# Electronic Supporting Information

**Manuscript**: Synthetic studies on the reverse antibiotic natural products, the nybomycins

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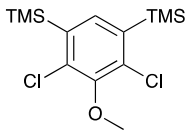
**Synthetic Procedures**

(4,6-Dichloro-5-methoxy-1,3-phenylene)bis(trimethylsilane) (**19**).




**20** was obtained following experimental procedures previously described by Hergenrother and co-workers and their spectroscopic data correspond with those reported.[1,2]

LDA Prep

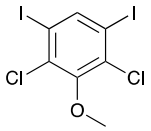
To a stirred solution of diisopropylamine (17.8 mL) in dry tetrahydrofuran (THF) (132.2 mL) at -78 °C (dry ice, isopropanol (IPA) bath) was added *n*-butyl lithium (*n*-BuLi) (2.5 M, 100 mL) dropwise. The solution was stirred for 30 min at -78 °C then transferred to an ice bath for temporary storage.

Reaction

To a stirred solution of 2,6-dichloroanisole (13.6 mL, 99 mmol) in dry THF (80 mL), under $N_2$, at -78 °C (dry ice, IPA bath) was added fresh LDA (1 M, 118.6 mL, 119 mmol) dropwise. The reaction mixture was stirred for 3 h taking care to keep the temperature between -78 °C to -65 °C. After this time had passed, TMSCl (15.0 mL, 119 mmol) was added dropwise and stirred for 1 h, keeping the temperature below -65 °C. The second portion of LDA (1 M, 128.5 mL, 129 mmol) was then added dropwise and stirred for 3.5 h. After the allotted time, TMSCl (17.5 mL, 129 mmol) was added and stirred for 18 h, while slowly allowing to -40 °C.

Water (50 mL) was added to quench the reaction. This turned the cloudy yellow solution to clear and colourless. HCl (1 M, 100 mL) was added and the product was extracted with EtOAc (2 x 150 mL). The organic phases were combined and washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The afforded the title compound **19** (33.4 g, quantitative yield) as an off white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.27 (s, 1H), 3.89 (s, 3H), 0.37 (s, 18H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 151.8, 138.6, 136.9, 136.6, 60.5, -0.6. TOF MS ES$^+$ (m/z): $[M+]^+$ calc'd for $C_{13}H_{22}OCl_2Si_2$: 320.0586; found: 320.0590.

2,4-dichloro-1,5-diiodo-3-methoxybenzene (**5**)



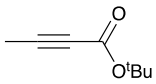

**5** was obtained following experimental procedures previously described by Hergenrother and co-workers and their spectroscopic data correspond with those reported.[1,2]

To a stirred solution of ICl (1 M in DCM, 100 mL, 97 mmol) at 0 °C was added 4,6-dichloro-5-methoxy-1,3-phenylene)bis(trimethylsilane) (**19**) (21.8 g, 67.8 mmol) in DCM (80 mL) dropwise, taking care to control the exotherm. After the addition was complete, the reaction mixture was stirred at room temperature for 2 h.

After completion of the reaction, monitored by TLC (100 % pentane), $NaHSO_3$ (10 % in water, 60 mL) was added to quench the reaction. The desired product was extracted with EtOAc (2 x 80 mL) and the organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated.

The crude product was purified by recrystallization from hexane. This yielded 2,4-dichloro-1,5-diiodo-3-methoxybenzene (**5**) (25.0 g, 86 %) as yellow needles. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.17 (s, 1H), 3.90 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 152.6, 144.3, 135.0, 97.6, 60.8. TOF MS ES$^+$ (m/z): [M+]$^+$ calc'd for $C_7H_4OCl_2I_2$: 427.7729; found: 427.7712.

*tert*-Butyl but-2-ynoate (**17**)

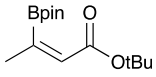



**17** was obtained following experimental procedures previously described by Otaka and co-workers.[3]

To a stirred solution of 1-bromoprop-1-ene (9.7 mL, 113.6 mmol) in dry THF (120 mL) under $N_2$ at -78 °C was added nBuLi (2.5 M in hexanes, 100 mL, 250.0 mmol) dropwise. The reaction mixture was stirred for 3 h at -78 °C. After this time had passed, $Boc_2O$ (38.4 g, 176.0 mmol) in dry THF (42 mL) was added at -78 °C dropwise. After the addition was complete the reaction mixture was warmed slowly to room temperature overnight.

After this time had passed, the reaction mixture was quenched with water (300 mL) and extracted with DCM (2 x 300 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude reaction product was purified using a silica plug flushing with 100 % pentane then eluting the title compound with 10 % $Et_2O$ in pentane. This yielded tert-butyl but-2-ynoate (**17**) (15.6 g, 98 %) as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.95 (s, 3H), 1.48 (s, 9H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 152.9, 83.1, 83.0, 73.9, 27.5, 3.9. TOF MS ES$^+$ (m/z): [M+]$^+$ calc'd for $C_8H_{13}O_2$: 141; found: 141.

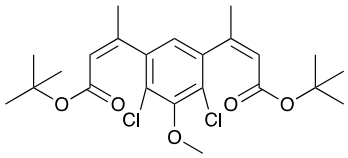
*tert*-Butyl (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (**18**)




To a stirred solution of ethyl but-2-ynoate (**17**) (8 g, 57.1 mmol) in dry THF (80 mL, degasses with $N_2$ for 45 min) under $N_2$ at 0 °C was added trimethylphosine (1 M in toluene, 11.4 mL, 11.4 mmol) and pinacolborane (11.4 mL, 114.3 mmol) slowly. The reaction mixture was stirred for 5 min at 0 °C the allowed to warm to room temperature and stirred for 18 h.

After completion of the reaction monitored by TLC (10 % $Et_2O$ in pentane) the reaction mixture was concentrated under reduced pressure and the resulting solid was purified using a silica plug flushing with 100 % pentane then eluting the title compound with 10 % $Et_2O$ in pentane. This yielded *tert*-butyl (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (**18**) (7.9 g, 52 %) as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.95 (q, J = 1.7 Hz, 1H), 1.91 (d, J = 1.7 Hz, 3H), 1.45 (s, 9H), 1.34 (s, 12H). $^{13}$C NMR (101 MHz, $CHCl_3$) $\delta$ 167.7, 152.2, 128.7, 83.6, 80.5, 28.2, 24.7, 20.4. $^{11}$B NMR (128 MHz, $CDCl_3$) $\delta$ 31.1. TOF MS ES$^+$ (m/z): $[M+]^+$ calc'd for $C_{14}H_{26}BO_4$: 269.1924; found: 269.1932.

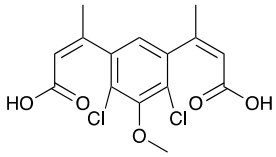
Di-*tert*-butyl 3,3'-(4,6-dichloro-5-methoxy-1,3-phenylene)(2*Z*,2'*Z*)-bis(but-2-enoate) (**20**)



To a stirred solution of 2,4-dichloro-1,5-diiodo-3-methoxybenzene (**5**) (5.0 g, 11.7 mmol) in degasses (for 15 min with $N_2$) DME (100 mL) and water (10 mL) under $N_2$ was added *tert*-butyl (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (**18**) (7.0 g, 26.2 mmol), $K_2CO_3$ (9.7 g, 69.9 mmol) and $Pd(Cl)_2$dppf (1.7 g, 2.3 mmol). The reaction mixture was stirred for 18 h at 85 $^oC$.

After completions of the reaction monitored by TLC (100 % DCM), the reaction was concentrated. The resulting solid was partitioned between DCM (100 mL) and water (100 mL). The layers were separated, and the aqueous phase was extracted with DCM (2 x 100 mL). The organic phases were then combined, washed with brine (150 mL), dried over $MgSO_4$, filtered and then concentrated under reduced pressure. The crude solid was purified by column chromatography starting with 100% DCM and then using 10% EtOAc in DCM. The product containing fractions were combined and concentrated to yield di-*tert*-butyl 3,3'-(4,6-dichloro-5-methoxy-1,3-phenylene)(2*Z*,2'*Z*)-bis(but-2-enoate) (**20**) (4.5 g, 84 %) off-white crystalline solid. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.60 (s, 1H), 5.90 (q, *J* = 1.5 Hz, 2H), 3.92 (s, 3H), 2.08 (d, *J* = 1.5 Hz, 6H), 1.22 (s, 18H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 164.5, 152.4, 149.2, 140.8, 124.9, 122.8, 121.7, 80.2, 60.7, 27.9, 26.0. TOF MS $ES^+$ (m/z): $[M+]^+$ calc'd for $C_{23}H_{30}O_5NaCl_2$: 479.1368; found: 479.1374.

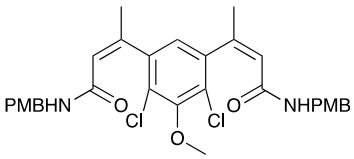
(2*Z*,2'*Z*)-3,3'-(4,6-Dichloro-5-methoxy-1,3-phenylene)bis(but-2-enoic acid) (**16**)




To a stirred solution of di-*tert*-butyl 3,3'-(4,6-dichloro-5-methoxy-1,3-phenylene)(I)-bis(but-2-enoate) (**20**) (52 mg, 0.114 mmol) in DCM (1 mL) was added TFA (1 mL). The reaction mixture was stirred for 2 h at room temperature.

After completions of the reaction monitored by TLC (100 % DCM), the reaction was partitioned between DCM (15 mL) and NaOH (1M, 15 mL). The layers were separated, and the aqueous phase was extracted with DCM (2 x 20 mL). The aqueous phase was then acidified with HCL (1M, 30 mL) and extracted with DCM (2 x 30 mL). These organic extracts were combined, washed with water (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. This afforded the desired product (**16**) (37 mg, 94 %) as a white crystalline solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.52 (s, 1H), 5.97 (d, J = 1.6 Hz, 2H), 3.78 (s, 3H), 2.12 (d, J = 1.5 Hz, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 170.8, 153.7, 152.5, 139.9, 125.0, 120.3, 60.6, 26.4. TOF MS ES$^+$ (m/z): $[M+CH_3CN+Na]^+$ calc'd for $C_{17}H_{17}NO_5NaCl_2$: 408.0381; found: 408.0383.

(2*Z*,2'*Z*)-3,3'-(4,6-Dichloro-5-methoxy-1,3-phenylene)bis(*N*-(4-methoxybenzyl)but-2-enamide) (**3**)

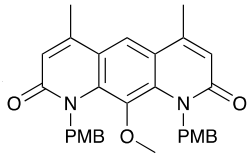



To a stirred solution of (2*Z*,2'*Z*)-3,3'-(4,6-dichloro-5-methoxy-1,3-phenylene)bis(but-2-enoic acid) (**16**) (1.8 g, 5.20 mmol) in dry DCM (30 mL) under $N_2$ at 0 °C was added oxalyl chloride (2.6 mL, 31.22 mmol) dropwise. The reaction mixture was warmed to room temperature and stirred for 4 h. After this time had passed, the reaction mixture was concentrated under reduced pressure and the atmosphere was changed to $N_2$. The residue was re-dissolved in dry DCM (30 mL) and cooled to 0 °C. $H_2NPMB$ (1.7 mL, 13.01 mmol) the $NEt_3$ (1.8 mL, 13.01 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 18 h.

