Concise Total Synthesis of Trichodermamides A, B and C Enabled by an Efficient Construction of the 1,2-Oxazadecaline Core

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General Procedures

Materials and methods: Anhydrous dichloromethane, tetrahydrofuran, toluene and diethyl ether were collected under argon from an LC Technologies solvent purification system, having been passed through two columns packed with molecular sieves. *N,N*-Dimethylformamide, acetonitrile, *sym*-collidine, pyridine, cyclohexane, dimethyl sulfoxide, benzene and trifluorotoluene were dried over 3 Å molecular sieves. 2,2,6,6-Tetramethylpiperidine was freshly distilled from calcium hydride before use. Benzoquinone was sublimed and stored at –20 °C. *N,O*-Bis(trimethylsilyl)acetamide (BTSA) was freshly distilled before use. Phenylselenol,[1] iodosobenzene,[2] tetrakis(triphenylphosphine)palladium(0),[3] and *N*,*N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-ethylenediaminomanganese(III) chloride (**23**),[4] were prepared according to the literature procedures. All other chemicals were used as commercially available. All reactions were conducted with continuous magnetic stirring under an atmosphere of argon in oven-dried glassware. Reactions were monitored by ^{1}H NMR or by TLC on silica gel-coated glass plates (Merck Kieselgel 60 F254) until deemed complete. Plates were visualized under ultraviolet light (254 nm) and by staining with ceric ammonium molybdate (CAM) or potassium permanganate.

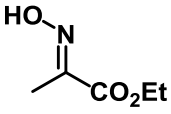
Purification: Column chromatography was performed using CombiFlash Rf-200 (Teledyne-Isco) automated flash chromatography system with hand-packed RediSep columns.

Characterization: ^{1}H, ^{13}C, NMR spectra were recorded at 500 MHz (^{1}H), 125 MHz (^{13}C) on the Agilent Inova 500 instrument in $CDCl_3$ solutions with and without tetramethylsilane (TMS) as an internal standard unless specified otherwise. Chemical shifts (δ) are reported in parts per million (ppm) from the residual solvent peak and coupling constants (*J*) in Hz. Proton multiplicity is assigned using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint.), septet (sept.), multiplet (m), broad (br).

Infrared measurements were carried out neat on a Bruker Vector 22 FT-IR spectrometer fitted with a Specac diamond attenuated total reflectance (ATR) module.

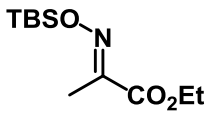
Experimental Procedures

Ethyl 2-(hydroxyimino)propanoate[5] (16a)



To a solution of ethyl pyruvate (24.8 mL, 300 mmol) in ethanol (50 mL) at 23 °C was added hydroxylamine (19.6 mL, 360 mmol, 1.2 equiv., 50% solution in water). After 12 h the solution was concentrated under reduced pressure and azeotroped to yield oxime **16a** (38.4 g, 98%) as a colorless solid. – m.p. 94–96 °C (Lit: 94 °C[5]). – ^{1}H NMR (500 MHz, $CDCl_3$): 10.22–9.87 (1 H, br s), 4.30 (2 H, q, *J* = 7 Hz), 2.10 (3 H, s), 1.34 (3 H, t, *J* = 7 Hz) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): 163.7, 149.3, 61.8, 14.0, 10.2 ppm. – IR: 3025, 2992, 1636, 1477, 1310, 1153 cm^{-1}.

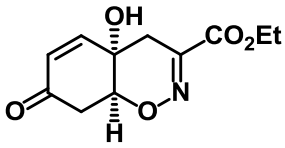
Ethyl 2-[(*tert*-butyldimethylsilyloxy)imino]propanoate (16c)



To a solution of oxime **16a** (15 g, 114.5 mmol) in dichloromethane (60 mL) at 0 °C was added 4-(dimethylamino)pyridine (698 mg, 5.72 mmol, 5 mol %), imidazole (12.5 g, 183.2 mmol, 1.6 equiv.), and *tert*-butyldimethylsilyl chloride (18.9 g, 126.0 mmol, 1.1 equiv.). The reaction mixture was stirred at 23 °C for 1 h, and then heated at 35 °C for 12 h. The reaction mixture was diluted with water (50 mL), the layers separated, and the organic layer was washed with water (2 × 50 mL). The combined aqueous layers were extracted with dichloromethane

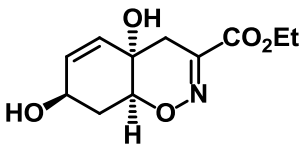
(2 × 50 mL), and the combined organic layers dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield oxime **16c** (27.35 g, 98%) a colorless oil. – ^{1}H NMR (500 MHz, $CDCl_3$): 4.32–4.27 (2 H, q. *J* = 7 Hz), 2.08 (3 H, s), 1.34 (3 H, t, *J* = 7 Hz), 0.96 (9 H, s), 0.24 (6 H, s) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): 164.0, 153.6, 61.0, 25.7, 17.9, 13.9, 10.9, –5.5 ppm. – IR: 3033, 2956, 2931, 2859, 1605, 1473, 1464, 1252, 1176, 1151, 961 cm^{-1}. – MS (ESI): 246.0 [M+H$^+$]. – HRMS: calcd. for $C_{11}H_{24}NO_3Si^+$ 246.1520, found 246.1170 [M+H$^+$].

(4a*S,8a*S**)-Ethyl 4a-hydroxy-7-oxo-4a,7,8,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxylate (15)**



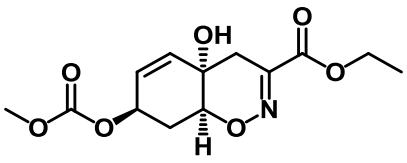
To a solution of 2,2,6,6-tetramethylpiperidine (15.2 mL, 89.8 mmol) in THF (160 mL) was added *n*-butyllithium (34.3 mL, 85.7 mmol) dropwise over 10 min at –78 °C. The reaction mixture was allowed to warm up to room temperature over 1 h and then cooled to –78 °C. A solution of (**16c**) (10 g, 40.8 mmol) in THF (80 mL) was added dropwise over 10 min. The reaction was stirred for 2 h at –78 °C, then a solution of freshly sublimed benzoquinone (4.4 g, 40.8 mmol) in THF was added dropwise over 10 min. The reaction was stirred at –78 °C for an additional 2 h, then a solution of acetic acid (9.5 mL, 163.2 mmol) in THF (10 mL) was added, and the mixture was warmed up to room temperature. The mixture was concentrated on Celite and purified by silica gel column chromatography (hexanes/5% v/v triethylamine in ethyl acetate) to yield (**15**) (8.6 g, 88%) as a brown oil, which was used in the next step without further purification. It can be additionally purified by suspending the oil in *t*-butyl methyl ether and precipitating the product with hexanes to give enone **15** as a colorless solid. – m.p. 100–104°C. – ^{1}H NMR (500 MHz, d_6-DMSO): 6.86–6.84 (1 H, dd, *J* = 10, 2 Hz), 6.03 (1 H, s), 5.91–5.88 (1 H, d, *J* = 10 Hz), 4.32 (1 H, m), 4.24–4.19 (2 H, q, *J* =10 Hz), 2.93–2.89 (1 H, dd, *J* = 20, 5 Hz), 2.74–2.70 (1 H, d, *J* = 20 Hz), 2.60–2.55 (2 H, m), 1.35 (3 H, t, *J* = 5 Hz) ppm. – ^{13}C NMR (125 MHz, d_6-DMSO): 195.2, 162.5, 149.2, 147.7, 130.3, 77.1, 62.6, 62.5, 38.3, 32.4, 14.0 ppm. – IR: 3363, 2983, 2935, 1725, 1681, 1275 cm^{-1}. – MS (ESI): 240.0 [M+H$^+$]. – HRMS: calcd. for $C_{11}H_{14}NO_5^+$ 240.0866, found 240.0860 [M+H$^+$].

(4a*S,7*R**,8a*S**)-Ethyl 4a,7-dihydroxy-4a,7,8,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxylate (S1)**



To a solution of enone **15** (10.0 g, 41.8 mmol) in a 1:1 v/v mixture of THF and glacial acetic acid (210 mL) at 0 °C was added freshly pulverized cerium chloride heptahydrate (27.0 g 71.4 mmol). The mixture was purged with argon for 45 min. Freshly pulverized potassium borohydride (5.6 g, 104.5 mmol) was added in five portions over 50 min. The mixture was vigorously stirred for 1 h, and the reaction was monitored by ^{1}H NMR of an aliquot after solvent evaporation in high vacuum. To this mixture was added chloroform (500 mL), and the resulting suspension was filtered through a pad of Celite. The Celite pad was washed with chloroform (250 mL), and the combined filtrate was concentrated in vacuo to afford pale a yellow oil. The product was purified by dissolving in dichloromethane (15 mL) followed by precipitation with hexanes (200 mL). The crude material was dried in high vacuum to afford diol **S1** (9.0 g, 37.62 mmol, 90%) as a pale yellow glassy and hydroscopic solid. – m.p. 130–135 °C – ^{1}H NMR (500 MHz, d_6-DMSO): 5.22 (1 H, dd, *J* = 10, 2.5 Hz), 5.11 (1 H, d, *J* = 10 Hz), 3.77 (1 H, m), 3.75 (2 H, q, *J* = 5 Hz), 3.60 (1 H, d, *J* = 10 Hz), 2.12–2.04 (1 H, dd, *J* = 19.5, 10 Hz), 1.83–1.19 (1 H, d, *J* = 10 Hz), 1.71–1.69 (1 H, m), 0.99 (1 H, m), 0.78 (3 H, t, *J* = 5 Hz) ppm. – ^{13}C NMR (125 MHz, d_6-DMSO): 163.4, 146.9, 133.3, 132.3, 77.2, 65.5, 63.3, 61.6, 36.9, 31.2, 14.4 ppm. – IR: 3345, 2984, 2935, 1718, 1599 cm^{-1}. – MS (ESI): 242.1 [M+H^{+}]. – HRMS: calcd. for $C_{11}H_{16}NO_5^{+}$ 242.1023, found 242.1036 [M+H^{+}].

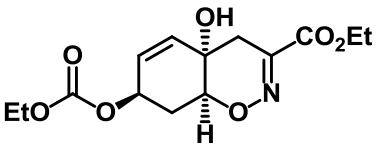
(4a*S,7*R**,8a*S**)-Ethyl 7-((methoxycarbonyl)oxy)-4a-hydroxy-4a,7,8,8a-tetrahydro-4H-benzo[*e*][1,2]oxazine-3-carboxylate (20a)**



To a solution of diol **S1** (0.5 g, 2.08 mmol) in a 2:1 v/v mixture of toluene and dichloromethane (21 mL) at 0 °C was added pyridine (0.30 mL, 3.3 mmol). After stirring for 5 min, methyl chloroformate (0.24 mL, 3.1 mmol) was added dropwise within 1 min. The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into a separatory funnel containing a 1M aqueous solution of potassium hydrogen sulfate (10 mL). The organic portion was

separated, and the aqueous phase was further extracted with toluene (2 × 20 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give carbonate **20a** as a viscous oil, which crystallized upon standing (0.6 g, 2.00 mmol, 96%) – ^{1}H NMR (500 MHz, $CDCl_3$): 5.88 (1 H, d, *J* = 6 Hz), 5.86 (1 H, d, *J* = 6 Hz), 5.23–5.22 (1 H, m), 4.25 (2 H, q, *J* = 5 Hz), 4.12 (1 H, dd, *J* = 5, 2 Hz), 3.69 (3 H, s), 2.69 (1 H, dd, *J* = 20, 5 Hz), 2.52 (1 H, dddd, *J* = 13, 11, 5, 3 Hz), 2.45–2.41 (1 H, d, *J* = 20 Hz), 1.96 (1 H, d, *J* = 5 Hz), 1.86–1.80 (1 H, ddd, *J* = 13, 11, 5 Hz), 1.28–1.30 (3 H, t, *J* = 5 Hz) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): 162.8, 155.0, 147.2, 134.6, 127.4, 76.1, 70.7, 63.4, 62.2, 54.9, 31.8, 31.3, 14.1 ppm. – IR: 3404, 2987, 1737, 1707, 1372, 1253 cm^{-1}. – MS (ESI): 299.1 [M^+]. – HRMS: calcd. for $C_{13}H_{18}NO_7^+$ 300.1078, found 300.1073 [$M+H^+$].

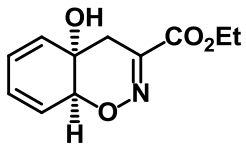
(4a*S,7*R**,8a*S**)-Ethyl 7-((ethoxycarbonyl)oxy)-4a-hydroxy-4a,7,8,8a-tetrahydro-4H-benzo[*e*][1,2]oxazine-3-carboxylate (20b)**



To a solution of diol **S1** (5.0 g, 20.8 mmol) in a 2:1 v/v mixture of toluene and dichloromethane (208 mL) at 0 °C was added pyridine (2.7 mL 33.3 mmol). After stirring for over 5 min, ethyl chloroformate (3.0 mL, 31.2 mmol) was added dropwise over 5 min. The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into a separatory funnel containing a 1M aqueous solution of potassium hydrogen sulfate (100 mL). The organic portion was separated, and the aqueous phase was further extracted with toluene (2 × 100 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give carbonate **20b** as a viscous oil (5.5 g, 17.68 mmol, 85%). – ^{1}H NMR (500 MHz, d_6-DMSO): 5.94–5.92 (1 H, dd, *J* = 10, 2 Hz), 5.77–5.75 (1 H, dd, *J* = 10, 3 Hz), 5.29–5.26 (1 H, m), 4.30–4.26 (2 H, q, *J* = 5 Hz), 4.18 (2 H, q, *J* = 5 Hz), 3.01 (1 H, s), 2.75–2.71 (1 H, dd, *J* = 20, 5 Hz), 2.58 (1 H, m), 2.49–2.45 (1 H, d, *J* = 20 Hz), 2.02 (1 H, d, *J* = 5 Hz), 1.86–1.80 (1 H, ddd, *J* = 13, 11, 5 Hz), 1.33–1.30 (3 H, t, *J* = 5 Hz), 1.28–1.25 (3 H, t, *J* = 5 Hz) ppm. – ^{13}C NMR (125 MHz, d_6-DMSO): 163.0, 154.6, 147.3, 134.9, 127.4, 76.2, 70.7, 64.4, 63.4, 62.3, 31.8, 31.5, 14.3, 14.2. ppm. – IR: 3404, 2987, 1737, 1707,

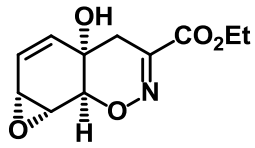
1372, 1253 cm^{-1}. – MS (ESI): 314.1 [M+H^+]. – HRMS: calcd. for $C_{14}H_{20}NO_7^+$ 314.1234, found 314.1227 [M+H^+].

(4a*S,8a*S**)-Ethyl 4a-hydroxy-4a,8a-dihydro-4H-benzo[*e*][1,2]oxazine-3-carboxylate (21)**



Carbonate (**20b**) (2.0 g, 6.4 mmol) was dissolved in toluene (32 mL), and the solution was degassed by bubbling argon for ~15 min. Freshly distilled *N,O*-bis(trimethylsilyl)acetamide (BTSA) (1.4 mL, 7.0 mmol) was added, and the mixture was continuously degassed for an additional 20 min. Tetrakis(triphenylphosphine)palladium (0.74 g 0.64 mmol) was added, and the mixture was stirred for 10 min. The mixture was directly loaded onto a silica gel column (12 g silica gel) and eluted with a 70:30 v/v mixture of hexanes and 5 vol % solution of triethylamine in ethyl acetate to give diene **21** as a pale yellow viscous oil (1.3 g, 5.76 mmol, 90%). – ^{1}H NMR (500 MHz, $CDCl_3$): 5.96–5.87 (4 H, m), 4.74 (1 H, m), 4.25 (2 H, q, *J* = 10 Hz), 2.75 (1 H, d, *J* = 15 Hz), 2.55 (1 H, br s), 2.45 (1 H, dd, *J* = 15, 5 Hz), 1.28 (3 H, t, *J* = 10 Hz) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): 163.0, 150.3, 134.4, 129.2, 126.7, 124.7, 80.1, 66.0 62.3, 29.0, 14.2 ppm. – IR: 3349, 3051, 2984, 1714, 1602, 1256 cm^{-1}. – MS (ESI): 246.0 [M+Na^+]. – HRMS: calcd. for $C_{11}H_{14}NO_4^+$ 224.0917, found 224.0917 [M+H^+].

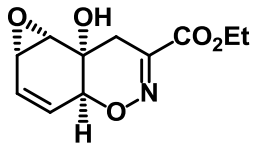
(4a*S,6a*R**,7a*R**,7b*S**)-Ethyl 4a-hydroxy-4a,6a,7a,7b-tetrahydro-4*H*-oxireno[2',3':3,4]benzo[1,2-e][1,2]oxazine-3-carboxylate (22b)**



To a solution of diene **21** (1.0 g, 4.5 mmol) in a mixture of trifluorotoluene (12 mL) and cyclohexane (12 mL), was added simultaneously *N*,*N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-ethylenediaminomanganese(III) chloride (**23**) (0.26 g, 0.5 mmol) and iodosobenzene (1.1 g, 4.9 mmol). The mixture was stirred at room temperature for 30 min and then directly loaded on a silica gel column (12 g silica gel). The product was eluted with a 3:1 v/v mixture of hexanes and ethyl acetate to give the distal epoxide **22b** (0.53 g, 2.19 mmol) and the proximal epoxide **22a** (0.18 g, 0.77 mmol). Total yield (70%).

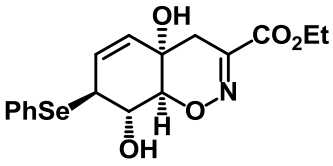
Distal epoxide (**22b**): ^{1}H NMR (500 MHz, $CDCl_3$): 6.20 (1 H, dd, *J* = 10, 5 Hz), 5.76 (1 H, d, *J* = 10 Hz), 4.25 (2 H, q, *J* = 5 Hz), 4.20 (1 H, s), 3.92 (1 H, dd, *J* = 5, 5 Hz), 3.50 (1 H, dd, 5, 5 Hz), 2.82 (1 H, br s), 2.77–2.81 (1 H, d, *J* = 20 Hz), 2.88–2.48 (1 H, d, *J* = 20 Hz) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): 162.7, 148.5, 136.4, 128.6, 73.5, 62.5, 62.2, 54.2, 47.3, 33.8, 14.2 ppm. – IR: 3354, 2932, 2836, 2552, 1711, 1669, 1606, 1290, 1104 cm^{-1}. – MS (ESI): 240.0 [$M+H^+$]. – HRMS: calcd. for $C_{11}H_{14}NO_5^+$ 240.0866, found 240.0864 [$M+H^+$].

(1a*S,3a*S**,7a*S**,7b*S**)-Ethyl 7a-hydroxy-3a,7,7a,7b-tetrahydro-1a*H*-oxireno[2',3':5,6]benzo[1,2-e][1,2]oxazine-6-carboxylate (22a)**



Proximal epoxide (**22a**): ^{1}H NMR (500 MHz, $CDCl_3$): 6.07–6.04 (1 H, ddd, *J* = 9.5, 4, 3 Hz), 5.95–5.93 (1 H, ddd, *J* = 10, 3, 2 Hz), 4.66 (1 H, m), 4.33 (2 H, qd, *J* = 7.5, 3 Hz), 3.68 (1 H, d, *J* = 4 Hz), 3.49–3.47 (1 H, td, *J* = 4, 2 Hz), 2.64–2.60 (1 H, dd, *J* = 19, 2 Hz), 2.26–2.22 (1 H, d, *J* = 19 Hz), 1.37–1.34 (3 H, t, *J* = 7.5 Hz) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): 162.8, 148.1, 135.8, 128.3, 126.2, 76.3, 66.6, 58.3, 49.2, 26.9, 14.1 ppm. – IR: 3356, 2932, 2838, 2552, 1710, 1669, 1606, 1290, 1104 cm^{-1}. – MS (ESI): 239.0 [M^+]. – HRMS: calcd. for $C_{11}H_{14}NO_5^+$ 240.0866, found 240.0863 [$M+H^+$].

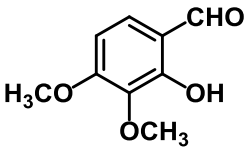
(4a*S,7*S**,8*S**,8a*S**)-Ethyl 4a,8-dihydroxy-7-(phenylselanyl)-4a,7,8,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxylate (24)**



The distal epoxide **22b** (0.5 g, 2.1 mmol) was dissolved in THF (11 mL) and cooled to 0 °C. Sodium bicarbonate (0.88 g, 10.5 mmol) was added. To the mixture, was added phenylselenol (0.49 g, 3.2 mmol) dropwise and the mixture was stirred for 1 h at 0 °C. The reaction mixture was partitioned between ethyl acetate (20 mL) and water (10 mL), and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (2 × 20 mL), and the combined organic fractions were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The resulting oil was washed with hexanes (3 × 15 mL) and dried in high vacuum to give the desired selenide **24** (0.79 g, 1.99 mmol, 95%). – ^{1}H NMR (500 MHz, ***d*$_6$-acetone**): 7.49 (2 H, d,

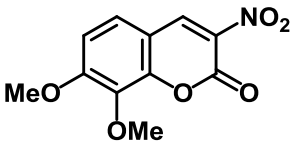
J = 10 Hz), 7.26 (1 H, t, *J* = 10 Hz), 7.20 (2 H, t, *J* = 10 Hz), 5.69–5.67 (1 H, dd, *J* = 10, 2.5 Hz), 5.58 (1 H, dd, *J* = 10, 2 Hz), 4.79 (1 H, s), 4.32 (1 H, s), 4.12–4.08 (2 H, q, *J* = 7 Hz), 3.91–3.89 (1 H, dd, *J* = 9.5, 2 Hz), 3.59 (1 H, s), 2.25 (1 H, dd, *J* = 19, 2 Hz), 1.18 (1 H, d, *J* = 19 Hz), 1.18 (3 H, t, *J* = 7 Hz). – ^{1}H NMR (500 MHz, **$CDCl_3$**): 7.61–7.57 (3 H, m), 7.27–7.26 (2 H, m), 5.82 (1 H, dd, *J* = 10, 5 Hz), 5.65 (1 H, d, *J* = 10 Hz), 4.26 (2 H, m), 4.3 (1 H, m), 3.72 (1 H, m), 2.44 (1 H, d, *J* =19.5 Hz), 2.01 (1 H, d, *J* = 19.5 Hz), 1.31 (3 H, m) ppm. – ^{13}C NMR (125 MHz, **$CDCl_3$**): 162.3, 147.6, 136.6, 131.8, 131.3, 129.0, 128.9, 127.6, 81.1, 69.9, 63.7, 62.1, 45.6, 31.6, 13.9 ppm. – IR: 3353, 2931, 2831, 1714, 1609, 1290 cm^{-1}. – MS (ESI): 398.1 [M+H^{+}]. – HRMS: calcd. 398.0501, found 398.1007 [M+H^{+}].

2-Hydroxy-3,4-dimethoxybenzaldehyde[6] (S2)



To a solution of 2,3,4-trimethoxybenzaldehyde (10.0 g, 51.0 mmol) in dry benzene (100 mL) was added aluminum chloride (8.1 g, 61.2 mmol) in two portions. The mixture was gently heated at reflux under an atmosphere of argon until viscous oil separated out (15 min). The reaction mixture was cooled to room temperature and quenched with a 1M solution of potassium hydrogen sulfate (50 mL), which was stirred until all solids dissolved. The organic phase was separated and the resulting aqueous phase was extracted with benzene (2 × 100 mL). The combined benzene portion was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford aldehyde **S2** as a colorless solid (9.2 g, 50.49 mmol, 99%). – m.p. 70–80 °C. – ^{1}H NMR (500 MHz, $CDCl_3$): 11.20 (1 H, br s), 9.76 (1 H, s), 7.29 (1 H, d, *J* = 10 Hz), 6.61 (1 H, d, *J* = 10 Hz), 3.95 (3 H, s), 3.91 (3 H, s) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): 195.1, 159.6, 155.9, 136.4, 130.4, 116.8, 104.2, 60.9, 56.5 ppm. – IR: 2991, 2939, 2839, 1632, 1661, 1588, 1442, 1256, 1088, 694 cm^{-1}.

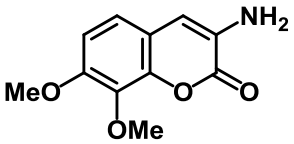
3-Nitro-7,8-methoxy-2*H*-chromen-2-one[6a] (S3)



To a solution of aldehyde **S2** (4.1 g, 22.5 mmol) in dry benzene (80 mL) at room temperature was added simultaneously piperidine (0.4 g, 4.5 mmol) and ethyl nitroacetate (3.0 g, 22.5 mmol). The flask was fitted to a Dean-Stark trap apparatus containing 3 Å molecular

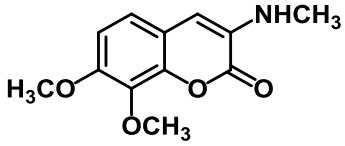
sieves in the burette. The reaction mixture was slowly warmed up to reflux within 1 h, and then refluxed overnight. It was then kept at 4 °C until a significant amount of a yellow solid precipitated (~2 h). The precipitated product was filtered, and the filtrate was partially concentrated to induce crystallization that produced an additional crop of the product. This process was repeated three times. The combined solids were air-dried to give nitrocoumarin **S3** (5.1 g, 20.25 mmol, 90%). – m.p. 200–204 °C. – ^{1}H NMR (500 MHz, ***d*$_6$-DMSO**): 9.19 (1 H, s), 7.78–7.76 (1 H, d, *J* = 10 Hz), 7.29–7.27 (1 H, d, *J* = 10 Hz), 3.97 (3 H, s), 3.83 (3 H, s) ppm. – ^{1}H NMR (500 MHz, **CDCl$_3$**): 8.73 (1 H, s), 7.44 (1 H, d, *J* = 10 Hz), 6.83 (1 H, d, *J* = 10 Hz), 4.03 (3 H, s), 4.01 (3 H, s) ppm. – ^{13}C NMR (125 MHz, ***d*$_6$-DMSO**): 159.0, 151.9, 148.3, 144.4, 134.9, 131.7, 127.7, 111.2, 110.8, 60.9, 56.9 ppm. – ^{13}C NMR (125 MHz, **CDCl$_3$**): 159.6, 151.7, 149.0, 143.1, 136.3, 131.9, 126.5, 110.8, 110.3, 61.6, 56.8 ppm. – IR: 3080, 2939, 2846, 1740, 1591, 1554 cm^{-1}.

3-Amino-7,8-methoxy-2*H*-chromen-2-one[6a] (25a)



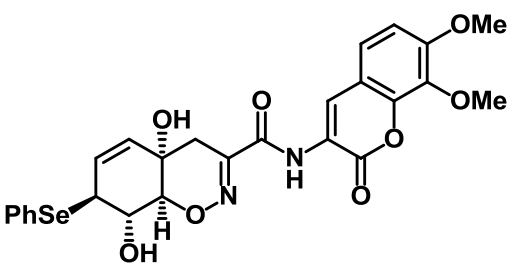
A mixture of nitrocoumarin **S3** (4.1 g, 16.3 mmol) and 10% palladium on activated charcoal (0.2 g) in ethanol (40 mL) was loaded in a Parr hydrogenator and degassed three time with hydrogen gas. The hydrogen pressure was adjusted to 25 psi, and the flask was shaken overnight at room temperature. The reaction mixture was filtered through a pad of Celite, and the pad was washed with ethanol. The filtrate was concentrated in vacuo to give aminocoumarin **25a** as a yellow solid (3.4 g, 15.48 mmol, 95%). – m.p. 185–187 °C. – ^{1}H NMR (500 MHz, ***d*$_6$-DMSO**): 7.10 (1 H, d, *J* = 10 Hz), 6.96 (1 H, d, *J* = 10 Hz), 6.68 (1 H, *d, J* = 10 Hz), 5.41 (2 H, s), 3.82 (3 H, s), 3.80 (3 H, s) ppm. – ^{1}H NMR (500 MHz, **CDCl$_3$**): 6.96 (1 H, d, *J* = 10 Hz), 6.83 (1 H, d, *J* = 10 Hz), 4.10 (2 H, s), 3.98 (3 H, s), 3.90 (3 H, s) ppm. – ^{13}C NMR (125 MHz, ***d*$_6$-DMSO**): 159.0, 150.9, 142.2, 135.8, 131.4, 119.7, 116.6, 110.1, 109.5, 61.1, 56.6 ppm. – ^{13}C NMR (125 MHz, **CDCl$_3$**): 159.2, 151.8, 143.1, 136.3, 129.9, 119.4, 115.8, 112.0, 109.3, 61.5, 56.5 ppm. – IR: 3471, 3367, 2924, 2824, 1696, 1621, 1502 cm^{-1}. – MS (ESI) 221.0 [M^{+}]. – HRMS: calcd. for $C_{11}H_{11}NO_4$ 221.0688, found 221.0681 [M^{+}].

7,8-Dimethoxy-3-(*N*-methylamino)-2*H*-chromen-2-one (25b)



To a solution of aminocoumarin **25a** (1.0 g, 4.52 mmol) in *N*,*N*-dimethylformamide (10 mL) was added freshly pulverized potassium carbonate (3.1 g, 22.6 mmol), and iodomethane (0.6 mL, 9 mmol), and the sealed vessel was allowed to stir at room temperature for 24 hours. The reaction mixture was partitioned between ethyl acetate (40 mL) and water (15 mL). The organic phase was separated and the aqueous phase was extracted in ethyl acetate (2 × 50 mL). The combined organic portions were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford an orange solid. The solid was dissolved in ethyl acetate (5 mL) and the desired material was precipitated with hexanes (10 mL). The supernatant was decanted and the material was washed with *tert*-butyl methyl ether (2 × 10 mL). The material was dried in vacuo to give **25b** as an orange powder (0.95 g, 4.0 mmol, 95%). Additional purification was performed by silica gel chromatography using 30 vol % solution of ethyl acetate in hexanes as an eluent. – m.p. 155–160 °C. – ^{1}H NMR (500 MHz, $CDCl_3$): 7.10 (1 H, d, *J* = 10 Hz), 6.96 (1 H, d, *J* = 10 Hz), 6.68 (1 H, d, *J* = 10 Hz), 5.41 (2 H, s), 3.82 (3 H, s), 3.80 (3 H, s) ppm. –^{13}C NMR (125 MHz, $CDCl_3$): 159.3, 151.0, 141.9, 136.4, 132.3, 119.2, 116.6, 109.4, 106.3, 61.4, 56.5, 29.8 ppm. – IR: 3472, 3367, 2924, 2824, 1696, 1621, 1502 cm^{-1}. – MS (ESI): 235.1 [M^+]. – HRMS: calcd. for $C_{12}H_{14}NO_4^+$ 236.0917, found: 236.0911 [$M+H^+$].

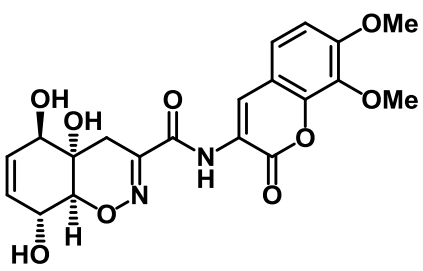
(4a*S,7*S**,8*S**,8a*S**)-*N*-(7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)-4a,8-dihydroxy-7-(phenylselanyl)-4a,7,8,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxamide (26)**



To a solution of selenide **24** (0.51 g, 1.3 mmol) in dichloromethane (7 mL) was added 3 Å molecular sieves (30 mg). The mixture was stirred until all the starting material dissolved. Sodium trimethylsilanolate (0.14 g, 1.3 mmol) was added, and the reaction mixture was stirred until the entire mixture gelated (10 min). Methanol (0.2 mL) was added to the gel, and the mixture was swirled until a solution was formed. The mixture was azeotroped with

benzene (4 × 2 mL), and methanesulfonic acid (94 μL, 0.9 mmol) and dichloromethane (2 mL) were added. The mixture was concentrated in vacuo and azeotroped with benzene (2 × 2 mL). To the resulting solid material was added (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) (0.53 g, 1.4 mmol), *sym*-collidine (0.17 g, 0.9 mmol) and aminocoumarin **25a** (0.31 g, 0.9 mmol). *N,N*-Dimethylformamide (10 mL) was added, and the mixture was stirred at room temperature overnight. Water (20 mL) was added, and the precipitated solid was isolated by filtration through a G4 fritted-glass funnel. The precipitate was washed with water (5 × 5 mL) and the solid was dissolved in ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give an oily material. The desired product was isolated by dissolving the oil in dichloromethane and precipitating the product with hexanes. The purification procedure was repeated to give selenide **26** (0.49 g, 1.22 mmol, 94%). – ^{1}H NMR (500 MHz, $CDCl_3$): 9.30 (1 H, s), 8.50 (1 H, s), 7.52 (2 H. d, *J* = 5 Hz), 7.31 (1 H, t, *J* = 5 Hz), 7.24 (2 H, t, *J* = 5 Hz), 7.14 (1 H, d, *J* = 9 Hz), 6.86 (1 H, d, *J* = 9 Hz), 5.85–5.83 (1 H, dd, *J* = 10, 3 Hz), 5.66–5.64 (1 H, dd, *J* = 10, 5 Hz), 5.23 (1 H, s), 4.08–4.07 (1 H, d, *J* = 4 Hz), 3.93 (3 H, s), 3.88 (3 H, s), 3.83 (1 H, d, *J* = 4 Hz), 3.75 (1 H, m), 3.66 (1 H, m), 2.54 (1 H, d, *J* = 20 Hz), 1.41–1.38 (1 H, d, *J* = 19.5 Hz) ppm. –^{13}C NMR (125 MHz, $CDCl_3$): 160.3, 158.9, 158.1, 154.3, 148.2, 144.2 136.7, 131.6, 129.4, 129.2, 126.7, 124.5, 122.5, 121.1, 114.1, 109.5, 81.3, 70.3, 64.2, 61.6, 56.5, 45.7, 30.3, 29.7 ppm. – IR: 3355, 2932, 2836, 1710, 1668, 1607, 1289 cm^{-1}. – MS (ESI): 572.0 [M^{+}]. – HRMS: calcd. for $C_{26}H_{25}N_2O_8Se^{+}$ 573.0771, found 573.0776 [M+H^{+}].

