Intramolecular 4 + 3 Cycloadditions. Cycloaddition Reactions of Cyclic Alkoxyallylic and Oxyallylic Cations

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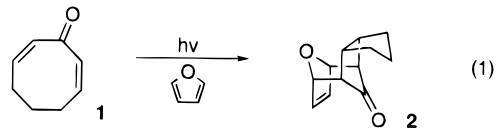
Abstract: The intramolecular 4 + 3 cycloaddition of oxyallylic and alkoxyallylic cations has been studied. Cyclopentenyl oxyallylic cations tethered to a furan by a three or four carbon chain react with high stereoselectivity via a compact (endo) transition state analogous to that seen in intermolecular cycloadditions. Six- through eight-membered oxyallylic cations react differently and give increasingly larger amounts of cycloadduct derived from extended (exo) transition states. This has been rationalized on the basis of ring strain in the endo transition states in this series. Cyclodecenyl oxyallylic cations are sickle-shaped and stereoselectively undergo cycloaddition via extended transition states to a furan diene tethered by three carbons. Cyclododecenyl oxyallylic cations behave similarly, although the evidence suggests that a small amount of W-shaped cation also is formed. Cyclic alkoxyallylic sulfones give rise to the corresponding cations upon treatment with $TiCl_4$, and the latter give rise to cycloadducts via apparent intramolecular 4 + 3 cycloadditions in variable yields. Side product formation in certain cases provides evidence for the intermediacy of cationic species which may also be important in the formation of the cycloadducts themselves.

Introduction

The 4 + 3 cycloaddition reaction of allylic cations and dienes is a powerful method for the construction of seven-membered rings.[1] In its intramolecular form, it has not received the amount of attention of its counterpart, the intramolecular Diels−Alder reaction.[2,3] We are engaged in a program of study of the intramolecular 4 + 3 cycloaddition reaction.[4] This report details our studies of the intramolecular cycloaddition reactions of cyclic cations.

The use of cyclic cations as dienophiles has been the subject of only a few studies. Among the earliest and most interesting routes to such cations are those involving photochemical electrocyclic reactions of dienones. For example, Crandall and co-workers reported that irradiation of 2,7-cyclooctadienone in the presence of furan gave adduct **2**.[5] Similar irradiation of



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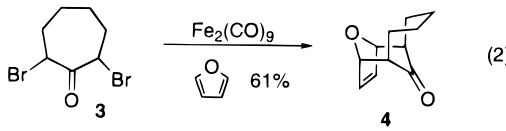
cyclohexadienones and pyrones also led to cycloadduct formation.[6] More recently, Schultz and West have developed intramolecular reactions based on a photochemical approach.[7]

Thermal approaches to cyclic allylic cations for 4 + 3 cycloaddition have also been developed. Reductive debromination of α,α′-dibromoketones has been reported in this regard.[8] For example, Noyori reported that treatment of **3** with $Fe_2(CO)_9$ in the presence of excess furan resulted in the formation of **4** with complete stereocontrol in 61% yield.[8a] Hoffmann made



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use of a different reductive dehalogenation protocol in a study of cyclic oxyallylic cations of varying ring size.[8c] Base-mediated dehydrohalogenation as a means of oxyallyl generation

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(3) For reviews of intramolecular Diels−Alder reactions, see: (a) Roush, W. R. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI: Greenwich, CT, 1990; Vol. 2, pp 91−146. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, Chapter 4.4.

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(5) Crandall, J. K.; Haseltine, R. P. *J. Am. Chem. Soc.* **1968**, *90*, 6251.

(6) (a) Barber, L. L.; Chapman, O. L.; Lassila, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 3664. (b) Chapman, O. L.; Clardy, J. C.; McDowell, T. L.; Wright, H. E. *J. Am. Chem. Soc.* **1973**, *95*, 5086. (c) Barltrop, J. A.; Day, A. C.; Samuel, C. J. *J. Am. Chem. Soc.* **1979**, *101*, 7521.

(7) (a) Schultz, A. G.; Reilly, J. *J. Am. Chem. Soc.* **1992**, *114*, 5068. (b) Schultz, A. G.; Macielag, M.; Plummer, M. *J. Org. Chem.* **1988**, *53*, 391. (c) West, F. G.; Hartker-Karger, C.; Koch, D. J.; Kuehn, C. E.; Arif, A. M. *J. Org. Chem.* **1993**, *58*, 6795.

