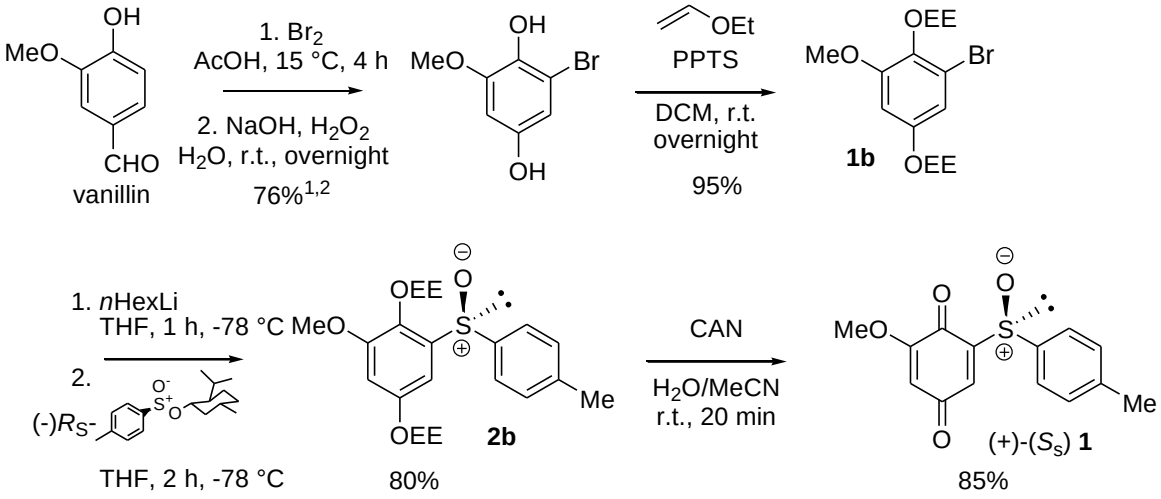
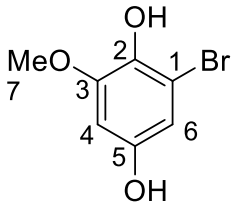
Supporting info

Preparation of (+)-(*Ss*)-1 :



Starting 2-bromo-6-methoxy-1,4-hydroquinone was prepared according to Cross[1] and Nolan[2] protocols



MM: 219.04 g.mol^{-1}

$C_7H_7O_3Br$

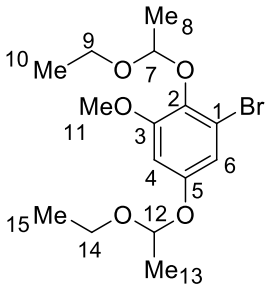
R_f: 0.46 (cyclohexane/AcOEt: 5/5)

^{1}H NMR (400 MHz, acetone-d_6): δ (ppm) **8.07** (s, 1H, O*H*), **7.47** (s, 1H, O*H*), **6.58** (d, 1H, C^6*H*, *J*=3Hz), **6.49** (d, 1H, C^4*H*, *J*=3Hz), **3.81** (s, 3H, C^7*H*$_3$)

^{13}C NMR (100 MHz, acetone-d_6): δ (ppm) **151.1** (C_q), **149.0** (C_q), **137.7** (C_q), **110.4** (*C*H), **108.5** (*C*H), **100.1** (C_q), **56.0** (*C*H$_3$)

IR: ν (cm^{-1}) **3500-3000** (OH), **1274** (O-C^{ar}), **1198** (O-C^{ar}), **1165** (O-C^{ar}), **1038** (O-CH_3), **820** (C^{ar}-Br)

