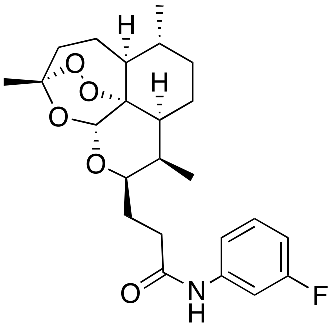
Supporting Information

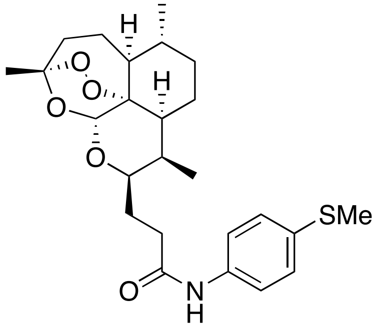
Malaria-Infected Mice are Completely Cured by One 6 mg/kg Oral Dose of a New Monomeric Trioxane Sulfide Combined with Mefloquine

Rachel D. Slack, Bryan T. Mott, Lauren E. Woodard, Abhai Triphati, David Sullivan,
Elizabeth Nenortas, Theresa A. Shapiro, and Gary H. Posner

Supporting Information Table of Contents:

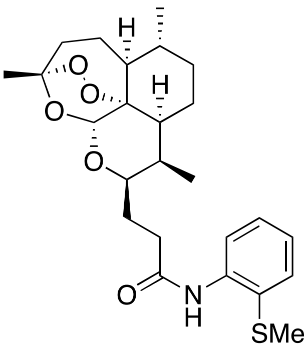


Synthesis of 3-artefanilide **12b.** A flame dried 5 mL RBF was charged carboxylic acid monomer **11** (30 mg, 0.088 mmol), EDC (27 mg, 0.14 mmol), and HOBt (15 mg, 0.11 mmol). CH_2Cl_2 (2.5 mL) was then added and the mixture was stirred for an hour at which time, 3-fluoroaniline (32 μL, 0.33 mmol) was added by syringe. The reaction was allowed to stir at room temperature for 3 hours. It was then quenched with 1N HCl, extracted with dichloromethane (3 x 5 mL), washed with brine, dried over magnesium sulfate and evaporated. The crude product was purified by preparative thin layer chromatography (silica gel, 40% EtOAc/Hexanes) to afford **12b** as an amorphous, white solid (20 mg, 0.050 mmol, 57%). FT-IR (thin film, cm^{-1}) 3330, 2962, 2876, 1700, 1679, 1614, 1542, 1491, 1441, 1376, 1318, 1275, 1261, 1189, 1138, 1116, 1095, 1052, 1008. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06 (bs, 1H), 7.51 (m, 1H), 7.20 (m, 2H), 6.75 (m, 1H), 5.35 (s, 1H), 4.17 (m, 1H), 2.73 (m, 1H), 2.61 (m, 1H), 2.50 (m, 1H), 2.37-2.29 (m, 1H), 2.04-1.79 (m, 5H), 1.66-1.58 (m, 2H), 1.49-1.22 (m, 7H, including singlet at 1.37), 0.96-0.94 (m, 4H), 0.88 (d, 3H, J= 7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.5, 162.9 (d, J_{C-F} = 24.2 Hz), 139.7 (d, J_{C-F} = 11 Hz), 129.9 (d, J_{C-F} = 8 Hz), 115.0, 110.6 (d, J_{C-F} = 22 Hz), 107.4 (d, J_{C-F} = 11 Hz), 107.1 (d, J_{C-F} = 10 Hz), 103.5, 88.9, 81.1, 76.1 (d, J_{C-F} = 8 Hz), 52.3, 44.3, 37.4, 36.5, 36.1, 34.4, 30.2, 26.0 (d, J_{C-F} = 5 Hz), 24.9 (d, J_{C-F} = 8 Hz), 24.6, 20.1, 13.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.3; $[\alpha]_D^{24}$ = +25 (c = 0.14, $CHCl_3$). HRMS (FAB) m/z calculated for $C_{24}H_{33}FNO_5$ $(M+H)^+$ 434.2343, found 434.2344.

