Supporting Information for

Singlet oxygen initiated cascade transformation of a simple difuran into the key ABC motif of the pectenotoxins

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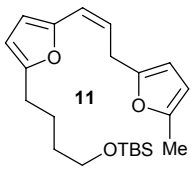
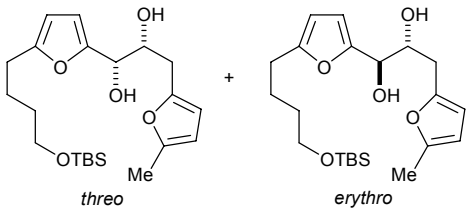
Part A: Experimental procedures



To a mixture of the phosphonium salt **10** (chewing gum-like material that is very difficult to handle, 1.15 g, 2.3 mmol) in anhydrous THF (8 mL) at 0 °C, was added a solution of *n*-BuLi (1.64 mL, 1.4 M in hexane, 2.3 mmol). The reaction mixture was warmed to room temperature and stirred for 1.5 h after which time all the gummy material had been consumed. The red colored solution was re-cooled to 0 °C and a solution of the aldehyde **13** (0.68 g, 2.3 mmol) in anhydrous THF (8 mL) was added. The reaction was warmed to room temperature and stirred for 2 h. The reaction mixture was concentrated to half its previous volume and then diluted with petroleum ether (50 mL). The $Ph_3P{=}O$ that was precipitated was removed by filtration and the remaining solution was concentrated in *vacuo* and purified by column chromatography (silica gel, petroleum ether:EtOAc = 1:0 → 50:1) to afford olefin **11** (*cis*:*trans* = 2:1, 0.63 g, 73 %).

cis-**11:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.23 (td, J_1 = 11.6 Hz, J_2 = 1.8 Hz, 1H), 6.20 (d, J = 3.0 Hz, 1H), 6.00 (d, J = 3.0 Hz, 1H), 5.93 (d, J = 3.0 Hz, 1H), 5.87 (d, J = 2.7 Hz, 1H), 5.62 (td, J_1 = 11.6 Hz, J_2 = 7.1 Hz, 1H), 3.79 (brd, J = 7.1 Hz, 2H), 3.64 (t, J = 6.3 Hz, 2H), 2.66 (t, J = 7.5 Hz, 2H), 2.27 (s, 3H), 1.71 (m, 2H), 1.59 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 152.6, 151.2, 150.5, 123.9, 118.6, 110.5, 106.5, 106.0, 105.6, 62.8, 32.2, 28.4, 27.9, 25.9 (3C), 24.3, 18.3, 13.5, -5.3 (2C) ppm; HRMS (TOFMS ES+): calcd for $C_{22}H_{34}O_3NaSi$: 397.2175 $[M + Na]^+$; found: 397.2169.



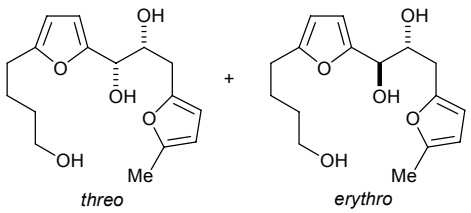
threo *erythro*

To a solution of olefin **11** (*cis*:*trans* = 2:1, 248 mg, 0.66 mmol) in *t*-BuOH:H_2O (4 mL:4 mL), at 0 °C, were added methanosulfonyl amide (MSA, 63 mg, 0.66 mmol) and AD-mix-β (three portions of 700 mg, added every 12 h). The reaction mixture was allowed to warm to room temperature and was stirred for a total of 60 h. EtOAc (5 mL) was then added, followed by Na_2SO_3 (3.5 g), and the stirring was continue for 1 h until compete separation of the two phases was seen. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 4 mL). The combined organic phases were dried with Na_2SO_4 and concentrated in *vacuo*. Flash column chromatography (silica gel, petroleum ether:EtOAc = 20:1 → 5:1) afforded 166 mg of the corresponding diol (62 %, *erythro*/*threo* = 1:2.6), as well as 50 mg (20 %) of the starting olefin (exclusively *cis*).

When the recovered *cis*-**11** was resubjected to the same SAD conditions a 2.5:1 mixture of *erythro*/*threo* 1,2-diols was formed.

Threo diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.23 (d, *J* = 3.3 Hz, 1H), 5.97 (d, *J* = 2.7 Hz, 1H), 5.94 (d, *J* = 3.0 Hz, 1H), 5.86 (d, *J* = 2.1 Hz, 1H), 4.49 (d, *J* = 6.0 Hz, 1H), 4.18 (m, 1H), 3.62 (t, *J* = 6.3 Hz, 2H), 2.76 (m, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 1.68 (m, 2H), 1.57 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 151.6, 151.1, 150.0, 108.5, 108.0, 106.1, 105.5, 72.0, 70.3, 62.8, 32.2, 32.0, 27.7, 25.9 (3C), 24.2, 18.3, 13.5, -5.3 (2C) ppm; HRMS (TOFMS ES+): calcd for $C_{22}H_{36}O_5NaSi$: 431.2230 $[M + Na]^+$; found: 431.2244.

Erythro diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.26 (d, *J* = 3.3 Hz, 1H), 5.99 (d, *J* = 3.0 Hz, 1H), 5.96 (d, *J* = 3.3 Hz, 1H), 5.87 (d, *J* = 2.1 Hz, 1H), 4.65 (d, *J* = 4.8 Hz, 1H), 4.19 (m, 1H), 3.62 (t, *J* = 6.3 Hz, 2H), 2.78 (m, 2H), 2.63 (t, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 1.68 (m, 2H), 1.57 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 151.3 (2C), 150.2, 108.7, 108.0, 106.1, 105.5, 72.1, 70.3, 62.8, 32.2, 31.5, 27.7, 25.9 (3C), 24.2, 18.3, 13.5, -5.3 (2C) ppm; HRMS (TOFMS ES+): calcd for $C_{22}H_{36}O_5NaSi$: 431.2230 $[M + Na]^+$; found: 431.2244.



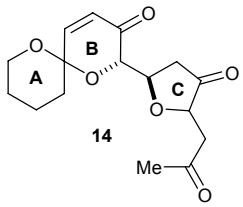
threo *erythro*

To a solution of 1,2-diol prepared above (*erythro*/*threo* = 1:2.6, 164 mg, 0.40 mmol) in anhydrous THF (8 mL), at 0 °C, TBAF (480 μL of 1.0 M solution in THF, 0.48 mmol) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 5 h after which it was partitioned between EtOAc (10 mL) and H_2O (10 mL). The layers were separated and the aqueous

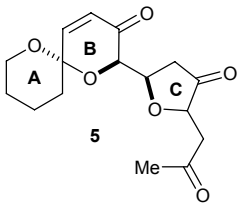
phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in *vacuo*. The residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1 → 1:2) to afford difuran-triol **6** (105 mg, 89 %, *erythro*/*threo* = 1:2.6). When the same reaction conditions were applied to a 2.5:1 *erythro/threo* mixture of the 1,2-diol, a 2.5:1 *erythro/threo* mixture of difuran-triol **6** was isolated.