After the allocated time had passed, the reaction mixture was partitioned between DCM (50 mL) and HCl (1M, 80 mL). The layers were separated and the organic phase was washed with water (80 mL), brine (80 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude solid was purified by column chromatography using 100 % DCM then 25 % EtOAc in DCM as the eluent system. The product containing fractions were combined and concentrated to yielded (2*Z*,2'*Z*)-3,3'-(4,6-dichloro-5-methoxy-1,3-phenylene)bis(*N*-(4-methoxybenzyl)but-2-enamide) (**3**) (2.05 g, 3.52 mmol, 68 %) as an off white solid. $^1$H NMR (400 MHz, DMSO-*d6*) $\delta$ 7.03 (d, J = 8.4 Hz, 4H), 6.80 (d, J = 8.4 Hz, 5H), 6.07 (d, J = 1.7 Hz, 2H), 4.09 (d, J = 6.0 Hz, 4H), 3.75 (s, 3H), 3.70 (s, 6H), 2.01 – 1.93 (m, 6H). $^{13}$C NMR (101 MHz, DMSO-*d6*) $\delta$ 164.3, 158.6, 145.0, 140.8, 131.8, 129.3, 128.9, 124.3, 123.8, 123.5, 114.0, 61.0, 55.5, 41.7, 25.7. TOF MS ES$^+$ (m/z): $[M+Na]^+$ calc'd for $C_{31}H_{32}N_2O_5NaCl_2$: 605.1586; found: 605.1594.

The spectroscopic data correspond with those previously reported.[4]

10-Methoxy-1,9-bis(4-methoxybenzyl)-4,6-dimethylpyrido[3,2-*g*]quinoline-2,8(1*H*,9*H*)-dione (**11**)

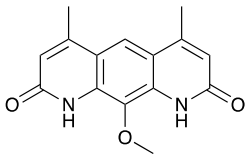



**11** was obtained following experimental procedures previously described by Hergenrother and co-workers and their spectroscopic data correspond with those reported.[4]

To a stirred solution of (2*Z*,2'*Z*)-3,3'-(4,6-dichloro-5-methoxy-1,3-phenylene)bis(*N*-(4-methoxybenzyl)but-2-enamide) (**3**) (60 mg, 0.103 mmol) in dry *i*-PrOH (5 mL) under $N_2$ was added $K_2CO_3$ (86 mg, 0.619 mmol), Xphos (5 mg, 0.010 mmol) and Xphos G2 Pd (8 mg, 0.010 mmol). The reaction mixture was heated at 90 °C for 18 h.

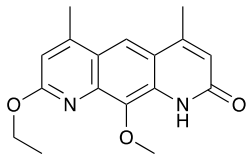
After completion of the reaction, monitored by TLC (100 % DCM), the solvent was removed under reduced pressure. The resulting solid was portioned between DCM (20 mL) and water (20 mL). The layers were separated and the organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude solid was purified by column chromatography using 100 % DCM then 25 % EtOAc in DCM as the eluent. The product containing fractions were combined and concentrated. The resulting solid was triturated with pentane (10 mL) to yield 10-methoxy-1,9-bis(4-methoxybenzyl)-4,6-dimethylpyrido[3,2-*g*]quinoline-2,8(1*H*,9*H*)-dione (**11**) (52 mg, 0.102 mmol, 99 %) as an off white solid. $^1$H NMR (400 MHz, $CHCl_3$) $\delta$ 7.62 (s, 1H), 7.01 (d, J = 8.1 Hz, 4H), 6.74 (d, J = 8.3 Hz, 4H), 6.59 (d, J = 1.3 Hz, 2H), 5.79 – 5.18 (m, 4H), 3.73 (s, 6H), 2.90 (s, 3H), 2.48 (d, J = 1.2 Hz, 6H). $^{13}$C NMR (101 MHz, $CHCl_3$) $\delta$ 164.1, 158.4, 146.2, 136.5, 130.2, 128.3, 120.8, 119.6, 116.8, 113.6, 61.7, 55.2, 29.7, 19.1. TOF MS ES$^+$ (m/z): [M+]$^+$ calc'd for $C_{31}H_{31}N_2O_5$: 511.2233; found: 511.2213.

10-Methoxy-4,6-dimethylpyrido[3,2-*g*]quinoline-2,8(1*H*,9*H*)-dione (**21**)



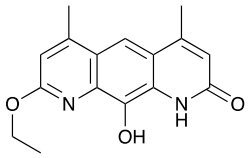
10-Methoxy-1,9-bis(4-methoxybenzyl)-4,6-dimethylpyrido[3,2-*g*]quinoline-2,8(1*H*,9*H*)-dione (**11**) (236 mg, 0.463 mmol) was dissolved in TFA (2.3 mL) and stirred for 18 h. After this time had passed water (30 mL) was added and the precipitated was collected *via* filtration and dried under vacuum. The solid was then triturated with $Et_2O$ (10 mL) and the resulting solid was dried under vacuum. This yielded 10-methoxy-4,6-dimethylpyrido[3,2-*g*]quinoline-2,8(1*H*,9*H*)-dione (**21**) (122 mg, 0.452 mmol, 98 %) as an off white solid. $^1$H NMR (400 MHz, DMSO-*d6*) $\delta$ 11.20 (s, 2H), 7.74 (s, 1H), 6.36 (t, J = 1.6 Hz, 2H), 3.74 (s, 3H), 2.49 (s, 6H). $^{13}$C NMR (101 MHz, DMSO-*d6*) $\delta$ 161.9, 148.2, 132.8, 130.8, 119.9, 116.8, 115.7, 61.4, 18.5. TOF MS ES$^+$ (m/z): [M+]$^+$ calc'd for $C_{15}H_{15}N_2O_3$: 271.1083; found: 271.1082.

8-Ethoxy-10-methoxy-4,6-dimethylpyrido[3,2-*g*]quinolin-2(1*H*)-one (**22**)



To a stirred solution of 10-methoxy-4,6-dimethylpyrido[3,2-*g*]quinoline-2,8(1*H*,9*H*)-dione (**21**) (200 mg, 0.735 mmol) in DMSO (10 mL) under $N_2$ was added $K_2CO_3$ (203 mg, 1.471 mmol) and EtI (59 μL, 0.735 mmol). The reaction mixture was heated at 70 °C for 18 h. After this time had passed, water (80 mL) was added and the precipitate was collected *via* filtration and dried under vacuum. The afforded 8-ethoxy-10-methoxy-4,6-dimethylpyrido[3,2-*g*]quinolin-2(1*H*)-one (**22**) (129 mg, 0.433 mmol, 59 %) as an white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.14 (s, 1H), 7.87 (s, 1H), 6.72 (d, J = 1.1 Hz, 1H), 6.54 – 6.50 (m, 1H), 4.57 (q, J = 7.1 Hz, 2H), 4.28 (s, 3H), 2.66 (d, J = 1.1 Hz, 3H), 2.57 (d, J = 1.2 Hz, 3H), 1.47 (t, J = 7.1 Hz, 3H). TOF MS ES$^+$ (m/z): [M+]$^+$ calc'd for $C_{17}H_{19}N_2O_3$: 299.34; found: 299.14.

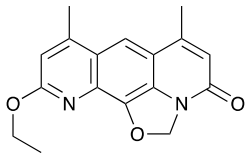
8-Ethoxy-10-hydroxy-4,6-dimethylpyrido[3,2-*g*]quinolin-2(1*H*)-one (**23**)




To a stirred solution of 8-ethoxy-10-methoxy-4,6-dimethylpyrido[3,2-*g*]quinolin-2(1*H*)-one (**22**) (298 mg, 0.993 mmol) in dry DCM (10 ml) under $N_2$ at 0 °C was added $BBr_3$ (1 M in DCM, 5.9 mL, 0.880 mmol) dropwise. After the addition was complete the reaction mixture was allowed to warm to room temperature and stirred for 18 h.

After the completion of the reaction, monitored by TLC (100 % EtOAc), water (60 mL) was added to the reaction mixture and the resulting precipitate was isolated *via* filtration. The solid was dried under vacuum then washed through the filter with DCM: MeOH (100 mL, 4:1). The solvent was removed from the filtrate to afford 8-ethoxy-10-hydroxy-4,6-dimethylpyrido[3,2-*g*]quinoline-2(1*H*)-one (**23**) (115 mg, 0.405 mmol, 41 %) as an off white solid. $^{1}$H NMR (400 MHz, DMSO-*d6*) $\delta$ 10.57 (s, 1H), 9.66 (s, 1H), 7.69 (s, 1H), 6.79 (d, J = 1.2 Hz, 1H), 6.42 (s, 1H), 4.62 (q, J = 7.0 Hz, 2H), 2.64 (d, J = 1.1 Hz, 3H), 2.53 (d, J = 1.2 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (101 MHz, DMSO-*d6*) $\delta$ 161.8, 161.6, 153.7, 153.1, 148.6, 136.7, 135.0, 125.5, 121.5, 120.6, 112.5, 110.3, 62.0, 55.4, 19.2, 18.8, 15.0. TOF MS ES$^{+}$ (m/z): $[M+]^{+}$ calc'd for $C_{16}H_{16}N_2O_3$: 285.32; found: 285.13.

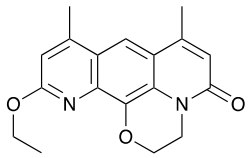
10-Ethoxy-6,8-dimethyl-2*H*,4*H*-oxazolo[5,4,3-*ij*]pyrido[3,2-*g*]quinoline-4-one (**24**)



To a stirred solution of 8-ethoxy-10-hydroxy-4,6-dimethylpyrido[3,2-*g*]quinoline-2(1*H*)-one (**23**) (12 mg, 0.042 mmol) in DMSO (0.5 mL) under $N_2$ was added 1,1-dibromomethane (29 μL, 0.420 mmol) and $K_2CO_3$ (35 mg, 0.252 mmol). The reaction mixture was heated at 85 °C for 18 h.

After the completion of the reaction, monitored by TLC (10 % MeOH in DCM), the reaction mixture was partitioned between EtOAc (20 mL) and water (20 mL). The layers were separated and the organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude solid was then purified using preparative TLC using 10 % MeOH in DCM as the eluent. This yielded 10-ethoxy-6,8-dimethyl-2*H*,4*H*-oxazolo[5,4,3-*ij*]pyrido[3,2-*g*]quinoline-4-one (**24**) (1.8 mg, 0.006 mmol, 14 %) as a light yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.58 (s, 1H), 6.69 (d, J = 1.2 Hz, 1H), 6.48 (s, 2H), 6.47 (q, J = 1.4 Hz, 1H), 4.54 (q, J = 7.1 Hz, 2H), 2.64 (dd, J = 2.8, 1.1 Hz, 3H), 2.54 (d, J = 1.3 Hz, 3H), 1.44 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.7, 158.6, 147.8, 147.6, 142.5, 131.6, 130.0, 124.4, 122.2, 115.5, 113.5, 110.9, 86.9, 62.1, 19.9, 18.1, 14.6. TOF MS ES$^+$ (m/z): [M+]$^+$ calc'd for $C_{17}H_{17}N_2O_3$: 297.1239; found: 297.1235.

