Neighboring Group Participation in Lewis Acid-Promoted [3 + 4] and [3 + 5] Annulations. The Stereocontrolled Synthesis of Tricyclic Ethers

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Received May 18, 1993•

A variety of 1,4- and 1,5-keto aldehydes derived from cycloalkanes are coupled with the bis(trimethylsilyl) enol ether of methyl acetoacetate in the presence of either TMSOTf or $TrSbCl_6$ to generate tricyclic ethers. The reactions proceed with excellent regiochemical control by a mechanism involving neighboring group participation. This mechanism involves initial formation of a bicyclic oxocarbenium ion intermediate from the keto aldehyde substrates. The geometries of selected bicyclic intermediates have been optimized using the AM1 method allowing successful prediction of the stereochemical outcomes in the cyclization in most cases. Epimerization of α-chiral keto aldehyde substrates does not appear to occur in these Lewis acid-promoted annulation reactions.

There exists a growing number of naturally occurring compounds containing highly functionalized seven-[1] and eight-membered[2] ring systems. Because of the therapeutic value of these compounds, the stereoselective construction of medium-sized ring systems is of great interest. Thus, although considerable effort has been invested in the synthesis of five- and six-membered carbocycles wherein both regiochemical and stereochemical control can be achieved in a predictable fashion, relatively few annulative methods exist for the stereoselective synthesis of seven-[3] and eight-membered[4] carbocycles. In principle, the synthesis of these rings sizes can be accomplished by the reaction of a 1,3-dianionic synthon with a 1,4- or 1,5-dielectrophilic substrate. However, in the absence of other control elements, the coupling of two such species is disfavored by entropic factors as well as by developing transannular interactions.[5] In addition, the two nucleophilic sites of the dianionic synthon and the two electrophilic sites of the dielectrophile must have differential reactivities in order to react in proper sequence, thereby providing high regioselectivity. If new stereogenic centers are created in the cyclization, relative asymmetric induction must also be controlled.

We recently reported the efficient construction of seven- and eight-membered carbocycles using Lewis acid-promoted [3 + 4] and [3 + 5] annulation reactions by processes which avoided the potential pitfalls mentioned above.[6] Highly functionalized bicyclic ethers were obtained in the coupling of 1,4- or 1,5-dielectrophiles with bis(trimethylsilyl) enol ethers derived from 1,3-keto esters or 1,3-diketones (eq 1). In general, trimethylsilyl trifluoromethanesulfonate (TMSOTf)[7] (15–25 mol %) was the optimum Lewis acid for the annulation of 1,4-keto aldehydes, 1,4-diketones, and 1,5-diketones with the bis(trimethylsilyl) enol ether of methyl acetoacetate (1). In

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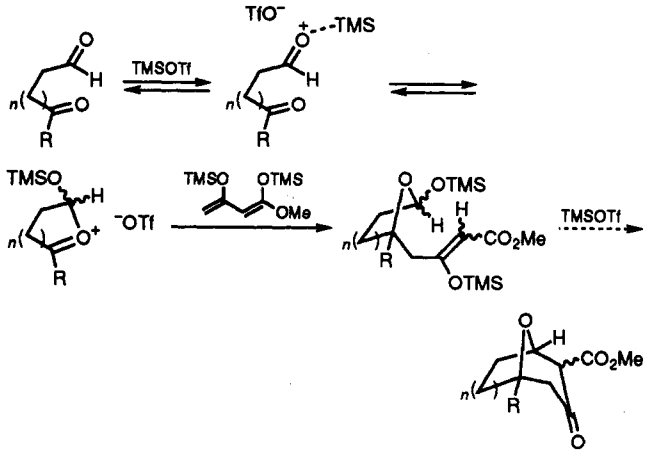
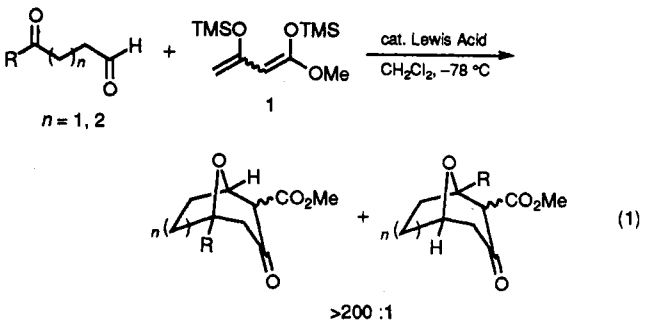
Scheme I

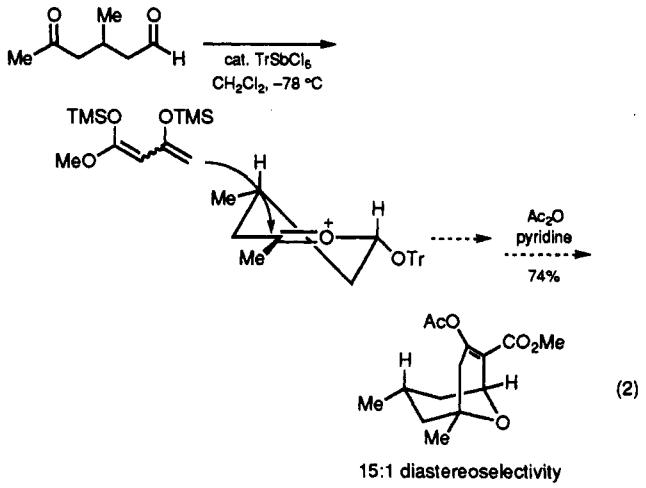


the case of 1,5-keto aldehydes, trityl hexachloroantimonate ($TrSbCl_6$)[8] (5–6 mol %) provided the best yields of the corresponding bicyclic ethers.



The success of this annulative method relies on a mechanism involving neighboring group participation (Scheme I).[9] This mechanism accounts for the unusually high regioselectivity obtained in these annulation reactions. For example, in annulations employing keto aldehyde substrates (eq 1), the regiochemistry observed was a result of initial attack of the more nucleophilic carbon (i.e., the terminal carbon) of the bis(trimethylsilyl) enol ether dinucleophile[10] at the ketone carbonyl carbon of the dielectrophile. Rationalization for this observation involved initial Lewis acid activation of the sterically less hindered aldehyde followed by intramolecular attack of the ketone carbonyl oxygen at this activated center, generating a cyclic oxocarbenium ion.[11] The ketone center on the cyclic oxocarbenium ion was thus activated toward nucleophilic attack. Subsequent reaction of the bis(trimethylsilyl) enol ether at this site provided a neutral acetal intermediate, which, after ring closure via a second cyclic oxocarbenium ion, generated the observed bicyclic product. The neighboring group participation mechanism thus explained the rather unusual relative reactivity of the two carbonyl groups in the dielectrophile.

The presence of a cyclic intermediate in this type of mechanism also provided a means for excellent stereochemical control in the annulation of chiral dielectrophiles with the bis(trimethylsilyl) enol ether 1. Conformational analysis of the proposed oxocarbenium ion intermediate allowed accurate prediction of the stereochemical outcome in the resulting bicyclic ether.[6] For example, stereoelectronically favored axial attack[12] of the nucleophile onto the energetically favored six-membered oxocarbenium ion conformer provided the C-7 exo-methyl-substituted bicyclic ether as the major diastereomer (eq 2).



To further demonstrate the synthetic potential of these annulation reactions, experiments involving the stereocontrolled synthesis of tricyclic ethers were performed. Thus, a variety of 1,4- and 1,5-keto aldehydes derived from cycloalkanes were coupled with bis(trimethylsilyl) enol ether 1, providing tricyclic ring systems. Neighboring group participation in such substrates was anticipated to permit regiochemical control in the cyclization. Conformational analysis of the bicyclic oxocarbenium ion intermediate was expected to allow prediction of stereochemistry in the resulting tricyclic ethers. The amount of strain energy involved in the formation of these intermediates was anticipated to be a critical factor in these annulations. An activated, cyclic intermediate calculated to possess a great deal of strain may not be able to form under the reaction conditions, and one might expect poor regioselectivity or a lack of annulation products in these instances. Epimerization of acid-sensitive α-chiral keto aldehyde substrates under the Lewis acidic conditions was also a concern. In order to explore these reactions in more detail, a variety of 1,4- and 1,5-keto aldehydes derived from cycloalkanes were synthesized and annulated with 1. The results of these studies are reported herein.

Results and Discussion

Regiochemical control in the annulative process was first examined by cyclization of 1,1-disubstituted cyclopentanes (2) and cyclohexanes (3). The cyclopentane derivatives

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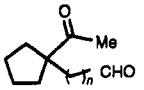
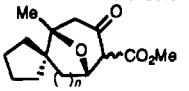
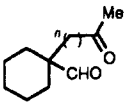
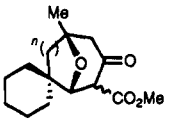
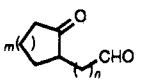
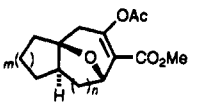
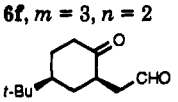
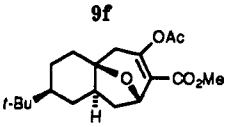
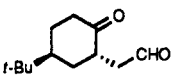
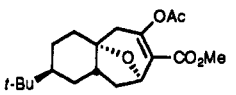
Table I. Lewis Acid Promoted Annulation of 1,4- and 1,5-Dielectrophiles with 1[a]

entry	substrate	product	% isoltd yield[b] (%)	diastereoselectivity[c]
				
1	**2a**, $n = 1$	**4a**	76	>200:1[d]
2	**2b**, $n = 2$	**4b**	79	>200:1[d]
				
3	**3a**, $n = 1$	**5a**	75	>200:1[d]
4	**3b**, $n = 2$	**5b**	63	>200:1[d]
				
5	**6a**, $m = 1, n = 1$	**9a**	52	2.5:1[d]
6	**6b**, $m = 1, n = 2$	**9b**	67	>120:1
7	**6c**, $m = 2, n = 1$	**9c**	87	>200:1
8	**6d**, $m = 2, n = 2$	**9d**	67	6:1
9	**6e**, $m = 3, n = 1$	**9e**	75	43:1
10	**6f**, $m = 3, n = 2$	**9f**	0	
				
11	**6g**	**9g**	74	>200:1
				
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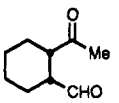
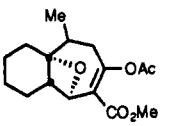
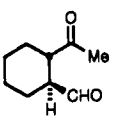
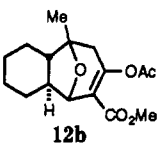
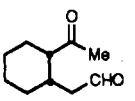
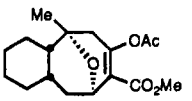
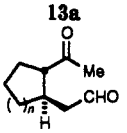
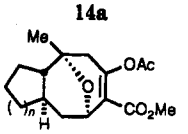
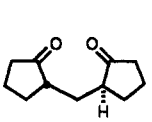
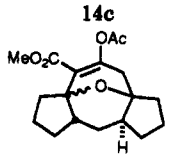
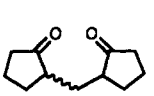
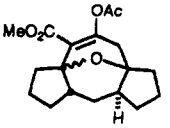
				
13	**11a**	**12a**	79	>200:1
				
14	**11b**	**12b**	0	
				
15	**13a**	**14a**	70	>100:1
				
16	**13b**, $n = 2$	**14b**	57	4:1
17	**13c**, $n = 1$	**14c**	<20	
				
18	**15a**	**16a**	45	2.5:1
				
19	**15a** and **15b**	**16a**	30	2:1

[a] TMSOTf was utilized in the annulation of 1,4-keto aldehydes. Annulation of 1,5-keto aldehydes employed $TrSbCl_6$ as the Lewis Acid. [b] Refers to yields of purified products as a mixture of diastereomers. 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. [c] Diastereoselectivities and regioselectivities were determined by fused silica capillary GLC or by NMR. [d] This ratio refers to regioselectivity.