Threo **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.24 (d, *J* = 3.0 Hz, 1H), 5.98 (d, *J* = 3.0 Hz, 1H), 5.95 (d, *J* = 3.3 Hz, 1H), 5.87 (d, *J* = 2.7 Hz, 1H), 4.50 (d, *J* = 6.0 Hz, 1H), 4.18 (m, 1H), 3.63 (t, *J* = 6.3 Hz, 2H), 2.76 (m, 2H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 1.71 (m, 2H), 1.61 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0, 151.7, 151.3, 150.0, 108.6, 108.1, 106.2, 105.7, 72.0, 70.3, 62.5, 32.1 (2C), 27.7, 24.1, 13.5 ppm; HRMS (TOFMS ES+): calcd for $C_{16}H_{22}O_5Na$: 317.1365 $[M + Na]^+$; found: 317.1361.

Erythro **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.26 (d, *J* = 3.0 Hz, 1H), 5.99 (d, *J* = 3.0 Hz, 1H), 5.97 (d, *J* = 3.3 Hz, 1H), 5.88 (d, *J* = 2.4 Hz, 1H), 4.64 (d, *J* = 4.8 Hz, 1H), 4.19 (m, 1H), 3.64 (t, *J* = 6.3 Hz, 2H), 2.79 (m, 2H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 2.04 (brs, -OH), 1.72 (m, 2H), 1.63 (m, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0, 151.4, 151.3, 150.1, 108.8, 108.0, 106.2, 105.7, 72.4, 70.3, 62.5, 32.1, 31.5, 27.7, 24.1, 13.5 ppm; HRMS (TOFMS ES+): calcd for $C_{16}H_{22}O_5Na$: 317.1365 $[M + Na]^+$; found: 317.1361.



14



5

A solution of difuran-triol **6** (*threo*/*erythro* = 2.6:1, 25 mg, 0.085 mmol) in MeOH (3 mL) containing rose bengal as photosensitizer (10^{-4} M) was placed in a test tube and cooled to 0 ºC. O_2 was bubbled through the solution immediately before and during its irradiation with a xenon Variac Eimac Cermax 300 W visible light lamp. Complete consumption of the starting material was observed by TLC after 2 mins irradiation. The solution was irradiated for one extra minute after which time the reaction TLC showed no further changes. This is indicative of the fact that both the furan rings in the starting compound **6** had been successfully oxidized in the initial 2 min irradiation period.

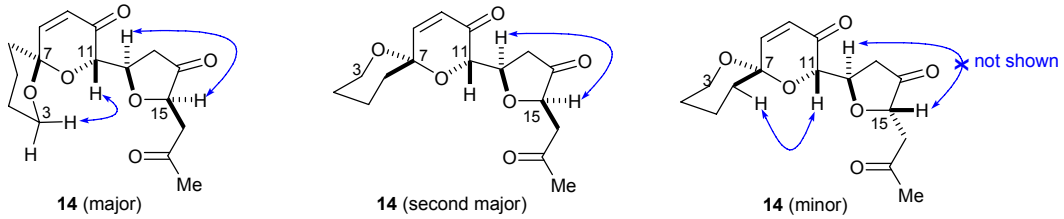
The reaction mixture was transferred to a round bottom flask and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$, concentrated once again in *vacuo* and was left for 2 h under high vacuum to ensure complete removal of MeOH. The crude mixture of dihydroperoxides **B** was dissolved in either $CDCl_3$ or $CHCl_3$ or CH_2Cl_2 (2 mL) and an excess of Me_2S (50 µL) was then added. The solution was stirred for 72 h at room temperature, after which time the DMS/DMSO ratio as well as the amount of MeOH produced remained unchanged (based ^{1}H NMR monitoring when $CDCl_3$ was used as solvent). The solution was then diluted with 2 mL of CH_2Cl_2 and *p*-TsOH•H_2O (3.0 mg, 0.016 mmol) was

added. The reaction was stirred at room temperature for 3 h, after which time the complicated TLC (before addition of *p*-TsOH•H_2O) had become much simpler (it now contained mainly one less polar spot). The reaction solution was concentrated in *vacuo* and purified by flash column chromatography (silica gel, hexane:EtOAc = 3:1 → 1:2) to afford pure compound **14** (13.4 mg, 51 %, mixture of three diastereoisomers in 5:3:2 ratio) accompanied by compound **5** (4.7 mg, 18 %, mixture of two diastereoisomers in 7:3 ratio).

When the photooxidation was run with a 2.5:1 *erythro/threo* mixture of difuran-triol **6**, 49 % of compound **5** (mixture of two diastereoisomers in 7:3 ratio), accompanied by 19 % of compound **14** (mixture of three diastereoisomers in 5:3:2 ratio) were isolated.

14: ^{1}H NMR (300 MHz, $CDCl_3$), diastereoisomer 1 (major): δ = 6.70 (d, J = 10.2 Hz, 1H), 6.10 (d, J = 10.2 Hz, 1H), 5.24 (ddd, J_1 = 9.6 Hz, J_2 = 3.0 Hz, J_3 = 1.8 Hz, 1H), 4.30 (d, J = 1.8 Hz, 1H), 4.15 (t, J = 4.2 Hz, 1H), 2.11 (s, 3H) ppm; Diastereoisomer 2 (second major): δ = 6.72 (d, J = 10.2 Hz, 1H), 6.08 (d, J = 10.2 Hz, 1H), 5.01 (dt, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 4.34 (d, J = 3.0 Hz, 1H), 4.24 (dd, J_1 = 6.2 Hz, J_2 = 4.2 Hz, 1H), 2.12 (s, 3H) ppm; Diastereoisomer 3 (minor): δ = 6.76 (d, J = 10.2 Hz, 1H), 6.09 (d, J = 10.2 Hz, 1H), 5.17 (td, J_1 = 9.0 Hz, J_2 = 2.8 Hz, 1H), 4.27 (t, J = 4.5 Hz, 1H), 4.10 (d, J = 2.8 Hz, 1H), 2.10 (s, 3H) ppm; The remaining resonances of the three inseparable diastereoisomers are partially overlapped as follows: δ = 3.88 – 3.60 (m, 2H of each diastereoisomer), 3.25 – 2.35 (m, 4H of each diastereoisomer), 1.93 – 1.50 (m, 6H of each diastereoisomer) ppm; ^{13}C NMR (75 MHz, $CDCl_3$), diastereoisomer 1 (major): δ = 215.3, 204.7, 194.1, 148.3, 127.6, 93.3, 77.7, 76.2, 74.1, 63.1, 45.8, 37.5, 34.3, 30.1, 24.4, 17.9 ppm; Diastereoisomers 2 and 3: δ = 215.3, 213.5, 204.8, 204.4, 193.9, 193.8, 150.5, 148.4, 127.6, 127.2, 95.2, 93.5, 80.3, 76.4, 76.1, 75.1, 74.8, 73.8, 63.0, 62.2, 45.8, 45.0, 37.7, 37.6, 34.3, 34.1, 30.4, 29.9, 24.4, 24.2, 18.6, 17.8 ppm; HRMS (TOFMS ES+): calcd for $C_{16}H_{20}O_6Na$: 331.1158 $[M + Na]^+$; found: 331.1152.

