Electronic Supplementary Information

Total synthesis of (±)-leuconolam: intramolecular allylic silane addition to a maleimide carbonyl group

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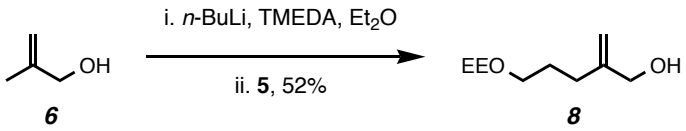
Contents of Supplementary Information

General Experimental Information

All reactions were performed under a dry nitrogen or argon atmosphere unless otherwise noted. All glassware was flame- and/or oven-dried before use. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), and toluene were dried through Al_2O_3 columns. All other reagents and solvents were used as received. (Chloromethyl)trimethylsilane was purchased from Gelest. $Ti(O\text{-}iPr)_4$, $TiCl_4$, $BF_3{\cdot}OEt_2$ and $MeAlCl_2$ were purchased from Sigma-Aldrich. TMSOTf was prepared from tetramethylsilane and TfOH.[1] Thin layer chromatography (TLC) was performed using TLC plastic sheets with F_{254} indicator and visualized with UV-light or staining with either potassium permanganate or anisaldehyde. Flash column purifications were performed using 40-63 μm silica gel. Medium pressure liquid chromatography (MPLC) purifications were performed using glass columns, dry packed with 25-35 μm particle size silica gel. Melting point data were collected on a Köfler hot stage and are uncorrected. NMR spectra were determined in $CDCl_3$ unless otherwise noted. ^{1}H NMR spectra were acquired at 500 MHz. ^{13}C NMR spectra were acquired at 125 or 75 MHz. Chemical shifts (δ) for ^{1}H NMR spectra are referenced to TMS at δ = 0.00 ppm, to CHD_2COCD_3 at δ = 2.04, or to CHD_2OD at δ = 3.31 ppm. ^{13}C NMR spectra are referenced to $CDCl_3$ at δ = 77.23 ppm, to $(CD_3)_2CO$ at δ = 29.9 ppm, to CD_3OD at δ = 49.15 ppm, or to $(CD_3)_2SO$ at δ = 39.51 ppm. The following abbreviations are used to describe NMR resonances: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sext (sextet), m (multiplet), br (broad), and nfom (non-first order multiplet). Coupling constants (*J*) are reported in Hz. Infrared spectra were recorded on an FT-IR spectrometer; the most intense and/or diagnostic peaks are reported; and all spectra were collected in attenuated total reflectance (ATR) mode as thin films on a germanium window. Low-resolution GC-MS data (LRMS) were recorded at 70 eV. High-resolution mass spectra (HRMS) in the ESI mode were recorded on a time of flight instrument with 20,000 resolving power (FWHM) using either PEG or PPG as internal calibration standards.

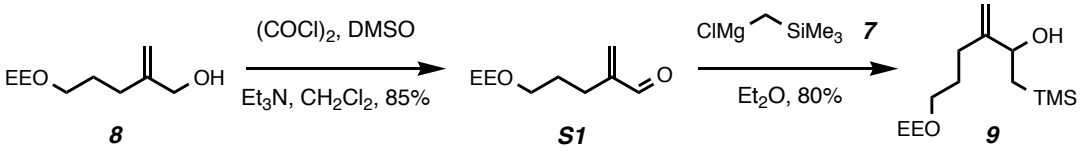
5-(1-Ethoxyethoxy)-2-methylenepentan-1-ol (8).



To a flame-dried 500 mL three-necked round-bottomed flask equipped with a mechanical stirrer, an addition funnel and a vacuum trap was added *n*-BuLi (2.5 M in hexanes, 82 mL, 205 mmol, 2.2 equiv). The flask was placed in an ice bath and attached to a vacuum pump at ca. 5 mm Hg. Approximately 60 mL of hexane was collected in the vacuum trap over 20 min. The resulting thick yellow residue was re-dissolved by dropwise addition of Et_2O (60 mL) at 0 °C over 10 min. The solution was cooled to –78 °C and treated with TMEDA (28 mL, 186 mmol, 2.0 equiv) followed by a solution of methallyl alcohol (**6**, 7.8 mL, 93 mmol, 1.0 equiv) in Et_2O (70 mL). The reaction mixture was stirred at –10 °C for 12 h and then treated with the bromide **5** (neat, 20.2 g, 102 mmol, 1.1 equiv) at –78 °C. The resulting mixture was stirred at 0 °C for 12 h, after which it was quenched by addition of saturated aqueous NH_4Cl (100 mL) at the same temperature. The biphasic mixture was stirred for 1 h and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude material by silica gel chromatography gave the title product **8** (6.9 g, 52%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (s, 1H), 4.88 (s, 1H), 4.68 (q, J = 5.5, 1H), 4.07 (s, 2H), 3.65 (dq, J = 9.5, 7.0 Hz, 1H), 3.60 (dt, J = 9.5, 7.0 Hz, 1H), 3.49 (dq, J = 9.5, 7.0 Hz, 1H), 3.44 (dt, J = 9.5, 7.0 Hz, 1H), 2.34 (br s, 1H), 2.14 (t, J = 7.0, 2H), 1.75 (p, J = 7.0 Hz, 2H), 1.31 (d, J = 5.5 Hz, 3H), and 1.21 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 148.6, 109.6, 99.7, 65.9, 64.9, 60.9, 29.7, 28.0, 20.0, and 15.4; **IR** (neat): 3430, 3079, 2976, 2932, and 2875 cm^{-1}; **HRMS** (ESI): calcd for $C_{10}H_{20}O_3$•Na^+ 211.1305, found 211.1304; and **TLC**: R_f = 0.3 (Hex/EtOAc = 5:1).

(±)-6-(1-Ethoxyethoxy)-3-methylene-1-(trimethylsilyl)hexan-2-ol (9).



In a flame-dried 500 mL three-necked round-bottomed flask equipped with a stir bar, an addition funnel, and a thermometer, $(COCl)_2$ (4.9 mL, 58 mmol, 1.2 equiv) was added followed by CH_2Cl_2 (110 mL). The solution was cooled to –78 °C and DMSO (4.4 mL, 62 mmol, 1.3 equiv) was added by use of a syringe pump over 20-25 min, during which the reaction temperature was maintained at around –65 °C. After being stirred for 30 min at the same temperature, the reaction mixture was treated with a solution of the primary alcohol **8** (6.9 g, 48 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at ca. –65 °C. The reaction mixture became inhomogeneous over the course of 4 h, after which it was treated with Et_3N (neat, 20.2 mL, 144 mmol, 3.0 equiv) and stirred for 6 h. The resulting slurry was allowed to warm to 0 °C, diluted with CH_2Cl_2 (100 mL), and quenched with saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude material was purified by distillation at 65-68 °C under 1 mm Hg pressure to afford the aldehyde **S1** (5.8 g, 85%) as a pale yellow oil.

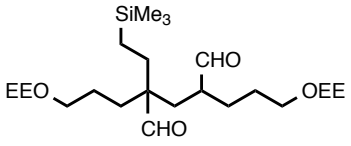
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 6.29 (s, 1H), 6.03 (s, 1H), 4.68 (q, J = 5.5 Hz, 1H), 3.65 (dq, J = 9.5, 7.0 Hz, 1H), 3.59 (dt, J = 9.5, 6.5 Hz, 1H), 3.48 (dq, J = 9.5, 7.0 Hz, 1H), 3.45 (dt, J = 9.5, 6.5 Hz, 1H), 2.34 (t, J = 7.5 Hz, 2H), 1.74 (p, J = 6.5, 2H), 1.31 (d, J = 5.5 Hz, 3H), and 1.21 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 194.6, 149.8, 134.2, 99.7, 64.4, 60.8, 27.9, 24.7, 19.9, and 15.3; **IR** (neat): 2977, 2932, 2874, 1693, and 1379 cm^{-1}; **HRMS** (ESI): calcd for $C_{10}H_{18}O_3$•Na^+ 209.1148, found 209.1146; and **TLC**: R_f = 0.3 (Hex/EtOAc = 11:1).

(Trimethylsilyl)methylmagnesium chloride solution (**7**) was prepared in the following manner. To a stirred suspension of freshly ground magnesium turnings (1.7 g, 72.0 mmol, 1.2 equiv) in Et_2O (20 mL) in a flame-dried round-bottomed Schlenk flask was added (chloromethyl)trimethylsilane (1.4 mL, 10 mmol, 0.2 equiv). Formation of the Grignard reagent, detected by prolonged vigorous bubbling and gray coloring of the mixture, was initiated by gentle external heating in an oil bath that was held at 45-50 °C. Additional alkyl chloride (7 mL, 50 mmol, 0.8 equiv) was slowly added as a solution in Et_2O (30 mL) at a rate to maintain a gentle reflux. The resulting suspension was stirred at room temperature for 24 h to afford 35 mL of an ethereal solution of **7** (ca. 1.7 M, measured by titration with *sec*-BuOH using a phenanthroline indicator).

To a flame-dried 250 mL round-bottomed flask equipped with a stir bar and an addition funnel, was introduced a solution of aldehyde **S1** (5.8 g, 41.0 mmol, 1. equiv) in Et_2O (100 mL). The solution was cooled to –78 ^oC and the addition funnel was filled with the Grignard reagent **7** (1.7 M, 29 mL, 50 mmol, 1.2 equiv) by use of a cannula, which was then added to the solution dropwise. The resulting mixture was allowed to warm to –10 °C and was stirred for an additional 3 h. The reaction mixture was quenched by the addition of water (50 mL). The biphasic mixture was stirred for 30 min and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by MPLC (10:1 hex/EtOAc) gave the title compound **9** (8.9 g, 80%) as a yellow oil.

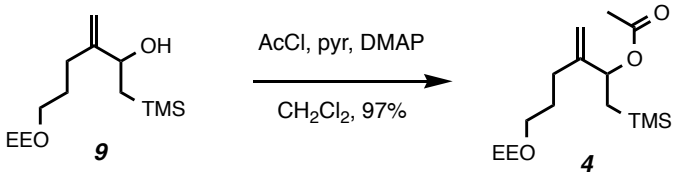
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.79 (s, 1H), 4.68 (q, *J* = 5.5 Hz, 1H), 4.29 (t, *J* = 7.5 Hz 1H), 3.68-3.60 (overlapped m, 2H), 3.52-3.44 (overlapped m, 2H), 2.21 (dt, *J* = 15.5, 8.0 Hz, 1H), 2.09 (dt, *J* = 15.5, 8.0 Hz, 1H), 1.79 (p, *J* = 7.0 Hz, 2H), 1.65 (br s, 1H), 1.32 (d, *J* = 5.5 Hz, 3H), 1.21 (t, *J* = 7.5 Hz, 3H), 0.97 (dd, *J* = 14.5, 6.5 Hz, 1H), 0.96 (dd, *J* = 14.5, 8.0 Hz, 1H), and 0.04 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.55, 153.51, 109.1, 99.8, 74.2, 65.24/65.1, 61.0/60.9, 28.5/28.4, 27.5/27.3, 24.69/24.68, 20.09/20.07, 15.5, and -0.7; **IR** (neat): 2950, 2898, 1734, 1645, 1444, 1380 1248, 1132, 1091, 1054, and 859 cm^{-1}; and **TLC**: R_f = 0.35 (Hex/EtOAc = 11:1); and **HRMS** (ESI): calcd for $C_{14}H_{30}O_3Si•Na^+$ 297.1856, found 297.1870.

Evidence was seen for the presence of ca. 15% of an aldehydic byproduct, to which we have tentatively assigned the structure **S2**; **^{1}H NMR** (500 MHz, $CDCl_3$) δ : 9.98 (s), 9.84 s), 9.70 (d, *J* = 3.0 Hz, 2x1H), 4.72 (q), 3.78 (m), 3.56 (m), 2.04-1.82 (m), 1.7-1.5 (m), 0.49-0.33 (m), and -0.02 (s); **^{13}C NMR** (125 MHz, $CDCl_3$) δ : 204.3, 100.3/100.0, 65.4/65.3, 61.8/ 61.4, 24.8/24.7, 24.5, 23.7, 22.2/22.1, 19.9, 15.39/15.36, 9.24/9.22, and -1.94.



S2

(±)-6-(1-Ethoxyethoxy)-3-methylene-1-(trimethylsilyl)hexan-2-yl acetate (4).

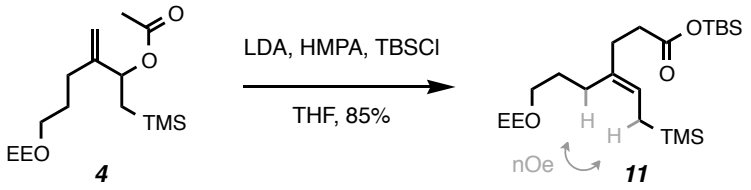


9 ***4***

To a solution of **9** (8.9 g, 33 mmol, 1.0 equiv), pyridine (3.9 mL, 50 mmol, 1.5 equiv), and DMAP (0.8 g, 6.6 mmol, 0.2 equiv) in CH_2Cl_2 (100 mL) was added acetyl chloride (2.8 mL, 40 mmol, 1.2 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched by the addition of water (30 mL); the organic layers were combined, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (8:1 hex/EtOAc) to give the allylic ester **4** (10 g, 97%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (br t, J = 8.5 Hz, 1H), 5.04 (s, 1H), 4.85 (s, 1H), 4.69 (q, J = 5.5 Hz, 1H), 3.66 (br dq, J = 10.0, 7.0 Hz, 1H), 3.60 (br dt, J = 10.5, 6.5 Hz, 1H), 3.50 (br dq, J = 10.0, 7.0 Hz, 1H), 3.45 (br dt, J = 10.5, 6.5 Hz, 1H), 2.12$^+$ (dt, J = 17, 8.5 Hz, 1H), 2.12$^-$ (dt, J = 18, 6.5 Hz, 1H), 2.02 (s, 3H), 1.76$^+$ (dp, J = 13.5, 6.5 Hz, 1H), 1.76$^-$ (dp, J = 13.5, 6.5 Hz, 1H), 1.31 (d, J = 5.5 Hz, 3H), 1.21 (t, J = 7.5 Hz, 3H), 1.09 (dd, J = 14.5, 8.5 Hz, 1H), 1.03 (dd, J = 14.5, 7.0 Hz, 1H), and 0.01 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.1, 149.0, 110,7, 99.6, 75.8, 64.9, 60.8, 27.9, 27.7, 22.2, 21.5, 19.9, 15.3, and -1.1; **IR** (neat): 2975, 2952, 2897, 1740, 1370, and 1248 cm^{-1}; **HRMS** (ESI): calcd for $C_{16}H_{32}O_4Si{\bullet}Na^+$ 339.1962, found 339.1982; and **TLC**: R_f = 0.4 (Hex/EtOAc = 8:1).

(*E*)-*tert*-Butyldimethylsilyl 7-(1-thoxyethoxy)-4-[2-(trimethylsilyl)ethylidene]heptanoate (11).

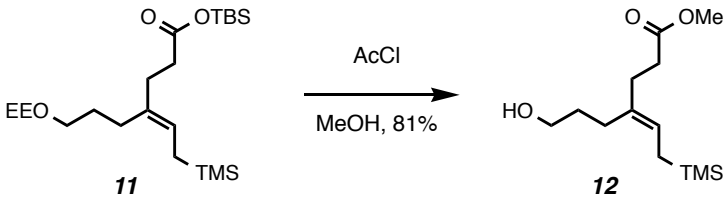


To a solution of LDA (1.0 M, 38 mL, 38 mmol, 1.2 equiv), which was prepared by addition of *n*-BuLi (2.5 M, 15 mL, 38 mmol, 1.2 equiv) to a solution of diisopropylamine (6 mL, 42 mmol, 1.3 equiv) in THF (17 mL) at –20 °C, was added the acetate **4** (10 g, 32 mmol, 1.0 equiv) at –78 °C. The mixture was stirred at the same temperature for 30 min after which a solution of TBSCl (6.3 g, 42 mmol, 1.3 equiv) in THF (10 mL) was added dropwise. The resulting solution was allowed to warm to room temperature over 1 h and was stirred for 24 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (50 mL) at 0 °C. The biphasic mixture was stirred for 30 min and extracted with EtOAc. The combined organic layers were

washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude material by silica gel chromatography gave the silyl ester **11** (11.7 g, 85%) as a yellow oil. This product could be stored as a stock solution in EtOAc (ca. 0.1 M) in a freezer (ca. –15 °C) for more than a year.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.21 (t, *J* = 8.5 Hz, 1H), 4.68 (q, *J* = 5.5 Hz, 1H), 3.65 (dq, *J* = 9.5, 7.0 Hz, 1H), 3.56 (dt, *J* = 9.5, 6.5 Hz, 1H), 3.49 (dq, *J* = 9.5, 7.0 Hz, 1H), 3.40 (dt, *J* = 9.5, 6.5 Hz, 1H), 2.40 (nfom, 2H), 2.30 (br t, *J* = 8 Hz, 2H), 2.07 (dt, *J* = 13.5, 7.5 Hz, 1H), 2.02 (dt, *J* = 13.5, 7.5 Hz, 1H), 1.63 (br p, *J* = 7, 2H), 1.41 (d, *J* = 8.5 Hz, 2H), 1.31 (d, *J* = 5.5 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 0.94 (s, 9H), 0.26 (s, 6H), and -0.02 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.2, 134.9, 121.7, 99.8, 65.4, 60.9, 35.6, 32.2, 28.6, 26.5, 25.8, 20.1, 18.6, 17.8, 15.6, and -1.51; **IR** (neat): 2954, 2928, 2898, 2860, 1721, 1251, 1135, 1091, 1060, and 842 cm^{-1}; **HRMS** (ESI): calcd for $C_{22}H_{46}O_4Si_2 \bullet Na^+$ 453.2827, found 453.2797; and **TLC**: R_f = 0.5 (Hex/EtOAc = 2:1).

(*E*)-Methyl 7-Hydroxy-4-[2-(trimethylsilyl)ethylidene]heptanoate (12).