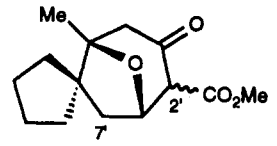
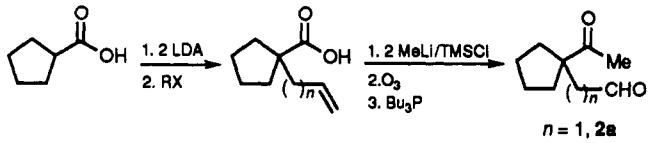
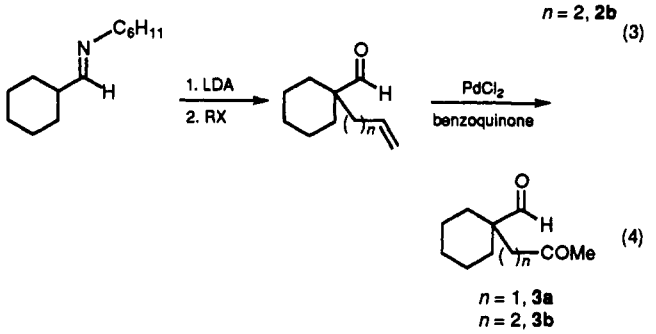


Figure 1. Compound **4a**.

were prepared by alkylation of the dianion derived from cyclopentanecarboxylic acid.[13] Formation of the methyl ketone,[14] followed by oxidative cleavage of the double bond,[15] provided the desired 1,4- and 1,5-keto aldehydes **2** (eq 3). The cyclohexane substrates were synthesized by

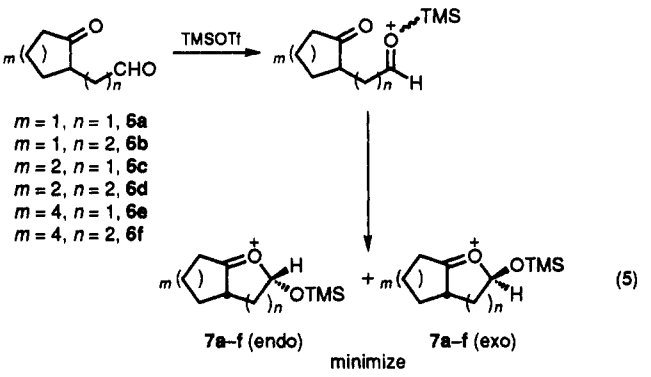




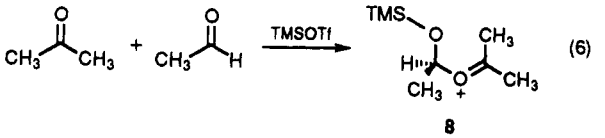
alkylation of the cyclohexylimine derived from cyclohexylcarboxaldehyde[16] with allyl bromide or 4-bromo-1-butene, followed by Wacker oxidation (eq 4).[17] TMSOTf-promoted or $TrSbCl_6$-promoted annulation (for 1,4-keto aldehyde substrates or 1,5-keto aldehyde substrates, respectively) with the dinucleophilic synthon **1** cleanly provided the corresponding spirocyclic compounds in good yield (63–79%, Table I, entries 1–4). Only one regioisomer was detected by both GLC and NMR, and this isomer resulted from initial attack of the bis(trimethylsilyl) enol ether at the ketone carbon of the dielectrophiles in accordance with the neighboring group participation mechanism.

Structural assignments were made in these cases by ^1H NMR. Each tricyclic product exists as a mixture of three isomers: the enol tautomer plus the keto esters with both exo and endo substitution of the methoxycarbonyl unit. For example, in compound **4a**, 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 ^1H NMR (Figure 1). On the other hand, H-1′ couples to both exo protons H-7′ and H-2′ and appears as a multiplet in the enol-substituted methoxycarbonyl epimer of the β-keto ester. These signals were comparable to those obtained for the previously studied bicyclic ether systems.[6]

Stereochemical control in the synthesis of tricyclic ethers was investigated by the annulation of a series of 2-substituted cycloalkanones **6** with **1**. TMSOTf-activation of the aldehyde carbonyl group followed by intramolecular attack of the ketone oxygen onto the aldehyde carbon was postulated to provide the proposed bicyclic oxocarbenium ion intermediate **7** (eq 5). AM1 calculations[18] were



performed on these bicyclic intermediates in order to generate optimized geometries, allowing us to predict the stereochemical outcome in the cyclization.[19] Because the trimethylsiloxy group can be situated in either the exo or endo orientation in the bicyclic intermediate, both isomers were minimized and their energies compared. Some insight regarding the proposed neighboring group participation mechanism was also expected from these calculations. If neighboring group participation was occurring in these compounds, one might expect a significant bonding interaction between the ketone oxygen and the activated aldehyde carbonyl group. Examination of interatomic distances (between the ketone oxygen and the aldehyde carbon) and bond orders provided this information. For comparative purposes, an intermolecular interaction which modeled the proposed intermediates was investigated in an acyclic system via AM1 calculations. TMSOTf-activation of acetaldehyde followed by attack of the ketone oxygen in acetone provided the theoretical complex **8** (eq 6). The geometry of this ion was minimized



in order to acquire parameters to compare with those obtained from the bicyclic intermediates **7**. Results obtained after minimization of the acyclic complex **8** are given in Table II. The distance between the ketone oxygen and the aldehyde carbon was approximately 1.51 Å, and the bond order was about 0.7. We therefore expected comparable values from other keto aldehyde substrates if the neighboring group participation mechanism was favorable.

Calculations performed on bicyclic intermediates **7a–f** suggested that neighboring group participation would be favorable in all the compounds examined with the exception of **7a** and the exo isomer **7b** (Table II). For each isomer of compound **7a**, the calculated distance between the ketone oxygen and aldehyde carbon was almost 2.5 Å and the bond order was only about 0.03, suggesting little bonding interaction between these two atoms. This result was expected because the bicyclic oxocarbenium ion derived from 1,4-keto aldehyde **6a** possessed a great deal

(13) Creger, P. L. *Org. Synth.* **1970**, *50*, 58.
(14) Rubottom, G. M.; Kim, C.-W. *J. Org. Chem.* **1983**, *48*, 1550.
(15) Patel, D. V.; VanMiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603.
(16) Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517.
(17) Tsuji, J. *Synthesis* **1984**, 369.
(18) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(19) Ampac version 2.10 was utilized for these calculations.

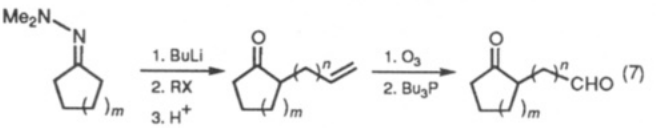
Table II. Results from AM1 Calculations

substrate[a]	ΔH_f (kcal/mol)	C–O distance[b] (Å)	C–O bond order[c]
7a (exo)	10.7	2.476	0.027
7a (endo)	12.5	2.457	0.028
7b (exo)	−0.52	2.384	0.040
7b (endo)	3.03	1.569	0.64
7c (exo)	5.07	1.625	0.59
7c (endo)	1.81	1.720	0.50
7d (exo)	−8.26	1.556	0.65
7d (endo)	−9.30	1.538	0.68
7e (exo)	−6.41	1.596	0.63
7e (endo)	−3.41	1.572	0.65
7f (exo)	−13.6	1.539	0.67
7f (endo)	−15.1	1.525	0.70
8	4.58	1.512	0.71

[a] Substrate obtained after minimization of the bicyclic intermediate when the trimethylsiloxy group was placed in either the exo or endo orientation. [b] Distance between the ketone oxygen and the aldehyde carbon. [c] Bond order between the ketone oxygen and the aldehyde carbon.

of strain energy. On the other hand, we anticipated neighboring group participation in the other keto aldehydes examined (**6b–e**) because the bicyclic intermediates derived from these compounds appear to possess relatively little strain. With the exception of the exo isomer of **7b**, the AM1 calculations confirmed these notions. Carbon–oxygen distances and bond orders were similar to those observed for complex **8**, suggesting a bonding interaction between the ketone oxygen and the aldehyde carbon in the anticipated intermediates (Table II). These theoretical results are compared to the experimental findings in the following paragraphs.

The series of 2-substituted cycloalkanones **6** required for the synthetic studies were generated by alkylation of the dimethylhydrazone-protected cycloalkanone[20] followed by deprotection[21] and ozonolysis (eq 7). Annulation



6

with the bis(trimethylsilyl) enol ether **1** and derivatization of the resulting epimerizable β-keto ester to the enol acetate allowed determination of the diastereoselectivity in the reactions.

The [3 + 4] annulation of 2-(2-oxoethyl)cyclohexanone (**6a**) with **1** provided only a 2.5:1 mixture of regioisomers in 52% yield (Table I, entry 5). Utilizing $TrSbCl_6$ as the Lewis acid in this reaction did not improve the regioselectivity or yield. These results could be rationalized with support from the AM1 calculations, which indicated little bonding interaction between the ketone oxygen and the Lewis acid-activated aldehyde carbon (Table II). Perhaps neighboring group participation was not particularly effective in this system, enabling substantial initial nucleophilic attack at the aldehyde.

The analogous cyclohexanone system **6c**, however, provided excellent results when annulated with **1**. Complete stereochemical as well as regiochemical control was obtained in the cyclization (Table I, entry 7). The extremely high regiochemical and stereochemical control observed in this cyclization was attributed to neighboring group participation, as suggested by the AM1 calculations

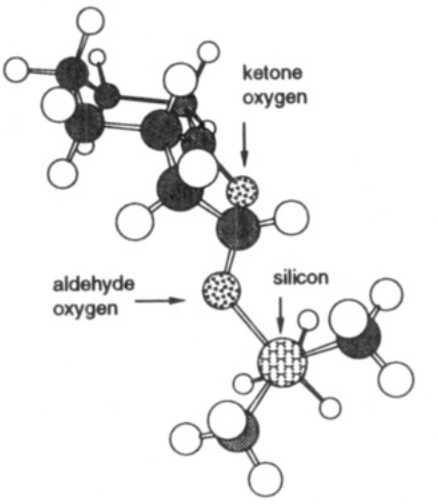


Figure 2. Optimized geometry of **7c** (endo).

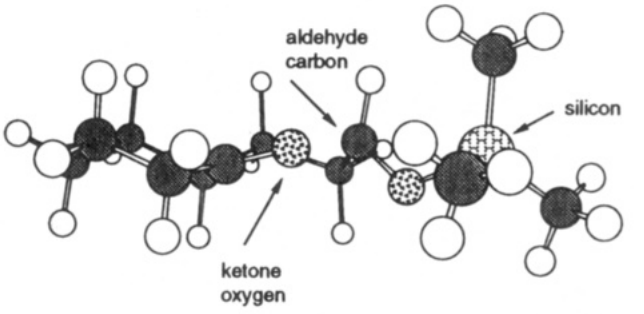


Figure 3. Optimized geometry of **7d** (exo).

(Table II). Thus, the stereochemistry of the tricyclic ether **9c** was predicted by examining the optimized geometry of the energetically favored isomer **7c** (endo) (Figure 2). Nucleophilic attack from the convex face of the intermediate at the activated ketone provided the observed stereochemistry as shown in Table I.

The low diastereoselectivity (6:1) obtained in the [3 + 5] annulation of 2-(3-oxopropyl)cyclohexanone (**6d**) with **1** (Table I, entry 8) was also explained by examination of the TMSOTf-activated keto aldehyde intermediate **7d** calculated with AM1 (Table II).[22] Because the energies of the two limiting isomers were similar, both were examined to evaluate stereochemical control in the tricyclic product. The optimized geometry of the intermediate derived from **6d** (exo) (Figure 3) was flatter than that derived from **6c** (Figure 2). The nucleophile could therefore access either face of the ketone carbonyl group to generate both stereoisomers. The endo isomer was expected to allow some selectivity in the addition of the nucleophile because of the convex nature of the intermediate (Figure 4). The nucleophile should prefer to attack from the top face of this intermediate to provide the major diastereomer shown in Table I (entry 8). These combined results would explain the low selectivities observed in this reaction.

The [3 + 5] annulation of the analogous cyclopentanone derivative (**6b**) provided improved diastereoselectivities. A single regioisomer was obtained as a >120:1 mixture of diastereomers (Table I, entry 6). For this example, the

(20) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3.
(21) Ballini, R.; Petrini, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2563.