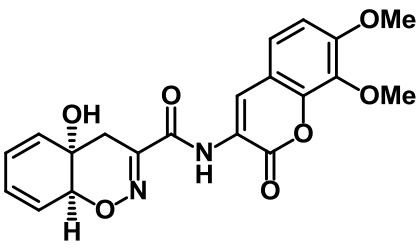
Trichodermamide A (1)



Selenide **26** (0.23 g, 0.4 mmol) was dissolved in THF (8 mL), and to this solution was added pyridine (0.16 mL 0.2 mmol). The mixture was stirred at 0 °C for 5 min. 30% Aqueous solution of hydrogen peroxide (1.6 mL, 20.1 mmol) was added, and the reaction mixture was stirred for 20 min. The reaction mixture was treated with a saturated aqueous solution of sodium thiosulfate (2 mL) and partitioned between a

saturated aqueous solution of sodium bicarbonate (3 mL) and ethyl acetate (50 mL). The aqueous portion was extracted with ethyl acetate (3 × 20 mL). The combined organic fractions were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a pale yellow oily material. Trichodermamide A (**1**) was isolated by dissolving the oil in ethyl acetate (5 mL) and precipitating the product with hexanes (20 mL). (0.16 g, 90% yield). –^{1}H NMR (500 MHz, **10 vol % *d*$_6$-DMSO in CDCl$_3$**): 9.48 (1 H, s), 8.62 (1 H, s), 7.24 (1 H, d, *J* = 8.5 Hz), 6.96 (1 H, d, *J* = 8.5 Hz), 5.62 (1 H, dd, *J* = 10.5, 4 Hz), 5.57 (1 H, dd, *J* = 10.5, 3.5 Hz), 5.18 (m, OH), 4.97(1 H, m), 4.51 (1 H, m) 4.48, (1 H, s), 4.22 (1 H, dd, J = 5.8, 2 Hz), 4.11 (1 H, br s), 3.98 (3 H, s), 3.95 (3 H, s), 2.72 (1 H, d, *J* = 19.5 Hz), 2.26 (1 H, d, *J* = 19.5 Hz) ppm. – ^{13}C NMR (125 MHz, **10 vol % *d*$_6$-DMSO in CDCl$_3$**) 160.9, 157.6, 153.6, 149.9, 143.4, 135.4, 129.2, 127.4, 123.4, 122.2, 120.7, 113.6, 109.2, 83.4, 73.5, 67.6, 66.1, 60.9, 55.9, 23.5. IR: 3356, 2939, 2842, 2842, 1714, 1677, 1607, 1524 cm^{-1}. – MS (ESI) 433.1 [M^{+}]. – HRMS: calcd. for $C_{20}H_{21}N_2O_9^+$ 433.1242, found 433.1244 [M+H^{+}].

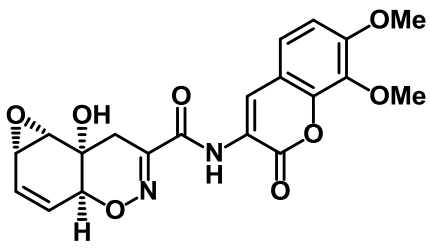
(4a*S,8a*S**)-*N*-(7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)-4a-hydroxy-4a,8a-dihydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxamide (27)**



To a solution of diene **21** (0.3 g, 1.3 mmol) in dichloromethane (7 mL) was added 3 Å molecular sieves (30 mg). The reaction mixture was stirred until the starting material dissolved. Sodium trimethylsilanolate (0.15 g, 1.3 mmol) was added, and the reaction mixture was stirred until the solution gelated (over 10 min) Methanol (0.2 mL) was added to the gel, and the mixture was swirled until a solution was formed. The mixture was azeotroped with benzene (4 × 2 mL), and methanesulfonic acid (0.13 g, 1.3 mmol) and dichloromethane (2 mL) were added. The mixture was concentrated in vacuo and azeotroped with benzene (2 × 2 mL). To the resulting solid material was added (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) (0.51 g, 1.3 mmol), *sym*-collidine (0.16 g, 1.3 mmol) and aminocoumarin **25a** (0.3 g, 1.3 mmol). *N,N*-Dimethylformamide (10 mL) was added, and the mixture was stirred at room temperature overnight. Water (20 mL) was added, and

the precipitated solid was isolated by filtration through a G4 fritted-glass funnel. The precipitate was washed with water (5 × 5 mL), and the solid was dissolved in ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give an oily material. The desired product was isolated by dissolving the oil in dichloromethane and precipitating amide **27** with hexanes as a colorless solid (0.36 g, 0.91 mmol, 70%). – m.p. 118–123°C. – ^{1}H NMR (500 MHz, $CDCl_3$): 9.31 (1 H, s), 8.52 (1 H, s), 7.11 (1 H, d, *J* = 10 Hz), 6.83 (1 H, d, *J* = 10 Hz), 6.00–5.99 (4 H, m), 4.73 (1 H, m), 3.91 (3 H, s), 3.87 (3 H, s), 2.64 (1 H, d, *J* = 10 Hz), 2.55–2.51 (1 H, dd, *J* = 10, 5 Hz) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): 161.1, 158.2, 154.3, 151.0, 144.4, 136.33, 134.4, 128.7, 127.1, 125.0, 124.6, 122.7, 121.3, 114.3, 109.6, 79.9, 65.9, 61.8, 56.6, 27.6 ppm. – IR: 3356, 2943, 2835, 1714, 1681, 1606, 1521 cm^{-1}. – MS (ESI) 398.0 [M^+]. – HRMS: calcd. for $C_{20}H_{19}N_2O_7^+$ 399.1187, found 399.1175 [$M+H^+$].

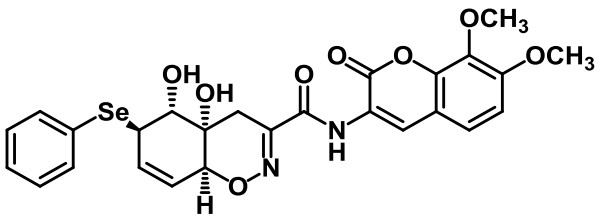
(1a*S,3a*S**,7a*S**,7b*S**)-*N*-(7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)-7a-hydroxy-3a,7,7a,7b-tetrahydro-1a*H*-oxireno[2',3':5,6]benzo[1,2-*e*][1,2]oxazine-6-carboxamide (28)**



To a solution of amide **27** (0.3 g, 0.7 mmol) in dichloromethane (4 mL) containing sodium bicarbonate (0.1 g, 1.1 mmol) was added a 32 wt % solution of peracetic acid in acetic acid (0.24 mL, 1.1 mmol) at 0 °C. The mixture was stirred for 1 h, and then concentrated in vacuo. The resulting oil was azeotroped with benzene (3 × 10 mL) then dissolved in dichloromethane (1 mL). Addition of hexanes (10 mL) led to precipitation of epoxide **28** (0.29 g, 0.69 mmol, 99%). – m.p. 118–123 °C. – ^{1}H NMR (500 MHz, **$CDCl_3$**): 9.41 (1 H, s), 8.59 (1 H, s), 7.19 (1 H, d, *J* = 5 Hz), 6.91 (1 H, d, *J* = 5 Hz), 6.10–6.07 (1 H, ddd, *J* = 10, 4.4, 3.5 Hz), 5.97–5.95 (1 H, ddd, *J* = 10, 4.4, 2 Hz), 4.7 (1 H, m), 3.99 (3 H, s), 3.95 (3 H, s), 3.73 (1 H, d, *J* = 4.4 Hz), 3.52–3.51 (1 H, ddd, *J* = 5.5, 4, 2 Hz), 3.49 (1 H, s), 2.76–2.75 (1 H, dd, *J* = 19.5, 2 Hz), 2.28–2.24 (1 H, d, *J* =19.5 Hz) ppm. – ^{1}H NMR (500 MHz, ***d_6*-acetone**): 9.34 (1 H, s), 8.57 (1 H, s), 7.40 (1 H, d, *J* = 9 Hz), 7.14 (1 H, d, *J* = 9 Hz), 6.15–6.13 (1 H, ddd, *J* = 10, 4.4, 3.5 Hz), 5.92–5.90 (1 h, ddd, *J* = 10, 4.4, 2 Hz), 4.66 (1 H, m), 3.96 (3 H, s), 3.90 (3 H, s), 3.72 (1 H, d, *J* = 4.4 Hz),

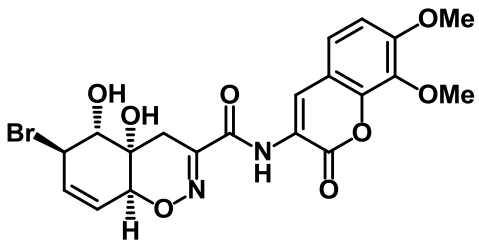
3.61 (1 H, m), 3.52 (1 H, s), 2.72–2.68 (1 H, dd, *J* = 19.5, 2 Hz), 2.24–2.20 (1 H, d, *J* =19.5 Hz) ppm. – ^{13}C NMR (125 MHz, **$CDCl_3$**): 162.7, 159.8, 156.3, 150.7, 146.0, 138.0, 137.2, 128.8, 125.2, 124.6, 123.2, 116.0, 111.8, 78.4, 67.3, 62.4, 60.5, 57.8, 50.7, 26.8 ppm. – IR: 3759, 1712, 1683 1625, 1075 cm^{-1}. – MS (ESI) 414.1 [M^+]. – HRMS: calcd. for $C_{20}H_{19}N_2O_8^+$ 415.1136, found 415.1193 [$M+H^+$].

(4a*S,5*R**,6*R**,8a*S**)-*N*-(7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)-4a,5-dihydroxy-6-(phenylselanyl)-4a,5,6,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxamide (29)**



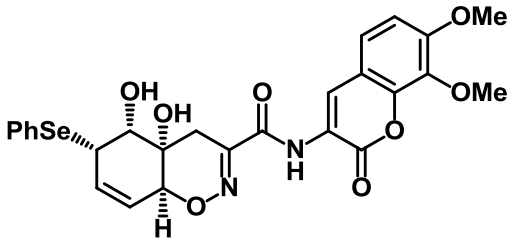
Epoxide **28** (100 mg, 0.24. mmol) was dissolved in degassed THF (2 mL), and the solution was additionally degassed by bubbling argon for ~5 min. Freshly prepared phenylselenol (80 mg, 0.48 mmol) and tetrakis(triphenylphosphine)palladium (27 mg, 0.024 mmol) were added simultaneously. The mixture was stirred for 15 min and partitioned between ethyl acetate (10 mL) and water (3 mL). The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford the crude material that was washed with hexanes (2 × 15 mL). The material was taken up in dichloromethane (5 mL) and loaded directly onto a silica gel column (4 g silica gel). The impurities were eluted with a 70:30 v/v mixture of hexanes-ethyl acetate and the desired material was eluted with a 10 vol % solution of acetone in ethyl acetate to give *trans*-selenide **29** (1.3 g, 5.76 mmol, 95%). – ^{1}H NMR (500 MHz, **25% d_6-DMSO in $CDCl_3$**): 9.29 (1 H, s), 8.55 (1 H, s), 7.54 (2 H, d, *J* = 5 Hz), 7.23–7.21 (3 H, m), 7.16 (1 H, d, *J* = 5 Hz), 6.89 (1 H, d, *J* = 6 Hz), 6.04 (1 H, dd, *J* = 9.5, 2.5 Hz), 5.67–5.66 (1 H, dddd, *J* = 9.5, 6, 4, 2 Hz), 4.83 (1 H, s), 4.52 (1 H, s), 4.12 (1 H, d, *J* = 4 Hz), 3.95 (1 H, m), 3.90 (3 H, s), 3.89 (3 H, s), 3.64 (1 H, m), 3.30 (1 H, d, *J* = 19.5 Hz), 2.40 (1 H, d, *J* = 19.5 Hz) ppm. – ^{13}C NMR (125 MHz, **25 vol % d_6-DMSO in $CDCl_3$**): 160.8 157.9, 154.0, 150.8, 143.9, 135.9, 135.2, 134.6, 131.3, 128.9, 127.8 124.1, 122.5, 121.8, 121.0, 113.0, 109.4, 75.7, 71.5, 66.8, 61.3, 56.3, 46.2, 29.2 ppm. – IR: 3357, 2933, 2839, 1711, 1669, 1606, 1289 cm^{-1}. – MS (ESI): 572.0 [M^+]. – HRMS: calcd. for $C_{26}H_{25}N_2O_8Se^+$ 573.0771, found 573.0765 [$M+H^+$].

(4a*S,5*R**,6*R**,8a*S**)-6-bromo-*N*-(7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)-4a,5-dihydroxy-4a,5,6,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxamide (S4)**



To a solution of lithium bromide (0.13 g, 0.31 mmol) in THF (3 mL), was added copper dibromide (0.16 g, 0.73 mmol). This mixture was stirred for 10 min, and a solution of epoxide **28** (0.2 g, 0.48 mmol) in THF (4 mL) was added dropwise within 5 min. The reaction mixture was stirred for 1 h. The reaction mixture was poured into a separatory funnel containing saturated aqueous ethylenediaminetetraacetic acid disodium salt (EDTA) solution (15 mL) and ethyl acetate (50 mL). The organic portion was separated and the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic fractions were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude material. Bromohydrin **S4** was purified by washing with hexanes. (0.13 g, 0.27 mmol, 86%). – m.p. 120–123 °C. – ^{1}H NMR (500 MHz, $CDCl_3$): 9.27 (1 H, s), 8.53 (1 H, s), 7.36 (1 H, d, *J* = 9 Hz), 7.07 (1 H, d, *J* = 9 Hz), 6.15–6.12 (1 H, dd, *J* = 10, 2.5 Hz), 5.86–5.83 (1 H, ddd, *J* = 10, 6.5, 2.5 Hz), 4.8 (1 H, br s), 4.77 (1 H, m), 4.2 (1 H, d, *J* = 4.5 Hz), 3.90 (3 H, s), 3.85 (3 H, s), 3.81 (1 H, d, *J* = 5.5 Hz), 3.42 (1 H, d, *J* = 19.5 Hz), 2.45 (1 H, d, *J* = 19.5 Hz) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): 160.5, 157.9, 157.8, 154.4, 151.1, 144.1, 136.1, 135.1, 123.3, 122.9, 114.1, 109.9, 75.6, 73.7, 67.4, 60.5, 55.9, 53.1, 48.9, 22.4 ppm. – IR: 3367, 2928, 2842, 1714, 1677, 1606, 1524 cm^{-1}. – MS (ESI): 495.0 [$M+H^+$]. – HRMS: calcd. for $C_{20}H_{20}BrN_2O_8^+$ 495.0398, found 495.0384 [$M+H^+$].

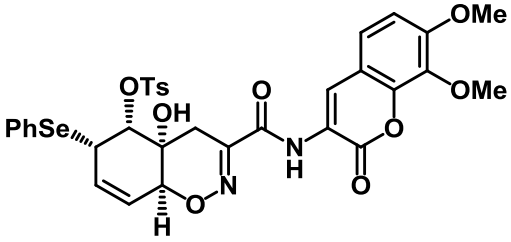
(4a*S,5*R**,6*S**,8a*S**)-*N*-(7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)-4a,5-dihydroxy-6-(phenylselanyl)-4a,5,6,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxamide (S5)**



Phenylselenol (0.14 g, 0. 28 mmol) and 1,8-bis(dimethylamino)naphthalene (**30**) (0.1 g, 0.5 mmol) were mixed under argon, and to this mixture was added THF (2 mL) at 0 °C. A solution of bromohydrin **S4** (0.22 g, 0.44 mmol) in THF (4 mL) was added dropwise over a period of 5 min. The reaction mixture was warmed up

to 4 °C over 2 h. The reaction mixture was partitioned between ethyl acetate (50 mL) and saturated aqueous solution of sodium bicarbonate (10 mL), and the organic portion was separated. The aqueous phase was further extracted with ethyl acetate (2 × 20 mL), and combined organic fractions were dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and washed with hexanes (3 × 5 mL) to give selenide **S5** (0.129 g, 0.23 mmol, 80%). – ^{1}H NMR (500 MHz, $CDCl_3$): 9.22 (1 H, s), 8.45 (1 H, s), 7.53 (2 H, t, *J* = 5 Hz), 7.28 (1 H, d, *J* = 9 Hz), 7.20 (3 H, m), 7.00 (1 H, d, *J* = 9 Hz), 5.92–5.90 (1 H, dd, *J* = 10, 3 Hz), 5.51–5.48 (1 H, dd, *J* = 10, 5 Hz), 4.57 (1 H, m), 4.17 (1 H, m), 4.04 (1 H, m), 3.83 (3 H, s), 3.78 (3 H, s), 2.86 (1 H, d, *J* = 20 Hz), 2.37–2.33 (1 H, d, *J* = 19.5 Hz) ppm. – ^{13}C NMR (125 MHz, 20 vol % CD_3OD in $CDCl_3$): 161.1, 158.2, 154.2, 149.6, 144.0, 135.8, 134.2, 132.4, 131.3, 129.1, 129.9, 127.8, 127.6, 124.6, 112.7, 113.9, 109.6, 75.8, 70.6, 67.2, 61.3, 56.2, 46.1, 26.2 ppm. – IR: 3356, 2932, 2838, 1710, 1669, 1606, 1289 cm^{-1}. – MS (ESI): 572.0 [M^{+}]. – HRMS: calcd. for $C_{26}H_{25}N_2O_8Se^{+}$ 573.0771, found 573.0771 [M+H^{+}].

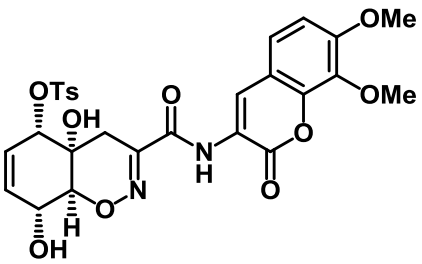
(4a*R,5*R**,6*S**,8a*S**)-3-((7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)carbamoyl)-4a-hydroxy-6-(phenylselanyl)-4a,5,6,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazin-5-yl 4-methylbenzenesulfonate (31)**



A solution of selenide **S5** (0.18 g, 0.31 mmol) in pyridine (4 mL) was added to solid *p*-toluenesulfonic anhydride (0.4 g, 1.3 mmol) at 0 °C. The reaction mixture was allowed to warm up to 4 °C over 2 h. The reaction mixture was diluted with cold (4°C) saturated aqueous solution of sodium bicarbonate (5 mL) and extracted with ethyl acetate (3 × 20 mL). The combined ethyl acetate extracts were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The resulting material was azeotroped with hexane (3 × 5 mL) until complete removal of the pyridine, then dissolved in ethyl acetate and precipitated with hexanes to afford tosylate **31** (0.23 g, 0.31 mmol, 99%). – m.p. 105–107 °C. – ^{1}H NMR (500 MHz, $CDCl_3$): 9.22 (1 H, s), 8.53 (1 H, s), 7.69 (2 H, d, *J* = 8 Hz), 7.52 (2 H, d, *J* = 8 Hz), 7.28 (3 H, m), 7.17 (4 H, m), 6.85–6.83 (1 H, dd, *J* = 8.5 Hz), 6.05–6.02 (1 H, dd, *J* = 9.5, 4.5 Hz), 5.67 (1 H, dd, *J* =

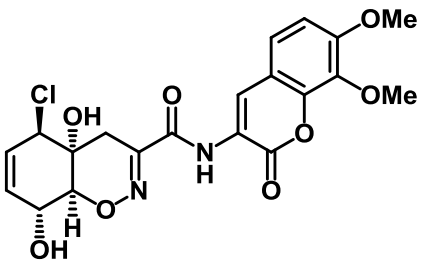
9.5, 4.0 Hz), 4.80–4.79 (1 H, d, *J* = 5 Hz), 4.18 (1 H, d, *J* = 4 Hz), 3.98 (1 H, s), 3.92 (3 H, s), 3.87 (3 H, s), 2.92 (1 H, d, *J* = 19.5 Hz), 2.40 (1 H, d, *J* = 19.5 Hz), 2.24 (3 H, s) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): 160.1, 157.9, 154.3, 149.9, 145.5, 144.2, 136.2, 135.6, 135.0, 134.1, 132.3, 130.0, 129.7, 129.4, 128.4, 128.1, 124.5, 122.6, 121.0, 114.0, 109.5, 77.7, 75.6, 67.1, 61.6, 56.4, 43.8, 28.6, 21.7 ppm. – IR: 3356, 2939, 1714, 1684, 1521 cm^{-1}. – MS (ESI): 726.1 [M$^+$]. – HRMS: calcd. for $C_{33}H_{30}N_2O_{10}SSe$ 726.0786, found 726.0786 [M$^+$].

(4a*R,5*S**,8*R**,8a*S**)-3-((7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)carbamoyl)-4a,8-dihydroxy-4a,5,8,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazin-5-yl 4-methylbenzenesulfonate (S6)**



To a solution of tosylate **31** (0.1 g, 0.14 mmol) in THF (3 mL) was added pyridine (60 μL, 0.6 mmol) at 0 °C. The mixture was stirred for 2 min, and a 30% aqueous solution of hydrogen peroxide (140 μL) was added. The reaction was stirred for 30 min, and then partitioned between ethyl acetate (20 mL) and a saturated aqueous solution of sodium bicarbonate (5 mL). The mixture was extracted with ethyl acetate (3 × 10 mL), and the combined ethyl acetate extracts were washed with a saturated aqueous solution of sodium bicarbonate (2 × 5 mL), dried over anhydrous sodium sulfate, filtered and then concentrated under reduced pressure. The crude material was dissolved in ethyl acetate, and the product was precipitated with hexanes to give diol **S6** (0.065 g, 0.11 mmol, 79%). – ^{1}H NMR (500 MHz, $CDCl_3$): 9.23 (1 H, s), 8.52 (1 H, s), 7.73–7.72 (2 H, d, *J* = 5 Hz), 7.28–7.27 (2 H, d, *J* = 5 Hz), 7.14–7.12 (1 H, d, *J* = 8.5 Hz), 6.8–6.85 (1 H, d, *J* = 9 Hz), 5.90–5.87 (1 H, dd, *J* = 10.5, 2.5 Hz), 5.46–5.43 (1 H, dd, *J* = 10.5, 2 Hz), 4.68 (1 H, m), 4.18 (1 H, m), 4.04 (1 H, m), 3.93 (3 H, s), 3.88 (3 H, s), 2.67–2.63 (1 H, d, *J* = 19.5 Hz), 2.45–2.41 (1 H, d, *J* = 19.5 Hz), 2.32 (3 H, s) ppm. – ^{13}C NMR (125 MHz, d_6-DMSO): 159.9, 158.0, 154.3, 149.9, 145.7, 144.2, 136.2, 132.6, 131.3, 130.2, 128.0, 124.6, 123.7, 122.6, 121.0, 114.0, 109.5, 79.1, 65.4, 65.0, 61.6, 56.4, 29.9 29.7, 21.8 ppm. – IR: 3367, 2928, 2850, 1714, 1677, 1602, 1524, 1461 cm^{-1}. – MS (ESI): 586.0 [M$^+$]. – HRMS: calcd. for $C_{27}H_{27}N_2O_{11}S^+$ 587.1330, found 587.1340 [M+H$^+$].

Trichodermamide B (2)

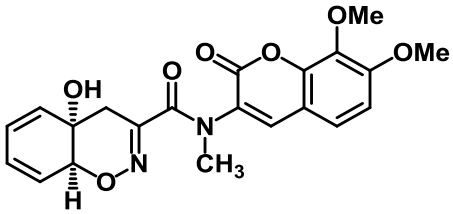


Tosylate **S6** (30 mg, 0.05 mmol) was dissolved in dimethyl sulfoxide (2 mL). To this solution, was added a solution of calcium chloride (0.7 g, 7 mmol) in dimethyl sulfoxide (3 mL). The reaction mixture was stirred overnight at room temperature, and poured into an Erlenmeyer flask containing water (30 mL). This mixture was stirred until precipitation of the crude material occurred. The precipitate was filtered through a fritted-glass funnel and washed with water (3 × 10 mL). The solid was dissolved in ethyl acetate (20 mL). The solution was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give trichodermamide B (~90% pure). The minor byproduct was inseparable by column chromatography (on silica gel, alumina, as well as reversed-phase chromatography).

Purification by in-situ derivatization: The crude mixture was dissolved in dichloromethane (5 mL) and 3 Å molecular sieves were added. The mixture was cooled to 0 °C, then triethylamine (0.14 mL, 1.1 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.13 mL, 0.6 mmol) were added. The mixture was stirred for 30 min, and then treated with a saturated aqueous solution of sodium bicarbonate (10 mL). The mixture was extracted with ethyl acetate (30 mL), and the organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The resulting material was dissolved in benzene (0.5 mL) and passed through a silica gel column (1:10 mixture of ethyl acetate and hexanes). The material was then dissolved in acetonitrile (0.3 mL) and 48% HF solution (0.2 mL) was added. The mixture was allowed to stir overnight at room temperature and then poured into a vial containing solid sodium bicarbonate. Ethyl acetate was added to this mixture. The ethyl acetate phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford a waxy material. The material was washed with freshly distilled pentane (2 × 5 mL) to give trichodermamide B (17 mg, 0.035 mmol, 70%). – ^{1}H NMR (500 MHz, **10 vol % d_6-DMSO in $CDCl_3$**): 9.49 (1 H, s), 8.65 (1 H, s), 7.27 (1 H, d, *J* = 10 Hz), 6.98 (1 H, d, *J* = 10 Hz), 5.70–5.66 (3 H, m), 5.36 (1 H, br s), 5.15 (1 H, br s), 4.92 (1 H, s), 4.33 (1 H, dd, *J* = 10, 5 Hz), 4.18 (1 H, m), 4.01 (3 H, s), 3.99 (3 H, s), 2.89 (1 H, dd, *J* =

19, 2 Hz), 2.30 (1 H, d, *J* = 19 Hz) ppm. – ^{1}H NMR (500 MHz, **25 vol % CD_3OD in $CDCl_3$**): 8.48, (1 H, s), 7.11 (1 H, d, *J* = 10 Hz), 6.82 (1 H, d, *J* =10 Hz), 5.54 (1 H, ddd, *J* = 10, 5, 5 Hz), 5.47 (1 H, ddd, *J* = 10, 2, 2 Hz), 4.69 (1 H, ddd, *J* = 5, 5, 5 Hz), 4.09 (1 H, dd, *J* =10, 5 Hz), 4.03 (1 H, dddd, *J* = 10, 5, 5, 5 Hz), 3.85 (3 H, s), 3.82 (3 H, s), 2.72 (1 H, dd, *J* = 20, 5 Hz), 2.18 (1 H, d, *J* = 20 Hz) ppm. – ^{13}C NMR (125 MHz, **10 vol % *d_6*-DMSO in $CDCl_3$**): 160.7, 157.8, 153.8, 149.6, 143.7, 135.7, 129.2, 127.3, 123.9, 122.3, 120.8, 113.7, 109.3, 84.0, 67.3, 65.6, 64.8, 61.1, 56.1, 24.9 ppm. – ^{13}C NMR (125 MHz, **25 vol % CD_3OD in $CDCl_3$**): 160.9, 158.1, 154.0, 149.4, 143.7, 135.6, 128.4, 127.6, 124.6, 122.5, 120.6, 113.7, 109.4, 83.6, 67.3, 65.9, 64.3, 60.0, 55.9, 24.7 ppm. – IR: 3188, 2924, 2850, 1718, 1677, 1606, 1524, 1461 cm^{-1}. – MS (ESI): 450.1 [$M+H^+$]. – HRMS: calcd. for $C_{20}H_{20}ClN_2O_8^+$ 451.0903, found 451.0888 [$M+H^+$].

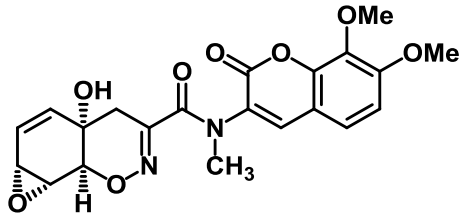
(4a*S,8a*S**)-*N*-(7,8-Dimethyoxy-2-oxo-2*H*-chromen-3-yl)-4a-hydroxy-*N*-methyl-4a,8a-dihydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxamide (S7)**



To a solution of diene **27** (400 mg, 1.00 mmol) in acetone (10 mL) was added freshly pulverized potassium carbonate (0.69 g, 5 mmol) and 18-crown-6 (264 mg, 1.00 mmol). The reaction mixture was stirred for 5 min, then iodomethane (4 mL, 65 mmol) was added. The reaction mixture was stirred for 48 hours at 40 °C. The mixture was partitioned between ethyl acetate (100 mL) and water (20 mL). The organic phase was separated and the aqueous phase was extracted in ethyl acetate (2 × 50 mL). The combined organic fractions were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford an orange solid. The solid was dissolved in ethyl acetate (5 mL) and the desired material was precipitated with hexanes (10 mL). The supernatant was decanted and the material was washed with hexanes (2 × 10 mL). The material was dried in vacuo to give **S7** (390 mg, 0.96 mmol, 95%). – ^{1}H NMR (500 MHz, $CDCl_3$): 7.64 (1 H, s), 7.19 (1 H, d, *J* = 10 Hz), 6.92 (1 H, d, *J* = 10 Hz), 5.95–5.92 (3 H, m), 5.76 (1 H, m), 4.57 (1 H, br s), 3.97 (3 H, s), 3.96 (3 H, s), 3.87–3.83 (1 H, m), 3.35 (3 H, s), 2.81 (1 H, br m), 2.54 (1 H, br m) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): 165.0, 155.6, 154.8, 146.3, 136.2, 134.1, 128.6, 128.5, 126.5, 126.5, 124.1, 123.0, 113.6, 109.4, 78.9, 66.4, 61.5, 56.5, 37.4,

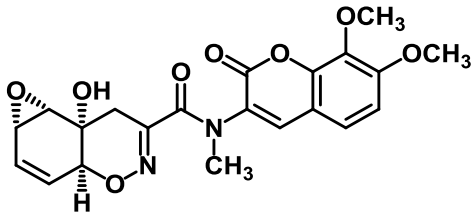
29.7, 29.3 ppm. – IR: 3363, 2943, 2850, 1718, 1651, 1606, 1506, 1290 cm^{-1}. – MS (ESI): 413.1 [M+H^+]. – HRMS: calcd. for $C_{21}H_{21}N_2O_7^+$ 413.1343, found 413.1310 [M+H^+].

(4a*S,6a*R**,7a*R**,7b*S**)-*N*-(7,8-dimethoxy-2-oxo-2*H*-chromen-3-yl)-4a-hydroxy-*N*-methyl-4a,6a,7a,7b-tetrahydro-4*H*-oxireno[2',3':3,4]benzo[1,2-*e*][1,2]oxazine-3-carboxamide (32)**



To a stirring solution of diene **S7** (0.1 g, 0.24 mmol) in dichloromethane (6 mL) at room temperature was added simultaneously catalyst **23** (14 mg, 0.024 mmol) and iodosobenzene (54 mg, 0.266 mmol). Stirring was continued for 30 min and the mixture was loaded on a silica gel column (4 g silica gel). The desired material was eluted with 1:1 v/v mixture of hexanes and ethyl acetate to give the distal epoxide **32** (40 mg, 0.093 mmol) and the proximal epoxide **S8** (30 mg, 0.07 mmol) as orange oils. Total yield 68%. Distal epoxide **32**: ^{1}H NMR (500 MHz, $CDCl_3$): 7.47 (1 H, s), 7.11 (1 H, d, *J* = 10 Hz), 6.85 (1 H, d, *J* = 10 Hz), 6.12 (1 H, dd, *J* = 10, 5 Hz), 5.88 (1 H, br d, *J* = 10 Hz), 4.09 (1 H, s), 3.92 (3 H, s), 3.89 (3 H, s), 3.74 (1 H, dd, *J* = 5, 4 Hz) 3.38 (1 H, m), 3.28 (3 H, s), 2.63 (1 H, br d), 1.50 (1 H, br d) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): 164.6, 159.0, 155.5, 152.0, 146.3, 136.9, 136.3, 132.1, 128.6, 127.4, 123.0, 113.5, 109.3, 72.7, 62.2, 61.5, 56.5, 54.0, 47.2, 37.6, 33.4 ppm. – IR: 3345, 2932, 2850, 1722, 1658, 1606, 1509, 1286 cm^{-1}. – MS ESI: 428.1 [M^+]. – HRMS: calcd. for $C_{21}H_{21}N_2O_8^+$ 429.1292, found 429.1292 [M+H^+].

