

Design, Synthesis, Derivatization, and Structure–Activity Relationships of Simplified, Tricyclic, 1,2,4-Trioxane Alcohol Analogues of the Antimalarial Artemisinin

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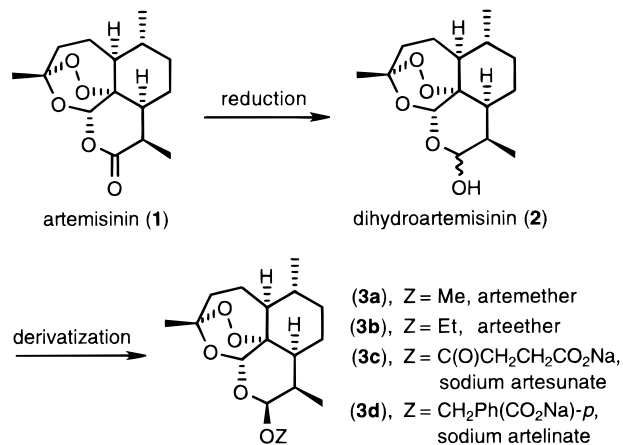
Novel C₄-(hydroxyalkyl)trioxanes **5d** and **5e** were designed and synthesized based on an understanding of the molecular mechanism of action of similar 1,2,4-trioxanes structurally related to the antimalarial natural product artemisinin (**1**). In vitro efficacies of these two new pairs of C₄-diastereomers against chloroquine-sensitive *Plasmodium falciparum* support conclusions about the importance to antimalarial activity of formation of a C₄ radical by a 1,5-hydrogen atom abstraction. Derivatives **6**, **7**, and **21** of C_{4β}-substituted trioxane alcohols **4a**, **5d**, and **5e** were prepared, each in a single-step, high-yielding transformation. Four of these new analogues, **6a–c** and **7**, are potent in vitro antimalarials, having 140 to 50% of the efficacy of the natural trioxane artemisinin (**1**).

Introduction

The chemotherapy of malaria has been aided by the relatively recent discovery and development of natural and synthetic endoperoxides. The parasites that cause this disease, genus *Plasmodium*, are becoming increasingly resistant to traditional therapies such as chloroquine and other alkaloids, sulfonamides (e.g., sulfadoxine), and diaminopyrimidines (e.g., pyrimethamine).^{1,2} The spread of multidrug resistance is particularly troublesome with *Plasmodium falciparum*, which causes cerebral malaria^{3,4} and other very serious consequences and is responsible for nearly all of the annual 1–3 million deaths attributed to malaria.^{5,6} Research into endoperoxide antimalarials began with isolation of the 1,2,4-trioxane artemisinin (qinghaosu, **1**) in 1972 as the active ingredient in a tea of *Artemisia annua* leaves used for thousands of years in China and southeast Asia to treat fever.^{7,8} Subsequent work on semisynthetic derivatives of lactone-reduced dihydroartemisinin (**2**) produced artemether (**3a**) and arteether (**3b**) as oil-soluble analogues and yielded artesunate (**3c**) and artelinate (**3d**) as water-soluble formulations (Scheme 1).^{9,10} Several million doses of these compounds have been given in Asia, Africa, and Central America,¹¹ and they are at various stages of formal clinical development as new malaria therapies.^{12–15}

Artemisinin-type antimalarials seem to act by releasing a cascade of potentially cytotoxic intermediates¹⁶ after activation of the crucial oxygen–oxygen bond by ferrous species¹⁷ found in the parasite and/or in the erythrocytes they infect.^{18,19} These peroxides cause gross morphological changes in malaria parasites,^{20,21} and biochemical evidence points to protein alkylation

Scheme 1



as part of the way in which damage is exacted on the invaders.²² In addition, various studies indicate that artemisinin may covalently bond to the porphyrin portion of heme,^{23,24} and a recent report characterizes the first artemisinin–porphyrin adduct formed during a heme model degradation.²⁵

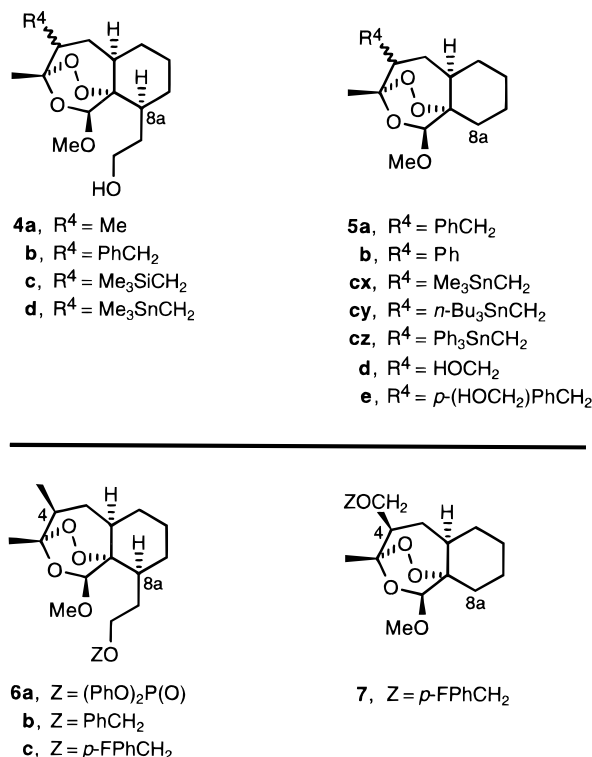
A desire to further probe structure–activity relationships (SAR) and to delve in more detail into the molecular events following initial iron(II) activation of the peroxide bond led many researchers in the past decade to synthesize modified tetracyclic artemisinin structures^{26–31} as well as numerous simplified trioxane analogues.^{32–35} These studies have produced promising therapeutic leads^{36,37} and have been used to develop a **chemical** understanding of how endoperoxide antimalarials kill *Plasmodia*.^{16,38,39} Evidence gathered from these investigations indicates that oxygen- and carbon-centered radicals,^{40–43} one or more high-valent iron oxo species, and reactive electrophilic alkylating species, such as epoxides and dicarbonyl compounds, are formed during iron(II)-induced decomposition of these systems.¹⁶

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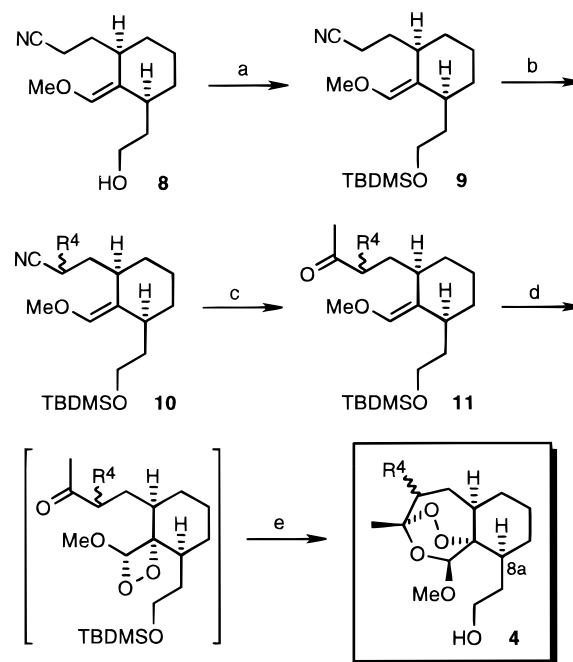
**Figure 1.**

In this paper, we do the following: (1) report full details on a series of C_4 -alkylated trioxanes **4** and **5a–c** (Figure 1) that demonstrated the central role of an intermediate carbon-centered radical in the mechanism of action of this class of compounds; (2) introduce C_4 -(hydroxyalkyl)trioxanes **5d** and **5e** that were designed to combine those structural characteristics of the first series that are associated with high antimalarial activity; (3) show that derivatization of $C_{4\beta}$ diastereomers of two of these trioxane alcohols **4a** and **5d** produces potent antimalarials **6** and **7**; and (4) make SAR generalizations related to the novel analogues reported herein.

Chemistry

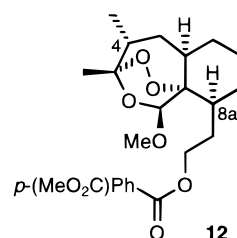
Synthesis of C_4 -substituted, C_{8a} -(hydroxyethyl)trioxanes **4**^{41,44} proceeded from alcohol **8** (Scheme 2), synthesized in three steps from commercial cyclohexanone as described previously by this group.³⁵ Protection of this free alcohol as its silyl ether **9** allowed for smooth alkylation of the conjugate base of the nitrile. The desired functionality at what will become C_4 in the final product was then introduced with the appropriate alkylating agent. Treatment of alkylated nitriles **10** with methyllithium produced ketones **11** as precursors to the target trioxanes. On the basis of the Jefford protocol,⁴⁵ addition of photochemically generated singlet oxygen to the enol ether portion of these ketones produced intermediate dioxetanes that were rearranged in situ to the corresponding trioxanes with a Lewis acid (silyl triflate)^{35,45} and then desilylated to produce the desired C_4 -alkylated trioxane alcohols **4** as mixtures of diastereomers at C_4 . These diastereomers were separated by HPLC. Assignment of stereochemistry was based on a series of rules developed using NMR spectroscopy and relative polarity,⁴⁶ relating to an X-ray

Scheme 2



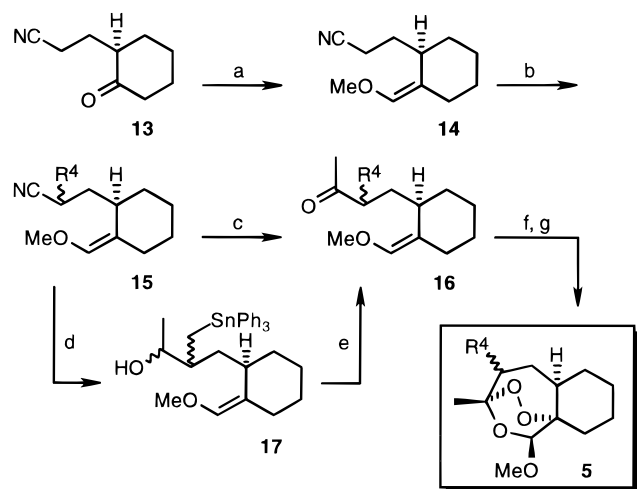
^a Reagents: (a) TBDMSOTf/2,6-lutidine, 91%; (b) 1. LDA, 2. R^4 -X, 59–94%; (c) MeLi, 68–94%; (d) $^1\text{O}_2$; (e) 1. TBDMSOTf, 2. Et_3N , 3. Bu_4NF , 8–21% from **11**.

crystal structure of monomethyl terephthalate ester **12**,⁴⁷ made from $C_{4\alpha}$ -methyl- C_{8a} -(hydroxyethyl)trioxane **4a**.



