derivative of TTX (8).[24] These derivatives were considered to be compounds at different stages of progressive oxidation or their derivatives as in the case of chiriquitoxin. While the structural variations found in the past are limited to the 6,11-position, i.e. the branching portion, the newly discovered compound 2 is the first TTX derivative which lacks an oxygen function on the ring. It seems to indicate that TTX is indeed formed by the stepwise oxidation of an alicyclic system as suggested by Yasumoto et al. (pathways b in Scheme I)[18] and excludes one of the earlier speculations[14] that TTX is formed by the condensation of arginine and a branched sugar (pathway a in Scheme I).

Another important aspect of compound 2 is the possible implication of the *N*-hydroxy compounds' participation in the toxigenesis of certain organisms. *N*-Hydroxy derivatives play an important role in the toxigenesis of other guanidine-containing toxins.[25,26] Those compounds have been shown to lose the hydroxy group reductively in biological systems. A typical example is the conversion of neosaxitoxin to saxitoxin by shellfish or bacteria.[26,27] Recently many strains of bacteria including several types of strains of marine bacteria have been reported to produce TTX. They include *Vibrio* spp., *Aeromonas* spp., *Alteromaonas* spp., *Photobacterium* sp., *Escherichia coli*, *Bacillus* sp., *Moraxella* spp., *Pseudomonas* spp., *Listonella* sp., and *Acinetobacter* sp.[8-11,28] These rather astounding reports on the production of TTX by a wide variety of bacteria ranging from Gram-negative and Gram-positive bacteria to actinomycetes have led to the speculation that there are rather ubiquitous precursors of TTX, which can be easily transformed to TTX by subtle structural modifications. In this regard, the finding that marine sediments contain appreciable amounts of TTX may be very significant.[29]

In our earlier experiments,[13,14] we fed various putative precursors to the newts *T. torosa* and *T. granulosa* under various conditions. All the experiments gave negative results. Attempts were made to incorporate highly radioactive acetate as a general metabolic precursor. We also tried [*guanido*-^{14}C]arginine, because, in our studies of saxitoxin biosynthesis, we learned that the guanidine group of arginine could be a universal source of guanidine group.[30] However, in both cases, when exhaustively purified, the isolated TTX samples were completely devoid of radioactivity, despite the fact that other general metabolites such as cholesterol and amino acids isolated in the experiments were significantly labeled. We also carried out similar experiments with Gram-negative bacteria isolated from the intestinal flora of the newts, which seemed to produce a tetrodotoxin-like substance.[12,14] However, again, the tetrodotoxin fraction isolated and purified by adding pure tetrodotoxin did not carry any radioactivity. All these results seemed to suggest the absence of de novo synthesis of TTX in the organisms, although, in our experiments, the newts sustained a high level of toxicity for 1-2 years and, moreover, there is evidence that they were constantly excreting small amounts of TTX in captivity. All these contradictory observations may be understandable, if there are compounds in the newts which can be easily transformed to TTX. *N*-Hydroxyl derivatives or deoxy compounds such as 2 certainly qualify as such precursors.

Conclusion

Despite numerous efforts over the years, the biosynthesis of TTX remains a mystery. All conventional approaches to the biosynthetic studies, including feeding experiments with the alleged TTX-producing organisms, have so far failed. Only some speculations have been made from the structural features of TTX and its derivatives. Of these compounds, the newly discovered compound, which lacks two oxygen functions on the carbon skeleton, seems to be the most informative with regard to the molecular origin of this most noted natural product. As to the biological origin of the alleged precursors of TTX, the question still remains unsolved. However, given the fact that low levels of TTX are widely found in a variety of organisms, they have to be derived from some very common sources and converted to TTX or its precursors in the organisms.

Acknowledgment. This research was supported by NIH Grant R37 GM 28754, which is greatly appreciated.

Supplementary Material Available: ^{13}C, ^{13}C DEPT, ^{1}H, and ^{1}H-^{1}H COSY spectra of compound 2 (16 pages). Ordering information is given on any current masthead page.

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Neighboring Group Participation in Lewis Acid-Promoted [3 + 4] and [3 + 5] Annulations. The Synthesis of Oxabicyclo[3.*n*.1]alkan-3-ones

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Abstract: Lewis acids are employed as catalysts in the annulation of 1,4- and 1,5-dicarbonyl dielectrophiles with bis(trimethylsilyl) enol ethers of β-diketones and β-keto esters. A variety of 2-(alkoxycarbonyl)-*m*-oxabicyclo[3.*n*.1]alkan-3-ones can be constructed by this process in which two new carbon-carbon bonds are generated. Unusually high regiocontrol is observed, and good to excellent stereochemical control can be achieved at virtually every position on the new carbocycles. Intramolecular neighboring group participation is proposed to explain the unusually high selectivities attained in the annulation reaction.

With increasing frequency, molecules possessing seven-[2] and eight-membered-ring[3] substructural units are being discovered and evaluated for their potential use as therapeutic agents. Unlike the syntheses of five- and six-membered rings, wherein a variety

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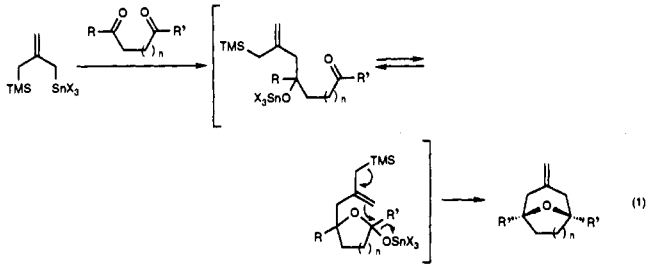
of general approaches can be utilized to create nearly every imaginable substitution pattern and stereochemical outcome, efficient syntheses of seven- and eight-membered rings are less commonplace. In particular, entropic factors and developing transannular interactions provide severe impediments to the formation of these medium-membered-ring systems in cyclization reactions.[4] Other problems surface when annulative approaches to these systems are considered. Thus, although several annulation approaches to seven-membered rings have been developed, few allow a command over both regiochemistry in unsymmetrical cases or predictable control of stereochemistry.[5] Efficient construction of eight-membered rings via annulative methods is even rarer.[6] In this article we outline an annulative route to seven- and eight-membered rings permitting good to excellent stereochemical control over nearly all of the newly formed stereogenic centers of the carbocycle formed. The success of the method relies on a novel use of neighboring group participation to control both regiochemistry and stereochemistry.

A very simplistic annulative approach to medium-sized rings would involve the reaction of dianionic synthons with dielectrophilic substrates.[7] In considering such strategies, there are several potential pitfalls to overcome in order for the methods to be practical. In addition to the inherent problem of generating a medium-sized ring, the annulation approach requires that the two nucleophilic sites of the dianionic synthon react in proper sequence with the dielectrophile to provide high regioselectivity. Furthermore, if new stereogenic centers are created, relative asymmetric induction must be controlled. Regiochemical and stereochemical problems can be particularly acute when the dielectrophile is a dicarbonyl substrate. Not only must one somehow distinguish between two very similar electrophiles in order to control regiochemistry but the conversion of two prochiral centers to stereogenic centers has the potential to create enormous stereochemical difficulties as well.

Our initial success in overcoming these problems was achieved by utilizing a trimethylenemethane dianionic synthon in conjunction with various dicarbonyl dielectrophiles.[6j] This method took advantage of an intermediate generated by intramolecular hemiketalization, permitting construction of both seven- and eight-membered rings (eq 1). Although this strategy proved very successful, recognition that the symmetrical nature of the trimethylenemethane dianionic synthon limited application to minimally functionalized, symmetrical systems led us to explore a second generation of dianionic synthons: i.e., β-dicarbonyl 1,3-dianion equivalents.



(1)

The reactivity of bis(trimethylsilyl) enol ethers (**4**) has been well-documented. In all cases, the terminal carbon (C-4) reacts first with appropriate electrophiles.[8] The discrete reactivity of the two nucleophilic sites in these 1,3-dianionic synthons was anticipated to permit the formation of unsymmetrical bicyclic ring systems when reacted with 1,4-dielectrophiles in which the two electrophilic units exhibited sufficiently different reactivities. The bis(trimethylsilyl) enol ether of methyl acetoacetate (**4a**) was previously shown to act as a 1,3-dianionic synthon in [3 + 3] and [4 + 2] annulation reactions.[9] Its reactivity in [3 + 4] and [3 + 5] annulation processes had not been fully developed when we undertook our studies, although a precedent for such annulations had been established by Chan and co-workers.[6i,10] Molander and Andrews further showed that high yields could be attained in the cyclization of symmetrical 1,4- and 1,5-diketones with $TiCl_4$ [eq 2, $R_1 = R_4(R_5) = Me$].[11] Good regiocontrol was achieved in the annulation of 1,4-keto acetals with **4a** and $TiCl_4$. However, the analogous reaction with 1,4-keto aldehydes gave poor regiose-

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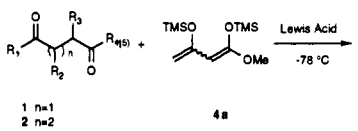
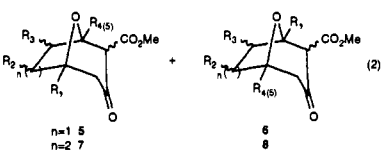
Table I. TMSOTf-Promoted Annulation of 1,4-Dicarbonyl Substrates (1) with 4a

substrate	product	R_1	R_2	R_3	R_4	% isoltd yield (5)[a]	diastereoselectivity[b] (regioselectivity)
1a	5a	Me	H	H	Me	56	
1b	5b	Me	H	H	H	53	(>200:1)
1c	5c	*n*-Pr	H	H	H	78–90	(>200:1)
1d	5d	Ph	H	H	H	87	(>200:1)
1e	5e	*t*-Bu	H	H	H	88	(>200:1)
1f	5f	*t*-Bu	H	H	Me	74	(28:1)
1g	5g	Ph	H	H	Me	66	(17:1)[c]
1h	5h	*i*-Pr	H	H	Me	60	(6.5:1)[c]
1i	5i	*n*-Pr	H	H	Me	58	(5:1)[c]
1j	5j	Et	Me	H	H	77	5.4:1[c]
1k	5k	Me	Ph	H	H	68	15:1[c]
1l	5l	*i*-Bu	*i*-Pr	H	H	77	15.6:1[c]
1m	5m	Ph	OMe	H	H	40	1.4:1[c]
1n	5n	Me	H	Me	H	75	13.5:1[c]
1o	5o	Me	H	*i*-Pr	H	87	27.3:1[c]
1p	5p	Ph	H	Me	H	79	15.2:1[c]
1q	5q	Ph	H	*i*-Pr	H	68	>160:1[c]

[a] Refers to yields of purified products as a mixture of diastereomers. All of these compounds have been fully characterized spectroscopically (^{1}H NMR, ^{13}C NMR, IR), and elemental composition has been established by combustion analysis and/or exact mass. [b] Diastereoselectivities and regioselectivities were determined by fused silica capillary GLC analysis or by ^{1}H NMR. [c] The crude bicyclic keto ester 5 was first derivatized to the corresponding enol acetate for determination of yield and diastereoselectivity.

lectivity. Furthermore, 1 equiv of the $TiCl_4$ "catalyst" was required for these reactions, creating difficulties in workup. Finally, the bis(trimethylsilyl) enol ethers themselves react with $TiCl_4$, and many of the reactions exhibited capricious behavior.



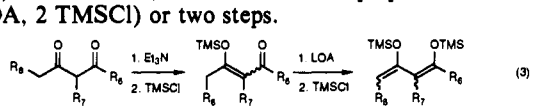


(2)

In order to solve these problems and explore further the scope of this particular annulative approach to medium-sized rings, a survey was performed in which the Lewis acid promoter for the reaction was systematically varied. Trimethylsilyl trifluoromethanesulfonate (TMSOTf)-promoted cyclizations of 1,4-keto aldehydes with **4a** (generating bicyclic ethers **5**) proved superior to those performed with $TiCl_4$, providing predictably high regio- and stereocontrol (eq 2, R_4 = H) in virtually every case.[12] Herein we report the full details of these [3 + 4] and [3 + 5] annulation reactions.

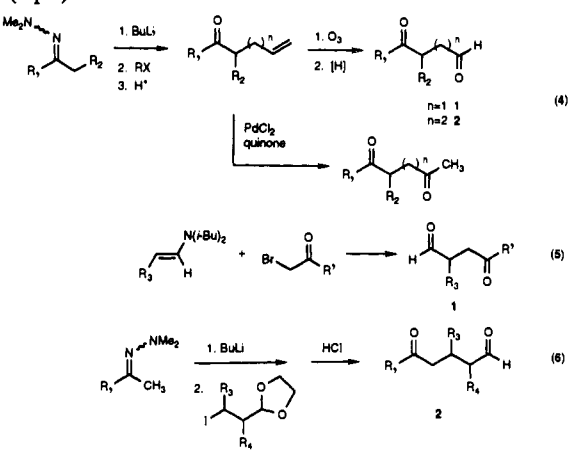
Results and Discussion

In order to explore the scope of the [3 + 4] and [3 + 5] annulation reactions, several starting 1,4- and 1,5-dielectrophiles and bis(trimethylsilyl) enol ethers (**4**) were synthesized. Optimum yields of bis(trimethylsilyl) enol ethers of β-keto esters were generally achieved by using a two-step process involving initial formation of a trimethylsilyl enol ether (**3**, eq 3).[13] Bis(trimethylsilyl) enol ethers of β-diketones could be prepared in either one (2 LDA, 2 TMSCl) or two steps.



(3)

Several methods were employed in the synthesis of the necessary dielectrophiles. Alkylation of ketone dimethylhydrazones[14] with allyl bromide or 4-bromobutene followed by deprotection[15] and ozonolysis[16] provided a variety of 1,4- and 1,5-keto aldehydes (**1** and **2**, eq 4). Wacker oxidation of the intermediate alkenone provided 1,4- and 1,5-diketones.[17] Alternatively, unsubstituted 1,4-keto aldehydes could be prepared by alkylation of the hydrazone with bromoacetaldehyde dimethyl acetal followed by deprotection.[18] Preparation of 2-substituted 1,4-keto aldehydes was achieved by alkylation of aldehyde enamines with α-bromo ketones (eq 5).[19] Several different 1,5-keto aldehydes were also prepared by alkylation of dimethylhydrazones with 2-(2-iodoethyl)-1,3-dioxolane[20] followed by acid hydrolysis of the protecting groups (eq 6).



(4)

(5)

(6)

Subjection of these substrates to reaction with the bis(trimethylsilyl) enol ethers in the presence of TMSOTf provided high yields of the desired products. Optimum results in the [3 + 4] annulation reaction occur under dilute conditions at −78 °C utilizing 10–20 mol % TMSOTf. The dinucleophilic synthon and the catalyst were each prepared as 0.1 M solutions in CH_2Cl_2 and were added sequentially to the 1,4-keto aldehyde in CH_2Cl_2 (0.1 M). The bicyclic ethers (**5**, eq 2, R_4 = H) were formed regioisomerically pure (with initial attack of the dinucleophilic synthon at the ketone!) in 53–90% isolated yields (Table I, **5b–e**). Each bicyclic product exists as a mixture of three isomers: the enol

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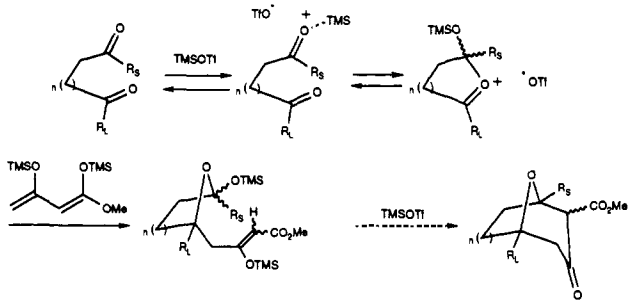
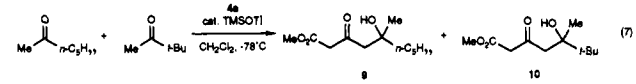
Scheme I



and the keto esters with both exo and endo substitution of the methoxycarbonyl unit. The bridgehead hydrogen (H-1) couples only to exo proton H-7 in the exo-substituted keto ester and the enol, generating two distinct doublets in the ^{1}H NMR. On the other hand, H-1 couples to both exo protons H-7 and H-2 and appears as a multiplet in the endo-substituted methoxycarbonyl epimer of the β-keto ester. The three signals collapse to one doublet in the ^{1}H NMR upon derivatization of the mixture to the enol acetate. A mixture of regioisomers **5** and **6** was generated using $TiCl_4$ as the Lewis acid in the [3 + 4] annulation reaction. In the regioisomer not generated by TMSOTf catalysis (**6**, initial attack of **4a** at the aldehyde of **1**), the bridgehead proton (H-5) appears as a multiplet in the ^{1}H NMR, coupled to exo protons H-4 and H-6. This regioisomer was undetected by both ^{1}H NMR and GLC in the crude reaction mixtures of TMSOTf-promoted annulations.

The unanticipated regiochemistry observed in these annulation reactions led us to consider the mechanism by which the final products were generated. The [3 + 4] annulation was investigated by examining the TMSOTf-promoted reaction of **4a** with symmetrical and unsymmetrical 1,4-diketones (Table I, **5a**,**f**–**i**). Chemoselectivity was first investigated in an intermolecular competition study. The reaction of **4a** with a 1:1 mixture of 2-heptanone and pinacolone in the presence of catalytic TMSOTf produced a 20:1 mixture of two alcohols in 66% isolated yield. As expected, the major product (**9**) was the alcohol formed from attack of **4a** on 2-heptanone (eq 7). The Lewis acid therefore



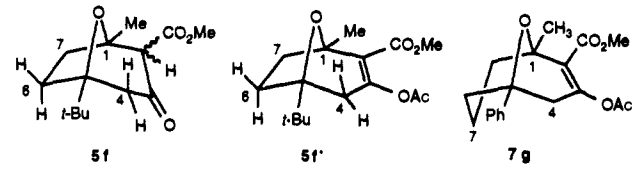
(7)

preferentially activates the less hindered ketone. However, cyclization of **4a** with 6,6-dimethyl-2,5-heptanedione (**1f**) again provided a quite unanticipated result. The major regioisomer generated was that owing to initial attack of the terminal carbon of **4a** at the more hindered carbonyl center of the dielectrophile (Table I, **5f**). This surprising regiochemistry, as well as that observed for the keto aldehyde dielectrophiles described above, can be explained by an unprecedented neighboring group participation mechanism (Scheme I). Activation of the less hindered ketone (or aldehyde)[21] by TMSOTf triggers formation of a cyclic oxocarbenium ion[22] via intramolecular attack of the more hindered carbonyl at the activated center.[12,23] Subsequent nucleophilic attack at the electronically activated oxocarbenium ion center would provide a neutral acetal intermediate which suffers further ring closure by TMSOTf-promoted cyclization, thereby providing the observed bicyclic ether. It is important to note that this sequence of events thus reverses the normal relative reactivity of the initial carbonyl units in the dielectrophile.

Further evidence for the role of intramolecular activation of electrophilic substrates in these processes derives from a competitive rate study between a dicarbonyl dielectrophile (4-oxoheptanal, **1c**) and 2-heptanone. Treatment of a 1:1 molar mixture of these electrophiles with 1 equiv of **4a** in the presence of TMSOTf provides a 57% isolated yield of **5c**. There is no trace of the product resulting from simple addition of the bis(trimethylsilyl) enol ether to 2-heptanone.

The regiochemistry of the bicyclic ethers was determined by examining nuclear Overhauser enhancements (NOE) obtained upon irradiation of the methyl or the *tert*-butyl group in the keto ester **5f** and its enol acetate derivative (**5f'**). Irradiation of the C-1 methyl singlet in both the enol acetate and the keto ester resulted in NOE enhancement of the methoxycarbonyl singlet. Enhancement was also observed for the C-2 *exo*-H in the bicyclic keto ester. Irradiation of the *tert*-butyl signal in both the bicyclic keto ester and its enol acetate derivative resulted in enhanced signals for protons at C-4 and C-6 (Table II).

Table II. NOE Data on Diketone Annulation Products

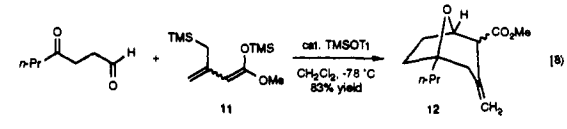


5f **5f'** **7g**

		% NOE					
compd	irrad	CO_2Me	exo-H_2	exo-H_4	endo-H_4	exo-H_6	exo-H_8
5f	C_1 Me	3.9	10.4				
5f	*t*-Bu			2.9	1.8	2.4	
5f'	C_1 Me	0.8					
5f'	*t*-Bu			7.2	6.1	8.1	
7g	C_1 Me	1					5.6

The propensity for these processes to provide this unusual regioselectivity is exceedingly high, and attempts at reversing the regiochemistry in the [3 + 4] annulation reaction met with little success. None of the Lewis acids surveyed generated **6** with high selectivity. The 1,4-dielectrophile was altered in an attempt to increase reactivity at C-1. Use of 1,4-keto acetal substrates was first attempted because it had been previously reported that TMSOTf activates acetals in preference to ketones and aldehydes.[24] Nevertheless, the annulation proceeded to afford the same regioisomer (**5**) as that obtained with 1,4-keto aldehydes. Again, neighboring group participation would explain this result. Preferential activation of the acetal by TMSOTf followed by intramolecular attack of the ketone carbonyl would generate the cyclic oxocarbenium ion. Nucleophilic attack and subsequent ring closure as explained earlier would lead to the observed product. Annulation of 1,4-ketal aldehydes and 1,4-ketal acetals gave similar results.

Alteration of the dinucleophilic synthon was also investigated. It had been previously reported that the 1,3-dianionic synthon **11** reacts initially to some degree at the internal carbon.[8d] It was envisioned that annulation of **11** with a 1,4-keto aldehyde should provide the "opposite" regioisomeric product from that observed with the bis(trimethylsilyl) enol ether dinucleophilic synthons. Reaction, however, occurred with the allyltrimethylsilane nucleophile attacking the ketone carbonyl first (γ attack) to afford **12** as a 1:1 mixture of ester epimers (eq 8). Regiochemistry was determined by ozonolysis of the double bond to provide **5c**.