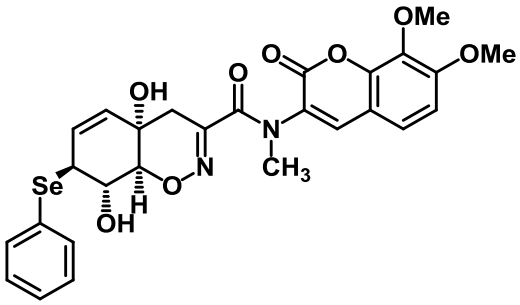
(1a*S,3a*S**,7a*S**,7b*S**)-*N*-(7,8-dimethoxy-2-oxo-2*H*-chromen-3-yl)-7a-hydroxy-*N*-methyl-3a,7,7a,7b-tetrahydro-1a*H*-oxireno[2',3':5,6]benzo[1,2-*e*][1,2]oxazine-6-carboxamide (S8)**



^{1}H NMR (500 MHz, $CDCl_3$): 7.58 (1 H, s), 7.19 (1 H, d, *J* = 10 Hz), 6.93 (1 H, d, *J* = 10 Hz), 6.02 (1 H, m), 6.00 (1 H, m), 5.66 (1 H, br m), 4.47 (1 H, br s), 3.98 (3 H, s), 3.96 (3 H, s), 3.64 (1 H, d, *J* = 5 Hz), 3.43

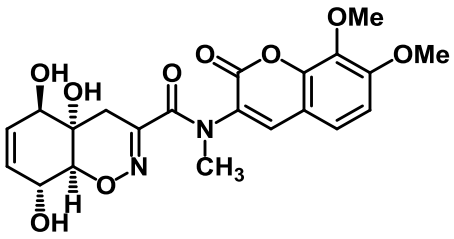
(1 H, m), 3.34 (3 H, s), 2.66 (1 H, br d), 1.62 (1 H, br m) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): 165.1, 161.9, 155.7, 146.3, 136.9, 136.2, 129.5, 128.4, 126.2, 123.0, 113.5, 109.5, 75.7, 72.7, 66.4, 61.5, 58.4, 56.5, 49.0, 37.3, 27.1 ppm. – IR: 3345, 2934, 2851, 1726, 1659, 1607, 1507, 1286 cm^{-1}. – MS ESI: 428.1 [M^+]. – HRMS: calcd. for $C_{21}H_{21}N_2O_8^+$ 429.1292, found 429.1292 [$M+H^+$].

(4a*S*,7*S***,8*S***,8a*S***)-*N*-(7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)-4a,8-dihydroxy-*N*-methyl-7-(phenylselanyl)-4a,7,8,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxamide (S9)**



The distal epoxide **32** (25 mg, 0.058 mmol) was dissolved in THF (2 mL) and cooled to 0 °C. Potassium carbonate (16 mg, 0.115 mmol) and phenylselenol (61 mg, 0.39 mmol) were simultaneously added and the mixture was stirred for 15 min at 0 °C, and then warmed up to 4 °C. The reaction mixture was partitioned between ethyl acetate (40 mL) and water (10 mL), and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (2 × 20 mL), and the combined organic portions were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The resulting oil was washed with hexanes (3 × 15 mL) and dried in high vacuum to give the desired selenide **S9** (32 mg, 0.054 mmol, 93%). – ^{1}H NMR (500 MHz, $CDCl_3$): 7.60–7.55 (3 H, m), 7.36–7.16 (4 H, m), 6.89 (1 H, d, *J* = 10 Hz), 5.74 (1 H, m), 5.63 (1 H, m), 3.96 (3 H, s), 3.92 (3 H, s), 3.81 (1 H, m), 3.64 (1 H, m), 3.32 (3 H, s), 2.48 (1 H, m), 1.85 (1 H, d, *J* = 19.5 Hz) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): 164.7, 159.1, 155.6, 150.7, 146.3, 136.7, 136.1, 132.1, 131.5, 130.9, 129.3, 129.1, 128.7, 127.7, 123.1, 113.5, 109.5, 80.6, 70.9, 63.8, 61.6, 56.5, 45.7, 37.4, 31.9 ppm. – IR: 3308, 2932, 2835, 1710, 1647, 1606, 1509, 1286 cm^{-1}. – MS (ESI): 587.1 [$M+H^+$]. – HRMS: calcd. for $C_{27}H_{27}N_2O_8Se^+$ 587.0927, found 587.0944 [$M+H^+$].

Trichodermamide C (3)



Selenide **S9** (40 mg, 0.07 mmol) was dissolved in THF (3 mL) and to this solution was added pyridine (22 μL, 0.28 mmol). The mixture was stirred at 0 °C for 5 min. A 30% aqueous solution of hydrogen peroxide (100 μL, 1.28 mmol) was added, and the reaction mixture was stirred for 20 min. The reaction mixture was treated with a saturated aqueous solution of sodium thiosulfate (2 mL) and partitioned between a saturated aqueous solution of sodium bicarbonate (3 mL) and ethyl acetate (50 mL). The organic portion was extracted (3 × 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a pale yellow oily material. The material was purified by silica gel chromatography (eluted with 10 vol % acetone solution in ethyl acetate) to afford trichodermamide C (**3**) (30 mg, 97%). – ^{1}H NMR (500 MHz, d_6-DMSO): 8.02 (1 H, s), 7.39 (1 H, d, J = 10 Hz), 7.15 (1 H, d, J = 10 Hz), 5.41 (1 H, d, J = 10 Hz), 5.34 (1 H, br d, J = 10 Hz), 5.14 (1 H, br d), 5.13 (1 H, br s), 4.93 (1 H, br s), 4.12 (1 H, br m), 3.91 (3 H, s), 3.83 (3 H, s) 3.75 (1 H, d, J = 7.2 Hz), 3.67 (1 H, br s) 3.21 (3 H, s), 2.37 (1 H, br d), 2.01 (1 H, br d, J = 19.5 Hz) ppm. – ^{13}C NMR (125 MHz, d_6-DMSO): 165.4, 158.4, 155.0, 151.8, 145.9, 137.1, 135.2, 129.9, 127.8, 127.8, 123.5, 113.4, 109.9, 82.8, 73.3, 67.2, 66.6, 60.8, 56.4, 36.3, 24.3 ppm. – IR: 3308, 2932, 2835, 1710, 1647, 1606, 1509, 1286 cm^{-1}. – MS (ESI): 447.1 [M^{+}]. – HRMS: calcd. for $C_{21}H_{23}N_2O_9^+$ 447.1398, found 447.1382.

X-Ray Crystallographic Data

(4a*S,8a*S**)-Ethyl 4a-hydroxy-7-oxo-4a,7,8,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxylate (15)**

CCDC Nr.: 1064083

Bond precision:	C–C = 0.0020 Å	Wavelength = 0.71073	
Cell:	a = 11.542(6)	b = 9.880(3)	c = 9.996(3)
α = 90	β = 104.510(5)	γ = 90	
Temperature:	98 K		
	Calculated	Reported	

Volume	1103.5(7)	1103.5(7)
Space group	P 21/c	P21/c
Hall group	-P 2ybc	-P 2ybc
Moiety formula	$C_{11}H_{13}NO_5$	$C_{11}H_{13}NO_5$
Sum formula	$C_{11}H_{13}NO_5$	$C_{11}H_{13}NO_5$
M_r	239.22	239.22
D_x, $g{\cdot}cm^{-3}$	1.440	1.440
Z	4	4
Mu (mm^{-1})	0.115	0.115
F000	504.0	504.0
F000′	504.31	
h, k, l_{max}	14, 12, 12	14, 12, 12
N_{ref}	2535	2520
T_{min}, T_{max}	0.973, 0.983	0.890, 1.000
T_{min}′	0.964	

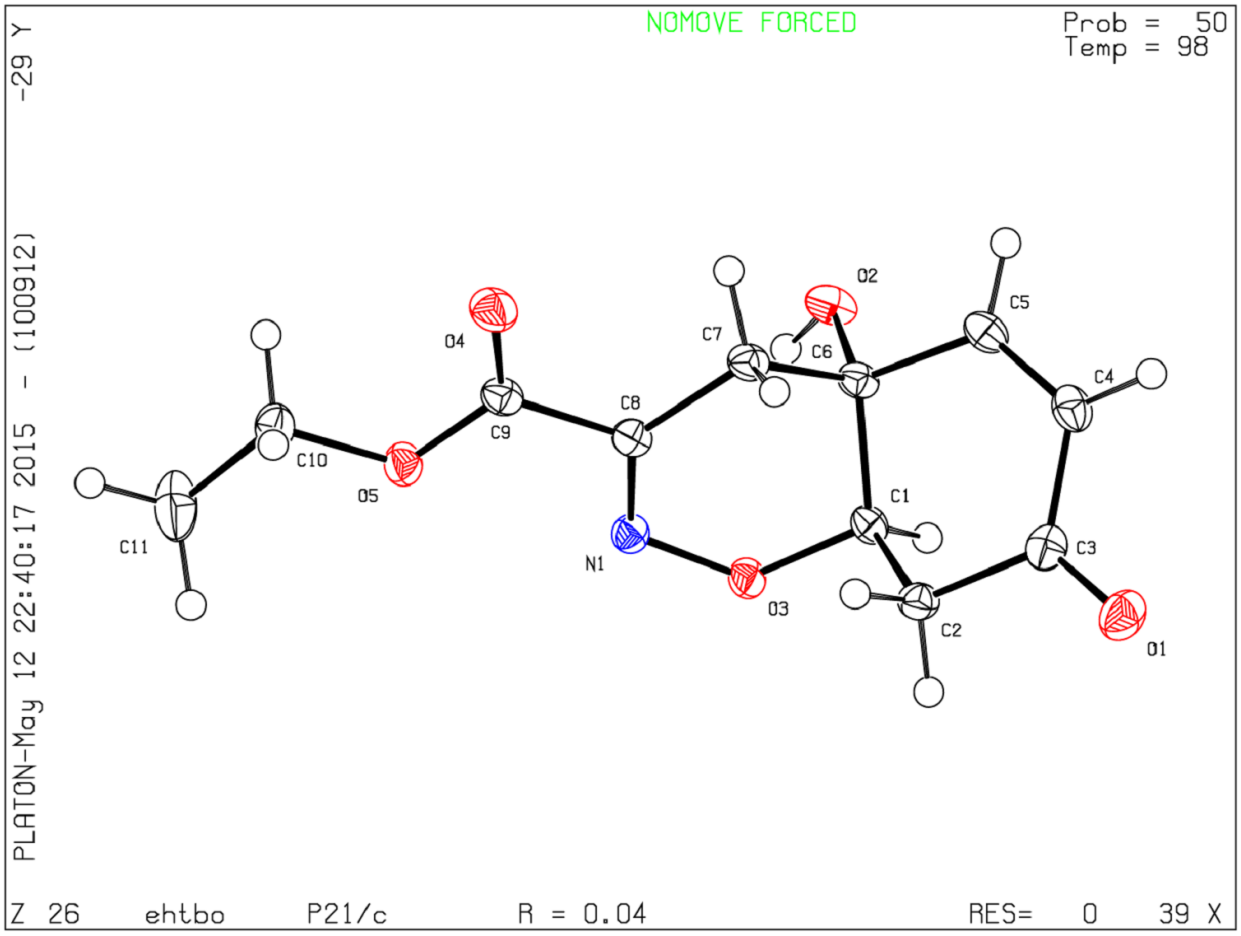
Correction method = # Reported T Limits: T_{min} = 0.890, T_{max} = 1.000

AbsCorr = MULTI-SCAN

Data completeness = 0.994 Theta(max) = 27.500

R(reflections) = 0.0439 (2381) wR2(reflections) = 0.0983(2520)

S = 1.010 Npar = 193



(4a*S*,7*R***,8a*S***)-Ethyl 7-((methoxycarbonyl)oxy)-4a-hydroxy-4a,7,8,8a-tetrahydro-4H-benzo[*e*][1,2]oxazine-3-carboxylate (20a)**

CCDC Nr.: 1064084

Bond precision: C–C = 0.0052 Å Wavelength = 0.71073

Cell:	a = 8.837(3)	b = 9.595(3)	c = 16.405(6)
	α = 90	β = 90	γ = 90
Temperature:	98 K		

	Calculated	Reported
Volume	1391.0(8)	1391.0(8)
Space group	P 21 21 21	P2(1) 2(1)
Hall group	P 2ac 2ab	
Moiety formula	$C_{13}H_{17}NO_7$	$C_{13}H_{17}NO_7$
Sum formula	$C_{13}H_{17}NO_7$	$C_{13}H_{17}NO_7$
M_r	299.28	299.28

D_x, g·cm^{-3}	1.429	1.429
Z	4	4
Mu (mm^{-1})	0.117	0.117
F000	632.0	632.0
F000′	632.41	
h, k, l_{max}	10, 11, 19	10, 11, 19
N_{ref}	2459 [1436]	2449
T_{min}, T_{max}	0.976, 0.985	0.762, 1.000
T_{min}′	0.972	

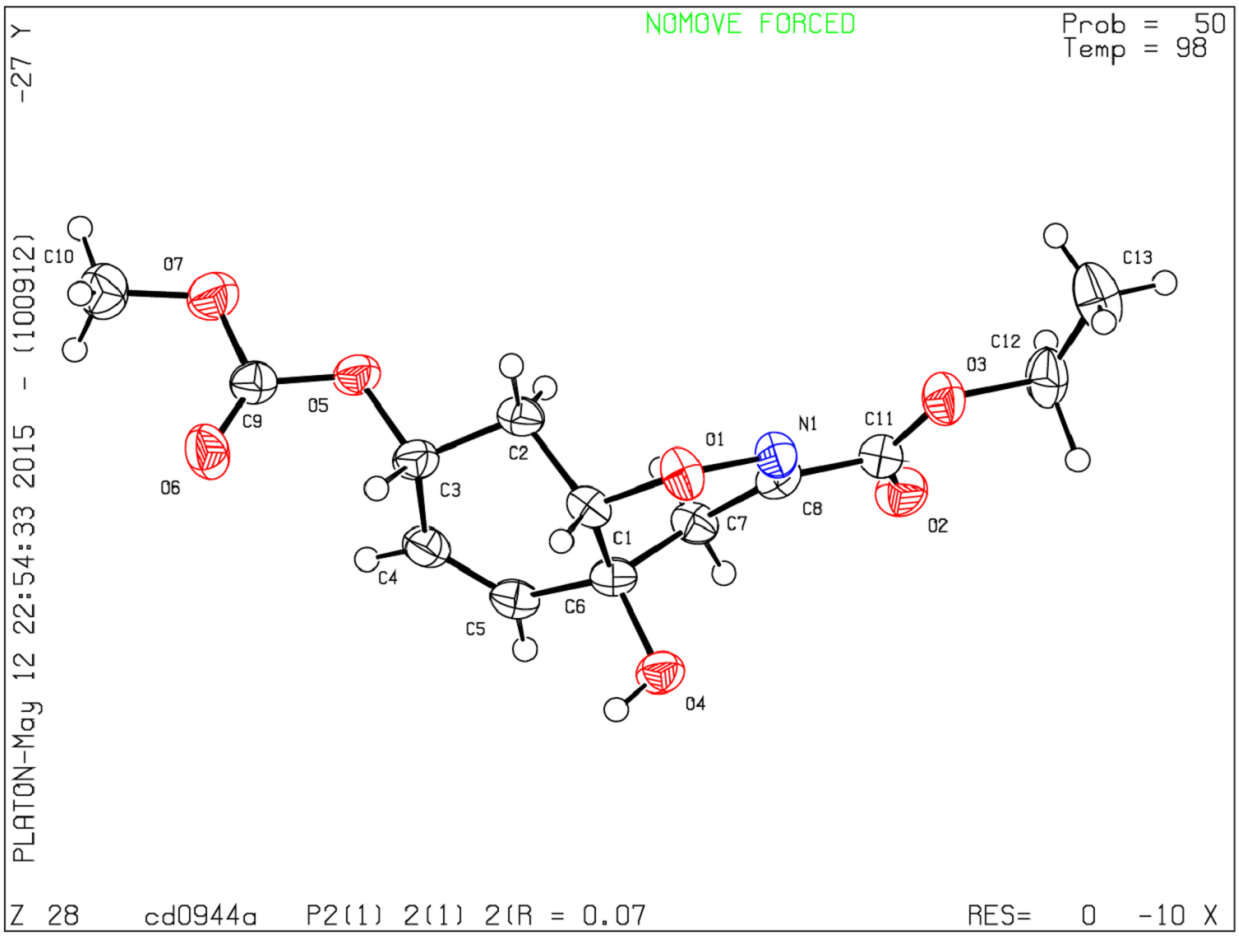
Correction method = # Reported T Limits: T_{min} = 0.762, T_{max} = 1.000

AbsCorr = MULTI-SCAN

Data completeness = 1.71/1.00 Theta(max) = 25.050

R(reflections) = 0.0671 (2303) wR2(reflections) = 0.1314(2449)

S = 1.003 Npar = 214



3-Amino-7,8-methoxy-2*H*-chromen-2-one (25a)

CCDC Nr.: 1400041

Bond precision:	C–C = 0.0016 Å		Wavelength = 0.71073
Cell:	a=8.7284(13)	b=7.9180(12)	c=14.286(2)
	α = 90	β = 93.316(3)	γ = 90
Temperature:	98 K		

	Calculated	Reported
Volume	985.7(3)	985.7(3)
Space group	P 21/n	P2(1)/n
Hall group	-P 2yn	-P 2yn
Moiety formula	$C_{11}H_{11}NO_4$	$C_{11}H_{11}NO_4$
Sum formula	$C_{11}H_{11}NO_4$	$C_{11}H_{11}NO_4$
M_r	221.21	221.21
D_x, g·cm^{-3}	1.491	1.491
Z	4	4

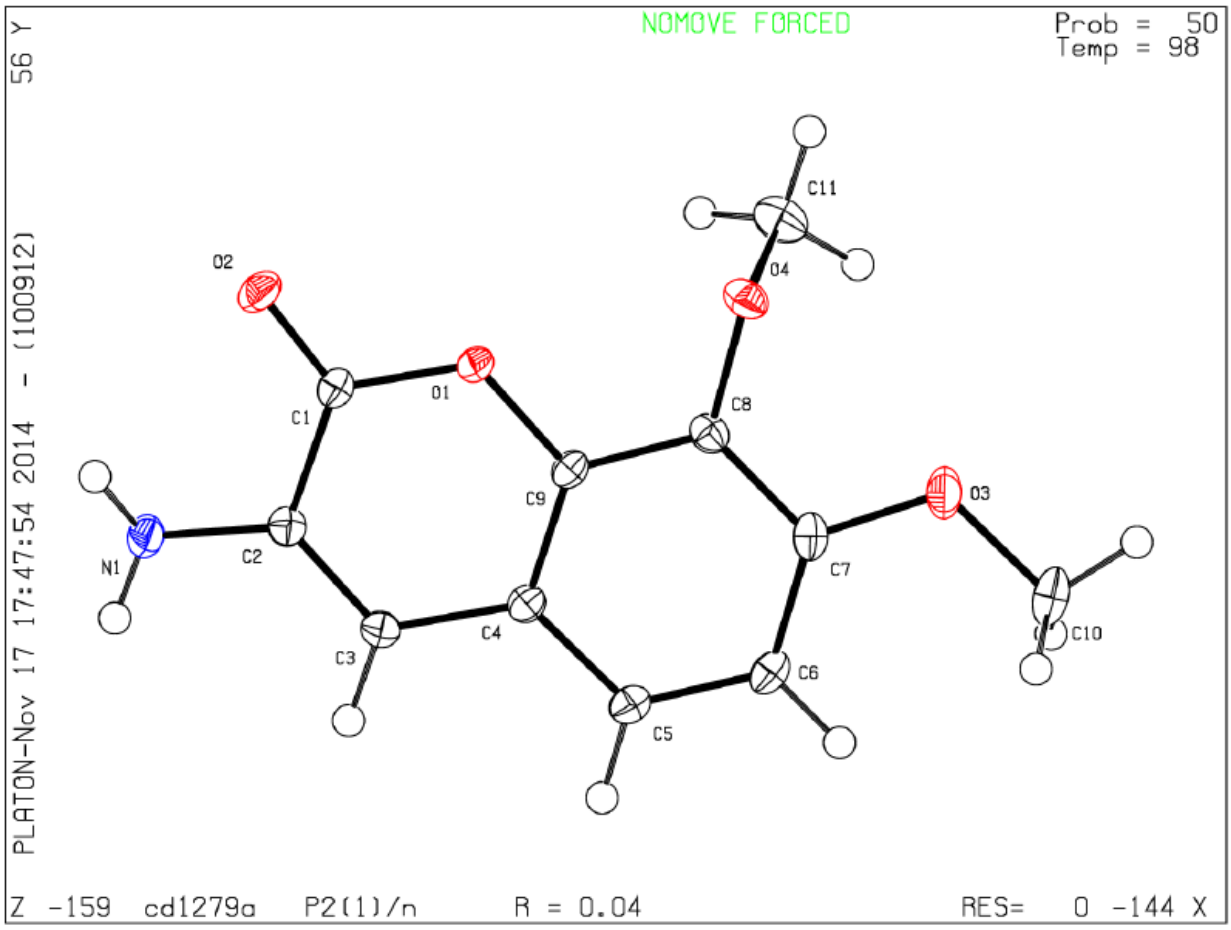
Mu (mm^{-1})	0.115	0.115
F000	464.0	464.0
F000′	464.27	
h, k, l_{max}	11, 10, 18	11, 10, 18
N_{ref}	2270	2243
T_{min}, T_{max}	0.977, 0.983	0.813, 1.000
T_{min}′	0.961	

Correction method = MULTI-SCAN

Data completeness = 0.988 Theta(max) = 27.500

R(reflections) = 0.0433 (2062) wR2(reflections) = 0.1105 (2243)

S = 1.001 Npar = 178



7,8-Dimethoxy-3-(*N*-methylamino)-2*H*-chromen-2-one (25b)

CCDC Nr.: 1064085

Bond precision:	C–C = 0.0029 Å		Wavelength = 0.71073
Cell:	a=23.444(5)	b=6.9509(14)	c=17.543(4)
	α = 90	β = 127.51(3)	γ = 90
Temperature:	98 K		

	Calculated	Reported
Volume	2267.7(12)	2267.8(11)
Space group	C 2/c	C 1 2/c 1
Hall group	-C 2yc	-C 2yc
Moiety formula	$C_{12}H_{13}NO_4$	$C_{12}H_{13}NO_4$
Sum formula	$C_{12}H_{13}NO_4$	$C_{12}H_{13}NO_4$
M_r	235.23	235.23

D_x, g·cm^{-3}	1.378	1.378
Z	8	8

Mu (mm^{-1})	0.104	0.104
F000	992.0	992.0
F000′	992.56	
h, k, l_{max}	28, 8, 21	28, 8, 21
N_{ref}	2240	2234
T_{min}, T_{max}	0.981, 0.990	0.673, 1.000
T_{min}′	0.979	

Correction method = # Reported T Limits: T_{min} = 0.673, T_{max} = 1.000

AbsCorr = MULTI-SCAN

Data completeness = 0.997 Theta(max) = 25.998

R(reflections) = 0.0411 (1587) wR2(reflections) = 0.1191 (2234)

S = 1.056 Npar = 157

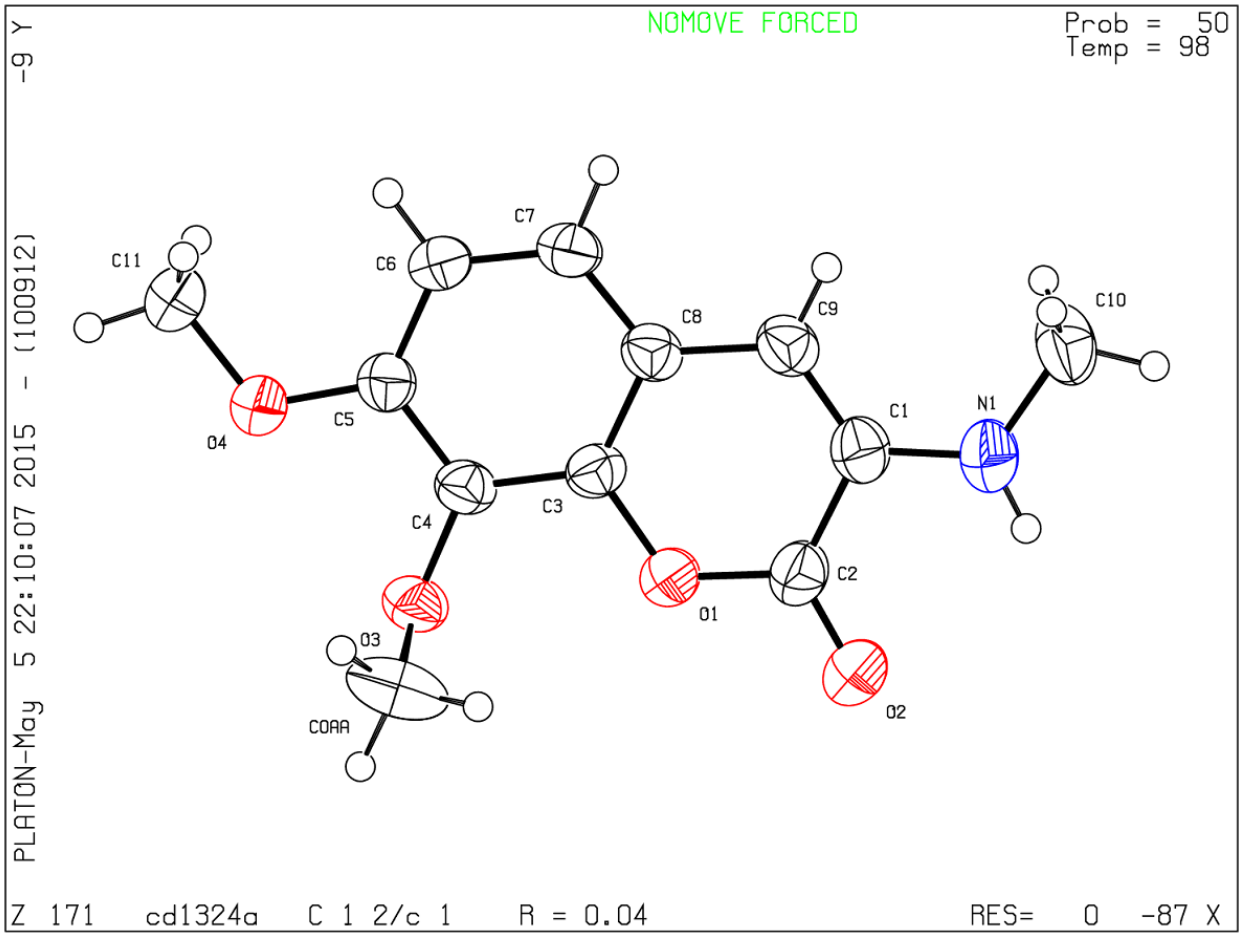
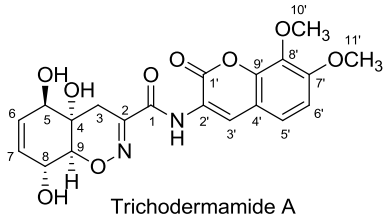


Table S1. Comparison of the ^{1}H NMR Data of the Synthetic Trichodermamide A with the ^{1}H NMR Data Reported for Trichodermamide A Isolated from *Trichoderma Sp.*[a]

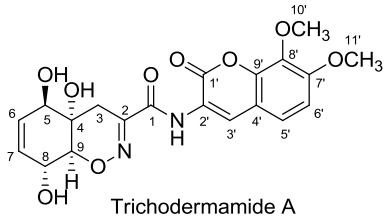


Trichodermamide A

Entry	δ_H, ppm		$\Delta\delta_H$	Position
	Synthetic	Lit.[7]		
1	9.48	9.48	0.00	NH
2	8.62	8.62	0.00	H-3′
3	7.14	7.24	0.10	H-5′
4	6.96	6.96	0.00	H-6′
5	5.62	5.62	0.00	H-6
6	5.57	5.57	0.00	H-7
7	4.48	4.47	0.01	H-5
8	4.22	4.22	0.00	H-9
9	4.11	4.11	0.00	H-8
10	3.98	3.98	0.00	CH_3-10′
11	3.95	3.96	-0.01	CH_3-11′
12	2.72	2.72	0.00	H-3a
13	2.26	2.26	0.00	H-3b

[a] Samples were dissolved in a 10 vol % solution of d_6-DMSO in $CDCl_3$.

Table S2. Comparison of the ^{13}C NMR Data of the Synthetic Trichodermamide A with the ^{13}C NMR Data Reported for Trichodermamide A Isolated from *Trichoderma Sp.*[a]

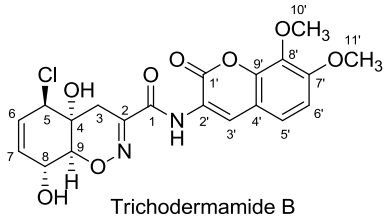


Trichodermamide A

Entry	δ_C, ppm		$\Delta\delta_C$	Position
	Synthetic	Lit.[7]		
1	160.9	160.9	0.0	1
2	157.6	157.7	-0.1	1′
3	153.6	153.6	0.0	7′
4	149.9	149.9	0.0	2
5	143.4	143.5	-0.1	9′
6	135.4	135.6	-0.2	8′
7	129.2	129.1	0.1	6
8	127.4	127.4	0.0	7
9	123.4	123.5	-0.1	3′
10	122.2	122.1	0.1	5′
11	120.7	120.7	0.0	2′
12	113.6	113.7	-0.1	4′
13	109.2	109.2	0.0	6′
14	83.4	83.3	0.1	9
15	73.5	73.7	-0.2	5
16	67.6	67.8	-0.2	4
17	66.1	66.1	0.0	8
18	60.9	60.9	0.0	11′
19	55.9	56.0	-0.1	10′
20	23.5	23.7	-0.2	3

[a] Samples were dissolved in a 10 vol % solution of d_6-DMSO in $CDCl_3$.

Table S3. Comparison of the ^{1}H NMR Data of the Synthetic Trichodermamide B with the ^{1}H NMR Data Reported for Trichodermamide B Isolated from *Trichoderma Sp.*[a]

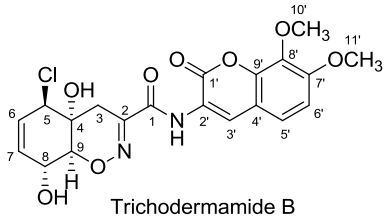


Trichodermamide B

Entry	δ_H, ppm		$\Delta\delta_H$	Position
	Synthetic	Lit.[7]		
1	9.49	9.49	0.00	NH
2	8.65	8.63	0.02	H-3′
3	7.27	7.23	0.04	H-5′
4	6.98	6.94	0.04	H-6′
5	5.66	5.66	0.01	H-6, H-7
6	4.92	4.90	0.02	H-5
7	4.33	4.32	0.01	H-9
8	4.18	4.18	0.00	H-8
9	4.01	3.99	0.02	CH_3-10′
10	3.99	3.96	0.03	CH_3-11′
11	2.89	2.89	0.00	H-3a
12	2.30	2.30	0.00	H-3b

[a] Samples were dissolved in a 10 vol % solution of d_6-DMSO in $CDCl_3$.

Table S4. Comparison of the ^{13}C NMR Data of the Synthetic Trichodermamide B with the ^{13}C NMR Data Reported for Trichodermamide B Isolated from *Trichoderma Sp.*[a]

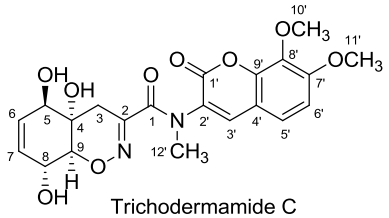


Trichodermamide B

Entry	δ_C, ppm		$\Delta\delta_C$	Position
	Synthetic	Lit.[7]		
1	160.7	160.7	0.0	1
2	157.8	157.8	0.0	1′
3	153.8	153.8	0.0	7′
4	149.6	149.6	0.0	2
5	143.7	143.7	0.0	9′
6	135.7	135.7	0.0	8′
7	129.2	129	0.2	6
8	127.3	127.4	-0.1	7
9	123.9	123.9	0.0	3′
10	122.3	122.3	0.0	5′
11	120.8	120.8	0.0	2′
12	113.7	113.8	-0.1	4′
13	109.3	109.2	0.1	6′
14	84.0	83.9	0.1	9
15	67.3	67.3	0.0	5
16	65.6	65.6	0.0	4
17	64.8	64.6	0.2	8
18	61.1	61.2	-0.1	11′
19	56.1	56.1	0.0	10′
20	24.9	25.1	-0.2	3

[a] Samples were dissolved in a 10 vol % solution of d_6-DMSO in $CDCl_3$.

Table S5. Comparison of the ^{1}H NMR Data of the Synthetic Trichodermamide C with the ^{1}H NMR Data Reported for Trichodermamide C Isolated from *Eupenicillium sp.*[a]

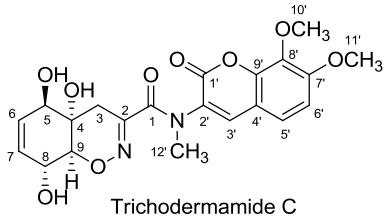


Trichodermamide C

Entry	δ_H, ppm		$\Delta\delta_H$	Position
	Synthetic	Lit.[8]		
1	8.02	8.02	0.00	H-3′
2	7.39	7.40	-0.01	H-5′
3	7.15	7.16	-0.01	H-6′
4	5.41	5.41	0.00	H-6
5	5.34	5.35	-0.01	H-7
6	4.12	4.12	0.00	H-5
7	3.91	3.91	0.00	CH_3-10′
8	3.83	3.83	0.00	CH_3-11′
9	3.75	3.75	0.00	H-9
10	3.67	3.68	-0.01	H-8
11	3.21	3.21	0.00	CH_3-12′
12	2.37	2.38	-0.01	H-3a
13	2.01	2.01	0.00	H-3b

[a] Samples were dissolved in d_6-DMSO. Data were collected at 30 ^{o}C.