Construction of most⁴⁸ C_4 -alkylated, C_{8a} -unsubstituted trioxanes **5** began with Wittig olefination of commercially available 2-(2'-cyanoethyl)cyclohexanone (**13**)⁴⁹ to produce known enol ether **14**^{34,45} (Scheme 3). The presence of added lithium chloride during ylide formation increased the ratio of desired *Z*-diastereomer: undesired *E*-diastereomer from 1:1 to 2.5:1 with a good overall yield.^{50,51} α -Deprotonation of the nitrile moiety of enol ether **14** followed by coupling with suitable electrophiles provided diastereomeric mixtures of substituted nitriles **15** that were usually converted directly into trioxane precursor ketones **16** by treatment with methyllithium. However, $C_{4\beta}$ -(triphenylstannyl)methyl nitrile **15cz**, isolated as a single diastereomer, did not react with methyllithium, possibly due to the large steric bulk of the C_4 substitution. To reach the desired ketone system **16cz**, nitrile **15cz** was instead reduced to the corresponding aldehyde that was immediately treated with methylmagnesium bromide to produce secondary alcohols **17**. Swern oxidation^{52,53} produced ketone **16cz** in equal overall yield to methyllithium addition to the other C_4 -stannylmethyl-substituted nitriles **15cx** and **15cy**. With precursor ketones **16** in hand, singlet oxygen-mediated dioxetane formation followed by silyl

Scheme 3



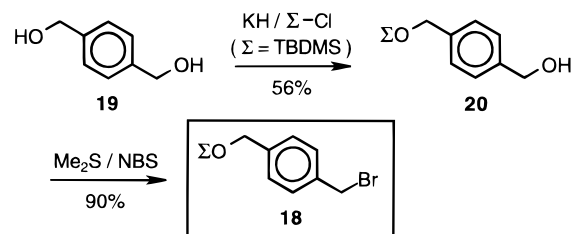
^a Reagents: (a) $\text{Ph}_3\text{PCH}_2\text{OMeCl/LHMDS/LiCl}$, 77%; (b) 1. LDA, 2. $\text{R}^4\text{-X}$, 41% to quantitative; (c) MeLi, 43–98%; (d) 1. DIBAL-H, 2. MeMgBr, 65%; (e) 1. DMSO/(CF_3CO)₂O, 2. Et₃N, 89%; (f) 1. ¹O₂, 2. TBDMSOTf, 3. Et₃N, 10–74%; (g) for **5d** and **5e**, *n*-Bu₄NF, 61–66%.

triflate-induced rearrangement provided trioxanes **5a–c** directly and produced trioxane silyl ethers that were desilylated without isolation to give trioxane alcohols **5d** and **5e**. In most cases, ketones **16** were transformed into trioxanes without prior separation of diastereomers, and the resulting mixtures of diastereomeric trioxanes were then easily separated by HPLC. For C₄-stannylmethyl ketones **16c**, however, diastereomers were separated **prior** to singlet oxygenation, and trioxanes **5c** were thus formed as single diastereomers. The stereochemistries of these analogues **5** were assigned as with trioxanes **4**, according to the same spectroscopy- and polarity-based rules,⁴⁶ with a crystal structure of C_{4α}-phenyltrioxane **5b** as confirmation.^{41,48}

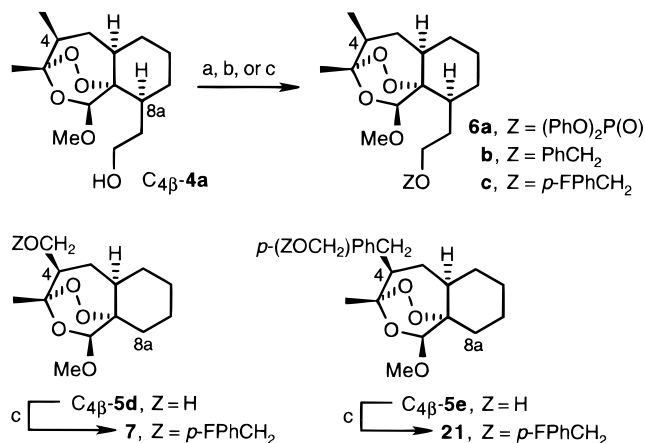
Synthesis of C₄-(hydroxyalkyl)trioxanes **5d**⁵⁴ and **5e** required alkylation of the nitrile anion of enol ether **14** by the appropriate masked hydroxyalkyl species and protection of the newly introduced hydroxyl group for the balance of the synthesis (Scheme 3). En route to C₄-(hydroxymethyl)trioxanes **5d**, addition of gaseous formaldehyde (cracked at 160 °C in line with the reaction)⁵⁵ produced diastereomeric C₄-hydroxymethyl nitriles that were silylated to give C₄-(silyloxy)methyl nitriles **15d**. The hydroxymethylation reaction was sensitive to the temperature profile after addition of formaldehyde, with a 2 h warming from –78 °C to room temperature giving double the yield over all other conditions evaluated. Toward C₄-(*p*-(hydroxymethyl)-benzyl)trioxanes **5e**, substituted nitriles **15e** were formed with protection already in place using *p*-(silyloxy)-methylbenzyl bromide **18**. This alkylating agent was made by monoprotection (monosilylation)⁵⁶ of 1,4-bis-(hydroxymethyl)benzene (**19**) followed by conversion of the remaining free benzyl alcohol into its benzyl bromide^{57,58} (Scheme 4). C₄-(Silyloxy)alkyl nitriles **15d** and **15e** were then carried forward in protected form according to the Scheme 3, with a final fluoride ion-induced desilylation to afford desired trioxane alcohols **5d** and **5e**.

Several of the trioxane alcohols discussed in this paper were derivatized (Scheme 5). C_{4β}-Methyl-C_{8α}-

Scheme 4



Scheme 5



^a Reagents: (a) $(\text{PhO})_2\text{POCl}/\text{Et}_3\text{N}/\text{DMAP}$, 86%; (b) KHMDS/ PhCH_2Br , 81%; (c) KHMDS or NaH/ $p\text{-FPhCH}_2\text{Br}$, 72–91%.

(hydroxyethyl)trioxane **4a** was transformed into its diphenyl phosphate ester **6a**, benzyl ether **6b**, and *p*-fluorobenzyl ether **6c**. Phosphate ester **6a** was made by reaction with the corresponding chlorophosphate. Ethers **6b** and **6c** were prepared by Williamson coupling⁵⁹ with the appropriate benzyl bromides. Both C_{4β}-(hydroxyalkyl)trioxanes **5d** and **5e** were derivatized as their *p*-fluorobenzyl ethers **7** and **21**, respectively, in the same fashion.

SAR Results and Discussion

Chemical degradation studies on artemisinin and on a number of first generation analogues have permitted development of a unified scheme for their mechanism of action¹⁶ (Scheme 6). This mechanistic view considers iron(II) association with either oxygen-1 or -2 of the peroxide bond¹⁷ of simplified trioxane **A**. If iron were to remain with oxygen-1, the resulting oxy radical **B** could collapse to a carbonyl followed either (i) by homolytic cleavage of the C₃–C₄ bond and ring closure to form ring-contracted product **C** or (ii) by fragmentation and loss of methyl formate to form diketone **D**. If iron were associated with oxygen-2, the resulting oxy radical **E** could either (iii) abstract the α-face hydrogen atom from C₄ (a 1,5-shift) to form carbon radical **F**, which can rearrange to epoxide **G** and then ultimately to hydroxylated product **H**, or (iv) collapse to carbonyl initiating loss of methyl formate to form diketone **D**. The rearrangement of carbon radical **F** to epoxide **G** can occur either directly or via β-scission of a high-valent iron oxo species followed by a rebound epoxidation process. We have previously provided evidence, through reporter reactions indicative of intermediate high-valent iron oxo species, that the β-scission pathway is active in chemical degradations both of artemisinin⁶⁰ and of related trioxane analogues.⁴⁴

Scheme 6

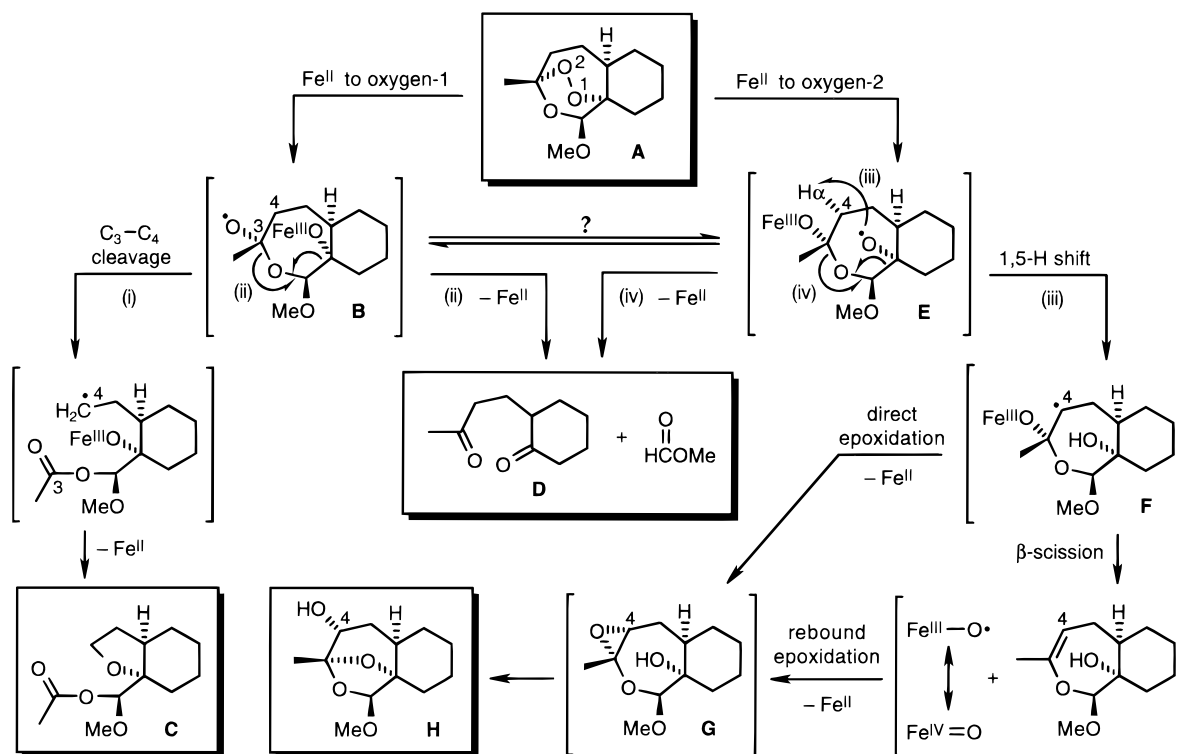


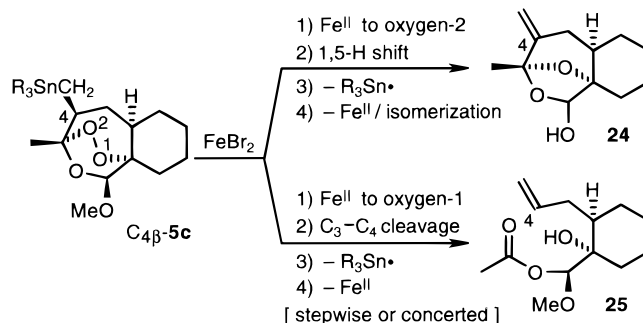
Table 1.^a In Vitro Antimalarial Activities of C₄-Substituted Trioxanes against Chloroquine-Sensitive *P. falciparum* (NF54)⁶⁴

trioxane	R ⁴	IC ₅₀ (nM)	
		C _{4β}	C _{4α}
4a	Me	7.7	1300
4b	PhCH ₂	8.3	1700
4c	Me ₃ SiCH ₂	240	>2500
4d	Me ₃ SnCH ₂	>2500	
22	H		120
5a	PhCH ₂	310	>2500
5b	Ph	2000	>2500
5cx	Me ₃ SnCH ₂	>2500	
5cy	<i>n</i> -Bu ₃ SnCH ₂	>2500	
5cz	Ph ₃ SnCH ₂	>2500	
5d	HOCH ₂	230	>2500
5e	<i>p</i> -(HOCH ₂)PhCH ₂	600	>2500
23	H	960	
artemisinin (1)			9.9