(22) In order to simplify the calculation, the trimethylsilyl-activated aldehyde was utilized for the optimization (instead of triphenylmethyl). Both Lewis acids provided identical diastereoselectivities in the cyclization.

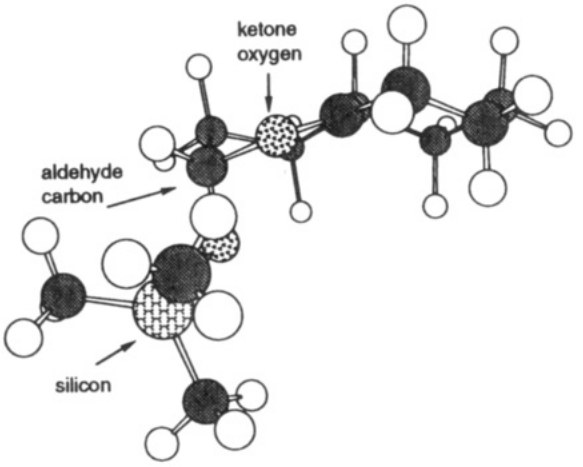


Figure 4. Optimized geometry of **7d** (endo).

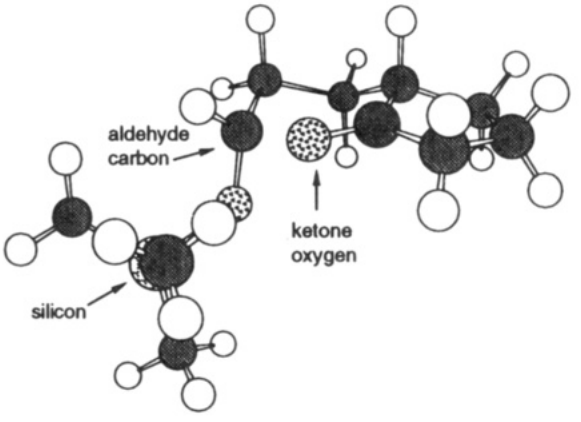


Figure 5. Optimized geometry of **7b** (endo).

results obtained from the AM1 calculations do not agree with the experimental observations. For the more energetically favored exo isomer **7b**, the carbon–oxygen distance and bond order obtained from these calculations indicate little bonding interaction between these atoms, suggesting a lack of neighboring group participation (Table II). On the other hand, according to the AM1 results, a strong bonding interaction is apparent in the less energetically favored endo isomer (Table II). Nevertheless, a bicyclic intermediate is assumed to form under the reaction conditions, and the stereochemical outcome was predicted by examining the optimized geometry of the endo isomer **7b** (Figure 5). With nucleophilic attack from the convex face of the intermediate, the ether bridge would lie trans to the methine hydrogen at the ring juncture in the tricyclic product. An X-ray crystal structure of the major diastereomer confirmed our stereochemical predictions.[23] These results provide an indication of the limits of calculational methods in predicting solution chemistry of reactive intermediates. Thus, although the calculations provided a useful guideline for most of the substrates, it is clear that caution must be exercised because total reliability of these methods cannot reasonably be expected.

In continuing the synthetic studies, the [3 + 4] and [3 + 5] annulations of cyclooctanone derivatives were also explored. Annulation of **6e** with **1** provided a 43:1 mixture

(23) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

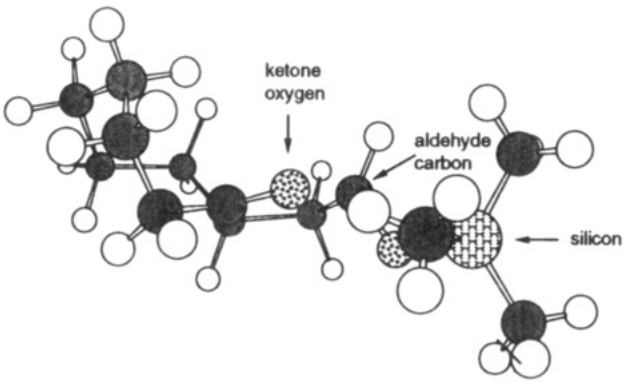
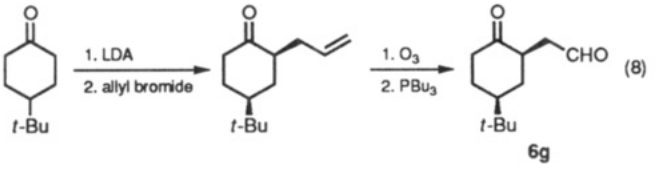


Figure 6. Optimized geometry of **7e** (exo).

of diastereomers in 75% yield (Table I, entry 9). The stereochemical outcome for this substrate was predicted from the optimized geometry of the trimethylsilyl-activated 1,4-keto aldehyde **7e** (Table II, Figure 6). Nucleophilic attack at the ketone carbonyl group from the convex face of the more energetically favored exo isomer was expected to provide the stereochemistry shown in Table I for the major diastereomer of compound **9e**. Surprisingly, annulation of **6f** generated none of the desired tricyclic ether (Table I, entry 10). TMSOTf and $TrSbCl_6$ were utilized as Lewis acids in the reaction, and both provided similar, disappointing results.

Because we were interested in determining if epimerization was a problem in the annulation reaction, two isomeric 4-*tert*-butylcyclohexanone derivatives were prepared and cyclized. The cis isomer (**6g**) was synthesized by alkylation of 4-*tert*-butylcyclohexanone (LDA) with allyl bromide, followed by oxidative cleavage of the double bond (eq 8). Alkylation of the dimethylhydrazone of 4-*tert*-butylcyclohexanone and hydrolysis[21] provided the trans-substituted cyclohexanone as the major stereoisomer (eq 9). Ozonolysis allowed access to **6h**.



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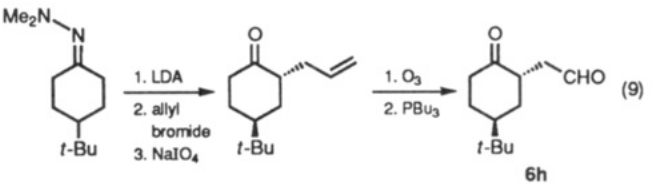


(9)

The more stable cis isomer (**6g**) reacted cleanly to provide the tricyclic ether (**9g**) as a single diastereomer by NMR (Table I, entry 11). The trans derivative (**6h**), when treated only with catalytic TMSOTf, epimerized to the cis isomer at −78 °C. Nevertheless, epimerization was avoided in the annulation and only the expected tricyclic product (**9h**) was obtained as a single diastereomer (Table I, entry 12).

Several more sensitive 1,2-disubstituted cycloalkane derivatives were annulated to examine whether epimerization would pose problems in these reactions. The *cis*- and *trans*-2-acetylcyclohexanecarboxaldehydes (**11a** and **11b**) were prepared by the method of Corey and Boger (eq

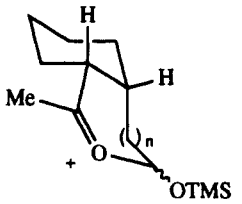
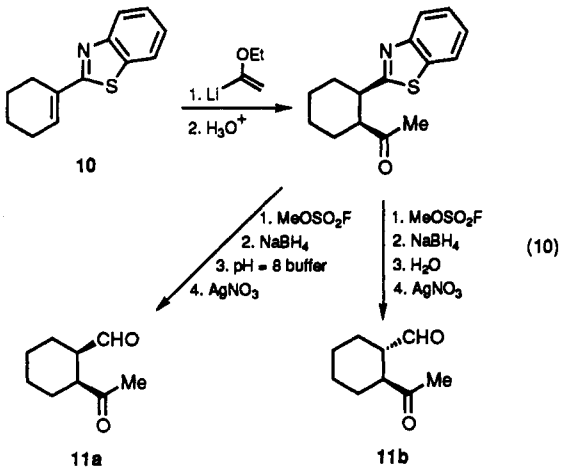


Figure 7. Proposed bicyclic intermediate derived from **11a** (n = 0) or **13a** (n = 1).

10).[24] Stereocontrolled addition of 1-ethoxyvinyllithium[25] onto 1-(2-benzothiazolyl)-1-cyclohexene (**10**)[24b] provided, after hydrolysis of the vinyl ether, the cis-keto benzothiazole. N-Methylation of the benzothiazole and reduction

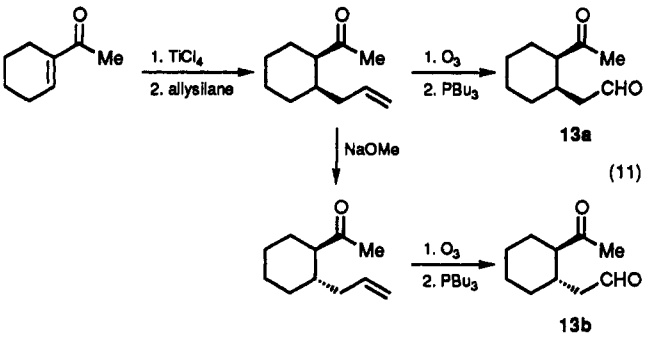


of the iminium salt provided the N-methylbenzothiazoline, which, upon silver(I)-promoted hydrolysis, generated the desired cis-1,4-keto aldehyde **11a**. When the $NaBH_4$ reduction of the iminium salt was not quenched with a buffer solution, the trans isomer **11b** was isolated (eq 10).

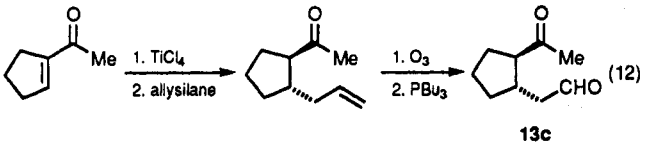
The cis isomer **11a** reacted cleanly with 1 to provide tricyclic ether **12a** as a single stereoisomer in 79% yield (Table I, entry 13). The stereochemistry was predicted by examination of the proposed bicyclic intermediate derived from the keto aldehyde (Figure 7). Nucleophile attack from the convex face of this intermediate (or top face of the ketone as shown in Figure 7) generates a trans relationship between the ether bridge and the methine hydrogens at the ring junctures.

The more stable trans isomer (**11b**) was also reacted with 1 under identical reaction conditions. However, no annulation products were isolated from this reaction (Table I, entry 14). The apparent lack of neighboring group participation was expected based on geometric constraints present in this system. The bicyclic intermediate and the resulting product would each contain a trans-fused six-five ring system. The lack of tricyclic products was attributed to the increased strain energy present in this geometry. It appeared that epimerization of the 1,4-keto aldehydes was not occurring in these systems because no annulation products were detected.

$TrSbCl_6$-promoted annulations of related 1,5-keto aldehydes were also investigated. The requisite substrates were synthesized via $TiCl_4$-promoted conjugate addition



of allylsilane onto 1-acetyl-1-cyclohexene (eq 11).[26] Ozonolysis provided the desired cis-1,5-keto aldehyde **13a** as the major stereoisomer. The *cis*-1-acetyl-2-(2-propenyl)-cyclohexane was epimerized to the more stable trans isomer for preparation of **13b**. Attempts to utilize the same methodology for the synthesis of the analogous *cis*-cyclopentyl compound provided the undesired trans isomer as the major product (14:1, eq 12). Compound **13c** was prepared from this intermediate.



Annulation of **13c** with 1 led to a complex mixture of compounds in low yields (<20%) which were not characterized (Table I, entry 17). To further complicate matters, the isolated material was contaminated with triphenylmethyl compounds. The poor reactivity of **13c** can be compared to that of **11b**. Both the bicyclic intermediates and products derived from these substrates would possess a large amount of ring strain.

By contrast, the *cis*-cyclohexyl derivative **13a** cyclized with 1 to provide the desired tricyclic ether **14a** as a >100:1 mixture of stereoisomers (Table I, entry 15). The geometry of the proposed bicyclic intermediate was examined using molecular models in order to predict the stereochemical outcome (Figure 7). Nucleophilic attack from the convex face of the ion was expected to generate the stereoisomer shown in Table I. This prediction was verified by single-crystal X-ray analysis of the major diastereomer of **14a**.[23]

Annulation of the corresponding trans isomer **13b** with 1 provided low diastereoselectivities. A 4:1 mixture of stereoisomers was obtained in this reaction (Table I, entry 16). Molecular models of the bicyclic intermediate show that it is flatter than the oxocarbenium ion derived from **13a**. The geometry of the bicyclic intermediate derived from this substrate can be compared to that derived from **6d** because each resembles a *trans*-decalin system. The nucleophile can attack from either face of the ketone carbonyl group in this intermediate, generating a mixture of products. Epimerization under the Lewis acidic reaction conditions apparently did not occur in the cyclization of either **13a** or **13b**.