Table S6. Comparison of the ^{13}C NMR Data of the Synthetic Trichodermamide C with the ^{13}C NMR Data Reported for Trichodermamide C Isolated from *Eupenicillium sp.*[a]



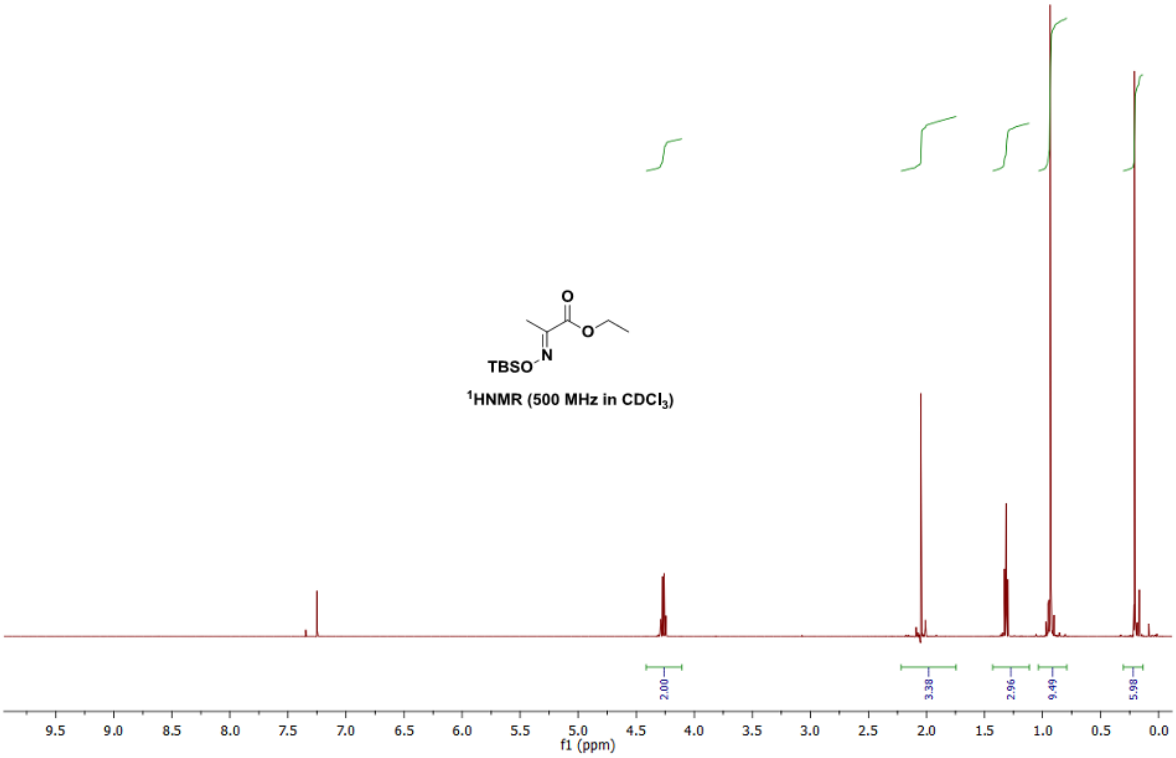
Trichodermamide C

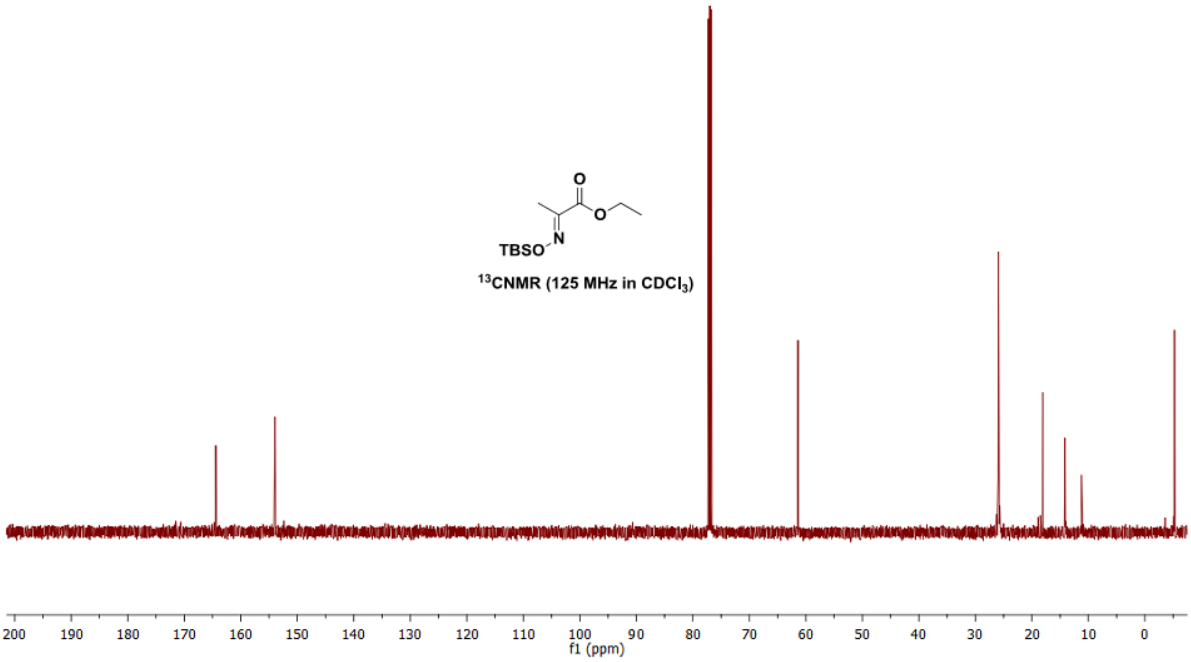
Entry	δ_C, ppm		$\Delta\delta_C$	Position
	Synthetic	Lit.[8]		
1	165.4	165.4	0.0	1
2	158.4	158.5	-0.1	1′
3	155.0	155.0	0.0	7′
4	151.8	151.8	0.0	2
5	145.9	145.9	0.0	9′
6	137.1	137.0	0.1	8′
7	135.2	135.2	0.0	6
8	129.9	129.9	0.0	7
9	127.8	127.8	0.0	3′
10	127.8	127.8	0.0	5′
11	123.5	123.5	0.0	2′
12	113.4	113.5	-0.1	4′
13	109.9	109.9	0.0	6′
14	82.8	82.8	0.0	9
15	73.3	73.4	-0.1	5
16	67.3	67.2	0.1	4
17	66.6	66.6	0.0	8
18	60.8	60.8	0.0	11′
19	56.4	56.4	0.0	10′
20	36.3	36.3	0.0	12′
21	24.3	24.3	0.0	3

[a] Samples were dissolved in d_6-DMSO. Data were collected at 30 °C.

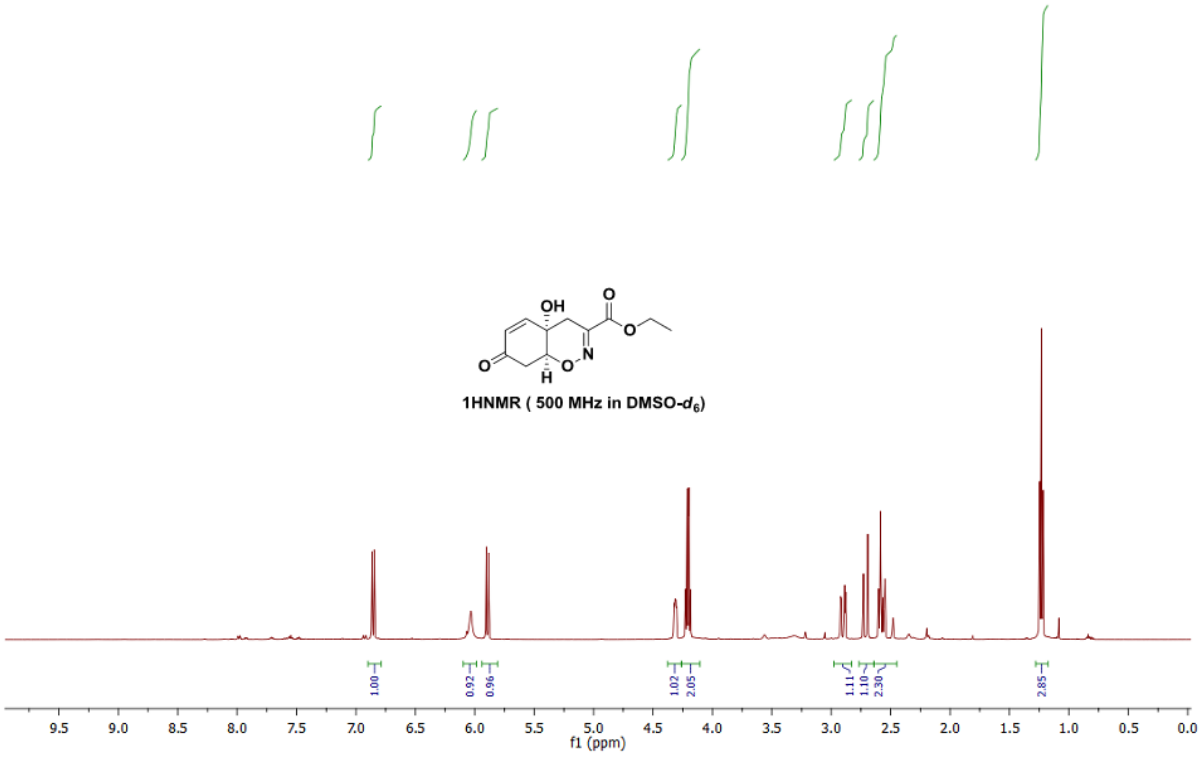
^{1}H and ^{13}C NMR Spectroscopic Data

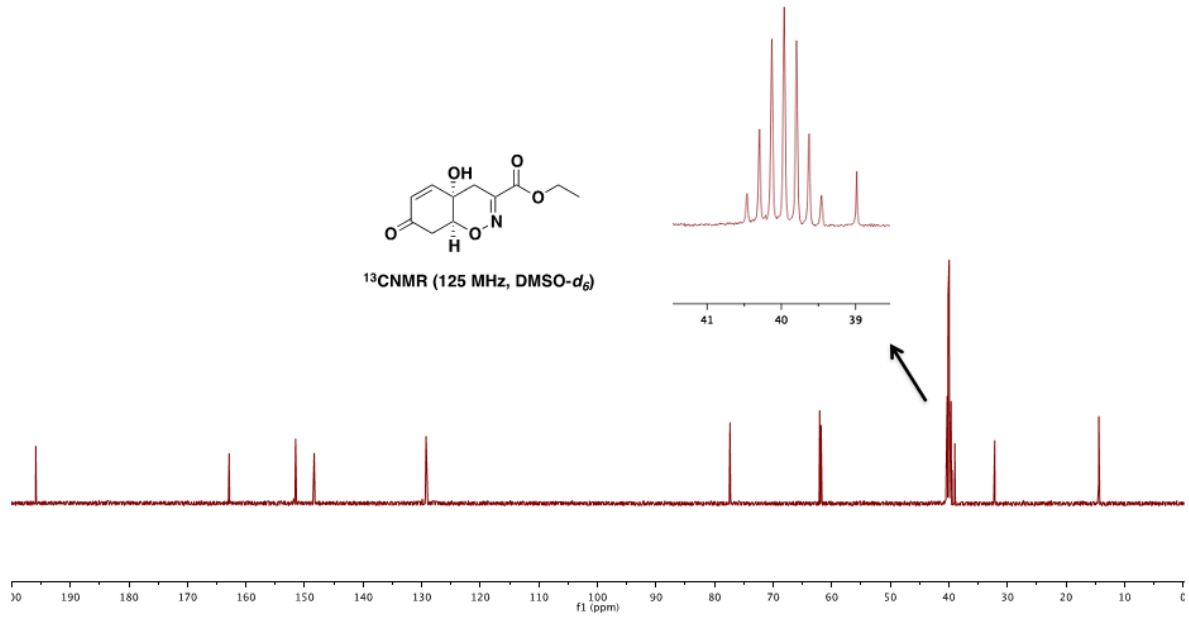
Ethyl 2-[(*tert*-butyldimethylsilyloxy)imino]propanoate (16c)



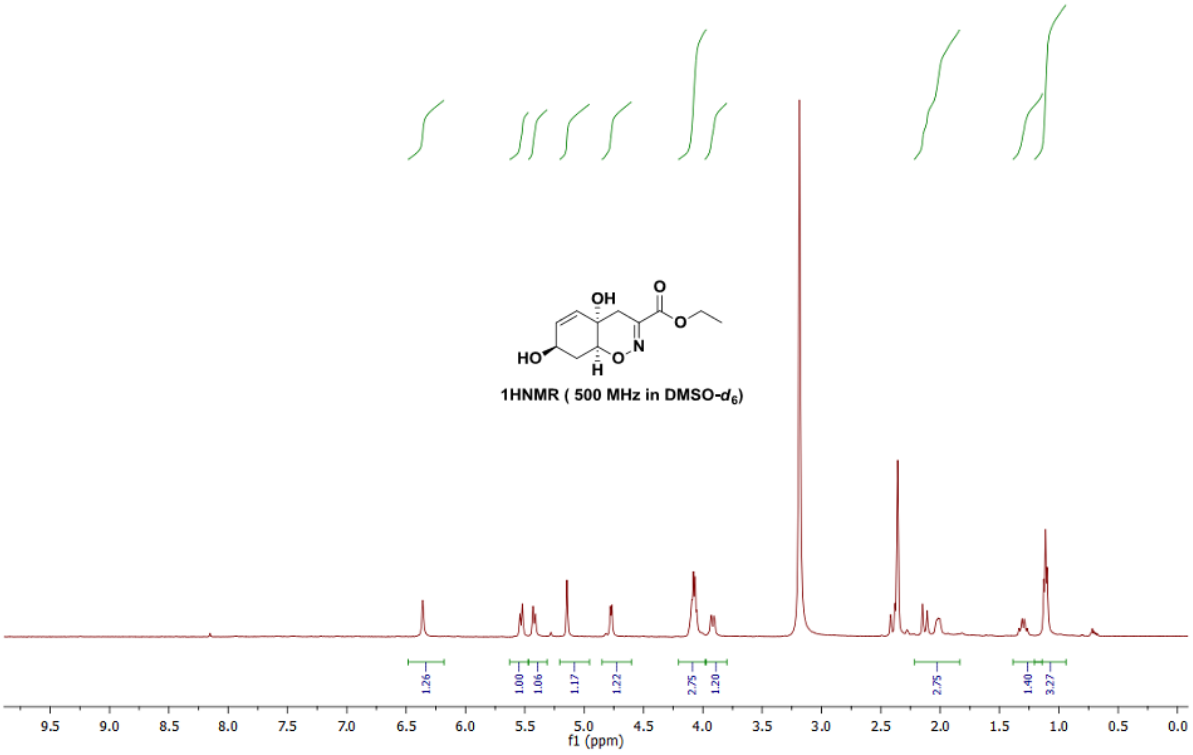


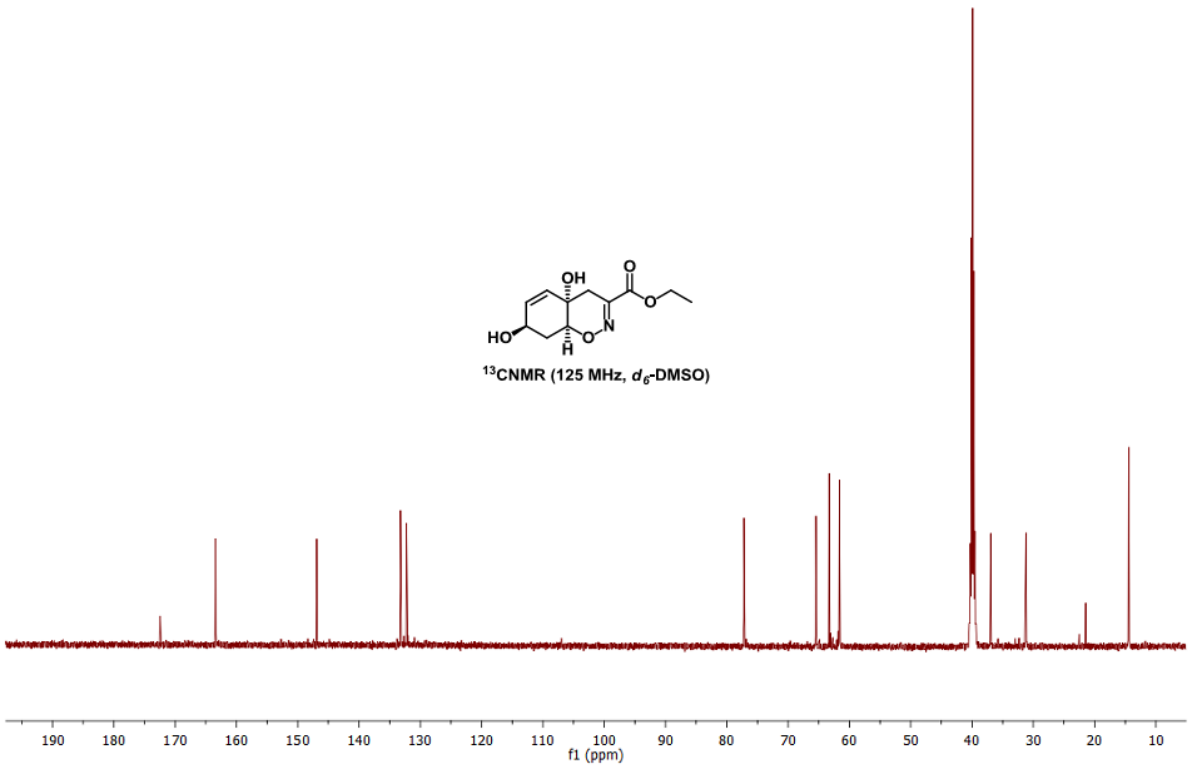
(4a*S,8a*S**)-Ethyl 4a-hydroxy-7-oxo-4a,7,8,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxylate (15)**



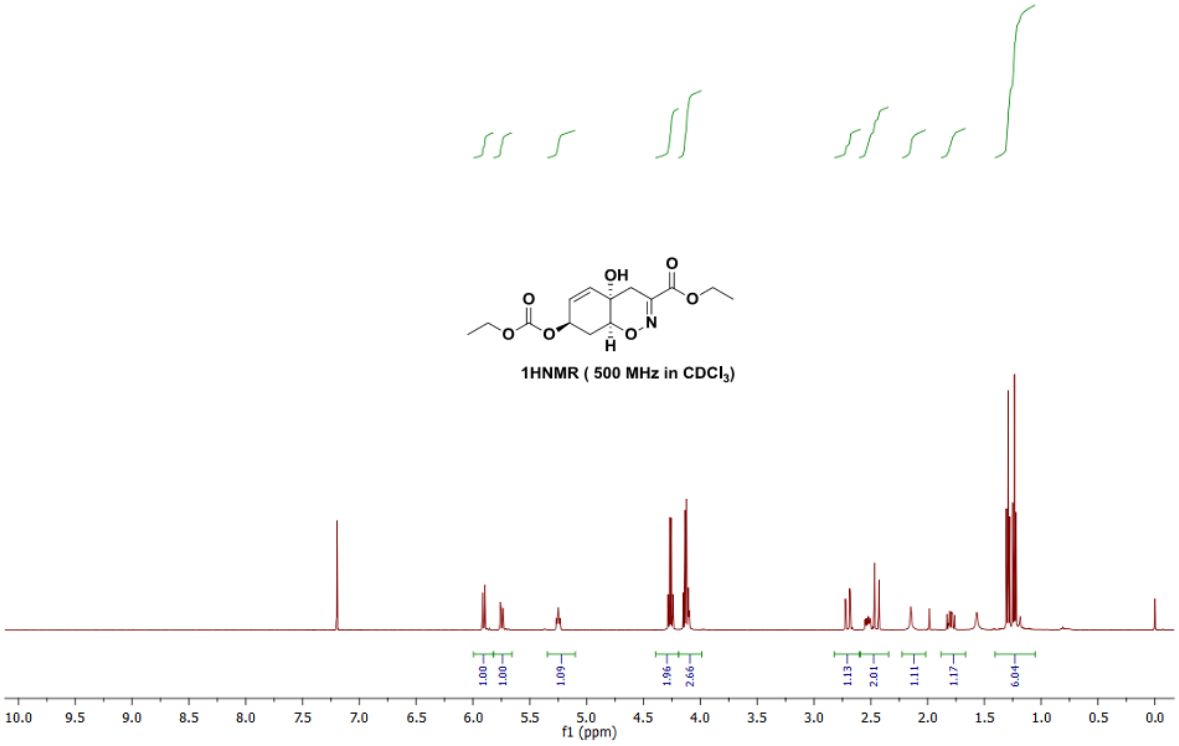


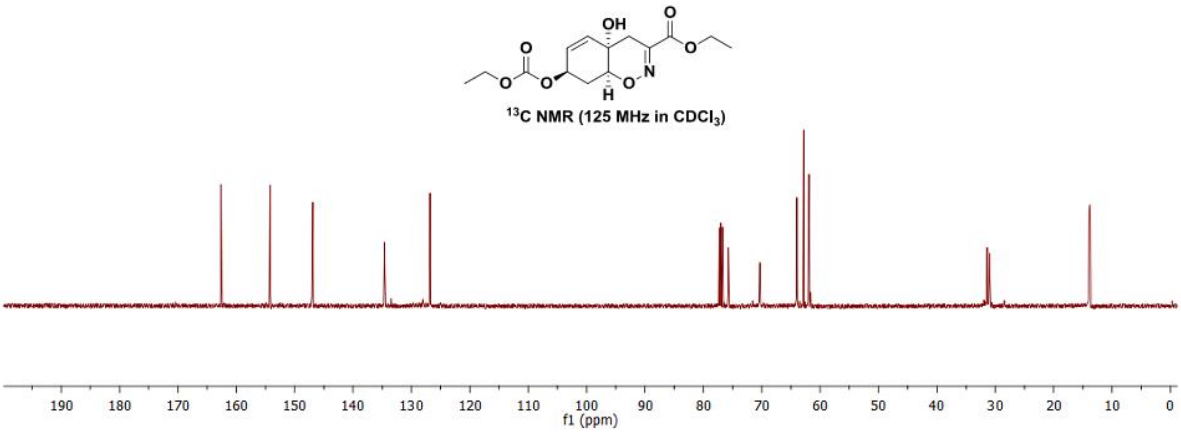
(4a*S,7*R**,8a*S**)-Ethyl 4a,7-dihydroxy-4a,7,8,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxylate (S1)**



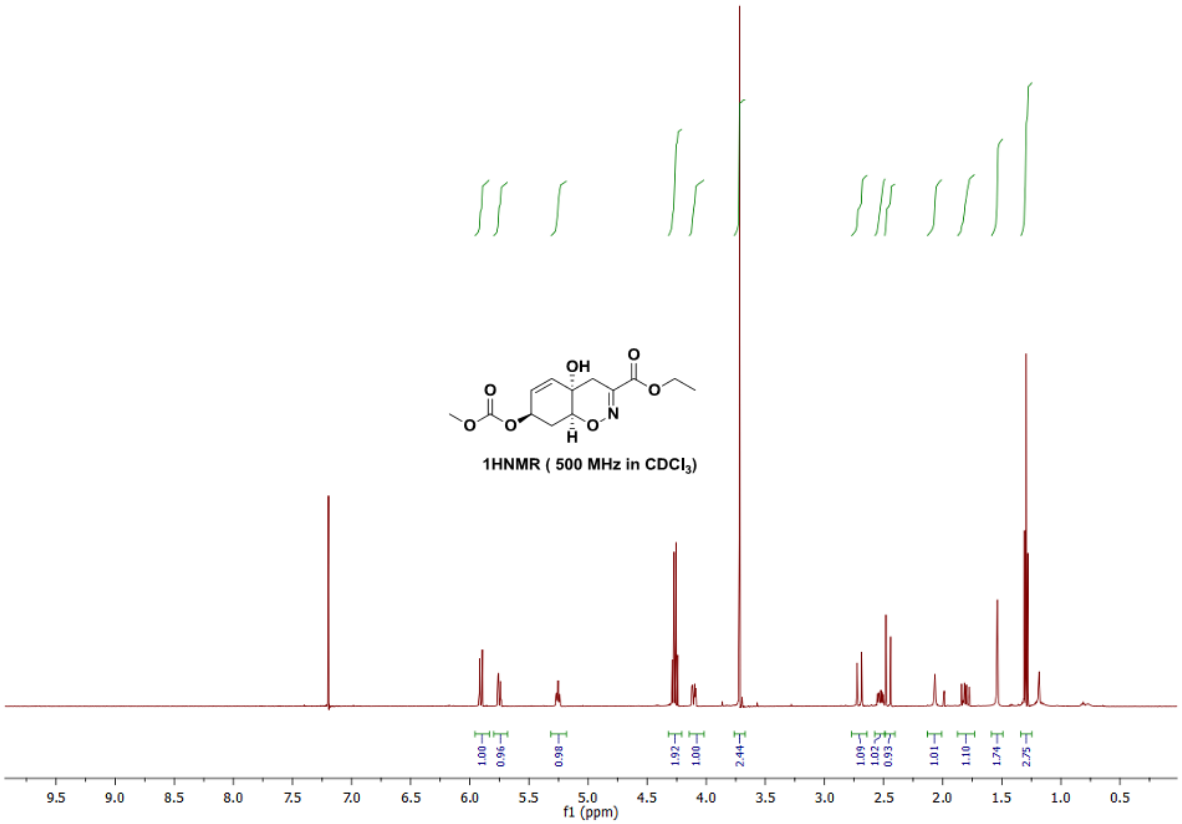


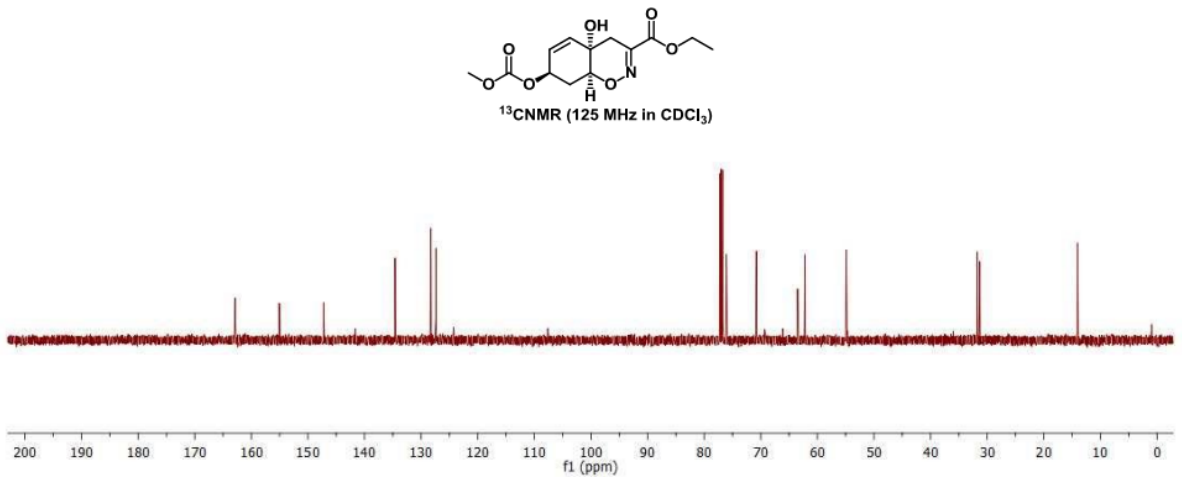
(4a*S*,7*R***,8a*S***)-Ethyl 7-((ethoxycarbonyl)oxy)-4a-hydroxy-4a,7,8,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxylate (20b)**



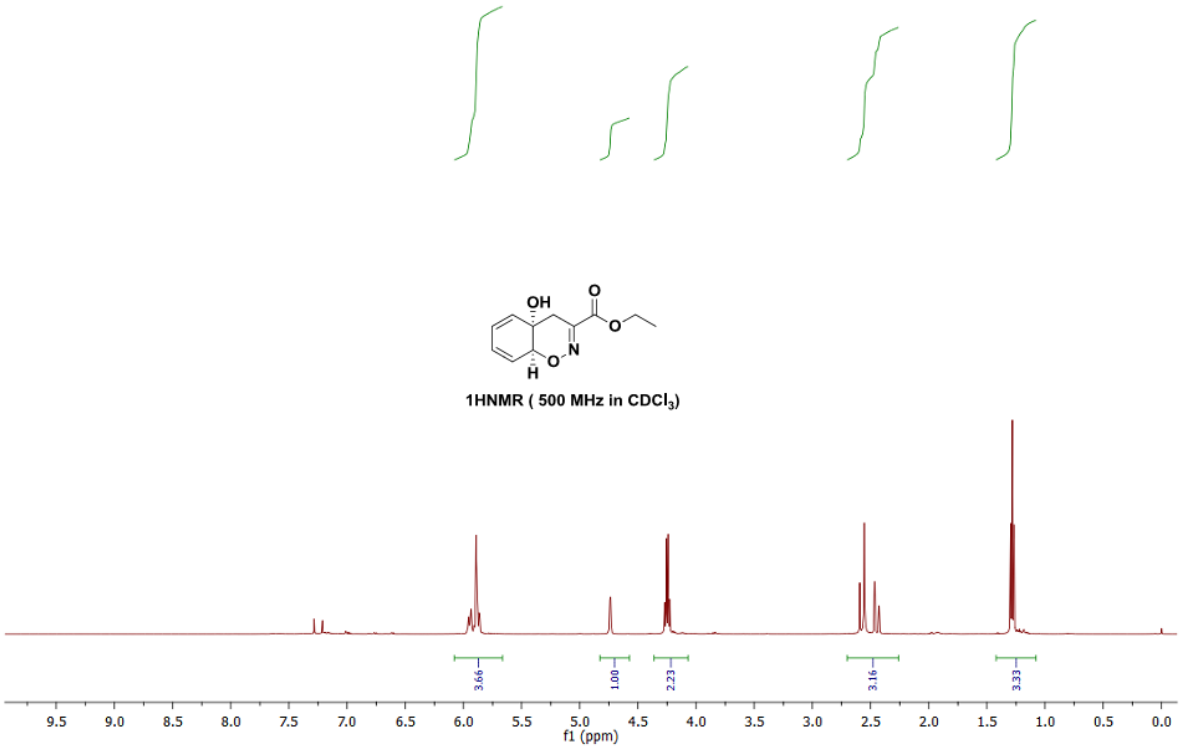


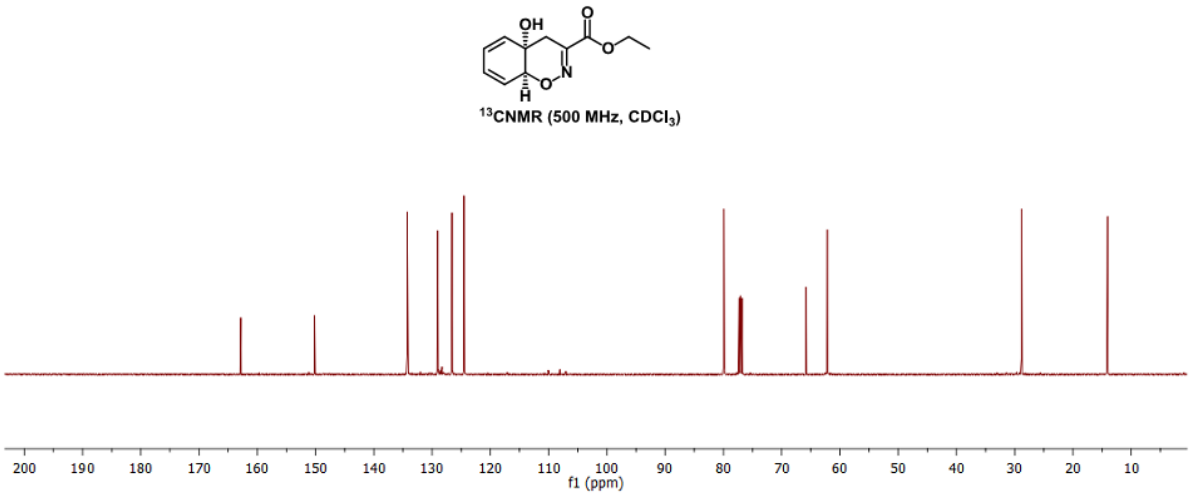
(4a*S*,7*R***,8a*S***)-Ethyl 7-((methoxycarbonyl)oxy)-4a-hydroxy-4a,7,8,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxylate (20a)**



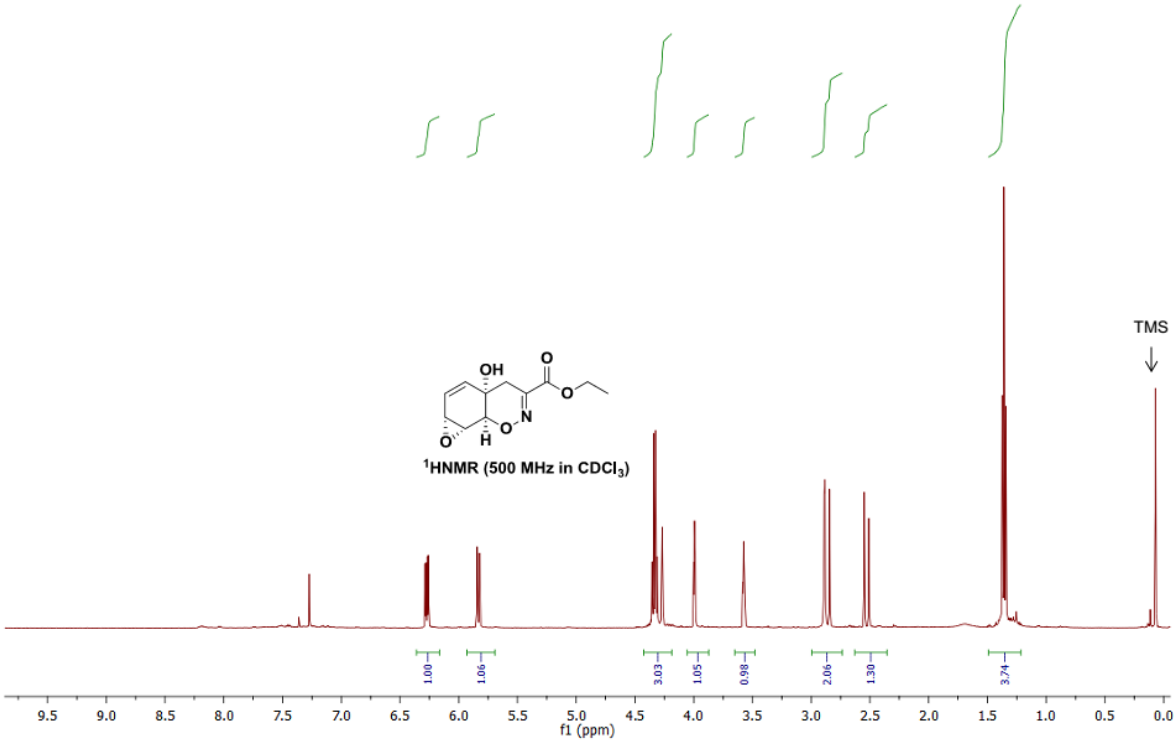


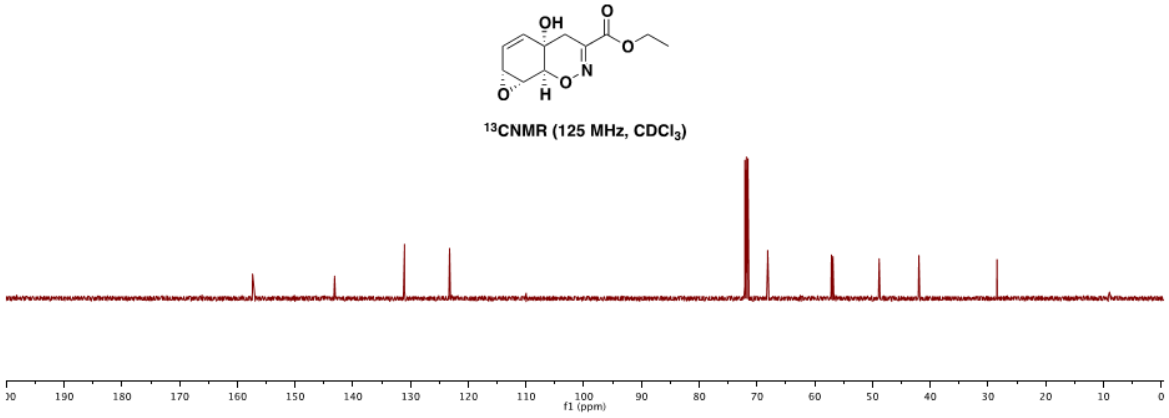
(4a*S,8a*S**)-Ethyl 4a-hydroxy-4a,8a-dihydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxylate (21)**