^a Antimalarial activity was determined by the method of Desjardins,⁶⁵ as modified by Milhous,⁶⁶ with details as reported previously.⁶⁷ The standard deviation for each set of quadruplicates was an average of 8% (≤31%) of the mean. *R*² values for the fitted curves were ≥0.992.

C₄-Alkylated trioxanes **4** and **5a–c** (Table 1) demonstrated the importance to antimalarial activity of the 1,5-hydrogen atom abstraction pathway and helped identify restrictions on intermediate carbon-centered radicals such as **F**.^{41,47} Indeed, substitution at C₄ dramatically modulates the in vitro antimalarial activity

Scheme 7



of the analogues. Considering the simple alkyl groups methyl and benzyl in trioxanes **4a**, **4b**, and **5a**, C_{4β} substitution (encourages formation of the C₄ radical) increases antimalarial activity over C₄-unsubstituted trioxanes **22** and **23**, whereas C_{4α} substitution (prevents formation of the C₄ radical) decreases efficacy relative to these parent systems. In contrast, with analogues whose C_{4β} substitution stabilizes the resulting tertiary radical **more** than simple alkyl,^{61,62} as in C₄-((trimethylsilyl)methyl)trioxanes **4c** and C₄-phenyltrioxanes **5b**, antimalarial potency is actually **lowered** compared to that of the C₄-unsubstituted systems.

C_{4β}-(Stannylmethyl)trioxanes **4d** and **5c** were designed to **intercept** a C₄ radical like **F** by elimination of R₃Sn•,⁶³ preventing β-scission of a high-valent iron oxo species and thereby interrupting this degradation pathway.⁶⁰ Reaction of iron(II) with all three C_{4β}-(stannylmethyl)-C_{8a}-unsubstituted-trioxanes **5c** in fact produced, as one of two major products, the expected exocyclic olefin-containing system **24** (Scheme 7). Interestingly, C_{4β}-(stannylmethyl)trioxanes **4d** and **5c** are inactive (Table 1), despite their structural similarity to

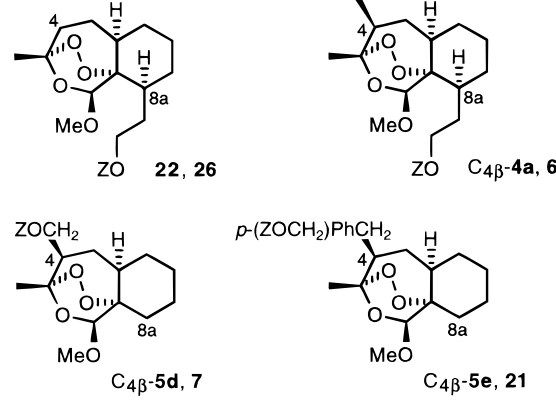
other active analogues (e.g. C_{4β}-(silylmethyl)trioxane **4c**), indicating that intermediates along the route from carbon radical **F** to hydroxylated product **H** are significant in conveying antimalarial efficacy.

An additional relationship between structure and activity stands out from this original series of simplified trioxanes. Comparison of the antimalarial efficacies of various C₄-substituted and -unsubstituted systems with and without a C_{8a}-hydroxyethyl moiety (e.g., **4b** versus **5a**, and **22** versus **23**) reveals that those with the hydroxyalkyl group present are more active than those without. Unfortunately, the synthesis of these systems is longer, especially for C₄-substituted trioxanes **4** since attachment of the C_{8a} functionality is a separate step from C₄ alkylation^{41,47} (Scheme 2). C₄-(Hydroxyalkyl)-trioxanes **5d** and **5e** were designed to incorporate in **one chemical step** favorable C₄ substitution and the presence of a hydroxyalkyl moiety. In vitro antimalarial testing of C₄-(hydroxymethyl)trioxanes **5d** and C₄-(*p*-(hydroxymethyl)benzyl)trioxanes **5e** revealed two structure–activity generalizations (Table 1). First, these new systems further bolster conclusions that a C₄ radical like **F** is important for antimalarial activity. Noting that these trioxanes contain simple alkyl groups at C₄ like trioxanes **4a**, **4b**, and **5a**, (1) C_{4β}-substituted diastereomers (that encourage a 1,5-hydrogen atom transfer) are more active than their C_{4α}-substituted analogues (that block this shift), and (2) C_{4β} diastereomers of these trioxanes are more active than the unsubstituted parent trioxane **22** while C_{4α} systems are less active. The second structure–activity relationship is that C₄-hydroxyalkyl substitution is less effective than at C_{8a} in enhancing antimalarial activity. While C_{4β}-substituted C_{8a}-(hydroxyethyl)trioxanes **4a** and **4b** are potent antimalarials, C_{4β}-(hydroxyalkyl)trioxanes **5d** and **5e** are not.

In general, derivatives of C₄-unsubstituted trioxane alcohol **22** are substantially more active than the free alcohol. Indeed, diphenyl phosphate ester **26a**, benzyl ether **26b**, and *p*-fluorobenzyl ether **26c** are potent in vitro antimalarials,³⁵ having 70% to 30% the efficacy of artemisinin (Table 2). Dramatically, phosphate ester **26a** and benzyl ether **26b** are as efficacious as arteether (**3b**) in vivo against chloroquine-resistant *P. falciparum* in *Aotus* monkeys.³⁷ In addition, *p*-fluorobenzyl ether **26c** is gametocytocidal in vitro with a potency an order of magnitude higher than artemisinin.⁶⁸

All of the new derivatives reported in Table 2, with the exception of ether **21** and of alcohols C_{4β}-**5d** and C_{4β}-**5e**, are potent antimalarials, with in vitro efficacies from 140 to 50% of artemisinin. In addition, *p*-fluorobenzyl ether **6c** has comparable activity to artemisinin in killing gametocytes⁶⁹ and thus, as with ether **26c**, is a potential therapy for interrupting the transmission of malaria from humans back to mosquitoes.⁷⁰ In examining structure–activity relationships based on these derivatives, it is apparent that for C_{4β}-methyl-C_{8a}-(hydroxyethyl)trioxane **4a** derivatization does not significantly increase its efficacy as it did with C₄-unsubstituted trioxane alcohol **22**. On the other hand, with C_{4β}-(hydroxyalkyl)trioxanes **5d** and **5e**, antimalarial activity of *p*-fluorobenzyl ethers **7** and **21** was increased. This jump in potency was more dramatic with ether **7**, with 12 times higher activity than its

Table 2.^a In Vitro Antimalarial Activities of Derivatives of Trioxane Alcohols against Chloroquine-Sensitive *P. falciparum* (NF54)⁶⁴



trioxane	Z	IC ₅₀ (nM)
26a	(PhO) ₂ P(O)	14
26b	PhCH ₂	25
26c	<i>p</i> -FPhCH ₂	31
22	H	120
6a	(PhO) ₂ P(O)	6.9
6b	PhCH ₂	11
6c	<i>p</i> -FPhCH ₂	13
C _{4β} - 4a	H	7.7
7	<i>p</i> -FPhCH ₂	19
C _{4β} - 5d	H	230
21	<i>p</i> -FPhCH ₂	240
C _{4β} - 5e	H	600
artemisinin (1)		9.9

^a Antimalarial activity was determined by the method of Desjardins,⁶⁵ as modified by Milhous,⁶⁶ with details as reported previously.⁶⁷ The standard deviation for each set of quadruplicates was an average of 8% (≤31%) of the mean. *R*² values for the fitted curves were ≥0.991.

parent alcohol **5d** and with one-half the efficacy of artemisinin.

Conclusions

On the basis of in vitro antimalarial activities of our original C₄-alkylated trioxanes **4** and **5a–c**, we have designed and synthesized C₄-(hydroxyalkyl)trioxanes **5d** and **5e**, incorporating those structural features from the first series most beneficial to antimalarial efficacy. The active C_{4β}-diastereomers of these systems are available in six and five chemical steps, respectively, in 13% and 12% overall yields. These new trioxane alcohols provide additional support for the importance to antimalarial activity of a C₄ radical formed by 1,5-hydrogen atom abstraction (Scheme 6, oxygen-2 pathway). Derivatives of C_{4β}-methyl-C_{8a}-(hydroxyethyl)trioxane **4a**, itself having 130% the potency of artemisinin, are highly efficacious antimalarials. While C_{4β}-(hydroxymethyl)- and C_{4β}-(*p*-(hydroxymethyl)benzyl)trioxanes **5d** and **5e** show only modest activity, one derivative, *p*-fluorobenzyl ether **7**, is quite potent and available in fewer chemical transformations than derivatives of C_{4β}-alkylated C_{8a}-(hydroxyalkyl)trioxanes. These qualitative SAR generalizations may aid in subsequent design of additional endoperoxide antimalarials as chemotherapeutic agents to combat multidrug-resistant malaria.