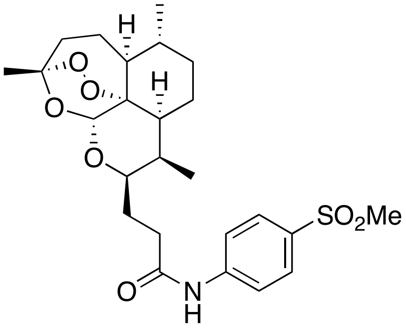


<u>Synthesis of 4-arteSanilide **12c**</u>. To a flame dried 10 mL round bottom flask was added carboxylic acid monomer **11** (16 mg, 0.047 mmol), EDC (9.9 mg, 0.052 mmol), HOBt (7.0 mg, 0.052 mmol), and CH_2Cl_2 (1 mL). The reaction was stirred for 1 hour before commercially available 4-aminothioanisole (6.9 μL, 0.056 mmol) was added dropwise and stirred for an additional 18 hours at room temperature until TLC analysis indicated consumption of starting material. The reaction was quenched with brine (3 mL), and extracted with CH_2Cl_2 (3 x 3 mL). The resulting organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by preparative thin layer chromatography (silica gel, 40% ethyl acetate/hexanes) to afford **12c** as a colorless, amorphous solid as a colorless, amorphous solid (83% yield, 18.0 mg, 0.039). FT-IR (thin film, cm^{-1}) 3313, 2939, 2874, 1663, 1614, 1543, 1509, 1451, 1406, 1377, 1212, 1124, 1091, 1055, 1012, 876, 835, 754 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 7.72 (bs, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 5.34 (s, 1H), 4.18 (m, 1H), 2.73 (m, 1H), 2.63-2.46 (m, 2H), 2.46 (m, 3H), 2.33 (td, J = 14.4, 4.0 Hz, 1H), 2.05-1.79 (m, 5H), 1.68-1.58 (m, 5H), 1.45-1.22 (m, 2H), 1.39 (s, 3H), 0.96 (d, J = 6 Hz, 3H), 0.89 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 157.9, 139.4, 134.2, 123.8, 121.6, 115.3, 103.4, 88.9, 81.1, 76.1, 52.3, 44.3, 37.4, 36.7, 35.2, 34.3, 30.9, 30.1, 26.0, 24.8, 24.6, 19.9, 19.3, 13.0; $[a]_D^{22} = +60$ (c = 0.47, $CHCl_3$); HRMS *m/z* calculated $C_{25}H_{36}SNO_5$

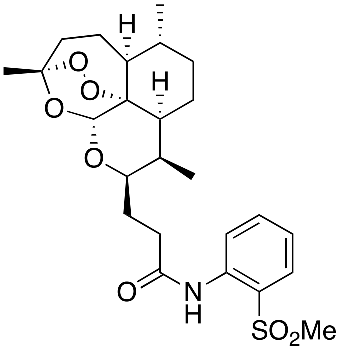
$(M + H)^+$ 463.2392, found 463.2388.



Synthesis of 2-arteSanilide **12e**. To a flame dried 10 mL round bottom flask was added carboxylic acid monomer **11** (20 mg, 0.059 mmol), EDC (12.4 mg, 0.065 mmol), HOBt (8.7 mg, 0.065 mmol), and CH_2Cl_2 (1 mL). The reaction was stirred for 1 hour before commercially available 2-aminothioanisole (8.9 µL, 0.071 mmol) was added dropwise and stirred for an additional 18 hours at room temperature until TLC analysis indicated consumption of starting material. The reaction was quenched with brine (3 mL), and extracted with CH_2Cl_2 (3 x 3 mL). The resulting organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by preparative thin layer chromatography (silica gel, 40% ethyl acetate/hexanes) to afford **12e** as a colorless, amorphous solid (86% yield, 23.3 mg, 0.051 mmol). FT-IR (thin film, cm^{-1}) 3336, 2920, 1688, 1579, 1511, 1433, 1376, 1296, 1124, 1092, 1058, 1011, 945; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32 (bs, 1H), 7.46 (d, J = 7.2 Hz, 2H), 7.27 (t, J = 8.8 Hz, 1H), 7.05 (t, J = 7.2 Hz, 1H), 5.34 (s, 1H), 4.16 (m, 1H), 2.75 (m, 2H), 2.51 (m, 2H), 2.37 (s, 3H), 2.32 (m, 1H), 2.08-1.79 (m, 4H), 1.69-1.57 (m, 2H), 1.52-1.21 (m, 4H), 1.38 (s, 3H), 0.95 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 138.4, 132.8, 128.8, 125.3, 124.2, 120.8, 103.3, 88.8, 81.1, 75.5, 52.4, 44.4, 37.4, 36.5, 35.7, 34.5, 30.2, 26.1, 26.1, 24.9, 24.7, 20.2, 18.9, 13.1; $[a]_D^{26}$ = +52.3 (c = 0.63, $CHCl_3$). HRMS *m*/*z* for $C_{25}H_{36}SNO_5$(M+H) calculated 463.2392 found 463.2395.