1-bromo-2,5-bis(1-ethoxyethoxy)-3-methoxybenzene **1b**



MM: 363.25 $g.mol^{-1}$

$C_{15}H_{23}O_5Br$

Into a 100 mL two-neck flask under argon atmosphere, 1.415 g of 2-bromo-6-methoxy-1,4-hydroquinone (6.46 mmol, 1.00 eq.) were suspended into 25 mL of anhydrous dichloromethane. To that suspension, 3.4 mL of ethyl vinyl ether (35.6 mmol, 5.5 eq.) were added dropwise and, after five minutes, 42 mg of *p*-tolylsulfonic acid (PPTS) (0.167 mmol, 0.025 eq.) were added. The solid was solubilized after 30 minutes. The reaction was stirred overnight at room temperature. A solution of saturated $NaHCO_3$ was used to quench the reaction. The phases were separated and the aqueous phase was extracted with diethyl ether. The organic phases were gathered and dried over $MgSO_4$, then filtered off and the solvents were evaporated. The crude was purified by filtration over a silica gel pad, using a cyclohexane/diethyl ether mixture in 4/1 ratio as eluent. The solvents were evaporated to give 2.344 g (quantitative) of **1b** as a yellow oil (95%).

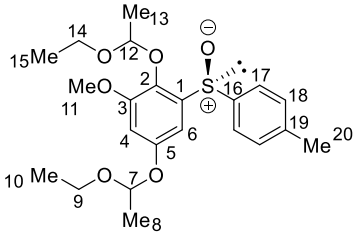
R_f: 0.65 (cyclohexane/AcOEt: 1/1)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) **6.77** (d, 1H, *J*=2Hz, C^6H), **6.56** (d, 1H, *J*=2Hz, C^4H), **5.40-5.21** (m, 2H, C^7H + $C^{12}H$), **3.80** (s, 3H, $C^{11}H_3$), **3.82-3.51** (m, 4H, C^9H_2 + $C^{14}H_2$), **1.50-1.42** (m, 6H, C^8H_3 + $C^{13}H_3$), **1.28-1.15** (m, 6H, $C^{10}H_3$ + $C^{15}H_3$)

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) **150.9** (C_q), **147.2** (C_q), **138.3** (2xC_q), **113.1** (CH_{arom}), **110.1** (C_q-Br), **108.2** (CH_{arom}), **101.5** (CH_{acet}), **100.1** (CH_{acet}), **62.2** (OCH_2), **61.0** (OCH_2), **56.1** (OCH_3), **20.3** (CH_3), **20.2** (CH_3), **15.2** (CH_3), **15.1** (CH_3).

IR: ν (cm^{-1}) **1198-1040** (multiple peaks corresponding to ether groups), **988-891** (multiple peaks corresponding to acetal groups), **820** (C^{ar}-Br)

2,5-bis(1-ethoxyethoxy)-3-methoxy-1 [(*S*)-4-methylbenzenesulfinyl]benzene **2b**



MM: 422.54 $g.mol^{-1}$

$C_{22}H_{30}O_6S$

Into a 100 mL two-neck flask under argon atmosphere, 1.60 mL of a 2.5 M *n*-hex-lithium solution in hexane (4.00 mmol, 1.0 eq) were dissolved in 15 mL of anhydrous THF and cooled down to -78 °C. A solution of 1.423 g of bromide **1b** (3.919 mmol, 1.0 eq.), dissolved in 25 mL of anhydrous THF, was added dropwise to the *n*-hex-lithium solution. The golden mixture was stirred for one hour at -78 °C. Into a 250 mL two-neck flask under argon atmosphere, 1.399 g of (-)-menthyl *p*-tolylsulfinate (4.76 mmol, 1.2 eq.) was dissolved in 45 mL of anhydrous THF and cooled down to -78 °C. The organo-lithium solution was quickly cannulated over the sulfinate solution and the final mixture was stirred for two hours at -78 °C. The solution was allowed to warm up to room temperature and quenched with distilled water. The phases were separated and the aqueous phase was extracted with diethyl ether. The organic phase was dried over $MgSO_4$, filtered off and evaporated. The crude was purified by

chromatography on silica gel (cyclohexane/AcOEt: 9/1 → 8/2) to give 1.3 g (80%) of **2b** as a golden oil.

