Malaria-Infected Mice Are Cured by Oral Administration of New Artemisinin Derivatives

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In four or five chemical steps from the 1,2,4-trioxane artemisinin, a new series of 23 trioxane dimers has been prepared. Eleven of these new trioxane dimers cure malaria-infected mice via oral dosing at 3 × 30 mg/kg. The clinically used trioxane drug sodium artesunate prolonged mouse average survival to 7.2 days with this oral dose regimen. In comparison, animals receiving no drug die typically on day 6–7 postinfection. At only 3 × 10 mg/kg oral dosing, seven dimers prolong the lifetime of malaria-infected mice to days 14–17, more than double the chemotherapeutic effect of sodium artesunate. Ten new trioxane dimers at only a single oral dose of 30 mg/kg prolong mouse average survival to days 8.7–13.7, and this effect is comparable to that of the fully synthetic trioxolane drug development candidate OZ277, which is in phase II clinical trials.

Introduction

Malaria still causes widespread morbidity and mortality.[1–3] Standard antimalarial drugs such as chloroquine are rapidly becoming ineffective due to malaria parasite widespread resistance.[4] A new class of antimalarial 1,2,4-trioxane drugs has emerged from traditional Chinese herbal remedies.[5–11] Although extremely fast-acting, the antimalarial effect of natural trioxane artemisinin (**1**) and its daughter trioxanes artemether (**1b**) and sodium artesunate (**1c**) is not long lasting; when these trioxanes are used as monotherapy, recrudescence of malaria parasites often occurs.[5–11] Therefore, the World Health Organization (WHO) has recommended, and most countries where malaria is endemic have adopted, use of artemisinin combination therapy (ACT), combining a trioxane with an alkaloidal antimalarial such as lumefantrine or amodiaquine.[12–15] Recently, we have discovered that the antimalarial effect of some artemisinin-derived trioxane dimers strongly prolongs mouse survival.[16] Even when used in vivo as monotherapy, these trioxane dimers cure malaria-infected mice after only a single subcutaneous dose.[16] Curing malaria-infected animals via oral administration of an antimalarial is an even more demanding and more desirable goal. Now we report on a series of 23 new trioxane dimers **6**–**28**, 11 of which cure 100% of the malaria-infected mice when administered orally at 3 × 30 mg/kg.

Results and Discussion

Chemistry. Scheme 1 outlines the chemical conversions[17] of natural trioxane **1** into previously described[18] dimeric trioxane ketone **2**, diol **3**, primary alcohol **4**, and carboxylic acid **5**. Based on recent reports that optimal antimalarial oral efficacy was achieved with trioxanes of relatively high lipophilicity (log $P \approx 8$),[16,19] we designed and prepared the following lipophilic trioxane dimers,[20] each in only one additional chemical step: hydrazone LH-isobu-ketone-isoniaz-hydrazone (**6**), ketals LH-isobudiol-acetal-form (**7**), WC-isobudiol-ketal-CB (**8**), LH-isobudiol-ketal-cyclohex-4-one (**9**), LW-isobudiol-ketal-4-THP (**10**), SS-isobudiol-ketal-4-pipC(O)Ph (**11**), LW-isobudiol-ketal-4-pipC(O)OEt (**12**), AU-isobudiol-ketal-pipC(O)NHCH$_3$ (**13**), and LH-isobudiol-ketal-4-SO$_2$-pyran (**14**), ethers WC-isobudiol-OCH$_2$Pyr (**15**)[16] and ASK-isobudiol-C(O)Ph (**16**), carboxylate ester KSP-isobudiol-OCH$_2$CCCH$_2$OBn-pF (**17**), ether WC-isobu-OCH$_2$Tol (**18**),[16] thiophosphate ester WM-isobu-CH$_2$OP(S)(OEt)$_2$ (**19**), carbamate AU-isobu-OC(O)NEt$_2$ (**20**), amides AU-isobu-C(O)NHCH$_2$Cyc-hex (**21**), SS-isobu-C(O)NH-Neop (**22**), ASR-isobuCONHCH$_2$Pyr (**23**), JGD-isobu-C(O)NHCH$_2$(4-C(O)OMe)Ph (**24**), WC-isobuC(O)NH-Bn-pMe (**25**), and WC-isobuC(O)NH-(*S*)-CH(Me)-(Ph-pF) (**26**), and oxadiazoles RS-isobu-3-Me-1,2,4-oxadiazole (**27**) and RS-isobu-5-*p*-FPh-1,3,4-oxadiazole (**28**). Of critical importance, none of these final transformations destroyed the essential peroxide pharmacophore within these dimer 1,2,4,-trioxanes. All of these new trioxane dimers are amorphous solids. All are stable neat at 60 °C for ≥24 h. All are stable for at least 12 h at room temperature in 80/20 DMSO/water at pH 7.4, and all except **6** are also stable in 80/20 DMSO/water at pH 2.0.

Biology. Following standard procedure,[21] trioxane dimers **6**–**28** were formulated in 70/30 Tween 80/ethanol and diluted 10× with water before oral administration to NMRI mice that were infected intravenously on day 0 with the *Plasmodium berghei* GFP ANKA malaria strain (2 × 10^7 parasitized erythrocytes, donation from AP Waters and CJ Janse, Leiden University). The mice ($n = 3$ per group) were treated orally with either three doses (24, 48, and 72 h postinfection) or a single dose (24 h postinfection) of trioxane dimer with a volume of 10 mL/kg. Two widely accepted measures of the efficacy of a drug are lowering blood parasitemia levels and raising animal survival times as compared to animals receiving no drug. Animals receiving no drug die typically 6–7 days postinfection. An accepted yardstick of cure (i.e., 100% efficacy) is survival of animals to day 30 postinfection,

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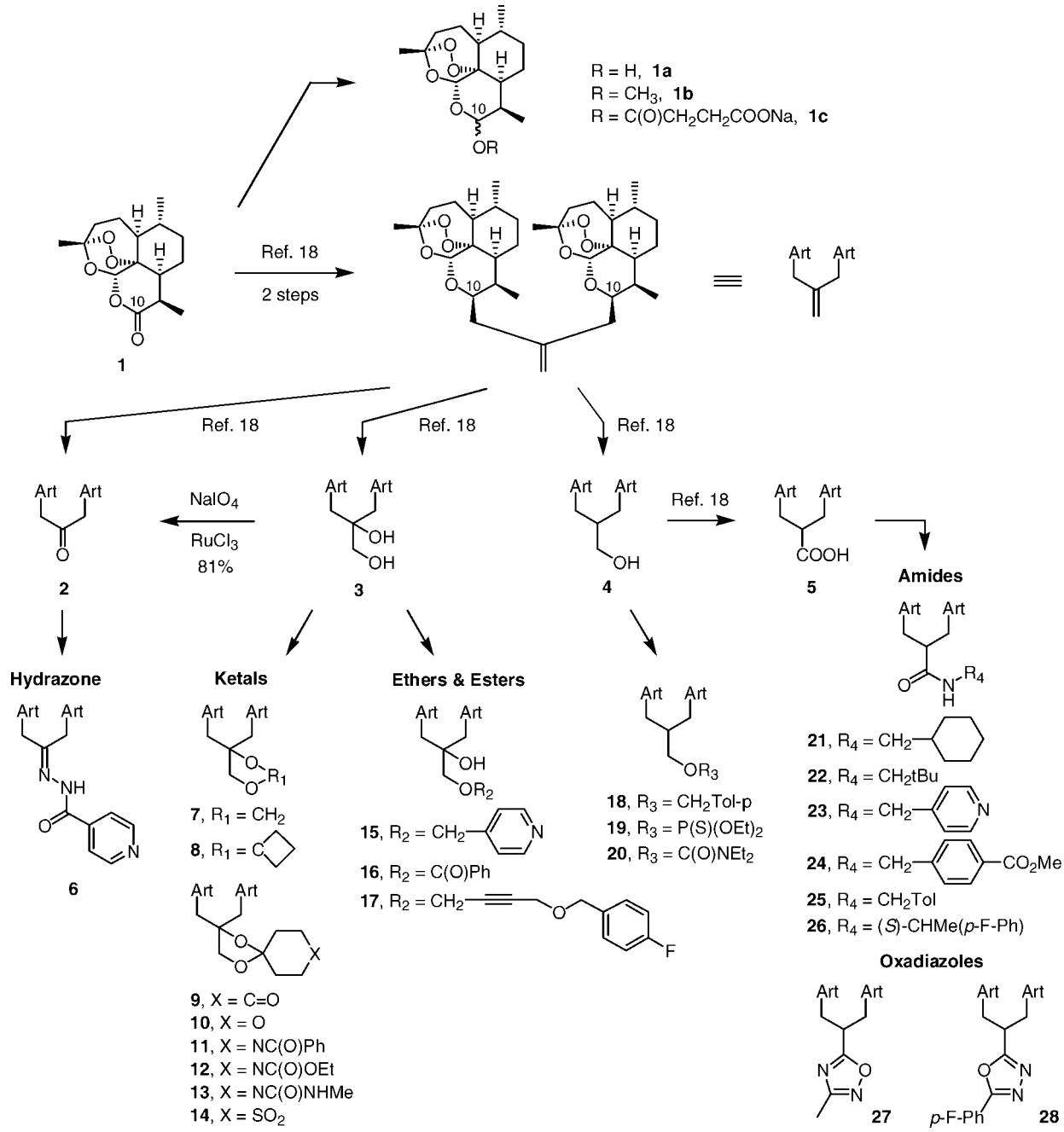
Scheme 1. First Generation Artemisinin Dimers and Scheme for Synthesis of New Artemisinin Dimers



