

## Supporting Information

### Enantioselective Synthesis of Antibiotic Inducing Gamma-Butenolides from *Streptomyces rochei* and Derivatives

Haylie E. Hennigan<sup>1</sup>, Manuela Frias-Gomez<sup>1</sup>, Kylie G. Castator<sup>1</sup>, Lauren E. Wilbanks<sup>1</sup>, Caroline Zu<sup>1</sup>, Gracie Sanders<sup>1</sup>, and Elizabeth I. Parkinson<sup>1,2,\*</sup>

<sup>1</sup>James Tarpo Jr. and Margaret Tarpo Department of Chemistry, Purdue University, West Lafayette, IN, USA

<sup>2</sup>Borch Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, , West Lafayette, IN, USA

\*corresponding author: eparkins@purdue.edu

## Table of Contents

<b>Chemistry Methods</b> .....	<b>3</b>
General Remarks.....	3
Figure S1: Alkynylation Optimizations .....	3
General Procedure 1 (GP1): Enantioselective Alkynylation of 4-methylfuran-3-carbaldehyde	3
General Procedure 2 (GP2): Synthesis of Ligands .....	4
Figure S2: Synthesis of SRB1-11 .....	6
General Procedure 3 (GP3): Silyl Protection of Propargyl Alcohols .....	7
General Procedure 4 (GP4): Hydrogenation of Propargyl Silylethers.....	9
General Procedure 5 (GP5): Conversion of Methyl Esters to Weinreb Amides .....	11
General Procedure 6 (GP6): Alkylation of Weinreb Amides .....	12
General Procedure 7 (GP7): Synthesis of Grignard Reagents .....	12
Figure S3: Synthetic route to SRB10 and SRB11 .....	17
General Procedure 8 (GP8): Deprotection of Silyl Ethers.....	18
General Procedure 9 (GP9): Photo-oxidation of Furyl Alcohols.....	23
Figure S4: Initial Route to access SRB1 .....	29
<b>Biological Materials and Methods</b> .....	<b>34</b>
Figure S5. Plasmid map used for the SrrA-GFP reporter assay, with BioBrick parts and their corresponding IDs. <sup>5</sup> .....	34
Figure S6. SrrA GFP reporter assay results. ....	35
Table S1. Dose-response results of SrrA GFP reporter assay. ....	35
Figure S7. SRB1 regioisomer specific GFP activation.....	36
Table S2. Strains and plasmids used in this study .....	36
Table S3. Relevant sequences to this study .....	37
Table S4. Primer sequences used in this study .....	38
Strains, Media and Cloning conditions.....	38
SrrA GFP Assay Vector Cloning.....	39
GFP Induction Protocol and Flow cytometry Analysis .....	39
<b>References</b> .....	<b>39</b>
<b>Spectral Data</b> .....	<b>40</b>
Chiral HPLC Traces.....	40
<sup>1</sup> H and <sup>13</sup> C Spectra .....	46

# Chemistry Methods

## General Remarks

All reactions were performed in flame-dried glassware under an atmosphere of nitrogen unless otherwise noted. All reagents and solvents, unless otherwise stated, were purchased from Sigma Aldrich, Thermo Fisher, TCI, Oakwood, or Aaron Chemicals and used without further purification. The solvents tetrahydrofuran (THF), dichloromethane (DCM), toluene, and *N,N*-dimethylformamide (DMF) were dried with an Inert PurSolv solvent purifying system. The reactions were monitored using thin layer chromatography (TLC) plates, Silica gel 60 F<sub>254</sub> (20 cm x 20 cm), were purchased from Supelco. Purification via column chromatography was performed with silica gel (230-400 mesh) purchased from Silicycle. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on a Bruker 500 MHz or a Bruker 800 MHz spectrometer in chloroform-*d*. Chemical shifts ( $\delta$ ) are reported in parts per million (ppm) relative to chloroform (7.26 ppm). Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). IR spectra were taken on a Nicolet FTIR spectrometer. Optical rotations were measured from a Rudolph Autopol III S2 polarimeter. Chiral HPLC data was obtained from an Agilent 1220 Infinity LC using a Chiralpak AD-H column with the given conditions.

## Figure S1: Alkynylation Optimizations

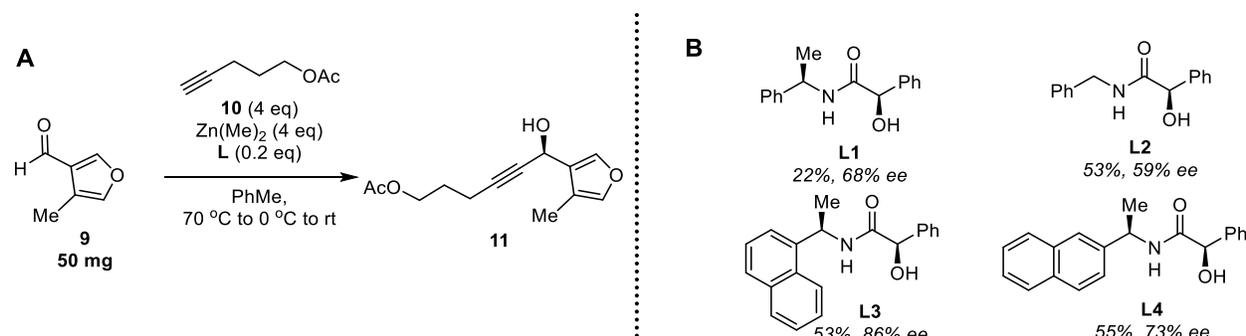
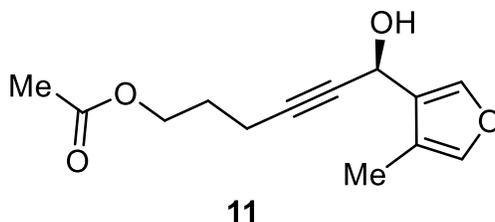


Figure S1 Ligand scan on a model system for the enantioselective alkynylation. Enantiomeric excess was determined by Chiral HPLC.

## General Procedure 1 (GP1): Enantioselective Alkynylation of 4-methylfuran-3-carbaldehyde

This was performed following the procedure developed by Blay and coworkers.<sup>1</sup> To a round bottom flask, equipped with a stir bar, was added alkyne (2.725 mmol, 4 equiv.) and toluene (15 mL). Dimethylzinc (10.901 mmol, 4 equiv.) was added dropwise to the flask over 10 minutes. The reaction was allowed to stir at room temperature for 1 h. In a separate conical flask was added the ligand **L** (0.545 mmol, 0.2 equiv.) and toluene (2 mL). The dispersion was heated to 70 °C in a silicone oil bath for 10 minutes or until **L** had completely dissolved. This solution was then quickly transferred to the first flask, and the reaction was heated at 70 °C. After 1 hour at this temperature, the reaction was brought to 0 °C in an ice bath and a solution of aldehyde<sup>2</sup> (2.725 mmol, 1 equiv.) in toluene (2 mL) was added dropwise over 10 minutes. The reaction was allowed to stir at room temperature for 14 hours, or until the aldehyde was consumed by TLC. The reaction was brought to 0 °C and quenched with 1M HCl (30 mL) *caution: reaction exotherms*. The phases were then separated, and the aqueous phase was extracted with EtOAc (30 mL x 2). Organic phases were combined, dried with MgSO<sub>4</sub>, gravity filtered, and concentrated under reduced pressure to afford a crude oil which was then purified on silica gel.



**(R)-6-hydroxy-6-(4-methylfuran-3-yl)hex-4-yn-1-yl acetate (11)** was prepared using aldehyde, **9** (50 mg, 0.454 mmol), pent-4-yn-1-yl acetate (240.6 mg, 1.816 mmol), dimethyl zinc (1M in heptanes, 1.82 mL, 1.816 mmol), and **L3** (55.6 mg, 0.182 mmol), and purified in 3:1 Hexanes:EtOAc to afford a pale-yellow oil, (57 mg, 53%). Enantiomeric excess was determined by chiral HPLC ( $t_R$  (major) = 6.64 min and  $t_R$  (minor) = 7.26 min, 86% ee).

**TLC:**  $R_f$  = 0.23 (3:1 Hexanes:EtOAc, visualized with ceric ammonium nitrate (CAN))

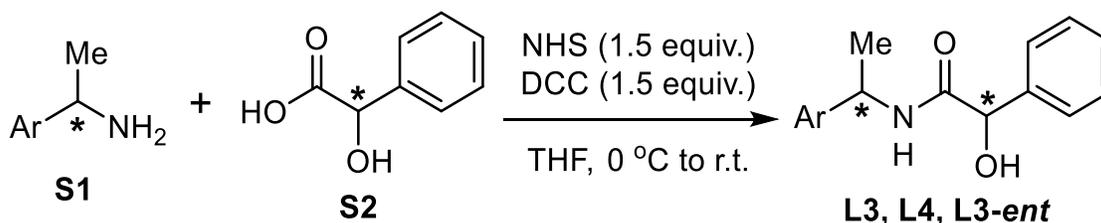
**$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.45 (s, 1H), 7.17 (s, 1H), 5.34 (s, 1H), 4.17 (t,  $J$  = 6.1 Hz, 2H), 2.36 (dt,  $J$  = 7.1, 2.0 Hz, 2H), 2.08 (s, 3H), 2.05 (s, 3H), 1.87 (p,  $J$  = 6.5 Hz, 2H).

**$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  171.09, 140.77, 140.71, 126.38, 119.10, 84.29, 80.12, 63.04, 56.90, 27.62, 20.94, 15.53, 8.18.

**FTIR** (neat):  $\nu$  1547.12  $\text{cm}^{-1}$ , 1737.69  $\text{cm}^{-1}$ , 3412.81  $\text{cm}^{-1}$

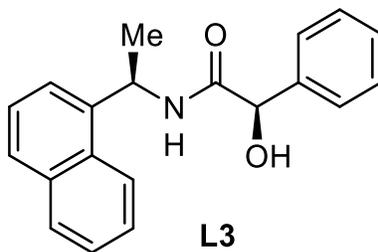
**HRMS** (ACPI+): calcd for  $\text{C}_{13}\text{H}_{15}\text{O}_3$  [ $\text{M}-\text{OH}$ ] $^-$  219.1027, found 219.1025 (-0.91 ppm)

$[\alpha]_D^{22}$ : -30.67°,  $c$  = 0.58 ( $\text{CHCl}_3$ )



### General Procedure 2 (GP2): Synthesis of Ligands

The synthesis of ligands **L1** and **L2** have been previously reported, and their spectra correspond to that reported in the literature.<sup>3</sup> Mandelic acid (**S2**, 5.84 mmol, 1 equiv.), amine (**S1**, 5.84 mmol, 1 equiv.), and *N*-hydroxysuccinimide (NHS, 8.76 mmol, 1.5 equiv.) were stirred in THF (60 mL) at 0 °C in a round bottom flask shielded from light. *N,N*-dicyclohexylcarbodiimide (DCC, 8.76 mmol, 1.5 equiv.) was added in one portion. The reaction was allowed to warm to room temperature and stirred overnight. The resulting solids were vacuum filtered, and the cake was washed with THF (30 mL, 2x). The filtrate was diluted with EtOAc (100 mL) and washed successively with a saturated solution of  $\text{NaHCO}_3$  (60 mL),  $\text{diH}_2\text{O}$  (60 mL), and 1M HCl (60 mL). The organic phase was then dried with  $\text{Na}_2\text{SO}_4$ , gravity filtered, and concentrated under reduced pressure. The resulting crude oil was purified via silica gel chromatography.



**(R)-2-hydroxy-N-((R)-1-(naphthalen-1-yl)ethyl)-2-phenylacetamide (L3)** was prepared using (R)-1-(1-naphthyl)ethylamine (0.94 mL, 5.84 mmol, 1 equiv.), (R)-mandelic acid (0.89 g, 5.84 mmol, 1 equiv.), NHS (1.01 g, 8.76 mmol, 1.5 equiv.), and DCC (1.82 g, 8.76 mmol, 1.5 equiv.) and purified in 3:2 Hexanes:EtOAc to afford a white solid (815 mg, 46%).

**TLC:**  $R_f = 0.32$  (3:2 Hex:EA, visualized with CAN)

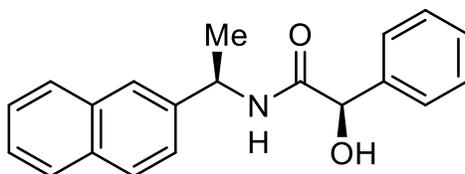
**$^1\text{H NMR}$  (500 MHz, DMSO)**  $\delta$  8.45 (d,  $J = 8.1$  Hz, 1H), 8.09 (dd,  $J = 6.1, 3.1$  Hz, 1H), 7.93 (dd,  $J = 6.0, 3.3$  Hz, 1H), 7.81 (d,  $J = 8.2$  Hz, 1H), 7.54 (d,  $J = 6.8$  Hz, 1H), 7.51 (dd,  $J = 6.3, 3.3$  Hz, 2H), 7.45 (d,  $J = 8.1$  Hz, 3H), 7.33 (t,  $J = 7.1$  Hz, 2H), 7.27 (dt,  $J = 7.3, 1.1$  Hz, 1H), 6.12 (d,  $J = 5.1$  Hz, 1H), 5.73 (p,  $J = 7.0$  Hz, 1H), 4.99 (d,  $J = 5.1$  Hz, 1H), 1.52 (d,  $J = 6.8$  Hz, 3H).

**$^{13}\text{C NMR}$  (126 MHz, DMSO)**  $\delta$  171.60, 141.75, 140.38, 133.82, 130.84, 129.10, 128.40, 127.87, 127.79, 127.10, 126.62, 126.05, 125.86, 123.62, 123.09, 73.89, 44.26, 21.94.

**FTIR** (neat):  $\nu$  1514.56  $\text{cm}^{-1}$ , 1657.20  $\text{cm}^{-1}$ , 3304.89  $\text{cm}^{-1}$

**HRMS** (ESI+): calcd for  $\text{C}_{20}\text{H}_{20}\text{NO}_2$   $[\text{M}+\text{H}]^+$  306.1489, found 306.1491 (0.65 ppm)

$[\alpha]_D^{23}$ :  $-135.11^\circ$ ,  $c = 0.29$  ( $\text{CHCl}_3$ )



**L4**

**(R)-2-hydroxy-N-((R)-1-(naphthalen-2-yl)ethyl)-2-phenylacetamide (L4)** was prepared using (R)-1-(2-naphthyl)ethylamine (100 mg, 0.58 mmol, 1 equiv.), (R)-mandelic acid (88 mg, 0.58 mmol, 1 equiv.), NHS (101 mg, 0.88 mmol, 1.5 equiv.), and DCC (182 mg, 0.88 mmol, 1.5 equiv.) and purified in 3:2 Hexanes:EtOAc to afford a white solid (70 mg, 40%).

**TLC:**  $R_f = 0.30$  (3:2 Hexanes:EtOAc, visualized with CAN)

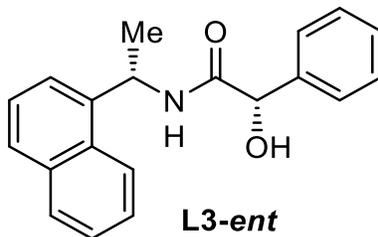
**$^1\text{H NMR}$  (500 MHz, DMSO)**  $\delta$  8.40 (d,  $J = 7.7$  Hz, 1H), 7.83 (t,  $J = 9.1$  Hz, 2H), 7.75 (d,  $J = 6.6$  Hz, 1H), 7.68 (s, 1H), 7.46 (d,  $J = 10.9$  Hz, 5H), 7.33 (t,  $J = 7.5$  Hz, 2H), 7.27 (d,  $J = 8.1$  Hz, 1H), 6.09 (d,  $J = 5.2$  Hz, 1H), 5.07 (p,  $J = 6.6$  Hz, 1H), 4.98 (d,  $J = 5.2$  Hz, 1H), 1.48 (d,  $J = 7.0$  Hz, 3H).

**$^{13}\text{C NMR}$  (126 MHz, DMSO)**  $\delta$  171.81, 142.42, 141.85, 133.29, 132.51, 128.43, 128.27, 128.04, 127.92, 127.88, 127.08, 126.57, 126.08, 125.48, 124.37, 73.89, 48.16, 24.96, 22.52.

**FTIR** (neat):  $\nu$  1525.60  $\text{cm}^{-1}$ , 1657.73  $\text{cm}^{-1}$ , 3318.62  $\text{cm}^{-1}$

**HRMS** (ESI+): calcd for  $\text{C}_{20}\text{H}_{20}\text{NO}_2$   $[\text{M}+\text{H}]^+$  306.1489, found 306.1495 (1.96 ppm)

$[\alpha]_D^{24}$ :  $-7.56^\circ$ ,  $c = 0.37$  ( $\text{CHCl}_3$ )



**L3-ent**

**(S)-2-hydroxy-N-((S)-1-(naphthalen-1-yl)ethyl)-2-phenylacetamide (L3-ent)** was prepared using (S)-1-(1-naphthyl)ethylamine (0.47 mL, 2.92 mmol, 1 equiv.), (S)-mandelic acid (444 mg, 2.92 mmol, 1 equiv.), NHS (504 mg, 4.38 mmol, 1.5 equiv.), and DCC (907 mg, 4.38 mmol, 1.5 equiv.) and purified in 3:2 Hexanes:EtOAc to afford a white solid, (479 mg, 54%).

**TLC:**  $R_f = 0.32$  (3:2 Hexanes:EtOAc, visualized with CAN)

**<sup>1</sup>H NMR (500 MHz, DMSO)** δ 8.45 (d, *J* = 7.9 Hz, 1H), 8.08 (dd, *J* = 6.3, 3.7 Hz, 1H), 7.94 (dd, *J* = 6.0, 3.6 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 7.3 Hz, 1H), 7.52 (dd, *J* = 6.3, 3.3 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 3H), 7.33 (t, *J* = 7.0 Hz, 2H), 7.27 (dt, *J* = 7.2, 1.3 Hz, 1H), 6.12 (d, *J* = 4.9 Hz, 1H), 5.73 (p, *J* = 7.6 Hz, 1H), 4.99 (d, *J* = 5.4 Hz, 1H), 1.52 (d, *J* = 7.2 Hz, 3H).

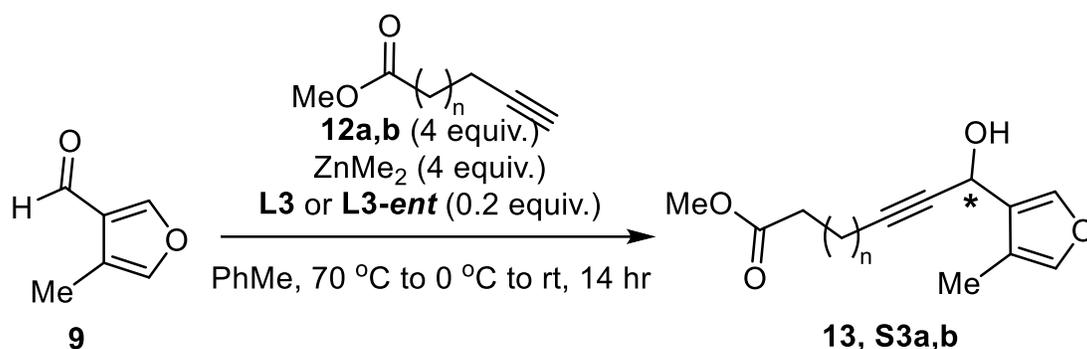
**<sup>13</sup>C NMR (126 MHz, DMSO)** δ 171.60, 141.75, 140.38, 133.82, 130.84, 129.10, 128.40, 127.87, 127.79, 127.10, 126.62, 126.05, 125.86, 123.62, 123.09, 73.89, 44.25, 21.94.

**FTIR** (neat): ν 1517.12 cm<sup>-1</sup>, 1657.14 cm<sup>-1</sup>, 3301.42 cm<sup>-1</sup>

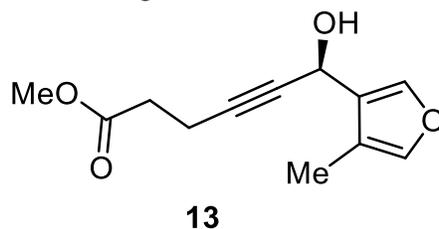
**HRMS** (ESI+): calcd for C<sub>20</sub>H<sub>20</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 306.1489, found 306.1493 (1.31 ppm)

**[α]<sub>D</sub><sup>24</sup>**: +130.25°, *c* = 0.31 (CHCl<sub>3</sub>)

### Figure S2: Synthesis of SRB1-11



The alkylation was performed according to GP1.



**Methyl (*R*)-6-hydroxy-6-(4-methylfuran-3-yl)hex-4-ynoate (**13**)** was prepared according to GP1 with **9** (300 mg, 2.77 mmol), 4-pentynoic acid methyl ester, **12a** (1.22 g, 10.90 mmol), dimethylzinc, (1.2M in toluene, 9.08 mL, 10.90 mmol), and **L3** (166 mg, 0.55 mmol) in toluene (30 mL). The reaction was purified in 3:1 Hexanes:EtOAc to afford a pale-yellow oil (473 mg, 78%). Enantiomeric excess was determined by chiral HPLC (*t*<sub>major</sub> = 5.33 min, *t*<sub>minor</sub> = 6.32 min, 92% ee). **TLC**: R<sub>f</sub> = 0.2 (3:1 Hexanes:EtOAc, visualized with CAN)

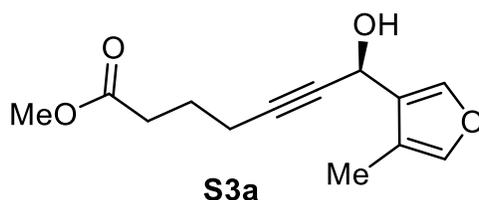
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.44 (s, 1H), 7.16 (s, 1H), 5.32 (s, 1H), 3.70 (s, 3H), 2.57 (s, 4H), 2.07 (m, 3H), 1.48 (s, 1H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 172.29, 140.87, 140.67, 126.28, 119.12, 83.70, 80.12, 56.84, 51.86, 33.21, 14.72, 8.15.

**FTIR** (neat): ν 1736.20 cm<sup>-1</sup>, 3443.41 cm<sup>-1</sup>

**HRSM (UPLCMS)**: *m/z* calc'd for C<sub>12</sub>H<sub>15</sub>O<sub>4</sub> [M+H]<sup>+</sup> 223.0965, found 223.0960 (-1.1 ppm)

**[α]<sub>D</sub><sup>21</sup>**: -8.46, *c* = 2.21 (CHCl<sub>3</sub>)



**Methyl (R)-7-hydroxy-7-(4-methylfuran-3-yl)hept-5-ynoate (S3a)** was prepared according to GP1 with **9** (250 mg, 2.27 mmol), methyl hex-5-ynoate, **12b** (1.14 g, 9.08 mmol), dimethylzinc, 1.2M in toluene (7.5 mL, 9.08 mmol), and **L3** (139 mg, 0.45 mmol) in toluene (20 mL). The reaction was purified in 3:1 Hexanes:EtOAc to afford a pale-yellow oil (290 mg, 54%). Enantiomeric excess was determined by Chiral HPLC ( $t_{\text{major}} = 5.91$  min,  $t_{\text{minor}} = 6.40$  min, 88% ee).

**TLC:** Rf = 0.26 (3:1 Hex:EA, visualized with CAN)

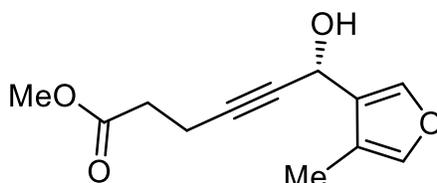
**<sup>1</sup>H NMR:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.44 (s, 1H), 7.17 (s, 1H), 5.33 (d, *J* = 5.6 Hz, 1H), 3.68 (s, 3H), 2.45 (t, *J* = 7.5 Hz, 2H), 2.33 (dt, *J* = 6.9, 1.6 Hz, 2H), 2.08 (s, 3H), 1.97 (d, *J* = 6.3 Hz, 1H), 1.87 (t, *J* = 7.3 Hz, 2H).

**<sup>13</sup>C NMR:** <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 173.53, 140.78, 140.69, 126.41, 119.12, 84.54, 80.24, 56.90, 51.54, 32.87, 23.71, 18.22, 8.18

**FTIR** (neat): ν 1735.65 cm<sup>-1</sup>, 3413.44 cm<sup>-1</sup>

**HRSM (UPLCMS):** *m/z* calc'd for C<sub>13</sub>H<sub>18</sub>O<sub>4</sub> [M+H]<sup>+</sup> 237.1121, found 237.1115 (-2.6 ppm)

$[\alpha]_D^{21}$ : -25.39, *c* = 0.47 (CHCl<sub>3</sub>)



**S3b**

**Methyl (S)-6-hydroxy-6-(4-methylfuran-3-yl)hex-4-ynoate (S3b)** was prepared according to GP1 with **9** (200 mg, 1.82 mmol), 4-pentynoic acid methyl ester, **12a** (815 mg, 7.27 mmol), dimethylzinc, (1.2M in toluene, 6.10 mL, 7.27 mmol), and **L3-ent** (111 mg, 0.36 mmol) in toluene (20 mL). The reaction was purified in 3:1 Hexanes:EtOAc to afford a pale-yellow oil (254 mg, 62%). Enantiomeric excess was determined by chiral HPLC ( $t_{\text{major}} = 6.32$  min,  $t_{\text{minor}} = 5.34$  min, 92% ee).

**TLC:** Rf = 0.19 (3:1 Hexanes:EtOAc, visualized with CAN)

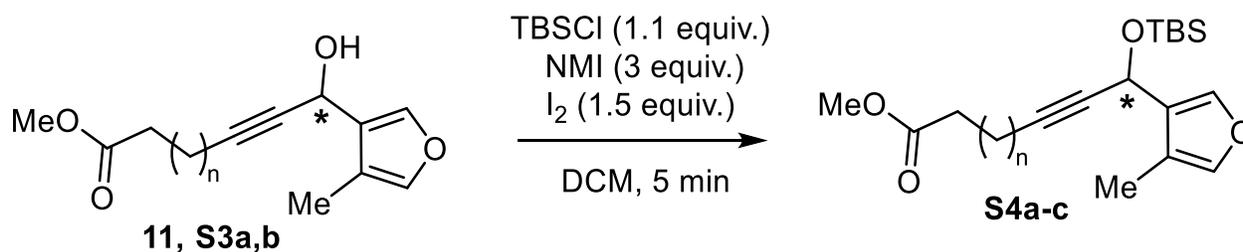
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.44 (s, 1H), 7.17 (s, 1H), 5.32 (s, 1H), 3.70 (s, 3H), 2.62 – 2.53 (m, 4H), 2.07 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 172.28, 140.88, 140.68, 126.27, 119.12, 83.72, 80.10, 56.86, 51.86, 33.21, 31.62, 14.72, 8.15.

**FTIR** (neat): ν 1736.70 cm<sup>-1</sup>, 3372.24 cm<sup>-1</sup>

**HRSM (ESI +):** *m/z* calc'd for C<sub>12</sub>H<sub>14</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup> 245.0784, found 245.0785 (-2.4 ppm)

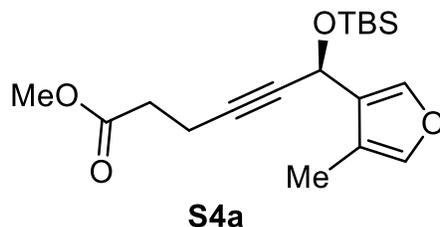
$[\alpha]_D^{21}$ : +8.00, *c* = 0.25 (CHCl<sub>3</sub>)



### General Procedure 3 (GP3): Silyl Protection of Propargyl Alcohols

A solution of propargyl alcohol (1.80 mmol, 1 equiv.) and N-methylimidazole (5.40 mmol, 3 equiv.) in DCM (18 mL) were stirred in a round bottom flask. Iodine (2.70 mmol, 1.5 equiv.) followed by TBSCl (1.98 mmol, 1.5 equiv.) was added to the flask and the reaction was stirred for 5 minutes

before the solvent was removed *in vacuo*. The resulting brown oil was dissolved in EtOAc (20 mL) and transferred to a separatory funnel containing a saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (20 mL). The phases were mixed until the color disappeared. The aqueous phase was removed and the EtOAc was washed with diH<sub>2</sub>O (20mL). The organic phase was removed and dried with MgSO<sub>4</sub>, gravity filtered, and concentrated. The resulting crude oil was *immediately* purified on a short plug of silica.



**Methyl (R)-6-((tert-butyldimethylsilyl)oxy)-6-(4-methylfuran-3-yl)hex-4-ynoate (S4a)** was prepared according to GP3 with **13** (400 mg, 1.80 mmol), *N*-methylimidazole (0.43 mL, 5.40 mmol), iodine (685 mg, 2.70 mmol), and TBSCl (298 mg, 1.98 mmol) in DCM (18 mL). The reaction was purified in 19:1 Hexanes:EtOAc to afford a pale-yellow oil (464 mg, 77%).

**TLC:** R<sub>f</sub>: 0.32 (19:1 Hexanes: EtOAc, visualized with KMnO<sub>4</sub>)

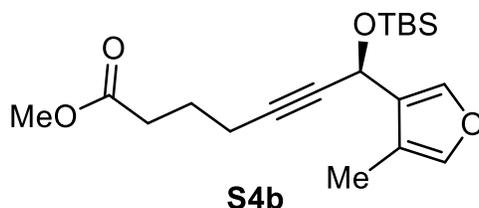
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.35 (s, 1H), 7.13 (s, 1H), 5.36 (s, 1H), 3.69 (s, 3H), 2.57 – 2.52 (m, 4H), 2.04 (s, 3H), 0.90 (s, 10H), 0.14 (s, 3H), 0.12 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 172.27, 140.31, 140.18, 127.05, 119.03, 83.04, 80.93, 57.78, 51.78, 33.24, 25.80, 18.23, 14.74, 8.39, -4.41, -4.83.

**FTIR** (neat): ν 1742.59 cm<sup>-1</sup>

**HRSM (ESI +):** m/z calcd for C<sub>18</sub>H<sub>28</sub>NaO<sub>4</sub>Si [M+Na]<sup>+</sup> 359.1649, found 359.1652 (0.7 ppm)

[α]<sub>D</sub><sup>21</sup>: -25.09, c = 0.51 (CHCl<sub>3</sub>)



**methyl (R)-7-((tert-butyldimethylsilyl)oxy)-7-(4-methylfuran-3-yl)hept-5-ynoate (S4b)** was prepared according to GP3 with **S3a** (112 mg, 0.47mmol), *N*-methylimidazole (0.11 mL, 1.40 mmol), iodine (180 mg, 0.71 mmol), and TBSCl (107 mg, 0.71 mmol) in DCM (4.7mL). The reaction was purified in 3:1 Hexanes:EtOAc to afford a pale-yellow oil (112 mg, 68%).

**TLC:** R<sub>f</sub> = 0.29 (19:1 Hexanes:EtOAc, visualized with KMnO<sub>4</sub>)

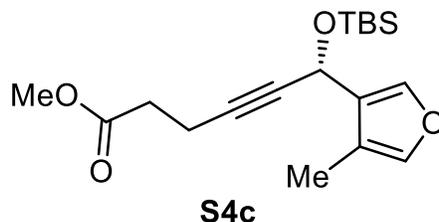
**<sup>1</sup>H NMR:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.35 (s, 1H), 7.14 (s, 1H), 5.37 (s, 1H), 3.67 (s, 3H), 2.43 (t, *J* = 7.6 Hz, 2H), 2.30 (dd, *J* = 7.0, 1.8 Hz, 2H), 2.05 (s, 3H), 1.84 (d, *J* = 7.1 Hz, 2H), 0.90 (s, 9H), 0.13 (d, *J* = 9.4 Hz, 6H).

**<sup>13</sup>C NMR:** <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 173.53, 140.33, 140.10, 127.20, 119.02, 83.86, 81.07, 57.83, 51.58, 32.85, 25.80, 23.77, 18.23, 8.43, -4.42, -4.82.

**FTIR** (neat): ν 1735.65 cm<sup>-1</sup>

**HRSM (UPLCMS):** m/z calc'd for C<sub>19</sub>H<sub>30</sub>NaO<sub>4</sub>Si [M+Na]<sup>+</sup> 373.1806, found 373.1785 (-5.6 ppm)

[α]<sub>D</sub><sup>21</sup>: -22.04, c = 0.48 (CHCl<sub>3</sub>)



**Methyl (S)-6-((tert-butyldimethylsilyl)oxy)-6-(4-methylfuran-3-yl)hex-4-ynoate (S5c)** was prepared according to GP3 with **S3b** (250 mg, 1.13 mmol), *N*-methylimidazole (0.27 mL, 3.38 mmol), iodine (428 mg, 1.69 mmol), and TBSCl (187 mg, 1.24 mmol) in DCM (10 mL). The reaction was purified in 19:1 Hexanes:EtOAc to afford a pale-yellow oil (233 mg, 62%).

**TLC:**  $R_f$ : 0.40 (19:1 Hexanes: EtOAc, visualized with  $\text{KMnO}_4$ )

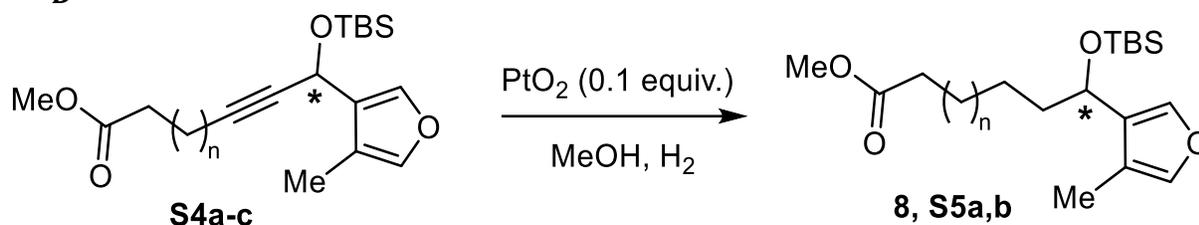
**$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 (s, 1H), 7.13 (s, 1H), 5.36 (s, 1H), 3.69 (s, 3H), 2.55 (m, 4H), 2.04 (s, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H).

**$^{13}\text{C NMR}$**  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  172.27, 140.31, 140.18, 127.05, 119.03, 83.04, 80.93, 57.78, 51.77, 33.24, 25.80, 18.23, 14.73, 8.39, -4.41, -4.83.

**FTIR** (neat):  $\nu$  1741.47  $\text{cm}^{-1}$

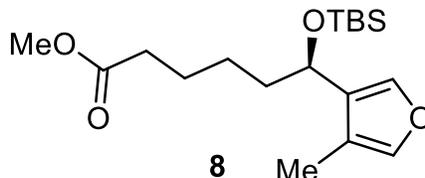
**HRSM (ESI +):**  $m/z$  calcd for  $\text{C}_{18}\text{H}_{28}\text{NaO}_4\text{Si}$   $[\text{M}+\text{Na}]^+$  359.1649, found 359.1651 (0.6 ppm)

$[\alpha]_D^{22}$ : +18.91,  $c$  = 0.55 ( $\text{CHCl}_3$ )



#### General Procedure 4 (GP4): Hydrogenation of Propargyl Silylethers

In a round bottom flask equipped with a stir bar was dissolved silyl protected propargyl alcohol (1.37 mmol, 1 equiv.) in MeOH (14 mL). The solution was sparged with a nitrogen balloon for 10 minutes.  $\text{PtO}_2$  (0.14 mmol, 0.1 equiv.) was then added to the vessel and sparged with a nitrogen balloon for an additional 10 minutes. Then the solution was sparged for 30 minutes with a hydrogen balloon. After which, the vent needle was removed, and the reaction was stirred under an atmosphere of hydrogen for 30 minutes. The reaction was then vacuum filtered over a short pad of celite and the celite cake was washed with EtOAc (20 mL x 2). The filtrate was concentrated under reduced pressure to afford the crude material which was purified on a plug of silica.



**Methyl (R)-6-((tert-butyldimethylsilyl)oxy)-6-(4-methylfuran-3-yl)hexanoate (8)** was prepared according to GP4 with **S4a** (460 mg, 1.37 mmol) and platinum (VI) dioxide (31 mg, 0.14 mmol), in MeOH (14 mL). The reaction was purified in 19:1 Hexanes:EtOAc to afford a clear oil (233 mg, 62%).

**TLC:**  $R_f$ : 0.43 (19:1 Hexanes: EtOAc, visualized with  $\text{KMnO}_4$ )

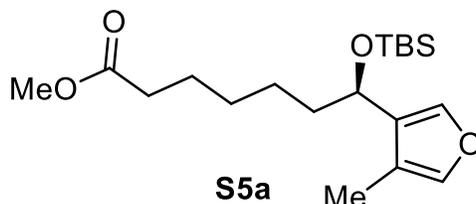
**$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.20 (s, 1H), 7.11 (s, 1H), 4.59 (t,  $J$  = 7.0 Hz, 1H), 3.65 (s, 3H), 2.29 (d,  $J$  = 7.4 Hz, 2H), 2.00 (s, 3H), 1.80 – 1.67 (m, 1H), 1.67 – 1.57 (m, 3H), 1.44 – 1.35 (m, 1H), 1.35 – 1.22 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), -0.09 (s, 3H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  174.16, 140.10, 139.68, 129.09, 118.53, 67.72, 51.46, 38.29, 34.11, 25.82, 25.16, 24.87, 18.18, 8.82, -4.71, -5.08.

FTIR (neat):  $\nu$  1741.61  $\text{cm}^{-1}$

HRSM (ESI +):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{32}\text{NaO}_4\text{Si}$   $[\text{M}+\text{Na}]^+$  363.1962, found 363.1966 (1.1 ppm)

$[\alpha]_D^{23}$ : +28.72,  $c$  = 0.63 ( $\text{CHCl}_3$ )



**Methyl (R)-7-((tert-butyldimethylsilyl)oxy)-7-(4-methylfuran-3-yl)heptanoate (S5a)** was prepared according to GP4 with **S4b** (160 mg, 0.46 mmol), and platinum (VI) dioxide (10 mg, 0.05 mmol), in MeOH (4.6 mL). The reaction was purified in 3:1 Hexanes:EtOAc to afford a pale-yellow oil (11 mg, 68%).

TLC:  $R_f$  = 0.29 (19:1 Hexanes:EtOAc, visualized with  $\text{KMnO}_4$ )

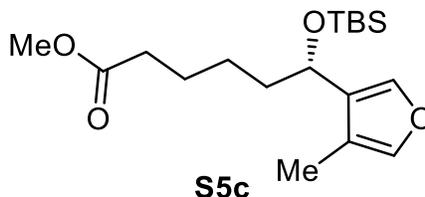
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19 (s, 1H), 7.11 (s, 1H), 4.58 (t,  $J$  = 5.4 Hz, 1H), 3.66 (s, 3H), 2.29 (t,  $J$  = 7.5 Hz, 2H), 2.01 (s, 3H), 1.77 – 1.21 (m, 8H), 0.87 (s, 9H), 0.02 (s, 3H), -0.09 (s, 3H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.53, 140.33, 139.63, 127.20, 118.57, 67.85, 51.46, 38.56, 34.06, 29.03, 25.83, 25.29, 24.96, 8.84, -4.70, -5.06.

FTIR (neat):  $\nu$  1731.79  $\text{cm}^{-1}$

HRSM (UPLCMS):  $m/z$  calc'd for  $\text{C}_{19}\text{H}_{34}\text{NaO}_4\text{Si}$   $[\text{M}+\text{Na}]^+$  377.2119, found 377.2133 (3.9 ppm)

$[\alpha]_D^{21}$ : +3.71,  $c$  = 0.37 ( $\text{CHCl}_3$ )



**Methyl (S)-6-((tert-butyldimethylsilyl)oxy)-6-(4-methylfuran-3-yl)hexanoate (S5b)** was prepared according to GP4 with **S4c** (220 mg, 0.65 mmol) and platinum (VI) dioxide (15 mg, 0.07 mmol), in MeOH (7 mL). The reaction was purified in 19:1 Hexanes:EtOAc to afford a clear oil (143 mg, 64%).

TLC:  $R_f$  = 0.39 (19:1 Hexanes:EtOAc, visualized with  $\text{KMnO}_4$ )

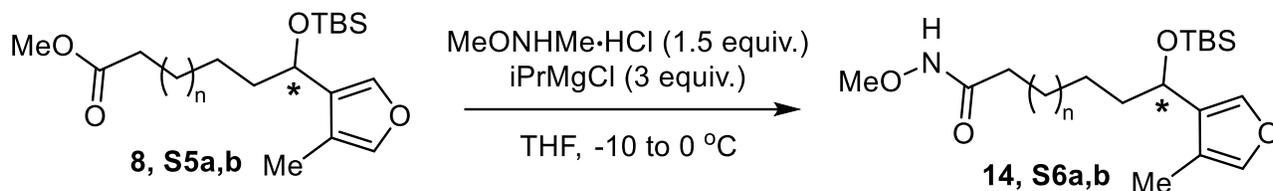
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19 (s, 1H), 7.11 (s, 1H), 4.59 (dd,  $J$  = 7.1, 5.4 Hz, 1H), 3.65 (s, 3H), 2.29 (t,  $J$  = 7.5 Hz, 2H), 2.00 (s, 3H), 1.78 – 1.67 (m, 1H), 1.67 – 1.57 (m, 3H), 1.44 – 1.33 (m, 1H), 1.33 – 1.22 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), -0.09 (s, 3H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  174.16, 140.09, 139.68, 129.09, 118.53, 67.72, 51.46, 38.29, 34.11, 25.90, 25.86, 25.82, 25.16, 24.87, 8.83, -4.71, -5.08.

FTIR (neat):  $\nu$  1741.69  $\text{cm}^{-1}$

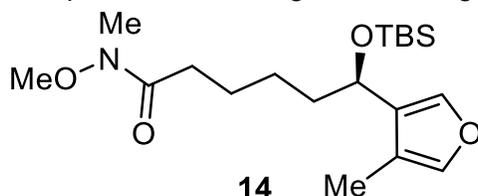
HRSM (ESI +):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{40}\text{NaO}_4\text{Si}$   $[\text{M}+\text{Na}]^+$  363.1962, found 363.1965 (-0.8 ppm)

$[\alpha]_D^{22}$ : -36.49,  $c$  = 0.20 ( $\text{CHCl}_3$ )



### General Procedure 5 (GP5): Conversion of Methyl Esters to Weinreb Amides

A solution of methyl ester (0.59 mmol, 1 equiv.) and *N,O*-dimethylhydroxyamine hydrochloride (0.88 mmol, 1.5 equiv.) in THF (6 mL) was stirred at -10 °C in a salt-ice bath. Once at temperature, *i*PrMgCl (1.76 mmol, 3 equiv.) was added dropwise over 10 min. The reaction was then stirred in a 4 °C refrigerator for 3 hours, or until the methyl ester was consumed by TLC. The reaction was then diluted with EtOAc (6 mL) and quenched with a saturated solution of NH<sub>4</sub>Cl (10 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (10 mL x 2). Combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, gravity filtered, and concentrated under reduced pressure. The crude material was purified via silica gel chromatography.



**(R)-6-((tert-butyldimethylsilyl)oxy)-N-methoxy-N-methyl-6-(4-methylfuran-3-yl)hexanamide (14)** was prepared according to GP5 with **12** (275 mg, 0.81 mmol), Weinreb salt (118 mg, 1.21 mmol), and *i*PrMgCl (2M in Et<sub>2</sub>O, 1.21 mL, 2.42) in THF (8 mL). The reaction was purified in 4:1 Hexanes:EtOAc to afford a clear oil (270 mg, 90%).

**TLC:** R<sub>f</sub> = 0.36 (4:1 Hexanes:EtOAc, visualized in KMnO<sub>4</sub>)

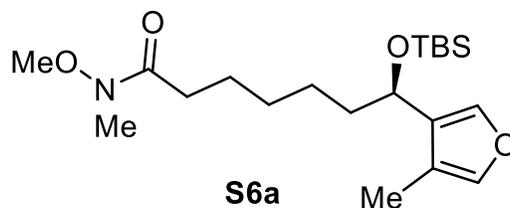
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.19 (s, 1H), 7.11 (s, 1H), 4.60 (s, 1H), 3.66 (s, 3H), 3.17 (s, 3H), 2.39 (s, 2H), 2.01 (s, 3H), 1.74 (s, 1H), 1.63 (s, 3H), 1.47 – 1.20 (m, 2H), 0.87 (d, *J* = 1.1 Hz, 9H), 0.02 (s, 3H), -0.09 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 174.68, 140.06, 139.67, 129.18, 118.60, 67.76, 61.21, 38.50, 31.90, 29.72, 25.83, 25.47, 24.56, 18.20, 8.84, -4.71, -5.05.

**FTIR** (neat): ν 1668.81 cm<sup>-1</sup>

**HRMS (UPLCMS):** *m/z* calcd for C<sub>19</sub>H<sub>36</sub>NO<sub>4</sub>Si [M+H]<sup>+</sup> 370.2408, found 370.2411 (0.8 ppm)

[α]<sub>D</sub><sup>23</sup>: +28.53, *c* = 0.69 (CHCl<sub>3</sub>)



**(R)-7-((tert-butyldimethylsilyl)oxy)-N-methoxy-N-methyl-7-(4-methylfuran-3-yl)heptanamide (S6a)** was prepared according to GP5 with **S5a** (110 mg, 0.31 mmol), Weinreb salt (46 mg, 0.47 mmol), and *i*PrMgCl (2M in THF, 0.47 mL, 0.93 mmol) in THF (3.1 mL). The reaction was purified in 3:1 Hexanes:EtOAc to afford a pale-yellow oil (115 mg, 96%).

**TLC:** R<sub>f</sub> = 0.24 (4:1 Hex:EA, visualized with KMnO<sub>4</sub>)

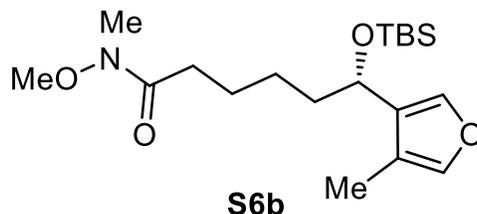
**<sup>1</sup>H NMR:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.19 (s, 1H), 7.10 (s, 1H), 4.58 (t, *J* = 5.5 Hz, 1H), 3.66 (s, 3H), 3.16 (s, 3H), 2.39 (t, *J* = 7.3 Hz, 2H), 2.00 (s, 3H), 1.77 – 1.67 (m, 1H), 1.67 – 1.56 (m, 3H), 1.44 – 1.24 (m, 4H), 0.86 (s, 9H), 0.02 (s, 3H), -0.10 (s, 3H).

<sup>13</sup>CNMR: (126 MHz, CDCl<sub>3</sub>) δ 174.73, 140.00, 139.61, 129.31, 118.59, 67.91, 61.18, 38.67, 31.83, 29.30, 25.83, 25.48, 24.64, 18.20, 8.83, -4.71, -5.05.

FTIR (neat): ν 1666.22 cm<sup>-1</sup>

HRSM (UPLCMS): m/z calc'd for C<sub>19</sub>H<sub>30</sub>NO<sub>4</sub>NaSi [M+Na]<sup>+</sup> 406.2384, found 406.2372 (-3.0 ppm)

[α]<sub>D</sub><sup>21</sup>: +68.00, c = 0.51 (CHCl<sub>3</sub>)



**(S)-6-((tert-butyldimethylsilyl)oxy)-N-methoxy-N-methyl-6-(4-methylfuran-3-yl)hexanamide (S6b)** was prepared according to GP5 with **S5b** (130 mg, 0.382 mmol),

Weinreb salt (56 mg, 0.573 mmol), and iPrMgCl, (2M in Et<sub>2</sub>O, 0.57 mL, 1.146) in THF (4 mL). The reaction was purified in 4:1 Hexanes:EtOAc to afford a clear oil (94 mg, 66%).

TLC: R<sub>f</sub> = 0.29 (4:1 Hex:EA, visualized in KMnO<sub>4</sub>)

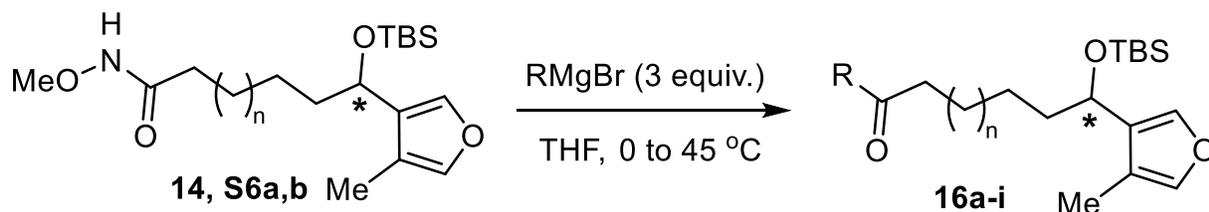
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.19 (s, 1H), 7.11 (s, 1H), 4.60 (dd, J = 7.1, 5.4 Hz, 1H), 3.67 (s, 3H), 3.17 (s, 3H), 2.40 (t, J = 7.5 Hz, 2H), 2.01 (s, 3H), 1.81 – 1.68 (m, 1H), 1.68 – 1.59 (m, 3H), 1.47 – 1.36 (m, 1H), 1.36 – 1.24 (m, 2H), 0.87 (s, 9H), 0.02 (s, 3H), -0.09 (s, 3H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 174.66, 140.05, 139.66, 129.17, 118.59, 67.76, 61.20, 38.50, 31.90, 29.72, 25.83, 25.47, 24.56, 18.19, 8.84, -4.71, -5.05.

FTIR (neat): ν 1666.17 cm<sup>-1</sup>

HRMS (UPLCMS): m/z calcd for C<sub>19</sub>H<sub>36</sub>NO<sub>4</sub>Si [M+H]<sup>+</sup> 370.2408, found 370.2420 (3.3 ppm)

[α]<sub>D</sub><sup>23</sup>: -38.50, c = 1.41 (CHCl<sub>3</sub>)



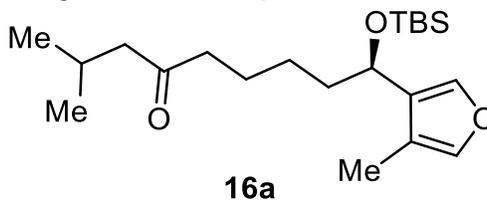
### General Procedure 6 (GP6): Alkylation of Weinreb Amides

A solution of Weinreb amide (0.27 mmol, 1 equiv.) in THF (3 mL) was stirred at 0 °C in an ice bath. Either a commercially available or freshly prepared (see general procedure 7) solution of Grignard reagent (0.81 mmol, 3 equiv.) was added to the reaction dropwise at 0 °C. After addition the reaction was heated to 45 °C and allowed to stir until the amide was consumed by TLC (1-6 hours). The reaction was then cooled to 0 °C, diluted with EtOAc (3 mL), and quenched with a saturated solution of NH<sub>4</sub>Cl (6 mL). The aqueous phase was extracted with EtOAc (6 mL x 2). The organic phases were combined, dried with Na<sub>2</sub>SO<sub>4</sub>, gravity filtered, and concentrated under reduced pressure. The resulting crude oil was purified on silica gel.

### General Procedure 7 (GP7): Synthesis of Grignard Reagents

In a flame-dried, two neck conical flask equipped with a stir-bar and fitted with a reflux condenser and septa was added magnesium turnings (1.08 mmol, 5 equiv.). The vessel was placed under vacuum and flame-dried for 5 minutes. Immediately after, a small crystal of iodine

(0.02 mmol, 0.1 equiv.) was added under an atmosphere of nitrogen. The flask was then rinsed with THF (1 mL) and heated to 65 °C. The alkyl bromide (0.87 mmol, 4 equiv.) was then added dropwise to the mixture over 10 minutes. The reaction was allowed to reflux for two hours and was used immediately once brought to room temperature.



**(R)-9-((tert-butyldimethylsilyl)oxy)-2-methyl-9-(4-methylfuran-3-yl)nonan-4-one (16a)** was prepared according to GP6 with **14** (270 mg, 0.73 mmol) and *i*BuMgBr (1.62M in Et<sub>2</sub>O, 1.35 mL, 2.19 mmol) in THF (7 mL). The reaction was purified in 19:1 Hexanes:EtOAc to afford a clear oil (203 mg, 76%).

**TLC:**  $R_f$  = 0.31 (19:1 Hexanes:EtOAc, visualized in KMnO<sub>4</sub>)

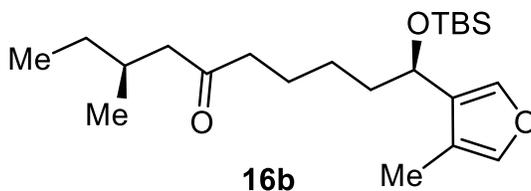
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.19 (s, 1H), 7.11 (s, 1H), 4.59 (t,  $J$  = 5.8 Hz, 1H), 2.35 (t,  $J$  = 7.2 Hz, 2H), 2.24 (d,  $J$  = 6.6 Hz, 2H), 2.12 (hept,  $J$  = 6.5 Hz, 1H), 2.00 (s, 3H), 1.77 – 1.65 (m, 1H), 1.65 – 1.51 (m, 3H), 1.41 – 1.30 (m, 1H), 1.30 – 1.18 (m, 1H), 0.90 (d,  $J$  = 6.6 Hz, 6H), 0.87 (s, 9H), 0.02 (s, 3H), -0.10 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  211.01, 140.08, 139.66, 129.14, 118.54, 67.75, 51.90, 43.31, 38.51, 25.83, 25.28, 24.64, 23.64, 22.61, 18.19, 8.83, -4.71, -5.07.

**FTIR** (neat):  $\nu$  1713.62 cm<sup>-1</sup>

**HRMS (UPLCMS):**  $m/z$  calcd for C<sub>21</sub>H<sub>39</sub>O<sub>3</sub>Si [M+H]<sup>+</sup> 367.2663, found 367.2660 (-0.7 ppm)

$[\alpha]_D^{21}$ : +24.22,  $c$  = 0.71 (CHCl<sub>3</sub>)



**(3S,10R)-10-((tert-butyldimethylsilyl)oxy)-3-methyl-10-(4-methylfuran-3-yl)decan-5-one (16b)** was prepared according to GP6 with **14** (70 mg, 0.19 mmol) and Grignard reagent prepared via GP7 (magnesium (18 mg, 0.76 mmol), (2S)-1-bromo-2-methylbutane (0.06 mL, 0.57 mmol), and iodine (5 mg, 0.02 mmol) in THF (1 mL)) in THF (1 mL). The reaction was purified in 9:1 Hexanes:EtOAc to afford a clear oil (32 mg, 45%).

**TLC:**  $R_f$  = 0.50 (9:1 Hexanes:EtOAc, visualized in KMnO<sub>4</sub>)

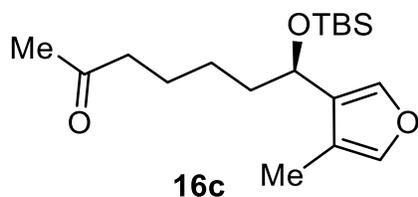
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.19 (s, 1H), 7.11 (s, 1H), 4.59 (t,  $J$  = 5.6 Hz, 1H), 2.43 – 2.30 (m, 3H), 2.18 (dd,  $J$  = 15.9, 8.2 Hz, 1H), 2.00 (s, 3H), 1.90 (h,  $J$  = 6.8 Hz, 1H), 1.79 – 1.67 (m, 1H), 1.67 – 1.48 (m, 4H), 1.42 – 1.22 (m, 5H), 1.22 – 1.11 (m, 1H), 0.96 – 0.79 (m, 16H), 0.02 (s, 3H), -0.09 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  211.26, 140.08, 139.66, 129.15, 118.54, 67.76, 50.00, 43.36, 38.52, 30.87, 29.56, 25.83, 25.28, 23.67, 19.42, 18.19, 11.35, 8.84, -4.71, -5.07.

**FTIR** (neat):  $\nu$  1713.09 cm<sup>-1</sup>

**HRMS (ESI+):** calcd for C<sub>22</sub>H<sub>40</sub>O<sub>3</sub>SiNa [M+Na]<sup>+</sup> 403.2644, found 403.2637 (-1.74 ppm)

$[\alpha]_D^{25}$ : +23.04,  $c$  = 0.36 (CHCl<sub>3</sub>)



**(R)-7-((tert-butyldimethylsilyl)oxy)-7-(4-methylfuran-3-yl)heptan-2-one (16c)** was prepared according to GP6 with **14** (70 mg, 0.19 mmol) and MeMgBr (3M in Et<sub>2</sub>O, 0.20 mL, 0.57 mmol) in THF (2 mL). The reaction was purified in 9:1 Hexanes:EtOAc to afford a clear oil (55 mg, 90%).

**TLC:** R<sub>f</sub> = 0.36 (9:1 Hexanes:EtOAc, visualized in KMnO<sub>4</sub>)

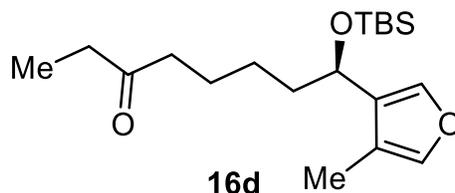
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.19 (s, 1H), 7.11 (s, 1H), 4.59 (dd, *J* = 7.2, 5.6 Hz, 1H), 2.40 (t, *J* = 7.5 Hz, 2H), 2.12 (s, 3H), 2.00 (s, 3H), 1.80 – 1.67 (m, 1H), 1.66 – 1.50 (m, 4H), 1.41 – 1.31 (m, 1H), 1.30 – 1.20 (m, 2H), 0.87 (s, 9H), 0.02 (s, 3H), -0.09 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 209.05, 140.10, 139.67, 129.11, 118.53, 67.72, 43.76, 38.46, 29.89, 25.82, 25.18, 23.72, 18.19, 8.84, -4.71, -5.06.

**FTIR** (neat): ν 1718.49 cm<sup>-1</sup>

**HRMS (ESI+):** calcd for C<sub>18</sub>H<sub>32</sub>O<sub>3</sub>SiNa [M+Na]<sup>+</sup> 347.2018, found 347.2014 (-1.2 ppm)

[α]<sub>D</sub><sup>21</sup>: +22.85, *c* = 0.28 (CHCl<sub>3</sub>)



**(R)-8-((tert-butyldimethylsilyl)oxy)-8-(4-methylfuran-3-yl)octan-3-one (16d)** was prepared according to GP6 with **14** (60 mg, 0.16 mmol) and EtMgBr (3M in Et<sub>2</sub>O, 0.16 mL, 0.47 mmol) in THF (2 mL). The reaction was purified in 17:3 Hexanes:EtOAc to afford a clear oil (47 mg, 85%).

**TLC:** R<sub>f</sub> = 0.27 (19:1 Hexanes:EtOAc, visualized in KMnO<sub>4</sub>)

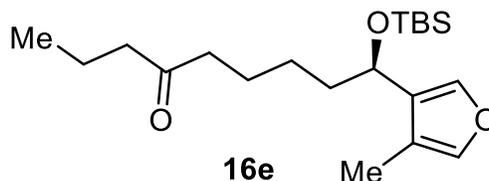
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.19 (s, 1H), 7.11 (s, 1H), 4.59 (t, *J* = 6.2 Hz, 1H), 2.39 (p, *J* = 6.2 Hz, 4H), 2.00 (s, 3H), 1.76 – 1.67 (m, 1H), 1.67 – 1.51 (m, 4H), 1.40 – 1.29 (m, 1H), 1.31 – 1.20 (m, 1H), 1.04 (t, *J* = 6.5 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), -0.10 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 211.74, 140.09, 139.67, 129.13, 118.54, 67.74, 42.38, 38.48, 35.93, 25.82, 25.28, 23.81, 18.19, 8.83, 7.86, -4.71, -5.07.

