A Practical, Enantioselective Synthetic Route to a Key Precursor to the Tetracycline Antibiotics

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Organic Letters

Supporting Information

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General Experimental Procedures. All reactions were performed in flame-dried glassware fitted with rubber septa under a positive pressure of argon, 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. Analytical thin-layer chromatography 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 (UV), and then were stained by submersion in aqueous ceric ammonium molybdate solution (CAM), basic aqueous potassium permanganate ($KMnO_4$), or an acidic solution of *p*-anisaldehyde in ethanol, followed by brief heating on a hot plate (~170 °C, 10–15 s). Flash-column chromatography was performed as described by Still et al.,[1] employing silica gel (60-Å pore size, 32–63 μm, standard grade, Sorbent Technologies). Acetone cooling baths were cooled to the appropriate temperature by addition of small portions of dry ice.

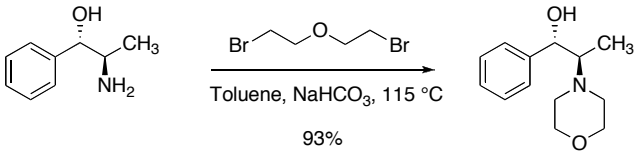
Materials. Commercial reagents and solvents were used with the following exceptions. Tetrahydrofuran and 1,4-dioxane were distilled under nitrogen from sodium-benzophenone ketyl. The molarity of commercial solutions of *n*-butyllithium was determined by titration against standard solutions of diphenylacetic acid (average of three determinations).[2]

Instrumentation. Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian Mercury 400 (400 MHz), Varian INOVA 500 (500 MHz), or Varian INOVA 600 (600 MHz) NMR spectrometers at 25 °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, C_6HD_5: δ 7.15). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, and coupling constant (*J*) in Hertz (Hz). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian Mercury 400 (100 MHz) or Varian INOVA 500 (125 MHz) NMR spectrometers at 25 °C. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.0, C_6D_6: δ 128). Samples for infrared (IR) spectroscopy were prepared as neat films by evaporation of dichloromethane solutions; infrared spectra were recorded using a Perkin–Elmer 1600 FT-IR spectrophotometer and were referenced to an internal polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}) and intensity of absorption (s = strong, m = medium, w = weak, br = broad). High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facility.

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.
[2] Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

Procedures for the Synthesis of the Tetracycline Precursor 1.

(1*S*,2*R*)-2-Morpholin-4-yl-1-phenylpropanol[3]



A 500-mL, single-necked, round-bottomed flask containing a Teflon-coated magnetic stirring bar was charged with (1*S*,2*R*)-norephedrine (36.2 g, 239 mmol, 1 equiv), 2-bromoethyl ether (65.7 g, 263 mmol, 1.10 equiv), sodium bicarbonate (44.3 g, 527 mmol, 2.20 equiv) and toluene (191 mL), then was fitted with a reflux condensor and the system was flushed with argon. The reaction flask was heated at 115 °C in an oil bath for 22.5 h. The product mixture was allowed to cool to 23 °C, then was filtered, and the filtrate was washed with water (100 mL). The product was extracted from the organic solution into aqueous citric acid solution (30% by weight, 2 x 200 mL). The combined citric acid layers were cooled in an ice-water bath and aqueous sodium hydroxide solution (6 N) was added slowly to the cooled solution to an endpoint of pH 13. The resulting basic aqueous mixture was extracted with toluene (3 x 300 mL). The toluene layers were combined and the combined solution was washed sequentially with water (200 mL) and saturated aqueous sodium chloride solution (300 mL). The washed product solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated (bath temp 45 °C), furnishing (1*S*,2*R*)-2-morpholin-4-yl-1-phenylpropanol (49.5 g, 93%) as a white, crystalline solid (mp = 77 °C).

^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.32-7.20 (m, 5H, Ar**H**), 4.88 (d, 1H, *J* = 3.9 Hz, C**H**OH), 3.69 (t, 4H, *J* = 4.88 Hz, C**H$_2$**OC**H$_2$**), 3.57 (br s, 1H, O**H**), 2.67-2.52 (5H, m, CH_3C**H**NR_2, C**H$_2$**NC**H$_2$**), 0.82 (3H, d, *J* = 6.8 Hz, C**H$_3$**).	
^{13}C NMR (100 MHz, $CDCl_3$), δ:	141.8, 128.0, 126.8, 125.8, 71.6, 67.3, 64.8, 50.8, 9.7.	
IR (neat), cm^{-1}:	3425 (bs), 2960 (m), 2908 (m), 2855 (m), 2816 (m), 1450 (s), 1116 (s).	
HRMS (ESI):	Calcd for $(C_{13}H_{19}NO_2+H)^+$:	222.1494
	Found:	222.1487

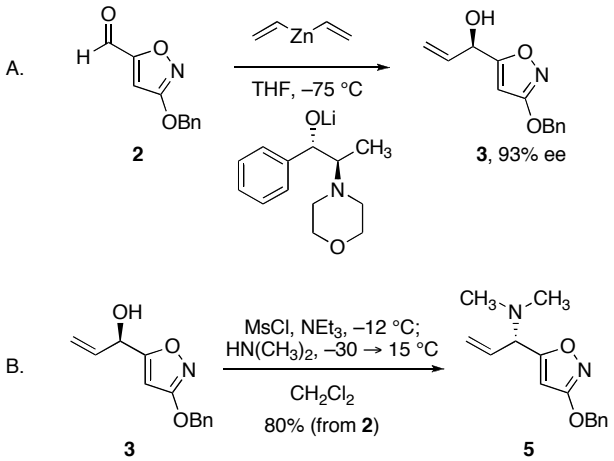
Divinylzinc

A special reaction flask was constructed for this transformation (see photograph on following page). Briefly, the side of a 5-L, two-necked, round-bottomed flask was fused to a coarse-fritted vacuum filtration funnel (~2-L volume, projecting at an angle of ~45° from the center neck). The center neck of the flask was oriented vertically, then was fitted with a mechanical stirrer. The side neck of the flask was fitted with a rubber septum. The joint of the fritted funnel was fitted with a 50-mL round-bottomed flask and a balloon of argon was affixed to the gas inlet adapter. The system was flame-dried and flushed with argon. The reaction flask was charged with a solution of zinc chloride in ethyl ether (1.0 M, 1 L, 1 mol, 1 equiv) through the side neck via cannula. A solution of vinylmagnesium bromide in tetrahydrofuran (1.0 M, 2 L, 2 mol, 2 equiv) was then added via cannula over 2.5 h (23 °C). A gray solid precipitated during and throughout the addition. After completion of the addition, the reaction mixture was stirred at 23 °C for 2 h,

[3] This procedure was modeled after that published for the alkylation of norephedrine with 1,4-dibromobutane: Pierce, M. E.; Parsons, R. L. Jr.; Radesca, L. A.; Lo, Y. S.; Silverman, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Morgan, S. J.; Davis, W. P.; Confalone; Chen, C.-y.; Tillyer, R. D.; Frey, L.; Tan, L.; Xu, F.; Zhao, D.; Thompson, A. S.; Corley, E. G.; Grabowski, E. J. J.; Reamer, R.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 8536-8543.

then dioxane (600 mL) was added via cannula.[4] The reaction mixture was stirred at 23 °C for 1 h. The 50-mL flask was replaced with a 3-L, single-necked, flame-dried flask and the mechanical stirrer was removed and replaced by a glass stopper. A positive pressure of argon was applied through the septum on the side-joint, and the entire apparatus was then turned 135° to allow the reaction mixture to filter into the 3-L flask. The resulting clear, yellow solution was used directly in the next reaction (theoretically, 0.28 M in divinylzinc, 2.25 L). We have found that it is possible to store the solution of divinylzinc at –20 °C for (at least) 2 months without diminution of the yield or enantioselectivity of the subsequent addition reaction.

(*S*)-Tertiary Amine **5**



[4] von dem Bussche-Hünnefeld, J. L.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719–5730.

A. A 12-L, Morton-style, four-necked flask was equipped with a mechanical stirrer, an internal thermocouple, and three rubber septa. The reaction flask was flushed with argon, then was charged with a solution of (1*S*,2*R*)-2-morpholin-4-yl-1-phenylpropanol (163.3 g, 738 mmol, 2.00 equiv) in toluene (2.0 L). The solution was cooled to 0 °C in an acetone bath, and a solution of *n*-butyllithium in hexanes (2.50 M, 295 mL, 738 mmol, 2.00 equiv) was added to the cooled solution via cannula. The reaction solution was stirred for an additional 30 min at 0 °C after the addition, and then a solution of divinylzinc (0.28 M, prepared as described above, 2.64 L, 738 mmol, 2.0 equiv) was added via cannula over 70 min. The reaction mixture was stirred at 0 °C for 1 h, then was cooled to an internal temperature of –75 °C by addition of dry ice to the cooling bath. A solution of aldehyde **2**[5] (75 g, 369 mmol, 1 equiv) in toluene (300 mL) was added to the reaction mixture at –75 °C over 50 min via cannula. The reaction mixture was stirred at –75 °C for 40 min, and the cooling bath was removed. When the reaction mixture had warmed to –30 °C, aqueous citric acid solution (30% by weight, 2 L) was added. The biphasic mixture was allowed to warm to 23 °C and the layers were separated. The organic layer was washed sequentially with water (700 mL) and brine (700 mL), then was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated (30-40 Torr, 45 °C bath temp) to furnish the allylic alcohol **3** (93% ee by Mosher ester[6] analysis) as a pale yellow oil, used directly in the next reaction without further purification. An analytical sample was prepared by flash-column chromatography on silica gel (30% ethyl acetate-hexanes) to furnish the allylic alcohol **3** as a clear, colorless oil.

B. A 12-L, Morton-style, four-necked flask was equipped with a mechanical stirrer, an internal thermocouple, and three rubber septa. The reaction flask was flushed with argon, then was charged with a solution of the unpurified allylic alcohol **3** (369 mmol, 1 equiv) and triethylamine (67.3 mL, 480 mmol, 1.30 equiv) in dichloromethane (3.7 L). The solution was cooled to –12 °C in an acetone bath and methanesulfonyl chloride (33.5 mL, 424 mmol, 1.15 equiv) was added dropwise via syringe. After stirring at –12 °C for 30 min, the reaction mixture was cooled to –30 °C by addition of small portions of dry ice to the cooling bath and then a solution of dimethylamine in tetrahydrofuran (2.0 M, 1.1 L, 2.2 mol, 6.0 equiv) was added via cannula over 70 min. The reaction mixture was allowed to warm slowly to 15 °C over 7 h, then was concentrated to a volume of 1.5 L. The concentrated solution was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.05 M, 2 L) and dichloromethane (1.5 L). The aqueous layer was separated and extracted with dichloromethane (1 L). The organic layers were combined and the combined layers were dried over sodium sulfate. The solids were filtered and the filtrate was concentrated. The residue obtained was partitioned between ethyl ether (700 mL) and aqueous hydrochloric acid solution (1.0 M, 1 L). The acidic extract was cooled in an ice-water bath and the cooled solution was brought to pH 13 by slow addition of aqueous sodium hydroxide solution (6.0 M). The resulting basic aqueous mixture was extracted with ethyl ether (2 x 700 mL) and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution, then were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue was purified by flash-column chromatography on silica gel (3% methanol-dichloromethane) to furnish the (*S*)-allylic amine **5** (76.3 g, 80% over two steps) as a pale yellow oil.

Recovery of (1*S*,2*R*)-2-morpholin-4-yl-1-phenylpropanol. The aqueous citric acid layer from part A was cooled in an ice-water bath and the cooled solution was brought to pH 13 by slow addition of aqueous sodium hydroxide solution (6 N). The resulting basic aqueous mixture was extracted with toluene (2 x 1.5 L). The toluene layers were combined and the combined solution was washed sequentially with water (500 mL) and saturated aqueous sodium chloride solution (500 mL). The washed solution was dried over sodium sulfate and the solids were filtered. The filtrate was concentrated (30-40 Torr, bath temp 45 °C) to furnish (1*S*,2*R*)-2-morpholinyl-1-phenylpropanol (161.5 g, 99%) as a white, crystalline solid.