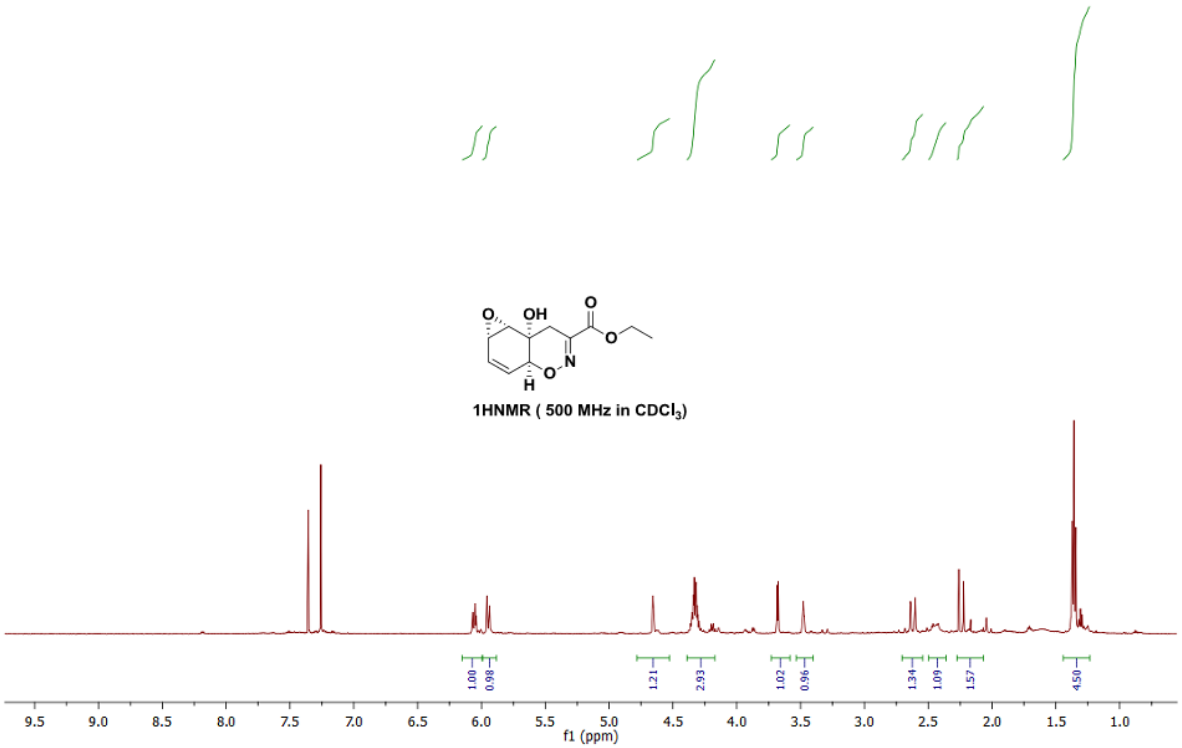


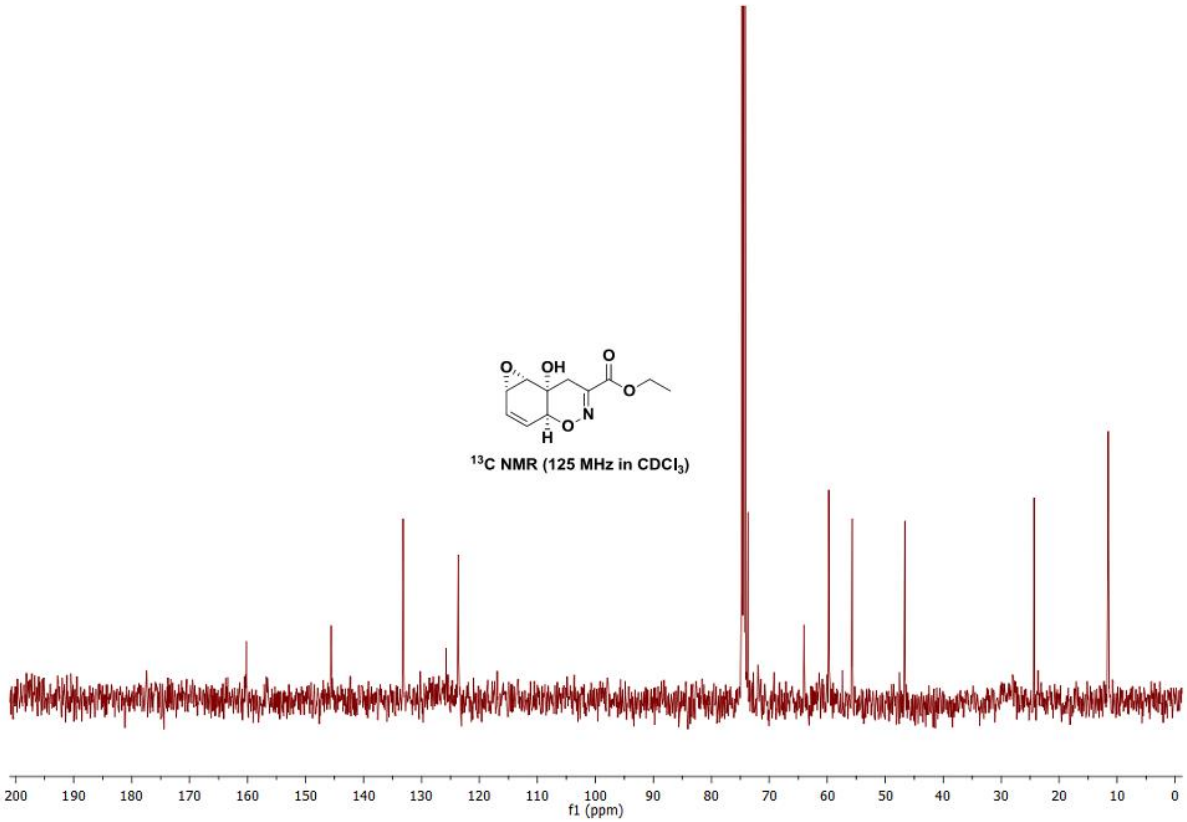
(4a*S*,6a*R***,7a*R***,7b*S***)-Ethyl 4a-hydroxy-4a,6a,7a,7b-tetrahydro-4*H*-oxireno[2',3':3,4]benzo[1,2-e][1,2]oxazine-3-carboxylate (22b)**



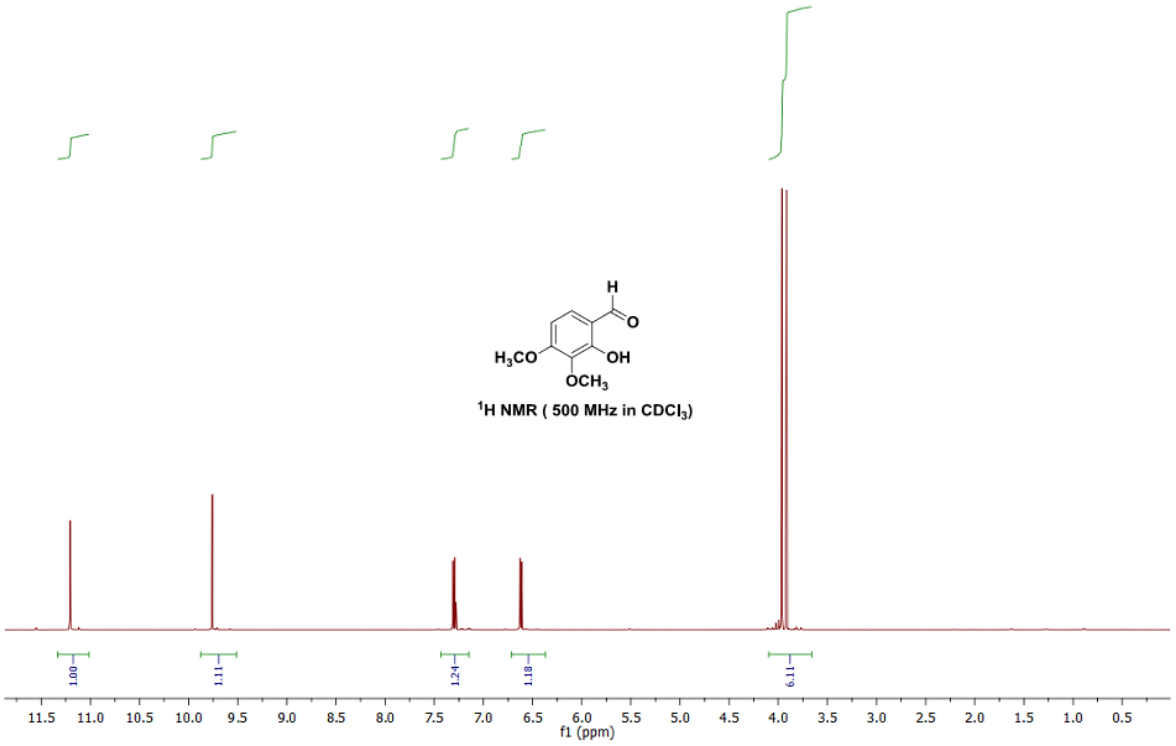


(1a*S,3a*S**,7a*S**,7b*S**)-Ethyl 7a-hydroxy-3a,7,7a,7b-tetrahydro-1a*H*-oxireno[2',3':5,6]benzo[1,2-e][1,2]oxazine-6-carboxylate (22a)**

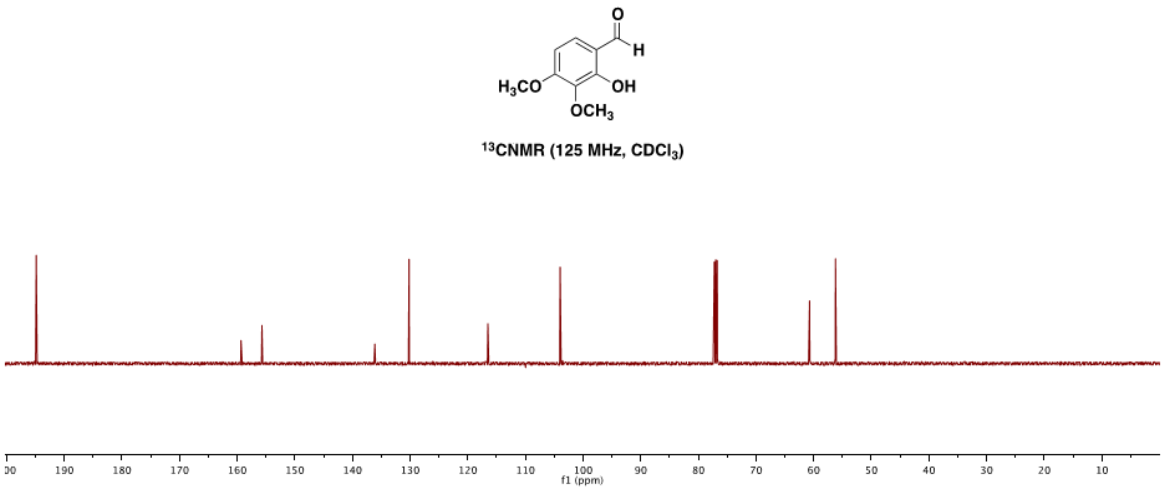




2-Hydroxy-3,4-dimethoxybenzaldehyde (S2)

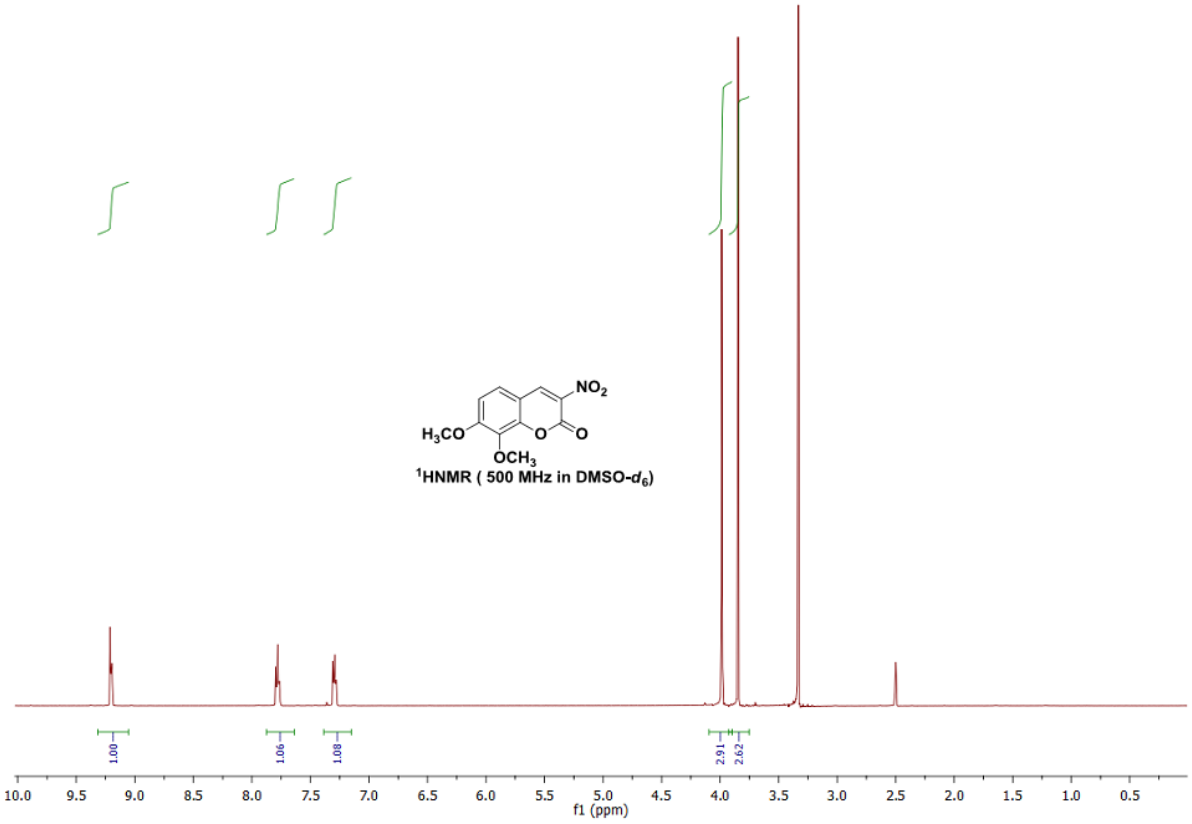


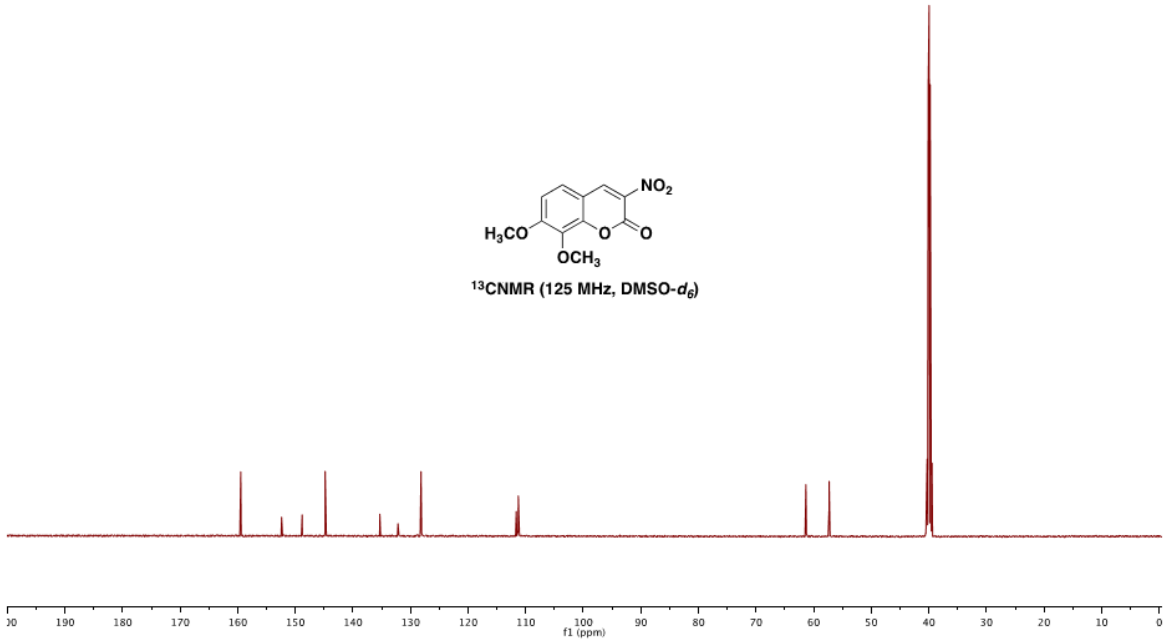
^{1}H NMR (500 MHz in $CDCl_3$)



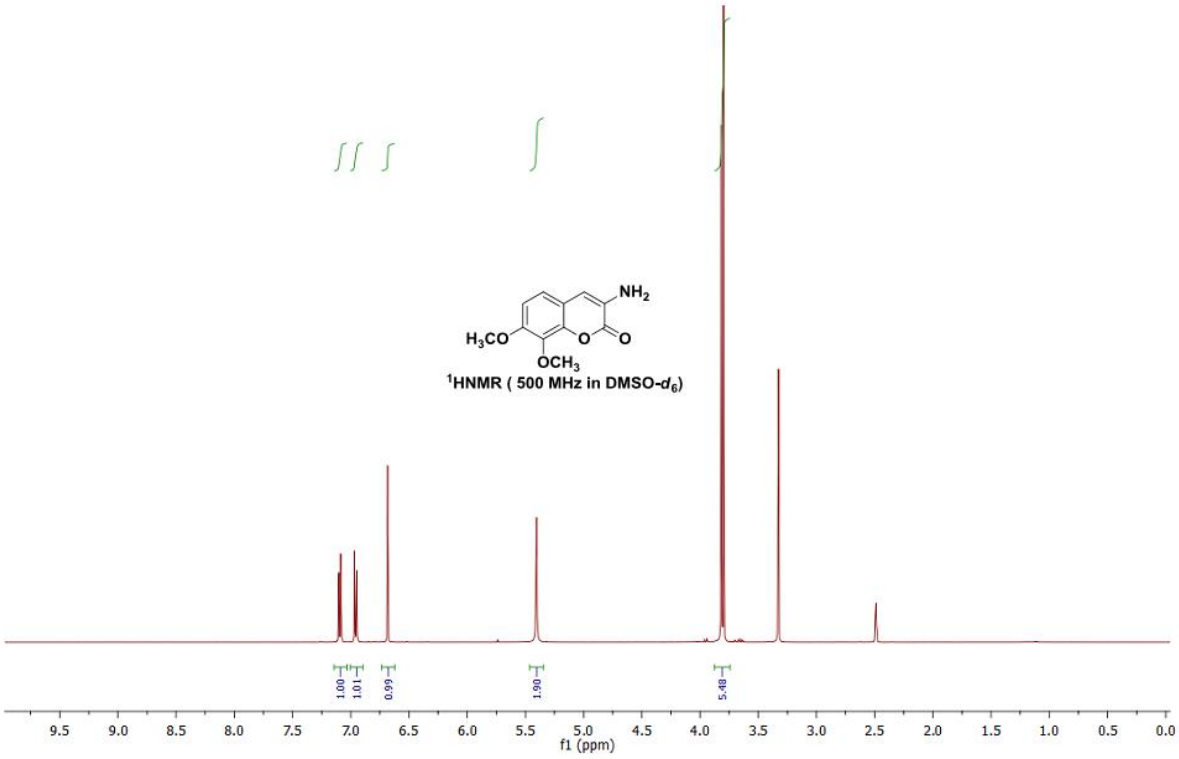
^{13}CNMR (125 MHz, $CDCl_3$)

3-Nitro-7,8-methoxy-2*H*-chromen-2-one (S3)

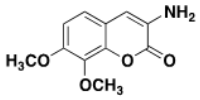




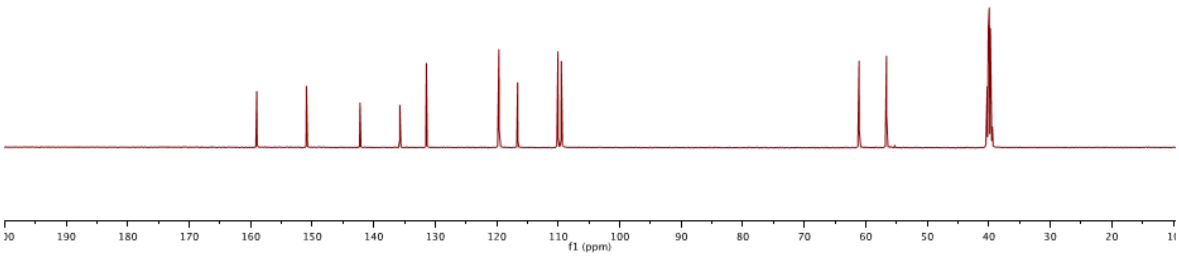
3-Amino-7,8-methoxy-2*H*-chromen-2-one (25a)



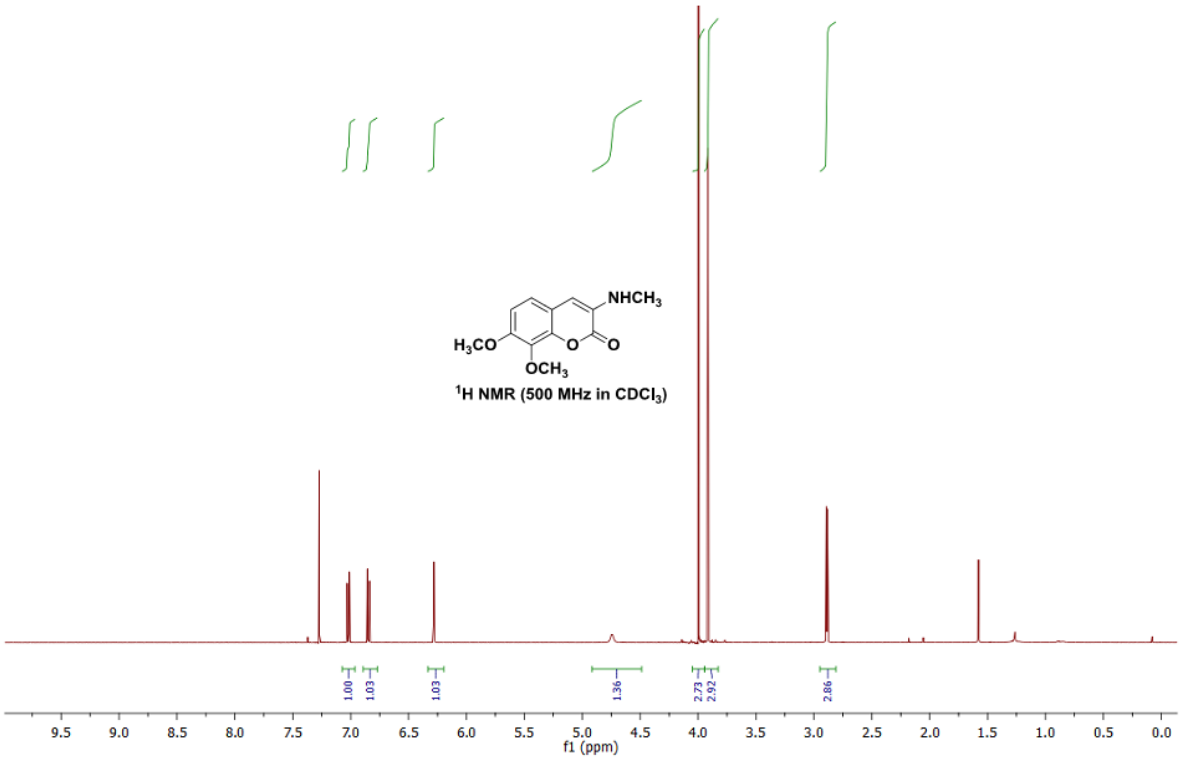
^{1}HNMR (500 MHz in DMSO-d_6)

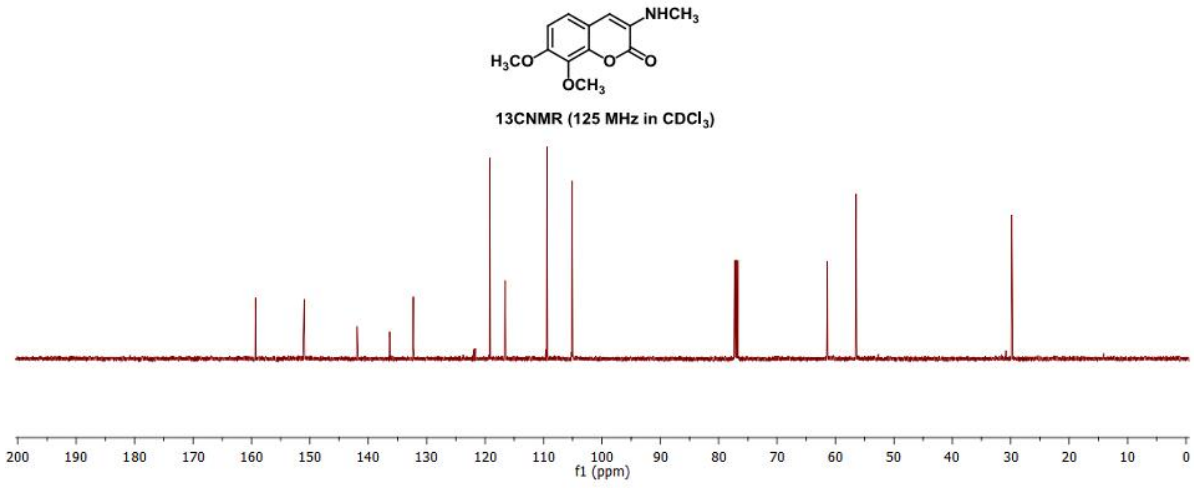


^{13}CNMR (125 MHz, DMSO-d_6)

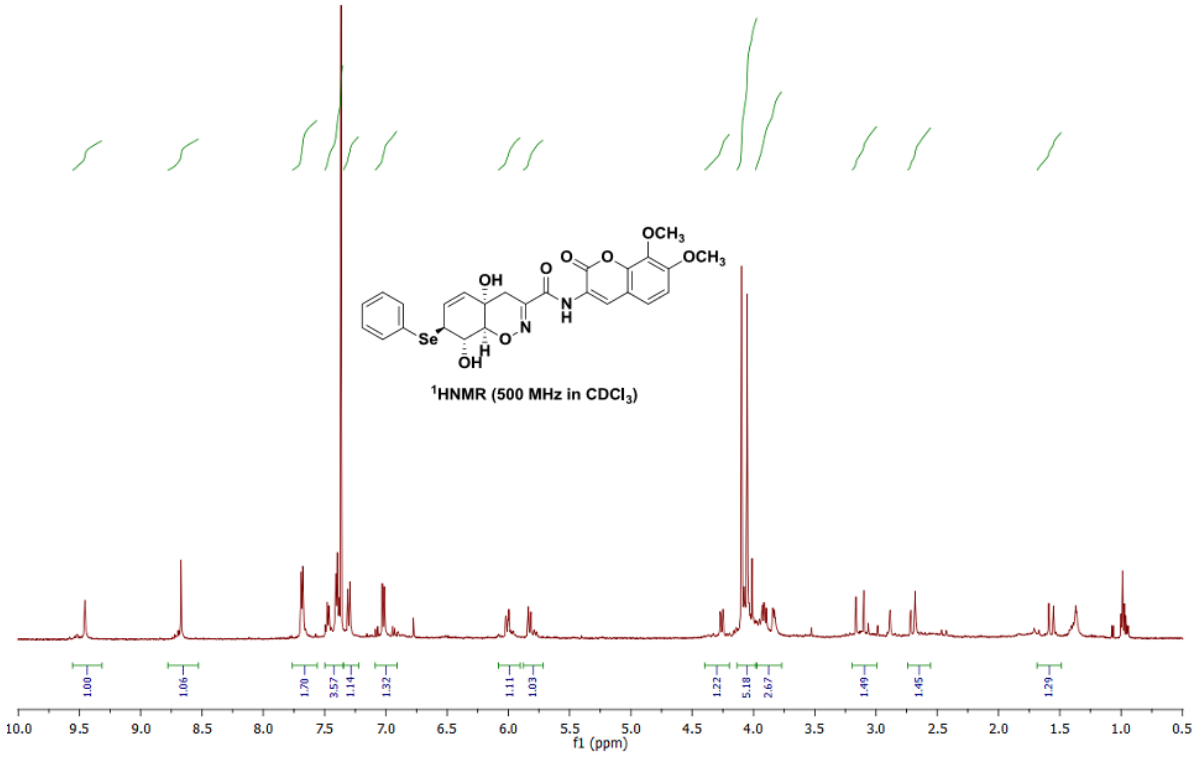


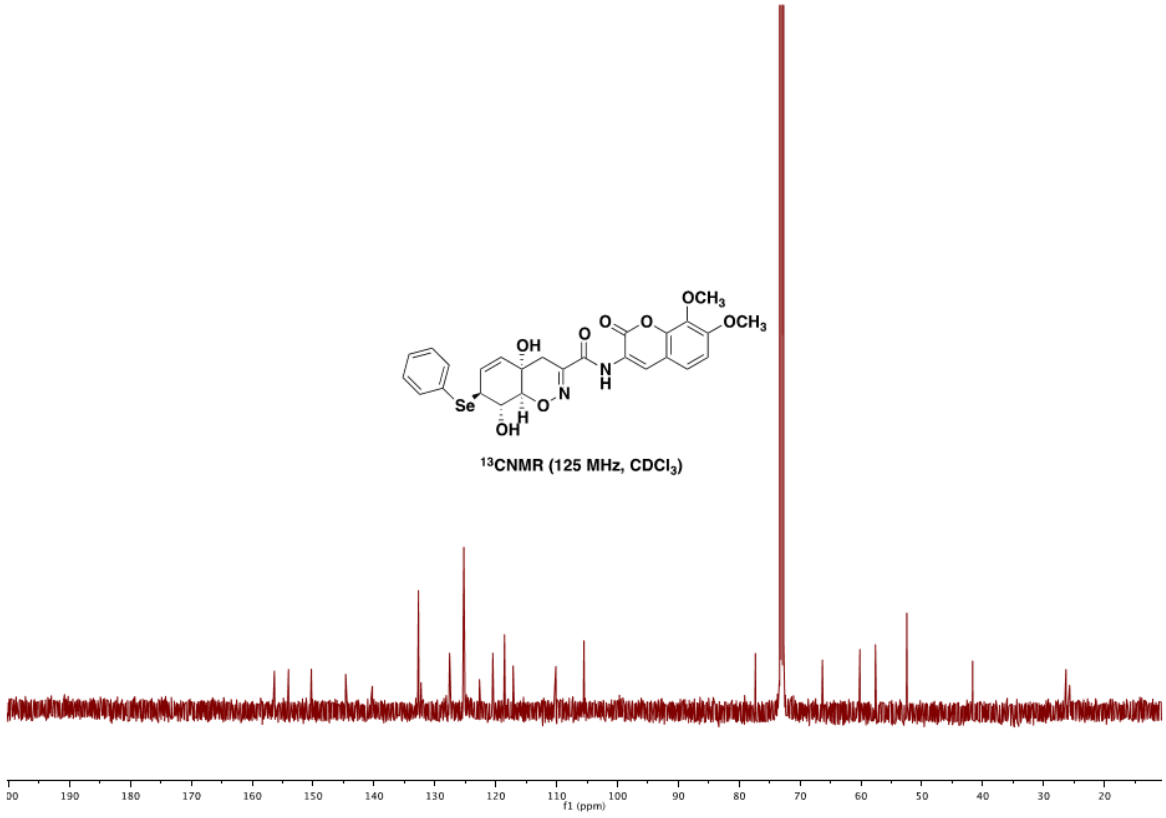
7,8-Dimethoxy-3-(methylamino)-2*H*-chromen-2-one (25b)