**FTIR** (neat): ν 1714.59 cm<sup>-1</sup>

**HRMS (ESI +):** *m/z* calcd for C<sub>19</sub>H<sub>34</sub>NaO<sub>3</sub>Si [M+H]<sup>+</sup> 361.2175, found 361.2177 (0.6 ppm)

[α]<sub>D</sub><sup>23</sup>: +27.56, *c* = 0.37 (CHCl<sub>3</sub>)



**(R)-9-((tert-butyldimethylsilyl)oxy)-9-(4-methylfuran-3-yl)nonan-4-one (16e)** was prepared according to GP6 with **14** (80 mg, 0.22 mmol) and Grignard reagent prepared via GP5 (magnesium (26 mg, 1.08 mmol), 1-bromopropane (0.08 mL, 0.87 mmol), and iodine (6 mg, 0.02 mmol) in THF (1 mL)) in THF (1 mL). The reaction was purified in 19:1 Hexanes:EtOAc to afford a clear oil (56 mg, 73%).

**TLC:** R<sub>f</sub> = 0.30 (19:1 Hexanes:EtOAc, visualized in KMnO<sub>4</sub>)

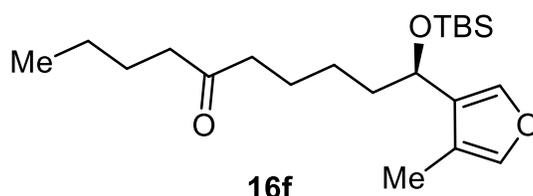
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.19 (s, 1H), 7.11 (s, 1H), 4.59 (dd, *J* = 7.2, 5.5 Hz, 1H), 2.35 (d, *J* = 7.4 Hz, 4H), 2.00 (s, 3H), 1.79 – 1.66 (m, 1H), 1.66 – 1.48 (m, 6H), 1.41 – 1.30 (m, 1H), 1.31 – 1.21 (m, 2H), 0.90 (d, *J* = 7.4 Hz, 4H), 0.87 (s, 9H), 0.02 (s, 3H), -0.09 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 211.31, 140.08, 139.67, 129.13, 118.54, 67.74, 44.78, 42.79, 38.50, 25.82, 25.28, 23.72, 18.19, 17.33, 13.78, 8.84, -4.71, -5.06.

**FTIR** (neat): *v* 1707.95 cm<sup>-1</sup>, 3413.22 cm<sup>-1</sup>

**HRMS (ESI+)**: calcd for C<sub>20</sub>H<sub>36</sub>NaO<sub>3</sub>Si [M+Na]<sup>+</sup> 375.2331, found 375.2322 (-2.40 ppm)

$[\alpha]_D^{22}$ : 27.05, *c* = 0.17 (CHCl<sub>3</sub>)



**(R)-10-((tert-butyldimethylsilyl)oxy)-10-(4-methylfuran-3-yl)decan-5-one (16f)** was prepared according to GP6 with **14** (60 mg, 0.16 mmol) and Grignard reagent prepared via GP7 (magnesium (20 mg, 0.81 mmol), 1-bromobutane (0.07 mL, 0.65 mmol), and iodine (4 mg, 0.02 mmol) in THF (1.5 mL)) in THF (1 mL). The reaction was purified in 17:3 Hexanes:EtOAc to afford a clear oil (32 mg, 54%).

**TLC**: R<sub>f</sub> = 0.30 (19:1 Hex:EA, visualized in KMnO<sub>4</sub>)

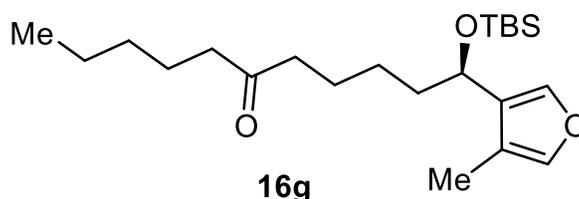
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.18 (s, 1H), 7.10 (s, 1H), 4.58 (dd, *J* = 7.2, 5.7 Hz, 1H), 2.37 (d, *J* = 7.3 Hz, 4H), 2.00 (s, 3H), 1.79 – 1.64 (m, 1H), 1.67 – 1.44 (m, 6H), 1.41 – 1.14 (m, 6H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), -0.10 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 211.42, 140.08, 139.66, 129.13, 118.53, 67.74, 42.75, 42.59, 38.49, 26.01, 25.82, 25.28, 23.74, 22.39, 18.18, 13.87, 8.83, -4.72, -5.07.

**FTIR** (neat): *v* 1714.21 cm<sup>-1</sup>

**HRMS (UPLCMS)**: *m/z* calcd for C<sub>21</sub>H<sub>39</sub>O<sub>3</sub>Si [M+H]<sup>+</sup> 367.2663, found 367.2659 (-1.1 ppm)

$[\alpha]_D^{22}$ : +23.52, *c* = 1.36 (CHCl<sub>3</sub>)



**(R)-1-((tert-butyldimethylsilyl)oxy)-1-(4-methylfuran-3-yl)undecan-6-one (16g)** was prepared according to GP6 with **14** (80 mg, 0.27 mmol) and Grignard reagent prepared via GP7 (magnesium (26 mg, 1.08 mmol), 1-bromopentane (0.10 mL, 0.87 mmol), and iodine (6 mg, 0.02 mmol) in THF (1.5 mL)) in THF (1 mL). The reaction was purified in 19:1 Hexanes:EtOAc to afford a clear oil (81 mg, 98%).

**TLC**: R<sub>f</sub> = 0.50 (19:1 Hexanes:EtOAc, visualized in KMnO<sub>4</sub>)

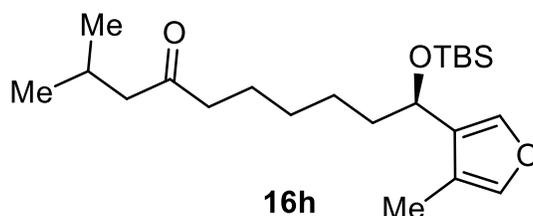
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.19 (s, 1H), 7.11 (s, 1H), 4.59 (t, *J* = 5.3 Hz, 1H), 2.36 (dd, *J* = 7.2, 3.3 Hz, 4H), 2.00 (s, 3H), 1.71 (s, 2H), 1.55 (s, 6H), 1.26 (s, 7H), 0.88 (d, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), -0.10 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 211.48, 140.08, 139.66, 129.13, 118.54, 67.74, 42.85, 42.76, 38.49, 31.46, 25.82, 25.28, 23.74, 23.59, 22.47, 18.19, 13.93, 8.83, -4.72, -5.07.

**FTIR** (neat): *v* 1714.53 cm<sup>-1</sup>

**HRMS (ESI+)**: calcd for C<sub>22</sub>H<sub>40</sub>O<sub>3</sub>SiNa [M+Na]<sup>+</sup> 403.2639, found 403.2633 (-2.72 ppm)

$[\alpha]_D^{23}$ : +18.00, *c* = 0.10 (CHCl<sub>3</sub>)



**(R)-10-((tert-butyldimethylsilyloxy)-2-methyl-10-(4-methylfuran-3-yl)decan-4-one (16h)** was prepared according to GP6 with **S6a** (110 mg, 0.30 mmol), and *i*BuMgBr (1.62M in EtO, 0.56 mL, 0.91 mmol) in THF (3.0 mL). The reaction was purified in 3:1 Hexanes:EtOAc to afford a pale-yellow oil (77 mg, 62%).

**TLC:**  $R_f = 0.32$  (19:1 Hexanes:EtOAc, visualized with  $\text{KMnO}_4$ )

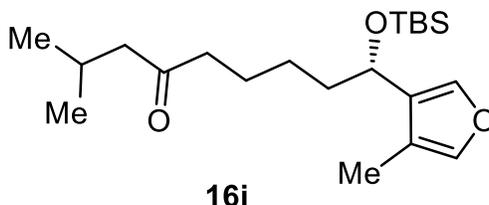
**$^1\text{H NMR}$ :**  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19 (s, 1H), 7.11 (s, 1H), 4.58 (dd,  $J = 6.9, 5.6$  Hz, 1H), 2.35 (t,  $J = 7.5$  Hz, 2H), 2.25 (d,  $J = 7.0$  Hz, 2H), 2.12 (m, 1H), 2.00 (s, 3H), 1.59 – 1.50 (m, 6H), 1.31 – 1.22 (m, 5H), 0.91 (d,  $J = 6.6$  Hz, 8H), 0.87 (s, 9H), 0.02 (s, 3H), -0.09 (s, 3H).

**$^{13}\text{C NMR}$ :**  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  211.15, 140.04, 139.63, 129.26, 118.57, 67.88, 51.87, 43.26, 38.58, 29.11, 25.83, 25.42, 24.65, 23.73, 22.62, 18.20, 8.83, -4.70, -5.06

**FTIR** (neat):  $\nu$  1712.51  $\text{cm}^{-1}$

**HRSM (UPLCMS):**  $m/z$  calc'd for  $\text{C}_{19}\text{H}_{30}\text{NaO}_4\text{Si}$   $[\text{M}+\text{Na}]^+$  403.2639, found 403.2621 (-4.4 ppm)

$[\alpha]_D^{21}$ : +11.50,  $c = 0.31$  ( $\text{CHCl}_3$ )



**(S)-9-((tert-butyldimethylsilyloxy)-2-methyl-9-(4-methylfuran-3-yl)nonan-4-one (16i)** was prepared according to GP6 with **S6b** (50 mg, 0.14 mmol) and *i*BuMgBr (1.62M in  $\text{Et}_2\text{O}$ , 0.25 mL, 0.41 mmol) in THF (2 mL). The reaction was purified in 19:1 Hexanes:EtOAc to afford a clear oil (36 mg, 72%).

**TLC:**  $R_f = 0.42$  (19:1 Hexanes:EtOAc, visualized in  $\text{KMnO}_4$ )

**$^1\text{H NMR}$ :**  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19 (s, 1H), 7.11 (s, 1H), 4.59 (t,  $J = 6.0$  Hz, 1H), 2.35 (t,  $J = 7.4$  Hz, 2H), 2.24 (d,  $J = 7.4$  Hz, 2H), 2.12 (hept,  $J = 6.5$  Hz, 1H), 2.00 (s, 3H), 1.77 – 1.66 (m, 1H), 1.65 – 1.49 (m, 4H), 1.42 – 1.30 (m, 1H), 1.30 – 1.18 (m, 2H), 0.89 (d,  $J = 6.5$  Hz, 7H), 0.87 (s, 9H), 0.02 (s, 3H), -0.09 (s, 3H).

**$^{13}\text{C NMR}$ :**  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  211.04, 140.08, 139.66, 129.14, 118.54, 67.75, 51.90, 43.32, 38.51, 25.83, 25.28, 24.65, 23.64, 22.61, 18.19, 8.83, -4.71, -5.07.

**FTIR** (neat):  $\nu$  1713.61  $\text{cm}^{-1}$

**HRMS (ESI+):** calc'd for  $\text{C}_{21}\text{H}_{38}\text{NaO}_3\text{Si}$   $[\text{M}+\text{Na}]^+$  389.2488, found 389.2486 (-0.51 ppm)

$[\alpha]_D^{21}$ : -32.07,  $c = 0.29$  ( $\text{CHCl}_3$ )

**Figure S3: Synthetic route to SRB10 and SRB11**

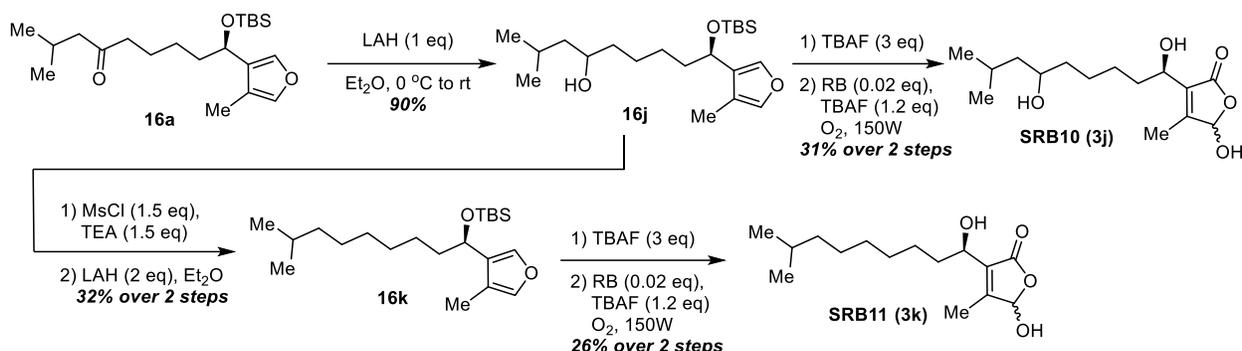
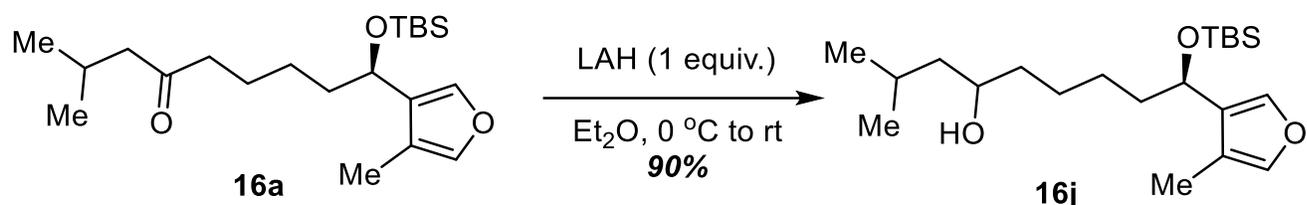


Figure 2 Synthetic route to SRB10 and SRB11



**(9R)-9-((tert-butyldimethylsilyl)oxy)-2-methyl-9-(4-methylfuran-3-yl)nonan-4-ol (16j)**

A dispersion of lithium aluminum hydride (LAH, 4 mg, 0.11 mmol, 1 equiv.) in Et<sub>2</sub>O (0.3 mL) was stirred at 0 °C. A solution of **16a** (40 mg, 0.11 mmol, 1 equiv.) in Et<sub>2</sub>O (0.3 mL) was added dropwise. The reaction was stirred at room temperature. Upon consumption of the ketone by TLC, two crystals of Na<sub>2</sub>SO<sub>4</sub> 10H<sub>2</sub>O were added and stirred. The dispersion was then filtered over a plug of cotton and concentrated. The filtrate was purified on silica gel in 9:1 Hexanes:EtOAc to afford a clear oil (36 mg, 90%).

**TLC:** R<sub>f</sub> = 0.26 (9:1 Hex:EA, visualized in KMnO<sub>4</sub>)

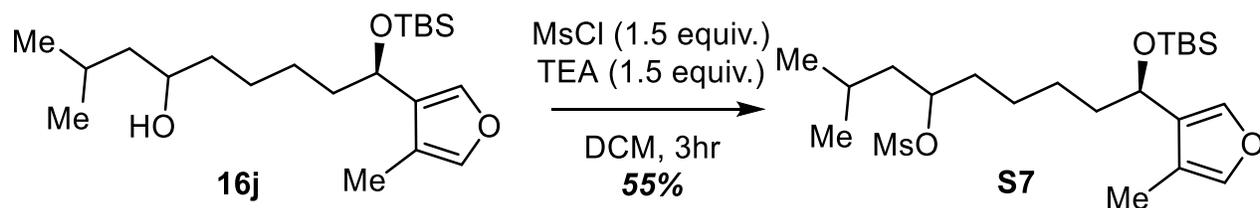
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.19 (s, 1H), 7.11 (s, 1H), 4.59 (d, *J* = 5.9 Hz, 1H), 3.65 (s, 1H), 2.01 (s, 3H), 1.84 – 1.67 (m, 2H), 1.66 – 1.57 (m, 1H), 1.47 – 1.18 (m, 10H), 0.91 (t, *J* = 6.9 Hz, 6H), 0.87 (s, 9H), 0.03 (s, 3H), -0.09 (s, 3H).

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 140.04, 139.63, 129.29, 118.59, 69.95, 67.90, 46.86, 38.73, 38.07, 25.84, 25.48, 24.65, 23.51, 22.07, 18.21, 8.84, -4.70, -5.05.

**FTIR (neat):** ν 1257.02 cm<sup>-1</sup>, 1462.34 cm<sup>-1</sup>, 3340.26 cm<sup>-1</sup>

**HRMS (ESI+):** calcd for C<sub>15</sub>H<sub>25</sub>O<sub>2</sub> [M-OTBS] 237.1860, found 237.1843 (-7.17 ppm)

**[α]<sub>D</sub><sup>22</sup>:** +8.84°, *c* = 0.26 (CHCl<sub>3</sub>)



**(9R)-9-((tert-butyldimethylsilyl)oxy)-2-methyl-9-(4-methylfuran-3-yl)nonan-4-yl**

**methanesulfonate (S7)** To a stirring solution of **16j** (20 mg, 0.05 mmol, 1 equiv.) in DCM (0.5 mL) at 0 °C in an ice bath was added methanesulfonyl chloride (0.01 mL, 0.08 mmol, 1.5 equiv.) followed by triethylamine (0.01 mL, 0.081 mmol, 1.5 equiv.). The reaction turned yellow and was stirred at room temperature for 3 hours. The reaction was then brought to 0 °C, diluted with DCM (1.5 mL) and quenched with diH<sub>2</sub>O (2 mL). The DCM layer was separated and the aqueous phase

was extracted with DCM (2 x 2 mL). Combined organic layers were dried with MgSO<sub>4</sub>, filtered, and concentrated to afford a yellow oil which was immediately purified on a plug of silica in 9:1 Hexanes:EtOAc to afford a clear oil (13 mg, 55%).

**TLC:** R<sub>f</sub> = 0.26 (9:1 Hexanes:EtOAc, visualized in KMnO<sub>4</sub>)

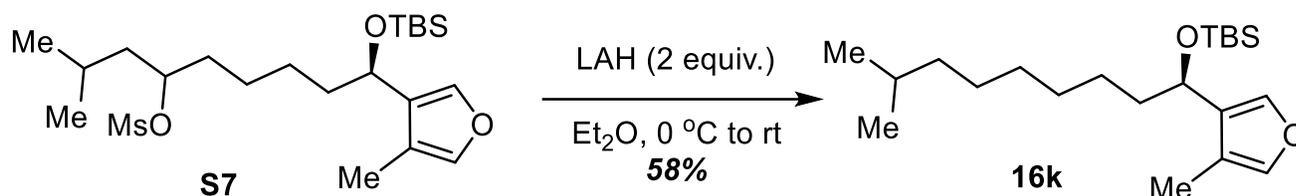
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.20 (s, 1H), 7.11 (s, 1H), 4.77 (p, *J* = 5.8 Hz, 1H), 4.59 (t, *J* = 6.2 Hz, 1H), 2.98 (s, 3H), 2.01 (s, 3H), 1.77 – 1.57 (m, 7H), 1.48 – 1.33 (m, 5H), 1.33 – 1.19 (m, 3H), 0.94 (t, *J* = 7.1 Hz, 6H), 0.87 (s, 9H), 0.03 (s, 3H), -0.09 (s, 3H).

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 140.10, 139.67, 129.16, 118.53, 82.62, 67.82, 43.57, 38.83, 38.53, 35.06, 25.83, 25.45, 24.50, 22.90, 22.19, 18.20, 8.84, -4.71, -5.06.

**FTIR (neat):** ν 1175.58 cm<sup>-1</sup>, 1341.98 cm<sup>-1</sup>

**HRMS (ACPI+):** calcd for C<sub>16</sub>H<sub>27</sub>O<sub>4</sub>S [M-OTBS]<sup>-</sup> 315.1636, found 315.1618 (-5.71 ppm)

**[α]<sub>D</sub><sup>22</sup>:** +11.53°, *c* = 0.26 (CHCl<sub>3</sub>)



#### (R)-tert-butyldimethyl((8-methyl-1-(4-methylfuran-3-yl)nonyl)oxy)silane (**16k**)

A dispersion of LAH (3.5 mg, 0.09 mmol, 2 equiv.) in Et<sub>2</sub>O (0.3 mL) was stirred at 0 °C. A solution of **S7** (20 mg, 0.05 mmol, 1 equiv.) in Et<sub>2</sub>O (0.3 mL) was added dropwise. The reaction was stirred at room temperature overnight. Upon consumption of the ketone by TLC, two crystals of Na<sub>2</sub>SO<sub>4</sub> 10H<sub>2</sub>O were added and stirred. The dispersion was then filtered over a plug of cotton and concentrated. The filtrate was purified on silica gel in 9:1 Hexanes:EtOAc to afford a clear oil (9 mg, 58%).

**TLC:** R<sub>f</sub> = 0.30 (100% Hex, visualized in KMnO<sub>4</sub>)

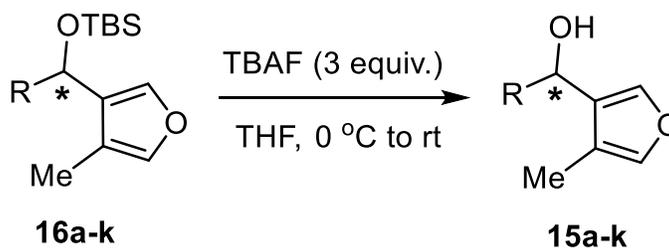
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.20 (s, 1H), 7.11 (s, 1H), 4.59 (t, *J* = 5.7 Hz, 1H), 2.01 (s, 3H), 1.77 – 1.64 (m, 1H), 1.64 – 1.55 (m, 1H), 1.51 (hept, *J* = 6.6 Hz, 2H), 1.40 – 1.18 (m, 12H), 1.15 (q, *J* = 6.2 Hz, 3H), 0.97 – 0.72 (m, 17H), 0.03 (s, 3H), -0.08 (s, 3H).

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 139.98, 139.60, 129.42, 118.64, 67.97, 39.04, 38.81, 29.88, 29.73, 29.52, 27.97, 27.35, 25.84, 25.66, 22.66, 18.21, 8.84, -4.69, -5.04.

**FTIR (neat):** ν 1256.58 cm<sup>-1</sup>, 1462.45 cm<sup>-1</sup>

**HRMS:** calcd for C<sub>15</sub>H<sub>25</sub>O [M-OTBS]<sup>-</sup> 221.1911, found 221.1907 (-1.80 ppm)

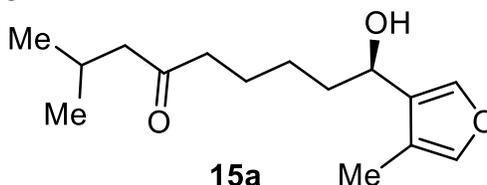
**[α]<sub>D</sub><sup>22</sup>:** +38.35°, *c* = 0.61 (CHCl<sub>3</sub>)



#### General Procedure 8 (GP8): Deprotection of Silyl Ethers

A solution of silyl ether (0.05 mmol, 1 equiv.) in THF (1 mL) was brought to 0 °C in an ice bath. TBAF, (1M in THF, 0.16 mmol, 3 equiv.) was then added and the reaction was stirred at room temperature. After 1.5 h, or once the silyl ether was consumed by TLC, the reaction was diluted

with EtOAc (3 mL) and quenched with diH<sub>2</sub>O (3 mL). The phases were removed, and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, gravity filtered, and concentrated under reduced pressure. The resulting crude oil was then loaded onto a pre-equilibrated silica gel column and eluted in Hexanes:EtOAc to afford a clear oil.



**(R)-9-hydroxy-2-methyl-9-(4-methylfuran-3-yl)nonan-4-one (15a)** was prepared according to GP8 with **16a** (50 mg, 0.136 mmol) and TBAF, (1M in THF, 0.41 mL, 0.41 mmol) in THF (2 mL). The reaction was purified in 4:1 Hexanes:EtOAc to afford a clear oil (26 mg, 76%).

**TLC:** R<sub>f</sub> = 0.26 (4:1 Hexanes:EtOAc, visualized in KMnO<sub>4</sub>)

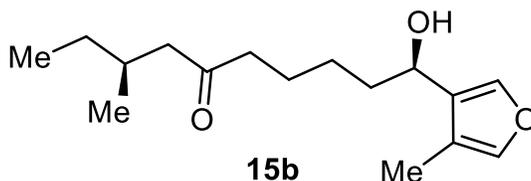
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.29 (s, 1H), 7.16 (s, 1H), 4.61 (t, *J* = 6.3 Hz, 1H), 2.39 (t, *J* = 7.4 Hz, 2H), 2.26 (d, *J* = 7.2 Hz, 2H), 2.12 (hept, *J* = 6.9 Hz, 1H), 2.04 (s, 3H), 1.87 – 1.69 (m, 2H), 1.70 – 1.50 (m, 2H), 1.50 – 1.41 (m, 1H), 1.41 – 1.26 (m, 1H), 0.90 (d, *J* = 6.9 Hz, 6H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 210.99, 140.38, 139.56, 128.78, 118.94, 66.61, 51.92, 43.18, 36.77, 25.53, 24.66, 23.44, 22.61, 8.56.

**FTIR** (neat): ν 1707.93 cm<sup>-1</sup>, 3405.86 cm<sup>-1</sup>

**HRMS (UPLCMS):** *m/z* calcd for C<sub>15</sub>H<sub>25</sub>O<sub>3</sub> [M+H]<sup>+</sup> 253.1798, found 253.1791 (-2.7 ppm)

[α]<sub>D</sub><sup>22</sup>: +26.96, *c* = 0.33 (CHCl<sub>3</sub>)



**(3S,10R)-10-hydroxy-3-methyl-10-(4-methylfuran-3-yl)decan-5-one (15b)** was prepared according to GP8 with **16b** (15 mg, 0.04 mmol) and TBAF (1M in THF, 0.12 mL, 0.12 mmol) in THF (1 mL). The reaction was purified in 17:3 Hexanes:EtOAc to afford a clear oil (9 mg, 86%).

**TLC:** R<sub>f</sub> = 0.24 (3:1 Hexanes:EtOAc, visualized in KMnO<sub>4</sub>)

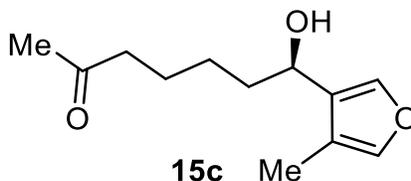
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.30 (s, 1H), 7.16 (s, 1H), 4.61 (t, *J* = 7.0 Hz, 1H), 2.53 – 2.32 (m, 3H), 2.19 (dd, *J* = 15.7, 8.1 Hz, 1H), 2.04 (s, 3H), 1.91 (h, *J* = 6.6 Hz, 1H), 1.84 – 1.70 (m, 3H), 1.68 – 1.56 (m, 3H), 1.51 – 1.40 (m, 1H), 1.31 (s, 4H), 1.20 (hept, *J* = 6.9 Hz, 1H), 0.94 – 0.77 (m, 6H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 211.22, 140.38, 139.56, 128.77, 118.94, 66.61, 50.02, 43.22, 36.77, 30.88, 29.56, 25.53, 23.46, 19.42, 11.35, 8.56.

**FTIR** (neat): ν 1708.48 cm<sup>-1</sup>, 3406.51 cm<sup>-1</sup>

**HRMS (ESI +):** calcd for C<sub>16</sub>H<sub>26</sub>NaO<sub>3</sub> 289.1780, found 289.1782 (0.69 ppm)

[α]<sub>D</sub><sup>23</sup>: +20.35, *c* = 0.28 (CHCl<sub>3</sub>)



**(R)-7-hydroxy-7-(4-methylfuran-3-yl)heptan-2-one (15c)** was prepared according to GP8 with **16c** (40 mg, 0.12 mmol) and TBAF (1M in THF, 0.37 mL, 0.37 mmol) in THF (1 mL). The reaction was purified in 3:1 Hexanes:EtOAc to afford a clear oil (12 mg, 45%).

**TLC:**  $R_f$  = 0.18 (7:3 Hex:EA, visualized in  $\text{KMnO}_4$ )

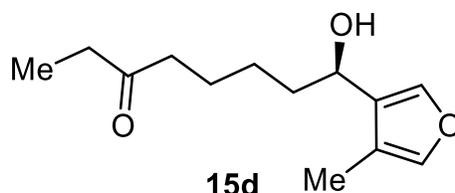
**$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 (s, 1H), 7.16 (s, 1H), 4.62 (t,  $J$  = 5.9 Hz, 1H), 2.44 (t,  $J$  = 7.0 Hz, 2H), 2.13 (s, 3H), 2.04 (s, 3H), 1.86 – 1.70 (m, 2H), 1.70 – 1.52 (m, 5H), 1.52 – 1.41 (m, 1H), 1.41 – 1.28 (m, 1H).

**$^{13}\text{C NMR}$**  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  208.98, 140.40, 139.57, 128.76, 118.93, 66.62, 43.61, 36.73, 29.94, 25.47, 23.52, 8.57.

**FTIR** (neat):  $\nu$  1709.68  $\text{cm}^{-1}$ , 3413.17  $\text{cm}^{-1}$

**HRMS (UPLCMS):**  $m/z$  calcd for  $\text{C}_{12}\text{H}_{19}\text{O}_3$   $[\text{M}+\text{H}]^+$  211.1329, found 211.1335 (2.9 ppm)

$[\alpha]_D^{23}$ : +19.22,  $c$  = 0.77 ( $\text{CHCl}_3$ )



**(R)-8-hydroxy-8-(4-methylfuran-3-yl)octan-3-one (15d)** was prepared according to GP8 with **16d** (20 mg, 0.06 mmol) and TBAF (1M in THF, 0.18 mL, 0.18 mmol) in THF (0.8 mL). The reaction was purified in 3:1 Hexanes:EtOAc to afford a clear oil (7 mg, 54%).

**TLC:**  $R_f$  = 0.16 (4:1 Hex:EA, visualized in  $\text{KMnO}_4$ )

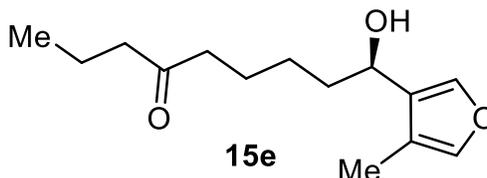
**$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 (s, 1H), 7.15 (s, 1H), 4.61 (t,  $J$  = 6.2 Hz, 1H), 2.41 (q,  $J$  = 7.3 Hz, 4H), 2.03 (s, 3H), 1.84 – 1.72 (m, 2H), 1.71 – 1.54 (m, 3H), 1.54 – 1.40 (m, 1H), 1.40 – 1.28 (m, 1H), 1.04 (t,  $J$  = 7.3 Hz, 3H).

**$^{13}\text{C NMR}$**  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  211.69, 140.37, 139.56, 128.77, 118.94, 66.60, 42.23, 36.76, 35.96, 25.56, 23.60, 8.56, 7.86.

**FTIR** (neat):  $\nu$  1709.75  $\text{cm}^{-1}$ , 34106.37  $\text{cm}^{-1}$

**HRMS (ESI +):**  $m/z$  calcd for  $\text{C}_{13}\text{H}_{20}\text{NaO}_3$   $[\text{M}+\text{Na}]^+$  247.1310, found 247.1308 (-0.8 ppm)

$[\alpha]_D^{22}$ : +24.28,  $c$  = 0.42 ( $\text{CHCl}_3$ )



**(R)-9-hydroxy-9-(4-methylfuran-3-yl)nonan-4-one (15e)** was prepared according to GP8 with **16e** (50 mg, 0.14 mmol) and TBAF (1M in THF, 0.43 mL, 0.43 mmol) in THF (1.5 mL). The reaction was purified in 4:1 Hexanes:EtOAc to afford a clear oil (26 mg, 76%).

**TLC:**  $R_f$  = 0.25 (4:1 Hex:EA, visualized in  $\text{KMnO}_4$ )

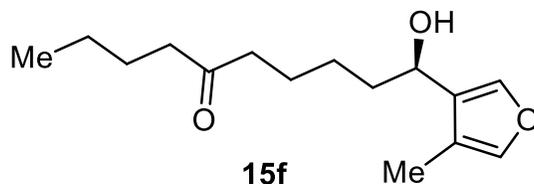
**$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 (s, 1H), 7.16 (s, 1H), 4.61 (d,  $J$  = 8.2 Hz, 1H), 2.41 (d,  $J$  = 6.9 Hz, 2H), 2.36 (d,  $J$  = 7.4 Hz, 2H), 2.04 (s, 3H), 1.84 – 1.71 (m, 2H), 1.68 – 1.54 (m, 5H), 1.50 – 1.40 (m, 1H), 1.40 – 1.29 (m, 1H), 0.90 (d,  $J$  = 7.4 Hz, 3H).

**$^{13}\text{C NMR}$**  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  211.25, 140.37, 139.56, 128.78, 118.94, 66.61, 44.80, 42.64, 36.76, 25.55, 23.51, 17.33, 13.78, 8.56.

**FTIR** (neat):  $\nu$  1707.95  $\text{cm}^{-1}$ , 3413.22  $\text{cm}^{-1}$

**HRMS (ESI+):** calcd for  $\text{C}_{14}\text{H}_{22}\text{NaO}_3$  261.1467, found 261.1458 (-3.44 ppm)

$[\alpha]_D^{23}$ : +21.86,  $c$  = 16 ( $\text{CHCl}_3$ )



**(R)-10-hydroxy-10-(4-methylfuran-3-yl)decan-5-one (15f)** was prepared according to GP8 with **16f** (30 mg, 0.082 mmol) and TBAF, 1M in THF (0.25 mL, 0.246 mmol) in THF (1 mL). The reaction was purified in 4:1 Hexanes:EtOAc to afford a clear oil (15 mg, 71%).

**TLC:**  $R_f = 0.22$  (4:1 Hex:EA, visualized in  $\text{KMnO}_4$ )

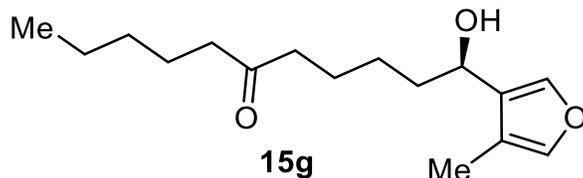
**$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 (s, 1H), 7.15 (s, 1H), 4.60 (t,  $J = 6.6$  Hz, 1H), 2.39 (p,  $J = 7.0$  Hz, 4H), 2.03 (s, 3H), 1.85 – 1.67 (m, 3H), 1.67 – 1.58 (m, 2H), 1.54 (p,  $J = 7.6$  Hz, 2H), 1.50 – 1.38 (m, 1H), 1.38 – 1.23 (m, 3H), 0.89 (t,  $J = 7.3$  Hz, 3H).

**$^{13}\text{C NMR}$**  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  211.41, 140.35, 139.55, 128.78, 118.94, 66.58, 42.61, 36.76, 29.71, 26.00, 25.54, 23.53, 22.38, 13.87, 8.56.

**FTIR** (neat):  $\nu$  1708.89  $\text{cm}^{-1}$ , 3411.99  $\text{cm}^{-1}$

**HRMS (UPLCMS):**  $m/z$  calcd for  $\text{C}_{15}\text{H}_{25}\text{O}_3$   $[\text{M}+\text{H}]^+$  253.1798, found 253.1791 (-2.9 ppm)

$[\alpha]_D^{22}$ : +18.15,  $c = 0.98$  ( $\text{CHCl}_3$ )



**(R)-1-hydroxy-1-(4-methylfuran-3-yl)undecan-6-one (15g)** was prepared according to GP8 with **16g** (75mg, 0.20 mmol) and TBAF (1M in THF, 0.59 mL, 0.59 mmol) in THF (2 mL). The reaction was purified in 4:1 Hexanes:EtOAc to afford a clear oil (34 mg, 65%).

**TLC:**  $R_f = 0.30$  (4:1 Hex:EA, visualized in  $\text{KMnO}_4$ )

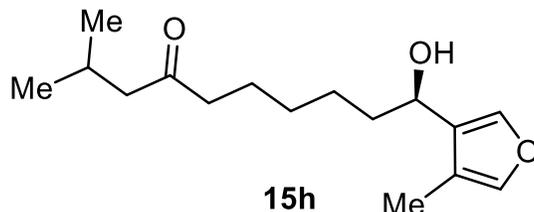
**$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 (s, 1H), 7.16 (s, 1H), 4.62 (dd,  $J = 10.3, 6.4$  Hz, 1H), 2.40 (dt,  $J = 17.3, 7.4$  Hz, 4H), 2.04 (s, 3H), 1.86 – 1.70 (m, 2H), 1.70 – 1.50 (m, 7H), 1.50 – 1.39 (m, 1H), 1.39 – 1.18 (m, 5H), 0.89 (t,  $J = 6.5$  Hz, 3H).

**$^{13}\text{C NMR}$**  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  211.40, 140.39, 139.56, 128.77, 118.94, 66.62, 42.89, 42.61, 36.76, 31.46, 25.55, 23.59, 23.53, 22.47, 13.93, 8.57.

**FTIR** (neat):  $\nu$  1708.89  $\text{cm}^{-1}$ , 3411.99  $\text{cm}^{-1}$

**HRMS (ESI+):**  $m/z$  calcd for  $\text{C}_{16}\text{H}_{26}\text{NaO}_3$  290.1858  $[\text{M}+\text{Na}]^+$ , found 290.1848 (-1.6 ppm)

$[\alpha]_D^{22}$ : + 31.78,  $c = 0.28$  ( $\text{CHCl}_3$ )



**(R)-10-hydroxy-2-methyl-10-(4-methylfuran-3-yl)decan-4-one (15h)** was prepared according to GP8 with **16h** (70 mg, 0.18 mmol), and TBAF (1M in THF, 0.55 mL, 0.55 mmol) in THF (2.0mL). The reaction was purified in 3:1 Hexanes:EtOAc to afford a pale-yellow oil (28 mg, 60%).

**TLC:**  $R_f = 0.21$  (4:1 Hex:EA, visualized with CAN)

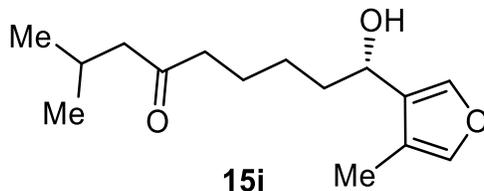
**$^1\text{H NMR}$** :  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 (s, 1H), 7.16 (s, 1H), 4.60 (t,  $J = 6.7$  Hz, 1H), 2.37 (t,  $J = 7.4$  Hz, 2H), 2.26 (d,  $J = 7.0$  Hz, 2H), 2.13 (hept,  $J = 6.8$  Hz, 1H), 2.04 (s, 3H), 1.82 – 1.71 (m, 3H), 1.62 – 1.51 (m, 5H), 1.37 – 1.30 (m, 4H), 0.91 (d,  $J = 6.6$  Hz, 6H).

**<sup>13</sup>CNMR:** <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 211.08, 140.36, 139.55, 128.85, 118.96, 66.80, 51.89, 43.20, 36.84, 29.07, 25.73, 24.65, 23.65, 22.62, 8.57.

**FTIR** (neat): ν 1731.79 cm<sup>-1</sup>, 3502.15 cm<sup>-1</sup>

**HRSM (UPLCMS):** m/z calc'd for C<sub>16</sub>H<sub>26</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup> 289.1774, found 289.1796 (-7.6 ppm)

$[\alpha]_D^{21}$ : +5.58, c = 0.56 (CHCl<sub>3</sub>)



**(S)-9-hydroxy-2-methyl-9-(4-methylfuran-3-yl)nonan-4-one (15i)** was prepared according to GP8 with **16i** (30 mg, 0.08 mmol) and TBAF (1M in THF, 0.25 mL, 0.25 mmol) in THF (1 mL). The reaction was purified in 4:1 Hexanes:EtOAc to afford a clear oil (15 mg, 73%).

**TLC:** R<sub>f</sub> = 0.37 (4:1 Hex:EA, visualized in KMnO<sub>4</sub>)

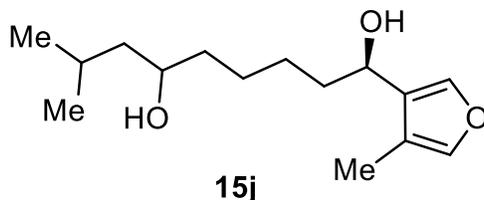
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.29 (s, 1H), 7.15 (s, 1H), 4.60 (t, *J* = 6.4 Hz, 1H), 2.38 (t, *J* = 7.4 Hz, 2H), 2.25 (d, *J* = 6.9 Hz, 2H), 2.12 (hept, *J* = 6.7 Hz, 1H), 2.03 (s, 3H), 1.83 – 1.68 (m, 3H), 1.68 – 1.54 (m, 2H), 1.49 – 1.39 (m, 1H), 1.39 – 1.26 (m, 1H), 0.90 (d, *J* = 6.7 Hz, 6H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 211.01, 140.35, 139.55, 128.78, 118.94, 66.58, 51.91, 43.18, 36.77, 25.52, 24.65, 23.44, 22.60, 8.56.

**FTIR** (neat): ν 1705.66 cm<sup>-1</sup>, 3407.46 cm<sup>-1</sup>

**HRMS (ESI+):** clacd for C<sub>15</sub>H<sub>24</sub>NaO<sub>3</sub> 275.1623, found 275.1622 (-0.36 ppm)

$[\alpha]_D^{21}$ : -14.90, c = 1.00 (CHCl<sub>3</sub>)



**(1R)-8-methyl-1-(4-methylfuran-3-yl)nonane-1,6-diol (15j)** was prepared according to GP8 with **16j** (46 mg, 0.12 mmol), and TBAF (1M in THF, 0.37 mL, 0.37 mmol) in THF (1.2mL). The reaction was purified in 3:1 Hexanes:EtOAc to afford a pale-yellow oil (27 mg, 84%).

**TLC:** R<sub>f</sub> = 0.39 (3:2 Hex:EA, visualized with CAN)

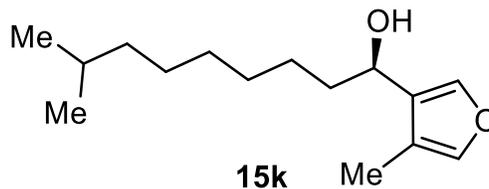
**<sup>1</sup>H NMR:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.30 (s, 1H), 7.16 (s, 1H), 4.61 (td, *J* = 6.0, 1.4 Hz, 1H), 3.72 – 3.62 (m, 1H), 2.04 (s, 3H), 1.86 – 1.72 (m, 3H), 1.58 – 1.33 (m, 10H), 1.28 – 1.18 (m, 3H), 0.91 (t, *J* = 7.0 Hz, 6H).

**<sup>13</sup>CNMR:** <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 140.35, 139.55, 128.87, 118.97, 69.92, 66.83, 46.90, 37.96, 36.99, 26.01, 25.51, 24.66, 23.51, 22.09, 8.58.

**FTIR** (neat): ν 3365.23 cm<sup>-1</sup>

**HRSM (UPLCMS):** m/z calc'd for C<sub>16</sub>H<sub>26</sub>NaO<sub>5</sub> [M+Na]<sup>+</sup> 277.1774, found 277.1788 (5.0 ppm)

$[\alpha]_D^{21}$ : +8.43, c = 0.39 (CHCl<sub>3</sub>)



**(R)-8-methyl-1-(4-methylfuran-3-yl)nonan-1-ol (15k)** was prepared according to GP8 with **16k** (9 mg, 0.03 mmol) and TBAF (1M in THF, 0.08 mL, 0.08 mmol) in THF (0.5 mL). The reaction was purified in 9:1 Hexanes:EtOAc to afford a clear oil (3 mg, 60%).

**TLC:**  $R_f = 0.25$  (9:1 Hex:EA, visualized in CAN)

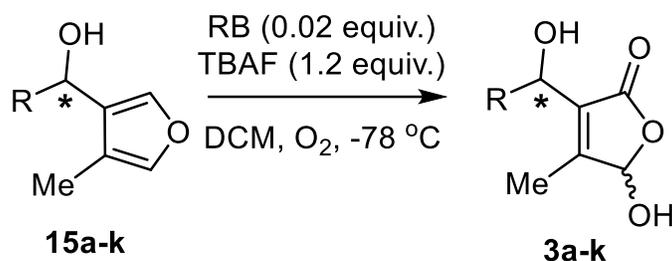
**$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.30 (s, 1H), 7.16 (s, 1H), 4.60 (q,  $J = 6.2$  Hz, 1H), 2.05 (s, 3H), 1.81 – 1.73 (m, 2H), 1.53 – 1.39 (m, 3H), 1.36 – 1.27 (m, 5H), 1.16 (q,  $J = 6.6$  Hz, 2H), 0.87 (d,  $J = 6.9$  Hz, 6H).

**$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  140.32, 139.55, 128.92, 119.02, 66.92, 39.03, 37.09, 29.86, 29.54, 27.97, 27.34, 25.96, 22.66, 8.57.

**FTIR** (neat):  $\nu$  1467.26  $\text{cm}^{-1}$ , 3347.98  $\text{cm}^{-1}$

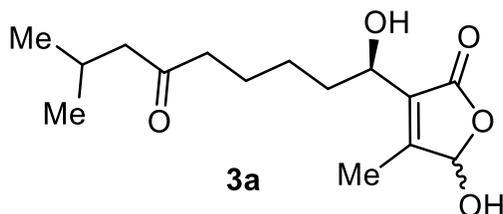
**HRMS** :  $m/z$  calcd for  $\text{C}_{15}\text{H}_{25}\text{O}$   $[\text{M}-\text{OH}]^-$  221.1911, found 221.1902 (-4.07 ppm)

$[\alpha]_D^{22}$  : +10.40,  $c = 0.25$  ( $\text{CHCl}_3$ )



### General Procedure 9 (GP9): Photo-oxidation of Furyl Alcohols

A solution of furyl alcohol (0.03 mmol, 1 equiv.) in DCM (1 mL) was cooled to  $-78$  °C in an isopropanol-dry ice bath. A solution of TBAF (1 M in THF, 0.05 mmol, 1.2 equiv.) was added followed by Rose Bengal (0.002 mmol, 0.05 equiv.). The reaction turned vibrant pink and was shielded from light. The solution was sparged with a nitrogen balloon for 10 minutes, then sparged with an oxygen balloon for an additional 10 minutes. After which, a 150W white light bulb was introduced and the reaction was stirred in the light. The reaction was allowed to slowly warm to  $-20$  °C. After 2 hours, or consumption of the furyl alcohol by TLC, the reaction was filtered over a short pad of silica. The silica cake was then washed with EtOAc (10 mL, 2x) and the filtrate was concentrated under reduced pressure. The resulting pale-pink crude oil was loaded onto a pre-equilibrated silica gel column, and eluted in 1:1 Hexanes:EtOAc to afford a clear oil.



**5-hydroxy-3-((R)-1-hydroxy-8-methyl-6-oxononyl)-4-methylfuran-2(5H)-one (3a)** was prepared according to GP9 with **15a** (20 mg, 0.08 mmol), TBAF (1M in THF, 0.10 mL, 0.10 mmol), and Rose Bengal (2 mg, 0.002 mmol) in DCM (1 mL). The reaction was purified in 2:3 Hexanes:EtOAc to afford a clear oil (14 mg, 64%) as a 7:1 mix of the  $\alpha$ : $\beta$  substituted regioisomers. The regioisomers were then separated via preparative high performance liquid chromatography (HPLC).

The HPLC separation of the two regioisomers was performed on a 150 mm length  $\times$  21.2 mm inner diameter, 5- $\mu\text{m}$  particle size Luna Omega Polar C18 100 A column with mobile phase A ( $\text{H}_2\text{O}$  with 0.1% formic acid) and mobile phase B (acetonitrile with 0.1% formic acid). The flow rate

was 20 ml min<sup>-1</sup>. The linear gradient was as follows: 0–1 min, 5% B, 1–12 min, gradient to 50% B, 12–14 min, 50% B, 14–18 min, gradient to 95% B, 18–21 min, 95% B, 21–21.10, gradient to 5% B, 21.10–25 min, 5% B. The wavelengths of 254nm and 217nm were used to determine regioisomer separation.

Ultra-high performance liquid chromatography mass spectrometry (UPLC-MS) analyses were performed of the photooxidation product in addition to the two separated regioisomers using a Waters ACQUITY UPLC in line with an ACQUITY RDa Detector and an Acquity UPLC BEH C18 1.7  $\mu$ m diameter, 2.1 x 50mm column. Waters\_connect (Unifi) software v.3.0.0.15 was used in the analyses of the spectra. The spectra was obtained using using mobile phases of H<sub>2</sub>O+0.1% formic acid (A) and acetonitrile+0.1% formic acid (B). The elution gradient was as follows: 0-1 min, 5% B, 1-7 min, gradient to 95% B, 7-8 min, 95% B, 8-8.10 min, gradient to 5% B, 8.10 to 10 min, 5% B. Data can be found in Figures S17-19.

**TLC:** R<sub>f</sub> = 0.19 (2:3 Hex:EA, visualized in CAN)

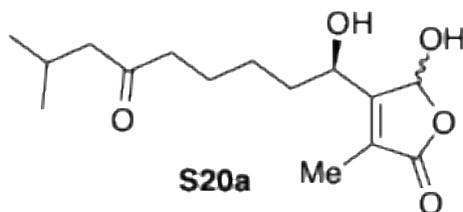
**<sup>1</sup>H NMR** (800 MHz, CDCl<sub>3</sub>)  $\delta$  5.84 (s, 1H), 5.18 (s, 1H), 4.48 (t, *J* = 6.4 Hz, 1H), 3.05 (s, 1H), 2.39 (dt, *J* = 7.0, 1.6 Hz, 2H), 2.26 (dd, *J* = 7.0, 1.8 Hz, 2H), 2.07 (s, 3H), 1.89 – 1.66 (m, 3H), 1.60 – 1.50 (m, 2H), 1.40 – 1.32 (m, 1H), 1.27 – 1.19 (m, 1H), 0.90 (dd, *J* = 6.6, 1.5 Hz, 6H).

**<sup>13</sup>C NMR** (201 MHz, CDCl<sub>3</sub>)  $\delta$  212.37, 171.49, 157.61, 130.00, 98.89, 66.42, 51.98, 42.79, 35.63, 29.71, 24.75, 24.67, 23.06, 22.55, 11.58.

**FTIR** (neat):  $\nu$  1708.65 cm<sup>-1</sup>, 1749.15 cm<sup>-1</sup>, 3340.16 cm<sup>-1</sup>

**HRMS (UPLCMS):** *m/z* calcd for C<sub>15</sub>H<sub>25</sub>O<sub>5</sub> [M+H]<sup>+</sup> 285.1697, found 285.1690 (-2.11 ppm)

$[\alpha]_D^{21}$ : +20.83, *c* = 0.39 (CHCl<sub>3</sub>) lit +18.4, *c* = 0.86 (CHCl<sub>3</sub>)<sup>4</sup>



**5-hydroxy-4-((*R*)-1-hydroxy-8-methyl-6-oxononyl)-3-methylfuran-2(5*H*)-one (r3a)** was prepared according to GP9 with **15a** (20 mg, 0.08 mmol), TBAF (1M in THF, 0.10 mL, 0.10 mmol), and Rose Bengal (2 mg, 0.002 mmol) in DCM (1 mL). The reaction was purified in 2:3 Hexanes:EtOAc to afford a clear oil (14 mg, 64%) as a 7:1 mix of the  $\alpha$ : $\beta$  substituted regioisomers. The minor regioisomer was then separated out via prep HPLC.

**TLC:** R<sub>f</sub> = 0.19 (2:3 Hex:EA, visualized in CAN)

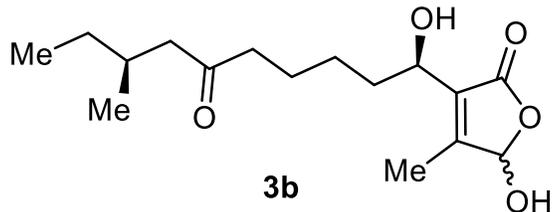
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.14 (t, *J* = 5.7 Hz, 1H), 4.79 – 4.67 (m, 1H), 4.43 (d, *J* = 6.4 Hz, 1H), 4.13 (d, *J* = 7.4 Hz, 1H), 2.75 (d, *J* = 5.4 Hz, 1H), 2.43 (t, *J* = 6.8 Hz, 2H), 2.27 (d, *J* = 7.1 Hz, 2H), 1.89 (d, *J* = 5.7 Hz, 3H), 1.86 – 1.60 (m, 4H), 1.51 – 1.22 (m, 4H), 0.92 (d, *J* = 6.7 Hz, 6H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) (reported as mixture of epimers at C4)  $\delta$  211.76, 211.46, 172.00, 171.70, 158.98, 156.86, 127.57, 126.54, 96.57, 96.44, 68.16, 67.56, 51.92, 42.83, 42.72, 35.51, 25.46, 24.70, 22.88, 22.57, 8.98, 8.88.

**FTIR** (neat):  $\nu$  1710.58 cm<sup>-1</sup>, 1754.93 cm<sup>-1</sup>, 3320.87 cm<sup>-1</sup>

**HRMS (UPLCMS):** *m/z* calcd for C<sub>15</sub>H<sub>25</sub>O<sub>5</sub> [M+H]<sup>+</sup> 285.1697, found 285.1698 (0.5 ppm)

$[\alpha]_D^{21}$ : -57.00, *c* = 0.072 (CHCl<sub>3</sub>)



**5-hydroxy-3-((1R,8S)-1-hydroxy-8-methyl-6-oxodecyl)-4-methylfuran-2(5H)-one (3b)** was prepared according to GP9 with **15b** (5 mg, 0.02 mmol), TBAF (1M in THF, 0.02 mL, 0.02 mmol), and Rose Bengal (1 mg, 0.001 mmol) in DCM (0.5 mL). The reaction was purified in 1:1 Hexanes:EtOAc to afford a clear oil (5 mg, 95%) as a 9:1 mix of the  $\alpha$ : $\beta$  substituted regioisomers. **TLC**:  $R_f$  = 0.25 (2:3 Hex:EA, visualized in CAN)

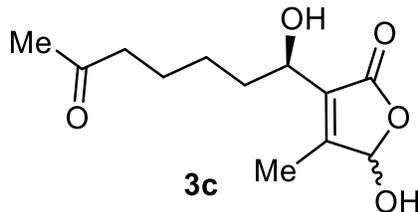
**$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ , only the signals for the  $\alpha$  regioisomer are given)  $\delta$  5.85 (s, 1H), 5.22 (s, 0.6H, C4-OH), 4.93 (s, 0.4H, C4-OH), 4.49 (s, 1H), 3.01 (s, 1H), 2.51 – 2.30 (m, 3H), 2.19 (dd,  $J$  = 15.3, 7.7 Hz, 1H), 2.08 (s, 3H), 1.95 – 1.77 (m, 3H, exp. 2H), 1.79 – 1.64 (m, 3H, exp. 2H), 1.64 – 1.46 (m, 3H, exp. 2H), 1.46 – 1.09 (m, 6H, exp. 3H), 0.87 (t,  $J$  = 7.3 Hz, 7H, exp. 6H).

**$^{13}\text{C NMR}$**  (126 MHz,  $\text{CDCl}_3$ )  $\delta$   $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  212.86, 171.45, 157.45, 129.97, 98.93, 66.42, 50.06, 42.73, 35.68, 30.92, 29.53, 24.65, 23.02, 19.39, 11.62, 11.33.

**FTIR** (neat):  $\nu$  1708.35  $\text{cm}^{-1}$ , 1745.23  $\text{cm}^{-1}$ , 3348.10  $\text{cm}^{-1}$

**HRMS (ESI+)**:  $m/z$  calcd for  $\text{C}_{16}\text{H}_{27}\text{O}_5$   $[\text{M}+\text{H}]^+$  299.1853, found 299.1859 (-2.0 ppm)

$[\alpha]_D^{21}$ : +19.43,  $c$  = 0.35 ( $\text{CHCl}_3$ ) lit +22.4,  $c$  = 0.80 ( $\text{CHCl}_3$ )<sup>4</sup>



**5-hydroxy-3-((R)-1-hydroxy-6-oxoheptyl)-4-methylfuran-2(5H)-one (3c)** was prepared according to GP9 with **15c** (10 mg, 0.05 mmol), TBAF (1M in THF, 0.06 mL, 0.06 mmol), and Rose Bengal (1 mg, 0.001 mmol) in DCM (0.5 mL). The reaction was purified in 2:3 Hexanes:EtOAc to afford a clear oil (5 mg, 95%) as a 6:1 mix of the  $\alpha$ : $\beta$  substituted regioisomers. **TLC**:  $R_f$  = 0.10 (2:3 Hex:EA, visualized in CAN)

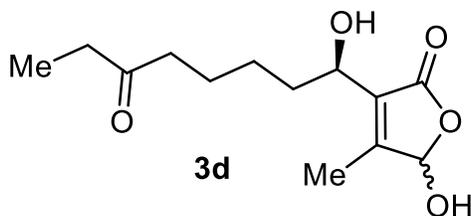
**$^1\text{H NMR}$**  (800 MHz,  $\text{CDCl}_3$ , only the signals for the  $\alpha$  regioisomer are given)  $\delta$  5.87 (s, 1H), 5.25 (s, 0.5H, C4-OH), 5.08 (s, 0.5H, C4-OH), 4.51 (s, 1H), 3.09 (d,  $J$  = 23.9 Hz, 1H), 2.56 – 2.41 (m, 2H), 2.16 (d,  $J$  = 12.0 Hz, 3H), 2.10 (d,  $J$  = 13.4 Hz, 3H), 1.96 – 1.67 (m, 5H, exp. 2H), 1.67 – 1.54 (m, 3H, exp. 1H), 1.54 – 1.34 (m, 2H, exp. 1H), 1.34 – 1.17 (m, 2H).

**$^{13}\text{C NMR}$**  (201 MHz,  $\text{CDCl}_3$ )  $\delta$  210.47, 171.52, 157.56, 129.99, 98.90, 66.40, 43.30, 35.67, 30.03, 24.80, 23.03, 11.63.

**FTIR** (neat):  $\nu$  1704.37  $\text{cm}^{-1}$ , 1745.05  $\text{cm}^{-1}$ , 3347.48  $\text{cm}^{-1}$

**HRMS (ESI+)**:  $m/z$  calcd for  $\text{C}_{12}\text{H}_{18}\text{NaO}_5$  265.1052, found 265.1047 (-1.89 ppm)

$[\alpha]_D^{21}$ : +30.51,  $c$  = 0.33 ( $\text{CHCl}_3$ )



**5-hydroxy-3-((R)-1-hydroxy-6-oxooctyl)-4-methylfuran-2(5H)-one (3d)** was prepared according to GP9 with **15d** (5 mg, 0.02 mmol), TBAF (1M in THF, 0.03 mL, 0.03 mmol), and Rose Bengal (1 mg, 0.001 mmol) in DCM (0.5 mL). The reaction was purified in 2:3 Hexanes:EtOAc to afford a clear oil (3 mg, 59%) as a 6:1 mix of the  $\alpha$ : $\beta$  substituted regioisomers.

**TLC:**  $R_f$  = 0.18 (2:3 Hex:EA, visualized in CAN)

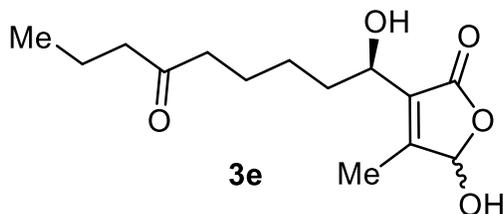
**$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ , only the signals for the  $\alpha$  regioisomer are given)  $\delta$  5.85 (s, 1H), 5.68 (s, 1H), 4.48 (d,  $J$  = 6.7 Hz, 1H), 3.30 (s, 1H), 2.42 (t,  $J$  = 6.2 Hz, 5H, exp 4H), 2.07 (s, 3H), 1.87 – 1.74 (m, 2H, exp 1H), 1.74 – 1.65 (m, 1H), 1.65 – 1.50 (m, 3H, exp 2H), 1.45 – 1.31 (m, 2H, exp 1H), 1.31 – 1.17 (m, 3H, exp 1H), 1.02 (t,  $J$  = 6.7 Hz, 4H, exp 3H).

**$^{13}\text{C NMR}$**  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  213.26, 171.69, 158.03, 129.98, 98.94, 66.37, 41.90, 36.06, 35.56, 24.86, 23.28, 11.60, 7.81.

