Antroquinonol A: Scalable Synthesis and Biology of a Phase-2 Drug Candidate

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SUPPORTING INFORMATION

Part 1: Experimental Procedures and Characterization Data

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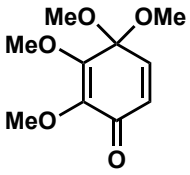
General Experimental. All reactions were carried out under an inert argon atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Dry dichloromethane (DCM), tetrahydrofuran (THF), toluene (PhMe) and were obtained by passing the previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using UV light as the visualising agent and an acidic solution of *p*-anisaldehyde and heat, or $KMnO_4$ and heat as developing agents. Flash silica gel chromatography was performed using E. Merck silica gel (60, particle size 0.043–0.063 mm). Chiral HPLC was performed using a Hitachi LaChrom Elite HPLC system. NMR spectra were recorded on Bruker DRX-600 and AMX-400 instruments and were calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ @ 7.26 ppm ^{1}H-NMR, 77.16 ppm ^{13}C-NMR). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra

(HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionisation time-of-flight (ESI-TOF) reflectron experiments. Optical rotations were obtained on a Perkin-Elmer 341 polarimeter. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected.



SI1

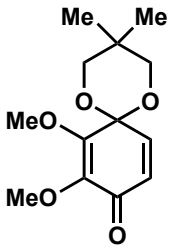
2,3,4,4-tetramethoxycyclohexa-2,5-dien-1-one SI1. To a flame-dried 250 mL round-bottomed flask equipped with a stir bar were added 2,3,4-trimethoxybenzaldehyde **11** (10.00 g, 50.97 mmol, 1.00 equiv), MeOH (100 mL), and H_2SO_4 (1.0 mL, 18 mmol, 0.35 equiv). The reaction flask was cooled to 0 ºC, upon which H_2O_2 (35% in H_2O; 5.67 mL, 65.85 mmol, 1.3 equiv) was added. The reaction flask was removed from the ice-water bath and the mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc (300 mL) and was washed with $NaHCO_3$ (sat. aq.: 200 mL) followed by brine (200 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated to give crude phenol.

The crude phenol (~10 g) was dissolved in MeOH (175 mL) and was cooled to 0°. A solution of (diacetoxyiodo)benzene (19.2 g, 59.5 mmol) in MeOH (150 mL) was added dropwise over 30 min. The reaction flask was then stirred for an additional hour at 0° before $NaHCO_3$ (sat. aq.; 300 mL) was added. The MeOH was removed on a rotary evaporator before the mixture was diluted with EtOAc (300 mL). The two resulting layers were separated, and the aqueous layer was extracted again with EtOAc (200 mL). It was then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to yield a red liquid. Column chromatography (SiO_2, 1:5 to 1:3 Et_2O/hexanes) provided an orange, slightly viscous liquid (7.97 g, 73 %).

Appearance: Orange liquid

All spectroscopic data matched the reported lit.[1]

TLC: R_f = 0.25 (1:3 Et_2O/hexanes, UV active, stains orange upon *vanillin* staining).



12

7,8-dimethoxy-3,3-dimethyl-1,5-dioxaspiro[5.5]undeca-7,10-dien-9-one 12. To a flame-dried 250 mL round bottom flask equipped with stir bar were added **SI1** (5.0 g, 23.34 mmol, 1.0 equiv), toluene (150 mL), 2,2-dimethyl-1,3-propanediol (4.86 g, 46.68 mmol, 2.0 equiv) and finally pyridinium *p*-toluenesulfonate (586.0 mg, 2.334 mmol, 0.1 equiv). This mixture was then heated to 60 ºC and stirred for one hour during which time the reaction turned an orange-red color. The vessel was then allowed to cool to room temperature, diluted with EtOAc (100 mL) and washed with $NaHCO_3$ (200 mL) followed with brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo* to give a crude solid. The product was purified by recrystallization from 20% Et_2O/Hex (12 mL per 1 g of crude) which provided white needles (5.16 g, 87%).

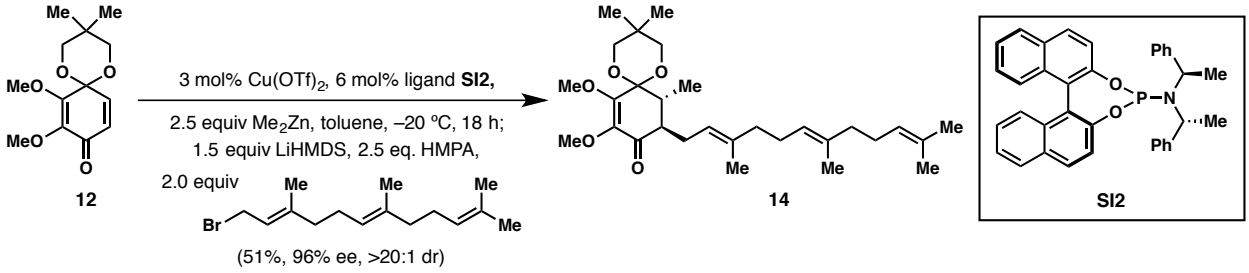
Appearance: White needles (MP = 33–35 ºC)

TLC: R_f = 0.30 (1:3 Et_2O/hexanes, UV active, stains dark green upon *vanillin* staining).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 10.4 Hz, 1 H), 6.10 (d, *J* = 10.4 Hz, 1 H), 4.17 (s, 3H), 3.82 (d, *J* = 11.4 Hz, 2 H), 3.74 (s, 3 H), 3.70 (d, *J* = 11.4 Hz, 2 H), 1.28 (s, 3 H), 0.89 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 183.3, 157.6, 137.4, 135.4, 126.8, 92.3, 72.0, 61.5, 61.1, 30.3, 22.8, 22.5 ppm.

HRMS (ESI-TOF): calc'd for $C_{13}H_{18}O_5$ [M+H^+] 254.1232, found 255.1229.



(11*R*)-7,8-dimethoxy-3,3,11-trimethyl-10-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-1,5-dioxaspiro[5.5]undec-7-en-9-one (+)-14. To a flame-dried 100 mL round-bottomed flask equipped with a stir bar were added copper(II) trifluoromethanesulfonate (42.6 mg, 0.118 mmol, 0.03 equiv), (S,R,R) phosphoramidite ligand **SI2**[2] (127.6 mg, 0.236 mmol, 0.06 equiv) and finally toluene (12 mL). This solution was stirred for one hour at room temperature under argon atmosphere before being cooled to –25 ºC. To this cooled solution was added spiroketal **12** (1.000 g, 3.93 mmol, 1.00 equiv) as a solution in 5 mL toluene and then dimethylzinc (1.2 M in toluene, 8.19 mL, 9.83 mmol, 2.50 equiv) dropwise over 15 minutes during which time the reaction turns a bright yellow color. This reaction was stored in a –20 ºC freezer for 18 hours. The reaction vessel was then placed in an ice water bath before lithium bis(trimethylsilyl)amide (1.0 M in THF, 5.90 mL, 5.90 mmol, 1.50 equiv), hexamethylphosphoramide (1.71 mL, 9.83 mmol, 2.50 equiv), and farnesyl bromide (2.13 mL, 7.87 mmol, 2.00 equiv) were added sequentially. The reaction was stirred at 0 ºC for 3 hours before being diluted with Et_2O (60 mL) and quenched with NH_4Cl (sat. aq.; 100 mL). The layers were separated and the aqueous layer was extracted two times with Et_2O (100 mL). All the organic layers were combined and then washed with water twice (100 mL) followed by brine (100 mL), and dried over $MgSO_4$. Evaporation *in vacuo* resulted in a clear yellow, non-viscous liquid. Column chromatography (SiO_2, 1:5 to 1:4 Et_2O/hexanes) provided a colorless, slightly viscous liquid (951.4 mg, 51 %).

Appearance: colorless oil.

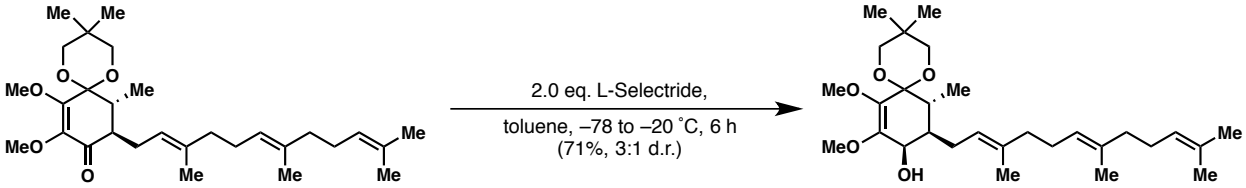
TLC: R_f = 0.65 (1:3 Et_2O/hexanes, UV active, stains dark blue upon *vanillin* staining).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.09–5.05 (m, 2 H), 5.00 (t, *J* = 7.1 Hz, 1 H), 4.10–4.06 (m, 4 H), 3.67–3.64 (m, 4 H), 3.55 (dd, *J* = 10.8, 1.2 Hz, 1 H), 3.43 (dd, *J* = 10.8, 1.2 Hz, 1 H), 2.69 (m, 1 H), 2.37–2.27 (m, 3 H), 2.07–1.94 (m, 8 H), 1.68 (s, 3 H), 1.62 (s, 3 H), 1.60 (s, 3 H), 1.58 (s, 3 H), 1.11–1.09 (m, 6 H), 0.88 (s, 3 H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 196.7, 163.2, 137.6, 137.5, 135.2, 131.4, 124.5, 124.2, 120.7, 97.1, 73.6, 71.3, 60.9, 60.5, 49.9, 40.0, 39.9, 38.6, 29.7, 27.8, 26.9, 26.8, 25.9, 23.4, 22.8, 17.8, 16.5, 16.1, 13.8 ppm.

