Orally Active, Antimalarial, Anticancer, Artemisinin-Derived Trioxane Dimers with High Stability and Efficacy

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In only two steps and in 70% overall yield, naturally occurring trioxane artemisinin (**1**) was converted on a gram scale into C-10-carba trioxane dimer **3**. This new, very stable dimer was then transformed easily in one additional step into four different dimers **4**−**7**. Alcohol and diol dimers **4** and **5** and ketone dimer **7** are 10 times more antimalarially potent in vitro than artemisinin (**1**), and alcohol and diol dimers **4** and **5** are strongly growth inhibitory but not cytotoxic toward several human cancer cell lines. Water-soluble carboxylic acid derivatives **8a** and **9** were easily prepared in one additional step from dimers **4** and **5**. Carboxylic acid dimers **8a** and **9** are thermally stable even at 60 °C for 24 h, are more orally efficacious as antimalarials in rodents than either artelinic acid or sodium artesunate, and are strongly inhibitory but not cytotoxic toward several human cancer cell lines.

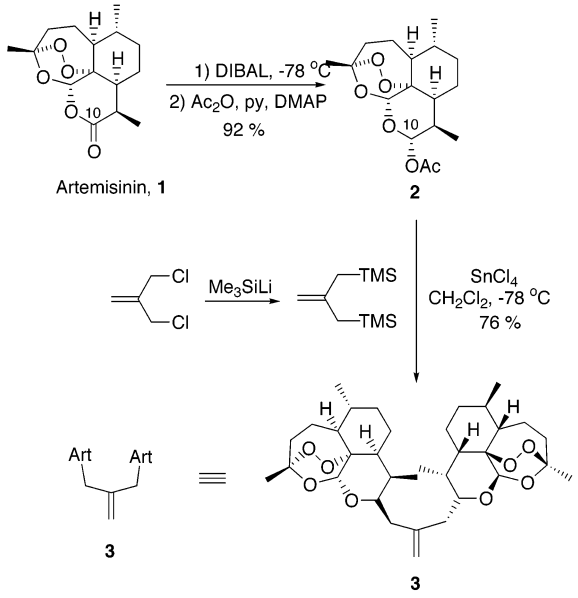
Introduction

Several 1,2,4-trioxane dimers have high in vitro antimalarial, antiproliferative, and antitumor activities,[1−5] and one has high in vivo anticancer activity.[6] When such dimers are semisynthesized from the natural Chinese antimalarial trioxane artemisinin (**1**), C-10 acetal derivatives are often unstable (i.e., easily hydrolyzed) in water.[4,7] Therefore, making hydrolytically stable C-10 non-acetal carba derivatives has become a high priority internationally.[7−16] Important also for development of practical new antimalarial drugs is keeping their synthesis short and their cost low.

Results

Pursuing our interest in trioxane dimers,[4−6] we now describe high-yield conversion of easily prepared C-10 acetate **2** in one step directly into C-10 non-acetal trioxane dimer **3** (Scheme 1). Inspiration for this bis-allylation of C-10 acetate **2** was based on the pioneering trioxane monoallylations of Ziffer[9] and O'Neill[17,18] using allylsilane and based also on allylic bis-silane chemistry.[19] The requisite allylic bis-silane was easily prepared in one step from the corresponding commercial allylic dichloride (Scheme 1); in the presence of tin tetrachloride, the allylic bis-silane converted acetate **2** on a gram scale into dimer **3**, characterized by ^{1}H NMR spectroscopy as done before in structurally related trioxanes.[20,21] This double-substitution reaction undoubtedly proceeded sequentially via initial monoallylation, producing an intermediate C-10 trioxane allylic silane that then reacted with another molecule of trioxane acetate **2** to form the product dimer **3**. This new dimer **3**, with an unsaturated three-carbon atom linker between the two trioxane units, is stable in air and light at room temperature for at least 6 months, and its preparation on a much larger industrial scale should be feasible.

Scheme 1



In contrast to most simple peroxides that are easily cleaved by reducing agents and by reactive organometallics,[22] the peroxide linkage in artemisinin-like trioxanes is relatively inert.[23] Therefore, we have been able to perform several different chemical transformations chemospecifically involving only the linker isobutylene carbon−carbon double bond in dimer **3** (Scheme 2). Borane reduction and in situ oxidation produced bis-trioxane primary alcohol **4**. Dihydroxylation using catalytic osmium tetroxide gave bis-trioxane vicinal diol **5**. Dimethyldioxirane formed bis-trioxane epoxide **6**. Oxi-