(*R*)-Allylic Alcohol **3**

TLC (30% ethyl acetate-hexanes)	R_f = 0.25 (UV, CAM).
^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.43-7.34 (m, 5H, Ar**H**), 6.04 (ddd, 1H, *J* = 17.1, 10.3, 5.9 Hz, CH_2=C**H**), 5.87 (s, 1H, Isox**H**), 5.46 (d, 1H, *J* = 17.1, *trans*-CH**H**=CH), 5.34 (d, 1H, *J* = 10.3 Hz, *cis*-

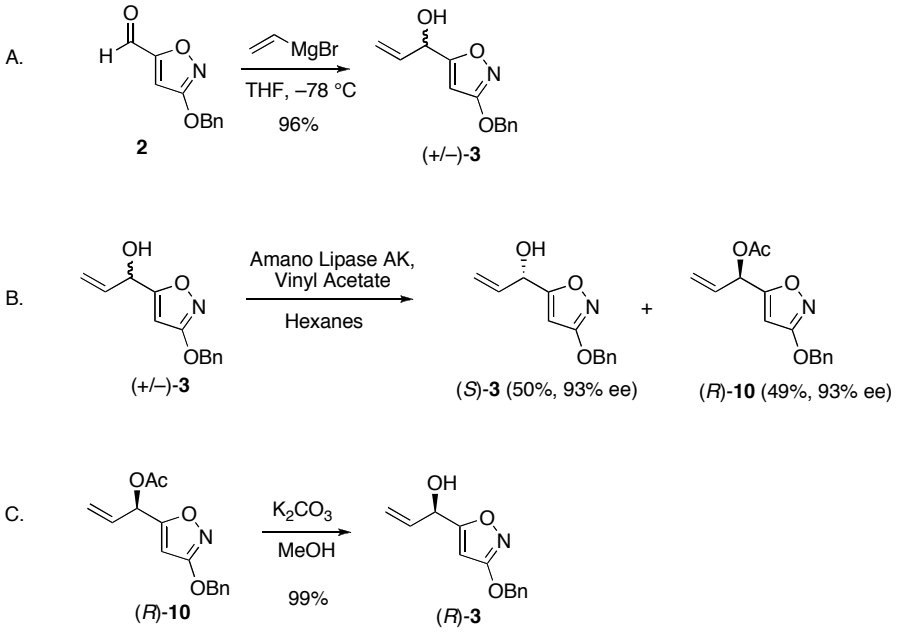
[5] Riess, R.; Schon, M.; Laschat, S.; Jager, V. *Eur. J. Org. Chem.* **1998**, 473-479.
[6] Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.

	CH**H**=CH), 5.24 (s, 2H, OC**H**$_2$Ar), 5.22 (t, 1H, *J* = 5.34 Hz, C**H**OH), 2.25 (br s, 1H, O**H**).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	173.3, 171.6, 135.7, 135.3, 128.6, 128.5, 128.2, 118.0, 92.9, 71.6, 68.3.
IR (neat), cm^{-1}:	3361 (bs), 1615 (s), 1503 (s), 1451 (s), 1364 (s) 1216 (w), 1119 (w), 1036 (s), 986 (s), 932 (s).
HRMS (ESI):	Calcd for $(C_{13}H_{13}NO_3+H)^+$: 232.0973
	Found: 232.0973

(*S*)-Allylic Amine **5**

TLC (40% acetone-hexanes)	R_f = 0.42 (UV, CAM).
^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.46-7.36 (m, 5H, Ar**H**), 5.94 (m, 1H, CH_2=C**H**), 5.81 (s, 1H, Isox**H**), 5.32-5.29 (m, 2H, C**HH**=CH), 5.26 (s, 2H, OC**H**$_2$Ar), 4.00 (d, 1H, *J* = 7.8 Hz, C**H**N(CH$_3$)$_2$), 2.27 (s, 6H, N(C**H**$_3$)$_2$).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	172.5, 171.6, 135.8, 134.1, 128.6, 128.5, 128.3, 119.5, 93.9, 71.5, 66.3, 42.3.
IR (neat), cm^{-1}:	2946 (w), 2869 (w), 2827 (w), 2782 (w), 1607 (s), 1501 (s), 1449 (s), 1366 (s), 1138 (w), 1036 (s), 992 (s), 926 (s).
HRMS (ESI):	Calcd for $(C_{15}H_{18}N_2O_2+H)^+$: 259.1446
	Found: 259.1436

Alternative Preparation of (*R*)-Allylic Alcohol **3**



A. A 200-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was flame-dried, then flushed with argon. The flask was charged with a solution of aldehyde **2** (3.70 g, 18.2 mmol, 1 equiv) in tetrahydrofuran (36 mL). The solution was cooled to –78 °C in a dry ice-acetone bath, then a solution of vinylmagnesium bromide in tetrahydrofuran (1.0 M, 36.5 mL, 36.4 mmol, 2.0 equiv) was added via syringe. The reaction solution was stirred at –78 °C for 40 min and the cooling bath was removed. Saturated aqueous ammonium chloride (50 mL) was added and the product solution was extracted with ethyl acetate (50 mL). The organic layer was washed with saturated aqueous sodium chloride (40 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography on silica gel (30 % ethyl acetate-hexanes) to furnish the (±)-allylic alcohol **3** (4.04 g, 96%) as a clear, colorless oil.

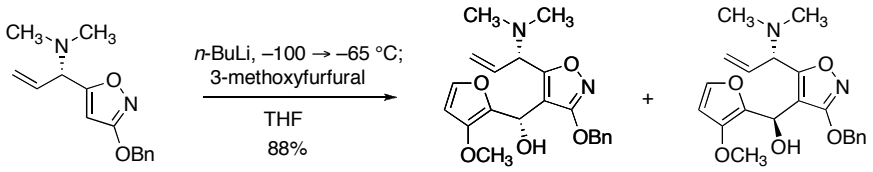
B. A 100-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was flame-dried, then flushed with argon. The flask was charged with a solution of (±)-allylic alcohol **3** (1.00 g, 4.30 mmol, 1 equiv) in hexanes (17 mL). Vinyl acetate (3.40 mL, 36.9 mmol, 8.57 equiv), 4 Å molecular sieves (65 mg), and Amano Lipase AK (125 mg) were then added to the solution sequentially at 23 °C. After stirring for 52.5 h, the reaction mixture was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate-hexanes, grading to 35% ethyl acetate-hexanes) to furnish separately the *R*-allylic acetate **10** (583 mg, 49%, 93% ee by the Mosher method[6] on the corresponding alcohol) as a clear, colorless oil and the *S*-allylic alcohol **3** (500 mg, 50%, 93% ee by the Mosher method) as a clear, colorless oil.

C. A 25-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was flame-dried, then flushed with argon. The flask was charged a solution of (*R*)-allylic acetate **10** (583 mg, 2.14 mmol, 1 equiv) in methanol (7.1 mL). Solid potassium carbonate (445 mg, 3.20 mmol, 1.50 equiv) was added to the solution in one portion at 23 °C. After stirring for 17 min, the reaction mixture was partitioned between water (100 mL) and ethyl ether (100 mL). The layers were separated and the organic layer was washed with saturated aqueous sodium chloride solution (50 mL). The washed layer was dried over sodium sulfate and the solids were filtered. The filtrate was concentrated to furnish the (*R*)-allylic alcohol **3** (490 mg, 99%) as a clear, colorless oil.

(*R*)-Allylic Acetate **10**

TLC (40% ethyl acetate-hexanes)	R_f = 0.50 (UV, CAM).
^{1}HNMR (500 MHz, $CDCl_3$), δ:	7.45-7.35 (m, 5H, Ar**H**), 6.28 (d, 1H, *J* = 6.8 Hz, C**H**OAc), 6.01 (ddd, 1H, *J* = 17.1, 10.3, 6.8 Hz, CH_2=C**H**), 5.91 (s, 1H, Isox**H**), 5.46 (d, 1H, *J* = 17.1, *trans*-CH**H**=CH), 5.40 (d, 1H, *J* = 10.3 Hz, *cis*-CH**H**=CH), 5.26 (s, 2H, OC**H$_2$**Ar), 2.13 (s, 3H, C(O)C**H$_3$**).
^{13}CNMR (100 MHz, $CDCl_3$), δ:	171.4, 169.6, 169.3, 135.6, 131.4, 128.6, 128.5, 128.2, 120.0, 94.5, 71.6, 68.2, 20.8.
IR (neat), cm^{-1}:	1746 (s), 1619 (m), 1507 (s), 1451 (m), 1368 (s), 1027 (m), 980 (m), 904 (s).
HRMS (ESI):	Calcd for $(C_{15}H_{15}NO_4+H)^+$: 274.1079
	Found: 274.1091

Diels–Alder Precursors **7**



An oven-dried, 5-L, three-necked, round-bottomed flask was equipped with a mechanical stirrer, two rubber septa, and an internal thermocouple, and the flask was charged with a solution of isoxazole **5** (74.5 g, 288 mmol, 1 equiv) in tetrahydrofuran (1.44 L). The solution was cooled to –100 °C in a bath of ethanol cooled with liquid dinitrogen, and a solution of *n*-butyllithium in hexanes (2.41 M, 138 mL, 332 mmol, 1.15 equiv) was added dropwise over 50 min to the cooled solution. The resulting dark-yellow solution was allowed to warm to –65 °C over 22 min, at which point the mixture had become reddish-brown. The mixture was stirred at –65 °C for 80 min and then a solution of 3-methoxyfurfural (40 g, 317 mmol, 1.1 equiv, vide infra) in tetrahydrofuran (350 mL) was added dropwise via cannula over 30 min. The reaction mixture was allowed to warm to –50 °C over 50 min and aqueous potassium phosphate solution (pH 7.0, 0.05 M, 1.5 L) was added. The product solution was extracted with dichloromethane (1 x 2 L, 2 x 700 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The solids were filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography on silica gel (70% ethyl ether-pentane) to furnish the Diels–Alder precursors **7** (97.6 g, 88%, 1.3:1 mixture of (*S*)- and (*R*)- epimers, respectively) as a pale red oil. In practice, the two

epimers were not separated nor further purified prior to use in the subsequent Diels–Alder reaction. Analytical samples of the pure epimers were obtained by radial chromatography (50% acetone-hexanes).

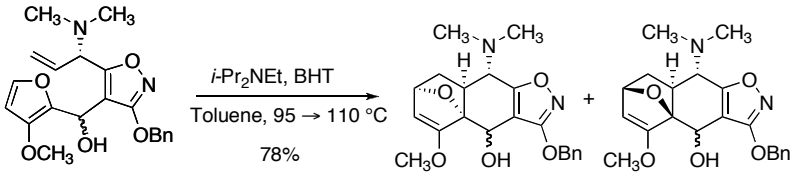
(*S*)-Alcohol **7**

TLC (60% diethyl ether-pentane)	R_f = 0.16 (UV, CAM)
^{1}H NMR (500 MHz, $CDCl_3$), δ:	8.15 (s, 1H, O**H**), 7.33-7.23 (m, 5H, Ar**H**), 7.13 (d, 1H, *J* = 1.95, Fur**H**), 6.23 (d, 1H, *J* = 1.95, Fur**H**), 6.23-6.10 (ddd, 1H, *J* = 17.1, 9.8, 9.8 Hz, CH_2=C**H**), 5.76 (s, 1H, C**H**OH), 5.38-5.35 (m, 2H, C**HH**=CH), 5.16 (AB quartet, 2H, *J* = 12.2 Hz, Δν = 8.1 Hz, -OC**H$_2$**Ar), 4.00 (d, 1H, *J* = 9.3 Hz, C**H**N$(CH_3)_2$), 3.59 (s, 3H, OC**H$_3$**), 2.32 (s, 1H, CHN(C**H$_3$**)$_2$).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	169.1, 167.8, 144.5, 140.4, 137.9, 135.9, 132.1, 128.3, 128.0, 127.5, 121.0, 107.0, 102.7, 71.1, 68.3, 58.9, 58.3, 42.1.
IR (neat), cm^{-1}:	2875 (w), 2846 (w), 2792 (w), 1632 (m), 1511 (m), 1451 (m), 1368 (m), 1106 (m), 1040 (m), 905 (s).
HRMS (ESI):	Calcd for $(C_{21}H_{24}N_2O_5+H)^+$: 385.1763 Found: 385.1747

