J. Med. Chem. **1998,** *41,* 940−951

Orally Active Antimalarial 3-Substituted Trioxanes: New Synthetic Methodology and Biological Evaluation

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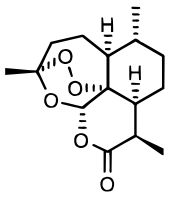
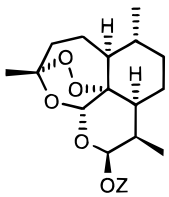
Received October 9, 1997

On the basis of a mechanistic understanding of the mode of action of artemisinin-like antimalarials, a series of structurally simple 3-aryl-1,2,4-trioxanes **5** was designed and was prepared in three to five operations from commercial reactants. The 3-aryl group was attached in each case as a nucleophile. In an electronically complementary fashion, 3-(fluoroalkyl)-trioxanes **6** were prepared via attachment of electrophilic fluoroalkyl esters. Both in vitro and in vivo antimalarial evaluations of these new trioxanes showed 12β-methoxy-3-aryltrioxanes **5g**, **5j**, **5k**, and **5l** to be highly potent, with crystalline fluorobenzyl ether trioxane **5k** especially potent even when administered to rodents orally. As shown by rearrangement of hexamethyl Dewar benzene into hexamethylbenzene, iron-induced degradation of some of these 3-aryltrioxanes **5** involves generation of high-valent iron oxo species that might kill malaria parasites.

Approximately 300−400 million people worldwide now have malaria, and each year 1−3 million, mostly children, die from this infectious disease.[1,2] Complicating chemotherapy treatment of malaria patients is the rapidly spreading multidrug resistance of parasites to standard quinoline-based antimalarial drugs such as chloroquine and mefloquine.[3,4] A new class of nonalkaloidal antimalarial compounds was identified by organic chemists in the 1970s based on ancient Chinese herbal medicine; characteristic of these potent and fast-acting antimalarials is their chemically unusual 1,2,4-trioxane pharmacophore unit.[5−8] Clinically used examples of such trioxanes derived from *Artemisia annua* (qinghao) are natural artemisinin (qinghaosu, **1**) and semisynthetic artemether (**2**) and artesunic acid (**3**) as well as promising artelinic acid (**4**).[5−7] Much structure−activity relationship (SAR) study has been done,[9] leading to an understanding of the fundamental biological[10] and chemical mechanisms[11] of action of such trioxanes.



artemisinin (**1**)



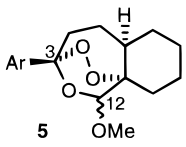
(**2**), Z = Me, artemether

(**3**), Z = C(O)$CH_2CH_2CO_2H$, artesunic acid

(**4**), Z = $CH_2Ph(CO_2H)$-*p*, artelinic acid

Malaria parasites inside human erythrocytes digest hemoglobin as a source of amino acids. In the presence of a trioxane, this process inadvertently causes the parasites' own death.[10,11] This self-destruction of the parasite schizonts in the human erythrocytic stage of their life cycle involves a cascade of chemical reactions triggered by the iron(II)[12,13] liberated during hemoglobin degradation.[11] Iron(II) reduces the peroxide bond in the trioxane antimalarial drug to form sequentially potentially lethal oxygen-centered free radicals, carbon-centered free radicals, high-valent iron oxo species, and reactive epoxides;[13] any one of these reactive intermediates, or a combination of them, may kill the parasite by alkylating or oxidizing critical biomolecules,[14,15] thereby disrupting vital biochemical processes.

On the basis of our understanding at the molecular level of the chemical cascade leading from antimalarial trioxane to these various cytotoxic intermediates,[13] we have designed a series of structurally simple 3-**aryl**trioxanes (**5**). We anticipated that the 3-aryl substituent would facilitate progression through this cascade by



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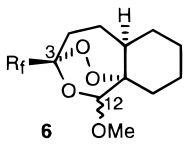
a, Ar = Ph
b, Ar = *p*-PhPh
c, Ar = 1-naphthyl
d, Ar = *p*-ClPh
e, Ar = *p*-MeOPh
f, Ar = 2-furyl
g, Ar = *p*-$HOCH_2$Ph
h, Ar = *p*-$MeOCH_2$Ph
i, Ar = *p*-MeOC(O)OCH_2Ph
j, Ar = *p*-MeC(O)OCH_2Ph
k, Ar = *p*-(*p*′-$FPhCH_2OCH_2$)Ph
l, Ar = *p*-FPh
m, Ar = *p*-F-*o*-MePh
n, Ar = *p*-CF_3Ph



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a, R_f = $CF_3CH_2CH_2$
b, R_f = FCH_2

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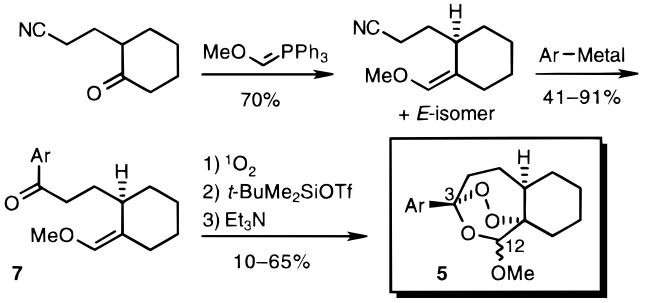
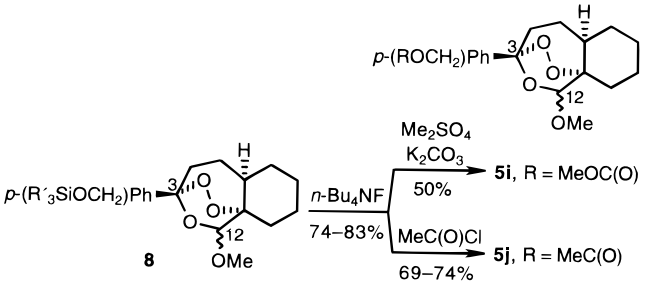
S0022-2623(97)00686-9 CCC: $15.00
Published on Web 02/12/1998

Scheme 1



Scheme 2



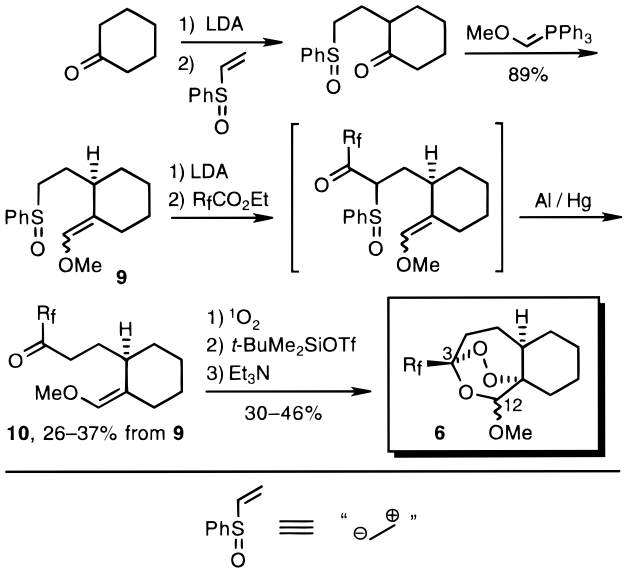
resonance stabilization of adjacent unsaturation and, therefore, would lead to larger amounts of cytotoxic intermediates and thus to more potent antimalarial trioxanes. The first 3-aryltrioxane reported was prepared in the Jefford group.[16] Also, based on the often pharmacologically beneficial effect of a drug having a fluorine atom in place of a hydrogen atom[17] and on the established importance of 3-alkyl substituents for high antimalarial activity,[18,19] we have prepared 3-(fluoroaryl)trioxanes **5k**−**5n** and 3-(**fluoroalkyl**)trioxanes **6**.[20] Preparation of 3-(fluoroalkyl)trioxanes **6** illustrates new synthetic methodology that significantly broadens the scope of accessible fluorinated targets by allowing not only fluorinated **nucleophiles** to be used (see Scheme 1) but now also more readily available fluorinated **electrophiles** (see Scheme 3).

Chemistry

Three-step syntheses of most of the 3-aryltrioxanes **5** are summarized in Scheme 1. For benzylic alcohol trioxanes **5g**, ketone precursor **7g** was prepared as the corresponding silyl ether and thus one more step was needed to liberate the benzylic hydroxyl group directly from silylated benzylic alcohol trioxanes **8**. For those 3-aryltrioxanes **5i** and **5j** that were prepared by acylation of the primary alcohol group of 3-(*p*-hydroxymethyl)phenyl trioxanes **5g**, one additional step was used (Scheme 2). Thus, in only three to five chemical operations, 3-aryltrioxanes **5a**−**n** were synthesized in racemic form in quantities up to a few hundred milligrams. Scale-up should be feasible. The 12α- and 12*β*-methoxy diastereomers were separated chromatographically and were distinguished by high-field ^{1}H and ^{13}C NMR spectroscopy.[21]

In contrast to Scheme 1 in which an aryl **nucleophile** was used to attach the aryl group to the cyclohexane side chain, Scheme 3 represents complementary synthetic methodology in which a fluoroalkyl **electrophile** was used. This flexibility in choice of either a nucleophile or an electrophile considerably broadens the

Scheme 3



variety of 3-substituents than can be incorporated into such trioxanes. Thus, 3-(fluoroalkyl)trioxanes **6a** and **6b** were conveniently prepared via Scheme 3 using readily available **electrophilic** fluorinated esters; corresponding fluorinated organometallic reagents for use in Scheme 1 are neither readily available nor easy to prepare. Finally, in Scheme 3, the commercially available phenyl vinyl sulfoxide serves effectively as the synthetic equivalent of a 2-carbon synthon that is **electrophilic** at one end and **nucleophilic** at the other.

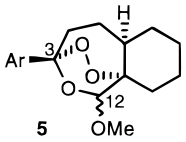
Biology

Following our previously described protocol,[22] we evaluated in vitro the chemical structure−antimalarial activity relationships of these 3-substituted trioxanes in chloroquine-sensitive *Plasmodium falciparum* (NF54)[23] parasites. The results of this evaluation are tabulated in Table 1.

Many general observations arise from examination of the in vitro antimalarial data in Table 1: (1) of the 29 3-substituted trioxanes, 23 have IC_{50} values of less than 100 nM, and 12 have IC_{50} values of less than 50 nM, compared to the 9.2 nM IC_{50} value for artemisinin; (2) several of these trioxanes have IC_{50} values ranging from 15 to 30 nM (in bold); (3) the 12*β*-methoxy diastereomers are equally or more potent than the corresponding 12α-methoxy diastereomers; (4) a *p*-fluoro substituent adds very little to in vitro antimalarial activity (cf. trioxanes **5a** and **5l**); (5) the steric hindrance of an *o*-methyl substituent as in 3-aryltrioxanes **5m** does not change antimalarial potency relative to its non-ortho-methylated analogues **5l**; (6) the nature of the halogen substituent, fluoro or chloro, does not have a strong effect (cf. **5d** vs **5l**); and (7) although oxygen-containing 3-aryltrioxanes such as anisole **5e** and furan **5f** are poor antimalarials, oxygen-containing benzylic trioxanes **5g**−**k** are potent antimalarials.

