

Supplementary Materials for
Enantioselective Total Synthesis of (+)-KB343

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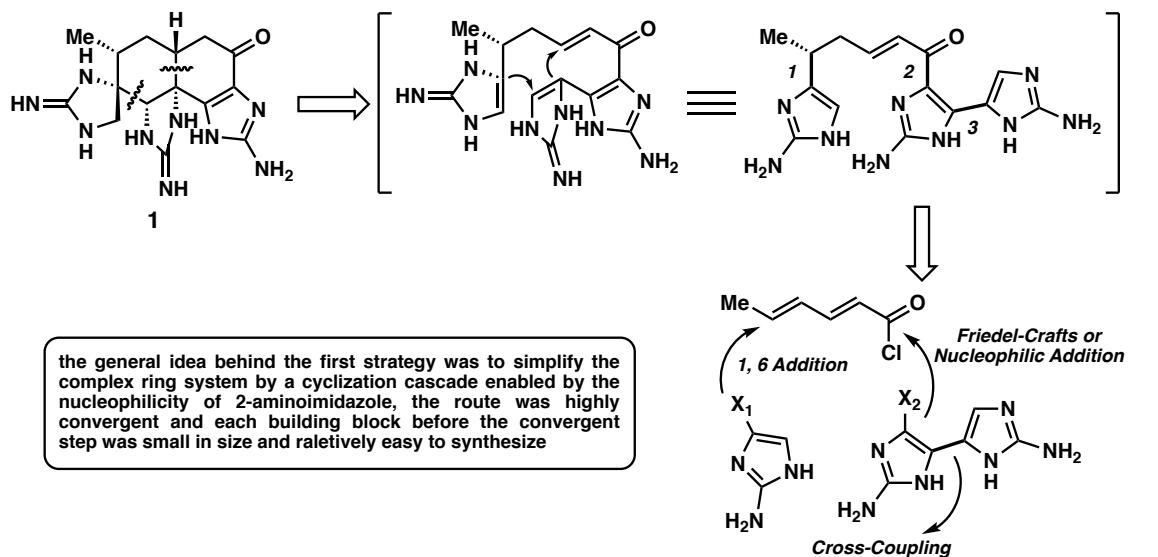
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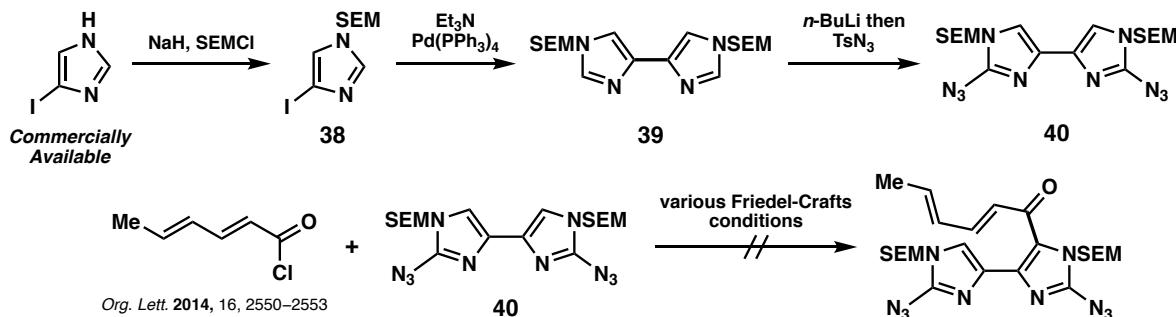
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I) Brief Summary of Failed routes

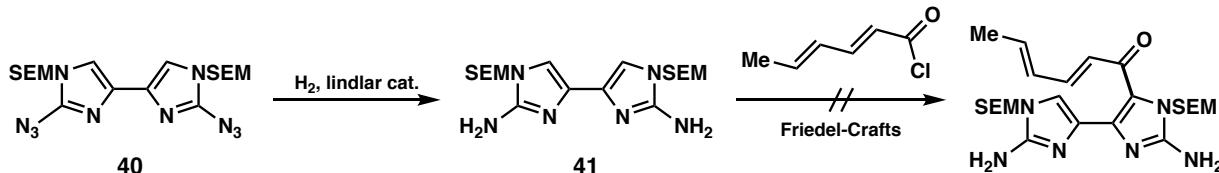
the general disconnection of the first route



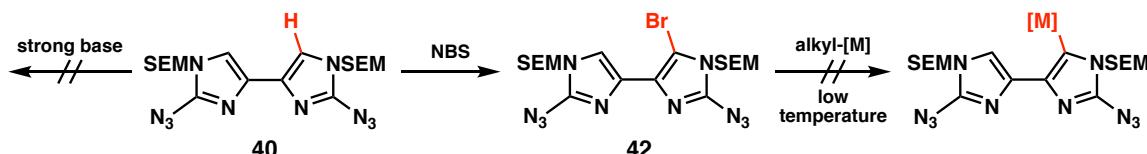
Attempts to form the bond 2



Substrate 40 failed to engage in Friedel-Crafts reaction. At ambient temperature, no conversion was observed and decomposition started to happen when elevated temperature was applied. One possible reason for the failure was that the substrate 40 was not electron-rich enough and maybe the reactivity can be improved if the azido group was reduced to free amino group.

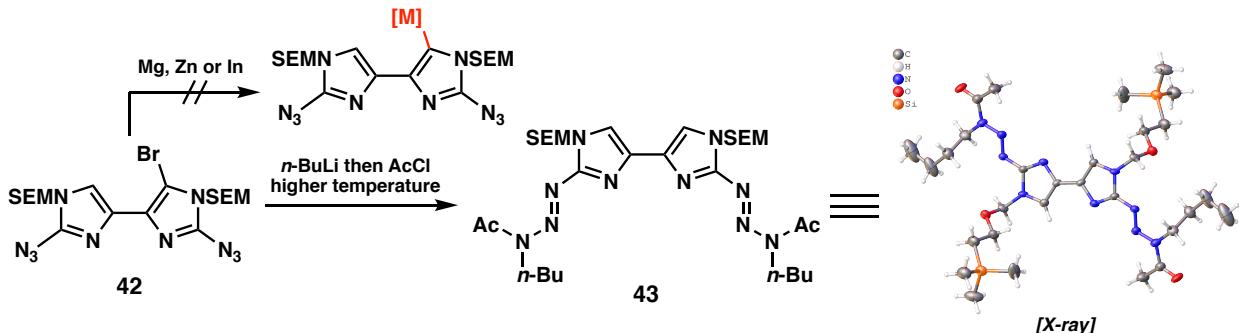


Substrate 41 turned out to be extremely difficult to handle, it's high polarity and low solubility rendered itself very hard to purify and monitor. Unfortunately, we did not observe any desired product formation under Friedel-Crafts conditions. The reaction usually turned into a black tar very quickly and the black tar did not dissolve in anything. Presumably the substrate 41 was highly sensitive and quickly decomposed into unidentifiable polymers.

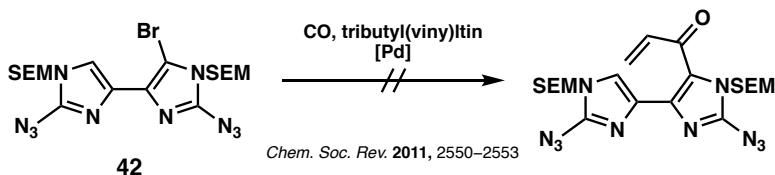


A different way to improve the nucleophilicity of 40 was to convert one of the C(sp²)-H bond into a highly polarized C(sp²)-[M] bond which should behave as an efficient nucleophile. Direct deprotonation by strong base led to either no reaction or decomposition. Alternatively, we can halogenate the C-H bond and subsequently convert it to the organometallic intermediate of interest via metal-halogen exchange mechanism. Unfortunately 42 was quite inert and no conversion was observed at low temperature (-78 °C ~ -40 °C).

Figure S1: General disconnection of Gen 1 and C-C bond formation problems



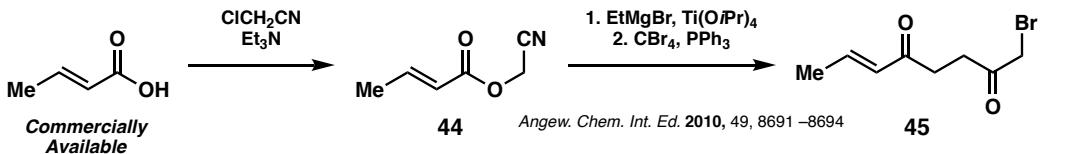
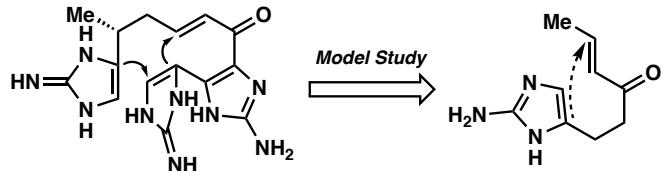
At higher temperature ($> -40^{\circ}\text{C}$), we started to observe decomposition of 42. In order to elucidate what caused the decomposition (the instability of desired intermediate or undesired reaction between 42 and strong base), we decided to trap the putative organometallic intermediate by adding AcCl into the reaction mixture. We successfully isolated a new product whose structure turned out to be 43 as shown. Direct metal insertion also failed.



The C-Br bond in 42 can also be utilized as a cross-coupling handle. Unfortunately, both carbonylative Stille-coupling and reductive cross-coupling failed to deliver any desired product.

Model study for the cyclization

We already encountered many difficulties at the early stage of the route however we have a much more important question to answer—whether the late-stage cyclization cascade was a viable design or not. We decided to test the key step on simple model substrate first.



Unfortunately, we screen a large variety of acid and base and no desired product was detected. Under forcing conditions (elevated temperature, excess activators, high concentration and etc.), we only observed decomposition. Presumably the desired product was never formed in the reaction and the 2-imidazole moiety was not stable enough for harsher conditions or desired product was formed but was not stable and quickly transformed into other byproducts.

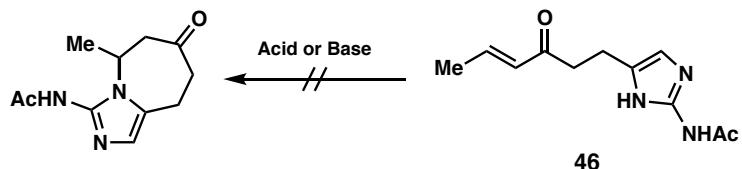
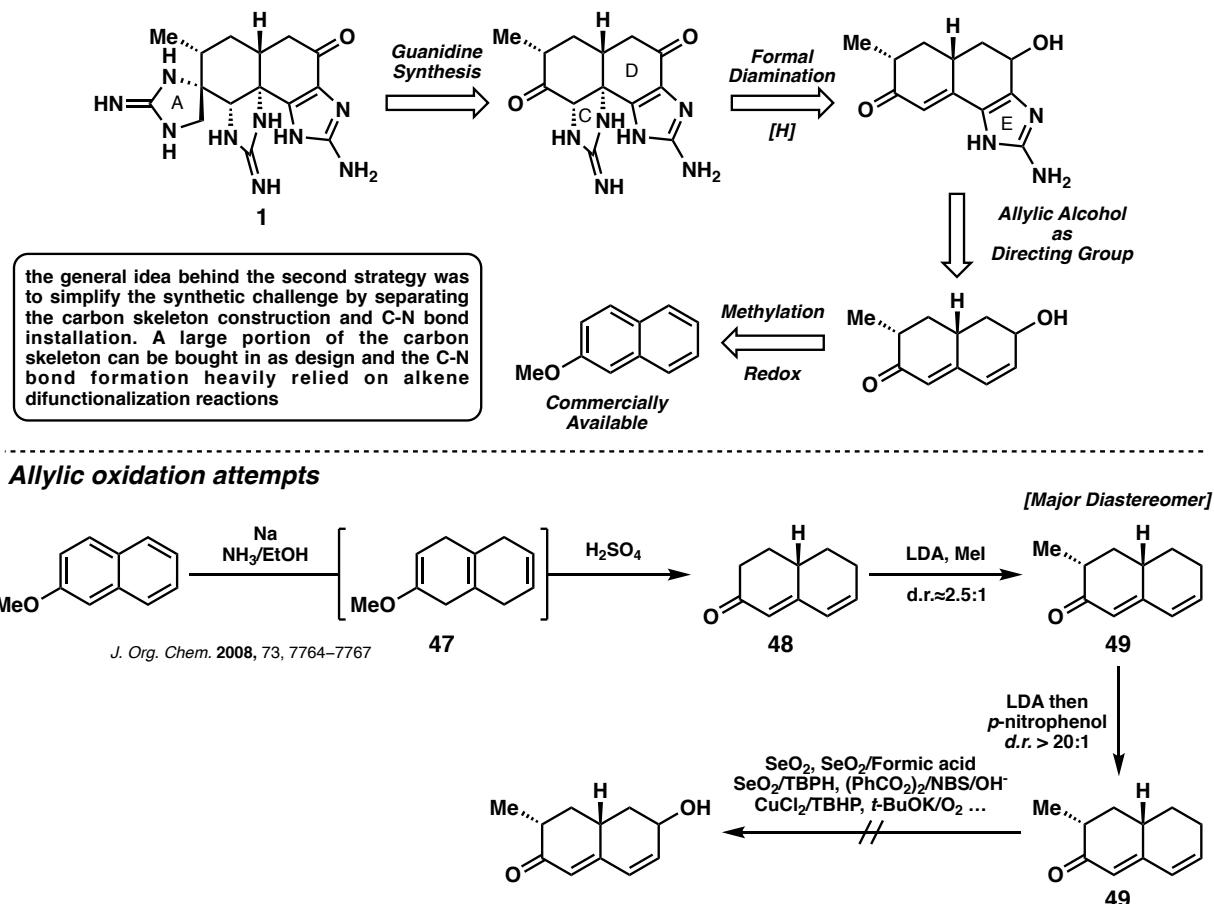
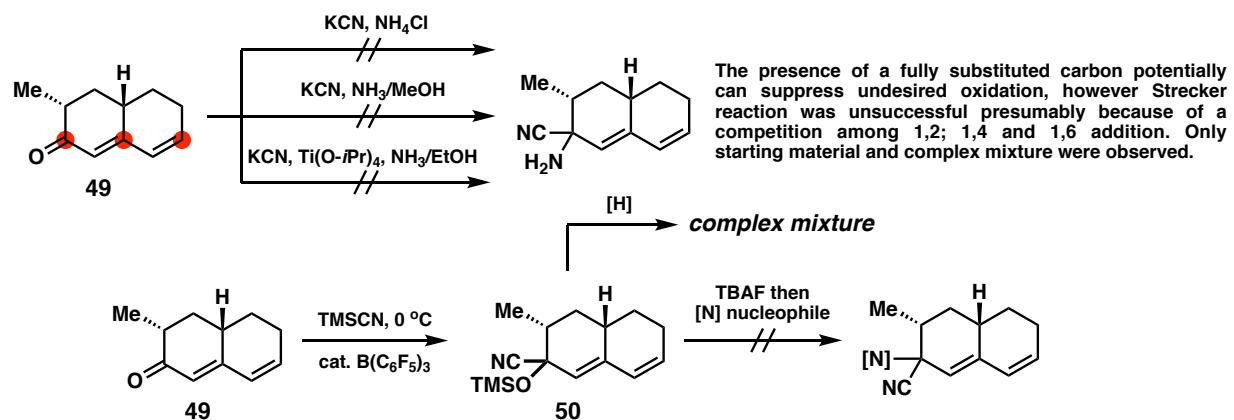


Figure S2: C-C bond formation problem and failed cyclization

the general disconnection of the second route

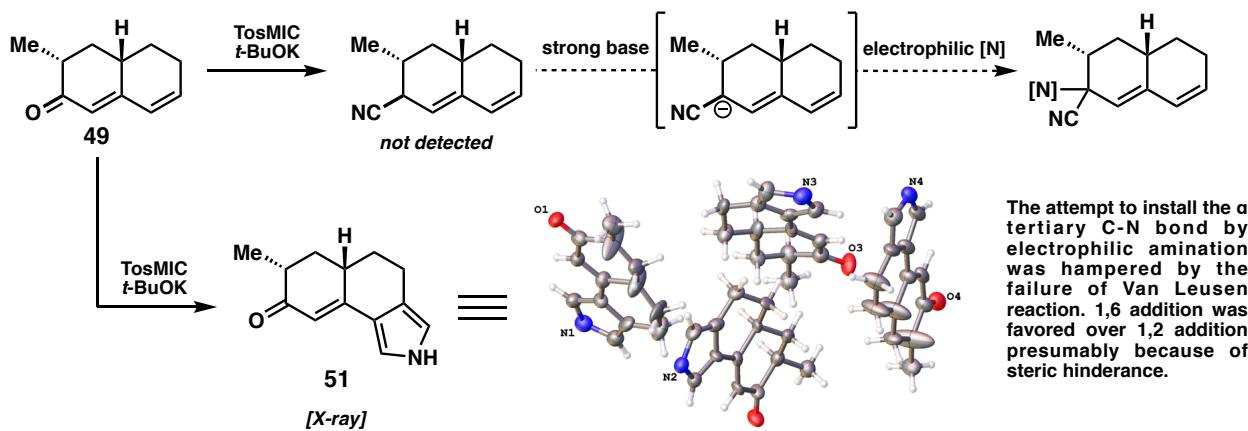


Attempts to avoid unproductive oxidation

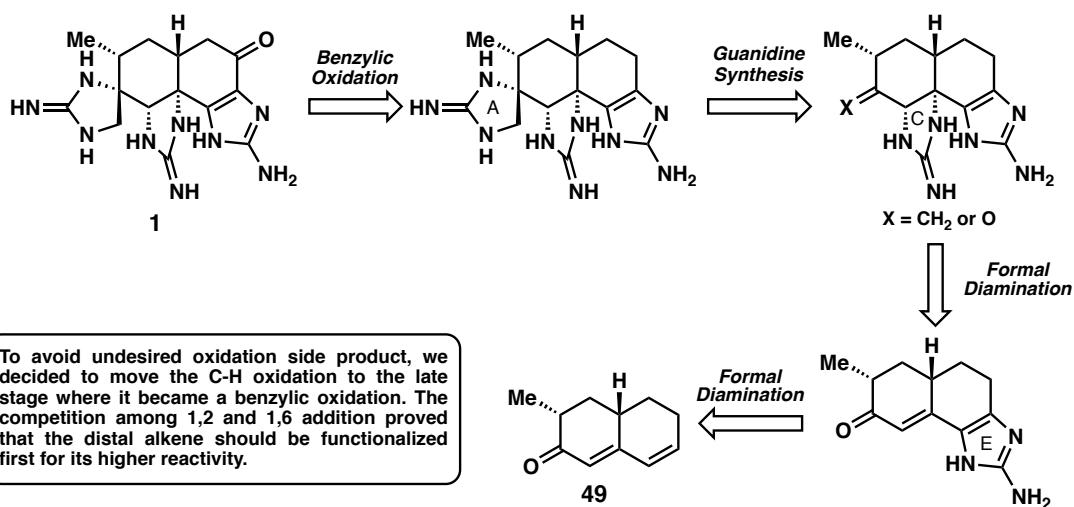


All attempts to install the α tertiary C-N bond by substitution of the tertiary alcohol failed presumably because of the steric hindrance and the electron-withdrawing cyano group. Reduction of the cyano group led to complex mixture presumably because of undesired elimination reactions.

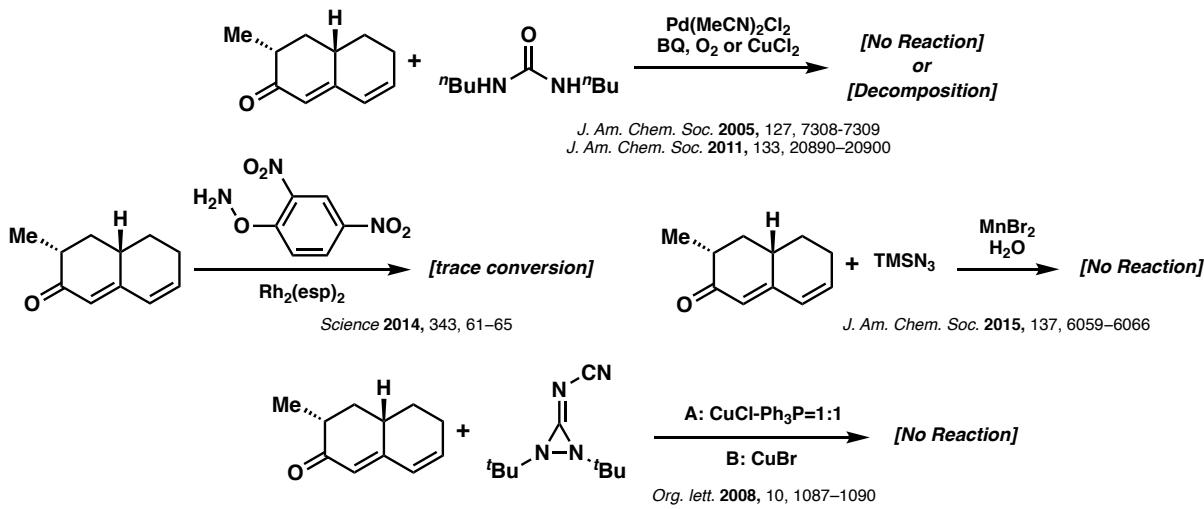
Figure S3: General disconnection of Gen 2 and oxidation problems



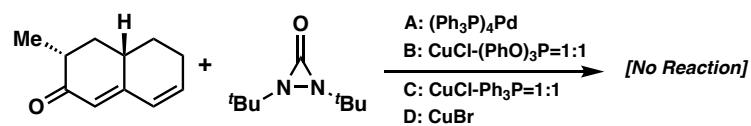
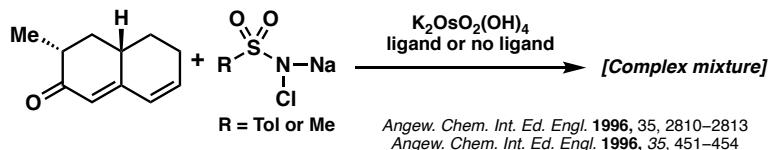
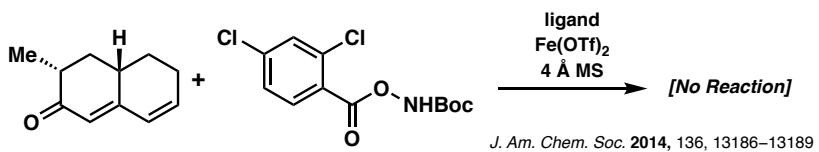
Modification of the second route



A brief summary of failed olefin (formal) difunctionalization



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Successful diazidation followed by other problems

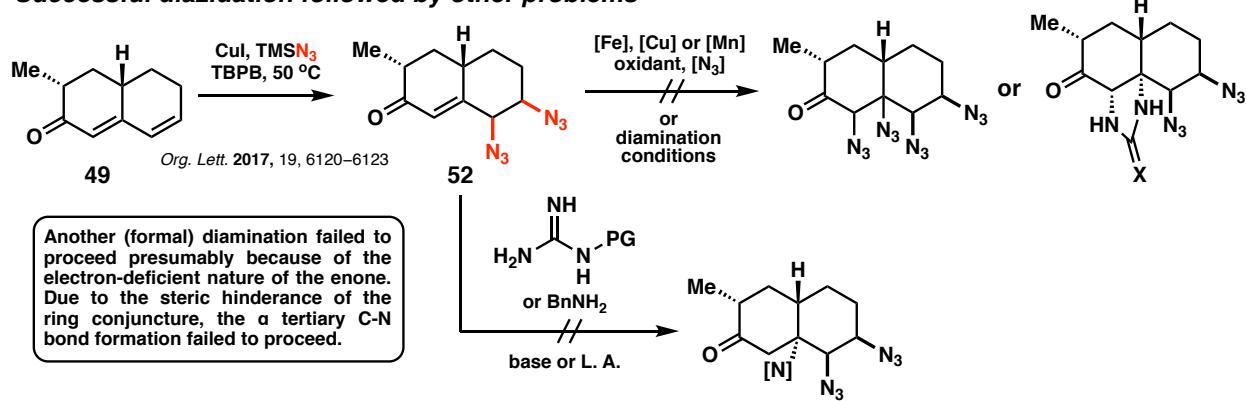
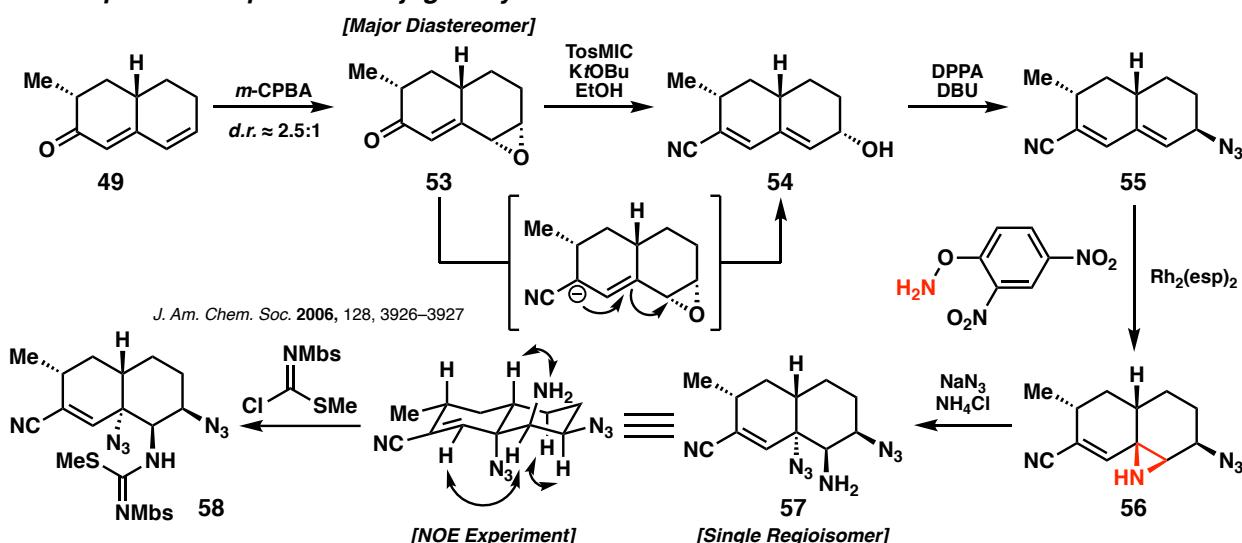


Figure S4: Difunctionalization problems

Attempts to transport the conjugate system



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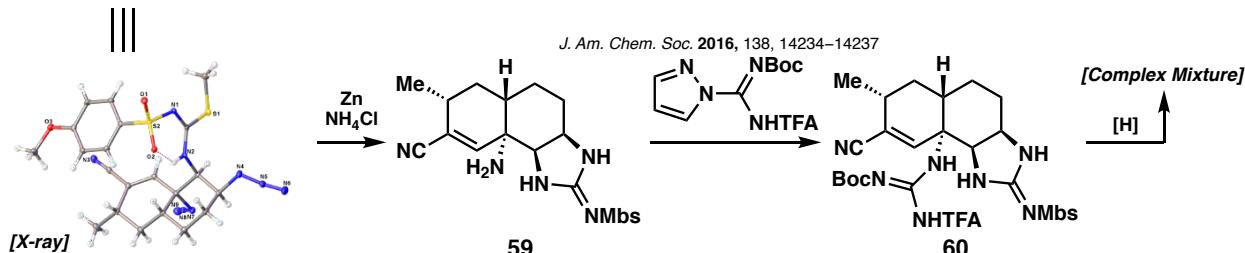
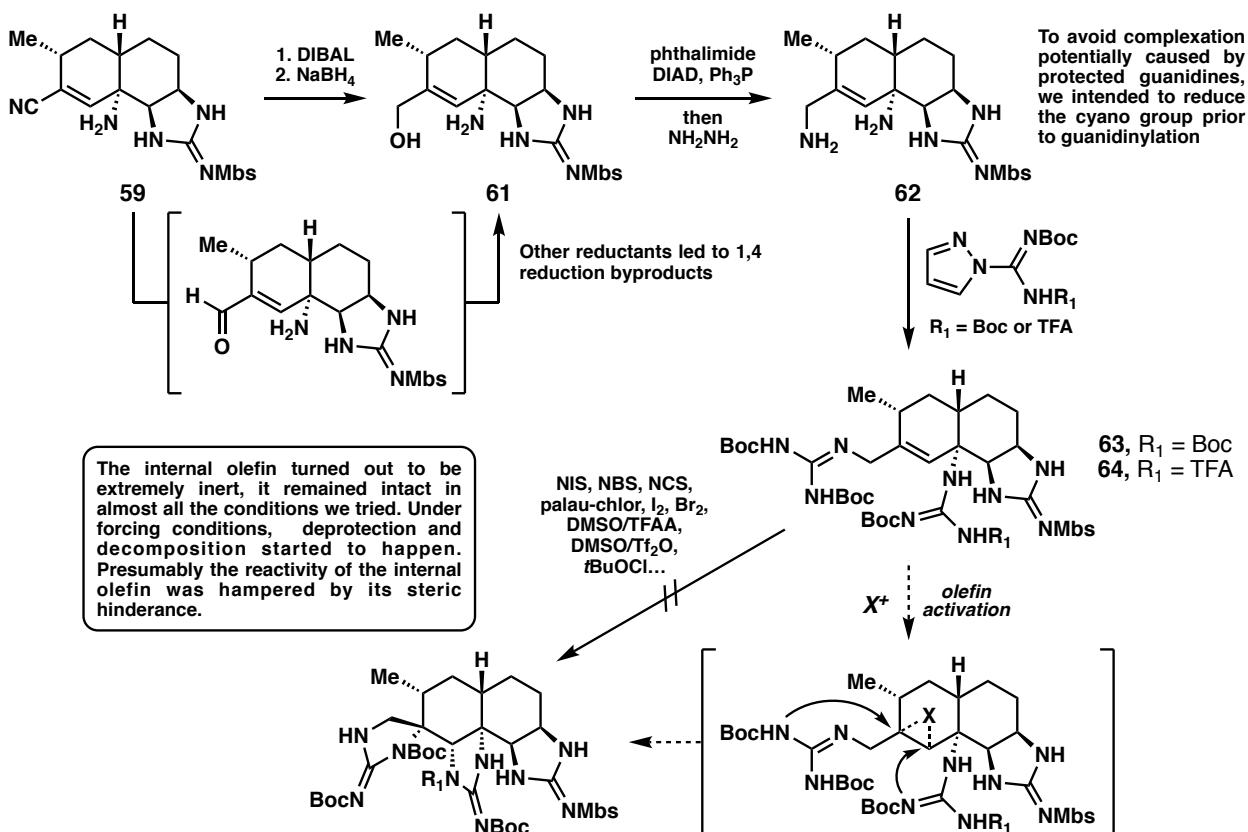


Figure S5: Olefin transportation

Double cyclization investigation



Other tactical approaches

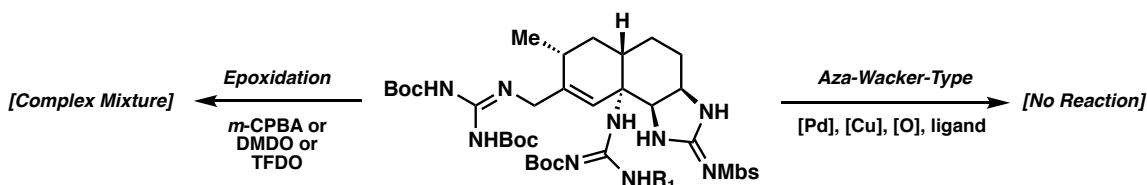


Figure S6: Double cyclization investigation

Attempts to relieve steric hinderance and following failures

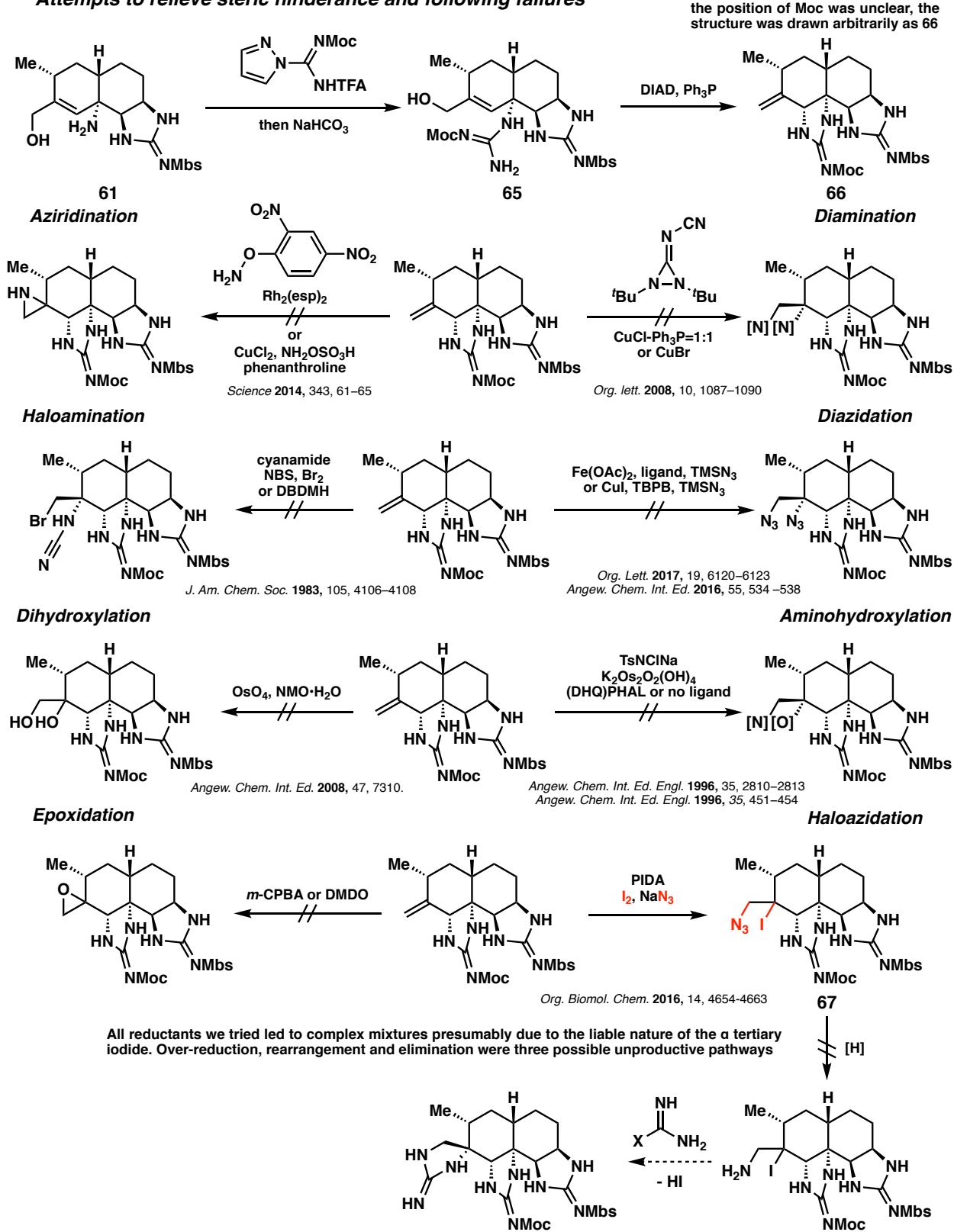
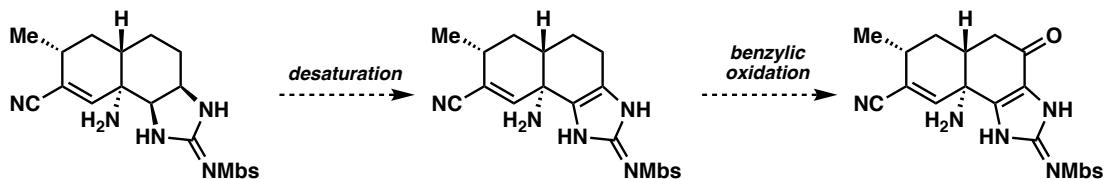


Figure S7: Exocyclic olefin functionalization

Desaturation attempts



There were two key oxidation state adjustments we needed to realize for the completion of the synthesis. The desaturation should have strong thermodynamic driving force theoretically and would set the stage for the ensuing benzylic oxidation

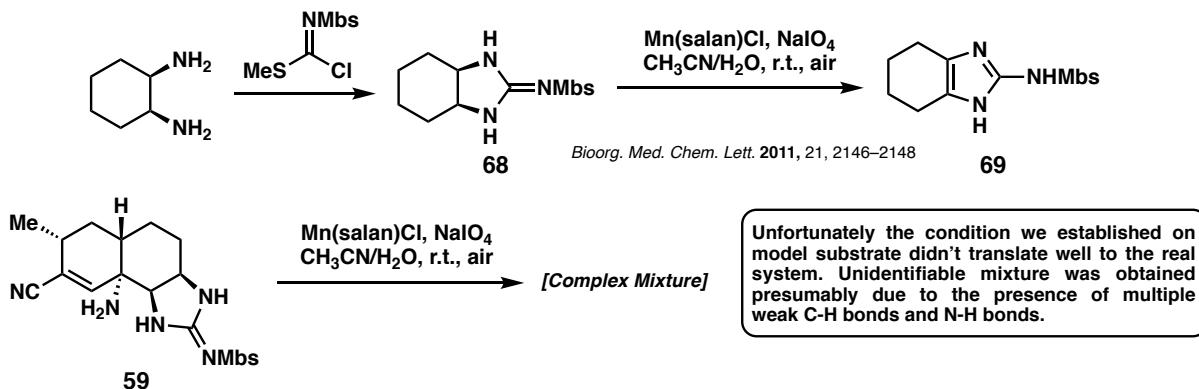


Figure S8: Desaturation attempts

the general disconnection of the third route

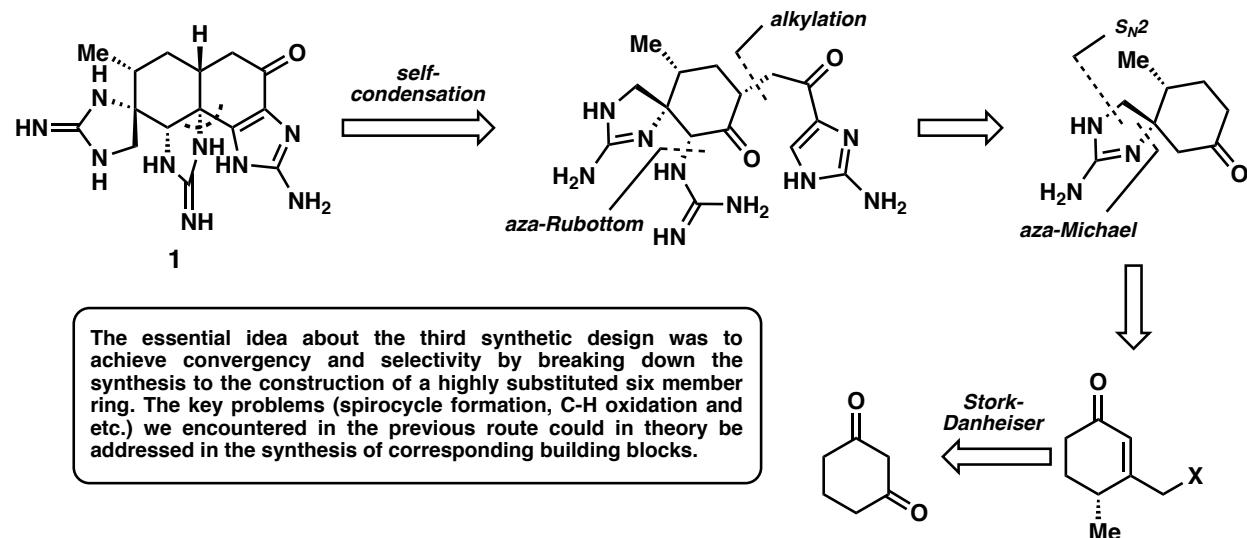
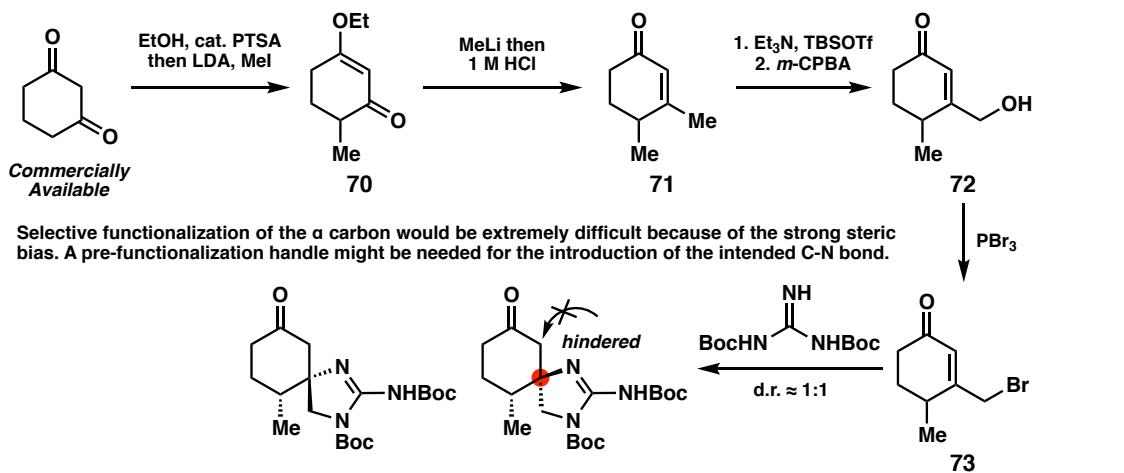
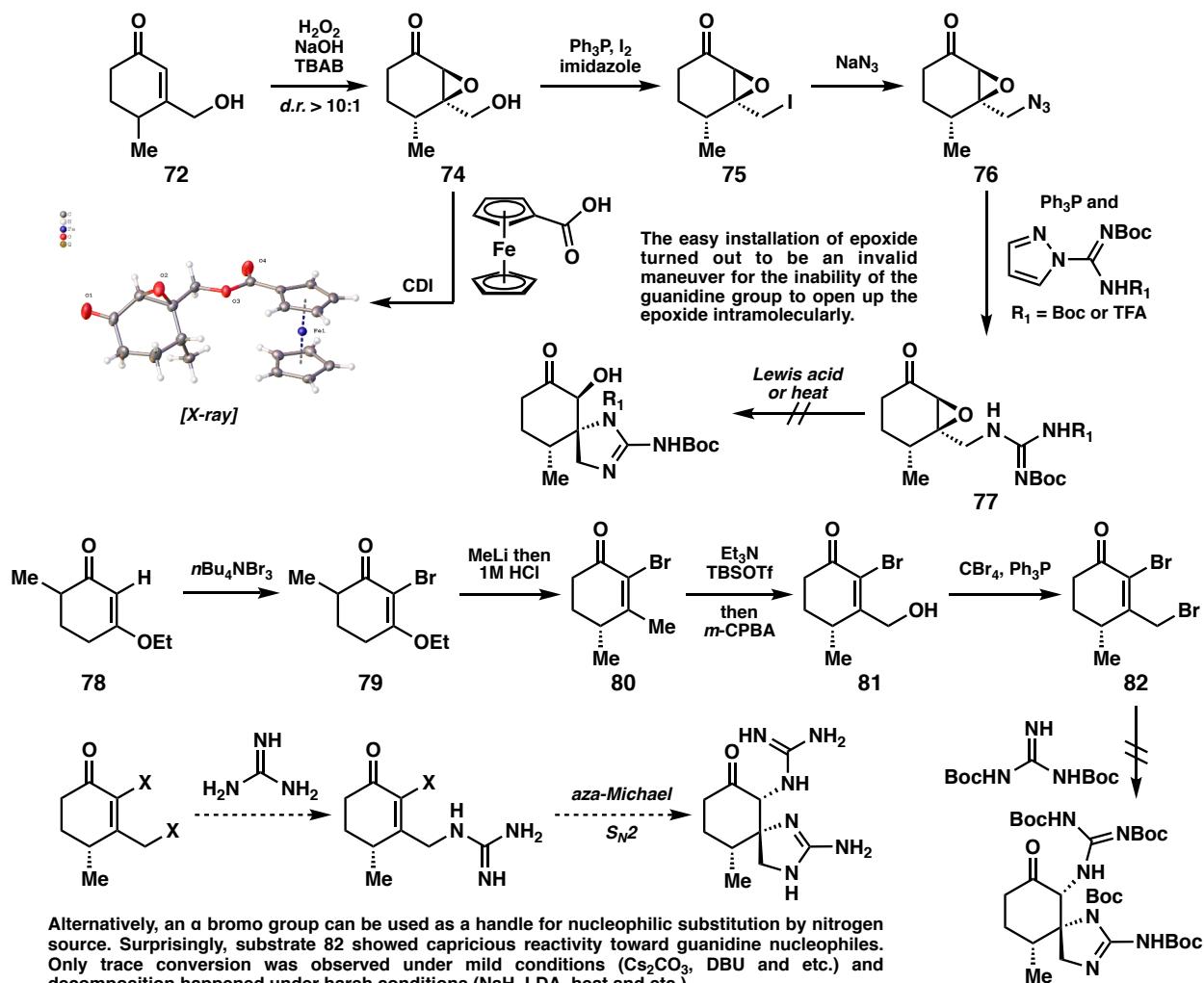