(*R*)-Alcohol **7**

TLC (60% diethyl ether-pentane)	R_f = 0.16 (UV, CAM)
^{1}H NMR (500 MHz, $CDCl_3$), δ:	8.09 (s, 1H, O**H**), 7.33-7.23 (m, 5H, Ar**H**), 7.12 (d, 1H, *J* = 1.95, Fur**H**), 6.25 (d, 1H, *J* = 1.95, Fur**H**), 6.19-6.10 (ddd, 1H, *J* = 16.9, 9.6, 9.6 Hz, CH_2=C**H**), 5.72 (s, 1H, C**H**OH), 5.41-5.37 (m, 2H, C**HH**=CH), 5.20 (AB quartet, 2H, *J* = 12.2 Hz, Δν = 8.1 Hz, -OC**H$_2$**Ar), 4.18 (d, 1H, *J* = 9.6 Hz, C**H**N$(CH_3)_2$), 3.61 (s, 3H, OC**H$_3$**), 2.32 (s, 1H, CHN(C**H$_3$**)$_2$).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	169.1, 168.6, 144.2, 140.2, 138.8, 135.9, 131.3, 128.3, 128.1, 127.6, 121.3, 107.3, 102.9, 71.1, 67.8, 59.1, 57.9, 41.9.
IR (neat), cm^{-1}:	2875 (w), 2846 (w), 2792 (w), 1632 (m), 1511 (m), 1451 (m), 1368 (m), 1106 (m), 1040 (m), 905 (s).
HRMS (ESI):	Calcd for $(C_{21}H_{24}N_2O_5+H)^+$: 385.1763 Found: 385.1747

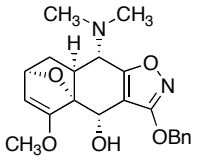
Diels–Alder Adducts



A 5-L, two-necked, round-bottomed flask was charged with a solution of Diels–Alder precursors **7** (97.6 g, 254 mmol, 1 equiv) and 2,6-di-*tert*-butyl-4-methylphenol (200 mg) in toluene (2.54 L). The solution was cooled to 0 °C in an ice-water bath and vacuum was applied (~1 Torr). After 60 min, argon (1 atm) was introduced. *N,N*-diisopropylethylamine (88.5 mL, 508 mmol, 2.00 equiv) was added, the flask was equipped with a reflux condensor and a thermometer, and the reaction mixture was heated at 95 °C in a heating mantle. After stirring for 105 h, the reaction mixture was further heated at 110 °C for 23 h. The reaction solution was cooled to 23 °C and the cooled product mixture was loaded directly onto a plug of silica gel (14 cm diameter, 17 cm length). The reaction solvent (toluene) was eluted with 15% acetone-hexanes; grading to 65% acetone-hexanes led to elution of the Diels–Alder products (76.6 g, 78%). The diastereomeric mixture was subjected to Swern oxidation in the next step, without further purification. Analytical samples of the four Diels–Alder products were prepared by radial chromatography (20% acetone-dichloromethane grading to 30% acetone-dichloromethane).

TLC (50% acetone-hexanes) R_f = 0.23-0.35 (all isomers) (UV, CAM).

Endo Adduct from (*S*)-alcohol **7**

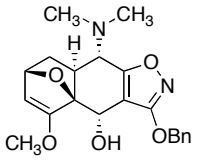


^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.48 (d, 2H, *J* = 7.7 Hz, Ar**H**), 7.41-7.35 (m, 3H, Ar**H**), 5.33 (s, 2H, OC**H$_2$**Ar), 5.23 (d, 1H, *J* = 2.4 Hz, C**H**=COCH$_3$), 5.03 (d, 1H, *J* = 2.4 Hz, C**H**OH), 5.00 (dd, 1H, *J* = 4.4, 2.4 Hz, C**H**CH=COCH$_3$), 3.44 (s, 3H, OC**H$_3$**), 3.10 (d, 1H, *J* = 11.2 Hz, C**H**N(CH$_3$)$_2$), 2.82 (ddd, 1H, *J* = 11.2, 9.3, 4.4 Hz, C**H**CHN(CH$_3$)$_2$), 2.48 (s, 6H, CHN(C**H$_3$**)$_2$), 2.35 (ddd, 1H, *J* = 11.2, 9.3, 4.4 Hz, C**H**HCHCHN(CH$_3$)$_2$), 2.28 (d, 1H, *J* = 2.4 Hz, O**H**), 1.38 (dd, 1H, *J* = 11.2, 4.4 Hz, CH**H**CHCHN(CH$_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 173.5, 169.5, 162.8, 135.8, 128.5, 128.5, 128.4, 128.3, 108.5, 102.2, 87.4, 79.3, 71.6, 64.2, 58.9, 57.5, 41.9, 34.4, 33.0.

HRMS (ESI): Calcd for $(C_{21}H_{24}N_2O_5+H)^+$: 385.1763
Found: 385.1752

Exo Adduct from (*S*)-alcohol **7**

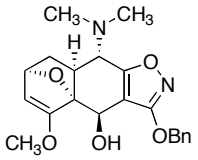


^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.45 (d, 2H, *J* = 7.3 Hz, Ar**H**), 7.39-7.33 (m, 3H, Ar**H**), 5.30 (s, 2H, OC**H$_2$**Ar), 5.28 (d, 1H, *J* = 1.9 Hz, C**H**=COCH$_3$), 5.17 (s, 1H, C**H**OH), 4.88 (dd, 1H, *J* = 4.4, 2.0 Hz, C**H**CH=COCH$_3$), 3.79-3.77 (m, 2H, O**H**, C**H**N(CH$_3$)$_2$), 3.68 (s, 3H, OC**H$_3$**), 2.43-2.38 (m, 7H, CHN(C**H$_3$**)$_2$, C**H**CHN(CH$_3$)$_2$), 2.24 (dd, 1H, *J* = 11.5, 8.1 Hz, C**H**HCHCHN(CH$_3$)$_2$), 1.96 (ddd, 1H, *J* = 11.2, 3.9, 3.9 Hz, CH**H**CHCHN(CH$_3$)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$), δ: 169.9, 169.1, 166.7, 135.8, 128.5, 128.3, 128.3, 106.9, 103.7, 86.7, 76.9, 71.5, 65.5, 61.4, 58.1, 43.4, 41.9, 35.5.

HRMS (ESI): Calcd for $(C_{21}H_{24}N_2O_5+H)^+$: 385.1763
Found: 385.1776

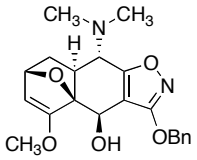
Endo Adduct from (*R*)-alcohol **7**



^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.49 (d, 2H, *J* = 7.0 Hz, Ar**H**), 7.40-7.34 (m, 3H, Ar**H**), 5.36-5.31 (m, 3H, OC**H$_2$**Ar, C**H**=COCH$_3$), 5.07 (dd, 1H, *J* = 9.0, 2.0 Hz, C**H**OH), 4.99 (dd, 1H, *J* = 4.1, 2.2 Hz, C**H**CH=COCH$_3$), 3.57 (s, 3H, OC**H$_3$**), 3.22 (dd, 1H, *J* = 11.2, 2.0 Hz, C**H**N(CH$_3$)$_2$), 2.48 (s, 1H, *J* = 9.0 Hz, O**H**), 2.43-2.33 (m, 7H, CHN(C**H$_3$**)$_2$, C**H**CHN(CH$_3$)$_2$), 2.31 (ddd, 1H, *J* =

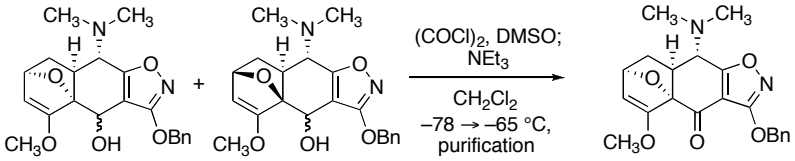
	11.5, 9.3, 4.1 Hz, C**H**HCHCHN$(CH_3)_2$), 1.40 (dd, 1H, *J* = 11.5, 3.9 Hz, CH**H**CHCHN$(CH_3)_2$).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	171.4, 169.3, 162.5, 135.8, 128.6, 128.5, 128.4, 128.2, 108.5, 103.4, 90.0, 79.1, 71.6, 65.1, 63.7, 57.9, 41.8, 41.8, 33.1.
HRMS (ESI):	Calcd for $(C_{21}H_{24}N_2O_5+H)^+$: 385.1763
	Found: 385.1755

Exo Adduct from (*R*)-alcohol **7**



^{1}H NMR (500 MHz, C_6D_6), δ:	7.35 (d, 2H, *J* = 7.3 Hz, Ar**H**), 7.08 (t, 2H, *J* = 7.8 Hz, Ar**H**), 7.03 (t, 1H, *J* = 7 Hz, Ar**H**), 5.57 (dd, 1H, *J* = 9.8, 2.0 Hz, C**H**OH), 5.31 (AB quartet, 2H, *J* = 12.2 Hz, Δν = 15.1 Hz, -OC**H$_2$**Ar), 4.62 (dd, 1H, *J* = 4.1, 2.0 Hz, C**H**CH=COCH$_3$), 4.59 (d, 1H, *J* = 2.0 Hz, C**H**=COCH$_3$), 3.52 (dd, 1H, *J* = 9.8, 2.0 Hz, C**H**N$(CH_3)_2$), 3.02 (s, 3H, OC**H$_3$**), 2.58 (d, 1H, *J* = 9.8 Hz, O**H**), 2.23 (s, 6H, CHN(C**H$_3$**)$_2$), 2.02 (ddd, 1H, *J* = 9.8, 7.8, 2.4 Hz, C**H**CHN$(CH_3)_2$), 1.78 (ddd, 1H, *J* = 11.6, 4.1, 2.4 Hz, C**H**HCHCHN$(CH_3)_2$), 1.69 (dd, 1H, *J* = 11.6, 7.8 Hz, CH**H**CHCHN$(CH_3)_2$).
^{13}C NMR (100 MHz, C_6D_6), δ:	170.5, 169.6, 164.5, 136.7, 128.6, 128.3, 128.3, 107.9, 101.3, 89.1, 77.9, 71.6, 64.7, 59.4, 57.1, 42.7, 41.7, 40.2.
HRMS (ESI):	Calcd for $(C_{21}H_{24}N_2O_5+H)^+$: 385.1763
	Found: 385.1751

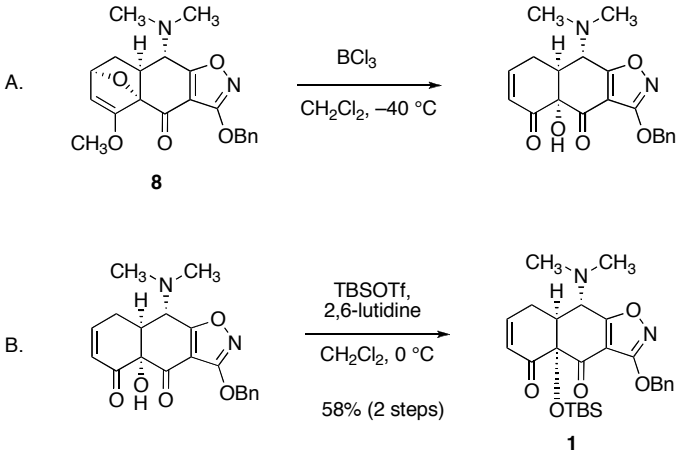
Ketone (**8**)



A 5-L, three-necked, round-bottomed flask was oven-dried then flushed with argon. The flask was equipped with a mechanical stirrer, two rubber septa, and an internal thermocouple, then was charged with a solution of oxalyl chloride (24.6 mL, 279 mmol, 1.40 equiv) in dichloromethane (1 L). The solution was cooled to –78 °C in a dry ice-acetone bath. A solution of dimethyl sulfoxide (35.3 mL, 498 mmol, 2.50 equiv) in dichloromethane (500 mL) was added dropwise over 90 min. After 10 min, a solution of the Diels–Alder adducts from the experiment above (76.6 g, 199 mmol, 1 equiv) in dichloromethane (500 mL) was added to the cold reaction solution dropwise via cannula. The flask containing the Diels–Alder adducts was rinsed with dichloromethane (25 mL) and the rinse solution was transferred to the reaction flask via cannula. The reaction solution was stirred at –78 °C for 25 min and then triethylamine (139 mL, 995 mmol, 5.00 equiv) was added. The reaction solution then was allowed to warm to –65 °C over 80 min and saturated aqueous sodium bicarbonate solution (700 mL) was added. The product solution was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.05 M, 500 mL) and dichloromethane (750 mL). The aqueous layer was extracted with dichloromethane (500 mL). The organic layers were combined and the combined layers were dried over sodium sulfate. The solids were filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography on silica gel (30% acetone-hexanes, grading to 50% acetone-hexanes) to furnish the ketone **8**, a single, pure diastereomer (55.4 g, 73%) as a pale yellow solid.

