Electronic Supplementary Material (ESI) for Chemical Communications.

The Base-Catalysed Tamura Cycloaddition Reaction: Calculation, Mechanism, Isolation of Intermediates and Asymmetric Catalysis

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Supplementary Information

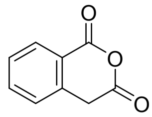
1 Experimental Section

1.1 General

Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400 MHz and Bruker Avance II 600MHz spectrometers, using as solvent $CDCl_3$ or DMSO-d_6 and referenced relative to residual $CHCl_3$ (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm). Chemical shifts are reported in ppm and coupling constants (*J*) in Hertz. Carbon NMR spectra were recorded on the same instruments (100.6 MHz and 150.9 MHz respectively) with total proton decoupling. HSQC, HMBC, NOESY and TOCSY NMR experiments were used to aid assignment of NMR peaks when required. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. A Waters micromass LCT-tof mass spectrometer was used in ESI positive and ESI negative modes for electrospray ionization mass spectrometry. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualised by UV irradiation and $KMnO_4$ staining. Anhydrous CH_2Cl_2, THF and diethyl ether were obtained from a Pure Solv MD-4EN solvent purification system.

1.2 Synthesis of anhydrides

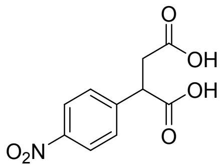
isochroman-1,3-dione (Homophthalic anhydride) **1**



A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with homophthalic acid (2.00 g, 11.1 mmol). Acetic anhydride (25 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at 80 °C for 2 h. The excess acetic anhydride was removed *in vacuo* and the solid obtained was triturated with diethyl ether (10 mL), filtered and dried under vacuum to afford homophthalic anhydride (**1**) as an off white solid (1.53 g, 85%). Spectral data for this compound were consistent with those in the literature.[1]

M.p. 141-142 °C (lit.[1] m.p. 140-144 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.05 (d, *J* = 7.9 Hz, 1H), 7.75 (app. t, 1H), 7.52 (app. t, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 4.28 (s, 2H).

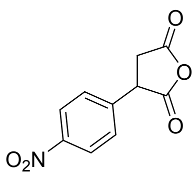
2-(4-Nitrophenyl)succinic acid (*p*-Nitrophenyl succinic acid) **S1**



A three-necked oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar was fitted with a thermometer and charged with fuming nitric acid (30 mL) and cooled to 0 °C. Phenylsuccinic acid (10.0 g, 51.5 mmol) was added portionwise, maintaining a temperature below 20 °C. The solution was allowed to stir at 0 °C for 2 h, then crushed ice (30 g) and water (20 mL) were added to the reaction mixture. The white precipitate formed was filtered, washed with water, dried, and then recrystallised from water to obtain **S1** as a white solid (7.2 g, 58%). Spectral data for this compound were consistent with those in the literature.[2]

M.p. 232-234 °C (lit.[2] 233-235 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.60 (br s, 2H), 8.19 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 4.10 (dd, *J* = 9.7, 5.5 Hz, 1H), 3.00 (d, *J* = 17.0, 9.7 Hz, 1H), 2.64 (dd, *J* = 17.0, 5.5 Hz, 1H).

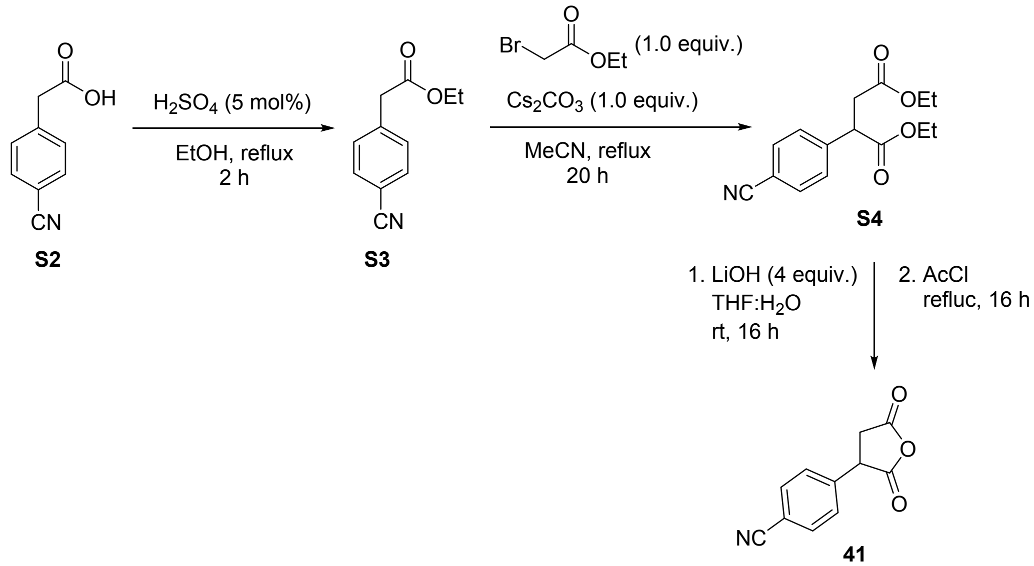
3-(4-Nitrophenyl)dihydrofuran-2,5-dione (*p*-Nitrophenyl succinic anhydride) **36**



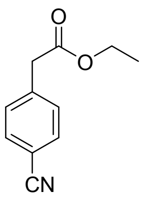
An oven-dried 50 mL round-bottomed flask containing a magnetic stirring bar was charged with **S1** (2.0 g, 8.36 mmol). Freshly distilled acetyl chloride (15 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at reflux under an argon atmosphere for 16 h. The acetyl chloride was then removed *in vacuo* to obtain a dark yellow oil that was purified by passing it through a plug of silica eluting with hexanes:EtOAc (1:1; *v/v*), followed by several azeotropic distillations with $CHCl_3$ on a rotary evaporator (5 x 5 mL) to afford **36** as a light yellow solid (1.20 g, 65%). Spectral data for this compound were consistent with those found in the literature.[2]

M.p. 66-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 4.51 (dd, *J* = 10.4, 7.2 Hz, 1H), 3.56 (dd, *J* = 18.8, 10.4 Hz, 1H), 3.18 (dd J = 18.8, 7.2 Hz, 1H).

General sequence for the synthesis of 4-(cyano)phenylsuccinic anhydride 41



Ethyl (4-cyanophenyl)acetate (S3)

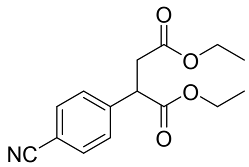


An oven-dried round-bottomed flask equipped with a magnetic stirring bar under an argon atmosphere was charged with 4-(cyano)phenylacetic acid **S2** (2.00 g, 12.4 mmol). EtOH (25 mL) and conc. H_2SO_4 (5 mol%) were subsequently added, the flask fitted with a condenser and the mixture heated under reflux for 2 hours. The solution was then allowed to cool to room temperature and concentrated *in vacuo.* The resulting residue was dissolved in EtOAc, washed once with $NaHCO_3$ (10% *w/v*), dried over $MgSO_4$ and reduced *in vacuo* to afford **S3** as a colourless oil (2.06 g, 88%).

Spectral data for this compound were consistent with those found in the literature.[3]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 6.5 Hz, 2H), 7.41 (d, *J* = 6.7 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); LRMS (ESI): calcd. For $[M+H]^+$ $C_{11}H_{11}NO_2$ Requires: 189.08, found: 189.08.

Diethyl (4-cyanophenyl)succinate (S4)

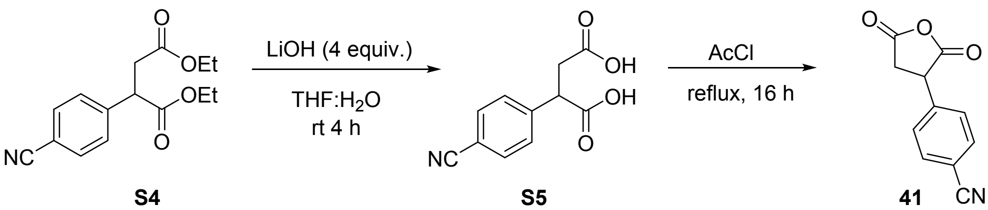


To an oven-dried round-bottomed flask equipped with a magnetic stirring bar under an argon atmosphere was added ester **S3** (2.00 g, 10.6 mmol) and caesium carbonate (3.45 g, 10.6 mmol) followed by MeCN (27 mL) and ethyl bromoacetate (1.18 mL, 10.6 mmol). The flask was then fitted with a condenser and heated at 80 °C for 16 h. The mixture was then cooled to room temperature, diluted with water and extracted three times with EtOAc. The combined organics were dried over $MgSO_4$, reduced *in vacuo* and purified by flash column chromatography to afford **S4** as a yellow oil (2.62g, 90%).

Spectral data for this compound were consistent with those found in the literature.[4]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 4.16 – 4.11 (m, 5H), 3.18 (dd, *J* = 17.0, 9.4 Hz, 1H), 2.68 (dd, *J* = 17.0, 6.1 Hz, 1H), 1.20 (m, 6H).; LRMS (ESI): calcd. For $[M+H]^+$ $C_{15}H_{18}NO_4$ Requires: 276.12, found: 276.12.

4-(2,5-Dioxotetrahydrofuran-3-yl)benzonitrile (41)

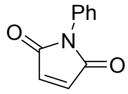


To a round-bottomed flask containing di-ester **S4** (2.60 g, 9.44 mmol) was added THF (24 mL) and water (7 mL) followed by lithium hydroxide (1.36 g, 38.0 mmol). The mixture was allowed to stir at room temperature until disappearance of the starting material was observed by TLC (~4 h). The reaction mixture was then acidifed with an aqueous HCl solution (2N) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Mg_2SO_4 and reduced *in vacuo* to yield the di-acid **S5** as a white solid (1.90 g). **S5** Was transferred to an oven-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar, followed by the addition of freshly distilled acetyl chloride (20 mL). The resulting mixture was heated under reflux for 16 h, the volatiles removed *in vacuo* and the residue stirred with a small amount of diethyl ether which caused precipitation of the anhydride **41** as a white solid (1.28 g, 67% over two steps).

M.p. 103-105 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.73 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 4.44 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.52 (dd, *J* = 18.8, 10.5 Hz, 1H), 3.14 (dd, *J* = 18.8, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.3, 168.2, 139.2, 133.2, 128.3, 117.9, 113.0, 46.3, 36.1; IR (neat): 3007, 2944, 2237, 1775, 1711, 1421, 1215, 1069, 1040, 924, 838 cm^{-1}; HRMS (ESI): calcd. For $[M-H]^-$ $C_{11}H_6NO_3$ Requires: 200.0353, found: 200.0346.

1.3 Synthesis of maleimides

1-phenyl-1H-pyrrole-2,5-dione (*N*-Phenyl maleimide) **14**

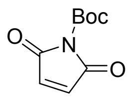


Step 1. To a three-necked 100 mL round-bottomed flask equipped with a magnetic stirring bar was added maleic anhydride (10.0 g, 102.0 mmol) in diethyl ether (125 mL). When all the maleic anhydride had dissolved, a solution of aniline (9.30 mL, 103.0 mmol) in diethyl ether (12 mL) was added drop-wise over 30 minutes. The resulting thick suspension was stirred at room temperature for 1 h and then cooled to 0 °C before being filtered to obtain the maleanilic acid as a fine powder, suitable for use in the next step without need for further purification.

Step 2. To a 100 mL round-bottomed flask equipped with a magnetic stirring bar was added the maleanilic acid followed by acetic anhydride (35 mL) and anhydrous sodium acetate (3.30 g, 40.2 mmol). The flask was fitted with a reflux condenser and the suspension dissolved by heating at 100 °C for 30 minutes. The reaction mixture was allowed to cool until mildly warm, and then poured onto ice water (100 mL). The precipitated product was collected by suction filtration, washed with ice-cold water (3 x 20 mL) and once with petroleum ether (50 mL), taken up in CH_2Cl_2 (20 mL), and dried over anhydrous Mg_2SO_4, then reduced *in vacuo*. Recrystallization of the crude solid from EtOAc/hexanes afforded **14** as canary yellow needles (7.70 g, 43%). Spectral data for this compound were consistent with those in the literature.[5]

M.p. 80 – 83 °C (lit.[6] 83 – 84 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 – 7.44 (m, 2H), 7.37 – 7.34 (m, 3H), 6.84 (s, 2H).

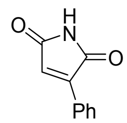
tert-butyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate (*N*-Boc maleimide) **26**



To a solution of maleimide (1.00 g, 10.3 mmol) in anhydrous CH_2Cl_2 (20 mL) was added di-*tert*-butyl dicarbonate (2.25 g, 10.3 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP; 126 mg, 1.03 mmol) at room temperature. After stirring the mixture for 10 min, the solvent was removed *in vacuo* and the crude residue purified by column chromatography on silica gel eluting with hexanes/EtOAc (4:1; *v/v*) to give **26** as a beige solid (1.81 g, 89%). Spectral data for this compound were consistent with those in the literature.[7]

M.p. 63 – 65 °C (lit[7] 62 64 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (s, 2H), 1.59 (s, 9H).

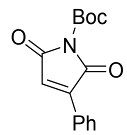
3-phenyl-1H-pyrrole-2,5-dione S6



To a 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged phenylmaleic anhydride (5.0 g, 28.7 mmol) and anhydrous ammonium acetate (5.53 g, 71.8 mmol). Glacial acetic acid was added (8 mL) and the mixture was heated under reflux for 3 h. The solvent was removed *in vacuo* and the crude residue purified by flash column chromatography on silica gel eluting with hexanes/EtOAc (4/1;*v/v*) to give **S6** as a beige solid (3.53 g, 71%).

M.p. 165 – 168 °C (lit.[8] 167 – 168 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.02 (s, 1H), 8.01 – 7.94 (m, 2H), 7.52 – 7.46 (m, 3H), 7.16 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.2, 171.8, 143.1, 130.8, 129.0, 128.8, 128.6, 125.9; IR (neat): 3179, 1709, 1594, 1447, 1343, 1127, 974, 873, 789 cm^{-1}; HRMS (ESI): calcd. For $[M-H]^-$ $C_{10}H_6NO_2$ Requires: 172.0404, found: 172.0412.

tert-butyl 2,5-dioxo-3-phenyl-2,5-dihydro-1H-pyrrole-1-carboxylate (*N*-Boc-α-phenyl maleimide) **21**

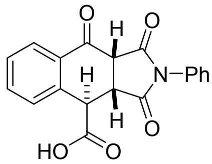


To a solution of 2-phenylmaleimide **S6** (1.48 g, 8.5 mmol) in anhydrous CH_2Cl_2 (17 mL) was added di-*t*-butyl dicarbonate (1.86 g, 8.5 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP; 104 mg, 0.85 mmol) at room temperature. After stirring the mixture for 10 min, the solvent was removed *in vacuo* and the crude residue purified by column chromatography on silica gel eluting with hexanes/EtOAc (4/1;*v/v*) to give **21** as a white solid (1.38 g, 60%).

M.p. 85 – 87 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 – 7.89 (m, 2H), 7.54 – 7.45 (m, 3H), 6.81 (s, 1H), 1.62 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 165.9, 146.2, 144.5, 131.9, 129.2, 129.0, 128.1, 125.2, 85.5, 28.0; IR (neat): 2985, 2942, 1796, 1756, 1708, 1617, 1315, 1283, 1250, 1147, 1006, 836, 788 cm^{-1}; HRMS (ESI): calcd. For $[M+Na]^+$ $C_{15}H_{15}NNaO_4$ requires: 296.0893, found: 296.0897.

1.4 Synthesis of Tamura cycloadducts

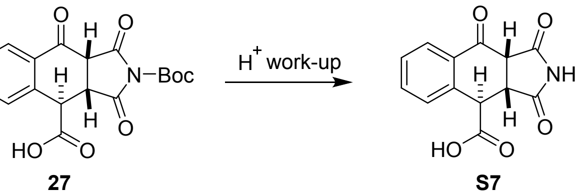
1,3,9-trioxo-2-phenyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[*f*]isoindole-4-carboxylic acid 24



To an oven-dried 10 mL round-bottomed flask equipped with a magnetic stirring bar under an argon atmosphere was added *N*-phenylmaleimide **14** (85.2 mg, 0.492 mmol) and homophthalic anhydride **1** (79.8 mg, 0.492 mmol) in THF (5.0 mL). *N,N*-diisopropylethylamine (17.2 μL, 0.0984 mmol – 20 mol %) was added *via* syringe and the resulting mixture was allowed to stir for 20 h at room temperature. The reaction mixture was then diluted with EtOAc (15 mL) and extracted with an aqueous solution of $NaHCO_3$ (3 x 15 mL, 10% *w/v*). The combined aqueous extracts were adjusted to pH~2 with aqueous HCl (2.0 N), then extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo* to yield **24** as a yellow solid (140.0 mg, 85%).

M.p. 108 – 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.63 (ddd *J* = 7.7, 7.7, 1.2 Hz, 1H), 7.46 - 7.57 (m, 2H), 7.32 - 7.45 (m, 3H), 7.10 (dd, *J* = 8.2, 1.7 Hz, 2H), 5.89 (br s, 1H), 4.70 (d, *J* = 1.3 Hz, 1H), 4.40 (d, *J* = 8.6 Hz, 1H), 4.03 (dd, *J* = 8.6, 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.4, 175.3, 175.1, 169.5, 135.6, 135.2, 131.7, 131.2, 130.3, 129.8, 129.1, 129.0, 128.5, 126.0, 52.6, 42.9, 41.2; IR (neat): 3200, 3070, 1708, 1597, 1497, 1456, 1381, 1158, 1006, 745, 690, 616, 555 cm^{-1}; HRMS (ESI): calcd. For $[M + Na]^+$ $C_{19}H_{13}NO_5Na$ requires: 358.0691, found: 358.0696.

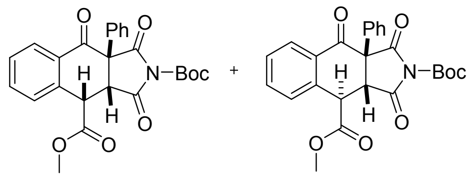
2-(tert-butoxycarbonyl)-1,3,9-trioxo-2,3,3a,4,9,9a-hexahydro-1H-benzo[*f*]isoindole-4-carboxylic acid 27



To an oven-dried 10 mL round-bottomed flask equipped with a magnetic stirring bar under an argon atmosphere was added *N*-Boc maleimide **26** (48.5 mg, 0.246 mmol) and homophthalic anhydride **1** (39.9 mg, 0.246 mmol) in THF (2.5 mL, 0.1 M). *N,N*-diisopropylethylamine (8.6 μL, 0.0492 mmol – 20 mol%) was added *via* syringe and the resulting mixture was allowed to stir at room temperature until full conversion to **27** was observed by ^{1}H NMR spectroscopic analysis (20 h). The reaction mixture was then diluted with EtOAc (15 mL) and extracted with an aqueous solution of $NaHCO_3$ (3 x 15 mL, 10% *w/v*). The combined aqueous extracts were adjusted to pH 1 with concentrated HCl and left to stir overnight at room temperature. The mixture was then extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo* to yield the carboxylic acid **S7** as a white solid (47.8 mg, 75%).

M.p. 204 - 206 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.64 (s, 1H), 7.70 – 7.66 (m, 2H), 7.54 – 7.48 (m, 2H), 4.30, (d, J = 1.6 Hz, 1H), 4.05 (d, J = 8.4 Hz, 1H), 3.97 (dd, J = 8.4, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.0, 178.2, 172.7, 172.0, 137.5, 134.5, 132.0, 129.8, 129.0, 127.0, 54.5, 43.2, 42.2; IR (neat): 3231, 3100, 1789, 1702, 1599, 1455, 1370, 1339, 1301, 1249, 1155, 1125, 1030, 928, 869, 716 cm^{-1}; HRMS (ESI): calcd. For $[M + H]^+$ $C_{13}H_{10}NO_5$ requires: 260.0565, found: 260.0553.

2-(tert-butyl) 4-methyl 1,3,9-trioxo-9a-phenyl-1,3,3a,4,9,9a-hexahydro-2H-benzo[f]isoindole-2,4-dicarboxylate 35



35a **35b**

To an oven-dried 10 mL round-bottomed flask equipped with a magnetic stirring bar under an argon atmosphere was added *N*-Boc, *α*-phenyl maleimide **21** (67.2 mg, 0.246 mmol) and homophthalic anhydride **1** (39.9 mg, 0.246 mmol) in THF (2.5 mL, 0.1 M). *N*-methyl pyrrolidine (25. 6 μL, 0.0492 mmol – 20 mol%) was added *via* syringe and the resulting mixture allowed to stir at room temperature until the formation of a white precipitate was observed (~1 h). An aqueous solution of citric acid (5 % *w/v*) was added drop-wise until the precipitate dissolved, then the mixture was diluted with EtOAc (20 mL) and washed with deionised water (5 x 5 mL). The organic layer was dried with $MgSO_4$, reduced *in vacuo* and the crude solid was placed in an oven dried 10 mL round-bottomed flask equipped with a magnetic stirring bar under an argon atmosphere. The solid was dissolved in THF (2.5 mL, 0.1 M), then anhydrous MeOH (750 μL, 18.5 mmol) and trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 μL, 0.300 mmol) were added *via* syringe at 0 °C, and the mixture was allowed to stir for 30 min. The solvent was then removed *in vacuo* and the crude residue purified by flash column chromatography on silica gel to afford **35a** and **35b** as white solids (102.8 mg, 93% combined yield).

35a (64.1 mg, 58%).

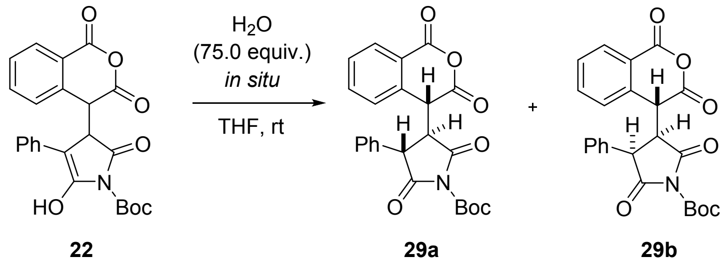
M.p. 185 – 187 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (dd, J = 7.7, 1.1 Hz, 1H), 7.62 (ddd J = 7.7, 7.7, 1.2 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.46 (ddd, J = 7.7, 7.7, 1.2 Hz, 1H), 7.34 – 7.26 (m, 5H), 4.59 (d, J = 6.6 Hz, 1H), 4.07 (d, J = 6.6 Hz, 1H), 3.63 (s, 3H), 1.59 (s, 9H) ; ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 187.7, 171.5, 171.2, 167.8, 146.1, 137.0, 135.2, 134.4, 133.3, 129.7, 129.6, 129.4, 128.8, 128.7, 126.5, 86.8, 59.6, 53.3, 49.9, 45.0, 27.9 ; IR (neat): 2976, 1806, 1768, 1753, 1719, 1599, 1449, 1372, 1258, 1243, 1147, 1086, 888, 829, 703 cm^{-1}; HRMS (ESI): calcd. For $[M+Na]^+$ $C_{25}H_{23}NO_7Na$ requires: 472.1385, found: 472.1367.

35b (38.7 mg, 35%).
M.p. 118 – 120 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 7.8, 1.2 Hz., 1H), 7.67 (ddd, *J* = 7.8, 7.8, 1.2 Hz, 1H), 7.53 (ddd, *J* = 7.8, 7.8, 1.2 Hz 1H), 7.41 (d , *J* = 7.8 Hz, 1H), 7.40 – 7.29 (m, 3H), 7.26 – 7.23 (m, 2H), 4.64 (2, *J* = 1.9 Hz, 1H), 4.19 (d, *J* = 1.9 Hz, 1H), 3.32 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.7, 171.1, 170.0, 168.3, 145.4, 137.0, 136.2, 135.3, 131.5, 130.7, 129.5, 129.2, 128.9, 128.4, 128.1, 126.3, 126.2, 87.2, 64.5, 52.8, 52.0, 41.9, 27.7; IR (neat): 2984, 1815, 1772, 1729, 1679, 1599, 1480, 1371, 1297, 1252, 1231, 1139, 1015, 910, 898, 837, 729, 697 cm^{-1}; HRMS (ESI): calcd. For $[M-H]^-$ $C_{25}H_{23}NO_7$ requires: 448.1402, found: 448.1419.

1.5 Synthesis of Michael adducts and derivatives

***Tert*-butyl 3-(1,3-dioxoisochroman-4-yl)-2,5-dioxo-4-phenylpyrrolidine-1-carboxylate 29**



To an oven dried 10 mL round-bottomed flask equipped with a magnetic stirring bar under an argon atmosphere was added homophthalic anhydride **1** (79.8 mg, 0.492 mmol), **21** (134.4 mg, 0.492 mmol) and 4-iodoanisole (57.6 mg, 0.123 mmol) as an internal standard. The solids were dissolved in THF (2.5 mL, 0.1 M), then *N,N*-diisopropylethylamine (17.2 µL, 0.0984 mmol – 20 mol%) was added dropwise *via* syringe and the mixture was allowed to stir at room temperature until full conversion to the enol **22** was observed by ^{1}H NMR spectroscopic analysis with respect to internal standard (94%). Addition of water (0.664 mL, 75.0 equiv.) followed by overnight stirring at room temperature revealed the formation of *ca*. 10% of the keto-Michael adduct **29**. The reaction mixture was diluted with EtOAc (20 mL) and washed with an aqueous solution of $NaHCO_3$ (3 x 15 mL, 10% *w/v*). The organic layer was dried with $MgSO_4$ and reduced *in vacuo* to afford **29** as a yellow solid (mixture of diastereomers, 30.4 mg, 0.0698 mmol, 14%). The diastereomers were separated by the employment of an automated flash chromatographic purification system (Biotage SP4) using a high performance prepacked silica cartridge (Biotage SNAP 10 g), eluting the mixture in gradient of EtOAc from 100% hexanes according the following developed method.

Flow: 10 ml/min; Unit: CV = column volume = 15 ml = 1 min. Gradient: 100% hexanes for 3 CV; from 0% EtOAc in hexanes to 35% EtOAc in hexanes in 24 CV.

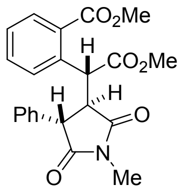
29a (10.5 mg, 5%)

M.p. 54 – 56 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.78 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H), 7.55 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H), 7.23 – 7.16 (m, 3H), 7.94 – 7.91 (m, 2H), 4.34 (d, *J* = 7.4 Hz, 1H), 4.23 (d, *J* = 8.4 Hz, 1H), 4.01 (dd, *J* = 8.4, 7.4 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.7 (2), 170.9 (2), 145.4, 134.9, 133.9, 133.7, 132.7, 131.1, 129.2 (2), 129.1, 128.5, 128.0, 86.1, 51.9, 45.1, 41.3, 27.6; IR (neat cm^{-1}): 3071, 2981, 2939, 1811, 1766, 1723, 1687, 1598, 1491, 1454, 1370, 1318, 1252, 1143, 1001, 912, 838, 729, 699.

29b (8.7 mg, 4%)

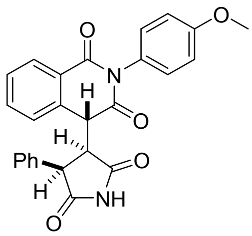
M.p. >60 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.68 (ddd, *J* = 7.3, 7.3,1.3 Hz, 1H), 7.48 (t, *J* = 7.3, 1H), 7.31 – 7.24 (m, 3H), 7.17 – 7.14 (m, 2H), 4.60 (d, *J* = 2.8 Hz, 1H), 4.47 (d, *J* = 8.7 Hz, 1H), 3.85 (dd, *J* = 8.7, 2.8 Hz, 1H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1 (2), 172.1, 171.7, 145.8, 136.8, 134.8, 133.9, 131.4, 129.2, 129.1 (2), 128.2, 128.0, 127.5, 86.8, 49.5, 44.9, 42.4, 27.7; IR (neat cm^{-1}): 3064, 2983, 1808, 1766, 1719, 1683, 1596, 1495, 1449, 1369, 1315, 1254, 1213, 1140, 1030, 949, 909, 800, 729, 695.