Experimental Section

General. The following applies unless otherwise noted: Reactions were run in flame-dried round-bottomed flasks under an atmosphere of ultrahigh purity (UHP) argon. Di-

ethyl ether (ether) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl prior to use. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride prior to use. All other compounds were purchased from Aldrich Chemical Co. and used without further purification. Analytical thin-layer chromatography (TLC) was conducted with silica gel 60 F₂₅₄ plates (250 μm thickness, Merck). Column chromatography was performed using short path silica gel (particle size <230 mesh), flash silica gel (particle size 400–230 mesh), or Florisil (200 mesh). Yields are not optimized. Purity of products was judged to be >95% based on their chromatographic homogeneity. High-performance liquid chromatography (HPLC) was carried out with a Rainin HPLX system equipped with two 25 mL/min preparative pump heads using Rainin Dynamax 10 mm \times 250 mm (semipreparative) columns packed with 60 Å silica gel (8 μm pore size), either as bare silica or as C-18-bonded silica. Melting points were measured using a Mel-Temp metal-block apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained either on a Varian XL-400 spectrometer, operating at 400 MHz for ^1H and 100 MHz for ^{13}C or on a Varian XL-500 spectrometer, operating at 500 MHz for ^1H and 125 MHz for ^{13}C . Chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrometer. Resonances are reported in wavenumbers (cm^{-1}). Low- and high-resolution mass spectra (LRMS and HRMS) were obtained with electronic or chemical ionization (EI or CI) either (1) at Johns Hopkins University on a VG Instruments 70-S spectrometer run at 70 eV for EI and run with ammonia (NH_3) as a carrier gas for CI or (2) at the University of Illinois at Champaign–Urbana on a Finnigan-MAT CH5, a Finnigan-MAT 731, or a VG Instruments 70-VSE spectrometer run at 70 eV for EI and run with methane (CH_4) for CI. Combustion analyses were conducted by Atlantic Microlab (Norcross, GA).

General Procedure 1: Formation of Lithium Diisopropylamide (LDA). To a -78°C solution of diisopropylamine (1.2 equiv based on 1.0 equiv of substrate) in THF (volume needed to make the final concentration of LDA 0.25–0.50 M) was added via syringe recently titrated *n*-butyllithium (1.1 equiv, originally 1.6 M in hexanes). This mixture was stirred at -78°C for 5 min and then warmed to room temperature and stirred for 20 min.

General Procedure 2: Trioxane Formation by Singlet Oxygenation. A sulfonation (three-necked) flask was fitted with a gas inlet line, an outlet line with stopcock, and a septum. To this flask was added solid methylene blue (ca. 5 mg) followed by a solution of the starting ketone (1.0 equiv) in CH_2Cl_2 (0.01 M). The resulting solution was cooled to -78°C while UHP oxygen passed through a drying column was bubbled (ca. 2–3 mL/s) through the solution. The reaction mixture was then irradiated with UV light (medium-pressure Hg lamp) with continuous O_2 bubbling until TLC analysis showed >95% consumption of starting material (typically 1–2 h). After irradiation, an argon source was introduced through the septum, the outlet stopcock was closed, and the gas inlet line was replaced with a stopper. To this reaction mixture, still at -78°C , was then added by cannula a -78°C solution of TBDMSOTf (1.1 equiv) in CH_2Cl_2 (0.50 M). The resulting solution was stirred for approximately 8 h at -78°C . At that time, the reaction was quenched by addition via syringe over 2 min of Et_3N (neat, 3.3 equiv). The mixture was allowed to warm to at least -20°C slowly over at least 2 h and was then concentrated under reduced pressure.

General Procedure 3: Desilylation by Fluoride Ion. To a solution of starting silyl ether (1.0 equiv) in THF (0.33 M) at 0°C was added a 0°C solution of *n*-Bu₄NF (monohydrate, 2–3 equiv) in THF (0.67 M). The resulting solution was stirred at 0°C until the starting material was consumed (generally at least 1 h). The reaction was quenched with H_2O and then diluted with appropriate volumes of ether and H_2O . The organic phase was separated, and the aqueous phase was

extracted with appropriate volumes of ether. The organic portions were combined, washed with saturated aqueous NaCl, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure.

General Procedure 4: Iron(II)-Induced Trioxane Degradation. To a stirred suspension of FeBr_2 (2.0 equiv) in THF (0.5 mL) was added dropwise a solution of trioxane (1.0 equiv) in THF (0.5 mL). The mixture was stirred for 10–30 min and then diluted with water (1 mL) and Et_2O (10 mL). The ethereal phase was washed with water (2 mL \times 3), dried over MgSO_4 , filtered, and concentrated in vacuo to give a crude product.

C_{8a}-(Silyloxy)ethyl Nitrile 9. To a mixture of TBDMSOTf (3.50 mL, 15.2 mmol) and 2,6-lutidine (2.35 mL, 20.2 mmol) in CH_2Cl_2 (10 mL) at 0°C was added via cannula a solution of alcohol **8**³⁵ (2.13 g, 9.54 mmol) in CH_2Cl_2 (10 mL). This reaction was allowed to warm to room temperature and was stirred for 3 h. The resulting mixture was cooled to 0°C and was quenched with water (20 mL) and diluted with ether (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether (20 mL \times 2). The combined organic portions were washed with brine (40 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (short path, 2% EtOAc/hexanes) to afford the desired product **9** (2.93 g, 8.68 mmol, 91%) as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 5.87 (s, 1 H), 3.58 (dt, J = 13.2, 3.6 Hz, 2 H), 3.52 (s, 3 H), 2.80 (m, 1 H), 2.31 (m, 2 H), 2.22 (m, 1 H), 1.88 (m, 1 H), 1.75 (m, 1 H), 1.70–1.48 (m, 6 H), 1.42 (m, 2 H), 0.90 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.3, 120.6, 118.3, 61.5, 59.3, 38.3, 33.8, 32.9, 31.7, 31.3, 30.8, 30.2, 26.0, 18.0, 15.7, -5.3 ; IR (CHCl_3) 2246, 1661 cm^{-1} ; LRMS (EI, rel intensity) 337 (M^+ , 1), 322 ($\text{M} - \text{CH}_3^+$, 4), 280 (100), 248 (20), 174 (24), 151 (41), 123 (21), 89 (75), 73 (32); HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{28}\text{NSiO}_2$ ($\text{M} - t\text{-Bu}^+$) 294.1889, found 294.1889.

C₄-Methyl C_{8a}-(Silyloxy)ethyl Nitriles 10a. To a freshly prepared solution of LDA (9.55 mmol) in THF/hexanes (45 mL/6 mL) at -78°C was added a precooled solution of nitrile **9** (2.93 g, 8.68 mmol) in THF (7 mL) via cannula. This mixture was warmed to room temperature, stirred for 10 min, and cooled back to -78°C . The resulting solution was treated with methyl iodide (0.165 mL, 2.65 mmol) via syringe. This reaction was stirred at -78°C for 30 min, allowed to slowly warm to room temperature over 8 h, quenched with water (30 mL), and diluted with ether (30 mL). The organic layer was separated, and the aqueous layer was extracted with ether (30 mL \times 2). The combined organic portions were washed with brine (60 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (short path, 10% EtOAc/hexanes) to afford the desired product **10a** (2.88 g, 8.19 mmol, 94%), a 1:1 mixture of diastereomers, as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 5.85 (s, 2 H), 3.55 (m, 4 H), 3.54 (s, 3 H), 3.52 (s, 3 H), 2.90 (m, 1 H), 2.56 (m, 1 H), 2.40 (m, 1 H), 1.95 (m, 1 H), 1.72–1.20 (m, 22 H), 1.34 (d, J = 6.8 Hz, 3 H), 1.29 (d, J = 7.2 Hz, 3 H), 0.902 (s, 9 H), 0.899 (s, 9 H), 0.06 (s, 12 H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.2, 143.0, 124.0, 123.8, 119.0, 118.9, 61.6, 61.4, 59.3 (2), 40.0, 38.9, 38.1, 38.0, 34.1, 33.8, 32.2, 32.1, 31.9, 31.8, 31.1, 30.7, 25.9 (2), 24.3, 23.4, 18.7, 18.0, 17.7, -5.3 (2); IR (CHCl_3) 2238, 1661 cm^{-1} ; LRMS (CI, NH_3 , rel intensity) 369 ($\text{M} + \text{NH}_4^+$, 1), 352 ($\text{M} + \text{H}^+$, 100), 294 (11); HRMS (CI, NH_3) m/z calcd for $\text{C}_{18}\text{H}_{32}\text{NSiO}_2$ ($\text{M} - \text{CH}_3^+$) 322.2202, found 322.2202.

C₄-Methyl C_{8a}-(Silyloxy)ethyl Ketones 11a. To a solution of C₄-methyl nitriles **10a** (1.53 g, 4.36 mmol) in ether (20 mL) at -78°C was added via syringe MeLi (1.5 M in ether, 9.30 mL, 14.0 mmol). After being stirred for 1 h at -78°C , the reaction was slowly warmed to room temperature over 2 h. The mixture was cooled back to -78°C and quenched with water (20 mL) and diluted with ether (50 mL). The organic phase was separated, and the aqueous phase was extracted with ether (30 mL \times 2). The organic portions were combined and washed with brine (40 mL), dried over anhydrous MgSO_4 ,

filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (short path, 10% EtOAc/hexanes) to afford the desired product **11a** (1.41 g, 3.83 mmol, 88%), a 1:1 mixture of diastereomers, as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 5.82 (s, 1 H), 5.81 (s, 1 H), 3.59 (m, 4 H), 3.51 (s, 3 H), 3.48 (s, 3 H), 2.82 (m, 1 H), 2.74 (m, 1 H), 2.55 (m, 1 H), 2.46 (m, 1 H), 2.20 (m, 2 H), 2.14 (s, 3 H), 2.13 (s, 3 H), 1.94–1.80 (m, 2 H), 1.69–1.26 (m, 18 H), 1.13 (d, J = 6.8 Hz, 3 H) 1.06 (d, J = 7.2 Hz, 3 H) 0.91 (s, 9 H), 0.90 (s, 9 H), 0.06 (s, 6 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 213.6, 212.9, 142.7, 142.5, 120.1, 120.0, 61.7, 61.6, 59.1, 59.0, 45.8, 45.1, 38.3, 38.2, 37.7, 37.1, 33.9, 33.8, 32.0, 31.9, 31.5, 31.4, 30.6, 29.0, 28.8, 28.5, 26.0 (2), 17.7, 17.6, 17.5, 16.2, –5.3 (2); IR (CHCl_3) 1714, 1661 cm^{-1} ; LRMS (CI, NH_3 , rel intensity) 386 ($\text{M} + \text{NH}_4^+$, 3), 369 ($\text{M} + \text{H}^+$, 100), 351 (10), 334 (19); HRMS (CI, NH_3) m/z calcd for $\text{C}_{21}\text{H}_{41}\text{NSiO}_3$ ($\text{M} + \text{NH}_4^+$) 369.2825, found 369.2831.