Figure S9: General disconnection of Gen 3

Spirocycle formation



Pre-functionalization handle test



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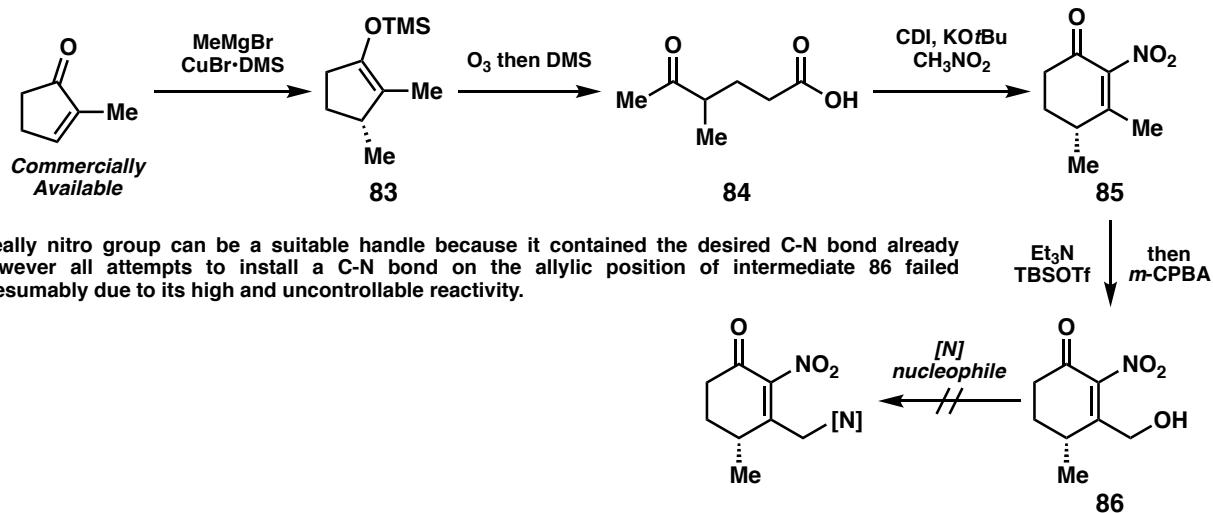
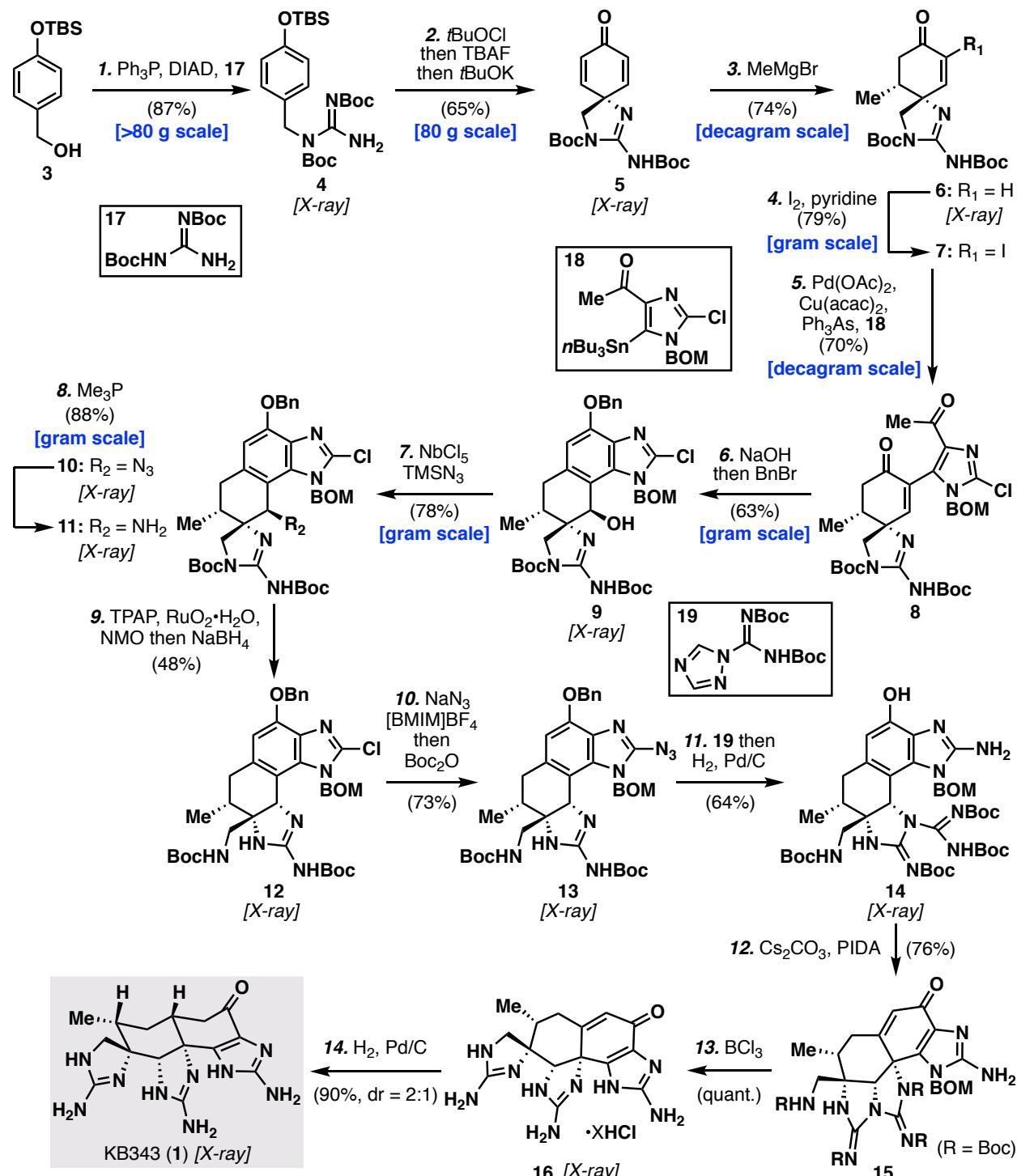


Figure S10: Problematic C-N bond formation

II) General Experimental

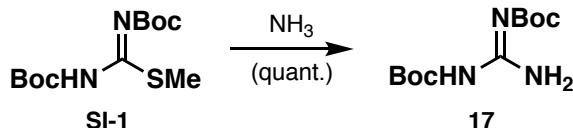
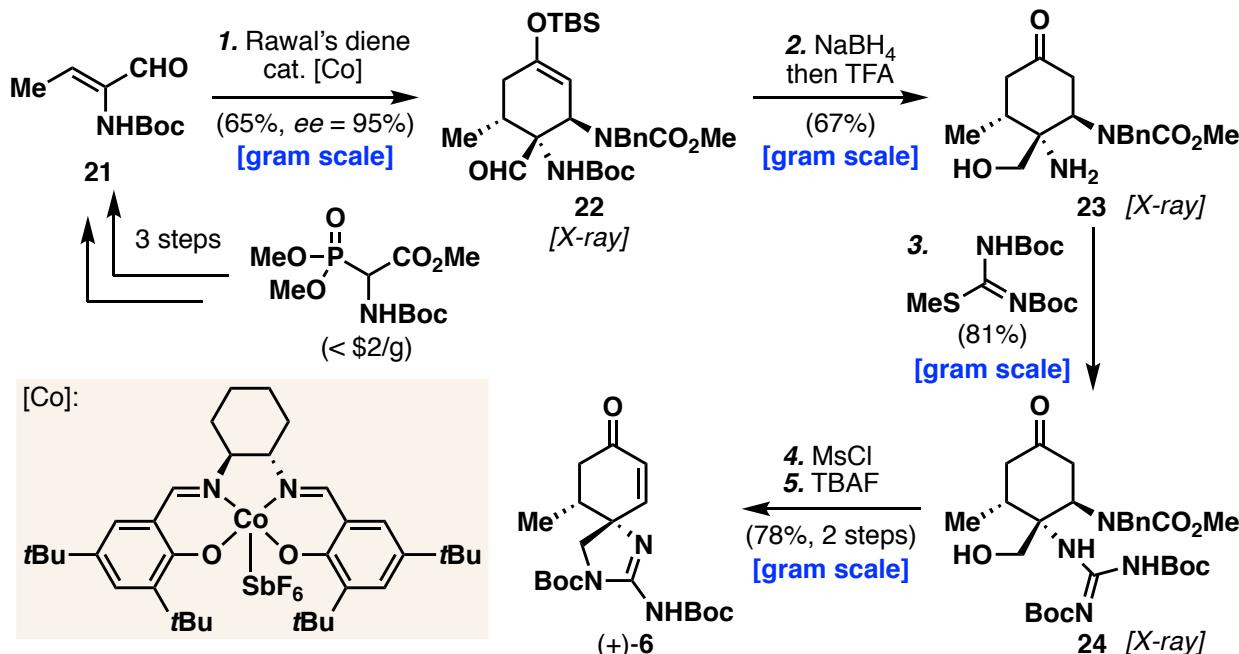
All reactions were carried out under an inert argon atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Dry acetonitrile (MeCN), dichloromethane (DCM), diethyl ether (Et₂O), tetrahydrofuran (THF), toluene (PhMe), dimethylformamide (DMF), benzene, and triethylamine (Et₃N) were obtained by passing the previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using UV light as the visualizing agent and/or phosphomolybdic acid and heat as a developing agent. Flash silica gel chromatography was performed using E. Merck silica gel (60, particle size 0.043 – 0.063 mm). NMR spectra were recorded on Bruker DRX-600 and AMX-400 instruments and were calibrated using residual undeuterated solvent as an internal reference (CDCl₃: ¹H NMR δ = 7.26 ppm, ¹³C NMR δ = 77.16 ppm; acetone-d₆: ¹H NMR δ = 2.05 ppm, ¹³C NMR δ = 49.84 ppm; CD₃OD: ¹H NMR δ = 3.31 ppm, ¹³C NMR δ = 49.00 ppm). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = quint, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time-of-flight (ESI-TOF) reflectron experiments. Phenomenex Luna C18 column (250*4.6 mm) and H₂O/MeCN/TFA were used as stationary and mobile phase respectively for HPLC purification.

III) Experimental Details of the Final Route



Reagents and conditions: (1) Ph_3P (1.15 equiv), DIAD (1.15 equiv), **17** (1.1 equiv) THF, 0 °C to rt, 3 h. (2) $t\text{BuOCl}$ (1.05 equiv), TBAF (1.05 equiv), $t\text{BuOK}$ (1.05 equiv), THF, rt, 8 to 10 h. (3) MeMgBr (5 equiv), THF/HMPA (6.5:1), -40 °C to 0 °C, 1 h. (4) I_2 (1.5 equiv), pyridine, rt, 24 h. (5) $\text{Pd}(\text{OAc})_2$ (0.12 equiv), $\text{Cu}(\text{acac})_2$ (0.6 equiv), Ph_3As (0.24 equiv), **18** (1.35 equiv), THF, 64 °C, 14 h. (6) NaOH (1.5 equiv), $\text{THF}/\text{H}_2\text{O}$ (1:1), 0 °C to 15 °C, 10 h then BnBr (4 equiv), 15 °C, 3 h. (7) NbCl_5 (0.25 equiv), TMSN_3 (12 equiv), MeCN/DCM (7:1), rt, 21 h. (8) Me_3P (2 equiv), NaOH (1 equiv), THF/H₂O (4:1), 0 °C, 40 min. (9) NMO (5 equiv), $\text{RuO}_2 \cdot \text{H}_2\text{O}$ (1.2 equiv), TPAP (0.7 equiv), 4 Å MS (50 w%), DCM, rt, 1 h then 4 Å MS (50 w%), DCM, rt, 1 h.

NaBH_4 (5 equiv), MeOH , 0°C , 15 min. (10) NaN_3 (50 equiv), $[\text{BMIM}] \text{BF}_4^-$, 70°C , 21 h then Boc_2O (3 equiv), Et_3N (5 equiv), DCM , 0°C , 40 min. (11) 19 (2.3 equiv), MeNO_2 , 60°C , 18 h then H_2 (1 atm), Pd/C (10 wt.%), MeOH , rt, 2.5 h. (12) Cs_2CO_3 (1.05 equiv), PIDA (1.05 equiv), HFIP, 0°C , 1 h. (13) BCl_3 (6.5 equiv), DCM , 0°C , 1 h then MeOH , rt, 24 h. (14) H_2 (1 atm), Pd/C (5 wt.%), TfOH (5 equiv), MeOH , -10°C , 15 d. Abbreviations: DIAD = diisopropyl azodicarboxylate; TBAF = tetra-*n*-butylammonium fluoride; TPAP = tetrapropylammonium perruthenate; NMO = N-methylmorpholine N-oxide; $[\text{BMIM}] \text{BF}_4^-$ = 1-butyl-3-methylimidazolium tetrafluoroborate; PIDA = (diacetoxyiodo)benzene; THF = tetrahydrofuran; HMPA = hexamethylphosphoramide; DCM = dichloromethane; MS = molecular sieve.



Experimental: To a 2 L round bottom flask fixed with a stir-bar, was added **SI-1** (150.0 g, 517.0 mmol) then MeOH (600 ml) and THF (400 ml) were added. The mixture was stirred at room temperature and NH_3 gas was bubbled into the mixture till all solids were dissolved then moved the flask into an oil bath and heat it to 50°C for 12 h (open air). Upon completion, the flask was removed from the oil bath and allowed to cool. The solvent was then removed under reduced pressure to give a huge chunk of white solid. Smash the aforementioned solid with a big spatula then leave the solid under high vacuum

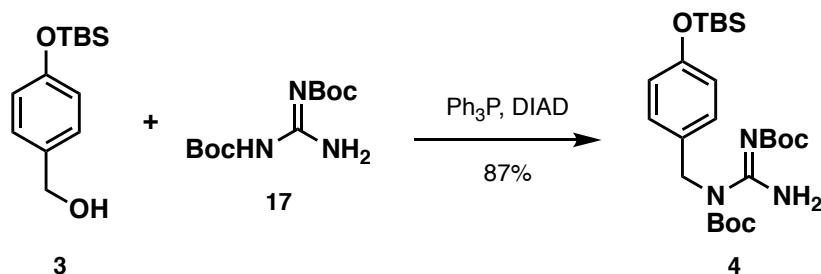
overnight to remove residual solvent. The desired product **17** (134.0 g, quantitative yield) was obtained and used directly in the next step without further purification.

Physical State: white solid;

m.p.: 131-133 °C;

R_f Value: 0.37 (ethyl acetate:hexane = 1:2);

The ¹H and ¹³C NMR spectra and HRMS data match with reported data in *J. Org. Chem.* **1998**, *63*, *12*, 3804-3805.



Experimental: **3** (83.3 g, 350.0 mmol), **17** (99.8 g, 385.0 mmol, 1.1 eq), triphenylphosphine (105.6 g, 402.5 mmol, 1.15 eq) and dry THF (1.2 L, 0.29 M) were added to a flame-dried 2 L round bottom flask fixed with a stir-bar. Backfill the flask with argon and cool it down to 0 °C. Start stirring at 0 °C. Start adding DIAD (81.4 g, 402.5 mmol, 1.15 eq) dropwise when the mixture became homogeneous. After the addition of DIAD was completed, the flask was warmed up to room temperature gradually. Upon completion (it usually takes about 2 to 3 hours), the solvent was then removed under reduced pressure to give the crude reaction mixture as a yellow oil. The crude product was purified via flash column chromatography (ethyl acetate and hexane as the eluents) yielding **4** (145.9 g, 87% yield) as a white solid.

Physical State: white solid;

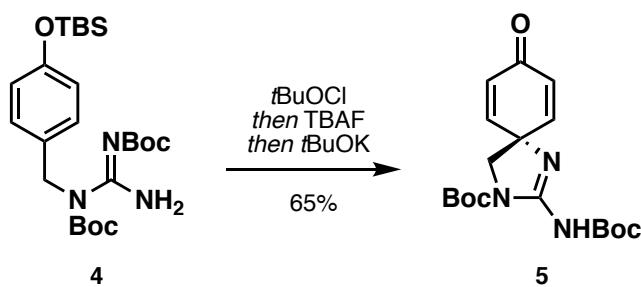
m.p.: 106-108 °C;

R_f Value: 0.83 (ethyl acetate:hexane = 1:2);

¹H NMR (600 MHz, CDCl₃) δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 5.09 (s, 2H), 1.49 (s, 9H), 1.32 (s, 9H), 0.97 (s, 9H), 0.17 (s, 6H).;

¹³C NMR (151 MHz, CDCl₃) δ 164.0, 161.1, 155.2, 154.7, 131.9, 128.4, 119.9, 84.0, 79.0, 47.2, 28.5, 27.9, 25.8, 18.4, -4.3 ppm.;

HRMS (m/z) calc'd for C₂₄H₄₂N₃O₅Si⁺ [M+H]⁺ 480.2888, found 480.2878



Experimental: **4** (80 g, 166.9 mmol) and dry THF (900 ml, 0.19 M) were added to a flame-dried 2 L round bottom flask fixed with a stir bar then the flask was backfilled with argon. Start stirring at room temperature and add *t*BuOCl (19.0 g, 175.3 mmol, 1.05 eq) in one portion when the mixture became homogeneous. After the completion of the addition of *t*BuOCl, wait for 20 mins then add TBAF in one portion (175.3 ml of 1 M solution in THF, 1.05 eq). Wait for another 30 mins then add *t*BuOK (175.3 ml of 1 M solution in THF, 1.05 eq) in one portion and let the reaction keep stirring for 8 to 10 hours. Upon completion, sat. NH₄Cl solution was added into the reaction mixture and the organic layer and the aqueous layer were separated. The aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with brine then dried over MgSO₄. After removing MgSO₄ by filtration, the solvent was removed under reduced pressure to give the crude reaction mixture as a yellow oil. The crude product was purified via flash column chromatography (ethyl acetate and hexane as the eluents) yielding **5** (39.4 g, 65% yield) as an off-white solid.

Physical State: off-white solid;

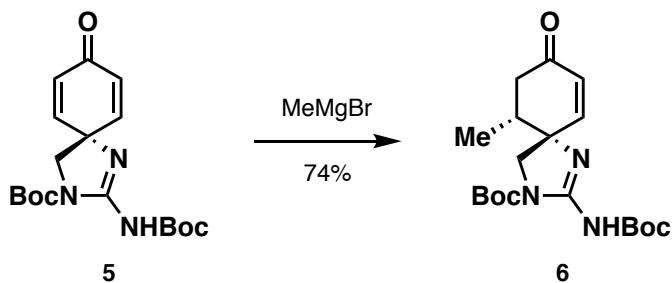
m.p.: 126-128 °C;

R_f Value: 0.12 (ethyl acetate:hexane = 2:3);

¹H NMR (600 MHz, CDCl₃) δ 6.76 (d, *J* = 10.0 Hz, 2H), 6.22 (d, *J* = 10.0 Hz, 2H), 3.74 (s, 2H), 1.53 (s, 9H), 1.49 (s, 9H).;

¹³C NMR (151 MHz, CDCl₃) δ 185.3, 152.0, 152.0, 149.3, 149.1, 128.3, 84.6, 82.3, 63.9, 53.1, 28.12, 28.10 ppm.;

HRMS (m/z) calc'd for C₁₈H₂₆N₃O₅⁺ [M+H]⁺ 364.1867, found 364.1873



Experimental: The cyclized product **5** (11 g, 30.3 mmol) was placed in a flame-dried 1 L round bottom flask fixed with a stir bar. The flask was placed under vacuum and backfilled with argon. Dry THF (525 ml) and dry HMPA (81 ml) were added into the flask via syringe. Start stirring at room temperature and then cool the reaction down to -40 °C after the mixture became homogeneous. Add methylmagnesium bromide (50.5 ml of 3 M solution in Et₂O, 5 eq) dropwise into the mixture. Wait for 30 mins after the completion of the addition of methylmagnesium bromide then warm the reaction mixture up to 0 °C. Wait for another 30 mins then add sat. NH₄Cl solution to quench the reaction. Extract the aqueous layer with ethyl acetate twice then combine all organic layers which were then washed with 10% LiCl solution for three times.

The organic layer was first dried over MgSO₄ which was then removed by filtration. The solvent was removed under reduced pressure to give the crude reaction mixture as a yellow solid. Add ethyl acetate (35 ml) and hexane (175 ml) into the resulting solid and heat the mixture with a heat gun to dissolve the solid as much as possible. Let the mixture cool down to room temperature gradually and wait for an hour (white solid will precipitate). Filter the mixture to collect some product as white solid (6.0 g) and the filtrate was concentrated under reduced pressure. The residual crude material was purified by flash

column chromatography (acetone and hexane as eluents) to yield desired product (2.5 g). The combined yield is 74%.

Physical State: white solid;

m.p.: >220 °C (decomp.);

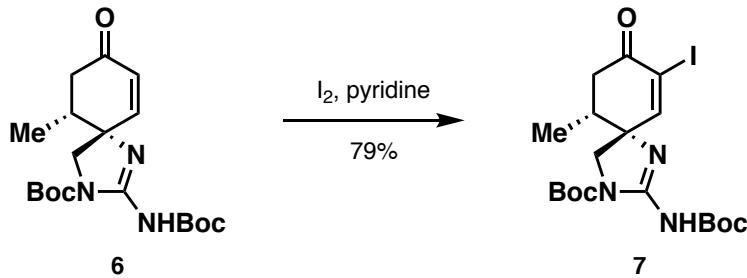
R_f Value: 0.18 (ethyl acetate:hexane = 2:3);

¹H NMR (600 MHz, CDCl₃) δ 6.55 (d, J = 10.0 Hz, 1H), 6.02 (d, J = 10.0 Hz, 1H), 3.93 – 3.43 (br, 2H), 2.82 (s, 1H), 2.38 (s, 1H), 2.18 (s, 1H), 1.54 (s, 9H), 1.50 (s, 9H), 0.98 (d, J = 6.6 Hz, 3H);

¹³C NMR (151 MHz, CDCl₃) δ 199.7, 152.2, 151.3, 149.5, 146.8, 129.0, 84.0, 81.9, 66.8, 54.5, 42.4, 39.0, 28.2, 15.1 ppm. (two peaks belonging to the two Boc tert-butyl groups overlap);

Optical Rotation: [α]_D²⁵ = +107.5° (c = 0.24 g / 100 mL, CHCl₃);

HRMS (m/z) calc'd for C₁₉H₃₀N₃O₅⁺ [M+H]⁺ 380.2180, found 380.2188



Experimental: **6** (1.5 g, 4.0 mmol) was added into a flame-dried 50 ml round bottom flask fixed with a stir bar. The flask was placed under vacuum and backfilled with argon. Dry pyridine (10 ml) was added into the flask via syringe. Start stirring at room temperature and wait for 10 mins add iodine (1.51 g, 5.9 mmol, 1.5 eq) into the flask in one portion. Keep stirring for 24 h then add sat. Na₂SO₃ to quench the reaction. The aqueous layer was separated and extracted with ethyl acetate twice. Combine all the organic layers and removed the solvent under reduced pressure. The crude reaction mixture was dissolved in ethyl acetate (65 ml) and HCl solution (0.5 M in H₂O) was added at room temperature dropwise into the mixture till the pH value of the organic layer turned 7 to 8. The aqueous

layer was discarded and the organic layer was dried over MgSO_4 first then concentrated under reduced pressure and the resulting material was purified by flash column chromatography (ethyl acetate and hexane as eluents) to yield **7** (1.58 g, 79% yield).

Physical State: off-white solid;

m.p.: >220 °C (decomp.);

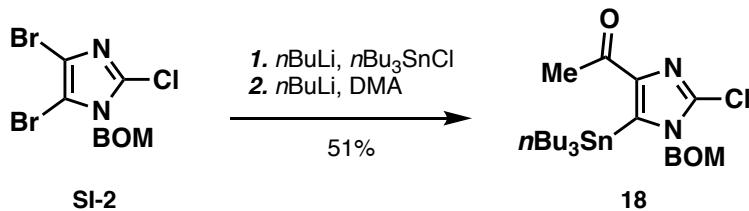
R_f Value: 0.58 (ethyl acetate:hexane = 2:3);

¹H NMR (600 MHz, CDCl_3) δ 9.64 (s, 1H), 7.36 (s, 1H), 3.66 (s, 2H), 2.99 (t, J = 14.3 Hz, 1H), 2.59 (d, J = 16.2 Hz, 1H), 2.21 (s, 1H), 1.53 (s, 9H), 1.49 (s, 9H), 1.00 (d, J = 6.7 Hz, 3H).;

¹³C NMR (151 MHz, CDCl_3) δ 192.5, 159.4, 152.1, 149.5, 147.3, 105.9, 84.3, 82.1, 70.5, 54.0, 41.2, 39.3, 28.2, 14.9 ppm. (two peaks belonging to the two Boc tert-butyl groups overlap);

Optical Rotation: $[\alpha]_D^{25} = +83.9^\circ$ ($c = 0.38$ g / 100 mL, CHCl_3);

HRMS (m/z) calc'd for $\text{C}_{19}\text{H}_{29}\text{IN}_3\text{O}_5^+$ [M+H]⁺ 506.1146, found 506.1169



Experimental: **SI-2** (13.2 g, 35 mmol) was added into a flame-dried 500 ml round bottom flask fixed with a stir bar. The flask was evacuated and backfilled with argon (in a balloon) three times. Dry THF (250 ml) was added into the flask via syringe. Dissolve all the solid at room temperature then cool the mixture to -78 °C. Add $n\text{BuLi}$ (14.7 ml of 2.5 M solution in hexane, 1.05 eq) into the mixture slowly (the colorless solution then turns orange after addition) and wait for 20 mins after the completion of the addition of $n\text{BuLi}$. Add $n\text{Bu}_3\text{SnCl}$ (10.0 ml, 36.8 mmol, 1.05 eq) into the mixture in one portion and then wait for 30 mins. Add another dose of $n\text{BuLi}$ (14.7 ml of 2.5 M solution in hexane, 1.05 eq) into the mixture slowly and wait for 30 mins after the completion of the addition of $n\text{BuLi}$. Add N,N-

Dimethylacetamide (8.1 ml, 87.5 mmol, 2.5 eq) into the mixture in one portion and then wait for 1 hour. Upon completion, add sat. NH₄Cl into the mixture to quench the reaction and remove the cold bath to let the reaction gradually warm up to room temperature. The aqueous layer was separated and extracted with diethyl ether once then combine all organic layers and wash with brine once. The resulting organic layer was dried over MgSO₄ then the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (diethyl ether and hexane as the eluents) yielding **18** (9.8 g, 51% yield) as a colorless oil.

The preparation of **SI-2** can be found in *J. Org. Chem.* **2009**, *74*, 995-1006.

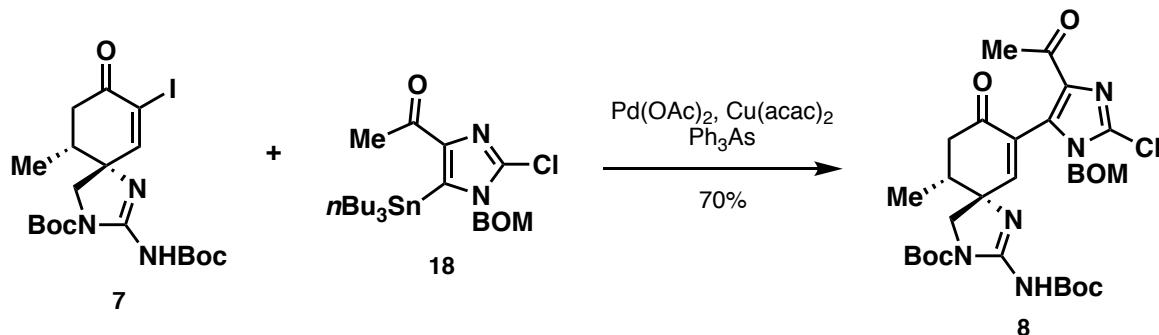
Physical State: colorless oil;

R_f Value: 0.59 (acetone:hexane = 2:7);

¹H NMR (600 MHz, CDCl₃) δ 7.39 – 7.26 (m, 5H), 5.38 (s, 2H), 4.45 (s, 2H), 2.52 (s, 3H), 1.55 – 1.41 (m, 6H), 1.31 (h, J = 6.9 Hz, 6H), 1.23 – 1.10 (m, 6H), 0.86 (t, J = 7.3 Hz, 9H).;

¹³C NMR (151 MHz, CDCl₃) δ 195.0, 149.2, 142.8, 136.5, 135.5, 128.6, 128.2, 127.5, 75.3, 70.4, 29.1, 27.3, 26.5, 13.7, 11.5 ppm.;

HRMS (m/z): calc'd for C₂₅H₄₀CIN₂O₂Sn⁺ [M+H]⁺ 555.1800, found 555.1807



Experimental: **7** (10.0 g, 19.8 mmol), **18** (14.8 g, 26.7 mmol, 1.35 eq) and triphenylarsine (1.5 g, 4.8 mmol, 0.24 eq) was added into a flame-dried 500 ml round bottom flask fixed with a stir-bar. The flask was evacuated and backfilled with argon (in a balloon) three times. Dry THF (150 ml) was added into the flask via syringe. Start stirring at room

temperature then add palladium(II) acetate (533 mg, 2.4 mmol, 0.12 eq) and copper(II) acetylacetonate (3.1 g, 11.9 mmol, 0.6 eq) into the flask in one portion. Heat the reaction to 64 °C and keep stirring for 14 h. Upon completion, remove the oil bath and let the reaction gradually cool down to room temperature. Remove the THF under reduced pressure and re-dissolve the resulting crude mixture in DCM (250 ml). Transfer the reaction mixture into a separatory funnel and wash the organic layer with “copper sequester” (sat. NH₄Cl:30% ammonia hydroxide = 9:1), 20% KF solution in H₂O and brine sequentially. The organic layer was dried over MgSO₄ then the solvent was removed under reduced pressure. The resulting crude reaction mixture was purified via flash column chromatography (ethyl acetate, DCM and hexane as the eluents) to give the desired product (8.9 g, 70% yield) as a yellow solid.

Physical State: yellow solid;

m.p.: 83-85 °C;

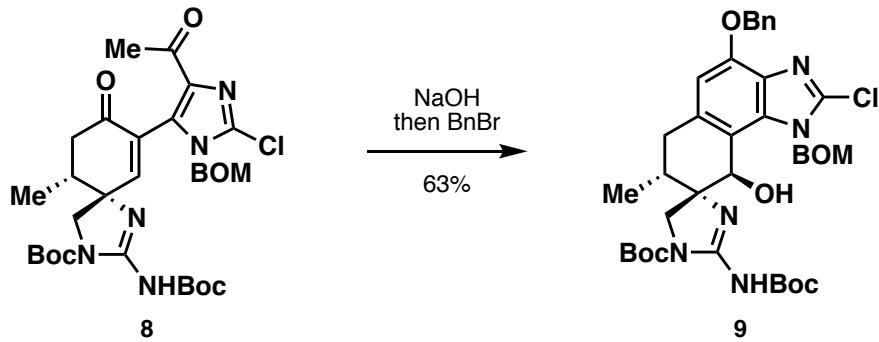
R_f Value: 0.15 (ethyl acetate:hexane = 2:3);

¹H NMR (600 MHz, CDCl₃) δ 7.38 – 7.21 (m, 5H), 6.78 (s, 1H), 5.32 (d, J = 10.2 Hz, 1H), 5.19 – 5.07 (br, 1H), 4.48 (s, 2H), 3.85 – 3.73 (br, 2H), 2.94 – 2.81 (br, 1H), 2.67 – 2.57 (br, 1H), 2.50 (s, 3H), 2.43 – 2.33 (br, 1H), 1.53 (s, 9H), 1.48 (s, 9H), 1.11 (d, J = 6.8 Hz, 3H).;

¹³C NMR (151 MHz, CDCl₃) δ 195.7, 194.1, 154.5, 152.1, 149.5, 147.1, 138.1, 136.3, 133.2, 131.7, 128.6, 128.2, 127.8, 84.2, 81.8, 73.9, 71.0, 67.7, 54.0, 42.4, 38.4, 28.2, 28.2, 27.5, 15.0 ppm. (one sp² carbon peak either is missing or overlaps with other peaks);

Optical Rotation: [α]_D²⁵ = +21.6° (c = 0.56 g / 100 mL, CHCl₃);

HRMS (m/z) calc'd for C₃₂H₄₁CIN₅O₇⁺ [M+H]⁺ 642.2689, found 642.2693



Experimental: **8** (1.1 g, 1.7 mmol) was placed in a 250 ml round bottom flask fixed with a stir bar and flushed with argon 3 times. THF (50 ml) and H₂O (50 ml) was added into the flask and stirring was started. The resulting solution was cooled down to 0 °C in an ice bath and 2 M NaOH solution (1.3 ml, 1.5 eq.) was added into the mixture slowly within 5 mins. Let the reaction run overnight and the temperature of ice bath will increase to 15 °C over the course of 10 h. Upon completion, BnBr (1.17 g, 6.9 mmol, 4 eq) was added into the reaction mixture in one portion then keep stirring for 3 h at 15 °C. Upon completion, 0.5 M HCl in H₂O was added carefully till the pH value of the organic layer became 7. The aqueous layer was separated and extracted with ethyl acetate twice. All the organic layers were combined and washed with brine then dried over MgSO₄. The solvent was removed under reduced pressure to give an off-white solid which was purified by flash column chromatography (DCM, acetone and hexane as eluents) give the desired product (790 mg). The combined yield is 63%.

Physical State: white solid;

m.p.: >220 °C (decomp.);

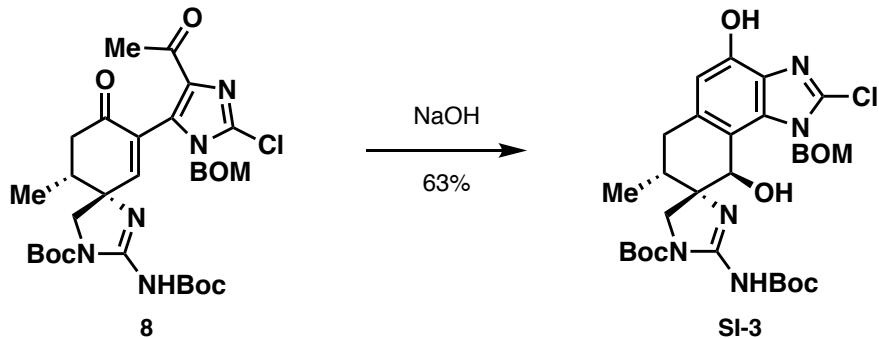
R_f Value: 0.20 (acetone:hexane = 1:4);

¹H NMR (600 MHz, CDCl₃) δ 8.62 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.41 – 7.32 (m, 3H), 7.24 – 7.10 (m, 5H), 6.43 (s, 1H), 5.96 (d, *J* = 12.0 Hz, 1H), 5.65 (d, *J* = 12.0 Hz, 1H), 5.23 (d, *J* = 12.1 Hz, 1H), 5.17 (d, *J* = 12.1 Hz, 1H), 5.03 (s, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 3.98 (d, *J* = 12.0 Hz, 1H), 3.86 (d, *J* = 12.0 Hz, 1H), 2.82 (d, *J* = 12.6 Hz, 1H), 2.68 (dd, *J* = 16.5, 11.5 Hz, 1H), 2.42 – 2.32 (m, 1H), 1.53 (s, 9H), 1.39 (s, 9H), 0.97 (d, *J* = 6.6 Hz, 3H);

¹³C NMR (151 MHz, CDCl₃) δ 164.3, 160.1, 149.4, 148.6, 139.3, 136.5, 136.0, 134.3, 133.0, 131.4, 128.7, 128.6, 128.2, 128.1, 127.6, 127.5, 112.8, 107.3, 82.7, 79.2, 74.2, 71.0, 70.7, 69.3, 61.6, 51.5, 34.9, 30.2, 28.3, 28.2, 14.1 ppm.;

Optical Rotation: [α]_D²⁵ = +6.1° (c = 0.41 g / 100 mL, CHCl₃);

HRMS (m/z) calc'd for C₃₉H₄₇CIN5O₇⁺ [M+H]⁺ 732.3159, found 732.3140



Experimental: **8** (3.2 g, 5.0 mmol) was placed in a 500 ml round bottom flask fixed with a stir bar and flushed with argon 3 times. THF (150 ml) and H₂O (150 ml) was added into the flask and stirring was started. The resulting solution was cooled down to 0 °C in an ice bath and 2 M NaOH solution (3.7 ml, 1.5 eq.) was added into the mixture slowly within 5 mins. Let the reaction run overnight and the temperature of ice bath will increase to 15 °C over the course of 8 h. Upon completion, 0.5 M HCl in H₂O was added carefully till the pH value of the organic layer became 7. The aqueous layer was separated and extracted with ethyl acetate twice. All the organic layers were combined and washed with brine then dried over MgSO₄. The solvent was removed under reduced pressure to give an off-white solid. Add DCM (20 ml) and hexane (80 ml) to the crude material and heat it with a heat gun to dissolve the solid as much as possible then let it gradually cool down to room temperature (white solid will precipitate). Filter the mixture to collect some product (1.6 g) and the filtrate was concentrated under reduced pressure. The residual crude material was purified by flash column chromatography (DCM, acetone and hexane as eluents) give the desired product (416 mg). The combined yield is 63%.

Physical State: white solid;

m.p.: >220 °C (decomp.);

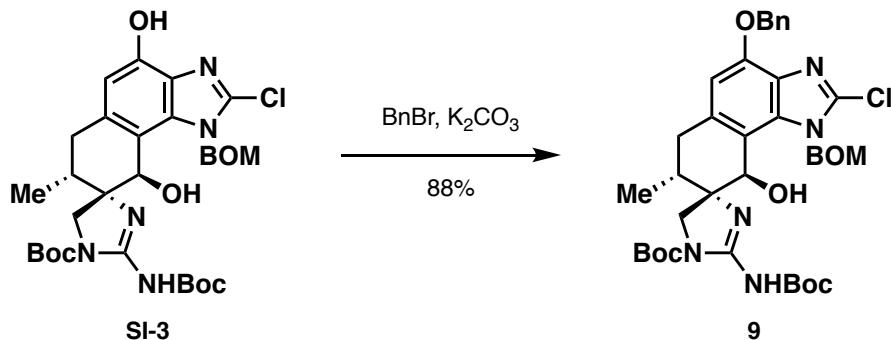
R_f Value: 0.51 (DCM:acetone = 8:1);

¹H NMR (600 MHz, CDCl₃) δ 7.35 – 7.15 (m, 5H), 6.37 (s, 1H), 5.96 – 5.67 (br, 2H), 5.06 (s, 1H), 4.56 (s, 2H), 4.13 – 3.66 (m, 2H), 2.78 (s, 2H), 2.40 (s, 1H), 1.54 (s, 9H), 1.40 (s, 9H), 1.04 (d, J = 6.5 Hz, 3H).

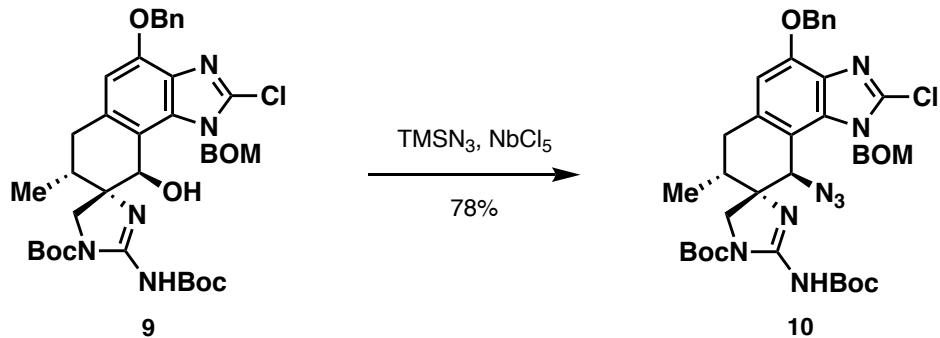
¹³C NMR (151 MHz, CDCl₃) δ 146.9, 138.8, 136.2, 133.8, 130.1, 128.6, 128.2, 127.8, 109.3, 83.1, 74.3, 70.7, 69.6, 52.0, 34.8, 30.6, 28.3, 28.2, 14.3 ppm. (5 sp² carbon peaks either are or overlapping with other peaks, 2 sp³ fully substituted carbon peaks either are missing or overlapping with other peaks);

Optical Rotation: [α]_D²⁵ = -20.5° (c = 0.20 g / 100 mL, CHCl₃);

HRMS (m/z) calc'd for C₃₂H₄₁CIN₅O₇⁺ [M+H]⁺ 642.2689, found 642.2675



Experimental: **SI-3** (3.2 g, 5.0 mmol), BnBr (2.6 g, 15.0 mmol, 3 eq) and potassium carbonate (3.4 g, 25.0 mmol, 5 eq) was placed in a 250 ml round bottom flask fixed with a stir bar. Acetone (125 ml) was added and stirring was started. The reaction was heated to 60 °C and kept being stirred for 2 h. Upon completion, the solid in the reaction mixture was filtered off and the solvent was removed under reduced pressure to give the crude material which was purified by flash column chromatography (acetone and hexane as eluents) to yield the product **9** (3.2 g, 88% yield).



Experimental: **9** (3.7 g, 5.1 mmol) and TMSN_3 (1.7 g, 15.2 mmol, 3 eq) were placed in a 500 ml flame-dried round bottom flask fixed with a stir-bar and placed under argon. Dry DCM (35 ml) and MeCN (245 ml) were added to the flask and stirring was started at room temperature. NbCl_5 (205.0 mg, 0.8 mmol, 0.15 eq) was added into the reaction mixture in one portion. After 7 h, TMSN_3 (2.6 g, 22.8 mmol, 4.5 eq) and NbCl_5 (68.3 mg, 0.3 mmol, 0.05 eq) were added into the reaction mixture sequentially. After 4 h, TMSN_3 (2.6 g, 22.8 mmol, 4.5 eq) and NbCl_5 (68.3 mg, 0.3 mmol, 0.05 eq) were added into the reaction mixture sequentially then wait for 10 h. Upon completion, sat. NaHCO_3 solution was added to quench the reaction. The aqueous layer was separated and extracted with ethyl acetate twice. All organic layers were combined and washed with brine then dried over MgSO_4 . The solvent was removed under reduced pressure to give the crude material which was purified by flash column chromatography (acetone and hexane as eluents) to yield the product **10** (3.0 g, 78% yield).

Physical State: white solid;

m.p.: 178–180 °C;

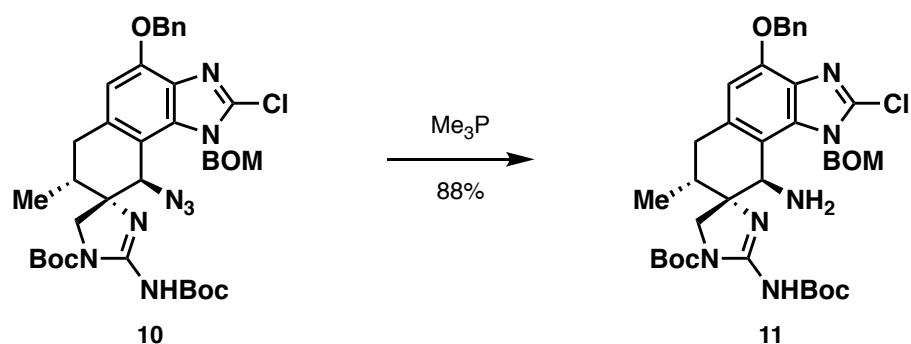
R_f Value: 0.58 (ethyl acetate:hexane = 2:3);

¹H NMR (600 MHz, CDCl_3) δ 7.52 – 7.47 (m, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.22 – 7.16 (m, 3H), 6.58 (s, 1H), 5.85 (d, J = 12.1 Hz, 1H), 5.78 (d, J = 12.1 Hz, 1H), 5.31 (s, 2H), 5.00 – 4.88 (br, 1H), 4.52 (s, 2H), 4.01 – 3.71 (br, 2H), 3.04 – 2.76 (br, <1H, the two protons on C4 do not show up well), 2.23 (s, 1H), 1.56 (s, 9H), 1.40 (s, 9H), 1.05 (s, 3H).;

¹³C NMR (151 MHz, CDCl₃) δ 159.7, 150.5, 148.5, 139.6, 136.6, 136.2, 134.6, 133.9, 132.0, 128.7, 128.6, 128.1, 127.6, 106.8, 83.3, 79.7, 73.8, 70.9, 70.7, 62.2, 52.1, 34.8, 32.0, 28.3, 28.2, 14.4 ppm. (5 peaks belonging to 5 sp² carbon atoms either are missing or overlap with other peaks);

Optical Rotation: [α]_D²⁵ = +24.0° (c = 0.47 g / 100 mL, CHCl₃);

HRMS (m/z) calc'd for C₃₉H₄₆CIN₈O₆⁺ [M+H]⁺ 757.3223, found 757.3214



Experimental: **10** (1.1 g, 1.5 mmol) was placed in a 250 ml flame-dried round bottom flask fixed with a stir-bar and placed under argon. THF (60 ml) and H₂O (15 ml) was added to the flask via syringe and the solution was cooled down to 0 °C. Trimethylphosphine (2.9 ml of 1 M solution in THF, 2.9 mmol, 2 eq) was added into the reaction mixture dropwise. After 30 mins, NaOH (1.5 ml of 1 M solution in H₂O, 1.5 mmol, 1 eq) was added into the reaction mixture slowly via syringe. Wait for 10 mins after the completion of addition of the NaOH solution then add H₂O to quench the reaction. The aqueous layer was separated and extracted with ethyl acetate twice. All organic layers were combined and washed with brine then dried over MgSO₄. The solvent was removed under reduced pressure to give the crude material which was then dissolved in hexane (20 ml) and ethyl acetate (5 ml). The mixture was heated by a heat gun to dissolve the solid as much as possible then let the mixture cool down to room temperature gradually (white solid will precipitate). Filter the mixture to collect some product (818 mg) and the filtrate was concentrated under reduced pressure. The residual crude material was purified by flash column chromatography (acetone and hexane as eluents) give the desired product (117 mg). The combined yield is 88%.

Physical State: white solid;

m.p.: >220 °C (decomp.);

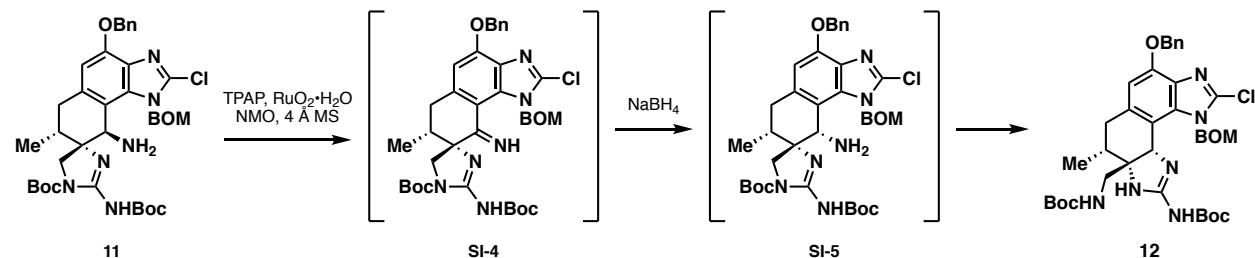
R_f Value: 0.21 (ethyl acetate:hexane = 2:3);

¹H NMR (600 MHz, CDCl₃) δ 8.64 (s, 1H), 7.49 (d, *J* = 7.1 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.32 – 7.27 (m, 3H), 7.26 – 7.19 (m, 3H), 6.49 (s, 1H), 6.06 (d, *J* = 11.8 Hz, 1H), 5.80 (d, *J* = 11.9 Hz, 1H), 5.32 (d, *J* = 12.3 Hz, 1H), 5.25 (d, *J* = 12.2 Hz, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.41 (s, 1H), 3.87 (d, *J* = 11.3 Hz, 1H), 3.79 (d, *J* = 11.4 Hz, 1H), 2.89 (dd, *J* = 17.8, 4.6 Hz, 1H), 2.71 (dd, *J* = 17.2, 12.5 Hz, 1H), 2.38 – 2.27 (m, 1H), 1.53 (s, 9H), 1.40 (s, 9H), 1.02 (d, *J* = 6.5 Hz, 3H).;

¹³C NMR (151 MHz, CDCl₃) δ 164.2, 159.8, 149.4, 148.6, 139.6, 136.9, 136.2, 134.5, 132.3, 131.3, 128.8, 128.7, 128.4, 128.0, 127.9, 127.6, 115.1, 107.0, 82.9, 79.2, 74.5, 70.8, 70.8, 62.4, 53.8, 52.1, 34.9, 30.0, 28.3, 28.2, 14.4 ppm.;

Optical Rotation: [α]_D²⁵ = +33.0° (c = 0.10 g / 100 mL, CHCl₃);

HRMS (m/z) calc'd for C₃₉H₄₈ClN₆O₆⁺ [M+H]⁺ 731.3318, found 731.3323



Experimental: 11 (66 mg, 0.09 mmol), NMO (53 mg, 0.45 mmol, 5 eq), ruthenium(IV) oxide monohydrate (16.3 mg, 0.11 mmol, 1.2 eq) and 4 Å molecular sieves (33 mg) were added to a 50 ml flame-dried round bottom flask fixed with a stir-bar and placed under argon. Dry DCM (2.5 ml) was added via syringe and the stirring was started. TPAP (15.8 mg, 0.05 mmol, 0.5 eq) was added into the reaction mixture in one portion. After 30 mins, TPAP (6.4 mg, 0.02 mmol, 0.2 eq) was added into the reaction mixture in one portion. After 30 mins, half of the DCM in the reaction mixture was removed by blowing air onto the reaction surface. The reaction was then cooled down to 0 °C and MeOH (2.5 ml) and

silica gel (660 mg) were added into the reaction mixture. NaBH₄ (17.1 mg, 5 eq) was added into the reaction in one portion and stirred for 30 mins. Upon the completion of the reaction, the mixture was filtered through a short path of celite which was quenched by aq. NH₄Cl solution. The aqueous layer was separated from the organic layer. The aqueous layer was extracted by DCM twice and all organic layers were combined and concentrated under reduced vacuum. The crude material was quickly purified by flash column chromatography (ethyl acetate and hexane as eluents first then switch to chloroform and acetone as eluents) to yield the desired product **12** (31.6 mg, 48% yield over two steps).