(8)

Stereoselectivity in the [3 + 4] annulations was investigated by utilizing a series of chiral, racemic 1,4-keto aldehydes. In order

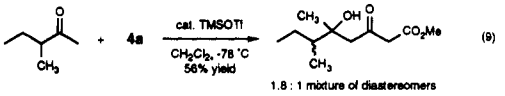
(21) (a) Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 2650. (b) Maruoka, K.; Araki, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3101. (c) Maruoka, K.; Nagahara, S.; Yamamoto, H. *Tetrahedron Lett.* **1990**, *31*, 5475.

(22) Spectroscopic evidence for this type of cationic intermediate has been gathered by Professor Stephen Castellino (private communication).

(23) Lewis acid-promoted intramolecular neighboring group participation has recently been demonstrated to provide an alternative means of obtaining high regio- and stereocontrol in carbon–carbon-bond-forming reactions. (a) Molander, G. A.; Bobbitt, K. L.; Murray, C. K. *J. Am. Chem. Soc.* **1992**, *114*, 2759. (b) Molander, G. A.; Haar, J. P., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 3608.

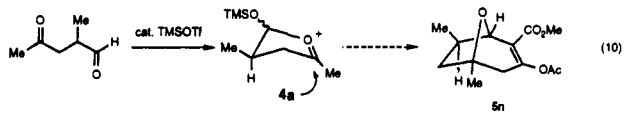
(24) (a) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259. (b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.

to deduce selectivities at the new stereocenter, the epimerizable center was removed by derivatization to the enol acetate. The observed stereoselectivities (5.4:1 to >160:1) were much higher than that achieved in the intermolecular reaction of **4a** with a simple acyclic ketone like 3-methyl-2-pentanone (1.8:1, eq 9), again suggesting the presence of a cyclic intermediate and reinforcing the idea of neighboring group participation. 1,3-Asymmetric



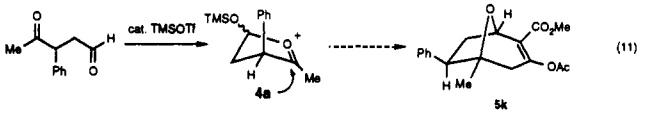
(9)

induction was examined by reaction of 2-substituted 1,4-keto aldehydes with **4a** to afford the corresponding bicyclic ethers with excellent stereoselectivities (13.5:1 to >160:1, Table I, **5n–q**). The substituent at the new stereocenter (C-7) was determined to be exo by examination of coupling constants in the ^{1}H NMR. Molecular models indicate that coupling of the bridgehead proton, H-1, should occur only with the exo proton at C-7. In the major diastereomer (**5n**), H-1 appears as a singlet in the ^{1}H NMR. The C-7 methyl group must therefore be in the exo position. H-1 in the minor diastereomer appears as a doublet (J = 5.86 Hz) in the ^{1}H NMR, coupling to the exo proton H-7 (methyl group endo). The stereoselectivity can be explained by preferential formation of an oxocarbenium ion which places the methyl substituent in the pseudoequatorial position. Pseudoaxial attack of **4a** would provide the observed major diastereomer (eq 10).



(10)

Annulation of 3-substituted 1,4-keto aldehydes (1,2-asymmetric induction) provided bicyclic ethers with good selectivity (5.4:1 to 15.6:1, Table I, **5j–l**). An X-ray crystal structure of **5k** indicated that the C-6 phenyl substituent in the major diastereomer is oriented exo on the bicyclic ether product. The stereochemistry can be explained by formation of an oxocarbenium ion which places the phenyl group in a pseudoaxial orientation. Pseudoaxial attack of the nucleophile would provide the observed major diastereomer (eq 11). Placing the phenyl group in the pseudo-



(11)

equatorial position would sterically hinder approach of the nucleophile to the electrophilic carbon. The two opposing effects (either placing the phenyl group in the pseudoaxial position or inhibiting the nucleophile's trajectory) probably compete with one another and contribute to the lower stereoselectivities observed as compared to the 1,3-asymmetric induction outlined above. This same trend was noted by Reissig and co-workers in the Lewis acid-catalyzed formation of disubstituted tetrahydrofuran derivatives from γ-lactols.[25] In those studies, boron trifluoride etherate was employed to promote allyltrimethylsilane substitution of methyl-substituted 2-hydroxytetrahydrofurans. The 4-methyl-substituted γ-lactol exhibited a 19:1 diastereoselectivity as compared to only a 2:1 diastereoselectivity observed for the 3-methyl-substituted γ-lactol. Five-membered-ring oxocarbenium ion transition-state models similar to those described herein were first proposed by Reissig and co-workers in their related study.[25]

Attempts at functionalizing the bicyclic ether system by incorporating heteroatoms into the dielectrophiles met with little success. The annulation of 3-methoxy-4-oxo-4-phenylbutanal (**1m**) provided only a 40% yield of the corresponding cyclization product as a 1.4:1 mixture of stereoisomers (Table I, **5m**). Competition for the Lewis acid may be occurring in this system. Replacement of the methoxy group with a less Lewis basic protected ether, such as a triphenylmethoxy or a *tert*-butyldimethylsiloxy group, did not seem to improve the results. Partial deprotection occurred under the reaction conditions.

(25) Schmitt, A.; Reissig, H.-U. *Synlett* **1991**, 40.

Table III. TMSOTf-Promoted Annulation of 4-Oxoheptanal with **4**

entry	substrate	product	R_6	R_7	% isoltd yield (**13** + **14**)[a]	**13**:**14**[b]
1	**4b**	**13b** + **14b**	OEt	H	84	
2	**4c**	**13c** + **14c**	O-*t*-Bu	H	80	
3	**4d**	**13d** + **14d**	Me	H	77	
4	**4e**	**13e** + **14e**	*t*-Bu	H	89	
5	**4f**	**13f** + **14f**	Me	Me	73	>40:1
6	**4g**	**13g** + **14g**	*t*-Bu	Me	80	1.3:1
7	**4h**	**13h** + **14h**	OEt	Me	76	1:>35
8	**4i**	**13i** + **14i**	OEt	*i*-Pr	73	1:25
9	**4j**	**13j** + **14j**	OCH_2CH_2		75	1:1.3

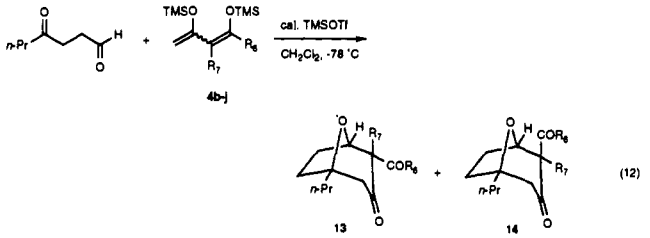
[a] Refers to yields of purified products as diastereomeric mixtures. All of these compounds have been fully characterized spectroscopically (^{1}H NMR, ^{13}C NMR, IR), and elemental composition has been established by combustion analysis and/or exact mass. [b] Diastereoselectivities and regioselectivities were determined by fused silica capillary GLC analysis.

Table IV. TMSOTf-Promoted Annulation of 4-Oxoheptanal with **4**

entry	substrate	product	R_8	% isoltd yield[a]	**15**:**16**[b]
1	**4k**	**15k** + **16k**	Me	72	5.4:1
2	**4l**	**15l** + **16l**	Et	60	16.5:1
3	**4m**	**15m** + **16m**	allyl	62	13.4:1
4	**4n**	**15n** + **16n**	Bn	64	34:1

[a] Refers to yields of purified products as diastereomeric mixtures. All of these compounds have been fully characterized spectroscopically (^{1}H NMR, ^{13}C NMR, IR), and elemental composition has been established by combustion analysis and/or exact mass. [b] Diastereoselectivities were determined by fused silica capillary GLC analysis.

Alternative bis(trimethylsilyl) enol ethers (**4b–e**, eq 12) employed in the [3 + 4] annulation reaction allow access to diverse bicyclic keto esters and diketones (Table III, entries 1–4). Stereoselectivities utilizing 2-substituted β-dicarbonyl dianionic synthons (**4f–j**) with 4-oxoheptanal in the presence of TMSOTf were also studied. One unusual feature of these reactions is that



(12)

the products derived from the reaction of 2-substituted bis(trimethylsilyl) enol ethers derived from β-keto esters (Table III, entries 7–9) have the opposite relative stereochemistry as that obtained by reaction of analogous 3-substituted bis(trimethylsilyl) enol ethers of β-diketones (Table III, entries 5 and 6). Relative stereochemistry was determined by alkylation of the appropriate bicyclic ether to generate the exo 2-substituted product (**13**). This product was identical to the major isomer isolated in the annulation of 4-oxoheptanal with bis(trimethylsilyl) enol ethers of 3-substituted β-diketones. The alkylation product, however, was the minor isomer obtained in the annulation utilizing 2-substituted bis(trimethylsilyl) enol ethers of β-keto esters. The annulation reaction appears to be under kinetic control because no epimerization occurred when products were resubjected to the reaction conditions. Although the origin of this phenomenon is as yet unknown, the ability to access both stereoisomeric product manifolds with functionalized quarternary stereogenic centers is impressive and potentially useful.

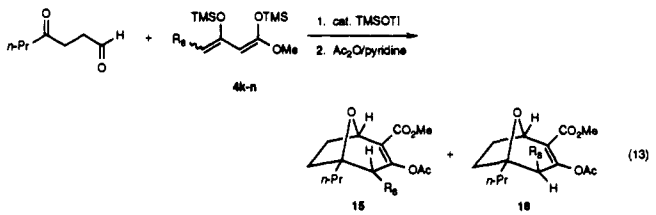
Substitution at the terminus of the bis(trimethylsilyl) enol ether (**4k–n**) allowed control of stereochemistry at C-4 of the bicyclic ether. Annulation of the bis(trimethylsilyl) enol ether of methyl 3-oxopentanoate (Table IV, entry 1) provided a 5.4:1 mixture of

Table V. Lewis Acid-Promoted Annulation of 1,5-Dicarbonyl Substrates (**2**) with **4a**

entry	product	R_1	R_2	R_3	R_4	R_5	% isoltd yield[a]	diastereoselectivity[b] (regioselectivity)
1	**7a**	Me	H	H	H	H	72	(>200:1)
2	**7b**	*n*-Pr	H	H	H	H	88	(>200:1)
3	**7c**	*i*-Pr	H	H	H	H	76	(>200:1)
4	**7d**	Ph	H	H	H	H	91	(>200:1)
5	**7e**	*t*-Bu	H	H	H	H	51	(>200:1)
6	**7f**	Me	H	H	H	Me	82	
7	**7g**	Ph	H	H	H	Me	69	(6:1)[c]
8	**19h**	Me	H	Me	H	Me	80	30:1[c]
9	**19i**	Et	Me	H	H	H	87	2:1[c]
10	**19j**	*i*-Pr	Me	H	H	H	56	2.8:1[c]
11	**19k**	Ph	Me	H	H	H	83	>200:1[c]
12	**19l**	Me	H	Me	H	H	74	14.8:1[c]
13	**19m**	Me	H	Ph	H	H	70	6:1[c]
14	**19n**	Ph	H	Me	H	H	78	>200:1[c]
15	**19o**	Me	H	H	Me	H	82	6.8:1[c]
16	**19p**	Ph	H	H	Me	H	60	8.2:1[c]
17	**19q**	Me	H	H	Ph	H	60	13.4:1[c]

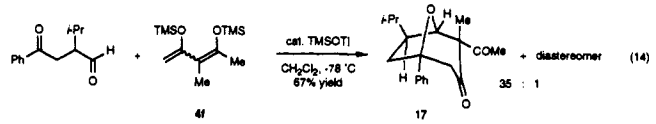
[a] Refers to yields of purified product as a mixture of diastereomers. Reactions in entries 6–8 were performed utilizing TMSOTf as a Lewis acid catalyst. All other reactions were performed utilizing $TrSbCl_6$ as a promoter. All of these compounds have been fully characterized spectroscopically (^1H NMR, ^{13}C NMR, IR), and elemental composition has been established by combustion analysis and/or exact mass. [b] Diastereoselectivities and regioselectivities were determined by fused silica capillary GLC analysis or by ^1H NMR. [c] The crude bicyclic keto ester was first derivatized to the corresponding enol acetate for determination of yield and diastereoselectivity.

stereoisomers (eq 13). Stereochemistry was determined by alkylation of the dianion of bicyclic ether **5c** (2 equiv of base, MeI) to provide (after formation of the enol acetate) the exo 4-methyl-substituted bicyclic ether **16**. This product was the minor diastereomer in the annulation reaction. Again, no epimerization occurred when the initial annulation products were resubjected to the experimental conditions. Additional substituted bis(trimethylsilyl) enol ethers were annulated with 4-oxoheptanal to afford the corresponding bicyclic compounds with high diastereoselectivities (13.4:1 to 34:1, Table IV, entries 2–4).



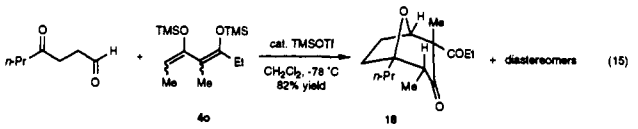
(13)

Two reactions were performed to demonstrate that stereochemical control at four centers on the bicyclic ring could be achieved in the annulation reactions. Thus, reaction of 2-isopropyl-4-oxo-4-phenylbutanal with **4f** generated the corresponding bicyclic ether **17** in 67% yield as a 35:1 mixture of two diastereomers (eq 14). Stereochemistry at C-7 was determined from coupling constants in the ^1H NMR as earlier explained. The *exo*-methyl configuration at C-2 was determined by comparison of chemical shifts with similar systems. The C-2 *exo*-methyl group typically falls around 1.6 ppm in the ^1H NMR (see spectral data for **17**, **13f**, and **13g**). The *endo*-methyl group, however, occurs further upfield in the ^1H NMR (1.17 ppm for **14g**). The oxygen bridge presumably causes a downfield shift for exo substituents.



(14)

Good selectivity was also achieved in the cyclization of 4-oxoheptanal with the bis(trimethylsilyl) enol ether of 4-methyl-3,5-heptanedione (**4o**), affording **18** as the major diastereomer (a 110:9:1.2:1 mixture of diastereomers was generated) in 82% yield (eq 15). The configuration at C-2 in the major diastereomer was determined from the chemical shift of the methyl singlet (1.59 ppm). Stereochemistry at C-4 was determined by comparison of the exo H-4 chemical shift (2.90 ppm) with that recorded for **15k** (quartet at 2.88 ppm). The chemical shift of endo H-4 (**16k**) falls further upfield (~2.05 ppm).[10] *W*-coupling of H-4 (J = 1.5 Hz) with H-6 could also be detected in the ^1H NMR of **18**, lending further support for the exo orientation of H-4.



(15)

Initial results obtained in the TMSOTf-promoted [3 + 5] annulation of 1,5-keto aldehydes were disappointing. Only a 28% yield of the corresponding bicyclic ether was achieved when **4a** was annulated with 5-oxooctanal and catalytic TMSOTf. However, utilization of catalytic (5–6 mol %) trityl hexachloroantimonate ($TrSbCl_6$)[26] with various 1,5-keto aldehydes and **4a** provided the bicyclic ethers (**7**) in 51–91% yields (Table V, entries 1–5). Again, only one regioisomer was detected (R_5 = H, eq 2). In the [3 + 5] annulation reaction of 1,5-keto aldehydes, the bicyclic ether isolated exists primarily in the enol form as deduced by NMR.

When utilizing 1,5-diketones in the [3 + 5] annulation reaction with **4a**, TMSOTf again proved to be the ideal catalyst. $TrSbCl_6$ provided only a 55% yield of the bicyclic ether (**7f**) when 2,6-octanedione was annulated with **4a**. A yield of 82% was attained when TMSOTf catalyzed the same reaction (Table V, entry 6). Chemoselectivity was examined with one unsymmetrical diketone. A 6:1 mixture of regioisomers (**7**:**8**, eq 2) was isolated when 6-phenyl-2,6-hexanedione was annulated with **4a** (Table V, entry 7). Regiochemistry was determined by nuclear Overhauser enhancement in the manner described earlier for compound **5f** (Table II).

Investigations were carried out on the [3 + 5] annulation series to determine the relative asymmetric induction that could be achieved by placing substituents at three different centers (R_2, R_3, and R_4, eq 16) on the dicarbonyl substrate. One can predict the outcome of each reaction by analyzing conformations of the proposed cyclic oxocarbenium ion intermediate (eq 16). Substituents R_3 and R_4 should reside in the more favorable equatorial orientation, thereby locking the intermediate in a relatively rigid half-chair conformation. This tenet, combined with stereoelectronically favored axial attack[27] of **4a** on the oxocarbenium ion, should serve to predict the stereochemical outcome of the annulations in a completely reliable manner. As described below, the

(26) Kobayashi, S.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 1535.

(27) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983. (b) Nasipuri, D. *Stereochemistry of Organic Compounds*; Wiley: New York, 1991. (c) Davis, A. B.; Hegarty, S. C. *J. Am. Chem. Soc.* **1992**, *114*, 2745.

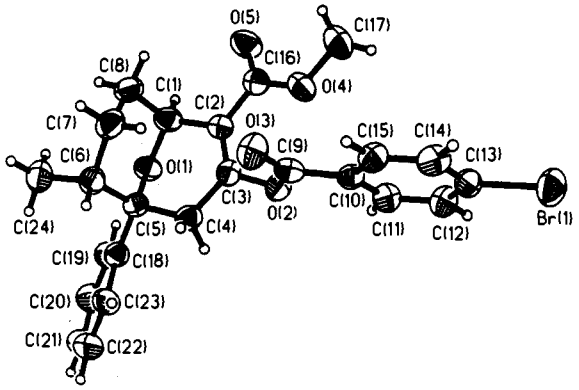


Figure 1. ORTEP diagram of compound **20**.

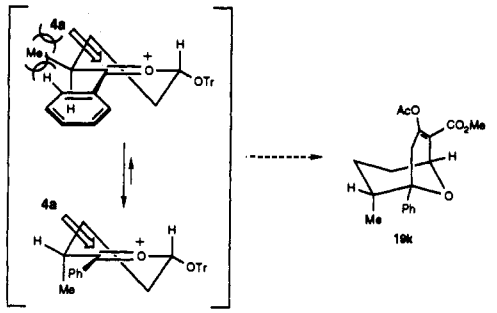
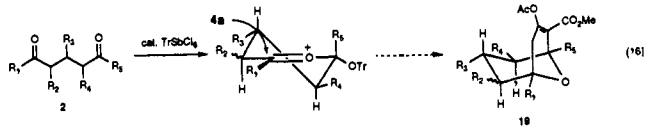


Figure 2. Proposed intermediates for synthesis of bicyclic ether **19k**.

situation with substituent R_2 is somewhat more complicated. In any event, it is useful to note that in reactions of **4a** with chiral dielectrophiles, all of the stereochemistry is established in the initial carbon–carbon-bond-forming reaction. Thus a high degree of relative asymmetric induction is imperative in this step in order for high overall selectivity to be established.



(16)

Annulation of 4-methyl-5-oxo-5-phenylpentanal with **4a** in the presence of $TrSbCl_6$ provided a single diastereomer in 83% yield (Table V, entry 11). Preparation of the crystalline *p*-bromobenzoyl ester derivative (**20**, Figure 1) provided crystals suitable for X-ray structure determination. This analysis revealed that the C-6 methyl group was oriented exo on the bicyclic ring. These results can be explained in the following manner: Formation of the intermediate oxocarbenium ion places significant positive charge adjacent to the phenyl group. Conjugation of the aryl unit with this charged center serves to lock the phenyl ring in a plane with the oxocarbenium ion in order to increase orbital overlap. This conformation creates severe steric interactions ($A^{1,2}$ strain[27b,28]) between the bulky phenyl ring and any substituent oriented pseudoequatorially on the adjacent carbon of the cyclic oxocarbenium ion (Figure 2). Furthermore, axial attack of the nucleophile on the oxocarbenium ion would be sterically hindered by an adjacent pseudoequatorial substituent. However, placing the methyl group in the pseudoaxial position relieves both of these interactions. Unhindered axial attack of the nucleophile on this conformation of the phenyl-substituted oxocarbenium ion generates the observed exo diastereomer (**19k**).

In contrast to the phenyl-substituted keto aldehyde dielectrophile, $TrSbCl_6$-promoted reaction of 4-substituted 1,5-keto aldehydes with **4a** provided low diastereoselectivities (2:1 to 2.8:1, Table V, entries 9 and 10) in the annulation process. Because the two diastereomers were inseparable in both cases, the relative stereochemistry of the major isomer was not determined. The poor selectivities observed in compounds **19i** and **19j** can be rationalized using conformational arguments based upon their respective oxocarbenium ion intermediates. Placing the methyl substituent (R_2 in eq 16) in the pseudoequatorial orientation again results in a steric interaction between this group and the incoming nucleophile and also creates some $A^{1,2}$ strain (but not nearly as great as in the phenyl-substituted keto aldehyde).[27b,28] Consequently, this transition state competes with that of one placing the methyl substituent in the pseudoaxial orientation, thereby contributing to the low diastereoselectivities observed.

In contrast to the poor 1,2 relative asymmetric induction generally observed, excellent 1,3-diastereoselectivity could be achieved (6:1 to >200:1, Table V, entries 8 and 12–14). Annulation of the symmetrical diketone, 4-methyl-2,6-heptanedione with **4a** in the presence of TMSOTf provided a 30:1 mixture of diastereomers. The relative stereochemistry of the major diastereomer was determined by single-crystal X-ray analysis of **19h**. This examination revealed that the major diastereomer possesses an exo C-7 methyl group, as predicted by the oxocarbenium ion intermediate (eq 16). That 1,3 relative asymmetric induction is higher than that of 1,2 relative asymmetric induction lends further support to the involvement of neighboring group participation. Unlike acyclic stereochemical control, where proximity of the determinative stereogenic center to the prostereogenic center is critical for high relative asymmetric induction, for cyclic intermediates conformational effects override proximity as the predominant factor in determining both the sense and magnitude of relative asymmetric induction.[29]

The sense and magnitude of 1,4-asymmetric induction were determined by annulation of 2-methyl-5-oxohexanal with **4a** in the presence of $TrSbCl_6$ (6.8:1, Table V, entry 15). An X-ray crystal structure of the major stereoisomer (**19o**) indicated that the methyl group resides endo in the final product. This stereochemistry was also correctly predicted by the proposed intermediate as outlined above (R_4 equatorial in the transition state, eq 16). Again as a consequence of the cyclic nature of the intermediate, superb 1,4-asymmetric induction (6.8:1 to 13.4:1, Table V, entries 15–17) was achieved in the [3 + 5] annulation reaction.