C₄-Methyl-C_{8a}-(hydroxyethyl)trioxanes C_{4a}-4a and C_{4 β} -4a. C₄-Methyl ketones **11a** (790 mg, 2.14 mmol) were treated according to general procedure 2 (70 mL of CH_2Cl_2 , 3.0 equiv of Et_3N). Purification of the crude material by column chromatography (Florisil, 2% EtOAc/hexanes) afforded the corresponding trioxane silyl ethers (260 mg, 0.649 mmol, 30%) as a 1:1 mixture of diastereomers. This material was immediately treated according to general procedure 3. The crude product was purified by column chromatography (Florisil, 10% EtOAc/hexanes) to give the desired C₄-methyl-C_{8a}-(hydroxyethyl)trioxanes **4a** (132 mg, 0.461 mmol, 71%), a 1:1 mixture of diastereomers, as a colorless oil. These diastereomers were separated by HPLC (silica, 40% EtOAc/hexanes, 3.0 mL/min, 254 nm) to give C_{4a}-methyltrioxane alcohol **4a** and C_{4 β} -methyltrioxane alcohol **4a**.

C_{4a}-4a: t_R = 11.8 min; ^1H NMR (400 MHz, CDCl_3) δ 5.17 (d, J = 1.2 Hz, 1 H), 3.78 (m, 1 H), 3.66 (m, 1 H), 3.49 (s, 3 H), 2.28 (m, 1 H), 2.06 (m, 1 H), 1.88–1.20 (m, 11 H), 1.37 (s, 3 H), 1.19 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 106.7, 99.6, 85.3, 61.6, 56.6, 45.3, 42.4, 33.9, 31.3, 30.2, 25.3, 24.6, 22.0, 21.9, 14.6.

C_{4 β} -4a: t_R = 12.4 min; ^1H NMR (400 MHz, CDCl_3) δ 5.21 (d, J = 1.2 Hz, 1 H), 3.78 (m, 1 H), 3.66 (m, 1 H), 3.50 (s, 3 H), 2.44 (m, 1 H), 2.06 (m, 1 H), 1.90–1.20 (m, 11 H), 1.30 (s, 3 H), 0.98 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 107.6, 100.1, 84.9, 61.6, 56.8, 47.5, 41.6, 39.9, 37.3, 33.9, 30.9, 30.2, 25.2, 23.2, 19.2.

4a: IR (CHCl_3) 3683, 3395 cm^{-1} ; LRMS (CI, NH_3 , rel intensity) 304 ($\text{M} + \text{NH}_4^+$, 41), 287 ($\text{M} + \text{H}^+$, 1) 272 (17), 237 (49), 209 (53), 137 (100); HRMS (CI, NH_3) m/z calcd for $\text{C}_{15}\text{H}_{30}\text{NO}_5$ ($\text{M} + \text{NH}_4^+$) 304.2124, found 304.2129.

C₄-Benzyl-C_{8a}-(Silyloxy)ethyl Nitriles 10b. To a freshly prepared solution of LDA (4.34 mmol) in THF/hexanes (30 mL/3 mL) at -78°C was added a precooled solution of nitrile **9** (1.33 g, 3.95 mmol) in tetrahydrofuran (5 mL) via cannula. The resulting mixture was warmed to 0°C , stirred for 15 min, and cooled back to -78°C . The solution was treated with benzyl bromide (0.495 mL, 4.19 mmol) via syringe. The reaction was allowed to warm to room temperature over 4 h, quenched with H_2O (30 mL), and diluted with ether (30 mL). The organic phase was separated, and the aqueous portion was extracted with ether (25 mL \times 2). The organic phases were combined, washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. Purification of the crude product by column chromatography (flash gel, 1% EtOAc/hexanes) afforded the desired product **10b** (1.56 g, 3.65 mmol, 92%), a 1:1 mixture of diastereomers, as a colorless oil.

C₄-Benzyl-C_{8a}-(Silyloxy)ethyl Ketones 11b. To a 0°C solution of C₄-substituted nitriles **10b** (1.56 g, 3.65 mmol) in ether (30 mL) was added by syringe MeLi (1.4 M in ether, 7.80 mL, 10.9 mmol). The resulting mixture was warmed to room temperature and stirred for 2 h. The reaction was then cooled to 0°C , quenched with H_2O (20 mL), and diluted with ether (40 mL). The organic layer was separated, and the aqueous layer was extracted with ether (30 mL \times 2). The combined organic layers were washed with brine (30 mL), dried over

anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (flash gel, 2% EtOAc/hexanes) to afford the desired ketones **11b** (1.48 g, 3.33 mmol, 91%), a 1:1 mixture of diastereomers, as a colorless oil.

C₄-Benzyl-C_{8a}-(hydroxyethyl)trioxanes C_{4a}-4b and C_{4 β} -4b. Ketones **11b** (644 mg, 1.46 mmol) were treated according to general procedure 2 (5.0 equiv Et_3N). The crude product was purified by column chromatography (Florisil, 2% EtOAc/hexanes) to afford a 1:1 mixture of the corresponding trioxane silyl ethers (320 mg, 0.671 mmol, 46%). This material was immediately treated according to general procedure 3 to afford the desired C₄-benzyl-C_{8a}-(hydroxyethyl)trioxanes **4b** (113 mg, 0.312 mmol, 46%), a 1:1 mixture of diastereomers, as a colorless oil. These diastereomers were separated by HPLC (silica, 40% EtOAc/hexanes, 3.0 mL/min, 254 nm) to give C_{4a}-benzyltrioxane alcohol **4b** and C_{4 β} -benzyltrioxane alcohol **4b**.

C₄-Silylmethyl-C_{8a}-(Silyloxy)ethyl Nitriles 10c. To a freshly prepared solution of LDA (1.95 mmol) in THF/hexanes (7.0 mL/1.4 mL) at -78°C was added a precooled solution of nitrile **9** (618 mg, 1.83 mmol) in THF (2 mL). The resulting mixture was warmed to room temperature, stirred for 10 min, and then cooled back to -78°C . To this solution was added (trimethylsilyl)methyl bromide (0.270 mL, 1.89 mmol). The reaction was slowly warmed to room temperature over 3 h and stirred for an additional hour before being cooled to -78°C and quenched with H_2O (10 mL). The resulting mixture was diluted with ether (20 mL), the organic layer was separated, and the aqueous layer was extracted with ether (20 mL \times 2). The combined organic portions were washed with brine (30 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (flash gel, 10% EtOAc/hexanes) to afford the desired product **10c** (727 mg, 1.72 mmol, 94%), a 1:1 mixture of diastereomers, as a colorless oil.

C₄-Silylmethyl-C_{8a}-(Silyloxy)ethyl Ketones 11c. To a solution of C₄-silylmethyl nitriles **10c** (933 mg, 2.20 mmol) in ether (8 mL) at -78°C was added via syringe MeLi (1.6 M in ether, 4.2 mL, 6.7 mmol). The reaction was warmed to room temperature, stirred for 2 h, then cooled back to -78°C , and quenched with H_2O . The resulting mixture was warmed to room temperature and diluted with water (10 mL) and with ether (30 mL), the organic layer was separated, and the aqueous layer was extracted with ether (20 mL \times 2). The combined organic portions were washed with brine (40 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (flash gel, 10% EtOAc/hexanes) to afford the desired ketones **11c** (909 mg, 2.06 mmol, 94%), a 1:1 mixture of diastereomers, as a colorless oil.

C₄-(Silylmethyl)-C_{8a}-(hydroxyethyl)trioxanes C_{4a}-4c and C_{4 β} -4c. Ketones **11c** (816 mg, 1.85 mmol) were treated according to general procedure 2 (4 h irradiation, 1.5 equiv of TBDMSOTf). The crude product was purified by column chromatography (Florisil, 5% EtOAc/hexanes) to afford a 1:1 mixture of the corresponding trioxane silyl ethers (520 mg, 1.10 mmol, 59%) that were immediately treated according to general procedure 3. Purification of the crude material by column chromatography (Florisil, 15% EtOAc/hexanes) gave C₄-(silylmethyl)-C_{8a}-(hydroxyethyl)trioxanes **4c** (104 mg, 0.290 mmol, 26%), a 1:1 mixture of diastereomers, as a colorless oil. This mixture was separated by HPLC (silica, 40% EtOAc/hexanes, 3.0 mL/min, 254 nm) to give C_{4a}-(silylmethyl)trioxane alcohol **4c** and C_{4 β} -(silylmethyl)trioxane alcohol **4c**.

C₄-Stannylmethyl-C_{8a}-(Silyloxy)ethyl Nitriles 10d. To a freshly prepared solution of LDA (5.16 mmol) in THF/hexanes (15 mL/3 mL) at -78°C was added dropwise a solution of nitrile **9** (1.45 g, 4.30 mmol) in THF (3 mL). After 15 min of stirring at -78°C , the solution was allowed to warm to 0°C and was then recooled to -78°C . A solution of $\text{Me}_3\text{SnCH}_2\text{I}$ (1.45 g, 4.73 mmol) in THF (3 mL) was then added, the cold bath was removed, and stirring was continued for 1.5 h. The reaction was quenched with saturated NH_4Cl (25 mL) and diluted with Et_2O (100 mL). The phases were separated,

and the ethereal solution was washed with water (20 mL \times 2), dried over MgSO_4 , filtered, and concentrated in vacuo. Column chromatography of the residue (flash gel, 5% Et_2O /hexanes) provided the desired product (1.30 g, 2.53 mmol, 59%), a 1:1 mixture of diastereomers, as a colorless oil.

C_4 -Stannylmethyl $\text{C}_{8\alpha}$ -(Silyloxy)ethyl Ketones **11d.** To a -78°C solution of C_4 -stannylmethyl nitriles **10d** (1.20 g, 2.37 mmol) in Et_2O (15 mL) was added dropwise MeLi (1.4 M in Et_2O , 8.40 mL, 11.8 mmol) over 10 min. The cooling bath was removed, and stirring was continued for 1.5 h before the reaction was quenched with water (10 mL) and diluted with Et_2O (50 mL). The phases were separated, and the ethereal phase was washed with water (10 mL), dried over MgSO_4 , and concentrated in vacuo. Column chromatography (flash gel, 5% Et_2O /hexanes) of the residue provided the desired product **11d** (0.860 g, 1.62 mmol, 68%), a 1:1 mixture of diastereomers, as a colorless oil.

$\text{C}_{4\beta}$ -(Stannylmethyl)- $\text{C}_{8\alpha}$ -(hydroxyethyl)trioxane **4d.** C_4 -Stannylmethyl ketones **11d** (450 mg, 0.850 mmol) were treated according to general procedure 2 (60 mL of CH_2Cl_2 , 3.0 equiv of Et_3N). The residue was purified by column chromatography (flash gel, hexanes \rightarrow 5% Et_2O /hexanes) to provide the desired trioxane silyl ethers (132 mg, 0.234 mmol, 28%). This material was immediately treated according to general procedure 3. Column chromatography of the crude product (flash gel, 25% \rightarrow 75% Et_2O /hexanes) gave a 10:1 mixture of $\text{C}_{4\beta}$ -(stannylmethyl)- $\text{C}_{8\alpha}$ -(hydroxyethyl)trioxane **4d** and its $\text{C}_{4\alpha}$ -stannylmethyl epimer (32 mg total mass, 0.071 mmol, 30%) as an oil. Purification of the major diastereomer by HPLC (silica, 35% EtOAc /hexanes, 3 mL/min, 254 nm) provided $\text{C}_{4\beta}$ -(stannylmethyl)trioxane alcohol **4d**: $t_R = 12.3$ min.