The [3 + 5] annulation of one symmetrical bicyclic ketone (**15**) was examined to investigate the synthesis of a tetracyclic ether. The starting substrate was prepared as a 1:1 mixture of *dl* (**15a**) and meso (**15b**) stereoisomers by condensation of [(*N*,*N*-dimethylamino)methyl]cyclo-

(24) (a) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 13. (b) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 5.
(25) Soderquist, J. A.; Hsu, G. J.-H. *Organometallics* **1982**, *1*, 830.
(26) Sakurai, H.; Hosomi, A.; Hayashi, J. *Org. Synth.* **1990**, *7*, 443.

pentanone with cyclopentanone.[27] The *dl*-isomer was obtained by fractional recrystallization. The stereochemical configuration of **15a** was determined by single-crystal X-ray analysis.[23]

Annulation of **15a** with the bis(trimethylsilyl) enol ether 1 provided the tetracyclic ether **16a** as a 2.5:1 mixture of diastereomers in low yield (Table I, entry 18). The stereochemical relationship of the methine protons was inferred from the stereochemistry of the starting diketone. The relative configuration of the ether bridge for the major diastereomer was not determined for this example. The isomeric mixture (**15a**:**15b**, 1:1) was also annulated with 1. Surprisingly, the identical products obtained for the annulation of only **15a** were obtained when the mixture was annulated (2:1 mixture of diastereomers) (Table I, entry 19). Treatment of a 1:1 mixture of **15a** and **15b** with TMSOTf at −78 °C resulted in no epimerization. It appears that the meso compound does not cyclize under the reaction conditions.

Conclusions

Several 1,4- and 1,5-keto aldehydes were cyclized with the bis(trimethylsilyl) enol ether 1 to provide highly functionalized tricyclic ethers. In general, the reactions proceeded in good yield, and the cyclized products were obtained with excellent regioselectivity. Attack of the bis-(trimethylsilyl) enol ether occurred at the activated ketone carbonyl group first, in accordance with the neighboring group participation mechanism.

Annulation was hindered if the cyclized oxocarbenium ion intermediate or the product contained a great deal of ring strain. On the other hand, if the bicyclic intermediate was relatively free of strain, a mechanism involving neighboring group participation was possible. This idea was supported by AM1 calculations performed on selected oxocarbenium ion intermediates. A small interatomic distance and significant bond order between the ketone oxygen and the aldehyde carbon was attributed to neighboring group participation. The stereochemical outcome in the final tricyclic product was successfully predicted by examining facial selectivity in nucleophilic attack on the proposed intermediates.

Experimental Section

Reagents. Tetrahydrofuran (THF) was distilled immediately prior to use from benzophenone ketyl under argon. 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,[28] and all reactions were carried out under argon.

1-(3-Butenyl)cyclopentanecarboxylic Acid (2b Precursor). To a solution of diisopropylamine (4.3 g, 43 mmol) in THF (60 mL) at 0 °C was slowly added *n*-BuLi (1.6 M in hexanes, 26.0 mL, 41.6 mmol). After 30 min, cyclopentanecarboxylic acid (2.250 g, 19.71 mmol) in THF (10 mL) was slowly added.[13] The solution was warmed to 50–60 °C for 30 min. The reaction was cooled to 0 °C, and 4-bromo-1-butene (2.7 g, 20 mmol) was added. The reaction was warmed to room temperature and was stirred for 20 h. A 0.5 M aqueous NaOH solution was added, and the organic solution was further extracted with 0.5 M NaOH (3×). The aqueous layer was washed with Et_2O and was made acidic with concentrated HCl. The product was extracted into CH_2Cl_2. The organic solution was dried ($MgSO_4$), filtered, and concentrated. Kugelrohr distillation provided 2.907 g of a clear and colorless liquid which contained approximately 10% starting cyclopentanecarboxylic acid (1.254 g), ot < 80 °C/0.15 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 12.2 (bs, 1H), 5.78 (m, 1 H), 4.96 (m, 2 H), 2.13 (m, 2 H), 2.01 (m, 2 H), 1.66 (m, 6 H), 1.46 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.09, 138.32, 114.52, 53.62, 38.11, 36.06, 30.18, 25.18, 24.97.

1-Acetyl-1-(3-butenyl)cyclopentane (2b Precursor). The product mixture (1.254 g, 7.454 mmol) was dissolved in THF (57.0 mL) and cooled to 0 °C, and MeLi (1.4 M in pentane, 21.0 mL, 29.4 mmol) was rapidly added.[14] The reaction was stirred for 2 h at 0 °C, and TMSCl (17.1 g, 158 mmol) was added. The reaction was warmed to room temperature and was stirred for 1 h. A solution of 1 M aqueous HCl (60 mL) was added. The product was extracted into Et_2O, and the ethereal solution was washed with H_2O. The solution was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (5:1 hexanes/EtOAc) provided the ketone (566 mg, 46%) as a clear and colorless liquid: ^1H NMR (300 MHz, $CDCl_3$): δ 5.75 (m, 1 H), 4.92 (m, 2 H), 2.12 (s, 3 H), 2.03 (m, 2 H), 1.85 (m, 2 H), 1.73–1.55 (m, 6 H), 1.42 (m, 2 H).

1-Formyl-1-(2-propenyl)cyclohexane (3a precursor). The following describes the general procedure for the synthesis of 1-formyl-1(alkenyl)cyclohexanes. To a solution of diisopropylamine (3.8 g, 37 mmol) in THF (40 mL) at 0 °C was slowly added *n*-BuLi (1.6 M in hexanes, 21.0 mL, 33.6 mmol). After 30 min, the cyclohexylimine of cyclohexylcarboxaldehyde (5.944 g, 30.75 mmol) was added dropwise.[16] The yellow solution was stirred for 1 h, and allyl bromide (or 4-bromo-1-butene) (4.2 g, 35 mmol) was slowly added. After 21 h, the reaction was warmed to room temperature and was concentrated in vacuo. THF (100 mL) and 1 M aqueous oxalic acid solution (50 mL) were added, and the mixture was stirred for 4 h. The reaction was concentrated, and the product was extracted into Et_2O. The ethereal extracts were washed with aqueous $NaHCO_3$ (5%) followed by brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Kugelrohr distillation provided the product (2.998 g, 64%) that was used without further purification, ot 40–48 °C/0.25 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.36 (s, 1 H), 5.56 (m, 1 H), 4.94 (m, 2 H), 2.09 (d, J = 7.6 Hz, 2 H), 1.79 (m, 2 H), 1.48 (m, 3 H), 1.23 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.59, 132.56, 118.10, 49.42, 40.59, 30.56, 25.77, 25.45, 24.81, 22.26.

1-Formyl-1-(3-butenyl)cyclohexane (3b Precursor). Following the general procedure described above, the title compound was isolated in 43% yield. The purity was 80% by GLC, ot 42–50 °C/0.15 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.37 (s, 1 H), 5.68 (m, 1 H), 4.91 (m, 2 H), 1.86 (m, 4 H), 1.49 (m, 5 H), 1.23 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.85, 138.19, 114.72, 49.40, 35.53, 30.87, 27.70, 25.84, 25.65, 24.88, 22.42.

2-(2-Propenyl)cyclohexanone (6c Precursor). To a solution of the dimethylhydrazone of cyclohexanone (4.420 g, 31.52 mmol) in THF (40 mL) at 0 °C was slowly added *n*-BuLi (1.6 M in hexanes, 24.0 mL, 38.4 mmol).[20] After 45 min, allyl bromide (4.8 g, 39 mmol) was slowly added, and the solution was warmed to room temperature. After the solution was stirred for 3 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 (15 g) were added to the residue, and the mixture was stirred for 17 h.[21] The resin was removed by filtration through Celite, and the solution was concentrated. The residue was diluted with CH_2Cl_2, and the aqueous layer was removed. The organic solution was dried ($MgSO_4$), filtered, and concentrated. Kugelrohr distillation provided the title compound (3.589 g, 82%) as a clear and colorless liquid. The purity of the ketone was 93% by GLC, ot 34–40 °C/0.2 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 5.69 (m, 1 H), 4.93 (m, 2 H), 2.40 (m, 1 H), 2.26 (m, 2 H), 2.08–1.77 (m, 4 H), 1.58 (m, 2 H), 1.29 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.35, 136.38, 116.07, 50.09, 41.88, 33.61, 33.22, 27.78, 24.79.

2-(3-Butenyl)cyclohexanone (6d Precursor). The following describes the general procedure for the synthesis of 5-alken-1-ones. To a solution of the dimethylhydrazone of cyclohexanone (4.438 g, 31.65 mmol) in THF (40 mL) at 0 °C was slowly added *n*-BuLi (1.6 M in hexanes, 23.0 mL, 36.8 mmol).[20] After 1 h, 4-bromo-1-butene (5.0 g, 37 mmol) was slowly added, and the

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

solution was warmed to room temperature. After the solution was stirred for 2 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 (15 g) were added to the residue, and the mixture was stirred for 17 h.[21] The resin was removed by filtration through Celite, and the solution was concentrated. The residue was diluted with CH_2Cl_2, and the aqueous layer was removed. The organic solution was dried ($MgSO_4$), filtered, and concentrated. Kugelrohr distillation provided the title compound (3.774 g, 78%) as a clear and colorless liquid. The purity of the ketone was 94% by GLC, ot 40–48 °C/0.15 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 5.76 (m, 1 H), 4.96 (m, 2 H), 2.30 (m, 3 H), 2.05 (m, 4 H), 1.87 (m, 2 H), 1.66 (m, 2 H), 1.37 (m, 1 H), 1.24 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.98, 138.36, 114.53, 49.64, 41.88, 33.70, 31.02, 28.29, 27.84, 24.75.

2-(3-Butenyl)cyclopentanone (6b Precursor). Following the general procedure described above, the title compound was isolated in 70% yield. The purity was >95% by GLC, ot < 44 °C/0.15 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 5.39 (m, 1 H), 4.95 (m, 2 H), 2.35–1.90 (m, 7 H), 1.90–1.63 (m, 2 H), 1.48 (m, 1 H), 1.29 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 221.30, 138.01, 114.99, 48.34, 38.04, 31.50, 29.44, 28.73, 20.60.

2-(2-Propenyl)cyclooctanone (6e Precursor). The dimethylhydrazone of cyclooctanone (1.192 g, 7.084 mmol) was added dropwise to freshly prepared LDA (8.0 mmol) in THF (10–15 mL) at 0 °C.[20] After 2 h, allyl bromide (980 mg, 8.09 mmol) was slowly added, and the reaction was warmed to room temperature. After 19 h, H_2O was added, and the aqueous layer was extracted with EtOAc. The combined organic layers were concentrated, the crude product was dissolved in acetone (50 mL), and wet Amberlyst-15 resin (9.6 g) was added.[21] After 21 h, the mixture was filtered through Celite and was concentrated. Purification by flash chromatography (9:1 hexanes/EtOAc) provided the alkylated cycloalkanone in 93% yield (1.100 g). ^1H NMR (300 MHz, $CDCl_3$): δ 5.67 (m, 1 H), 4.98 (m, 2 H), 2.62 (m, 1 H), 2.24 (m, 3 H), 2.00 (m, 2 H), 1.80 (m, 2 H), 1.67–1.35 (m, 6 H), 1.21 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 219.49, 136.00, 116.50, 50.08, 42.28, 36.43, 32.17, 27.38, 25.41, 25.14, 24.64.