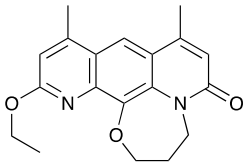
11-Ethoxy-7,9-dimethyl-2,3-dihydro-5*H*-[1,4]oxazino[2,3,4-*ij*]pyrido[3,2-*g*]quinolin-5-one (**25**)



To a stirred solution of 8-ethoxy-10-hydroxy-4,6-dimethylpyrido[3,2-*g*]quinoline-2(1*H*)-one (**23**) (16 mg, 0.056 mmol) in DMSO (0.5 mL) under $N_2$ was added 1,2-dibromoethane (48 μL, 0.559 mmol) and $K_2CO_3$ (46 mg, 0.336 mmol). The reaction mixture was heated at 85 °C for 18 h.

After the completion of the reaction, monitored by TLC (10 % MeOH in DCM), the reaction mixture was partitioned between EtOAc (20 mL) and water (20 mL). The layers were separated and the organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude solid was then purified using preparative TLC using 10 % MeOH in DCM as the eluent. This yielded 11-ethoxy-7,9-dimethyl-2,3-dihydro-5*H*-[1,4]oxazino[2,3,4-*ij*]pyrido[3,2-*g*]quinolin-5-one (**25**) (2.3 mg, 0.007 mmol, 13 %) as an off-white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.79 (s, 1H), 6.79 (d, J = 1.2 Hz, 1H), 6.61 (d, J = 1.3 Hz, 1H), 4.67 – 4.58 (m, 4H), 4.38 (t, J = 4.7 Hz, 2H), 2.70 (d, J = 1.0 Hz, 3H), 2.60 (d, J = 1.2 Hz, 3H), 1.49 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 163.0, 160.3, 147.2, 147.1, 136.9, 136.6, 125.0, 121.6, 120.6, 119.0, 113.6, 112.2, 64.4, 61.9, 39.7, 19.4, 19.1, 14.7. TOF MS ES$^+$ (m/z): [M+]$^+$ calc'd for $C_{18}H_{19}N_2O_3$ 311.1396; found: 311.1397.

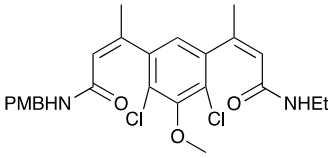
12-Ethoxy-8,10-dimethyl-3,4-dihydro-2*H*,6*H*-[1,4]oxazepino[2,3,4-*ij*]pyrido[3,2-*g*]quinolin-6-one (**26**)



To a stirred solution of 8-ethoxy-10-hydroxy-4,6-dimethylpyrido[3,2-*g*]quinoline-2(1*H*)-one (**23**) (20 mg, 0.069 mmol) in DMF (1 mL) under $N_2$ was added 1,3-dibromopropane (7 μL, 0.069 mmol) and $K_2CO_3$ (58 mg, 0.420 mmol). The reaction mixture was heated at 85 °C for 18 h.

After the completion of the reaction, monitored by TLC (10 % MeOH in DCM), the reaction mixture was partitioned between EtOAc (20 mL) and water (20 mL). The layers were separated and the organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude solid was then purified using preparative TLC using 5 % MeOH in DCM as the eluent. This yielded 11-ethoxy-7,9-dimethyl-2,3-dihydro-5*H*-[1,4]oxazino[2,3,4-*ij*]pyrido[3,2-*g*]quinolin-5-one (**26**) (4.0 mg, 0.012 mmol, 18 %) as an off-white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.78 (s, 1H), 6.74 (q, J = 1.1 Hz, 1H), 6.55 (q, J = 1.2 Hz, 1H), 4.67 (t, J = 5.9 Hz, 2H), 4.59 (q, J = 7.1 Hz, 2H), 4.52 (t, J = 6.8 Hz, 2H), 2.65 (d, J = 1.1 Hz, 3H), 2.52 (d, J = 1.2 Hz, 3H), 2.43 – 2.35 (m, 2H), 1.45 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 163.1, 162.8, 147.0, 146.5, 142.5, 140.7, 132.1, 122.0, 121.0, 120.5, 114.1, 113.5, 72.0, 61.9, 42.3, 27.9, 19.4, 19.0, 14.7. TOF MS ES$^+$ (m/z): [M+]$^+$ calc'd for $C_{19}H_{21}N_2O_3$ 325.1552; found: 325.1550.

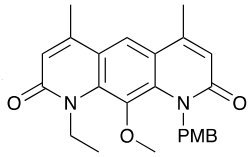
(*Z*)-3-(2,4-Dichloro-3-methoxy-5-((*Z*)-4-((4-methoxybenzyl)amino)-4-oxobut-2-en-2-yl)phenyl)-*N*-ethylbut-2-enamide (**27**)




To a stirred solution of (2*Z*,2'*Z*)-3,3'-(4,6-Dichloro-5-methoxy-1,3-phenylene)bis(but-2-enoic acid) (**16**) (20 mg, 0.058 mmol) in dry DCM (0.5 mL) under $N_2$ was added oxalyl chloride (41 μL, 0.349 mmol) dropwise. The reaction mixture was stirred at room temperature for 4 h. After this time had passed, the reaction mixture was concentrated under reduced pressure and the atmosphere was changed to $N_2$. The residue was re-dissolved in dry DCM (1 mL) and cooled to 0 °C. $NH_2Et$ (2M in THF, 29 μL, 0.058 mmol), $NH_2PMB$ (8 μL, 0.058 mmol) and $NEt_3$ (41 μL, 0.291 mmol) were added sequentially. After the last addition the reaction mixture was allowed to warm to room temperature and stirred for 18 h.

After the reaction was complete, monitored by TLC (1:1 DCM: EtOAc), the reaction mixture was partitioned between DCM (20 mL) and HCl (1 M, 20 mL). The layers were separated and the aqueous phase was extracted with DCM (2 x 20 mL). The organic phases were then combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The resulting solid was purified by column chromatography using 100 % DCM then 1:1 DCM: EtOAc as the eluent. The yielded (*Z*)-3-(2,4-dichloro-3-methoxy-5-((*Z*)-4-((4-methoxybenzyl)amino)-4-oxobut-2-en-2-yl)phenyl)-*N*-ethylbut-2-enamide (**27**) (12 mg, 0.024 mmol, 42 %) as an off-white solid. $^1$H NMR (400 MHz, DMSO-*d6*) δ 7.07 – 7.02 (m, 2H), 6.84 – 6.79 (m, 2H), 6.76 (br. s, 1H), 6.07 (q, J = 1.4 Hz, 1H), 5.98 (q, J = 1.5 Hz, 1H), 4.11 (d, J = 5.9 Hz, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 2.96 (q, J = 7.0 Hz, 2H), 2.02 (d, J = 1.5 Hz, 3H), 1.97 (s, 3H), 0.89 (t, J = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, DMSO-*d6*) *δ* 163.9, 163.7, 158.1, 153.3, 151.2, 144.6, 140.3, 131.4, 128.7, 128.5, 128.4, 123.9, 123.8, 123.3, 123.1, 113.6, 113.5, 60.2, 55.0, 41.3, 33.1, 25.2, 25.2, 14.6. TOF MS ES$^+$ (m/z): [M+]$^+$ calc'd for $C_{25}H_{29}N_2O_4Cl_2$ 491.1504; found: 419.1987.

1-Ethyl-10-methoxy-9-(4-methoxybenzyl)-4,6-dimethylpyrido[3,2-g]quinoline-2,8(1*H*,9*H*)-dione (**28**)

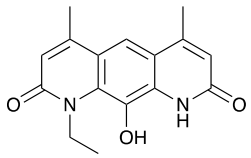



**28** was obtained following experimental procedures previously described by Hergenrother and co-workers.[2]

To a stirred solution of (*Z*)-3-(2,4-dichloro-3-methoxy-5-((*Z*)-4-((4-methoxybenzyl)amino)-4-oxobut-2-en-2-yl)phenyl)-*N*-ethylbut-2-enamide (**27**) (11 mg, 0.022 mmol) in dry *i*-PrOH (1 mL) under $N_2$ was added $K_2CO_3$ (19 mg, 0.135 mmol), Xphos (1 mg, 0.002 mmol) and Xphos G2 Pd (2 mg, 0.002 mmol). The reaction mixture was heated at 90 °C for 18 h.

After completion of the reaction, monitored by TLC (100 % EtOAc), the solvent was removed under reduced pressure. The resulting solid was partitioned between DCM (20 mL) and water (20 mL). The layers were separated and the organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 1-ethyl-10-methoxy-9-(4-methoxybenzyl)-4,6-dimethylpyrido[3,2-g]quinoline-2,8(1*H*,9*H*)-dione (**28**) (8 mg, 0.019 mmol, 85 %). This material was used in the next step without further purification. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.64 (s, 1H), 7.08 – 7.02 (m, 2H), 6.74 – 6.70 (m, 2H), 6.64 (d, J = 1.3 Hz, 1H), 6.51 (t, J = 1.3 Hz, 1H), 5.36 (d, J = 14.9 Hz, 2H), 4.18 (dq, J = 13.6, 6.8 Hz, 2H), 3.70 (s, 3H), 3.31 (s, 3H), 2.52 (d, J = 1.2 Hz, 3H), 2.45 (d, J = 1.2 Hz, 3H), 1.08 – 1.04 (m, 3H). TOF MS ES$^+$ (m/z): [M+]$^+$ calc'd for $C_{25}H_{27}N_2O_4$ 419.1971; found: 419.1987.

1-Ethyl-10-hydroxy-4,6-dimethylpyrido[3,2-*g*]quinoline-2,8(1*H*,9*H*)-dione (**29**)

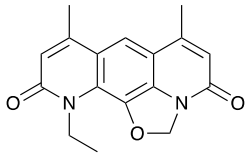



**29** was obtained following experimental procedures previously described by Hergenrother and co-workers.[2]

To a round bottom flask containing 1-ethyl-10-methoxy-9-(4-methoxybenzyl)-4,6-dimethylpyrido[3,2-g]quinoline-2,8(1*H*,9*H*)-dione (**28**) (8 mg, 0.019 mmol) was added HBr (48 %, aq., 1 mL).

The reaction mixture was stirred and heated at reflux (110 °C) for 18 h. After completion of the reaction monitored by TLC (100 % EtOAc) water (20 mL) and the resulting precipitate was isolate *via* filtration. This afforded 1-ethyl-10-hydroxy-4,6-dimethylpyrido[3,2-*g*]quinoline-2,8(1*H*,9*H*)-dione (**29**) (5 mg, 0.017 mmol, 91 %) as an off-white solid. $^{1}$H NMR (400 MHz, DMSO-*d6*) $\delta$ 7.65 (s, 1H), 6.93 (s, 1H), 6.44 (d, J = 1.3 Hz, 1H), 6.40 (d, J = 1.3 Hz, 1H), 4.59 (q, J = 6.8 Hz, 2H), 2.49 – 2.49 (m, 3H, under DMSO), 2.47 (d, J = 1.2 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H). TOF MS ES$^{-}$ (m/z): [M-]$^{-}$ calc'd for $C_{16}H_{15}N_2O_3$ 283.32; found: 283.1.