Physical State: off-white solid;

m.p.: >150 °C (decomp.);

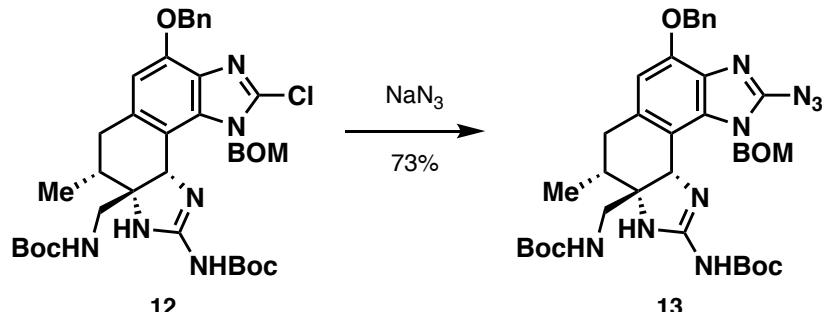
R_f Value: 0.17 (MeOH:DCM = 1:15);

¹H NMR (600 MHz, CDCl₃) δ 7.50 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.35 – 7.28 (m, 6H), 6.58 (s, 1H), 6.05 (d, *J* = 12.2 Hz, 1H), 5.85 (s, 1H), 5.57 (d, *J* = 12.2 Hz, 1H), 5.34 (s, 2H), 5.26 (s, 1H), 4.72 (d, *J* = 12.7 Hz, 1H), 4.42 (d, *J* = 12.8 Hz, 1H), 3.38 (dd, *J* = 14.6, 5.0 Hz, 1H), 3.38 (dd, *J* = 15.0, 8.6 Hz, 1H), 2.78 (t, *J* = 13.6 Hz, 1H), 2.44 (dd, *J* = 14.9, 3.1 Hz, 1H), 1.66 – 1.58 (m, 1H), 1.40 (s, 9H), 1.39 (s, 9H), 1.06 (d, *J* = 6.7 Hz, 3H).;

¹³C NMR (151 MHz, CDCl₃) δ 163.6, 161.8, 157.2, 149.4, 139.7, 137.9, 136.9, 136.3, 134.7, 132.1, 128.7, 128.7, 128.4, 128.3, 128.0, 127.5, 111.0, 107.1, 79.9, 79.0, 73.7, 70.9, 70.2, 65.0, 54.4, 46.3, 36.7, 35.7, 28.4, 28.4, 15.6 ppm.;

Optical Rotation: [α]_D²⁵ = -98.2° (c = 0.11 g / 100 mL, CHCl₃);

HRMS (m/z) calc'd for C₃₉H₄₈CIN₆O₆⁺ [M+H]⁺ 731.3318, found 731.3312



Experimental: **12** (400 mg, 0.55 mmol) and NaN₃ (1.78 g, 27.39 mmol, 50 eq) were added to a 50 ml flame-dried round bottom flask fixed with a stir-bar and placed under argon. 1-Butyl-3-methylimidazolium tetrafluoroborate (11 ml) was added into the reaction mixture via syringe and the stirring was started. The reaction mixture was heated to 70 °C and kept being stirred for 21 h. Upon completion, the reaction mixture was cooled down to room temperature gradually. Dry DCM (11 ml) was added into the reaction mixture then cool the reaction mixture down to 0 °C. Et₃N (277 mg, 2.73 mmol, 5 eq) and Boc₂O (359 mg, 1.64 mmol, 3 eq) were added into the reaction mixture sequentially. After 40 mins, sat. NaHCO₃ was added to quench the reaction. The aqueous layer was separated and extracted with DCM for three times. All the organic layers were combined and washed with H₂O twice and brine sequentially then dried over MgSO₄. The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (ethyl acetate and hexane as eluents first then switch to chloroform and acetone as eluents) to yield the product **13** (295 mg, 73% yield).

Physical State: pink solid;

m.p.: >150 °C (decomp.);

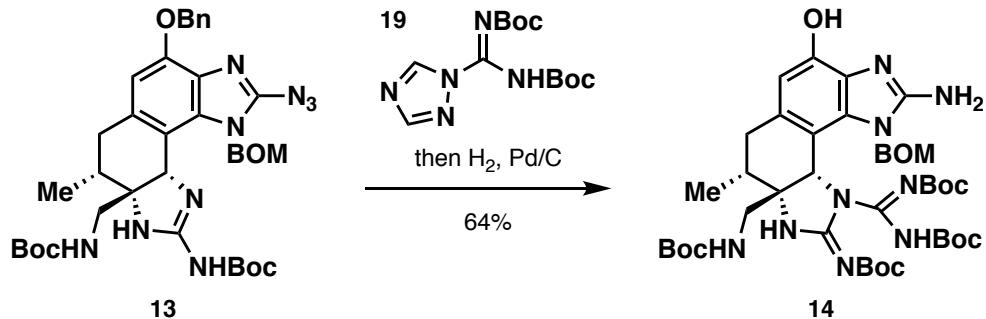
R_f Value: 0.17 (MeOH:DCM = 1:15);

¹H NMR (600 MHz, CDCl₃) δ 7.50 (d, *J* = 7.0 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.34 – 7.29 (m, 6H), 6.55 (s, 1H), 5.87 (s, 1H), 5.85 (d, *J* = 12.5 Hz, 1H), 5.37 (s, 2H), 5.34 (d, *J* = 12.3 Hz, 1H), 4.69 (d, *J* = 12.6 Hz, 1H), 4.41 (d, *J* = 12.6 Hz, 1H), 3.40 (dd, *J* = 14.6, 5.2 Hz, 1H), 3.35 – 3.23 (m, 1H), 2.75 (dd, *J* = 14.9, 12.4 Hz, 1H), 2.42 (dd, *J* = 15.0, 3.1 Hz, 1H), 1.69 – 1.62 (m, 1H), 1.39 (s, 9H), 1.37 (s, 9H), 1.07 (d, *J* = 6.7 Hz, 3H).;

¹³C NMR (151 MHz, CDCl₃) δ 161.8, 159.5, 157.3, 148.9, 146.6, 137.1, 136.3, 136.0, 133.8, 131.7, 128.7, 128.6, 128.4, 128.3, 127.9, 127.3, 110.5, 107.2, 80.2, 79.9, 72.4, 70.9, 70.5, 65.6, 54.7, 46.4, 36.3, 35.5, 28.4, 28.2, 15.5 ppm.;

Optical Rotation: [α]_D²⁵ = -127.3° (c = 0.15 g / 100 mL, CHCl₃);

HRMS (m/z) calc'd for C₃₉H₄₈N₉O₆⁺ [M+H]⁺ 738.3722, found 738.3703



Experimental: **13** (220 mg, 0.30 mmol) and **19** (121 mg, 0.39 mmol, 1.3 eq) were added to a 25 ml flame-dried round bottom flask fixed with a stir-bar and placed under argon. Dry nitromethane (6 ml) was added into the reaction via syringe and the stirring was started. The reaction mixture was heated to 60 °C and kept being stirred for 8 h. Add **19** (93 mg, 0.30 mmol, 1 eq) into the reaction mixture and wait for 10 h. The solvent was removed under reduced pressure and the crude material was left under vacuum overnight. Catalytic Pd/C (40 mg, 10 wt.%) was added to the dry crude material and the flask was placed under vacuum then backfilled with hydrogen gas (in a balloon) for three times. Add dry MeOH (3 ml) into the flask and start stirring at temperature. After 2.5 h, the balloon was removed and the reaction mixture was filtered through a short path of celite which was washed by DCM and MeOH twice. The combined solvent was then removed under reduced pressure and the crude material was purified by flash column chromatography (DCM and MeOH as eluents) to yield the product **14** (165 mg, 64% yield).

Physical state: off-white solid;

m.p.: 128-130 °C;

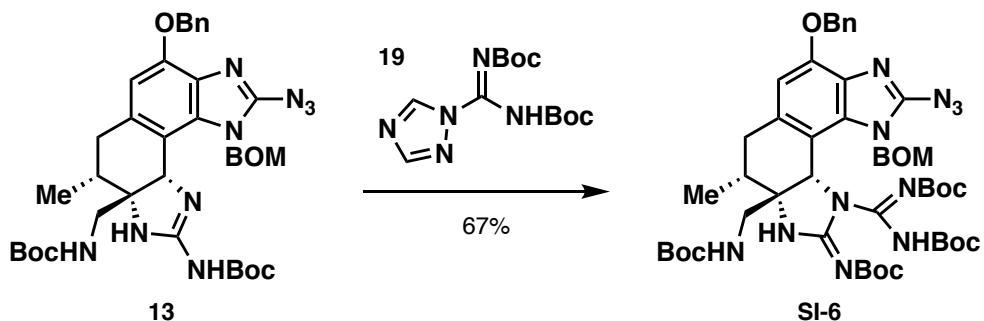
R_f Value: 0.27 (MeOH:DCM = 1:15);

¹H NMR (600 MHz, Acetone-d₆) δ 11.63 (s, 1H), 8.83 (s, 1H), 7.29 (s, 5H), 6.88 (d, J = 12.7 Hz, 1H), 6.48 (s, 1H), 5.82 – 5.69 (m, 3H), 4.74 (d, J = 11.0 Hz, 1H), 4.54 (d, J = 10.8 Hz, 1H), 3.39 (dd, J = 14.8, 7.7 Hz, 1H), 2.82 (t, J = 13.4 Hz, 1H), 2.49 (dd, J = 14.9, 5.1 Hz, 1H), 2.43 (dd, J = 14.5, 3.0 Hz, 1H), 1.43 (s, 10H), 1.42 (s, 9H), 1.35 (s, 9H), 1.31 (s, 9H), 1.14 (d, J = 6.8 Hz, 3H). (one proton peak overlaps with one of the four peaks belonging to the four Boc tert-butyl groups);

¹³C NMR (151 MHz, Acetone-d₆) δ 162.5, 161.3, 158.6, 158.4, 157.4, 153.5, 150.6, 146.8, 146.2, 137.7, 134.7, 129.3, 129.0, 126.5, 110.1, 106.7, 81.8, 79.5, 79.3, 79.0, 74.5, 71.7, 66.3, 58.5, 44.6, 39.5, 35.7, 28.5, 28.3, 28.1, 15.0 ppm. (One sp² carbon peak either is missing or overlaps with other peaks, one Boc tert-butyl group peak overlaps with other Boc tert-butyl group peaks);

Optical Rotation: [α]_D²⁰ = -50.0° (c = 0.31 g / 100 mL, CHCl₃);

HRMS (m/z): calc'd for C₄₃H₆₀N₉O₁₀ [M-H]⁻ 862.4469, found 862.4443



Experimental: **13** (220 mg, 0.30 mmol) and **19** (121 mg, 0.39 mmol, 1.3 eq) were added to a 25 ml flame-dried round bottom flask fixed with a stir-bar and placed under argon. Dry nitromethane (6 ml) was added into the reaction via a syringe then the stirring was started. The reaction mixture was heated to 60°C and kept being stirred for 8 h. Add **19** (93 mg, 0.30 mmol, 1 eq) into the reaction mixture and wait for 10 h. The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (ethyl acetate and hexane as eluents) to yield the product **SI-6** (197 mg, 67% yield).

Physical state: pink solid;

m.p.: >150 °C (decomp.);

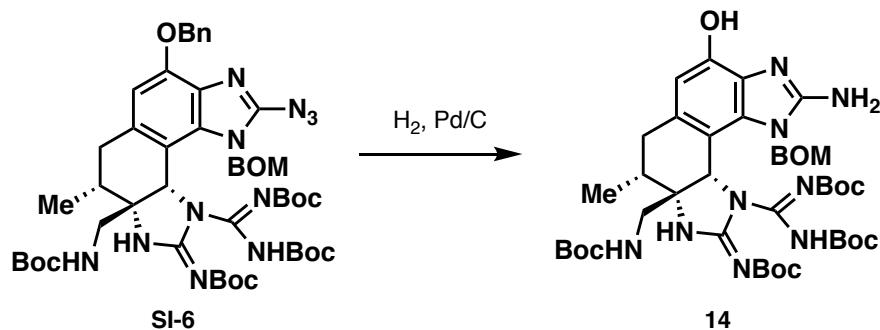
R_f Value: 0.59 (ethyl acetate:hexane = 2:1);

¹H NMR (600 MHz, CDCl₃) δ 11.68 – 11.09 (br, 1H), 8.80 (s, 1H), 7.53 (d, J = 7.0 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 6.2 Hz, 1H), 7.30 – 7.26 (m, 3H), 7.15 (dd, J = 6.5, 2.9 Hz, 2H), 6.92 (d, J = 12.3 Hz, 1H), 6.56 (s, 1H), 5.60 (s, 1H), 5.43 (d, J = 12.2 Hz, 1H), 5.35 (q, J = 11.8 Hz, 2H), 5.05 (t, J = 6.0 Hz, 1H), 4.48 (d, J = 10.9 Hz, 1H), 4.31 (d, J = 11.0 Hz, 1H), 3.32 (dd, J = 14.9, 7.5 Hz, 1H), 2.97 (t, J = 12.0 Hz, 1H), 2.35 (dd, J = 14.7, 3.1 Hz, 1H), 2.07 (dd, J = 15.0, 5.6 Hz, 1H), 1.47 – 1.28 (m, 37H), 1.12 (d, J = 6.7 Hz, 3H);

¹³C NMR (151 MHz, CDCl₃) δ 161.5, 160.1, 158.9, 156.6, 154.9, 149.6, 147.2, 146.1, 138.7, 137.2, 135.9, 135.7, 130.9, 128.8, 128.7, 128.6, 128.5, 127.9, 127.5, 108.0, 106.5, 81.8, 79.7, 79.5, 79.2, 74.1, 71.4, 71.0, 65.5, 57.2, 43.5, 38.7, 35.6, 28.2, 28.1, 28.0, 14.8 ppm. (One Boc tert-butyl group peak overlaps with other peaks);

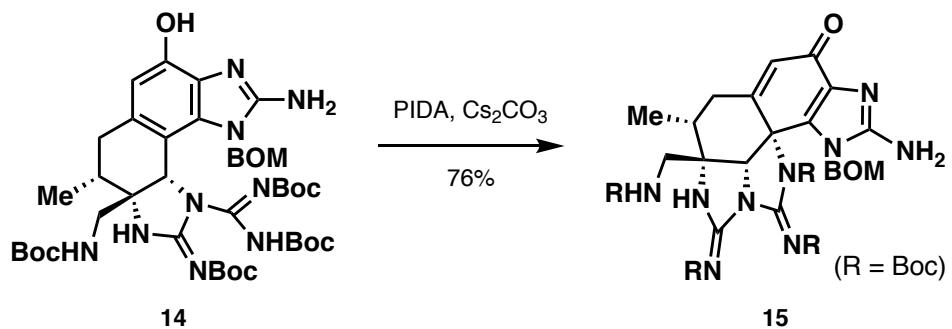
Optical Rotation: [α]_D²⁵ = -231.0° (c = 0.10 g / 100 mL, CHCl₃);

HRMS (m/z) calc'd for C₅₀H₆₆N₁₁O₁₀ [M+H]⁺ 980.4989, found 980.4971



Experimental: To a 10 ml flame-dried tube fixed with a stir-bar was added **SI-6** (70 mg, 0.07 mmol) and palladium on carbon (10 wt. %, 12 mg). The tube was place under vacuum and backfilled with H₂ (in a balloon) for three times. Dry MeOH (0.8 ml) was then added into the reaction mixture via syringe and the stirring was started at room temperature. After 3 h, the reaction was diluted with DCM (1.5 ml) and methanol (1.5 ml) and filtered through a short pad of celite which was then washed with DCM (1.5 ml)

and methanol (1.5 ml). The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (DCM and methanol as eluents) to yield the desired product **14** (56 mg, 91% yield).



Experimental: **14** (50 mg, 0.06 mmol), (diacetoxyiodo)benzene (20 mg, 0.06 mmol, 1.05 eq) and cesium carbonate (20 mg, 0.06 mmol, 1.05 eq) were added into a 10 ml flame-dried tube fixed with a stir bar. The tube was place under vacuum and backfilled with argon. The reaction was cooled down to 0°C and HFIP (0.65 ml) was added in one portion then the stirring was started (The color of the reaction mixture turned from colorless to green then yellow in the end). After 45 mins, the reaction mixture was diluted with DCM and washed with H₂O and sat. NaHCO₃ solution sequentially then dried over MgSO₄. The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (DCM and methanol as eluents) to yield the desired product **15** (38 mg, 76% yield).

Physical State: yellow foam;

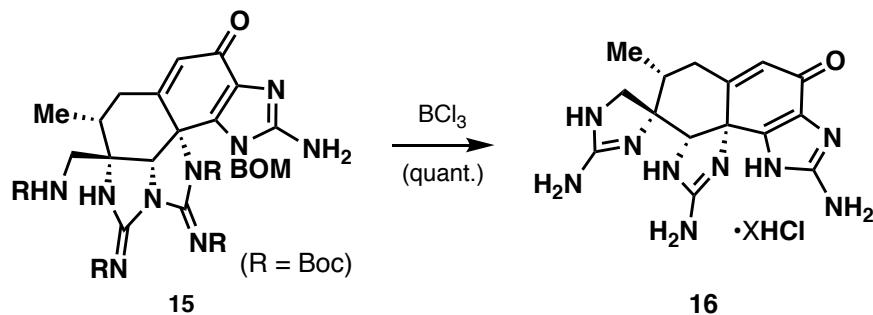
R_f Value: 0.36 (MeOH:DCM = 1:15);

¹H NMR (600 MHz, Acetone-d₆) δ 7.50 (d, J = 7.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.31 – 7.27 (m, 1H), 6.27 – 6.16 (br, 1H), 6.14 (s, 1H), 6.02 – 5.92 (br, 2H), 5.38 (d, J = 10.5 Hz, 1H), 5.33 (d, J = 10.5 Hz, 1H), 4.98 (s, 1H), 4.80 (d, J = 11.3 Hz, 1H), 4.76 (d, J = 11.3 Hz, 1H), 3.41 – 3.31 (m, 1H), 3.10 (d, J = 11.1 Hz, 1H), 2.48 (d, J = 12.0 Hz, 1H), 2.25 – 2.12 (m, 2H), 1.51 (s, 9H), 1.47 (s, 9H), 1.29 (s, 9H), 1.10 (s, 12H);

¹³C NMR (151 MHz, Acetone-d₆) δ 179.9, 158.2, 157.4, 153.7, 153.1, 149.3, 138.2, 135.6, 134.8, 129.1, 129.0, 128.5, 128.1, 84.7, 80.8, 79.9, 79.6, 73.6, 71.5, 68.7, 61.1, 48.7, 42.8, 34.1, 28.4, 28.3, 27.6, 16.9 ppm. (three peaks belonging to three sp² carbon atoms and one peak belonging to one sp³ carbon atom either are missing or overlap with other peaks);

Optical Rotation: [α]_D²⁰ = -4.2° (c = 0.26 g / 100 mL, CHCl₃);

HRMS (m/z): calc'd for C₄₃H₆₀N₉O₁₀⁺ [M+H]⁺ 862.4458, found 862.4475

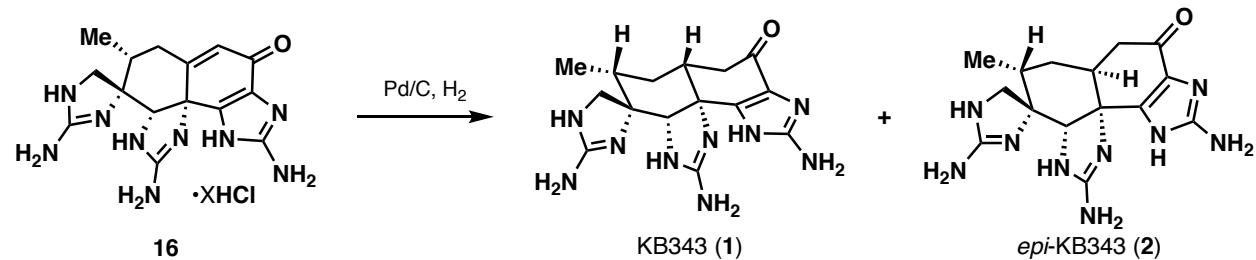


Experimental: The starting material **15** (17.2 mg, 0.02 mmol) was dissolved in DCM (0.2 mL) and cooled down to 0 °C then the stirring was started. To the aforementioned solution was added BCl₃ (0.13 ml of 1 M solution in DCM, 6.5 eq). After 1 h, the cold bath was removed and H₂O (2 ml) was added to the reaction in one portion. The reaction was kept being stirred and allowed to warm up to room temperature. The organic phase and the aqueous phase were separated and the latter was washed with Et₂O twice. The water in the aqueous phase was removed under reduced pressure to yield a yellow solid which was dissolved in MeOH (1 ml) and kept being stirred at room temperature for 24 h. The reaction mixture was then concentrated under reduced pressure to yield **16** (9.0 mg, quantitative), which was used directly without further purification.

Physical State: yellow to orange solid;

m.p.: >220 °C (decomp.);

¹H NMR (600 MHz, Methanol-d₄) δ 6.30 (d, J = 1.6 Hz, 1H), 4.41 (s, 1H), 3.62 (d, J = 10.9 Hz, 1H), 3.53 (d, J = 10.9 Hz, 1H), 2.69 (dd, J = 14.3, 5.2 Hz, 1H), 2.60 (ddd, J = 14.0, 11.3, 1.8 Hz, 1H), 2.11 (dq, J = 12.0, 6.3 Hz, 1H), 1.20 (d, J = 6.9 Hz, 3H).;
¹³C NMR (151 MHz, Methanol-d₄) δ 175.0, 161.9, 161.2, 154.5, 151.5, 129.6, 122.8, 118.8, 69.1, 68.1, 61.0, 53.8, 41.2, 35.1, 16.1 ppm.;
Optical Rotation: [α]_D²⁰ = +106.7° (c = 0.045 g / 100 mL, MeOH);
HRMS (m/z) calc'd for C₁₅H₂₀N₉O₁⁺ [M+H]⁺ 342.1785, found 342.1785



Experimental: **16** (2.5 mg, 0.006 mmol), Pd/C (0.9 mg, 5 wt.%) and a clean stir-bar were placed in a flame-dried tube which was connected to vacuum and backfilled with H₂ gas (in a balloon) for three times. The reaction tube was cooled down to -10 °C in a cold bath and MeOH (0.52 ml) with TfOH (2.5 μl, 5 eq) was then added into the mixture slowly in one portion. Start stirring and keep the reaction under the same temperature for 15 d. After the reaction completed, the cold bath and the H₂ balloon were removed. The reaction mixture was then filtered through a short path of celite and washed with MeOH with 0.5% TFA (1 ml) twice. The organic phases were combined and concentrated under reduced pressure. The resulting crude material was dissolved in H₂O with 0.5% TFA (1 ml) and purified by reversed phase HPLC (H₂O/MeCN as mobile phase and 0.1% TFA was used as buffer). The fractions containing desired product and the other diastereomer were combined separately and concentrated under reduced pressure to give **1** (1.5 mg) a white powder and **2** (0.7 mg) as a white powder.

Product 1

Physical State: white solid;

m.p.: >220 °C (decomp.);

¹H NMR (600 MHz, CD₃CN) δ 9.57 (s, 1H), 9.23 (s, 1H), 8.04 – 7.94 (br, 2H), 7.91 (s, 1H), 7.41 (s, 1H), 7.06 (s, 2H), 6.49 – 6.29 (br, 1H), 6.30 – 6.04 (m, 1H), 6.04 – 5.76 (br, 1H), 4.13 (s, 1H), 3.70 (d, J = 10.9 Hz, 1H), 3.58 (d, J = 11.1 Hz, 1H), 2.79 – 2.71 (m, 1H), 2.65 (dd, J = 17.3, 12.4 Hz, 1H), 2.55 (dd, J = 17.3, 3.5 Hz, 1H), 1.84 – 1.75 (m, 1H), 1.57 – 1.44 (m, 2H), 0.97 (d, J = 6.6 Hz, 3H);

¹³C NMR (151 MHz, CD₃CN) δ 185.8, 162.2, 161.0, 151.5, 141.3, 122.9, 68.9, 63.8, 63.1, 52.9, 41.0, 40.4, 38.8, 30.1, 14.7 ppm;

Optical Rotation: [α]_D²⁰ = +90.2° (c = 0.051 g / 100 mL, H₂O);

CD (H₂O) λ_{ext} : 206 (+13.83), 287 (-3.03), 318 (+6.30);

HRMS (m/z) calc'd for C₁₅H₂₂N₉O₁⁺ [M+H]⁺ 344.1942, found 344.1944

Product 2

Physical State: white solid;

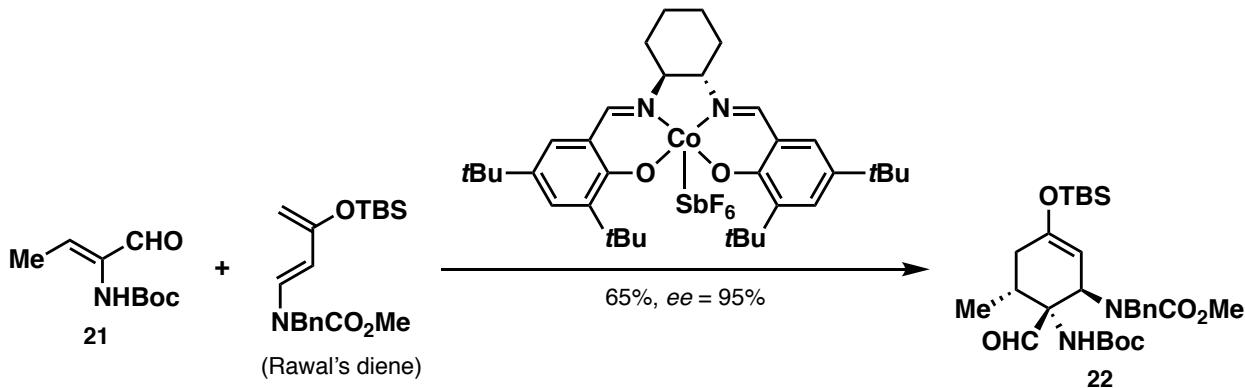
m.p.: >220 °C (decomp.);

¹H NMR (600 MHz, Methanol-d₄) δ 4.42 (s, 1H), 3.67 (q, J = 10.9 Hz, 2H), 2.89 (dd, J = 17.1, 4.7 Hz, 1H), 2.75 (dq, J = 10.7, 5.7 Hz, 1H), 2.59 (dd, J = 17.1, 5.8 Hz, 1H), 1.84 (dq, J = 13.7, 6.6 Hz, 1H), 1.74 (ddd, J = 14.8, 8.8, 6.1 Hz, 1H), 1.62 (ddd, J = 15.0, 9.0, 6.3 Hz, 1H), 1.08 (d, J = 6.7 Hz, 3H);

¹³C NMR (151 MHz, Methanol-d₄) δ 185.5, 161.5, 160.6, 154.2, 144.0, 123.7, 66.9, 66.0, 62.2, 53.4, 40.8, 37.6, 34.7, 32.0, 15.1 ppm;

Optical Rotation: [α]_D²⁰ = +30.0° (c = 0.100 g / 100 mL, H₂O);

HRMS (m/z) calc'd for C₁₅H₂₂N₉O₁⁺ [M+H]⁺ 344.1942, found 344.1942



Experimental: To a stirred solution of (*S,S*)-Co(III)-Salen-SbF₆ (227.0 mg, 0.27 mmol, 0.05 eq) and oven-dried powdered 4Å MS (1 g) in 3 mL DCM was added aldehyde **21** (1.0 g, 5.4 mmol, 1.0 eq) at 0 °C, the resulting mixture was stirred at 0 °C for 10 min. Rawal's diene (2.8 g, 8.1 mmol, 1.5 eq) was then added and the resultant mixture was stirred at the same temperature for 45 h. Upon completion, the solid was removed by filtration through celite and washed with DCM (30 mL). The filtrate was concentrated and the residue was purified by flash column chromatography (SiO₂, 15:1 → 6:1 hexane/EtOAc) to give cycloadduct **22** (1.89 g, 65% yield) as a yellow solid.

The enantiomeric excess (ee) of compound **22** was determined to be 95% ee by ¹H NMR analysis of the corresponding Mosher ester, as described by Rawal (*J. Am. Chem. Soc.* **2000**, *122*, 7843-7844). The synthesis of the corresponding Mosher ester is shown in Page 40.

Physical State: yellow solid;

m.p.: 167-169 °C;

R_f Value: 0.57 (ethyl acetate:hexane = 1:4);

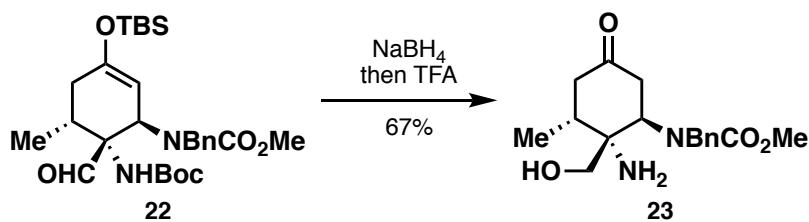
¹H NMR (600 MHz, CDCl₃) δ 9.71 (s, 1H), 7.27 (t, *J* = 7.7 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 2H), 5.84 (s, 1H), 5.21 (s, 1H), 4.55 (d, *J* = 17.0 Hz, 1H), 4.50 (s, 1H), 4.13 (d, *J* = 16.8 Hz, 1H), 3.61 (s, 3H), 2.77 – 2.64 (m, 1H), 2.59 (d, *J* = 18.2 Hz, 1H), 1.82 (dd, *J* = 18.2, 6.1 Hz, 1H), 1.44 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.78 (s, 9H), -0.16 (s, 3H), -0.20 (s, 3H);

¹³C NMR (151 MHz, CDCl₃) δ 199.8, 158.9, 155.4, 155.3, 139.1, 128.5, 126.7, 125.5, 97.9, 80.4, 67.7, 57.0, 53.4, 48.2, 34.7, 29.9, 28.4, 25.5, 17.9, 17.1, -4.7, -5.0 ppm.;

Optical Rotation: [α]_D²⁵ = -77.8° (c = 2.50 g / 100 mL, CHCl₃);

Enantiomeric excess: 95% (as determined via ¹H NMR analysis of the corresponding Mosher ester);

HRMS (m/z) calc'd for C₂₈H₄₅N₂O₆Si⁺ [M+H]⁺ 533.3041, found 533.3039



Experimental: To a solution of **22** (1.1 g, 2.07 mmol, 1.0 eq) in MeOH/THF (v/v = 2:1, 90 mL) was added NaBH₄ (102.0 mg, 2.69 mmol, 1.3 eq) slowly at 0 °C, the reaction mixture was then warmed to room temperature and stirred for 40 min. The reaction mixture was quenched with 5 mL acetone and stirred at room temperature for 10 min. Solvent was removed under reduced pressure and the crude mixture was placed under high vacuum for 2 h to give the primary alcohol intermediate.

A solution of TFA (4.7 mL, 62.0 mmol, 30.0 eq) in 33 mL DCM was added to the above obtained crude alcohol and the resulting reaction mixture was stirred at room temperature for 20 min. Half of TFA and DCM was removed under reduced pressure, 50 mL DCM was added and the remaining TFA was neutralized with sat. aq. NaHCO₃. The aqueous layers were extracted with DCM (4×50 mL) and the combined organic layers were washed with brine and dried over Na₂SO₄. Removal of the solvent under reduced pressure afforded the crude product which was purified by flash chromatography (SiO₂, 3:1 hexane/acetone to 20:1 hexane/acetone→10:1 DCM/MeOH) to afford **23** (443.0 mg, 67%) as an off-white solid.

Physical State: off-white solid;

m.p.: 90–92 °C;

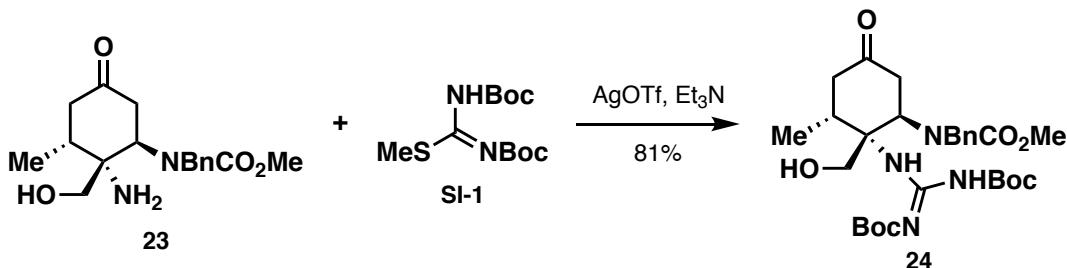
R_f Value: 0.23 (acetone:hexane = 1:1);

¹H NMR (600 MHz, CD₃CN) δ 7.33 (t, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.24 – 7.12 (br, 2H), 5.16 – 4.70 (br, 1H), 4.62 – 4.36 (br, 1H), 3.65 – 3.37 (m, 6H), 2.81 – 2.60 (br, 1H), 2.16 – 2.14 (4H, overlapping with water peak), 0.86 (d, *J* = 6.6 Hz, 3H).;

¹³C NMR (151 MHz, CD₃CN) δ 207.4, 158.2, 139.7, 129.5, 128.4, 128.1, 66.1, 62.0, 58.8, 53.8, 53.1, 45.4, 42.0, 32.8, 15.5 ppm.;

Optical Rotation: [α]_D²⁵ = –28.4° (c = 0.19 g / 100 mL, CHCl₃);

HRMS (m/z) calc'd for C₁₇H₂₅N₂O₄⁺ [M+H]⁺ 321.1809, found 321.1816



Experimental: A solution of amine **23** (1.35 g, 4.2 mmol, 1.0 eq), **SI-1** (2.08 g, 7.2 mmol, 1.7 eq), oven-dried powdered 4Å MS (1.35 g) in 70 mL DCM was added Et₃N (2.4 mL, 16.9 mmol, 4.0 eq) at room temperature, the reaction mixture was stirred at the same temperature for 10 min. AgOTf (1.52 g, 5.9 mmol, 1.4 eq) was added and stirred was continued for another 30 min. Solid was removed by filtration through Celite and washed with DCM (30 mL). The filtrate was concentrated and the residue was purified by flash column chromatography (SiO₂, 15:1→10:1 hexanes/acetone) to give compound **24** (1.92 g, 81% yield) as an off-white solid.

Physical State: off-white solid;

m.p.: 145–147 °C;

R_f Value: 0.41 (acetone:hexane = 1:4);

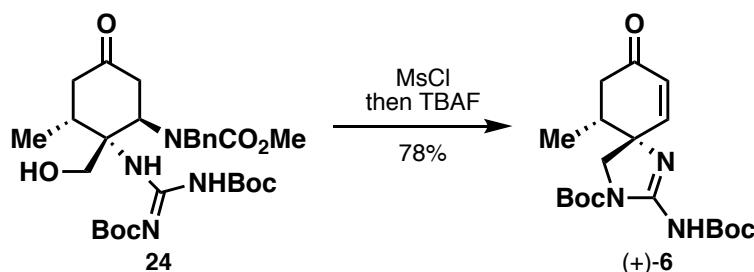
¹H NMR (600 MHz, CDCl₃) δ 11.42 (s, 1H), 8.99 (s, 1H), 7.35 – 7.23 (m, 5H), 5.08 – 4.92 (m, 2H), 4.59 (s, 1H), 4.14 (d, *J* = 12.1 Hz, 1H), 3.83 (t, *J* = 11.2 Hz, 1H), 3.73 (s, 3H),

2.78 (s, 1H), 2.59 (d, J = 18.0 Hz, 1H), 2.25 (dd, J = 17.9, 7.3 Hz, 1H), 2.16 – 2.04 (m, 2H), 1.51 (s, 9H), 1.44 (s, 9H), 0.95 (d, J = 6.9 Hz, 3H);

^{13}C NMR (151 MHz, CDCl_3) δ 204.4, 161.5, 158.2, 156.5, 153.3, 138.2, 128.8, 128.6, 127.7, 84.6, 80.1, 67.9, 64.7, 54.7, 53.0, 53.0, 43.8, 41.2, 34.9, 28.2, 28.0, 14.8 ppm.;

Optical Rotation: $[\alpha]_D^{25} = +4.5^\circ$ ($c = 0.31$ g / 100 mL, CHCl_3);

HRMS (m/z) calc'd for $\text{C}_{28}\text{H}_{43}\text{N}_4\text{O}_8^+$ [M+H]⁺ 563.3075, found 563.3068

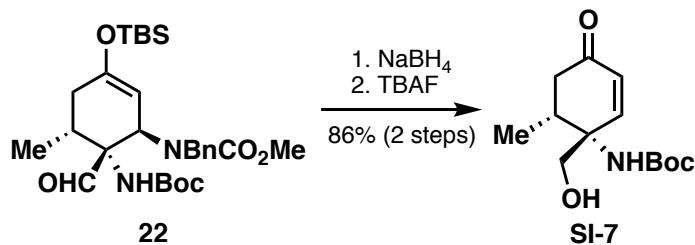


Experimental: A solution of **24** (2.08 g, 3.7 mmol, 1.0 eq) and Et_3N (3.1 mL, 22.2 mmol, 6.0 eq) in 61 mL DCM was added MsCl (0.55 mL, 7.4 mmol, 2.0 eq) at 0 °C, the reaction mixture was stirred at 0 °C for 0.5 h. MsCl (0.55 mL, 7.4 mmol, 2.0 eq) was added again and stirring was continued for 1 h at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with DCM (3×30 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 . Removal of the solvent under reduced pressure afforded the crude residue which was used directly in the next step without further purification.

To a solution of the crude mesylate obtained above in 53 mL THF was added TBAF (5.6 mL, 1 M in THF, 5.6 mmol, 1.5 eq) at 0 °C, the reaction mixture was stirred at the same temperature for 0.5 h. Another portion of TBAF (5.6 mL, 1 M in THF, 5.6 mmol, 1.5 eq) was added and the mixture was warmed to room temperature, stirring was continued for another 1 h at room temperature. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 . Removal of the solvent under reduced pressure afforded

the crude residue, which was purified by flash chromatography (SiO_2 , 4:1 \rightarrow 1:1 hexanes: EtOAc) to furnish compound (+)-**6** (1.1 g, 78%) as a white solid.

The enantiomeric excess of compound (+)-**6** was determined to be 95% ee via chiral HPLC analysis.



Experimental: To a solution of **22** (80.0 mg, 0.15 mmol, 1.0 eq) in MeOH/THF (v/v 2:1, 4.5 mL) was added NaBH_4 (7.4 mg, 0.20 mmol, 1.3 eq) slowly at 0°C , the reaction mixture was then warmed to room temperature and stirred for 40 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with DCM (3×10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 . Removal of the solvent under reduced pressure afforded the crude product which was directly used in the next step.

To a solution of the above obtained free alcohol intermediate in 3 mL THF under argon was added TBAF (1.0 mol/L in THF, 0.2 mL, 0.2 mmol, 1.3 eq) at room temperature. The reaction mixture was stirred at the same temperature for 20 min and quenched with sat. aq. NH_4Cl solution. The aqueous layers were extracted with EtOAc (3×15 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4 . Removal of the solvent under reduced pressure afforded the crude product which was purified by flash chromatography (SiO_2 , 4:1 \rightarrow 3:1 hexanes/EtOAc to 4:1 \rightarrow 3:1 hexanes/acetone) to afford **SI-7** (33.0 mg, 86%) as a colorless liquid over two steps.

Physical State: colorless liquid

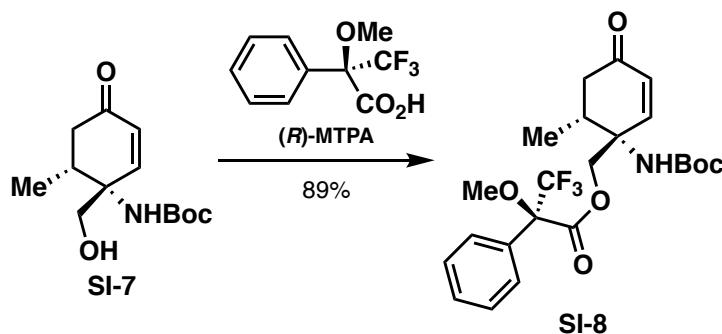
R_f Value: 0.23 (hexanes/acetone: 2/1)

Optical Rotation: $[\alpha]_D^{25} = +42.7^\circ$ ($c = 0.26$ g / 100 mL, CHCl_3)

¹H NMR (600 MHz, CDCl₃) δ 6.91 (d, *J* = 10.3 Hz, 1H), 6.03 (d, *J* = 10.2 Hz, 1H), 4.91 (s, 1H), 4.04 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.74 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.68 (br s, 1H), 2.66 – 2.58 (m, 1H), 2.53 (dd, *J* = 17.2, 4.8 Hz, 1H), 2.40 (dd, *J* = 17.2, 7.9 Hz, 1H), 1.43 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 198.4, 156.0, 148.9, 129.4, 80.8, 66.9, 58.7, 42.1, 34.0, 28.4, 15.7.

HRMS (m/z) calc'd for C₁₃H₂₂NO₄ [M-Boc+2H]⁺ 156.1019, found 156.1021.



Experimental: A solution of **SI-7** (23.0 mg, 0.09 mmol, 1.0 eq), (*R*)-MTPA (31.7 mg, 0.135 mmol, 1.5 equiv), DCC (55.7 mg, 0.27 mmol, 3.0 eq) and DMAP (2.2 mg, 0.018 mmol, 0.2 equiv) in 3 mL DCM was stirred at room temperature for 20 min. Solid was removed by filtration through Celite and the reaction mixture was quenched with sat. aq. NaHCO₃ solution. The aqueous layers were extracted with DCM (3×10 mL) and the combined organic layers were washed with brine and dried over Na₂SO₄. Removal of the solvent under reduced pressure afforded the crude product **which was subjected to ¹H NMR analysis to show a dr of 35.9:1, the ee of SI-7 was thus determined to be 95%**.

Furthermore, the crude mixture was purified by flash chromatography (SiO₂, 6:1→4:1 hexanes/EtOAc) to afford **SI-8** (38.0 mg, 89%) as a colorless liquid.

Physical State: colorless liquid

R_f Value: 0.57 (hexanes/EtOAc: 2/1)

Optical Rotation: [α]_D²⁵ = +25.8° (c = 1.60 g / 100 mL, CHCl₃)

¹H NMR (600 MHz, CDCl₃) δ 7.48 (d, *J* = 7.6 Hz, 2H), 7.43 – 7.37 (m, 3H), 6.89 (d, *J* = 10.4 Hz, 1H), 5.98 (d, *J* = 10.3 Hz, 1H), 4.92 (d, *J* = 11.1 Hz, 1H), 4.65 (s, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 3.50 (s, 3H), 2.49 – 2.36 (m, 3H), 1.41 (s, 9H), 1.01 (d, *J* = 6.6 Hz, 3H).

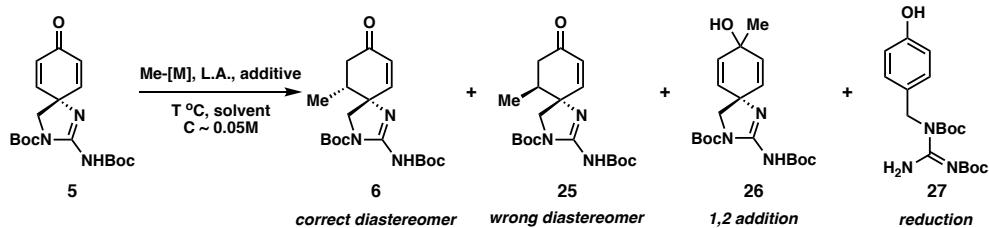
¹³C NMR (151 MHz, CDCl₃) δ 197.5, 166.2, 154.6, 148.2, 131.9, 130.1, 130.0, 128.7, 127.4, 123.3 (**CF₃**, q, *J* = 288.4 Hz), 84.8 (**C**, q, *J* = 27.9 Hz), 80.7, 66.8, 56.2, 55.6, 41.5, 34.2, 28.4, 15.2.

¹⁹F NMR (376 MHz, CDCl₃) δ -74.0.

HRMS (m/z) calc'd for C₂₃H₂₉F₃NO₆ [M-Boc+2H]⁺ 372.1417, found 372.1427.

