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Synthesis and Antimalarial Activities of Structurally Simplified 1,2,4-Trioxanes Related to Artemisinin

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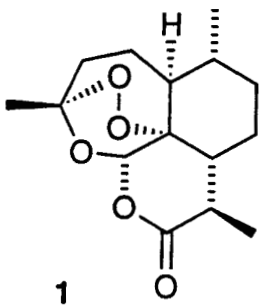
ABSTRACT

Eleven derivatives of the clinically useful, antimalarial, 1,2,4-trioxane artemisinin have been synthesized in only several steps from commercial cyclohexanones. Of these simple, tricyclic 1,2,4-trioxanes, 10 showed considerable in vitro antimalarial activity, with one being as potent as artemisinin. Some structure-activity relationship generalizations are made from this series of artemisinin analogs. Triethylsilyl hydrotrioxide ($Et_3SiOOOH$), prepared in situ from ozone and triethylsilane, is shown to be a mild, fast-acting, and effective dioxetane-forming reagent with vinyl ethers and with a vinyl thioether on relatively small (50–100 mg) scale.

INTRODUCTION

Malaria is an infectious disease that kills 1–2 million people each year; children especially are at risk [1]. International efforts at preventing the spread of malaria by using bed nets [2] and by developing prophylactic vaccines [3] are underway. Although chemotherapy for malaria patients has been effective, malaria parasites are developing rapidly increasing multidrug resistance to such standard medicines as the natural alkaloid quinine and the synthetic alkaloid chloroquine [4]. Therefore, a worldwide search has been mounted seeking new classes of nonalkaloidal antimalarial compounds to which malaria parasites are not (yet) resistant. Indigenous practitioners of Chinese folk medicine have used an extract of the qinghao plant (*Artemisia annua* L. *compositae*) for more than a thousand years as a treatment for fevers, including malaria fever [5]. In 1972, the active component of this tea brew was isolated and identified as the nonalkaloidal, sesquiterpene lactone, 1,2,4-trioxane artemisinin (qinghaosu, **1**) [6].



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In China during the past 20 years, well over 1 million malaria patients have been cured by treatment with artemisinin or one of its semisynthetic derivatives. No serious side effects of this medical regimen have been reported [7,8]. Many acres of

Dedicated to Prof. Shigeru Oae on the occasion of his seventy-fifth birthday.

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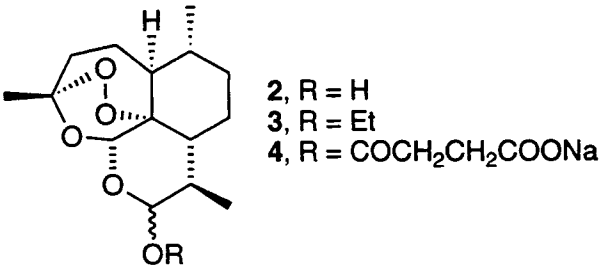
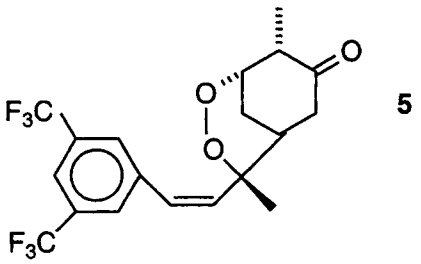
land are used to grow *Artemisia annua* as a supply for artemisinin or one of its semisynthetic derivatives. Organic chemists have devised various syntheses of artemisinin as well as of dihydroartemisinin (**2**) and its O-derivatives [9–22]. Indeed, dihydroartemisinin O-ethyl ether (arteether, **3**) and the water-soluble O-succinate half-ester sodium salt (sodium artesunate, **4**), more easily administered to patients than artemisinin, are now undergoing full clinical evaluation under World Health Organization auspices. Also, phase III clinical trials are now underway for the structurally related, laboratory-synthesized, peroxide arteflene (**5**) [23]. The peroxide linkages in these antimalarial drugs **1–5** are thought to be the trigger, activated by iron-induced reduction inside the malaria parasite, that releases plasmocidal-free radical intermediates [24–26].



2, R = H
3, R = Et
4, R = $COCH_2CH_2COONa$



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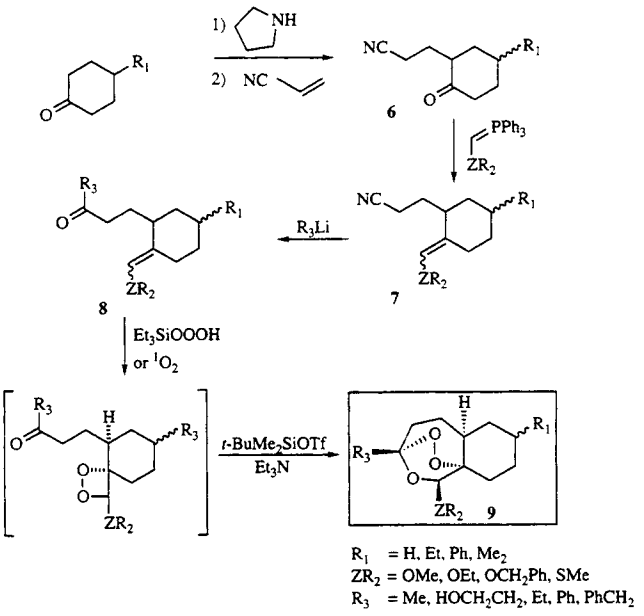
Various structurally simplified 1,2,4-trioxanes have been synthesized to probe structure-activity relationships (SARs) [27], to determine what is the essential pharmacophore, and to generate sufficiently simple and inexpensive analogs that would be accessible and economically reasonable by large-scale industrial synthesis [9–22]. Toward these goals, in 1991, we reported in preliminary fashion syntheses of two new, simple 1,2,4-trioxanes [28]. Herein, we disclose full details of synthesis and *in vitro* antimalarial assays of 11 different, structurally simplified versions of artemisinin, leading to some qualitative SAR generalizations.

RESULTS AND DISCUSSIONS

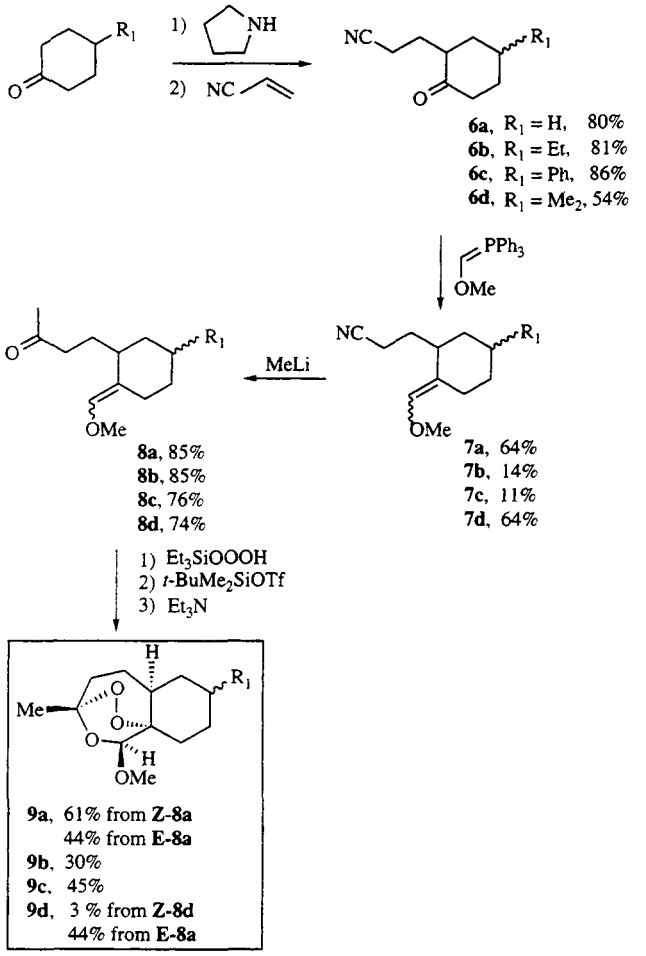
Following the seminal work in Geneva on conversion of keto vinyl ethers into 1,2-dioxetanes and then skeletal rearrangement into 1,2,4-trioxanes [19], we used the transformations outlined in Scheme 1 to prepare three series of structurally simplified 1,2,4-trioxanes in only four steps from commer-