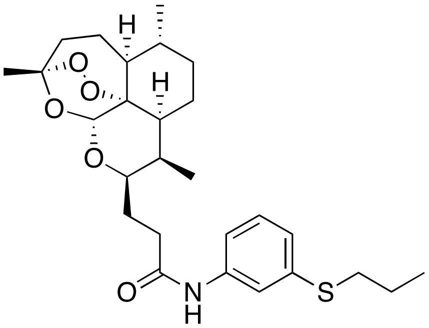


Synthesis of 4-sulfone **12i**. To a stirring solution of 4-arteSanilide **12c** (16.6 mg, 0.036 mmol) in CH_2Cl_2 (1 mL) was added *m*-CPBA (≤77%, 17.7 mg, 0.079 mmol). The reaction was stirred for 2 hours before TLC analysis indicated consumption of starting material, at which point it was quenched with saturated $NaHSO_3$ and extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were washed with saturated $NaHSO_3$ and saturated $NaHCO_3$, dried with $MgSO_4$, and concentrated under reduced pressure. The crude oil was purified by preparative thin layer chromatography (silica gel, 50% EtOAc/Hexanes) to afford **12i** as a colorless, amorphous solid (91% yield, 16.2 mg, 0.033 mmol). FT-IR (thin film, cm^{-1}) 3691, 3371, 3745, 3317, 2939, 2361, 1668, 1608, 1542, 1493, 1454, 1428, 1376, 1285, 1211, 1152, 1090, 1088, 1054; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.12 (bs, 1H) 7.86 (d, J = 6.6 Hz, 2H), 7.77 (d, J = 6.6 Hz, 2H), 5.36 (s, 1H), 4.22 (dd, J = 9.6, 6.6 Hz, 1H), 3.03 (s, 3H), 2.73 (q, J = 4.8 Hz, 2H), 2.60 (t, J = 4.8 Hz, 2H), 2.38 (td, J = 10.2, 2.8 Hz, 1H), 2.07 (m, 2H), 2.35 (m, 1H), 1.94 (m, 2H), 1.81 (m, 1H), 1.63 (m, 2H), 1.41 (s, 3H), 1.28 (m, 3H), 0.96 (d, J = 4.5 Hz, 3H), 0.87 (d, J = 6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 143.2, 134.8, 128.6, 122.2, 119.6, 103.5, 89.1, 81.1, 76.1, 57.3 52.2, 44.7, 44.2, 37.5, 36.4, 35.9, 34.3, 30.5, 26.0, 25.0, 24.6, 24.5, 20.4, 12.9; $[a]_D^{23}$ = +43 (c = 0.38, $CHCl_3$); HRMS *m/z* for $C_{25}H_{35}SNO_7Na(M+Na)^+$ calculated 516.2032 found 516.2029.



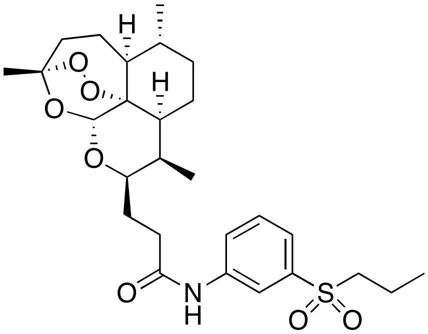
Synthesis 2-sulfone **12k**. To a stirring solution of 2-arteSanilide **12e** (3.5 mg, 0.0078 mmol) in CH_2Cl_2 (0.5 mL) was added *m*-CPBA (≤77%, 3.7 mg, 0.017 mmol) and stirred for 2.5 hours until TLC analysis indicated the consumption of starting material. The reaction was quenched with saturated $NaHSO_3$ and extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were washed with saturated $NaHSO_3$ and saturated $NaHCO_3$, dried with $MgSO_4$, and concentrated under reduced pressure. The crude oil was purified by preparative thin layer chromatography (silica gel, 50% EtOAc/Hexanes) to afford **12k** as colorless, amorphous solid (93% yield, 3.5 mg, 0.0071 mmol). FT-IR (thin film, cm^{-1}) 3329, 2893, 2468, 1666, 1599, 1542, 1493, 1454, 1428, 1376, 1285, 1261, 1208, 1156, 1123, 1090, 1032, 1009; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.50 (bs, 1H), 7.85 (dd, J = 7.8, 1.2 Hz, 1H), 7.61 (t, J = 7.2 Hz, 1H), 7.22 (t, J = 7.2, 1H), 5.32 (s, 1H), 4.15 (dd, J = 9.6, 6.6 Hz, 1 H), 3.09 (m, 2H), 2.72 (m, 2H), 2.52 (m, 1H), 2.43 (s, 3H) 2.31 td, J = 14.1, 3.6 1H), 2.07 (m, 2H), 2.07 (m, 2H), 1.70 (m, 3H), 1.71 (m, 4H), 1.34 (s, 3H), 0.94 (d, J = 6 Hz, 3H), 0.88 (d, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$)