$\text{C}_{4\alpha}$ -Methyltrioxane Monomethyl Terephthalate Ester **12.** Monomethyl terephthalate (17 mg, 0.096 mmol), 4-(*N,N*-dimethylamino)pyridine (DMAP, 18.8 mg, 0.154 mmol), dicyclohexylcarbodiimide (23.8 mg, 0.116 mmol), and CH_2Cl_2 (2 mL) were mixed at 0°C , warmed to room temperature, stirred for 30 min, and cooled back to 0°C . To this mixture was added via cannula a solution of $\text{C}_{4\alpha}$ -methyl- $\text{C}_{8\alpha}$ -(hydroxyethyl)trioxane **4a** (11 mg, 0.038 mmol) in CH_2Cl_2 (0.5 mL). After 10 min at 0°C , the reaction was warmed to room temperature and stirred for an additional 30 min. The solvent was then removed under reduced pressure. The resulting residue was purified by column chromatography (Florisil, 5% EtOAc /hexanes) to afford the desired product **12** (13.6 mg, 0.030 mmol, 79%) as a white solid: mp 116.0 – 117.0°C . A crystal of ester **12** suitable for X-ray analysis was obtained by recrystallization from hexane.⁷¹

Enol Ether **14.** A 1.0 L round-bottomed flask was charged with (methoxymethyl)triphenylphosphonium chloride (37.4 g, 109 mmol) and LiCl (3.84 g, 91.0 mmol). The mixture of solids was flame-dried under vacuum just until it was a dry, loose powder. After cooling, the flask was flushed with argon, and THF (450 mL) was added. This slurry was cooled to -78°C , and LHMDS (1.0 M in THF, 200 mL, 200 mmol) was added via cannula. The mixture was stirred at -78°C for 15 min, then warmed to room temperature, and stirred for 2 h. The resulting brick red solution was cooled back to -78°C , and a precooled solution of 2-(2'-cyanoethyl)cyclohexanone (**13**, 13.7 g, 90.6 mmol) in THF (200 mL) was added via cannula. This reaction was stirred at -78°C for 15 min, then warmed to room temperature, and stirred for 8 h, and finally quenched at room temperature with H_2O (10 mL) and then further diluted with H_2O (50 mL) after 10 min of stirring. As much of the organic layer as possible was decanted, and the remaining organic/aqueous mixture was diluted with ether (100 mL). The phases were separated, and the aqueous was washed with ether (100 mL). The organic portions were combined, washed with saturated aqueous NaCl, dried over MgSO_4 , filtered, and concentrated under reduced pressure. ^1H NMR of the crude mixture showed a 2.5:1.0 ratio of *Z*-enol ether to *E*-enol ether. The material was filtered through a plug of flash gel to afford the mixture of enol ethers (12.5 g, 69.7 mmol, 77%) as a yellow oil. Further purification by column chromatography (flash gel, 1% \rightarrow 10% EtOAc /hexanes)

afforded the desired *Z*-enol ether **14** (8.62 g, 48.1 mmol, 53%, less polar) as a pale yellow oil. The spectroscopic data were consistent with those reported previously.^{34,45}

C_4 -Benzyl Nitriles **15a.** To a solution of LDA (3.5 mmol) in THF/hexanes (0.70 mL/2.8 mL) at -78°C was added via cannula a precooled solution of enol ether **14** (567 mg, 3.16 mmol) in THF (29 mL). After 5 min of stirring at -78°C , the reaction mixture was warmed to room temperature and stirred for 20 min. This bright yellow enolate solution was cooled to -78°C , and benzyl bromide (0.39 mL, 3.3 mmol) was added via syringe over 2 min. The blue-green mixture was stirred at -78°C for 1 h, warmed to room temperature over 1 h, and stirred for 2 h. This orange solution was cooled to 0°C and quenched by addition of H_2O (5 mL). The resulting solution was diluted with H_2O (50 mL) and ether (30 mL). The organic phase was separated, and the aqueous phase was extracted with ether (50 mL \times 2). The organic portions were combined, washed with saturated aqueous NaCl, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (short path, 5% \rightarrow 10% EtOAc /hexanes) to give the desired product **15a** (840 mg, 3.1 mmol, 99%), a 1:1 diastereomeric mixture, as a yellow oil.

C_4 -Benzyl Ketones **16a.** To a solution of C_4 -benzyl nitriles **15a** (830 mg, 3.08 mmol) in ether (30 mL) at -78°C was added via syringe MeLi (6.6 mL, 9.2 mmol) over 5 min. The mixture was stirred at -78°C for 30 min then warmed to room temperature and stirred for 6 h. The turbid reaction mixture was cooled to 0°C and quenched by addition of H_2O (5 mL). The resulting solution was diluted with H_2O (50 mL) and ether (30 mL). The organic phase was separated, and the aqueous phase was extracted with ether (50 mL \times 2). The organic portions were combined, washed with saturated aqueous NaCl, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (short path, 5% \rightarrow 10% EtOAc /hexanes) to give the desired product **16a** (736 mg, 2.57 mmol, 84%), a 1:1 diastereomeric mixture, as an orange oil.

C_4 -Benzyltrioxanes $\text{C}_{4\alpha}$ -5a** and $\text{C}_{4\beta}$ -**5a**.** C_4 -Benzyl ketones **16a** (350 mg, 1.22 mmol) were treated according to general procedure 2. The resulting blue-green syrup was crudely purified by column chromatography (florisil, 1% \rightarrow 20% EtOAc /hexanes) to give the desired product **5a** (290 mg, 0.911 mmol, 74%), a 1:1 mixture of diastereomers, as a yellow oil. These trioxane diastereomers were separated by HPLC (silica, 3% EtOAc /hexanes, 3.0 mL/min, 260 nm) to afford $\text{C}_{4\alpha}$ -benzyltrioxane **5a** and $\text{C}_{4\beta}$ -benzyltrioxane **5a** as white solids:

Trioxane $\text{C}_{4\alpha}$ -**5a**: $t_R = 12.9$ min; mp = 81.5 – 82.5°C .

Trioxane $\text{C}_{4\beta}$ -**5a**: $t_R = 15.1$ min; mp = 121.0 – 123.0°C .

C_4 -(Trimethylstannyl)methyl Ketones $\text{C}_{4\beta}$ -16cx** and $\text{C}_{4\alpha}$ -**16cx**.** To a freshly prepared solution of LDA (17.3 mmol) in THF/hexane (45 mL/17 mL) at -78°C was added dropwise a solution of enol ether **14** (3.00 g, 14.5 mmol) in THF (10 mL). After 10 min of stirring at -78°C , the solution was allowed to warm to 0°C and then recooled to -78°C . A solution of $\text{Me}_3\text{SnCH}_2\text{I}$ (4.88 g, 15.9 mmol) in THF (10 mL) was added, and stirring was continued for 2 h. The reaction was quenched with saturated NH_4Cl (25 mL) and diluted with Et_2O (200 mL). The ethereal solution was washed with water (50 mL \times 2), dried over MgSO_4 , filtered, and concentrated in vacuo to provide the desired C_4 -alkylated nitriles (5.57 g, 15.6 mmol, $>100\%$), a 1:1 mixture of diastereomers, which was essentially pure by TLC and was used without further purification.

To a -78°C solution of the above C_4 -alkylated nitriles (5.30 g, 14.9 mmol) in Et_2O (50 mL) was added dropwise MeLi (1.4 M in Et_2O , 49.0 mL, 68.6 mmol) over 10 min. The cooling bath was removed, and stirring was continued for 1.5 h before the reaction was quenched with water (50 mL) and diluted with Et_2O (100 mL). The phases were separated, and the ethereal phase was washed with water (50 mL), dried over MgSO_4 , and concentrated in vacuo. Chromatography (flash gel, hexanes \rightarrow 10% EtOAc /hexanes) of the residue provided $\text{C}_{4\beta}$ -(trimethylstannyl)methyl ketone **16cx** (less polar, 910 mg, 2.44 mmol,

17%) and a 1:4 mixture of $C_{4\beta}$ -**16cx** and $C_{4\alpha}$ -(trimethylstannyl)-methyl ketone **16cx** (1.43 g total mass, 3.83 mmol, 26%).

$C_{4\beta}$ -(Trimethylstannyl)methyltrioxane 5cx. $C_{4\beta}$ -Alkylated ketone **16cx** (490 mg, 1.22 mmol) was treated according to general procedure 2 (50 mL of CH_2Cl_2 , 2.5 equiv of Et_3N). Chromatography of the residue (flash gel, hexanes \rightarrow 5% Et_2O /hexanes) provided the desired trioxane $C_{4\beta}$ -(trimethylstannyl)-methyltrioxane **5cx** (124 mg, 0.306 mmol, 25%) as a white solid: mp 44.0–46.0 °C.

C_4 -(Tributylstannyl)methyl Nitriles 15cy. To a freshly prepared solution of LDA (20.2 mmol) in THF/hexanes (50 mL/13 mL) at $-78^\circ C$ was added dropwise a solution of enol ether **14** (3.50 g, 16.9 mmol) in THF (10 mL). After 15 min of stirring at $-78^\circ C$, the solution was allowed to warm to $0^\circ C$ and then recooled to $-78^\circ C$. A solution of Bu_3SnCH_2I (8.00 g, 18.6 mmol) in THF (10 mL) was added, the cold bath was removed, and stirring was continued for 1.5 h. The reaction was quenched with saturated NH_4Cl (25 mL) and diluted with ether (200 mL). After separation of phases, the ethereal solution was washed with water (50 mL \times 2), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue (flash gel, hexanes \rightarrow 25% Et_2O /hexanes) provided the desired product **15cy** (6.20 g, 12.9 mmol, 72%), a 1:1 mixture of diastereomers, as a colorless oil.

C_4 -(Tributylstannyl)methyl ketones $C_{4\beta}$ -16cy** and $C_{4\alpha}$ -**16cy**.** To a $-78^\circ C$ solution of C_4 -alkylated nitriles **15cy** (5.70 g, 11.2 mmol) in Et_2O (50 mL) was added dropwise MeLi (1.4 M in Et_2O , 39.9 mL, 55.9 mmol) over 10 min. The bath was removed, and stirring was continued for 1.5 h before the reaction was quenched with water (50 mL) and diluted with Et_2O (100 mL). The phases were separated, and the ethereal portion was washed with water (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Column chromatography (flash gel, hexanes \rightarrow 20% $EtOAc$ /hexanes) of the residue provided $C_{4\beta}$ -(tributylstannyl)methyl ketones **16cy** (less polar, 2.90 g, 5.81 mmol, 52%) and $C_{4\alpha}$ -(tributylstannyl)methyl ketones **16cy** (more polar, 2.52 g, 5.05 mmol, 46%) as colorless oils.