Detailed NOE studies for the structural assignment of the three diastereoisomeres. Only relevant diagnostic NOEs are shown.

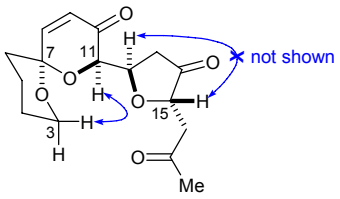


14 (major) **14** (second major) **14** (minor)

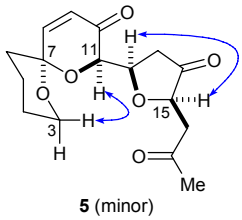
5: ^{1}H NMR (300 MHz, $CDCl_3$), major: δ = 6.72 (d, J = 10.2 Hz, 1H), 6.00 (d, J = 10.2 Hz, 1H), 5.12 (ddd, J_1 = 9.3 Hz, J_2 = 3.3 Hz, J_3 = 2.4 Hz, 1H), 4.74 (d, J = 2.4 Hz, 1H), 4.39 dd, (J_1 = 5.2 Hz, J_2 = 3.7 Hz, 1H), 2.17 (s, 3H) ppm; minor: δ = 6.72 (d, J = 10.2 Hz, 1H), 6.01 (d, J = 10.2 Hz, 1H), 4.91 (dt, J_1 = 7.1 Hz, J_2 = 2.7 Hz, 1H), 4.69 (d, J = 2.7 Hz, 1H), 4.19 dd, (J_1 = 6.3 Hz, J_2 = 3.6 Hz, 1H), 2.17 (s, 3H) ppm; The remaining resonances of the two inseparable diastereoisomers are partially overlapped as follows: δ = 3.85 – 3.70 (m, 2H of major + 2H of minor), 3.06 – 2.40 (m, 4H of major + 4H of

minor), 1.93 – 1.55 (m, 6H of major + 6H of minor) ppm; ^{13}C NMR (75 MHz, $CDCl_3$), major: δ = 215.0, 204.7, 194.6, 148.9, 127.2, 93.5, 77.2, 76.0, 74.8, 63.0, 45.8, 36.5, 33.8, 30.1, 24.4, 18.2 ppm; minor: δ = 215.0, 204.7, 194.6, 148.9, 127.2, 93.5, 77.2, 74.5, 73.5, 62.7, 44.9, 35.8, 34.0, 29.7, 24.5, 17.7 ppm; HRMS (TOFMS ES+): calcd for $C_{16}H_{20}O_6Na$: 331.1158 $[M + Na]^+$; found: 331.1152.

Detailed NOE studies for the structural assignment of the two diastereoisomeres. Only relevant diagnostic NOEs are shown.

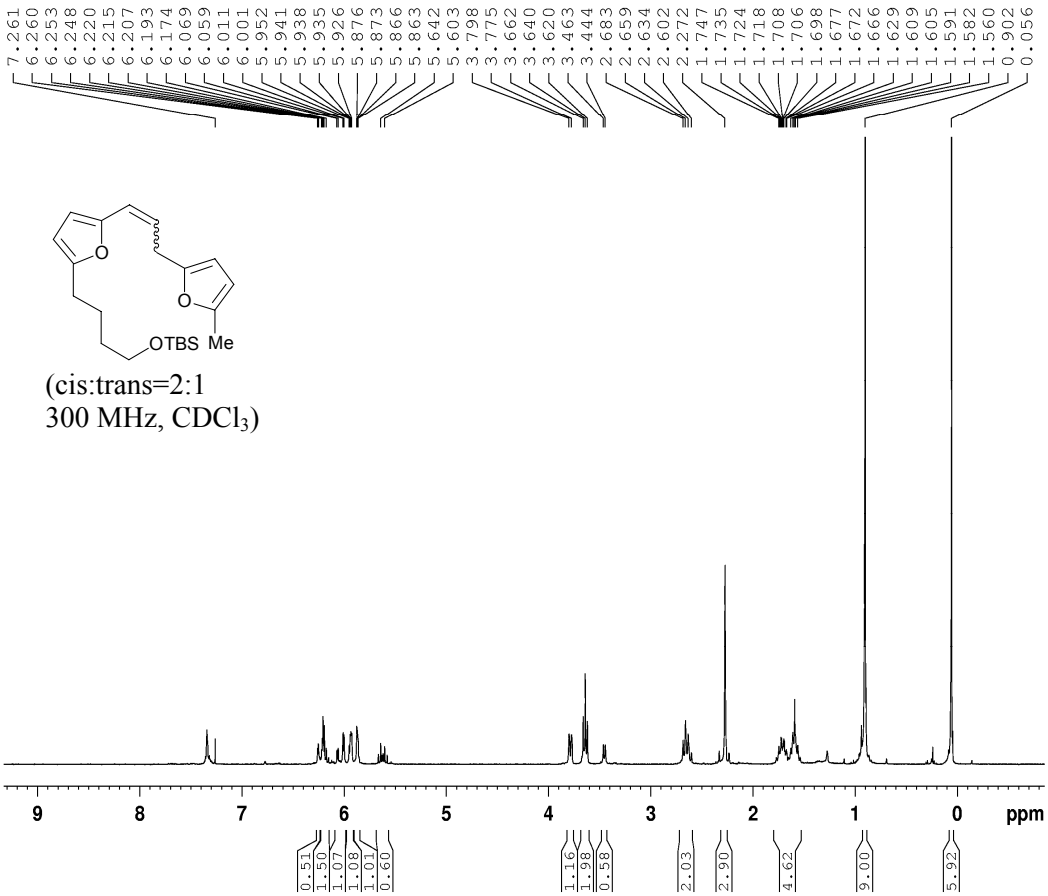


5 (major)

