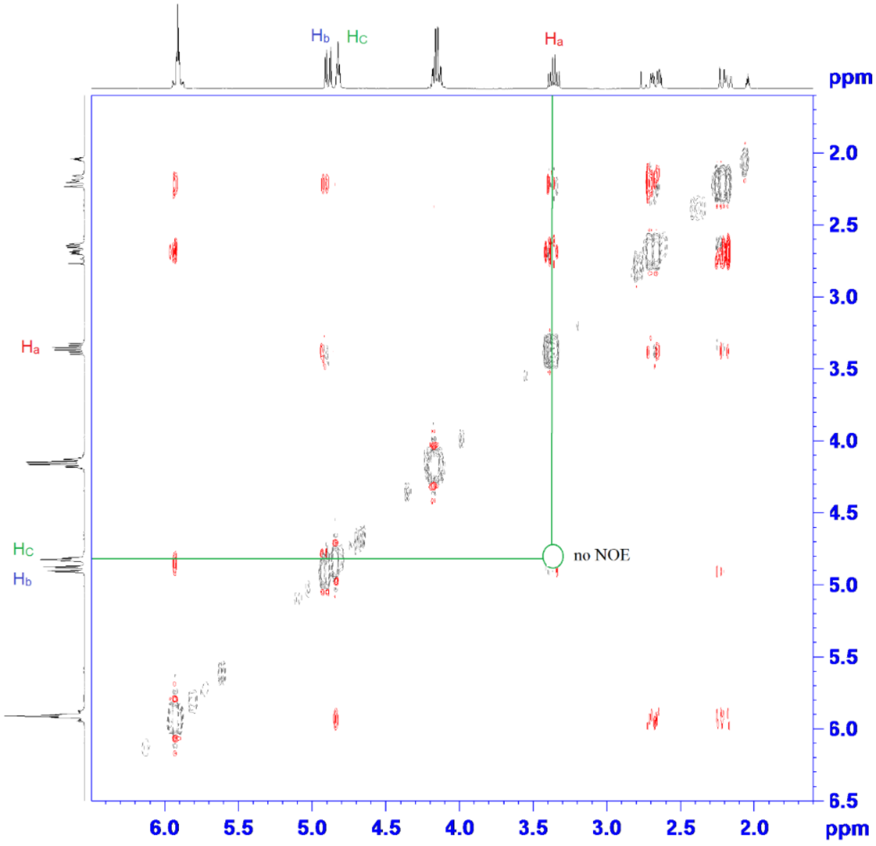
24a

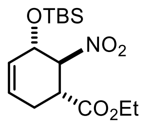
(±)-Ethyl (1*R*,5*R*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-6-nitrocyclohex-3-ene-1-carboxylate (24a): IR ν_{max} (neat)/cm^{-1}: 2958 (w), 2930 (w), 2891 (w), 2858 (w), 1734 (s), 1557 (s), 1473 (w), 1379 (m), 1297 (m), 1256 (s), 1184 (s), 1117 (s), 1086 (s), 1032 (m), 955 (s), 891 (m), 827 (s), 777 (s), 747 (m), 701 (m); ^{1}H NMR (400 MHz, acetone-*d*$_6$) δ 5.97–5.87 (m, 2H), 4.89 (dd, *J* = 11.8, 4.0 Hz, 1H), 4.82 (t, *J* = 3.9 Hz, 1H), 4.22–4.07 (m, 2H), 3.36 (td, *J* = 11.7, 6.0 Hz, 1H), 2.67 (ddd, *J* = 18.4, 6.0, 4.0 Hz, 1H), 2.27–2.11 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.83 (s, 9H), 0.09 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.7, 128.3, 126.3, 86.0, 65.5, 60.7, 37.3, 28.9, 25.1, 17.6, 13.5, -4.8, -6.2; LRMS (ESI, m/z): calcd for $C_{15}H_{27}NO_5SiNa^+$, [M + Na$^+$], 352.2, found 352.2.

The stereochemistry of **24a** was determined by *NOE* analysis: there is no *NOE* observed between H_a and H_c.

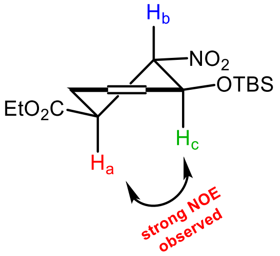


24a



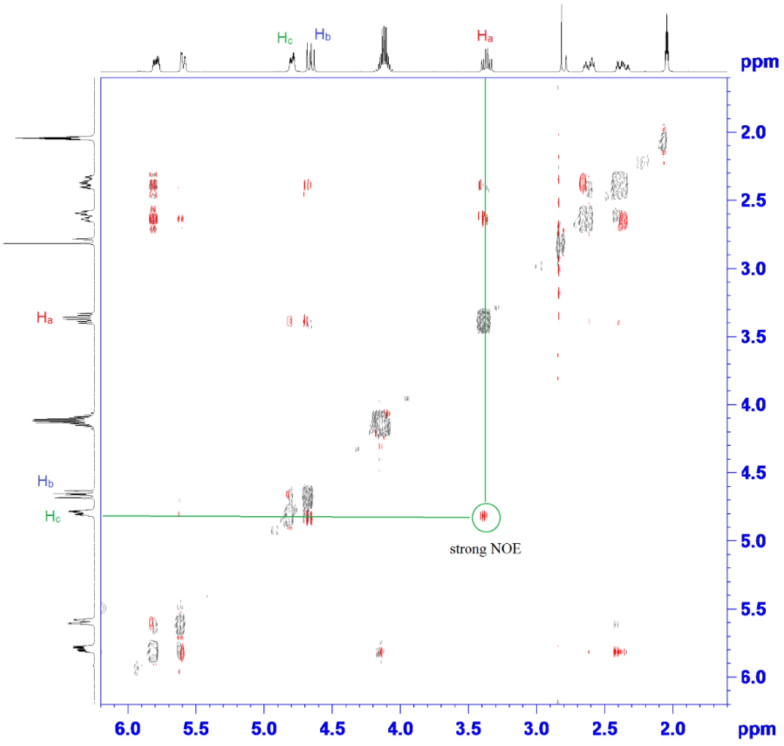


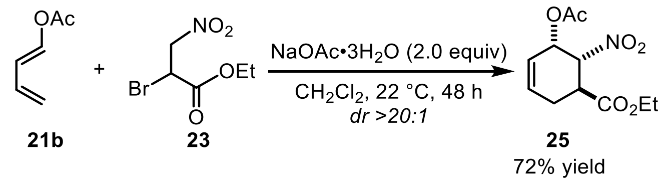
24b



(±)-Ethyl (1*R*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-6-nitrocyclohex-3-ene-1-carboxylate (24b): IR ν_{max} (neat)/cm^{-1}: IR ν_{max} (neat)/cm^{-1}: 2959 (w), 2931 (w), 2859 (w), 1737 (s), 1557 (s), 1387 (m), 1264 (s), 1239 (s), 1198 (m), 1101 (s), 1022 (m), 976 (m), 890 (m), 839 (s), 778 (s), 736 (s); ^{1}H NMR (400 MHz, acetone-d_6) δ 5.79 (dtd, *J* = 6.9, 4.6, 2.2 Hz, 1H), 5.62–5.56 (m, 1H), 4.83–4.77 (m, 1H), 4.66 (dd, *J* = 11.8, 8.6 Hz, 1H), 4.19–4.04 (m, 2H), 3.37 (td, *J* = 11.6, 6.0 Hz, 1H), 2.62 (dddd, *J* = 10.7, 6.4, 3.4, 1.6 Hz, 1H), 2.37 (dddd, *J* = 14.1, 11.4, 5.9, 2.7 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 170.5, 128.9, 125.9, 89.6, 71.3, 61.0, 42,4, 28.1, 25.1, 17.6, 13.4, -5.4, -6.2; LRMS (ESI, m/z): calcd for $C_{15}H_{27}NO_5SiNa^+$, [M + Na$^+$], 352.2, found 352.2.

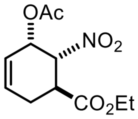
The stereochemistry of **24b** was determined by *NOE* analysis: there is a strong *NOE* observed between H_a and H_c.





(*E*)-Buta-1,3-dien-1-yl acetate **21b** was prepared through a known literature procedure.[3]

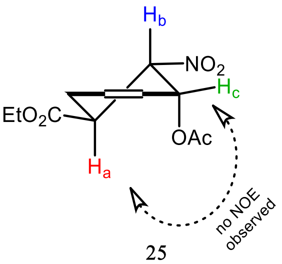
To an oven-dried 500 mL round bottom flask equipped with a stir bar was added finely ground $NaOAc\cdot3H_2O$ (43.1 g, 316.8 mmol, 2.0 equiv). The flask was evacuated and backfilled with N_2. Subsequently, anhydrous CH_2Cl_2 (244 mL), (*E*)-buta-1,3-dien-1-yl acetate **21b** (26.6 g, 237.6 mmol, 1.5 equiv) and ethyl 2-bromo-3-nitropropanoate **23** (35.8 g, 158.4 mmol, 1.0 equiv) were added. The reaction mixture was stirred at room temperature for 48 h until **23** was fully consumed (monitored by TLC). The reaction mixture was filtered and the solid was washed with CH_2Cl_2 (100 mL). The combined CH_2Cl_2 filtrate was washed with brine (100 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the crude product was recrystallized from ethanol (100 mL) to furnish the desired product **25** (29.3 g, 72%, *dr* >20:1, m.p. 75–76 ºC).



25

(±)-Ethyl (1*R*,5*R*,6*S*)-5-acetoxy-6-nitrocyclohex-3-ene-1-carboxylate (**25**): IR ν_{max} (neat)/cm^{-1}: 2979 (w), 1737 (s), 1559 (s), 1373 (m), 1226 (s), 1186 (s), 1027 (m), 924 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10–5.90 (m, 2H), 5.84–5.68 (m, 1H), 4.93 (dd, *J* = 12.1, 4.2 Hz, 1H), 4.32–4.12 (m, 2H), 3.45 (td, *J* = 11.8, 6.2 Hz, 1H), 2.80–2.66 (m, 1H), 2.33–2.19 (m, 1H), 1.99 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 169.4, 131.2, 122.6, 83.3, 65.8, 61.6, 38.0, 28.9, 20.6, 14.1; LRMS (ESI, m/z): calcd for $C_{11}H_{15}NO_6Na^+$, [M + Na$^+$], 280.1, found 280.1.

The stereochemistry of **25** was determined by *NOE* analysis: there is no *NOE* observed between H_a and H_c.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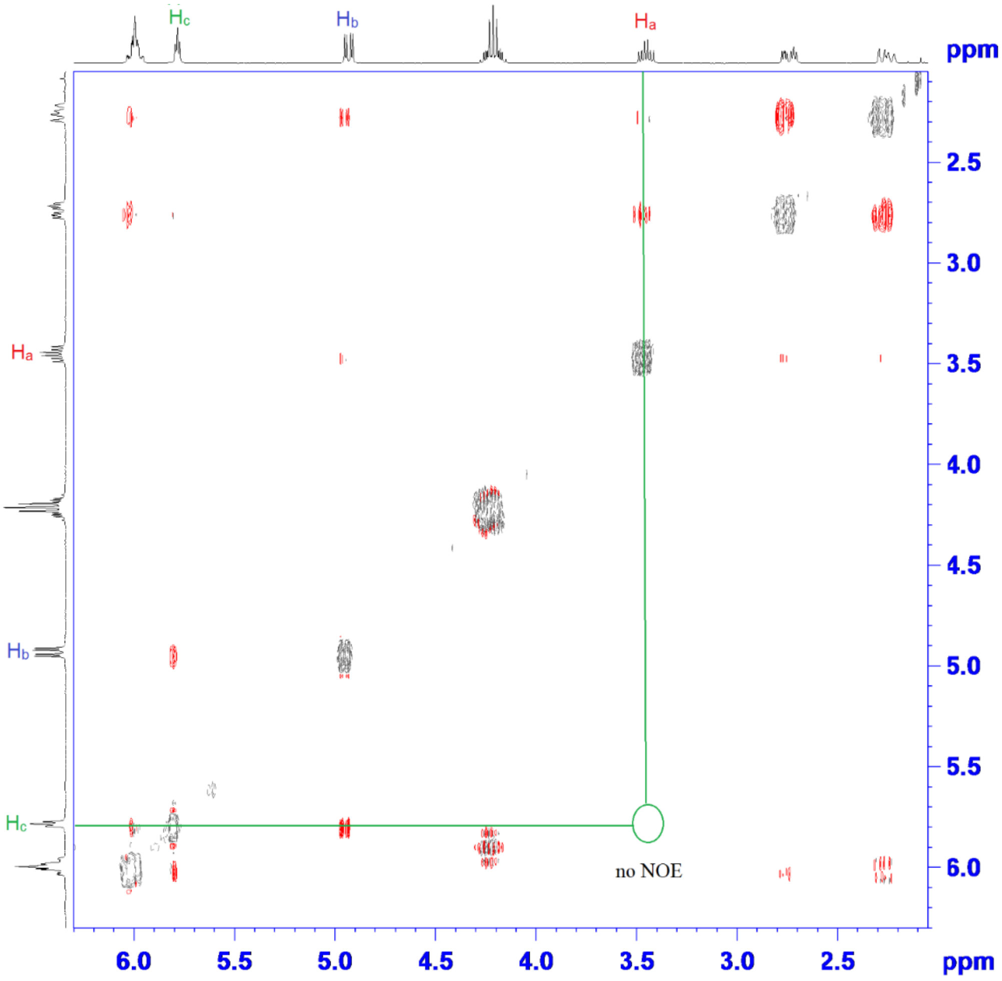
NO_2
H_c
EtO_2C
OAc
H_a
no NOE observed

25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H_b
H_a
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3.0
3.5
4.0
4.5
5.0
5.5
6.0
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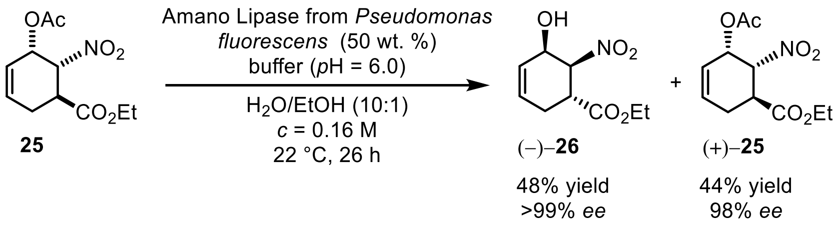
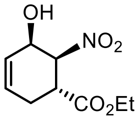
H_b
H_c
no NOE
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm

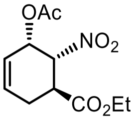


To a 100 mL round bottom flask were added Amano Lipase *from Pseudomonas fluorescens* (1.0 g, 50 wt. %), **25** (2.0 g, 7.8 mmol, 1.0 equiv), aqueous citric acid–Na_2HPO_4 buffer (44.2 mL, *p*H = 6.0, *c* = 0.037 M) and ethanol (4.4 mL). The mixture was stirred at room temperature for 26 h. EtOAc (30 mL) was added to dilute the reaction. The organic phase was separated from the aqueous phase and the aqueous phase was further extracted with EtOAc (30 mL×4). The combined organic phase was washed with brine (30 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 50:1 to 2:1) to afford the hydrolyzed product (–)–**26** as colorless oil (804 mg, 48% yield, >99% *ee*) along with the enantio-enriched starting material (+)–**25** (880 mg, 44% yield, 98% *ee*), which was further purified by recrystallization from ethanol (10 mL) to furnish the enantio-enriched starting material (+)–**25** as a white solid (800 mg, 40% yield, >99% *ee*, m.p. 75–76 ºC).



(–)–**26**

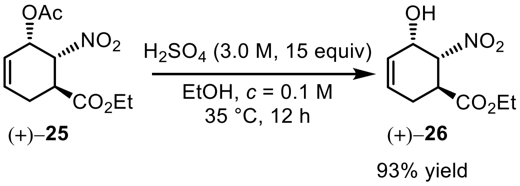
Ethyl (1*R*,5*R*,6*S*)-5-hydroxy-6-nitrocyclohex-3-ene-1-carboxylate ((–)–**26**): $[\alpha]_D^{20}$ = –294.5° (*c* 1.03, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 3442 (br), 2983 (w), 2930 (w), 1726 (s), 1551 (s), 1379 (m), 961 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 5.96–5.89 (m, 2H), 4.83 (dd, *J* = 11.6, 4.0 Hz, 1H), 4.81–4.76 (m, 1H), 4.27–4.14 (m, 2H), 3.38 (td, *J* = 11.5, 6.0 Hz, 1H), 2.67 (ddd, *J* = 18.4, 6.0, 3.9 Hz, 1H), 2.44 (d, *J* = 4.1 Hz, 1H), 2.27–2.14 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 129.5, 125.7, 86.1, 64.4, 61.5, 37.4, 29.0, 14.0; LRMS (ESI, m/z): calcd for $C_9H_{13}NO_5Na^+$, [M + Na$^+$], 238.1, found 238.1.



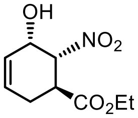
(+)–**25**

Ethyl (1*S*,5*S*,6*R*)-5-acetoxy-6-nitrocyclohex-3-ene-1-carboxylate ((+)–**25**): $[\alpha]_D^{20}$ = +363.1 ° (*c* 1.18, CHCl$_3$).

Note: (+)–**25** is unstable under the HPLC separation conditions; therefore, *ee* analysis was carried out after an additional step of acid hydrolysis.



To a 100 mL round bottom flask were added (+)–**25** (2.0 g, 7.8 mmol, 1.0 equiv), EtOH (39 mL) and H$_2$SO$_4$ (39 mL, 3.0 M, 116.7 mmol, 15 equiv). The mixture was stirred at 35 °C for 12 h. EtOAc (50 mL) was added to dilute the reaction. The organic phase was separated from the aqueous phase and the aqueous phase was further extracted with EtOAc (30 mL×3). The combined organic phase was washed with brine (50 mL) and dried over Na$_2$SO$_4$. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 50:1 to 2:1) to afford the hydrolyzed product (+)–**26** as colorless oil (1.56 g, 93% yield).



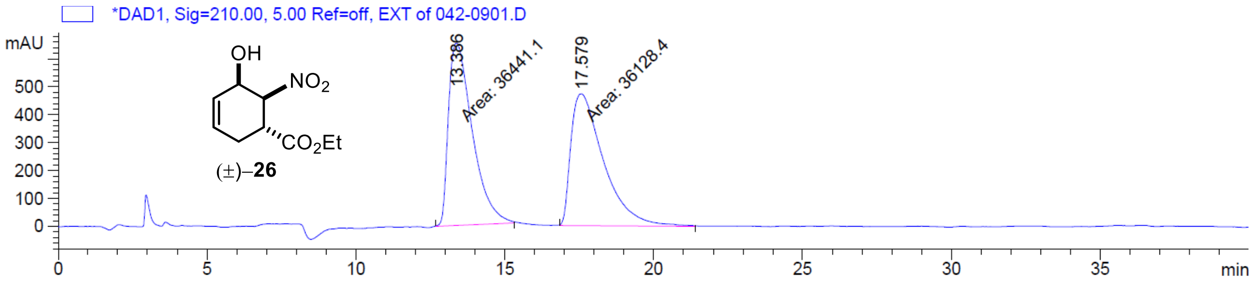
(+)–**26**

Ethyl (1*S*,5*S*,6*R*)-5-hydroxy-6-nitrocyclohex-3-ene-1-carboxylate ((+)–**26**): $[\alpha]_D^{20}$ = +294.5 ° (*c* 1.03, CHCl$_3$).

The *ee* of compounds (–)–**26** and (+)–**26** were determined by Chiral HPLC analysis (Chiral AD-H column, 10% isopropanol in hexanes, flow rate = 1.0 mL/min, UV detection at 210 nm). t_r

(compound (–)–**26**) = 13.4 min, >99% *ee*; t_r (compound (+)–**26**) =17.6 min, 98% *ee* or >99% *ee* (after recrystallization).

***Racemic sample* (±)–26**



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   2  17.579 MM    1.2739 3.61284e4   472.65869  49.7846

Totals :                  7.25695e4  1126.13037
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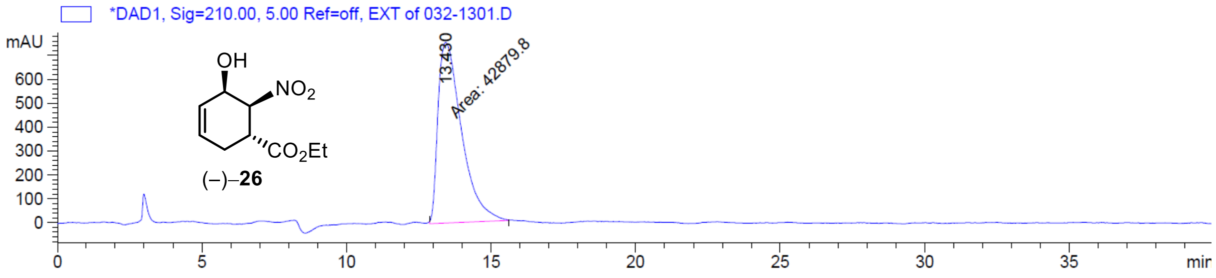
***Enantio-enriched sample* (–)–26 (>99% *ee*)**



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Totals :                  4.28798e4  757.81018
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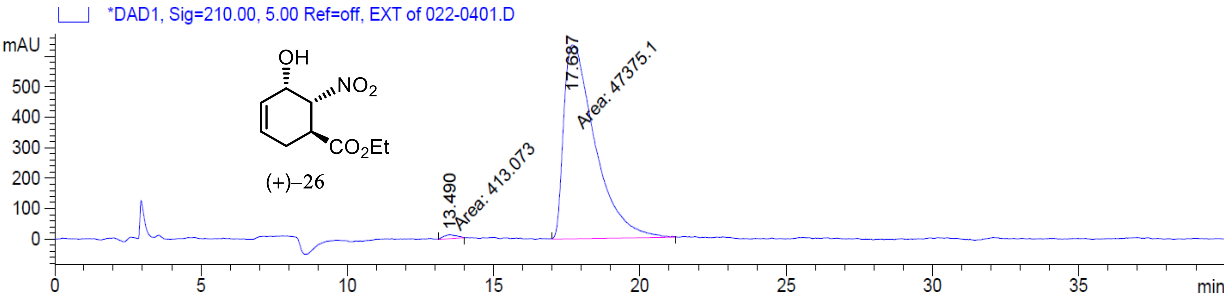
Enantio-enriched sample (+)–**26** (98% *ee*): hydrolysis product of (+)–**25** (98% *ee*) that is directly obtained after the kinetic resolution.



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Totals :                  4.77881e4  649.81106
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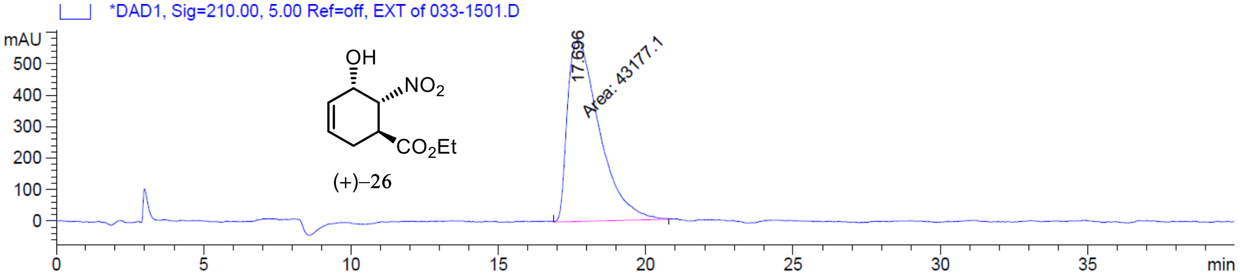
Enantio-enriched sample (+)–**26** (>99% *ee*): hydrolysis product of (+)–**25** (>99% *ee*) that is obtained after the recrystallization following the kinetic resolution.



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 Signal has been modified after loading from rawdata file!

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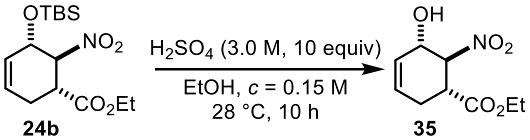
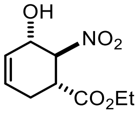


24b **35**

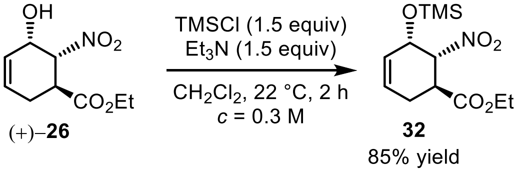
92% yield

To a 50 mL round bottom flask were added **24b** (659 mg, 2.0 mmol, 1.0 equiv) and EtOH (6.7 mL), then aqueous H_2SO_4 solution (6.7 mL, 3.0 M, 20.0 mmol, 10 equiv) was added. The mixture was stirred at 28 °C for 10 h. EtOAc (15 mL) was added to dilute the reaction. The organic phase was separated from the aqueous phase and the aqueous phase was further extracted with EtOAc (10 mL×3). The combined organic phase was washed with brine (20 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 50:1 to 3:1) to afford the hydrolyzed product **35** as colorless oil (396 mg, 92% yield).

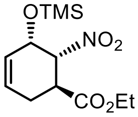


35

(±)-Ethyl (1*R*,5*S*,6*S*)-5-hydroxy-6-nitrocyclohex-3-ene-1-carboxylate (35): IR ν_{max} (neat)/cm^{-1}: 3456 (br), 1723 (s), 1550 (s), 1373 (m), 1297 (m), 1240 (s), 1186 (s), 1018 (s), 959 (m), 722 (m), 678 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.79 (dtd, *J* = 6.9, 4.5, 2.1 Hz, 1H), 5.66 (ddd, *J* = 10.0, 3.4, 2.2 Hz, 1H), 4.72 (dd, *J* = 11.4, 8.5 Hz, 1H), 4.69–4.60 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.29 (td, *J* = 11.3, 6.0 Hz, 1H), 3.17 (d, *J* = 6.0 Hz, 1H), 2.59 (dddd, *J* = 12.3, 6.3, 3.0, 1.4 Hz, 1H), 2.32 (dddd, *J* = 17.3, 11.2, 5.8, 2.8 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.1, 128.0, 126.4, 89.0, 69.9, 61.7, 42.0, 28.0, 13.8; LRMS (ESI, m/z): calcd for $C_9H_{13}NO_5Na^+$, [M + Na$^+$], 238.1, found 238.1.

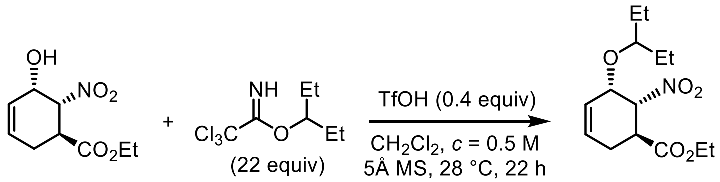


To a flame-dried 50 mL round bottom flask was added (+)–**26** (861 mg, 4.0 mmol, 1.0 equiv). After the flask was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (13 mL) was added via a syringe and the mixture was cooled down to 0 ºC. Subsequently, Trimethylsilyl chloride (0.76 mL, 6.0 mmol, 1.5 equiv) was added to the flask followed by Et_3N (0.83 mL, 6.0 mmol, 1.5 equiv). The reaction mixture was stirred at 22 ºC for 2 h until (+)–**26** was fully consumed (monitored by TLC). Saturated aqueous NH_4Cl solution (5 mL) was added to quench the reaction. The organic phase was separated from aqueous phase and the aqueous phase was further extracted with CH_2Cl_2 (10 mL×3). The combined organic phase was washed with brine (20 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 100:1 to 10:1) to afford the desired product **32** as colorless oil (977 mg, 85% yield).



32

Ethyl (1*S*,5*S*,6*R*)-6-nitro-5-((trimethylsilyl)oxy)cyclohex-3-ene-1-carboxylate (32): $[\alpha]_D^{20}$ = +298.3° (*c* 1.03, CHCl$_3$). IR ν_{max} (neat)/cm^{-1}: 2961 (w), 2113 (w), 1732 (s), 1556 (s), 1380 (s), 1298 (m), 1253 (s), 1184 (s), 1085 (s), 954 (s), 841 (s), 747 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 9.8, 4.8, 2.0 Hz, 1H), 5.81–5.73 (m, 1H), 4.79–4.71 (m, 2H), 4.26–4.10 (m, 2H), 3.53–3.37 (m, 1H), 2.70–2.61 (m, 1H), 2.23–2.09 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 128.1, 126.5, 86.1, 65.1, 61.2, 37.2, 29.1, 14.0, -0.1; LRMS (ESI, m/z): calcd for $C_{12}H_{21}NO_5SiNa^+$, [M + Na$^+$], 310.1, found 310.1.

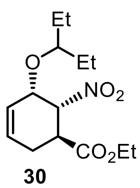


(+)–**26** **51** **30**

81% yield

Pentan-3-yl 2,2,2-trichloroacetimidate **51** was prepared through a known procedure.[4]

To an oven-dried 25 mL round bottom flask equipped with a stir bar were added (+)–**26** (430 mg, 2.0 mmol, 1.0 equiv) and 5 Å molecular sieves powder (500 mg). After the flask was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (4.0 mL) and freshly distilled pentan-3-yl 2,2,2-trichloroacetimidate **51** (7.7 mL, 44 mmol, 22 equiv) were added. The reaction was cooled to 0 °C and TfOH (71 μL, 0.8 mmol, 0.4 equiv) was added. After the addition of TfOH, the reaction mixture was warmed up to 28 ºC and stirred at this temperature for 22 h until (+)–**26** was fully consumed (monitored by TLC). The mixture was cooled to 0 ºC, and Et_3N (0.28 mL, 2.0 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added to quench the reaction. The mixture was filtered and the solid was washed with CH_2Cl_2 (10 mL×4). The filtrate was concentrated *in vacuo* and the residue was purified through column chromatography (hexanes/EtOAc: from 100:1 to 10:1) to afford the desired product **30** as colorless oil (462 mg, 81% yield).

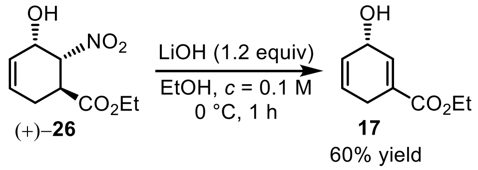


30

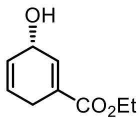
Ethyl (1*S*,5*S*,6*R*)-6-nitro-5-(pentan-3-yloxy)cyclohex-3-ene-1-carboxylate (30): $[\alpha]_D^{20}$ = +306.4° (*c* 1.02, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 2966 (w), 2936 (w), 2878 (w), 1733 (s), 1557 (s), 1463 (m), 1379 (s), 1298 (m), 1263 (m), 1184 (s), 1116 (m), 1077 (s), 1061 (s), 1032 (s), 978 (s), 913 (m), 731 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94–5.78 (m, 2H), 4.76 (dd, *J* = 12.0, 4.2 Hz, 1H), 4.47 (t, *J* = 4.4 Hz, 1H), 4.22–4.08 (m, 2H), 3.51–3.37 (m, 1H), 3.27–3.16 (m, 1H), 2.70–2.56 (m, 1H), 2.20–2.07 (m, 1H), 1.47–1.30 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.79 (t, *J* = 7.4 Hz, 3H), 0.73 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 128.6, 125.2, 85.0, 81.7, 69.2, 61.1, 37.5, 29.0, 26.3, 25.4, 13.9, 9.1, 9.0; LRMS (ESI, m/z): calcd for $C_{14}H_{23}NO_5Na^+$, [M + Na$^+$], 308.1, found 308.1.

D. Iron-Catalyzed Stereoselective Diazidation of Highly Functionalized Substrates for the Synthesis of 3·2TsOH

a. Initial Attempts for the Direct Diazidation of a Chiral 1,4-Cyclohexadiene 17

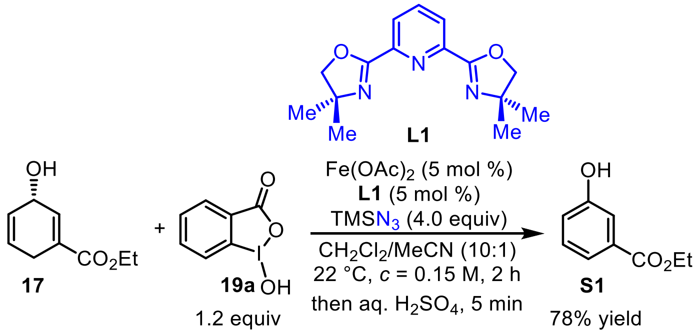


To a flame-dried 50 mL round bottom flask were added (+)–**26** (430 mg, 2.0 mmol, 1.0 equiv) and EtOH (20 mL). After the vial was moved to ice-bath, LiOH (58 mg, 2.4 mmol, 1.2 equiv) was added portion-wise and the mixture was stirred at 0 ºC for 1 h until the starting material was fully consumed (monitored by TLC). AcOH (23 μL, 0.4 mmol, 0.2 equiv) was added to quench the reaction. EtOH was removed *in vacuo*, and the residue was diluted with EtOAc (10 mL) and water (10 mL). The organic phase was separated from aqueous phase and the aqueous phase was further extracted with EtOAc (10 mL×2). The combined organic phase was dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 30:1 to 3:1) to afford the desired product **17** as colorless oil (202 mg, 60% yield).



17

Ethyl (*S*)-3-hydroxycyclohexa-1,4-diene-1-carboxylate (17): $[\alpha]_D^{20}$ = +10.2° (*c* 1.03, $CHCl_3$); IR ν_{max} (neat)/cm^{-1}: 3438 (br), 2985 (w), 1724 (s), 1541 (s), 1355 (m), 950 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (dq, *J* = 3.6, 1.8 Hz, 1H), 5.95 (dtd, *J* = 10.1, 3.3, 1.4 Hz, 1H), 5.89–5.83 (m, 1H), 4.75–4.68 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.97–2.89 (m, 1H), 2.80 (ddtd, *J* = 9.7, 5.1, 3.5, 1.9 Hz, 1H), 2.31 (br, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 136.6, 129.6, 126.5, 126.2, 62.7, 60.7, 25.9, 14.1; LRMS (ESI, m/z): calcd for $C_9H_{12}O_3Na^+$, [M + Na$^+$], 191.1, found 191.1.



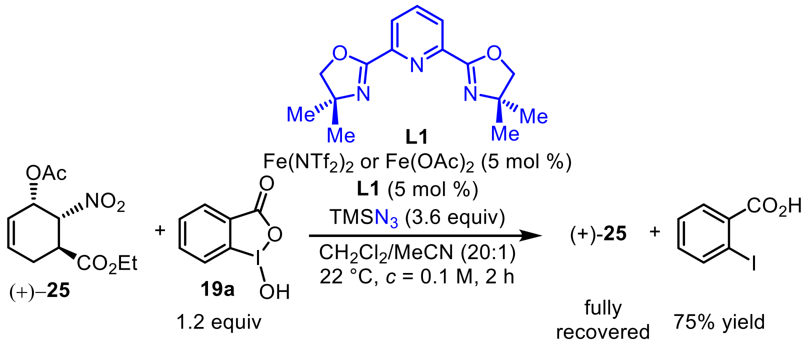
2,6-Bis(4,4-dimethyl-4,5-dihydrooxazol-2-yl)pyridine **L1** was prepared through a known procedure.[5]

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OAc)_2$ (5.2 mg, 0.03 mmol, 5 mol %) and the ligand **L1** (8.2 mg, 0.03 mmol, 5 mol %). After this vial was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (0.6 mL) and MeCN (0.4 mL) were added via syringes and the mixture was stirred at room temperature for 10 min. To a second flame-dried sealable 2-dram vial (vial **B**) equipped with a stir bar was added **17** (101 mg, 0.6 mmol, 1.0 equiv) and benziodoxole **19a** (190 mg, 0.72 mmol, 1.2 equiv). After this vial was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (3 mL), and freshly distilled $TMSN_3$ (315 μL, 2.4 mmol, 4.0 equiv) were added to vial **B** via syringes. After the reaction mixture was cooled to 0 °C, the catalyst solution in vial **A** was added to vial **B** drop-wise. Upon the completion of addition, the mixture was warmed up to room temperature and stirred for additional 2 h. The reaction was quenched with saturated $NaHCO_3$ solution (2 mL), and the organic phase was separated from the aqueous phase, which was further extracted with CH_2Cl_2 (2 mL×3), the combined organic layer was washed with aqueous H_2SO_4 (1 M, 3 mL), brine (3 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 30:1 to 5:1) to afford the product **S1** as a white solid (78 mg, 78% yield) which is a known compound.[6]

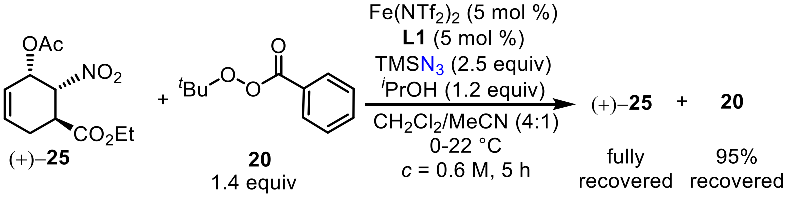
Safety Warning: Standard precautions with regard to handling $TMSN_3$ should be taken during the reaction. For safely handling $TMSN_3$, see the MSDS sheet at http://www.sigmaaldrich.com/catalog/product/aldrich/155071

Recent process safety accessement for the iron-catalyzed olefin diazidation demonstrated that most diazides (C/N ratio > 1.5) are thermally stable and they do not decompose until 200 °C;[7] however, they are moderately shock-sensitive: colorless diazides as liquid and foams turned dark-black after Drop Weight Test.[7] Therefore, mechanical impact should be minimized during product isolation and purification.

b. Initial Attempts for the Direct Diazidation of Highly Functionalized Cyclic Allylic Alcohols under the Standard Iron-Catalyzed Reaction Conditions



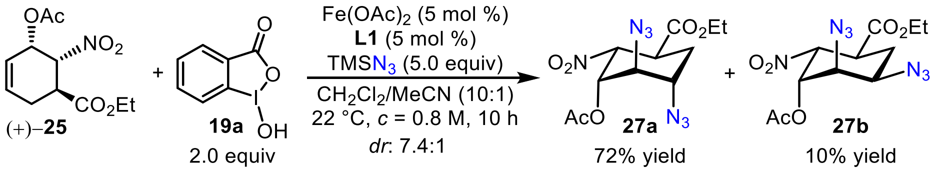
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(NTf_2)_2$ or $Fe(OAc)_2$ (0.02 mmol, 5 mol %) and **L1** (5.5 mg, 0.02 mmol, 5 mol %). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stir bar were added (+)**-25** (103 mg, 0.4 mmol, 1.0 equiv) and **19a** (127 mg, 0.48 mmol, 1.2 equiv). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (3.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. Freshly distilled $TMSN_3$ (189 μL, 1.44 mmol, 3.6 equiv) was added to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 2 h and TLC showed that no new spot was generated, then the reaction was quenched with saturated $NaHCO_3$ solution (0.5 mL) and further diluted with CH_2Cl_2 (5 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/EtOAc: from 100:1 to 3:1) to afford the starting material (+)**-25** (100 mg, >95% recovered) and 2-iodobenzoic acid (74 mg, 75% yield).



Note: Commercially available *tert*-butyl peroxybenzoate **20** (*Luperox® P*) is viscous liquid and it should be vigorously degassed (purging by N_2 for 15 min) and used as stock solution in CH_2Cl_2.

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(NTf_2)_2$ (31 mg, 0.05 mmol, 5 mol %) and **L1** (14 mg, 0.05 mmol, 5 mol %). After this vial was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (0.6 mL) and MeCN (0.3 mL) were added via syringes and the mixture was stirred at room temperature for 10 min. A second flame-dried sealable 3-dram vial (vial **B**) equipped with a stir bar was evacuated and backfilled with N_2 twice. *tert*-Butyl peroxybenzoate **20** (*Luperox® P*, 272 mg, 1.4 mmol, 1.4 equiv) in anhydrous CH_2Cl_2 (0.7 mL, *c* = 2.0 M) was added to vial **B**. Both solutions in vial **A** and vial **B** were degassed with brief evacuation and then backfilling with N_2. (+)-**25** (257 mg, 1.0 mmol, 1.0 equiv), ^{i}PrOH (92 μL, 1.2 mmol, 1.2 equiv) and freshly opened $TMSN_3$ (328 μL, 2.5 mmol, 2.5 equiv) were added to vial **B** at 0 °C. Subsequently, the catalyst solution in vial **A** was added to vial **B** using a syringe pump within 20 min. The reaction mixture was warmed up to 22 °C and kept stirring for 5 h and TLC showed that no new spot was generated. The reaction was quenched with saturated $NaHCO_3$ solution (2 mL), the organic phase was separated from the aqueous phase, which was further extracted with CH_2Cl_2 (2 mL×3), the combined organic layer was washed with brine (3 mL), and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography to afford the starting material (+)-**25** (249 mg, >95% recovered) and **20** (258 mg, >95% recovered).

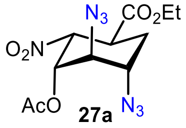
c. Reinvented Iron-Catalyzed Diazidation with Benziodoxole that is Effective for Highly Functionalized (+)–25



To a flame-dried 250 mL round bottom flask equipped with a stir bar were added $Fe(OAc)_2$ (169 mg, 0.97 mmol, 5 mol %), **L1** (265 mg, 0.97 mmol, 5 mol %), (+)–**25** (5.0 g, 19.44 mmol, 1.0 equiv) and benziodoxole **19a** (10.3 g, 38.9 mmol, 2.0 equiv). After the flask was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (20 mL) and MeCN (2.0 mL) were added via syringes and the mixture was stirred at room temperature for 10 min. Subsequently, freshly opened $TMSN_3$ (12.8 mL, 97.2 mmol, 5.0 equiv) was added to the flask at room temperature within 8 h using a syringe pump. The reaction mixture was stirred for additional 2 h until (+)–**25** was fully consumed (monitored by TLC). The reaction was carefully quenched with saturated $NaHCO_3$ solution (50 mL) to remove any residual hydrazoic acid and further diluted with Et_2O (160 mL), the resulting suspension was stirred vigorously for 10 min. The mixture was filtered and the solid was washed with Et_2O (20 mL×2). The combined filtrate was washed with saturated $NaHCO_3$ solution (100 mL), brine (100 mL) and dried over Na_2SO_4. The mixture was filtered through a silica gel pad (*ca.* 6 cm long × 6 cm diameter) and the pad was washed with ether (100 mL×3). After concentration *in vacuo*, the crude diazidation product **27a** and the other diastereomer **27b** were obtained as a yellow solid, which could be used in the next step without further purification. The crude yield and *dr* value were obtained by quantitative ^{1}H NMR experiment using 1,3,5-trimethylbenzene as an internal standard (85% NMR yield, *dr*: 7.4:1). For characterization purposes, the crude product was purified through column chromatography (hexanes/EtOAc: from 20:1 to 6:1) to afford the desired product **27a** as a white solid (4.78 g, 72% yield) along with the undesired diazidation product **27b** (0.66 g, 10% yield) as yellow oil.

Safety Warning: Standard precautions with regard to handling $TMSN_3$ should be taken during the reaction. For safely handling $TMSN_3$, see the MSDS sheet at http://www.sigmaaldrich.com/catalog/product/aldrich/155071

Recent process safety accessement for the iron-catalyzed olefin diazidation demonstrated that most diazides (C/N ratio > 1.5) are thermally stable and they do not decompose until 200 °C;[7] however, they are moderately shock-sensitive: colorless diazides as liquid and foams turned dark-black after Drop Weight Test.[7] Therefore, mechanical impact should be minimized during product isolation and purification.



27a

Ethyl (1*S*,2*R*,3*S*,4*R*,5*S*)-3-acetoxy-4,5-diazido-2-nitrocyclohexane-1-carboxylate (27a): $[\alpha]_D^{20}$ = –6.4° (*c* 1.13, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 2966 (w), 2098 (s), 1748 (s), 1727 (s), 1557 (s), 1383 (m), 1232 (s), 1189 (s), 1042 (m), 1024 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (dd, *J* = 6.8, 4.3 Hz, 1H), 5.23 (dd, *J* = 6.7, 4.3 Hz, 1H), 4.32–4.16 (m, 3H), 3.68 (q, *J* = 6.1 Hz, 1H), 3.46 (q, *J* = 6.4 Hz, 1H), 2.21 (t, *J* = 6.1 Hz, 2H), 2.12 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.4, 81.8, 69.6, 62.4, 60.9, 57.8, 39.0, 27.4, 20.5, 14.0; LRMS (ESI, m/z): calcd for $C_{11}H_{15}N_7O_6Na^+$, [M + Na$^+$], 364.1, found 364.1.

The stereochemistry of compound **27a** was determined by X-ray crystallographic analysis. (**Figure S1**)

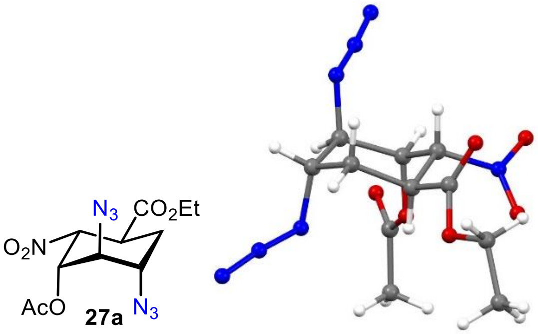
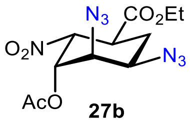


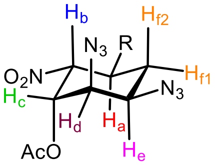
Figure S1. The X-ray Crystal Structure of ethyl (1*S*,2*R*,3*S*,4*R*,5*S*)-3-acetoxy-4,5-diazido-2-nitrocyclohexane-1-carboxylate **27a**



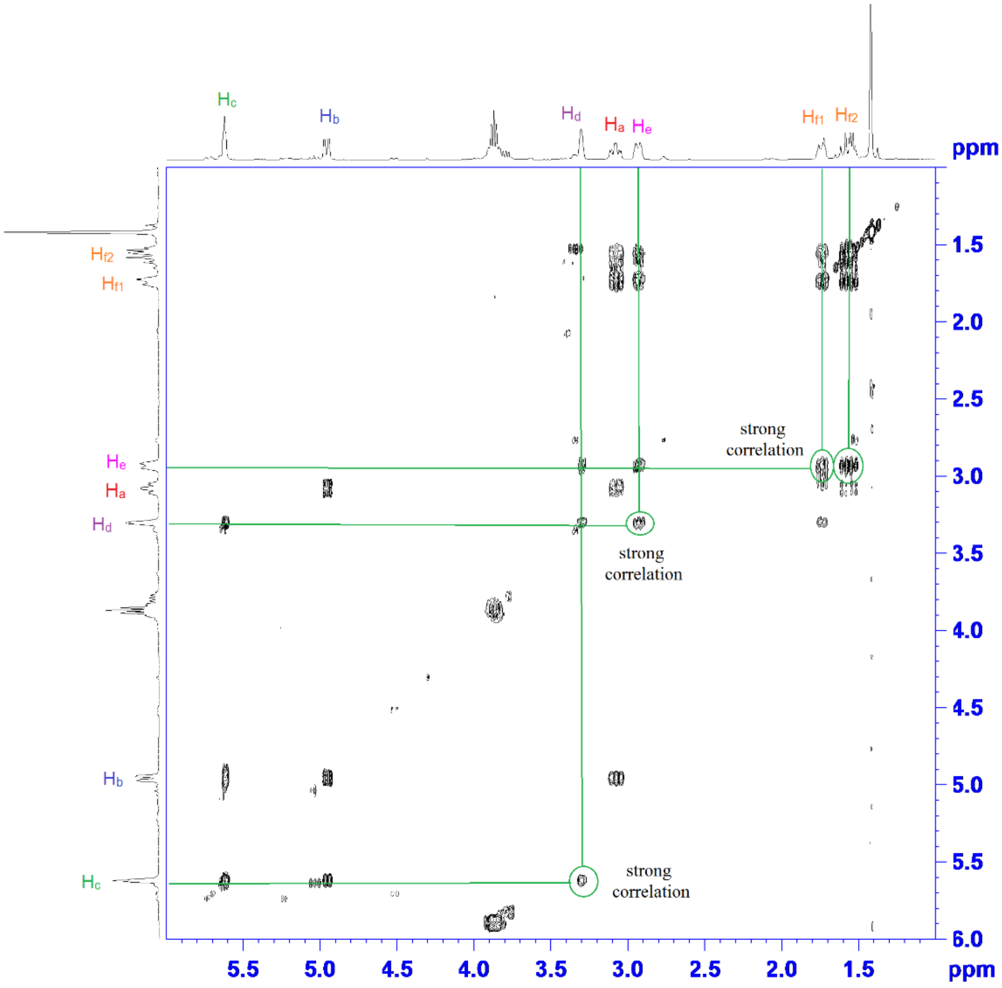
27b

Ethyl (1*S*,2*R*,3*S*,4*R*,5*R*)-3-acetoxy-4,5-diazido-2-nitrocyclohexane-1-carboxylate (27b): $[\alpha]_D^{20}$ = –12.4° (*c* 1.05, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 2967 (w), 2097 (s), 1746 (s), 1728 (s), 1557 (s), 1383 (m), 1232 (s), 1190 (s), 1045 (m), 1022 (m), 942 (m); ^{1}H NMR (400 MHz, benzene-*d*$_6$) δ 5.62 (t, *J* = 3.6 Hz, 1H), 4.96 (dd, *J* = 11.1, 2.7 Hz, 1H), 3.95–3.84 (m, 2H), 3.35–3.29 (m, 1H), 3.08 (td, *J* = 12.3, 4.3 Hz, 1H), 2.99–2.88 (m, 1H), 1.76–1.72 (m, 1H), 1.62–1.49 (m, 1H), 1.42 (s, 3H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, benzene-*d*$_6$) δ 170.2, 167.6, 80.7, 69.6, 61.5, 60.6, 56.5, 39.7, 26.2, 19.4, 13.6; LRMS (ESI, m/z): calcd for $C_{11}H_{15}N_7O_6Na^+$, [M + Na$^+$], 364.1, found 364.1.

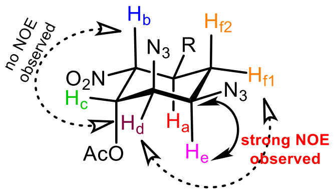
The full assignment of ^{1}H NMR of **27b** was carried out through ^{1}H–^{1}H COSY analysis: there are strong correlations between H_e and H_{f1}/H_{f2}, H_e and H_d, as well as H_d and H_c.



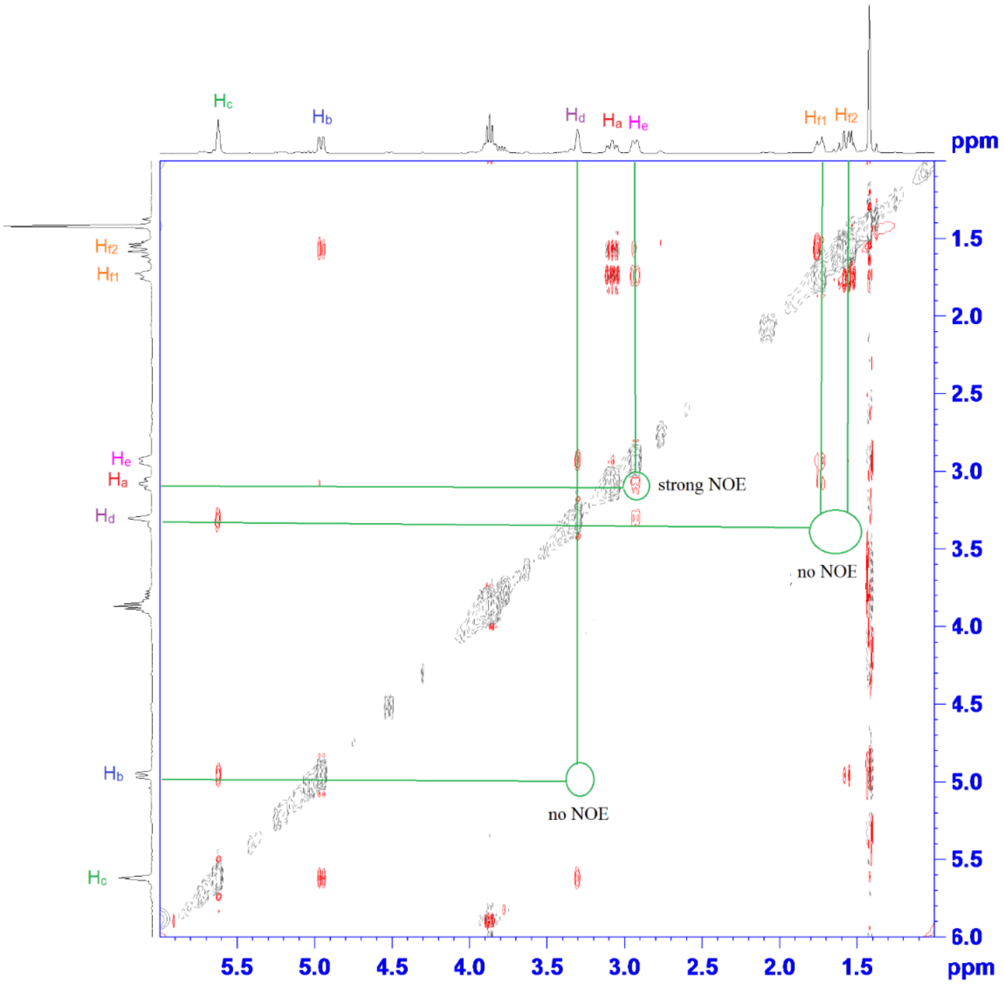
27b
R: CO_2Et

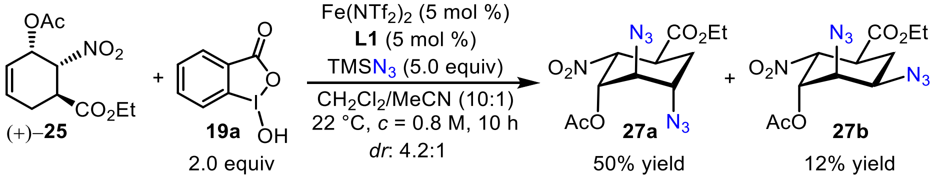


The stereochemistry of **27b** was determined by *NOE* analysis: there is a strong *NOE* between H_a and H_e; however, there is no *NOE* observed either between H_d and H_f, or between H_d and H_b.