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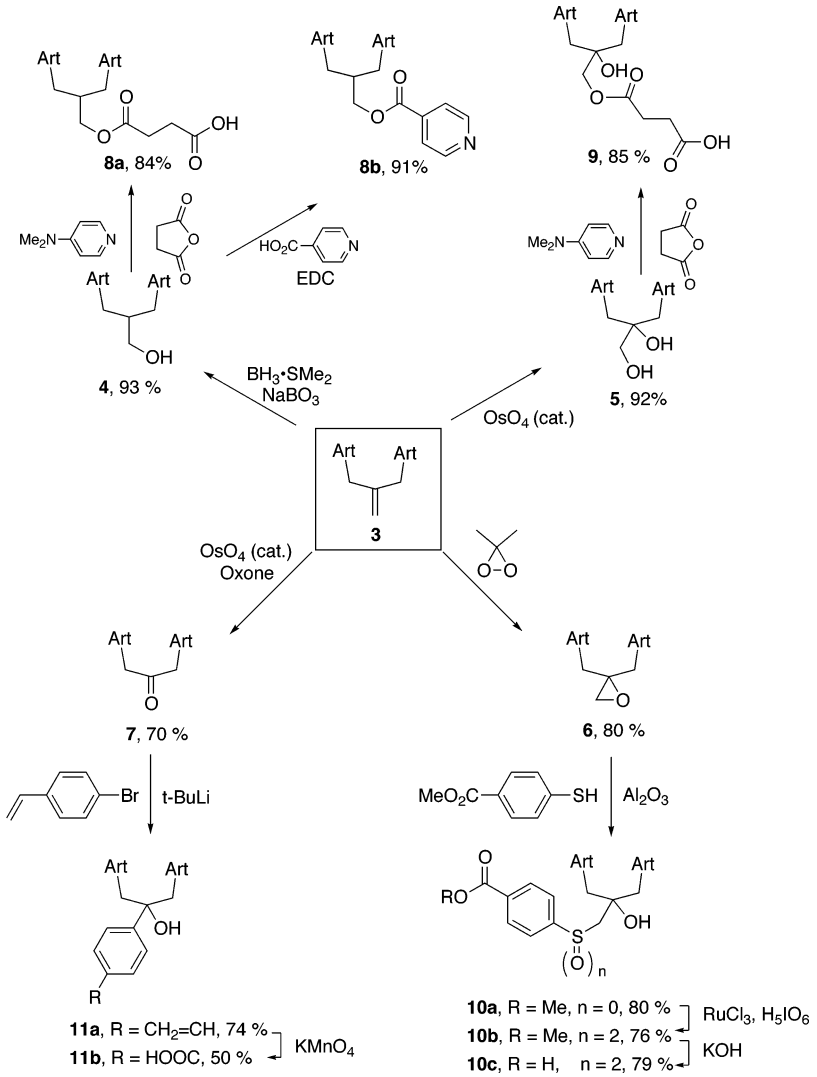
Scheme 2



dative cleavage using catalytic osmium tetroxide and oxone led to bis-trioxane ketone **7**. Bis-trioxanes **4**−**7** are stable even when heated neat in air for 24 h at 60 °C; ^{1}H NMR spectrometry showed less than 5% decomposition under these accelerated aging conditions.

To illustrate further the chemical stability of the peroxide unit in these trioxane dimers and especially to generate some water-soluble dimers that can be easily administered in vivo, we have converted each of the dimers **4**−**7** into a carboxylic acid (Scheme 2). Primary alcohol **4** opened succinic anhydride to form bis-artesunate **8a** in high yield. Esterification of primary alcohol **4** gave isonicotinate ester **8b**. Diol **5** opened succinic anhydride to produce the tertiary alcohol primary succinate ester **9**. Epoxide **6** reacted chemospecifically with a substituted benzenethiol in the presence of chromatographic alumina[24] to give β-hydroxysulfide **10a** in high yield; sulfide to sulfone oxidation gave dimer benzoate ester **10b** that was saponified into benzoic acid **10c**. Finally, ketone **7** underwent chemospecific addition of styryllithium to afford styryl tertiary alcohol **11a**; oxidative cleavage of the styrene double bond produced benzoic acid **11b**. Each of these new carboxylic acid dimers is at least as soluble in water buffered at pH 7.4 as is the antimalarial drug candidate artelinic acid,[25] and tertiary alcohol primary succinate ester **9** is close to 30 times more water-soluble than artelinic acid. Trioxane dimer carboxylic acids **8a**, **9**, and **10c** are stable in air even at 60 °C for 24 h; ^{1}H NMR spectrometry indicated <5% decomposition under these conditions.

Table 1. Antimalarial Activities in Vitro[a]

trioxane	IC_{50} (nM)	trioxane	IC_{50} (nM)
3	24	**8b**	1.7
4	0.87	**9**	3.0
5	0.59	**10c**	2.4
6	2.8	**11b**	2.1
7	0.91	artemisinin	9.0 ± 1.9
8a	2.0		

[a] The standard deviation for each set of quadruplicates was an average of 9% (≤22%) of the mean. R^2 values for the fitted curves were ≥0.987. Artemisinin activity is the mean ± standard deviation of the concurrent control (n = 10).

By use of our standard assay,[26] the antimalarial potencies of these dimers in vitro against chloroquine-sensitive *Plasmodium falciparum* (NF 54) parasites were determined to be as shown in Table 1. In sharp contrast to the potencies of the natural trioxane artemisinin (IC_{50} = 9.0 nM) and of the initial olefinic dimer **3** (IC_{50} = 24 nM), alcohol and diol dimers **4** and **5** and ketone dimer **7** all have substantially enhanced potencies, with IC_{50} values below 1 nM. Also, water-soluble

Table 2. Antimalarial Efficacies in Vivo[a]

trioxane carboxylic acid	administration route	ED_{50}[b]	ED_{90}[b]	% parasite suppression at 10 mg/kg
8a	iv	2.2	6.3	81.0
	po	9.0	15.0	79.2
artelinic acid	iv	11.0	25.0	54.7
sodium artesunate	po	10.0	39.0	52.8
9	iv	2.4	11.0	83.4
	po	4.8	34.0	55.4
10c	iv	2.7	10.0	83.4
	po	7.5	35.0	46.1
artelinic acid	iv	5.6	43.0	42.4
sodium artesunate	po	5.5	70.0	50.9

[a] Reference 27. [b] mg kg^{-1} day^{-1} × 4 days.

carboxylic acid dimers **8a**, **9**, **10c**, and **11b** all are several times more potent than artemisinin (**1**).