1-(2-Benzothiazolyl)cyclohexene (10). To a solution of Eaton's reagent (60 mL) was added 1-(2-benzothiazolyl)-1-hydroxycyclohexane (5.970 g, 25.59 mmol).[24b] The mixture was heated to about 60 °C for 21 h. The reaction was cooled to room temperature and was added dropwise to saturated aqueous $NaHCO_3$ (300 mL). After being stirred for 10 min, the aqueous solution was washed with Et_2O. The combined ethereal layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (10:1 hexanes/EtOAc) provided the title compound as a white solid (5.299 g, 96%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, J = 8.0 Hz, 1 H), 7.76 (d, J = 7.8 Hz, 1 H), 7.39 (m, 1 H), 7.27 (m, 1 H), 6.74 (m, 1 H), 2.66 (m, 2 H), 2.23 (m, 2 H), 1.76 (m, 2 H), 1.66 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.26, 153.55, 133.92, 133.78, 133.16, 125.62, 124.58, 122.58, 121.06, 26.12, 25.76, 22.02, 21.67.

***cis*-2-Acetyl-1-(2-benzothiazolyl)cyclohexane (11a and 11b Precursor).** To a solution of ethyl vinyl ether (2.9 g, 40 mmol) in THF (20.0 mL) at −78 °C was slowly added *t*-BuLi (1.5 M in pentane, 19.2 mL, 32.6 mmol).[25] The reaction mixture was warmed slowly to 0 °C over 1.25 h and was added dropwise to 1-(2-benzothiazolyl)cyclohexene (1.075 g, 4.99 mmol) in THF (40.0 mL) at −78 °C.[24a] After the mixture was stirred for 2 h, MeOH (7.0 mL) was added, and the reaction mixture was poured into a pH = 7.0 phosphate buffer. The product was extracted into Et_2O, and the ethereal layers were washed with brine. The solution was concentrated in vacuo, and the residue was dissolved in THF (20 mL) and H_2O (5 mL). A 0.020 M HCl solution (35.0 mL) was added, and the mixture was stirred for 15 h. EtOAc was added, and the layers were separated. The aqueous layer was further washed with EtOAc. The combined organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on neutral alumina using a solvent gradient (hexanes to 6:1 hexanes/EtOAc) provided the title compound (1.220 g, 94%) which was >95% cis by ^{13}C NMR. ^1H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J = 8.0 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H), 7.38 (m, 1 H), 7.28 (m, 1 H), 3.39 (td, J = 11, 3.9 Hz, 1 H), 3.18 (m, 1 H), 2.16 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.09, 174.95, 152.67, 134.75, 125.69, 124.61, 122.58, 121.49, 54.85, 43.67, 33.50, 29.43, 29.23, 25.57, 25.31.

***cis*-1-Acetyl-2-(2-propenyl)cyclohexane (13a Precursor).** The following describes the general procedure for the synthesis of 1-acetyl-2-(2-propenyl)cycloalkanes. A solution of 1-acetyl-1-cyclohexene (3.347 g, 26.95 mmol) and CH_2Cl_2 (75 mL) was cooled to −78 °C, and $TiCl_4$ (6.0 g, 32 mmol) was added.[26] A yellow precipitate formed. The reaction was stirred for 5 min, and allyltrimethylsilane (4.575 g, 40.04 mmol) in CH_2Cl_2 (40 mL) was added dropwise. The purple solution was stirred for 30 min, and H_2O (50 mL) was added. The mixture was warmed to room temperature and was diluted with Et_2O. The aqueous layer was washed with Et_2O, and the ethereal layers were dried ($MgSO_4$), filtered, and concentrated. Kugelrohr distillation provided the desired product (2.939 g, 66%) as an approximate 6:1 mixture of cis/trans isomers ot < 52 °C/0.2 mmHg. ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer): δ 5.62 (m, 1 H), 4.92 (m, 2 H), 2.55 (m, 1 H), 2.05 (s, 3 H), 2.04 (m, 1 H), 1.95 (m, 1 H), 1.78 (m, 2 H), 1.56 (m, 3 H), 1.41–1.23 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer): δ 211.48, 137.29, 115.88, 52.67, 36.61, 33.58, 28.87, 28.28, 23.96, 21.82, 21.78.

***trans*-1-Acetyl-2-(2-propenyl)cyclopentane (13c Precursor).** Prepared from 1-acetyl-1-cyclopentene[29] by the general procedure described above. The title compound was isolated as an approximate 14:1 mixture of trans/cis isomers in 80% yield. ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer): δ 5.70 (m, 1 H), 4.95 (m, 2 H), 2.47 (m, 1 H), 2.22 (m, 1 H), 2.10 (s, 3 H), 2.07 (m, 2 H), 1.83 (m, 2 H), 1.61 (m, 3 H), 1.24 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer): δ 211.42, 137.26, 115.77, 57.70, 41.53, 39.59, 32.12, 29.82, 29.23, 24.80.

***trans*-1-Acetyl-2-(2-propenyl)cyclohexane (13b Precursor).** Na (160 mg, 6.96 mmol) was dissolved in MeOH (20 mL). The *cis*-1-acetyl-2-(2-propenyl)cyclohexane (860 mg, 5.17 mmol) was added, and the solution was stirred at room temperature for 3 days and then heated at reflux for 24 h. The reaction was cooled, and H_2O was added. The product was extracted into CH_2Cl_2, and the organic solution was dried ($MgSO_4$), filtered, and concentrated to provide a yellow liquid that consisted of an approximate 8:1 mixture of trans/cis isomers. ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer): δ 5.71 (m, 1 H), 4.94 (m, 2 H), 2.19 (m, 1 H), 2.11 (s, 3 H), 2.03 (m, 1 H), 1.88–1.65 (m, 6 H), 1.22 (m, 3 H), 0.92 (m, 1 H).

***trans*-4-*tert*-Butyl-2-(2-propenyl)cyclohexanone (6h Precursor).** To a solution of diisopropylamine (2.6 g, 26 mmol) in THF (25 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 14.4 mL, 23.0 mmol). After 30 min, the dimethylhydrazone of 4-*tert*-butylcyclohexanone (4.138 g, 21.08 mmol) was added dropwise.[30] After 17 h, the reaction was cooled to −78 °C, and allyl bromide (2.8 g, 23 mmol) was added. After 1 h, the solution was warmed to 0 °C and was stirred for 3.5 h. The reaction was quenched (pH = 7.0 phosphate buffer), and the aqueous layer was extracted with EtOAc. The combined organic layers were concentrated, and the residue was dissolved in MeOH (300 mL) and pH = 7.0 phosphate buffer (100 mL). $NaIO_4$ (18 g) dissolved in H_2O (100 mL) was added, and the mixture was stirred for 19 h. The solids were filtered off through Celite, and the solution was concentrated. Flash chromatography (7:1 hexanes/EtOAc) provided the alkylated cycloalkanone as an approximate 3.4:1 mixture of trans/cis isomers (2.887 g, 70%). ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer): δ 5.01 (m, 1 H), 4.98 (m, 2 H), 2.34 (m, 4 H), 2.22 (m, 1 H), 1.96 (m, 1 H), 1.82 (m, 1 H), 1.63–1.37 (m, 3 H), 0.85 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer): δ 215.07, 135.43, 116.87, 48.48, 41.00, 38.49, 35.42, 32.35, 30.18, 27.55, 27.31.

1-Acetyl-1-(2-oxoethyl)cyclopentane (2a). A solution of 1-acetyl-1-(2-propenyl)cyclopentane[30] (750 mg, 4.93 mmol) in MeOH (3 mL) and CH_2Cl_2 (15 mL) was cooled to −78 °C, and O_3 was bubbled into the solution until a blue color persisted. The solution was purged with Ar until colorless, and Zn (800 mg, 12.2 mmol) and AcOH (5.0 mL, 87 mmol) were added.[15] The reaction was warmed to room temperature and was stirred for 30 min. The product was extracted into CH_2Cl_2, and the organic solution

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(30) Prepared by Caroline Bogdasarian.

was washed with aqueous $NaHCO_3$ (5%). The solution was dried (K_2CO_3), filtered, and concentrated. Kugelrohr distillation provided the keto aldehyde (640 mg, 84%), ot 60–64 °C/0.1 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.60 (m, 1 H), 2.66 (s, 2 H), 2.12 (s, 3 H), 1.97 (m, 2 H), 1.66 (m, 4 H), 1.52 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.34, 201.20, 56.51, 51.18, 35.72, 25.57, 25.32, 25.07.

1-Formyl-1-(2-oxopropyl)cyclohexane (3a). The following describes the general procedure for the synthesis of 1-formyl-1-(oxoalkyl)cyclohexanes. The 1-formyl-1-(2-propenyl)cyclohexane (2.801 g, 18.40 mmol) was added dropwise to a mixture of $PdCl_2$ (345 mg, 1.94 mmol), benzoquinone (2.238 g, 20.70 mmol), and 10 mL of a 7:1 DMF/H_2O solution.[17] The reaction was stirred for 3–4 h and was poured into 3 M HCl. The product was extracted into Et_2O, and the ethereal extracts were washed three times with aqueous NaOH (10%) followed by brine. The organic extracts were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (3:1 hexanes/EtOAc) followed by Kugelrohr distillation provided **3a** (1.680 g, 54%) as a clear and colorless liquid, ot 62–70 °C/0.2 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.59 (s, 1 H), 2.62 (s, 2 H), 2.00 (s, 3 H), 1.72 (m, 2 H), 1.30 (m, 8 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.59, 206.38, 50.66, 47.01, 30.99, 30.19, 25.21, 21.78.

1-Formyl-1-(3-oxobutyl)cyclohexane (3b). Following the general procedure described above, **3b** was isolated in 46% yield, ot 71–78 °C/0.15 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.27 (s, 1 H), 2.22 (m, 2 H), 2.01 (s, 3 H), 1.78 (m, 2 H), 1.62 (m, 2 H), 1.45 (m, 3 H), 1.16 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.88, 206.46, 48.79, 37.29, 30.72, 29.82, 28.83, 25.44, 22.22.

2-(2-Oxoethyl)cyclohexanone (6c). The following describes the general procedure for the synthesis of 1,4- and 1,5-keto aldehydes. O_3 was bubbled into a −78 °C solution of 2-(2-propenyl)cyclohexanone (1.818 g, 13.15 mmol) in CH_2Cl_2/MeOH (5:1, 42 mL) containing catalytic $NaHCO_3$ until the blue color persisted. The solution was purged with Ar until colorless, and PBu_3 (3.2 g, 16 mmol) was slowly added. The solution was warmed to room temperature and was stirred for 2 h. The volatiles were removed in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) followed by Kugelrohr distillation provided **6c** as a clear and colorless liquid (1.681 g, 91%). The purity was 99% by GLC, ot 60–66 °C/0.2 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.70 (s, 1 H), 2.84 (m, 2 H), 2.30 (m, 2 H), 2.04 (m, 2 H), 2.18 (m, 1 H), 1.80 (m, 1 H), 1.62 (m, 2 H), 1.34 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.70, 200.70, 45.23, 43.39, 41.52, 33.78, 27.49, 24.98.

1-Acetyl-1-(3-oxopropyl)cyclopentane (2b). Following the general procedure described above, **2b** was isolated in 45% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 9.60 (m, 1 H), 2.66 (s, 2 H), 2.12 (s, 3 H), 1.97 (m, 2 H), 1.66 (m, 4 H), 1.52 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.34, 201.10, 56.51, 51.18, 35.72, 25.57, 25.32, 25.07.

2-(3-Oxopropyl)cyclopentanone (6b). Following the general procedure described above, **6b** was isolated in 43% yield, ot 50–57 °C/0.15 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.71 (t, J = 1.46 Hz, 1 H), 2.52 (m, 2 H), 2.32–1.90 (m, 6 H), 1.72 (m, 1 H), 1.60 (m, 1 H), 1.45 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.24, 201.78, 47.92, 41.51, 37.86, 29.56, 21.91, 20.44.

2-(3-Oxopropyl)cyclohexanone (6d). Following the general procedure described above, **6d** was isolated in 84% yield. The purity was 96% by GLC, ot 68–75 °C/0.15 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.65 (t, J = 1.3 Hz, 1 H), 2.42 (m, 2 H), 2.22 (m, 3 H), 1.95 (m, 3 H), 1.76 (m, 1 H), 1.52 (m, 3 H), 1.29 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.33, 202.10, 49.52, 41.91, 41.48, 34.03, 27.75, 24.83, 21.85.