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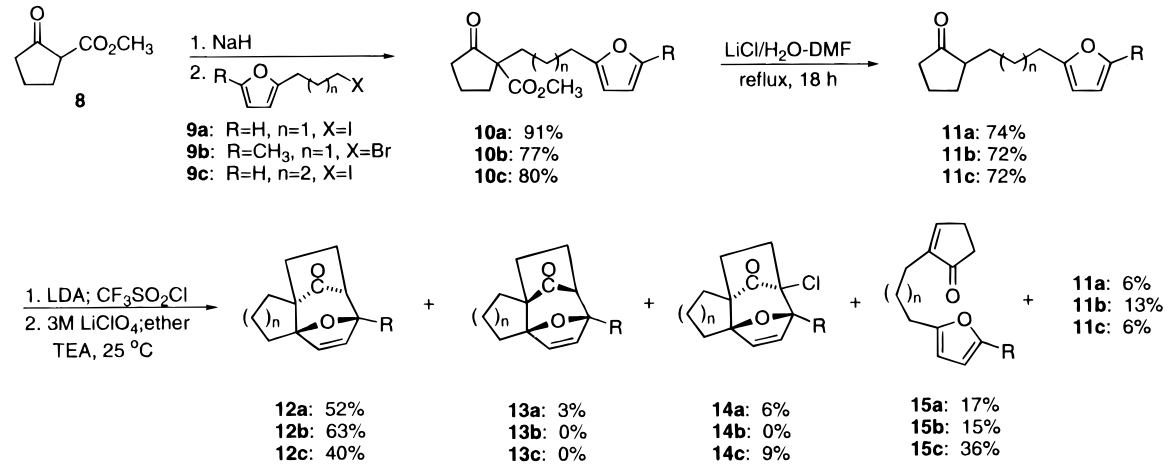
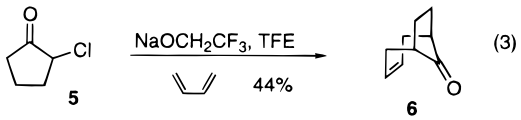
Scheme 1



was used by Föhlisch.[9] For example, treatment of α-chlorocyclopentanone with sodium trifluoroethoxide in trifluoroethanol gave **6** in 44% yield.[9a] More recently, certain limitations to



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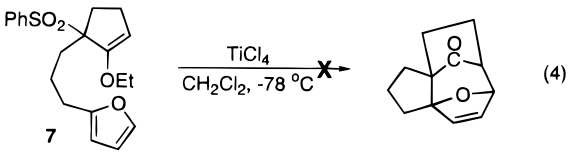
this type of approach have been reported.[9c] Levisalles reported that a steroidal cyclic sulfite gave a 4 + 3 cycloadduct with furan.[10] Schmid demonstrated that chloroenamines react with silver salts in the presence of dienes to give 4 + 3 cycloadducts.[11] This methodology has been used by Cha in an approach to natural products.[12]

Our work began as a general approach to the synthesis of complex polycyclic systems using the intramolecular 4 + 3 cycloaddition reaction. In particular, we had the goal of using the methodology to prepare cyclooctanoids and ingenanes.[4b,c]

Results and Discussion

We initially planned to adapt our alkoxyallylic sulfone methodology to cyclic systems.[4j] However, treatment of **7** with $TiCl_4$ under typical reaction conditions resulted in the formation of a small amount of a carbonyl-containing product which was clearly not a cycloadduct by NMR. We therefore sought to use a methodology which would give rise to the intermediates suitable for cycloaddition but under much milder conditions.[13] We chose to use the methodology introduced by Föhlisch.[14]



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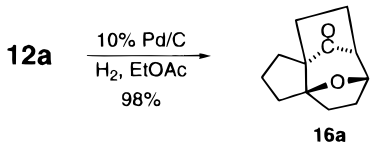
Reaction of keto ester **8** with sodium hydride and alkylation of the resulting enolate with 2-(3-iodopropyl)furan gave **10a** in 91% yield. Krapcho decarboalkoxylation afforded ketone **11a** in 74% yield.[15] Treatment of ketone **11a** with LDA and triflyl chloride produced the corresponding α-chloroketone.[16] This was immediately dissolved without purification in a 3 M ethereal solution of $LiClO_4$ containing 3 equiv of triethylamine. Stirring for several hours and workup resulted in the isolation of cycloadducts **12a** and **13a** as a 15:1 mixture of diastereomers in 55% yield. The ratio of diastereomers for this and all other reactions was determined by ^1H NMR of the crude reaction mixture. Also isolated were the chlorinated cycloadduct **14a**, enone **15a**, and the starting ketone in 6%, 17%, and 6% yields, respectively. The major isomer of the cycloadduct mixture, **12a**, was characterized by spectral data analysis (^1H, ^{13}C NMR; IR; MS). The structure of **12a** was confirmed and its stereochemistry defined by X-ray analysis of the corresponding dihydro derivative **16a**.[4b] The structure of **14a** was also assigned on



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the basis of spectroscopic data and its stereochemistry assigned on the basis of that seen in **12a**. The formation of **14a** is doubtless due to some dichlorination of ketone **11a**. Such a compound would be expected to lead to **14a** and accounts for the recovered ketone.

Avoiding the competitive formation of enone **15a** has not been experimentally addressed. In the presence of base, oxyallyl **17a**, a plausible intermediate in this reaction, may undergo either cycloaddition or a bimolecular elimination reaction. The hydrogens flanking the oxyallylic cation are approximately parallel to the π system of the cation and stereoelectronically poised to undergo elimination.[17] The formation of α,β-

(9) (a) Föhlisch, B.; Joachimi, R. *Chem. Ber.* **1987**, *96*, 5466. (b) Föhlisch, B.; Gottsein, W.; Kaiser, R.; Wanner, I. *Tetrahedron Lett.* **1980**, *21*, 1951. (c) Föhlisch, B.; Joachimi, R.; Reiner, S. *J. Chem. Soc. (S)* **1993**, 253. (d) Matzinger, P.; Eugster, C. M. *Helv. Chim. Acta* **1979**, *62*, 2325.

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(11) (a) Schmid, R.; Schmid, H. *Helv. Chim. Acta* **1974**, *57*, 1883. (b) Ernst, B.; Ganter, C. *Helv. Chem. Acta* **1978**, *61*, 1775.