δ 171.6, 139.0, 135.2, 130.0, 125.5, 123.8, 122.9, 120.6, 103.3, 88.8, 82.0, 75.4, 57.8, 52.4, 44.4, 37.2, 36.7, 36.1, 35.2, 30.6, 26.4, 24.9, 24.7, 20.0, 12.9; $[\alpha]_D^{22}$ = +58 (c = 0.32, $CHCl_3$); HRMS *m*/*z* for $C_{25}H_{35}NO_7SNa$(M+Na) calculated 516.2032 found 516.2037.

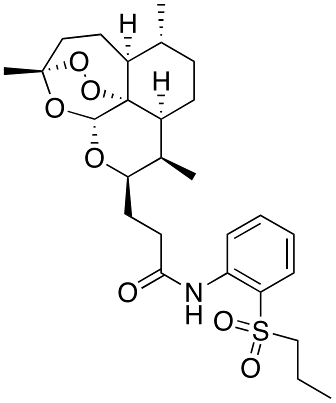


<u>Synthesis of 3-*n*-propyl sulfide **12l**.</u> To a 10 mL round bottom flask was added carboxylic acid monomer **11** (20 mg, 0.059 mmol), EDC (12.4 mg, 0.065 mmol), HOBt (10.8 mg, 0.065 mmol), and 3-*n*-propylsulfanylaniline (10.8 mg, 0.065 mmol). CH_2Cl_2 (1.5 mL) was then added and the reaction was allowed to stir at room temperature for 8 hours. It was then quenched with brine, extracted with CH_2Cl_2 (3 x 3 mL), and dried over $MgSO_4$, and evaporated. The crude product was purified by preparative thin layer chromatography (silica gel, 30% EtOAc/Hexanes) to afford **12l** as a colorless, amorphous solid (79% yield, 22.7 mg, 0.046 mmol). FT-IR (thin film, cm^{-1}) 3310, 2958, 2874, 1668, 1594, 1479, 1456, 1418, 1376, 1295, 1252, 1186, 1123, 1090, 1055, 1011, 876, 824, 779, 665; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 (bs, 1H), 7.56 (s, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 5.32 (s, 1H), 4.17 (m, 1H), 2.88 (t, 7.2 Hz, 2H), 2.72 (m, 1H), 2.62-2.43 (m, 2H), 2.32 (m, 1H), 2.03-1.77 (m, 5H), 1.70-1.53 (m, 3H), 1.65 (sex, J = 7.2 Hz, 2H), 1.48-1.20 (m, 4H), 1.37 (s, 3H), 1.00 (t, J = 7.2 Hz, 3H),

0.92 (d, J = 8.8 Hz, 3H), 0.87 (J = 10.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) 171.3, 138.6, 137.9, 129.1, 124.2, 119.6, 117.0 103.4, 89.0, 81.1, 75.8, 52.3, 44.3, 37.4, 36.5, 36.1, 35.4, 34.4, 30.2, 26.1, 25.1, 24.9, 24.7, 22.4, 20.2, 13.4, 13.0; $[a]_D^{26}$ = +36.4 (c = 0.40, $CHCl_3$); ESI-HRMS *m/z* for $C_{27}H_{40}NO_5S(M+H)^+$ calc. 490.2633, found 490.2640.