2-(2-Oxoethyl)cyclooctanone (6e). Following the general procedure described above, **6e** was isolated in 87% yield, ot 60–72 °C/0.1 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.67 (s, 1 H), 3.32 (m, 1 H), 3.09 (m, 1 H), 2.75 (m, 1 H), 2.41 (dd, J = 18.3, 3.9 Hz, 1 H), 2.26 (m, 1 H), 2.11 (m, 1 H), 1.95–1.32 (m, 8 H), 0.98 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.98, 200.57, 46.46, 42.57, 42.32, 32.68, 27.55, 24.36, 24.15, 23.76.

2-(3-Oxopropyl)cyclooctanone (6f). Following the general procedure described above, **6f** was prepared from 2-(3-butenyl)-cyclooctanone[31] in 66% yield, ot 66–76 °C/0.1 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.65 (m, 1 H), 2.51 (m, 1 H), 2.29 (m, 4 H), 1.82 (m, 4 H), 1.68–1.28 (m, 7 H), 1.14 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 219.41, 201.79, 49.36, 41.97, 41.57, 32.65, 27.08, 25.24, 25.21, 24.44, 24.18.

***cis*-4-*tert*-Butyl-2-(1-oxoethyl)cyclohexanone (6g).** Following the general procedure described above, **6g** was isolated in 54% yield. The purity was 99% by GLC, ot < 120 °C/0.2 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.72 (s, 1 H), 2.86 (m, 2 H), 2.33 (m, 2 H), 2.19 (m, 1 H), 2.06 (m, 2 H), 1.57 (m, 1 H), 1.36 (m, 1 H), 1.18 (m, 1 H), 0.83 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.11, 200.78, 46.81, 44.58, 43.62, 40.86, 34.80, 32.26, 28.30, 27.46. IR (neat): 2958, 2869, 1713, 1396, 1367, 1228, 1148 cm^{-1}.

***trans*-4-*tert*-Butyl-2-(2-oxoethyl)cyclohexanone (6h).** Following the general procedure described above, **6h** was isolated in 89% yield as an approximate 1.3:1 mixture of trans/cis diastereomers. Further flash chromatography followed by preparative HPLC (9:1 hexanes/EtOAc) provided the trans diastereomer (197 mg) as a clear and colorless liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 9.70 (s, 1 H), 2.96 (m, 1 H), 2.76 (m, 1 H), 2.39 (m, 2 H), 2.18 (m, 1 H), 1.81 (m, 2 H), 1.67–1.33 (m, 3 H), 0.81 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.52, 200.36, 43.71, 42.32, 41.26, 38.43, 32.77, 29.06, 26.87, 23.17.

***cis*-1-Acetyl-2-(2-oxoethyl)cyclohexane (13a).** Following the general procedure described above, **13a** was isolated as an approximate 20:1 cis/trans mixture of products in 62% yield, ot 59–70 °C/0.15 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.65 (d, J = 0.98 Hz, 1 H), 2.56 (m, 2 H), 2.39 (m, 2 H), 2.06 (s, 3 H), 1.69–1.18 (m, 8 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.37, 201.75, 52.24, 44.29, 30.26, 29.62, 29.06, 24.47, 23.81, 22.07.

***trans*-1-Acetyl-2-(1-oxoethyl)cyclohexane (13b).** Following the general procedure described above, **13b** was isolated as a mixture of isomers in 56% yield. Additional flash chromatography provided a >25:1 mixture of trans/cis keto aldehydes as indicated by ^{13}C NMR. ^1H NMR (300 MHz, $CDCl_3$): δ 9.55 (m, 1 H), 2.14 (m, 4 H), 2.01 (s, 3 H), 1.83 (m, 1 H), 1.76 (m, 3 H), 1.15 (m, 3 H), 0.92 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.80, 201.80, 56.17, 48.77, 32.75, 31.64, 29.44, 28.85, 25.30, 25.24.

***trans*-1-Acetyl-2-(2-oxoethyl)cyclopentane (13c).** Following the general procedure described above, **13c** was isolated in 81% yield. The purity was >95% as indicated by NMR, ot 80–88 °C/0.2 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.66 (t, J = 1.8 Hz, 1 H), 2.60 (m, 1 H), 2.46 (m, 2 H), 2.11 (s, 3 H), 1.94 (m, 2 H), 1.64 (m, 4 H), 1.21 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.46, 201.88, 57.88, 49.02, 35.54, 32.38, 29.63, 28.98, 24.47.

2-(2-Oxoethyl)cyclopentanone (6a). A solution of the dimethylhydrazone of cyclopentanone (5.424 g, 42.30 mmol) in THF (40 mL) was cooled to 0 °C, and *n*-BuLi (1.6 M in hexanes, 31.0 mL, 49.6 mmol) was added dropwise.[20] After 20 min, allyl bromide (6.0 g, 49.7 mmol) was slowly added and the reaction was warmed to room temperature. The reaction was quenched after 1.5 h by pouring into saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to provide a yellow liquid (8.041 g). The crude alkylation product was dissolved in a 1:1 mixture of CH_2Cl_2 and MeOH (100 mL), and this solution was cooled to −78 °C. O_3 was added until a blue color persisted. The solution was purged with Ar, and Bu_3P (24 g, 148 mmol) was slowly added. The mixture was warmed to room temperature and was stirred overnight. The reaction was concentrated in vacuo and was purified by flash chromatography (3:1 hexanes/EtOAc) followed by Kugelrohr distillation to provide a clear and colorless oil (3.410 g, 63%), ot <70 °C/0.2 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.66 (s, 1 H), 2.78 (m, 1 H), 2.43 (m, 2 H), 2.38–1.93 (m, 4 H), 1.73 (m, 1 H), 1.44 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 219.32, 200.11, 43.39, 43.36, 36.93, 29.14, 20.54.

***cis*-2-Acetylcyclohexanecarboxaldehyde (11a).** To a solution of *cis*-2-acetyl-1-(2-benzothiazolyl)cyclohexane (1.594 g, 6.146 mmol) in CH_2Cl_2 (25.0 mL) was added $MeSO_3F$ (850 mg, 7.42 mmol).[24b] The reaction was stirred for 4 h and was

(31) Prepared by Craig Tanner.

concentrated in vacuo. The white solid was suspended in absolute EtOH (6.0 mL), acetone (3.6 g, 63 mmol) was added, and the mixture was cooled to −78 °C. A solution of $NaBH_4$ (700 mg, 18.5 mmol) in EtOH (24.0 mL) at −78 °C was added dropwise, and the reaction was stirred for 30 min. The mixture was poured into a mixture of saturated aqueous NH_4Cl/NH_4OH solution (pH ≈ 8) and Et_2O. The aqueous layer was washed with Et_2O, and the combined ethereal layers were washed with brine. The organic solution was dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in CH_3CN (100 mL) and a pH = 7.0 phosphate buffer (30 mL). $AgNO_3$ (1.6 g, 9.4 mmol) in H_2O (15 mL) was added, and the mixture was stirred for 15 min. A second portion of $AgNO_3$ (1.6 g, 9.4 mmol) in H_2O (15 mL) was added. After 15 min, Et_3N (620 mg, 6.17 mmol) was added. After 10 min, the reaction was filtered through Celite with the aid of Et_2O. Brine was added, and the resulting AgCl was filtered off through Celite. The product was extracted into Et_2O, and the organic solution was dried ($MgSO_4$), filtered, and concentrated. Kugelrohr distillation provided **11a** as a clear and colorless liquid (722 mg, 76%) which was >90% cis by NMR, ot <80 °C/0.15 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.62 (s, 1 H), 2.79 (m, 1 H), 2.55 (m, 1 H), 2.15 (s, 3 H), 1.94 (m, 2 H), 1.79 (m, 2 H), 1.43 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.79, 203.90, 49.81, 48.93, 27.56, 26.11, 23.92, 23.76, 23.67.

***trans*-2-Acetylcyclohexanecarboxaldehyde (11b).** The procedure for the preparation of **11a** was followed with the following exception. The *N*-methylbenzothiazolium fluorosulfonate (3.43 mmol) was suspended in EtOH (17.0 mL), and acetone (2.0 g, 34 mmol) and $NaBH_4$ (391 mg, 10.3 mmol) were added at −78 °C. After 30 min, the reaction was poured into CH_2Cl_2 and brine. The product was extracted into CH_2Cl_2. The organic solution was dried ($MgSO_4$), filtered, and concentrated. The silver-promoted hydrolysis was performed as usual to provide **11b** as a clear and colorless liquid (438 mg, 83%) which was >92% trans by NMR, ot <80 °C/0.15 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 9.52 (s, 1 H), 2.62 (m, 2 H), 2.16 (s, 3 H), 2.08 (m, 1 H), 1.96 (m, 1 H), 1.78 (m, 2 H), 1.12 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.93, 203.04, 50.91, 49.94, 28.63, 28.12, 25.30, 25.02, 24.89.

2,2′-Methylenebis(cyclopentanone) (15a and 15b). Prepared by the method of Gill and co-workers[27] as a 1:1 mixture of diastereomers in 80% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 2.18–1.82 (m, 10.5 H), 1.66 (m, 3 H), 1.54 (m, 2 H), 1.39 (m, 2 H), 1.18 (m, 0.5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.54, 220.48, 46.84, 46.59, 37.69, 37.66, 29.93, 29.71, 29.53, 29.29, 20.32, 20.30.

Fractional recrystallization (2X) from petroleum ether provided the *dl*-stereoisomer (**15a**). Stereochemistry was determined by X-ray analysis, mp 73.8–75.0 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.14–1.87 (m, 10 H), 1.66 (m, 2 H), 1.53 (t, J = 6.6 Hz, 2 H), 1.38 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.43, 46.81, 37.66, 29.69, 29.27, 20.28.

General Procedure for the Preparation of Bicyclic Ethers (4a and 5a). A 0.1 M solution of TMSOTf (15–30 mol %) in CH_2Cl_2 was added to a 0.1 M solution of the dielectrophile (1 equiv) in CH_2Cl_2 at −78 °C. After 3 min, a 0.1 M solution of the bis(trimethylsilyl) enol ether (1) (1.0–1.2 equiv) in CH_2Cl_2 was added dropwise. The reaction was stirred for 5 h and was quenched by rapid addition of a pH = 7.0 phosphate buffer. After the mixture was warmed to room temperature, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (3:1 hexanes/EtOAc) followed by Kugelrohr distillation to provide the bicyclic ether.

Spiro[cyclopentane-1,6′-2′-(methoxycarbonyl)-5′-methyl-8′-oxabicyclo[3.2.1]octan]-3′-one (4a). Following the general procedure described above, **2a** (144 mg, 0.934 mmol) was annulated with **1** (253 mg, 0.971 mmol) in the presence of TMSOTf (35 mg, 0.16 mmol) to provide **4a** as a clear and colorless oil (179 mg, 76%) ot 96–104 °C/0.15 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 11.4 (s, 0.1 H, enol), 4.90 (d, J = 8.8 Hz, 0.5 H, exo), 4.78 (d, J = 6.6 Hz, 0.1 H, enol), 4.68 (m, 0.4 H, endo), 3.69 (s) and 3.68 (s, 3 H total), 3.64 (d, J = 3.4 Hz, 0.4 H, endo), 3.07 (s, 0.5 H, exo), 2.60–2.28 (m, 2 H), 2.05 (m, 1 H), 1.89–1.29 (m, 9 H), 1.25 (s), 1.24 (s), and 1.19 (s, 3 H total). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.78, 202.27, 170.45, 168.53, 168.38, 103.84, 85.50, 84.73, 81.98, 75.07, 74.13, 70.31, 62.71, 61.67, 56.28, 55.77, 55.15, 52.70, 52.43, 52.07, 51.87, 51.23, 48.71, 43.48, 42.76, 40.66, 38.17, 36.56, 36.52, 35.63, 34.05, 33.75, 23.30, 22.59, 22.54, 22.39, 22.26, 22.21, 22.04, 21.50, 21.26. IR (neat): 2956, 1739, 1716, 1660, 1622, 1446, 1216, 1027 cm^{-1}. LRMS (EI^+) m/e: 194 (M − 58, 38), 136 (81), 109 (44), 108 (40), 94 (74), 67 (94), 43 (100). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.96; H, 8.06.