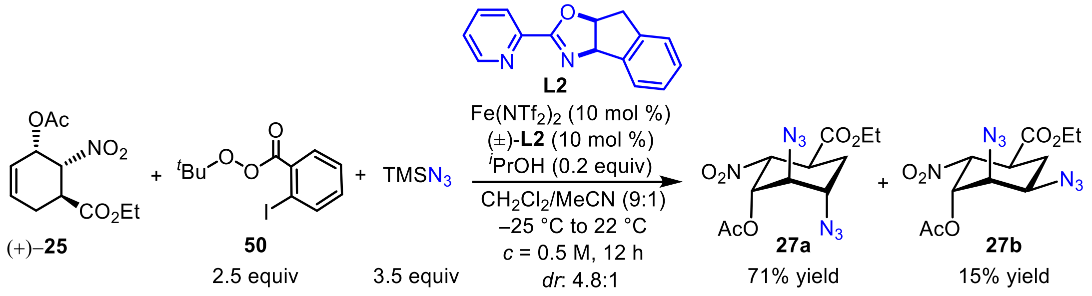
27b
R:CO_2Et





To a flame-dried sealable 2-dram vial equipped with a stir bar were added $Fe(NTf_2)_2$ (30.8 mg, 0.05 mmol, 5 mol %), **L1** (13.7 mg, 0.05 mmol, 5 mol %), (+)–**25** (257 mg, 1.0 mmol, 1.0 equiv) and benziodoxole **19a** (528 mg, 2.0 mmol, 2.0 equiv). After the flask was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (1.1 mL) and MeCN (0.11 mL) were added via syringes and the mixture was stirred at room temperature for 10 min. Subsequently, freshly opened TMSN$_3$ (656 μL, 5.0 mmol, 5.0 equiv) was added to the flask at room temperature within 8 h using a syringe pump. The reaction mixture was stirred for additional 2 h until (+)–**25** was fully consumed (monitored by TLC). The reaction was carefully quenched with saturated NaHCO$_3$ solution (3 mL) to remove any residual hydrazoic acid and further diluted with Et$_2$O (8 mL), the resulting suspension was stirred vigorously for 10 min. The mixture was filtered and the solid was washed with Et$_2$O (5 mL×2). The combined filtrate was washed with saturated NaHCO$_3$ solution (10 mL), brine (10 mL) and dried over Na$_2$SO$_4$. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 100:1 to 10:1) to afford the desired diazidation product **27a** as white foam (171 mg, 50% yield) along with the other diastereomer **27b** as colorless oil (41 mg, 12% yield).

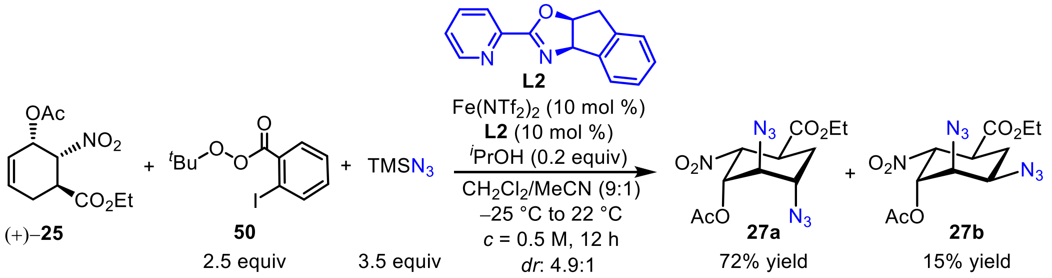
d. Reinvented Iron-Catalyzed Diazidation with Peroxyesters that is Effective for Highly Functionalized (+)–25

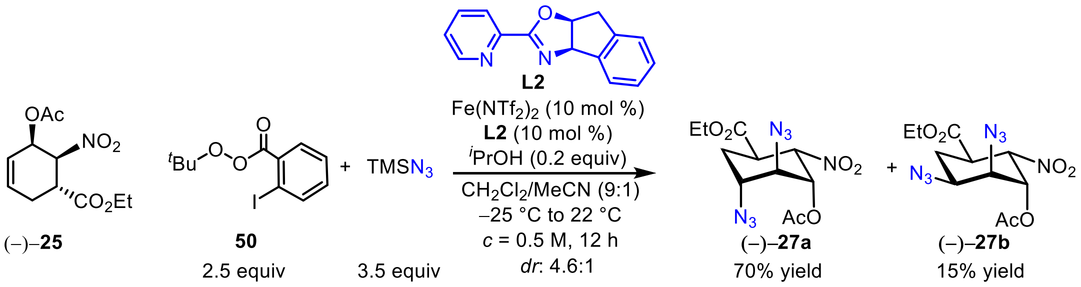


tert-Butyl 2-iodobenzoperoxoate **50** and **L2** were prepared through a known procedure.[8]

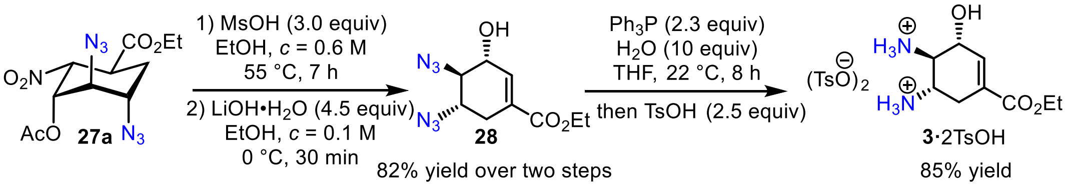
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added Fe(NTf$_2$)$_2$ (62 mg, 0.1 mmol, 10 mol %) and ligand (±)-**L2** (24 mg, 0.1 mmol, 10 mol %). After this vial was evacuated and backfilled with N$_2$ twice, anhydrous CH$_2$Cl$_2$ (0.6 mL) and MeCN (0.2 mL) were added via syringes and the mixture was stirred at room temperature for 10 min. To a second flame-dried sealable 2-dram vial (vial **B**) equipped with a stir bar was added (+)–**25** (257 mg, 1.0 mmol, 1.0 equiv) and *tert*-butyl 2-iodobenzoperoxoate **50** (800 mg, 2.5 mmol, 2.5 equiv). After this vial was evacuated and backfilled with N$_2$ twice, anhydrous CH$_2$Cl$_2$ (1.2 mL), isopropanol (15 μL, 0.2 mmol, 0.2 equiv) and freshly distilled TMSN$_3$ (460 μL, 3.5 mmol, 3.5 equiv) were added to vial **B** via syringes. After the reaction mixture was cooled to –25 °C, the catalyst solution in vial **A** was added to vial **B** using a syringe pump within 0.5 h. Then the reaction mixture was warmed up to 22 °C and kept stirring for 12 h. CH$_2$Cl$_2$ (4 mL) and saturated NaHCO$_3$ solution (3 mL) were added to quench the reaction and to remove any residual hydrazoic acid. The organic phase was separated from the aqueous phase, and it was washed with saturated Na$_2$CO$_3$ solution (2 mL), brine (2 mL), and dried over Na$_2$SO$_4$. After concentration *in vacuo*, the *dr* was obtained by quantitative ^{1}H NMR experiment using 1,3,5-trimethylbenzene as an internal standard (88% NMR yield, *dr*: 4.8:1). The crude product was purified through column chromatography (hexanes/EtOAc: from 20:1 to 6:1) to afford the desired pure product **27a** as white foam (243 mg, 71% yield) along with the other diastereomer **27b** as yellow oil (51 mg, 15% yield).

Note: no significant match/mismatch effect was observed when (+)–**25** and (–)–**25** were used during the iron-catalyzed diazidation using chiral ligand **L2**.

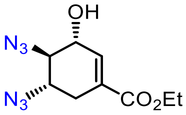




e. Synthesis of 3·2TsOH from the Olefin Diazidation Product



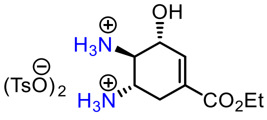
To an oven-dried 250 mL round bottom flask was added the diazidation product **27a** (4.9 g, 14.4 mmol, 1.0 equiv). After the flask was evacuated and backfilled with N_2 twice, EtOH (24 mL) and methanesulfonic acid (2.81 mL, 43.2 mmol, 3.0 equiv) were added via syringes. The mixture was warmed up to 55 ºC and stirred at this temperature for 7 h until the starting material was fully consumed (monitored by TLC). The reaction mixture was moved to ice-bath and diluted with EtOH (120 mL). Subsequently, $LiOH·H_2O$ (2.72 g, 64.8 mmol, 4.5 equiv) was added portion-wise and the mixture was stirred at 0 ºC for additional 30 min until the intermediate was consumed (monitored by NMR). AcOH (1.24 mL, 21.6 mmol, 1.5 equiv) was added to quench the reaction. EtOH was removed *in vacuo*, and the residue was diluted with EtOAc (50 mL) and water. The organic phase was separated from aqueous phase and the aqueous phase was further extracted with EtOAc (50 mL×2). The combined organic phase was dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 30:1 to 3:1) to afford the desired product **28** as yellow oil (2.99 g, 82% yield over two steps).



28

Ethyl (3*R*,4*R*,5*S*)-4,5-diazido-3-hydroxycyclohex-1-ene-1-carboxylate (28): $[\alpha]_D^{20}$ = –102° (*c* 0.75, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 3435 (br), 2981 (w), 2103 (s), 1704 (m), 1656 (w), 1250 (s), 1089 (m), 1043 (m), 981 (w); ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (s, 1H), 4.33–4.28 (m, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.60 (td, *J* = 10.2, 5.9 Hz, 1H), 3.48–3.40 (m, 1H), 2.93 (dd, *J* = 18.1, 5.8 Hz, 1H), 2.58–2.57 (m, 1H), 2.39–2.29 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 137.8, 128.5, 70.8, 68.2, 61.5, 59.6, 30.1, 14.1; LRMS (ESI, m/z): calcd for $C_9H_{12}N_6O_3Na^+$, [M + Na$^+$], 275.1, found 275.1.

To a 100 mL round bottom flask with a stir bar was added **28** (2.99 g, 11.9 mmol, 1.0 equiv). After the flask was evacuated and backfilled with N_2 twice, THF (50 mL) and H_2O (2.1 mL, 118.6 mmol, 10 equiv) were added via syringes. Subsequently, Ph_3P (7.15 g, 27.3 mmol, 2.3 equiv) in THF (20 mL) was added drop-wise to the reaction at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 8 h (monitored by IR until the absorption of azido groups disappeared). The mixture was then concentrated *in vacuo* and the residue was further dissolved in Et_2O (30 mL). This solution was added drop-wise to another solution of TsOH·H_2O (5.6 g, 29.7 mmol, 2.5 equiv) in Et_2O (60 mL). The reaction was kept stirring for 1 h and the white precipitate was collected by filtration, washed with Et_2O (10 mL×3) and dried *in vacuo*. The diaminium product **3**·2TsOH was obtained as a white solid (5.5 g, 85% yield, m.p. 220–222 ºC).



3·2TsOH

Ethyl (3*R*,4*R*,5*S*)-4,5-diamino-3-hydroxycyclohex-1-ene-1-carboxylate (**3·2TsOH**): $[\alpha]_D^{20}$ = +2.1° (*c* 1.05, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 3328 (br), 2861 (br), 1721 (m), 1536 (m), 1250 (m), 1195 (s), 1162 (s), 1123 (s), 1034 (s), 1009 (s), 808 (s), 684 (s); ^1H NMR (400 MHz, D_2O) δ 7.56 (d, *J* = 8.1 Hz, 4H), 7.24 (d, *J* = 8.0 Hz, 4H), 6.74 (s, 1H), 4.45 (d, *J* = 6.5 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.79 (td, *J* = 9.4, 6.0 Hz, 1H), 3.44 (dd, *J* = 10.0, 8.2 Hz, 1H), 2.86 (dd, *J* = 17.9, 5.9 Hz, 1H), 2.49 (dd, *J* = 18.0, 8.8 Hz, 1H), 2.27 (s, 6H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, D_2O) δ 166.8, 142.5, 139.4, 137.0, 129.4, 127.3, 125.3, 66.6, 62.5, 53.9, 46.7, 27.4, 20.5, 13.2; LRMS (ESI, m/z): calcd for $C_9H_{17}N_2O_3^+$, [M – 2TsOH + H^+], 201.1, found 201.1.

E. Safety Assessment of the Olefin Diazidation Product Using Differential Scanning Calorimetry (DSC) and Drop Weight Test (DWT)

a. Differential Scanning Calorimetry (DSC)

The DSC measurements were performed in a Mettler 821e using 40 µL aluminum punctured crucibles under nitrogen atmosphere or 60 µL high pressure (gold-plated) steel crucibles under air atmosphere. All measurements were carried out at a heating rate of 5 K/min.

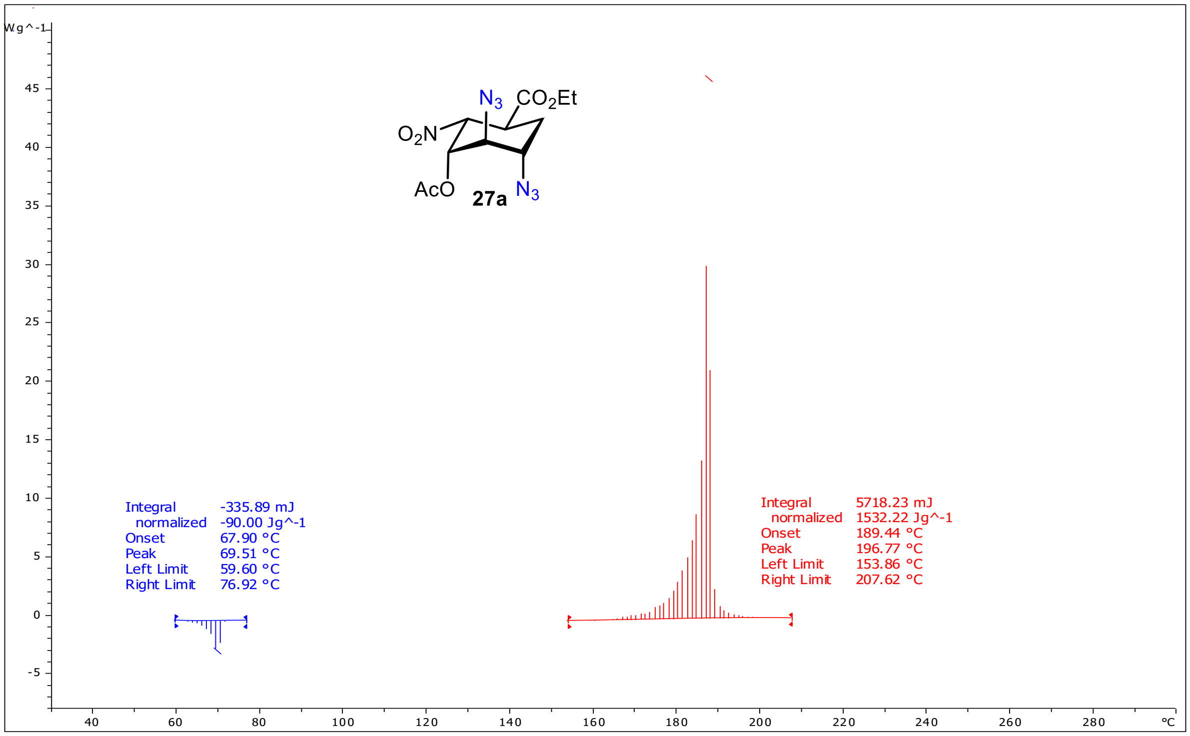


Figure S2. DSC Heating Curve of Diazide **27a** in Aluminum Pan

The diazide **27a** is stable towards the DSC (heating rate = 5K/min) under 160 °C. It melts around 69 °C and starts to decompose at 189 °C.

Given the high energy released above 189 °C, careful handling of **27a** at room temperature is strongly recommended.

b. Mechanical Impact Sensitivity

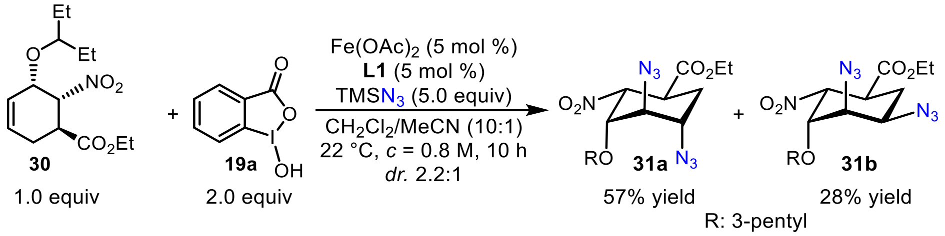
The Fall Hammer Test (Drop Hammer) designed to determine the sensitivity of potentially high explosive compounds was carried out in accordance to the UN Recommendation on the Transport of Dangerous Goods, Manual of Tests and Criteria–Test 3 (a) (ii) as well as EN 13631–4.

The limiting impact energy is determined as the lowest energy at which a flash, flame, or explosion is observed. The test is used to assess the sensitivity of the test material to drop-weight impact.

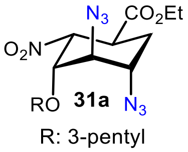
The determination of the sensitivity to impact stimuli is one of the most important characteristics of energetic materials such as the diazides, which can be heat and shock-sensitive and can explosively decompose with little input of external energy. This determination is necessary to evaluate their safety in handling, processing or transportation. The tested substances were analyzed by dropping 5 Kg from 0.80 m height, i.e., 400 Kg×cm (40 Newton).

The diazide **27a** is stable towards DWT, while the colorless crystalline solid turns to white powder.

F. Substrate Structure–Diazidation Stereoselectivity Relationship Studies

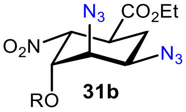


To a flame-dried sealable 2-dram vial equipped with a stir bar were added $Fe(OAc)_2$ (8.7 mg, 0.05 mmol, 5 mol %), **L1** (13.7 mg, 0.05 mmol, 5 mol %), **30** (285 mg, 1.0 mmol, 1.0 equiv) and benziodoxole **19a** (528 mg, 2.0 mmol, 2.0 equiv). After the flask was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (1.1 mL) and MeCN (0.11 mL) were added via syringes and the mixture was stirred at room temperature for 10 min. Subsequently, freshly opened $TMSN_3$ (656 μL, 5.0 mmol, 5.0 equiv) was added to the flask at room temperature within 8 h using a syringe pump. The reaction mixture was stirred for additional 2 h until **30** was fully consumed (monitored by TLC). The reaction was carefully quenched with saturated $NaHCO_3$ solution (3 mL) to remove any residual hydrazoic acid and further diluted with Et_2O (8 mL), the resulting suspension was stirred vigorously for 10 min. The mixture was filtered and the solid was washed with Et_2O (5 mL×2). The combined filtrate was washed with saturated $NaHCO_3$ solution (10 mL), brine (10 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the *dr* was obtained by quantitative ^1H NMR experiment using 1,3,5-trimethylbenzene as an internal standard (87% NMR yield, *dr*: 2.2:1). The crude product was purified through column chromatography (hexanes/EtOAc: from 100:1 to 10:1) to afford the desired diazidation product **31a** as colorless oil (211 mg, 57% yield) along with the other diastereomer **31b** as colorless oil (103 mg, 28% yield).



Ethyl (1*S*,2*R*,3*S*,4*R*,5*S*)-4,5-diazido-2-nitro-3-(pentan-3-yloxy)cyclohexane-1-carboxylate (31a): $[\alpha]_D^{20} = +4.3°$ (*c* 1.20, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 2970 (w), 2941 (w), 2881 (w), 2105 (s), 1731 (s), 1558 (s), 1448 (m), 1375 (m), 1264 (s), 1191 (s), 1094 (s), 1020 (m), 736 (s); ^1H

NMR (400 MHz, $CDCl_3$) δ 5.17 (dd, *J* = 5.6, 4.4 Hz, 1H), 4.28–4.18 (m, 2H), 4.06 (t, *J* = 7.2 Hz, 1H), 3.98 (dd, *J* = 7.1, 4.3 Hz, 1H), 3.46 (dd, *J* = 13.2, 7.0 Hz, 1H), 3.42–3.32 (m, 2H), 2.23–2.13 (m, 2H), 1.66–1.54 (m, 2H), 1.53–1.41 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 83.3, 82.8, 74.1, 63.4, 62.2, 58.1, 39.3, 27.4, 25.1, 24.9, 14.0, 8.9, 8.8; LRMS (ESI, m/z): calcd for $C_{14}H_{23}N_7O_5Na^+$, [M + Na^+], 392.2, found 392.2.

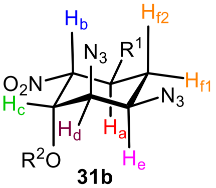


31b

R: 3-pentyl

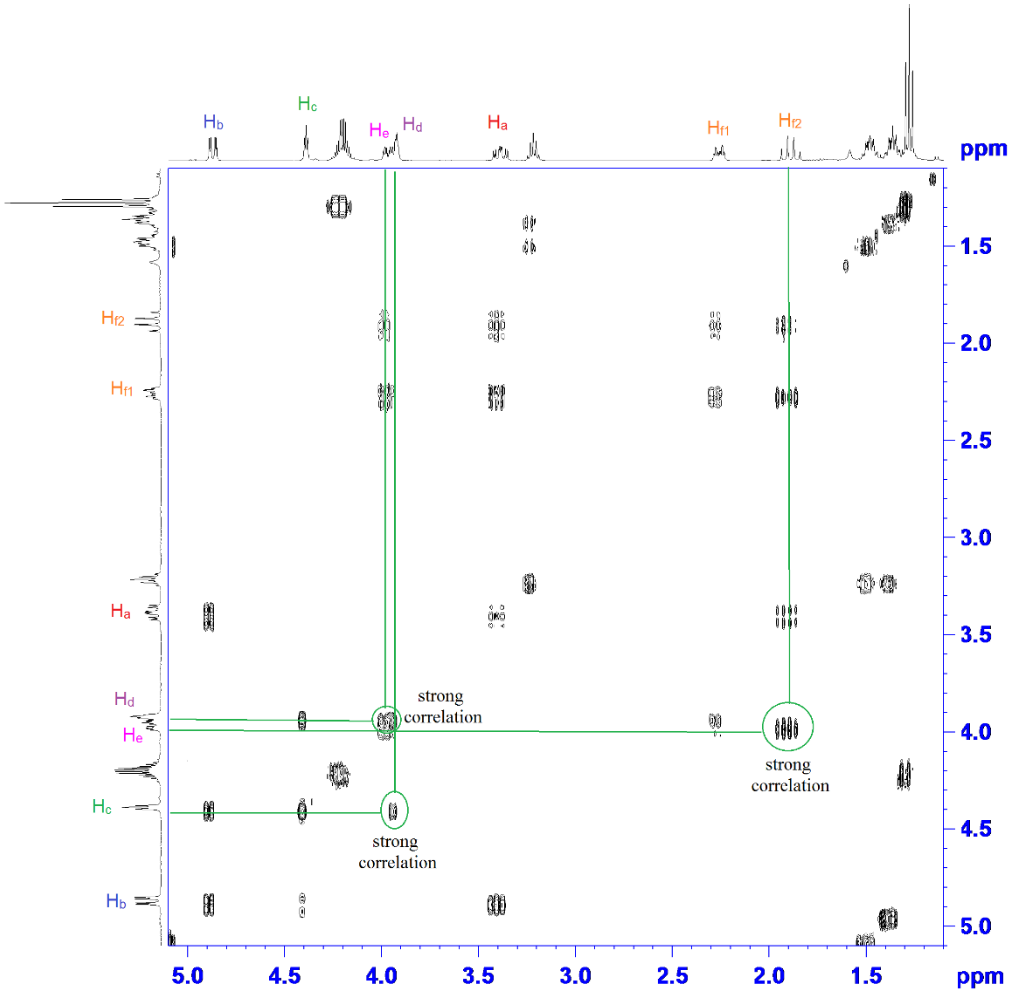
Ethyl (1*S*,2*R*,3*S*,4*R*,5*R*)-4,5-diazido-2-nitro-3-(pentan-3-yloxy)cyclohexane-1-carboxylate (31b): $[\alpha]_D^{20}$ = –45.1° (*c* 1.13, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 2971 (w), 2937 (w), 2879 (w), 2105 (s), 1733 (s), 1558 (s), 1462 (m), 1377 (m), 1293 (m), 1266 (s), 1248 (s), 1186 (s), 1093 (s), 991 (m), 737 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 4.87 (dd, *J* = 11.5, 3.1 Hz, 1H), 4.39 (t, *J* = 3.6 Hz, 1H), 4.27–4.12 (m, 2H), 4.00–3.94 (m, 1H), 3.93–3.91 (m, 1H), 3.39 (ddd, *J* = 13.2, 11.5, 4.3 Hz, 1H), 3.22 (quint, *J* = 5.7 Hz, 1H), 2.26 (dtd, *J* = 12.8, 4.3, 1.3 Hz, 1H), 1.94–1.84 (m, 1H), 1.53–1.42 (m, 2H), 1.41–1.32 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.74 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 83.5, 82.0, 75.4, 62.4, 61.7, 56.7, 39.2, 26.5, 25.8, 24.9, 14.0, 9.6, 8.7; LRMS (ESI, m/z): calcd for $C_{14}H_{23}N_7O_5Na^+$, [M + Na^+], 392.2, found 392.2.

The full assignment of ^1H NMR of **31b** was carried out through ^1H–^1H COSY NMR analysis: there are strong correlations between H_e and H_{f2}, H_e and H_d, as well as H_d and H_c. (See below)

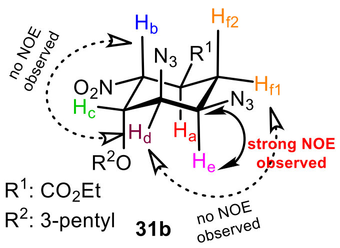


31b

R^1: CO_2Et, R^2: 3-pentyl

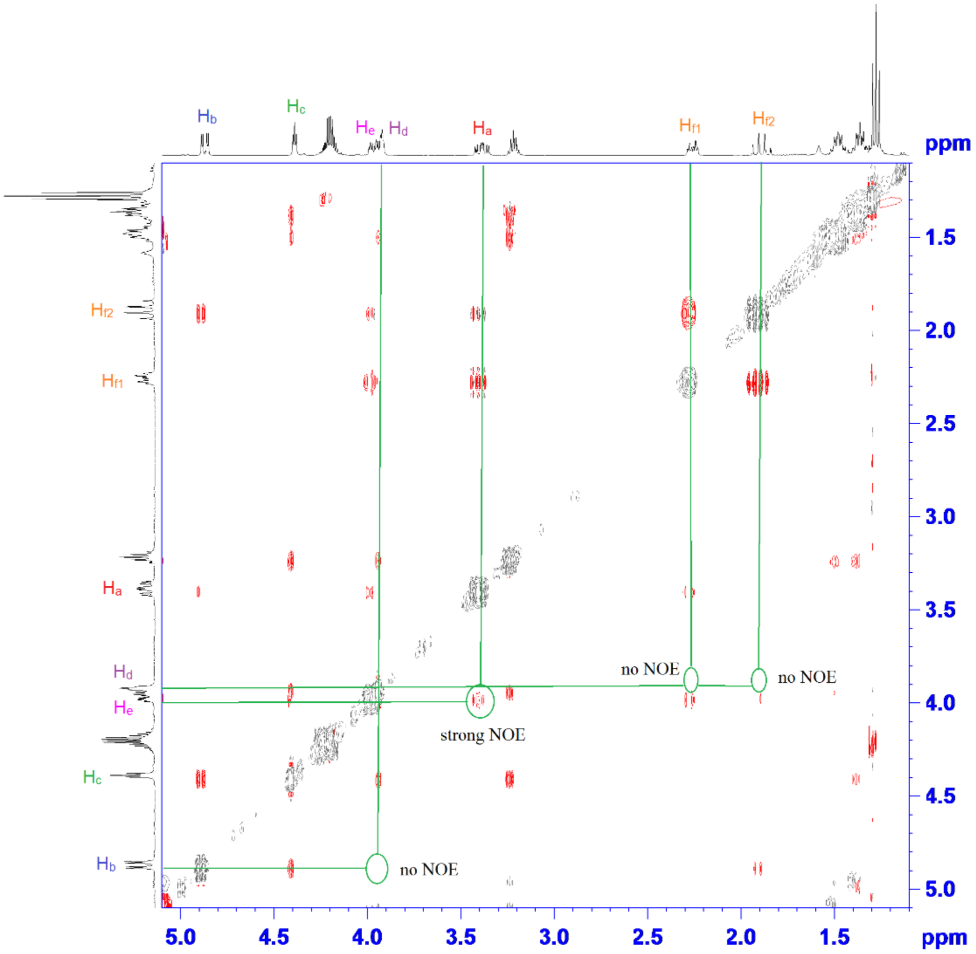


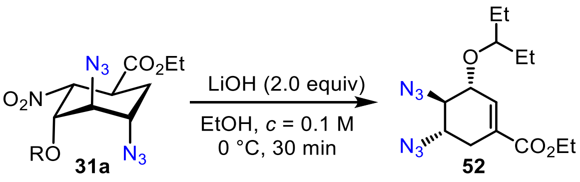
The stereochemistry of **31b** was determined by *NOE* analysis: there is strong *NOE* observed between H_a and H_e. However, no *NOE* is observed either between H_d and H_f, or H_d and H_b. (See below)



R^1: CO_2Et
R^2: 3-pentyl

31b

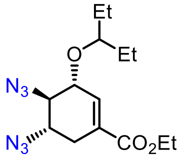




31a
R: 3-pentyl

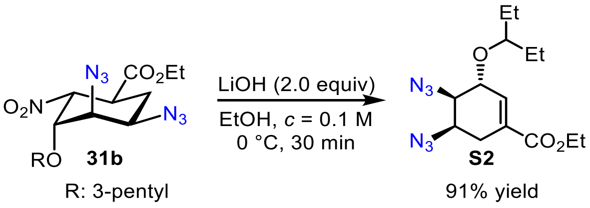
52
92% yield

To a 25 mL round bottom flask were added the diazidation product **31a** (200 mg, 0.54 mmol, 1.0 equiv) and EtOH (5.4 mL). After the flask was moved to ice-bath, LiOH (26 mg, 1.08 mmol, 2.0 equiv) was added portion-wise and the mixture was stirred at 0 ºC for 30 min until the starting material **31a** was fully consumed (monitored by TLC). AcOH (31 μL, 0.54 mmol, 1.0 equiv) was added to quench the reaction. EtOH was removed *in vacuo*, and the residue was diluted with EtOAc (8 mL) and water (8 mL). The organic phase was separated from aqueous phase and the aqueous phase was further extracted with EtOAc (8 mL×2). The combined organic phase was dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 30:1 to 3:1) to afford the desired product **52** as yellow oil (160 mg, 92% yield).

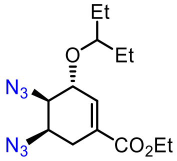


52

Ethyl (3*R*,4*R*,5*S*)-4,5-diazido-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (52): $[\alpha]_D^{20}$ = –140.2° (*c* 1.00, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 2970 (w), 2937 (w), 2878 (w), 2103 (s), 1714 (s), 1464 (w), 1368 (w), 1248 (s), 1089 (m), 1057 (s), 984 (w), 734 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 6.76–6.74 (m, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.00 (ddd, *J* = 7.7, 3.7, 1.9 Hz, 1H), 3.50–3.37 (m, 3H), 2.92–2.84 (m, 1H), 2.32–2.17 (m, 1H), 1.66–1.49 (m, 4H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.6 Hz, 3H), 0.93 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 136.8, 128.2, 82.3, 76.3, 67.6, 61.2, 59.7, 30.2, 26.3, 25.5, 14.2, 9.5, 9.4; LRMS (ESI, m/z): calcd for $C_{14}H_{22}N_6O_3Na^+$, [M + Na$^+$], 345.2, found 345.2.

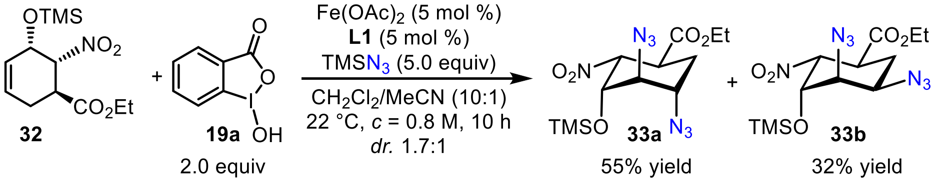


To a flame-dried sealable 2-dram vial equipped with a stir bar were added the diazidation product **31b** (100 mg, 0.27 mmol, 1.0 equiv) and EtOH (2.7 mL). After the vial was moved to ice-bath, LiOH (13 mg, 0.54 mmol, 2.0 equiv) was added portion-wise and the mixture was stirred at 0 ºC for 30 min until the starting material **31b** was fully consumed (monitored by TLC). AcOH (16 µL, 0.27 mmol, 1.0 equiv) was added to quench the reaction. EtOH was removed *in vacuo*, and the residue was diluted with EtOAc (5 mL) and water (5 mL). The organic phase was separated from aqueous phase and the aqueous phase was further extracted with EtOAc (5 mL×2). The combined organic phase was dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 30:1 to 3:1) to afford the desired product **S2** as colorless oil (79 mg, 91% yield).

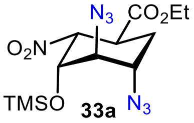


S2

Ethyl (3*R*,4*R*,5*R*)-4,5-diazido-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (S2): $[\alpha]_D^{20}$ = –107.1° (*c* 1.00, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 2971 (w), 2935 (w), 2878 (w), 2101 (s), 1714 (s), 1653 (w), 1463 (w), 1253 (s), 1232 (s), 1098 (s), 1054 (s), 952 (m), 756 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (dt, *J* = 3.4, 1.7 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.16–4.09 (m, 1H), 4.01 (ddd, *J* = 6.1, 5.0, 2.5 Hz, 1H), 3.71 (dt, *J* = 8.1, 4.1 Hz, 1H), 3.41 (quint, *J* = 5.8 Hz, 1H), 2.74–2.65 (m, 1H), 2.57 (ddt, *J* = 18.3, 6.1, 1.4 Hz, 1H), 1.63–1.51 (m, 4H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.6 Hz, 3H), 0.92 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 135.0, 128.9, 82.2, 72.9, 63.2, 61.1, 57.9, 27.7, 26.3, 25.8, 14.2, 9.7, 9.3; LRMS (ESI, m/z): calcd for $C_{14}H_{22}N_6O_3Na^+$, [M + Na$^+$], 345.2, found 345.2.

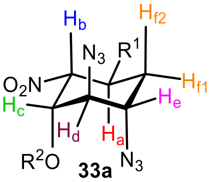


To a flame-dried sealable 2-dram vial equipped with a stir bar were added $Fe(OAc)_2$ (8.7 mg, 0.05 mmol, 5 mol %), **L1** (13.7 mg, 0.05 mmol, 5 mol %), **32** (287 mg, 1.0 mmol, 1.0 equiv) and benziodoxole **19a** (528 mg, 2.0 mmol, 2.0 equiv). After the flask was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (1.1 mL) and MeCN (0.11 mL) were added via syringes and the mixture was stirred at room temperature for 10 min. Subsequently, freshly opened $TMSN_3$ (656 μL, 5.0 mmol, 5.0 equiv) was added to the flask at room temperature within 8 h using a syringe pump. The reaction mixture was stirred for additional 2 h until **32** was fully consumed (monitored by TLC). The reaction was carefully quenched with saturated $NaHCO_3$ solution (3 mL) to remove any residual hydrazoic acid and further diluted with Et_2O (8 mL), the resulting suspension was stirred vigorously for 10 min. The mixture was filtered and the solid was washed with Et_2O (5 mL×2). The combined filtrate was washed with saturated $NaHCO_3$ solution (10 mL), brine (10 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the *dr* was obtained by quantitative ^1H NMR experiment using 1,3,5-trimethylbenzene as an internal standard (88% NMR yield, *dr*: 1.7:1). the crude product was purified through column chromatography (hexanes/EtOAc: from 100:1 to 10:1) to afford the desired diazidation product **33a** as colorless oil (204 mg, 55% yield) along with the other diastereomer **33b** as colorless oil (119 mg, 32% yield).



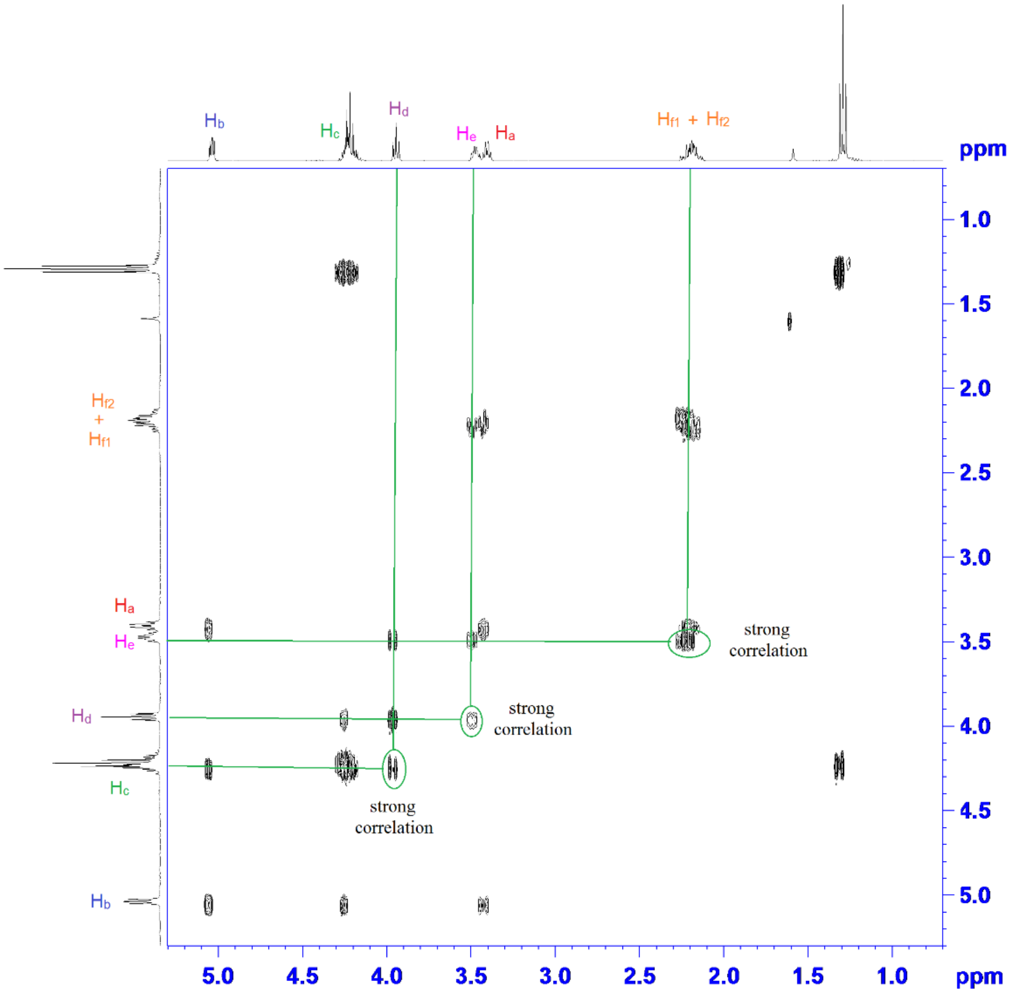
Ethyl (1*S*,2*R*,3*S*,4*R*,5*S*)-4,5-diazido-2-nitro-3-((trimethylsilyl)oxy)cyclohexane-1-carboxylate (33a): $[\alpha]_D^{20}$ = +17.2° (*c* 1.00, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 2961 (w), 2104 (s), 1730 (s), 1558 (s), 1446 (w), 1376 (m), 1253 (s), 1189 (s), 1115 (s), 1022 (m), 843 (s), 756 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 5.04 (dd, *J* = 5.9, 4.4 Hz, 1H), 4.30–4.14 (m, 3H), 3.95 (t, *J* = 6.9 Hz, 1H), 3.47 (td, *J* = 7.4, 4.9 Hz, 1H), 3.41 (dd, *J* = 12.0, 6.0 Hz, 1H), 2.28–2.09 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 85.0, 70.4, 64.4, 62.1, 57.6, 38.8, 27.6, 14.0, -0.5; LRMS (ESI, m/z): calcd for $C_{12}H_{21}N_7O_5SiNa^+$, [M + Na$^+$], 394.1, found 394.1.

The full assignment of ^{1}H NMR of **33a** was carried out through ^{1}H–^{1}H COSY NMR analysis: there are strong correlations between H_e and H_{f1}/H_{f2}, H_e and H_d, as well as H_d and H_c.

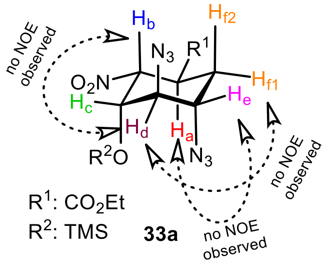


33a

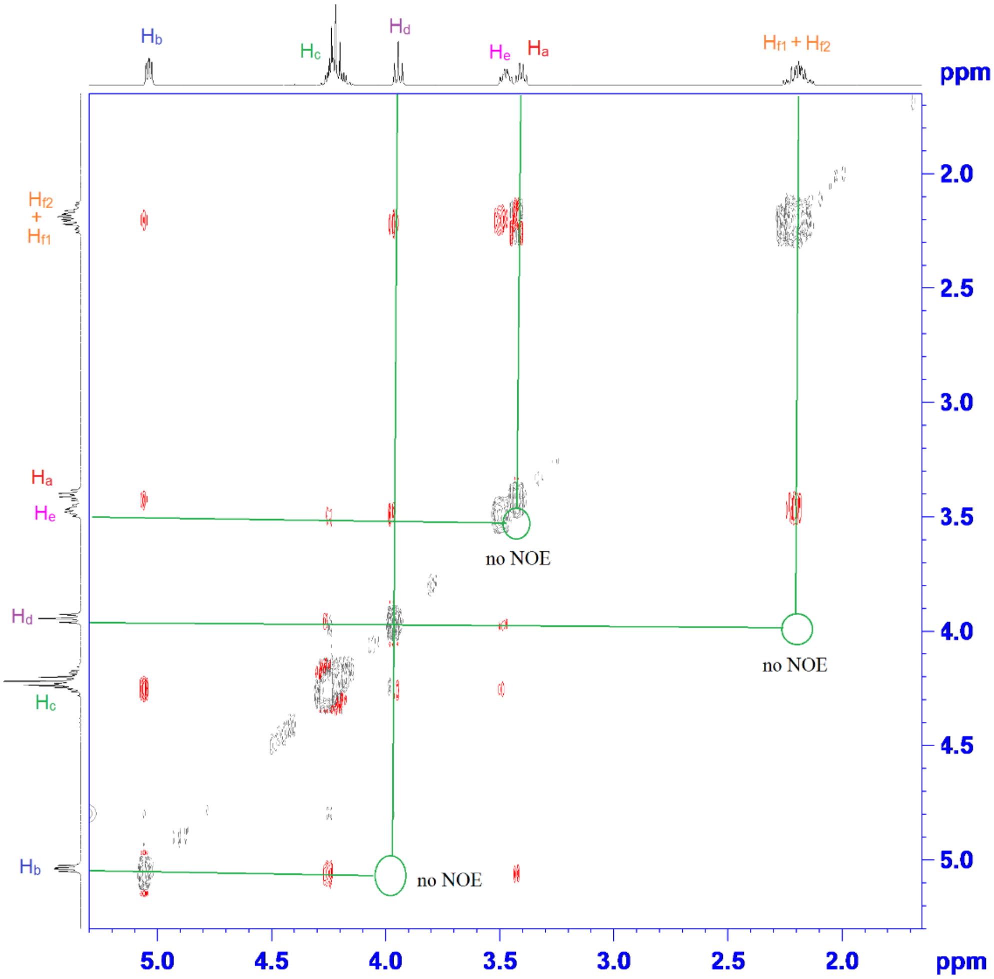
R^1: CO$_2$Et, R^2: TMS

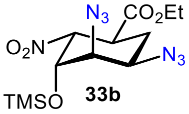


The stereochemistry of **33a** was determined by *NOE* analysis: there is no significant *NOE* observed between H_a and H_e, H_d and H_f, or H_d and H_b.



33a

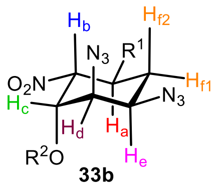




33b

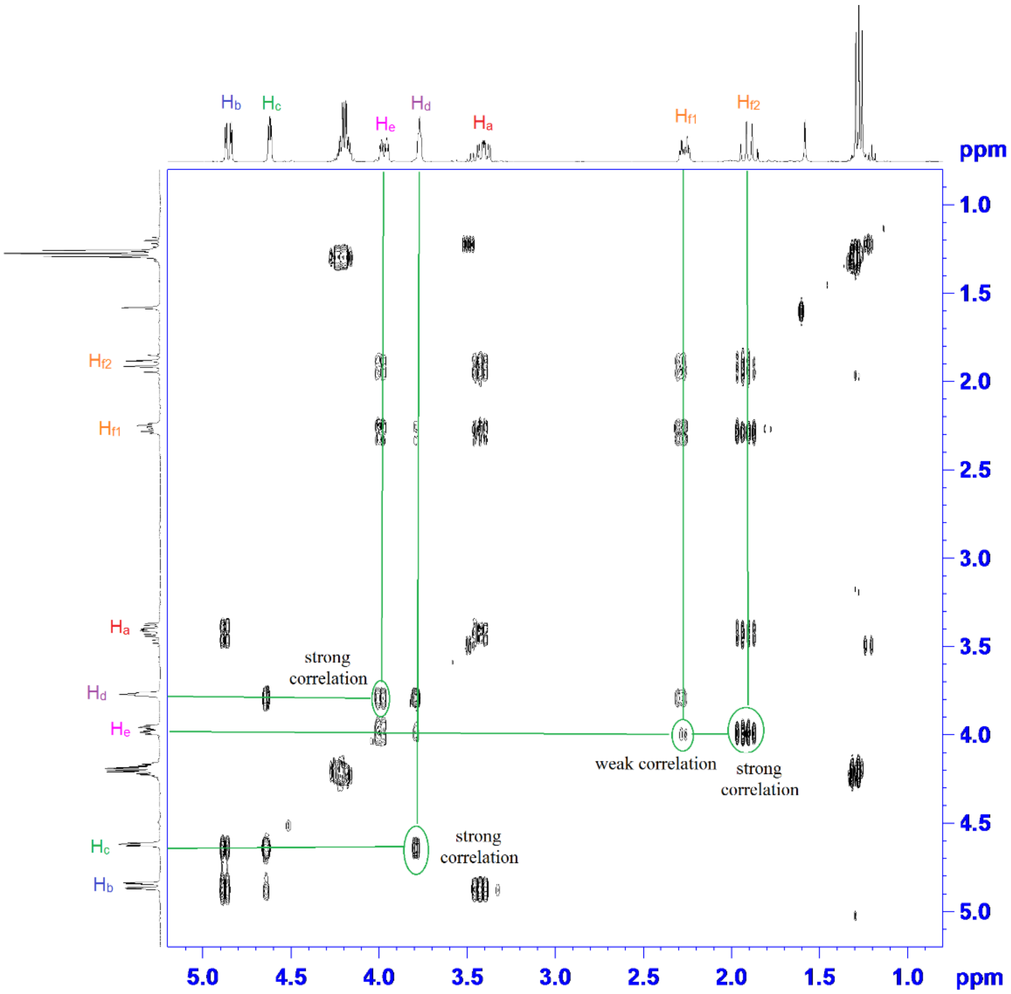
Ethyl (1*S*,2*R*,3*S*,4*R*,5*R*)-4,5-diazido-2-nitro-3-((trimethylsilyl)oxy)cyclohexane-1-carboxylate (33b): $[\alpha]_D^{20}$ = –61.4° (*c* 1.33, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 2961 (w), 2106 (s), 1733 (s), 1557 (s), 1386 (m), 1254 (s), 1186 (s), 1110 (s), 991 (m), 844 (s), 737 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (dd, *J* = 11.3, 2.7 Hz, 1H), 4.62 (dd, *J* = 3.9, 3.0 Hz, 1H), 4.26–4.14 (m, 2H), 4.00–3.93 (m, 1H), 3.80–3.73 (m, 1H), 3.45–3.34 (m, 1H), 2.30–2.21 (m, 1H), 1.96–1.81 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 82.9, 71.3, 64.5, 61.7, 56.2, 38.7, 26.5, 14.0, -0.4; LRMS (ESI, m/z): calcd for $C_{12}H_{21}N_7O_5SiNa^+$, [M + Na$^+$], 394.1, found 394.1.

The full assignment of ^{1}H NMR of **33b** was carried out through ^{1}H–^{1}H COSY NMR analysis: there are strong correlations between H_e and H_{f2}, H_e and H_d, as well as H_d and H_c.

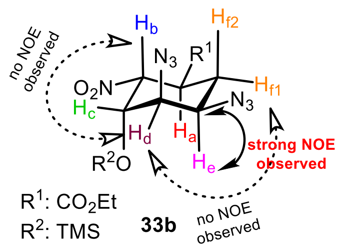


33b

R^1: CO$_2$Et, R^2: TMS

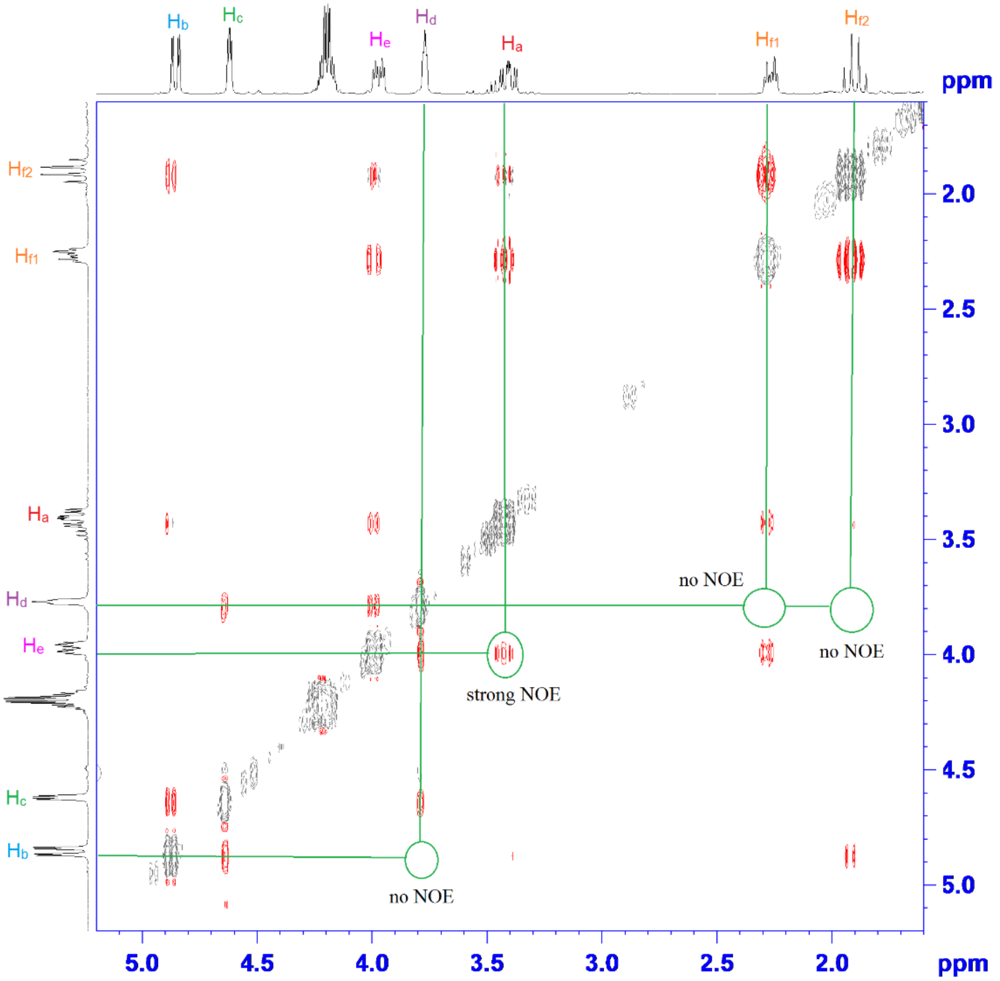


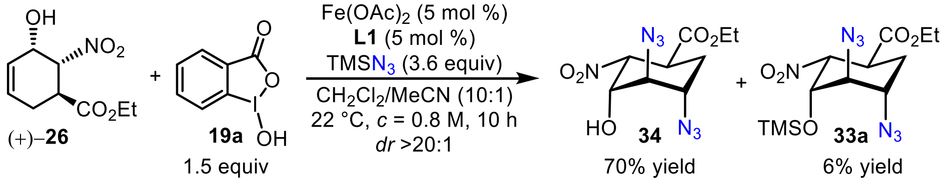
The stereochemistry of **33b** was determined by *NOE* analysis: there is a strong *NOE* observed between H$_a$ and H$_e$. However, no *NOE* is observed either between H$_d$ and H$_f$, or H$_d$ and H$_b$.