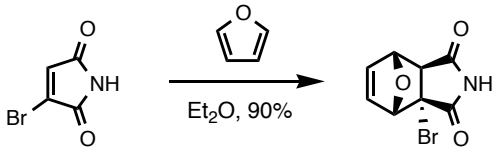
11 ***12***

To a solution of **11** (2.0 g, 4.7 mmol, 1.0 equiv) in MeOH (17 mL) was added acetyl chloride (5.1 mL, 5.6 mmol, 1.2 equiv) at –10 °C. The resulting solution was stirred at room temperature for 4 h. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL) and diluted with EtOAc (50 mL). The organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Removal of the residual solvent under high vacuum afforded the alcohol **12** (1.1 g, 81%), which was used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.22 (t, *J* = 8.5 Hz, 1H), 3.66 (s, 3H), 3.65 (t, *J* = 6.5 Hz, 2H), 2.49-2.46 (m, 2H), 2.33 (br t, *J* = 7 Hz, 2H), 2.07 (br t, *J* = 8 Hz, 2H), 1.64 (br p, *J* = 7 Hz, 2H), 1.42 (d, *J* = 8.5 Hz, 2H), and -0.02 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.1, 134.6, 122.2, 63.1, 51.7, 33.7, 31.9, 31.2, 26.0, 18.6, and -1.6; **IR** (thin film): 3442, 2952, 2895, 2861, 1741,

1438, 1248, 1155, 1058, and 851 cm^{-1}; **HRMS** (ESI): calcd for $C_{13}H_{26}O_3Si•Na^+$ 281.1543, found 281.1550; **TLC**: R_f = 0.35 (2:1 Hex/EtOAc).

(±)-(3a*S*,4*S*,7*R*,7a*S*)-3a-Bromo-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (13b)



13b

To a stirred suspension of 2-bromomaleimide[2] (4.0 g, 22.7 mmol, 1 equiv) in Et_2O (6 mL) in a culture tube was added freshly distilled furan (16.5 mL, 227 mmol, 10 equiv). The tube was sealed and placed in an 80 °C temperature oil bath. The reaction mixture became homogenous after being stirred for ca. 3 h. The culture tube was removed from the hot bath after 4 days, and the reaction content was concentrated under reduced pressure in a water bath that was held at 35-40 °C. Subsequent removal of the residual ether under high vacuum afforded the exo-imide **13b** (4.9 g, 90%) as a light beige amorphous solid, which was used in the next step without further purification.

mp: 167-172 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.19 (br s, 1H), 6.68-6.56 (nfom, 2H), 5.33 (dd *J* = 1.0, 1.0, 1H), 5.31 (dd *J* = 1.0, 1.0, 1H), and 2.89 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.95, 172.94, 136.8 136.7, 83.4, 82.8, 57.1, and 56.1; **IR** (thin film): 3184, 3089, 1781, 1714, 1345, 1161, and 1032 cm^{-1}; **HRMS** (ESI): calcd for $C_8H_5{}^{79}BrNO_3^-$ 241.9458, found 241.9473, and calcd for $C_8H_5{}^{81}BrNO_3^-$ 243.9437, found 243.9447; and **TLC**: R_f = 0.2 (2:1 Hex/EtOAc).

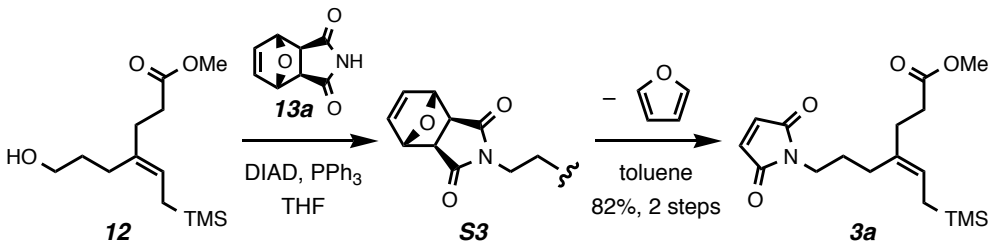
General Procedure for the Mitsunobu Reaction

To a solution of PPh_3 (1.5 equiv) in THF (0.3 M) at –10 °C was added a solution of the alcohol **12** (1 equiv) in THF (0.3 M). The mixture was stirred for 5 min and treated with the imide (**13a** or **13b**, 1.3 equiv). To the resulting solution was added di-isopropyl azodicarboxylate (DIAD, 1.5 equiv) dropwise. The reaction mixture was stirred at –10 °C for 1 h and diluted with hexane. The precipitated material was filtered, and the filtrate was concentrated under reduced pressure. The crude material was purified by silica gel chromatography to provide the retro-Diels-Alder reaction precursor.

General Procedure for the Retro-Diels-Alder (RDA) Reaction

The precursor obtained following the above procedure was dissolved in toluene (0.05 M) at room temperature and transferred into a culture tube. The tube was kept in a 100 °C temperature oil bath until no starting material was observed by TLC. The reaction mixture was allowed to cool to room temperature and was concentrated under reduced pressure. The residue was left under high vacuum for 12 h to afford the desired maleimides **3a** or **3b** in 80 or 82% yield, respectively, from the alcohol **12**. Unlike **3b**, the protiomaleimide **3a** was purified by silica gel chromatography to remove the reduced dicarboxylate by-product that co-eluted with the **S3** after the Mitsunobu reaction.

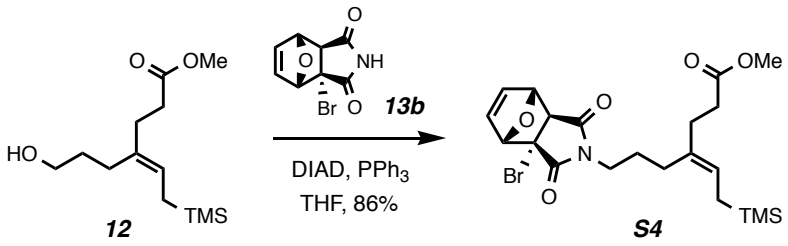
(*E*)-Methyl 7-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-4-[2-(trimethylsilyl)ethylidene]-heptanoate (3a).



The primary alcohol **12** was subjected to the Mitsunobu conditions with the furan protected imide **13a** following the general procedure described above. The resulting intermediate **S3** was subjected to the RDA conditions as described above to afford the title symmetric maleimide **3a** in 82% overall yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.70 (s, 2H), 5.21 (t, J = 8.5 Hz, 1H), 3.65 (s, 3H), 3.51 (br t, J = 7.5 Hz, 2H), 2.39 (m, 2H), 2.31 (br t, J = 7.5 Hz, 2H), 1.98 (br t, J = 8 Hz, 2H), 1.64 (br p, J = 7 Hz, 2H), 1.37 (dt, J = 8.5, 1.0 Hz, 2H), and -0.03 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.0, 171.0, 134.3, 133.7, 122.5, 51.7, 38.1, 33.6, 31.8, 27.1, 27.07, 18.7, and -1.6; **IR** (thin film): 2952, 1737, 1707, 1409, 1247, 1154, 855, and 838 cm^{-1}; **HRMS** (ESI): calcd for $C_{17}H_{27}NO_4Si•Na^+$ 360.1602, found 360.1586; **TLC:** R_f = 0.6 (2:1 Hex/EtOAc).

(±)-(*E*)-Methyl 7-[(3a*S*,4*S*,7*R*,7a*S*)-3a-Bromo-1,3-dioxo-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindol-2(3*H*)-yl]-4-[2-(trimethylsilyl)ethylidene]heptanoate (S4).



Protected imide **S4** was synthesized as a yellow oil in 86% yield from **12** following the general Mitsunobu displacement procedure described above.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.65 (br s, 2H), 5.27 (s, 1H), 5.26 (s, 1H), 5.20 (t, *J* = 8.5 Hz, 1H), 3.65 (s, 3H), 3.54 (t, *J* = 7.0 Hz, 2H), 2.85 (s, 1H), 2.40-2.36 (m, 2H), 2.29 (br t, *J* = 7.5 Hz, 2H), 1.96 (br t, *J* = 8 Hz, 2H), 1.65 (br p, *J* = 7 Hz, 2H), 1.37 (d, *J* = 8.5 Hz, 2H), and -0.04 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.0, 173.5, 173.4, 136.69, 136.68, 133.5, 122.7, 83.3, 82.7, 56.0, 55.4, 51.7, 40.0, 33.6, 31.8, 26.8, 26.0, 18.7, and -1.6; **IR** (thin film): 2952, ca. 1730 (sh), 1711, 1163, and 855 cm^{-1}; **HRMS** (ESI): calcd for $C_{21}H_{30}{}^{79}BrNO_5Si{\bullet}Na^+$ 506.0969, found 506.0960, and calcd for $C_{21}H_{30}{}^{81}BrNO_5Si{\bullet}Na^+$ 508.0949, found 508.0942; and **TLC:** R_f = 0.55 (2:1 Hex/EtOAc).

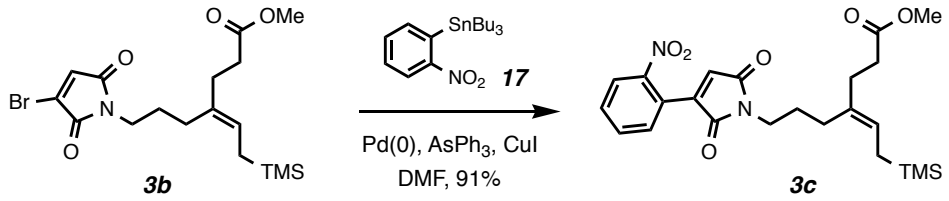
(*E*)-Methyl 7-(3-Bromo-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-4-[2-(trimethylsilyl)-ethylidene]heptanoate (3b).

The bromomaleimide **3b** was obtained as a brown oil in ca. 95% yield from **S4** following the general RDA procedure described above.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (s, 1H), 5.22 (t, *J* = 8.5 Hz, 1H), 3.65 (s, 3H), 3.55 (br t, *J* = 7.5 Hz, 2H), 2.41-2.36 (m, 2H), 2.30 (br t, *J* = 7.5 Hz, 2H), 1.99 (br t, *J* = 8 Hz, 2H), 1.69-1.63 (br p, *J* = 7 Hz, 2H), 1.36 (d, *J* = 8.5 Hz, 2H), and -0.03 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ

173.9, 168.8, 165.5, 133.5, 132.0, 131.6, 122.7, 51.8, 39.1, 33.6, 31.7, 27.0 (br), 18.8, and -1.6; **IR** (thin film): 2951, ca. 1730 (sh), 1715, 1398, 1245, 1155, and 851 cm^{-1}; **HRMS** (ESI): calcd for $C_{17}H_{26}{}^{79}BrNO_4Si{\bullet}Na^+$ 438.0707, found 438.0713, and calcd for $C_{17}H_{26}{}^{81}BrNO_4Si{\bullet}Na^+$ 440.0687, found 440.0709; and **TLC:** R_f = 0.65 (2:1 Hex/EtOAc).

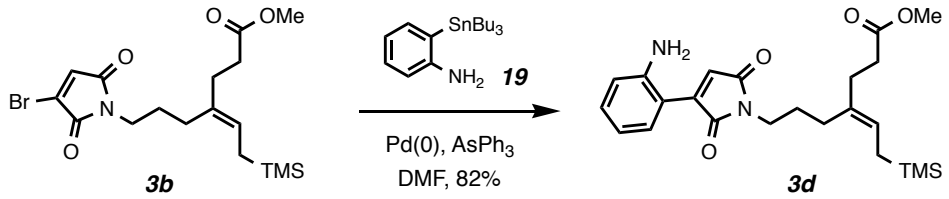
(*E*)-Methyl 7-[3-(2-Nitrophenyl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl]-4-[2-(trimethylsilyl)ethylidene]heptanoate (3c).



To a solution of **3b** (0.20 g, 0.50 mmol, 1.0 equiv) in DMF (0.5 mL) was added *o*-tributylstannyl-2-nitrobenzene[3] (**17**, 0.30 g, 0.75 mmol, 1.5 equiv). The resulting solution was purged with Ar for 15 min and treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (0.05 g, 0.05 mmol, 0.1 equiv), $AsPh_3$ (0.06 g, 0.20 mmol, 0.4 equiv), and CuI (0.2 g, 0.10 mmol, 0.2 equiv) all at once. The mixture was purged with Ar for an additional 15 min and was stirred at room temperature under an Ar atmosphere for 24 h. The reaction mixture was poured into water (ca. 5 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude material by silica gel chromatography gave the imide **3c** (0.21 g, 91%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.74 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.67 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.47 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.68 (s, 1H), 5.22 (tt, *J* = 8.5, 1.0 Hz, 1H), 3.65 (s, 3H), 3.57 (t, *J* = 7.5 Hz, 2H), 2.41-2.37 (m, 2H), 2.32 (br tt, *J* = 8.0, 1.0 Hz, 2H), 2.01 (nfom, 2H), 1.69 (nfom, 2H), 1.40 (d, *J* = 8.5 Hz, 2H), and -0.04 (s, 9H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 173.9, 170.0, 168.8, 148.3, 145.6, 134.0, 133.6, 131.6, 131.5, 126.4, 125.2, 124.7, 122.5, 51.7, 38.6, 33.6, 31.8, 27.0, 26.9, 18.6, and -1.7; **IR** (thin film): 2953, 1734, 1710, 1526, 1404, 1352, 1247, 1155, and 855cm^{-1}; **HRMS** (ESI): calcd for $C_{23}H_{30}N_2O_6Si{\bullet}Na^+$ 481.1765, found 481.1771.

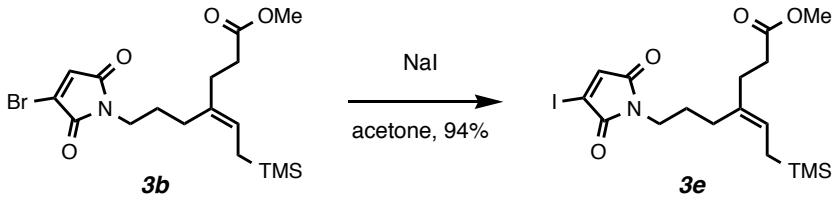
(*E*)-Methyl 7-[3-(2-Aminophenyl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl]-4-[2-(trimethylsilyl)ethylidene]heptanoate (3d).



To a solution of **3b** (0.20 g, 0.50 mmol, 1.0 equiv) in DMF (0.5 mL) was added *o*-tributylstannyl-2-aminobenzene[4] (**19**, 0.25 g, 0.65 mmol, 1.3 equiv). The resulting solution was purged with Ar for 15 min and $Pd_2(dba)_3 \cdot CHCl_3$ (0.05 g, 0.05 mmol, 0.1 equiv) and $AsPh_3$ (0.06 g, 0.20 mmol, 0.4 equiv) were added all at once. The mixture was purged with Ar for an additional 15 min, and the mixture was stirred at room temperature under an Ar atmosphere for 12 h. The reaction mixture was poured into water (ca. 5 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude material by silica gel chromatography gave **3d** (0.17 g, 82%) as an orange oil. This compound was also prepared from **3c** by $SnCl_2$-mediated (3.0 equiv) reduction in EtOH (0.5 M) at 50 °C in ca. 16 h.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.23 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 6.82 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H), 6.76 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.73 (s, 1H), 5.22 (t, *J* = 8.5 Hz, 1H), 4.32 (br s, 2H), 3.65 (s, 3H), 3.57 (br t, *J* = 7.5 Hz, 2H), 2.42-2.38 (m, 2H), 2.32 (br t, *J* = 7.5 Hz, 2H), 2.02 (br t, *J* = 8 Hz, 2H), 1.71 (br p, *J* = 7 Hz, 2H), 1.39 (d, *J* = 8.5 Hz, 2H), and -0.03 (s, 9H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 174.0, 171.4, 171.0, 146.5, 144.5, 133.7, 132.2, 131.4, 125.5, 122.5, 119.0, 117.3, 114.8, 51.7, 38.4, 33.6, 31.8, 27.1 (br), 18.7, and -1.6; **IR** (thin film): 2952, 1737, 1702, 1626, 1441, 1404, 1248, 1156, and 854 cm^{-1}; **HRMS** (ESI): calcd for $C_{23}H_{32}N_2O_4Si \bullet Na^+$ 451.2024, found 451.2022.

(*E*)-Methyl 7-(3-Iodo-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-4-[2-(trimethylsilyl)ethylidene]heptanoate (3e).



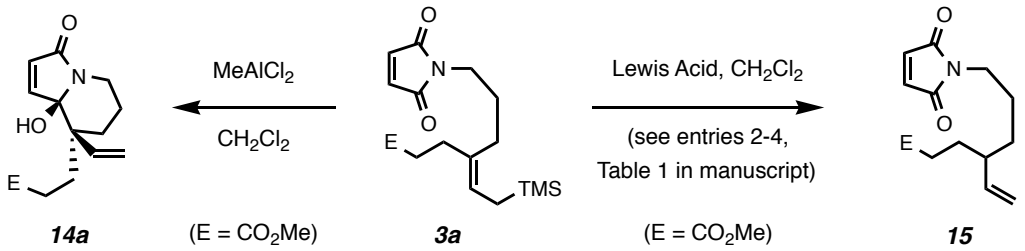
To a solution of the bromomaleimide **3b** (1.0 g, 2.4 mmol, 1.0 equiv) in acetone (20 mL) was added NaI (2.0 g, 13 mmol, 5.5 equiv) at room temperature. The resulting suspension was heated to reflux in a sealed culture tube for 36 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure to afford the iodide **3e** (1.1 g, 94%) as a red oil, which was used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (s, 1H), 5.22 (t, J = 8.5 Hz, 1H), 3.65 (s, 3H), 3.56 (br t, J = 7.5 Hz, 2H), 2.40-2.36 (m, 2H), 2.30 (br t, J = 7.5 Hz, 2H), 1.98 (br t, J = 8 Hz, 2H), 1.65 (br p, J = 7 Hz, 2H), 1.37 (d, J = 8.5 Hz, 2H), and -0.03 (s, 9H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 173.9, 170.0, 166.9, 140.7, 133.5, 122.7, 107.5, 51.8, 39.3, 33.6, 31.7, 27.00, 26.97, 18.8, and -1.6; **IR** (thin film): 2952, ca. 1730 (sh), 1711, 1440, 1398, 1247, 1155, and 853 cm^{-1}; **HRMS** (ESI): calcd for $C_{17}H_{26}INO_4Si{\bullet}Na^+$ 486.0568, found 486.0539; and **TLC:** R_f = 0.65 (2:1 Hex/EtOAc).