The in vivo antimalarial efficacies of water-soluble dimer carboxylic acids **8a**, **9**, and **10c** (**11b** not tested), as measured in mice according to a published protocol,[27] are shown in Table 2 as two separate groups of experiments. In all cases, these water-soluble dimeric trioxanes are more efficacious than the drug candidate artelinic acid administered intravenously (iv) and more efficacious than the clinically used drug sodium artesunate administered orally (po). At a dose of 10 mg/kg of mouse body weight, each of the dimeric trioxanes **8a**, **9**, and **10c** suppressed *P. berghei* NY malaria parasite growth considerably better (>80%) than did artelinic acid or sodium artesunate. Neither overt toxicity nor behavioral modification was observed in the mice due to drug administration in any of these experiments.

Preliminary growth inhibitory activities at nanomolar to micromolar concentrations, measured in vitro as described previously using a diverse panel of human cancer cell lines in the National Cancer Institute's (NCI's) Developmental and Therapeutic Program,[28] indicate that diol dimer **5** is selectively and strongly growth inhibitory but not lethal (very low LC_{50} values) to the renal cancer cell line ACHN. The epoxide dimer **6** and the ketone dimer **7** are less inhibitory. Without being cytotoxic (very low LC_{50} values), water-soluble dimer **9** is especially selective and potent at inhibiting growth of only colon cancer KM 12 cells, central nervous system SF-295 cells, and ovarian cancer OVCAR-3 cells. Water-soluble dimers **8a** and **10c** are also not cytotoxic but are somewhat less selective than dimer **9** in cancer cell growth inhibition.

In conclusion, new C-10 non-acetal trioxane dimer **3**, easily prepared on a gram scale and thermally stable, can be used to make a diverse series of three-carbon-atom-linked oxygenated dimers **4**−**7** without destroying the critical pharmacophore peroxide bond. Each of the new trioxane dimers **4**, **5**, and **7** is 10 times more antimalarially potent in vitro than the natural trioxane artemisinin (**1**), and alcohol and diol dimers **4** and **5** are strongly growth inhibitory but not cytotoxic toward several human cancer cell lines. Moreover, water-soluble trioxane dimers **8a**, **9**, and **10c** are orally active new antimalarials that are more efficacious than artelinic acid, are more efficacious than sodium artesunate in mice, and also are selective and potent inhibitors of cancer cell growth without being cytotoxic. These semisynthetic new chemical entities **4** and **5** and especially easily synthesized [four steps from natural artemisinin (**1**)] dimer carboxylic acids **8a** and **9**, therefore, deserve further preclinical evaluation as potential drug candidates for chemotherapy of malaria and cancer.[29−32]

Experimental Section

Synthesis of α-Dihydroartemisinin Acetate (2).[33] A 250 mL round-bottomed flask was charged with artemisinin (**1**) (1.49 g, 5.29 mmol, 1.0 equiv) and anhydrous dichloromethane (45.0 mL), and this solution was cooled to −78 °C. DIBAL, 1.0 M, in toluene (6.5 mL, 6.5 mmol, 1.2 equiv) was added dropwise at −78 °C. Upon the complete consumption of starting material (about an hour, checked by TLC), pyridine (1.50 mL, 18.5 mmol, 3.5 equiv) and 4-(*N*,*N*-dimethylamino)-pyridine (780 mg, 6.36 mmol, 1.2 equiv) were added. Then acetic anhydride (2.00 mL, 21.2 mmol, 4.0 equiv) was added at −78 °C. The reaction mixture was stirred vigorously at −78 °C for 3 h and slowly warmed to room temperature and stirred overnight. The reaction was quenched with 20 mL of saturated NH_4Cl. Then the organic layer was separated and washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (14% EtOAc/hexanes) to afford the desired product **2** (1.60 g, 4.90 mmol, 92%) as a white solid: mp = 129−132 °C (ref 34, 128−129 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (d, J = 9.6 Hz, 1H), 5.44 (s, 1H), 2.60−2.51 (m, 1H), 2.41−2.33 (m, 1H), 2.12 (s, 3H), 1.43 (s, 3H), 0.96 (d, J = 6.0 Hz, 3H), 0.84 (d, J = 7.2 Hz, 3H).

Synthesis of Trioxane Isobutylene Dimer 3. A solution of dihydroartemisinin acetate **2** (2.18 g, 6.68 mmol) and the allylic bis-silane linker (1.14 g, 5.70 mmol) in dry dichloromethane (120 mL) was cooled to −78 °C. Tin(IV) chloride (6.7 mL, 6.7 mmol, 1.0 M solution in dichloromethane) was further diluted with dry dichloromethane (7 mL) and was added to the reaction mixture by cannula in a dropwise manner. The reaction mixture was stirred at −78 °C for 1 h, at which time TLC confirmed the complete consumption of starting material. Water (10 mL) was added, and the reaction mixture was allowed to warm to room temperature. Additional water (50 mL) was added, and the organics were extracted with dichloromethane (3 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo to give a solid. Gradient column chromatography on silica, eluting with 5−10% ethyl acetate in hexanes isolated the trioxane isobutylene dimer **3** as a white solid (1.52 g, 2.58 mmol, 76%): mp = 132−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (s, 2H), 4.87 (s, 2H), 4.30 (ddd J = 10.4, 5.6, 4.0 Hz, 2H), 2.75−2.67 (m, 2H), 2.61−2.54 (m, 2H), 2.37−2.23 (m, 4H), 2.04−1.98 (m, 2H), 1.91−1.84 (m, 2H), 1.81−1.75 (m, 2H), 1.67−1.56 (m, 4H), 1.52−1.32 (m, 12H, including singlet at 1.39), 1.23−1.20 (m, 2H), 0.94 (d, J = 6.0 Hz, 6H), 0.90 (d, J = 7.6 Hz, 6H), 0.98−0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 113.1, 103.1, 88.6, 81.2, 75.5, 52.4, 44.5, 37.1, 36.7, 35.2, 34.5, 30.6, 26.2, 24.7, 24.6, 20.2, 13.3; IR($CHCl_3$) 3060, 2938, 2875, 1641, 1451, 1375, 1121, 1092, 1054, 1007, 878, 732 cm^{-1}; HRMS (ES) m/z calcd for $C_{34}H_{52}O_8$-Na (M + Na) 611.3560, found 611.3555. Anal. ($C_{34}H_{52}O_8$) C, H.