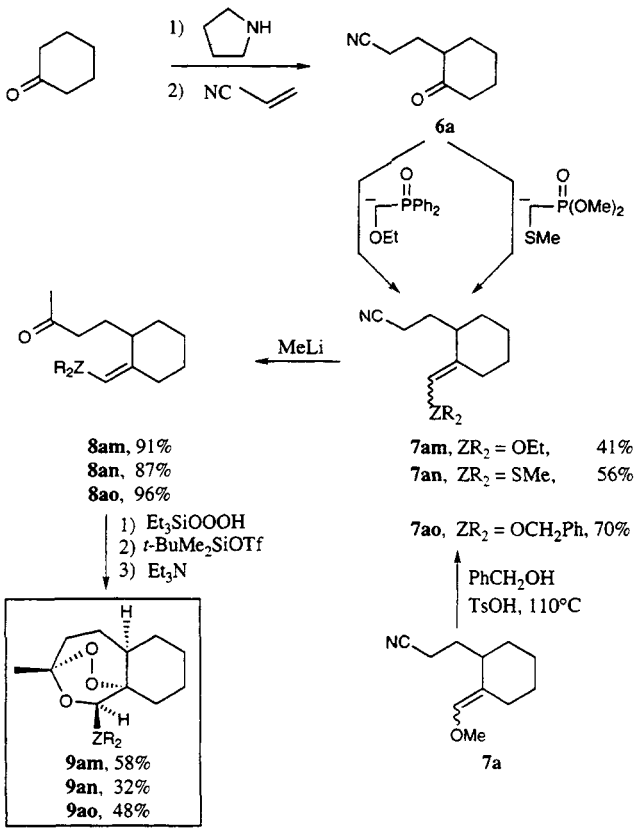
SCHEME 1

cial cyclohexanones. In the first series, only R_1 was varied. In the second series, only the acetal group ZR_2 was changed; and, in the third series, only the bridgehead R_3 group was altered.

Enamine alkylation of cyclohexanone and of its 4-substituted derivatives according to literature precedent [29] gave 2-cyanoethylcyclohexanones **6a–d** in 54–86% yields (Scheme 2). Wittig methoxymethylenation [30], using phenyllithium rather than the standard *n*-butyllithium to generate the phosphonium ylide, gave the vinyl ethers **7a** and **7d** in 64% yields as a roughly 1:1 mixture of geometric isomers that were easily separated by column chromatography; the 4-monosubstituted cyclohexane systems **7b** and **7c**, isolated in low yields, were difficult to purify because of the additional R_1-bearing stereogenic center. Methyllithium addition to nitriles **7** generated methyl ketones **8** in 74–85% yields. Using our protocol with the new dioxetane-forming reagent triethylsilyl hydrotrioxide ($Et_3SiOOOH$) [28], keto vinyl ethers **8** were converted into 1,2,4-trioxanes **9** in 3–61% yields. To compare $Et_3SiOOOH$ with singlet molecular oxygen ($^1O_2$) [31], keto vinyl ether *Z*-**8a** was treated separately with each of these oxygenating reagents. In contrast to the very rapid (<1 minute) $Et_3SiOOOH$ reaction that gave trioxane **9a** exclusively in 61% yield, the slower (>2 hours) $^1O_2$ reaction gave a 48% yield of trioxane **9a** plus 18% of its methoxy epimer. Noteworthy but still preplexing is the effect of vinyl ether geometry on the yield of trioxane; vinyl ethers *Z*-**8a** and *E*-**8a** gave trioxane **9a** in 61 and 44% yields, respectively, but vinyl ethers *Z*-**8d** and *E*-**8d** gave trioxane **9d** in 3 and 44% yields, respectively. The geometry of vinyl ethers



SCHEME 2

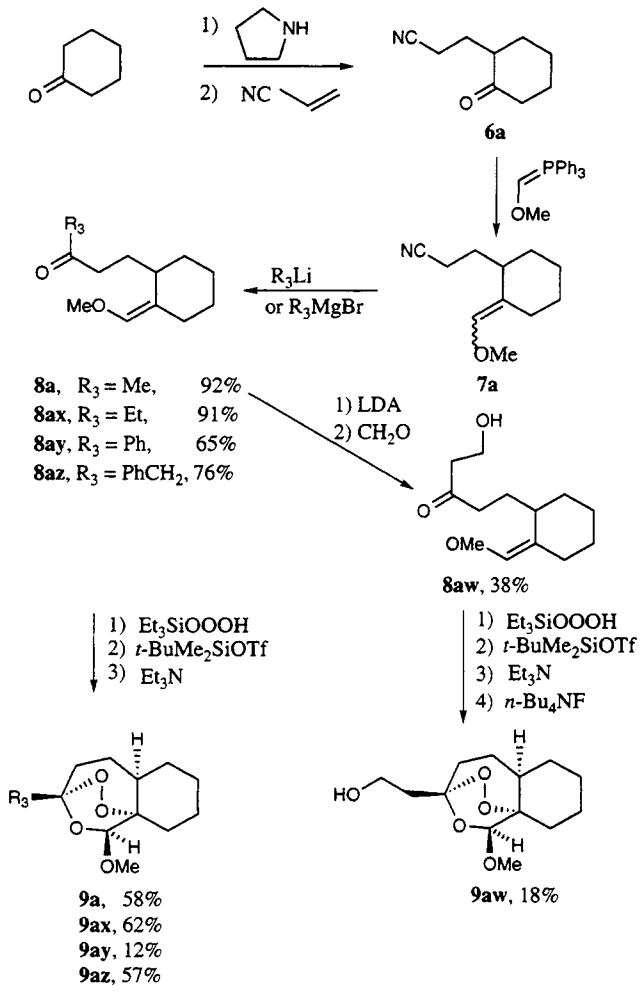


SCHEME 3

7 and **8** was determined by ^{1}H NMR spectroscopy (see the Experimental section). The orientation of the methoxy group in trioxanes **9** was assigned in many cases by considering the stereochemical relationship of the acetal hydrogen atom with the methine hydrogen atom three carbon atoms away; ^{1}H NMR W-coupling [32] (between the two hydrogen atoms shown explicitly in structure **9**) of 0.9–1.6 Hz was observed in 7 of the 11 trioxanes **9**.

Enamine alkylation of cyclohexanone followed by R_2Z-methylenation [33] gave vinyl ether **7am** and vinyl thioether **7an** as a mixture of geometric isomers in 41 and 56% yields, respectively (Scheme 3). Vinyl ether exchange [34] allowed conversion of methyl vinyl ether **7a** into benzyl vinyl ether **7ao** in 70% yield. Column chromatography allowed easy separation of the geometric isomers of these vinyl ethers, and subsequent reactions were performed on the *Z*-isomers only. Addition of methyllithium to the nitrile group of the cyanoethyl substituent gave methyl ketones **8am–8ao** in 87–96% yields. Treatment with triethylsilyl hydrotrioxide [35] produced 1,2,4-trioxanes **9am–9ao** in 32–58% yields. Noteworthy is the formation of only diastereomer **9am** and **9ao** in this dioxetane-mediated process, whereas in the case of methylthio-trioxane **9an**, two diastereomers were formed, differing only in the orientation of the methylthio group, with only that **9an** diastereomer shown in Scheme 3 showing a ^{1}H NMR W-coupling between the two hydrogen atoms shown explicitly in structure **9an**; this mixture of diastereomeric trioxanes was formed also when the geometric isomer of the precursor vinyl thioether (i.e., *E*-**8ao**) was used. It is possible that the sulfur atom in the intermediate methylthio-substituted dioxetane provided sufficient stabilization for adjacent carbocation (i.e., zwitterion) formation to allow bond rotation leading to the mixture of trioxanes.

Enamine alkylation of cyclohexanone followed by Wittig methoxymethylenation, chromatographic separation of geometric isomers, and then nitrile addition using either organolithium (MeLi, PhLi) or organomagnesium halide (EtMgBr, $PhCH_2MgCl$) reagents gave *Z*-enol ether ketones **8ax–8az** (Scheme 4). Regioselective deprotonation of methyl ketone **8a** followed by reaction of the enolate with formaldehyde gave aldol product hydroxyethyl ketone **8aw**. Reaction of these enol ether ketones with $Et_3SiOOOH$ proceeded smoothly to generate the methyl, ethyl, and benzyl trioxanes **9a**, **9ax**, and **9az** [36], but low yields (12–18%) of



SCHEME 4

trioxanes were obtained from phenyl ketone **8ay** and hydroxyethyl ketone **8aw**. Also, the corresponding sterically hindered *t*-butyl ketone enol ether failed to produce any trioxane. Comparing the effectiveness of $Et_3SiOOOH$ with that of $^1O_2$ to convert phenyl ketone vinyl ether **8ay** into phenyl trioxane **9ay**, we found in this case that $^1O_2$ produced trioxane **9ay** (^1H NMR W-coupling J = 1.5 Hz) in higher yield (30%) than did $Et_3SiOOOH$ but accompanied by 12% of the trioxane having the opposite orientation of the acetal methoxy group, paralleling earlier results [19].