Conclusions

The Lewis acid-promoted [3 + 4] and [3 + 5] annulation reactions of dicarbonyl substrates with bis(trimethylsilyl) enol ether dinucleophilic synthons have been showcased as an efficient means of synthesizing a variety of bicyclic ether ring systems. High regiocontrol and stereocontrol are attained in these cyclizations wherein multiple stereogenic centers are generated. A mechanism involving intramolecular neighboring group participation has been proposed to explain the results obtained in this study. Through this unique mechanism, predictably high regioselectivity and stereoselectivity are achieved via an unprecedented reactivity pattern.

Experimental Section

Reagents. Tetrahydrofuran (THF) was distilled immediately prior to use from benzophenone ketyl under Ar. CH_2Cl_2 was stirred over sulfuric acid, decanted, and stirred over K_2CO_3. It was distilled from CaH_2 onto 4-Å molecular sieves and was stored over 4-Å molecular sieves. Standard benchtop techniques were employed for handling air-sensitive reagents,[30] and all reactions were carried out under Ar.

General Procedure for the Synthesis of 4-Alken-1-ones and 5-Alken-1-ones. To a solution of dimethylhydrazone (19 mmol) in THF (20 mL) at 0 °C was added 14.0 mL of *n*-BuLi (1.6 M in hexanes, 22.4 mmol) dropwise.[14] After 40 min, allyl bromide (4-alken-1-one) or 4-bromo-1-butene (5-alken-1-one) (23 mmol) was slowly added, and the solution was warmed to room temperature. After stirring for 1.5–16 h, H_2O was added and the product was extracted into EtOAc. The volatiles were removed in vacuo. Acetone (100 mL) and wet Amberlyst-15 (8 g) were added to the residue.[15] The mixture was stirred until no starting material

(28) (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859. (c) Potapov, V. M. *Stereochemistry*; Mir Publishers: Moscow, 1978.

(29) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036.

(30) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975.

was present by GLC. The resin was removed by filtration through Celite and the solution was concentrated. The product was purified by flash chromatography.

7-Octen-4-one was isolated in 68% yield. The purity of the ketone was >95% by GLC: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (m, 1 H), 4.95 (m, 2 H), 2.46 (t, J = 6.8 Hz, 2 H), 2.38–2.26 (m, 4 H), 1.56 (m, 2 H), 0.87 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.16, 137.12, 114.99, 44.62, 41.61, 27.61, 17.06, 13.54.

2,2-Dimethyl-6-hepten-3-one was isolated in 60% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 1 H), 4.98 (m, 2 H), 2.55 (m, 2 H), 2.27 (m, 2 H), 1.12 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.19, 137.66, 115.03, 44.02, 35.69, 27.91, 26.36; IR ($CHCl_3$) 2960, 1700, 1640, 1470, 910 cm^{-1}.

1-Phenyl-4-penten-1-one was isolated in 88% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (m, 2 H), 7.52–7.40 (m, 3 H), 5.86 (m, 1 H), 5.02 (m, 2 H), 3.04 (t, J = 7.4 Hz, 2 H), 2.46 (m, 2 H).

2-Methyl-6-hepten-3-one was isolated in 62% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (m, 1 H), 4.85 (m, 2 H), 2.42 (m, 2 H), 2.17 (m, 2 H), 0.95 (d, J = 6.8 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.54, 137.24, 114.88, 40.61, 39.20, 27.57, 17.97.

4-Methyl-6-hepten-3-one was isolated in 67% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (m, 1 H), 4.95 (m, 2 H), 2.54 (m, 1 H), 2.38 (m, 2 H), 2.30 (m, 1 H), 2.01 (m, 1 H), 1.00 (d, J = 7.1 Hz, 3 H), 0.96 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.36, 135.71, 116.57, 45.55, 37.08, 34.29, 16.01, 7.49.

2-Methyl-7-octen-3-one was isolated in 57% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (m, 1 H), 4.95 (m, 2 H), 2.56 (m, 1 H), 2.42 (t, J = 7.3 Hz, 2 H), 2.02 (m, 2 H), 1.64 (m, 2 H), 1.05 (d, J = 6.7 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.76, 138.13, 115.10, 40.80, 39.33, 33.08, 22.66, 18.18.

1-Phenyl-5-hexen-1-one was isolated in 68% yield. The purity was 99% by GLC: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (m, 2 H), 7.56–7.40 (m, 3 H), 5.85–5.76 (m, 1 H), 4.97 (m, 2 H), 2.95 (t, J = 7.3 Hz, 2 H), 2.09 (m, 2 H), 1.83 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.25, 138.05, 137.05, 132.90, 128.54, 128.00, 115.26, 37.62, 33.11, 23.20.

2-Methyl-1-phenyl-5-hexen-1-one was isolated in 93% yield. The purity was 89% by GLC: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (m, 2 H), 7.42 (m, 3 H), 5.78 (m, 1 H), 4.98 (m, 2 H), 3.50 (m, 1 H), 2.08 (m, 2 H), 1.95 (m, 1 H), 1.53 (m, 1 H), 1.19 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.29, 138.10, 136.68, 132.84, 128.60, 128.23, 115.12, 39.64, 32.52, 31.39, 17.19.

General Procedure for the Synthesis of 1,1-Dimethoxy-4-alkanones. A solution of dimethylhydrazone (6.435 g, 40 mmol) in THF (50 mL) was cooled to 0 °C, and 26.0 mL of *n*-BuLi (1.6 M in hexanes, 42 mmol) was added dropwise. After the mixture was stirred for 25 min, bromoacetaldehyde dimethyl acetal (8.6 g, 47 mmol) was quickly added and the solution was warmed to room temperature. The reaction was quenched with H_2O after 18 h, and the product was extracted into Et_2O. The ethereal solution was washed with brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in CH_2Cl_2 (100 mL) and MeOH (100 mL), and O_3 was bubbled into the solution at −78 °C until it turned blue. The solution was purged with Ar until colorless, and excess Me_2S was added. After the solution was warmed to room temperature, the volatiles were removed in vacuo. The residue was dissolved in pentane and washed with water followed by brine. The organic solution was dried ($MgSO_4$) and concentrated. The ketone was purified by flash chromatography (3:1 hexanes/EtOAc).

1,1-Dimethoxy-4-phenyl-4-butanone was isolated as a yellow-orange liquid in 52% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (m, 2 H), 7.50–7.37 (m, 3 H), 4.42 (t, J = 5.5 Hz, 1 H), 3.29 (s, 6 H), 3.00 (t, J = 7.2 Hz, 2 H), 2.00 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.44, 136.82, 132.91, 128.46, 127.91, 103.82, 53.10, 33.09, 26.78.

1,1-Dimethoxy-5,5-dimethyl-4-hexanone was isolated in 37% yield as a yellow liquid which was 91% pure by GLC: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32 (t, J = 5.5 Hz, 1 H), 3.28 (s, 6 H), 2.52 (t, J = 7.2 Hz, 2 H), 1.82 (q, J = 7.2 Hz, 2 H), 1.10 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.10, 103.70, 52.87, 43.85, 30.92, 26.17, 25.11.

2,4-Dimethyl-4-pentenal. The cyclohexyl imine of propanal (1.912 g, 13.73 mmol) was added dropwise to a freshly prepared solution of LDA (14.4 mmol) in THF (20 mL) at 0 °C. The solution was stirred at 0 °C for 2.5 h, and 1-iodo-2-methyl-2-propene (2.953 g, 15.68 mmol) was slowly added. After 1 h, the solution was quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine and dried ($MgSO_4$). The material was purified by flash chromatography (5:1 hexanes/EtOAc) followed by Kugelrohr distillation to yield the title compound as a clear and colorless liquid (0.580 g, 38%): ot 46–54 °C/8 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, J = 1.7 Hz, 1 H), 4.79 (s, 1 H), 4.70 (s, 1 H), 2.58–2.38 (m, 2 H), 2.42 (m, 1 H), 1.70 (s, 3 H), 1.05 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.86, 142.18, 112.77, 44.12, 38.78, 22.16, 13.18.

3-Phenyl-5-hexen-2-one. To a solution of oil-free NaH (709 mg, 29.5 mmol) in THF (40 mL) at 0 °C was added phenylacetone[31] (3.0913 g, 23.040 mmol) dropwise. Allyl bromide (3.39 g, 28 mmol) was slowly added after 0.5 h, and the solution was warmed to room temperature. After 45 min, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (4:1 hexanes/EtOAc) provided the title compound as a yellow liquid (3.6154 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.22 (m, 5 H), 5.68 (m, 1 H), 4.97 (m, 2 H), 3.72 (t, J = 7.6 Hz, 1 H), 2.82 (m, 1 H), 2.46 (m, 1 H), 2.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.64, 138.37, 135.75, 128.91, 128.26, 127.34, 116.57, 59.37, 36.06, 28.99.

2-Methoxy-1-phenyl-4-penten-1-one. To a solution of freshly prepared LDA (34.7 mmol) in THF (35 mL) at −78 °C was added 2-methoxyacetophenone (4.32 g, 28.7 mmol) dropwise. After 25 min, allyl bromide (4.2 g, 35 mmol) was slowly added and the solution was warmed to room temperature. The reaction was quenched with H_2O after 18 h, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (3:1 hexanes/EtOAc, 6:1 hexanes/EtOAc) provided the title compound as a pale yellow liquid (3.543 g, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (m, 2 H), 7.56 (m, 1 H), 7.46 (m, 2 H), 5.86 (m, 1 H), 5.08 (m, 2 H), 4.56 (m, 1 H), 3.39, (s, 3 H), 2.58 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.49, 135.04, 133.24, 133.08, 128.48, 128.46, 117.60, 83.80, 57.40, 36.97.

General Procedure for the Preparation of 1,4-Keto Aldehydes. Method A.[16a,b] O_3 was bubbled into a −78 °C solution of the 4-alken-1-one (54 mmol) in CH_2Cl_2/MeOH (1:1, 160 mL) containing catalytic $NaHCO_3$ until the blue color persisted. The solution was purged with Ar until colorless, and excess Me_2S was added. The solution was warmed to room temperature and stirred for 5 h. The volatiles were removed in vacuo, and the residue was purified by flash chromatography followed by Kugelrohr distillation.

Method B.[16c] The ozonolysis was performed utilizing MeOH as the solvent. No $NaHCO_3$ was added to the solution. The solution was purged with Ar until colorless, and Zn (3.5 equiv) and AcOH (16 equiv) were added. The mixture was warmed to room temperature and stirred for 2 h. Water was added and the solution was decanted from the zinc. The aqueous solution was extracted with CH_2Cl_2, and the combined extracts were washed with water and aqueous $NaHCO_3$ (5%). The solution was dried (K_2CO_3), filtered, and concentrated. The residue was purified by flash chromatography followed by Kugelrohr distillation.

Method C. The ozonolysis was performed as described in method A except PBu_3 (1.5–2 equiv) was employed as the reducing reagent. The solution was stirred at room temperature for 1 h, and the volatiles were removed in vacuo. The keto aldehyde was purified by flash chromatography followed by Kugelrohr distillation.

4-Oxopentanal (1b) was prepared by method A in 54% yield: ot 100–105 °C/20 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1 H), 2.65 (s, 4 H), 2.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.47, 200.52, 37.16, 35.26, 29.52; IR (neat) 2909, 2836, 1714, 1407, 1366, 1169 cm^{-1}; MS (EI$^+$) m/e 101 (4), 99 (4), 72 (18), 43 (100).

4-Oxoheptanal (1c) was prepared by method A in 30% yield. The purity was >95% as indicated by GLC: ot <60 °C/0.5 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1 H), 2.58 (s, 4 H), 2.30 (t, J = 7.3 Hz, 2 H), 1.46 (q, J = 7.3 Hz, 2 H), 0.76 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.62, 200.47, 44.18, 37.07, 34.29, 16.92, 13.29; IR (neat) 2964, 1716, 1460, 1386, 1128, 1023 cm^{-1}; MS (EI$^+$) m/e 129 (18), 100 (20), 85 (58), 71 (57), 57 (22), 43 (100).

3-Methyl-4-oxohexanal (1j) was prepared by method **B** in 22% yield. The purity was 94% by GLC: ot 86–90 °C/8 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1 H), 3.03–2.83 (m, 2 H), 2.58–2.38 (m, 3 H), 1.10 (d, J = 6.8 Hz, 3 H), 1.03 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.33, 200.65, 46.71, 39.70, 34.08, 16.79, 7.64; IR ($CDCl_3$) 2974, 1713, 1460 cm^{-1}.

4-Oxo-3-phenylpentanal (1k) was prepared by method **B** in 83% yield: ot 76–82 °C/0.25 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1 H), 7.41–7.22 (m, 5 H), 4.28 (dd, J = 4.2, 9.8 Hz, 1 H), 3.46 (dd, J = 9.8, 18.6 Hz, 1 H), 2.69 (dd, J = 4.2, 18.6 Hz, 1 H), 2.12 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.14, 199.80, 137.36, 128.97, 127.96, 127.47, 52.45, 46.25, 28.36.

3-Methoxy-4-oxo-4-phenylbutanal (1m) was prepared by method B in 65% yield: ot 79–82 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (t, J = 1.3 Hz, 1 H), 7.77 (m, 2 H), 7.36 (m, 1 H), 7.24 (m, 2 H), 4.91 (t, J = 6.1 Hz, 1 H), 3.16 (s, 3 H), 2.67 (m, 2 H); ^{13}C NMR (75

(31) Prepared by PDC oxidation of *sec*-phenethyl alcohol: Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

MHz, $CDCl_3$) δ 198.81, 197.90, 134.57, 133.64, 128.66, 128.56, 77.90, 57.42, 44.92.

2-Methyl-4-oxopentanal (1n) was prepared by method C in 22% yield: ot 76–80 °C/8 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1 H), 2.85 (m, 2 H), 2.42 (m, 1 H), 2.15 (s, 3 H), 1.10 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.38, 203.23, 43.80, 41.38, 29.95, 13.27; IR ($CDCl_3$) 2968, 1713, 1364, 1171 cm^{-1}.

General Procedure for the Preparation of 1,4-Keto Aldehydes (1d and 1e). A solution of 1,1-dimethoxy-4-alkanone (24 mmol) was dissolved in $CHCl_3$ (70 mL), and 1:1 mixture of CF_3CO_2H/H_2O (35 mL) was added.[18] The solution was stirred for 2 h and the layers were separated. The aqueous layer was extracted into $CHCl_3$, and the combined organic layers were washed with aqueous $NaHCO_3$ (5%) followed by brine. The solution was dried (K_2CO_3) and concentrated in vacuo. The keto aldehyde was purified by flash chromatography followed by Kugelrohr distillation.

4-Oxo-4-phenylbutanal (1d) was isolated in 54% yield. The purity was 97% by GLC: ot 100–110 °C/0.06 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1 H), 7.95 (m, 2 H), 7.54 (m, 1 H), 7.44 (m, 2 H), 3.30 (t, J = 6.2 Hz, 2 H), 2.90 (t, J = 6.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.49, 197.55, 136.05, 132.92, 128.28, 127.67, 37.09, 30.59; IR (neat) 3062, 2908, 2831, 1717, 1684, 1398, 1209, 983, 692 cm^{-1}; MS (EI^+) m/e 178 (14), 163 (11), 134 (30), 105 (100), 77 (73), 51 (28).

5,5-Dimethyl-4-oxohexanal (1e) was isolated in 44% yield. The purity was 98% by GLC: ot 40–44 °C/0.3 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1 H), 2.78 (m, 2 H), 2.68 (m, 2 H), 1.14 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.93, 200.78, 43.86, 37.52, 29.06, 26.42; IR (neat) 2969, 1704, 1661, 1478, 1366, 1092 cm^{-1}; MS (EI^+) m/e 140 (5), 114 (10), 85 (36), 57 (100), 41 (38).

General Procedure for the Preparation of 2-Substituted 1,4-Keto Aldehydes.[19] A solution of the diisobutyl enamine of the aldehyde (9 mmol) and the α-bromo ketone (6 mmol) in benzene (3 mL) was stirred at room temperature for 22 h. H_2O was added and the layers were separated. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography followed by Kugelrohr distillation provided the 1,4-keto aldehyde.

2-Isopropyl-4-oxopentanal (1o). The reaction was performed neat, and **1o** was isolated in 34% yield: ot 42–48 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1 H), 2.82 (m, 2 H), 2.26 (m, 1 H), 2.12 (s, 3 H), 2.09 (m, 1 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.83 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.98, 203.71, 52.48, 38.43, 30.04, 27.35, 20.24, 19.12.

2-Methyl-4-oxo-4-phenylbutanal (1p) was isolated in 63% yield. The purity was >98% by GLC: ot 83–88 °C/0.5 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1 H), 7.88 (m, 2 H), 7.48 (m, 1 H), 7.37 (m, 2 H), 3.40 (dd, J = 6.4, 17.3 Hz, 1 H), 2.96 (m, 2 H), 1.14 (d, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.25, 197.60, 136.36, 133.11, 128.44, 127.86, 41.35, 39.13, 13.41.

2-Isopropyl-4-oxo-4-phenylbutanal (1q) was isolated in 72% yield. The purity was 96% by GLC: ot 94–100 °C/0.15 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1 H), 7.95 (m, 2 H), 7.58–7.39 (m, 3 H), 3.49 (dd, J = 9.3, 17.8, Hz, 1 H), 3.10 (m, 1 H), 2.88 (dd, J = 3.7, 17.8 Hz, 1 H), 2.22 (m, 1 H), 1.03 (d, J = 6.8 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.84, 198.34, 136.68, 133.19, 128.56, 128.04, 52.46, 34.16, 27.77, 20.34, 19.44.

Preparation of 3-Isopropyl-6-methyl-4-oxoheptanal (1l). To a solution of LDA (37.4 mmol) in THF (50 mL) at −78 °C was slowly added 2,6-dimethyl-4-heptanone (4.7259 g, 33.225 mmol). After 0.5 h, allyl bromide (4.7 g, 39 mmol) was added dropwise, and the reaction was warmed to room temperature. The reaction was quenched with saturated aqueous NH_4Cl after 21 h, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in CH_2Cl_2 (100 mL), and MeOH (20 mL) and $NaHCO_3$ (100 mg) were added. O_3 was bubbled into the mixture at −78 °C until it turned blue. Argon was bubbled into the solution until colorless, and excess Me_2S (5.0 mL) was added. The reaction was warmed to room temperature and stirred for 22 h. The volatiles were removed in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) followed by Kugelrohr distillation provided **1l** as a clear and colorless liquid (3.4059 g, 56%): ot 62–70 °C/0.15 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1 H), 2.91 (m, 2 H), 2.46 (dd, J = 6.3, 17.1 Hz, 1 H), 2.31 (m, 2 H), 2.19–1.92 (m, 2 H), 0.90 (d, J = 7.0 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.83 (d, J = 6.6 Hz, 3 H), 0.73 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.73, 201.08, 51.37, 51.31, 40.58, 28.48, 23.83, 22.48, 22.43, 22.36, 21.05, 18.10.

General Procedure for the Preparation of 1,4- and 1,5-Diketones.[17a] A solution of alkenone (18.3 mmol), p-benzoquinone (2.00 g, 18.5 mmol), and DMF (25 mL) was prepared in a 3-neck round-bottom flask equipped with a condenser and a thermometer. $PdCl_2$ (470 mg, 2.65 mmol) was added followed by H_2O (1.5 mL). The solution was heated to 70 °C, and H_2O (1.0 mL) was added at 0.5-h intervals for 1.5 h. After heating for 3 h, the mixture was cooled and H_2O was added. The product was extracted with pentane, and the combined pentane layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The diketone was purified by flash chromatography (3:1 hexanes/EtOAc) followed by Kugelrohr distillation.

6,6-Dimethyl-2,5-heptanedione (1f) was isolated in 49% yield: ot <80 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 2.72 (m, 2 H), 2.63 (m, 2 H), 2.14 (s, 3 H), 1.10 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.68, 207.52, 43.81, 36.88, 30.50, 29.98, 26.45; IR (neat) 2970, 1706, 1479, 1365, 1162, 1087, 995 cm^{-1}; MS (EI^+) m/e 141 (0.4), 123 (0.5), 99 (100), 81 (2), 71 (10), 57 (23), 43 (19).

5-Phenyl-2,5-pentanedione (1g) was isolated in 50% yield: ot 110–120 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (m, 2 H), 7.52 (m, 1 H), 7.44 (m, 2 H), 3.23 (t, J = 6.3 Hz, 2 H), 2.84 (t, J = 6.3 Hz, 2 H), 2.21 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.26, 198.47, 136.56, 133.08, 128.50, 127.96, 36.89, 32.27, 29.94.

6-Methyl-2,5-heptanedione (1h) was isolated in 47% yield: ot <60 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 2.65 (s, 4 H), 2.59 (m, 1 H), 1.06 (s, 3 H), 1.05 (d, J = 7.0 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.33, 207.43, 40.72, 36.81, 33.74, 29.92, 18.18; IR (neat) 2971, 1711, 1362 cm^{-1}; MS (EI^+) m/e 143 (100), 142 (2), 125 (10), 99 (82), 71 (22), 43 (36).

2,5-Octanedione (1i) was isolated in 43% yield: ot <60 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 2.61 (m, 4 H), 2.37 (t, J = 7.3 Hz, 2 H), 2.12 (s, 3 H), 1.53 (m, 2 H), 0.84 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.42, 207.17, 44.66, 36.69, 35.88, 29.74, 17.08, 13.49; IR (neat) 2964, 1716 cm^{-1}; MS (EI^+) m/e 143 (100), 142 (8), 114 (12), 99 (51), 71 (48), 43 (66).