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(13) We have treated **12a** with $TiCl_4$ and found that it does not give the same product as that from the reaction of **7**. Studies of the reactions of the cycloadducts with Lewis acids continue and will be reported elsewhere.

(14) (a) Kaiser, R.; Föhlisch, B. *Helv. Chim. Acta* **1990**, *73*, 1504. (b) Föhlisch, B.; Hetter, R. *Chem. Ber.* **1984**, *117*, 2580. (c) Föhlisch, B.; Flogaus, R.; Oexle, J.; Schädel, A. *Tetrahedron Lett.* **1984**, *25*, 1773. (d) Föhlisch, B.; Gehrlach, E.; Herter, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 137.

(15) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *48*, 138.

(16) Wender P. A.; Holt, D. A. *J. Am. Chem. Soc.* **1985**, *107*, 7771.

(17) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, U.K., 1983; p 190.

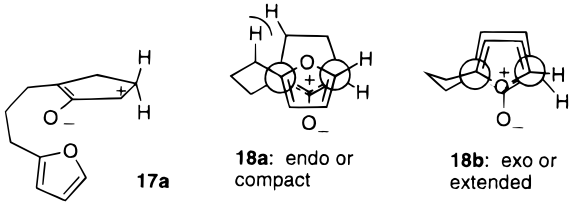


Figure 1. Plausible transition state structures for the formation of **12a** and **13a**.

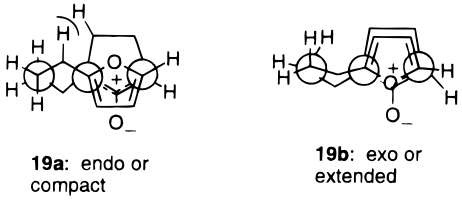


Figure 2. Plausible transition state structures for the formation of **12c** and **13c**.

unsaturated ketones from α-halo precursors may proceed by a similar mechanism.[18b] Further, analogues of **17** are putative intermediates in the Nazarov cyclization which leads to cyclopentenones.[18a]

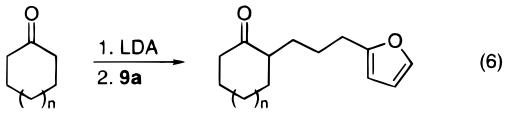
The stereochemistry of **12a** is that expected on the basis of precedent.[9a] Assuming a concerted reaction, two approaches of diene to dienophile are possible: an endo or compact approach leading to the observed major product **12a** or an extended or exo approach leading to **13a** (Figure 1). In the exo approach, there are steric (eclipsing) interactions between the furan ring and the methylene groups on the cyclopentenyl ring. Further, dipole−dipole repulsion is evident, though in a very polar medium it may not be a severe problem. In the endo approach, a repulsive interaction between a hydrogen on the tether and one on the cyclopentenyl ring should exist. Overall, it appears that the unfavorable electronic and steric effects associated with the exo approach are sufficient to make the endo approach favored to a considerable extent.

The stereoselection observed in intermolecular cycloadditions of cyclopentenyl and larger oxyallylic cations with furans has been rationalized as arising from secondary orbital interactions and steric effects.[1] Interestingly, West observed poor endo/exo selectivity in related intramolecular cycloadditions and rationalized this result on the basis of unfavorable steric interactions between the oxyallylic cation and the tether.[7c]

The cyclization of ketone **11b** proceeded in a manner analogous to that of **11a**. However, no chlorinated cycloadduct was found. Only one stereoisomer of cycloadduct **12b** was detected, and its structural and stereochemical assignment was based on analogy to **12a**. Enone **15b** and recovered ketone were obtained in 15% and 13% yields, respectively.

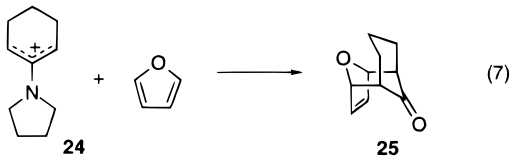
Adding an additional methylene group to the tether joining cation and diene places entropic demands on the cycloaddition which have deleterious effects. The cycloadduct from ketone **11c** was obtained in only 40% yield along with a 9% yield of the chlorinated cycloadduct **14c**. The elimination product was obtained in 36% yield. As expected, as the entropic demands on the cycloaddition grow, elimination becomes increasingly competitive.

The structure of **12c** was confirmed and its stereochemistry established by X-ray crystallographic analysis.[19] As in the case of **12a**, two transition states can be envisaged on the basis of the assumption of a concerted reaction (Figure 2). The endo transition state is once again favored. Untoward steric interactions and dipole−dipole repulsion are at a minimum, and the incipient six-membered ring takes on a chair conformation. In **19b**, the steric and electronic problems found in **18b** are present. The incipient six-membered ring is also forced into a boat conformation.[20] We set out to establish some generality with respect to ring size of the oxyallylic species. The precursors for this study were prepared by simple alkylation of the appropriate ketone enolates (eq 6). Dialkylation was a significant problem, but no attempt was made to optimize the alkylation and the dialkylation products were not rigorously characterized.