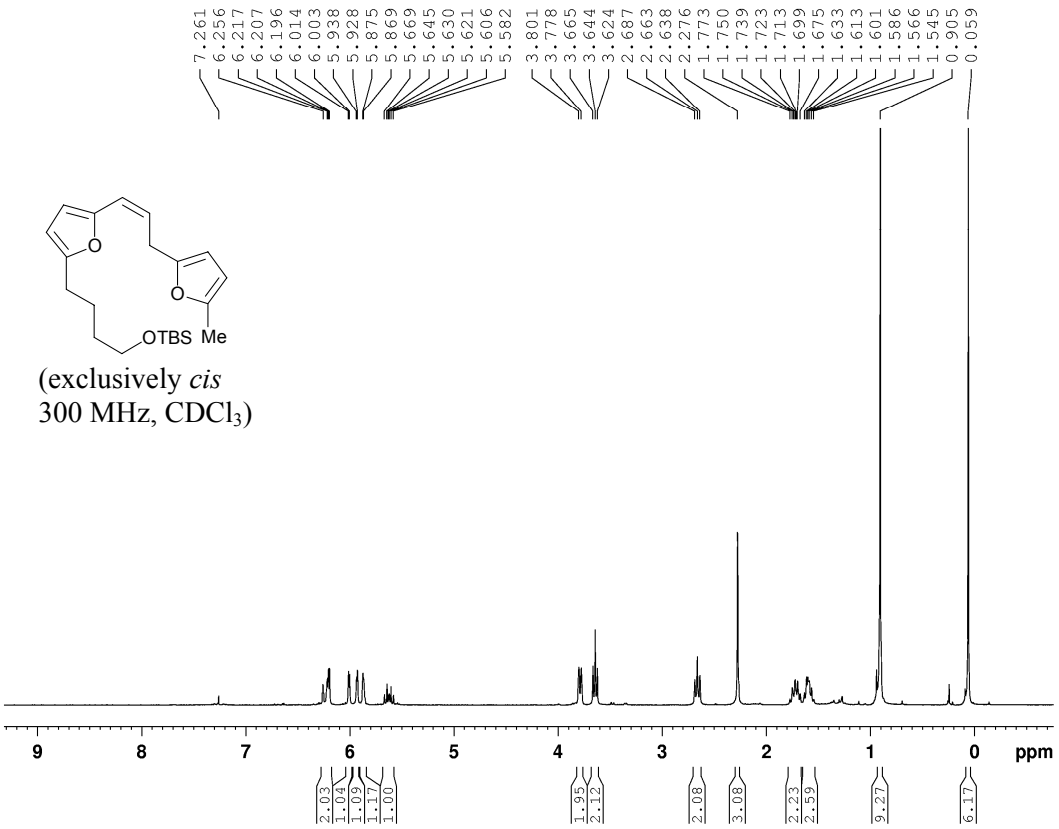


5 (minor)

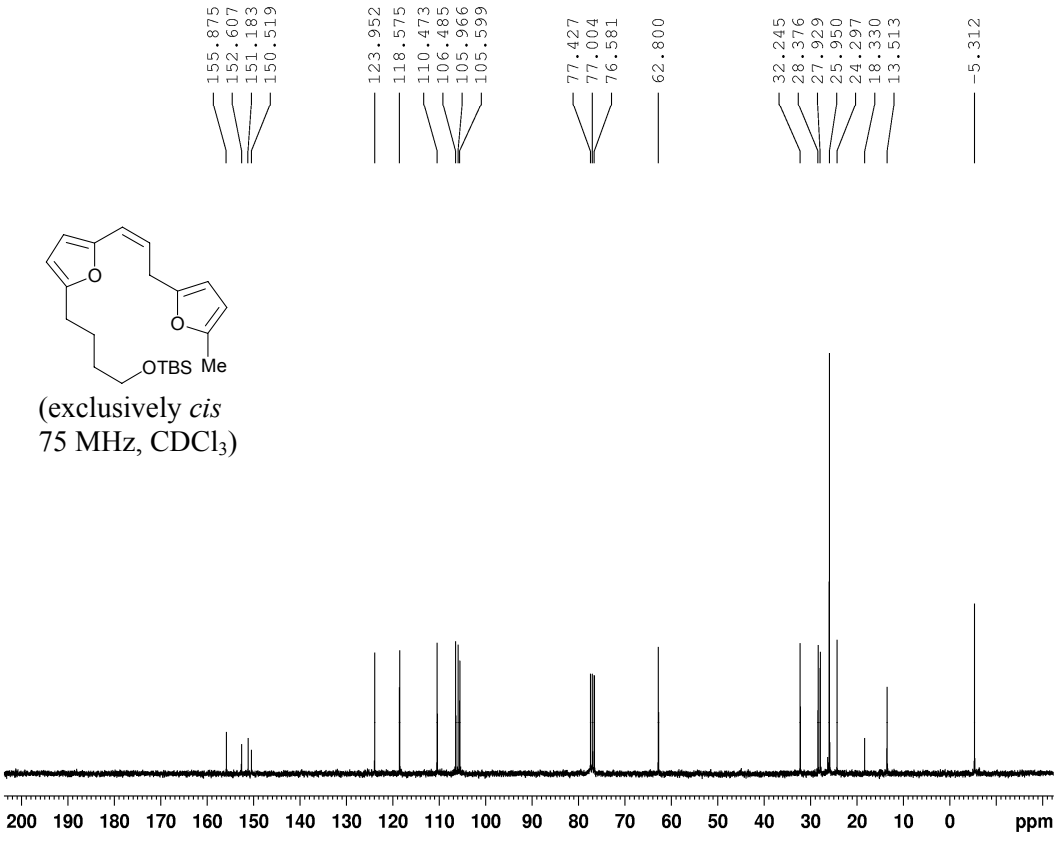
Part B: Copies of ^{1}H and ^{13}C NMR spectra



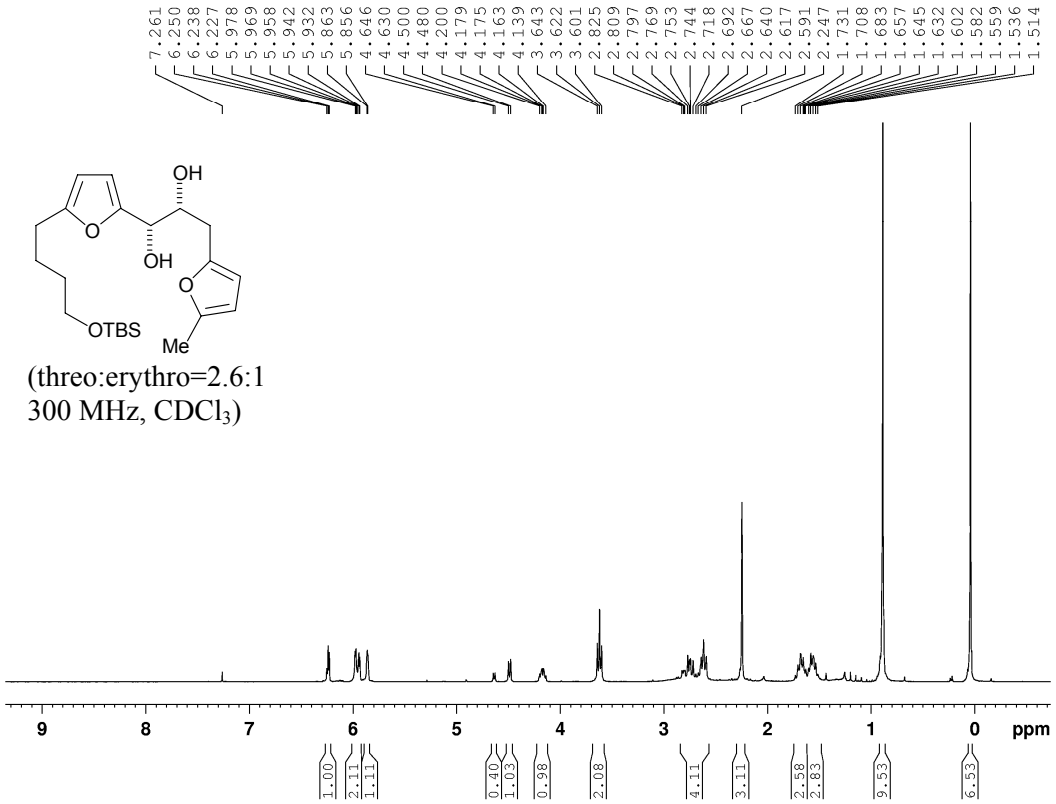
(cis:trans=2:1
300 MHz, $CDCl_3$)