Methyl 2-(2-methoxy-1-(1-methyl-2,5-dioxo-4-phenylpyrrolidin-3-yl)-2-oxoethyl)benzoate 30



To an oven dried 10 mL round-bottomed flask equipped with a magnetic stirring bar under an argon atmosphere was added homophthalic anhydride **1** (79.8 mg, 0.492 mmol), **21** (134.4 mg, 0.492 mmol) and 4-iodoanisole (57.6 mg, 0.246 mmol) as an internal standard. The solids were dissolved in THF (5.0 mL, 0.1 M), then *N,N*-diisopropylethylamine (17.2 µL, 0.0984 mmol – 20 mol%) was added *via* syringe and the mixture was allowed to stir at room temperature until full conversion to the enol **22** was observed by ^{1}H NMR spectroscopic analysis with respect to internal standard (3 d). Deionised water (1.32 mL, 75.0 equiv.) was added to the reaction mixture and it was allowed to stir overnight at room temperature. The mixture was then diluted with EtOAc (30 mL) and extracted with an aqueous solution of $NaHCO_3$ (3 x 10 mL, 10% *w/v*). The aqueous extracts were adjusted to pH 2 using 2N HCl and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and reduced *in vacuo* to afford a white solid, to which was added THF (5.0 mL, 0.1 M) followed by the addition of anhydrous MeOH (1.50 mL, 36.9 mmol, 75 equiv.) and trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 300 µL, 0.590 mmol, 1.2 equiv.) *via* syringe at 0 °C. After 30 min the solvent was removed *in vacuo* and the crude residue purified by flash column chromatography on silica gel to afford **30** as a white solid (*dr* = 95:5, 62.0 mg, 32%).
M.p. 110 – 112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.12 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.12 – 7.06 (m, 3H), 6.74 – 6.66 (m, 2H), 5.13 (d, *J* = 8.2, 1H), 3.86 – 3.75 (m, 5H), 3.72 (s, 3H), 3.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 176.9, 172.6, 167.9, 136.9, 135.9, 132.0, 130.6, 130.1, 129.6, 128.7, 127.9, 127.8, 127.5, 52.7, 52.5, 51.7, 51.1, 46.4, 25.3; IR (neat): 2950, 1778, 1735, 1690, 1435, 1383, 1280, 1249, 1229, 1130, 1080, 984, 751, 701 cm^{-1}; HRMS (ESI): calcd. For $[M + H]^+$ $C_{22}H_{22}NO_6$ requires: 396.1432, found: 396.1442.

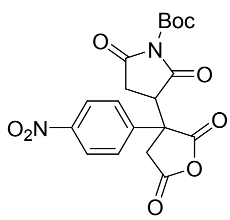
4-(2,5-dioxo-4-phenylpyrrolidin-3-yl)-2-(4-methoxyphenyl)isoquinoline-1,3(2H,4H)-dione 32



To an oven-dried 10 mL round-bottomed flask equipped with a magnetic stirring bar under an argon atmosphere was added homophthalic anhydride **1** (39.9 mg, 0.246 mmol), and **21** (67.2 mg, 0.246 mmol) in dry THF (2.5 mL, 0.1 M). The flask was fitted with a reflux condenser and the contents heated to 80 °C, followed by the addition of *N,N*-diisopropylethylamine (8.6 μL, 0.0492 mmol – 20 mol%). Reflux was maintained until full conversion to the keto-Michael adduct **29b** was observed by ^{1}H NMR spectroscopic analysis (20 h), at which point anisidine (30.3 mg, 0.246 mmol) was added and the reaction mixture refluxed for a further 20 h. The solvent was then removed *in vacuo* and the crude residue purified by column chromatography to afford **32** as a white solid (45.5 mg, 42%).

M.p. >165 °C (dec.) ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.68 (ddd, *J* = 7.8, 7.8, 1.3 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.33 – 7.24 (m, 3H), 7.24 – 7.19 (m, 2H), 7.13 (d, *J* = 9.1 Hz, 2H), 6.93 (d, *J* = 9.1 Hz, 2H), 4.71 (d, *J* = 1.8 Hz, 1H), 4.59 (d, *J* = 8.5 Hz, 1H), 3.98 (dd, *J* = 8.5, 1.8 Hz, 1H), 3.82 (s, 3H), 1.70 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.8, 175.7, 175.4, 159.7, 137.4, 135.1, 134.8, 131.4, 129.5, 129.3, 129.0, 128.2, 128.0, 127.6, 127.5, 124.1, 114.6, 77.3, 55.6, 50.1, 44.3, 42.2; IR (neat): 3011, 2967, 2932, 2835, 1781, 1706, 1596, 1517, 1385, 1251, 1181, 1027, 932, 826 cm^{-1}.

tert-butyl 3-(3-(4-nitrophenyl)-2,5-dioxotetrahydrofuran-3-yl)-2,5-dioxopyrrolidine-1-carboxylate 37

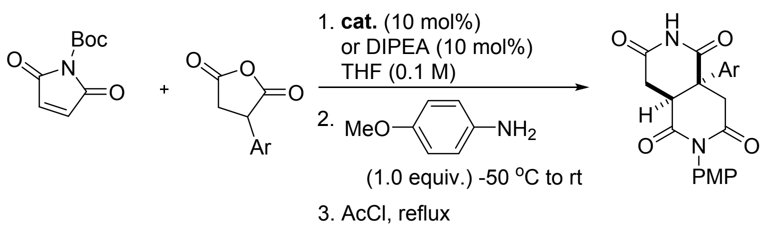


To an oven-dried 10 mL round-bottomed flask equipped with a magnetic stirring bar under an argon atmosphere was added *N*-Boc maleimide **26** (48.5 mg, 0.246 mmol) and *p*-nitrophenylsuccinic anhydride **36** (54.4 mg, 0.246 mmol) in THF (2.5 mL). *N,N*-diisopropylethylamine (8.6 μL, 0.0492 mmol – 20 mol%) was added *via* syringe and the resulting mixture was allowed to stir for 20 h at room temperature. The solution was chilled on ice and an excess of water was added quickly (~2 mL), followed by etching of the inside of the flask with a spatula. The precipitate formed was collected by suction filtration and washed with cold diethyl ether (~5 mL) to afford **37** as a white solid (30.9 mg, 31%).

M.p. 134 - 136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 2H), 3.79 (d, *J* = 18.9 Hz, 1H), 3.73 (dd, *J* = 9.6, 6.9 Hz, 1H), 3.62 (d, *J* = 18.9 Hz, 1H), 2.88 (dd, *J* = 18.9, 9.6 Hz, 1H), 2.61 (dd, *J* = 18.9, 6.9 Hz, 1H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 171.2, 169.0, 166.3, 148.7, 145.2, 140.0, 128.2, 125.0, 87.8, 53.8, 47.6, 39.1, 32.1, 27.9; IR (neat): 2988, 1812, 1785, 1765, 1713, 1521, 1345, 1322, 1232, 1147, 1099, 1068, 942, 730 cm^{-1}; HRMS (ESI): calcd. For $[M-H]^-$ $C_{19}H_{17}N_2O_9$ requires: 417.0940, found: 417.0947.

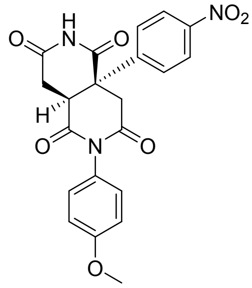
1.6 Development of an asymmetric variant

General procedure I: General procedure for the derivatisation of Michael adducts as *bis*-imides



To an oven-dried 10 mL carousel tube equipped with a magnetic stir bar under an argon atmosphere was charged *N*-boc maleimide **26** (48.5 mg, 0.246 mmol) and the relevant phenylsuccinic anhydride derivative (0.246 mmol). Anhydrous THF (2.5 mL, 0.1 M) was subsequently added and the reaction adjusted to the relevant temperature, then left to stir for 30 min. The relevant catalyst (10 mol%) or DIPEA (20 mol%) was added and the reaction allowed to stir until deemed complete by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. When complete, the mixture was cooled to -50 °C, allowed to equilibrate for 30 minutes, then *p*-anisidine (**31**, 30.3 mg, 0.246 mmol) added in one go. After 1 hour the reaction mixture was allowed to warm to room temperature. EtOAc (10 mL) was added, and the relevant acid extracted with aqueous $NaHCO_3$ (5 % *w/v,* 3 x 5 mL). The combined aqueous extracts were acidified to pH 2 using aqueous HCl (2N), then extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, concentrated *in vacuo* and the crude carboxylic acid transferred to an oven-dried 5 mL round-bottomed flask equipped with a magnetic stir bar. Freshly distilled acetyl chloride was added *via* syringe (2.5 mL), the flask fitted with a condenser and the reaction mixture heated under reflux overnight. The volatiles were then removed *in vacuo* and the crude residue purified by flash column chromatography to afford the relevant *bis*-imide.

(*S*,*S*)-2-(4-Methoxyphenyl)-4a-(4-nitrophenyl)tetrahydro-2,6-naphthyridine-1,3,5,7(2H,6H)-tetraone (40)

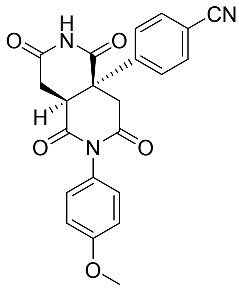


Synthesised according to general procedure I using *p*-nitrophenylsuccinic anhydride **36** (54.4 mg, 0.246 mmol) to afford **40** as a white solid (62.5 mg, 60%). M.p. 148-150 °C. $[\alpha]_D^{20}$ = -75.2 (c = 0.08, $CHCl_3$).

CSP-HPLC analysis. ACQUITY UPC^2 Trefoil CEL1, 2.5 μm (3.0 x 100 mm). ABPR: 1500 (psi). A = CO_2 / B = MeOH/IPA (1:1 *v/v*), column temperature: 30 °C, UV detection at 230 nm, retention times: 5.515 min (major enantiomer) and 5.981 min (major enantiomer).

M.p. 148-150 °C; $[\alpha]_D^{20}$ = -75.2 (c = 0.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.8 Hz, 2H), 8.03 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2 H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.82 (s, 3H), 3.71 – 3.60 (m, 2H), 3.42 (dd, *J* = 19.2, 4.9 Hz, 1H), 3.35 (d, *J* = 19.2 Hz, 1H), 3.09 (dd, *J* = 19.2, 12.7 Hz, 1H), 1.62 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 170.1, 167.9, 167.7, 160.0, 148.2, 140.2, 128.8, 128.0, 126.0, 125.0, 114.9, 55.5, 46.6, 44.6, 41.8, 30.4; IR (neat): 3462, 1736, 1720, 1531, 1508, 1351, 1360, 1205, 1215; HRMS (ESI): calcd. For $[M-H]^-$ $C_{21}H_{16}N_3O_7$ requires: 422.0994, found: 422.0995.

4-((*S*,*S*)-2-(4-methoxyphenyl)-1,3,5,7-tetraoxooctahydro-2,6-naphthyridin-4a(2H)-yl)benzonitrile (43)

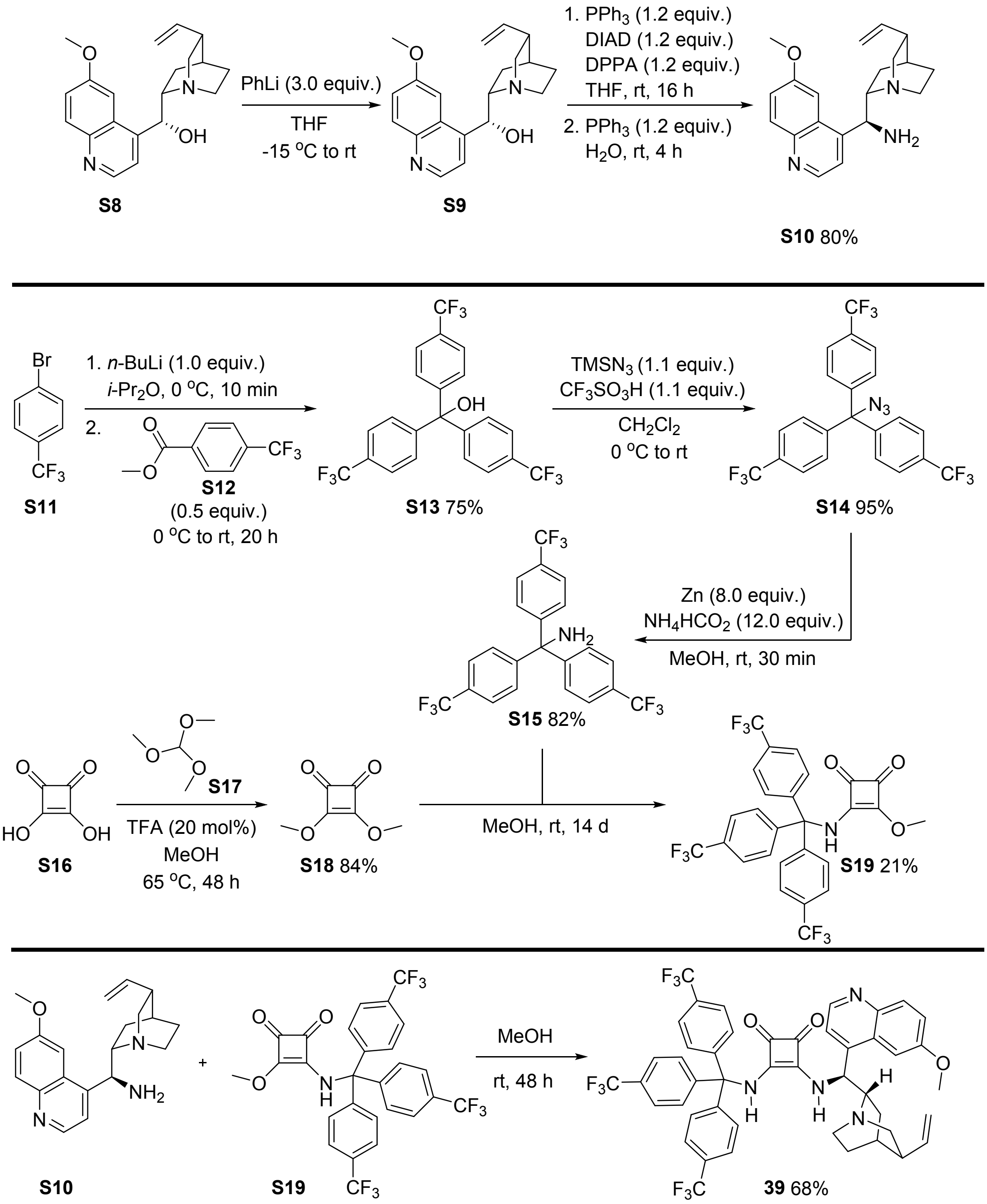


Synthesised according to general procedure I using 4-(cyano)phenylsuccinic anhydride **41** (49.6 mg, 0.246 mmol) to afford **43** as a white solid (47.6 mg, 48%).

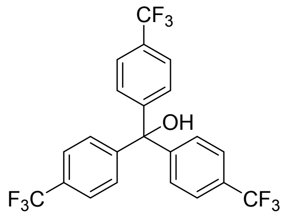
HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5 μm (3.0 x 100 mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol/MeCN/IPA (1:1:1 *v/v/v*), column temperature: 30 °C, UV detection at 230 nm, retention times: 4.034 min (minor enantiomer) and 4.917 min (major enantiomer).

M.p. 159-162 °C; $[\alpha]_D^{20}$ = -20.9 (c = 0.02, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.02 (br s, 1H), 7.77 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 6.99 – 6.92 (m, 2H), 6.87 – 6.78 (m, 2H), 3.82 (s, 3H), 3.69 – 3.61 (m, 2H), 3.43 (dd, *J* = 19.4, 5.3 Hz, 1H), 3.34 (d, *J* = 19.4 Hz, 1H), 3.09 (dd *J* = 19.4, 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 170.1, 168.0, 167.8, 160.0, 138.4, 133.5, 128.7, 127.6, 126.1, 117.3, 114.9, 114.0, 55.5, 46.6, 44.5, 41.7, 30.4; IR (neat): 3016, 2970, 2232, 1739, 1684, 1510, 1254, 1365, 1217, 1206, 1027; HRMS (ESI): calcd. For $[M-H]^-$ $C_{22}H_{17}N_3O_5$ requires: 402.1095, found: 402.1082.

Synthesis of catalyst **39**



Tris(4-(trifluoromethyl)phenyl)methanol (S13)

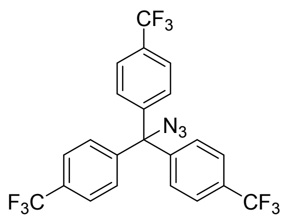


A 100 mL oven dried three-neck round-bottomed flask containing a stirring bar was charged with methyl 4-bromobenzotrifluoride (**S11**, 5.8 g, 25.72 mmol). Anhydrous diisopropyl ether (30 mL) was then added via syringe and the solution was cooled to -10 °C. A solution of n-butyl lithium (1.6 M in hexanes, 17.6 mL, 28.17 mmol) was added dropwise via syringe and the reaction was stired for 30 min. A solution of methyl 4- (trifluoromethyl)benzoate (**S12**, 2.5 g, 12.25 mmol) in dry diisopropyl ether (5 mL) was added dropwise *via* syringe at -10 °C and the resulting solution was allowed warm to room temperature and stirred for 16 h. The reaction mixture was then quenched with water (20 mL), acidified with aqueous HCl (2 N), and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a residue that was purified by flash column chromatography to afford **S13** (4.26 g, 75%) as a light yellow solid.

Spectral data for this compound were consistent with those in the literature.[9]

M.p. 91-93 °C (lit.[10] M.p. 92-93 °C); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.3 Hz, 6H), 7.42 (d, *J* = 8.3 Hz, 6H), 2.87 (bs, 1H).

4,4',4''-(Azidomethanetriyl)tris((trifluoromethyl)benzene) (S14)

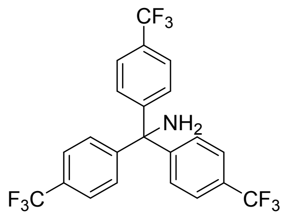


A 250 mL oven dried three-neck round-bottomed flask containing a stirring bar was charged with alcohol **S13** (4.00 g, 8.61 mmol). Anhydrous CH_2Cl_2 (90 mL) was then added *via* syringe and the resulting solution was cooled to -10 °C. Triflic acid (835 µL, 9.47 mmol) was added *via* syringe and the reaction was stirred for 15 min. Trimethylsilyl azide (1.3 mL, 9.47 mmol) was added dropwise *via* syringe at -10 °C and the resulting solution was allowed to warm to room temperature and stirred for 30 min. After disappearance of the starting material was observed by TLC (~30 min), the reaction mixture was poured onto ice (~ 100 g). The product was extracted with dichloromethane (4 x 50 mL) and the combined organic layers dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a residue that was purified by flash column chromatography to afford **S14** as a white solid (4.01 g, 95%).

Spectral data for this compound were consistent with those in the literature.[9]

M.p. 71-73 °C (lit.[9] M.p. 70-72 °C); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.3 Hz, 6H), 7.43 (d, *J* = 8.3 Hz, 6H).

Tris(4-(trifluoromethyl)phenyl)methanamine (S15)

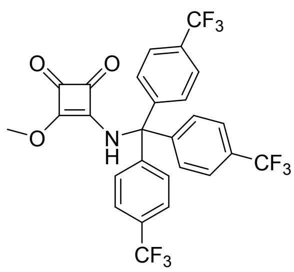


A 100 mL oven dried round-bottomed flask containing a stirring bar was charged with azide **S14** (3.50 g, 7.37 mmol), activated zinc powder (1.92 g, 29.5 mmol) and ammonium formate (1.86 g, 29.5 mmol). Dry MeOH (29.5 mL - 0.25 M) was added *via* syringe and the reaction mixture stirred at room temperature under an argon atmosphere until completion of the reaction was observed by TLC analysis (~ 1 h. The reaction mixture was then filtered through a Celite pad, washed with CH_2Cl_2 (10 mL), then the combined filtrates were concentrated *in vacuo*. The resulting residue was taken up in CH_2Cl_2 (30 mL), washed with a saturated brine solution (2 x 20 mL) then with water (2 x 20 mL). The organic layer was subsequently dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a residue which was purified by flash column chromatography to afford **S15** as a white solid (2.81 g, 82%).

Spectral data for this compound were consistent with those in the literature.[9]

M.p. 80-82 °C (lit.[9] M.p. 82-84 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.3 Hz, 6H), 7.43 (d, *J* = 8.3 Hz, 6H), 2.31 (bs, 2H).

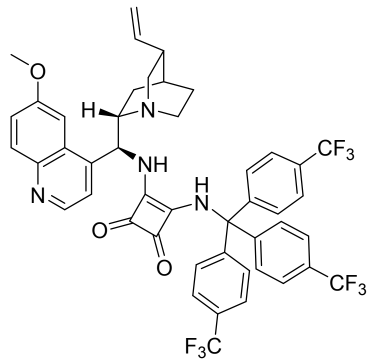
3-Methoxy-4-((tris(4-(trifluoromethyl)phenyl)methyl)amino)cyclobut-3-ene-1,2-dione (S19)



An oven-dried 25 mL round-bottomed flask equipped with a magnetic stirring bar under an argon atmosphere was charged with **S18** (500 mg, 3.52 mmol) and amine **S15** (1.63 g, 3.52 mmol). Anhydrous MeOH (4 mL) was subsequently added *via* syringe and the resulting suspension allowed

to stir at room temperature for 14 days. The solvent was then removed *in vacuo* and the resulting residue purified by flash column chromatography to afford **S19** as a white solid (421 mg, 21%).
Spectral data for this compound were consistent with those in the literature.[9]
M.p. 91-93 °C (lit.[9] M.p. 94-98 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.3 Hz, 6H), 7.27 (d, *J* = 8.3 Hz, 6H), 6.90 (bs, 1H), 3.85 (bs, 1H).

3-(((S)-(6-Methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-4-((tris(4-(trifluoromethyl)phenyl)methyl)amino)cyclobut-3-ene1,2-dione (39)



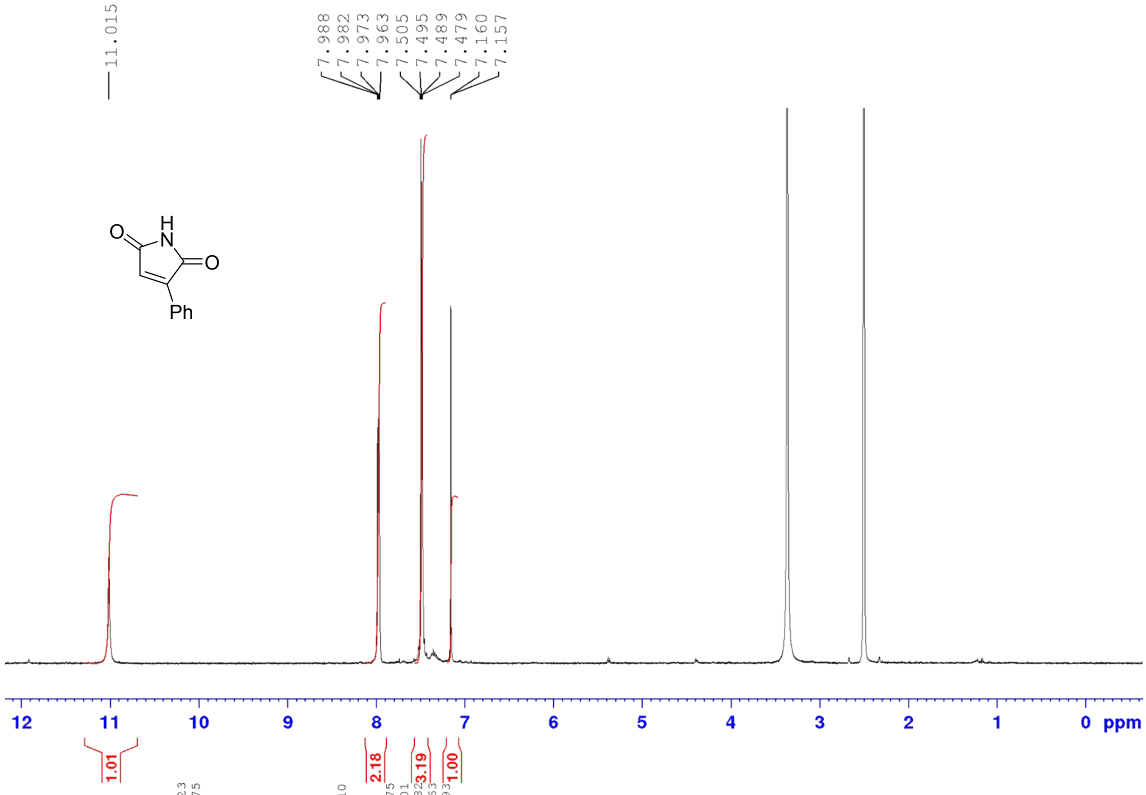
A 10 mL oven dried round-bottomed flask containing a stirring bar was charged with **S15** (800 mg, 2.47 mmol) and **S19** (142 mg, 2.47 mmol). Dry MeOH (5 mL) was added *via* syringe and the reaction mixture was placed under an argon atmosphere. The solution was stirred at room temperature for 48 h. The solvent was subsequently removed *in vacuo* and the residue purified by flash column chromatography to afford **49** as a pale yellow solid (1.45 g, 68%).
Spectal data for this compound were consistent with those in the literature.[9]

M.p. 209-211 °C (dec.) (lit.[9] M.p. 212-214 °C (dec.)); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.56 (bs, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.58 - 7.56 (m, 7H), 7.52 (bs, 1H), 7.33 (d, *J* = 9.0 Hz, 1H), 7.30 - 7.18 (m, 6H), 6.43 (bs, 1H), 5.67 - 5.58 (m, 2H), 4.96 - 4.92 (m, 2H), 3.92 (s, 3H), 3.03 - 2.98 (m, 2H), 2.45 - 2.42 (m, 3H), 2.27 - 2.19 (m, 1H), 1.64 - 1.58 (m, 1H), 1.57 - 1.49 (m, 2H), 1.29 - 1.23 (m, 2H).