**FTIR** (neat):  $\nu$  1705.10  $\text{cm}^{-1}$ , 1745.14  $\text{cm}^{-1}$ , 3374.08  $\text{cm}^{-1}$

**HRMS (UPLCMS):**  $m/z$  calcd for  $\text{C}_{13}\text{H}_{20}\text{NaO}_5$   $[\text{M}+\text{Na}]^+$  279.1208, found 279.1192 (-5.7 ppm)

$[\alpha]_D^{21}$ : +30.45,  $c$  = 0.22 ( $\text{CHCl}_3$ )



**5-hydroxy-3-((R)-1-hydroxy-6-oxononyl)-4-methylfuran-2(5H)-one (3e)** was prepared according to GP9 with **15e** (10 mg, 0.04 mmol), TBAF (1M in THF, 0.05 mL, 0.05 mmol), and Rose Bengal (1 mg, 0.001 mmol) in DCM (0.5 mL). The reaction was purified in 2:3 Hexanes:EtOAc to afford a clear oil (10 mg, 84%) as a 6:1 mix of the  $\alpha$ : $\beta$  substituted regioisomers.

**TLC:**  $R_f$  = 0.21 (2:3 Hex:EA, visualized in CAN)

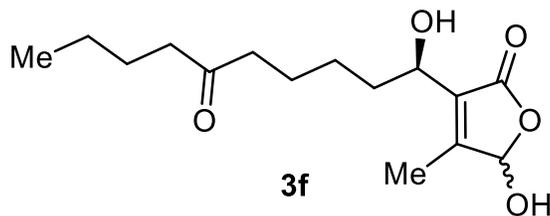
**$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ , only the signals for the  $\alpha$  regioisomer are given)  $\delta$  5.85 (s, 1H), 5.25 (s, 0.5H, C4-OH), 4.99 (s, 0.5H, C4-OH), 4.64 – 4.34 (m, 1H), 3.16 – 2.95 (m, 1H), 2.47 – 2.33 (m, 5H, exp. 4H), 2.08 (s, 3H), 1.87 – 1.78 (m, 1H), 1.78 – 1.65 (m, 2H, exp. 1H), 1.65 – 1.47 (m, 5H, exp 4H), 1.47 – 1.16 (m, 4H, exp. 2H), 0.93 – 0.85 (m, 4H, exp. 3H).

**$^{13}\text{C NMR}$**  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  212.91, 171.47, 157.53, 130.14, 98.95, 66.41, 44.86, 42.33, 35.63, 24.65, 23.05, 17.27, 13.74, 11.63.

**FTIR** (neat):  $\nu$  1704.54  $\text{cm}^{-1}$ , 1746.56  $\text{cm}^{-1}$ , 3377.45  $\text{cm}^{-1}$

**HRMS (ESI+):**  $m/z$  calcd for  $\text{C}_{14}\text{H}_{23}\text{O}_5$   $[\text{M}+\text{H}]^+$  271.1540 found 271.1532 (-2.9 ppm)

$[\alpha]_D^{21}$ : +11.40,  $c$  = 0.64 ( $\text{CHCl}_3$ )



**5-hydroxy-3-((R)-1-hydroxy-6-oxodecyl)-4-methylfuran-2(5H)-one (3f)** was prepared according to GP9 with **15f** (12 mg, 0.05 mmol), TBAF (1M in THF, 0.06 mL, 0.06 mmol), and Rose Bengal (1 mg, 0.001 mmol) in DCM (0.5 mL). The reaction was purified in 2:3 Hexanes:EtOAc to afford a clear oil (5 mg, 95%) as an 8:1 mix of the  $\alpha$ : $\beta$  substituted regioisomers.

**TLC:**  $R_f$  = 0.28 (2:3 Hex:EA, visualized in CAN)

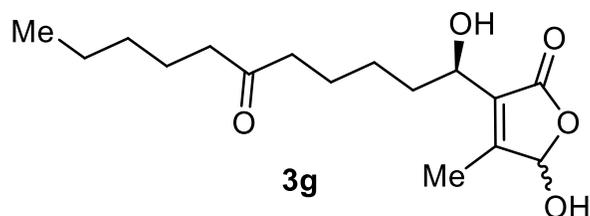
**$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ , only the signals for the  $\alpha$  regioisomer are given)  $\delta$  5.84 (s, 1H), 5.53 (s, 1H), 4.48 (s, 1H), 3.21 (s, 1H), 2.40 (p,  $J$  = 7.4 Hz, 4H), 2.07 (s, 3H), 1.93 – 1.81 (m, 1H), 1.78 – 1.62 (m, 2H, exp 1H), 1.62 – 1.45 (m, 5H, exp 4H), 1.45 – 1.11 (m, 6H, exp 4H), 0.89 (t,  $J$  = 7.4 Hz, 3H).

**$^{13}\text{C NMR}$**  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  212.99, 171.62, 157.89, 129.99, 98.93, 66.40, 42.72, 42.26, 35.60, 25.94, 24.82, 23.20, 22.33, 13.85, 11.60.

**FTIR** (neat):  $\nu$  1704.58  $\text{cm}^{-1}$ , 1745.35  $\text{cm}^{-1}$ , 3373.99  $\text{cm}^{-1}$

**HRMS (UPLCMS):**  $m/z$  calcd for  $\text{C}_{15}\text{H}_{25}\text{O}_5$   $[\text{M}+\text{H}]^+$  285.1697 found 285.1689 (-2.5 ppm)

$[\alpha]_D^{21}$ : +29.50,  $c$  = 0.20 ( $\text{CHCl}_3$ )



**5-hydroxy-3-((R)-1-hydroxy-6-oxoundecyl)-4-methylfuran-2(5H)-one (3g)** was prepared according to GP9 with **15g** (30 mg, 0.11 mmol), TBAF (1M in THF, 0.13 mL, 0.13 mmol), and Rose Bengal (2 mg, 0.002 mmol) in DCM (1 mL). The reaction was purified in 2:3 Hexanes:EtOAc to afford a clear oil (26 mg, 79%) as a 6:1 mix of the  $\alpha$ : $\beta$  substituted regioisomers.

**TLC:**  $R_f$  = 0.29 (2:3 Hex:EA, visualized in CAN)

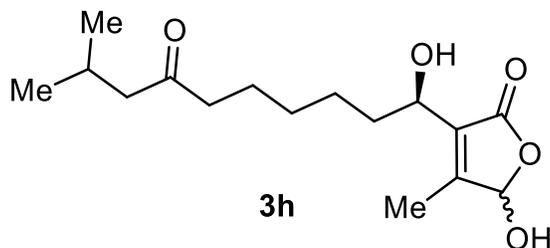
**$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ , only the signals for the  $\alpha$  regioisomer are given)  $\delta$  5.86 (s, 1H), 4.48 (t,  $J$  = 7.0 Hz, 1H), 2.47 – 2.34 (m, 4H), 2.07 (s, 3H), 1.86 – 1.78 (m, 1H), 1.75 – 1.64 (m, 1H), 1.61 – 1.48 (m, 4H), 1.42 – 1.33 (m, 1H), 1.33 – 1.19 (m, 6H, exp. 5H), 0.88 (t,  $J$  = 6.8 Hz, 3H).

**$^{13}\text{C NMR}$**  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  212.58, 171.58, 157.71, 130.09, 99.20, 66.43, 42.98, 42.26, 35.63, 31.39, 24.82, 23.54, 23.20, 22.44, 13.92, 11.58.

**FTIR** (neat):  $\nu$  1706.75  $\text{cm}^{-1}$ , 1745.44  $\text{cm}^{-1}$ , 3384.24  $\text{cm}^{-1}$

**HRMS (UPLCMS):**  $m/z$  calcd for  $\text{C}_{16}\text{H}_{27}\text{O}_5$   $[\text{M}+\text{H}]^+$  299.1853 found 299.1840 (-4.5 ppm)

$[\alpha]_D^{21}$ : +12.04,  $c$  = 1.22 ( $\text{CHCl}_3$ )



**5-hydroxy-3-((R)-1-hydroxy-9-methyl-7-oxodecyl)-4-methylfuran-2(5H)-one (3h)** was prepared according to GP9 with **15h** (17 mg, 0.06 mmol), TBAF (1M in THF, 0.10 mL, 0.10 mmol), and Rose Bengal (1 mg, 0.001 mmol) in DCM (1.5 mL). The reaction was purified in 3:1 Hexanes:EtOAc to afford a pale-yellow oil (16 mg, 84%) as a 8:1 mix of the  $\alpha$ : $\beta$  substituted regioisomers.

**TLC:**  $R_f$  = 0.30 (2:3 Hex:EA, visualized with CAN)

**$^1\text{H NMR}$** :  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ , only the signals for the  $\alpha$  regioisomer are given)  $\delta$  5.85 (s, 1H), 4.47 (t,  $J$  = 7.0 Hz, 1H), 3.07 (s, 1H), 2.39 (t,  $J$  = 7.3 Hz, 2H), 2.27 (d,  $J$  = 6.9 Hz, 2H), 2.17

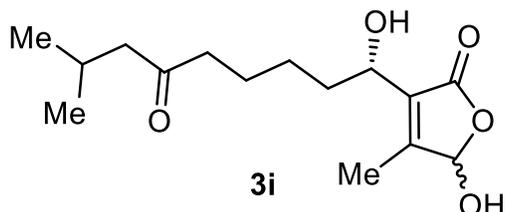
– 2.06 (m, 1H), 2.07 (s, 3H), 1.87 – 1.75 (m, 2H), 1.68 (s, 1H), 1.55 (p,  $J = 7.1$  Hz, 2H), 1.46 – 1.37 (m, 1H), 1.35 – 1.26 (m, 3H), 0.90 (d,  $J = 6.6$  Hz, 6H).

**$^{13}\text{C}$  NMR**:  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  212.46, 171.43, 157.22, 130.40, 98.74, 66.80, 51.87, 43.11, 36.09, 28.75, 24.95, 24.68, 23.27, 22.58, 11.53.

**FTIR** (neat):  $\nu$  1706.72  $\text{cm}^{-1}$ , 1747.22  $\text{cm}^{-1}$ , 3388.37  $\text{cm}^{-1}$

**HRSM (UPLCMS)**:  $m/z$  calc'd for  $\text{C}_{16}\text{H}_{26}\text{NaO}_5$   $[\text{M}+\text{Na}]^+$  321.1672 found 321.1663 (-2.9 ppm)

$[\alpha]_D^{21}$ : +5.54,  $c = 0.46$  ( $\text{CHCl}_3$ )



**5-hydroxy-3-((S)-1-hydroxy-8-methyl-6-oxononyl)-4-methylfuran-2(5H)-one (3i)** was prepared according to GP9 with **15i** (10 mg, 0.04 mmol), TBAF (1M in THF, 0.05 mL, 0.05 mmol), and Rose Bengal (1 mg, 0.001 mmol) in DCM (0.5 mL). The reaction was purified in 1:1 Hexanes:EtOAc to afford a clear oil (8 mg, 74%) as a 5:1 mix of the  $\alpha$ : $\beta$  substituted regioisomers.

**TLC**:  $R_f = 0.25$  (2:3 Hex:EA, visualized in CAN)

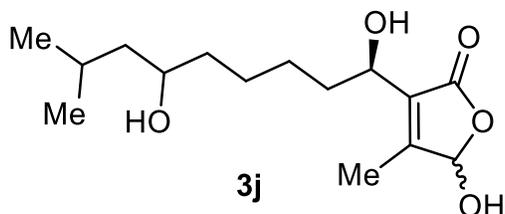
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ , only the signals for the  $\alpha$  regioisomer are given)  $\delta$  5.85 (s, 1H), 5.30 (s, 0.5H, C4-OH), 5.14 (s, 0.5H, C4-OH), 4.48 (s, 1H), 3.08 (s, 1H), 2.39 (t,  $J = 6.8$  Hz, 2H), 2.27 (d,  $J = 7.0$  Hz, 2H), 2.16 – 2.10 (m, 1H), 2.08 (s, 3H), 1.86 – 1.78 (m, 2H, exp. 1H), 1.78 – 1.65 (m, 1H), 1.65 – 1.50 (m, 3H, exp. 2H), 1.47 – 1.32 (m, 2H, exp. 1H), 1.32 – 1.16 (m, 3H, exp. 1H), 0.90 (d,  $J = 6.6$  Hz, 7H, exp. 6H).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  212.61, 171.52, 157.62, 130.04, 98.96, 66.45, 51.96, 42.74, 35.65, 29.72, 24.69, 23.04, 22.57, 11.62.

**FTIR** (neat):  $\nu$  1705.32  $\text{cm}^{-1}$ , 1746.13  $\text{cm}^{-1}$ , 3377.03  $\text{cm}^{-1}$

**HRMS (UPLCMS)**:  $m/z$  calc'd for  $\text{C}_{15}\text{H}_{25}\text{O}_5$   $[\text{M}+\text{H}]^+$  285.1697 found 285.1693 (-1.3 ppm)

$[\alpha]_D^{23}$ : -63.61,  $c = 0.55$  ( $\text{CHCl}_3$ )



**3-((1R)-1,6-dihydroxy-8-methylnonyl)-5-hydroxy-4-methylfuran-2(5H)-one (3j)** was prepared according to GP9 with **15j** (17 mg, 0.08 mmol), TBAF (1M in THF, 0.12 mL, 0.12 mmol), and Rose Bengal (2 mg, 0.001 mmol) in DCM (1.0 mL). The reaction was purified in 1:4 Hexanes:EtOAc to afford a pale-yellow oil (7 mg, 37%) as a 6:1 mix of the  $\alpha$ : $\beta$  substituted regioisomers.

**TLC**:  $R_f = 0.33$  (1:4 Hex:EA, visualized with CAN)

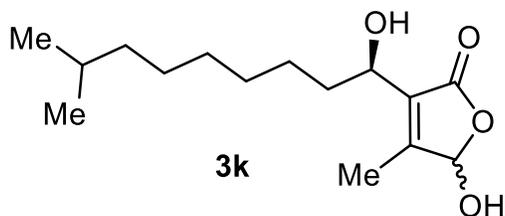
**$^1\text{H}$  NMR**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , only the signals for the  $\alpha$  regioisomer are given)  $\delta$  5.83 (s, 1H), 4.88 (s, 1H), 4.49 (s, 1H), 3.66 (s, 1H), 3.02 (s, 1H), 2.08 (s, 3H), 1.93 – 1.79 (m, 2H), 1.78 – 1.57 (m, 6H), 1.50 – 1.32 (m, 8H), 0.89 (t,  $J = 6.6$  Hz, 8H).

**$^{13}\text{C}$  NMR** (201 MHz,  $\text{CDCl}_3$ )  $\delta$  171.44, 157.24, 130.42, 98.59, 70.06, 66.73, 60.44, 46.84, 37.47, 35.81, 29.71, 25.21, 24.63, 23.44, 22.08, 14.20, 11.50.

**FTIR** (neat):  $\nu$  1745.29  $\text{cm}^{-1}$ , 3369.08  $\text{cm}^{-1}$

**HRSM (UPLCMS)**:  $m/z$  calc'd for  $\text{C}_{16}\text{H}_{26}\text{NaO}_5$   $[\text{M}+\text{Na}]^+$  309.1672 found 309.1678 (1.7 ppm)

$[\alpha]_D^{21}$ : +10.51,  $c = 0.18$  ( $\text{CHCl}_3$ )



**5-hydroxy-3-((R)-1-hydroxy-8-methylnonyl)-4-methylfuran-2(5H)-one (3k)** was prepared according to GP9 with **15k** (3 mg, 0.01 mmol), TBAF, 1M in THF (0.02 mL, 0.02 mmol), and Rose Bengal (1 mg, 0.001 mmol) in DCM (0.5 mL). The reaction was purified in 1:1 Hexanes:EtOAc to afford a clear oil (2 mg, 43%) as a 6:1 mix of the  $\alpha$ : $\beta$  substituted regioisomers.

**TLC:**  $R_f$  = 0.20 (1:1 Hex:EA, visualized in CAN)

**$^1\text{H NMR}$**  (800 MHz,  $\text{CDCl}_3$ ) only the signals for the  $\alpha$  regioisomer are given)  $\delta$  5.87 (t,  $J$  = 7.0 Hz, 1H), 4.48 (t,  $J$  = 4.4 Hz, 1H), 3.67 (br s, 0.5H), 3.59 (br s, 0.5H), 2.74 (br s, 1H), 2.07 (s, 3H), 1.87 – 1.78 (m, 2H, exp 1H), 1.73 – 1.63 (m, 2H, exp 1H), 1.54 – 1.47 (m, 3H, exp 2H), 1.47 – 1.36 (m, 3H, exp 2H), 1.36 – 1.20 (m, 17H, exp 4H), 1.20 – 1.12 (m, 4H, exp 3H), 0.86 (d,  $J$  = 6.5 Hz, 12H, exp 6H).

**$^{13}\text{C NMR}$**   $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  171.22, 156.62, 130.89, 98.45, 66.89, 38.98, 36.60, 29.79, 29.35, 27.95, 27.31, 25.54, 22.65, 11.39.

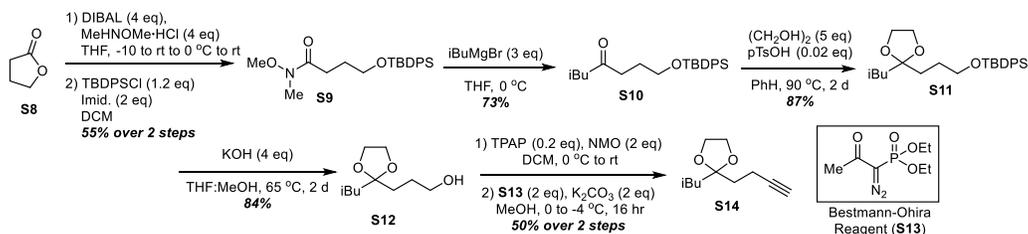
**FTIR** (neat):  $\nu$  1745.71  $\text{cm}^{-1}$ , 3348.24  $\text{cm}^{-1}$

**HRMS (UPLCMS):**  $m/z$  calcd for  $\text{C}_{15}\text{H}_{25}\text{O}_3$  [ $\text{M}-\text{OH}$ ] $^-$  253.1809, found 253.1799 (-3.95 ppm)

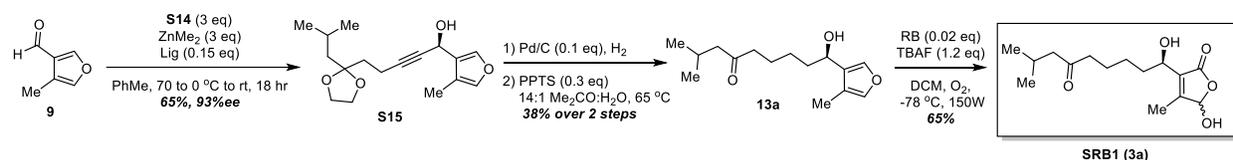
$[\alpha]_D^{22}$ : +13.33,  $c$  = 0.5 ( $\text{CHCl}_3$ )

### Figure S4: Initial Route to access SRB1

#### A) Side Chain



#### B) Convergence



**Figure S4a)** Forward route to accessing the alkyne sidechain of SRB1. **b)** Convergent route to access SRB1.

### Aminolysis of $\gamma$ -Butyrolactone and Tert-butyldiphenylsilyl protection



A two-neck flask equipped with a stir bar and fitted with an addition funnel was charged with *N,O*-dimethylhydroxylamine hydrochloride (9.06 g, 92.9 mmol, 4 equiv.), diluted with THF (100 mL) and brought to -10 °C in a salt-ice bath. Diisobutylaluminum hydride (DIBAL, 1M in toluene, 93 mL, 92.9 mmol, 4 equiv.) was added dropwise via addition funnel over 20 minutes and allowed to warm to room temperature. After 3 hours the reaction was brought to 0 °C in an ice bath and  $\gamma$ -butyrolactone, **S8** (2.00 g, 23.2 mmol, 1 equiv.) was added dropwise over 10 minutes and allowed to stir at room temperature. After two hours, the reaction was cooled to 0 °C and diluted with EtOAc (100 mL). A few drops of water were added to the reaction, causing vigorous bubbling. After the bubbling ceased, a saturated solution of Rochelle's salt (150 mL) was added. The emulsion was vigorously stirred for 30 minutes and moved to a separatory funnel. The organic phase was removed and the aqueous layer was extracted with EtOAc (100 mL x 5). The organic layers were combined, dried with Na<sub>2</sub>SO<sub>4</sub>, gravity filtered, and concentrated under reduced pressure to afford a viscous pale-yellow oil. Then the oil was dissolved in DCM (50 mL) and stirred in a round bottom flask. Imidazole (2.37g, 34.848 mmol, 1.5 equiv.) and TBDPSCI (9.00 mL, 34.848 mmol, 1.5 equiv.) were added successively and stirred overnight. The reaction was then quenched with a saturated solution of NH<sub>4</sub>Cl (50 mL). The aqueous phase was extracted with DCM (50 mL x 2). Combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, gravity filtered, and concentrated under reduced pressure. The crude oil was purified on silica gel in 17:3 Hexanes:EtOAc to afford **S9** as a clear oil (6.70 g, 73%).

**TLC:** R<sub>f</sub> = 0.25 (17:3 Hex:EA, visualized under UV)

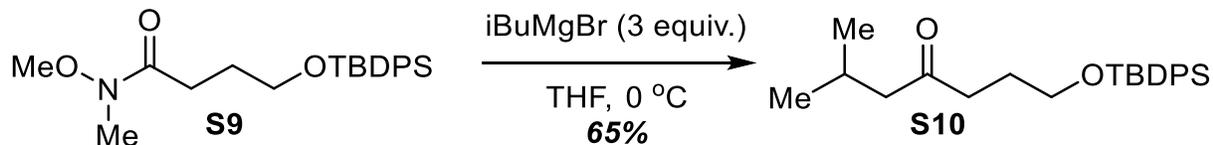
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  7.66 (dd, *J* = 7.4, 1.4 Hz, 4H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 4H), 3.73 (t, *J* = 5.9 Hz, 2H), 3.67 (s, 3H), 3.18 (s, 3H), 2.56 (t, *J* = 7.3 Hz, 2H), 1.90 (d, *J* = 6.1 Hz, 2H), 1.05 (s, 9H).

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta$  174.55, 135.59, 133.95, 129.60, 127.65, 63.29, 61.19, 32.23, 28.46, 27.57, 26.89, 19.27.

**FTIR** (neat):  $\nu$  1664.29 cm<sup>-1</sup>, 1108.89 cm<sup>-1</sup>

**HRMS** (ACPI+): calcd for C<sub>22</sub>H<sub>31</sub>NO<sub>3</sub>Si [M] 385.2146, found 385.2147 (0.25 ppm)

#### Alkylation of Weinreb Amide



**S9** (2.00 g, 5.01 mmol, 1 equiv.) was dissolved in THF (20 mL) and stirred at 0 °C in an ice bath. Isobutylmagnesium bromide (2M in Et<sub>2</sub>O, 7.51 mL, 15.0 mmol, 3 equiv.) was added dropwise. The reaction was then allowed to stir at room temperature. After consumption of the amide was observed on TLC, the reaction was brought to 0 °C, diluted with EtOAc (20 mL), and quenched with a saturated solution of NH<sub>4</sub>Cl (20 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (20 mL x 2). The combined organic layers were dried with MgSO<sub>4</sub>, gravity filtered, and concentrated under reduced pressure. The crude oil was purified on silica gel in 19:1 Hexanes:EtOAc to afford **S10** as a clear oil (1.26 g, 65%).

**TLC:** R<sub>f</sub> = 0.44 (19:1 Hex:EA, visualized under UV)

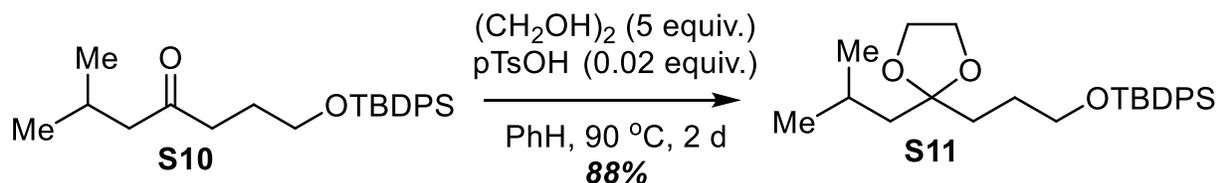
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.65 (d, *J* = 6.6 Hz, 4H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 4H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.50 (t, *J* = 7.0 Hz, 2H), 2.27 (d, *J* = 7.3 Hz, 2H), 2.13 (hept, *J* = 6.8 Hz, 1H), 1.82 (p, *J* = 6.5 Hz, 2H), 1.05 (s, 9H), 0.92 (d, *J* = 6.8 Hz, 6H).

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 210.83, 135.57, 133.87, 129.64, 127.67, 63.05, 51.94, 39.63, 26.89, 26.62, 24.69, 22.63, 19.25.

**FTIR** (neat): ν 1711.77 cm<sup>-1</sup>, 1110.81 cm<sup>-1</sup>

**HRMS** (ACPI+): calcd for C<sub>24</sub>H<sub>35</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 383.2401, found 383.2392 (-2.34 ppm)

#### Ketal Protection



A solution of **S10** (1.20 g, 2.73 mmol, 1 equiv.), ethylene glycol (0.78 mL, 13.6 mmol, 5 equiv.), and *p*-toluenesulfonic acid (10 mg, 0.06 mmol, 0.02 equiv.) in benzene (60 mL) was stirred at 95 °C in an oil bath in a round bottom flask equipped with a Dean-Stark apparatus and reflux condenser. After 2 days, the reaction was brought to room temperature and the solution was decanted into a separatory funnel containing Et<sub>2</sub>O (50 mL) and a saturated solution of NaHCO<sub>3</sub> (50 mL). The phases were mixed and separated. The aqueous phase was extracted with Et<sub>2</sub>O (50 mL x 2). Combined organic layers were dried with MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting crude oil was purified on silica gel in 19:1 Hexanes:EtOAc to afford **S11** as a clear oil (1.15 g, 88%).

**TLC:** R<sub>f</sub> = 0.44 (19:1 Hex:EA, visualized under UV)

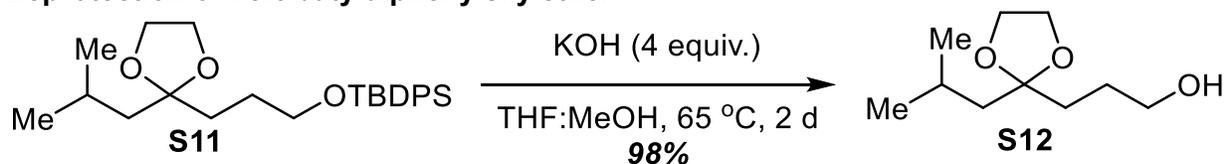
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.66 (d, *J* = 6.9 Hz, 4H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 4H), 4.06 – 3.75 (m, 4H), 3.67 (t, *J* = 6.7 Hz, 2H), 1.77 (hept, *J* = 6.7 Hz, 1H), 1.73 – 1.66 (m, 2H), 1.64 (s, 2H), 1.52 (d, *J* = 6.4 Hz, 2H), 1.05 (s, 9H), 0.95 (d, *J* = 6.4 Hz, 6H).

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 135.61, 134.10, 129.53, 127.61, 111.99, 64.55, 64.05, 45.21, 33.55, 27.20, 26.88, 24.08, 24.01, 19.24.

**FTIR** (neat): ν 1427.09 cm<sup>-1</sup>, 1105.03 cm<sup>-1</sup>, 701.97 cm<sup>-1</sup>

**HRMS** (ACPI+): calcd for C<sub>26</sub>H<sub>39</sub>O<sub>3</sub>Si [M+H]<sup>+</sup> 427.2663, found 427.2664 (-0.94 ppm)

#### Deprotection of Tert-butylidiphenylsilylether



A solution of **S11** (1.10 g, 2.50 mmol, 1 equiv.) and potassium hydroxide (0.56 g, 9.98 mmol, 4 equiv.) in diH<sub>2</sub>O (10 mL) were dissolved in a mixture of THF (35 mL) and MeOH (15 mL). The reaction was brought to 65 °C and stirred for 2 days or until the silyl ether was consumed by TLC. The reaction was brought to 0 °C and quenched with a saturated solution of NH<sub>4</sub>Cl (50 mL). During this the reaction turned deep magenta. The aqueous phase was extracted with DCM (50 mL x 3). The combined organic layers were dried with MgSO<sub>4</sub>, gravity filtered, and concentrated under reduced pressure. The resulting crude oil was purified via silica gel in 7:3 Hexanes:EtOAc to afford **S12** as a yellow oil (492 mg, 98%).

**TLC:** R<sub>f</sub> = 0.22 (7:3 Hex:EA, visualized under KMnO<sub>4</sub>)

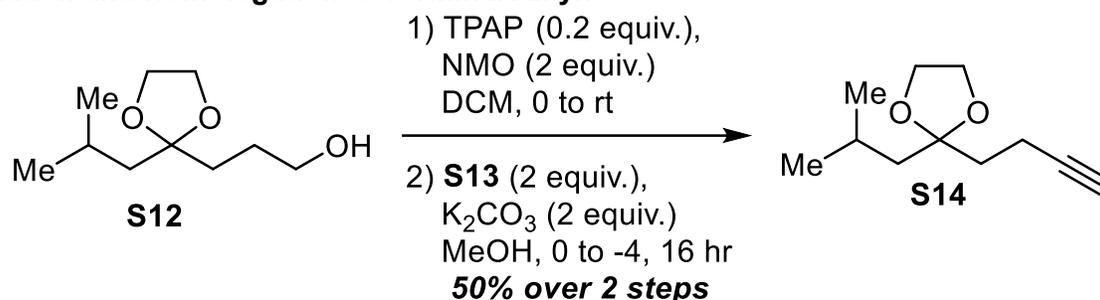
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 3.95 (s, 4H), 3.64 (t, *J* = 5.3 Hz, 2H), 2.01 (s, 1H), 1.83 – 1.70 (m, 3H), 1.66 (p, *J* = 6.3 Hz, 2H), 1.54 (d, *J* = 6.3 Hz, 2H), 0.95 (s, 6H).

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 111.90, 64.60, 63.21, 45.09, 34.01, 27.04, 24.15, 23.98.

**FTIR** (neat): ν 3405.73 cm<sup>-1</sup>, 1467.59 cm<sup>-1</sup>, 1060.67 cm<sup>-1</sup>, 948.82 cm<sup>-1</sup>

**HRMS** (ACPI-): calcd for C<sub>10</sub>H<sub>19</sub>O<sub>3</sub> [M-H]<sup>-</sup> 187.1340, found 187.1352 (6.41 ppm)

## Oxidation and Homologation to Terminal Alkyne



Tetrapropylammonium perruthenate (75 mg, 0.21 mmol, 0.2 equiv.) and *N*-methylmorpholine *N*-oxide (249 mg, 2.13 mmol, 2 equiv.) and crushed 4Å MS (200 mg) were added to a warm, freshly flame-dried round bottom flask, equipped with a stir bar. The vessel was placed under vacuum and allowed to cool to room temperature, after which, the vessel was charged with DCM (10 mL) under an atmosphere of nitrogen. A solution of alcohol, **S12** (200 mg, 1.06 mmol, 1 equiv.) in DCM (1 mL) was added dropwise. The reaction was allowed to stir at room temperature until the consumption of the starting alcohol was observed by TLC. The solution was then passed through a short plug of silica gel. The plug was washed with 4:1 pentane:Et<sub>2</sub>O (200 mL). The filtrate was then concentrated to a clear oil which was immediately dissolved in MeOH (1 mL) and added dropwise to a stirring solution of the Bestmann-Ohira reagent, **S13** (468 mg, 2.13 mmol, 2 equiv.) and potassium carbonate (281 mg, 2.13 mmol, 2 equiv.) in MeOH (10 mL) at 0 °C in an ice bath. The reaction was moved to a 4 °C refrigerator and stirred overnight. The reaction was quenched at 0 °C with a saturated solution of NH<sub>4</sub>Cl (10 mL) and extracted with Et<sub>2</sub>O (20 mL x 3). The combined organic layers were dried with MgSO<sub>4</sub>, gravity filtered, and concentrated under a stream of nitrogen gas. The resulting yellow oil was purified on a plug of silica gel in 9:1 pentanes:Et<sub>2</sub>O to afford the alkyne, **S15** as a clear oil (97 mg, 50% over 2 steps).

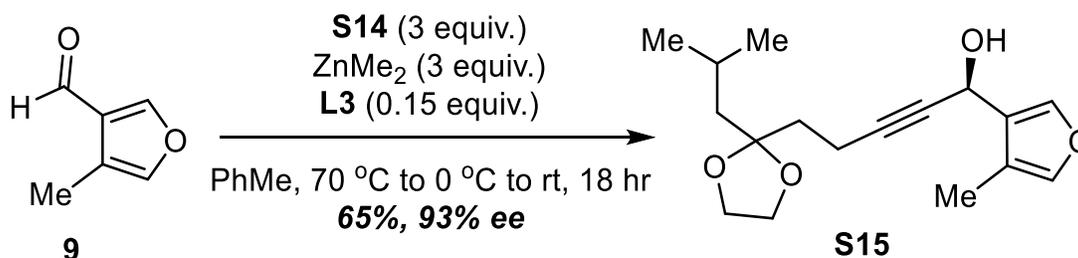
**TLC:** R<sub>f</sub> = 0.45 (9:1 pentane:Et<sub>2</sub>O, visualized with CAN)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 3.92 (d, *J* = 2.7 Hz, 4H), 2.31 – 2.19 (m, 2H), 1.92 (t, *J* = 2.7 Hz, 2H), 1.91 (d, *J* = 7.7 Hz, 1H), 1.77 (hept, *J* = 6.7 Hz, 1H), 1.51 (d, *J* = 6.3 Hz, 2H), 0.95 (d, *J* = 6.7 Hz, 6H).

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 110.90, 84.52, 77.28, 67.84, 64.73, 45.26, 36.29, 23.95, 13.12.

**FTIR** (neat): ν 2120.97 cm<sup>-1</sup>, 1261.24 cm<sup>-1</sup>, 1035 cm<sup>-1</sup>

**HRMS** (ACPI+): calcd for C<sub>11</sub>H<sub>19</sub>O<sub>2</sub> [M+H]<sup>+</sup> 183.1380, found 183.1376 (-2.18 ppm)



Prepared using GP1 with aldehyde **9** (30 mg, 0.27 equiv., 1 equiv.), alkyne **S14** (150 mg, 0.82 mmol, 3 equiv.), dimethylzinc (2M in toluene, 0.41 mL, 0.823 mmol, 3 equiv.), and **L3** (12.6 mg, 0.04 mmol, 0.15 equiv.). The reaction was purified in 4:1 Hexanes:EtOAc to afford **S15** as a pale-yellow oil (52 mg, 65%). Enantiomeric excess was determined by Chiral HPLC using a Diacel Chiralpak AD-H column in 15% isopropanol in hexanes over 10 min at 30 °C with detection at 217 nm, *t*<sub>R</sub> (major) = 6.64 min and *t*<sub>R</sub> (minor) = 7.26 min, 92%ee).

**TLC:** R<sub>f</sub> = 0.21 (4:1 Hex:EA, visualized with CAN)

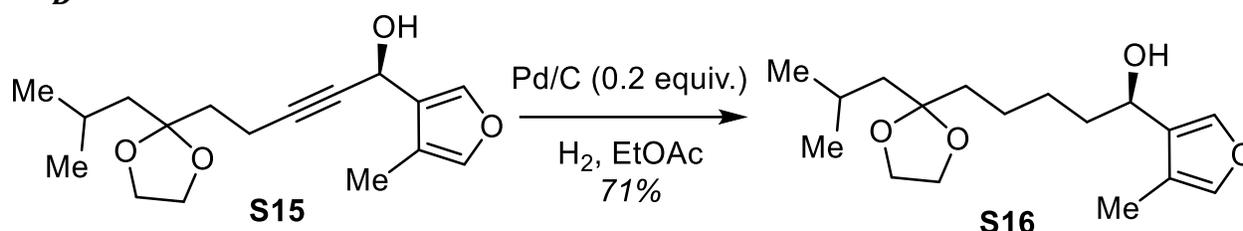
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.46 (s, 1H), 7.17 (s, 1H), 5.33 (s, 1H), 3.92 (d, *J* = 3.2 Hz, 5H), 2.32 (dt, *J* = 7.9, 1.9 Hz, 2H), 2.08 (s, 3H), 1.92 (t, *J* = 8.1 Hz, 2H), 1.76 (hept, *J* = 6.3 Hz, 1H), 1.51 (d, *J* = 5.9 Hz, 2H), 0.95 (d, *J* = 7.0 Hz, 6H).

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 140.85, 140.64, 126.51, 119.15, 110.91, 85.74, 79.00, 64.73, 56.97, 45.26, 36.31, 24.10, 23.96, 13.44, 8.21.

**FTIR (neat):** ν 3426.65 cm<sup>-1</sup>

**HRMS (ESI+):** calcd for C<sub>17</sub>H<sub>15</sub>O<sub>4</sub> [M+H]<sup>+</sup> 293.1753, found 293.1747 (2.13 ppm)

**[α]<sub>D</sub><sup>22</sup>:** -6.21, *c* = 0.29 (CHCl<sub>3</sub>)



A solution of **S15** (40 mg, 0.14 mmol, 1 equiv.), in EtOAc (3 mL) was sparged with nitrogen for 15 minutes. Palladium on carbon (4 mg, 0.03 mmol, 0.2 equiv.) was added and the vessel was sparged with nitrogen for another 15 minutes. The vessel was then sparged with hydrogen for 30 minutes, after which, the vent needle was removed, and the reaction was stirred for an additional hour under an atmosphere of hydrogen. The solution was vacuum filtered over a pad of celite and the filtrate was concentrated to afford **S16** as a clear oil (28 mg, 71%).

**TLC:** R<sub>f</sub> = 0.19 (4:1 Hex:EA, visualized with CAN)

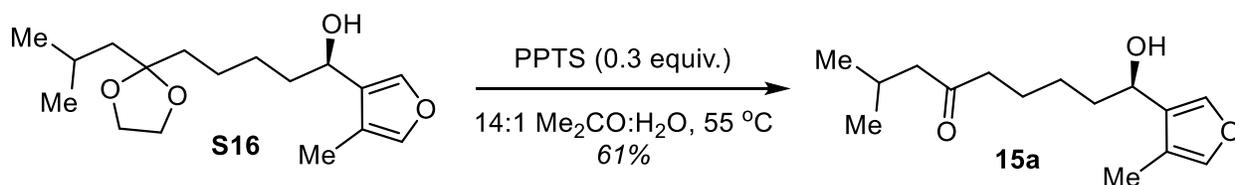
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.29 (d, *J* = 2.0 Hz, 1H), 7.15 (s, 1H), 4.60 (t, *J* = 7.0 Hz, 1H), 3.91 (d, *J* = 3.1 Hz, 4H), 2.04 (d, *J* = 1.3 Hz, 3H), 1.83 – 1.70 (m, 3H), 1.62 (t, *J* = 7.6 Hz, 4H), 1.51 (d, *J* = 6.1 Hz, 2H), 1.48 – 1.31 (m, 4H), 0.94 (d, *J* = 6.7 Hz, 6H).

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 140.32, 139.56, 128.85, 118.99, 111.97, 66.79, 64.60, 45.20, 37.34, 37.01, 26.19, 24.11, 24.04, 23.72, 8.57.

**FTIR (neat):** ν 3410.43 cm<sup>-1</sup>

**HRMS (ESI+):** *m/z* calcd for C<sub>17</sub>H<sub>23</sub>O<sub>4</sub> [M+H]<sup>+</sup> 297.2060, found 297.2055 (3.52 ppm)

**[α]<sub>D</sub><sup>22</sup>:** +7.56, *c* = 1.27 (CHCl<sub>3</sub>)



A solution of **S16** (30 mg, 0.10 mmol, 1 equiv.) and pyridinium p-toluenesulfonate (PPTS, 8 mg, 0.03 mmol, 0.3 equiv.) were refluxed in a solution of 14:1 acetone:diH<sub>2</sub>O (2 mL) for 2 hours. After which, the reaction was brought to room temperature, diluted with EtOAc (2 mL), and quenched with a saturated solution of sodium bicarbonate (2 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2 mL x 2). The combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, gravity filtered, and concentrated under reduced pressure. The resulting crude oil was purified on silica gel in 4:1 Hexanes:EtOAc to afford **15a** as a clear oil (16 mg, 61%).

**TLC:** R<sub>f</sub> = 0.26 (4:1 Hex:EA, visualized in KMnO<sub>4</sub>)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.29 (s, 1H), 7.16 (s, 1H), 4.61 (t, *J* = 6.3 Hz, 1H), 2.39 (t, *J* = 7.4 Hz, 2H), 2.26 (d, *J* = 7.2 Hz, 2H), 2.12 (hept, *J* = 6.9 Hz, 1H), 2.04 (s, 3H), 1.87 – 1.69 (m, 2H), 1.70 – 1.50 (m, 4H), 1.50 – 1.41 (m, 1H), 1.41 – 1.26 (m, 1H), 0.90 (d, *J* = 6.9 Hz, 6H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  210.99, 140.38, 139.56, 128.78, 118.94, 66.61, 51.92, 43.18, 36.77, 25.53, 24.66, 23.44, 22.61, 8.56.

FTIR (neat):  $\nu$  1707.93  $\text{cm}^{-1}$ , 3405.86  $\text{cm}^{-1}$

HRMS (UPLCMS):  $m/z$  calcd for  $\text{C}_{15}\text{H}_{25}\text{O}_3$   $[\text{M}+\text{H}]^+$  253.1798, found 253.1791 (-2.7 ppm)

$[\alpha]_D^{22}$ : +26.96,  $c$  = 0.33 ( $\text{CHCl}_3$ )

## Biological Materials and Methods

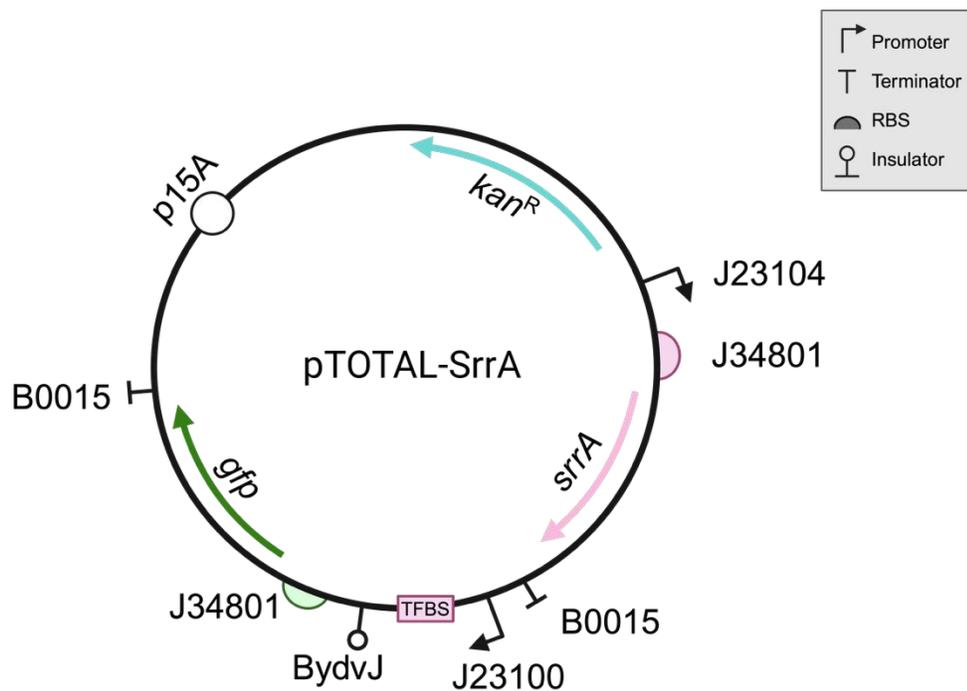
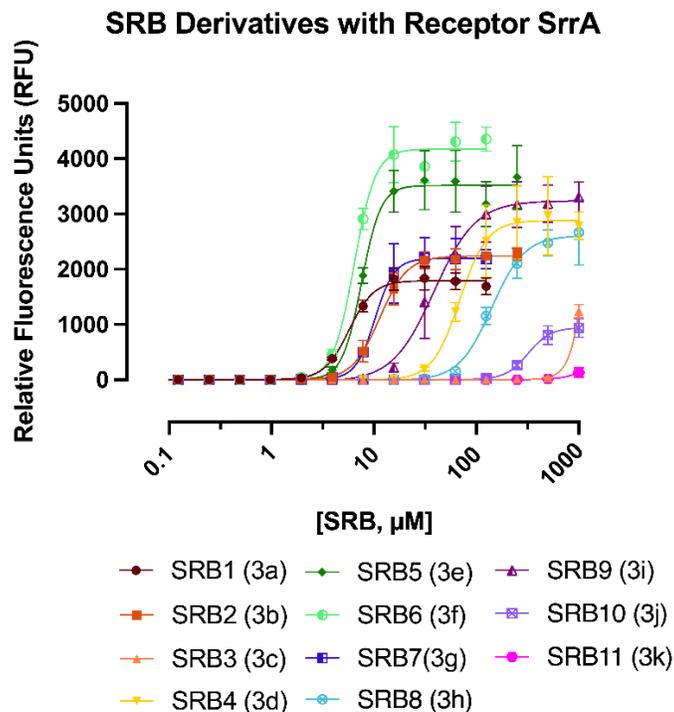


Figure S5. Plasmid map used for the SrrA-GFP reporter assay, with BioBrick parts and their corresponding IDs.<sup>5</sup>



**Figure S6. SrrA GFP reporter assay results.** Data represent the average of at least three independent biological replicates performed on separate days, with error bars showing the standard deviation (SD). The response is reported in relative fluorescence units (RFU). Dose-response curves were fitted using GraphPad Prism v10.6.0 with a four-parameter variable slope model (log[agonist] vs response).

**Table S1. Dose-response results of SrrA GFP reporter assay.** Missing values indicate dose-response curves that do not level off at the highest concentrations tested.  $K_D$ ,  $E_{\max}$ , and Hill coefficients were obtained by fitting experimental data to a four-parameter variable-slope (log[agonist] vs. response) model using GraphPad Prism v10.6.0. Area under the curve (AUC) values were calculated from the experimental data after normalizing the x-axis to  $\log_{10}([\text{SRB}]/K_D)$ . The AUC for each normalized curve was determined by trapezoidal integration over a range of  $-1.79$  to  $+0.85$  log units relative to  $K_D$ . For SRB3, SRB10, and SRB11, full sigmoidal dose-response curves were not obtained. Therefore, these derivatives were excluded from further analysis.

SRB	$K_D$ ( $\mu\text{M}$ )	$E_{\max}$ (RFU)	Average Baseline (RFU)	Hill Coefficient	Average Area Under the Curve (AUC)	Average $K_D$ ( $\mu\text{M}$ )	Average Experimental Maximum (RFU)	Average Fold Change
SRB1	5.71	1793	$0.82 \pm 0.22$	3.606	$1354 \pm 120$	$5.73 \pm 0.43$	$1876 \pm 184$	$2258 \pm 224$
SRB2	11.38	2238		3.10	$1646 \pm 225$	$11.56 \pm 1.74$	$2335 \pm 26$	$2833 \pm 31$
SRB3	>1000	--		--	--	>1000	$1241 \pm 119$	--
SRB4	68.76	2881		3.262	$1616 \pm 337$	$69.37 \pm 4.72$	$3041 \pm 641$	$3128 \pm 778$
SRB5	7.57	3516		4.63	$2196 \pm 184$	$7.52 \pm 0.56$	$3718 \pm 691$	$4818 \pm 721$
SRB6	6.41	4176		3.84	$2837 \pm 119$	$6.44 \pm 0.39$	$4448 \pm 594$	$5269 \pm 180$

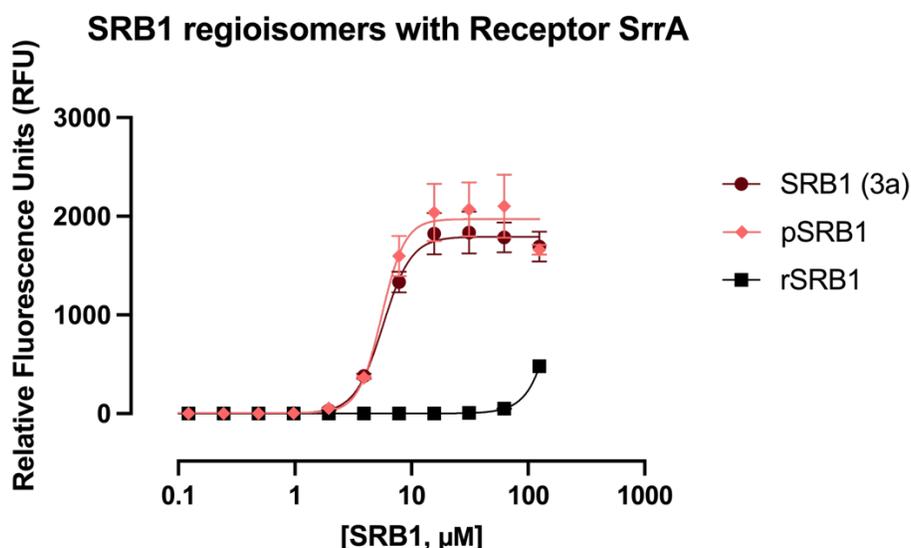
SRB7	10.21	2194		4.60	1739 ± 330	10.02 ± 1.43	2286 ± 148	2726 ± 376
SRB8	141	2608		2.71	719 ± 64	155.47 ± 26.56	2886 ± 310	3244 ± 296
SRB9	38.67	3238		2.13	3513 ± 415	38.92 ± 7.71	3305 ± 244	4347 ± 331
SRB10	>1000	--		--	--	>1000	972 ± 165	--
SRB11	>1000	--		--	--	>1000	130 ± 85	--

“Average  $K_D$  ( $\mu\text{M}$ )” represents the mean experimentally determined  $K_D$  across biological replicates.

“Average Baseline (RFU)” corresponds to the mean fluorescence of the DMSO control.

“Average Experimental Maximum (RFU)” is defined as the highest RFU value observed for each replicate.

“Average Fold Change” corresponds to the fold change for each biological replicate, calculated as the maximum response divided by the mean fluorescence of the DMSO control (0.82 RFU), and then averaged across replicates.



**Figure S7. SRB1 regioisomer specific GFP activation.** Biological activation was performed using both isolated regioisomers of SRB1 to evaluate individual activity. Full dose-response curves were performed in biological triplicated for each condition. Activation is driven by the favored SRB1 regioisomer (“pSRB1”) when compared to its regioisomer counterpart (“rSRB1”) that did not achieve a full dose-response curve within the tested concentration. SRB1 (3a) from Figure S6, exhibits a similar activation pattern as pSRB1. The dissociation constant ( $K_D$ ) of pSRB1 ( $5.55 \pm 0.05 \mu\text{M}$ ) is consistent with the one of SRB1 in Table S1. These results indicate that activation of the system is primarily driven by the desired SRB1 regioisomer, while its counterpart contributes minimally, if at all, to system activation.

**Table S2. Strains and plasmids used in this study**

	Strain or Plasmid	Relevant Characteristics	Source or Reference
Strains	NEB@5-alpha	fhuA2 $\Delta$ (argF-lacZ)U169 phoA glnV44 $\Phi$ 80 $\Delta$ (lacZ)M15	NEB

		<i>gyrA96 recA1 relA1 endA1 thi-1 hsdR17</i>	
	DH10B™	F– <i>mcrA</i> Δ( <i>mrr-hsdRMS-mcrBC</i> ) φ80/ <i>lacZ</i> ΔM15 Δ <i>lacX74 recA1 endA1 araD139</i> Δ ( <i>ara-leu</i> )7697 <i>galU galK</i> λ– <i>rpsL</i> (Str <sup>R</sup> ) <i>nupG</i>	Thermo Scientific™
Plasmids	pLW003		Wilbanks et al. 2023 <sup>6</sup>
	pET-28b(-)		Novagen
	pRF-ScbR		Addgene #49370 Stanton et al. 2013 <sup>7</sup>
	pTOTAL-SrrA		Wilbanks et al 2025 <sup>8</sup>

**Table S3. Relevant sequences to this study**

Coding Sequence	Promoter Region	GFP Promoter Region with SrrA Operator
Homologous Overhang	AatII/EcoR1	Sall/NdeI
caaagaggagaaagaattcATGGCACAAC AGGAACGTGCGATTTCGTACCCGCC GCGCGTTCTAGAAGCGGCAGCAA CGGTATTTGCCGAGCACGGTTATG CTGCCGCTACCGTGGCGGATATTTT AAAGGTGGCCGGACTGACTAAAGG CGCCCTGTACTTCCACTTTCCCAGT AAAGAAGCGCTTGCACGTGGCATT CTGGAGGCACAGGTGCCGCAACAG CTCGTTCCGCAGCAGCTGAAACTC CAGGAATGGGTAGATGCGGGTATG ACTCTGGCTCATCAGCTGCCGCGC GACCCTGTTCTGCGCGCGGGCGCC CGTTTGTGCGCTGAACATAACCGTA GCGAACAACATGGCAGCGCCTTCC CAACCTGGATCGCCTTTTCTGCCTC ATTGCTTGAACAGGCGAAACGGAAT GGTGAGGTCCTGGGGCACATAGAA CCGGCCGAAACCGCCGAATGCGTC CTCGGCTCCTTCCACGGCATTCAAC TTTTATCCCAATTGCAGACGAACTG GGCGGATATCGAGCAGCGTGCCAG CGCGCTGTTTAGGCATGTATTACCG GCAGTGGCGGTGCCAAGTGTGCTG GTGCGCTTAGACACAGCGCCTGAT CGAGGAGCCCGCGTCGTTGCAGAA CTGGAGGCGATGGCGGCGCAGCC	tcggatgacgtctaagaaacc attattatcatgacattaacctat aaaaataggcgtatcacgagg cagaattcagataaaaaaaaaat ccttagcttcgctaaggatgatt tctggctgcagttgacagctagc tcagtcctaggattgtgctagc ggatccaaagaggagaaaga attcatggca	agaggtgtcgactgacggctag ctgagtcctaggtacagtgctagc aggaatacaaaacagcttggtc ggtttgatattaagcttaggtgtct caaggtgcgtacctgactgatg agtccgaaaggacgaaacacc cctctacaaataatgtttaaag atctaaagaggagaaatagcat atgcgtaaa

GGATGGGCTGGCATCGCTGTCAAG CTAAaataagcggccac		
---	--	--

**Table S4. Primer sequences used in this study**

Primer Use	Primer Number	Sequence (5' → 3')
Amplify pLW0003 to replace chloramphenicol with kanamycin resistance	1	tttgatatcgagctcgcttgg
	2	gagtgccacctgacgtc
Amplification of kanamycin cassette from pET28b(-)	3	gaaccgtaaaaaggccggttgctggcggttttccataggctccgcc
	4	agatcaaaggatcttcttgagatcctttttt
Amplify pLW0003 for origin replacement with p15A	5	gaagatccttgatctttctacggg
	6	aaacgccagcaacgc
Amplify p15A origin	7	gaaccgtaaaaaggccggttgctggcggttttccataggctccgcc
	8	tgaccccgtagaaaagatcaaaggatcttcttgagatcgtttggtctgcg
Backbone forward for SrrA insertion	9	gaattctttctctcttttctagttaaac
Backbone reverse for SrrA insertion	10	gaattctttctctctttggatccg

### Strains, Media and Cloning conditions

For plasmid propagation, *E. coli* DH5 $\alpha$  (NEB, C2987H) was grown in Luria Broth (LB) medium supplemented with kanamycin (50  $\mu$ g/mL). *E. coli* DH10B (Thermo Scientific, EC0113) was used for fluorescence measurements. PCR amplifications were carried out using Q5 High-Fidelity 2X Master Mix (New England Biolabs, M0492S), with annealing temperatures and extension times selected according to the manufacturer's recommendations. Each template was amplified in triplicate 20  $\mu$ L reactions composed of 10  $\mu$ L master mix, 2  $\mu$ L forward/reverse primer mix (500  $\mu$ M each), 1  $\mu$ L plasmid template (1 ng/ $\mu$ L), and 7  $\mu$ L nuclease-free water. One reaction was performed using the annealing temperature given by NEB's calculator, a second reaction contained 3% DMSO at the same temperature, and the third followed a stepdown/touchdown protocol in which the annealing temperature was set 2  $^{\circ}$ C above the recommended temperature and reduced by 0.3  $^{\circ}$ C per cycle. Cycling conditions were 98  $^{\circ}$ C for 30 s; 30 cycles of 98  $^{\circ}$ C for 20 s, 60-70  $^{\circ}$ C for 15 s (stepdown when applicable), and 72  $^{\circ}$ C for 20 s per kb; followed by a final extension of 72  $^{\circ}$ C for 2 min and storage at 4  $^{\circ}$ C. PCR products were separated on 0.8% agarose gels with a GeneRuler 1 kb Plus ladder (Thermo Scientific, SM1331). Desired fragments were excised, pooled, and purified using Freeze 'N Squeeze<sup>TM</sup> DNA Gel Extraction Spin Columns (Bio-Rad, 7326165). The DNA flowthrough was precipitated by adding 900  $\mu$ L ice-cold 100% ethanol, 30  $\mu$ L 3 M sodium acetate, and 1  $\mu$ L GlycoBlue (Invitrogen, AM9516) for visualization, then centrifuged at 15,000 rpm, washed twice with 70% ethanol, and resuspended in 15  $\mu$ L nuclease-free water. For the isothermal assembly reactions, NEBuilder HiFi DNA Assembly Master Mix (NEB, E2621S) was used at a 3:1 insert-to-backbone ratio. Restriction-based cloning followed NEB protocols, where 1  $\mu$ g plasmid or insert was combined with 10X CutSmart buffer and 1  $\mu$ L of each enzyme in a 50  $\mu$ L reaction, incubated at 37  $^{\circ}$ C for 1 h, run on agarose gels, and purified as described above. Ligation was performed according to manufacturer protocol (New England Biolabs) except a 5:1 insert-to-vector ratio was used for the reaction. Transformations were carried out with DH5 $\alpha$  competent cells using the manufacturer protocol, and selected clones were verified by restriction digests and confirmed by Sanger sequencing (Azenta). For fluorescence assays, plasmids were introduced

into DH10B competent cells according to the supplier's protocol. A full list of strains, plasmids, primers, and DNA sequences used in this work is provided in **Tables S2-S4**.

### SrrA GFP Assay Vector Cloning

Construction of the pTOTAL-SrrA plasmid has been previously reported.<sup>8</sup> In brief, plasmid pLW0003 served as the starting backbone.<sup>6</sup> Primers 1/2 amplified pLW0003 to replace the chloramphenicol resistance with kanamycin resistance, obtained from pET-28b(-) using primers 3/4. Standard PCR, gel purification, isothermal assembly, and transformation protocols were followed as previously stated. The origin of replication (ori) was subsequently exchanged for the p15A ori, amplified from pRF-ScbR with primers 7/8 and assembled into the backbone amplified with primers 5/6.<sup>7</sup>

From this modified plasmid the "pTOTAL-SrrA" vector was generated in three sequential steps. First, the *gfp* promoter was replaced with a synthetic fragment (IDT) containing the BBa\_J23100 -10/-35 promoter, SrrA operator, BydVJ ribozyme sequence, and RBS BBa\_J34801 via Sall/NdeI restriction enzyme cloning. Second, the repressor promoter was inserted by EcoRI/AatII digestion and ligation with a synthesized SrrA promoter fragment (IDT). Finally, the synthesized SrrA coding sequence (IDT), designed with homologous overlaps, was assembled into the amplified backbone using primers 9/10.

### GFP Induction Protocol and Flow cytometry Analysis

The following methodology and analysis have been previously described by Wilbanks et al. (2025) and are detailed in the *Synthetic Molecule Induction Assay Protocol* and *Flow Cytometry Analysis sections*.<sup>8</sup> Briefly, overnight LB cultures were diluted into supplemented M9 medium, induced in 96-well plates with molecule (SRBs) at OD<sub>600</sub> ~0.1-0.2, and analyzed after a 5 h incubation by flow cytometry. Events were gated on a range of X axis FSC-W 1 to 100 using floreada.io. Mean fluorescence was quantified, and the background of vector-empty controls was subtracted. Data is presented as biological triplicate collected on separate days.