Synthesis of Bis-trioxane Primary Alcohol 4. A solution of trioxane isobutylene dimer **3** (0.89 g, 1.5 mmol) in dry tetrahydrofuran (25 mL) was cooled to 0 °C. Borane/dimethyl sulfide complex (2.0 M solution in diethyl ether, 0.90 mL, 1.80 mmol) was carefully added, and the reaction mixture was warmed to room temperature and stirred for 3 h. At this time TLC analysis confirmed that no starting material remained. A suspension of $NaBO_3 \cdot 4H_2O$ (1.17 g, 7.60 mmol) in water (12 mL) was slowly added, and the resulting suspension was stirred for 17 h. Water (10 mL) and dichloromethane (50 mL) were added, and organics were extracted with dichloromethane (3 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo to give a white solid. Gradient column chromatography on silica, eluting with 20%, 30%, and finally 40% ethyl acetate/petroleum ether isolated bis-trioxane primary alcohol **4** as a white solid (0.85 g, 1.40 mmol, 93%): mp = 81−82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.35 (s, 1H), 5.34 (s, 1H), 4.47−4.40 (m, 1H), 4.33 (qt, 1H, J = 6.0), 3.83−3.75 (m, 1H), 3.67−3.60 (m, 1H), 3.17 (dd, 1H, J = 7.6, J = 6.1), 2.64 (qt, 1H, J = 6.9),

2.59 (qt, 1H, $J = 6.9$), 2.32 (t, br, 2H, $J = 14.1$), 2.06−1.97 (m, 3H), 1.95−1.87 (m, 2H), 1.86−1.74 (m, 2H), 1.70−1.55 (m, 8H), 1.50−1.30 (m, 14H, including singlet at 1.40), 0.99−0.90 (m, 2H), 0.95 (d, 6H, $J = 5.8$), 0.87 (apparent t, 6H, $J = 6.9$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 103.12, 102.97, 89.47, 89.22, 81.11 (2), 73.86, 71.27, 65.12, 52.20, 52.07, 44.18, 44.01, 37.68, 37.46, 37.43, 36.52, 36.51, 34.40, 34.37, 31.26, 30.74 (2), 30.65, 25.95, 25.89, 24.83 (2), 24.73, 24.70, 20.15, 20.10, 12.89, 12.61; IR ($CHCl_3$) 3490 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{34}H_{54}O_9Na$ (M + Na) 629.3660, found 629.3697

Synthesis of Bis-trioxane Vicinal Diol 5. A 10 mL round-bottomed flask was charged with isobutylene dimer **3** (21.0 mg, 0.036 mmol, 1.0 equiv) and 4-methylmorpholine *N*-oxide (5.0 mg, 0.043 mmol, 1.2 equiv). The mixture was dissolved in acetone (2.0 mL). To this solution was added osmium tetroxide (0.016 mL, 25 mg/2 mL of aqueous solution, 0.02 equiv). The reaction mixture was stirred vigorously at room temperature for 24 h. The reaction mixture was quenched with saturated aqueous $NaHSO_3$ solution (2.0 mL) and stirred for an additional 30 min. Then the color turned to pale-orange. The reaction mixture was poured into a mixture of 20 mL of diethyl ether and 20 mL of saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (30 mL × 2). Then organic layer was combined and washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (50% EtOAc/hexanes) to afford the desired product **5** as a white solid (20.3 mg, 0.033 mmol, 92%): mp = 159−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 5.35 (s, 1H), 4.74−4.70 (m, 1H), 4.56−4.51 (m, 1H), 4.09 (s, 1H), 3.71−3.62 (m, 2H), 3.12 (t, $J = 7.2$ Hz, 1H), 2.64−2.52 (m, 2H), 2.36−2.26 (m, 2H), 2.04−1.99 (m, 2H), 1.96−1.63 (m, 12H), 1.46−1.20 (m, 14H, including two singlets at 1.40 and 1.39), 0.96 (d, $J = 6.0$ Hz, 3H), 0.95 (d, $J = 6.0$ Hz, 3H), 0.89 (d, $J = 7.6$ Hz, 3H), 0.88 (d, $J = 7.6$ Hz, 3H), 0.98−0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.0, 102.9, 89.7, 89.5, 81.1, 81.0, 74.7, 70.6, 70.5, 68.4, 52.0, 43.8, 43.7, 37.8, 37.5, 36.5, 34.9, 34.3, 31.0, 30.9, 25.91, 25.86, 24.9, 24.82, 24.75, 20.1, 12.5, 12.4; IR($CHCl_3$) 3499.4, 2951.2, 2875.8, 1452.9, 1377.5, 1207.4, 1108.3, 1053.5, 1009.0, 911.5, 878.2, 843.8, 731.6 cm^{-1}; HRMS (ES) *m/z* calcd for $C_{34}H_{54}O_{10}Na$ (M + Na) 645.3609, found 645.3559.