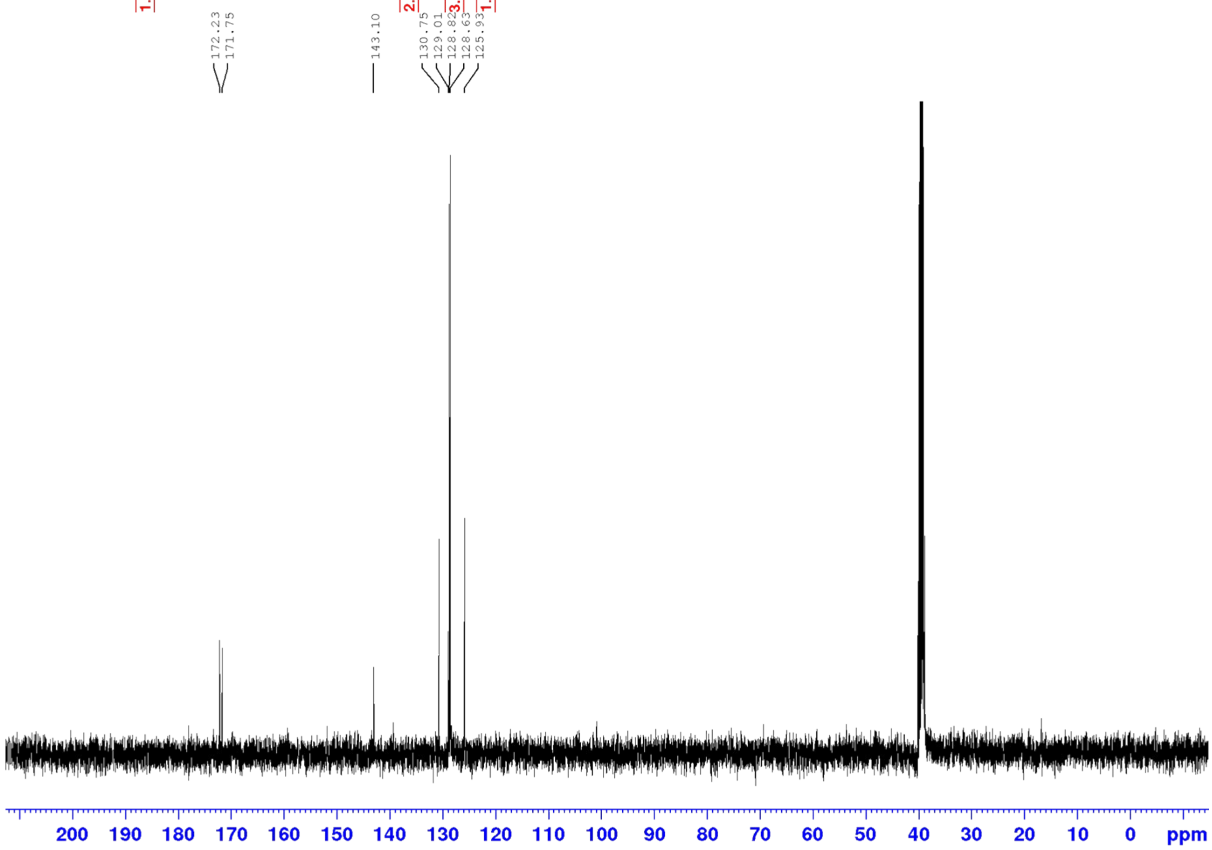
1.7 NMR Spectra

Note for each compound below the top figure is the ^{1}H NMR spectrum ($CDCl_3$ or DMSO-d_6, 400 MHz or 600 MHz) the bottom is the corresponding ^{13}C NMR spectrum ($CDCl_3$ or DMSO-d_6, 100 MHz)

S6

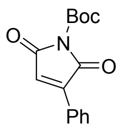


11.015
7.988
7.982
7.973
7.963
7.505
7.495
7.489
7.479
7.160
7.157
O
H
N
O
Ph
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.01
2.18
3.19
1.00

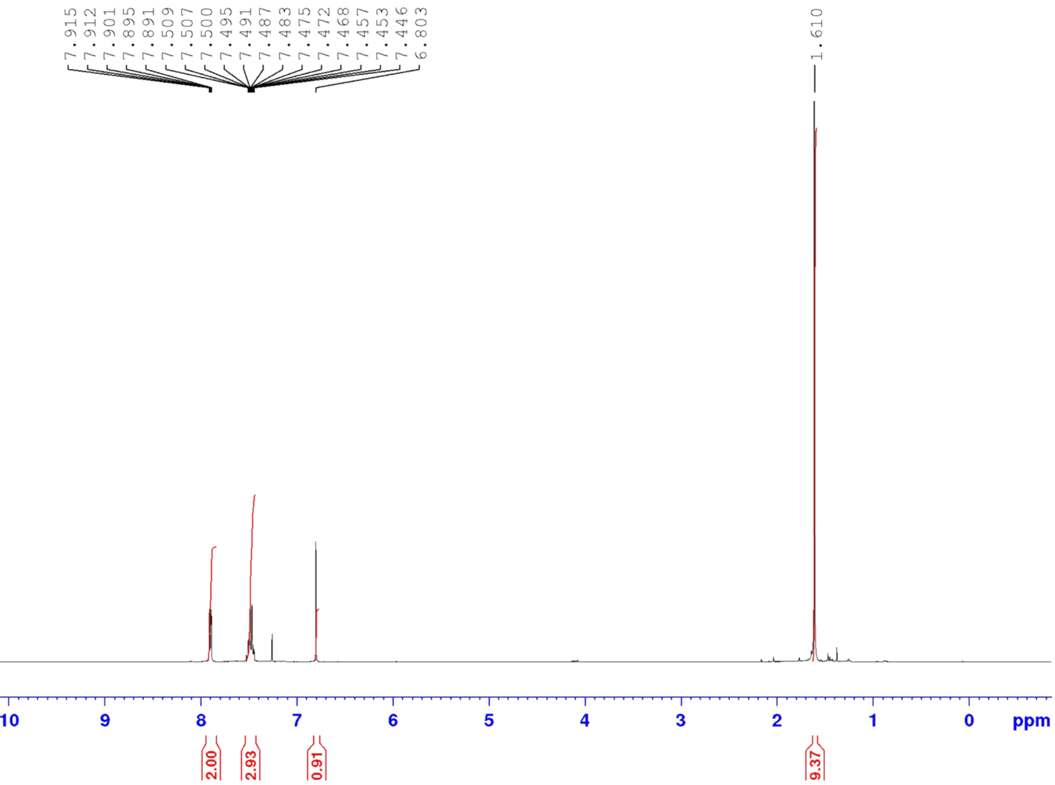


172.23
171.75
143.10
130.75
129.01
128.82
128.63
125.93
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

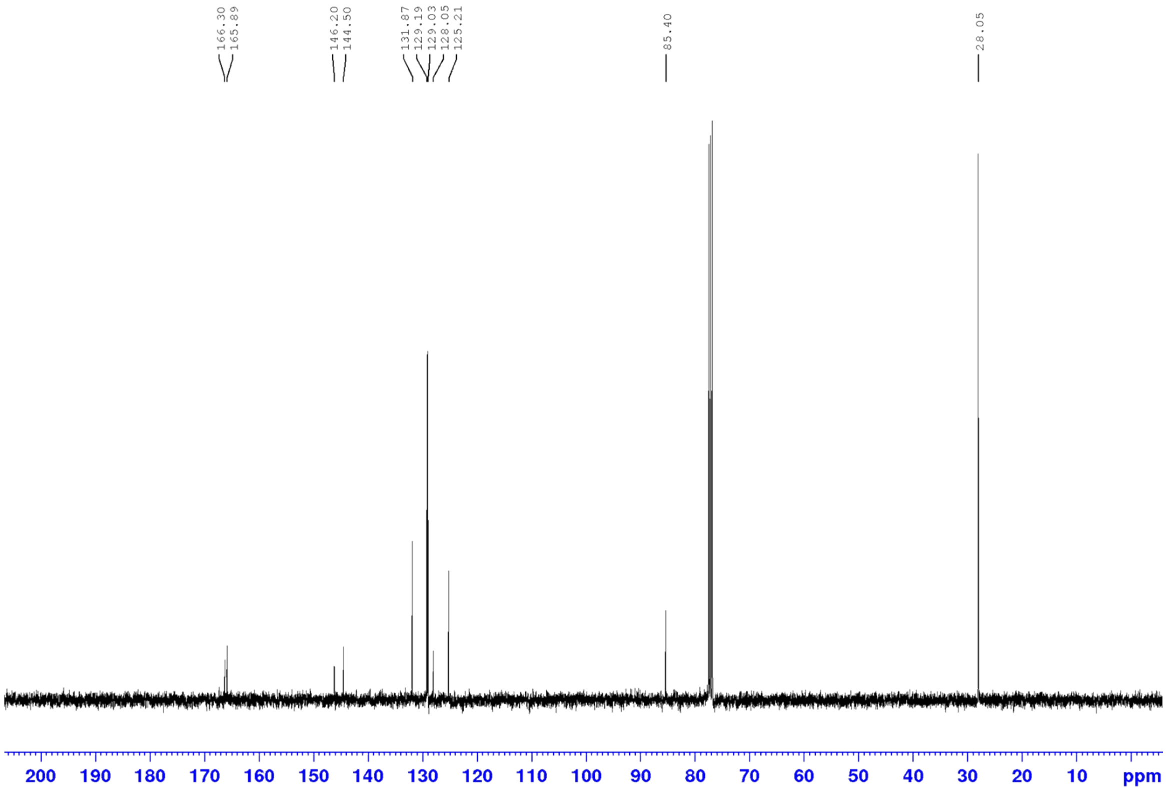
21



Boc
N
O
O
Ph

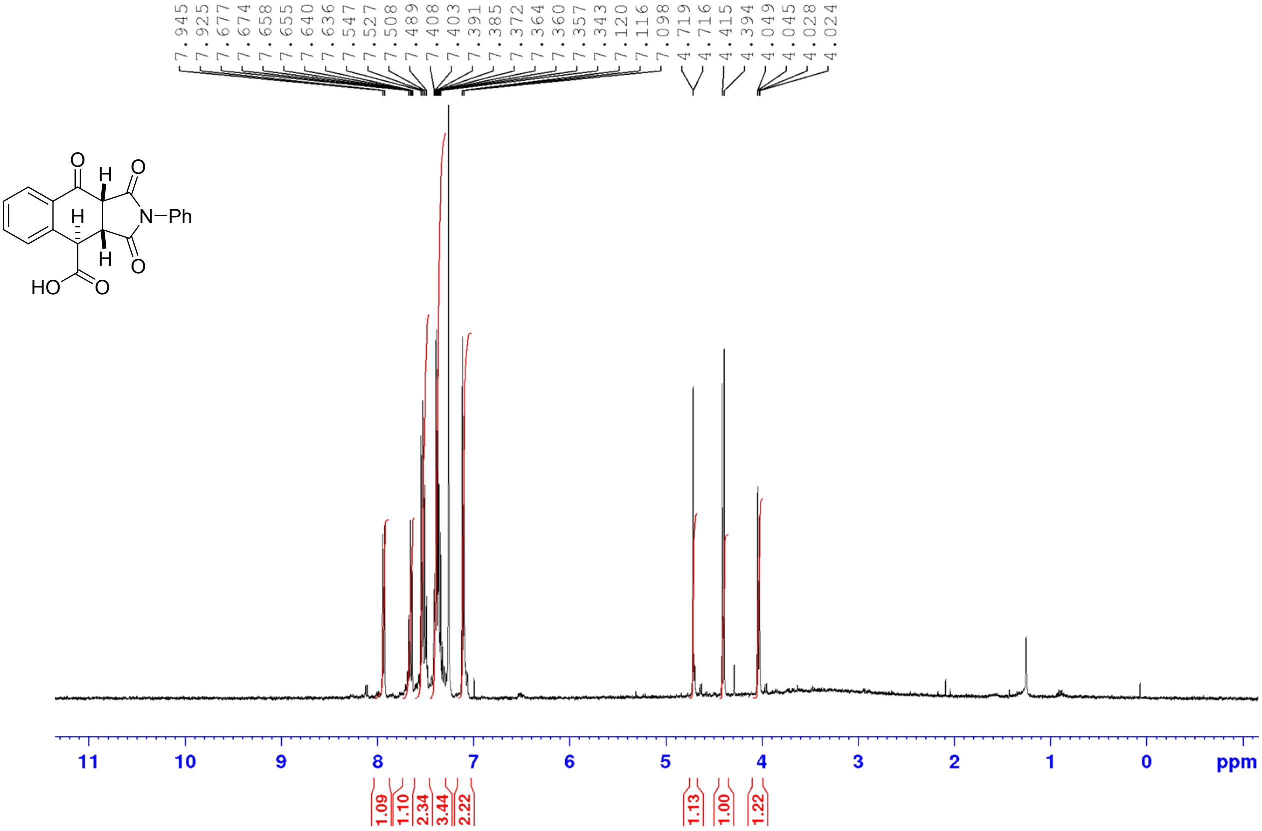


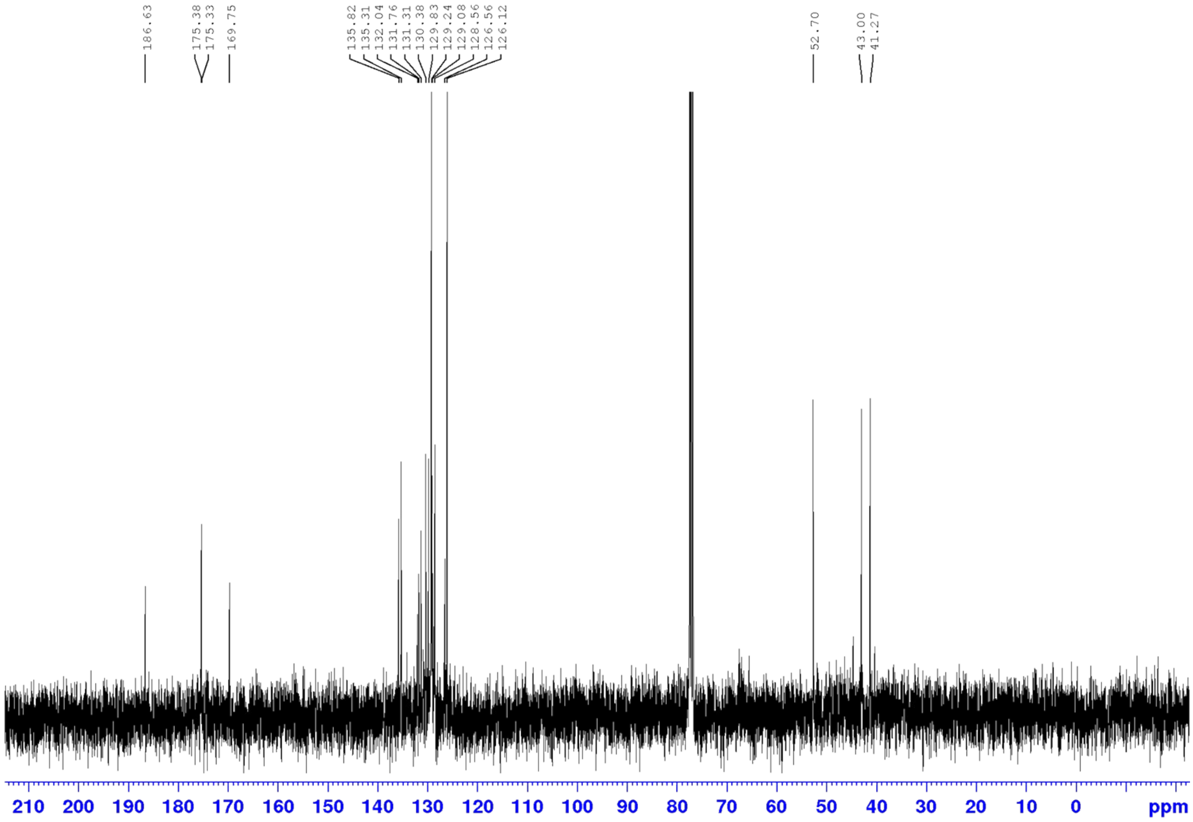
7.915
7.912
7.901
7.895
7.891
7.509
7.507
7.500
7.495
7.491
7.487
7.483
7.475
7.472
7.468
7.457
7.453
7.446
6.803
1.610
10 9 8 7 6 5 4 3 2 1 0 ppm
2.00
2.93
0.91
9.37



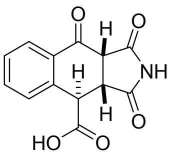
166.30
165.89
146.20
144.50
131.87
129.19
129.03
128.05
125.21
85.40
28.05
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

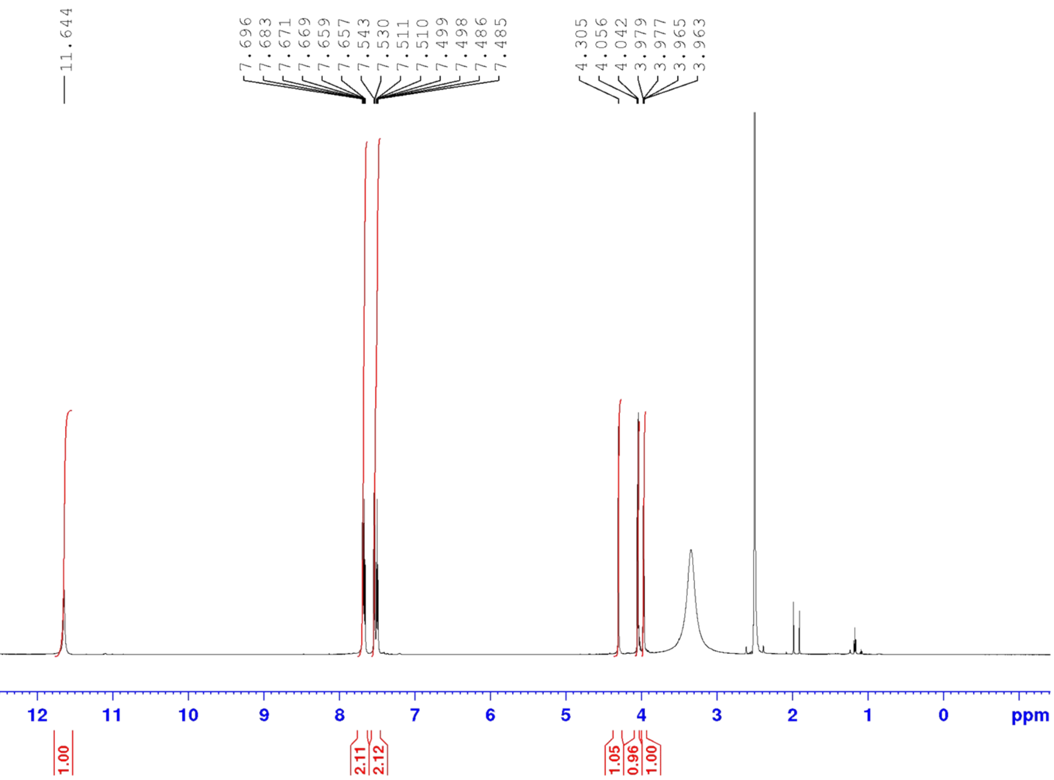
24

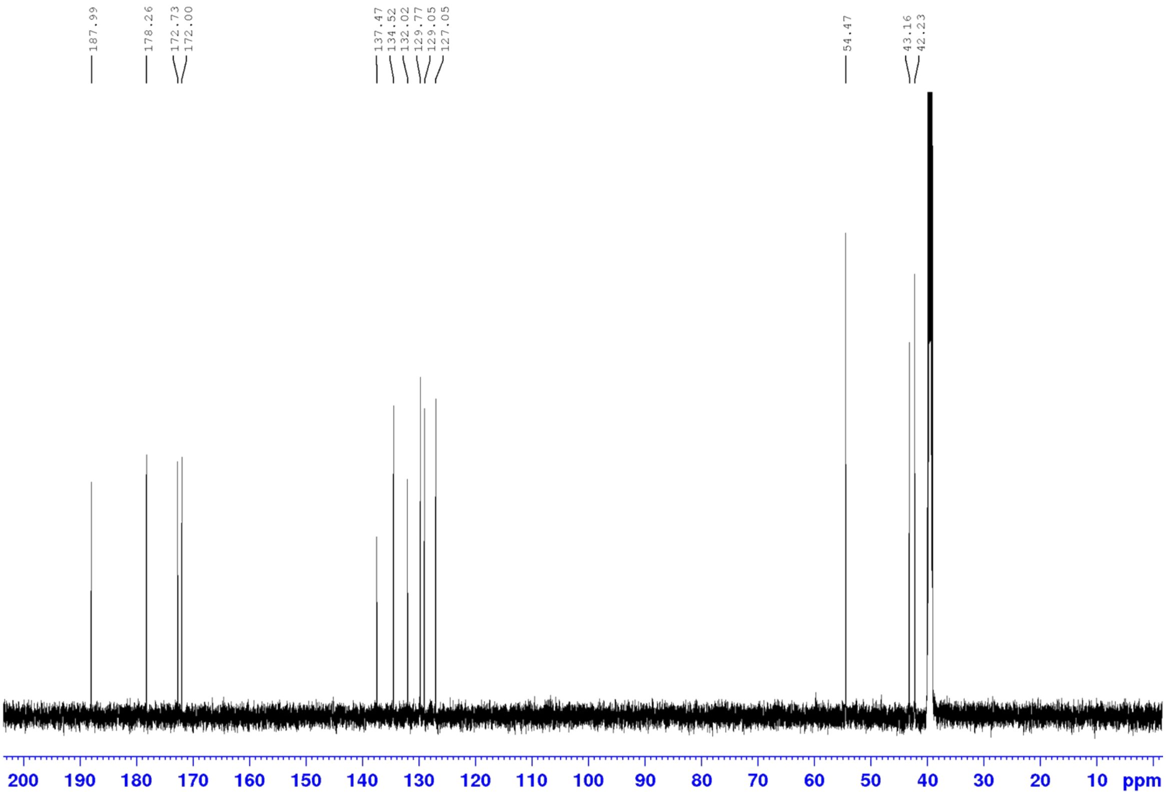

7.945
7.925
7.677
7.674
7.658
7.655
7.640
7.636
7.547
7.527
7.508
7.489
7.408
7.403
7.391
7.385
7.372
7.364
7.360
7.357
7.343
7.120
7.116
7.098
4.719
4.716
4.415
4.394
4.049
4.045
4.028
4.024
1.09
1.10
2.34
3.44
2.22
1.13
1.00
1.22
ppm


186.63
175.38
175.33
169.75
135.82
135.31
132.04
131.76
131.31
130.38
129.83
129.24
129.08
128.56
126.56
126.12
52.70
43.00
41.27
ppm

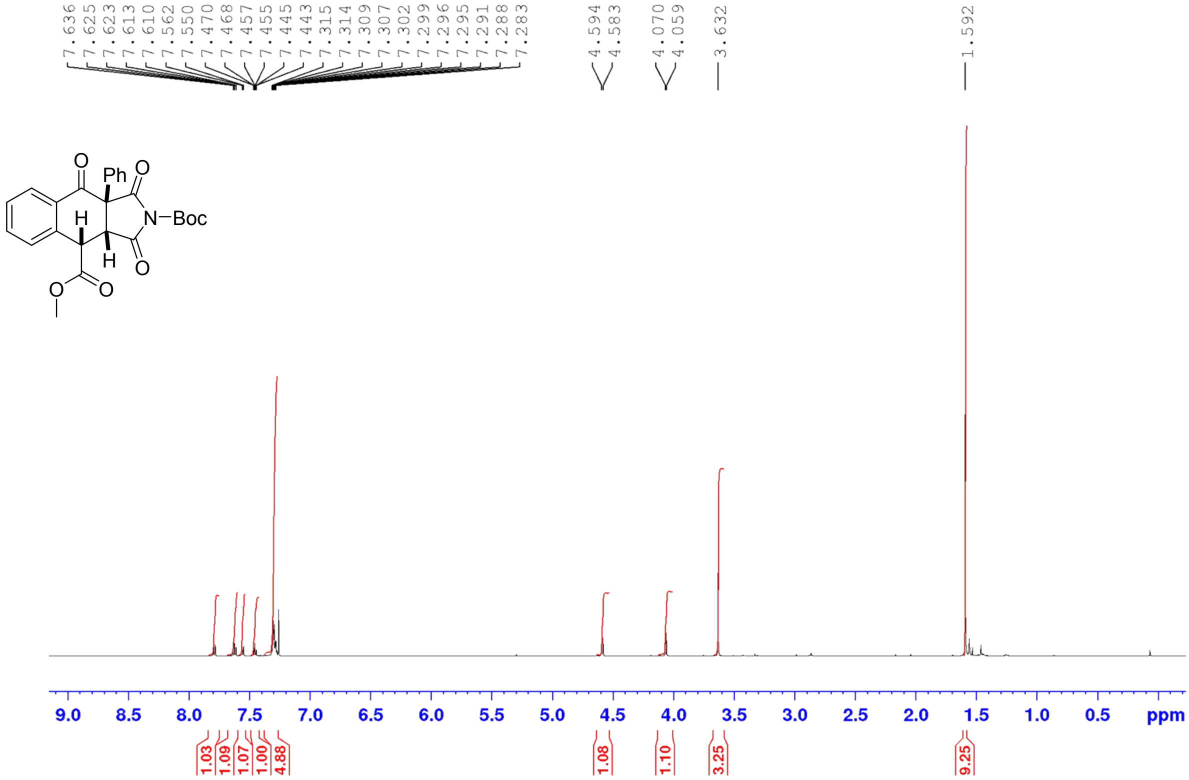
S7

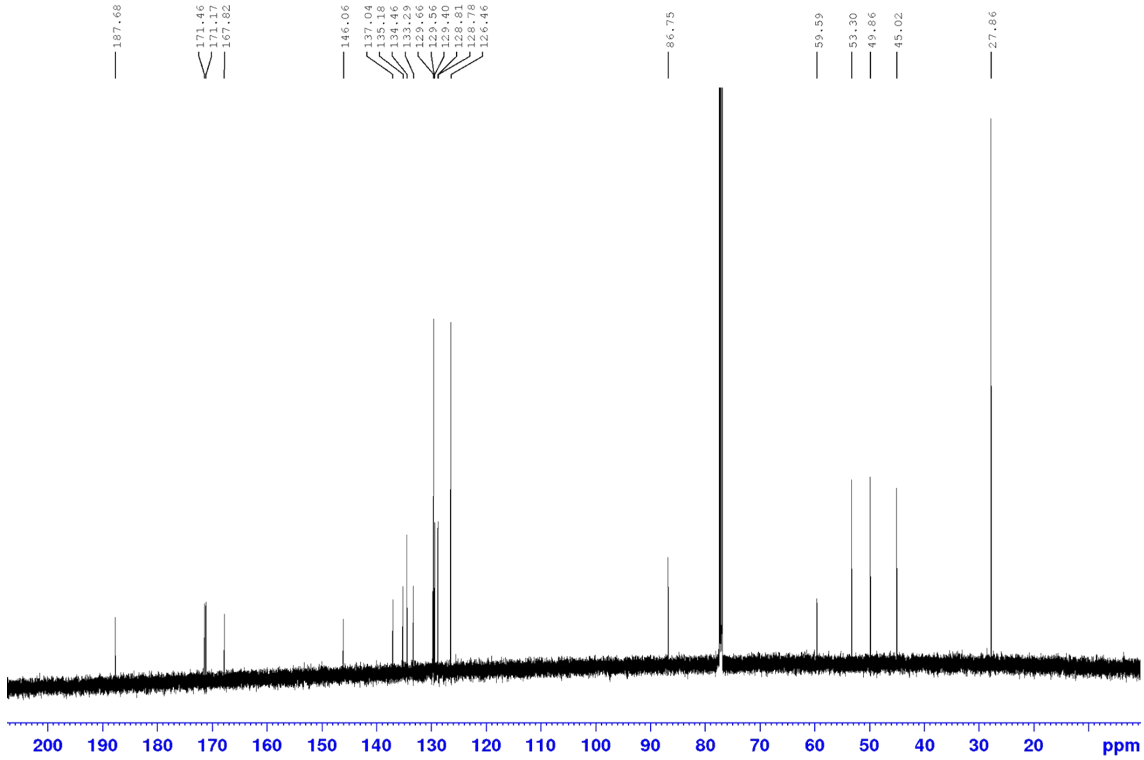



11.644
7.696
7.683
7.671
7.669
7.659
7.657
7.543
7.530
7.511
7.510
7.499
7.498
7.486
7.485
4.305
4.056
4.042
3.979
3.977
3.965
3.963
1.00
2.11
2.12
1.05
0.96
1.00
ppm