HRMS (ESI-TOF): calc'd for $C_{29}H_{46}O_5$ [M^+] 474.3345, found 474.3345.

Optical rotation: $[\alpha]_D^{20}$ (c = 0.088, MeOH) = +51.1º.



(9*R*,10*R*,11*R*)-7,8-dimethoxy-3,3,11-trimethyl-10-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-1,5-dioxaspiro[5.5]undec-7-en-9-ol (+)-SI3. To a flame-dried 50 mL round-bottomed flask equipped with a stir bar were added **(+)-14** (1.04 g, 2.190 mmol, 1.00 equiv) and toluene (12 mL). The resulting solution was cooled to -78 ºC before L-selectride (1.0 M in THF, 4.38 mL, 4.38 mmol, 2.00 equiv) was added dropwise. This reaction was stirred for 2 hours at –78 ºC before being allowed to warm to –20 ºC over 4 hours. The mixture was then diluted with Et_2O (60 mL) and was filtered on a silica plug. The plug was washed with 30% EtOAc/Hex (100 mL). The solvents were removed *in vacuo* and column chromatography (SiO_2, 1:4 to 1:2 Et_2O/hexanes) provided the product as a colorless oil (783 mg, 1.643 mmol, 75 %).

Appearance: colorless oil

TLC: R_f = 0.30 (1:3 Et_2O/hexanes, UV active, stains dark blue upon *anisaldehyde* staining).

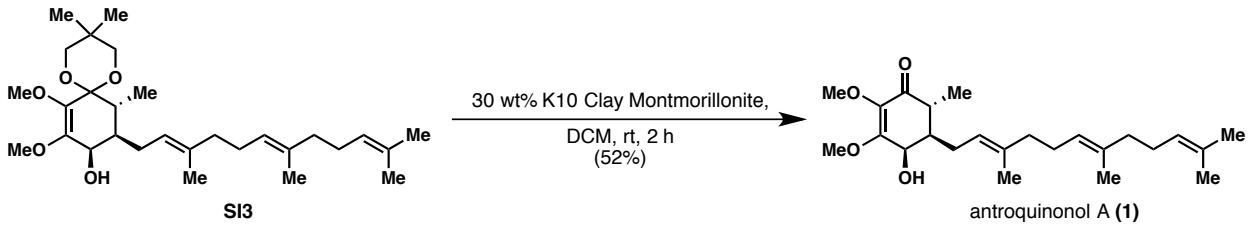
For the undesired diastereomer, R_f = *0.35*

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (t, *J* = 7.2 Hz, 1H), 5.09 (m, 2H), 4.25 (d, *J* = 10.4 Hz, 1H), 4.19 (t, *J* = 5.6, 3.4 Hz, 1H), 3.94 (d, *J* = 10.8 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.49 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.36 (dd, *J* = 10.8, 2.0 Hz, 1H), 2.23-1.92 (m, 10H), 1.83-1.74 (m, 2H), 1.68 (s, 3H), 1.66 (s, 3H), 1.59 (s, 6H), 1.16 (s, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.79 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 146.4, 144.3, 137.0, 135.3, 131.4, 124.5, 124.2, 122.6, 96.9, 73.8, 71.7, 66.5, 66.0, 59.9, 57.6, 40.6, 40.0, 39.9, 39.5, 29.5, 26.9, 26.8, 25.9, 23.9, 22.9, 17.8, 16.3, 16.2, 12.1 ppm.

HRMS (ESI-TOF): calc'd for $C_{29}H_{48}O_5$ [M^+] 476.3501, found 476.3502.

Optical rotation: $[\alpha]_D^{20}$ (c=0.00323, MeOH) = +80.2º.



(4*R*,5*R*,6*R*)-4-hydroxy-2,3-dimethoxy-6-methyl-5-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)cyclohex-2-en-1-one (+)-1. To a round-bottomed flask equipped with a stir bar were added **(+)-SI3** (783 mg, 1.64 mmol, 1.00 equiv) and dichloromethane (12 mL). The mixture was rapidly stirred at room temperature while K10 Clay Montmorillonite (228 mg, 30 wt%) was added. The heterogeneous mixture was stirred for 1 hour at room temperature. The mixture was then directly purified using column chromatography (SiO_2, 1:3 to 1:2 Et_2O/hexanes) provided a colorless, viscous liquid (333.6 mg, 52 %).

Appearance: clear oil

TLC: R_f = 0.25 (1:2 Et_2O/hexanes, UV active, stains dark blue upon *anisaldehyde* staining).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.16 (t, *J* = 7.2 Hz, 1H), 5.09 (t, *J* = 6.6 Hz, 2H), 4.35 (t, *J* = 3.6 Hz, 1H), 4.06 (s, 3H), 3.66 (s, 3H), 2.53 (m, 1H), 2.25 (t, *J* = 7.8 Hz, 2H), 2.13-2.02 (m, 6H), 2.00-1.95 (m, 2H), 1.75 (m, 1H), 1.68 (s, 3H), 1.66 (s, 3H), 1.60 (s, 6H), 1.17 (d, *J* = 6.6 Hz, 3H) ppm.

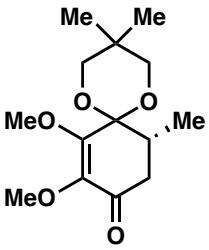
^{13}C NMR (150 MHz, $CDCl_3$): δ 197.3, 160.6, 138.2, 136.1, 135.5, 131.5, 124.5, 124.0, 121.1, 68.1, 60.8, 59.4, 43.5, 40.4, 40.0, 39.9, 27.2, 26.9, 26.6, 25.9, 17.8, 16.3, 16.2, 12.5 ppm.

HRMS (ESI-TOF): calc'd for $C_{24}H_{38}O_4$ [M^+] 390.2769, found 390.2770.

Optical rotation: $[\alpha]_D^{20}$ (c = 0.364, MeOH) = +52.0º.

*The enantiomer of **1**, **(-)-antroquinonol A,** was prepared from (-)-Enone **13** and tested for its oncological activity.

Optical rotation: $[\alpha]_D^{20}$ (c = 0.364, MeOH) = –57.1º.



13

(*R*)-7,8-dimethoxy-3,3,11-trimethyl-1,5-dioxaspiro[5.5]undec-7-en-9-one (+)-13. To a flame-dried 100 mL round-bottomed flask equipped with a stir bar were added copper(II) trifluoromethanesulfonate (42.6 mg, 0.118 mmol, 0.03 equiv), phosphoramidite ligand **SI2** (127.6 mg, 0.236 mmol, 0.06 equiv) and finally toluene (12 mL). This solution was stirred for one hour at room temperature under argon atmosphere before being cooled to –25 ºC. To this cooled solution was added spiroketal **12** (1.000 g, 3.93 mmol, 1.00 equiv) as a solution in 5 mL toluene and then dimethylzinc (1.2 M in toluene, 8.19 mL, 9.83 mmol, 2.50 equiv) dropwise over 15 minutes during which time the reaction turns a bright yellow color. This reaction was stored in a –20 ºC

freezer for 18 h. The mixture was then diluted with Et_2O (100 mL) and quenched with NH_4Cl (sat. aq.; 100 mL). The layers were separated and the aqueous layer was extracted two times with Et_2O (2x50 mL). The organic layers were combined and washed with NaOH (1M, 100 mL) and brine (100 mL), and then dried over anhydrous $MgSO_4$. Evaporation *in vacuo* resulted in a clear yellow, viscous liquid. Column chromatography (SiO_2, 1:5 to 1:4 Et_2O/hexanes) provided a white crystalline solid (584.2 mg, 55 %). ***(*R*)-7,8-dimethoxy-3,3,11-trimethyl-1,5-dioxaspiro[5.5]undec-7-en-9-one (-)-13** was prepared with an identical procedure but the opposite ligand enantiomer (R, S, S).

Appearance: White crystalline solid

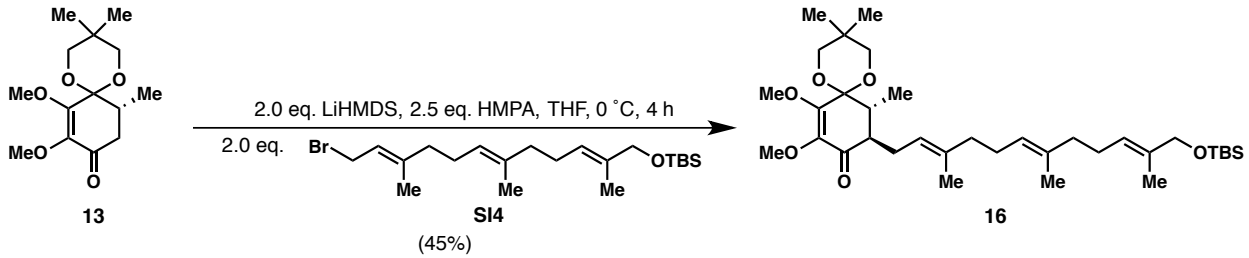
TLC: R_f = 0.35 (1:3 Et_2O/hexanes, UV active, stains orange upon *vanillin* staining).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11 (s, 3 H), 3.95 (d, *J* = 10.8 Hz, 1 H), 3.76 (d, *J* = 10.8 Hz, 1H), 3.67 (s, 3H), 3.58 (dd, *J* = 10.8, 1.2 Hz, 1 H), 3.51 (dd, *J* = 10.8, 1.2 Hz, 1 H), 2.62–2.49 (m, 2 H), 2.38–2.34 (m, 1 H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.06 (s, 3H), 0.95 (s, 3 H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 194.7, 162.9, 137.8, 97.4, 73.1, 71.5, 60.9, 60.8, 41.1, 35.5, 29.8, 23.2, 22.8, 14.5 ppm.