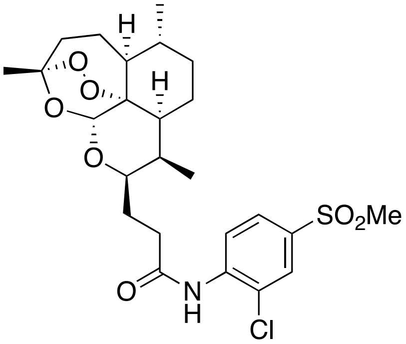


Synthesis of 3-*n*-propyl sulfone **12m**. To a stirring solution of 3-*n*-propyl sulfide **12l** (10 mg, 0.020 mmol) in CH_2Cl_2 (1 mL) was added *m*-CPBA (≤77%, 7.8 mg, 0.045 mmol). The solution was allowed to stir for 3 hours before it was quenched with saturated $NaHSO_3$ (3 mL) and extracted with CH_2Cl_2 (3 x 4 mL). The combined organic extracts were washed with saturated $NaHSO_3$ and saturated $NaHCO_3$, dried with $MgSO_4$, and concentrated under reduced pressure. The crude oil was purified by preparative thin layer chromatography (silica gel, 45% EtOAc/Hexanes) to afford **12m** as a colorless, amorphous solid (10.3 mg, 0.020 mmol, 97% yield). FT-IR (thin film, cm^{-1}) 3333, 2926, 2363, 1697, `595, 1540, 1478, 1420, 1376, 1302, 1250, 1139, 1091, 1054, 1010, 876, 757; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 (bs, 1H), 8.04 (m, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 5.36 (s, 1H), 4.21 (m, 1H), 3.08 (m, 2H), 2.75 (m, 1H), 2.67-2.52 (m, 2H), 2.34 (m, 1H), 2.06-1.79 (m, 5H), 1.75-1.62 (m, 4H), 1.49-1.19 (m, 5H), 1.31 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.91 (J = 7.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.8, 139.7, 139.3, 129.8, 124.8, 123.0, 119.0, 103.5, 89.0, 81.1, 57.8, 52.3, 44.3, 37.4, 36.5, 36.1, 34.4, 30.2, 29.7, 26.0, 25.0, 24.9, 24.7, 20.1, 16.5, 13.0, 12.9.; $[a]_D^{27}$ = +25.7 (c = 0.59, $CHCl_3$); ESI-HRMS *m*/*z* for $C_{27}H_{40}NO_7S(M+H)^+$ calc. 522.2523, found 522.2524.



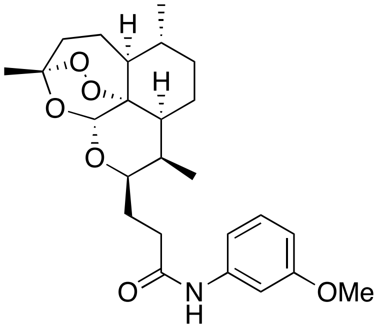
<u>Synthesis of 2-*n*-propyl sulfone **12n**.</u> To a 10 mL round bottom flask was added carboxylic acid monomer **11** (11.7 mg, 0.035 mmol), EDC (7.8 mg, 0.042 mmol), HOBt (1 mg, 6.9μmol), and 2-*n*-propylsulfenylaniline (6.9 mg, 0.042 mmol). CH_2Cl_2 (1 mL) was then added and the reaction was allowed to stir at room temperature for 20 hours. It was then quenched with brine (3 mL), extracted with CH_2Cl_2 (3 x 3 mL), dried over $MgSO_4$, and evaporated. The crude product was dissolved in CH_2Cl_2 (1 mL) and *m*-CPBA (≤77%, 16.9 mg, 0.076 mmol) was added. The resulting solution was allowed to stir for 1.5 hours before the reaction was quenched with $NaHSO_3$ (2 mL) and extracted with CH_2Cl_2 (3 x 4 mL). The combined organic extracts were washed with $NaHSO_3$ and $NaHCO_3$, dried with $MgSO_4$, and evaporated. The resulting crude oil was purified by preparative thin layer chromatography (silica gel, 50% EtOAc/Hexanes) to afford **12l** as a colorless, amorphous solid (57% yield over 2 steps, 10.2 mg, 0.020mmol). FT-IR (thin