In Table 1 are listed the in vitro antimalarial activities of trioxanes **9** against *Plasmodium falciparum* parasites using the semiautomated microdilution method of Desjardins et al. [37] as modified by Milhous et al. [38]. In this assay, the incorporation of [^{3}H]-hypoxanthine into *Plasmodium falciparum* parasites serves as an index of viability of the parasites. The drugs were tested against the African Sierra Leone (D-6) and the Indochina (W-2) clone of *P. falciparum* parasites. The African Sierra Leone clone is resistant to mefloquine but sensitive to chloroquine, quinine, sulfadoxine, and pyrimethamine, whereas the Indochina clone is resistant to chloroquine, quinine, sulfadoxine, and pyrimethamine but sensitive to mefloquine. The results of these in vitro assays, summarized in Table 1, were analyzed by fitting the radioactivity uptake vs. drug concentration data to four parameters logistic regression. The concentration of each drug required to produce 50% inhibition (IC_{50}) of uptake of [^{3}H]-hypoxanthine compared to control was then derived from the best-fit concentration-response curve.

The antimalarial activities of trioxanes **9** support the following comments: (1) 10 of these 11 structurally simplified, tricyclic analogs of artemisinin have considerable antimalarial activity, reinforcing the generalization [9–22] that the 1,2,4-trioxane unit is the essential pharmacophore; (2) some of these simple and easily prepared analogs are very potent (e.g., **9d** and especially **9ao**), with antimalarial activities similar to that of artemisinin; (3) the vast majority of these analogs are selectively active in the chloroquine-resistant W-2 Indochina clone of malaria parasites, a result that may be useful eventually in helping to elucidate the specificity or enhanced drug transport possibly involved in mediating drug resistance; (4) in series I, in which only the cyclohexyl R_1 group is varied, the most lipophilic derivatives **9c** (R_1 = Ph) and **9d** (R_1 = Me_2) are the most active; (5) in series II, in which only the acetal ZR_2 is varied, again the most lipophilic OCH_2Ph derivative **9ao** is the most active; (6) in this series II, thiomethyl acetal **9an** is quite active, indicating that a normally redox-sensitive sulfide functionality does not block antimalarial activity; (7) in series III, in which only the bridgehead R_3 substituent is varied, again the most lipophilic derivative **9ay** is the most active; and (8) in this series, the only inactive analog (**9az**) has a bridgehead benzyl group, and it may be that this group can be fragmented from the trioxane as a relatively stable benzyl-free radical after iron reduction of the trioxane into an oxy radical that rearranges into a carbon-centered radical β to the benzyl group [25].

In conclusion, 11 new, structurally simplified, tricyclic trioxanes, synthesized easily in only several steps from commercial cyclohexanones, have been shown to possess considerable *in vitro* antimalarial activities. From these results, qualitative SAR generalizations point to the importance of lipophilicity in increasing the likelihood that a new artemisinin analog will have strong antimalarial activity and indicate that structural variations at several different positions of simple trioxanes like **9** can be made without undermining antimalarial activity. Finally, these trioxane syntheses demonstrate further the usefulness of $Et_3SiOOOH$ as a new dioxetane-forming reagent, not involving $^1O_2$, especially with relatively small quantities (50–100

TABLE 1 In vitro Antimalarial Activities of Synthetic Trioxanes **9**

Trioxane	R_3	ZR_2	R_1	IC_{50} Values (ng/mL)	
				W-2 Indochina Clone	D_6 African Clone
Series I					
9a	Me	OMe	H	25.2	84.7
9b	Me	OMe	Et	5.2	65.1
9c	Me	OMe	Ph	6.4	25.1
9d	Me	OMe	Me_2	1.74	50.5
Series II					
9a	Me	OMe	H	25.2	84.7
9am	Me	OEt	H	3.9	25
9an	Me	SMe	H	6.8	17.4
9ao	Me	OCH_2Ph	H	0.86	13.9
Series III					
9a	Me	OMe	H	25.2	84.7
9aw	$HOCH_2CH_2$	OMe	H	62	255
9ax	Et	OMe	H	6.0	11.6
9ay	Ph	OMe	H	5.8	4.9
9az	$PhCH_2$	OMe	H	not	active
Artemisinin				0.65	1.56
Arteether				0.19	0.55

mg) of unhindered vinyl ethers and a vinyl thioether.

EXPERIMENTAL [25]

Trioxane 9a

Z- and E-2-(2-Cyanoethyl)-1-methoxymethylidenylcyclohexane (*Z- and E-***7a**). To a slurry of (Methoxymethyl)triphenylphosphonium chloride (24.365 g, 71 mmol) and dry THF (120 mL) was added via a cannula a 1.8 M phenyllithium solution (44 mL, 79 mmol) in cyclohexane/ether over 30 minutes at 0°C. The resultant red ylide solution was stirred for 3 hours at room temperature and then cooled to −78°C using a Dry Ice-acetone bath. To this ylide solution was added via a cannula 2-(2-cyanoethyl)cyclohexanone (**6a**, 8.67 g, 57.3 mmol) prepared by Stork's enamine alkylation procedure, in THF (30 mL) over 10 minutes. After being stirred for 1 hour at −78°C, the reaction mixture was warmed to room temperature over 2 hours, and stirred for 10 hours. This reaction mixture was treated with a 10% sulfuric acid solution (50 mL) at 0°C, and then diluted with water (100 mL) and ether (100 mL). The organic layer was separated and further extracted two times with ethyl ether (50 mL × 2). The combined organic layer was washed with saturated NaCl solution (100 mL), dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed at reduced pressure to yield a crude product. Chromatography on silica gel (10:90 = hexane; ethyl acetate) afforded a 1:1 mixture of the desired product (6.62 g, 64%). Further separation using a mixture of ethyl acetate and hexane (1:99) afforded pure *Z-***7a** (2.0 g), pure *E*-enol ether *E-***7a** (1.9 g), and an unseparated mixture of *Z-***7a** and *E-***7a** (2.4 g). *Z-***7a**: colorless liquid; FT-IR ($CHCl_3$, cm^{-1}) 2247.5, 1676.2; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.86 (d, J = 1.8 Hz, 1H), 3.52 (s, 3H), 2.91–2.87 (m, 1H), 2.28–2.23 (m, 2H), 1.98–1.87 (m, 3H), 1.76–1.44 (m, 6H), 1.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.37, 120.55, 116.96, 59.26, 32.57, 31.31, 28.02, 27.59, 26.34, 21.72, 15.24. *E-***7a**: colorless liquid; FT-IR ($CHCl_3$, cm^{-1}) 2246.7, 1676.0; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.81 (s, 1H), 3.56 (s, 3H), 2.42 (dt, J = 13.6, 3.6 Hz, 1H), 2.33 (m, 1H), 2.23 (m, 1H), 2.13 (m, J = 5.0 Hz, 1H), 1.98–1.89 (m, 2H), 1.81 (tdd, J = 12.7, 4.3, 1.8 Hz, 1H), 1.68–1.50 (m, 5H), 1.33 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.46, 119.99, 117.62, 59.49, 37.63, 32.80, 27.09, 26.97, 22.45, 21.97, 15.39.