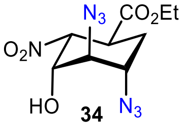
R^1: CO_2Et
R^2: TMS

33b





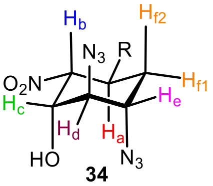
To a flame-dried 100 mL round bottom flask equipped with a stir bar were added Fe(OAc)$_2$ (61 mg, 0.35 mmol, 5 mol %), **L1** (95 mg, 0.35 mmol, 5 mol %), (+)–**26** (1.5 g, 6.97 mmol, 1.0 equiv) and benziodoxole **19a** (2.76 g, 10.46 mmol, 1.5 equiv). After the flask was evacuated and backfilled with N$_2$ three times, anhydrous CH$_2$Cl$_2$ (8 mL) and MeCN (0.8 mL) were added via syringes and the mixture was stirred at room temperature for 10 min. Subsequently, freshly opened TMSN$_3$ (3.3 mL, 25.1 mmol, 3.6 equiv) was added to the flask at room temperature within 8 h using a syringe pump. The reaction mixture was stirred for additional 2 h until (+)–**26** was fully consumed (monitored by TLC). The reaction was carefully quenched with saturated NaHCO$_3$ solution (20 mL) to remove any residual hydrazoic acid and further diluted with Et$_2$O (60 mL), the resulting suspension was stirred vigorously for 10 min. The mixture was filtered and the solid was washed with Et$_2$O (15 mL×2). The combined filtrate was washed with saturated NaHCO$_3$ solution (50 mL), brine (50 mL) and dried over Na$_2$SO$_4$. The mixture was filtered through a silica gel pad (*ca.* 6 cm long × 6 cm diameter) and the pad was washed with ether (50 mL×3). After concentration *in vacuo*, the crude diazidation products **34** and **33a** were obtained as yellow oil, *which could be used directly without further purification*. The crude yield of compound **34** and **33a** were obtained by quantitative ^{1}H NMR experiment using 1,3,5-trimethylbenzene as an internal standard (71% NMR yield for compound **34** and 7% NMR yield for compound **33a**). For characterization purposes, the crude mixture was purified through column chromatography (hexanes/EtOAc: from 20:1 to 6:1) to afford the desired product **34** as colorless oil (1.46 g, 70% yield) along with the *O*-TMS protected diazidation product **33a** as colorless oil (155 mg, 6% yield)



34

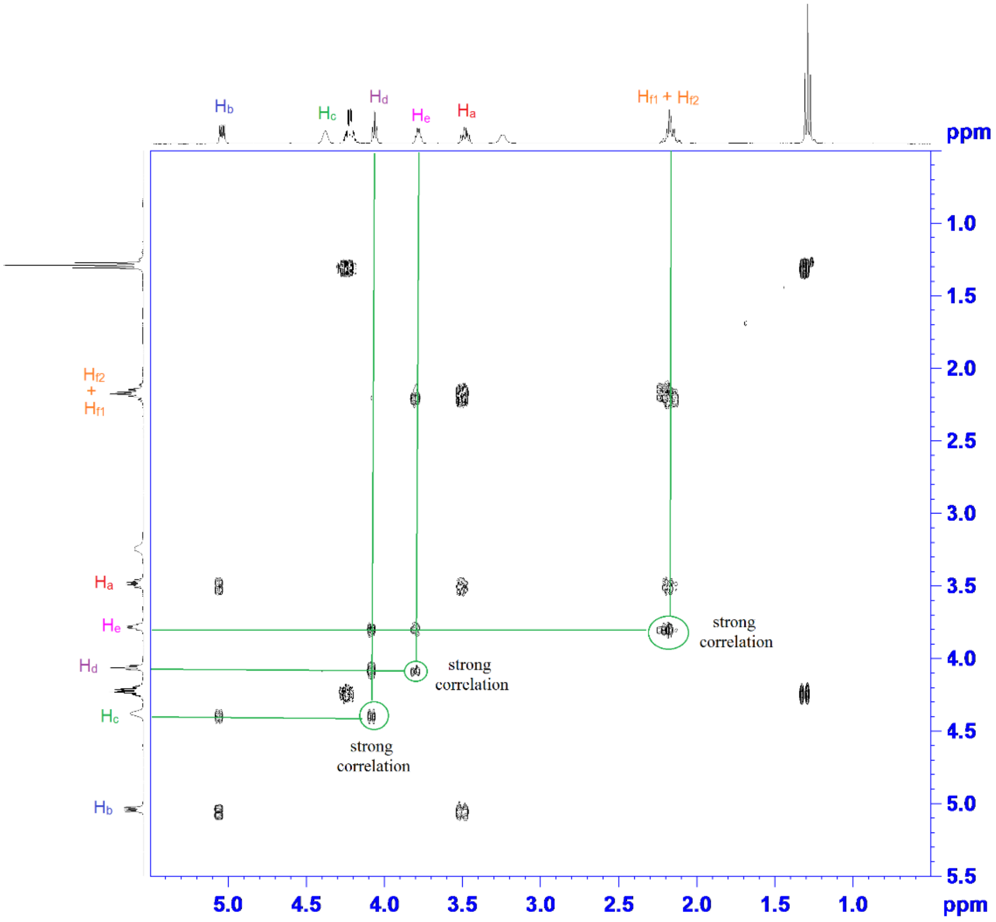
Ethyl (1*S*,2*R*,3*S*,4*R*,5*S*)-4,5-diazido-3-hydroxy-2-nitrocyclohexane-1-carboxylate (34): $[\alpha]_D^{20}$ = +4.2° (*c* 1.01, CHCl$_3$). IR ν_{max} (neat)/cm^{-1}: 3462 (w), 2920 (w), 2110 (s), 1729 (s), 1558 (s), 1377 (m), 1258 (s), 1200 (m), 1095 (m), 1021 (m), 955(w), 874 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (dd, *J* = 8.4, 3.9 Hz, 1H), 4.40–4.36 (m, 1H), 4.27–4.18 (m, 2H), 4.06 (t, *J* = 5.4 Hz, 1H), 3.78 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.48 (td, *J* = 8.7, 5.2 Hz, 1H), 3.24 (d, *J* = 7.0 Hz, 1H), 2.26–2.07 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 83.7, 70.0, 62.7, 62.2, 58.3, 37.4, 27.4, 14.0; LRMS (ESI, m/z): calcd for $C_9H_{13}N_7O_5Na^+$, [M + Na$^+$], 322.1, found 322.1.

The full assignment of ^{1}H NMR of **34** was carried out through ^{1}H–^{1}H COSY NMR analysis: there are strong correlations between H_e and H_{f1}/H_{f2}, H_e and H_d, as well as H_d and H_c.

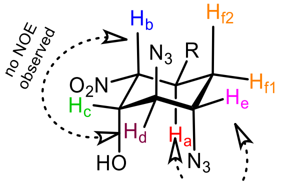


34

R: CO_2Et

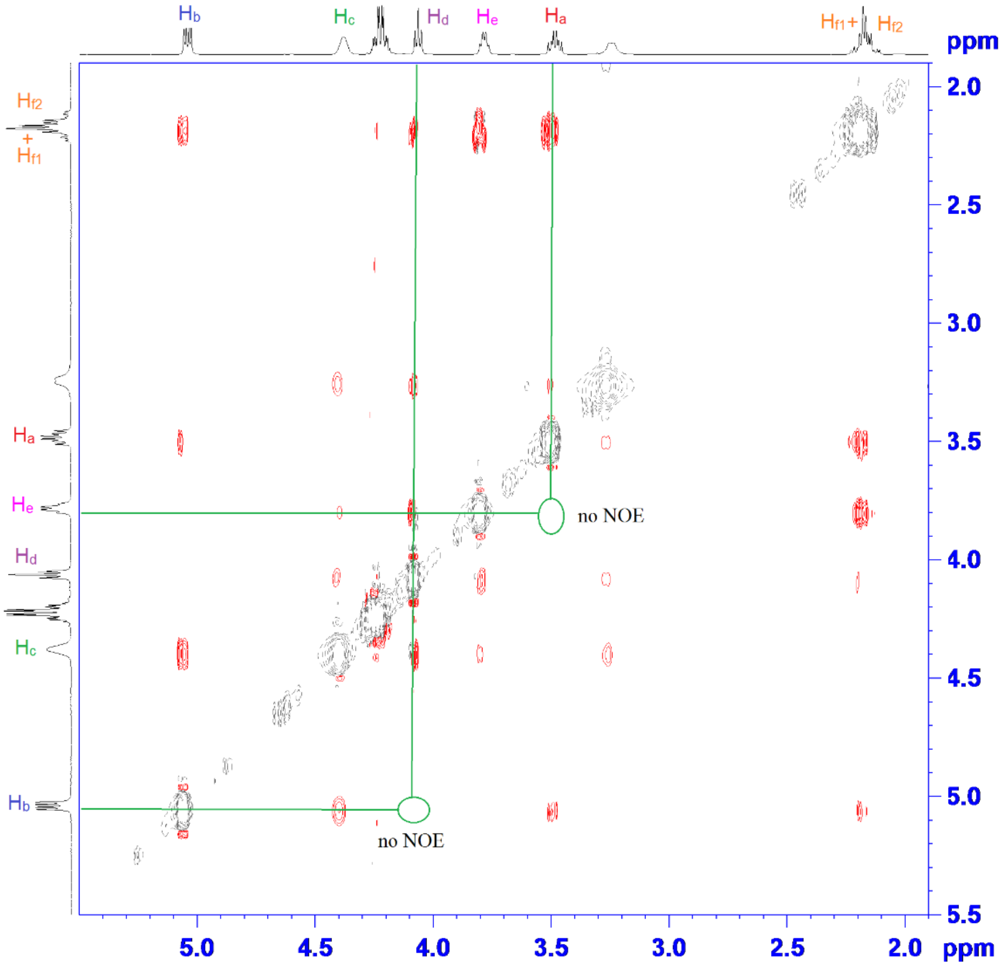


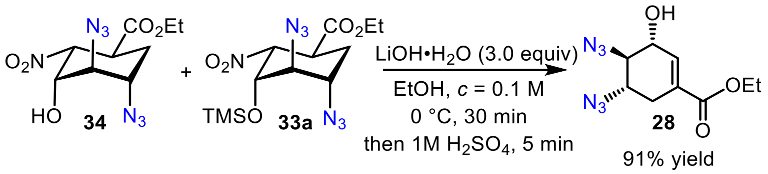
The stereochemistry of **34** was determined by *NOE* analysis: there is no significant *NOE* observed either between H_a and H_e, or H_d and H_b.



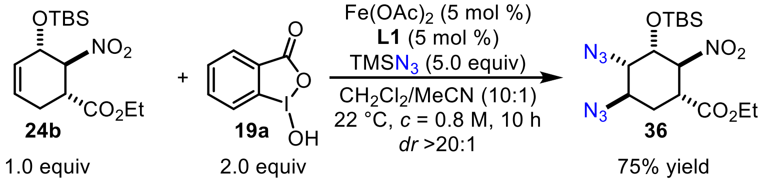
34

R: CO_2Et

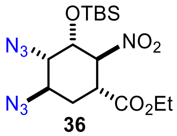




To a 100 mL round bottom flask were added the crude diazidation products **34** and **33a** (5.3 mmol, 1.0 equiv) obtained in last step and EtOH (53 mL). After the flask was moved to ice-bath, LiOH·H_2O (0.67 g, 15.9 mmol, 3.0 equiv) was added portion-wise and the mixture was stirred at 0 ºC for 30 min until the starting material was fully consumed (monitored by TLC). Aqueous H_2SO_4 solution (1 M, 26.5 mL, 26.5 mmol, 5.0 equiv) was added and stirred for 5 min. EtOH was removed *in vacuo*, and the residue was diluted with EtOAc (30 mL). The organic phase was separated from aqueous phase and the aqueous phase was further extracted with EtOAc (30 mL×2). The combined organic phase was dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 30:1 to 3:1) to afford the desired product **28** as yellow oil (1.21 g, 91% yield).



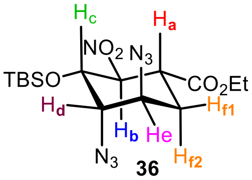
To a flame-dried sealable 2-dram vial equipped with a stir bar were added $Fe(OAc)_2$ (8.7 mg, 0.05 mmol, 5 mol %), **L1** (13.7 mg, 0.05 mmol, 5 mol %), **24b** (330 mg, 1.0 mmol, 1.0 equiv) and benziodoxole **19a** (528 mg, 2.0 mmol, 2.0 equiv). After the flask was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (1.1 mL) and MeCN (0.11 mL) were added via syringes and the mixture was stirred at room temperature for 10 min. Subsequently, freshly opened $TMSN_3$ (656 μL, 5.0 mmol, 5.0 equiv) was added to the flask at room temperature within 8 h using a syringe pump. The reaction mixture was stirred for additional 2 h until **24b** was fully consumed (monitored by TLC). The reaction was carefully quenched with saturated $NaHCO_3$ solution (3 mL) to remove any residual hydrazoic acid and further diluted with Et_2O (8 mL), the resulting suspension was stirred vigorously for 10 min. The mixture was filtered and the solid was washed with Et_2O (5 mL×2). The combined filtrate was washed with saturated $NaHCO_3$ solution (10 mL), brine (10 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 100:1 to 10:1) to afford the diazidation product **36** as a foam (310 mg, 75% yield).



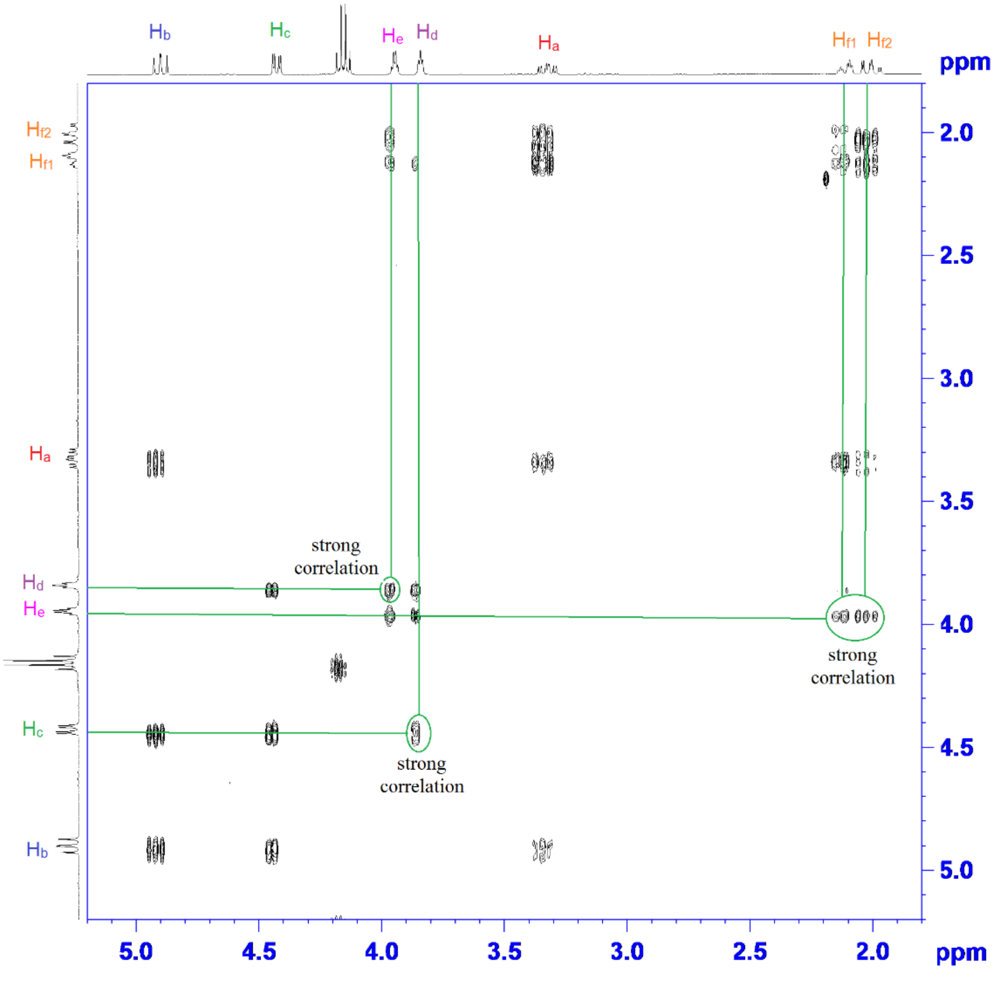
36

(±)-Ethyl (1*R*,2*S*,3*S*,4*S*,5*R*)-4,5-diazido-3-((*tert*-butyldimethylsilyl)oxy)-2-nitrocyclohexane-1-carboxylate (36): IR ν_{max} (neat)/cm^{-1}: 2933 (w), 2859 (w), 2107 (s), 1723 (s), 1556 (s), 1383 (m), 1257 (s), 1203 (s), 1107 (s), 1026 (m), 836 (s), 778 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (dd, *J* = 11.3, 9.9 Hz, 1H), 4.43 (dd, *J* = 9.9, 3.1 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.95 (dd, *J* = 6.6, 3.1 Hz, 1H), 3.84 (t, *J* = 3.0 Hz, 1H), 3.32 (ddd, *J* = 12.9, 11.5, 4.5 Hz, 1H), 2.15–2.07 (m, 1H), 2.01 (ddd, *J* = 14.7, 13.1, 3.0 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 87.0, 71.1, 63.7, 61.9, 58.7, 40.8, 26.3, 25.5, 17.9, 13.9, -4.3, -5.8; LRMS (ESI, m/z): calcd for $C_{15}H_{27}N_7O_5Na^+$, [M + Na^+], 436.2, found 436.2.

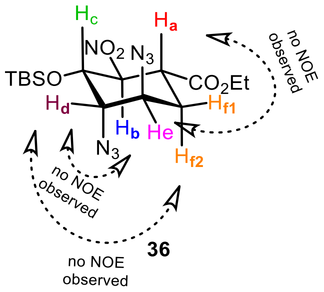
The full assignment of ^{1}H NMR of **36** was carried out through ^{1}H–^{1}H COSY NMR analysis: there are strong correlations between H_e and H_{f1}/H_{f2}, H_e and H_d, as well as H_d and H_c.



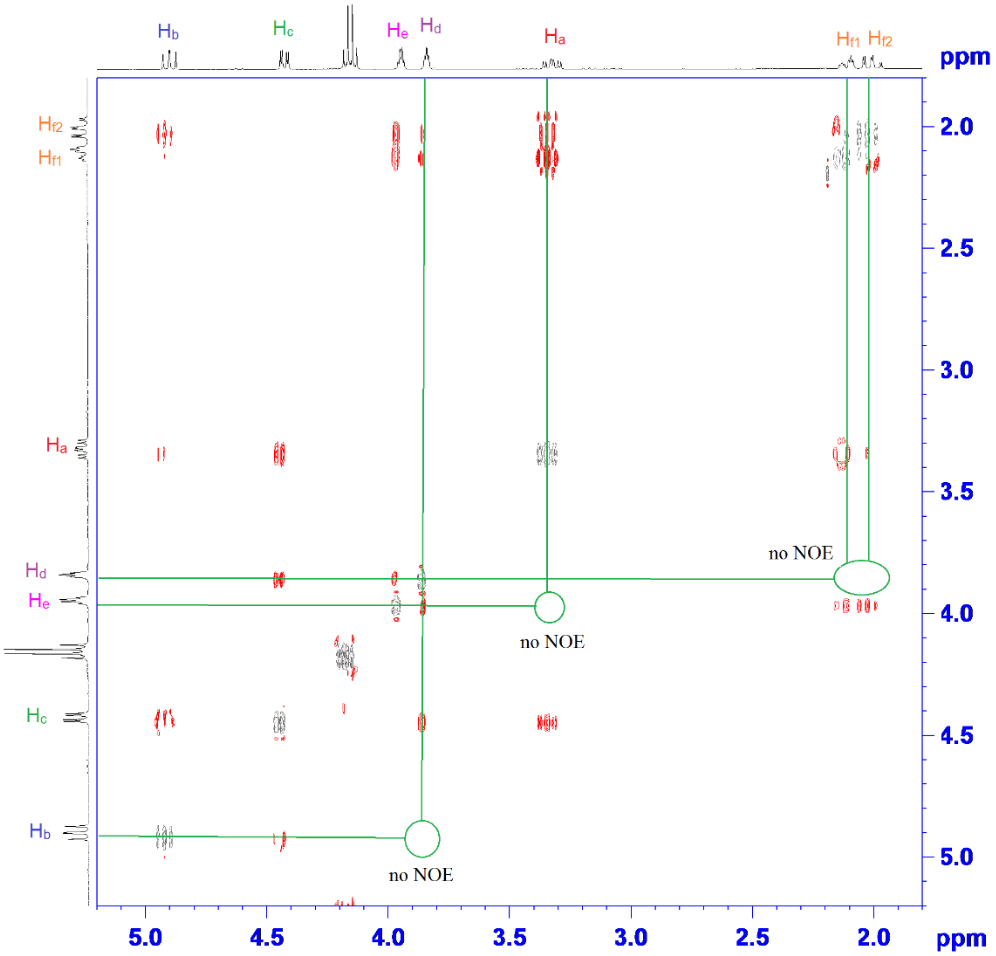
36

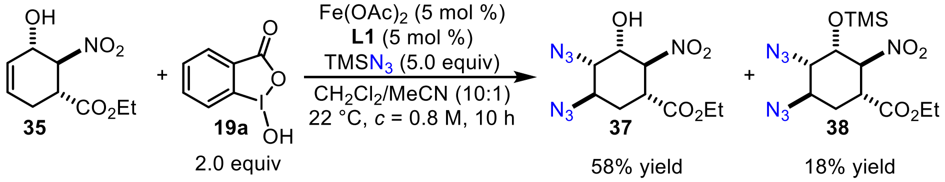


The stereochemistry of **36** was determined by *NOE* analysis: there is no significant *NOE* observed between H_a and H_e, H_d and $H_{b,}$ or H_d and H_f. (See below)

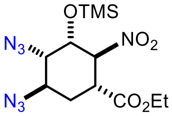


36





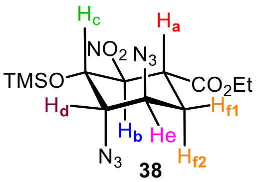
To a flame-dried sealable 2-dram vial equipped with a stir bar were added $Fe(OAc)_2$ (8.7 mg, 0.05 mmol, 5 mol %), **L1** (13.7 mg, 0.05 mmol, 5 mol %), **35** (215 mg, 1.0 mmol, 1.0 equiv) and benziodoxole **19a** (528 mg, 2.0 mmol, 2.0 equiv). After the flask was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (1.1 mL) and MeCN (0.11 mL) were added via syringes and the mixture was stirred at room temperature for 10 min. Subsequently, freshly opened $TMSN_3$ (656 μL, 5.0 mmol, 5.0 equiv) was added to the flask at room temperature within 8 h using a syringe pump. The reaction mixture was stirred for additional 2 h until **35** was fully consumed (monitored by TLC). The reaction was carefully quenched with saturated $NaHCO_3$ solution (3 mL) to remove any residual hydrazoic acid and further diluted with Et_2O (8 mL), the resulting suspension was stirred vigorously for 10 min. The mixture was filtered and the solid was washed with Et_2O (5 mL×2). The combined filtrate was washed with saturated $NaHCO_3$ solution (10 mL), brine (10 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 100:1 to 3:1) to afford the *O*-TMS protected diazidation product **38** as colorless oil (67 mg, 18% yield) along with the desired diazidation product **37** as colorless oil (174 mg, 58% yield).



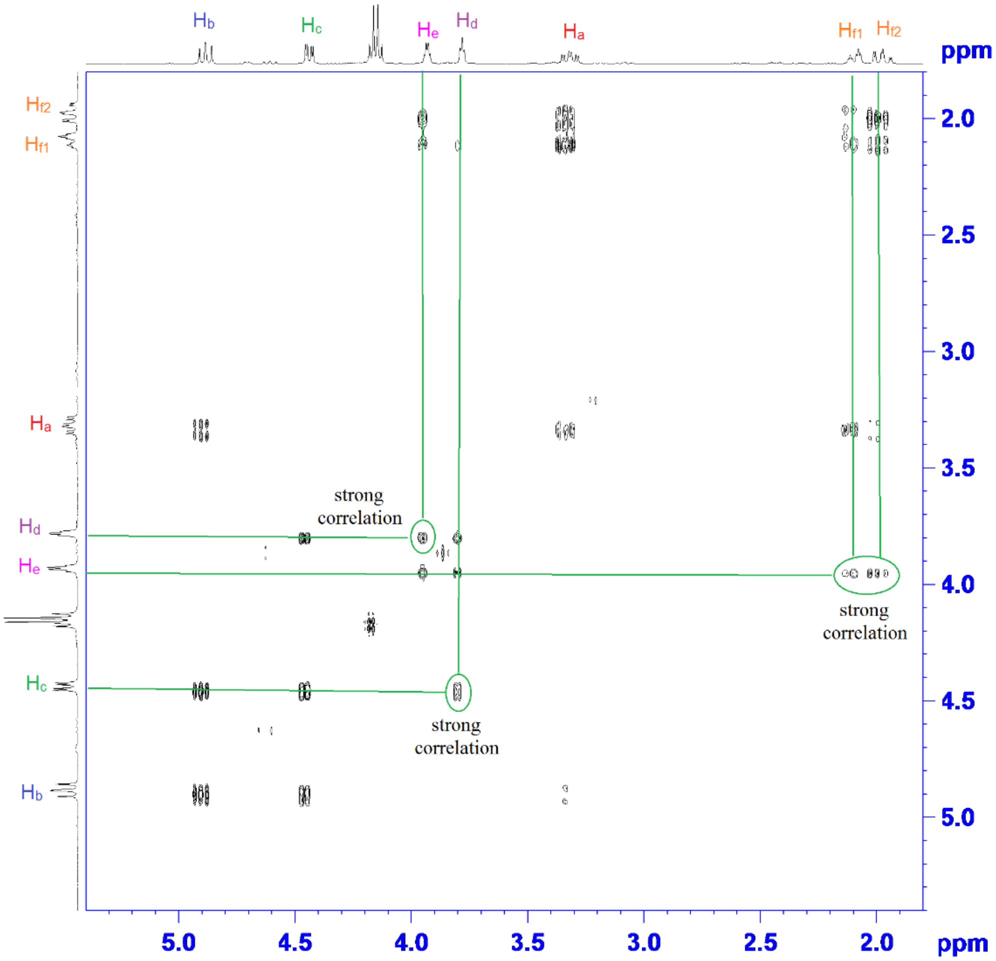
38

(±)-Ethyl (1*R*,2*S*,3*S*,4*S*,5*R*)-4,5-diazido-2-nitro-3-((trimethylsilyl)oxy)cyclohexane-1-carboxylate (38): IR ν_{max} (neat)/cm^{-1}: 2962 (w), 2095 (s), 1719 (s), 1554 (s), 1247 (s), 1204 (m), 1111 (s), 1025 (m), 842 (s), 751 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (dd, *J* = 11.2, 9.8 Hz, 1H), 4.44 (dd, *J* = 9.7, 3.3 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.93 (q, *J* = 3.3 Hz, 1H), 3.78 (t, *J* = 3.3 Hz, 1H), 3.32 (ddd, *J* = 12.7, 11.4, 4.4 Hz, 1H), 2.10 (dt, *J* = 6.7, 3.8 Hz, 1H), 2.03–1.93 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 87.2, 71.2, 63.7, 61.9, 58.5, 40.6, 26.3, 13.9, -0.5; LRMS (ESI, m/z): calcd for $C_{12}H_{21}N_7O_5SiNa^+$, [M + Na^+], 394.1, found 394.1.

The full assignment of ^{1}H NMR of **38** was carried out through ^{1}H–^{1}H COSY NMR analysis: there are strong correlations between H_e and H_{f1}/H_{f2}, H_e and H_d, as well as H_d and H_c.



38

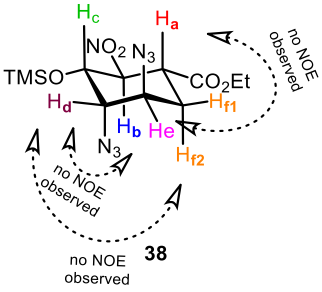


strong correlation

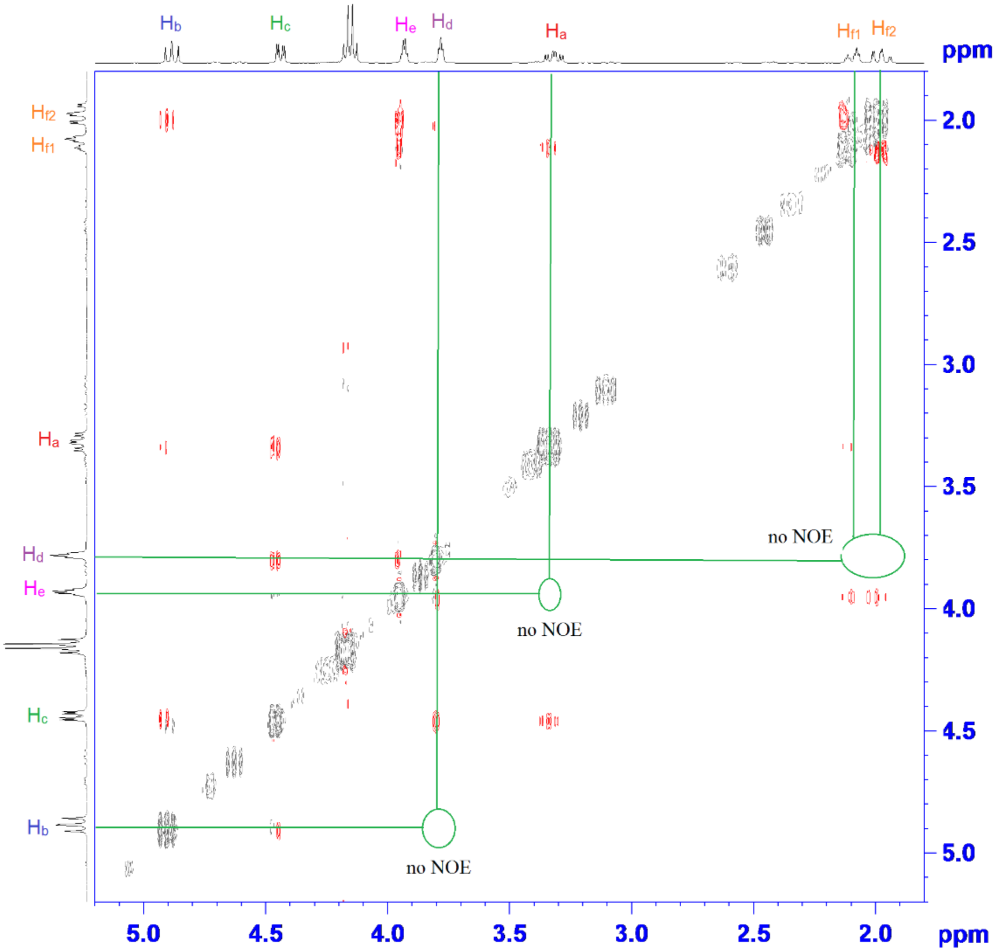
strong correlation

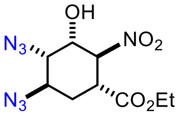
strong correlation

The stereochemistry of **38** was determined by *NOE* analysis: there is no significant *NOE* observed between H_a and H_e, H_d and H_b, or H_d and H_f. (See below)



38

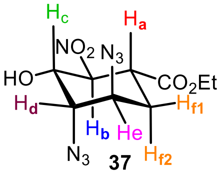




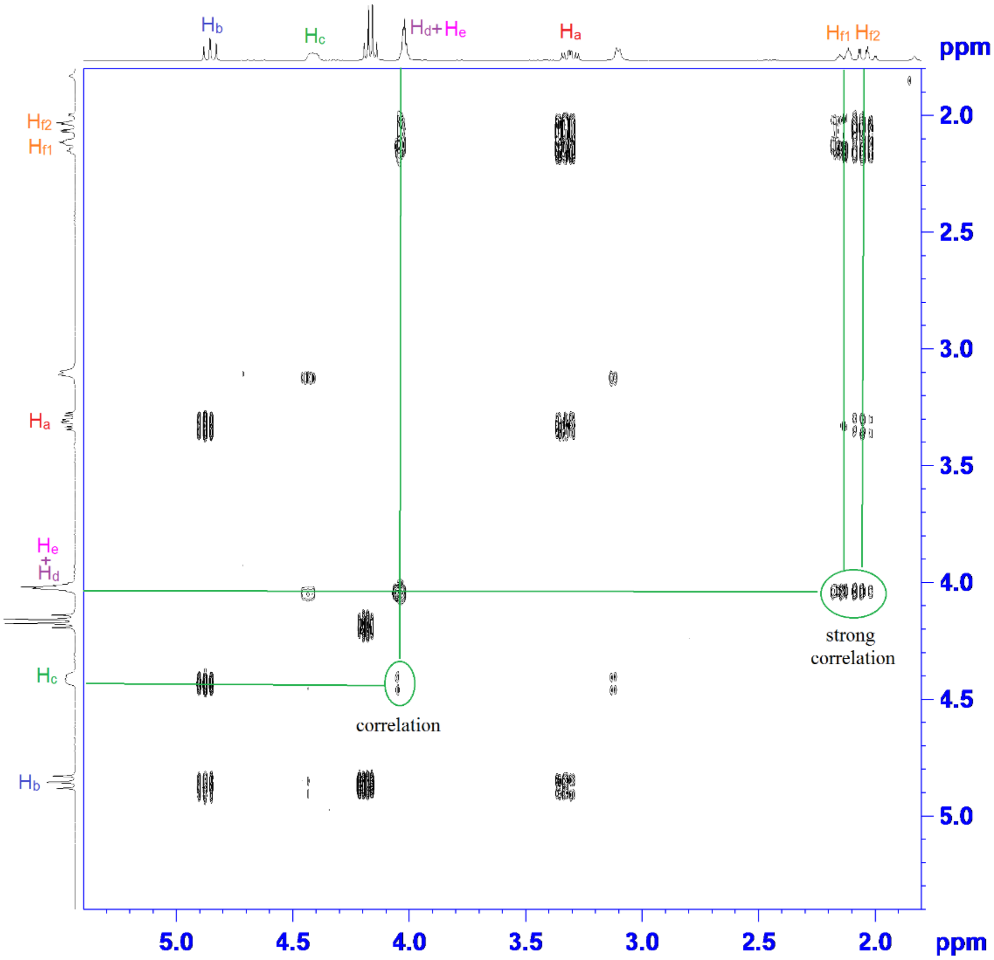
37

(±)-Ethyl (1*R*,2*S*,3*S*,4*S*,5*R*)-4,5-diazido-3-hydroxy-2-nitrocyclohexane-1-carboxylate (37): IR ν_{max} (neat)/cm^{-1}: 3433 (w), 3406 (w), 2099 (s), 1718 (s), 1556 (s), 1296 (m), 1236 (s), 1196 (s), 1080 (s), 1020 (m), 896 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90–4.81 (m, 1H), 4.45–4.37 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.06–3.98 (m, 2H), 3.36–3.25 (m, 1H), 3.10 (d, *J* = 5.8 Hz, 1H), 2.18–2.08 (m, 1H), 2.08–1.96 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 86.6, 69.4, 63.4, 62.1, 58.4, 40.3, 26.6, 13.9; LRMS (ESI, m/z): calcd for $C_9H_{13}N_7O_5Na^+$, [M + Na$^+$], 322.1, found 322.1.

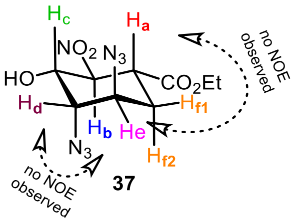
The full assignment of ^{1}H NMR of **37** was carried out through ^{1}H–^{1}H COSY NMR analysis: there are strong correlations between H_e and H_{f1}/H_{f2}, H_e and H_d, as well as H_d and H_c.


Hc
Ha
NO2
N3
HO
CO2Et
Hd
Hf1
Hb
He
N3
Hf2

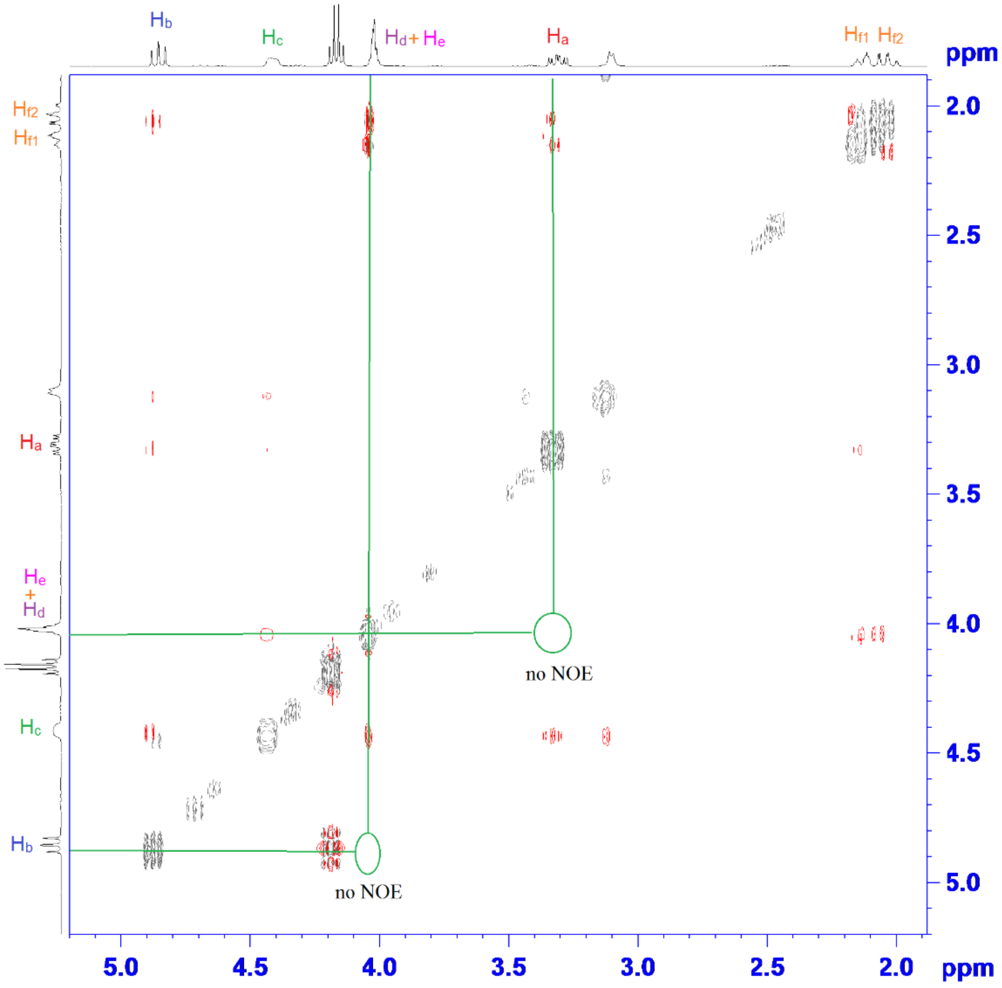
37


Hb
Hc
Hd+He
Ha
Hf1
Hf2
ppm
Hf2
Hf1
Ha
He
+
Hd
Hc
Hb
2.0
2.5
3.0
3.5
4.0
4.5
5.0
strong
correlation
correlation
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm

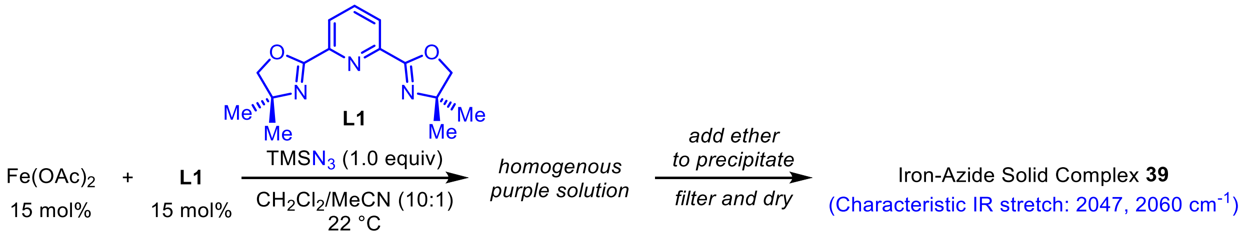
The stereochemistry of **37** was determined by *NOE* analysis: there is no significant *NOE* observed either between H_a and H_e or H_d and H_b.



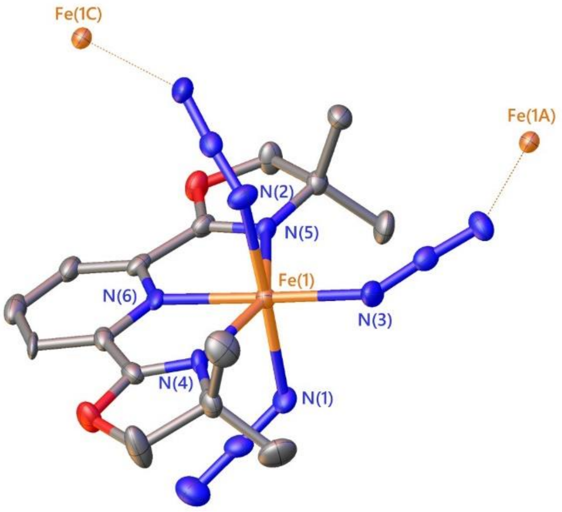
37



G. Catalyst Structure–Reactivity Relationship Studies



To a flame-dried 20 mL sealable test tube equipped with a stir bar were added $Fe(OAc)_2$ (87 mg, 0.5 mmol, 15 mol%) and ligand **L1** (137 mg, 0.5 mmol, 15 mol%). After the tube was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (8.0 mL) and MeCN (1.0 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. $TMSN_3$ (0.45 mL, 3.3 mmol, 1.0 equiv) was added to the catalyst solution and the mixture was stirred for additional 0.5 h. Ether (8 mL) was added drop-wise to the above solution while stirring and purple suspension started to precipitate out. The mixture was centrifuged and the supernatant was removed via a syringe. The solid residue was washed with ether (15 mL) and separated from the liquid by centrifuge. After Et_2O was removed via a syringe, the solid residue was further dried *in vacuo* to afford **39** as a purple solid (99 mg). The IR analysis of **39** shows characteristic azido-group absorption at 2047 cm^{-1} and 2060 cm^{-1}.



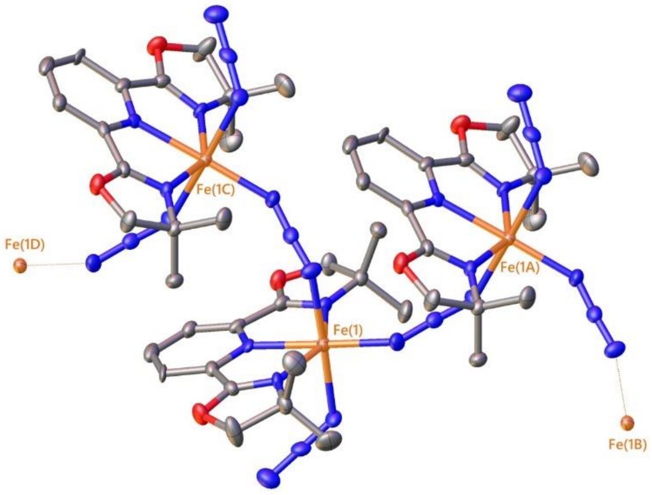
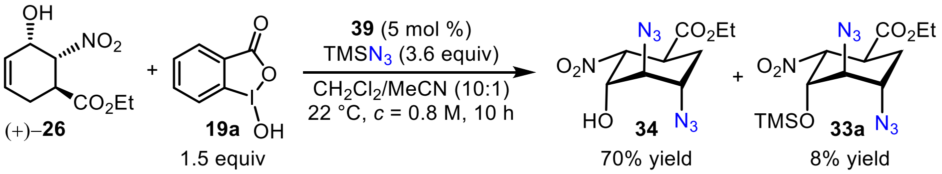
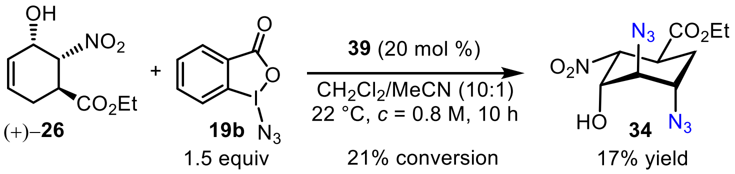


Figure S3. Solid-state structure of both the monomeric unit and the polymeric state of **39**. Solvate (CH_2Cl_2) and hydrogen atoms have been omitted for clarity. Ellipsoids are depicted at the 50% level.



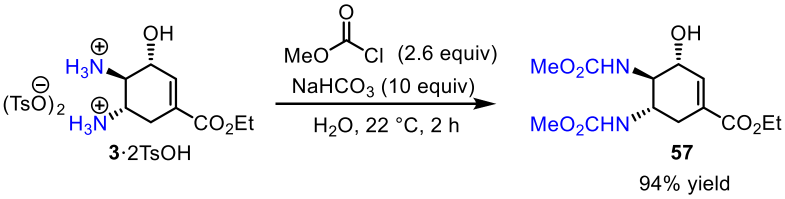
To a flame-dried sealable 2-dram vial equipped with a stir bar were added the solid catalyst **39** (23 mg, 0.05 mmol, 5 mol %), (+)–**26** (215 mg, 1.0 mmol, 1.0 equiv) and benziodoxole **19a** (396 mg, 1.5 mmol, 1.5 equiv). After the flask was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (1.1 mL) and MeCN (0.11 mL) were added via syringes and the mixture was stirred at room temperature for 10 min. Subsequently, freshly opened $TMSN_3$ (473 μL, 3.6 mmol, 3.6 equiv) was added to the flask at room temperature within 8 h using a syringe pump. The reaction mixture was stirred for additional 2 h until (+)–**26** was fully consumed (monitored by TLC). The reaction was carefully quenched with saturated $NaHCO_3$ solution (3 mL) to remove any residual hydrazoic acid and further diluted with Et_2O (8 mL), the resulting suspension was stirred vigorously for 10 min. The mixture was filtered and the solid was washed with Et_2O (5 mL×2). The combined filtrate was washed with saturated $NaHCO_3$ solution (10 mL), brine (10 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 20:1 to 6:1) to afford the desired product **34** as colorless oil (209 mg, 70% yield) along with the *O*-TMS protected diazidation product **33a** as colorless oil (30 mg, 8% yield).



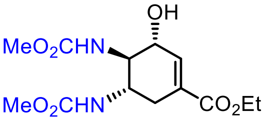
To a flame-dried sealable 2-dram vial equipped with a stir bar were added the solid catalyst **39** (90 mg, 0.2 mmol, 20 mol %), (+)–**26** (215 mg, 1.0 mmol, 1.0 equiv) and **19b** (434 mg, 1.5 mmol, 1.5 equiv). After the flask was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (1.1 mL) and MeCN (0.11 mL) were added via syringes and the mixture was stirred at room temperature for 10 h. The reaction was quenched with saturated $NaHCO_3$ solution (1 mL) and further diluted with Et_2O (8 mL), the resulting suspension was stirred vigorously for 10 min. The mixture was filtered and the solid was washed with Et_2O (5 mL×2). The combined filtrate was washed with saturated $NaHCO_3$ solution (10 mL), brine (10 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 20:1 to 6:1) to afford the desired product **34** as colorless oil (51 mg, 17% yield) along with the recovered starting material (+)-**26**.

H. Expedient Tamiflu Synthesis from 3·2TsOH and Related Synthetic Explorations

a. Expedient Tamiflu Synthesis from 3·2TsOH

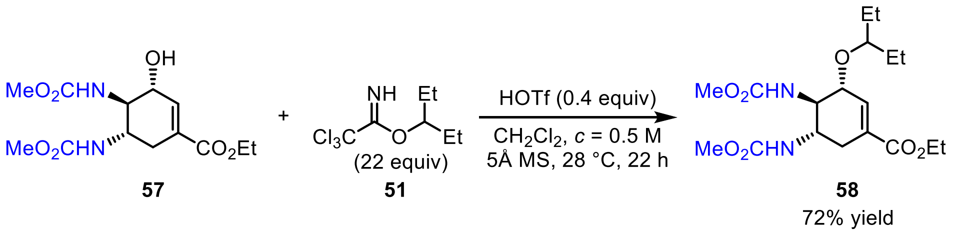


To a 100 mL round bottom flask with a stir bar were added **3**·2TsOH (5.36 g, 9.85 mmol, 1.0 equiv) and H_2O (60 mL). After the flask cooled to 0 °C, $NaHCO_3$ (8.3 g, 98.5 mmol, 10 equiv) was carefully added portion-wise. The resulting solution was stirred at 0 °C for 5 min and methyl chloroformate (1.98 mL, 25.6 mmol, 2.6 equiv) was added. The mixture was warmed up to room temperature and stirred for additional 2 h. EtOAc was added to the reaction mixture. The organic phase was separated from the aqueous phase and the aqueous phase was further extracted with EtOAc (30 mL×3). The combined organic phase was dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 50:1 to 2:1) to afford the desired product **57** as a white solid (2.93 g, 94% yield, m.p. 58–59 °C).

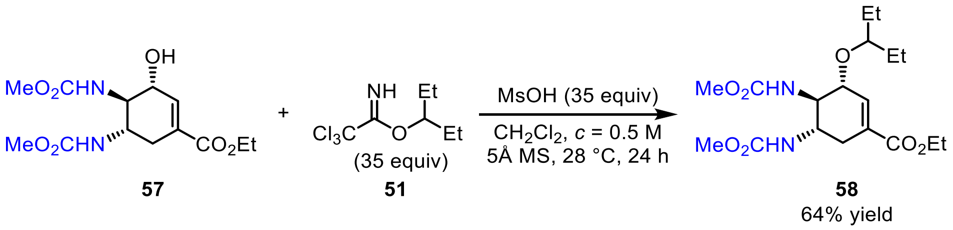


57

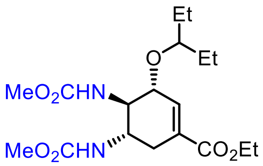
Ethyl (3*R*,4*R*,5*S*)-4,5-bis((ethoxycarbonyl)amino)-3-hydroxycyclohex-1-ene-1-carboxylate (57): $[\alpha]_D^{20}$ = –26.7° (*c* 0.325, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 3319 (m), 2981 (w), 1692 (s), 1533 (s), 1447 (w), 1372 (w), 1239 (s), 1039 (s), 986 (m), 861 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 5.92 (d, *J* = 8.6 Hz, 1H), 5.69 (d, *J* = 8.9 Hz, 1H), 4.29–4.28 (m, 1H), 4.26–4.21 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.82–3.71 (m, 1H), 3.61 (s, 3H), 3.60 (s, 3H), 3.59–3.53 (m, 1H), 2.79 (dd, *J* = 17.5, 5.1 Hz, 1H), 2.30–2.18 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 158.9, 157.7, 139.1, 128.7, 71.5, 61.0, 58.8, 52.5, 52.4, 49.9, 31.3, 14.1; LRMS (ESI, m/z): calcd for $C_{13}H_{21}N_2O_7^+$, $[M + H^+]$, 317.1, found 317.1.



To an oven-dried 50 mL round bottom flask equipped with a stir bar were added **57** (1.38 g, 4.36 mmol, 1.0 equiv) and 5 Å molecular sieves powder (1.5 g). After the flask was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (9.0 mL) and freshly distilled pentan-3-yl 2,2,2-trichloroacetimidate **51** (16.7 mL, 96.0 mmol, 22 equiv) were added. The reaction was cooled to 0 °C and TfOH (154 μL, 1.74 mmol, 0.4 equiv) was added. After the addition of TfOH, the reaction mixture was warmed up to 28 ºC and stirred at this temperature for 22 h until **57** was fully consumed (monitored by TLC). The mixture was cooled to 0 ºC, and Et_3N (0.6 mL, 4.36 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added to quench the reaction. The mixture was filtered and the solid was washed with CH_2Cl_2 (10 mL×4). The filtrate was concentrated *in vacuo* and the residue was purified through column chromatography (hexanes/EtOAc: from 30:1 to 2:1) to afford the desired product **58** as a white solid (1.21 g, 72% yield, m.p. 95–96 °C).

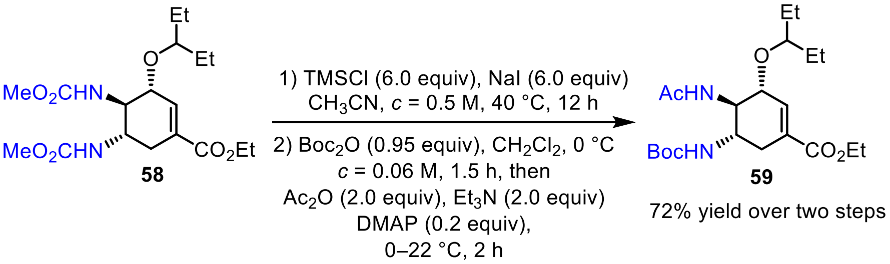


To an oven-dried 25 mL round bottom flask equipped with a stir bar were added **57** (158 mg, 0.5 mmol, 1.0 equiv) and 5 Å molecular sieves powder (200 mg). After the flask was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (1.0 mL) and freshly distilled pentan-3-yl 2,2,2-trichloroacetimidate **51** (3.1 mL, 17.5 mmol, 35 equiv) were added. The reaction was cooled to 0 °C and MsOH (1.15 mL, 17.5 mmol, 35 equiv) was added in 3 h using a syringe pump. After the addition of MsOH, the reaction mixture was warmed up to 28 ºC and stirred at this temperature for 24 h. The mixture was filtered and the solid was washed with CH_2Cl_2 (5 mL×4). The filtrate was concentrated *in vacuo* and the residue was purified through column chromatography (hexanes/EtOAc: from 30:1 to 2:1) to afford the desired product **58** as a white solid (124 mg, 64% yield, m.p. 95–96 °C).



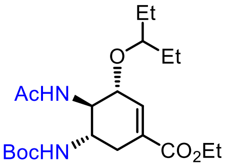
58

Ethyl (3*R*,4*R*,5*S*)-4,5-bis((methoxycarbonyl)amino)-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (**58**): $[\alpha]_D^{20}$ = –54.6° (*c* 0.85, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 3313 (m), 2921 (s), 1697 (s), 1544 (m), 1286 (m), 1231 (m), 1058 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 5.50 (s, 1H), 4.86 (d, *J* = 8.4 Hz, 1H), 4.19 (q, *J* = 6.7 Hz, 2H), 4.06–3.9 (m, 1H), 3.90–3.88 (m, 1H), 3.80–3.75 (m, 1H), 3.65 (s, 3H), 3.63 (s, 3H), 3.39 (quint, *J* = 5.6 Hz, 1H), 2.72 (dd, *J* = 17.1, 4.8 Hz, 1H), 2.36 (dd, *J* = 18.4, 8.0 Hz, 1H), 1.56–1.48 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.91–0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 157.5, 157.1, 136.8, 129.3, 82.4, 77.2, 75.1, 60.9, 55.2, 52.3, 52.1, 49.5, 30.4, 26.1, 25.7, 14.1, 9.3, 9.2; LRMS (ESI, m/z): calcd for $C_{18}H_{31}N_2O_7^+$, [M + H$^+$], 387.2, found 387.2.