HRMS (ESI-TOF): calc'd for $C_{14}H_{22}O_5$ [M^+] 270.1467, found 270.1467.

Optical rotation: $[\alpha]_D^{20}$ (c = 0.011, MeOH) = +98.2º.



(10*R*,11*R*)-10-((2*Z*,6*E*,10*E*)-12-((*tert*-butyldimethylsilyl)oxy)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-7,8-dimethoxy-3,3,11-trimethyl-1,5-dioxaspiro[5.5]undec-7-en-9-one (+)-16. To a flame-dried 100 mL round-bottomed flask equipped with a stir bar was added **13** (180 mg, 0.66 mmol, 1.00 equiv), dry THF (2 mL) and hexamethylphosphoramide (0.3 mL). The mixture was cooled to -30°C and lithium bis(trimethylsilyl)amide (1M in THF, 1.33 mL, 1.33 mmol, 2.00 equiv) was added dropwise. The reaction mixture was stirred at this temperature for 15 min before bromide **SI4** (554 mg, 1.33 mmol, 2.00 equiv) in dry THF (1 mL) was added dropwise. **SI4** was prepared by mesylation/bromination of the corresponding allylic alcohol[3] and was used without isolation or purification. The mixture was warmed to 0°C and stirred for 4 hours and then quenched with NH_4Cl (sat. aq.: 30 mL) and extracted twice with Et_2O (2x30 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified using column chromatography (15% EtOAc/Hex) to yield (+)-**16** (181.3 mg, 45 %) as a colorless oil.

Appearance: clear oil.

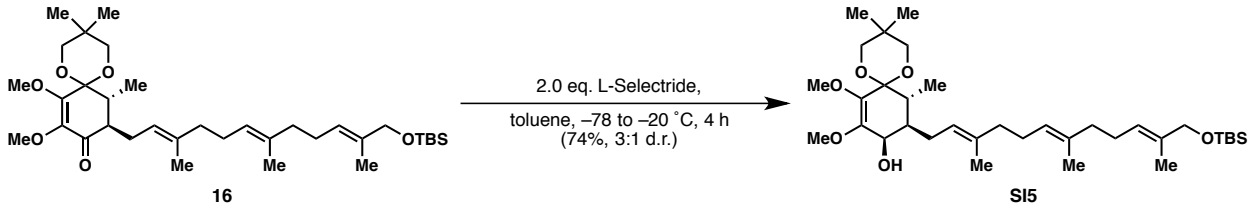
TLC: R_f = 0.65 (1:3 Et_2O/hexanes, UV active, stains dark blue upon *vanillin* staining).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.36 (t, J = 6.3 Hz, 1H), 5.08 (t, J = 6.3 Hz, 1H), 4.99 (t, J = 7.3 Hz, 1H), 4.09 (s, 3H), 4.07 (d, J = 10.7 Hz, 1H), 3.99 (s, 2H), 3.65 (d, J = 10.7 Hz, 1H), 3.63 (s, 3H), 3.55 (d, J = 10.7 Hz, 1H), 3.43 (d, J = 10.7 Hz, 1H), 2.70-2.66 (m, 1H), 2.39-2.34 (m, 1H), 2.33-2.25 (m, 2H), 2.15-1.92 (m, 8H), 1.61 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.09 (m, 6H), 0.90 (s, 9H), 0.88 (s, 3H), 0.05 (s, 6H)ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 196.7, 163.2, 137.5, 137.4, 135.0, 134.4, 124.5, 124.4, 120.7, 97.1, 73.6, 71.3, 68.8, 60.9, 60.5, 49.9, 40.0, 39.5, 38.5, 29.7, 27.8, 26.8, 26.3, 26.1, 23.4, 22.8, 18.6, 16.5, 16.1, 13.8, 13.6, -5.1 ppm.

HRMS (ESI-TOF): calc'd for $C_{35}H_{60}O_6Si$ [M^+] 604.4158, found 604.4159.

Optical rotation: $[\alpha]_D^{20}$ (c = 0.123, MeOH) = +25.9º



(9*R*,10*R*,11*R*)-10-((2*Z*,6*E*,10*E*)-12-((*tert*-butyldimethylsilyl)oxy)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-7,8-dimethoxy-3,3,11-trimethyl-1,5-dioxaspiro[5.5]undec-7-en-9-ol (+)-SI5. To a flame-dried 50 mL round-bottomed flask equipped with a stir bar were added **(+)-16** (100.0 mg, 0.165 mmol, 1.00 equiv) and toluene (1 mL). The resulting solution was cooled to -78 ºC before L-selectride (1.0 M in THF, 0.33 mL, 0.33 mmol, 2.00 equiv) was added dropwise. This reaction was stirred for 2 hours at –78 ºC before being allowed to warm to –20 ºC over 4 hours. The mixture was then diluted with Et_2O (3 mL) and was filtered on a silica plug. The plug was washed with 30% EtOAc/Hex (10 mL). The solvents were removed *in vacuo* and column chromatography (SiO_2, 1:4 to 1:2 Et_2O/hexanes) provided the product as a colorless, slightly viscous liquid (74.2 mg, 74 %).

Appearance: clear liquid

TLC: R_f = 0.30 (1:3 Et_2O/hexanes, UV active, stains dark blue upon *anisaldehyde* staining).

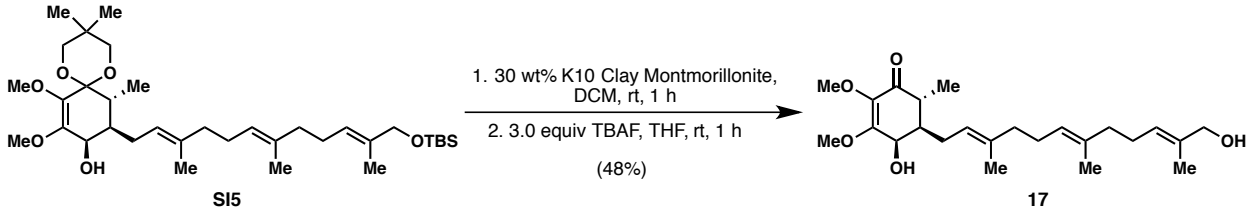
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.36 (dd, *J* = 6.8, 1.4 Hz, 1H), 5.19 (t, *J* = 6.8 Hz, 1H), 5.11 (t, *J* = 6.8 Hz, 1H), 4.25 (d, *J* = 10.4 Hz, 1H), 4.18 (t, *J* = 4.9 Hz, 1H), 3.99 (s, 2H), 3.94 (d, *J* = 10.4 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.49 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.36 (dd, *J* = 10.4, 2.0 Hz,

1H), 2.22-1.92 (m, 10H), 1.78 (m, 2H), 1.65 (s, 3H), 1.59 (s, 6H), 1.15 (s, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.79 (s, 3H), 0.05 (s, 6H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 146.3, 144.3, 136.9, 135.1, 134.4, 124.5, 124.4, 122.5, 96.9, 73.7, 71.7, 68.8, 66.5, 59.9, 57.6, 40.6, 40.0, 39.6, 39.5, 29.5, 26.9, 26.8, 26.3, 26.1, 23.9, 22.9, 18.6, 16.4, 16.1, 13.6, 12.1, -5.1 ppm.

HRMS (ESI-TOF): calc'd for $C_{35}H_{62}O_6Si$ [M+H$^+$] 607.4388, found 607.4389.

Optical rotation: $[\alpha]_D^{20}$ (c=0.0034, MeOH) = +61.76º.



(4*R*,5*R*,6*R*)-4-hydroxy-5-((2*Z*,6*E*,10*E*)-12-hydroxy-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-2,3-dimethoxy-6-methylcyclohex-2-en-1-one (+)-17. To a round-bottomed flask equipped with a stir bar were added **(+)-SI5** (50 mg, 0.08 mmol, 1.00 equiv) and dichloromethane (1 mL). The mixture was rapidly stirred at room temperature while K10 Clay Montmorillonite (15 mg, 30 wt%) was added. The heterogeneous mixture was stirred for 1 hour at room temperature. The mixture was then filtered through a glass-frit funnel and the resulting solution was concentrated *in* vacuo to give the crude mixture as a clear oil. The oil was dissolved in dry THF (1 mL) and TBAF (1M in THF, 0.24 mL, 0.24 mmol, 3.00 equiv) was added. The mixture was stirred for 1 h at room temperature before being directly purified by column chromatography (SiO_2, 1:9 to 3:5 EtOAc/Hex) to give the product as an oil (16.1 mg, 48 %).