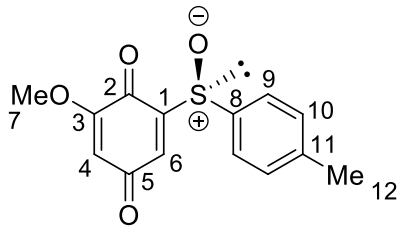
R_f: 0.56 (cyclohexane/Et_2O: 2/3)

$[\alpha]_D^{20}$= +171.7 (c=1, acetone)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) **7.63** (mc, 2H, 2xC^{17}*H*), **7.27** (mc, 2H, 2xC^{18}*H*), **7.05** (mc, 1H, C^6*H*), **6.66** (mc, 1H, C^4*H*), **5.59-5.31** (m, 2H, C^7*H* + C^{12}*H*), **3.81** (s, 3H, C^{11}*H*$_3$), **3.97-3.45** (m, 4H, C^9*H* + C^{14}*H*), **2.38** (s, 3H, C^{20}*H*$_3$), **1.48** (m, 6H, C^8*H*$_3$ + C^{13}*H*$_3$), **1.19** (m, 6H, C^{10}*H*$_3$ + C^{15}*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) **154.3** (*C*$_q$), **154.1** (*C*$_q$), **152.7** (*C*$_q$), **152.4** (*C*$_q$), **141.3**(*C*$_q$), **136.2** (*C*$_q$), **129.5** (2x*C*H$_{p\text{Tol}}$), **124.9** (2x*C*H$_{p\text{Tol}}$), **105.4** (*C*H$_{\text{arom}}$), **105.2** (*C*H$_{\text{arom}}$), **100.2** (*C*H$_{\text{acet}}$), **99.9** (*C*H$_{\text{acet}}$), **64.2** (O*C*H$_2$), **61.5** (O*C*H$_2$), **55.7** (O*C*H$_3$), **21.1** (*C*H$_3$), **20.6** (*C*H$_3$), **20.0** (*C*H$_3$), **15.2** (*C*H$_3$), **15.0** (*C*H$_3$).

(+)-3-methoxy-1-[(*S*)-4-methylbenzenesulfinyl]cyclohexa-1,3-diene-2,5-dione **1**



MM: 276.16 g.mol^{-1}

$C_{14}H_{12}O_4S$

Into a 50 mL flask, 604 mg of sulfoxide **2b** (1.43 mmol, 1.0 eq.) were dissolved in 15 mL of acetonitrile. A solution of 2.178 g of CAN (3.97 mmol, 2.8 eq.) dissolved in 10 mL of distilled water was quickly poured on the sulfoxide solution. After 20 minutes, a TLC analysis indicates the complete conversion of the starting material. The acetonitrile was evaporated and the aqueous residue was extracted with dichloromethane. The organic phase was dried

over $MgSO_4$, filtered off and evaporated to give 336 mg (70%) of **1** as a light orange oil which was crystallized in hot methanol.

Mp: 153 °C Litt: 154 °C[2]

R_f: 0.29 (cyclohexane/AcOEt: 2/1)

$[\alpha]_D^{20}$: +375 (c=1, chloroform) (Litt[2]: 373.8, c=1 chloroform)