20a: n=1, 53%
20b: n=2, 51%
20c: n=3, 51%
20d: n=5, 53%
20e: n=7, 53%

Chlorination of **20a** and cycloaddition under standard conditions resulted in the formation of a 54% yield (61% based on recovered starting material) of cycloadducts **21a**,**b** in a ratio of 1:2.5. The dramatic change in diastereomer distribution relative to cycloadducts **12a**/**13a** is noteworthy. The exo diastereomer **21b** is now favored. Control experiments suggest that this reaction is taking place under kinetic control. Treatment of a 1:1.6 mixture of **21a**,**b** under cycloaddition conditions resulted in no change in their relative ratio. The basis of this stereochemical change is not clear. This observation differs from results of intermolecular 4 + 3 cycloaddition reactions of cyclohexenyl cations. For example, Schmid found that the cyclohexenyl allylic cation **24** underwent 4 + 3 cycloaddition with furan to give 4 + 3 adducts which were obtained as a 97:3 mixture of diastereomers favoring the endo isomer **25**.[11]



24 **25**

Similar findings were reported by Föhlisch.[9] It seems clear that the change in stereoselectivity in the intramolecular 4 + 3 cycloaddition is due to the tether joining the cyclohexenyl oxyallylic cation and the furan. However, transition states leading to **21a**,**b** should not differ substantially from those leading to **12a** and **13a**. We believe that a major source of the disparity arises due to an increase in torsional strain in the transition state leading to **21a**.

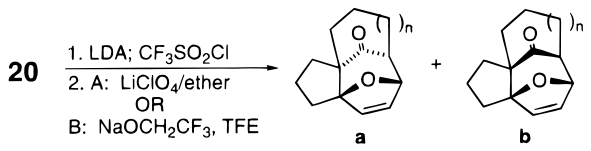
Molecular mechanics (PCMODEL, version 5) calculations on the cations **26a**−**d** show that as ring size increases the angle "a" decreases. This will have the effect of inducing strain in endo transition states in intramolecular 4 + 3 cycloaddition reactions by forcing the methylene groups adjacent to the diene

(18) (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, *45*, 1. (b) Warnhoff, E. W.; Martin, D. G.; Johnson, W. S. In *Organic Syntheses Collective Volume 4*; Rabjohn, N., Ed.; Wiley: New York, 1963; pp 162−66.

(19) Data on **12c**: MW = 204.27; space group $p21/c$; a = 7.0682(7) Å, b = 19.641(4) Å, c = 8.0446(9) Å, β = 110.980(4)°; V = 1042.8(3) Å^3; Z = 4; D_{calcd} = 1.301; radiation = Mo Kα (λ = 0.709 30) Å; m = 0.08 mm^{-1}; $F(000)$ = 440; temperature = 23/−1°; final R = 0.050 for 1056 reflections with $I > 2\sigma(I)$.

(20) As a cautionary note, it must be pointed out that we have not rigorously established that the cycloaddition reactions involving cyclopentenyl cations are under kinetic control or that the mechanism of the reaction is indeed concerted.

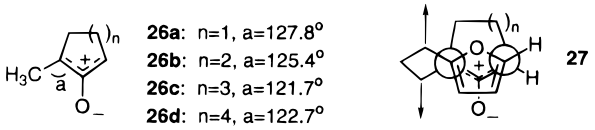
Table 1. Cycloaddition Results for **20a**−**c**



entry	*n*	educt	reagent	product	yield (%)[a]	ratio (a:b)
1	1	**20a**	A	**21**	54 (61)	1:2.5
2	2	**20b**	A	**22**	56 (66)	1:7.3
3	3	**20c**	A	**23**	17	1:9.5
4	3	**20c**	B	**23**	61 (69)	1:10.1

[a] Yield in parentheses based on recovered starting material.

and dienophile to move away from each other as shown in **27**. Exo transition states do not suffer from such strain.[21]



The structure of **21b** was determined by spectral data analysis (^{1}H, ^{13}C NMR; IR; MS). The stereochemistry of **21b** was assigned on the basis of an X-ray crystal structure.[22] Cycloadduct **21a** could not be isolated in pure form, and its structure is based on our conclusion that it is in fact a 4 + 3 cycloadduct by ^{1}H NMR and it must be isomeric to **21b**.

The cycloaddition of **20b** led to two cycloadducts in a ratio of 1:7.3 in 56% yield (66%, corrected). The increased torsional strain in the endo approach was expected to bias the cycloaddition toward an exo transition state. Indeed, the major product was the **22b**. The structure was determined by spectral and X-ray analysis.[23] This result differs from the results of similar intermolecular reactions and underscores the considerable effect that intramolecularity can have on simple diastereoselection. As shown in eq 2, Noyori and Ito showed that a cycloheptenyl oxyallylic cation reacts with furan to give a 4 + 3 cycloadduct possessing the endo stereochemistry exclusively.[8a,b] Hoffmann reported that a similar reaction proceeded to produce a 36:1 ratio of diastereomers.[8c]

The cyclization of substrate **20c** was not as straightforward. Chlorination proceeded uneventfully, but cyclization using 3 M ethereal $LiClO_4$ even up to reflux temperature was not effective in affording yields of cycloadducts in excess of 17%. Both **20c** and the corresponding chloroketone **28** were obtained in 16% and 41% yields, respectively. Changing the nature of the base had no effect on the outcome of the cycloaddition.[24] The recovery of chloroketone was telling, and we believe the reluctance of this species to undergo cyclization can be traced to its conformation.