Z-Methoxymethylidenyl-2-(3-oxobutyl)cyclohexane (*Z-***8a**). General Procedure. To a solution of *Z-***7a** (87.2 mg, 0.5 mmol) in dry ethyl ether (2 mL) was added via a gas-tight syringe a 0.8 M methyllithium solution (2.0 mL, 1.6 mmol) in ethyl ether over 2 minutes at −78°C under argon atmosphere. After being stirred for 10 minutes at −78°C, the reaction mixture was slowly warmed to room temperature, and stirred for 30 minutes. The reaction mixture was treated with water (5 mL) at −78°C and extracted two times with ethyl ether (10 mL × 2). The combined organic layer was washed with saturated NaCl solution (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure to yield a crude product. Chromatography on silica gel (2:98 = hexane;

ethyl acetate) afforded the desired product *Z*-**8a** (88.3 mg, 92%) as a colorless liquid; FT-IR ($CHCl_3$, cm^{-1}) 1707.8, 1678.5; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.796 (d, J = 1.82 Hz, 1H), 3.50 (s, 3H), 2.77 (m, 2H), 2.37 (m, 2H), 2.122 (s, 3H), 1.95–1.91 (m, 2H), 1.88–1.69 (m, 4H), 1.63–1.54 (m, 2H), 1.53–1.48 (m, 2H), 1.26–1.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.59, 140.22, 119.04, 59.06, 41.78, 32.29, 31.53, 29.89, 28.20, 26.30, 25.14, 21.48.

Methoxy-methyl-trioxane **9a**. *General Procedure.* To a freshly prepared $Et_3SiOOOH$ solution (3.2 mmol) in CH_2Cl_2 (80 mL) was cannulated enol ether *Z*-**8a** (63.7 mg, 0.32 mmol) in CH_2Cl_2 (3 mL) solution over 10 seconds at −78°C under nitrogen atmosphere. To the resultant solution, after being vigorously stirred for 30 minutes, was slowly added precooled (−78°C) *tert*-butyldimethylsilyl triflate (80 μL, 0.35 mmol) in CH_2Cl_2 (1.0 mL) over 1 minute. The resultant solution was stirred at −78°C for 2–3 hours, treated with triethylamine (680 μL, 4.9 mmol), and then slowly warmed to −20°C over 1 hour. The solution was transferred to a 100 mL one-necked round-bottom flask and concentrated to 1 mL under reduced pressure. ^1H NMR spectrum of the crude product indicated the exclusive formation of the desired 1,2,4-trioxane. Chromatography of the crude product on silica gel using a mixture of ethyl acetate and hexane (1:99) as an eluent gave pure 1,2,4-trioxane **9a** (>95% pure, 45.3 mg, 61%) as a white solid. Recrystallization of trioxane **9a** from hexane afforded a few milligrams of white crystals: mp 68–69°C (Ref. [19c] 74–75°C); FT-IR ($CHCl_3$, cm^{-1}) 3019.7, 2951.5, 2934.1, 2862.1, 1446.0, 1396.8, 1375.5, 1270.4, 1224.2, 1212.4, 1205.8, 1142.6, 1119.9, 1066.3, 1028.8, 1009.0, 972.2, 895.8, 876.7, 865.0, 815.8; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.928 (s, 1H), 2.302 (ddd, J = 14.70, 13.43, 3.76 Hz, 1H), 2.052 (ddd, J = 14.65, 4.4, 3.1 Hz, 1H), 1.84–1.86 (m, 1H), 1.836–1.803 (m, 1H), 1.67–1.45 (m, 7H), 1.397 (s, 3H), 1.28–1.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 104.931, 104.675, 83.404, 57.083, 47.440, 37.858, 35.687, 30.857, 26.810, 26.220, 25.046, 23.777; CIMS (NH_3, *rel* intensity) 246 (M + 18, 100) 229 (M + 1, 42), 214 (39), 211 (71), 197 (63), 196 (59), 186 (20), 179 (60), 169 (92), 151 (36), 138 (89), 125 (33). Anal. calcd for $C_{12}H_{20}O_4$: C, 63.10; H, 8.83. Found: C, 63.10; H, 8.83.

Trioxane **9b**

General Procedure. Enol ether **8b** (57.4 mg, 0.26 mmol) afforded trioxane **9b** (18.1 mg, 32%) along with the corresponding ozonide as a colorless oil; ^1H NMR ($CDCl_3$, 400 MHz) δ major isomer: 4.93 (d, J = 1.6 Hz, 1H), 3.51 (s, 3H), 2.30 (qd, J = 15.0, 4.2 Hz, 1H), 2.05 (dt, J = 15.0, 4.2 Hz, 1H), 1.91–1.46 (m, 10H), 1.397 (s, 3H), 1.38–1.16 (m, 3H), 0.877 (t, J = 7.2 Hz, 3H); minor isomer: 4.76 (s, 1H), 3.521 (s, 3H), 2.30 (qd, J = 15.0, 4.2 Hz, 1H), 2.05 (dt, J = 15.0, 4.2 Hz, 1H), 1.91–1.46 (m, 10H), 1.386 (s, 3H), 1.38–1.16 (m, 3H), 0.865 (t, J = 7.2 Hz, 3H): Ozonide: 2.41 (m, 1H), 2.30 (qd, J = 15.0, 4.2 Hz, 1H), 2.05 (dt, J = 15.0, 4.2 Hz, 1H), 1.91–1.46 (m, 10H), 1.499 (s, 3H), 1.38–1.16 (m, 3H), 0.895 (t, J = 7.2 Hz, 3H). Full characterization of trioxane **9b** was not done due to a limited amount of this material.

Trioxane **9c**

General Procedure. Enol ether **8c** (214.9 mg, 0.79 mmol) afforded trioxane **9c** (108.2 mg, 45%) along with the corresponding ozonide as a colorless oil; ^1H NMR ($CDCl_3$, 400 MHz) δ major isomer: 7.310–7.190 (m, 5H), 5.009 (d, J = 0.91 Hz, 1H), 3.588 (s, 3H), 2.60 (pt, J = 12.2, 3.8 Hz, 1H), 2.34 (ddd, J = 14.2, 13.8, 4.2 Hz, 1H), 2.08 (dt, J = 16.0, 3.8 Hz, 1H), 2.04–1.76 (m, 8H), 1.68–1.46 (m, 2H), 1.422 (s, 3H); minor isomer: 7.32–7.16 (m, 5H), 4.819 (s, 1H), 3.550 (s, 3H), 2.59–2.51 (m, 1H), 2.38–2.29 (m, 1H), 2.25–2.12 (m, 1H), 2.03–1.66 (m, 8H) 1.60–1.51 (m, 2H), 1.415 (s, 3H). Full characterization of trioxane **9c** was not done due to the limited amount of this compound available.

Trioxane **9d**

Nitrile 6d. To a mixture of sodium borohydride (8.3 g, 0.22 mol) and Cu(I)Br (15.2 g, 0.11 mol) in dry ether (200 mL) at 0°C was added 4,4-dimethyl-2-cyclohexenone (25.3 g, 0.20 mol) in dry ether (20 mL) via a cannula under argon atmosphere. The reaction mixture was slowly treated with methanol (70 mL) at 0°C, stirred for 3 hours at room temperature, and then mixed with a 10% sulfuric acid solution (100 mL) at 0°C. The crude alcohol after usual extractive workup was dissolved in acetone (100 mL), slowly added to a chromium (III) oxide solution (30.4 g, 0.2 mol) in 30% sulfuric acid solution (50 mL, 0.15 mol) at 0°C, and stirred for 1 hour at room temperature. The usual extractive workup with ethyl acetate afforded 4,4-dimethylcyclohexanone (24.30 g, 94%) as a major product. The 4,4-dimethylcyclohexanone in benzene was condensed with pyrrolidine (20 mL, 0.24 mol) to give the corresponding enamine, which was alkylated with acrylonitrile (15 mL, 0.23 mol) in *p*-dioxane and hydrolyzed with a 10% sulfuric acid solution (40 mL). Usual workup and vacuum distillation afforded 2-(2-cyanoethyl)-4,4-dimethylcyclohexanone (**6d**, 19.79 g, 54% based on 4,4-dimethylcyclohexenone); bp 108–120 (0.2–00.3 torr); FT-IR (neat, cm^{-1}) 2245.4, 1710.6; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.61 (m, 1H), 2.48 (d, J = 9.2 Hz, 2H), 2.27 (ddd, J = 13.7, 4.6, 2.3, Hz, 1H), 2.06 (m, 1H), 1.80–1.72 (m, 2H), 1.63 (td, J = 13.7, 4.6, 2H), 1.50–1.42 (m, 1H), 1.39 (t, J = 13.7 Hz, 1H), 1.25 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100

MHz) δ 212.28, 119.62, 46.69, 44.28, 39.99, 38.31, 31.20, 30.84, 25.45, 24.32, 15.11.