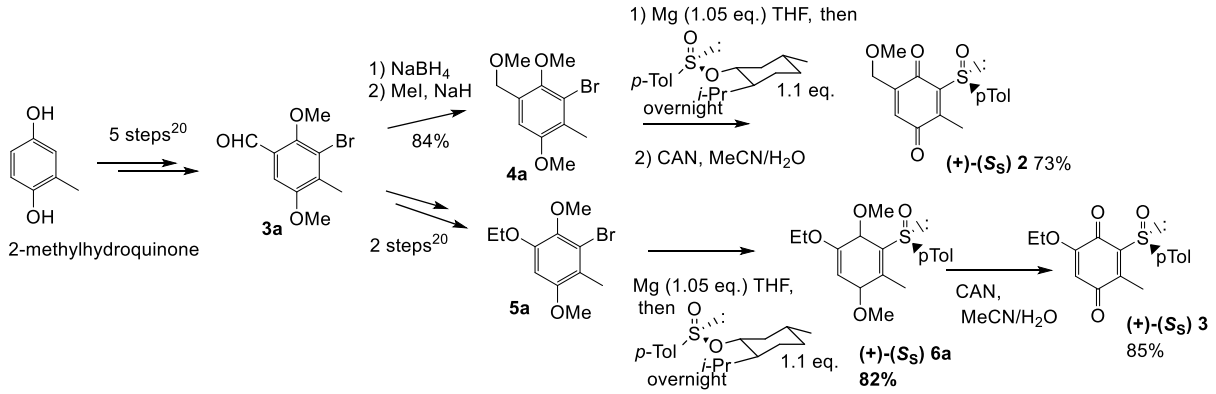
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) **7.51** (dd, 4H, A_2B_2 J = 8.1 Hz, Δν=65 Hz, 2 x C[9]*H*-2 x C[10]*H*), **7.29** (d, 1H, J = 2 Hz, C[6]*H*), **5.95** (d, 1H, J=2Hz, C[4]*H*), **3.79** (s, 3H, C[7]H_3), **2.38** (s, 3H, C[12]H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) **184.9** (*C*=O), **178.7** (*C*=O), **159.2** (C_q), **154.0** (C_q), **143.3** (C_q), **138.7**(C_q), **133.0** (*C*[6]H), **130.7** (2 x *C*[10]H), **126.2 (**2 x *C*[9]H), **108.8** (*C*[4]H), **57.1** (O*C*H_3), **21.9** (*C*H_3).

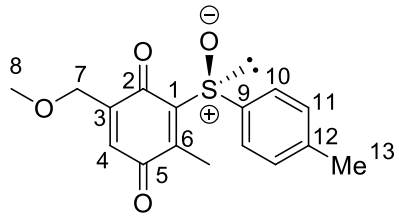
IR: ν (cm^{-1}) **1676** (C=O), **1634** (C=O), **1190** (O-C[ar]), **1079**, **1055**

Preparation of (+)-(*S*s) 2 and (+)-(*S*s) 3 :

Preparation of (+)-(*S*s) 2 :



(+)-3-methoxymethyl-6-methyl-1-[(*S*)-4-methylbenzenesulfinyl]cyclohexa-1,3-diene-2,5-dione **2**



MM: 304.18 g.mol^{-1}

$C_{16}H_{16}O_4S$

Mp: 108 °C

$[\alpha]_D^{20}$: +654 (c=0.15, chloroform).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) **7.43** (dd, 4H, A_2B_2 J = 8. Hz, Δν =83 Hz, 2 x C^9*H*-2 x C^{10}*H*), **6.82** (s, 1H, C^4*H*), **4.25** (dd, 2H, AB J = 3. Hz, Δν =8 Hz, C^7*H*$_2$), **3.43** (s, 3H, C^8*H*$_3$), **2.50** (s, 3H, C^{13}*H*$_3$), **2.40** (s, 3H, C^6*H*$_3$).

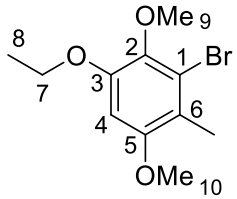
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) **185.5** (*C*=O), **184.1** (*C*=O), **147.3** (C_q), **146.0** (C_q), **145.6** (C_q), **141.9** (C_q), **139.5** (C_q), **131.8** (*C*^{4}H), **130.** (2 x *C*^{10}H), **125.0 (**2 x *C*^{9}H), **67.4** (O*C*H$_3$), **59.4** (*C*^{7}H$_2$), **21.4** (*C*H$_3$), **9.6** (*C*H$_3$).

Microanalysis: for $C_{16}H_{16}O_4S$, calculated: C: 63.14, H: 5.30, O: 21.03; found: C: 62.98, H: 5.41, O: 21.18

Preparation of (+)-(*Ss*) 3:

1-bromo-2,5-dimethoxy-3-hydroxy-6methyl benzene was prepared according to our previous paper[3]

