Diastereoselective Michael–Claisen Cyclizations of γ-Oxa-α,β Unsaturated Ketones En Route to 5-Oxatetracyclines

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Supporting Information

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General Experimental Procedures: All reactions were performed in round-bottom flasks fitted with rubber septa under a positive pressure of argon or nitrogen, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless-steel cannula. Organic solutions were concentrated by rotary evaporation (house vacuum, ca. 25–40 torr) at ambient temperature, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore-size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light, then were stained with either an aqueous sulfuric acid solution of ceric ammonium molybdate (CAM) or an aqueous sodium carbonate solution of potassium permanganate (KMnO4) then briefly heated on a hot plate. Flash-column chromatography was performed as described by Still et al.,[1] employing silica gel (60 Å, 32–63 μM, standard grade, Dynamic Adsorbents, Inc.).

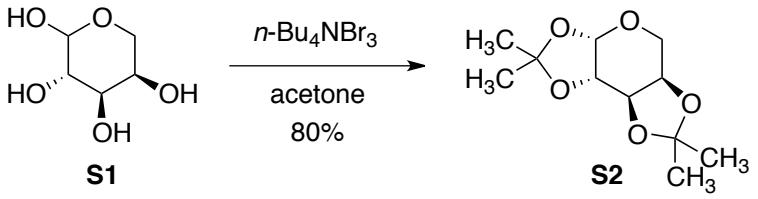
Materials: Dry solvents were purchased from the Aldrich Chemical Company in Sure/Seal^{TM} glass bottles and used without purification. All reagents were purchased and used without purification with the following exceptions: benzaldehyde, *tert*-butyldimethylsilyl trifluoromethanesulfonate and triethylsilyl trifluoromethanesulfonate were distilled under an atmosphere of argon. Tetramethylethylenediamine was distilled from calcium hydride under an atmosphere of argon. Trifluoromethanesulfonic anhydride was distilled from P_2O_5 under an atmosphere of argon. Lithium chloride was dried at 150 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 150 °C (760 mmHg); the hot, dried solid was flame dried under vacuum (0.1 mmHg) for 2−3 min immediately prior to use. Benzyl bromide was filtered neat through a column of oven-dried basic alumina immediately prior to use.

Instrumentation: Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian INOVA 500 (500 MHz) or 600 (600 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26; D_2HCOD: δ 3.31). Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), and coupling constant (*J*) in Hertz. Carbon

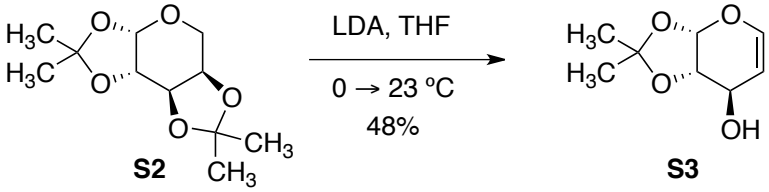
[1] Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Varian INOVA 500 (125 MHz) NMR spectrometer at 23 °C. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0; C_6D_6, δ 128.0). Infrared (IR) spectra were obtained using a Shimadzu 8400S FT-IR spectrometer and were referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facility. X-ray crystallographic analysis was performed at the Harvard University X-ray Crystallographic Laboratory by Dr. Shao-Liang Zheng.

Experimental Procedures and Characterization Data



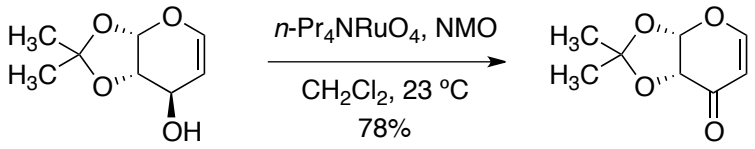
Bis-*O*-isopropylidene S2.[2] Tetrabutylammonium tribromide (1.29 g, 2.66 mmol, 0.040 equiv) was added in one portion to a white suspension of D-(–)-arabinose (**S1**, 10.0 g, 66.6 mmol, 1 equiv) in dry acetone (250 mL, dried over anhydrous calcium sulfate) at 23 ºC. The resulting mixture was stirred at 23 ºC for 2 d, whereupon triethylamine (1.00 mL) was added dropwise. The resulting yellow solution was concentrated. The crude product was purified by flash-column chromatography (2% acetone–hexanes initially, grading to 5% acetone–hexanes), affording bis-*O*-isopropylidene **S2** as a white solid (12.3 g, 80%). The characterization data obtained for **S2** were in agreement with those reported in the literature.[3]



Allylic alcohol S3.[4] A round-bottomed flask containing a solution of bis-*O*-isopropylidene **S2** (69.3 g, 301 mmol, 1 equiv) in tetrahydrofuran (1.00 L) was cooled at 0 ºC. A commercial solution of lithium diisopropylamide (2.0 M in tetrahydrofuran–heptane–ethylbenzene, 556 mL, 1.11 mol, 3.70 equiv) was added dropwise via cannula over 1.25 h to the cooled starting material solution. The resulting mixture was stirred for 30 min, whereupon the cooling bath was removed. The reaction mixture was allowed to warm to 23 ºC. After stirring at this temperature for 12 h, the reaction flask was cooled to 0 ºC and saturated ammonium chloride solution (500 mL) was added dropwise. The cooling bath was removed and the crude reaction mixture was concentrated to approximately 300 mL. The pH of the solution was adjusted to 5 by the dropwise addition of aqueous hydrochloric acid solution (1 N). The phases were separated and the aqueous phase was

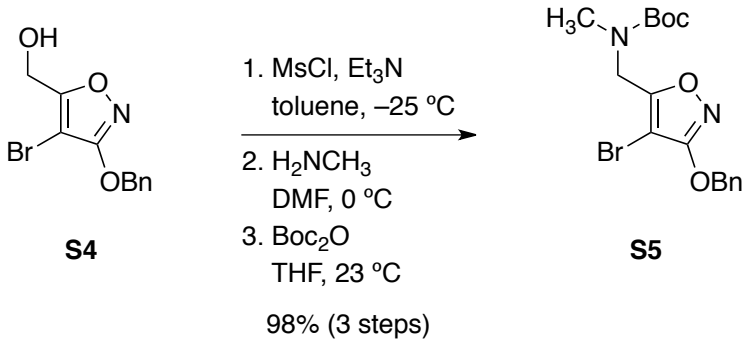
[2] This procedure is adapted from that of Khan et al.: Khan, A. T.; Khan, M. M.; Adhikary, A. *Carbohydr. Res.* **2011**, *346*, 673–677.
[3] Pedatella, S.; Guaragna, A.; D'Alonzo, D.; De Nisco, M.; Palumbo, G. *Synthesis* **2006**, *2*, 305–308.
[4] This procedure is adapted from that of Klemer et al.: Klemer, A.; Jung, G. *Chem. Ber.* **1981**, *114*, 1192–1195.

extracted with ether (3 × 400 mL). The organic extracts were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The product was purified by flash-column chromatography (20% ethyl ether–hexanes initially, grading to 60% ethyl ether–hexanes) to provide allylic alcohol **S3** as a pale yellow solid (24.7 g, 48%). TLC (30% ethyl acetate–hexanes): R_f = 0.22 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.34 (d, 1H, *J* = 6.3 Hz, OC(=CH)**H**), 5.44 (d, 1H, *J* = 2.9 Hz, OC**H**O), 4.96–4.93 (m, 1H, OC(=C**H**)H), 4.20–4.18 (m, 2H, $(CH_3)_2$COC**H**C, C**H**OH), 2.33 (d, 1H, *J* = 4.9 Hz, O**H**), 1.45 (s, 3H, $(CH_3)_2$C), 1.39 (s, 3H, $(CH_3)_2$C); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 143.2, 111.0, 99.0, 93.4, 77.9, 60.3, 27.7, 25.8. FTIR (neat), cm^{-1}: 3431 (br), 1651 (m), 1227 (s), 1076 (s), 1022 (s). HRMS (ESI): Calcd for $(C_8H_{13}O_4)^+$: 173.0814. Found: 173.0774.



S3 **6**

Dihydro-4-pyranone 6. Tetrapropylammonium perruthenate (3.80 g, 10.8 mmol, 0.100 equiv) was added portionwise over 1.5 h to a mixture of allylic alcohol **S3** (18.6 g, 108 mmol, 1 equiv), *N*-methylmorpholine *N*-oxide (19.0 g, 162 mmol, 1.50 equiv) and powdered 4Å molecular sieves (42.0 g) in anhydrous dichloromethane (270 mL) cooled at 0 ºC. The cooling bath was removed and the reaction mixture was allowed to warm to 23 ºC. After stirring at this temperature for 20 min, the reaction mixture was filtered through a thick pad of silica gel, washing with ethyl acetate. The filtrate was concentrated. The crude product was purified by flash-column chromatography (10% ethyl acetate–hexanes initially, grading to 25% ethyl acetate–hexanes), affording dihydro-4-pyranone **6** as a pale yellow solid (14.4 g, 78%). TLC (30% ethyl acetate–hexanes): R_f = 0.26 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.25 (d, 1H, *J* = 6.3 Hz, OC(=CH)**H**), 5.88 (d, 1H, *J* = 3.5 Hz, OC**H**O), 5.43 (dd, 1H, *J* = 6.4, 1.3 Hz, OC(=C**H**)H), 4.19 (dd, 1H, *J* = 3.6, 1.3 Hz, OC**H**C(O)), 1.52 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 186.3, 160.7, 113.3, 103.8, 101.0, 76.7, 27.4, 25.7. FTIR (neat), cm^{-1}: 1678 (s), 1599 (s), 1223 (s), 1032 (s). HRMS (ESI): Calcd for $(C_8H_{10}O_4Na)^+$: 193.0477. Found: 193.0465.



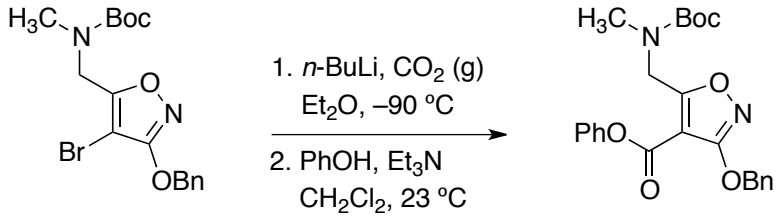
***tert*-Butyl ((3-Benzyloxy-4-bromoisoxazol-5-yl)methyl)(methyl)carbamate S4: Step 1, Mesylation.** Methanesulfonyl chloride (31.7 mL, 406 mmol, 1.70 equiv) was added dropwise by syringe over 15 min to a mechanically stirred solution of 3-benzyloxy-4-bromo-5-(hydroxymethyl)isoxazole[5] (**S4**, 67.9 g, 239 mmol, 1 equiv) and triethylamine (66.6 mL, 478 mmol, 2.00 equiv) in toluene (1.20 L) at −25 °C (cooled using an acetone cooling bath with temperature control by periodic addition of dry ice). After 30 min, ethyl ether (400 mL), water (400 mL) and 0.1 M pH 5 aqueous sodium citrate buffer (450 mL) were added sequentially. The cooling bath was removed and the reaction flask was allowed to warm to 23 °C. The layers were separated and the aqueous phase was extracted with ethyl ether (3 × 400 mL). The organic extracts were combined and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide (3-(benzyloxy)-4-bromoisoxazol-5-yl)methyl methanesulfonate (not shown) as a white solid (87 g). This material was used in the next transformation without further purification.

Step 2, Methylamine displacement. The unpurified mesylate (87 g) from step 1 above was dissolved in dimethylformamide (1.20 L) and the resulting solution was cooled to 0 ºC. A solution of methylamine in ethanol (33% w/w, 452 g, 4.80 mol, 20.0 equiv) was added to the solution of mesylate via cannula over 10 min. After 2 h, saturated aqueous sodium bicarbonate solution (350 mL), saturated aqueous sodium chloride solution (350 mL), and ethyl ether (500 mL) were added. The layers were separated. The aqueous phase was extracted with ethyl ether (3 × 400 mL). The organic extracts were combined and washed with water (3 × 500 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide 3-benzyloxy-4-bromo-5-(methylaminomethyl)isoxazole (not shown)

[5] Brubaker, J. D. A Practical Synthetic Route to Structurally Diverse Tetracycline Antibiotics. Ph.D. thesis, Harvard University, Cambridge, MA, 2007.

as a pale yellow oil (72 g). This material was used in the next transformation without further purification.

Step 3, *tert*-Butyl carbamate formation. To a solution of the unpurified methylamine (72 g) from step 2 above in tetrahydrofuran (600 mL) was added di-*tert*-butyl dicarbonate (112 mL, 481 mmol, 2.00 equiv). Immediately, gas evolution was observed. After 40 min, the solution was concentrated to give a pale yellow oil. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate–hexanes initially, grading to 15% ethyl acetate–hexanes) to provide isoxazole **S5** (94 g, 98% over 3 steps) as a clear and colorless oil. TLC (15% ethyl acetate–hexanes): R_f = 0.39 (UV, CAM). ^{1}H NMR (1.4 : 1 ratio of rotamers, asterisk (*) denotes minor rotamer, 500 MHz, $CDCl_3$), δ: 7.50–7.43 (m, 2H, Ar**H**), 7.44–7.33 (m, 3H, Ar**H**), 5.32 (s, 2H, OC**H**$_2$Ph), 4.51* (s, 2H, C**H**$_2$NCH$_3$Boc), 4.44 (s, 2H, C**H**$_2$NCH$_3$Boc), 2.94 (s, 3H, NC**H**$_3$), 2.89* (s, 3H, NC**H**$_3$), 1.47 (s, 9H, NC(O)O(C**H**$_3$)$_3$).^{13}C NMR (125 MHz, $CDCl_3$), δ: 168.3, 166.4, 155.3*, 154.7, 135.0, 128.4, 128.4, 128.0, 83.6*, 83.5, 80.4, 80.2*, 71.8, 43.9, 43.3*, 34.6, 28.2. FTIR (neat), cm^{-1}: 2980 (w), 2936 (w), 2253 (m), 1695 (s), 1616 (m), 1522 (s), 1479 (w), 1449 (s). HRMS (ESI): Calcd for $(C_{17}H_{21}N_2O_4BrNa)^+$: 419.0582, 421.0562. Found: 419.0556, 421.0539.



S5 **10**

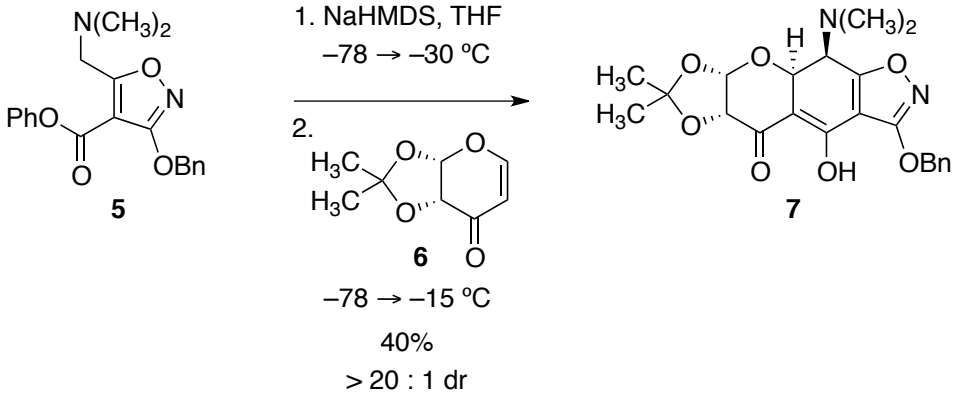
69% (2 steps)

Isoxazole 10: **Step 1, Carboxylation**. A titrated solution of *n*-butyllithium in hexanes (2.51 M, 56.6 mL, 142 mmol, 1.20 equiv) was added dropwise by cannula over 20 min to a solution of *tert*-butyl ((3-Benzyloxy-4-bromoisoxazol-5-yl)methyl)(methyl)carbamate (**S5**, 47.0 g, 118 mmol, 1 equiv) in ethyl ether (790 mL) cooled at –90 ºC. Upon addition of base, the solution turned light yellow. The internal reaction temperature was carefully maintained below –85 ºC. After the addition of *n*-butyllithium was completed, stirring was maintained for 15 min. Carbon dioxide gas was then bubbled through the reaction mixture using a stainless-steel needle. After 2 h, the stream of carbon dioxide gas was stopped and nitrogen gas was bubbled through the solution using a stainless-steel needle. The cooling bath was removed and the reaction flask was

allowed to slowly warm to 23 °C over the course of 2 h. The flow of nitrogen gas was then stopped. Hexanes (400 mL), ethyl acetate (200 mL), and 1 M aqueous sodium hydroxide solution (500 mL) were added in sequence. After stirring for 20 min, the layers were separated. The organic phase was extracted with 1 M aqueous sodium hydroxide solution (3 × 500 mL). The aqueous extracts were combined and the combined solution was cooled to 0 ºC with stirring. The pH of the solution was adjusted to 4.5 by the dropwise addition of concentrated hydrochloric acid. The solution was removed from the cooling bath and allowed to warm to 23 °C. The solution was saturated with solid sodium chloride and then extracted with dichloromethane (3 × 1 L). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide 3-benzyloxy-5-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)isoxazole-4-carboxylic acid (not shown) as an off-white solid (38.6 g). This material was used in the next transformation without further purification.

Step 2, Esterification. Bis(2-oxo-3-oxazolidinyl)phosphonic chloride (40.7 g, 160 mmol, 1.50 equiv) was added to a solution of triethylamine (44.5 mL, 319 mmol, 3.00 equiv) and the unpurified 3-benzyloxy-5-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)isoxazole-4-carboxylic acid (38.6 g, 106 mmol, 1 equiv) from step 1 above in dichloromethane (532 mL) cooled at 0 ºC. After stirring for 5 min, phenol (15.0 g, 160 mmol, 1.50 equiv) was added. The cooling bath was then removed and the reaction mixture was allowed to warm to 23 ºC. After stirring for 2 h at 23 ºC, the reaction was concentrated to give a thick yellow oil. The residue was diluted with ethyl ether (400 mL) and hexanes (200 mL) and was washed with half saturated aqueous sodium bicarbonate (3 × 1 L). The organic extract was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (100% hexanes initially, then grading to 30% ethyl ether–hexanes) to provide pure isoxazole **10** as a clear and colorless oil (32.2 g, 69% over two steps). TLC (40% ethyl ether–hexanes): R_f = 0.34 (UV, CAM). ^{1}H NMR (1 : 1 ratio of rotamers, asterisk (*) denotes rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.52–7.46 (m, 2H, Ar**H**), 7.45–7.30 (m, 5H, Ar**H**), 7.29–7.25 (m, 1H, Ar**H**), 7.17 (d, 2H, *J* = 7.9 Hz, Ar**H**), 5.40 (s, 2H, OC**H**$_2$Ph), 4.90* (s, 2H, C**H**$_2$NCH$_3$Boc), 4.82 (s, 2H, C**H**$_2$NCH$_3$Boc), 3.00 (s, 3H, NC**H**$_3$), 2.98* (s, 3H, NC**H**$_3$), 1.48* (s, 9H, NC(O)O(C**H**$_3$)$_3$) 1.43 (s, 9H, NC(O)O(C**H**$_3$)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 176.6, 176.4*, 168.8*, 168.6, 158.9, 155.4*, 154.8, 149.8, 135.2, 129.2, 128.2, 128.1, 127.4, 125.9, 121.3, 100.5*, 100.3, 80.3, 80.2*, 71.6, 45.5, 35.1, 28.0. FTIR (neat), cm^{-1}: 1749 (m), 1732 (m),

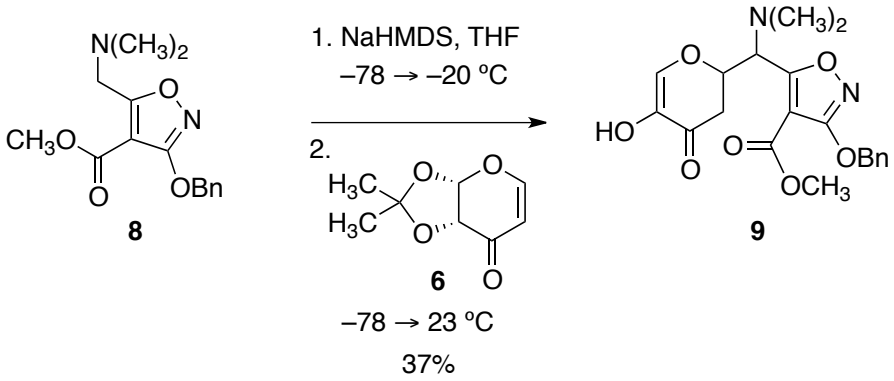
1699 (s), 1616 (m), 1591 (m), 1512 (s), 1452 (m), 1391 (m), 1368 (s). HRMS (ESI): Calcd for $(C_{24}H_{26}N_2O_6Na)^+$: 461.1689. Found: 461.1684.



Michael–Claisen cyclization product 7. A solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (1.00 M, 12.1 mL, 12.1 mmol, 2.05 equiv) was added dropwise via syringe to a solution of phenyl 3-benzyloxy-5-(dimethylaminomethyl)isoxazole-4-carboxylate **5**[6] (4.14 g, 11.8 mmol, 2.00 equiv) in tetrahydrofuran (100 mL) at –78 ºC. The resulting light brown solution was stirred at this temperature for 5 min, and then was warmed to –30 ºC. After stirring at –30 ºC for 40 min, the reaction solution turned orange and was cooled to –78 ºC. After stirring at this temperature for a further 5 min, a solution of pyrone **6** (1.00 g, 5.88 mmol, 1 equiv) in tetrahydrofuran (7.00 mL) was added dropwise via cannula to the orange anion solution at –78 ºC. The reaction mixture was stirred at this temperature for 5 min and then was allowed to warm to –15 ºC over 80 min. After stirring at –15 ºC for a further 2 h, saturated aqueous ammonium chloride solution (30 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. Water (150 mL) and ethyl acetate (200 mL) were added and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 × 200 mL). The organic extracts were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified first by flash-column chromatography (18% acetone–hexanes initially, grading to 24% acetone–hexanes), then by preparative HPLC on an Agilent Prep C18 column [10 μm, 250 x 21.2 mm, UV detection at 350 nm, solvent A: water, solvent B: methanol, gradient elution with 70–90% B over 50 min, flow rate: 15 mL/min, 5 batches]. Fractions eluting at 14–20 min were collected and concentrated, providing the Michael–Claisen cyclization product **7** as a yellow

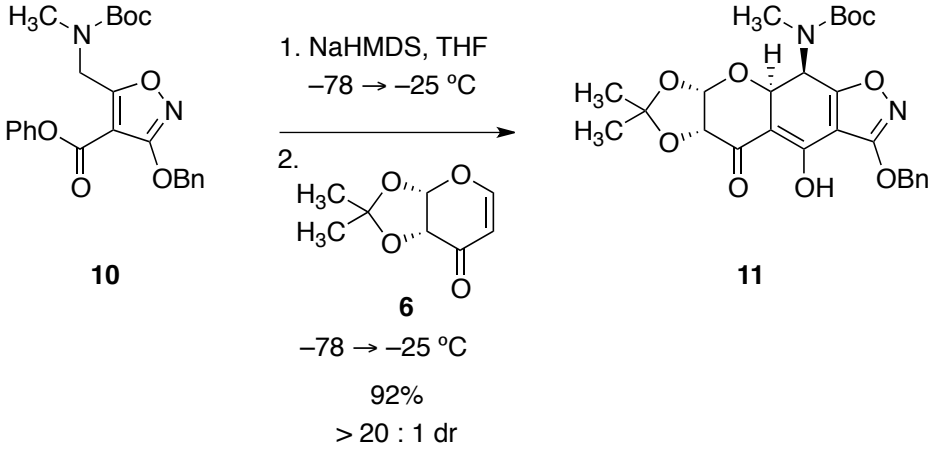
[6] Kummer, D. A.; Li, D.; Dion, A.; Myers, A. G. *Chem. Sci.* **2011**, *2*, 1710–1718.

solid (1.00 g, 40%). TLC (25% acetone–hexanes): R_f = 0.15 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 13.62 (s, 1H, br-s, 1H, O**H**), 7.49 (d, 2H, *J* = 7.8 Hz, Ar**H**), 7.40–7.34 (m, 3H, Ar**H**), 5.96 (d, 1H, *J* = 5.1 Hz, $(CH_3)_2COCHO$), 5.37 (s, 2H, OCH_2Ph), 5.10 (d, 1H, *J* = 7.2 Hz, $OCHCHN(CH_3)_2$), 4.54 (d, 1H, *J* = 4.9 Hz, $(CH_3)_2COCHC(O)$), 4.22 (d, 1H, *J* = 7.2 Hz, $CHN(CH_3)_2$), 2.32 (s, 6H, $N(CH_3)_2$), 1.42 (s, 6H, $(CH_3)_2C$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 182.3, 175.5, 167.3, 167.2, 134.7, 128.6, 128.5, 128.3, 109.5, 108.9, 106.5, 98.4, 72.6, 68.6, 64.6, 58.1, 42.1, 27.0, 26.8. FTIR (neat), cm^{-1}: 2932 (w), 1699 (s), 1649 (s), 1510 (s), 1250 (s), 1125 (s), 836 (s). HRMS (ESI): Calcd for $(C_{22}H_{24}N_2O_7)^+$: 429.1662. Found: 429.1656.



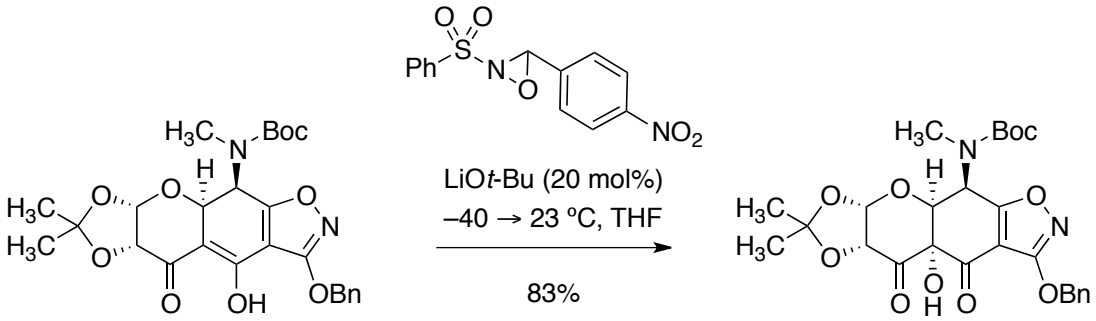
Fragmentation product 9. A solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (1.00 M, 197 μL, 0.197 mmol, 2.10 equiv) was added dropwise via syringe to a solution of methyl 3-benzyloxy-5-(dimethylaminomethyl)isoxazole-4-carboxylate **8** (54.6 mg, 0.188 mmol, 2.00 equiv) in tetrahydrofuran (1.5 mL) at –78 ºC. The resulting yellow solution was stirred at this temperature for 5 min, and then was warmed to –20 ºC. After stirring at –20 ºC for 30 min, the reaction solution was cooled to –78 ºC. After stirring at this temperature for a further 5 min, a solution of pyrone **6** (16.0 mg, 0.094 mmol, 1 equiv) in tetrahydrofuran (0.300 mL) was added dropwise via cannula to the anion solution at –78 ºC. The reaction mixture was stirred at this temperature for 5 min and then was allowed to warm to 23 ºC over 70 min. Aqueous dipotassium hydrogen phosphate buffer solution (pH 7.0, 0.2 M, 10 mL) and dichloromethane (10 mL) were added and the phases were separated. The aqueous phase was extracted with dichloromethane (2 × 10 mL). The organic extracts were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash-column chromatography (25% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes) to provide methyl ester **9** as a yellow solid (14.0 mg, 37%). TLC (30% ethyl acetate–hexanes): R_f = 0.09 (UV, CAM). ^{1}H NMR (500 MHz,

$CDCl_3$), δ: 7.49 (d, 2H, J = 7.8 Hz, Ar**H**), 7.44–7.33 (m, 3H, Ar**H**), 7.20 (s, 1H, =C**H**O), 5.36 (s, 2H, OC**H**$_2$Ph), 5.34 (br-s, 1H, O**H**), 4.92 (ddd, 1H, J = 13.7, 9.8, 3.7 Hz, OC**H**CHN$(CH_3)_2$), 4.80 (d, 1H, J = 9.8 Hz, OCHC**H**N$(CH_3)_2$), 3.86 (s, 3H, OC**H**$_3$), 2.98 (dd, 1H, J = 18.2, 3.3 Hz, OCHC**H**$_2$C=O), 2.74 (dd, 1H, J = 17.8, 13.7 Hz, OCHC**H**$_2$C=O), 2.26 (s, 6H, N(C**H**$_3)_2$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 187.5, 174.2, 168.8, 161.6, 145.0, 136.7, 135.4, 128.6, 128.4, 127.8, 104.3, 72.0, 62.3, 51.9, 42.1, 38.2. FTIR (neat), cm^{-1}: 1717 (m), 1674 (w), 1634 (w), 1613 (m), 1508 (m), 1173 (s), 1113 (s), 733 (s). HRMS (ESI): Calcd for $(C_{20}H_{23}N_2O_6)^+$: 403.1500. Found: 403.1524.



Michael-Claisen cyclization product 11. A solution of sodium bis(trimethylsilyl)amide (15.8 g, 86.4 mmol, 2.10 equiv) in tetrahydrofuran (50.0 mL) was added dropwise by cannula over 25 min to a solution of phenyl 3-benzyloxy-5-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)isoxazole-4-carboxylate (**10**, 36.1 g, 82.2 mmol, 2.00 equiv) in tetrahydrofuran (800 mL) at –78 °C. After stirring for 15 min, the reaction mixture was warmed to –25 °C over the course of 30 min. After stirring for 30 min at –25 ºC, the reaction mixture was cooled to –78 °C. After stirring at –78 ºC for a further 15 min, a solution of enone **6** (7.00 g, 41.1 mmol, 1 equiv) in tetrahydrofuran (25.0 mL) was added dropwise by cannula over the course of 15 min. After stirring for 20 min at –78 ºC, the reaction mixture was allowed to warm to –25 °C over 1.5 h. Stirring was then maintained at –25 ºC (temperature control by periodic addition of dry ice to an acetone cooling bath) for 2 h. Saturated aqueous ammonium chloride solution (800 mL) and saturated aqueous sodium chloride solution (400 mL) were added sequentially. The cooling bath was removed and the reaction mixture was allowed to warm to 23 °C. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 500

mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate–hexanes initially, then grading to 50% ethyl acetate–hexanes) to provide pure Michael-Claisen cyclization product **11** as a yellow foam (19.5 g, 92%). TLC (50% ethyl ether–hexanes): R_f = 0.17 (UV, CAM). ^{1}H NMR (1 : 1 ratio of rotamers, asterisk (*) denotes rotamer peaks, 500 MHz, $CDCl_3$), δ: 13.62 (br-s, 1H, O**H**), 7.54–7.44 (m, 2H, Ar**H**), 7.43–7.31 (m, 3H, Ar**H**), 6.03 (br-s, 1H, C**H**NCH$_3$Boc), 5.86 (d, 1H, *J* = 5.1 Hz, (CH$_3$)$_2$COC**H**O), 5.73* (br-s, 1H, C**H**NCH$_3$Boc), 5.38 (s, 2H, OC**H**$_2$Ph), 5.10 (br-s, 1H, OC**H**CHNCH$_3$Boc), 4.52 (d, 1H, *J* = 5.2 Hz, (CH$_3$)$_2$COC**H**C(O)), 2.58 (br-s, 3H, NC**H**$_3$), 1.49 (s, 9H, C(C**H**$_3$)$_3$), 1.44 (s, 3H, (C**H**$_3$)$_2$C), 1.43 (s, 3H, (C**H**$_3$)$_2$C). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 181.9, 175.4, 174.9*, 167.9, 167.3, 155.6, 155.0*, 134.7, 128.7, 128.6, 128.4, 109.7, 109.5, 106.1, 98.1, 81.3, 80.9*, 72.6, 68.7, 63.4, 63.2*, 49.0, 47.7*, 30.7, 30.2*, 28.2, 27.0, 26.7. FTIR (neat), cm^{-1}: 3532 (br-w), 2980 (m), 2936 (w), 1697 (s), 1651 (s), 1586 (m), 1512 (s), 1454 (m). HRMS (ESI): Calcd for $(C_{26}H_{31}N_2O_9)^+$: 515.2030. Found: 515.2019.

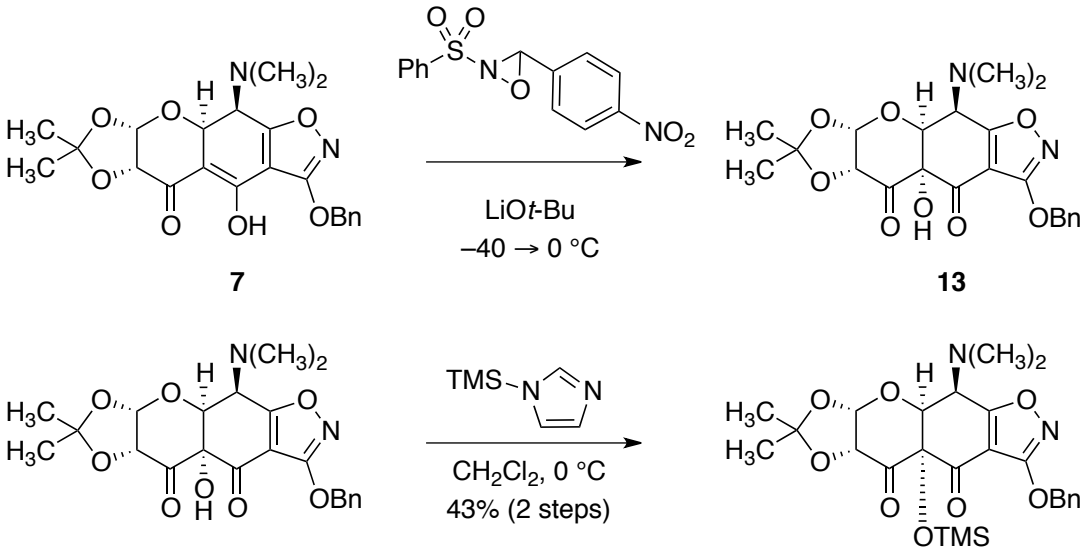


11 **12**

Alcohol 12. A solution of lithium *tert*-butoxide in tetrahydrofuran (0.5 M, 1.54 mL, 0.770 mmol, 0.20 equiv) was added dropwise by syringe to a solution of enol **11** (1.98 g, 3.85 mmol, 1 equiv) and 3-(4-nitrophenyl)-2-(phenylsulfonyl)-oxaziridine[6, 7] (1.53 g, 5.00 mmol, 1.30 equiv) in tetrahydrofuran (77.0 mL) at –40 ºC (cooled using an acetone bath with temperature control by periodic addition of dry ice). The reaction mixture was allowed to warm to 0 ºC over 2 h and then to 23 ºC over 3 h. Ethyl acetate (150 mL) and saturated aqueous ammonium chloride solution (200 mL) were then added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The organic layers were combined. The combined

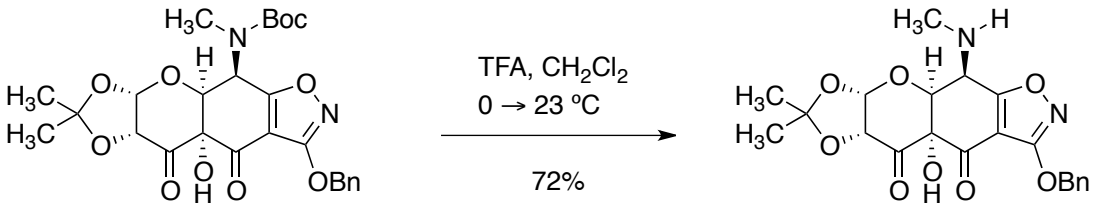
[7] Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Organic Syntheses* **1993**, *Coll. Vol. 8*, 546.

solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate–hexanes initially, then grading to 25% ethyl acetate–hexanes) to provide pure alcohol **12** as a yellow foam (1.70 g, 83%). TLC (30% ethyl acetate–hexanes): R_f = 0.40 (UV, CAM). ^{1}H NMR (3 : 1 ratio of rotamers, asterisk (*) denotes minor rotamer, 500 MHz, $CDCl_3$), δ: 7.50–7.45 (m, 2H), 7.42–7.34 (m, 3H), 6.30 (d, 1H, *J* = 3.4 Hz, C**H**NCH$_3$Boc), 5.99* (br-s, 1H, C**H**NCH$_3$Boc), 5.81 (d, 1H, *J* = 5.2 Hz, (CH$_3$)$_2$COC**H**O)), 5.37 (s, 2H, OC**H**$_2$Ph), 4.69 (d, 1H, *J* = 3.4 Hz, OC**H**CHNCH$_3$Boc), 4.59* (br-s, 1H, (CH$_3$)$_2$COC**H**C(O)), 4.57 (d, 1H, *J* = 5.2 Hz, (CH$_3$)$_2$COC**H**C(O)), 4.48* (br-s, 1H, O**H**), 4.46 (br-s, 1H, O**H**), 2.95* (s, 3H, NC**H**$_3$), 2.93 (s, 3H, NC**H**$_3$), 1.52 (s, 9H, C(C**H**$_3$)$_3$), 1.49* (s, 9H, C(C**H**$_3$)$_3$), 1.45 (s, 3H, (C**H**$_3$)$_2$C), 1.43 (s, 3H, (C**H**$_3$)$_2$C). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 201.7*, 201.4, 185.0, 184.9*, 176.8, 176.2*, 167.9, 155.8, 154.4*, 134.5, 128.5, 128.3, 128.1, 110.1, 105.6, 105.3*, 99.5, 99.4*, 82.9, 82.8*, 81.4*, 81.3, 77.4*, 77.3, 75.2, 72.4, 52.0*, 51.1, 33.7, 33.2*, 28.0, 27.3, 26.8. FTIR (neat), cm^{-1}: 3401 (br-m), 2982 (m), 2936 (m), 2833 (w), 1749 (s), 1697 (s), 1612 (m), 1514 (s), 1481 (s), 1454 (m). HRMS (ESI): Calcd for $(C_{26}H_{31}N_2O_{10})^+$: 531.1979. Found: 531.1970.



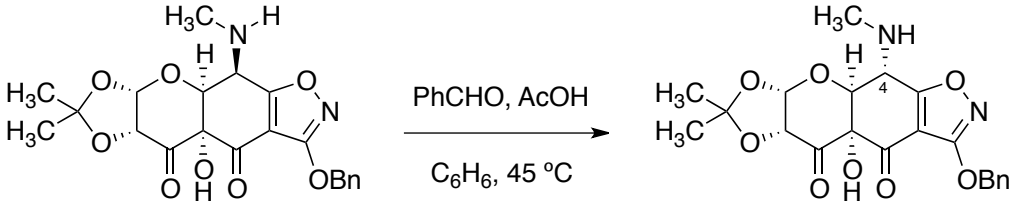
Trimethylsilyl ether 14: Step 1, hydroxylation. A commercial solution of lithium *tert*-butoxide in tetrahydrofuran (1.0 M, 305 μL, 0.305 mmol, 0.30 equiv) was added dropwise via syringe to a solution of Michael–Claisen cyclization product **7** (435 mg, 1.02 mmol, 1 equiv) and 3-(4-nitrophenyl)-2-(phenylsulfonyl)-oxaziridine[6,7] (404 mg, 1.32 mmol, 1.30 equiv) in tetrahydrofuran (6.0 mL) at –40 ºC (cooled using an acetone bath with temperature control by

periodic addition of dry ice). The reaction mixture was allowed to warm to –5 ºC over 30 min. After stirring at –5 ºC for 1 h, saturated aqueous sodium bicarbonate solution (40 mL) was added and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 × 40 mL). The organic extracts were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was partially purified by flash-column chromatography on silica gel (30% ethyl acetate–hexanes) to provide impure alcohol **13** (395 mg). **Step 2, silylation.** The impure hydroxylated product **13** (395 mg, 0.889 mmol, 1 equiv) was dissolved in dichloromethane (5.0 mL) and the resulting solution was cooled to 0 ºC. 1-(Trimethylsilyl)imidazole (652 µL, 4.44 mmol, 5.00 equiv) was added dropwise to the solution of hydroxylated product **13**. After stirring at 0 ºC for 1 h, the reaction mixture was diluted with dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL) was added dropwise over 5 min. The resulting mixture was allowed to warm to 23 ºC whereupon dichloromethane (10 mL) and water (10 mL) were added. The phases were separated and the aqueous phase was extracted with dichloromethane (20 mL). The organic extracts were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash-column chromatography on silica gel (12% ethyl acetate–hexanes initially, grading to 15% ethyl acetate–hexanes), providing trimethylsilyl ether **14** as a pale yellow solid (223 mg, 43% over two steps). TLC (15% ethyl acetate–hexanes): R_f = 0.18 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.46 (d, 2H, *J* = 7.3, Ar**H**), 7.38–7.32 (m, 3H, Ar**H**), 5.74 (d, 1H, *J* = 5.2 Hz, $(CH_3)_2COCHO$), 5.36 (s, 2H, OCH_2Ph), 4.79 (d, 1H, *J* = 3.0 Hz, $OCHCHN(CH_3)_2$), 4.48 (d, 1H, *J* = 5.2 Hz, $(CH_3)_2COCHC(O)$), 4.45 (d, 1H, *J* = 3.0 Hz, $CHN(CH_3)_2$), 2.62 (s, 6H, $N(CH_3)_2$), 1.43 (s, 3H, $(CH_3)_2C$), 1.41 (s, 3H, $(CH_3)_2C$), 0.08 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 200.9, 186.6, 179.4, 168.0, 134.8, 128.5, 128.5, 128.1, 109.9, 105.1, 99.3, 86.3, 77.3, 76.5, 72.4, 59.2, 43.3, 27.4, 26.9, 1.7. FTIR (neat), cm^{-1}: 1753 (m), 1703 (m), 1512 (s), 1157 (s), 1072 (s), 849 (s). HRMS (ESI): Calcd for $(C_{25}H_{33}N_2O_8Si)^+$: 517.2001. Found: 517.2022.