At least one of these 3-aryltrioxanes is effective also against another type of opportunistic infection. Preliminary L929 cell studies[24] with *p*-fluorophenyl-12*β*-methoxytrioxane **5l** indicate that it is as active as artemisinin at inhibiting growth of *Toxoplasma gondii*, a parasite that causes cerebral encephalitis in immu-

Table 1. [a] In Vitro Antimalarial Activitites



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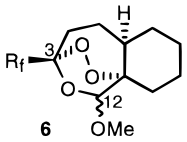

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trioxane	Ar or R_f	C_{12}-OMe	IC_{50} (nM)
5a	Ph	α	110
		β	38
5b	*p*-PhPh	α	76
		β	68
5c	1-naphthyl	α	170
		β	44
5d	*p*-ClPh	α	49
		β	55
5e	*p*-MeOPh		>2500[b]
5f	2-furyl	α	600
5g	*p*-$HOCH_2$Ph	α	78
		β	**15**
5h	*p*-$MeOCH_2$Ph	α	39
		β	51
5i	*p*-$MeOC(O)OCH_2$Ph	α	79
5j	*p*-$MeC(O)OCH_2$Ph	α	44
		β	**20**
5k	*p*-(*p*′-$FPhCH_2OCH_2$)Ph	α	42
		β	**23**
5l	*p*-FPh	α	65
		β	**30**
5m	*p*-F-*o*-MePh	α	99
		β	34
5n	*p*-CF_3Ph	α	39
		β	53
11	CH_3	*β*	960[c]
6a	$CF_3CH_2CH_2$	*β*	84[c]
6b	FCH_2	α	320[c]
		β	160[c]
artemisinin			**9.2**

[a] Antimalarial activity was determined as reported previously.[22] The standard deviation for each set of quadruplicates was an average of 10% (≤59%) of the mean. R^2 values for the fitted curves were ≥0.989. [b] 12-Methoxy stereochemistry not unambiguously determined. [c] Assay may underestimate the potency of these volatile compounds.

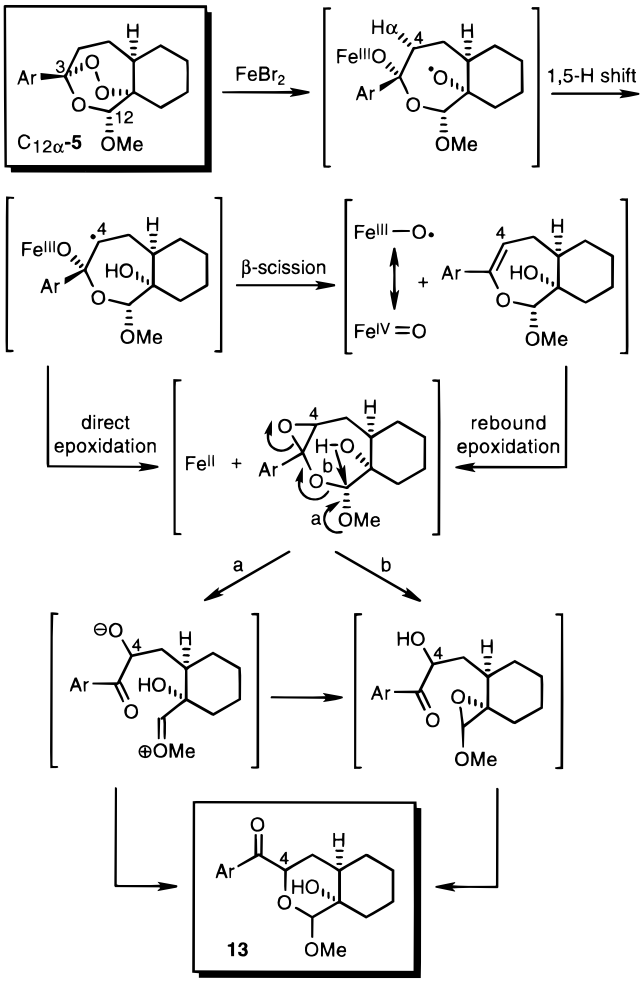
nocompromised individuals. In this cell assay, the therapeutic index (ratio of activity/toxicity) of fluorophenyl trioxane **5l** is better than that of atovaquone.

In the past, we have been successful in using in vitro antimalarial activities as a guide to select peroxides for in vivo antimalarial evaluation.[25] Preliminary assay of four 12*β*-methoxy-3-aryltrioxanes (**5g**, **5j**, **5k**, and **5l**) in a rodent system against chloroquine-sensitive *Plasmodium berghei* (N) using a previously described protocol[26] resulted in the data shown in Table 2. For convenience in comparing relative potencies of antimalarials having different molecular weights, ED_{50} and ED_{90} values are presented not only in the standard mg/kg terms but here also in *μ*mol/kg values. Several observations emerge: (1) these four simple synthetic trioxanes are potent antimalarials; (2) high levels of in vitro antimalarial activity correlate well with high in vivo antimalarial potencies; (3) especially noteworthy for ease of administration ultimately in clinical settings is the **oral activity** of these simple, crystalline trioxanes; and (4) structurally simple benzylic alcohol trioxane **5g**, acetate trioxane **5j**, and fluorobenzyl ether trioxane **5k** are up to twice as potent as the complex natural artemisinin (**1**). All of these orally active trioxanes are stable at 60 °C for at least 36 h. Thus, these preclinical in vivo results demonstrate the high antimalarial efficacy of simple 12*β*-methoxytrioxanes **5g**, **5j**, **5k**, and **5l**, and recent preliminary in vivo acute toxicity testing results highlight the relative safety of (fluorophenyl)trioxane **5l**. These new and easily prepared trioxanes, therefore, are promising lead compounds appropriate for clinical evaluation.

Mechanism of Action

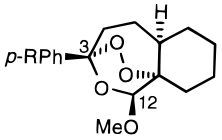
We have recently proposed a unified chemical mechanism to account for the ability of trioxanes to kill malaria parasites selectively.[11] According to this mechanism, the parasite's digestion of hemoglobin releases heme in which iron(II) reduces the trioxane's peroxide linkage to form oxy radicals. Critically for antimalarial activity, one type of such oxy radical then rearranges via a 1,5-hydrogen atom shift to form a carbon radical at C_4.[13] Therefore, we designed the 3-aryl trioxanes described here to facilitate the next *β*-scission step to form the arene-conjugated new carbon−carbon double bond shown in Scheme 4 and a strongly oxidizing and possibly cytotoxic high-valent iron oxo species.

Scheme 4



Evidence to support operation of this mechanism in iron(II)-initiated reduction of these 3-aryltrioxanes comes from three sources. First, 4*β*-methyl-3-phenyltrioxane **12** (forming a C_4-tertiary radical) has 5 times higher in vitro antimalarial activity than the corresponding 4-unsubstituted system 12α-methoxytrioxane **5a** (forming a

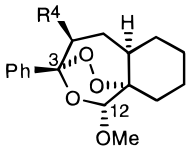
Table 2. In Vivo Antimalarial Activities



$C_{12\beta}$-trioxane	R	ED_{50}, mg/kg (μmol/kg)[a]		ED_{90}, mg/kg (μmol/kg)		IC_{50}, (nM)[b] in vitro
		subcutaneous	oral	subcutaneous	oral	
5g	$HOCH_2$	3.4 (11)	5.5 (17)	6.8 (21)	12 (37)	15
5j	$MeC(O)OCH_2$	2.8 (7.7)	14 (39)	6.0 (17)	22 (61)	20
5k	p'-$FPhCH_2OCH_2$	3.5 (8.2)	3.8 (8.9)	7.1 (17)	6.8 (16)	23
5l	F	6.8 (22)	10 (32)	13 (42)	23 (75)	30
	artemisinin	3.0 (11)	8.5 (30)	9.2		
	chloroquine	1.0 (1.9)	1.2 (2.3)	5.0		

[a] Four different doses (1, 3, 10, and 30 mg/kg) were administered each day for 4 days to five mice per dose regimen to establish the ED values indicated above via a previously reported protocol.[26] [b] In vitro antimalarial activity was determined as reported previously.[22]

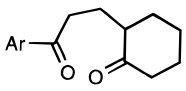
less stable C_4-secondary radical).[27] Second, iron(II)-induced degradation of 3-phenyl- and 3-(*p*-fluorophenyl)-12α-methoxytrioxanes **5a** and **5l** (see Scheme 4) in the



$C_{12\alpha}$-**5a**, R^4 = H IC_{50} = 110 nM
12, R^4 = Me IC_{50} = 21 nM

presence of hexamethyl Dewar benzene (HMDB) led to considerable rearrangement into hexamethylbenzene. This rearrangement is generally accepted as strong evidence for the intermediacy of one or more high-valent iron oxo species,[13] formed presumably as outlined in Scheme 4 via β-scission, along with a new styrene carbon−carbon double bond. Third, iron(II)-induced degradation of 12α-methoxytrioxane **5l** produced 1−2% of the C_4-oxygenated, structurally reorganized aryl ketone **13** as a single diastereomer.[28] Formation of this rearranged product, having the same molecular formula as its parent trioxane **5l**, may reasonably involve one or both of the epoxide intermediates shown in Scheme 4. Independent synthesis of the penultimate C_4-hydroxy epoxide (dimethyldioxirane reacting with the corresponding vinyl ether) showed that it rearranged spontaneously into aryl ketone **13**.

In contrast, iron(II)-mediated degradation of the 12β-diastereomers of 3-phenyl- and 3-(*p*-fluorophenyl)trioxanes did not produce any rearrangement of HMDB. Major products of these reactions were 1,5-diketones **14**.[19] These results indicate a dependence of the deg-



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radation pathway on the stereochemistry at C_{12}. 12β-Methoxy-3-aryltrioxanes may exert their antimalarial activity by acting as prodrugs for electrophilic diketones. The diketones arising from most of the 3-aryltrioxanes listed in Table 1 were thus tested for in vitro efficacy. These potential alkylating agents were generally inactive, with the exception of those arising from trioxane **5a** (1400 nM) and trioxane **5l** (1200 nM). The low antimalarial activity of these reactive diketones in unmasked form may be due to their reacting with other biomolecules before reaching the parasite targets.[19]

In summary, mechanism-based design has led to a series of structurally simple 3-aryl trioxanes that are efficacious in vivo as potent antimalarials even when administered orally to rodents. These trioxanes, therefore, are now excellent antimalarial drug candidates for further clinical evaluations as part of the worldwide effort to fight malaria via chemotherapy.

Experimental Section

General. Unless otherwise noted, the following applies: Reactions were run in flame-dried round-bottomed flasks under an atmosphere of ultra-high-purity (UHP) argon. Diethyl 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 F_{254} 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 × 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 ^{1}H and 100 MHz for ^{13}C, or on a Varian XL-500 spectrometer, operating at 500 MHz for ^{1}H 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 diisopropy-

lamine (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 2a: Ketone Synthesis (Lithium−Halogen Exchange). To a solution of aryl bromide (1.3 equiv) in ether (5 mL/mmol of nitrile) at −78 °C was added via syringe recently titrated *t*-BuLi (2.5 equiv, originally 1.6 M in ether) over 1 min. This solution was stirred at −78 °C for 30−60 min. To this mixture was added dropwise via cannula a −78 °C solution of nitrile starting material (1.0 equiv) in ether (5 mL/mmol). The reaction was stirred at −78 °C for 15 min, then warmed to room temperature over 1 h and stirred at that temperature until complete by TLC analysis (at least 1 h). At that time, the reaction was cooled back to 0 °C and quenched with dropwise addition of H_2O. The mixture was then diluted with H_2O and ether, the organic phase separated, and the aqueous phase extracted twice with ether. The organic portions were combined, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure.