(exclusively *cis*
300 MHz, $CDCl_3$)



(exclusively *cis*
75 MHz, $CDCl_3$)



(threo:erythro=2.6:1
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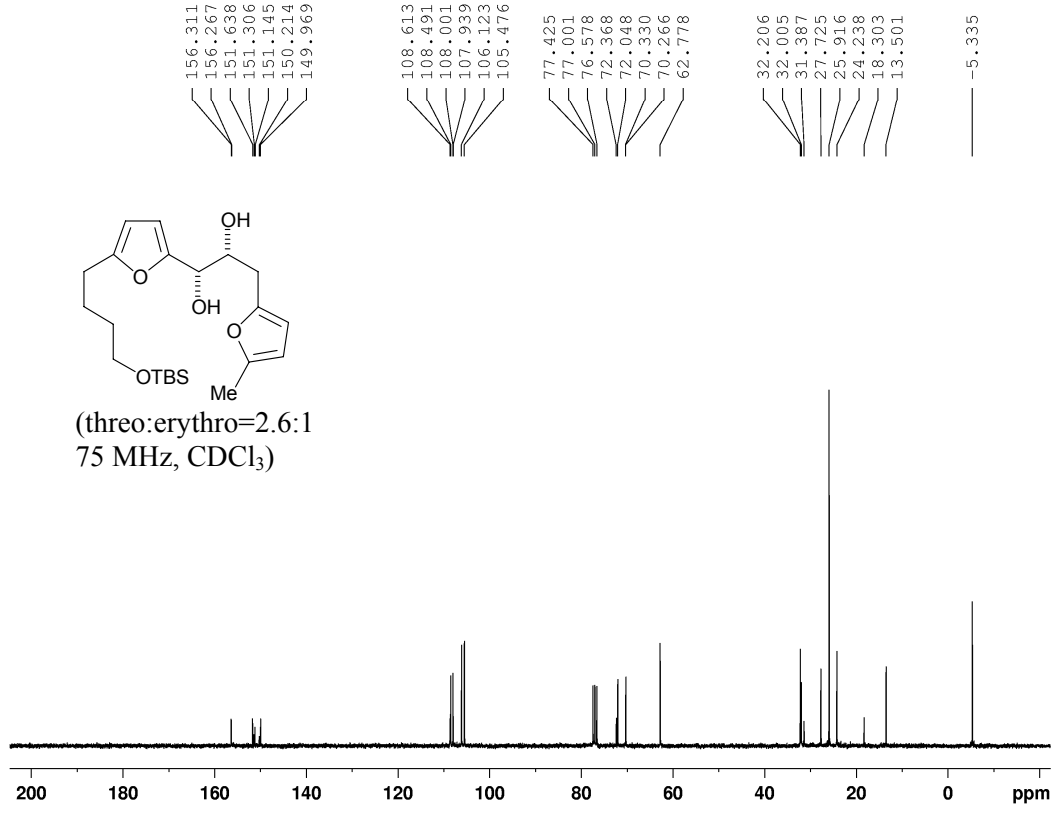

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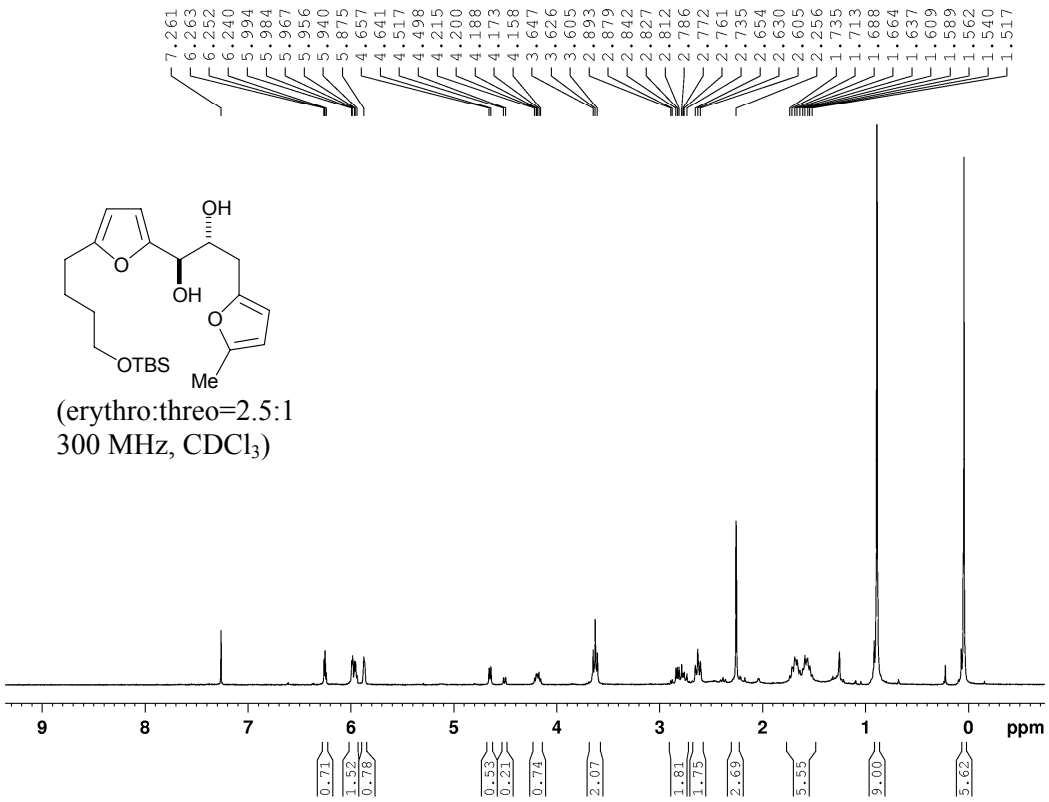
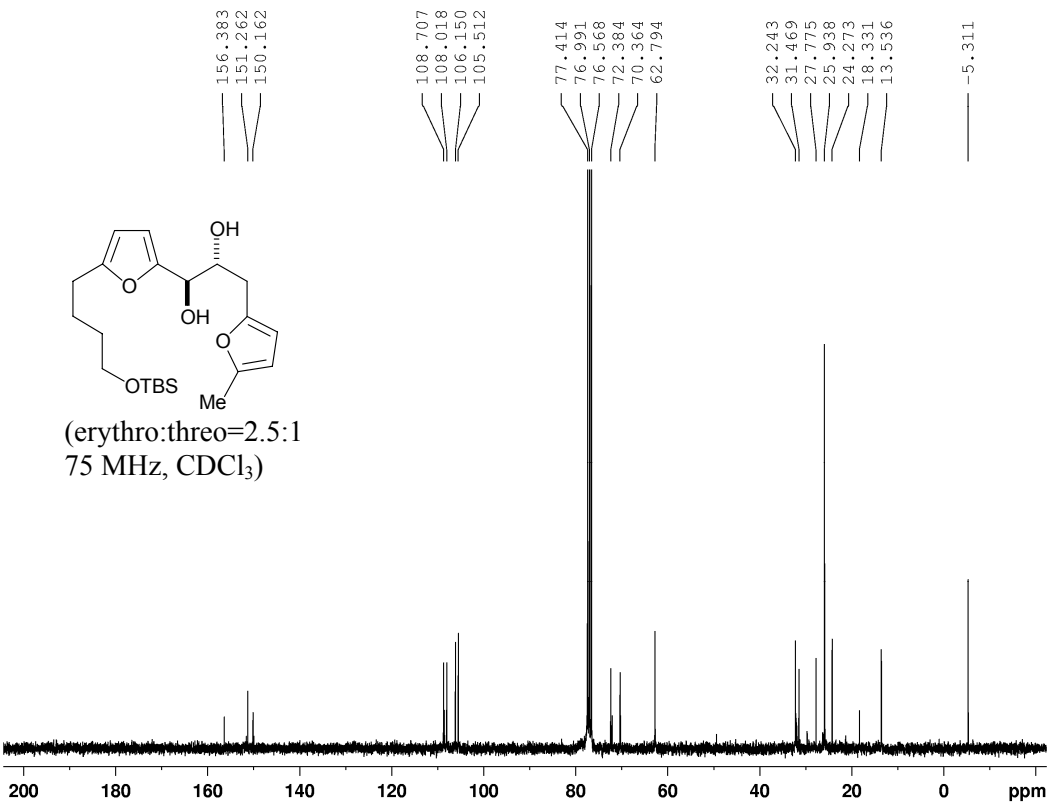
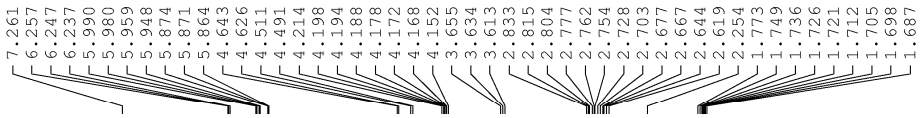
75 MHz, $CDCl_3$)