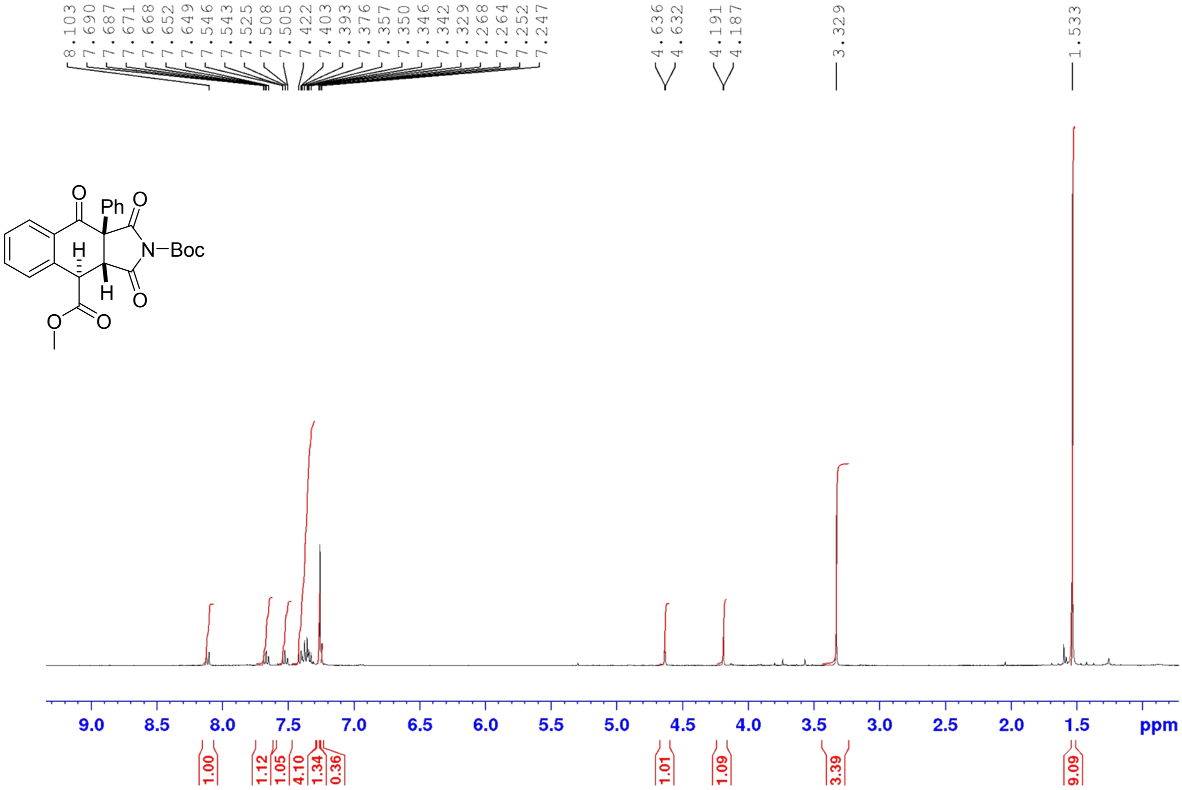

187.99
178.26
172.73
172.00
137.47
134.52
132.02
129.77
129.05
127.05
54.47
43.16
42.23
ppm

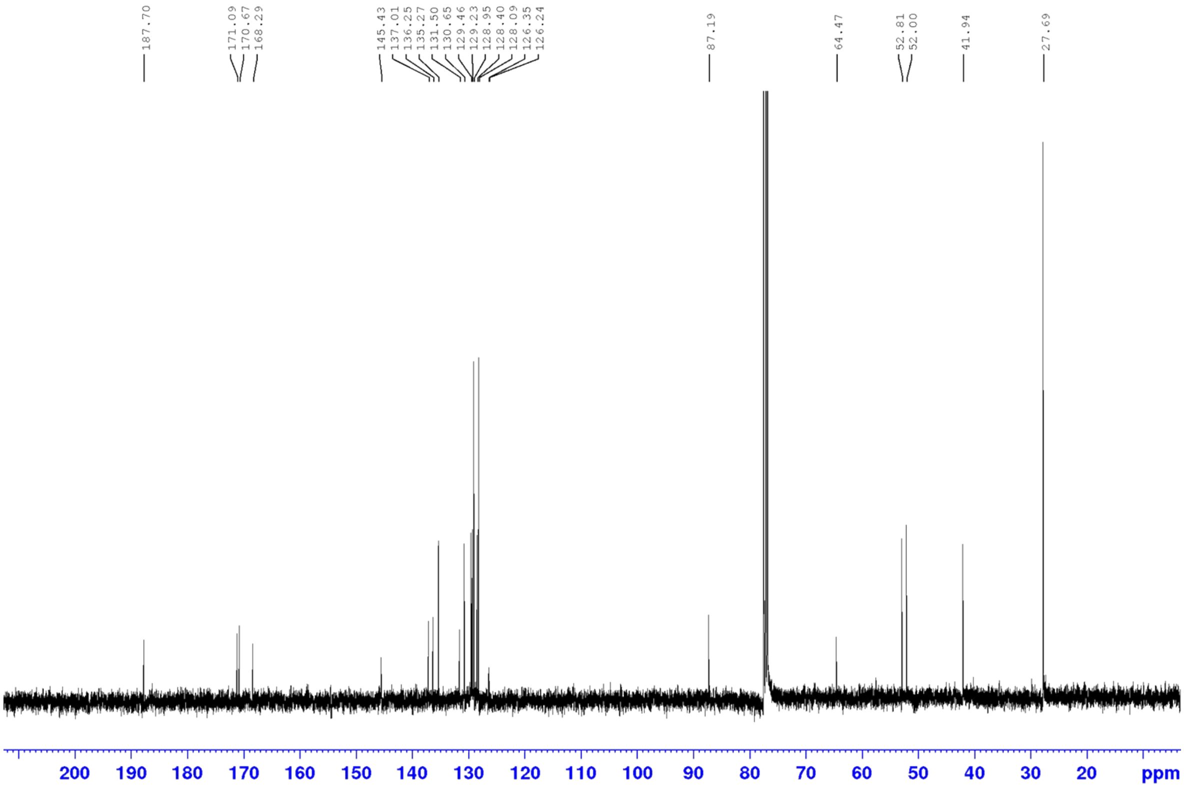
35a



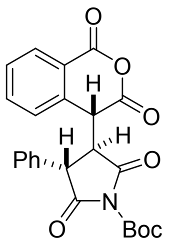


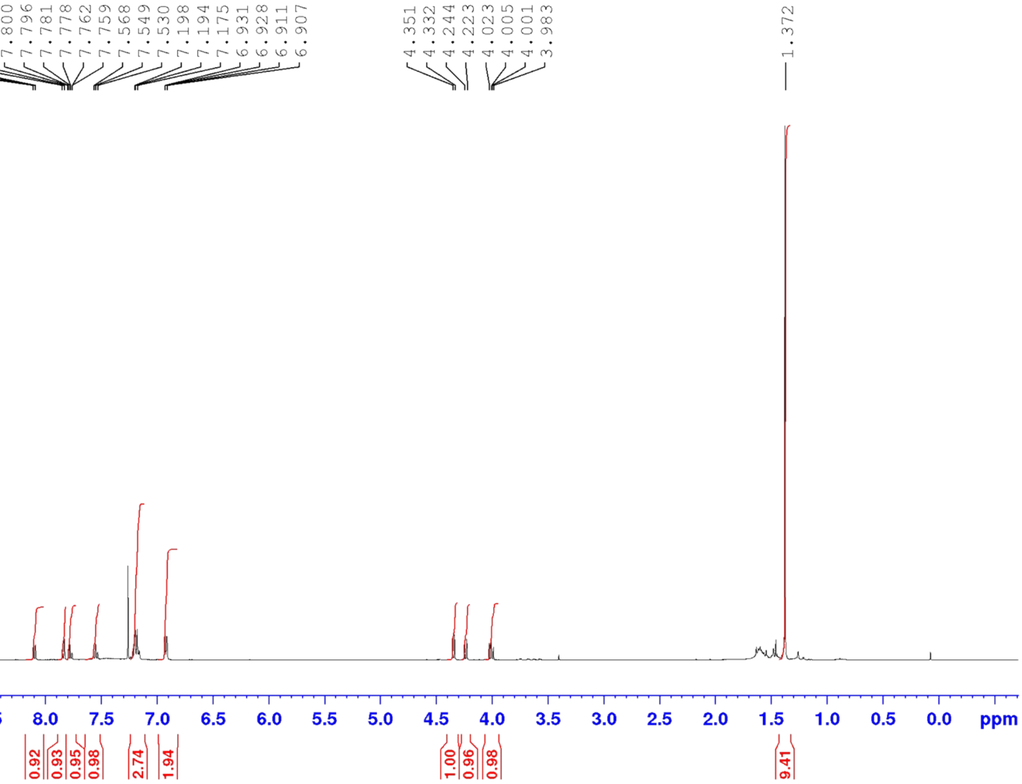
35b

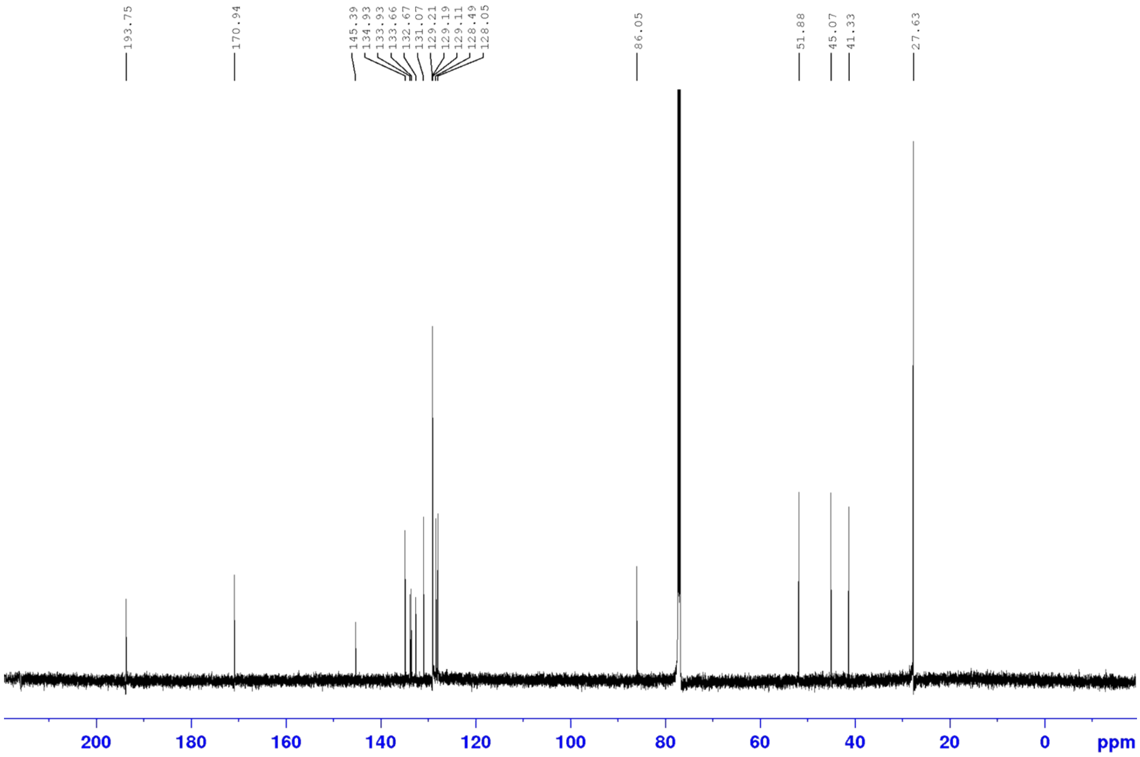

Ph
O
O
O
N−Boc
H
H
O
O
8.103
7.690
7.687
7.671
7.668
7.652
7.649
7.546
7.543
7.525
7.508
7.505
7.422
7.403
7.393
7.376
7.357
7.350
7.346
7.342
7.329
7.268
7.264
7.252
7.247
4.636
4.632
4.191
4.187
3.329
1.533
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
1.00
1.12
1.05
4.10
1.34
0.36
1.01
1.09
3.39
9.09


187.70
171.09
170.67
168.29
145.43
137.01
136.25
135.27
131.50
130.65
129.46
129.23
128.95
128.40
128.09
126.35
126.24
87.19
64.47
52.81
52.00
41.94
27.69
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

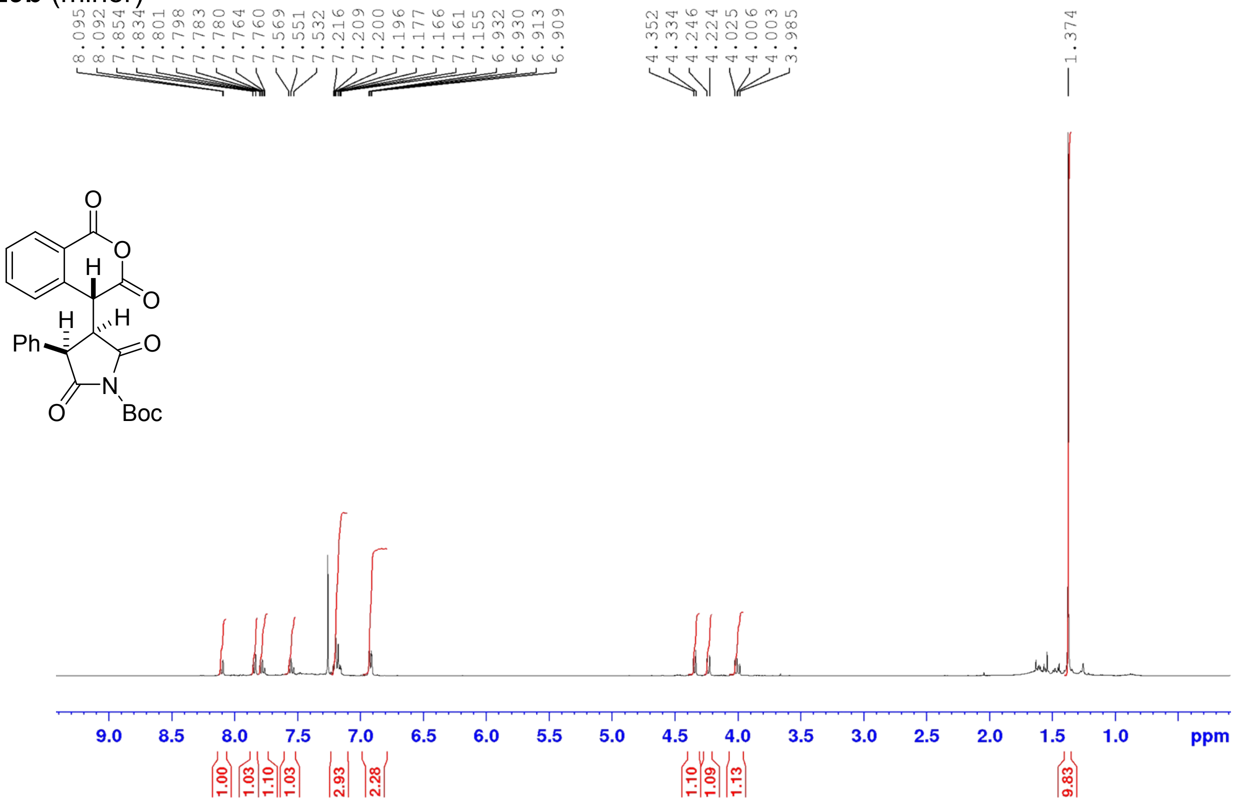
29a (major)

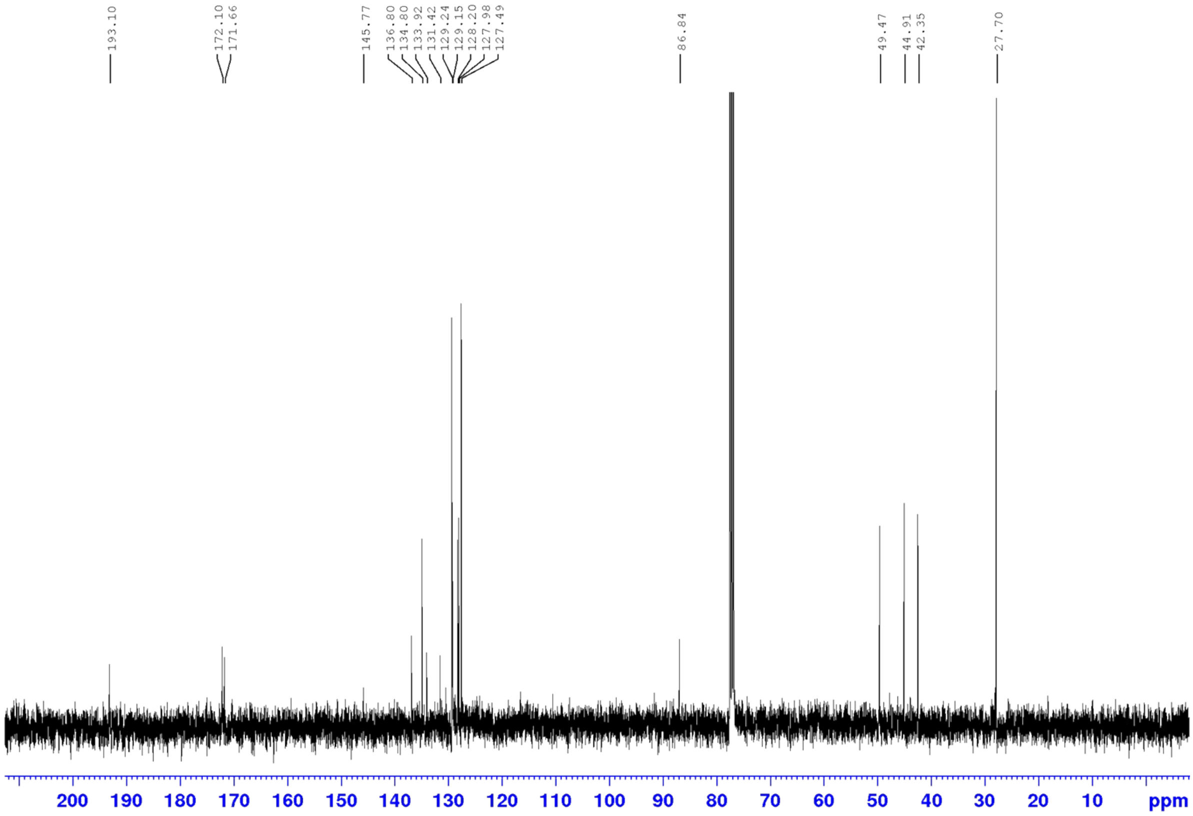

O
O
O
H
H
H
Ph
O
N
O
Boc


8.110
8.093
8.091
7.852
7.833
7.800
7.796
7.781
7.778
7.762
7.759
7.568
7.549
7.530
7.198
7.194
7.175
6.931
6.928
6.911
6.907
4.351
4.332
4.244
4.223
4.023
4.005
4.001
3.983
1.372
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 ppm
0.92
0.93
0.95
0.98
2.74
1.94
1.00
0.96
0.98
9.41

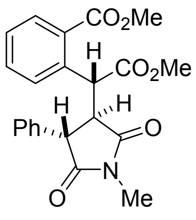

193.75
170.94
145.39
134.93
133.93
133.66
132.67
131.07
129.21
129.19
129.11
128.49
128.05
86.05
51.88
45.07
41.33
27.63
200 180 160 140 120 100 80 60 40 20 0 ppm

29b (minor)

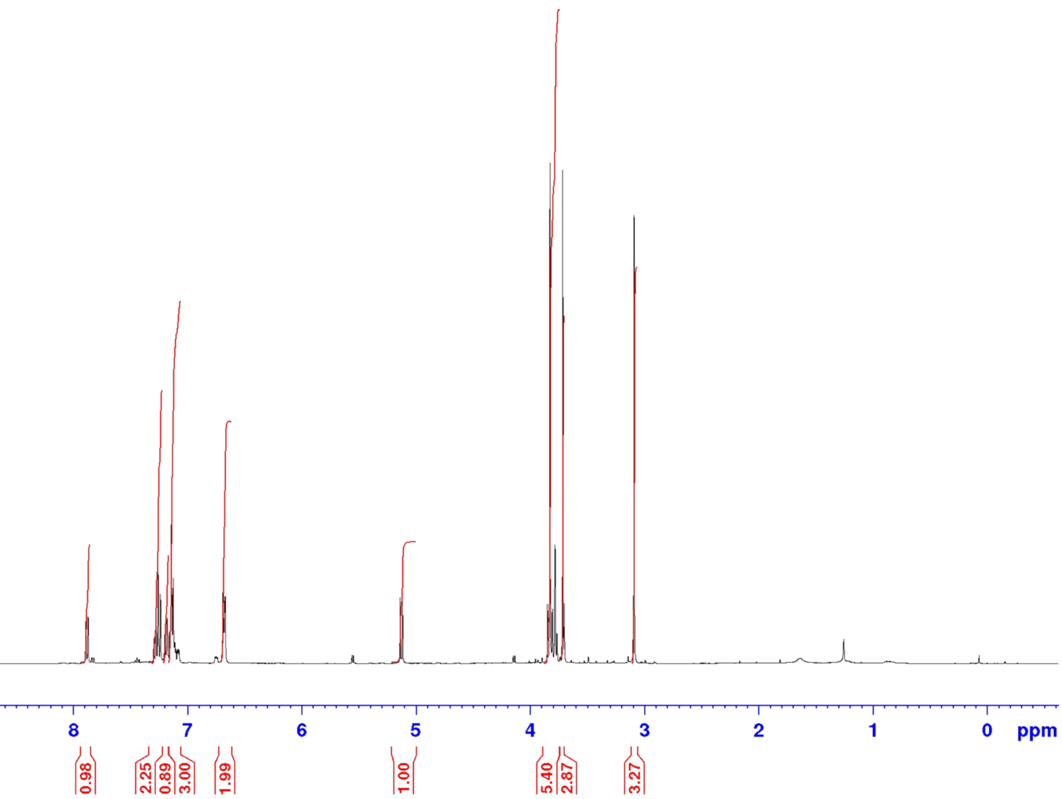

8.095
8.092
7.854
7.834
7.801
7.798
7.783
7.780
7.764
7.760
7.569
7.551
7.532
7.216
7.209
7.200
7.196
7.177
7.166
7.161
7.155
6.932
6.930
6.913
6.909
4.352
4.334
4.246
4.224
4.025
4.006
4.003
3.985
1.374
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.03
1.10
1.03
2.93
2.28
1.10
1.09
1.13
9.83

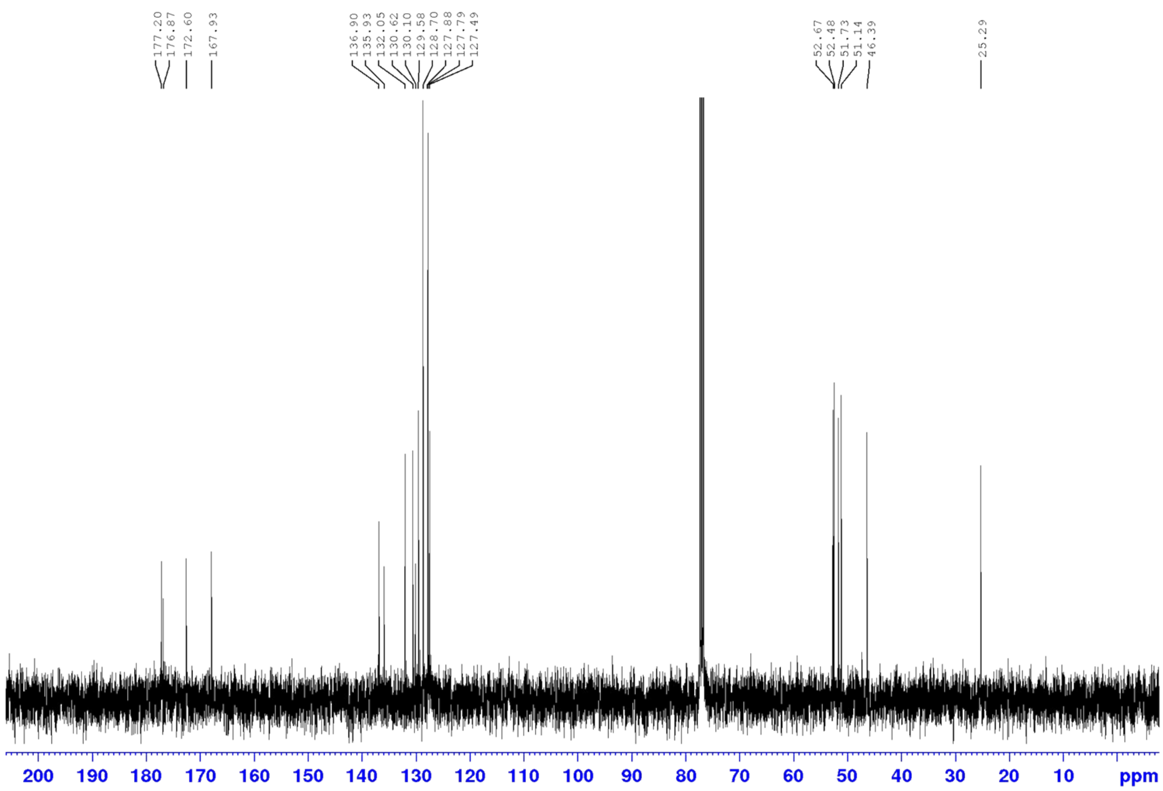

193.10
172.10
171.66
145.77
136.80
134.80
133.92
131.42
129.24
129.15
128.20
127.98
127.49
86.84
49.47
44.91
42.35
27.70
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