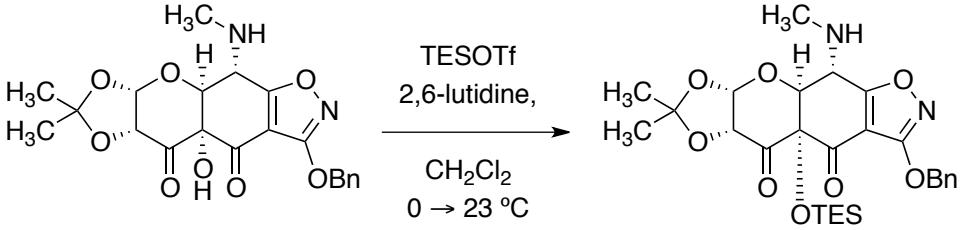
12 **17**

Amino alcohol 17 . Trifluoroacetic acid (20.2 mL, 263 mmol, 20.0 equiv) was added dropwise by syringe to alcohol **12** (6.97 g, 13.1 mmol, 1 equiv) in dichloromethane (263 mL) at 0 ºC. The reaction was allowed to warm gradually to 23 ºC. After stirring for 8 h, the reaction was cooled to 0 ºC and saturated aqueous sodium bicarbonate solution (400 mL) was added. The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 300 mL). The organic extracts were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate–hexanes initially, then grading to 60% ethyl acetate–hexanes) to provide pure amino alcohol **17** as a yellow foam (4.08 g, 72%). TLC (60% ethyl acetate–hexanes): R_f = 0.33 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.51–7.43 (m, 2H, Ar**H**), 7.42–7.31 (m, 3H, Ar**H**), 5.80 (d, 1H, *J* = 5.2 Hz, $(CH_3)_2COC\mathbf{H}O$), 5.36 (s, 2H, $OC\mathbf{H}_2Ph$), 4.68 (d, 1H, *J* = 3.4 Hz, $OC\mathbf{H}CHNHCH_3$), 4.55 (d, 1H, *J* = 5.2 Hz, $(CH_3)_2COC\mathbf{H}C(O)$), 4.45 (d, 1H, *J* = 3.4 Hz, $C\mathbf{H}NHCH_3$), 2.77 (s, 3H, $NC\mathbf{H}_3$), 1.44 (s, 3H, $(C\mathbf{H}_3)_2C$), 1.43 (s, 3H, $(C\mathbf{H}_3)_2C$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 202.4, 185.3, 180.5, 167.8, 134.7, 128.5, 128.4, 128.2, 110.2, 104.4, 99.6, 82.6, 75.3, 73.9, 72.4, 54.5, 34.3, 27.3, 26.8. FTIR (neat), cm^{-1}: 3345 (br-w), 2988 (m), 2940 (m), 2814 (w), 1746 (s), 1703 (s), 1604 (s), 1512 (s), 1483 (s). HRMS (ESI): Calcd for $(C_{21}H_{23}N_2O_8)^+$: 431.1454. Found: 431.1480.



Amino alcohol 18 . Benzaldehyde (8.81 mL, 86.9 mmol, 10.0 equiv) was added dropwise by syringe to amino alcohol **17** (3.74 g, 8.69 mmol, 1 equiv) in benzene (174 mL) at 23 ºC. Acetic acid (9.95 mL, 174 mmol, 20.0 equiv) was then added dropwise by syringe. The reaction mixture was then heated to 45 ºC. After stirring for 9 h at 45 ºC, the reaction was concentrated to give a brown oil. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate–hexanes initially, then grading to 60% ethyl acetate–hexanes) to provide epimer **18** (20:1 mixture of C4 epimers) as a yellow foam (1.77 g, 47%). TLC (60% ethyl acetate–hexanes): R_f = 0.40 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.51–7.45 (m, 2H, Ar**H**), 7.42–7.33 (m, 3H,

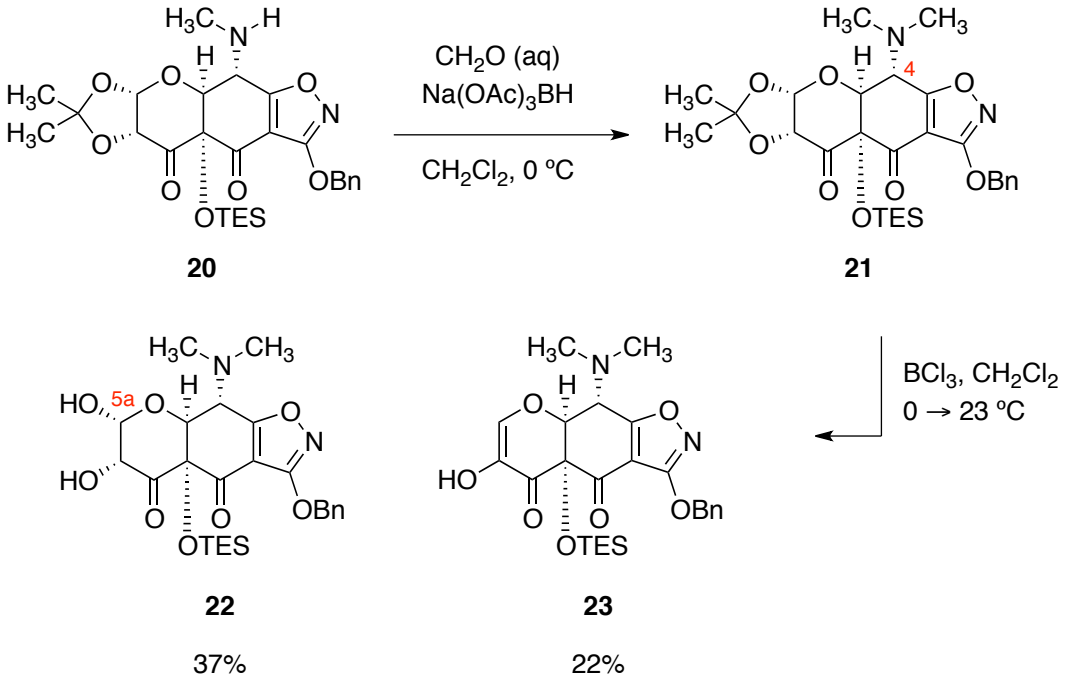
Ar**H**), 5.73 (d, *J* = 5.3 Hz, 1H, $(CH_3)_2COCHO$), 5.38 (s, 2H, OCH_2Ph), 4.67 (d, 1H, *J* = 2.1 Hz, $OCHCHNHCH_3$), 4.51 (d, 1H, *J* = 5.2 Hz, $(CH_3)_2COCHC(O)$), 4.05 (d, 1H, *J* = 2.0 Hz, $CHNHCH_3$), 2.69 (s, 3H, NCH_3), 1.44 (s, 3H, $(CH_3)_2C$), 1.43 (s, 3H, $(CH_3)_2C$). ^{13}C NMR (125 MHz, $CDCl_3$), δ:202.6, 185.2, 180.6, 167.9, 134.7, 128.7, 128.5, 128.3, 110.3, 103.9, 99.5, 81.6, 75.1, 74.7, 72.6, 56.3, 35.1, 27.5, 26.9. FTIR (neat), cm^{-1}: 3433 (w), 3335 (w), 1748 (s), 1699 (s), 1607 (s), 1512 (s). HRMS (ESI): Calcd for $(C_{21}H_{23}N_2O_8)^+$: 431.1454. Found: 431.1466.



18 **20**

73%

Silyl ether 20. Triethylsilyl trifluoromethanesulfonate (1.70 mL, 8.01 mmol, 2.00 equiv) was added to a solution of epimer **18** (1.72 g, 4.00 mmol, 1 equiv) and 2,6-lutidine (1.87 mL, 16.0 mmol, 4.00 equiv) in dichloromethane (40.0 mL) at 0 ºC. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After stirring for 2 h at 23 ºC, aqueous dipotassium hydrogen phosphate buffer solution (pH 7.0, 1 M, 200 mL) was added. The layers were separated and the aqueous phase was extracted with dichloromethane (1 × 200 mL) and ethyl acetate (2 × 200 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate–hexanes initially, then grading to 20% ethyl acetate–hexanes) to provide pure triethylsilyl ether **20** as a yellow foam (1.59 g, 73%). TLC (20% ethyl acetate–hexanes): R_f = 0.29 (UV, CAM). ^1H NMR (500 MHz, $CDCl_3$), δ: 7.49–7.45 (m, 2H, Ar**H**), 7.41–7.32 (m, 3H, Ar**H**), 5.67 (d, *J* = 5.2 Hz, 1H, $(CH_3)_2COCHO$), 5.39 (s, 2H, OCH_2Ph), 4.60 (d, 1H, *J* = 1.9 Hz, $OCHCHNHCH_3$), 4.46 (d, 1H, *J* = 5.2 Hz, $(CH_3)_2COCHC(O)$), 3.94 (app-s, 1H, $CHNHCH_3$), 2.66 (s, 3H, NCH_3), 1.43 (s, 3H, $(CH_3)_2C$), 1.42 (s, 3H, $(CH_3)_2C$), 0.86–0.77 (m, 9H, $SiCH_2CH_3$), 0.76–0.61 (m, 3H, $SiCH_2CH_3$), 0.57 (m, 3H, $SiCH_2CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 201.8, 186.1, 180.5, 167.8, 134.8, 128.5, 128.4, 128.0, 109.9, 103.6, 99.2, 84.9, 76.2, 75.5, 72.4, 56.8, 34.8, 27.4, 26.8, 6.6, 5.9. FTIR (neat), cm^{-1}: 3368 (m), 2953 (m), 2878 (m), 2810 (w), 1753 (s), 1701 (s), 1607 (m), 1512 (s), 1476 (m), 1454 (m). HRMS (ESI): Calcd for $(C_{27}H_{37}N_2O_8Si)^+$: 545.2319. Found: 545.2351.

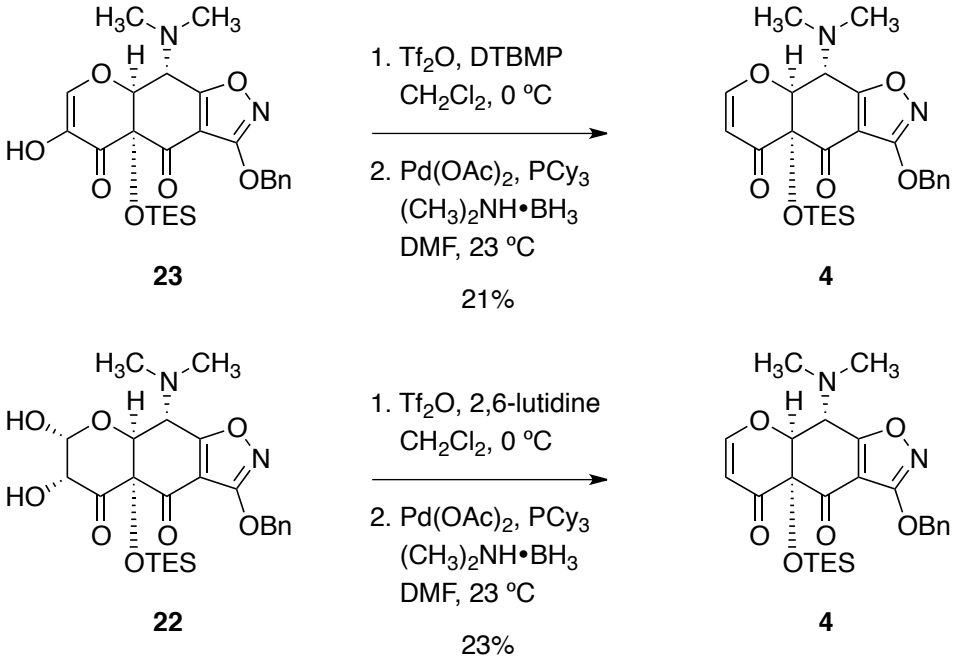


Enol 23 and diol 22: **Step 1, Reductive Amination.** To a solution of amine **20** (719 mg, 1.32 mmol, 1 equiv) in dichloromethane (33.0 mL) cooled at 0 ºC was added sodium triacetoxyborohydride (2.24 g, 10.6 mmol, 10.0 equiv) in one portion. After stirring for 1 min, aqueous formaldehyde (37% w/w, 393 µL, 1.32 mmol, 4.00 equiv) was added. After stirring for 30 min at 0 ºC, a second portion of sodium triacetoxyborohydride (560 mg, 2.64 mmol, 2.00 equiv) was added. After an additional 30 min of stirring at 0 ºC, saturated aqueous sodium bicarbonate solution (15 mL) was added. The reaction mixture was poured into water (15 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with saturated sodium chloride solution (3 × 50 mL) and dried over sodium sulfate. The dried solution was filtered. The filtrate was concentrated to provide crude amine **21** as a pale yellow oil as an inseparable 15:1 mixture of C4-epimers, which was used in the next step without further purification. For characterization purposes, a small amount of amine **21** was purified by preparative HPLC on a Waters SunFire Prep C18 column [5 µm, 250 × 19 mm, UV detection at 350 nm, solvent A: water, solvent B: acetonitrile, injection volume: 3.5 mL (2.8 mL water, 0.7 mL acetonitrile), gradient elution with 80→100% B over 40 min, flow rate: 15 mL/min]. Fractions eluting at 21–23 min were collected and concentrated, affording amine **21** as a clear oil. TLC (20% ethyl acetate–hexanes): R_f = 0.36 (UV, CAM). ^{1}H NMR (600 MHz, $CDCl_3$), δ: 7.49–7.44 (m, 2H, Ar**H**), 7.40–7.32 (m, 3H, Ar**H**), 5.67 (d, 1H, *J* =

5.2 Hz, $(CH_3)_2COCHO$), 5.39 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 5.37 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.58 (s, 1H, $OCHCHN(CH_3)_2$), 4.49 (d, 1H, *J* = 5.2 Hz, $(CH_3)_2COCHC(O)$), 4.11 (d, 1H, *J* = 1.0 Hz, $CHN(CH_3)_2$), 2.49 (s, 6H, $N(CH_3)_2$), 1.46 (s, 3H, $(CH_3)_2C$), 1.43 (s, 3H, $(CH_3)_2C$), 0.84–0.74 (m, 9H, $SiCH_2CH_3$), 0.72–0.61 (m, 3H, $SiCH_2CH_3$), 0.60–0.49 (m, 3H, $SiCH_2CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 202.5, 186.6, 178.9, 168.0, 134.9, 128.6, 128.5, 128.2, 110.0, 106.1, 99.1, 84.3, 76.6, 75.1, 72.4, 64.3, 43.5, 27.5, 27.0, 6.8, 6.0. FTIR (neat), cm^{-1}: 2953 (m), 2876 (m), 2793 (m), 2102 (w), 1751 (s), 1705 (s), 1609 (s), 1512 (s), 1473 (s), 1456 (s). HRMS (ESI): Calcd for $(C_{28}H_{39}N_2O_8Si)^+$: 559.2476. Found: 559.2483.

Step 2, Acetonide Cleavage. A solution of boron trichloride in dichloromethane (1.0 M, 3.84 mL, 3.84 mmol, 1.50 equiv) was added dropwise by syringe to a solution of crude amine **21** (1.43 g, 2.56 mmol, 1 equiv) in dichloromethane (51.2 mL) at 0 ºC. The cooling bath was removed and the reaction mixture was allowed to warm to 23 ºC. After 30 min, saturated sodium bicarbonate solution (100 mL) was added. The biphasic mixture was partitioned and the aqueous phase was extracted with dichloromethane (3 × 100 mL). The organic extracts were combined and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude reaction mixture was purified by flash-column chromatography on silica gel (5% acetone–hexanes initially, then grading to 30% acetone–hexanes) to provide pure enol **23** as a yellow foam (288 mg, 22%) and diol **22** as a yellow foam, which consists of a 5 : 1 inconsequential mixture of C5a anomers (479 mg, 37%). Enol **23**: TLC (30% acetone–hexanes): R_f = 0.38 (UV, CAM). ^1H NMR (600 MHz, $CDCl_3$), δ: 7.53–7.46 (m, 2H, Ar**H**), 7.41–7.33 (m, 3H, Ar**H**), 7.28 (s, 1H, =C**H**O), 5.35 (s, 2H, OCH_2Ph), 4.81 (d, 1H, *J* = 8.2 Hz, $OCHCHNCH_3CH_2Ph$), 4.79 (br-s, 1H, O**H**), 4.48 (d, 1H, *J* = 8.2 Hz, $CHNCH_3CH_2Ph$), 2.53 (s, 6H, NCH_3), 0.90 (t, 9H, *J* = 7.9 Hz, $SiCH_2CH_3$), 0.78–0.57 (m, 6H, $SiCH_2CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 182.5, 182.1, 178.1, 167.4, 142.9, 135.6, 134.7, 128.7, 128.6, 128.5, 108.6, 83.5, 80.9, 72.8, 59.8, 42.0, 6.9, 6.1. FTIR (neat), cm^{-1}: 3422 (br-m), 2955 (m), 2913 (m), 2876 (m), 2801 (w), 1721 (s), 1674 (m), 1628 (s), 1547 (m), 1514 (s), 1476 (m). HRMS (ESI): Calcd for $(C_{25}H_{33}N_2O_7Si)^+$: 501.2057. Found: 501.2092. Diol **22**: TLC (30% acetone–hexanes): R_f = 0.26 (UV, CAM). ^1H NMR (5 : 1 ratio of C5a anomers, asterisk (*) denotes minor anomer, 500 MHz, $CDCl_3$), δ: 7.51–7.42 (m, 2H, Ar**H**), 7.42–7.31 (m, 3H, Ar**H**), 5.48 (d, 1H, *J* = 4.5 Hz, HOC**H**O), 5.39 (s, 2H, OCH_2Ph), 4.65* (d, 1H, *J* = 7.9 Hz, HOC**H**O), 4.63 (s, 1H, $OCHCHN(CH_3)_2$), 4.37 (d, 1H, *J* = 4.4 Hz, HOC**H**C(O)), 4.19* (s, 1H, $OCHCHN(CH_3)_2$), 4.16*

(d, 1H, J = 7.8 Hz, HOC**H**C(O)), 4.12 (s, 1H, C**H**N(CH_3)$_2$), 3.97* (d, 1H, J = 0.9 Hz, C**H**N(CH_3)$_2$), 2.49 (s, 6H, N(C**H**$_3$)$_2$), 0.80 (t, 9H, J = 7.8 Hz, SiCH$_2$C**H**$_3$), 0.74–0.61 (m, 3H, SiC**H**$_2$CH$_3$), 0.61–0.48 (m, 3H, SiC**H**$_2$CH$_3$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 203.1, 186.2, 178.5, 168.0, 134.8, 128.6, 128.6, 128.2, 106.5, 94.6, 84.0, 75.3, 75.1, 72.5, 63.9, 43.2, 6.7, 5.9. FTIR (neat), cm^{-1}: 3449 (br-m), 2955 (s), 2876 (s), 2803 (w), 2100 (m), 1749 (s), 1703 (s), 1616 (s), 1514 (s), 1476 (s), 1371 (s). HRMS (ESI): Calcd for $(C_{25}H_{35}N_2O_8Si)^+$: 519.2163. Found: 519.2118.



Enone 4 from enol 23: **Step 1, Triflation.** Trifluoromethanesulfonic anhydride (18.4 µL, 0.109 mmol, 2.00 equiv) was added dropwise by syringe to a solution of enol **23** (27.3 mg, 54.5 µmol, 1 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (44.8 mg, 0.218 mmol, 4.00 equiv) in dichloromethane (500 µL) at 0 ºC. After 5 min, the reaction was concentrated to provide the crude vinyl triflate (**24**, not shown) as a light brown oil.

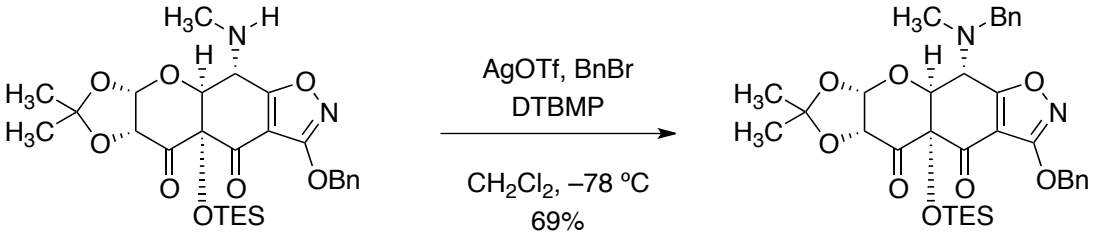
Step 2, Reduction. To a flask charged with tricyclohexylphosphine (12.2 mg, 43.5 µmol, 0.80 equiv) was added a solution of the crude vinyl triflate (**24**, not shown) from step 1 in dimethylformamide (5.40 mL) via cannula. Palladium(II) acetate (4.9 mg, 21.8 µmol, 0.40 equiv), and borane dimethylamine complex (16.1 mg, 0.273 mmol, 5.00 equiv) were then added. The resulting dark orange solution was stirred at 23 ºC for 5 min, at which point another portion of palladium(II) acetate (4.9 mg, 21.8 µmol, 0.40 equiv) was added. Immediately the solution

turned black. After 10 min, TLC indicated complete consumption of the starting material. The reaction mixture was cooled to 0 ºC and saturated aqueous sodium chloride solution (5 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl ether (3 × 20 mL). The combined organic extracts were washed with water (3 × 30 mL) and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes) to provide pure enone **4** (5.5 mg, 21%) as a brown foam.

Enone 2 from diol 22: **Step 1, Triflation.** Trifluoromethanesulfonic anhydride (114 µL, 0.675 mmol, 3.50 equiv) was added dropwise by syringe to a solution of diol **22** (100 mg, 0.193 mmol, 1 equiv) and 2,6-lutidine (112 µL, 0.964 mmol, 5.00 equiv) in dichloromethane (1.00 mL) at 0 ºC. After stirring for 5 min, the reaction was concentrated to provide the crude vinyl triflate (**24**, not shown) as a light brown oil.

Step 2, Reduction. To a flask charged with tricyclohexylphosphine (43.3 mg, 0.154 mmol, 0.80 equiv) was added a solution of the crude vinyl triflate (**24**, not shown) from step 1 in dimethylformamide (19.3 mL) via cannula. Palladium(II) acetate (17.3 mg, 77.2 µmol, 0.40 equiv), and borane dimethylamine complex (56.8 mg, 0.964 mmol, 5.00 equiv) were then added. The resulting dark orange solution was stirred at 23 ºC for 5 min, at which point another portion of palladium(II) acetate (17.3 mg, 77.2 µmol, 0.40 equiv) was added. Immediately the solution turned black. After 10 min, TLC indicated complete consumption of the starting material. The reaction mixture was cooled to 0 ºC and saturated aqueous sodium chloride solution (10 mL) was added. The layers were separated and the aqueous phase was extracted with ethyl ether (3 × 40 mL). The combined organic extracts were washed with water (3 × 50 mL) and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes) to provide pure enone **4** (21.5 mg, 23%) as a brown foam. TLC (30% ethyl acetate–hexanes): R_f = 0.20 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.51–7.46 (m, 2H, Ar**H**), 7.43–7.32 (m, 3H, Ar**H**), 7.30 (d, 1H, *J* = 6.2 Hz, =C**H**O), 5.58 (d, 1H, *J* = 6.2 Hz, =C**H**C(O)), 5.35 (s, 2H, OC**H**$_2$Ph), 4.92 (d, 1H, *J* = 8.7 Hz, OC**H**CHN(CH$_3$)$_2$), 4.41 (d, 1H, *J* = 8.7 Hz, C**H**N(CH$_3$)$_2$), 2.55 (s, 6H, N(C**H**$_3$)$_2$), 0.86 (t, 9H, *J* = 7.9 Hz, SiCH$_2$C**H**$_3$), 0.78–0.59 (m, 6H, SiC**H**$_2$CH$_3$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 186.4, 183.7, 177.6, 167.4, 159.8, 134.7, 128.6, 128.5, 108.6, 106.3, 83.4, 81.1, 72.7, 59.7, 41.9, 7.0, 6.2. FTIR (neat), cm^{-1}: 3067

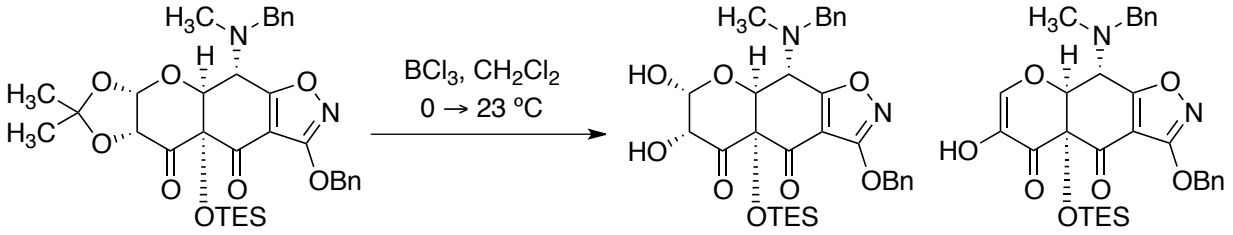
(w), 3036 (w), 2932 (s), 2876 (m), 2853 (m), 2799 (w), 1721 (s), 1678 (s), 1607 (s), 1599 (s), 1678 (m), 1514 (s), 1454 (s). HRMS (ESI): Calcd for $(C_{25}H_{33}N_2O_6Si)^+$: 485.2108. Found: 485.2160.



20 **S6**

Benzylamine S6. To a solution of amine **20** (557.2 mg, 1.02 mmol, 1 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (1.26 g, 6.14 mmol, 6.00 equiv) in dichloromethane (14.6 mL) at –78 ºC was added silver(I) trifluoromethanesulfonate (789 mg, 3.07 mmol, 3.00 equiv) in one portion. Benzyl bromide (377 µL, 3.17 mmol, 3.10 equiv) was then added dropwise by syringe. After stirring for 1 h, another portion of silver(I) trifluoromethanesulfonate (263 mg, 1.02 mmol, 1.00 equiv) and benzyl bromide (134 µL, 1.13 mmol, 1.10 equiv) were added sequentially. After stirring for a further hour, saturated aqueous ammonium chloride solution (50 mL) was added. The cooling bath was removed and the reaction mixture was allowed to warm to 23 ºC. The phases were partitioned and the organic layer was filtered through a pad of celite. The filtrate was washed with half-saturated aqueous ammonium chloride solution (1 × 100 mL). The aqueous layer was back-extracted with dichloromethane (2 × 100 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate–hexanes initially, then grading to 15% ethyl acetate–hexanes) to provide pure amine **S6** as a pale yellow foam (447 mg, 69%). TLC (20% ethyl acetate–hexanes): R_f = 0.5 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.50–7.43 (m, 2H, Ar**H**), 7.42–7.30 (m, 7H, Ar**H**), 7.30–7.22 (m, 1H, Ar**H**), 5.66 (d, 1H, *J* = 5.1 Hz, $(CH_3)_2COC\mathbf{H}O$), 5.38 (app-d, 2H, *J* = 2.3 Hz, $OC\mathbf{H}_2Ph$), 4.63 (d, 1H, *J* = 0.8 Hz, $OC\mathbf{H}CHNCH_3CH_2Ph$), 4.50 (d, 1H, *J* = 5.1 Hz, $(CH_3)_2COC\mathbf{H}C(O)$), 4.35 (d, 1H, *J* = 0.9 Hz, $C\mathbf{H}NCH_3CH_2Ph$), 3.86 (d, 1H, *J* = 13.5 Hz, $NC\mathbf{H}_2Ph$), 3.77 (d, 1H, *J* = 13.5 Hz, $NC\mathbf{H}_2Ph$), 2.41 (s, 3H, $NC\mathbf{H}_3$), 1.48 (s, 3H, $(C\mathbf{H}_3)_2C$), 1.44 (s, 3H, $(C\mathbf{H}_3)_2C$), 0.77 (t, *J* = 7.8 Hz, 9H, $SiCH_2C\mathbf{H}_3$), 0.71–0.59 (m, 3H, $SiC\mathbf{H}_2CH_3$), 0.52 (dq, *J* = 14.9, 7.8 Hz, 3H, $SiC\mathbf{H}_2CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 202.5, 186.4, 178.9, 167.9,

138.2, 134.8, 128.5, 128.4, 128.4, 128.3, 128.0, 127.3, 109.9, 106.2, 98.9, 84.2, 76.4, 75.3, 72.3, 63.2, 59.6, 39.6, 27.4, 26.9, 6.6, 5.8. FTIR (neat), cm^{-1}: 2955 (m), 2936 (m), 2876 (m), 2808 (w), 1751 (s), 1703 (s), 1609 (m), 1512 (s), 1478 (m), 1454 (m). HRMS (ESI): Calcd for $(C_{34}H_{43}N_2O_8Si)^+$: 635.2789. Found: 635.2805.

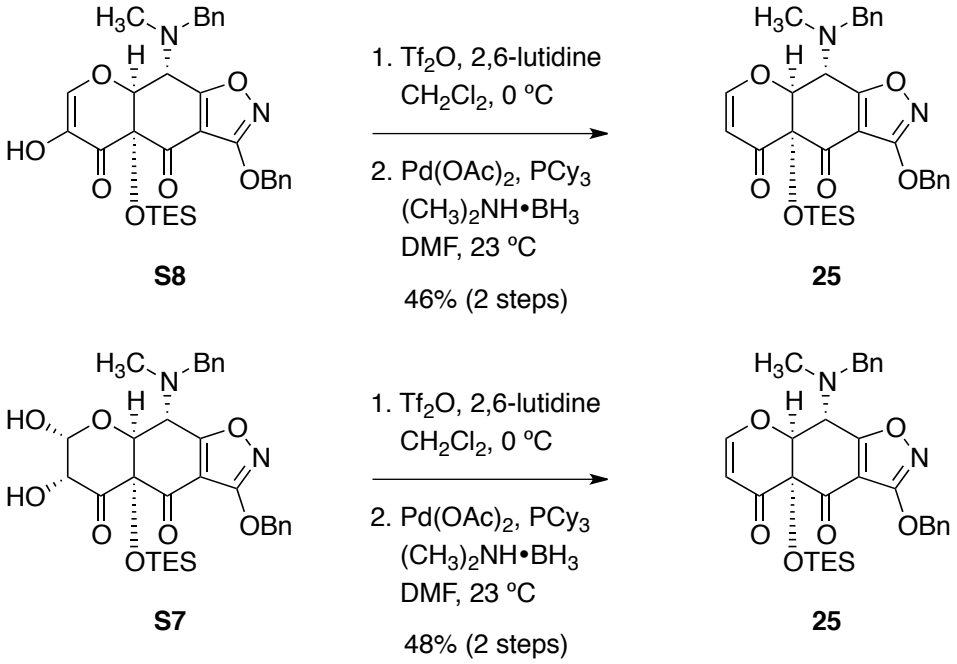


S6 **S7** **S8**

51% 14%

Enol S7 and diol S8. A solution of boron trichloride in dichloromethane (1.0 M, 1.06 mL, 1.06 mmol, 1.50 equiv) was added dropwise by syringe to a solution of amine (**S6**, 447 mg, 0.704 mmol, 1 equiv) in dichloromethane (14.1 mL) at 0 ºC. The cooling bath was removed and the reaction mixture was allowed to warm to 23 ºC. After 20 min, saturated sodium bicarbonate solution (50 mL) was added. The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% acetone–hexanes initially, then grading to 30% acetone–hexanes) to provide pure enol **S8** as a yellow foam (56.1 mg, 14%) and pure diol **S7** as a yellow foam (213 mg, 51%). Enol **S8**: TLC (30% acetone–hexanes): R_f = 0.44 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.52–7.47 (m, 2H, Ar**H**), 7.43–7.32 (m, 7H, Ar**H**), 7.32–7.27 (m, 1H, Ar**H**), 7.04 (s, 1H, =C**H**O), 5.36 (s, 2H, OC**H**$_2$Ph), 4.84 (d, 1H, *J* = 8.4 Hz, OC**H**CHNCH$_3$CH$_2$Ph), 4.61 (br-s, 1H, O**H**), 4.53 (d, 1H, *J* = 8.3 Hz, C**H**NCH$_3$CH$_2$Ph), 3.95 (d, 1H, *J* = 13.3 Hz, NC**H**$_2$Ph), 3.89 (d, 1H, *J* = 13.3 Hz, NC**H**$_2$Ph), 2.44 (s, 3H, NC**H**$_3$), 0.89 (t, *J* = 7.9 Hz, 9H, SiCH$_2$C**H**$_3$), 0.73–0.66 (m, 3H, SiC**H**$_2$CH$_3$), 0.66–0.57 (m, 3H, SiC**H**$_2$CH$_3$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 182.5, 181.9, 178.7, 167.4, 142.9, 137.6, 135.4, 134.7, 128.8, 128.7, 128.6, 128.6, 128.5, 127.8, 108.6, 84.0, 81.0, 72.7, 59.7, 56.7, 38.0, 6.9, 6.1. FTIR (neat), cm^{-1}: 3601 (br-m), 2955 (m), 2876 (m), 1721 (s), 1672 (m), 1628 (s), 1514 (s), 1474 (m), 1456 (m). HRMS (ESI): Calcd for $(C_{31}H_{37}N_2O_7Si)^+$: 577.2370. Found: 577.2382. Diol **S7**: TLC (30% acetone–hexanes): R_f = 0.33 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$), δ:

7.48–7.44 (m, 2H, Ar**H**), 7.41–7.30 (m, 7H, Ar**H**), 7.30–7.26 (m, 1H, Ar**H**), 5.46 (d, 1H, *J* = 4.5 Hz, HOC**H**O), 5.39 (s, 2H, OC**H**$_2$Ph), 4.66 (s, 1H, OC**H**CHNCH$_3$CH$_2$Ph), 4.37 (d, 1H, *J* = 4.5 Hz, HOC**H**C(O)), 4.31 (s, 1H, C**H**NCH$_3$CH$_2$Ph), 3.87 (d, 1H, *J* = 13.4 Hz, NC**H**$_2$Ph), 3.74 (d, 1H, *J* = 13.4 Hz, NC**H**$_2$Ph), 3.46 (br-s, 1H, O**H**), 3.23 (br-s, 1H, O**H**), 2.41 (s, 3H, NC**H**$_3$), 0.86–0.73 (m, 9H, SiCH$_2$C**H**$_3$), 0.72–0.59 (m, 3H, SiC**H**$_2$CH$_3$), 0.60–0.44 (m, 3H, SiC**H**$_2$CH$_3$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 203.4, 186.4, 179.4, 168.0, 138.2, 134.9, 128.8, 128.6, 128.5, 128.4, 128.2, 127.4, 106.3, 94.4, 84.1, 75.5, 75.1, 72.5, 62.7, 59.5, 39.6, 6.7, 5.9. FTIR (neat), cm^{-1}: 3435 (br-m), 3065 (w), 3034 (w), 2955 (m), 2911 (w), 2876 (m), 2808 (w), 1748 (s), 1703 (s), 1613 (m), 1514 (s), 1479 (m), 1454 (s). HRMS (ESI): Calcd for $(C_{31}H_{39}N_2O_8Si)^+$: 595.2476. Found: 595.2489.



Enone 25 from enol S8: **Step 1, Triflation.** Trifluoromethanesulfonic anhydride (31.3 µL, 0.185 mmol, 3.50 equiv) was added dropwise by syringe to a solution of enol **S8** (30.5 mg, 52.9 µmol, 1 equiv) and 2,6-lutidine (30.8 µL, 0.264 mmol, 5.00 equiv) in dichloromethane (500 µL) at 0 ºC. After stirring for 5 min, the reaction was concentrated to provide the crude vinyl triflate (not shown) as a light brown oil.

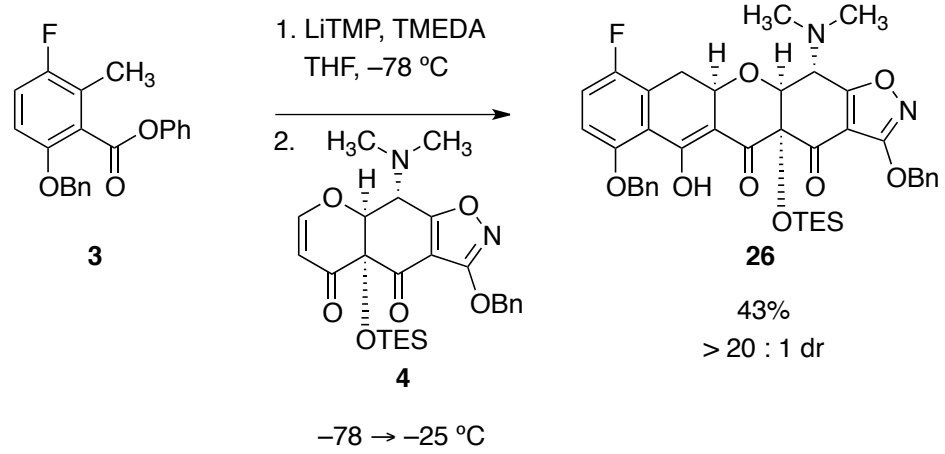
Step 2, Reduction. To a flask charged with tricyclohexylphosphine (11.9 mg, 42.4 µmol, 0.80 equiv) was added a solution of the crude vinyl triflate (not shown) from step 1 in dimethylformamide (5.30 mL) via cannula. Palladium(II) acetate (4.8 mg, 21.4 µmol, 0.40 equiv), and borane dimethylamine complex (15.6 mg, 0.265 mmol, 5.00 equiv) were then added.

The resulting dark orange solution was stirred at 23 ºC for 5 min, at which point another portion of palladium(II) acetate (4.8 mg, 21.4 μmol, 0.4 equiv) was added. Immediately the solution turned black. After 10 min, TLC indicated complete consumption of the starting material. The reaction mixture was cooled to 0 ºC and saturated aqueous sodium chloride solution (5 mL) was added. The layers were separated and the aqueous phase was extracted with ethyl ether (3 × 20 mL). The combined organic extracts were washed with water (3 × 30 mL) and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (100% hexanes initially, grading to 10% ethyl acetate–hexanes) to provide pure enone **25** (13.5 mg, 46%) as a brown foam.

Enone 25 from diol S7: **Step 1, Triflation.** Trifluoromethanesulfonic anhydride (99.0 μL, 0.587 mmol, 3.50 equiv) was added dropwise by syringe to a solution of diol **S7** (99.7 mg, 0.168 mmol, 1.0 equiv) and 2,6-lutidine (98.0 μL, 0.838 mmol, 5.00 equiv) in dichloromethane (1.00 mL) at 0 ºC. After 5 min, the reaction was concentrated to provide the crude vinyl triflate (not shown) as a light brown oil.