with no detectable malaria parasites in the animals' blood at that time. Average mouse survival times using two different oral dosing regimens are summarized in Table 1. The clinically used trioxane drug **1c** is included as a standard.[15] At an oral dose regimen of 3 × 30 mg/kg of trioxane dimers **7**–**10**, **12**–**15**, **18**, **20**, and **21**, all cured the malaria-infected mice; no parasites were detected in the blood of the surviving mice by using standard flow cytometry techniques.[21] To confirm the reliability of such flow cytometry for establishing cure on day 30 postinfection, blood from the surviving mice in two curative experiments (e.g., with dimers **10** and **21**) was inoculated into uninfected mice; no parasitemia developed in these mice even after 30 days. Neither overt toxicity nor behavioral changes attributable to trioxane drug administration were observed visually in any of the cured animals. The clinically used trioxane drug **1c** gave mouse average survival of 7.2 days with this oral dose regimen of 3 × 30 mg/kg. At a lower oral dose regimen of 3 × 10 mg/kg, trioxane dimers **6**–**7**, **9**–**13**, **15**, **20**, and **24** all prolonged mouse average survival to at least day 10, compared to day 6.5 average survival with the trioxane drug **1c** under this multiple dose regimen. At only a single oral dose of 1 × 30 mg/kg, trioxane dimers **6**, **9**–**12**, **15**, **20**, and **25**−**28** all prolonged mouse average survival at least as effectively as the fully synthetic trioxolane peroxide drug development candidate OZ277 maleate (**29**), which is in phase II clinical trials (Table 2).[22,23]

In summary, many of the artemisinin-derived antimalarial trioxane dimers described here are highly efficacious even when administered orally. When administered using three oral doses of 30 mg/kg, 11 of these dimers cure malaria-infected mice. These trioxane dimers are stable both thermally and hydrolytically. Further chemical structure−biological activity

Table 1. Antimalarial Oral Efficacy of Trioxane Dimers in *P. berghei*-Infected Mice

trioxane dimer	avg survival (days) after infection dose: 3 × 30 mg/kg	avg survival (days) after infection dose: 3 × 10 mg/kg	log *P* (calc)
6		17.7 (17, 18, 18)[a]	7.0
7	≥30	11.0 (11, 11, 11)	6.3
8	≥30	7.0 (7, 7, 7)	7.1
9	≥30	16.3 (17, 14, 18)	7.1
10	≥30	15.7 (16, 15, 16)	6.9
11		15.7 (16, 15, 16)	8.1
12	≥30	14.0 (14, 14, 14)	7.4
13	≥30	13.3 (12, 14, 14)	6.4
14	≥30	8.3 (8, 9, 8)	5.9
15	≥30	14.7 (30, 7, 7)	5.9
16	20.7	6.0 (6, 6, 6)	7.7
18	≥30	8.0 (8, 8, 8)	9.2
19	24.7	7.7 (8, 8, 7)	8.9
20	≥30	14.0 (14, 14, 14)	7.7
21	≥30	7.0 (7, 7, 7)	8.0
22	27.7	6.0 (6, 6, 6)	7.8
23	11.3	7.0 (7, 7, 7)	6.6
24		10.0 (11, 7, 12)	8.0
	Control		
vehicle (no drug)	6–7	6–7	
1c	7.2	6.5	3.0

[a] Actual mouse survival until day.

Table 2. Antimalarial Efficacy Using a Single Oral Dose of Trioxane Dimers in *P. berghei*-Infected Mice

trioxane dimer	avg survival (days) after infection dose: 1 × 30 mg/kg	% suppression of parasitemia (on day 3 post infection)
6	10.0 (10, 10, 10)[a]	99.4
9	8.3 (9, 9, 7)	99.6
10	9.0 (9, 9, 9)	99.5
11	10.0 (10, 10, 10)	99.0
12	8.7 (8, 9, 9)	99.6
15	10.0 (10, 10, 10)	99.2
17	6.3 (7, 5, 7)	88.0
20	11.7 (9, 13, 13)	99.3
25	10.3 (9, 8, 14)	99.0
26	12.7 (14, 14, 10)	98.9
27	13.7 (13, 13, 14)	98.9
28	10.0 (15, 7, 8)	98.8
	Control	
vehicle (no drug)	6–7	0
1c	7.6	92.0
29	8.2, 10.7[b]	99.7, 99.95[b]

[a] Actual mouse survival until day. [b] Data from Supporting Information in ref 22.

relationship (SAR) study is ongoing, aimed at developing trioxane dimers able to achieve the goal of a single oral dose cure.

Experimental Section[18]

The purity of all trioxane dimers was judged to be >98% based on HPLC analysis. Log *P* values were calculated by using MarvinSketch and a calculator plug-in by ChemAxon Kft.

Hydrazone 6. An oven-dried 10 mL flask was charged sequentially with trioxane dimer ketone **2** (151 mg, 0.25 mmol), EtOH (5 mL), isoniazid (105 mg, 0.76 mmol), and *p*-toluenesulfonic acid monohydrate (24 mg, 0.13 mmol). The reaction was stirred at room temperature (rt) for 2 h, and then the reaction was quenched with H_2O (10 mL). EtOAc (20 mL) was added to the mixture, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layer was dried ($MgSO_4$) and concentrated in vacuo. The purification of the crude product by column chromatography (1% Et_3N in EtOAc) gave **6** (156 mg, 86%) as an amorphous solid: $[\alpha]_D^{21} = -109$ (*c* 1.30, $CHCl_3$); IR (thin film) 2951, 2871, 1675, 1375, 1050, 1004, 754 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 10.73 (s, 1H), 8.76 (d, $J = 5.6$ Hz, 2H), 7.79 (d, $J = 5.6$ Hz, 2H), 5.66 (s, 1H), 5.48 (s, 1H), 4.66–4.65 (m, 1H), 2.97–2.24 (m, 8H), 2.18–1.66 (m, 8H), 1.57–1.22 (m including singlets at 1.33 and 1.31, 16H), 1.10–0.93 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 163.9, 162.6, 150.4, 121.9, 104.2, 103.9, 92.3, 92.2, 80.9, 80.8, 75.4, 72.9, 51.9, 51.8, 46.2, 45.9, 37.3, 37.2, 36.9, 36.3, 36.1, 34.1, 33.9, 33.6, 32.3, 31.5, 26.2, 25.3, 24.7, 24.6, 22.6, 21.6, 21.5, 20.3, 14.1, 13.9; HRMS (FAB) calculated for $C_{39}H_{56}N_3O_9$ [$(M + H)^+$] 710.4017, found 710.4009.

Acetal 7. To a solution of trioxane dimer diol **3** (50 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) was added paraformaldehyde (5 mg, 0.16 mmol) and *p*-toluenesulfonic acid monohydrate (3 mg, 0.02 mmol). The reaction was stirred at rt for 12 h. It was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic solution was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The purification of the crude product by column chromatography (elution with 25% EtOAc in hexane) gave **7** (38 mg, 72%) as an amorphous solid: $[\alpha]_D^{25} = +91$ (*c* 0.53, $CHCl_3$); IR (thin film) 2946, 2849, 1377, 1094, 1052, 1010, 941, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 (s, 1H), 5.34 (s, 1H), 4.99 (s, 1H), 4.96 (s, 1H), 4.50–4.46 (m, 1H), 4.29 (m, 1H), 3.86 (s, 2H), 2.73–2.64 (m, 1H), 2.35–2.20 (m, 3H), 2.02–1.96 (m, 3 H), 1.90–1.71 (m, 6H), 1.65–1.17 (m including singlets at 1.38 and 1.37, 19H), 0.97–0.83 (m including doublets at 0.94 with $J = 6.4$ Hz, 0.93 with $J = 6.4$ Hz, 0.87 with $J = 7.6$ Hz, and 0.84 with $J = 7.6$ Hz, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.2, 103.1, 94.6, 88.5, 82.2, 81.09, 81.07, 73.4, 72.2, 71.3, 52.4, 52.3, 44.6, 44.5, 37.3, 37.2, 36.7, 36.6, 35.4, 34.5, 34.4, 33.8, 30.7, 30.6, 26.1, 26.09, 24.6, 24.6, 24.5, 24.4, 20.2, 20.1, 13.4, 13.2; HRMS (FAB) calculated for $C_{35}H_{55}O_{10}$ [$(M + H)^+$] 635.3795, found 635.3765.