Synthesis of Bis-trioxane Epoxide 6. To a 25 mL round-bottomed flask was added isobutylene dimer **3** (34.1 mg, 0.058 mmol, 1.0 equiv) and anhydrous dichloromethane (10.0 mL). This solution was cooled to −78 °C. Dimethyldioxirane (3.8 mL, 0.29 mmol, 5.0 equiv, 0.08 M solution in acetone) was added rapidly. The mixture was then stirred for 30 min at −78 °C and was slowly warmed to room temperature while monitoring was done with TLC. Solvents were removed under reduced pressure, which afforded a yellow oil. The crude mixture was purified by flash column chromatography (20% EtOAc/hexanes) to afford the desired product **6** as a white solid (28.1 mg, 0.047 mmol, 80%): mp = 147−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (s, H), 5.43 (s, H), 4.45 (dd $J = 10.0$, 6.0 Hz, 1H), 4.22 (dd $J = 10.0$, 6.0 Hz, 1H), 2.82−2.72 (m, 2H), 2.68−2.62 (m, 3H), 2.43−2.33 (m, 3H), 2.02−1.97 (m, 2H), 1.88−1.82 (m, 2H), 1.75−1.70 (m, 2H), 1.62−1.58 (m, 2H), 1.54−1.26 (m, 17H, including singlet at 1.39), 0.98−0.88 (m, 3H), 0.93 (d, $J = 6.4$ Hz, 6H), 0.92 (d, $J = 6.4$ Hz, 6H), 0.80 (d, $J = 7.6$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.43, 103.40, 87.94, 87.93, 81.10, 81.07, 75.44, 74.37, 60.43, 54.46, 52.54, 52.50, 44.58, 36.91, 36.70, 34.40, 33.50, 33.01, 30.40, 30.36, 26.18, 24.45, 24.35, 24.32, 20.22, 20.19, 13.69, 13.51; IR($CHCl_3$) 2939, 2875, 1452, 1376, 1280, 1208, 1188, 1123, 1091, 1057, 1006, 941, 878, 754 cm^{-1}; HRMS (ES) *m/z* calcd for $C_{34}H_{52}O_9Na$ (M + Na) 627.3509, found 627.3478.

Synthesis of Bis-trioxane Ketone 7. Trioxane isobutylene dimer **3** (30 mg, 0.051 mmol) was dissolved in anhydrous DMF (0.250 mL). OsO_4 (0.1 mol %, 2.5% in *t*-BuOH) was added to it. The reaction mixture was stirred for 5 min, and oxone (63 mg, 0.2 mmol) was added to it in one portion. After the reaction mixture was stirred for 2 h, it was quenched with saturated aqueous Na_2SO_3 solution and stirred for an additional 1 h. The mixture was then diluted with water and extracted with dichloromethane. Flash column chromatography (25% EtOAc/hexanes) yielded the desired ketone **7** (21 mg, 0.035 mmol, 70%) as a white solid: mp = 120−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 2H), 4.75 (m, 2H), 2.90 (m, 2H), 2.75 (m, 2H), 2.59 (dd, 2H, $J = 15.6$ Hz, $J = 4$ Hz), 2.33 (dt, 2H, $J = 15.6$ Hz, $J = 4$ Hz), 2.04−1.96 (m, 2H), 1.94 (m, 2H), 1.79 (m, 2H), 1.68−1.57 (m, 6H), 1.48−1.22 (m, 14H, including singlet at 1.35), 0.99 (d, 6H, $J = 6.4$ Hz), 0.88 (d, 6H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 103.1, 88.9, 80.8, 71.2, 52.1, 44.1, 43.9, 37.3, 36.4, 34.3, 29.9, 25.9, 24.6, 24.4, 20.0, 13.0; IR($CHCl_3$) 1722 cm^{-1}; HRMS (ES) *m/z* calcd for $C_{33}H_{50}O_9Na$ (M + Na) 613.3347, found 613.3303.

Synthesis of Bis-trioxane Succinate Monoester 8a. To a solution of the bis-trioxane primary alcohol **4** (50 mg, 0.082 mmol) and succinic anhydride (24 mg, 0.24 mmol) in dichloromethane (10 mL) was added 4-(*N*,*N*-dimethylamino)pyridine (10 mg, 0.082 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for 12 h, after which TLC showed complete consumption of the starting materials. The mixture was then washed with brine and extracted with EtOAc (3 × 30 mL), and the crude mixture was purified by flash column chromatography (50% EtOAc/hexanes) to furnish the desired product **8a** as a white solid (40 mg, 0.068 mmol, 84%): mp = 77−80 °C; $[\alpha]^{23.9}_D$ 46.7 ($CHCl_3$, *c* 0.10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (s, 1H), 5.31 (s, 1H), 4.36 (m, 2H), 4.22 (m, 3H), 2.74−2.54 (m, 6H), 2.32 (m, 2H), 2.17 (m, 1H), 2.01 (m, 2H), 1.90 (m, 2H), 1.84−1.60 (m, 11H), 1.48−1.20 (m, 16H, including two singlets at 1.40 and 1.39), 1.00−0.80 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 172.0, 102.9, 103.6, 89.4, 88.5, 81.1, 74.1, 71.1, 67.1, 52.4, 52.1, 44.6, 44.1, 37.4, 37.3, 36.6, 36.5, 34.4, 34.3, 30.5, 30.4, 30.0, 29.7, 29.4, 29.0, 26.0, 25.9, 24.7, 20.3, 20.1, 13.3, 12.7; HRMS (ES) *m/z* calcd for $C_{38}H_{58}O_{12}Na$ (M + Na) 729.3820, found 729.3795. Anal. ($C_{38}H_{60}O_{13}$) C, H.