Step 2, Reduction. To a flask charged with tricyclohexylphosphine (37.7 mg, 0.134 mmol, 0.8 equiv) was added a solution of the crude vinyl triflate (not shown) from step 1 in dimethylformamide (16.8 mL) via cannula. Palladium(II) acetate (15.1 mg, 67.3 μmol, 0.40 equiv), and borane dimethylamine complex (49.5 mg, 0.839 mmol, 5.00 equiv) were then added. The resulting dark orange solution was stirred at 23 ºC for 5 min, at which point another portion of palladium(II) acetate (15.1 mg, 67.3 μmol, 0.40 equiv) was added. Immediately the solution turned black. After 10 min, TLC indicated complete consumption of the starting material. The reaction mixture was cooled to 0 ºC and saturated aqueous sodium chloride solution (10 mL) was added. The phases were separated and the aqueous layer was extracted with ethyl ether (3 × 40 mL). The combined organic layers were washed with water (3 × 50 mL) and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (100% hexanes initially, grading to 10% ethyl acetate–hexanes) to provide pure enone **25** (45.0 mg, 48%) as a brown foam. TLC (15% ethyl acetate–hexanes): R_f = 0.31 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.52–7.47 (m, 2H, Ar**H**), 7.44–7.31 (m, 7H, Ar**H**), 7.32–7.27 (m, 1H, Ar**H**), 7.05 (d, 1H, *J* = 6.1 Hz, =C**H**O), 5.36 (s, 2H, OC**H**$_2$Ph), 5.36 (d, 1H, *J* = 6.0 Hz, =C**H**C(O)), 4.97 (d, 1H, *J* = 8.5 Hz, OC**H**CHNCH$_3$CH$_2$Ph), 4.47 (d, 1H, *J* = 8.6 Hz, C**H**NCH$_3$CH$_2$Ph), 4.01 (d, 1H, *J* = 13.3 Hz,

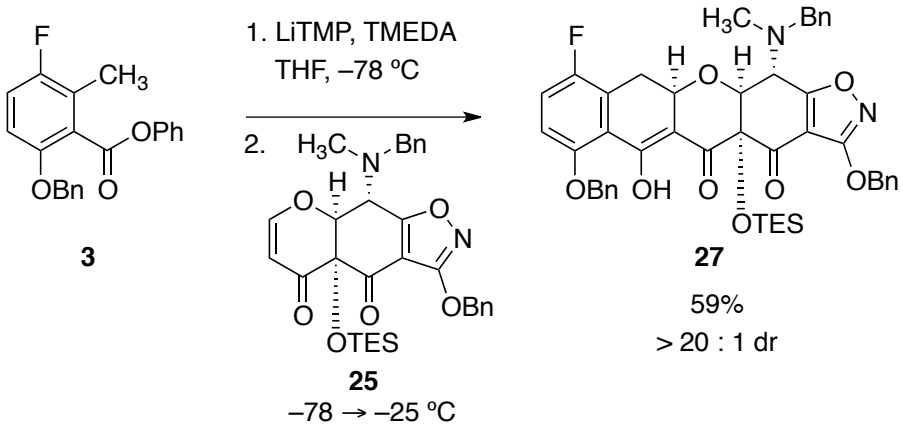
NC**H**$_2$Ph), 3.94 (d, 1H, J = 13.3 Hz, NC**H**$_2$Ph), 2.49 (s, 3H, NC**H**$_3$), 0.89 (t, 9H, J = 7.9 Hz, SiCH$_2$C**H**$_3$), 0.75–0.66 (m, 3H, SiC**H**$_2$CH$_3$), 0.66–0.58 (m, 3H, SiC**H**$_2$CH$_3$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 186.3, 183.8, 178.1, 167.4, 159.8, 137.6, 134.7, 128.9, 128.6, 128.6, 128.5, 128.5, 127.7, 108.7, 106.0, 83.8, 81.3, 72.7, 59.8, 56.3, 37.9, 7.0, 6.2. FTIR (neat), cm^{-1}: 3063 (w), 3034 (w), 2951 (m), 2926 (s), 2874 (m), 2853 (m), 1722 (s), 1678 (s), 1611 (s), 1599 (s), 1477 (s), 1454 (s). HRMS (ESI): Calcd for $(C_{31}H_{37}N_2O_6Si)^+$: 561.2421. Found: 561.2390.



Preparation of 0.48 M LiTMP solution in THF: A solution of *n*-butyllithium in hexanes (2.51 M, 400 µL, 1.00 mmol, 1 equiv) was added dropwise via syringe to a solution of 2,2,6,6-tetramethylpiperidine (188 µL, 1.10 mmol, 1.10 equiv) and triethylamine hydrochloride (1.40 mg, 10.2 µmol, 0.010 equiv) in tetrahydrofuran (1.50 mL) at –78 ºC. After stirring for 15 min, the resultant solution of lithium 2,2,6,6-tetramethylpiperidide was warmed to 0 ºC.

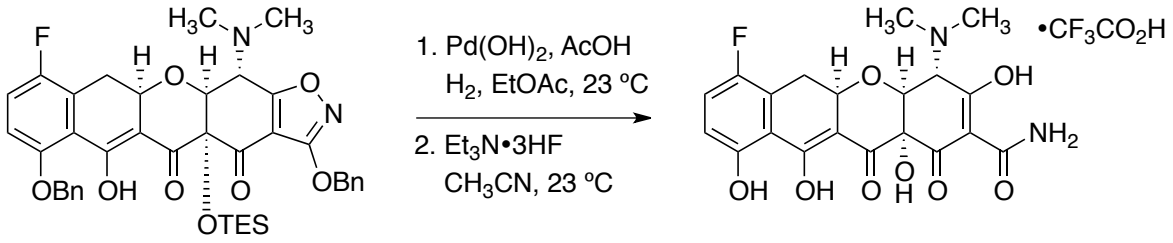
Cyclization product 26: A solution of lithium 2,2,6,6-tetramethylpiperidide in tetrahydrofuran (0.48 M, 130 µL, 0.062 mmol, 2.40 equiv) was added dropwise via syringe to a solution of *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (27.5 µL, 0.182 mmol, 7.00 equiv) and phenyl 6-(benzyloxy)-3-fluoro-2-methylbenzoate **3** (15.3 mg, 0.045 mmol, 2.10 equiv) in tetrahydrofuran (800 µL) at –78 ºC. The resulting deep-red mixture was stirred vigorously at –78 °C for 20 min. Then a solution of enone **4** (10.5 mg, 0.022 mmol, 1 equiv) in tetrahydrofuran (200 µL) was added dropwise via cannula. The resulting light-orange mixture was allowed to warm to –20 °C over 1.5 h. Saturated ammonium chloride solution (1 mL) and 1.0 M aqueous hydrochloric acid solution (0.5 mL) were then added. The cooling bath was removed and the reaction mixture was allowed to warm to 23 ºC. The biphasic mixture poured into water (5 mL) and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over

sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate–hexanes initially, grading to 25% ethyl acetate–hexanes) to provide pure cyclization product **26** (6.8 mg, 43%) as a light yellow foam. TLC (30% ethyl acetate–hexanes): R_f = 0.48 (UV, CAM). ^{1}H NMR (600 MHz, $CDCl_3$), δ: 15.73 (s, 1H, O**H**), 7.54–7.45 (m, 4H, Ar**H**), 7.44–7.35 (m, 4H, Ar**H**), 7.36–7.30 (m, 2H, Ar**H**), 7.13 (dd, 1H, *J* = 9.2, 8.1 Hz, FCC**H**), 6.88 (dd, 1H, *J* = 9.2, 4.4 Hz, FCCHC**H**), 5.41 (d, 1H, *J* = 12.1 Hz, OC**H**$_2$Ph), 5.37 (d, 1H, *J* = 12.1 Hz, OC**H**$_2$Ph), 5.24 (d, 1H, *J* = 12.2 Hz, OC**H**$_2$Ph), 5.16 (d, 1H, *J* = 12.3 Hz, OC**H**$_2$Ph), 4.75 (d, 1H, *J* = 10.9 Hz, OC**H**CH_2), 4.24 (s, 1H, OC**H**$CHN(CH_3)_2$), 4.10 (s, 1H, C**H**$N(CH_3)_2$), 3.33 (dd, 1H, *J* = 15.2, 5.6 Hz, OCHC**H**$_2$), 2.62–2.45 (m, 7H, OCHC**H**$_2$, $N(CH_3)_2$), 0.82 (t, 9H, *J* = 7.9 Hz, $SiCH_2CH_3$), 0.75–0.66 (m, 3H, $SiCH_2CH_3$), 0.66–0.54 (m, 3H, $SiCH_2CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 185.4, 183.4, 178.3, 178.2, 168.2, 155.3, 153.8 (d, *J* = 239.5 Hz), 136.3, 135.2, 128.6, 128.5, 128.4, 128.1, 128.0, 127.0, 126.0 (d, *J* = 18.7 Hz), 120.7 (d, *J* = 24.1 Hz), 120.3, 114.3 (d, *J* = 8.0 Hz), 107.3, 106.4, 79.1, 78.0, 72.2, 71.7, 71.2, 65.0, 43.2, 28.3, 6.8, 5.8. ^{19}F NMR (376 MHz, $CDCl_3$), δ: –125.44. FTIR (neat), cm^{-1}: 3067 (w), 3034 (w), 2955 (m), 2926 (s), 2876 (s), 2853 (m), 2793 (w), 2251 (w), 2100 (w), 1713 (s), 1609 (s), 1570 (m), 1512 (s), 1478 (s), 1454 (s). HRMS (ESI): Calcd for $(C_{40}H_{44}N_2O_8FSi)^+$: 727.2851. Found: 727.2816.



Preparation of 0.48 M LiTMP solution in THF: A solution of *n*-butyllithium in hexanes (2.51 M, 400 µL, 1.00 mmol, 1 equiv) was added dropwise via syringe to a solution of 2,2,6,6-tetramethylpiperidine (188 µL, 1.10 mmol, 1.10 equiv) and triethylamine hydrochloride (1.50 mg, 10.9 µmol, 0.010 equiv) in tetrahydrofuran (1.50 mL) at –78 ºC. After stirring for 15 min, the resultant solution of lithium 2,2,6,6-tetramethylpiperidide was warmed to 0 ºC.

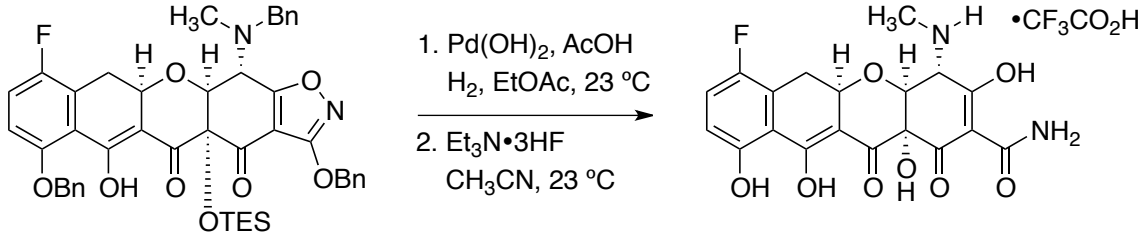
Cyclization product 27: A solution of lithium 2,2,6,6-tetramethylpiperidide in tetrahydrofuran (0.48 M, 130 μL, 62.5 μmol, 2.40 equiv) was added dropwise via syringe to a solution of *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (27.5 μL, 0.182 mmol, 7.00 equiv) and phenyl 6-(benzyloxy)-3-fluoro-2-methylbenzoate **3** (19.3 mg, 57.3 μmol, 2.20 equiv) in tetrahydrofuran (1.00 mL) at –78 ºC. The resulting deep-red mixture was stirred vigorously at –78 °C for 20 min. Then a solution of enone **25** (14.6 mg, 26.0 μmol, 1 equiv) in tetrahydrofuran (250 μL) was added dropwise via cannula. The resulting light-orange mixture was allowed to warm slowly to –20 °C over 1.5 h. Saturated ammonium chloride solution (1 mL) and 1.0 M aqueous hydrochloric acid solution (0.5 mL) were then added. The cooling bath was removed and the reaction mixture was allowed to warm to 23 ºC. The resulting biphasic mixture was poured into water (5 mL) and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (100% hexanes initially, grading to 10% acetone–hexanes) to provide pure cyclization product **27** (12.4 mg, 59%) as a light yellow foam. TLC (20% ethyl acetate–hexanes): R_f = 0.30 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 15.71 (s, 1H, O**H**), 7.53–7.46 (m, 4H, Ar**H**), 7.43–7.30 (m, 10H, Ar**H**), 7.27–7.24 (m, 1H, Ar**H**), 7.13 (dd, 1H, *J* = 9.1, 8.1 Hz, FCC**H**), 6.88 (dd, 1H, *J* = 9.3, 4.0 Hz, FCCHC**H**), 5.41 (d, 1H, *J* = 12.1 Hz, OC**H**$_2$Ph), 5.37 (d, 1H, *J* = 12.1 Hz, OC**H**$_2$Ph), 5.24 (d, 1H, *J* = 12.3 Hz, OC**H**$_2$Ph), 5.16 (d, 1H, *J* = 12.3 Hz, OC**H**$_2$Ph), 4.73 (dd, 1H, *J* = 13.2, 5.5 Hz, OC**H**CH$_2$), 4.28 (app-s, 2H, C**H**NCH$_3$CH$_2$Ph, OC**H**CHNCH$_3$CH$_2$Ph), 3.92 (d, 1H, *J* = 13.6 Hz, NC**H**$_2$Ph), 3.82 (d, 1H, *J* = 13.3 Hz, NC**H**$_2$Ph), 3.27 (dd, 1H, *J* = 14.9, 5.8 Hz, OCHC**H**$_2$), 2.44 (s, 3H, NC**H**$_3$), 2.40 (t, *J* = 14.6 Hz, 1H, OCHC**H**$_2$), 0.79 (t, *J* = 7.7 Hz, 9H, SiCH$_2$C**H**$_3$), 0.74–0.65 (m, 3H, SiC**H**$_2$CH$_3$), 0.63–0.55 (m, 3H, SiC**H**$_2$CH$_3$). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 185.4, 183.6, 178.6, 178.0, 168.2, 155.3 (d, *J* = 2.0 Hz), 153.8 (d, *J* = 239.5 Hz), 138.4, 136.3, 135.1, 128.8, 128.6, 128.5, 128.4, 128.4, 128.1, 128.0, 127.4, 127.0, 126.1 (d, *J* = 18.7 Hz), 120.7 (d, *J* = 24.1 Hz), 120.2 (d, *J* = 3.1 Hz), 114.3 (d, *J* = 7.8 Hz), 107.2, 106.6, 79.6, 78.2, 72.2, 71.6, 71.1, 63.7, 59.9, 39.5, 28.3, 6.8, 5.8. ^{19}F NMR (376 MHz, $CDCl_3$), δ: –126.14. FTIR (neat), cm^{-1}: 3065 (w), 3034 (w), 2953 (m), 2875 (m), 1713 (s), 1609 (s), 1510 (s), 1478 (s), 1452 (s), 1367 (s). HRMS (ESI): Calcd for $(C_{46}H_{48}N_2O_8FSi)^+$: 803.3164. Found: 803.3157.



26 **2**

5-Oxatetracycline 2: **Step 1, Hydrogenation .** Palladium hydroxide on carbon (20 wt%, 74.0 mg, 105 μmol, 3.5 equiv) was added in one portion to a solution of Michael–Claisen product **26** (21.9 mg, 30.1 μmol, 1 equiv) and acetic acid (69.0 μL, 1.20 mmol, 40.0 equiv) in ethyl acetate (6.50 mL) at 23 ºC. An atmosphere of hydrogen was introduced by briefly evacuating the flask, then flushing with pure hydrogen (1 atm) for 5 min. The yellow heterogeneous mixture was stirred at 23 ºC for 5 min, then was filtered through a plug of Celite®. The filtrate was concentrated to afford a yellow oil.

Step 2, **Silyl Group Cleavage**. Triethylamine trihydrofluoride (368 μL, 2.26 mmol, 75.0 equiv) was added to a solution of the crude hydrogenation product in acetonitrile (3.50 mL) at 23 ºC. The reaction mixture was stirred at 23 ºC for 15 min. Methoxytrimethylsilane (1.80 mL) was then added. The resulting mixture was concentrated. The product was purified by preparative HPLC on a Waters SunFire Prep C18 column [5 μm, 250 × 19 mm, UV detection at 350 nm, solvent A: 0.1% trifluoroacetic acid in water, solvent B: 0.1% trifluoroacetic acid in acetonitrile, injection volume: 3.5 mL (3.3 mL water, 0.2 mL acetonitrile), gradient elution with 20→70% B over 50 min, flow rate: 15 mL/min]. Fractions eluting at 12.5–13.5 min were collected and concentrated, affording C5-oxatetracycline trifluoroacetate **2** as a yellow solid (3.3 mg, 20% over two steps). ^{1}H NMR (500 MHz, CD_3OD, trifluoroacetate), δ: 7.31 (t, 1H, J = 9.0 Hz, FCC**H**), 6.86 (dd, 1H, J = 9.2, 4.0 Hz, FCCHC**H**), 3.38 (dd, 1H, J = 15.0, 5.4 Hz, OCHC**H**$_2$), 3.10 (br-s, 6H, N(C**H**$_3$)$_2$), 2.56 (t, 1H, J = 13.9 Hz, OCHC**H**$_2$). Three additional signals (OC**H**CH$_2$, C**H**N(CH$_3$)$_2$, and OC**H**CHN(CH$_3$)$_2$) are hidden beneath the residual HDO signal (δ: 4.90). ^{13}C NMR (125 MHz, CD_3OD, trifluoroacetate), δ: 193.3, 192.6, 186.5, 174.8, 171.8, 159.8, 153.9 (d, J = 236.8 Hz), 125.4 (d, J = 18.9 Hz), 125.2 (d, J = 25.2 Hz), 118.5 (d, J = 7.5 Hz), 116.9, 108.2, 96.1, 74.8, 72.4, 72.3, 66.5, 44.2, 42.6, 30.7. ^{19}F (376 MHz, CD_3OD, trifluoroacetate), δ: –76.29 (C**F**$_3$COOH), –129.27 (C**F**). FTIR (neat), cm^{-1}: 3392 (m), 2502 (s), 2243 (w), 2139 (w), 2075 (s), 1672 (s). HRMS (ESI): Calcd for $(C_{20}H_{20}N_2O_8F_1)^+$: 435.1204. Found: 435.1168.



27 **28**

Oxatetracycline 28: **Step 1, Hydrogenation.** Palladium hydroxide on carbon (20% wt, 68.6 mg, 97.6 μmol, 4.00 equiv) was added in one portion to a solution of Michael–Claisen product **27** (19.6 mg, 2.44 μmol, 1 equiv) and acetic acid (28.0 μL, 0.488 mmol, 20.0 equiv) in ethyl acetate (5.00 mL) at 23 ºC. An atmosphere of hydrogen was introduced by briefly evacuating the flask, then flushing with pure hydrogen (1 atm) for 5 min. The yellow heterogeneous mixture was stirred at 23 ºC for an additional 10 min, and then was filtered through a plug of Celite®. The filtrate was concentrated, affording a yellow oil.

Step 2, **Silyl Group Cleavage**. Triethylamine trihydrofluoride (298 μL, 1.83 mmol, 75.0 equiv) was added to a solution of the crude hydrogenation product from step 1 in acetonitrile (2.40 mL) at 23 ºC. The reaction mixture was stirred at 23 ºC for 15 min. Methoxytrimethylsilane (1.60 mL) was then added. The resulting mixture was concentrated. The product was purified by preparative HPLC on a Waters SunFire Prep C18 column [5 μm, 250 × 19 mm, UV detection at 350 nm, solvent A: 0.1% trifluoroacetic acid in water, solvent B: 0.1% trifluoroacetic acid in acetonitrile, injection volume: 3.5 mL (3.3 mL water, 0.2 mL acetonitrile), gradient elution with 20→70% B over 50 min, flow rate: 15 mL/min]. Fractions eluting at 10.5–11.5 min were collected and concentrated, affording C5-oxatetracycline trifluoroacetate **28** as a yellow solid (4.0 mg, 30% over two steps). ^{1}H NMR (500 MHz, CD_3OD, trifluoroacetate), δ: 7.31 (t, 1H, J = 9.0 Hz, FCC**H**), 6.86 (dd, 1H, J = 9.4, 4.0 Hz, FCCHC**H**), 4.64 (d, 1H, J = 2.8 Hz, C**H**NHCH$_3$), 4.59 (d, 1H, J = 2.8 Hz, OC**H**CHNHCH$_3$), 3.42 (dd, 1H, J = 15.1, 5.5 Hz, OCHC**H**$_2$), 2.90 (s, 3H, NHC**H**$_3$), 2.58 (t, 1H, J = 13.9 Hz, OCHC**H**$_2$). One additional signal (OC**H**CH$_2$) is hidden beneath the residual HDO signal (δ: 4.88). ^{13}C NMR (125 MHz, CD_3OD, trifluoroacetate), δ: 193.0, 192.8, 187.7, 174.9, 171.9, 159.8, 153.9 (d, J = 235.9 Hz), 125.5 (d, J = 18.9 Hz), 125.2 (d, J = 26.5 Hz), 118.4, 117.0, 108.5, 95.8, 74.4, 72.8, 71.8, 60.6, 32.1, 28.2. ^{19}F NMR (471 MHz, CD_3OD, trifluoroacetate), δ: –73.28 (C**F**$_3$COOH), –126.29 (C**F**). FTIR (neat), cm^{-1}: 3397

(s), 2928 (w), 2855 (w), 2509 (s), 2241 (w), 2075 (m), 1670 (s), 1628 (s). HRMS (ESI): Calcd for $(C_{19}H_{18}N_2O_8F)^+$: 421.1047. Found: 421.1044.

Computational Analysis of Compounds 1, 4, 13, 14, 17 and their derivatives

Calculations were performed using the Gaussian 09 program[8] on the Odyssey cluster at Harvard University Research Computing group. Molecular geometries were optimized using density functional theory (DFT) with the B3LYP/6-31g(d) basis set.[9] The benzyloxy group of the isoxazole functionality was simplified to a methoxy group to minimize computational time. To evaluate the validity of the computational method, the computed, simplified structures of the AB enone (**1**) and compound **13** were superimposed with their solid-state structures[10], obtained through X-ray crystallography. The resulting images, rendered using MacPyMOL, are depicted in Figure S1.

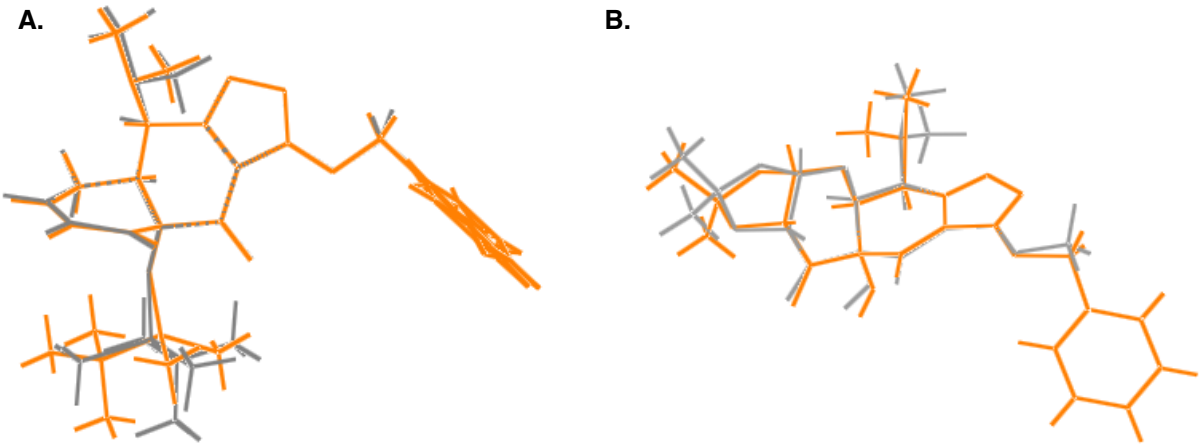


Figure S1. (A) Comparison of the X-ray crystallographic structure of the AB enone (**1**, depicted in orange) and its simplified structure (the benzyloxy group of the isoxazole functionality was simplified to a methoxy group, depicted in gray), calculated with the B3LYP/6-31g(d) basis set. (B) Comparison of the X-ray crystallographic structure of **13** (depicted in orange) and its simplified structure (depicted in gray), calculated with the B3LYP/6-31g(d) basis set.

The relative energies of compounds **1**, **4**, **13**, **14**, **17, S9–10** and their C4-epimers were determined from the electronic energies of stationary points located at the B3LYP/6-31g(d) level of theory. Optimized geometries of compounds **1**, **4**, **13**, **14**, **17, S9–10** and their C4-epimers are shown in Figure S2–S5.

[8] Frisch, M. J.; *et al*. Gaussian 09; Gaussian, Inc.: Wallingford, CT, 2009.
[9] (a) Lee, C.; Yang, W.; Parr, R. G., *Physical Review B* **1988**, *37*, 785- 789; (b) Becke, A. D., *The Journal of Chemical Physics* **1993**, *98*, 5648- 5652.
[10] Sun, C.; Wang, Q.; Brubaker, J. D.; Wright, P. M.; Lerner, C. D.; Noson, K.; Charest, M.; Siegel, D. R.; Wang, Y. M.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 17913

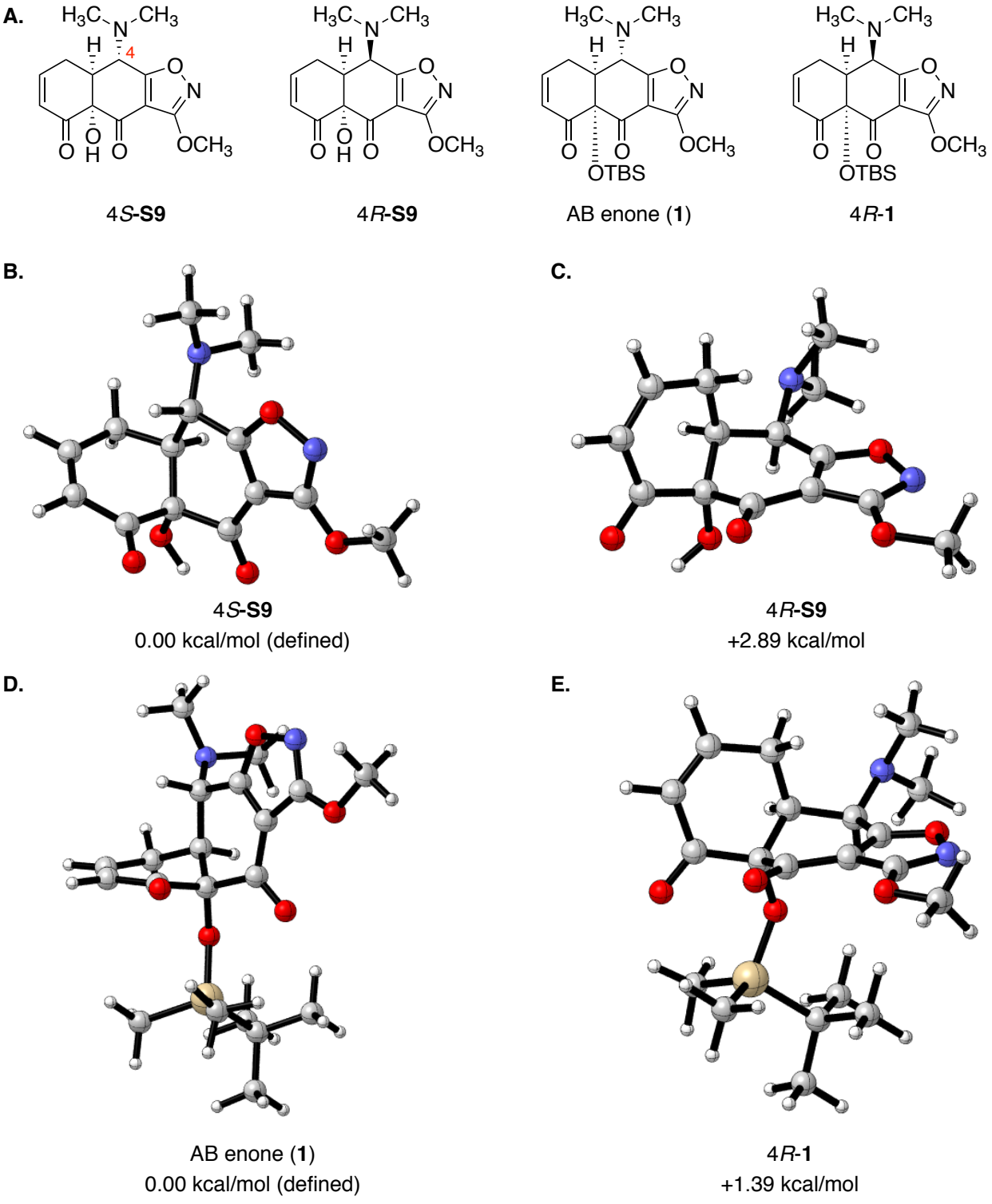


Figure S2. (A) Chemical structures of computed 5-carba-AB enone derivatives. (B)–(E) Optimized geometries and relative energies of compounds **S9**, AB enone (**1**), and their C4-epimers.

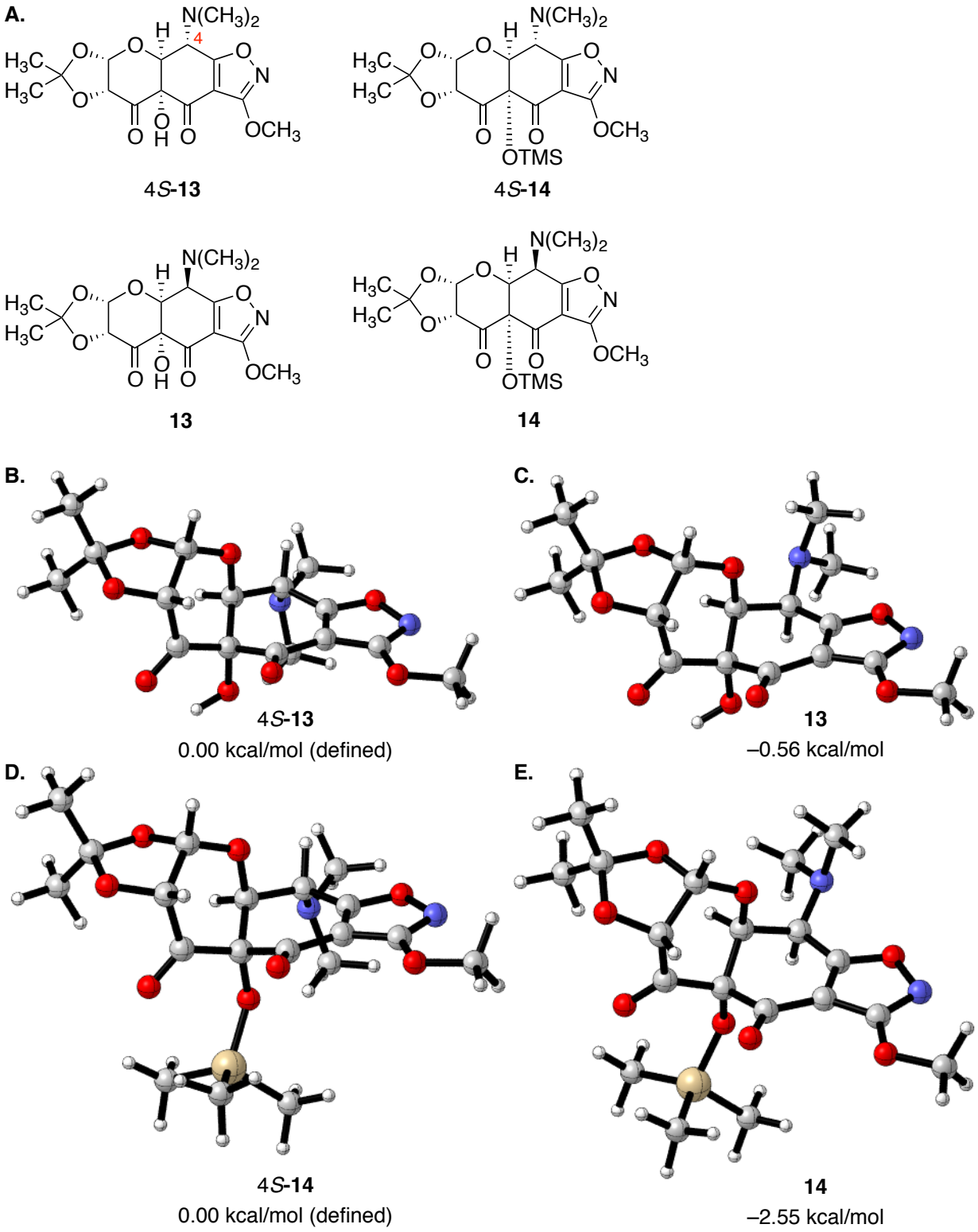


Figure S3. (A) Chemical structures of computed 5-oxa-AB enone derivatives. (B)–(E) Optimized geometries and relative energies of compounds **13**, **14**, and their C4-epimers.

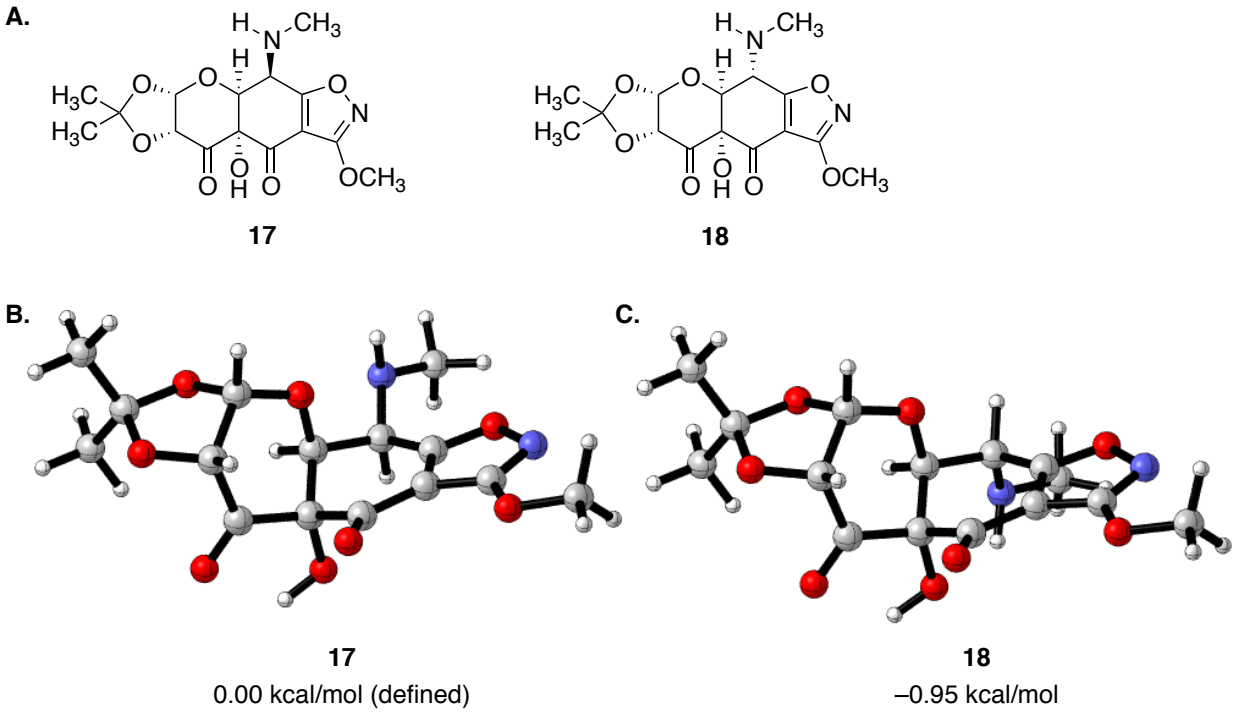


Figure S4. (A) Chemical structures of computed 5-oxa-AB enone precursors **17** and **18**. (B)–(C) Optimized geometries and relative energies of compounds **17** and **18**.

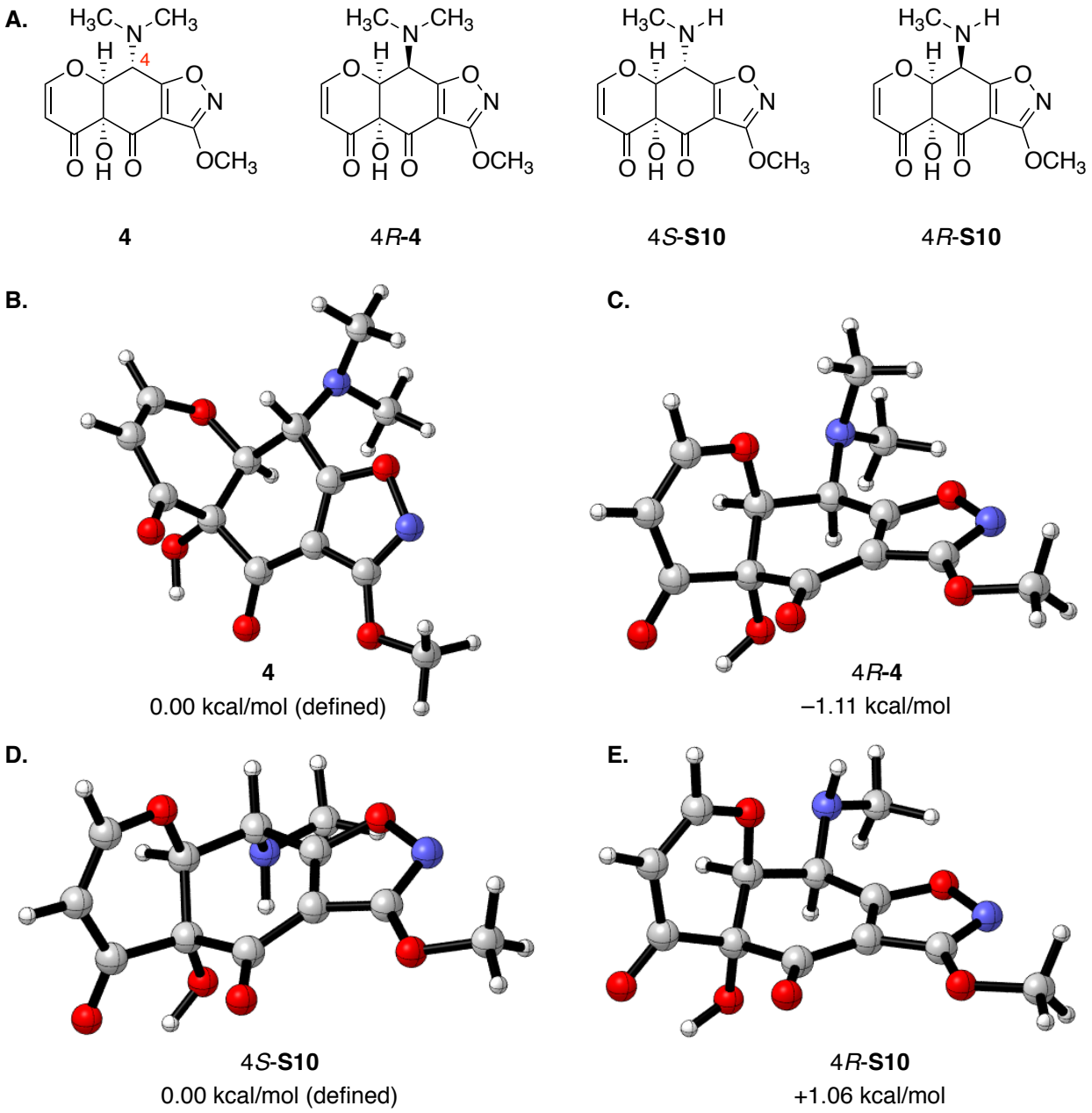


Figure S5. (A) Chemical structures of computed 5-oxa-AB enone derivatives. (B)–(E) Optimized geometries and relative energies of compounds **4**, **S10**, and their C4-epimers.

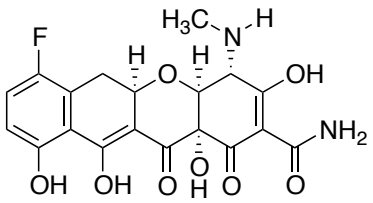
Minimum Inhibitory Concentration (MIC) Values

MIC values were used to determine the efficacy of a particular antibiotic by measuring its ability to inhibit growth at a range of different concentrations.

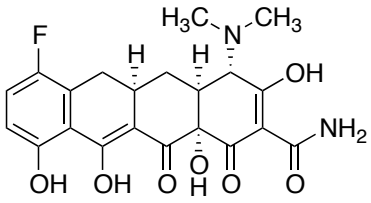
A 96-well plate (cat. No. 351172. Falcon, Corning, NY) was prepared by first adding 100 µL of media to wells in columns 2–10, rows B–G, and 98.4 µL of media to wells in column 11, rows B–G. An additional 93.6 µL of media was then added to wells in column 2, rows B–G, followed by 6.4 µL of drug solution (2.0 mg/mL in 50% dimethyl sulfoxide (DMSO)/water). A serial dilution was performed across the plate to column 10, discarding the final 100 µL of media. 1.6 µL of DMSO was added to wells in column 11, rows B–G, to serve as controls. 200 µL of media was added to all remaining empty wells (column 1 and 12, rows A–H; column 2–11, rows A and H).

Cells were prepared by reinoculating an overnight culture into fresh media (lysogeny broth (LB) for *E. coli* strain MC4100, tryptic soy broth (TSB) for *S. aureus* (Newman)) until they reached an OD_{600} = ~ 0.6. The log-phase cells were then diluted 60-fold in a fresh media reservoir to reach an OD_{600} = ~ 0.01. 100-µL aliquots of cells from the media reservoir were then added to wells in columns 2–11, rows B–G in the 96-well plate to provide a final drug concentration of 32 µg/mL in column 2, rows B–G. The plate was shaken at 37 ºC until the cells in the DMSO control wells (column 11, rows B–G) reached an OD_{600} = ~ 1.0 (~18 h for *E. coli* strain MC4100, ~11 h for *S. aureus* (Newman)).

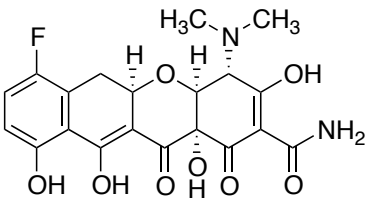
A 1 mg/mL aqueous solution of thiazolyl blue tetrazolium bromide (MTT) was prepared and 50 µL of this solution as added to each well in columns 2–11, rows B–G. Following incubation for a further 1 h at 23 ºC, MICs were determined by measuring the first well that stained successfully (indicating respiration by the organism). The drug concentration present in the last well in which the stain did not appear provided the MIC value for a particular drug molecule in this bacterial strain. The final MIC value for each drug was an average of two runs, each verified by a duplicate (two rows for each small molecule) and the growth of bacteria in the absence of small molecule was confirmed using a DMSO control (column 11, rows B–G).