1-Phenyl-1,5-hexanedione (7g) was isolated in 25% yield: ot <140 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (m, 2 H), 7.50–7.37 (m, 3 H), 2.96 (t, J = 7.1 Hz, 2 H), 2.52 (t, J = 7.1 Hz, 2 H), 2.09 (s, 3 H), 1.96 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.50, 199.75, 136.78, 133.06, 128.57, 128.00, 42.49, 37.29, 29.84, 18.08.

General Procedure for the Preparation of 1,5-Keto Aldehydes. To a solution of the dimethylhydrazone (1 equiv) at 0 °C was added n-BuLi (1.2 equiv) dropwise.[14] After 40 min, the iodo acetal[20] (1.2 equiv) was added slowly, and the ice bath was removed. The reaction was quenched with H_2O and the aqueous layer was extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered, and concentrated. To the residue was added 0.5 M HCl (167 mL), and the mixture was stirred for 30–60 min until no starting material remained by GLC. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with H_2O and aqueous $NaHCO_3$ (5%). The organic solution was dried (K_2CO_3), filtered, and concentrated. Flash chromatography followed by Kugelrohr distillation provided the 1,5-keto aldehydes.

5-Oxohexanal (2a). Using the general procedure described above, the dimethylhydrazone of acetone was alkylated (16 h) with 2-(2-iodoethyl)-1,3-dioxolane to provide **2a** as a clear and colorless liquid in 15% yield. The purity was >95% by GLC: ot 40–50 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (t, J = 1.3 Hz, 1 H), 2.42 (m, 4 H), 2.07 (s, 3 H), 1.82 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.91, 201.83, 42.75, 42.12, 29.77, 15.83.

5-Oxooctanal (2b). Using the general procedure described above, the dimethylhydrazone of 2-pentanone was alkylated (15 h) with 2-(2-iodoethyl)-1,3-dioxolane to provide **2b** as a clear and colorless liquid in 60% yield: ot 44–60 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (t, J = 1.5 Hz, 1 H), 2.43 (m, 4 H), 2.32 (t, J = 7.3 Hz, 2 H), 1.84 (m, 2 H), 1.53 (m, 2 H), 0.85 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.26, 201.93, 44.64, 42.90, 41.21, 17.14, 15.91, 13.59.

6,6-Dimethyl-5-oxoheptanal (2e). Using the general procedure described above, the dimethylhydrazone of pinacolone was alkylated (40 h) with 2-(2-iodoethyl)-1,3-dioxolane to provide **2e** as a clear and colorless liquid in 55% yield: ot 62–68 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (t, J = 1.5 Hz, 1 H), 2.49 (t, J = 7.1 Hz, 2 H), 2.40 (td, J = 7.1, 1.5 Hz, 2 H), 1.82 (m, 2 H), 1.06 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.19, 202.10, 43.94, 42.96, 35.08, 26.23, 16.18.

4-Methyl-5-oxoheptanal (2i). Using the general procedure described above, the dimethylhydrazone of 3-pentanone was alkylated (20 h) with 2-(2-iodoethyl)-1,3-dioxolane to provide **2i** as a clear and colorless liquid in 61% yield. The purity was >95% by GLC: ot 66–74 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (t, J = 1.5 Hz, 1 H), 2.61–2.22 (m, 5 H), 1.91 (m, 1 H), 1.62 (m, 1 H), 1.05 (d, J = 7.1 Hz, 3 H), 0.98 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.45, 201.81, 44.82, 41.34, 34.26, 24.62, 16.57, 7.60.

4,6-Dimethyl-5-oxoheptanal (2j). Using the general procedure described above, the dimethylhydrazone of 2-methyl-3-pentanone was alkylated (40 h) with 2-(2-iodoethyl)-1,3-dioxolane to provide **2j** as a clear

and colorless liquid in 63% yield. The purity was >95% by GLC: ot 66–72 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (t, J = 1.5 Hz, 1 H), 2.67 (m, 2 H), 2.32 (m, 2 H), 1.89 (m, 1 H), 1.61 (m, 1 H), 1.02 (d, J = 7.3 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H), 0.99 (d, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.47, 201.75, 43.11, 41.40, 39.36, 24.64, 18.22, 17.97, 16.84.

3-Methyl-5-oxohexanal (2l). Using the general procedure described above, the dimethylhydrazone of acetone was alkylated (19 h) with 2-(2-iodo-2-methylethyl)-1,3-dioxolane[32] to provide **2l** as a clear and colorless liquid in 21% yield. The purity was >95% by GLC: ot 46–50 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (t, J = 1.8 Hz, 1 H), 2.50 (m, 1 H), 2.43 (m, 1 H), 2.35 (m, 2 H), 2.25 (m, 1 H), 2.05 (s, 3 H), 0.91 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.60, 201.83, 50.12, 49.77, 30.21, 23.79, 20.03.

3-Methyl-5-oxo-5-phenylpentanal (2n). Using the general procedure described above, the dimethylhydrazone of acetophenone was alkylated (18 h) with 2-(2-iodo-2-methylethyl)-1,3-dioxolane[32] to provide **2n** in 60% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, J = 1.7 Hz, 1 H), 7.92 (m, 2 H), 7.51 (m, 1 H), 7.42 (m, 2 H), 3.00 (m, 1 H), 2.86 (m, 1 H), 2.74 (m, 1 H), 2.54 (m, 1 H), 2.35 (m, 1 H), 1.03 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.91, 199.02, 136.85, 133.07, 128.53, 127.95, 50.34, 44.74, 24.36, 20.20.

2-Methyl-5-oxohexanal (2o). Using the general procedure described above, the dimethylhydrazone of acetone was alkylated (24 h) with 2-(2-iodo-1-methylethyl)-1,3-dioxolane[33] to provide **2o** as a clear and colorless liquid in 35% yield. The purity was >95% by GLC: ot 58–66 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (t, J = 1.7 Hz, 1 H), 2.41 (t, J = 7.1 Hz, 2 H), 2.28 (m, 1 H), 2.06 (s, 3 H), 1.86 (m, 1 H), 1.57 (m, 1 H), 1.02 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.85, 204.39, 45.33, 40.35, 29.81, 23.86, 13.29.

2-Phenyl-5-hexenal. The dimethylhydrazone of phenylacetaldehyde (4.427 g, 27.29 mmol) was added dropwise to a solution of freshly prepared LDA (30.4 mmol) in THF (40 mL) at 0 °C. After 2 h, the solution was cooled to −78 °C and 4-bromo-1-butene (4.3 g, 32 mmol) was slowly added. The solution was warmed to room temperature and stirred overnight. The reaction was quenched with H_2O and the product was extracted into EtOAc. The organic solution was concentrated in vacuo. Acetone (75 mL) and wet Amberlyst-15 (12 g) were added to the residue. The mixture was heated at reflux until no starting material remained by GLC (4 h). The reaction was cooled and filtered through Celite. H_2O was added and the product was extracted into CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Short-path distillation provided the title compound as a clear and colorless liquid (2.299 g, 48%). The purity was >95% by NMR: bp 59–64 °C/0.1 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (d, J = 1.7 Hz, 1 H), 7.38 (m, 3 H), 7.23 (m, 2 H), 5.80 (m, 1 H), 5.05 (m, 2 H), 3.58 (m, 1 H), 2.22 (m, 1 H), 2.01 (m, 2 H), 1.86 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.61, 137.50, 136.14, 129.05, 128.87, 127.58, 115.55, 58.21, 30.82, 28.65.

4-Phenyl-6-hepten-2-one.[34] A solution of benzalacetone (5.911 g, 40.43 mmol) in CH_2Cl_2 (75 mL) was cooled to −40 °C. $TiCl_4$ (7.8 g, 41 mmol) was slowly added, and the dark red solution was stirred for 5 min. Allyltrimethylsilane (5.95 g, 52.1 mmol) in CH_2Cl_2 (40 mL) was added dropwise over 15 min. After 20 min, H_2O was added and the mixture was warmed to room temperature. Et_2O was added and the layers were separated. The aqueous layer was extracted with Et_2O, and the combined ethereal layers were washed with saturated aqueous $NaHCO_3$ followed by brine. The solution was dried ($MgSO_4$), filtered, and concentrated. Distillation through a 3-in. Vigreux column provided the alkenone as a clear and colorless liquid (6.302 g, 83%). The purity was 97% by GLC: bp 64–74 °C/0.1 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 2 H), 7.22 (m, 3 H), 5.68 (m, 1 H), 5.03 (m, 2 H), 3.30 (m, 1 H), 2.79 (m, 2 H), 2.40 (m, 2 H), 2.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.65, 144.01, 136.11, 128.42, 127.40, 126.38, 116.71, 49.36, 40.75, 40.56, 30.54.

4-Methyl-2,6-heptanedione was prepared as previously described:[35] ot 58–64 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48–2.27 (m, 5 H), 2.04 (s, 6 H), 0.85 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.09, 49.92, 30.12, 25.13, 19.95.

General Procedure for the Synthesis of 1,5-Keto Aldehydes.[16c] A solution of the 5-alken-1-one (8 mmol) in MeOH (20 mL) and CH_2Cl_2 (4 mL) was cooled to −78 °C. O_3 was bubbled into the solution until it turned blue. The solution was purged with Ar until colorless, and Zn (1.3 g, 20 mmol) and AcOH (8.0 mL) were added. The mixture was warmed to room temperature and stirred for 1–3 h. Water was added and the product was extracted into CH_2Cl_2. The combined organic layers were washed with water followed by aqueous $NaHCO_3$ (5%). The solution was dried (K_2CO_3), filtered, and concentrated. The product was purified by flash chromatography followed by Kugelrohr distillation.

6-Methyl-5-oxoheptanal (2c) was isolated in 79% yield: ot 56–62 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, J = 1.5 Hz, 1 H), 2.51 (m, 1 H), 2.47 (m, 4 H), 1.84 (m, 2 H), 1.03 (d, J = 6.8 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.94, 202.02, 42.95, 40.75, 38.78, 18.09, 15.96.

5-Oxo-5-phenylpentanal (2d) was isolated in 72% yield: ot 90–100 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, J = 1.5 Hz, 1 H), 7.91 (m, 2 H), 7.51 (m, 1 H), 7.42 (m, 2 H), 3.01 (m, 2 H), 2.55 (td, J = 7.1, 1.2 Hz, 2 H), 2.04 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.03, 199.35, 136.66, 133.12, 128.58, 127.94, 42.95, 37.16, 16.38.

4-Methyl-5-oxo-5-phenylpentanal (2k) was isolated in 72% yield: ot 107–112 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1 H), 7.93 (m, 2 H), 7.53 (m, 1 H), 7.43 (m, 2 H), 3.53 (m, 1 H), 2.47 (m, 2 H), 2.12 (m, 1 H), 1.78 (m, 1 H), 1.19 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.48, 201.85, 136.20, 133.11, 128.69, 128.25, 41.31, 39.42, 25.25, 17.51.

Preparation of 5-Oxo-3-phenylhexanal (2m). The general ozonolysis procedure described above was followed with the following exceptions. The solvent mixture employed was CH_2Cl_2/MeOH (5:1) and catalytic $NaHCO_3$ was added. PBu_3 (1.5 equiv) was utilized for reduction of the ozonide. Upon stirring for 2 h, the solution was concentrated. The residue was purified by flash chromatography (2:1 hexanes/EtOAc, 3:1 hexanes/EtOAc) followed by Kugelrohr distillation to provide **2m** as a clear and colorless oil (82%): ot 88–93 °C/0.1 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (t, J = 1.7 Hz, 1 H), 7.33–7.20 (m, 5 H), 3.78 (m, 1 H), 2.78 (m, 4 H), 2.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.63, 200.94, 142.86, 128.66, 127.16, 126.79, 49.43, 49.34, 34.86, 30.22.

Preparation of 5-Oxo-2-Phenylhexanal (2q).[17b] To a mixture of $PdCl_2$ (170 mg, 0.956 mmol), *p*-benzoquinone (1.546 g, 14.30 mmol), DMF (7.0 mL), and H_2O (1.0 mL) was added 5-phenyl-6-hepten-2-one (2.186 g, 12.55 mmol) dropwise. The mixture was stirred for 2.5 h and poured into 10% HCl. The product was extracted into Et_2O, and the combined ethereal layers were washed with H_2O, aqueous $NaHCO_3$ (5%), and brine. The solution was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (3:1 hexanes/EtOAc) followed by Kugelrohr distillation provided the 1,5-keto aldehyde as a pale yellow oil (1.166 g, 49%): ot <100 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (d, J = 1.5 Hz, 1 H), 7.28 (m, 3 H), 7.10 (m, 2 H), 3.52 (m, 1 H), 2.33 (m, 2 H), 2.26 (m, 1 H), 2.01 (s, 3 H), 1.90 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.81, 200.14, 135.57, 129.12, 128.79, 127.73, 57.75, 40.29, 29.78, 23.36.

General Procedure for the Synthesis of Trimethylsilyl Enol Ethers. To a vigorously stirred solution of the 1,3-diketone or 1,3-keto ester (1 equiv) in dry hexanes was added triethylamine (1.2 equiv) followed by TMSCl (1.1 equiv). A thick white precipitate formed. After the mixture was stirred overnight, the salts were filtered off with the aid of hexanes. Concentration followed by Kugelrohr distillation provided the trimethylsilyl enol ethers. Isomeric ratios were estimated from NMR data.

Methyl 3-(Trimethylsiloxy)but-2-enoate (3a) was isolated as a 2:1 mixture of isomers in 78% yield from methyl acetoacetate: ot 96–100 °C/25 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (s) and 5.50 (s, 1 H total), 3.58 (s) and 3.57 (s, 3 H total), 2.19 (s) and 1.82 (s, 3 H total), 0.19 (s, 9 H); IR (neat) 2959, 1705, 1626, 1446, 1279, 1132, 1004 cm^{-1}.

Ethyl 3-(Trimethylsiloxy)but-2-enoate (3b) was isolated as a 2:1 mixture of isomers in 75% yield from ethyl acetoacetate: ot 50–58 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (s) and 5.02 (s, 1 H total), 4.05 (q, J = 7.1 Hz, 2 H), 2.20 (s) and 1.83 (s, 3 H total), 1.19 (m, 3 H), 0.21 (s) and 0.20 (s, 9 H total); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.54, 167.91, 165.50, 164.49, 100.30, 99.65, 59.15, 58.90, 24.23, 20.53, 14.29, 14.26, 0.42, 0.028.

***tert*-Butyl 3-(Trimethylsiloxy)but-2-enoate (3c)** was isolated as a 4:1 mixture of isomers in 68% yield from *tert*-butyl acetoacetate: ot 58–64 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (s) and 4.93 (s, 1 H total), 2.14 (s) and 1.78 (s, 3 H total), 1.39 (s) and 1.38 (s, 9 H total), 0.18 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.27, 167.50, 164.90, 163.20, 101.92, 101.55, 78.97, 78.65, 28.27, 28.24, 24.20, 20.39, 0.52, 0.12; IR ($CDCl_3$) 2979, 1698, 1623, 1256, 1133 cm^{-1}.

4-(Trimethylsiloxy)pent-3-en-2-one (3d)[36] was isolated as a 3:1 mixture of isomers in 70% yield from 2,4-pentanedione: ot 90–100 °C/30 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.49 (s) and 5.26 (s, 1 H total), 2.16 (s, 3 H), 2.02 (s) and 1.94 (s, 3 H total), 0.22 (s) and 0.18 (s, 9 H

(32) Prepared by the method of Larson and Klesse[20] from crotonaldehyde.
(33) Prepared by the method of Larson and Klesse[20] from methacrolein.
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total); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.33, 169.10, 111.56, 108.12, 31.61, 21.03, 0.68, 0.021.

Trimethylsilyl enol ether of 5,5-dimethyl-2,4-hexanedione (3e) was isolated as a 3:1 mixture of isomers[37] in 82% yield from 5,5-dimethyl-2,4-hexanedione:[38] ot 58–64 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (s) and 5.64 (s, 1 H total), 2.22 (s) and 1.92 (s, 3 H total), 1.08 (s) and 1.06 (s, 9 H total), 0.25 (s) and 0.23 (s, 9 H total); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 205.30, 169.92, 103.92, 43.35, 26.81, 21.34, 0.17; IR ($CDCl_3$) 2967, 1671, 1583, 1390, 1256 cm^{-1}.

3-Methyl-4-(trimethylsiloxy)pent-3-en-2-one (3f) was isolated as a 1:1 mixture of isomers in 71% yield from 3-methyl-2,4-pentanedione: ot 44–70 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (m, 6 H), 1.73 (m, 1.5 H), 1.61 (m, 1.5 H), 0.18 (s) and 0.14 (s, 9 H total); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.29, 159.98, 116.79, 116.60, 29.96, 21.66, 13.21, 0.82, 0.61.

Ethyl 2-Methyl-3-(trimethylsiloxy)but-2-enoate (3h) was isolated as a mixture of isomers in 81% yield from ethyl 3-methylacetoacetate: ot 52–60 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 4.10 (q, J = 7.1 Hz, 2 H), 2.22 (d, J = 1.2 Hz, 3 H), 1.72 (d, J = 1.2 Hz, 3 H), 1.24 (t, J = 7.1 Hz, 3 H), 0.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.77, 161.22, 109.05, 59.61, 21.48, 14.27, 12.35, 0.73.

3-[1-(Trimethylsiloxy)ethylidene]dihydro-2(3*H*)-furanone (3j). Via the general procedure described above, the title compound was prepared in 75% yield: ot <100 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (t, J = 7.8 Hz, 2 H), 2.80 (td, J = 1.9, 7.8 Hz, 2 H), 2.29 (t, J = 1.9 Hz, 3 H), 0.23 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.34, 162.44, 104.68, 64.23, 26.03, 18.49, 0.85; IR (neat) 2961, 1734, 1654, 1378, 1278, 1032 cm^{-1}.

Methyl 3-(Trimethylsiloxy)pent-2-enoate (3k) was isolated as a 3:1 mixture of isomers in 68% yield from methyl 3-oxopentanoate: ot 50–58 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 5.03 (s) and 4.95 (s, 1 H total), 3.55 (s, 3 H), 2.61 (q, J = 7.3 Hz) and 2.03 (q, J = 7.3 Hz, 2 H total), 0.99 (t, J = 7.3 Hz) and 0.98 (t, J = 7.3 Hz, 3 H total), 0.17 (s) and 0.16 (s, 9 H total); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.62, 169.70, 167.80. 166.03, 98.17, 97.66, 50.36, 50.21, 31.04, 26.38, 11.06, 10.88, 0.32, 0.17.

Methyl 3-(Trimethylsiloxy)hex-2-enoate (3l) was isolated as a 2:1 mixture of isomers in 98% yield from methyl 3-oxohexanoate:[39] ot 90–100 °C/15 mmHg; ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 5.04 (s, 1 H), 3.62 (s, 3 H), 2.65 (m, 2 H), 1.51 (m, 2 H), 0.90 (t, J = 7.3 Hz, 3 H), 0.23 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 173.64, 168.09, 98.41, 50.58, 34.94, 20.20, 13.64, 0.01.

Methyl 3-(Trimethylsiloxy)hepta-2,6-dienoate (3m) was isolated as a mixture of isomers (4:1 by GLC) in 81% yield from methyl 3-oxohept-6-enoate.[39] The purity was 99% by GLC: ot 66–80 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 5.80 (m, 1 H), 4.98 (m, 3 H), 3.63 (s, 3 H), 2.79 (t, J = 7.6 Hz, 2 H), 2.23 (m, 2 H), 0.24 (s, 9 H).

Methyl 3-(Trimethylsiloxy)-5-phenylpent-2-enoate (3n) was isolated as a 3:1 mixture of isomers in 96% yield from methyl 3-oxo-5-phenylpentanoate:[39] ot 120–124 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 7.22 (m, 5 H), 5.06 (s, 1 H), 3.64 (s, 3 H), 3.02 (m, 2 H), 2.82 (m, 2 H), 0.23 (s, 9 H).

Methyl 3-Methyl-4-(trimethylsilyl)but-2-enoate.[40] A solution of [(trimethylsilyl)methyl]magnesium chloride (19.0 mL, 1.0 M in Et_2O, 19.0 mmol) was added dropwise to CuI (4.0 g, 21.0 mmol) in THF (20 mL) at −78 °C. The reaction was stirred for 1.5 h between −65 and −40 °C. Methyl 2-butynoate (2.0 g, 20.0 mmol) was added at −78 °C, and the ice bath was allowed to warm slowly. The solution turned bright yellow at approximately −5 °C, indicating reaction had occurred. The reaction was poured into a mixture of saturated aqueous NH_4Cl (10 mL) and NH_4OH (40 mL). The aqueous mixture was extracted with Et_2O, and the combined ethereal layers were washed with aqueous NH_4OH (~20%) until the washings were no longer blue. The organic layer was washed with H_2O and dried (Na_2SO_4). Kugelrohr distillation provided the title compound as a clear and colorless liquid (1.8077 g, 51%) as a 3:1 mixture of isomers by GLC. The purity was 98% by GLC: ot 56–64 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 5.45 (m, 1 H), 3.63 (s, 3 H), 2.14 (m, 3 H), 1.72 (s, 2 H), 0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 167.33, 161.06, 112.44, 50.49, 33.70, 21.47, −1.44.

General Procedure for the Synthesis of Bis(trimethylsilyl) Enol Ethers. The trimethylsilyl enol ether (1 equiv) was added dropwise to a freshly prepared solution of LDA (1.1 equiv) in THF at −78 °C. After 30 min, TMSCl (1.2 equiv) was slowly added and the reaction was warmed to 0 °C. After 1 h, the volatiles were removed in vacuo and the salts were suspended in dry hexanes. The mixture was filtered and concentrated. Products derived from β-keto esters with boiling points <80 °C and from β-diketones were further purified by Kugelrohr distillation. Bis(trimethylsilyl) enol ethers of β-keto esters cannot be heated above 80 °C because rearrangements occur.[41] The final products sometimes contained impurities, and further purification was not attempted because of air sensitivity and thermal instability.