Synthesis of Bis-trioxane Isonicotinate Ester Dimer 8b. To a stirring suspension of dimer alcohol **4** (30.4 mg, 0.050 mmol) and isonicotinic acid (20.1 mg, 0.163 mmol) in dry dichloromethane (1 mL) was added 4-(*N*,*N*-dimethylamino)-pyridine (23.5 mg, 0.192 mmol) and 1-(3-(dimethylamino)-propyl)-3-ethylcarbodiimide (EDC) hydrochloride (39.2 mg, 0.204 mmol). A further 1.5 mL of dry dichloromethane was added to wash down the flask walls, and the reaction mixture was stirred at room temperature for 3 h, at which time TLC analysis showed full consumption of starting material. Water (5 mL), saturated $NaHCO_3$ solution (5 mL), and dichloromethane (5 mL) were added, and the organics were extracted with dichloromethane (3 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo to give a white solid. Gradient column chromatography on silica (crude was dry-loaded), eluting first with 25% ethyl acetate in petrol and then 30% ethyl acetate in petrol, isolated the isonicotinate dimer **8b** as a white solid (32.6 mg, 0.046 mmol, 91%); mp = 74−78 °C; $[\alpha]^{24.5}_D$ 77.8 ($CHCl_3$, *c* 0.06); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (s, br, 2H), 7.86 (s, br, 2H), 5.33 (s, 1H), 5.29 (s, 1H), 4.55 (s, 1H), 4.54 (s, 1H), 4.51−4.44 (m, 1H), 4.37−4.30 (m, 1H), 2.70 (st, 1H, $J = 7.0$), 2.59 (st, 1H, $J = 7.0$), 2.45−2.36 (m, br, 1H), 2.31 (td, 2H, $J = 14.0$, $J = 3.7$), 2.05−1.96 (m, 2H), 1.95−1.73 (m, 6H), 1.69−1.50 (m, 6H), 1.41−1.15 (m, 14H, including two singlets at 1.40 and 1.39), 0.98−0.92 (m, 2H), 0.96 (d, 3H, $J = 5.9$), 0.94 (d, 3H, $J = 5.9$), 0.88 (d, 3H, $J = 7.4$), 0.87 (d, 3H, $J = 7.4$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.99, 150.49 (2), 137.93, 122.91 (2), 103.16, 102.87, 89.52, 88.83, 81.12, 81.11, 73.23, 70.83, 68.10, 52.30, 52.07, 44.32, 44.06, 37.50, 37.47, 36.64, 36.54, 34.42, 34.39, 33.95, 30.61, 30.58, 30.49, 30.15, 26.02, 26.01, 24.97, 24.89, 24.76, 24.67, 20.17, 20.10, 13.08, 12.72; IR ($CHCl_3$) 2942, 1866, 1726, 1452, 1407, 1372, 1321, 1276, 1210, 1123, 1106, 1057, 1046, 1006, 931, 876, 756, 707 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{40}H_{57}NO_{10}Na$ (M + Na) 734.3875, found 734.3855. Anal. ($C_{40}H_{57}NO_{10}$) C, H.

Synthesis of Tertiary Alcohol Primary Succinate Ester 9. A 25 mL round-bottomed flask was charged with vicinal diol **5** (52.9 mg, 0.085 mmol, 1.0 equiv) and anhydrous dichloromethane (3.0 mL). To this solution, succinic anhydride

(25.5 mg, 0.255 mmol, 3.0 equiv) and 4-*N*,*N*-(dimethylamino)-pyridine (10.4 mg, 0.085 mmol, 1.0 equiv) were added, and the reaction mixture was stirred for 24 h at room temperature while being monitored by TLC. Upon complete consumption of starting material, the reaction mixture was poured into a mixture of 30 mL of dichloromethane and 30 mL of saturated aqueous NH_4Cl solution. Then the organic layer was separated and washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (2-propanol/dichloromethane/ethyl acetate, 1:3:18) to afford the desired product **9** as a white solid (52.0 mg, 0.071 mmol, 85%): mp = 95−97 °C; $[\alpha]^{23.5}_D$ 56.6 ($CHCl_3$, *c* 0.16); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (s, 1H), 5.34 (s, 1H), 4.61−4.52 (m, 2H), 4.29 (ABq, J_{AB} = 18.8 Hz, $\Delta\nu_{AB}$ = 11.6 Hz, 2H), 2.72−2.66 (m, 4H), 2.58−2.50 (m, 2H), 2.36−2.24 (m, 2H), 2.04−1.58 (m, 13H), 1.46−1.18 (m, 17H, including two singlets at 1.40 and 1.39), 0.95 (d, J = 6.0 Hz, 6H), 0.88 (d, J = 7.6 Hz, 3H), 0.87 (d, J = 7.6 Hz, 3H), 0.98−0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 171.7, 103.2, 102.9, 89.6, 89.0, 81.1, 81.0, 73.3, 70.6, 70.3, 68.6, 52.1, 51.9, 44.1, 43.7, 37.5, 36.6, 36.5, 36.3, 35.1, 34.4, 34.3, 30.8, 30.7, 29.2, 29.1, 25.9, 25.8, 24.8, 24.7, 20.2, 20.1, 12.8, 12.5; IR($CHCl_3$) 3502, 2950, 2872, 1737, 1713, 1453, 1378, 1208, 1168, 1106, 1054, 1009, 942, 878, 844, 735 cm^{-1}; HRMS (ES) *m*/*z* calcd for $C_{38}H_{58}NaO_{13}$ (M + Na) 745.3769, found 745.3726. Anal. ($C_{38}H_{58}O_{13}$) C, H.

Water Solubility Test. To a 1 dram vial, 0.5 mL of pH 7.4 phosphate buffer solution and 2 mg of trioxane dimer were added, and the mixture was vigorously stirred for 1 h. In some cases, compound was added again until there was remaining compound that was not dissolved. Then the solution was transferred via pipet into a small sintered glass filter. The filtrate was evaporated under reduced pressure, and the weight was measured. The buffer solution (0.5 mL for blank run) was dried, and the weight was measured. The weight of phosphate blank was subtracted from the observed weight for the trioxane dimer. Succinate ester **9** had a solubility of 16.6 mg/mL, compared to 0.6 mg/mL for artelinic acid.