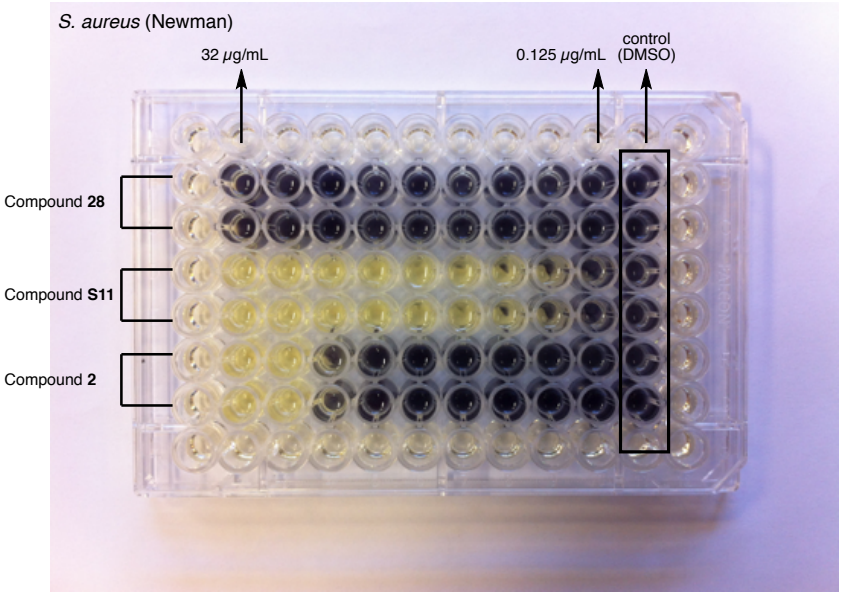
compound **28**

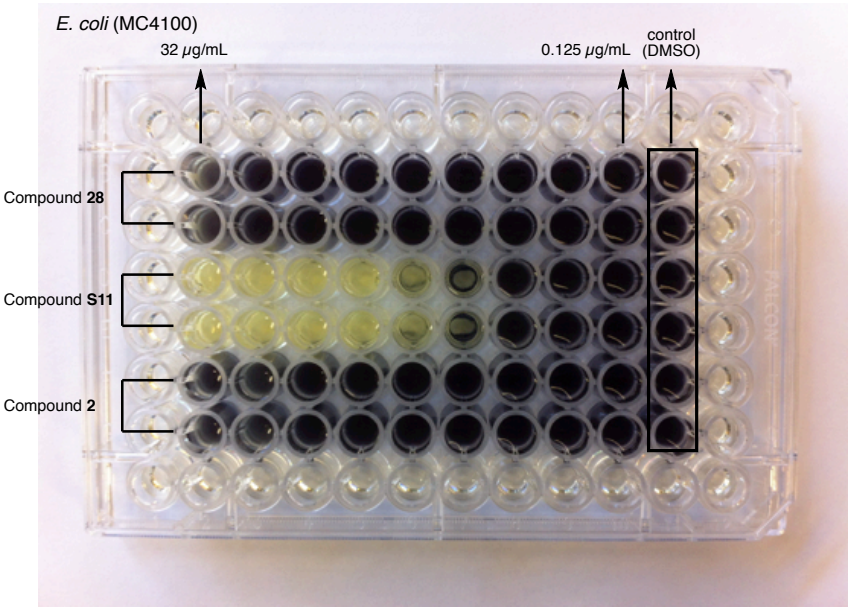


7-fluorominocycline (**S11**)



compound **2**





X-Ray Crystallography of amino alcohol 13: Data of a crystal mounted on a diffractometer was collected at 180 K. The intensities of the reflections were collected by means of a Bruker APEX II DUO CCD diffractometer (Cu_{K_α} radiation, λ=1.54178 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at 30°, 55°, 80° and 115° in 2θ. Data integration down to 0.84 Å resolution was carried out using SAINT V7.46 A with reflection spot size optimization.[11] Absorption corrections were made with the program SADABS.[11] The structure was solved by the direct methods procedure and refined by least-squares methods again F^2 using SHELXS-97 and SHELXL-97.[12] Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table 1, geometric parameters are shown in Table 2, and hydrogen-bond parameters are listed in Table 3. The Ortep plots produced with SHELXL-97 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.[13]

Table 1. Experimental details

Crystal data	
Chemical formula	$C_{22}H_{24}N_2O_8$
M_r	444.43
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	100
a, *b*, *c* (Å)	9.5161 (2), 17.6610 (3), 13.0462 (2)
b (°)	107.255 (1)
V (Å^3)	2093.91 (7)
Z	4
Radiation type	Cu *K*a
m (mm^{-1})	0.91
Crystal size (mm)	0.03 × 0.01 × 0.01
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector diffractometer

[11] Bruker AXS APEX II, Bruker AXS, Madison, Wisconsin, 2009.
[12] G. M. Sheldrick, Acta Cryst. 2008, A64, 112-122.
[13] Accelrys DS Visualizer v2.0.1, Accelrys Software. Inc., 2007.

Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.973, 0.991
No. of measured, independent and observed [$I > 2s(I)$] reflections	33387, 6774, 6441
R_{int}	0.038
Refinement	
$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.028, 0.066, 1.05
No. of reflections	6774
No. of parameters	593
No. of restraints	1
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$D\rho_{max}$, $D\rho_{min}$ (e Å^{-3})	0.17, -0.15
Absolute structure	Flack H D (1983), Acta Cryst. A39, 876-881
Flack parameter	0.02 (10)

Computer programs: *APEX2* v2009.3.0,[11] *SAINT* 7.46A,[11] *SHELXS97*,[12] *SHELXL97*,[12] Bruker *SHELXTL*.[12]

Table 2. Geometric parameters (Å, º)

C1—N1	1.307 (2)	C31—N3	1.315 (2)
C1—O1	1.328 (2)	C31—O11	1.328 (2)
C1—C2	1.429 (3)	C31—C32	1.423 (3)
C2—C11	1.360 (3)	C32—C41	1.351 (3)
C2—C3	1.447 (3)	C32—C33	1.460 (2)
C3—O2	1.217 (2)	C33—O12	1.213 (2)
C3—C4	1.549 (3)	C33—C34	1.546 (3)
C4—O3	1.408 (2)	C34—O13	1.407 (2)
C4—C5	1.521 (2)	C34—C35	1.526 (3)
C4—C9	1.542 (2)	C34—C39	1.551 (2)
C5—O4	1.202 (2)	C35—O14	1.205 (2)
C5—C6	1.527 (3)	C35—C36	1.519 (3)
C6—O5	1.407 (2)	C36—O15	1.404 (2)
C6—C8	1.531 (2)	C36—C38	1.523 (2)
C6—H6	1.0000	C36—H36	1.0000
C7—O5	1.434 (2)	C37—O15	1.442 (2)
C7—O6	1.446 (2)	C37—O16	1.446 (2)

C7—C20	1.505 (3)	C37—C49	1.501 (3)
C7—C19	1.511 (3)	C37—C50	1.514 (3)
C8—O7	1.394 (2)	C38—O17	1.398 (2)
C8—O6	1.416 (2)	C38—O16	1.423 (2)
C8—H8	1.0000	C38—H38	1.0000
C9—O7	1.429 (2)	C39—O17	1.425 (2)
C9—C10	1.550 (2)	C39—C40	1.549 (2)
C9—H9	1.0000	C39—H39	1.0000
C10—N2	1.464 (2)	C40—N4	1.472 (2)
C10—C11	1.501 (3)	C40—C41	1.494 (3)
C10—H10	1.0000	C40—H40	1.0000
C11—O8	1.330 (2)	C41—O18	1.333 (2)
C12—O1	1.456 (2)	C42—O11	1.457 (2)
C12—C13	1.502 (3)	C42—C43	1.501 (3)
C12—H12A	0.9900	C42—H42A	0.9900
C12—H12B	0.9900	C42—H42B	0.9900
C13—C18	1.380 (3)	C43—C44	1.393 (3)
C13—C14	1.394 (3)	C43—C48	1.397 (3)
C14—C15	1.390 (3)	C44—C45	1.390 (3)
C14—H14	0.9500	C44—H44	0.9500
C15—C16	1.367 (4)	C45—C46	1.375 (3)
C15—H15	0.9500	C45—H45	0.9500
C16—C17	1.372 (3)	C46—C47	1.389 (3)
C16—H16	0.9500	C46—H46	0.9500
C17—C18	1.387 (3)	C47—C48	1.382 (3)
C17—H17	0.9500	C47—H47	0.9500
C18—H18	0.9500	C48—H48	0.9500
C19—H19A	0.9800	C49—H49A	0.9800
C19—H19B	0.9800	C49—H49B	0.9800
C19—H19C	0.9800	C49—H49C	0.9800
C20—H20A	0.9800	C50—H50A	0.9800
C20—H20B	0.9800	C50—H50B	0.9800
C20—H20C	0.9800	C50—H50C	0.9800
C21—N2	1.458 (3)	C51—N4	1.468 (2)
C21—H21A	0.9800	C51—H51A	0.9800
C21—H21B	0.9800	C51—H51B	0.9800
C21—H21C	0.9800	C51—H51C	0.9800

C22—N2	1.466 (3)	C52—N4	1.476 (3)
C22—H22A	0.9800	C52—H52A	0.9800
C22—H22B	0.9800	C52—H52B	0.9800
C22—H22C	0.9800	C52—H52C	0.9800
N1—O8	1.448 (2)	N3—O18	1.4343 (19)
O3—H3	0.90 (3)	O13—H13	0.87 (3)
N1—C1—O1	125.05 (17)	N3—C31—O11	123.85 (16)
N1—C1—C2	112.66 (17)	N3—C31—C32	112.13 (16)
O1—C1—C2	122.21 (16)	O11—C31—C32	123.94 (16)
C11—C2—C1	103.57 (16)	C41—C32—C31	104.02 (15)
C11—C2—C3	123.97 (18)	C41—C32—C33	122.80 (16)
C1—C2—C3	132.43 (17)	C31—C32—C33	133.18 (16)
O2—C3—C2	125.31 (18)	O12—C33—C32	125.09 (17)
O2—C3—C4	121.30 (17)	O12—C33—C34	121.96 (16)
C2—C3—C4	113.37 (15)	C32—C33—C34	112.84 (15)
O3—C4—C5	112.00 (14)	O13—C34—C35	111.76 (14)
O3—C4—C9	110.37 (14)	O13—C34—C33	106.97 (14)
C5—C4—C9	108.76 (14)	C35—C34—C33	108.32 (15)
O3—C4—C3	107.42 (15)	O13—C34—C39	109.47 (14)
C5—C4—C3	107.85 (15)	C35—C34—C39	108.37 (14)
C9—C4—C3	110.41 (14)	C33—C34—C39	111.98 (14)
O4—C5—C4	121.55 (17)	O14—C35—C36	121.70 (17)
O4—C5—C6	121.48 (16)	O14—C35—C34	120.63 (17)
C4—C5—C6	116.96 (15)	C36—C35—C34	117.67 (14)
O5—C6—C5	112.59 (15)	O15—C36—C35	112.00 (14)
O5—C6—C8	103.25 (14)	O15—C36—C38	103.00 (14)
C5—C6—C8	113.72 (14)	C35—C36—C38	112.57 (15)
O5—C6—H6	109.0	O15—C36—H36	109.7
C5—C6—H6	109.0	C35—C36—H36	109.7
C8—C6—H6	109.0	C38—C36—H36	109.7
O5—C7—O6	105.33 (14)	O15—C37—O16	105.64 (13)
O5—C7—C20	108.47 (16)	O15—C37—C49	111.96 (15)
O6—C7—C20	109.71 (16)	O16—C37—C49	108.52 (16)
O5—C7—C19	111.26 (16)	O15—C37—C50	107.28 (16)
O6—C7—C19	108.58 (16)	O16—C37—C50	110.39 (15)
C20—C7—C19	113.20 (19)	C49—C37—C50	112.81 (17)

O7—C8—O6	111.22 (14)	O17—C38—O16	111.08 (14)
O7—C8—C6	115.42 (15)	O17—C38—C36	115.21 (15)
O6—C8—C6	103.12 (15)	O16—C38—C36	102.20 (14)
O7—C8—H8	108.9	O17—C38—H38	109.4
O6—C8—H8	108.9	O16—C38—H38	109.4
C6—C8—H8	108.9	C36—C38—H38	109.4
O7—C9—C4	107.08 (14)	O17—C39—C40	106.40 (13)
O7—C9—C10	106.36 (14)	O17—C39—C34	108.99 (14)
C4—C9—C10	113.55 (14)	C40—C39—C34	113.84 (14)
O7—C9—H9	109.9	O17—C39—H39	109.2
C4—C9—H9	109.9	C40—C39—H39	109.2
C10—C9—H9	109.9	C34—C39—H39	109.2
N2—C10—C11	113.77 (15)	N4—C40—C41	112.22 (14)
N2—C10—C9	116.78 (15)	N4—C40—C39	117.08 (15)
C11—C10—C9	106.17 (14)	C41—C40—C39	107.96 (14)
N2—C10—H10	106.5	N4—C40—H40	106.3
C11—C10—H10	106.5	C41—C40—H40	106.3
C9—C10—H10	106.5	C39—C40—H40	106.3
O8—C11—C2	110.96 (17)	O18—C41—C32	110.79 (16)
O8—C11—C10	123.03 (16)	O18—C41—C40	121.42 (15)
C2—C11—C10	125.95 (16)	C32—C41—C40	127.66 (16)
O1—C12—C13	108.31 (15)	O11—C42—C43	109.34 (14)
O1—C12—H12A	110.0	O11—C42—H42A	109.8
C13—C12—H12A	110.0	C43—C42—H42A	109.8
O1—C12—H12B	110.0	O11—C42—H42B	109.8
C13—C12—H12B	110.0	C43—C42—H42B	109.8
H12A—C12—H12B	108.4	H42A—C42—H42B	108.3
C18—C13—C14	118.0 (2)	C44—C43—C48	118.93 (18)
C18—C13—C12	119.89 (17)	C44—C43—C42	122.94 (17)
C14—C13—C12	122.12 (19)	C48—C43—C42	118.09 (16)
C15—C14—C13	120.4 (2)	C45—C44—C43	119.91 (18)
C15—C14—H14	119.8	C45—C44—H44	120.0
C13—C14—H14	119.8	C43—C44—H44	120.0
C16—C15—C14	120.5 (2)	C46—C45—C44	120.73 (18)
C16—C15—H15	119.7	C46—C45—H45	119.6
C14—C15—H15	119.7	C44—C45—H45	119.6
C15—C16—C17	119.7 (2)	C45—C46—C47	119.86 (19)

C15—C16—H16	120.2	C45—C46—H46	120.1
C17—C16—H16	120.2	C47—C46—H46	120.1
C16—C17—C18	120.1 (2)	C48—C47—C46	119.89 (19)
C16—C17—H17	119.9	C48—C47—H47	120.1
C18—C17—H17	119.9	C46—C47—H47	120.1
C13—C18—C17	121.22 (18)	C47—C48—C43	120.66 (18)
C13—C18—H18	119.4	C47—C48—H48	119.7
C17—C18—H18	119.4	C43—C48—H48	119.7
C7—C19—H19A	109.5	C37—C49—H49A	109.5
C7—C19—H19B	109.5	C37—C49—H49B	109.5
H19A—C19—H19B	109.5	H49A—C49—H49B	109.5
C7—C19—H19C	109.5	C37—C49—H49C	109.5
H19A—C19—H19C	109.5	H49A—C49—H49C	109.5
H19B—C19—H19C	109.5	H49B—C49—H49C	109.5
C7—C20—H20A	109.5	C37—C50—H50A	109.5
C7—C20—H20B	109.5	C37—C50—H50B	109.5
H20A—C20—H20B	109.5	H50A—C50—H50B	109.5
C7—C20—H20C	109.5	C37—C50—H50C	109.5
H20A—C20—H20C	109.5	H50A—C50—H50C	109.5
H20B—C20—H20C	109.5	H50B—C50—H50C	109.5
N2—C21—H21A	109.5	N4—C51—H51A	109.5
N2—C21—H21B	109.5	N4—C51—H51B	109.5
H21A—C21—H21B	109.5	H51A—C51—H51B	109.5
N2—C21—H21C	109.5	N4—C51—H51C	109.5
H21A—C21—H21C	109.5	H51A—C51—H51C	109.5
H21B—C21—H21C	109.5	H51B—C51—H51C	109.5
N2—C22—H22A	109.5	N4—C52—H52A	109.5
N2—C22—H22B	109.5	N4—C52—H52B	109.5
H22A—C22—H22B	109.5	H52A—C52—H52B	109.5
N2—C22—H22C	109.5	N4—C52—H52C	109.5
H22A—C22—H22C	109.5	H52A—C52—H52C	109.5
H22B—C22—H22C	109.5	H52B—C52—H52C	109.5
C1—N1—O8	104.29 (14)	C31—N3—O18	104.38 (13)
C21—N2—C10	111.45 (15)	C51—N4—C40	111.14 (14)
C21—N2—C22	109.98 (16)	C51—N4—C52	110.08 (15)
C10—N2—C22	117.13 (14)	C40—N4—C52	116.75 (14)
C1—O1—C12	116.77 (15)	C31—O11—C42	115.91 (14)

C4—O3—H3	109.9 (18)	C34—O13—H13	106.9 (17)
C6—O5—C7	108.05 (13)	C36—O15—C37	108.05 (13)
C8—O6—C7	109.74 (13)	C38—O16—C37	108.24 (13)
C8—O7—C9	115.50 (14)	C38—O17—C39	115.65 (13)
C11—O8—N1	108.48 (13)	C41—O18—N3	108.61 (13)
N1—C1—C2—C11	2.3 (2)	N3—C31—C32—C41	3.0 (2)
O1—C1—C2—C11	-174.62 (17)	O11—C31—C32—C41	-173.92 (16)
N1—C1—C2—C3	-175.66 (19)	N3—C31—C32—C33	-176.46 (18)
O1—C1—C2—C3	7.5 (3)	O11—C31—C32—C33	6.6 (3)
C11—C2—C3—O2	-168.86 (19)	C41—C32—C33—O12	-166.79 (18)
C1—C2—C3—O2	8.7 (3)	C31—C32—C33—O12	12.6 (3)
C11—C2—C3—C4	12.8 (3)	C41—C32—C33—C34	17.0 (2)
C1—C2—C3—C4	-169.64 (19)	C31—C32—C33—C34	-163.66 (18)
O2—C3—C4—O3	-95.7 (2)	O12—C33—C34—O13	-96.5 (2)
C2—C3—C4—O3	82.68 (18)	C32—C33—C34—O13	79.89 (17)
O2—C3—C4—C5	25.2 (2)	O12—C33—C34—C35	24.1 (2)
C2—C3—C4—C5	-156.42 (15)	C32—C33—C34—C35	-159.49 (15)
O2—C3—C4—C9	143.88 (18)	O12—C33—C34—C39	143.59 (17)
C2—C3—C4—C9	-37.7 (2)	C32—C33—C34—C39	-40.0 (2)
O3—C4—C5—O4	14.3 (2)	O13—C34—C35—O14	15.6 (2)
C9—C4—C5—O4	136.56 (18)	C33—C34—C35—O14	-102.0 (2)
C3—C4—C5—O4	-103.7 (2)	C39—C34—C35—O14	136.33 (18)
O3—C4—C5—C6	-166.24 (15)	O13—C34—C35—C36	-164.94 (15)
C9—C4—C5—C6	-44.0 (2)	C33—C34—C35—C36	77.47 (19)
C3—C4—C5—C6	75.77 (19)	C39—C34—C35—C36	-44.2 (2)
O4—C5—C6—O5	-35.2 (2)	O14—C35—C36—O15	-31.4 (2)
C4—C5—C6—O5	145.32 (15)	C34—C35—C36—O15	149.19 (15)
O4—C5—C6—C8	-152.22 (17)	O14—C35—C36—C38	-146.88 (18)
C4—C5—C6—C8	28.3 (2)	C34—C35—C36—C38	33.7 (2)
O5—C6—C8—O7	-151.86 (15)	O15—C36—C38—O17	-156.30 (15)
C5—C6—C8—O7	-29.5 (2)	C35—C36—C38—O17	-35.5 (2)
O5—C6—C8—O6	-30.37 (17)	O15—C36—C38—O16	-35.74 (17)
C5—C6—C8—O6	91.94 (17)	C35—C36—C38—O16	85.08 (17)
O3—C4—C9—O7	-176.43 (14)	O13—C34—C39—O17	178.49 (14)
C5—C4—C9—O7	60.32 (18)	C35—C34—C39—O17	56.37 (18)
C3—C4—C9—O7	-57.82 (18)	C33—C34—C39—O17	-63.05 (18)

O3—C4—C9—C10	-59.34 (19)	O13—C34—C39—C40	-62.92 (19)
C5—C4—C9—C10	177.42 (15)	C35—C34—C39—C40	174.96 (14)
C3—C4—C9—C10	59.28 (19)	C33—C34—C39—C40	55.5 (2)
O7—C9—C10—N2	-60.33 (19)	O17—C39—C40—N4	-50.47 (19)
C4—C9—C10—N2	-177.85 (15)	C34—C39—C40—N4	-170.53 (15)
O7—C9—C10—C11	67.73 (17)	O17—C39—C40—C41	77.28 (17)
C4—C9—C10—C11	-49.79 (19)	C34—C39—C40—C41	-42.77 (19)
C1—C2—C11—O8	-1.9 (2)	C31—C32—C41—O18	-2.6 (2)
C3—C2—C11—O8	176.28 (17)	C33—C32—C41—O18	176.91 (16)
C1—C2—C11—C10	175.38 (17)	C31—C32—C41—C40	173.18 (17)
C3—C2—C11—C10	-6.5 (3)	C33—C32—C41—C40	-7.3 (3)
N2—C10—C11—O8	-29.2 (2)	N4—C40—C41—O18	-34.4 (2)
C9—C10—C11—O8	-158.99 (16)	C39—C40—C41—O18	-164.85 (15)
N2—C10—C11—C2	153.90 (18)	N4—C40—C41—C32	150.24 (17)
C9—C10—C11—C2	24.1 (2)	C39—C40—C41—C32	19.7 (2)
O1—C12—C13—C18	143.90 (18)	O11—C42—C43—C44	-10.8 (2)
O1—C12—C13—C14	-36.4 (2)	O11—C42—C43—C48	171.70 (16)
C18—C13—C14—C15	1.1 (3)	C48—C43—C44—C45	1.0 (3)
C12—C13—C14—C15	-178.61 (19)	C42—C43—C44—C45	-176.51 (18)
C13—C14—C15—C16	0.0 (3)	C43—C44—C45—C46	-0.1 (3)
C14—C15—C16—C17	-0.6 (3)	C44—C45—C46—C47	-0.9 (3)
C15—C16—C17—C18	0.1 (3)	C45—C46—C47—C48	0.9 (3)
C14—C13—C18—C17	-1.6 (3)	C46—C47—C48—C43	0.0 (3)
C12—C13—C18—C17	178.11 (19)	C44—C43—C48—C47	-0.9 (3)
C16—C17—C18—C13	1.0 (3)	C42—C43—C48—C47	176.68 (18)
O1—C1—N1—O8	175.07 (17)	O11—C31—N3—O18	174.81 (16)
C2—C1—N1—O8	-1.7 (2)	C32—C31—N3—O18	-2.11 (19)
C11—C10—N2—C21	176.40 (15)	C41—C40—N4—C51	-179.95 (15)
C9—C10—N2—C21	-59.3 (2)	C39—C40—N4—C51	-54.3 (2)
C11—C10—N2—C22	-55.7 (2)	C41—C40—N4—C52	-52.6 (2)
C9—C10—N2—C22	68.5 (2)	C39—C40—N4—C52	73.1 (2)
N1—C1—O1—C12	-4.1 (3)	N3—C31—O11—C42	-8.9 (3)
C2—C1—O1—C12	172.35 (17)	C32—C31—O11—C42	167.68 (16)
C13—C12—O1—C1	-148.03 (16)	C43—C42—O11—C31	-144.68 (16)
C5—C6—O5—C7	-91.18 (16)	C35—C36—O15—C37	-90.26 (17)
C8—C6—O5—C7	31.89 (18)	C38—C36—O15—C37	30.95 (18)
O6—C7—O5—C6	-21.19 (19)	O16—C37—O15—C36	-14.48 (18)

C20—C7—O5—C6	-138.59 (16)	C49—C37—O15—C36	103.47 (17)
C19—C7—O5—C6	96.28 (19)	C50—C37—O15—C36	-132.25 (15)
O7—C8—O6—C7	142.43 (15)	O17—C38—O16—C37	150.94 (14)
C6—C8—O6—C7	18.15 (18)	C36—C38—O16—C37	27.55 (17)
O5—C7—O6—C8	0.52 (19)	O15—C37—O16—C38	-9.60 (18)
C20—C7—O6—C8	117.08 (17)	C49—C37—O16—C38	-129.83 (16)
C19—C7—O6—C8	-118.74 (17)	C50—C37—O16—C38	106.06 (18)
O6—C8—O7—C9	-65.49 (19)	O16—C38—O17—C39	-62.13 (19)
C6—C8—O7—C9	51.5 (2)	C36—C38—O17—C39	53.4 (2)
C4—C9—O7—C8	-67.14 (18)	C40—C39—O17—C38	172.73 (14)
C10—C9—O7—C8	171.14 (14)	C34—C39—O17—C38	-64.12 (18)
C2—C11—O8—N1	0.9 (2)	C32—C41—O18—N3	1.48 (19)
C10—C11—O8—N1	-176.38 (16)	C40—C41—O18—N3	-174.63 (15)
C1—N1—O8—C11	0.48 (19)	C31—N3—O18—C41	0.43 (18)

Table 3. Hydrogen-bond parameters

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
O3—H3···N4^{i}	0.90 (3)	2.03 (3)	2.893 (2)	161 (3)
O13—H13···N2^{ii}	0.87 (3)	2.12 (3)	2.915 (2)	151 (2)

Symmetry code(s): (i) *x*+1, *y*, *z*; (ii) *x*-1, *y*, *z*-1.

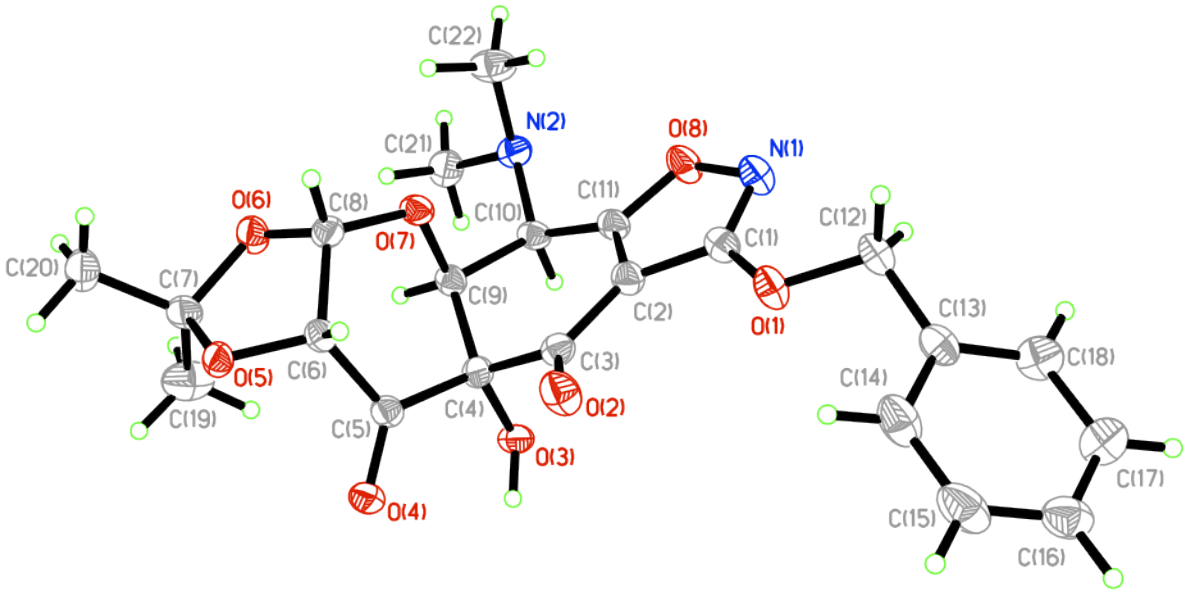


Figure 1a

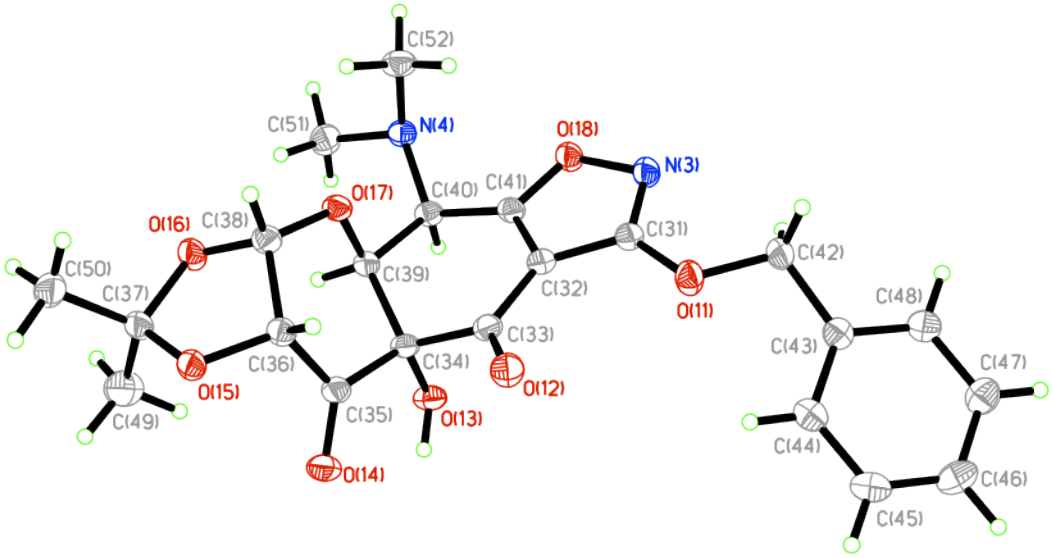


Figure 1b

Figure 1. Perspective views showing 50% probability displacement.

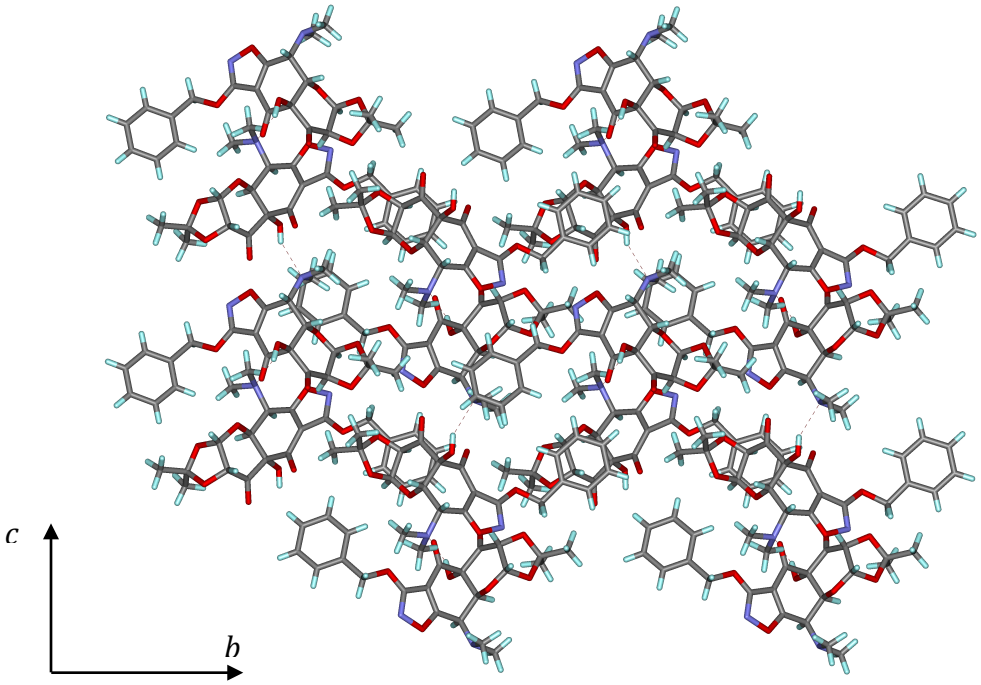
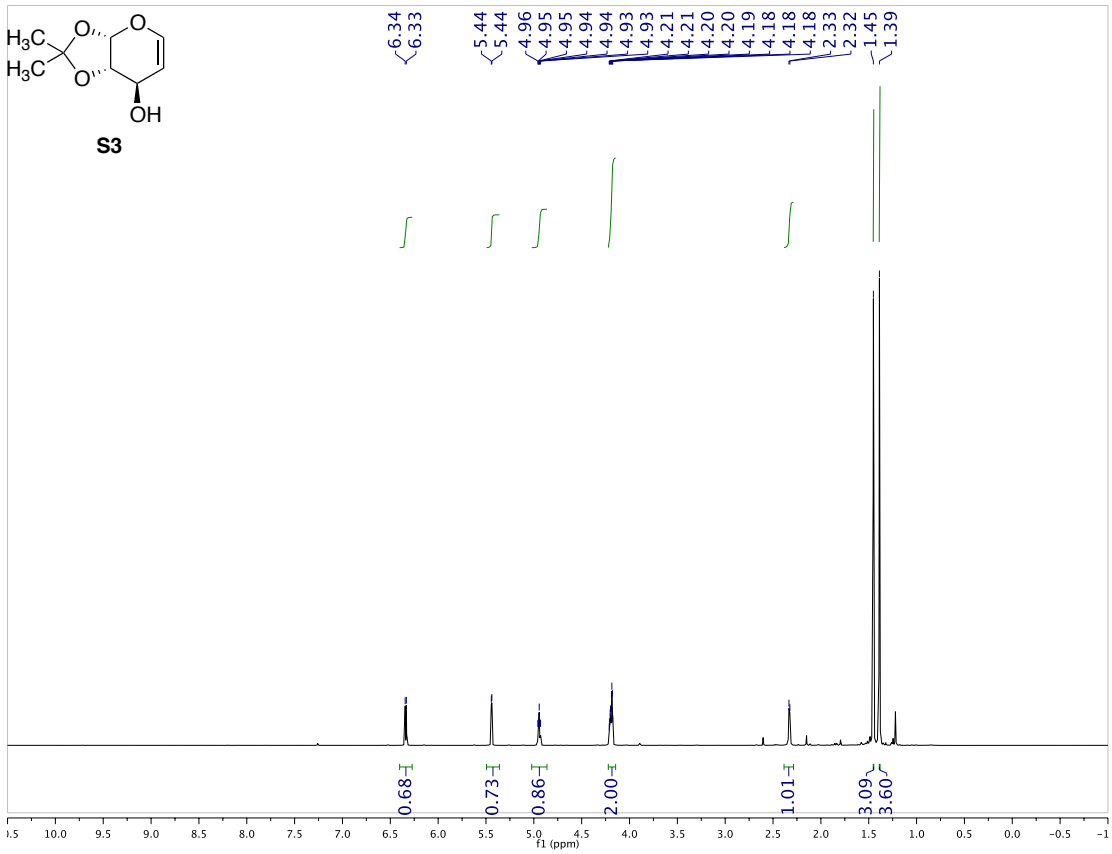


Figure 2. Three-dimensional supramolecular architecture viewed along the *a*-axis direction.