Although the stereochemistry of **28** was not confirmed, from what is known about the alkylation of kinetic enolates of

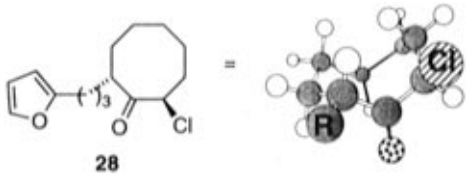
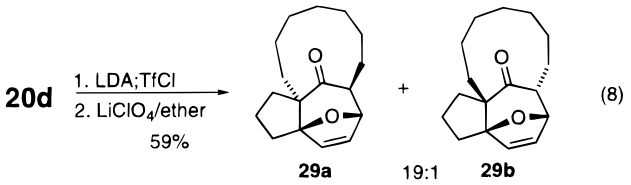


Figure 3.

2-alkylcyclooctanones, it is likely that the stereochemistry of **28** is as shown in Figure 3.[25] In this conformation, both hydrogens α to the carbonyl group are parallel to the carbon−oxygen bond, not perpendicular to it, as would be required for a facile deprotonation. Thus, **28** would have to undergo a conformational change in order to form the enolate precursor to the oxyallylic cation. We concluded that the use of a stronger base might prove more effective in siphoning off any reactive conformer present in solution and improve conversion rates and cycloadduct yield. Stirring chloroketone **28** in the presence of a trifluoroethanol solution of sodium trifluoroethoxide gave cycloadducts **23a**,**b** in 61% yield (69% based on recovered starting material) in a ratio of 1:10.1.

The structure and stereochemistry of the major cycloadduct were determined by spectroscopic analysis. The stereochemical assignments of both **23a** and **23b** were established by comparison of certain resonances in their ^{1}H NMR spectra with other 4 + 3 cycloadducts whose structures were firmly established by X-ray crystallography. It was observed in the ^{1}H NMR spectra of all of the cycloadducts that the olefinic protons H_a and H_b in the exo isomers resonated at lower field than the corresponding protons in the endo isomers (Table 2). This same pattern was also observed for the chemical shift of the proton on the methine of the oxygen bridge (H_c). This trend in the chemical shift was also observed by Hoffmann in his study of intermolecular cycloaddition of cyclic oxyallylic cations with furan.[8c]

Cycloadducts **29a**,**b** were obtained in 59% yield (67% based on recovered starting material) as a 19:1 mixture of isomers by ^{1}H NMR deom **20d**. The major isomer in the mixture was



(8)

characterized spectroscopically and crystallographically.[26] This demonstrated that **29a** possessed a B_{ae} conformation.[27]

The minor isomer **29b** could not be isolated in pure form. However, inspection of an ^{1}H NMR of a mixture of **29a**,**b** showed a signal for the methine proton at 4.71 ppm as a doublet of doublets (J = 1.8, 2.9 Hz). If it is assumed that the smaller coupling constant involves the adjacent olefinic proton, coupling to the α-ketone proton amounts to about 3 Hz. This is the value that Hoffmann found for coupling between the axial proton H_a and the methine proton H_b in adducts such as **30**, which possess

(21) Other factors could certainly be involved. Further studies are needed to paint a complete picture of the basis of simple diastereoselection in these reactions.

(22) Data on **21b**: MW = 218.29; space group $p21/n$; a = 11.9350(20) Å, b = 11.9910(20) Å, c = 7.8920(20) Å, b = 99.512(5)°; V = 1113.9(4) Å^3; Z = 4; D_{calcd} = 1.302 g·cm^{-3}; m = 0.64 mm^{-1}; $F(000)$ = 471.95; radiation = Cu Kα (λ = 1.540 56) Å; temperature = 23/−1°; final R = 0.041 for 2095 reflections with $I > 2.5\sigma(I)$.

(23) Data on **22b**: MW = 204.27; space group $p21/n$; a = 8.6163(10) Å, b = 11.4938(6) Å, c = 22.0340(20) Å, β = 100.800(4)°; V = 2143.5(3) Å^3; Z = 8; $F(000)$ = 871.90; D_{calcd} = 1.26 g·cm^{-3}; radiation = Cu Ka (λ = 1.540 56) Å; temperature = 23/−1°; final R = 0.049 for 2831 reflections with $I > 2.0\sigma(I)$.

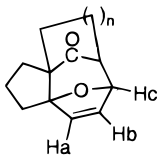
(24) Base (yield, **23a**:**23b**): pyridine (12%, 1:9.3); diisopropylethylamine (11%, 1:9.8); 2,6-lutidine (9%, 1:9.8); 2,6-di-*tert*-butylpyridine (11%, 1:9.6).

(25) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

(26) Harmata, M.; Elomari, S.; Barnes, C. L. *Acta Crystallogr., C* (submitted).

(27) This nomenclature was introducted by Hoffmann and Vinter.[8c] The first letter denotes the conformation of the tetrahydropyranone portion of the molecule, boat (B) or chair (C). The subscripts describe the orientation of the polymethylene chain joining the positions α to the carbonyl group of the tetrahydropyranone, axial (a) and/or equatorial (e).