IV) Optimization Tables

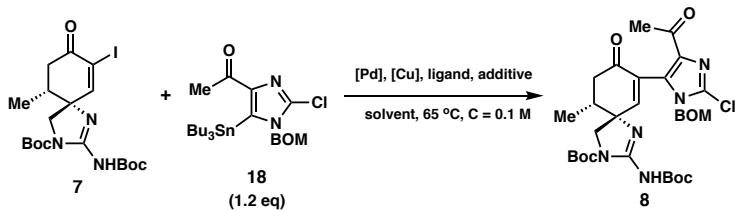
Methyl conjugate addition (step 3)



Me-[M]	Lewis acid (L.A.)	Additive	Temperature	Solvent	^a Result
CuI (1 eq), ^b MeLi (1 eq)	none	none	-78 °C	THF	N. R.
CuI (1 eq), MeLi (2 eq)	none	none	0 °C	THF	N. R.
CuBr·DMS (1 eq), MeLi (2 eq)	none	none	-20 °C → r.t.	THF	N. R.
CuCN (2 eq), MeLi (2 eq)	none	none	0 °C	THF	N. R.
CuI (1.5 eq), MeLi (3 eq)	TMSCl (2 eq)	none	-78 °C	Et ₂ O	N. R.
CuI (1.5 eq), MeLi (3 eq)	TMSOTf (2 eq)	none	0 °C	Et ₂ O	trace conversion
CuI (1.5 eq), MeLi (3 eq)	BF ₃ ·Et ₂ O (2 eq)	none	-78 °C	Et ₂ O/THF	5, 25 and 27
CuI (1.5 eq), MeLi (3 eq)	BF ₃ ·Et ₂ O (2 eq)	none	-20 °C	Et ₂ O/THF	25, 27 and de-Boc
CuI (1.5 eq), MeLi (3 eq)	BF ₃ ·Et ₂ O (2 eq)	HMPA (5 eq)	-40 °C	Et ₂ O/THF	25, 26 and 27
CuI (1.5 eq), MeLi (3 eq)	BF ₃ ·Et ₂ O (2 eq)	Bu ₃ P (2 eq)	-40 °C	Et ₂ O/THF	5 and de-Boc
CuI·P(OEt) ₃ (3 eq), MeLi (6 eq)	BF ₃ ·Et ₂ O (3 eq)	none	-78 °C	Et ₂ O/THF	25 and de-Boc
CuI (1.5 eq), MeLi (3 eq)	(C ₆ F ₅) ₃ B (eq)	none	-40 °C → r.t.	Et ₂ O/THF	messy
CuI (1 eq), ^c MeMgBr (2 eq)	TiCl ₄ (1 eq)	none	-40 °C → r.t.	Et ₂ O/THF	27
Ni(acac) ₂ (0.2 eq), ^d Me ₂ Zn (2 eq)	LiBr (1 eq)	none	0 °C → r.t.	toluene/THF	5 and 27
Cu(OTf) ₂ (0.2 eq), Me ₂ Zn (2 eq)	ⁱ BBBr ₃ (1 eq)	none	0 °C	toluene/THF	5 and 27
Ni(acac) ₂ (0.2 eq), ^e Me ₃ Al (1 eq)	none	none	0 °C → r.t.	toluene/THF	5 and 27
CuBr (0.2 eq), Me ₃ Al (1 eq)	none	none	0 °C → r.t.	toluene/THF	5 and 27
MeMgBr (1.5 eq)	none	^f LiHMDS (1 eq)	-40 °C	Et ₂ O/THF	^h 33%, d.r. > 20:1
MeLi (1.5 eq)	none	LiHMDS (1 eq)	-40 °C → r.t.	Et ₂ O/THF	5 and 26
Me ₂ Zn (1.5 eq)	none	LiHMDS (1 eq)	-40 °C → r.t.	toluene/THF	N. R.
CuI (1.5 eq), MeLi (3 eq)	none	LiHMDS (1 eq)	-40 °C → r.t.	Et ₂ O/THF	messy
MeMgBr (2.1 eq)	none	none	-40 °C → 0 °C	Et ₂ O/THF	42%, d.r. > 20:1
MeMgBr (5 eq)	none	^g HMPA:THF=1:12	-40 °C → 0 °C	Et ₂ O/THF	57%, d.r. > 20:1
MeMgBr (5 eq)	none	HMPA:THF=1:6.5	-40 °C → 0 °C	Et ₂ O/THF	72%, d.r. > 20:1

Note: a) the qualitative results were obtained by TLC, LCMS and crude NMR; b) 1.6 M Et₂O solution; c) 3.0 M Et₂O solution; d) 2.0 M toluene solution; e) 2.0 M toluene solution; f) 1.0 M THF solution; g) volume ratio; h) isolation yield of 6, d.r. was determined by crude NMR.; i) 1.0 M DCM solution

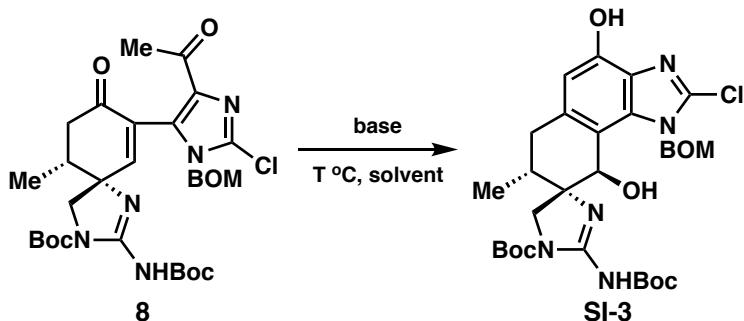
Stille cross-coupling (step 5)



[Pd]	[Cu]	Ligand	Additive	Solvent	^a Result
Pd(PPh ₃) ₄ (10 mol%)	none	none	none	THF	N. R.
Pd(PPh ₃) ₄ (10 mol%)	CuI (10 mol%)	none	none	THF	trace
Pd(Ph ₃ P) ₂ Cl ₂ (10 mol%)	CuI (50 mol%)	none	none	MeCN	< 10%
Pd[(o-Tol) ₃ P]Cl ₂ (10 mol%)	CuI (50 mol%)	none	none	MeCN	trace
Pd(PPh ₃) ₄ (10 mol%)	CuI (50 mol%)	none	CsF (1 eq)	THF	< 10%
Pd(PPh ₃) ₄ (10 mol%)	CuI (50 mol%)	none	LiCl (3 eq)	THF	< 10%
Pd(PPh ₃) ₄ (10 mol%)	CuI (50 mol%)	none	^b [Ph ₂ PO ₂][nBu ₄ N] (1 eq)	THF	< 10%
Pd(OAc) ₂ (10 mol%)	CuI (50 mol%)	SPhos (20 mol%)	none	THF	< 10%
Pd(OAc) ₂ (10 mol%)	CuI (50 mol%)	XPhos (20 mol%)	none	THF	< 10%
Pd(OAc) ₂ (10 mol%)	CuI (50 mol%)	(2-furyl) ₃ P (20 mol%)	none	THF	33%
Pd(OAc) ₂ (10 mol%)	CuI (50 mol%)	(2-thienyl) ₃ P (20 mol%)	none	THF	21%
Pd(OAc) ₂ (10 mol%)	CuI (50 mol%)	XantPhos (20 mol%)	none	THF	trace
Pd(OAc) ₂ (10 mol%)	CuI (50 mol%)	JohnPhos (20 mol%)	none	THF	trace
Pd(OAc) ₂ (10 mol%)	CuI (50 mol%)	(4-FPh) ₃ P (20 mol%)	none	THF	11%
Pd(OAc) ₂ (10 mol%)	CuI (50 mol%)	Ph ₃ As (20 mol%)	none	THF	40%
Pd(OAc) ₂ (10 mol%)	Cu(MeCN) ₄ PF ₆ (50 mol%)	(2-furyl) ₃ P (20 mol%)	none	THF	trace
Pd(OAc) ₂ (10 mol%)	CuBr (50 mol%)	(2-furyl) ₃ P (20 mol%)	none	THF	21%
Pd(OAc) ₂ (10 mol%)	CuTc (50 mol%)	(2-furyl) ₃ P (20 mol%)	none	THF	20%
Pd(OAc) ₂ (10 mol%)	Cu(acac) ₂ (50 mol%)	Ph ₃ As (20 mol%)	none	THF	59%
Pd(OAc) ₂ (12 mol%)	Cu(acac) ₂ (60 mol%)	Ph ₃ As (24 mol%)	none	THF	c70%

Note: a) the reactions were stopped after 16 h, "trace" means that 8 can only be detected on LCMS, the numbers were isolation yields of 8 and "< 10%" means that 8 can be seen on TLC but barely on crude NMR; b) see Chem. Commun. 2008, 2873-2875; c) 1.35 eq of 18 was used

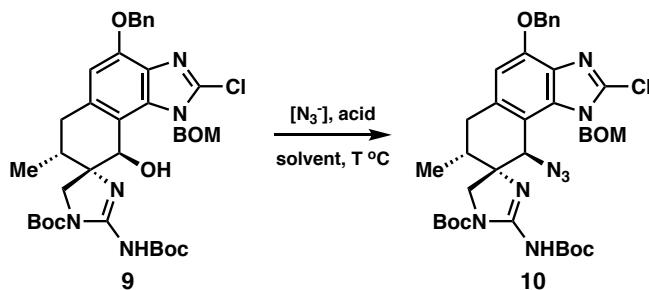
Aldol condensation (step 6 without one-pot Bn protection)



Base	Temperature	Solvent	^a Result
^b KOtBu (1 eq)	r.t.	tBuOH	messy
KOtBu (2 eq)	r.t.	tBuOH	messy
KOtBu (2 eq)	r.t.	THF	8 and SI-3 (32%)
NaNH ₂ (2 eq)	r.t.	THF	8 and SI-3 (trace)
KOtBu (2 eq) + ^c NH ₃ (2 eq)	r.t.	THF	messy
^b NaHMDS (2 eq)	r.t.	THF	8 and SI-3 (23%)
NaOMe (2 eq)	r.t.	MeOH	Boc deprotection
^b LiHMDS (2 eq)	-78 °C	THF	messy
^b KHMDS (2 eq)	-78 °C	THF	messy
DBU (2 eq)	80 °C	toluene	Boc deprotection
^d KOH (1.5 eq)	r.t.	^e THF/H ₂ O	41%
^d LiOH (1.5 eq)	r.t.	THF/H ₂ O	messy
^d NaOH (1.5 eq)	r.t.	THF/H ₂ O	46%
NaOH (1.5 eq)	r.t.	^e dioxane/H ₂ O	14%
NaOH (1.5 eq)	r.t.	^e acetone/H ₂ O	45%
NaOH (1.5 eq)	r.t.	^f DMF/H ₂ O	34%
NaOH (1.5 eq)	0 °C → r.t.	THF/H ₂ O	f 66%

Note: *a*) the numbers in parentheses were obtained by isolation; *b*) 1.0 M THF solution; *c*) 0.4 M THF solution; *d*) 2.0 M H₂O solution; *e*) volume ratio = 1:1; *f*) the yield slightly drops on gram scale

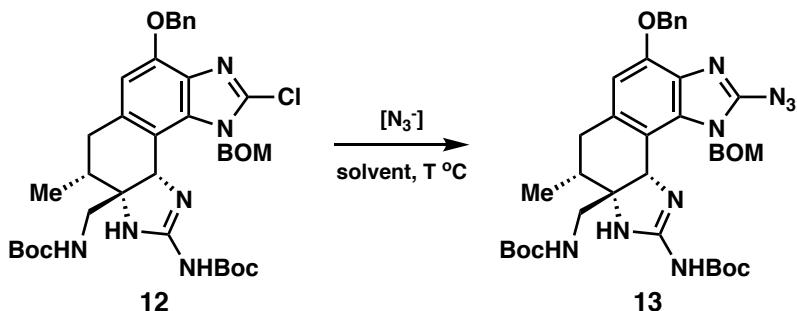
Benzyllic azidation (step 7)



[N ₃ ⁻]	Acid	Temperature	Solvent	^a Result
NaN ₃ (2 eq)	BF ₃ ·Et ₂ O (2 eq)	80 °C	dioxane	decomp.
NaN ₃ (2 eq)	BF ₃ ·Et ₂ O (2 eq)	r.t.	dioxane	Boc deprotection
TMSN ₃ (2 eq)	Zn(OTf) ₂ (10 mol%)	r.t.	DCM	Boc deprotection
TMSN ₃ (2 eq)	Zn(OTf) ₂ (1 eq)	40 °C	DCM	Boc deprotection
TMSN ₃ (2 eq)	BF ₃ ·Et ₂ O (2 eq)	0 °C	DCM	Boc deprotection
TMSN ₃ (2 eq)	InBr ₃ (10 mol%)	r.t.	DCM	Boc deprotection
TMSN ₃ (2 eq)	NaAuCl ₄ (10 mol%)	r.t.	DCM	Boc deprotection
TMSN ₃ (2 eq)	Bi(OTf) ₃ (10 mol%)	r.t.	DCM	^b 9 and 10 (trace)
TMSN ₃ (2 eq)	NbCl ₅ (10 mol%)	r.t.	DCM	9 and 10 (15%)
TMSN ₃ (2 eq)	NbCl ₅ (10 mol%)	r.t.	MeCN	9 and 10 (27%)
NaN ₃ (2 eq)	NbCl ₅ (10 mol%)	r.t.	MeCN	9 and 10 (trace)
TBAN ₃ (2 eq)	NbCl ₅ (10 mol%)	r.t.	MeCN	9 and 10 (28%)
TMSN ₃ (2 eq)	NbCl ₅ (25 mol%)	r.t.	MeCN	^c 39%
TMSN ₃ (2 eq)	NbCl ₅ (50 mol%)	r.t.	MeCN	^d 36%
TMSN ₃ (2 eq)	NbCl ₅ (1 eq)	r.t.	MeCN	^d 36%
TMSN ₃ (2.5 eq)	NbCl ₅ (15 mol%)	r.t.	^e MeCN/DCM	^e 54%
TMSN ₃ (7 eq)	NbCl ₅ (20 mol%)	r.t.	MeCN/DCM	^f 78%

Note: a) the reactions were stopped after 8 h; b) the numbers in parentheses were obtained by isolation of 10, “trace” means that 10 can be detected on LCMS but barely seen on TLC; c) there was significant amount of 9 left and Boc-deprotection happened; d) no 9 left but there was significant amount of Boc-deprotection byproduct; e) the reaction was stopped after 16 h; f) slightly longer time and more TMSN₃ and NbCl₅ would be needed for gram scale reaction; e) the volume ratio = 7:1

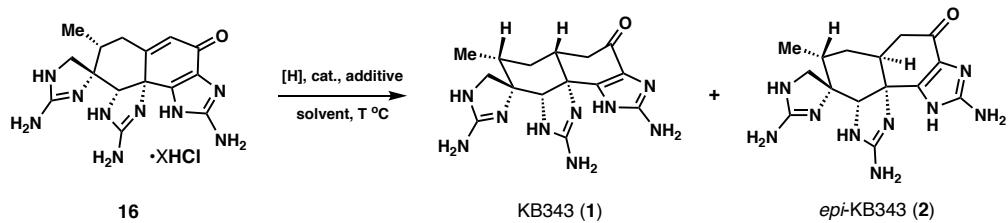
S_NAr reaction (step 10)



[N ₃ ⁻]	Temperature	Solvent	^a Result
NaN ₃ (4 eq)	80 °C	MeCN	N. R.
NaN ₃ (4 eq)	70 °C	DMF	trace
TMSN ₃ (4 eq)	70 °C	DMF	trace
^b NaN ₃ (10 eq)	70 °C	DMF	Boc deprotection + trace 13
NaN ₃ (10 eq)	75 °C	^c acetone/H ₂ O	Boc deprotection
NaN ₃ (10 eq)	75 °C	MeOH	Boc deprotection + trace 13
TBAN ₃ (10 eq)	70 °C	DMF	Boc deprotection + trace 13
NaN ₃ (10 eq)	70 °C	MeCN	Boc deprotection + trace 13
^b NaN ₃ (10 eq)	75 °C	MeCN	^d 19%
NaN ₃ (8 eq)	70 °C	MeNO ₂	Boc deprotection + trace 13
NaN ₃ (8 eq)	70 °C	DMSO	^d 20%
NaN ₃ (8 eq)	70 °C	sulfolane	^d 28%
NaN ₃ (8 eq)	70 °C	[BMIM][BF ₄]	^d 39%
NaN ₃ (8 eq)	70 °C	HFIP	Boc deprotection
NaN ₃ (8 eq)	^f 100 °C	[BMIM][BF ₄]	Boc deprotection
NaN ₃ (10 eq)	75 °C	[BMIM][OTf]	Boc deprotection
LiN ₃ (10 eq)	75 °C	[BMIM][BF ₄]	^d 42%
KN ₃ (10 eq)	75 °C	[BMIM][BF ₄]	Boc deprotection + trace 13
NaN ₃ (50 eq)	70 °C	[BMIM][BF ₄]	^e 73%

Note: a) the reactions were stopped after 16 h, the numbers were isolation yield of 13 and “trace” means that only a small peak of 13 can be detected on LCMS; b) 10 eq of 15-crown-5 was added; c) the volume ratio = 1:1 ; d) there was significant amount of Boc deprotection byproduct; e) longer reaction time was needed and (Boc)₂O and Et₃N were added after the reaction

1,4 reduction of the enone (step 14)

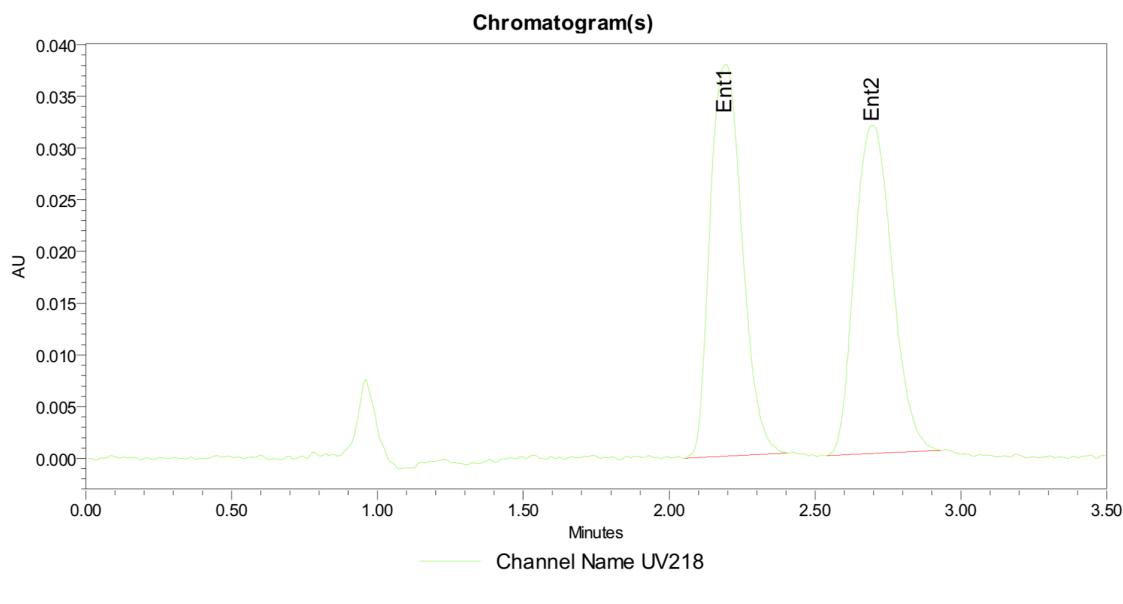


cat.	δ [H]	additive	solvent	Temperature	^a Result (1 : 2)
Pd(OH) ₂ /C (20 wt.%)	H ₂	none	MeOH	r.t.	1 : 5.7
Pd/C (10 wt.%)	H ₂	none	MeOH	r.t.	1 : 2.6
Rh/Al ₂ O ₃ (5 wt.%)	H ₂	none	MeOH	r.t.	1 : 9.7
RhCl(PPh ₃) ₃	H ₂	none	MeOH	r.t.	low conversion
[Rh(cod)Cl] ₂	H ₂	Ph ₃ P, AgBF ₄	^f MeOH/DCM	r.t.	low conversion
pyrrolidine	Hantzsch ester	AlCl ₃	MeCN	80 °C	low conversion
Cu(OAc) ₂	PMHS	tBuOH	^f EtOH/toluene	r.t.	N. R.
NiCl ₂ ·6H ₂ O	NaBH ₄	none	MeOH	-78 °C	1 : 2.2
Fe(acac) ₃	PhSiH ₃	PhSH	EtOH	r.t.	^c only 2
Mn(dpm) ₃	PhSiH ₃	TBHP	ⁱ PrOH	r.t.	^c 16
none	^d Sml ₂	none	H ₂ O	r.t.	^c 16
none	Mg	HCl	MeOH	r.t.	^c 16
L ₁ -Pd(OTf) ₂ ·H ₂ O	EtOH	4 Å MS	EtOH	r.t.	low conversion
Pd/BaSO ₄ (5 wt.%)	H ₂	none	MeOH	r.t.	1 : 2.5
bakers' yeast	D-glucose	pH buffer	EtOH	40 °C	N. R.
(MeCN) ₂ Rh(cod)BF ₄	Et ₃ SiH	(+)-DIOP	MeOH	r.t.	^c only 2
L ₂ Rh(cod)BF ₄	Et ₃ SiH	none	MeOH	r.t.	^c only 2
RhCl(PPh ₃) ₃	Et ₃ SiH	none	MeOH	r.t.	^e only 2
CuCl ₂	NaBH ₄	none	MeOH	0 °C	1 : 6.5
Pd/C (10 wt.%)	H ₂	none	MeOH	0 °C	1 : 1.4
Pd/C (10 wt.%)	H ₂	none	MeOH	-20 °C	^c 1 : 8.4
Pd/C (10 wt.%)	H ₂	none	MeOH	40 °C	1 : 2.8
Pd/C (10 wt.%)	H ₂	none	H ₂ O	r.t.	1 : 13.1
Pd/C (10 wt.%)	H ₂	none	EtOH	r.t.	^c 1 : 2.8
Pd/C (10 wt.%)	H ₂	none	ⁱ PrOH	r.t.	N. R.
Pd/C (10 wt.%)	H ₂	none	TFA	r.t.	N. R.
Pd/C (5 wt.%)	H ₂	none	MeOH	r.t.	1 : 1.7
Pd/C (5 wt.%)	H ₂	none	MeOH	0 °C	1.1 : 1
Pd/C (5 wt.%)	H ₂	none	MeOH	-10 °C	^e 1.3 : 1
Pd/C (5 wt.%)	H ₂	^g AgSbF ₆	MeOH	r.t.	1 : 1.7
Pd/C (5 wt.%)	H ₂	^g AgOTs	MeOH	r.t.	^e 1 : 1.5
Pd/C (5 wt.%)	H ₂	^g AgOTf	MeOH	r.t.	1.1 : 1
Pd/C (5 wt.%)	H ₂	^g AgTFA	MeOH	r.t.	^e 1.1 : 1
Pd/C (5 wt.%)	H ₂	^h BBBr ₃	MeOH	r.t.	1 : 2.0
Pd/C (5 wt.%)	H ₂	^g AgOTf	MeOH	0 °C	^e 1.9 : 1
Pd/C (5 wt.%)	H ₂	^g AgOTf	MeOH	-10 °C	^e 2.0 : 1
Pd/C (5 wt.%)	H ₂	TfOH	MeOH	0 °C	1.7 : 1
Pd/C (5 wt.%)	H ₂	TfOH	MeOH	-10 °C	2 : 1

Note: a) the reactions were stopped after 8 h unless stated otherwise, the product ratio was calculated based on LC trace integration or isolation yield, "low conversion" means that LCMS trace mainly showed the peak of 16; b) H₂ balloon was used unless stated otherwise; c) significant amount of re-aromatized byproduct was generated; d) 0.1 M THF solution; e) significant amount of 16 was left after the reaction; f) the volume ration is 9:1; g) the silver salt was added to the MeOH solution of 16 before the hydrogenation to exchange the counter ion and the resulting AgCl precipitation was removed by filtration; h) BBBr₃ was used in the previous deprotection step to generate the HBr salt; m) the reaction was stopped after 7 d; n) the reaction was stopped after 15 d; L₁ = (S)-BINAP; L₂ = (R,R)-Et-DuPhos.

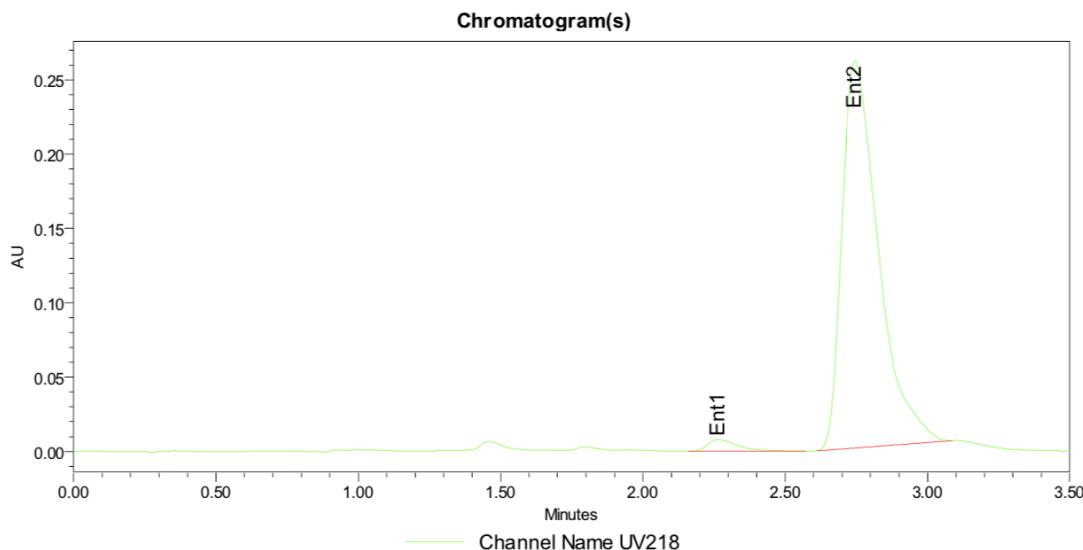
V) ee Determination

The LC trace of the racemic 6



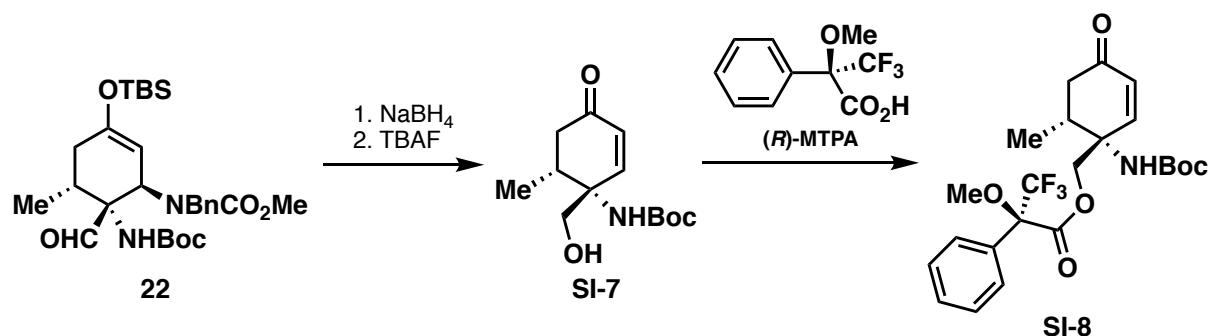
Peak Info								
	Channel Name	Name	RT	Area	Height (μ V)	ent1	ent2	ee
1	UV218	Ent1	2.19	289503	37916	50.44	49.56	0.88
2	UV218	Ent2	2.70	284454	31754	50.44	49.56	0.88

The LC trace of the enantio-enriched 6

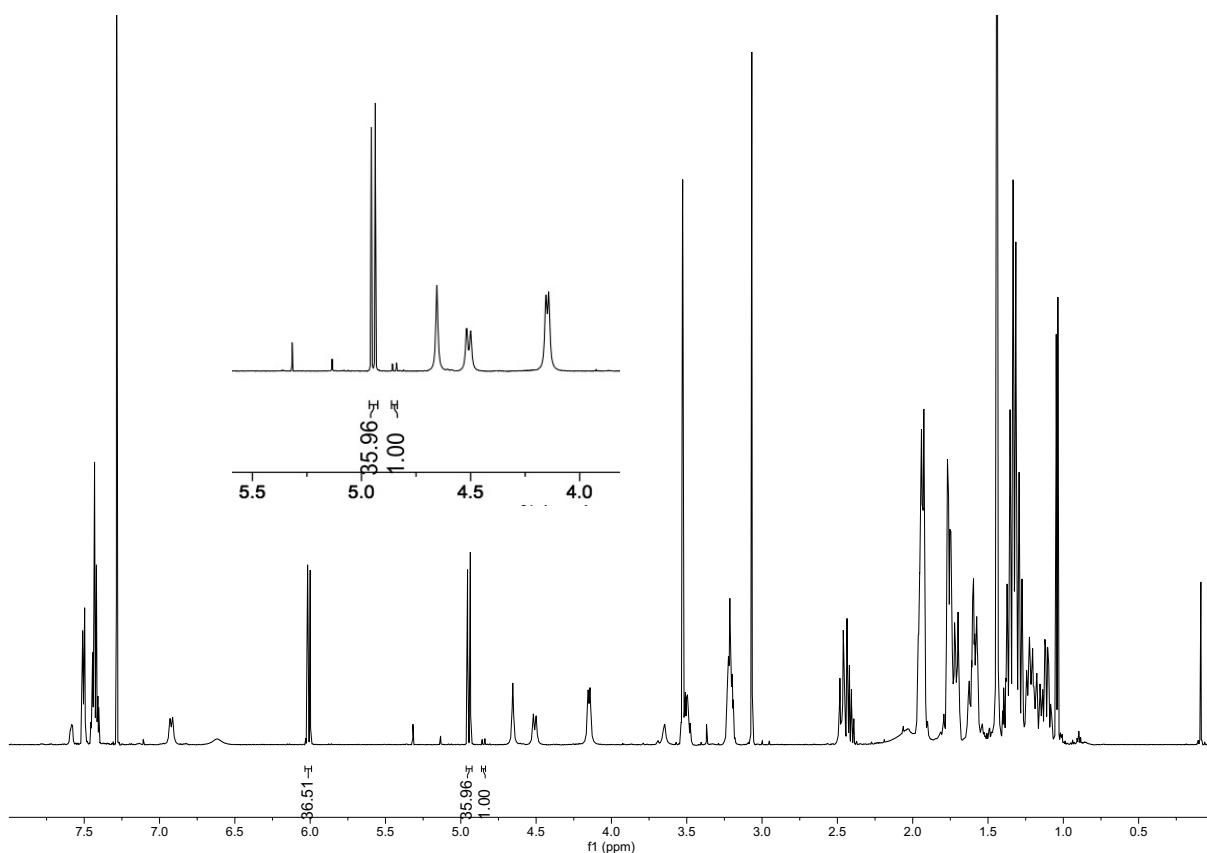


Peak Info								
	Channel Name	Name	RT	Area	Height (μ V)	ent1	ent2	ee
1	UV218	Ent1	2.26	59080	8024	2.49	97.51	-95.02
2	UV218	Ent2	2.74	2313405	260503	2.49	97.51	-95.02

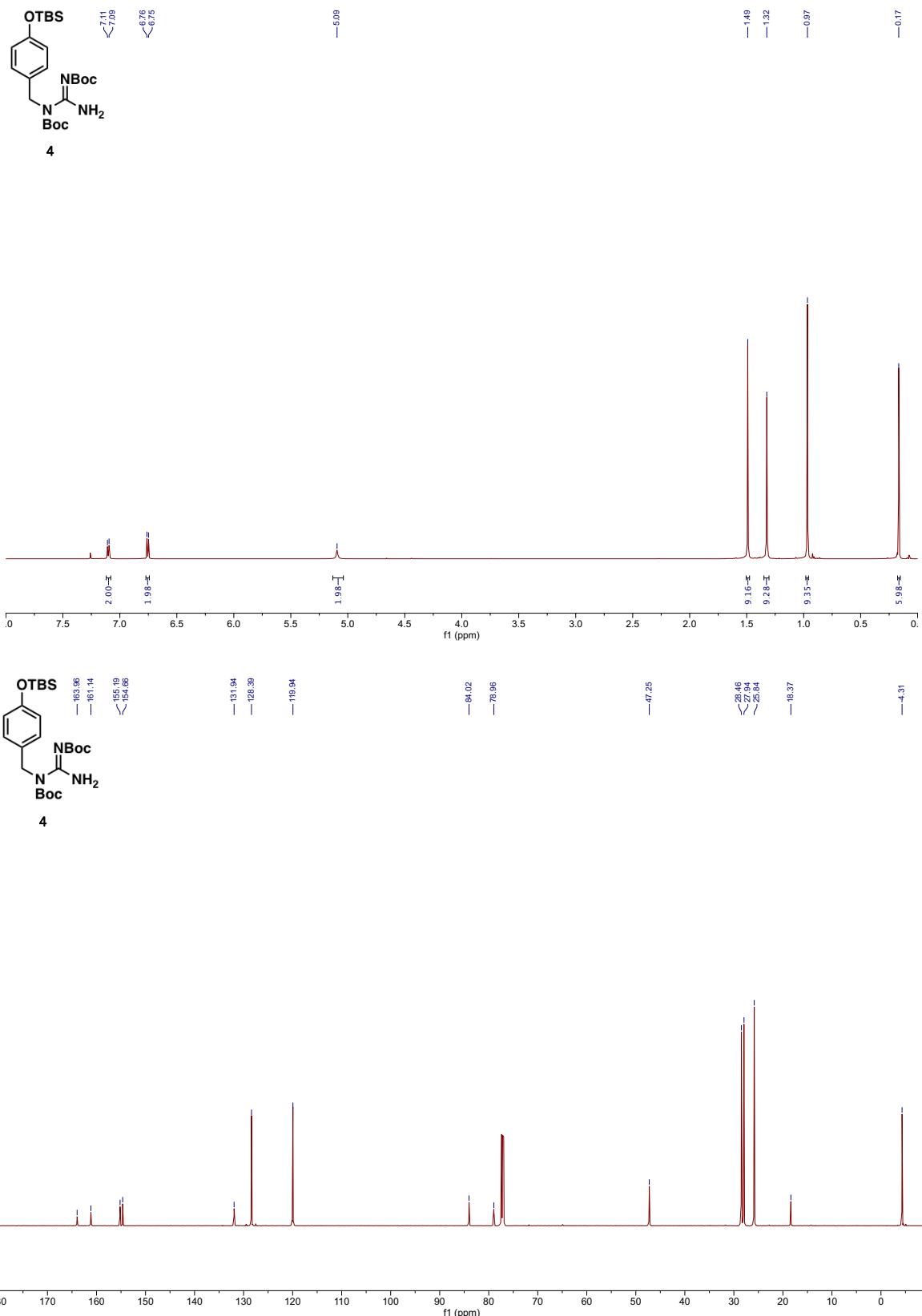
The synthesis of the Mosher's acid ester

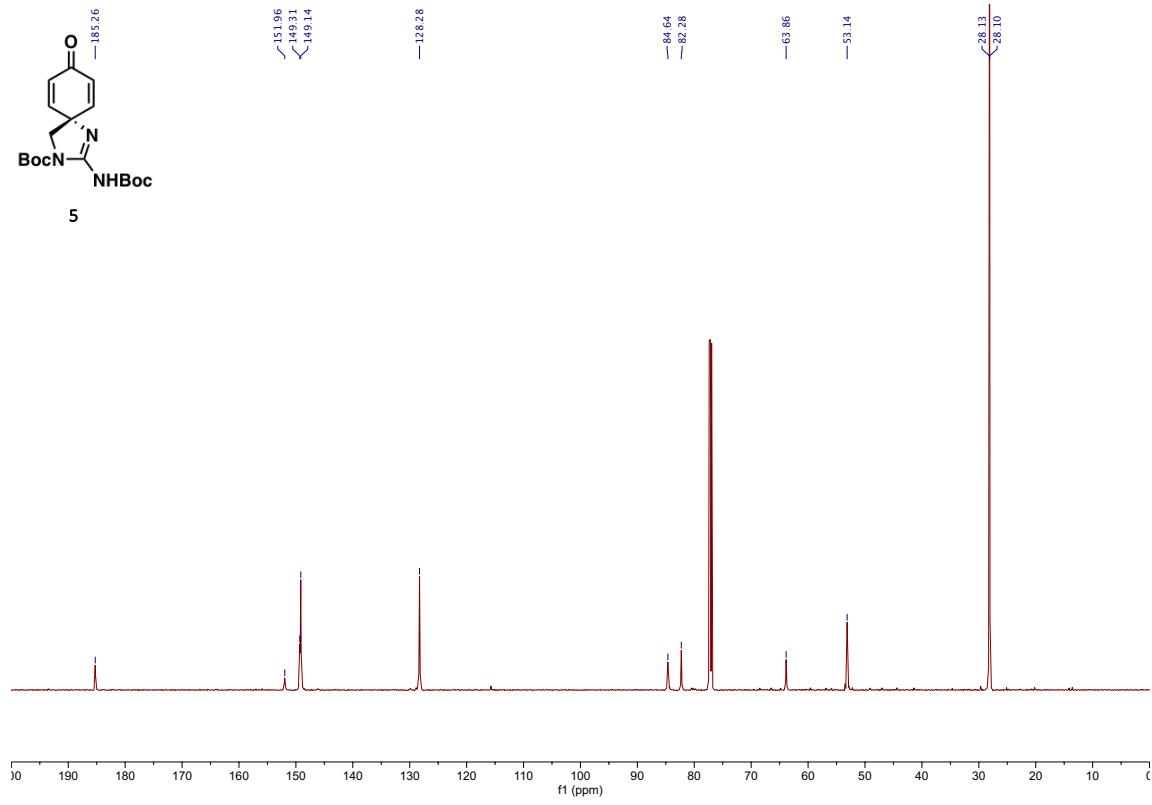
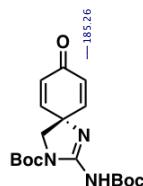
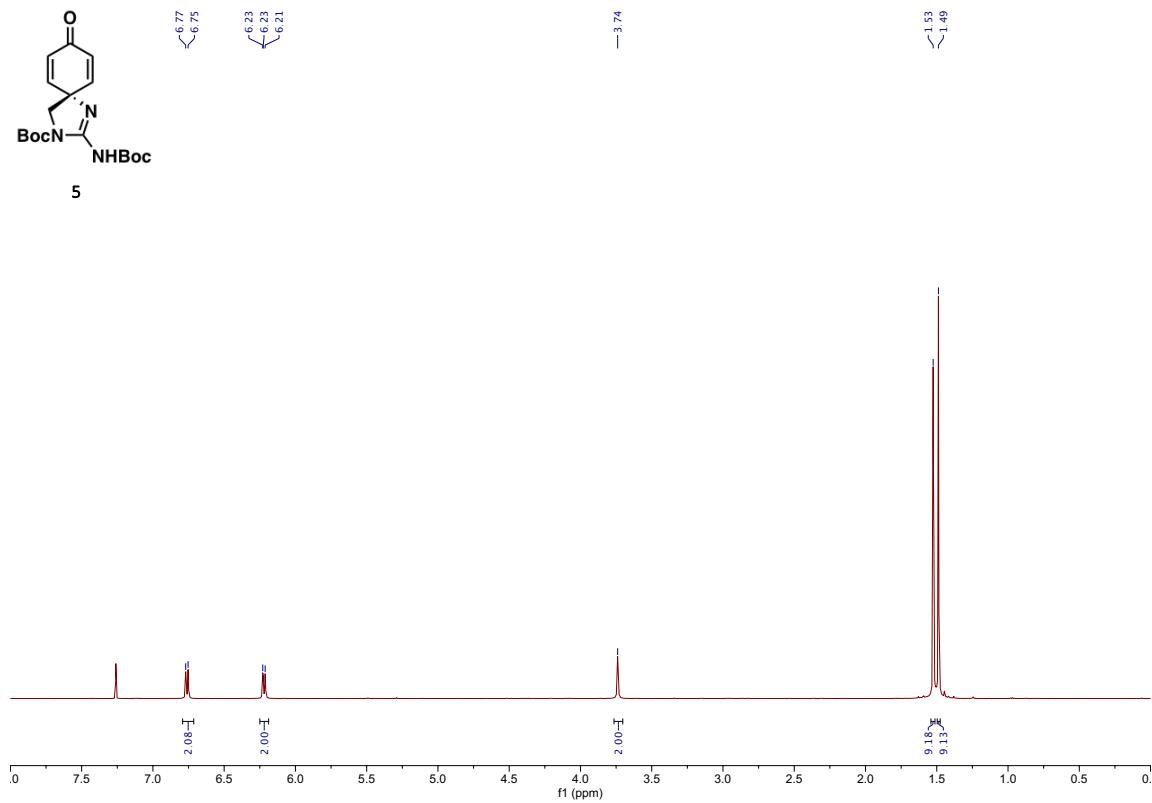
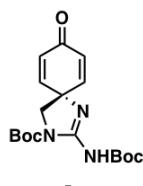


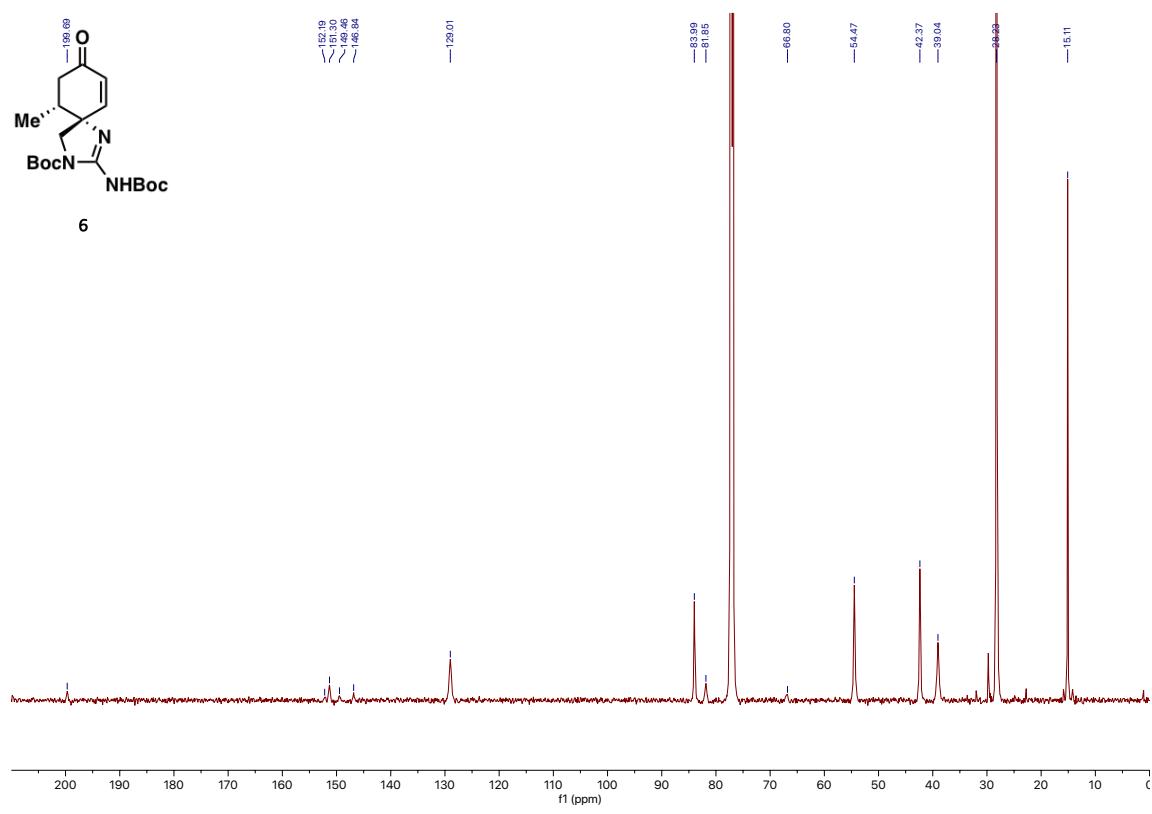
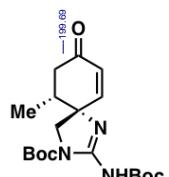
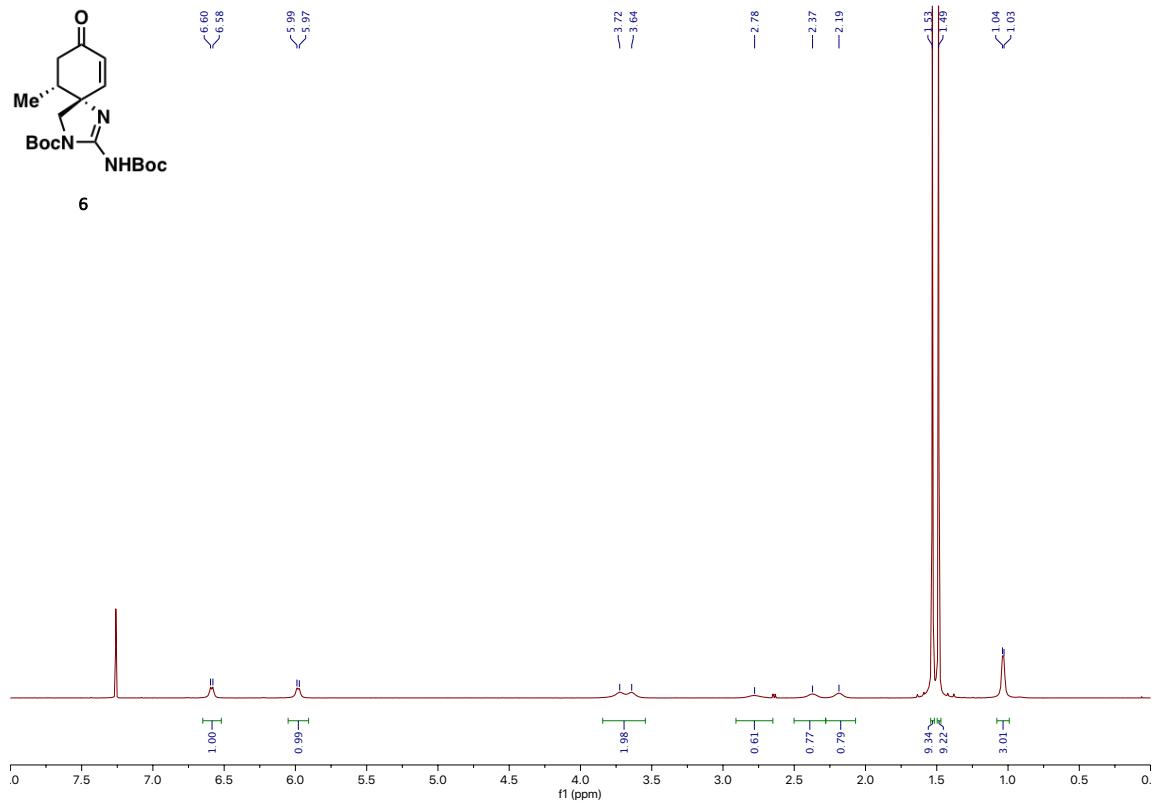
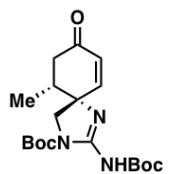
The ¹H NMR integration of Mosher's acid ester for ee measurement

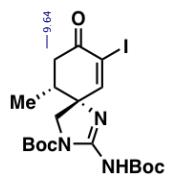


VI) NMR Spectra

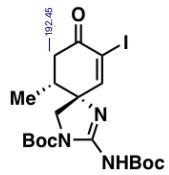
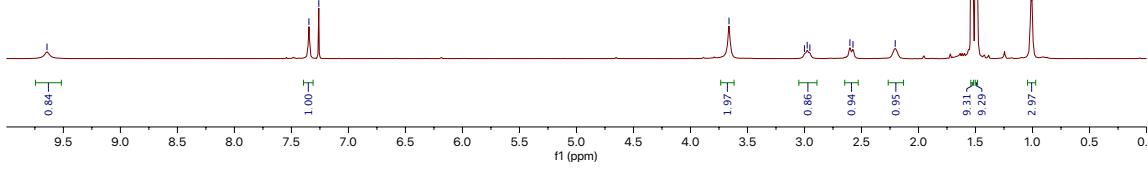