^{1}H NMR and ^{13}C NMR Spectra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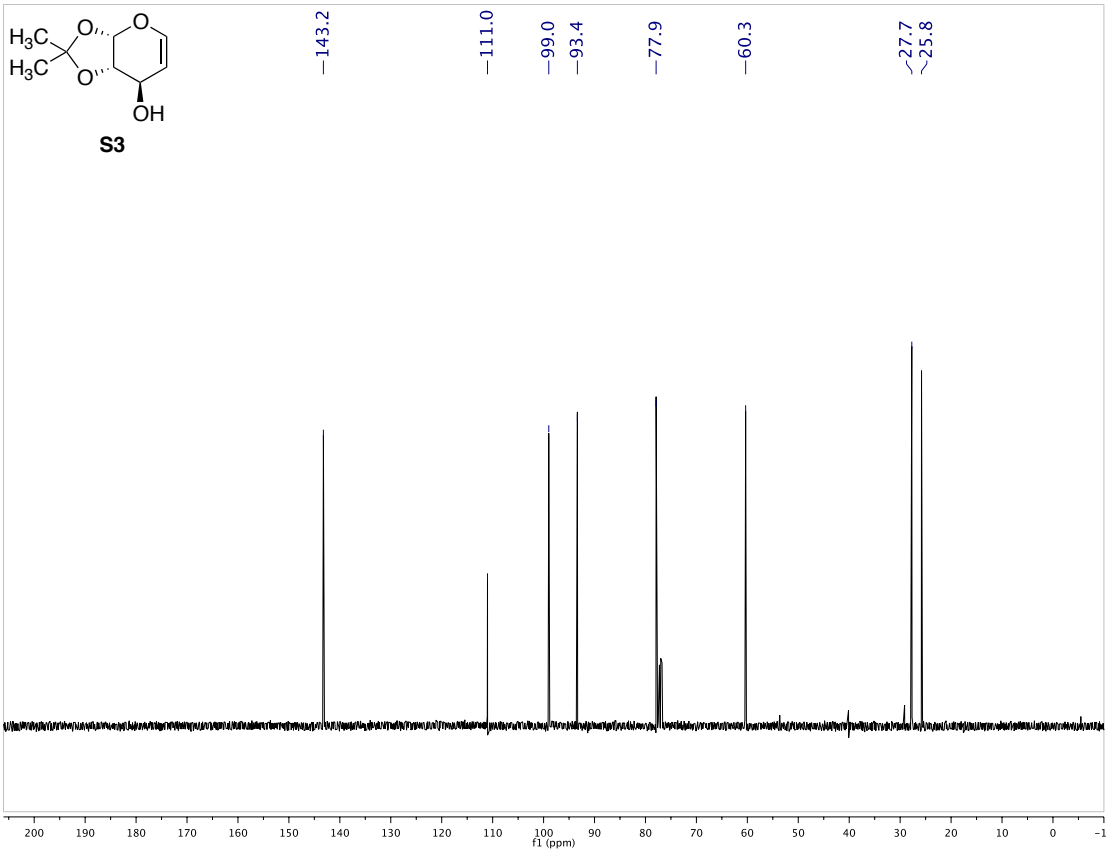
6.33
5.44
5.44
4.96
4.95
4.95
4.94
4.94
4.93
4.93
4.21
4.21
4.20
4.20
4.19
4.18
4.18
2.33
2.32
1.45
1.39
0.68
0.73
0.86
2.00
1.01
3.09
3.60
f1 (ppm)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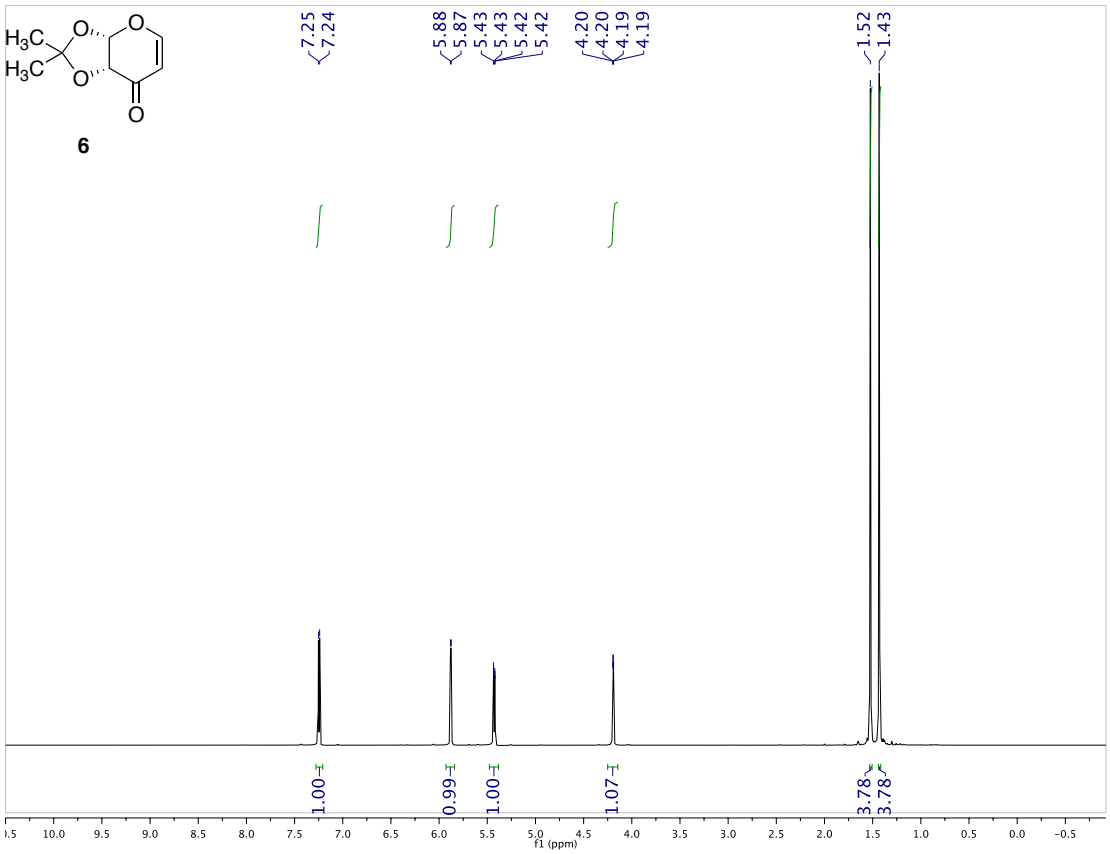
99.0
93.4
77.9
60.3
27.7
25.8
f1 (ppm)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5.42
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4.19
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0.99
1.00
1.07
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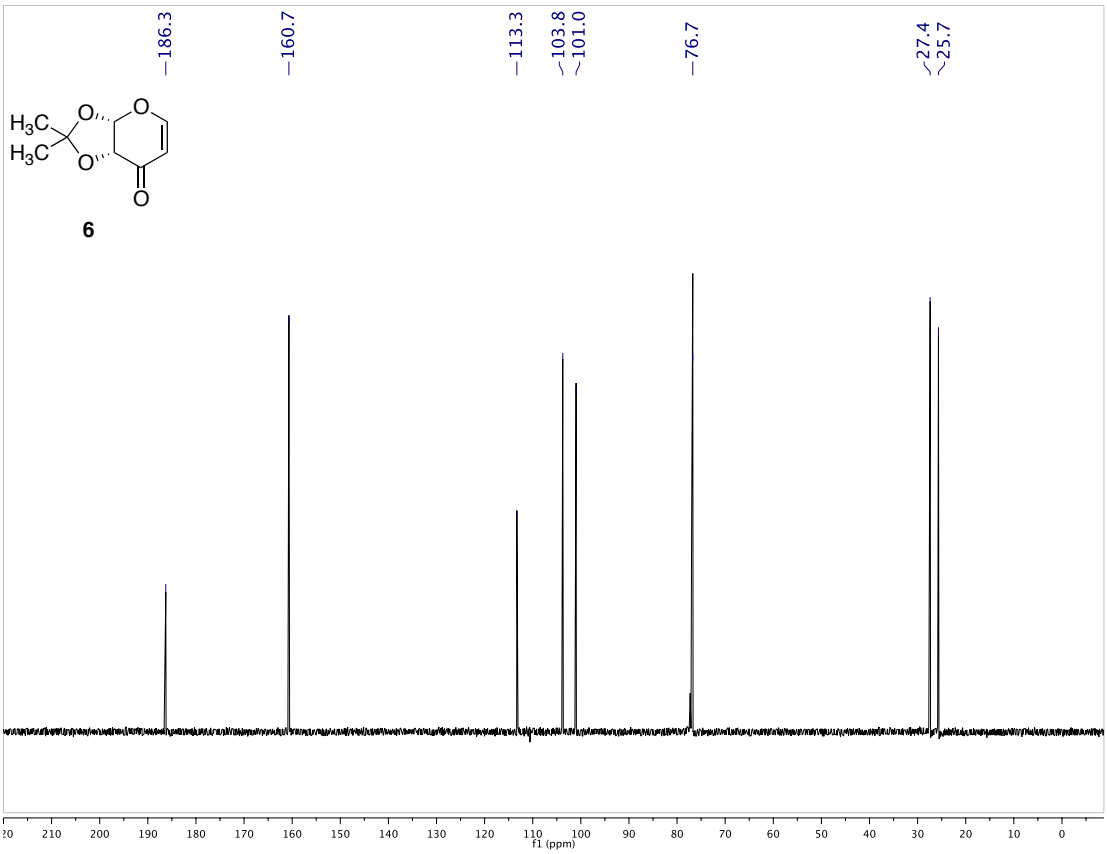
3.78
f1 (ppm)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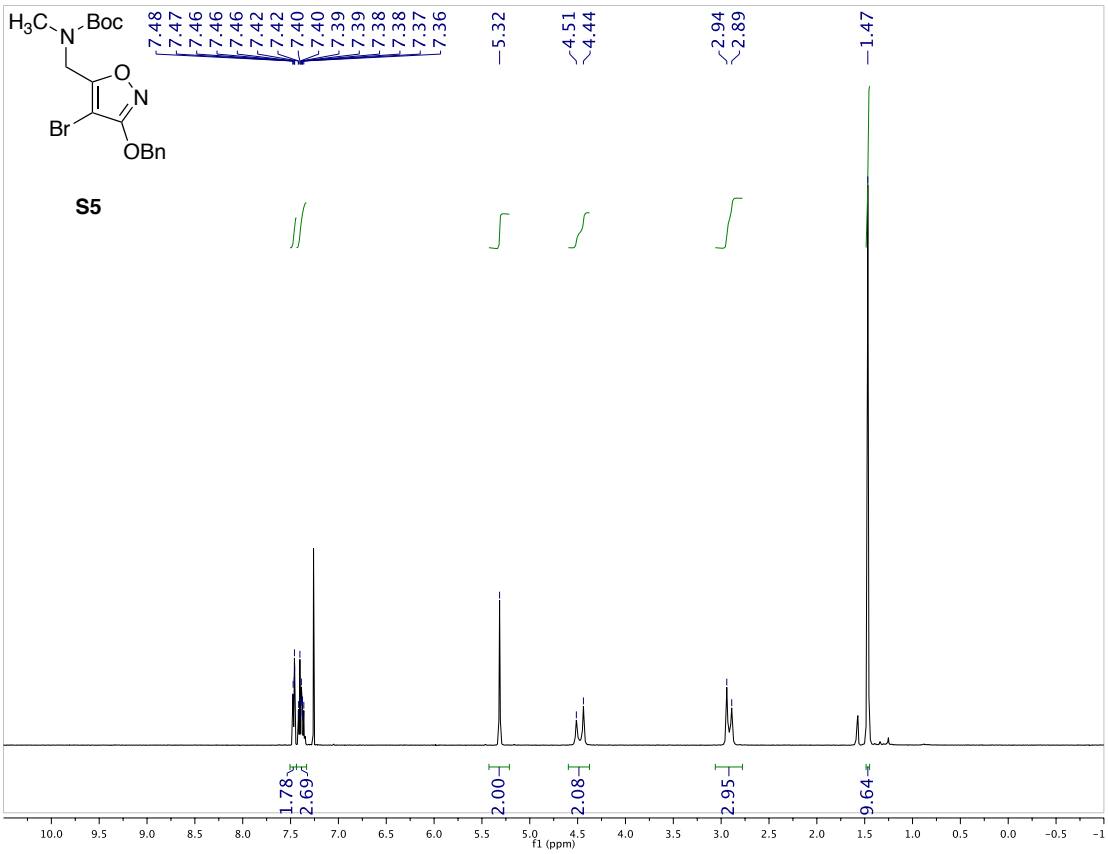
f1 (ppm)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O
N
Br
OBn
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7.42
7.40
7.40
7.39
7.39
7.38
7.38
7.37
7.36
5.32
4.51
4.44
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1.78
2.69
2.00
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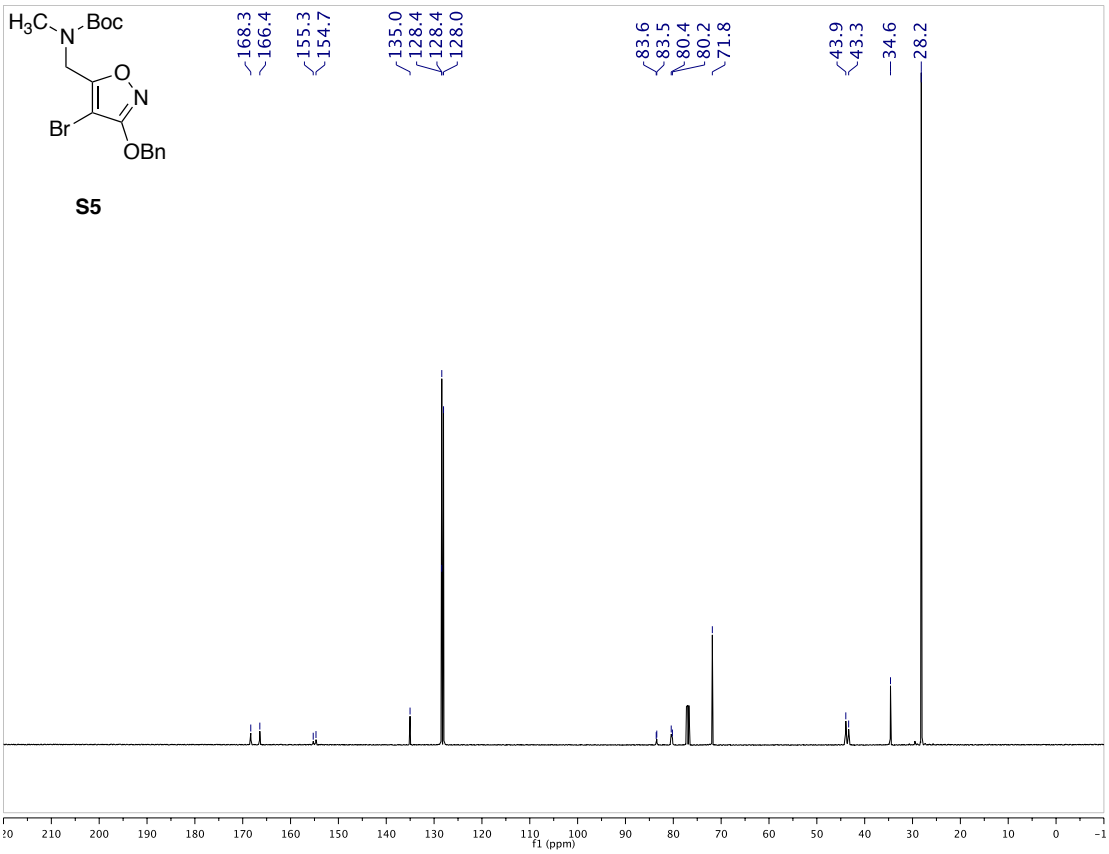
2.95
9.64
f1 (ppm)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Boc
O
N
Br
OBn
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154.7
135.0
128.4
128.4
128.0
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34.6
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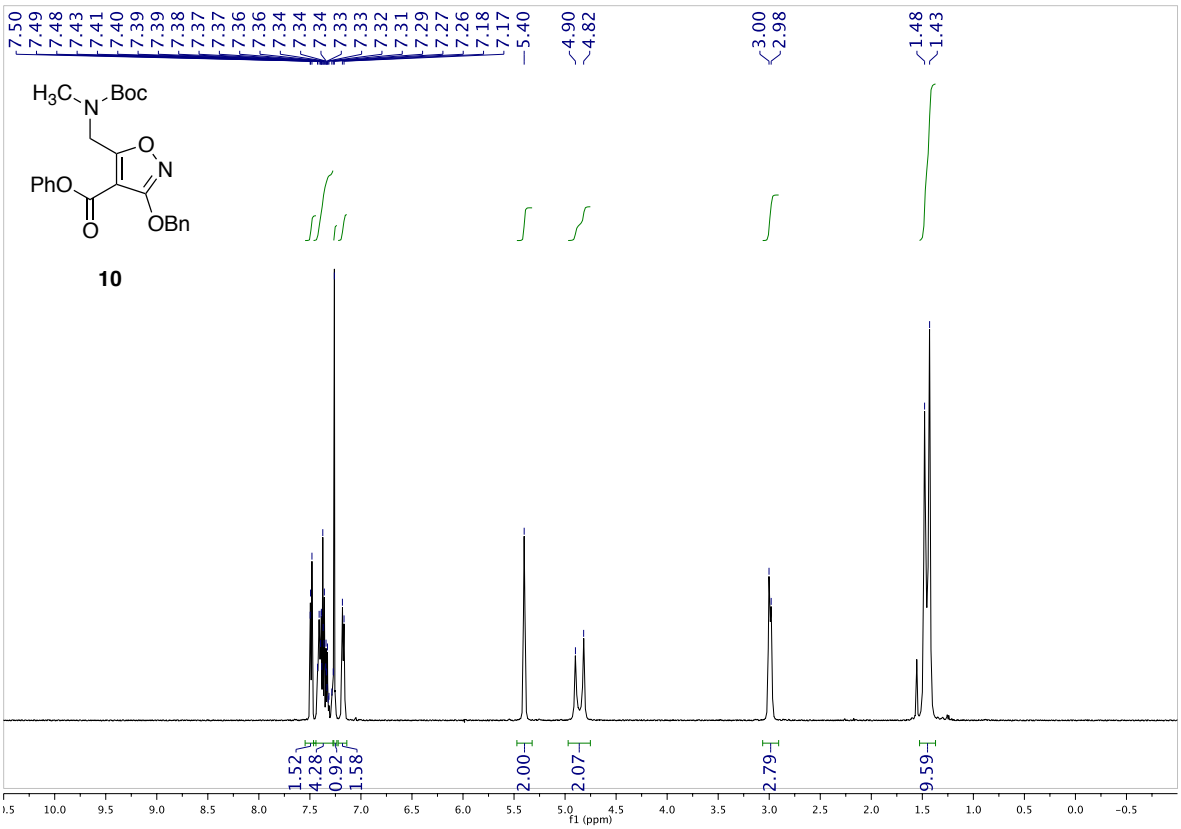
f1 (ppm)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7.34
7.34
7.34
7.33
7.33
7.32
7.31
7.29
7.27
7.26
7.18
7.17
5.40
4.90
4.82
3.00
2.98
1.48
1.43
H3C
N
Boc
O
N
PhO
O
OBn
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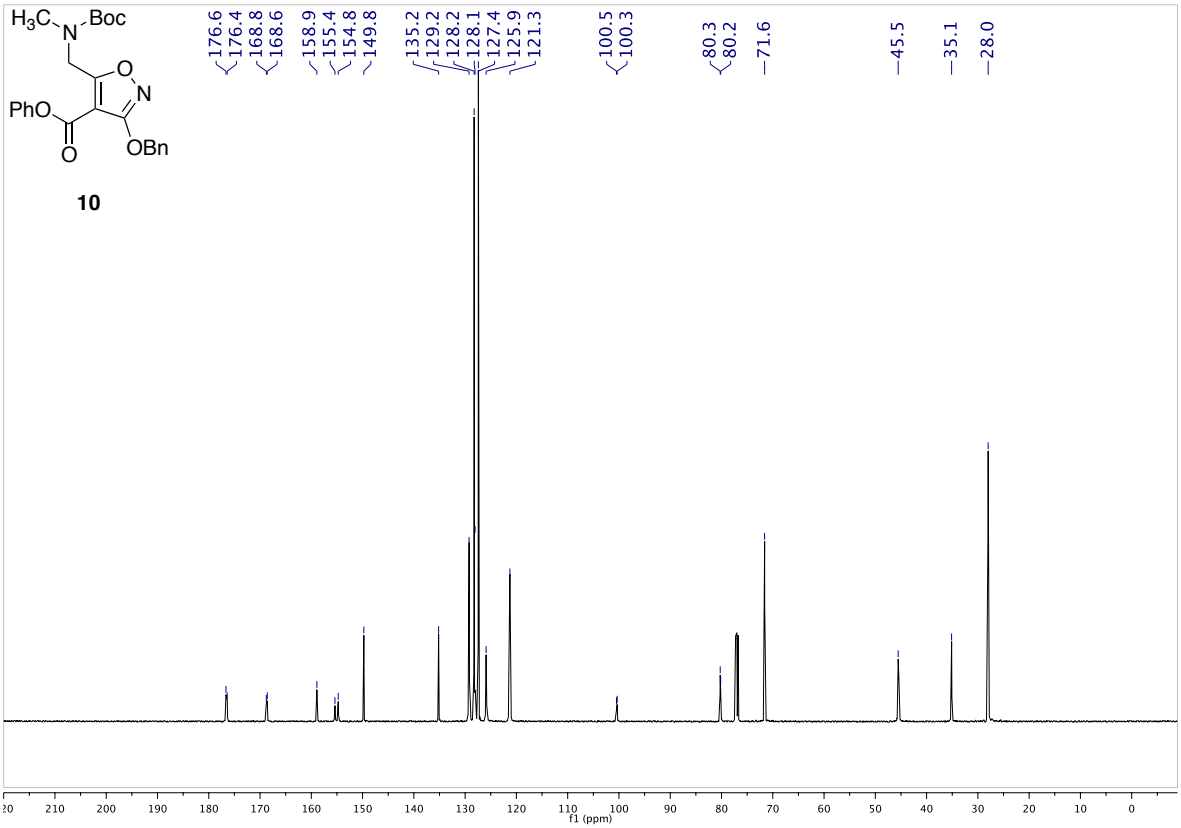
f1 (ppm)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Boc
O
N
PhO
O
OBn
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154.8
149.8
135.2
129.2
128.2
128.1
127.4
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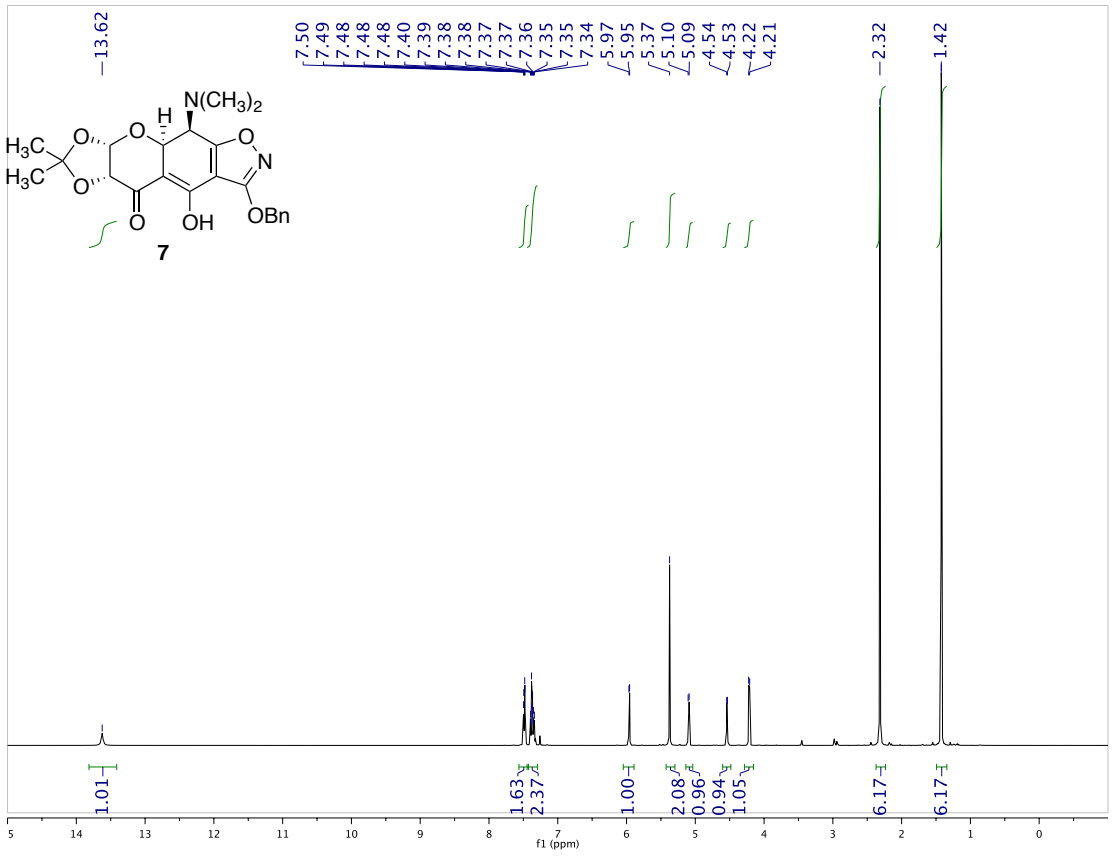
45.5
35.1
28.0
f1 (ppm)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7.36
7.35
7.35
7.34
5.97
5.95
5.37
5.10
5.09
4.54
4.53
4.22
4.21
2.32
1.42
N(CH3)2
H
H3C
H3C
O
O
O
O
O
N
O
OH
OBn
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1.00
2.08
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0.94
1.05
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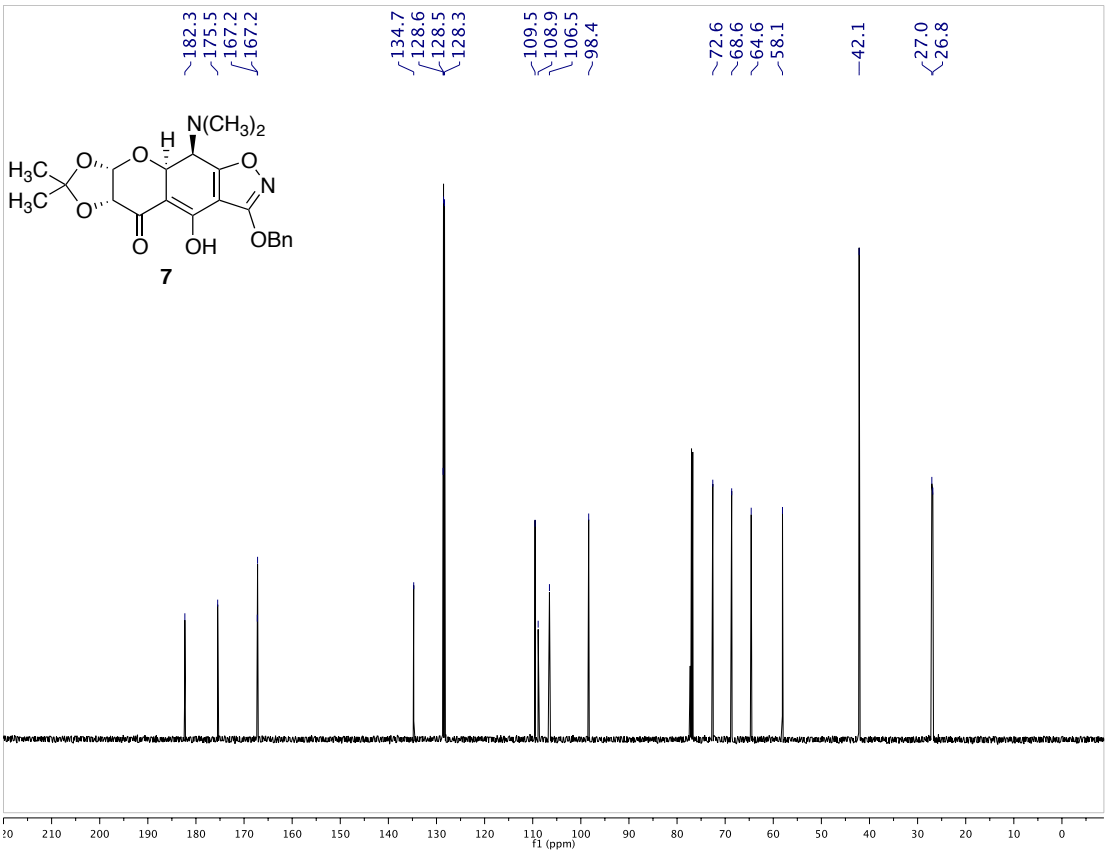
6.17
f1 (ppm)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134.7
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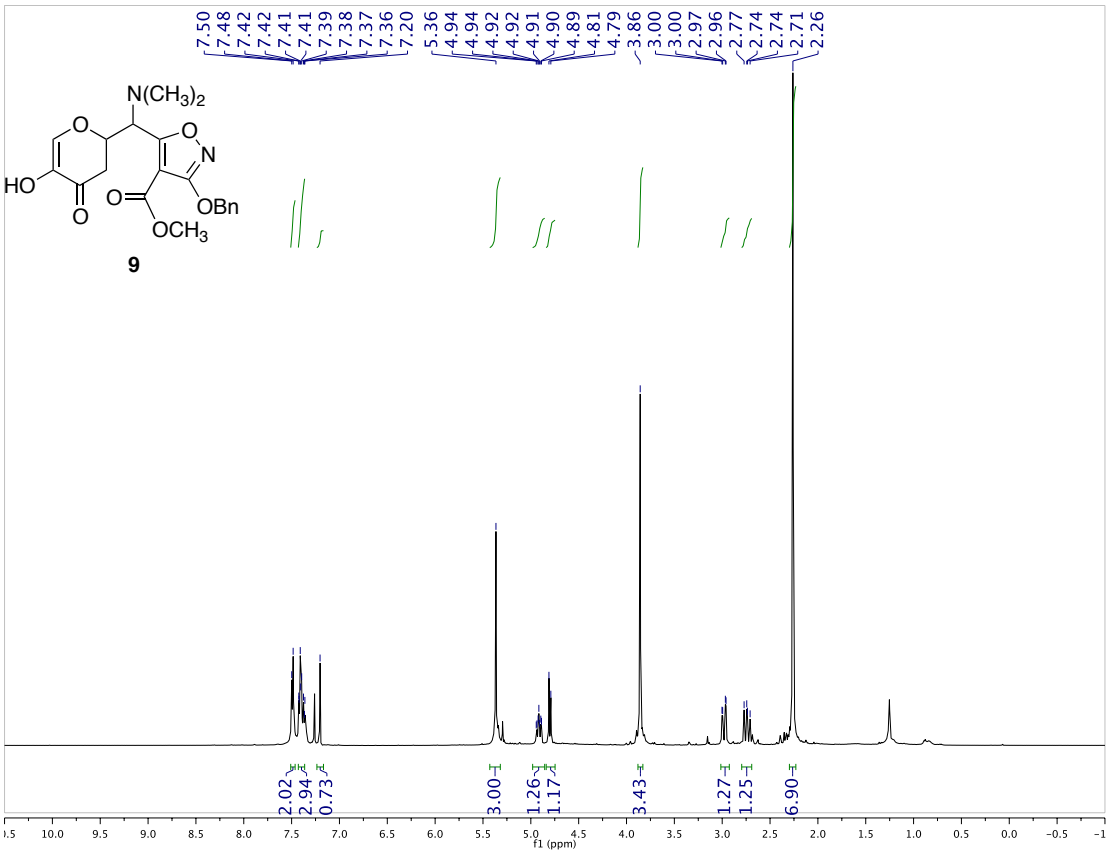
128.3
109.5
108.9
106.5
98.4
72.6
68.6
64.6
58.1
42.1
27.0
26.8
N(CH3)2
H
H3C
H3C
O
O
O
O
O
N
O
OH
OBn
7
f1 (ppm)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7.36
7.20
5.36
4.94
4.94
4.92
4.92
4.91
4.90
4.89
4.81
4.79
3.86
3.00
3.00
2.97
2.96
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2.71
2.26
N(CH3)2
HO
O
O
O
N
O
OBn
OCH3
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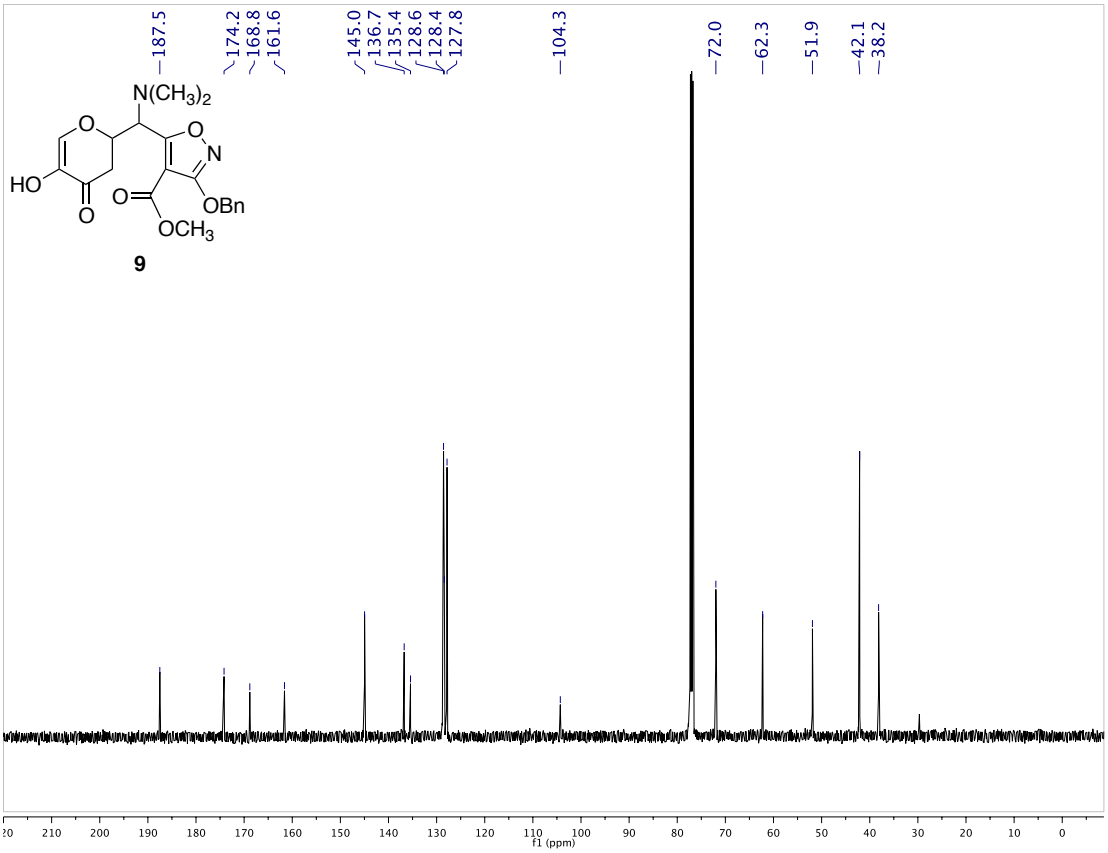
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135.4
128.6
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127.8
104.3
72.0
62.3
51.9
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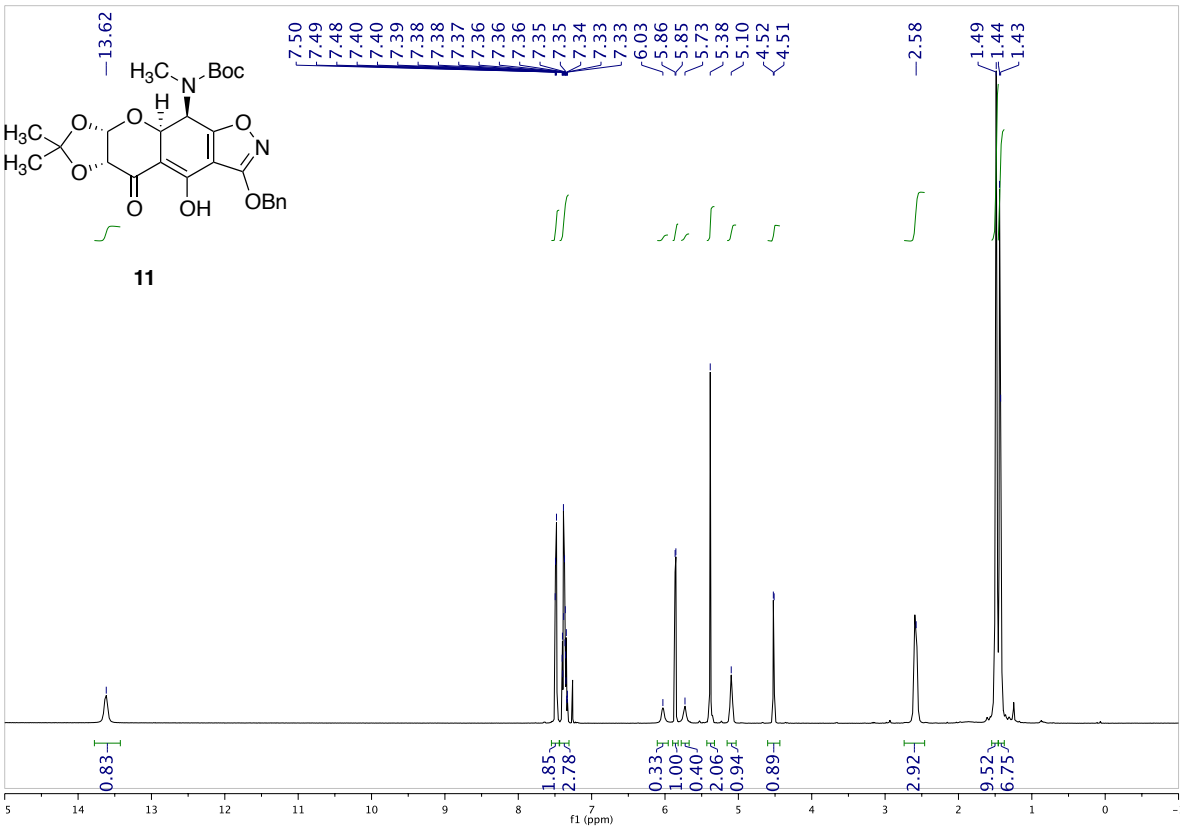
38.2
N(CH3)2
HO
O
O
O
N
O
OBn
OCH3
9
f1 (ppm)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5.86
5.85
5.73
5.38
5.10
4.52
4.51
2.58
1.49
1.44
1.43
0.83
1.85
2.78
0.33
1.00
0.40
2.06
0.94
0.89
2.92
9.52
6.75
f1 (ppm)
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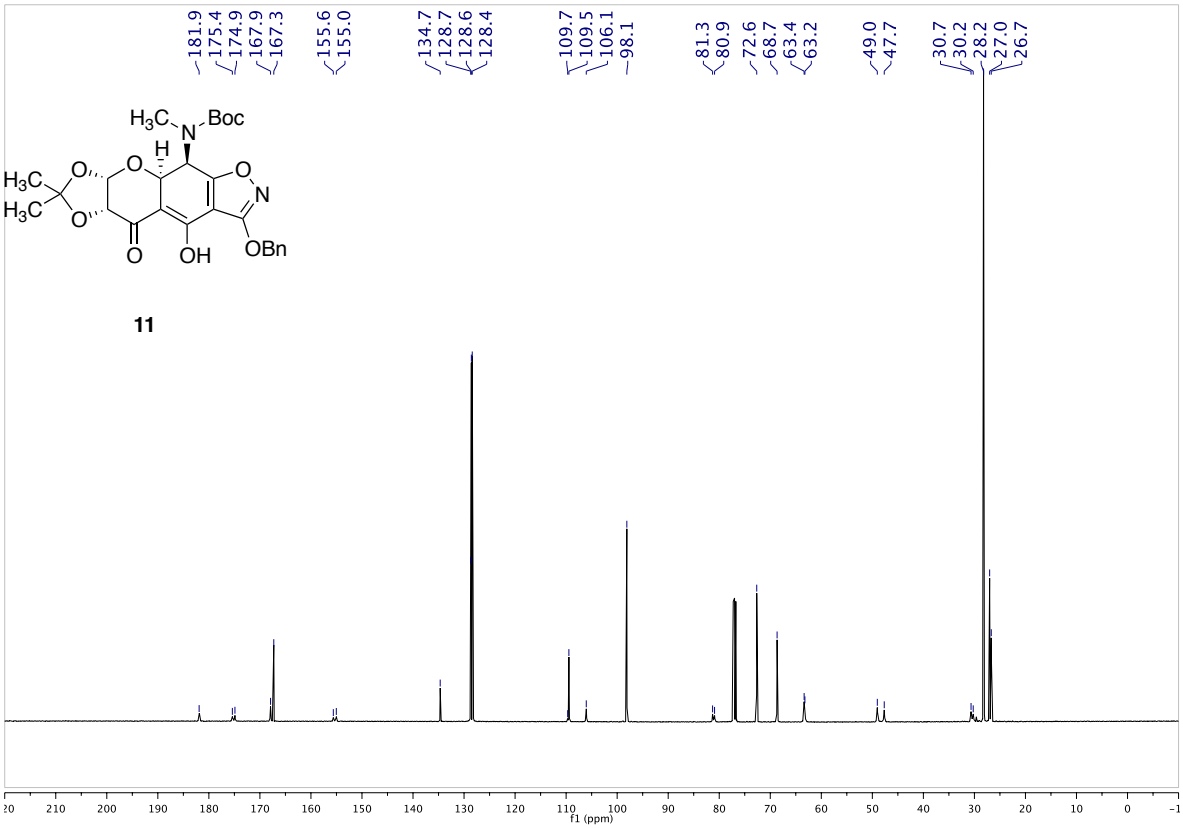
Boc
H
O
O
H3C
H3C
O
O
O
N
O
OH
OBn
11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109.5
106.1
98.1
81.3
80.9
72.6
68.7
63.4
63.2
49.0
47.7
30.7
30.2
28.2
27.0
26.7
f1 (ppm)
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O
O
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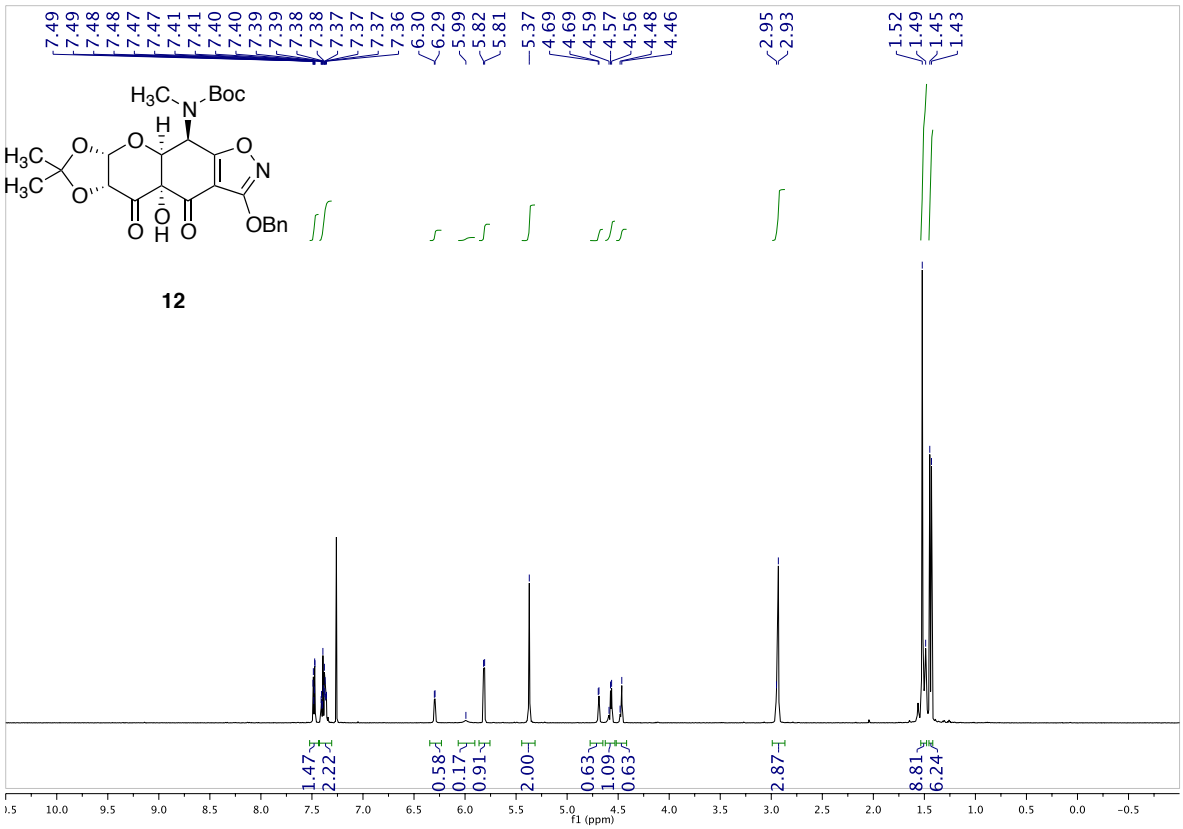
O
O
O
N
O
OH
OBn
11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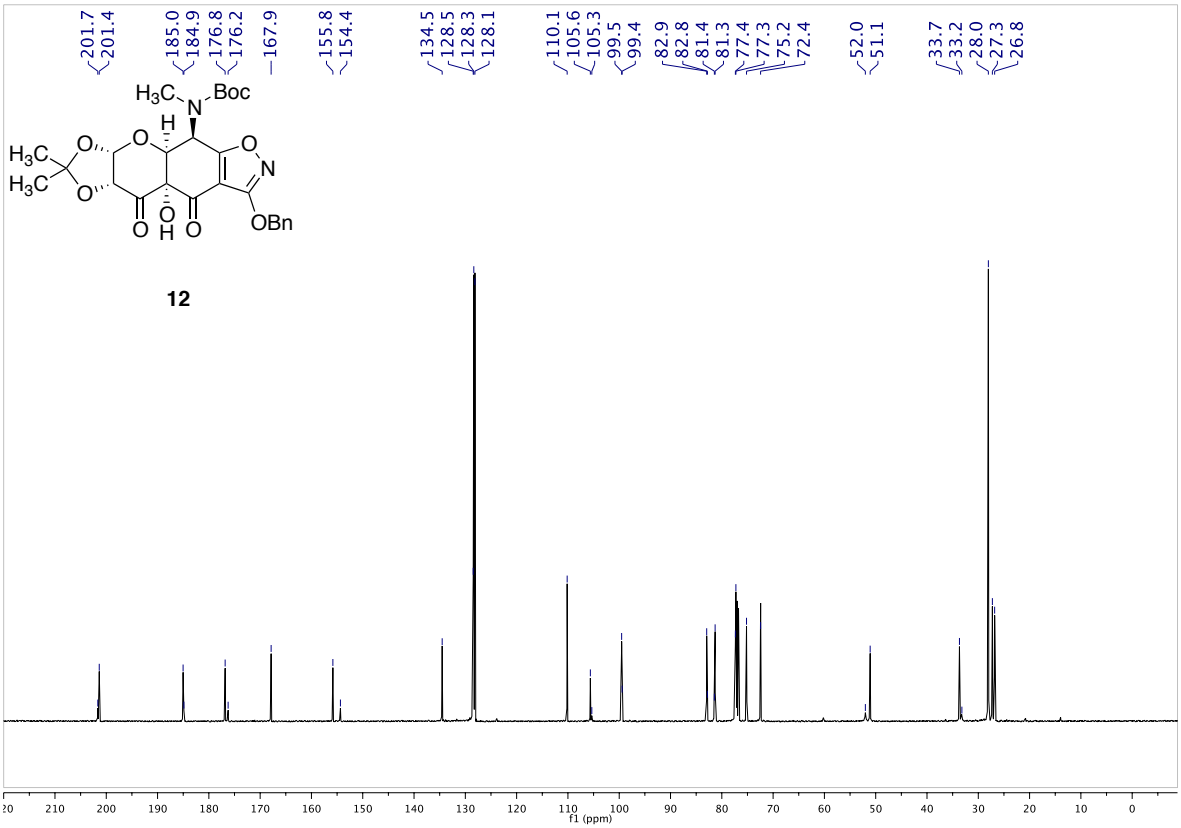
H3C N Boc H O O H3C H3C O O O H O O O N OBn
12
1.47 2.22 0.58 0.17 0.91 2.00 0.63 1.09 0.63 2.87 8.81 6.24
f1 (ppm)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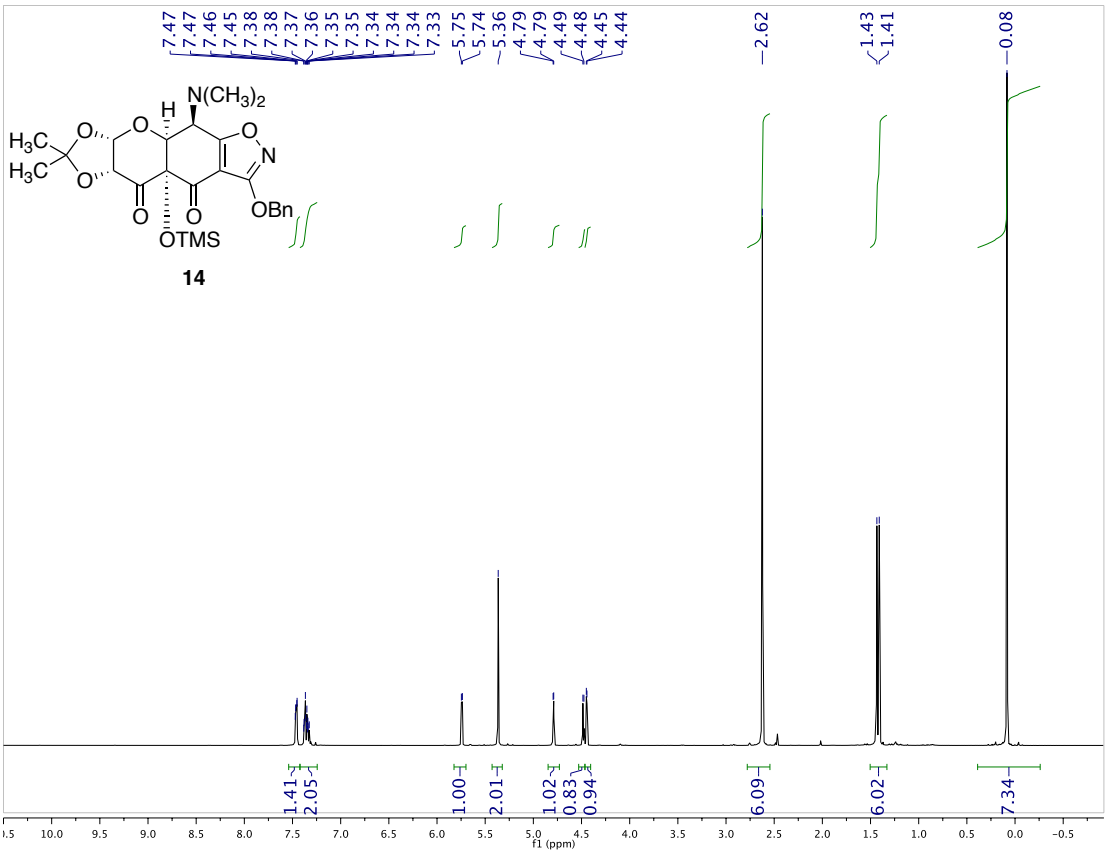
f1 (ppm)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5.75
5.74
5.36
4.79
4.79
4.49
4.48
4.45
4.44
2.62
1.43
1.41
0.08
N(CH3)2
H
H3C
H3C
O
O
O
O
O
N
O
O
OBn
OTMS
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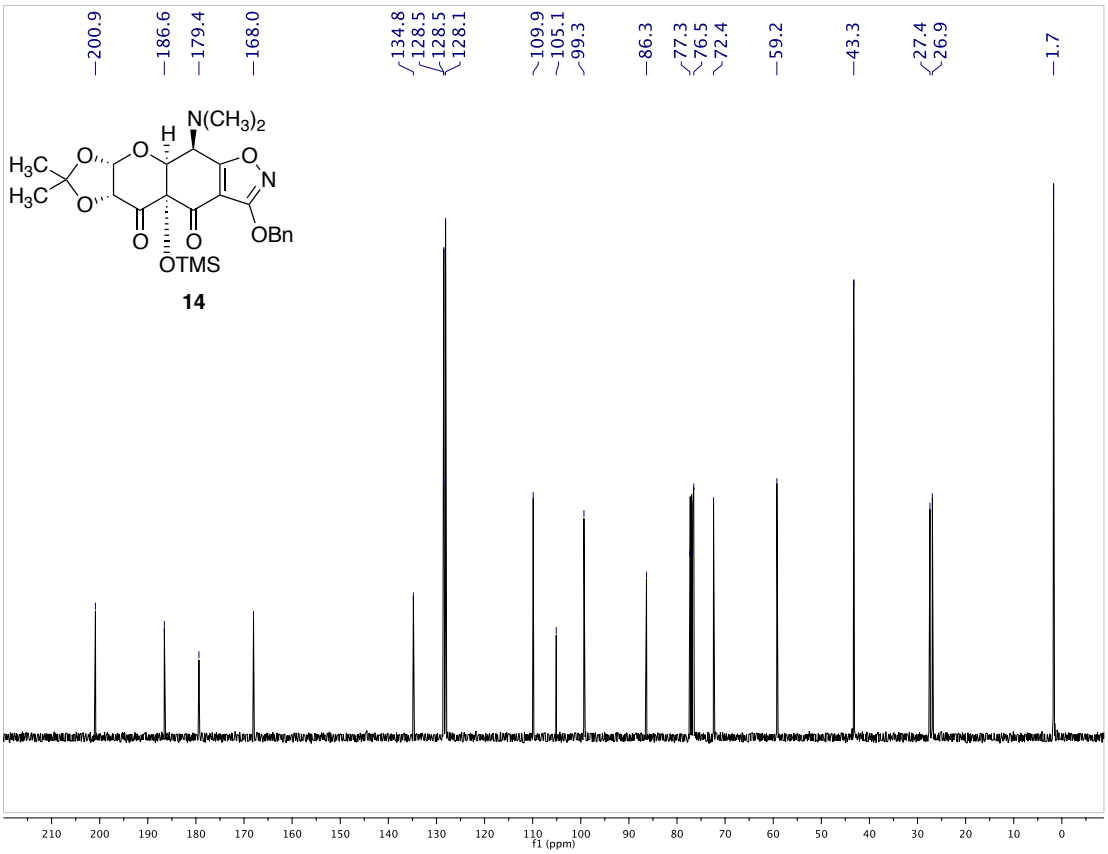
1.00
2.01
1.02
0.83
0.94
6.09
6.02
7.34
f1 (ppm)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105.1
99.3
86.3
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76.5
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59.2
43.3
27.4
26.9
1.7
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O
O
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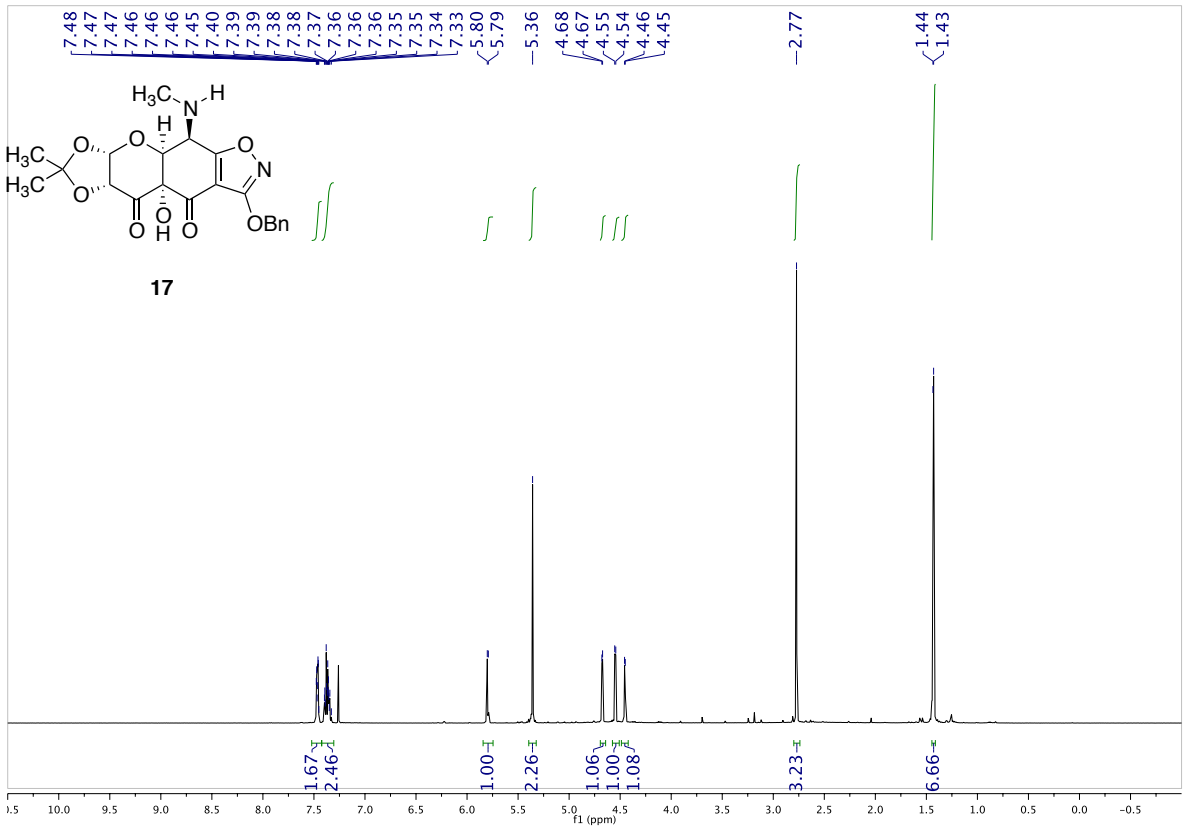
OTMS
14
f1 (ppm)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O
O
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O
H
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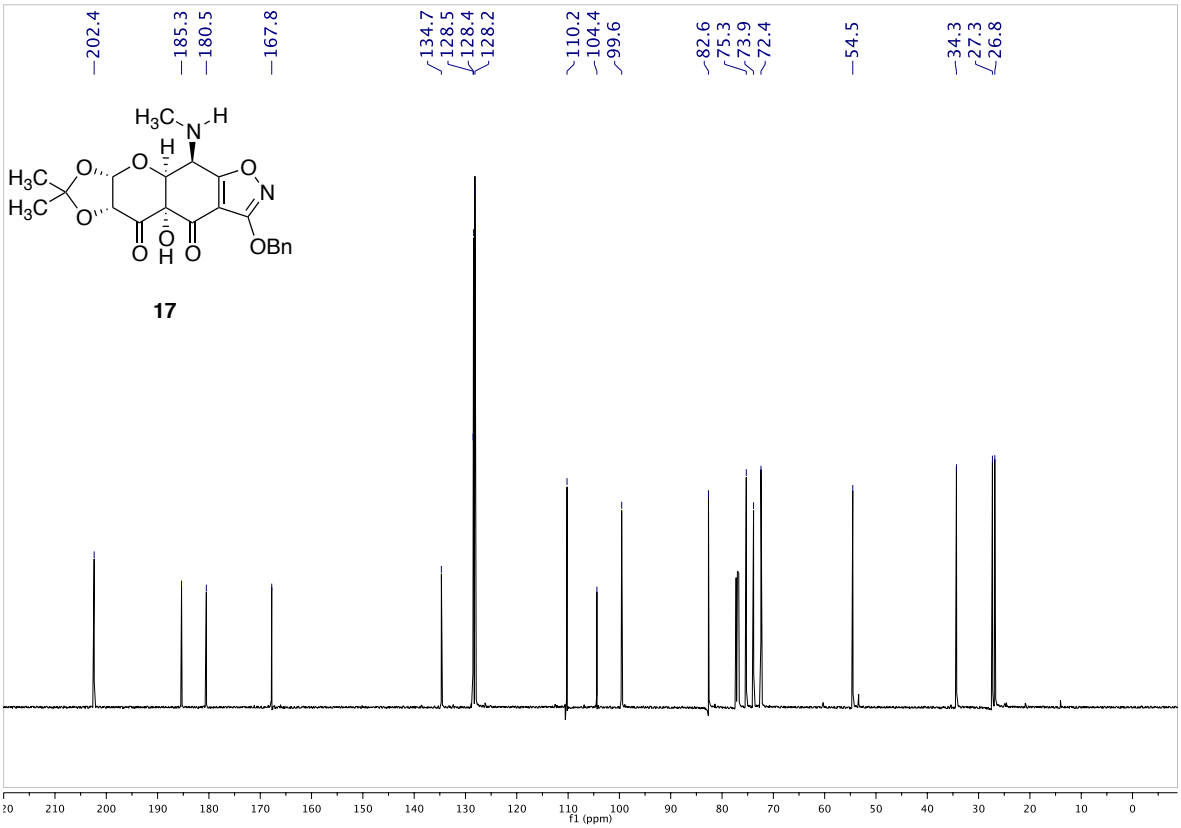
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27.3
26.8
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H3C
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O
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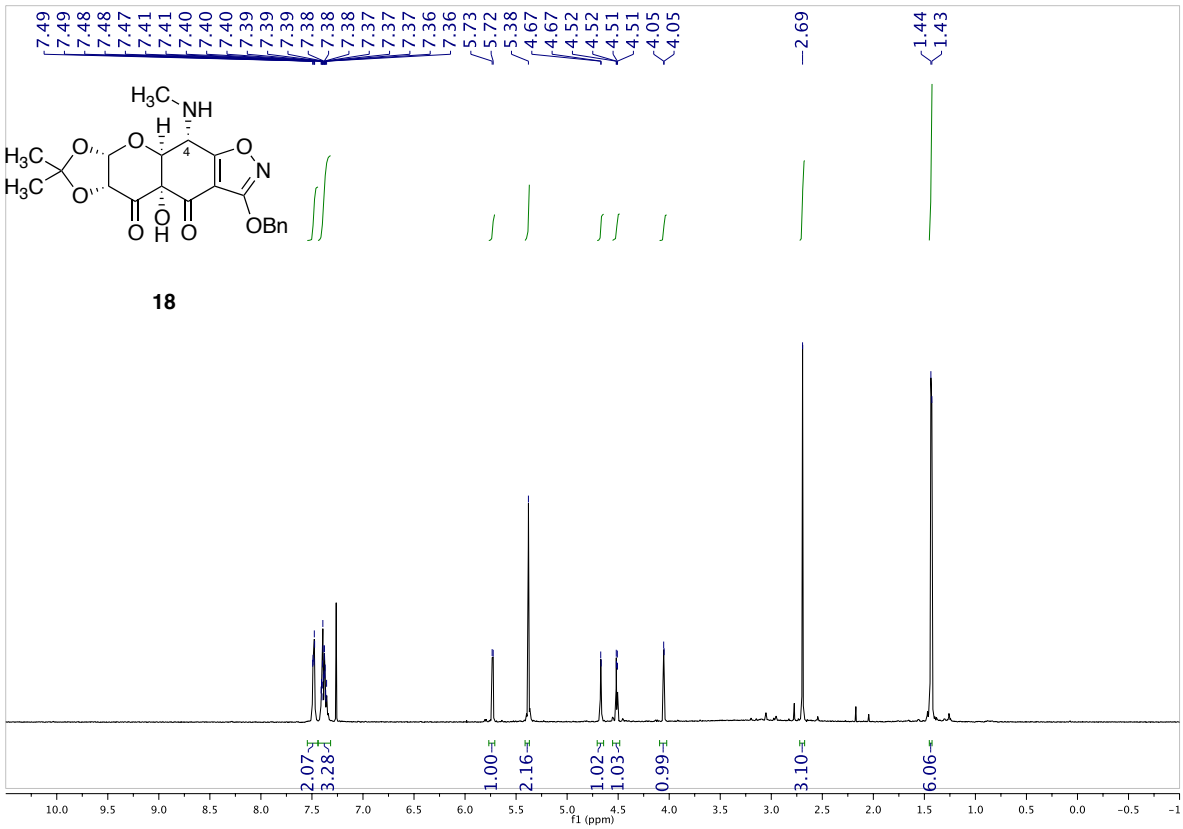
OBn
17
f1 (ppm)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4.05
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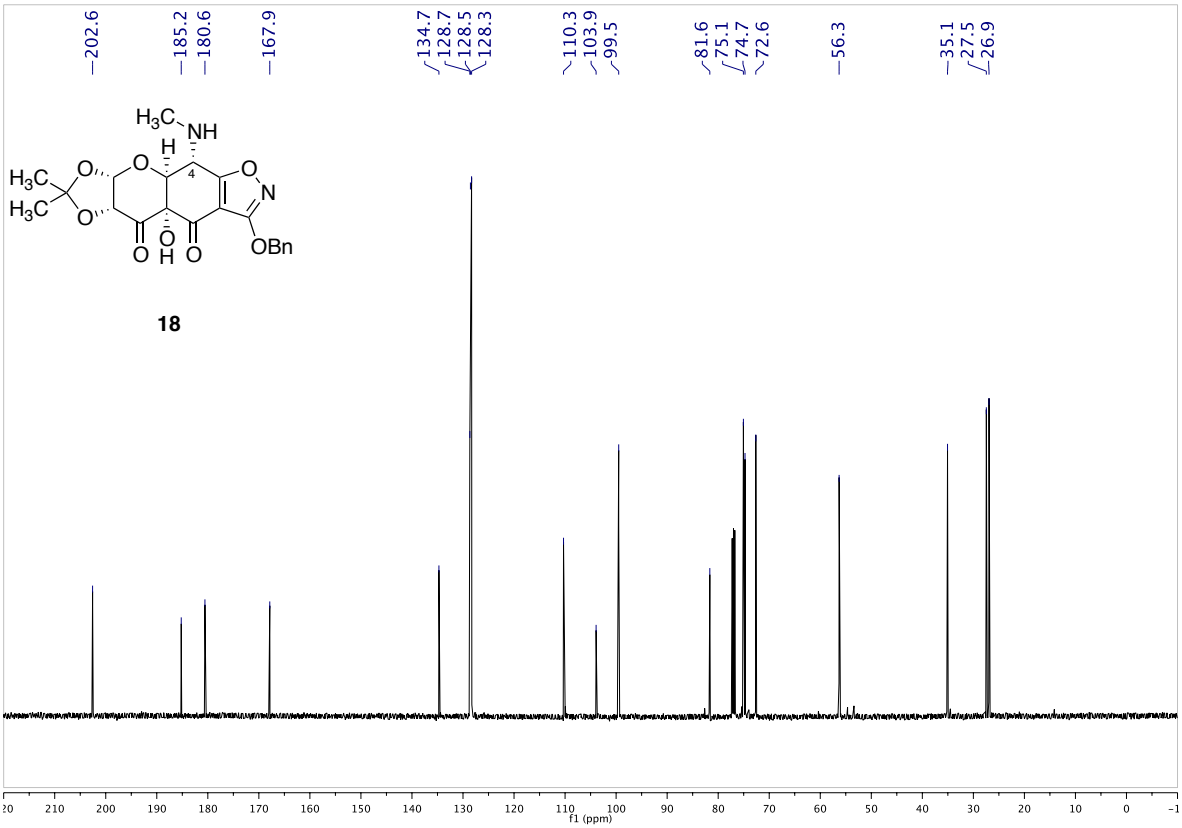
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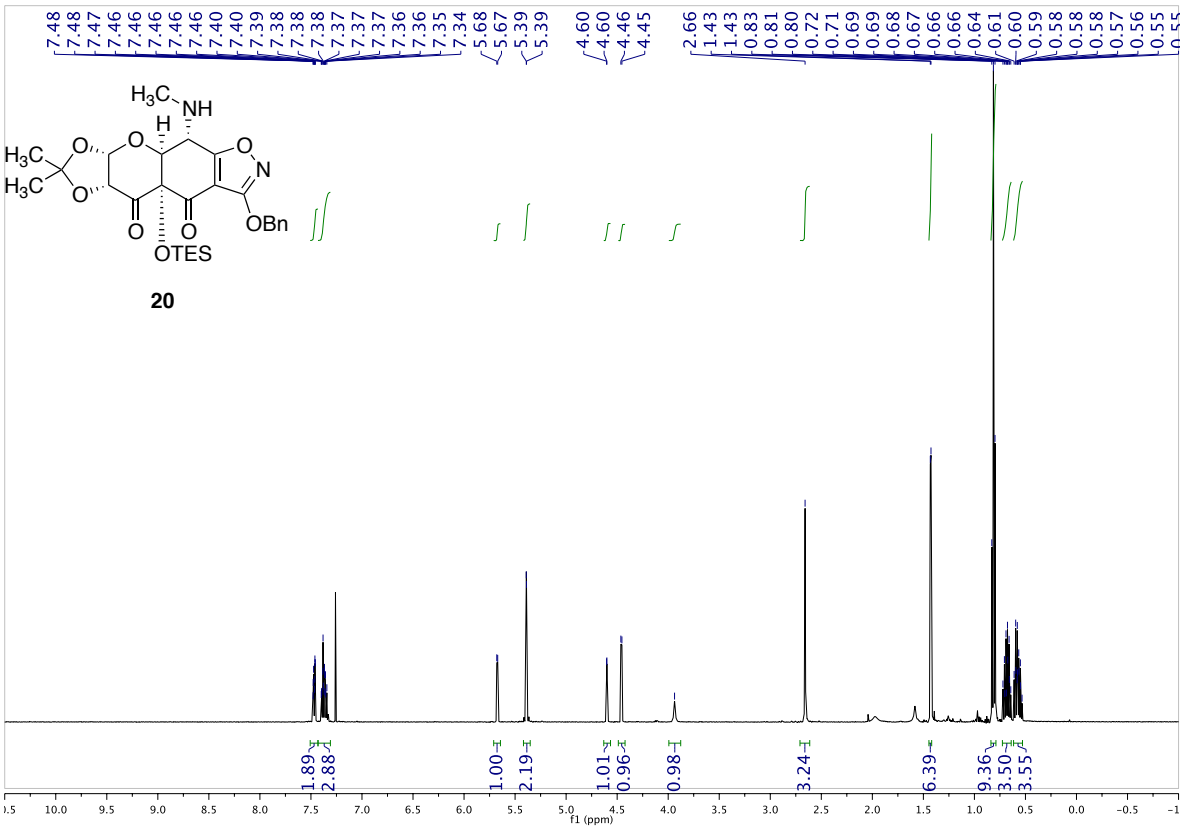
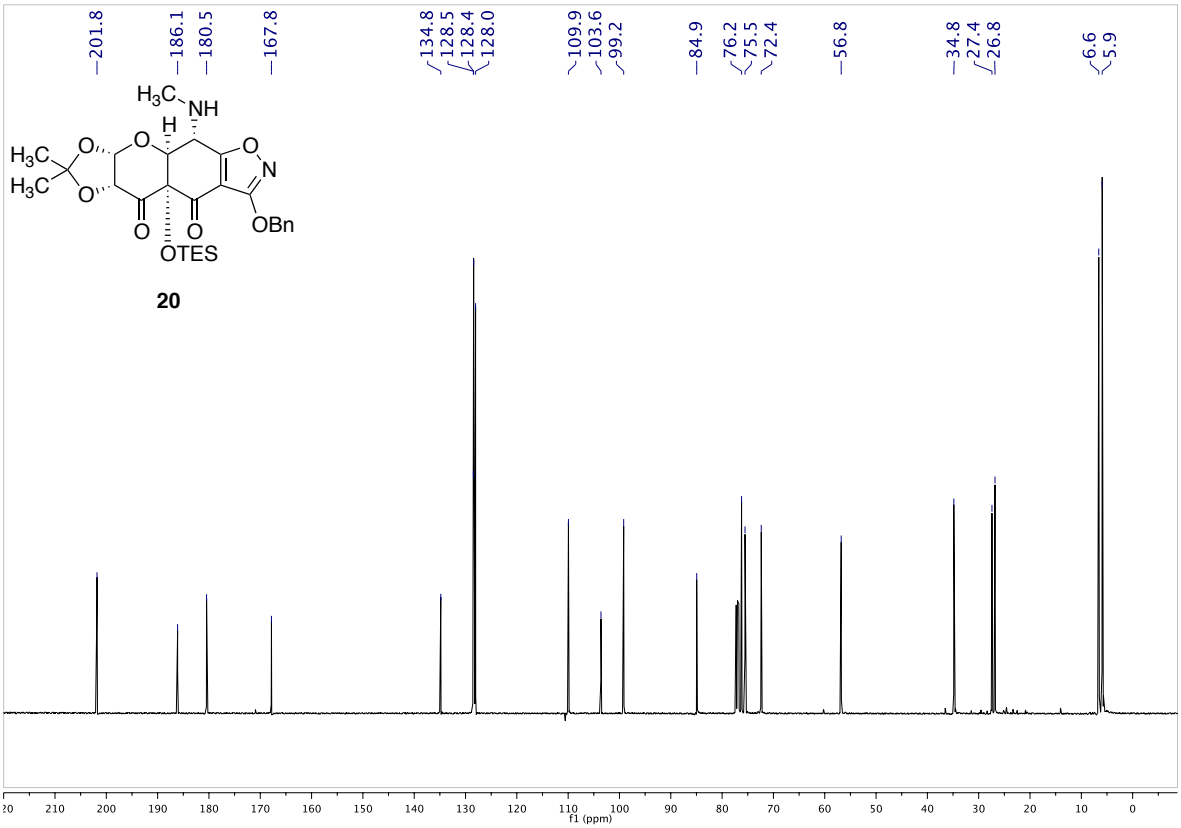
72.6
56.3
35.1
27.5
26.9
18
f1 (ppm)