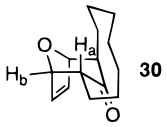
Table 2. Chemical Shift Data for Selected Cycloadducts



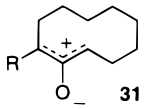
cycloadduct	*n*	type[a]	δH_a (ppm)[b]	δH_b (ppm)[b]	δH_c (ppm)[b]
12a	1	endo	6.09	6.28	4.69
13a	1	exo	6.41	6.48	5.04
21a	2	endo	6.23	6.38	4.94
21b	2	exo	6.46	6.64	5.02
22a	3	endo	6.02	6.33	4.72
22b	3	exo	6.40	6.54	4.95
23a	4	endo	6.05	6.29	4.67
23b	4	exo	6.37	6.49	4.94

[a] Refers to the relationship between the oxygen and carbonyl bridges of the cycloadducts. [b] In $CHCl_3$, downfield from TMS.

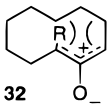
the C_{ae} conformation. Hence, we tentatively assigned the structure of the minor isomer as **29b**.



30



31

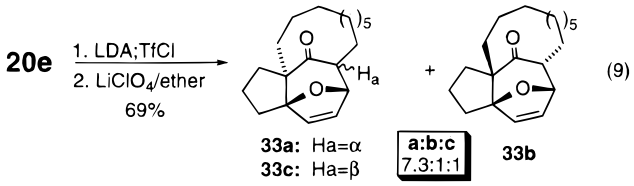


32

The inside−outside stereochemistry of **29a**/**b** suggests strongly that the products are derived from a sickle-shaped cation **31** through an exo transition state. An isomeric cation **32** is probably considerably higher in energy for steric reasons. In an earlier report, we raised the question of whether a U-shaped cation might be preferred over the sickle-shaped species on the basis of MNDO calculations.[4b] Recently, theoretical studies by Hoffmann and Vinter have provided strong support for the idea that the products in the cyclodecanone series arise from a sickle-shaped cation as those same authors concluded in their seminal paper.[8c,28]

Three products were obtained in 69% yield (72% based on recovered ketone) in a ratio of 7.3:1:1 from **20e**. The structure and stereochemistry of **33a** were secured by X-ray analysis.[29] As in **29a**, the tetrahydropyranone ring possesses the B_{ae} conformation.

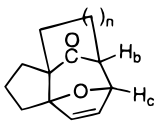
The two minor cycloadducts were obtained as an inseparable mixture (1:1). Recrystallization from hexanes and X-ray analysis of a randomly chosen single crystal gave a structure for **33b** (C_{ae}).[30] It is to be noted that such a recrystallization



(9)

gave crystals as well as an oily material. An ^1H NMR spectrum of the crystals contaminated with some of this oily material showed an isomer ratio of 3:1. It was assumed that the major isomer in this mixture was **33b**. The olefinic protons of the major component of this mixture appeared at 6.23 ppm (dd, J = 1.8, 5.8 Hz) and 6.07 ppm (d, J = 5.8 Hz). The methine of the ether bridge appeared as a doublet of doublets at 4.68 ppm (J = 1.8, 3.6 Hz). The olefinic protons of the minor component appeared at 6.40 ppm (dd, J = 2.1, 5.9 Hz) and 6.26 ppm (d, J = 5.9 Hz). The corresponding bridge methine proton resonated at 4.89 ppm (dd, J = 2.1, 7.9 Hz). These data suggest that the major component of the mixture is indeed **33b** and that the minor component possesses structure **33c** (B_{aa} conformation).

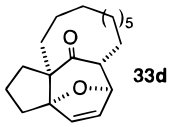
Table 3. Coupling Constants (H_a/H_b) for Selected Cycloadducts



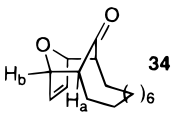
cycloadduct	*n*	type[a]	conformation	J_{H_a/H_b} (Hz)
12a	1	endo	C_{aa}	3.7
13a	1	exo	B_{aa}	7.8
21a	2	endo	C_{aa}	0.0
21b	2	exo	B_{aa}	8.7
22a	3	endo	C_{aa}	0.0
22b	3	exo	B_{aa}	8.6
23a	4	endo	C_{aa}	1.2
23b	4	exo	B_{aa}	8.0
29a	6	exo	B_{ae}	2.2
29b	6	endo	C_{ae}	2.9
31a	8	exo	B_{ae}	2.0
31b	8	endo	C_{ae}	3.6
31c	8	exo	B_{aa}	7.9

[a] Refers to the relationship between the oxygen and carbonyl bridges of the cycloadducts.

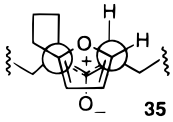
This conclusion is based on good literature precedent. In their study of the intermolecular 4 + 3 cycloaddition of cyclic oxyallyls and furans, Hoffmann and Vinter observed coupling constants of 7.5−8.5 Hz between protons H_a and H_b in cycloadducts such as **34**, possessing the B_{aa} conformation.[8c] The



33d



34



35

observed coupling constants between the same two protons in all other conformations ranged between 0.4 and 3.5 Hz. We also observed this same trend (Table 3). Thus, the large coupling constant (7.9 Hz) observed between the appropriate protons in **33c** implies that the structure is as shown and the compound possesses a B_{aa} conformation. Subjecting the 3:1 mixture of **33b**,**c** to the cyclization conditions for 86 h or treatment with sodium methoxide in methanol at room temperature for 2 days resulted in no change in composition. Refluxing a 1:2 mixture of **33b**,**c** in methanolic sodium methoxide resulted in no change in the composition of the mixture as evidenced by ^1H NMR. Further, **33a** was recovered unchanged after being stirred under the cyclization conditions for 23 days or refluxed with methanolic sodium methoxide. These data suggest that cycloadduct formation is under kinetic control.