General Procedure for the Allylative Ring Closure

A solution of the allylation precursor imide (1 equiv) in CH_2Cl_2 (0.05 M) was treated with $MeAlCl_2$ (1.6 M, 4 equiv) in hexane at room temperature. The resulting mixture was stirred at the same temperature for 10-60 min until TLC analysis indicated full conversion of the starting imide. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and the mixture was extracted with EtOAc. The organic layers were combined, washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude material was purified by trituration using a 3:1 mixture of Hex/EtOAc. The product was left as an amorphous solid that was of suitable purity (^{1}H NMR analysis) for use in the next experiment without further purification. In the case of **3d**, the amino ester regioisomeric products **14d** and **iso-14d** were separated by silica gel chromatography using EtOAc as the eluent.

(±)-(8*R*,8a*R*)-Methyl 3-(8a-Hydroxy-3-oxo-8-vinyl-3,5,6,7,8,8a-hexahydroindolizin-8-yl)propanoate (14a).



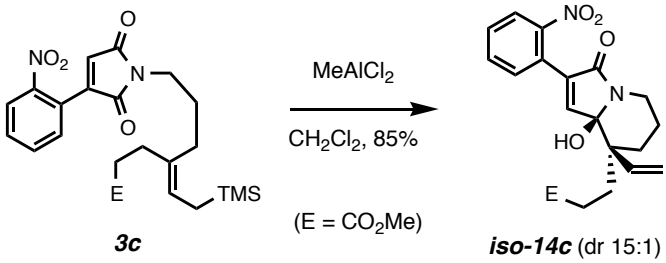
The imide **3a** (100 mg) was subjected to the general allylative cyclization procedure, which afforded the carbinolamide **14a** (69 mg, dr 42:1, 88%) as a white solid. Under the conditions of entries 2-4 in Table 1 of the manuscript, varying amounts of the imide **15** were obtained, following chromatographic purification on SiO_2.

14a: ^{1}**H NMR** (500 MHz, $CDCl_3$): δ 6.97 (d, *J* = 6.0 Hz, 1H), 6.17 (d, *J* = 6.0 Hz, 1H), 5.87 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.40 (d, *J* = 11.0 Hz, 1H), 5.21 (d, *J* = 17.5 Hz, 1H), 4.07 (dd, *J* = 13.0, 5.5 Hz, 1H), 3.63 (s, 3H), 2.95 (ddd, *J* = 13.0, 13.0, 4.5 Hz, 1H), 2.54 (br s, 1H), 2.09 (dt, *J* = 15.5, 5.5 Hz, 1H), 2.09-2.02 (m, 2H), and 1.67-1.43 (m, 5H); ^{13}**C NMR** (125 MHz, $CDCl_3$): δ 173.8, 167.7, 146.9, 140.6, 128.6, 117.4, 91.9, 51.9, 46.2, 35.2, 28.7, 25.6, 24.3, and 20.1; **IR** (thin film): 3330, 2950, 2926, 2873, 1736, 1684, 1433, 1172, 1057, and 913 cm^{-1}; **HRMS** (ESI): calcd for $C_{14}H_{19}NO_4$•Na^+ 288.1206, found 288.1201; **TLC:** R_f = 0.2 (EtOAc).

(±)-Methyl 7-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-4-vinylheptanoate (15).

Isolated as a yellow oil in 43-95% yield (Table 1 in manuscript). ^{1}**H NMR** (500 MHz, $CDCl_3$): δ 6.69 (s, 1H), 5.43 (ddd, *J* = 17.0, 10.0, 9.0 Hz, 1H), 5.03 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.98 (dd, *J* = 17.0, 2.0 Hz, 1H), 3.66 (s, 3H), 3.49 (t, *J* = 7.0 Hz, 2H), 2.32 (ddd, *J* = 16.0, 9.0, 5.5 Hz, 1H), 2.24 (ddd, *J* = 16.0, 9.0, 7.0 Hz, 1H), 1.93 (ddddd, *J* = 9.5, 9.5, 9.5, 4.5, 4.5 Hz, 1H), 1.71 (dddd, *J* = 13.5, 9.0, 7.0, 4.5 Hz, 1H), 1.68-1.46 (m, 4H), 1.36 (nfom, 1H), and 1.29-1.20 (nfom, 1H); ^{13}**C NMR** (125 MHz, $CDCl_3$): δ 174.4, 171.1, 141.5, 134.2, 116.4, 51.7, 43.7, 38.0, 32.10, 32.06, 30.0, and 26.4; **IR** (thin film): 2927, 2852, 1734, 1706, 1409, 1254, 1172, 831, and 696 cm^{-1}; **HRMS** (ESI): calcd for $C_{14}H_{19}NO_4$•Na^+ 288.1206, found 288.1217; **TLC:** R_f 0.65 (2:1 Hex/EtOAc).

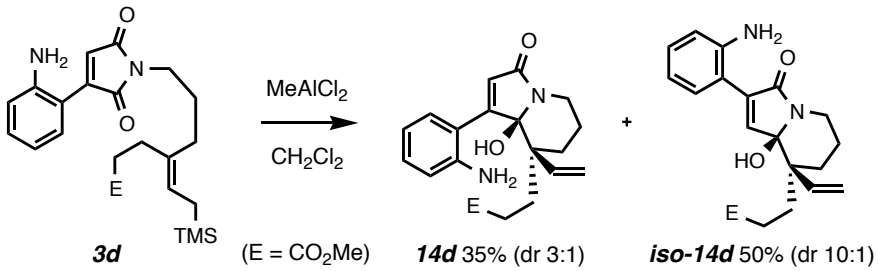
(±)-Methyl 3-[(8*R*,8a*R*)-8a-Hydroxy-2-(2-nitrophenyl)-3-oxo-8-vinyl-3,5,6,7,8,8a-hexahydroindolizin-8-yl]propanoate (iso-14c).



The imide **3c** (100 mg) was subjected to the general allylative cyclization reaction, which afforded the carbinolamide **iso-14c** (70 mg, 85%) as a pale yellow solid.

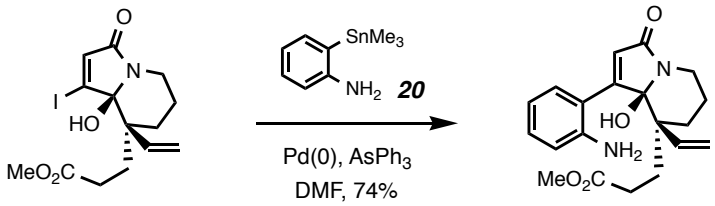
mp: 178-180 °C; ^{1}H **NMR** (500 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.61 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.53 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.39 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.98 (s, 1H), 5.93 (dd, *J* = 17.5, 11.0, Hz, 1H), 5.38 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.21 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.03 (dddd, *J* = 13.0, 5.5, 1.0, 1.0 Hz, 1H), 3.62 (s, 3H), 3.00 (ddd, *J* = 13.0, 13.0, 4.0 Hz, 1H), 2.99 (br s, 1H), 2.13-2.04 (m, 3H), 1.82 (ddd, *J* = 15.0, 10.0, 6.5, 1H), 1.77-1.71 (nfom, 1H), and 1.67-1.50 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.8, 165.0, 148.9, 140.6, 140.5, 138.6, 133.3, 131.8, 130.0, 126.8, 124.8, 117.2, 90.3, 51.9, 46.9, 35.8, 28.8, 25.5, 24.5, and 20.1; **IR** (thin film): 2962, 2917, 2849, 1731, 1650, 1527, 1431, 1352, 1260, 1094, 1073, 1021, and 797 cm^{-1}; **HRMS** (ESI): calcd for $C_{20}H_{22}N_2O_6$•Na^+ 409.1370, found 409.1388; and **TLC:** R_f = 0.3 (EtOAc).

(±)-Methyl 3-[(8*R*,8a*R*)-8a-Hydroxy-2-(2-aminophenyl)-3-oxo-8-vinyl-3,5,6,7,8,8a-hexahydroindolizin-8-yl]propanoate (14d).



The imide **3d** (100 mg) was subjected to the general allylative cyclization procedure, which afforded the carbinolamide **14d** (28 mg, dr 3:1, 35%) and **iso-14d** (47 mg, dr 10:1 by ^{1}H NMR, 50%), each as a yellow waxy material.

The desired amide **14d** was synthesized in 74% yield (cf. Scheme 4 in manuscript) using the following procedure:



14e ***14d***

To a solution of **14e** (dr = 15:1, see page 18, 120 mg, 0.30 mmol, 1.0 equiv) in DMF (1.5 mL) was added *o*-trimethylstannyl-2-aminobenzene[4] (**20**, 100 mg, 0.39 mmol, 1.3 equiv). The resulting solution was purged with Ar for 15 min and $Pd_2(dba)_3 \cdot CHCl_3$ (31 mg, 0.03 mmol, 0.1 equiv) and $AsPh_3$ (37 mg, 0.12 mmol, 0.4 equiv) were added all at once. The mixture was purged with Ar for an additional 15 min and stirred at room temperature for 12 h. The reaction mixture was poured into water (ca. 3 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography using EtOAc as the eluent.

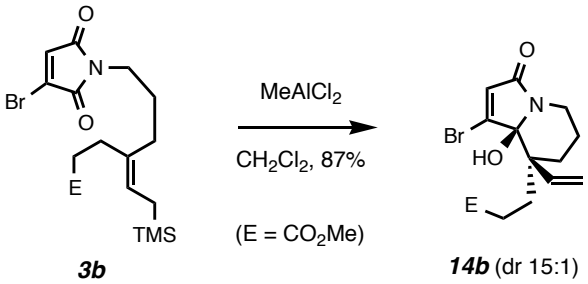
14d: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.19 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 6.83 (dd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.74 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.17 (s, 1H), 5.36 (dd, *J* = 17.5, 11.0, Hz, 1H), 5.03 (dd, *J* = 11.0, 1.0 Hz, 1H), 4.98 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.60-4.20 (very br s), 4.11 (dddd, *J* = 13.0, 5.5, 1.5, 1.5 Hz, 1H), 3.61 (s, 3H), 2.99 (ddd, *J* = 13.0, 13.0, 4.0 Hz, 1H), 2.11 (nfom, 1H), 2.05-1.93 (m, 2H), and 1.67-1.43 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.8, 167.3, 159.5, 143.8, 139.5, 130.7, 130.6, 127.4, 121.6, 119.8, 118.0, 117.6, 94.0, 51.9, 47.6, 35.6, 28.6, 25.5, 24.7, and 20.2; **IR** (thin film): 3354 (br), 2949, 1734, 1676, 1672, 1434, 1419, 1289, 1202, 1172, 1048, 928, 841, 754, and 673 cm^{-1}; **LC-LRMS** [ESI + APCI]: 339.0 $(M - OH)^+$ and 677.3 $(2M - H_2O - OH)^+$; **HRMS** (ESI): calcd for $C_{20}H_{24}N_2O_4 \bullet Na^+$ 379.1628, found 379.1636; and **TLC:** R_f = 0.3 (EtOAc).

(±)-Methyl 3-[(8*R*,8a*R*)-2-(2-Aminophenyl)-8a-hydroxy-3-oxo-8-vinyl-3,5,6,7,8,8a-hexahydroindolizin-8-yl]propanoate (iso-14d).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (ddd, *J* = 7.5, 1.5, 0.5 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 6.86 (s, 1H), 6.76 (br dd, *J* = 7.5, 7.5 Hz, 1H), 6.67 (br d, *J* = 8.0 Hz, 1H), 5.90 (dd, *J* =

17.5, 11.0, Hz, 1H), 5.34 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.16 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.45-4.01 (very br s), 4.02 (ddd, *J* = 13.0, 5.5, 1.0 Hz, 1H), 3.60 (s, 3H), 2.97 (ddd, *J* = 13.0, 13.0, 4.0 Hz, 1H), 2.14-2.00 (m, 3H), and 1.65-1.40 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.8, 167.2, 142.0, 140.7, 139.2, 131.0, 130.8, 130.4, 129.2, 125.6, 119.6, 117.0, 90.1, 51.9, 48.6, 35.6, 28.8, 25.6, 24.4, and 20.2; **IR** (thin film): 2959, 1731, 1680, 1628, 1432, 1277, 1261, 763, and 753 cm^{-1}; **HRMS** (ESI): calcd for $C_{20}H_{24}N_2O_4$•Na^+ 379.1628, found 379.1643; and **TLC:** R_f = 0.65 (EtOAc).

(±)-Methyl 3-[(8*R*,8a*S*)-1-Bromo-8a-hydroxy-3-oxo-8-vinyl-3,5,6,7,8,8a-hexahydroindolizin-8-yl]propanoate (14b).

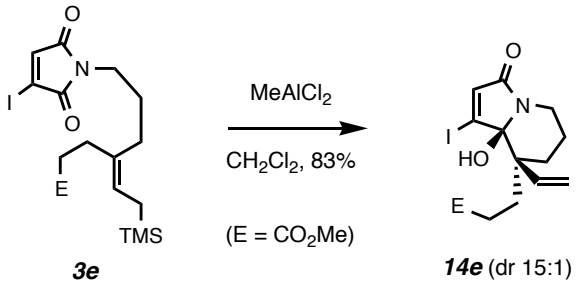


3b ***14b*** (dr 15:1)

The imide **3b** (100 mg) was subjected to the general allylative cyclization procedure, which afforded the carbinolamide **14b** (72 mg, dr 15:1, 87%) as a white solid.

mp: 187-190 °C; **^{1}H NMR** (500 MHz, d_6-Acetone): δ 6.43 (s, 1H), 6.36 (dd, *J* = 17.5, 11.0, Hz, 1H), 5.25 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.15 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.06 (dddd, *J* = 13.0, 5.5, 1.5, 1.5 Hz, 1H), 3.58 (s, 3H), 2.92 (ddd, *J* = 13.0, 13.0, 4.0 Hz, 1H), 2.21-2.01 (m, 3H), 1.64-1.53 (m, 4H), and 1.51-1.41 (nfom, 1H); **^{13}C NMR** (125 MHz, d_6-Acetone): δ 174.0, 165.5, 143.9, 141.0, 130.4, 116.7, 93.0, 51.8, 47.4, 36.2, 29.0, 26.5, 26.0, and 20.7; **IR** (thin film): 2919, 2848, 1736, 1711, 1673, 1268, and 847 cm^{-1}; **HRMS** (ESI): calcd for $C_{14}H_{18}{}^{79}BrNO_4$•$Na^+$ 366.0311, found 366.0295, and calcd for $C_{14}H_{18}{}^{81}BrNO_4$•$Na^+$ 368.0291, found 368.0286; and **TLC:** R_f = 0.20 (EtOAc).

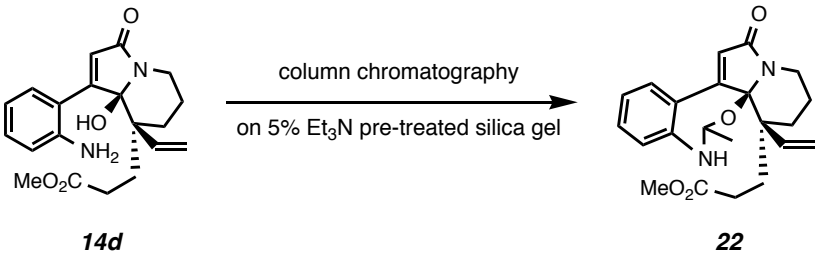
(±)-Methyl 3-[(8*R*,8a*S*)-8a-Hydroxy-1-iodo-3-oxo-8-vinyl-3,5,6,7,8,8a hexahydro-indolizin-8-yl]propanoate (14e).



The imide **3e** (100 mg) was subjected to the general allylative cyclization procedure, which afforded the carbinolamide **14e** (70 mg, dr 15:1, 83%) as a white solid.

mp: 145-148 °C; **^{1}H NMR** (500 MHz, d_6-Acetone): δ 6.69 (s, 1H), 6.46 (dd, *J* = 17.5, 11.0, Hz, 1H), 5.26 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.18 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.07 (dddd, *J* = 13.0, 5.5, 1.5, 1.5 Hz, 1H), 3.58 (s, 3H), 2.95 (td, *J* = 13.0, 4.0 Hz, 1H), 2.20-2.13 (m, 3H), and 1.64-1.52 (m, 4H), and 1.51-1.40 (nfom, 1H); **^{13}C NMR** (125 MHz, d_6-Acetone): δ 173.1, 165.2, 141.1, 139.2, 122.7, 117.1, 51.8, 46.5, 36.5, 30.5, 29.0, 27.0, 25.9, and 20.6; **IR** (thin film): 2948, 2918, 2850, 1730, 1699, 1672, 1434, 1419, 1245, 1202, 1170, 1053, and 914 cm^{-1}; **HRMS** (ESI): calcd for $C_{14}H_{18}INO_4$•Na^+ 414.0173, found 414.0204; and **TLC:** R_f = 0.25 (EtOAc).

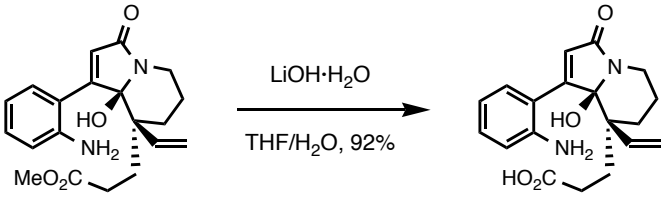
(±)-Methyl 3-{(7*R*,7a*S*,9*R*)-9-Methyl-2-oxo-7-vinyl-4,5,6,7,9,10-hexahydro-2H-benzo[4,5][1,3]-oxazepino[7,6-*i*]indolizin-7-yl}propanoate (22).