20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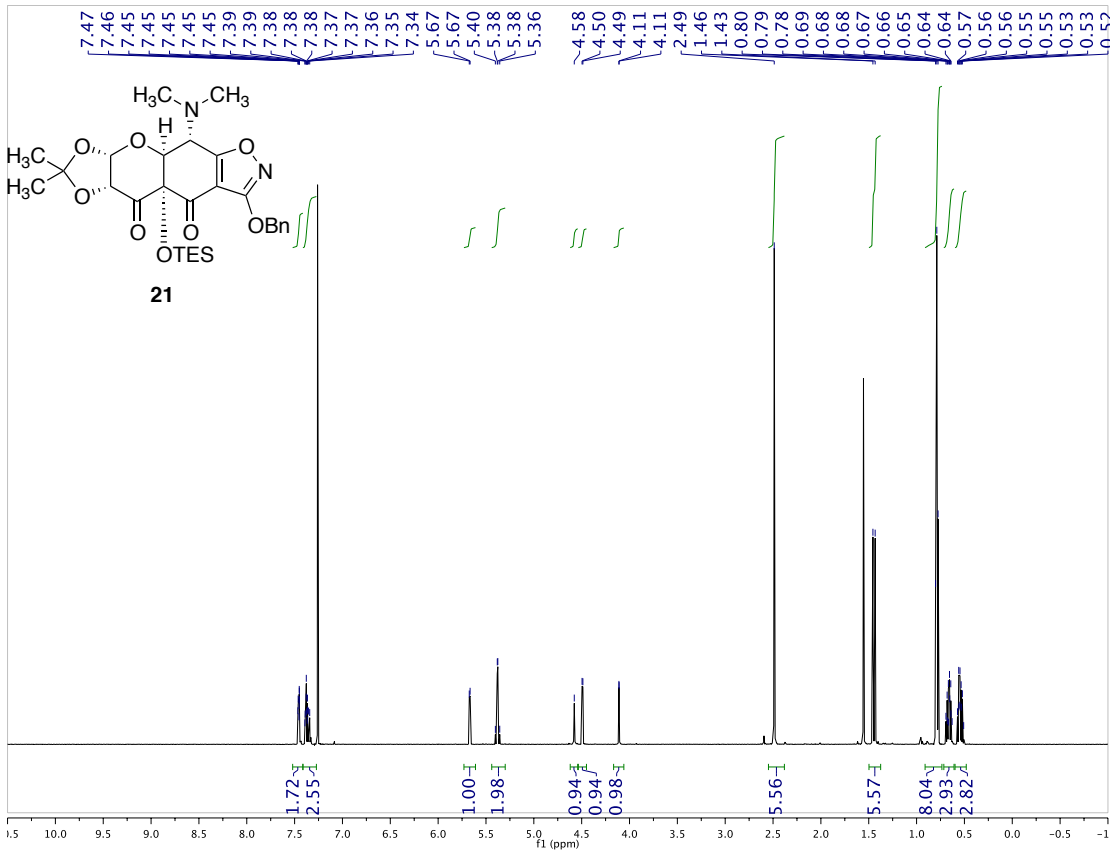
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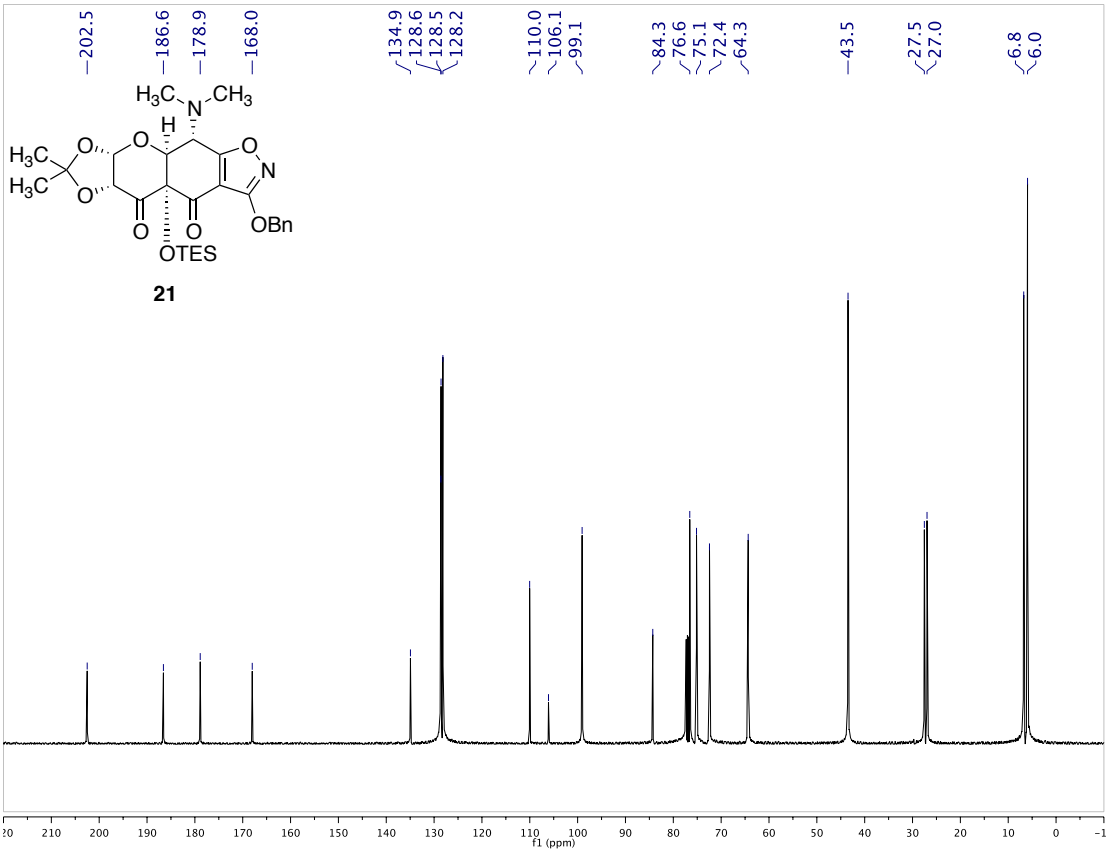
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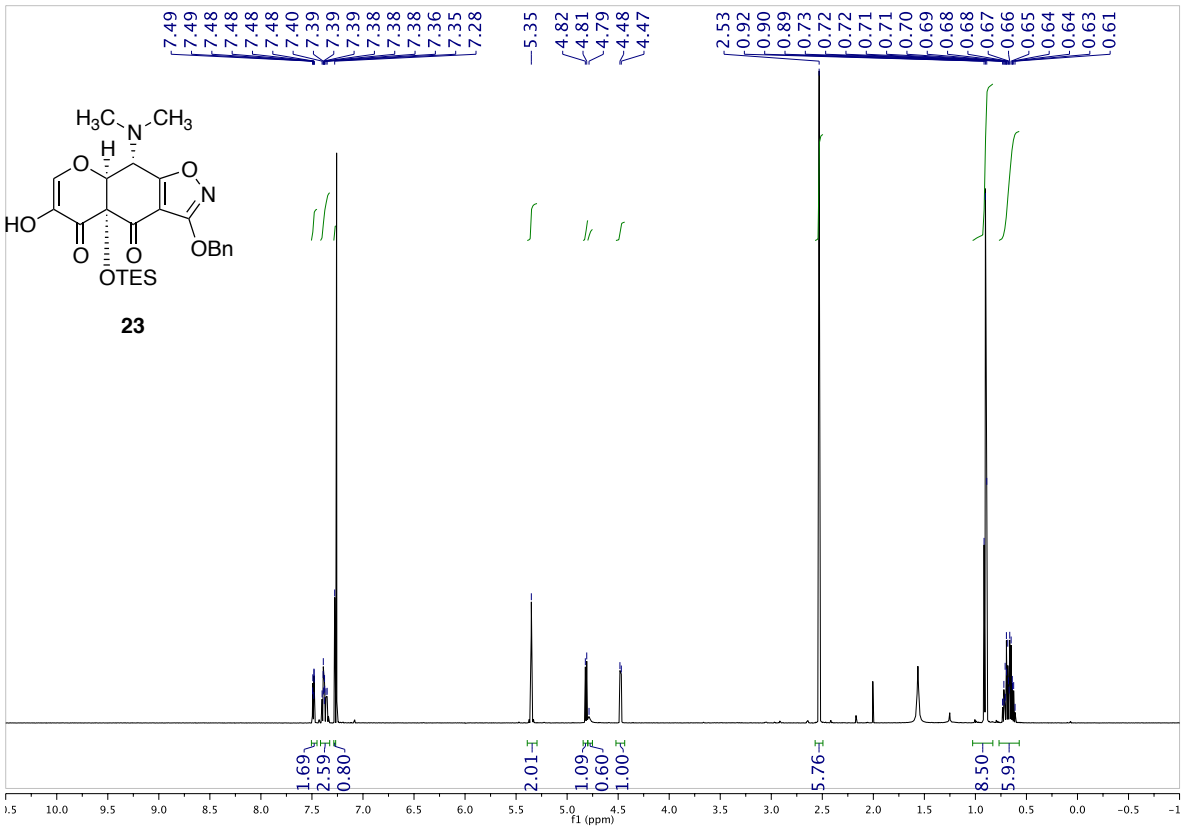
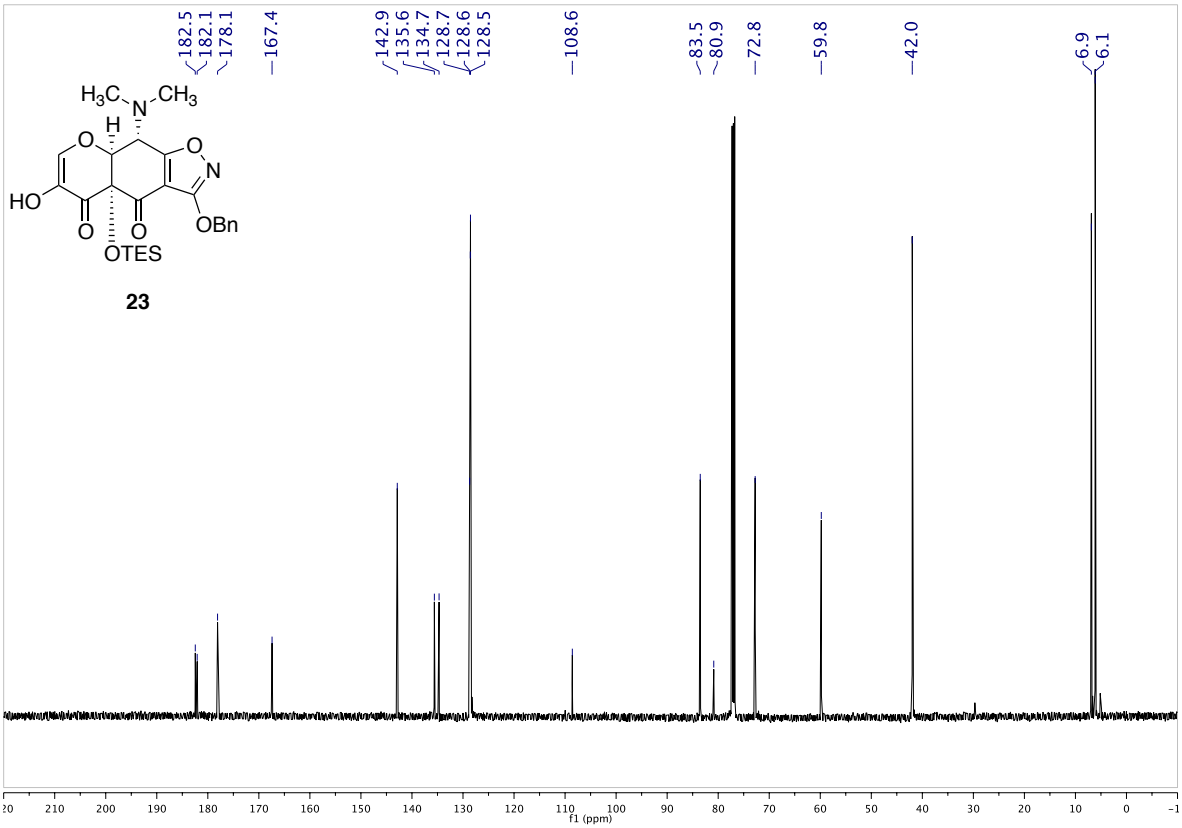

7.49
7.49
7.48
7.48
7.48
7.48
7.40
7.39
7.39
7.39
7.38
7.38
7.38
7.36
7.35
7.28
5.35
4.82
4.81
4.79
4.48
4.47
2.53
0.92
0.90
0.89
0.73
0.72
0.72
0.71
0.71
0.70
0.69
0.68
0.68
0.67
0.66
0.65
0.64
0.64
0.63
0.61
1.69
2.59
0.80
2.01
1.09
0.60
1.00
5.76
8.50
5.93
f1 (ppm)