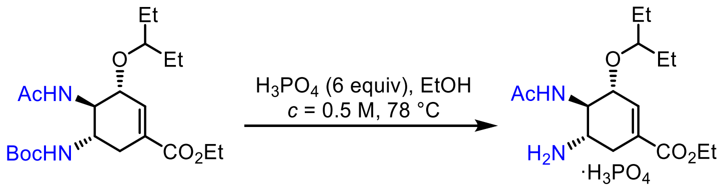
To a flame-dried 50 mL round bottom flask equipped with a stir bar were **58** (1.0 g, 2.6 mmol, 1.0 equiv) and anhydrous NaI (2.34 g, 15.6 mmol, 6.0 equiv). After this flask was evacuated and backfilled with N_2 twice, anhydrous MeCN (5.2 mL) was added followed by drop-wise addition of freshly distilled TMSCl (1.98 mL, 15.6 mmol, 6.0 equiv) via a syringe. The mixture was warmed up to 40 ºC and stirred at this temperature for 12 h in dark. The reaction was cooled down to 0 °C and diluted with CH_2Cl_2 (30 mL). Saturated Na_2CO_3 solution (10 mL), H_2O (5 mL) and saturated $Na_2S_2O_3$ solution (2 mL) were added and the mixture was stirred for additional 5 min. The organic phase was separated from the aqueous phase and the aqueous phase was further extracted with CH_2Cl_2 (80 mL×3). The combined organic phase was washed with water (10 mL×2), brine (10 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the crude diamine product will be used directly in the next step without further purification.

To an oven-dried 100 mL round bottom flask equipped with a stir bar was added the crude diamine product obtained in last step. The flask was evacuated and backfilled with N_2 twice and then anhydrous CH_2Cl_2 (40 mL) was added. Subsequently, a solution of Boc_2O (546 mg, 2.5 mmol, 0.95 equiv) in CH_2Cl_2 (2 mL) was added to the flask at 0 ºC within 40 min using a syringe pump. The mixture was warmed up to room temperature and stirred for additional 1 h (monitored by TLC until the diamine starting material was consumed). Et_3N (0.72 mL, 5.2 mmol, 2.0 equiv), Ac_2O (0.49 mL, 5.2 mmol, 2.0 equiv) and a solution of DMAP (64 mg, 0.5 mmol, 0.2 equiv) in CH_2Cl_2 (0.5 mL) were added to the above mixture at 0 ºC. The reaction mixture was warmed up to room temperature and kept stirring for additional 2 h until the intermediate was consumed (monitored by TLC). Saturated $NaHCO_3$ solution (10 mL) was added to quench the reaction. The organic phase was separated from the aqueous phase and the aqueous phase was extracted with CH_2Cl_2 (30 mL×2). The combined organic phase was washed with brine (10 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 30:1 to 2:1) to afford the desired product **59** as a white solid (772 mg, 72% yield over two steps, m.p. 141–142 °C).



59

Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-((*tert*-butoxycarbonyl)amino)-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (**59**): $[\alpha]_D^{20}$ = –77.0° (*c* 1.06, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 3313 (m), 2971 (m), 2932 (m), 1681 (s), 1654 (s), 1544 (m), 1297 (m), 1242 (s), 1051 (m), 1013 (m), 943 (m), 733(m); ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 5.89 (d, *J* = 9.0 Hz, 1H), 5.17 (d, *J* = 9.1 Hz, 1H), 4.25–4.15 (m, 2H), 4.06 (dd, *J* = 18.5, 9.0 Hz, 1H), 3.97–3.95 (m, 1H), 3.78 (qd, *J* = 9.7, 5.4 Hz, 1H), 3.36 (quint, *J* = 5.6 Hz, 1H), 2.73 (dd, *J* = 17.8, 5.0 Hz, 1H), 2.43–2.20 (m, 1H), 1.97 (s, 3H), 1.62–1.45 (m, 4H), 1.41 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.89–0.81 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 166.0, 156.3, 137.6, 129.3, 82.2, 79.7, 75.9, 61.0, 54.4, 49.0, 30.9, 28.3, 26.1, 25.7, 23.4, 14.2, 9.5, 9.2; LRMS (ESI, m/z): calcd for $C_{21}H_{37}N_2O_6^+$, [M + H^+], 413.3, found 413.3.

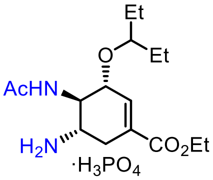


59

1 (Tamiflu®)

83% yield

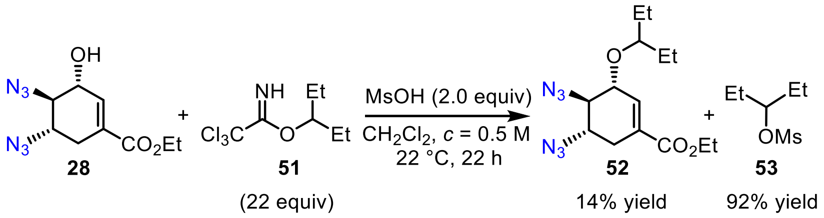
To an oven-dried 10 mL round bottom flask equipped with a stir bar was added **59** (1.21 g, 2.9 mmol). The flask was evacuated and backfilled with N_2 twice and then EtOH (4 mL) was added. Subsequently, H_3PO_4 (1.08 mL, 17.6 mmol, 6.0 equiv) in EtOH (1.8 mL) was added to the flask at room temperature using a syringe. The mixture was warmed up to 78 ºC and stirred for additional 12 h (monitored by TLC until the starting material was consumed). The mixture was then cooled to 0 ºC and stirred for 3 h with precipitates generated. The reaction mixture was filtered and the solid was washed with cold acetone (2.0 mL×3). The solid was collected and dried *in vacuo* to afford the desired product **1** (Tamiflu) as a white solid (1.0 g, 83% yield, m.p. 188–190 °C).



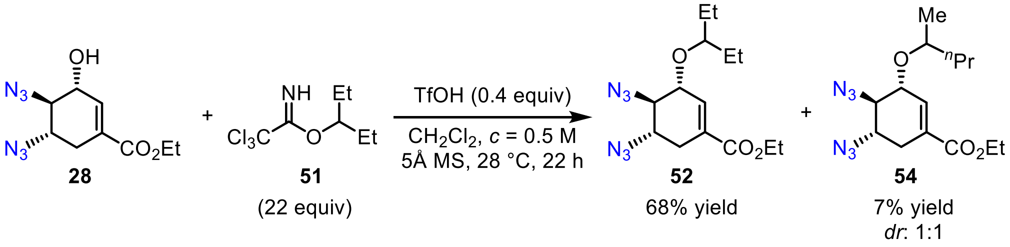
1 (Tamiflu®)

Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(pentan-3-yloxy) cyclohex-1-ene-1-carboxylate (**Tamiflu**, **1**): $[\alpha]_D^{20}$ = –30° (c 1.01, H_2O). IR ν_{max} (neat)/cm^{-1}: 3347 (m), 3169 (br), 2966 (w), 2937 (w), 2874 (w), 1716 (s), 1656 (s), 1549 (s), 1243 (s), 1120 (s), 952 (s), 850 (m) ; ^{1}H NMR (400 MHz, D_2O) δ 6.85 (s, 1H), 4.33 (d, J = 8.8 Hz, 1H), 4.25 (dt, J = 7.2, 5.3 Hz, 2H), 4.05 (dd, J = 11.6, 8.8 Hz, 1H), 3.62–3.53 (m, 2H), 2.96 (dd, J = 17.0, 5.6 Hz, 1H), 2.55–2.45 (m, 1H), 2.08 (s, 3H), 1.60–1.40 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H), 0.90–0.76 (m, 6H); ^{13}C NMR (100 MHz, D_2O) δ 175.2, 167.3, 137.9, 127.5, 84.2, 75.0, 62.3, 52.6, 49.0, 28.1, 25.4, 25.0, 22.3, 13.2, 8.5, 8.4; LRMS (ESI, m/z): calcd for $C_{16}H_{29}N_2O_4^+$, [M – H_3PO_4 + H$^+$], 313.2, found 313.2.

b. Related Synthetic Explorations

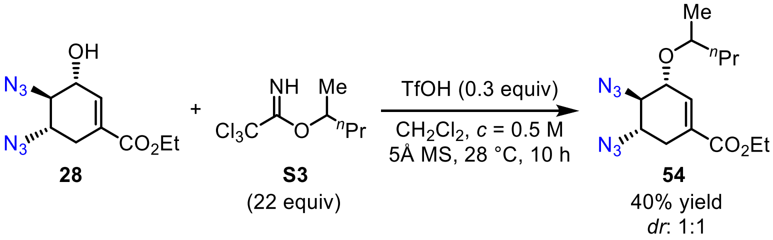


To an oven-dried 25 mL round bottom flask equipped with a stir bar were added **28** (504 mg, 2.0 mmol, 1.0 equiv) and 5 Å molecular sieves powder (500 mg). After the flask was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (4.0 mL) and freshly distilled pentan-3-yl 2,2,2-trichloroacetimidate **51** (7.7 mL, 44 mmol, 22 equiv) were added. The reaction was cooled to 0 °C and MsOH (260 μL, 4.0 mmol, 2.0 equiv) was added. After the addition of MsOH, the reaction mixture was warmed up to 22 ºC and stirred at this temperature for 22 h. The mixture was cooled to 0 ºC, and Et_3N (0.28 mL, 2.0 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added to quench the reaction. The mixture was filtered and the solid was washed with CH_2Cl_2 (7 mL×4). The filtrate was concentrated *in vacuo* and the residue was purified through column chromatography (hexanes/EtOAc: from 100:1 to 10:1) to afford the desired product **52** as colorless oil (90 mg, 14% yield) along with the side product **53** as colorless oil (306 mg, 92% yield) which is a known compound.[9]

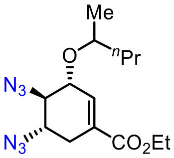


To an oven-dried 25 mL round bottom flask equipped with a stir bar were added **28** (504 mg, 2.0 mmol, 1.0 equiv) and 5 Å molecular sieves powder (500 mg). After the flask was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (4.0 mL) and freshly distilled pentan-3-yl 2,2,2-trichloroacetimidate **51** (7.7 mL, 44 mmol, 22 equiv) were added. The reaction was cooled to 0 °C and TfOH (71 μL, 0.8 mmol, 0.4 equiv) was added. After the addition of TfOH, the reaction mixture was warmed up to 28 ºC and stirred at this temperature for 22 h until **28** was fully consumed (monitored by TLC). The mixture was cooled to 0 ºC, and Et_3N (0.28 mL, 2.0 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added to quench the reaction. The mixture was filtered and the solid was washed with CH_2Cl_2 (7 mL×4). The filtrate was concentrated *in vacuo* and the residue was purified through column chromatography (hexanes/EtOAc: from 100:1 to 10:1) to afford an inseparable mixture of **52** and **54** as colorless oil (484 mg, 75% yield, **52**:**54** = 10:1).

Note: in order to confirm the structure of **54**, it was independently synthesized from **S3**. The conversion from **52** to **54** under the reaction condition was corroborated by a TfOH-catalyzed control experiment.



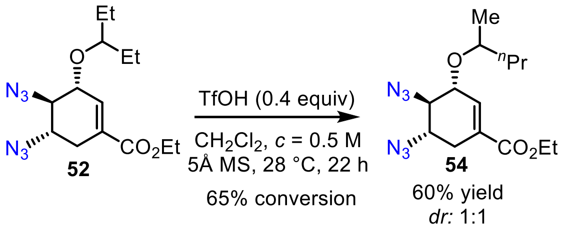
To a flame-dried sealable 3-dram vial equipped with a stir bar were added **28** (252 mg, 1.0 mmol, 1.0 equiv) and 5 Å molecular sieves powder (250 mg). After the flask was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (2.0 mL) and freshly distilled pentan-2-yl 2,2,2-trichloroacetimidate **S3** (3.84 mL, 22 mmol, 22 equiv) were added. The reaction was cooled to 0 °C and TfOH (27 μL, 0.3 mmol, 0.3 equiv) was added. After the addition of TfOH, the reaction mixture was warmed up to 28 ºC and stirred at this temperature for 10 h. The mixture was cooled to 0 ºC, and Et_3N (0.14 mL, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added to quench the reaction. The mixture was filtered and the solid was washed with CH_2Cl_2 (5 mL×4). The filtrate was concentrated *in vacuo* and the residue was purified through column chromatography (hexanes/EtOAc: from 100:1 to 10:1) to afford the product **54** as colorless oil (129 mg, 40% yield, *dr*. 1:1).



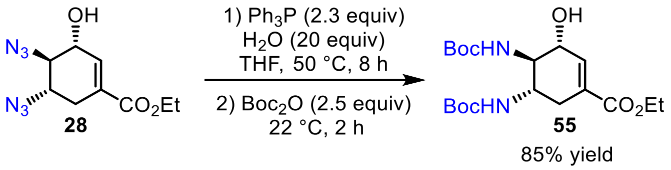
54

dr: 1:1

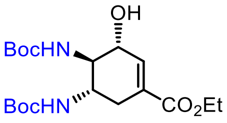
Ethyl (3*R*,4*R*,5*S*)-4,5-diazido-3-(pentan-2-yloxy)cyclohex-1-ene-1-carboxylate (54): IR ν_{max} (neat)/cm^{-1}: IR ν_{max} (neat)/cm^{-1}: 2958 (w), 2932 (w), 2877 (w), 2103 (s), 1714 (s), 1656 (w), 1369 (w), 1248 (s), 1090 (m), 1062 (s), 735 (s); *Diastereomer 1:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (t, *J* = 2.0 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.08–4.01 (m, 1H), 3.75 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.52–3.35 (m, 2H), 2.91–2.84 (m, 1H), 2.31–2.16 (m, 1H), 1.69–1.49 (m, 2H), 1.45–1.37 (m, 2H), 1.29 (t, *J* = 6.4 Hz, 3H), 1.25 (d, *J* = 6.4 Hz, 3H), 0.97–0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 137.3, 128.2, 76.8, 76.2, 67.7, 61.2, 59.7, 39.2, 30.3, 20.7, 18.7, 14.2, 14.1; *Diastereomer 2:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (t, *J* = 2.1 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.98 (ddd, *J* = 7.9, 3.7, 1.9 Hz, 1H), 3.68 (dt, *J* = 12.2, 6.0 Hz, 1H), 3.52–3.35 (m, 2H), 2.90–2.84 (m, 1H), 2.31–2.18 (m, 1H), 1.49–1.33 (m, 4H), 1.29 (t, *J* = 6.4 Hz, 3H), 1.21 (d, *J* = 6.0 Hz, 3H), 0.97–0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 136.5, 128.2, 76.4, 75.5, 67.0, 61.2, 59.3, 38.7, 30.2, 19.2, 18.7, 14.2, 14.1; LRMS (ESI, m/z): calcd for $C_{14}H_{22}N_6O_3Na^+$, [M + Na^+], 345.2, found 345.2.



To a flame-dried sealable 3-dram vial equipped with a stir bar were added **52** (100 mg, 0.31 mmol, 1.0 equiv) and 5 Å molecular sieves powder (100 mg). After the flask was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (0.6 mL) was added. The reaction was cooled to 0 °C and TfOH (11 μL, 0.12 mmol, 0.4 equiv) was added. The reaction mixture was warmed up to 28 ºC and stirred at this temperature for 22 h, then the mixture was cooled to 0 ºC, and Et_3N (43 μL, 0.31 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added to quench the reaction. The mixture was filtered and the solid was washed with CH_2Cl_2 (5 mL×4). The filtrate was concentrated *in vacuo* and the residue was purified through column chromatography (hexanes/EtOAc: from 100:1 to 10:1) to afford the inseparable mixture of product **54** and the starting material **52**, which were analyzed by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard (60% NMR yield for compound **54** with *dr*. 1:1 and 35% NMR yield for the starting material **52**).

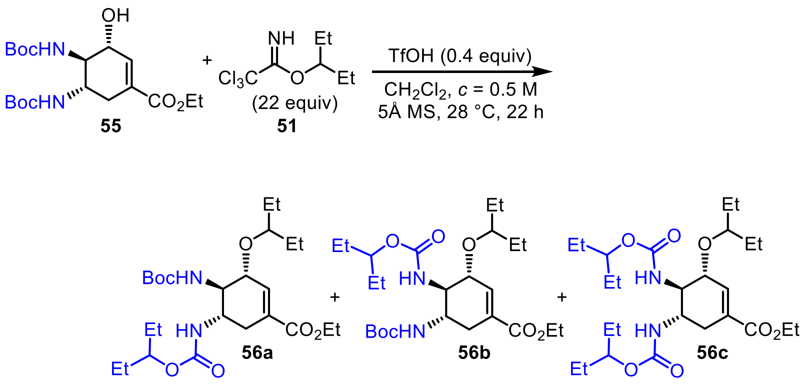


To a 50 mL round bottom flask with a stir bar was added **28** (504 mg, 2.0 mmol, 1.0 equiv). After the flask was evacuated and backfilled with N_2 twice, THF (15 mL) and H_2O (0.72 mL, 40 mmol, 20 equiv) were added via syringes. Subsequently, Ph_3P (1.2 g, 4.6 mmol, 2.3 equiv) in THF (5 mL) was added drop-wise to the reaction at 0 °C. The reaction mixture was warmed up to 50 °C and stirred for 8 h (monitored by IR until the absorption of azido groups disappeared). The reaction mixture was cooled to room temperature, then Boc_2O (1.09 g, 5.0 mmol, 2.5 equiv) in THF (5 mL) was added, the reaction mixture was stirred for 2 h at 22 °C. The mixture was concentrated *in vacuo* and re-dissolved in EtOAc (20 mL) and H_2O (10 mL), The organic phase was separated from the aqueous phase and the aqueous phase was further extracted with EtOAc (10 mL×3). The combined organic phase was dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (hexanes/EtOAc: from 50:1 to 2:1) to afford the desired product **55** as a white solid (681 mg, 85% yield, m.p. 118–120 °C).



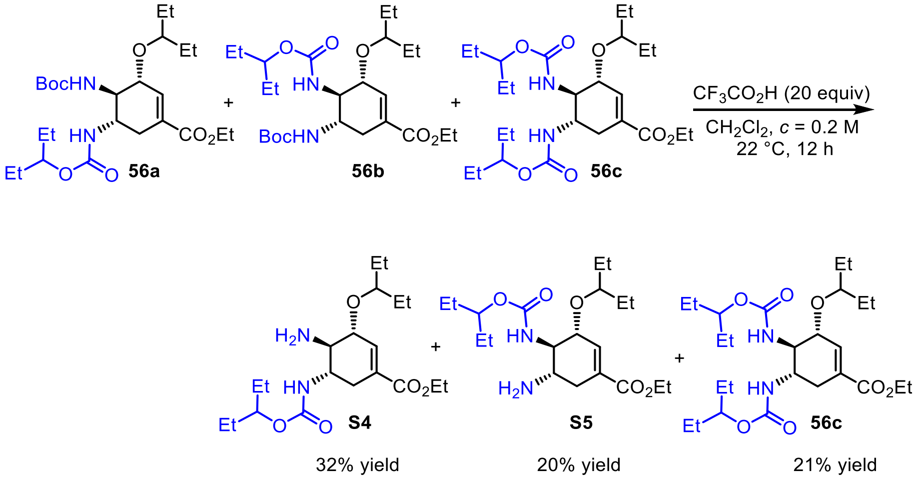
55

Ethyl (3*R*,4*R*,5*S*)-4,5-bis((*tert*-butoxycarbonyl)amino)-3-hydroxycyclohex-1-ene-1-carboxylate (55): $[\alpha]_D^{20}$ = –12.2° (*c* 1.35, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 3346 (m), 1714 (m), 1680 (s), 1528 (s), 1364 (m), 1314 (m), 1243 (s), 1166 (s), 1073 (m), 1016 (m), 967 (m), 780 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (t, *J* = 2.2 Hz, 1H), 5.72 (d, *J* = 6.8 Hz, 1H), 4.87 (d, *J* = 8.8 Hz, 1H), 4.32–4.25 (m, 1H), 4.24–4.12 (m, 3H), 3.84–3.71 (m, 1H), 3.53–3.42 (m, 1H), 2.82 (dd, *J* = 17.5, 5.1 Hz, 1H), 2.17 (ddt, *J* = 17.3, 10.9, 3.1 Hz, 1H), 1.44 (s, 9H), 1.43 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 158.4, 156.9, 138.8, 128.2, 80.3 (two carbons overlapped each other), 73.3, 61.0, 59.9, 48.4, 31.3, 28.3 (two carbons overlapped each other), 14.1; LRMS (ESI, m/z): calcd for $C_{19}H_{32}N_2O_7Na^+$, [M + Na$^+$], 423.2, found 423.2.

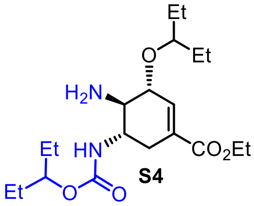


To a flame-dried sealable 3-dram vial equipped with a stir bar were added **55** (401 mg, 1.0 mmol, 1.0 equiv) and 5 Å molecular sieves powder (400 mg). After the vial was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (2.0 mL) and freshly distilled pentan-3-yl 2,2,2-trichloroacetimidate (3.84 mL, 22 mmol, 22 equiv) were added. The reaction was cooled to 0 °C and TfOH (36 μL, 0.4 mmol, 0.4 equiv) was added. After the addition of TfOH, the reaction mixture was warmed up to 28 ºC and stirred at this temperature for 22 h until **55** was fully consumed (monitored by TLC). The mixture was cooled to 0 ºC, and Et_3N (0.14 mL, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added to quench the reaction. The mixture was filtered and the solid was washed with CH_2Cl_2 (5 mL×4). The filtrate was concentrated *in vacuo* and the residue was purified through column chromatography (hexanes/EtOAc: from 100:1 to 10:1) to afford inseparable mixture of **56a** and **56b** and **56c** as viscous oil.

Note: in order to confirm the structures of **56a, 56b** and **56c**, They were further treated with TFA to afford **S4** and **S5**.



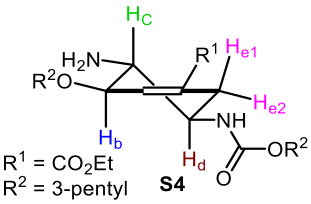
To a flame-dried sealable 3-dram vial equipped with a stir bar were added the inseparable products obtained in last step. After the vial was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (5.0 mL) was added. The reaction was cooled to 0 °C and TFA (1.53 mL, 20 mmol, 20 equiv) was added, then the reaction mixture was warmed up to 22 ºC and stirred at this temperature for 12 h. The mixture was concentrated *in vacuo* and the residue was re-dissolved in CH_2Cl_2 (10 mL), washed with saturated $NaHCO_3$ solution (3 mL), the organic phase was dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified through column chromatography (CH_2Cl_2/MeOH: from 100:1 to 10:1) to afford the product **S4** as a white solid (123 mg, 32% yield, m.p. 75–77 °C), product **S5** as viscous oil (77 mg, 20% yield) and recover product **56c** as a white solid (105 mg, 21% yield, m.p. 118–120 °C).



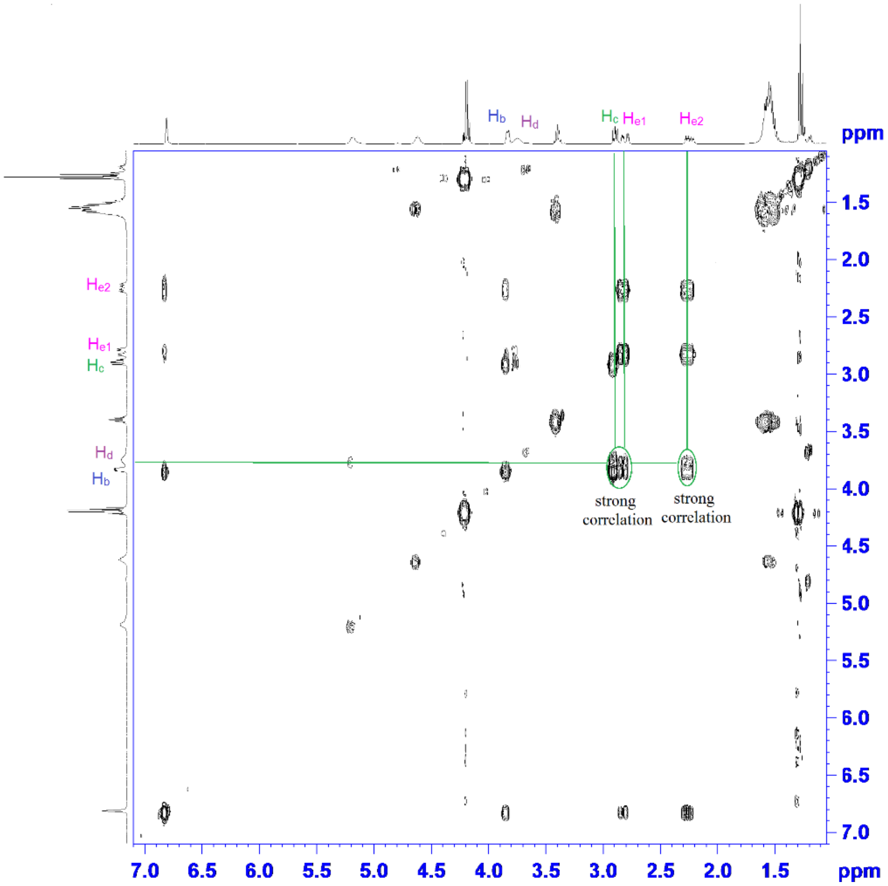
S4

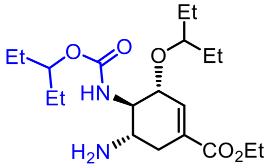
Ethyl (3*R*,4*R*,5*S*)-4-amino-3-(pentan-3-yloxy)-5-(((pentan-3-yloxy)carbonyl)amino) cyclohex-1-ene-1-carboxylate (S4): IR ν_{max} (neat)/cm^{-1}: 2967 (m), 2941 (w), 2878 (w), 1714 (s), 1693 (s), 1556 (s), 1463 (m), 1262 (s), 1237 (s), 1226 (s), 1155 (m), 1099 (s), 1043 (s), 1013 (s), 940 (s), 756 (m), 734 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 1H), 5.19 (d, *J* = 6.0 Hz, 1H), 4.69–4.54 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.88–3.80 (m, 1H), 3.79–3.58 (m, 1H), 3.40 (quint, *J* = 5.7 Hz, 1H), 2.89 (dd, *J* = 9.4, 6.9 Hz, 1H), 2.81 (dd, *J* = 17.9, 5.4 Hz, 1H), 2.25 (ddt, *J* = 18.0, 8.5, 2.6 Hz, 1H), 1.66–1.45 (m, 10H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.94–0.86 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 156.7, 136.5, 129.3, 81.3, 78.3, 77.2, 60.8, 54.9, 50.4, 30.5, 26.6 (two carbons overlapped each other), 26.3, 25.7, 14.2, 9.6 (two carbons overlapped each other), 9.5 (two carbons overlapped each other); LRMS (ESI, m/z): calcd for $C_{20}H_{36}N_2O_5Na^+$, [M + Na$^+$], 407.3, found 407.3.

Note: The structure of **S4** was further confirmed by ^1H–^1H COSY NMR analysis: there are strong correlations observed between H_d and H_{e1}/H_{e2} as well as H_d and H_c.



S4



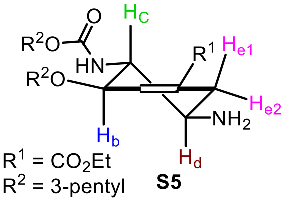


S5

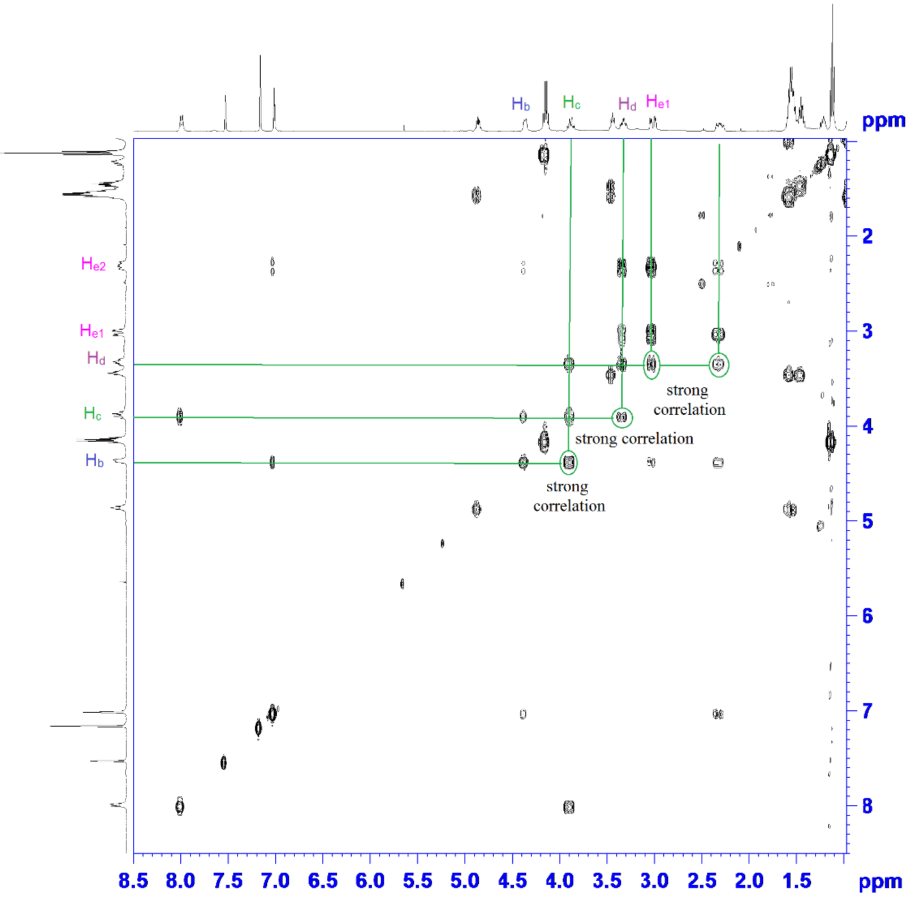
Ethyl (3*R*,4*R*,5*S*)-5-amino-3-(pentan-3-yloxy)-4-(((pentan-3-yloxy)carbonyl)amino) cyclohex-1-ene-1-carboxylate (S5): IR ν_{max} (neat)/cm^{-1}: 2965 (m), 2936 (w), 2878 (w), 1712 (s), 1690 (s), 1533 (s), 1463 (m), 1290 (m), 1231 (s), 1118 (s), 1052 (s), 925 (m), 773 (m), 733 (m);

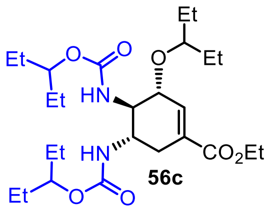
^{1}H NMR (400 MHz, pyridine-d_5) δ 7.99 (d, *J* = 8.9 Hz, 1H), 7.01 (t, *J* = 2.0 Hz, 1H), 4.91–4.80 (m, 1H), 4.38–4.37 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.88 (dd, *J* = 19.3, 9.0 Hz, 1H), 3.44 (dt, *J* = 11.0, 5.5 Hz, 1H), 3.38–3.25 (m, 1H), 3.02 (dd, *J* = 17.7, 4.8 Hz, 1H), 2.38–2.22 (m, 1H), 1.64–1.39 (m, 8H), 1.12 (t, *J* = 7.1 Hz, 3H), 0.99–0.74 (m, 12H); ^{13}C NMR (100 MHz, pyridine-d_5) δ 166.3, 157.7, 138.8, 129.7, 81.6, 76.1 (two carbons overlapped each other), 60.5, 60.3, 50.7, 34.2, 26.9, 26.8, 26.2, 25.9, 14.1, 9.6 (two carbons overlapped each other), 9.5, 9.4; LRMS (ESI, m/z): calcd for $C_{20}H_{36}N_2O_5Na^+$, [M + Na$^+$], 407.3, found 407.3.

Note: The structure of **S5** was further confirmed by ^{1}H–^{1}H COSY NMR analysis: there are strong correlations observed between H_d and H_{e1}/H_{e2}, H_d and H_c, as well as H_b and H_c.



S5





Ethyl (3*R*,4*R*,5*S*)-3-(pentan-3-yloxy)-4,5-bis(((pentan-3-yloxy)carbonyl)amino)cyclohex-1-ene-1-carboxylate (56c): IR ν_{max} (neat)/cm^{-1}: 3297 (m), 2967 (m), 2940 (w), 2879 (w), 1728 (m), 1674 (s), 1537 (s), 1462 (m), 1282 (s), 1242 (s), 1229 (s), 1057 (s), 992 (m), 926 (m), 775 (m), 732 (m); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.79 (s, 1H), 5.46 (d, *J* = 8.1 Hz, 1H), 4.75 (d, *J* = 8.4 Hz, 1H), 4.61–4.55 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.99–3.95 (m, 1H), 3.89 (dd, *J* = 16.0, 7.3 Hz, 1H), 3.81–3.78 (m, 1H), 3.40 (quint, *J* = 5.4 Hz, 1H), 2.84–2.65 (m, 1H), 2.32 (dd, *J* = 17.6, 8.0 Hz, 1H), 1.65–1.42 (m, 12H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.97–0.73 (m, 18H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 166.1, 157.3, 156.7, 136.9, 129.5, 82.2, 77.6, 77.2, 75.6, 60.9, 54.8, 49.6, 30.9, 26.6, 26.5 (two carbons overlapped each other), 26.4, 26.1, 25.8, 14.2, 9.5 (three carbons overlapped), 9.4, 9.3 (two carbons overlapped each other); LRMS (ESI, m/z): calcd for $C_{26}H_{46}N_2O_7Na^+$, [M + Na$^+$], 521.3, found 521.3.

I. References

(1) Trost, B. M.; Chupak, L. S.; Lübbers, T. "Short Preparation of (*S*)-(*E*)-1-(*O*-Methylmandeloxy)butadiene." *J. Org. Chem.* **1997**, *62*, 736.

(2) Pritchard, R. G.; Stoodley, R. J.; Yuen, W.-H. "Studies Related to Carba-pyranoses: Synthesis of Acetylated Derivatives of 4-Amino-2,4-Dideoxy-3-*O*-(β-*d*-glucopyranosyl)-β-*l*-(and β-*d*-) altrocarba-pyranose from a *d*-Glucose Template." *Org. Biomol. Chem.* **2005**, *3*, 162.

(3) Banks, R. E.; Miller, J. A.; Nunn, M. J.; Stanley, P.; Weakley, T. J. R.; Ullah, Z. "Diels-Alder Route to Potential Trichothecene Precursors." *J. Chem. Chem., Perkin Trans. 1.* **1981**, 1096.

(4) Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. "Synthesis of Tamiflu and its Phosphonate Congeners Possessing Potent Anti-Influenza Activity." *J. Am. Chem. Soc.* **2007**, *129*, 11892.

(5) Lu, D.-F.; Zhu, C.-L.; Jia, Z.-X.; Xu, H. "Iron(II)-Catalyzed Intermolecular Amino-Oxygenation of Olefins through the N–O Bond Cleavage of Functionalized Hydroxylamines." *J. Am. Chem. Soc.* **2014**, *136*, 13186.

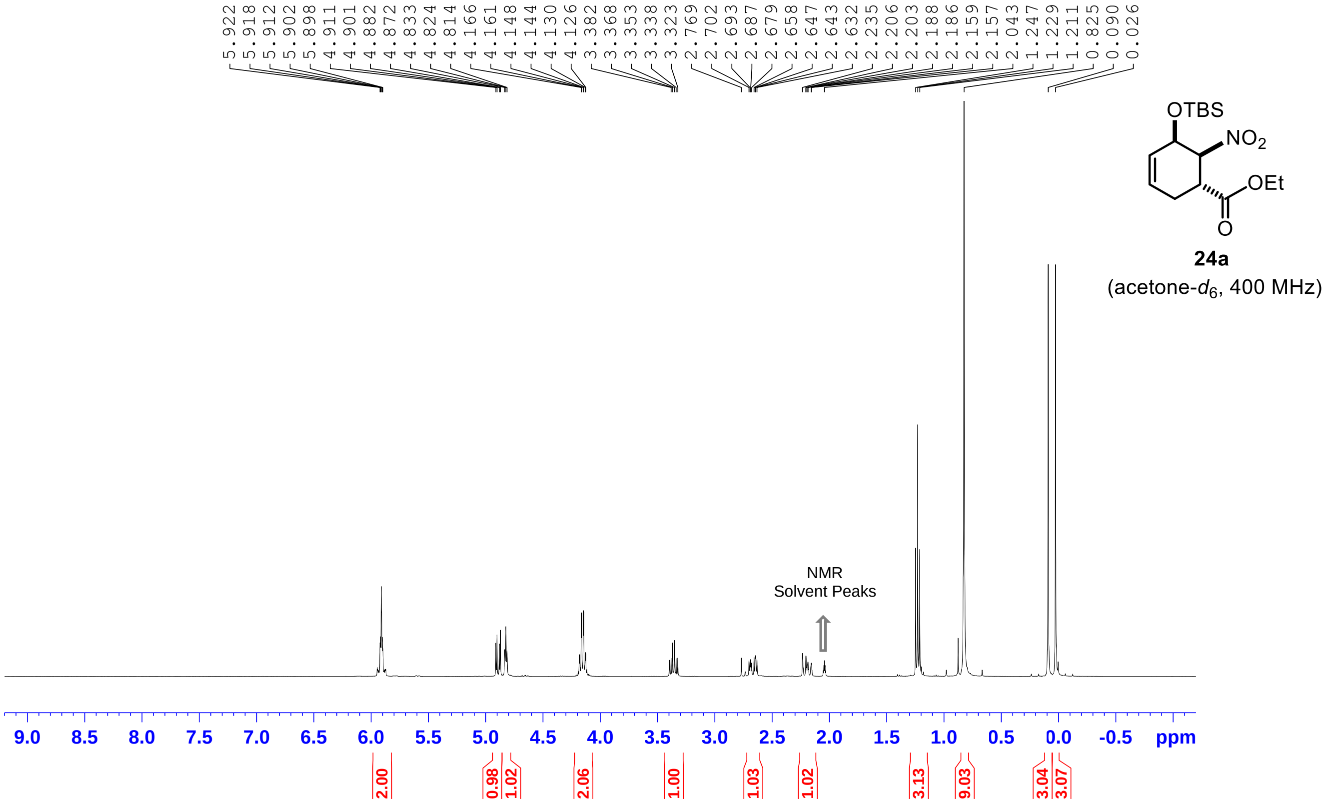
(6) Magano, J.; Chen, M. H.; Clark, J. D.; Nussbaumer, T. "2-(Diethylamino)ethanethiol, a New Reagent for the Odorless Deprotection of Aromatic Methyl Ethers." *J. Org. Chem.* **2006**, *71*, 7103.

(7) Zhu, H.-T.; Arosio, L.; Villa, R.; Nebuloni, M.; Xu, H. "Process Safety Assessment of the Iron-Catalyzed Direct Olefin Diazidation for the Expedient Synthesis of Vicinal Primary Diamines." *Org. Process Res. Dev.* **2017**, *21*, 2068.

(8) Shen, S.-J.; Zhu, C.-L.; Lu, D.-F.; Xu, H. "Iron-Catalyzed Direct Olefin Diazidation via Peroxyester Activation Promoted by Nitrogen-Based Ligands." *ACS Catal.* **2018**, *8*, 4473.

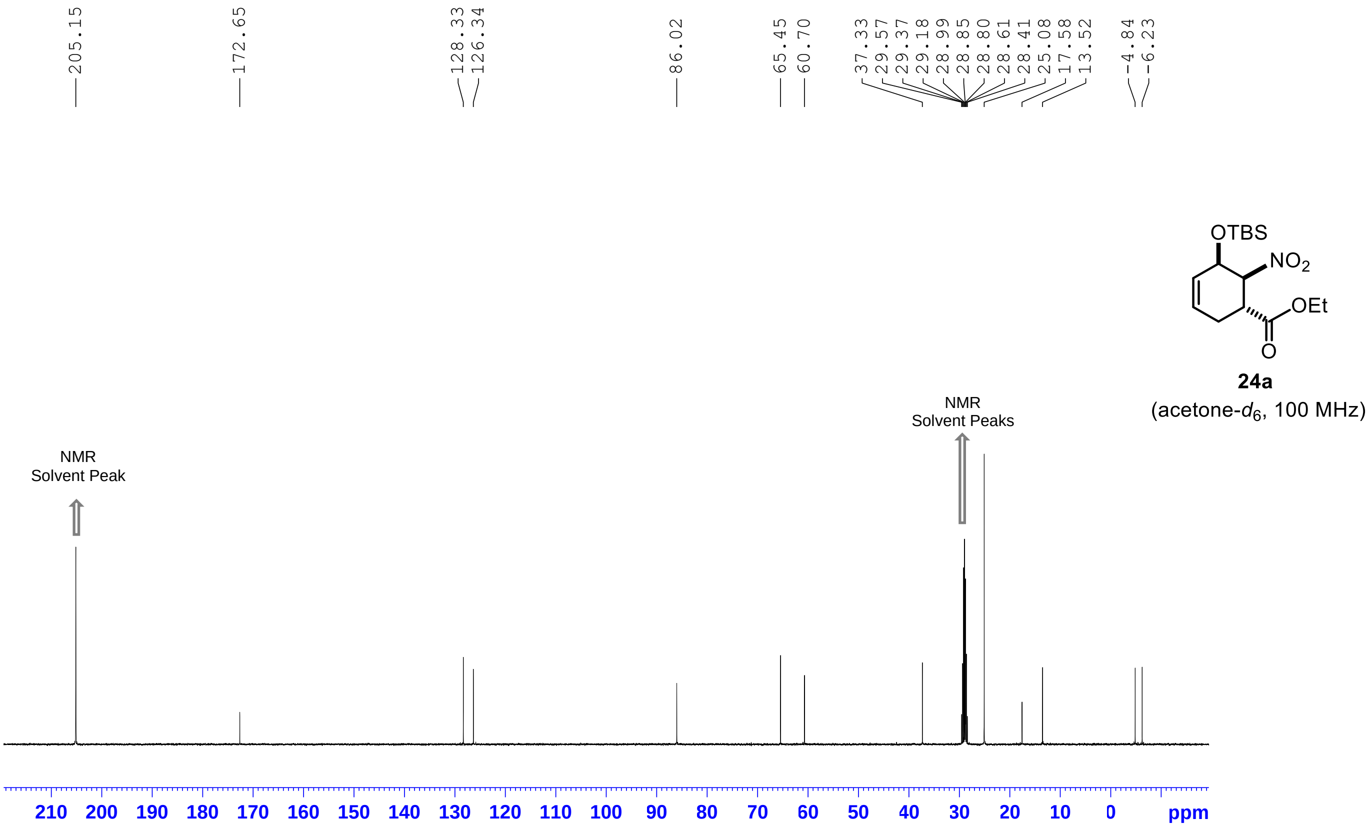
(9) Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. "New, Efficient Synthesis of Oseltamivir Phosphate (Tamiflu) via Enzymatic Desymmetrization of a meso-1,3-Cyclohexanedicarboxylic Acid Diester." *J. Org. Chem.* **2008**, *73*, 4895.

J. NMR Spectra



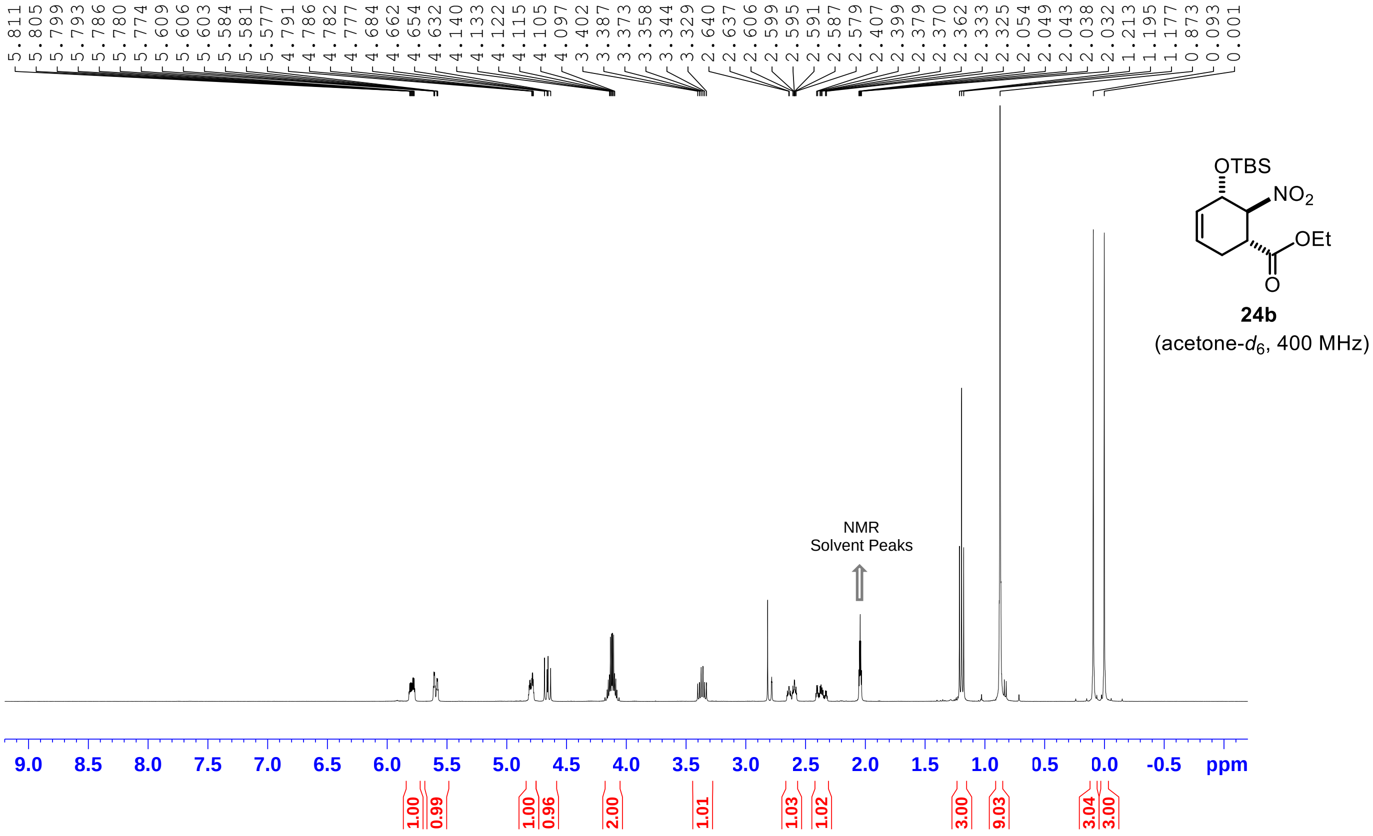
24a

(acetone-d_6, 400 MHz)



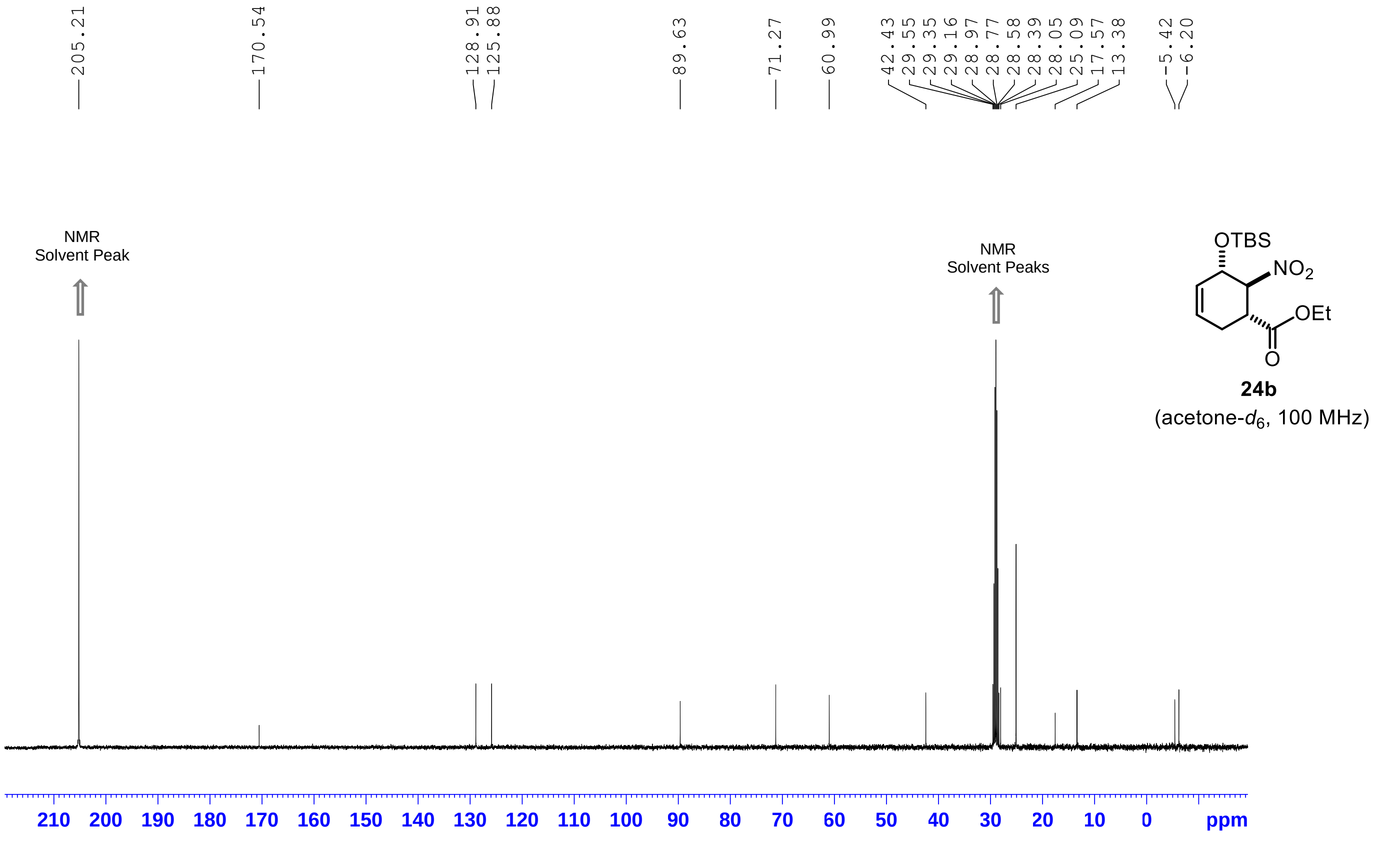
24a

(acetone-d_6, 100 MHz)



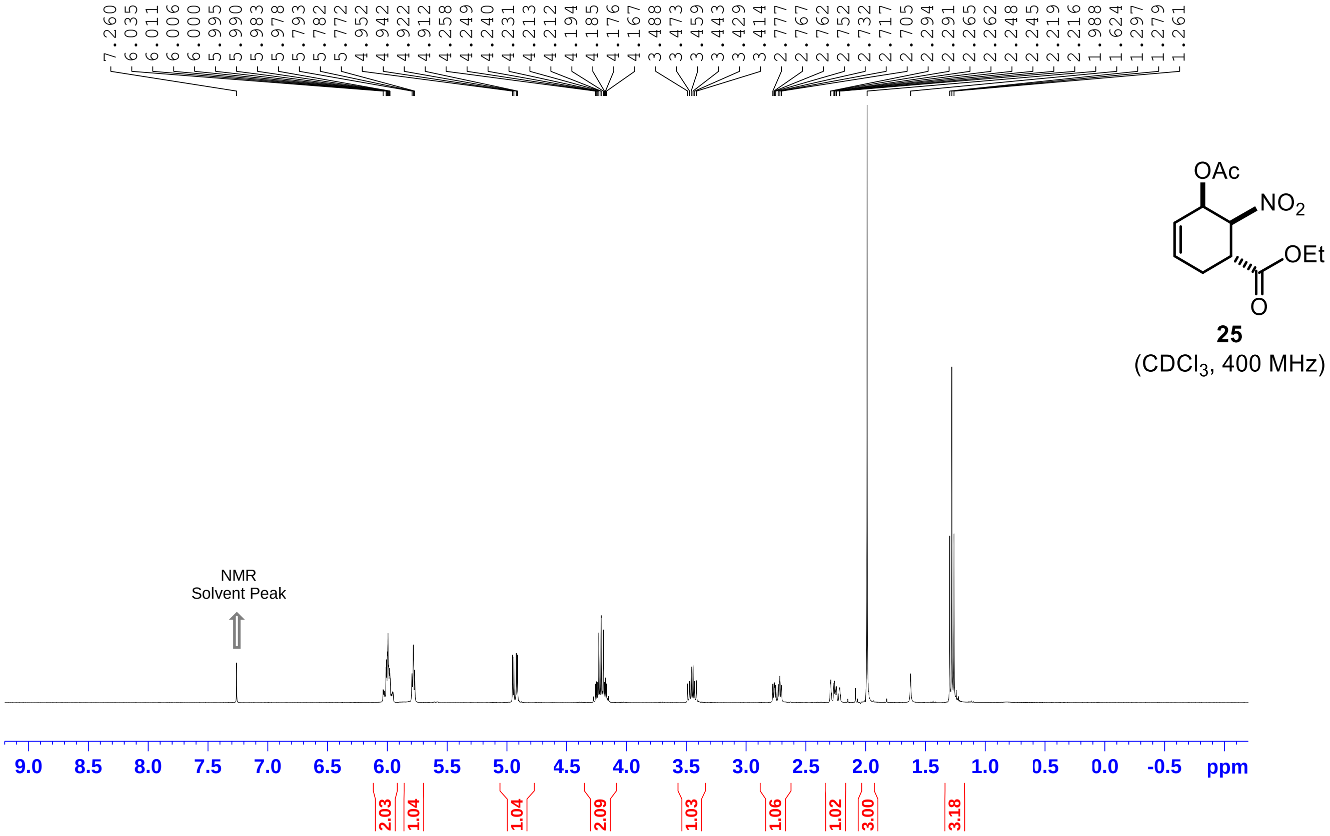
24b

(acetone-d_6, 400 MHz)