30

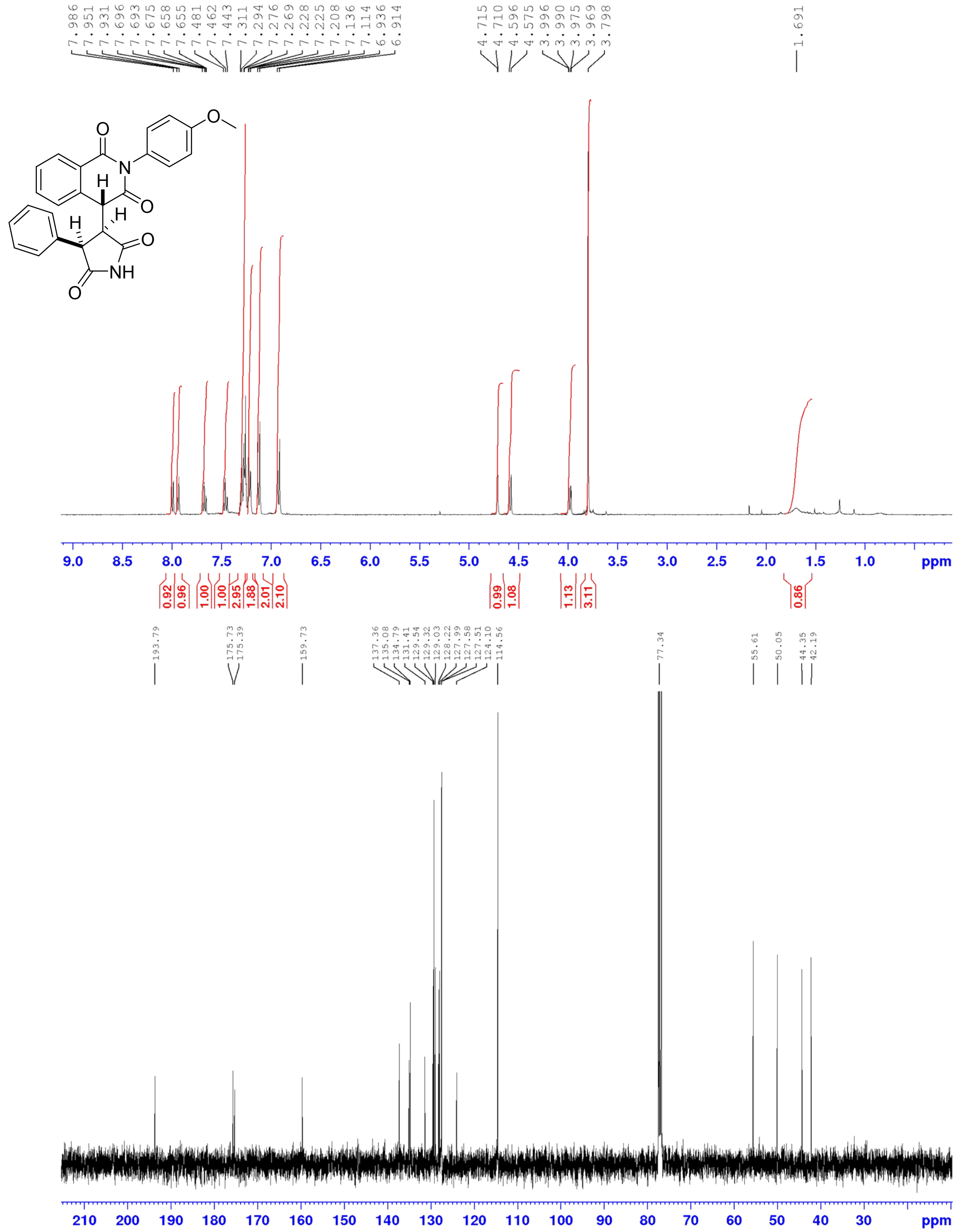

CO2Me
H
CO2Me
H
H
Ph
O
N
O
Me

95:5 *dr*

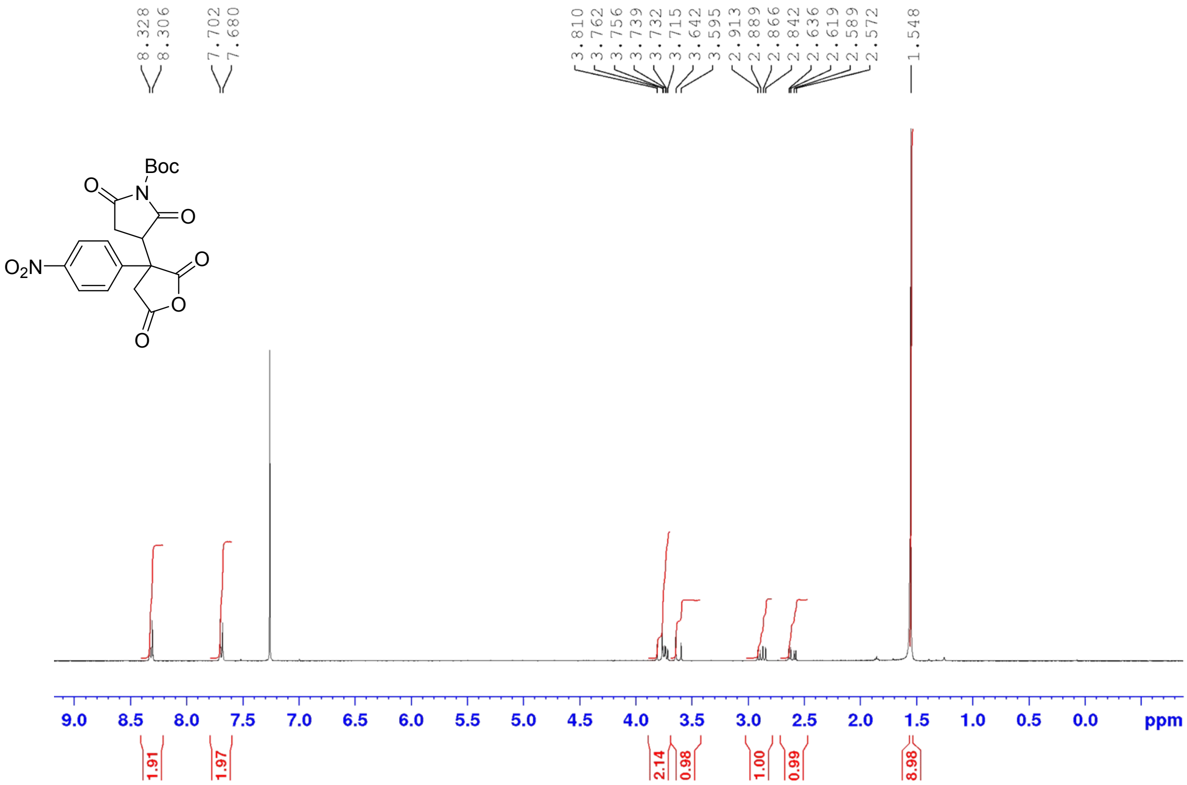

9
8
7
6
5
4
3
2
1
0
ppm
0.98
2.25
0.89
3.00
1.99
1.00
5.40
2.87
3.27

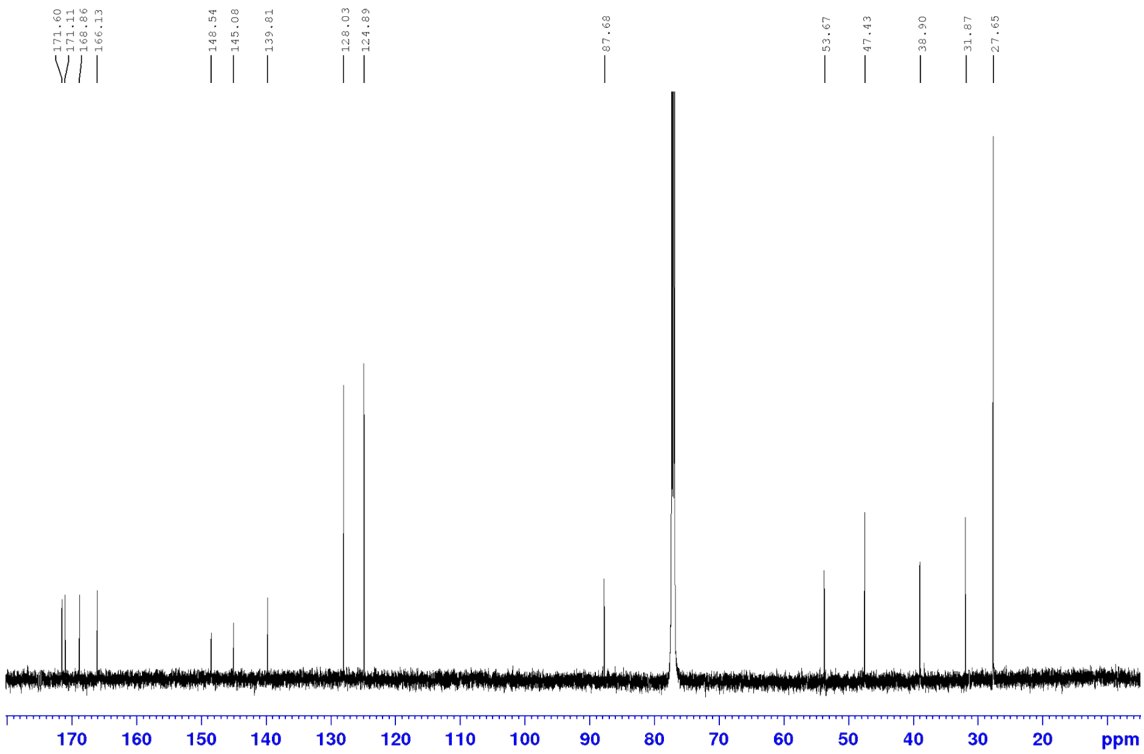

177.20
176.87
172.60
167.93
136.90
135.93
132.05
130.62
130.10
129.58
128.70
127.88
127.79
127.49
52.67
52.48
51.73
51.14
46.39
25.29
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

32

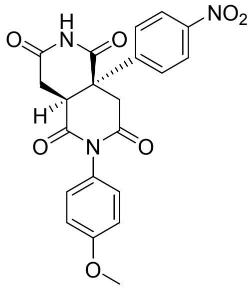


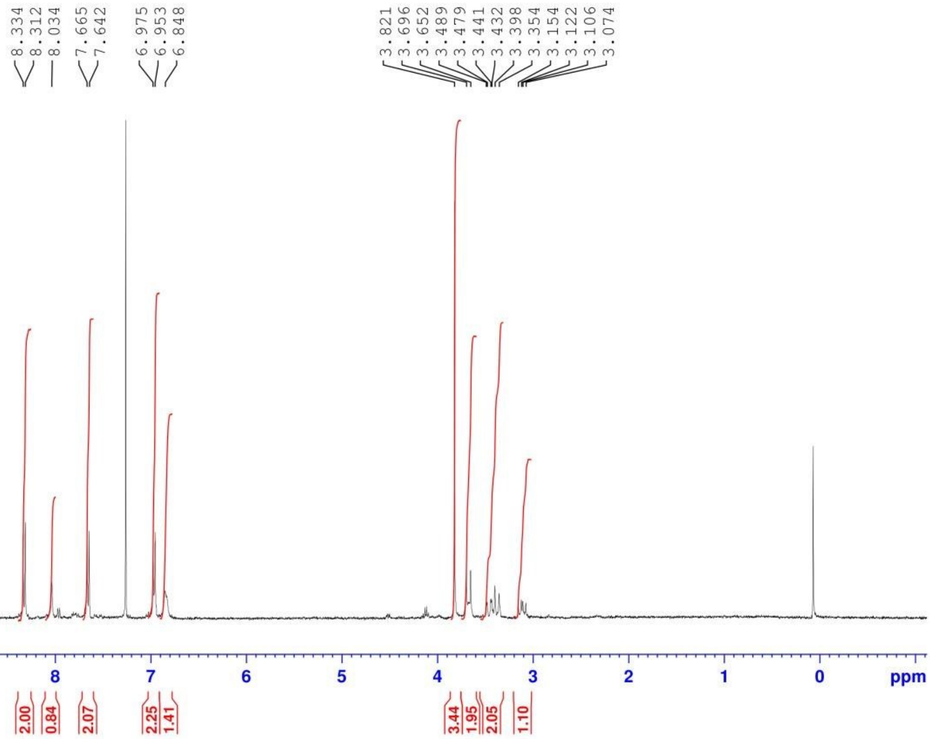
37

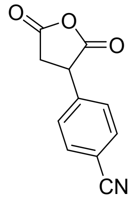

Boc
O
N
O
O₂N
O
O
O
8.328
8.306
7.702
7.680
3.810
3.762
3.756
3.739
3.732
3.715
3.642
3.595
2.913
2.889
2.866
2.842
2.636
2.619
2.589
2.572
1.548
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.91
1.97
2.14
0.98
1.00
0.99
8.98

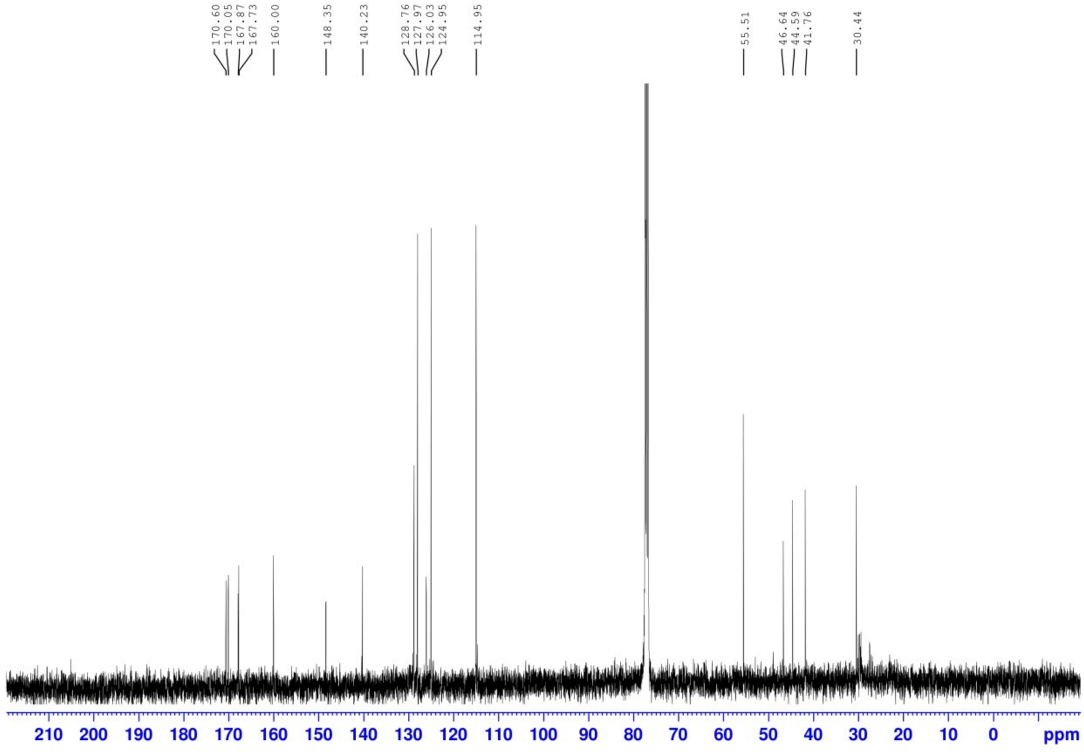

171.60
171.11
168.86
166.13
148.54
145.08
139.81
128.03
124.89
87.68
53.67
47.43
38.90
31.87
27.65
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

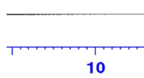
40

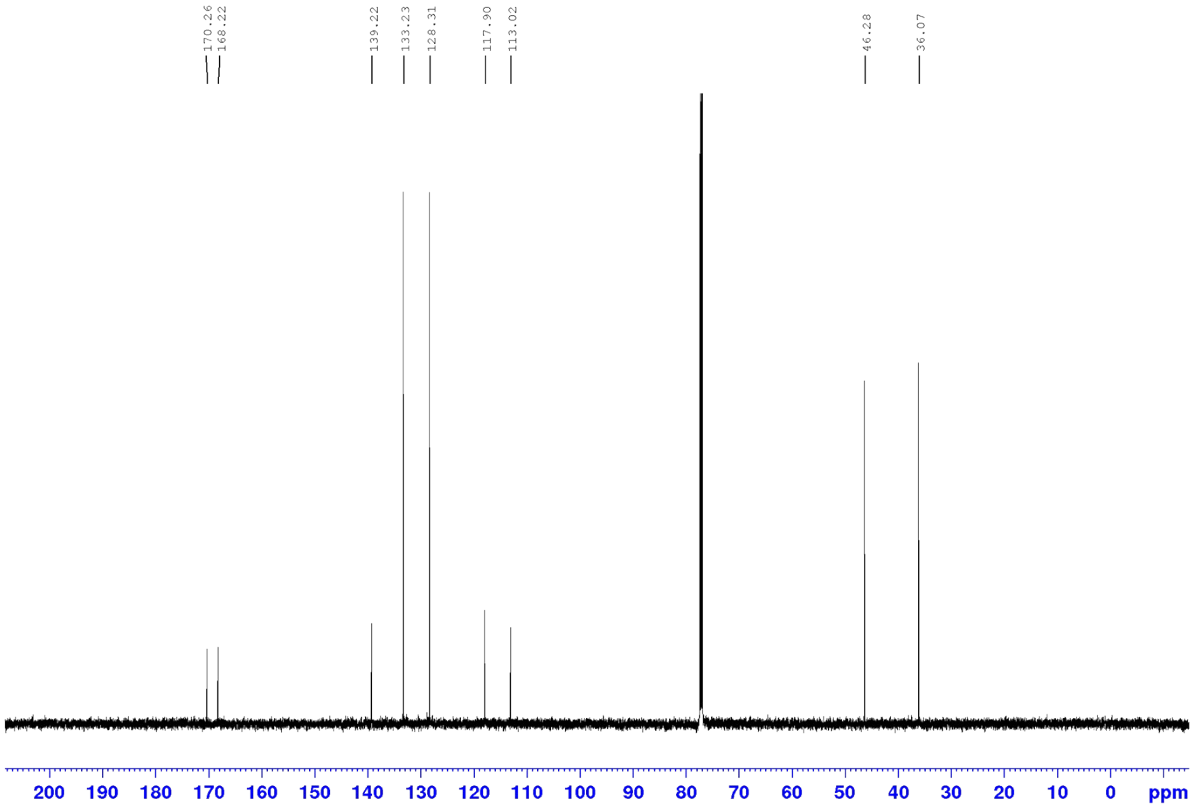



8.334 8.312 8.034 7.665 7.642 6.975 6.953 6.848
3.821 3.696 3.652 3.489 3.479 3.441 3.432 3.398 3.354 3.154 3.122 3.106 3.074
2.00 0.84 2.07 2.25 1.41 3.44 1.95 2.05 1.10
ppm

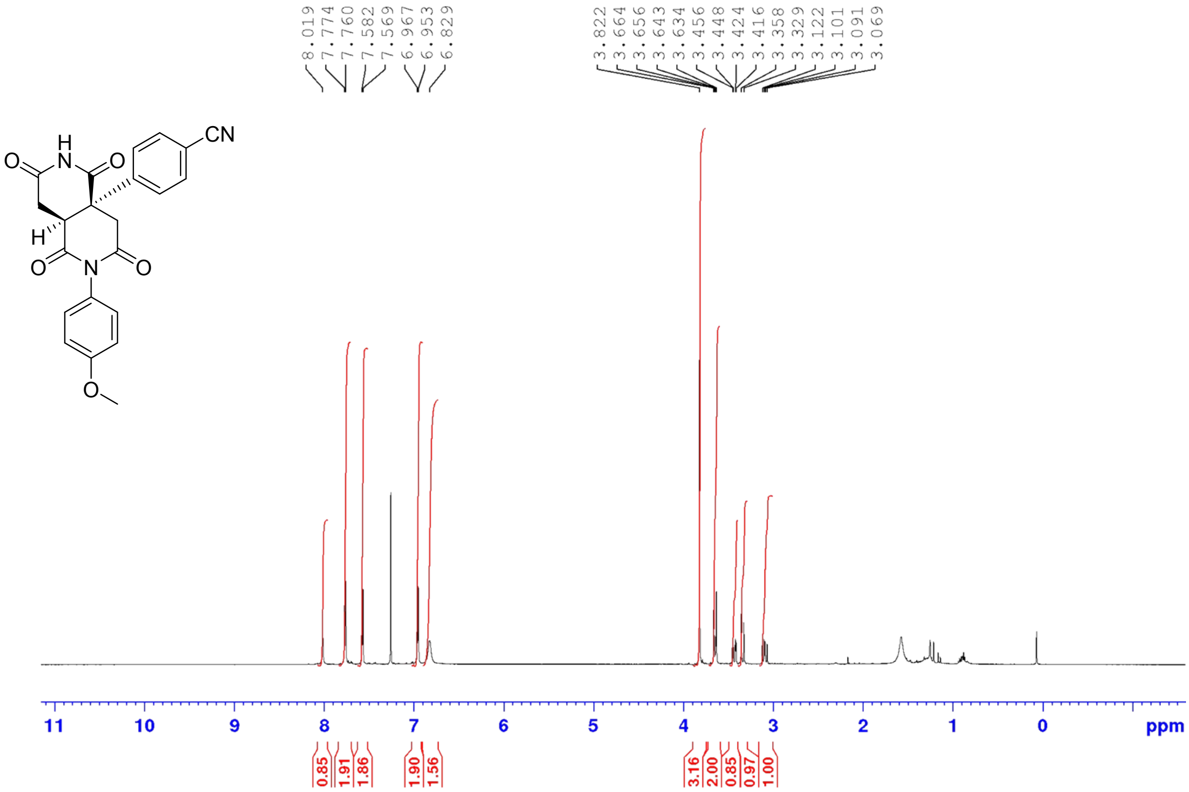


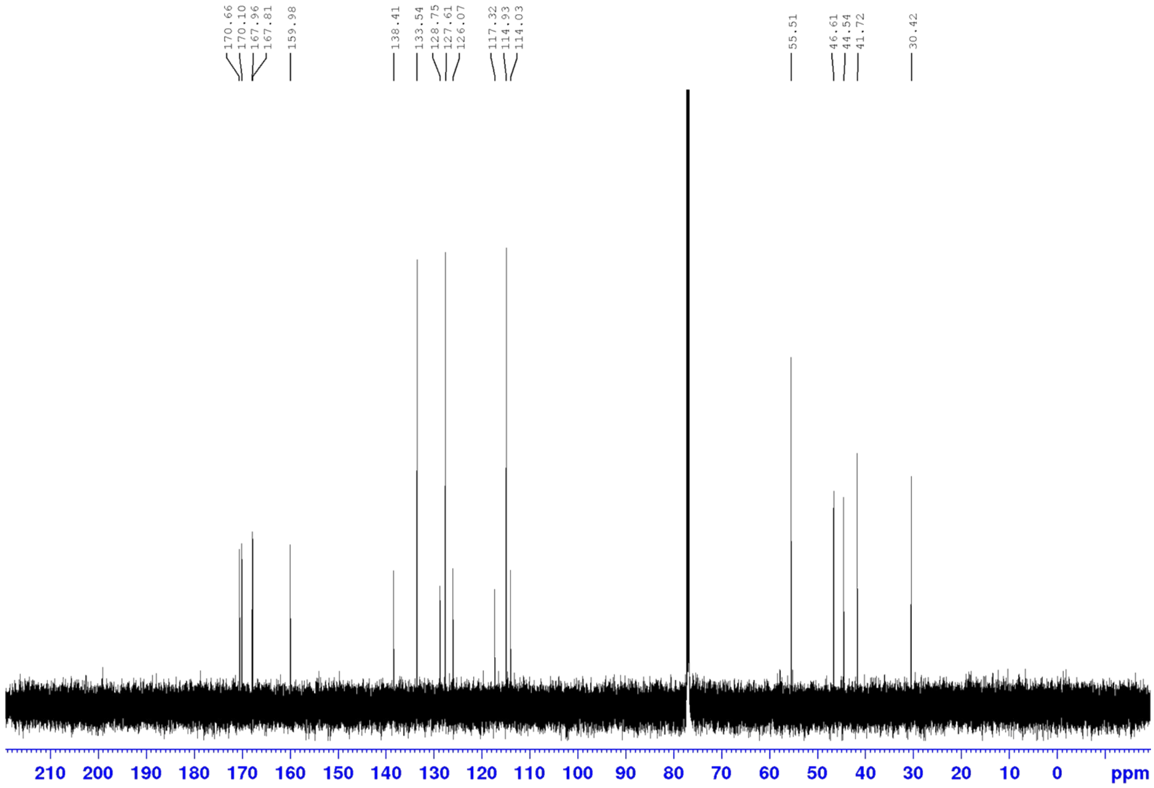

170.60 170.05 167.87 167.73 160.00 148.35 140.23 128.76 127.97 126.03 124.95 114.95 55.51 46.64 44.59 41.76 30.44
ppm




170.26
168.22
139.22
133.23
128.31
117.90
113.02
46.28
36.07
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

43


CN
H
O
N
O
H
O
N
O
O
8.019
7.774
7.760
7.582
7.569
6.967
6.953
6.829
3.822
3.664
3.656
3.643
3.634
3.456
3.448
3.424
3.416
3.358
3.329
3.122
3.101
3.091
3.069
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.85
1.91
1.86
1.90
1.56
3.16
2.00
0.85
0.97
1.00


170.66
170.10
167.96
167.81
159.98
138.41
133.54
128.75
127.61
126.07
117.32
114.93
114.03
55.51
46.61
44.54
41.72
30.42
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

1.8 HPLC chromatograms

Product **40**

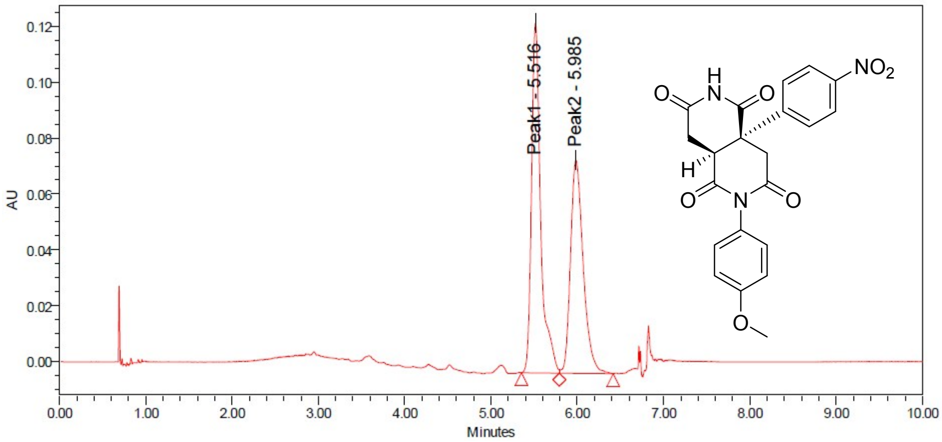
Study Conditions

Instrument: ACQUITY UPC^2
Chiral stationary phase: ACQUITY UPC^2 Trefoil CEL1, 2.5 μm 3.0 x 100 mm column
Detection: UV 254 nm with PDA detector
Mobile phase: A = CO_2, B = Methanol/IPA (1:1 *v/v*)
Column temperature: 30 °C
Inlet pressure: 1500 (psi)

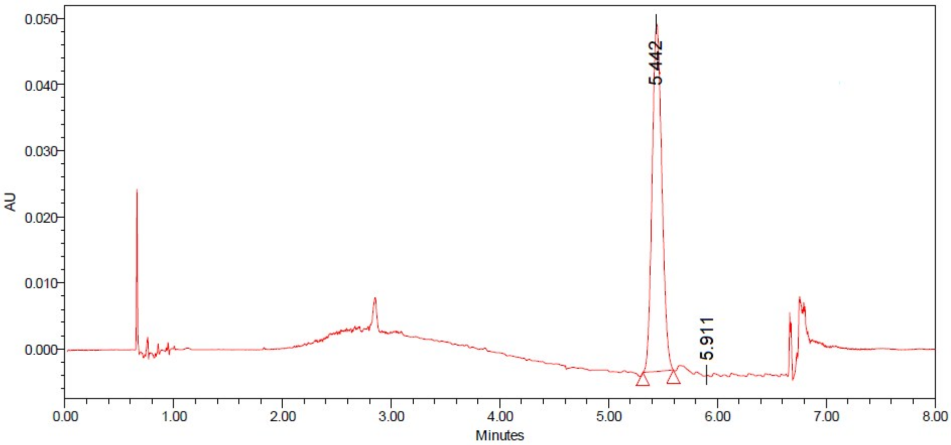
Gradient table

	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	97.0	3.0	Initial
2	10.00	1.200	40.0	60.0	6

Racemic:



Enantioselective: >99% ee



Peak results: Racemic		
	Ret. Time (min)	**Rel. Area (%)**
1	5.516	54.22
2	5.985	45.78

Peak results: Enantioselective		
	Ret. Time (min)	**Rel. Area (%)**
1	5.442	99.98
2	5.911	0.02

Product **43**

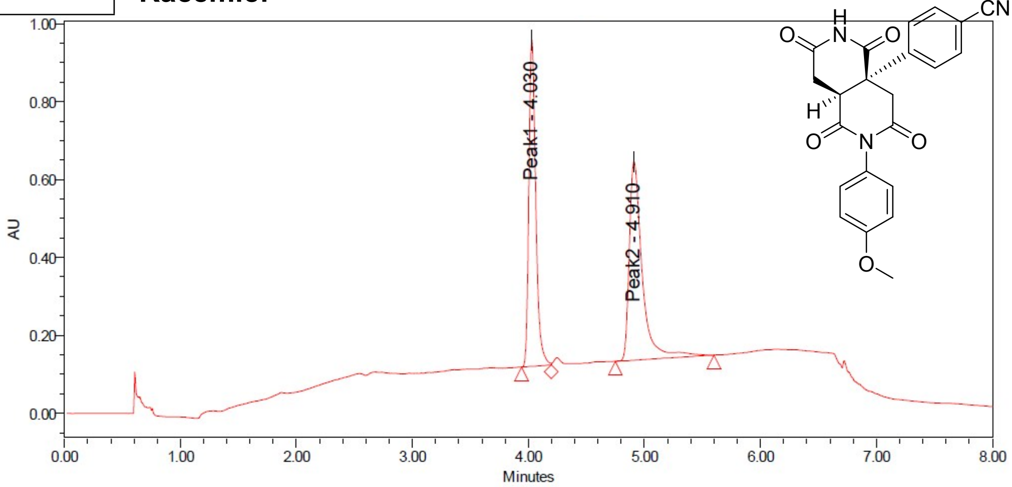
Study Conditions

Instrument: ACQUITY UPC[2]
Chiral stationary phase: ACQUITY UPC[2] Trefoil AMY1, 2.5 μm 3.0 x 100 mm column
Detection: UV 254 nm with PDA detector
Mobile phase: A = CO_2, B = Ethanol/MeCN/IPA (1:1:1 *v/v/v*)
Column temperature: 30 °C
Inlet pressure: 1500 (psi)