Spiro[cyclohexane-1,7′-2′-(methoxycarbonyl)-5′-methyl-8′-oxabicyclo[3.2.1]octan]-3′-one (5a). Following the general procedure described above, **3a** (160 mg, 0.951 mmol) was annulated with **1** (274 mg, 1.05 mmol) in the presence of TMSOTf (41 mg, 0.18 mmol) to provide **5a** as a clear and colorless oil (191 mg, 75%), ot 80–94 °C/0.1 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 11.91 (bs, 0.8 H, enol), 4.51 (s, 0.2 H, exo), 4.38 (s, 0.8 H, enol), 3.75 (s) and 3.73 (s, 3 H total), 3.34 (s, 0.2 H, exo), 2.71 (d, J = 15.0 Hz, 0.2 H, exo), 2.50 (dd, J = 0.98, 17.8 Hz, 0.8 H, enol), 2.34 (d, J = 15.0 Hz, 0.2 H, exo), 2.08 (d, J = 17.8 Hz, 0.8 H, enol), 1.70 (m, 1 H), 1.52 (m, 2 H), 1.43–1.08 (m, 9 H), 1.41 (s) and 1.38 (s, 3 H total). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.98, 170.98, 170.58, 169.45, 100.91, 85.73, 85.70, 81.93, 80.41, 79.05, 57.50, 54.72, 52.60, 52.50, 51.18, 47.65, 46.90, 46.55, 43.96, 38.77, 36.92, 32.80, 27.53, 27.01, 25.86, 25.39, 24.06, 23.87, 22.52, 22.44. IR (neat): 2930, 1742, 1716, 1651, 1614, 1445, 1247, 1064 cm^{-1}. LRMS (EI^+) m/e: 208 (M − 58, 67), 165 (100), 151 (69), 122 (47), 107 (46), 81 (76), 67 (60), 43 (94). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.32. Found: C, 67.61; H, 8.38.

General Procedure for the Synthesis of Bicyclic Ethers 9a, 9c, 9e, 9g, 9h, and 12a. 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 or TLC. The solution was purified by flash chromatography followed by Kugelrohr distillation to provide the bicyclic ethers.

(1*R,3*R**,5*S**)-10-Acetoxy-11-(methoxycarbonyl)-2-oxatricyclo[5.3.1.0^{1,5}]undec-10-ene (9a).** Following the general procedure described above, **6a** (124 mg, 0.983 mmol) was annulated with **1** (273 mg, 1.05 mmol) in the presence of TMSOTf (36 mg, 0.16 mmol) to provide **9a** as a clear and colorless oil (137 mg, 52%). The product consisted of a 2.5:1 mixture of regioisomers as indicated by GLC and NMR, ot 112–120 °C/0.1 mmHg. ^1H NMR (300 MHz, $CDCl_3$) (major regioisomer): δ 4.91 (d, J = 5.8 Hz, 1 H), 3.66 (s, 3 H), 2.79 (d, J = 17.8 Hz, 1 H), 2.42 (m, 1 H), 2.15 (s, 3 H), 2.05 (d, J = 17.8 Hz, 1 H), 1.98–1.57 (m, 6 H), 1.38 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) (major regioisomer): δ 168.34, 163.63, 155.34, 122.38, 91.03, 74.59, 51.49, 45.95, 45.12, 40.35, 36.55, 32.94, 24.57, 20.78. IR (neat): 2952, 1766, 1721, 1654, 1181 cm^{-1}. HRMS: calcd for $C_{14}H_{18}O_5$ 266.1154, found 266.1129. LRMS (EI^+) m/e: 266 (5), 224 (76), 207 (23), 181 (22), 123 (16), 95 (11), 81 (11), 55 (13), 43 (100). Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 62.36; H, 6.82.

(1*R,3*R**,5*S**)-11-Acetoxy-12-(methoxycarbonyl)-2-oxatricyclo[6.3.1.0^{1,5}]dodec-11-ene (9c).** Following the general procedure described above, **6c** (144 mg, 1.03 mmol) was annulated with **1** (279 mg, 1.07 mmol) in the presence of TMSOTf (34 mg, 0.15 mmol) to provide **9c** as one diastereomer by GLC (251 mg, 87%, clear and colorless oil), ot 120–126 °C/0.1 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 4.89 (d, J = 6.8 Hz, 1 H), 3.63 (s, 3 H), 2.35 (d, J = 18.3 Hz, 1 H), 2.19 (m, 1 H), 2.10 (s, 3 H), 2.03 (d, J = 18.3 Hz, 1 H), 1.97 (m, 1 H), 1.84 (m, 1 H), 1.74 (m, 1 H), 1.62 (m, 1 H), 1.59–1.38 (m, 4 H), 1.14 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.15, 163.32, 154.84, 123.61, 79.88, 71.87, 51.37, 43.75, 43.72, 41.51, 31.82, 29.40, 20.66, 20.23, 18.61. IR (neat): 2931, 1769, 1720, 1664, 1436, 1364, 1209, 1006 cm^{-1}. LRMS (EI^+) m/e: 280 (2), 238 (87), 206 (32), 188 (58), 181 (43), 141 (48), 129 (23), 95 (28), 43 (100). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 63.94; H, 7.13.

(1*R,3*R**,5*S**)-13-Acetoxy-14-(methoxycarbonyl)-2-oxatricyclo[8.3.1.0^{1,5}]tetradec-13-ene (9e).** Following the general procedure described above, **6e** (154 mg, 0.915 mmol) was annulated with **1** (247 mg, 0.948 mmol) in the presence of TMSOTf (32 mg, 0.14 mmol) to provide **9e** as a clear and colorless oil (213 mg, 75%). The product consisted of a 43:1 mixture of diastereomers as indicated by GLC, ot < 126 °C/0.1 mmHg. ^1H NMR

(300 MHz, $CDCl_3$): δ 4.74 (d, J = 6.3 Hz, 1 H), 3.65 (s, 3 H), 2.51 (d, J = 18.1 Hz, 1 H), 2.44 (dd, J = 8.5, 12.0 Hz, 1 H), 2.14 (s, 3 H), 2.10 (d, J = 18.1 Hz, 1 H), 1.98 (m, 2 H), 1.77–1.31 (m, 10 H), 1.22 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.29, 163.45, 154.76, 121.70, 83.06, 70.95, 51.44, 48.07, 45.45, 42.09, 32.04, 31.64, 31.20, 26.01, 25.96, 24.28, 20.78. IR (neat): 2922, 1766, 1714, 1666, 1435, 1360, 1171 cm^{-1}. LRMS (EI+) m/e: 308 (10), 266 (100), 234 (29), 216 (26), 181 (46), 141 (23), 121 (17) 95 (12), 81 (22), 67 (21), 55 (38), 43 (90). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.13; H, 7.98.

(1*R,3*R**,5*S**,7*S**)-7-*tert*-Butyl-11-acetoxy-12-(methoxycarbonyl)-2-oxatricyclo[6.3.1.0^{1,5}]dodec-11-ene (9g).** Following the general procedure described above, **6g** (159 mg, 0.810 mmol) was annulated with 1 (238 mg, 0.914 mmol) in the presence of TMSOTf (29 mg, 0.13 mmol) to provide **9g** as a clear and colorless oil (207 mg, 76%). The product was isolated as a single diastereomer as indicated by NMR, ot < 134 °C/0.15 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 4.96 (d, J = 6.8 Hz, 1 H), 3.68 (s, 3 H), 2.41 (d, J = 18.4 Hz, 1 H), 2.28 (dd, J = 3.4, 20.3 Hz, 1 H), 2.15 (s, 3 H), 2.08 (d, J = 18.4 Hz, 1 H), 1.96 (m, 2 H), 1.81–1.63 (m, 2 H), 1.60–1.40 (m, 2 H), 1.35–1.29 (m, 1 H), 1.05–0.86 (m, 2 H), 0.80 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.35, 163.46, 155.08, 124.11, 79.86, 72.07, 51.56, 44.74, 44.71, 43.46, 33.96, 32.66, 32.62, 27.13, 21.62, 20.84. IR (CH_2Cl_2): 2953, 1766, 1719, 1662, 1437, 1365, 1177 cm^{-1}. LRMS (CI+) m/e: 337 (41), 323 (29), 305 (60), 295 (85), 277 (100), 245 (74), 219 (38), 181 (50), 141 (30), 123 (19), 103 (57), 57 (69), 41 (91). Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.71; H, 8.34.

(1*R,3*R**,5*S**,7*R**)-7-*tert*-Butyl-11-acetoxy-12-(methoxycarbonyl)-2-oxatricyclo[6.3.1.0^{1,5}]dodec-11-ene (9h).** Following the general procedure described above, **6h** (112 mg, 0.571 mmol) was annulated with 1 (172 mg, 0.660 mmol) in the presence of TMSOTf (1.0 mL of a 0.1 M CH_2Cl_2 solution) to provide **9h** as a white solid (104 mg, 54%). The product was isolated as a single diastereomer as indicated by NMR. ^1H NMR (300 MHz, $CDCl_3$): δ 4.90 (d, J = 6.3 Hz, 1 H), 3.68 (s, 3 H), 2.47 (d, J = 17.9 Hz, 1 H), 2.34–2.10 (m, 2 H), 2.15 (s, 3 H), 2.00 (d, J = 17.9 Hz, 1 H), 1.92–1.73 (m, 2 H), 1.70–1.38 (m, 3 H), 1.38–1.15 (m, 3 H), 0.78 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.36, 163.60, 154.66, 122.58, 80.28, 72.43, 51.54, 43.86, 42.04, 39.84, 36.55, 32.68, 29.54, 26.88, 26.64, 20.84, 19.02. IR (CH_2Cl_2): 2950, 1768, 1723, 1662, 1436, 1364, 1171 cm^{-1}. LRMS (EI+) m/e: 336 (6), 294 (68), 276 (58), 244 (55), 219 (27), 181 (49), 160 (24), 141 (40), 107 (12), 91 (19), 79 (18), 57 (81), 43 (100). Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.56; H, 8.34.

(1*R,3*R**,4*S**,9*S**)-11-Acetoxy-12-(methoxycarbonyl)-1-methyl-2-oxatricyclo[6.3.1.0^{4,9}]dodec-11-ene (12a).** Following the general procedure described above, **11a** (121 mg, 0.785 mmol) was annulated with 1 (215 mg, 0.825 mmol) in the presence of TMSOTf (26 mg, 0.12 mmol). The enol acetate was isolated (183 mg, 79%) as a >200:1 mixture of diastereomers, ot 108–114 °C/0.07 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 4.44 (s, 1 H), 3.66 (s, 3 H), 2.44 (d, J = 17.8 Hz, 1 H), 2.29 (m, 1 H), 2.17 (m, 1 H), 2.13 (s, 3 H), 2.01 (d, J = 17.8 Hz, 1 H), 1.69–1.47 (m, 3 H), 1.47–1.25 (m, 4 H), 1.29 (s, 3 H), 1.18 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.35, 163.60, 154.81, 121.18, 81.24, 77.20, 51.48, 48.52, 45.53, 42.68, 25.88, 22.76, 21.67, 21.30, 21.23, 20.76. IR (neat): 2934, 1762, 1722, 1661, 1436, 1361, 1296, 1084 cm^{-1}. LRMS (EI+) m/e: 251 (M − 43, 4), 234 (12), 202 (13), 169 (100), 137 (10), 79 (8), 67 (9), 43 (49). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.38; H, 7.73.

General Procedure for the Preparation of Bicyclic Ethers (4b and 5b). $TrSbCl_6$ (5–6 mol %) in CH_2Cl_2 was added to a 0.1 M solution of the 1,5-dicarbonyl substrate (1 equiv) in CH_2Cl_2 at −78 °C. After 3 min, a 0.1 M solution of the bis(trimethylsilyl) enol ether 1 (1.0–1.2 equiv) in CH_2Cl_2 was added dropwise. The reaction mixture was stirred for 5 h and was quenched by rapid addition of a pH = 7.0 phosphate buffer. After the mixture was warmed to room temperature, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) 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.