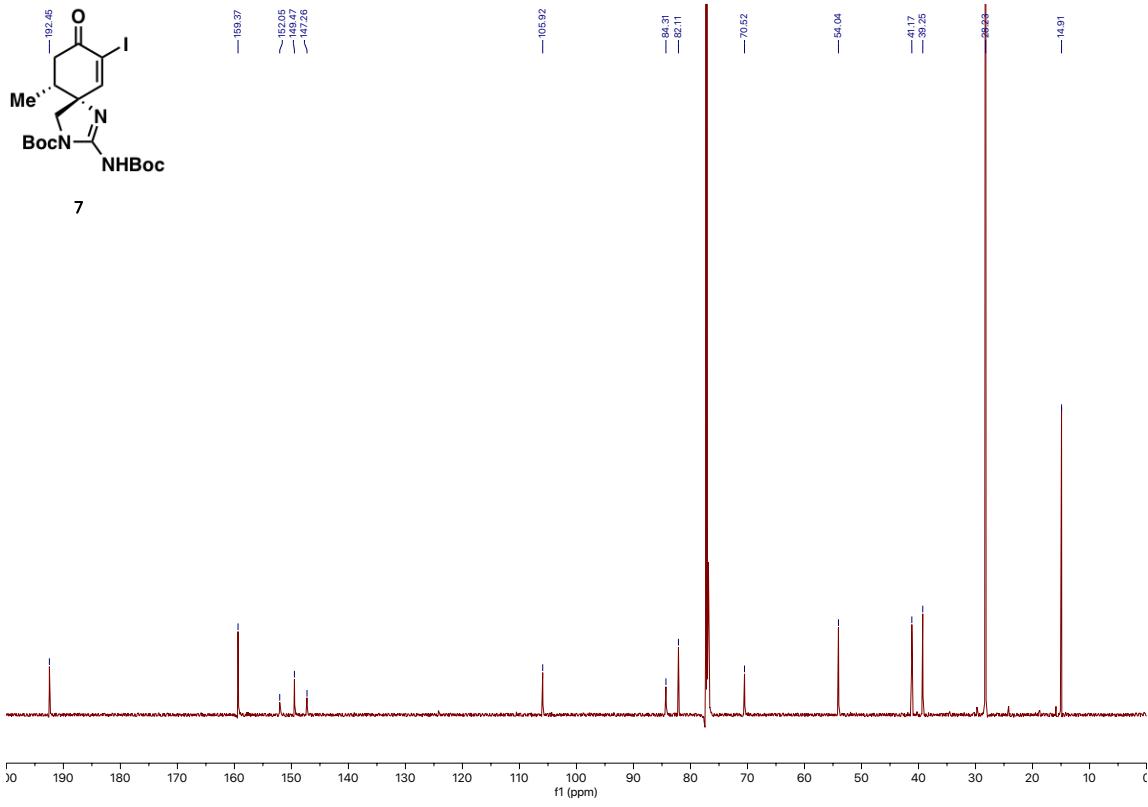


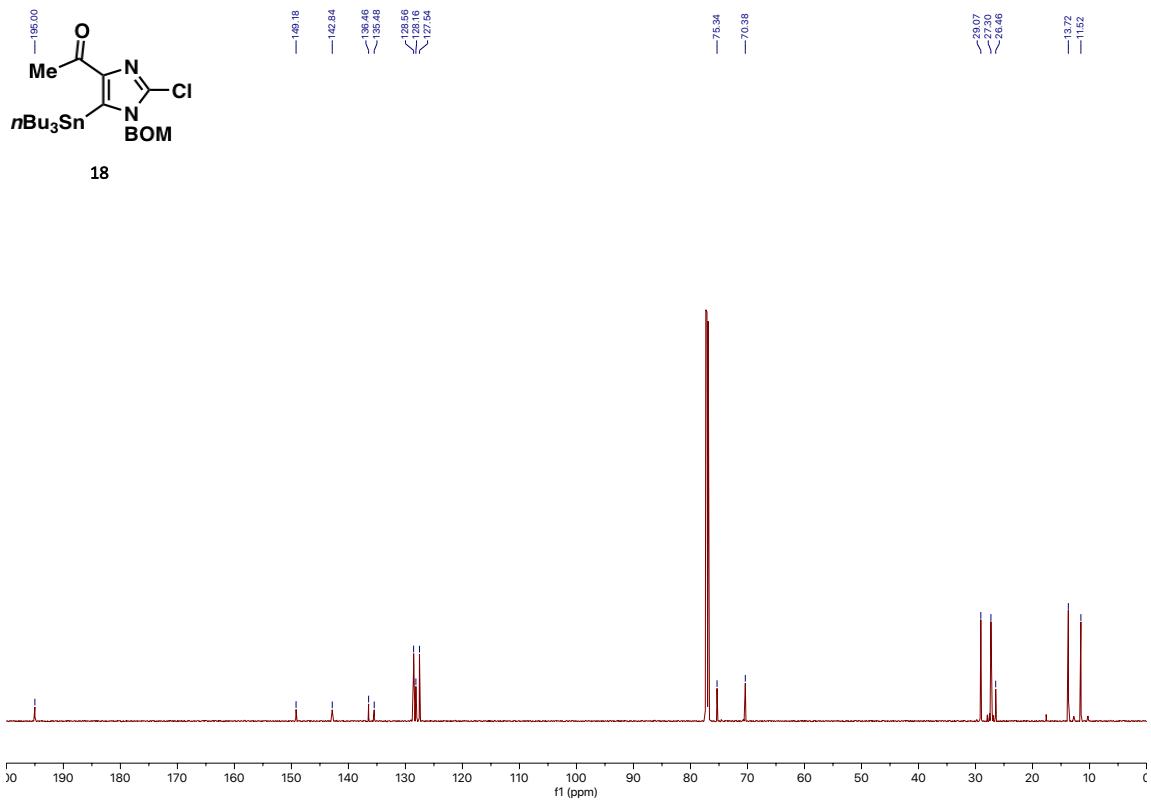
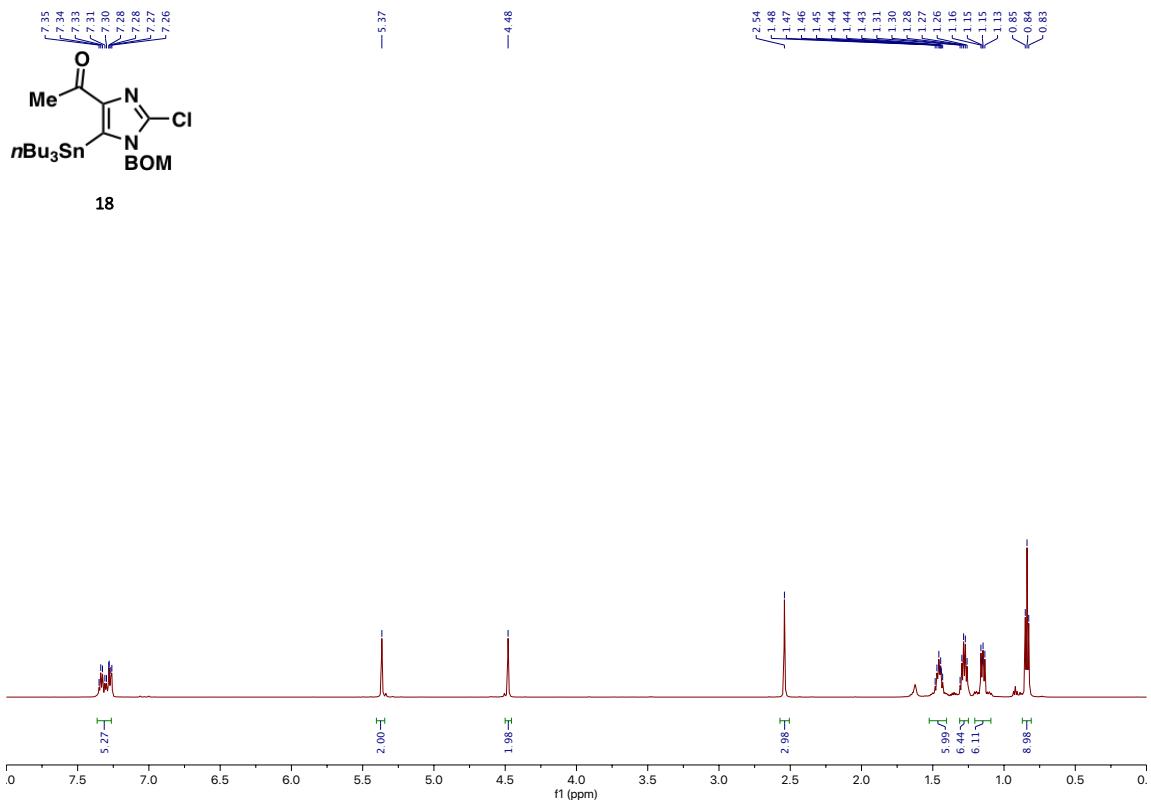


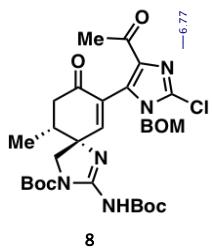
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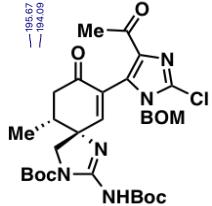
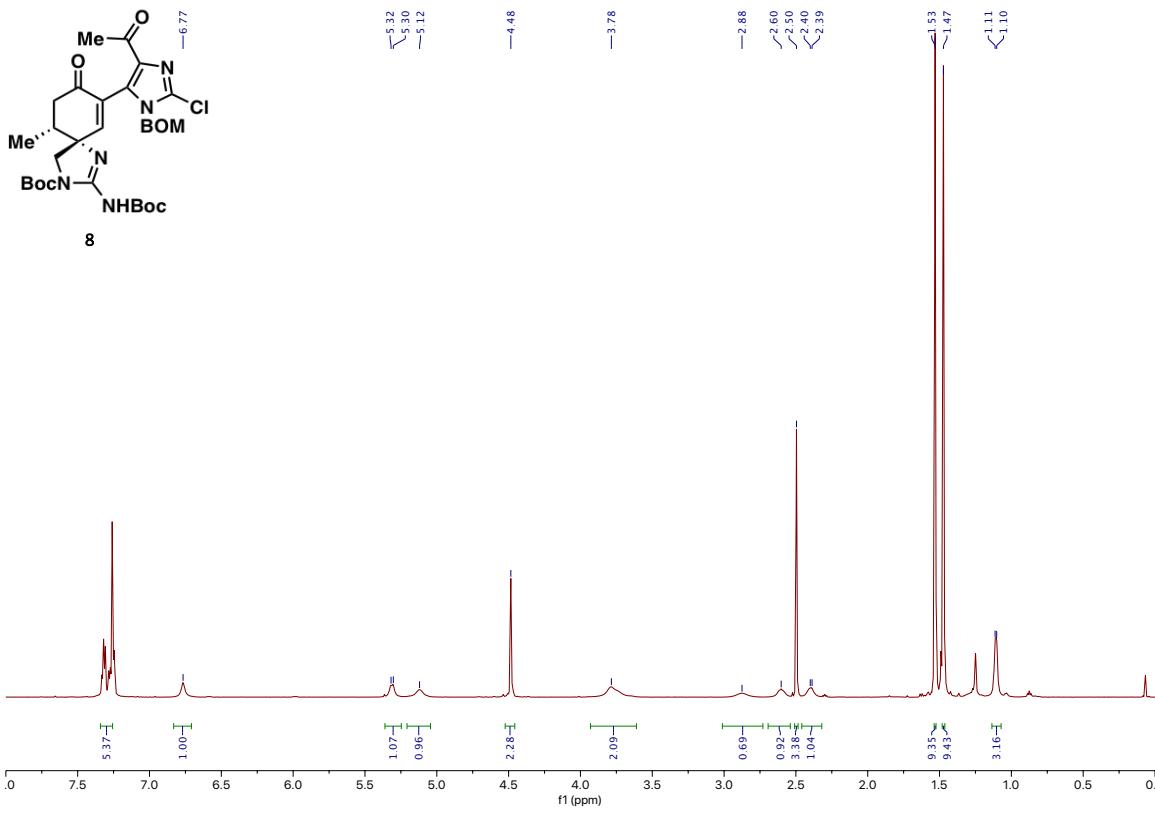
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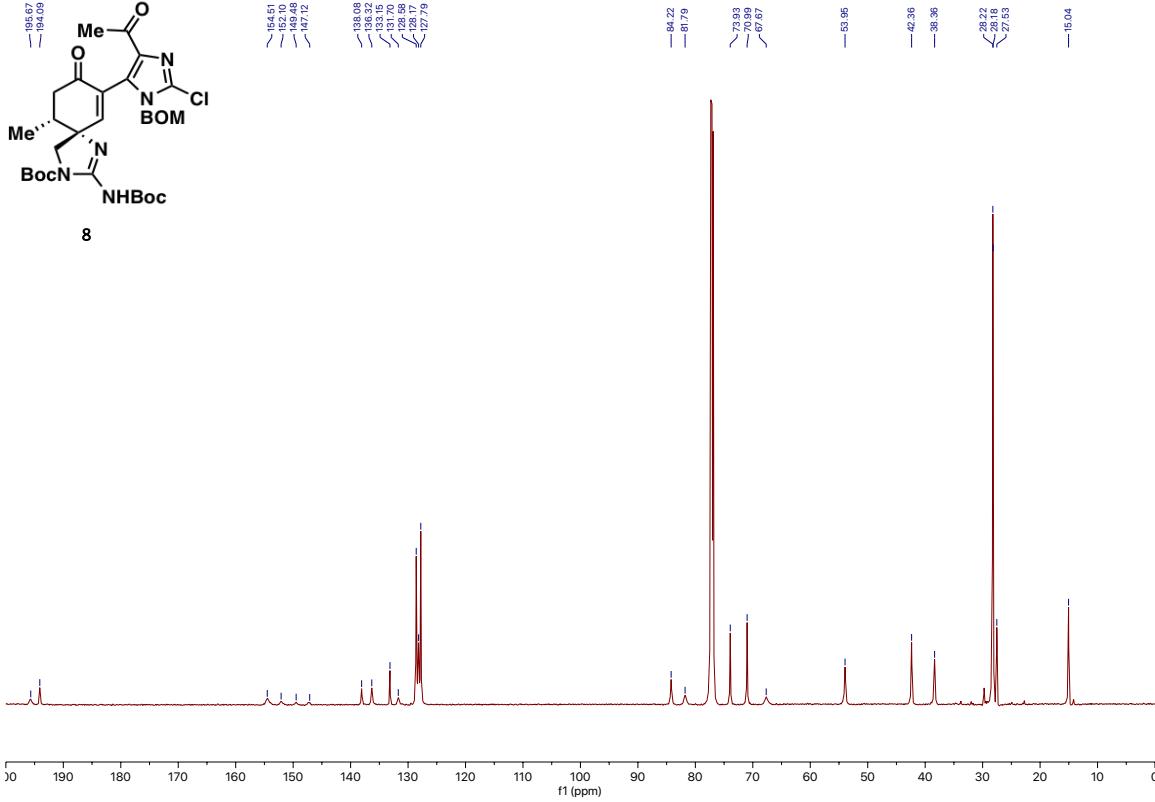


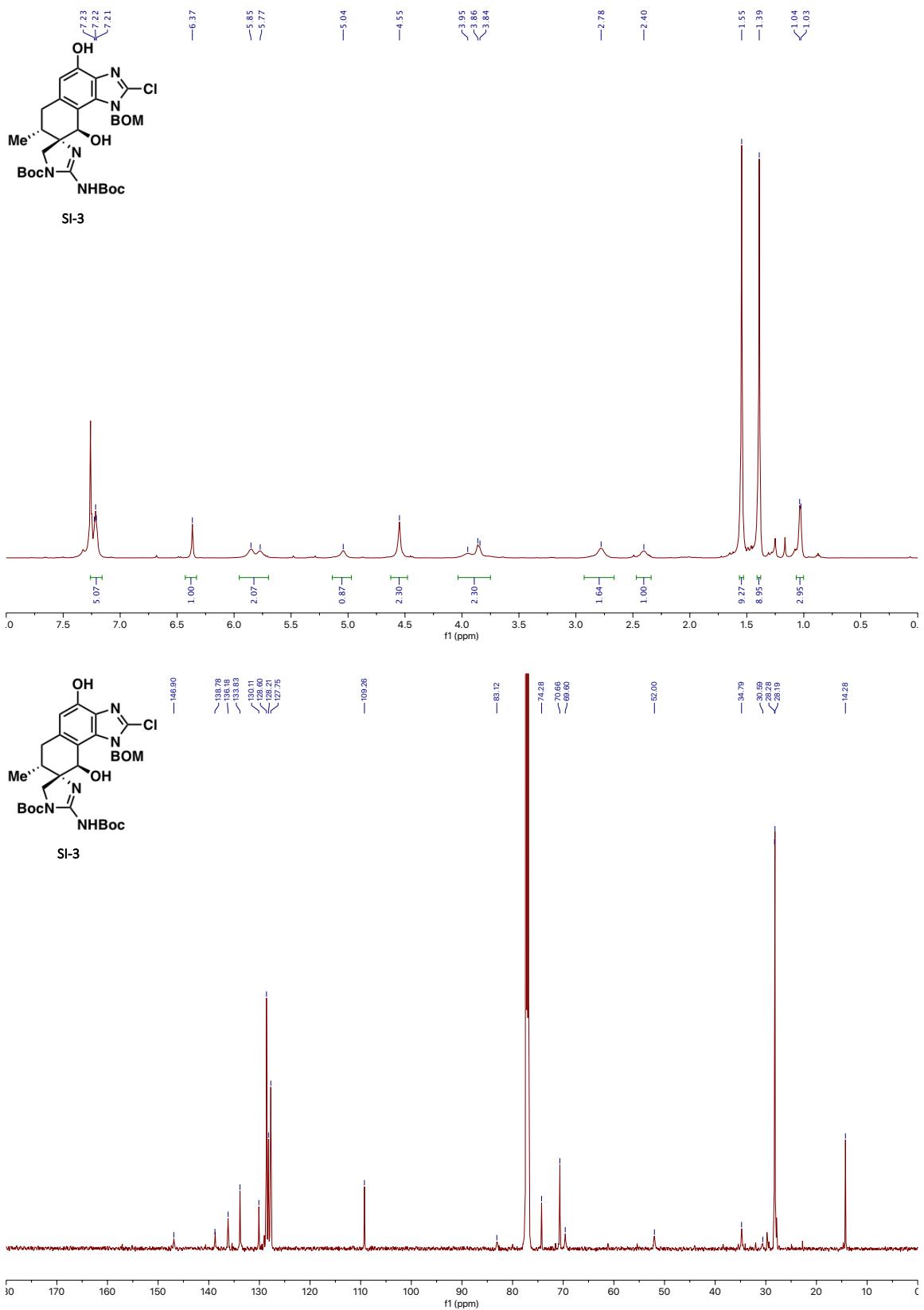


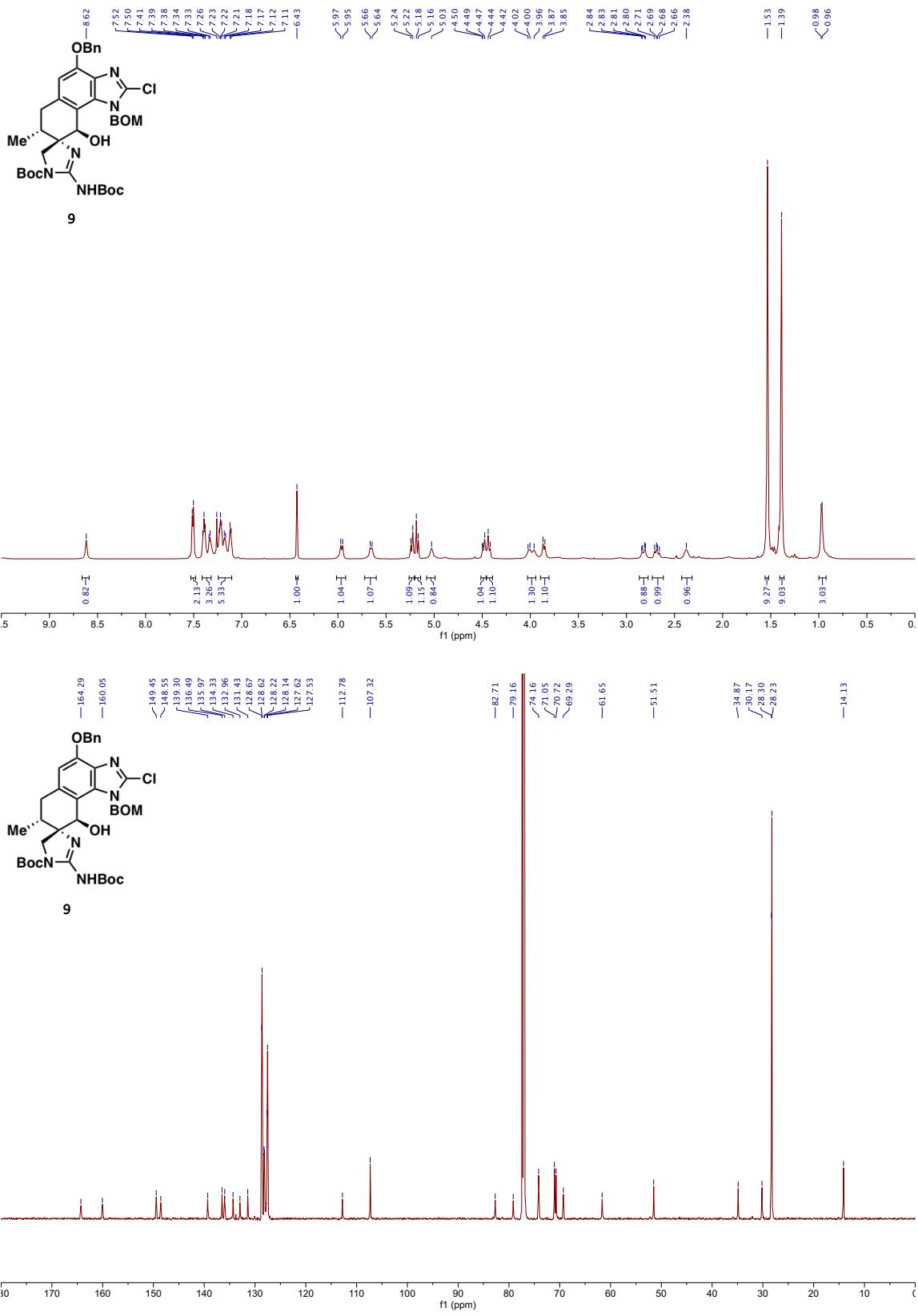
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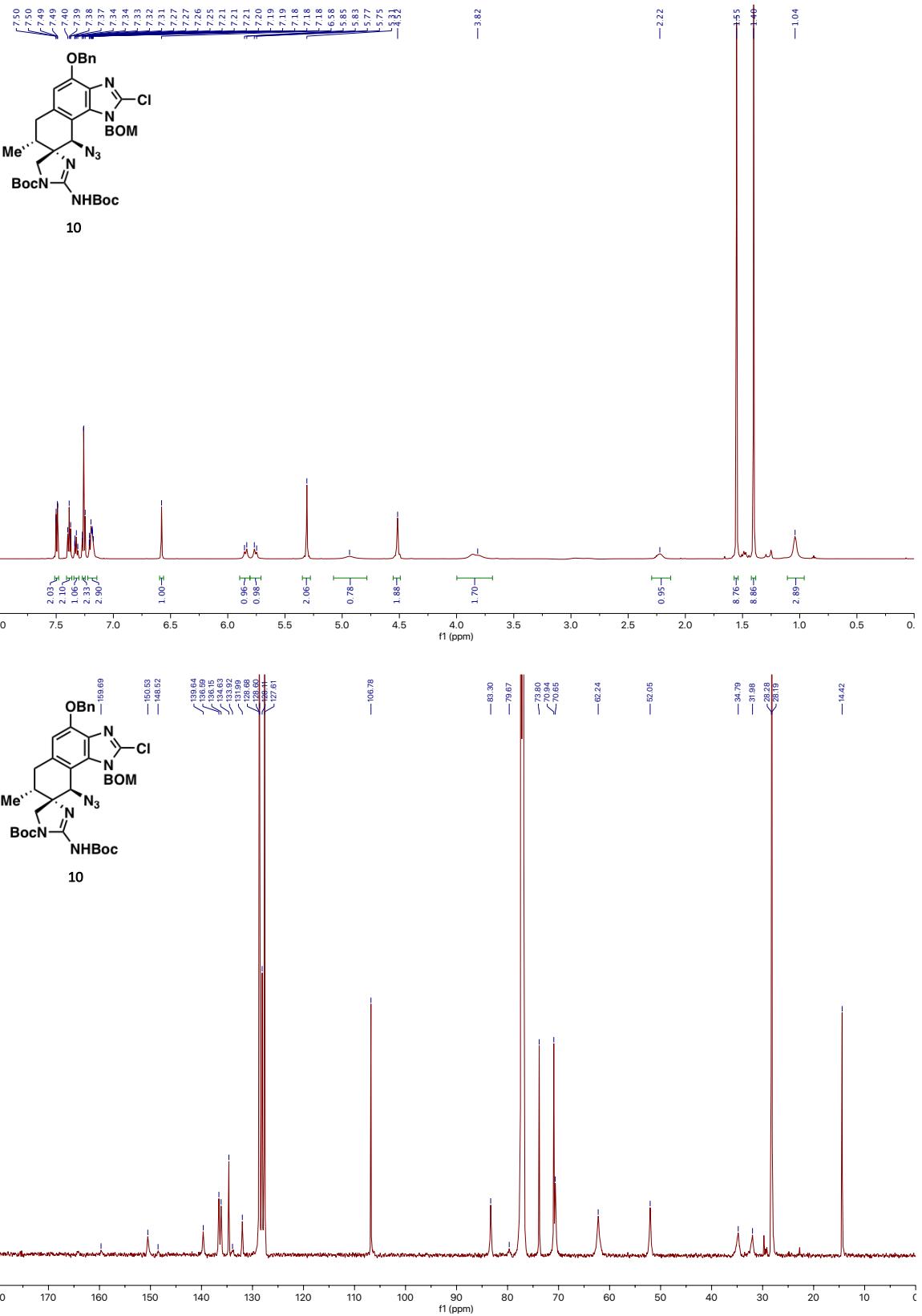


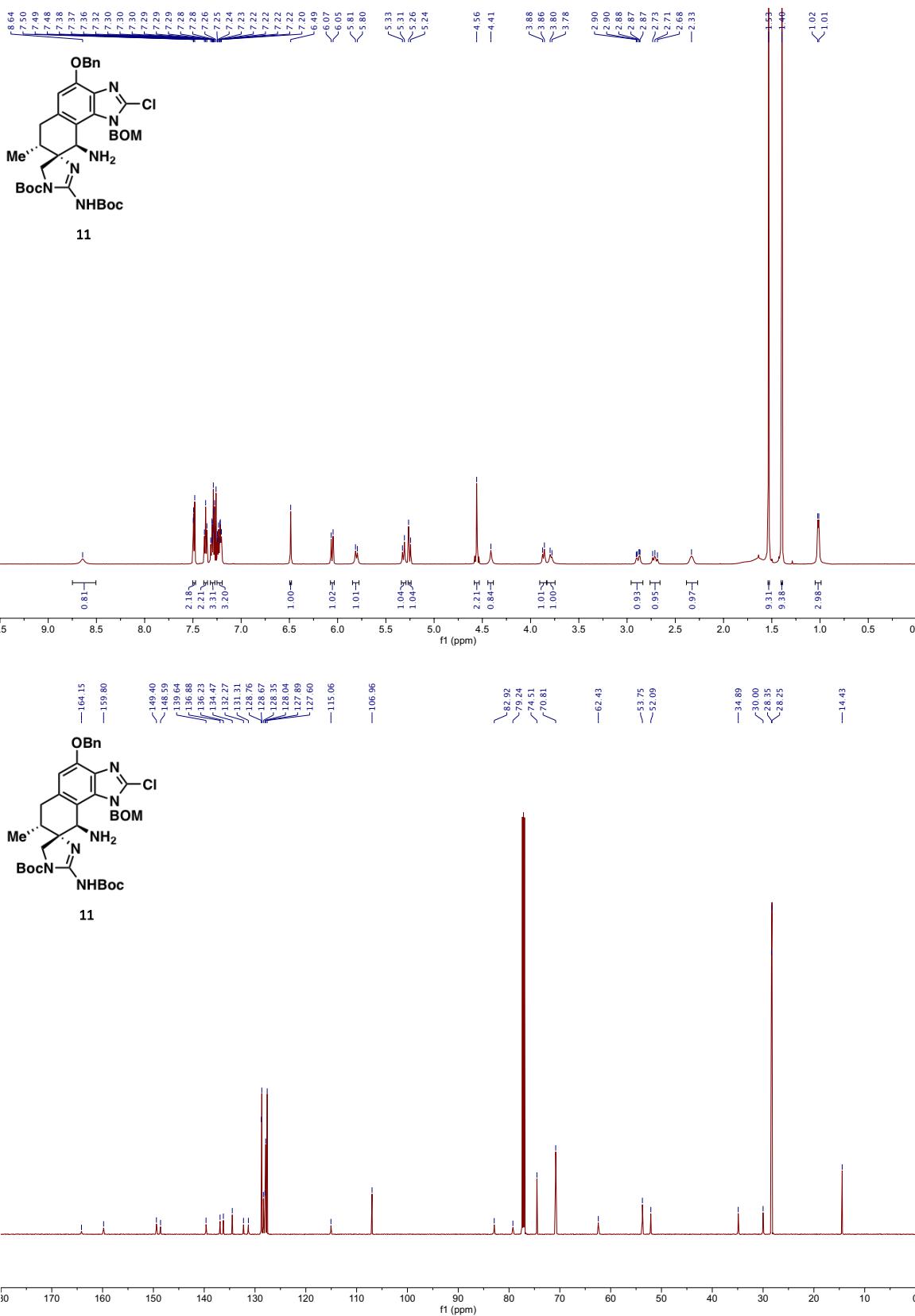
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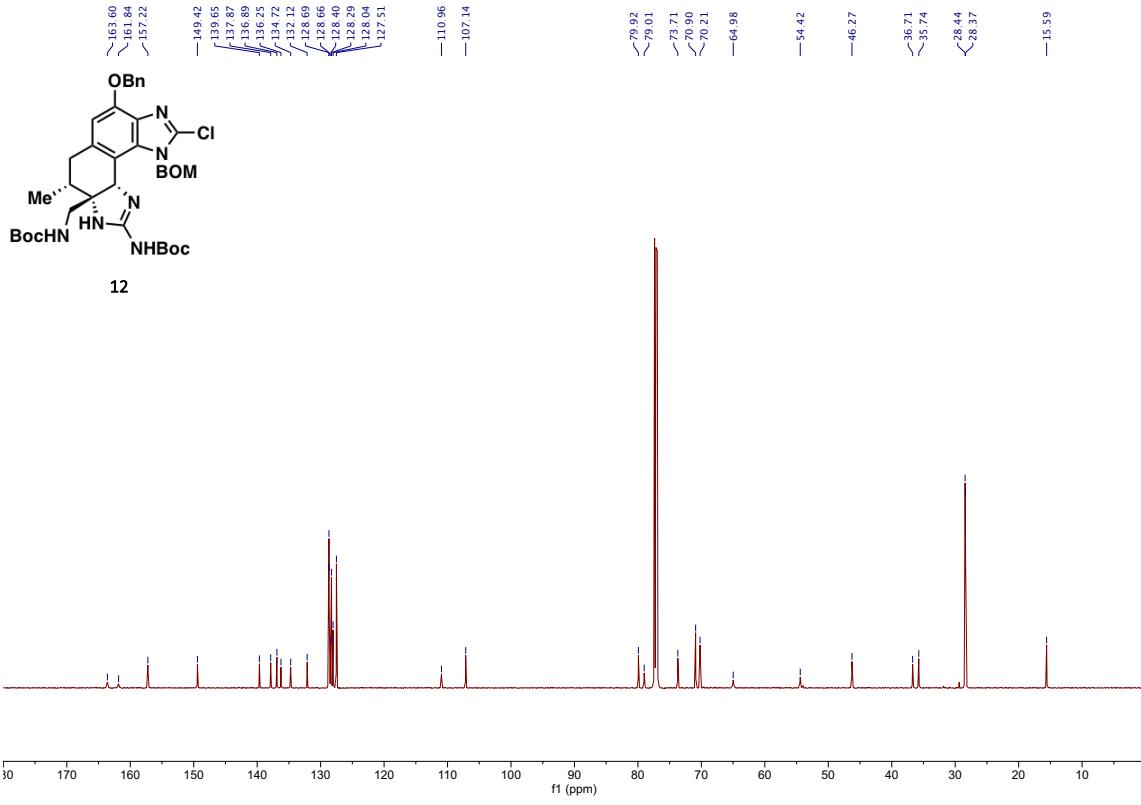
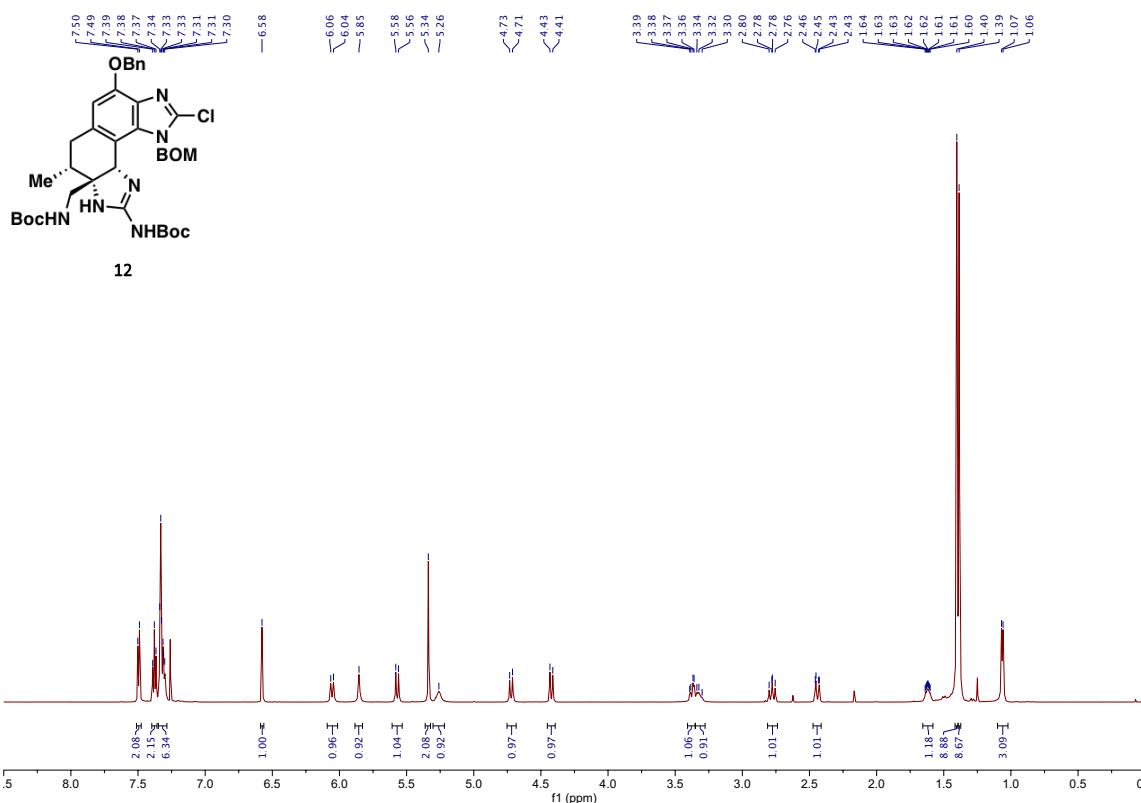


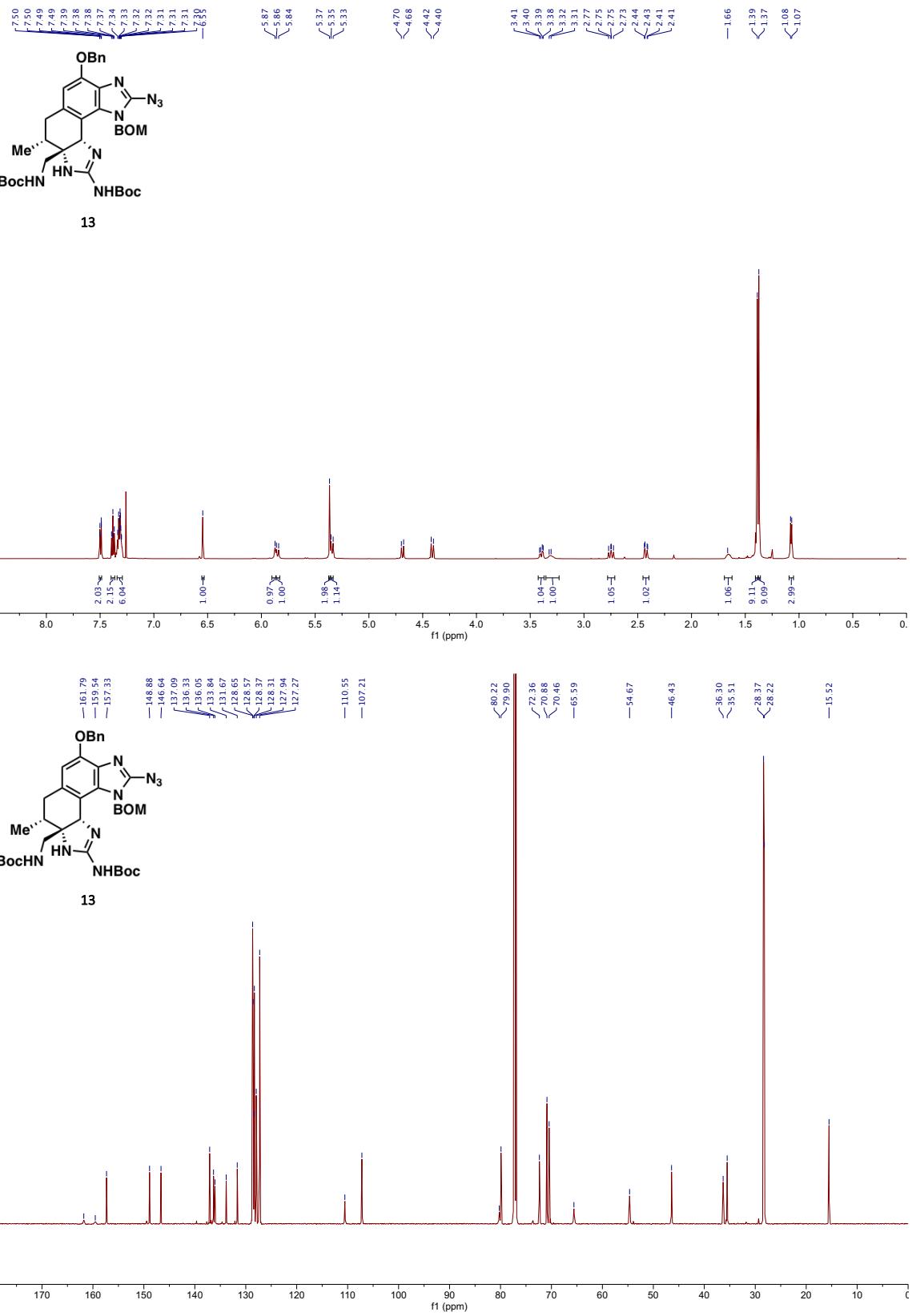


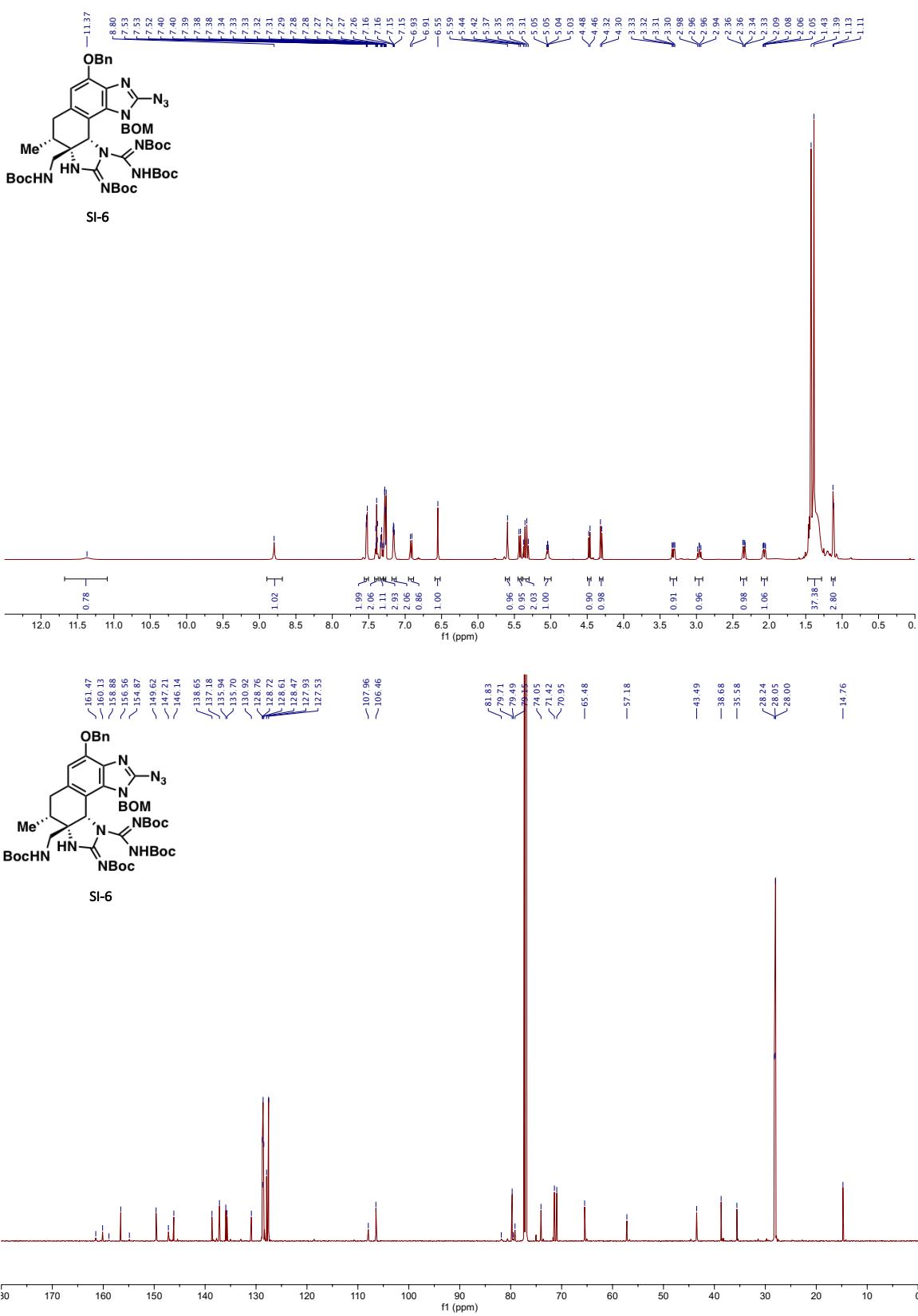


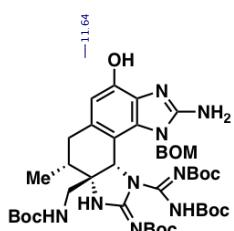




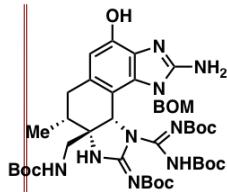
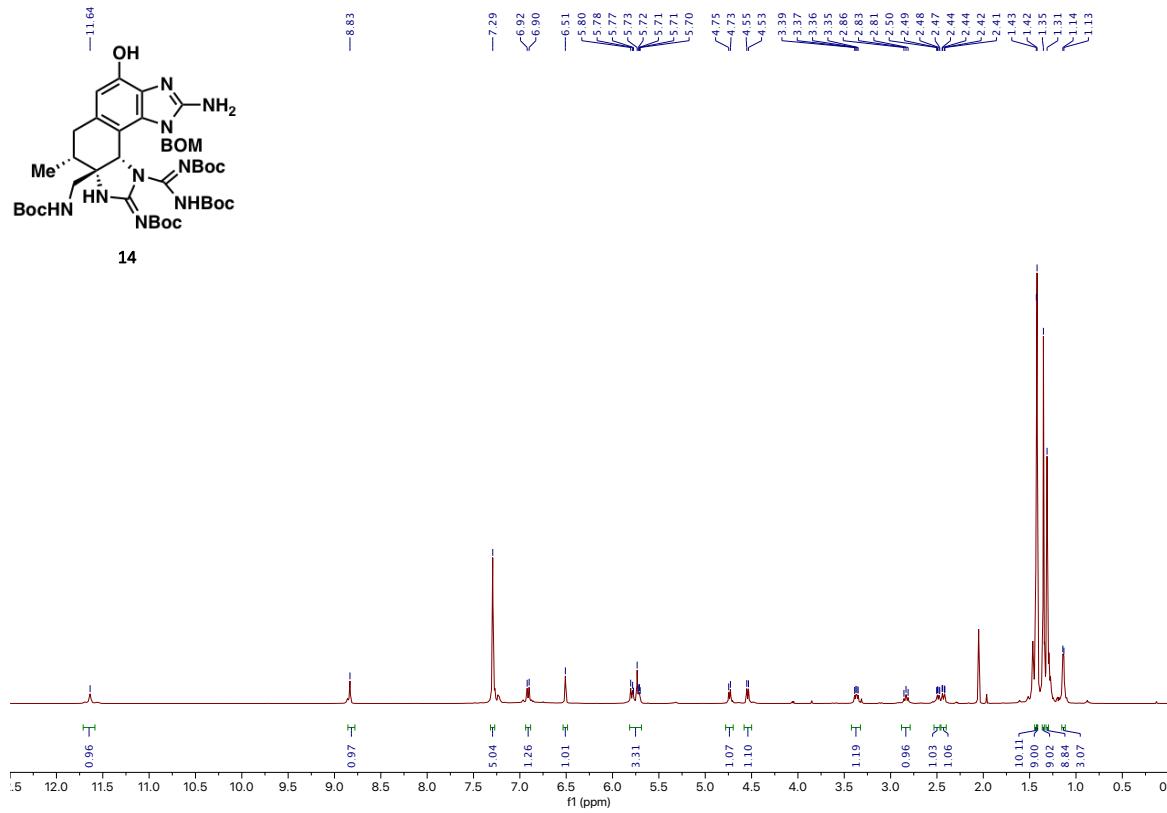