Appearance: clear oil

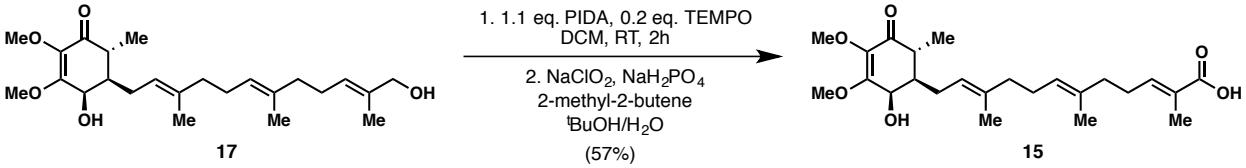
TLC: R_f = 0.25 (1:2 Et_2O/hexanes, UV active, stains dark blue upon *anisaldehyde* staining).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.41 (dd, *J* = 7.2, 1.3 Hz, 1H), 5.19 (dd, *J* = 7.2, 1.3 Hz, 1H), 5.12 (dd, *J* = 7.2, 1.3 Hz, 1H), 4.38 (d, *J* = 3.5 Hz, 1H), 4.09 (s, 3H), 4.02 (s, 2H), 3.69 (s, 3H), 2.56 (m, 1H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.20-2.00 (m, 8H), 1.77 (m, 1H), 1.68 (s, 3H), 1.63 (s, 3H), 1.58 (s, 3H), 1.20 (d, *J* = 6.9 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 197.3, 160.6, 138.1, 136.1, 135.0, 134.8, 126.0, 124.4, 121.2, 69.1, 68.1, 60.8, 59.5, 43.6, 40.5, 40.0, 39.4, 27.1, 26.5, 26.2, 16.3, 16.1, 13.9, 12.5 ppm.

HRMS (ESI-TOF): calc'd for $C_{24}H_{38}O_5$ [M+H$^+$] 407.2792, found 407.2793.

Optical rotation: $[\alpha]_D^{20}$ (c=0.0027, MeOH) = +58.5º.



(2*E*,6*E*,10*Z*)-12-((1*R*,2*R*,6*R*)-2-hydroxy-3,4-dimethoxy-6-methyl-5-oxocyclohex-3-en-1-yl)-2,6,10-trimethyldodeca-2,6,10-trienoic acid (+)-15. To a round-bottomed flask equipped with a stir bar were added **(+)-17** (7 mg, 0.017 mmol, 1.00 equiv), DCM (0.7 mL), TEMPO (0.5 mg, 0.0003 mmol, 0.20 equiv) and (bisacetoxyiodo)benzene (5.6 mg, 0.019 mmol, 1.10 equiv) at room temperature. The mixture was stirred until complete conversion of the alcohol (4 h). The mixture was then filtered on a silica plug and the plug was washed with 1:1 EtOAc/Hex (20 mL). The solvents were removed *in vacuo* and the crude mixture was dissolved in ^{t}BuOH/H_2O (4:1, 1 mL). 2-methyl-2butene (0.1 mL, excess) was added followed by NaH_2PO_4 (14.3 mg, 0.119 mmol, 7.00 equiv) and finally $NaClO_2$ (10.8 mg, 0.119 mmol, 7.00 equiv). The reaction mixture was stirred overnight and then diluted with EtOAc and washed with brine. The organic layer was

separated, dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The crude product was purified using preparative TLC (SiO_2, 7:3 EtOAc/Hex) to give the product as an oil (4.1 mg, 57 %).

Appearance: clear oil

TLC: R_f = 0.25 (1:2 Et_2O/hexanes, UV active, stains dark blue upon *anisaldehyde* staining).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 (t, *J* = 7.3 Hz, 1H), 5.18 (t, *J* = 7.3 Hz, 1H), 5.11 (m, 1H), 4.37 (d, *J* = 3.4 Hz, 1H), 4.06 (s, 3H), 3.66 (s, 3H), 2.58-2.48 (m, 1H), 2.34-2.17 (m, 4H), 2.15-1.98 (m, 7H), 1.83 (s, 3H), 1.64 (s, 3H), 1.61 (s, 3H), 1.17 (d, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 197.3, 171.4, 160.5, 144.8, 137.8, 136.1, 134.0, 126.9, 125.2, 121.4, 68.1, 60.8, 59.5, 43.7, 40.5, 39.9, 38.2, 27.3, 27.0, 26.3, 16.2, 16.0, 12.6, 12.3 ppm.

HRMS (ESI-TOF): calc'd for $C_{24}H_{36}O_6$ [M^+] 420.2511, found 420.2512.

Optical rotation: $[\alpha]_D^{20}$ (c=0.0029, MeOH) = +55.1°.

References:

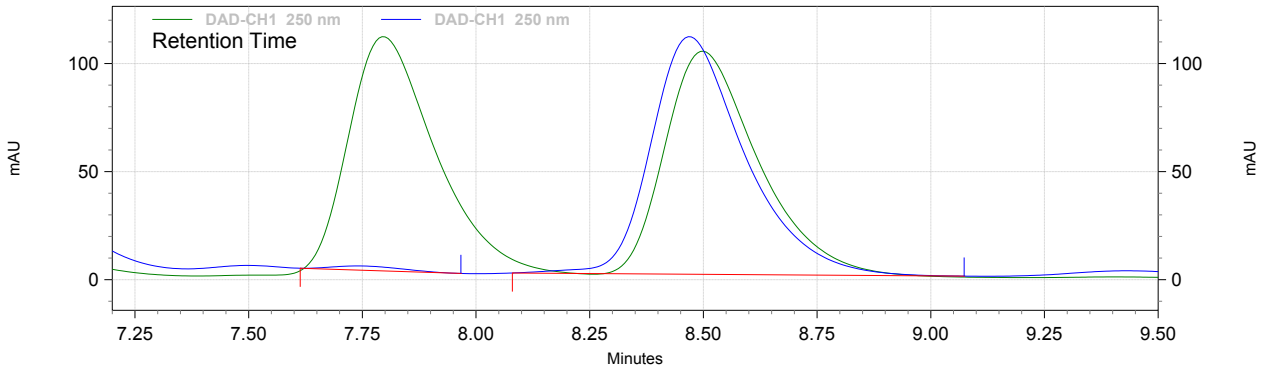
(1) Jim-Min F., *et al.*, *Org. Biomol. Chem.,* **2015**, *13*, 5510-5519.

(2) d'Augustin, M.; Palais, L., Alexakis A. *Angew. Chem. Int. Ed.*, **2005**, *44*, 1376–1378.

(3) Marshall, J. A.; Jenson, T. M.; DeMoff, B. S. *J. Org. Chem.* **1987**, *52*, 3860–3866.

Chiral HPLC for (+)-**13:**

ADH Column, 20% Ethyl Acetate in Hexanes, 0.8 mL/minute flow rate



DAD-CH1 250 nm Results

Retention Time	Area	Area %	Height	Height %
7.740	100807	1.28	9464	1.73
8.467	7750301	98.72	538609	98.27
Totals	7851108	100.00	548073	100.00

X-ray crystallographic data for (+)-**13**:

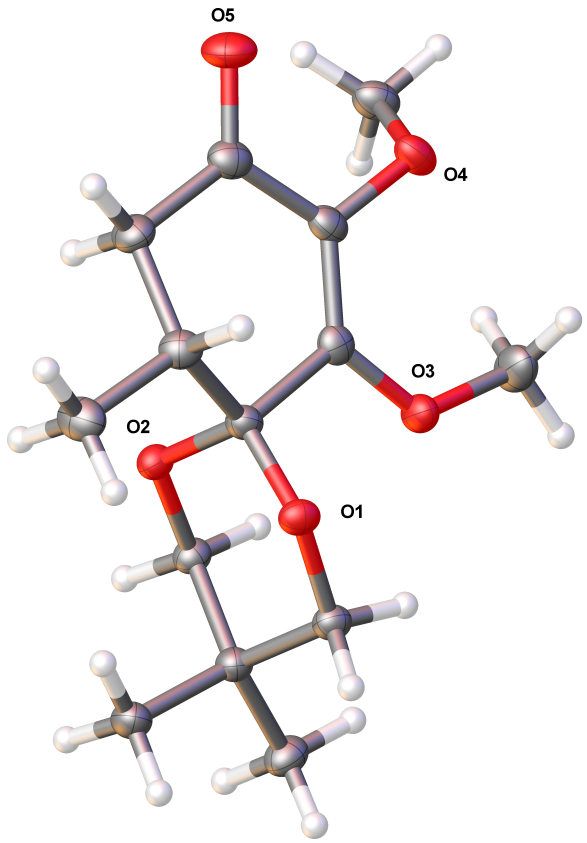


Table S1. Crystal data and structure refinement for Baran480.