General Procedure 2b: Ketone Synthesis (Sulfoxide Alkylation/Reduction). To a freshly prepared solution of LDA (1.1 equiv) in THF/hexanes (0.25 M) at −78 °C was added dropwise by cannula a −78 °C solution of sulfoxide substrate (1.0 equiv) in THF (0.67 M). The mixture was allowed to warm to −35 °C over 2 h, was stirred for an additional hour, and was cooled back to −78 °C. A solution of fluoroalkyl ester (1.4 equiv) in THF (3.3 M) was added via cannula. The resulting reaction mixture was stirred at −78 °C for 1 h and then warmed to −35 °C over 2 h. After being stirred at that temperature for an additional 2 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc, dried over anhydrous $MgSO_4$, and concentrated to give a crude acylated sulfoxide.

Aluminum foil (10 equiv based on estimated yield of sulfoxide) was cut into small strips, submerged for 15 s in an aqueous mercury(II) chloride solution (2% w/v), and then rinsed well with absolute ethanol and then with ether. The resulting aluminum/mercury amalgam was snipped with scissors into a 0 °C solution of the above acylated sulfoxide in aqueous THF (90%, THF/H_2O, 2.0 mL/mmol of aluminum foil). This reaction was stirred at 0 °C for 1.5 h. Anhydrous $MgSO_4$ was then added to the resulting gray slurry, and this mixture was filtered with copious ether rinses. The combined organic washes were concentrated under reduced pressure.

General Procedure 3a: 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 **just** until TLC analysis showed >95% consumption of starting material (typically 20−60 min). 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 3b: Trioxane Formation: Proton Sponge Modification. This procedure is identical to general procedure 3a, with the following modifications. CH_2Cl_2 (anhydrous, 99.8%, packaged in Sure/Seal bottle) was purchased from Aldrich (27,099-7) and used without further purification. The TBDMSOTf solution (1.3 equiv, 0.50 M in CH_2Cl_2) also contained 2,6-di-*tert*-butyl-4-methylpyridine (0.25 equiv). The reaction was quenched with Et_3N (neat, 3.9 equiv).

General Procedure 4: 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 Bu_4NF (monohydrate, 1.5 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 (3 mL) 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.

***p*-Biphenyl Ketone 7b.** To a solution of 4-bromobiphenyl (770 mg, 3.30 mmol) in ether (4 mL) at 0 °C was added *n*-BuLi (1.25 M in hexanes, 2.5 mL, 3.1 mmol) via syringe. This solution was stirred at 0 °C for 5 min, then warmed to room temperature and stirred for 1 h. The resulting greenish gray turbid mixture was added dropwise via cannula (without cooling) to a −78 °C solution of (*Z*)-methoxyethylidene-2-(2′-cyanoethyl)cyclohexanone[16,29] (370 mg, 2.06 mmol) in ether (14 mL). The reaction mixture turned bright orange and fumed extensively during the addition. The mixture was stirred at −78 °C for 5 min, then warmed to room temperature and stirred for 3 h. At that time, the reaction was quenched with H_2O (3 mL) and then diluted with ether (50 mL) and H_2O (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 $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (short path, 1% → 10% EtOAc/hexanes) to give the desired product **7b** (282 mg, 2.53 mmol, 41%) as a light pink solid: mp = 93.0−94.5 °C.

3-(*p*-Biphenyl)trioxanes $C_{12\alpha}$-5b and $C_{12\beta}$-5b. *p*-Biphenyl ketone **7b** (190 mg, 0.565 mmol) was treated according to general procedure 3a. The crude reaction mixture was purified by column chromatography (Florisil, 1% → 10% EtOAc/hexanes) to give 12α-methoxytrioxane **5b** (90 mg, 0.24 mmol, 43%), 12*β*-methoxytrioxane **5b** (45 mg, 0.324 mmol, 22%), impure diketone **14b**, and an impure mixture of mono- and di-O-silylated species arising from **14b**. The latter material was treated according to general procedure 4 (excess Bu_4NF). The crude product from this reaction was combined with the other portion of impure diketone **14b** and purified by column chromatography (flash gel, 5% → 50% EtOAc/hexanes) to give diketone **14b** (36 mg, 0.117 mmol, 21%).

Further purification of trioxane $C_{12\alpha}$-**5b** by HPLC (silica, 85% CH_2Cl_2/hexanes, 2.5 mL/min, 274 nm, t_R = 15.8 min) afforded a white solid: mp = 163.5−165.0 °C.

Further purification of trioxane $C_{12\beta}$-**5b** by HPLC (silica, 3% EtOAc/hexanes, 3.0 mL/min, 274 nm, t_R = 9.9 min) afforded a white solid: mp = 146.0−147.0 °C.

Further purification of diketone **14b** by HPLC (silica, 15% EtOAc/hexanes, 3.0 mL/min, 274 nm, t_R = 18.9 min) afforded a white solid: mp = 76.0−76.5 °C.

1-Naphthyl Ketone 7c. (*Z*)-Methoxyethylidene-2-(2′-cyanoethyl)cyclohexanone[16,29] (500 mg, 2.79 mmol) was treated according general procedure 2a using 1-naphthyl bromide. Analysis of the crude product by TLC and then by ^1H NMR revealed the almost exclusive presence of a stable imine corresponding to the desired ketone. A small amount of hydrolysis was evident by TLC. Accordingly, this material was dissolved in 5% EtOAc/hexanes (20 mL) and slurried with short path silica (10 g) for 8 h, at which time TLC analysis indicated complete hydrolysis of imine to ketone. This solution was filtered and concentrated and the resulting oil was purified by column chromatography (flash gel, 1% → 10% EtOAc/hexanes) to give the desired product **7c** (695 mg, 2.25 mmol, 81%) as a pale yellow oil.

3-(1-Naphthyl)trioxanes $C_{12\alpha}$-5c and $C_{12\beta}$-5c. 1-Naphthyl ketone **7c** (310 mg, 1.00 mmol) was treated according to general procedure 3a. The crude reaction mixture was purified

by column chromatography (Florisil, 1% → 10% EtOAc/hexanes) to give 12α-methoxytrioxane **5c** (138 mg, 0.405 mmol, 40%), 12β-methoxytrioxane **5c** (66 mg, 0.19 mmol, 19%), impure diketone **14c**, and an impure mixture of mono- and di-O-silylated species arising from **14c**. The latter material was treated according to general procedure 4 (excess Bu_4NF). The crude product from this reaction was combined with the other portion of impure diketone **14c** and purified by column chromatography (flash gel, 5% → 50% EtOAc/hexanes) to give diketone **14c** (91 mg, 0.32 mmol, 32%).

Further purification of trioxane $C_{12\alpha}$-**5c** by HPLC (silica, 98% CH_2Cl_2/hexanes, 2.0 mL/min, t_R = 13.6 min) afforded a white solid: mp = 110−112 °C.

Further purification of trioxane $C_{12\beta}$-**5c** by HPLC (silica, 40% CH_2Cl_2/hexanes, 3.0 mL/min, 274 nm, t_R = 14.5 min) afforded a white solid: mp = 154.5−155.0 °C.

Further purification of diketone **14c** by HPLC (silica, 15% EtOAc/hexanes, 3.0 mL/min, 280 nm, t_R = 19.0 min) afforded a white solid: mp = 80.0−81.5 °C.

***p*-Chlorophenyl Ketone 7d.** To a slurry of (methoxymethyl)triphenylphosphonium chloride (16.7 g, 48.8 mmol) in THF (200 mL) at −78 °C was added PhLi (1.8 M in 70% cyclohexane/ether, 25.3 mL, 45.6 mmol) via syringe. The resulting dark red mixture was stirred at −78 °C for 15 min, warmed to room temperature, and stirred for 3 h. This solution was cooled back to −78 °C, and a precooled solution of 2-(2′-carbomethoxyethyl)cyclohexanone[30] (6.00 g, 32.6 mmol) in THF (100 mL) was added via cannula. The mixture was stirred at −78 °C for 1 h, warmed to room temperature, and stirred for 12 h. The reaction was quenched with H_2O (10 mL) and further diluted with H_2O (100 mL). After 10 min of stirring, the organic layer was decanted. The aqueous portion was extracted with ether (2 × 50 mL). 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 (flash gel, 1% → 20% EtOAc/hexanes) to give the desired enol ethers (5.68 g, 26.8 mmol, 82%), a 1:1 mixture of diastereomers, as a colorless liquid.

To a 0 °C solution of (*p*-chlorophenyl)magnesium bromide (1.0 M in ether, 5.65 mL, 5.65 mmol) in benzene (7.0 mL) was added via syringe Et_3N (2.35 mL, 17.0 mmol). This mixture was stirred at 0 °C for 10 min, and then a precooled solution of the above enol ethers (600 mg, 2.83 mmol) in benzene (14 mL) was added via cannula. The reaction was stirred at 0 °C for 3 h, quenched with dropwise addition of H_2O (3 mL), and then diluted with ether (50 mL) and H_2O (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 $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was filtered through a plug of short path silica to afford the corresponding ketones (566 mg, 1.93 mmol, 68%) as a 1:1 mixture of diastereomers. This mixture was separated by column chromatography (short path, 1% → 10% EtOAc/hexanes) to give the desired *Z*-enol ether isomer **7d**, which solidified slowly at room temperature over several days: mp = 38.0−39.5 °C.

3-(*p*-Chlorophenyl)trioxanes $C_{12\alpha}$-5d and $C_{12\beta}$-5d. *p*-Chlorophenyl ketone **7d** (235 mg, 0.802 mmol) was treated according to general procedure 3a. The crude reaction mixture was purified by column chromatography (Florisil, 1% → 10% EtOAc/hexanes) to give 12α-methoxytrioxane **5d** (73 mg, 0.22 mmol, 28%), 12β-methoxytrioxane **5d** (84 mg, 0.26 mmol, 32%), impure diketone **14d**, and an impure mixture of mono- and di-O-silylated species arising from **14d**. The latter material was treated according to general procedure 4 (excess Bu_4NF). The crude product from this reaction was combined with the other portion of impure diketone **14d** and purified by column chromatography (flash gel, 5% → 50% EtOAc/hexanes) to give diketone **14d** (45 mg, 0.17 mmol, 21%).

Further purification of trioxane $C_{12\alpha}$-**5d** by HPLC (silica, 100% CH_2Cl_2, 2.0 mL/min, 264 nm, t_R = 20.4 min) afforded a white solid: mp = 94.0−95.0 °C.

Further purification of trioxane $C_{12\beta}$-**5d** by HPLC (silica, 80% CH_2Cl_2/hexanes, 2.0 mL/min, 264 nm, t_R = 9.5 min) afforded a white solid: mp = 93.0−95.0 °C.

Further purification of diketone **14d** by HPLC (silica, 15% EtOAc/hexanes, 3.0 mL/min, 264 nm, t_R = 17.1 min) afforded a white solid: mp = 71.5−73.5 °C.

***p*-Methoxyphenyl Ketone 7e.** (*Z*)-Methoxyethylidene-2-(2′-cyanoethyl)cyclohexanone[16,29] (300 mg, 1.67 mmol) was treated according general procedure 2a (1.6 equiv of aryl bromide, 1.5 equiv of *t*-BuLi) using *p*-methoxyphenyl bromide. The crude product was purified by column chromatography (flash gel, 1% → 20% EtOAc/hexanes) to give the desired product **7e** (323 mg, 1.12 mmol, 67%) as a colorless oil.