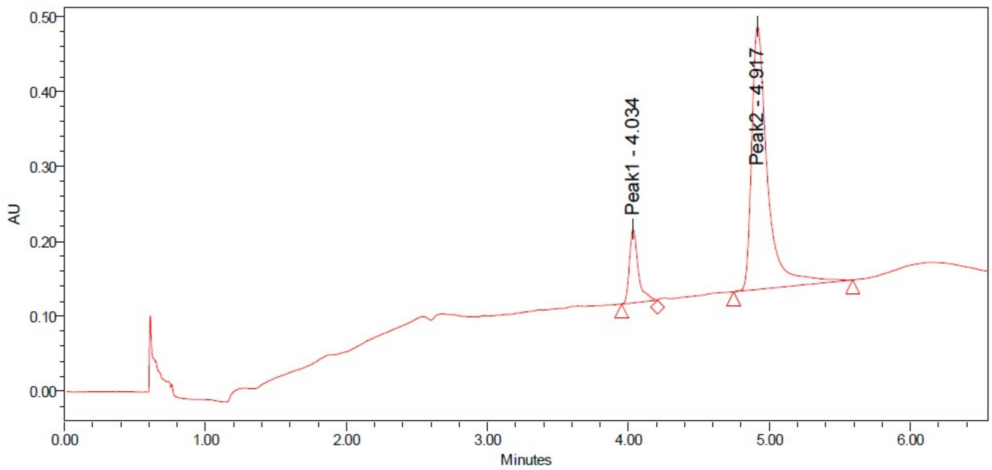
Gradient table

	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	97.0	3.0	Initial
2	4.50	1.200	40.0	60.0	6
3	6.00	1.200	40.0	60.0	6
4	8.00	1.200	97.0	3.0	6

Racemic:



Enantioselective: 71% ee

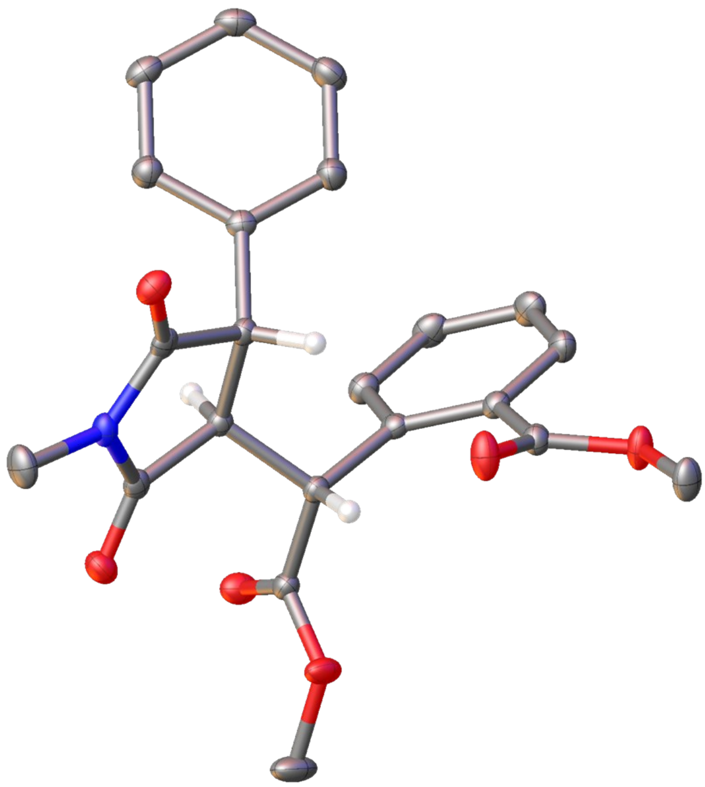


Peak results: Racemic		
	Ret. Time (min)	**Rel. Area (%)**
1	4.030	46.50
2	4.910	53.50

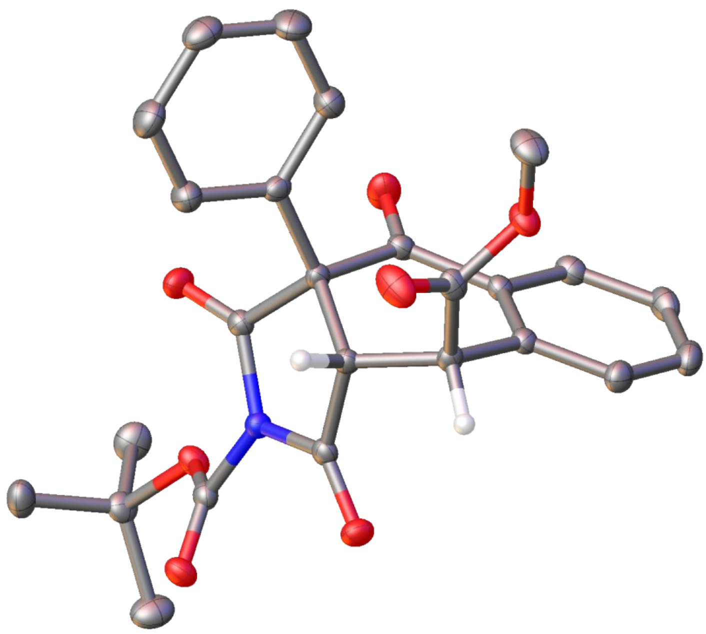
Peak results: Enantioselective		
	Ret. Time (min)	**Rel. Area (%)**
1	4.034	13.49
2	4.917	86.51

1.9 Crystal structures

30



35b



The X-ray structural analysis of **30** and **35b** were performed on a Bruker D8 Quest Eco at 100(2) K with an Oxford Cryosystems cryostat, with samples mounted on a MiTeGen microloop using Mo Kα radiation (λ = 0.71073 Å). Bruker APEX[11] software was used to collect and reduce data and determine the space group. Absorption corrections were applied using SADABS.[12] The structures were solved with the XT structure solution program[13] using Intrinsic Phasing and refined with the XL refinement package[14] using Least Squares minimisation in Olex2.[15] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned to calculated positions using a riding model with appropriately fixed isotropic thermal parameters.

In **30**, there are two independent molecules in the asymmetric unit with identical chirality. The Model has chirality at C5, R; C5A, R; C16, S; C16A, S; C17, S; C17A, S. In **35b**, the Model has Chirality at C5, S; C14, R; C15, S (centrosymmetric space group).

Crystal data and refinement parameters are shown in Table S1 and the crystallographic data, CCDC 1865406 and 1865407, can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data-request/cif.

Table S1. Crystal data and structure refinement parameters

Identification code	**30**	**35b**
Empirical formula	$C_{22}H_{21}NO_6$	$C_{25}H_{23}NO_7$
Formula weight	395.40	449.44
Temperature (K)	100(2)	100(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
a (Å)	11.4121(3)	7.8998(2)
b (Å)	11.4588(3)	11.8254(4)
c (Å)	15.1821(4)	12.5588(4)
α (°)	82.2960(10)	77.6681(13)
β (°)	79.7080(10)	78.7428(13)
γ (°)	78.8140(10)	76.0758(13)
Volume (Å^3)	1906.11(9)	1099.60(6)
Z	4	2
ρ (calculated) (Mg/m^3)	1.378	1.357
Absorption coefficient (mm^{-1})	0.101	0.100
F(000)	832	472
Crystal size (mm^3)	0.32 x 0.17 x 0.11	0.3 x 0.15 x 0.12
Reflections collected	61470	21416
Independent reflections	9558 [R(int) = 0.0489]	5326 [R(int) = 0.0398]
Completeness to theta = 25.242°	99.9 %	99.9 %
Max. and min. transmission	0.7457 and 0.7003	0.7456 and 0.7085
Data / restraints / parameters	9558 / 0 / 529	5326 / 0 / 302

Goodness-of-fit on F^2	1.014	1.014
Final R indices [I>2σ(I)]	R1 = 0.0407, wR2 = 0.0918	R1 = 0.0401, wR2 = 0.0911
R indices (all data)	R1 = 0.0575, wR2 = 0.0999	R1 = 0.0599, wR2 = 0.1010
Largest diff. peak and hole (e.$Å^{-3}$)	0.316 and -0.263	0.315 and -0.235
CCDC no.	1865406	1865407

(*S*,*S*)-40

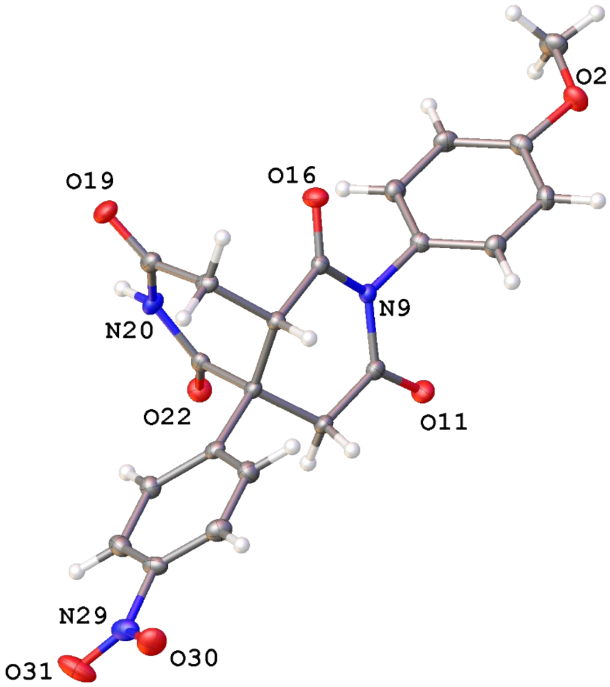


Table S2 Crystal data and structure refinement parameters for **(*S*,*S*)-40**

Empirical formula	$C_{21}H_{17}N_3O_7$	
Formula weight	423.38	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 6.6218(12) Å	α= 90°.
	b = 11.9315(18) Å	β= 98.905(5)°.
	c = 11.960(2) Å	γ = 90°.
Volume	933.6(3) $Å^3$	
Z	2	
Density (calculated)	1.506 Mg/m^3	
Absorption coefficient	0.115 mm^{-1}	
F(000)	440	

Crystal size	0.286 x 0.245 x 0.109 mm^3
Theta range for data collection	3.114 to 28.824°.
Index ranges	$-8\leq h\leq 8$, $-16\leq k\leq 16$, $-16\leq l\leq 16$
Reflections collected	19135
Independent reflections	4860 [R(int) = 0.0425]
Completeness to theta = 25.242°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7458 and 0.7039
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4860 / 2 / 285
Goodness-of-fit on F^2	1.030
Final R indices [$I>2\sigma(I)$]	R1 = 0.0347, wR2 = 0.0753
R indices (all data)	R1 = 0.0450, wR2 = 0.0802
Absolute structure parameter	-0.2(4)
Largest diff. peak and hole	0.196 and -0.202 e.$Å^{-3}$
CCDC no.	1938123

Computational Study

The geometry of the isolated molecules as well as those of the different stationary structures of the free-energy profile were optimised by using the wb97-xD[16] density functional theory (DFT) approach, which is a long-range corrected hybrid density functional including empirical atom-atom dispersion correction, with standard 6-311++G(d,p)[17, 18] basis sets. Vibrational analyses were performed to confirm that the different optimised structures corresponded to true minima of the free-energy profile or to transition states. To assess the connectivity between each transition states and the minima to which it evolves, intrinsic reaction coordinates (IRC) calculations have been performed. All these calculations were carried out with the Gaussian09 program.[19] The self-consistent reaction field (SCRF) calculations using the PCM solvation model were carried out screening the complete free-energy profile of all the reactions involved in this study. The dielectric constant in the PCM calculations was set to $\varepsilon = 2.379$ to simulate tetrahydrofuran (THF) similar to the solvent medium used in the experimental studies.

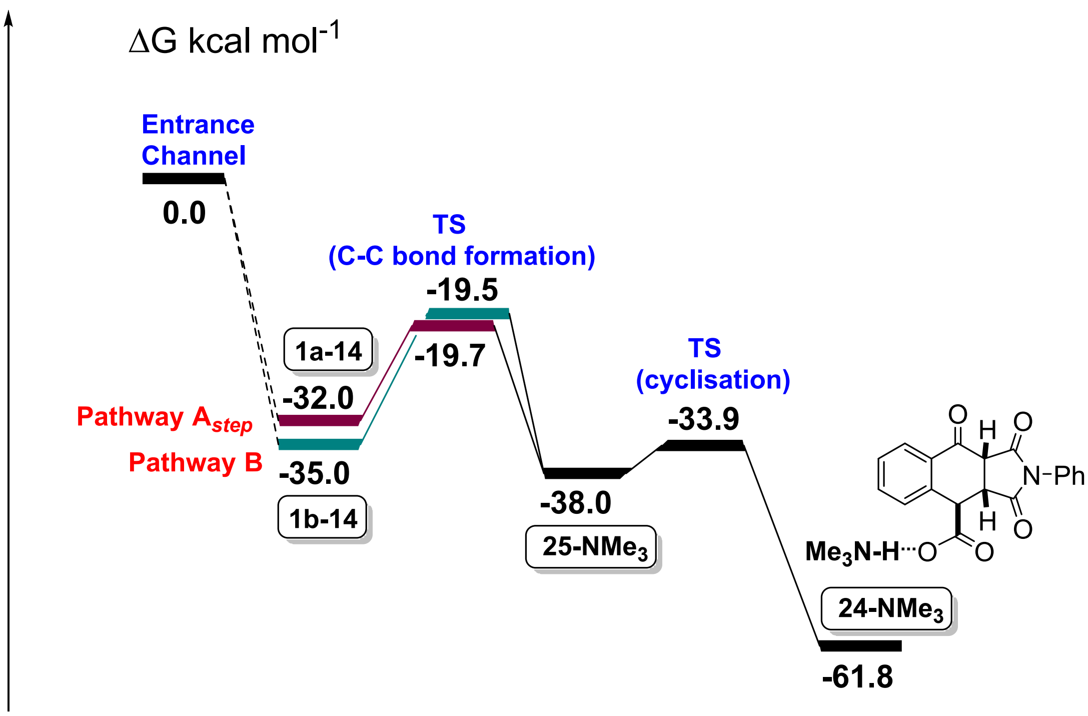


Fig. S1. Free energy profile for Pathways A and B for *N*-phenylmaleimide (**14**) at wb97-xD/6-311++G(d,p) computational level in PCM-THF.

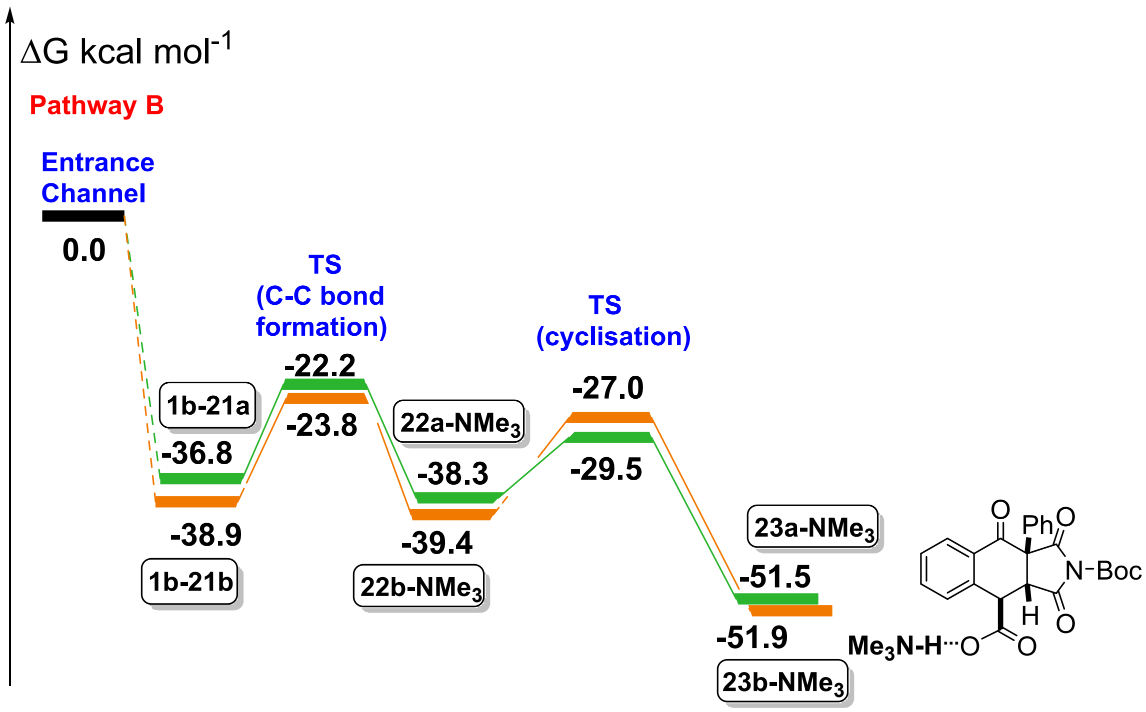
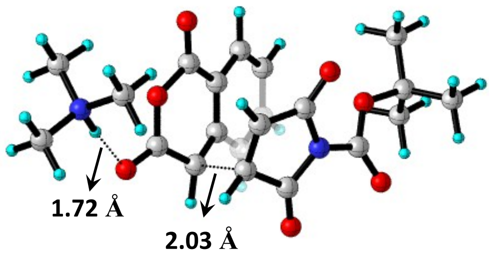
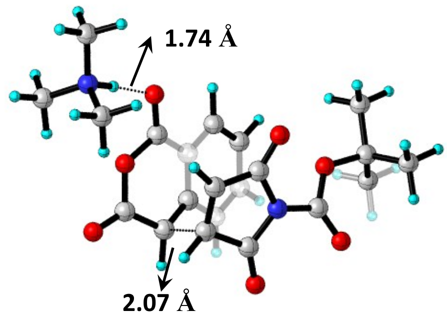


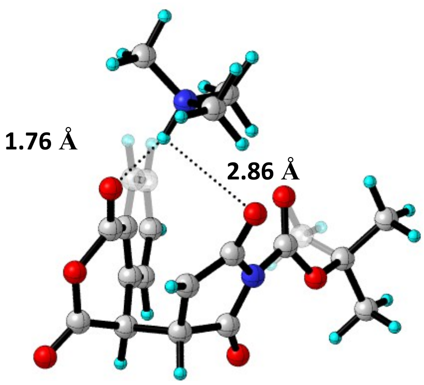
Fig. S2. Free energy profile for Pathway B (formation of both diastereomers) for the *N*-Boc-α-phenylmaleimide at wb97-xD/6-311++G(d,p) computational level in PCM-THF.



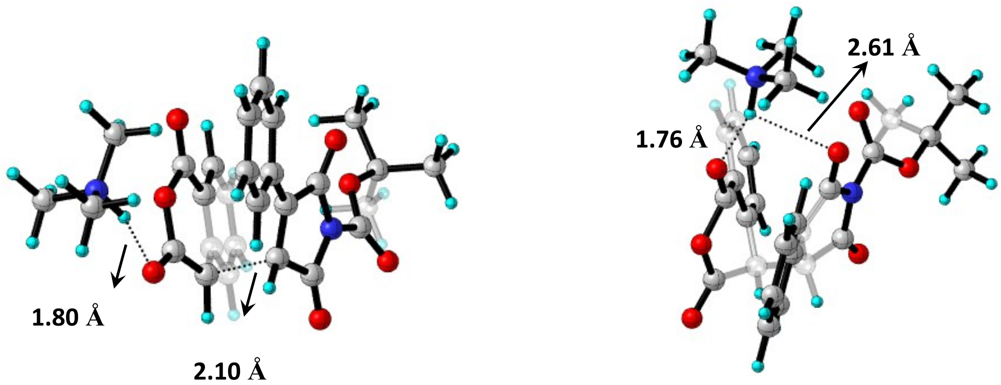
TS C-C bond formation **1a-26**



TS C-C bond formation **1b-26**



TS cyclisation **28-NMe$_3$**



TS C-C bond formation **1b-26** TS cyclisation **22b-NMe$_3$**

Fig. S3. Optimised geometries for the different TSs involving the *N*-Boc maleimide (**26**) and *N*-Boc-α-phenylmaleimide (**21**) at wb97-xD/6-311++G(d,p) computational level in PCM-THF in the presence of Trimethylamine (TMA).

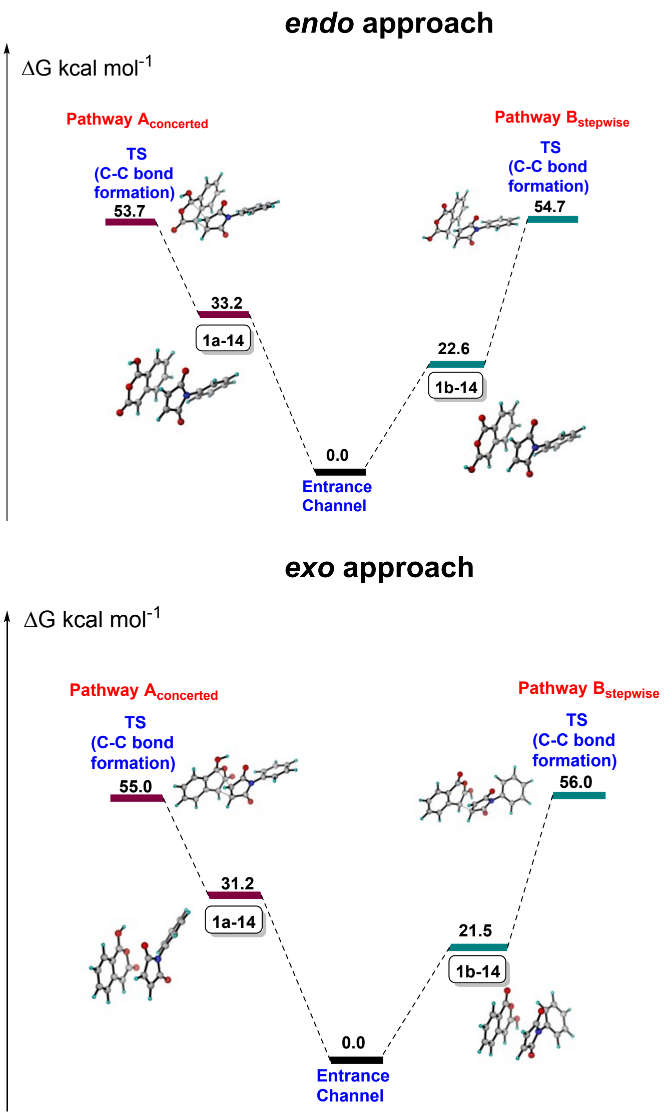


Fig. S4. Optimised geometries and free energy profiles for the first step of the reaction involving *N*-phenylmaleimide (**14**) and either enol **1a** or **1b** at wb97-xD/6-311++G(d,p) computational level in PCM-o-dichlorobenzene at 200ºC, absence of base.

Table S3. DFT Optimised Geometries (Cartesian Coordinates in Å) of the Stationary Points in PCM-THF.

PES Fig. 2 **Pathway** A

1a-26

C 0.8415172218 -1.7447706059 -0.4160841144
C -0.446632798 -1.8893702364 0.3218285051
C 0.6392485173 -1.0183215915 -1.5096136738
H 1.7520932815 -2.196784093 -0.0534286179
C -0.7930500672 -0.6309349558 -1.5937086413
H 1.344085729 -0.7261449375 -2.2729702281
N -1.4130203055 -1.1769175313 -0.4347593324
O -0.6332325187 -2.4740106672 1.3505033328
O -1.3272614844 -0.0278540381 -2.4817723052
C -2.7900700518 -1.1411741922 -0.1032716502
O -3.2975480604 -1.9613811486 0.6131002697
O -3.3634763861 -0.114968143 -0.6861561036
C -4.8189649848 0.1073881523 -0.6201302473
C -5.5504789484 -1.0845496151 -1.2265343421
C -5.2389840176 0.3793794997 0.8192137349
C -4.994749069 1.3497447729 -1.4823598278
H -5.1641035266 -1.2992284501 -2.2258950493
H -5.452987993 -1.9749476847 -0.6062283995
H -6.6113578443 -0.838974397 -1.315829697
H -5.089813209 -0.4950846837 1.4512815218
H -4.6730186611 1.2185153762 1.2283093344
H -6.2990346709 0.6442179077 0.8323147144
H -6.0475348841 1.6400040416 -1.4969241238
H -4.4077034496 2.1788119151 -1.0818976932
H -4.6694645153 1.1557280359 -2.5063772601
C 1.6453552368 0.2663115239 1.7978760545
C 0.4511496427 0.971905082 1.5426145639
C 2.7506606323 0.3808796489 0.9605663435
C -0.686389886 0.864447358 2.3891058835
C 0.3263952512 1.8000398246 0.3989785673
C -1.8414451654 1.5456364014 2.1052555824
H -0.6262341924 0.227415393 3.264478952
C -0.870558134 2.4915329231 0.1236614174
C 1.459648115 1.9348948884 -0.4745373649
C -1.9454198137 2.3728938077 0.9656787308
H -2.6930073877 1.443428506 2.7700401311
H -0.9215870116 3.1079758966 -0.7660673584
H -2.8696473758 2.8973917992 0.7559500097
O 1.5168628484 2.6226841318 -1.4978080939
O 3.8544572986 -0.1474421795 0.9948293645
O 2.5794490373 1.2585697174 -0.1563396402
H 1.7321692464 -0.3840710706 2.6576618765
H 3.0604687666 2.4669425594 -2.1998529764
N 4.0243912638 2.34653625 -2.6008788418
C 4.2091581717 0.8969093094 -2.8643711724
H 4.0847420365 0.3604144803 -1.9257336296

TS C-C

C -0.6418357012 2.1415175286 -1.1466687862
C 0.8440256173 2.3740247807 -1.1366833222
C -0.860405526 0.9134092585 -1.7654108208
H -1.2814368511 3.0092555281 -1.250181293
C 0.3768719618 0.2458917428 -1.9950406003
H -1.7985237062 0.5135982657 -2.1138827002
N 1.4198398948 1.1668742569 -1.5376243847
O 1.4192595989 3.3795074195 -0.8028523569
O 0.6223298466 -0.8172767211 -2.5276386089
C 2.8024689923 0.9170036532 -1.4928046792
O 3.6290129301 1.7794394105 -1.6483051523
O 3.0201134283 -0.3569939124 -1.237323002
C 4.368289573 -0.9380607216 -1.2750918665
C 4.9861754981 -0.7331433924 -2.6538022706
C 5.2201646945 -0.3465284285 -0.1577607808
C 4.0949268552 -2.414781458 -1.0219661623
H 4.3154581103 -1.1131696279 -3.4281045068
H 5.1977161319 0.3178893982 -2.8473265222
H 5.9239853205 -1.2915471587 -2.7076436306
H 4.7210217275 -0.4737527192 0.8054972227
H 6.1756935078 -0.8757057532 -0.121262762
H 5.412935901 0.7128910379 -0.3223536336
H 5.0369812809 -2.9678251137 -1.0200193944
H 3.6061829514 -2.5513890599 -0.0550654711
H 3.4475044261 -2.8234624 -1.8003837482
C -0.8709508211 2.0798968959 0.9134646572
C 0.0375144107 1.0475844646 1.3406141649
C -2.2687478692 1.7645057524 0.853142304
C 1.3116895135 1.3256003986 1.8692388857
C -0.3090206773 -0.2929647064 1.1060773832
C 2.184890741 0.2977045891 2.1495821267
H 1.5982618726 2.3558519577 2.0459309314
C 0.5948903076 -1.3331436701 1.3772756842
C -1.6486594336 -0.5944444838 0.6407126869
C 1.8327124586 -1.0386657806 1.8995613395
H 3.1599853253 0.5258908468 2.5654526097
H 0.2968412408 -2.3554580243 1.1791411465
H 2.5350736075 -1.8333481636 2.120840844
O -2.0750648512 -1.6949066265 0.327526851
O -3.214881097 2.5168119088 0.8453667126
O -2.5682520703 0.414746805 0.6617060297
H -0.653726837 3.1043866949 1.1911302889
H -3.7230220456 -1.604306331 -0.2213667252
N -4.7101802637 -1.49054497 -0.5439025926
C -5.1846221202 -2.8173300092 -1.0113692657
H -4.5459656256 -3.1516700316 -1.8266614726