Report date	2014-10-23	
Identification code	CCDC 1417155	
Empirical formula	C14 H22 O5	
Molecular formula	C14 H22 O5	
Formula weight	270.31	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 5.9867(7) Å	α= 90°.
	b = 13.6517(15) Å	β= 97.160(6)°.
	c = 8.5379(9) Å	γ = 90°.
Volume	692.35(13) $Å^3$	
Z	2	
Density (calculated)	1.297 Mg/m^3	
Absorption coefficient	0.807 mm^{-1}	

F(000)	292
Crystal size	0.161 x 0.124 x 0.053 mm^3
Crystal color, habit	Colorless Block
Theta range for data collection	5.221 to 68.188°.
Index ranges	-7<=h<=7, -16<=k<=16, -10<=l<=9
Reflections collected	9241
Independent reflections	2497 [R(int) = 0.0348]
Completeness to theta = 68.000°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.3201 and 0.2216
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2497 / 1 / 177
Goodness-of-fit on F^2	1.096
Final R indices [I>2sigma(I)]	R1 = 0.0287, wR2 = 0.0737
R indices (all data)	R1 = 0.0291, wR2 = 0.0743
Absolute structure parameter	0.04(7)
Extinction coefficient	n/a
Largest diff. peak and hole	0.145 and -0.177 e.$Å^{-3}$

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Baran480. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	8990(2)	4660(1)	6411(2)	20(1)
O(2)	5285(2)	4390(1)	5200(1)	19(1)
O(3)	6719(2)	6302(1)	6895(2)	23(1)
O(4)	3845(2)	6235(1)	9392(2)	24(1)
O(5)	2507(3)	4414(1)	10195(2)	32(1)
C(1)	6697(3)	4573(2)	6633(2)	19(1)
C(2)	5859(3)	5484(2)	7457(2)	20(1)
C(3)	4455(3)	5418(2)	8584(2)	21(1)
C(4)	3624(3)	4468(2)	9089(2)	24(1)
C(5)	4233(4)	3581(2)	8193(2)	25(1)
C(6)	6579(3)	3660(2)	7668(2)	23(1)
C(7)	7185(4)	2728(1)	6841(3)	29(1)

C(8)	6210(4)	7271(2)	7386(3)	33(1)
C(9)	1521(3)	6497(2)	8975(2)	26(1)
C(10)	9553(3)	5232(1)	5090(2)	20(1)
C(11)	8032(3)	5012(1)	3557(2)	19(1)
C(12)	5603(3)	5049(1)	3928(2)	19(1)
C(13)	8377(4)	5803(2)	2344(2)	26(1)
C(14)	8578(4)	4007(2)	2913(2)	25(1)

Table S3. Bond lengths [Å] and angles [°] for Baran480.

O(1)-C(1)	1.414(2)	C(13)-H(13A)	0.9800
O(1)-C(10)	1.446(2)	C(13)-H(13B)	0.9800
O(2)-C(1)	1.420(2)	C(13)-H(13C)	0.9800
O(2)-C(12)	1.440(2)	C(14)-H(14A)	0.9800
O(3)-C(2)	1.343(2)	C(14)-H(14B)	0.9800
O(3)-C(8)	1.432(2)	C(14)-H(14C)	0.9800
O(4)-C(3)	1.385(2)		
O(4)-C(9)	1.438(2)	C(1)-O(1)-C(10)	118.32(13)
O(5)-C(4)	1.226(2)	C(1)-O(2)-C(12)	114.81(14)
C(1)-C(2)	1.543(3)	C(2)-O(3)-C(8)	123.95(16)
C(1)-C(6)	1.534(3)	C(3)-O(4)-C(9)	112.57(15)
C(2)-C(3)	1.357(3)	O(1)-C(1)-O(2)	112.49(14)
C(3)-C(4)	1.473(3)	O(1)-C(1)-C(2)	111.67(15)
C(4)-C(5)	1.501(3)	O(1)-C(1)-C(6)	105.12(15)
C(5)-H(5A)	0.9900	O(2)-C(1)-C(2)	110.01(15)
C(5)-H(5B)	0.9900	O(2)-C(1)-C(6)	106.78(15)
C(5)-C(6)	1.530(3)	C(6)-C(1)-C(2)	110.55(15)
C(6)-H(6)	1.0000	O(3)-C(2)-C(1)	110.28(15)
C(6)-C(7)	1.521(3)	O(3)-C(2)-C(3)	127.40(18)
C(7)-H(7A)	0.9800	C(3)-C(2)-C(1)	122.32(17)
C(7)-H(7B)	0.9800	O(4)-C(3)-C(4)	116.34(16)
C(7)-H(7C)	0.9800	C(2)-C(3)-O(4)	121.68(18)
C(8)-H(8A)	0.9800	C(2)-C(3)-C(4)	121.85(17)
C(8)-H(8B)	0.9800	O(5)-C(4)-C(3)	120.99(19)
C(8)-H(8C)	0.9800	O(5)-C(4)-C(5)	122.3(2)
C(9)-H(9A)	0.9800	C(3)-C(4)-C(5)	116.67(16)
C(9)-H(9B)	0.9800	C(4)-C(5)-H(5A)	109.1
C(9)-H(9C)	0.9800	C(4)-C(5)-H(5B)	109.1
C(10)-H(10A)	0.9900	C(4)-C(5)-C(6)	112.46(16)
C(10)-H(10B)	0.9900	H(5A)-C(5)-H(5B)	107.8
C(10)-C(11)	1.528(3)	C(6)-C(5)-H(5A)	109.1
C(11)-C(12)	1.528(2)	C(6)-C(5)-H(5B)	109.1
C(11)-C(13)	1.528(3)	C(1)-C(6)-H(6)	107.9
C(11)-C(14)	1.529(3)	C(5)-C(6)-C(1)	109.64(15)
C(12)-H(12A)	0.9900	C(5)-C(6)-H(6)	107.9
C(12)-H(12B)	0.9900	C(7)-C(6)-C(1)	112.39(15)

C(7)-C(6)-C(5)	110.94(17)	C(11)-C(12)-H(12B)	109.5
C(7)-C(6)-H(6)	107.9	H(12A)-C(12)-H(12B)	108.1
C(6)-C(7)-H(7A)	109.5	C(11)-C(13)-H(13A)	109.5
C(6)-C(7)-H(7B)	109.5	C(11)-C(13)-H(13B)	109.5
C(6)-C(7)-H(7C)	109.5	C(11)-C(13)-H(13C)	109.5
H(7A)-C(7)-H(7B)	109.5	H(13A)-C(13)-H(13B)	109.5
H(7A)-C(7)-H(7C)	109.5	H(13A)-C(13)-H(13C)	109.5
H(7B)-C(7)-H(7C)	109.5	H(13B)-C(13)-H(13C)	109.5
O(3)-C(8)-H(8A)	109.5	C(11)-C(14)-H(14A)	109.5
O(3)-C(8)-H(8B)	109.5	C(11)-C(14)-H(14B)	109.5
O(3)-C(8)-H(8C)	109.5	C(11)-C(14)-H(14C)	109.5
H(8A)-C(8)-H(8B)	109.5	H(14A)-C(14)-H(14B)	109.5
H(8A)-C(8)-H(8C)	109.5	H(14A)-C(14)-H(14C)	109.5
H(8B)-C(8)-H(8C)	109.5	H(14B)-C(14)-H(14C)	109.5
O(4)-C(9)-H(9A)	109.5		
O(4)-C(9)-H(9B)	109.5		
O(4)-C(9)-H(9C)	109.5		
H(9A)-C(9)-H(9B)	109.5		
H(9A)-C(9)-H(9C)	109.5		
H(9B)-C(9)-H(9C)	109.5		
O(1)-C(10)-H(10A)	109.0		
O(1)-C(10)-H(10B)	109.0		
O(1)-C(10)-C(11)	112.98(14)		
H(10A)-C(10)-H(10B)	107.8		
C(11)-C(10)-H(10A)	109.0		
C(11)-C(10)-H(10B)	109.0		
C(10)-C(11)-C(13)	108.96(16)		
C(10)-C(11)-C(14)	110.69(16)		
C(12)-C(11)-C(10)	107.25(15)		
C(12)-C(11)-C(13)	109.26(15)		
C(12)-C(11)-C(14)	110.90(15)		
C(13)-C(11)-C(14)	109.74(16)		
O(2)-C(12)-C(11)	110.74(14)		
O(2)-C(12)-H(12A)	109.5		
O(2)-C(12)-H(12B)	109.5		
C(11)-C(12)-H(12A)	109.5		

Table S4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Baran480. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	16(1)	25(1)	20(1)	1(1)	3(1)	1(1)
O(2)	18(1)	20(1)	18(1)	1(1)	2(1)	-2(1)
O(3)	26(1)	17(1)	27(1)	-3(1)	9(1)	-1(1)
O(4)	21(1)	29(1)	22(1)	-7(1)	2(1)	4(1)
O(5)	35(1)	38(1)	25(1)	5(1)	13(1)	2(1)
C(1)	18(1)	20(1)	18(1)	-1(1)	4(1)	1(1)
C(2)	18(1)	22(1)	19(1)	-1(1)	-2(1)	1(1)
C(3)	21(1)	26(1)	17(1)	-4(1)	1(1)	2(1)
C(4)	23(1)	30(1)	18(1)	1(1)	1(1)	2(1)
C(5)	30(1)	23(1)	24(1)	4(1)	8(1)	-3(1)
C(6)	24(1)	24(1)	21(1)	4(1)	3(1)	2(1)
C(7)	38(1)	21(1)	29(1)	4(1)	8(1)	5(1)
C(8)	35(1)	20(1)	46(1)	-5(1)	15(1)	0(1)
C(9)	21(1)	32(1)	24(1)	-2(1)	4(1)	5(1)
C(10)	18(1)	23(1)	20(1)	0(1)	4(1)	-1(1)
C(11)	20(1)	20(1)	18(1)	0(1)	5(1)	-1(1)
C(12)	19(1)	20(1)	18(1)	3(1)	2(1)	-1(1)
C(13)	27(1)	27(1)	24(1)	5(1)	4(1)	-4(1)
C(14)	26(1)	25(1)	25(1)	-4(1)	9(1)	-2(1)

Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Baran480.