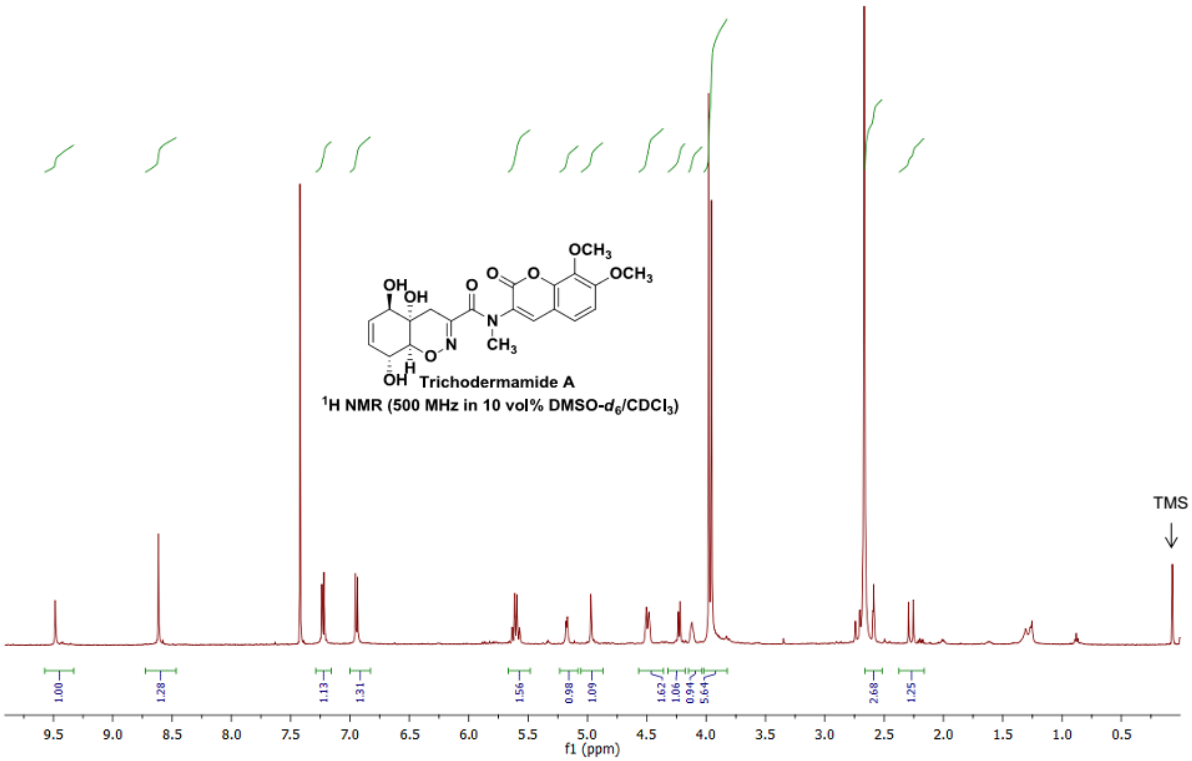


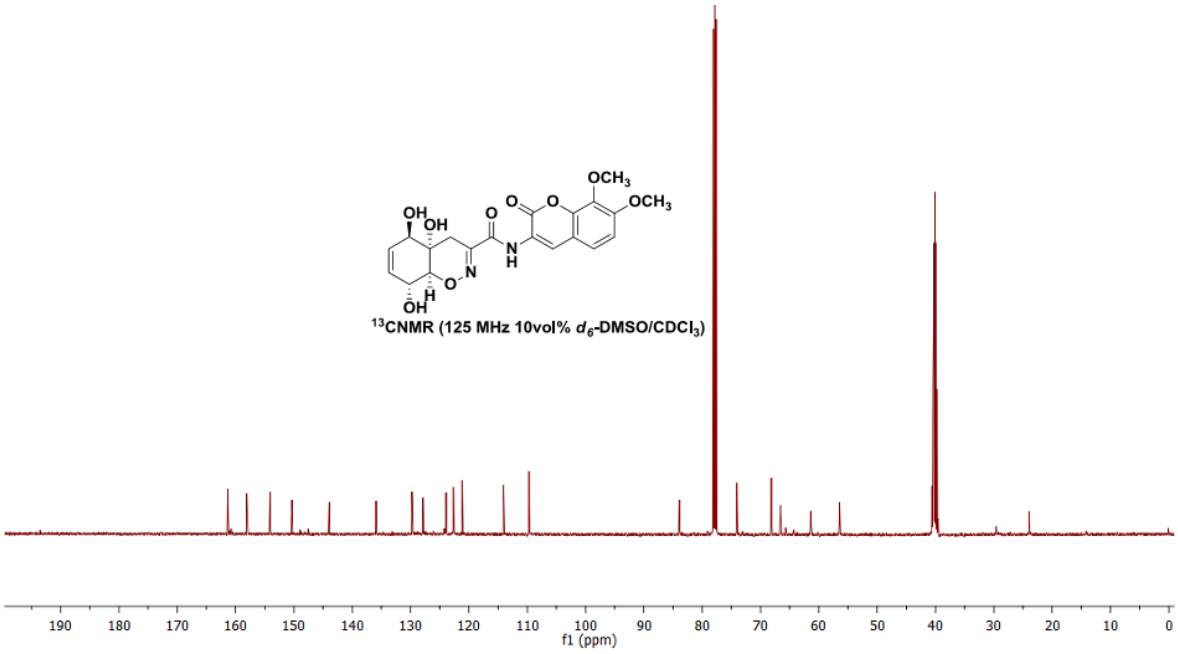
(4a*S,7*S**,8*S**,8a*S**)-*N*-(7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)-4a,8-dihydroxy-7-(phenylselanyl)-4a,7,8,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxamide(26)**

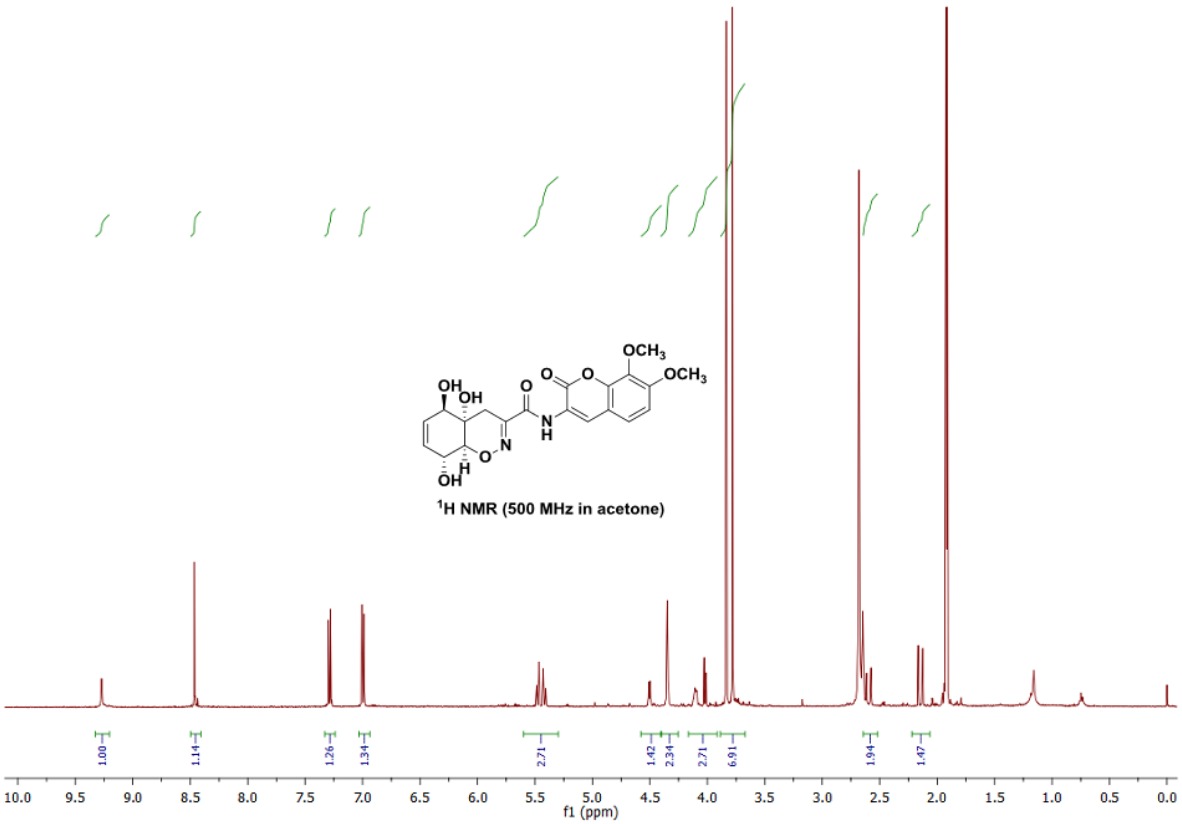




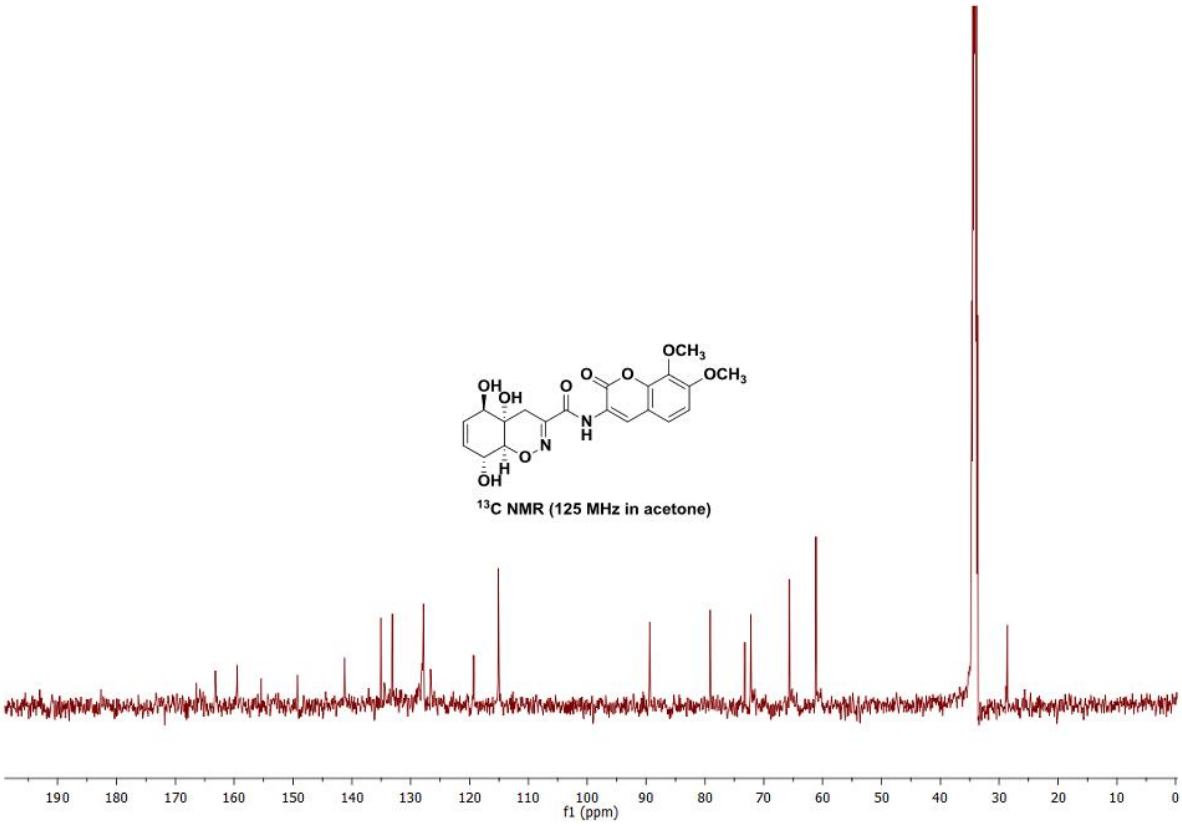
Trichodermamide A (1)





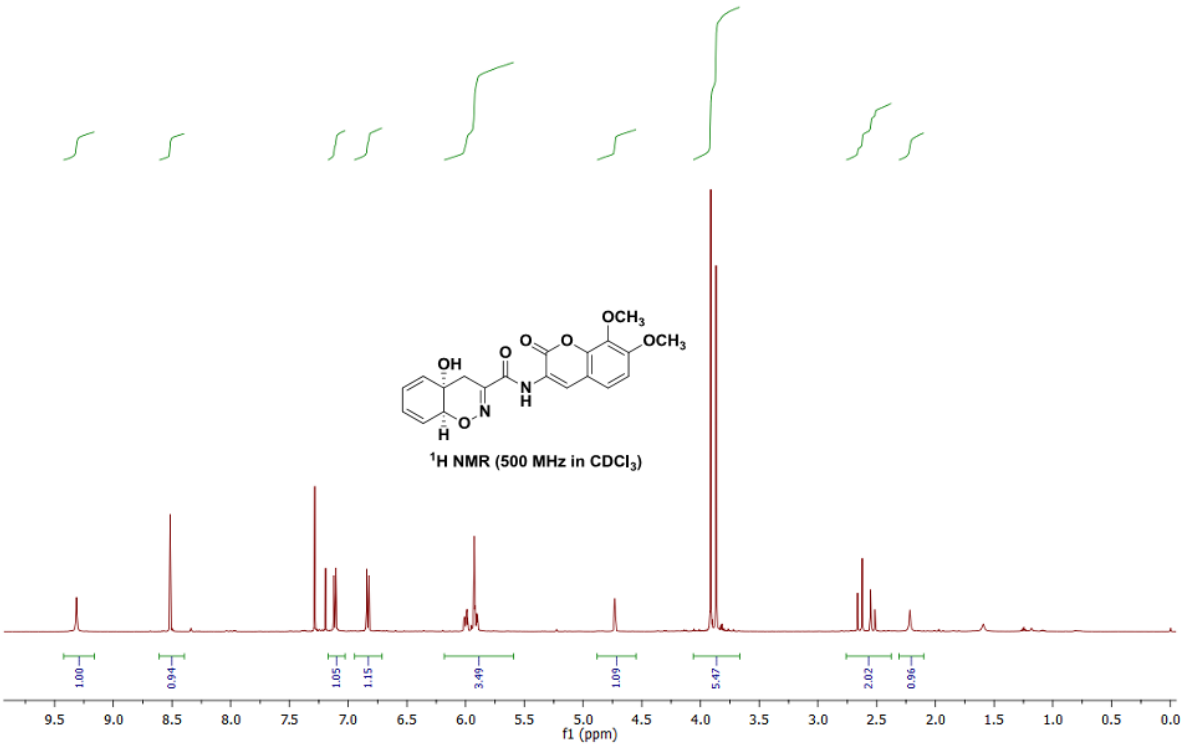


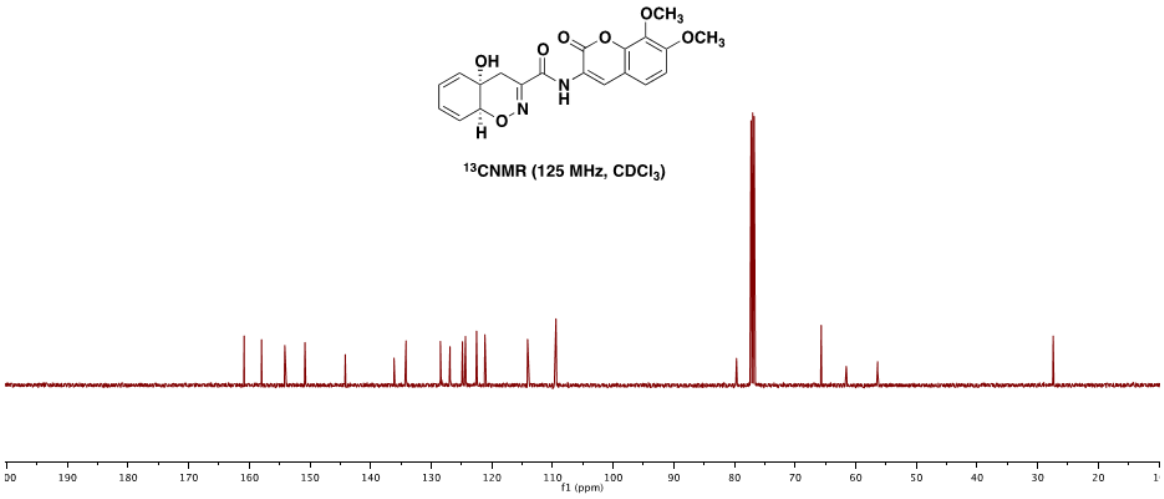
^{1}H NMR (500 MHz in acetone)



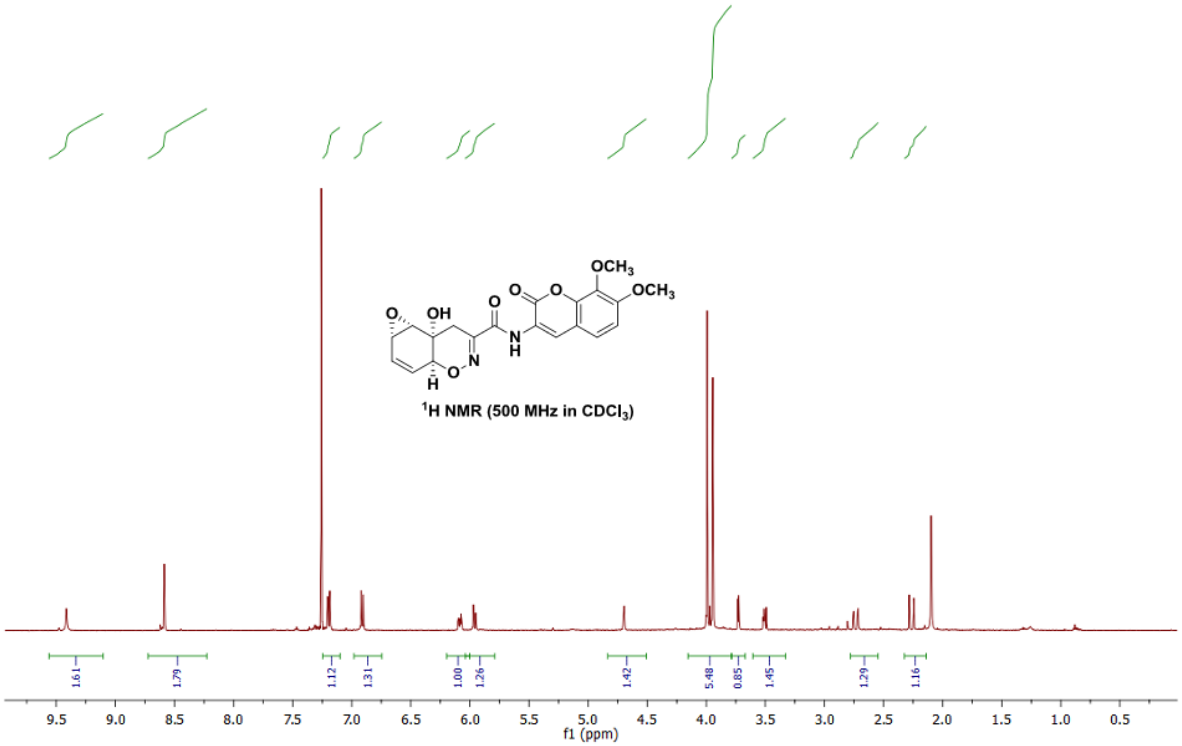
^{13}C NMR (125 MHz in acetone)

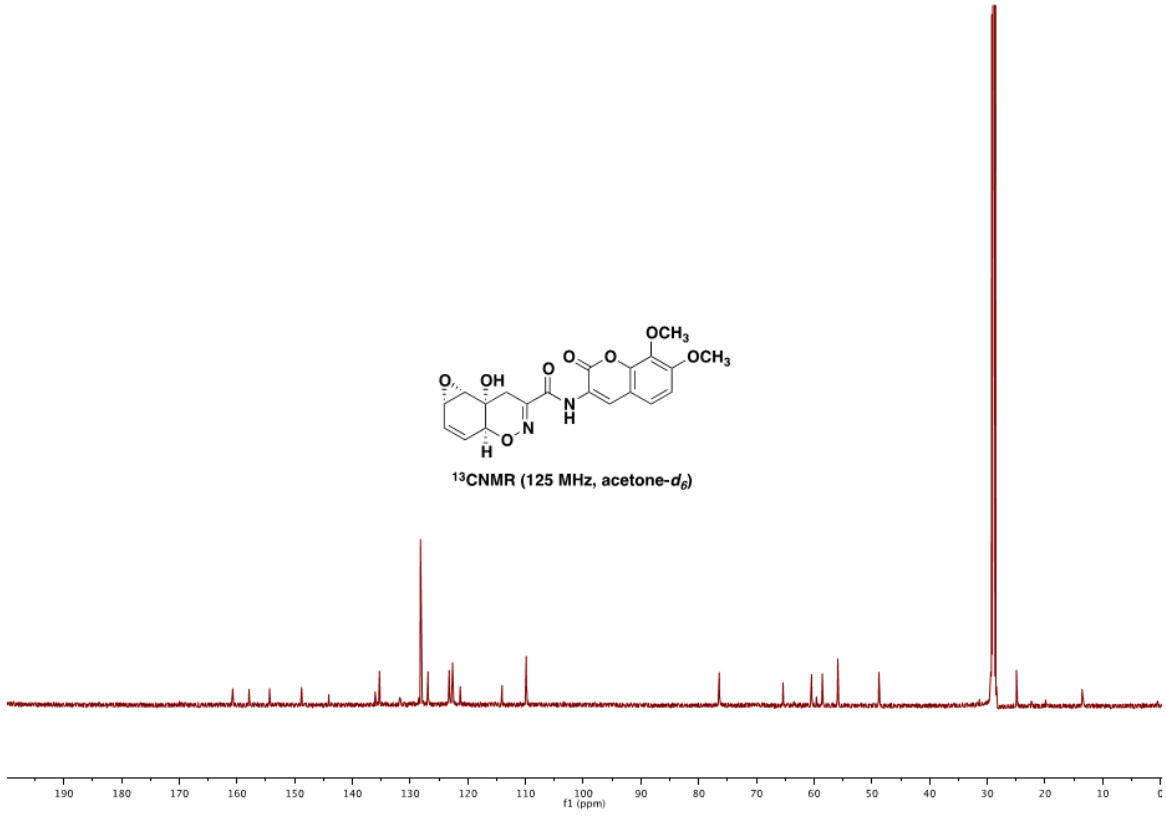
(4a*S*,8a*S***)-*N*-(7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)-4a-hydroxy-4a,8a-dihydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxamide (27)**



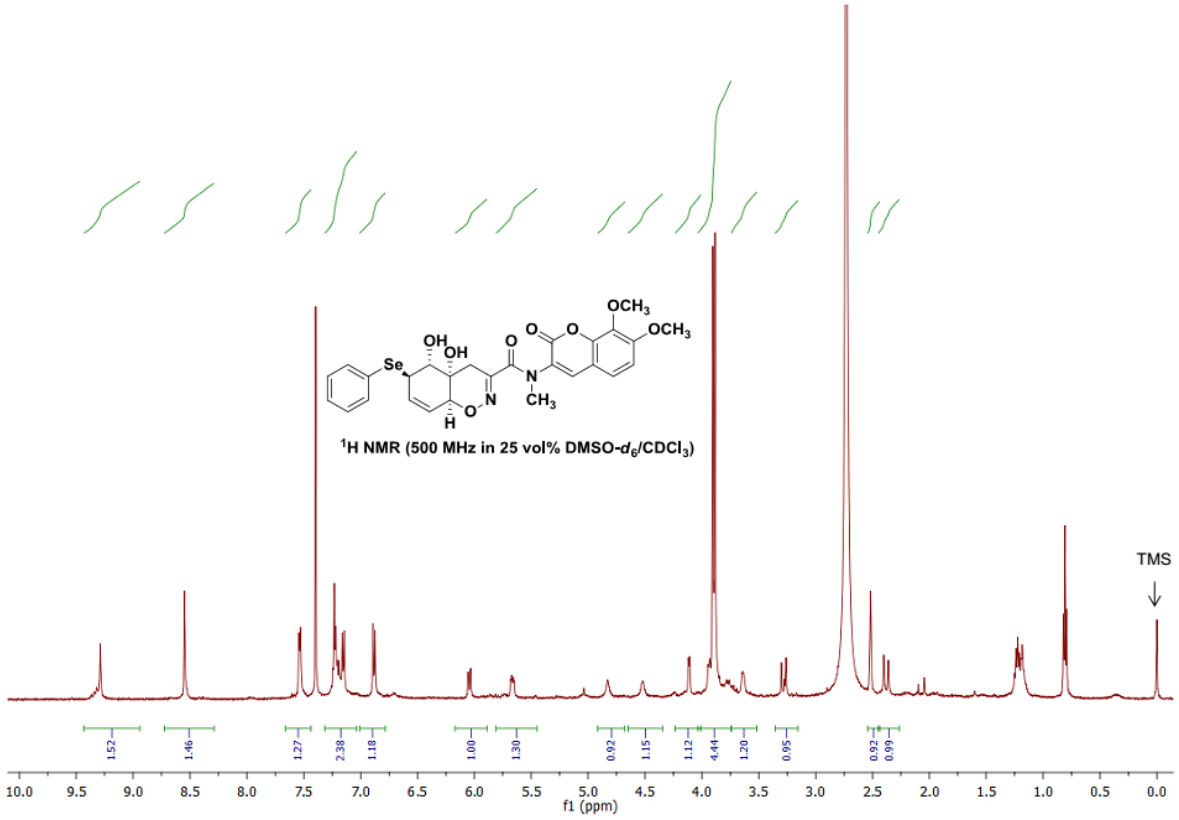


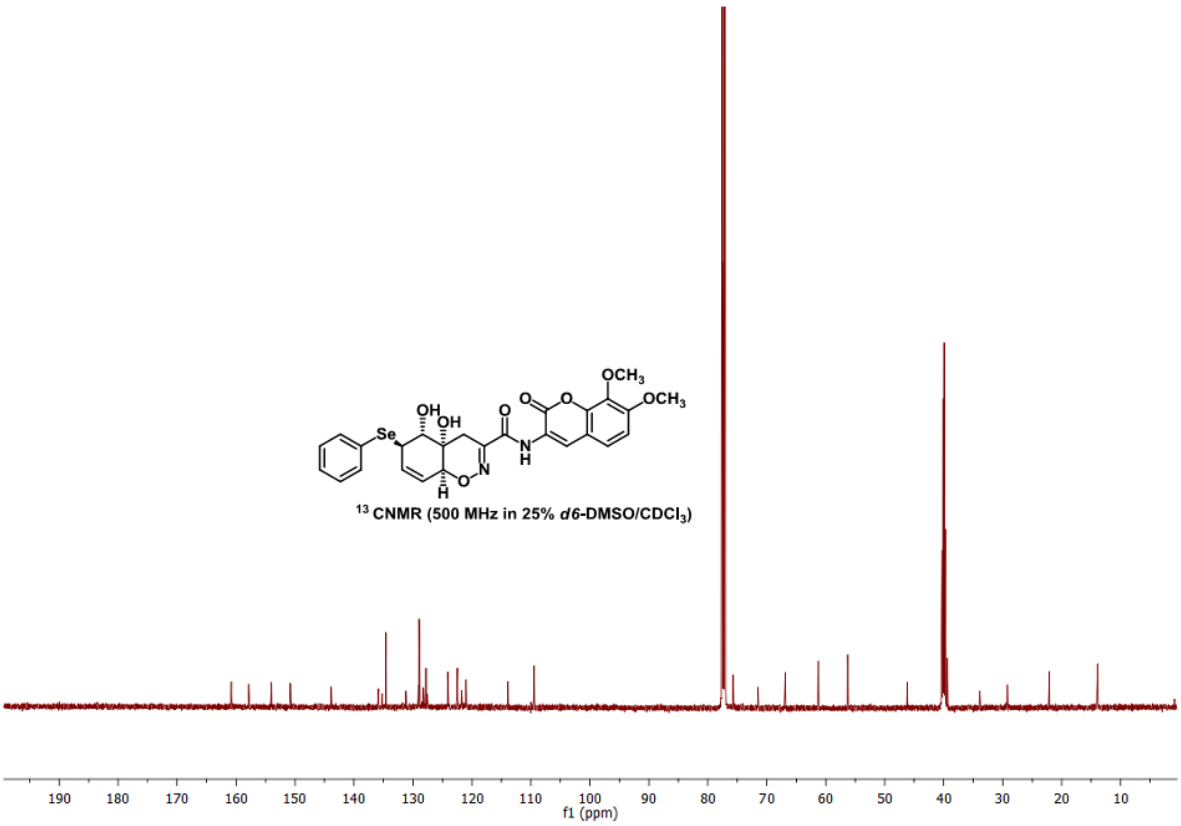
(1a*S*,3a*S***,7a*S***,7b*S***)-*N*-(7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)-7a-hydroxy-3a,7,7a,7b-tetrahydro-1a*H*-oxireno[2',3':5,6]benzo[1,2-e][1,2]oxazine-6-carboxamide (28)**



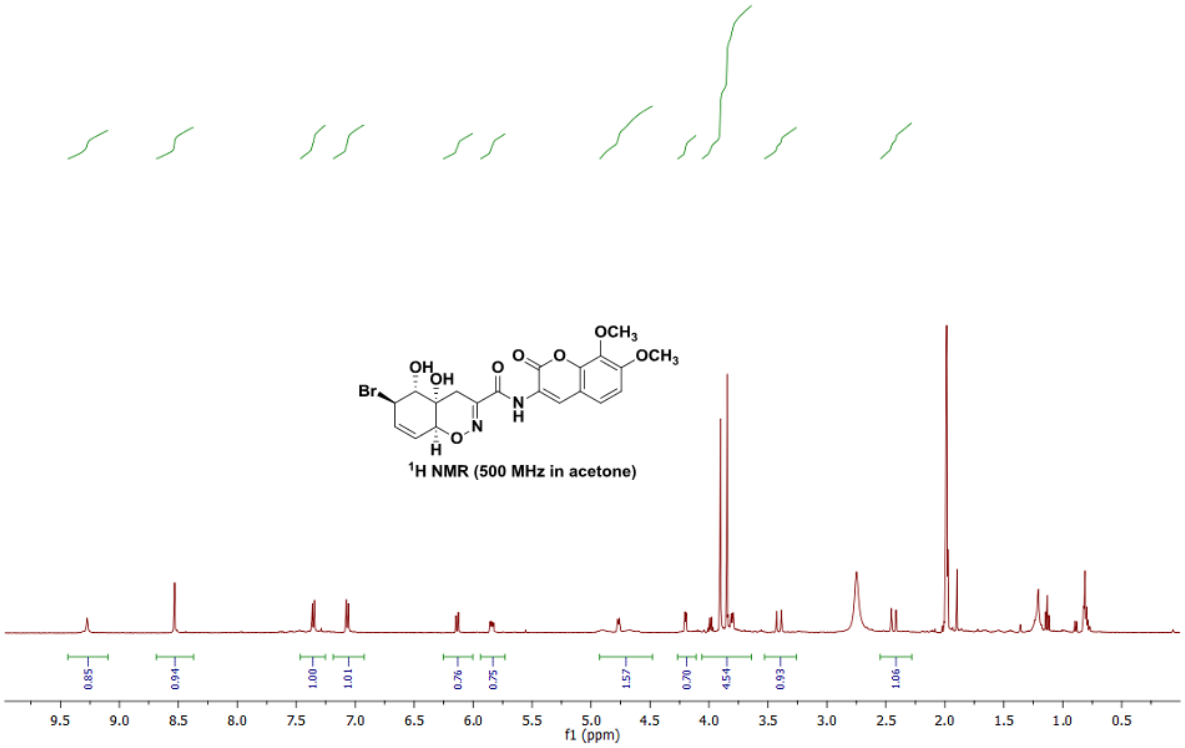


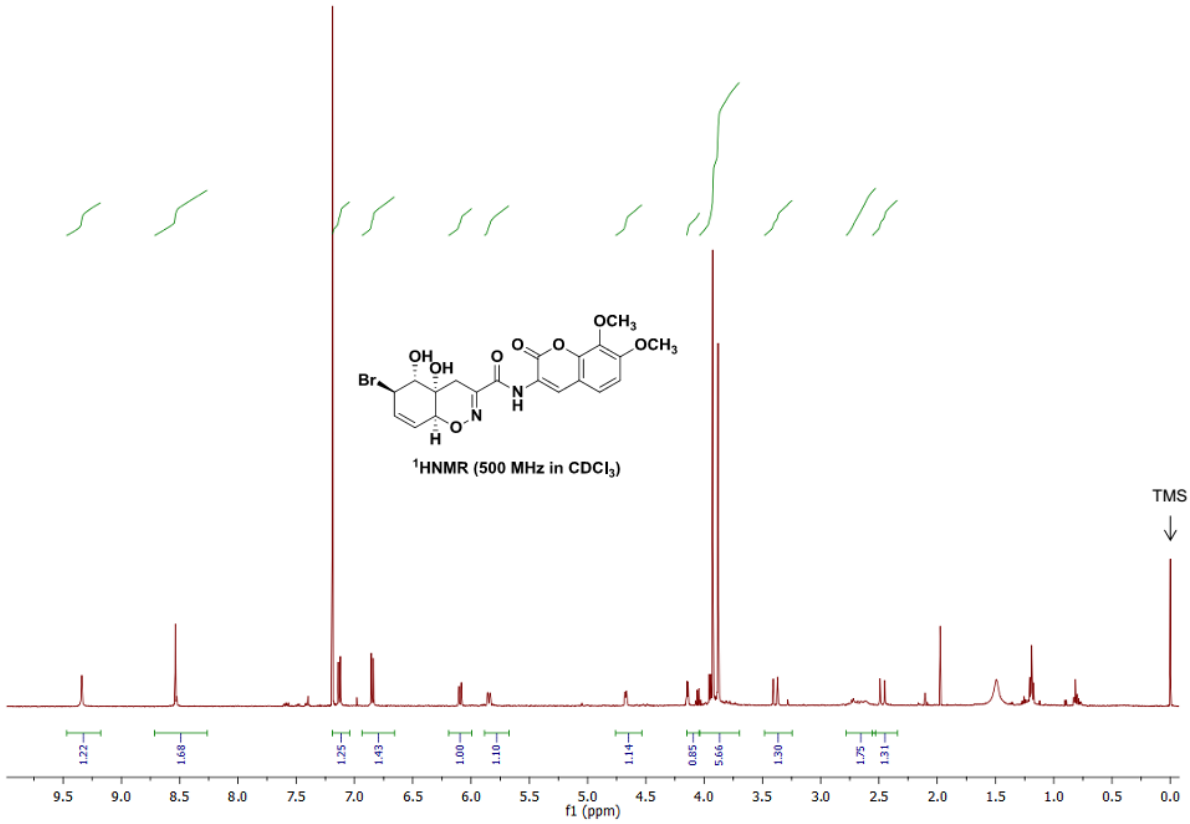
(4a*S,5*R**,6*R**,8a*S**)-*N*-(7,8-dimethoxy-2-oxo-2*H*-chromen-3-yl)-4a,5-dihydroxy-6-(phenylselanyl)-4a,5,6,8a-tetrahydro-4*H*-benzo[e][1,2]oxazine-3-carboxamide (29)**