11-Ethyl-6,8-dimethyl-11-hydro-2H,4H-oxazolo[5,4,3-ij]pyrido[3,2-*g*]quinoline-4,10-dione (**30**)

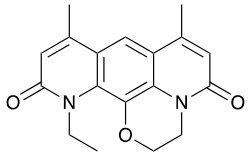


**30** was obtained following experimental procedures previously described by Hergenrother and co-workers and their spectroscopic data correspond with those reported.[5]

To a stirred solution of 1-ethyl-10-hydroxy-4,6-dimethylpyrido[3,2-*g*]quinoline-2,8(1*H*,9*H*)-dione (**29**) (5 mg, 0.017 mmol) in DMSO (0.5 mL) under $N_2$ was added $K_2CO_3$ (14 mg, 0.105 mmol) and dibromomethane (12 μL, 0.175 mmol). The reaction mixture was heated at 85 °C for 18 h.

After completion of the reaction monitored by TLC (10 % MeOH in DCM) the reaction mixture was partitioned between DCM (20 mL) and water (20 mL). The layers were separated and the organic phase was washed with brine (20 mL), dried oved $MgSO_4$, filtered and concentrated under reduced pressure. The resulting solid was purified by preparative TLC using 5 % MeOH in DCM as the eluent (ran twice). This yielded 11-ethyl-6,8-dimethyl-11-hydro-2H,4H-oxazolo[5,4,3-ij]pyrido[3,2-*g*]quinoline-4,10-dione (**30**) (1.7 mg, 33 %) as an off white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.48 (s, 1H), 6.52 (d, J = 1.3 Hz, 1H), 6.47 (q, J = 1.2 Hz, 1H), 6.41 (s, 2H), 4.54 (q, J = 7.0 Hz, 2H), 2.52 (d, J = 1.2 Hz, 3H), 2.50 (d, J = 1.2 Hz, 3H), 1.37 (t, J = 7.0 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 161.7, 158.7, 147.6, 146.7, 135.1, 132.4, 125.1, 121.4, 121.1, 120.8, 113.6, 113.4, 86.1, 40.3, 20.3, 18.0, 15.0. TOF MS ES$^+$ (m/z): [M+]$^+$ calc'd for $C_{17}H_{17}N_2O_3$: 297.1239; found: 297.1234.

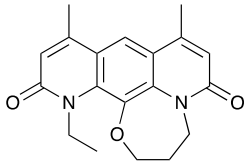
12-Ethyl-7,9-dimethyl-2,3-dihydro-5*H*-[1,4]oxazino[2,3,4-*ij*]pyrido[3,2-*g*]quinoline-5,11(12*H*)-dione (**31**)



To a stirred solution of 1-ethyl-10-hydroxy-4,6-dimethylpyrido[3,2-*g*]quinoline-2,8(1*H*,9*H*)-dione (**29**) (20 mg, 0.069 mmol) in dry DMF (1 mL) under $N_2$ was added $K_2CO_3$ (58 mg, 0.420 mmol) and 1,2-dibromoethane (6 μL, 0.069 mmol). The reaction mixture was heated at 110 °C for 18 h.

After completion of the reaction monitored by TLC (10 % MeOH in DCM) the reaction mixture was partitioned between DCM (20 mL) and water (20 mL). The layers were separated and the organic phase was washed with brine (20 mL), dried oved $MgSO_4$, filtered and concentrated under reduced pressure. The resulting solid was purified by preparative TLC using 5 % MeOH in DCM as the eluent (ran twice). This yielded 12-ethyl-7,9-dimethyl-2,3-dihydro-5*H*-[1,4]oxazino[2,3,4-*ij*]pyrido[3,2-*g*]quinoline-5,11(12*H*)-dione (**31**) (6.5 mg, 28 %) as an off white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.58 (s, 1H), 6.56 (d, J = 1.3 Hz, 2H), 4.60 (q, J = 6.9 Hz, 2H), 4.42 (t, J = 4.8 Hz, 2H), 4.32 (dd, J = 5.4, 4.1 Hz, 2H), 2.52 (d, J = 1.2 Hz, 3H), 2.48 (d, J = 1.2 Hz, 3H), 1.41 (t, J = 6.9 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 163.2, 160.5, 146.6, 145.7, 130.8, 130.3, 127.9, 121.1, 119.8, 118.8, 116.7, 114.2, 63.7, 42.3, 40.0, 19.4, 19.0, 15.4. TOF MS ES$^+$ (m/z): [M+]$^+$ calc'd for $C_{18}H_{19}N_2O_3$: 311.1396; found: 311.1387.

13-Ethyl-8,10-dimethyl-3,4-dihydro-2*H*,6*H*-[1,4]oxazepino[2,3,4-*ij*]pyrido[3,2-*g*]quinoline-6,12(13*H*)-dione (**32**)



To a stirred solution of 1-ethyl-10-hydroxy-4,6-dimethylpyrido[3,2-*g*]quinoline-2,8(1*H*,9*H*)-dione (**29**) (20 mg, 0.069 mmol) in dry DMF (1 mL) under $N_2$ was added $K_2CO_3$ (58 mg, 0.420 mmol) and 1,3-dibrompropane (7 μL, 0.069 mmol). The reaction mixture was heated at 110 °C for 18 h.

After completion of the reaction monitored by TLC (10 % MeOH in DCM) the reaction mixture was partitioned between DCM (20 mL) and water (20 mL). The layers were separated and the organic phase was washed with brine (20 mL), dried oved $MgSO_4$, filtered and concentrated under reduced pressure. The resulting solid was purified by preparative TLC using 5 % MeOH in DCM as the eluent (ran twice). This yielded 13-ethyl-8,10-dimethyl-3,4-dihydro-2*H*,6*H*-[1,4]oxazepino[2,3,4-*ij*]pyrido[3,2-*g*]quinoline-6,12(13*H*)-dione (**32**) (10.1 mg, 44 %) as an off white solid. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.55 (s, 1H), 6.54 (d, J = 1.2 Hz, 1H), 6.53 (d, J = 1.2 Hz, 1H), 4.67 – 4.59 (m, 2H), 4.50 (q, J = 6.9 Hz, 2H), 4.35 (t, J = 6.7 Hz, 2H), 2.47 (d, J = 1.2 Hz, 3H), 2.46 (d, J = 1.2 Hz, 3H), 2.37 (p, J = 6.5 Hz, 2H), 1.44 (t, J = 6.8 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 163.7, 162.6, 146.4, 145.7, 137.7, 134.3, 134.3, 121.2, 120.6, 119.2, 118.5, 115.1, 72.3, 44.1, 42.0, 27.3, 19.4, 19.2, 15.0. TOF MS ES$^+$ (m/z): [M+]$^+$ calc'd for $C_{19}H_{21}N_2O_3$: 325.1552; found: 325.1553.

## Microbiology Protocols

Experimental procedures previously described by Sridhar and co-workers.[6]

Disc preparations

Antibiotics were dissolved in $CHCl_3$ to make up 1 mmol and 10 mmol solutions. 20 μL of each solution was loaded onto a 6 mm whatmann paper disc (sterilised by autoclave) in a glass petri dish (sterilised by autoclave). 7 discs were used per antibiotic per concentration. The glass petri dishes containing the antibiotic discs were transferred to the oven (37 °C) for 30 min to dry.

Kirby-Bauer disc diffusion method[7,8]

The bacterial strains used were a fluoroquinolone sensitive (FQS) S. *aureus* strain, SH1000 and a fluoroquinolone resistant (FQR) S. *aureus* strain USA300 JE2. Cultures were streaked on Mueller-Hinton agar plates to single colonies to check purity and grown in the oven (37 °C) for 24 h. A single colony was taken and dissolved in sterilised Mueller-Hinton broth (10 mL) and grown in the incubator (37 °C) with aeration for 6 h to create the inoculum culture. The inoculum culture was then diluted with PBS to a turbidity of 0.5 Mcfarland standard solution. A Mueller-Hinton agar plate was then inoculated with the inoculum culture using a sterilised swap, swapping in three directions for even coverage on the plate. 7 antibiotic discs were transferred to the plate and the plate was incubated in the oven (37 °C) for 24 h. After this time the zone of inhibition was measured for each disc.

## References


1 J. S. Bair, R. Palchaudhuri and P. J. Hergenrother, 2010, **132**, 5469–5478.

2 E. I. Parkinson, J. S. Bair, M. Cismesia and P. J. Hergenrother, *ACS Chem. Biol.*, 2013, **8**, 2173–2183.

3 A. Otaka, E. Mitsuyama, T. Kinoshita, H. Tamamura and N. Fujii, *J. Org. Chem.*, 2000, **65**, 4888–4899.

4 P. J. Hergenrother, D. A. Boothman, J. S. Bair, R. Palchaudhuri, WO 2013/056073 A1, 2013.

5 P. J. Hergenrother, E. I. Parkinson, J. S. Bair, WO 2015/142952 A1, 2015.

6 N. Vineetha, R. A. Vignesh and D. Sridhar, *Int. J. Appl. Res.*, 2015, **1**, 624–631.

7 B. AW, P. DM and K. WM, *AMA. Arch. Intern. Med.*, 1959, **104**, 208–216.

8 A. W. Bauer, J. C. Sherris, M. Turck and W. M. M. Kirby, *Am. J. Clin. Pathol.*, 1966, **45**, 493–496.

**Failed Reaction Conditions**

Scheme 1 – Unsuccessful Suzuki-Miyaura cross-coupling of **1** and **2** to form **3.**