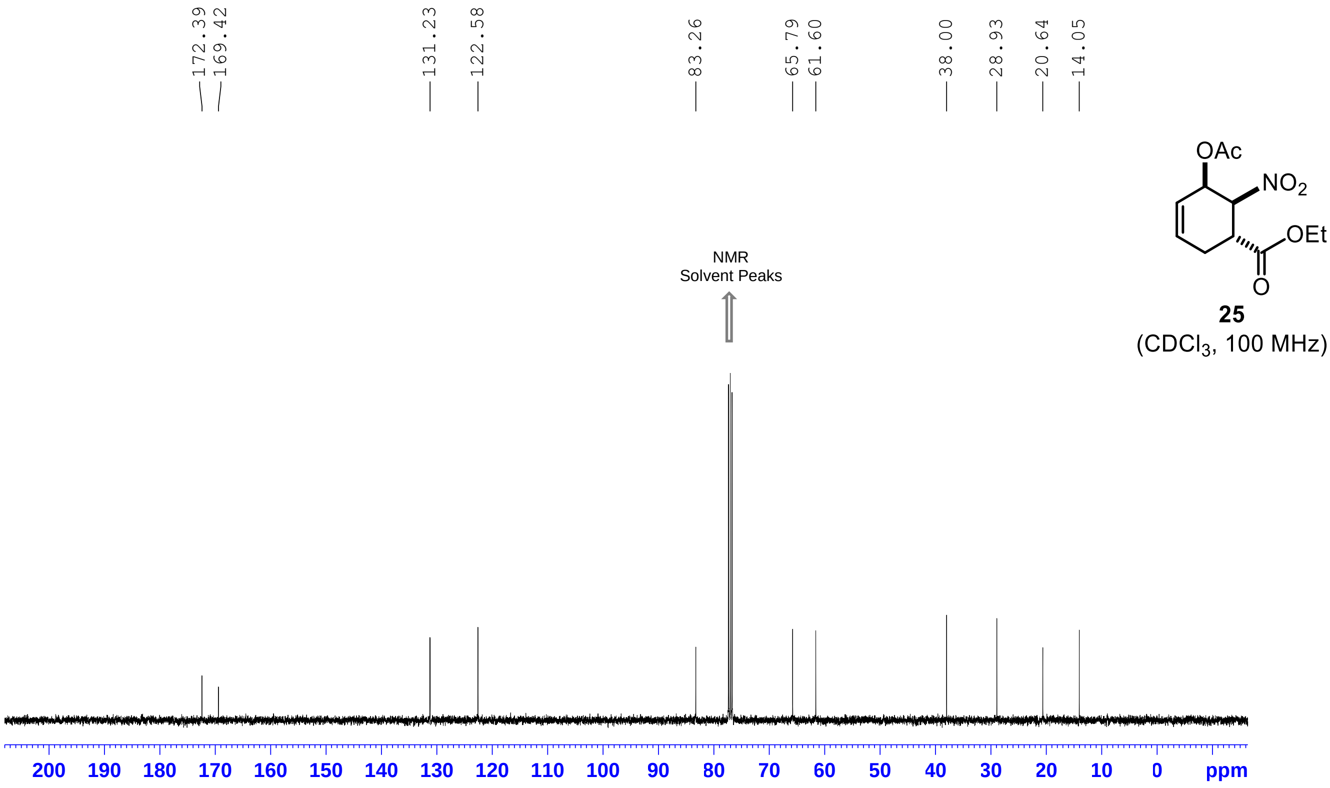
24b

(acetone-d_6, 100 MHz)



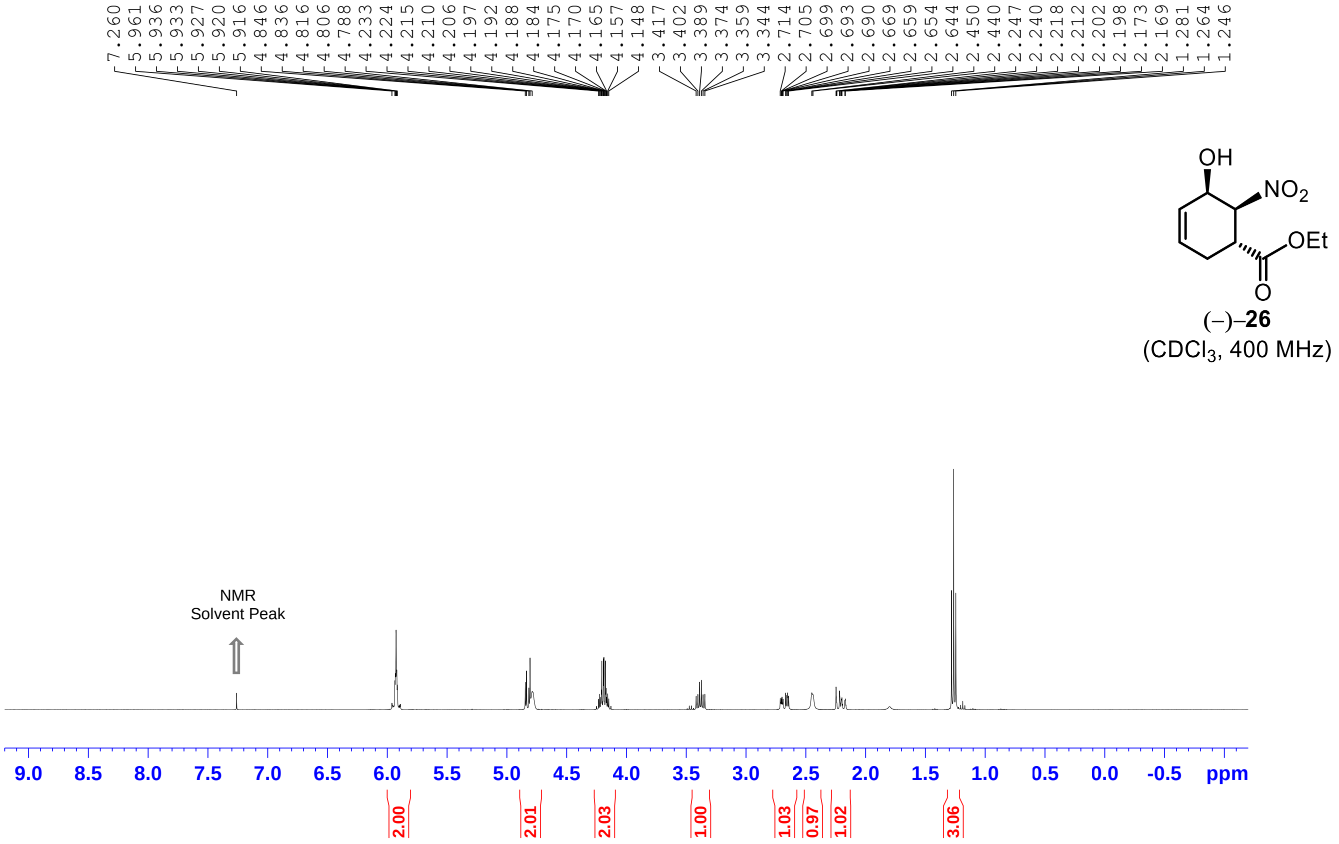
25

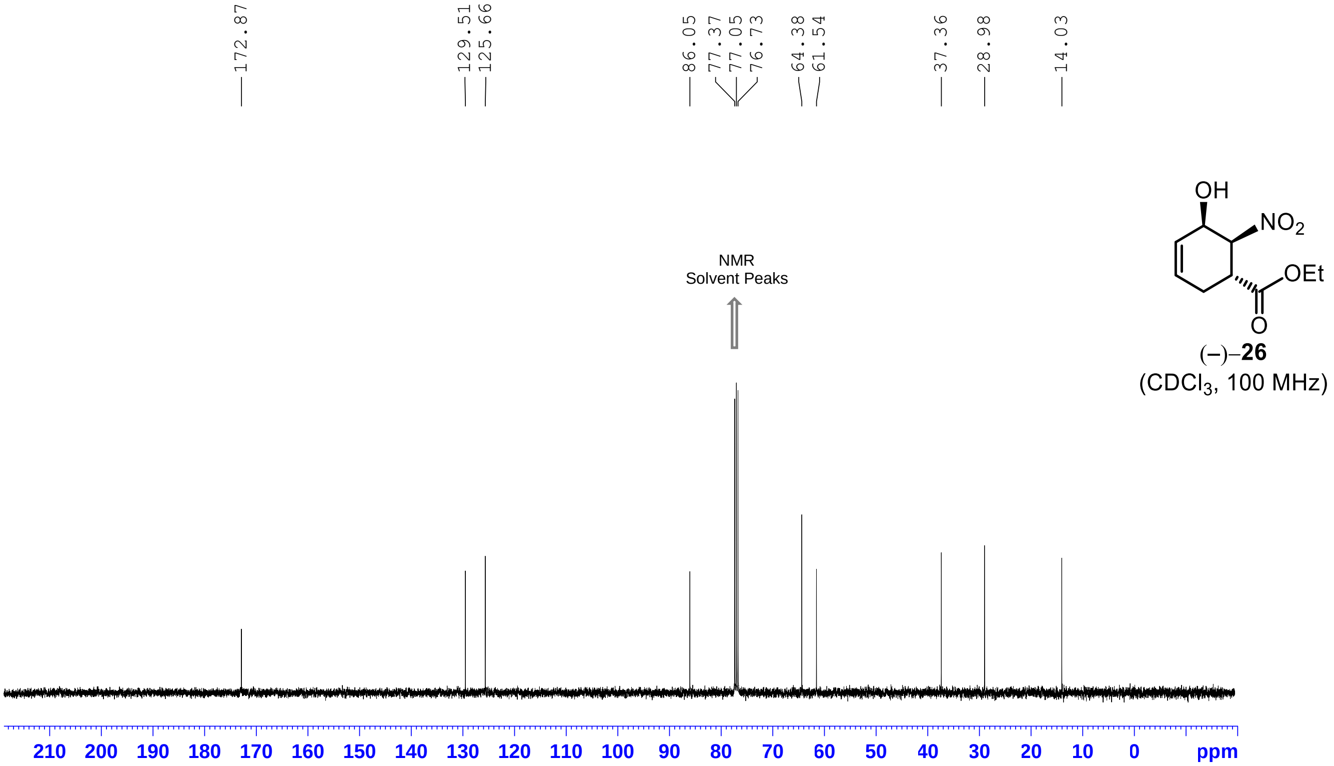
(CDCl$_3$, 400 MHz)

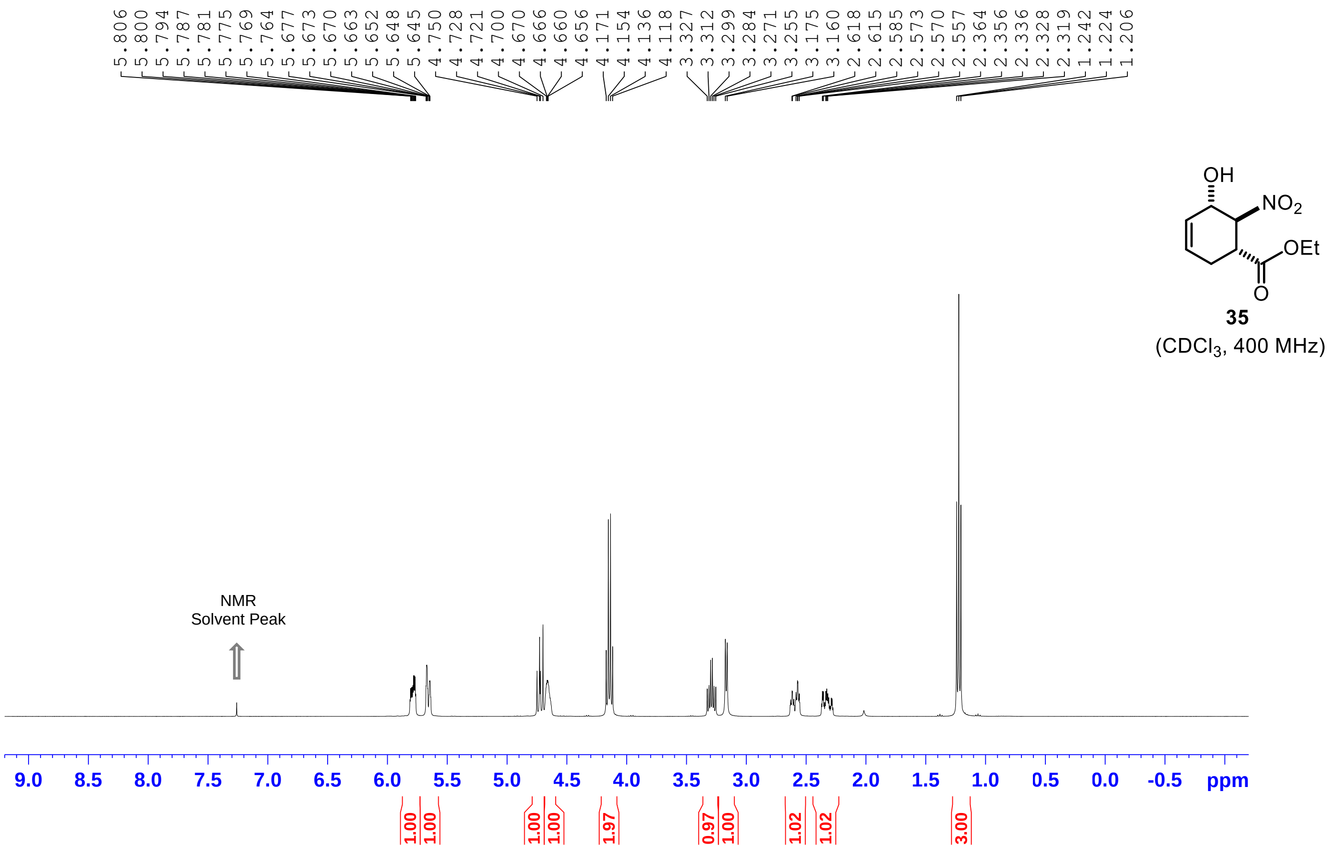


25

(CDCl$_3$, 100 MHz)

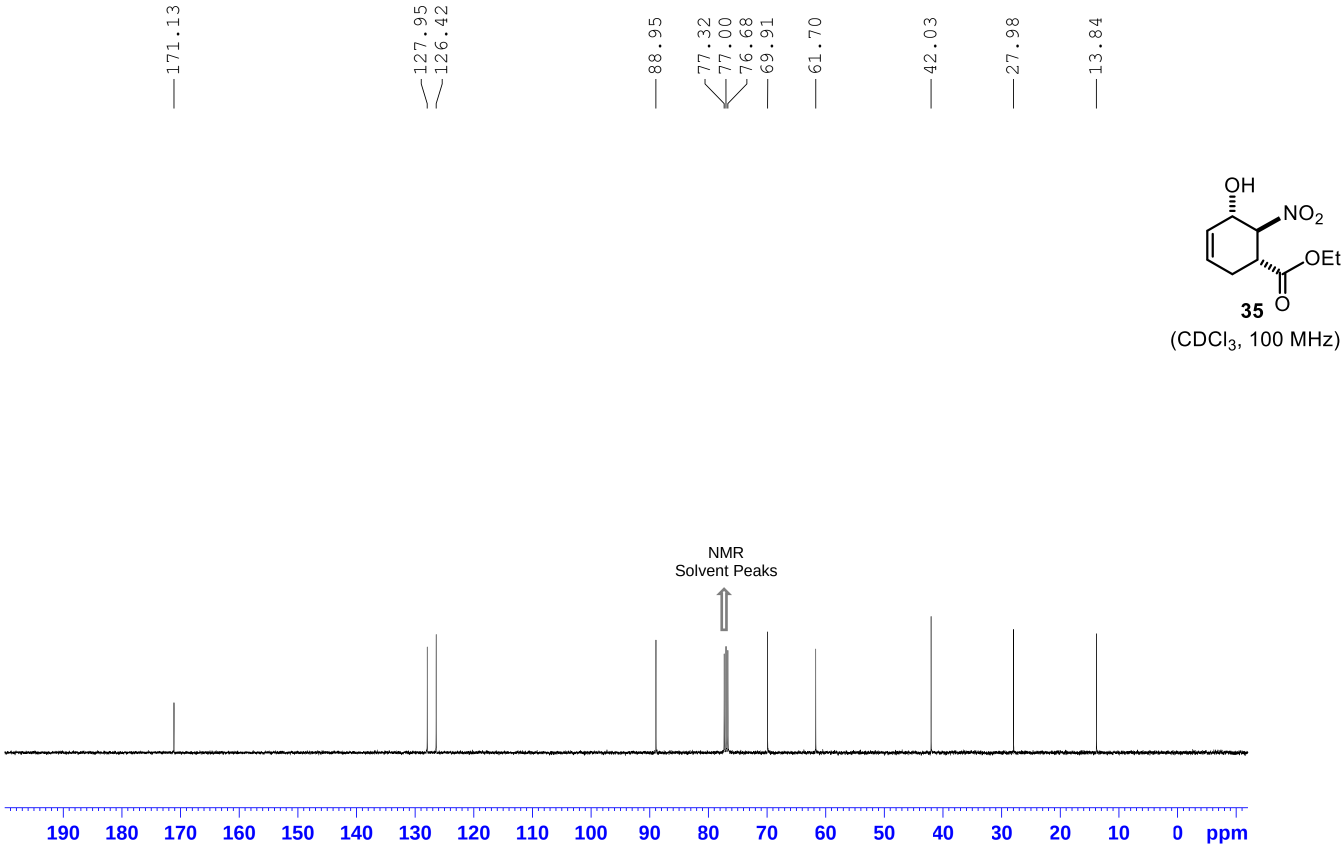

7.260
5.961
5.936
5.933
5.927
5.920
5.916
4.846
4.836
4.816
4.806
4.788
4.233
4.224
4.215
4.210
4.206
4.197
4.192
4.188
4.184
4.175
4.170
4.165
4.157
4.148
3.417
3.402
3.389
3.374
3.359
3.344
2.714
2.705
2.699
2.693
2.690
2.669
2.659
2.654
2.644
2.450
2.440
2.247
2.240
2.218
2.212
2.202
2.198
2.173
2.169
1.281
1.264
1.246
OH
NO2
OEt
O
(–)–26
(CDCl3, 400 MHz)
NMR
Solvent Peak
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
-0.5
ppm
2.00
2.01
2.03
1.00
1.03
0.97
1.02
3.06


172.87
129.51
125.66
86.05
77.37
77.05
76.73
64.38
61.54
37.36
28.98
14.03
OH
NO2
OEt
O
(–)–26
(CDCl3, 100 MHz)
NMR
Solvent Peaks
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



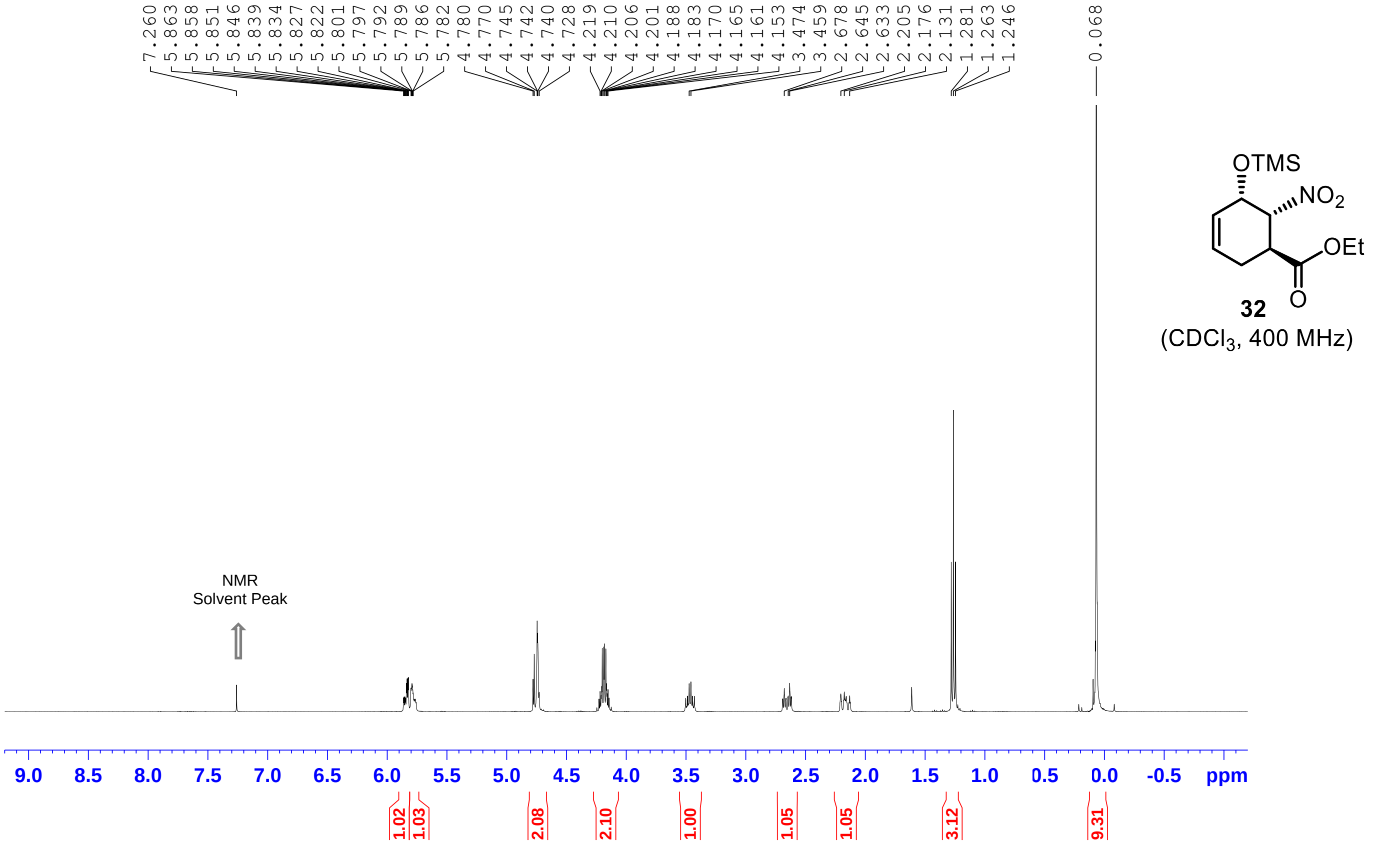
35

($CDCl_3$, 400 MHz)



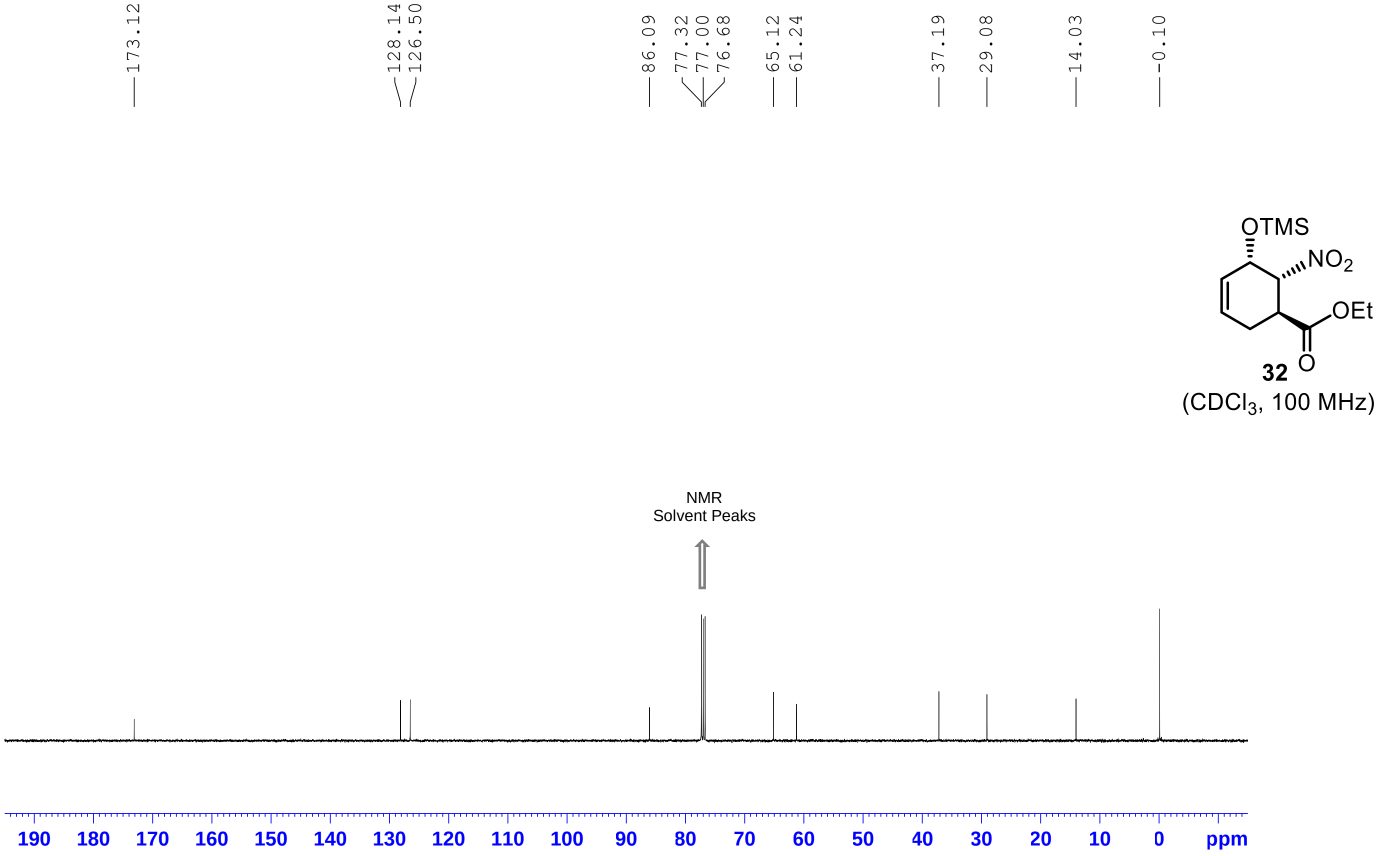
35

($CDCl_3$, 100 MHz)



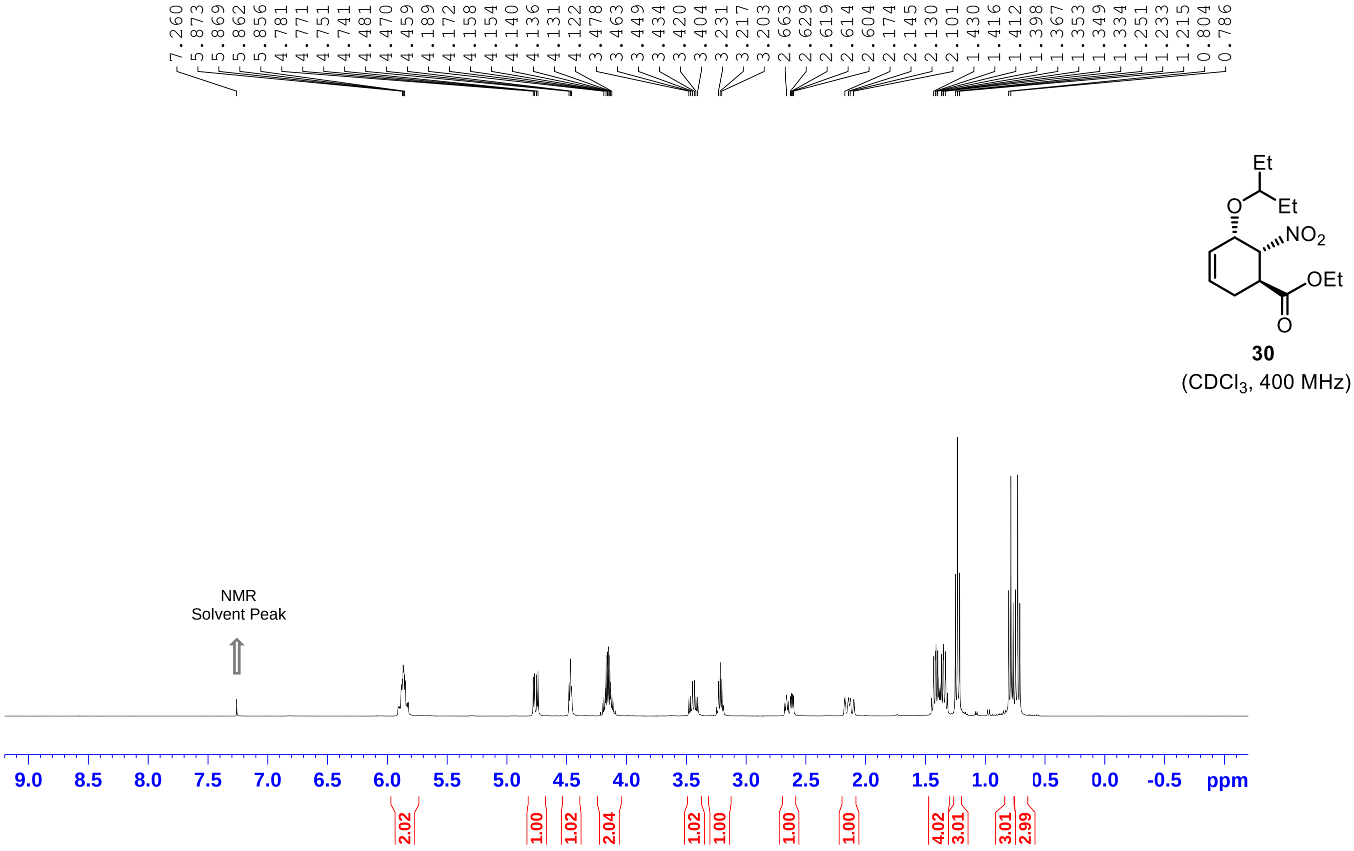
32

(CDCl$_3$, 400 MHz)



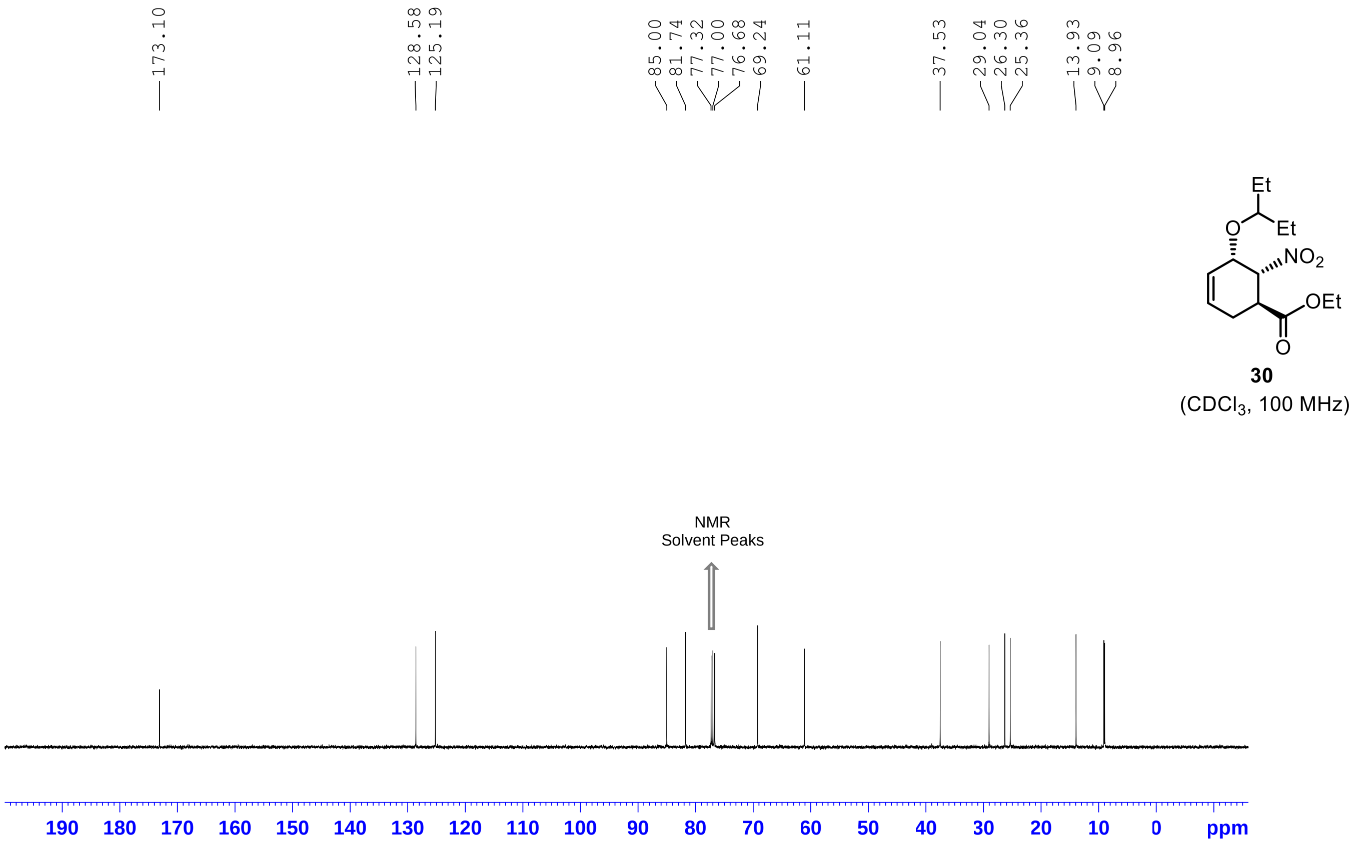
32

(CDCl$_3$, 100 MHz)



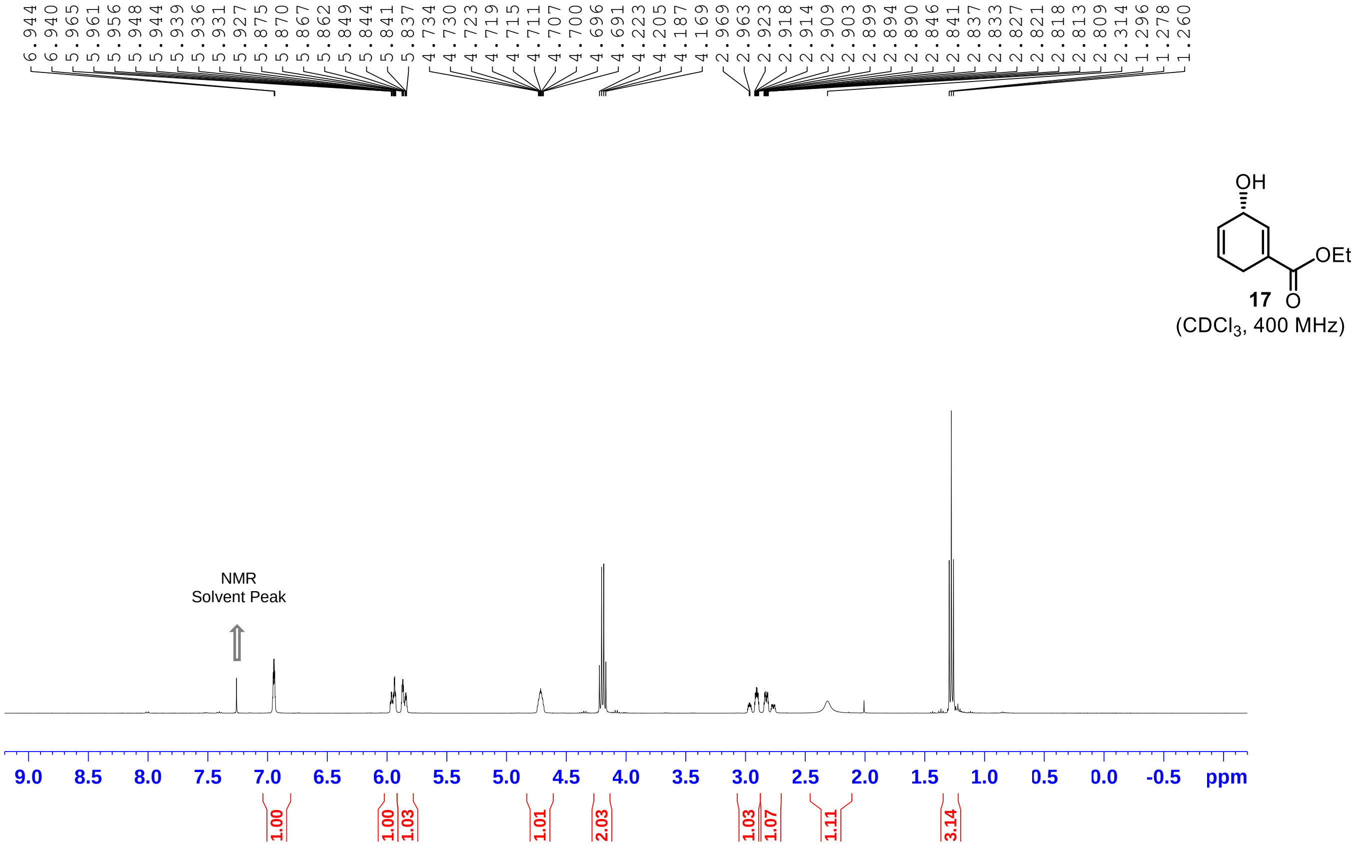
30

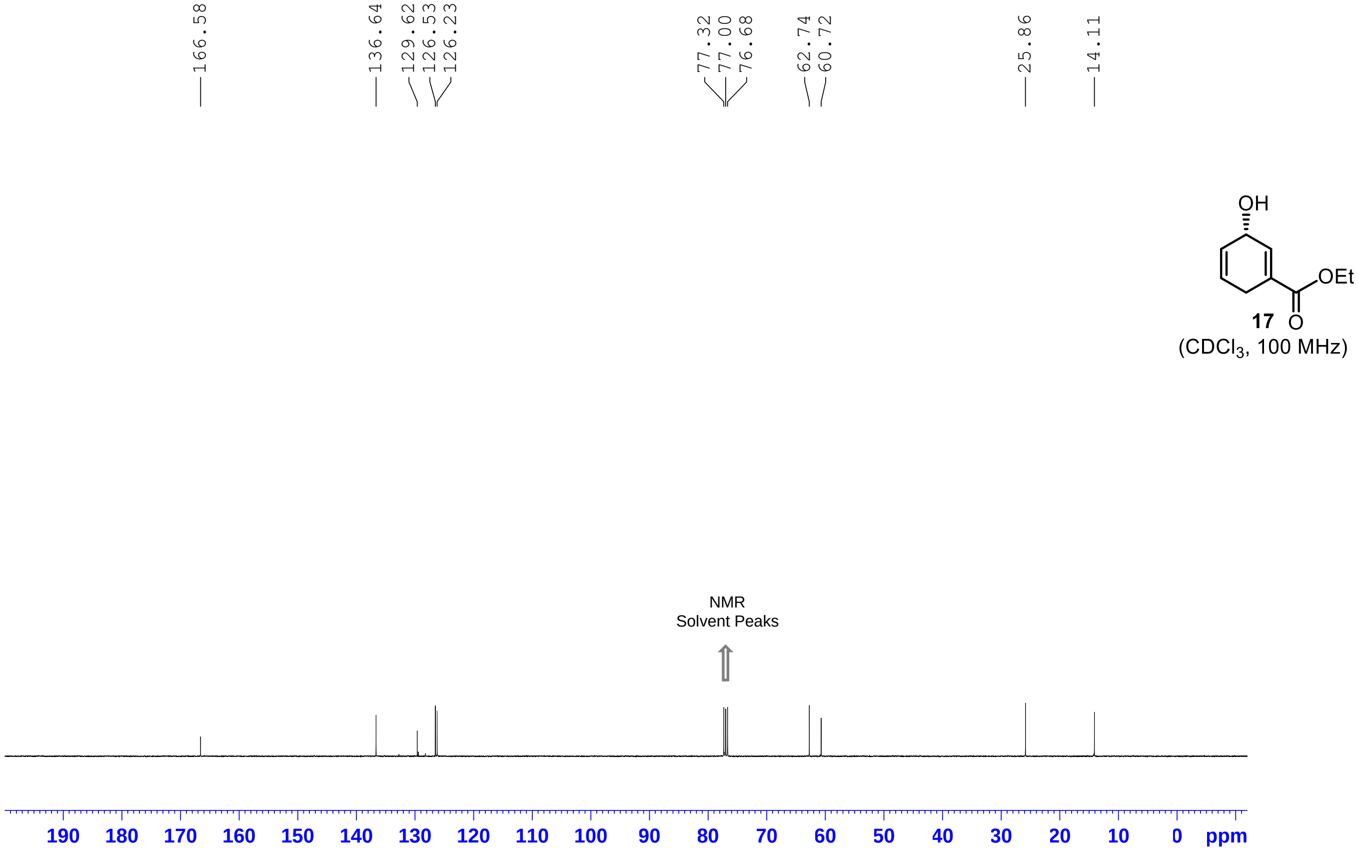
($CDCl_3$, 400 MHz)

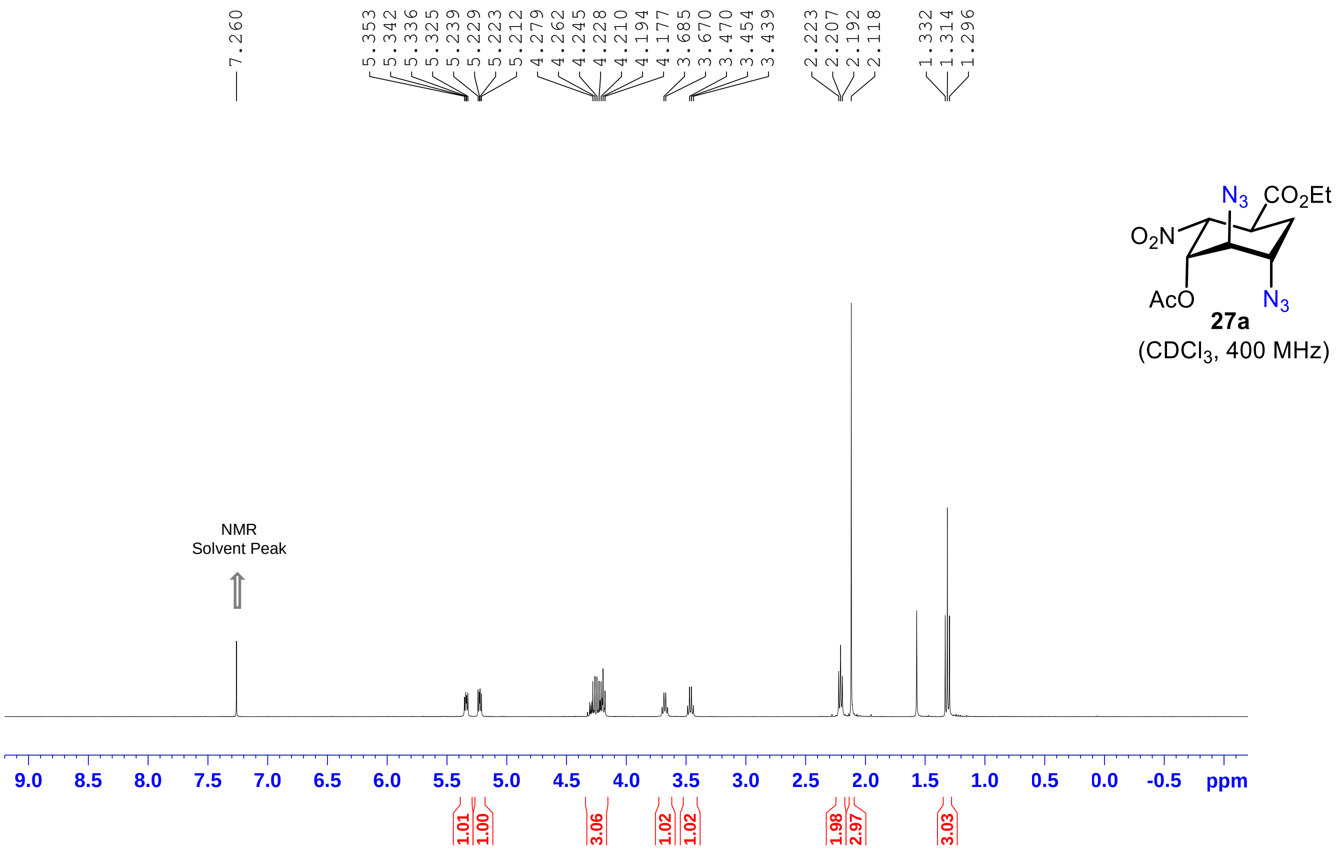


30

($CDCl_3$, 100 MHz)

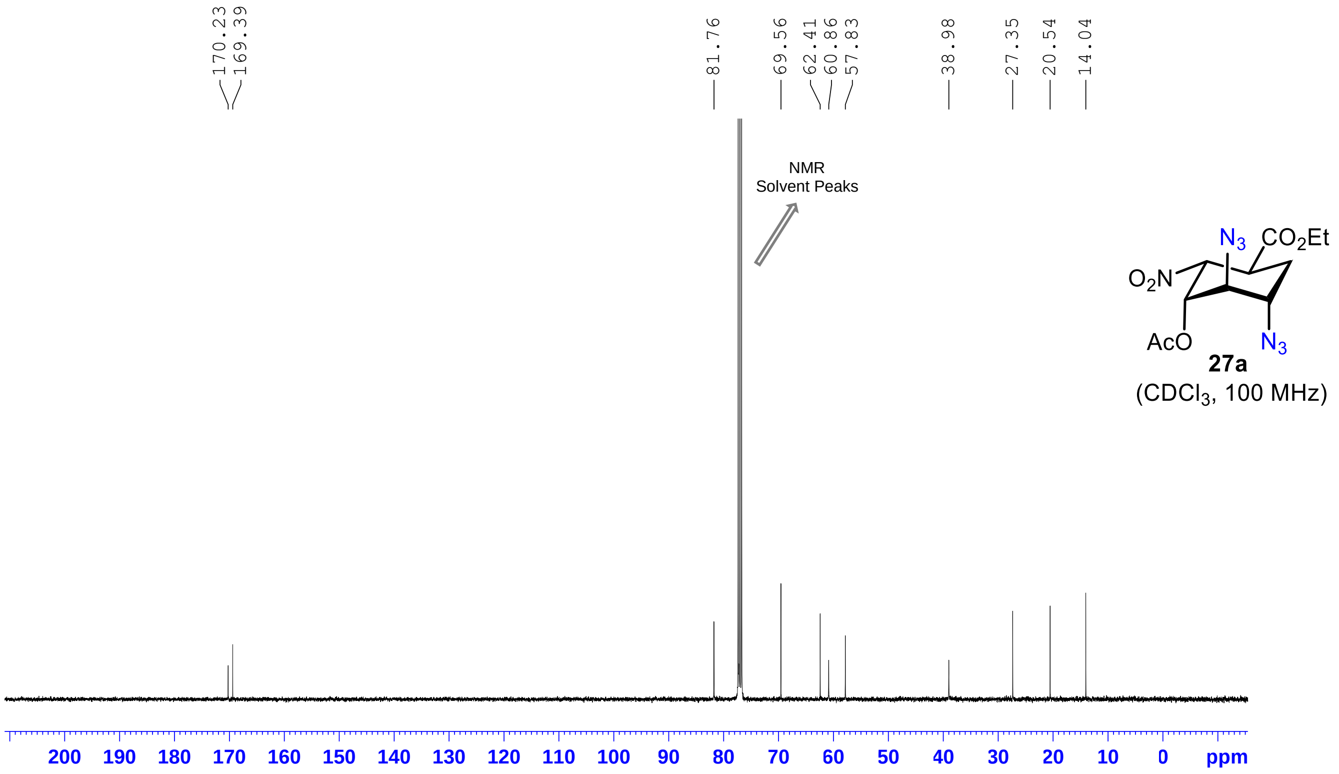

6.944
6.940
5.965
5.961
5.956
5.948
5.944
5.939
5.936
5.931
5.927
5.875
5.870
5.867
5.862
5.849
5.844
5.841
5.837
4.734
4.730
4.723
4.719
4.715
4.711
4.707
4.700
4.696
4.691
4.223
4.205
4.187
4.169
2.969
2.963
2.923
2.918
2.914
2.909
2.903
2.899
2.894
2.890
2.846
2.841
2.837
2.833
2.827
2.821
2.818
2.813
2.809
2.314
1.296
1.278
1.260
OH
OEt
17
O
(CDCl$_3$, 400 MHz)
NMR
Solvent Peak
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
-0.5
ppm
1.00
1.00
1.03
1.01
2.03
1.03
1.07
1.11
3.14


166.58
136.64
129.62
126.53
126.23
77.32
77.00
76.68
62.74
60.72
25.86
14.11
OH
OEt
17
O
(CDCl$_3$, 100 MHz)
NMR
Solvent Peaks
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



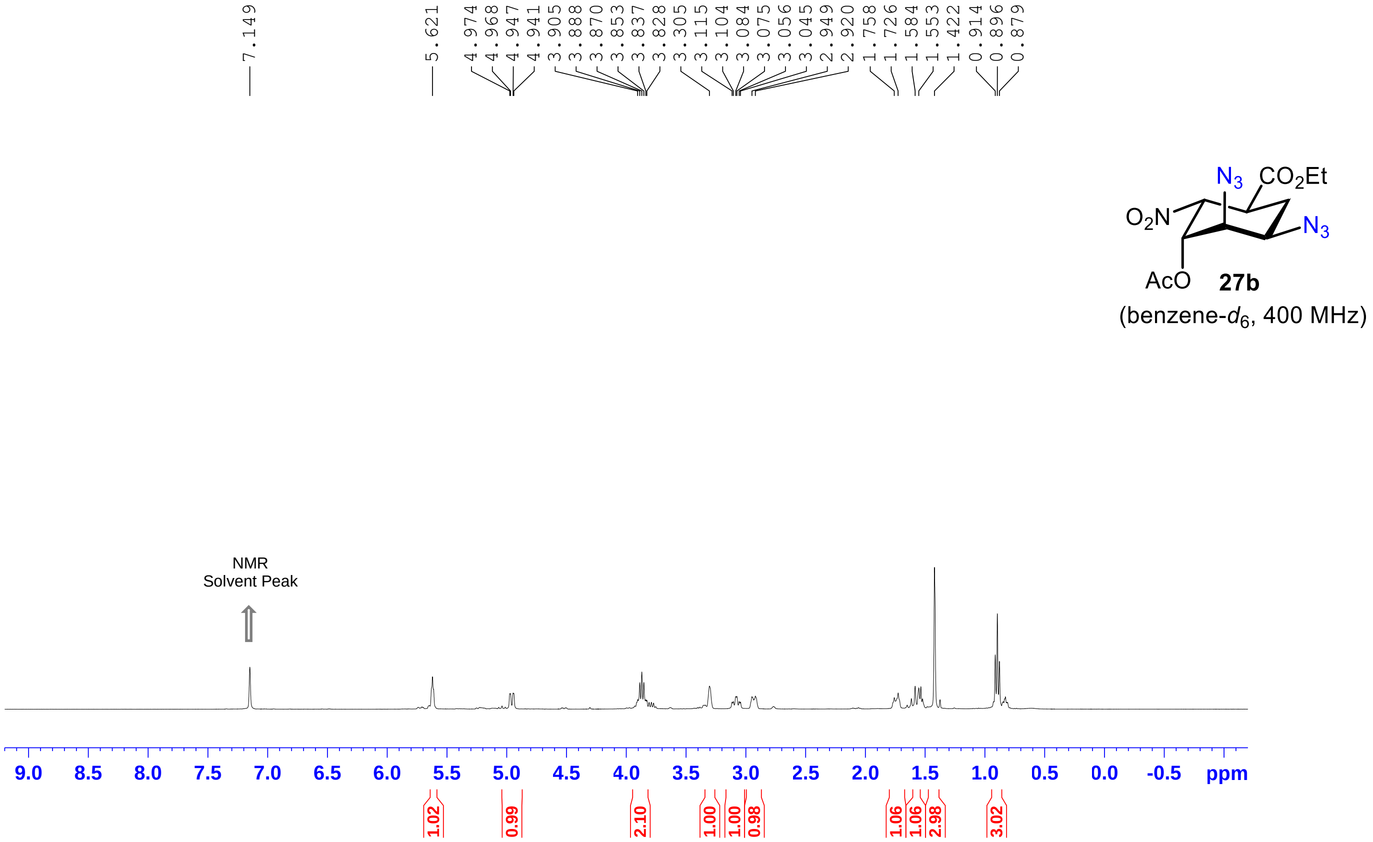
27a

($CDCl_3$, 400 MHz)