film, cm^{-1}) 3345, 2931, 2349, 1688, 1601, 1539, 1476, 1428, 1391, 1266, 1212, 1061, 1012; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (bs, 1H), 8.50 (d, J = 8.4 Hz, 1H), 7.85 (dd, J = 10.4, 1.6 Hz, 1H), 7.61 (t, J = 7.2 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 5.32 (s, 1H), 4.15 (m, 1H), 3.09 (m, 2H), 2.72 (m, 2H), 2.52 (m, 1H), 2.31 (m, 1H), 2.13-1.56 (m, 5H), 1.73 (t, J = 7.8 Hz, 2H), 1.72-1.62 (m, 4H), 1.46-1.18 (m, 3H), 1.35 (s, 3H), 1.00 (t, J = 7.5 Hz, 3H), 0.95 (d, J = 6.0 Hz, 3H), 0.91 (J = 8.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.6, 137.5, 135.2, 130.0, 125.5, 123.8, 122.9, 103.3, 88.8, 81.1, 75.4, 57.8, 52.4, 44.4, 37.4, 36.5, 36.1, 34.4, 30.2, 26.1, 25.5, 24.7, 24.6, 20.2, 16.2, 13.1, 12.9; $[a]_D^{27}$ = +25.7 (c = 0.59, $CHCl_3$); ESI-HRMS *m/z* for $C_{27}H_{40}NO_7S(M+H)^+$ calculated 522.2525, found 522.2521.

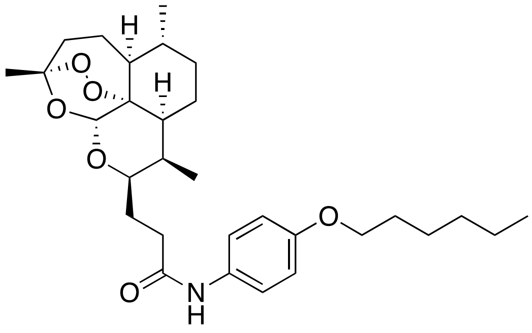


<u>Synthesis of 2-chloro-4-sulfone **12o**.</u> To a flame dried 10 mL round bottom flask charged with carboxylic acid monomer **11** (33.5 mg, 0.098 mmol) and N-methylmorpholine (12 μL, 0.108 mmol) in anhydrous THF (1 mL) was added isobutyl chloroformate (13 μL, 0.108 mmol) at -40ºC. The solution was stirred for 1 hour. Meanwhile, in a flame dried 10 mL pear shaped flask, *n*Buli (1.4 M in toluene, 0.41 mL, 0.57 mmol) was added to a solution of commercially available 2,4-bis(methylsulfonyl)aniline (121.5 mg, 0.59 mmol) in THF (2 mL) at -78ºC. The solution was stirred for 20 minutes before it was warmed to

0ºC, at which point it was stirred for an additional 10 minutes. This anilide solution was then pre-cooled to -40ºC and slowly added to former reaction via cannula. The reaction was stirred for 5 hours at -40ºC before it was quenched with saturated NH_4Cl (5 mL). The mixture was extracted with EtOAc (3 x 4 mL), washed with brine, and purified by thin layer chromatography (45% EtOAc/Hexanes) to afford **12o** as a colorless amorphous solid (37% yield, 19.2 mg, 0.036 mmol). FT-IR (thin film, cm^{-1}) 3328, 2931, 1672, 1598, 1538, 1463, 1439, 1376, 1311, 1239, 1141, 1058, 1008, 878. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.58 (bs, 1H), 7.83 (d, J = 6.6 Hz, 1H), 7.59 (s, 1H), 7.22 (dd, J = 7.1, 2.2 Hz, 1H), 5.31 (s, 1H), 4.15 (m, 1H), 3.09 (m, 2H), 2.72 (m, 1H), 2.31 (m, 2H), 2.63 (s, 3H), 2.35 (m, 3H), 2.03-1.66 (m, 4H), 1.40 (s, 3H) 1.39-1.17 (m, 4H), 0.93 (d, J = 7.2 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 136.6, 134.8, 134.3, 130.1, 128.9, 122.1, 118.9, 112.2, 69.6, 56.8, 56.4, 53.6, 47.2, 46.4, 41.1, 39.4, 36.2, 35.1, 33.6, 27.9, 24.1, 22.8, 19.8, 12.8; $[a]_D^{23}$ = +33 (c = 0.56, $CHCl_3$); HRMS *m*/*z* calculated for $C_{25}H_{34}ClNO_7S$(M+H) 528.1823, found 528.1828.