Isolated as a pale yellow, waxy material in ca. 10% when the amino ester **14d** was subjected to a column chromatography purification using 5% Et_3N pre-treated silica gel and EtOAc eluent. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.19 (d, *J* = 7.0, 1H), 7.18 (td, *J* = 8.0, 1.5 Hz, 1H), 6.81 (td, *J* = 7.5, 1.0 Hz, 1H), 6.54 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.28 (s, 1H), 5.37 (dd, *J* = 17.5, 11.0, Hz, 1H), 5.09

(dq, 8.0, 5.5 Hz, 1H), 4.85 (dd, *J* = 11.0, 1.0 Hz, 1H), 4.79 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.15 (dddd, 13.0, 5.5, 1.5, 1.5 Hz, 1H), 3.61 (s, 3H), 2.99 (td, *J* = 13.0, 4.0 Hz, 1H), 2.10 (m, 1H), 1.98 (dd, *J* = 10.0, 8.0 Hz, 2H), and 1.53-1.41 (m, 2H), and 1.38 (d, *J* = 5.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.9, 167.1, 160.3, 144.3, 139.3, 131.0, 129.2, 125.8, 119.64, 119.61. 116.5, 115.9, 100.0, 78.6, 51.8, 48.1, 35.7, 28.7, 25.4, 25.2, 21.9, and 20.1; **IR** (thin film): 3318 (br), 2948, 1737, 1676, 1487, 1169, 1048, and 757 cm^{-1}; **HRMS** (ESI): calcd for $C_{22}H_{26}N_2O_4$•Na^+ 405.1785, found 405.1807; and **TLC:** R_f = 0.4 (EtOAc).

(±)-3-[(8*R*,8a*S*)-1-(2-Aminophenyl)-8a-hydroxy-3-oxo-8-vinyl-3,5,6,7,8,8a-hexahydro-indolizin-8-yl]propanoic acid (S5).

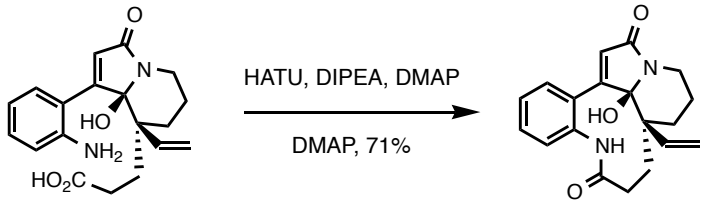


14d ***S5***

To a solution of the amino ester **14d** (80 mg, 0.22 mmol, 1 equiv) in THF/H_2O (3:1, 2.2 mL) was added LiOH·H_2O (28 mg, 0.66 mmol, 3 equiv) at room temperature. The reaction mixture was stirred for 6 h, diluted with EtOAc, and treated with AcOH dropwise until the pH was lowered to neutrality. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the amino acid **S5** (70 mg, 92%) as a pale yellow solid. The crude material, which retained ethyl acetate solvent even after being kept under vacuum for a day, was used in the next step without further purification.

mp: 185-187 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.15 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 6.75 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.71 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.21 (s, 1H), 5.44 (dd, *J* = 17.5, 11.0 Hz, 1H), 4.99 (dd, *J* = 11.0, 1.0 Hz, 1H), 4.94 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.14 (br dd, *J* = 13.5, 5.0 Hz, 1H), 3.03 (ddd, *J* = 13.0, 13.0, 4.5 Hz, 1H), 2.16-1.91 (m, 3H), and 1.70-1.37 (m, 5H). **^{13}C NMR** (125 MHz, d_6-DMSO): δ 174.3, 166.0, 146.0, 140.1, 130.5, 129.81, 129.75, 125.1, 118.2, 115.6, 115.5, 115.0, 92.9, 46.3, 34.5, 28.2, 24.7, 24.3, and 19.7; **IR** (thin film): 3431 (br), 2921, 1713, 1680, 1051, 1026, 1006, 824, and 762 cm^{-1}; **HRMS** (ESI): calcd for $C_{19}H_{21}N_2O_4^-$ 341.1507, found 341.1487.

(±)-(8a*R*,12a*S*,14b*S*)-8a-Ethyl-7,8,8a,10,11,12a-hexahydro-12a-hydroxyindolizino[8,1-ef][1]benzazonine-6,13(5H,9H)-dione (21).



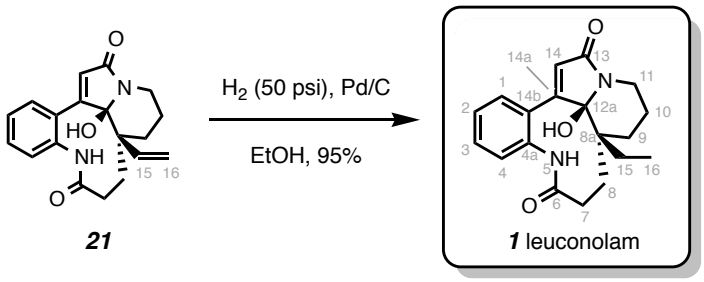
S5 ***21***

To a solution of the amino acid **S5** (55 mg, 0.16 mmol, 1 equiv) in DMF (3.0 mL) was added DIPEA (23 mg, 0.18 mmol, 1.1 equiv), DMAP (4 mg, 0.03 mmol, 0.2 equiv), and HATU (80 mg, 0.21 mmol, 1.3 equiv) at room temperature. The reaction solution was stirred for 6 h and quenched by addition of water. The resulting mixture was extracted with EtOAc and the organic layer was washed with brine and concentrated under reduced pressure. The crude material was purified by silica gel chromatography with 10:1 EtOAc/MeOH to provide the macrolactam **21** (37 mg, 71%) as a white solid.

mp: >250 °C; assignments of resonances in both ^{1}H and ^{13}C NMR spectra (acquired in CD_3OD) were guided by analysis of the HMBC (page 73) and HSQC (page 74) data. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.0 Hz, 1H), 7.41 (app t, *J* = 7.0 Hz, 1H), 7.35 (app t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 6.17 (dd, *J* = 18.0, 11.5, Hz, 1H), 5.95 (s, 1H), 4.98 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 18.0 Hz, 1H), 4.00 (br m, 1H), 2.91 (br m, 1H), 2.36 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.19-2.13 (m, 1H), 2.02-1.91 (m, 2H), and 1.63-1.49 (m, 3H), and 1.43 (br d, *J* = 13.0 Hz, 1H); **^{1}H NMR** (500 MHz, CD_3OD): δ 7.92 (dd, *J* = 7.5, 1.5 Hz, 1H, H4), 7.48 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H, H3), 7.40 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, H4), 7.27 (dd, *J* = 7.5, 1.0 Hz, 1H, H1), 6.30 (dd, *J* = 18.0, 11.5, Hz, 1H, H15), 6.00 (s, 1H, H14), 4.90 (dd, *J* = 11.5, 1.0 Hz, 1H, H16Z), 4.83 (dd, *J* = 18.0, 1.0 Hz, 1H, H16E), 4.07 (dddd, 13.0, 5.0, 1.5, 1.5, 1H, H11), 3.01 (ddd, *J* = 13.0, 13.0, 4.5, 1H, H11'), 2.42 (ddd, *J* = 14.5, 8.0, 1.0 Hz, 1H, H7), 2.21 (ddd, *J* = 14.0, 14.0, 4.5, 1H, H9), 1.94 (ddd, *J* = 14.0, 12.5, 1.5 Hz, 1H H7'), 1.91 (br dd, *J* = 15.5, 7.5 Hz, 1H, H8), 1.76 (ddd, *J* = 15.5, 12.5, 1.0 Hz, 1H, H8'), 1.71-1.57 (br m, 2H, H10 and H10'), and 1.44 (br d, *J* = 13.0 Hz, 1H, H9'); **^{13}C NMR** (125 MHz, CD_3OD): δ 180.6 (C6), 168.6 (C13), 158.1 (C14a), 142.4 (C15), 138.0 (C4a), 133.8 (C14b), 131.4 (C3), 130.6 (C4), 129.6 (C14), 128.00 (C2), 127.96 (C1), 115.3 (C16), 94.3 (12a), 50.3 (C11), 37.8 (C9), 36.4 (C11), 30.4 (C7), 29.6 (C8),

and 21.6 (C10); **IR** (thin film): 3257 (br), 2929, 2888, 1678, 1441, 1040, and 1026 cm^{-1}; **LC-LRMS** [ESI + APCI] 325.0 $(M–OH)^+$, and 357.0 $(M–OH+MeOH)^+$; and **HRMS** (ESI): calcd for $C_{19}H_{20}N_2O_3•Na^+$ 347.1366, found 347.1361.

(±)-(8a*R*,12a*S*,14b*S*)-8a-Ethyl-7,8,8a,10,11,12a-hexahydro-12a-hydroxyindolizino[8,1-*ef*][1]benzazonine-6,13(5H,9H)-dione; (±)-Leuconolam [(±)-1].

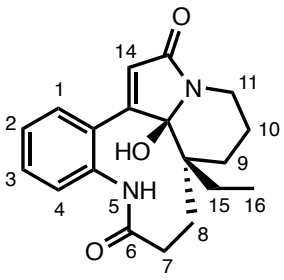


The 15,16-dehydro-macrolactam **21** (20 mg, 0.06 mmol, 1 equiv) was diluted in EtOH (0.1 M) and transferred into a high-pressure glass reaction vessel[5] equipped with a stir bar. To this mixture was added Pd on activated carbon (10%, 30 mg, 0.30 mmol, 5 equiv). The vessel was sealed and H_2 gas (50 psi) was introduced. The mixture was stirred at room temperature for 5 h. The excess pressure in the reaction vessel was released and the resulting suspension was filtered through a plug of Celite (EtOH as eluent). The filtrate was concentrated under reduced pressure and the crude material was purified by silica gel chromatography with EtOAc/MeOH (5:1) to give leuconolam [**(±)-1**, 19 mg, 95%] as a white solid.

mp: >250 °C (263-264 °C[6]); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.42 (td, *J* = 7.5, 1.5 Hz, 1H), 7.36 (td, *J* = 7.5, 1.5 Hz, 1H), 7.20 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.19 (br s, N*H*), 5.86 (s, 1H), 4.05 (br d, *J* = 12.0 Hz 1H), 3.58-3.49 (br s, O*H*), 2.90 (ddd, *J* = 13.0, 9.5, 7.0 Hz, 1H), 2.17 (br dd, *J* = 14.5, 7.5 Hz, 1H), 2.04 (br dd, *J* = 13.5, 13.5 Hz, 1H), 1.81-1.69 (m, 2H), 1.63-1.44 (m, 4H), 1.32-1.24 (m, 2H), and 0.58 (t, *J* = 7.5 Hz, 3H); **^{1}H NMR** (500 MHz, 5:95 v/v d_6-DMSO/$CDCl_3$): δ 7.88 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.66 (br s, N*H*), 7.40 (td, *J* = 7.5, 1.5 Hz, 1H), 7.33 (td, *J* = 7.5, 1.5 Hz, 1H), 7.24 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.96 (s, 1H), 4.72 (br s, O*H*), 4.08 (br d, *J* = 12.0 Hz 1H), 2.94 (ddd, *J* = 13.0, 9.5, 7.0 Hz, 1H), 2.18 (br dd, *J* = 14.0, 7.0 Hz, 1H), 2.03 (br dd, *J* = 13.0, 13.0 Hz, 1H), 1.83-1.72 (m, 2H), 1.62-1.43 (m, 4H), 1.32-1.25 (m, 2H), and 0.57 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 177.6, 166.4, 156.0, 135.8, 133.8, 129.6, 129.5, 128.7, 126.6, 126.5, 93.6, 45.2, 35.5, 32.6, 28.0, 25.9, 24.6, 20.2, and

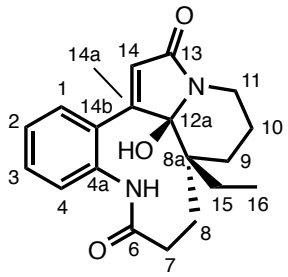
7.4; **IR** (thin film): 3227 (br), 2889, 1681, 1438, 1040, 1026, and 761 cm^{-1}; **LC-LRMS** [ES + APCI] 327.0 $(M–OH)^+$, 359.0 $(M–OH+MeOH)^+$, and 653.3 $(2M–H_2O–OH)^+$; **HRMS** (ESI, PPG calibrant): calcd for $C_{19}H_{22}N_2O_3•Na^+$ 349.1523, found 349.1539.

Table S1. Comparison of the ^{1}H NMR spectral data of natural (Goh[6]) and synthetic [Banwell[7] and this work] leuconolam (**1**) and, to emphasize the differences, of 12a-*epi*-leuconolam.[6]

	Proton #	Goh (400 MHz) [a]	Banwell (300 MHz) [a]	this work (500 MHz) [a]	this work (500 MHz) [b]	12a-*epi*-**1** (270 MHz) [a]
 ***1*** leuconolam						
	1	7.20	7.18	7.20	7.24	7.45
	2	7.33 [c]	7.35 [c]	7.36	7.33	7.33
	3	7.33 [c]	7.35 [c]	7.42	7.40	7.12
	4	7.92	7.88	7.88	7.88	8.16
	5 (N*H*)	7.89	7.51	7.19	7.66	–
	7	2.14	2.05	2.17	2.18	3.16
	7'	2.00	2.05	2.04	2.03	2.66
	8	1.65-1.37	1.85-1.05	1.63-1.44	1.83-1.72	2.13-2.03
	8'	1.65-1.37	1.85-1.05	1.63-1.44	1.62-1.43	2.13-2.03
	9	1.79	1.85-1.05	1.81-1.69	1.83-1.72	1.79-1.30
	9'	1.65-1.37	1.85-1.05	1.81-1.69	1.62-1.43	1.79-1.30
	10	1.65-1.37	1.85-1.05	1.63-1.44	1.62-1.43	1.79-1.30
	10'	1.65-1.37	1.85-1.05	1.63-1.44	1.62-1.43	1.79-1.30
	11	3.98	4.00	4.05	4.08	4.44
	11'	2.96	2.92	2.90	2.94	3.07
	14	5.79	5.77	5.86	5.96	6.20
	15 (2H)	1.65-1.37	1.85-1.05	1.32-1.24	1.32-1.25	1.79-1.30
	16 (3H)	0.55	0.55	0.58	0.57	0.73
	O*H*	–	–	3.58-3.49	4.74-4.71	–

[a] Measured in $CDCl_3$. [b] Measured in 5:95 v/v d_6-DMSO/$CDCl_3$. [c] H2 and H3 were observed as a single resonance.

Table S2. Comparison of the ^{13}C NMR spectral assignments of natural (Goh[6]) and synthetic [Banwell[7] and this work] leuconolam (**1**).

	Carbon #	Goh (22.5 MHz) [a]	Banwell (75 MHz) [a]	this work (125 MHz) [b]	12a-*epi*-**1** (22.5 MHz) [a]
 ***1*** leuconolam	**1**	129.3	129.7	129.5	124.2
	2	126.6	126.5	126.6	121.4
	3	129.4	129.9	129.6	131.4
	4	126.3	127.2	126.5	115.8
	4a	135.0	135.2	135.8	148.6
	6	177.8	177.8	177.6	175.8
	7	32.1	32.5	32.6	34.1
	8	25.4	25.8	25.9	30.4
	8a	44.9	45.3	45.2	44.5
	9	24.5	24.5	24.6	26.1
	10	19.7	20.1	20.2	16.8
	11	35.3	35.7	35.5	37.0
	12a	93.6	94.0	93.6	93.6
	13	166.5	166.7	166.4	173.2
	14	128.1	128.6	128.7	118.1
	14a	155.6	156.0	156.0	164.1
	14b	133.1	133.5	133.8	123.4
	15	27.3	27.9	28.0	33.0
	16	6.9	7.4	7.4	8.2

[a] Measured in ca. $CDCl_3$; assignments for C1 and C3 and for C2 and C4 may be interchanged. [b] Measured in 10:90 v/v d_6-DMSO/$CDCl_3$.