H 3.4615882651 0.5746890356 -3.5875799383
H 5.2088308985 0.735011003 -3.2669575008
C 4.0938326224 3.1456731318 -3.8484702681
H 3.3341663367 2.7859775885 -4.540068386
H 3.9088074806 4.1912563255 -3.6092631624
H 5.0838702343 3.0318743346 -4.2898994996
C 4.9841954146 2.8325597981 -1.576527248
H 4.7843242115 3.8845562799 -1.3799317009
H 4.8398591201 2.2488958666 -0.6698339705
H 5.9987140119 2.706912375 -1.9546044709
PES Fig. 2 **Pathway** B
1b-26
H 4.7580550328 -0.3465290685 0.3082305866
N 5.4550722367 -0.3657742701 -0.4995755801
C 6.6071091047 -1.1847427654 -0.0559213618
H 6.256551334 -2.189537231 0.1741868368
H 7.3525214181 -1.2216369186 -0.8507962552
H 7.0361951196 -0.733108364 0.8370203372
C 4.7622734747 -0.9728923406 -1.6607311966
H 4.4095429055 -1.9646563897 -1.3805337752
H 3.9182236133 -0.3396764016 -1.9268972033
H 5.4583578665 -1.0470651146 -2.496696799
C 5.8475199319 1.036733211 -0.7766281309
H 4.9528895166 1.5976599856 -1.0395125295
H 6.2976175004 1.4586989414 0.1205382381
H 6.565188261 1.0534708526 -1.5975096273
C 0.7196434916 -1.997193887 0.1249867208
C -0.5915123065 -1.9258381629 0.8323219181
C 0.5903199336 -1.4768814273 -1.0896157089
H 1.5907427545 -2.4225062437 0.6000148729
C -0.8144873765 -1.0313144816 -1.2940144082
H 1.328804593 -1.3684838654 -1.8695218832
N -1.4951325136 -1.3151023928 -0.0756928282
O -0.8348101577 -2.2965037205 1.9449982706
O -1.2858307506 -0.5742554333 -2.2960590452
C -2.8732590249 -1.136141342 0.2006991518
O -3.4334739367 -1.7386873465 1.0762350959
O -3.3845899238 -0.2526015524 -0.6235934026
C -4.830204975 0.0301615503 -0.664967407
C -5.5922069165 -1.2440786123 -1.010106635
C -5.2834309296 0.6423326043 0.6547234148
C -4.9304257406 1.0452993603 -1.7952152542
H -5.1881228868 -1.6924310037 -1.9210335951
H -5.5465884088 -1.9729998457 -0.2014857293
H -6.639992748 -0.9918684158 -1.1891827765
H -5.1828816655 -0.0624965316 1.4790506001
H -4.7047791966 1.5413633184 0.8764021678
H -6.334457987 0.9277249984 0.5650252688
H -5.9729071922 1.3430459067 -1.927544442
H -4.3390588269 1.9340534847 -1.5653313317
H -4.5661816546 0.6159879049 -2.7306102801
H -5.1297263254 -3.5232638817 -0.1849640722
H -6.2141168501 -2.7233959104 -1.3559199152
C -4.6989099669 -0.4924706245 -1.6445141953
H -4.2901436556 0.4399332701 -1.2599370445
H -4.0792265211 -0.8708958018 -2.4556042569
H -5.7197569042 -0.3413875842 -1.9944026064
C -5.4926280289 -0.9993478619 0.6202606619
H -5.439857796 -1.739936539 1.4162852754
H -5.0559693463 -0.0607816918 0.9547427826
H -6.5271769248 -0.8509128855 0.3121921539

TS C-C
H -4.7763896937 -0.6547773857 -0.5020023273
N -5.443515661 -1.0306978677 0.2115355233
C -5.7573258366 0.0676887342 1.1607331281
H -6.2145214773 0.8881377841 0.610216733
H -6.44713845 -0.3060477112 1.9171333968
H -4.8295284571 0.4001989675 1.621338864
C -6.6496648073 -1.4970150989 -0.5169542538
H -7.1029870651 -0.6486480119 -1.0263236709
H -6.3520177229 -2.249352734 -1.2450886634
H -7.3538758294 -1.9241742531 0.1965886632
C -4.7448379642 -2.1508717336 0.8924763976
H -4.4740704449 -2.8983794757 0.1489070862
H -3.8501333446 -1.7583332159 1.3715682374
H -5.4132236866 -2.5852309979 1.6353675367
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C -0.5382582241 -1.8513590245 0.0530589239
H -1.3768081102 -1.9875826044 -1.9748842817
C 0.8095672451 -1.7110830479 0.4822692769
H -1.3108092387 -2.2209780375 0.7079687327
N 1.5785915585 -1.3516839298 -0.7166312796
O 1.0725845833 -1.2253113632 -2.9873230708
O 1.3350442061 -1.9119280515 1.5585724499
C 2.9410219426 -1.0078720168 -0.7669335697
O 3.6489127783 -1.2608456421 -1.7086076654
O 3.2772509468 -0.3653628054 0.3325283792
C 4.6672269804 -0.0061388959 0.6378375758
C 5.5352549801 -1.2587897517 0.6777043939
C 5.1712295384 1.0208828573 -0.3694964147
C 4.543321003 0.6105712655 2.0248391091
H 5.1011492613 -1.9985150154 1.3545602614
H 5.6492294677 -1.7016090852 -0.3113010531
H 6.5253905916 -0.9894152989 1.0535779786
H 4.4903025122 1.8738389699 -0.4111636142
H 6.1525909543 1.3805251462 -0.0500349299
H 5.2625534907 0.5885667223 -1.365249792
H 5.5239423299 0.9450105548 2.3708188007
H 3.8680087231 1.4682269462 1.9980333101
H 4.1489913113 -0.1199876597 2.7340284711

C 1.5297874697 0.3651509397 2.0264153823
C 0.4104513758 1.0806480224 1.5235332557
C 2.6744298472 0.2381229633 1.2746454714
C -0.7920179968 1.2156226683 2.2585302639
C 0.4527795852 1.6560978159 0.2344632217
C -1.8680126339 1.8876104578 1.7291410697
H -0.8563187022 0.7703556745 3.2451179491
C -0.6563095295 2.338645311 -0.2926690236
C 1.6661276408 1.540542299 -0.5561236995
C -1.8102486906 2.4579189522 0.4444209686
H -2.7790672486 1.9718797061 2.3121825778
H -0.5815309449 2.7588523166 -1.2885706502
H -2.6708451545 2.9750504375 0.0379080123
O 1.8564137018 1.9912934323 -1.6664869515
O 3.7376998106 -0.3717217541 1.5311669495
O 2.6991746311 0.8526030579 0.0155843866
H 1.4986888686 -0.1061262901 2.998825522

28-NMe_3

C 0.817060705 -1.5571144835 0.9899562112
C -0.65274484 -1.840648705 1.2965163526
C 0.8741834306 -1.5616411551 -0.4985142416
H 1.4421557892 -2.313400737 1.4730388102
C -0.3759719918 -1.6875995447 -1.0250004316
H 1.7807786786 -1.6367219057 -1.0799299437
N -1.3239229378 -1.7787129225 0.0880597912
O -1.133640155 -1.9948797394 2.3942843056
O -0.8155018443 -1.8143023191 -2.201662505
C -2.7098659284 -1.5473597721 0.0028099931
O -3.5198370585 -2.1292437666 0.676910537
O -2.9398074087 -0.5849065839 -0.8718027426
C -4.2974896655 -0.1871889033 -1.2615597236
C -5.0629797005 -1.3848754032 -1.812130773
C -4.9999164784 0.4613098903 -0.0746715511
C -4.032930404 0.8351436461 -2.3592449567
H -4.4858906454 -1.8723781551 -2.6017244518
H -5.2860831836 -2.1126258307 -1.0329519774
H -6.0045758362 -1.0345078785 -2.2419225167
H -4.4080838941 1.2981533983 0.3029669159
H -5.9704930053 0.844390376 -0.3994440125
H -5.1595557636 -0.2557239666 0.7298932738
H -4.97839024 1.255745069 -2.7088739183
H -3.4053611455 1.6459839314 -1.9817010942
H -3.5300836123 0.3609164824 -3.2052960967
C 1.1631096432 -0.1765382621 1.6959991397
C 0.2225128631 0.9100855888 1.2692251246
C 2.5833734203 0.1428539619 1.3333623649
C -0.9519428501 1.1930958859 1.9601805352
C 0.4943973102 1.5927614657 0.085829094
C -1.8426052068 2.1311005287 1.4570027413
H -1.1740009862 0.6670494556 2.8808222302
C -0.4035565869 2.5302762192 -0.4258999636
C -1.2691716788 0.3611812683 -1.6736632165
C -0.3409855873 1.2101806598 -0.9589229012
C -2.5584880624 0.1732787279 -1.0928026854
C 0.7446572766 1.8386474638 -1.5899262132
C -0.4658860318 1.3231513252 0.4328124279
C 1.658087158 2.5564005634 -0.8461925702
H 0.8589310685 1.7470438863 -2.6639612646
C 0.4762701619 2.0402390448 1.1838530036
C -1.6323263975 0.7498674775 1.0978034996
C 1.5309688351 2.6565124806 0.5462662961
H 2.4855402069 3.0460717108 -1.347534782
H 0.3536665801 2.1076921285 2.2579602538
H 2.2578921137 3.2213112386 1.1176719986
O -1.8526450111 0.7022403812 2.2785852794
O -3.5775276735 -0.2153176892 -1.6551745533
O -2.6583910505 0.3147598473 0.2639281344
H -1.2599209035 0.3873873038 -2.7566791948

TS cyclisation

C 0.3398879829 -2.0047012526 -1.5976171518
C -1.0693440966 -1.4976016049 -1.3101608626
C 1.1340147683 -0.7711130809 -1.82783371
H 0.3185577986 -2.7135510369 -2.4280461629
C 0.332855603 0.3588984202 -1.6617735502
N -0.9814432816 -0.1089108112 -1.2121378082
O -2.0399939096 -2.1889533778 -1.1276868317
O 0.5519147602 1.5553466516 -1.8390643707
C -1.8999460436 0.7260868313 -0.550274113
O -1.5548800274 1.6807416513 0.0984057013
O -3.1331296378 0.3011236058 -0.7455018884
C -4.2551075879 0.7881209688 0.0716941057
C -3.9676487259 0.5103787688 1.5435082939
C -4.5117312834 2.2642634659 -0.2088498157
C -5.4164129617 -0.0654294985 -0.42086191
H -3.7306162865 -0.5465479093 1.6879954004
H -3.1392522589 1.1146823031 1.9129114916
H -4.8589983865 0.7468900637 2.1295380429
H -3.6953454204 2.8877215393 0.1527640345
H -4.6398768394 2.4303313029 -1.2812650255
H -5.4337439464 2.5646354506 0.2953983314
H -6.3245895149 0.2012255043 0.1243403833
H -5.5891681446 0.1012216254 -1.486302803
H -5.2093614161 -1.1253811738 -0.2608505336
C 0.8007938474 -2.812883403 -0.3009969823
C 0.5609954792 -1.9637009658 0.9076034429
C 2.2739718473 -3.0645537944 -0.4646246522
C -0.5027978733 -2.1300314161 1.7883869542
C 1.4063787113 -0.8658366799 1.0480206971
C -0.7057053367 -1.2019871922 2.801746862
H -1.1757484277 -2.9712457374 1.6690705716
C 1.20739766 0.0615644285 2.0666109985
C 2.5256274833 -0.7382034311 0.0942970359

C 1.7711724071 1.3539330437 -0.6071601421
C -1.5764815176 2.7941399392 0.2603800472
H -2.7544541447 2.34624972 2.0021082215
H -0.1642513605 3.0520706502 -1.3445881043
H -2.2799376971 3.5220539655 -0.1262694843
O 2.0412614925 1.7071112501 -1.7223457717
O 3.5492273342 -0.1685654184 1.9641433033
O 2.7812090017 0.7672764742 0.1250923947
H 1.1231633586 -0.3339299498 2.7736784114
H -0.1768290805 -1.0354402829 -3.3190397918
N 0.1766523327 -0.4963946652 -4.1867719502
C 1.6525976775 -0.6104465946 -4.2155010677
H 2.0583556902 -0.1373359094 -3.3228021299
H 1.9226064656 -1.6654511114 -4.2346539794
H 2.0382356052 -0.1120490527 -5.1060653058
C -0.4486516311 -1.1501327623 -5.3580689631
H -1.531191075 -1.0979311181 -5.2520620356
H -0.1357812992 -0.641453274 -6.2709290094
H -0.1359071466 -2.192691382 -5.3876019979
C -0.263446564 0.9099375768 -4.0422944083
H -1.3453230257 0.9275854995 -3.9223455874
H 0.2155858432 1.3352769155 -3.1624597825
H 0.0251932221 1.473743291 -4.9305812069

27-NMe_3

H 4.782173828 -1.0714607445 0.699795225
N 5.4853103816 -0.7522470645 -0.0412124841
C 4.7700730691 0.2308118924 -0.8920841
H 4.3965668482 1.0378846179 -0.2616959159
H 5.4566359349 0.6267223777 -1.6411032992
H 3.9338174049 -0.2722679055 -1.3742015097
C 6.6265223687 -0.1316425912 0.6685216966
H 6.2589465551 0.7058147028 1.2595457527
H 7.0782495918 -0.873128919 1.3252434471
H 7.3590972662 0.2181996162 -0.059433768
C 5.8898955026 -1.9482412845 -0.8162215041
H 6.3822458992 -2.6512909184 -0.1460756391
H 4.990634373 -2.4026796061 -1.2275091041
H 6.5735593872 -1.649296157 -1.6117007808
C 0.0495760808 -1.4327320591 0.7075943437
C -1.2192603188 -0.8842241676 1.3379406796
C -0.1437574844 -1.2568947265 -0.8034242895
H 0.0773886897 -2.4976759232 0.9498326003
C -1.5858711974 -0.7815649617 -0.9702694347
H -0.0276976237 -2.1860183874 -1.3586418293
N -2.1150710994 -0.5795788358 0.3076219575
O -1.4555161118 -0.7597423243 2.5089822168
O -2.1674056033 -0.5697147947 -1.9978871514
C -3.4238983575 -0.0328095797 0.5481928666
O -3.5752395222 0.9680186942 1.1870338759
O -4.3182676117 -0.7990259298 -0.0200602381
C -5.7521318055 -0.4203228331 -0.0763250431
C 0.1480407801 -0.1085426682 2.9429337786
H -1.533718369 -1.3307833259 3.4891839976
H 1.8962126275 0.8893962916 2.1818120633
H -0.0139398934 0.6053507461 3.7418920156
O 3.2588204846 0.2325759106 -0.0065808088
O 2.7818648228 -4.1129201622 -0.7517689955
O 3.0659973156 -1.9665432658 -0.3235238313
H 0.2787862504 -3.766344314 -0.255770025
H 2.7252846731 1.9142256022 -0.0104540767
N 2.7278432281 2.9532610933 0.0271964545
C 3.8216844135 3.3356531932 0.9539523865
H 3.6211304441 2.9097722761 1.9356877945
H 4.7615242615 2.9439654496 0.56951386
H 3.8654182812 4.4226167153 1.0204342408
C 2.993228265 3.4299868769 -1.3562078676
H 2.1880888989 3.0703546347 -1.9922182692
H 3.0372248016 4.5189780387 -1.3479892952
H 3.9456752956 3.0189206532 -1.6867674722
C 1.3991928293 3.4113603884 0.5156599605
H 1.3718651238 4.5004248017 0.4726435721
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C -6.3232172288 -0.3812562521 1.3349518519
C -5.8927255982 0.907095132 -0.8099270744
C -6.3565236213 -1.5592927584 -0.8835938013
H -6.1352224332 -1.326788534 1.8487674467
H -5.8989736787 0.4351641679 1.9181721188
H -7.4040720378 -0.236133318 1.269558116
H -5.4003332867 0.8579387632 -1.7837144263
H -6.9547548935 1.1047962258 -0.9722053872
H -5.4737345568 1.7334055111 -0.2363105778
H -7.4291649578 -1.3919256267 -1.0008596834
H -5.9009097628 -1.611255987 -1.874514339
H -6.2069364163 -2.5144920135 -0.3758382459
C 1.2896328306 -0.7631362181 1.3035875233
C 1.4649541192 0.6365768992 0.7694645757
C 2.5893226842 -1.5203612625 0.9394707424
C 1.9402938689 1.6734044689 1.5687587982
C 1.2682913581 0.8698709036 -0.597265692
C 2.209995458 2.9180649849 1.0161043937
H 2.1073865178 1.4958102741 2.6249053752
C 1.5512378992 2.1194906824 -1.1523085755
C 0.7609314484 -0.2182413274 -1.4683618
C 2.0188575479 3.144304163 -0.3465293224
H 2.5729772633 3.719156413 1.6501387701
H 1.3904013884 2.2730789569 -2.2129965799
H 2.2282636598 4.1188845996 -0.7714223121
O 0.9768089915 -0.2626296931 -2.6580705245
O 3.5780475647 -1.2884361437 1.6930195429
O 2.5963343281 -2.2044367016 -0.0948126969
H 1.1961910985 -0.7346514972 2.3895272126

PES Fig. S1 **Pathway** A

1a-14

H 4.7580550328 -0.3465290685 0.3082305866
N 5.4550722367 -0.3657742701 -0.4995755801
C 6.6071091047 -1.1847427654 -0.0559213618
H 6.256551334 -2.189537231 0.1741868368
H 7.3525214181 -1.2216369186 -0.8507962552
H 7.0361951196 -0.733108364 0.8370203372
C 4.7622734747 -0.9728923406 -1.6607311966
H 4.4095429055 -1.9646563897 -1.3805337752
H 3.9182236133 -0.3396764016 -1.9268972033
H 5.4583578665 -1.0470651146 -2.496696799
C 5.8475199319 1.036733211 -0.7766281309
H 4.9528895166 1.5976599856 -1.0395125295
H 6.2976175004 1.4586989414 0.1205382381
H 6.565188261 1.0534708526 -1.5975096273
C 0.7196434916 -1.997193887 0.1249867208
C -0.5915123065 -1.9258381629 0.8323219181
C 0.5903199336 -1.4768814273 -1.0896157089
H 1.5907427545 -2.4225062437 0.6000148729
C -0.8144873765 -1.0313144816 -1.2940144082

TS C-C

H -4.7763896937 -0.6547773857 -0.5020023273
N -5.443515661 -1.0306978677 0.2115355233
C -5.7573258366 0.0676887342 1.1607331281
H -6.2145214773 0.8881377841 0.610216733
H -6.44713845 -0.3060477112 1.9171333968
H -4.8295284571 0.4001989675 1.621338864
C -6.6496648073 -1.4970150989 -0.5169542538
H -7.1029870651 -0.6486480119 -1.0263236709
H -6.3520177229 -2.249352734 -1.2450886634
H -7.3538758294 -1.9241742531 0.1965886632
C -4.7448379642 -2.1508717336 0.8924763976
H -4.4740704449 -2.8983794757 0.1489070862
H -3.8501333446 -1.7583332159 1.3715682374
H -5.4132236866 -2.5852309979 1.6353675367
C -0.651564851 -1.5414978276 -1.3042879269
C 0.7488614551 -1.3702852235 -1.8344452284
C -0.5382582241 -1.8513590245 0.0530589239
H -1.3768081102 -1.9875826044 -1.9748842817
C 0.8095672451 -1.7110830479 0.4822692769

H 1.328804593 -1.3684838654 -1.8695218832
N -1.4951325136 -1.3151023928 -0.0756928282
O -0.8348101577 -2.2965037205 1.9449982706
O -1.2858307506 -0.5742554333 -2.2960590452
C -2.8732590249 -1.136141342 0.2006991518
O -3.4334739367 -1.7386873465 1.0762350959
O -3.3845899238 -0.2526015524 -0.6235934026
C -4.830204975 0.0301615503 -0.664967407
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C -5.2834309296 0.6423326043 0.6547234148
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H -5.5465884088 -1.9729998457 -0.2014857293
H -6.639992748 -0.9918684158 -1.1891827765
H -5.1828816655 -0.0624965316 1.4790506001
H -4.7047791966 1.5413633184 0.8764021678
H -6.334457987 0.9277249984 0.5650252688
H -5.9729071922 1.3430459067 -1.927544442
H -4.3390588269 1.9340534847 -1.5653313317
H -4.5661816546 0.6159879049 -2.7306102801
C 1.5297874697 0.3651509397 2.0264153823
C 0.4104513758 1.0806480224 1.5235332557
C 2.6744298472 0.2381229633 1.2746454714
C -0.7920179968 1.2156226683 2.2585302639
C 0.4527795852 1.6560978159 0.2344632217
C -1.8680126339 1.8876104578 1.7291410697
H -0.8563187022 0.7703556745 3.2451179491
C -0.6563095295 2.338645311 -0.2926690236
C 1.6661276408 1.540542299 -0.5561236995
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H -0.5815309449 2.7588523166 -1.2885706502
H -2.6708451545 2.9750504375 0.0379080123
O 1.8564137018 1.9912934323 -1.6664869515
O 3.7376998106 -0.3717217541 1.5311669495
O 2.6991746311 0.8526030579 0.0155843866
H 1.4986888686 -0.1061262901 2.998825522

H -1.3108092387 -2.2209780375 0.7079687327
N 1.5785915585 -1.3516839298 -0.7166312796
O 1.0725845833 -1.2253113632 -2.9873230708
O 1.3350442061 -1.9119280515 1.5585724499
C 2.9410219426 -1.0078720168 -0.7669335697
O 3.6489127783 -1.2608456421 -1.7086076654
O 3.2772509468 -0.3653628054 0.3325283792
C 4.6672269804 -0.0061388959 0.6378375758
C 5.5352549801 -1.2587897517 0.6777043939
C 5.1712295384 1.0208828573 -0.3694964147
C 4.543321003 0.6105712655 2.0248391091
H 5.1011492613 -1.9985150154 1.3545602614
H 5.6492294677 -1.7016090852 -0.3113010531
H 6.5253905916 -0.9894152989 1.0535779786
H 4.4903025122 1.8738389699 -0.4111636142
H 6.1525909543 1.3805251462 -0.0500349299
H 5.2625534907 0.5885667223 -1.365249792
H 5.5239423299 0.9450105548 2.3708188007
H 3.8680087231 1.4682269462 1.9980333101
H 4.1489913113 -0.1199876597 2.7340284711
C -1.2691716788 0.3611812683 -1.6736632165
C -0.3409855873 1.2101806598 -0.9589229012
C -2.5584880624 0.1732787279 -1.0928026854
C 0.7446572766 1.8386474638 -1.5899262132
C -0.4658860318 1.3231513252 0.4328124279
C 1.658087158 2.5564005634 -0.8461925702
H 0.8589310685 1.7470438863 -2.6639612646
C 0.4762701619 2.0402390448 1.1838530036
C -1.6323263975 0.7498674775 1.0978034996
C 1.5309688351 2.6565124806 0.5462662961
H 2.4855402069 3.0460717108 -1.347534782
H 0.3536665801 2.1076921285 2.2579602538
H 2.2578921137 3.2213112386 1.1176719986
O -1.8526450111 0.7022403812 2.2785852794
O -3.5775276735 -0.2153176892 -1.6551745533
O -2.6583910505 0.3147598473 0.2639281344
H -1.2599209035 0.3873873038 -2.7566791948

PES Fig. S1 **Pathway** B

1b-14

C 0.6514206313 -1.5580225357 -0.7099887686
C -0.5787725179 -1.8798675484 0.0754461792
C 0.3404483497 -0.660692584 -1.6394826672
H 1.5993426269 -2.0299413981 -0.4998601447
C -1.1070617727 -0.3228865643 -1.5216755328
H 0.9716521071 -0.2017240125 -2.3851071185
N -1.6054244058 -1.0894156951 -0.4571146337
O -0.6936057414 -2.6745649071 0.9729867671
O -1.7436349746 0.4415896146 -2.2004229352
C 1.5725108002 0.2349243241 1.7282165089
C 0.4578006718 1.0646558518 1.4894207525

TS C-C

C 0.019400548 -0.2390080169 -1.9309092552
C -1.4757250974 -0.3731865181 -1.7812393359
C 0.3860255361 0.9128607983 -1.2380580649
H 0.456444375 -0.5706588847 -2.8647814729
C -0.7366026546 1.4172670288 -0.5141339909
H 1.3412043556 1.4117006095 -1.2449245336
N -1.8641856666 0.5825623697 -0.864515175
O -2.1980971897 -1.1640162658 -2.3493884182
O -0.8372770205 2.3634426337 0.2480919602
C 0.5489782032 -1.9792516016 -0.9480510591
C -0.0483771966 -1.846393752 0.3545504259

C 2.6913485329 0.2627247318 0.9007079637
C -0.6858286328 1.0611129975 2.3332113438
C 0.4244192595 1.9302796229 0.3673633786
C -1.7716408871 1.8500535218 2.0531597211
H -0.6888058186 0.4129317899 3.2032899841
C -0.7002998319 2.7345050475 0.0964328186
C 1.5759351978 1.9828518652 -0.4894133593
C -1.7943723631 2.6955257778 0.9225377798
H -2.6352446175 1.817837936 2.7092167735
H -0.6838209723 3.3710301104 -0.780293201
H -2.6662935467 3.3032704456 0.7143403914
O 1.7110545879 2.7032224727 -1.4836025691
O 3.7392476291 -0.368792453 0.9291514578
O 2.6183537095 1.1861271126 -0.1923882542
H 1.5900330091 -0.4407828414 2.5725824909
H 3.2410092226 2.4809553434 -2.1453822986
N 4.2046472886 2.3300411025 -2.5405311968
C 4.2894154199 0.903424937 -2.9420538914
H 4.1042966437 0.2898513465 -2.0623030209
H 3.5349969538 0.7084817263 -3.7027588177
H 5.283286394 0.7065613954 -3.3439565167
C 4.3551600093 3.2419146281 -3.7000316509
H 3.5897970981 3.0047436377 -4.4369109724
H 4.2327228013 4.2684538312 -3.3595641623
H 5.345768846 3.1086903334 -4.1347380452
C 5.1721386098 2.6450805382 -1.4590703458
H 5.0288871072 3.6802036701 -1.1534664287
H 4.9783418471 1.9779494723 -0.6217396274
H 6.1845276718 2.5022673385 -1.8368824833
C -2.9659340503 -1.1355532375 -0.0451850531
C -3.9775767158 -1.1952339428 -1.0002961946
C -3.2793635124 -1.1344460417 1.3107475349
C -5.3050331982 -1.2335849429 -0.5925217999
H -3.7300656939 -1.2053923256 -2.0534765546
C -4.6089890404 -1.1919547317 1.7081749593
H -2.4889628709 -1.0925601096 2.046352667
C -5.6254058538 -1.2341321373 0.7605025221
H -6.0898275062 -1.2710656291 -1.3392303291
H -4.8481764625 -1.1975053126 2.7654548313
H -6.6622643792 -1.2706024522 1.0746580879