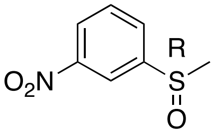


Synthesis of 3-methyl ether **12p**. To a flame dried 10 mL round bottom flask was added carboxylic acid monomer **11** (25 mg, 0.073 mmol), EDC (15.4 mg, 0.081 mmol), HOBt (10.9 mg, 0.081 mmol), and CH_2Cl_2 (1 mL). The reaction was stirred for 1 hour before commercially available *m*-anisidine (9.2 µL, 0.081 mmol) was added dropwise and stirred for an additional 5 hours at room temperature until TLC analysis indicated consumption of starting material. The reaction was quenched with brine (3 mL), and extracted with CH_2Cl_2 (3 x 3 mL). The resulting organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by preparative thin layer chromatography (silica gel, 40% ethyl acetate/hexanes) to afford **12p** as a colorless, amorphous solid (92% yield, 29.9 mg, 0.067 mmol). FT-IR (thin film, cm^{-1}) 3317, 2939, 1668, 1608, 1542, 1493, 1454, 1428, 1376, 1285, 1261, 1208, 1156, 1123, 1090, 1053, 1011; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (bs, 1H), 7.34 (s, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.63 (dd, J = 8.0, 2.0 Hz, 1H), 5.35 (s, 1H), 4.16 (m, 1H), 3.79 (s, 3H), 2.76-2.60 (m, 2H), 2.47 (m, 1H), 2.33 (m, 1H), 2.04-1.78 (m, 6H), 1.67-1.53 (2H), 1.49-1.18 (4H), 1.38 (s, 3H), 0.94 (d, J = 10.8 Hz, 3H), 0.89 (J = 7.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.6, 160.3, 139.6, 129.7, 11.9, 110.0, 105.4, 103.7, 89.1, 81.3, 75.9, 55.4, 52.6, 44.6, 37.5, 36.6, 35.9, 34.4, 30.3, 36.1, 25.0, 24.9, 24.7, 20.2, 13.0; $[a]_D^{25}$ = +45.6 (c = 1.36, $CHCl_3$); ESI-HRMS *m/z* for $C_{25}H_{36}NO_6(M+H)^+$ calc. 446.2549, found 446.2546.



Synthesis of 4-hexyl ether **12q**

To a flame dried 10 mL round bottom flask was added carboxylic acid monomer **11** (20 mg, 0.059 mmol, 1.0 eq), EDC (11 mg, 0.07 mmol, 1.2), HOBt (9.5 mg, 0.07 mmol, 1.2 eq), and CH_2Cl_2 (1 mL). The reaction was stirred for 1 hour before commercially available 4-(hexyloxy)aniline (13.5 mg, 0.07 mmol, 1.2 eq) was added dropwise and stirred for an additional 5 hours at room temperature until TLC analysis indicated consumption of starting material. The reaction was quenched with brine (3 mL), and extracted with CH_2Cl_2 (3 x 3 mL). The resulting organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by preparative thin layer chromatography (silica gel, 40% ethyl acetate/hexanes) to afford **12q** as a colorless, amorphous solid (60% yield, 18.0 mg, 0.035 mmol). FT-IR (cm^{-1}) 3308, 2935, 2871, 1658, 1603, 1542, 1510, 1453, 1412, 1377, 1240, 1173, 1124, 1090, 1056, 1011, 937, 876, 828, 754; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1 H), 7.41 (d, *J* = 8.91 Hz, 2 H), 6.82 (d, *J* = 8.91 Hz, 2 H), 5.34 (s, 1 H), 4.15 (ddd, *J* = 11.01, 6.02, 1.86 Hz, 1 H), 3.91 (t, *J* = 6.57 Hz, 2 H), 2.79 - 2.70 (m, 1 H), 2.64 - 2.55 (m, 1 H), 2.50 - 2.40 (m, 1 H), 2.33 (td, *J* = 13.91, 3.69 Hz, 1 H), 2.05 – 1.95 (m, 2 H), 1.94 - 1.86 (m, 2 H), 1.84 - 1.71 (m, 3 H), 1.67 - 1.55 (m, 2 H), 1.46 - 1.41 (m, 3 H), 1.38 (s, 4 H), 1.36 - 1.29 (m, 5 H), 1.28 - 1.22 (m, 2 H), 0.95 (d, *J* = 5.87 Hz, 4 H), 0.89 (t, *J* = 6.76 Hz, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 155.8, 131.1, 121.7, 114.7, 103.5, 88.9, 81.2, 76.1, 68.3, 52.4, 44.4, 37.4, 36.5, 35.7, 34.4, 31.6, 30.2, 29.3, 26.1, 25.7, 25.0, 24.9, 24.7, 22.6, 20.2, 14.1, 13.2; $[\alpha]_D^{25}$ +43.78 (c = 0.1.245, $CHCl_3$); ESI-HRMS m/z $(M + H)^+$ for $C_{30}H_{46}NO_6$ calc. 516.3331, found = 516.3326.