*Enol Ethers Z- and E-***7d**. To a slurry of (methoxymethyl)triphenyl-phosphonium chloride (3.43 g, 10.0 mmol) in dry THF (20 mL) was added via a cannula a 1.58 M *n*-butyllithium solution (6.3 mL, 10.0 mmol) in hexane over 30 minutes at 0°C. The resultant red ylide solution was stirred for a further 4 hours at room temperature and then cooled to 0°C. To this ylide solution was added via a cannula 2-(2-cyanoethyl)-4,4-dimethylcyclohexanone (**6d**, 1.19 g, 6.6 mmol) in THF (5 mL) over 10 minutes. After being stirred for 1 hour at 0°C, the reaction mixture was warmed to room temperature over 2 hours and stirred for 24 hours. This reaction mixture was mixed with water (10 mL) at 0°C and extracted two times with ethyl ether (30 mL × 2). The combined organic layer was washed with saturated NaCl solution (30 mL), dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed at reduced pressure to yield a crude product. Chromatography on silica gel (10:90 = hexane: ethyl acetate) afforded a 1:1 mixture of the desired product **6d** (881 mg, 64%). *Z*-**6d**: FT-IR (neat, cm^{-1}) 2245, 1677; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.83 (s, 1H), 3.51 (s, 3H), 2.60 (m, 1H), 2.40–2.26 (m, 2H), 2.11–1.95 (m, 2H), 1.89–1.81 (m, 1H), 1.76–1.67 (m, 1H), 1.44–1.25 (m, 4H), 0.95 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.44, 120.65, 117.00, 59.27, 45.12, 40.76, 34.26, 30.75, 30.34, 29.34, 29.25, 25.33, 15.94; EIMS (*rel* intensity) 207 (23), 153 (100), 121 (73), 97 (63), 86 (40), 84 (55), 67 (14), 41 (20); HRMS (EI) calcd for $C_{13}H_{21}NO$: 207.1623. Found 207.1625. *E*-**6d** (*E*-isomer); FT-IR (neat, cm^{-1}) 2245, 1678; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.63 (s, 1H), 3.56 (s, 3H), 2.58 δ (dt, *J* = 13.1, 4.4 Hz, 1H), 2.39 (m, 2H), 2.15 (m, 1H), 1.94 (m, 1H), 1.83 (m, 1H), 1.59–1.46 (m, 3H), 1.41 (dtd, *J* = 13.1, 4.4, 2.2 Hz, 1H), 1.19 (td, *J* = 12.4, 4.4 Hz, 1H), 0.97 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.47, 120.00, 119.74, 59.44, 46.64, 39.66, 31.78, 30.87, 27.84, 25.91, 21.33, 15.09.

*Ketones Z- and E-***8d**. Addition of a 1.2 M methyllithium solution (10.0 mL, 12.0 mmol) in ether to nitrile *Z/E*-**7d** (881.0 mg, 4.25 mmol) in ether (10 mL) at −78°C yielded a mixture (707.9 mg, 76%) of *Z*-**8d** and *E*-**8d**. Further separation using a mixture of ethyl acetate and hexane (1:99) afforded pure isomers as colorless liquids *Z*-**8d**; FT-IR (neat, cm^{-1}) 1715.7, 1677.7; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.720 (s, 1H), 3.417 (s, 3H), 2.48 (m, *J* = 5.1 Hz, 1H), 2.360 (t, *J* = 7.5 Hz, 2H), 2.049 (s, 3H), 1.97 (m, 1H), 1.83 (s, 1H), 1.72 (dt, *J* = 7.5, 5.1 Hz, 1H), 1.59 (m, 1H), 1.29 (m, 3H), 1.15 (m, 1H), 0.912 (s, 3H), 0.801 (s, 3H); ^{13}C NMR ($CHCl_3$, 100 MHz) δ 209.87, 139.89, 118.94, 59.19, 44.93, 42.76, 41.00, 33.95, 31.55, 30.77, 29.90, 28.92, 28.39, 24.96. *E*-**8d** (*E*-isomer); FT-IR (neat, cm^{-1}) 1717, 1678; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.633 (s, 1H), 3.513 (s, 3H), 2.60 (dt, *J* = 15.0, 4.0 Hz, 1H), 2.45 (m, 2H), 2.117 (s, 3H), 1.92 (s, 1H), 1.80 (m, 1H), 1.70 (m, 1H), 1.39 (m, 4H), 1.12 (m, 1H), 0.909 (s, 3H), 0.860 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHZ) δ 209.13, 138.37, 121.27, 59.42, 47.44, 41.79, 39.89, 35.34, 32.36, 30.97, 30.02, 25.65, 25.38, 21.77.

Trioxane **9d**. *General Procedure.* Trioxane **9d** (21.3 mg, 42%) was obtained from enol ether *E*-**8d** (45.8 mg, 0.26 mmol) as a colorless oil; FT-IR ($CDCl_3$, cm^{-1}) 3013.0, 2954.0, 2865.6, 1470.6, 1451.7, 1386.5, 1375.4, 1254.7, 1226.9, 1218.0, 1205.4, 1166.5, 1150.8, 1123.6, 1093.7, 1049.1, 1017.1, 994.9, 971.9, 941.3, 885.9, 869.3, 830.3, 628.2; ^1H NMR ($CDCl_3$, 400 MHz) δ major isomer: 4.89 (d, *J* = 1.46 Hz, 1H), 3.51 (s, 3H), 2.29 (ddd, *J* = 14.7, 13.4, 3.9 Hz, 1H), 2.06 (dt, *J* = 14.7, 3.9 Hz, 1H), 1.95–1.84 (m, 1H), 1.80 (qd, *J* = 13.4, 4.0 Hz, 1H), 1.70–1.38 (m, 5H), 1.40 (s, 3H), 1.29–1.22 (m, 2H), 0.93 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 104.90, 104.85, 83.49, 57.10, 43.98, 43.04, 37.94, 36.33, 32.23, 31.84, 29.60, 26.59, 26.27, 24.53; HRMS (CI) calcd for $C_{14}H_{28}NO_5$ (M + 18) 274.2018. Found 274.2020. A very low yield (3%) of trioxane **9d** was obtained from *Z*-**8d**.

Trioxane **9am**

*Z- and E-2-(2-Cyanoethyl)-1-ethoxymethylidenylcyclohexane (Z- and E-***7am**). To a solution of diphenyl(ethoxymethyl)phosphine oxide (7.02 g, 27.0 mmol) in dry THF (100 mL) was added via a cannula an LDA solution, *in situ* prepared from diisopropylamine (4.8 mL, 34.0 mmol) in dry THF (30 mL) and a 1.5 M *n*-butyllithium (22 mL, 33.0 mmol) in hexane at 0°C, over 20 minutes under argon atmosphere. The resultant red ylide solution was treated via a cannula with 2-(2′-cyanoethyl)cyclohexanone (**6a**) (5.67 g, 37.5 mmol, 1.4 equiv) in THF (20 mL) over 10 minutes. After being stirred for 1 hour at −78°C, the reaction mixture was warmed to room temperature over 2 hours and stirred for 48 hours. This reaction mixture was mixed with water (10 mL) at 0°C and extracted with ethyl ether (30 mL × 2) to yield a crude product. Chromatography on silica gel (10:90 = hexane: ethyl acetate) afforded a 1:1 mixture of the desired products *Z*- and *E*-**7am** (2.147 g, 41%). Further separation using a mixture of ethyl acetate and hexane (2:98) afforded pure *Z*-isomer *Z*-**7am** (972.3 mg), pure *E*-enol ether *E*-**7am** (902.8 mg), and an unseparated mixture of geometric isomers (271.7 mg). *Z*-**7am**: colorless liquid; FT-IR ($CH-Cl_3$, cm^{-1}) 2246.8, 1673.0; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.917 (d, *J* = 1.7, Hz, 1H), 3.711 (dq, *J* = 7.04, 3.2 Hz, 2H), 2.92 (m, 1H), 2.29–2.24 (m, 2H), 2.00–1.83 (m, 4H), 1.76–1.62 (m, 2H), 1.59–1.52 (m, 2H), 1.51–1.43 (m, 2H), 1.28–1.19 (m, 1H), 1.224 (t, *J* = 7.05 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.89, 120.54, 116.74,

67.20, 32.55, 31.31, 28.00, 27.63, 26.39, 21.72, 15.17, 15.12; MS (rel intensity) 193 (M, 15), 139 (100), 111 (41), 93 (23), 67 (80), 55 (24); HRMS calcd for $C_{12}H_{19}NO$ 193.1471. Found 193.1467. *E*-**7am**: colorless liquid; FT-IR ($CHCl_3$, cm^{-1}) 3019.9, 2931.0, 2857.5, 2245.9, 1673.7, 1447.0, 1380.3, 1183.5, 1145.2, 1121.6; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.861 (s, 1H), 3.753 (q, J = 7.0 Hz, 2H), 2.45 (dt, J = 8.0, 3.0 Hz, 1H), 2.37–2.18 (m, 2H), 2.13 (m, 2H), 1.95–1.89 (m, 2H), 1.82 (m, 1H), 1.70–1.59 (m, 2H), 1.538 (m, 2H), 1.38–1.20 (m, 1H), 1.243 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.97, 120.02, 117.72, 67.41, 37.67, 32.82, 27.08, 26.97, 22.42, 21.03, 15.39, 15.17.