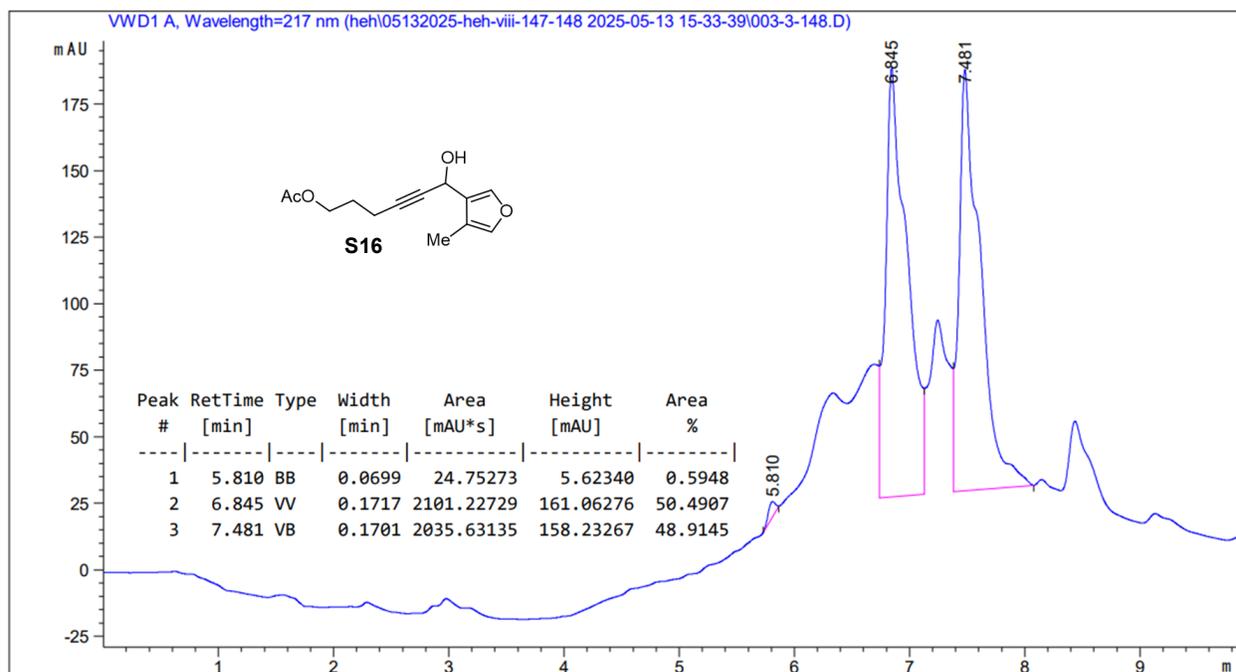
## References

- (1) Blay, G.; Fernández, I.; Marco-Aleixandre, A.; Pedro, J. R. Mandelamide–Zinc-Catalyzed Enantioselective Alkyne Addition to Heteroaromatic Aldehydes. *J. Org. Chem.* **2006**, *71* (17), 6674–6677. <https://doi.org/10.1021/jo0610255>.
- (2) Silva, A. L.; Toscano, R. A.; Maldonado, L. A. An Enantioselective Approach to Furanoeremophilanes: (+)-9-Oxoeryopsin. *J. Org. Chem.* **2013**, *78* (11), 5282–5292. <https://doi.org/10.1021/jo400399q>.
- (3) Blay, G.; Fernández, I.; Hernández-Olmos, V.; Marco-Aleixandre, A.; Pedro, J. R. Enantioselective Addition of Dimethylzinc to Aldehydes Catalyzed by *N*-Substituted Mandelamide-Ti(IV) Complexes. *Tetrahedron Asymmetry* **2005**, *16* (11), 1953–1958. <https://doi.org/10.1016/j.tetasy.2005.04.011>.
- (4) Arakawa, K.; Tsuda, N.; Taniguchi, A.; Kinashi, H. The Butenolide Signaling Molecules SRB1 and SRB2 Induce Lankacidin and Lankamycin Production in *Streptomyces Rochei*. *ChemBioChem* **2012**, *13* (10), 1447–1457. <https://doi.org/10.1002/cbic.201200149>.
- (5) Shetty, R. P.; Endy, D.; Knight, T. F. Engineering BioBrick Vectors from BioBrick Parts. *J. Biol. Eng.* **2008**, *2* (1), 5. <https://doi.org/10.1186/1754-1611-2-5>.
- (6) Wilbanks, L. E.; Hennigan, H. E.; Martinez-Brokaw, C. D.; Lakkis, H.; Thormann, S.; Eggly, A. S.; Buechel, G.; Parkinson, E. I. Synthesis of Gamma-Butyrolactone Hormones Enables Understanding of Natural Product Induction. *ACS Chem. Biol.* **2023**, *18* (7), 1624–1631. <https://doi.org/10.1021/acscchembio.3c00241>.

- (7) Stanton, B. C.; Nielsen, A. A. K.; Tamsir, A.; Clancy, K.; Peterson, T.; Voigt, C. A. Genomic Mining of Prokaryotic Repressors for Orthogonal Logic Gates. *Nat. Chem. Biol.* **2014**, *10* (2), 99–105. <https://doi.org/10.1038/nchembio.1411>.
- (8) Wilbanks, L. E.; Roberts, C. B.; Frias-Gomez, M.; Hennigan, H. E.; Castator, K. G.; Budimir, Z. L.; Zu, C.; Parkinson, E. I. Streptomyces Autoregulator Biosensors from Natural Product Cluster-Situated Regulators. *bioRxiv* September 5, 2025, p 2025.09.05.673737. <https://doi.org/10.1101/2025.09.05.673737>.

## Spectral Data

### Chiral HPLC Traces



**Figure S8** Chiral HPLC conditions were optimized with **S16** using a Diacel Chiralpak AD-H column using a gradient of 5% to 95% isopropanol in hexanes over 10 min at 30 °C with detection at 217 nm. Compound **S16** was synthesized according to GP1 with a mix of **L3** and **L3-ent**. The spectral data corresponds to that of **11**.

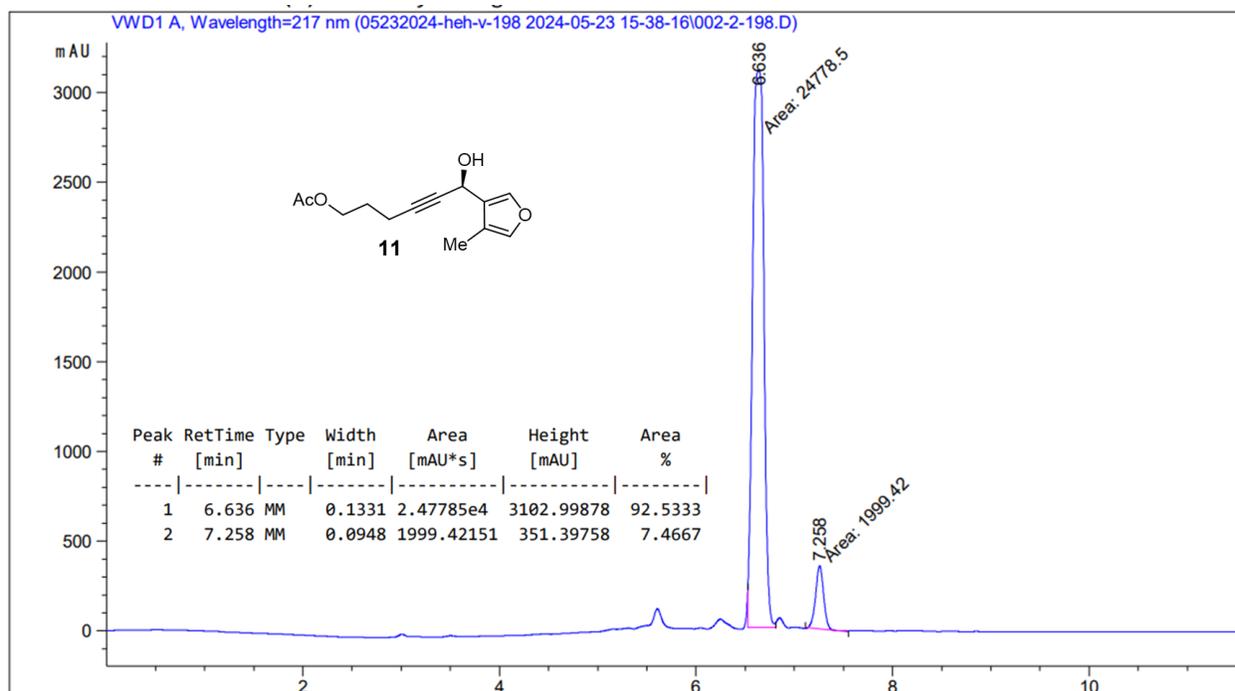


Figure S9 Enantiomeric excess of **11** was determined by Chiral HPLC using a Diacel Chiralpak AD-H column using a gradient of 5% to 95% isopropanol in hexanes over 10 min at 30 °C with detection at 217 nm,  $t_R$  (major) = 6.64 min and  $t_R$  (minor) = 7.26 min.

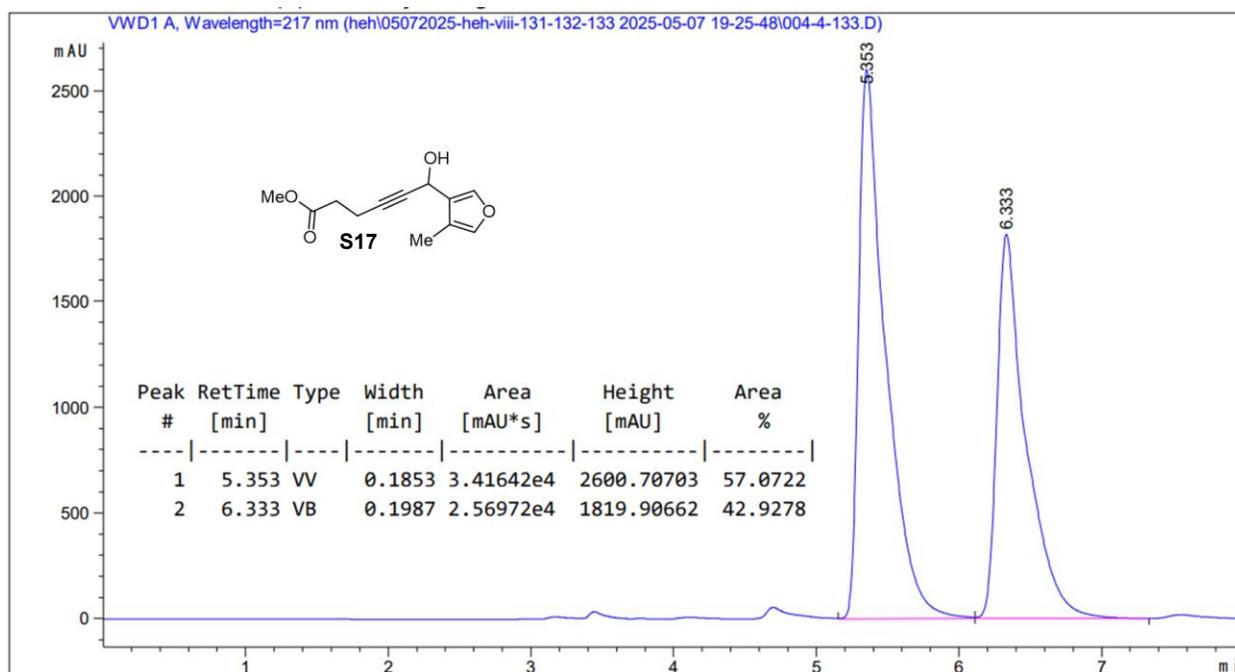


Figure S10 Chiral HPLC conditions were optimized with **17** using a Diacel Chiralpak AD-H column in 25% isopropanol in hexanes over 8 min at 30 °C with detection at 217 nm. Compound **20** was synthesized according to GP 1 with a mix of ligands **L3** and **L3-ent**. The spectral data corresponds with **13**.

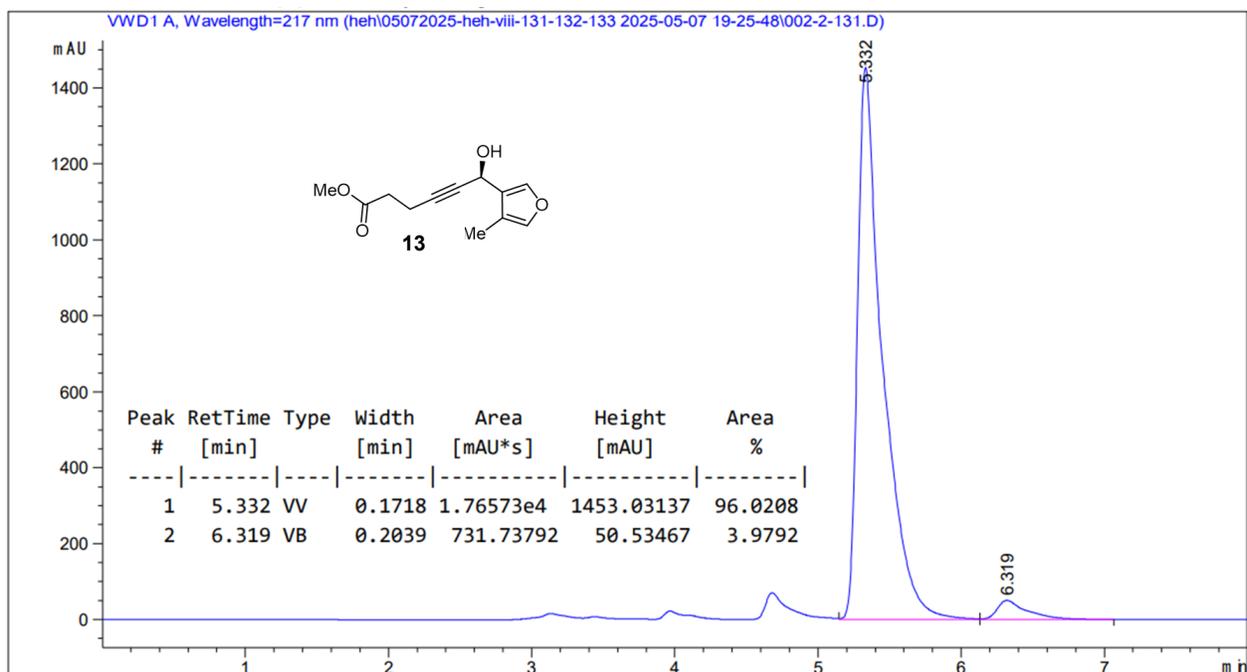


Figure S11 Enantiomeric excess of **13** was determined by chiral HPLC using a Diacel Chiralpak AD-H column column in 25% isopropanol in hexanes over 8 min at 30 °C with detection at 217 nm,  $t_R$  (major) = 5.33 min and  $t_R$  (minor) = 6.32 min

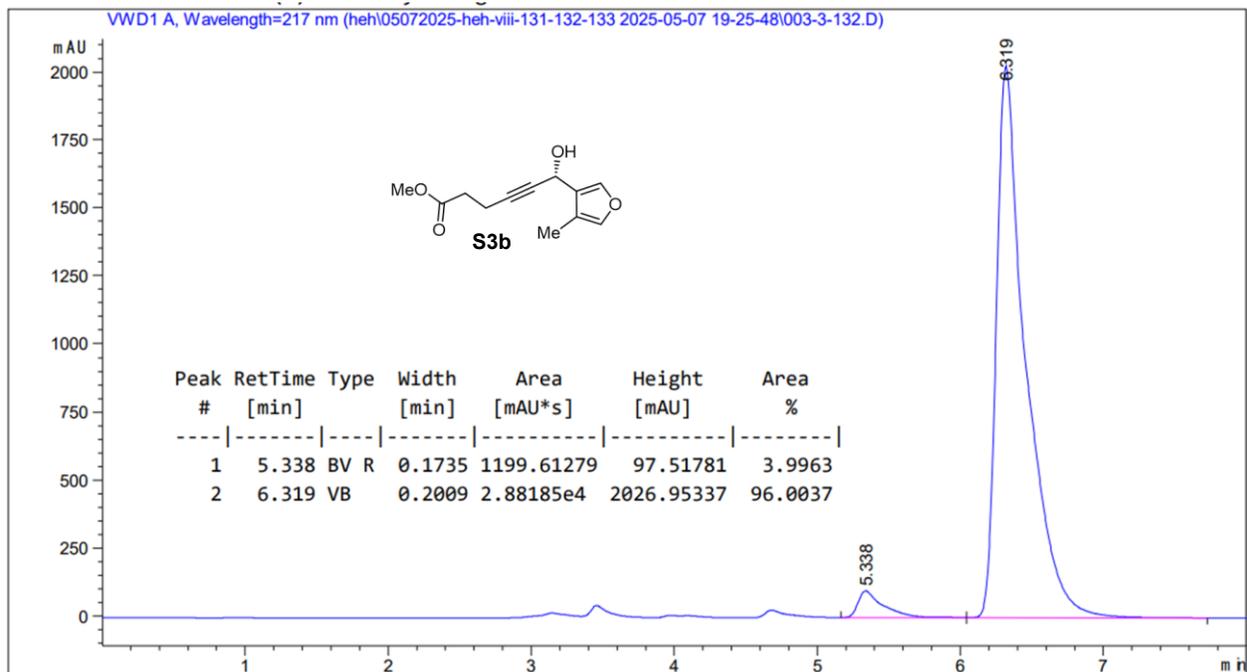
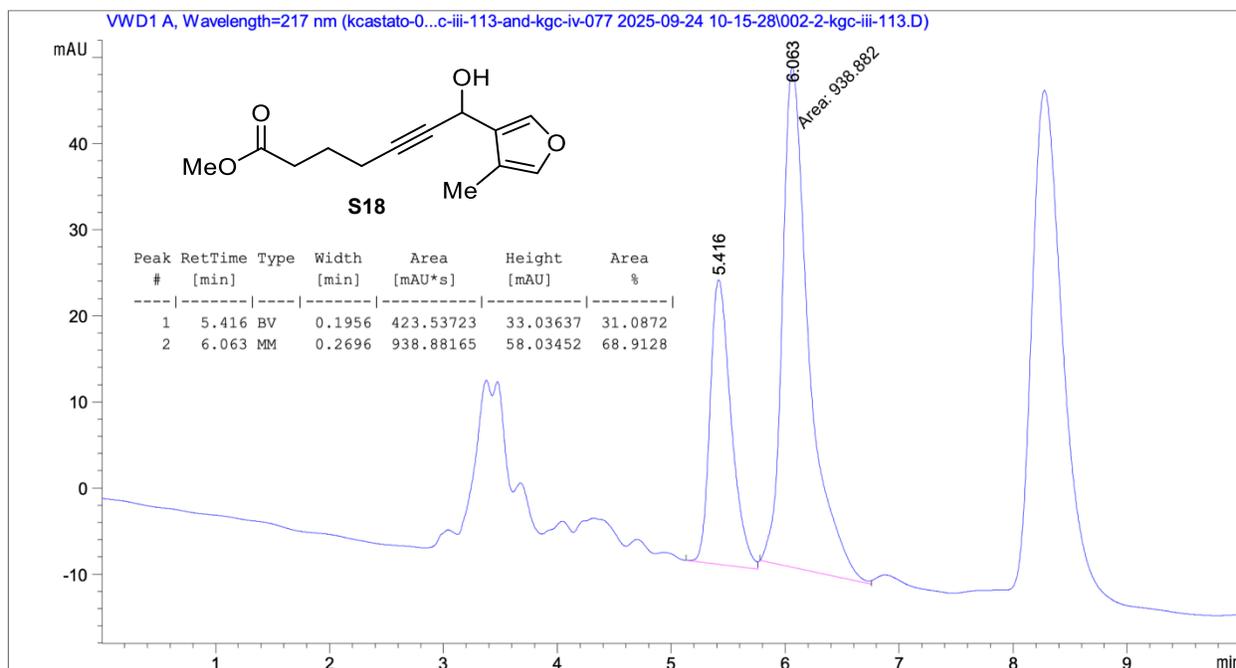
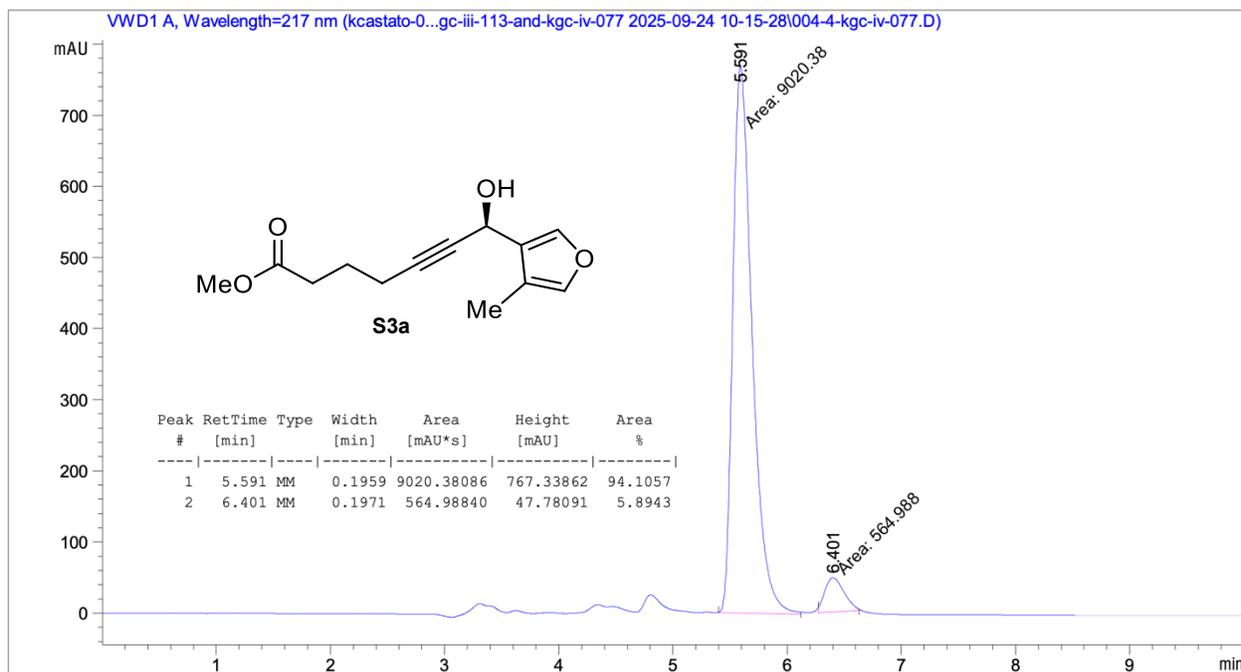


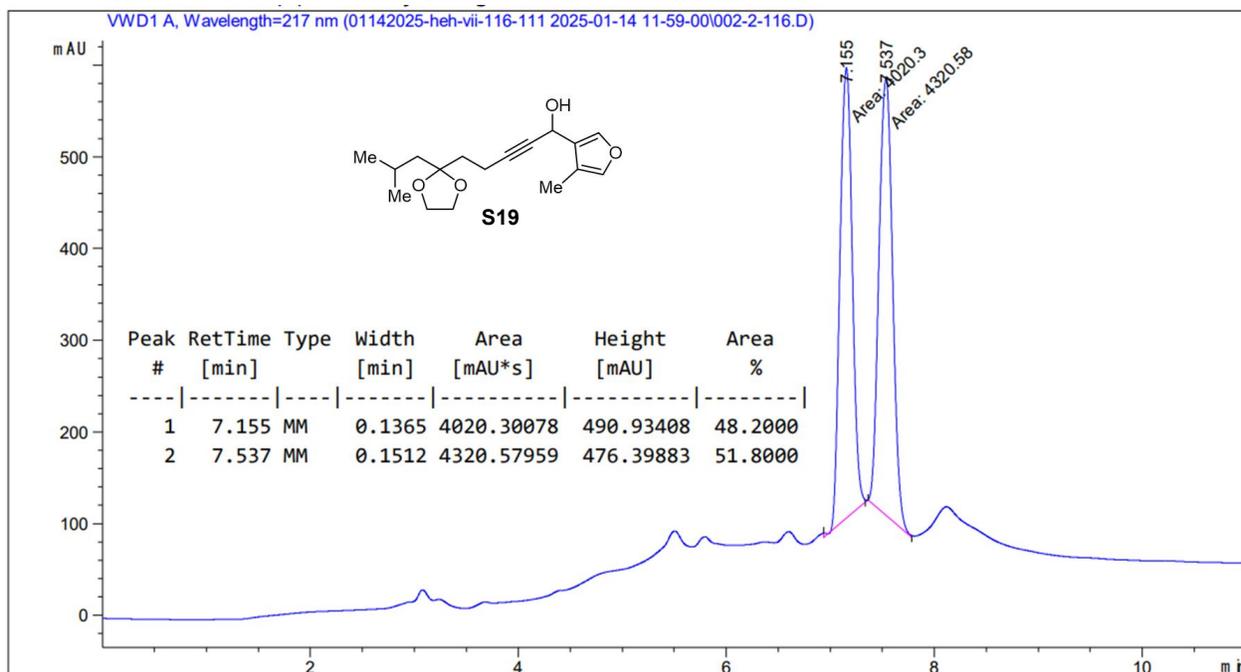
Figure S12 Enantiomeric excess of **S3b** was determined by chiral HPLC using a Diacel Chiralpak AD-H column column in 25% isopropanol in hexanes over 8 min at 30 °C with detection at 217 nm,  $t_R$  (major) = 6.32 min and  $t_R$  (minor) = 5.34 min



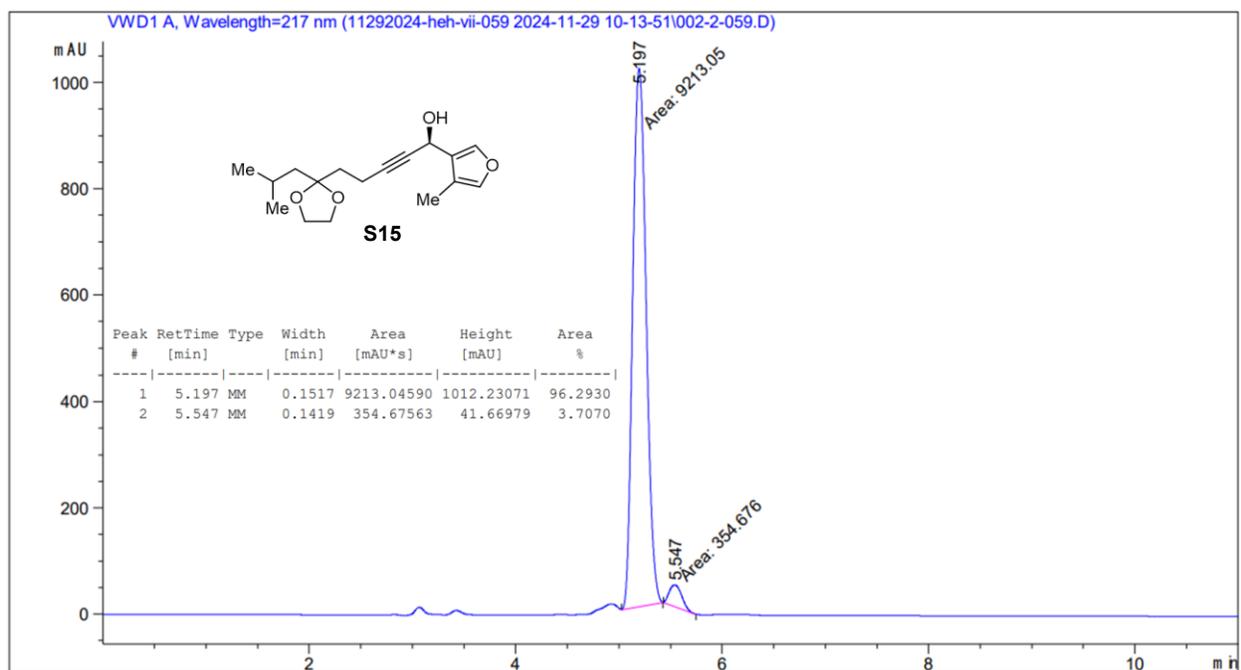
**Figure S13** Chiral HPLC conditions were optimized with **S18** using a Diacel Chiralpak AD-H column in 25% isopropanol in hexanes over 10 min at 30 °C with detection at 217 nm. Compound **S18** was synthesized according to GP 1 with a mix of ligands **L3** and **L3-ent**. The spectral data corresponds with **S3a**.



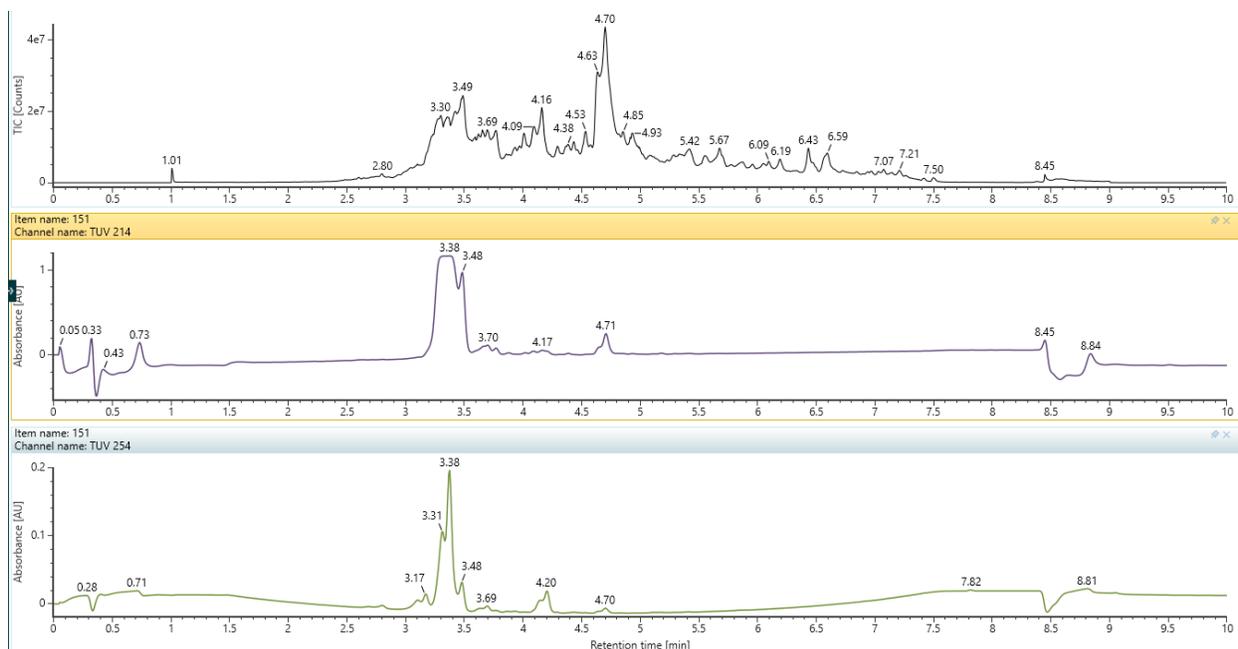
**Figure S14** Enantiomeric excess of **S4a** was determined by chiral HPLC using a Diacel Chiralpak AD-H column column in 25% isopropanol in hexanes over 10 min at 30 °C with detection at 217 nm,  $t_R$  (major) = 5.59 min and  $t_R$  (minor) = 6.40 min.



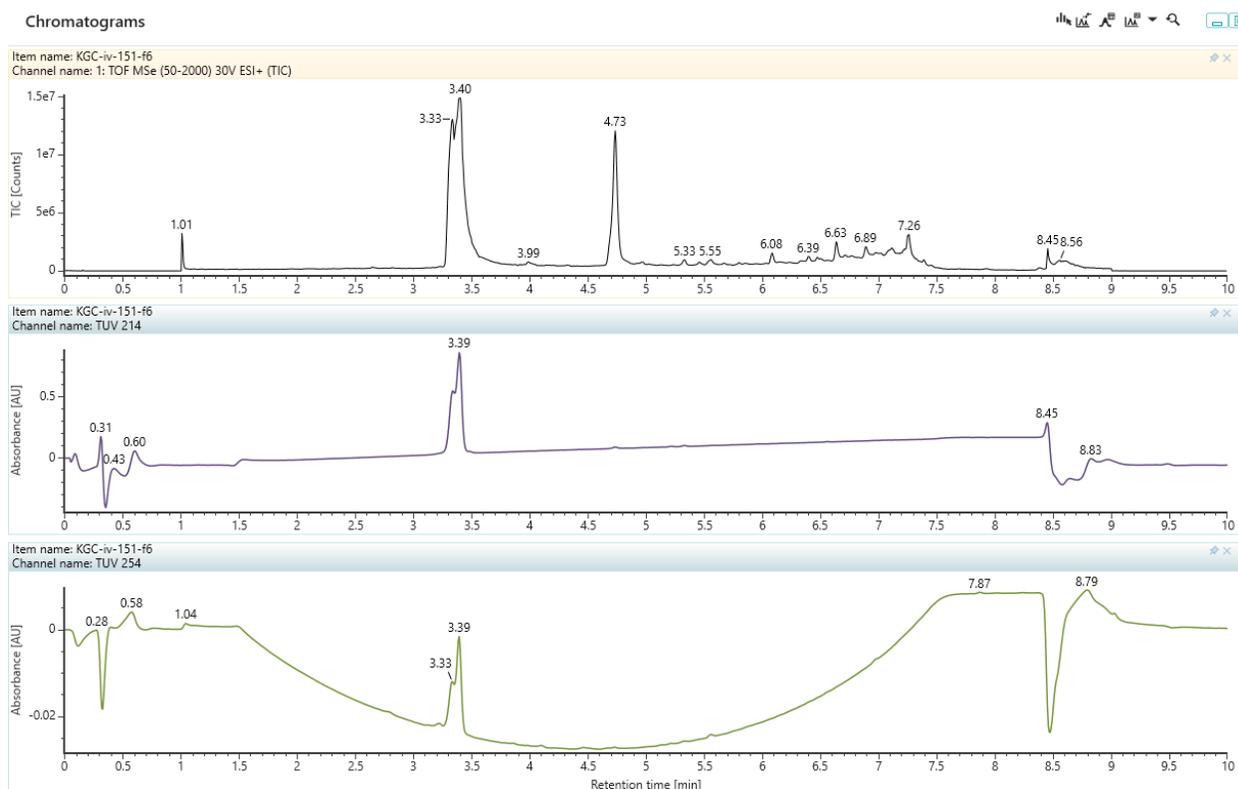
**Figure S15** Chiral HPLC conditions were optimized with **S19** using a Diacel Chiralpak AD-H column in 15% isopropanol in hexanes over 10 min at 30 °C with detection at 217 nm. Compound **S19** was synthesized according to GP E.2 with a mix of ligands **L3** and **L3-ent**. The spectral data matches that of **S15**.



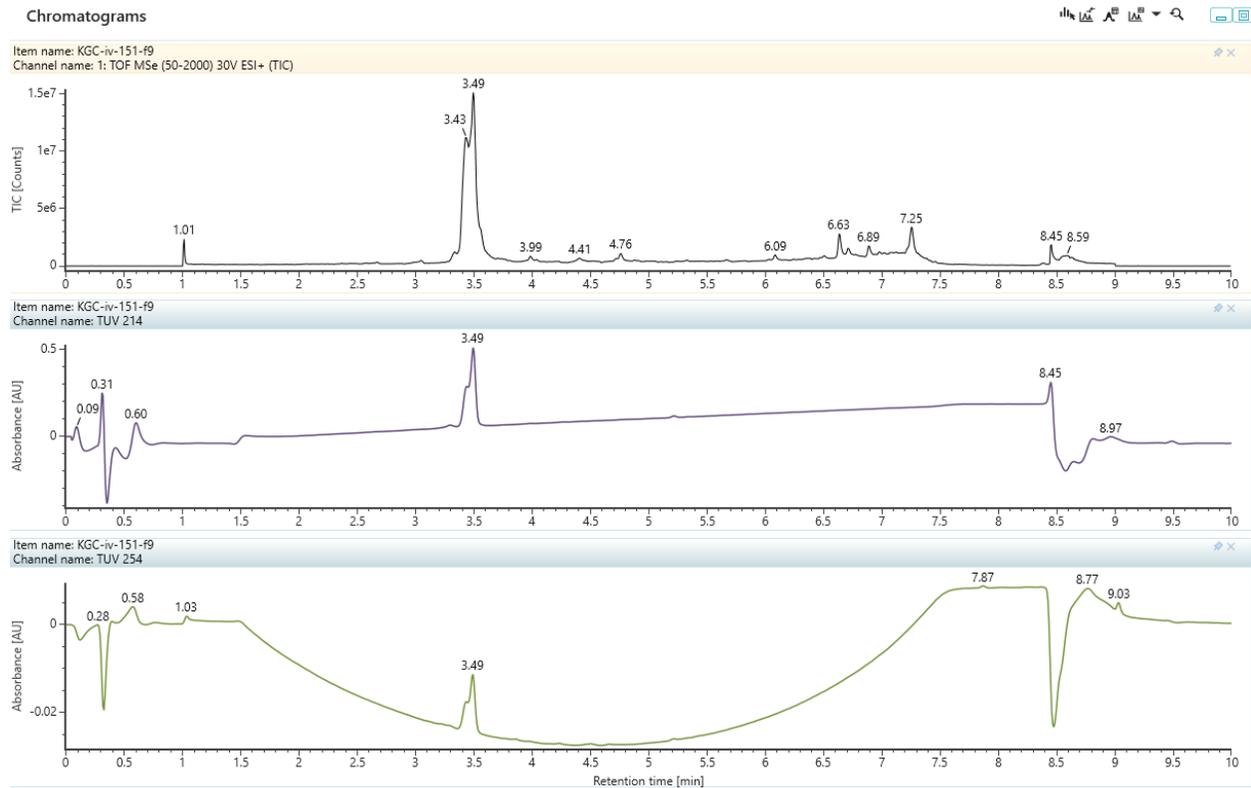
**Figure S16** Enantiomeric excess of **S15** was determined by Chiral HPLC using a Diacel Chiralpak AD-H column in 15% isopropanol in hexanes over 10 min at 30 °C with detection at 217 nm,  $t_R$  (major) = 5.20 min and  $t_R$  (minor) = 5.55 min



**Figure S17** UPLC-MS trace of photooxidation product, mix between SRB 1 and its regioisomer. Elution of SRB 1 (3a) at 3.38 min and elution of its regioisomer S20a at 3.48.



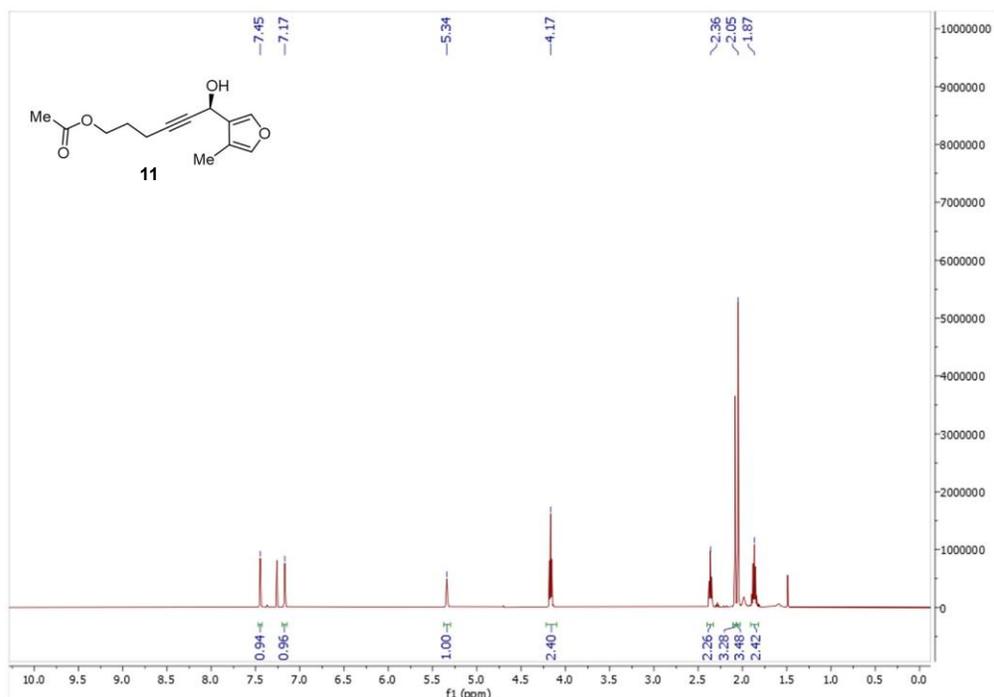
**Figure S18** UPLC-MS trace of SRB 1 (3a) after HPLC purification. Elution of the two epimers at C4 at 3.33 and 3.40 min.



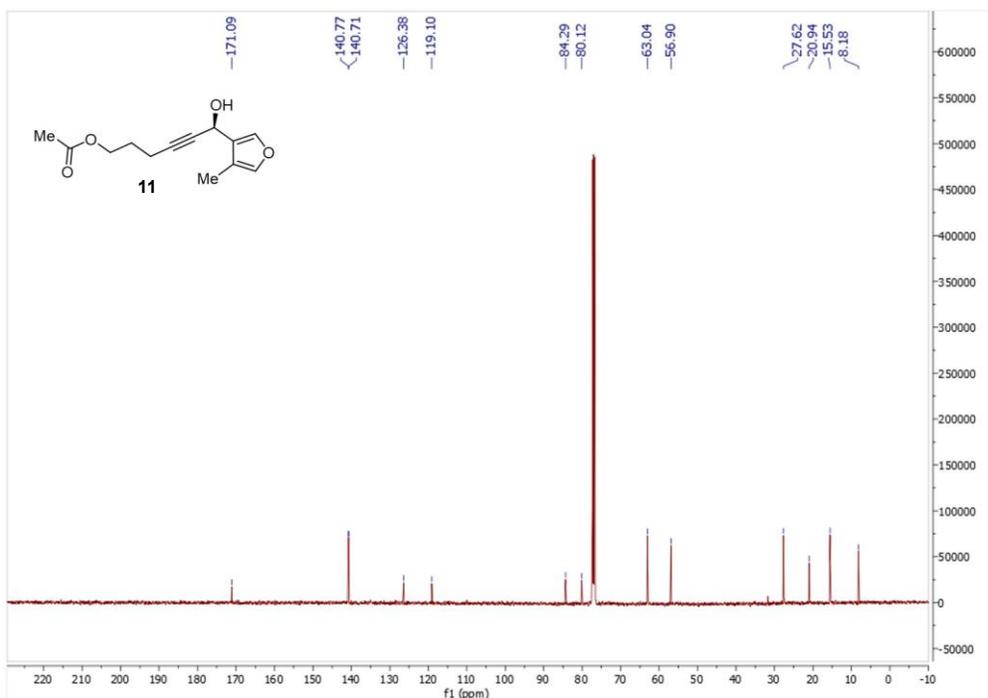
**Figure S19** UPLC-MS trace of the regioisomer of SRB 1 (S20a) after HPLC purification. Elution of the two epimers at C4 at 3.43 and 3.49 min.

## <sup>1</sup>H and <sup>13</sup>C Spectra

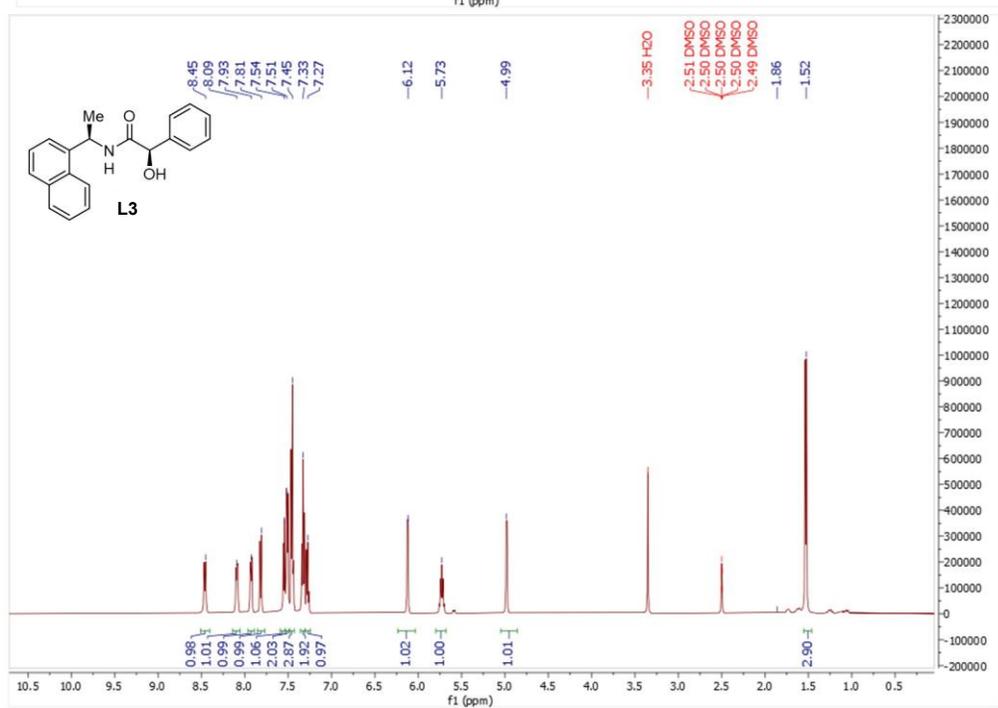
<sup>1</sup>H (500 MHz) of **11**



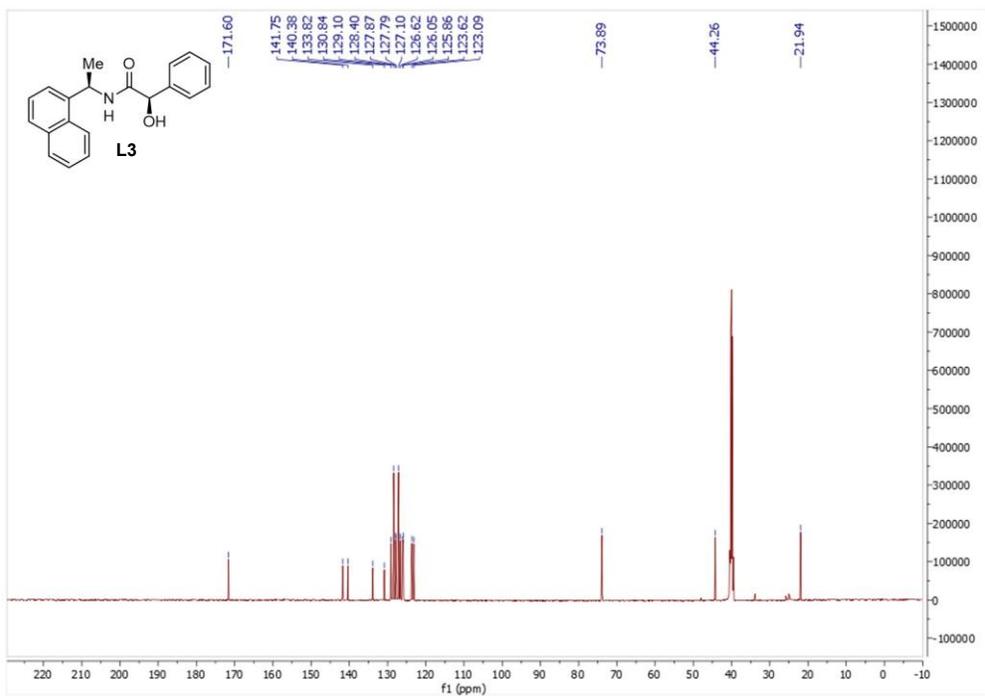
$^{13}\text{C}$  (126 MHz) of **11**



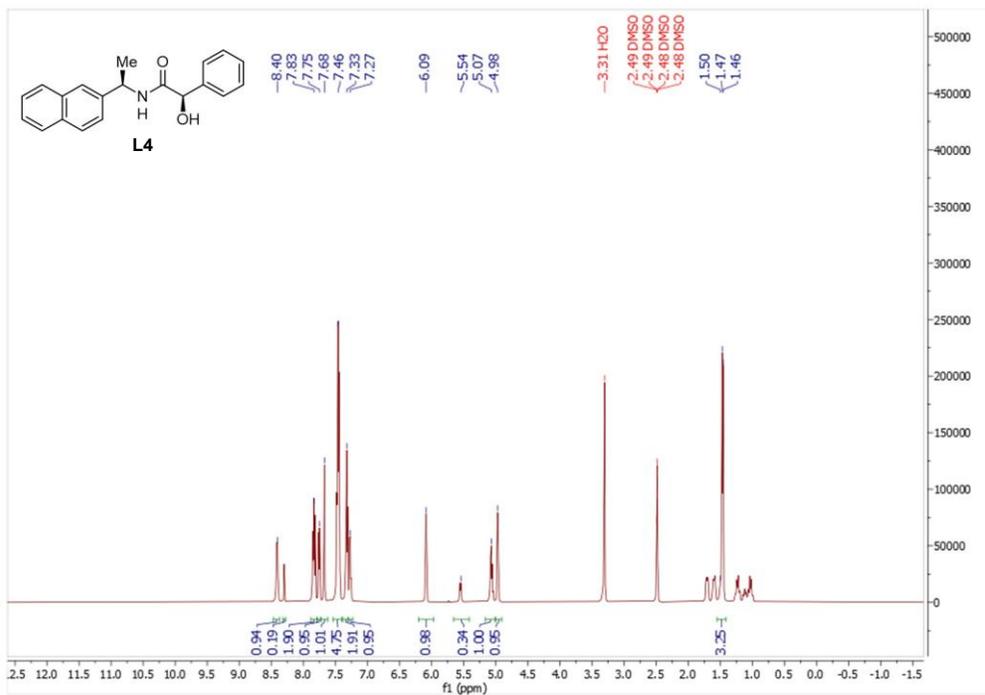
$^1\text{H}$  (500 MHz) of **L3**



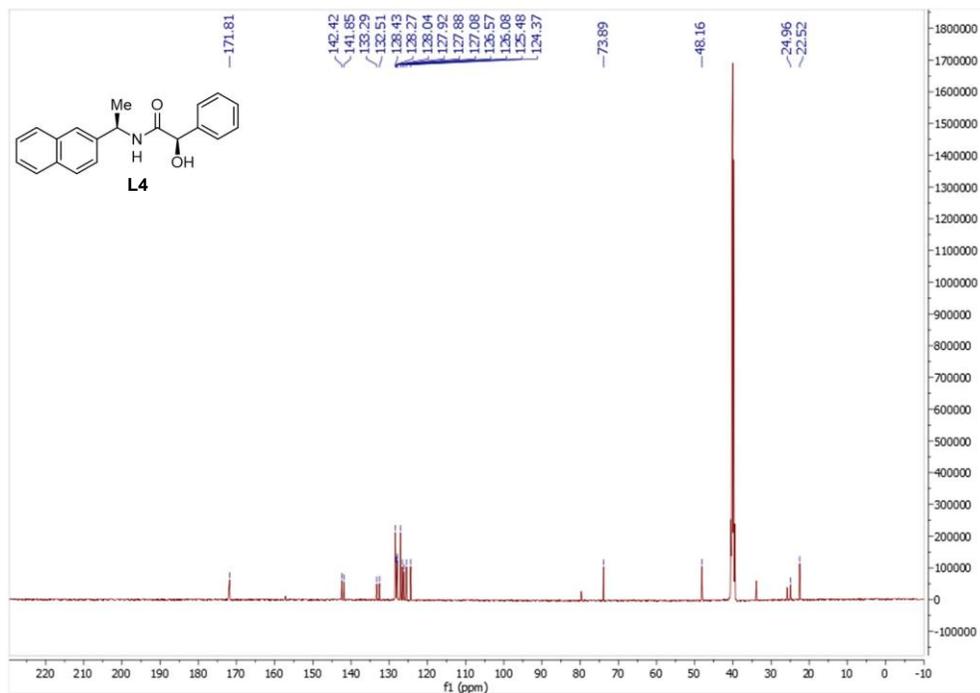
$^{13}\text{C}$  (126 MHz) of L3



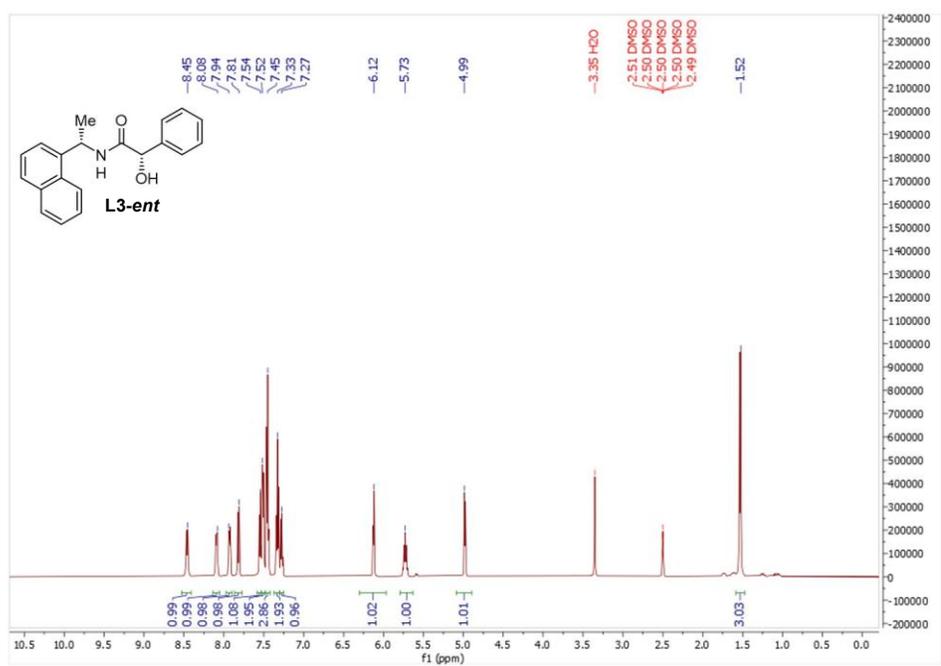
$^1\text{H}$  (500 MHz) of L4



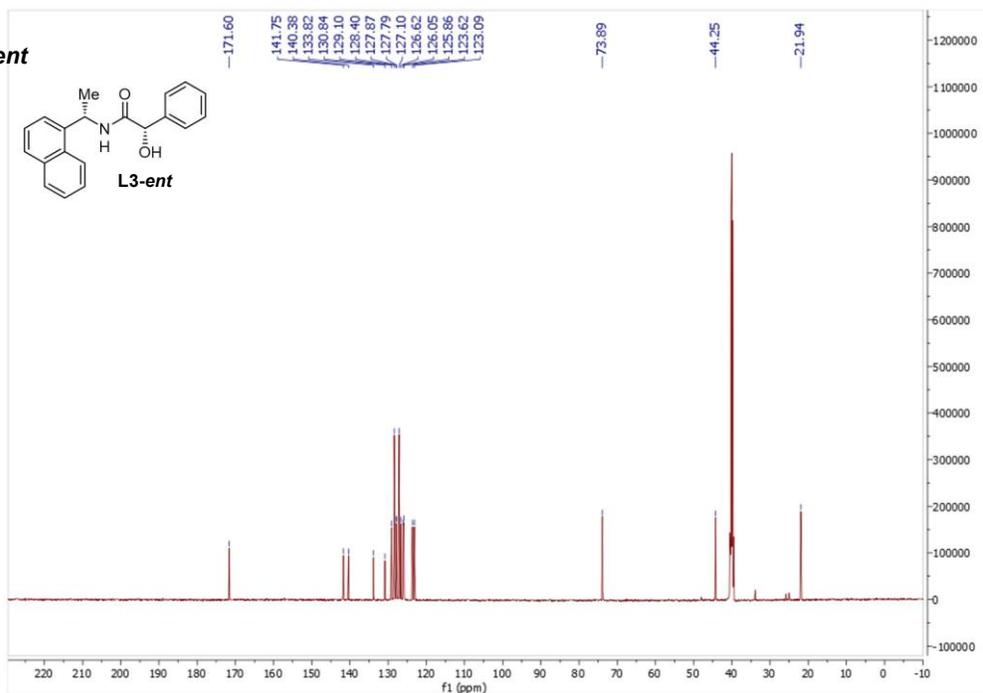
$^{13}\text{C}$  (126 MHz) of **L4**



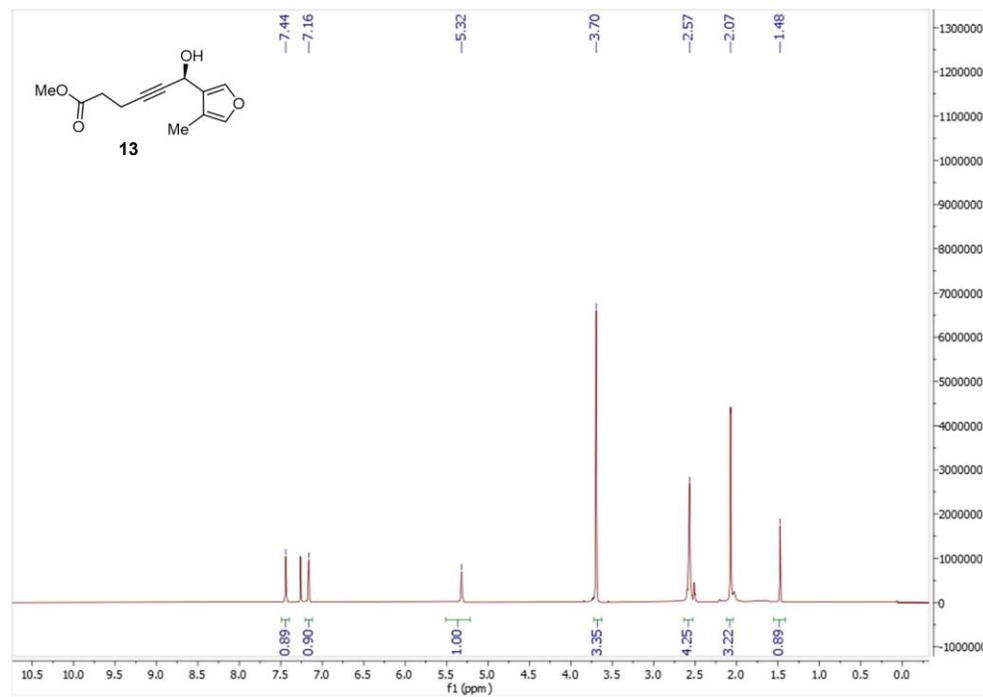
$^1\text{H}$  (500 MHz) of **L3-ent**



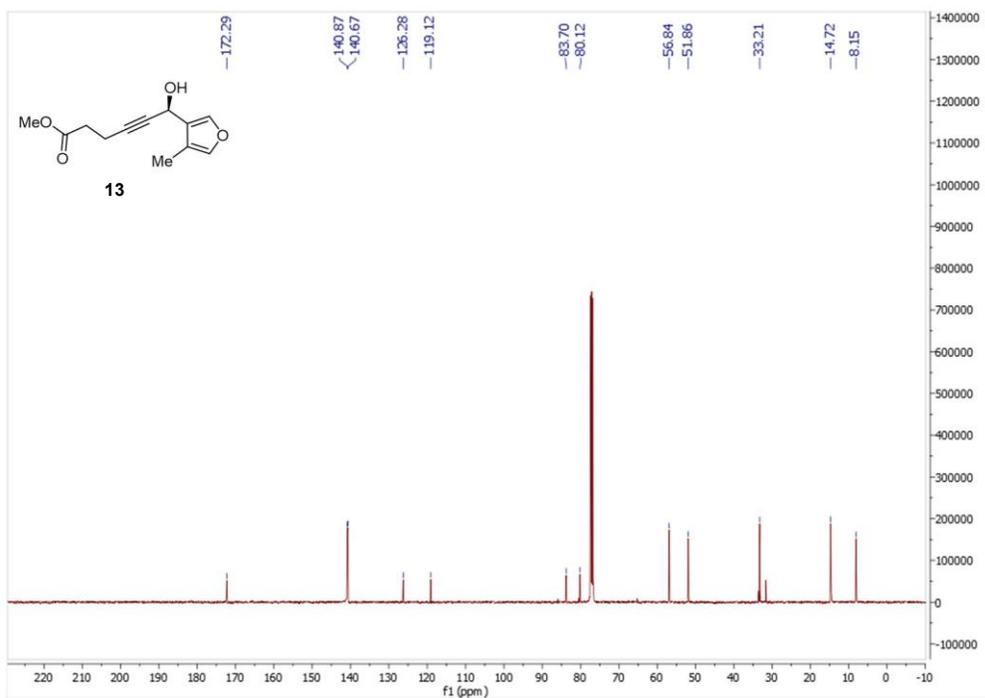
$^{13}\text{C}$  (126 MHz) of **L3-ent**