Spiro[cyclopentane-1,6′-3′-hydroxy-2′-(methoxycarbonyl)-5′-methyl-9′-oxabicyclo[3.3.1]non-2′-ene] (4b). Following the general procedure described above, **2b** (150 mg, 0.892 mmol) was annulated with 1 (266 mg, 1.02 mmol) in the presence of $TrSbCl_6$ (32 mg, 0.055 mmol) to provide a clear and colorless oil (187 mg, 79%) which consisted primarily of the enol epimer, ot 106–116 °C/0.07 mmHg. ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer): δ 11.80 (s, 1 H), 4.68 (d, J = 4.4 Hz, 1 H), 3.69 (s, 3 H), 2.38 (d, J = 19.3 Hz, 1 H), 2.22 (d, J = 19.3 Hz, 1 H), 1.96 (m, 2 H), 1.60 (m, 2 H), 1.50–1.17 (m, 8 H), 1.12 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer): δ 171.30, 170.18, 99.58, 75.82, 66.91, 51.23, 48.49, 37.17, 37.00, 33.92, 30.44, 27.54, 26.87, 25.48. IR (neat): 2946, 1741, 1716, 1666, 1628, 1442, 1309, 1240 cm^{-1}. LRMS (EI+) m/e: 266 (8), 184 (12), 169 (100), 142 (40), 110 (10), 82 (11), 67 (15), 43 (27). Anal. Calcd for $C_{15}H_{22}O_5$: C, 67.64; H, 8.32. Found: C, 67.78; H, 8.54.

Spiro[cyclohexane-1,8′-2′-(methoxycarbonyl)-5′-methyl-9′-oxabicyclo[3.3.1]non-3′-one] (5b). Following the general procedure described above, **3b** (150 mg, 0.823 mmol) was annulated with 1 (215 mg, 0.825 mmol) in the presence of $TrSbCl_6$ (41 mg, 0.18 mmol) to provide **5b** as a clear and colorless oil (146 mg, 63%), ot 87–100 °C/0.1 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 4.44 (s, 0.3 H, exo), 4.34 (s, 0.7 H, enol), 3.74 (s) and 3.72 (s, 3 H total), 3.45 (s, 0.3 H, exo), 2.70 (dd, J = 1.2, 15.6 Hz, 0.3 H, exo), 2.38 (d, J = 19.0 Hz, 0.7 H, enol), 2.31 (m, 0.3 H, exo), 2.14 (d, J = 19.0 Hz, 0.7 H, enol), 2.07 (m, 1 H), 1.69 (m, 2 H), 1.50 (m, 2 H), 1.44–1.09 (m, 8 H), 1.29 (s) and 1.26 (s, 3 H total), 0.86 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.55, 171.81, 171.22, 169.96, 98.61, 80.68, 75.84, 74.47, 70.47, 54.98, 52.73, 51.07, 50.99, 39.25, 36.03, 35.85, 35.14, 34.34, 34.00, 32.65, 32.34, 31.86, 30.83, 30.42, 26.88, 26.33, 26.06, 23.13, 21.69, 21.04, 20.99, 20.75. IR (neat): 2924, 1740, 1716, 1652, 1621, 1446, 1238, 1036 cm^{-1}. LRMS (EI+) m/e: 222 (M − 58, 33), 179 (22), 164 (27), 136 (29), 113 (58), 96 (66), 81 (100), 71 (26), 43 (73). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.62; H, 8.61.

General Procedure for the Synthesis of Bicyclic Ethers 9b, 9d, 14a, and 14b. 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 or TLC. The solution was purified by flash chromatography followed by Kugelrohr distillation to provide the bicyclic ethers.

(1*R,3*R**,5*S**)-11-Acetoxy-12-(methoxycarbonyl)-2-oxatricyclo[6.3.1.0^{1,5}]dodec-11-ene (9b).** Following the general procedure described above, **6b** (114 mg, 0.813 mmol) was annulated with 1 (233 mg, 0.894 mmol) in the presence of $TrSbCl_6$ (28 mg, 0.048 mmol) to provide **9b** as a >120:1 mixture of diastereomers as indicated by GLC (152 mg, 67%). Recrystallization from Et_2O/petroleum ether provided crystals suitable for X-ray analysis, mp 70.8–73.1 °C, ot < 100 °C/0.1 mmHg. ^1H NMR (300 MHz, $CDCl_3$): δ 4.80 (bs, 1 H), 3.65 (s, 3 H), 2.61 (dd, J = 1.2, 18.8 Hz, 1 H), 2.17 (s, 3 H), 2.02 (d, J = 18.8 Hz, 1 H), 1.98 (m, 2 H), 1.89–1.56 (m, 7 H), 1.45 (m, 1 H), 1.40 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.55, 163.50, 155.92, 117.86, 78.96, 69.20, 51.52, 43.54, 40.12, 37.51, 28.72, 21.59, 21.13, 20.82, 17.76. IR (CH_2Cl_2): 2948, 1762, 1718, 1670, 1438, 1364, 1175, 1041 cm^{-1}. LRMS (EI+) m/e: 280 (4), 238 (100), 181 (82), 150 (13), 123 (7), 79 (12), 67 (10), 43 (52). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.19; H, 7.25.

(1*R,3*R**,6*S**)-12-Acetoxy-13-(methoxycarbonyl)-2-oxatricyclo[7.3.1.0^{1,6}]tridec-12-ene (9d).** Following the general procedure described above, **6d** (142 mg, 0.921 mmol) was annulated with 1 (269 mg, 1.03 mmol) in the presence of $TrSbCl_6$ (35 mg, 0.061 mmol) to provide **9d** as a clear and colorless oil (182 mg, 67%). The enol acetate was isolated as a 6:1 mixture of diastereomers by ^{13}C NMR, ot < 140 °C/0.3 mmHg. ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer): δ 4.86 (d, J = 3.9 Hz, 1 H), 3.65 (s, 3 H), 2.17 (s, 3 H), 2.14 (m, 2 H), 2.02 (m, 2 H), 1.77 (m, 1 H), 1.66 (m, 2 H), 1.45 (m, 2 H), 1.26 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer): δ 168.48, 163.40, 156.30, 118.44, 71.46, 69.49, 51.44, 41.74, 40.16, 39.94, 27.14, 25.44, 22.41, 21.42, 21.26, 20.76. IR (CH_2Cl_2): 2939, 1762, 1717, 1673, 1364, 1204, 1107, 1002 cm^{-1}. LRMS (EI+) m/e: 294 (5), 252 (100), 235 (9), 220 (19), 202 (21), 181 (75), 149 (5), 123 (7), 91 (6), 79 (9), 67 (10), 55 (8), 43 (43). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.36; H, 7.46.

(1*R,3*R**,5*S**,10*S**)-12-Acetoxy-13-(methoxycarbonyl)-1-methyl-2-oxatricyclo[7.3.1.0^{5,10}]tridec-12-ene (14a).** Following the general procedure described above, **13a** (128 mg, 0.761 mmol) was annulated with 1 (211 mg, 0.810 mmol) in the presence of $TrSbCl_6$ (30 mg, 0.052 mmol) to provide **14a** as a white solid (165 mg, 70%). Analysis by GLC indicated that the cis/trans ratio of products was 32:1. The cis product was isolated as a >100:1 mixture of diastereomers. Recrystallization provided crystals suitable for X-ray analysis, mp 101.7–104.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.88 (d, J = 4.6 Hz, 1 H), 3.65 (s, 3 H), 2.35 (d, J = 19.2 Hz, 1 H), 2.29 (m, 1 H), 2.18 (d, J = 19.2 Hz, 1 H), 2.17 (s, 3 H), 2.12 (m, 1 H), 1.73 (m, 1 H), 1.56–1.13 (m, 7 H), 1.16 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.44, 163.40, 156.46, 118.84, 73.45, 69.29, 51.46, 45.58, 41.81, 31.19, 27.24, 26.92, 26.13, 25.06, 21.41, 20.74, 20.54. IR (CH_2Cl_2): 2926, 1765, 1716, 1670, 1364, 1217, 1204, 1089 cm^{-1}. LRMS (EI$^+$) m/e: 309 (M + 1, 7), 266 (9), 249 (12), 169 (100), 142 (16), 43 (32). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.05; H, 7.88.

(1*R,3*R**,5*S**,10*R**)-12-Acetoxy-13-(methoxycarbonyl)-1-methyl-2-oxatricyclo[7.3.1.0^{5,10}]tridec-12-ene (14b).** Following the general procedure described above, **13b** (163 mg, 0.969 mmol) was annulated with 1 (272 mg, 1.04 mmol) in the presence of $TrSbCl_6$ (37 mg, 0.064 mmol) to provide **14b** as a clear and colorless oil which solidified on standing (170 mg, 57%). Analysis by GLC indicated that the trans/cis ratio of products was 38:1. The trans product existed of a 4:1 mixture of diastereomers, mp 73.0–75.8 °C, ot < 130 °C/0.1 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer): 4.83 (bs, 1 H), 3.64 (s, 3 H), 2.30 (d, J = 19.2 Hz, 1 H), 2.17 (s, 3 H), 2.09 (d, J = 19.2 Hz, 1 H), 1.73 (m, 1 H), 1.56 (m, 4 H), 1.19 (m, 3 H), 1.18 (s, 3 H), 0.94 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer): δ 168.57, 163.37, 156.10, 118.64, 73.69, 69.14, 52.38, 51.47, 36.02, 34.93, 33.16, 31.42, 28.58, 27.48, 26.61, 25.85, 20.73. IR (CH_2Cl_2): 2927, 1770, 1715, 1668, 1448, 1362, 1203, 1084 cm^{-1}. LRMS (EI$^+$) m/z: 308 (3), 252 (12), 169 (100), 142 (20), 79 (5), 67 (10), 55 (8), 43 (44). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 65.96; H, 7.88.

Annulation of 15a with 1 (16a). TMSOTf (10 mg, 0.050 mmol) in CH_2Cl_2 (0.050 mL) was added to a solution of **15a** (66 mg, 0.37 mmol) in CH_2Cl_2 (3.6 mL) at −78 °C. A solution of 1 (100 mg, 0.384 mmol) in CH_2Cl_2 (3.8 mL) was added dropwise, and the reaction was stirred for 5 h. The keto ester was isolated as described in the general procedure and was dissolved in pyridine (3–5 mL). Ac_2O (1 mL) and catalytic DMAP were added, and the mixture was heated at 80 °C for 16 h. Flash chromatography (5:1 hexanes/EtOAc) provided **16a** (53 mg, 45%) as an approximate 2.5:1 mixture of diastereomers as determined by ^{13}C NMR. ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer): δ 3.69 (s, 3 H), 2.57 (d, J = 17.3 Hz, 1 H), 2.11 (s, 3 H), 1.91 (d, J = 17.3 Hz, 1 H), 1.94–1.35 (m, 13 H), 1.22 (m, 1 H), 0.99 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer): δ 168.51, 165.84, 149.68, 125.75, 82.24, 79.92, 51.50, 44.22, 41.34, 40.29, 39.70, 39.01, 33.65, 32.98, 30.25, 24.55, 22.97, 20.80. IR (CH_2Cl_2): 2952, 1761, 1720, 1435, 1266, 1011 cm^{-1}. HRMS: calcd for $C_{18}H_{24}O_5$ 320.1624, found 320.1636. LRMS (EI$^+$) m/e: 320 (8), 278 (100), 246 (52), 218 (32), 195 (39), 169 (90), 150 (25), 121 (19), 79 (33), 43 (79).

Annulation of 15a and 15b with 1 (16a). Following the procedure described above, a 1:1 mixture of **15a** and **15b** (182 mg, 1.01 mmol) was annulated with 1 (289 mg, 1.11 mmol) in the presence of TMSOTf (1.6 mL of a 0.1 M CH_2Cl_2 solution) over 5 h. The enol acetate **16a** (96 mg, 30%) was isolated as an approximate 2:1 mixture of diastereomers as determined by ^{13}C NMR. Spectral data was identical to that described above.

Acknowledgment. We are grateful to Viloya S. Allured for the X-ray crystal structures, to Professor Dale Boger for his advice regarding the synthesis of **11a**, and to Ruben Tommasi for his assistance with the AM1 calculations. We also thank the National Science Foundation and the National Institutes of Health for their generous support of this research.

Supplementary Material Available: NMR data for starting keto aldehyde substrates and for compound **16a** (40 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.