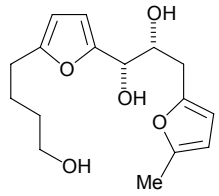


(erythro:threo=2.5:1
300 MHz, $CDCl_3$)



(erythro:threo=2.5:1
75 MHz, $CDCl_3$)





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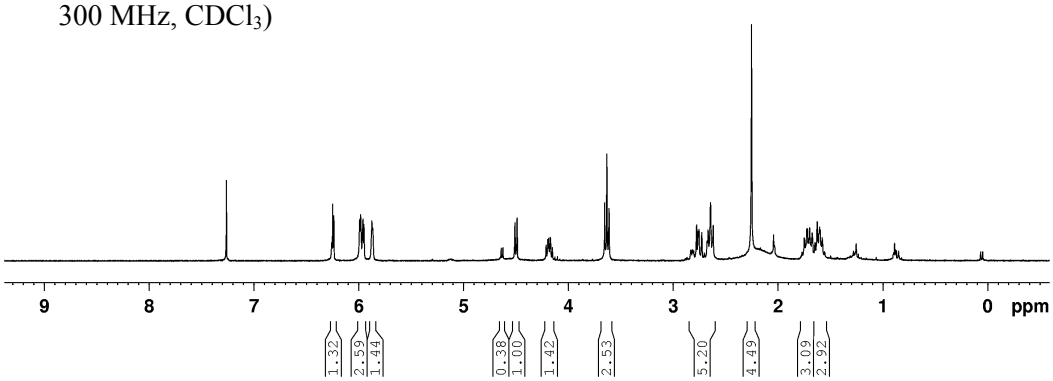
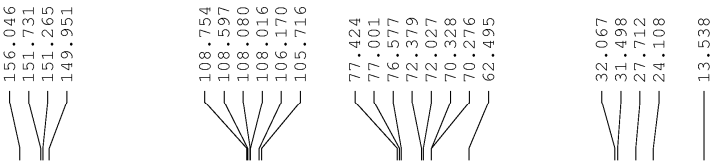
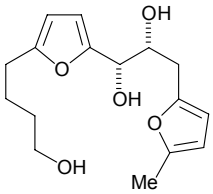
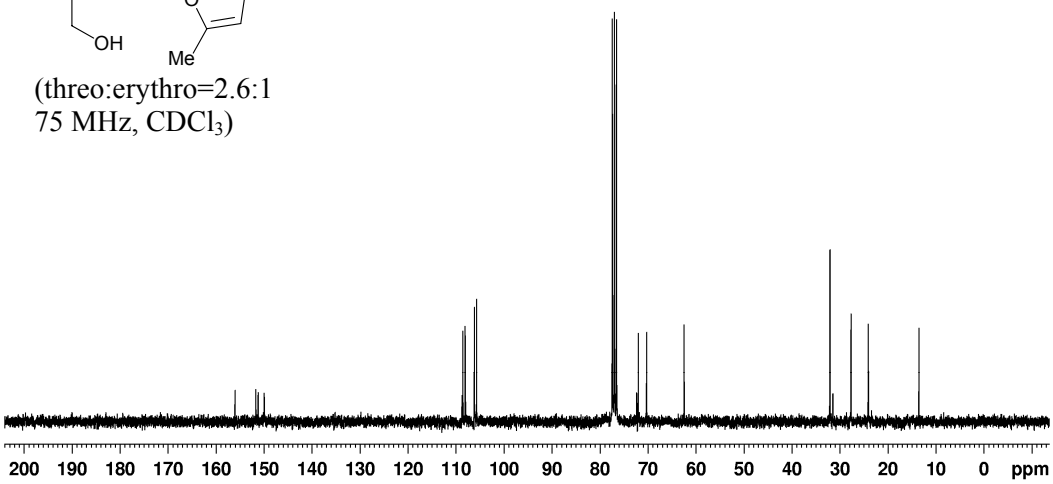
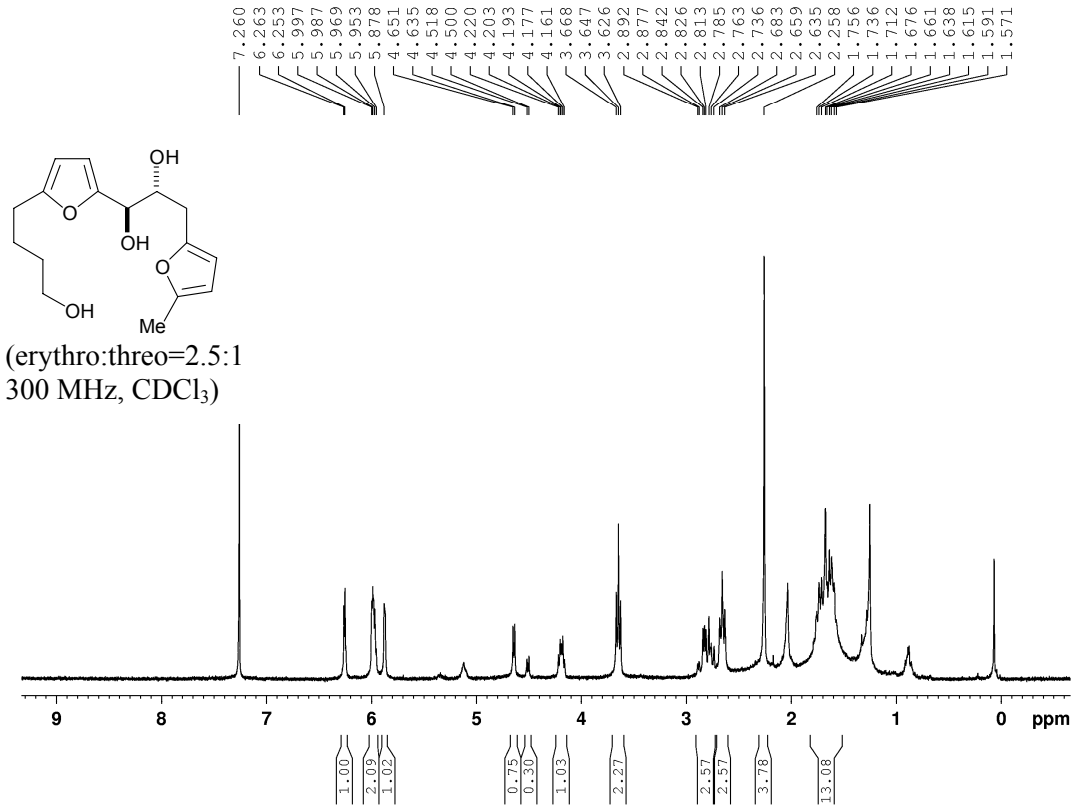