Z-1-Ethoxymethylidenyl-2-(3-oxobutyl)cyclohexane (*Z*-**8am**). General Procedure. Addition of a 0.8 M methyllithium solution (10.0 mL, 8.0 mmol) in ether to nitrile *Z*-**7am** (586.1 mg, 3.0 mmol) in ether (10 mL) yielded ketone *Z*-**8am** (581.9 mg, 91 %) as a colorless liquid; FT-IR ($CHCl_3$, cm^{-1}) 1707.4, 1676.0; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.849 (s, 1H), 3.687 (q, J = 7.0 Hz, 2H), 2.80 (m, 1H), 2.37–2.31 (m, 2H), 2.13 (s, 3H), 2.00–1.91 (m, 1H), 1.88–1.87 (m, 2H), 1.75–1.69 (m, 1H), 1.63–1.48 (m, 6H), 1.216 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.66, 138.77, 119.14, 67.00, 41.83, 32.40, 31.59, 29.88, 28.28, 26.44, 25.25, 21.54. EIMS (*rel* intensity) 210 (M, 15), 164 (2), 152 (100), 139 (43), 123 (36), 111 (30), 93 (29), 79 (16), 67 (63); HRMS calcd for $C_{13}H_{22}O_2$ 210.1620. Found 210.1623.

Trioxane **9am**. *General Procedure.* Enol Ether *Z*-**8am** (36.8 mg, 0.17 mmol) gave a pure 1,2,4-trioxane **9am** (>95% pure, 24.7 mg, 58%) as a colorless gum. Recrystallization from hexane gave pure white crystals: mp 60–61°C; FT-IR ($CHCl_3$, cm^{-1}) 3019.7, 2934.1, 2862.5, 1446.0, 1374.0, 1141.9, 1119.9, 1065.5, 1027.3, 1005.3, 971.5; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.04 (d, J = 1.3 Hz, 1H), 3.967 (dq, J = 4.0, 14.0 Hz, 1H), 3.54 (dq, J = 9.5, 7.1 Hz, 1H), 2.30 (ddd, J = 14.5, 13.5, 3.8 Hz, 1H), 2.05 (dt, J = 14.0, 4.0 Hz, 1H), 1.88–1.80 (m, 2H), 1.76–1.56 (m, 6H), 1.56–1.48 (m, 1H), 1.385 (s, 3H), 1.253 (t, J = 7.1 Hz, 3H), 1.28–1.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 104.89, 103.03, 83.35, 65.39, 47.45, 37.87, 35.73, 30.88, 26.81, 26.23, 25.11, 23.92, 15.27; CIMS (NH_3 rel intensity) 260 (M + 18, 37), 243 (M + 1, 20), 225 (51), 210 (33), 197 (56), 179 (30), 169 (100), 152 (49); HRMS calcd. for $C_{13}H_{23}O_4$ (M + H) 243.1596. Found 243.1596. Anal. calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 69.14; H, 9.10.

Trioxane **9an**

*Enol Thioether Z- and E-***7an**. *General Procedure.* To a solution of dimethyl methylthiomethylphosphonate (4.847 g, 24.4 mmol) in dry THF (30 mL) at −78°C was added a 1.6 M *n*-butyllithium solution (15.3 mL, 24.4 mmol) in hexane over 30 minutes. The resultant red ylide solution was stirred for 10 minutes and then warmed to −40°C over 10 minutes in order to complete the ylide formation and then recooled to −78°C. To the ylide solution was added via a cannula 2-(2'-cyanoethyl)cyclohexanone (**6a**, 3.046 g, 20.1 mmol) in THF (10 mL) over 20 minutes. After being stirred for 10 minutes at −78°C, the reaction mixture was warmed to room temperature over 0.5 hours, stirred for 3 hours at room temperature, and then refluxed for 2 hours. The reaction mixture was cooled to 0°C, mixed with water (30 mL), and concentrated under reduced pressure. Chromatography on silica gel (10:90 = hexane: ethyl acetate) afforded an inseparable mixture of the desired product *Z/E*-**7an** (2.645 g, 56%, *Z*:*E* = 1:9) as a colorless oil. *Z*-isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 5.615 (s, 1H), 2.38–2.21 (m, 3H), 2.27 (s, 3H), 2.13–1.93 (m, 2H), 1.81–1.39 (m, 8H).

*Z- and E-***8an**. *General Procedure.* Addition of a 1.3 M methyllithium solution (22 mL, 28.6 mmol) in ether to nitrile *Z/E*-**7an** (2.4562 g, 12.5 mmol) in dry ether (10 mL) at −78°C gave a mixture of methyl ketone *Z*-**8an** and *E*-**8an** (2.3192 g, 87%). *Z*-**8an**; FT-IR (neat, cm^{-1}) 1714.3, 1619.8; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.609 (d, J = 1.6 Hz, 1H), 2.72 (m, 1H), 2.50–2.33 (m, 2H), 2.232 (s, 3H), 2.20–2.10 (m, 1H), 2.04 (dm, J = 12.8 Hz, 1H), 1.94–1.84 (m, 1H), 1.78–1.72 (m, 1H), 1.70–1.62 (m, 3H), 1.59–1.47 (m, 2H), 1.32–1.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHZ) δ 209.325, 141.807, 118.999, 41.620, 37.343, 32.072, 31.554, 30.032, 28.124, 25.426, 20.871, 17.298. EIMS (*rel* intensity) 212 (M, 17), 195 (2), 164 (22), 139 (100), 121 (21), 106 (34), 93 (48), 79 (19), 61 (15), 43 (56); HRMS calcd for $C_{12}H_{20}OS$ 212.1235. Found 212.1237. *E*-**8an**: FT-IR (neat, cm^{-1}) 1713.8, 1679.1; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.510 (s, 1H), 2.394 (t, J = 7.8 Hz, 2H), 2.255 (s, 3H), 2.140 (s, 3H), 2.28–2.15 (m, 1H), 2.11–2.04 (m, 1H), 1.94–1.84 (m, 1H), 1.71–1.37 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.117, 141.984, 117.454, 43.541, 41.816, 33.330, 30.834, 28.153, 27.212, 25.649, 22.978, 17.312.

Trioxane **9an**. *From Z-***8an**. *General Procedure.* Enol ether *Z*-**8an** (40.8 mg, 0.19 mmol) gave an isomeric mixture of 1,2,4-trioxane **9an** (major:minor = 8:2, 16.9 mg, 36%) as a colorless oil; FT-IR (neat, cm^{-1}) 2989.7, 2928.0, 2875.0, 1460.7, 1450.4, 1372.5, 1250.6, 1203.6, 1158.1, 1137.5, 1114.0, 1069.9, 1061.1, 1030.3, 1002.4, 973.0, 893.6, 856.9, 792.3, 742.3; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.182 (d, J = 1.6 Hz, 1H), 2.318 (s, 3H), 2.10–2.00 (m, 2H), 1.92–1.80 (m, 1H), 1.78–1.40 (m, 6H), 1.388 (s, 3H), 1.44–1.15 (m, 4H); HRMS (CI, NH_3) calcd for $C_{12}H_{21}O_2$ 245.1211. Found 245.1212.