$C_{4\alpha}$ -(Tributylstannyl)methyltrioxane $C_{4\alpha}$ -5cy**.** $C_{4\alpha}$ -Alkylated ketone **16cy** (650 mg, 1.30 mmol) was treated according to general procedure 2 (60 mL of CH_2Cl_2 , 3.6 equiv of Et_3N). The material was concentrated and the residue purified by column chromatography (flash gel, hexanes \rightarrow 5% Et_2O /hexanes) provided the desired $C_{4\alpha}$ -(tributylstannyl)-methyltrioxane **5cy** (70 mg, 0.13 mmol, 10%) as a colorless oil.

$C_{4\beta}$ -(Tributylstannyl)methyltrioxane $C_{4\beta}$ -5cy**.** $C_{4\beta}$ -Alkylated ketone **16cy** (730 mg, 1.40 mmol) was treated according to general procedure 2 (60 mL of CH_2Cl_2 , 3.6 equiv of Et_3N). The material was concentrated in vacuo, and the residue purified by column chromatography (flash gel, hexanes \rightarrow 5% Et_2O /hexanes) provided $C_{4\beta}$ -tributylstannylmethyl trioxane **5cy** (349 mg, 0.657 mmol, 45%) as a colorless oil.

$C_{4\beta}$ -(Triphenylstannyl)methyl Nitrile 15cz. To a freshly prepared solution of LDA (17.4 mmol) in THF/hexanes (50 mL/2.5 mL) was added dropwise over 5 min a solution of enol ether **14** (3.00 g, 14.5 mmol) in THF (10 mL). This mixture was stirred at $-78^\circ C$ for 15 min, the cooling bath was removed, and stirring was continued for 15 min. The resulting solution was cooled back to $-78^\circ C$, and a solution of Ph_3SnCH_2I (7.86 g, 15.9 mmol) in THF (10 mL) was added via cannula. The reaction was stirred at $-78^\circ C$ for 3 h, warmed to room temperature, stirred for an additional hour, and quenched with NH_4Cl (25 mL). The mixture was then diluted with ether (200 mL), the phases were separated, and the ethereal solution was washed with saturated aqueous $NaHCO_3$ (50 mL) and water (50 mL \times 2), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue (flash gel, 10% Et_2O /hexanes) provided the desired $C_{4\beta}$ -substituted product **15cz** (3.23 g, 5.96 mmol, 41%): mp = 103.5–105.0 °C.

$C_{4\beta}$ -(Triphenylstannyl)methyl Ketone 16cz. To a $-78^\circ C$ solution of $C_{4\beta}$ -alkylated nitrile **15cz** (2.00 g, 3.50 mmol) in toluene (20 mL) was added dropwise DIBAL-H (1.0 M in hexanes, 3.85 mL, 3.85 mmol). The mixture was stirred at $-78^\circ C$ for 1 h and then allowed to warm to room temperature

over 2 h. The reaction was quenched with MeOH (1.5 mL) followed by water (1.5 mL). Stirring was continued for 20 min over which time a white precipitate formed from the initially gelatinous mixture. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was quickly eluted through a short pad of flash gel (10% Et_2O /hexanes) to provide the desired aldehyde (>90% pure, 1.81 g, 3.32 mmol, 95%) that was used without further purification.

To a $-78^\circ C$ solution of the above $C_{4\beta}$ -substituted aldehydes (1.73 g, 3.17 mmol) in THF (25 mL) was added dropwise MeMgBr (1.4 M in Et_2O , 6.4 mL, 9.0 mmol). The resulting solution was stirred at $-78^\circ C$ for 1 h, allowed to warm to room temperature, and stirred for a further 30 min. The reaction was quenched with water (10 mL) and diluted with ether (50 mL), and the phases were separated. The ethereal phase was washed with saturated NH_4Cl (10 mL \times 2) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography (flash gel, 15% Et_2O /hexanes) provided the desired alcohols **17** (1.20 g, 2.14 mmol, 68%), a 3:1 diastereomeric mixture, as a thick colorless oil.

To a $0^\circ C$ solution of DMSO (0.553 mL, 7.80 mmol) in CH_2Cl_2 (10 mL) was added a solution of trifluoroacetic anhydride (0.826 mL, 5.85 mmol) in CH_2Cl_2 (3 mL) dropwise. The solution was stirred for 15 min. A solution of alcohols **17** (1.15 g, 1.95 mmol) in CH_2Cl_2 (3 mL) was then added dropwise. Stirring was continued for 30 min, and Et_3N (1.90 mL, 13.6 mmol) was added. The solution was allowed to warm to room temperature and stirred further for 20 min. The mixture was diluted with Et_2O (70 mL), washed with water (25 \times 2 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography (flash gel, 10% Et_2O /hexanes) provided the desired $C_{4\beta}$ -alkylated ketone **16cz** (0.970 g, 1.73 mmol, 89%) as a colorless oil.

$C_{4\beta}$ -(Triphenylstannyl)methyltrioxane 5cz. $C_{4\beta}$ -substituted ketone **16cz** (650 mg, 1.16 mmol) was treated according to general procedure 2 to give the desired $C_{4\beta}$ -(triphenylstannyl)methyltrioxane **5cz** (135 mg, 0.228 mmol, 20%) as a colorless oil.

C_4 -(Hydroxymethyl)trioxanes $C_{4\alpha}$ -5d** and $C_{4\beta}$ -**5d**.** We have previously reported preparation and characterization of intermediates en route to C_4 -(hydroxymethyl)trioxanes **5d**.⁵⁴ Conditions for formation and separation of these trioxanes, as well as characterization of $C_{4\beta}$ -(hydroxymethyl)trioxane **5d** itself, were also reported at that time. We include in the Supporting Information the latter information, along with data for the previously unreported $C_{4\alpha}$ -(hydroxymethyl)trioxane **5d**, for convenience.

C_4 -(Silyloxy)methyl ketones **16d** (200 mg, 0.585 mmol) were treated according to general procedure 2. The resulting blue syrup was purified by column chromatography (Florisil, 1% \rightarrow 10% $EtOAc$ /hexanes) to give the corresponding trioxane silyl ethers, a 1:1 mixture of diastereomers (ca. 140 mg, 0.376 mmol, 64%), as a yellow oil. A portion of this material (44 mg, 0.12 mmol) was treated according to general procedure 3. This crude product was purified by column chromatography (Florisil, 1% \rightarrow 20% $EtOAc$ /hexanes) to give the desired trioxane alcohols **5d** (20 mg, 0.078 mmol, 66%), a 1:1 diastereomeric mixture, as a colorless oil. These trioxane alcohols were separated by HPLC (silica, 5% *i*-PrOH/hexanes, 3.0 mL/min, 230 nm) to afford $C_{4\alpha}$ -(hydroxymethyl)trioxane **5d** and $C_{4\beta}$ -(hydroxymethyl)trioxane **5d** as white solids:

Trioxane $C_{4\alpha}$ -**5d**: t_R = 14.1 min; mp = 97.0–99.0 °C.

Trioxane $C_{4\beta}$ -**5d**: t_R = 16.2 min; mp = 101.0–102.0 °C.

p -(Silyloxy)methylbenzyl Alcohol 20 (Beilstein 4863197). Sodium hydride (60% in mineral oil, 1.6 g, 40 mmol) was washed with anhydrous hexanes (5 mL \times 2) and dried in vacuo. This gray powder was suspended in THF (80 mL) at room temperature, and solid 1,4-bis(hydroxymethyl)benzene (5.0 g, 36 mmol) was added in three portions over 3 min. The reaction was stirred for 45 min at which time it was a milky white. To this alkoxide mixture was added TBDMSCl (5.7 g, 38 mmol) as a solid in three portions over 3 min. This addition was highly exothermic. The reaction was stirred for 1 h. At that time, the still turbid mixture was quenched with H_2O (5

mL) and then diluted with H₂O (100 mL) and ether (100 mL). The organic phase was separated, and the aqueous phase was extracted with ether (100 mL × 2). The organic portions were combined, washed with saturated aqueous NaCl, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. This crude product was purified by column chromatography (short path, 1% → 50% EtOAc/hexanes) to give the desired product **20** (5.1 g, 20 mmol, 56%).

***p*-((Silyloxy)methyl)benzyl Bromide 18.** To a solution of *N*-bromosuccinimide (4.2 g, 24 mmol) in CH₂Cl₂ (75 mL) at 0 °C was added via syringe over several minutes dimethyl sulfide (2.1 mL, 29 mmol). The bright yellow turbid mixture was stirred at 0 °C for 10 min and then was cooled to −20 °C. At this temperature, a precooled solution of *p*-((silyloxy)methyl)benzyl alcohol **20** (4.0 g, 16 mmol) in CH₂Cl₂ (8 mL) was added via cannula. The resulting mixture was warmed to 0 °C, kept at this temperature for 15 min, then warmed to room temperature, and stirred for 2 h. At that time, the reaction was quenched with H₂O (5 mL) and then diluted with H₂O (100 mL) and CH₂Cl₂ (50 mL). The organic phase was separated, and the aqueous phase was extracted with CH₂Cl₂ (100 mL). The organic portions were combined, washed with saturated aqueous NaCl, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. This crude product was purified by column chromatography (Florisil, 1% → 5% EtOAc/hexanes) to give the desired product **18** (4.5 g, 14 mmol, 90%) as a colorless oil. It should be noted that benzyl bromide **18** is extremely unstable to unmodified silica, with 95% of the material decomposing upon chromatography on short path silica gel. As indicated above, Florisil was suitable for this purification.

***C*₄-(*p*-((Silyloxy)methyl)benzyl) Nitriles 15e.** To a freshly prepared solution of LDA (3.36 mmol) in THF/hexanes (6.5 mL/2.4 mL) at −78 °C was added via cannula a precooled solution of enol ether **14** (540 mg, 3.01 mmol) in THF (23 mL). After 5 min of stirring at −78 °C, the reaction mixture was warmed to room temperature and stirred for 15 min. This golden brown enolate solution was cooled to −78 °C, and a 1 M THF solution of *p*-((silyloxy)methyl)benzyl bromide **18** at room temperature was added via syringe over 2 min. The mixture was stirred at −78 °C for 1 h, warmed to room temperature over 1 h, and stirred at room temperature for 2 h. The reaction was cooled to 0 °C and quenched by dropwise addition of H₂O (3 mL). The resulting mixture was diluted with H₂O (50 mL) and ether (50 mL). The organic phase was separated, and the aqueous phase was extracted with ether (50 mL × 2). The organic portions were combined, washed with saturated aqueous NaCl, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. This crude product was purified by column chromatography (short path, 1% → 10% EtOAc/hexanes) to give the desired product **15e** (1.09 g, 2.63 mmol, 88%), a 1:1 diastereomeric mixture, as a yellow oil.