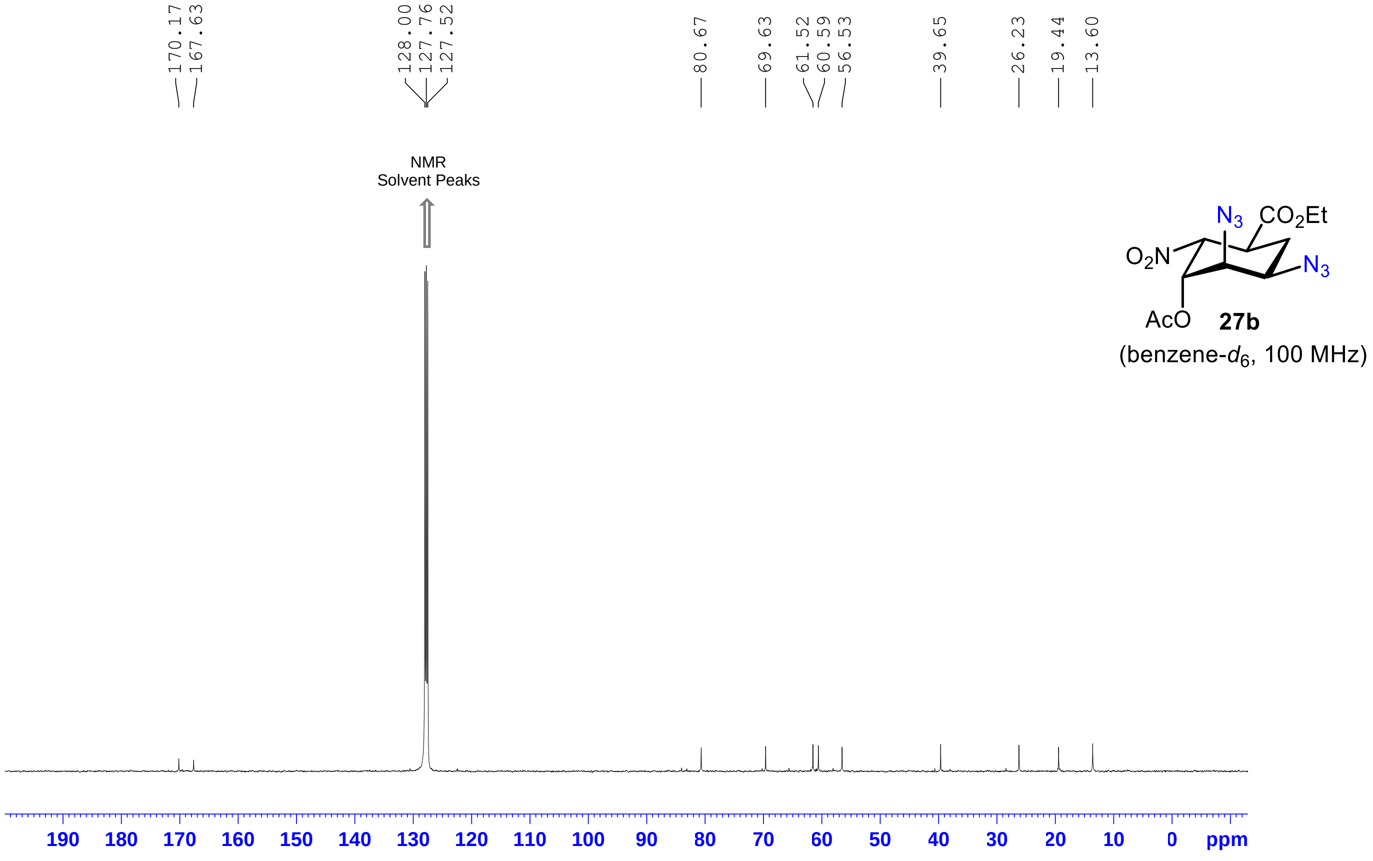
27a

($CDCl_3$, 100 MHz)



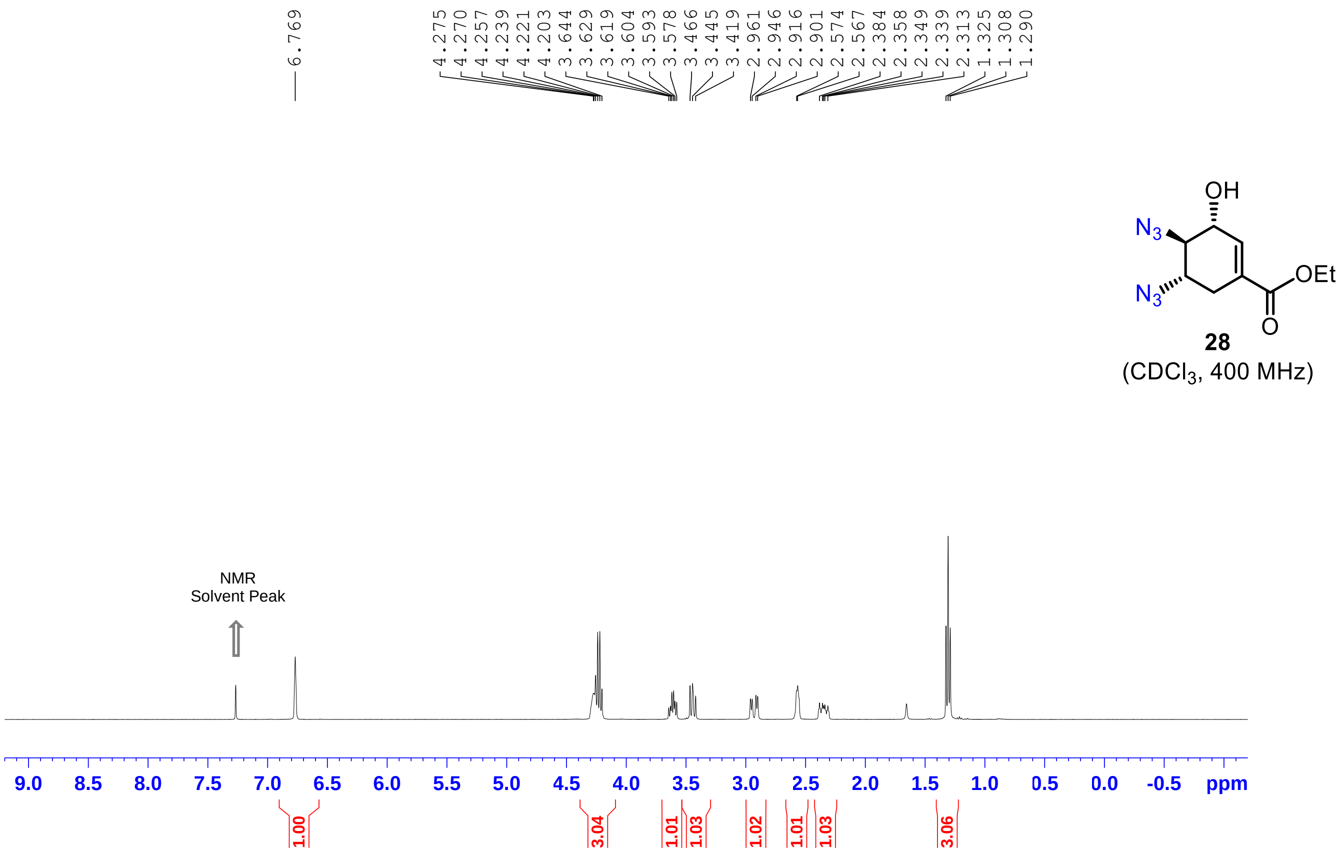
27b

(benzene-d_6, 400 MHz)



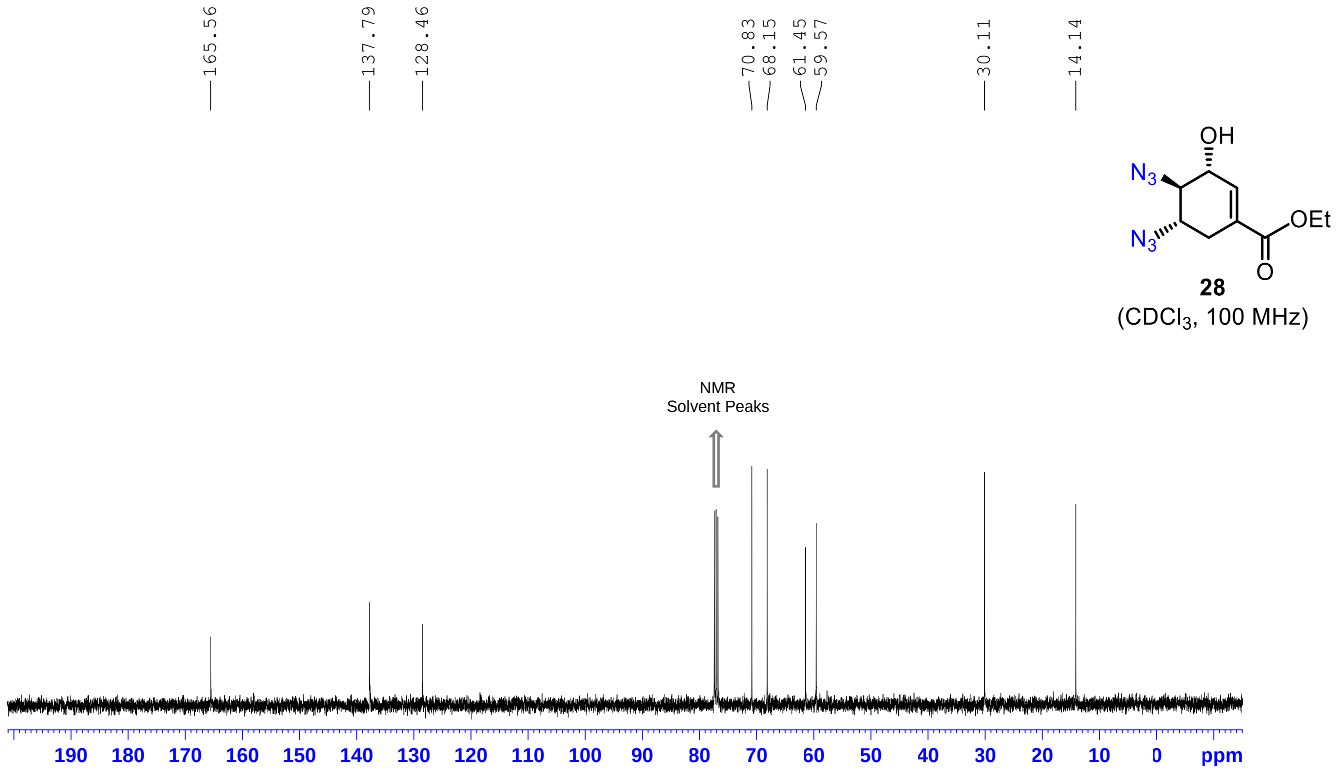
27b

(benzene-d_6, 100 MHz)



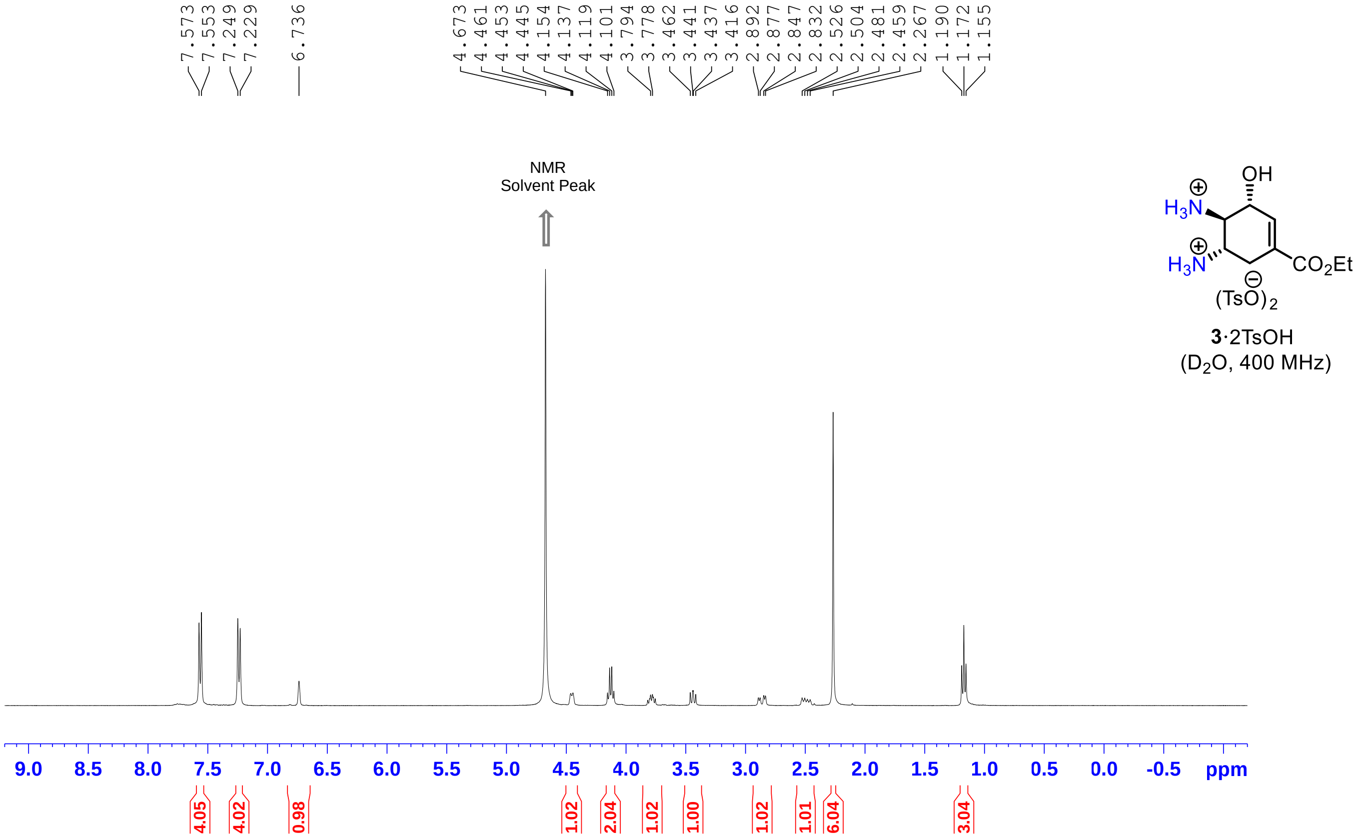
28

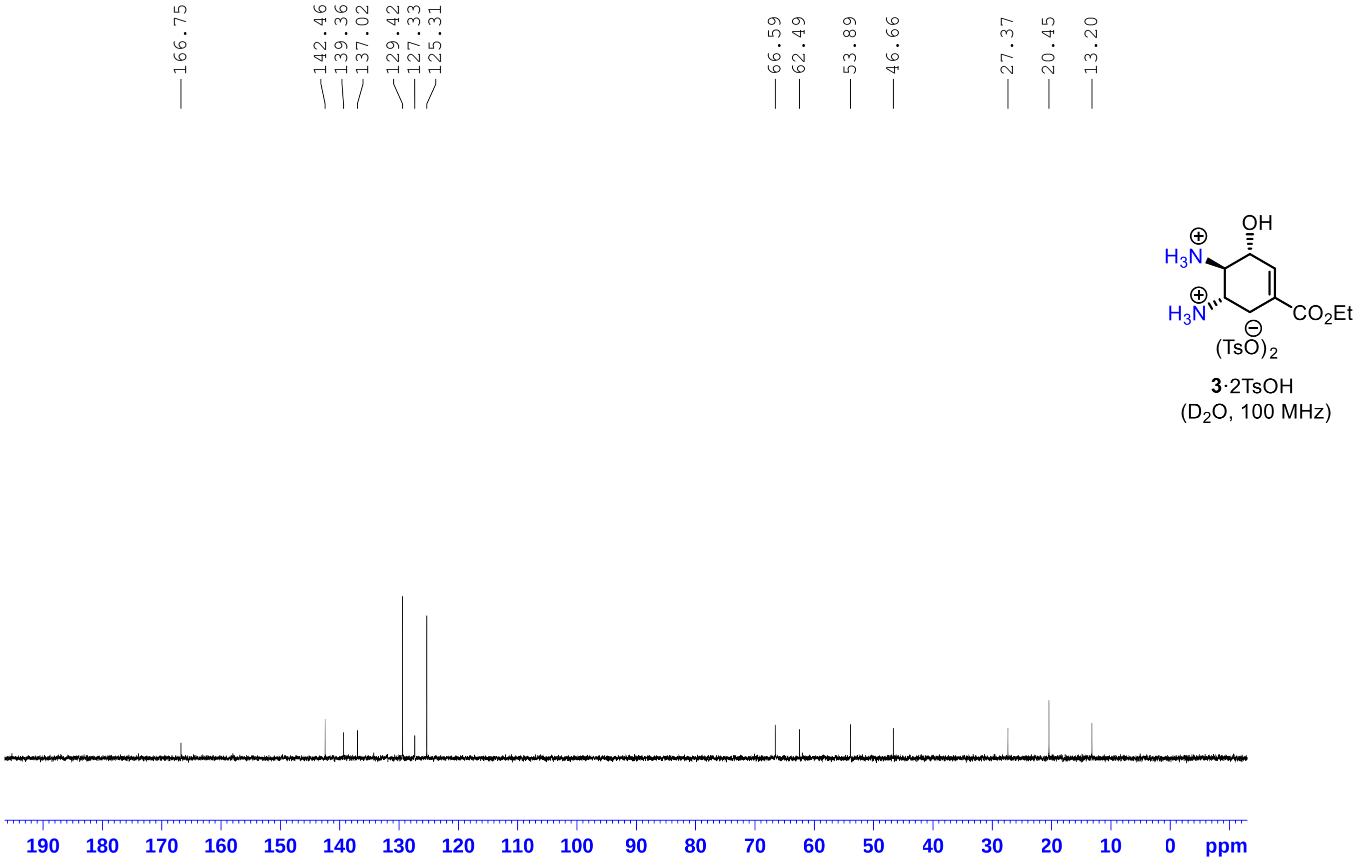
($CDCl_3$, 400 MHz)

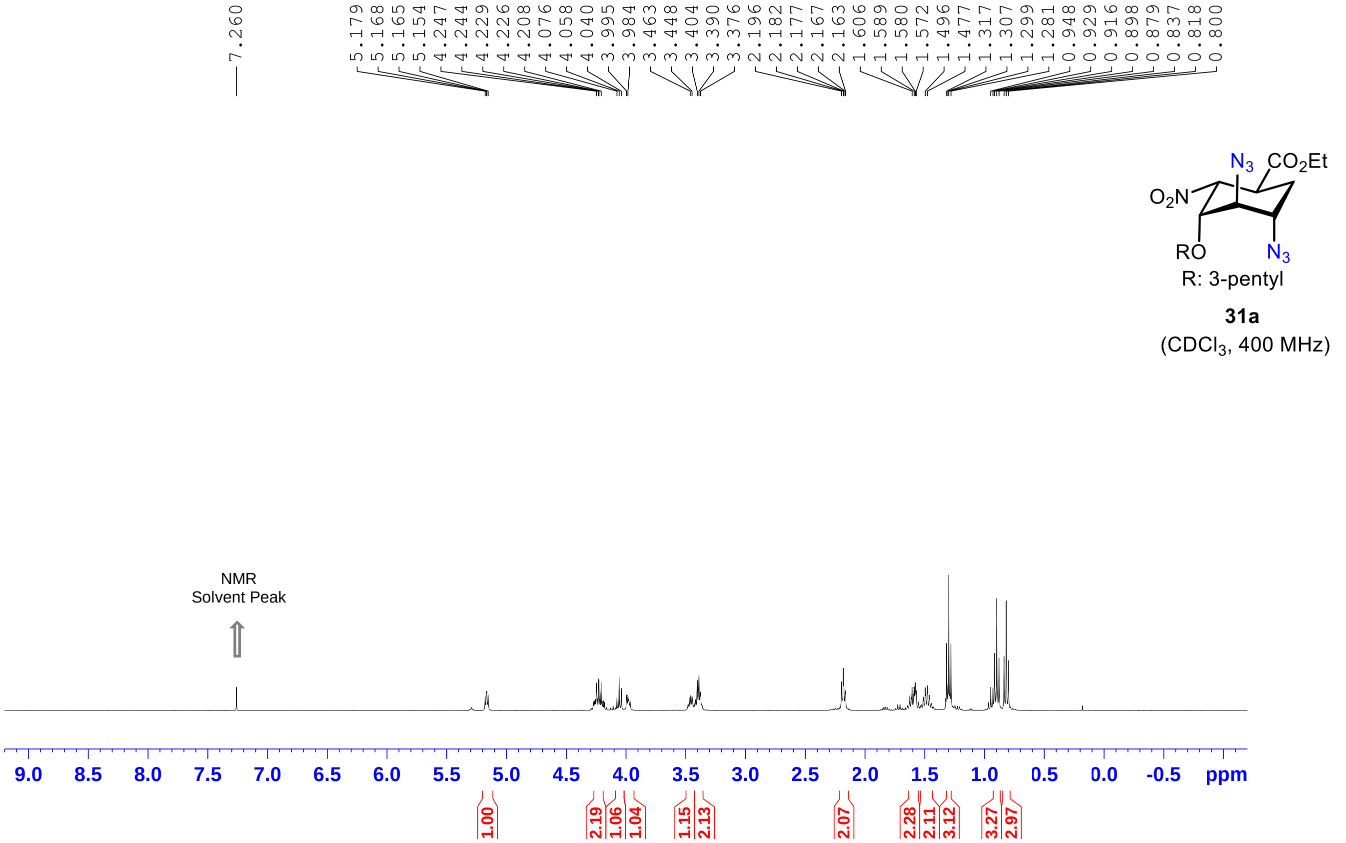


28

($CDCl_3$, 100 MHz)

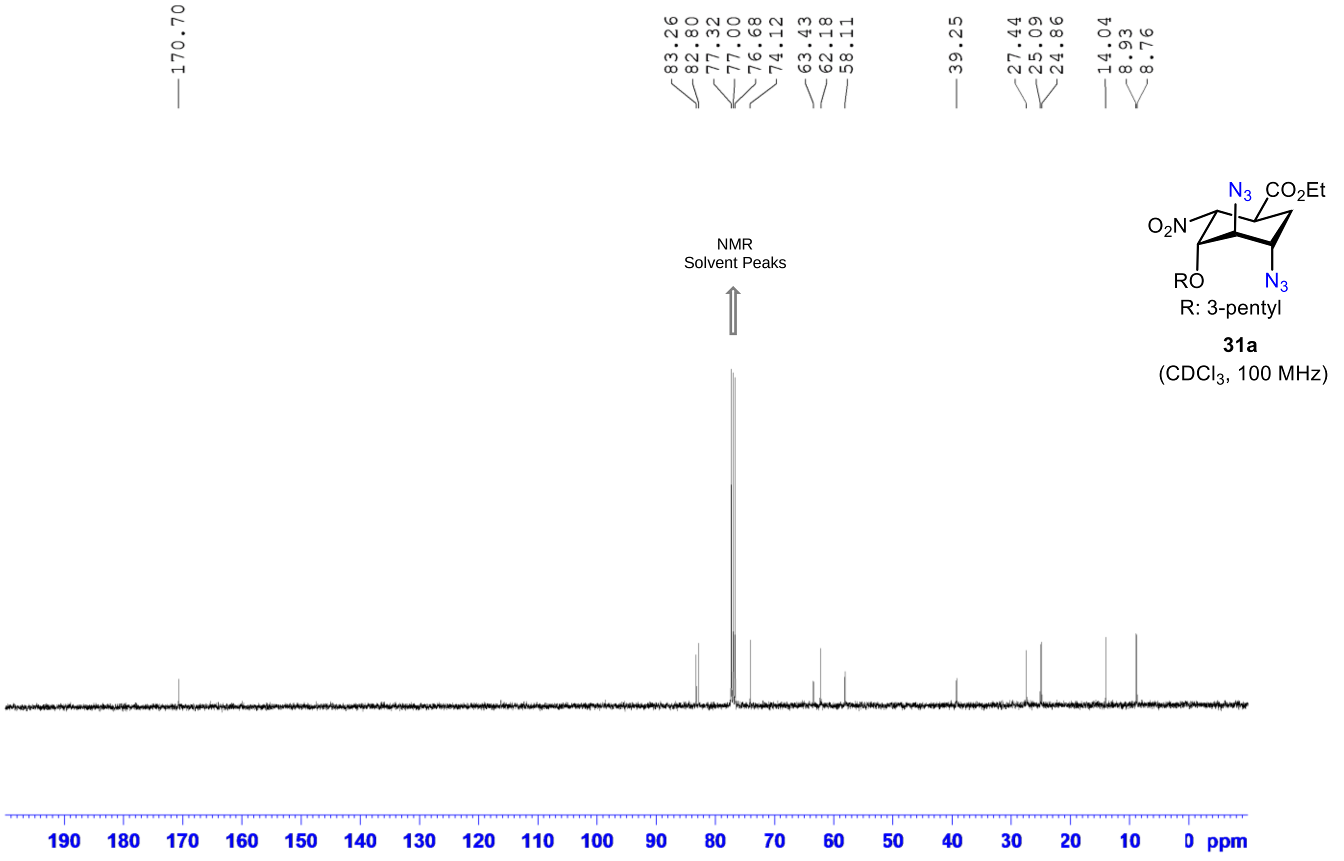

7.573
7.553
7.249
7.229
6.736
4.673
4.461
4.453
4.445
4.154
4.137
4.119
4.101
3.794
3.778
3.462
3.441
3.437
3.416
2.892
2.877
2.847
2.832
2.526
2.504
2.481
2.459
2.267
1.190
1.172
1.155
NMR
Solvent Peak
OH
H_3N^+
H_3N^+
CO_2Et
$(TsO^-)_2$
3·2TsOH
(D_2O, 400 MHz)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
4.05
4.02
0.98
1.02
2.04
1.02
1.00
1.02
1.01
6.04
3.04


166.75
142.46
139.36
137.02
129.42
127.33
125.31
66.59
62.49
53.89
46.66
27.37
20.45
13.20
OH
H_3N^+
H_3N^+
CO_2Et
$(TsO^-)_2$
3·2TsOH
(D_2O, 100 MHz)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



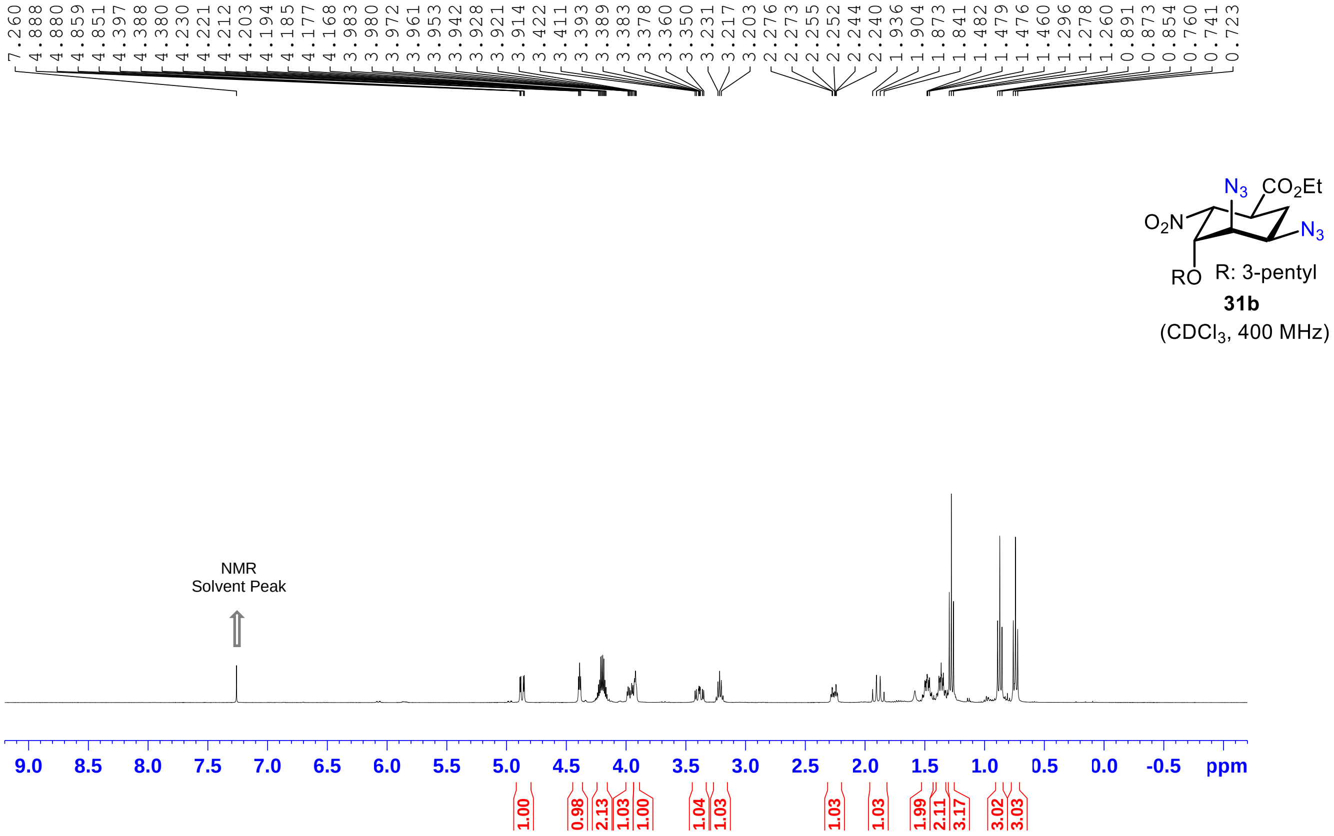
31a

(CDCl$_3$, 400 MHz)



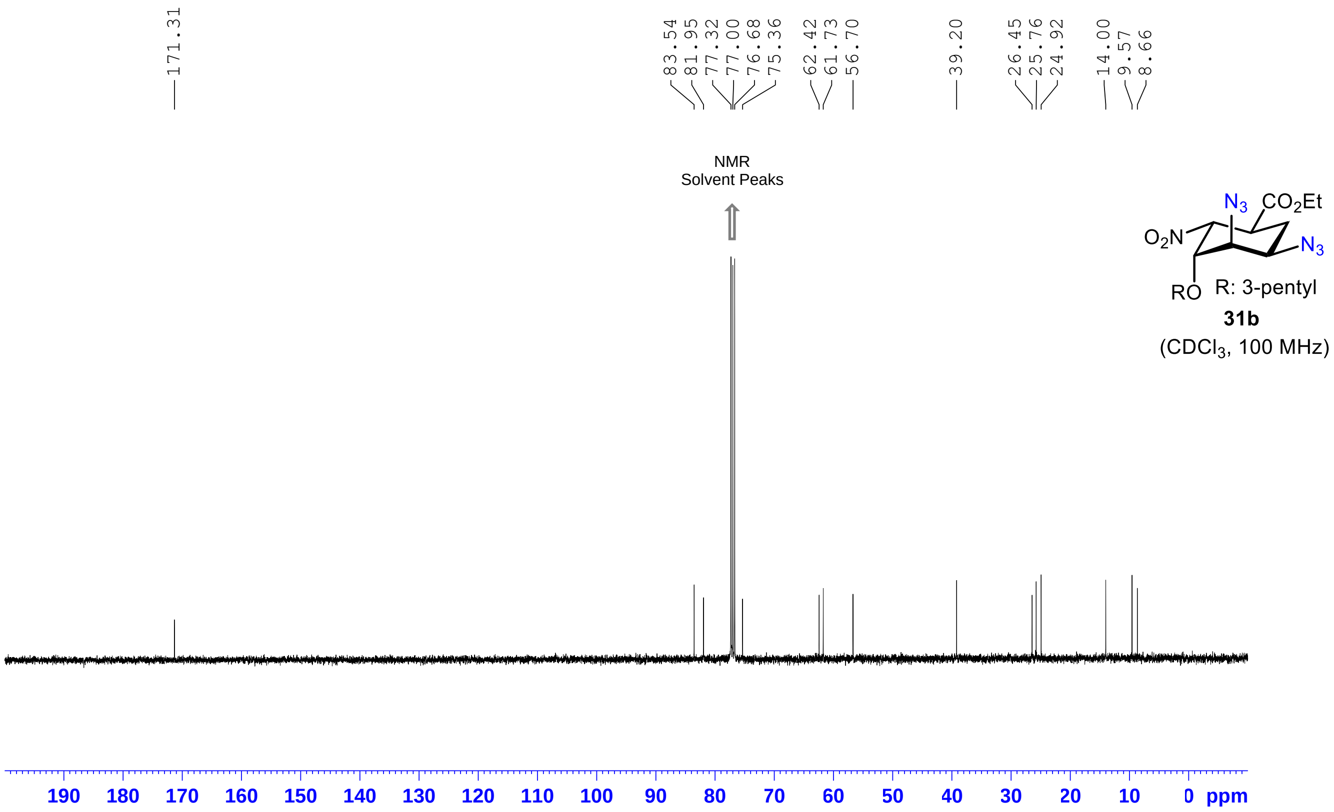
31a

(CDCl$_3$, 100 MHz)



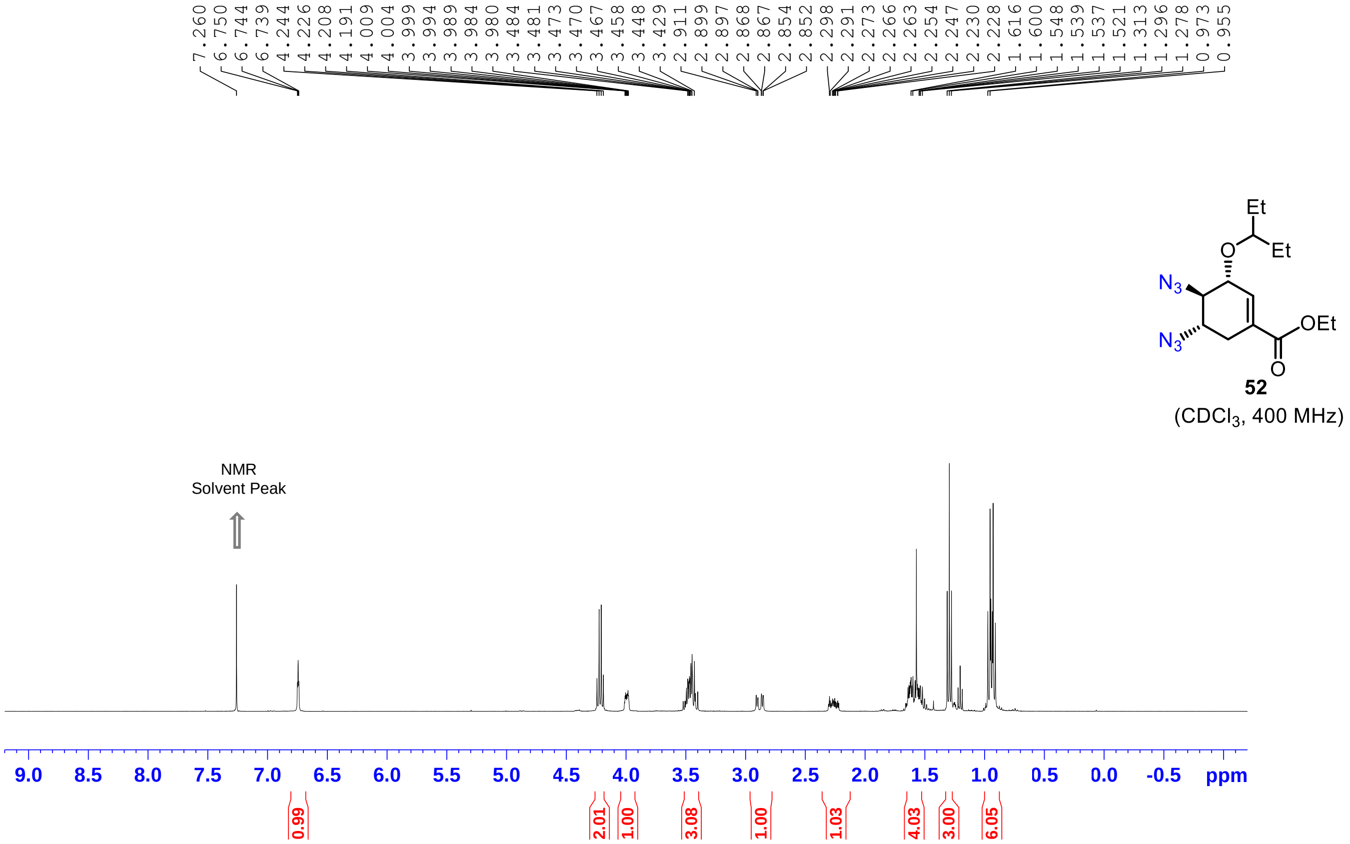
31b

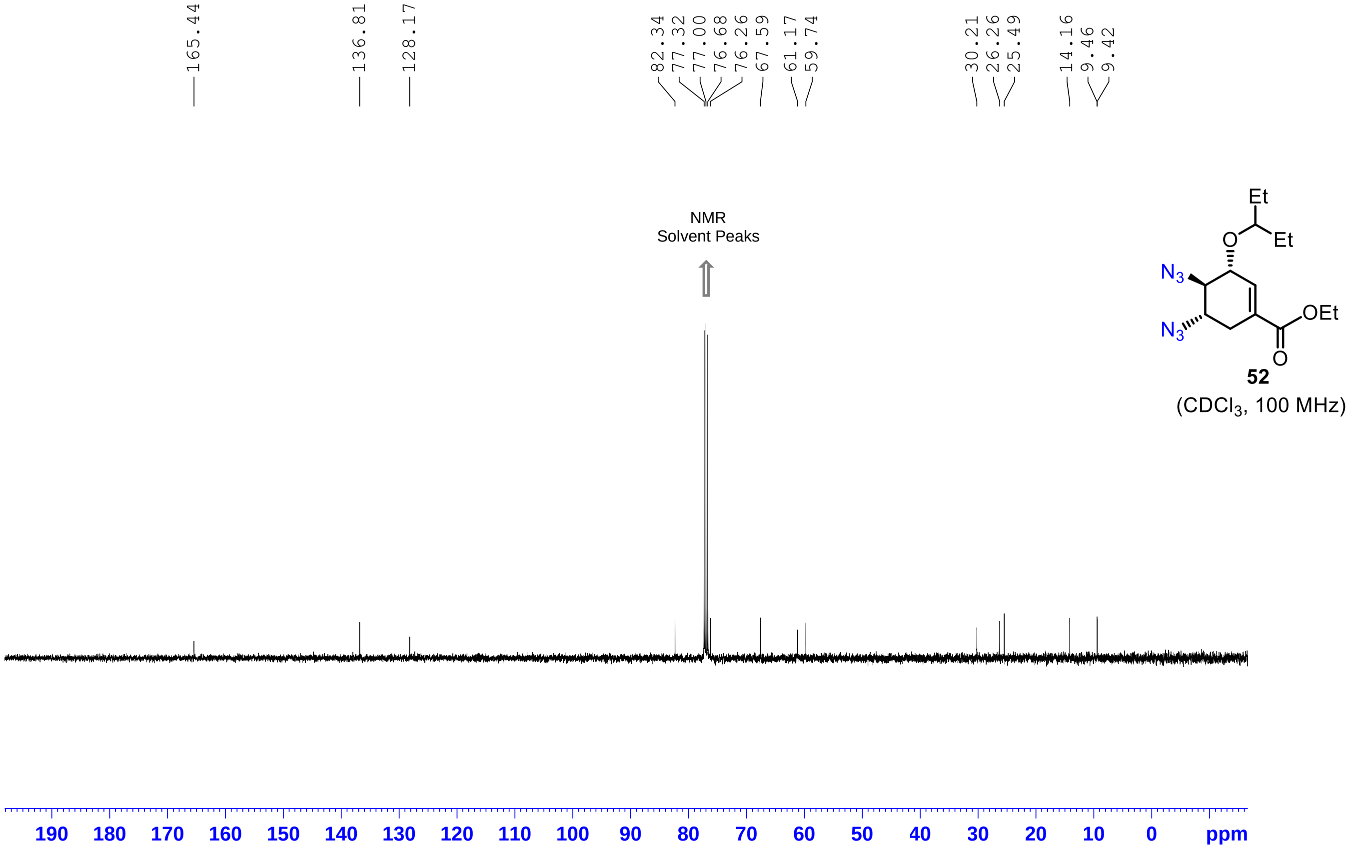
(CDCl$_3$, 400 MHz)

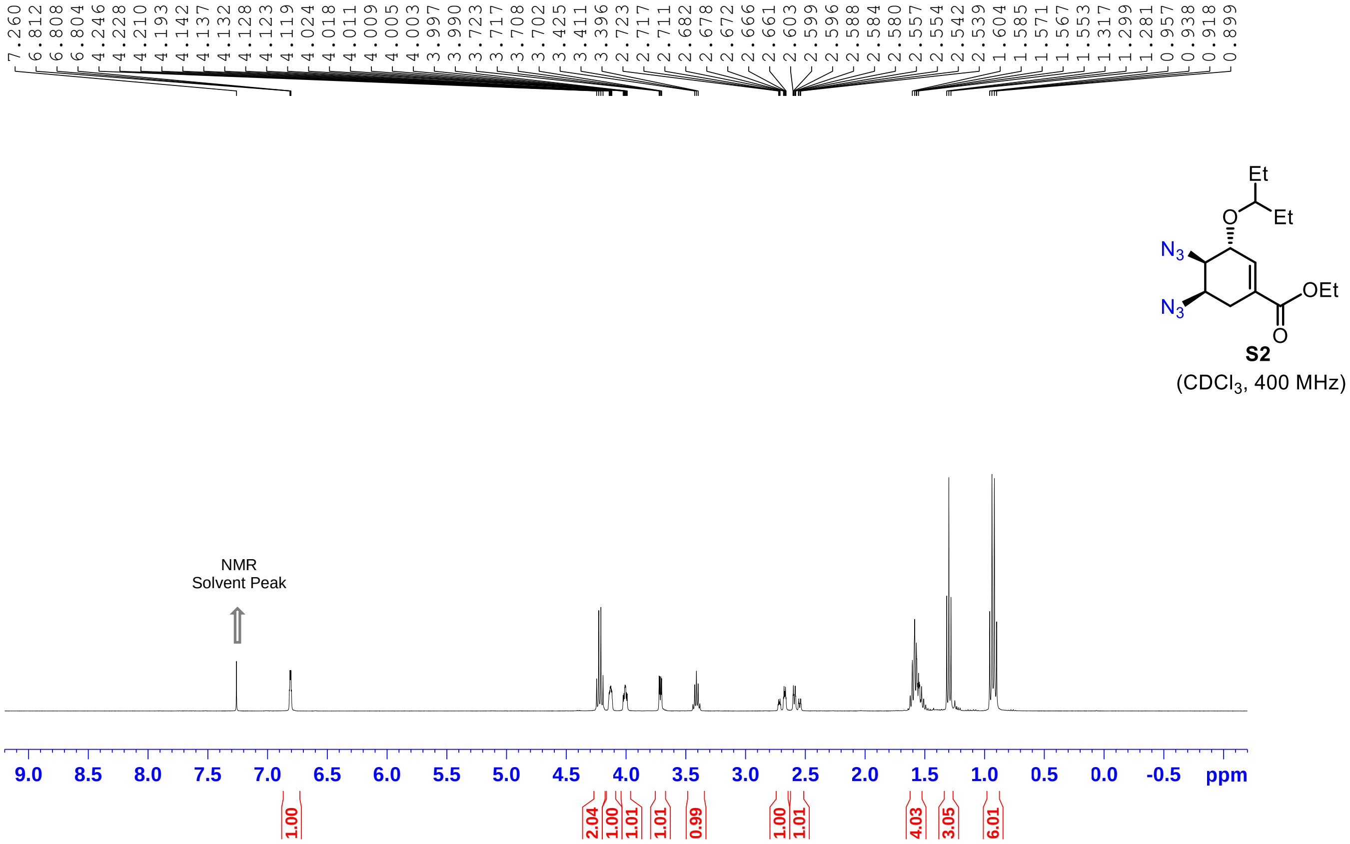


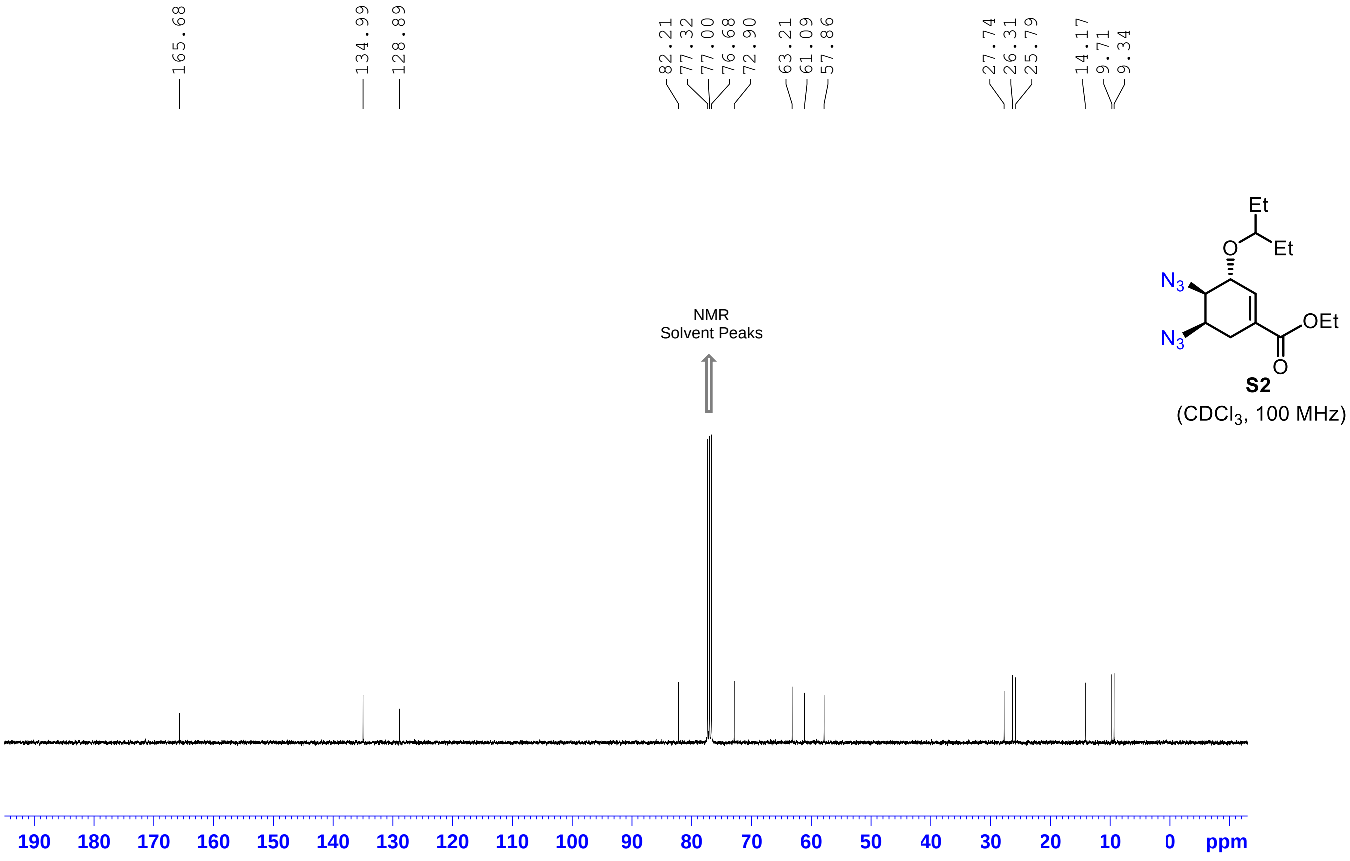
31b

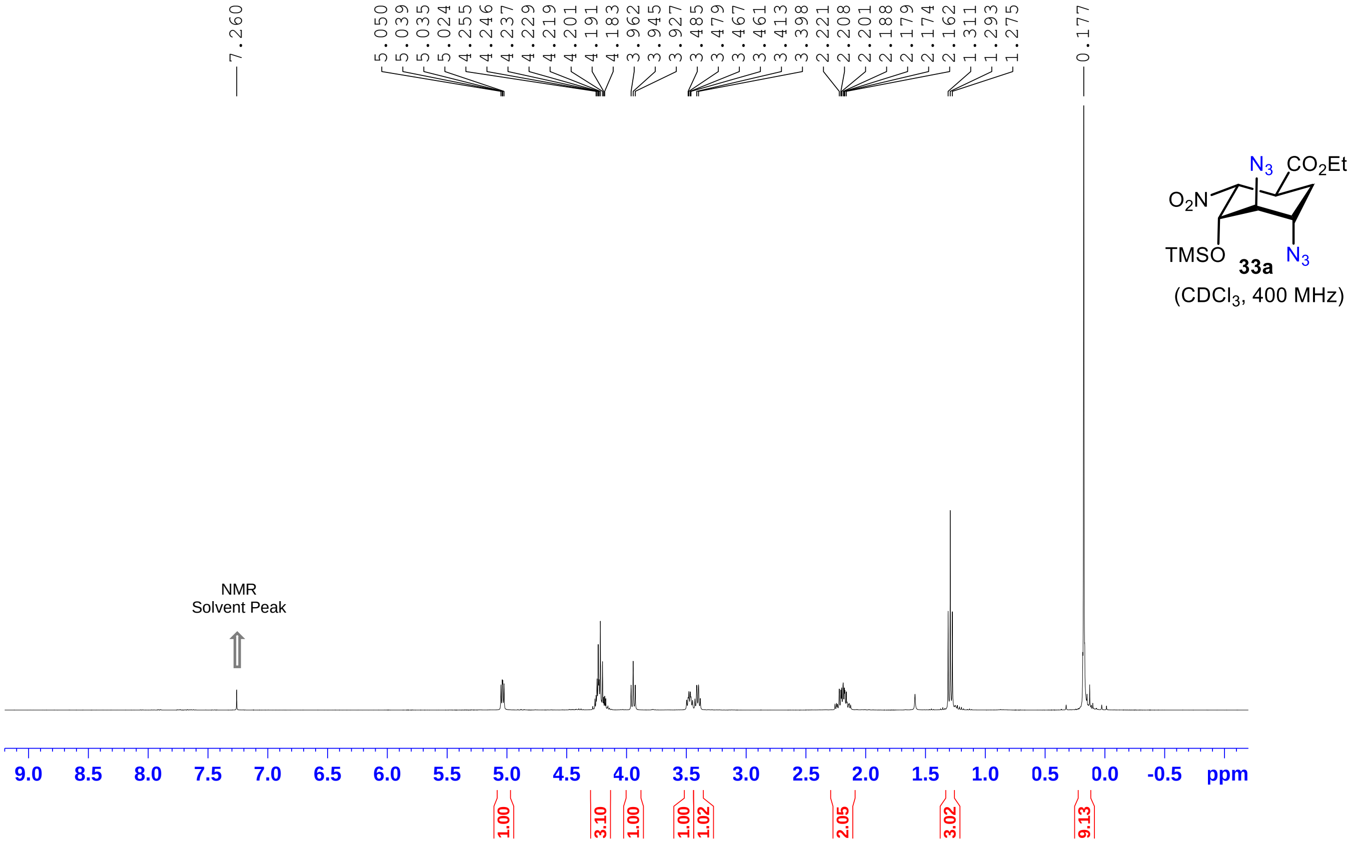
(CDCl$_3$, 100 MHz)

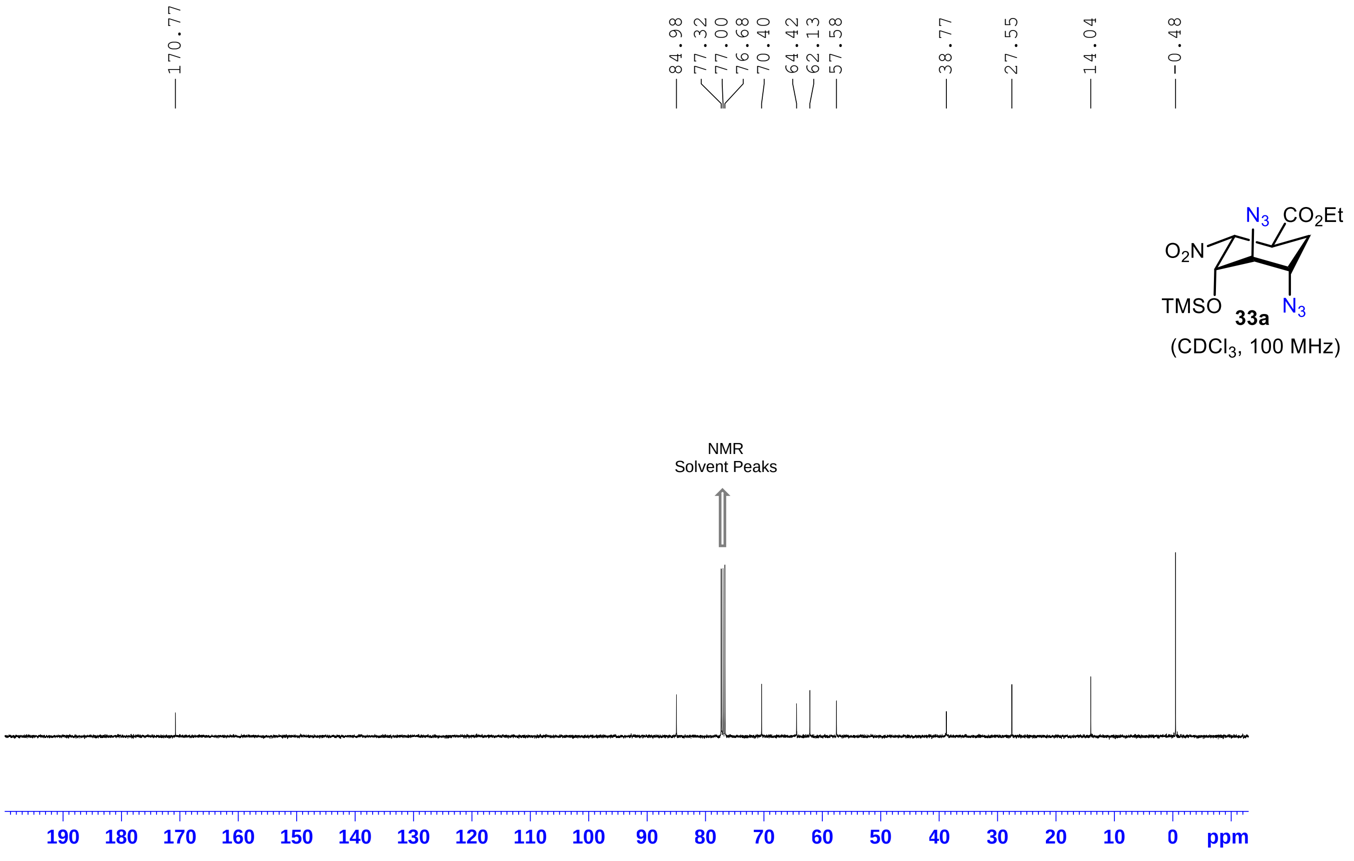

7.260
6.750
6.744
6.739
4.244
4.226
4.208
4.191
4.009
4.004
3.999
3.994
3.989
3.984
3.980
3.484
3.481
3.473
3.470
3.467
3.458
3.448
3.429
2.911
2.899
2.897
2.868
2.867
2.854
2.852
2.298
2.291
2.273
2.266
2.263
2.254
2.247
2.230
2.228
1.616
1.600
1.548
1.539
1.537
1.521
1.313
1.296
1.278
0.973
0.955
Et
O
Et
N_3
N_3
OEt
O
52
($CDCl_3$, 400 MHz)
NMR
Solvent Peak
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
-0.5
ppm
0.99
2.01
1.00
3.08
1.00
1.03
4.03
3.00
6.05