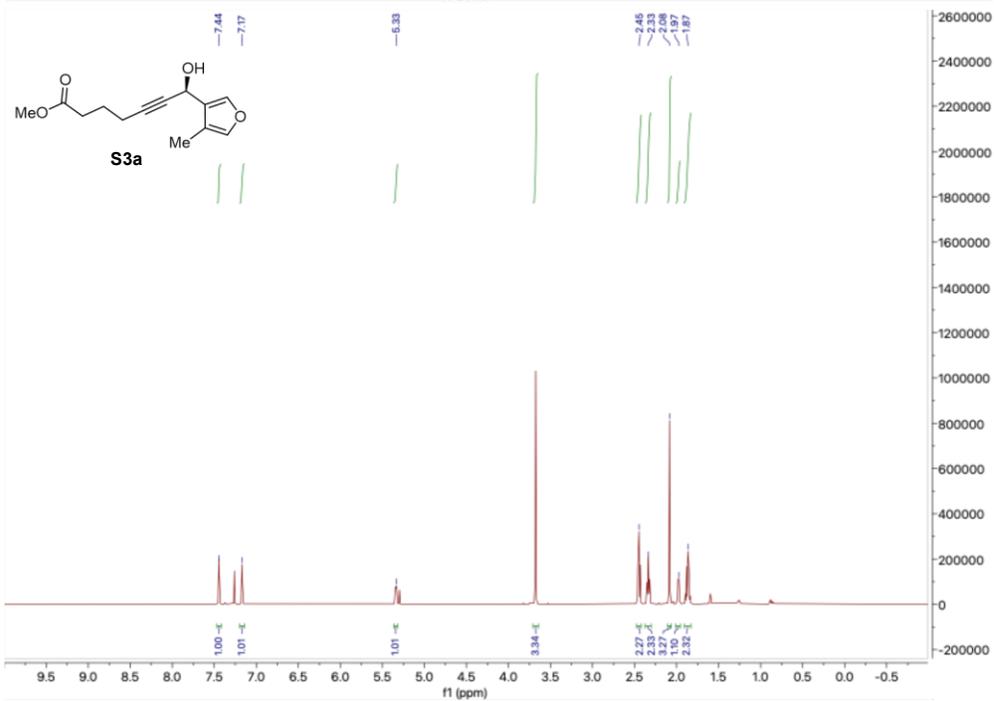
$^1\text{H}$  (500 MHz) of **13**



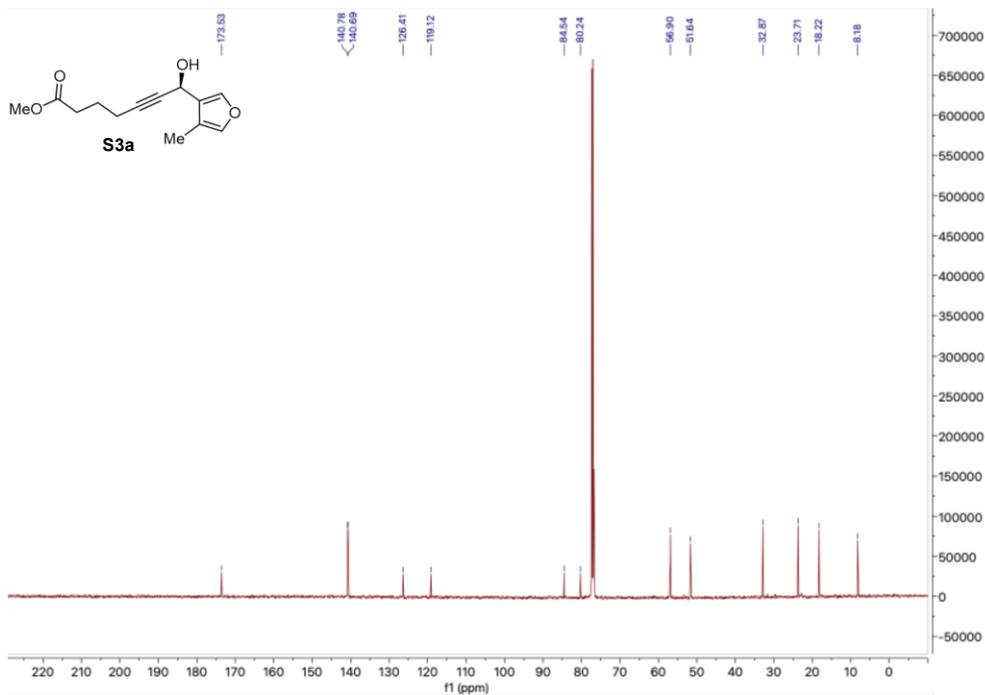
<sup>13</sup>C (126 MHz) of **13**



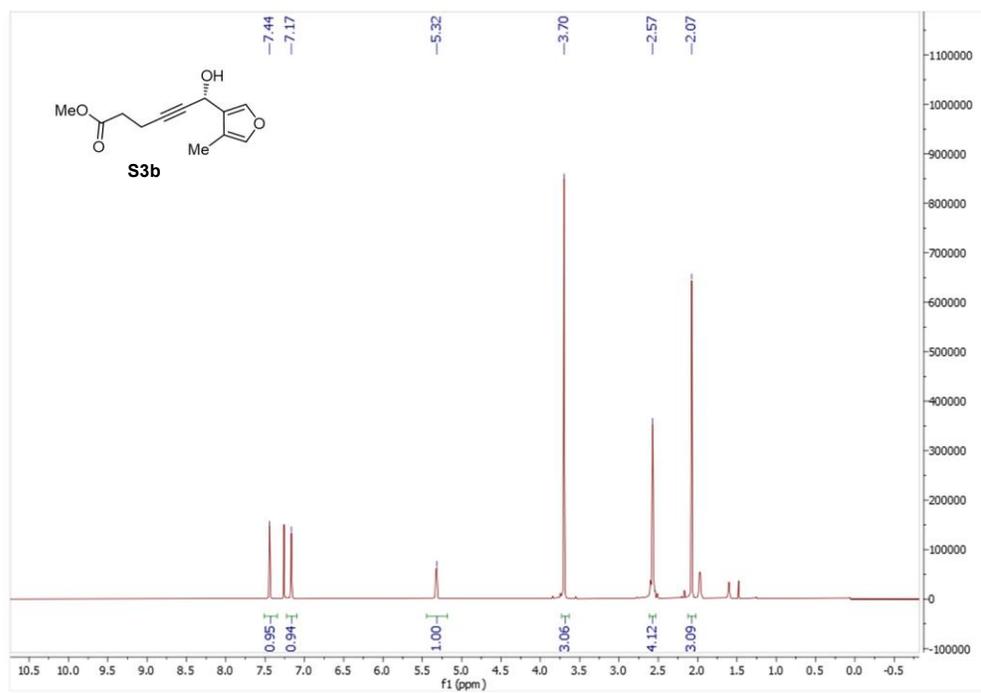
<sup>1</sup>H (500 MHz) of **S3a**



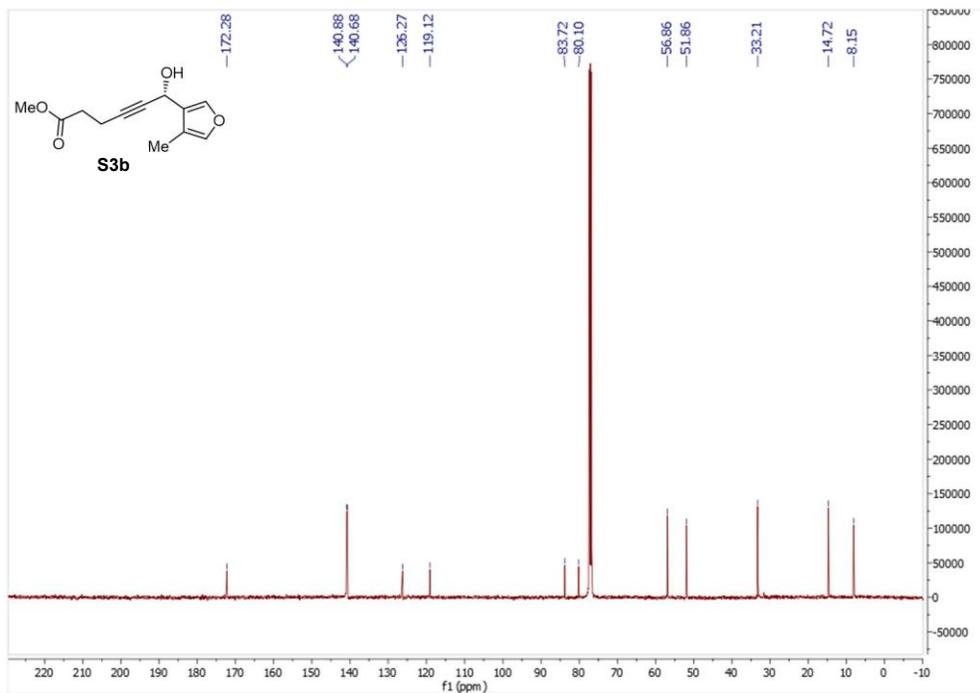
$^{13}\text{C}$  (126 MHz) of **S3a**



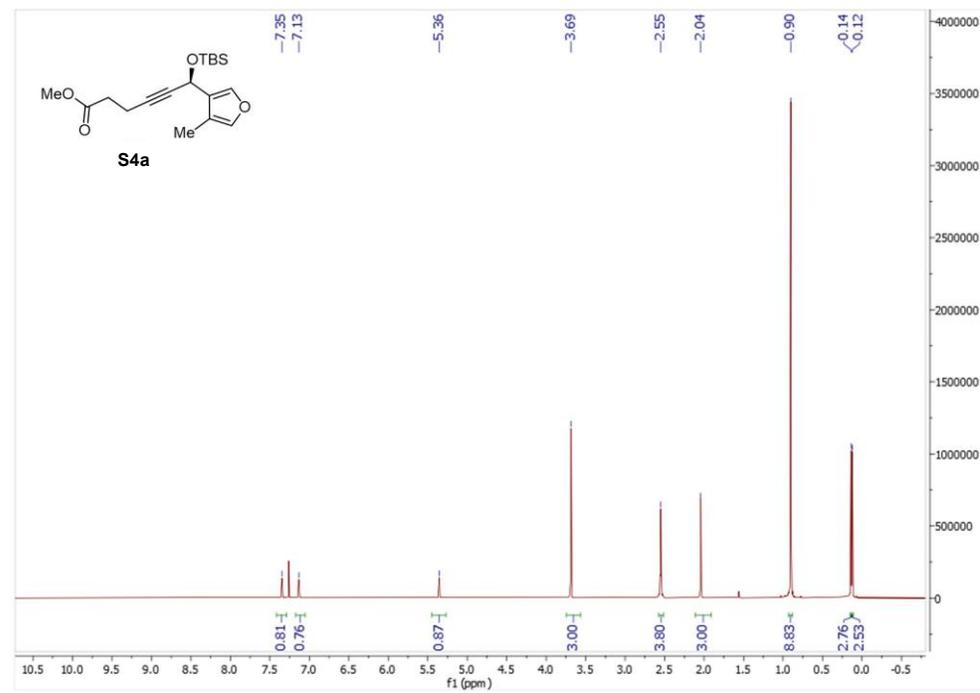
$^1\text{H}$  (500 MHz) of **S3b**



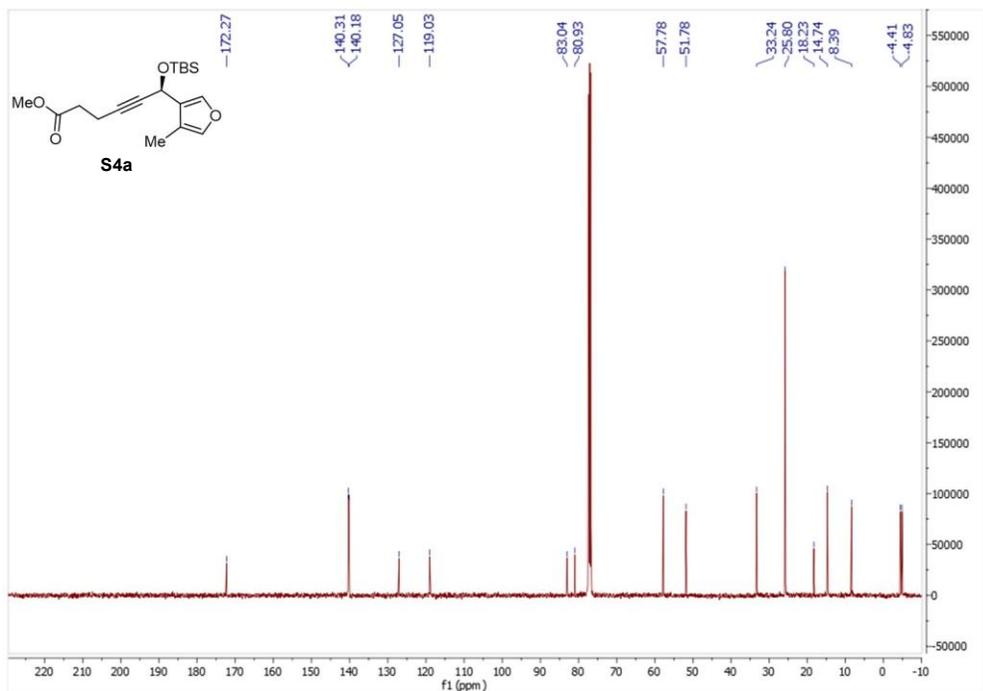
$^{13}\text{C}$  (126 MHz) of **S3b**



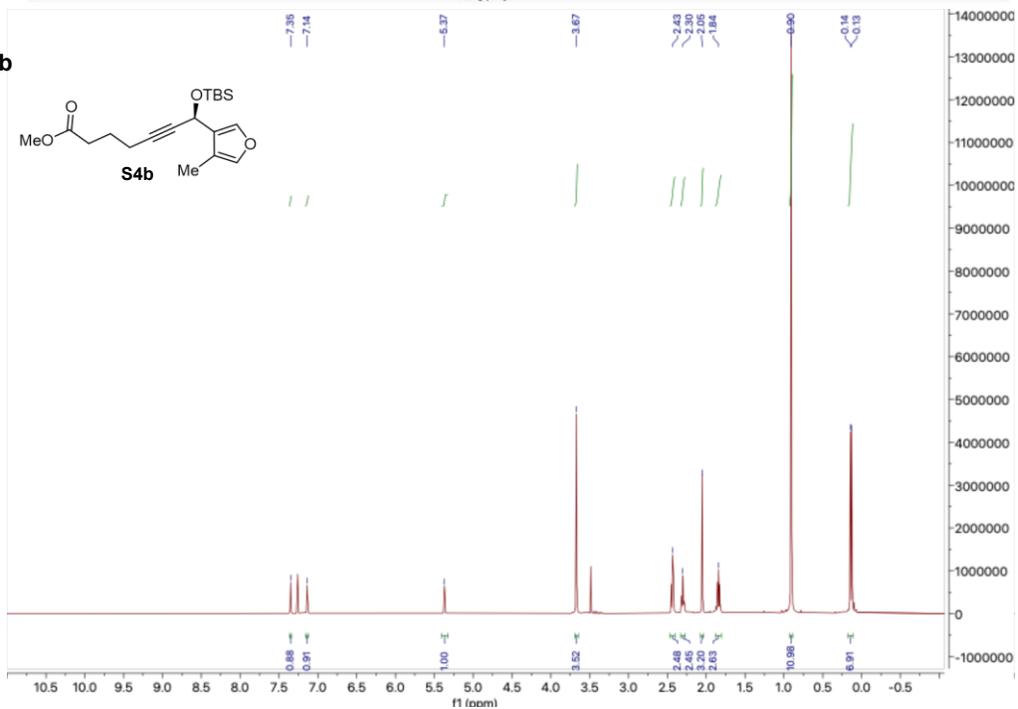
$^1\text{H}$  (500 MHz) of **S4a**



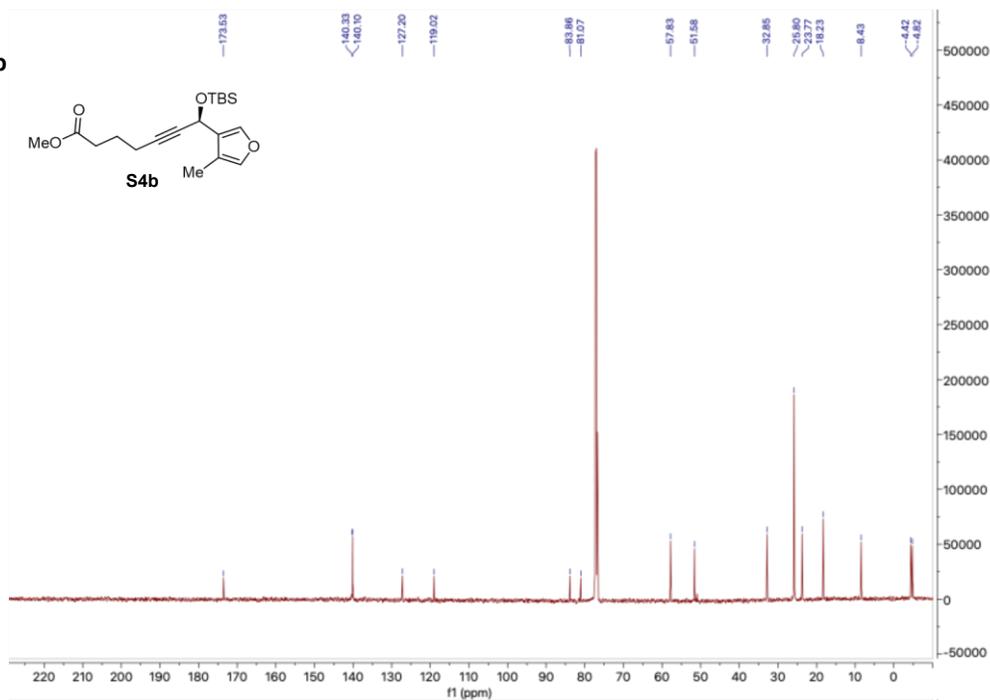
<sup>13</sup>C (126 MHz) of **S4a**



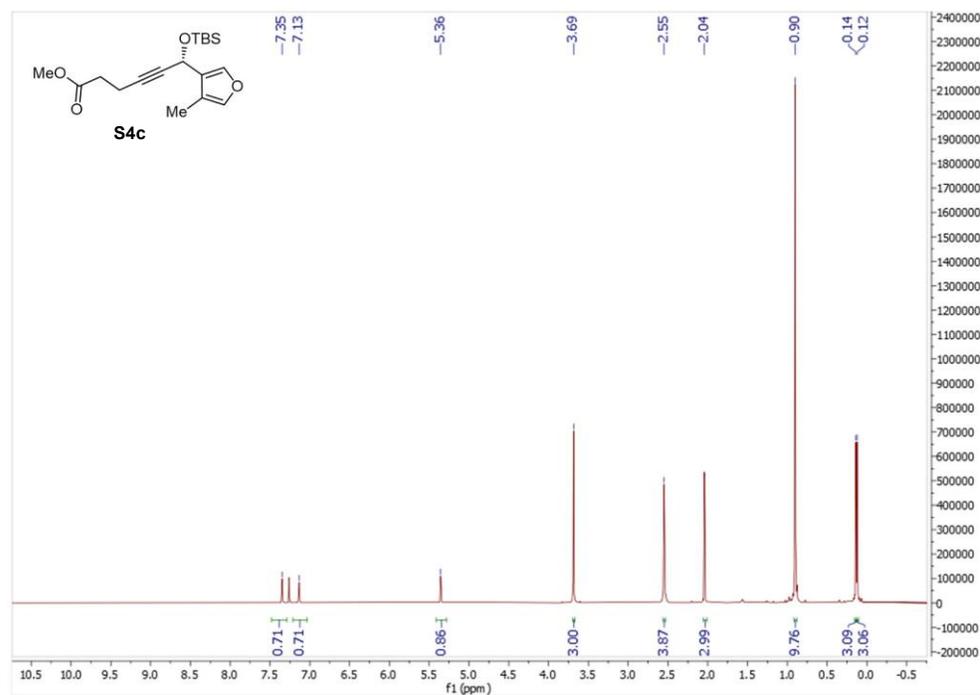
<sup>1</sup>H (500 MHz) of **S4b**



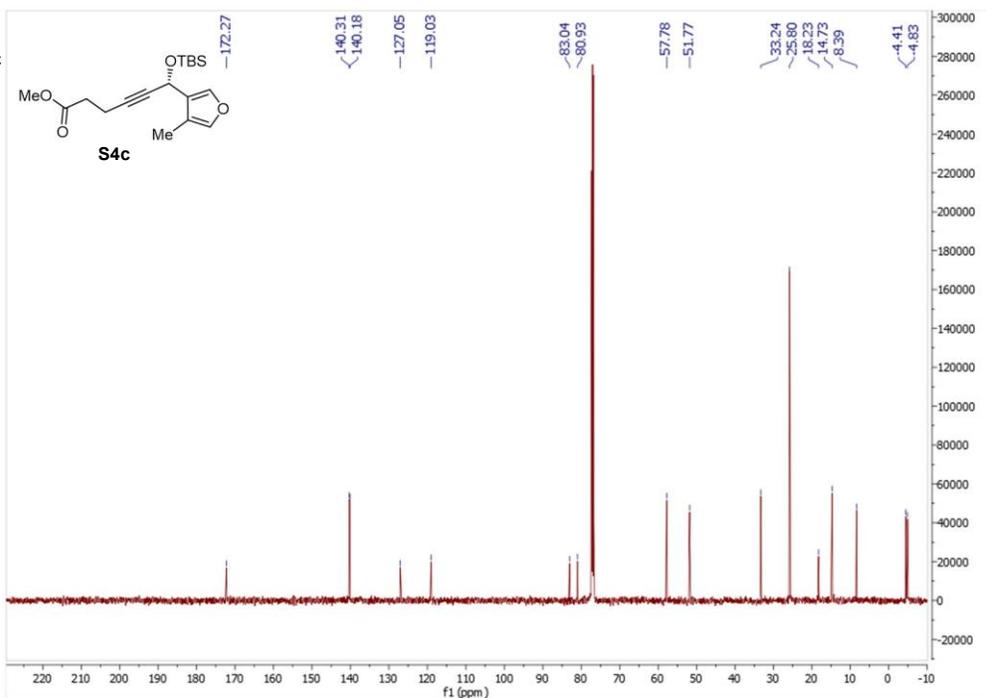
$^{13}\text{C}$  (126 MHz) of **S4b**



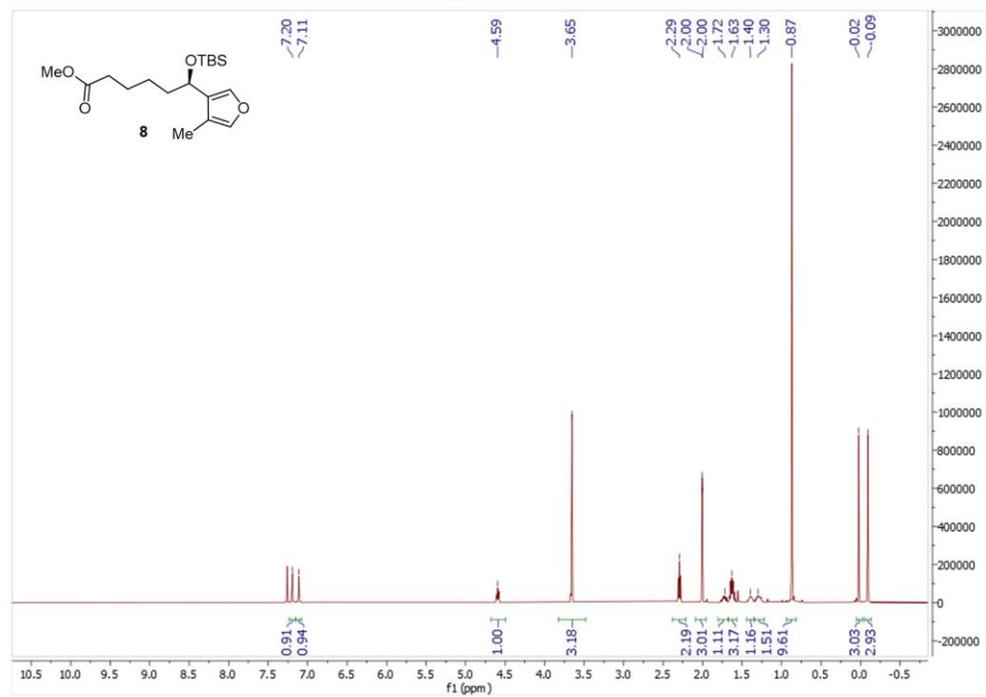
$^1\text{H}$  (500 MHz) of **S4c**



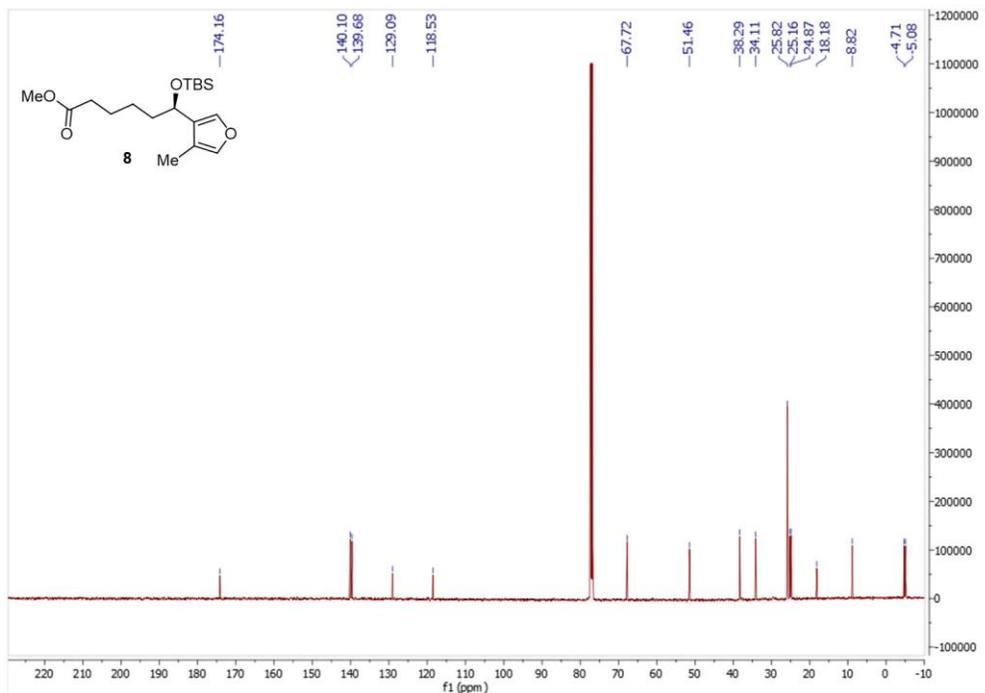
$^{13}\text{C}$  (126 MHz) of **S4c**



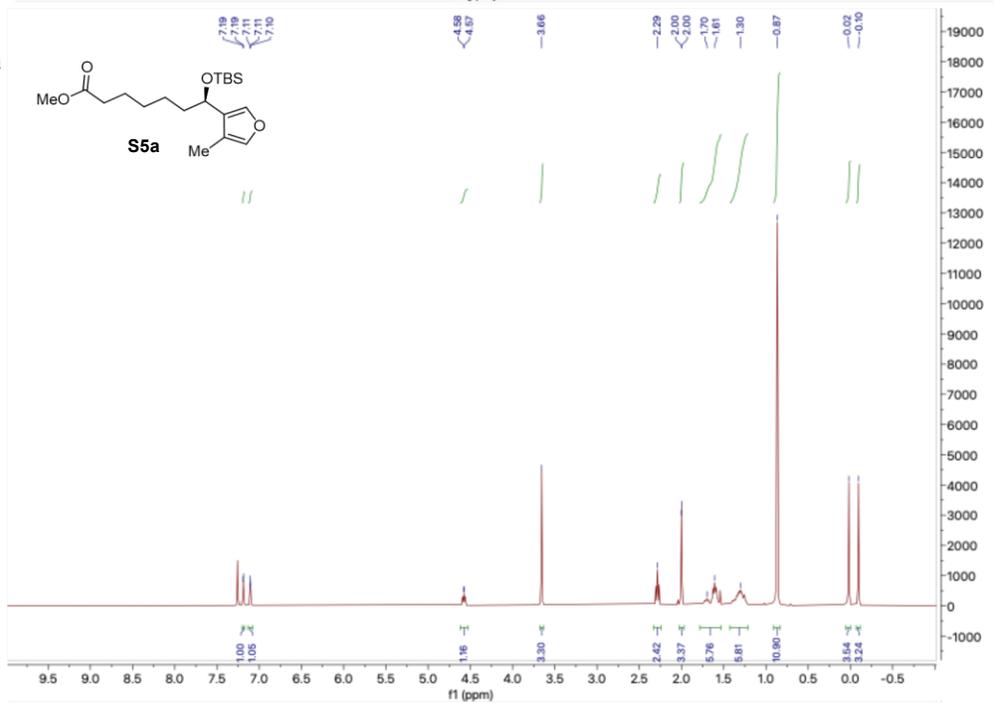
$^1\text{H}$  (500 MHz) of **8**



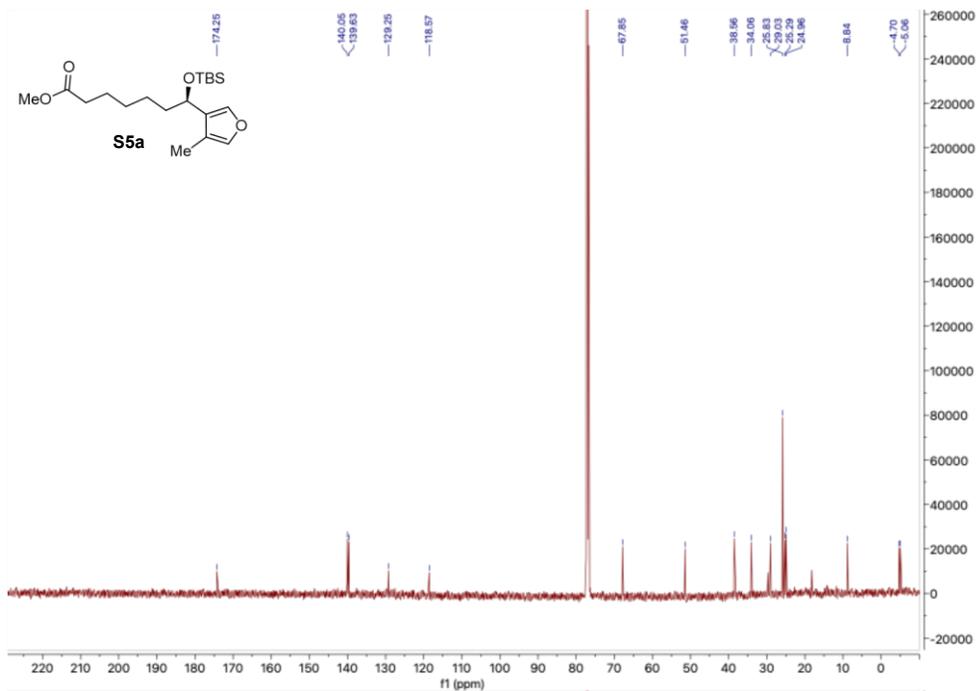
$^{13}\text{C}$  (126 MHz) of **8**



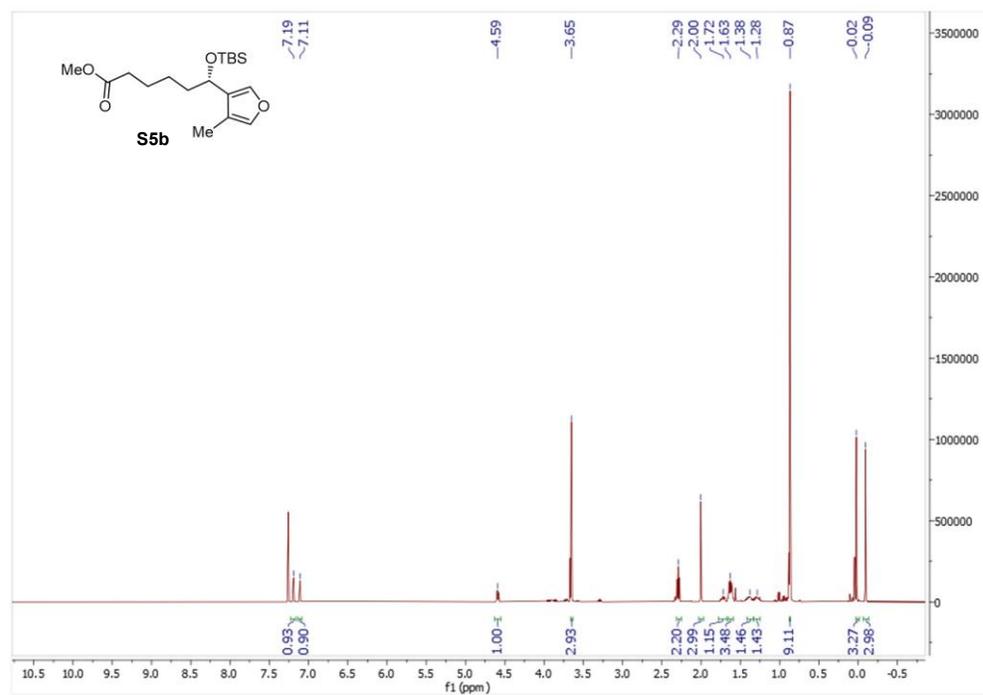
$^1\text{H}$  (500 MHz) of **S5a**



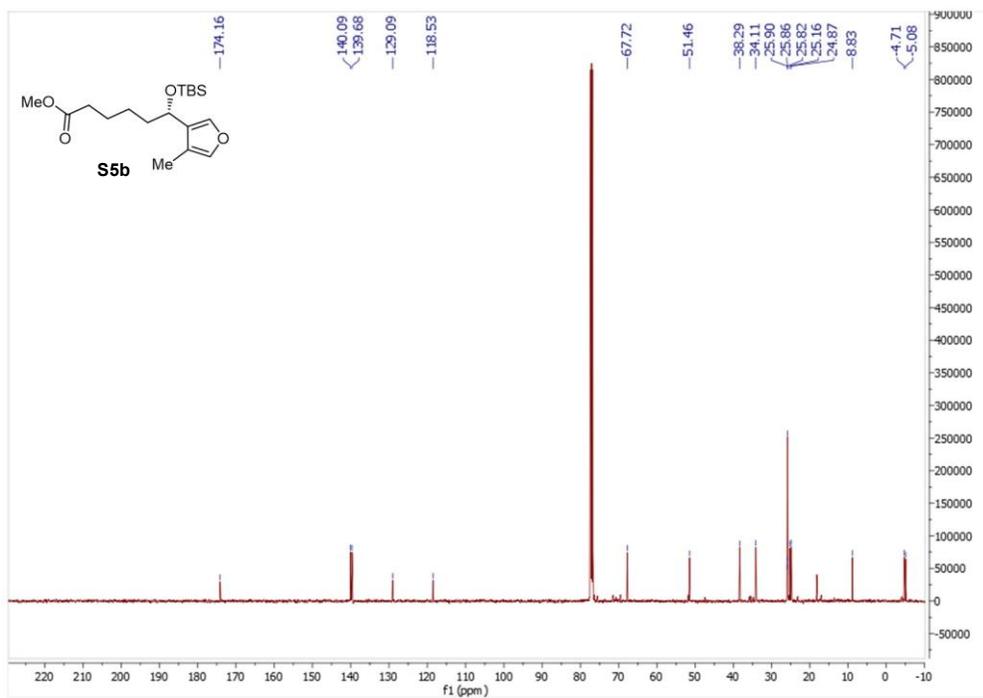
$^{13}\text{C}$  (126 MHz) of **S5a**



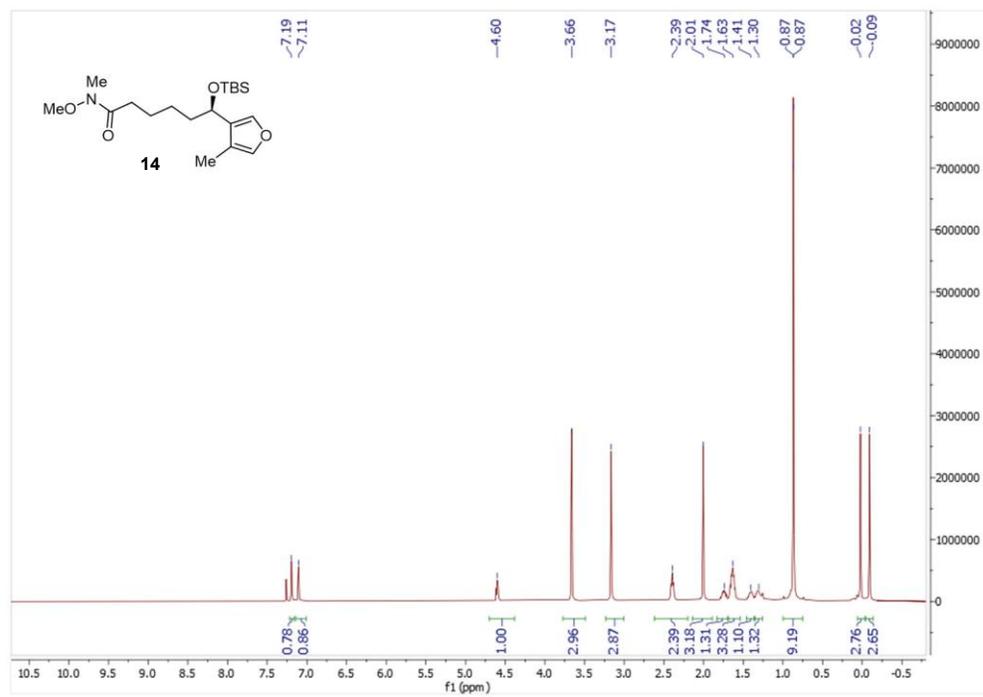
$^1\text{H}$  (500 MHz) of **S5b**



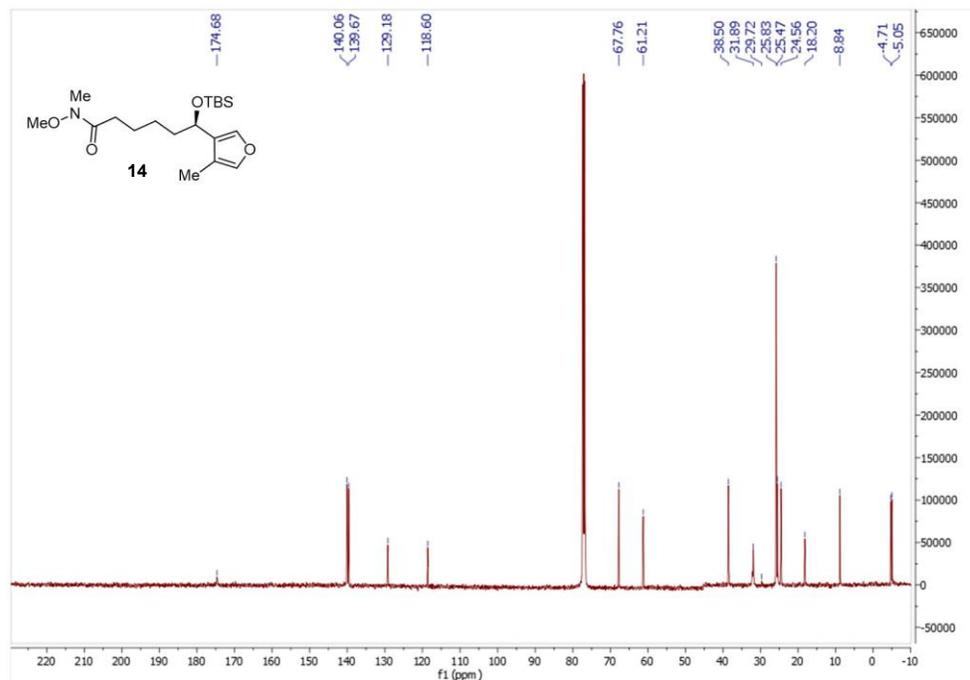
$^{13}\text{C}$  (126 MHz) of **S5c**



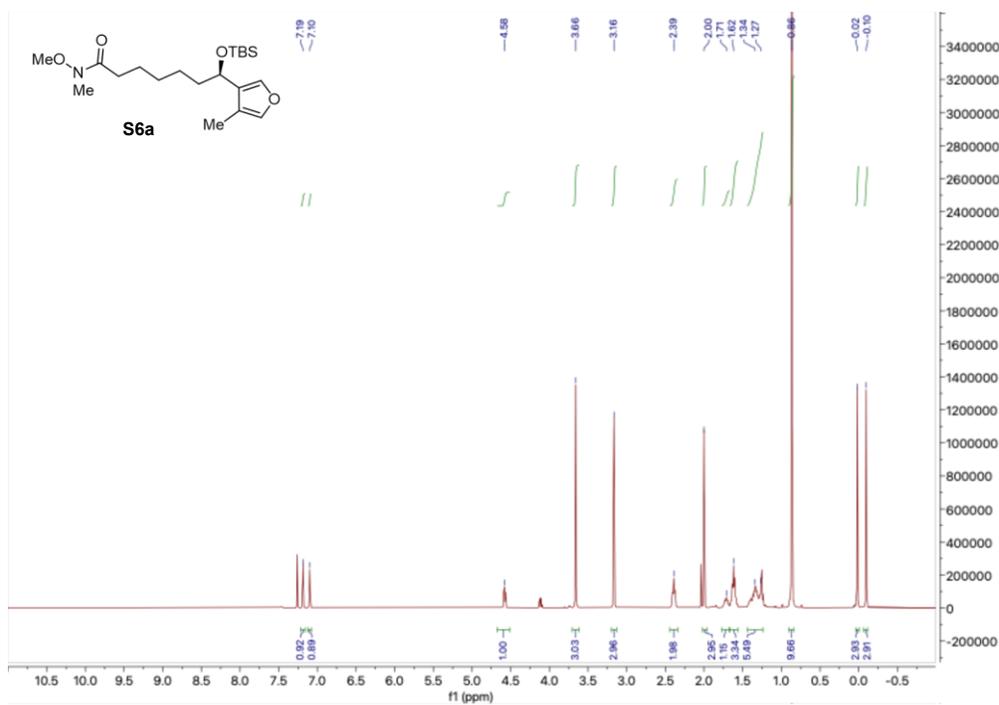
$^1\text{H}$  (500 MHz) of **14**



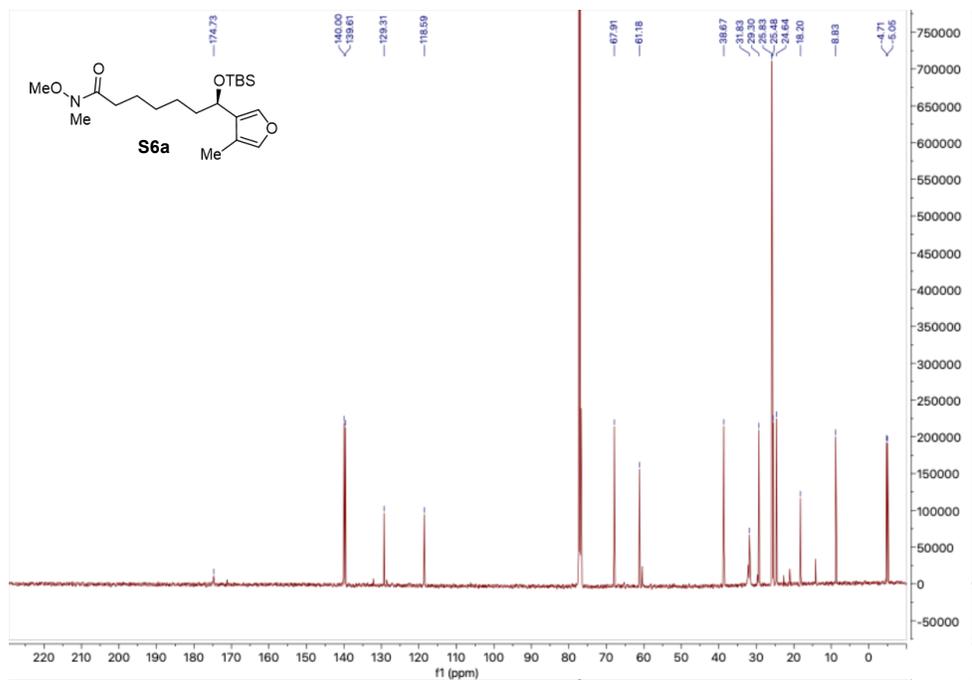
$^{13}\text{C}$  (500 MHz) of **14**



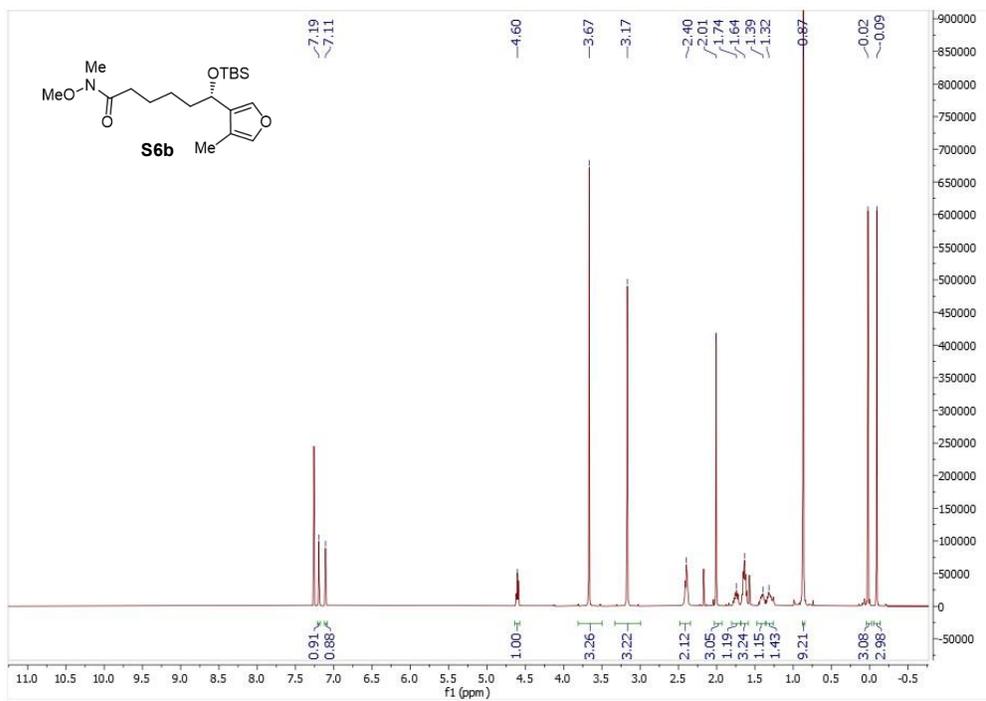
$^1\text{H}$  (500 MHz) of **S6a**



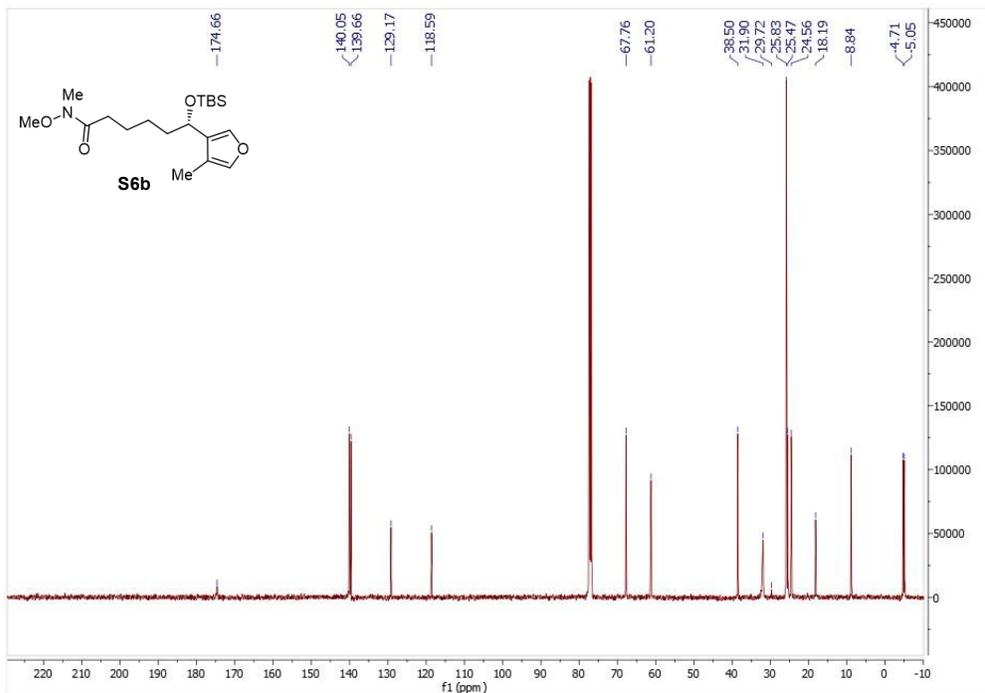
$^{13}\text{C}$  (126 MHz) of **S6a**



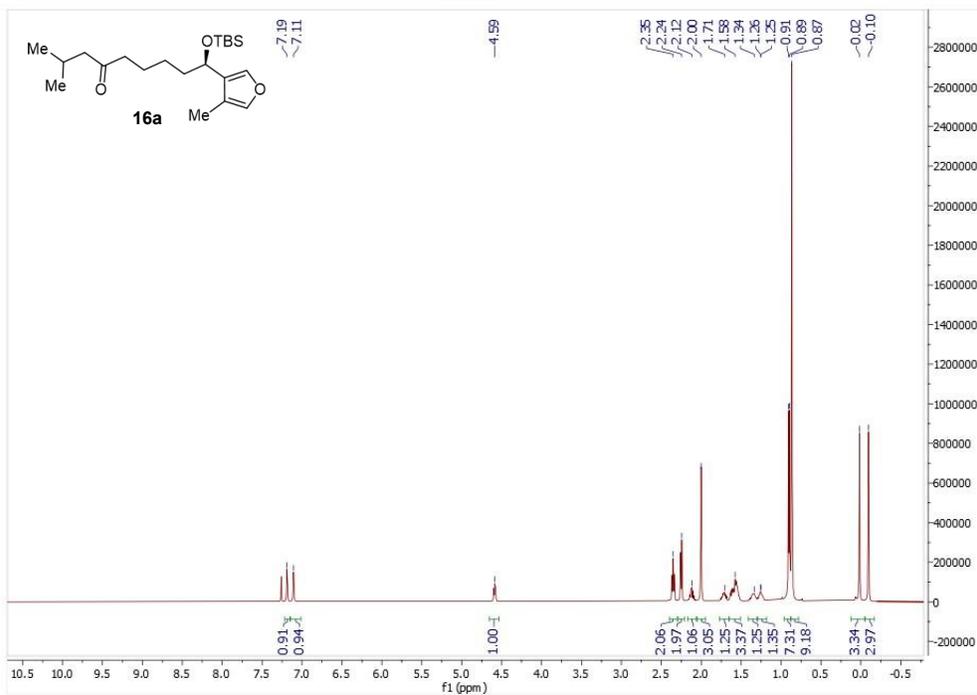
$^1\text{H}$  (500 MHz) of **S6b**



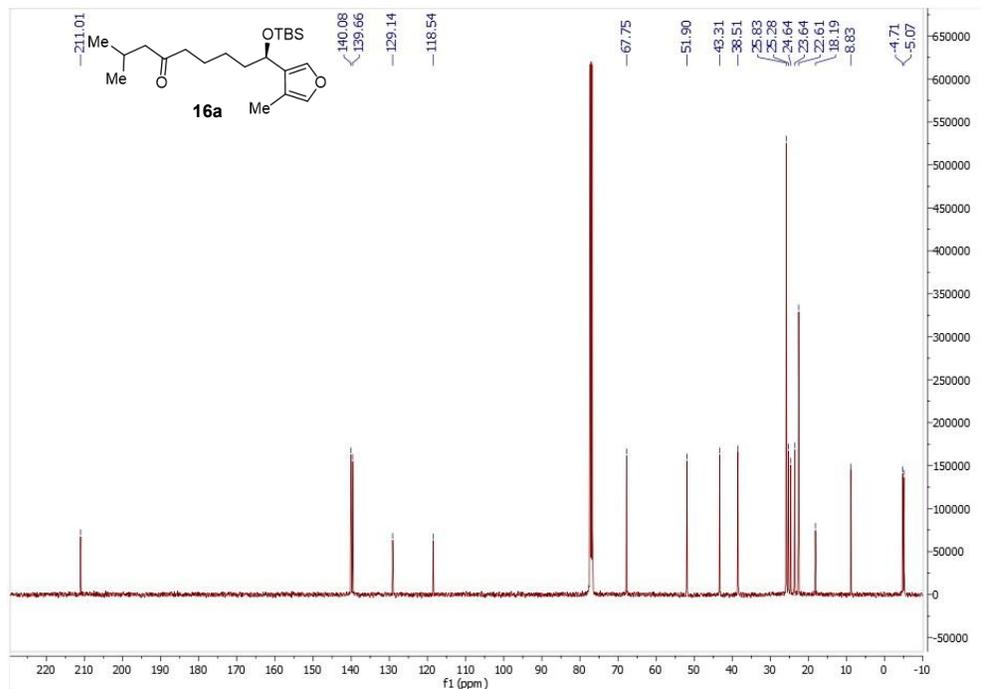
$^{13}\text{C}$  (126 MHz) of **S6b**



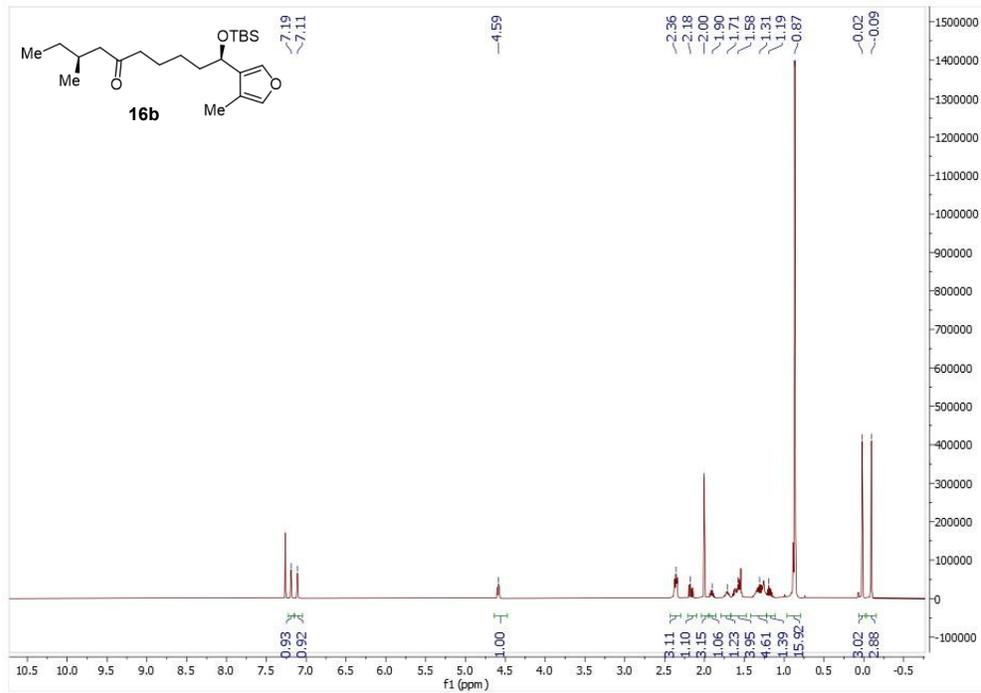
$^1\text{H}$  (500 MHz) of **16a**