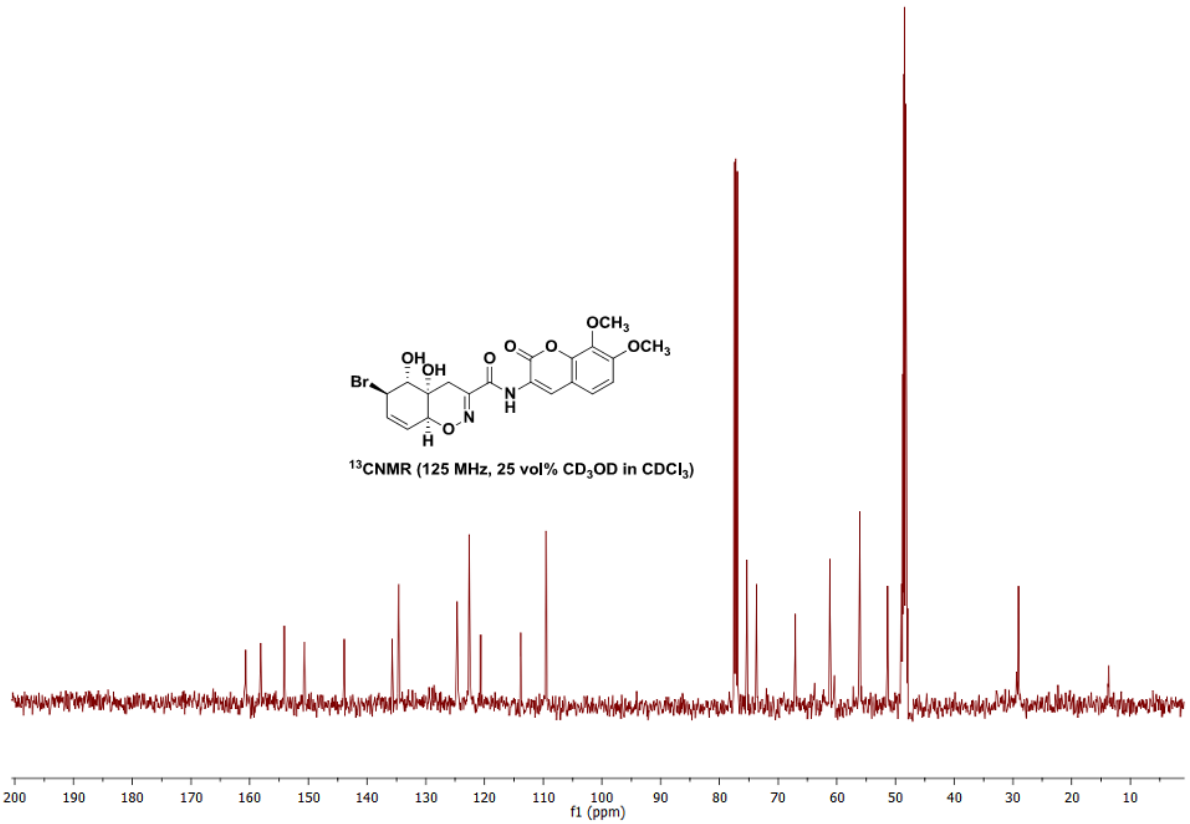




(4a*S,5*R**,6*R**,8a*S**)-6-bromo-*N*-(7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)-4a,5-dihydroxy-4a,5,6,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxamide (S4)**

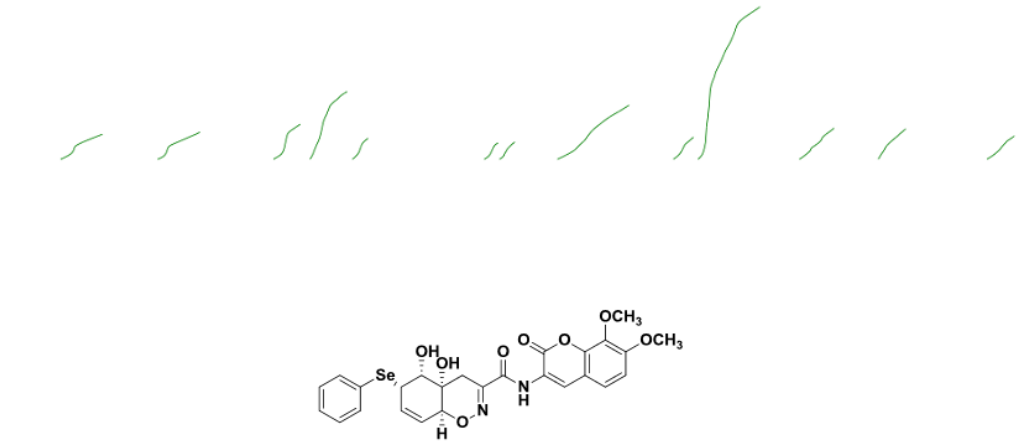




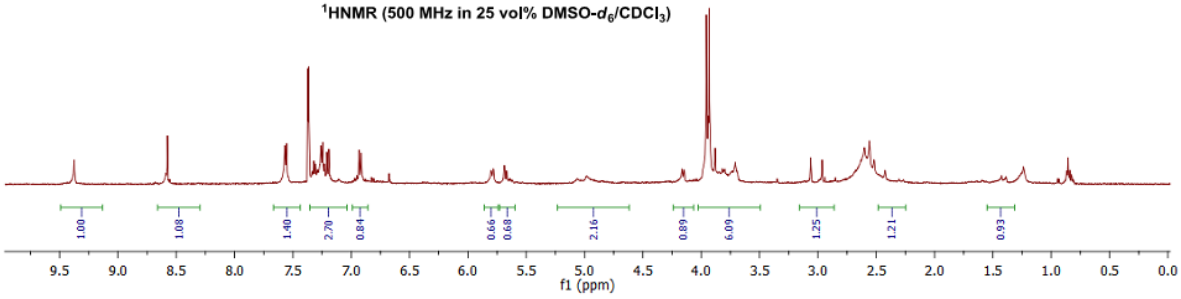


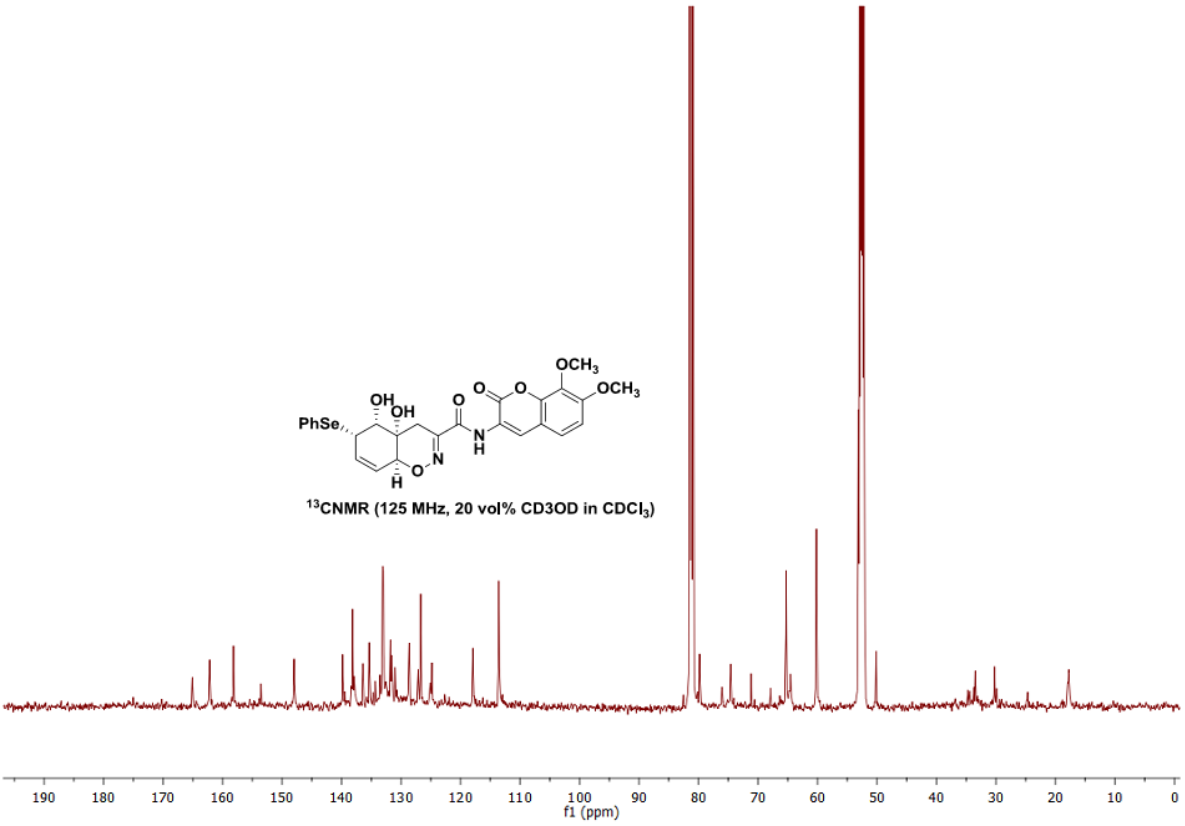
^{13}CNMR (125 MHz, 25 vol% CD_3OD in $CDCl_3$)

(4a*S,5*R**,6*S**,8a*S**)-*N*-(7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)-4a,5-dihydroxy-6-(phenylselanyl)-4a,5,6,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazine-3-carboxamide (S5)**



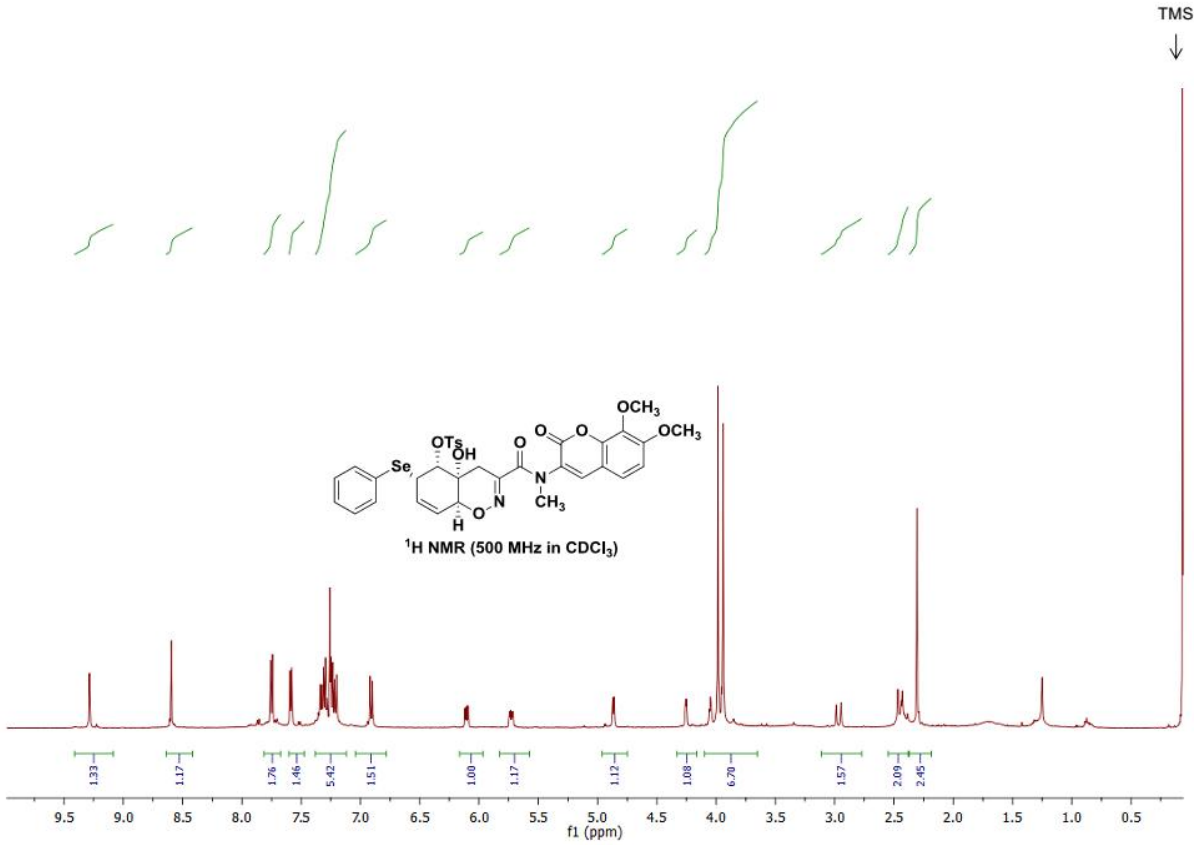
^{1}HNMR (500 MHz in 25 vol% DMSO-d_6/$CDCl_3$)

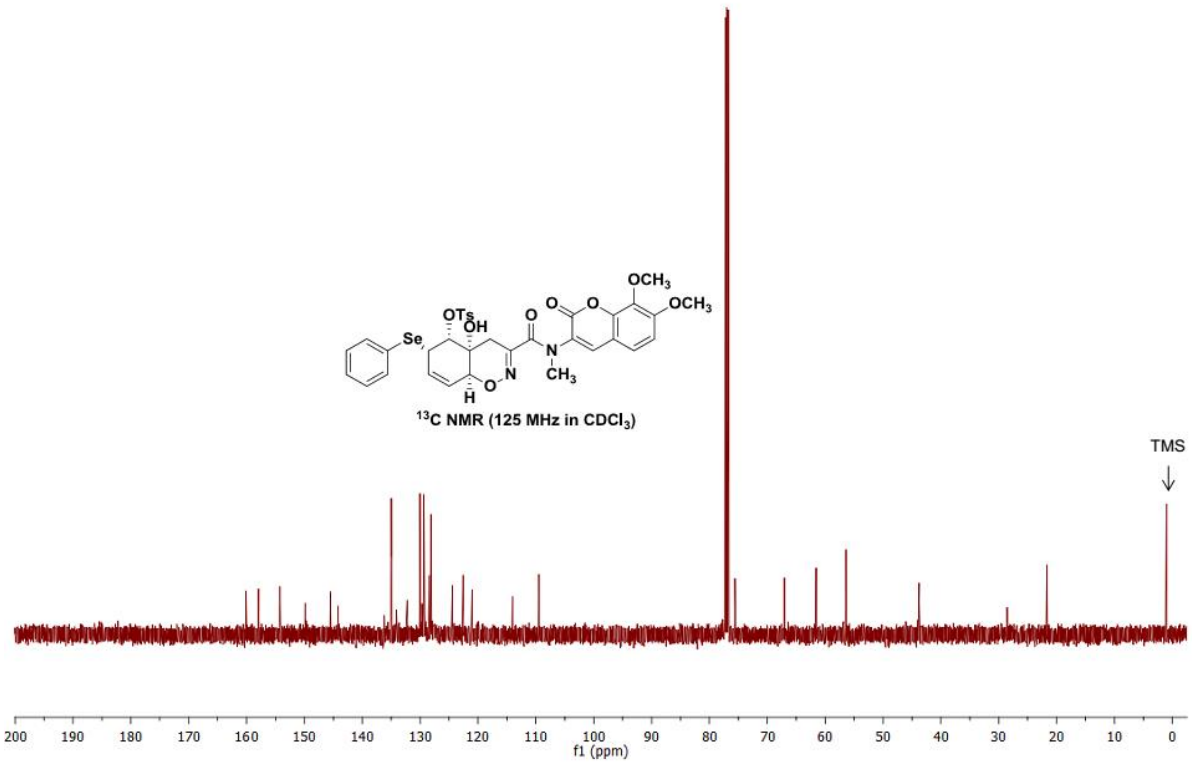




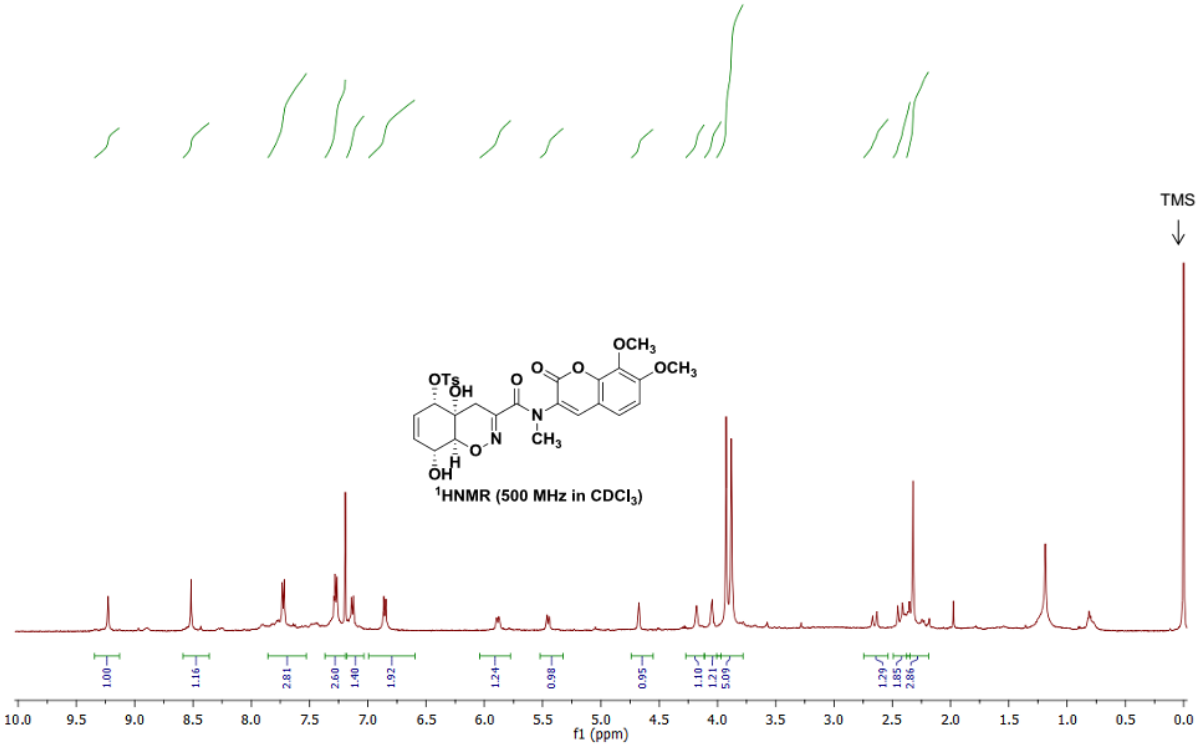
^{13}CNMR (125 MHz, 20 vol% CD3OD in $CDCl_3$)

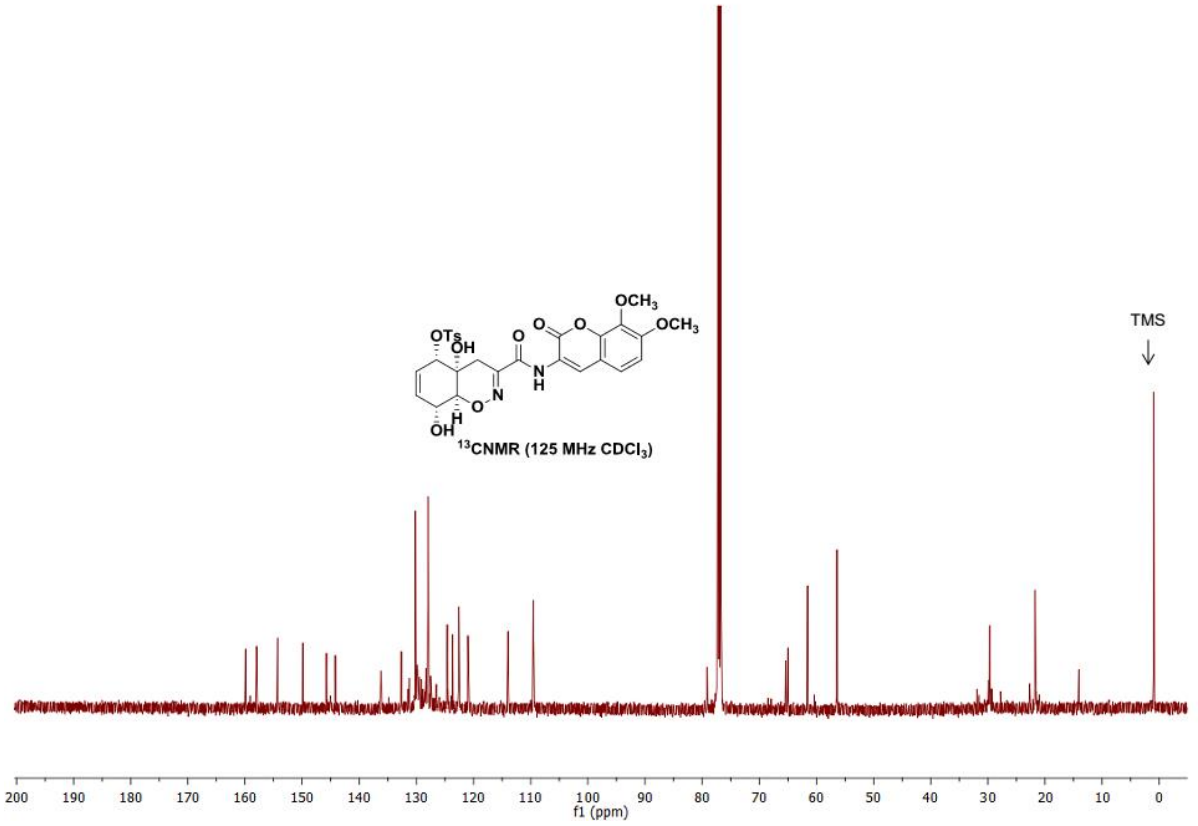
(4a*R,5*R**,6*S**,8a*S**)-3-((7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)carbamoyl)-4a-hydroxy-6-(phenylselanyl)-4a,5,6,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazin-5-yl 4-methylbenzenesulfonate (31)**



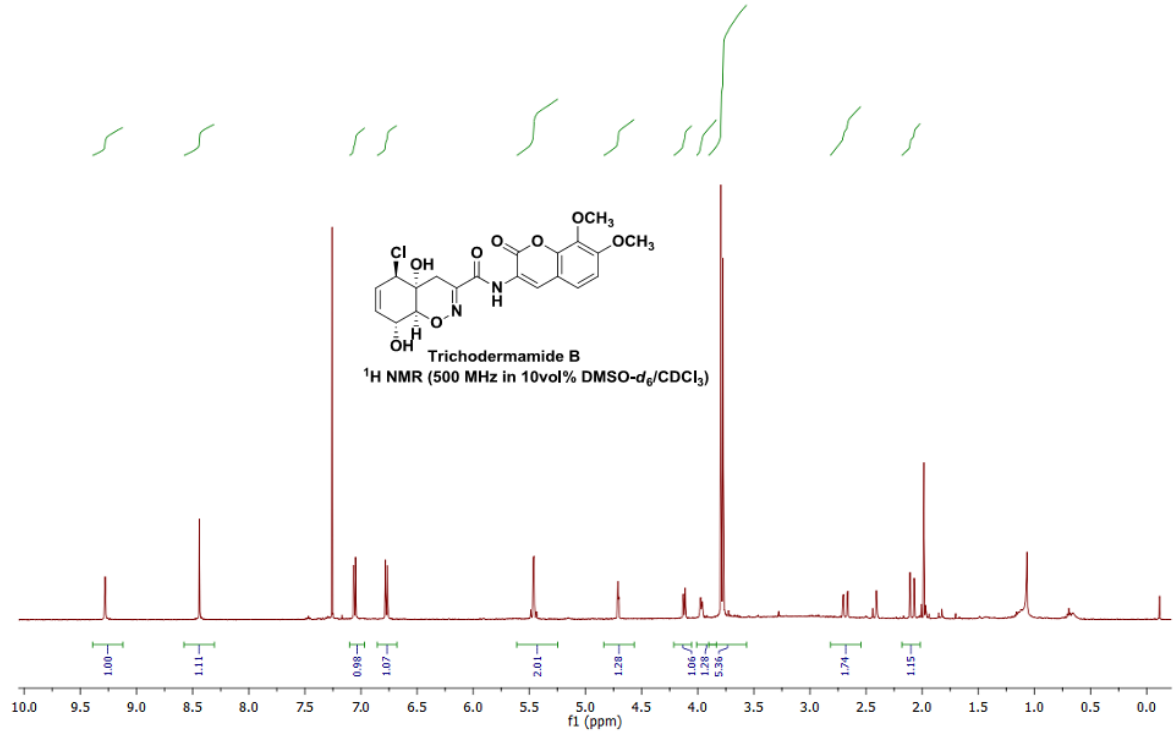


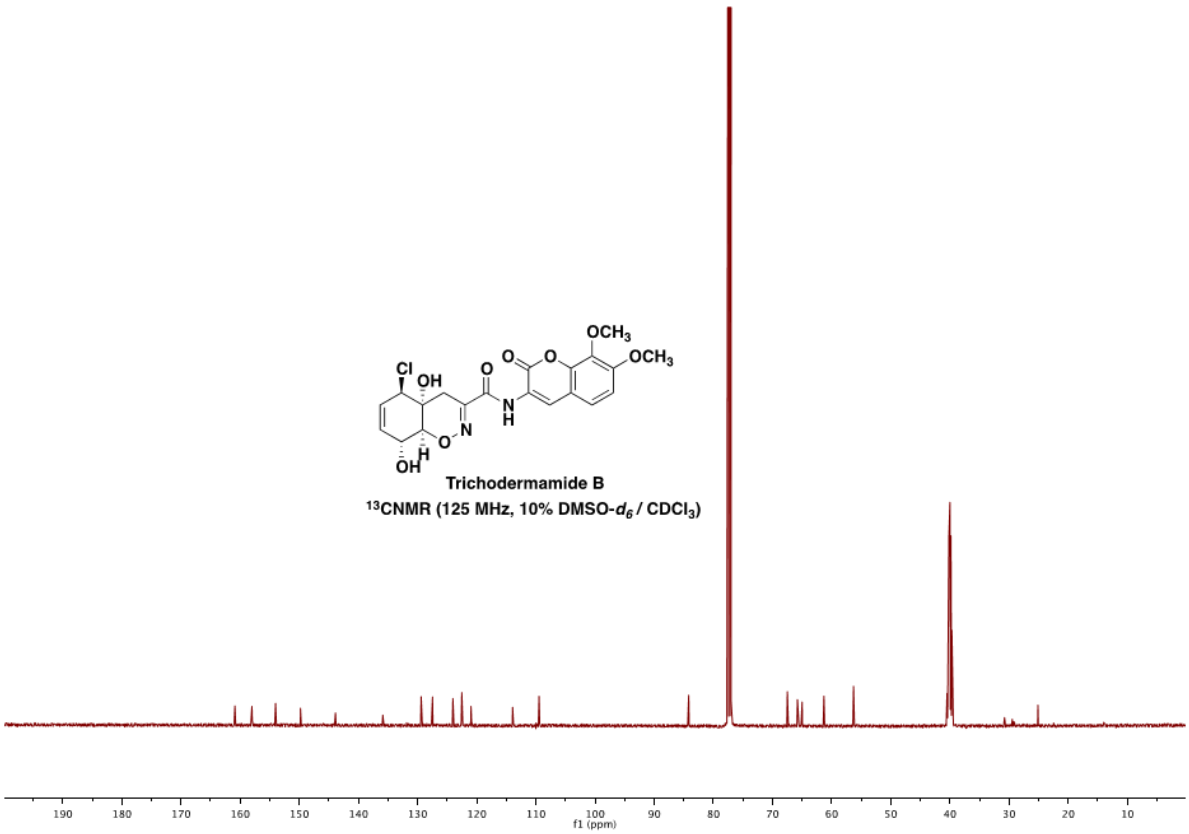
(4a*R,5*S**,8*R**,8a*S**)-3-((7,8-Dimethoxy-2-oxo-2*H*-chromen-3-yl)carbamoyl)-4a,8-dihydroxy-4a,5,8,8a-tetrahydro-4*H*-benzo[*e*][1,2]oxazin-5-yl 4-methylbenzenesulfonate (S6)**

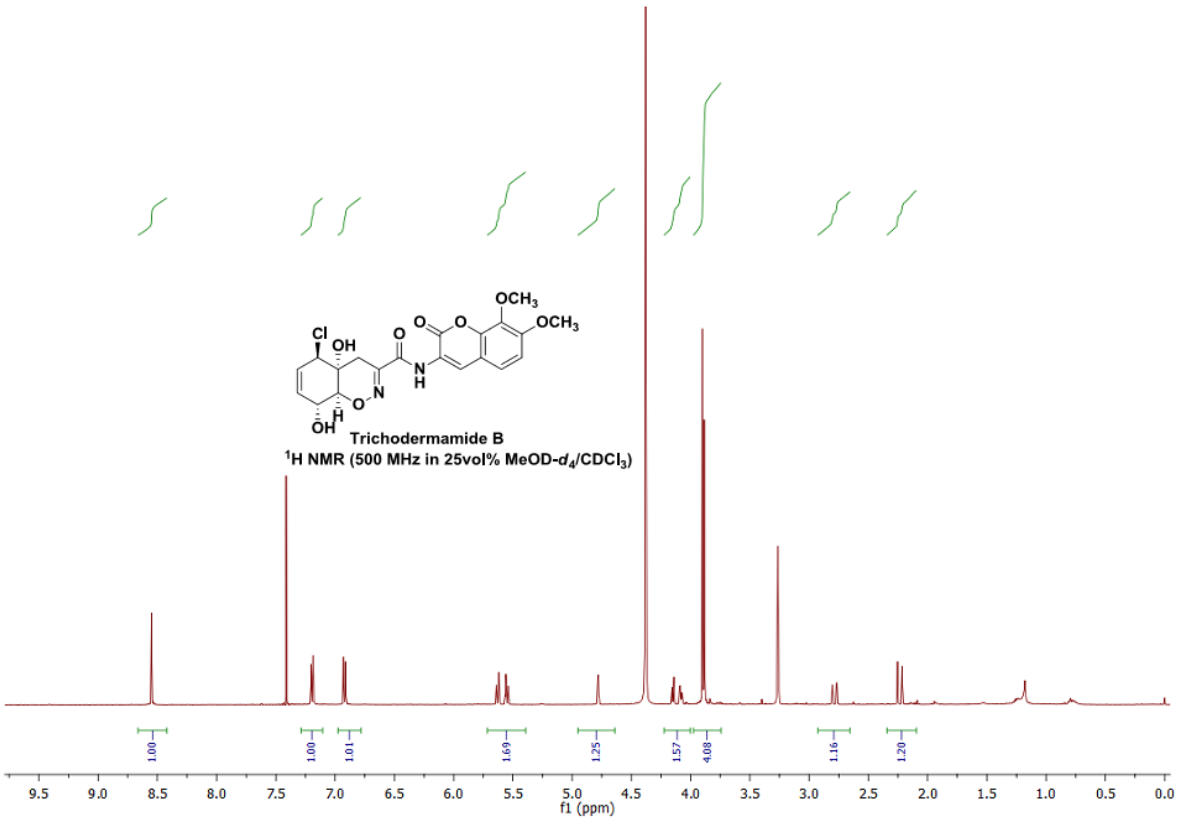


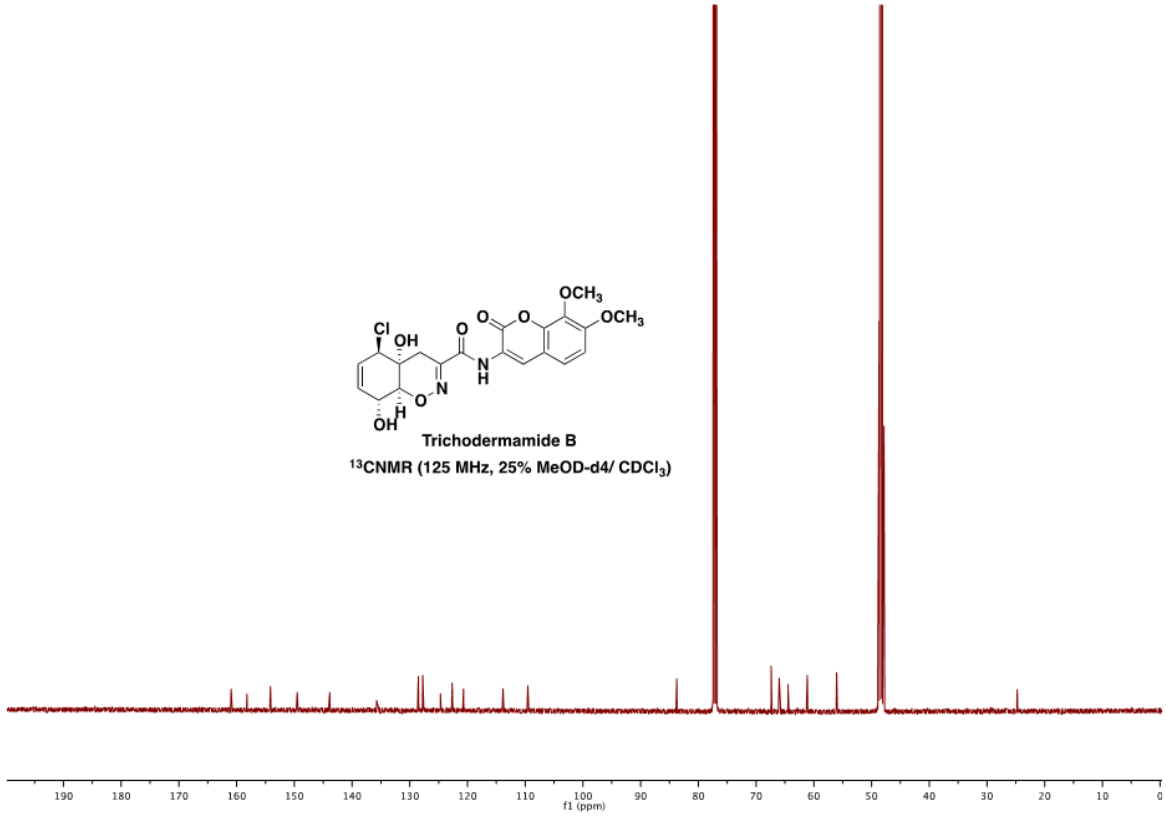


Trichodermamide B (2)