Synthesis of β-Hydroxysulfide Ester 10a. A 50 mL round-bottomed flask was charged with bis-trioxane epoxide **6** (80.0 mg, 0.132 mmol, 1.0 equiv), methyl 4-mercaptobenzoate (44.4 mg, 0.264 mmol, 2.0 equiv), and neutral aluminum oxide (1.0 g, type W 200 super I, Woelm Pharma, Germany), and then anhydrous diethyl ether (10.0 mL) was added to make a slurry, which was stirred for 3 h at room temperature while being monitored by TLC. Upon complete consumption of starting material, the reaction mixture was filtered through a Celite pad and the solid was washed with ethyl acetate (30 mL × 2) and then concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (25% EtOAc/hexanes) to afford the desired product **10a** as a sticky solid (81.2 mg, 0.105 mmol, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (ABq, J_{AB} = 8.4 Hz, $\Delta\nu_{AB}$ = 154.4 Hz, 4H), 5.36 (s, 1H), 5.35 (s, 1H), 4.69 (dd, J = 10.4, 6.0 Hz, 1H), 4.69 (dd, J = 10.0, 6.0 Hz, 1H), 3.88 (s, 3H), 3.52 (ABq, J_{AB} = 12.4 Hz, $\Delta\nu_{AB}$ = 44.4 Hz, 2H), 2.65−2.55 (m, 1H), 2.52−2.42 (m, 1H), 2.34−2.24 (m, 2H), 2.08−1.58 (m, 12H), 1.46−1.18 (m, 10H, including two singlets at 1.36 and 1.31), 0.94 (d, J = 6.0 Hz, 6H), 0.85 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 7.2 Hz, 3H), 0.98−0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 145.0, 129.6, 127.7, 126.4, 102.9, 102.8, 89.7, 89.3, 81.1, 81.0, 74.9, 70.8, 70.5, 52.1, 51.9, 43.9, 43.6, 42.4, 38.3, 37.4, 36.5, 36.4, 36.1, 34.4, 34.3, 30.8, 30.7, 26.0, 25.9, 24.8, 24.7, 20.1, 20.0, 12.7, 12.4; IR ($CHCl_3$) 3498, 2951, 2876, 1721, 1594, 1430, 1377, 1276, 1182, 1110, 1054, 1008, 942, 880, 845, 762, 736 cm^{-1}.

Synthesis of β-Hydroxysulfone Ester 10b.[35] A 50 mL round-bottomed flask was charged with β-hydroxysulfide ester **10a** (40.0 mg, 0.052 mmol, 1.0 equiv), which was then dissolved in tetrachloromethane (1.5 mL). Then acetonitrile (1.5 mL) and H_2O (2.3 mL) were added. To the reaction mixture ruthenium(III) chloride hydrate (catalytic amount) and periodic acid (23.7 mg, 0.104 mmol, 2.0 equiv) was added. (Upon addition of ruthenium chloride, the solution was turned black.) After the mixture was stirred for 30 min at room temperature, 30 mL of diethyl ether was added and the resulting mixture was stirred for an additional 10 min. Then, the reaction mixture was dried over $MgSO_4$ and filtered through a Celite pad. The solid was washed with ethyl acetate (30 mL) and then concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (30% EtOAc/hexanes) to afford the desired product **10b** as a white solid (32.0 mg, 0.040 mmol, 76%): mp = 115−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (ABq, J_{AB} = 8.4 Hz, $\Delta\nu_{AB}$ = 73.6 Hz, 4H), 5.70 (s, 1H), 5.36 (s, 1H), 5.19 (dd, J = 10.8, 6.0 Hz, 1H), 4.88 (s, 1H), 4.58 (dd, J = 9.6, 6.4 Hz, 1H), 3.95 (s, 3H), 3.81 (ABq, J_{AB} = 13.6 Hz, $\Delta\nu_{AB}$ = 278.4 Hz, 2H), 2.90−2.82 (m, 1H), 2.70−2.56 (m, 2H), 2.43−2.30 (m, 2H), 2.20−1.20 (m, 22H, including two singlets at 1.54 and 1.24), 0.96 (d, J = 6.0 Hz, 6H), 0.93 (d, J = 8.0 Hz, 3H), 0.88 (d, J = 7.6 Hz, 3H), 0.98−0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 145.3, 134.3, 129.9, 128.5, 103.6, 102.8, 90.1, 88.5, 81.2, 73.6, 71.6, 71.1, 60.1, 52.6, 52.5, 51.8, 45.0, 43.3, 39.5, 37.5, 37.3, 36.5, 34.5, 34.3, 30.5, 30.4, 26.4, 26.0, 25.0, 24.8, 24.6, 24.3, 20.3, 20.0, 13.7, 11.9; IR ($CHCl_3$) 3458, 2951, 2875, 1731, 1435, 1377, 1320, 1280, 1153, 1105, 1051, 1015, 911, 880, 733 cm^{-1}; HRMS (ES) *m*/*z* calcd for $C_{42}H_{60}NaO_{13}S$ (M + Na) 827.3646, found 827.3661.