3-(*p*-Methoxyphenyl)trioxane 5e. *p*-Methoxyphenyl ketone **5** (300 mg, 1.04 mmol) was treated according to general procedure 3a. The crude reaction mixture was purified by column chromatography (Florisil, 1% → 10% EtOAc/hexanes) to give trioxane **5e** (140 mg, 0.437 mmol, 42%), with ambiguous relative stereochemistry, impure diketone **14e**, and an impure mixture of mono- and di-O-silylated species arising from **14e**. The latter material was treated according to general procedure 4 (excess Bu_4NF). The crude product from this reaction was combined with the other portion of impure diketone **14e** and purified by column chromatography (flash gel, 5% → 50% EtOAc/hexanes) to give diketone **14e** (94 mg, 0.36 mmol, 35%).

Further purification of trioxane **5e** by HPLC (silica, 5% EtOAc/hexanes, 3.0 mL/min, 254 nm, t_R = 19.0 min) afforded a white solid: mp = 84.5−85.0 °C. Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.47; H, 7.57. Found: C, 67.54; H, 7.57. Note that this combustion analysis rules out the deoxytrioxane product. Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.02; H, 7.96.

Further purification of diketone **14e** by HPLC (silica, 25% EtOAc/hexanes, 3.0 mL/min, 274 nm, t_R = 16.6 min) afforded a white solid: mp = 104.0−105.0 °C.

2-Furyl Ketone 7f. To a solution of furan (0.525 mL, 7.25 mmol) in THF (8 mL) at 0 °C was added via syringe *n*-BuLi (5.6 mL, 1.25 M solution in hexanes, 7.0 mmol). The mixture was stirred at 0 °C for 2 h, then warmed to room temperature, and stirred for 1 h. This solution was then cooled back to 0 °C, and a solution of (*Z*)-methoxyethylidene-2-(2′-cyanoethyl)-cyclohexanone[16,29] (500 mg, 2.79 mmol) in THF (4 mL) at 0 °C was added via cannula. The reaction immediately turned bright orange. After 5 min at 0 °C, the mixture was warmed to room temperature and stirred for 6 h, at which time it was dark red. The reaction was then quenched with H_2O (3 mL) and diluted with ether (20 mL) and H_2O (20 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 $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (20 g flash gel, 1% → 20% EtOAc/hexanes) to give the desired product **7f** (296 mg, 1.19 mmol, 43%) as a yellow oil.

3-(2-Furyl)trioxane 5f. 2-Furyl ketone **7f** (250 mg, 1.01 mmol) was treated according to general procedure 3a. The crude reaction mixture was purified by column chromatography (Florisil, 1% → 20% EtOAc/hexanes) to give 12α-methoxytrioxane **5f** (45 mg, 0.16 mmol, 16%), impure diketone **14f**, and an impure mixture of mono- and di-O-silylated species arising from **14f**. The latter material was treated according to general procedure 4 (excess Bu_4NF). The crude product from this reaction was combined with the other portion of impure diketone **14f** and purified by column chromatography (flash gel, 5% → 50% EtOAc/hexanes) to give diketone **14f** (121 mg, 0.549 mmol, 54%).

Further purification of trioxane **5f** by HPLC (silica, 5% EtOAc/hexanes, 4.0 mL/min, 254 nm, t_R = 14.2 min) afforded a white solid: mp = 110.5−112.0 °C.

Further purification of diketone **14f** by HPLC (silica, 10% *i*-PrOH/hexanes, 3.0 mL/min, 264 nm, t_R = 12.0 min) afforded a white solid: mp = 48.5−49.5 °C.

***p*-(Silyloxymethyl)phenyl Ketone 7g.** To a solution of *p*-hydroxymethylphenyl bromide (4.75 g, 25.4 mmol) and

imidazole (2.59 g, 38.0 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added via dropping funnel a solution of *tert*-butyldimethylsilyl chloride (4.59 g, 30.5 mmol). The resulting solution was kept for 5 min at 0 °C, then warmed to room temperature, and stirred for 20 min. The reaction was then quenched with H_2O (10 mL) and diluted with 10% aqueous HCl (100 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (100 mL × 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 Kügelrohr distillation (160−180 °C, 0.9 Torr) to give the desired silyl ether (7.21 g, 23.9 mmol, 94%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 2 H), 7.20 (m, 2 H), 4.69 (s, 2 H), 0.95 (d, J = 0.8 Hz, 9 H), 0.11 (d, J = 0.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 131.2, 127.6, 120.5, 64.3, 25.9, 18.4, −5.2. These spectroscopic data are consistent with those reported previously.[31,32]

(*Z*)-Methoxyethylidene-2-(2′-cyanoethyl)cyclohexanone[16,29] (500 mg, 2.79 mmol) was treated according to general procedure 2a with the above *p*-(silyloxymethyl)phenyl bromide. The crude product was purified by column chromatography (flash gel, 1% → 10% EtOAc/hexane) to give the desired product **7g** (776 mg, 1.92 mmol, 69%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 2 H), 7.39 (m, 2 H), 5.79 (d, J = 1.6 Hz, 1 H), 4.78 (s, 2 H), 3.41 (s, 3 H), 2.99−2.83 (m, 3 H), 2.00 (m, 2 H), 1.80 (m, 1 H), 1.74 (m, 2 H), 1.65 (m, 1 H), 1.52 (m, 3 H), 1.26−1.15 (m, 1 H), 0.95 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 146.3, 140.3, 136.0, 128.0, 125.6, 118.9, 64.4, 59.0, 36.8, 32.6, 31.6, 28.2, 26.4, 25.8, 21.6, 18.3, −5.3; IR (neat) 3001, 2928, 2856, 1684, 1609, 1462, 1256, 1124, 1094, 839 cm^{-1}; LRMS (EI, rel intensity) 402 (M^+, 2), 370 (6), 249 (6), 223 (12), 138 (100); HRMS (EI) *m*/*z* calcd for (M^+) 402.2590, found 402.2594.

3-(*p*-(Hydroxymethyl)phenyl)trioxanes $C_{12\alpha}$-5g and $C_{12\beta}$-5g. *p*-(Silyloxymethyl)phenyl ketone **7g** (430 mg, 1.07 mmol) was treated according to general procedure 3b. The crude reaction mixture was purified by column chromatography (Florisil, 1% → 20% EtOAc/hexanes) to give a silylated 12α-methoxytrioxane (115 mg, 0.264 mmol, 25%), a silylated 12β-methoxytrioxane (129 mg, 0.296 mmol, 28%), an impure *p*-(silyloxymethyl)phenyl diketone, and an impure mixture of mono- and di-O-silylated species arising from this diketone. Portions of the trioxanes (100 mg, 0.230 mmol of $C_{12\alpha}$ analogue; 75 mg, 0.17 mmol of $C_{12\beta}$ analogue) were individually desilylated according to general procedure 4. The resulting crude products were purified separately by column chromatography (Florisil each, 5% → 50% EtOAc/hexanes) to give 12α-methoxytrioxane **5g** (60 mg, 0.19 mmol, 83%) and 12β-methoxytrioxane **5g** (40 mg, 0.12 mmol, 71%). All diketone-containing material was combined and was treated according to general procedure 4 (excess Bu_4NF). The crude product was purified by column chromatography (flash gel, 5% → 50% EtOAc/hexanes) to give diketone **14g** (52 mg, 0.20 mmol, 19%).

Further purification of trioxane $C_{12\alpha}$-**5g** by HPLC (silica, 10% *i*-PrOH/hexanes, 3.0 mL/min, 254 nm, t_R = 14.4 min) afforded a white solid: mp = 140−142 °C (broad); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2 H), 7.34 (m, 2 H), 5.18 (s, 1 H), 4.68 (s, 2 H), 3.61 (s, 3 H), 2.83 (ddd, J = 14.4, 13.6, 4.0 Hz, 1 H), 2.41 (m, 1 H), 2.26 (ddd, J = 14.8, 4.8, 2.4 Hz, 1 H), 1.89 (m, 1 H), 1.82−1.69 (m, 5 H), 1.67−1.56 (m, 1 H), 1.33−1.15 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 139.7, 126.5, 125.5, 103.8, 96.0, 83.6, 64.8, 55.9, 45.3, 37.5, 33.3, 32.5, 27.1, 25.2, 23.1; IR ($CHCl_3$) 3608, 3506, 3031, 3012, 2934, 2864, 1451, 1347, 1272, 1100, 1012 cm^{-1}; LRMS (CI, NH_3, rel intensity) 321 (M + H^+, 63), 289 (22), 261 (100), 138 (24); HRMS (CI, NH_3) *m*/*z* calcd for $C_{18}H_{25}O_5$ (M + H^+) 321.1702, found 321.1709.

Further purification of trioxane $C_{12\beta}$-**5g** by HPLC (silica, 5% *i*-PrOH/hexanes, 3.0 mL/min, 254 nm, t_R = 18.6 min) afforded a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2 H), 7.35 (m, 2 H), 5.14 (d, J = 1.2 Hz, 1 H), 4.69 (d, J = 3.2 Hz, 2 H), 3.65 (s, 3 H), 2.78 (ddd, J = 14.8, 13.2, 3.6 Hz, 1 H), 2.29 (ddd, J = 14.4, 4.4, 3.2 Hz, 1 H), 2.02−1.89 (m, 2 H), 1.81−1.59 (m, 8 H), 1.30 (apparent dt, J_d = 4.8 Hz, J_t = 13.6 Hz, 1 H), 1.20 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 140.1, 126.7, 125.5, 105.1, 105.0, 83.8, 64.9, 57.1, 47.4, 39.1, 35.6, 30.8, 26.8, 25.0, 23.8; IR ($CHCl_3$) 3608, 3473, 3031, 3012, 2933, 2863, 1446, 1277, 1104, 1036, 960 cm^{-1}; LRMS (CI, NH_3, rel intensity) 321 (M + H^+, 100), 261 (68), 138 (34); HRMS (CI, NH_3) *m*/*z* calcd for $C_{18}H_{25}O_5$ (M + H^+) 321.1702, found 321.1700.

Further purification of diketone **14g** by HPLC (silica, 20% *i*-PrOH/hexanes, 3.0 mL/min, 270 nm, t_R = 10.6 min) afforded a white solid: mp = 50.0−51.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (m, 2 H), 7.45 (m, 2 H), 4.77 (d, J = 5.2 Hz, 2 H), 3.04 (ddABq, J_d = 8.4, 6.0 Hz, J_{AB} = 16.8 Hz, $\Delta\nu_{AB}$ = 64.4 Hz, 2 H), 2.43 (m, 2 H), 2.31 (m, 1 H), 2.19−2.03 (m, 3 H), 1.99 (br m, 1 H), 1.87 (m, 1 H), 1.75−1.62 (m, 3 H), 1.46 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5, 200.0, 146.2, 135.8, 128.3, 126.5, 64.4, 49.9, 42.2, 36.3, 34.6, 28.1, 25.0, 24.5; IR ($CHCl_3$) 3611, 3489, 3029, 3011, 2939, 2864, 1704, 1681, 1610, 1450, 1233, 1014 cm^{-1}; LRMS (EI, rel intensity) 260 (M^+, 5), 242 (10), 150 (84), 135 (100), 107 (13), 89 (15), 77 (11); HRMS (EI) *m*/*z* calcd for $C_{16}H_{20}O_3$ (M^+) 260.1412, found 260.1417.