1,3-Bis(trimethylsiloxy)-1-methoxybuta-1,3-diene (4a)[13a] was isolated as a mixture of isomers in 81% yield from **3a**: ot 52–60 °C/0.06 mmHg; ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 4.42 (s, 1 H), 4.08 (s, 1 H), 3.88 (s, 1 H), 3.49 (s, 3 H), 0.19 (s, 9 H), 0.15 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diasteromer) δ 158.57, 153.33, 89.23, 77.59, 54.83, 0.33, 0.10; IR (neat) 2964, 1708, 1652, 1444, 1388, 1252, 1196, 1093 cm^{-1}.

1,3-Bis(trimethylsiloxy)-1-ethoxybuta-1,3-diene (4b) was isolated as a 3:1 mixture of isomers in 92% yield from **3b**: ot <80 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 4.42 (s, 1 H), 4.08 (m) and 4.06 (m, 2 H total), 3.72 (q, J = 7.0 Hz, 2 H), 1.25 (t, J = 7.0 Hz, 3 H), 0.20 (s), 0.16 (s), 0.15 (s), and 0.12 (s, 18 H total); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 157.59, 153.50, 88.07, 77.86, 63.42, 14.24, 0.46, 0.14.

1,3-Bis(trimethylsiloxy)-1-*tert*-butoxybuta-1,3-diene (4c) was isolated as a 6:1 mixture of isomers in 99% yield from **3c**: ^1H NMR (300 MHz, $CDCl_3$) δ 4.47 (s, 1 H), 4.19 (d, J = 1.4 Hz, 1 H), 4.13 (d, J = 1.4 Hz, 1 H), 1.40 (s) and 1.29 (s, 9 H total), 0.18 (s), 0.15 (s), 0.13 (s), and 0.10 (s, 18 H total); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 153.62, 153.14, 91.03, 89.50, 79.56, 28.35, 0.50 0.10; IR ($CDCl_3$) 2962, 1699, 1643, 1369, 1252, 1152 cm^{-1}.

2,4-Bis(trimethylsiloxy)penta-1,3-diene (4d)[13a] was isolated as a 1:1 mixture of isomers in 85% yield from **3d**: ot 50–60 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 5.17 (s) and 4.29 (s, 1 H total), 4.71 (m) and 4.09 (d, J = 13.2 Hz, 2 H total), 1.98 (s) and 1.83 (s, 3 H total), 0.21 (s), 0.19 (s), 0.18 (s), and 0.17 (s, 18 H total); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.52, 152.67, 152.44, 150.67, 108.52, 107.08, 93.34, 23.73, 19.88, 0.82, 0.30, 0.11, −0.01.

2,4-Bis(trimethylsiloxy)-5,5-dimethylhexa-1,3-diene (4e) was isolated as a single isomer in 88% yield from **3e**: ot 58–62 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (s, 1 H), 4.44 (s, 1 H), 4.33 (s, 1 H), 1.05 (d, J = 0.73 Hz, 9 H), 0.21 (d, J = 0.73 Hz, 9 H), 0.18 (d, J = 0.98 Hz, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.48, 153.26, 103.58, 95.10, 36.98, 28.48, 1.29, 0.28.

2,4-Bis(trimethylsiloxy)-3-methylpenta-1,3-diene (4f) was isolated as a 1.4:1 mixture of isomers in 96% yield from **3f**: ot 52–60 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 4.41 (s), 4.31 (s), 4.30 (s), and 4.11 (s, 2 H total), 1.96 (s) and 1.80 (s, 3 H total), 1.63 (m, 3 H), 0.17 (s) and 0.15 (s, 18 H total); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.84, 155.44, 146.29, 144.54, 115.00, 112.22, 94.33, 93.97, 20.45, 19.66, 15.42, 14.19, 0.76, 0.70, 0.06, 0.04.

1,3-Bis(trimethylsiloxy)-1-ethoxy-2-methylbuta-1,3-diene (4h). Via the general procedure described above, the title compound was prepared as a 4:1 mixture of isomers in 99% yield from **3h**: ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 4.41 (s, 1 H), 4.27 (s, 1 H), 3.72 (q, J = 7.0 Hz, 2 H), 1.63 (s, 3 H), 1.25 (t, J = 7.0 Hz, 3 H), 0.20 (s, 9 H), 0.17 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 155.76, 151.08, 95.50, 93.12, 64.24, 14.82, 13.17, 0.12, 0.05.

4-[1-(Trimethylsiloxy)ethenyl]-5-(trimethylsiloxy)-2,3-dihydrofuran (4j). Via the general procedure described above, the title compound was prepared in 93% yield from **3j**: ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (t, J = 8.9 Hz, 2 H), 3.93 (s, 1 H), 3.85 (s, 1 H), 2.69 (t, J = 8.9 Hz, 2 H), 0.23 (s, 9 H), 0.18 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.12, 153.32, 86.86, 81.73, 66.05, 30.17, 0.38, 0.043; IR ($CHCl_3$) 2961, 1734, 1671, 1404, 1253, 1062 cm^{-1}.

1,3-Bis(trimethylsiloxy)-1-methoxypenta-1,3-dlene (4k)[36] was isolated as a 1.3:1 mixture of isomers in 90% yield from **3k**: ot <80 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (q, J = 6.8 Hz, 1 H), 3.84 (s) and 3.60 (s, 1 H total), 3.46 (s) and 3.43 (s, 3 H total), 1.52 (d, J = 6.8 Hz) and 1.48 (d, J = 6.8 Hz, 3 H total), 0.17 (s), 0.14 (s), 0.12 (s), and 0.10 (s, 18 H total); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 157.03, 145.39, 102.09, 78.00, 54.70, 11.02, 0.44, 0.30.

1,3-Bis(trimethylsiloxy)-1-methoxyhexa-1,3-diene (4l). Via the general procedure described above, the title compound was prepared as a 4:1

(37) It is not clear from the spectral data whether these are regioisomers or stereoisomers.

(38) Prepared from acetone dimethylhydrazone and trimethylacetyl chloride: Enders, D.; Weuster, P. *Tetrahedron Lett.* **1978**, 2853.

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mixture of isomers in 76% yield from **3l**: ot <66 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84 (t, J = 7.1 Hz, 1 H), 3.86 (s, 1 H), 3.50 (s, 3 H), 2.05 (m, 2 H), 0.92 (t, J = 7.6 Hz, 3 H), 0.21 (s), 0.19 (s), 0.16 (s), and 0.15 (s, 18 H total); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 157.12, 143.94, 108.38, 77.94, 54.76, 18.99, 14.64, 0.47, 0.36.

1,3-Bis(trimethylsiloxy)-1-methoxyhepta-1,3,6-triene (4m) was isolated as a 5:1 mixture of isomers in 76% yield from **3m**: ot <66 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (m, 1 H), 5.05–4.85 (m, 3 H), 3.88 (s, 1 H), 3.51 (s, 3 H), 2.80 (m, 2 H), 0.21 (s), 0.20 (s), 0.17 (s), and 0.16 (s, 18 H total); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 157.51, 145.32, 138.43, 113.57, 105.34, 77.76, 54.78, 30.04, 0.52, 0.36.

1,3-Bis(trimethylsiloxy)-1-methoxy-5-phenylpenta-1,3-diene (4n) was isolated as a mixture of isomers in 100% yield from **3n**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 5 H), 5.05 (t, J = 7.3 Hz, 1 H), 3.92 (s, 1 H), 3.52 (s, 3 H), 3.42 (d, J = 7.3 Hz, 2 H), 0.20 (s), 0.19 (s), 0.18 (s), and 0.16 (s, 18 H total).

2,4-Bis(trimethylsiloxy)-3,5,5-trimethylhexa-1,3-diene (4g). 3,5,5-Trimethyl-2,4-hexanedione[42] (848 mg, 5.43 mmol) was added dropwise to a freshly prepared solution of LDA (13.0 mmol) in THF (30 mL) at −78 °C. After 30 min, TMSCl (1.7 g, 16 mmol) was slowly added, and the solution was stirred for 50 min at 0 °C. The volatiles were removed in vacuo, and the salts were filtered off with the aid of hexanes. Concentration followed by Kugelrohr distillation provided **4g** as a yellow liquid comprising a 1.8:1 mixture of isomers (1.410 g, 86%): ot 70–78 °C/0.3 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (s), 4.09 (s), and 4.03 (s, 2 H total), 1.76 (s) and 1.67 (s, 3 H total), 1.16 (s) and 1.14 (s, 9 H total), 0.20 (s), 0.18 (s), 0.15 (s), and 0.14 (s, 18 H total); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.38, 158.34, 155.25, 154.50, 114.33, 113.48, 93.80, 92.76, 37.83, 36.88, 29.67, 29.55, 19.44, 16.95, 1.08, 0.93, 0.24, 0.12.

1-Ethoxy-2-isopropyl-1,3-bis(trimethylsiloxy)buta-1,3-diene (4i). Ethyl 2-isopropylacetoacetate[43] (1.154 g, 6.700 mmol) was added dropwise to a freshly prepared solution of LDA (14 mmol) in THF (35 mL) at −78 °C. After 30 min, TMSCl (1.6 g, 15 mmol) was slowly added. The solution was warmed to 0 °C and stirred for a total of 1 h. The volatiles were removed in vacuo, and the solids were filtered off with the aid of hexanes. The solution was concentrated to provide **4i** as a yellow liquid (2.006 g, 94%) comprising a 1.3:1 mixture of isomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (d, J = 3.5 Hz, 1 H), 4.05 (d, J = 3.5 Hz, 1 H), 3.77 (qd, J = 2.7, 7.1 Hz, 2 H), 2.70 (m) and 2.58 (m, 1 H total), 1.17 (m, 3 H), 0.97 (d, J = 6.8 Hz, 6 H), 0.18 (s), 0.17 (s), 0.16 (s), and 0.15 (s, 18 H total); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.63, 154.32, 150.89, 150.04, 106.62, 106.46, 94.19, 94.09, 65.58, 63.92, 27.17, 27.04, 21.82, 21.45, 14.79, 0.14, 0.11; IR ($CDCl_3$) 2961, 1669, 1653, 1291, 1252 cm^{-1}.

4-Methyl-3,5-bis(trimethylsiloxy)hepta-2,4-diene (4o). 4-Methyl-3,5-heptanedione (550 mg, 3.87 mmol) was added dropwise to a freshly prepared solution of LDA (8.3 mmol) in THF (15 mL) at −78 °C. After 35 min, TMSCl (0.86 g, 7.9 mmol) was slowly added and the solution was stirred for 1 h at 0 °C. The volatiles were removed in vacuo, and the salts were filtered off with the aid of hexanes. Concentration followed by Kugelrohr distillation provided **4o** as a yellow liquid (1.027 g, 92%): ot 60–64 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 4.66 (q, J = 6.6 Hz, 1 H), 2.08 (q, J = 7.6 Hz, 2 H), 1.63 (s, 3 H), 1.54 (d, J = 6.6 Hz, 3 H), 1.00 (t, J = 7.6 Hz, 3 H), 0.13 (s, 9 H), 0.12 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 148.82, 148.50, 112.11, 105.54, 26.09, 15.65, 11.29, 10.77, 0.84, 0.29.

1-Methoxy-3-[(trimethylsilyl)methyl]-1-(trimethylsiloxy)buta-1,3-diene (11) was isolated predominantly as a single isomer in 98% yield from methyl 3-methyl-4-(trimethylsilyl)but-2-enoate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (d, J = 2.6 Hz, 1 H), 4.37 (d, J = 2.6 Hz, 1 H), 4.05 (s, 1 H), 3.52 (s, 3 H), 1.75 (s, 2 H), 0.22 (s, 9 H), −0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.09, 141.04, 104.83, 80.93, 54.88, 27.54, 1.60, 0.48.

General Procedure for the Preparation of Bicyclic Ethers. A 0.1 M solution of TMSOTf (15–30 mol %) in CH_2Cl_2 was added to a 0.1 M solution of the 1,4-dicarbonyl substrate (1 equiv) in CH_2Cl_2 at −78 °C. After 3 min, a 0.1 M solution of the appropriate bis(trimethylsilyl) enol ether (1.0–1.2 equiv) in CH_2Cl_2 was added dropwise. The reaction was stirred for 3.5–5 h and quenched by rapid addition of pH 7.0 phosphate buffer. Upon warming to room temperature, the layers were separated and the aqueous layer was extracted with $CHCl_3$ or CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (3:1 hexanes/EtOAc) followed by Kugelrohr distillation to provide the bicyclic ether. Compounds **5a–f** and **7f** existed as a mixture of diastereomers (enol, exo, and endo) because of the epimerizable center at C-2 and the ability of the keto ester to enolize.

2-(Methoxycarbonyl)-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-one (5a) was isolated in 56% yield: ot 70–80 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72 (s) and 3.68 (s, 3 H total), 3.45 (s) and 3.13 (s, 1 H total), 2.91 (m) and 2.45 (m, 1 H total), 2.61 (m, 0.5 H), 1.86–1.68 (m, 3.5 H), 1.44 (s), 1.43 (s), and 1.41 (s, 6 H total); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.77, 202.38, 168.69, 167.71, 83.69, 82.45, 82.12, 82.02, 66.69, 66.54, 53.38, 52.78, 52.12, 51.82, 37.84, 36.82, 36.38, 33.72, 26.00, 25.96, 25.03, 24.30; IR (neat) 2975, 2882, 1735, 1717, 1436, 1329, 1158 cm^{-1}; HRMS calcd for $C_{11}H_{16}O_4$ 212.1048, found 212.1032; LRMS (EI$^+$) m/e 212 (8), 181 (17), 96 (54), 69 (23), 43 (100); purity >98% by GLC.

2-(Methoxycarbonyl)-5-methyl-8-oxabicyclo[3.2.1]octan-3-one (5b) was isolated in 53% yield: ot 80–90 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.57 (s, 0.2 H, enol), 4.97 (d, J = 8.0 Hz, 0.2 H, enol), 4.87 (d, J = 5.6 Hz, 0.55 H, exo), 4.74 (m, 0.25 H, endo), 3.73 (s), 3.72 (s), and 3.71 (s, 3 H total), 3.67 (m, 0.25 H, endo), 3.11 (s, 0.55 H, exo), 2.72 (d, J = 14.9 Hz, 1 H), 2.55 (m, 1 H), 2.46–2.01 (m, 2 H), 1.91–1.60 (m, 2 H), 1.43 (s), 1.42 (s), and 1.40 (s, 3 H total); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.14, 201.62, 170.19, 169.85, 168.53, 168.20, 103.53, 82.92, 82.24, 79.08, 76.47, 72.35, 62.64, 61.48, 54.31, 54.00, 52.50, 51.90, 51.29, 43.63, 36.10, 35.66, 35.37, 34.95, 29.06, 27.96, 26.48, 25.74, 25.60; IR (neat) 2973, 1741, 1718, 1654, 1622, 1444, 1249, 1062 cm^{-1}; LRMS (EI$^+$) m/e 198 (18), 169 (53), 116 (51), 82 (65), 69 (34), 43 (100). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.59; H, 7.46.

2-(Methoxycarbonyl)-5-propyl-8-oxabicyclo[3.2.1]octan-3-one (5c) was isolated in 78–90% yield: ot 80–85 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.56 (bs, 0.3 H, enol), 4.96 (d, J = 8.0 Hz, 0.3 H, enol), 4.86 (d, J = 5.8 Hz, 0.5 H, exo), 4.74 (m, 0.2 H, endo), 3.72 (s), 3.70 (s), and 3.69 (s, 3 H total), 3.67 (m, 0.2 H, endo), 3.10 (s, 0.5 H, exo), 2.70 (dd, J = 0.73, 15.6 Hz, 1 H), 2.54 (m, 1 H), 2.45–2.02 (m, 4 H), 1.89–1.60 (m, 4 H), 1.40 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.59, 202.52, 170.23, 170.02, 168.59, 168.22, 103.60, 85.44, 84.76, 81.58, 77.25, 76.30, 71.96, 62.92, 61.71, 52.49, 52.28, 51.90, 51.29, 42.11, 41.85, 41.37, 35.85, 33.88, 33.62, 33.05, 28.80, 27.65, 17.39, 17.25, 17.23, 14.48, 14.37, 14.31; IR (neat) 2958, 2874, 1744, 1719, 1658, 1620, 1443, 1245, 1066 cm^{-1}; LRMS (EI$^+$) m/e 226 (26), 197 (51), 110 (59), 71 (100), 55 (43), 43 (92). Anal. Calcd for $C_{15}H_{16}O_4$: C, 63.70; H, 8.02. Found: C, 63.75; H, 7.98.

2-(Methoxycarbonyl)-5-phenyl-8-oxabicyclo[3.2.1]octan-3-one (5d) was isolated in 87% yield: ot 100–105 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.60 (s, 0.3 H, enol), 7.38–7.20 (m, 5 H), 5.15 (d, J = 7.8 Hz, 0.3 H, enol), 5.08 (d, J = 4.9 Hz, 0.4 H, exo), 4.94 (m, 0.3 H, endo), 2.81 (m, 0.3 H, endo), 3.75 (s), 3.74 (s), and 3.72 (s, 3 H total), 3.22 (s, 0.4 H, exo), 2.92 (dd, J = 2.0, 16.4 Hz, 1 H), 2.70 (m, 1 H), 2.50 (d, J = 16.4 Hz, 1 H), 2.38–1.92 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.62, 201.09, 170.23, 169.43, 168.48, 168.17, 128.55, 128.49, 128.41, 127.55, 127.50, 127.10, 124.40, 124.28, 124.41, 103.56, 86.13, 85.43, 82.42, 62.90, 61.72, 55.44, 54.94, 52.64, 52.08, 51.47, 44.38, 37.02, 36.59, 36.03, 35.93, 28.86, 27.75; IR ($CHCl_3$) 2960, 1740, 1720, 1660, 1260, 1200 cm^{-1}; LRMS (EI$^+$) m/e 260 (22), 143 (44), 105 (100), 77 (42). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.20; H, 6.30.

5-*tert*-Butyl-2-(methoxycarbonyl)-8-oxabicyclo[3.2.1]octan-3-one (5e) was isolated in 88% yield: ot 90–98 °C/0.5 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.63 (s, 0.3 H, enol), 4.94 (d, J = 7.3 Hz, 0.3 H, enol), 4.86 (d, J = 4.9 Hz, 0.5 H, exo), 4.72 (m, 0.2 H, endo), 3.72 (s) and 3.71 (s, 3 H total), 3.64 (m, 0.2 H, endo), 3.10 (s, 0.5 H, exo), 2.88–2.75 (m, 1 H), 2.62–2.32 (m, 1 H), 2.07–1.65 (m, 3 H), 1.55–1.45 (m, 1 H), 0.95 (s) and 0.94 (s, 9 H total); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.74, 203.14, 171.01, 170.36, 168.72, 168.36, 103.14, 90.14, 89.55, 86.10, 72.26, 62.70, 61.49, 52.46, 51.92, 51.28, 49.39, 49.09, 38.26, 36.19, 35.55, 35.50, 30.04, 29.60, 29.33, 28.99, 28.10, 25.14, 25.07, 24.83; IR ($CHCl_3$) 2960, 1740, 1720, 1660, 1620, 1440, 1265 cm^{-1}; LRMS (EI$^+$) m/e 240 (12), 109 (33), 57 (100), 43 (48). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.91; H, 8.45.

5-*tert*-Butyl-2-(methoxycarbonyl)-1-methyl-8-oxabicyclo[3.2.1]octan-3-one (5f) was isolated in 74% yield as a 28:1 mixture of regioisomers: ot 88–96 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 3.66 (s, 3 H), 3.11 (s, 1 H), 3.04 (dd, J = 1.7, 14.3 Hz, 1 H), 2.34 (d, J = 14.3 Hz, 1 H), 2.14–1.92 (m, 2 H), 1.82–1.61 (m, 2 H), 1.38 (s, 3 H), 0.95 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 205.41, 167.85, 89.27, 82.32, 66.61, 51.99, 47.72, 37.67, 35.52, 30.37, 25.04, 24.08; IR (neat) 2986, 1736, 1716, 1323, 1197, 1161, 1043 cm^{-1}; LRMS (EI$^+$) m/e 254 (3), 169 (9), 138 (60), 101 (40), 69 (42), 57 (100), 43 (42). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.17; H, 8.94.

(42) Prepared from 5,5-dimethyl-2,4-hexanedione[38] and MeI: Kirschleger, B.; Queignec, R. *C. R. Acad. Sci., Ser. 3* **1985**, 143.

(43) Prepared from ethyl acetoacetate and isopropyl iodide.[42]

2-(Methoxycarbonyl)-3-methylene-5-propyl-8-oxabicyclo[3.2.1]octane (12). Following the general procedure described above, 4-oxoheptanal (82 mg, 0.65 mmol) was annulated with **11** (197 mg, 0.762 mmol) in the presence of TMSOTf (23 mg, 0.10 mmol) over 4.5 h to provide **12** (121 mg, 83%, clear and colorless liquid) as a 1:1 mixture of ester diastereomers: ot 66–80 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.00–4.77 (m, 2.5 H), 4.46 (dd, J = 2.9, 7.1 Hz, 0.5 H), 3.69 (s, 3 H), 3.38 (s) and 2.92 (s, 1 H total), 2.49 (m, 0.5 H), 2.23 (d, J = 13.7 Hz, 0.5 H), 2.16–2.02 (m, 0.5 H), 2.11 (d, J = 13.7 Hz, 1 H), 2.02–1.83 (m, 1 H), 1.71–1.45 (m, 4.5 H), 1.34 (m, 2 H), 0.91 (t, J = 7.2 Hz) and 0.89 (t, J = 7.2 Hz, 3 H total); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.08, 171.78, 140.21, 140.16, 115.37, 111.56, 84.41, 84.27, 77.56, 76.64, 55.34, 53.29, 51.96, 51.37, 45.42, 43.64, 41.61, 41.49, 33.30, 32.53, 29.38, 27.62, 17.60, 17.49, 14.61, 14.56; IR (neat) 2957, 1738, 1465, 1435, 1243, 1165, 1028, 896 cm^{-1}; HRMS calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1414; LRMS (EI$^+$) m/e 224 (37), 207 (18), 193 (27), 165 (14), 147 (19), 114 (48), 93 (34), 79 (32), 71 (98), 55 (23), 43 (100).