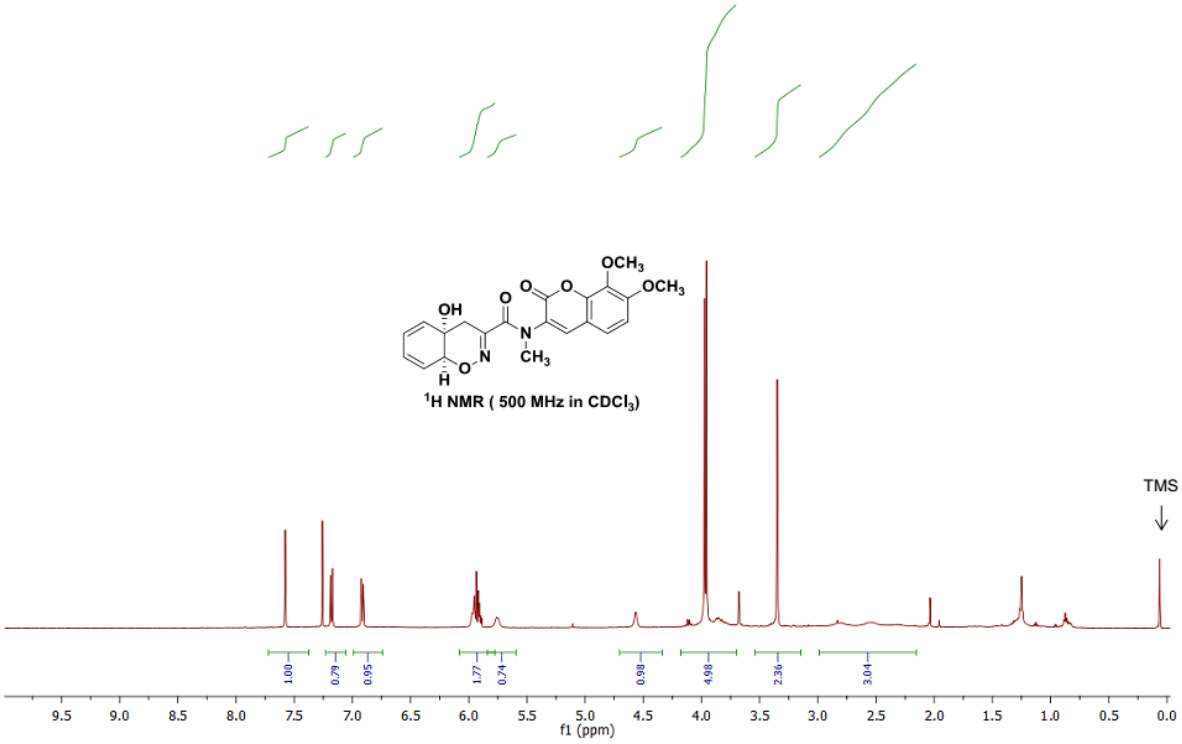


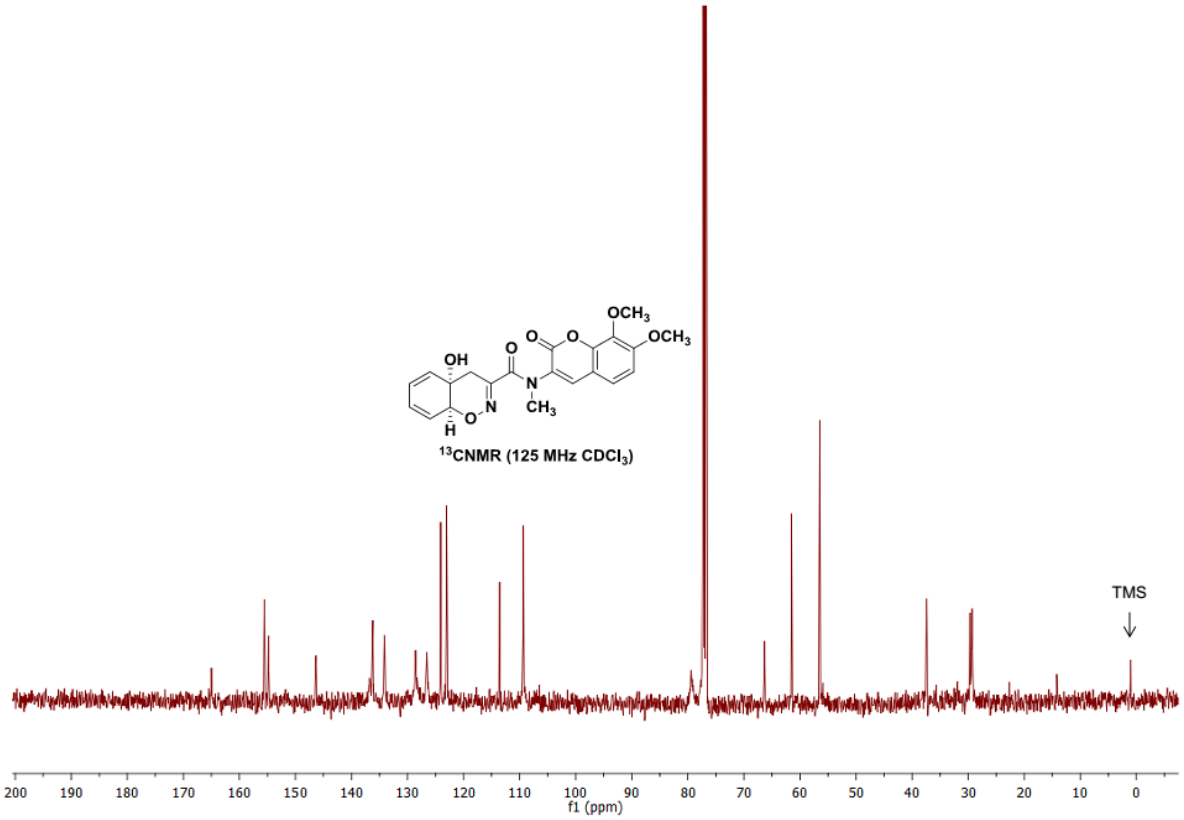



Trichodermamide B
^{1}H NMR (500 MHz in 25vol% MeOD-d_4/$CDCl_3$)
1.00
1.00
1.01
1.69
1.25
1.57
4.08
1.16
1.20
f1 (ppm)

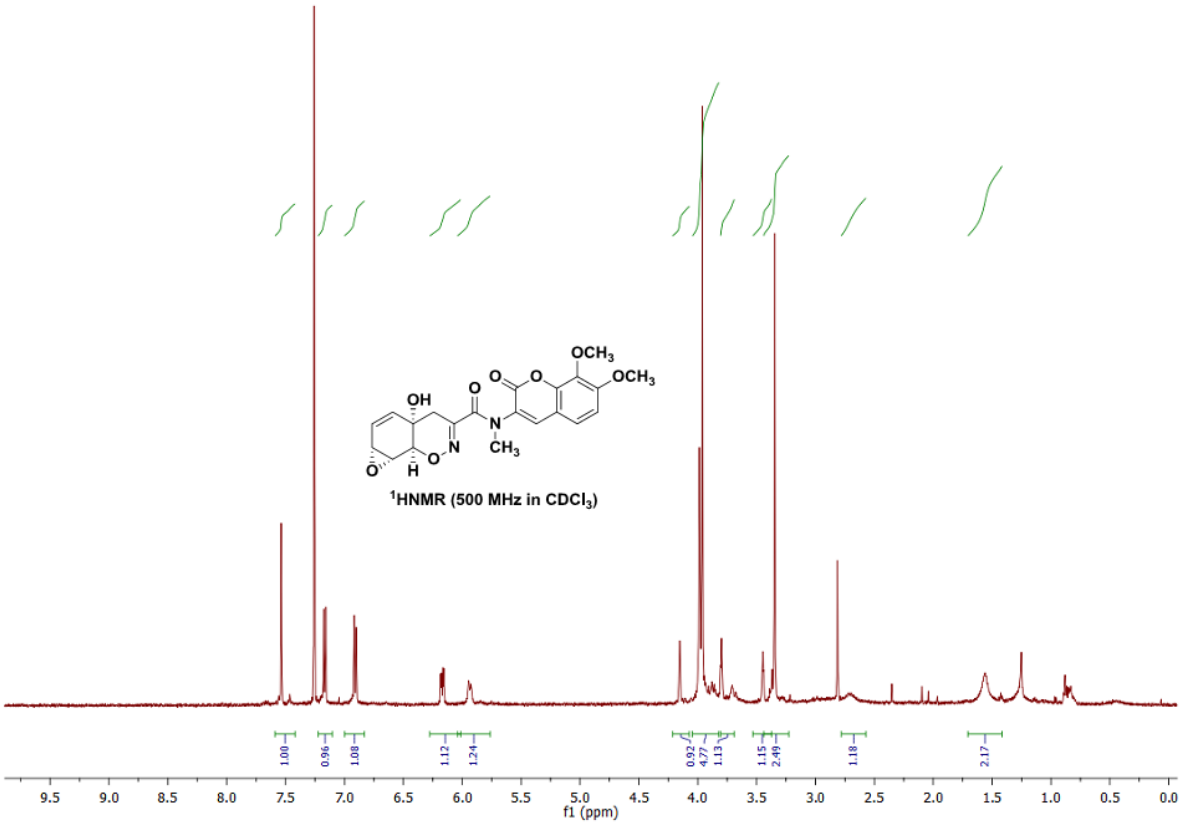

Trichodermamide B
^{13}CNMR (125 MHz, 25% MeOD-d4/ $CDCl_3$)
f1 (ppm)

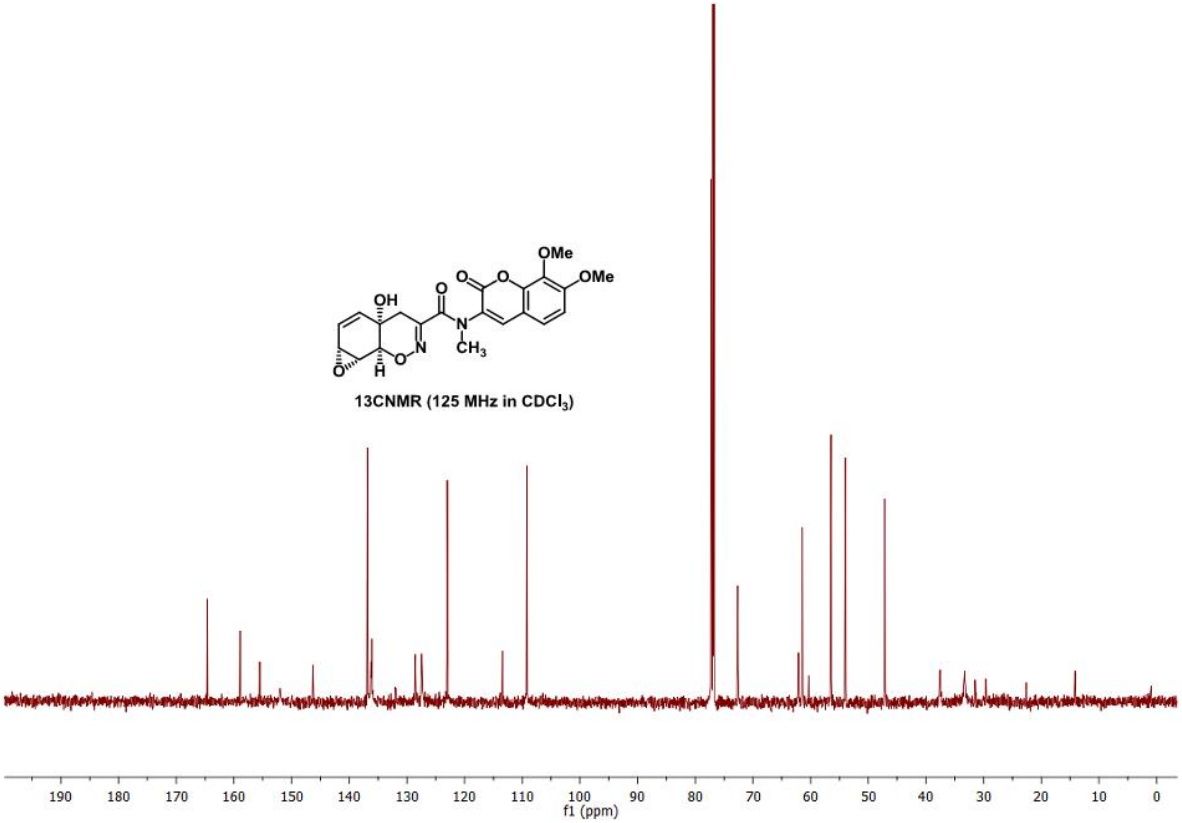
(4a*S,8a*S**)-*N*-(7,8-dimethyoxy-2-oxo-2*H*-chromen-3-yl)-4a-hydroxy-*N*-methyl-4a,8a-dihydro-4*H*-benzo[e][1,2]oxazine-3-carboxamide (S7)**



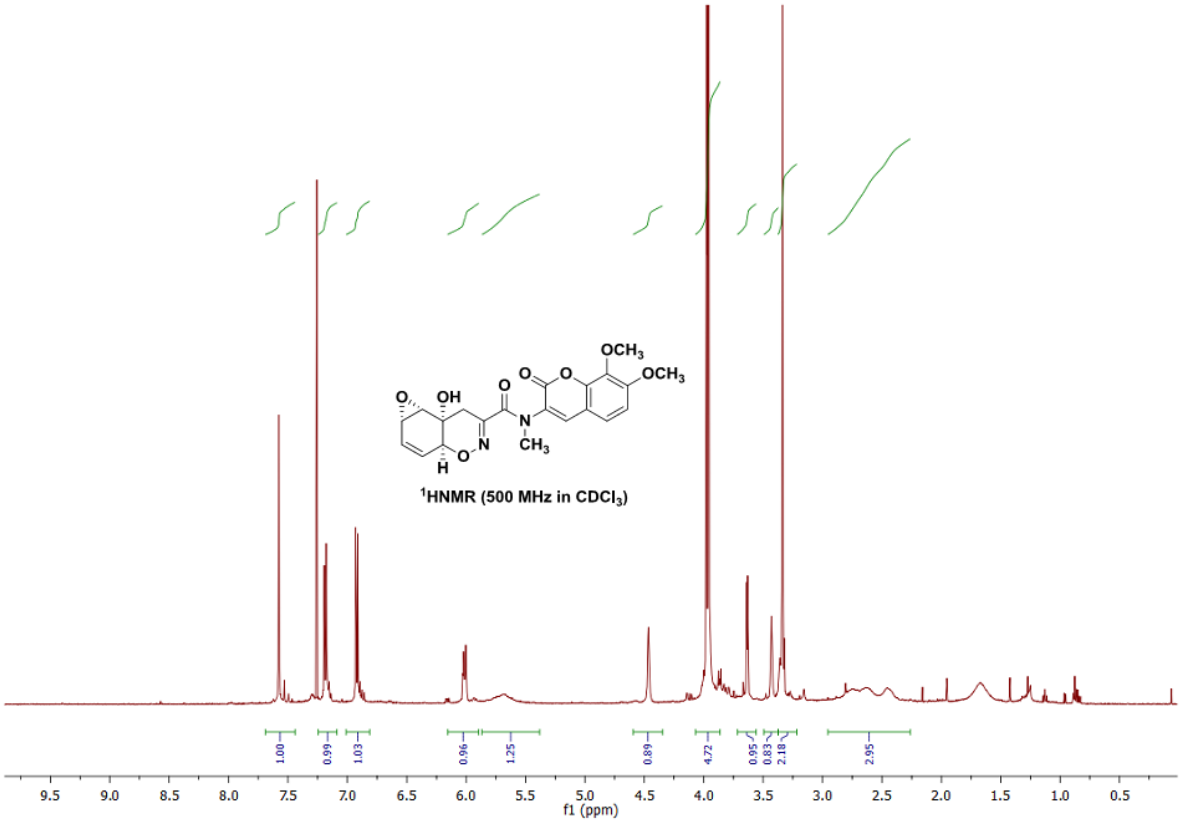


(4a*S*,6a*R***,7a*R***,7b*S***)-*N*-(7,8-dimethoxy-2-oxo-2*H*-chromen-3-yl)-4a-hydroxy-*N*-methyl-4a,6a,7a,7b-tetrahydro-4*H*-oxireno[2',3':3,4]benzo[1,2-e][1,2]oxazine-3-carboxamide (32)**

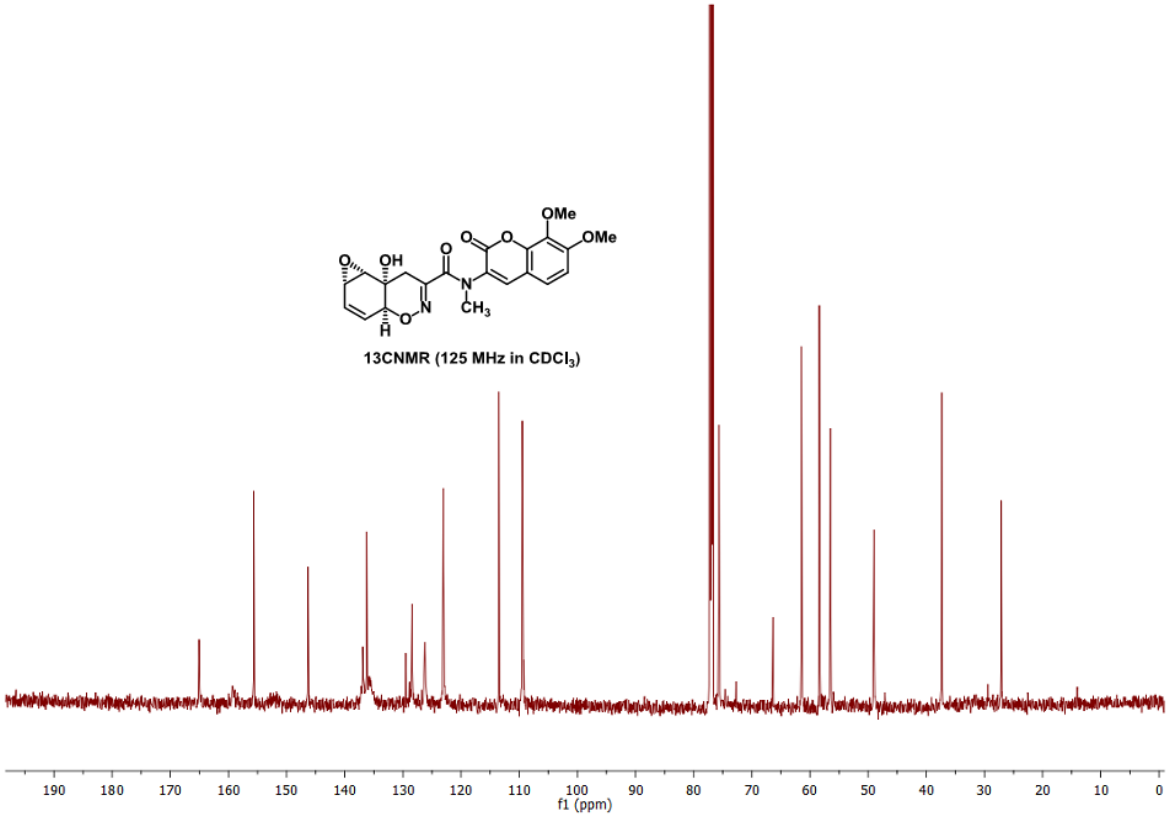




(1a*S,3a*S**,7a*S**,7b*S**)-*N*-(7,8-dimethoxy-2-oxo-2*H*-chromen-3-yl)-7a-hydroxy-*N*-methyl-3a,7,7a,7b-tetrahydro-1a*H*-oxireno[2',3':5,6]benzo[1,2-e][1,2]oxazine-6-carboxamide (S8)**

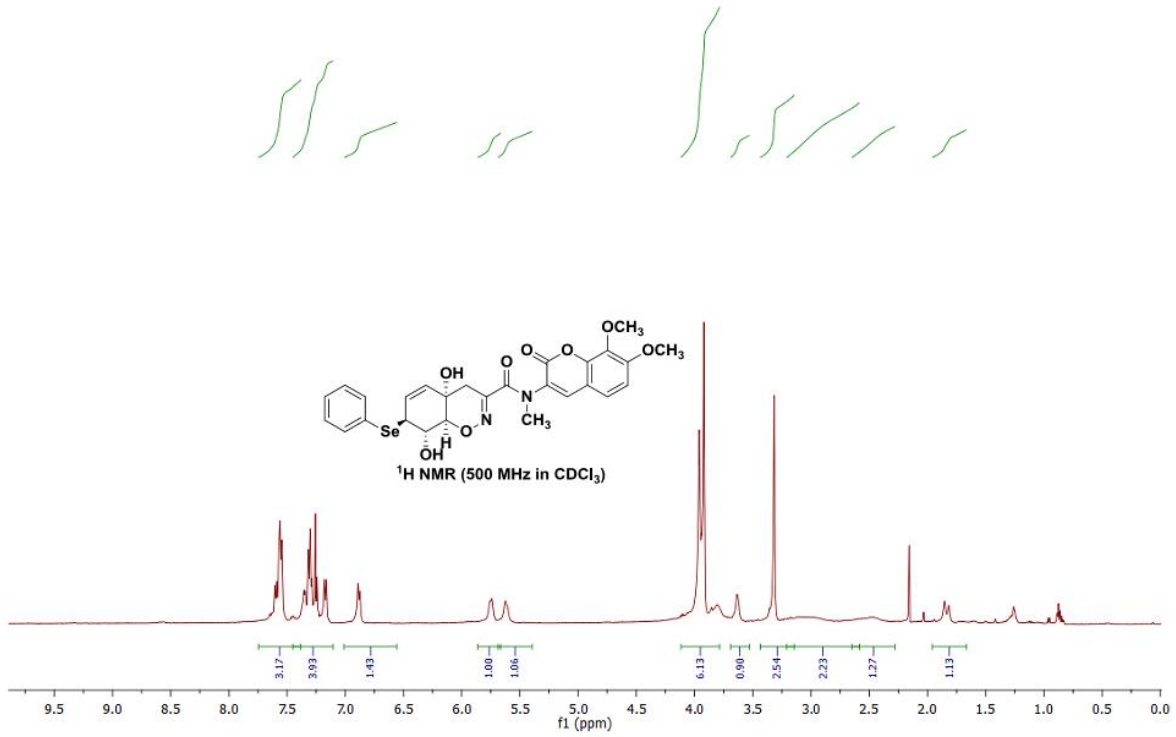


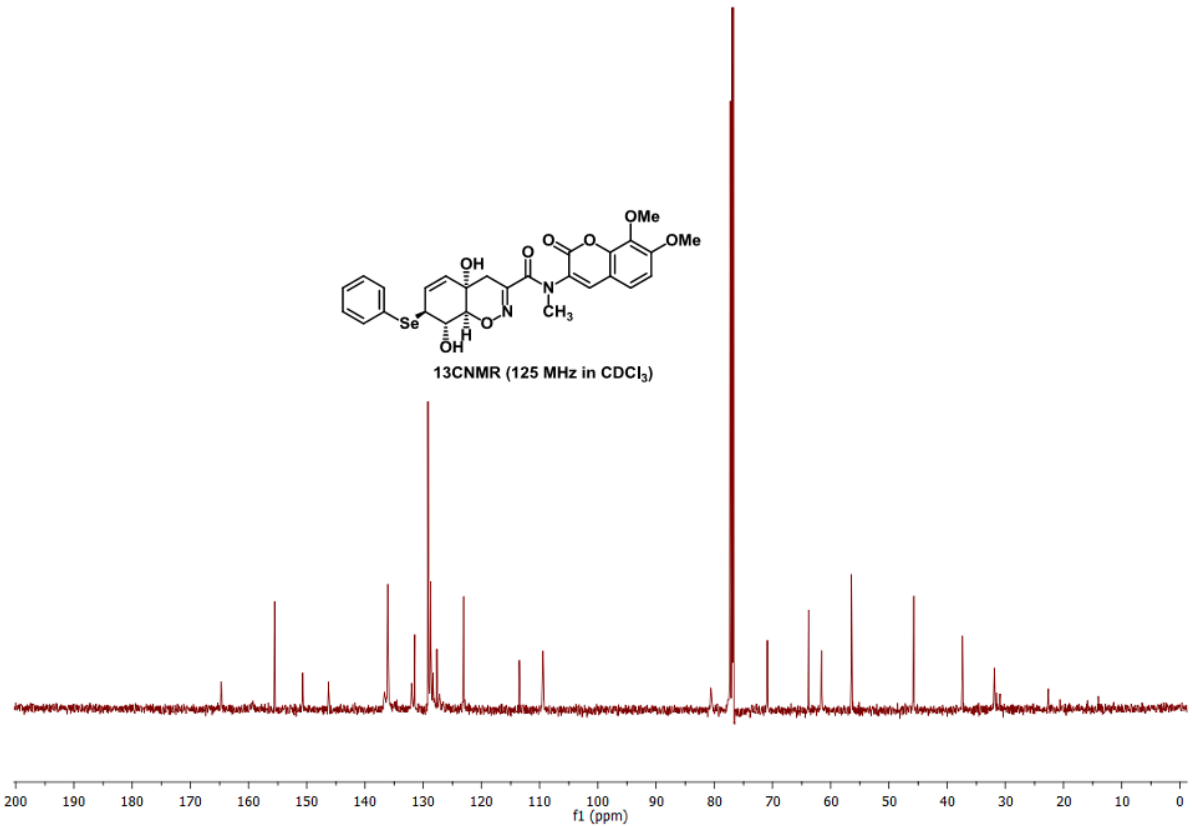
^{1}HNMR (500 MHz in $CDCl_3$)



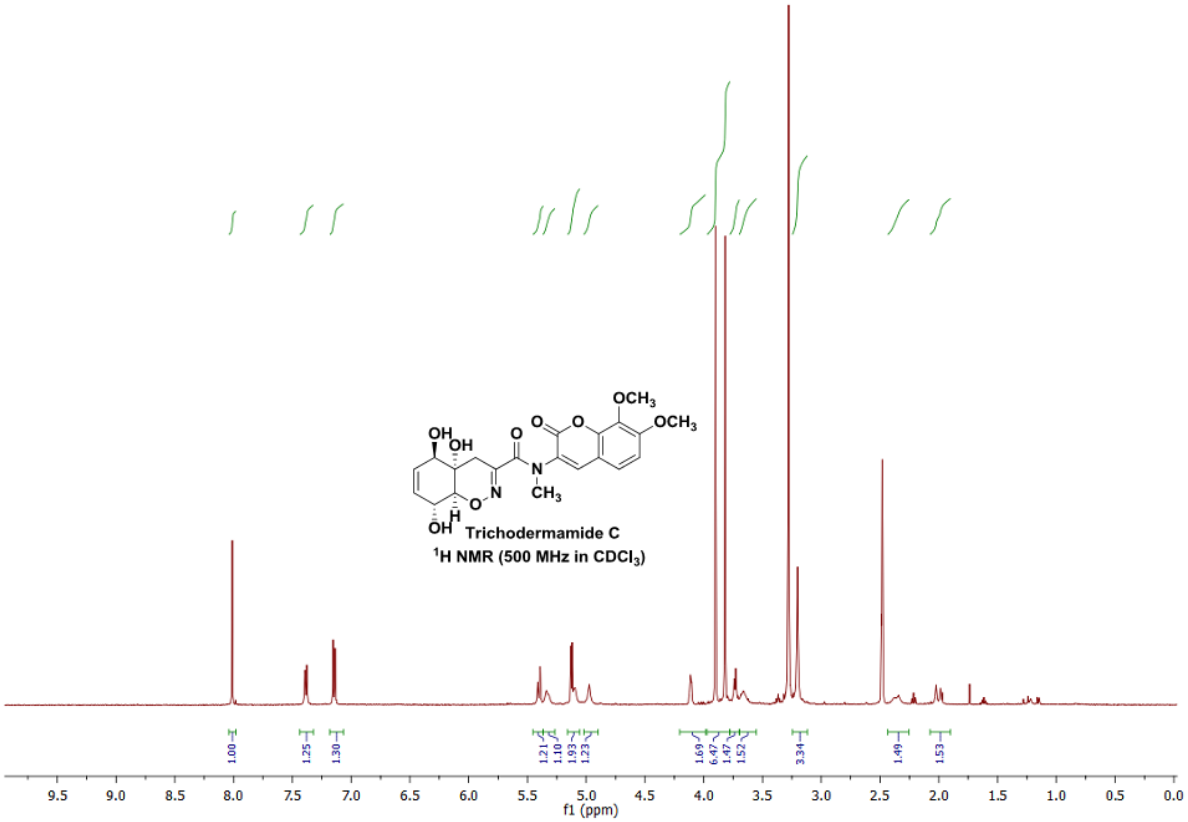
13CNMR (125 MHz in $CDCl_3$)

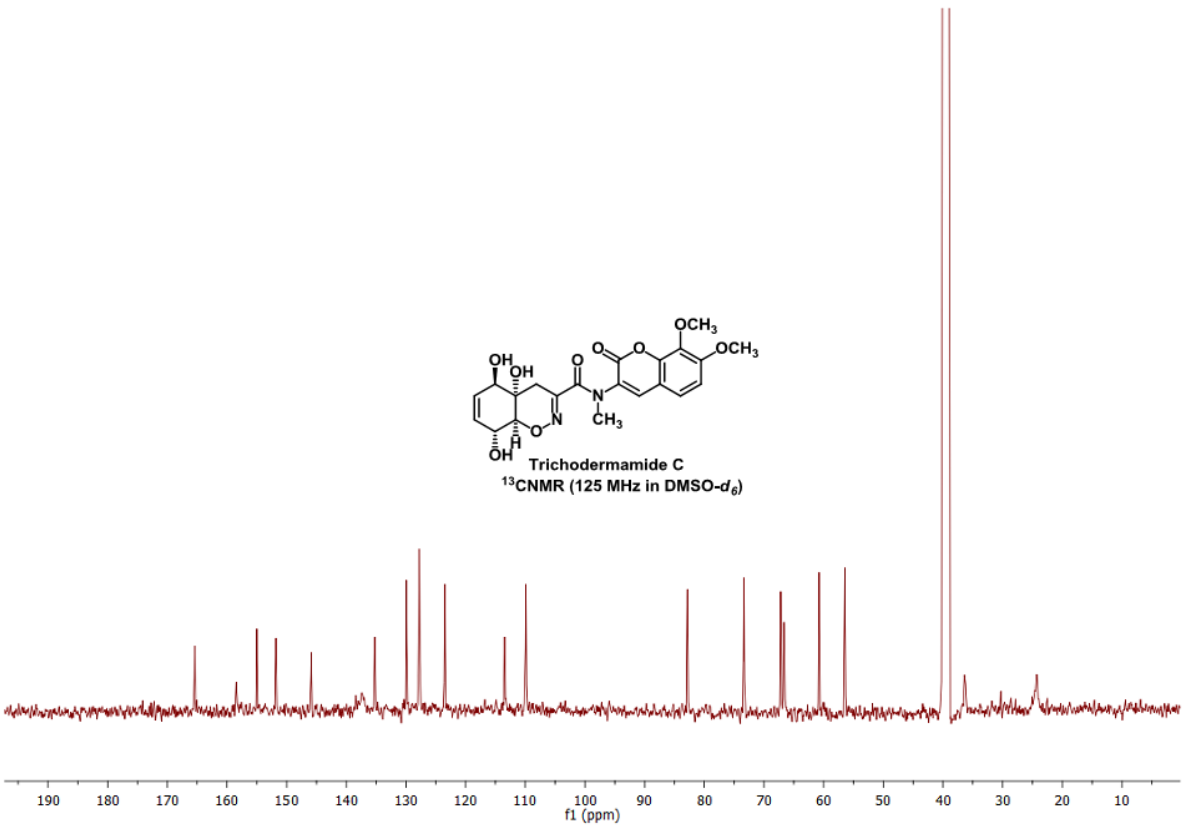
(4a*S*,7*S***,8*S***,8a*S***)-*N*-(7,8-dimethoxy-2-oxo-2*H*-chromen-3-yl)-4a,8-dihydroxy-*N*-methyl-7-(phenylselanyl)-4a,7,8,8a-tetrahydro-4*H*-benzo[e][1,2]oxazine-3-carboxamide (S9)**





Trichodermamide C (3)





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