1-bromo-2,5-bis(methoxy)-3-ethoxy-6-methylbenzene **5a**



MM: 274.98 g mol^{-1}

$C_{11}H_{15}O_3Br$

1-bromo-2,5-dimethoxy-3-hydroxy-6methyl benzene 12.035 g (48.73 mmol, 1 equiv.) was dissolved in CH_2Cl_2 200 mL and stirred with an aqueous solution of sodium hydroxide (3.250 g, 81.3 mmol, 1.67 equiv.). 1.12 mL (990 mg, 2.45 mmol, 0.05 equiv.) of Aliquat® 336 were added in the mixture followed by 12.6 mL (15.08 g, 97.86 mmol, 2 equiv.) of diethyl sulfate. The mixture was vigorously stirred until disappearance of starting phenol controlled by TLC. Then 2 g of solid NaOH were added and the mixture was stirred at room temperature overnight. Aqueous phase was extracted with 2x200 mL of dichloromethane and the combined organic phases were washed with brine (2x100 mL). The organic phase was dried over $MgSO_4$, filtered off and evaporated to give 14.5 g of crude which was flash chromatographied on silica gel (hexane/Et_2O: 3/2) to afford 14 g (91%) of **5a** as white crystals.

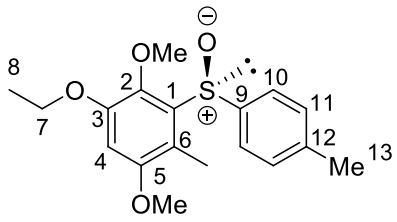
R_f: 0.6 (cyclohexane/Et_2O: 3/1)

Mp: 63 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) **6.39** (s, 1H, C^4*H*), **4.11** (q, 2H, *J*=7Hz, C^7*H*$_2$), **3.79** (s, 3H, C^9*H*$_3$), **3.78** (s, 3H, C^{10}*H*$_3$), **2.24** (s, 3H, C^6*H*$_3$), **1.41** (t, 3H, *J*=7.0 Hz, C^8*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) **154.2** (*C*$_q$), **151.3** (*C*$_q$), **140.3** (*C*$_q$), **121.5** (*C*$_q$), **119.2** (*C*$_q$-Br), **96.7** (*C*H$_{arom}$), **66.7** (*C*^{7}H$_2$), **60.5.** (O*C*H$_3$), **56.4** (O*C*H$_3$), **15.1** (*C*^{6}H$_3$), **9.4**. (*C*^{8}H$_3$).

2,5-dimethoxy-3-ethoxy-6-methyl-1 [(*S*)-4-methylbenzenesulfinyl]benzene **6a**



MM: 334.20 g mol^{-1}

$C_{18}H_{20}O_4S$

A THF solution (30 mL) of bromotoluene **5a** (5 g, 18.2 mmol, 1 equiv.) was added dropwise under argon to an anhydrous THF (30 mL) suspension of magnesium slurry (460 mg, 1.05 equiv.). When the formation of the Grignard reagent was completed, the solution was cooled to 0 °C and cannulated to a THF (50 mL) solution of 5.6 g of (-)-menthyl *p*-tolylsulfinate (19.2 mmol, 1.05 eq.) under argon at 0 °C. The solution was allowed to warm up to room temperature and quenched with a saturated solution of NH_4Cl (100 mL). Aqueous phase was extracted three times with diethyl ether (100 mL) and the combined organic phases were treated with brine (200 mL), dried over MgSO4, filtered off and concentrated to afford a waxy solid which after trituration with Et_2O (100 mL) delivered 4.98g of **6a** as white needles (82%).