***p*-(Methoxymethyl)phenyl Ketone 7h.** To a room temperature suspension of *p*-(hydroxymethyl)phenyl bromide (3.0 g, 16 mmol) in methyl iodide (10 g, 160 mmol) was added just enough CH_2Cl_2 to dissolve ca. 90% of the solid (ca. 5 mL). To this rapidly stirring mixture was added solid *n*-Bu_4NI (300 mg, 0.80 mmol) followed immediately by NaOH (50% aqueous, 6.2 mL, 80 mmol). After 3 h, the mixture was diluted with H_2O (50 mL) and CH_2Cl_2 (50 mL). The organic phase was separated, and the aqueous phase was washed with CH_2Cl_2 (50 mL). 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 (flash gel, 1% → 5% EtOAc/hexanes) to give the desired methyl ether (3.0 g, 15 mmol, 93%) as a colorless oil. Its spectroscopic data are consistent with those reported previously.[33,34]

(*Z*)-Methoxyethylidene-2-(2′-cyanoethyl)cyclohexanone[16,29] (1.00 g, 5.58 mmol) was treated according to general procedure 2a with the above (methoxymethyl)phenyl bromide. The crude product was purified by column chromatography (flash gel, 1% → 20% EtOAc/hexane) to give the desired product **7h** (925 mg, 3.06 mmol, 55%) as a colorless oil.

3-(*p*-(Methoxymethyl)phenyl)trioxanes $C_{12\alpha}$-5h and $C_{12\beta}$-5h. *p*-(Methoxymethyl)phenyl ketone **7h** (230 mg, 0.792 mmol) was treated according to general procedure 3b. The crude reaction mixture was purified by column chromatography (Florisil, 1% → 20% EtOAc/hexanes) to give 12α-methoxytrioxane **5h** (39 mg, 0.12 mmol, 21%), 12β-methoxytrioxane **5h** (19 mg, 0.057 mmol, 10%), impure diketone **14h**, and an impure mixture of mono- and di-O-silylated species arising from **14h**. The latter material was treated according to general procedure 4 (excess Bu_4NF). The crude product from this reaction was combined with the other portion of impure diketone **14h** and purified by column chromatography (flash gel, 5% → 50% EtOAc/hexanes) to give diketone **14h** (99 mg, 0.36 mmol, 66%).

Further purification of trioxane $C_{12\alpha}$-**5h** by HPLC (silica, 5% EtOAc/CH_2Cl_2, 3.0 mL/min, 254 nm, t_R = 11.4 min) afforded a white solid: mp = 96.0−97.0 °C. Further purification of trioxane $C_{12\beta}$-**5h** by HPLC (silica, 10% EtOAc/hexanes, 2.5 mL/min, 254 nm, t_R = 16.0 min) afforded a white solid: mp = 69.0−70.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2 H), 7.32 (m, 2 H), 5.14 (d, J = 1.2 Hz, 1 H), 4.46 (s, 2 H), 3.65 (s, 3 H), 3.37 (s, 3 H), 2.78 (ddd, J = 14.4, 13.2, 3.6 Hz, 1 H), 2.30 (ddd, J = 13.6, 4.4, 3.2 Hz, 1 H), 2.02−1.89 (m, 2 H), 1.81−1.59 (m, 7 H), 1.30 (apparent dt, J_d = 4.8 Hz, J_t = 13.6 Hz, 1 H), 1.20 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 138.6, 127.3, 125.2, 105.0, 104.9, 83.7, 74.1, 58.0, 57.1, 47.4, 39.1, 35.6, 30.7, 26.8, 25.0, 23.8; IR ($CHCl_3$) 3032, 3012, 2933, 2862, 1447, 1277, 1104, 1016 cm^{-1}; LRMS (CI, NH_3, rel intensity) 335 (M + H^+, 37), 275 (100); HRMS (CI, NH_3) *m*/*z* calcd for $C_{19}H_{27}O_5$ (M + H^+) 335.1858, found 335.1860.

Further purification of diketone **14h** by HPLC (silica, 25% EtOAc/hexanes, 3.0 mL/min, 284 nm, t_R = 19.8 min) afforded a white solid: mp = 41.5−42.5 °C.

3-(*p*-(Carbomethoxyoxymethyl)phenyl)trioxane 5i. To a 0 °C slurry of $C_{12\alpha}$-methoxytrioxane benzyl alcohol **5g** (32 mg, 0.10 mmol) and K_2CO_3 (414 mg, 3.00 mmol) in acetone (10 mL) was added Me_2SO_4 (0.33 mL, 3.5 mmol). The resulting mixture was warmed to room temperature. After 3 h, no reaction was evident by TLC analysis. The mixture was then heated to reflux. After 6 h, all acetone had boiled away. The reaction had partially but cleanly proceeded according to TLC. Additional Me_2SO_4 (0.33 mL, 3.5 mmol) was added, and the mixture was refluxed for an additional 12 h. The reaction was then cooled to room temperature and diluted with H_2O (5 mL) and $CHCl_3$ (5 mL). The phases were separated, and the aqueous phase was extracted with $CHCl_3$ (5 mL). The combined organic portions were washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (Florisil, 1% → 20% EtOAc/hexanes) to give $C_{12\alpha}$-methoxytrioxane carbonate **5i** (19 mg, 0.050 mmol, 50%). Further purification of this material by HPLC (silica, 10% EtOAc/CH_2Cl_2, 2.0 mL/min, 264 nm, t_R = 9.5 min) afforded a white solid: mp = 113.5−114.0 °C.

3-(*p*-(Acetoxymethyl)phenyl)trioxanes 5j. C_3-(*p*-(Hydroxymethyl)phenyl)trioxanes **5g** were individually treated according to the following procedure: To a solution of trioxane alcohol (32 mg, 0.10 mmol $C_{12\alpha}$-**5g**; 29 mg, 0.091 mmol $C_{12\beta}$-**5g**) in CH_2Cl_2 (0.10 M) was added DMAP (ca. 0.2 equiv, catalytic) as a solid followed by Et_3N (1.2 equiv) via syringe. The resulting solution was cooled to 0 °C and acetyl chloride (1.2 equiv) was added via syringe. The reaction was stirred at 0 °C for 15−20 min, quenched with dropwise addition of H_2O (1 mL), then diluted with CH_2Cl_2 (2 mL) and H_2O (2 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 mL). The combined organic portions were washed with saturated aqueous NaCl (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude products were purified separately by column chromatography (Florisil each, 1% → 10% EtOAc/hexanes) to give 12α-methoxytrioxane acetate **5j** (28 mg, 0.077 mmol, 77%) and 12*β*-methoxytrioxane acetate **5j** (24 mg, 0.066 mmol, 73%).

Further purification of $C_{12\alpha}$-**5j** by HPLC (silica, 60% MeO*t*-Bu/CH_2Cl_2, 2.5 mL/min, 264 nm, t_R = 8.5 min) afforded a white solid: mp = 71.0−72.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2 H), 7.34 (br d, 2 H), 5.17 (s, 1 H), 5.10 (s, 2 H), 3.60 (s, 3 H), 2.82 (ddd, J = 13.2, 13.6, 3.6 Hz, 1 H), 2.41 (m, 1 H), 2.24 (ddd, J = 14.4, 4.8, 2.4 Hz, 1 H), 2.10 (s, 3 H), 1.89 (m, 1 H), 1.82−1.70 (m, 4 H), 1.68−1.55 (m, 1 H), 1.30−1.15 (M, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 140.5, 136.3, 127.9, 125.5, 103.8, 96.1, 83.7, 65.8, 56.0, 45.4, 37.6, 33.4, 32.5, 27.2, 25.3, 23.1, 21.0; IR ($CHCl_3$) 3020, 2934, 2863, 1736, 1451, 1224, 1100, 1014, 754, 668 cm^{-1}; LRMS (CI, CH_4, rel intensity) 363 (M + H$^+$, 4), 331 (17), 303 (89), 243 (100), 177 (23), 125 (33), 109 (66), 61 (53); HRMS (CI, CH_4) m/z calcd for $C_{20}H_{27}O_6$ (M + H$^+$) 363.1808, found 363.1804.

Further purification of $C_{12\beta}$-**5j** by HPLC (silica, 10% EtOAc/hexanes, 2.5 mL/min, 264 nm, t_R = 11.0 min) afforded a white solid: mp = 85.0−85.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2 H), 7.34 (m, 2 H), 5.13 (d, J = 1.2 Hz, 1 H), 5.10 (s, 2 H), 3.64 (s, 3 H), 2.77 (ddd, J = 14.8, 13.6, 4.0 Hz, 1 H), 2.28 (ddd, J = 14.8, 4.4, 3.2 Hz, 1 H), 2.10 (s, 3 H), 2.02−1.89 (m, 2 H), 1.81−1.59 (m, 7 H), 1.30 (apparent dt, J_d = 5.2 Hz, J_t = 13.6 Hz, 1 H), 1.21 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 140.8, 136.4, 128.0, 125.4, 105.0, 104.9, 83.8, 65.8, 57.1, 47.4, 39.1, 35.6, 30.8, 26.8, 25.0, 23.8, 21.0; IR ($CHCl_3$) 3030, 2934, 2862, 1736, 1446, 1380, 1234, 1104, 1016 cm^{-1}; LRMS (CI, NH_3, rel intensity) 380 (M + NH_4^+, 12), 363 (M + H$^+$, 81), 320 (M$^+$ − O_2, 15), 303 (100), 260 (36), 138 (20); HRMS (CI, NH_3) m/z calcd for $C_{20}H_{27}O_6$ (M + H$^+$) 363.1808, found 363.1814.

***p*-(*p*′-Fluorobenzyloxymethyl)phenyl Ketone (7k).** To a rapidly stirring room temperature slurry of *p*-hydroxymethylphenyl bromide (5.0 g, 27 mmol) in *p*-fluorobenzyl bromide (6.6 mL, 53 mmol) was added NaOH (50% aqueous, 10.5 mL, 134 mmol) followed immediately by solid *n*-Bu_4NI (494 mg, 1.34 mmol). After 1 h, the mixture was diluted with H_2O (50 mL) and CH_2Cl_2 (50 mL). The organic phase was separated, and the aqueous phase was washed with CH_2Cl_2 (50 mL). 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 Kügelrohr distillation (175 °C, 0.9 Torr) to give the desired ether (7.43 g, 25.2 mmol, 93%) as a white solid: mp = 37.5−38.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 2 H), 7.31 (m, 2 H), 7.24 (m, 2 H), 7.04 (m, 2 H), 4.50 (s, 2 H), 4.49 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (d, J_{C-F} = 244 Hz), 137.1, 133.7 (d, J_{C-F} = 3.0 Hz), 131.5, 129.5 (d, J_{C-F} = 7.6 Hz), 129.3, 121.5, 115.2 (d, J_{C-F} = 21.3 Hz), 71.5, 71.3; IR (neat) 3044, 2923, 2859, 1603, 1509, 1223, 1086, 1012, 824 cm^{-1}; LRMS (EI, rel intensity) 294/296 (M$^+$, 3), 185/187 (8), 169/171 (29), 109 (100), 91 (52); HRMS (EI) m/z calcd for $C_{14}H_{12}O^{79}BrF$ (M$^+$) 294.0056, found 294.0054.