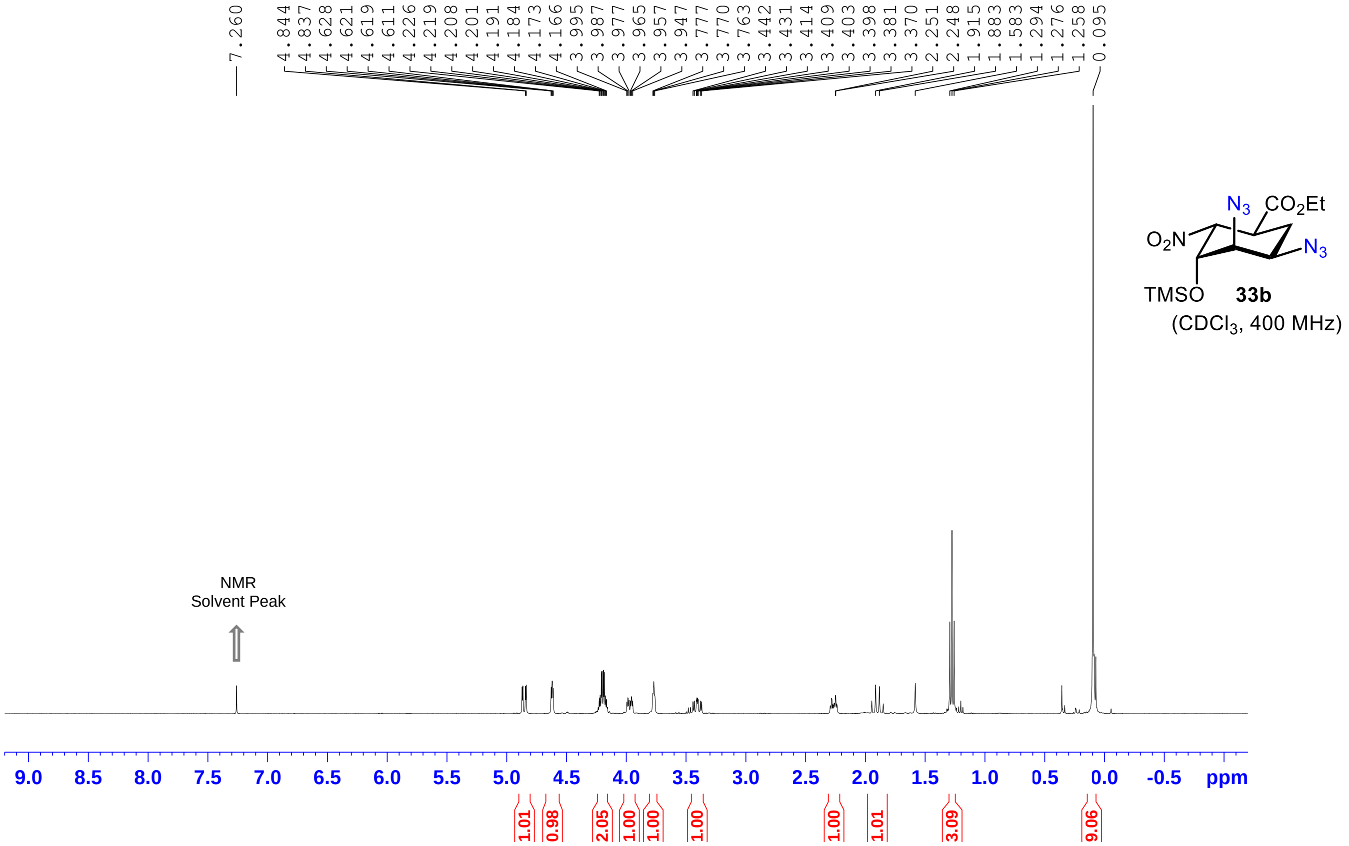

165.44
136.81
128.17
82.34
77.32
77.00
76.68
76.26
67.59
61.17
59.74
30.21
26.26
25.49
14.16
9.46
9.42
Et
O
Et
N_3
N_3
OEt
O
52
($CDCl_3$, 100 MHz)
NMR
Solvent Peaks
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


7.260
6.812
6.808
6.804
4.246
4.228
4.210
4.193
4.142
4.137
4.132
4.128
4.123
4.119
4.024
4.018
4.011
4.009
4.005
4.003
3.997
3.990
3.723
3.717
3.708
3.702
3.425
3.411
3.396
2.723
2.717
2.711
2.682
2.678
2.672
2.666
2.661
2.603
2.599
2.596
2.588
2.584
2.580
2.557
2.554
2.542
2.539
1.604
1.585
1.571
1.567
1.553
1.317
1.299
1.281
0.957
0.938
0.918
0.899
Et
O
Et
N3
OEt
N3
O
S2
(CDCl3, 400 MHz)
NMR
Solvent Peak
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
-0.5
ppm
1.00
2.04
1.00
1.01
1.01
0.99
1.00
1.01
4.03
3.05
6.01


165.68
134.99
128.89
82.21
77.32
77.00
76.68
72.90
63.21
61.09
57.86
27.74
26.31
25.79
14.17
9.71
9.34
Et
O
Et
N3
OEt
N3
O
S2
(CDCl3, 100 MHz)
NMR
Solvent Peaks
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

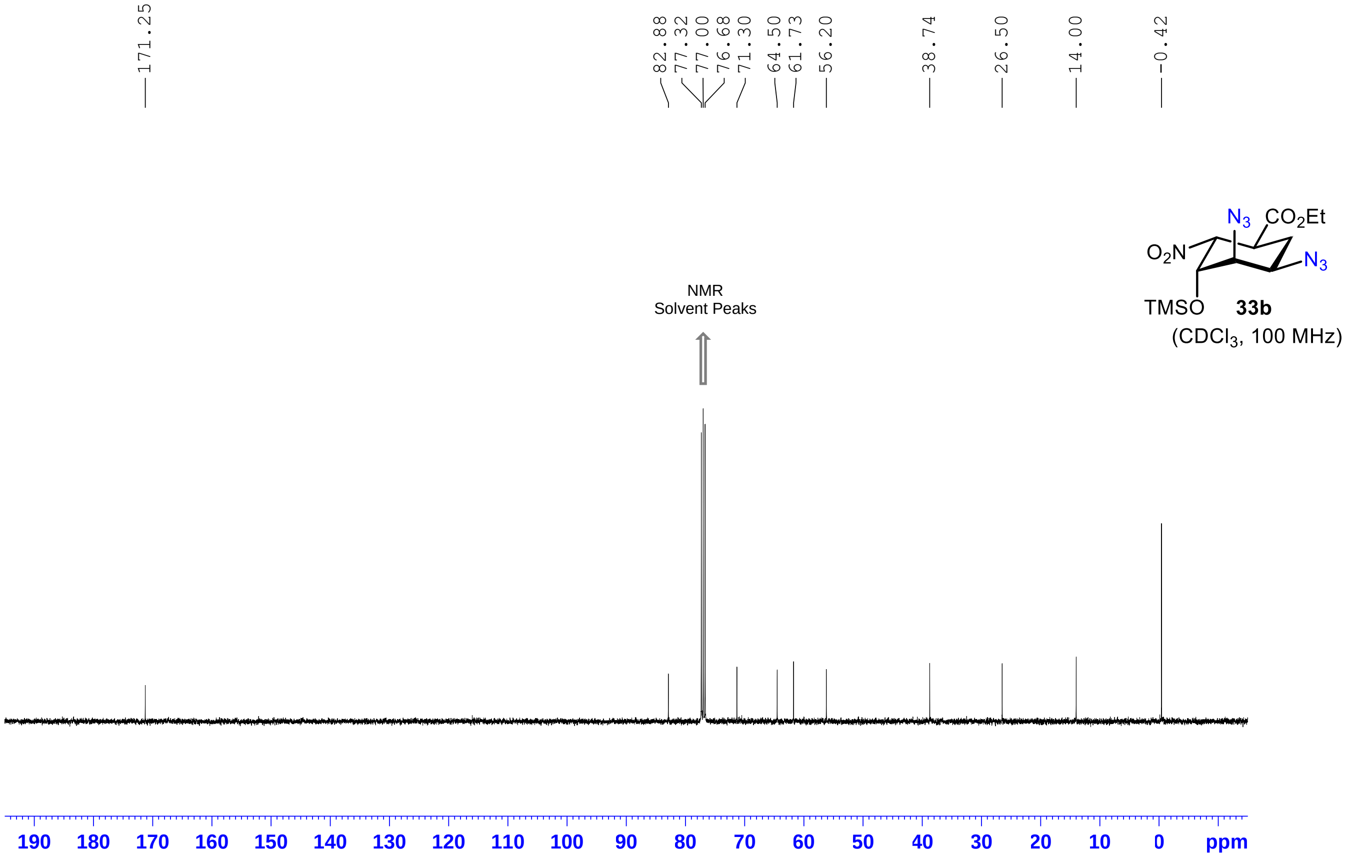

7.260
5.050
5.039
5.035
5.024
4.255
4.246
4.237
4.229
4.219
4.201
4.191
4.183
3.962
3.945
3.927
3.485
3.479
3.467
3.461
3.413
3.398
2.221
2.208
2.201
2.188
2.179
2.174
2.162
1.311
1.293
1.275
0.177
N_3
CO_2Et
O_2N
TMSO
33a
N_3
($CDCl_3$, 400 MHz)
NMR
Solvent Peak
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
1.00
3.10
1.00
1.00
1.02
2.05
3.02
9.13


170.77
84.98
77.32
77.00
76.68
70.40
64.42
62.13
57.58
38.77
27.55
14.04
-0.48
N_3
CO_2Et
O_2N
TMSO
33a
N_3
($CDCl_3$, 100 MHz)
NMR
Solvent Peaks
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



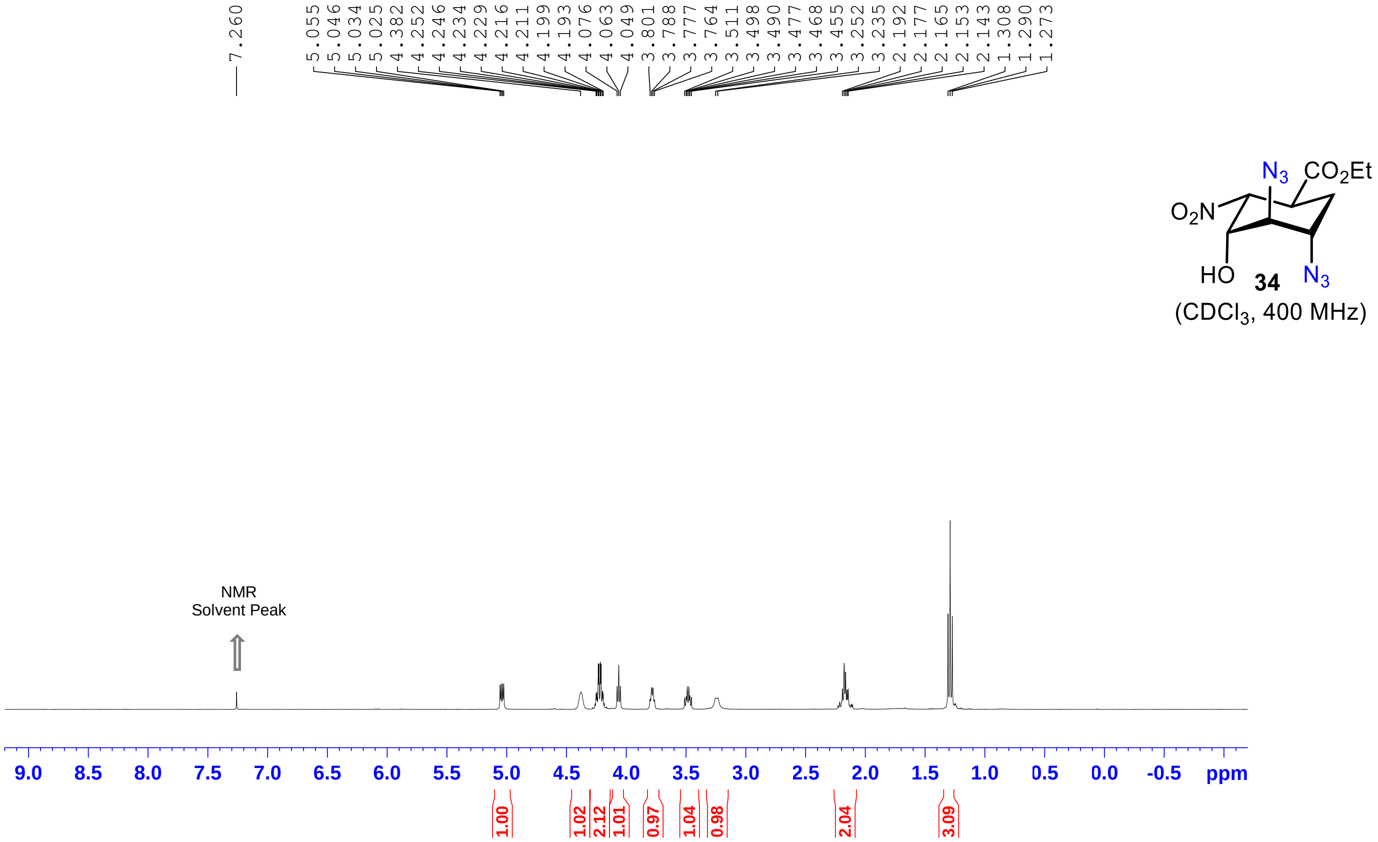
33b

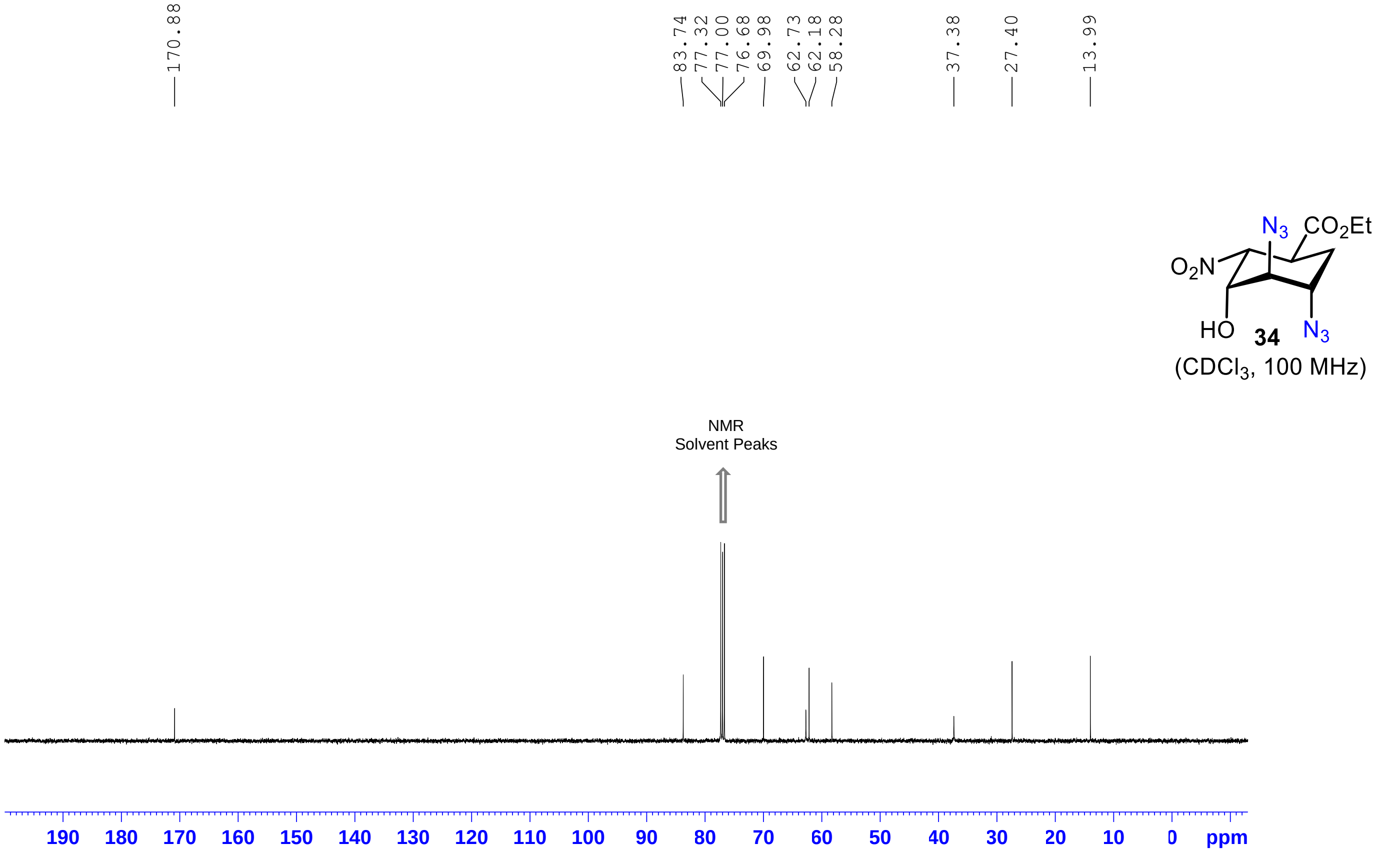
($CDCl_3$, 400 MHz)

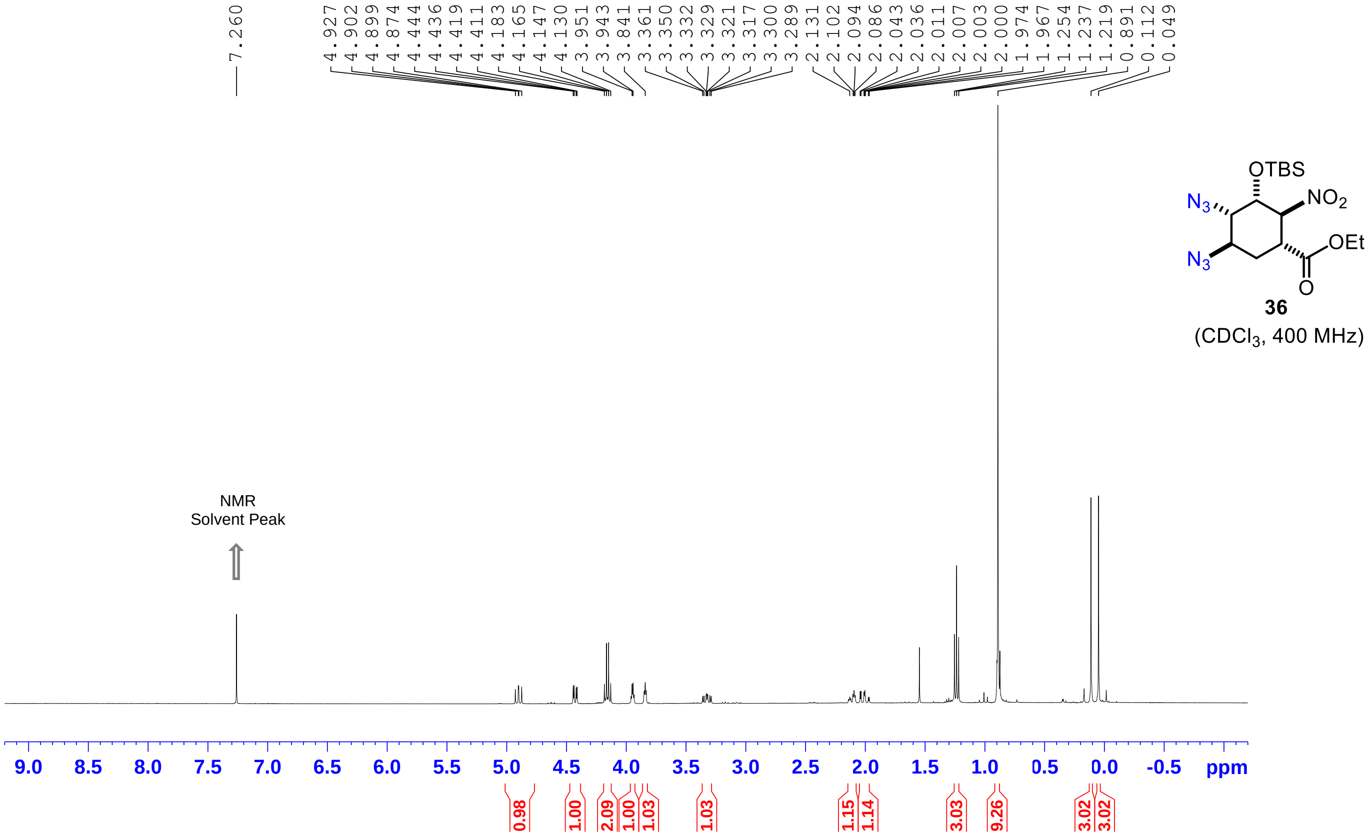


33b

($CDCl_3$, 100 MHz)

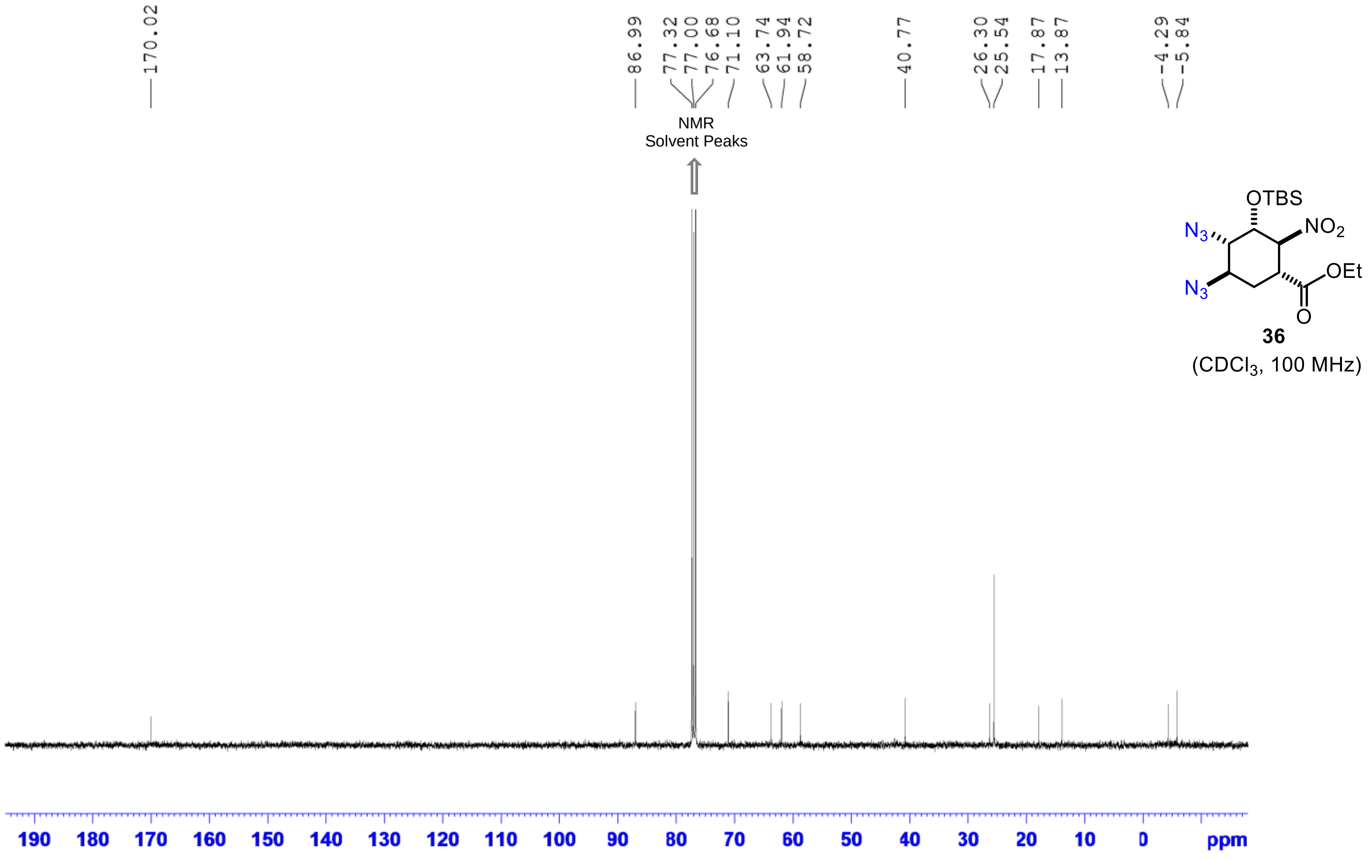

7.260
5.055
5.046
5.034
5.025
4.382
4.252
4.246
4.234
4.229
4.216
4.211
4.199
4.193
4.076
4.063
4.049
3.801
3.788
3.777
3.764
3.511
3.498
3.490
3.477
3.468
3.455
3.252
3.235
2.192
2.177
2.165
2.153
2.143
1.308
1.290
1.273
N3
CO2Et
O2N
HO
34
N3
(CDCl3, 400 MHz)
NMR
Solvent Peak
9.0
8.5
8.0
7.5
7.0
6.5
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
-0.5
ppm
1.00
1.02
2.12
1.01
0.97
1.04
0.98
2.04
3.09


170.88
83.74
77.32
77.00
76.68
69.98
62.73
62.18
58.28
37.38
27.40
13.99
N3
CO2Et
O2N
HO
34
N3
(CDCl3, 100 MHz)
NMR
Solvent Peaks
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



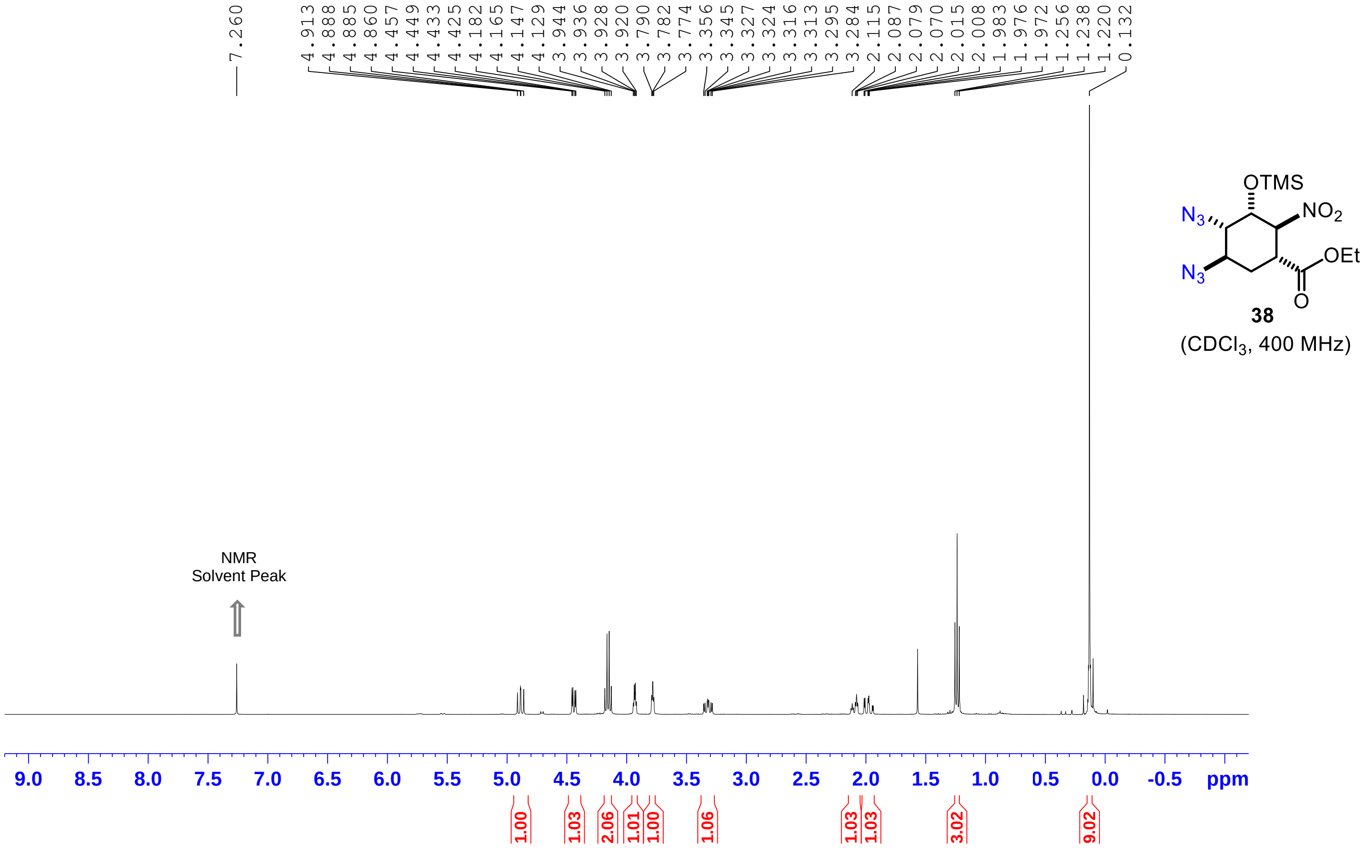
36

($CDCl_3$, 400 MHz)



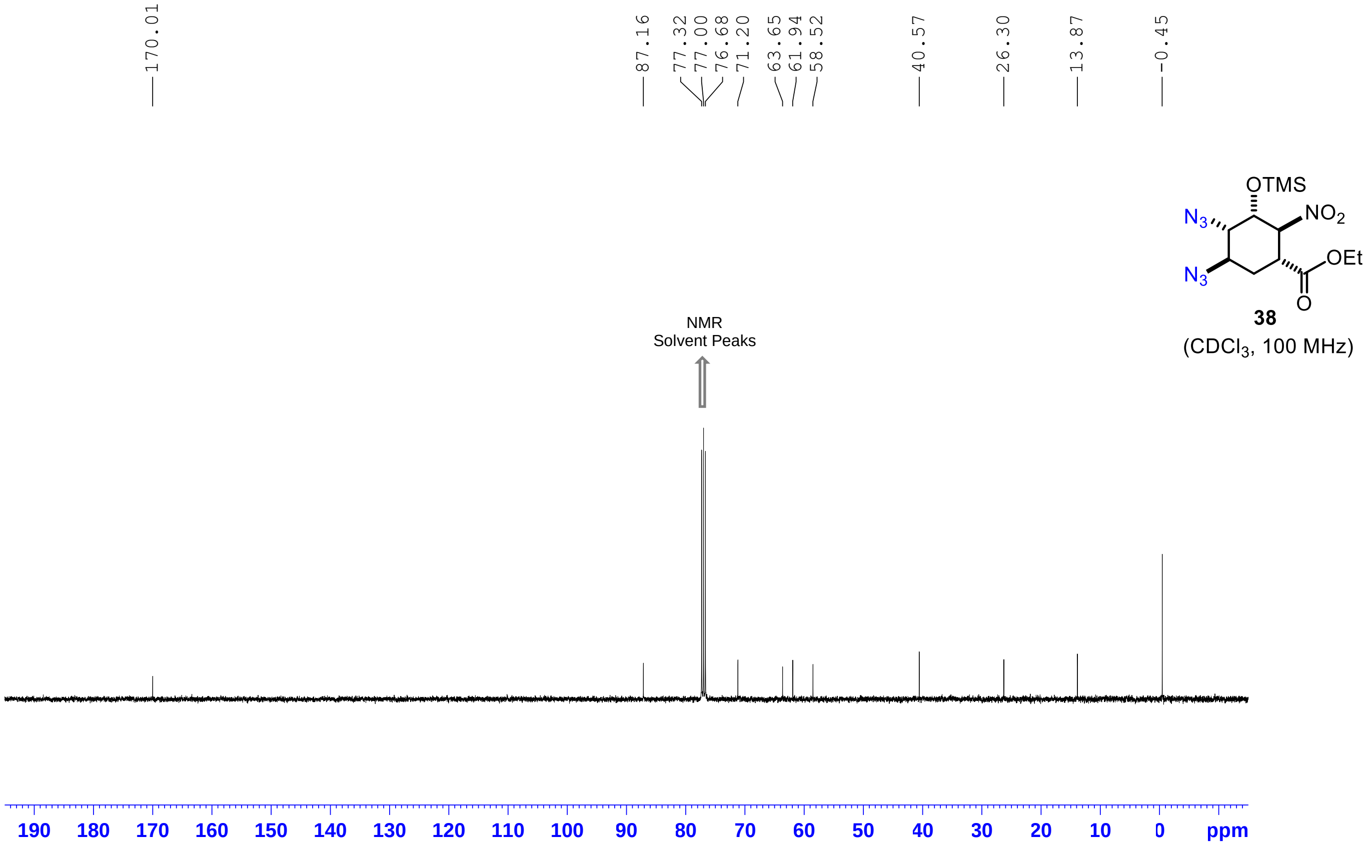
36

($CDCl_3$, 100 MHz)



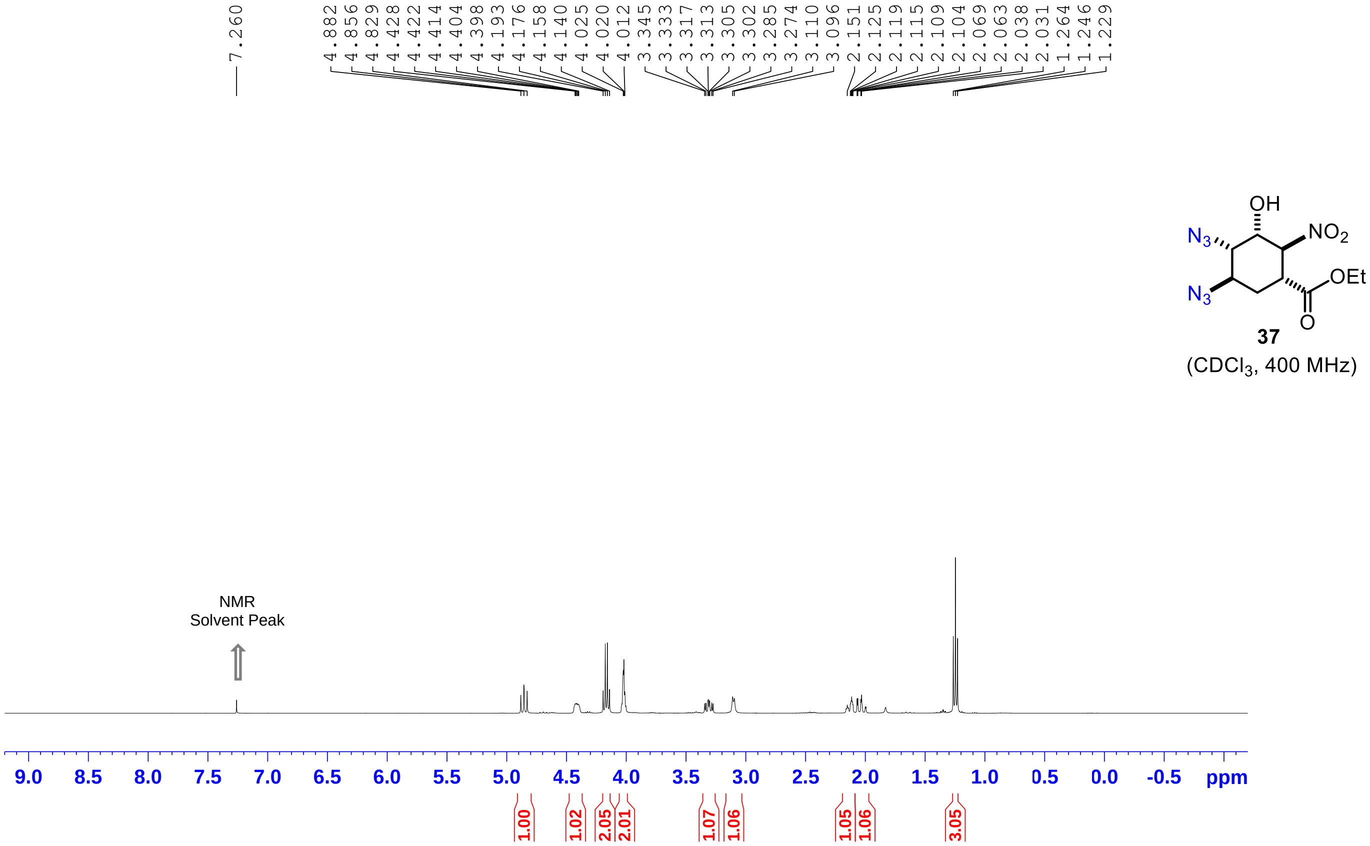
38

($CDCl_3$, 400 MHz)



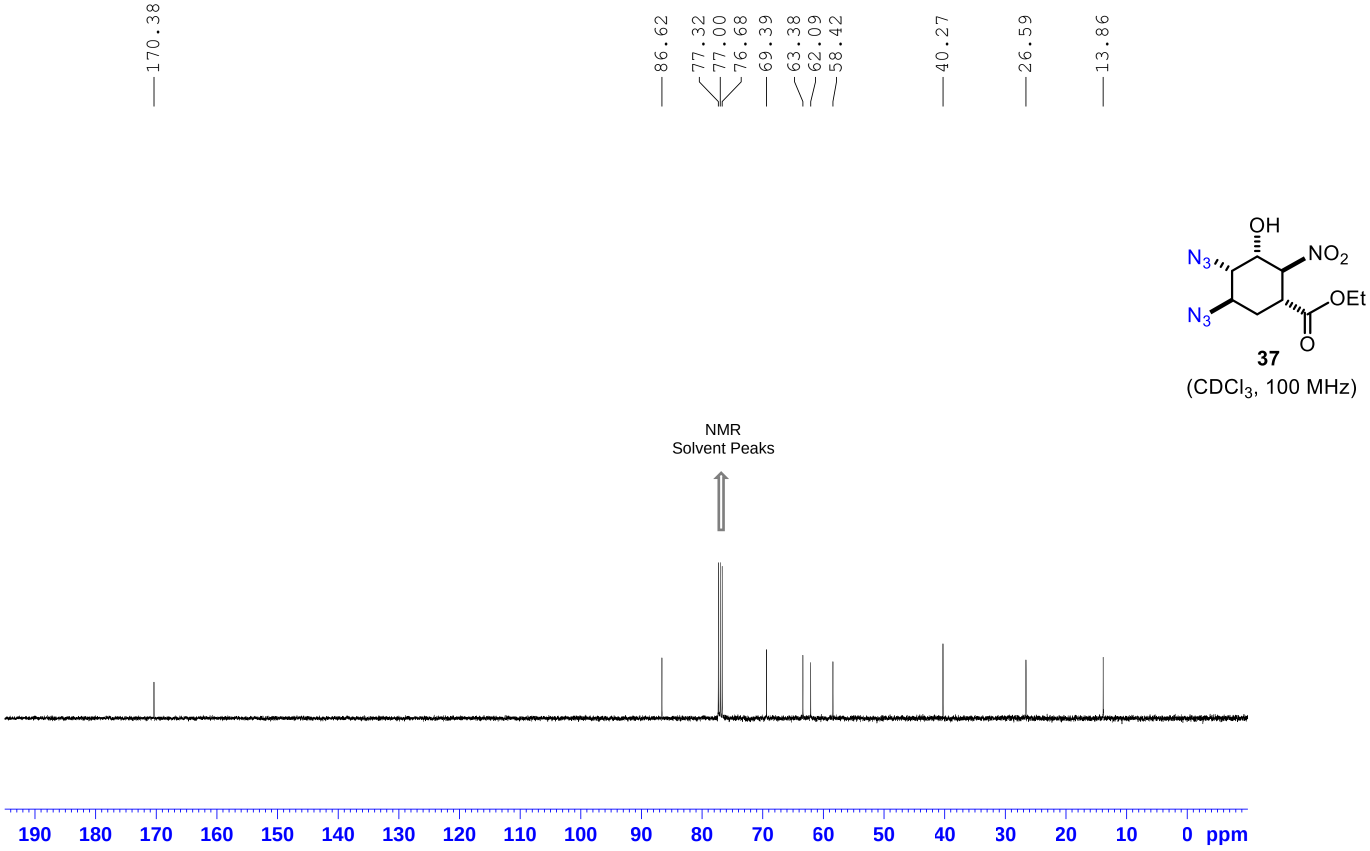
38

($CDCl_3$, 100 MHz)



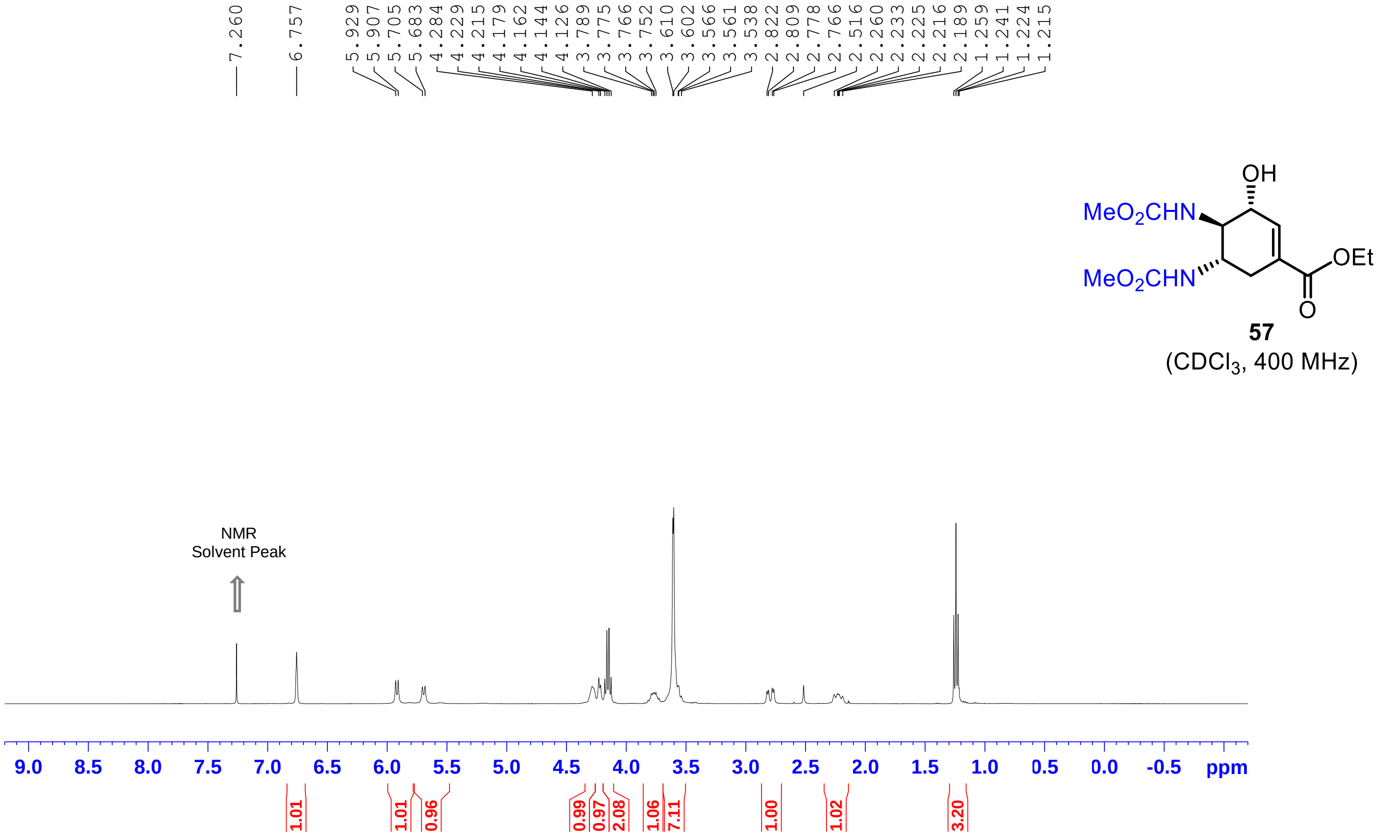
37

($CDCl_3$, 400 MHz)

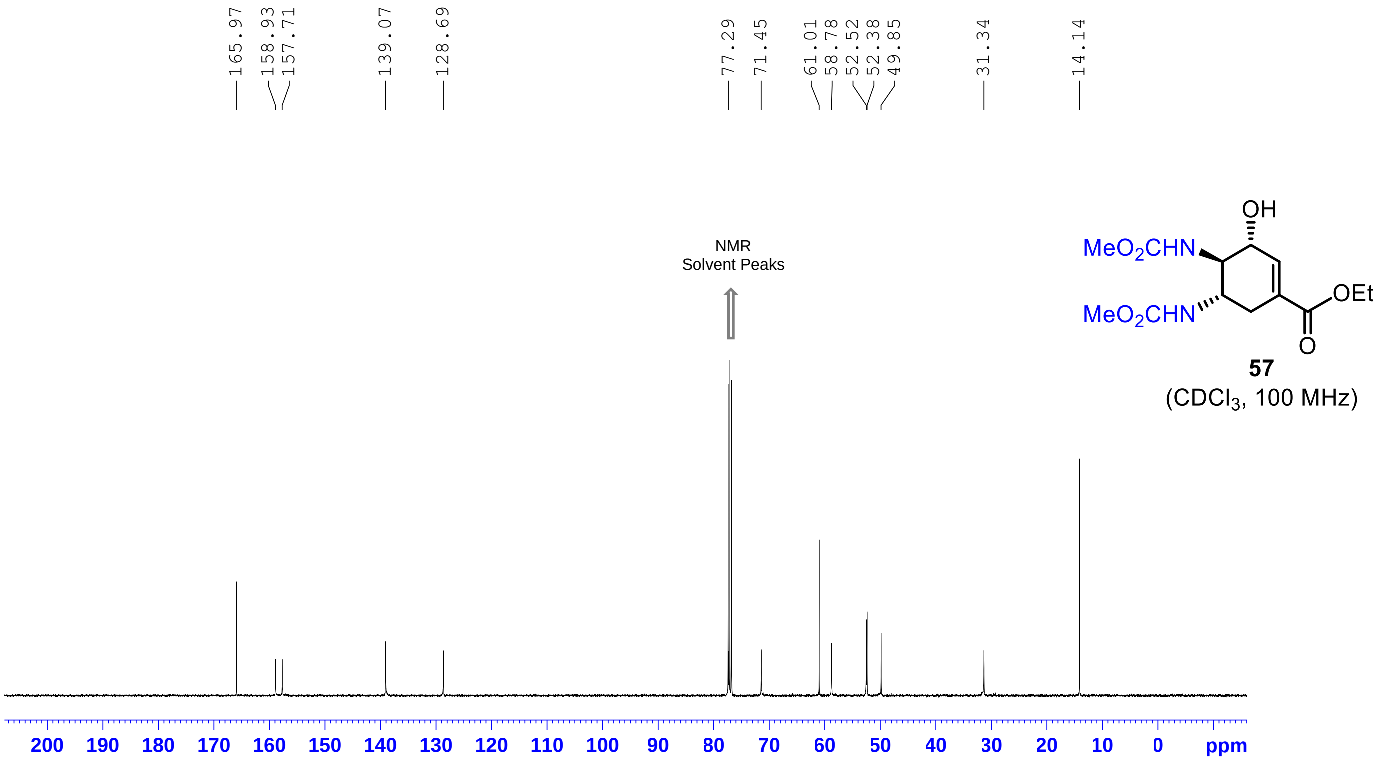


37

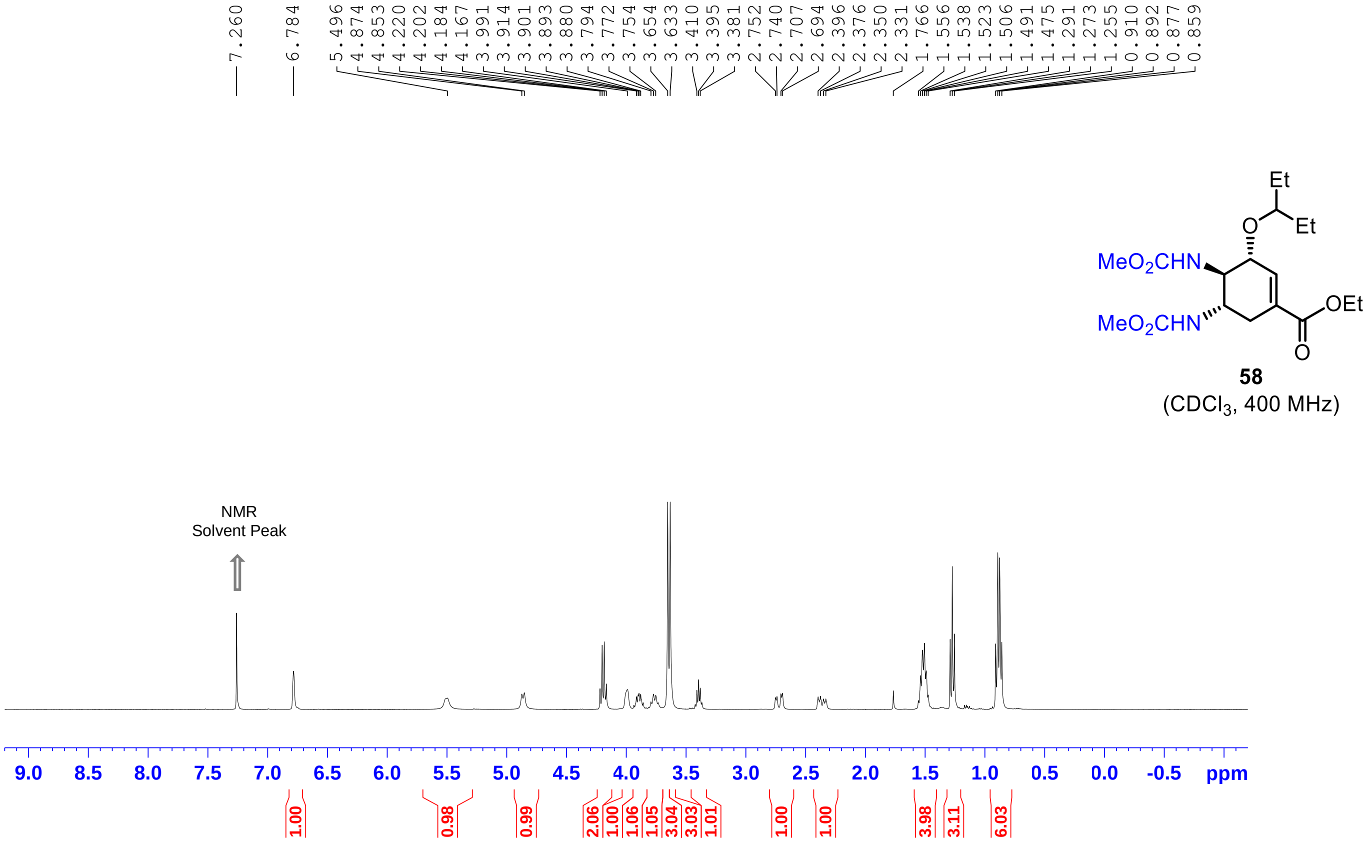
($CDCl_3$, 100 MHz)



57
($CDCl_3$, 400 MHz)

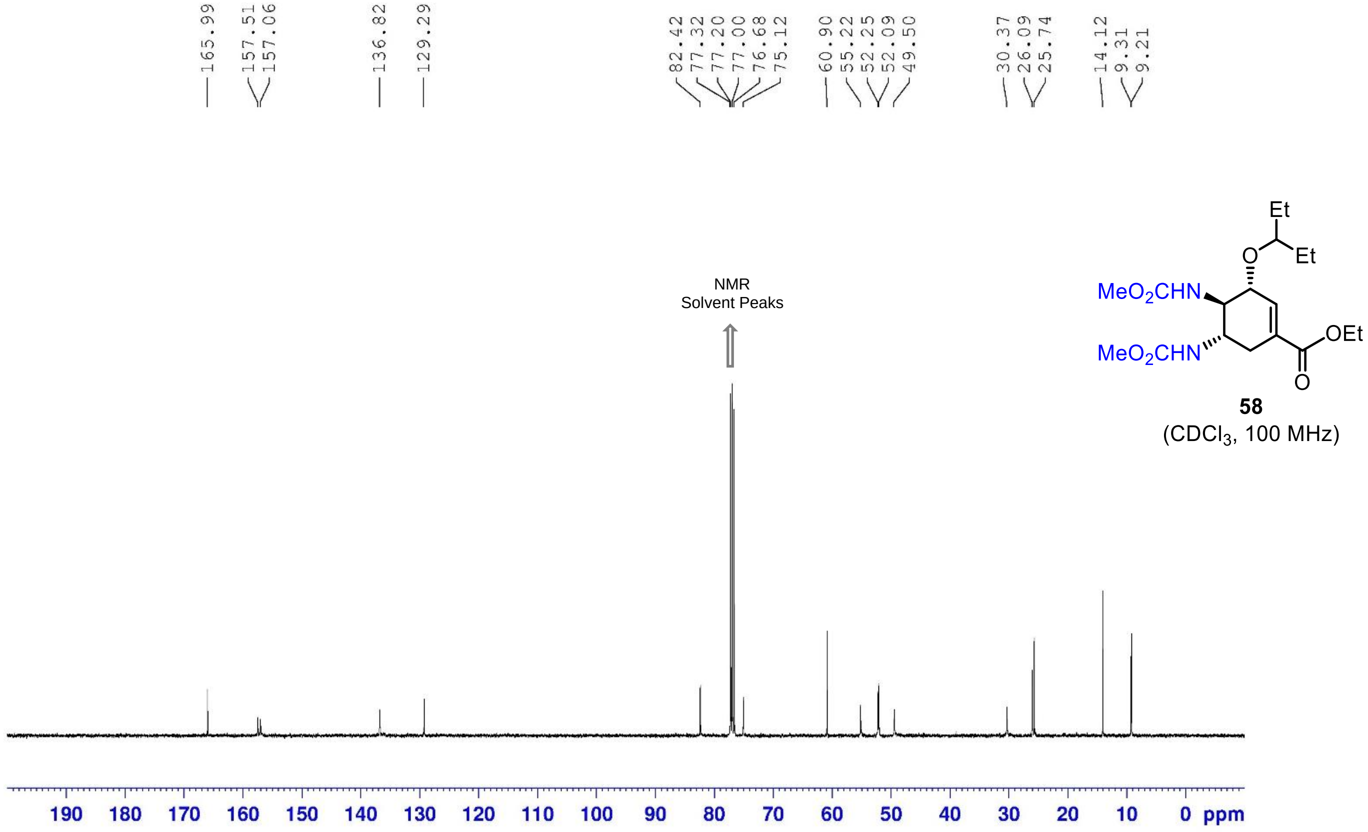


57
($CDCl_3$, 100 MHz)