TLC (50% acetone-hexanes)	R_f = 0.33 (UV, CAM).
^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.51 (d, 2H, *J* = 6.8 Hz, Ar**H**), 7.40-7.34 (m, 3H, Ar**H**), 5.37 (AB quartet, 2H, *J* = 12.2 Hz, Δν = 9.0 Hz, -OC**H**$_2$Ar), 5.31 (d, 1H, *J* = 2.0 Hz, C=C**H**), 5.05 (dd, 1H, *J* = 4.4, 2.4 Hz, C=CHC**H**), 3.52 (s, 3H, OC**H**$_3$), 3.46 (d, 1H, *J* = 11.2 Hz, C**H**$(NCH_3)_2$), 2.81 (ddd, 1H, *J* = 11.2, 9.0, 4.9 Hz, C**H**CH$(NCH_3)_2$), 2.49 (s, 6H, NC**H**$_3)_2$), 2.37 (ddd, 1H, *J* = 11.2, 9.0, 4.4 Hz, C**H**HCHCHN$CH_3)_2$), 1.49 (dd, 1H, *J* = 11.2, 4.9 Hz, C**H**HCHCHN$CH_3)_2$).
^{13}C NMR (100 MHz, C_6D_6), δ:	184.5, 184.2, 167.5, 161.5, 135.1, 128.5, 128.5, 128.2, 110.5, 102.3, 89.5, 79.7, 72.3, 64.6, 57.8, 44.1, 41.8, 32.8.
IR (neat), cm^{-1}:	2944 (w), 2875 (w), 2838 (w), 2796 (w), 1710 (s), 1632 (s), 1580 (s), 1505 (s), 1453 (s), 1370 (m), 1339 (m), 1308 (m), 1023 (m), 949 (s).
HRMS (ESI):	Calcd for $(C_{21}H_{22}N_2O_5+H)^+$: 383.1607
	Found: 383.1593

Tetracycline Precursor **1**



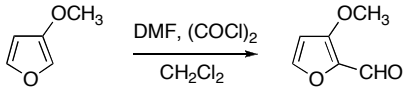
A. A 3-L, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was flame-dried, then flushed with argon. The flask was charged with a solution of ketone **8** (55.4 g, 145 mmol, 1 equiv) in dichloromethane (1.45 L). The reaction flask was cooled to –40 °C in an acetone bath and a solution of boron trichloride in dichloromethane (1.0 M, 435 mL, 435 mmol, 3.00 equiv) was added to the cooled solution. The yellow reaction mixture was stirred for 25 min, a solution of dipotassium hydrogenphosphate (120 g) in water (1 L) was added, and the cooling bath was removed. The reaction mixture was adjusted to pH 7 with additional aqueous dipotassium hydrogenphosphate solution. The biphasic mixture was partitioned and the aqueous layer was extracted with dichloromethane (1 L). The organic layers were combined and the combined layers were dried over sodium sulfate. The solids were filtered and the filtrate was concentrated for use directly in the subsequent silylation reaction.

B. A 3-L, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was flame-dried, then flushed with argon. The flask was charged with a solution of the residue obtained above (step A) in dichloromethane (1.45 L). The solution was cooled in an ice-water bath. 2,6-Lutidine (33.5 mL, 305 mmol, 2.10 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (53.3 mL, 232 mmol, 1.6 equiv) were added sequentially to the cooled solution. The reaction solution was stirred at 0 °C for 15 min and the cooling bath was removed. The reaction solution was stirred at 23 °C for 20 min,

then was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.05 M, 1 L) and dichloromethane (500 mL). The aqueous layer was separated and extracted with dichloromethane (500 mL). The organic layers were combined and the combined layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography on silica gel (100% dichloromethane, grading to 2% ethyl acetate-dichloromethane) to furnish the tetracycline precursor **1** (40.2 g, 58% over two steps) as a light-yellow foam. The light-yellow foam was recrystallized from ethyl acetate-hexanes (1:4 by volume, 250 mL total volume) to give 27 g of an off-white solid (mp = 150–151 °C). The mother liquor was concentrated and the residue obtained was further recrystallized to give 7.2 g (2nd crop, mp = 150–151 °C) and 1.9 g (3rd crop, mp = 149–150 °C) of product **1**.

TLC (20% ethyl acetate-hexanes)	R_f = 0.34 (UV, CAM).
^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.51 (d, 2H, *J* = 1.5 Hz, Ar**H**), 7.50-7.34 (m, 3H, Ar**H**), 6.94 (m, 1H, =C**H**CH_2), 6.10 (ddd, 1H, *J* = 10.3, 1.5, 1.5 Hz, =C**H**C(O)), 5.36 (m, 2H, OC**H**$_2$Ph), 3.79 (d, 1H, *J* = 10.7 Hz, C**H**N$(CH_3)_2$), 2.83 (m, 2H, =CHC**H**$_2$), 2.78 (m, 1H, C**H**CHN$(CH_3)_2$), 2.46 (s, 6H, N(C**H**$_3)_2$), 0.84 (s, 9H, SiC(C**H**$_3)_3$), 0.27 (s, 3H, SiC**H**$_3$), 0.06 (s, 3H, SiC**H**$_3$).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	193.4, 187.9, 181.6, 167.7, 149.5, 135.2, 128.8, 128.8, 128.8, 128.6, 108.6, 83.5, 72.8, 59.8, 48.1, 42.2, 26.3, 25.8, 19.3, –2.2, –3.8.
IR (neat), cm^{-1}:	2942 (s), 1719 (s), 1678 (s), 1602 (m), 1510 (s), 1053 (s), 733 (s).
HRMS (ESI):	Calcd for $(C_{26}H_{34}N_2O_5+H)^+$: 483.2315
	Found: 483.2310

3-Methoxyfurfural (**6**)

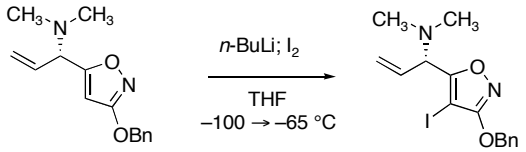


6

A 3-L, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was flame-dried, then flushed with argon. The flask was charged with a solution of *N*,*N*-dimethylformamide (31.9 mL, 413 mmol, 1.35 equiv) in dichloromethane (1.2 L). The solution was cooled to 0 °C in an acetone bath, and oxalyl chloride (32.5 mL, 367 mmol, 1.2 equiv) was added over 16 min. Vigorous gas evolution accompanied the latter addition, and a white solid precipitated. After stirring for 20 min, the reaction mixture was cooled to –40 °C by addition of dry ice to the cooling bath and a solution of 3-methoxyfuran[7] (30 g, 306 mmol, 1 equiv) in dichloromethane (100 mL) was added via cannula. The reaction mixture became dark brown during the addition. After stirring for 20 min, the cooling bath was removed and saturated aqueous sodium bicarbonate solution (1.5 L) was added. The biphasic mixture was stirred vigorously for 6 hours, then was partitioned. The aqueous layer was extracted with dichloromethane (2 x 800 mL). The organic layers were combined and the combined layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography on silica gel (100% ethyl ether) to furnish 3-methoxyfurfural **6** (21.2 g, 55%) as a pale-yellow solid.

TLC (30% ethyl acetate-hexanes)	R_f = 0.14 (UV, CAM).
^{1}H NMR (500 MHz, $CDCl_3$), δ:	9.5 (s, 1H, **H**C=O), 7.45 (d, 1H, *J* = 2.0 Hz, Fur**H**), 6.35 (d, 1H, *J* = 2.0 Hz, Fur**H**), 3.86 (s, 3H, OC**H$_3$**).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	173.9, 158.6, 148.2, 137.4, 102.3, 58.9.
IR (neat), cm^{-1}:	3131 (w), 2945 (w), 2838 (w), 2808 (w), 1653 (s), 1586 (s), 1469 (s), 1426 (s), 1364 (s), 1269 (s), 1109 (s), 988 (m).
HRMS (ESI):	Calcd for $(C_6H_6O_3+H)^+$: 127.0935
	Found: 127.0936

Iodide (**9**)



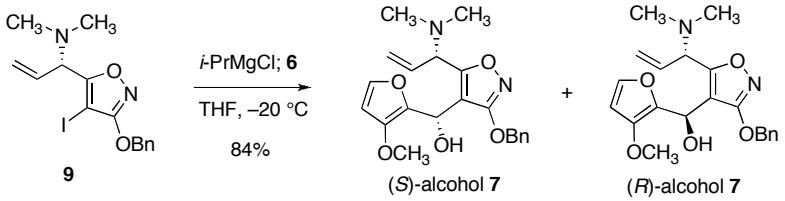
5 **9**

A 200-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was flame-dried, then flushed with argon. The flask was charged with a solution of isoxazole **5** (2.00 g, 7.75 mmol, 1 equiv) in tetrahydrofuran (52 mL). The solution was cooled to –100°C in a liquid dinitrogen-ethanol bath, then a solution of *n*-butyllithium in hexanes (2.50 M, 3.56 mL, 8.91 mmol, 1.15 equiv) was added dropwise over 9 min. The reaction solution was warmed to –65 °C over 15 min. The mixture was stirred at –65 °C for 60 min, then a solution of iodine (2.56 g, 10.1 mmol, 1.30 equiv) in tetrahydrofuran (25 mL) was added via cannula. The reaction solution was stirred at –65 °C for 15 min, and the cooling bath was removed. The product solution was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.05 M, 25 mL), saturated aqueous sodium thiosulfate solution (25 mL), and ethyl acetate (150 mL). The organic layer was washed with saturated aqueous sodium chloride solution and the washed solution was dried over sodium sulfate. The solids were filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography on silica gel (40% ethyl acetate-hexanes) to furnish the iodide **9** (1.97 g, 66%) as a pale yellow solid.

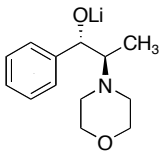
[7] (a) Meister, C.; Scharf, H.-D. *Synthesis* **1981**, 737-739. (b) Meister, C.; Scharf, H.-D. *Synthesis* **1981**, 733-736.

TLC (40% ethyl acetate-hexanes)	R_f = 0.32 (UV, CAM).
^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.47 (d, 2H, *J* = 7.3 Hz, Ar**H**), 7.42-7.36 (m, 3H, Ar**H**), 6.03 (ddd, 1H, *J* = 17.6, 10.3, 7.8 Hz, CH_2=C**H**), 5.34-5.27 (m, 4H, C**H**H=CH, OC**H$_2$**Ar), 4.06 (d, 1H, *J* = 7.8 Hz, C**H**N(CH_3)$_2$), 2.29 (s, 6H, N(C**H$_3$**)$_2$).
^{13}C NMR (125 MHz, C_6D_6), δ:	171.7, 170.9, 135.7, 134.4, 128.8, 128.7, 128.3, 119.7, 72.2, 66.8, 43.2.
IR (neat), cm^{-1}:	3033 (w), 2981 (m), 2949 (m), 2866 (m), 2824 (m), 2779 (m), 1596 (s), 1508 (s), 1455 (s), 1437 (s), 1361 (s), 1254 (m), 1088 (s).
HRMS (ESI):	Calcd for $(C_{15}H_{17}IN_2O_2+H)^+$: 385.0413
	Found: 385.0415