Ketal 8. To a solution of trioxane dimer diol **3** (70 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added cyclobutanone (100 μL, 1.30 mmol) and *p*-toluenesulfonic acid monohydrate (2 mg, 0.01 mmol). The reaction was stirred at rt for 48 h. It was concentrated and purified by flash column chromatography (elution with EtOAc/hexane = 1:10) on silica gel to give **8** (73 mg, 96%) as an amorphous solid: $[\alpha]_D^{24} = +74$ (*c* 0.50, $CHCl_3$); IR (thin film) 2944, 2873, 1377, 1282, 1052, 1008, 879 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.52 (s, 1H), 5.40 (s, 1H), 4.86 (m, 1H), 4.53 (m, 1H), 4.24 (d, $J = 8.4$ Hz, 1H), 3.98 (d, $J = 8.0$ Hz, 1H), 2.90 (m, 1H), 2.78 (m, 1H), 2.63–2.27 (m, 6H), 2.13 (d, $J = 13.6$ Hz, 2H), 1.85–0.55 (m including a singlet at 1.40, 42H); ^{13}C NMR (100 MHz, C_6D_6) δ 109.7, 103.2, 102.9, 101.1, 89.2, 89.2, 83.6, 81.0, 80.9, 73.0, 72.0, 71.3, 52.7, 52.6, 45.1, 44.8, 38.0, 37.9, 37.5, 37.4, 37.3, 37.1, 35.5, 34.8, 34.7, 31.2, 26.3, 25.2, 24.8, 24.8, 20.3, 20.2, 13.5, 13.2, 12.1; HRMS (FAB) calculated for $C_{38}H_{59}O_{10}$ [$(M + H)^+$] 675.4108, found 675.4084.

Ketal 9. To a solution of trioxane dimer diol **3** (50 mg, 0.08 mmol) in CH_2Cl_2 (3 mL) was added 1,4-cyclohexanedione (90 mg, 0.80 mmol) and *p*-toluenesulfonic acid monohydrate (3 mg, 0.02 mmol). The reaction was stirred at rt for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic solution was washed with brine, dried ($MgSO_4$), and concentrated. The purification of the crude product by column chromatography (elution with 25% EtOAc in hexane) gave **9** (45 mg, 78%) as an amorphous solid: $[\alpha]_D^{21} = +70$ (*c* 0.75, $CHCl_3$); IR (thin film) 2938, 2880, 2359, 2320, 1712, 1635, 1587, 1558, 1442, 1374, 1316, 1249, 1220, 1181, 1114, 1046, 1008, 959, 921, 872, 834, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 5.35 (s, 1H), 4.62–4.58 (m, 1H), 4.26–4.23 (m, 1 H), 4.08 (d, $J = 8.8$ Hz, 1H), 3.96 (d, $J = 8.8$ Hz, 1H), 2.75 (sextet, $J = 7.2$ Hz, 1 H), 2.68–2.55 (m, 3H), 2.48–2.40 (m, 2 H), 2.36–2.22 (m, 3H), 2.11–1.69 (m, 12H), 1.65–1.21 (m including singlets at 1.37 and 1.35, 19H), 0.92–0.80 (m including a doublet at 0.93 with $J = 6.0$ Hz, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 107.2, 103.3, 102.8, 88.8, 88.2, 83.4, 81.1, 81.0, 73.3, 72.6, 70.8, 52.4, 52.2, 44.7, 44.2, 38.22, 38.2, 37.3, 37.2, 37.1, 36.59, 36.55, 35.9,

34.7, 34.5, 34.4, 34.3, 30.9, 30.7, 30.3, 26.1, 26.0, 24.6, 24.59, 24.4, 20.2, 13.4, 13.2, 11.1; HRMS (FAB) calculated for $C_{40}H_{61}O_{11}$ [(M + H)$^+$] 717.4214, found 717.4181.

Ketal 10. *p*-Toluenesulfonic acid monohydrate (3 mg, 0.02 mmol) was added to a solution of trioxane dimer diol **3** (50 mg, 0.08 mmol) and tetrahydro-4*H*-pyran-4-one (15 μL, 0.16 mmol) in CH_2Cl_2 (2 mL). The reaction was stirred overnight at rt. The solution was washed with saturated aqueous $NaHCO_3$ (5 mL), water (5 mL), and brine (5 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (silica gel, 33% EtOAc in hexane) to afford **10** (30 mg, 54%) as an amorphous solid: $[\alpha]_D^{25} = +74$ (*c* 0.42, $CHCl_3$); IR (thin film) 2953, 2873, 1712, 1453, 1376 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 5.35 (s, 1H), 4.59 (m, 1H), 4.19 (m, 1H), 4.00 (d, $J = 8.8$ Hz, 1H), 3.89 (d, $J = 8.8$ Hz, 1H), 3.75 (m, 4H), 2.79–2.64 (m, 2H), 2.37–2.27 (m, 3H), 2.04–1.16 (m including singlets at 1.38 and 1.36, 31H), 0.94–0.81 (m including a doublet at 0.95 with $J = 6.4$ Hz, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.2, 103.1, 102.8, 88.2, 87.9, 82.7, 80.9, 80.8, 72.6, 72.5, 71.2, 65.8, 65.7, 52.3, 52.1, 44.6, 44.3, 37.9, 37.0, 36.9, 36.7, 36.7, 36.4, 36.4, 34.6, 34.3, 34.2, 30.7, 30.4, 25.9, 25.9, 24.4, 24.1, 20.0, 20.0, 13.5, 13.3; HRMS (FAB) calculated for $C_{39}H_{61}O_{11}$ [(M + H)$^+$] 705.4214, found 705.4214.

Ketal 11. To a solution of trioxane dimer diol **3** in THF (2 mL) at 0 °C was added *N*-benzoyl piperidinone (41 mg, 0.20 mmol) and triethylorthoformate (1.0 mL, 6.0 mmol). The mixture was warmed to rt and stirred for 24 h. It was quenched by addition of cold water (10 mL), and layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic solution was washed with water (5 mL) and 5% aqueous $NaHCO_3$ (5 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated to give the crude product that was purified by flash column chromatography (eluted with 50% EtOAc in hexane) to afford **11** (27 mg, 85%) as an amorphous solid: $[\alpha]_D^{25} = +234$ (*c* 0.75, $CHCl_3$); IR (thin film) 2947, 2876, 1631, 1437, 1379, 1350, 1293, 1113, 1092, 1048, 1013, 934, 868, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 5H), 5.34 (s, 2H), 4.60–4.56 (dd, $J = 6.0$, 10.4 Hz, 1H), 4.23–4.21 (m, 1H), 4.05–3.91 (m, 3H), 3.8–3.69 (s, 1H), 3.50–3.47 (m, 2H), 2.79–2.61 (m, 2H), 2.32–2.28 (m, 2H), 2.01–1.19 (m including a singlet at 1.36, 32H), 0.95–0.88 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 136.1, 129.5, 128.4, 126.8, 107.1, 103.3, 102.9, 88.7, 88.2, 83.3, 81.1, 81.3, 77.3, 73.0, 72.7, 71.0, 53.5, 52.4, 52.3, 45.7, 44.8, 44.3, 40.2, 37.3, 37.2, 36.6, 35.8, 34.5, 34.4, 30.9, 30.7, 26.1, 24.6, 24.4, 20.2, 20.2, 13.7, 13.3; HRMS (FAB) calculated for $C_{46}H_{66}N_3O_{11}$ [(M + H)$^+$] 808.4636, found 808.4655.

Ketal 12. *p*-Toluenesulfonic acid monohydrate (1 mg, 5 μmol) was added to a solution of trioxane dimer diol **3** (20 mg, 0.03 mmol) and 1-carbethoxy-4-piperidone (10 μL, 0.06 mmol) in CH_2Cl_2 (1 mL). The reaction was stirred overnight at rt. The solution was washed with saturated aqueous $NaHCO_3$ (5 mL), water (5 mL), and brine (5 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (silica gel, 29% EtOAc in hexane) to afford **12** (17 mg, 67%) as an amorphous solid: $[\alpha]_D^{24} = +75$ (*c* 0.62, $CHCl_3$); IR (thin film) 2927, 2875, 1697, 1435, 1378, 1350, 1279, 1240, 1112, 1055, 1011 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 5.35 (s, 1H), 4.58 (m, 1H), 4.20 (m, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 4.01 (d, $J = 8.8$ Hz, 1H), 3.89 (d, $J = 8.8$ Hz, 1H), 3.61–3.47 (m, 4H), 2.77–2.65 (m, 2H), 2.37–2.23 (m, 3H), 2.04–1.14 (m including singlets at 1.39 and 1.36, 34H), 0.95–0.84 (m including a doublet at 0.94 with $J = 6.0$ Hz, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 107.2, 103.4, 103.0, 88.5, 88.2, 83.1, 81.1, 81.1, 72.8, 71.3, 61.3, 52.5, 52.3, 44.8, 44.5, 41.8, 37.3, 37.2, 37.0, 36.7, 36.6, 35.7, 34.5, 34.4, 30.9, 30.7, 29.7, 26.1, 26.1, 24.6, 24.4, 20.2, 20.2, 14.7, 14.2, 13.7, 13.4; HRMS (FAB) calculated for $C_{42}H_{66}NO_{12}$ [(M + H)$^+$] 776.4585, found 776.4597.