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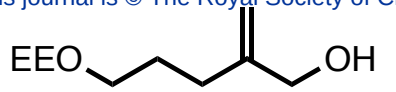

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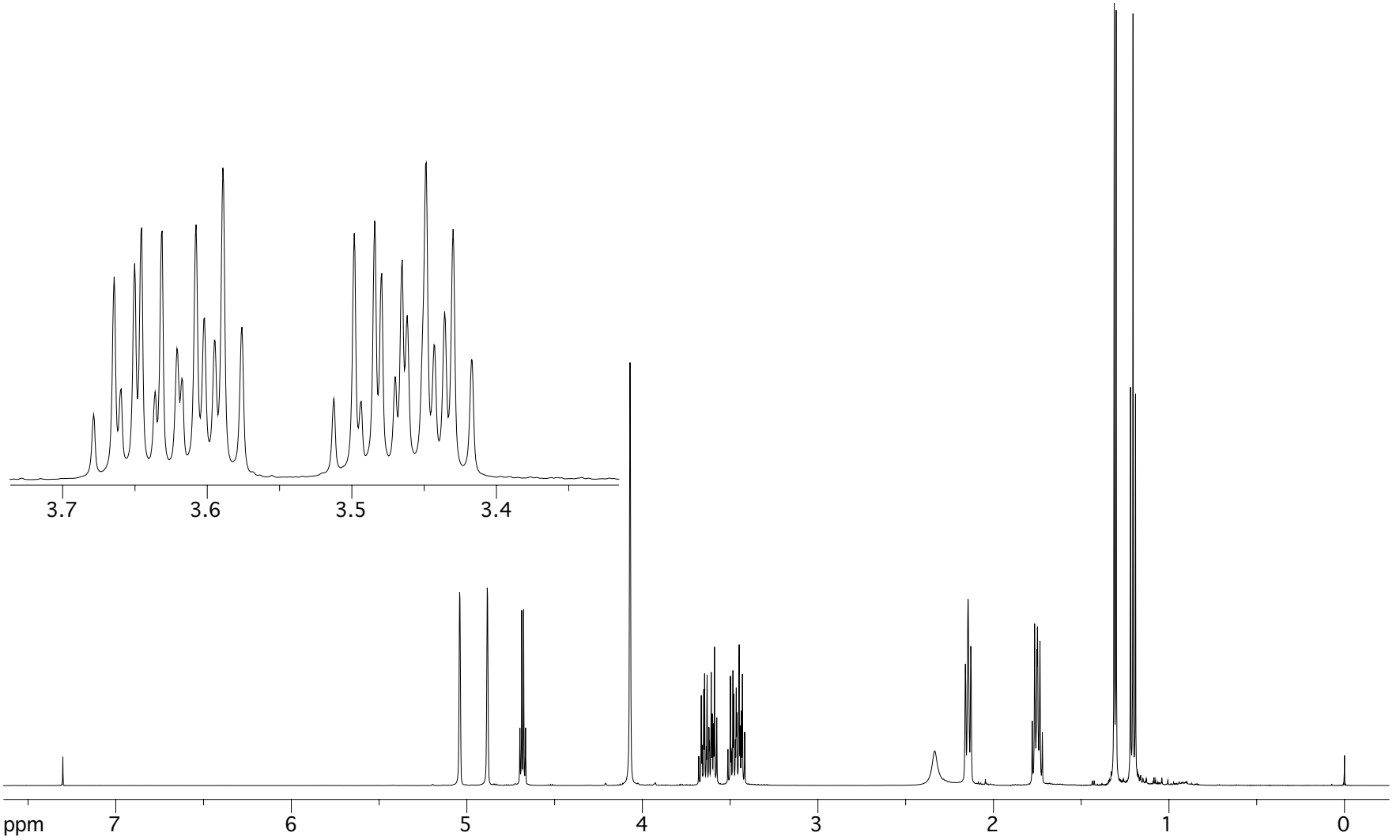

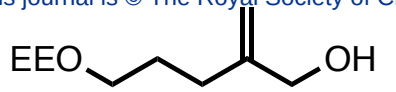

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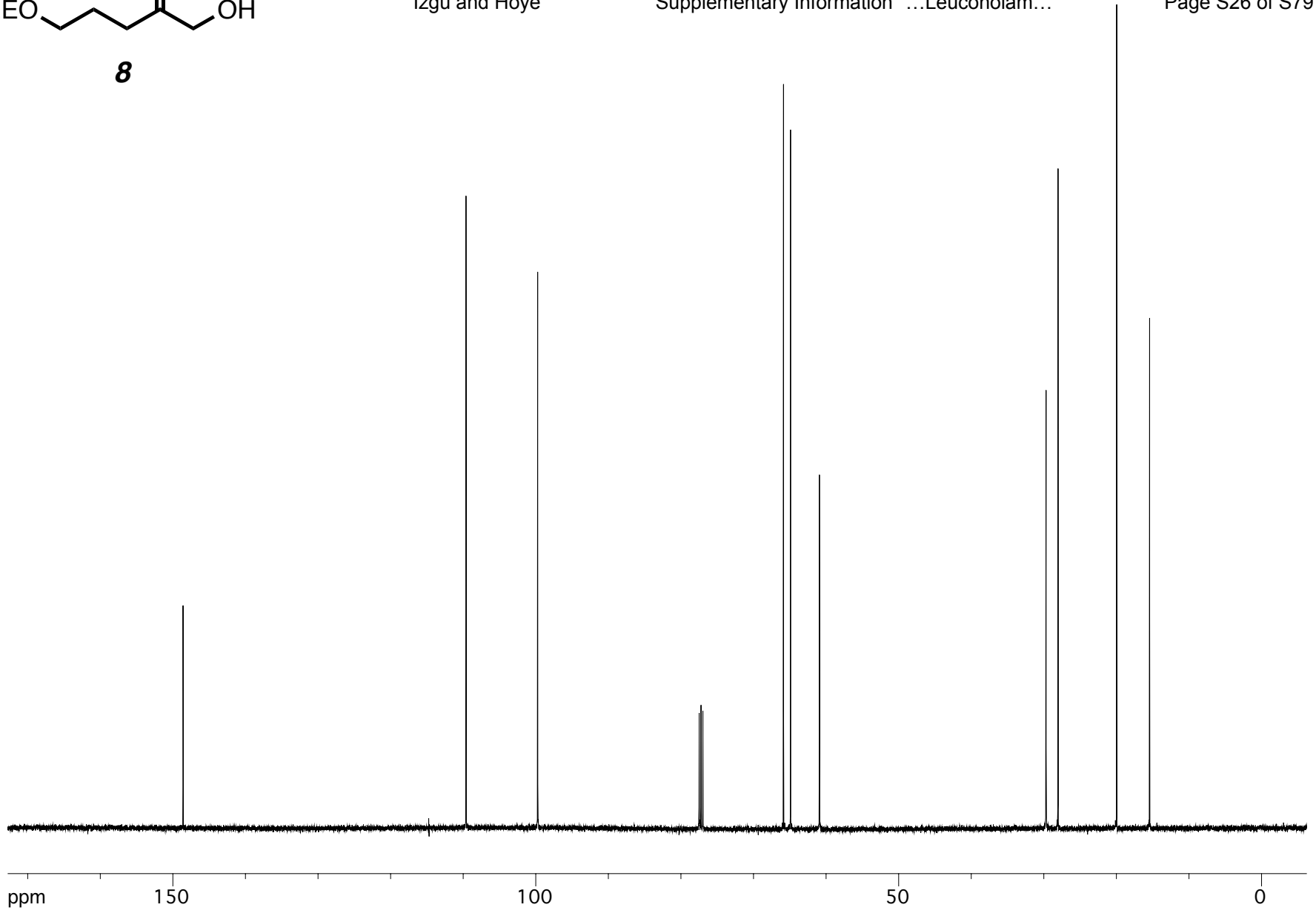
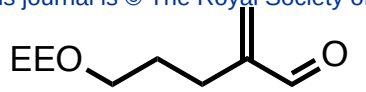
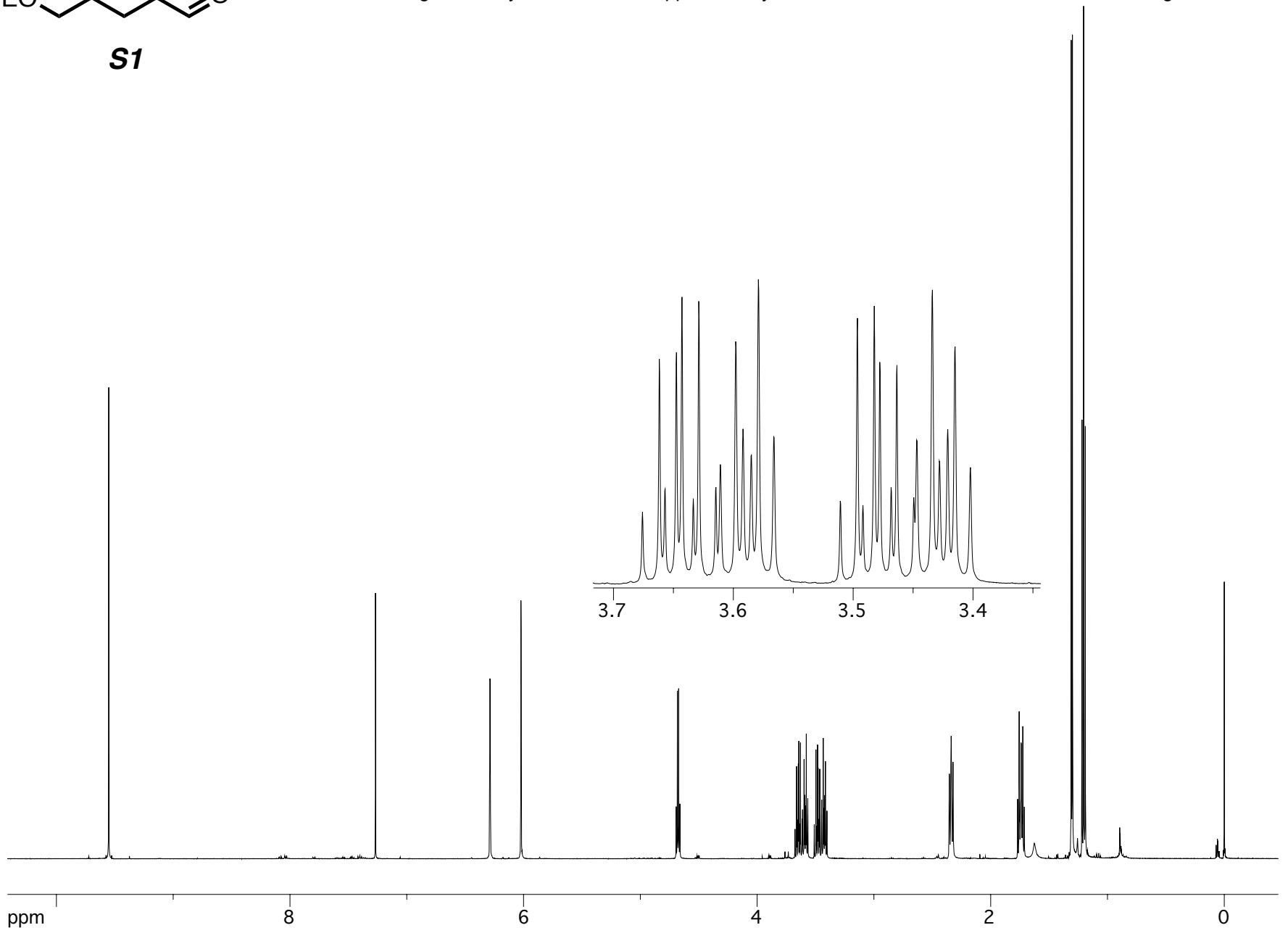
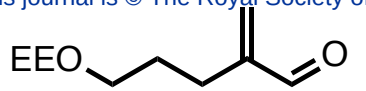




S1





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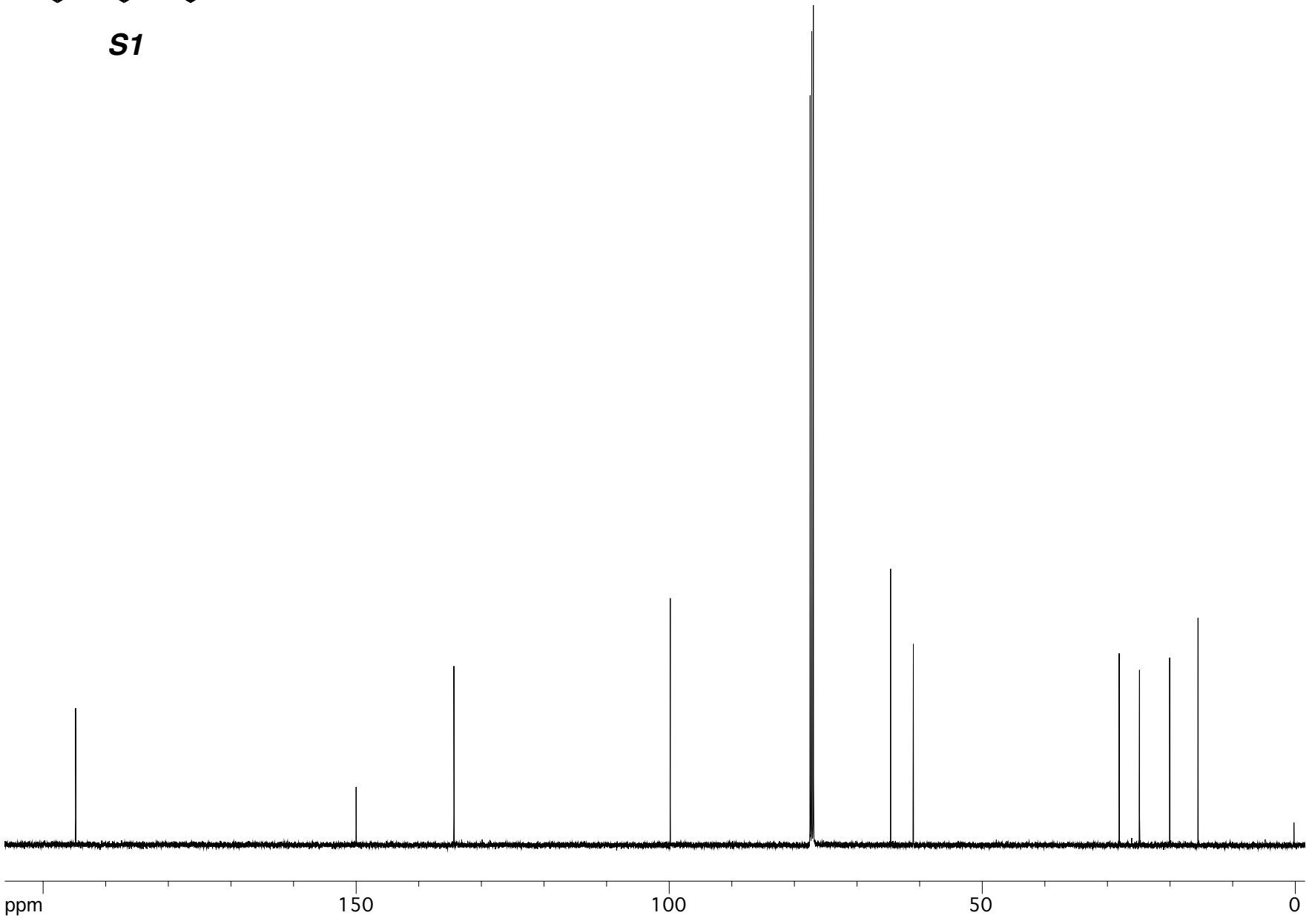

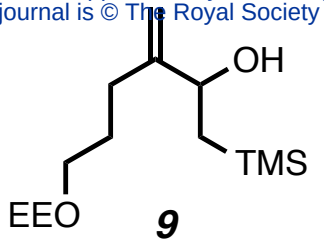

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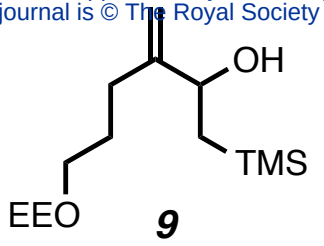

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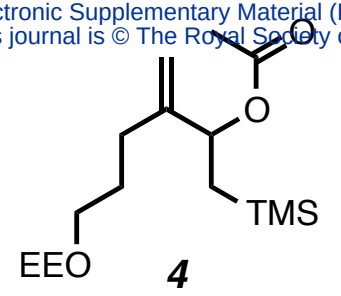

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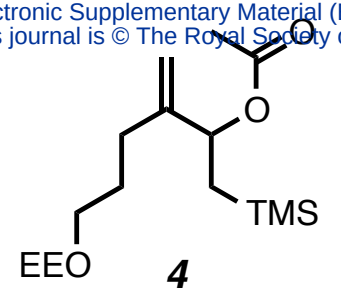

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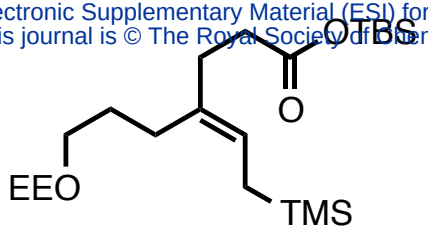

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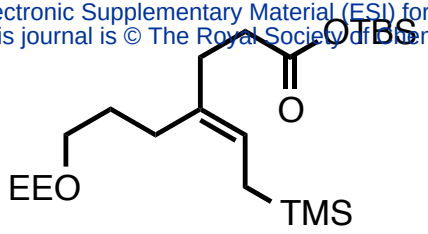

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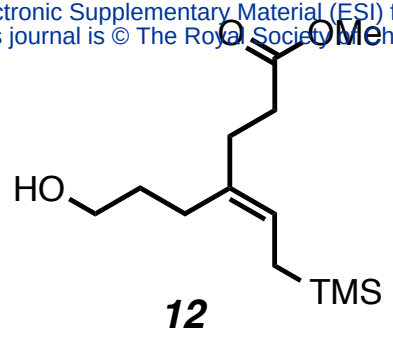

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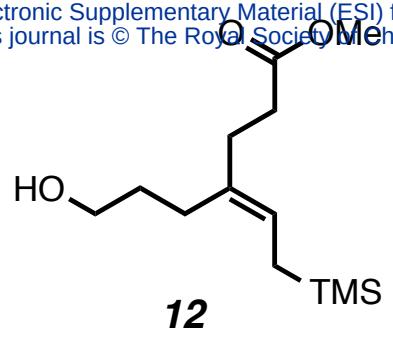

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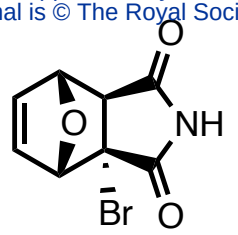

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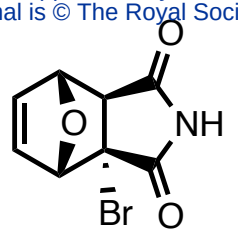
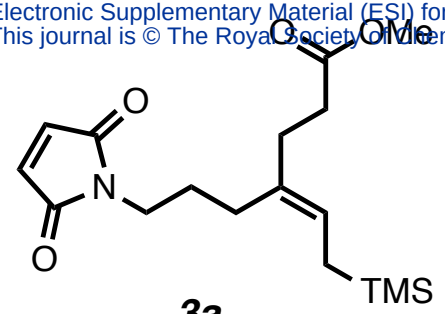


13b



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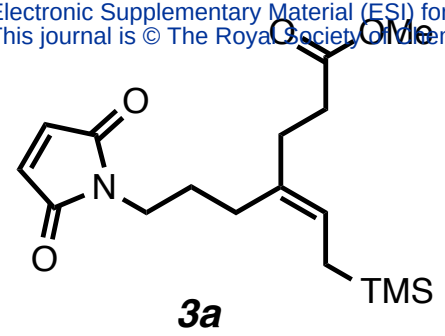