Diels Alder Precursors **7**



A 5-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was flame-dried, then flushed with argon. The flask was charged with a solution of iodide **9** (49 mg, 0.13 mmol, 1 equiv) in tetrahydrofuran (850 μL). The solution was cooled to –20 °C in an acetone bath, then a solution of isopropylmagnesium chloride in tetrahydrofuran (2.0 M, 96 μL, 0.19 mmol, 1.5 equiv) was added dropwise. The resulting pale-yellow solution was stirred for 40 min, then a solution of 3-methoxyfurfural (27 mg, 0.22 mmol, 1.7 equiv) in tetrahydrofuran (450 μL) was added dropwise via cannula. The reaction mixture was stirred for 5 min, then aqueous potassium phosphate solution (pH 7.0, 0.05 M, 4 mL) was added. The product solution was extracted with dichloromethane (2 x 10 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The solids were filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography on silica gel (70% ethyl ether-pentane) to furnish the Diels-Alder precursors **7** (41 mg, 84%, 1.8:1 mixture of epimers) as a pale yellow oil. The product provided spectroscopic data identical to those presented above save for differences attributable to the varying ratio of product diastereomers.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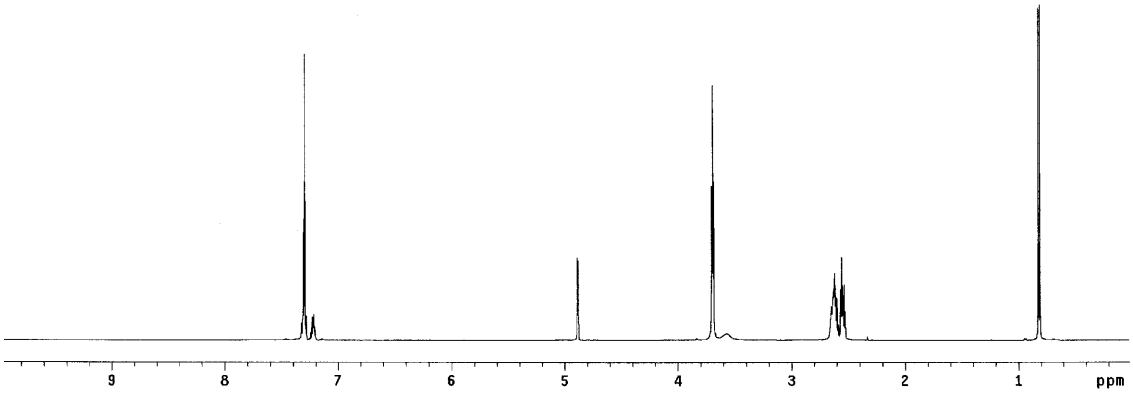
CH3
N
O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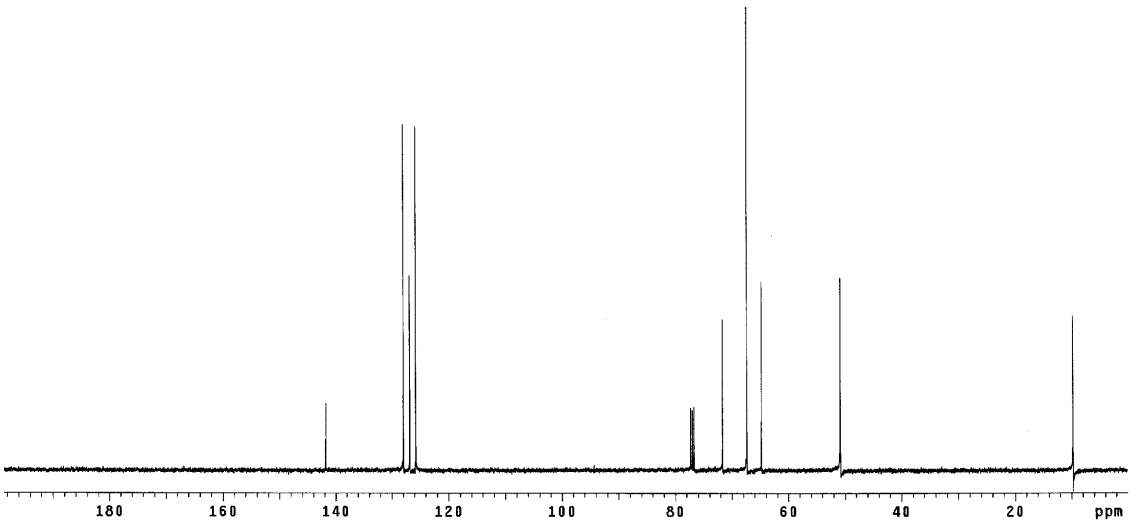
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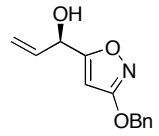
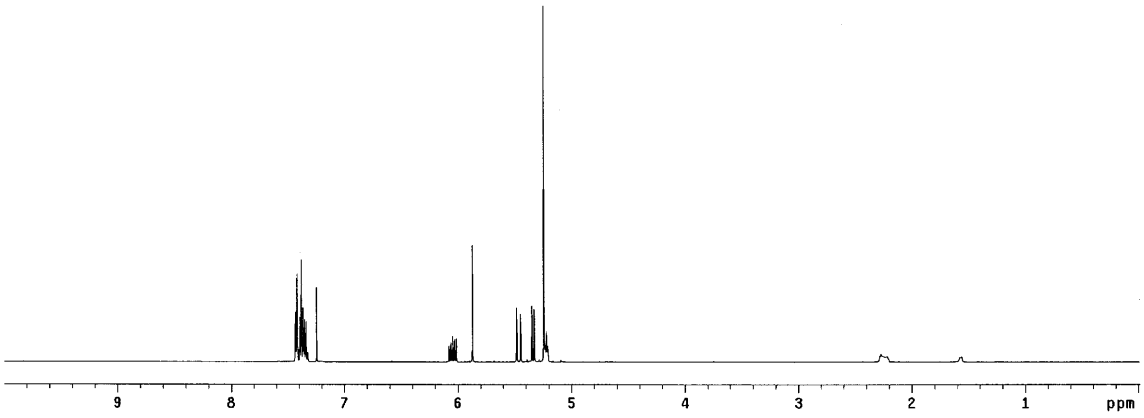
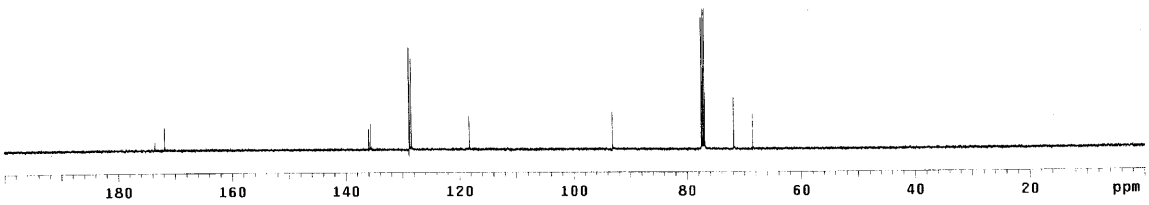
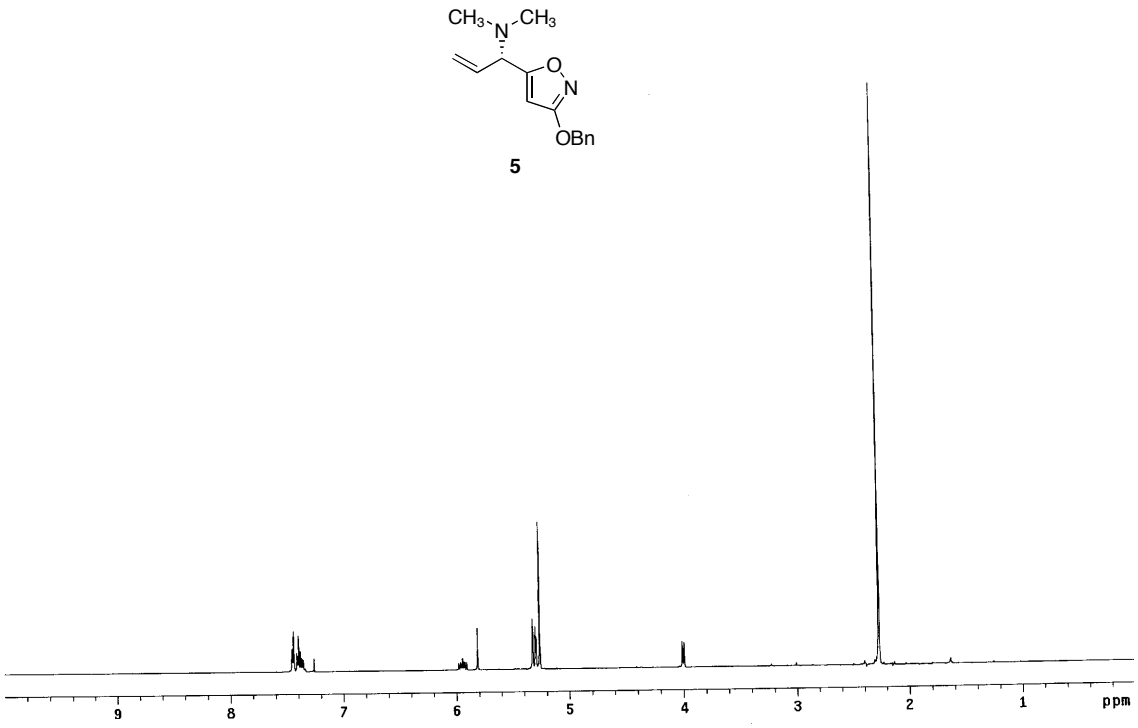


3



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ppm

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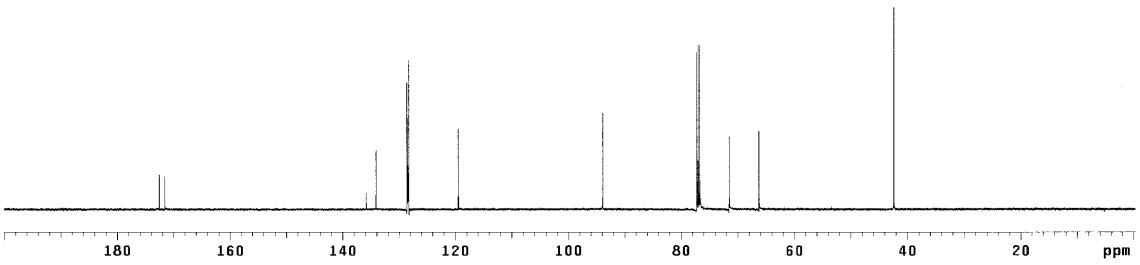
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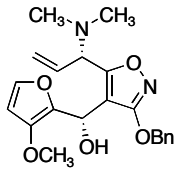
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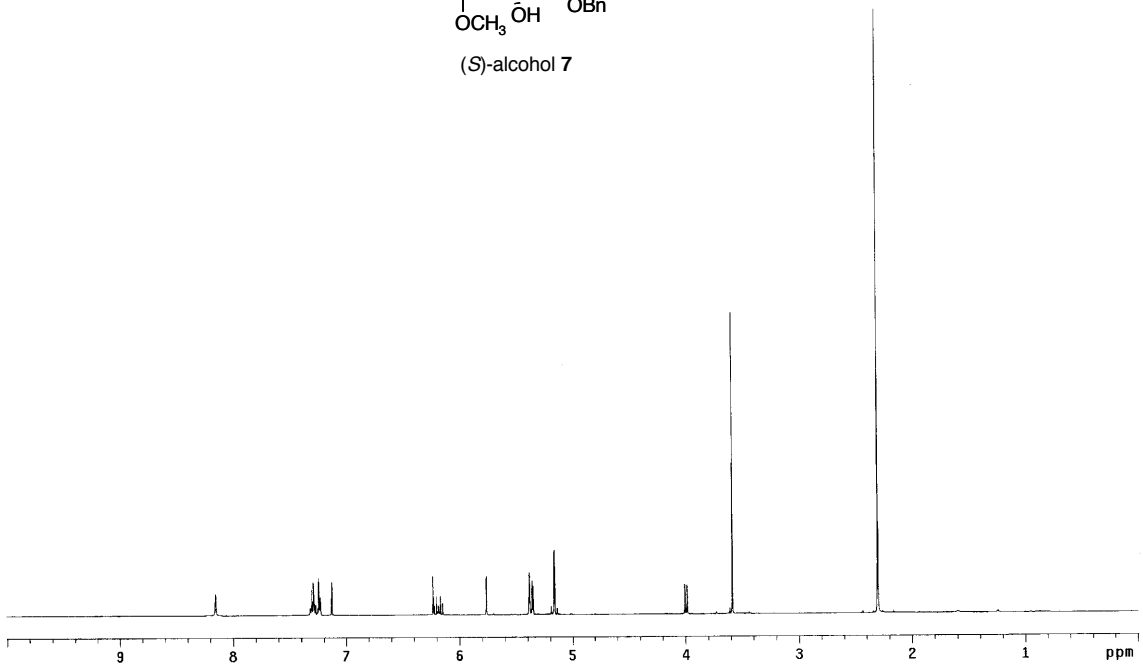
OBn
OCH3
OH