(*Z*)-Methoxyethylidene-2-(2′-cyanoethyl)cyclohexanone[16,29] (1.00 g, 5.58 mmol) was treated according to general procedure 2a with the above *p*-(*p*′-fluorobenzyloxymethyl)phenyl bromide. The crude product was purified by column chromatography (flash gel, 1% → 20% EtOAc/hexane) to give the desired product **7k** (1.68 g, 4.24 mmol, 76%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2 H), 7.43 (br d, 2 H), 7.33 (m, 2 H), 7.04 (m, 2 H), 5.79 (d, J = 2.0 Hz, 1 H), 4.59 (s, 2 H), 4.53 (s, 2 H), 3.42 (s, 3 H), 2.92 (m, 3 H), 2.00 (m, 2 H), 1.83−1,70 (m, 3 H), 1.64 (m, 1 H), 1.60−1.48 (m, 4 H), 1.28−1.15 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 162.3 (d, J_{C-F} = 244 Hz), 143.0, 140.4, 136.6, 133.6 (d, J_{C-F} = 3.1 Hz), 129.4 (d, J_{C-F} = 8.4 Hz), 128.2, 127.3, 119.0, 115.3 (d, J_{C-F} = 51.1 Hz), 71.7, 71.5, 59.1, 36.9, 32.6, 31.7, 28.3, 26.4, 25.8, 21.6; IR (neat) 3058, 2927, 2854, 1681, 1608, 1510, 1224, 1124, 826; LRMS (EI, rel intensity) 396 (M$^+$, 1), 138 (100), 123 (11), 109 (20); HRMS (EI) m/z calcd for $C_{25}H_{29}O_3F$ (M$^+$) 396.2101, found 396.2101.

3-(*p*-(*p*′-Fluorobenzyloxymethyl)phenyl)trioxanes $C_{12\alpha}$-5k and $C_{12\beta}$-5k. *p*-(*p*′-Fluorobenzyloxymethyl)phenyl ketone **7k** (175 mg, 0.441 mmol) was treated according to general procedure 3b. The crude reaction mixture was purified by column chromatography (Florisil, 1% → 20% EtOAc/hexanes) to give 12α-methoxytrioxane **5k** (58 mg, 0.14 mmol, 13%), 12*β*-methoxytrioxane **5k** (65 mg, 0.15 mmol, 14%), impure diketone **14k**, and an impure mixture of mono- and di-O-silylated species arising from **14k**. The latter material was treated according to general procedure 4 (excess Bu_4NF). The crude product from this reaction was combined with the other portion of impure diketone **14k** and purified by column chromatography (flash gel, 5% → 50% EtOAc/hexanes) to give diketone **14k** (217 mg, 0.589 mmol, 55%).

Further purification of trioxane $C_{12\alpha}$-**5k** by HPLC (silica, 20% EtOAc/CH_2Cl_2, 1.5 mL/min, 274 nm, t_R = 9.5 min) afforded a white solid: mp = 90.0−91.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2 H), 7.33 (m, 4 H), 7.03 (m, 2 H), 5.18 (s, 1 H), 4.54 (s, 2 H), 4.49 (s, 2 H), 3.62 (s, 3 H), 2.84 (ddd, J = 14.8, 13.2, 3.6 Hz, 1 H), 2.42 (m, 1 H), 2.27 (ddd, J = 14.4, 4.8, 2.4 Hz, 1 H), 1.90 (m, 1 H), 1.83−1.71 (m, 4 H), 1.70−1.59 (m, 1 H), 1.33−1.16 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, J_{C-F} = 244 Hz), 139.8, 138.5, 133.7 (d, J_{C-F} = 3.0 Hz), 129.3 (d, J_{C-F} = 8.3 Hz), 127.2, 125.3, 115.0 (d, J_{C-F} = 21.3), 103.7, 95.9, 83.3, 71.5, 71.1, 55.8, 45.2, 37.4, 33.2, 32.3, 27.0, 25.1, 23.0; IR ($CHCl_3$) 3019, 2933, 2863, 1511, 1210, 1100, 1013, 752 cm^{-1}; LRMS (CI, CH_4, rel intensity) 427 (M − H$^+$, 3), 397 (15), 369 (33), 243 (58), 169 (24), 125 (29), 109 (100), 61 (81); HRMS (CI, CH_4) m/z calcd for $C_{25}H_{28}O_5F_1$ (M − H$^+$) 427.1921, found 427.1910.

Further purification of trioxane $C_{12\beta}$-**5k** by HPLC (silica, 5% EtOAc/hexanes, 4.0 mL/min, 264 nm, t_R = 14.5 min) afforded a white solid: mp = 59.0−61.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2 H), 7.32 (m, 4 H), 7.03 (m, 2 H), 5.14 (d, J = 1.2 Hz, 1 H), 4.54 (s, 2 H), 4.48 (s, 2 H), 3.64 (s, 3 H), 2.78 (ddd, J = 14.4, 13.2, 3.6 Hz, 1 H), 2.29 (ddd, J = 14.8, 4.4, 3.2 Hz, 1 H), 2.02−1.89 (m, 2 H), 1.81−1.59 (m, 5 H), 1.20 (apparent

dt, J_d = 5.2 Hz, J_t = 13.6 Hz, 1 H) overlapping 1.21 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (d, J_{C-F} = 244 Hz), 140.2, 138.6, 133.8 (d, J_{C-F} = 3.0 Hz), 129.5 (d, J_{C-F} = 8.4 Hz), 127.5, 125.4, 115.2 (d, J_{C-F} = 21.3 Hz), 105.1, 150.0, 83.8, 71.7, 71.3, 57.2, 47.5, 39.1, 65.6, 30.8, 26.8, 25.1, 23.8; IR ($CHCl_3$) 3034, 3011, 2933, 2862, 1604, 1511, 1230, 1139, 1104, 785 cm^{-1}; LRMS (CI, NH_3, rel intensity) 429 (M + H$^+$, 20), 397 (5), 369 (100), 154 (14), 126 (13); HRMS (CI, NH_3) *m/z* calcd for $C_{25}H_{30}O_5F$ (M + H$^+$) 429.2077, found 429.2088.

Further purification of diketone **14k** by HPLC (silica, 30% EtOAc/hexanes, 3.0 mL/min, 260 nm, t_R = 12.5 min) afforded a cloudy film: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2 H), 7.44 (br d, 2 H), 7.33 (m, 2 H), 7.05 (m, 2 H), 4.59 (s, 2 H), 4.53 (s, 2 H), 3.04 (ddABq, J_d = 8.4, 6.4 Hz, J_{AB} = 17.2 Hz, $\Delta\nu_{AB}$ = 64.8 Hz, 2 H), 2.43 (m, 2 H), 2.31 (m, 1 H), 2.19−2.04 (m, 3 H), 1.88 (m, 1 H), 1.75−1.64 (m, 3 H), 1.46 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 199.8, 162.3 (d, J_{C-F} = 244 Hz), 143.4, 136.1, 133.6 (d, J_{C-F} = 3.1 Hz), 129.4 (d, J_{C-F} = 8.3 Hz), 128.3, 127.4, 115.3 (d, J_{C-F} = 21.3), 71.7, 71.4, 50.0, 42.2, 36.4, 34.6, 28.1, 25.1, 24.6; IR ($CHCl_3$) 3029, 3012, 2939, 2863, 1705, 1681, 1609, 1511, 1231, 1086, 826, 668 cm^{-1}; LRMS (EI, rel intensity) 368 (M$^+$, 6), 258 (71), 242 (47), 148 (47), 133 (100), 123 (54), 109 (83), 77 (33); HRMS (EI) *m/z* calcd for $C_{23}H_{25}O_3F$ (M$^+$) 368.1788, found 368.1785.

***p*-Fluorophenyl Ketone 7l.** (*Z*)-Methoxyethylidene-2-(2′-cyanoethyl)cyclohexanone[16,29] (732 mg, 4.08 mmol) was treated according to general procedure 2a (1.5 equiv of aryl bromide, 1.4 equiv of *t*-BuLi) using *p*-fluorophenyl bromide. The crude product was purified by column chromatography (flash gel, 1% → 5% EtOAc/hexanes) to give the desired product **7l** (1.03 g, 3.73 mmol, 91%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2 H), 7.11 (m, 2 H), 5.79 (d, J = 2.0 Hz, 1 H), 3.41 (s, 3 H), 2.97−2.81 (m, 3 H), 2.00 (m, 2 H), 1.82 (m, 1 H), 1.74 (m, 2 H), 1.65 (m, 1 H), 1.53 (m, 3 H), 1.21 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 165.3 (d, J_{C-F} = 253 Hz), 140.4, 133.7 (d, J_{C-F} = 3.0 Hz), 130.4 (d, J_{C-F} = 9.1 Hz), 118.8, 115.3 (d, J_{C-F} = 22.0 Hz), 59.0, 36.6, 32.5, 31.6, 28.2, 26.4, 25.7, 21.6; IR (neat) 3068, 2927, 2853, 1683, 1598, 1506, 1232, 1124, 836 cm^{-1}; LRMS (EI, rel intensity) 276 (M$^+$, 7), 244 (4), 138 (100), 123 (24), 95 (15); HRMS (EI) *m/z* calcd for $C_{17}H_{21}O_2F$ (M$^+$) 276.1525, found 276.1532.

3-(*p*-Fluorophenyl)trioxanes $C_{12\alpha}$-5l and $C_{12\beta}$-5l. *p*-Fluorophenyl ketone **3** (270 mg, 0.977 mmol) was treated according to general procedure 3a. The crude reaction mixture was purified by column chromatography (Florisil, 1% → 10% EtOAc/hexanes) to give 12α-methoxytrioxane **5l** (60 mg, 0.19 mmol, 20%), 12*β*-methoxytrioxane **5l** (100 mg, 0.324 mmol, 33%), impure diketone **14l**, and an impure mixture of mono- and di-O-silylated species arising from **14l**. The latter material was treated according to general procedure 4 (excess Bu_4NF). The crude product from this reaction was combined with the other portion of impure diketone **14l** and purified by column chromatography (flash gel, 5% → 50% EtOAc/hexanes) to give diketone **14l** (78 mg, 0.314 mmol, 32%).

Further purification of trioxane $C_{12\alpha}$-**5l** by HPLC (C-18, 10% water/methanol, 3.0 mL/min, 260 nm, t_R = 9.3 min) afforded a white solid: mp = 97.0−98.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2 H), 7.03 (m, 2 H), 5.17 (s, 1 H), 3.61 (s, 3 H), 2.83 (ddd, J = 14.4, 13.2, 3.6 Hz, 1 H), 2.41 (m, 1 H), 2.25 (ddd, J = 14.4, 4.8, 2.4 Hz, 1 H), 1.89 (m, 1 H), 1.82−1.70 (m, 4 H), 1.62 (m, 1 H), 1.30−1.15 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (d, J_{C-F} = 246 Hz), 136.4 (d, J_{C-F} = 3.0 Hz), 127.4 (d, J_{C-F} = 8.3 Hz), 115.0 (d, J_{C-F} = 22.0 Hz), 103.6, 96.2, 83.6, 56.1, 45.3, 37.5, 33.3, 32.5, 27.1, 25.2, 23.1; IR ($CHCl_3$) 3032, 2934, 2863, 1604, 1512, 1452, 1235, 1101 cm^{-1}; LRMS (CI, NH_3, rel intensity) 326 (M + NH_4^+, 19), 309 (M + H$^+$, 86), 277 (30), 249 (100), 138 (18); HRMS (CI, NH_3) *m/z* calcd for $C_{17}H_{22}O_4F$ (M + H$^+$) 309.1502, found 309.1503.