(+)-(*R*)-**14**

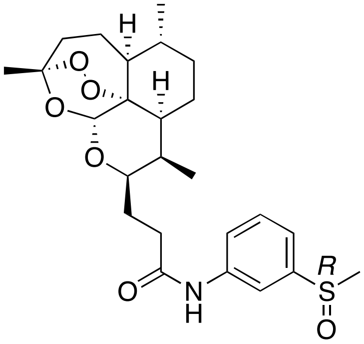
Synthesis of sulfoxide (+)-(*R*)-**14**

Commercially available racemic sulfide **13** (500 mg, 2.96 mmol) was dissolved in HOAc:MeOH (1:3, 6 mL), and H_2O_2 (30% in H_2O, 2 mL) was added at room temperature. The reaction was allowed to stir for 24 hours before it was quenched with saturated $NaHCO_3$ (8 mL) at 0ºC, and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The resulting solid was purified by column chromatography (silica gel, 20-40% EtOAc/Hexanes) to afford racemic sulfoxide **14** as a colorless solid (91% yield, 499.0 mg, 2.69 mmol). Sulfoxide (+)-(*R*)-**14** was resolved by chiral HPLC (Regis Whelk-01 (S,S); 20% IPA in hexanes; detection wavelength 254 nm; flow rate = 2.5 mL/min) t_r = 82.0 min (*R*)-enantiomer and 95.7 min (*S*)-enantiomer. Spectral and physical properties match that which has been reported in the literature.[1] $[\alpha]_D^{22.4} = +123.7$ ($CHCl_3$, 0.80).

(+)-(*R*)-**15**

Synthesis of sulfenyl aniline (+)-(*R*)-**15**

To a suspension of Raney nickel (catalytic) and (+)-(*R*)-**14** (20 mg, 0.11 mmol) in MeOH (1 mL) was added hydrazine (0.5 mL). The reaction was stirred for 18 hours before it was filtered through celite and washed with MeOH (3 x 5 mL). The filtrate was diluted with saturated NH_4Cl (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with saturated NH_4Cl and brine, dried with $MgSO_4$, and concentrated under reduced pressure. Crude sulfoxide (+)-(*R*)-**15** was purified by column chromatography (silica gel, 1-10% MeOH/CH_2Cl_2) to afford (+)-(*R*)-**15** as a colorless solid (81% yield, 13.5 mg, 0.087 mmol). Spectral and physical properties match that which has been reported in the literature.[2] $[\alpha]_D^{23} = +177.2$ ($CHCl_3$, c = 0.11).



Synthesis of 3-(*R*)-sulfoxide **12h**

Carboxylic acid **5** (15 mg, 0.043 mmol), EDC (10.0 mg, 0.052 mmol), and HOBt (7.1 mg, 0.052 mmol) were dissolved in CH_2Cl_2 (2 mL) in a 10 mL round bottom flask. The solution was stirred for 15 minutes at room temperature before (+)-**15** (8.1 mg, 0.052 mmol) was added. The reaction was allowed to stir for 36 hours before it was quenched with brine (3 mL) and extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The resulting crude oil was purified by preparative thin layer chromatography (silica gel, 100% EtOAc) to afford sulfoxide diastereomer **12h** (48% yield, mg, 10.1 mg, 0.021 mmol).

References

(1) Tohma, H.; Takizawa, S.; Watanabe, H; Fukuoka, Y.; Maegawa, T.; Kita, Y.

Hypervalent Iodine(V)-Induced Asymmetric Oxidation of Sulfides to Sulfoxides Mediated by Reversed Micelles: Novel Nonmetallic Catalytic System. *J. Org.Chem.*, **1999**, *64*, 3519-3523.

(2)Folli, U.; Iarossi, D; Taddei, F. Intramolecular hydrogen bonds in aromatic sulphoxides: ^{1}H nuclear magnetic resonance and acidity constant measurements. *J. Chem. Soc., Perkin Trans. 2*, 1973, 848-853.