***C*₄-(*p*-((Silyloxy)methyl)benzyl) Ketones 16e.** To a solution of *C*₄-substituted nitriles **15e** (1.00 g, 2.42 mmol) in ether (20 mL) at −78 °C was added via syringe MeLi (1.4 M in ether, 5.2 mL, 7.3 mmol) over 5 min. The resulting mixture was stirred at −78 °C for 10 min and then warmed to room temperature and stirred for 3 h. At that time, the reaction was cooled to 0 °C and quenched with dropwise addition of H₂O (1 mL). The resulting mixture was diluted with H₂O (25 mL) and ether (25 mL). The organic phase was separated, and the aqueous phase was extracted with ether (25 mL × 2). The organic portions were combined, washed with saturated aqueous NaCl, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. This crude product was purified by column chromatography (short path, 1% → 20% EtOAc/hexanes) to give the desired product **16e** (700 mg, 1.63 mmol, 68%), a 1:1 diastereomeric mixture, as a yellow oil.

***C*₄-(*p*-(Hydroxymethyl)benzyl)trioxanes C_{4α}-5e and C_{4β}-5e.** *C*₄-Substituted ketones **16e** (440 mg, 1.02 mmol) were treated according to general procedure 2. The resulting blue syrup was purified by column chromatography (Florisil, 1% → 20% EtOAc/hexanes) to give the corresponding trioxane silyl

ethers, a 1:1 mixture of diastereomers (ca. 310 mg, 0.670 mmol, 65%), as a dark yellow oil. This material was combined with that from a second singlet oxygenation/silyl triflate rearrangement (total mass, 440 mg, 0.951 mmol) and was treated according to general procedure 3. This crude product was purified by column chromatography (Florisil, 5% → 50% EtOAc/hexanes) to give the desired products **5e**, a 1:1 diastereomeric mixture (201 mg, 0.580 mmol, 61%), as a colorless oil. These trioxane alcohol diastereomers were separated by HPLC (C-18, 20% H₂O/MeOH, 3.0 mL/min, 254 nm) to afford C_{4α}-(*p*-(hydroxymethyl)benzyl)trioxane **5e** as a white solid and C_{4β}-(*p*-(hydroxymethyl)benzyl)trioxane **5e** as a colorless oil:

Trioxane C_{4α}-**5e**: *t*_R = 20.8 min; mp = 99.5–100.0 °C.

Trioxane C_{4β}-**5e**: *t*_R = 18.9 min.

C_{4β}-Methyltrioxane Phosphate Ester 6a. To a 0 °C solution of redistilled diphenyl chlorophosphate (8 μL, 0.04 mmol) and DMAP (2.6 mg, 0.021 mmol) in CH₂Cl₂ (0.5 mL) was added via syringe Et₃N (6 μL, 0.04 mmol). This mixture was allowed to stir at room temperature for 40 min before a solution of C_{4β}-methyl-C_{8α}-(hydroxyethyl)trioxane **4a** (5.0 mg, 0.017 mmol) in CH₂Cl₂ (0.5 mL) was added via cannula. The reaction was stirred at room temperature for 5 h and then diluted with water (10 mL) and ether (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether (5 mL × 2). The combined organic portions were washed with brine (10 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified column chromatography (Florisil, 20% EtOAc/hexanes) to afford the desired product **6a** (7.8 mg, 0.015 mmol, 86%) as a colorless oil. This material was further purified by HPLC (silica, 20% EtOAc/hexanes, 3.0 mL/min, 254 nm): *t*_R = 20.3 min.

C_{4β}-Methyltrioxane Benzyl Ether 6b. To a 0 °C solution of C_{4β}-methyl-C_{8α}-(hydroxyethyl)trioxane **4a** (76.2 mg, 0.266 mmol) in THF (2 mL) was added via syringe KHMDS (0.50 M in toluene, 2.66 mL, 1.33 mmol). This mixture was stirred for 10 min at 0 °C, and then benzyl bromide (48 μL, 0.040 mmol) was added via syringe. The resulting solution was stirred at 0 °C for 30 min, then warmed to room temperature, and stirred for 2 h. The reaction was cooled back to 0 °C, quenched with water (5 mL), and diluted with ether (5 mL). The organic layer was separated, and the aqueous layer was extracted with ether (10 mL × 2). The combined organic portions were washed with brine (5 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. Column chromatography of the crude material (Florisil, 1% → 4% EtOAc/hexanes) afforded the desired product **6b** (80.9 mg, 0.215 mmol, 81%) as a colorless oil.

C_{4β}-Methyltrioxane *p*-Fluorobenzyl Ether 6c. To a 0 °C solution of C_{4β}-methyl-C_{8α}-(hydroxyethyl)trioxane **4a** (7.1 mg, 0.022 mmol) in THF (1 mL) was added via syringe KHMDS (0.50 M in toluene, 0.30 mL, 0.15 mmol). This mixture was stirred for 10 min at 0 °C, and *p*-fluorobenzyl bromide (8.0 μL, 0.065 mmol) was added via syringe. The resulting solution was stirred at 0 °C for 30 min, then warmed to room temperature, and stirred for 18 h. The reaction was then quenched with water (2 mL) at 0 °C and diluted with ether (2 mL). The organic layer was separated, and the aqueous layer was extracted with ether (5 mL × 2). The combined organic portions were washed with brine (5 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. Column chromatography of the crude material (Florisil, 10% EtOAc/hexanes) afforded the desired product **6c** (7.8 mg, 0.020 mmol, 91%) as a colorless oil. This material was further purified by HPLC (silica, 3% EtOAc/hexanes, 3.0 mL/min, 254 nm): *t*_R = 10.6 min.

C_{4β}-(((*p*-Fluorobenzyl)oxy)methyl)trioxane 7. In a flame-dried 1 dram vial under argon, sodium hydride (60% in mineral oil, 22 mg, 0.55 mmol) was washed with anhydrous hexanes (1 mL × 2) and dried in vacuo. This gray powder was cooled to 0 °C, and a room temperature solution of C_{4β}-(hydroxymethyl)trioxane **5d** (28 mg, 0.11 mmol) in DMF (0.75 mL) was added dropwise via syringe directly onto the solid. Vigorous release of gas occurred immediately. The flask containing the

starting alcohol was washed with DMF (0.30 mL), and this rinse was also added via syringe to the reaction. After 10 min at 0 °C, the mixture was warmed to room temperature and stirred for roughly 45 min, as which time bubbling had ceased. This dark beige turbid solution was cooled to 0 °C, and *p*-fluorobenzyl bromide (68 μ L, 0.55 mmol) was added neat dropwise via syringe. The mixture was stirred at 0 °C for 10 min, then warmed to room temperature, and stirred for 3 h, during which time its color slowly faded. The reaction was then cooled back to 0 °C, quenched with dropwise addition of H₂O (1 mL), and diluted with H₂O (2 mL) and ether (5 mL). The organic phase was separated, and the aqueous phase was extracted with ether (5 mL). The organic portions were combined, washed with saturated aqueous NaCl, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. This crude product was purified by column chromatography (Florisil, 1% \rightarrow 5% EtOAc/hexanes) to give the desired product **7** (29 mg, 0.079 mmol, 72%) as a colorless oil. This material was further purified by HPLC (silica, 5% EtOAc/hexanes, 3.5 mL/min, 254 nm, t_R = 14.4 min) to afford a colorless oil.

C₄₀-(*p*-(Fluorobenzyloxy)methyl)benzyl)trioxane **21.** In a flame-dried 1 dram vial under argon, sodium hydride (14 mg, 60% in mineral oil, 0.35 mmol) was washed with anhydrous hexanes (1 mL \times 2) and dried in vacuo. This gray powder was cooled to 0 °C, and a room temperature solution of C₄₀-(*p*-(hydroxymethyl)benzyl)trioxane **5e** (25 mg, 0.072 mmol) in DMF (0.50 mL) was added dropwise via syringe directly onto the solid. Vigorous release of gas occurred immediately. The flask containing the starting alcohol was washed with DMF (0.25 mL), and this solution was also added via syringe to the reaction. After 10 min at 0 °C, the mixture was warmed to room temperature and stirred for roughly 45 min, at which time bubbling had ceased. This beige turbid solution was cooled to 0 °C, and *p*-fluorobenzyl bromide (43 μ L, 0.35 mmol) was added neat dropwise via syringe. The color of the reaction faded immediately. The mixture was stirred at 0 °C for 10 min, then warmed to room temperature, and stirred for 1 h. The reaction was then cooled back to 0 °C, quenched with dropwise addition of H₂O (1 mL), and diluted with H₂O (2 mL) and ether (5 mL). The organic phase was separated, and the aqueous phase was extracted with ether (5 mL). The organic portions were combined, washed with saturated aqueous NaCl, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. This crude product was purified by column chromatography (Florisil, 1% \rightarrow 10% EtOAc/hexanes) to give the desired product **21** (28 mg, 0.061 mmol, 85%) as a colorless oil. This material was further purified by HPLC (silica, 5% EtOAc/hexanes, 3.0 mL/min, 254 nm, t_R = 22.7 min) to afford a colorless oil.

Degradation of C₄₀-(Trimethylstannyl)methyl)trioxane **5cx.** The aforementioned trioxane (10 mg, 0.023 mmol) was treated according to general procedure 4. ¹H NMR of the crude mixture indicated a 1:5 ratio of exocyclic olefin **24**:acetate **25**. This material was purified by column chromatography (flash gel, 5% \rightarrow 25% Et₂O/hexanes) to afford olefin **24** (0.7 mg, 0.003 mmol, 14%) as a white solid and acetate **25** (4.0 mg, 0.017 mmol, 72%) as an oil.

Exocyclic olefin **24**: mp 138.0–140.0 °C.

Degradation of C₄₀-(Tributylstannyl)methyl)trioxane **5cy.** The aforementioned trioxane (11 mg, 0.020 mmol) was treated according to general procedure 4. ¹H NMR of the mixture indicated a 1:5 ratio of exocyclic olefin **24**:acetate **25**.

Degradation of C₄₀-(Triphenylstannyl)methyl)trioxane **5cy.** The aforementioned trioxane (10 mg, 0.017 mmol) was treated according to general procedure 4. ¹H NMR of the mixture indicated a 1:10 ratio of exocyclic olefin **24**:acetate **25**.

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Supporting Information Available: X-ray crystallographic data for ester **12**, and ¹H and ¹³C NMR, IR, and mass spectral data for all compounds in the text except for those leading to and including trioxanes **4a** (Scheme 2) that are described in the Experimental Section (24 pages). Ordering information is given on any current masthead page.

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