(*S*)-alcohol **7**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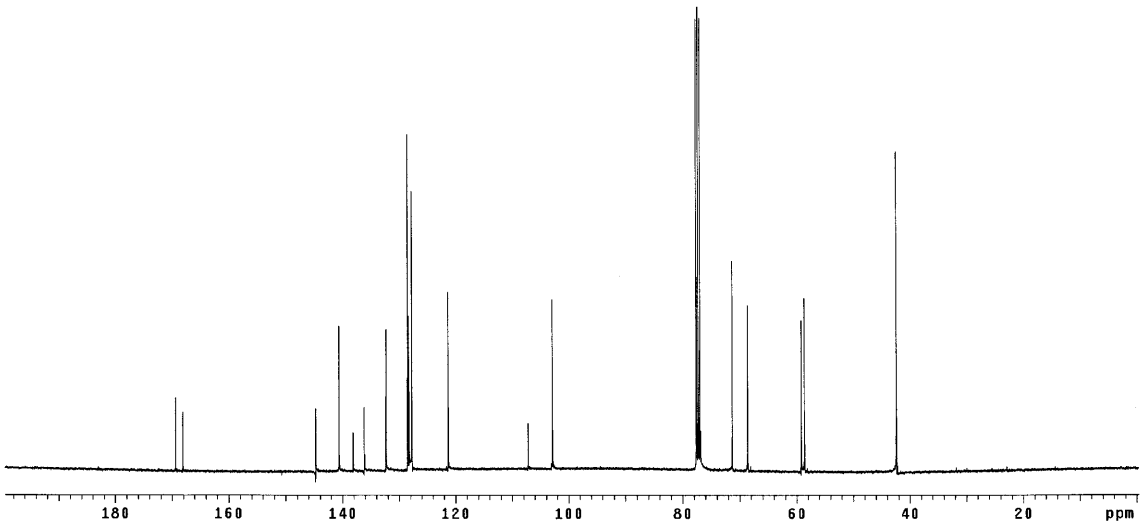
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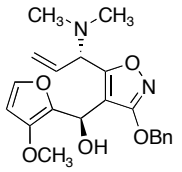
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OH
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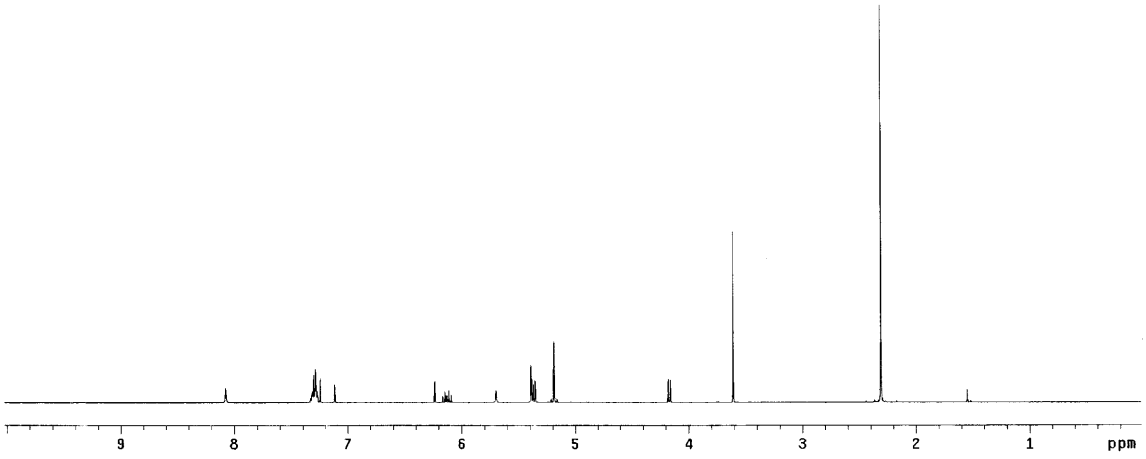
(*R*)-alcohol **7**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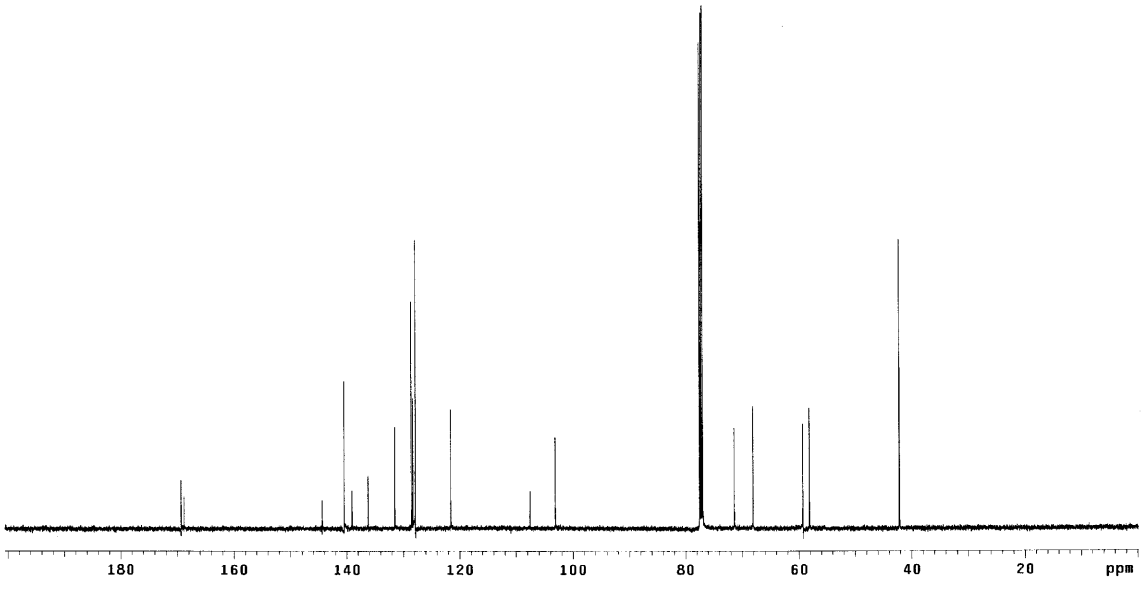
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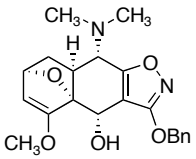
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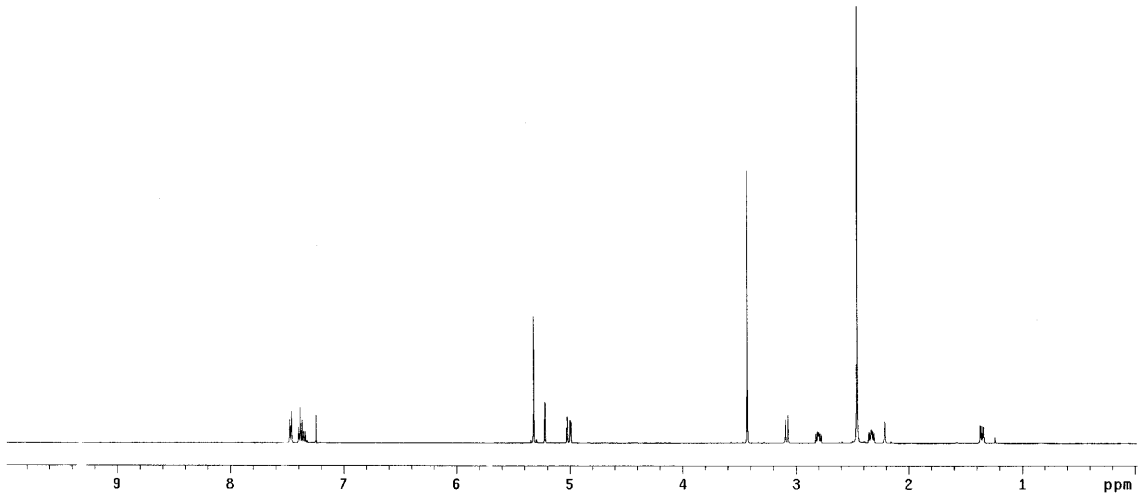
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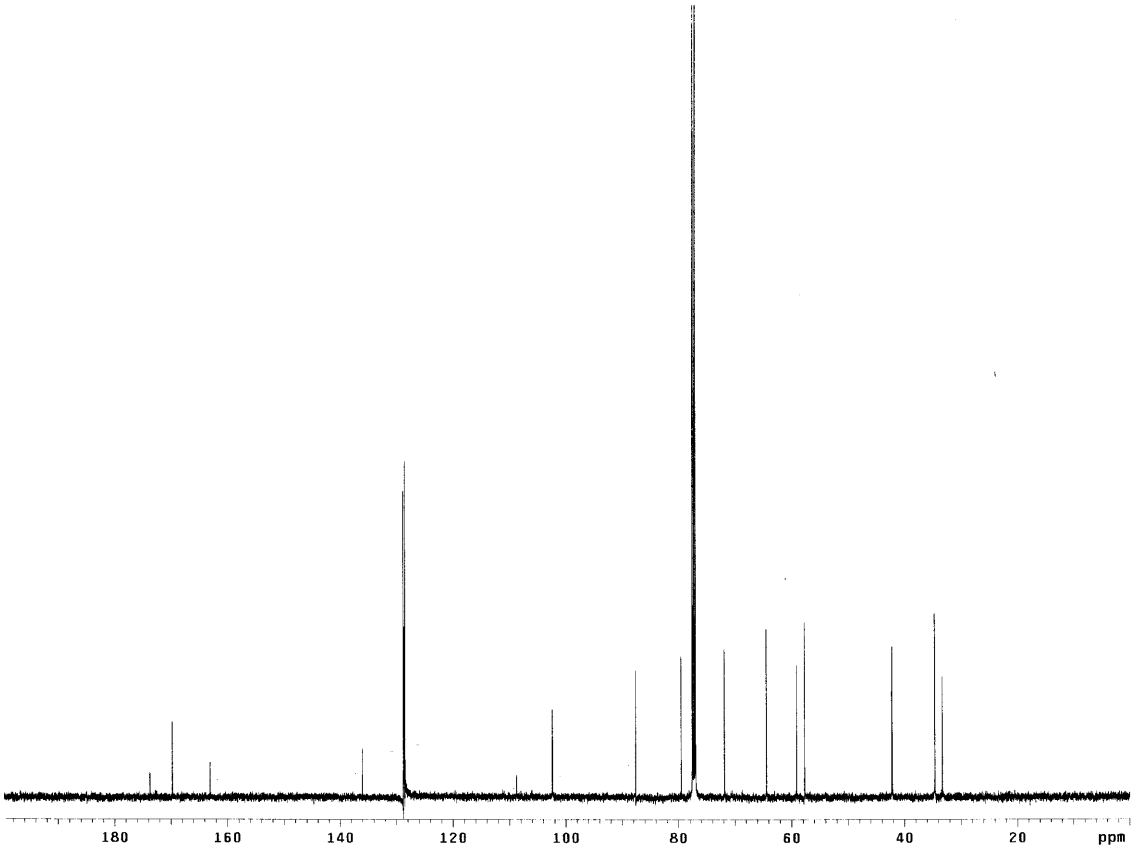