Further purification of trioxane $C_{12\beta}$-**5l** by HPLC (C-18, 2% water/methanol, 3.0 mL/min, 270 nm, t_R = 6.3 min) afforded a white solid: mp = 87.0−88.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 2 H), 7.03 (m, 2 H), 5.13 (d, J = 1.2 Hz), 3.64 (s, 3 H), 2.78 (ddd, J = 14.4, 13.2, 3.6 Hz, 1 H), 2.28 (ddd, J = 14.4, 4.8, 3.2 Hz, 1 H), 2.01−1.87 (m, 2 H), 1.80−1.59 (m, 7 H), 1.30 (apparent dt, J_d = 4.8 Hz, J_t = 13.6 Hz, 1 H), 1.21 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (d, J_{C-F} = 246 Hz), 136.7 (d, J_{C-F} = 3.0 Hz), 127.2 (d, J_{C-F} = 8.4 Hz), 115.0 (d, J_{C-F} = 21.2 Hz), 105.1, 104.7, 83.7, 57.1, 47.4, 39.1, 35.6, 30.8, 26.8, 25.0, 23.8; IR ($CHCl_3$) 3034, 3012, 2934, 2863, 1604, 1512, 1447, 1235, 1139, 1106 cm^{-1}; LRMS (CI, NH_3, rel intensity) 326 (M + NH_4^+, 12), 309 (M + H$^+$, 100), 277 (11), 249 (71), 138 (17); HRMS (CI, NH_3) *m/z* calcd for $C_{17}H_{22}O_4F$ (M + H$^+$) 309.1502, found 309.1506.

Further purification of diketone **14l** by HPLC (silica, 8% EtOAc/hexanes, 4.0 mL/min, 270 nm, t_R = 18.2 min) afforded a white solid: mp = 63.0−64.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (m, 2 H), 7.12 (m, 2 H), 3.02 (dd AB q, J_d = 8.8, 6.0 Hz, J_{AB} = 16.8 Hz, $\Delta\nu_{AB}$ = 70.8 Hz, 2 H), 2.48−2.27 (m, 3 H), 2.18−2.03 (m, 3 H), 1.88 (m, 1 H), 1.76−1.64 (m, 3 H), 1.46 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 198.6, 165.6 (d, J_{C-F} = 253 Hz), 133.1 (d, J_{C-F} = 3.0 Hz), 130.7 (d, J_{C-F} = 9.1 Hz), 115.5 (d, J_{C-F} = 22.0 Hz), 49.9, 42.2, 36.3, 34.6, 28.1, 25.1, 24.6; IR ($CHCl_3$) 3022, 2940, 2863, 1705, 1683, 1599, 1508, 1224, 1156, 764 cm^{-1}; LRMS (EI, rel intensity) 248 (M$^+$, 8), 138 (100), 123 (54), 95 (21); HRMS (EI) *m/z* calcd for $C_{15}H_{17}O_2F$ (M$^+$) 248.1213, found 248.1216.

***p*-Fluoro-*o*-methylphenyl Ketone 7m.** (*Z*)-Methoxyethylidene-2-(2′-cyanoethyl)cyclohexanone[16,29] (450 mg, 2.51 mmol) was treated according to general procedure 2a (1.6 equiv of aryl bromide, 1.5 equiv of *t*-BuLi) using *p*-fluoro-*o*-methylphenyl bromide. The crude product was purified by column chromatography (short path, 1% → 20% EtOAc/hexanes) to give the desired product **7m** (476 mg, 1.64 mmol, 65%) as a pale yellow oil.

3-(*p*-Fluoro-*o*-methylphenyl)trioxanes $C_{12\alpha}$-5m and $C_{12\beta}$-5m. *p*-Fluoro-*o*-methylphenyl ketone **7m** (230 mg, 0.792 mmol) was treated according to general procedure 2a. The crude reaction mixture was purified by column chromatography (Florisil, 1% → 20% EtOAc/hexanes) to give 12α-methoxytrioxane **5m** (40 mg, 0.12 mmol, 16%), 12*β*-methoxytrioxane **5m** (50 mg, 0.16 mmol, 20%), impure diketone **14m**, and an impure mixture of mono- and di-O-silylated species arising from **14m**. The latter material was treated according to general procedure 4 (excess Bu_4NF). The crude product from this reaction was combined with the other portion of impure diketone **14m** and purified by column chromatography (flash gel, 5% → 50% EtOAc/hexanes) to give diketone **14m** (116 mg, 0.442 mmol, 56%).

Further purification of trioxane $C_{12\alpha}$-**5m** by HPLC (silica, 4% EtOAc/hexanes, 3.0 mL/min, 254 nm, t_R = 13.7 min) afforded a white solid: mp = 112.0−113.0 °C.

Further purification of trioxane $C_{12\beta}$-**5m** by HPLC (silica, 1% EtOAc/hexanes, 3.0 mL/min, 254 nm, t_R = 10.4 min) afforded a white solid: mp = 97.0−99.0 °C.

Further purification of diketone **14m** by HPLC (silica, 10% EtOAc/hexanes, 4.0 mL/min, 264 nm, t_R = 18.8 min) afforded a white solid: mp = 38.5−39.5 °C.

***p*-Trifluoromethylphenyl Ketone 7n.** (*Z*)-Methoxyethylidene-2-(2′-cyanoethyl)cyclohexanone[16,29] (400 mg, 2.23 mmol) was treated according to general procedure 2a using methyl *p*-(trifluoromethyl)phenyl bromide. The crude product was purified by column chromatography (flash gel, 1% → 20% EtOAc/hexanes) to afford the desired product **7n** (557 mg, 1.71 mmol, 77%) as a yellow oil.

3-(*p*-(Trifluoromethyl)phenyl) trioxanes $C_{12\alpha}$-5n and $C_{12\beta}$-5n. *p*-(Trifluoromethyl)phenyl ketone **7n** (390 mg, 1.09 mmol) was treated according to general procedure 3a. The crude reaction mixture was purified by column chromatography (Florisil, 1% → 20% EtOAc/hexanes) to give $C_{12\alpha}$-methoxytrioxane **5n** (13 mg, 0.033 mmol, 3%), $C_{12\beta}$-methoxytrioxane **5n** (30 mg, 0.077 mmol, 7%) impure diketone **14n**, and an impure mixture of mono- and di-O-silylated species arising from **14n**. The latter material was treated according to general procedure 4 (excess Bu_4NF). The crude product from this reaction was combined with the other portion of impure diketone **14n** and purified by column chromatography (flash gel, 5% → 50% EtOAc/hexanes) to give diketone **14n** (216 mg, 0.724 mmol, 66%).

Further purification of trioxane $C_{12\alpha}$-**5n** by HPLC (silica, 5% EtOAc/hexanes, 3.0 mL/min, 254 nm, t_R = 12.7 min) afforded a white solid: mp = 137.0−138.0 °C.

Further purification of trioxane $C_{12\beta}$-**5n** by HPLC (silica, 3% EtOAc/hexanes, 3.0 mL/min, 254 nm, t_R = 7.3 min) afforded a white solid: mp = 97.0−98.0 °C.

Further purification of diketone **14n** by HPLC (silica, 20% EtOAc/hexanes, 3.0 mL/min, 284 nm, t_R = 12.6 min) afforded a white solid: mp = 53.5−54.0 °C.

Sulfoxide Enol Ether 9. To a suspension of (methoxymethyl)triphenylphosphonium chloride (1.42 g, 4.14 mmol) in THF (15 mL) at −78 °C was added dropwise via syringe PhLi (1.77 M in 70% cyclohexane/ether, 2.34 mL, 4.14 mmol). This mixture was warmed to room temperature and stirred for 3 h. The resulting dark red solution was cooled to −78 °C, and a solution of 2-(2′-phenylsulfoxyethyl)cyclohexanone[35] (0.650 g, 2.60 mmol) in THF (10 mL) was added dropwise by cannula. The resulting mixture was then allowed to warm to room temperature over 5 h and was stirred for an additional 5 h. At that time, the reaction was quenched with H_2O (25 mL), extracted with EtOAc, dried over anhydrous $MgSO_4$, and concentrated. Purification by column chromatography (flash gel, 50% EtOAc/hexanes) afforded the desired product **9** (644 mg, 2.32 mmol, 89%) as a roughly equal mixture of the four diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 8 H), 7.51 (m, 12 H), 5.81 (s, 1 H), 5.80 (s, 1 H), 5.71 (s, 1 H), 5.69 (s, 1 H), 3.53 (s, 3 H), 3.52 (s, 3 H), 3.49 (s, 3 H), 3.47 (s, 3 H), 2.96 (m, 1 H), 2.75 (m, 8 H), 2.25 (m, 2 H), 2.10−1.20 (m, 41 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 143.99, 143.97, 143.88, 140.67, 140.65, 139.89, 139.86, 130.9, 130.8, 130.7, 130.6, 129.1, 129.0, 128.97, 124.1, 123.99, 123.98, 123.92, 118.8, 118.0, 117.9, 59.4, 59.21, 59.18, 55.8, 55.7, 55.5, 55.3, 38.3, 37.9, 33.4, 33.3, 32.4, 31.9, 31.53, 31.46, 28.1, 27.0, 26.3, 26.2, 24.1, 23.7, 23.5, 23.4, 22.8, 22.43, 22.38, 21.54, 21.51; IR ($CHCl_3$) 2927, 2852, 1676, 1444, 1127, 1043, 748, 693 cm^{-1}; LRMS (CI, NH_3, rel intensity) 279 (M + H$^+$, 100), 265 (40); HRMS (CI, NH_3) *m/z* calcd for $C_{16}H_{23}SO_2$ (M + H$^+$) 279.1419, found 279.1423.

Trifluoropropyl Ketone 10a. Sulfoxide enol ether **9** (1.20 g, 4.32 mmol) was treated according to general procedure 2b using ethyl 4,4,4-trifluorobutyrate (acylated sulfoxide was passed through silica before reduction). Purification of the crude product by column chromatography (flash gel, 90% EtOAc/hexanes) afforded pure ketone **10a** (120 mg, 0.431 mmol, 37%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (d, J = 2.0 Hz, 1 H), 3.48 (s, 3 H), 2.75 (m, 1 H), 2.67 (m, 2 H), 2.47−2.30 (m, 4 H), 1.96−1.49 (m, 9 H), 1.25−1.13 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.6, 140.4, 127.0 (q, J_{C-F} = 276 Hz), 118.8, 59.1, 40.7, 35.0 (q, J_{C-F} = 2.2 Hz), 32.3, 31.7, 28.2, 27.9 (q, J_{C-F} = 29.8 Hz), 26.4, 25.2, 21.6; IR ($CHCl_3$) 2929, 2855, 1720, 1678, 1442, 1307, 1255, 1237, 1127, 1104 cm^{-1}; LRMS (EI, rel intensity) 278 (M$^+$, 9), 138 (100), 125 (44), 123 (12), 93 (10); HRMS (EI) *m/z* calcd for $C_{14}H_{21}O_2F_3$ (M$^+$) 278.1494, found 278.1499.

3-(Trifluoropropyl)trioxane 6a. Trifluoropropyl ketone **10a** (106 mg, 0.381 mmol) was treated according to general procedure 3a (irradiation for 2 h). The crude reaction mixture was purified by column chromatography (flash gel, 10% EtOAc/hexanes) to give $C_{12\beta}$-methoxytrioxane **6a** (36 mg, 0.116 mmol, 30%).