Ketal 13. 4-Oxo-piperidine-1-carbonyl chloride (0.100 g, 0.620 mmol) was dissolved in CH_2Cl_2 (1.50 mL). Methyl amine (2.0 M in THF, 1.50 mL, 3.09 mmol) was added to the solution. It was stirred for 16 h at rt and then quenched with H_2O (5 mL). Layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were washed with H_2O (1 × 10 mL), dried ($MgSO_4$), and concentrated. Purification of the crude product by column chromatography (10% hexane in EtOAc) gave 4-oxo-piperidine-1-carboxylic acid methylamide (43 mg, 45%) as a slightly yellow solid: mp 76–80 °C; IR (thin film) 3348, 2962, 2909, 2874, 1713, 1630, 1547, 1484, 1419, 1392, 1353, 1312, 1266, 1151, 1080, 982, 825, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (s, 1H), 3.65 (t, $J = 5.6$ Hz, 4H), 2.83–2.68 (m, 3H), 2.42 (t, $J = 6.0$ Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 158.1, 42.9, 40.9, 27.7; HRMS (FAB) calculated for $C_7H_{13}N_2O_2$ [(M + H)$^+$] 157.0977, found 157.0969. To a solution of trioxane dimer diol **3** (20 mg, 0.03 mmol) in CH_2Cl_2 (1.50 mL) was added 4-oxo-piperidine-1-carboxylic acid methylamide (41 mg, 0.26 mmol) and *p*-toluenesulfonic acid monohydrate (2 mg, 0.01 mmol). The reaction was stirred for 16 h at rt and then quenched with H_2O (3 mL). Layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried ($MgSO_4$) and concentrated. Purification of the crude product by column chromatography (100% EtOAc) gave **13** (19 mg, 76%) as an amorphous white solid: $[\alpha]_D^{22} = +55$ (*c* 0.90, $CHCl_3$); IR (thin film) 3346, 2956, 2926, 2873, 2850, 1629, 1544, 1449, 1379, 1350, 1251, 1119, 1092, 1051, 1009, 935, 877, 829, 769, 664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (s, 1H), 5.32 (s, 1H), 4.57–4.53 (m, 1H), 4.46–4.44 (m, 1H), 4.20–4.15 (m, 1H), 3.99 (d, $J = 9.2$ Hz, 1H), 3.88 (d, $J = 9.2$ Hz, 1H), 3.48–3.35 (m, 4H), 2.78–2.77 (d, $J = 4.4$ Hz, 3H), 2.75–2.70 (m, 1H), 2.67–2.62 (m, 1H), 2.34–2.19 (m, 3H), 2.19–1.92 (m, 4H), 1.88–1.83 (m, 2H), 1.77–1.71 (m, 4H), 1.68–1.60 (m, 3H), 1.56–1.44 (m, 5H), 1.40–1.29 (m including singlets at 1.37 and 1.33, 10H), 1.25–1.17 (m, 3H), 0.96–0.91 (m, 7H), 0.85–0.82 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 107.3, 103.4, 103.0, 88.6, 88.3, 83.1, 81.1, 81.1, 72.9, 72.7, 71.2, 52.5, 52.3, 44.8, 44.5, 42.1, 37.3, 37.2, 37.1, 36.9, 36.7, 35.7, 34.7, 34.5, 34.4, 30.9, 30.8, 30.7, 27.7, 26.2, 26.1, 24.6, 24.4, 20.3, 20.2, 19.1, 13.7, 13.4; HRMS (FAB) calculated for $C_{41}H_{65}N_2O_{11}$ [(M + H)$^+$] 761.4588, found 761.4610.

Ketal 14. To a solution of trioxane dimer diol **3** (50 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) was added tetrahydrothiopyran-4-one (18 mg, 0.16 mmol) and *p*-toluenesulfonic acid monohydrate (3 mg, 0.02 mmol), and it was stirred at rt for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic solution was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (elution with 25% EtOAc in hexane) to give a crude solid. To a mixture of oxone (410 mg, 0.69 mmol) in H_2O (2 mL) was cannulated the crude solid (49 mg, 0.07 mmol) in MeOH (4 mL). The reaction stirred at rt for 1.5 h. The insoluble solid was filtered off, and the filtrate was extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (30% EtOAc in hexane) gave **14** (46 mg, 88%) as an amorphous solid: $[\alpha]_D^{24} = +62$ (*c* 0.34, $CHCl_3$); IR (thin film) 2938, 2880, 2851, 2465, 2224, 1712, 1587, 1558, 1452, 1374, 1326, 1287, 1249, 1220, 1191, 1104, 1056, 1017, 940, 901, 882, 747, 660 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (s, 1H), 5.28 (s, 1H), 4.57–4.53 (m, 1H), 4.28–4.25 (m, 1H), 4.04 (d, $J = 9.0$ Hz, 1H), 3.91 (d, $J = 9.0$ Hz, 1H), 3.43–3.37 (m, 1H), 3.33–3.27 (m, 1H), 3.08–3.00 (m, 2H), 2.74–2.69 (m, 1 H), 2.49–2.44 (m, 1 H), 2.35–2.22 (m, 5 H), 2.03–1.89 (m, 5H), 1.89–1.47 (m, 10H), 1.47–1.15 (m including singlets at 1.38 and 1.36, 14H), 0.92–0.80 (m including doublets at 0.87 with $J = 7.6$ Hz and 0.84 with $J = 7.6$ Hz, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.8, 103.1, 102.3, 89.3, 88.0, 83.7, 80.8, 80.7, 73.3, 71.9, 68.9, 51.9, 51.6, 49.0, 48.7, 44.3, 43.3, 37.2, 37.14, 37.10, 36.2, 36.1, 34.2, 34.1, 33.9, 33.8, 33.6, 30.6, 30.4, 25.7, 25.6, 24.5, 24.4, 24.3, 24.1, 19.9, 19.7, 13.1, 12.2; HRMS (FAB) calculated for $C_{39}H_{61}O_{12}S$ [(M + H)$^+$] 753.3883, found 753.3875.

Ester 16. A 25 mL round-bottom flask was charged with trioxane dimer diol **3** (70 mg, 0.11 mmol), CH_2Cl_2 (5 mL), pyridine (22 μL, 0.56 mmol), and benzoyl chloride (0.33 μL, 0.56 mmol). The

reaction was stirred at rt for 2 h. Then, it was quenched with ice cold water (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organics were washed with aqueous citric acid (5%, 5 × 5 mL). The organic layer was dried ($MgSO_4$) and concentrated. The crude product was purified by flash silica gel column chromatography (40% EtOAc in hexane) to give **16** (64 mg, 80%) as an amorphous solid: $[\alpha]_D^{23} = +70$ (*c* 1.00, $CHCl_3$); IR (thin film) 3498, 2943, 2870, 1718, 1446, 1372, 1310, 1274, 1112, 907, 730, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H), 7.55–7.51 (m, 1H), 7.43–7.34 (m, 2H), 5.34 (s, 1H), 5.31 (s, 1H), 4.71 (dd, $J = 8.0$, 10.0 Hz, 1H), 4.61 (dd, $J = 8.0$, 10.0 Hz, 1H), 4.55 (s, 2H), 4.24 (bs, 1H), 2.66–2.54 (m, 2H), 2.32–2.24 (m, 2H), 2.15–1.75 (m, 10H), 1.68–1.62 (m, 4H), 1.42–1.18 (m including two singlets at 1.40 and 1.37, 14H), 0.96–0.86 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 132.5, 130.7, 129.5, 128.1, 103.6, 102.9, 89.4, 89.1, 80.9, 80.9, 73.8, 70.5, 70.4, 52.1, 51.9, 43.9, 43.8, 37.4, 37.4, 36.5, 36.5, 36.3, 35.0, 34.3, 34.3, 30.8, 30.7, 30.2, 25.9, 25.8, 24.8, 24.8, 24.6, 24.6, 20.0, 20.0, 12.7, 12.6; HRMS (FAB) calculated for $C_{41}H_{59}O_{11}$ $[(M + H)^+]$ 727.4057, found 727.4031; Anal. calculated for $C_{41}H_{58}O_{11}$ C, 67.75, H, 8.04, found C, 67.24, H, 8.09.