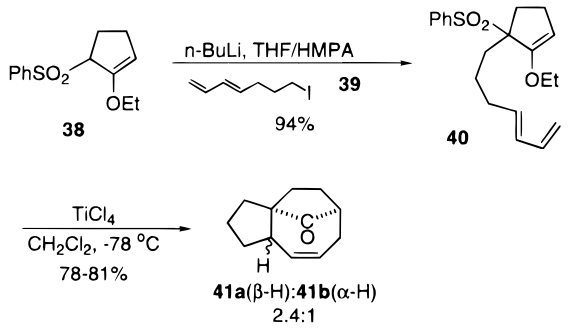
It would therefore appear that both **33a** and **33b** are formed via a sickle-shaped oxyallylic species, with the major cycloadduct **33a** being derived from an exo approach. While one might predict that **33c** is derived from an exo approach of a U-shaped cation, the absence of cycloadduct **33d** suggests that this is not the case. At least a small amount of this cycloadduct should have been formed if a U-shaped cation were an intermediate in the cycloaddition. On the other hand, molecular models suggest

(28) Goodman, J. M.; Hoffmann, H. M. R.; Vinter, J. G. *Tetrahedron Lett.* **1995**, *36*, 7757.

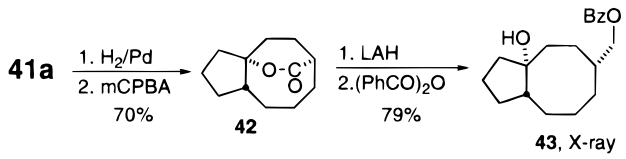
(29) Data on **33a**: MW = 288.43; space group $P21/c$; a = 18.497(6) Å, b = 8.770(4) Å, c = 10.650(3) Å, β = 106.320(20)°; V = 1658.0(10) Å^3; Z = 4; $F(000)$ = 632.22; m = 0.07 mm^{-1}; D_{calcd} = 1.155 g·cm^{-3}; radiation = Mo Kα (0.709 30) Å; temperature = 23/−1°; final R = 0.043 for 1886 reflections with $I > 2.0\sigma(I)$.

(30) Harmata, M.; Barnes, C. L.; Elomari, S. *J. Chem. Crystallogr.* (manuscript in preparation).

Scheme 2

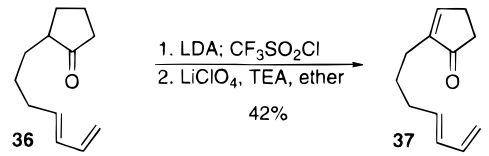


Scheme 3



that a W-shaped cation can only cyclize via a transition state such as **35** (assuming a concerted mechanism). This could give rise to a cycloadduct with a C_{ee} conformation. A ring flip would then lead to **33c** with the B_{aa} conformation. Such a process was proposed by Hoffmann and Vinter for the formation of **34**.

All of the cycloadditions discussed thus far involved furans as the diene component. In an effort to broaden the scope of the cycloaddition, we examined a few cycloadditions in which the diene component was a substituted butadiene. Our initial attempt to apply Föhlisch's methodology to this part of the study failed. Treatment of **36** according to our standard procedure resulted in the formation of enone **37** in 42% yield. Apparently



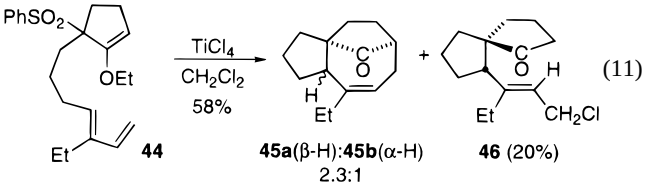
(10)

the tethered diene was not sufficiently nucleophilic to compete with elimination, at least under these reaction conditions, or the s-cis/s-trans conformational equilibrium of the diene was not conducive to cyclization.

We anticipated that the generation of a more reactive allylic cation in the absence of base would render the desired cycloaddition process tenable. The application of our alkoxyallylic sulfone methodology seemed appropriate despite the fact that it failed with substrate **7** (cf. eq 4). Thus, substrate **40** was prepared by the alkylation of **38**.[31,32] Treatment of **40** with $TiCl_4$ resulted in the formation of a 2.4:1 mixture of cycloadducts **41a**,**b** in 78−81% yield. The structures of both cycloadducts were determined from spectroscopic data. The stereochemistry of **41a** was determined by X-ray analysis of benzoate **43**. Hydrogenation of **41a** followed by treatment with mCPBA gave lactone **42** in 70% yield.[33] Lithium aluminum hydride reduction and selective benzoylation gave **43** in 79% yield. X-ray analysis of **43** proved its stereochemistry, and the stereochemistry of **41a** was assigned accordingly.[4b] On the basis of the assumption that **41a** was epimeric to **41b**, the latter's relative configuration was also established.

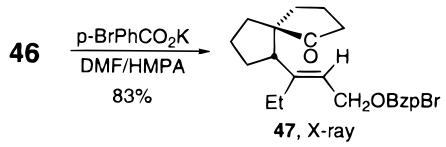
The mechanism of formation of the cycloadducts is open to some question. The high electrophilicity of the alkoxyallylic cation may predispose the system toward a stepwise cycloaddition process. Evidence for the intervention of stepwise processes in other systems has been obtained (*vide infra*). In any case, transition states leading to the epimeric cycloadducts **41a**,**b** are not sufficiently different in energy to lead to high simple diastereoselection. Circumventing this problem is a subject for future study.