Further purification of trioxane **6a** by HPLC (silica, 0.6% *i*-PrOH/hexanes, 3.0 mL/min, 235 nm, t_R = 5.4 min) afforded a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (s, 1 H), 3.52 (s, 3 H), 2.38−2.14 (m, 3 H), 2.00 (ddd, J = 14.4, 4.4, 3.2 Hz, 1 H), 1.93 (apparent dt, J_d = 10.8 Hz, J_t = 6.4 Hz, 1 H), 1.84 (m, 2 H), 1.70−1.53 (m, 8 H), 1.28−1.13 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.0 (q, J_{C-F} = 274 Hz), 104.8 (q, J_{C-F} = 3.1 Hz),104.3, 83.8, 57.1, 47.4, 36.9, 35.5, 32.1 (q, J_{C-F} = 2.3 Hz), 30.8, 27.7 (q, J_{C-F} = 29.6 Hz), 26.5, 25.0, 23.7; IR ($CHCl_3$) 2931, 2863, 1449, 1396, 1324, 1256, 1208, 1110, 1004, 968 cm^{-1}; LRMS (CI, NH_3, rel intensity) 328 (M + NH_4^+, 100), 311 (M + H$^+$, 63), 293 (27), 279 (27), 278 (M$^+$ − O_2, 6), 268 (71), 251 (92), 138 (13), 118 (22), 100 (37); HRMS (CI, NH_3) *m/z* calcd for $C_{14}H_{22}O_4F_3$ (M + H$^+$) 311.1470, found 311.1476.

Fluoromethyl Ketone 10b. Sulfoxide enol ether **9** (1.41 g, 5.07 mmol) was treated according to general procedure 2b using ethyl fluoroacetate (acylated sulfoxide was used crude in reduction). The crude product was purified by column chromatography (flash gel, 90% EtOAc/hexanes) to afford pure ketone **10b** (286 mg, 1.33 mmol, 26%) as an oil.

3-(Fluoromethyl)trioxanes $C_{12\alpha}$-6b and $C_{12\beta}$-6b. Fluoromethyl ketone **10b** (281 mg, 1.31 mmol) was treated according to general procedure 3a (20 mL CH_2Cl_2, irradiation for 2 h). The crude product was purified by column chromatography (flash gel, 10% EtOAc/hexanes) to give $C_{12\alpha}$-methoxytrioxane **6b** (17 mg, 0.069 mmol, 5%) and $C_{12\beta}$-methoxytrioxane **6b** (132 mg, 0.537 mmol, 41%).

Further purification of trioxane $C_{12\alpha}$-**6b** by recrystallization afforded a white solid: mp = 75.0−76.0 °C.

Further purification of trioxane $C_{12\beta}$-**6b** by recrystallization afforded a white solid: mp = 80.0−81.0 °C.

4β-Methyl-3-phenyl-12α-methoxytrioxane 12. To a freshly prepared solution of LDA (2.96 mmol) in THF/hexane (3.5 mL/2.5 mL) at −78 °C was added a precooled solution of (*Z*)-methoxyethylidene-2-(2′-cyanoethyl)cyclohexanone[16,29] (483 mg, 2.69 mmol) in THF (20 mL). After 5 min of stirring at −78 °C for 5 min, the reaction mixture was warmed to room temperature and stirred for 15 min. This bright yellow enolate solution was cooled to −78 °C, and methyl iodide (0.17 mL, 2.8 mmol) was added dropwise via syringe. After the addition, 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 addition of H_2O (5 mL). The resulting mixture was diluted with H_2O (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 $MgSO_4$, filtered, and concentrated under reduced pressure. This crude product was purified by column chromatography (short path, 1% → 5% EtOAc/hexane) to give the desired alkylated nitriles (472 mg, 2.44 mmol, 91%), a 1:1 diastereomeric mixture, as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (m, 2 H), 3.53 (s, 3 H), 3.51 (s, 3 H), 3.08 (m, 1 H), 2.96 (m, 1 H), 2.50 (m, 2 H), 2.10 (ddd, J = 13.6, 11.2, 5.2 Hz, 1 H), 2.00−1.80 (m, 4 H), 1.74 (m, 3 H), 1.63−1.50 (m, 7 H), 1.45 (m, 3 H), 1.32 (d, J = 2.8 Hz, 3 H), 1.30 (d, J = 3.2 Hz, 3 H), 1.22 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 141.0, 124.0, 123.5, 117.4, 117.1, 59.09, 59.08, 36.7, 35.4, 31.7, 31.4, 31.2, 30.1, 28.07, 28.06, 26.4, 26.2, 23.9, 22.8, 21.8, 21.4, 18.6, 17.3; IR (neat) 3057, 2930, 2854, 2238, 1677, 1449, 1240, 1129, 839 cm^{-1}; LRMS (EI, rel intensity) 193 (M$^+$, 11), 125 (100), 93 (24), 45 (12); HRMS (EI) *m/z* calcd for $C_{12}H_{19}NO$ (M$^+$) 193.1467, found 193.1469.

To a solution of these 4-methylated nitriles (100 mg, 0.517 mmol) in ether (4.5 mL) at −78 °C was added via syringe a solution of phenyllithium (1.8 M in 70% cyclohexane/ether, 0.86 mL, 2.6 mmol). This dark brown solution was stirred at −78 °C for 15 min, then warmed to room temperature, and stirred for 3 h. At that time, the reaction was cooled to 0 ° C and quenched by dropwise addition of H_2O (1 mL). The resulting mixture was diluted with H_2O (20 mL) and ether (20 mL). The organic phase was separated, and the aqueous phase was extracted with ether (20 mL × 2). The organic portions were combined, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. This crude product was purified by column chromatography (short path, 1% → 10% EtOAc/hexane) to give the desired ketones (138 mg, 0.507 mmol, 98%), a 2:1 diastereomeric mixture, as a yellow oil: *italics in NMR data indicate minor isomer where discernible,* ^{1}H NMR (400 MHz, $CDCl_3$) δ *7.97 (m, 2 H),* 7.92 (m, 2 H), *7.53 (m, 3 H),* 7.44 (m, 3 H), 5.69 (m, 2 H), 3.41 (m, 1 H) overlapping 3.37 (s, 3 H), *3.02 (m, 1 H) overlapping 3.01 (s, 3 H), 2.83 (m, 1 H),* 2.29 (ddd, J = 13.6, 12.4, 5.2 Hz, 1 H), 2.03−1.90 (m, 3 H), 1.83−1.69 (m, 5 H), *1.63 (m, 2 H),* 1.55−1.42 (m, 8 H), 1.27−1.12 (m, 2 H) overlapping 1.22 (d, J = 6.8 Hz, 3 H) and 1.17 *(d,* J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, *204.1,* 140.9, *140.0, 136.9,* 136.7, 132.4, *132.3,* 128.4, *128.28, 128.27,* 128.2, *118.9,*

118.7, 59.0, *58.4*, 39.1, *38.6*, 35.7, *34.5*, 32.4, *31.7*, 31.4, *30.9*, 28.4, *26.54*, 26.48, 21.63, *21.61*, *19.2*, 17.2; IR (neat) 3060, 2927, 2852, 1682 (2 peaks overlapping), 1579, 1448, 1205, 1128, 703 cm^{-1}; LRMS (EI, rel intensity) 272 (M^+, 2), 138 (100), 123 (16), 105 (23), 77 (28); HRMS (EI) *m/z* calcd for $C_{18}H_{24}O_2$ (M^+) 272.1776, found 272.1779.

This mixture of 4-methylated 3-phenyl ketones (100 mg, 0.367 mmol) was treated according to general procedure 3a. The crude reaction mixture was purified by column chromatography (Florisil, 1% → 20% EtOAc/hexanes) to give 4β-methyltrioxane **12** (23 mg, 0.076 mmol, 21%). Further purification of of this material by HPLC (silica, 3% EtOAc/hexanes, 2.0 mL/min, 254 nm, t_R = 26.1 min) afforded a white solid: mp = 105.0−106.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 2 H), 7.31 (m, 3 H), 5.14 (s, 1 H), 3.52 (s, 3 H), 7.85 (m, 1 H), 2.41 (m, 1 H), 1.83 (m, 2 H), 1.73 (m, 3 H), 1.40 (m, 1 H), 1.30−1.13 (m, 4 H), 0.48 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 128.3, 127.8, 125.7, 106.6, 95.5, 82.9, 55.7, 44.5, 40.0, 37.6, 33.3, 32.5, 25.3, 23.1, 21.2; IR ($CHCl_3$) 3032, 3012, 2933, 2861, 1450, 1262, 1094, 1010, 700 cm^{-1}; LRMS (CI, NH_3, rel intensity) 322 (M + NH_4^+, 25), 305 (M + H^+, 100), 245 (96), 168 (28), 138 (58), 105 (44); HRMS (CI, NH_3) *m/z* calcd for $C_{18}H_{25}O_4$ (M + H^+) 305.1753, found 305.1758.

Formation of Aryl Ketone 13 by Iron-Induced Degradation of 5l. To a stirred suspension of iron(II) bromide (0.10 g, 0.46 mmol) in THF (3 mL) at 0 °C was added a 0 °C solution of **5l** (0.20 g, 0.65 mmol) in THF (3.5 mL) via cannula. The reaction was stirred at 0 °C for 45 min and then slowly warmed to room temperature. When TLC indicated that all starting material was consumed (about 1 h), the reaction was quenched with H_2O (3 mL) and diluted with $CHCl_3$ (15 mL). The two layers were separated, and the aqueous was extracted with $CHCl_3$ (15 mL × 2). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude mixture of products.[28] Separation by column chromatography (Florisil, 1% → 30% EtOAc/hexanes) afforded impure **13** that was combined with another portion of impure **13** from a second degradation of **5l** (0.15 g, 0.49 mmol). Column chromatography of this combined sample (Florisil, 1% → 30% EtOAc/hexanes) provided aryl ketone **13** (7.5 mg, 0.024 mmol, 2% for both degradations). Further purification of this material by HPLC (silica, 10% *i*-PrOH/hexanes, 3.0 mL/min, 245 nm, t_R = 10.8 min) afforded a white solid: mp = 79.5−80.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (m, 2 H), 7.15 (m, 2 H), 5.16 (dd, J = 11.6, 2.8 Hz, 1 H), 4.38 (s, 1 H), 3.52 (s, 3 H), 2.23 (d, J = 2.0 Hz, 1 H), 2.10−2.00 (m, 4 H), 1.68 (m, 2 H), 1.45−1.39 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 165.8 (d, J_{C-F} = 253 Hz), 131.5 (d, J_{C-F} = 3.7 Hz), 131.4 (d, J_{C-F} = 9.1 Hz), 115.8 (d, J_{C-F} = 22.0 Hz), 104.8, 71.2, 69.8, 56.4, 36.0, 30.9, 29.1, 26.1, 21.0, 20.1; IR ($CHCl_3$) 3568, 3016, 2938, 2867, 1694, 1599, 1234, 1218, 758; LRMS (CI, NH_3, rel intensity) 326 (M + NH_4^+, 7), 309 (M + H^+, 6), 291 (4), 277 (100); HRMS (CI, NH_3) *m/z* calcd for $C_{17}H_{22}O_4F$ (M + H^+) 309.1502, found 309.1506.

Acknowledgment. We thank the NIH (AI-34885 and NCRR OPD-GCRC RR00722) and the Burroughs Wellcome Fund for financial support and Professor Wallace Peters and Mr. Brian Robinson for the in vivo antimalarial results reported here. We thank also the NIAID contract services for the preliminary in vivo acute toxicity experiments.

Supporting Information Available: ^{1}H and ^{13}C NMR, IR, and mass spectral data for those compounds for which such spectroscopic characterization is not provided in the experimental section of this paper (11 pages). Ordering information is given on any current masthead page.

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JM970686E