Ether 17. To a solution of 2-butyne-1,4-diol (500 mg, 5.81 mmol) in DMF (10 mL) was added NaH (60% dispersion in mineral oil, 140 mg, 3.48 mmol), and it was stirred at rt for 30 min. The mixture was cooled to 0 °C, and 4-fluorobenzyl bromide (428 μL, 3.48 mmol) was added dropwise. The solution was stirred for 14 h and then added to ice cold water (10 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were rinsed with ice–water (3 × 20 mL) and brine, dried ($MgSO_4$), and concentrated. Flash column chromatography (10–25% EtOAc in hexane) yielded mono 4-fluorobenzyl ether (320 mg, 28%) as a colorless oil: IR (thin film) 3440, 2871, 1603, 1510, 1349, 1223, 1073, 1029, 1007, 823, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 2H), 7.03 (m, 2H), 4.52 (s, 2H), 4.30 (m, 2H), 4.19 (m, 2H), 2.26 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, $J =$ 244 Hz), 133.0 (d, $J = 3$ Hz), 129.8 (d, $J = 8$ Hz), 115.3 (d, $J =$ 22 Hz), 84.9, 81.4, 70.9, 57.4, 50.9; HRMS (FAB) calculated for $C_{11}H_{11}FO_2$ $[(M + H)^+]$ 193.0665; found, 193.0666. To a solution of the mono 4-fluorobenzyl ether alcohol (295 mg, 1.52 mmol) in THF (20 mL) was added freshly ground KOH (681 mg, 12.16 mmol). The mixture was cooled to −30 °C, and tosylchloride (319 mg, 1.67 mmol) was added in one portion. After stirring at −30 °C for 3 h, the mixture was added to water (10 mL), and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were rinsed with brine, dried ($MgSO_4$), concentrated, and purified by flash column chromatography (25% EtOAc in hexane) to give 2-butyne-1-tosylate-4-*p*-fluorobenzyl ether (495 mg, 94%) as a colorless oil: IR (thin film) 2857, 1602, 1508, 1446, 1358, 1222, 1179, 1083, 1008, 947, 815, 662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.31 (m, 2H), 7.25 (m, 2H), 7.00 (m, 2H), 4.74 (t, $J = 1.6$ Hz, 2H), 4.42 (s, 2H), 4.05 (t, $J = 1.6$ Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, $J =$ 244 Hz), 145.1, 133.0 (d, $J = 3$ Hz), 129.8 (d, $J = 8$ Hz), 129.8, 128.1, 115.3 (d, $J = 22$ Hz), 85.3, 78.5, 70.9, 57.8, 57.0, 21.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −114.72 (septet, $J = 5.6$ Hz); HRMS (FAB) calculated for $C_{18}H_{16}FO_4S$ $[(M - H^+)]$ 347.0753, found 347.0746. To a solution of trioxane dimer diol **3** (35 mg, 0.056 mmol) in THF (1 mL) was added KH (30% dispersion in mineral oil, rinsed with hexane prior to use, 30 mg, 0.225 mmol), and the mixture was stirred at rt for 1 h. The mixture was cooled to 0 °C, and a solution of 2-butyne-1-tosylate-4-*p*-fluorobenzyl ether (130 mg, 0.373 mmol) in THF (1 mL) was added dropwise. The solution was warmed slowly to rt and stirred for 10 h. The reaction was added to ice cold water and extracted with CH_2Cl_2 (3 × 5 mL), dried ($MgSO_4$), and concentrated. The crude oil was purified by flash column chromatography (25% EtOAc in hexane) to give **17** (16 mg, 36% yield) as an amorphous white solid: $[\alpha]_D^{27} = +80$ (*c* 0.08, $CHCl_3$); IR (thin film) 3673, 2940, 2889, 1513, 1377, 1348, 1223, 1091, 1014, 844, 825, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.03 (m, 2H), 5.36 (s, 1H), 5.34 (s, 1H), 4.55 (m, 4H), 4.30 (m, 4H), 3.74 (d, $J = 9.2$ Hz, 1H), 3.66 (d, $J =$ 9.2 Hz, 1H), 2.64 (m, 2H), 2.31 (m, 2H), 1.88 (m, 9H), 1.62 (m, 5H), 1.4–1.19 (m including a singlet at 1.38, 14H), 0.97–0.79 (m including doublets at 0.94 with $J = 6.0$ Hz, 0.87 with $J = 7.2$ Hz, and 0.87 with $J = 7.6$ Hz, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, $J = 244$ Hz), 133.4 (d, $J = 3$ Hz), 129.9 (d, $J = 8$ Hz), 115.2 (d, $J = 22$ Hz), 103.1, 102.9, 89.4, 88.9, 83.5, 81.6, 81.1, 81.1, 74.0, 74.0, 71.2, 71.1, 70.7, 58.7, 57.5, 52.4, 52.2, 44.4, 44.0, 37.4, 37.4, 36.63, 36.63, 36.0, 35.3, 34.5, 34.5, 30.82, 30.82, 26.1, 26.0, 24.8, 24.8, 20.2, 20.1, 13.0, 12.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −115.16 (septet, $J = 5.6$ Hz); HRMS (FAB) calculated for $C_{45}H_{63}FO_{11}$ $[(M + H)^+]$ 799.4433, found 799.4445.

Thiophosphate ester 19. To a solution of trioxane dimer primary alcohol **4** (0.080 g, 0.13 mmol) in THF at 0 °C was added lithium hexamethyldisilane (1.0 M in THF, 0.20 mL, 0.20 mmol) dropwise over 1 min. After stirring for 10 min, diethyl chloro thiophosphate (52 μL, 0.33 mmol) was added neat. The reaction mixture was allowed to warm to rt and stir for 2 h before the reaction was quenched by the slow addition of H_2O (5 mL). The contents of the flask were extracted with CH_2Cl_2 (2 × 25 mL), washed with saturated aqueous $NaHCO_3$ (5 mL) and H_2O (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by silica gel chromatography (20% EtOAc in hexane) to give **19** as an amorphous white solid (56 mg, 56%): $[\alpha]_D^{23} = +59.2$ (*c* 3.30, $CHCl_3$); IR (thin film) 2943, 2872, 1737, 1443, 1378, 1102, 1002, 967 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (s, 1H), 5.28 (s, 1H), 4.42–4.32 (m, 1H), 4.27–4.15 (m, 3H), 4.15–4.04 (m, 4H), 2.74–2.50 (m, 2H), 2.37–2.13 (m, 3H), 2.02–1.17 (m including singlets at 1.38 and 1.37, and a triplet at 1.30 with $J = 6.9$ Hz, 34H), 0.97–0.77 (m including doublets at 0.93 with $J = 6.0$ Hz, 0.85 with $J = 7.5$ Hz, and 0.84 with $J = 7.5$ Hz, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.1, 102.8, 89.3, 88.6, 81.14, 81.07, 73.9, 71.2, 70.3 (d, $J = 5$ Hz), 64.1 (d, $J = 5$ Hz), 52.5, 52.2, 44.5, 44.2, 37.4, 37.3, 36.63, 36.57, 35.2, 35.1, 34.5, 34.4, 30.5, 30.4, 30.2, 29.6, 26.1 (d, $J = 3$ Hz), 24.82, 24.75, 24.70, 24.6, 20.2, 20.1, 15.9 (d, $J = 5$ Hz), 15.2, 13.2; HRMS (FAB) calculated for $C_{38}H_{64}O_{11}PS$ $[(M + H)^+]$ 759.3907, found 759.3896.

Carbamate 20. Trioxane dimer primary alcohol **4** (40 mg, 0.07 mmol) was dissolved in CH_2Cl_2 (0.8 mL). Sodium hydride (60% dispersion in mineral oil, 4 mg, 0.10 mmol) was added to the solution. After 1 h, diethylcarbamyl chloride (9 mg, 0.07 mmol) was added. The reaction was stirred for 16 h at rt, and then more sodium hydride (60% dispersion in mineral oil, 4 mg, 0.10 mmol) was added. After 16 h, the reaction was quenched with H_2O (10 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL) and ethyl acetate (2 × 10 mL). The combined organic layer was dried ($MgSO_4$) and concentrated. Purification of the crude product by column chromatography (60% EtOAc in hexane) gave **20** (32 mg, 70%) as an amorphous solid: $[\alpha]_D^{21} = +49.3$ (*c* 2.43, $CHCl_3$); IR (thin film) 2928, 2870, 1693, 1480, 1423, 1374, 1268, 1230, 1191, 1114, 1056, 998, 958, 950, 872, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.29 (m, 2H), 4.37–4.33 (m, 1H), 4.26–4.15 (m, 3H), 3.24 (m, 4H), 2.69 (sextet, $J = 6.4$ Hz, 1H), 2.59 (sextet, $J = 6.8$ Hz, 1H), 2.31–2.27 (m, 2H), 2.16 (m, 1H), 2.00–1.93 (m, 2H), 1.88–1.82 (m, 2H), 1.81–1.71 (m, 3H), 1.64–1.50 (m, 5H), 1.44–1.36 (m including singlets at 1.38 and 1.37, 9H), 1.33–1.17 (m, 6H), 1.09 (t, $J =$ 6.8 Hz, 6H), 0.95–0.92 (m, 7H), 0.86–0.82 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 103.2, 103.0, 88.2, 88.6, 81.2, 81.1, 73.6, 72.1, 67.4, 52.5, 52.3, 44.6, 44.4, 37.4, 37.3, 36.7, 36.6, 34.5, 34.4, 34.3, 30.8, 30.5, 30.4, 29.8, 26.1, 26.0, 24.8, 24.7, 24.6, 20.3, 20.2, 14.2, 13.3, 12.9; HRMS (FAB) calculated for $C_{39}H_{64}NO_{10}$ $[(M + H)^+]$ 706.4530, found 706.4540.