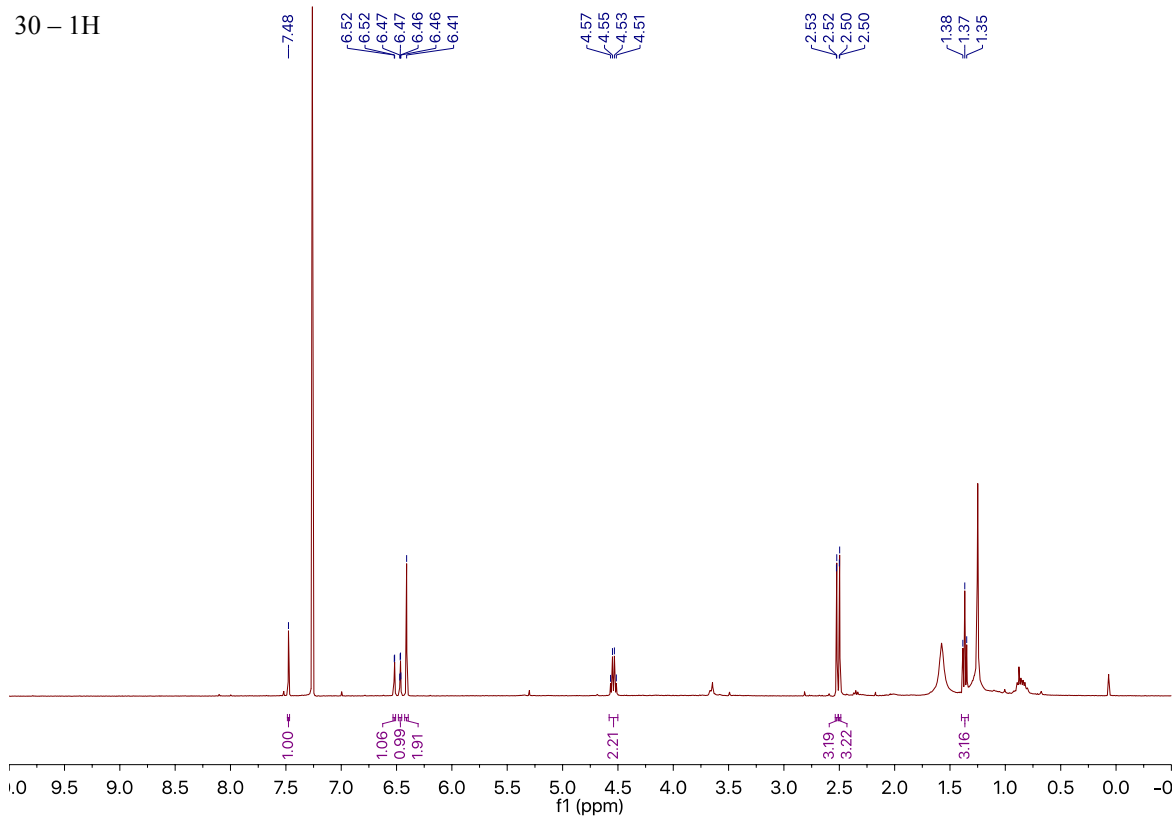
| Trial | Attempted Conditions |
|---|---|
| 1 | $Pd(dppf)Cl_2$, $K_2CO_3$, DME: $H_2O$ (9:1), 85 °C |
| 2 | $Pd(dppf)Cl_2$, $K_2CO_3$, DME: $H_2O$ (4:1), 85 °C |
| 3 | Pd G2 Xphos, Xphos, $CsCO_3$, DME: $H_2O$ (4:1), 90 °C |
| 4 | $Pd(dppf)Cl_2$, $K_2CO_3$, Dioxane: $H_2O$ (9:1), 90 °C |
| 5 | $Pd(dppf)Cl_2$, $K_3PO_4$, DME: $H_2O$ (9:1), 90 °C |
| 6 | $Pd(dppf)Cl_2$, $K_2CO_3$, DME: $H_2O$ (9:1), 87 °C, under microwave irradiation (1 h) |

Scheme 5 - Attempted synthesis of amide **3**. Converting ester **15** into acid **16**.

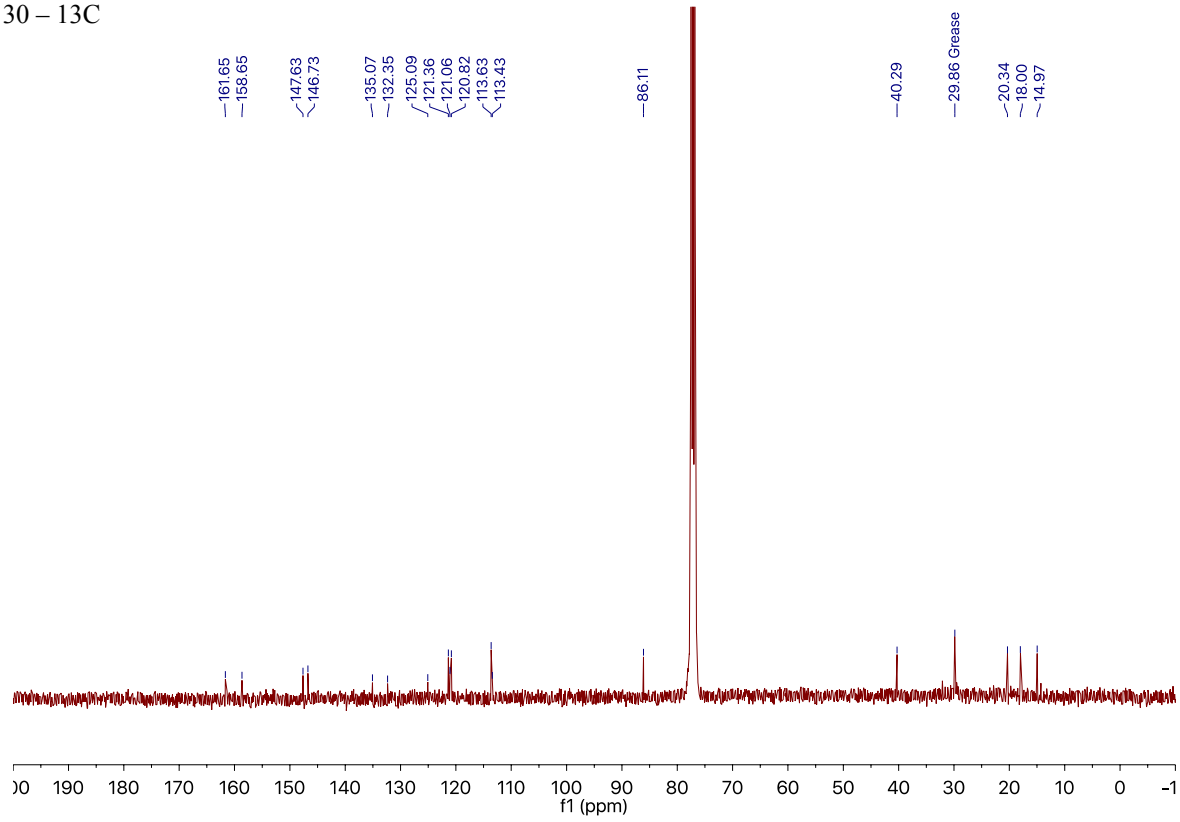
| Trial | Attempted Conditions |
|---|---|
| 1 | NaOH (1 M), MeOH, rt |
| 2 | NaOH (1 M), THF, EtOH, rt |
| 3 | NaOH (3 M), MeOH, THF, rt |
| 4 | LiOH (1 M), THF, $H_2O$, 60 °C |
| 5 | LiOH (1 M), EtOH, MeCN, rt |
| 6 | $K_2CO_3$, MeOH, $H_2O$, 40 °C |
| 7 | $NEt_3$, THF, $H_2O$, rt |
| 8 | $NEt_3$, $H_2O$, rt |
| 9 | HCl (1M), $H_2O$, 110 °C |
| 10 | HCl (conc), dioxane, 110 °C |
| 11 | TMSCl, NaI, MeCN, 85 °C |
| 12 | TBAH, MeCN, rt |
| 13 | KF, TBAF, THF, 70°C |
| 14 | TMSOK, THF, rt |
| 15 | $NH_4OH$, THF, $H_2O$, rt |