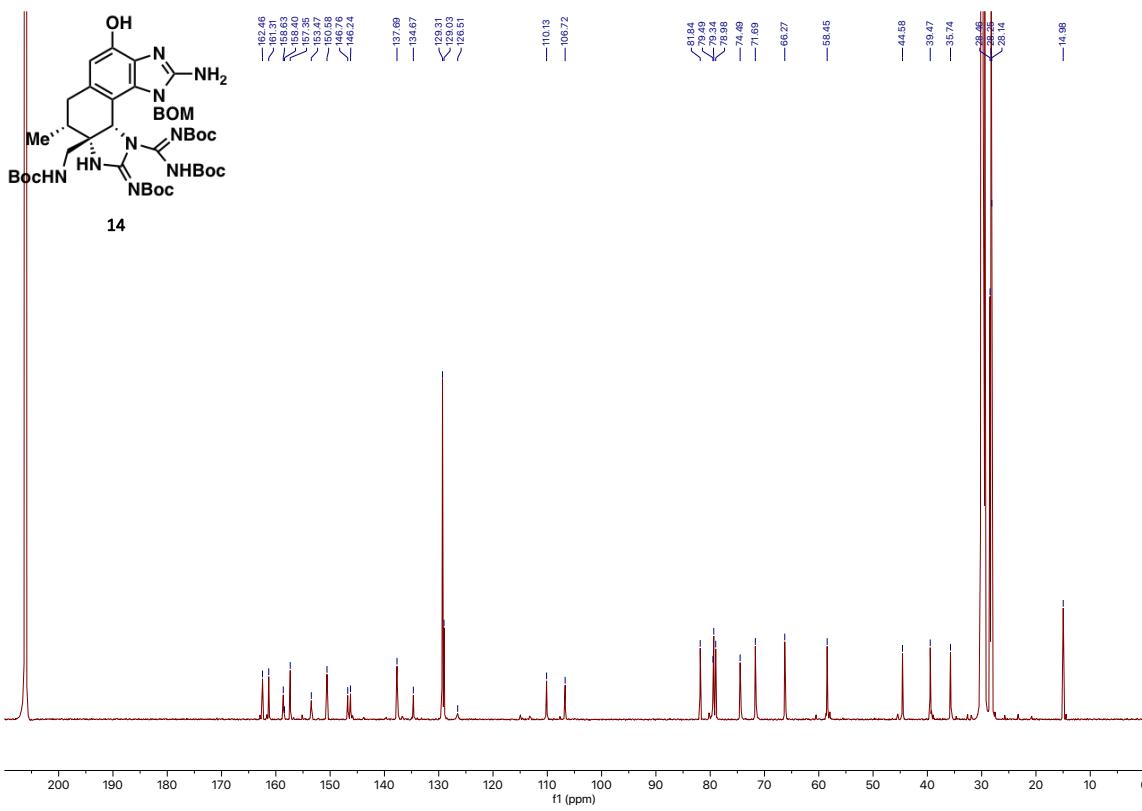


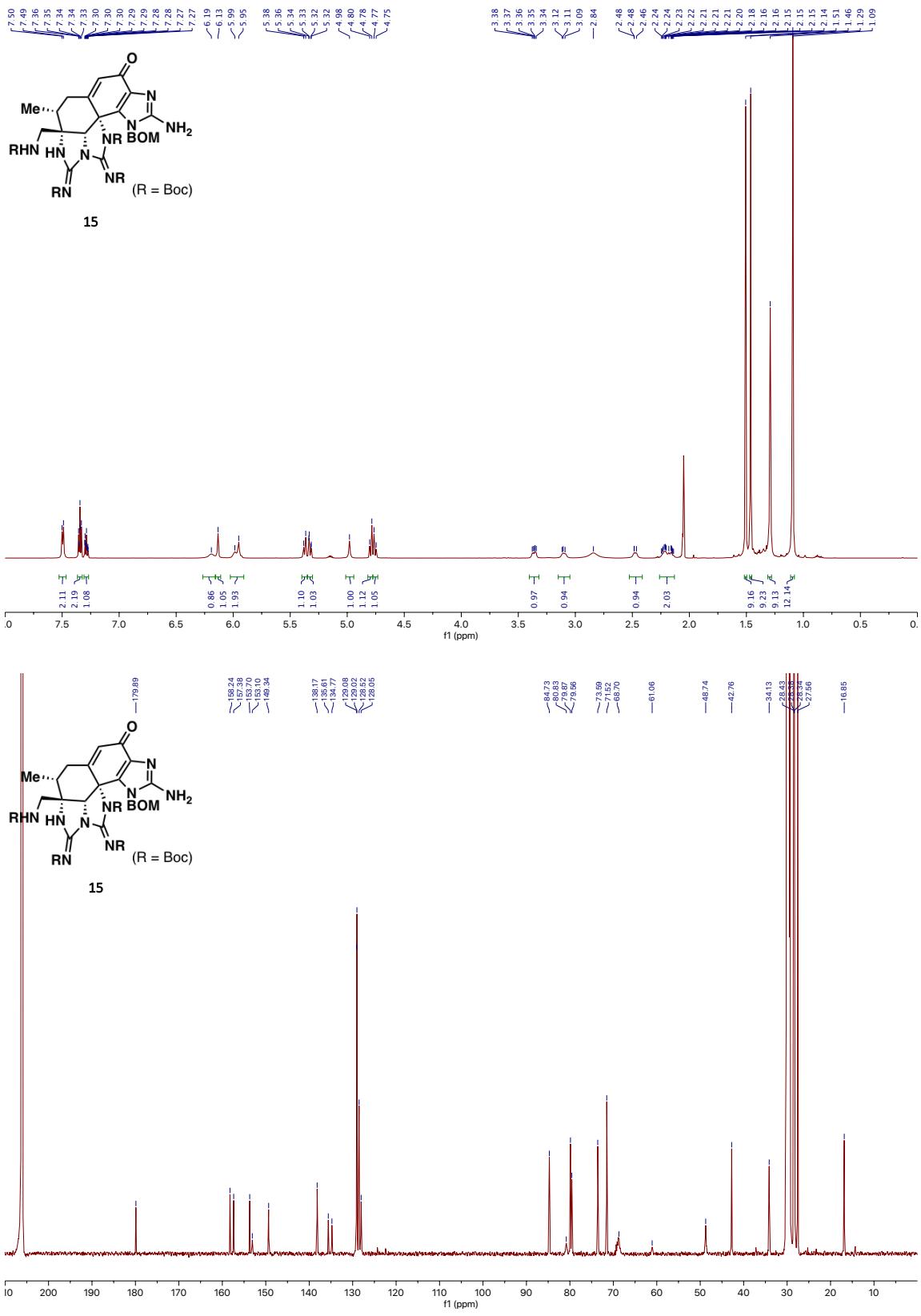


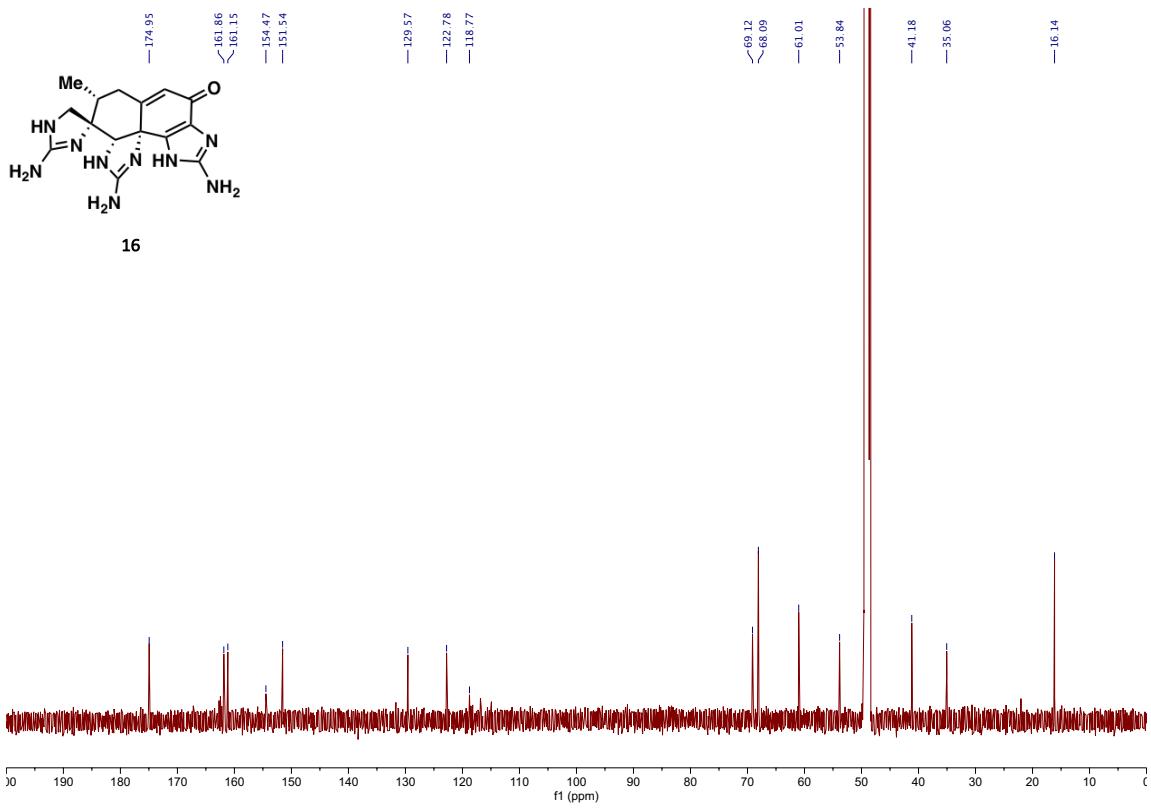
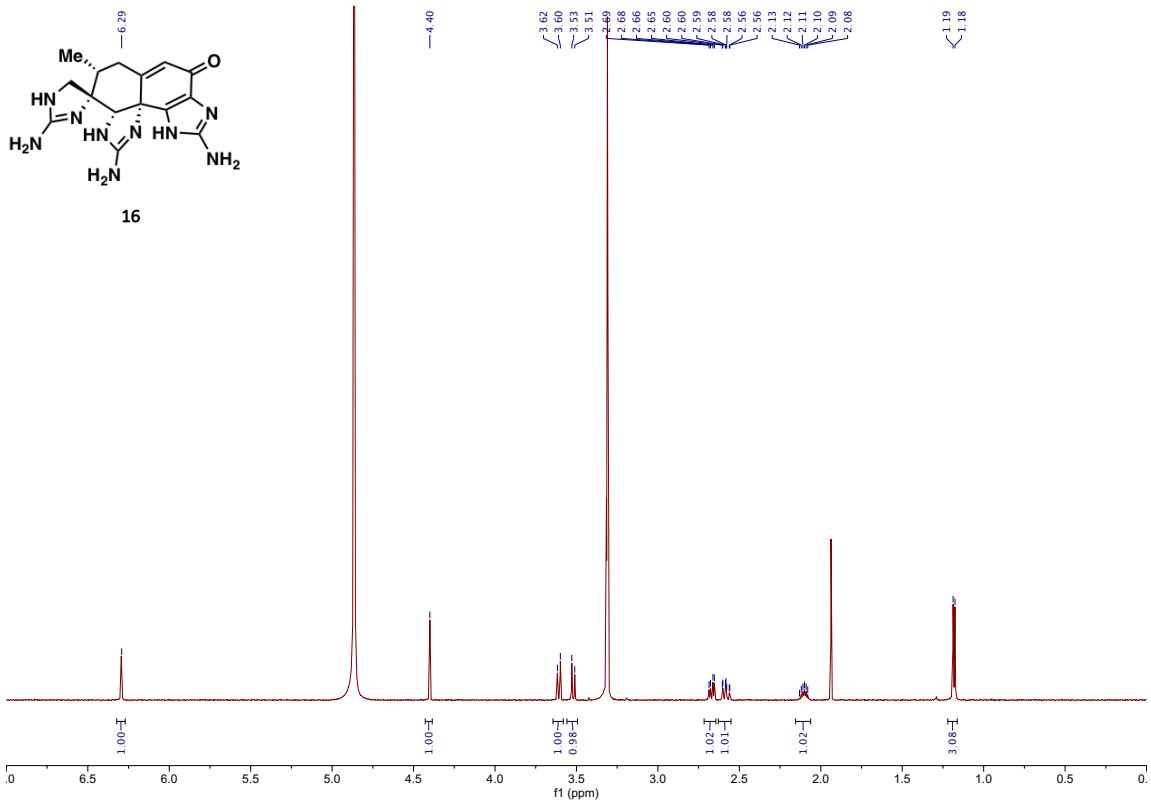
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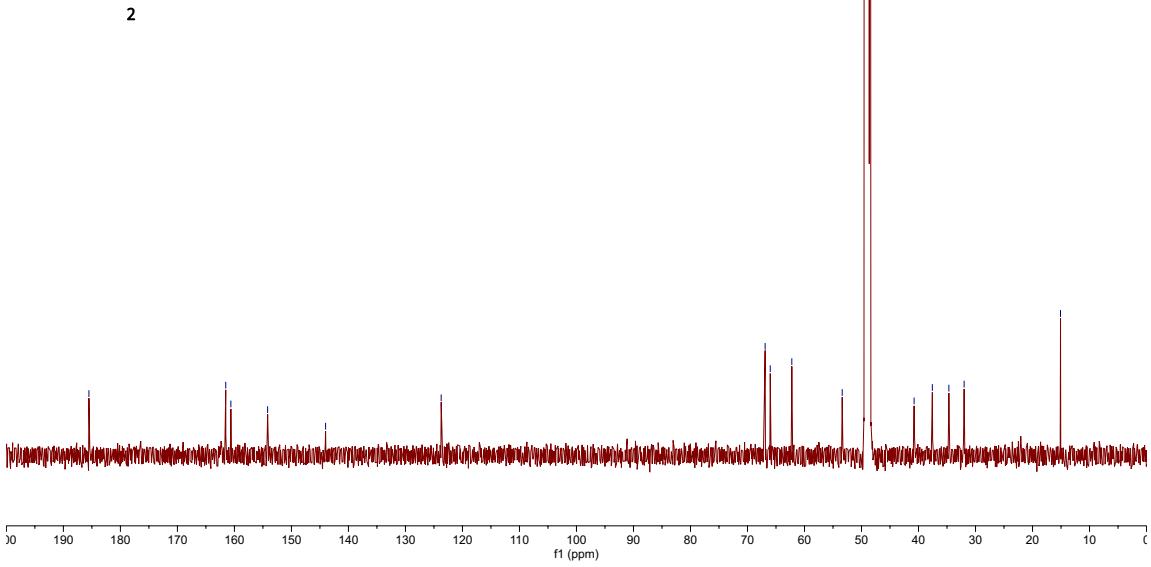
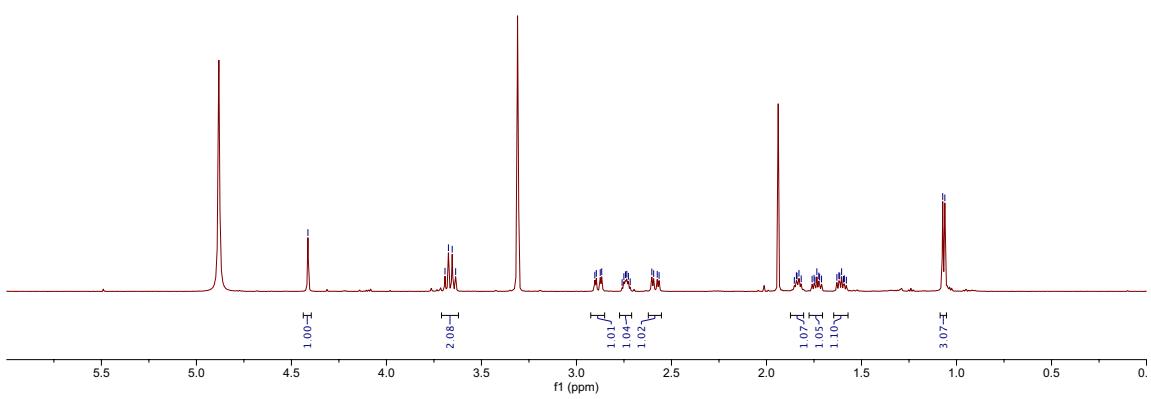
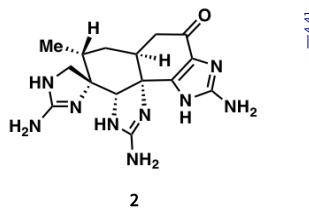


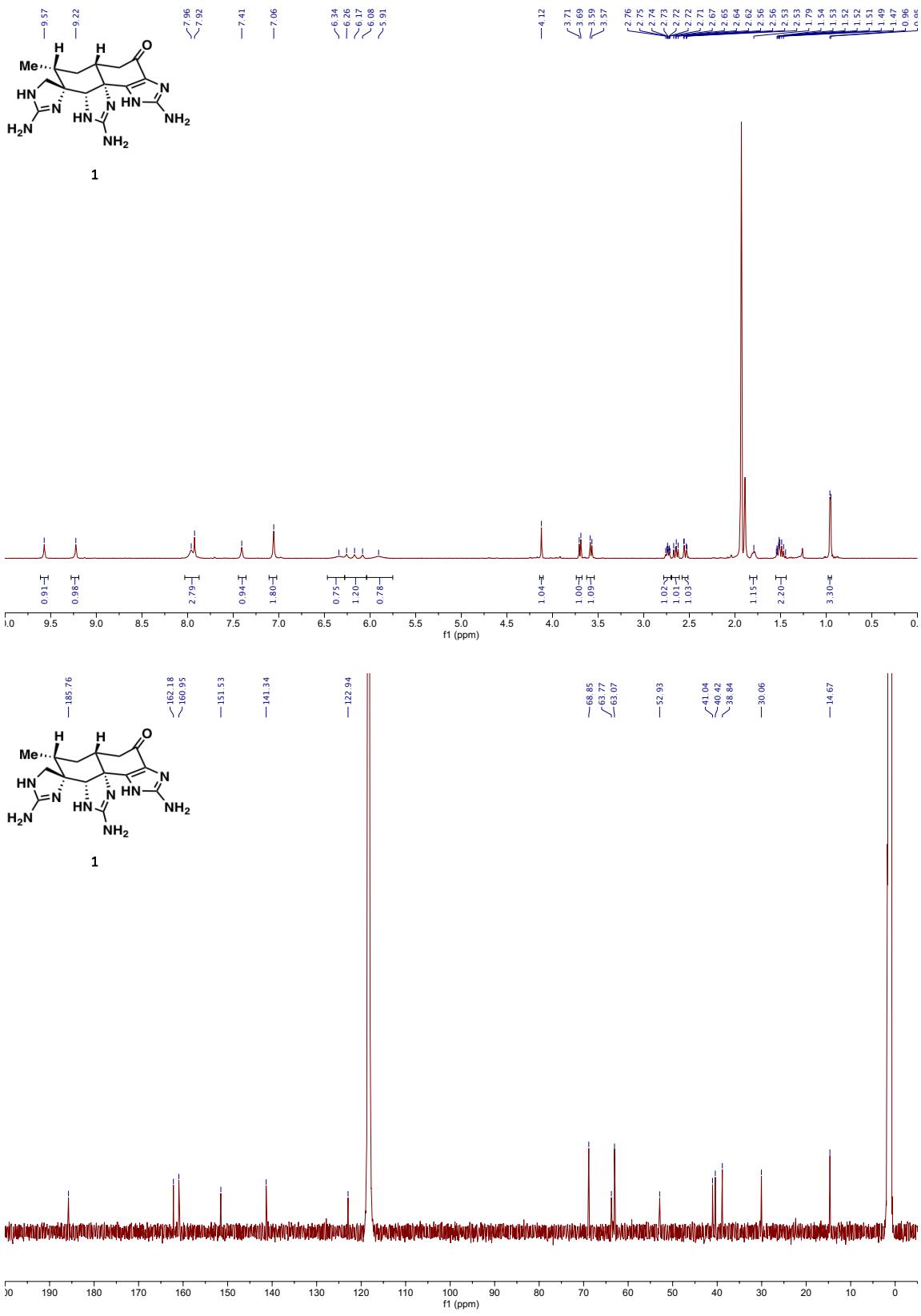
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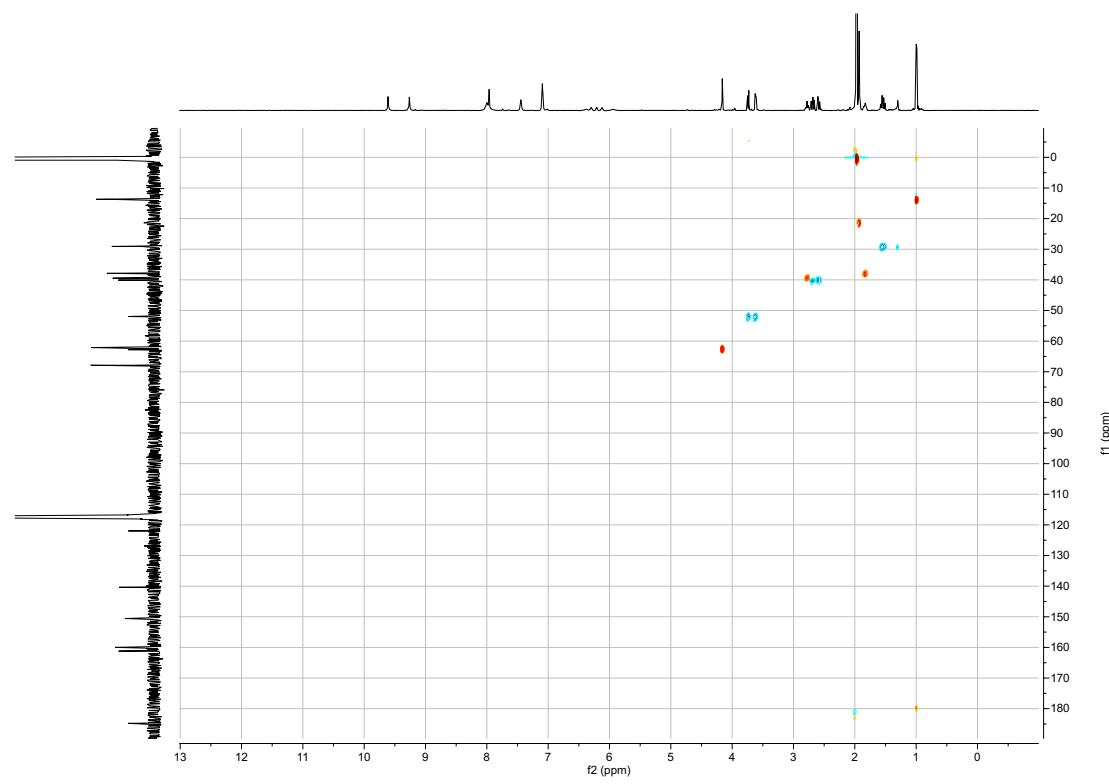




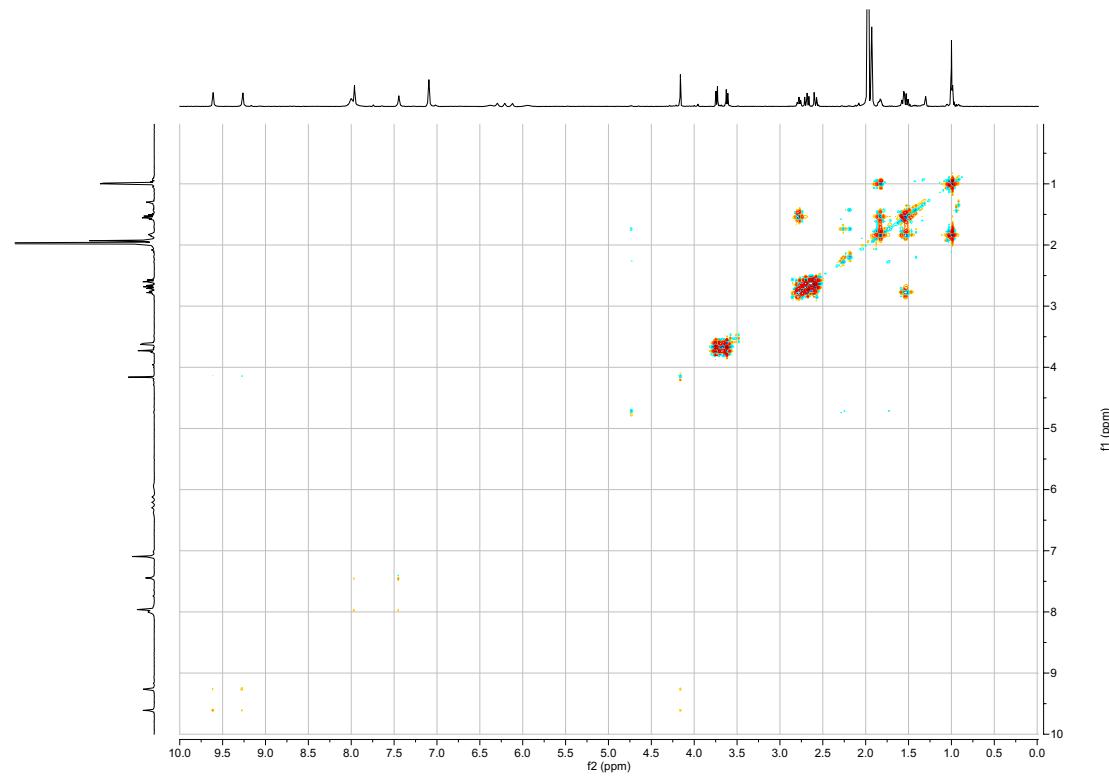




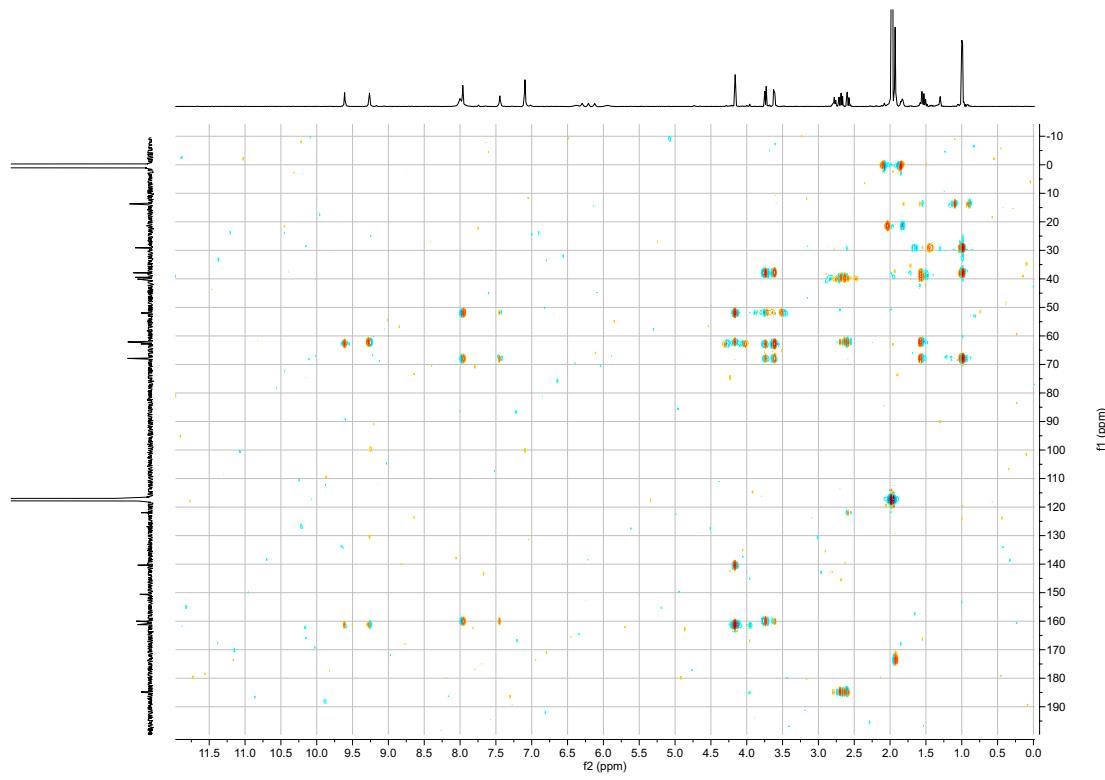
^{13}C - ^1H HSQC of **1** in acetonitrile- d_3



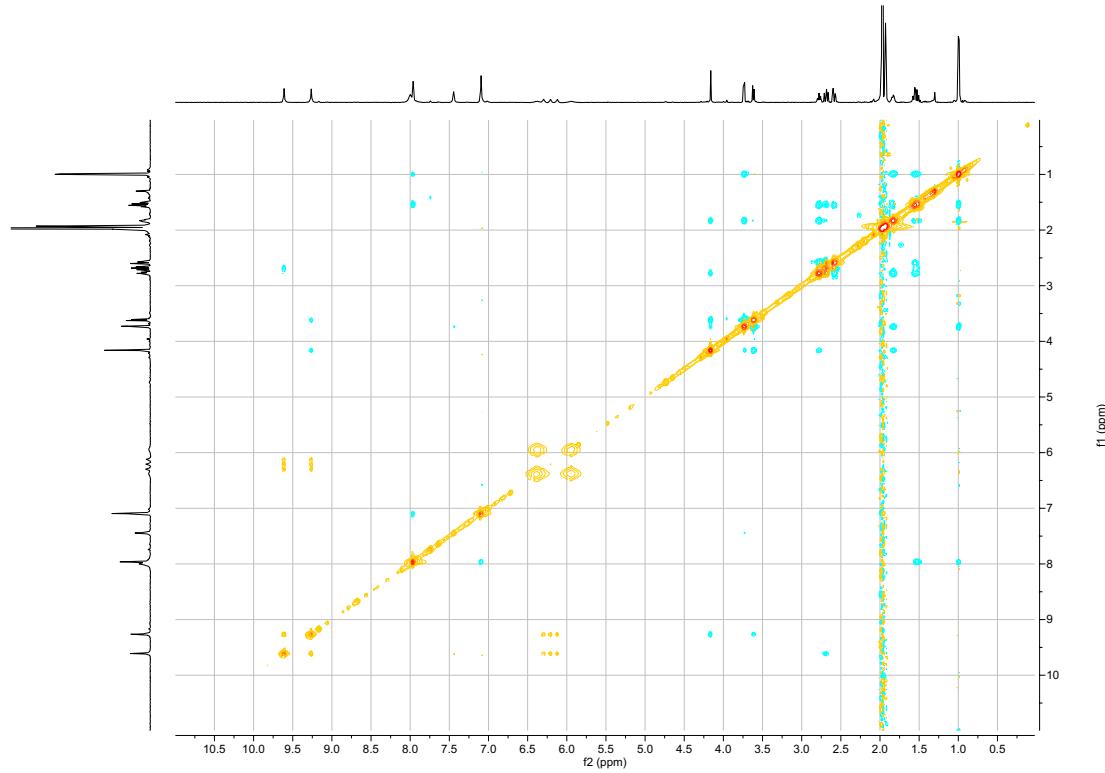
^1H - ^1H COSY of **1** in acetonitrile- d_3



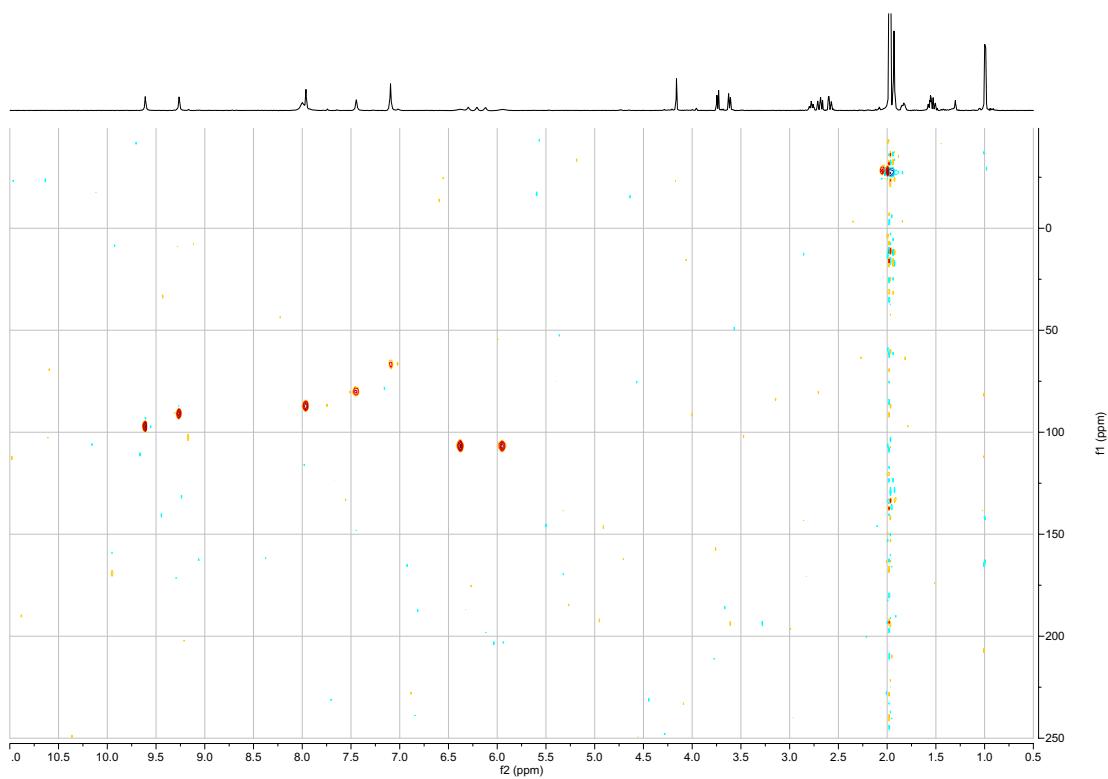
^{13}C - ^1H HMBC of **1** in acetonitrile- d_3



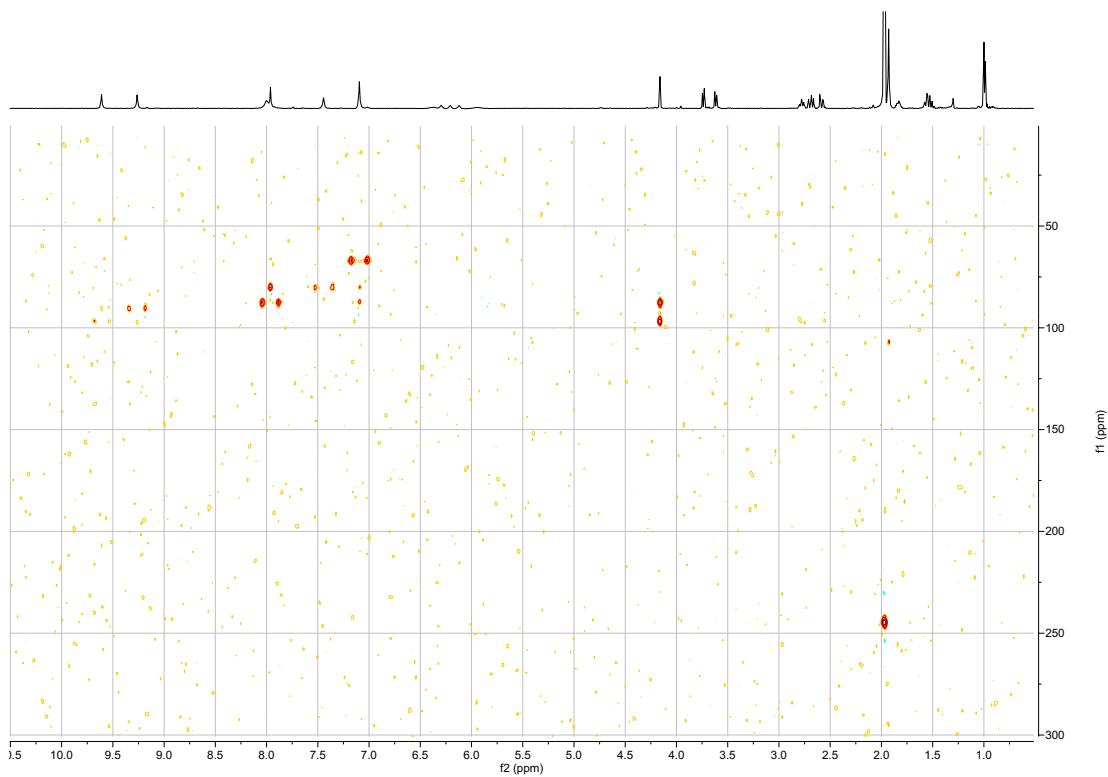
^1H - ^1H NOESY of **1** in acetonitrile- d_3

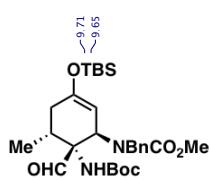


$^{15}\text{N}-^1\text{H}$ HSQC of **1** in acetonitrile- d_3

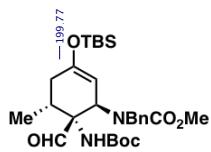
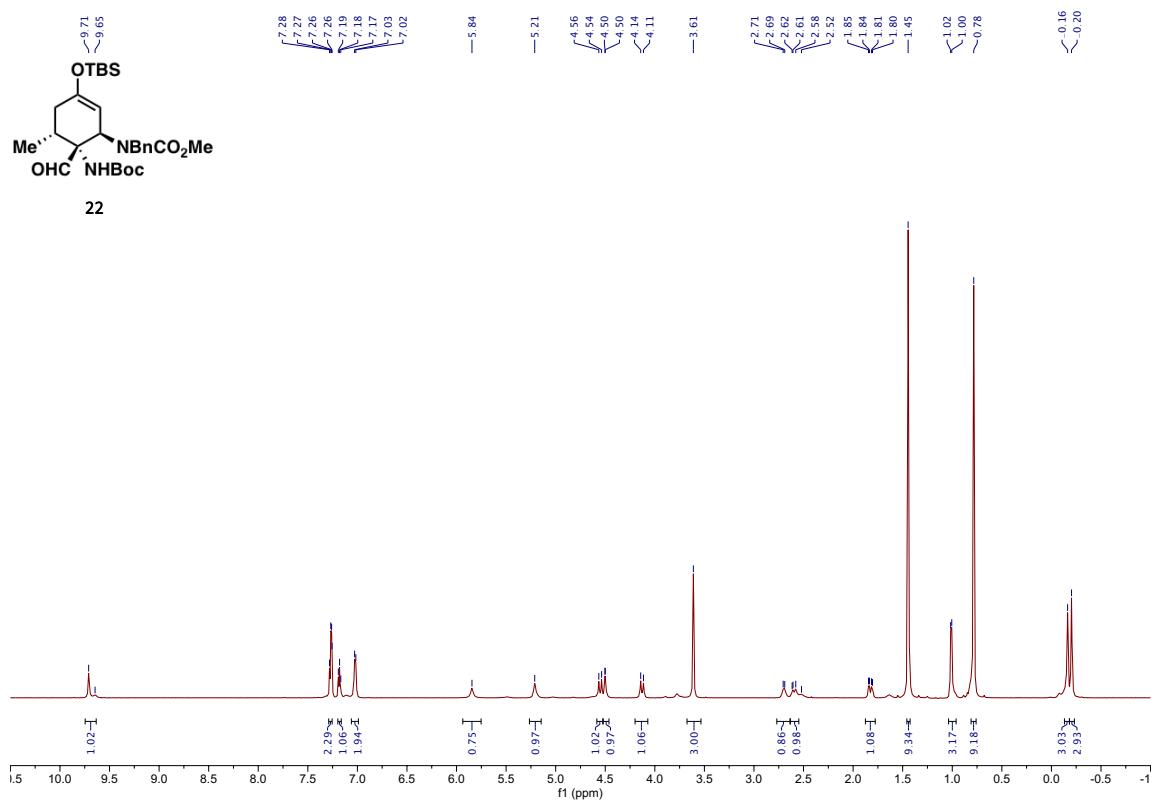


$^{15}\text{N}-^1\text{H}$ HMBC of **1** in acetonitrile- d_3

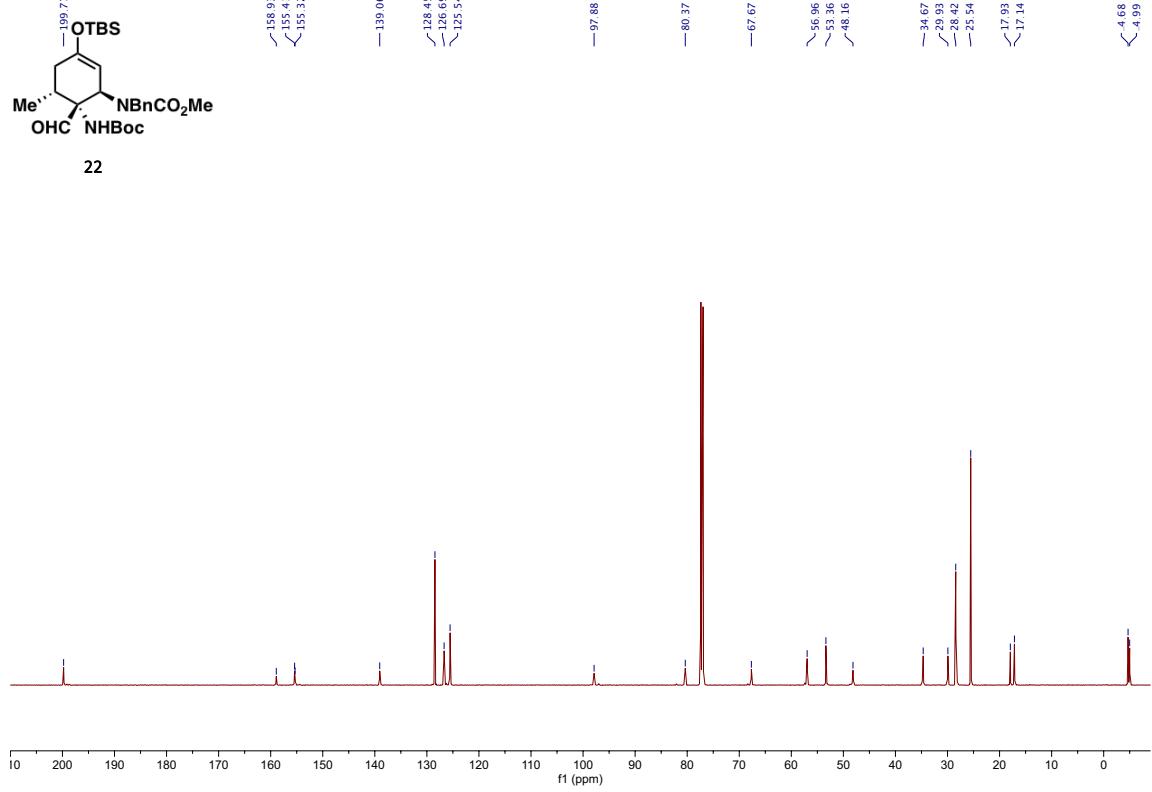


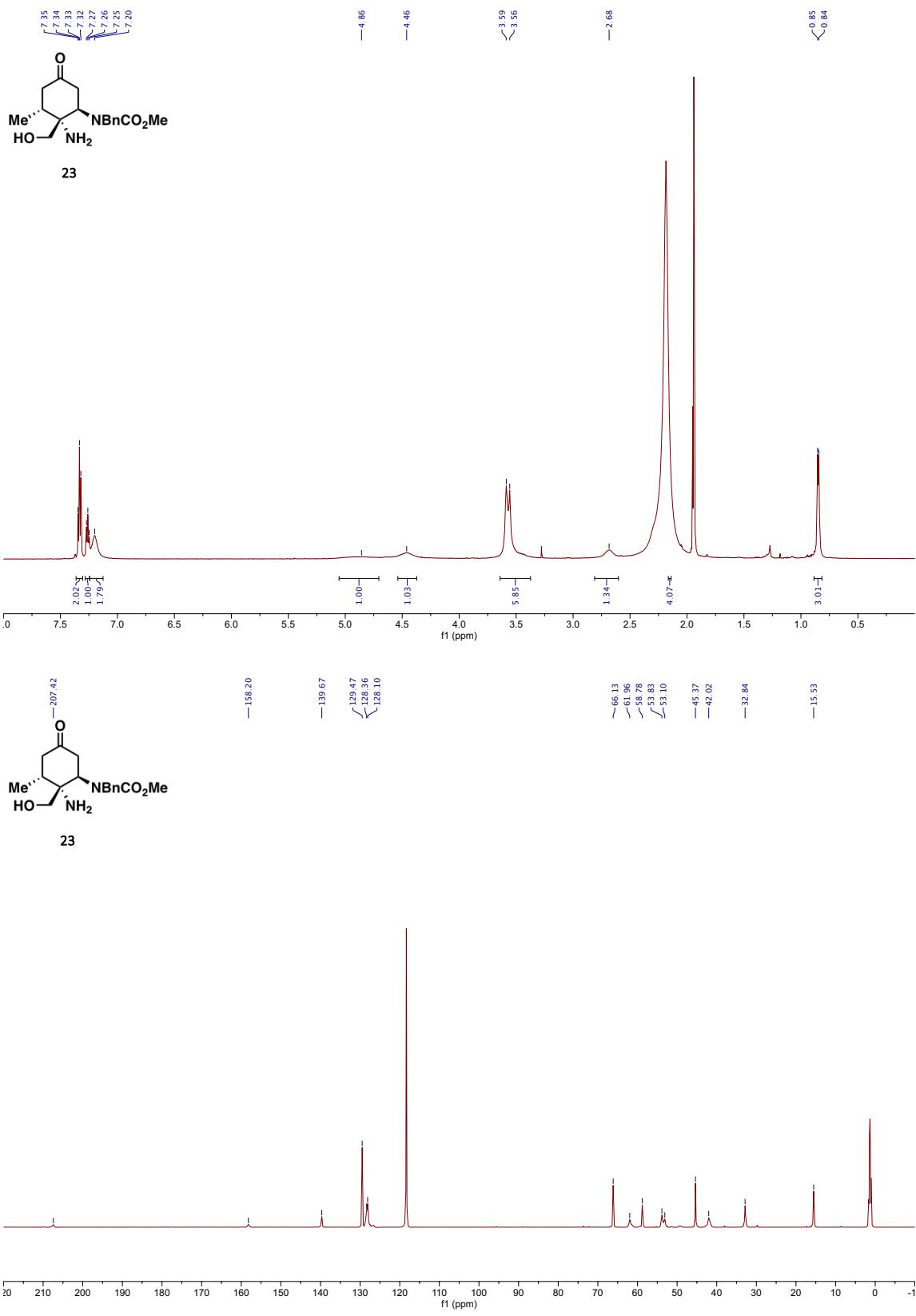


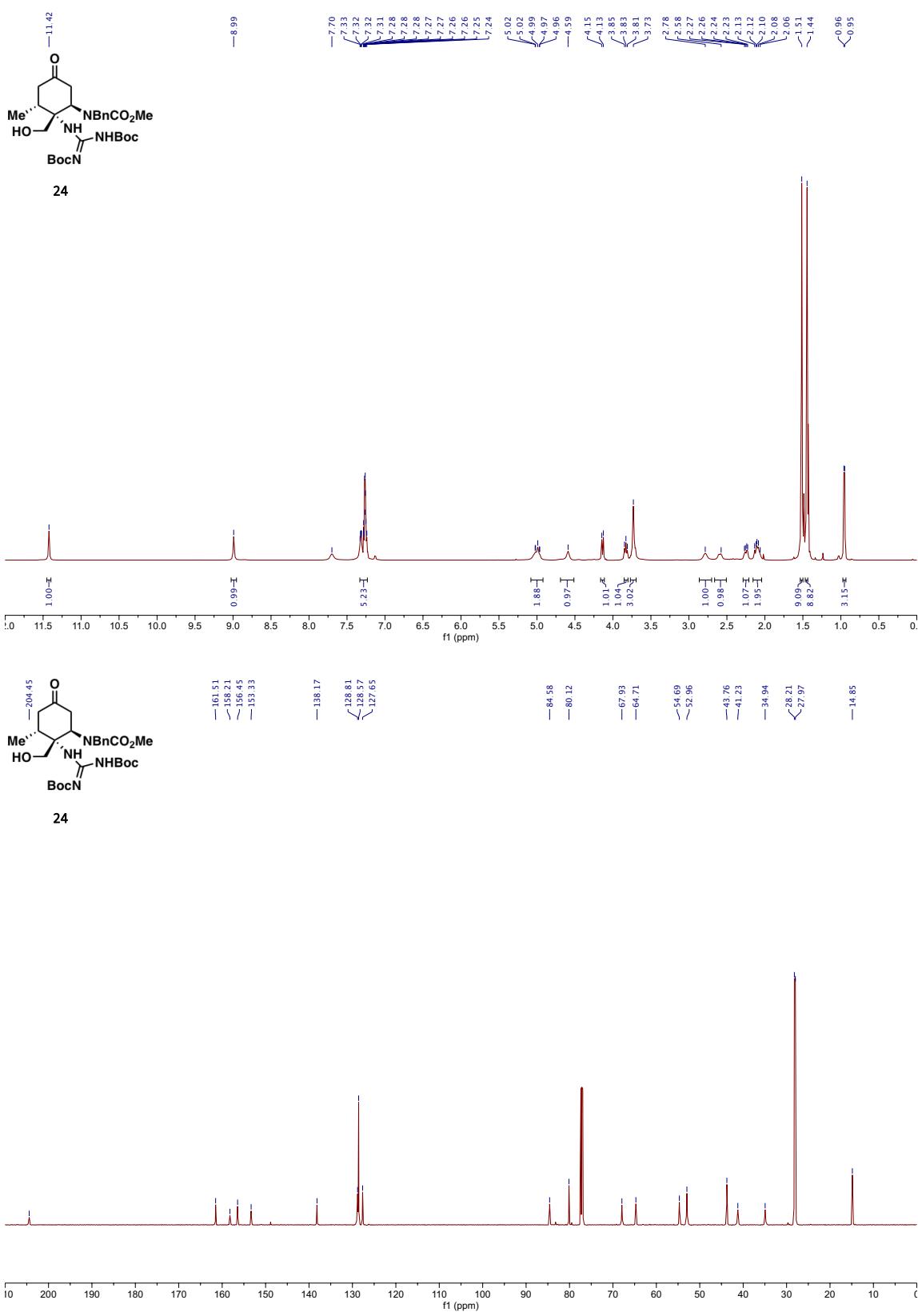
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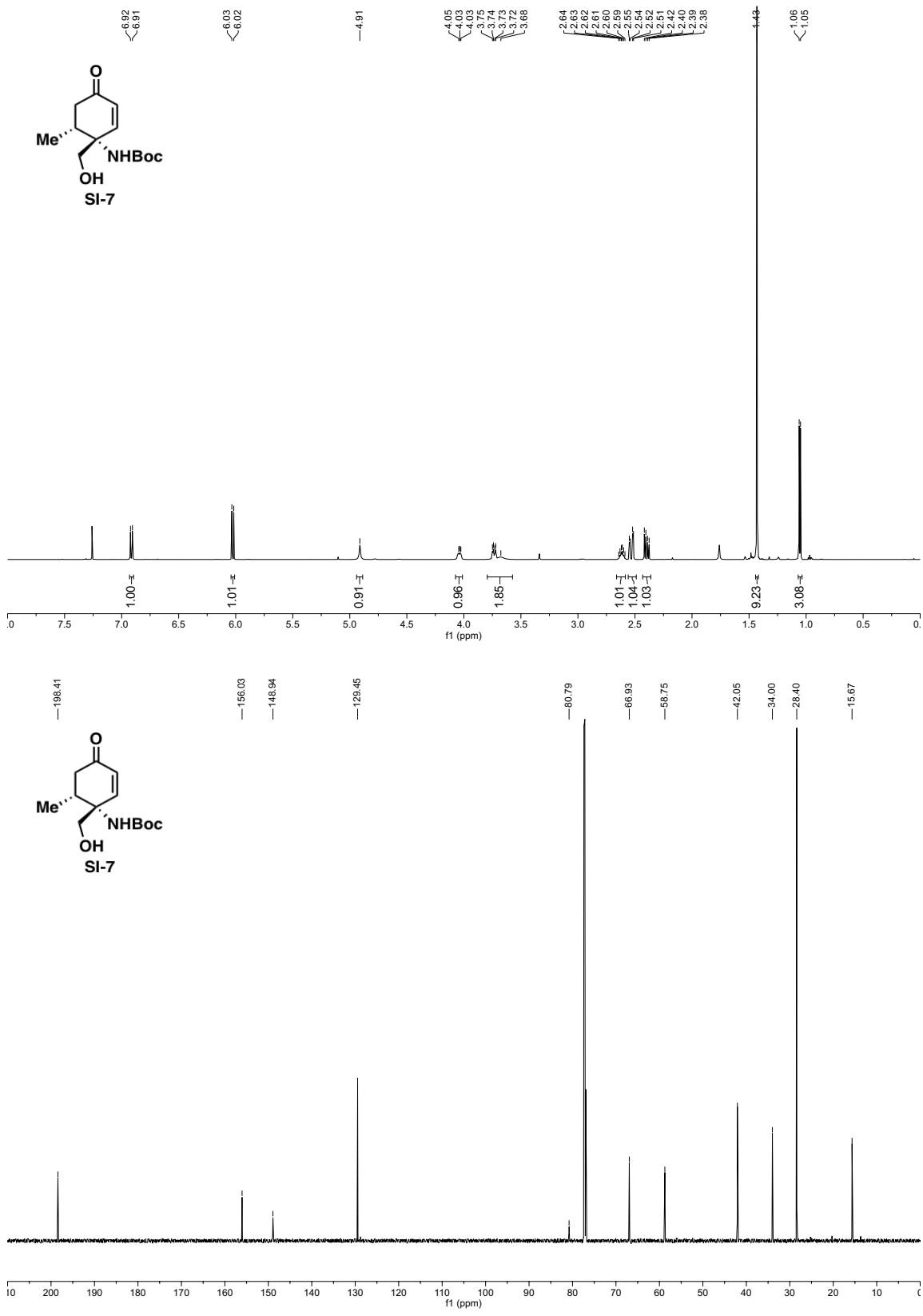