Amide 21. Trioxane dimer acid **5** (35 mg, 0.06 mmol) was dissolved in CH_2Cl_2 (1.5 mL). 1-(3-(Dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (13 mg, 0.07 mmol) and 1-hydroxybenzotriazole (10 mg, 0.07 mmol) were added. After 1 h, cyclohexanemethyl amine (23 mg, 0.17 mmol) was added to the reaction mixture. It was stirred for 3 h, and then the reaction was quenched with saturated aqueous NH_4Cl (3 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) and EtOAc (2 × 10 mL). The

combined organic solution was dried ($MgSO_4$) and concentrated. Purification of the crude product by column chromatography (30% EtOAc in hexane) gave **21** (39 mg, 93%) as an amorphous solid: $[\alpha]_D^{22} = +102$ (*c* 1.25, $CHCl_3$); IR (thin film) 2872, 2880, 2861, 1654, 1529, 1452, 1355, 1268, 1258, 1230, 1201, 1191, 1094, 1075, 1056, 1017, 959, 930, 863, 824, 815, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.05 (t, $J = 5.6$ Hz, 1H), 5.25 (s, 1H), 5.22 (s, 1H), 4.09–3.99 (m, 2H), 3.07 (t, $J = 6.0$ Hz, 2H), 2.75–2.65 (m, 2H), 2.55–2.49 (m, 1H), 2.34–2.25 (m, 2H), 2.14–2.04 (m, 1H), 2.03–1.95 (m, 3H), 1.90–1.78 (m, 3H), 1.77–1.59 (m, 11H), 1.54–1.41 (m, 6H), 1.39–1.34 (m including singlets at 1.38 and 1.36, 6H), 1.31–1.14 (m, 8H), 0.96–0.90 (m, 9H), 0.85–0.79 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 103.4, 88.5, 88.4, 81.2, 81.1, 76.1, 74.3, 52.6, 52.5, 46.0, 45.0, 44.7, 44.1, 37.7, 37.4, 37.3, 36.5, 34.7, 34.5, 32.8, 32.6, 31.6, 31.1, 31.0, 30.2, 29.9, 26.5, 26.3, 26.2, 25.9, 25.9, 25.3, 24.9, 24.8, 24.7, 24.6, 20.2, 14.3, 13.5, 13.2; HRMS (FAB) calculated for $C_{41}H_{66}NO_9$ [$(M + H)^+$] 716.4638, found 716.4745.

Amide 22. To a solution of trioxane dimer acid **5** (50 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (23 mg, 0.12 mmol) and hydroxybenzotriazole (16 mg, 0.12 mmol). The mixture was stirred for 2 h. The neopentylamine (0.041 mL, 0.49 mmol) was then added to the reaction mixture at 0 °C, and it was stirred overnight as it warmed to rt. The reaction was quenched by addition of H_2O (10 mL). It was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated to give the crude product, which was purified by flash column chromatography (eluted with 50% EtOAc in hexane to afford **22** (52 mg, 77%) as an amorphous solid: $[\alpha]_D^{25} = +110$ (*c* 0.50, $CHCl_3$); IR (thin film) 3338, 2953, 2870, 1664, 1447, 1380, 1212, 1094, 1011, 936, 877, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.11–6.08 (t, $J = 6.0$ Hz, 1H), 5.27 (s, 1H), 5.25 (s, 1H), 4.14–4.10 (m, 1H), 4.07–4.04 (m, 1H), 3.15 (dd, $J =$ 6.8, 13.6 Hz, 1H), 2.97 (dd, $J = 6.0$, 13.6 Hz, 1H), 2.78–2.70 (m, 2H), 2.59–2.52 (m, 1H), 2.36–2.26 (m, 2H), 2.18–2.07 (m, 1H), 2.03–1.97 (m, 2H), 1.90–1.71 (m, 6H), 1.68–1.61 (m, 2H), 1.55–1.18 (m including two singlets at 1.39 and 1.36, 17H), 0.96–0.90 (m including a singlet at 0.91, 17H), 0.85 (d, $J = 7.6$ Hz, 3H), 0.82 (d, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 103.5, 103.4, 88.4, 88.2, 81.2, 81.0, 76.0, 74.5, 52.6, 52.5, 50.8, 44.8, 44.7, 44.2, 37.4, 37.3, 36.5, 36.5, 34.5, 34.5, 32.4, 31.5, 30.2, 29.8, 27.4, 26.2, 26.1, 24.9, 24.7, 24.6, 24.5, 20.2, 20.2, 13.5, 13.3; HRMS (FAB) calculated for $C_{39}H_{64}NO_9$ [$(M + H)^+$] 690.4581, found 690.4595.

Amide 23. Trioxane dimer acid **5** (50 mg, 0.08 mmol), *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (19 mg, 0.10 mmol), and 1-hydroxybenzotriazole (13 mg, 0.10 mmol) were added to CH_2Cl_2 (4 mL). After stirring at 0 °C for 2 h, 4-(aminomethyl)pyridine (17 μL, 0.16 mmol) and triethylamine (45 μL, 0.32 mmol) were added. The reaction mixture was stirred at rt for 30 min, and then the reaction was quenched with 1% aqueous HCl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash column chromatography (100% EtOAc) to yield **23** (31 mg, 54%) as an amorphous solid: $[\alpha]_D^{22} = +100$ (*c* 0.05, $CHCl_3$); IR (thin film) 3311, 2938, 2875, 1669, 1603, 1530, 1453, 1417, 1377, 1253, 1187, 1093, 1052, 1012, 878, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63–8.48 (m, 2H), 7.35–7.28 (m, 2H), 6.35 (t, $J = 5.6$ Hz, 1H), 5.32 (s, 1H), 5.20 (s, 1H), 4.53 (dd, $J = 5.6$, 16.0 Hz, 1H), 4.41 (dd, $J = 5.6$, 16.0 Hz, 1H), 4.19–4.15 (m, 1H), 4.13–4.09 (m, 1H), 2.72–2.61 (m, 3H), 2.38–2.30 (m, 3H), 2.40–2.17 (m, 1H), 2.04–1.23 (m including singlets at 1.36 and 1.27, 26H), 0.97 (m, 8H), 0.90–0.82 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 149.8, 147.9, 123.5, 103.4, 88.7, 88.6, 81.2, 81.1, 73.5, 52.5, 52.4, 44.6, 44.5, 44.4, 42.9, 37.5, 37.3, 36.5, 34.5, 33.6, 33.0, 30.2, 29.9, 26.2, 26.2, 24.9, 24.8, 24.7, 24.6, 20.2, 13.5, 13.0; HRMS (FAB) calculated for $C_{40}H_{59}N_2O_9$ [$(M + H)^+$] 711.4221, found 711.4245.

Amide 24. To a solution of trioxane dimer acid **5** (50 mg, 0.08 mmol) in CH_2Cl_2 (5 mL) was added *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (61 mg, 0.32 mmol) and 1-hydroxybenzotriazole hydrate (12 mg, 0.09 mmol). After 1.5 h, methyl 4-(aminomethyl)benzoate hydrochloride (65 mg, 0.32 mmol) and Et_3N (44 μL, 0.39 mmol) were added. The reaction mixture was stirred overnight, and then the reaction was quenched by the addition of 1 N HCl (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash gradient column chromatography (silica gel, 3:2 then, 3:1 ether/petroleum ether) to give **24** (47 mg, 78%) as an amorphous solid: $[\alpha]_D^{25} = +56$ (*c* 0.50, $CHCl_3$); IR (thin film) 2950, 2360, 1722, 1672, 1279, 1106, 1052, 1012 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95–7.93 (d, $J = 8.1$ Hz, 2H), 7.41–7.39 (d, $J = 8.1$ Hz, 2H), 6.41–6.39 (t, $J = 4.8$ Hz, 1H), 5.26 (s, 1H), 5.15 (s, 1H), 4.48 (d, $J = 5.3$ Hz, 2H), 4.15–4.06 (m, 2H), 3.87 (s, 3H), 2.74–2.57 (m, 3H), 2.31–2.11 (m, 3H), 2.01–1.16 (m including singlets at 1.39 and 1.29, 27H), 0.93–0.82 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 166.9, 144, 129.8, 129, 127.9, 103.4, 103.3, 88.7, 88.5, 81.2, 81.1, 76.3, 73.7, 52.5, 52.4, 52.0, 44.6, 44.5, 44.2, 43.7, 37.4, 37.2, 36.5, 34.5, 33.3, 33.0, 30.2, 30.0, 26.2, 26.1, 24.9, 24.8, 24.7, 24.5, 20.2, 13.5, 13.0; HRMS (FAB) calculated for $C_{43}H_{62}NO_{11}$ [$(M + H)^+$] 768.4323, observed 768.4349.