Mp: 134 °C

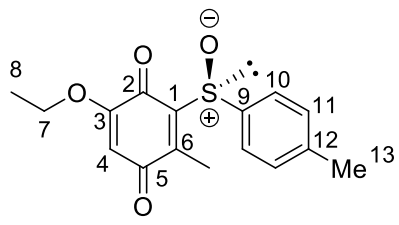
$[\alpha]_D^{20}$: -167.1 (c=1.21, acetone)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) **7.34** (dd, 4H, A_2B_2 *J* = 8 Hz, Δν =52 Hz, 2 x C^{10}*H*-2 x C^{11}*H*), **5.96** (s, 1H, C^4*H*), **4.08** (q, 2H, *J*=7Hz, C^7*H*$_2$), **3.84** (s, 3H, OC*H*$_3$), **3.78** (s, 3H, OC*H*$_3$), **2.51** (s, 3H, C^{13}*H*$_3$), **2.39** (s, 3H, C^6*H*$_3$), **1.49** (t, 3H, *J*=7.0 Hz, C^8*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) **154.6** (*C*$_q$), **151.0** (*C*$_q$), **141.7** (*C*$_q$), **141.0** (*C*$_q$), **139.3** (*C*$_q$), **137.5** (*C*$_q$), **129.6** (2 x *C*^{11}H), **124.7 (**2 x *C*^{10}H), **119.7** (*C*$_q$), **100.9** (*C*^{4}H), **65.7** (*C*^{7}H$_2$), **61.7** (O*C*H$_3$), **56.2** (O*C*H$_3$), **21.2** (*C*H$_3$), **9.9** (*C*H$_3$), **9.4** (*C*H$_3$).

Microanalysis: for $C_{18}H_{20}O_4S$, calculated: C: 64.65, H: 6.63, O: 19.14; found: C: 64.61, H: 6.68, O: 19.24

(+)-3-ethoxy-6-methyl-1-[(*S*)-4-methylbenzenesulfinyl]cyclohexa-1,3-diene-2,5-dione **3**



MM: 304.18 g mol^{-1}

$C_{16}H_{16}O_4S$

Into a 500 mL flask, 3 g of sulfoxide **6a** (9 mmol, 1.0 eq.) were dissolved in 150 mL of acetonitrile. A solution of 13.82 g of CAN (25.2 mmol, 2.8 eq.) dissolved in 100 mL of distilled water was quickly poured on the sulfoxide solution. After 20 minutes, a TLC analysis indicates the complete conversion of the starting material. The acetonitrile was evaporated and the aqueous residue was extracted with dichloromethane. The organic phase was dried over $MgSO_4$, filtered off and evaporated to give 2.325 mg (85%) of **3** as light orange needles after crystallization in hot methanol.

Mp: 142 °C

$[\alpha]_D^{20}$: +460.6 (c=1, dichloromethane).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) **7.47** (dd, 4H, A_2B_2 , *J* = 8 Hz, Δν =103 Hz, 2 x C^9*H*-2 x C^{10}*H*), **5.93** (s, 1H, C^4*H*), **3.97** (q, 2H, *J*=7Hz, C^7*H*$_2$), **2.50** (s, 3H, C^{13}*H*$_3$), **2.39** (s, 3H, C^6*H*$_3$), **1.45** (t, 3H, *J*=7.0 Hz, C^8*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) **185.4** (*C*=O), **179.2** (*C*=O), **157.1** (C_q), **148.0** (C_q), **144.5** (C_q), **141.7** (C_q), **139.5** (C_q), **130.1** (2 x *C*^{10}H), **124.9 (**2 x *C*^{9}H), **108.2** (*C*^{4}H), **65.6** (*C*^{7}H$_2$), **21.4** (*C*H$_3$), **13.8** (*C*H$_3$), **9.4** (*C*H$_3$).

Microanalysis: for $C_{16}H_{16}O_4S$, calculated: C: 63.14, H: 5.30, O: 21.03; found: C: 63.21, H: 5.39, O: 21.20

References:

1. Cross, B.E.; Zammit, L.J. Pigments of gnomonia erythrostoma—IV : The synthesis of 5,8-dibenzyloxy-3-hydroxy-6-methoxy-1,4-naphthoquinone. Tetrahedron 1976 Feb 12;32(13), 1587-90.

2. Noland WE, Kedrowski BL. Quinone approaches toward the synthesis of aflatoxin B(2). Org Lett. 2000 Jul 13;2(14):2109-11. PubMed PMID: 10891242.

3. Lanfranchi DA, Hanquet G. Asymmetric Diels-Alder reactions of a new enantiomerically pure sulfinylquinone: a straightforward access to functionalized Wieland-Miescher ketone analogues with (R) absolute configuration. J. Org. Chem. 2006 May 19;71(13):4854-61. PubMed PMID: 16776513