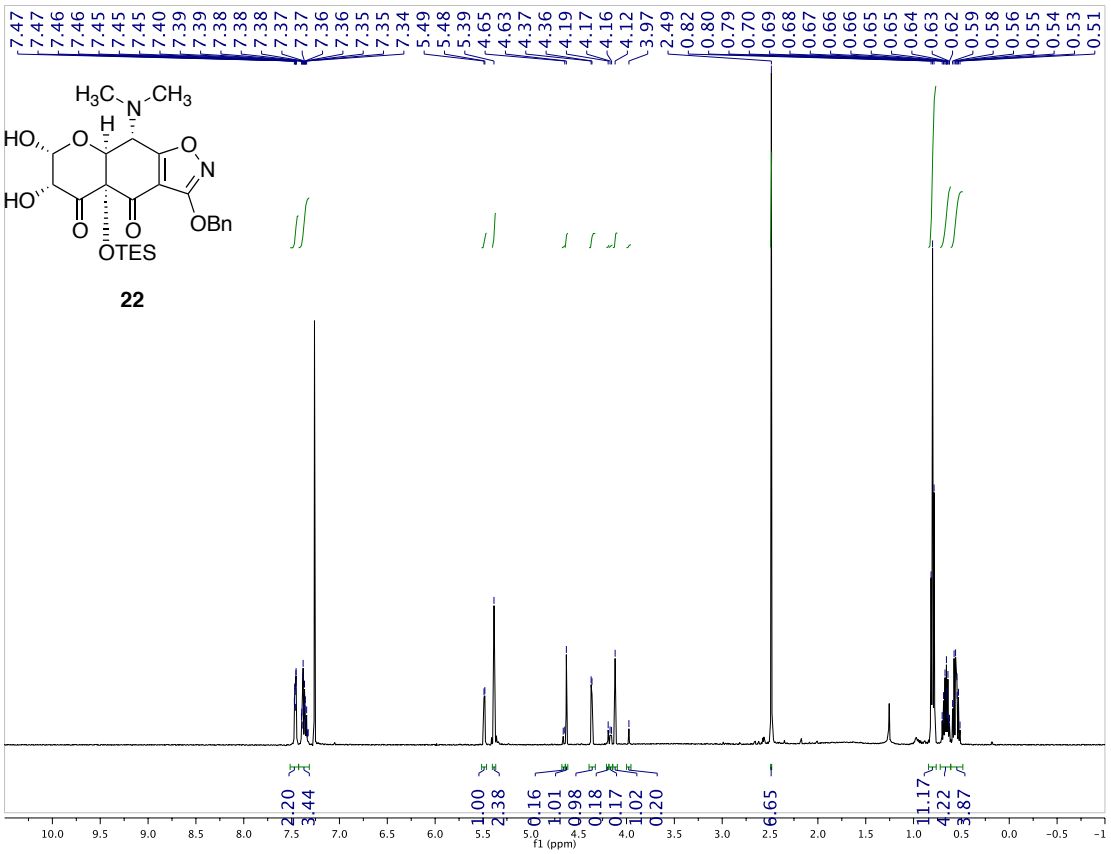
H3C
N
CH3
H
O
O
N
HO
O
O
OBn
OTES

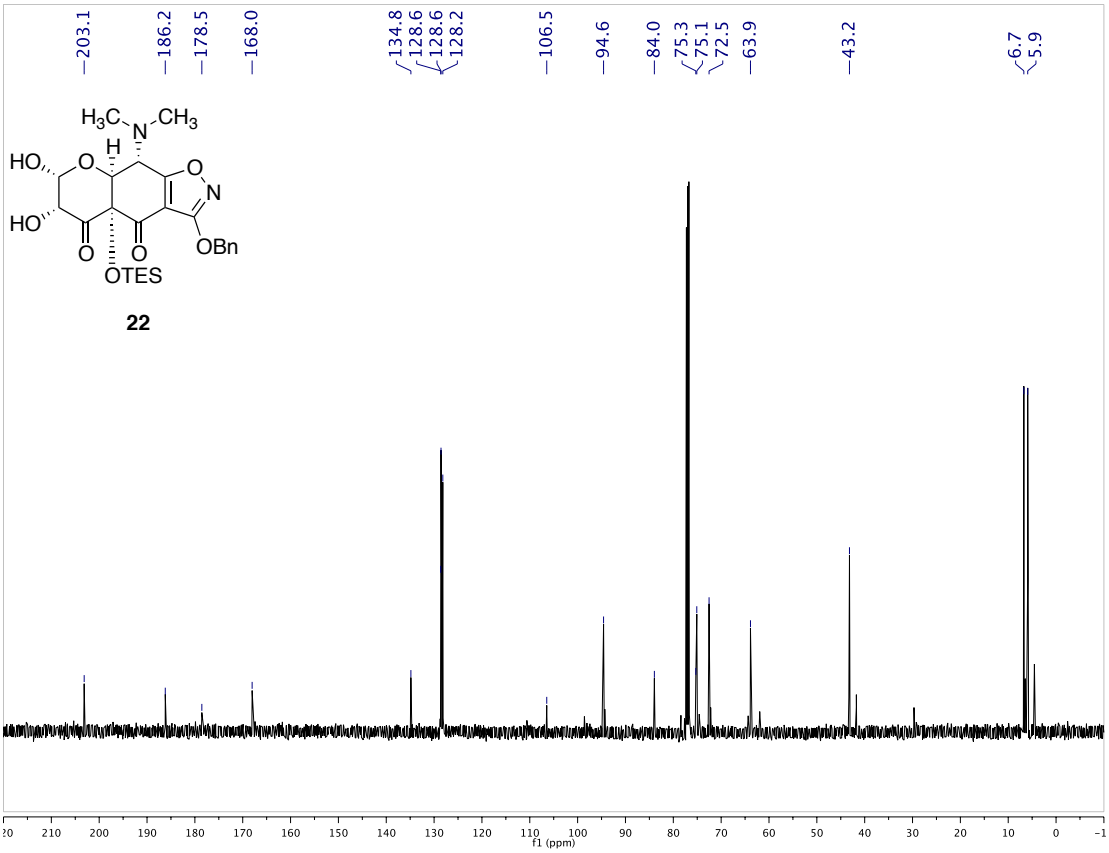
23

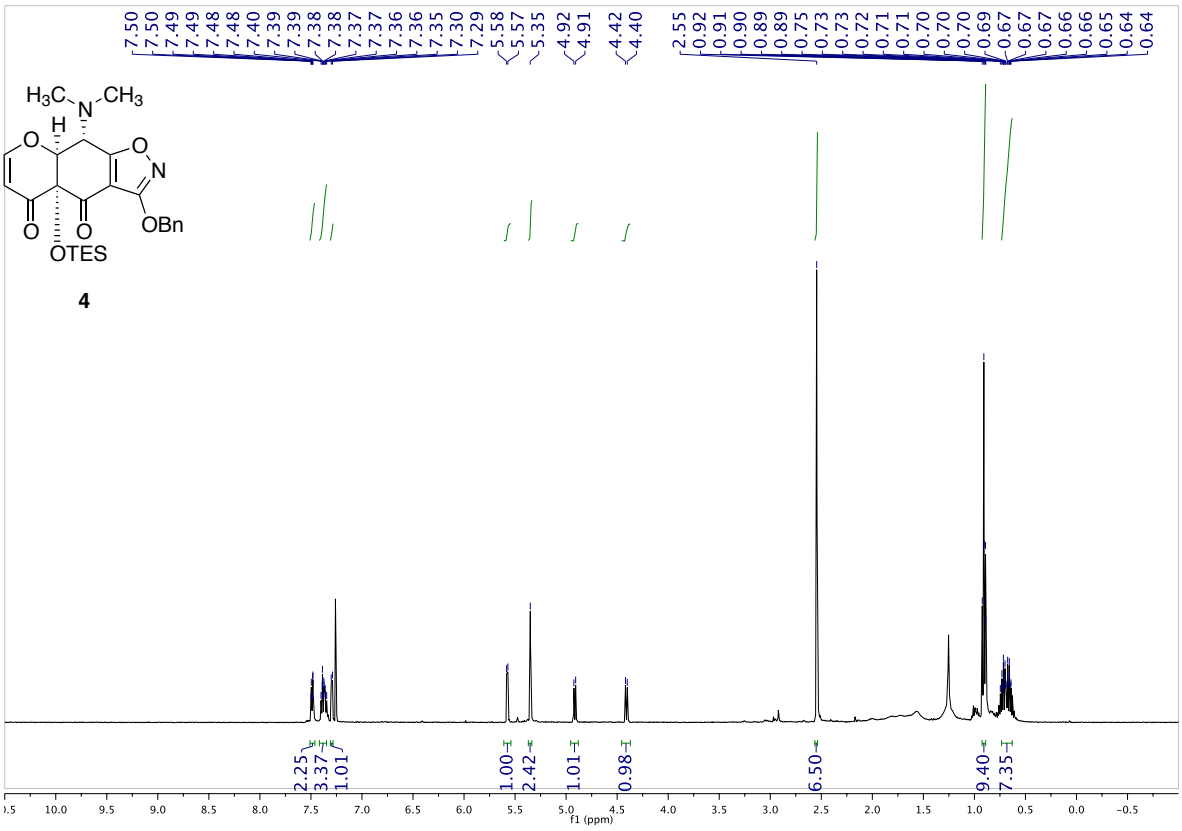

182.5
182.1
178.1
167.4
142.9
135.6
134.7
128.7
128.6
128.5
108.6
83.5
80.9
72.8
59.8
42.0
6.9
6.1
f1 (ppm)

H3C
N
CH3
H
O
O
N
HO
O
O
OBn
OTES

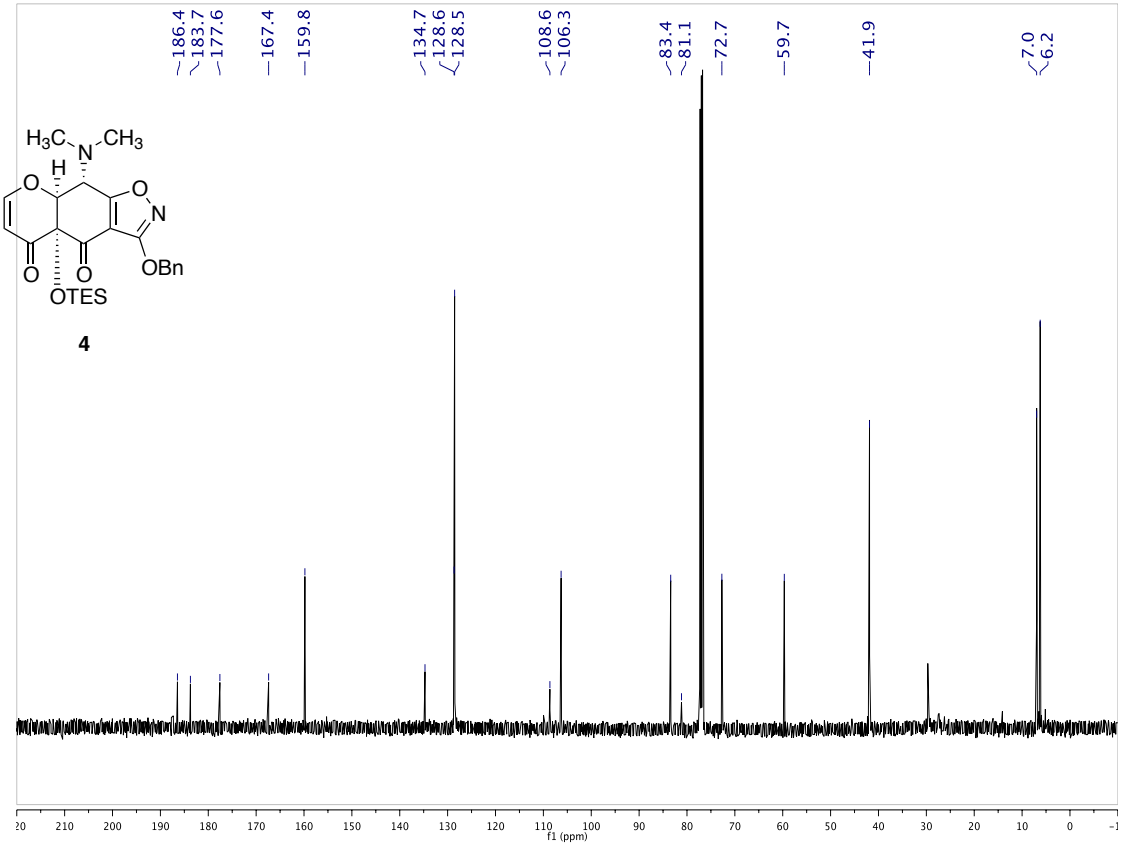
23


7.47 7.47 7.46 7.46 7.45 7.45 7.45 7.40 7.39 7.39 7.38 7.38 7.38 7.37 7.37 7.36 7.36 7.35 7.35 7.34 5.49 5.48 5.39 4.65 4.63 4.37 4.36 4.19 4.17 4.16 4.12 3.97 2.49 0.82 0.80 0.79 0.70 0.69 0.68 0.67 0.66 0.66 0.65 0.65 0.64 0.63 0.62 0.59 0.58 0.56 0.55 0.54 0.53 0.51
H3C N CH3
H
HO
O
O
N
HO
O
O
OBn
OTES
22
2.20 3.44 1.00 2.38 0.16 1.01 0.98 0.18 0.17 1.02 0.20 6.65 11.17 4.22 3.87
f1 (ppm)

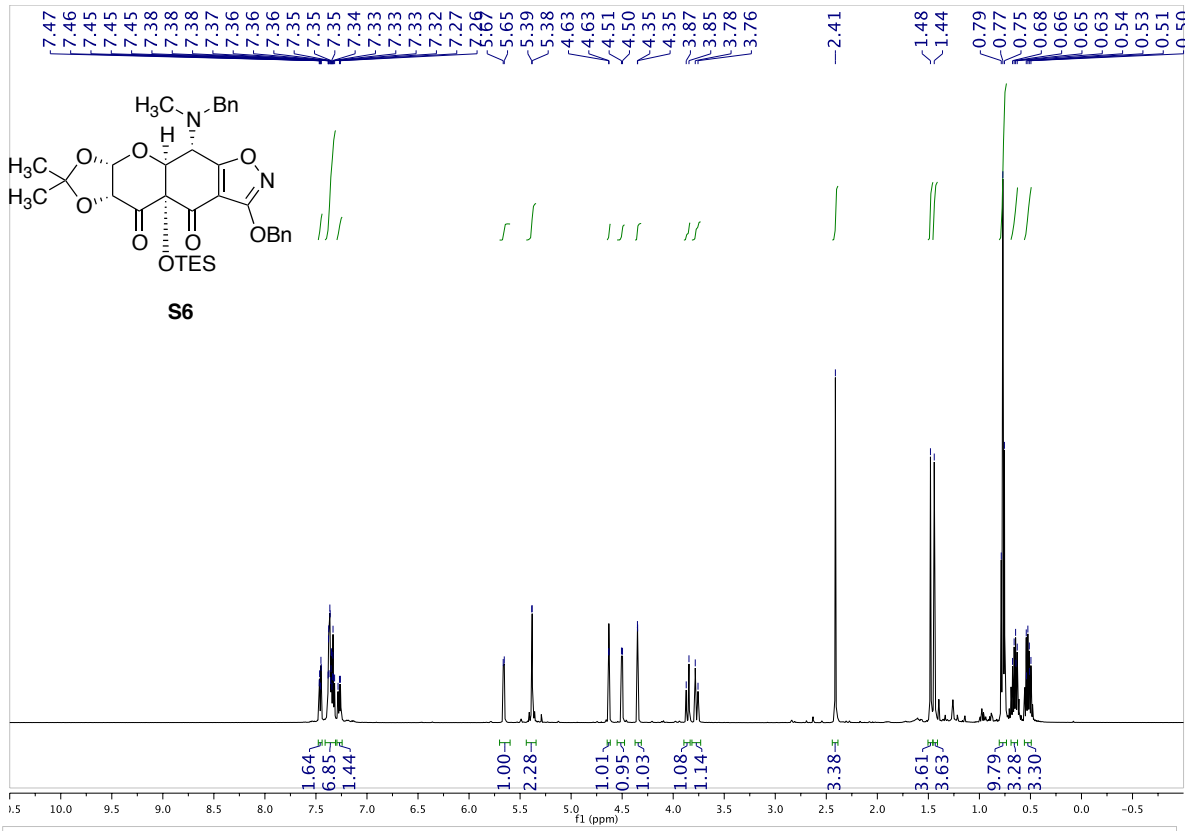

203.1 186.2 178.5 168.0 134.8 128.6 128.6 128.2 106.5 94.6 84.0 75.3 75.1 72.5 63.9 43.2 6.7 5.9
H3C N CH3
H
HO
O
O
N
HO
O
O
OBn
OTES
22
f1 (ppm)

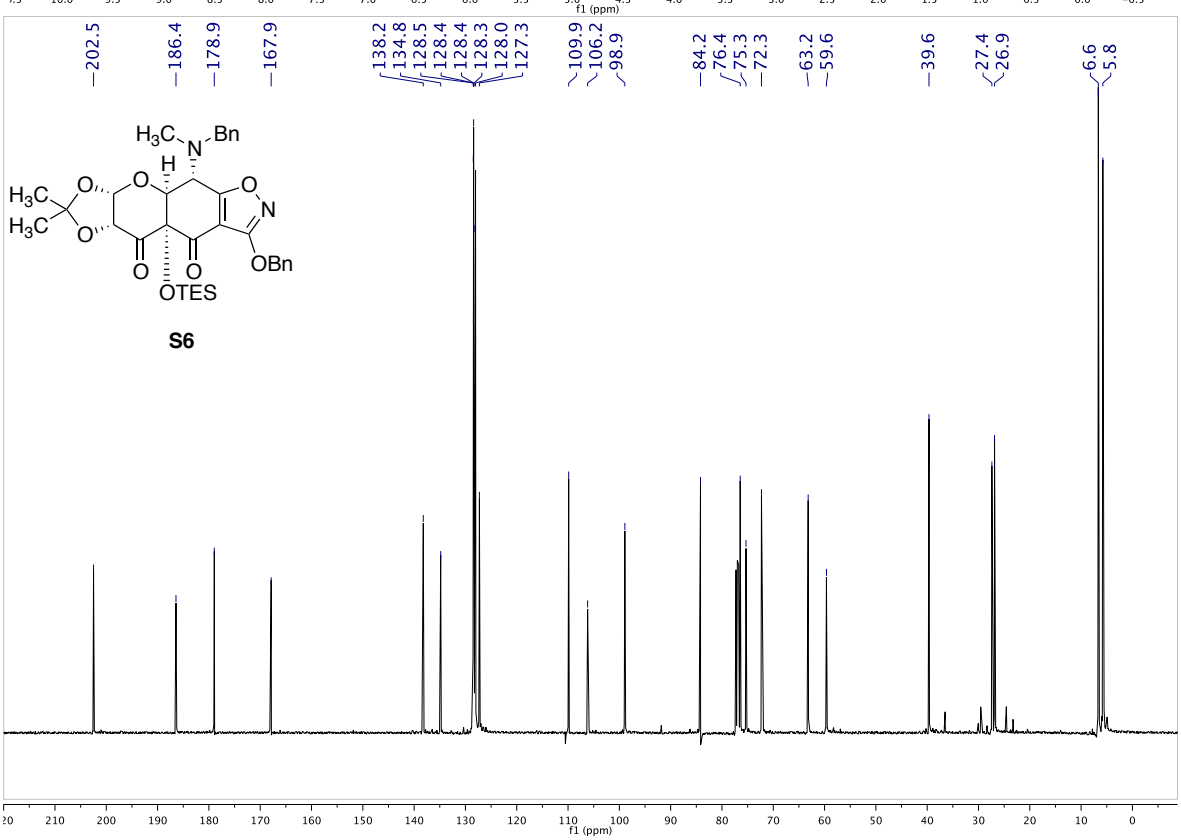

7.50 7.50 7.49 7.49 7.48 7.48 7.40 7.39 7.39 7.38 7.38 7.37 7.37 7.36 7.36 7.35 7.30 7.29
5.58 5.57 5.35
4.92 4.91
4.42 4.40
2.55 0.92 0.91 0.90 0.89 0.89 0.75 0.73 0.73 0.72 0.71 0.71 0.70 0.70 0.70 0.69 0.67 0.67 0.67 0.66 0.66 0.65 0.64 0.64
2.25 3.37 1.01 1.00 2.42 1.01 0.98 6.50 9.40 7.35
f1 (ppm)

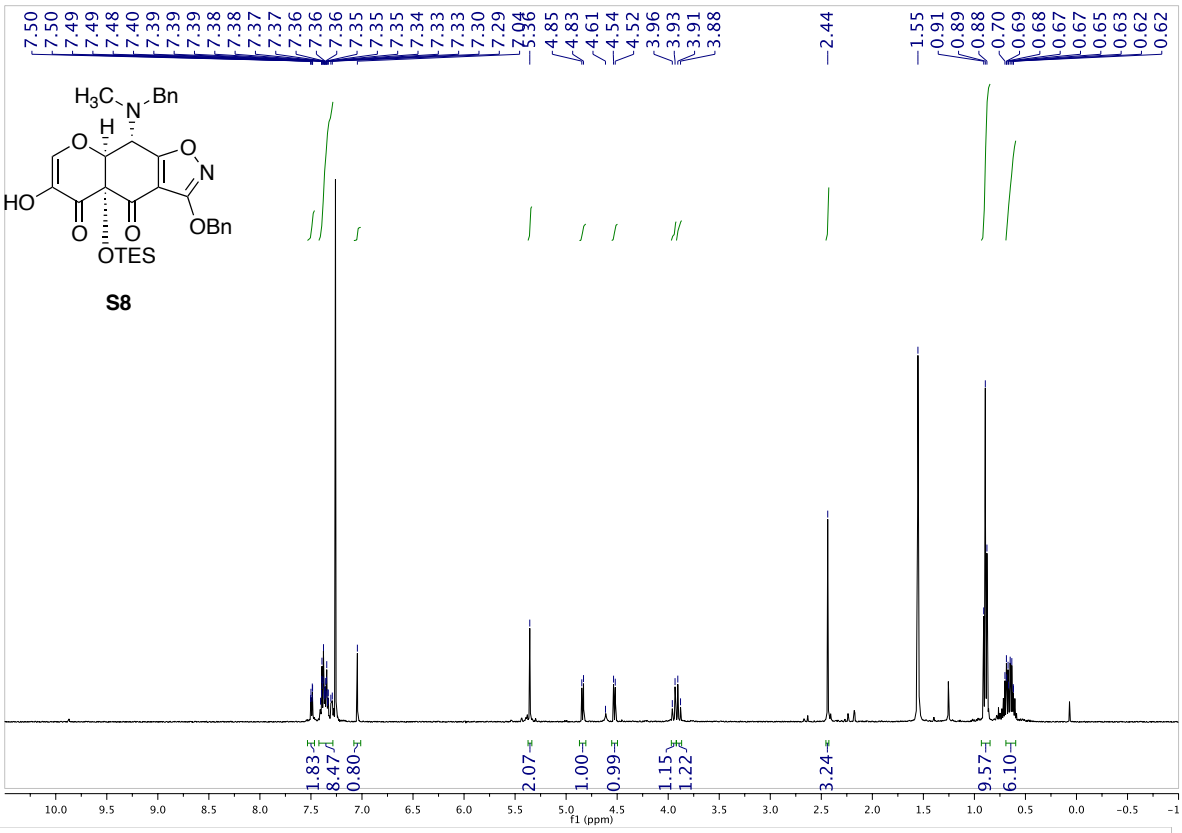
4

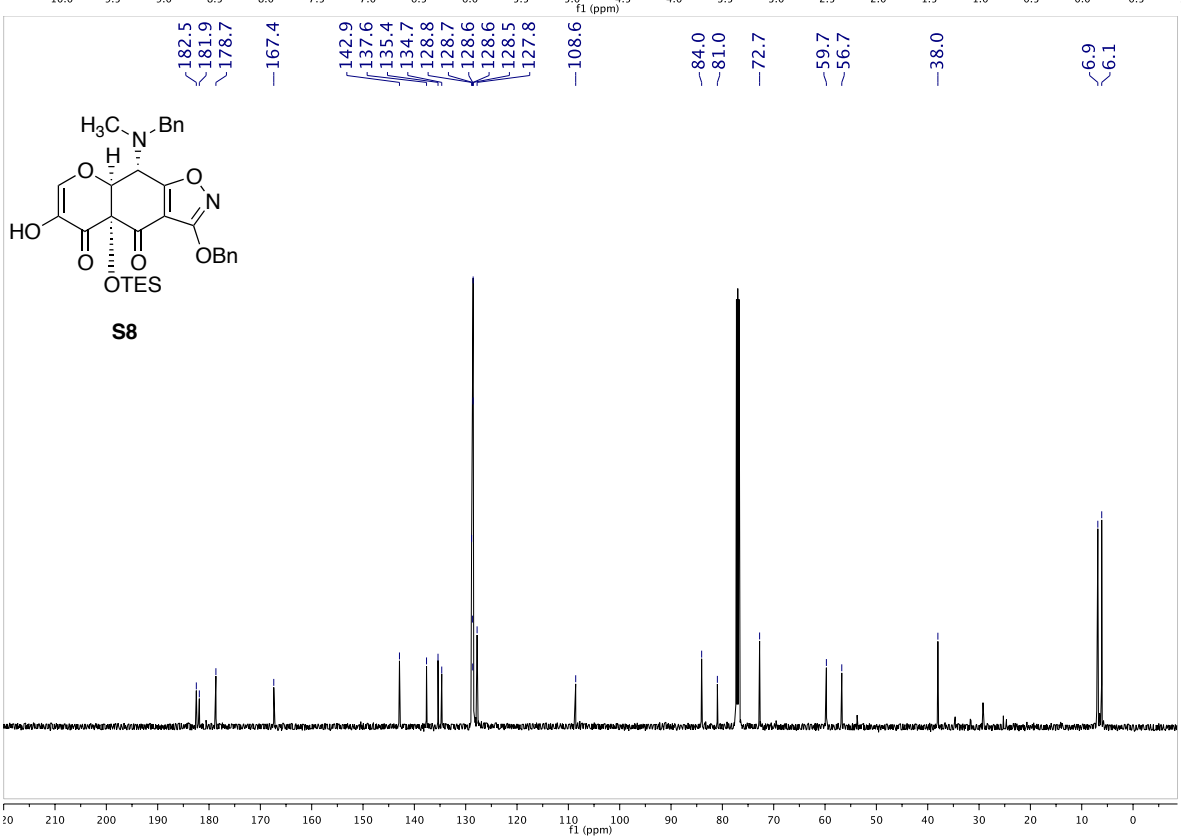

186.4 183.7 177.6 167.4 159.8 134.7 128.6 128.5 108.6 106.3 83.4 81.1 72.7 59.7 41.9 7.0 6.2
f1 (ppm)

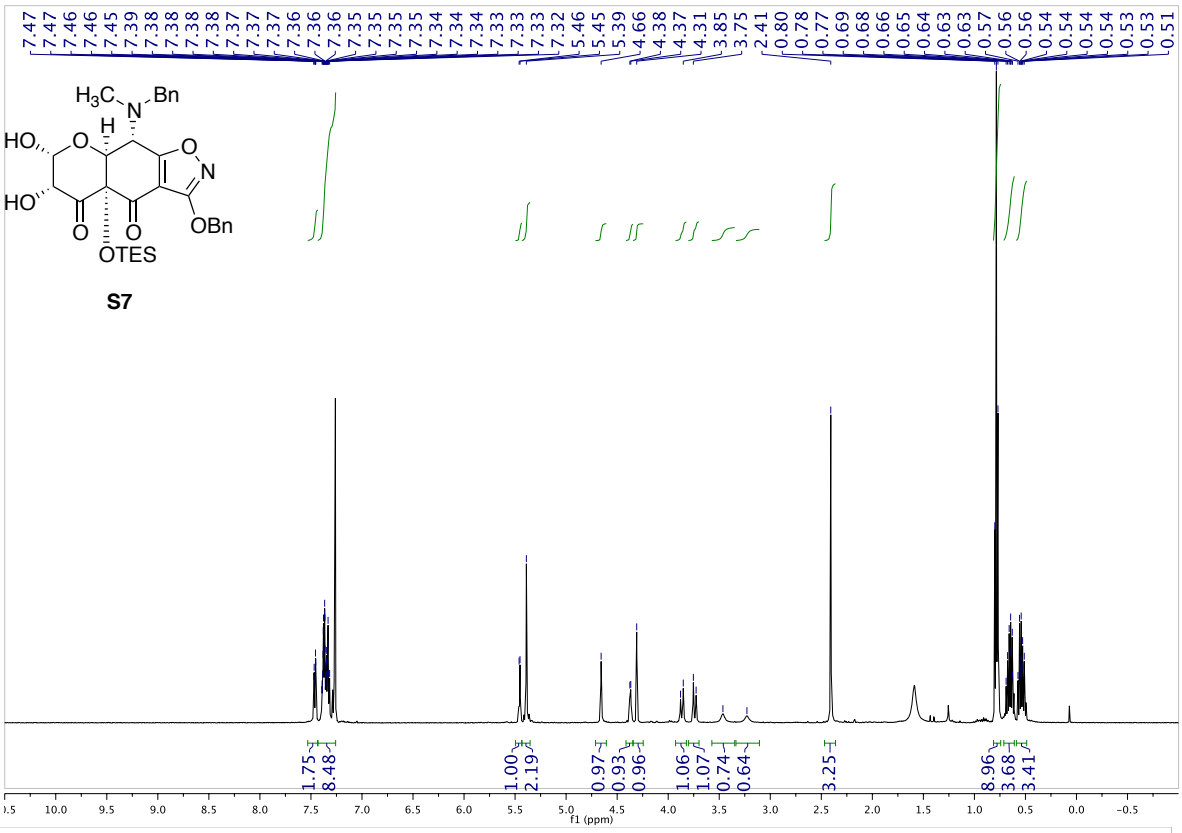
4

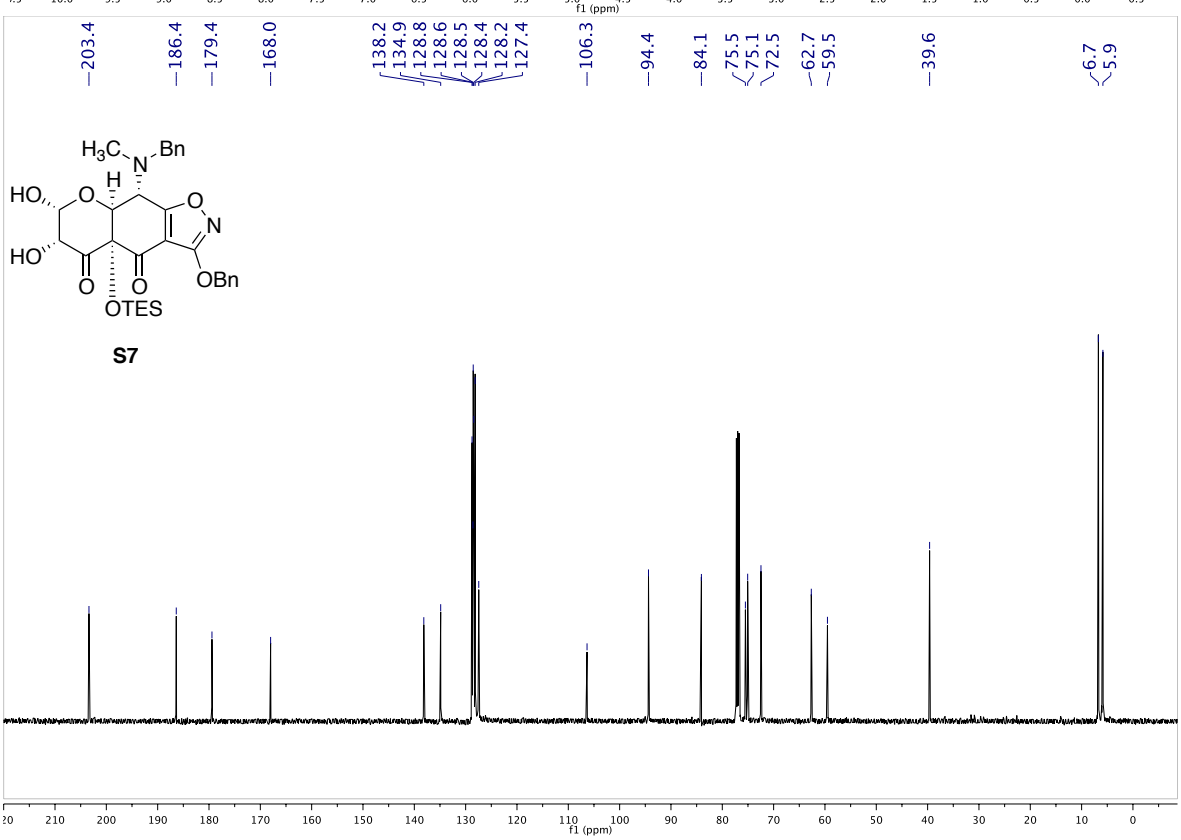

7.47 7.46 7.45 7.45 7.45 7.38 7.38 7.38 7.37 7.36 7.36 7.36 7.35 7.35 7.35 7.34 7.33 7.33 7.33 7.32 7.27 5.67 5.65 5.39 5.38 4.63 4.63 4.51 4.50 4.35 4.35 3.87 3.85 3.78 3.76 2.41 1.48 1.44 0.79 0.77 0.75 0.68 0.66 0.65 0.63 0.54 0.53 0.51
H3C N Bn H O O O N H3C H3C O O O O OBn OTES
S6
1.64 6.85 1.44 1.00 2.28 1.01 0.95 1.03 1.08 1.14 3.38 3.61 3.63 9.79 3.28 3.30
f1 (ppm)

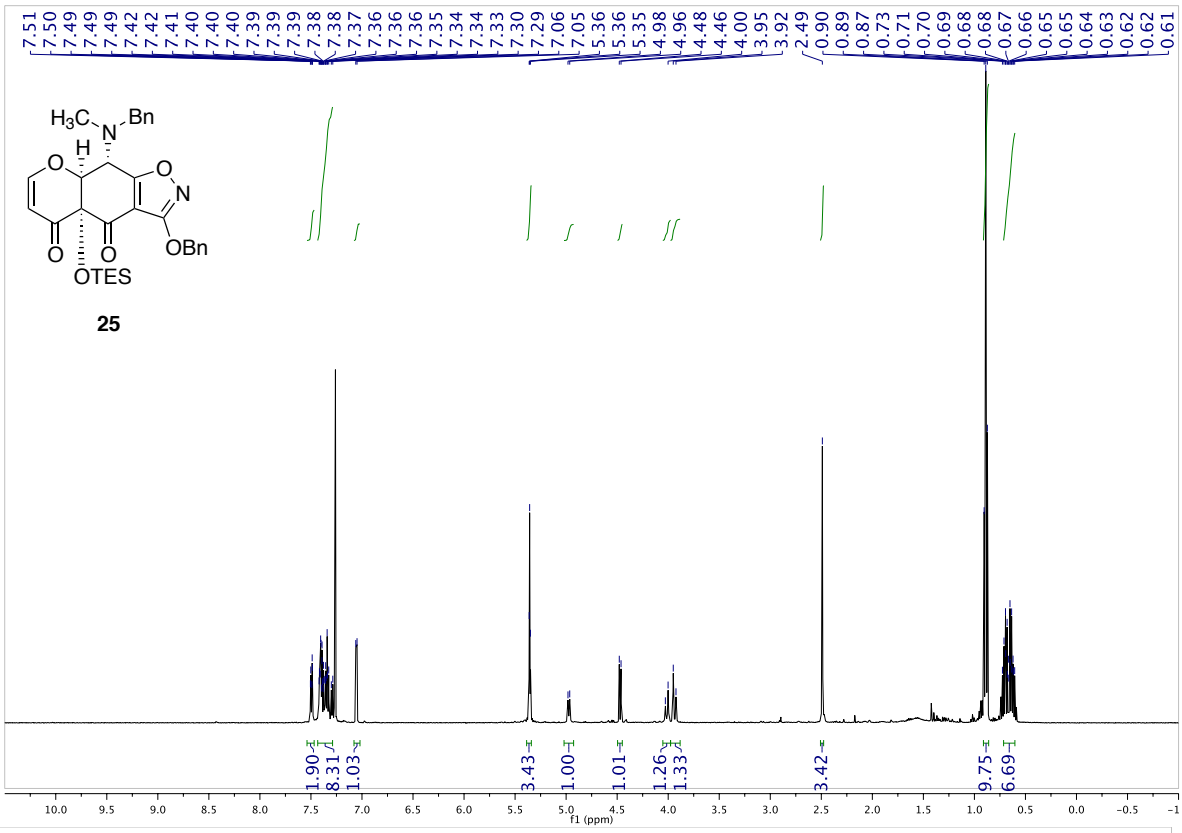

202.5 186.4 178.9 167.9 138.2 134.8 128.5 128.4 128.4 128.3 128.0 127.3 109.9 106.2 98.9 84.2 76.4 75.3 72.3 63.2 59.6 39.6 27.4 26.9 6.6 5.8
H3C N Bn H O O O N H3C H3C O O O O OBn OTES
S6
f1 (ppm)

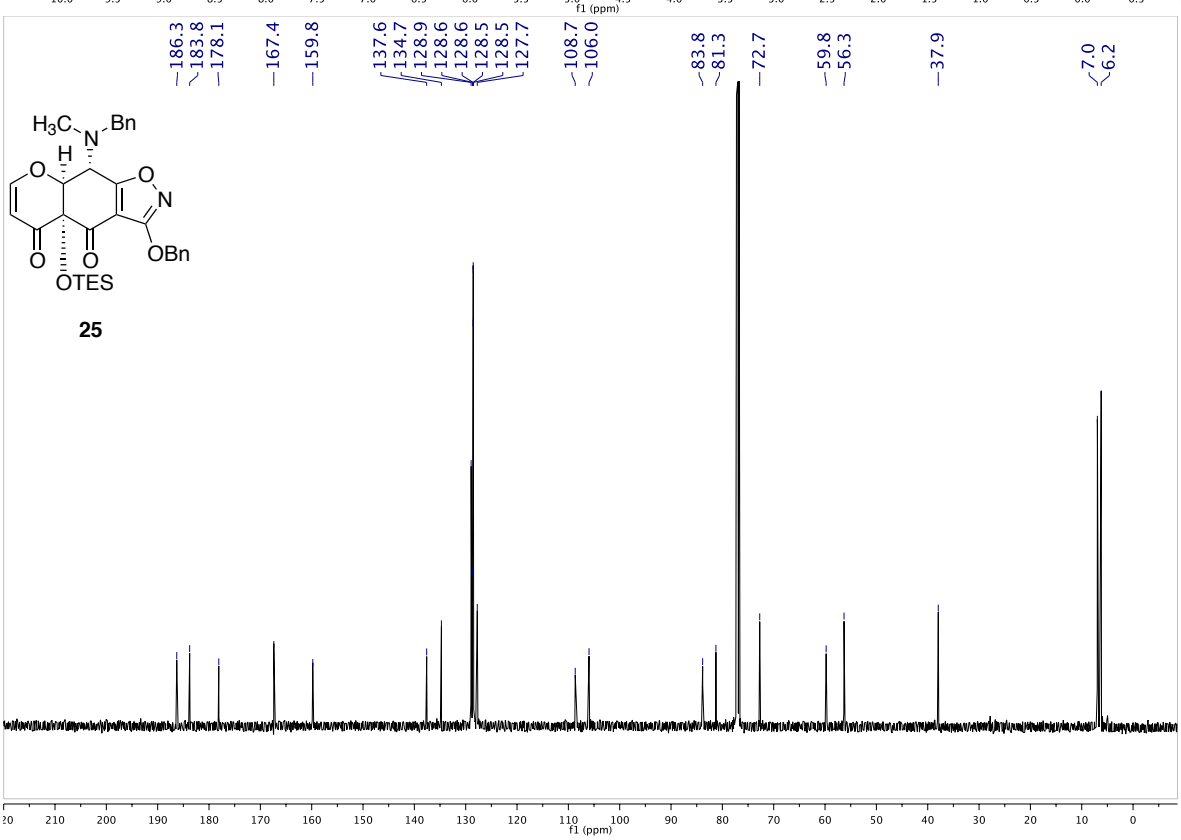

7.50 7.50 7.49 7.49 7.48 7.40 7.39 7.39 7.39 7.38 7.38 7.37 7.37 7.36 7.36 7.36 7.35 7.35 7.35 7.34 7.33 7.33 7.30 7.29 7.04 5.36 4.85 4.83 4.61 4.54 4.52 3.96 3.93 3.91 3.88 2.44 1.55 0.91 0.89 0.88 0.70 0.69 0.68 0.67 0.67 0.65 0.63 0.62 0.62
1.83 8.47 0.80 2.07 1.00 0.99 1.15 1.22 3.24 9.57 6.10
f1 (ppm)
S8

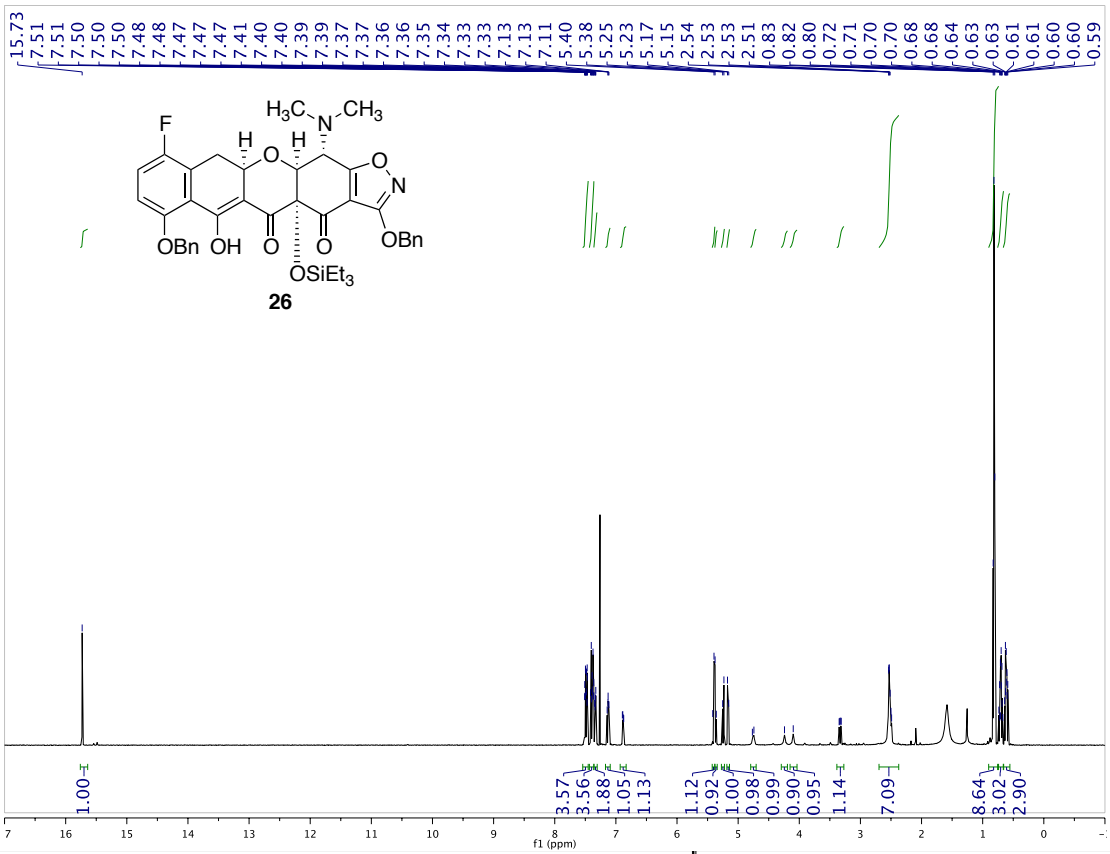

182.5 181.9 178.7 167.4 142.9 137.6 135.4 134.7 128.8 128.7 128.6 128.6 128.5 127.8 108.6 84.0 81.0 72.7 59.7 56.7 38.0 6.9 6.1
f1 (ppm)
S8