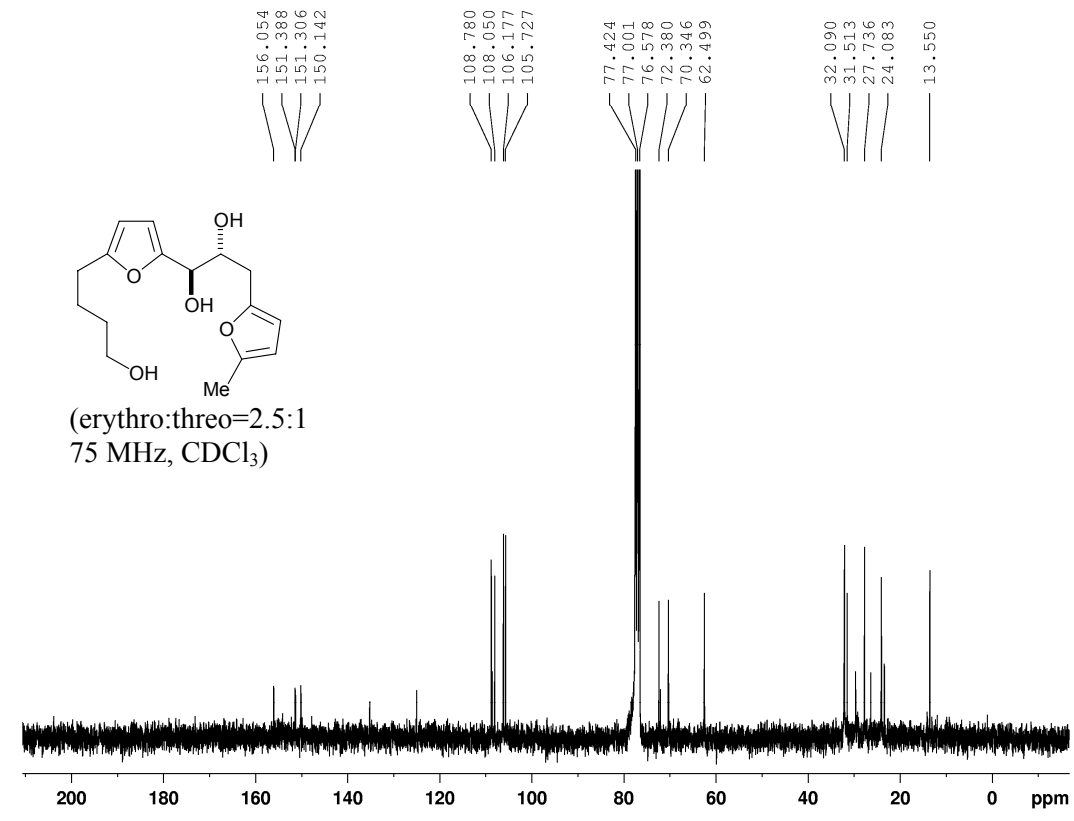


(threo:erythro=2.6:1
75 MHz, $CDCl_3$)

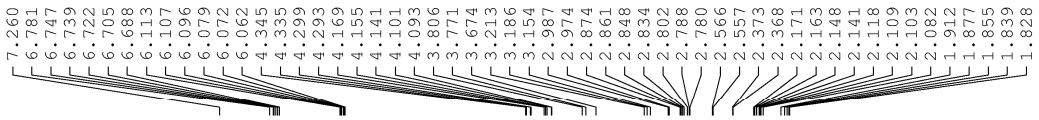


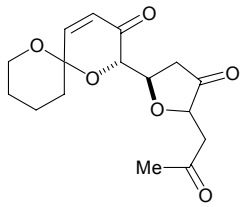


(erythro:threo=2.5:1
300 MHz, $CDCl_3$)