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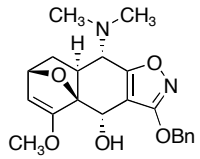
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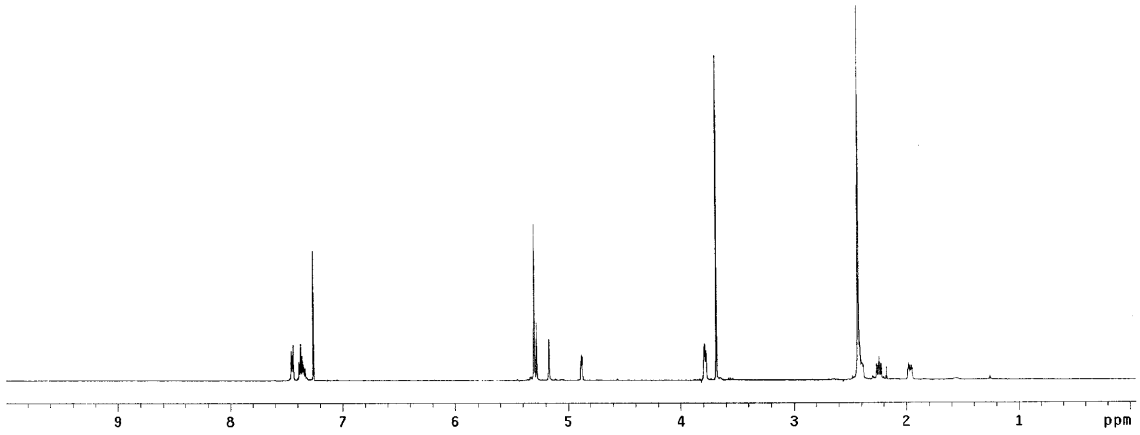
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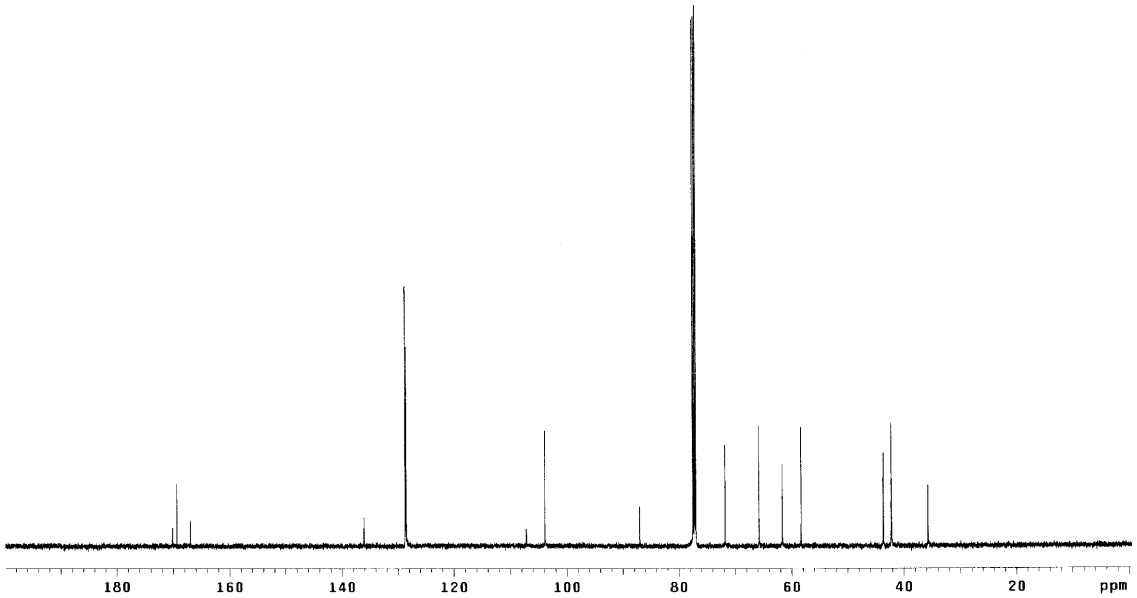
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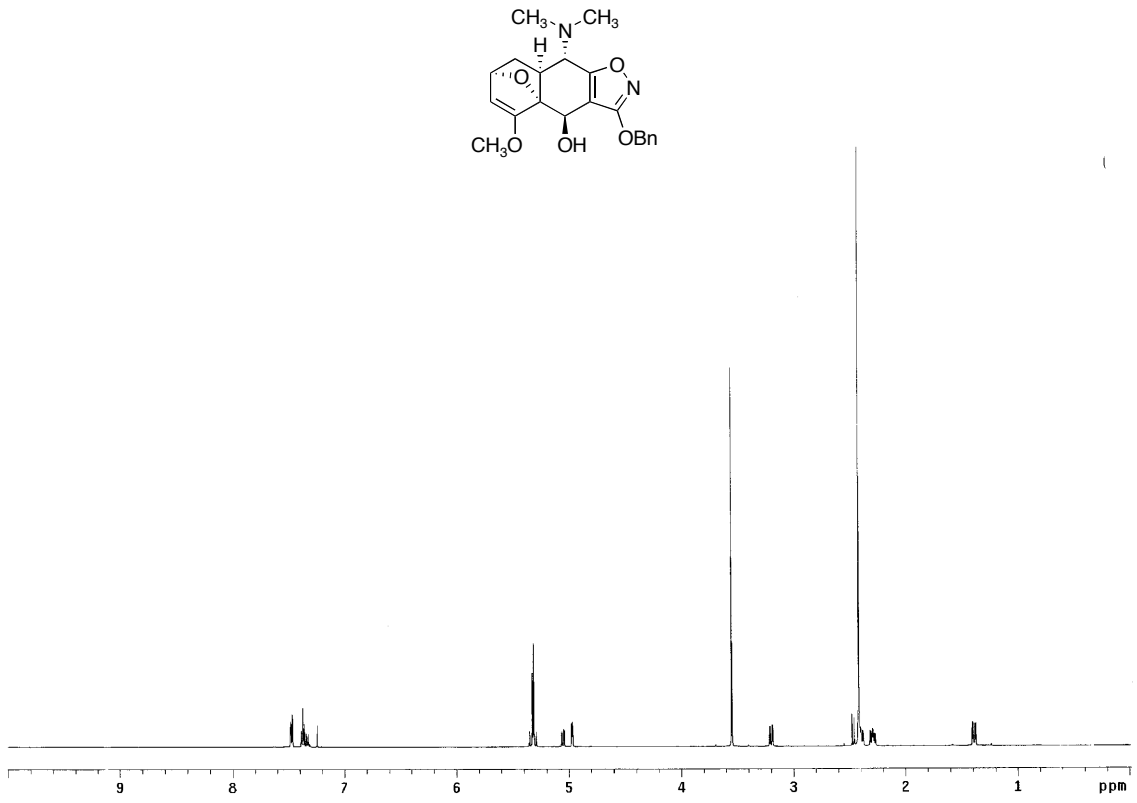
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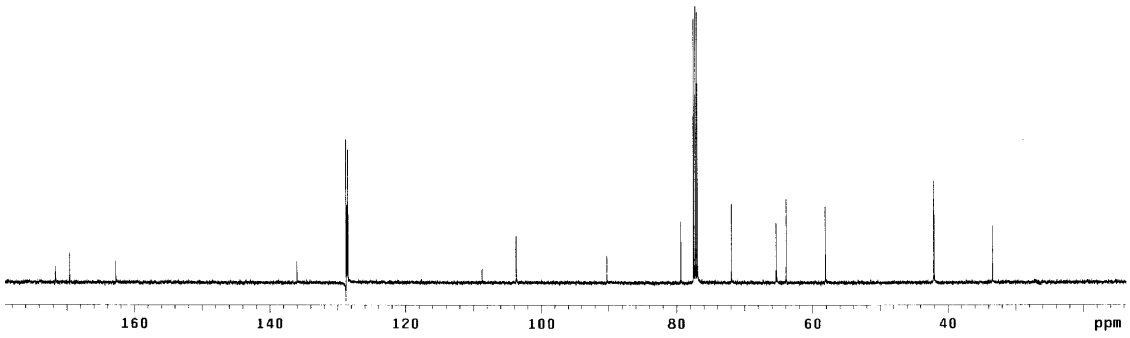
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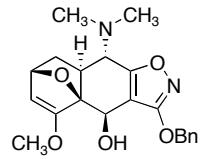
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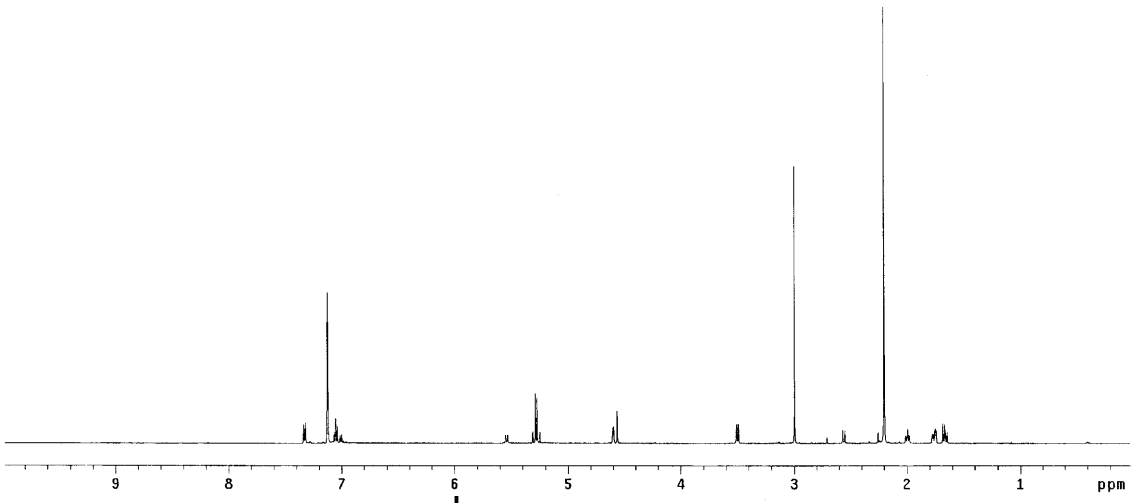