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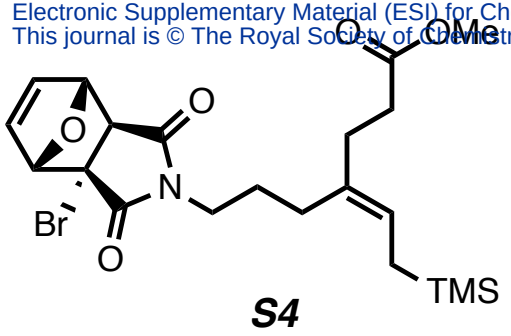

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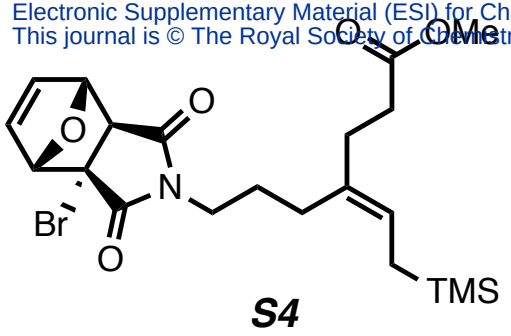

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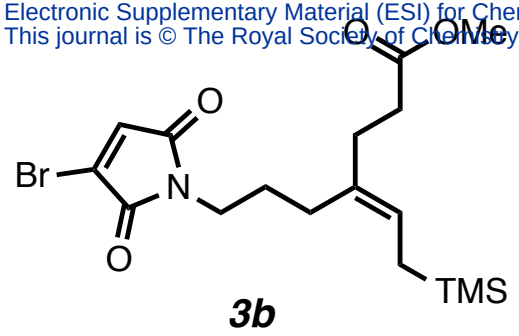

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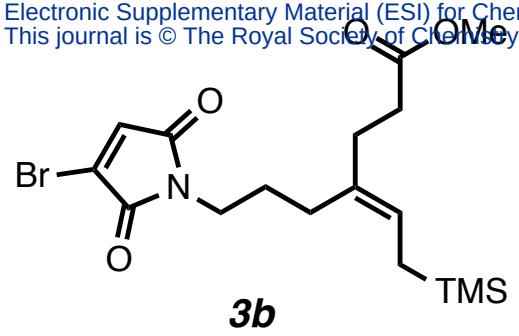

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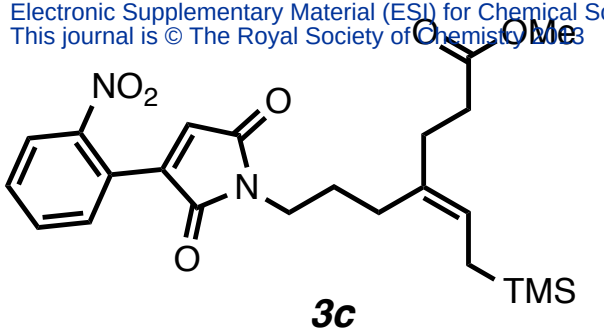

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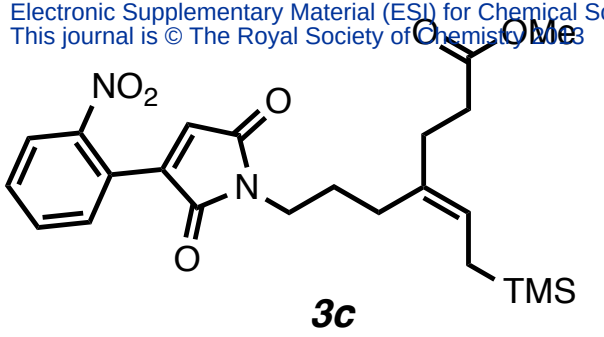

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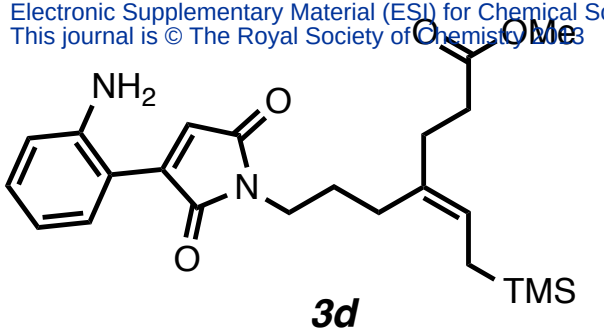

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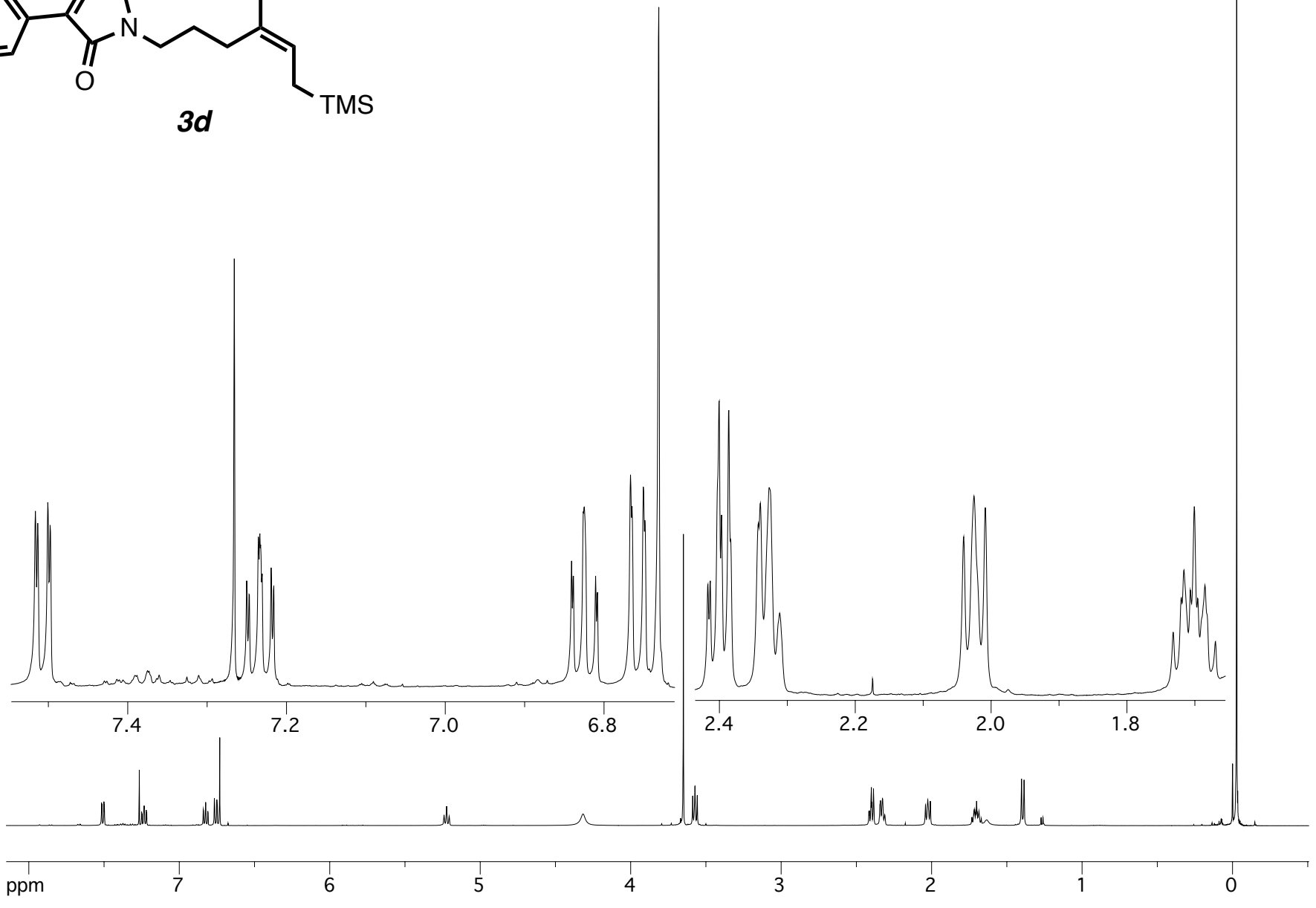

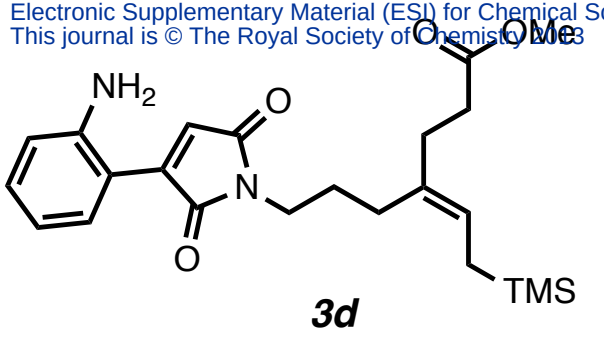

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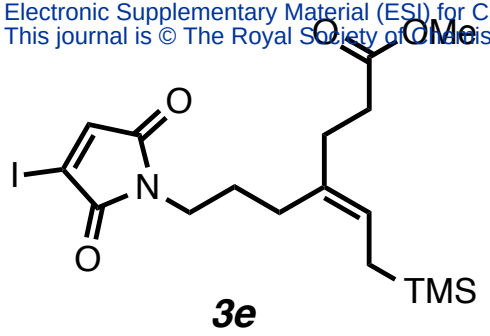

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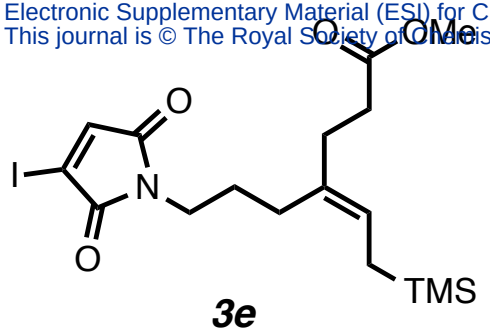

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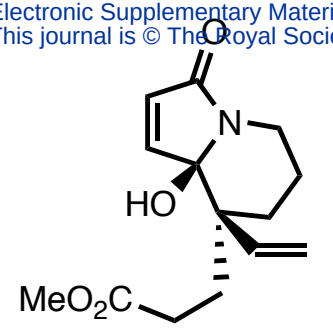

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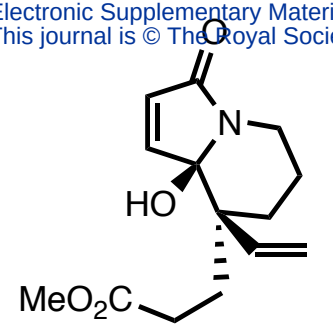

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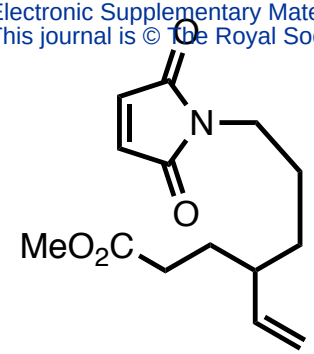

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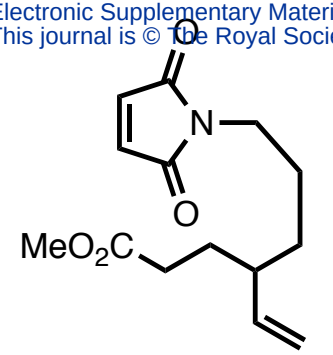

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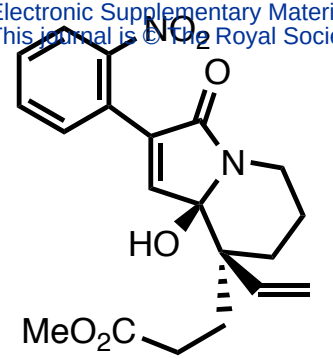
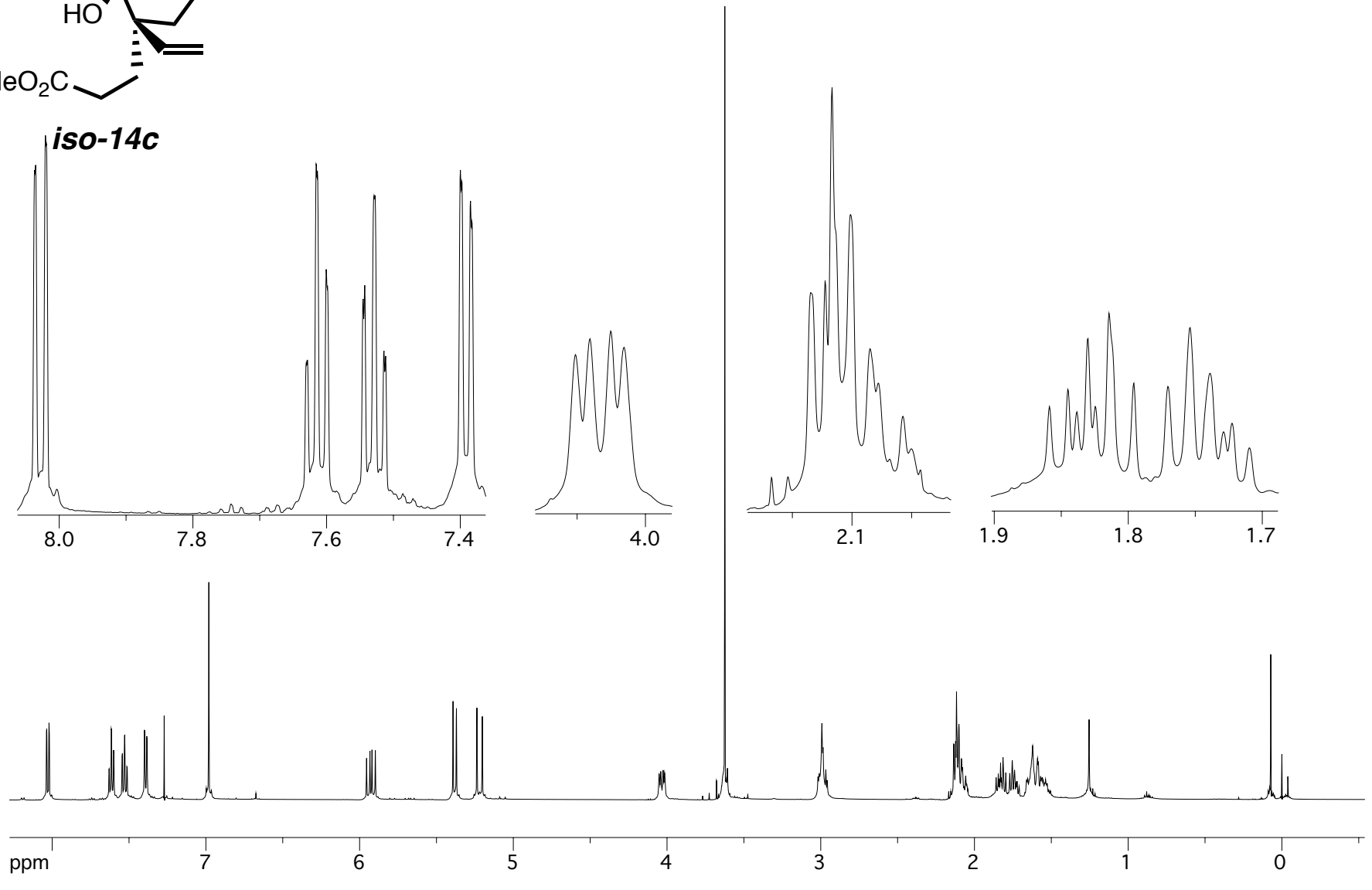
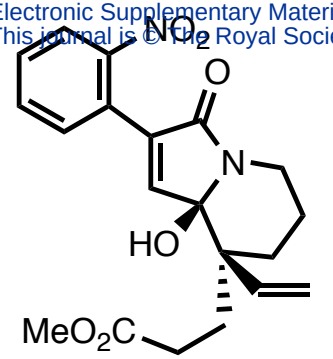


iso-14c





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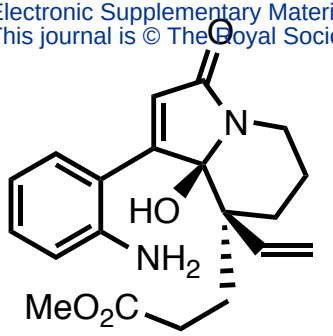

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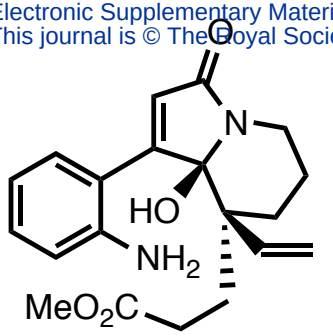

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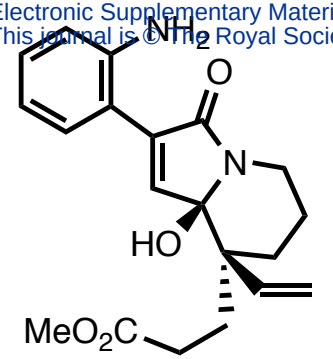