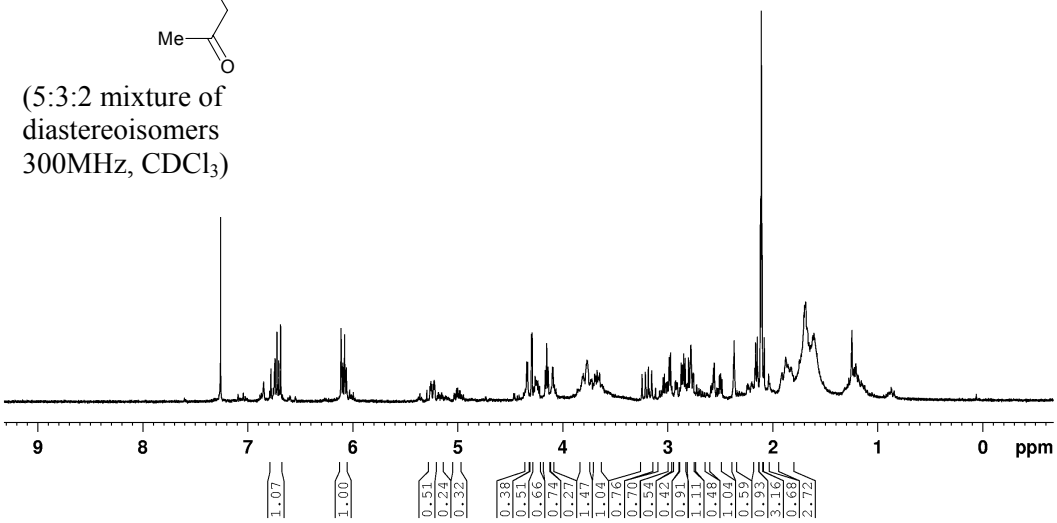


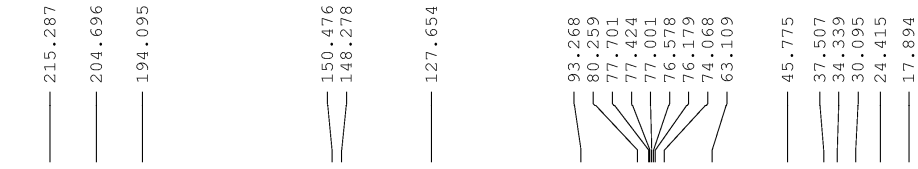
(erythro:threo=2.5:1
75 MHz, $CDCl_3$)

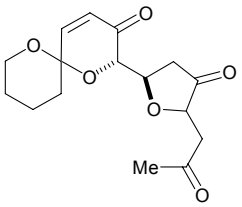




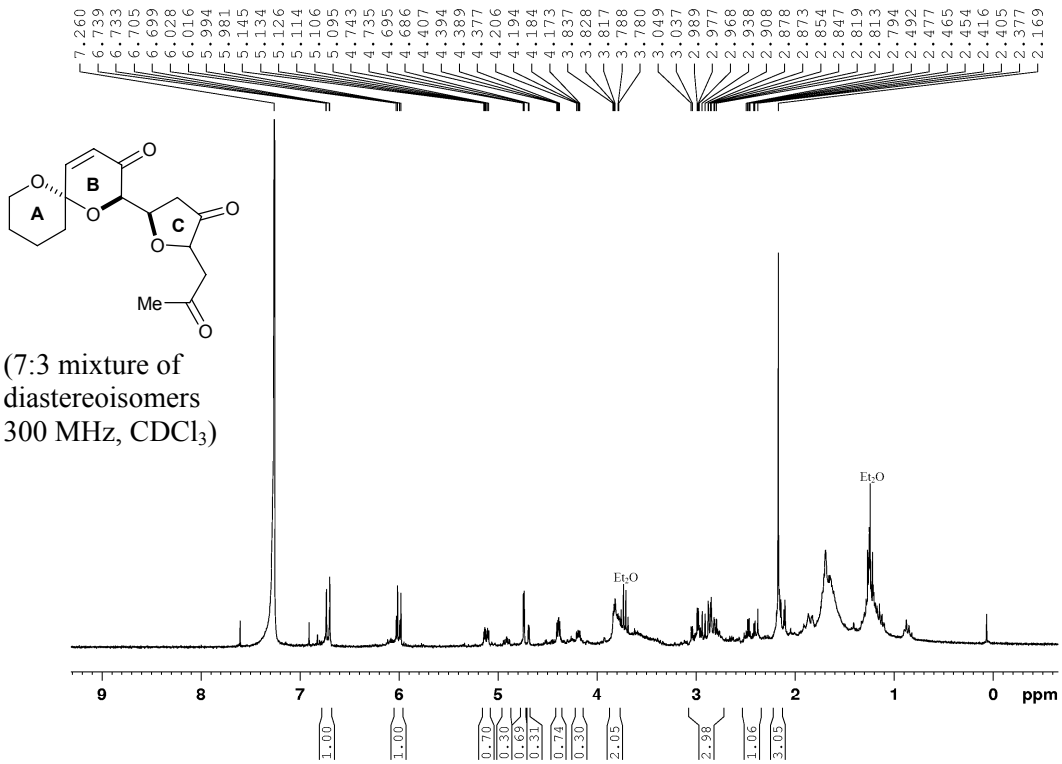
(5:3:2 mixture of diastereoisomers 300MHz, $CDCl_3$)



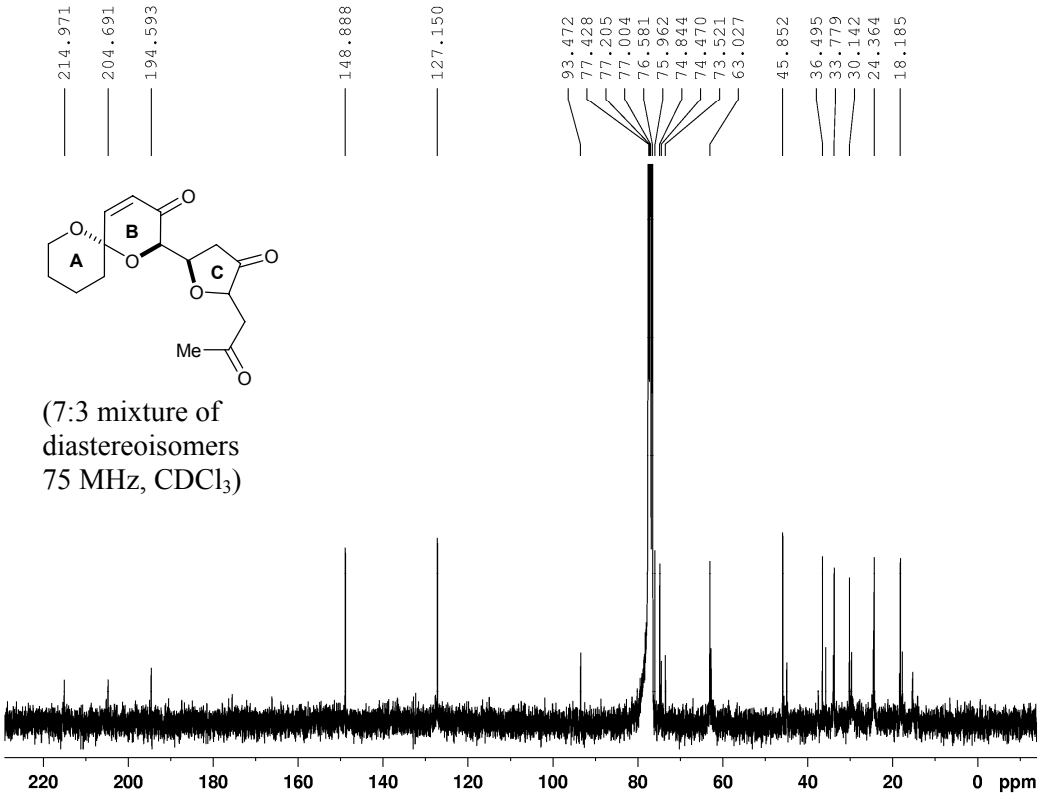




(5:3:2 mixture of diastereoisomers 75 MHz, $CDCl_3$)



(7:3 mixture of diastereoisomers 300 MHz, $CDCl_3$)



(7:3 mixture of diastereoisomers 75 MHz, $CDCl_3$)