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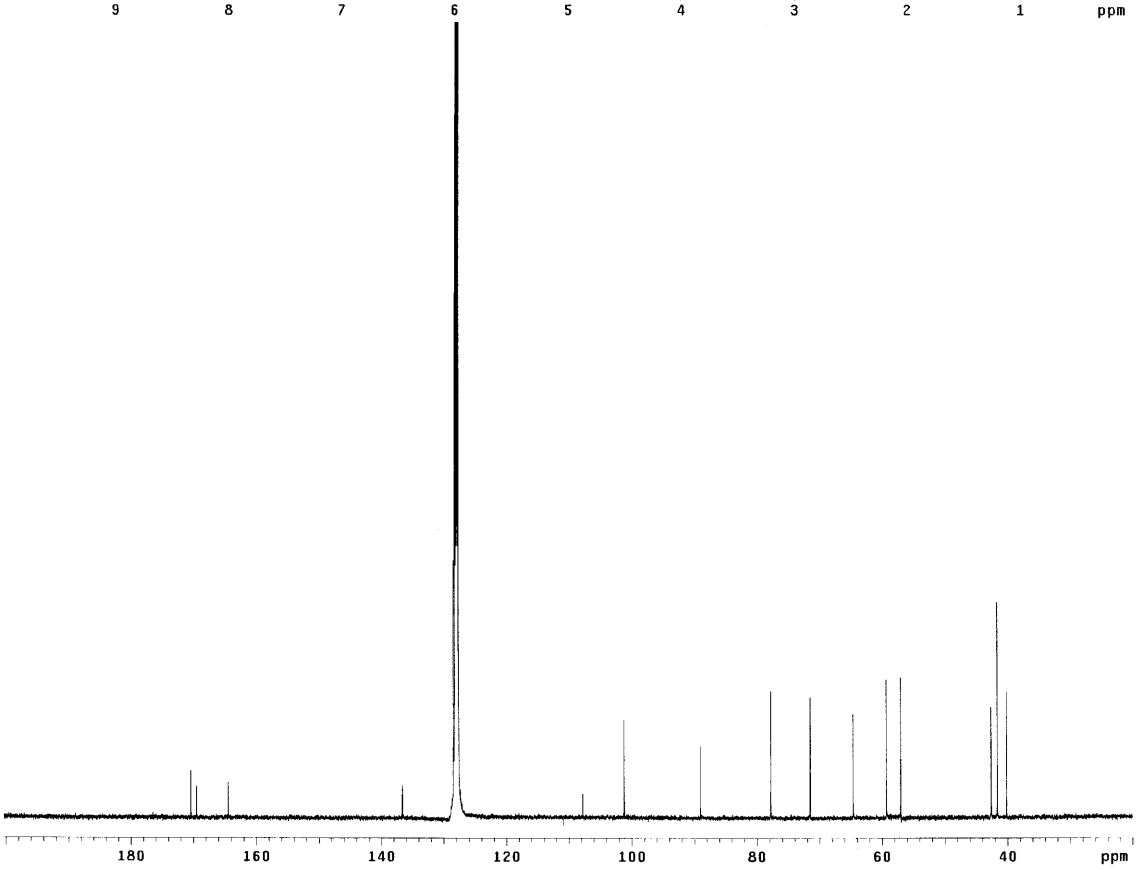
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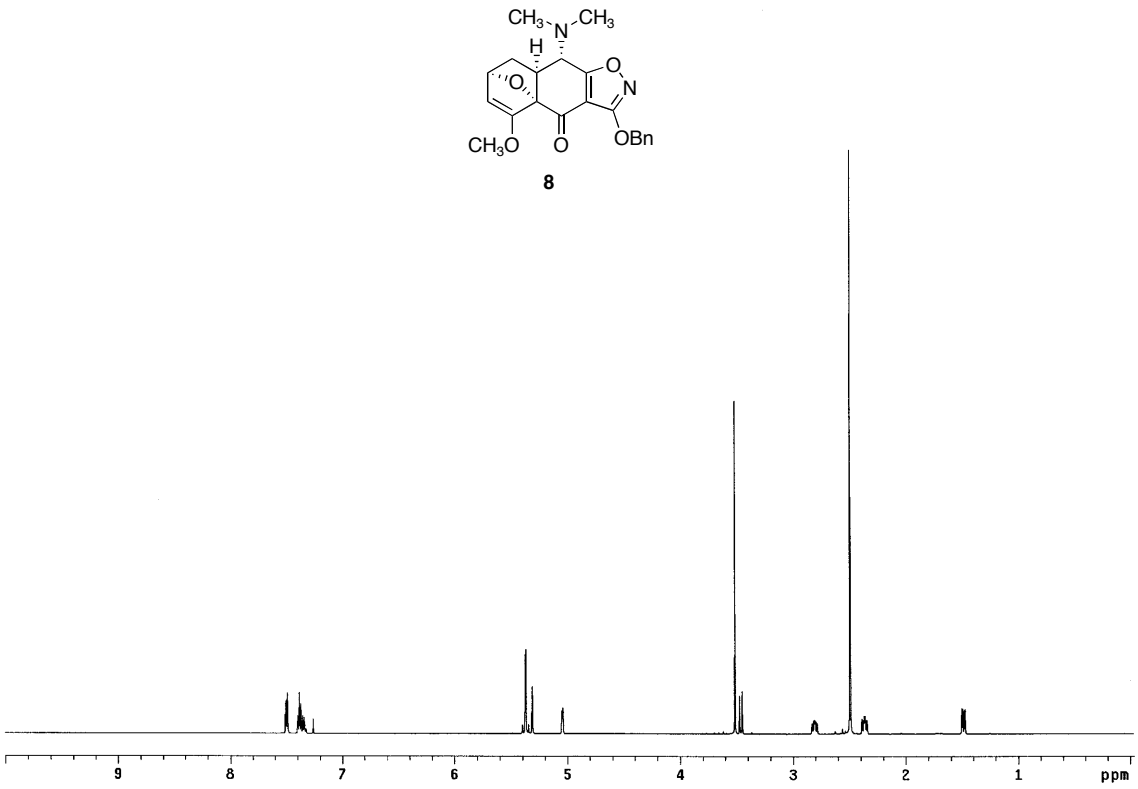
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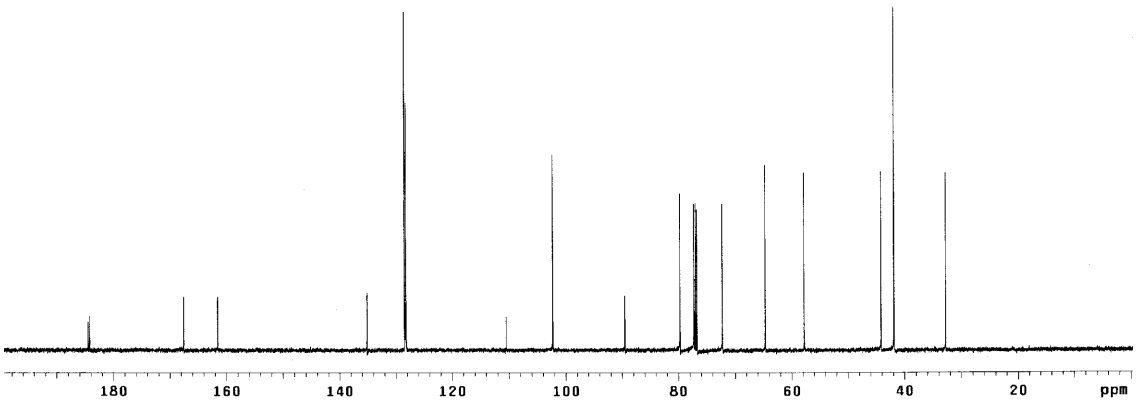
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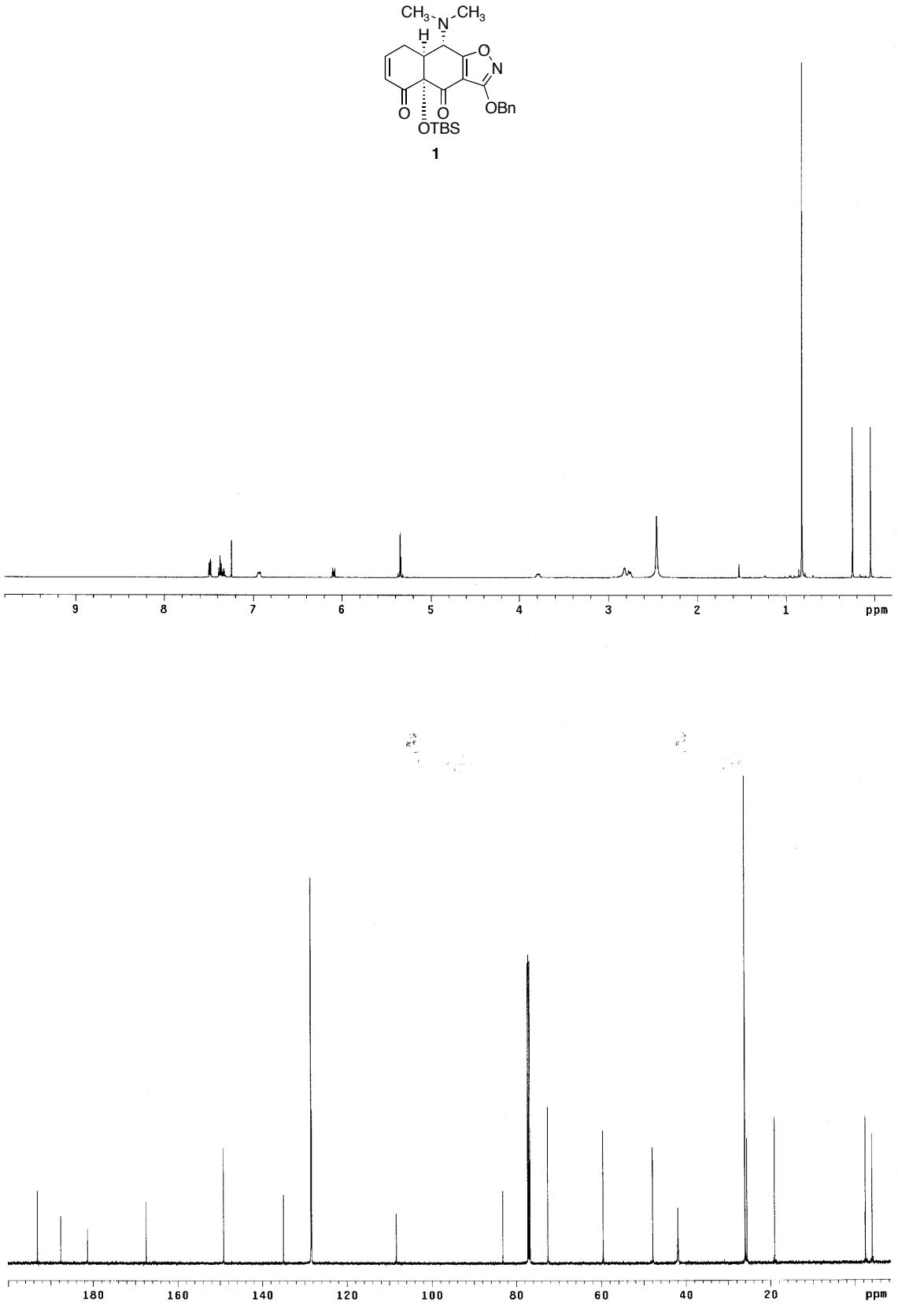
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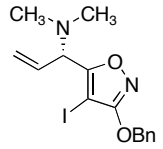
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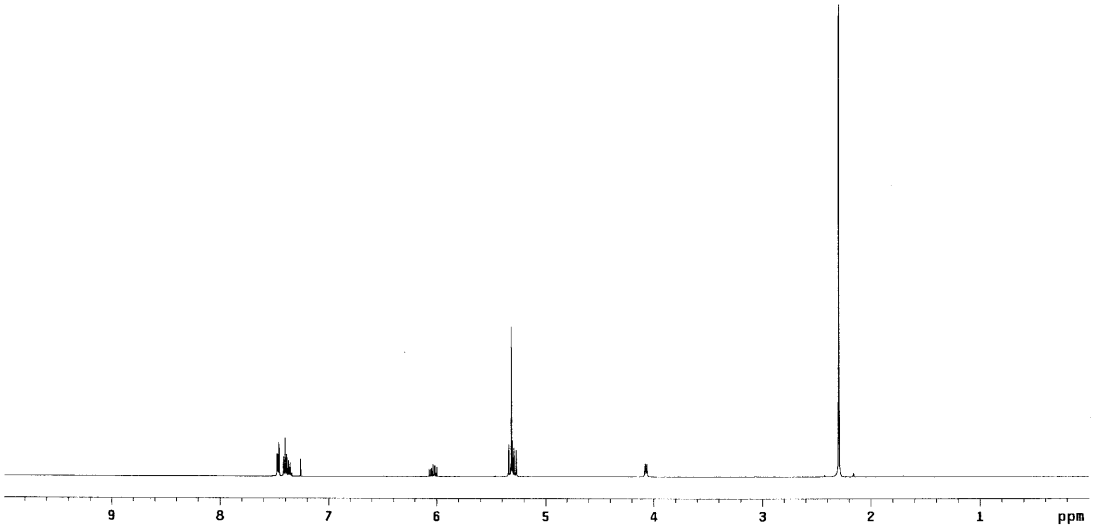
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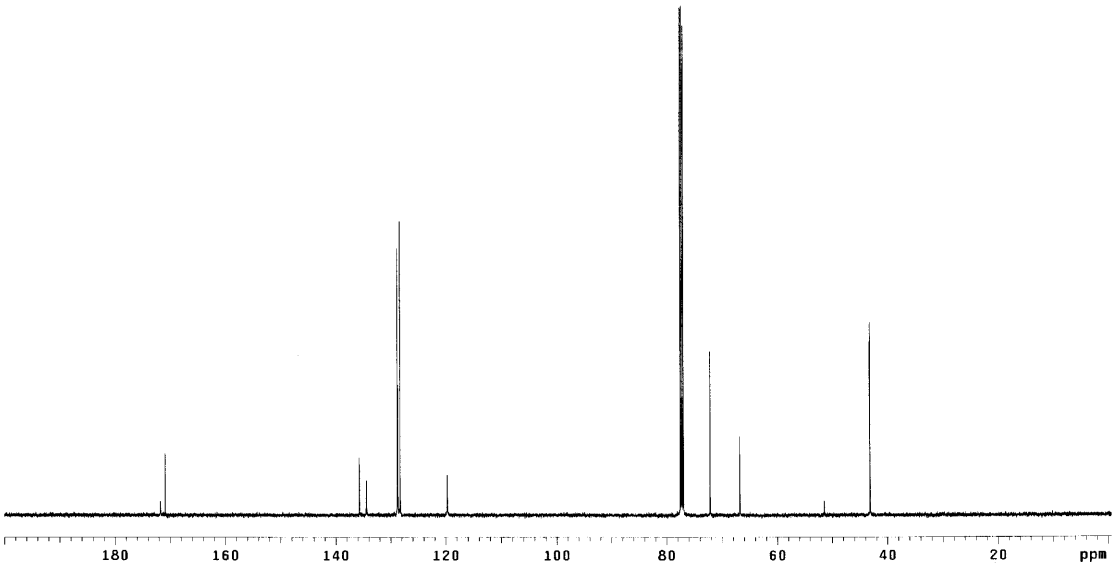
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