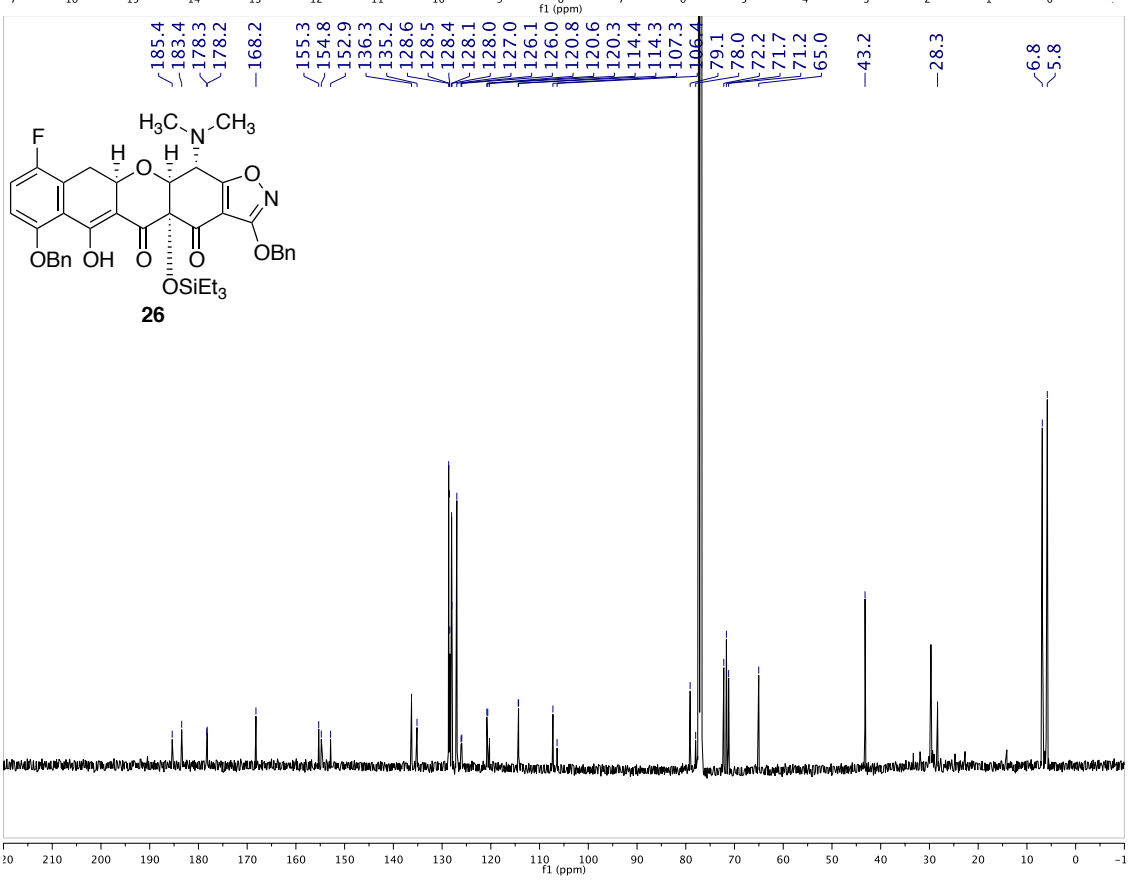

S7
f1 (ppm)

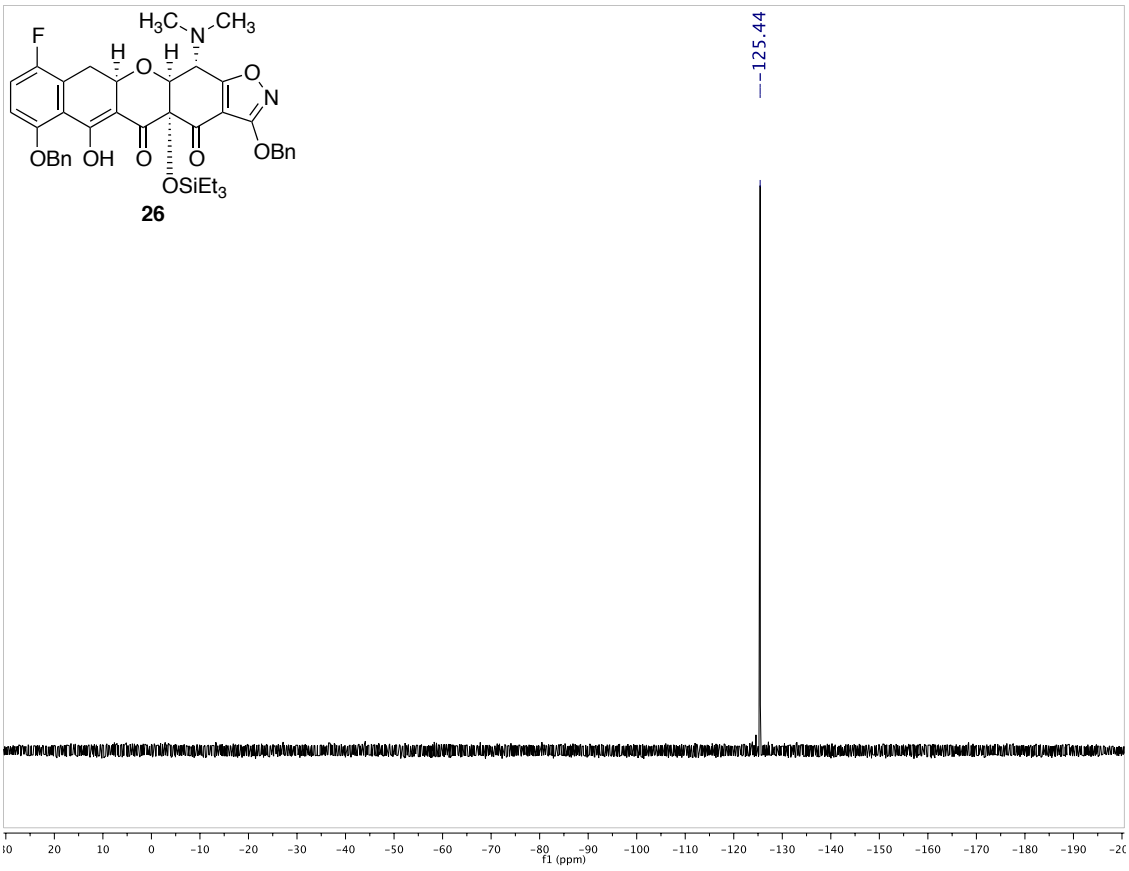

S7
f1 (ppm)

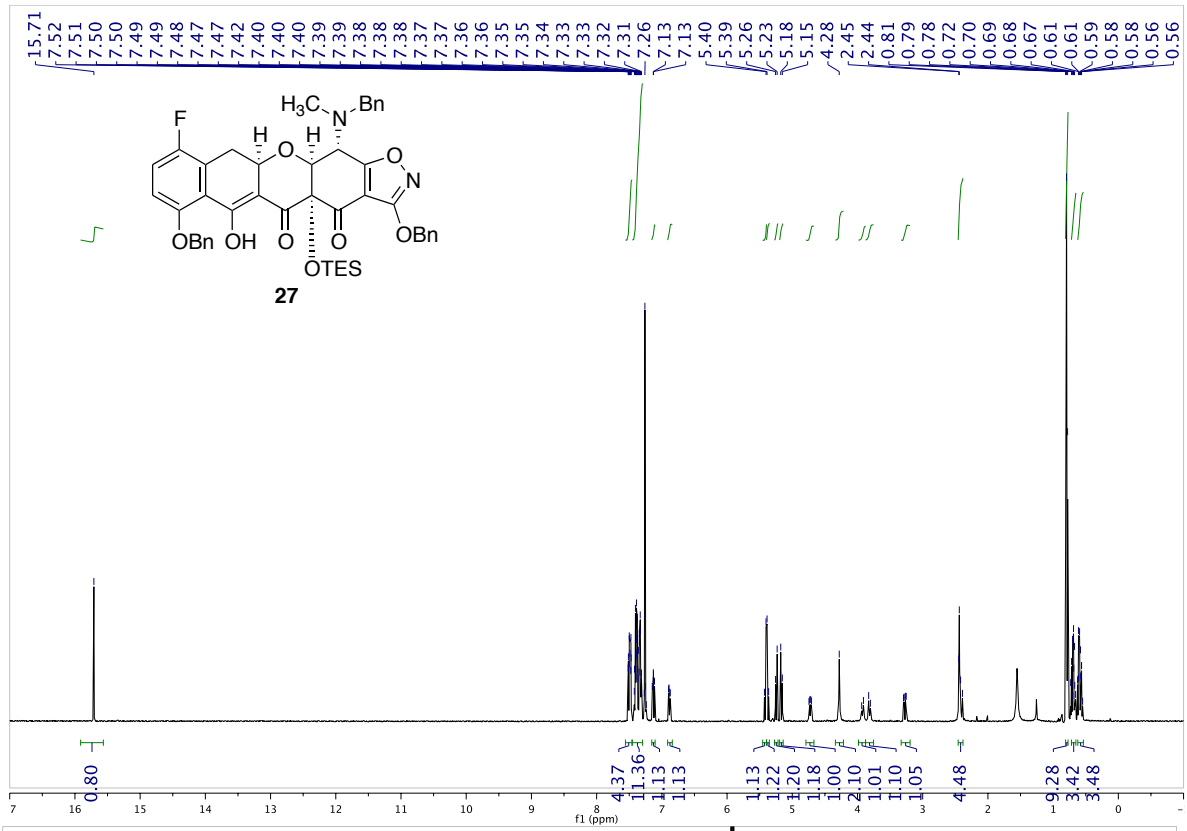

7.51 7.50 7.49 7.49 7.49 7.42 7.42 7.41 7.40 7.40 7.40 7.39 7.39 7.39 7.38 7.38 7.37 7.36 7.36 7.36 7.35 7.34 7.34 7.33 7.30 7.29 7.06 7.05 5.36 5.35 4.98 4.96 4.48 4.46 4.00 3.95 3.92 2.49 0.90 0.89 0.87 0.73 0.71 0.70 0.69 0.68 0.68 0.67 0.66 0.65 0.65 0.64 0.63 0.62 0.62 0.61
H3C N Bn
H
O
O
N
O
O
OBn
OTES
25
1.90 8.31 1.03 3.43 1.00 1.01 1.26 1.33 3.42 9.75 6.69
f1 (ppm)

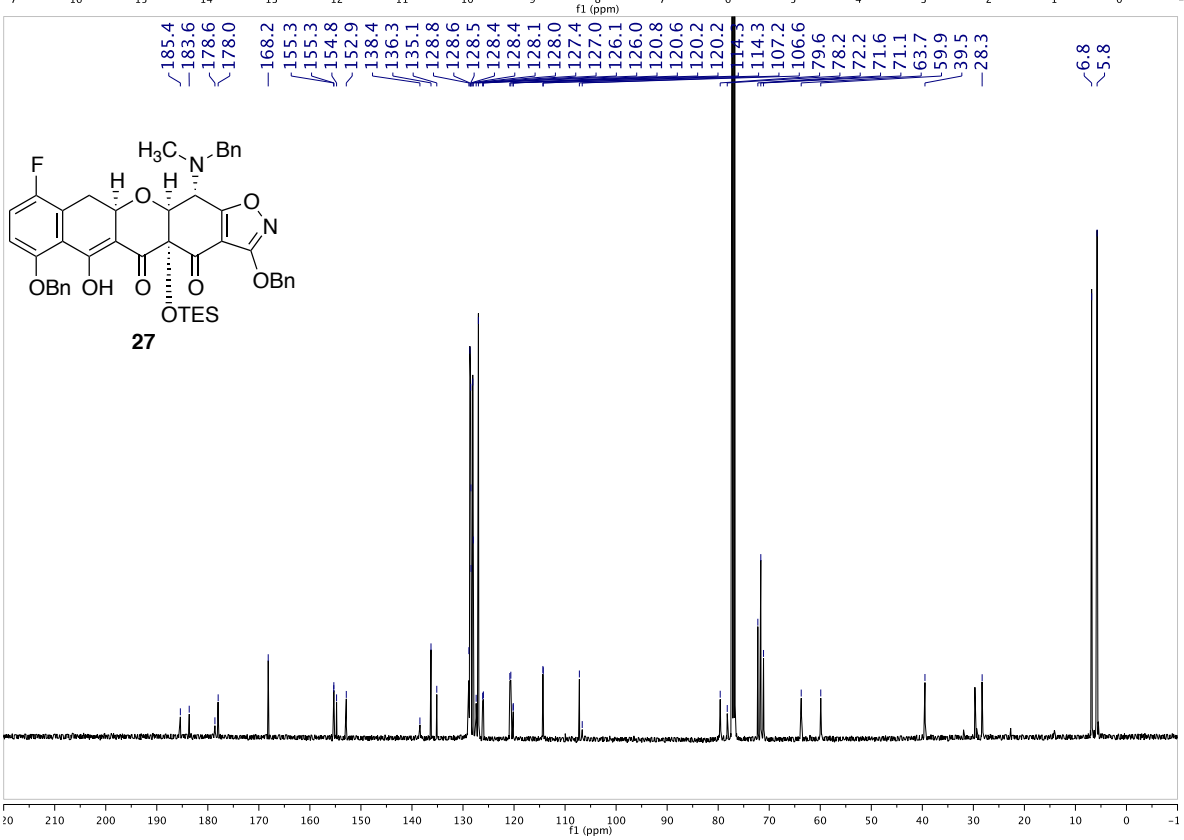

186.3 183.8 178.1 167.4 159.8 137.6 134.7 128.9 128.6 128.6 128.5 128.5 127.7 108.7 106.0 83.8 81.3 72.7 59.8 56.3 37.9 7.0 6.2
H3C N Bn
H
O
O
N
O
O
OBn
OTES
25
f1 (ppm)

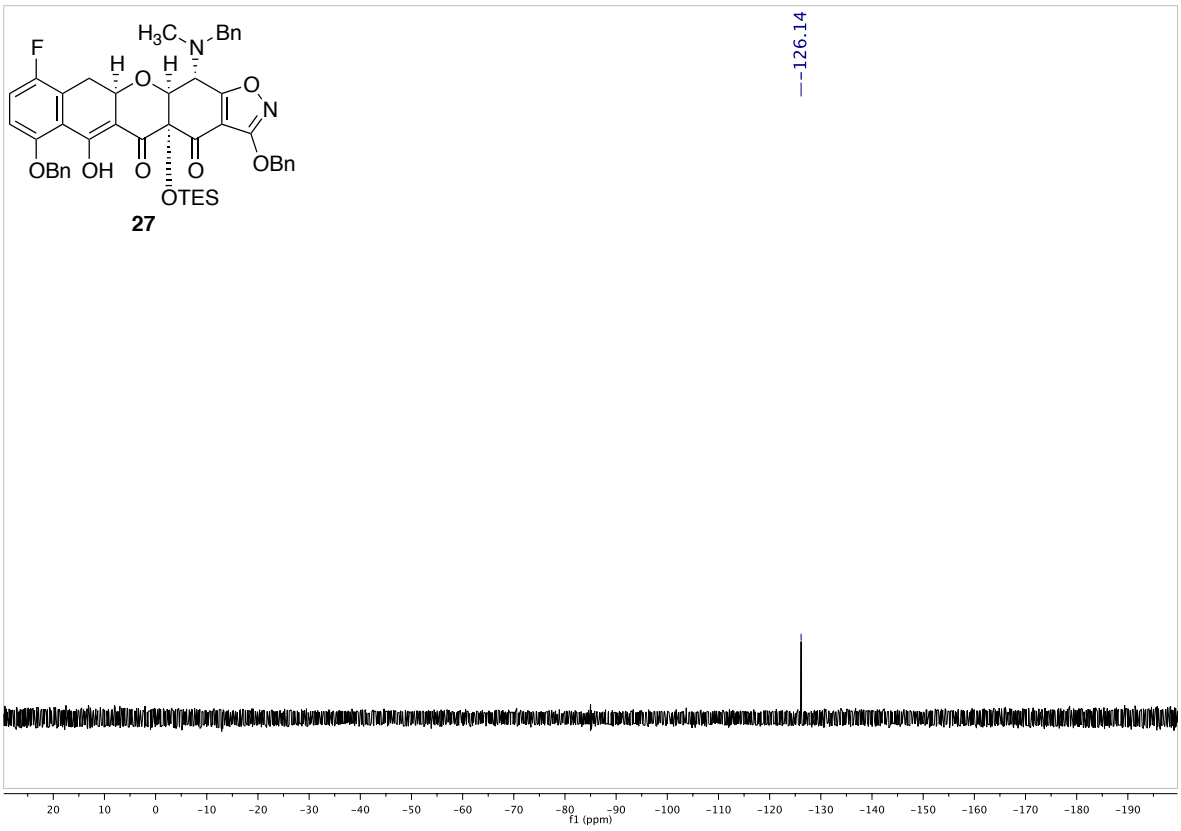

15.73 7.51 7.51 7.50 7.50 7.50 7.48 7.48 7.47 7.47 7.47 7.41 7.40 7.40 7.39 7.39 7.37 7.37 7.36 7.36 7.35 7.34 7.33 7.33 7.13 7.13 7.11 5.40 5.38 5.25 5.23 5.17 5.15 2.54 2.53 2.53 2.51 0.83 0.82 0.80 0.72 0.71 0.70 0.70 0.68 0.68 0.64 0.63 0.63 0.61 0.61 0.60 0.60 0.59
F
H
O
H
H_3C
N
CH_3
O
N
OBn
OH
O
O
OBn
$OSiEt_3$
26
1.00
3.57
3.56
1.88
1.05
1.13
1.12
0.92
1.00
0.98
0.99
0.90
0.95
1.14
7.09
8.64
3.02
2.90
f1 (ppm)

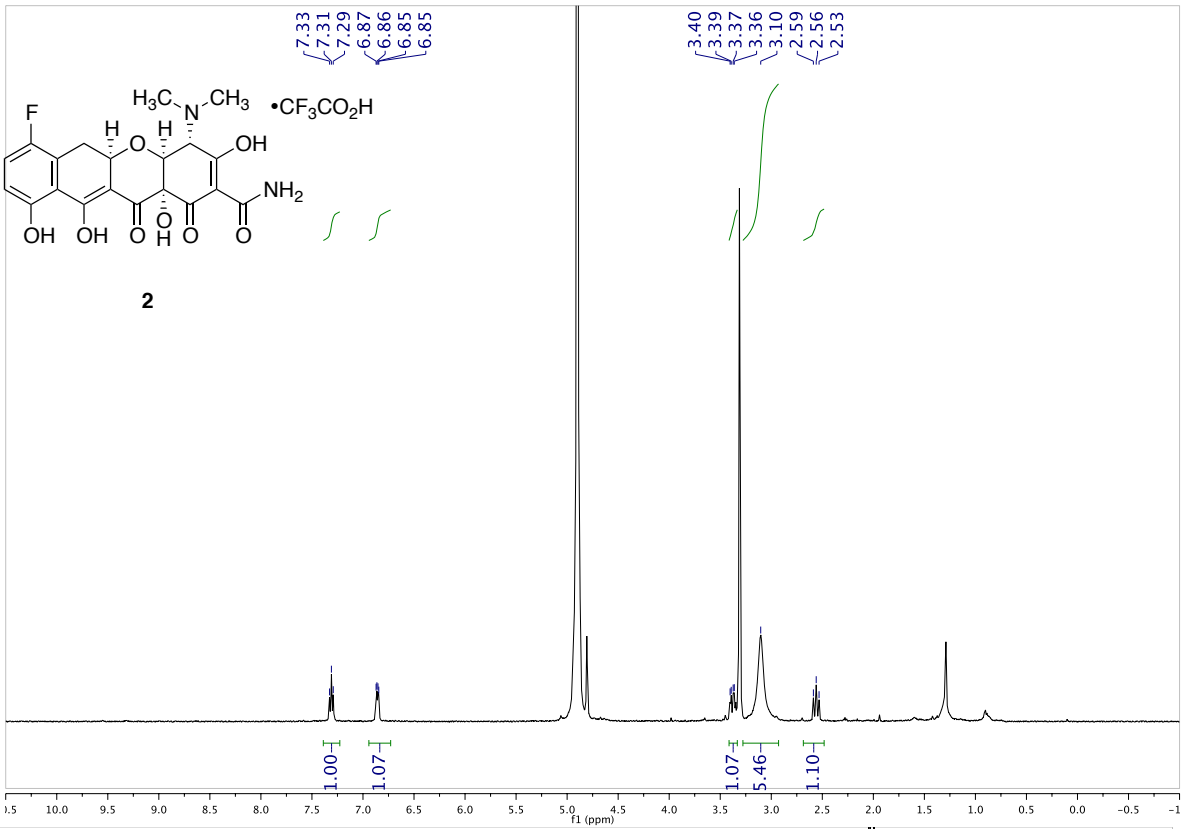

185.4 183.4 178.3 178.2 168.2 155.3 154.8 152.9 136.3 135.2 128.6 128.5 128.4 128.1 128.0 127.0 126.1 126.0 120.8 120.6 120.3 114.4 114.3 107.3 106.4 79.1 78.0 72.2 71.7 71.2 65.0 43.2 28.3 6.8 5.8
F
H
O
H
H_3C
N
CH_3
O
N
OBn
OH
O
O
OBn
$OSiEt_3$
26
f1 (ppm)

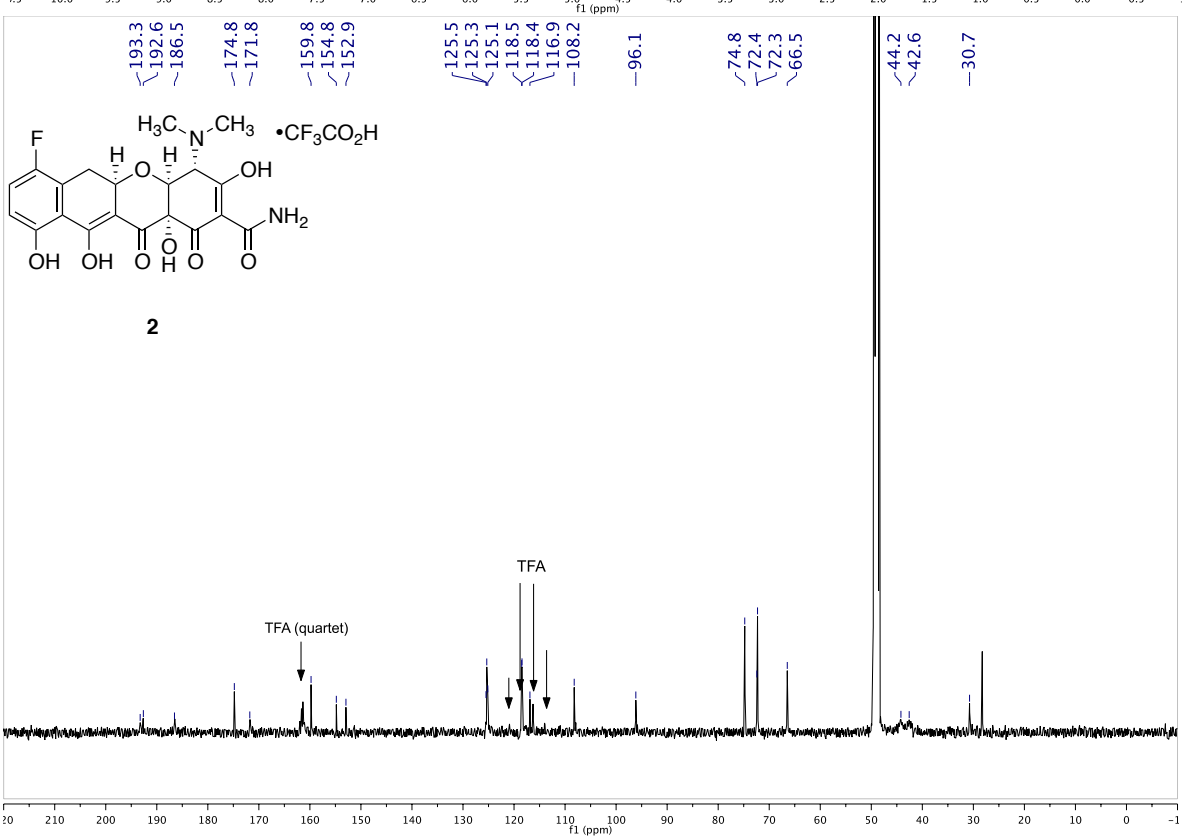

F
H
O
H
H_3C
N
CH_3
O
N
OBn
OH
O
O
OBn
$OSiEt_3$
26
-125.44
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

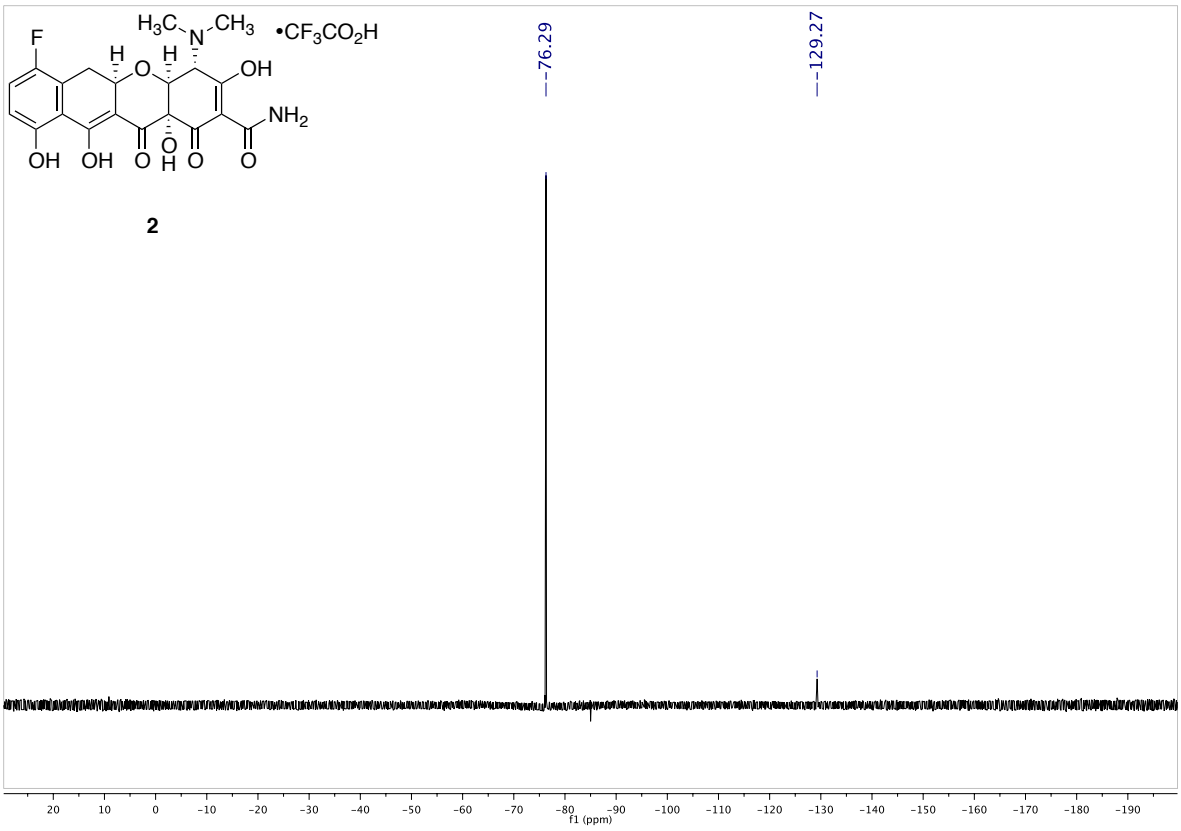

15.71
7.52
7.51
7.50
7.50
7.49
7.49
7.48
7.47
7.47
7.42
7.40
7.40
7.40
7.39
7.39
7.38
7.38
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.31
7.26
7.13
7.13
5.40
5.39
5.26
5.23
5.18
5.15
4.28
2.45
2.44
0.81
0.79
0.78
0.72
0.70
0.69
0.68
0.67
0.61
0.61
0.59
0.58
0.58
0.56
0.56
F
H3C
N
Bn
H
H
O
O
N
OBn
OH
O
O
OBn
OTES
27
0.80
4.37
11.36
1.13
1.13
1.13
1.22
1.20
1.18
1.00
2.10
1.01
1.10
1.05
4.48
9.28
3.42
3.48
f1 (ppm)

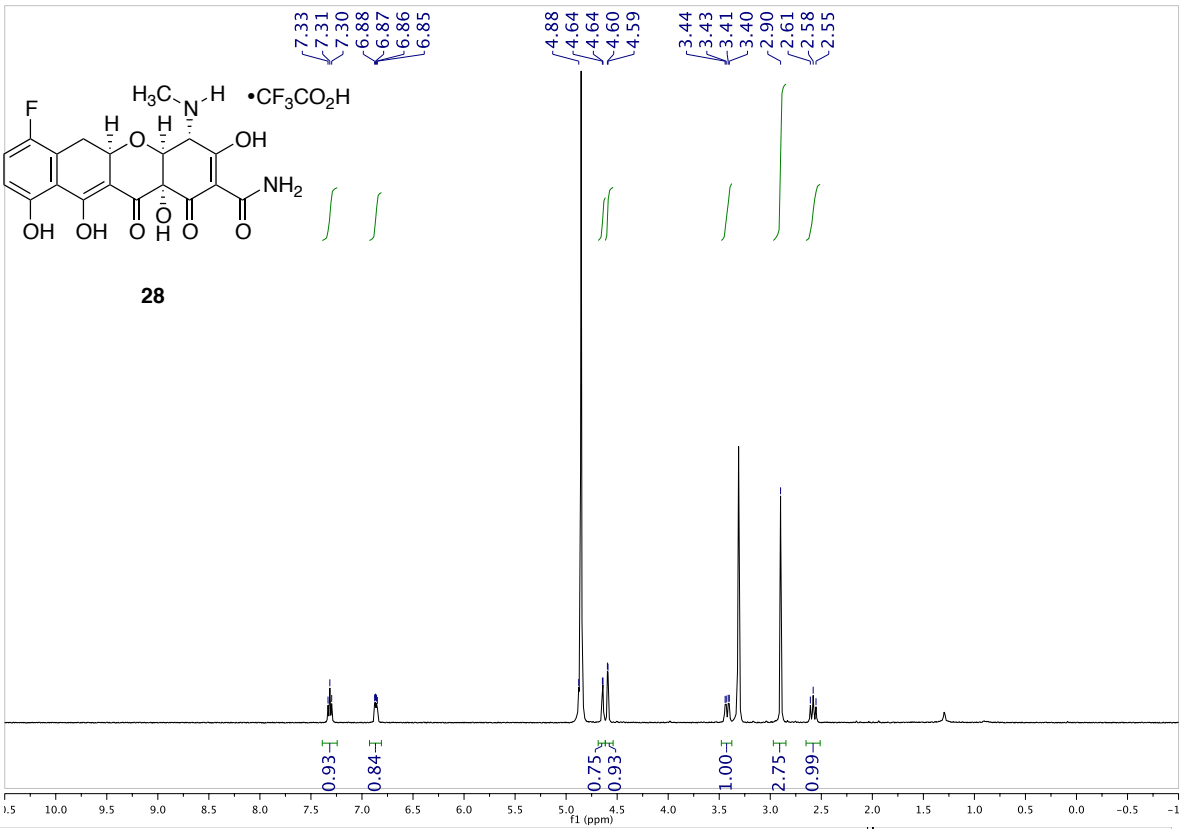

185.4
183.6
178.6
178.0
168.2
155.3
155.3
154.8
152.9
138.4
136.3
135.1
128.8
128.6
128.5
128.4
128.4
128.1
128.0
127.4
127.0
126.1
126.0
120.8
120.6
120.2
120.2
114.3
114.3
107.2
106.6
79.6
78.2
72.2
71.6
71.1
63.7
59.9
39.5
28.3
6.8
5.8
F
H3C
N
Bn
H
H
O
O
N
OBn
OH
O
O
OBn
OTES
27
f1 (ppm)


F
H3C
N
Bn
H
H
O
O
N
OBn
OH
O
O
OBn
OTES
27
−126.14
20
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
f1 (ppm)

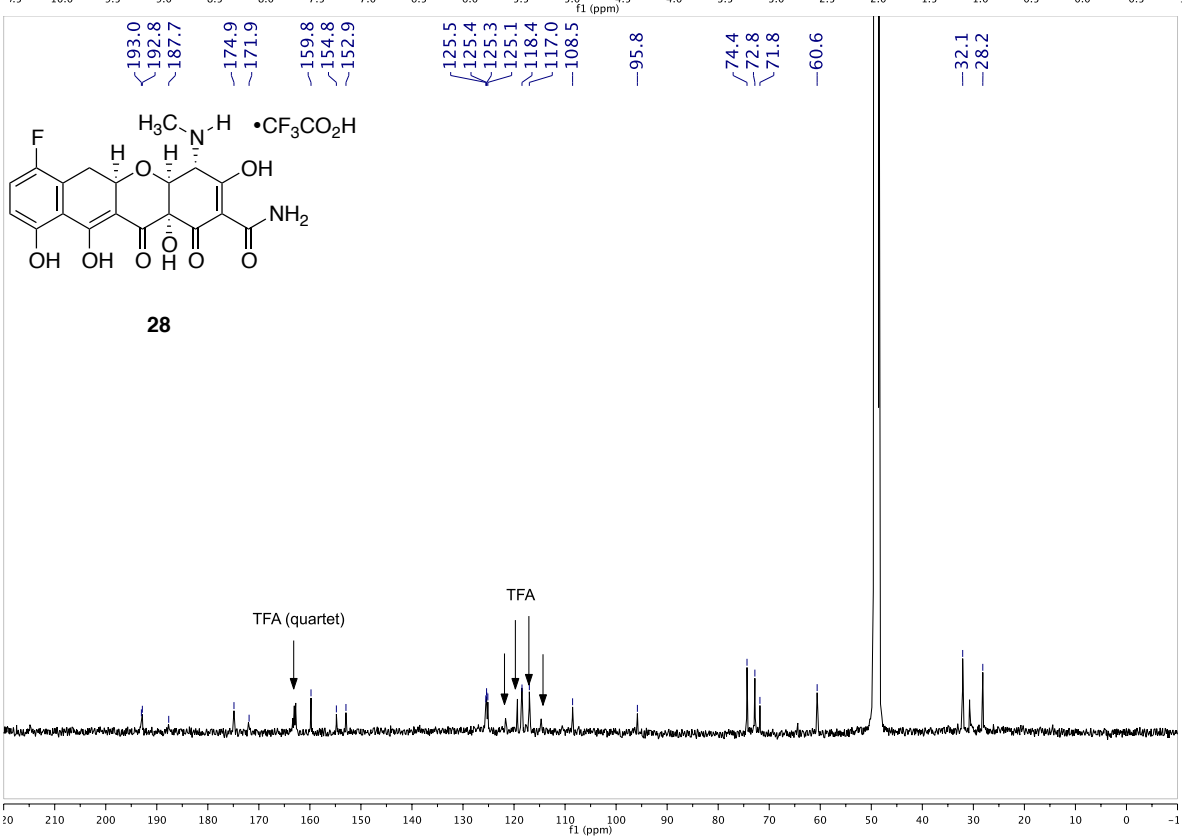

7.33
7.31
7.29
6.87
6.86
6.85
6.85
3.40
3.39
3.37
3.36
3.10
2.59
2.56
2.53
F
H
O
H
OH
NH2
OH
OH
O
O
H
O
O
O
H3C
N
CH3
•CF3CO2H
2
1.00
1.07
1.07
5.46
1.10
f1 (ppm)


193.3
192.6
186.5
174.8
171.8
159.8
154.8
152.9
125.5
125.3
125.1
118.5
118.4
116.9
108.2
96.1
74.8
72.4
72.3
66.5
44.2
42.6
30.7
F
H
O
H
OH
NH2
OH
OH
O
O
H
O
O
O
H3C
N
CH3
•CF3CO2H
2
TFA
TFA (quartet)
f1 (ppm)

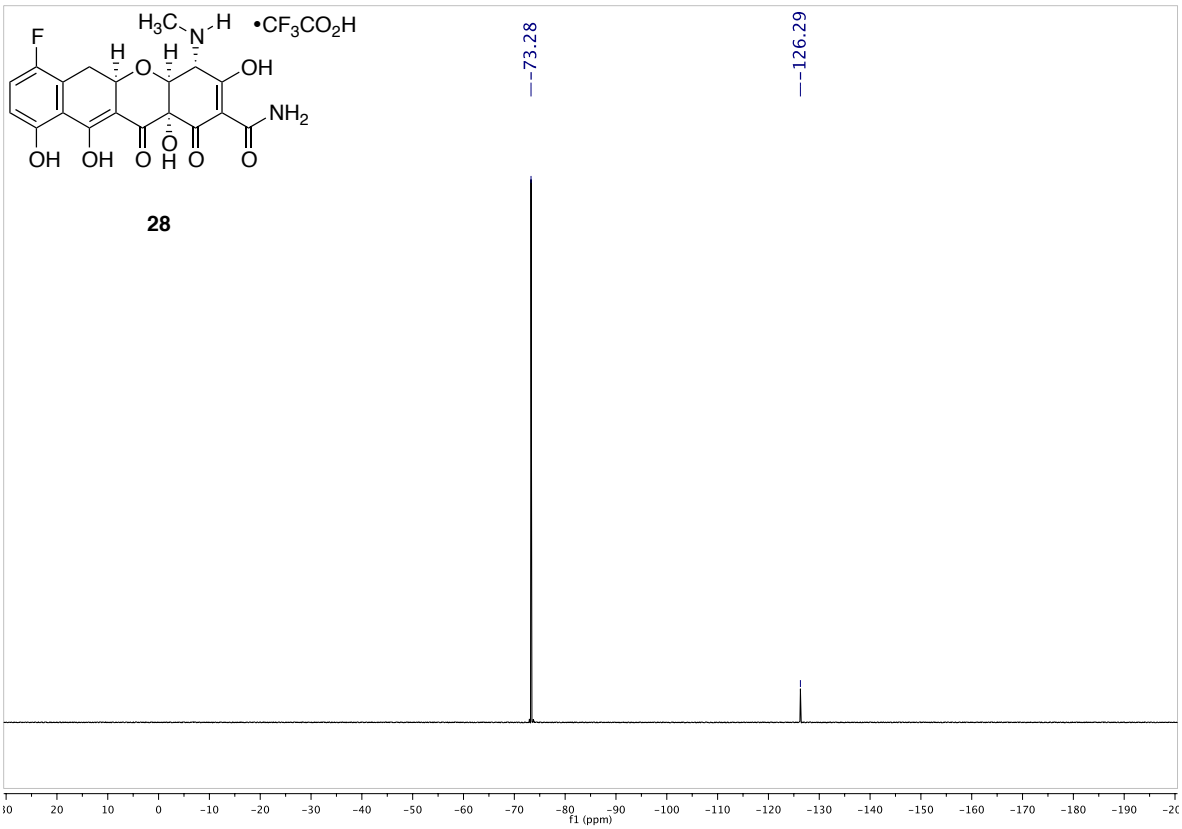

F
H
O
H
OH
NH2
OH
OH
O
H
O
O
O
•CF3CO2H
H3C
N
CH3
2
-76.29
-129.27
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


7.33
7.31
7.30
6.88
6.87
6.86
6.85
4.88
4.64
4.64
4.60
4.59
3.44
3.43
3.41
3.40
2.90
2.61
2.58
2.55
F
H
O
H
OH
NH2
OH
OH
O
H
O
O
H3C
N
H
•CF3CO2H
0.93
0.84
0.75
0.93
1.00
2.75
0.99
f1 (ppm)

28


193.0
192.8
187.7
174.9
171.9
159.8
154.8
152.9
125.5
125.4
125.3
125.1
118.4
117.0
108.5
95.8
74.4
72.8
71.8
60.6
32.1
28.2
TFA (quartet)
TFA
f1 (ppm)

28


F
H
O
H
OH
NH2
OH
OH
O
O
H
O
O
•CF3CO2H
H3C
N
H
28
-73.28
-126.29
f1 (ppm)