Synthesis of β-Hydroxysulfone Benzoic Acid 10c. A 10 mL round-bottomed flask was charged with β-hydroxysulfone ester **10b** (19.7 mg, 0.024 mmol, 1.0 equiv) and then dissolved in 2.5% KOH/MeOH (1.0 mL). This solution was stirred vigorously at room temperature while being monitored with TLC. Upon the complete consumption of starting material (about 3 h), the solution was evaporated to dryness under reduced pressure and then was dissolved in 10 mL of water. This solution was acidified with acetic acid until pH 4.0 was attained and was extracted with EtOAc (30 mL × 2). Then the organic layer was combined and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (2-propanol/dichloromethane/ethyl acetate, 1:3:18) to afford the desired product **10c** as a white solid (14.7 mg, 0.019 mmol, 79%): mp = 143−145 °C; $[\alpha]^{23.9}_D$ 105.2 ($CHCl_3$, *c* 0.07); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (ABq, J_{AB} = 8.4 Hz, $\Delta\nu_{AB}$ = 76.4 Hz, 4H), 5.71 (s, 1H), 5.38 (s, 1H), 5.19 (dd, J = 10.8, 6.4 Hz, 1H), 4.63 (dd, J = 9.2, 6.0 Hz, 1H), 3.82 (ABq, J_{AB} = 13.6 Hz, $\Delta\nu_{AB}$ = 266.4 Hz, 2H), 2.85−2.82 (m, 1H), 2.70−2.56 (m, 2H), 2.43−2.30 (m, 2H), 2.20−1.20 (m, 22H, including two singlets at 1.56 and 1.25), 0.96 (d, J = 6.0 Hz, 6H), 0.93 (d, J = 8.0 Hz, 3H), 0.88 (d, J = 7.6 Hz, 3H), 0.98−0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 145.7, 133.5, 130.4, 128.5, 103.8, 102.9, 90.1, 88.7, 81.3, 73.7, 71.8, 71.2, 60.2, 52.6, 51.9, 44.9, 43.3, 39.4, 37.5, 37.4, 37.3, 36.5, 34.5, 34.3, 30.6, 30.5, 26.1, 25.9, 25.0, 24.8, 24.5, 24.4, 20.2, 20.0, 13.6, 11.9; IR ($CHCl_3$) 3459, 2939, 2875, 1723, 1432, 1403, 1378, 1319, 1300, 1228, 1154, 1099, 1051, 1015, 911, 877, 732, 616 cm^{-1}; HRMS (ES) *m*/*z* calcd for $C_{41}H_{58}NaO_{13}S$ (M + Na) 813.3490, found 813.3500. Anal. ($C_{41}H_{58}O_{13}$) C, H.

Synthesis of Bis-trioxane Styryl Tertiary Alcohol 11a. A solution of styryllithium was prepared by adding *t*-BuLi (1.2 mL, 1.7 M in hexanes) to a solution of 4-bromostyrene (0.13 mL, 1 mmol) in diethyl ether (5.0 mL). The deep-red solution was stirred for 30 min to ensure complete formation of styryllithium. To a solution of ketone **7** (30 mg, 0.051 mmol) in THF was added a solution of styryllithium (0.35 mL, ∼0.07 mmol) at −78 °C, and the reaction mixture was stirred for 30 min at the same temperature. The reaction was then worked up by adding a saturated solution of ammonium chloride and extracting with dichloromethane. Flash column chromatography (10−15% EtOAc/petroleum ether) yielded the desired tertiary alcohol **11a** (26 mg, 0.037 mmol, 74%) as a viscous oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, 2H), 7.35 (d, 2H), 6.68 (dd, 1H), 5.70 (d, 1H), 5.35 (s, 2H), 5.2 (d, 2H), 4.46 (m, 1H), 4.19 (m, 1H), 2.78−2.42 (m, 4H), 2.32 (m, 2H), 2.17 (m, 1H), 2.01 (m, 2H), 1.90 (m, 4H), 1.84−1.60 (m, 11H), 1.48−1.20 (m, 16H, including singlet at 1.38), 1.00−0.80 (m, 12H).

Synthesis of Bis-trioxane Tertiary Alcohol Benzoic Acid 11b. Styryl tertiary alcohol **11a** (20 mg, 0.028 mmol) was dissolved in acetone (3 mL), and $KMnO_4$ was added to it as a

solid. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was then treated with 2-propanol to quench excess $KMnO_4$. The solvent was evaporated, and the product was washed with water and extracted with ethyl acetate. Flash column chromatography (90% EtOAc/petroleum ether) yielded the desired product **11b** (19 mg, 0.014 mmol, 50%) as a white solid: mp = 97−101 °C; $[\alpha]^{24.1}_D$ 17.6 ($CHCl_3$, *c* 0.06); ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 5.47 (s, 1H), 5.29 (s, 1H), 4.36 (m, 1H), 4.08 (m, 1H), 2.59−2.48 (m, 2H), 2.40−2.20 (m, 5H), 2.02−1.76 (m, 8H), 1.58−1.10 (m, 18H, including two singlets at 1.27 and 1.20), 1.00−0.70 (m, 14H); ^{13} C NMR (100 MHz, CD_3OD) δ 167.4, 132.5 130.6, 130.0, 127.7, 104.7, 104.6, 90.5, 89.9, 82.3, 82.1, 78.4, 74.1, 73.6, 54.1, 53.8, 46.4, 45.9, 43.4, 39.8, 38.6, 38.5, 37.8, 37.7, 35.9, 35.8, 32.1, 31.9, 26.4, 26.1, 26.0, 25.9, 25.8, 25.7, 20.8, 20.7, 13.9, 13.6; HRMS (ES) *m/z* calcd for $C_{40}H_{56}NaO_{11}$ (M + Na) 735.3715, found 735.3717.

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Supporting Information Available: Preliminary growth inhibitory activities at nanomolar to micromolar concentrations, measured in vitro using a diverse panel of human cancer cell lines in the National Cancer Institute's Developmental and Therapeutic Program, for compounds **5** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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