*From E-***8an**: *General Procedure.* Enol ether *E*-**8an** (65.8 mg, 0.31 mmol) gave an isomeric mixture of 1,2,4-trioxane **9an** (major:minor = 6:4, 34.1

mg, 45%). ^{1}H NMR spectroscopy showed that the major isomers from *Z*-**8an** and *E*-**8an** are the same. Major isomer: FT-IR (neat, cm^{-1}) 2989.7, 2933.9, 2857.5, 1447.8, 1383.3, 1272.8, 1031.2, 1002.7, 972.7, 945.7, 893.3, 875.3, 842.3, 825.9; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.183 (d, J = 1.6 Hz, 1H), 2.320 (s, 3H), 2.10–2.00 (m, 2H), 1.92–1.80 (m, 1H), 1.78–1.40 (m, 6H), 1.390 (s, 3H), 1.51–1.15 (m, 4H). Minor isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.058 (s, 1H), 2.314 (s, 3H), 2.10–2.00 (m, 2H), 1.92–1.80 (m, 1H), 1.78–1.40 (m, 6H), 1.383 (s, 3H), 1.51–1.15 (m, 4H).

Trioxane **9ao**

*Preparation of Z-***7ao** *and E-***7ao** *by Trans-Etherification.* A mixture of enol ether **7a** (606.2, 3.4 mmol), benzyl alcohol (425.0 mg, 3.9 mmol), and *p*-toluenesulfonic acid (10 mg) in toluene (20) was refluxed for 2 hours with distilling off of the methanol. The reaction mixture was concentrated and then separated by column chromatography to yield benzyl enol ether *Z*-**7ao** and *E*-**7ao** (E:Z = 1:1, 493.3 mg, 58%) as a colorless oil. *Z*-**7ao**: FT-IR (neat, cm^{-1}) 2243.5, 1675.6; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (m, 5H), 5.99 (d, J = 1.60 Hz, 1H), 4.71 (d, J = 6.0 Hz, 1H), 4.69 (d, J = 6.0 Hz, 1H), 2.95 (m, J = 12.0 Hz, 1H), 2.22–2.09 (m, 2H), 1.96–1.81 (m, 3H), 1.75–1.68 (m, 1H), 1.68–1.58 (m, 1H), 1.58–1.37 (m, 4H), 1.25–1.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.59, 137.54, 128.47, 127.93, 127.60, 120.61, 118.08, 112.59, 73.61, 32.75, 31.34, 28.02, 27.63, 26.39, 21.66, 15.18. *E*-**7ao**: FT-IR (neat, cm^{-1}) 2243.5, 1676.5; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (m, 5H), 5.91 (s, 1H), 4.77 (d, J = 6.0 Hz, 1H), 4.75 (d, J = 6.0 Hz, 1H), 2.51 (dt, J = 16.0, 4.2 Hz, 1H), 2.23–2.16 (m, 1H), 2.14–2.02 (m, 2H), 1.93–1.76 (m, 2H), 1.69–1.47 (m, 6H), 1.35–1.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.68, 137.64, 128.37, 127.77, 127.42, 119.91, 118.94, 73.51, 37.52, 32.66, 26.93, 26.85, 22.32, 22.07, 15.14.

*Ketone Z-***8ao**. *General Procedure.* To nitrile *Z*-**7ao** (119.8 mg, 0.47 mmol) in dry ether (3 mL) was added a 1.2 M methyllithium solution (1.2 mL, 1.4 mmol) at −78°C. The separation of the crude product with ethyl acetate and hexane (1:99) gave a pure methyl ketone *Z*-**8ao** (122.3 mg, 96%); FT-IR (neat, cm^{-1}) 1714.3, 1677.8, 1674.9; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.326 (m, 5H), 5.944 (d, J = 1.67 Hz, 1H), 4.71 (d, J = 6.0 Hz, 1H), 4.69 (d, J = 6.0 Hz, 1H), 2.85 (m, 1H), 2.42–2.26 (m, 2H), 2.046 (s, 3H), 1.98–1.89 (m, 1H), 1.89–1.75 (m, 2H); 1.75–1.68 (m, 1H), 1.62–1.41 (m, 5H), 1.23–1.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.662, 138.548, 137.833, 128.319, 127.686, 127.404, 120.135, 73.371, 41.863, 32.532, 31.597, 29.877, 28.234, 26.372, 25.166, 21.474①MS (*rel* intensity) 272 (M, 3), 214 (20), 181 (18), 162 (4), 135 (7), 121 (13), 91 (100), 79 (7), 77 (3), 65 (6); HRMS calcd for $C_{18}H_{24}O_2$ 272.1776. Found 272.1782.

Trioxane **9ao**. *General Procedure.* Enol ether *Z*-**8ao** (47.0 mg, 0.17 mmol) gave a pure 1,2,4-trioxane **9ao** (>95% pure, 25.2 mg, 48%) as a colorless oil; FT-IR (neat, cm^{-1}) 3066.4, 3031.2, 2990.0, 2928.3, 2860.7, 1607.6, 1587.0, 1497.5, 1453.5, 1446.1, 1373.8, 1206.1, 1160.1, 1140.3, 1118.4, 1064.7, 1030.7, 1006.6, 971.5, 897.0, 878.4, 734.8; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.28 (m, 5H), 5.148 (d, J = 0.92 Hz, 1H), 4.988 (d, J = 11.8 Hz, 1H), 4.575 (d, J = 12.7 Hz, 1H), 2.32 (ddd, J = 15.0, 14.2, 3.2 Hz, 1H), 2.08 (dt, J = 15.0, 3.2 Hz, 1H), 1.98–1.87 (m, 1H), 1.83–1.77 (dm, J = 15.0 Hz, 1H), 1.77–1.44 (m, 7H), 1.417 (s, 3H), 1.29–1.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.496, 128.334, 127.614, 127.707, 105.007, 102.071, 70.811, 47.465, 37.858, 35.542, 30.873, 26.802, 26.227, 24.963, 23.877; CIMS (NH_3, *rel* intensity) 322 (M + 18, 74.6), 305 (M + 1, 17.3), 287 (25.4), 272 (44.6), 214 (58.5), 197 (100), 181 (82.3), 169 (42.6), 151 (29.6), 108 (43.8), 91 (52.4); HRMS (CI, NH_3) calcd for $C_{18}H_{25}O_4$ (M + 1) 305.1753. Found 305.1755.

Trioxane **9aw**

Z-Methoxymethylidenyl-2-(5-hydroxy-3-oxo-pentyl)cyclohexane (*Z*-**8aw**). To an LDA solution prepared in situ from diisopropylamine (95 μL, 0.7 mmol) in dry ethyl ether (1.5 mL) and a 1.45 M *n*-butyllithium solution (480 μL, 0.7 mmol) in hexane was added ketone *Z*-**8a** (132.7 mg, 0.7 mmol) in ether (1.5 mL) via a cannula over 5 minutes. The resultant solution was stirred for an additional 30 minutes at −78°C and then treated with gaseous formaldehyde, generated in situ by heating paraformaldehyde (83.2 mg). This solution was stirred for an hour at −78°C and then mixed with water (5 mL). The organic layer was extracted three times with ethyl acetate (10 mL, × 3). The combined organic layer was washed with saturated NaCl solution (15 mL), dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed at reduced pressure to yield a crude product. Chromatography on silica gel (60:40 hexane: ethyl acetate) afforded 58.4 mg (38%) of the desired product (*Z*-**9aw**) as an oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.780 (d, J = 1.53 Hz, 1H), 3.813 (q, J = 5.61 Hz, 2H), 3.478 (s, 3H), 2.78 (m, 1H), 2.637 (t, J = 5.30 Hz, 2H), 2.39 (m, 2H), 2.00–2.66 (m, 4H), 1.66–1.35 (m, 6H), 1.19 (m, 1H).

Trioxane **9aw**. *General Procedure.* Enol ether *Z*-**8aw** (21.9 mg, 0.10 mmol) gave pure 1,2,4-trioxane **9aw** (>95% pure, 8.4 mg, 23%) as its *t*-butyl(dimethylsilyl) ether; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.895 (s, 1H), 3.84–3.71 (m, 2H), 3.511 (s, 3H), 2.26–2.13 (m, 1H), 2.05–2.00 (m, 1H), 1.948 (t, J = 7.2 Hz, 2H), 1.86–1.50 (m, 7H), 1.44–1.15 (m, 4H), 0.885 (s, 9H), 0.052 (s, 6H); HRMS calcd for $C_{19}H_{37O5}Si$ 373.2410. Found 373.2414. To this protected trioxane **9aw** (10.2 mg, 0.03 mmol) in dry ether (3 mL) was added a 1.0 M tetrabutylammo-

nium fluoride solution (50 μL, 0.05 mmol) in THF at room temperature. The resulting solution was stirred for 6 hours and then concentrated to give a crude product, which was directly separated by column chromatography to afford the corresponding deprotected trioxane **9aw** (5.2 mg, 74%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.977 (s, 1H), 3.812 (q, J = 6.11 Hz, 2H), 3.523 (s, 3H), 2.34–2.25 (m, 1H), 2.12–1.54 (m, 13H), 1.29–1.18 (m, 2H).