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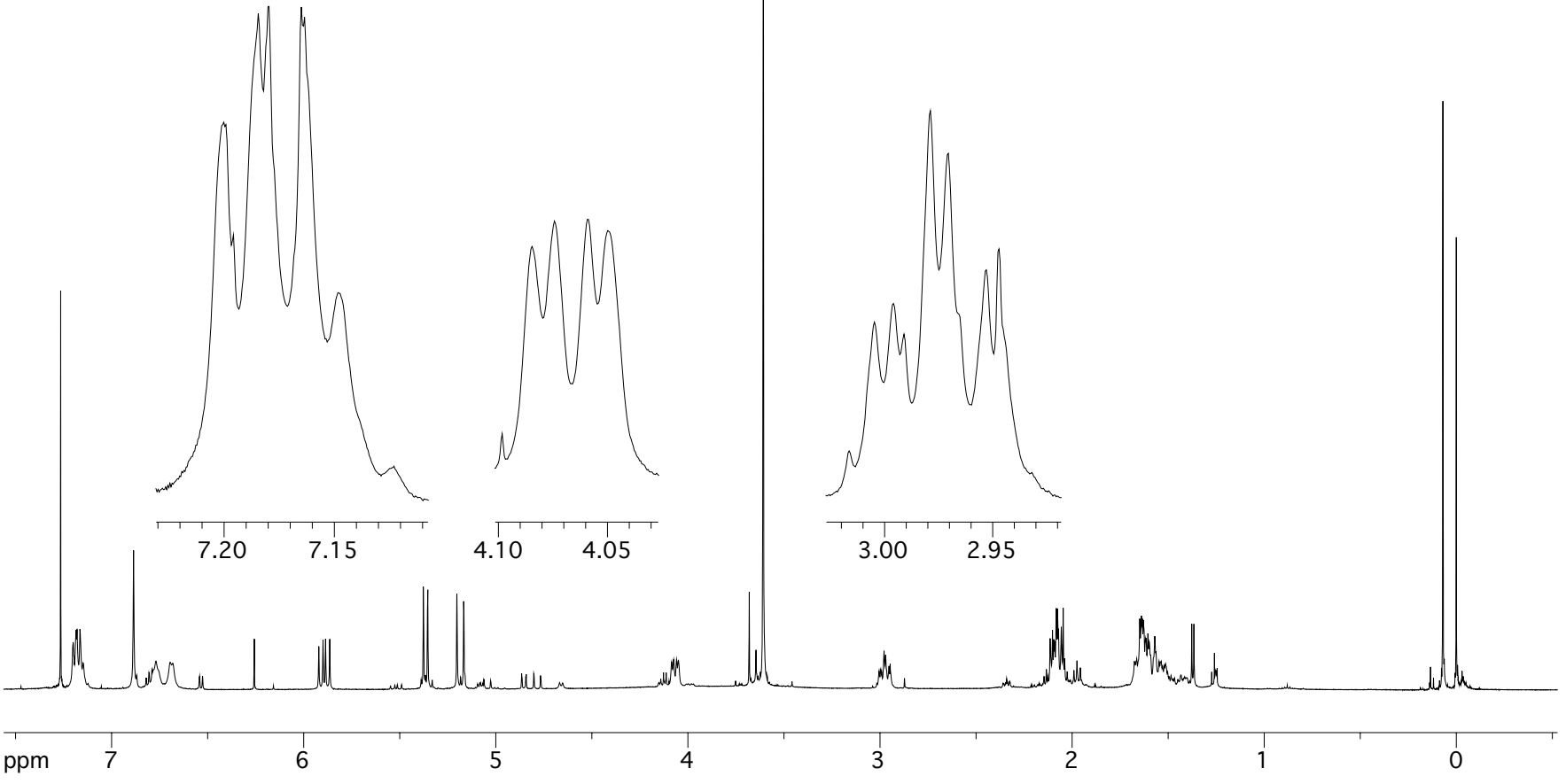

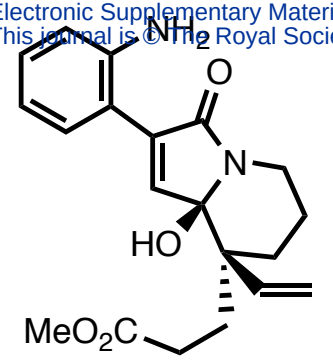

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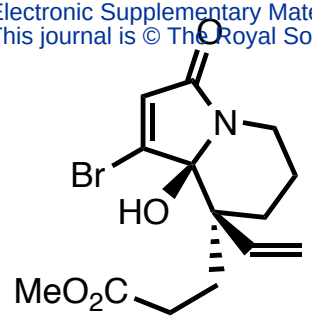
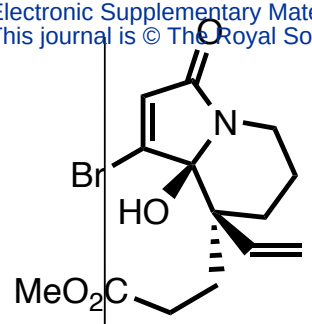


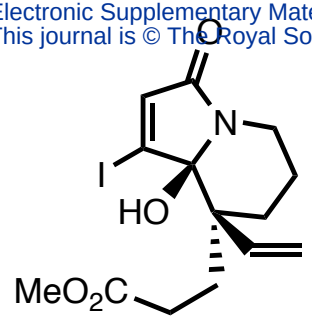
14b

★ d_5-acetone



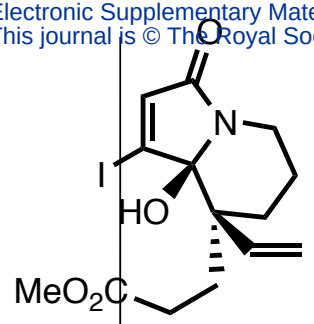
14b

★ d_6-acetone



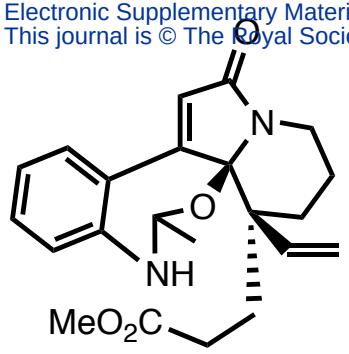
14e

★ d_5-acetone



14e

★ d_6-acetone



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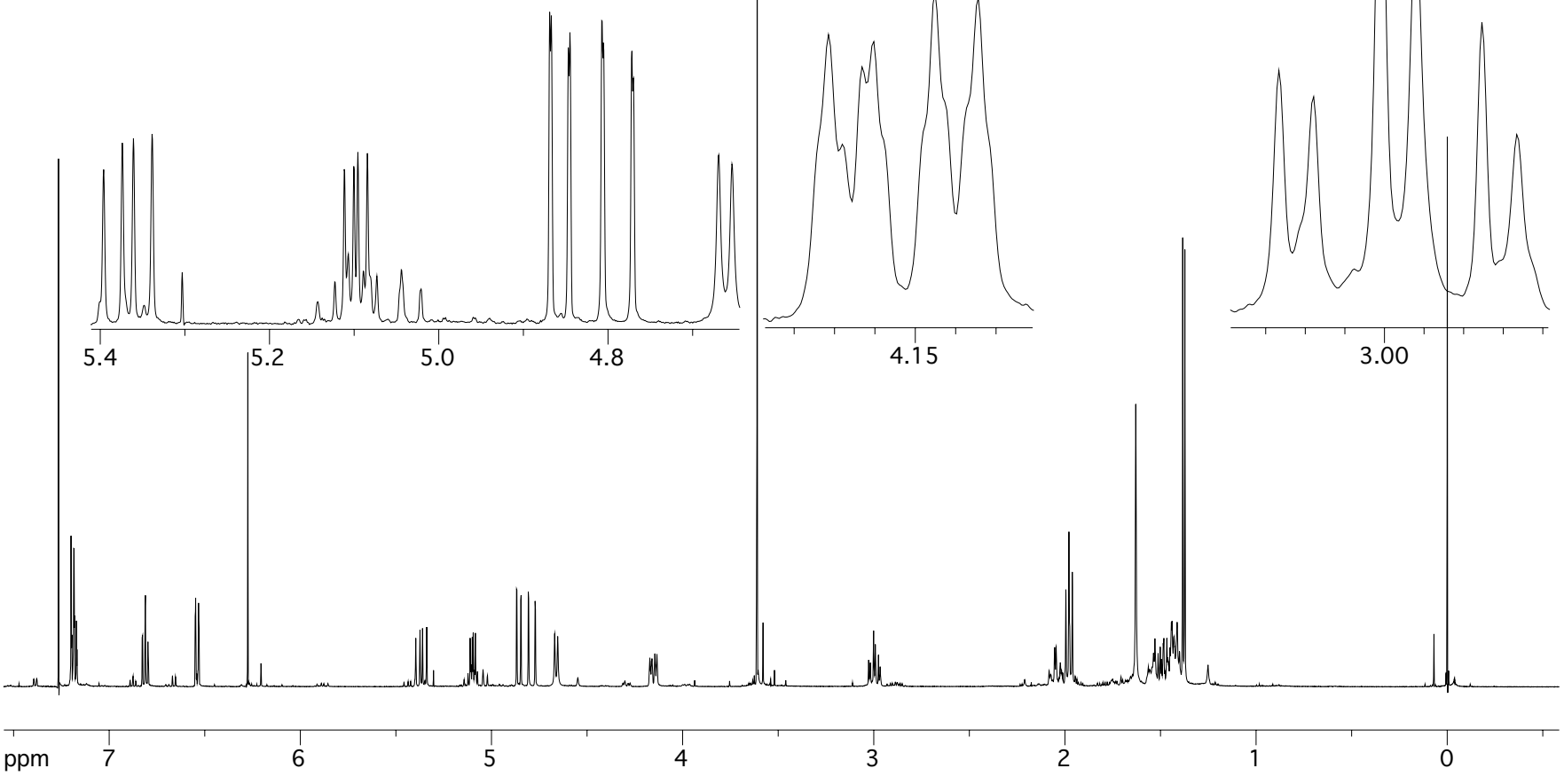

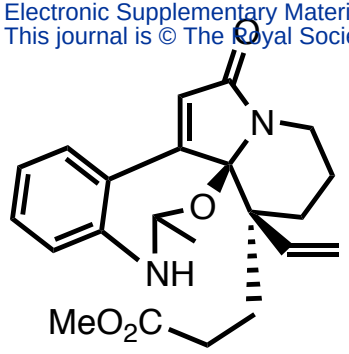

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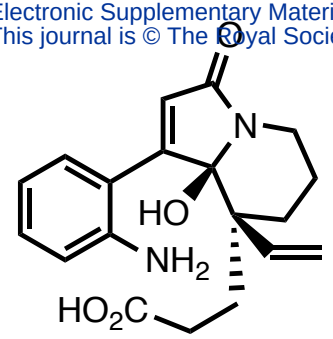
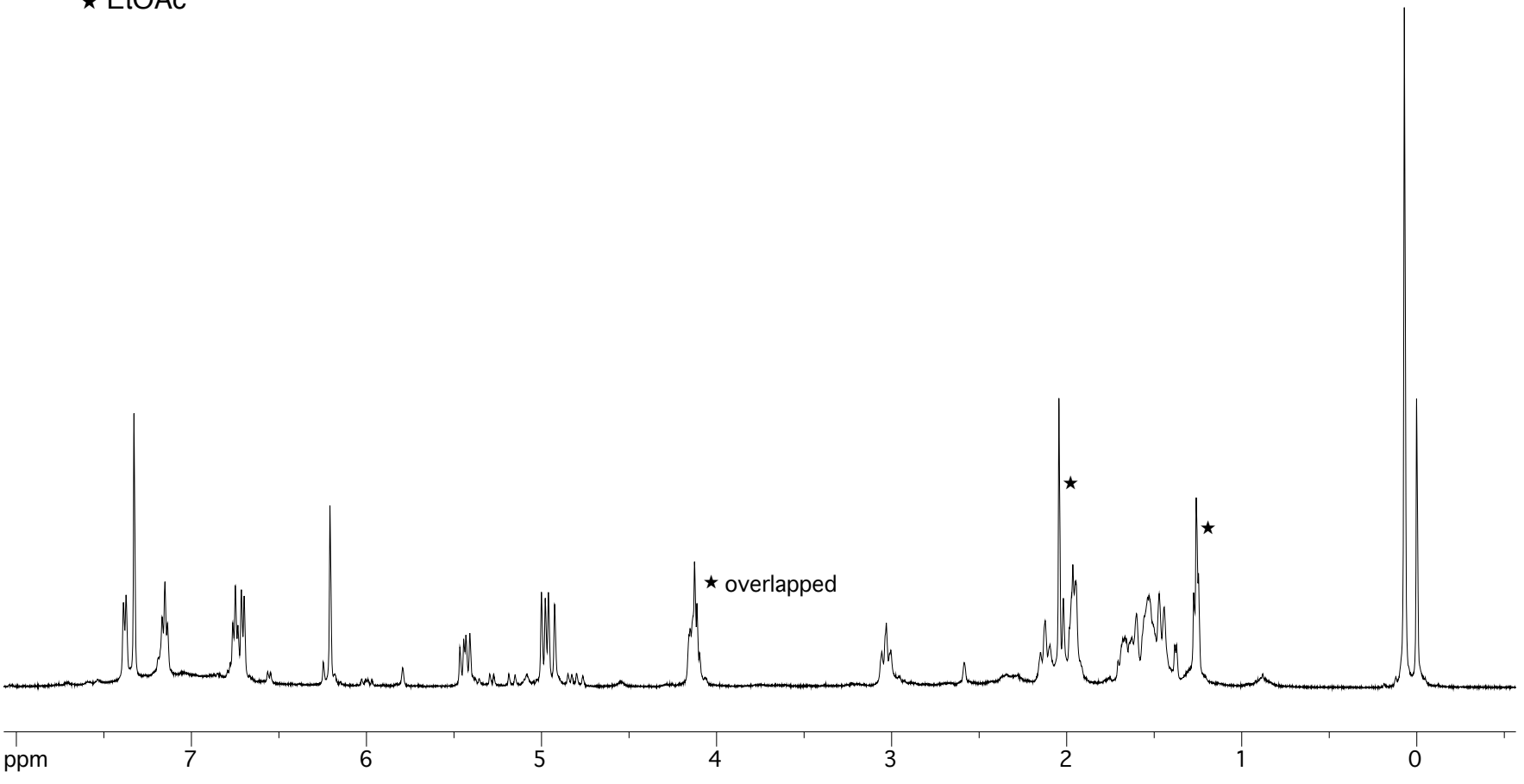
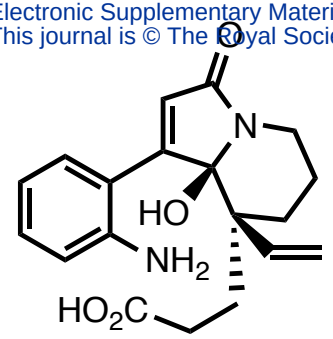