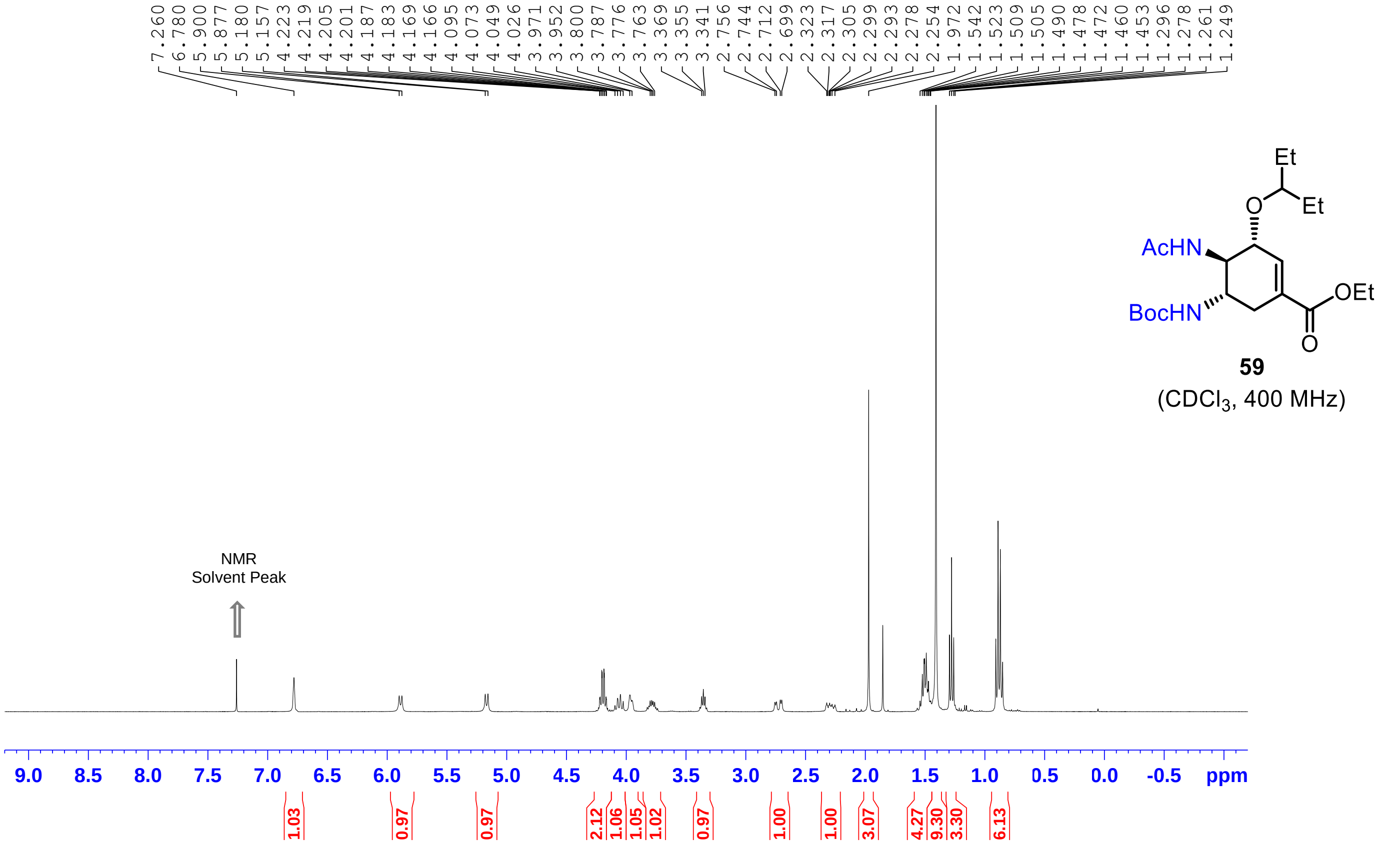
58

($CDCl_3$, 400 MHz)



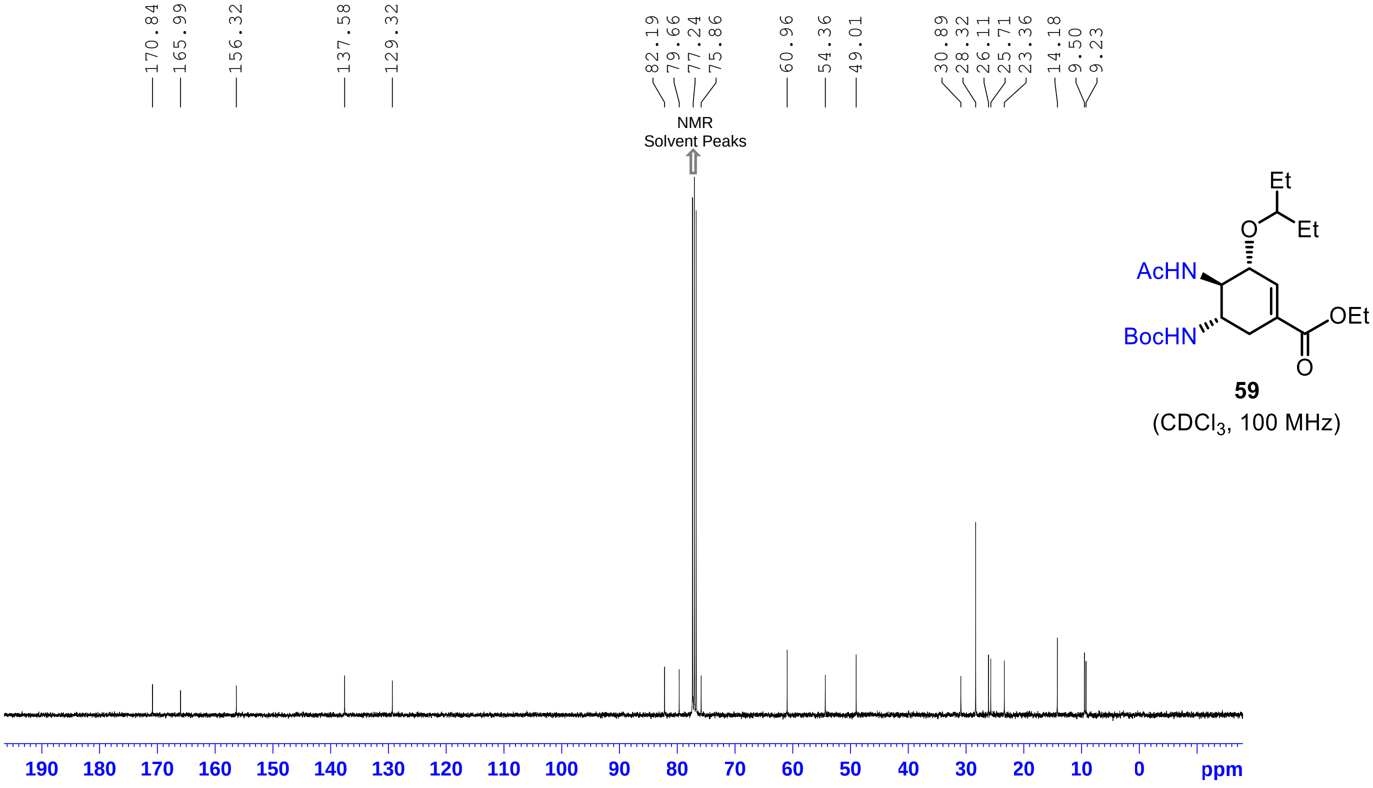
58

($CDCl_3$, 100 MHz)



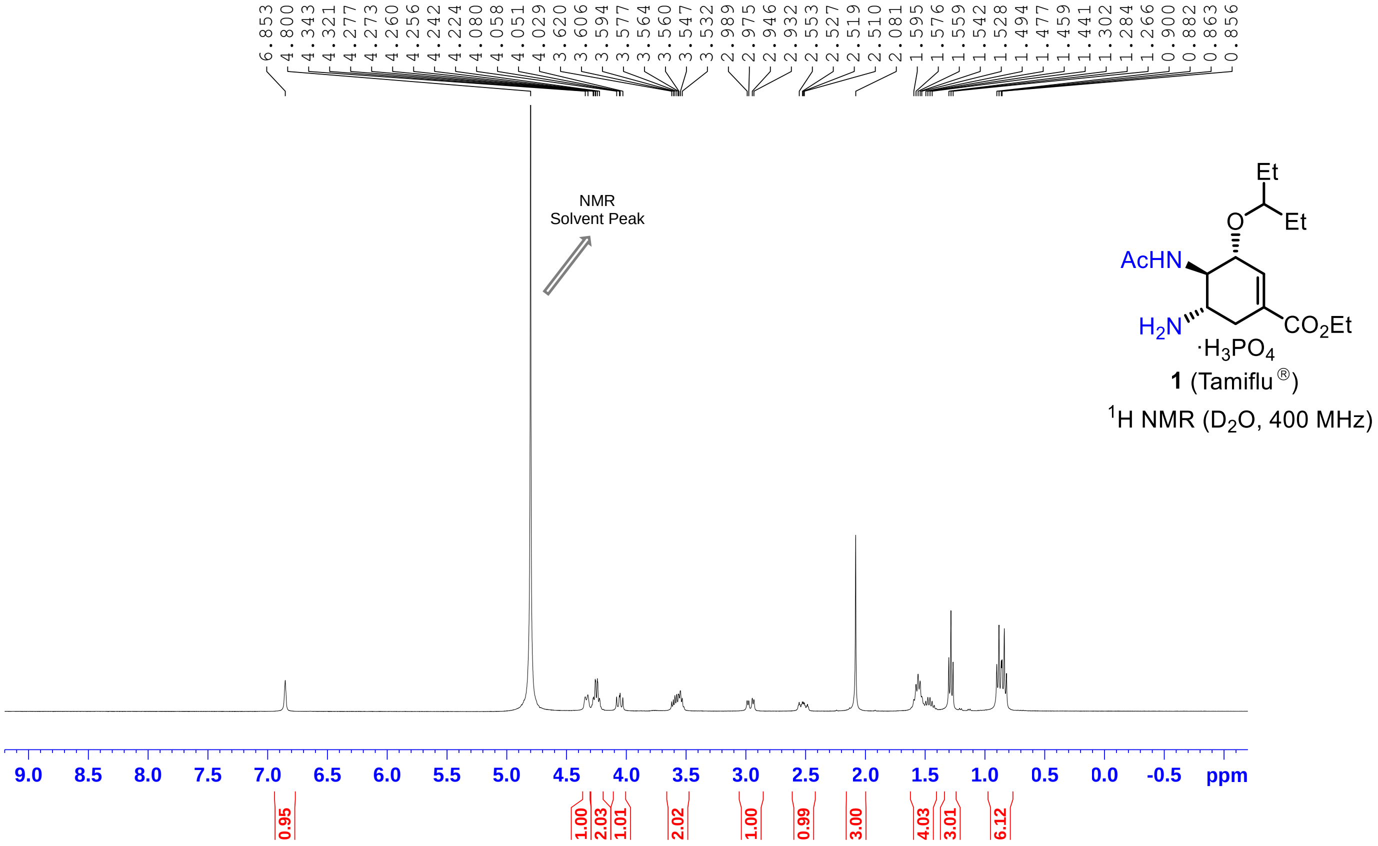
59

($CDCl_3$, 400 MHz)



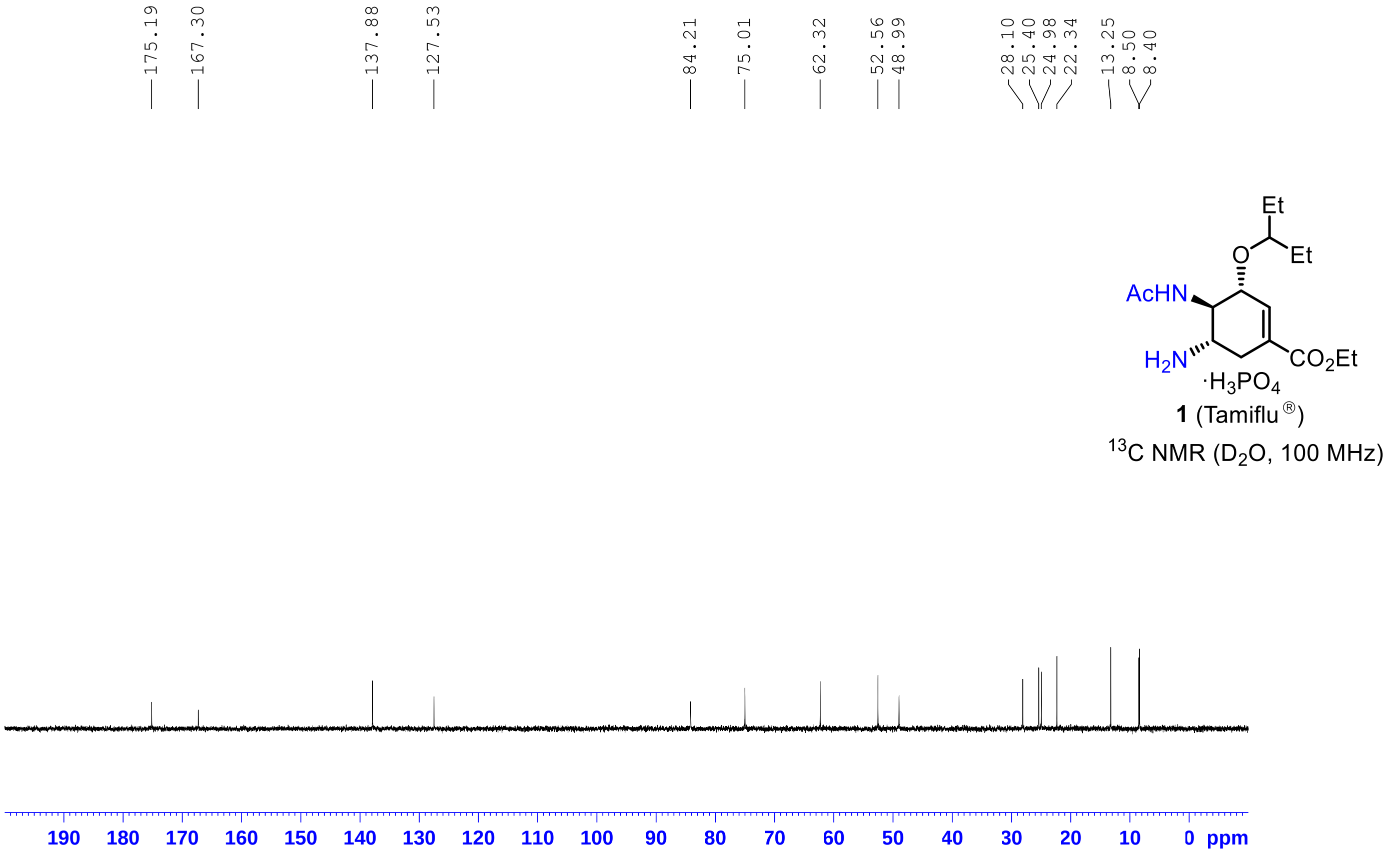
59

($CDCl_3$, 100 MHz)



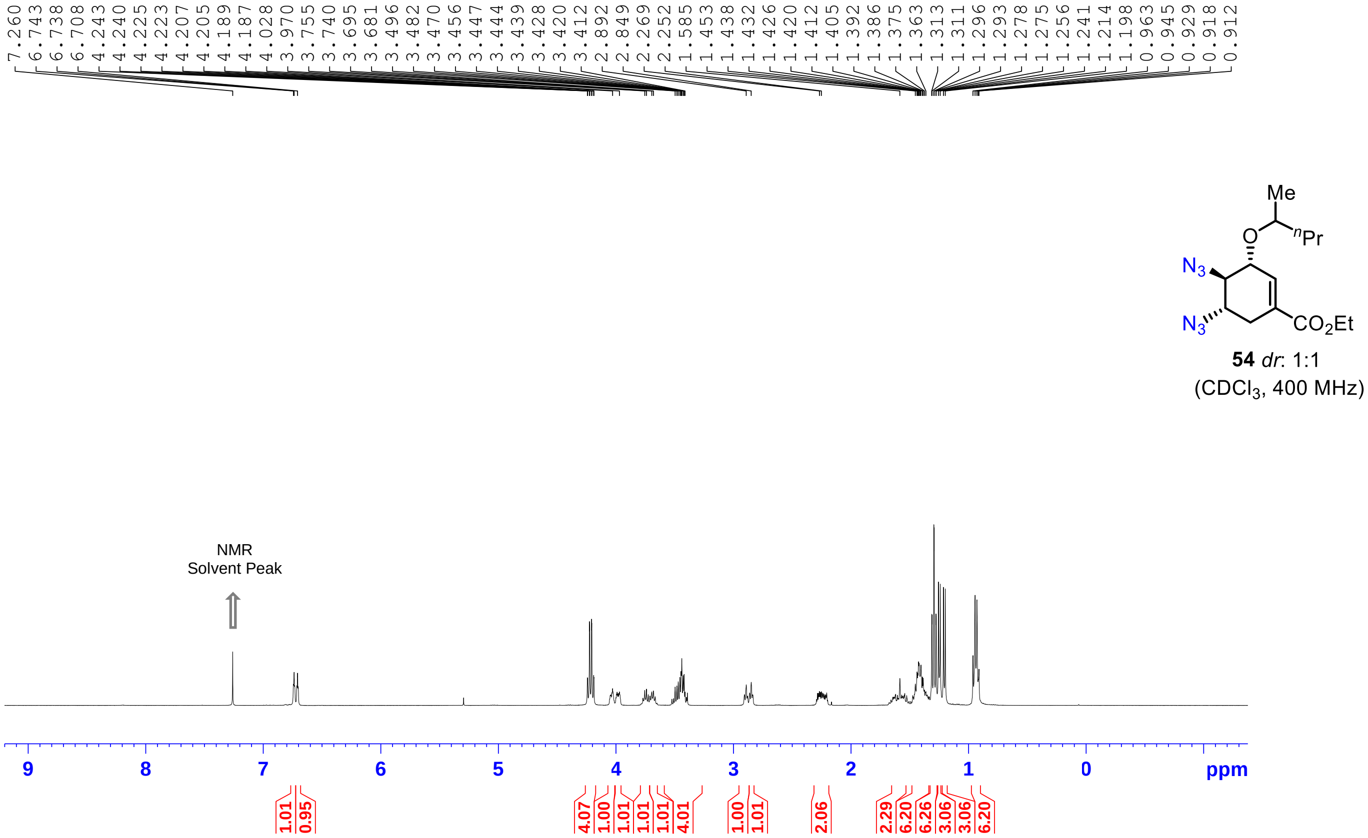
1 (Tamiflu®)

^1H NMR (D_2O, 400 MHz)

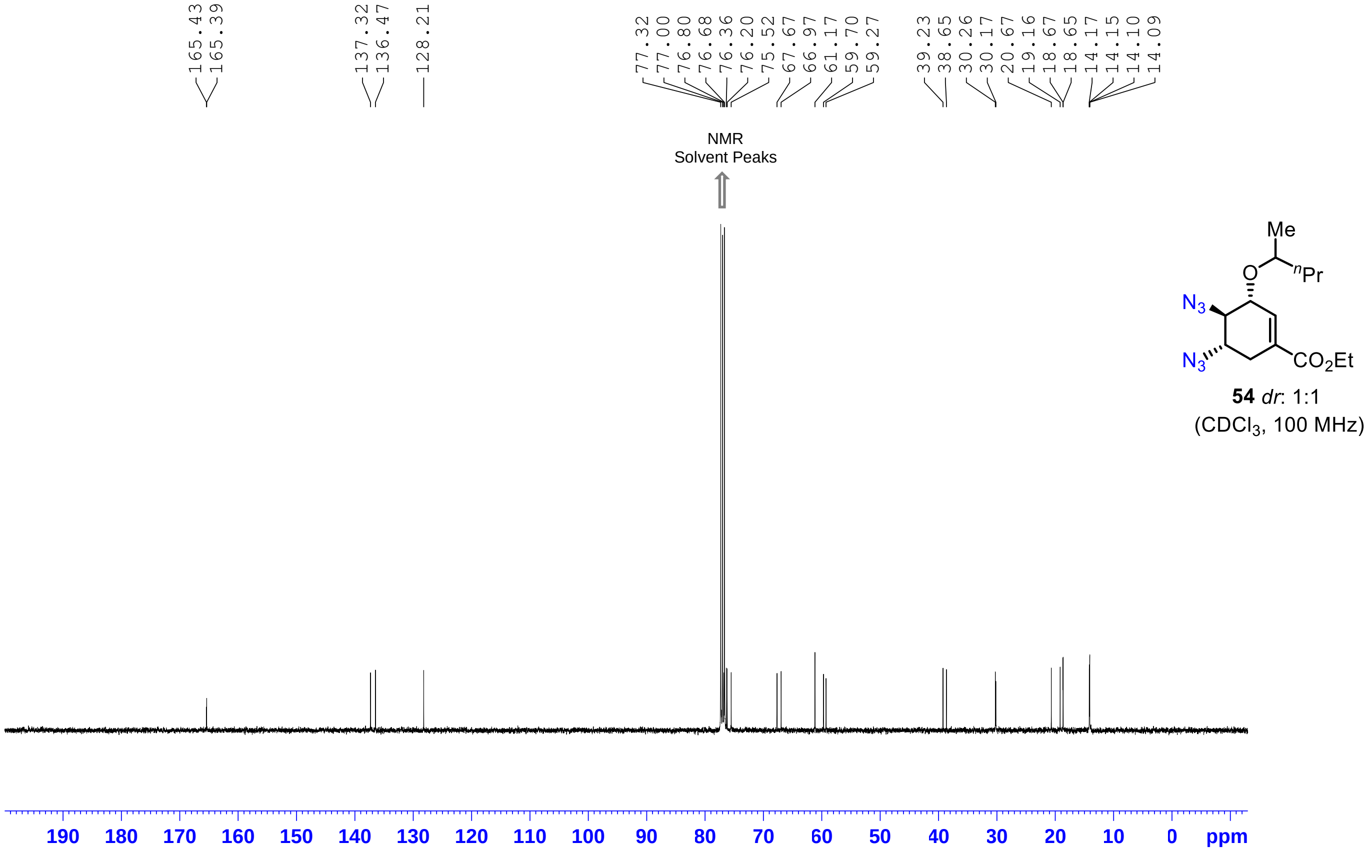


1 (Tamiflu®)

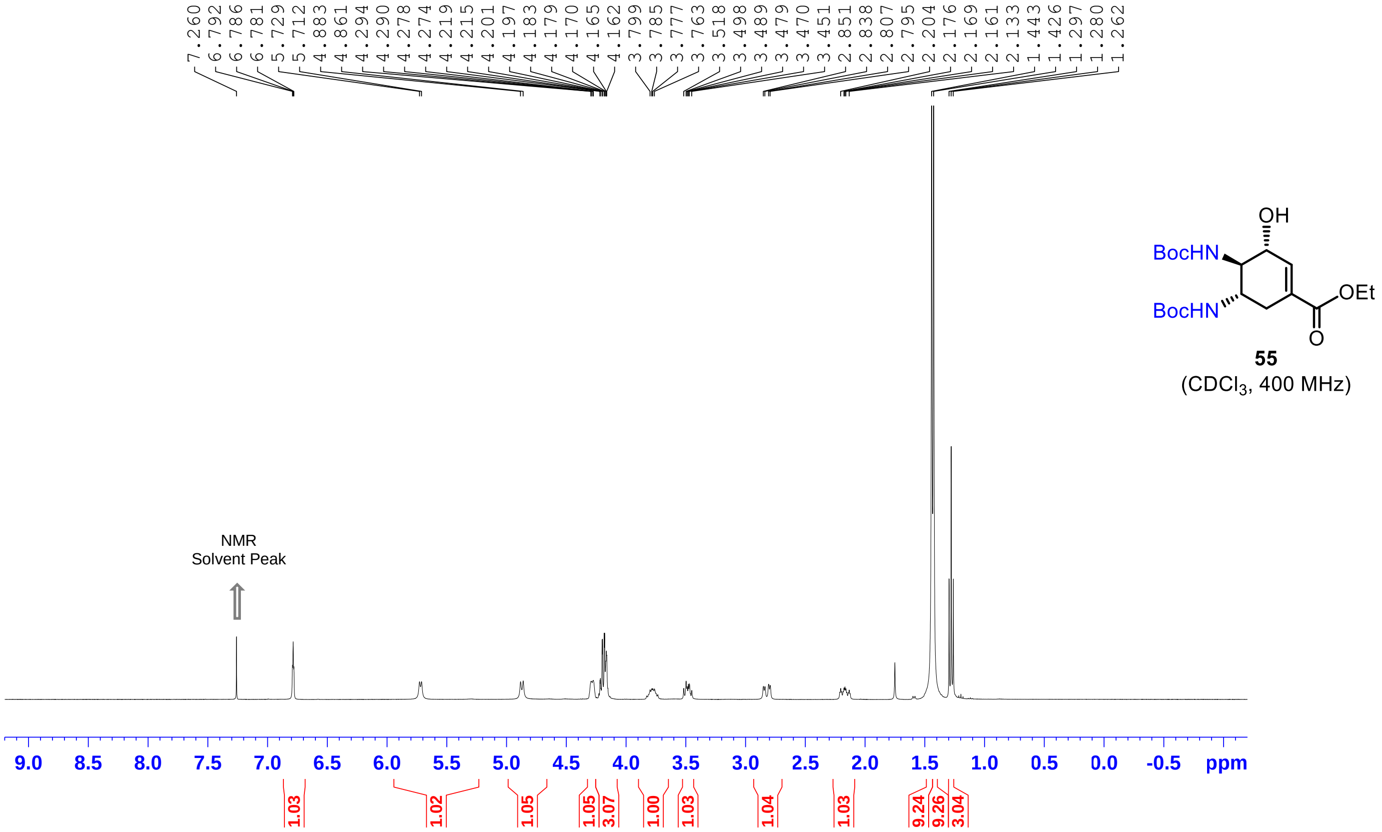
^{13}C NMR (D_2O, 100 MHz)



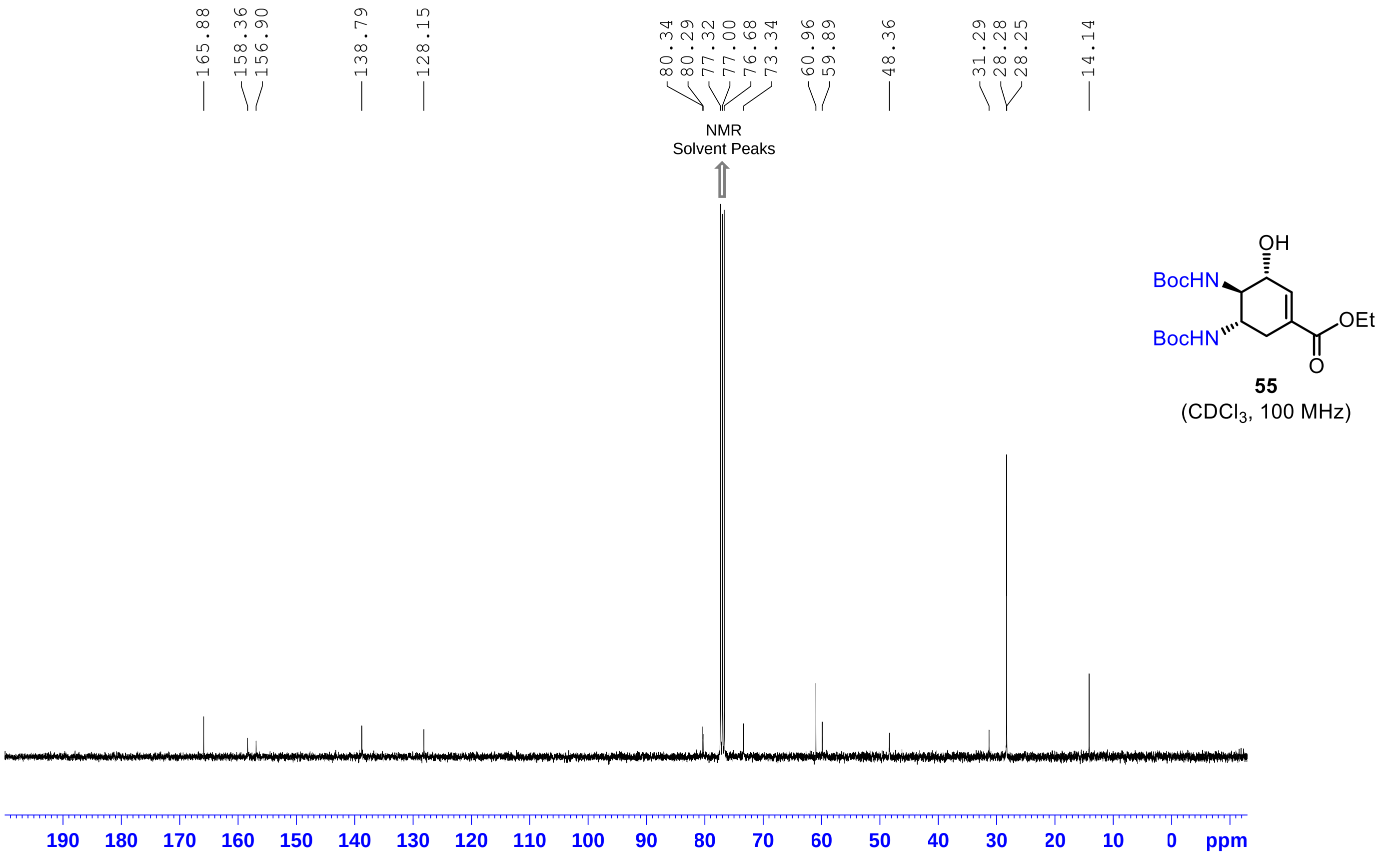
54 *dr*: 1:1
(CDCl$_3$, 400 MHz)



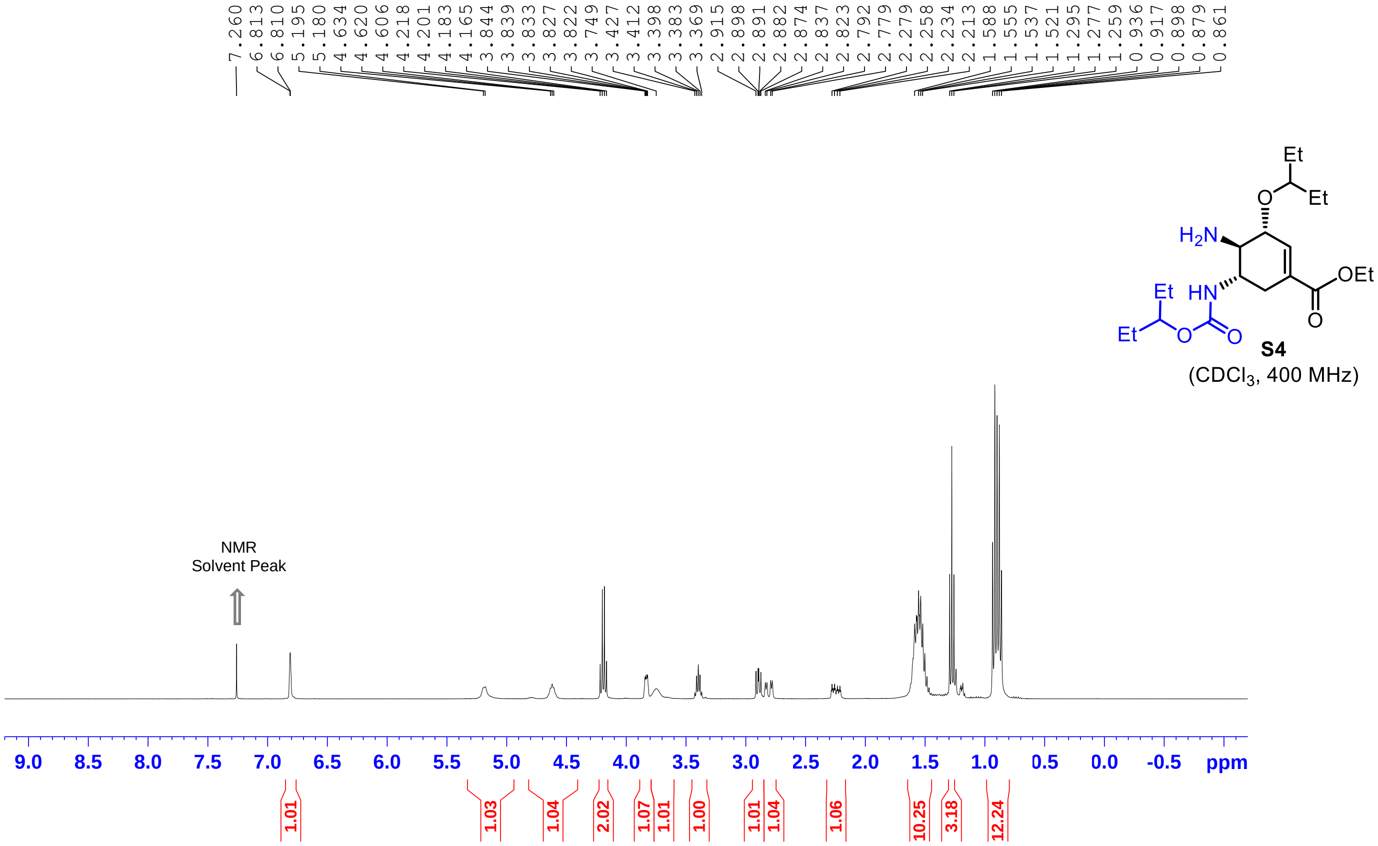
54 *dr*: 1:1
(CDCl$_3$, 100 MHz)

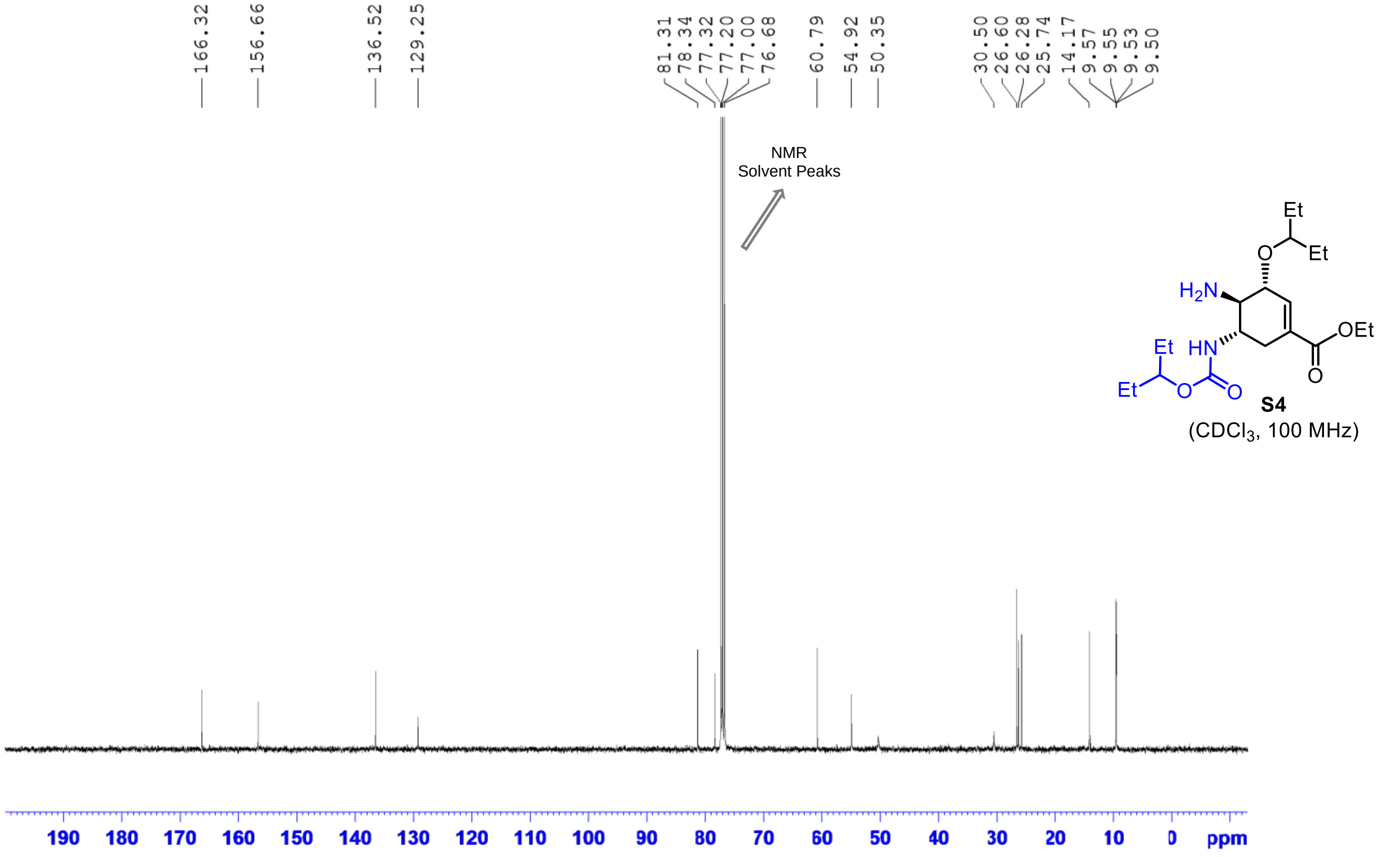


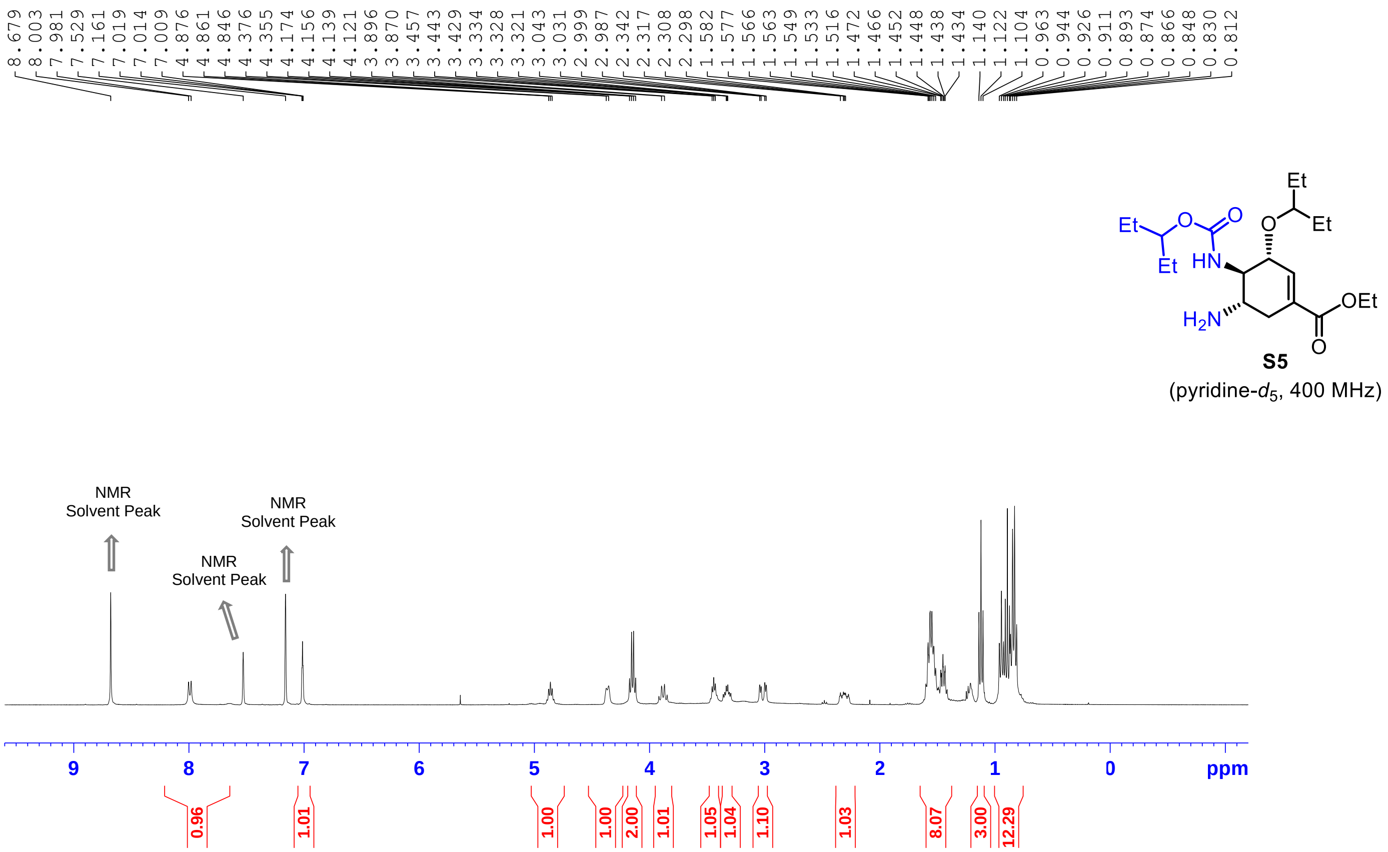
55
($CDCl_3$, 400 MHz)



55
($CDCl_3$, 100 MHz)

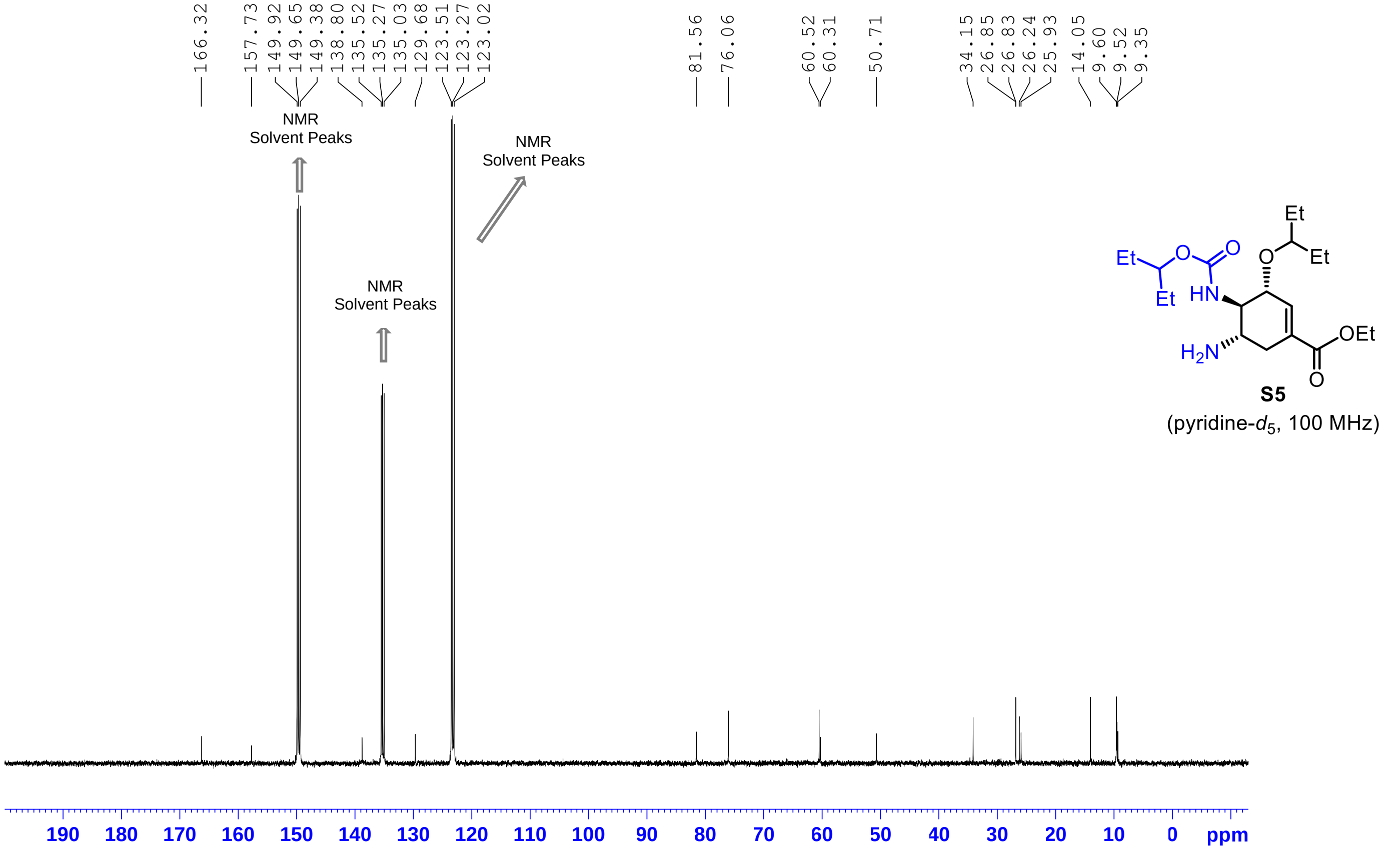

7.260
6.813
6.810
5.195
5.180
4.634
4.620
4.606
4.218
4.201
4.183
4.165
3.844
3.839
3.833
3.827
3.822
3.749
3.427
3.412
3.398
3.383
3.369
2.915
2.898
2.891
2.882
2.874
2.837
2.823
2.792
2.779
2.279
2.258
2.234
2.213
1.588
1.555
1.537
1.521
1.295
1.277
1.259
0.936
0.917
0.898
0.879
0.861
Et
O
Et
H_2N
OEt
Et
HN
O
Et
O
O
S4
($CDCl_3$, 400 MHz)
NMR
Solvent Peak
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
-0.5
ppm
1.01
1.03
1.04
2.02
1.07
1.01
1.00
1.01
1.04
1.06
10.25
3.18
12.24


166.32
156.66
136.52
129.25
81.31
78.34
77.32
77.20
77.00
76.68
60.79
54.92
50.35
30.50
26.60
26.28
25.74
14.17
9.57
9.55
9.53
9.50
NMR
Solvent Peaks
Et
O
Et
H_2N
OEt
Et
HN
O
Et
O
O
S4
($CDCl_3$, 100 MHz)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



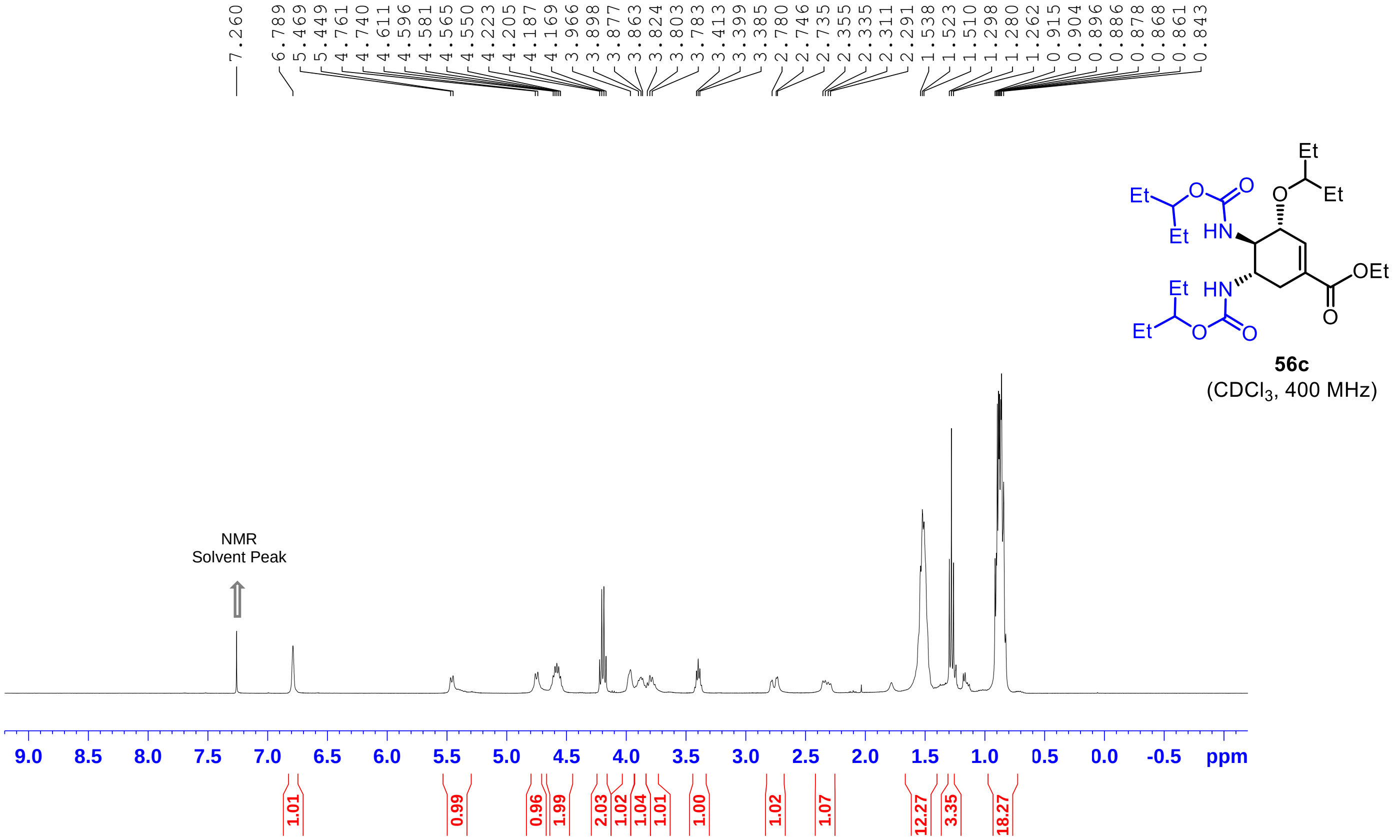
S5

(pyridine-d_5, 400 MHz)

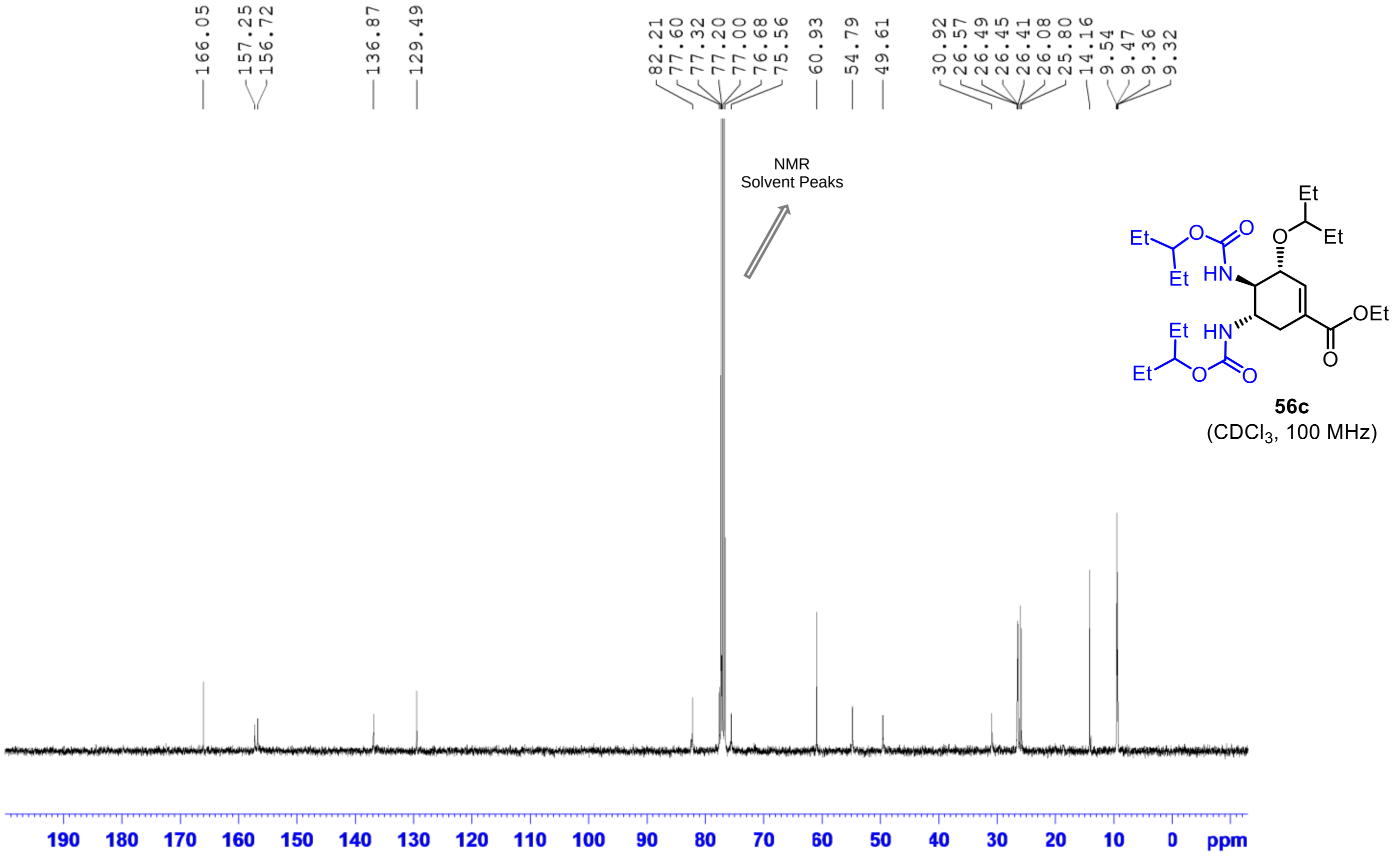


S5

(pyridine-d_5, 100 MHz)



56c
(CDCl$_3$, 400 MHz)



56c
(CDCl$_3$, 100 MHz)