## NMR Spectra

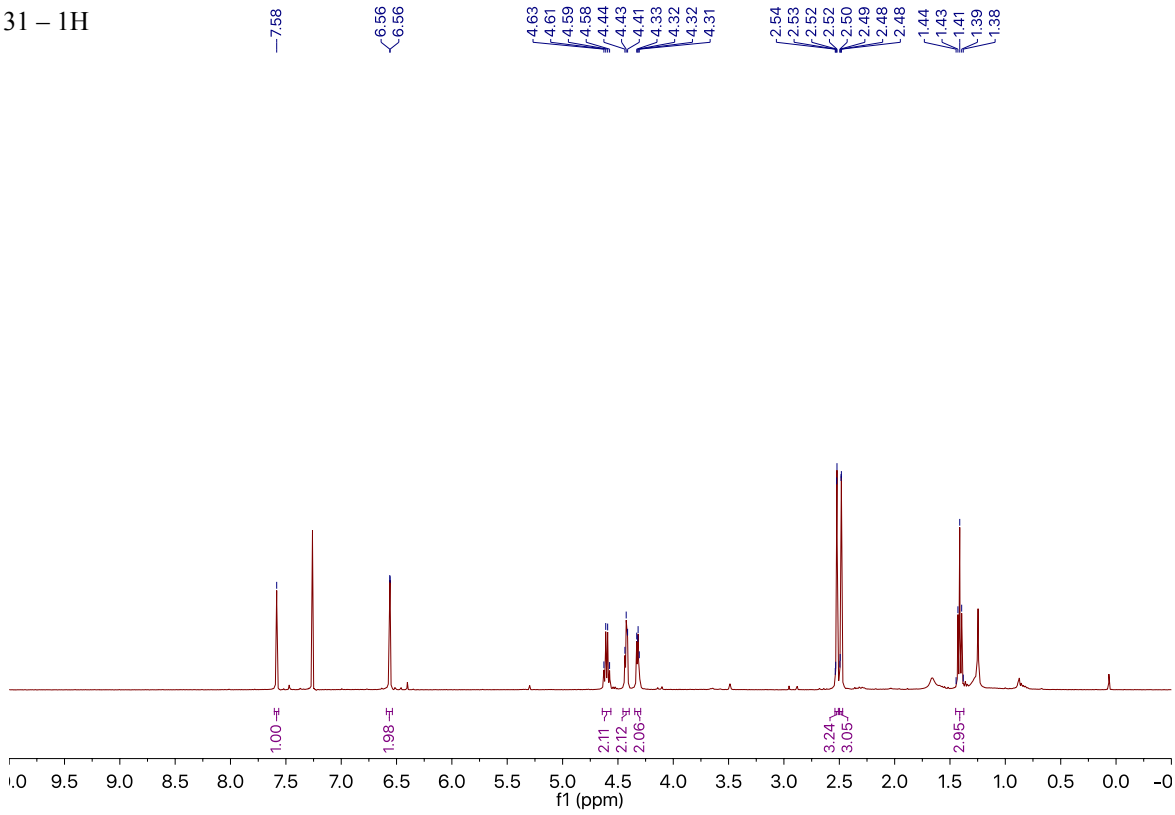
30 – 1H



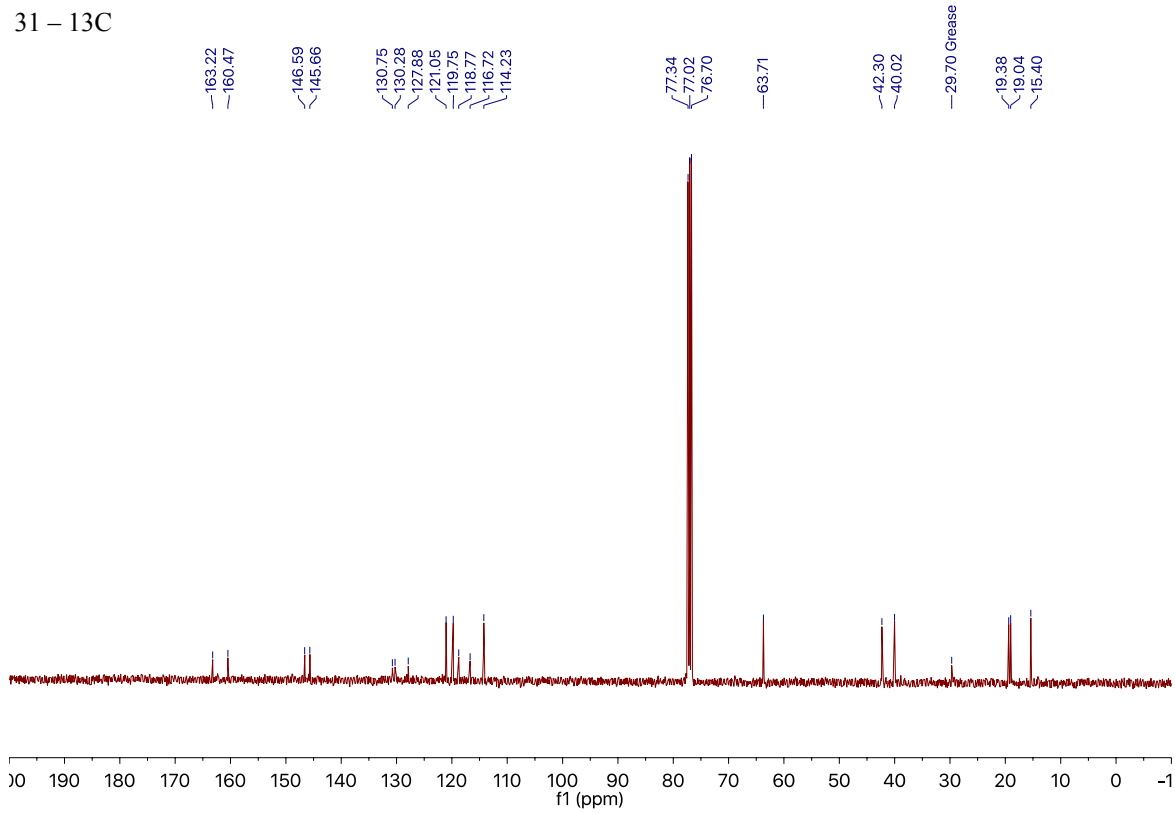

30 – 13C



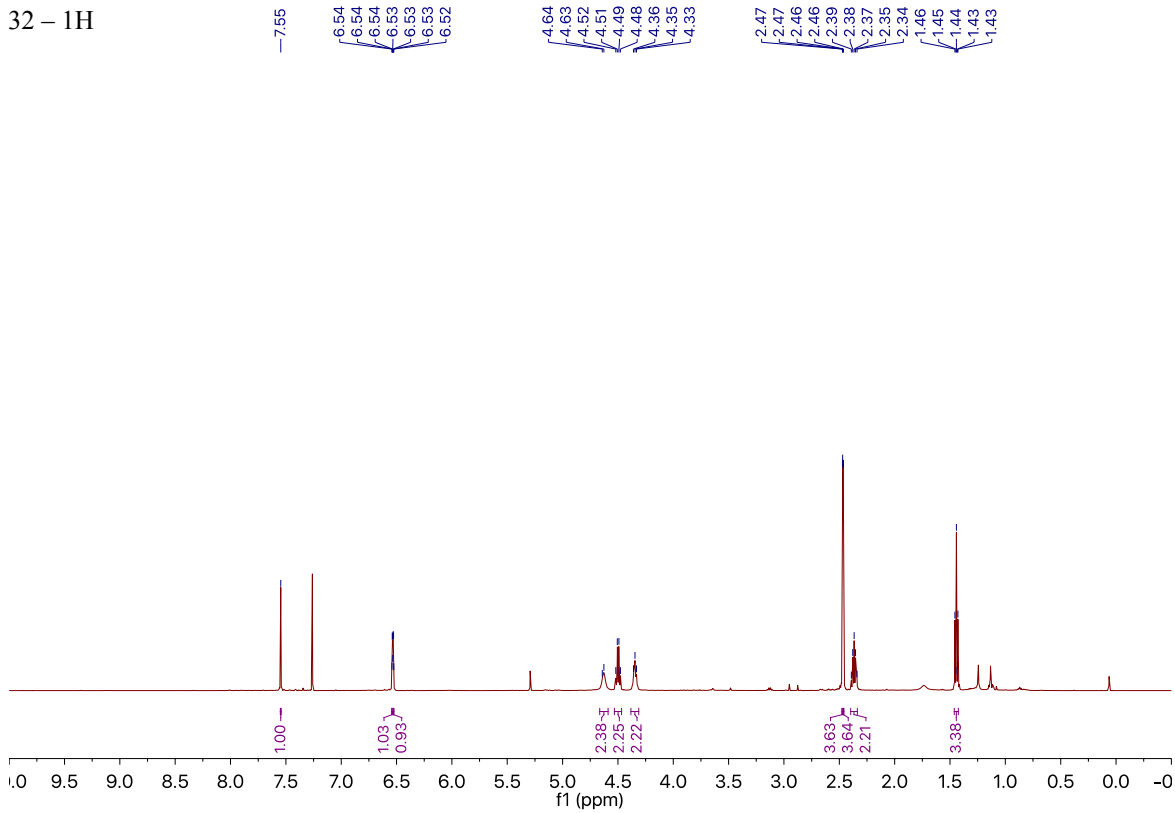
31 – 1H


7.58
6.56
6.56
4.63
4.61
4.59
4.58
4.44
4.43
4.41
4.33
4.32
4.32
4.31
2.54
2.53
2.52
2.52
2.50
2.49
2.48
2.48
1.44
1.43
1.41
1.39
1.38
1.00
1.98
2.11
2.12
2.08
3.24
3.05
2.95
f1 (ppm)

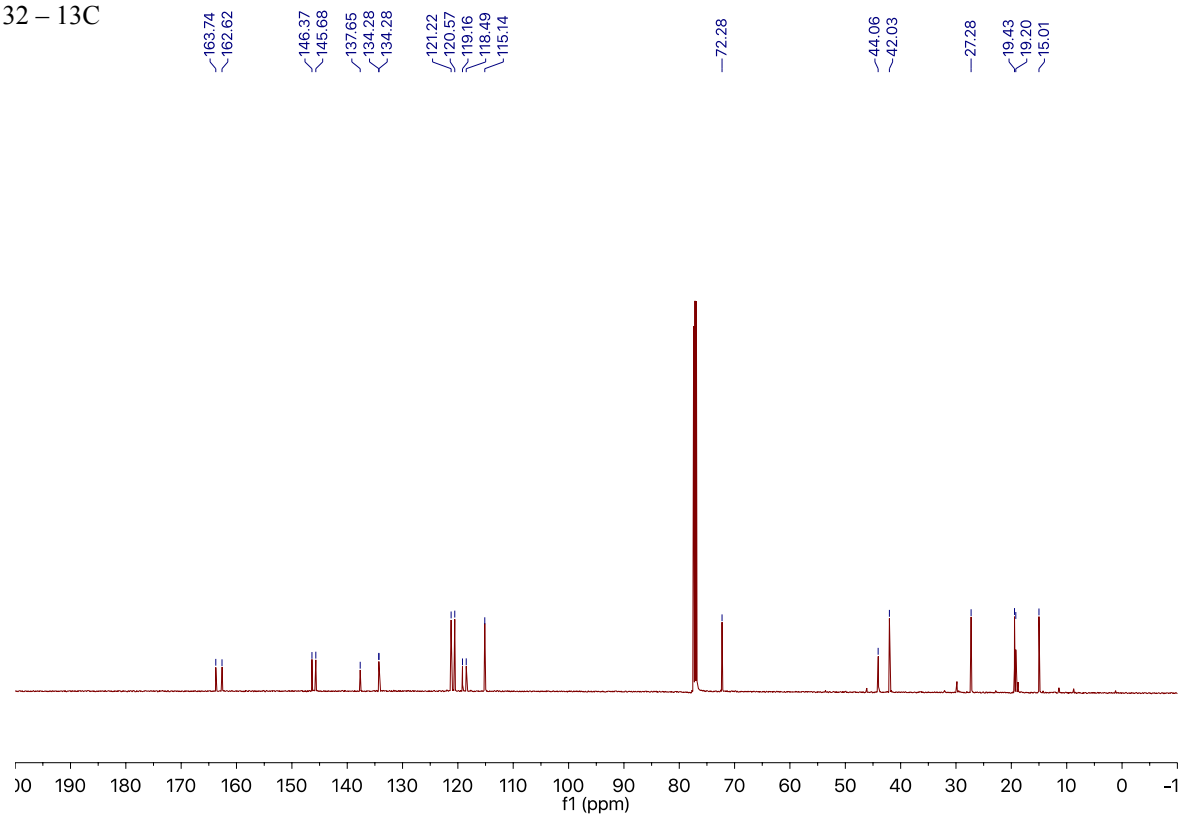
31 – 13C


163.22
160.47
146.59
145.66
130.75
130.28
127.88
121.05
119.75
118.77
116.72
114.23
77.34
77.02
76.70
63.71
42.30
40.02
29.70 Grease
19.38
19.04
15.40
f1 (ppm)

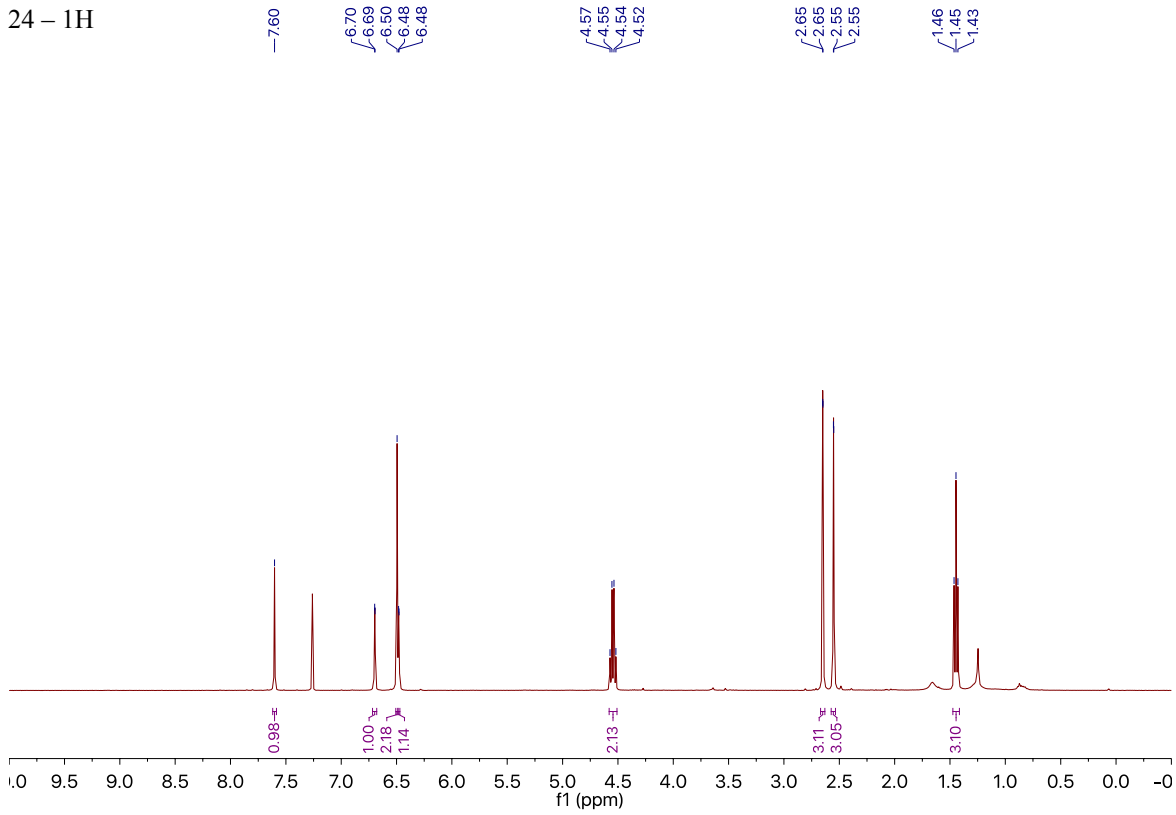
32 – 1H


7.55
6.54
6.54
6.54
6.53
6.53
6.52
4.64
4.63
4.52
4.51
4.49
4.48
4.36
4.35
4.33
2.47
2.47
2.46
2.46
2.39
2.38
2.37
2.35
2.34
1.46
1.45
1.44
1.43
1.43
1.00
1.03
0.93
2.38
2.25
2.22
3.63
3.64
2.21
3.38
f1 (ppm)