	x	y	z	U(eq)
H(5A)	3107	3493	7251	30
H(5B)	4176	2994	8869	30
H(6)	7690	3745	8635	27
H(7A)	6097	2620	5901	43
H(7B)	7151	2171	7561	43
H(7C)	8699	2793	6528	43
H(8A)	6900	7751	6740	49
H(8B)	6807	7361	8498	49
H(8C)	4574	7365	7254	49
H(9A)	1274	6695	7863	39
H(9B)	1139	7042	9639	39
H(9C)	565	5932	9137	39
H(10A)	11135	5097	4933	24
H(10B)	9434	5936	5341	24
H(12A)	5233	5725	4227	23
H(12B)	4571	4866	2976	23
H(13A)	7366	5681	1370	39
H(13B)	9942	5789	2117	39
H(13C)	8045	6447	2767	39
H(14A)	8486	3509	3729	38
H(14B)	10104	4015	2608	38
H(14C)	7496	3852	1988	38

in vitro/in vivo assays

in vitro cytotoxicity assay - Materials and Methods

All cell lines (A549, AsPC-1, HepG2, Hep3B, NCI-H441, LNCaP, MDA-MB-231 and PANC-1) were obtained from American Type Culture Collection (Manassas, VA). Cell lines were grown in RPMI 1640 media (Gibco) with 10% fetal bovine serum, heat inactivated (Sigma), 10mM HEPES (Gibco), and 1% penicillin/streptomycin (Gibco). All cell lines were maintained under routine maintenance conditions (37 ^{o}C, 5% CO2, high humidity).
An aliquot of each cell line was seeded to each well of a 384-well plate (Greiner) using the same growth media as outlined above. Cells were allowed to attach 24 hours before compound addition. Compounds were solubilized and serially diluted immediately prior to compound addition to cells. Following a 72 hour incubation with compound, cells were stained with CellTiter 96â Aqueous Non-Radioactive Cell Proliferation MTS stain (Promega) to determine in vitro cytotoxicity. Plates were incubated at 37 ^{o}C for 3hrs, and absorbance then measured at 492nm.

Assessment of *In Vivo* Antitumor Activity in the Subcutaneously Implanted Hep3B Hepatocellular Carcinoma Xenograft Model in NSG Mice.

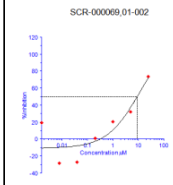
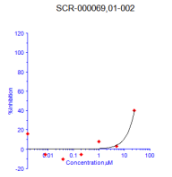
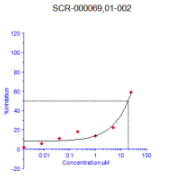
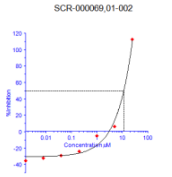
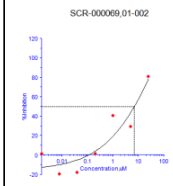
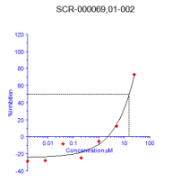
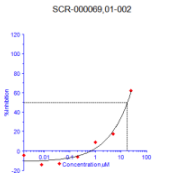
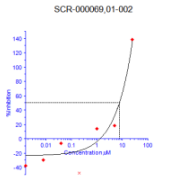
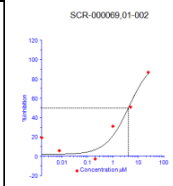
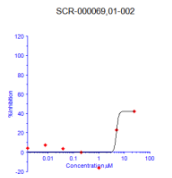
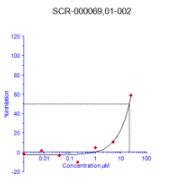
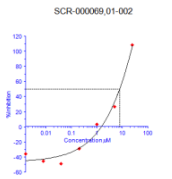
Female NSG (NOD.Cg-Prkdc^{scid} *Il2rg*tm^{1Wjl}/SzJ) mice, 6–8 weeks old, were obtained from the Jackson Laboratory. Animals were provided with food and water ad libitum and housed five per cage. Mice were maintained in accordance with Bristol-Myers Squibb's Institutional Animal Care and Use Committee in accordance with the American Association for Accreditation of Laboratory Animal Care (AAALAC) guidelines for the humane treatment and care of laboratory mice.
Hep3B tumor fragments maintained by serial passage *in vivo* were implanted subcutaneously in the hind flank using an 18 g trocar. Compound or vehicle dosing was initiated approximately two weeks post implant, when tumor sizes reached 75-100 mm^3. Compound 1in corn oil was administered intraperitoneally (i.p.) at 50 mg/kg on a QD × 14 schedule, whereas paclitaxel in Cremophor/EtOH (50:50 diluted 1:4 in saline prior to injection) was administered intravenously (i.v.) at its optimed (MTD) preclinical regimen of 24 mg/kg using a Q2D ´ 5 schedule. The vehicle control group was given corn oil. Tumor growth was assessed twice weekly by vernier caliper measurement. Group sizes were n = 6 with double sided tumor implants.
Antitumor activity was determined by calculating the maximum percent tumor growth inhibition (TGI) of treated animals using the formula: %TGI = $\{(C_t-T_t)/(C_t-C_0)\} \times 100$ where C_t = the median tumor volume (mm^3) of vehicle treated control (C) mice at time t. T_t = median tumor volume of treated (T) mice at time t. C_0 is the median tumor volume of control mice at time 0. Activity is defined as a continuous %TGI >70% for at least one tumor volume doubling time after the start of drug treatment. Standard error of the mean was calculated using IDBS EWorkBook built in software formula in Quantrix spreadsheets.

Cell Line	IC50 µM (72h)* duplicate data
MDA-MB-231	>25
HepG2	>25
LNCaP	>25
Hep 3B	8 ± 1.2
PANC-1	>25
AsPC-1	>25
A549	14.5 ± 1.1
H441	>25

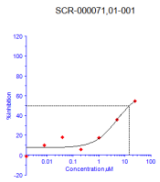
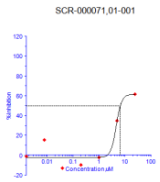
Table S6. Oncology panel *in vitro* data for (-)-Antroquinonol A (ent-**1**)
* incubation time. Source of cell lines: ATCC.

IC50 Curves for (1), (15) and enantiomer of antroquinonol (ent-1):

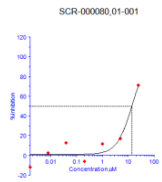
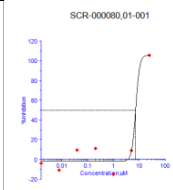
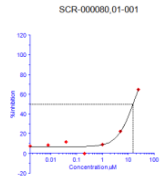
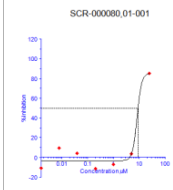
Compound 1

A549		LNCAP		MB-231		HEP3B	
IC50,uM	Graph	IC50,uM	Graph	IC50,uM	Graph	IC50,uM	Graph
8.95		>25		18.89		11.38	
6.95		15.59		17.84		7.61	
4.05		>25		21.06		7.82	

Compound 15

	A549
IC50,uM	Graph
14.88	
6.63	

Compound 1 - enantiomer

	A549		HEP3B
IC50,uM	Graph	IC50,uM	Graph
13.74		7.21	
15.26		8.91	

Experimental protocol for metabolite identification using mouse liver microsomes

MsLM incubation was carried out in 1 mg/ml microsomal proteins with 5 μM drug and 1 mM NADPH at 37 ^{o}C. LC/UV/MS analysis was done with Shimadzu LC-30AD LC pumps coupled with a SPD-M20A PDA detector and a Thermo LTQ Orbitrap mass spectrometer. The LC was run on a Water Acuity UPLC HSS T3 column (2.1x150 mm) in water/acetonitrile solvents and 0.1% formic acid at a flow rate of 0.5 ml/min. The LC gradient was a linear gradient of 25% - 98% acetonitrile in 9-min, after an initial ramp from 10% to 25% acetonitrile in 0.2-min. The UV traces exhibited in Fig. 2A were extracted at a wavelength range of 265 - 270 nm. A similar protocol was used for human and rat liver microsomes and for hepatocytes.

Metabolism of 1 in rat hepatocytes

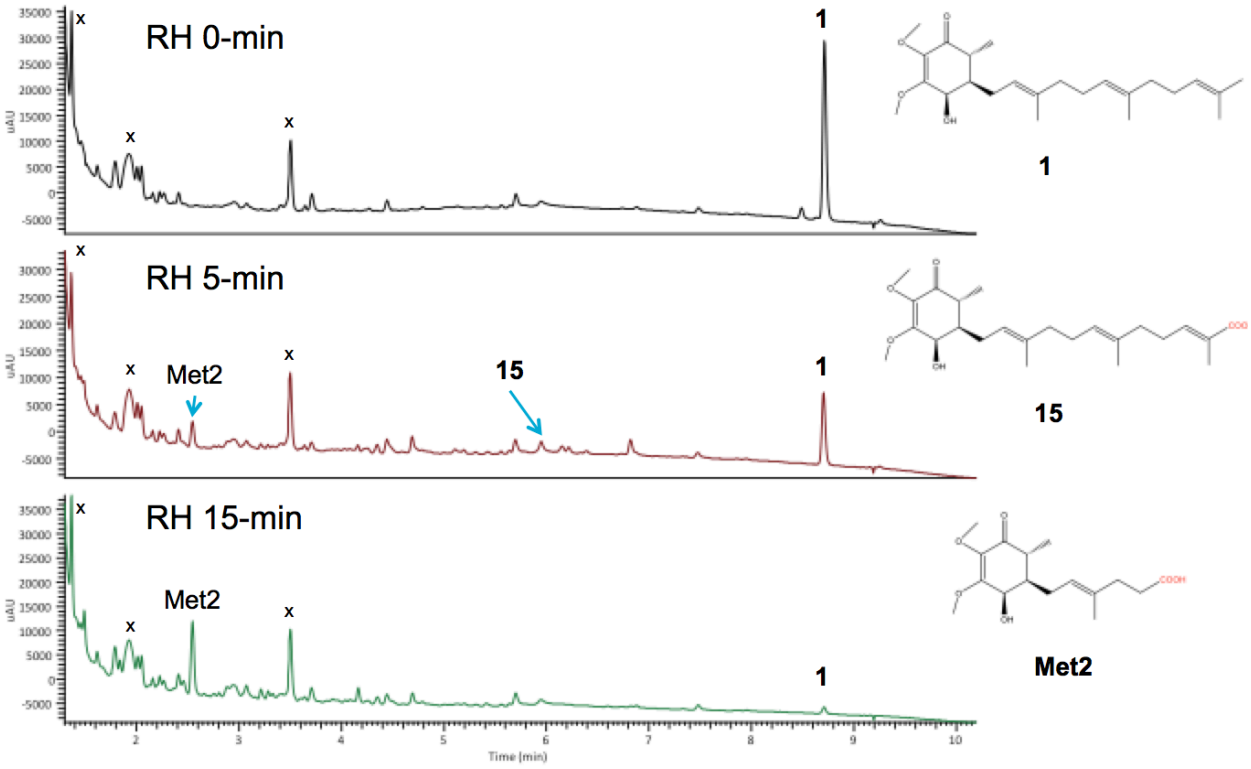


Figure S1. Major metabolite in Rat Hepatocytes was **Met2**
x = sample matrix peaks, not parent related; 5-µM drug, ~2 million cells/ml, UV 260-270nm.