(1*R,2*R**,5*S**,7*R**)-7-Isopropyl-2-methyl-2-(1-oxoethyl)-5-phenyl-8-oxabicyclo[3.2.1]octan-3-one (17).** The product consisted of two diastereomers in the ratio of 35:1 by GLC and was isolated in 67% yield: ot 86–100 °C/0.05 mmHg; mp 74.0–75.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 7.45–7.26 (m, 5 H), 4.43 (s, 1 H), 2.89 (dd, J = 2.2, 15.1 Hz, 1 H), 2.62 (d, J = 15.1 Hz, 1 H), 2.38 (s, 3 H), 2.18 (m, 1 H), 1.97 (m, 2 H), 1.72 (m, 1 H), 1.63 (s, 3 H), 0.86 (d, J = 5.4 Hz, 3 H), 0.84 (d, J = 5.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 208.71, 207.60, 144.14, 128.67, 128.53, 127.42, 124.20, 86.05, 83.78, 66.76, 52.24, 48.29, 39.43, 31.45, 29.61, 20.96, 20.60, 17.80; IR (CH_2Cl_2) 3063, 2962, 1701, 1449, 1355, 1233, 1094, 765, 587 cm^{-1}; LRMS (EI$^+$) m/e 300 (2), 257 (14), 215 (29), 186 (98), 171 (9), 135 (14), 123 (11), 118 (52), 105 (100), 91 (18), 77 (27), 43 (20). Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.76; H, 7.95.

(1*R,2*R**,4*R**,5*S**)-2,4-Dimethyl-2-(1-oxopropyl)-5-propyl-8-oxabicyclo[3.2.1]octan-3-one (18).** The product was generated as a mixture of four diastereomers in the ratio of 1:1.2:9.2:109.4 as determined by GLC and was isolated in 82% yield: ot 80–88 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 4.46 (d, J = 7.3 Hz, 1 H), 2.90 (qd, J = 6.7, 1.5 Hz, 1 H), 2.78 (dq, J = 17.6, 7.3 Hz, 1 H), 2.52 (dq, J = 17.6, 7.3 Hz, 1 H), 2.16 (m, 1 H), 1.66 (m, 3 H), 1.60–1.35 (m, 4 H), 1.59 (s, 3 H), 1.06 (t, J = 7.3 Hz, 3 H), 0.98 (t, J = 6.6 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 211.94, 210.62, 88.86, 80.66, 66.14, 49.32, 39.21, 34.14, 29.25, 28.60, 21.14, 16.85, 14.30, 8.69, 7.88; IR (neat) 2964, 1704, 1462, 1343, 1019, 969 cm^{-1}; HRMS calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1717; LRMS (EI$^+$) m/e 252 (14), 209 (36), 195 (48), 142 (47), 139 (34), 125 (78), 113 (83), 71 (55), 57 (100), 43 (52). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.58. Found: C, 70.80; H, 9.45.

2-(Methoxycarbonyl)-1,5-dimethyl-9-oxabicyclo[3.3.1]nonan-3-one (7f) was isolated in 82% yield: ot <106 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 3.66 (s, 3 H), 3.18 (s, 1 H), 2.84 (d, J = 14.7 Hz, 1 H), 2.31 (dd, J = 1.1, 14.7 Hz, 1 H), 1.59–1.43 (m, 6 H), 1.31 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 205.37, 168.30, 74.41, 73.61, 63.48, 52.14, 49.31, 37.74, 35.75, 30.46, 27.70, 17.63; IR (CH_2Cl_2) 2937, 1735, 1710, 1450, 1377, 1194, 1056 cm^{-1}; LRMS (EI$^+$) m/e 226 (16), 183 (21), 137 (36), 114 (84), 101 (86), 82 (91), 43 (100). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.75; H, 8.19.

2-(Ethoxycarbonyl)-5-propyl-8-oxabicyclo[3.2.1]octan-3-one (13b and 14b) was isolated as a mixture of epimers in 84% yield: ot 106–112 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.66 (bs, 0.3 H, enol), 4.95 (d, J = 8.1 Hz, 0.3 H, enol), 4.86 (d, J = 5.6 Hz, 0.5 H, exo), 4.72 (m, 0.2 H, endo), 4.24–4.10 (m, 2 H), 3.64 (d, J = 3.9 Hz, 0.2 H, endo), 3.10 (s, 0.5 H, exo), 2.74 (d, J = 16.4 Hz, 1 H), 2.55 (d, J = 16.4 Hz, 1 H), 2.36–1.87 (m, 3 H), 1.75–1.58 (m, 4 H), 1.40–1.20 (m, 4 H), 0.92 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.78, 202.17, 169.93, 169.90, 168.19, 167.82, 103.78, 85.44, 84.77, 81.60, 76.36, 72.00, 63.16, 61.83, 61.52, 60.92, 60.18, 52.55, 52.24, 42.16, 41.89, 41.44, 41.42, 35.85, 33.92, 33.67, 33.19, 28.82, 27.67, 17.42, 17.30, 17.26, 14.51, 14.39, 14.34, 14.22, 14.03, 13.93; IR ($CDCl_3$) 2960, 1738, 1720, 1246, 1188 cm^{-1}; HRMS calcd for $C_{13}H_{20}O_4$ 240.1362, found 240.1383; LRMS (EI$^+$) m/e 240 (19), 211 (38), 130 (60), 110 (93), 71 (100), 55 (38), 43 (79). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.43; H, 8.45.

2-(*tert*-Butoxycarbonyl)-5-propyl-8-oxabicyclo[3.2.1]octan-3-one (13c and 14c) was isolated as a mixture of epimers in 80% yield: ot 100–110 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.72 (bs, 0.3 H, enol), 4.90 (d, J = 7.8 Hz, 0.3 H, enol), 4.78 (d, J = 5.6 Hz, 0.5 H, exo), 4.69 (m, 0.2 H, endo), 3.54 (d, J = 3.9 Hz, 0.2 H, endo), 3.02 (s, 0.5 H, exo), 2.72 (d, J = 16.1 Hz) and 2.26 (d, J = 16.1 Hz, 1 H total), 2.52 (d, J = 16.1 Hz) and 2.01 (d, J = 16.1 Hz, 1 H total), 2.10–1.84 (m, 2 H), 1.73–1.55 (m, 4 H), 1.44 (s), 1.43 (s), and 1.42 (s, 9 H total), 1.34 (m, 2 H), 0.91 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.24, 202.59, 169.75, 169.11, 167.38, 167.18, 104.87, 85.37, 84.62, 82.37, 81.72, 81.62, 81.22, 77.69, 76.40, 72.30, 64.21, 62.52, 52.60, 51.87, 42.19, 41.55, 41.44, 35.74, 33.99, 33.71, 33.55, 28.69, 28.20, 27.99, 27.83, 27.63, 17.42, 17.38, 17.26, 14.52, 14.39, 14.35; IR ($CDCl_3$) 2960, 1732, 1651, 1456, 1251, 1157 cm^{-1}; LRMS (EI$^+$) m/e 269 (1), 268 (6), 195 (46), 183 (31), 169 (23), 110 (100), 81 (22), 71 (50), 57 (98), 43 (47). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.15; H, 8.97.

2-(1-Oxoethyl)-5-propyl-8-oxabicyclo[3.2.1]octan-3-one (13d and 14d) was isolated as a mixture of epimers in 77% yield: ot 90–100 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (d, J = 5.9 Hz, 1 H), 2.59 (dd, J = 1.2, 18.2 Hz, 1 H), 2.18 (m, 1 H), 2.11 (m, 1 H), 2.04 (s, 3 H), 1.89–1.72 (m, 3 H), 1.68–1.59 (m, 3 H), 1.42–1.34 (m, 2 H), 0.93 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.71, 113.11, 81.65, 73.42, 45.67, 42.13, 35.63, 33.63, 21.96, 17.23, 14.51; IR (neat) 2959, 2873, 1706, 1607, 1405, 1193, 1043 cm^{-1}; HRMS calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1278; LRMS (EI$^+$) m/e 210 (8), 181 (22), 167 (21), 125 (22), 97 (28), 71 (28), 43 (100). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.59; H, 8.74.

2-(2,2-Dimethyl-1-oxopropyl)-5-propyl-8-oxabicyclo[3.2.1]octan-3-one (13e and 14e) was isolated as a mixture of epimers in 89% yield: ot 100–108 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (d, J = 7.6 Hz, 0.2 H, exo), 4.49 (dd, J = 3.9, 7.3 Hz, 0.8 H, endo), 4.15 (d, J = 3.9 Hz, 0.8 H, endo), 3.67 (s, 0.2 H, exo), 2.45–2.38 (m, 1 H), 2.26 (m, 1 H), 2.16–1.88 (m, 2 H), 1.70–1.56 (m, 4 H), 1.37–1.26 (m, 2 H), 1.09 (s) and 1.02 (s, 9 H total), 0.87 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.24, 208.16, 205.16, 204.24, 85.38, 84.32, 76.21, 64.98, 62.11, 52.83, 52.69, 45.56, 45.00, 41.39, 41.36, 34.05, 32.99, 30.11, 27.63, 27.51, 25.93, 25.23, 17.35, 17.22, 14.39, 14.32; IR (neat) 2978, 1722, 1697, 1603, 1478, 1366, 1021 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.50; H, 9.54.

(1*R,2*R**,5*S**)-2-Methyl-2-(1-oxoethyl)-5-propyl-8-oxabicyclo-[3.2.1]octan-3-one (13f)** was isolated as a >40:1 mixture of diastereomers in 73% yield: ot 90–100 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (d, J = 7.6 Hz, 1 H), 2.67 (d, J = 14.3 Hz, 1 H), 2.29 (s, 3 H), 2.21–2.11 (m, 1 H), 2.16 (d, J = 14.3 Hz, 1 H), 1.69–1.58 (m, 5 H), 1.51 (s, 3 H), 1.37 (m, 2 H), 0.93 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.88, 208.64, 85.12, 80.11, 66.68, 49.81, 41.37, 33.48, 29.38, 28.61, 20.88, 17.49, 14.43; IR (neat) 2961, 2874, 1703, 1456, 1248, 1080 cm^{-1}; LRMS (EI$^+$) m/e 224 (0.6), 206 (0.6), 181 (26), 167 (37), 139 (12), 114 (48), 99 (100), 71 (17), 43 (50). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.51; H, 8.99.

2-(2,2-Dimethyl-1-oxopropyl)-2-methyl-5-propyl-8-oxabicyclo[3.2.1]-octan-3-one (13g and 14g) was isolated as a 1.3:1 mixture of diastereomers in 80% yield. The two diastereomers were separable by flash chromatography.

(1*R,2*R**,5*S**)-2-(2,2-Dimethyl-1-oxopropyl)-2-methyl-5-propyl-8-oxabicyclo[3.2.1]octan-3-one (13g):** ot 105–110 °C/0.3 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (d, J = 7.6 Hz, 1 H), 2.72 (dd, J = 1.6, 13.6 Hz, 1 H), 2.13 (d, J = 13.6 Hz, 1 H), 2.16–2.09 (m, 1 H), 1.69–1.52 (m, 5 H), 1.64 (s, 3 H), 1.45–1.31 (m, 2 H), 1.19 (s, 9 H), 0.92 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.65, 208.90, 86.32, 82.25, 68.72, 50.62, 45.59, 41.39, 33.47, 28.52, 28.30, 19.43, 17.55, 14.43; IR ($CDCl_3$) 2960, 1706, 1683, 1252, 1009 cm^{-1}; LRMS (EI$^+$) m/e 251 (3), 209 (72), 182 (31), 139 (26), 111 (52), 83 (66), 57 (100). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.44; H, 9.65.

(1*R,2*S**,5*S**)-2-(2,2-Dimethyl-1-oxopropyl)-2-methyl-5-propyl-8-oxabicyclo[3.2.1]octan-3-one (14g):** ot 110–116 °C/0.3 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (d, J = 8.3 Hz, 1 H), 2.61 (d, J = 14.2 Hz, 1 H), 2.30 (d, J = 14.2 Hz, 1 H), 2.03–1.91 (m, 1 H), 1.72–1.52 (m, 5 H), 1.37–1.28 (m, 2 H), 1.20 (s, 9 H), 1.17 (s, 3 H), 0.88 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.34, 207.34, 85.58, 80.19, 70.15, 52.44, 46.62, 41.34, 34.48, 28.80, 27.75, 17.48, 15.60, 14.38; IR ($CDCl_3$) 2960, 1724, 1687, 1185, 1042 cm^{-1}; LRMS (EI$^+$) m/e 266 (3), 209 (20), 164 (24), 139 (20), 111 (29), 83 (35), 71 (34), 57 (100). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.15; H, 9.65.

(1*R,2*S**,5*S**)-2-(Ethoxycarbonyl)-2-methyl-5-propyl-8-oxabicyclo-[3.2.1]octan-3-one (14h)** was isolated as a 35:1 mixture of diastereomers in 76% yield: ot 88–105 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (d, J = 7.8 Hz, 1 H), 4.23–4.01 (m, 2 H), 2.70 (d, J = 14.7 Hz, 1 H), 2.25 (d, J = 14.7 Hz, 1 H), 1.93 (m, 1 H), 1.59 (m, 5 H), 1.31 (m, 2 H), 1.18 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.48, 172.16, 85.03, 81.45, 62.24, 61.25, 51.33, 41.32, 33.76, 24.70, 17.34, 15.39, 14.29, 13.84; IR (neat) 2961, 2874, 1732, 1716, 1684, 1472, 1254, 1097 cm^{-1}; LRMS (EI$^+$) m/e 255 (0.1), 254 (6), 190 (11), 144 (100), 129 (26), 95 (60), 83 (45), 71 (35), 43 (34). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.24; H, 8.91.

(1*R,2*S**,5*S**)-2-(Ethoxycarbonyl)-2-isopropyl-5-propyl-8-oxabicyclo[3.2.1]octan-3-one (14i)** was isolated as a 25:1 mixture of diastereomers in 73% yield: ot 114–120 °C/0.2 mmHg; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 4.86 (d, J = 7.6 Hz, 1 H), 4.16 (m, 2 H), 2.73 (d, J = 14.0 Hz, 1 H), 2.23 (d, J = 14.0 Hz, 1 H), 2.15 (m, 1 H), 1.95 (m, 1 H), 1.65–1.51 (m, 5 H), 1.35–1.26 (m, 2 H), 1.21 (t, J = 7.2 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 6 H), 0.86 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.60, 170.36, 85.28, 80.30, 68.73, 60.76, 52.04, 41.36, 33.53, 27.78, 24.54, 20.00, 17.39, 16.66, 14.32, 14.07; IR ($CDCl_3$) 2964, 1709, 1237, 1028 cm^{-1}; LRMS (EI^+) m/e 283 (3), 282 (13), 237 (40), 194 (18), 172 (33), 157 (65), 141 (61), 123 (46), 95 (40), 71 (55), 43 (100). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.17; H, 9.29.

8′-Oxa-3′-oxo-5′-propylspiro[furan-2(3*H*),2′-bicyclo[3.2.1]octan]-5-(4*H*)-one (13j and 14j) was isolated as a 1.3:1 mixture of diastereomers in 75% yield: ot <150 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (d, J = 7.3 Hz, 0.5 H), 4.40 (d, J = 7.5 Hz, 0.5 H), 4.32–4.04 (m, 2 H), 3.08–2.90 (m, 1 H), 2.67–2.55 (m, 1.5 H), 2.41–2.31 (m, 1.5 H), 2.15–1.98 (m, 1 H), 1.86–1.54 (m, 5 H), 1.38 (m, 2 H), 0.92 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.95, 202.10, 173.14, 171.65, 85.38, 84.70, 79.74, 78.93, 64.98, 64.25, 61.82, 61.75, 50.91, 49.33, 41.26, 41.12, 34.16, 33.52, 32.98, 27.92, 26.64, 25.60, 17.27, 17.24, 14.33, 14.28; IR ($CDCl_3$) 2959, 1772, 1716, 1506, 1029 cm^{-1}; LRMS (EI^+) m/e 239 (92), 238 (18), 196 (19), 181 (11), 125 (100), 110 (52), 71 (54), 55 (52), 43 (100). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.86; H, 7.73.

(1*R,2*R**,5*S**)-2-(1-Oxoethyl)-2-methyl-5-propyl-8-oxabicyclo-[3.2.1]octan-3-one (13f).** A solution of NaH (7.0 mg, 0.29 mmol) and THF (1.0 mL) was cooled to 0 °C, and a solution of 2-(1-oxoethyl)-5-propyl-8-oxabicyclo[3.2.1]octan-3-one (**13d** and **14d**) (52 mg, 0.25 mmol) in THF (1.0 mL) was added dropwise. After 30 min, MeI (46 mg, 0.32 mmol) was added. The mixture was warmed to room temperature and stirred for 18 h. A pH 7.0 phosphate buffer was added, and the aqueous layer was washed with Et_2O. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (3:1 hexanes/EtOAc) followed by Kugelrohr distillation to provide **13f** as a pale yellow oil (47.6 mg, 86%), which was >96% pure by GLC analysis. The material was identical in all respects to that prepared above.

(1*R,2*R**,5*S**)-2-(Ethoxycarbonyl)-2-methyl-5-propyl-8-oxabicyclo-[3.2.1]octan-3-one (13h).** A solution of NaH (28 mg, 1.2 mmol) in THF (2.0 mL) was cooled to 0 °C, and a solution of 2-(ethoxycarbonyl)-5-propyl-8-oxabicyclo[3.2.1]octan-3-one (**13b** and **14b**) (167 mg, 0.695 mmol) in THF (2.0 mL) was added dropwise. The solution was stirred for 45 min and MeI (171 mg, 1.2 mmol) was added. After 18 h at room temperature, the reaction was quenched by addition of a pH 7.0 phosphate buffer. The aqueous layer was extracted with Et_2O, and the ethereal extracts were dried (Na_2SO_4) and concentrated. The product was purified by flash chromatography (3:1 hexanes/EtOAc) followed by Kugelrohr distillation to provide **13h** (120 mg, 68%) as a clear and colorless liquid: ot 90–100 °C/0.25 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 4.33 (dd, J = 1.8, 7.0 Hz, 1 H), 4.15 (q, J = 7.1 Hz, 2 H), 2.60 (d, J = 15.6 Hz, 1 H), 2.20 (d, J = 15.6 Hz, 1 H), 2.15–2.07 (m, 2 H), 1.72–1.56 (m, 4 H), 1.51 (s, 3 H), 1.42–1.28 (m, 2 H), 1.22 (t, J = 7.1 Hz, 3 H), 0.90 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.96, 170.68, 84.70, 80.53, 61.91, 60.94, 49.27, 41.40, 33.53, 27.96, 21.02, 17.32, 14.35, 13.95; IR (neat) 2960, 2874, 1716, 1456, 1268, 1076 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.09; H, 8.67.

(1*R,2*R**,5*S**)-2-(Ethoxycarbonyl)-2-isopropyl-5-propyl-8-oxabicyclo[3.2.1]octan-3-one (13i).** A solution of 2-(ethoxycarbonyl)-5-propyl-8-oxabicyclo[3.2.1]octan-3-one (**13b** and **14b**) (67 mg, 0.28 mmol), anhydrous K_2CO_3 (70 mg, 0.51 mmol), isopropyl iodide (68 mg, 0.40 mmol), and anhydrous toluene (3 mL) was heated at reflux for 45 h. The solution was cooled, water (35 mL) was added, and the product was extracted into Et_2O. The combined organic extracts were washed with brine and dried (Na_2SO_4), and the volatiles were removed in vacuo. The product was purified by flash chromatography (3:1 hexanes/EtOAc) followed by Kugelrohr distillation (31 mg, 39%): ot 114–120 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (d, J = 7.6 Hz, 1 H), 4.19 (m, 2 H), 2.73 (m, 1 H), 2.53 (dd, J = 1.6, 14.0 Hz, 1 H), 2.25 (d, J = 14.0 Hz, 1 H), 2.29–2.16 (m, 1 H), 1.85–1.52 (m, 5 H), 1.48–1.29 (m, 2 H), 1.27 (t, J = 7.3 Hz, 3 H), 0.94 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.67, 169.01, 85.82, 77.65, 70.50, 60.47, 51.15, 41.35, 33.41, 31.00, 28.80, 17.78, 17.56, 17.40, 14.45, 14.20; IR ($CDCl_3$) 2965, 1744, 1713, 1246, 907 cm^{-1}; LRMS (EI^+) m/e 283 (2), 282 (11), 237 (27), 172 (58), 157 (97), 141 (100), 123 (51), 111 (51), 71 (42), 43 (53). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.22. Found: C, 68.55; H, 9.28.

Methyl 5-Hydroxy-5-methyl-3-oxodecanoate (9). Using the general procedure described above, 2-heptanone (99.9 mg, 0.875 mmol) was reacted with **4a** (288.7 mg, 1.108 mmol) in the presence of TMSOTf (39.7 mg, 0.178 mmol) over 3.25 h to provide the alcohol (169.7 mg, 84%) as a clear and colorless liquid: ot 96–100 °C/0.3 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3 H), 3.45 (s, 2 H), 2.96 (bs, 1 H), 2.69 (d, J = 16.8 Hz, 1 H), 2.60 (d, J = 16.8 Hz, 1 H), 1.43 (m, 2 H), 1.26 (m, 6 H), 1.16 (s, 3 H), 0.82 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 204.33, 167.33, 71.74, 52.28, 52.15, 50.40, 42.12, 32.09, 26.60, 23.44, 22.46, 13.87; IR (neat) 3254, 2934, 1748, 1707, 1438, 1160 cm^{-1}; LRMS (EI^+) m/e 215 (3), 183 (8), 159 (50), 127 (100), 85 (52), 43 (88). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.26; H, 9.70.