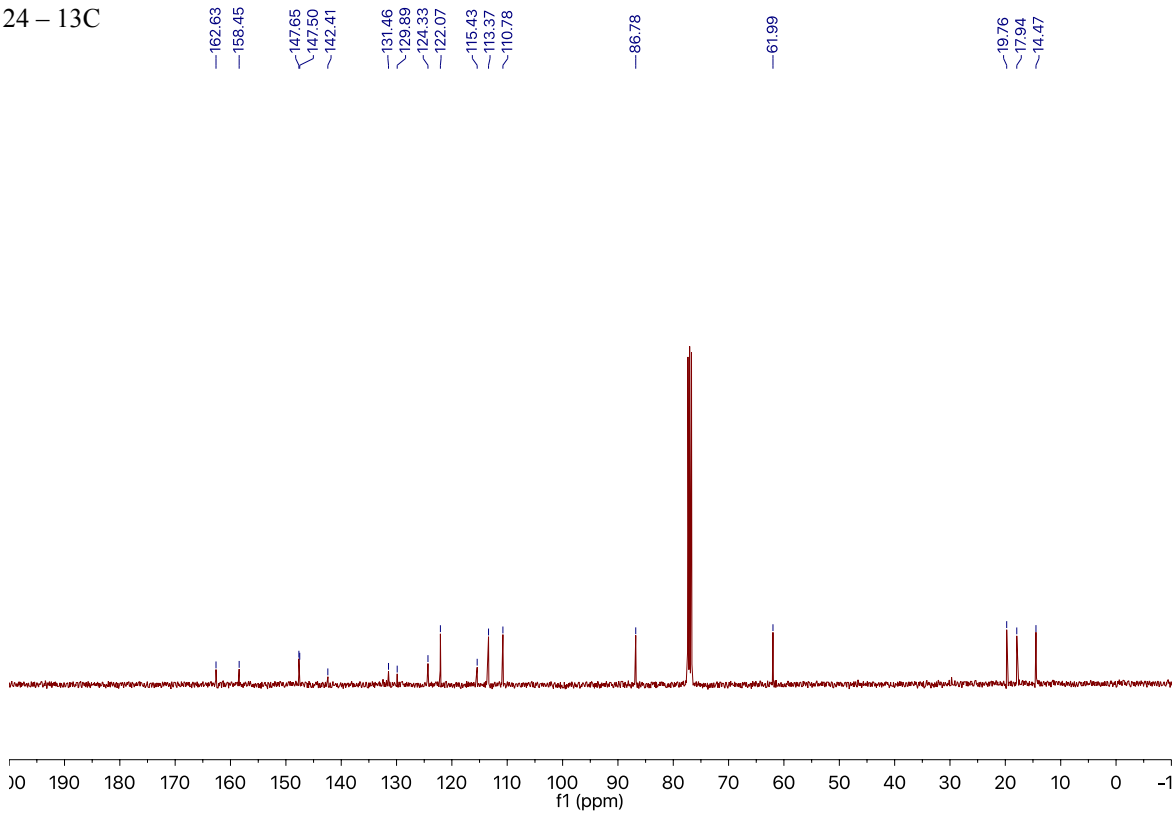
32 – 13C


163.74
162.62
146.37
145.68
137.65
134.28
134.28
121.22
120.57
119.16
118.49
115.14
72.28
44.06
42.03
27.28
19.43
19.20
15.01
f1 (ppm)

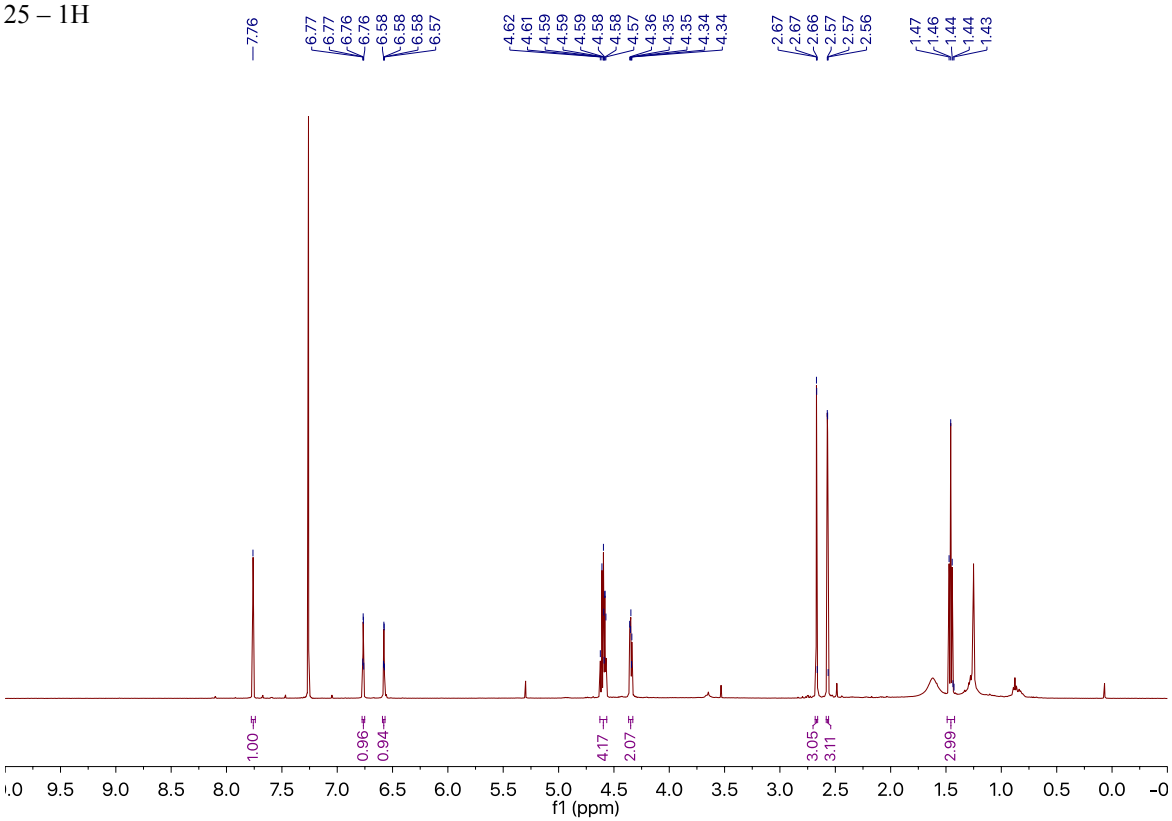
24 – 1H


7.60
6.70
6.69
6.50
6.48
6.48
4.57
4.55
4.54
4.52
2.65
2.65
2.55
2.55
2.55
1.46
1.45
1.43
0.98
1.00
2.18
1.14
2.13
3.11
3.05
3.10
f1 (ppm)

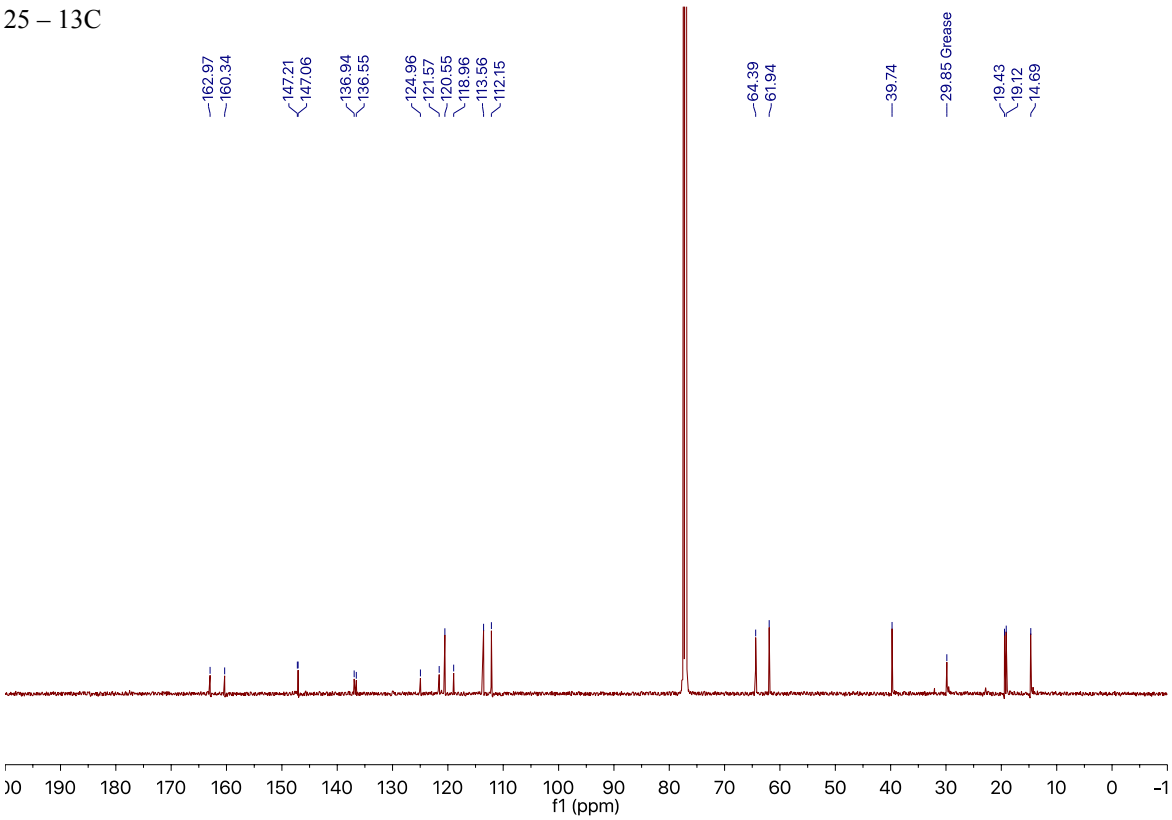
24 – 13C


162.63
158.45
147.65
147.50
142.41
131.46
129.89
124.33
122.07
115.43
113.37
110.78
86.78
61.99
19.76
17.94
14.47
f1 (ppm)