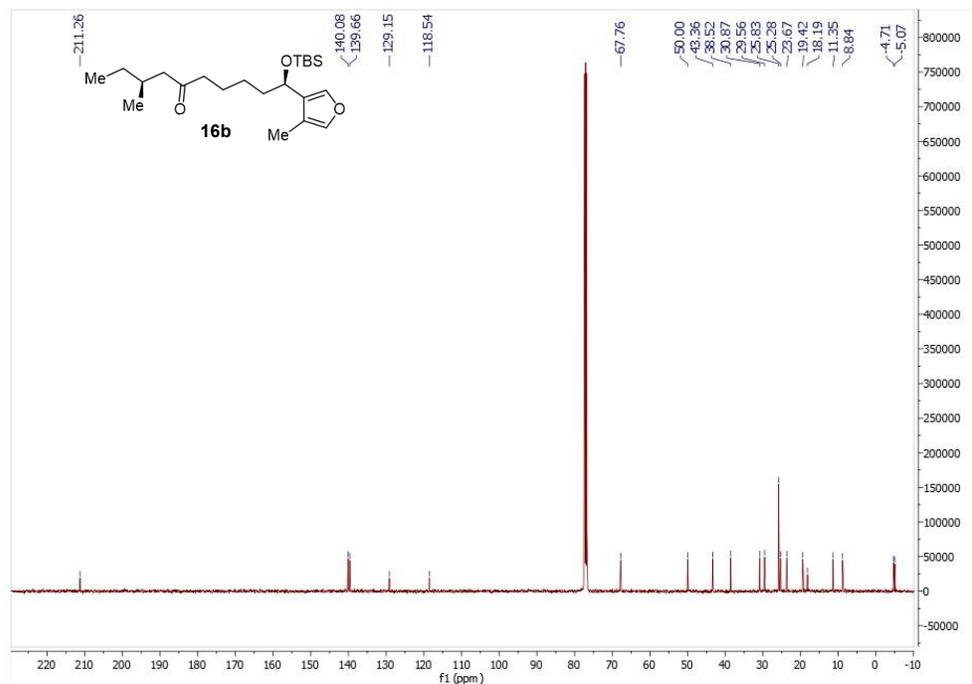
$^{13}\text{C}$  (126 MHz) of **16a**



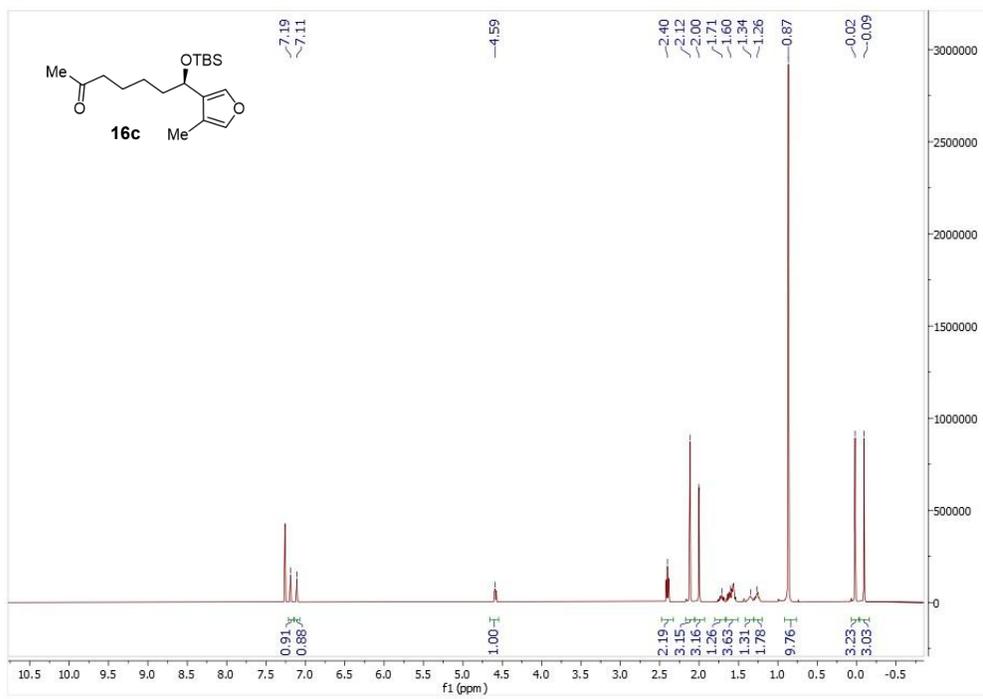
$^1\text{H}$  (500 MHz) of **16b**



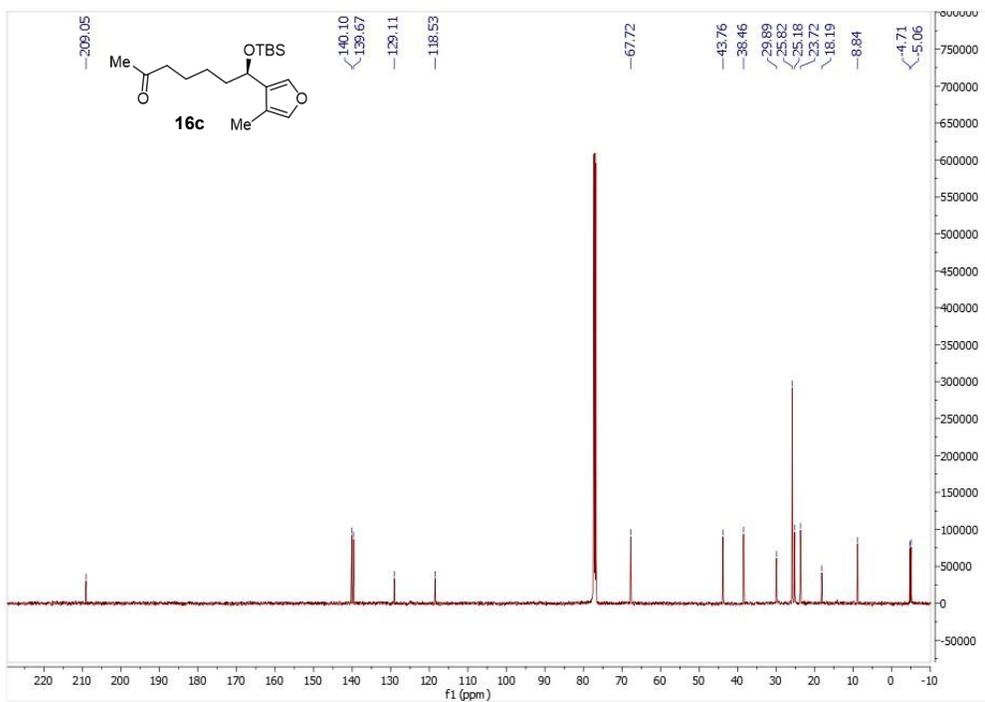
$^{13}\text{C}$  (126 MHz) of **16b**



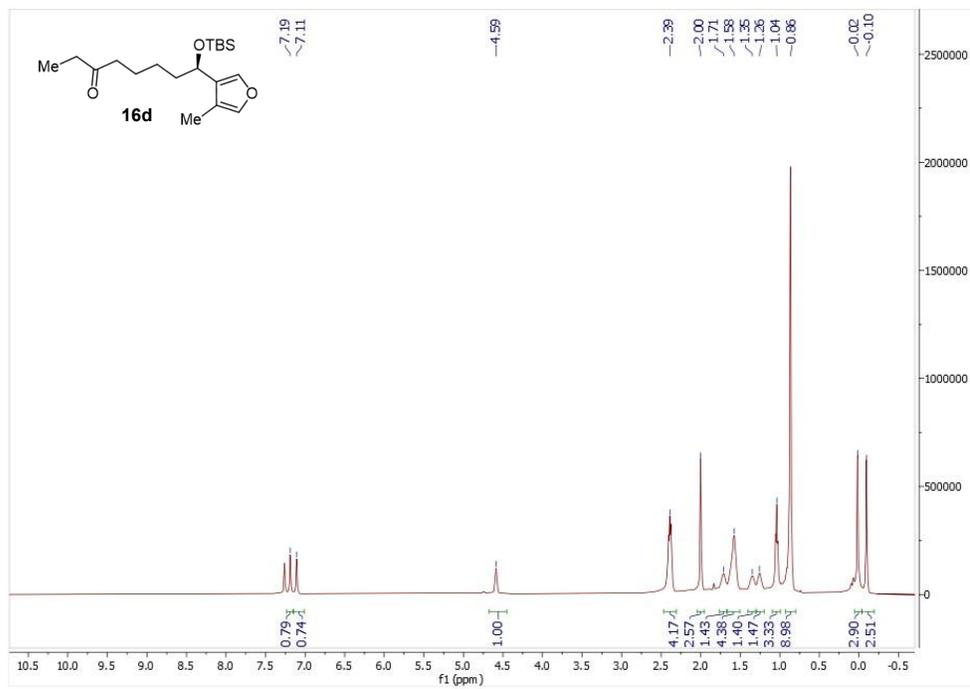
$^1\text{H}$  (500 MHz) of **16c**



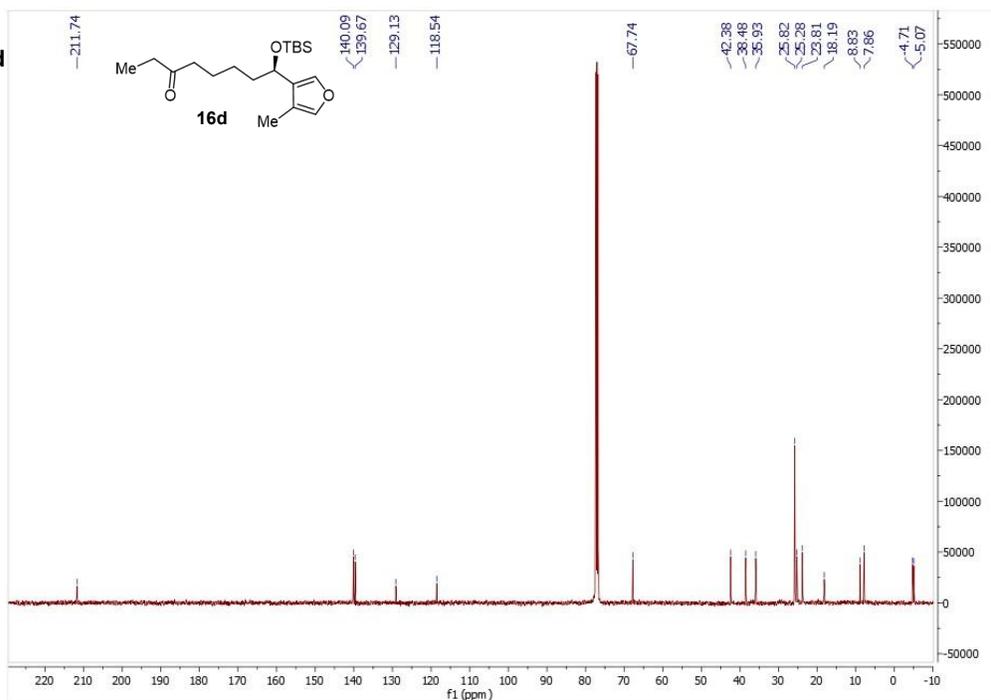
$^{13}\text{C}$  (126 MHz) of **16c**



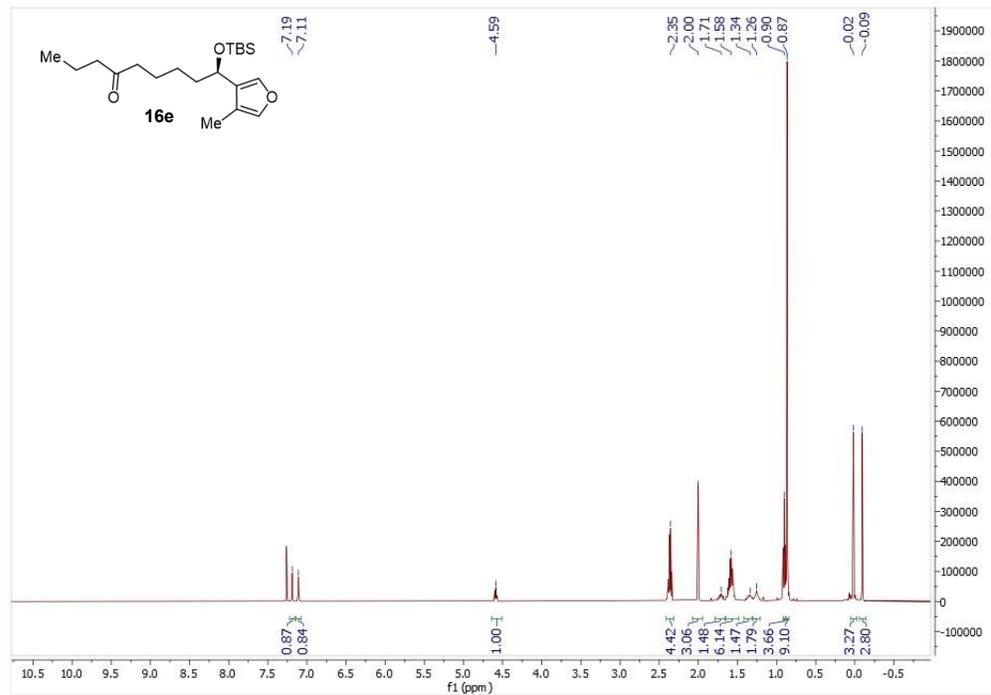
$^1\text{H}$  (500 MHz) of **16d**



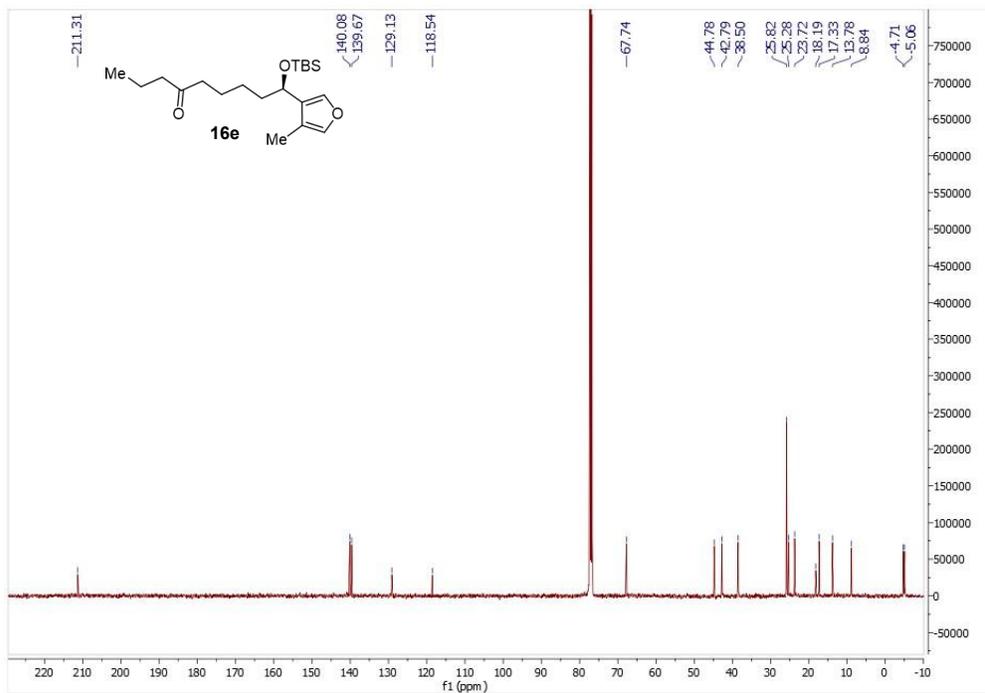
<sup>13</sup>C (126 MHz) of **16d**



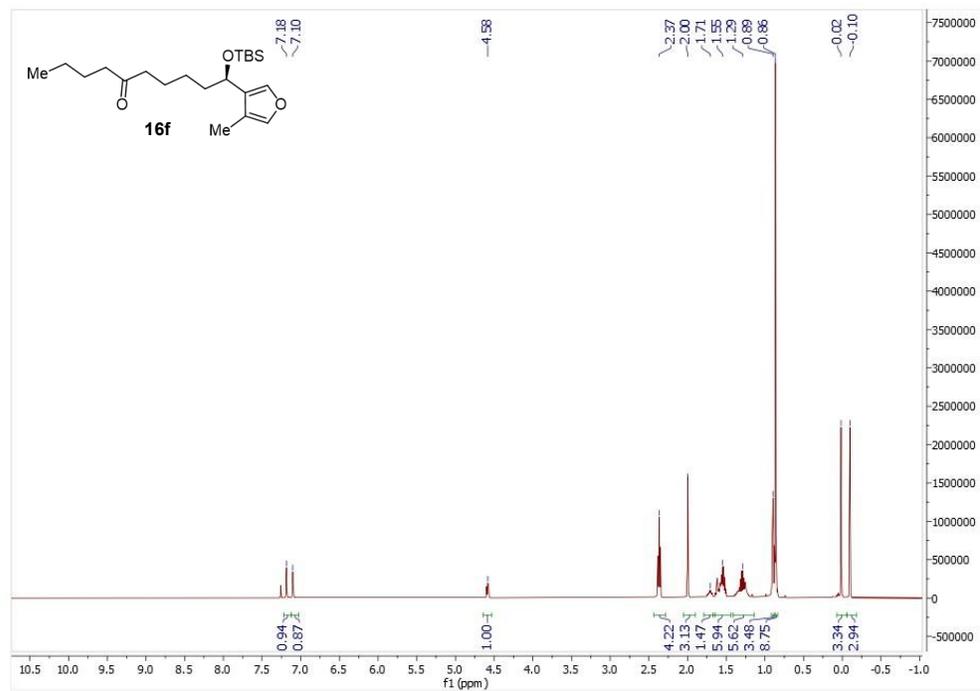
<sup>1</sup>H (500 MHz) of **16e**



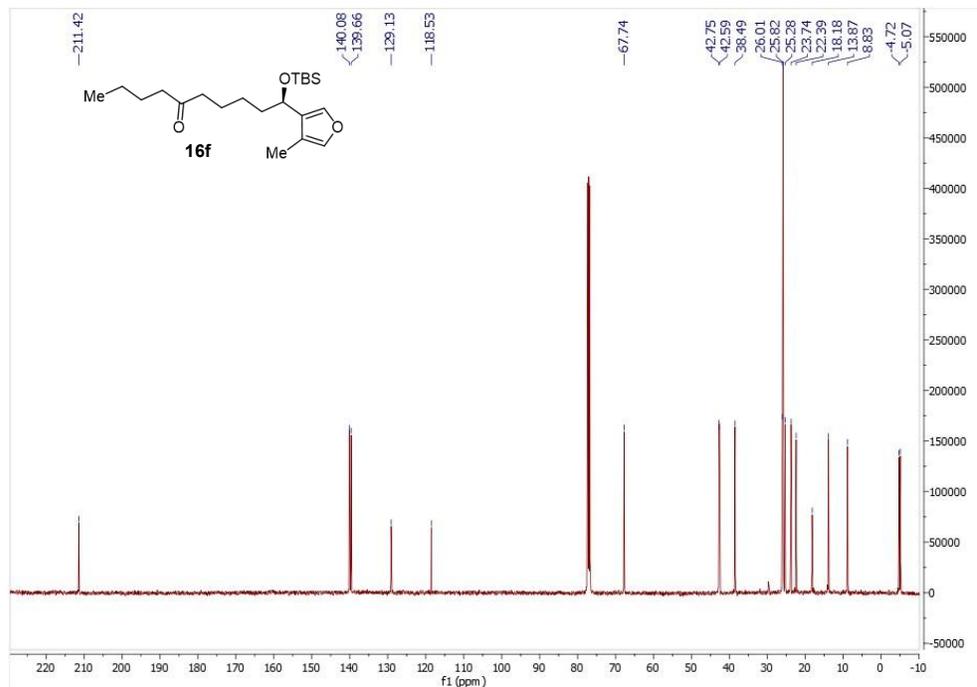
$^{13}\text{C}$  (126 MHz) of **16e**



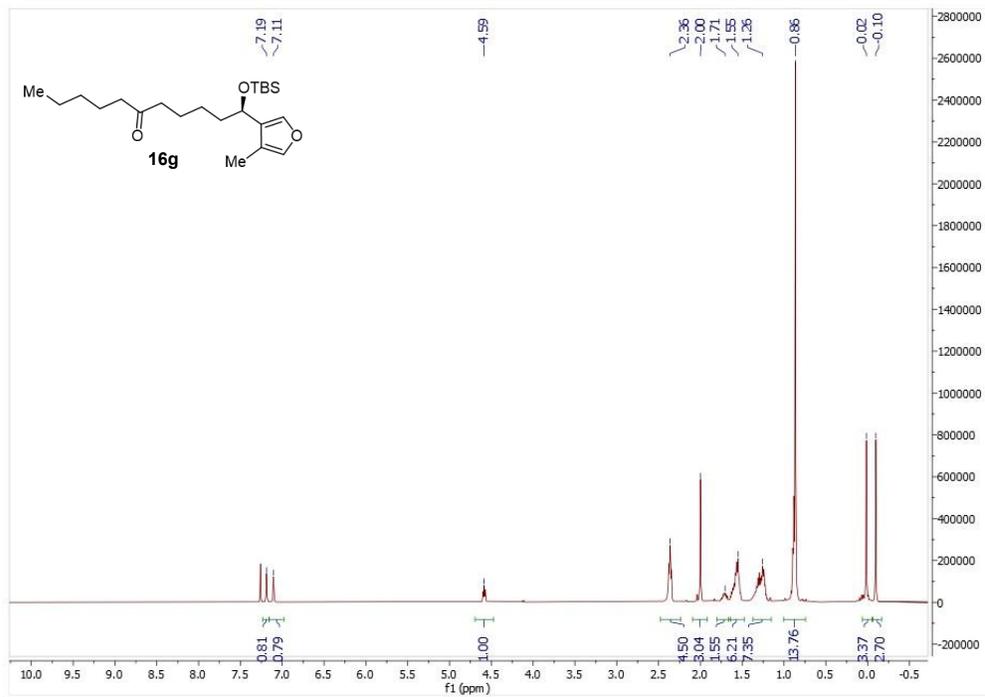
$^1\text{H}$  (500 MHz) of **16f**



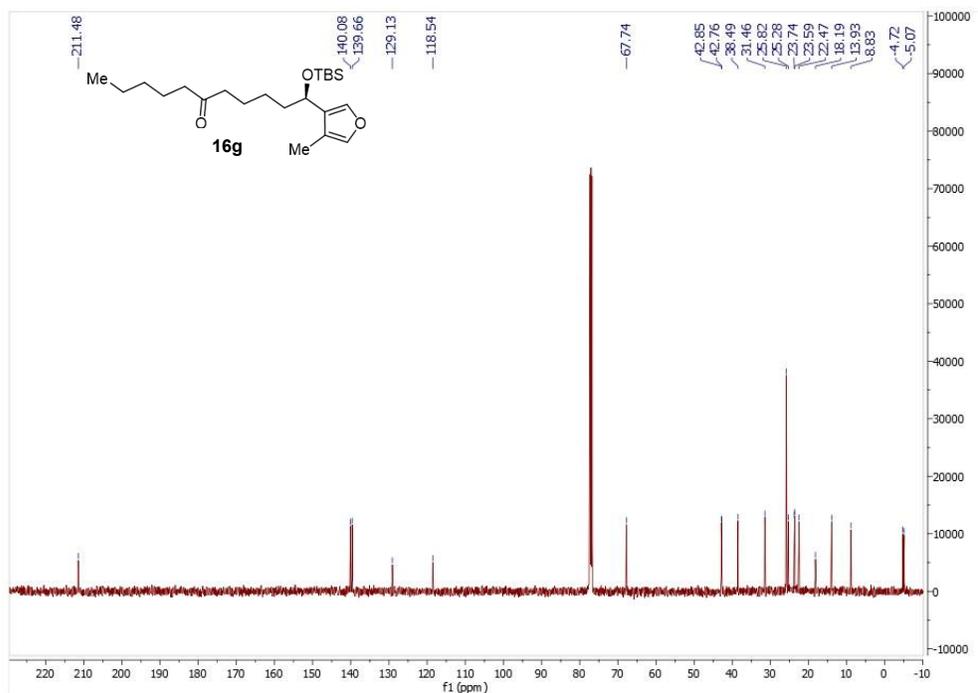
$^{13}\text{C}$  (126 MHz) of **16f**



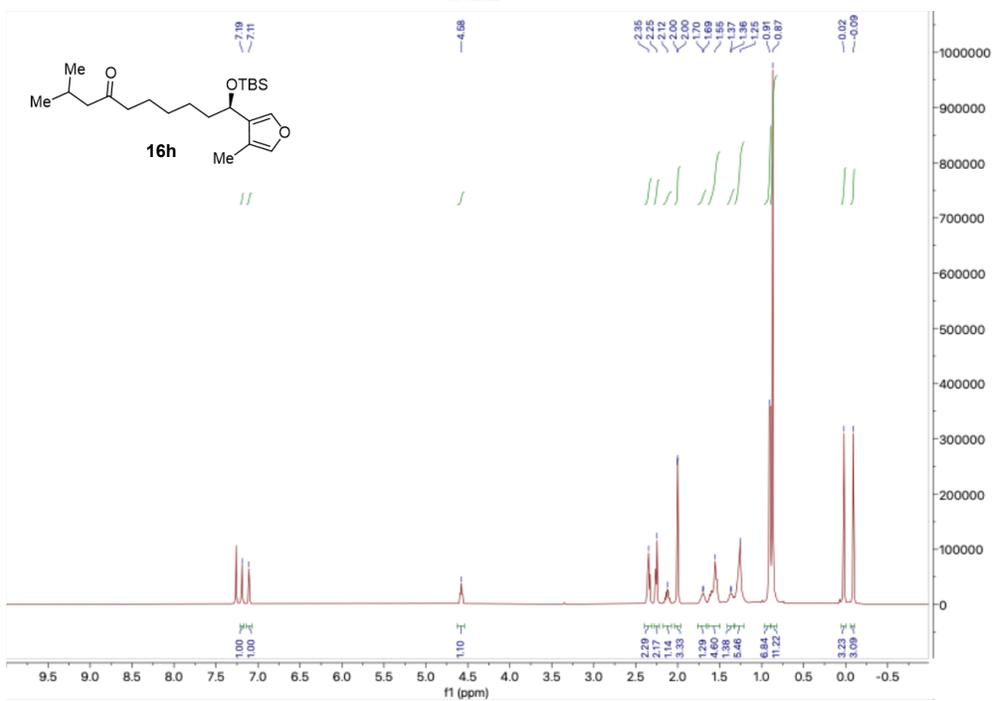
$^1\text{H}$  (500 MHz) of **16g**



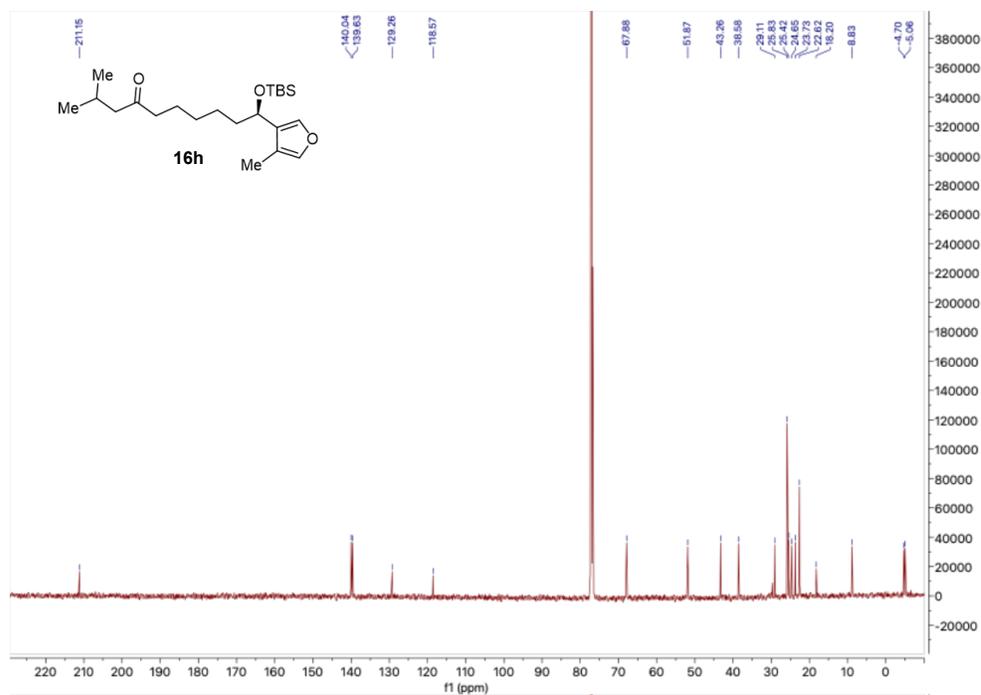
$^{13}\text{C}$  (126 MHz) of **16g**



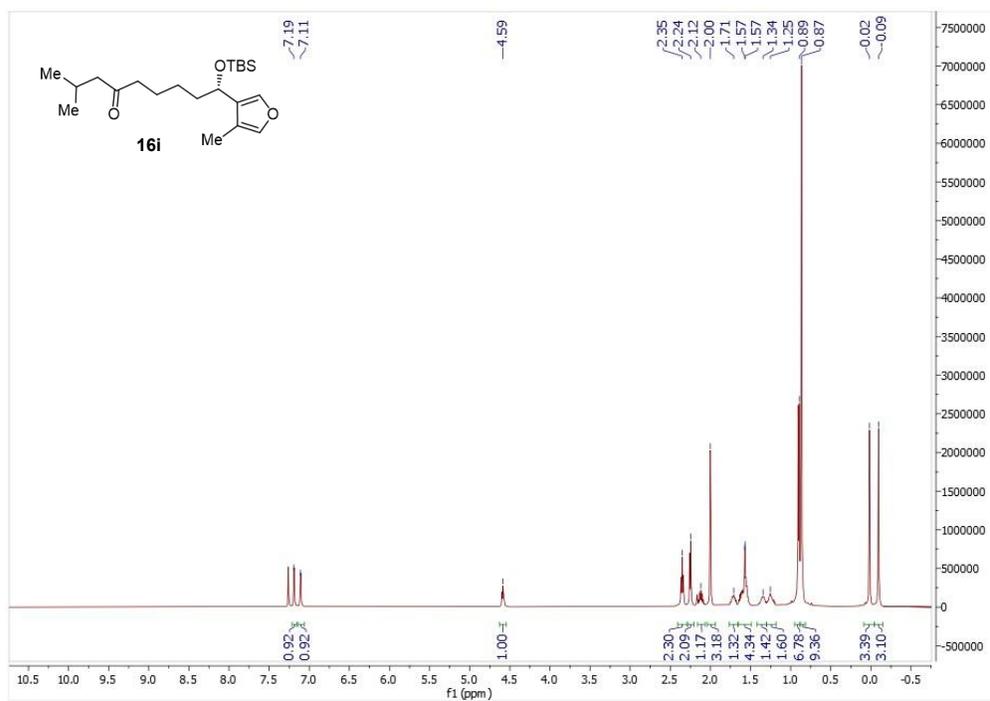
$^1\text{H}$  (500 MHz) of **16h**



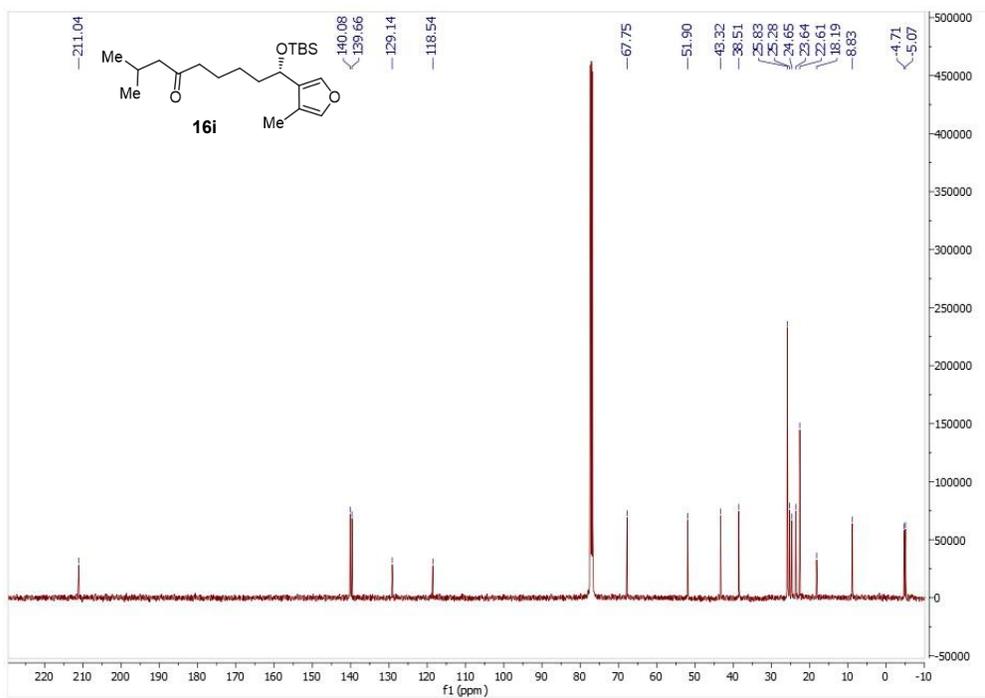
$^{13}\text{C}$  (126 MHz) of **16h**



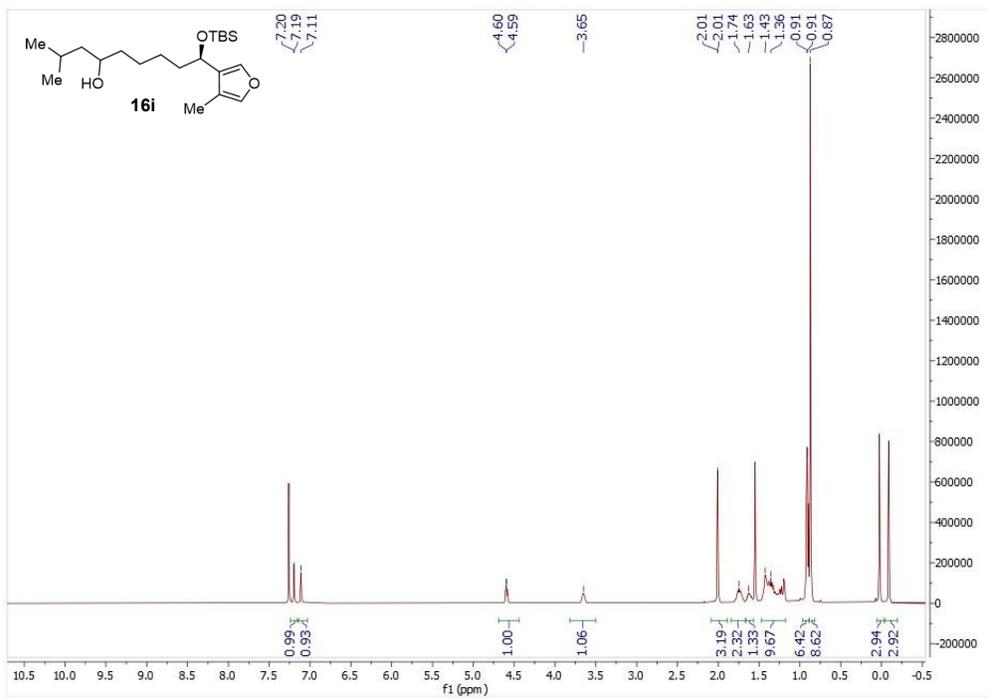
$^1\text{H}$  (500 MHz) of **16i**



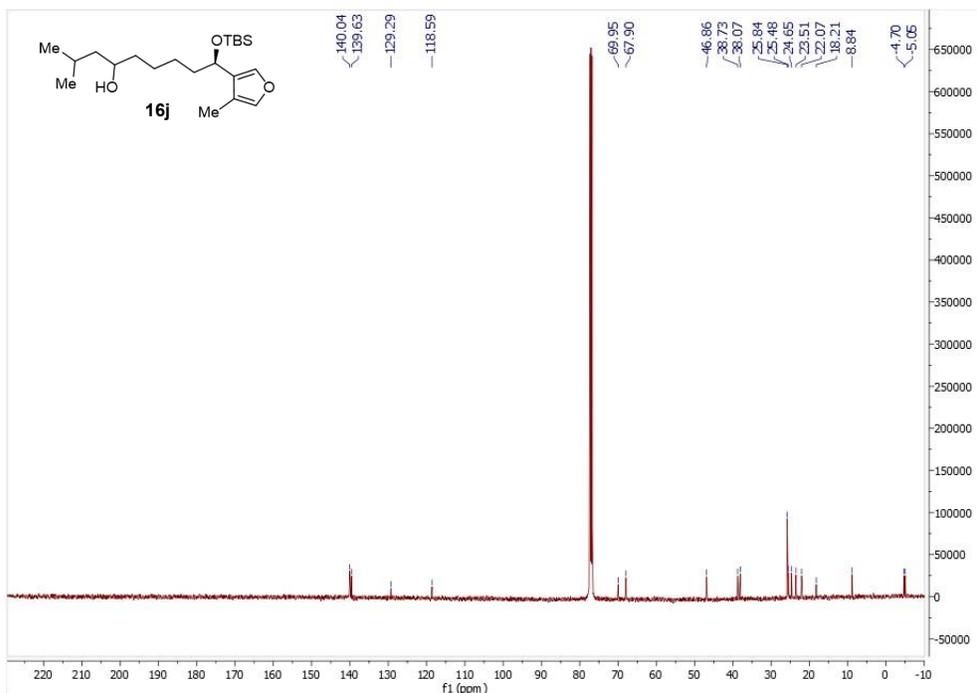
$^{13}\text{C}$  (126 MHz) of **16i**



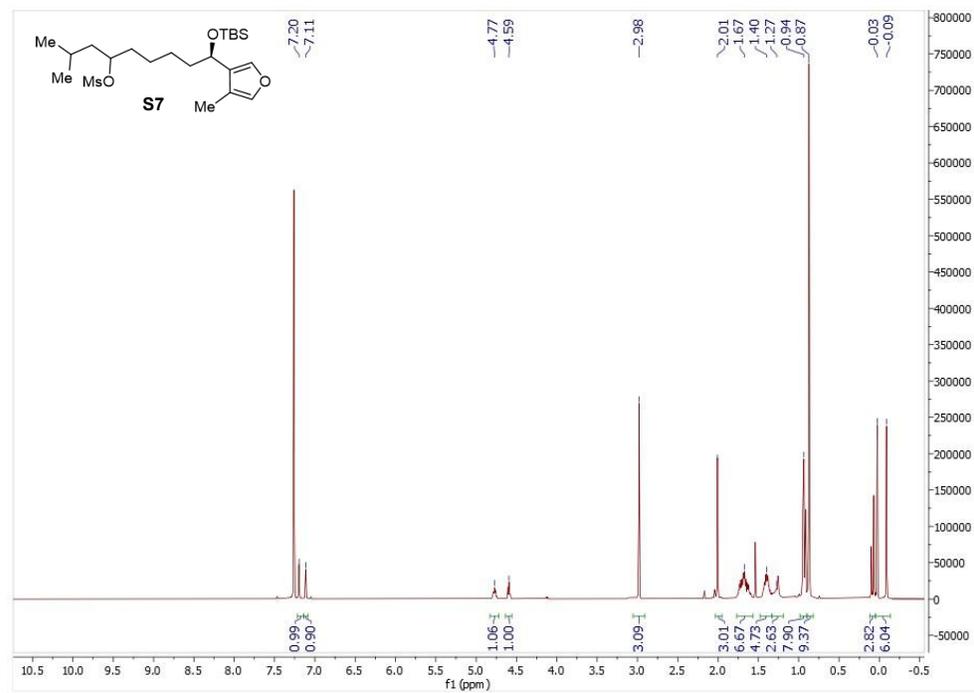
$^1\text{H}$  (500 MHz) of **16j**



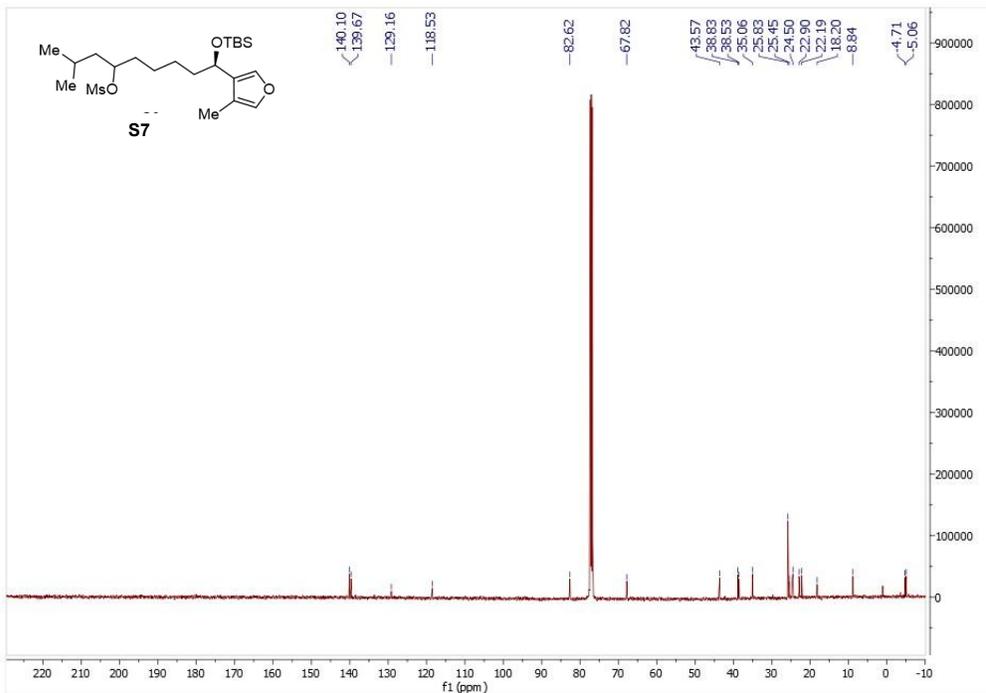
$^{13}\text{C}$  (126 MHz) of **16j**



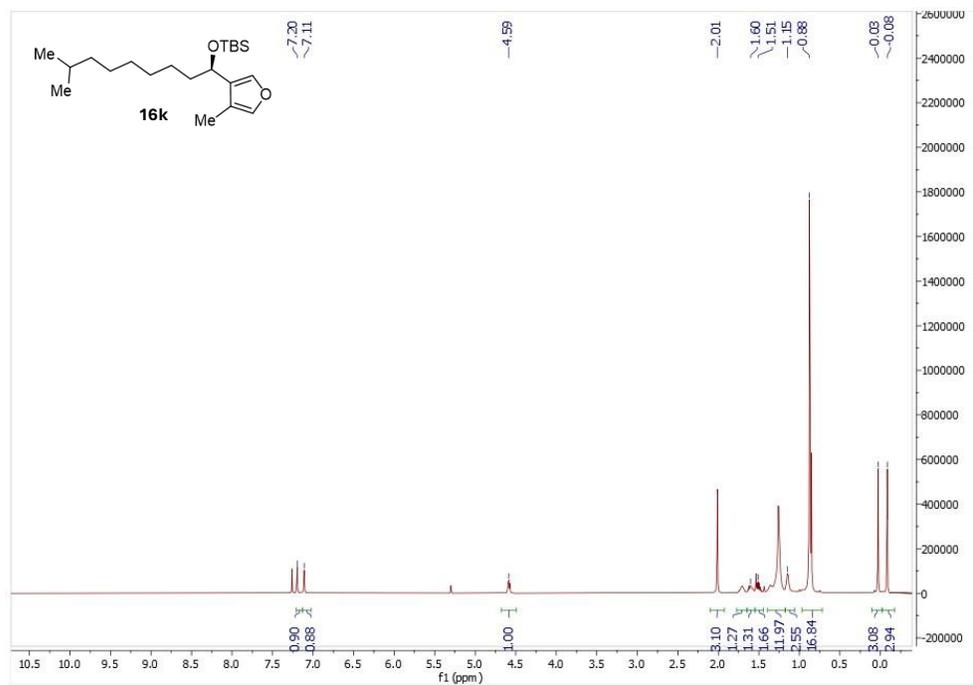
$^1\text{H}$  (500 MHz) of **S7**



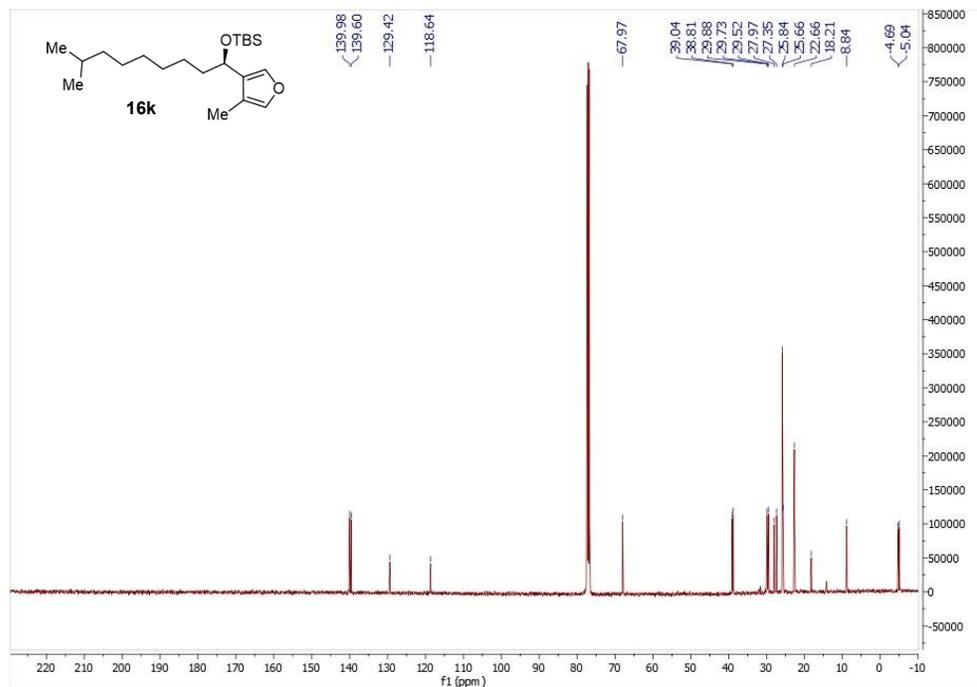
$^{13}\text{C}$  (126 MHz) of **S7**



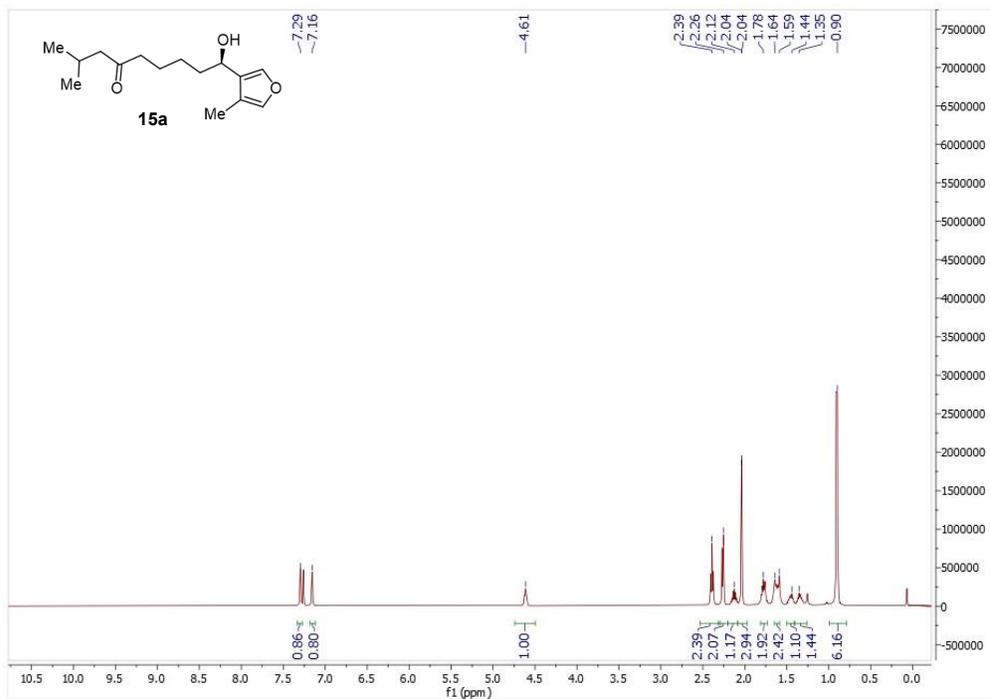
$^1\text{H}$  (500 MHz) of **16k**



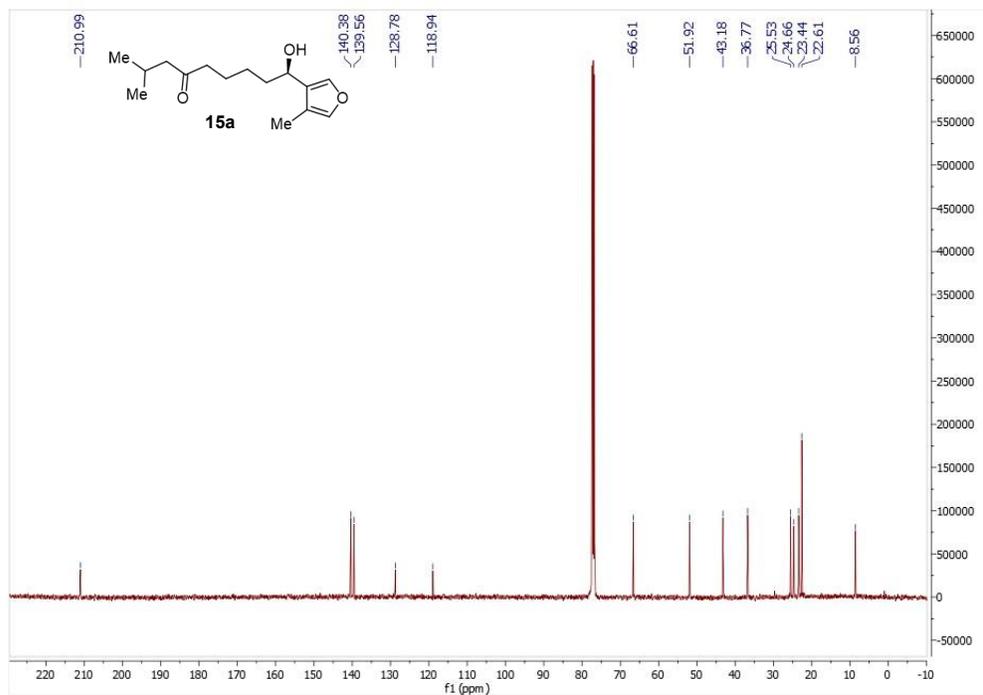
$^{13}\text{C}$  (126 MHz) of **16k**



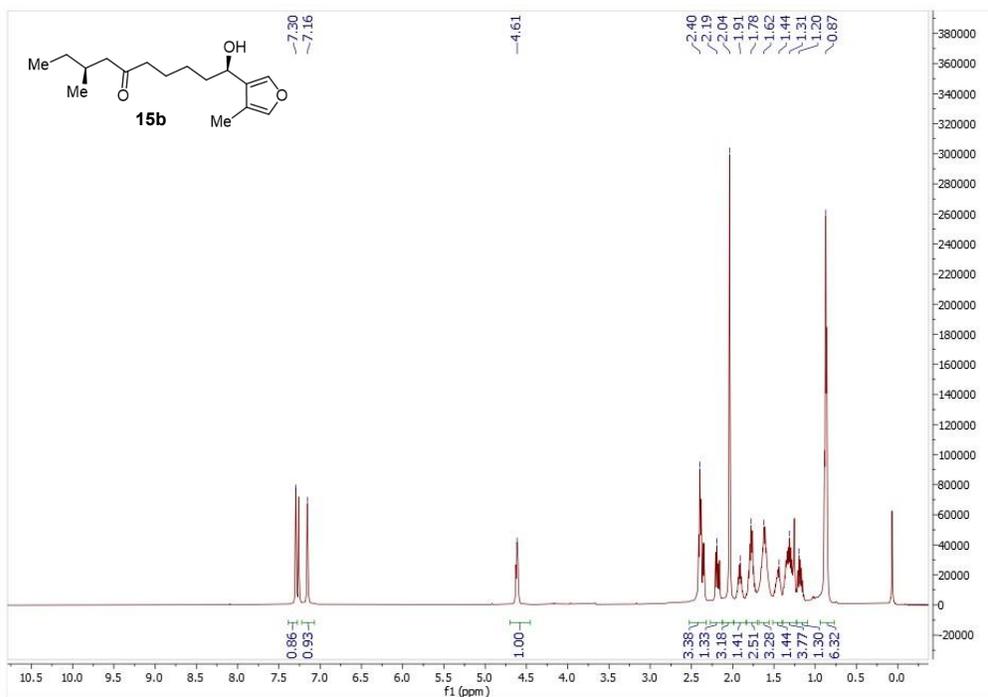
$^1\text{H}$  (500 MHz) of **15a**



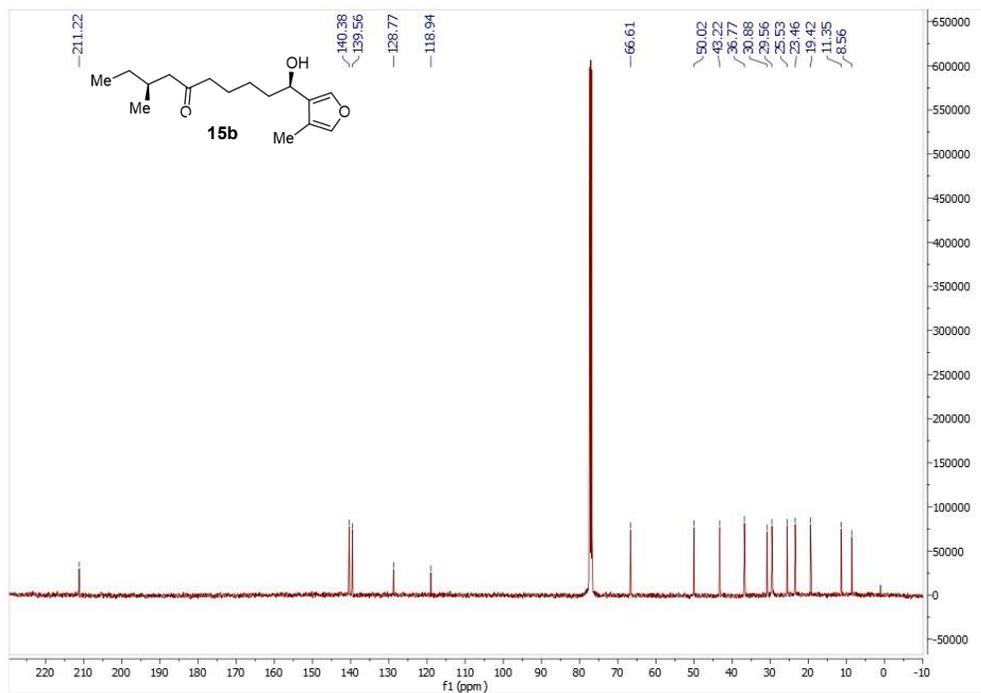