Amide 25. To a solution of trioxane dimer acid **5** (25 mg, 0.040 mmol) in CH_2Cl_2 (1 mL) were added *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (9 mg, 0.05 mmol) and 1-hydroxybenzotriazole (7 mg, 0.05 mmol). It was stirred at rt for 1 h. To the reaction was added 4-methylbenzylamine (15 μL, 0.12 mmol), and the solution was stirred for 3 h. Then, water (1 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic solution was dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (elution with EtOAc/hexane = 1:2) to give **25** (26 mg, 89%) as an amorphous white solid: $[\alpha]_D^{22} = +82$ (*c* 0.59, $CHCl_3$); IR (thin film) 2928, 2870, 1665, 1514, 1377, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 8.0$ Hz, 2H), 6.18 (t, $J = 5.2$ Hz, 1H), 5.27 (s, 1H), 5.20 (s, 1H), 4.40 (dd, $J = 4.8$, 15.2 Hz, 2H), 4.11 (m, 2H), 2.74 (sextet, $J = 7.2$ Hz, 1H), 2.67 (sextet, $J = 7.2$ Hz, 1H), 2.53 (m, 1H), 2.31 (dt, $J = 4.0$, 14.0 Hz, 2H), 2.31 (s, 3H), 2.17 (m, 1H), 2.03–1.17 (m including singlets at 1.37 and 1.27, 27H), 0.99–0.80 (m including doublets at 0.95 with $J = 5.2$ Hz, 0.94 with $J = 6.0$ Hz, 0.85 with $J = 8.0$ Hz, and 0.83 with $J = 8.4$ Hz, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 136.7, 135.4, 129.1, 128.1, 103.4, 103.3, 88.6, 88.4, 81.2, 81.0, 76.3, 73.9, 52.6, 52.4, 44.8, 44.6, 44.4, 43.8, 37.4, 37.2, 36.6, 36.5, 34.5, 34.5, 33.1, 32.9, 30.2, 30.0, 26.2, 26.0, 24.9, 24.8, 24.7, 24.5, 21.1, 20.2, 20.2, 13.5, 13.0; HRMS (FAB) calculated for $C_{42}H_{62}NO_9$ [$(M + H)^+$] 724.4425, found 724.4439.

Amide 26. To a solution of trioxane dimer acid **5** (25 mg, 0.040 mmol) in CH_2Cl_2 (1 mL) were added *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (9 mg, 0.05 mmol) and 1-hydroxybenzotriazole (7 mg, 0.05 mmol). It was stirred at rt for 1 h. To the reaction was added (*S*)-(−)-1-(4-fluorophenyl)ethylamine (15 μL, 0.12 mmol), and the solution was stirred for 3 h. Then, water (1 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic solution was dried ($MgSO_4$) and concentrated. The crude was purified by flash column chromatography (elution with EtOAc/hexane = 1:2) to give **26** (30 mg, 99%) as an amorphous white solid: $[\alpha]_D^{22} = +98$ (*c* 0.70, $CHCl_3$); IR (thin film) 2934, 2869, 1665, 1509, 1378, 1132, 1052, 1008 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, $J = 7.2$, 12.4 Hz, 2H), 6.99 (t, $J = 8.4$ Hz, 2H), 6.34 (d, $J = 7.6$ Hz, 1H), 5.28 (s, 1H), 5.27 (s, 1H), 5.07 (t, $J = 7.2$ Hz, 1H), 4.09 (m, 1H), 3.84 (m, 1H), 2.77 (sextet, $J = 6.0$ Hz, 1H), 2.59 (sextet, $J = 6.4$ Hz, 1H), 2.50 (m, 1H), 2.38–2.15 (m, 3H), 2.06–1.97 (m, 2H), 1.93–1.17 (m including d at 1.47 with $J = 6.8$ Hz, and singlets at 1.41 and 1.34, 28H), 0.99–0.89 (m including doublets at 0.95 with $J = 4.0$ Hz and 0.93 with $J = 3.6$

Hz, 8H), 0.83 (d, $J = 12.4$ Hz, 3H), 0.66 (d, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 161.8 (d, $J = 243$ Hz), 140.0 (d, $J = 3$ Hz), 127.9 (d, $J = 8$ Hz), 115.0 (d, $J = 21$ Hz), 103.6, 103.5, 88.4, 88.3, 81.2, 81.0, 76.9, 74.0, 52.6, 52.4, 48.5, 44.8, 44.7, 44.6, 37.4, 37.2, 36.6, 36.5, 34.5, 34.5, 33.5, 32.5, 30.1, 29.6, 26.2, 26.1, 24.8, 24.7, 24.7, 24.6, 22.4, 20.2, 13.7, 13.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −116.5; HRMS (FAB) calculated for $C_{42}H_{61}FNO_9$ $[(M + H)^+]$ 742.4330, found 742.4313.

Oxadiazole 27. To a solution of trioxane dimer acid **5** (80 mg, 0.13 mmol) in dimethylformamide (1 mL) at –10 °C was added a solution of *N*,*N*′-diisopropylcarbodiimide (24 μL, 0.15 mmol), 1-hydroxybenzotriazole (21 mg, 0.15 mmol), and *N*-hydroxyethanimidamide (11 mg, 0.15 mmol) in dimethylformamide (3 mL) over 20 min. The reaction was stirred for 20 min at –10 °C and slowly warmed to rt overnight. Volatile components were removed under reduced pressure, and the residue was dissolved in EtOAc (10 mL). The organic solution was subsequently washed with saturated aqueous $NaHCO_3$ (6 mL), H_2O (6 mL), aqueous $KHSO_4$ (0.5 M, 2 × 6 mL), and brine (6 mL) and dried ($MgSO_4$). The crude product was dissolved in THF (3 mL), and *n*-Bu_4NF in THF (1.0 M, 170 μL, 0.17 mmol) was added to the solution dropwise. The reaction mixture was stirred overnight and then poured into EtOAc (10 mL). It was washed with water (6 mL) and brine (6 mL) and dried ($MgSO_4$). The crude product was purified by column chromatography (EtOAc/hexane = 1:4) to give **27** (53 mg, 62%) as an amorphous white solid: $[\alpha]_D^{26} = +97$ (*c* 0.41, $CHCl_3$); IR (thin film) 2953, 2934, 2874, 1611, 1581, 1462, 1379, 1329, 1278, 1222, 1102, 1054, 1009, 943, 880, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (s, 1H), 5.11 (s, 1H), 4.21–4.25 (m, 1H), 4.09–4.15 (m, 1H), 3.51 (bs, 1H), 2.71–2.62 (m, 1H), 2.53–2.43 (m, 1H), 2.34 (s, 3H), 2.31–2.21 (m, 2H), 2.17–2.09 (m, 1H), 2.01–1.73 (m, 9H), 1.65–1.51 (m, 4H), 1.44–1.16 (m including singlets at 1.38 and 1.34, 14H), 0.94 (d, $J = 6.0$ Hz, 3H), 0.93 (d, $J = 6.0$ Hz, 3H), 0.92–0.88 (m, 2H), 0.84 (d, $J = 7.0$ Hz, 3H), 0.82 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.5, 166.6, 103.1, 102.8, 89.5, 88.3, 81.0, 80.9, 73.8, 70.9, 52.3, 51.9, 44.3, 43.8, 37.5, 37.3, 36.6, 36.5, 34.8, 34.4, 34.4, 34.2, 33.6, 30.4, 30.3, 25.8, 25.6, 24.8, 24.8, 24.7, 20.2, 20.0, 13.0, 12.3, 11.6; HRMS (FAB) calculated for $C_{36}H_{55}N_2O_9$ $[(M + H)^+]$ 659.3908, found 659.3901.