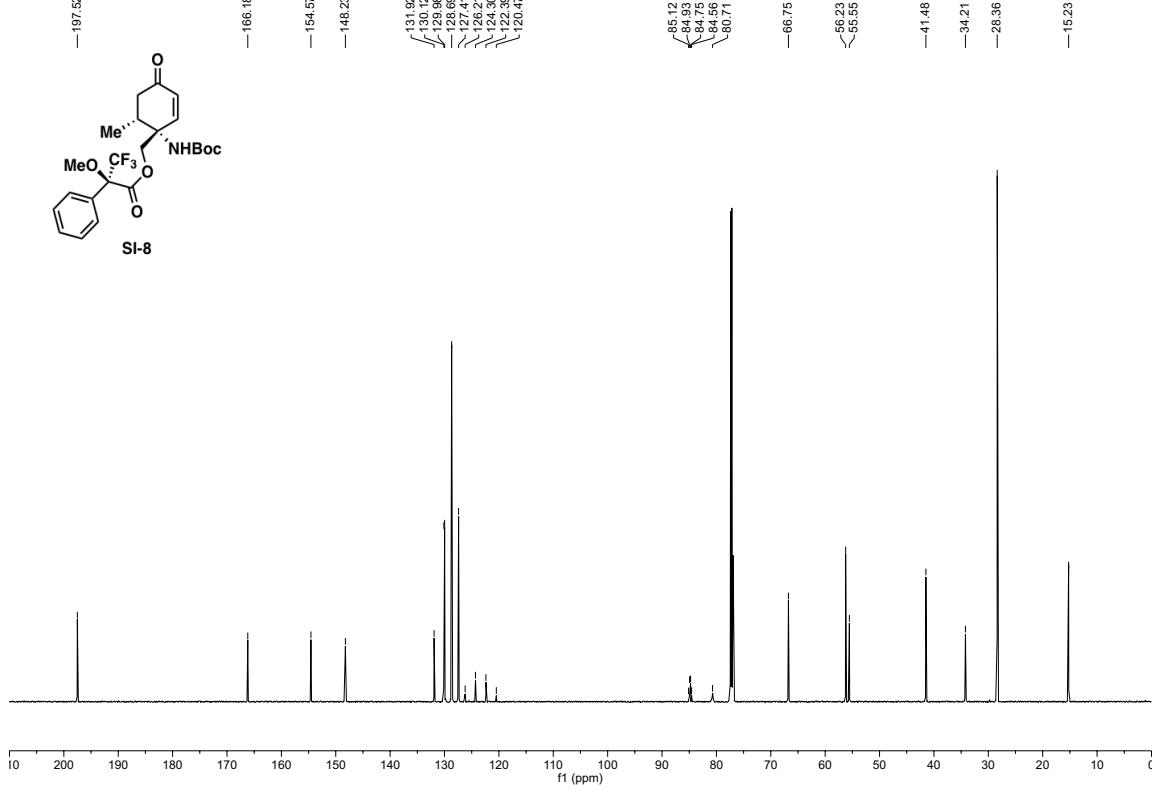
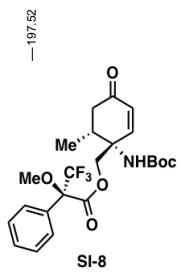
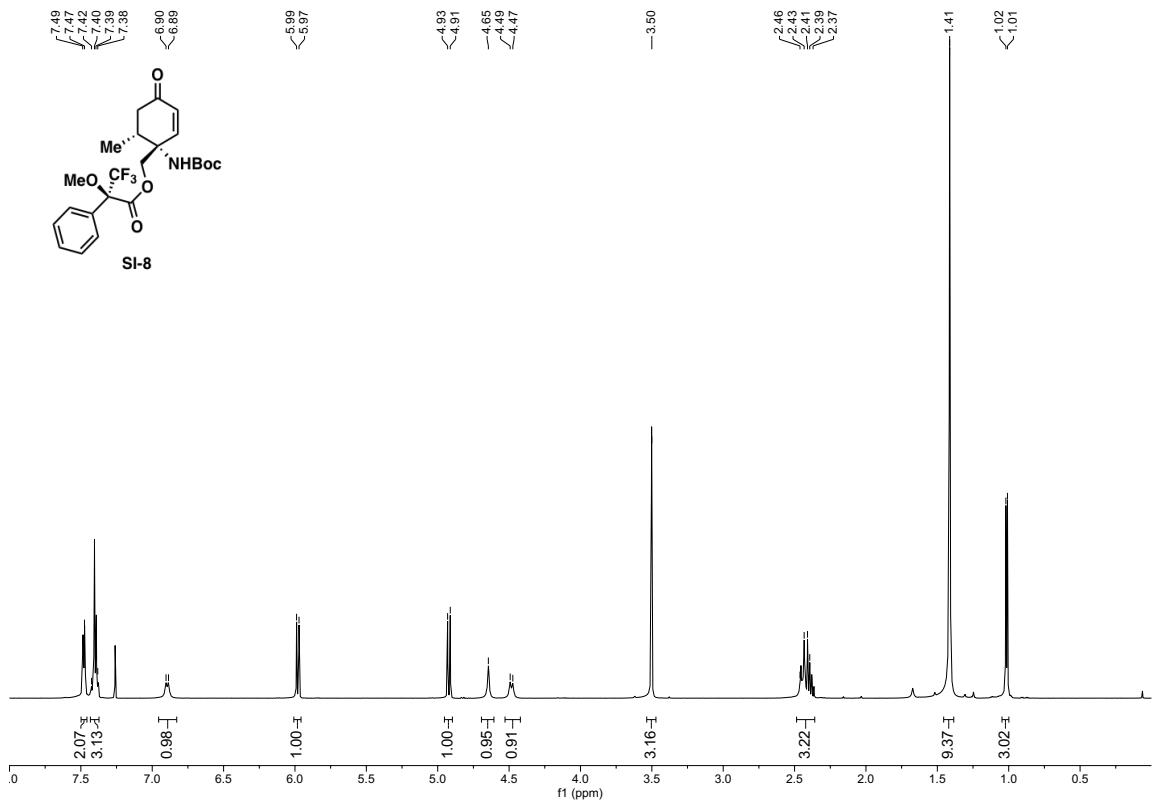
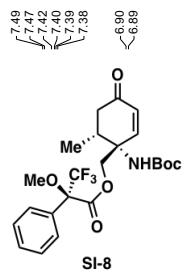
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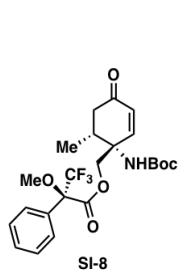




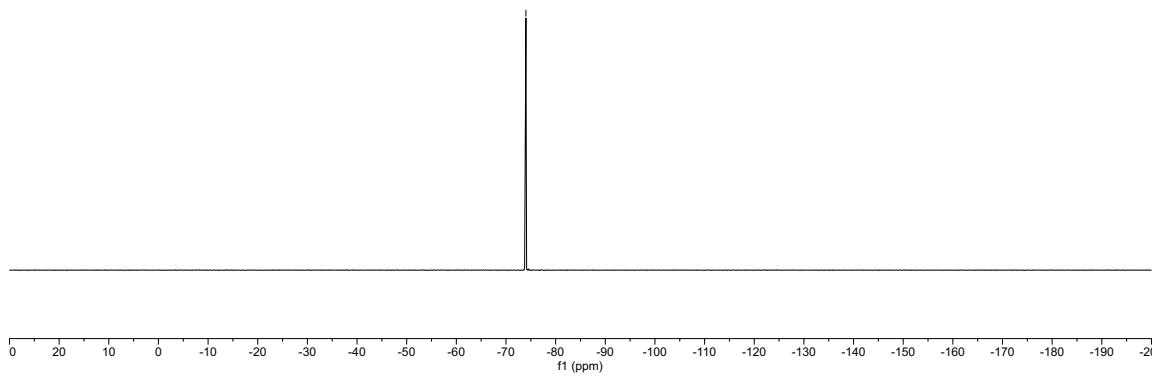








—74.01



VII) X-Ray Crystallography Data

Crystal structure of 4

The single crystal X-ray diffraction studies were carried out on a Bruker D8-Venture 3-circle diffractometer equipped with a Photon3 detector and Mo K_α radiation ($\lambda = 0.7107 \text{ \AA}$).

Crystals of the subject compound were used as received. A 0.2 x 0.22 x 0.18 mm piece of a colorless crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ω scans. Crystal-to-detector distance was 50 mm and exposure time was 1 and 3 seconds per frame using a scan width of 0.70°. Data collection was 99.9 % complete to 25.242° in θ . A total of 26049 reflections were collected covering the indices, -11≤=h≤=11, -13≤=k≤=13, -17≤=l≤=17. 5245 reflections were found to be symmetry independent, with a R_{int} of 0.0445. Indexing and unit cell refinement indicated a Primitive, Triclinic lattice. The space group was found to be **P-1**. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: Great data and refinement

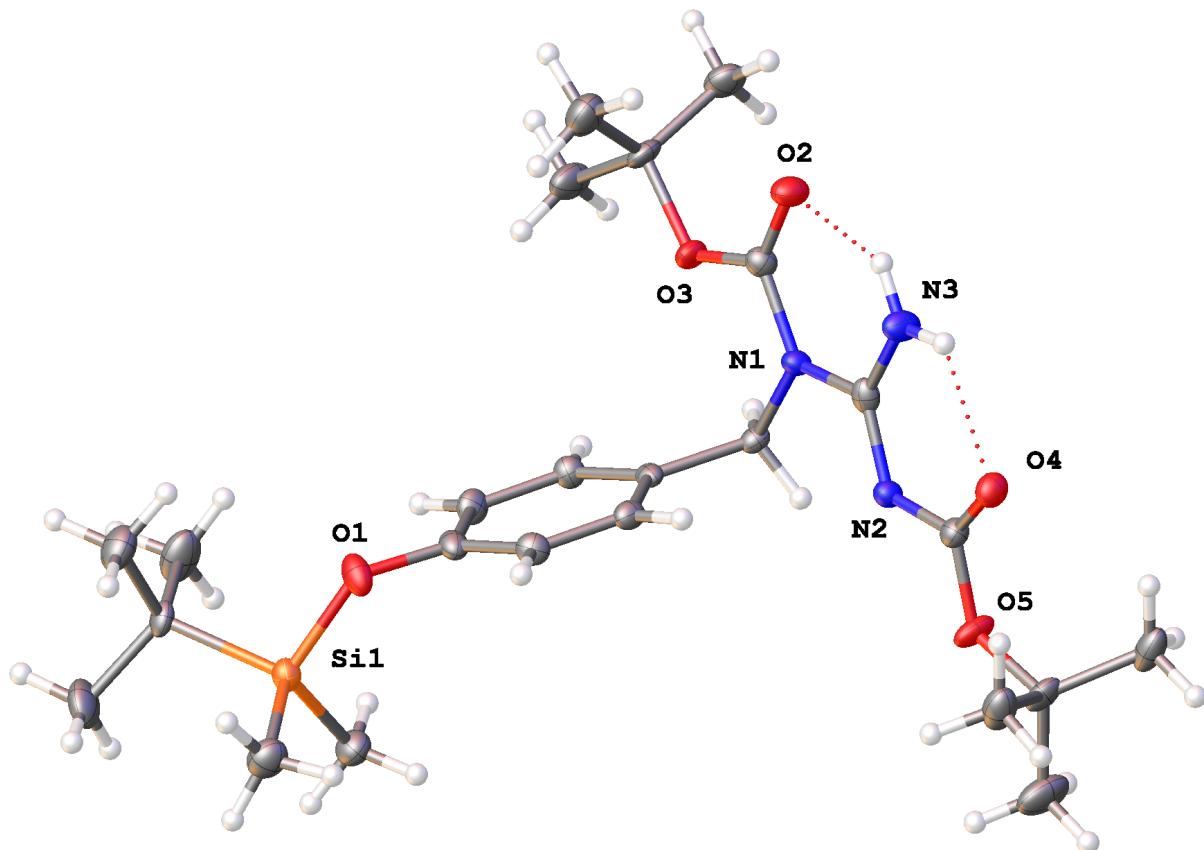


Table 1. Crystal data and structure refinement for Baran798.

Identification code	baran798		
Empirical formula	C ₂₄ H ₄₁ N ₃ O ₅ Si		
Formula weight	479.69		
Temperature	100 K		
Wavelength	0.71073 Å		
Crystal system	Triclinic		
Space group	P-1		
Unit cell dimensions	a = 9.7823(9) Å	α = 104.376(4)°.	
	b = 10.6555(14) Å	β = 94.049(4)°.	
	c = 14.0520(19) Å	γ = 102.846(4)°.	
Volume	1371.0(3) Å ³		
Z	2		
Density (calculated)	1.162 Mg/m ³		
Absorption coefficient	0.121 mm ⁻¹		
F(000)	520		

Crystal size	0.22 x 0.2 x 0.18 mm ³
Theta range for data collection	2.461 to 25.865°.
Index ranges	-11<=h<=11, -13<=k<=13, -17<=l<=17
Reflections collected	26049
Independent reflections	5245 [R(int) = 0.0445]
Completeness to theta = 25.242°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7453 and 0.7160
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5245 / 0 / 309
Goodness-of-fit on F ²	1.025
Final R indices [I>2sigma(I)]	R1 = 0.0361, wR2 = 0.0828
R indices (all data)	R1 = 0.0468, wR2 = 0.0878
Extinction coefficient	n/a
Largest diff. peak and hole	0.351 and -0.241 e.Å ⁻³

Crystal structure of 5

The single crystal X-ray diffraction studies were carried out on a Bruker SMART Pt135 CCD diffractometer equipped with Cu K_α radiation ($\lambda = 1.54178 \text{ \AA}$).

Crystals of the subject compound were used as received. A 0.25 x 0.25 x 0.08 mm piece of a colorless crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ω scans. Crystal-to-detector distance was 45 mm and exposure time was 1, 2, 3 or 5 seconds depending on the 2θ range per frame using a scan width of 1.25°. Data collection was 100 % complete to 67.679° in θ. A total of 35579 reflections were collected covering the indices, -121<=h<=21, -13<=k<=12, -12<=l<=12. 3765 reflections were found to be symmetry independent, with a R_{int} of 0.0401. Indexing and unit cell refinement indicated a Primitive, **Monoclinic** lattice. The space group was found to be **P2₁/c**. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: Great data! There is one copy of the compound in the asymmetric unit. The chemical formula of the compound is: C₁₈H₂₅N₃O₅

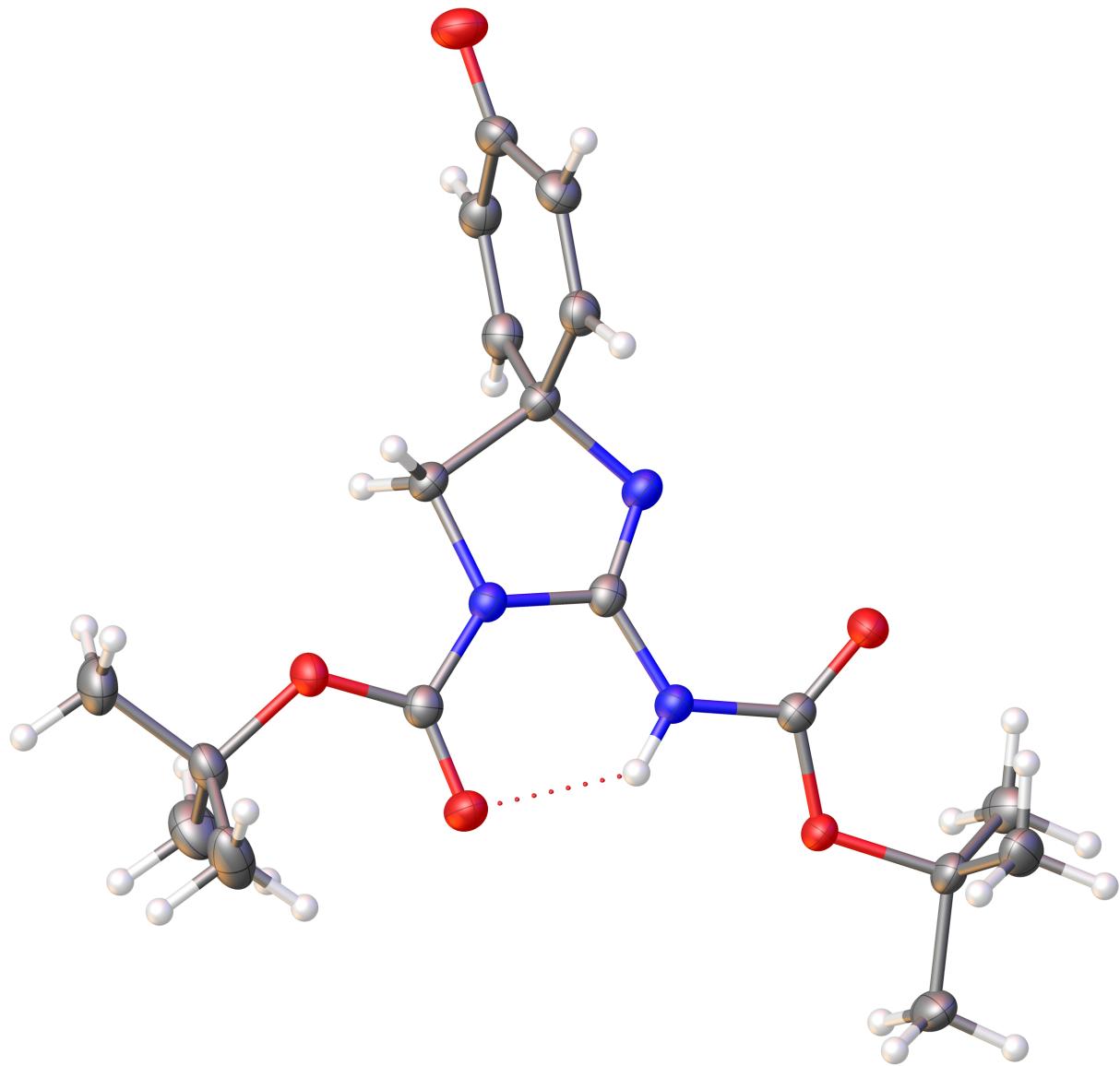


Table 1. Crystal data and structure refinement for Baran797.

Identification code	baran797_a	
Empirical formula	C ₁₈ H ₂₅ N ₃ O ₅	
Formula weight	363.41	
Temperature	100.15 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 17.5289(6) Å	α= 90°.
	b = 10.6163(4) Å	β= 92.3660(10)°.

	c = 10.5174(4) Å	$\gamma = 90^\circ$.
Volume	1955.54(12) Å ³	
Z	4	
Density (calculated)	1.234 Mg/m ³	
Absorption coefficient	0.751 mm ⁻¹	
F(000)	776	
Crystal size	0.25 x 0.25 x 0.08 mm ³	
Theta range for data collection	2.523 to 70.904°.	
Index ranges	-21<=h<=21, -13<=k<=12, -12<=l<=12	
Reflections collected	35579	
Independent reflections	3765 [R(int) = 0.0401]	
Completeness to theta = 67.679°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.5220 and 0.4423	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3765 / 0 / 241	
Goodness-of-fit on F ²	1.053	
Final R indices [I>2sigma(I)]	R1 = 0.0326, wR2 = 0.0839	
R indices (all data)	R1 = 0.0350, wR2 = 0.0866	
Largest diff. peak and hole	0.259 and -0.188 e.Å ⁻³	

Crystal structure of **6**

The single crystal X-ray diffraction studies were carried out on a Bruker X8 APEX II diffractometer equipped with Cu K_α radiation ($\lambda=1.54178$ Å).

Crystals of the subject compound were used as received (grow from THF).

A 0.200 x 0.200 x 0.165 mm colorless crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ϖ scans. Crystal-to-detector distance was 40 mm and exposure time was 2.0, 4.0 and 10.0 seconds (depending on the 2θ range) per frame using a scan width of 1.40°. Data collection was 99.4% complete to 67.500° in θ . A total of 14447 reflections were collected covering the indices, -48<=h<=49, -11<=k<=11, -13<=l<=11. 4041 reflections were found

to be symmetry independent, with a R_{int} of 0.0340. Indexing and unit cell refinement indicated a **C-centered, Monoclinic** lattice. The space group was found to be ***C2/c***. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. . Crystallographic data are summarized in Table 1.

Notes: 84/16 disorder, SAME command used to model

C2/c “Racemic” space group

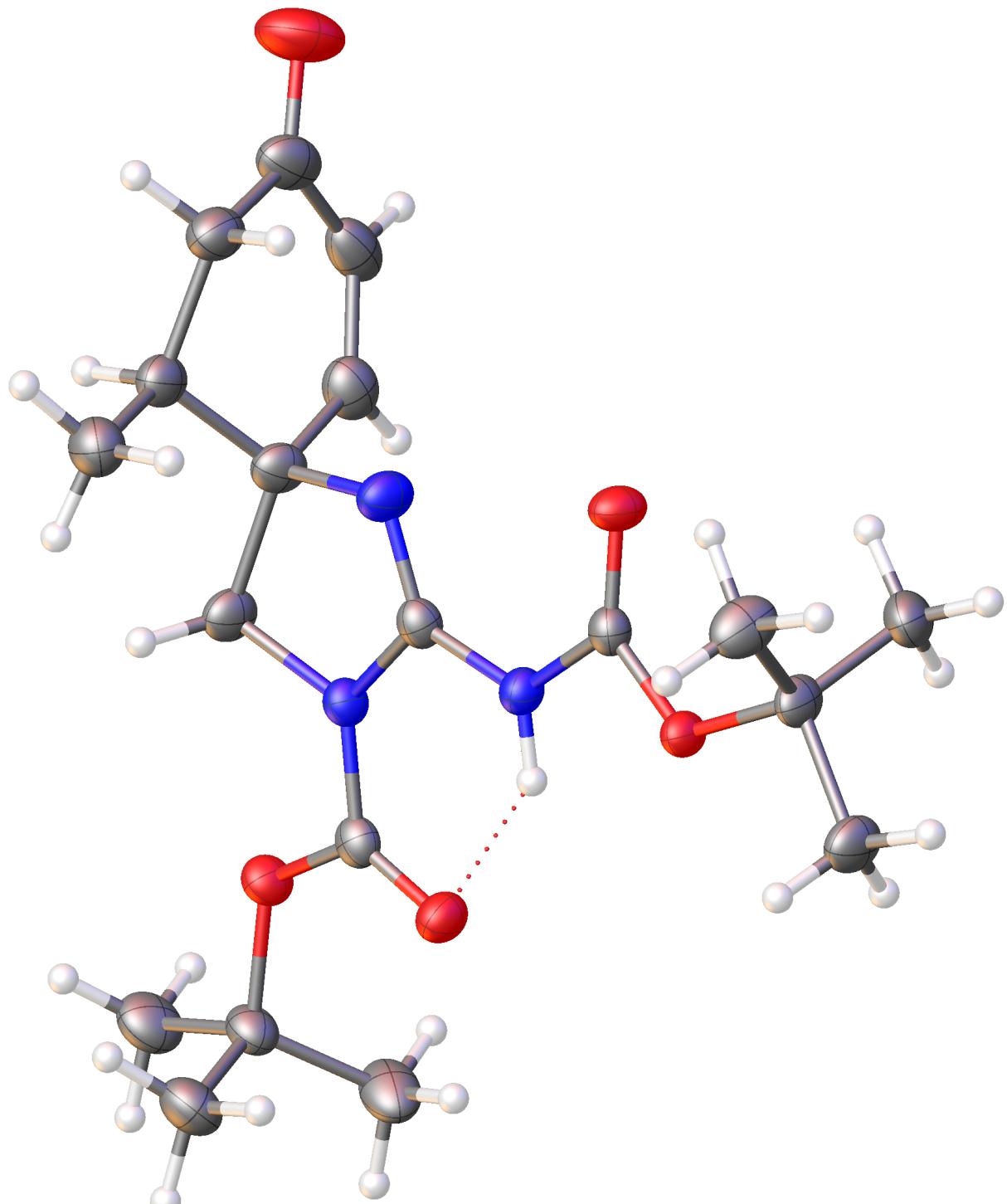


Table 1. Crystal data and structure refinement for Baran788_sq.

Report date 2021-07-13

Identification code baran788_sq

Empirical formula	C19 H29 N3 O5	
Molecular formula	C19 H29 N3 O5	
Formula weight	379.45	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C 1 2/c 1	
Unit cell dimensions	a = 41.1626(6) Å	α= 90°.
	b = 9.96190(10) Å	β= 97.5240(10)°.
	c = 10.9225(2) Å	γ = 90°.
Volume	4440.29(11) Å ³	
Z	8	
Density (calculated)	1.135 Mg/m ³	
Absorption coefficient	0.679 mm ⁻¹	
F(000)	1632	
Crystal size	0.2 x 0.2 x 0.165 mm ³	
Crystal color, habit	colorless block	
Theta range for data collection	2.165 to 68.839°.	
Index ranges	-48<=h<=49, -11<=k<=11, -13<=l<=11	
Reflections collected	14447	
Independent reflections	4041 [R(int) = 0.0340]	
Completeness to theta = 67.679°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7531 and 0.6095	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4041 / 95 / 319	
Goodness-of-fit on F ²	1.063	
Final R indices [I>2sigma(I)]	R1 = 0.0508, wR2 = 0.1236	
R indices (all data)	R1 = 0.0590, wR2 = 0.1286	
Largest diff. peak and hole	0.324 and -0.227 e.Å ⁻³	

Crystal structure of **9**

The single crystal X-ray diffraction studies were carried out on a Bruker Microstar APEX II CCD diffractometer equipped with Cu K_α radiation ($\lambda = 1.54178 \text{ \AA}$).

Crystals of the subject compound were used as received. A 0.21 x 0.12 x 0.02 mm piece of a crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ω scans. Crystal-to-detector distance was 40 mm and exposure time was 5, 8, 10, or 45 seconds depending on the 2θ range per frame using a scan width of 1.25°. Data collection was 99.8 % complete to 67.498° in θ . A total of 45318 reflections were collected covering the indices, $-18 \leq h \leq 18$, $-27 \leq k \leq 27$, $-14 \leq l \leq 14$. 7157 reflections were found to be symmetry independent, with a R_{int} of 0.0788. Indexing and unit cell refinement indicated a Primitive, **Monoclinic** lattice. The space group was found to be **P2₁/c**. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: Great data! The structure is racemic. There is one copy of the compound in the asymmetric unit. There is disordered solvent in the pores; solvent masking in Olex2 was used to account for 29 electrons in the asymmetric unit. The chemical formula for the compound is: C₃₉H₄₆ClN₅O₇

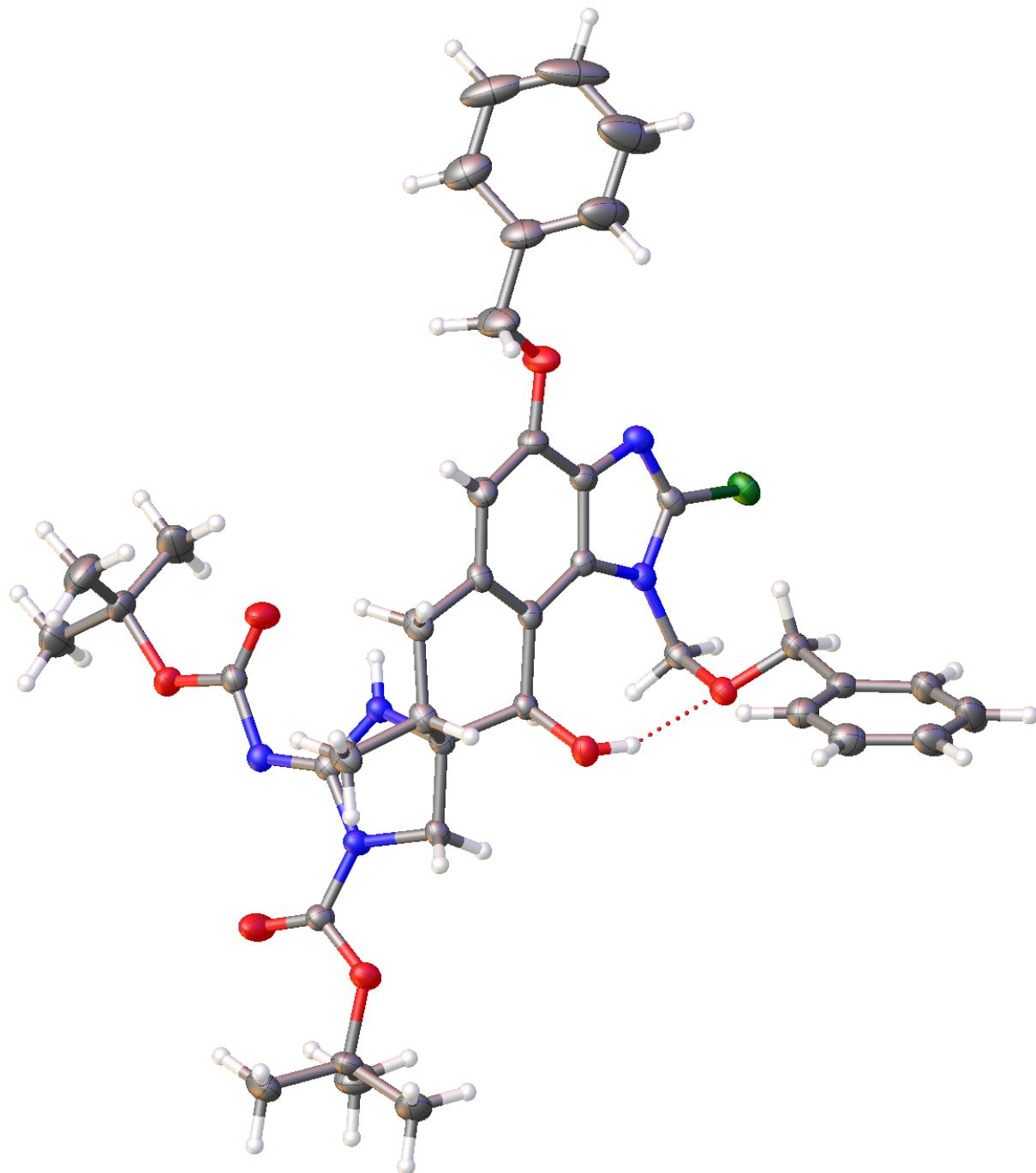


Table 1. Crystal data and structure refinement for Baran812.

Identification code	baran812_a
Empirical formula	C ₃₉ H ₄₆ ClN ₅ O ₇
Formula weight	732.26
Temperature	100.00 K
Wavelength	1.54178 Å

Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	$a = 15.7885(4)$ Å	$\alpha = 90^\circ$.
	$b = 23.1891(5)$ Å	$\beta = 111.2540(10)^\circ$.
	$c = 11.6962(3)$ Å	$\gamma = 90^\circ$.
Volume	$3990.96(17)$ Å ³	
Z	4	
Density (calculated)	1.219 Mg/m ³	
Absorption coefficient	1.280 mm ⁻¹	
F(000)	1552	
Crystal size	0.21 x 0.12 x 0.02 mm ³	
Theta range for data collection	3.003 to 67.498°.	
Index ranges	-18<=h<=18, -27<=k<=27, -14<=l<=14	
Reflections collected	45318	
Independent reflections	7157 [R(int) = 0.0788]	
Completeness to theta = 67.498°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7529 and 0.6490	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	7157 / 0 / 477	
Goodness-of-fit on F ²	1.020	
Final R indices [I>2sigma(I)]	R1 = 0.0444, wR2 = 0.1119	
R indices (all data)	R1 = 0.0621, wR2 = 0.1216	
Largest diff. peak and hole	0.274 and -0.261 e.Å ⁻³	

Crystal structure of **10**

The single crystal X-ray diffraction studies were carried out on a Bruker Microstar APEX II CCD diffractometer equipped with Cu K α radiation ($\lambda = 1.54178$ Å).

Crystals of the subject compound were used as received. A 0.12 x 0.02 x 0.02 mm piece of a crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ω scans. Crystal-to-detector distance was 40 mm and exposure time was 4, 6, 8, 12, 16, or 20 seconds depending on the 2 θ range per frame using a scan width of 1.40°. Data collection was 97.5 %

complete to 66.690° in θ . A total of 13897 reflections were collected covering the indices, $-16 \leq h \leq 16$, $-23 \leq k \leq 29$, $-13 \leq l \leq 12$. 6605 reflections were found to be symmetry independent, with a R_{int} of 0.0483. Indexing and unit cell refinement indicated a **Primitive, Monoclinic** lattice. The space group was found to be **P2₁/c**. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: Data quality wasn't great, but suitable for structural determination. X-ray induced decomposition of the azide was observed. Only the earlier runs were used for structural refinement. The crystal was racemic. There is one copy of the compound in the asymmetric unit. There is some positional disorder on the phenyl rings. The chemical formula for the compound is: C₃₉H₄₅ClN₈O₆

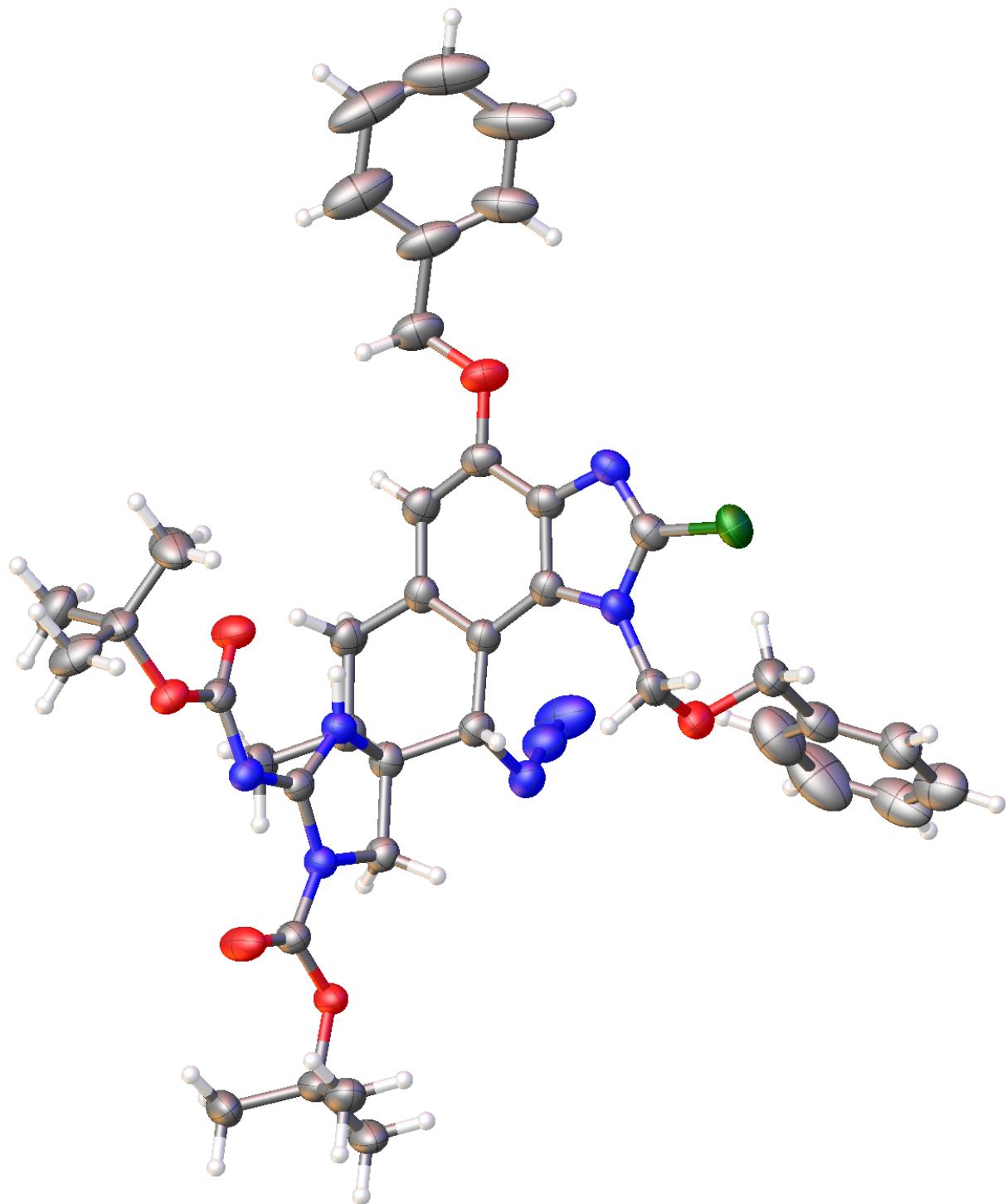


Table 1. Crystal data and structure refinement for Baran827.

Identification code	baran827_a
Empirical formula	C ₃₉ H ₄₅ ClN ₈ O ₆
Formula weight	757.28

Temperature	100.15 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 13.9341(10) Å b = 24.5490(16) Å c = 11.4004(8) Å	α= 90°. β= 101.314(3)°. γ = 90°.
Volume	3823.9(5) Å ³	
Z	4	
Density (calculated)	1.315 Mg/m ³	
Absorption coefficient	1.358 mm ⁻¹	
F(000)	1600	
Crystal size	0.12 x 0.02 x 0.02 mm ³	
Theta range for data collection	3.702 to 66.690°.	
Index ranges	-16<=h<=16, -23<=k<=29, -13<=l<=12	
Reflections collected	13897	
Independent reflections	6605 [R(int) = 0.0483]	
Completeness to theta = 66.690°	97.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.5201 and 0.4022	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	6605 / 120 / 568	
Goodness-of-fit on F ²	1.024	
Final R indices [I>2sigma(I)]	R1 = 0.0583, wR2 = 0.1537	
R indices (all data)	R1 = 0.0914, wR2 = 0.1746	
Extinction coefficient	0.00085(17)	
Largest diff. peak and hole	0.684 and -0.241 e.Å ⁻³	

Crystal structure of **11**

The single crystal X-ray diffraction studies were carried out on a Bruker Microstar APEX II CCD diffractometer equipped with Cu K_α radiation ($\lambda = 1.54178 \text{ \AA}$).

Crystals of the subject compound were used as received. A 0.15 x 0.075 x 0.05 mm piece of a crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2)

K using ϕ and ω scans. Crystal-to-detector distance was 40 mm and exposure time was 5, 10, 15, 20, or 30 seconds depending on the 2θ range per frame using a scan width of 1.50° . Data collection was 97.8 % complete to 67.679° in θ . A total of 45151 reflections were collected covering the indices, $-13 \leq h \leq 13$, $-17 \leq k \leq 17$, $-17 \leq l \leq 19$. 8779 reflections were found to be symmetry independent, with a R_{int} of 0.1001. Indexing and unit cell refinement indicated a **Triclinic** lattice. The space group was found to be **P-1**. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: Great data! The crystal was racemic. There is one copy of the compound in the asymmetric unit. The solvent is disordered, solvent masking in Olex2 was used to account for 100 electrons in the asymmetric unit. The chemical formula for the compound is: $C_{39}H_{47}ClN_6O_6$

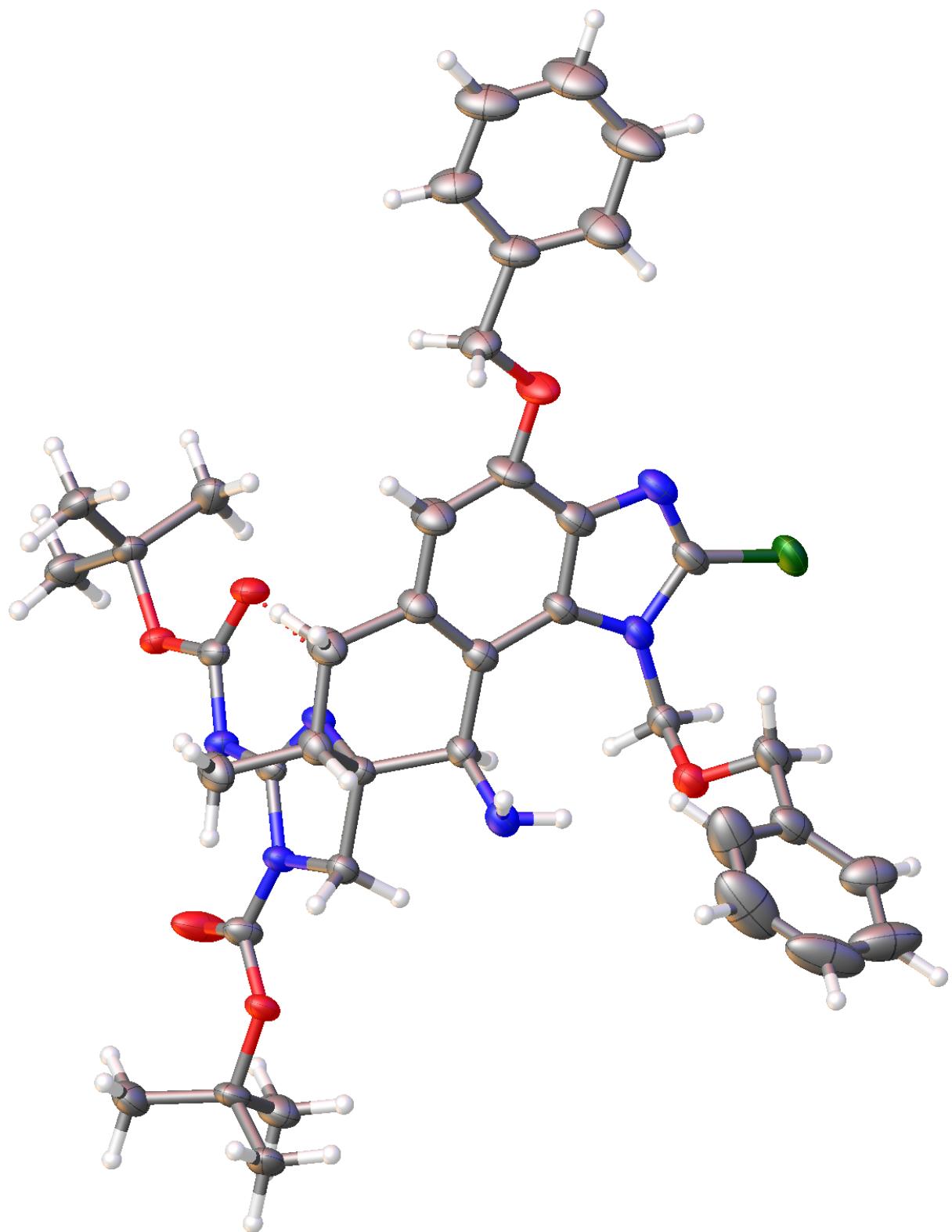


Table 1. Crystal data and structure refinement for Baran826.

Identification code	baran826_0m_a	
Empirical formula	C39 H47 Cl N6 O6	
Formula weight	731.27	
Temperature	100.15 K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.3820(5) Å	α= 71.878(3)°.
	b = 14.1916(6) Å	β= 87.765(3)°.
	c = 16.2248(7) Å	γ = 75.110(2)°.
Volume	2404.74(19) Å ³	
Z	2	
Density (calculated)	1.010 Mg/m ³	
Absorption coefficient	1.051 mm ⁻¹	
F(000)	776	
Crystal size	0.15 x 0.075 x 0.05 mm ³	
Theta range for data collection	2.868 to 69.800°.	
Index ranges	-13<=h<=13, -17<=k<=17, -17<=l<=19	
Reflections collected	45151	
Independent reflections	8779 [R(int) = 0.1001]	
Completeness to theta = 67.679°	97.8 %	
Absorption correction	None	
Max. and min. transmission	0.6616 and 0.5405	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	8779 / 121 / 555	
Goodness-of-fit on F ²	0.969	
Final R indices [I>2sigma(I)]	R1 = 0.0525, wR2 = 0.1340	
R indices (all data)	R1 = 0.0863, wR2 = 0.1506	
Largest diff. peak and hole	0.370 and -0.559 e.Å ⁻³	

Crystal structure of **12**

The single crystal X-ray diffraction studies were carried out on a Bruker D8-Venture 3-circle diffractometer equipped with a Photon3 detector and Mo K_α radiation ($\lambda = 0.7107 \text{ \AA}$).