25-NMe$_3$

C 0.817060705 -1.5571144835 0.9899562112
C -0.65274484 -1.840648705 1.2965163526
C 0.8741834306 -1.5616411551 -0.4985142416
H 1.4421557892 -2.313400737 1.4730388102
C -0.3759719918 -1.6875995447 -1.0250004316
H 1.7807786786 -1.6367219057 -1.0799299437
N -1.3239229378 -1.7787129225 0.0880597912
O -1.133640155 -1.9948797394 2.3942843056
O -0.8155018443 -1.8143023191 -2.201662505
C -2.7098659284 -1.5473597721 0.0028099931

C 1.9587276954 -1.7400320498 -1.0651407549
C -1.2453098669 -2.4903269081 0.7143868311
C 0.5191431532 -0.9376750038 1.2630470791
C -1.8473123114 -2.212135996 1.9221410365
H -1.6922599426 -3.1980922588 0.0251480603
C -0.1141902195 -0.6407719209 2.480461218
C 1.8075679378 -0.3551807053 0.9479723945
C -1.2936893002 -1.271266803 2.8059111329
H -2.7697986846 -2.7161152629 2.1884732741
H 0.3425306376 0.0766016087 3.1513159422
H -1.7887364785 -1.0525732907 3.7442104255
O 2.3996512978 0.4938434249 1.596344858
O 2.717215314 -2.0968191681 -1.936718092
O 2.5009791207 -0.8879522711 -0.1031776308
H 0.1671063684 -2.7425033634 -1.6156049374
H 3.8696460945 0.9431282985 0.7844180956
N 4.7615673827 1.1740402476 0.2917784973
C 5.3533074771 2.3499031997 0.978501479
H 4.6529165505 3.1806031502 0.9167176245
H 5.5334330929 2.0955472033 2.0212725084
H 6.2905642327 2.611314123 0.4883815626
C 4.426284503 1.4761554442 -1.1238407536
H 3.9625414629 0.5962037763 -1.5651006544
H 3.7373802246 2.3189122014 -1.1492310958
H 5.3431972009 1.7279154631 -1.6563660077
C 5.6313661024 -0.02598691 0.3967913766
H 5.8064471677 -0.2391761271 1.4498545983
H 5.1196477573 -0.863418848 -0.0729208047
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C -3.1967023224 0.7989712335 -0.4319452983
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C -5.0184369474 2.2981043511 0.0508533886
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C -5.3022968518 -0.0685413063 0.3524593436
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H -5.4129223351 3.3071852476 0.0934300173
H -5.9176490303 -0.9163789893 0.6322861556
H -6.83586898 1.3860977222 0.753002683

TS cyclisation

C 0.3398879829 -2.0047012526 -1.5976171518
C -1.0693440966 -1.4976016049 -1.3101608626
C 1.1340147683 -0.7711130809 -1.82783371
H 0.3185577986 -2.7135510369 -2.4280461629
C 0.332855603 0.3588984202 -1.6617735502
N -0.9814432816 -0.1089108112 -1.2121378082
O -2.0399939096 -2.1889533778 -1.1276868317
O 0.5519147602 1.5553466516 -1.8390643707
C -1.8999460436 0.7260868313 -0.550274113
O -1.5548800274 1.6807416513 0.0984057013

O -3.5198370585 -2.1292437666 0.676910537
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C -4.2974896655 -0.1871889033 -1.2615597236
C -5.0629797005 -1.3848754032 -1.812130773
C -4.9999164784 0.4613098903 -0.0746715511
C -4.032930404 0.8351436461 -2.3592449567
H -4.4858906454 -1.8723781551 -2.6017244518
H -5.2860831836 -2.1126258307 -1.0329519774
H -6.0045758362 -1.0345078785 -2.2419225167
H -4.4080838941 1.2981533983 0.3029669159
H -5.9704930053 0.844390376 -0.3994440125
H -5.1595557636 -0.2557239666 0.7298932738
H -4.97839024 1.255745069 -2.7088739183
H -3.4053611455 1.6459839314 -1.9817010942
H -3.5300836123 0.3609164824 -3.2052960967
C 1.1631096432 -0.1765382621 1.6959991397
C 0.2225128631 0.9100855888 1.2692251246
C 2.5833734203 0.1428539619 1.3333623649
C -0.9519428501 1.1930958859 1.9601805352
C 0.4943973102 1.5927614657 0.085829094
C -1.8426052068 2.1311005287 1.4570027413
H -1.1740009862 0.6670494556 2.8808222302
C -0.4035565869 2.5302762192 -0.4258999636
C 1.7711724071 1.3539330437 -0.6071601421
C -1.5764815176 2.7941399392 0.2603800472
H -2.7544541447 2.34624972 2.0021082215
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H -2.2799376971 3.5220539655 -0.1262694843
O 2.0412614925 1.7071112501 -1.7223457717
O 3.5492273342 -0.1685654184 1.9641433033
O 2.7812090017 0.7672764742 0.1250923947
H 1.1231633586 -0.3339299498 2.7736784114
H -0.1768290805 -1.0354402829 -3.3190397918
N 0.1766523327 -0.4963946652 -4.1867719502
C 1.6525976775 -0.6104465946 -4.2155010677
H 2.0583556902 -0.1373359094 -3.3228021299
H 1.9226064656 -1.6654511114 -4.2346539794
H 2.0382356052 -0.1120490527 -5.1060653058
C -0.4486516311 -1.1501327623 -5.3580689631
H -1.531191075 -1.0979311181 -5.2520620356
H -0.1357812992 -0.641453274 -6.2709290094
H -0.1359071466 -2.192691382 -5.3876019979
C -0.263446564 0.9099375768 -4.0422944083
H -1.3453230257 0.9275854995 -3.9223455874
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H 0.0251932221 1.473743291 -4.9305812069

24-NMe$_3$

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H 4.3965668482 1.0378846179 -0.2616959159
O -3.1331296378 0.3011236058 -0.7455018884
C -4.2551075879 0.7881209688 0.0716941057
C -3.9676487259 0.5103787688 1.5435082939
C -4.5117312834 2.2642634659 -0.2088498157
C -5.4164129617 -0.0654294985 -0.42086191
H -3.7306162865 -0.5465479093 1.6879954004
H -3.1392522589 1.1146823031 1.9129114916
H -4.8589983865 0.7468900637 2.1295380429
H -3.6953454204 2.8877215393 0.1527640345
H -4.6398768394 2.4303313029 -1.2812650255
H -5.4337439464 2.5646354506 0.2953983314
H -6.3245895149 0.2012255043 0.1243403833
H -5.5891681446 0.1012216254 -1.486302803
H -5.2093614161 -1.1253811738 -0.2608505336
C 0.8007938474 -2.812883403 -0.3009969823
C 0.5609954792 -1.9637009658 0.9076034429
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C 1.4063787113 -0.8658366799 1.0480206971
C -0.7057053367 -1.2019871922 2.801746862
H -1.1757484277 -2.9712457374 1.6690705716
C 1.20739766 0.0615644285 2.0666109985
C 2.5256274833 -0.7382034311 0.0942970359
C 0.1480407801 -0.1085426682 2.9429337786
H -1.533718369 -1.3307833259 3.4891839976
H 1.8962126275 0.8893962916 2.1818120633
H -0.0139398934 0.6053507461 3.7418920156
O 3.2588204846 0.2325759106 -0.0065808088
O 2.7818648228 -4.1129201622 -0.7517689955
O 3.0659973156 -1.9665432658 -0.3235238313
H 0.2787862504 -3.766344314 -0.255770025
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N 2.7278432281 2.9532610933 0.0271964545
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H 4.990634373 -2.4026796061 -1.2275091041
H 6.5735593872 -1.649296157 -1.6117007808
C 0.0495760808 -1.4327320591 0.7075943437
C -1.2192603188 -0.8842241676 1.3379406796
C -0.1437574844 -1.2568947265 -0.8034242895
H 0.0773886897 -2.4976759232 0.9498326003
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C -5.7521318055 -0.4203228331 -0.0763250431
C -6.3232172288 -0.3812562521 1.3349518519
C -5.8927255982 0.907095132 -0.8099270744
C -6.3565236213 -1.5592927584 -0.8835938013
H -6.1352224332 -1.326788534 1.8487674467
H -5.8989736787 0.4351641679 1.9181721188
H -7.4040720378 -0.236133318 1.269558116
H -5.4003332867 0.8579387632 -1.7837144263
H -6.9547548935 1.1047962258 -0.9722053872
H -5.4737345568 1.7334055111 -0.2363105778
H -7.4291649578 -1.3919256267 -1.0008596834
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C 1.4649541192 0.6365768992 0.7694645757
C 2.5893226842 -1.5203612625 0.9394707424
C 1.9402938689 1.6734044689 1.5687587982
C 1.2682913581 0.8698709036 -0.597265692
C 2.209995458 2.9180649849 1.0161043937
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C 0.7609314484 -0.2182413274 -1.4683618
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H 2.5729772633 3.719156413 1.6501387701
H 1.3904013884 2.2730789569 -2.2129965799
H 2.2282636598 4.1188845996 -0.7714223121
O 0.9768089915 -0.2626296931 -2.6580705245
O 3.5780475647 -1.2884361437 1.6930195429
O 2.5963343281 -2.2044367016 -0.0948126969

H 1.1961910985 -0.7346514972 2.3895272126

PES Fig. S2 **Pathway** A

Trans

1b-21b

H 4.3214477338 -1.2859243371 -0.690528115
N 5.1729048543 -0.8304975013 -0.2424941739
C 5.3876178339 -1.4737775155 1.0761183238
H 5.5372450693 -2.5417442753 0.9252404855
H 6.2685066802 -1.0356788793 1.5463080028
H 4.504422682 -1.3054739089 1.6885118598
C 6.3161019606 -1.0548134664 -1.1568145767
H 6.4703273383 -2.1263858262 -1.2722186605
H 6.0857627851 -0.6119390846 -2.1244248493
H 7.2098933345 -0.5921398354 -0.7375657061
C 4.8562203541 0.6100293447 -0.0941504057
H 4.6795485795 1.0353363897 -1.0801101245
H 3.9563044715 0.7066002437 0.5114587098
H 5.6951645989 1.1160378911 0.3850899542
C 0.2276862805 0.4963995112 -1.8841095604
C -1.1151936732 -0.078385972 -2.1205816526
C 0.213127353 1.2682938808 -0.7948658122
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C -1.1669442146 1.2101307691 -0.1966098596
N -1.9355486901 0.3754569647 -1.0525842456
O -1.4625502496 -0.752786701 -3.0492036075
O -1.5425204387 1.7628256066 0.7964320977
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O -3.8159465802 -0.8258252402 -1.5872426799
O -3.8990006026 0.8689540838 -0.0977719677
C -5.3297943979 0.7444341168 0.2355507752
C -6.1690276717 1.0250629213 -1.0050423541
C -5.6095564175 -0.62701173 0.8378268099
C -5.5139325696 1.8396148795 1.2774805525
H -5.8899250276 1.9864913554 -1.442889033
H -6.0503264387 0.2428122375 -1.7540684976
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H -4.9319534644 -0.81739207 1.6727967955
H -6.6341081306 -0.6419363462 1.2171856545
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H -6.5521926254 1.8516134419 1.6164077388
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H -5.2745245161 2.8169501369 0.8532200237
C 0.7878122535 -2.4670540757 -0.8480148862
C -0.2179159347 -2.308019037 0.1428699729
C 2.0417976487 -1.9322583868 -0.6632216272
C -1.5250754203 -2.8268775459 -0.0155181551
C 0.0559306983 -1.5922097402 1.3300310967
C -2.4860917264 -2.6211583757 0.9455906718
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C -0.9360980923 -1.3905732422 2.3031056519

TS C-C

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N -4.9801687729 -0.9507393547 -0.3385013827
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H -6.9981436908 -0.3641564361 -0.1775584413
C -4.6313583709 -0.0921495645 -1.5011450905
H -4.3661234897 0.8980612222 -1.1368648187
H -3.7802719228 -0.5273222117 -2.018189439
H -5.4985059032 -0.0362482952 -2.1595940065
C -0.2677925256 0.2647963729 1.8546571032
C 1.1848494177 0.1280882319 2.1874191886
C -0.3864317319 1.1377951139 0.76975463
H -0.9655157681 0.2078522805 2.6798682219
C 0.9324172564 1.3996799377 0.244563686
N 1.8702150098 0.7115867565 1.1242082654
O 1.660232267 -0.4146566399 3.1531967038
O 1.2984907832 2.1130563252 -0.6632258649
C 3.2690744196 0.6484153383 0.9721646504
O 4.0251933687 0.6147378791 1.9087138402
O 3.5791175398 0.6074209742 -0.3060928552
C 4.9690537008 0.704700512 -0.7725405998
C 5.5903132127 2.0074734762 -0.2813683955
C 5.7547559192 -0.5228143342 -0.325804127
C 4.8031577567 0.7206901484 -2.2861961821
H 4.9536115074 2.8542819466 -0.5487348335
H 5.7408896253 1.9991856778 0.7976784803
H 6.5605650691 2.1416993332 -0.7657584285
H 5.8618379975 -0.5537151268 0.7579970064
H 5.2551958246 -1.434037738 -0.6614732681
H 6.7494952946 -0.4901335082 -0.7772397118
H 5.7836807608 0.7827015737 -2.7636195098
H 4.3051060581 -0.1903045943 -2.6242051358
H 4.2056306782 1.5801805596 -2.5964950979
C -0.5427650461 -1.7562295155 1.3617562253
C 0.5015548589 -2.0574203012 0.4118171047
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C 1.7047167724 -2.6828347932 0.7845145577
C 0.3588385461 -1.6199885319 -0.9140836729
C 2.7113966401 -2.8584777672 -0.1414188026
H 1.8338029797 -3.0170382524 1.8073526954
C 1.3941810366 -1.7884940351 -1.8443794191

C 1.3989876396 -1.0929832302 1.5610220769
C -2.2029253277 -1.8920476301 2.1154018726
H -3.4832590397 -3.0192412985 0.792488598
H -0.6817096957 -0.8317206272 3.1961595663
H -2.9719103796 -1.7345205015 2.8621250037
O 1.8093697965 -0.5500801834 2.5661457972
O 3.0420651857 -1.9441172234 -1.4154048599
O 2.2886827776 -1.2570734674 0.5411651195
H 0.5848712646 -2.9961285849 -1.7687366264
C 1.2885059842 2.1087266288 -0.2575801684
C 2.1637575321 2.7445970514 -1.1454445061
C 1.4584873048 2.2927153875 1.1171030361
C 3.1912536354 3.545238486 -0.6682794871
H 2.0224608719 2.6259112822 -2.2140438099
C 2.4971219316 3.0843493992 1.5905107909
H 0.7940152795 1.802749143 1.8155172573
C 3.3624499913 3.7139193672 0.7025522751
H 3.8565723812 4.0407109615 -1.3661852733
H 2.6292390149 3.209249638 2.6588918459
H 4.165486569 4.3389450911 1.0767490862

22b-NMe$_3$
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C -0.6098405701 -1.6449094876 -1.5250779479
C 0.4993391071 0.2728037645 -0.6557622007
H 0.8915903877 -0.6318607443 -2.6271655154
C -0.7482185461 0.2009540439 -0.0939354549
N -1.4196940831 -0.9743437867 -0.6431982594
O -0.890662527 -2.6408293978 -2.1558839553
O -1.3578013647 0.9189469813 0.7448585156
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H -5.5955091347 -1.4151967355 -1.8239477439
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H -5.0573451184 1.4765209535 0.5013672486
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C 3.1780466737 -1.384633418 -1.6922755119
C 0.8376554336 -2.8937702559 0.9148758855
C 2.8242330788 -1.5685111278 1.1377120146

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H -2.8539377991 3.7269720653 -2.197966859
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N -1.157452 -0.420552 -0.950366
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O -3.339362 -0.365378 -1.446519
C -4.751773 0.026752 -1.285849
C -5.105027 0.056741 0.197115
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C -5.487567 -1.101942 -1.994842
H -4.832262 -0.889693 0.670229
H -4.602152 0.872982 0.715174
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H -6.073968 1.567934 -1.970331
H -6.564064 -0.923855 -1.945002
H -5.191869 -1.154567 -3.044869
H -5.268697 -2.060351 -1.519859
C 0.522764 -2.507246 1.042069
C -0.256585 -1.526428 1.867591
C 1.969775 -2.446195 1.471993
C -1.502321 -1.769688 2.432226
C 0.307197 -0.256542 1.946246

C 0.7847327129 -3.0331997365 2.2937460878
H 0.0808040871 -3.3662234312 0.299198845
C 2.7711336825 -1.7064014343 2.5264207963
C 3.9600573468 -0.8395812673 0.5487626305
C 1.7456101744 -2.4319961021 3.1050589991
H -0.013230934 -3.6154637221 2.7399311235
H 3.5420599209 -1.2456951734 3.1317024542
H 1.6966171167 -2.5429600372 4.1815295108
O 4.7994325375 -0.2417963117 1.1562778858
O 3.4478588697 -1.3655077513 -2.8580577725
O 4.1164577637 -0.9087586888 -0.8219768248
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C 2.3924266869 1.7337130811 -1.3448694196
C 1.5940241537 1.8800049582 0.9147723191
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H 2.3457705507 1.3034583801 -2.3402156328
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C 3.4041643293 3.302477188 0.1830602704
H 4.0160662216 3.0330310513 -1.8601475334
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H 4.1400343349 4.0700492372 0.3933328223
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H -3.4540542052 3.3487750304 0.9528117854
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23b-NMe_3

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C -0.355231 0.772667 2.60254
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C -1.597828 0.529714 3.169528
H -3.143188 -0.921111 3.522225
H 0.11596 1.743308 2.68993
H -2.12104 1.325594 3.686656
O 2.219248 1.009063 1.229343
O 2.660036 -3.397192 1.725398
O 2.487039 -1.201156 1.543612
H 0.160489 -3.527318 1.148961
H 1.502219 2.50588 0.654706
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H 2.691750047 -4.6232900172 3.1077276503

H -1.3212186035 -5.6295364119 1.9845176202
H 0.8375005977 -6.2682889762 3.028930269

Cis

1b-21a

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22a-NMe$_3$

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TS cyclisation

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O -0.3648626688 -0.5213814409 -2.4400937664

O -0.9515394589 -2.3518062917 -3.5813795702

Table S4. DFT Optimised Geometries (Cartesian Coordinates in Å) of the Constrained Transition States in PCM-THF.

TSC-C 1a-26 constrained geometry (ΔG= 25.3 Kcal/mol)
C -0.6138732975 1.1888247511 -1.8328027366
C 0.8837319022 1.2687901462 -1.9322399825
C -0.932271974 -0.1251401043 -1.3822437848
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C 0.2720677247 -0.8736412967 -1.1976163748
H -1.866430448 -0.6272349879 -1.5676241601
N 1.3670190446 0.0602916311 -1.4236266367
O 1.5379626823 2.2054952813 -2.3157958912
O 0.4437215695 -2.047245551 -0.9468559862
C 2.7317115366 -0.179686056 -1.1583332478
O 3.6195527504 0.2945523038 -1.817993527
O 2.8435865817 -0.9537991006 -0.1004414114
C 4.1409637781 -1.459432392 0.3677702197
C 4.8272147286 -2.2557091147 -0.7365150861
C 4.9898773175 -0.2956769893 0.8654542107
C 3.736711992 -2.37296171 1.5171474058
H 4.1536396923 -3.0243885349 -1.1232506151
H 5.1467777682 -1.6135862529 -1.5562612007
H 5.7071746035 -2.7503115671 -0.3180530093
H 4.4421942564 0.2766456419 1.6178396144
H 5.8996032809 -0.6883064508 1.3264414697
H 5.2705985956 0.3678530916 0.0479783971
H 4.6288955783 -2.8096024858 1.9716284036
H 3.1947364098 -1.8104620078 2.2799139858
H 3.0947644478 -3.1788413369 1.1554764921
C -0.9117914148 2.4883060854 -0.3419665464
C -0.0805881269 1.9629139357 0.7247480528
C -2.3425600168 2.2239656468 -0.2322099416
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C -0.4484084037 0.7194030719 1.252037439
C 1.9062056436 1.9180212629 2.0827191822
H 1.4241353561 3.5043365383 0.7181128452
C 0.3622385778 0.0687333491 2.1886489271
C -1.6863728799 0.1142672659 0.7665993907
C 1.5268287234 0.6764538621 2.6102608244
H 2.8274455592 2.3840876595 2.4138876246
H 0.0614911938 -0.899645044 2.5691244652
H 2.1547810536 0.190703772 3.3480250483
O -2.1147561796 -0.9905721658 1.1055562241
O -3.2450215435 2.9142389413 -0.6427791335
O -2.6621214361 1.0154382409 0.3225110748
H -0.6728376314 3.4661136634 -0.7439260098
H -3.5176964608 -1.5154318702 0.4409121302
N -4.4110954356 -1.9283047234 0.0595664743
C -5.4088774422 -0.8318628367 -0.0138988856
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H -4.0326880691 -3.7363875245 1.0658304498
H -4.9712324816 -2.5406550492 1.9932252427
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H -3.2932734277 -3.2032356423 -1.1885120085
H -5.0028926154 -2.9928969274 -1.6617591914

TSC-C 1a-14 constrained geometry (ΔG= -13.7 Kcal/mol)
C -0.0252219184 -1.9500629713 -1.6073160405
C -1.438011962 -1.5649979602 -1.2611885372
C 0.7335504053 -0.7411319229 -1.6416954479
H 0.0926670796 -2.745934568 -2.3340301401
C -0.1317416265 0.3478930269 -1.3191108231
H 1.6282452822 -0.5881488108 -2.2234140308
N -1.4179604717 -0.2040611453 -1.0140192851
O -2.4023223735 -2.2931665712 -1.1750360878
O 0.0903607262 1.5497160279 -1.276428341
C 0.452563757 -2.9648326649 0.0472612283
C 0.1986234024 -2.0137696457 1.1134362722
C 1.8594128953 -3.1581087257 -0.3054264322
C -0.8790452082 -2.1009619131 2.005554707
C 1.0317865708 -0.8910053884 1.1562896702
C -1.0796107723 -1.1050792142 2.9416303403
H -1.5461346709 -2.9541238545 1.9561123433
C 0.8210442417 0.116213229 2.1036918636
C 2.1210278971 -0.8042117652 0.1804470645
C -0.2216858535 0.0014466881 3.0007487508
H -1.9052502201 -1.1815893304 3.6397437678
H 1.498573534 0.9602544592 2.1423678382
H -0.3795156082 0.7671307209 3.7514814781
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O 2.3663325488 -4.1768992061 -0.7103681244
O 2.6356907491 -2.0362428337 -0.2356979788
H -0.1371420447 -3.8737575392 0.0207982661
H 2.5050814875 1.8300669718 -0.0854002312
N 2.6732174911 2.8519593935 -0.2012477903
C 2.7050900497 3.1181840212 -1.6767121379
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H 1.9515385076 3.8607486462 -1.9262467515
H 3.6907924488 3.4850370249 -1.9544941103
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H 3.920657019 2.8558110527 1.4965287478
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H 1.5937301032 3.3349804602 1.5425387714

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C -2.3877703459 1.4184629596 0.5117550041
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H -5.7983399342 1.089022623 -1.2771034891
H -3.3597993373 2.8424756599 1.7841636259
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References

1. Cornaggia, C.; Manoni, F.; Torrente, E.; Tallon, S.; Connon, S. J., A Catalytic Asymmetric Reaction Involving Enolizable Anhydrides. *Org. Lett.* **2012,** *14* (7), 1850-1853.
2. Manoni, F.; Cornaggia, C.; Murray, J.; Tallon, S.; Connon, S. J., Catalytic, enantio- and diastereoselective synthesis of [gamma]-butyrolactones incorporating quaternary stereocentres. *Chem. Commun.* **2012,** *48* (52), 6502-6504.
3. Wu, G.; Deng, Y.; Wu, C.; Zhang, Y.; Wang, J., Synthesis of α-Aryl Esters and Nitriles: Deaminative Coupling of α-Aminoesters and α-Aminoacetonitriles with Arylboronic Acids. *Angew. Chem. Int. Ed.* **2014,** *53* (39), 10510-10514.
4. Tan, D. Q.; Atherton, A. L.; Smith, A. J.; Soldi, C.; Hurley, K. A.; Fettinger, J. C.; Shaw, J. T., Synthesis of a γ-Lactam Library via Formal Cycloaddition of Imines and Substituted Succinic Anhydrides. *ACS Combinatorial Science* **2012,** *14* (3), 218-223.
5. Cava, M. P.; Deana, A. A.; Muth, K.; Mitchell, M. J., Fluoride ion catalyzed hydrolysis of carboxylic anhydrides. *Org. Synth.* **1961,** *41*, 93.
6. Garad, D. N.; Tanpure, S. D.; Mhaske, S. B., Radical-mediated dehydrative preparation of cyclic imides using (NH4)2S2O8–DMSO: application to the synthesis of vernakalant. *Beilstein J. Org. Chem.* **2015,** *11*, 1008-1016.
7. Sengoku, T.; Murata, Y.; Aso, Y.; Kawakami, A.; Inuzuka, T.; Sakamoto, M.; Takahashi, M.; Yoda, H., Indium-Catalyzed Amide Allylation of N-Carbonyl Imides: Formation of Azaspiro-γ-lactones via Ring Opening–Reclosure. *Org. Lett.* **2015,** *17* (23), 5846-5849.
8. Yang, Z.-H.; Chen, Z.-H.; An, Y.-L.; Zhao, S.-Y., Selective and tunable synthesis of 3-arylsuccinimides and 3-arylmaleimides from arenediazonium tetrafluoroborates and maleimides. *RSC Advances* **2016,** *6* (28), 23438-23447.
9. Claveau, R.; Twamley, B.; Connon, S. J., Dynamic kinetic resolution of bis-aryl succinic anhydrides: enantioselective synthesis of densely functionalised γ-butyrolactones. *Chem. Commun.* **2018,** *54* (26), 3231-3234.
10. Dünnebacke, D.; Neumann, W. P.; Penenory, A.; Stewen, U., Über sterisch gehinderte freie Radikale, XIX. Stabile 4,4′,4″-trisubstituierte Triphenylmethyl-Radikale. *Chem. Ber.* **1989,** *122* (3), 533-535.
11. Bruker APEX3 v2017.3-0. Bruker APEX3 v2017.3-0, Bruker AXS Inc: Madison, WI, USA. , 2017.
12. Bruker (2016/2). SADABS. Bruker SADABS v2017.3-0, Bruker AXS Inc: Madison, WI, USA. , 2016.
13. Sheldrick, G., SHELXT - Integrated space-group and crystal-structure determination. *Acta Crystallogr. Sect. A* **2015,** *71* (1), 3-8.
14. Sheldrick, G., A short history of SHELX. *Acta Crystallogr. Sect. A* **2008,** *64* (1), 112-122.

15. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H., OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* **2009,** *42* (2), 339-341.
16. Chai, J.-D.; Head-Gordon, M., Long-range corrected hybrid density functionals with damped atom-atom dispersion corrections. *Phys. Chem. Chem. Phys.* **2008,** *10* (44), 6615-6620.
17. Frisch, M. J.; Pople, J. A.; Binkley, J. S., Self-Consistent Molecular-Orbital Methods .25. Supplementary Functions for Gaussian-Basis Sets. *J. Chem. Phys.* **1984,** *80* (7), 3265-3269.
18. Ditchfield, R., Self-consistent perturbation theory of diamagnetism. *Mol. Phys.* **1974,** *27* (4), 789-807.
19. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Gaussian, Inc.: Wallingford CT, 2009.