<sup>13</sup>C (126 MHz) of **15a**



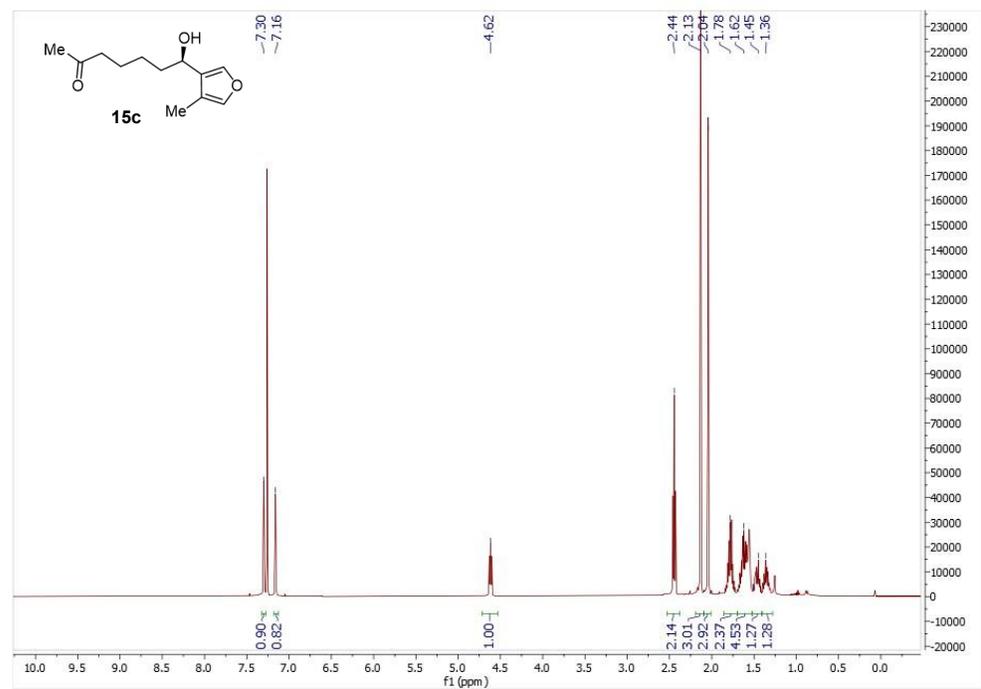
<sup>1</sup>H (500 MHz) of **15b**



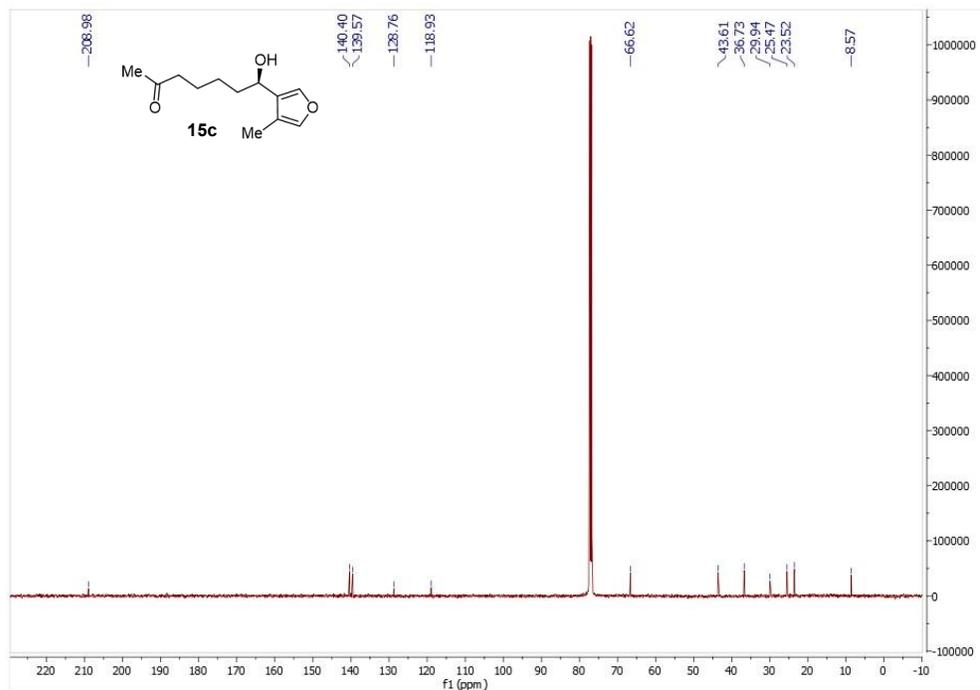
<sup>13</sup>C (126 MHz) of **15b**



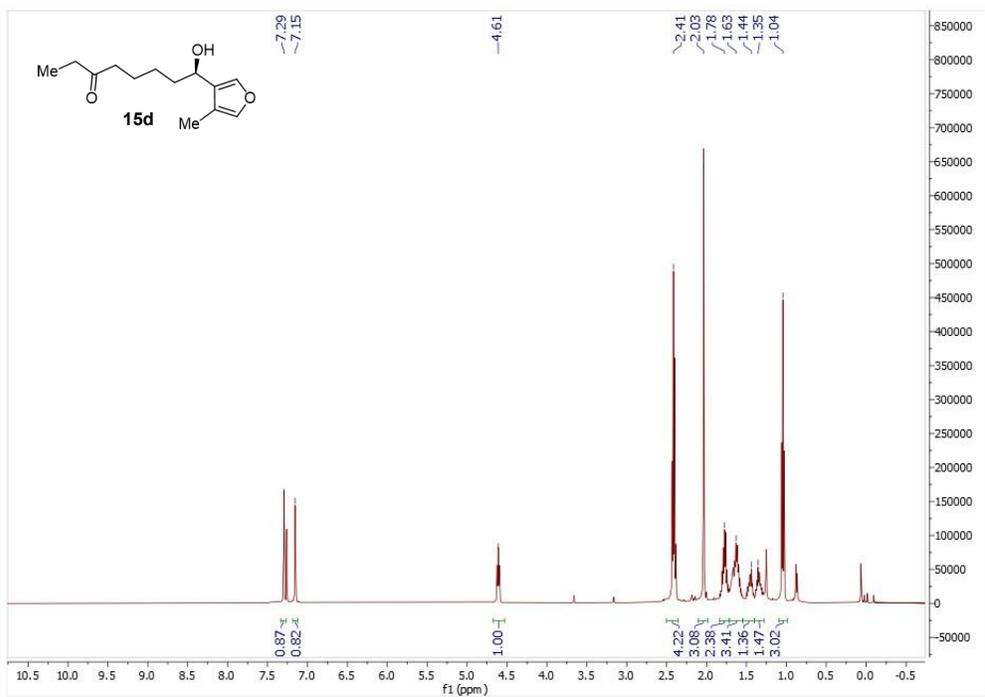
<sup>1</sup>H (500 MHz) of **15c**



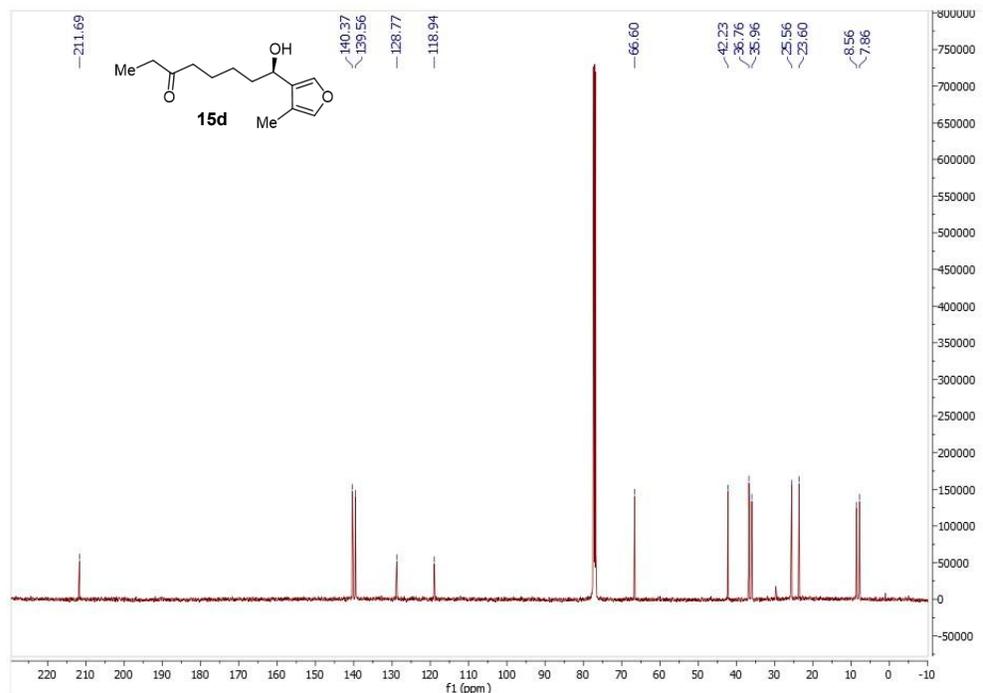
$^{13}\text{C}$  (126 MHz) of **15c**



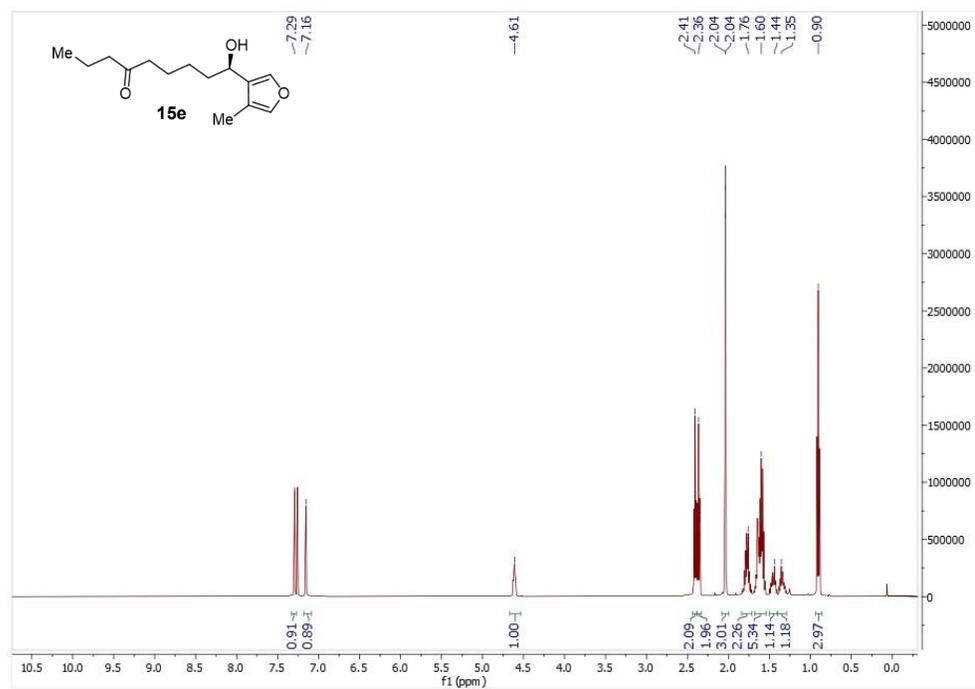
$^1\text{H}$  (500 MHz) of **15d**



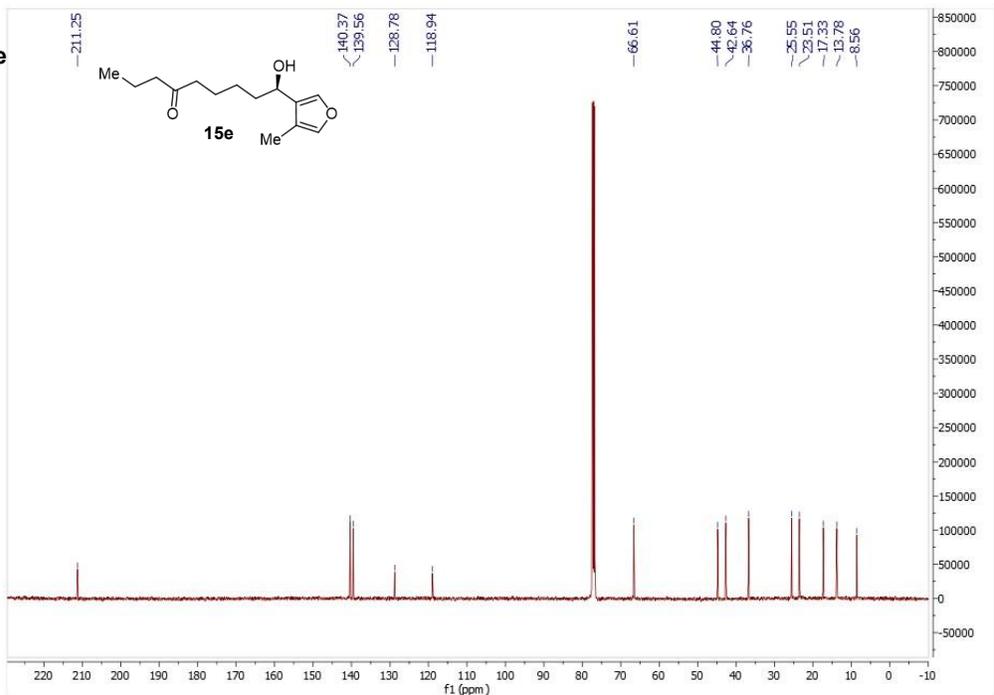
$^{13}\text{C}$  (126 MHz) of **15d**



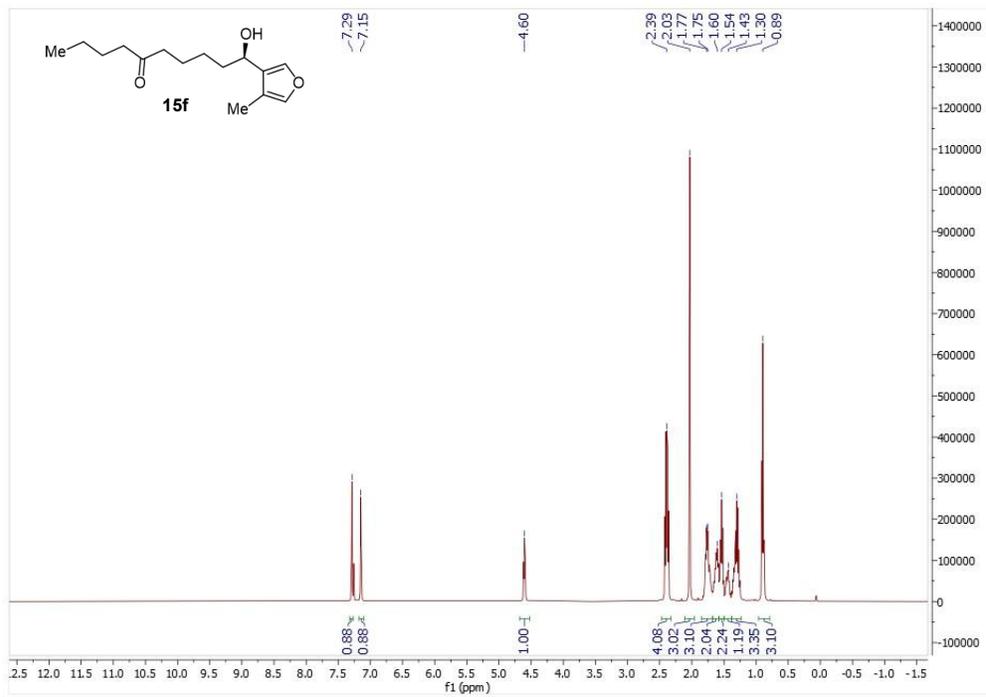
$^1\text{H}$  (500 MHz) of **15e**



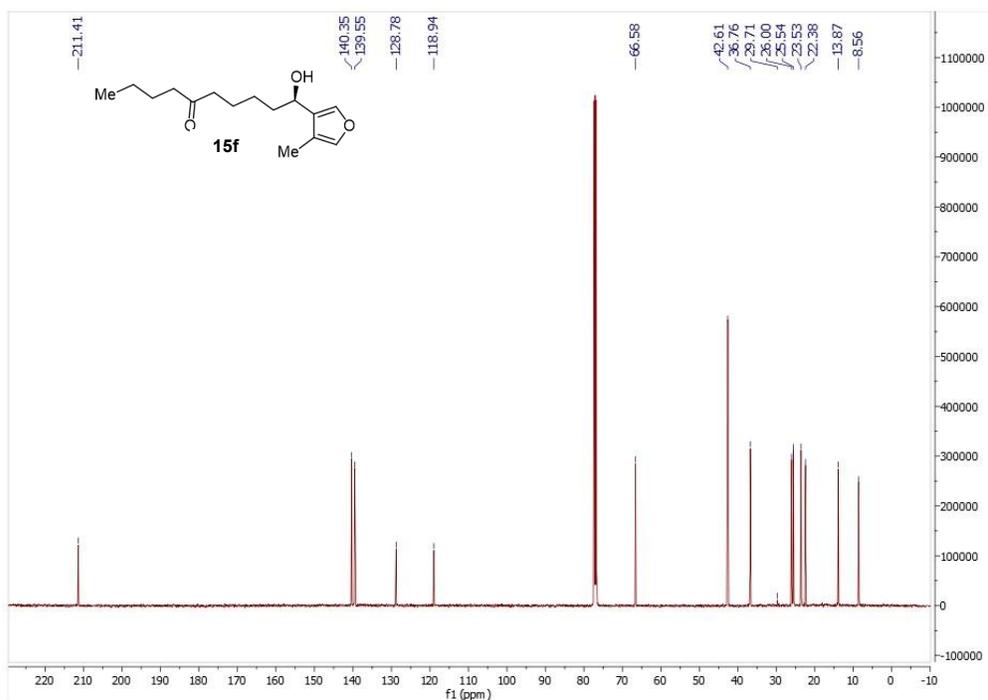
<sup>13</sup>C (126 MHz) of **15e**



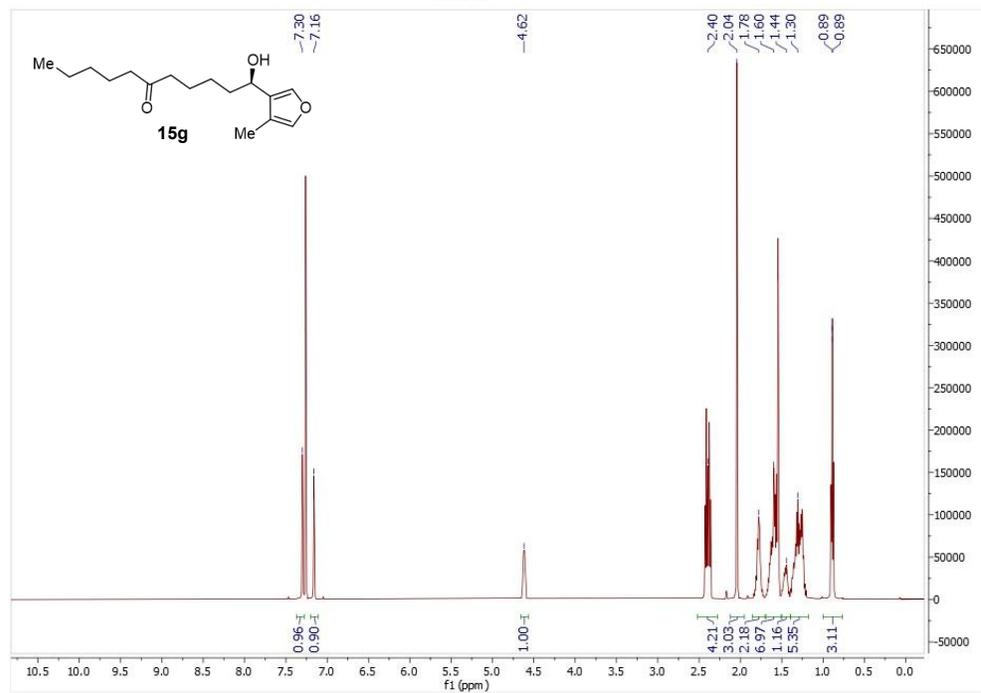
<sup>1</sup>H (500 MHz) of **15f**



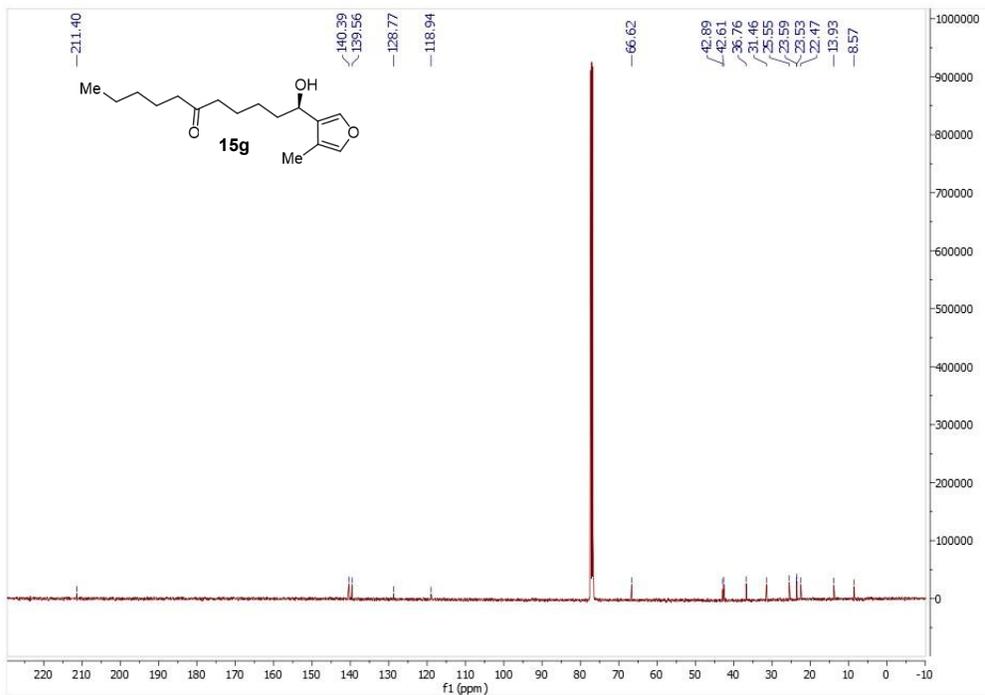
$^{13}\text{C}$  (126 MHz) of **15f**



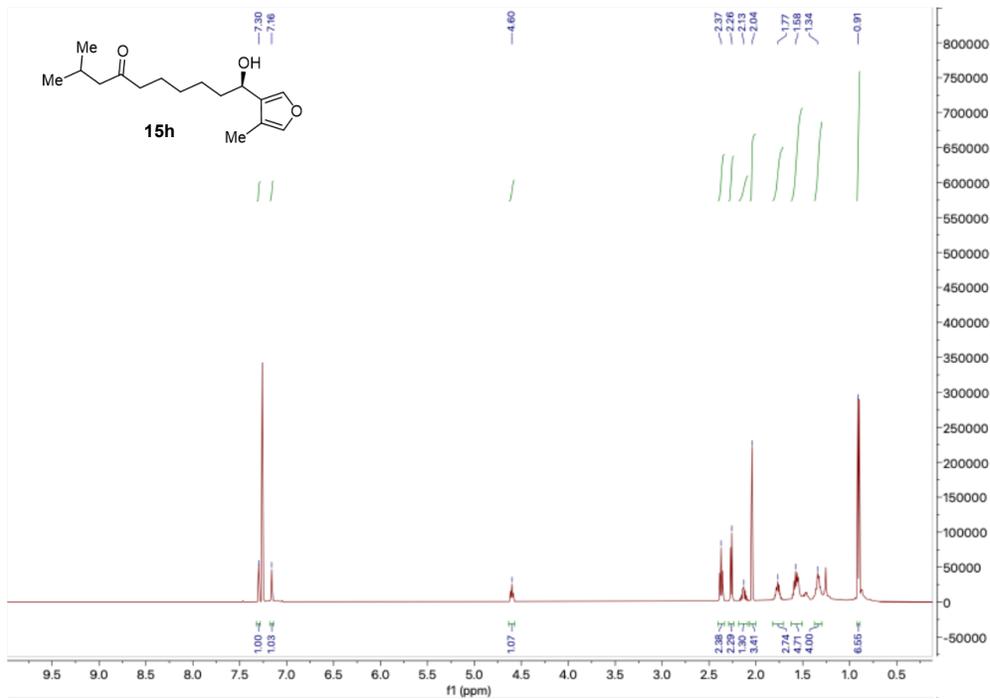
$^1\text{H}$  (500 MHz) of **15g**



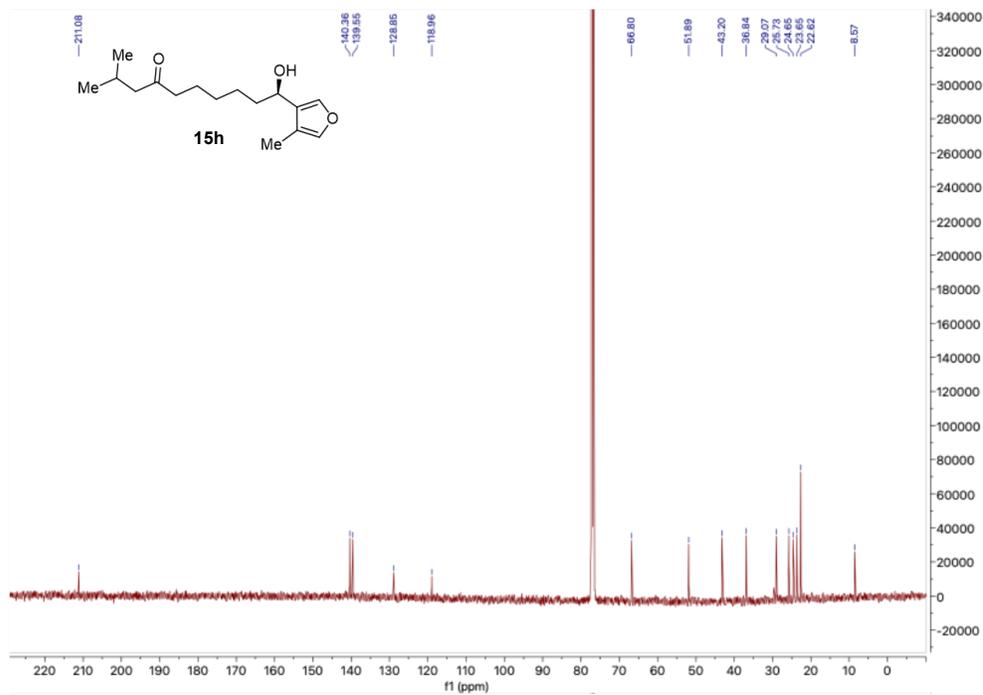
<sup>13</sup>C (126 MHz) of **15g**



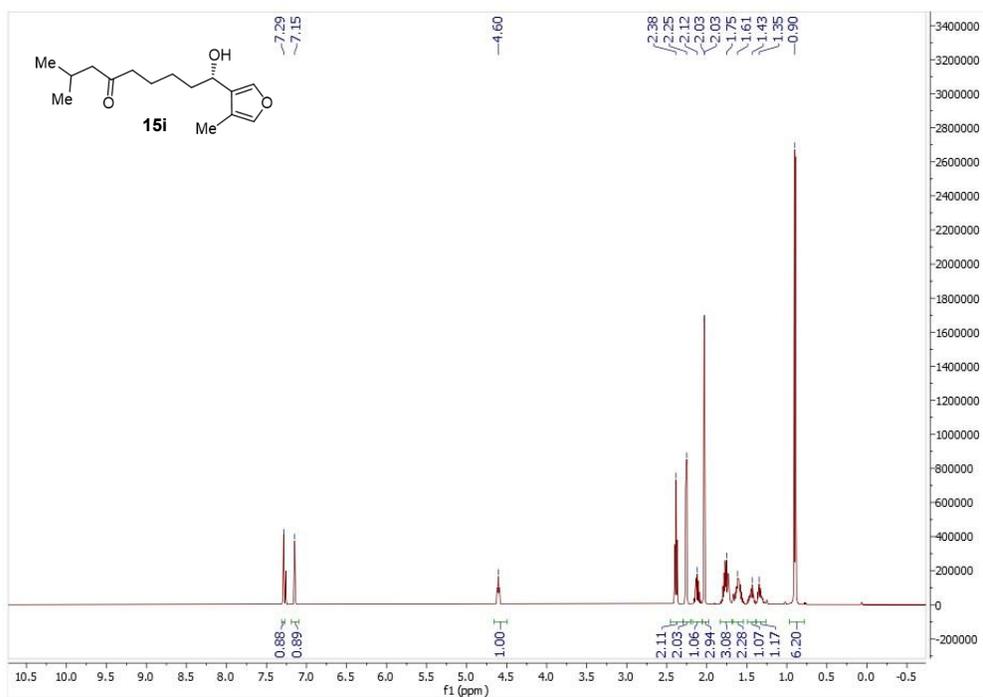
<sup>1</sup>H (500 MHz) of **15h**



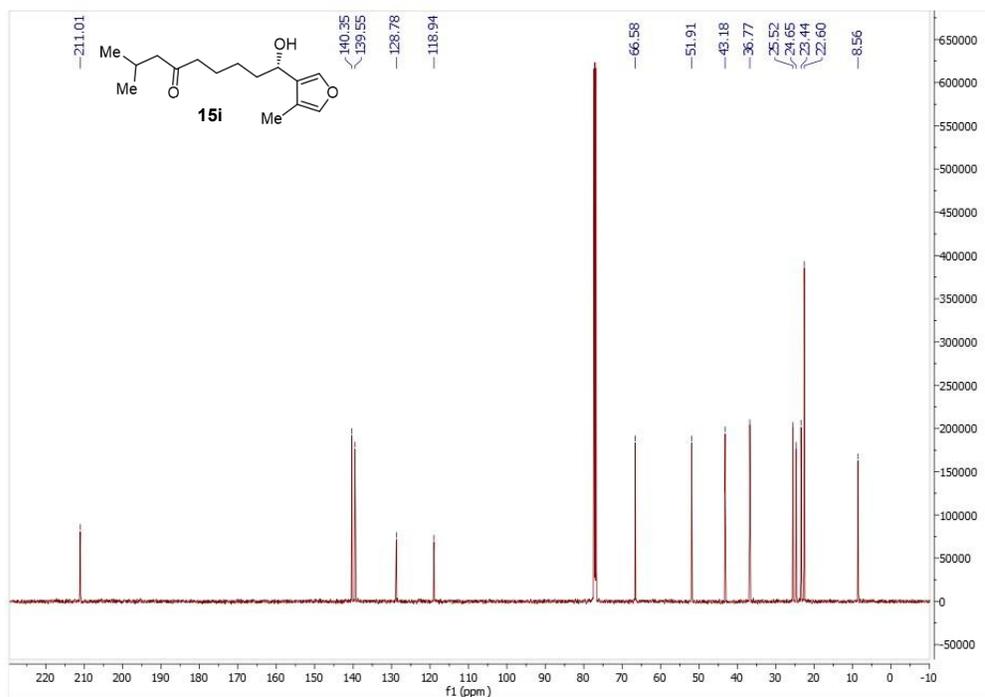
$^{13}\text{C}$  (126 MHz) of **15h**



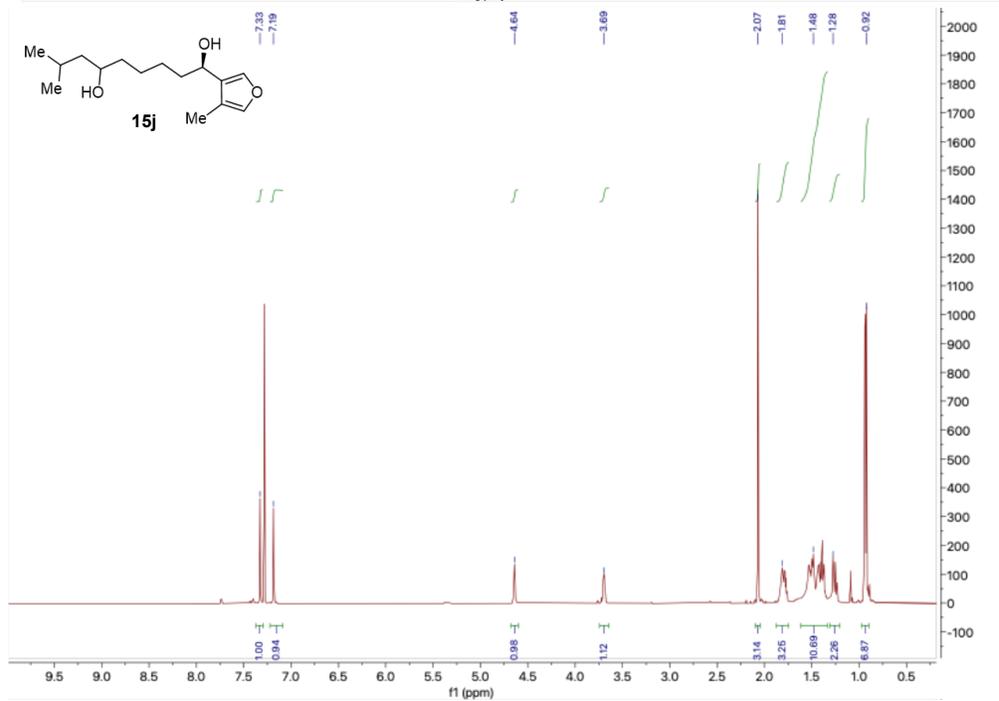
$^1\text{H}$  (500 MHz) of **15i**



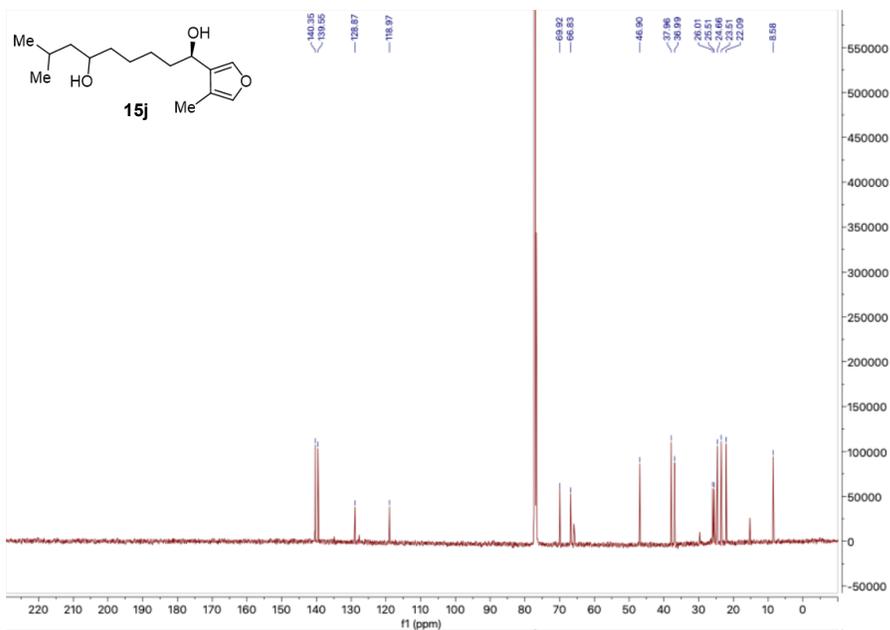
$^{13}\text{C}$  (126 MHz) of **15i**



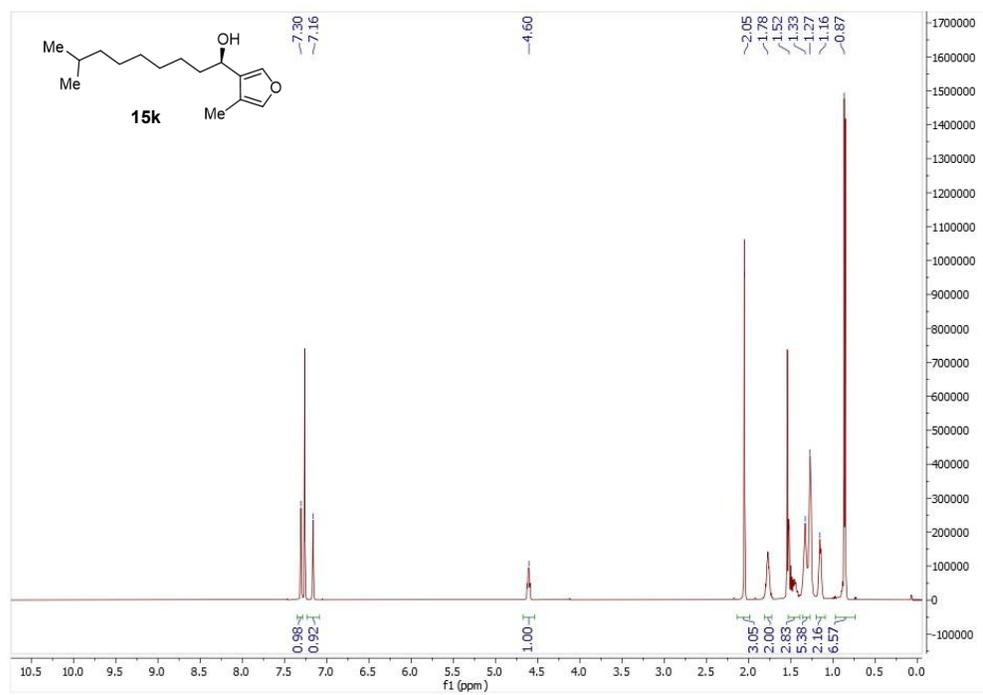
$^1\text{H}$  (500 MHz) of **15j**



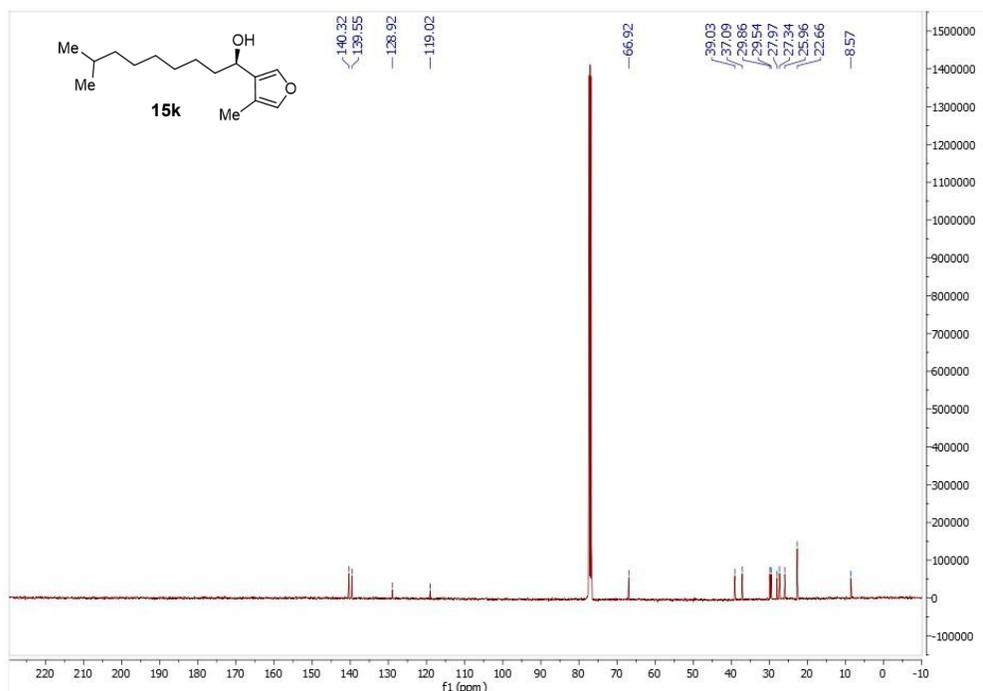
<sup>13</sup>C (126 MHz) of **15j**



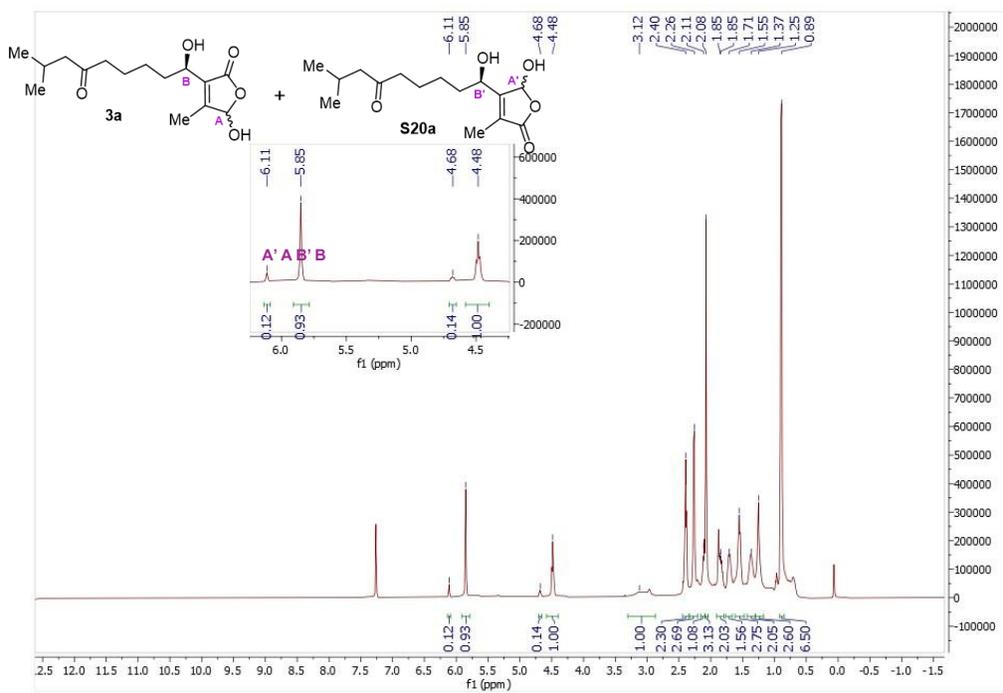
<sup>1</sup>H (500 MHz) of **15k**



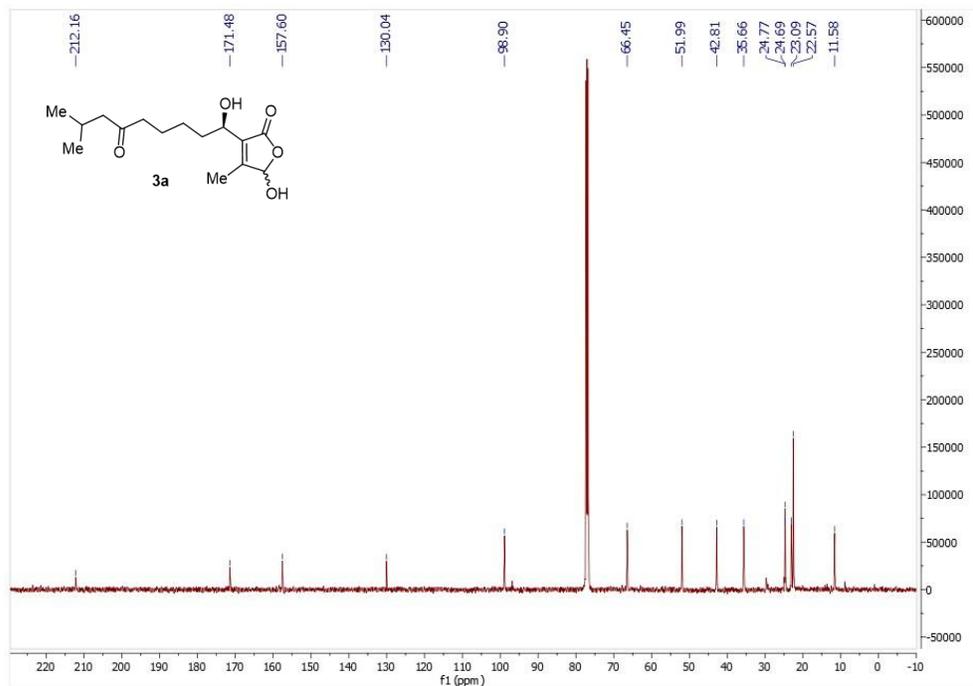
$^{13}\text{C}$  (126 MHz) of **15k**



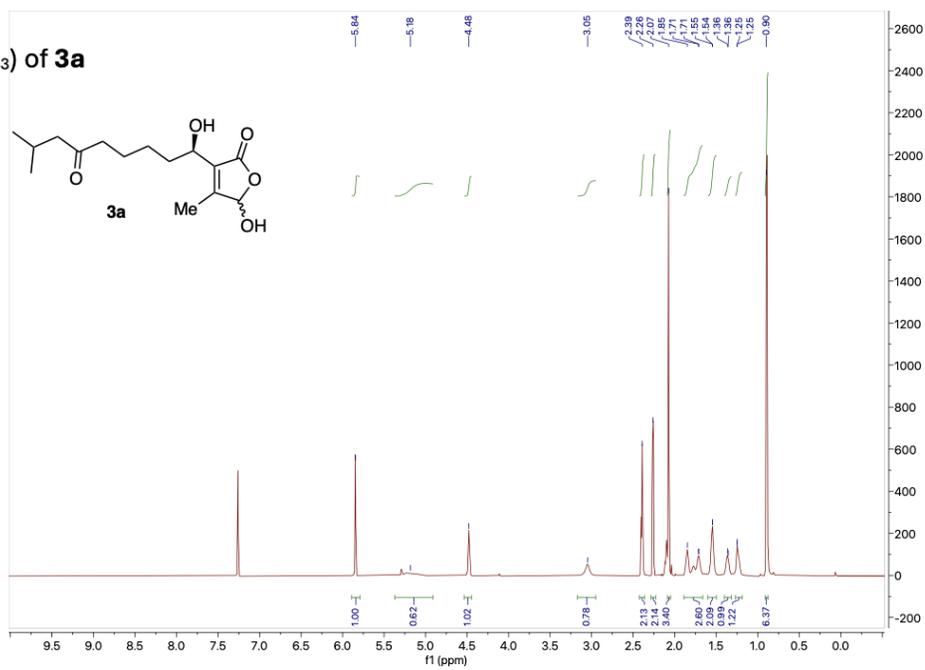
$^1\text{H}$  (500 MHz) of **3a**



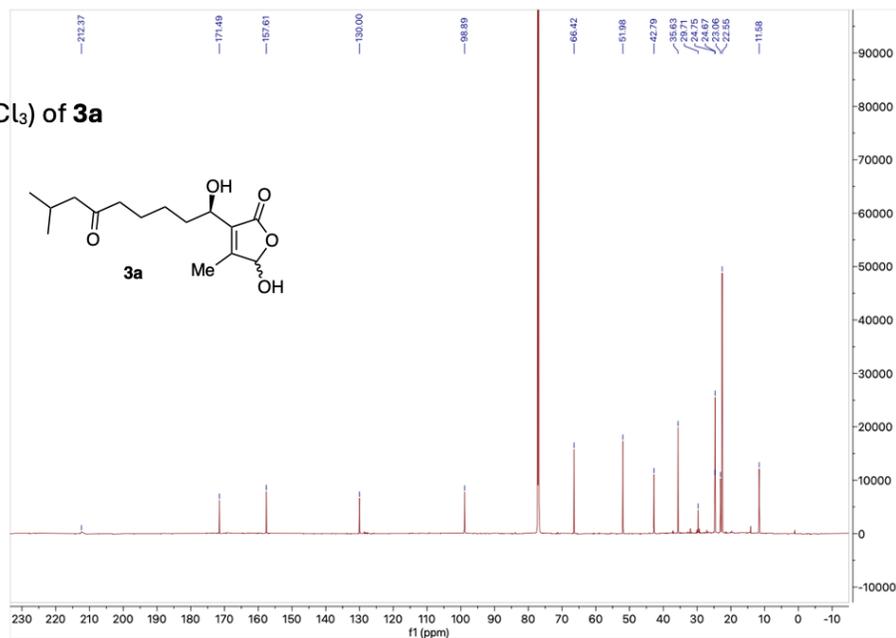
$^{13}\text{C}$  (126 MHz) of **3a**



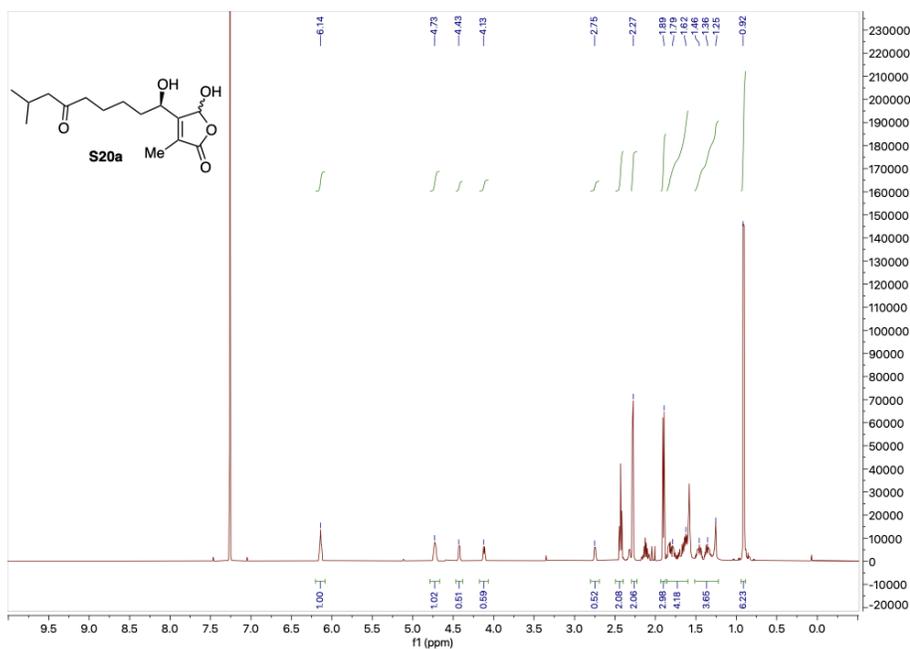
$^1\text{H}$  NMR (800 MHz,  $\text{CDCl}_3$ ) of **3a**



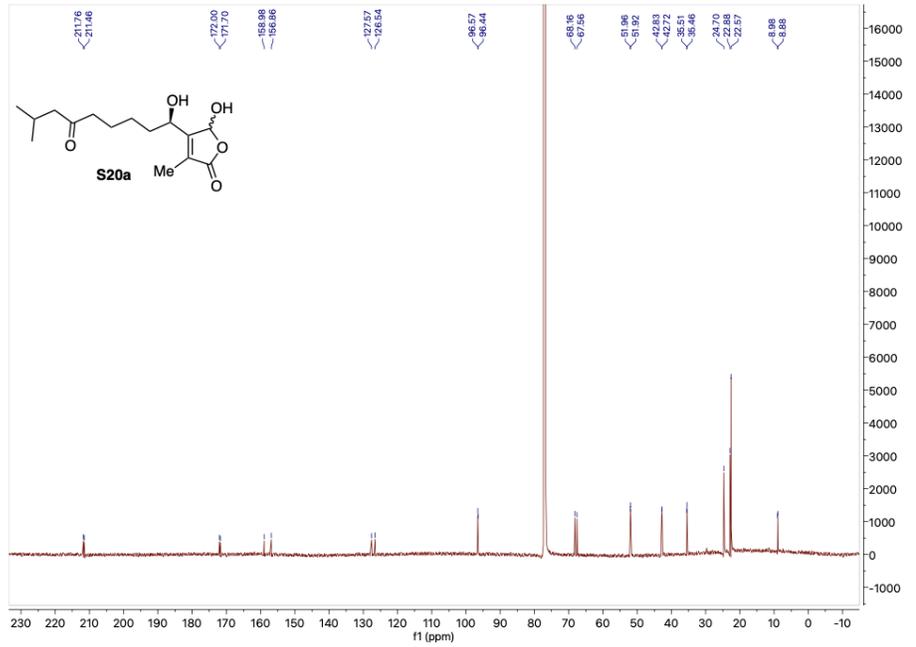
<sup>13</sup>C NMR (201 MHz, CDCl<sub>3</sub>) of **3a**