Competition Reaction between 2-Heptanone and Pinacolone with 4a. Using the general procedure, 2-heptanone (162 mg, 1.42 mmol) and pinacolone (144 mg, 1.44 mmol) were reacted with **4a** (386.7 mg, 1.484 mmol) in the presence of TMSOTf (56.2 mg, 0.253 mmol) over 3.5 h. Flash chromatography (2:1 hexanes/EtOAc) provided a 20:1 mixture (ratio determined by ^1H NMR) of the two alcohols (217.5 mg). The major product, methyl 5-hydroxy-5-methyl-3-oxodecanoate (**9**), had identical physical and spectral characteristics as the compound described above.

Methyl 5-Hydroxy-5,6-dimethyl-3-oxooctanoate. Using the general procedure described above, 3-methyl-2-pentanone (60.1 mg, 0.600 mmol) was annulated with **4a** (175.5 mg, 0.6738 mmol) in the presence of TMSOTf (0.12 mmol) over 4 h. Flash chromatography (2:1 hexanes/EtOAc) followed by Kugelrohr distillation provided the alcohol (72.1 mg, 56%) as a clear and colorless liquid (1.8:1 mixture of diastereomers): ot 76–82 °C/0.25 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 3 H), 3.48 (s, 2 H), 3.23 (bs, 1 H), 2.76 (d, J = 16.6 Hz) and 2.74 (d, J = 16.6 Hz, 1 H total), 2.63 (d, J = 16.6 Hz) and 2.60 (d, J = 16.6 Hz, 1 H total), 1.81–1.36 (m, 3 H), 1.13 (s) and 1.11 (s, 3 H total), 0.85 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 204.91, 167.41, 74.36, 52.37, 50.62, 49.68, 44.96, 24.71, 23.21, 12.91, 12.63; IR (neat) 3522, 2968, 1747, 1708, 1652, 1631, 1438, 1166 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.30; H, 9.02.

General Procedure for the Synthesis of Bicyclic Ethers 5j–q and 15k–n. The general procedure described above was followed with these exceptions. After flash chromatography, all fractions containing product were combined and concentrated. Pyridine (5–10 mL), catalytic DMAP, and Ac_2O (1.0 mL) were added. The mixture was stirred at room temperature for 17–24 h until starting material was no longer present as indicated by GLC. The solution was purified by flash chromatography followed by Kugelrohr distillation to provide the bicyclic ethers.

(1*R,5*S**,6*S**)-3-Acetoxy-5-ethyl-2-(methoxycarbonyl)-6-methyl-8-oxabicyclo[3.2.1]oct-2-ene (5j)** was isolated as a 5.4:1 mixture of diastereomers in 77% yield: ot 100–110 °C/0.2 mmHg; ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 4.87 (d, J = 6.3 Hz, 1 H), 3.68 (s, 3 H), 2.61 (d, J = 18.1 Hz, 1 H), 2.42–2.35 (m, 1 H), 2.16 (s, 3 H), 1.94 (d, J = 18.1 Hz, 1 H), 1.75–1.57 (m, 4 H), 0.94 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 188.44, 163.63, 155.09, 122.37, 82.94, 72.02, 51.53, 46.53, 41.17, 39.22, 27.15, 20.84, 17.38, 8.19; IR ($CDCl_3$) 2969, 1769, 1723, 1665, 1436, 1183 cm^{-1}; LRMS (EI^+) m/e 269 (0.5), 268 (3), 226 (13), 183 (100), 176 (18), 137 (30), 85 (9), 69 (17), 57 (17), 43 (39). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.69; H, 7.37.

(1*R,5*S**,6*S**)-3-Acetoxy-2-(methoxycarbonyl)-5-methyl-6-phenyl-8-oxabicyclo[3.2.1]oct-2-ene (5k)** was isolated as a 15:1 mixture of diastereomers in 68% yield. Recrystallization from Et_2O provided crystals suitable for X-ray structure determination: mp 90.0–90.1 °C; ot 148–156 °C/0.25 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.22 (m, 5 H), 5.22 (d, J = 6.3 Hz, 1 H), 3.79 (s, 3 H), 3.42 (t, J = 8.3 Hz, 1 H), 2.66 (m, 2 H), 2.51 (m, 1 H), 2.32 (d, J = 18.1 Hz, 1 H), 2.28 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.38, 163.42, 154.61, 142.22, 128.82, 128.19, 126.62, 122.26, 82.26, 72.99, 52.17, 51.60, 46.01, 45.29, 23.78, 20.81; IR (neat) 2951, 1770, 1717, 1662, 1436, 1363, 1175, 1033 cm^{-1}; LRMS (EI^+) m/e 317 (6), 274 (22), 242 (21), 225 (38), 170 (67), 115 (51), 91 (28), 43 (100). Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.44; H, 6.58.

(1*R,5*S**,6*S**)-3-Acetoxy-2-(methoxycarbonyl)-6-isopropyl-5-(2-methylpropyl)-8-oxabicyclo[3.2.1]oct-2-ene (51)** was isolated as a 15.6:1 mixture of diastereomers in 77% yield: ot 100–120 °C/0.15 mmHg; ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 4.88 (d, J = 6.1 Hz, 1 H), 3.66 (s, 3 H), 2.75 (d, J = 18.1 Hz, 1 H), 2.15 (s, 3 H), 2.19–1.82 (m, 5 H), 1.82 (d, J = 18.1 Hz, 1 H), 1.69–1.47 (m, 2 H), 0.96 (d, J = 6.4 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.85 (d, J = 6.6 Hz, 3 H), 0.81 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 168.32, 163.57, 155.19, 122.21, 83.12, 71.94, 53.00, 51.46, 42.60, 42.55, 38.77, 27.16, 25.31, 24.54, 24.24, 23.66, 20.81, 19.36; IR (neat) 2954, 1769, 1722, 1666, 1367, 1179, 1033 cm^{-1}; LRMS (EI^+) m/e 325 (32), 265 (90), 232 (45), 211 (100), 165 (18), 137 (8), 85 (62), 57 (56), 43 (83). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.97; H, 8.92.

3-Acetoxy-6-methoxy-2-(methoxycarbonyl)-5-phenyl-8-oxabicyclo-[3.2.1]oct-2-ene (5m) was isolated as a 1.4:1 mixture of diastereomers in 40% yield: ot <130 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.14 (m, 5 H), 5.13 (d, J = 6.6 Hz) and 5.00 (d, J = 6.6 Hz, 1 H

total), 3.88 (m) and 3.80 (d, J = 7.8 Hz, 1 H total), 3.63 (s) and 3.62 (s, 3 H total), 3.66 (m) and 3.21 (m, 1 H total), 3.25 (s) and 2.81 (s, 3 H total), 2.92 (d, J = 18.3 Hz), 2.72 (d, J = 18.3 Hz), 2.60 (m) and 2.48 (d, J = 18.3 Hz, 2 H total), 2.30 (m) and 1.85 (m, 1 H total), 2.10 (s) and 2.08 (s, 3 H total); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.36, 167.44, 163.43, 163.07, 155.65, 153.67, 144.26, 139.96, 128.30, 127.71, 127.23, 127.22, 125.58, 123.60, 122.68, 121.50, 88.22, 86.96, 85.08, 84.12, 72.74, 71.82, 58.39, 57.10, 51.61, 51.50, 45.04, 41.58, 39.43, 37.23, 20.70; IR (neat) 3060, 2950, 1770, 1722, 1667, 1436, 1297, 1168, 1052, 761 cm^{-1}; LRMS (EI$^+$) m/e 332 (1), 272 (5), 257 (23), 231 (30), 200 (25), 169 (10), 144 (5), 105 (100), 77 (29), 43 (35). Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.06. Found: C, 65.35; H, 6.15.

(1*R,5*S**,7*R**)-3-Acetoxy-2-(methoxycarbonyl)-5,7-dimethyl-8-oxabicyclo[3.2.1]oct-2-ene (5n)** was isolated as a 13.5:1 mixture of diastereomers in 75% yield: ot 98–102 °C/0.25 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 4.61 (s, 1 H), 3.67 (s, 3 H), 2.46 (m, 2 H), 2.14 (s, 3 H), 2.16 (m, 1 H), 1.99 (d, J = 17.8 Hz, 1 H), 1.39 (s, 3 H), 1.25 (dt, J = 1.8, 12.7 Hz, 1 H), 1.04 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 168.27, 163.61, 154.49, 121.95, 79.89, 79.52, 51.54, 44.54, 44.09, 43.55, 26.82, 21.63, 20.78; IR ($CDCl_3$) 2967, 1766, 1723, 1662, 1437, 1364, 1009 cm^{-1}; LRMS (EI$^+$) m/e 255 (0.2), 212 (4), 197 (3), 169 (100), 138 (15), 95 (4), 69 (8), 43 (24). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.13. Found: C, 61.67; H, 7.29.

(1*R,5*S**,7*R**)-3-Acetoxy-7-isopropyl-2-(methoxycarbonyl)-5-methyl-8-oxabicyclo[3.2.1]oct-2-ene (5o)** was isolated as a 27.3:1 mixture of diastereomers in 87% yield: ot 90–100 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 4.80 (s, 1 H), 3.67 (s, 3 H), 2.47 (dd, J = 1.7, 18.1 Hz, 1 H), 2.14 (s, 3 H), 2.05 (d, J = 18.1 Hz, 1 H), 2.03 (m, 2 H), 1.51 (m, 2 H), 1.38 (s, 3 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.82 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 168.35, 163.45, 154.55, 122.69, 79.71, 75.85, 57.21, 51.41, 43.24, 40.94, 31.66, 26.44, 20.82, 20.46, 20.22; IR (neat) 2960, 1765, 1724, 1663, 1436, 1364, 1247, 1031 cm^{-1}; HRMS calcd for $C_{15}H_{22}O_5$ 282.1467, found 282.1479; LRMS (EI$^+$) m/e 282 (22), 251 (18), 240 (100), 169 (100), 137 (12), 69 (10), 55 (10), 43 (50). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.36; H, 7.60.

(1*R,5*S**,7*R**)-3-Acetoxy-2-(methoxycarbonyl)-7-methyl-5-phenyl-8-oxabicyclo[3.2.1]oct-2-ene (5p)** was isolated as a 15.2:1 mixture of diastereomers in 79% yield: ot <150 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 7.33–7.10 (m, 5 H), 4.68 (s, 1 H), 3.64 (s, 3 H), 2.62 (d, J = 18.0 Hz, 1 H), 2.50 (m, 2 H), 2.39 (d, J = 18.0 Hz, 1 H), 2.09 (s, 3 H), 1.55 (m, 1 H), 1.00 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 168.28, 163.52, 154.15, 145.32, 128.35, 127.02, 123.93, 121.96, 83.13, 79.45, 51.61, 45.92, 44.13, 44.05, 21.57, 20.76; IR (CH_2Cl_2) 3029, 2958, 1766, 1723, 1662, 1362, 1052, 888 cm^{-1}; LRMS (EI$^+$) m/e 316 (28), 256 (15), 231 (36), 224 (28), 200 (19), 154 (17), 131 (8), 105 (100), 81 (10), 77 (28), 43 (35). Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.55; H, 6.35.

(1*R,5*S**,7*R**)-3-Acetoxy-7-isopropyl-2-(methoxycarbonyl)-5-phenyl-8-oxabicyclo[3.2.1]oct-2-ene (5q)** was isolated as a >160:1 mixture of diastereomers in 68% yield: mp 101.5–104.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 7.41–7.19 (m, 5 H), 5.06 (s, 1 H), 3.73 (s, 3 H), 2.69 (dd, J = 1.5, 18.1 Hz, 1 H), 2.52 (d, J = 18.1 Hz, 1 H), 2.48 (m, 1 H), 2.22 (m, 1 H), 2.19 (s, 3 H), 1.84 (dt, J = 2.4, 12.9 Hz, 1 H), 1.59 (m, 1 H), 0.94 (d, J = 6.6 Hz, 3 H), 0.82 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 168.45, 163.43, 154.26, 145.35, 128.38, 127.04, 123.92, 122.77, 83.04, 75.81, 57.16, 51.55, 43.95, 42.39, 31.65, 20.86, 20.50, 20.23; HRMS calcd for $C_{20}H_{24}O_5$ 344.1624, found 344.1664; LRMS (EI$^+$) m/e 344 (12), 284 (9), 231 (50), 157 (10), 129 (12), 105 (100), 91 (12), 77 (31), 43 (43). Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.18; H, 6.94.

(1*R,4*R**,5*S**)-3-Acetoxy-2-(methoxycarbonyl)-4-methyl-5-propyl-8-oxabicyclo[3.2.1]oct-2-ene (15k)** was isolated as a 5.4:1 mixture of diastereomers in 72% yield: ot 108–120 °C/0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88 (d, J = 4.6 Hz, 1 H), 3.66 (s) and 3.65 (s, 3 H total), 2.88 (q, J = 7.2 Hz, 1 H), 2.17 (s, 3 H), 2.08–1.93 (m, 3 H), 1.58–1.33 (m, 5 H), 1.06 (d, J = 6.8 Hz, 0.5 H), 0.94 (d, J = 7.3 Hz, 2.5 H), 0.89 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.60, 168.13, 163.79, 163.64, 158.52, 157.64, 120.86, 120.61, 85.16, 83.63, 73.87, 73.79, 51.49, 51.44, 44.73, 42.89, 39.35, 38.26, 35.78, 34.94, 33.18, 28.28, 20.89, 20.67, 17.19, 16.46, 14.55, 14.40, 13.16, 9.77; IR (neat) 2959, 1766, 1722, 1650, 1436, 1162 cm^{-1}; LRMS (EI$^+$) m/e 282 (8), 240 (26), 208 (27), 169 (58), 138 (69), 71 (67), 43 (100). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.47; H, 7.99.

(1*R,4*R**,5*S**)-3-Acetoxy-4-ethyl-2-(methoxycarbonyl)-5-propyl-8-oxabicyclo[3.2.1]oct-2-ene (15l)** was isolated as a 16.5:1 mixture of diastereomers in 60% yield: ot 93–100 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 4.87 (d, J = 4.9 Hz, 1 H), 3.66 (s, 3 H), 2.58 (d, J = 7.3 Hz, 1 H), 2.19 (s, 3 H), 1.97 (m, 3 H), 1.78–1.21 (m, 7 H), 1.02 (t, J = 7.3 Hz, 3 H), 0.90 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 168.25, 163.87, 158.45, 120.33, 85.41, 73.65, 51.47, 50.10, 39.50, 34.66, 29.21, 20.90, 19.49, 16.64, 15.36, 14.40; IR (neat) 2960, 2875, 1769, 1722, 1650, 1435, 1366, 1053, 885 cm^{-1}; LRMS (EI$^+$) m/e 296 (8), 254 (19), 222 (29), 183 (94), 168 (76), 152 (100), 136 (43), 81 (21), 71 (62), 43 (44). Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.88; H, 8.23.

(1*R,4*R**,5*S**)-3-Acetoxy-2-(methoxycarbonyl)-4-prop-2-enyl-5-propyl-8-oxabicyclo[3.2.1]oct-2-ene (15m)** was isolated as a 13.4:1 mixture of diastereomers in 62% yield: ot 100–106 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 5.71 (m, 1 H), 4.98 (m, 2 H), 4.87 (d, J = 5.1 Hz, 1 H), 3.65 (s, 3 H), 2.88 (m, 1 H), 2.35–1.97 (m, 5 H), 2.09 (s, 3 H), 1.80–1.49 (m, 3 H), 1.37 (m, 2 H), 0.88 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 168.22, 163.75, 157.56, 137.74, 121.02, 115.18, 85.16, 73.72, 51.47, 47.66, 39.52, 34.73, 30.63, 29.31, 20.80, 16.54, 14.33; IR (neat) 2959, 1770, 1722, 1651, 1435, 1360, 1257, 1044, 914 cm^{-1}; LRMS (EI$^+$) m/e 308 (2), 265 (40), 234 (46), 195 (48), 180 (75), 164 (59), 163 (83), 148 (100), 135 (37), 121 (32), 81 (37), 71 (58), 53 (20), 43 (78). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.42; H, 7.53.

(1*R,4*R**,5*S**)-3-Acetoxy-4-benzyl-2-(methoxycarbonyl)-5-propyl-8-oxabicyclo[3.2.1]oct-2-ene (15n)** was isolated as a 34:1 mixture of diastereomers in 64% yield: ot 120–130 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 7.34–7.18 (m, 5 H), 4.98 (d, J = 1.5 Hz, 1 H), 3.71 (s, 3 H), 3.37 (dd, J = 3.2, 9.0 Hz, 1 H), 2.80 (m, 2 H), 2.18 (m, 3 H), 1.74 (m, 3 H), 1.68 (s, 3 H), 1.53 (m, 2 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 168.08, 163.74, 157.64, 140.51, 128.45, 128.42, 126.03, 121.21, 85.16, 73.74, 51.46, 48.73, 39.57, 34.78, 32.58, 29.40, 20.10, 16.58, 14.35; IR (neat) 3086, 2957, 1770, 1722, 1650, 1435, 1360, 1165, 947, 699 cm^{-1}; LRMS (EI$^+$) m/e 326 (9), 315 (31), 284 (26), 230 (45), 198 (50), 165 (12), 131 (27), 91 (100), 71 (24), 43 (33). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.07; H, 7.07.

(1*R,4*S**,5*S**)-3-Acetoxy-2-(methoxycarbonyl)-4-methyl-5-propyl-8-oxabicyclo[3.2.1]oct-2-ene (16k).** A solution of **5c** (152.6 mg, 0.6744 mmol) in THF (2–3 mL) was added dropwise to oil-free NaH (26.5 mg, 1.104 mmol) in THF (2 mL) at 0 °C. After 1 h, the solution was cooled to −78 °C and LDA (1.2 mL, 0.6 M in THF, 0.72 mmol) was added dropwise. After 35 min, MeI (96 mg, 68 mmol) was added and the solution was warmed slowly to room temperature. H_2O was added after 5 h, and the layers were separated. The aqueous layer was extracted with Et_2O. The combined ethereal layers were dried (Na_2SO_4). The keto ester was isolated by flash chromatography (3:1 hexanes/EtOAc) and was dissolved in pyridine (3 mL). Ac_2O (1.0 mL) and catalytic DMAP were added and the reaction was stirred for 16 h. Flash chromatography (3:1 hexanes/EtOAc) followed by Kugelrohr distillation provided the enol acetate as a clear and colorless oil (122 mg, 64%): ot 90–96 °C/0.15 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.91 (m, 1 H), 3.68 (s, 3 H), 2.19 (s, 3 H), 2.04 (m, 3 H), 1.83 (m, 2 H), 1.77–1.58 (m, 1 H), 1.44 (m, 1 H), 1.26 (m, 2 H), 1.09 (d, J = 6.8 Hz, 3 H), 0.93 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.60, 163.79, 158.60, 120.89, 83.67, 73.81, 51.58, 44.74, 38.31, 35.82, 33.23, 20.96, 17.25, 14.61, 13.21; IR (neat) 2956, 1762, 1723, 1656, 1436, 1353, 1232, 885 cm^{-1}; LRMS (EI$^+$) m/e 282 (5), 240 (28), 211 (33), 190 (34), 169 (46), 154 (32), 138 (58), 71 (70), 43 (100). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.55; H, 7.80.

General Procedure for the Preparation of Enol Acetates 5g–i, 7g, and 19h. The general procedure was used with the following exception. To generate the enol acetate, the reaction mixture was heated at reflux for 3–10 h. Flash chromatography followed by Kugelrohr distillation provided the enol acetate.

3-Acetoxy-2-(methoxycarbonyl)-1-methyl-5-phenyl-8-oxabicyclo[3.2.1]oct-2-ene (5g) was isolated as a 17:1 mixture of regioisomers in 66% yield: ot 130–137 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major regioisomer) δ 7.32–7.09 (m, 5 H), 3.66 (s, 3 H), 2.74 (d, J = 17.2 Hz, 1 H), 2.52 (m, 1 H), 2.35 (d, J = 17.2 Hz, 1 H), 2.32 (m, 1 H), 2.08 (m, 1 H), 2.05 (s, 3 H), 1.83 (m, 1 H), 1.52 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major regioisomer) δ 168.25, 165.32, 150.65, 145.51, 128.31, 127.02, 126.10, 124.12, 82.22, 80.92, 51.55, 43.67, 42.66, 38.47, 21.55, 20.70; IR (neat) 3028, 2950, 1760, 1714, 1660, 1434, 1313, 1048, 761, 701 cm^{-1}; LRMS (EI$^+$) m/e 316 (7), 256 (26), 224 (100), 214 (5), 181 (14), 137 (14), 105 (89), 77 (17). Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.16; H, 6.25.

3-Acetoxy-5-isopropyl-2-(methoxycarbonyl)-1-methyl-8-oxabicyclo[3.2.1]oct-2-ene (5h) was isolated as a 6.5:1 mixture of regioisomers in 60% yield: ot 88–105 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major regioisomer) δ 3.69 (s, 3 H), 2.55 (d, J = 17.1 Hz, 1 H), 2.46 (m, 1 H), 2.10 (s, 3 H), 1.98 (d, J = 17.1 Hz, 1 H), 1.92–1.51 (m, 4 H), 1.45 (s, 3 H), 0.88 (d, J = 6.8 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$)

(major regioisomer) δ 168.29, 165.44, 151.55, 126.07, 84.27, 80.30, 51.42, 42.60, 39.30, 35.72, 31.93, 21.48, 20.73, 17.24, 16.44; IR (neat) 2963, 1766, 1721, 1662, 1435, 1243, 1061, 941 cm^{-1}; LRMS (EI^+) *m/e* 282 (1), 211 (19), 190 (100), 165 (40), 137 (18), 109 (12), 95 (11), 81 (8), 71 (28). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 64.11; H, 7.89.

3-Acetoxy-2-(methoxycarbonyl)-1-methyl-5-propyl-8-oxabicyclo-[3.2.1]oct-2-ene (5i) was isolated as a 5:1 mixture of regioisomers in 58% yield: ot <110 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) (major regioisomer) δ 3.69 (s, 3 H), 2.58 (d, *J* = 17.1 Hz, 1 H), 2.46 (m, 1 H), 2.10 (s, 3 H), 1.97 (d, *J* = 17.1 Hz, 1 H), 1.92–1.53 (m, 5 H), 1.48 (s, 3 H), 1.36 (m, 2 H), 0.90 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major regioisomer) δ 168.25, 165.42, 151.08, 126.11, 81.53, 80.27, 51.44, 42.57, 42.07, 41.51, 34.83, 21.48, 20.71, 17.09, 14.47; IR (neat) 2958, 1767, 1721, 1660, 1435, 1242, 1060, 942 cm^{-1}; LRMS (EI^+) *m/e* 282 (1), 211 (38), 190 (100), 165 (29), 137 (20), 123 (13), 109 (10), 95 (17), 81 (8), 71 (36). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.81. Found: C, 64.19; H, 8.21.