Oxadiazole 28. To a solution of the trioxane dimer acid **5** (70 mg, 0.11 mmol) and 1-hydroxybenzotriazole (18 mg, 0.13 mmol) in CH_2Cl_2 (4 mL) were added *N*,*N*′-diisopropylcarbodiimide (26 μL, 0.17 mmol) and 4-fluorobenzohydrazide (30 mg, 0.22 mmol), successively. The reaction mixture was stirred overnight. It was concentrated and redissolved in EtOAc (15 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (7 mL), H_2O (7 mL), aqueous $KHSO_4$ (0.5 M, 2 × 7 mL), and brine, dried ($MgSO_4$), and concentrated. The crude diacylhydrazine was dissolved in THF (7 mL), and methyl *N*-(triethylammoniumsulphonyl)carbamate (51 mg, 0.22 mmol) was added. The solution was stirred at 50 °C overnight. It was concentrated and redissolved in EtOAc (10 mL). The organic layer was washed with water (5 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (EtOAc/hexane = 1:7) to give **28** (33 mg, 40%) as an amorphous white solid: $[\alpha]_D^{26} = +56$ (*c* 0.56, CH_2Cl_2); IR (thin flim) 3064, 2939, 2871, 1611, 1499, 1450, 1377, 1226, 1094, 1053, 1011, 941, 879, 844, 751 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.06–8.02 (m, 2H), 7.18 (t, $J = 8.0$ Hz, 2H), 5.29 (s, 1H), 5.11 (s, 1H), 4.26–4.22 (m, 1H), 4.18–4.12 (m, 1H), 3.57–3.44 (m, 1H), 2.64 (dq, $J = 8.0$, 7.6 Hz, 1H), 2.50 (dq, $J = 8.0$, 7.6 Hz, 1H), 2.23–2.11 (m, 3H), 2.05–1.76 (m, 8H), 1.67–1.51 (m, 4H), 1.42–1.14 (m including s at 1.23, 12H), 1.11 (s, 3H), 0.98–0.88 (m including doublets at 0.95 with $J = 7.6$ Hz and 0.93 with $J = 8.0$ Hz, 8H), 0.88 (d, $J = 7.6$ Hz, 3H), 0.86 (d, $J = 8.0$ Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 170.4, 165.0 ($J = 252.0$ Hz), 164.0, 129.6 ($J = 8.0$ Hz), 121.8 ($J = 2.0$ Hz), 116.5 ($J = 23.0$ Hz), 103.6, 103.3, 90.0, 89.0, 81.5, 81.5, 74.3, 72.0, 53.0, 52.7, 45.0, 44.6, 38.1, 38.0, 37.2, 37.0, 35.0, 35.0, 34.3, 34.2, 33.9, 31.0, 30.9, 26.1, 26.1, 25.4, 25.4, 25.4, 25.2, 20.5, 20.4, 13.5, 12.9; ^{19}F NMR (282 MHz, CD_2Cl_2) δ –109.1; HRMS (FAB) calculated for $C_{41}H_{56}FN_2O_9$ $[(M + H)^+]$ 739.3970, found 739.3967.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all of the new trioxane dimers. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Ridley, R. G. Medical need, scientific opportunity, and the drive for antimalarial drugs. *Nature* **2002**, *415*, 686–693.
(2) Breman, J. G.; Alilio, M. S.; Mills, A. Conquering the intolerable burden of malaria: what's new, what's needed: a summary. *Am. J. Trop. Med. Hyg.* **2004**, *71*, 1–15.
(3) Snow, R. W.; Guerra, C. A.; Noor, A. M.; Myint, H. Y.; Hay, S. I. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. *Nature* **2005**, *434*, 214–217.
(4) Olliaro, P. L.; Boland, P. B. Clinical Public Health Implications of Antimalarial Drug Resistance. In *Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery*; Rosenthal, P. J., Ed.; Humana Press: Totowa, NJ, 2001; pp 65–83.
(5) Shizhen, L. *Compendium of Materia Medica (Bencao Gangmu)*; Foreign Languages Press: Beijing, China,first published in Chinese in 1593, translation published 2003.
(6) Klayman, D. L. Qinghaosu (artemisinin): an antimalarial drug from China. *Science* **1985**, *228*, 1049–1055.
(7) O'Neill, P. M.; Posner, G. H. A medicinal chemistry perspective on artemisinin and related endoperoxides. *J. Med. Chem.* **2004**, *47*, 2945–2964.
(8) Tang, Y.; Dong, Y.; Vennerstrom, J. L. Synthetic peroxides as antimalarials. *Med. Res. Rev.* **2004**, *24*, 425–448.
(9) Jefford, C. W. Synthetic peroxides as antimalarials. *Curr. Opin. Invest. Drugs (Thomson Sci.)* **2004**, *5*, 866–872.
(10) Haynes, R. K. From artemisinin to new artemisinin antimalarials: Biosynthesis, extraction, old and new derivatives, stereochemistry and medicinal chemistry requirements. *Curr. Top. Med. Chem.* **2006**, *6*, 509–537.
(11) Begue, J.-P.; Bonnet-Delpon, D. Fluoroartemisinins: metabolically more stable antimalarial artemisinin derivatives. *ChemMedChem* **2007**, *2*, 608–624.
(12) Ashley, E. A.; White, N. J. Artemisinin-based combinations. *Curr. Opin. Infect. Dis.* **2005**, *18*, 531–536.
(13) (a) Adjuik, M.; Babiker, A.; Garner, P.; Olliaro, P.; Taylor, W.; White, N. Artesunate combinations for treatment of malaria: meta-analysis. *Lancet* **2004**, *363*, 9–17. (b) Guthmann, J.-P.; Cohuet, S.; Rigutto, C.; Fortes, F.; Saraiva, N.; Kiguli, J.; Kyomuhendo, J.; Francis, M.; Noel, F.; Mulemba, M.; Balkan, S. High efficacy of two artemisinin-based combinations (artesunate + amodiaquine and artemether + lumefantrine) in Caala, Central Angola. *Am. J. Trop. Med. Hyg.* **2006**, *75*, 143–145.
(14) *Guidelines for the Treatment of Malaria*; World Health Organization: Switzerland, 2006.
(15) Myint, H. Y.; Ashley, E. A.; Day, N. P. J.; Nosten, F.; White, N. J. Efficacy and safety of dihydroartemisinin-piperaquine. *Trans. R. Soc. Trop. Med. Hyg.* **2007**, *101*, 858–866.
(16) Posner, G. H.; Paik, I.-H.; Chang, W.; Borstnik, K.; Sinishtaj, S.; Rosenthal, A. S.; Shapiro, T. A. Malaria-infected mice are cured by a single dose of novel artemisinin derivatives. *J. Med. Chem.* **2007**, *50*, 2516–2519.
(17) (a) For a scholarly review of synthesis of cyclic peroxides including 1,2,4-trioxanes, see: Korshin, E. E.; Bachi, M. D. Synthesis of Cyclic Peroxides. In *The Chemistry of Peroxides*; Rappoport, Z., Ed.; John Wiley & Sons Ltd.: Chichester, U.K., 2006; Vol. 2, pp 189–305. (b) Kim, B. J.; Sasaki, T. Recent progress in the synthesis of artemisinin and its derivatives. *Org. Prep. Proced. Int.* **2006**, *38*, 1–80.
(18) Posner, G. H.; Paik, I. H.; Sur, S.; McRiner, A. J.; Borstnik, K.; Xie, S.; Shapiro, T. A. Orally active, antimalarial, anticancer, artemisinin-derived trioxane dimers with high stability and efficacy. *J. Med. Chem.* **2003**, *46*, 1060–1065.
(19) Singh, C.; Kanchan, R.; Sharma, U.; Puri, S. K. New adamantane-based spiro 1,2,4-trioxanes orally effective against rodent and simian malaria. *J. Med. Chem.* **2007**, *50*, 521–527.
(20) Jung, M.; Lee, S.; Ham, J.; Lee, K.; Kim, H.; Kim, S. K. Antitumor activity of novel deoxoartemisinin monomers, dimers, and trimer. *J. Med. Chem.* **2003**, *46*, 987–994.

(21) Franke-Fayard, B.; Trueman, H.; Ramesar, J.; Mendoza, J.; van der Keur, M.; van der Linden, R.; Sinden, R. E.; Waters, A. P.; Janse, C. J. A *Plasmodium berghei* reference line that constitutively expresses GFP at a high level throughout the complete life cycle. *Mol. Biochem. Parasitol.* **2004**, *137*, 23–33.

(22) Vennerstrom, J. L.; Arbe-Barnes, S.; Brun, R.; Charman, S. A.; Chiu, F. C. K.; Chollet, J.; Dong, Y.; Dorn, A.; Hunziker, D.; Matile, H.; McIntosh, K.; Padmanilayam, M.; Santo, T. J.; Scheurer, C.; Scorneaux, B.; Tang, Y.; Urwyler, H.; Wittlin, S.; Charman, W. N. Identification of an antimalarial synthetic trioxolane drug development candidate. *Nature* **2004**, *430*, 900–904.

(23) Terzic, N.; Opsenica, D.; Milic, D.; Tinant, B.; Smith, K. S.; Milhous, W. K.; Solaja, B. A. Deoxycholic acid-derived tetraoxane antimalarials and antiproliferatives. *J. Med. Chem.* **2007**, *50*, 5118–5127.

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