Trioxane **9ax**

Z-Methoxymethylidenyl-2-(3-oxopentyl)cyclohexane (*Z*-**8ax**). General Procedure. Ketone *Z*-**8ax** (121.5 mg, 76%) was obtained from the reaction of nitrile *Z*-**7a** (136.4 mg, 0.76 mmol) in ether (5.0 mL) with a 3 M ethylmagnesium bromide solution (1.0 mL, 3.0 mmol) in ether for 30 hours at room temperature: colorless liquid; FT-IR ($CHCl_3$, cm^{-1}) 1707.1, 1678.1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.788 (d, J = 1.87 Hz, 1H), 3.493 (s, 3H), 2.76 (m, 1H), 2.408 (q, J = 7.5 Hz, 2H), 2.27–2.43 (m, 2H), 1.96 (m, 1H), 1.88–1.70 (m, 4H), 1.63–1.54 (m, 2H), 1.53–1.44 (m, 2H), 1.25–1.14 (m, 1H), 1.039 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.32, 140.12, 119.28, 59.13, 40.57, 35.86, 32.48, 31.62, 28.30, 26.39, 25.31, 21.55.

Trioxane **9ax**. *General Procedure.* Enol ether *Z*-**8ax** (64.9 mg, 0.31 mmol) gave a pure 1,2,4-trioxane **9ax** (>95% pure, 46.0 mg, 62%) as a colorless oil; FT-IR ($CHCl_3$, cm^{-1}) 3019.7, 2933.1, 2861.1, 1447.3, 1224.2, 1206.5, 1141.9, 1121.3, 1039.1, 1014.1, 930.4; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.921 (s, 1H), 3.525 (s, 3H), 2.22 (ddd, J = 14.1, 12.9, 3.5 Hz, 1H), 2.02 (ddd, J = 14.1, 13.0, 3.5 Hz, 1H), 1.88–1.72 (m, 2H), 1.72–1.50 (m, 6H), 1.69 (q, J = 7.4 Hz, 2H), 1.22 (qd, J = 13.5, 4.7 Hz, 1H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 106.15, 104.83, 83.54, 57.05, 47.47, 35.97, 35.60, 32.61, 30.81, 26.73, 25.07, 23.79, 6.97; CIMS (NH_3, *rel* intensity) 260 (M + 18, 15), 243 (M + 1, 13), 228 (10), 211 (22), 200 (27), 195 (24), 183 (100), 165 (20), 154 (25), 138 (8), 126 (20), 109 (5); HRMS calcd for $C_{13}H_{23}O_4$ (M + H) 243.1596. Found 243.1599.

Trioxane **9ay**

Z-Methoxymethylidenyl-2-(3-oxo-3-phenylpropyl)-cyclohexane (*Z*-**8ay**). General Procedure. Addition of a 1.8 M phenyllithium solution (10.0 mL, 18.0 mmol) in cyclohexane and ether to nitrile *Z*-**7a** (1.60 g. 8.9 mmol) in ether (10 mL) yielded ketone *Z*-**8ay** (1.50 g, 65%) as a colorless liquid; FT-IR ($CHCl_3$, cm^{-1}) 1678.1, 1598.8; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.934–7.533 (m, 2H), 7.533 (m, 1H), 7.444 (m, 2H), 5.790 (d, J = 1.49 Hz, 1H), 3.410 (s, 3H), 2.915 (m, 3H), 2.12 (m, 2H), 1.85–1.63 (m, 5H), 1.535 (m, 2H), 1.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.75, 140.40, 137.30, 132.52, 128.33, 127.91, 118.93, 58.97, 36.74, 32.53, 31.61, 28.20, 26.36, 25.72, 21.57.

Trioxane **9ay**. *General Procedure.* Using trimethylsilyl triflate (193 μL, 1.0 mmol) and stirring for only 20 minutes, enol ether *Z*-**8ay** (102.8 mg, 0.40 mmol) gave an inseparable mixture (95% pure, 26.8 mg, 23%) of 1,2,4-trioxane **9ay** and an ozonide. HPLC provided analytically pure trioxane **9ay** as a colorless oil; FT-IR ($CHCl_3$, cm^{-1}) 3019.4, 2935.3, 2859.7, 1598.5, 1449.9, 1370.1, 1351.3, 1274.3, 1224.2, 1206.8, 1137.5, 1105.2, 1017.8; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.550 (m, 2H), 7.375 (m, 3H), 5.144 (d, J = 1.5 H_3), 3.65 (s, 3H), 2.789 (m, 1H), 2.248–2.338 (m, 1H), 2.191–2.113 (m, 1H), 2.029–1.604 (m, 8H), 1.431–1.227 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 129.32, 128.71, 128.32, 128.16, 125.86, 125.81, 125.20, 110.18, 108.20, 105.07, 84.00, 82.40, 57.17, 47.46, 40.18, 39.14, 35.64, 33.61, 32.46, 30.82, 30.48, 26.85, 25.06, 24.94, 24.40, 23.85, 23.75; CIMS (NH_3, *rel* intensity) 291 (M + 1,2), 264 (10), 247 (62), 231 (100), 169 (12), 154 (25), 125 (33), 105 (52); HRMS calcd for $C_{17}H_{23}O_4$ (M+H) 291.1596. Found 291.1592.

Trioxane **9az**

Ketone Z-8az. Z-Methoxymethylidenyl-2-(3-oxo-4-phenylbutyl)cyclohexane (*Z*-**8az**). General Procedure. Ketone *Z*-**8az** (83.8 mg, 94%) was obtained from the reaction of nitrile *Z*-**7a** in ether (5.0 mL) with a 1.0 M benzylmagnesium chloride solution (2.0 mL, 2.0 mmol) in ether for 30 hours at room temperature: colorless liquid; FT-IR ($CHCl_3$, cm^{-1}) 1708.7, 1678.4, 1601.8; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.18 (m, 4H), 5.768 (d, J = 1.90 Hz, 1H), 3.678 (s, 3H), 3.464 (s, 3H), 2.74 (m, 1H), 2.40 (m, 2H), 1.92 (m, 1H), 1.86–1.68 (m, 3H), 1.62–1.44 (m, 4H), 1.28–1.14 (m, 2H).

Trioxane **9az**. *General Procedure.* Enol ether *Z*-**8az** (83.8 mg, 0.30 mmol) gave pure 1,2,4-trioxane **9az** (>95% pure, 53.0 mg, 57%) as a white solid. Recrystallization of the trioxane from hexane afforded a few milligrams of white crystalline **9az**: mp 126–127°C; FT-IR ($CHCl_3$ cm^{-1}) 3026.8, 3019.9, 3014.4, 2935.7, 2858.3, 1604.0, 1496.5, 1453.8, 1369.7, 1342.5, 1250.0, 1224.1, 1210.5, 1122.8, 1068.5, 1047.9, 995.0, 965.6, 901.0, 836.4; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (m, 5H), 4.89 (s, 1H), 3.53 (s, 3H), 3.03 (d, J = 14.2 Hz, 1H), 2.91 (d, J = 14.2 Hz, 1H), 2.07 (dd, J = 9.5, 3.4 Hz, 1H), 2.06 (dd, J = 8.3, 3.4 Hz, 1H), 1.85–1.46 (m, 8H), 1.27–1.11 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.98, 130.65, 127.95, 126.64, 105.66, 104.68, 83.84, 57.03, 47.38, 45.61, 36.16, 35.53, 30.76, 26.68, 25.03, 23.77; CIMS (NH_3, *rel* intensity) 322 (M + 18, 10), 305 (M + 1, 7), 278 (48) 261 (100), 23 (86), 231 (57), 225 (35), 188 (19), 171 (22), 153 (17), 139 (19), 125 (38), 108 (20), 91 (55). HRMS calcd for $C_{17}H_{25}O_4$ (M + 1) 305.1753. Found

305.1755. Anal. calcd for $C_{18}H_{24}O_4$: C, 71.03, H, 7.95. Found: C, 70.97, H, 7.93.

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