3-Acetoxy-2-(methoxycarbonyl)-1-methyl-5-phenyl-9-oxabicyclo-[3.3.1]non-2-ene (7g) was isolated as a 6:1 mixture of regioisomers in 69% yield: ot 136–150 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) (major regioisomer) δ 7.68–7.19 (m, 5 H), 3.74 (s, 3 H), 2.72 (d, *J* = 18.3 Hz, 1 H), 2.52 (d, *J* = 18.3 Hz, 1 H), 2.17 (s, 3 H), 2.13–1.56 (m, 6 H), 1.52 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major regioisomer) δ 168.36, 165.46, 151.60, 148.75, 128.23, 126.70, 125.37, 123.32, 73.98, 73.48, 51.55, 39.05, 38.85, 34.10, 26.06, 20.73, 17.81; IR ($CDCl_3$) 2951, 1758, 1717, 1436, 1338, 1221, 1051, 701 cm^{-1}; HRMS calcd for $C_{19}H_{22}O_5$ 330.1467, found 330.1460; LRMS (EI^+) *m/e* 330 (11), 287 (15), 245 (100), 213 (50), 172 (5), 147 (10), 105 (97), 91 (13), 77 (40).

(1*R,5*S**,7*R**)-3-Acetoxy-2-(methoxycarbonyl)-1,5,7-trimethyl-9-oxabicyclo[3.3.1]non-2-ene (19h)** was isolated as a 30:1 mixture of diastereomers in 80% yield. Recrystallization from hexanes/CH_2Cl_2 (10:1) provided crystals suitable for X-ray structure determination: ot 112–120 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3 H), 2.39 (d, *J* = 18.3 Hz, 1 H), 2.11–1.91 (m, 2 H), 2.09 (s, 3 H), 1.99 (d, *J* = 18.3 Hz, 1 H), 1.54 (m, 1 H), 1.32 (s, 3 H), 1.23 (s, 3 H), 1.00 (m, 2 H), 0.85 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.27, 165.53, 151.47, 123.38, 73.83, 70.85, 51.46, 46.61, 42.84, 38.63, 31.05, 25.91, 23.59, 21.77, 20.68; IR ($CDCl_3$) 2953, 1760, 1716, 1436, 1350, 1216, 1059, 913, 727 cm^{-1}; LRMS (EI^+) *m/e* 282 (3), 225 (11), 183 (100), 151 (39), 109 (3), 67 (2). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.80; H, 8.09.

General Procedure for the Synthesis of Bicyclic Ethers 7a–e. A solution of the 1,5-keto aldehyde (0.1 M in CH_2Cl_2) was cooled to −78 °C, and catalytic $TrSbCl_6$ (5–6 mol %) was added. A solution of the bis(trimethylsilyl) enol ether of methyl acetoacetate (1.05–1.2 equiv, 0.1 M in CH_2Cl_2) was added dropwise. After 5 h at −78 °C, a pH 7.0 phosphate buffer was added and the mixture was warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$). The product was purified by flash chromatography (3:1 hexanes/EtOAc) followed by Kugelrohr distillation. The bicyclic keto esters existed primarily in the enol form.

3-Hydroxy-2-(methoxycarbonyl)-5-methyl-9-oxabicyclo[3.3.1]non-2-ene (7a) was isolated in 72% yield: ot 86–92 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 11.88 (s, 1 H), 4.74 (bs, 1 H), 3.70 (s, 3 H), 2.38 (d, *J* = 18.8 Hz, 1 H), 2.14 (d, *J* = 18.8 Hz, 1 H), 1.81–1.42 (m, 6 H), 1.21 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.36, 170.24, 99.30, 70.26, 67.48, 51.29, 38.76, 38.14, 31.19, 28.09, 15.74; IR (neat) 2939, 1740, 1716, 1667, 1632, 1444, 1232, 1029, 819 cm^{-1}; HRMS calcd for $C_{12}H_{18}O_3$ 212.1049, found 212.1073; LRMS (EI^+) *m/e* 213 (3), 212 (1), 169 (100). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: 62.72; H, 7.79.

3-Hydroxy-2-(methoxycarbonyl)-5-propyl-9-oxabicyclo[3.3.1]non-2-ene (7b) was isolated in 88% yield: ot 98–104 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 11.89 (s, 1 H), 4.74 (d, *J* = 2.7 Hz, 1 H), 3.70 (s, 3 H), 2.42 (d, *J* = 18.8 Hz, 1 H), 2.08 (d, *J* = 18.8 Hz, 1 H), 1.79–1.26 (m, 10 H), 0.88 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.58, 170.28, 99.61, 72.26, 67.26, 51.29, 46.56, 37.05, 36.30, 28.49, 15.91, 15.51, 14.51; IR (neat) 2956, 1717, 1698, 1668, 1624, 1362, 1235, 1043, 818 cm^{-1}; LRMS (EI^+) *m/e* 241 (8), 240 (4), 197 (100), 165 (37), 137 (15), 123 (12), 95 (11), 81 (8), 71 (28). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.68; H, 8.40.

3-Hydroxy-5-isopropyl-2-(methoxycarbonyl)-9-oxabicyclo[3.3.1]non-2-ene (7c) was isolated in 76% yield: ot 86–92 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 11.91 (s, 1 H), 4.76 (s, 1 H), 3.71 (s, 3 H), 2.40 (d, *J* = 19.0 Hz, 1 H), 2.01 (d, *J* = 19.0 Hz, 1 H), 1.79–1.41 (m, 7 H), 0.85 (d, *J* = 6.9 Hz, 3 H), 0.848 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.87, 170.34, 99.78, 74.31, 67.24, 51.30, 39.47, 34.35, 33.10, 28.53, 16.28, 15.82, 15.37; IR (neat) 2948, 1741, 1716, 1667, 1626, 1443, 1272, 1076, 815 cm^{-1}; LRMS (EI^+) *m/e* 240 (4), 231 (18), 197 (100), 165 (52), 137 (22), 105 (29), 71 (31). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.94; H, 8.36.

3-Hydroxy-2-(methoxycarbonyl)-5-phenyl-9-oxabicyclo[3.3.1]non-2-ene (7d) was isolated in 91% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 11.97 (s, 1 H), 7.43–7.20 (m, 5 H), 5.05 (s, 1 H), 3.79 (s, 3 H), 2.76 (d, *J* = 18.8 Hz, 1 H), 2.66 (d, *J* = 18.8 Hz, 1 H), 1.99–1.86 (m, 3 H), 1.71–1.59 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.00, 170.19, 148.83, 128.36, 128.27, 126.74, 123.21, 99.40, 73.24, 67.56, 51.37, 39.47, 39.36, 28.22, 16.01; IR (neat) 3027, 2944, 1739, 1716, 1662, 1628, 1444, 1289, 1038, 810, 756, 700 cm^{-1}; LRMS (EI^+) *m/e* 274 (2), 243 (3), 231 (18), 105 (100), 91 (12), 77 (35), 51 (10). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.07; H, 6.68.

3-Hydroxy-2-(methoxycarbonyl)-5-*tert*-butyl-9-oxabicyclo[3.3.1]non-2-ene (7e) was isolated in 51% yield: ot 88–100 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 11.88 (s, 1 H), 4.73 (s, 1 H), 3.69 (s, 3 H), 2.64 (d, *J* = 19.3 Hz, 1 H), 1.92 (d, *J* = 19.3 Hz, 1 H), 1.70–1.39 (m, 6 H), 0.88 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.23, 170.29, 100.12, 75.98, 67.08, 51.22, 37.83, 33.21, 30.78, 28.74, 24.43, 24.40, 15.49; IR ($CDCl_3$) 2956, 1661, 1626, 1444, 1367, 1220, 1096, 926 cm^{-1}; LRMS (EI^+) *m/e* 197 (46), 165 (30), 125 (27), 97 (20), 57 (100). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.90; H, 8.54.

General Procedure for the Synthesis of Bicyclic Ethers 19i–q. The general procedure described above was followed with these exceptions. After purification by flash chromatography, all fractions containing product were concentrated and the residue was dissolved in pyridine (5 mL). Catalytic DMAP and Ac_2O (1.0 mL) were added, and the reaction was stirred until no starting material was observed by GLC. Flash chromatography (3:1 hexanes/EtOAc) followed by Kugelrohr distillation provided the enol acetate.

3-Acetoxy-5-ethyl-2-(methoxycarbonyl)-6-methyl-9-oxabicyclo-[3.3.1]non-2-ene (19i) was isolated as a 2:1 mixture of diastereomers in 87% yield: ot <120 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (d, *J* = 4.6 Hz) and 4.82 (d, *J* = 3.7 Hz, 1 H total), 3.66 (s) and 3.65 (s, 3 H total), 2.36 (d, *J* = 19.3 Hz, 1 H), 2.20 (s) and 2.19 (s, 3 H total), 2.17–1.81 (m, 3 H), 1.75–1.44 (m, 3 H), 1.42–1.38 (m, 2 H), 1.00 (d, *J* = 6.8 Hz) and 0.79 (d, *J* = 6.6 Hz, 3 H total), 0.87 (t, *J* = 7.3 Hz) and 0.79 (t, *J* = 7.6 Hz, 3 H total); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 168.60, 163.47, 156.66, 118.60, 74.91, 69.14, 51.51, 39.07, 33.99, 32.70, 22.57, 22.37, 20.83, 14.32, 6.62; IR (neat) 2949, 1767, 1723, 1673, 1436, 1260, 1046, 878 cm^{-1}; LRMS (EI^+) *m/e* 283 (4), 223 (10), 183 (100), 142 (40), 110 (13), 57 (47), 43 (59). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 64.12; H, 8.08.

3-Acetoxy-5-isopropyl-2-(methoxycarbonyl)-6-methyl-9-oxabicyclo-[3.3.1]non-2-ene (19j) was isolated as a 2.8:1 mixture of diastereomers in 56% yield: ot <120 °C/0.05 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (m, 1 H), 3.68 (s) and 3.67 (s, 3 H total), 2.22 (s) and 2.21 (s, 3 H total), 2.25–1.76 (m, 3 H), 1.69–1.31 (m, 5 H), 1.03 (d, *J* = 6.8 Hz), 0.94 (d, *J* = 6.8 Hz), 0.92 (d, *J* = 6.8 Hz), 0.86 (d, *J* = 6.8 Hz), 0.80 (d, *J* = 6.8 Hz) and 0.74 (d, *J* = 6.8 Hz, 9 H total); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 168.51, 163.51, 156.74, 118.74, 77.55, 68.57, 51.43, 36.04, 34.61, 30.84, 29.44, 24.38, 20.81, 16.60, 16.39, 16.37; IR (neat) 2962, 1768, 1721, 1674, 1436, 1260, 1092, 876 cm^{-1}; LRMS (EI^+) *m/e* 296 (4), 239 (10), 197 (100), 180 (21), 142 (18), 110 (5), 71 (35). Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.90; H, 8.55.

(1*R,5*S**,6*R**)-3-Acetoxy-2-(methoxycarbonyl)-6-methyl-5-phenyl-9-oxabicyclo[3.3.1]non-2-ene (19k)** was isolated as a single diastereoisomer in 83% yield: ot <170 °C/0.1 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.17 (m, 5 H), 5.14 (d, *J* = 4.6 Hz, 1 H), 3.73 (s, 3 H), 2.73 (d, *J* = 19.2 Hz, 1 H), 2.63 (d, *J* = 19.2 Hz, 1 H), 2.37 (m, 1 H), 2.22 (s, 3 H), 2.15 (m, 1 H), 2.05 (m, 1 H), 1.47 (m, 2 H), 0.66 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.60, 163.38, 156.06, 147.28, 128.15, 126.34, 123.35, 118.26, 75.89, 69.33, 51.58, 41.88, 38.20, 22.12, 22.11, 15.48; IR (CH_2Cl_2) 3026, 2948, 1770, 1721, 1674, 1436, 1245, 1174, 1062, 880 cm^{-1}; LRMS (EI^+) *m/e* 330 (6), 273 (9), 231 (100), 199 (6), 186 (3), 120 (7), 105 (69), 43 (20). Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.30; H, 6.89.

Preparation of (1*R,5*S**,6*R**)-3-(4-Bromobenzoyl)-2-(methoxycarbonyl)-6-methyl-5-phenyl-9-oxabicyclo[3.3.1]non-2-ene (20) for X-ray Crystallography.** The general procedure above was followed with these exceptions. Instead of Ac_2O, 4-bromobenzoyl chloride was utilized to derivatize the keto ester. Upon complete formation of the derivative (20 h, room temperature), water and Et_2O were added. The aqueous layer was washed with Et_2O, and the ethereal layers were washed several times with water followed by brine. The organic solution was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (4:1 hexanes/EtOAc) provided a white crystalline solid (424 mg, 84%). Recrystallization from Et_2O provided colorless needles suitable for X-ray crystallography: mp 163.9–164.1 °C; ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 7.94 (m, 2 H), 7.61 (d, *J* = 8.5 Hz, 2 H), 7.24 (m, 5 H), 5.18 (d, *J* =

4.6 Hz, 1 H), 3.58 (s, 3 H), 2.84 (d, J = 19.3 Hz, 1 H), 2.74 (d, J = 19.3 Hz, 1 H), 2.47 (m, 1 H), 2.19 (m, 1 H), 2.06 (m, 1 H), 1.51 (m, 2 H), 0.68 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 163.88, 163.36, 155.94, 147.24, 132.00, 131.93, 131.58, 128.91, 128.20, 128.12, 126.41, 123.38, 118.79, 76.08, 69.51, 51.66, 41.90, 38.28, 22.23, 22.17, 22.12, 22.07, 15.51; IR ($CDCl_3$) 3062, 2952, 1734, 1676, 1590, 1438, 1265, 1062, 921, 752, 650 cm^{-1}; HRMS calcd for $C_{24}H_{23}BrO_5$ 470.0729, found 470.0699; LRMS (EI$^+$) m/e 472 (5), 470 (5), 415 (42), 413 (42), 287 (13), 185 (99), 183 (100), 157 (12), 155 (12), 105 (36), 77 (18).

(1*R,5*S**,7*R**)-3-Acetoxy-2-(methoxycarbonyl)-5,7-dimethyl-9-oxabicyclo[3.3.1]non-2-ene (19l)** was isolated as a 14.8:1 mixture of diastereomers in 74% yield: ot 92–104 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 4.87 (d, J = 3.9 Hz, 1 H), 3.66 (s, 3 H), 2.32 (d, J = 19.1 Hz, 1 H), 2.16 (s, 3 H), 2.11 (d, J = 19.1 Hz, 1 H), 2.00 (m, 1 H), 1.60 (m, 2 H), 1.34 (td, J = 4.4, 12.6 Hz, 1 H), 1.23 (s, 3 H), 1.10 (t, J = 12.8 Hz, 1 H), 0.83 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 168.48, 163.37, 156.04, 118.91, 71.08, 69.46, 51.50, 47.11, 39.79, 36.01, 30.65, 21.77, 21.74, 20.75; IR (neat) 2952, 1767, 1723, 1708, 1670, 1436, 1256, 1106, 892 cm^{-1}; LRMS (EI$^+$) m/e 268 (1), 226 (4), 211 (6), 169 (100), 137 (17), 109 (4), 95 (2), 43 (16). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.78; H, 7.70.

(1*R,5*S**,7*R**)-3-Acetoxy-2-(methoxycarbonyl)-5-methyl-7-phenyl-9-oxablcyclo[3.3.1]non-2-ene (19m)** was isolated as a 6:1 mixture of diastereomers in 70% yield: ot 144–149 °C/0.13 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 7.35–7.14 (m, 5 H), 5.08 (d, J = 3.7 Hz, 1 H), 3.71 (s, 3 H), 3.37 (m, 1 H), 2.48 (d, J = 19.0 Hz, 1 H), 2.28 (d, J = 19.0 Hz, 1 H), 2.27 (s, 3 H), 2.51–1.61 (m, 4 H), 1.35 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 168.54, 163.20, 156.38, 144.85, 128.47, 127.08, 126.36, 118.76, 71.37, 69.54, 51.57, 46.08, 39.83, 34.57, 33.30, 30.64, 20.78; IR (CH_2Cl_2) 3028, 2932, 1765, 1721, 1670, 1436, 1364, 1106, 868 cm^{-1}; HRMS calcd for $C_{19}H_{22}O_5$ 330.1467, found 330.1458; LRMS (EI$^+$) m/e 330 (5), 288 (14), 270 (10), 238 (6), 169 (100), 137 (10), 104 (27), 91 (11), 69 (8), 43 (39). Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.56; H, 6.81.

(1*R,5*S**,7*R**)-3-Acetoxy-2-(methoxycarbonyl)-7-methyl-5-phenyl-9-oxabicyclo[3.3.1]non-2-ene (19n)** was isolated as a single diastereomer in 78% yield: ot 153–160 °C/0.1 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.21 (m, 5 H), 5.18 (d, J = 3.9 Hz, 1 H), 3.75 (s, 3 H), 2.66 (s, 2 H), 2.25 (m, 1 H), 2.23 (s, 3 H), 2.03 (dd, J = 2.93, 13.2 Hz, 1 H), 1.79 (m, 1 H), 1.52 (dt, J = 4.6, 12.9 Hz, 1 H), 1.33 (t, J = 12.9 Hz, 1 H), 0.93 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.58, 163.34, 155.83, 148.26, 128.29, 126.83, 123.23, 119.05, 74.14, 69.51, 51.60, 48.36, 40.38, 36.10, 22.07, 21.75, 20.76; IR (CH_2Cl_2) 2928, 1764, 1720, 1672, 1361, 1220, 1056, 891 cm^{-1}; LRMS (EI$^+$) m/e 330 (20), 288 (12), 231 (100), 199 (17), 169 (13), 137 (14), 105 (93), 77 (27), 43 (38). Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.18; H, 6.81.

(1*R,5*S**,8*S**)-3-Acetoxy-2-(methoxycarbonyl)-5,8-dimethyl-9-oxabicyclo[3.3.1]non-2-ene (19o)** was isolated as a 6.8:1 mixture of diastereomers in 82% yield: ot 96–105 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 4.83 (d, J = 4.2 Hz, 1 H), 3.62 (s, 3 H), 2.17 (d, J = 5.6 Hz, 2 H), 2.13 (s, 3 H), 1.90 (m, 1 H), 1.62–1.47 (m, 4 H), 1.19 (s, 3 H), 0.81 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 168.55, 164.13, 155.38, 117.14, 73.34, 70.40, 51.32, 39.44, 38.49, 34.10, 30.31, 23.93, 20.60, 17.42; IR (neat) 2931, 1770, 1721, 1672, 1436, 1260, 1155, 1040, 857 cm^{-1}; LRMS (EI$^+$) m/e 268 (2), 226 (2), 211 (9), 169 (100), 137 (15), 124 (5), 97 (27), 43 (13). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.72; H, 7.28.

(1*R,5*S**,8*S**)-3-Acetoxy-2-(methoxycarbonyl)-8-methyl-5-phenyl-9-oxabicyclo[3.3.1]non-2-ene (19p)** was isolated as an 8.2:1 mixture of diastereomers in 60% yield: ot <150 °C/0.05 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 7.33–7.12 (m, 5 H), 5.08 (d, J = 4.4 Hz, 1 H), 3.64 (s, 3 H), 2.60 (d, J = 19.0 Hz, 1 H), 2.50 (d, J = 19.0 Hz, 1 H), 2.13 (s, 3 H), 2.03 (m, 1 H), 1.94 (m, 1 H), 1.84–1.61 (m, 2 H), 1.53 (m, 1 H), 0.68 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 168.68, 164.14, 155.22, 148.13, 128.21, 126.76, 123.17, 117.30, 73.45, 73.43, 51.44, 40.16, 39.80, 34.29, 24.18, 20.64, 17.45; IR ($CDCl_3$) 3030, 2953, 1757, 1716, 1674, 1473, 1270, 1055, 885 cm^{-1}; LRMS (EI$^+$) m/e 330 (3), 273 (8), 231 (100), 199 (14), 187 (11), 151 (7), 129 (15), 115 (11), 105 (54), 103 (13), 77 (16), 43 (24). Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 68.87; H, 6.93.

(1*R,5*S**,8*S**)-3-Acetoxy-2-(methoxycarbonyl)-5-methyl-8-phenyl-9-oxabicyclo[3.3.1]non-2-ene (19q)** was isolated as a 13.4:1 mixture of diastereomers in 60% yield: ot <140 °C/0.15 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 7.29–7.14 (m, 5 H), 5.12 (d, J = 4.4 Hz, 1 H), 3.25 (m, 1 H), 2.98 (s, 3 H), 2.58 (m, 1 H), 2.36 (s, 2 H), 2.26 (s, 3 H), 1.77 (m, 3 H), 1.37 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 168.89, 163.12, 155.61, 140.72, 128.26, 126.60, 117.03, 74.04, 70.72, 50.73, 45.44, 39.52, 38.82, 30.30, 20.73, 20.14; IR (CH_2Cl_2) 3061, 2948, 1770, 1716, 1673, 1366, 1206, 1043, 863 cm^{-1}; LRMS (EI$^+$) m/e 330 (1), 288 (7), 270 (6), 211 (7), 169 (100), 137 (6), 104 (43), 91 (7), 43 (26). Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 68.76; H, 6.75.

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Supplementary Material Available: Listings of details of the X-ray crystallographic structure determinations for compounds **5k**, **19h**, **19o**, and **20** described within the text, including tables of structure data, atomic coordinates, bond lengths, and isotropic and anisotropic thermal parameters (46 pages); tables of observed and calculated structure factors (30 pages). Ordering information is given on any current masthead page.