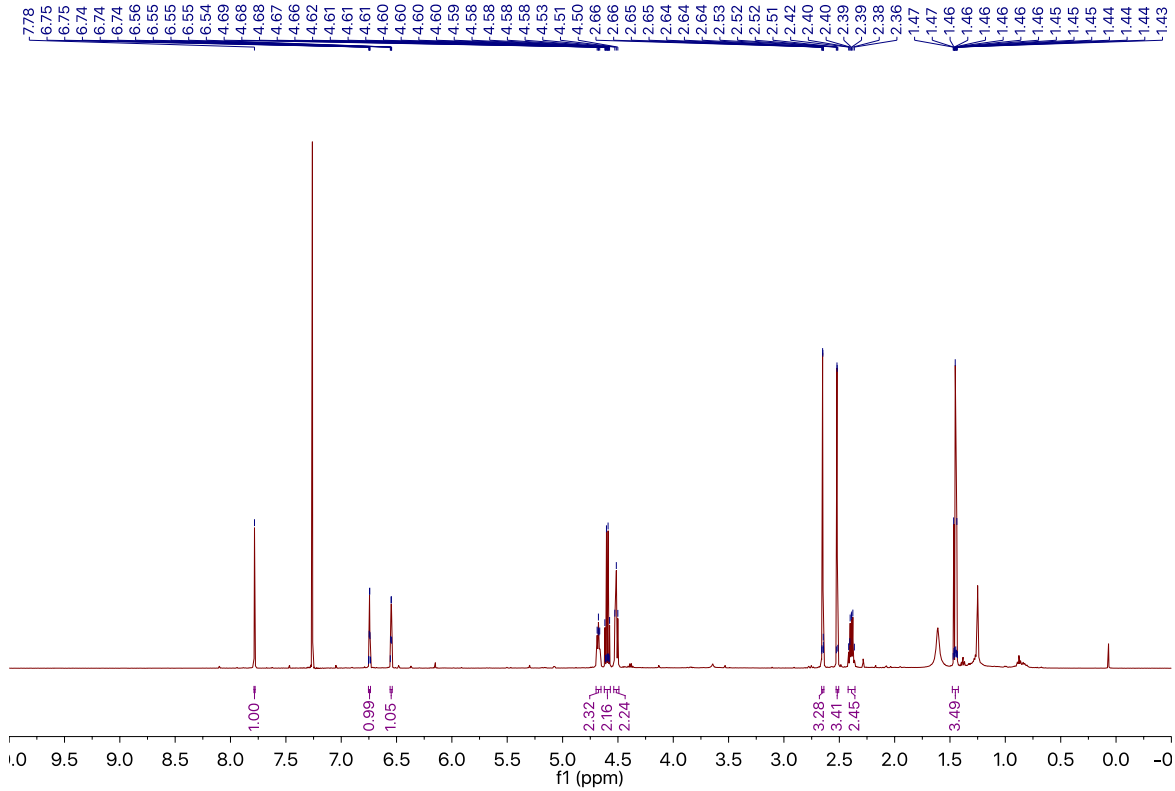
25 – 1H


7.76
6.77
6.77
6.76
6.76
6.58
6.58
6.58
6.57
4.62
4.61
4.59
4.59
4.59
4.58
4.58
4.57
4.36
4.35
4.35
4.34
4.34
2.67
2.67
2.66
2.57
2.57
2.56
1.47
1.46
1.44
1.44
1.43
1.00
0.96
0.94
4.17
2.07
3.05
3.11
2.99
f1 (ppm)

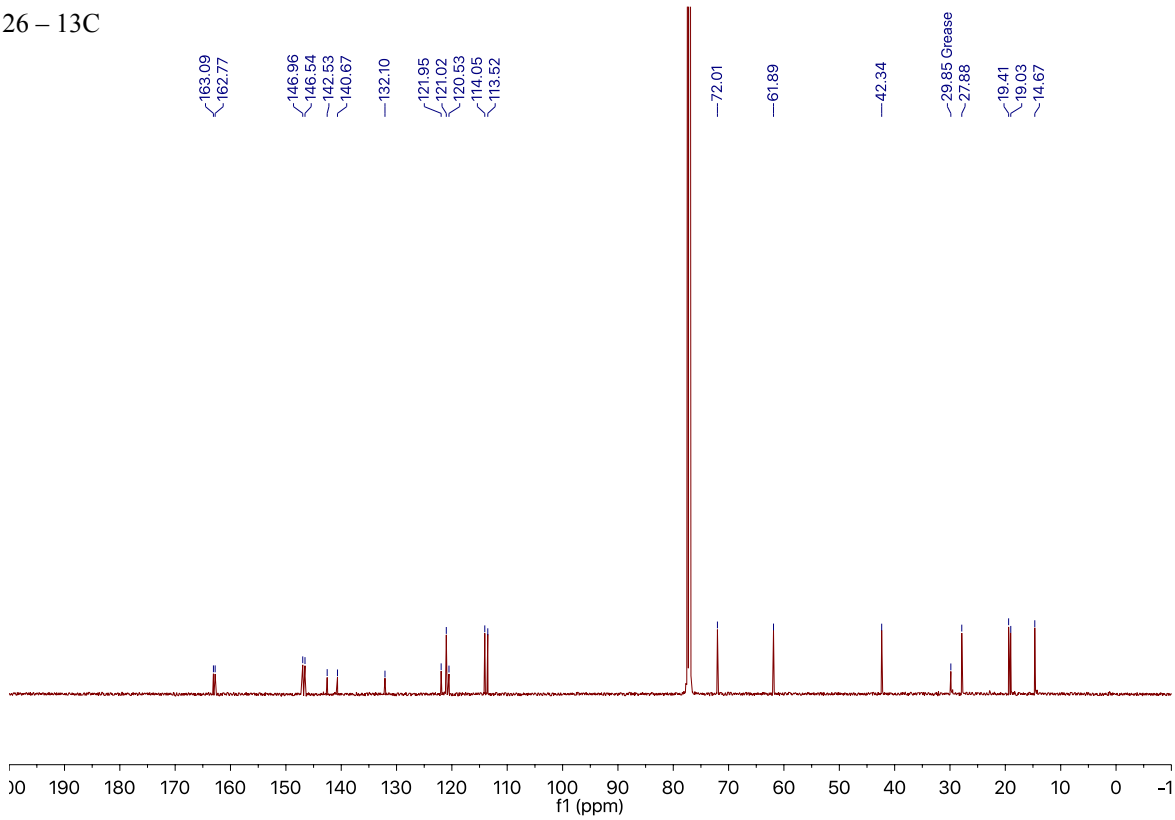
25 – 13C


162.97
160.34
147.21
147.06
136.94
136.55
124.96
121.57
120.55
118.96
113.56
112.15
64.39
61.94
39.74
29.85 Grease
19.43
19.12
14.69
f1 (ppm)

26 – 1H


7.78 6.75 6.75 6.74 6.74 6.56 6.55 6.55 6.55 6.54 4.69 4.68 4.68 4.67 4.66 4.62 4.61 4.61 4.61 4.60 4.60 4.60 4.60 4.60 4.59 4.58 4.58 4.58 4.58 4.53 4.51 4.50 2.66 2.66 2.65 2.65 2.64 2.64 2.64 2.53 2.52 2.52 2.51 2.42 2.40 2.40 2.39 2.39 2.38 2.36 1.47 1.47 1.46 1.46 1.46 1.46 1.46 1.45 1.45 1.45 1.44 1.44 1.44 1.43
1.00
0.99
1.05
2.32
2.16
2.24
3.28
3.41
2.45
3.49
f1 (ppm)

26 – 13C


163.09 162.77 146.96 146.54 142.53 140.67 132.10 121.95 121.02 120.53 114.05 113.52 72.01 61.89 42.34 29.85 Grease 27.88 19.41 19.03 14.67
f1 (ppm)

## X-Ray Crystallography

### The X-ray crystal structure of 18

*Crystal data for* **18**: $C_{14}H_{25}BO_4$, $M$ = 268.15, orthorhombic, $P2_12_12_1$ (no. 19), $a$ = 8.9148(5), $b$ = 9.6905(8), $c$ = 18.8528(13) Å, $V$ = 1628.7(2) Å$^3$, $Z$ = 4, $D_c$ = 1.094 g cm$^{-3}$, μ(Mo-Kα) = 0.077 mm$^{-1}$, $T$ = 173 K, colourless block, Agilent Xcalibur 3 E diffractometer; 2856 independent measured reflections ($R_{int}$ = 0.0331), $F^2$ refinement,[X1,X2] $R_1$(obs) = 0.0496, $wR_2$(all) = 0.1161, 2298 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, completeness to $\theta_{full}$(25.2°) = 98.3%], 202 parameters. The absolute structure of **18** could not be determined from the diffraction data [Flack parameter $x$ = –0.2(10)]. CCDC 1908213.

The $(CMe_2)_2$ portion of the $(CMe_2)_2O_2B$ ring in the structure of **18** was found to be disordered. Two orientations were identified of *ca*. 74 and 26% occupancy, their geometries were optimised, the thermal parameters of adjacent atoms were restrained to be similar, and only the non-hydrogen atoms of the major occupancy orientation were refined anisotropically (those of the minor occupancy orientation were refined isotropically).

### References


[X1] SHELXTL v5.1, Bruker AXS, Madison, WI, 1998.

[X2] SHELX-2013, G.M. Sheldrick, *Acta Cryst.*, 2015, **C71**, 3-8.


### Figures

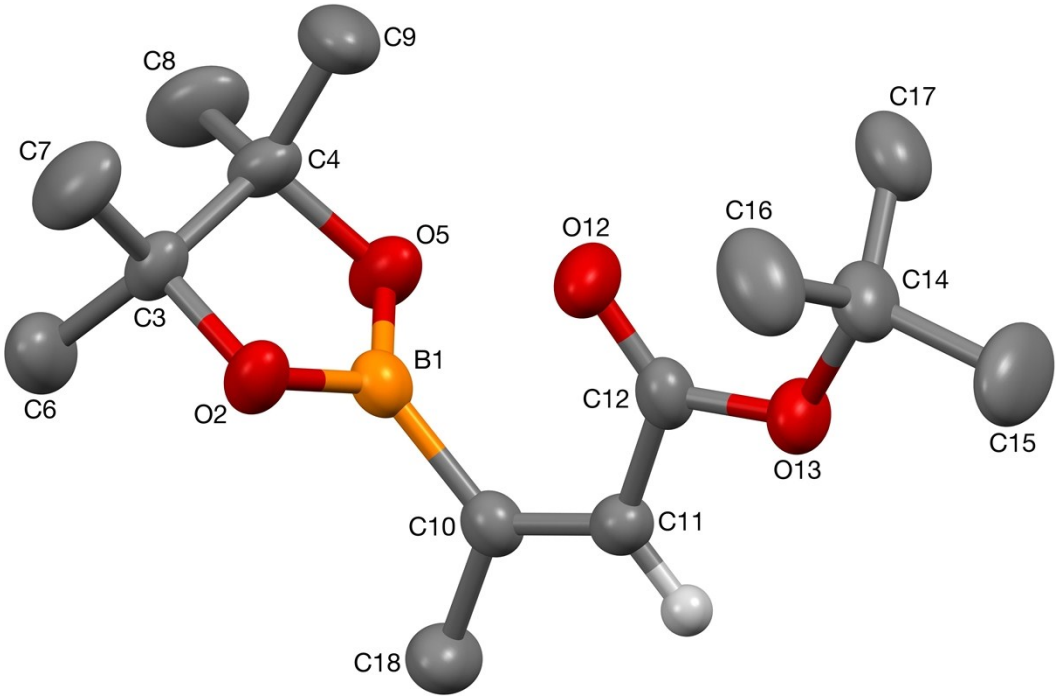



**Fig. S1** The crystal structure of **18** (50% probability ellipsoids).