Metabolism of 1 in human hepatocytes

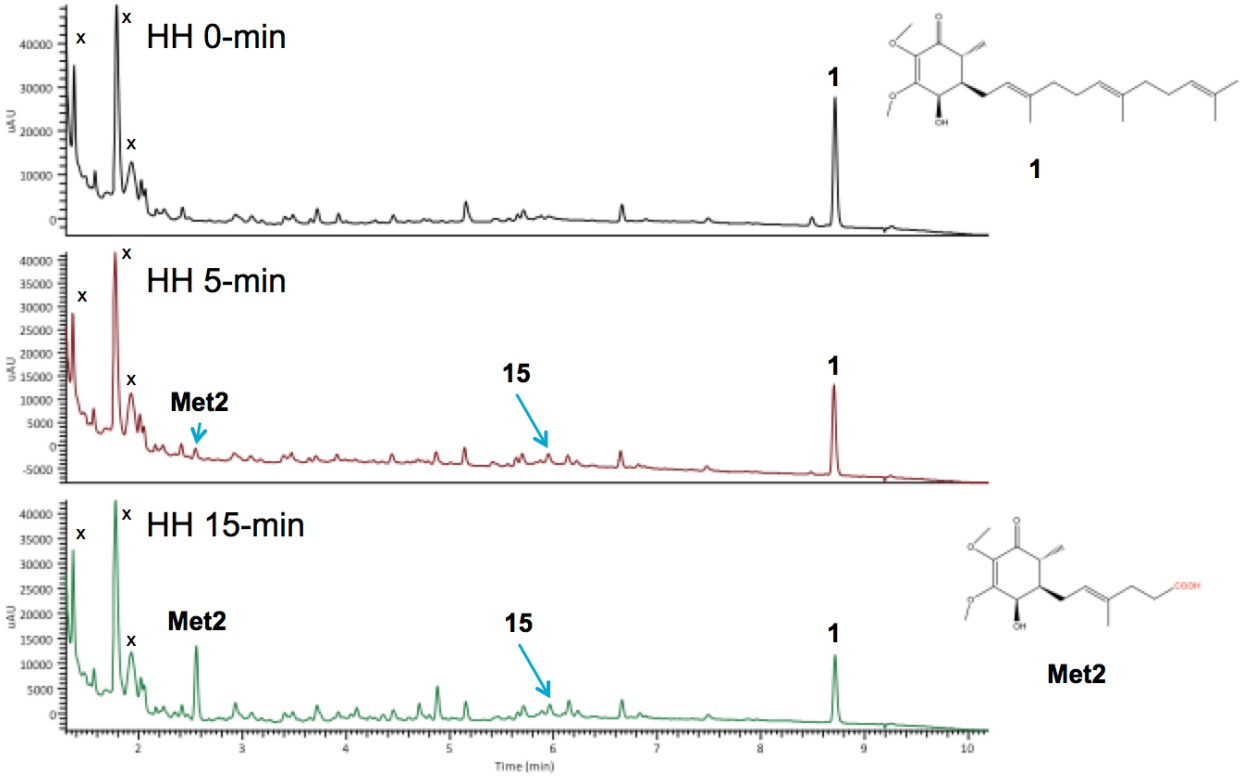


Figure S2. Major metabolite in Human Hepatocytes was **Met2.**
x = sample matrix peaks, not parent related; 5-µM drug, ~2 million cells/ml, UV 260-270nm.

Metabolism of 1 in mouse hepatocytes

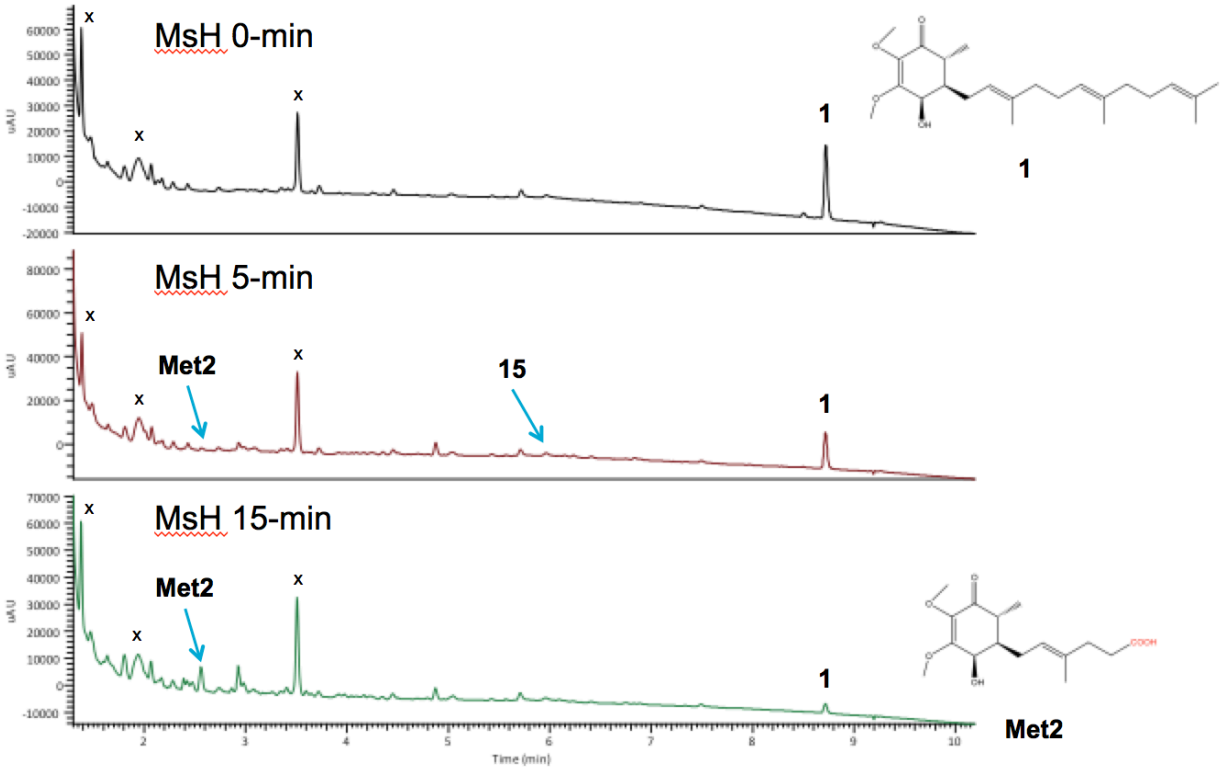


Figure S3. Major metabolite in Mouse Hepatocytes was **Met2**.
x = sample matrix peaks, not parent related; 5-µM drug, ~2 million cells/ml, UV 260-270nm.