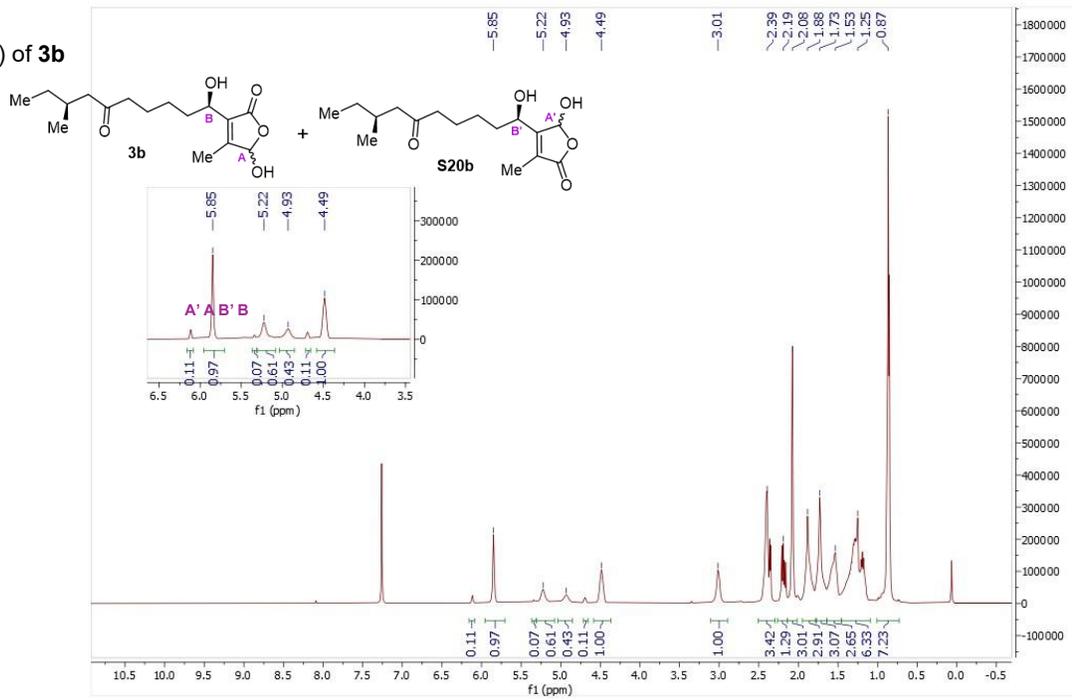
<sup>1</sup>H (500 MHz) of **S20a**



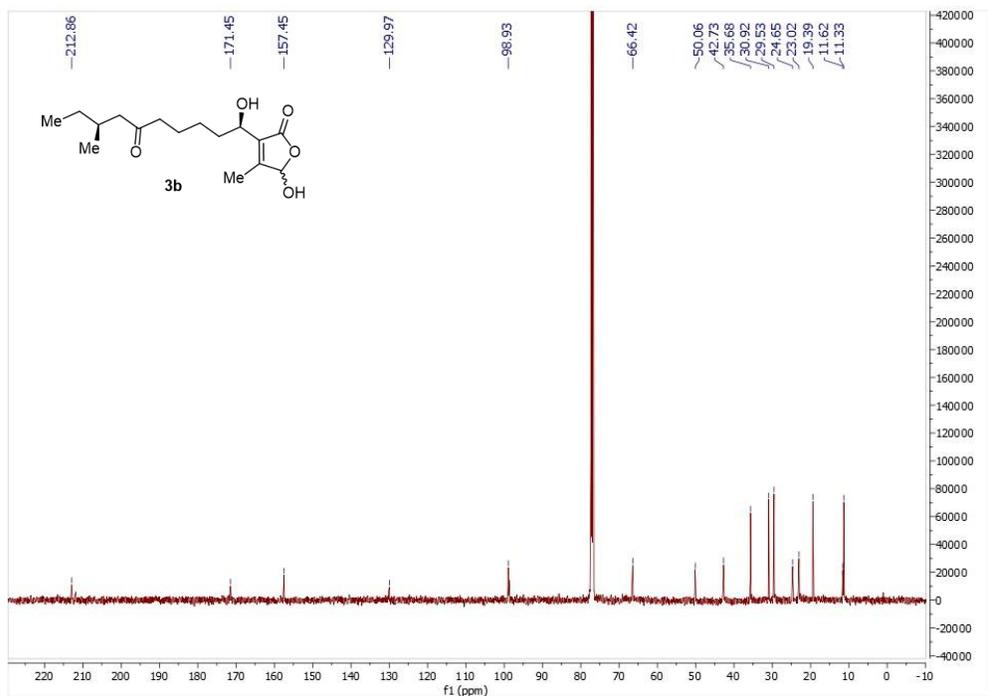
<sup>13</sup>C (126 MHz) of **S20a**



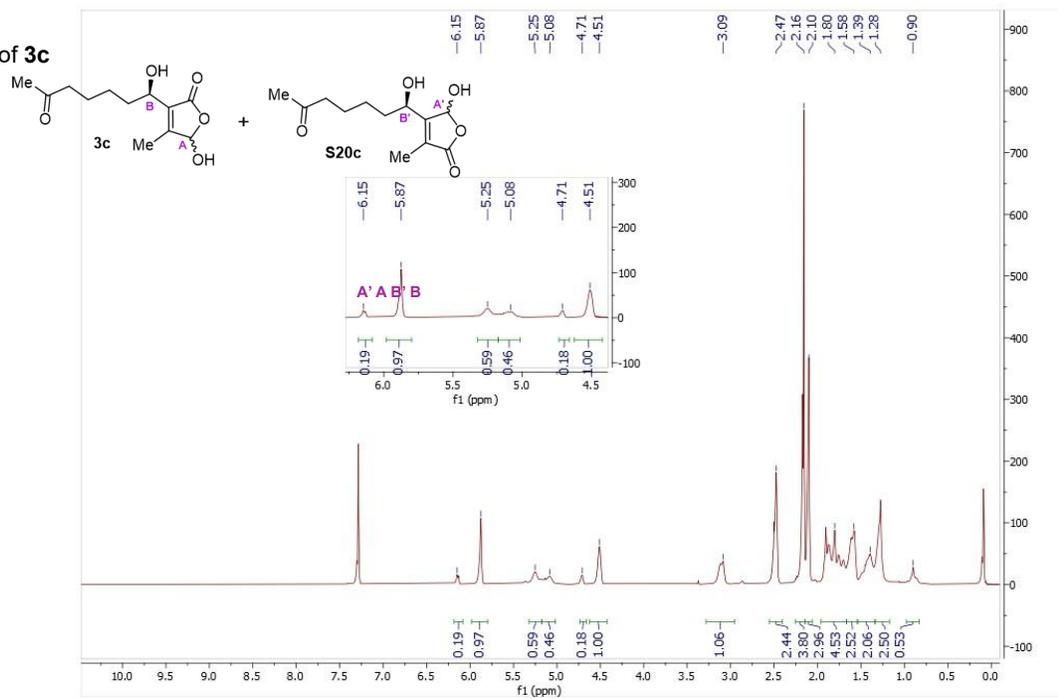
<sup>1</sup>H (500 MHz) of **3b**



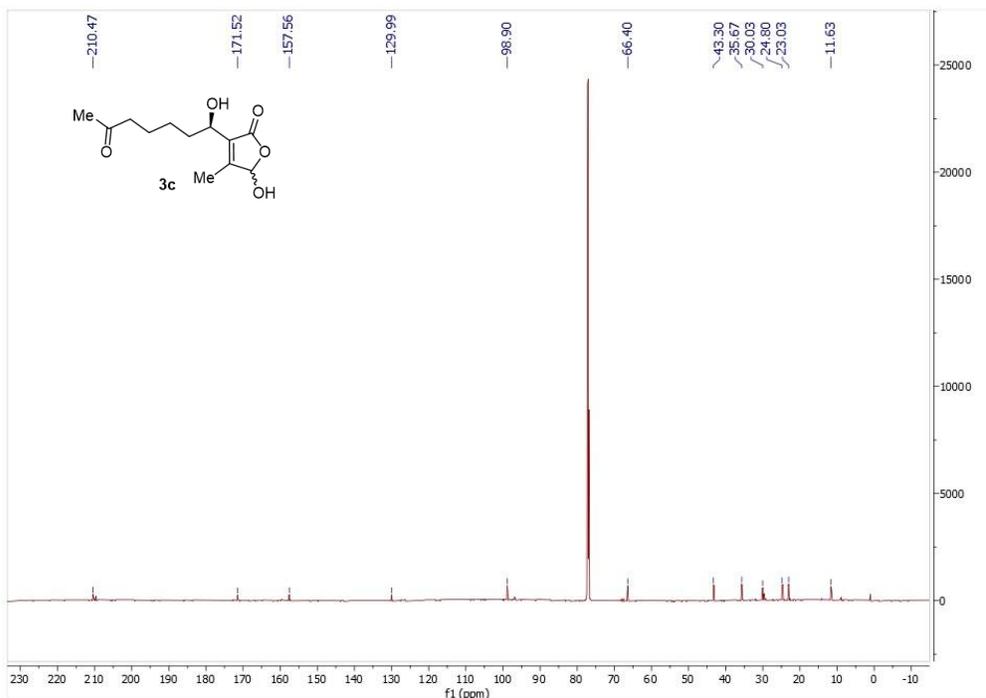
$^{13}\text{C}$  (126 MHz) of **3b**



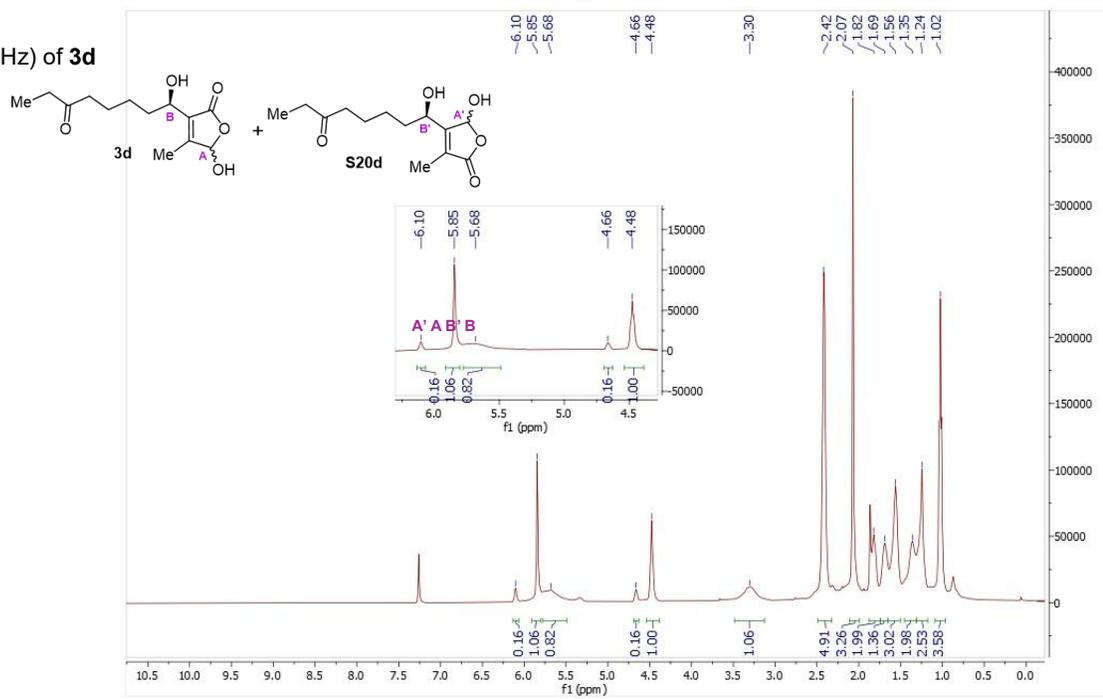
$^1\text{H}$  (500 MHz) of **3c**



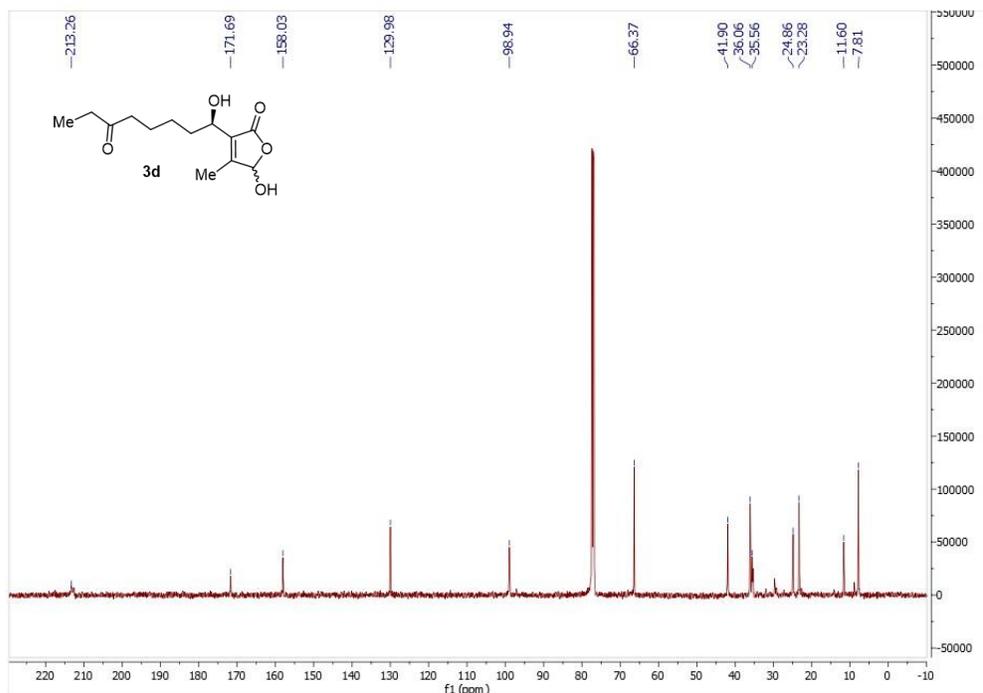
$^{13}\text{C}$  (126 MHz) of **3c**



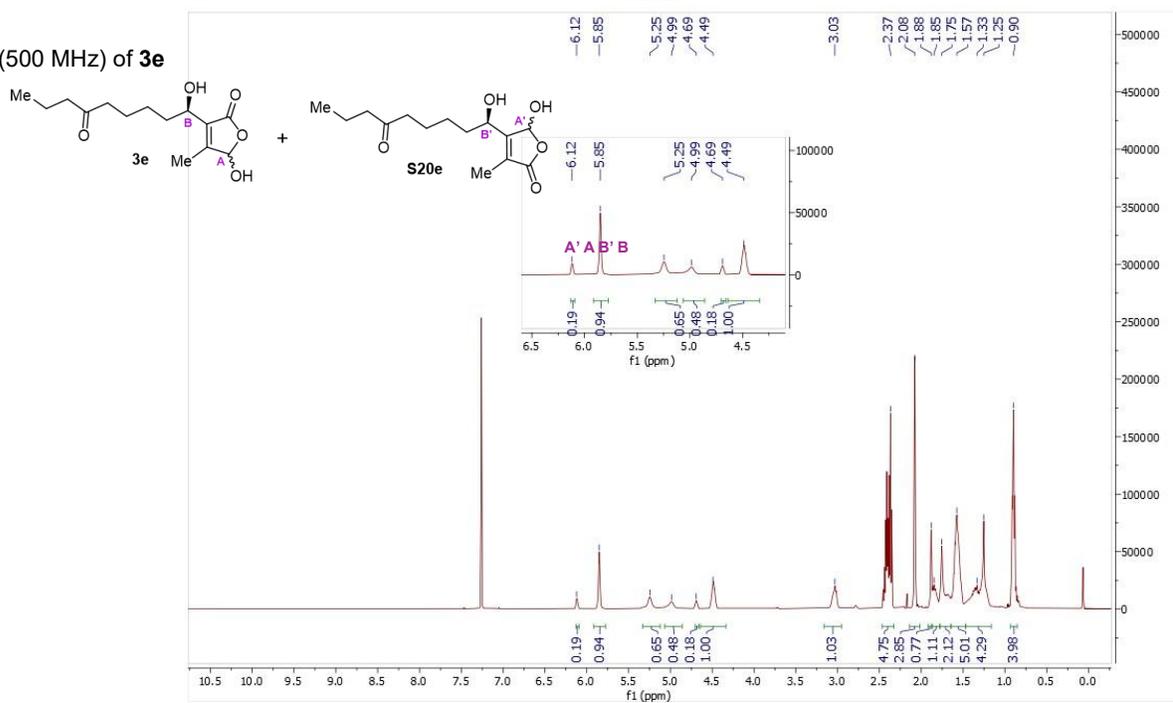
$^1\text{H}$  (500 MHz) of **3d**



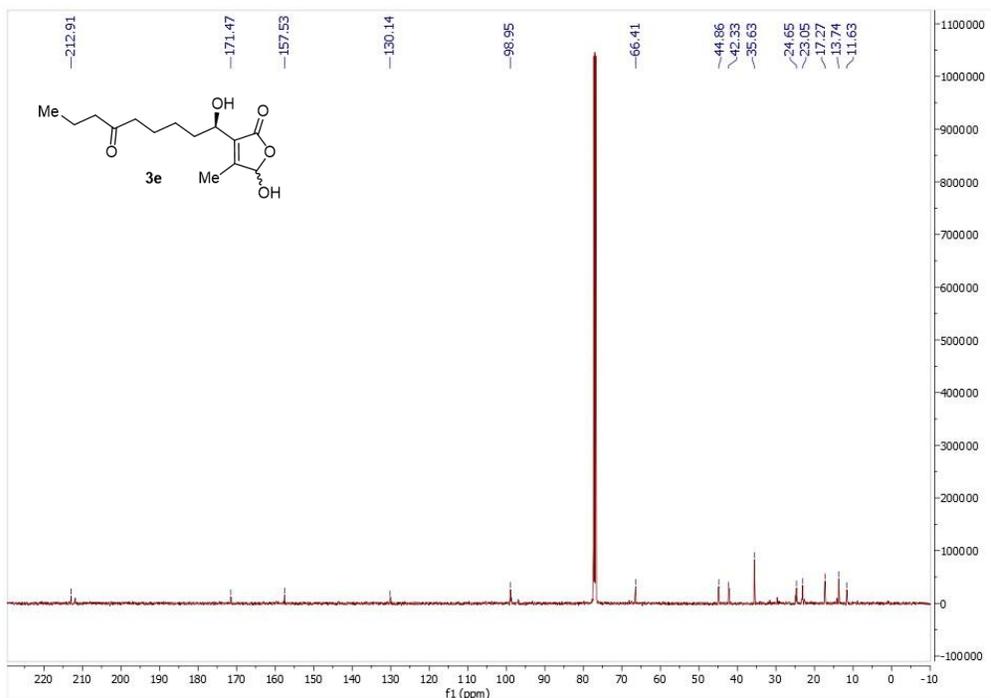
<sup>13</sup>C (126 MHz) of **3d**



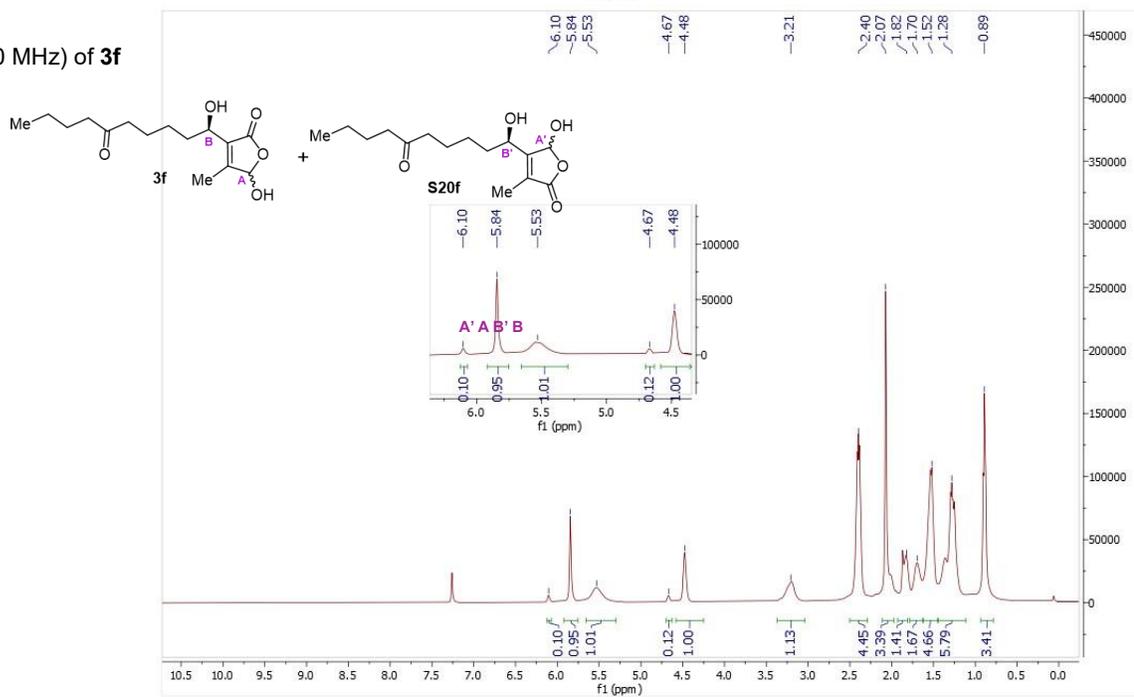
<sup>1</sup>H (500 MHz) of **3e**



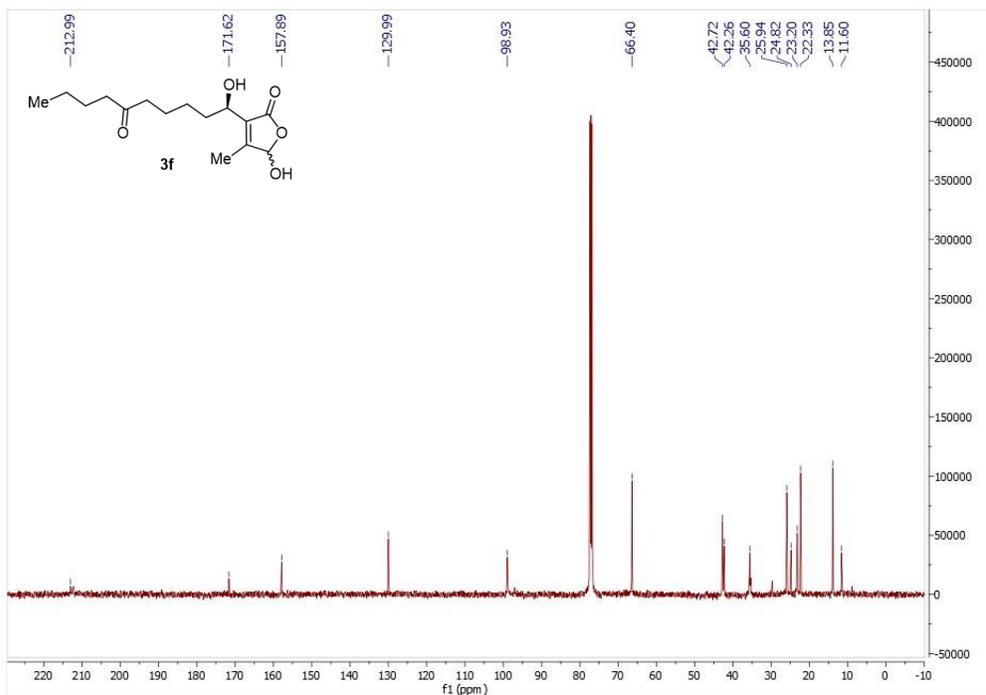
$^{13}\text{C}$  (126 MHz) of **3e**



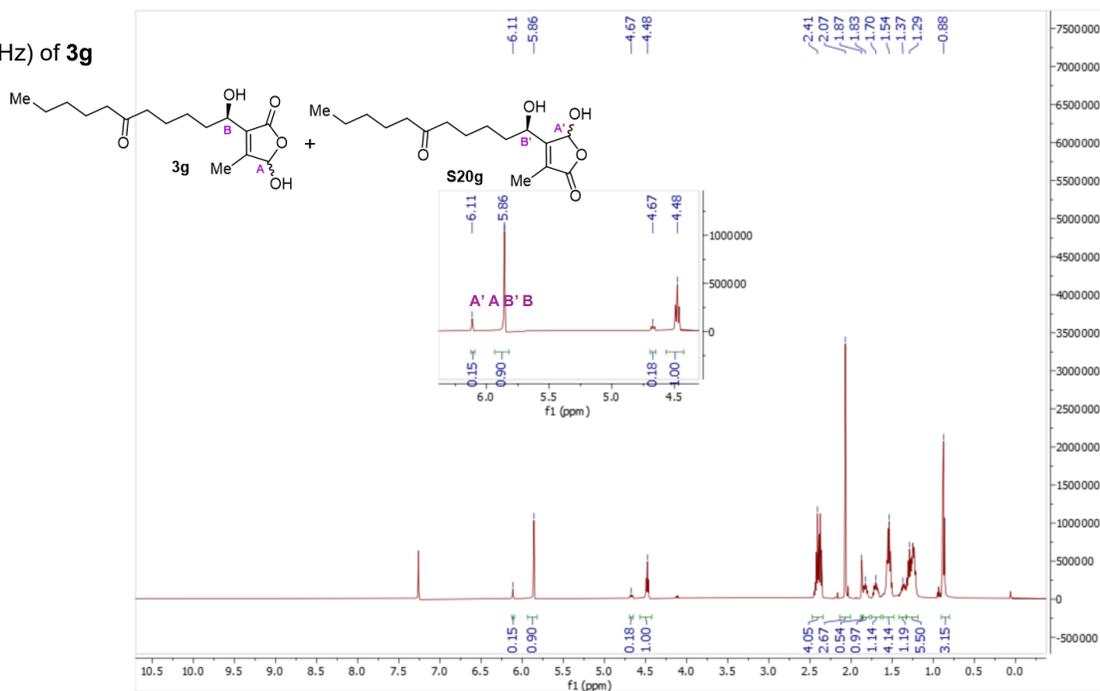
$^1\text{H}$  (500 MHz) of **3f**



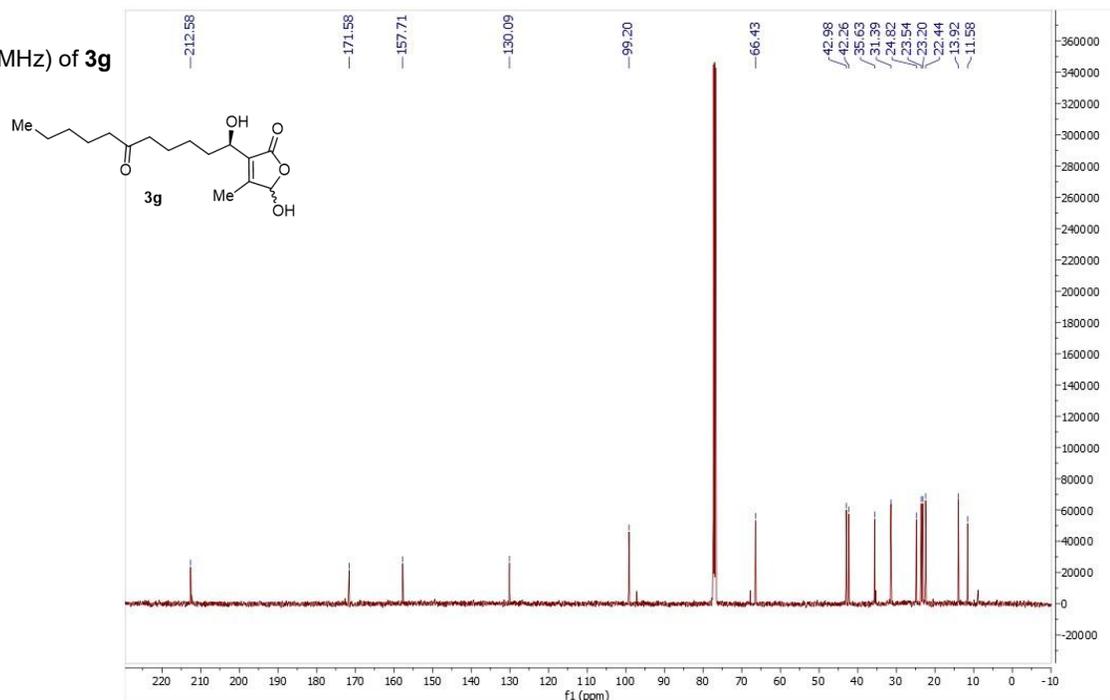
$^{13}\text{C}$  (126 MHz) of **3f**



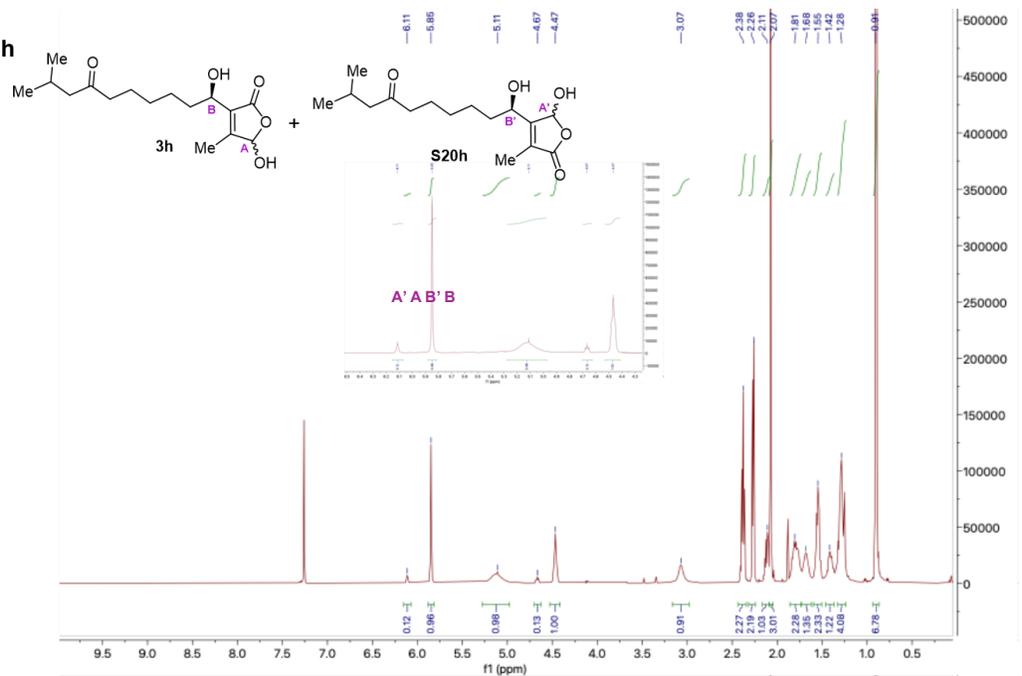
$^1\text{H}$  (500 MHz) of **3g**



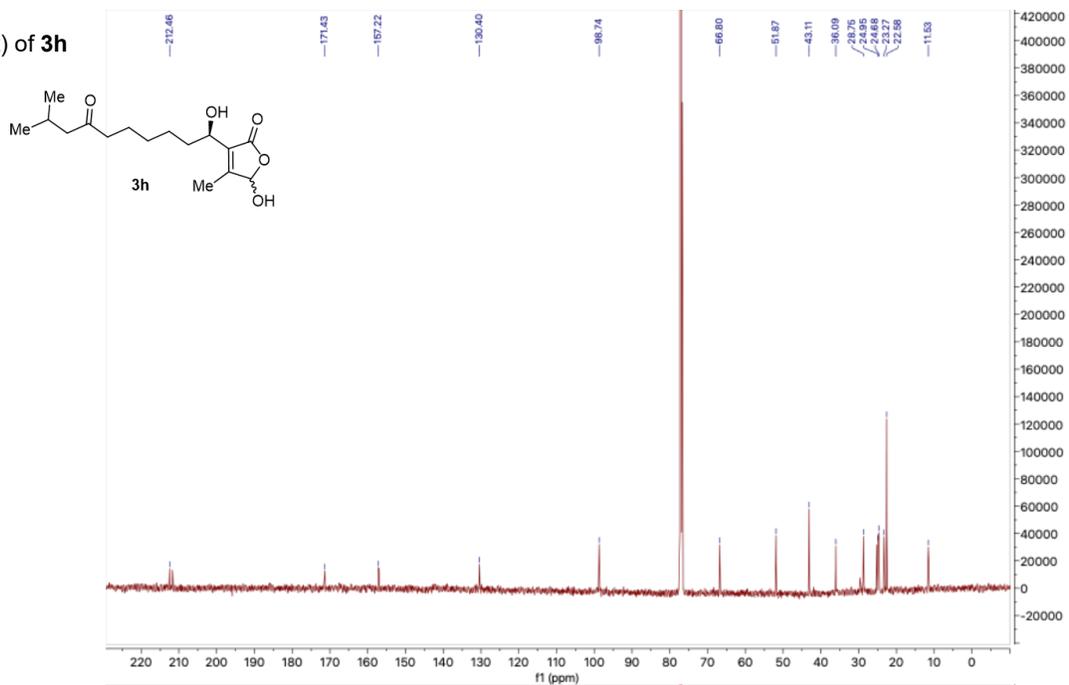
<sup>13</sup>C (126 MHz) of **3g**



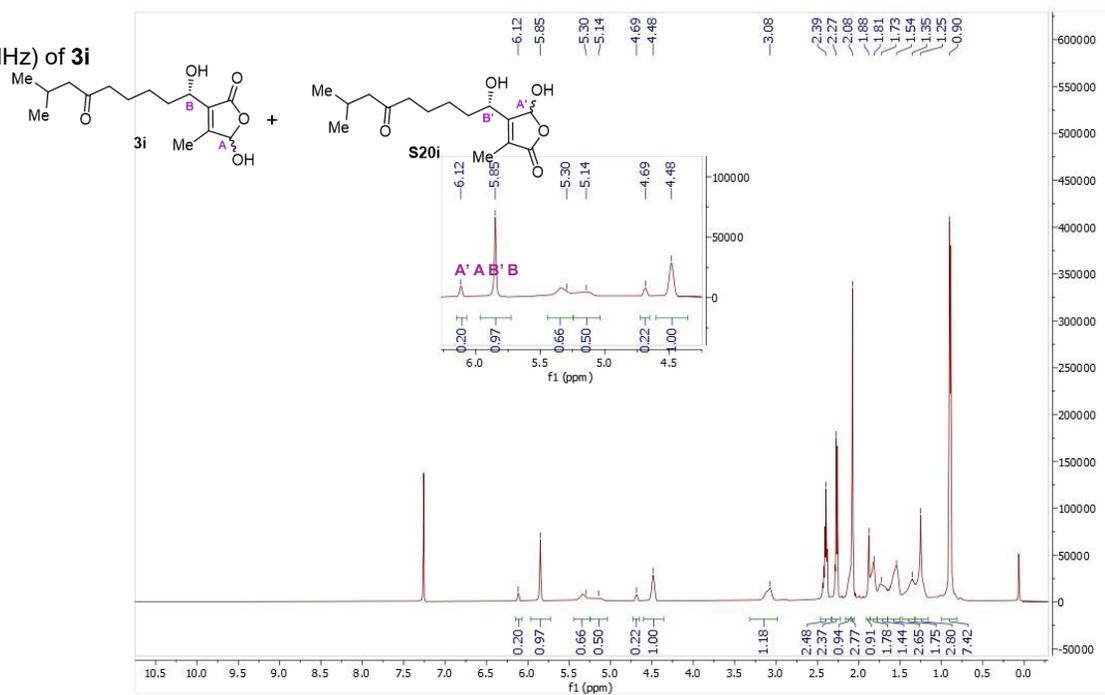
<sup>1</sup>H (500 MHz) of **3h**



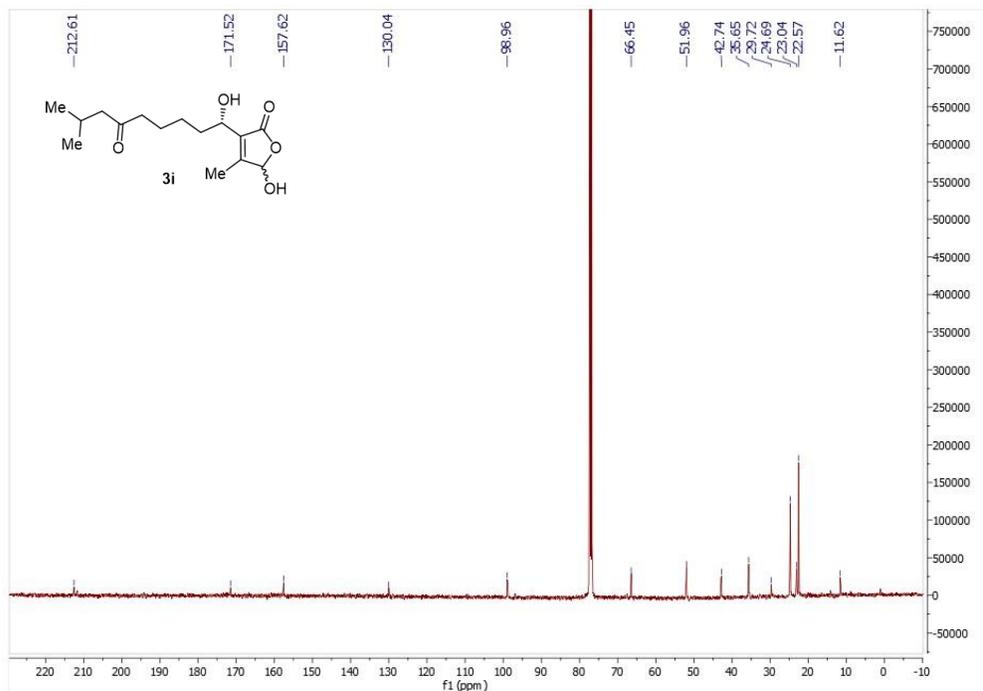
<sup>13</sup>C (126 MHz) of **3h**



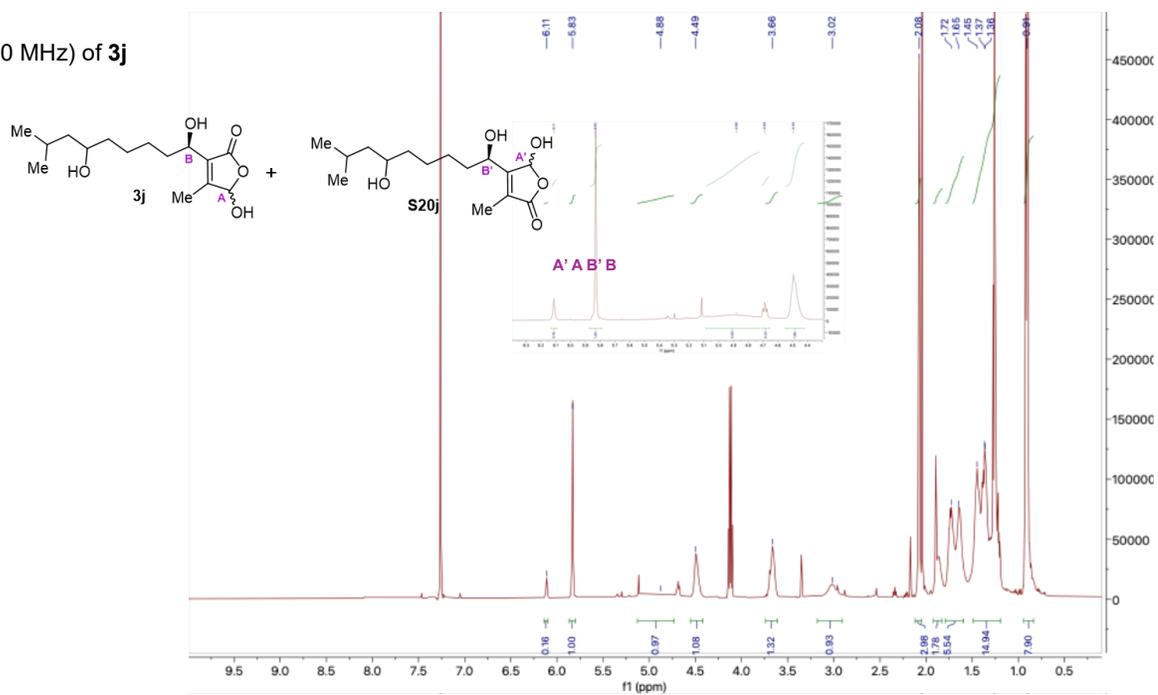
<sup>1</sup>H (500 MHz) of **3i**



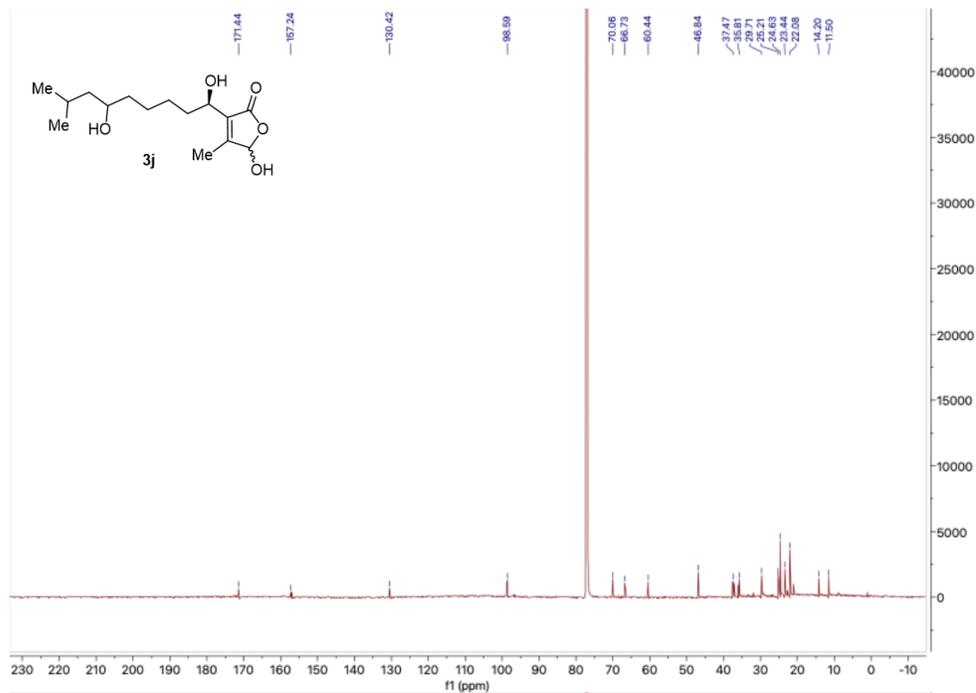
$^{13}\text{C}$  (126 MHz) of **3i**



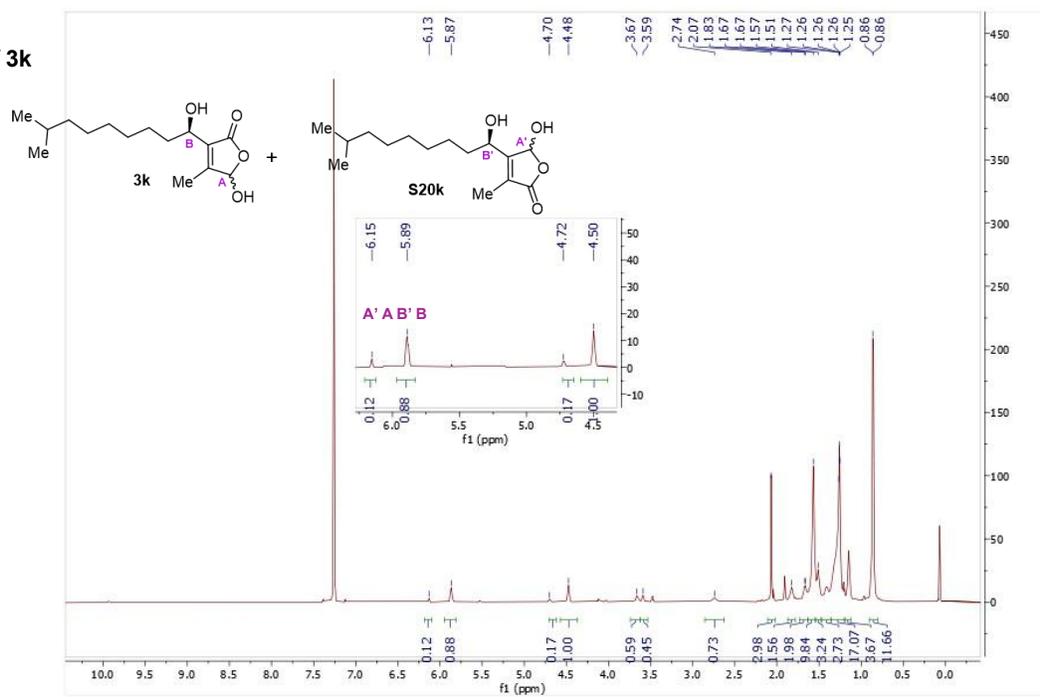
$^1\text{H}$  (500 MHz) of **3j**



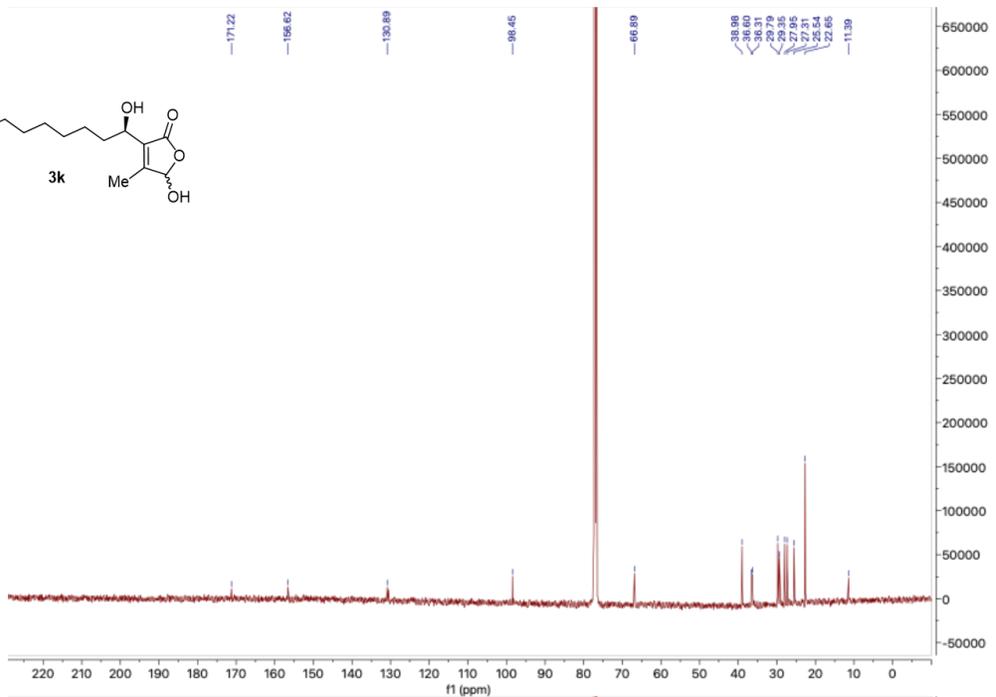
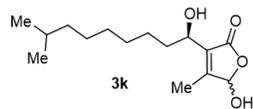
$^{13}\text{C}$  (126 MHz) of **3j**



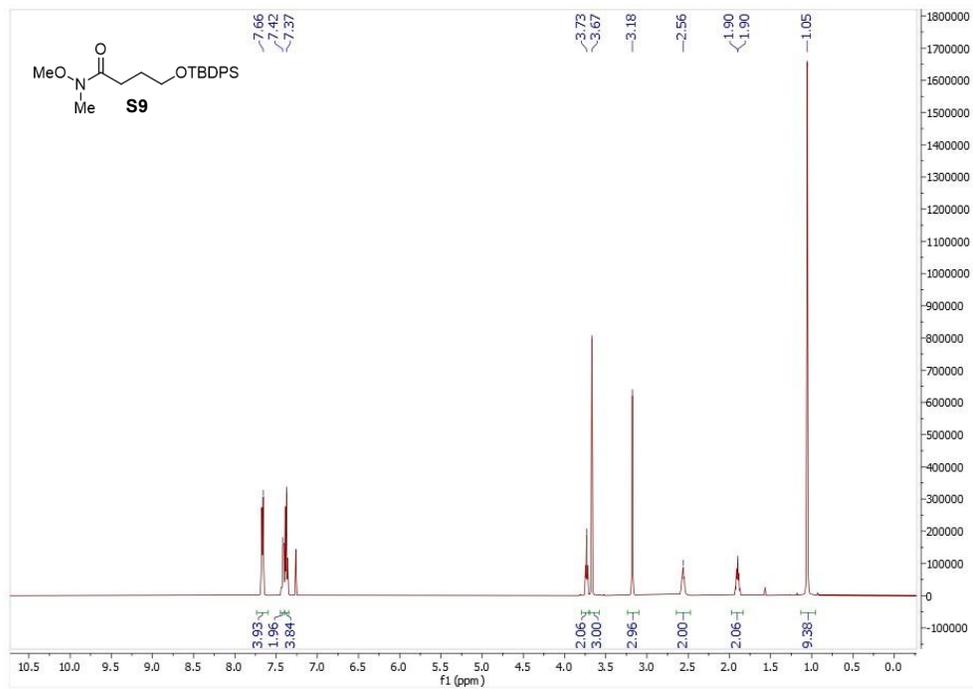
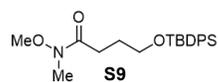
$^1\text{H}$  (500 MHz) of **3k**



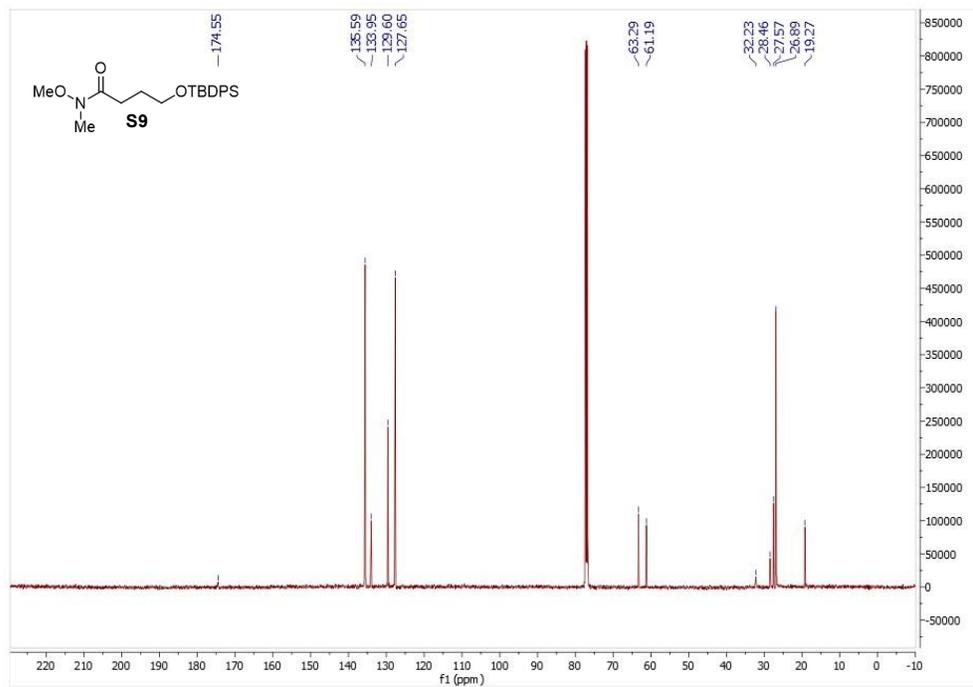
<sup>13</sup>C (126 MHz) of **3k**



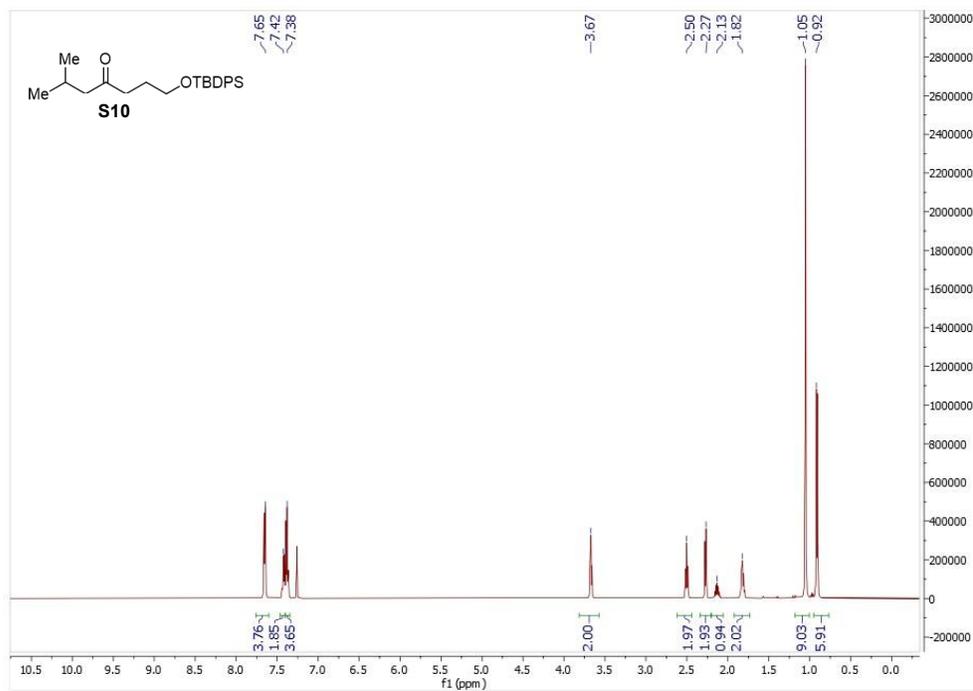
<sup>1</sup>H (500 MHz) of **S9**



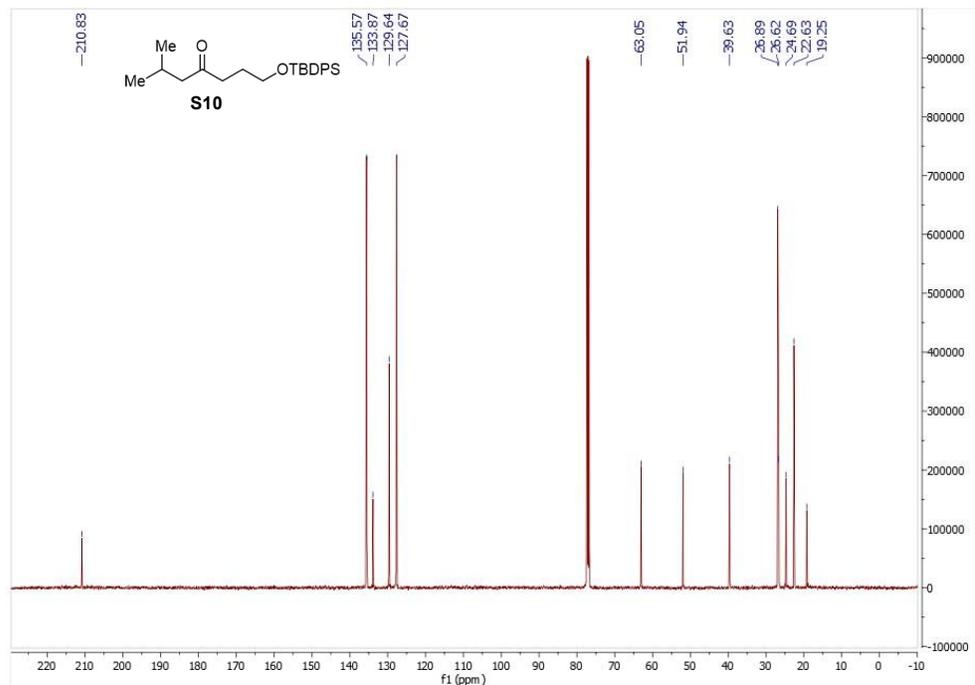
<sup>13</sup>C (126 MHz) of **S9**



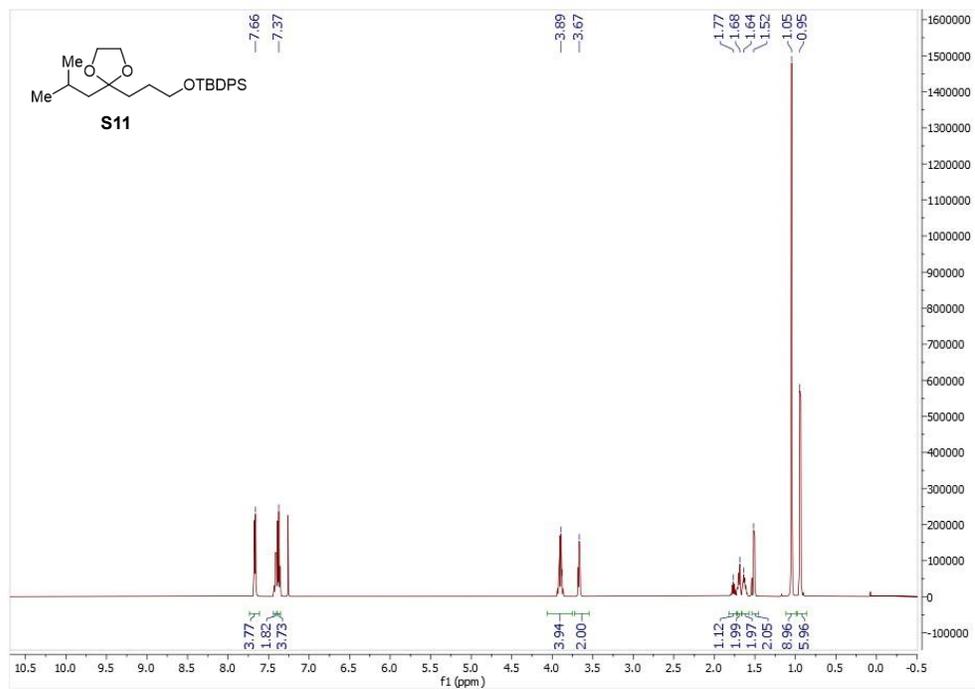
<sup>1</sup>H (500 MHz) of **S10**



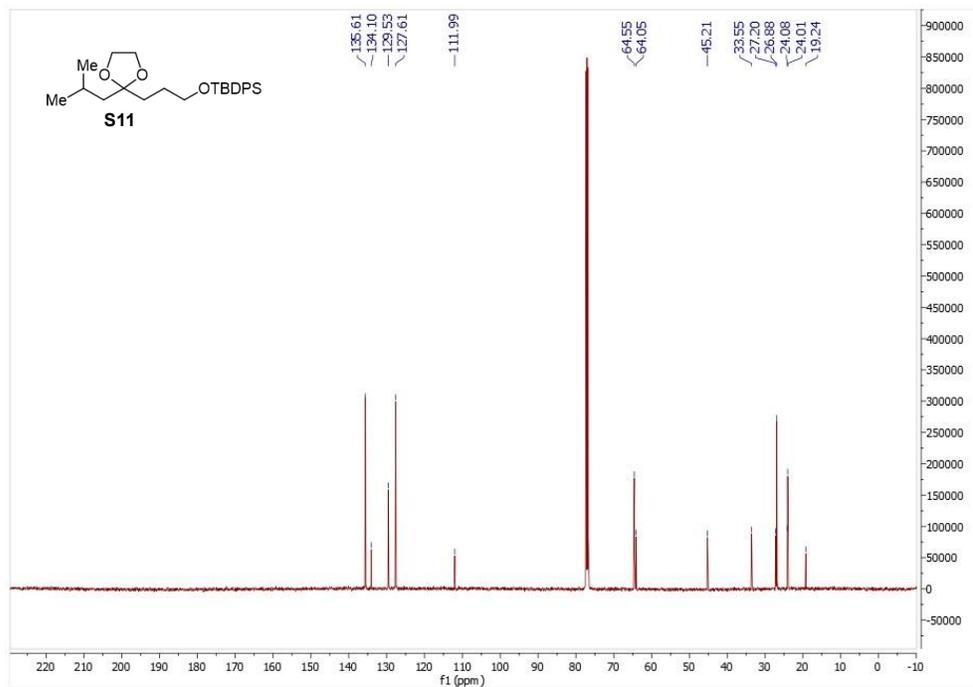
<sup>13</sup>C (126 MHz) of **S10**



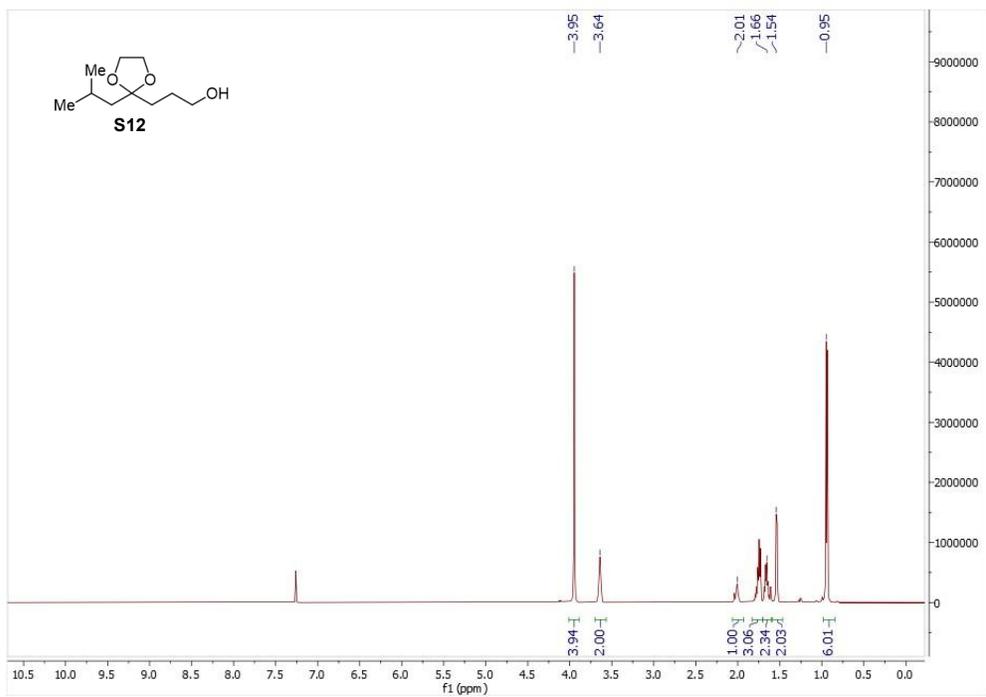
<sup>1</sup>H (500 MHz) of **S11**



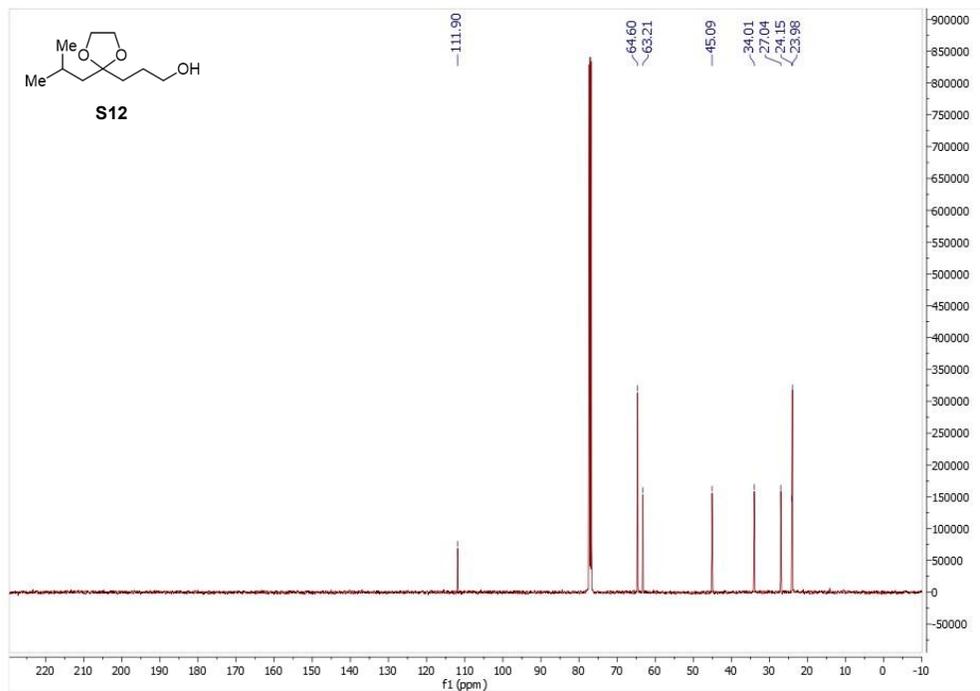
<sup>13</sup>C (126 MHz) of **S11**



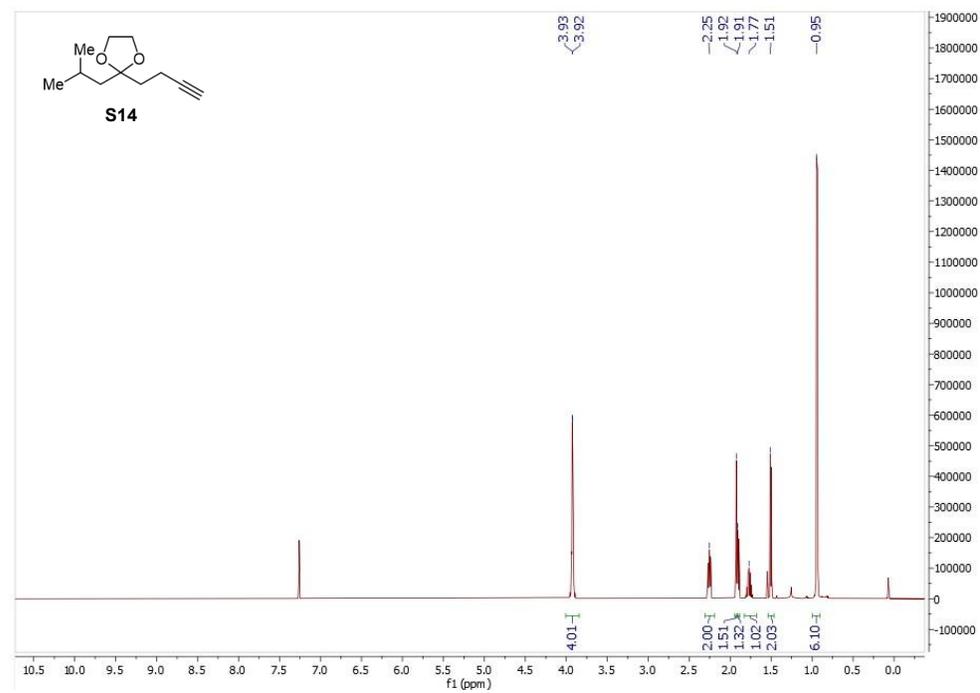
<sup>1</sup>H (500 MHz) of **S12**



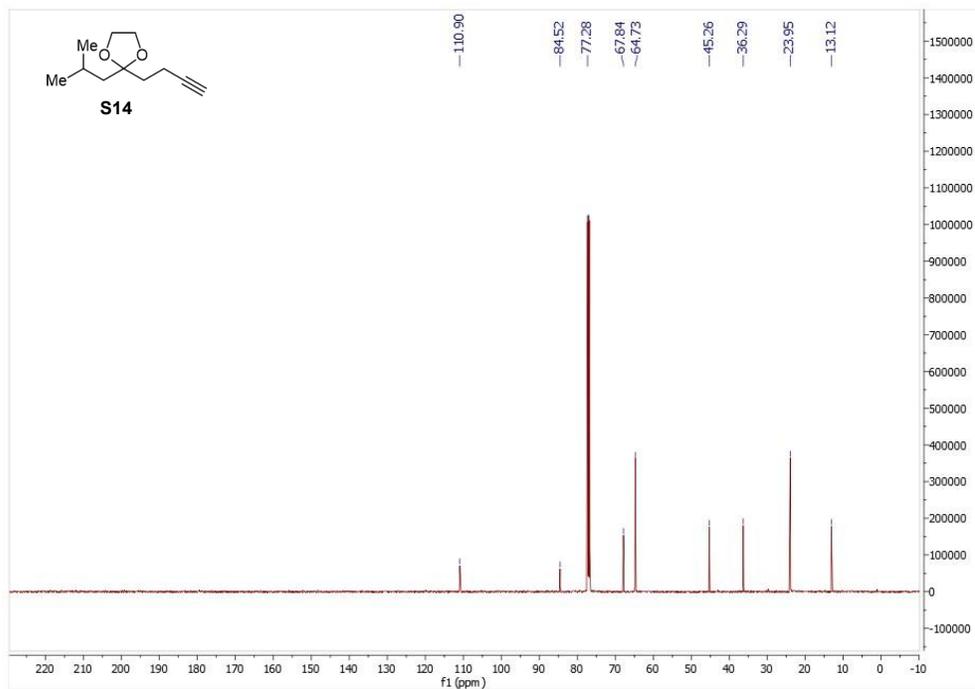
<sup>13</sup>C (126 MHz) of **S12**



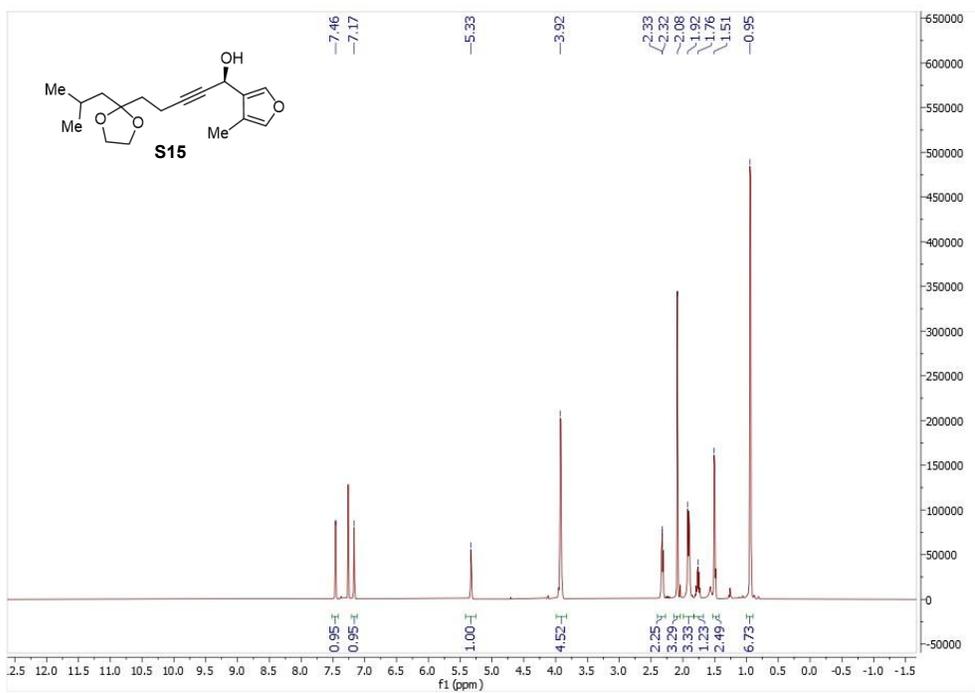
<sup>1</sup>H (500 MHz) of **S14**



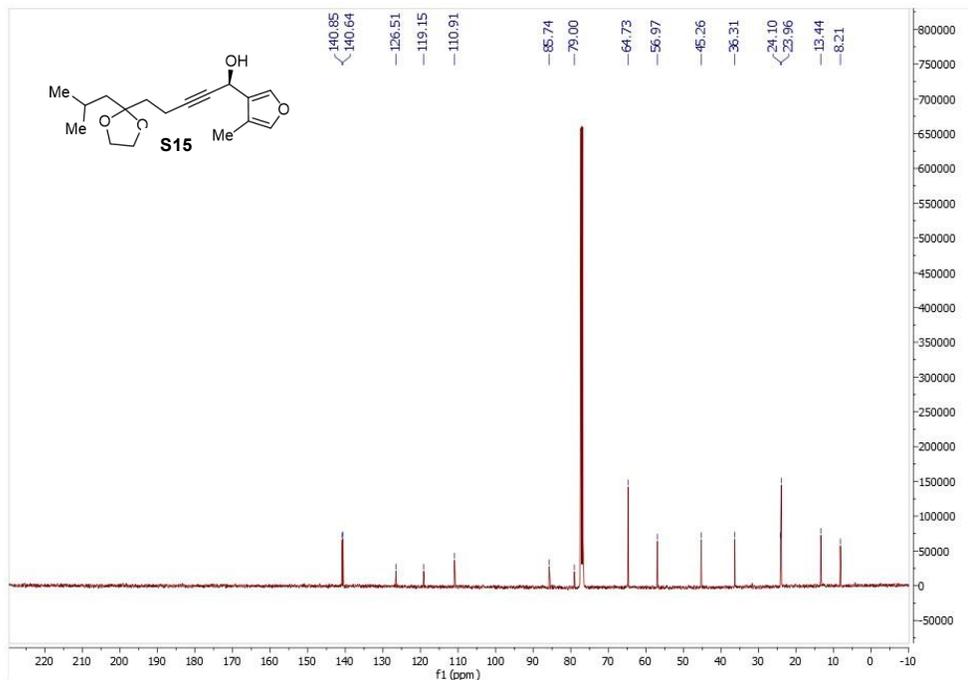
$^{13}\text{C}$  (126 MHz) of **S14**



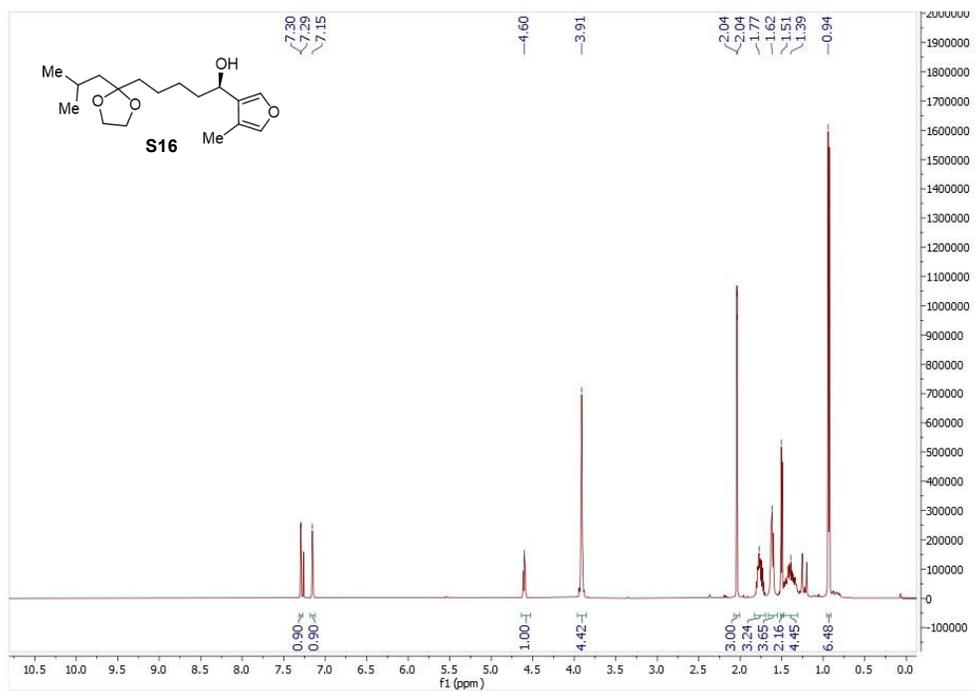
$^1\text{H}$  (500 MHz) of **S15**



<sup>13</sup>C (126 MHz) of **S15**



<sup>1</sup>H (500 MHz) of **S16**



$^{13}\text{C}$  (126 MHz) of **S16**