Crystals of the subject compound were used as received. A 0.2 x 0.14 x 0.045 mm piece of a crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ω scans. Crystal-to-detector distance was 50 mm and exposure time was 3 or 8 seconds depending on the 2θ range per frame using a scan width of 0.70°. Data collection was 99.9 % complete to 25.242° in θ . A total of 48063 reflections were collected covering the indices, $-13 \leq h \leq 14$, $-16 \leq k \leq 16$, $-16 \leq l \leq 16$. 7644 reflections were found to be symmetry independent, with a R_{int} of 0.0655. Indexing and unit cell refinement indicated a **Triclinic** lattice. The space group was found to be **P-1**. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: Great data! The crystal was racemic. There is one copy of the compound and one fumarate molecule in the asymmetric unit. Two of the protecting groups were positionally disordered. There is some disordered solvent in the pores that couldn't be adequately modeled; solvent masking in Olex2 was used to account for 6 electrons in the asymmetric unit. The chemical formula for the compound is: C₃₉H₄₈CIN₆O₆*CHO₂

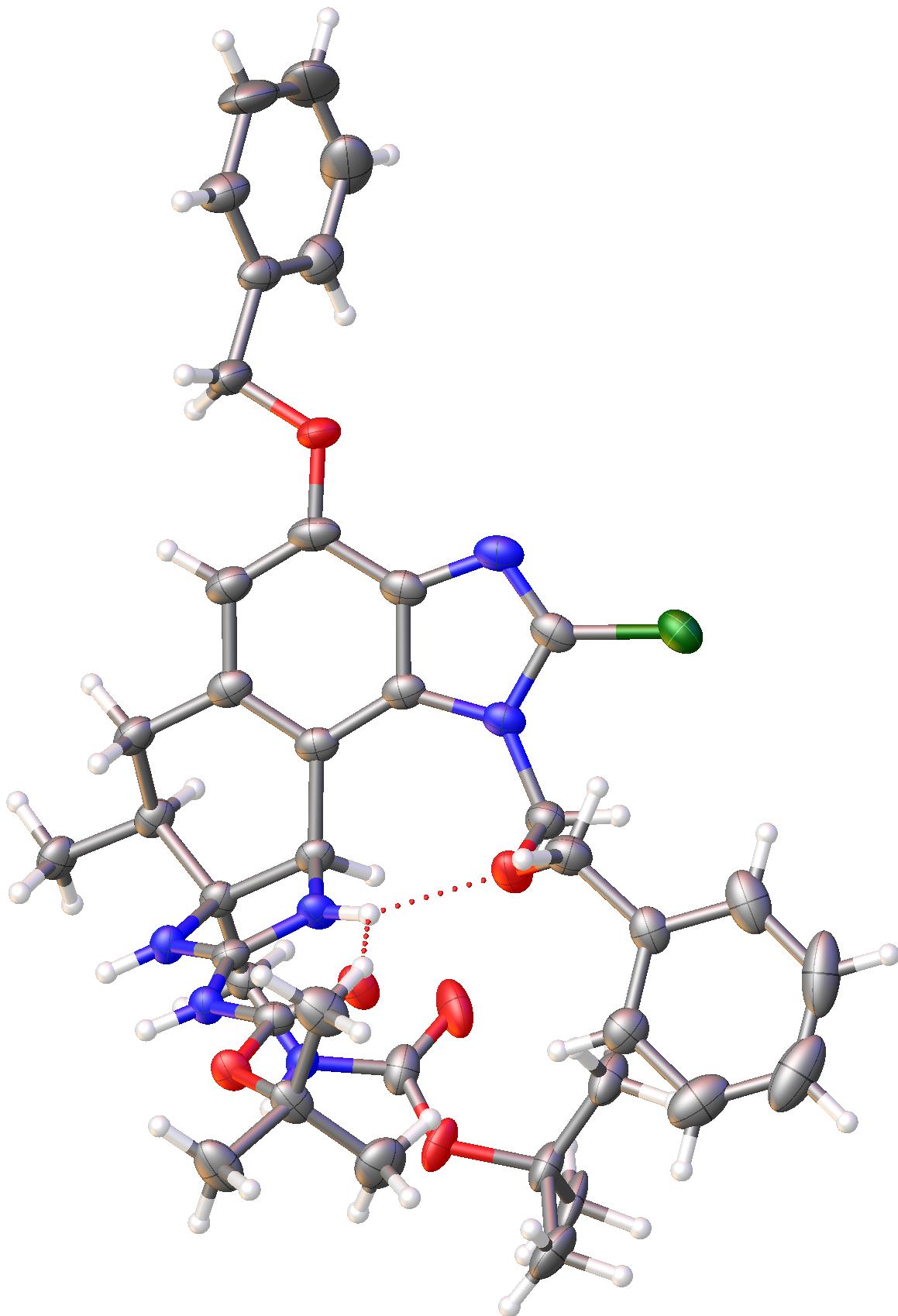


Table 1. Crystal data and structure refinement for Baran820.

Identification code	baran820		
Empirical formula	C40 H49 Cl N6 O8		
Formula weight	777.30		
Temperature	100.00 K		
Wavelength	0.71073 Å		
Crystal system	Triclinic		
Space group	P-1		
Unit cell dimensions	$a = 11.5330(7)$ Å	$\alpha = 85.000(2)^\circ$.	
	$b = 13.3566(8)$ Å	$\beta = 89.616(2)^\circ$.	
	$c = 13.8373(8)$ Å	$\gamma = 71.090(2)^\circ$.	
Volume	2008.3(2) Å ³		
Z	2		
Density (calculated)	1.285 Mg/m ³		
Absorption coefficient	0.154 mm ⁻¹		
F(000)	824		
Crystal size	0.2 x 0.14 x 0.045 mm ³		
Theta range for data collection	2.575 to 25.743°.		
Index ranges	-13<=h<=14, -16<=k<=16, -16<=l<=16		
Reflections collected	48063		
Independent reflections	7644 [R(int) = 0.0655]		
Completeness to theta = 25.242°	99.9 %		
Absorption correction	Semi-empirical from equivalents		
Max. and min. transmission	0.7453 and 0.6945		
Refinement method	Full-matrix least-squares on F ²		
Data / restraints / parameters	7644 / 12 / 605		
Goodness-of-fit on F ²	1.028		
Final R indices [I>2sigma(I)]	R1 = 0.0461, wR2 = 0.1054		
R indices (all data)	R1 = 0.0633, wR2 = 0.1138		
Largest diff. peak and hole	1.047 and -0.475 e.Å ⁻³		

Crystal structure of **13**

The single crystal X-ray diffraction studies were carried out on a Bruker D8-Venture 3-circle diffractometer equipped with a Photon3 detector and Mo K α radiation ($\lambda = 0.7107$ Å).

Crystals of the subject compound were used as received. A 0.2 x 0.2 x 0.2 mm piece of a crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ω scans. Crystal-to-detector distance was 50 mm and exposure time was 10 or 30 seconds depending on the 2θ range per frame using a scan width of 0.70°. Data collection was 99.7 % complete to 25.242° in θ . A total of 124401 reflections were collected covering the indices, $-16 \leq h \leq 16$, $-16 \leq k \leq 16$, $-28 \leq l \leq 28$. 16567 reflections were found to be symmetry independent, with a R_{int} of 0.1037. Indexing and unit cell refinement indicated a **Triclinic** lattice. The space group was found to be **P-1**. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: Data quality was poor but suitable for structural determination. The crystal is racemic. There are two copies of the compound and two copies of formic acid in the asymmetric unit. The chemical formula for the compound is: C₃₉H₄₇N₉O₆*CH₂O₂

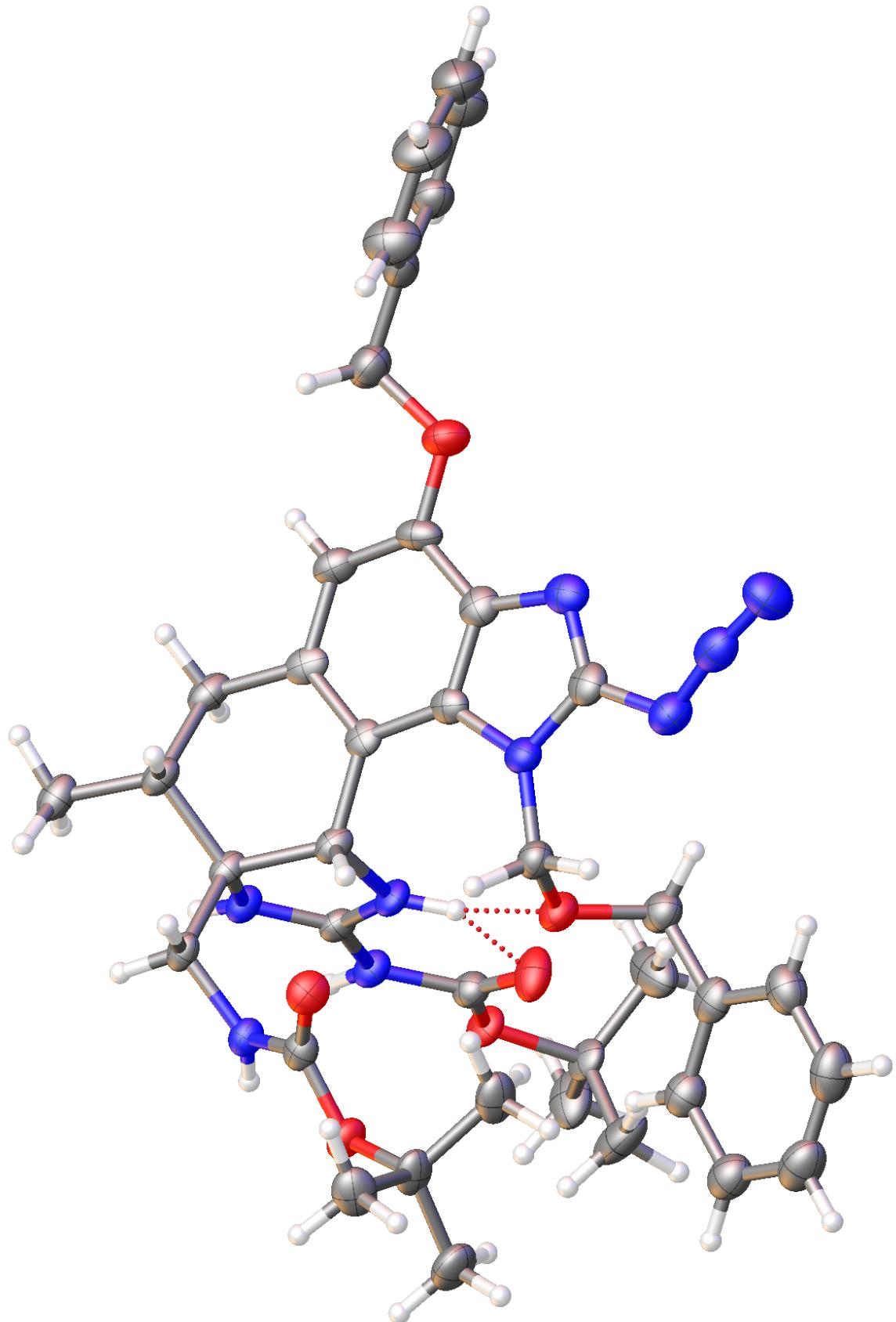


Table 1. Crystal data and structure refinement for Baran823.

Identification code	baran823_0m_a	
Empirical formula	C40 H49 N9 O8	
Formula weight	783.88	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 13.5233(12) Å	α= 85.802(3)°.
	b = 13.5646(12) Å	β= 75.750(3)°.
	c = 22.746(2) Å	γ = 88.073(3)°.
Volume	4032.7(6) Å ³	
Z	4	
Density (calculated)	1.291 Mg/m ³	
Absorption coefficient	0.092 mm ⁻¹	
F(000)	1664	
Crystal size	0.2 x 0.18 x 0.13 mm ³	
Theta range for data collection	2.464 to 26.517°.	
Index ranges	-16<=h<=16, -16<=k<=16, -28<=l<=28	
Reflections collected	124401	
Independent reflections	16567 [R(int) = 0.1037]	
Completeness to theta = 25.242°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.4908 and 0.4191	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	16567 / 0 / 1041	
Goodness-of-fit on F ²	1.067	
Final R indices [I>2sigma(I)]	R1 = 0.0943, wR2 = 0.1993	
R indices (all data)	R1 = 0.1550, wR2 = 0.2368	
Largest diff. peak and hole	0.903 and -0.334 e.Å ⁻³	

Crystal structure of **14**

The single crystal X-ray diffraction studies were carried out on a Bruker D8-Venture 3-circle diffractometer equipped with a Photon3 detector and Mo K_α radiation ($\lambda = 0.7107 \text{ \AA}$).

Crystals of the subject compound were used as received. A 0.17 x 0.07 x 0.02 mm piece of a crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ω scans. Crystal-to-detector distance was 50 mm and exposure time was 60 or 120 seconds per frame using a scan width of 0.70°. Data collection was 99.6 % complete to 22.029° in θ . A total of 229586 reflections were collected covering the indices, $-31 \leq h \leq 31$, $-23 \leq k \leq 23$, $-28 \leq l \leq 28$. 22316 reflections were found to be symmetry independent, with a R_{int} of 0.1413. Indexing and unit cell refinement indicated a **Primitive, Monoclinic** lattice. The space group was found to be **P2₁/c**. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: The data quality was very poor but suitable for structural determination. The crystal was racemic. There are three copies of the compound and one molecule of acetic acid in the asymmetric unit. The remaining solvent was disordered; solvent masking in Olex2 was used to account for 221 electrons in the asymmetric unit. There is some positional disorder on some of the BOC groups. The chemical formula for the compound is: C₄₅H₆₅N₉O₁₁

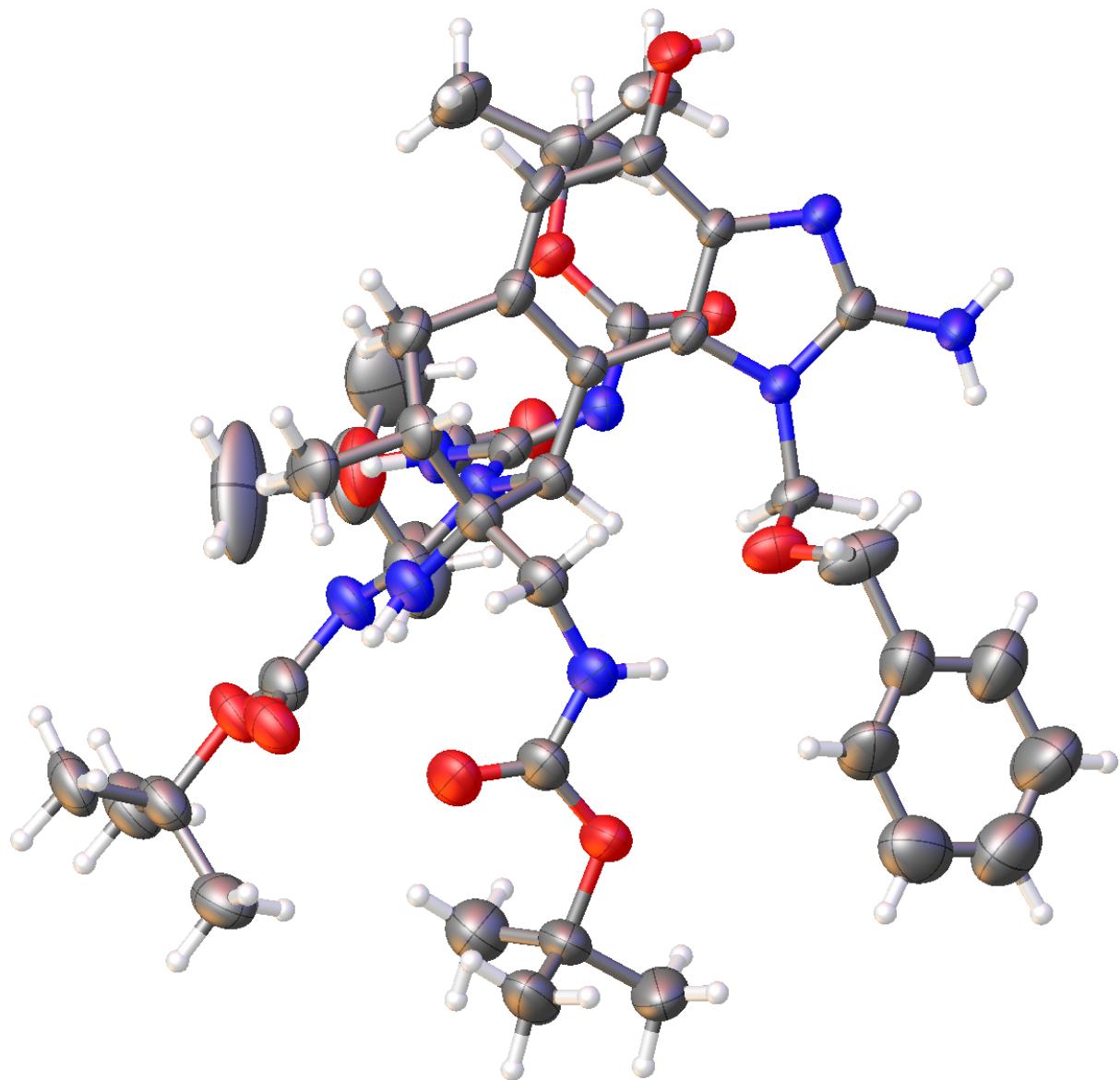


Table 1. Crystal data and structure refinement for Baran842.

Identification code	baran842	
Empirical formula	C45 H65 N9 O11	
Formula weight	908.06	
Temperature	100.15 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 29.5726(16) Å	α= 90°.
	b = 22.6244(13) Å	β= 96.670(2)°.
	c = 27.3861(15) Å	γ = 90°.
Volume	18199.0(17) Å ³	
Z	12	
Density (calculated)	0.994 Mg/m ³	
Absorption coefficient	0.072 mm ⁻¹	
F(000)	5832	
Crystal size	0.17 x 0.07 x 0.02 mm ³	
Theta range for data collection	2.443 to 22.029°.	
Index ranges	-31<=h<=31, -23<=k<=23, -28<=l<=28	
Reflections collected	229586	
Independent reflections	22316 [R(int) = 0.1434]	
Completeness to theta = 22.029°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.4882 and 0.4568	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	22316 / 69 / 1877	
Goodness-of-fit on F ²	1.021	
Final R indices [I>2sigma(I)]	R1 = 0.0633, wR2 = 0.1678	
R indices (all data)	R1 = 0.1064, wR2 = 0.1945	
Largest diff. peak and hole	0.655 and -0.342 e.Å ⁻³	

Crystal structure of **16**

The single crystal X-ray diffraction studies were carried out on a Bruker D8 Venture Ultra diffractometer equipped with Mo K _{α} radiation ($\lambda=0.71073 \text{ \AA}$).

Crystals of the subject compound were used as received (grow from Water / Acetone).

A 0.100 x 0.060 x 0.045 mm colorless block crystal was mounted on a Cryoloop with Paratone oil.

Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ω scans. Crystal-to-detector distance was 50 mm and exposure time was 3.0 seconds (depending on the 2θ range) per frame using a scan width of 0.70°. Data collection was 99.9% complete to 25.242° in θ . A total of 33126 reflections were collected covering the indices, -9≤h≤9, -13≤k≤13, -18≤l≤18. 4179 reflections were found to be symmetry independent, with a R_{int} of 0.0654. Indexing and unit cell refinement indicated a **Primitive, Triclinic** lattice. The space group was found to be **P-1**. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. . Crystallographic data are summarized in Table 1.

Notes: Excellent data and refinement,

2x “HCl” salt + water and acetone solvate

Disorders on hydrogen bonds, some positions are only ½ occupied

Pics contains only the “core” molecule

“racemic” space group

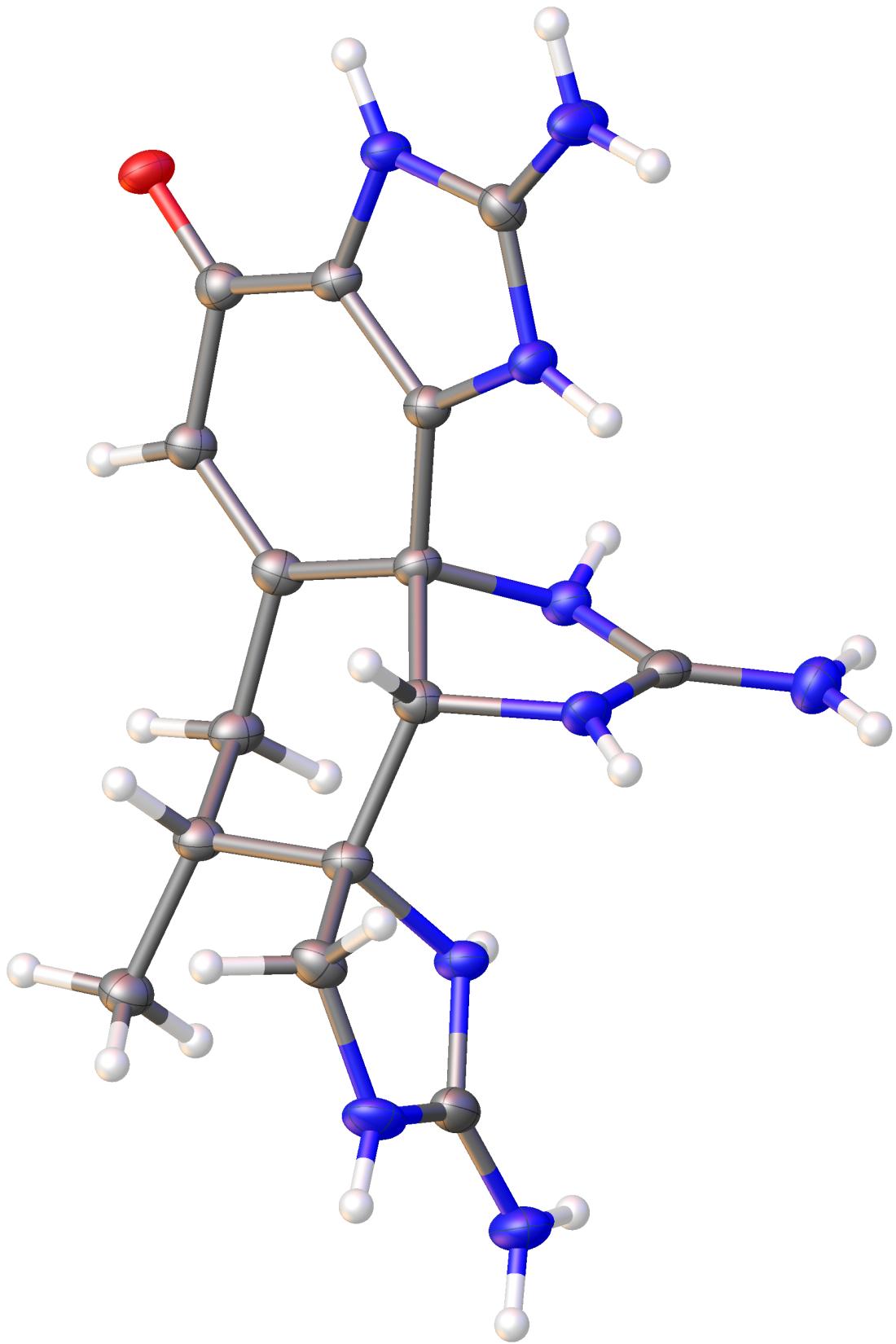


Table 1. Crystal data and structure refinement for Baran817.

Report date	2022-09-14	
Identification code	baran817	
Empirical formula	C18 H29 Cl2 N9 O3	
Molecular formula	C15 H21 N9 O, C3 H6 O, 2(Cl), H2 O	
Formula weight	490.40	
Temperature	100.00 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.6170(6) Å	α= 69.952(2)°.
	b = 11.0576(7) Å	β= 77.272(3)°.
	c = 15.0043(11) Å	γ = 73.027(2)°.
Volume	1125.25(14) Å ³	
Z	2	
Density (calculated)	1.447 Mg/m ³	
Absorption coefficient	0.330 mm ⁻¹	
F(000)	516	
Crystal size	0.1 x 0.06 x 0.045 mm ³	
Crystal color, habit	yellow block	
Theta range for data collection	2.821 to 25.492°.	
Index ranges	-9<=h<=9, -13<=k<=13, -18<=l<=18	
Reflections collected	33126	
Independent reflections	4179 [R(int) = 0.0654]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.6463 and 0.6142	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4179 / 3 / 304	
Goodness-of-fit on F ²	1.038	
Final R indices [I>2sigma(I)]	R1 = 0.0394, wR2 = 0.0947	
R indices (all data)	R1 = 0.0534, wR2 = 0.1038	
Largest diff. peak and hole	0.343 and -0.449 e.Å ⁻³	

Crystal structure of **1**

The single crystal X-ray diffraction studies were carried out on a Bruker D8-Venture 3-circle diffractometer equipped with a Photon3 detector and Mo K α radiation ($\lambda = 0.7107 \text{ \AA}$).

Crystals of the subject compound were used as received. A 0.25 x 0.23 x 0.18 mm piece of a crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ω scans. Crystal-to-detector distance was 50 mm and exposure time was 3, 6, or 8 seconds using a scan width of 0.70°. Data collection was 99.9 % complete to 25.242° in θ . A total of 66402 reflections were collected covering the indices, $-11 \leq h \leq 11$, $-32 \leq k \leq 32$, $-12 \leq l \leq 12$. 4920 reflections were found to be symmetry independent, with a R_{int} of 0.0480. Indexing and unit cell refinement indicated a Primitive, Monoclinic lattice. The space group was found to be **P2₁/m**. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: Great data! The crystal was racemic. There is one copy of the compound, 3 molecules of HCl, one molecule of H₂O, ~0.90 molecules of MeOH, and one molecule of acetone in the asymmetric unit. One of the Cl atoms is positionally disordered and was modeled over 4 positions. The MeOH is likely partially occupied.

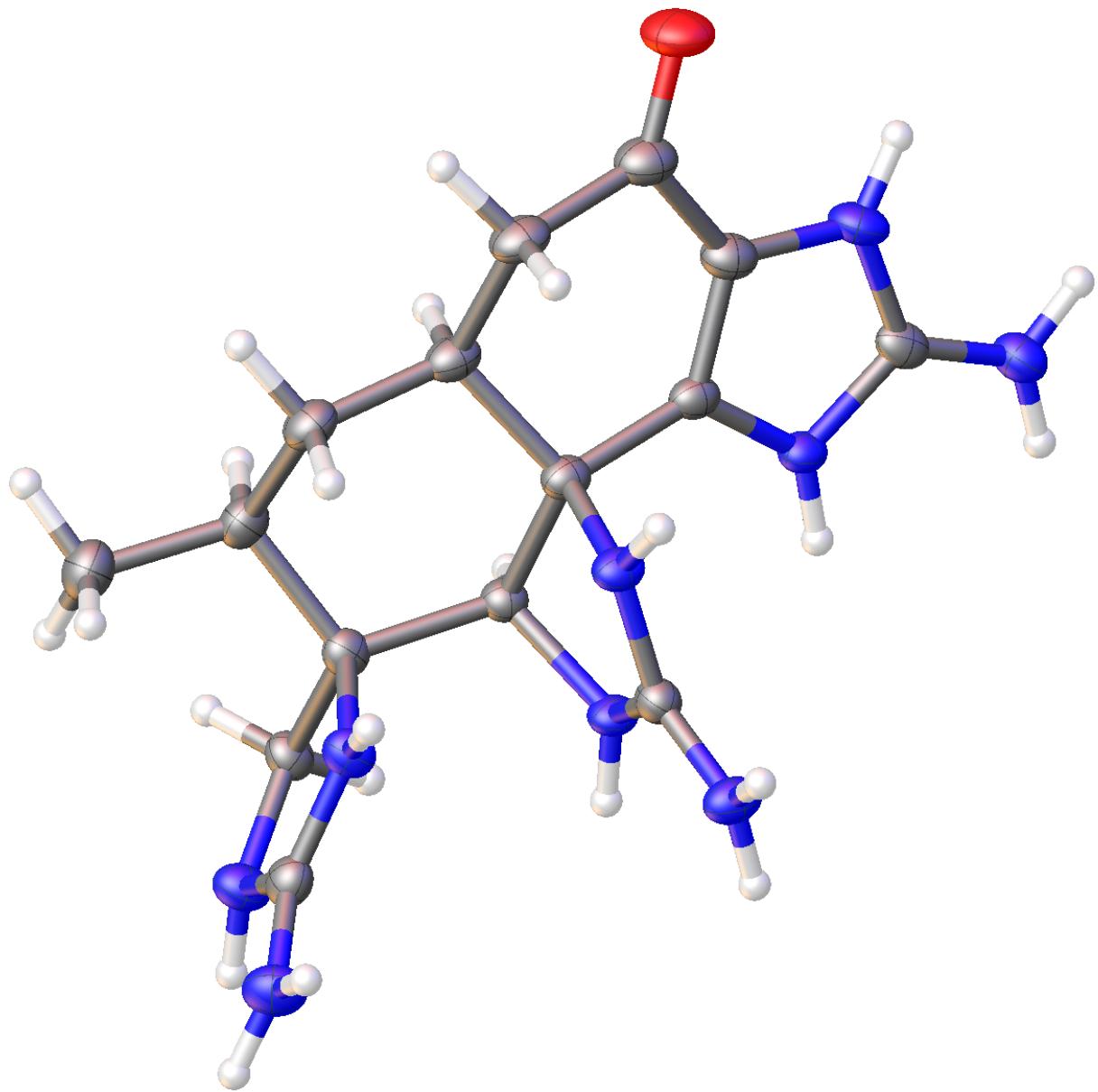


Table 1. Crystal data and structure refinement for Baran839.

Identification code	baran839_0m_a	
Empirical formula	C16.96 H30.83 Cl3 N9 O2.96	
Formula weight	514.49	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21/m 1	
Unit cell dimensions	a = 9.1372(4) Å	α= 90°.
	b = 25.8189(11) Å	β= 93.671(2)°.
	c = 9.9218(4) Å	γ = 90°.
Volume	2335.87(17) Å ³	
Z	4	
Density (calculated)	1.463 Mg/m ³	
Absorption coefficient	0.432 mm ⁻¹	
F(000)	1081	
Crystal size	0.25 x 0.23 x 0.18 mm ³	
Theta range for data collection	2.592 to 26.434°.	
Index ranges	-11<=h<=11, -32<=k<=32, -12<=l<=12	
Reflections collected	66402	
Independent reflections	4920 [R(int) = 0.0480]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.6465 and 0.6128	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4920 / 8 / 345	
Goodness-of-fit on F ²	1.126	
Final R indices [I>2sigma(I)]	R1 = 0.0446, wR2 = 0.1058	
R indices (all data)	R1 = 0.0524, wR2 = 0.1097	
Largest diff. peak and hole	0.713 and -0.367 e.Å ⁻³	

Crystal structure of 22

The single crystal X-ray diffraction studies were carried out on a Bruker Microstar APEX II CCD diffractometer equipped with Cu K α radiation ($\lambda = 1.54178 \text{ \AA}$).

Crystals of the subject compound were used as received. A 0.24 x 0.08 x 0.08 mm piece of a crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ω scans. Crystal-to-detector distance was 40 mm and exposure time was 2, 4, 5, 8, 10, 12, or 15 seconds depending on the 2θ range per frame using a scan width of 1.25°. Data collection was 96.3 % complete to 67.679° in θ . A total of 28328 reflections were collected covering the indices, $-7 \leq h \leq 7$, $-33 \leq k \leq 34$, $-17 \leq l \leq 18$. 9815 reflections were found to be symmetry independent, with a R_{int} of 0.0595. Indexing and unit cell refinement indicated a Primitive, **Monoclinic** lattice. The space group was found to be **P2₁**. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: Data quality was suitable for structural determination Absolute stereochemistry was conclusively assigned (Absolute Structure Parameter = 0.10(3)). There are two copies of the compound in the asymmetric unit. The crystal was a nonmerohedral twin; the smaller domain was ignored during integration. The chemical formula for the compound is: C₂₈H₄₄N₂O₆Si

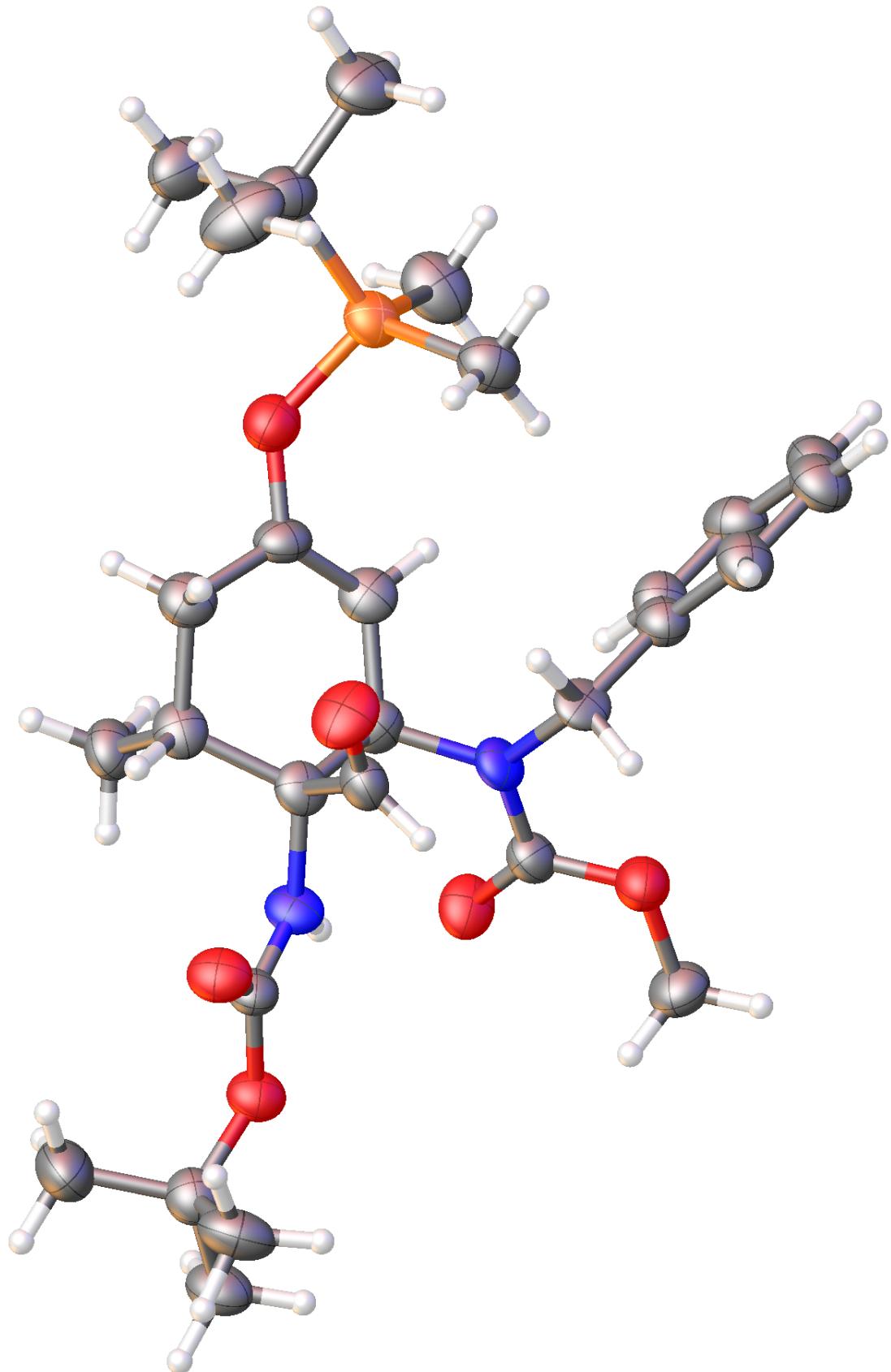


Table 1. Crystal data and structure refinement for Baran838.

Identification code	baran838_0m_a	
Empirical formula	C28 H44 N2 O6 Si	
Formula weight	532.74	
Temperature	100.15 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 6.3667(3) Å	α= 90°.
	b = 30.3360(16) Å	β= 92.895(2)°.
	c = 15.6780(8) Å	γ = 90°.
Volume	3024.2(3) Å ³	
Z	4	
Density (calculated)	1.170 Mg/m ³	
Absorption coefficient	1.017 mm ⁻¹	
F(000)	1152	
Crystal size	0.24 x 0.08 x 0.08 mm ³	
Theta range for data collection	2.822 to 66.679°.	
Index ranges	-7<=h<=7, -33<=k<=34, -17<=l<=18	
Reflections collected	28328	
Independent reflections	9815 [R(int) = 0.0595]	
Completeness to theta = 66.679°	96.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.4599	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	9815 / 1 / 687	
Goodness-of-fit on F ²	1.082	
Final R indices [I>2sigma(I)]	R1 = 0.0966, wR2 = 0.2453	
R indices (all data)	R1 = 0.1010, wR2 = 0.2480	
Absolute structure parameter	0.10(3)	
Largest diff. peak and hole	0.785 and -0.407 e.Å ⁻³	

Crystal structure of **23**

The single crystal X-ray diffraction studies were carried out on a Bruker Microstar APEX II CCD diffractometer equipped with Cu K α radiation ($\lambda = 1.54178 \text{ \AA}$).

Crystals of the subject compound were used as received. A 0.18 x 0.13 x 0.1 mm piece of a crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ω scans. Crystal-to-detector distance was 40 mm and exposure time was 5, 15, 20, or 30 seconds depending on the 2θ range per frame using a scan width of 1.25°. Data collection was 100 % complete to 67.679° in θ . A total of 24913 reflections were collected covering the indices, $-16 \leq h \leq 16$, $-7 \leq k \leq 7$, $-18 \leq l \leq 17$. 4910 reflections were found to be symmetry independent, with a R_{int} of 0.0760. Indexing and unit cell refinement indicated a Primitive, **Monoclinic** lattice. The space group was found to be **P2₁**. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: Great data! Absolute stereochemistry was assigned based on known stereocenters (Absolute Structure Parameter = 0.11(12)). There is one copy of the compound, two molecules of fumaric acid, and one molecule of MTBE in the asymmetric unit. The chemical formula for the compound is: C₁₇H₂₄N₂O₄*(CH₂O₂)₂*C₅H₁₂O

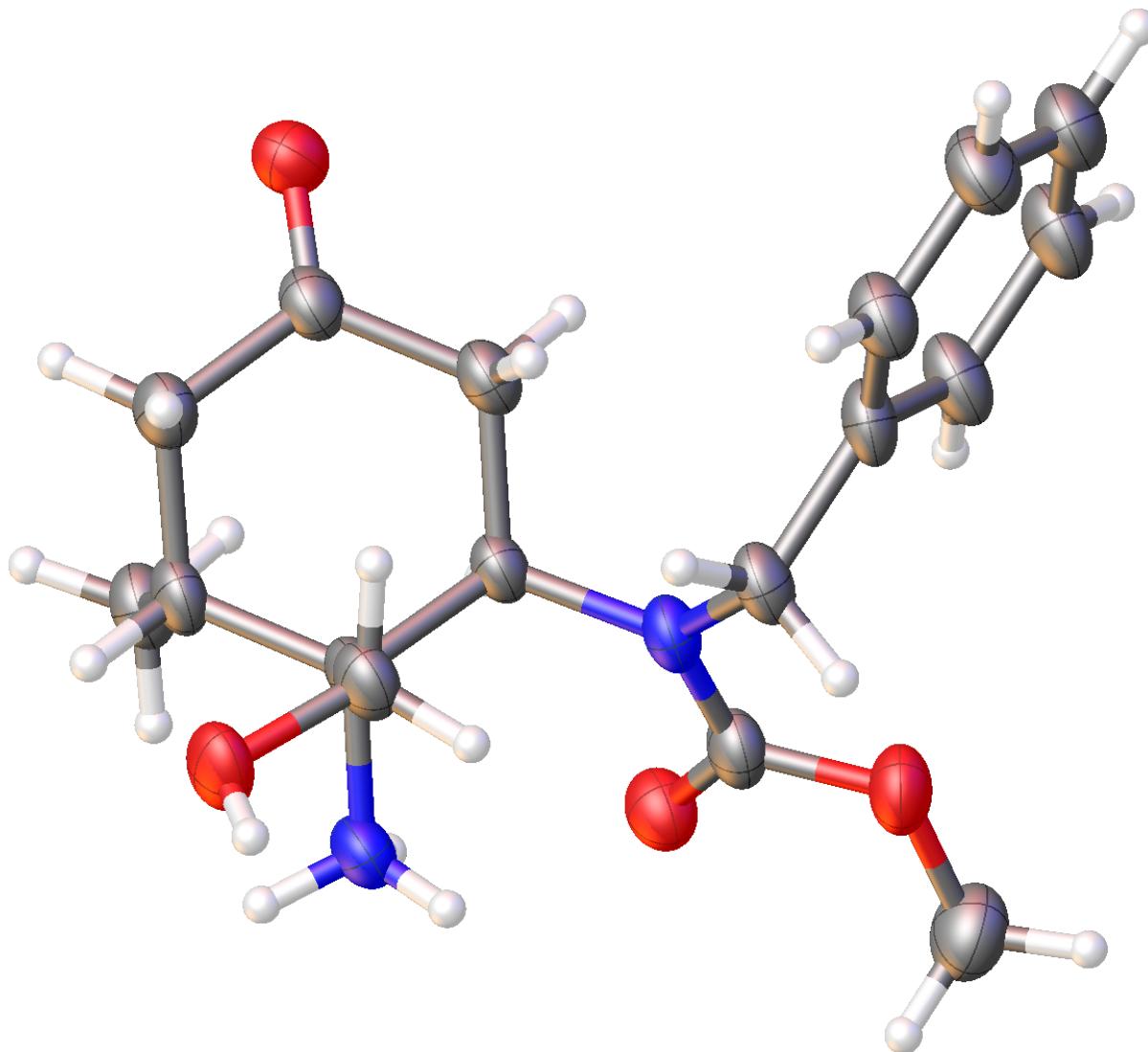


Table 1. Crystal data and structure refinement for Baran837.

Identification code	baran837_0m_a	
Empirical formula	C ₂₄ H ₄₀ N ₂ O ₉	
Formula weight	500.58	
Temperature	100.15 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 14.1346(8) Å	α = 90°.
	b = 6.4071(4) Å	β = 101.329(3)°.
	c = 15.0434(8) Å	γ = 90°.
Volume	1335.81(13) Å ³	

Z	2
Density (calculated)	1.245 Mg/m ³
Absorption coefficient	0.788 mm ⁻¹
F(000)	540
Crystal size	0.18 x 0.13 x 0.1 mm ³
Theta range for data collection	2.996 to 68.947°.
Index ranges	-16<=h<=16, -7<=k<=7, -18<=l<=17
Reflections collected	24913
Independent reflections	4910 [R(int) = 0.0760]
Completeness to theta = 67.679°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7532 and 0.4291
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4910 / 1 / 325
Goodness-of-fit on F ²	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0549, wR2 = 0.1435
R indices (all data)	R1 = 0.0635, wR2 = 0.1523
Absolute structure parameter	0.11(12)
Largest diff. peak and hole	0.342 and -0.225 e.Å ⁻³

Crystal structure of **24**

The single crystal X-ray diffraction studies were carried out on a Bruker SMART Pt135 CCD diffractometer equipped with Cu K α radiation ($\lambda = 1.54178 \text{ \AA}$).

Crystals of the subject compound were used as received. A 0.2 x 0.12 x 0.085 mm piece of a crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ω scans. Crystal-to-detector distance was 45 mm and exposure time was 4, 10, 16, or 20 seconds depending on the 2 θ range per frame using a scan width of 1.00°. Data collection was 99.9 % complete to 67.679° in θ . A total of 105604 reflections were collected covering the indices, $-15 \leq h \leq 15$, $-23 \leq k \leq 23$, $-15 \leq l \leq 15$. 11176 reflections were found to be symmetry independent, with a R_{int} of 0.0306. Indexing and unit cell refinement indicated a Primitive, **Monoclinic** lattice. The space group was found to be **P2₁**. The data were integrated using the Bruker SAINT Software program and scaled using the

SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014).

All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: Great data! Absolute stereochemistry was conclusively assigned (Absolute Structure Parameter = -0.01(8)). There are two copies of the compound in the asymmetric unit. The crystal was twinned; the .hkl5 file was used during refinement. There is some positional disorder on the alcohol. The chemical formula for the compound is: C₂₈H₄₂N₄O₈

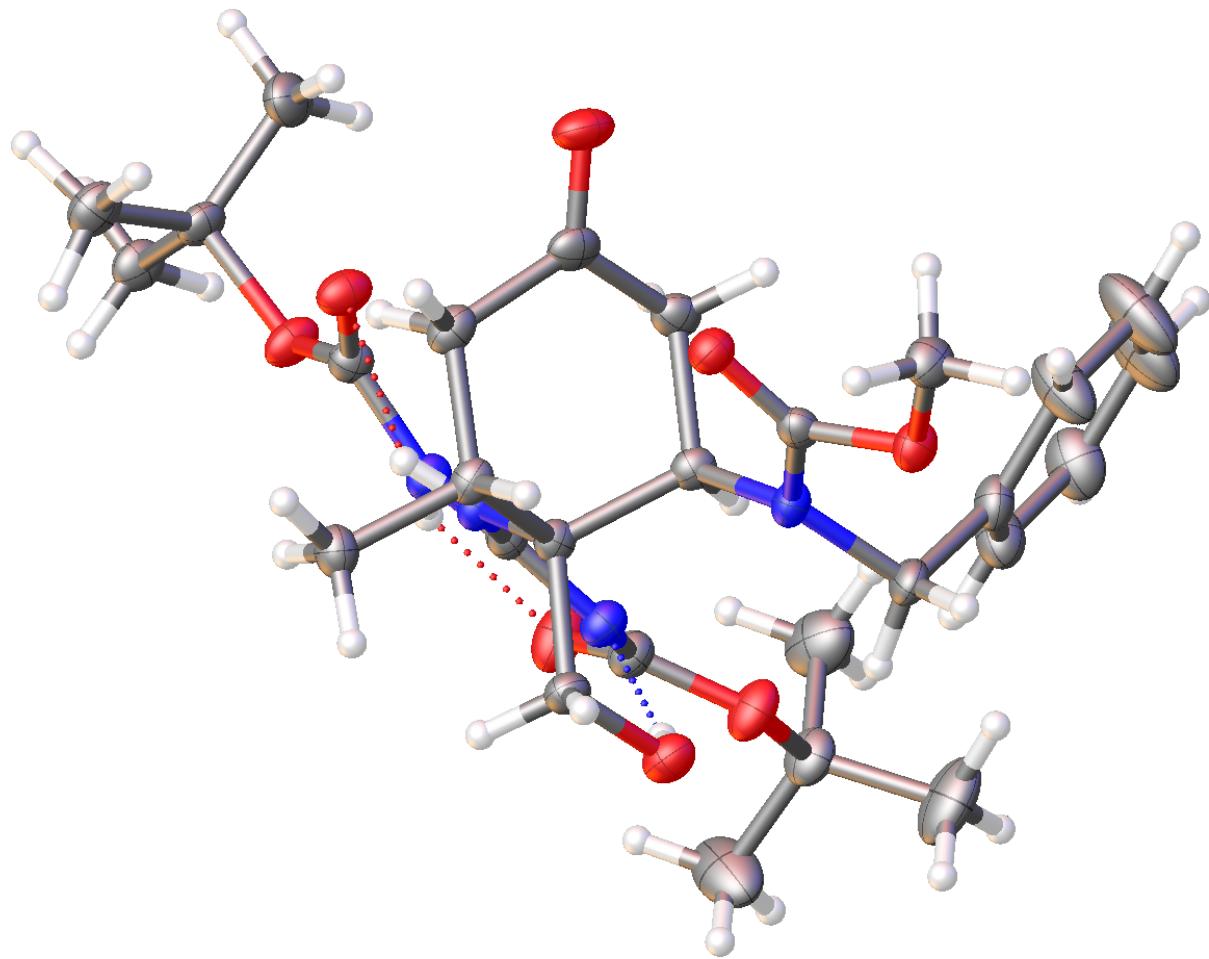


Table 1. Crystal data and structure refinement for Baran828.

Identification code	baran828		
Empirical formula	C ₂₈ H ₄₂ N ₄ O ₈		
Formula weight	562.65		
Temperature	100.15 K		
Wavelength	1.54178 Å		
Crystal system	Monoclinic		
Space group	P 1 21 1		
Unit cell dimensions	a = 12.3666(5) Å	α= 90°.	
	b = 19.0771(8) Å	β= 103.7210(10)°.	
	c = 13.0013(5) Å	γ = 90°.	
Volume	2979.7(2) Å ³		
Z	4		
Density (calculated)	1.254 Mg/m ³		
Absorption coefficient	0.761 mm ⁻¹		

F(000)	1208
Crystal size	0.2 x 0.12 x 0.085 mm ³
Theta range for data collection	3.499 to 70.168°.
Index ranges	-15<=h<=15, -23<=k<=23, -15<=l<=15
Reflections collected	105604
Independent reflections	11176 [R(int) = 0.0502]
Completeness to theta = 67.679°	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	11176 / 1 / 751
Goodness-of-fit on F ²	1.067
Final R indices [I>2sigma(I)]	R1 = 0.0364, wR2 = 0.0989
R indices (all data)	R1 = 0.0368, wR2 = 0.0994
Absolute structure parameter	-0.01(8)
Largest diff. peak and hole	0.305 and -0.212 e.Å ⁻³

VIII) CD Spectrum

The CD spectrum of synthetic (+)-KB343 was measured on JASCO J-1500 spectrometer in a 1-mm quartz cell at 25 °C. HPLC water was used as solvent and blank correction (just pure HPLC water) was applied. The sample concentration was 0.47 mM.