Metabolism of 1 in human liver microsomes

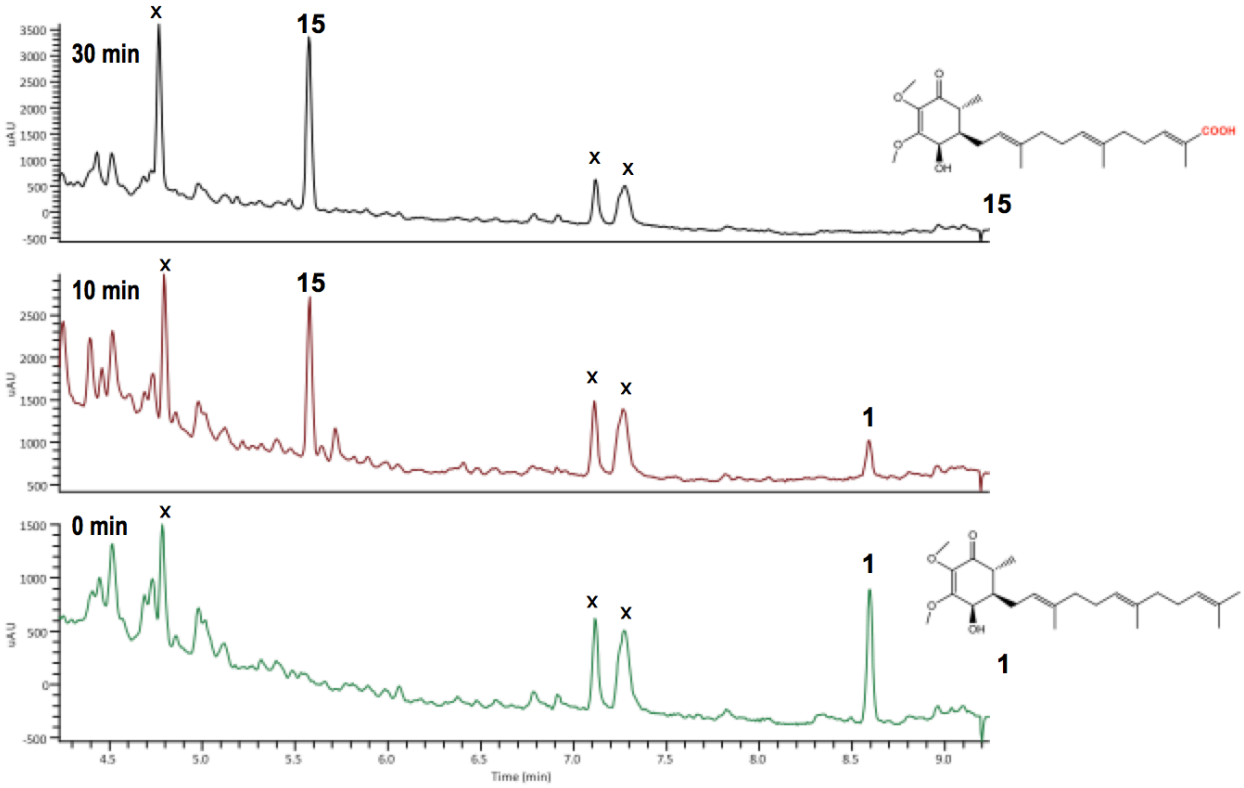


Figure S4. Major Metabolite in Human Liver Microsome was **15**.
x = sample matrix peaks, not parent related; 5-µM drug, 1-mg/ml microsomal protein, UV 265-270nm.

Mouse PK protocol: Compound **1** (50 mg/kg) was administered to male Balb/C mice (n = 3 per group, 20–25 g each) as an intraperitoneal injection (i.p) and oral (p.o) dose formulated in 100% Corn oil (10mL/kg). Blood samples (~15 μL) were obtained by retro-orbital bleeding at 0.5, 1, 2, 4, and 7 hours post dose. Aliquots of blood samples (15-μL) were spotted directly onto Ahlstrom 226 DBS cards (PerkinElmer, Waltham, MA, USA). Samples were dried in ambient air for at least 2 hours and stored at room temperature in sealed bags with desiccant until analysis. A 6-mm disc from the center of the dried spot (equivalent to 12.5 μL of blood) was punched with a BSD600 Duet Automated Punch Instrument (Luminex, Austin, TX, USA), and the sample was delivered into a 96 format filter plate. A 35 μL aliquot of water was added and vortexed for 5 minutes, followed by 85 μL of acetonitrile containing the internal standard. The filter plate was then vortexed for an additional 30 minutes, centrifuged and supernatant was analyzed via LC-MS/MS.

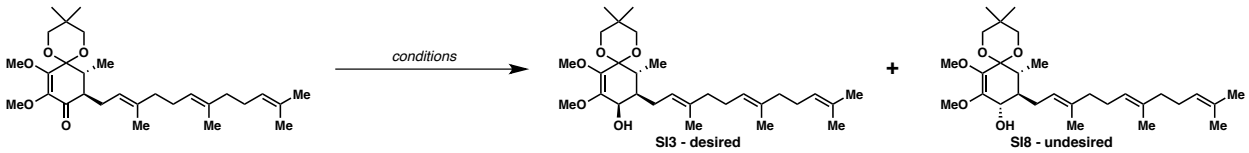
Raw data

Table 1: **Whole Blood Concentrations (nM) of compound 1 in Mice after a 50-mg/kg I ntraperitoneal (i.p.) injection**

Time (h)	Mouse A	Mouse B	Mouse C
0.5	243.9	241.1	271.0
1	418.2	398.5	320.9
2	321.2	509.6	428.3
4	316.6	333.8	342.4
7	434.1	256.4	186.1

Table 2: **Whole Blood Concentrations (nM) of compound 1 in Mice after a 50-mg/kg Oral (PO) Administration**

Time (h)	Mouse D	Mouse E	Mouse F
0.5	100.0	30.2	49.6
1	54.8	30.9	41.8
2	139.2	49.0	30.9
4	24.5	31.3	35.2
7	26.6	17.0	20.2



Entry	Conditions	Yield (%)*	d.r. (SI3:SI8)	Notes
1	1.3 eq. DIBAL-H, Et_2O, –78 ºC, 1 h	41	1:1.4	
2	1.3 eq. DIBAL-H, toluene, -78 ºC, 1 h	54	1:4	
3	1.3 eq. DIBAL-H, THF, -78 ºC, 6 h	27	1:2	~40% conversion
4	3.0 eq. DIBAL-H, 3.0 eq. $ZnCl_2$,THF, -78 ºC, 12 h	<5	n.d.	predominately elimination products
5	Red-Al, toluene, 0 ºC, 2 h	83	< 1:20	
6	$LiAlH(OtBu)_3$, THF, 0 ºC, 6 h	75	< 1:20	
7	2.0 eq. $NaBH_4$, DCM, MeOH, 0 ºC, 1 h	81	< 1:20	
8	2.0 eq. $LiBH_4$, 2.0 eq. $La(OTf)_3$, THF, 0 ºC	72	1:9	
9	2.0 eq. $LiBH_4$, 2.0 eq. $YbCl_3$, THF, 0 ºC	0	< 1:20	
10	2.0 eq. $LiBH_4$, 2.0 eq. $BiCl_3$, THF, 0 ºC	0	< 1:20	
11	3.0 eq. $LiBH_4$, 3.0 eq. MAD-Al, toluene, -78 ºC	0	n.d.	predominately elimination products
12	K-Selectride, THF, 0 ºC, 6 h	<5	n.d.	complicated mixture
13	L-Selectride, THF, 0 ºC, 6 h	<5	n.d.	<5% conversion
14	3.0 eq. L-Selectride, DCM, -78 ºC, 6 h	35	1:1.2	~50% conversion
15	3.0 L-Selectride, toluene, 0 ºC, 0.5 h	80	2:1	
16	2.0 L-Selectride, toluene, -78 ºC, 6 h	94	3:1	
17	2.5 eq. L-Selectride, 3.0 eq. $ZnCl_2$, toluene, -78 ºC, 3 h	64	< 1:20	
18	20 mol% (R)-2-methyl-CBS,1.2 eq. BH_3, THF, rt, 24 h	0	n.d.	<5% conversion
19	20 mol% (s)-2-methyl-CBS,1.2 eq. BH_3, THF, rt, 24 h	0	n.d.	<5% conversion
20	20 mol % $(PPh_3)_3RhCl$, 2.0 eq. Et_2SiH_2, benzene, 50 ºC, 18 h	n.d.	n.d.	<5% conversion
21	20 mol% $[Ir(cyclooctene)_2Cl]_2$, 2.0 eq. Ph_2SiH_2, benzene, 50 ºC, 24 h	n.d.	n.d.	<5% conversion
22	Ph_3BHK, THF, -78 to 0 ºC, 12 h	n.d.	< 1:20	~10% conversion

Figure S5. Screened conditions for reduction of **14**.

- = yield of mixture of diastereomers.

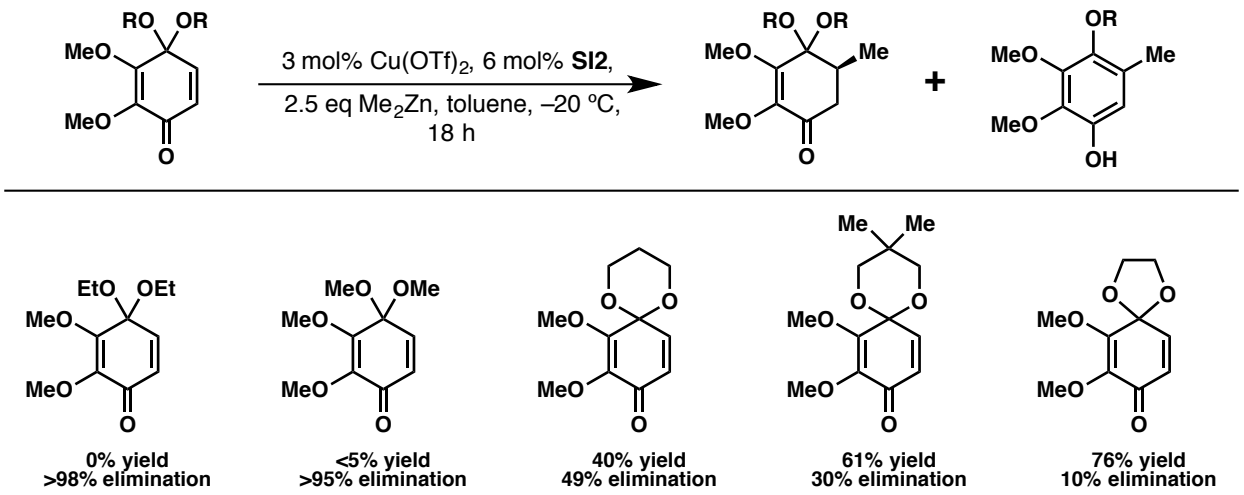


Figure S6. Screened ketal identity for conjugate additions.