S5

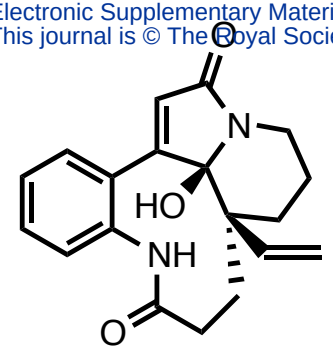
★ EtOAc





S5

★ d_6-DMSO

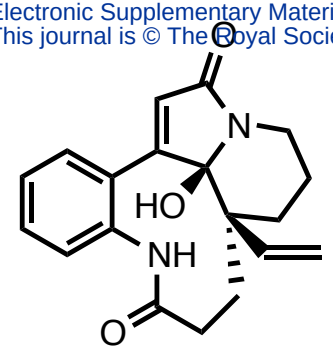


21

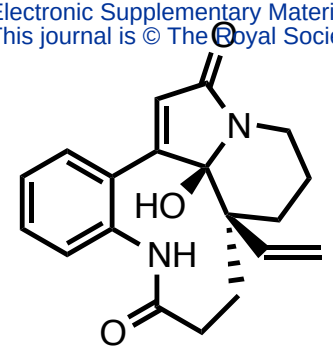
in $CDCl_3$

★ DMF

▼ MeOH

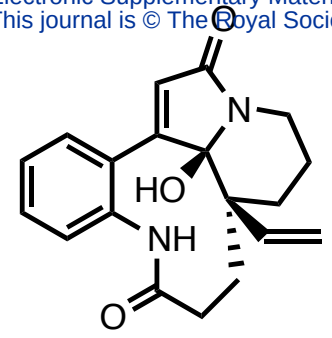


21
in CD_3OD

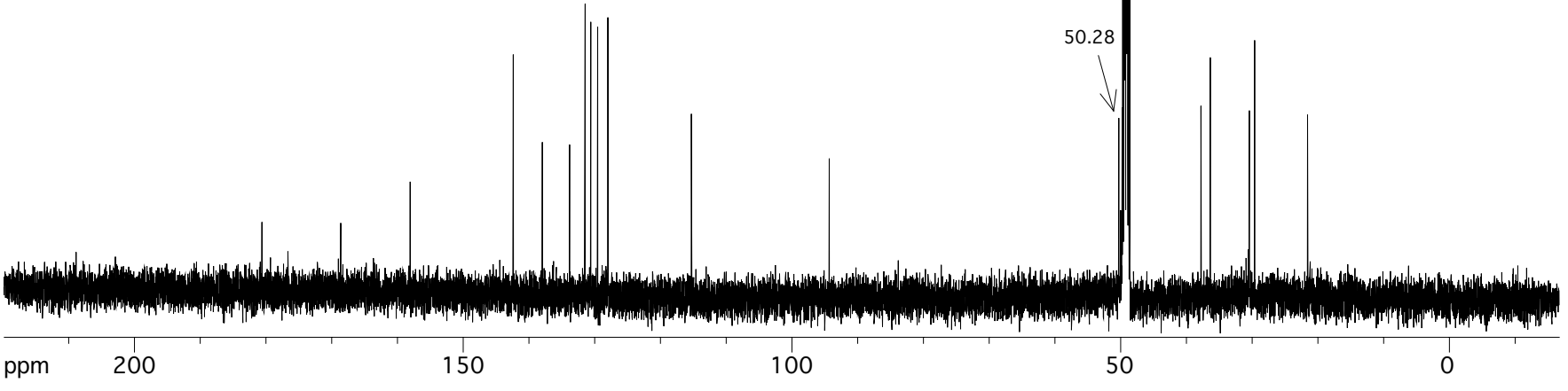


21

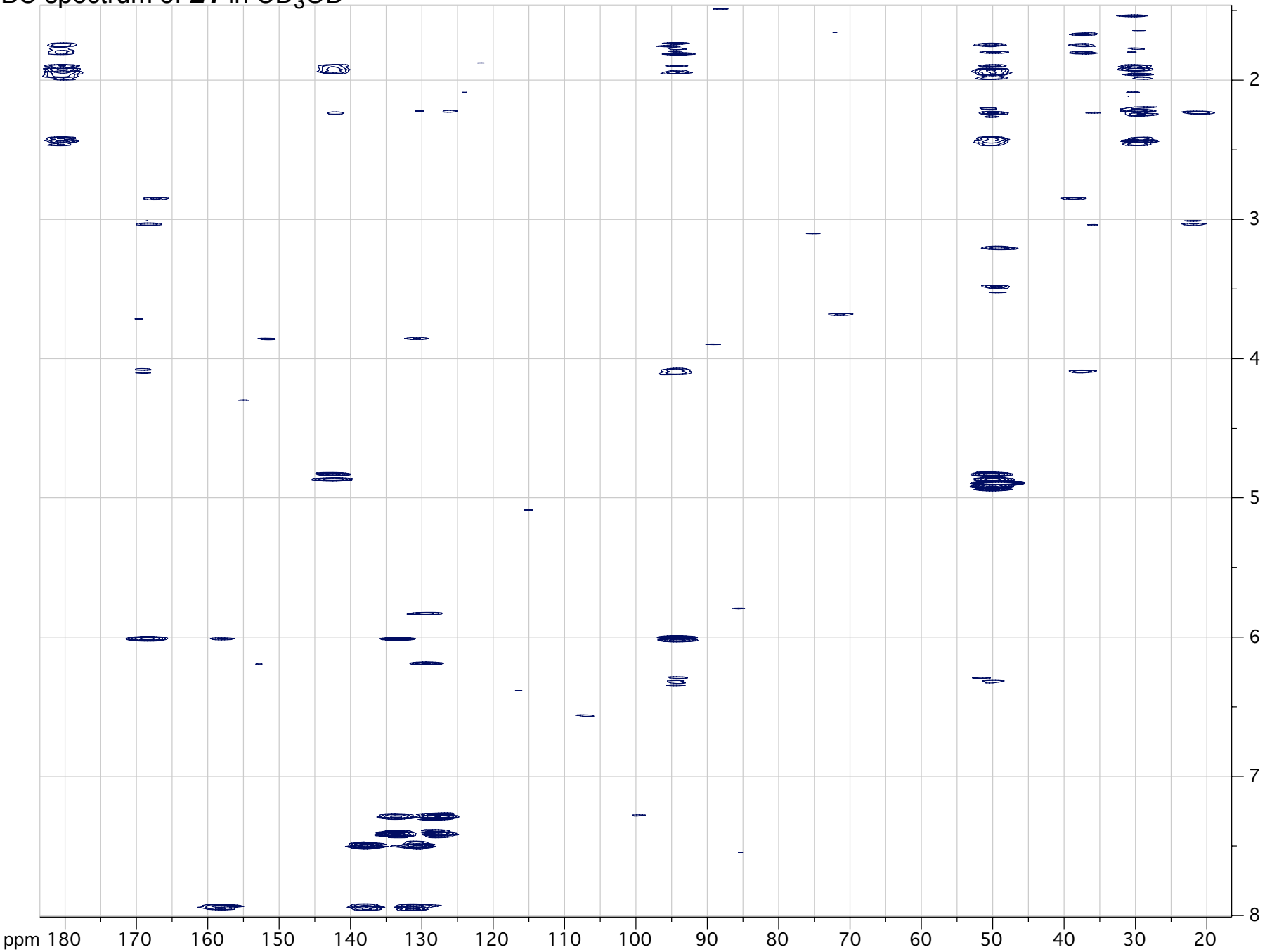
in CD_3OD (resolution enhanced)



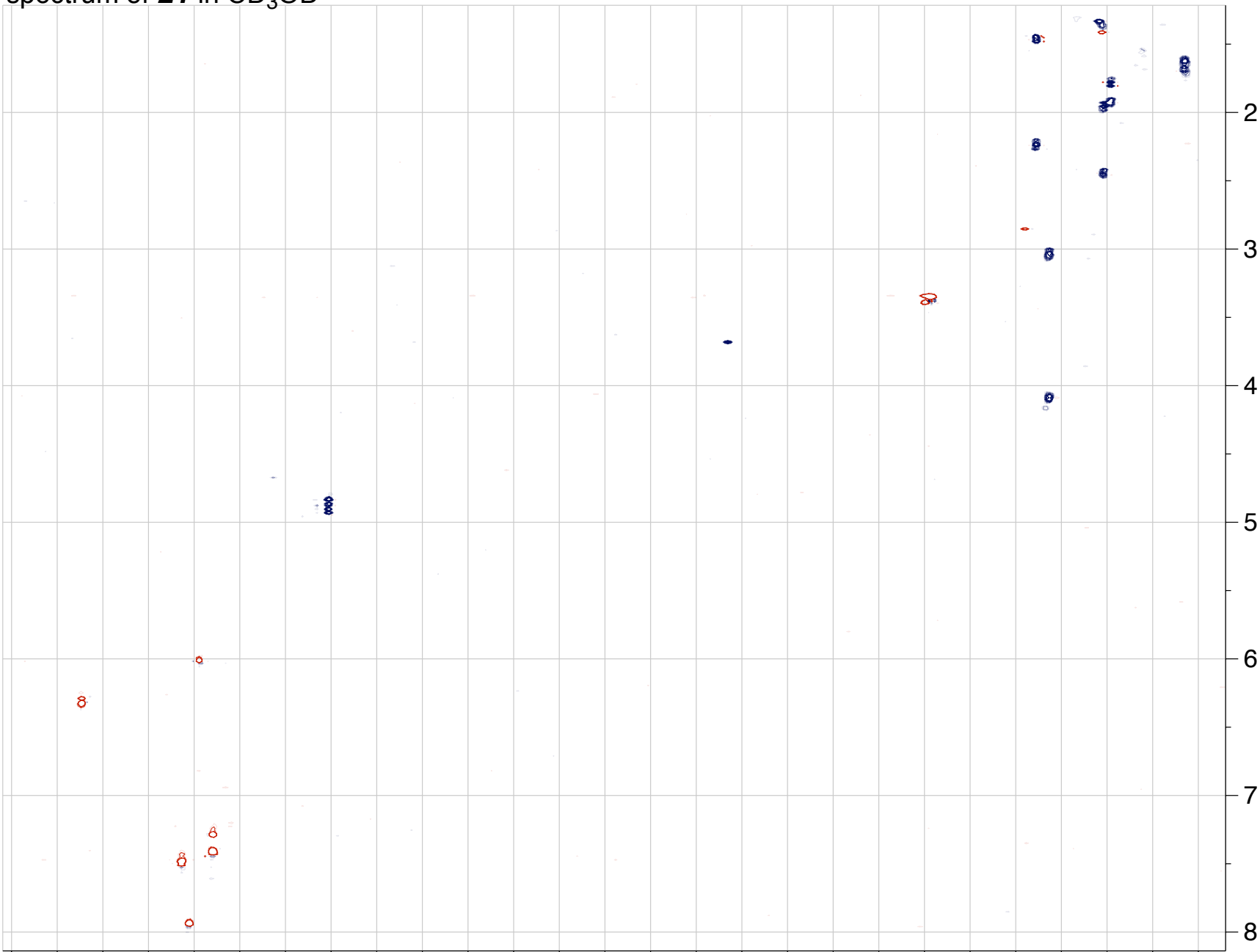
21
in CD_3OD



HMBC spectrum of ***21*** in CD_3OD

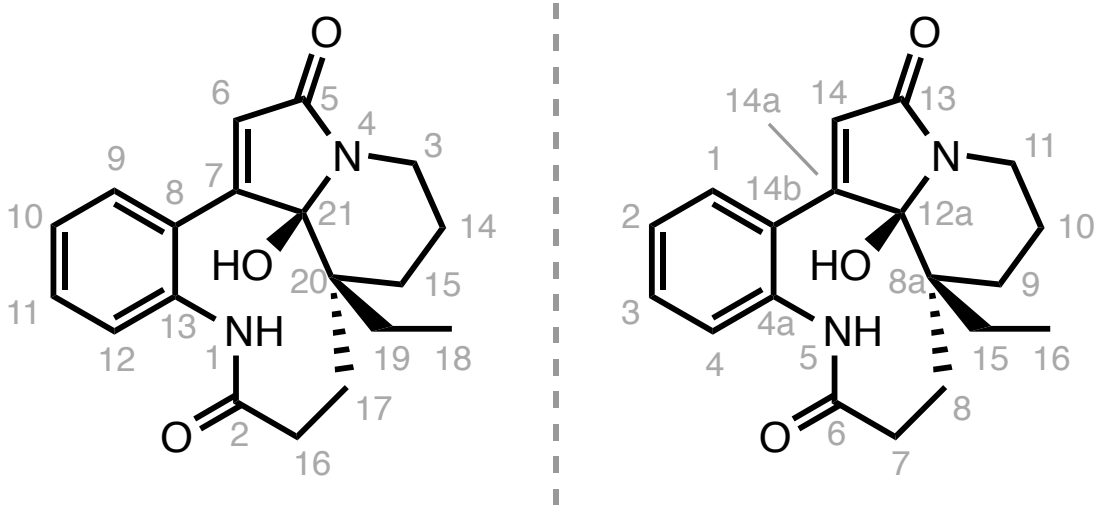


HSQC spectrum of ***21*** in CD_3OD



Numbering of leuconolam (***1***)

Goh *vs.* this work



S. H. Goh *et al.*

Graphic taken from S. H. Goh, A. R. M. Ali, W. H. Wong, Tetrahedron, 1989, 45, 7899–7920.

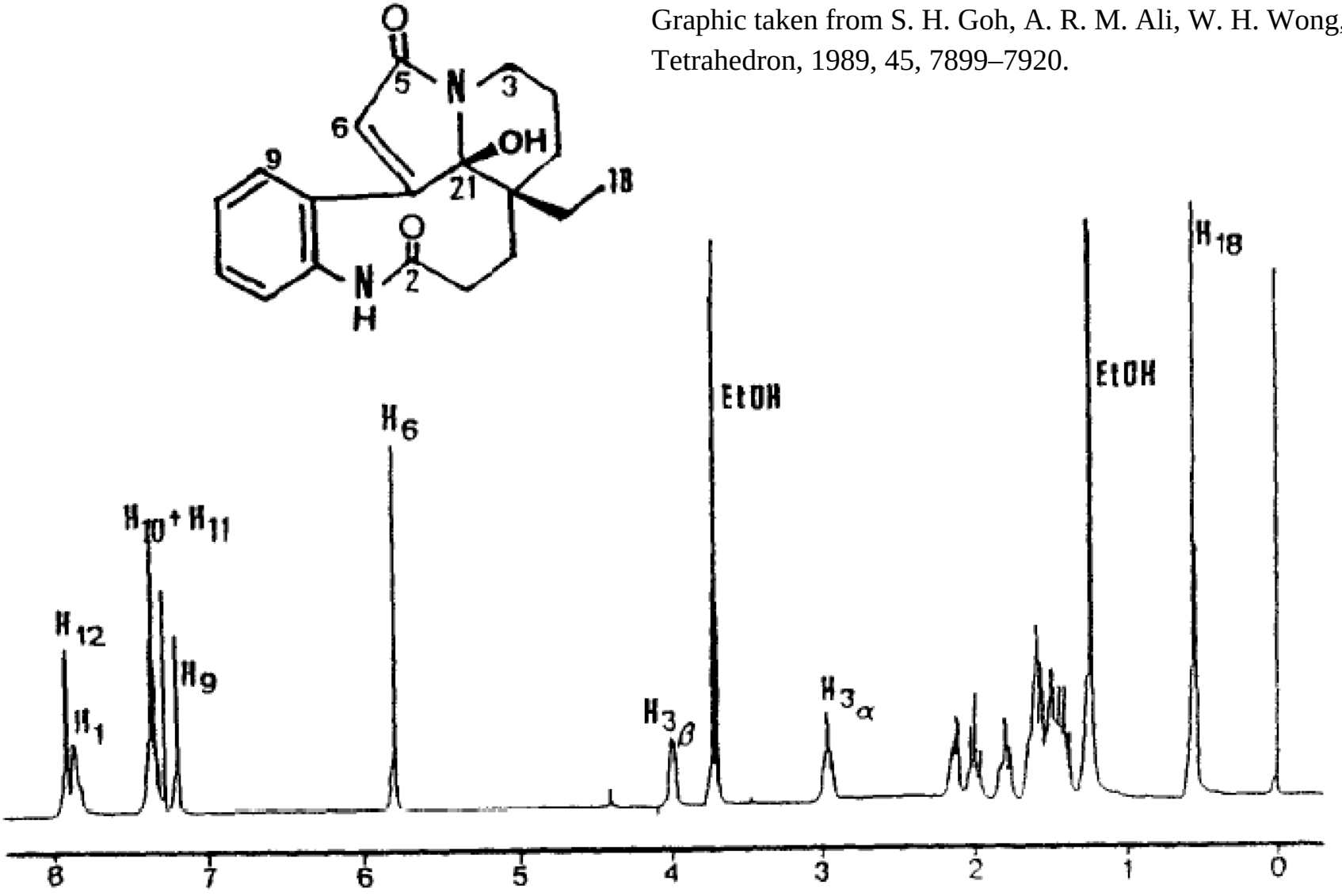
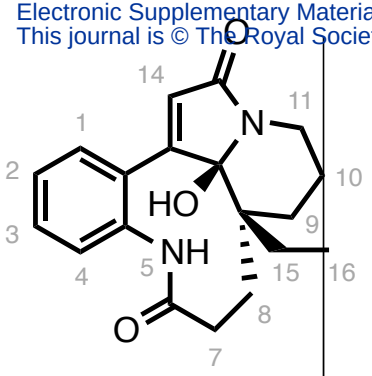
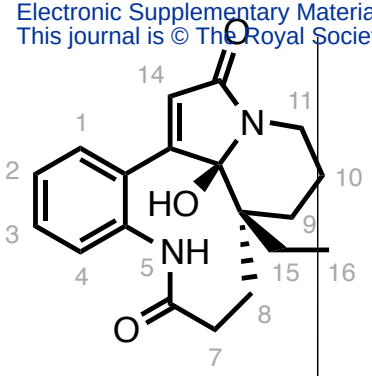


Figure 1 : 400 MHz HNMR Spectrum of Leuconolam in $CDCl_3$



1 leuconolam



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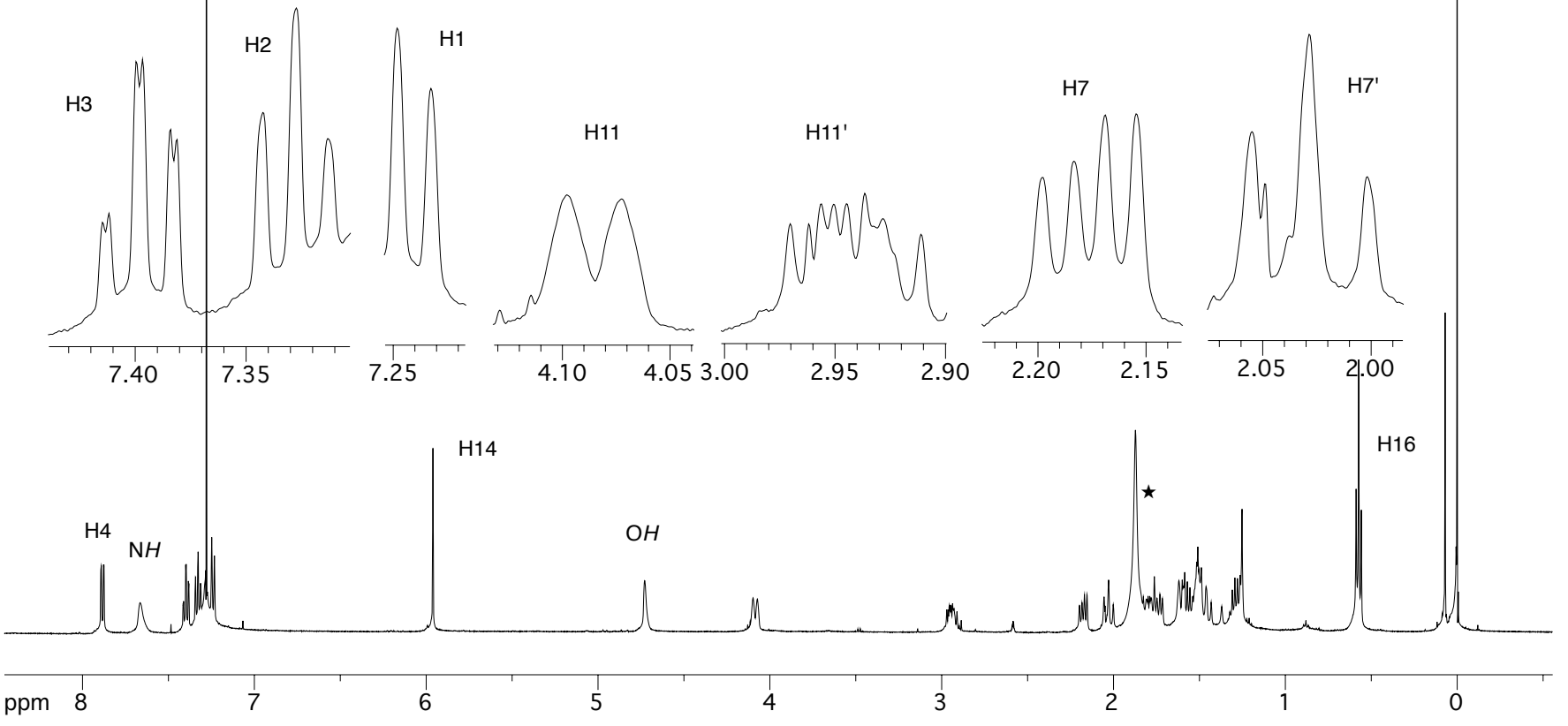
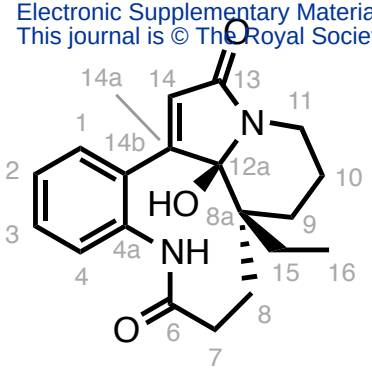
★ water in ca. 5:95 v/v d_6-DMSO/$CDCl_3$





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★ d_6-DMSO (ca. 10% in $CDCl_3$)