In order to begin to explore the scope of this reaction, substrate **44** was prepared and subjected to Lewis acid treatment.[34] Cycloadducts **45a**,**b** were obtained in 57% yield in a ratio of 2.3:1. The structures of these compounds were assigned in accord with **41a**,**b**. Interestingly, **46** occurred as a major side product in this reaction.



(11)

The structure of **46** could be deduced spectroscopically. The ^{1}H NMR spectrum showed an olefinic signal which appeared as a triplet at 5.47 ppm (J = 8.0 Hz). The two protons of the methylene group bearing the chlorine atom appeared as a multiplet between 4.15 and 4.70 ppm. The ^{13}C NMR spectrum showed 14 carbons including a carbonyl at 223.7 ppm and olefinic carbons at 148.1 and 121.6 ppm. Low-resolution mass spectrometry gave a parent ion peak (*m*/*e* 240) consistent with the formula $C_{14}H_{21}OCl$. Treatment of **46** with potassium *p*-bromobenzoate in DMF/HMPA resulted in the formation of **47**, whose structure and stereochemistry were established by X-ray analysis.[35]



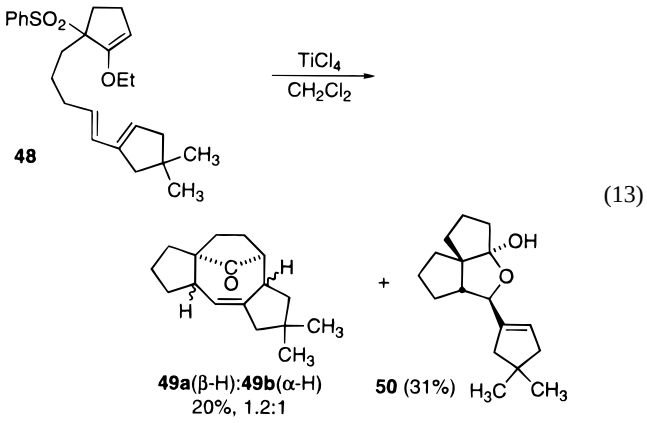
(12)

The formation of **46** suggests that a stepwise process may be involved in the formation of the cycloadducts. This is particularly true in the case of highly electrophilic dienophiles and nucleophilic dienes such as alkyl-substituted butadienes. However, while the postulation of an intermediate carbocation is tenable, the intervention of such an intermediate in the formation of **41** or **45** is by no means certain.

That cycloadduct formation is decreased when electrophilic addition becomes easier was further demonstrated by the attempted cycloaddition of **48**.[36] Treatment of this substrate with $TiCl_4$ resulted in the formation of cycloadducts **49a**,**b** in 11−20% yield in a ratio of 1.2:1. The major product of the reaction was hemiacetal **50**, formed in 27−31% yield.

The structure of **49a** was determined by standard spectral means. The ^{1}H NMR spectrum contained a signal for an olefinic proton at 5.23 ppm (J = 1.9 Hz). The ^{13}C NMR spectrum

(31) Funk, R. L.; Bolton, G. L.; Brummond, K. M.; Ellstead, K. E.; Stallman, J. B. *J. Am. Chem. Soc.* **1993**, *115*, 7024.
(32) Wulff, W. D.; Powers, T. S. *J. Org. Chem.* **1993**, *58*, 2381.
(33) Koch, S. S. C.; Chamberlin, R. *Synth. Commun.* **1989**, 289.
(34) For the experimental details of the preparation of the dienyl iodide used to make **44**, see the supporting information.
(35) Data on **47**: MW = 405.33; space group $P21/n$; a = 7.3050(20) Å, b = 10.5060(10) Å, c = 25.198(5) Å, β = 19024.8(20)°; V = 1924.8(7) Å^3; Z = 4; $F(000)$ = 840; m = 3.04 mm^{-1}; D_{calcd} = 1.399 g·cm^{-3}; radiation = Mo Kα (0.709 30) Å; temperature = 23/−1°; final R = 0.047 for 2537 reflections with $I > 2.0\sigma(I)$.
(36) For the experimental details of the preparation of the dienyl iodide used to make **48**, see the supporting information.



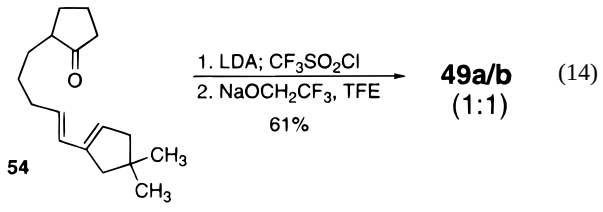
(13)

showed a signal for the carbonyl carbon at 217.2 ppm and two olefinic carbons at 143.7 and 124.0 ppm. The IR had a band at 1735 cm^{-1}, suggesting the presence of a cyclopentanone. Similar data were obtained for **49b**. In this case, however, the olefinic proton appeared at 5.57 ppm in the ^1H NMR spectrum. Indeed, it appears that endo isomers such as **41a**, **45a**, and **49a** all have their olefinic proton resonances at higher field than their corresponding exo isomers. This is presumably due to the fact that, in the "endo" series, the olefinic protons lie within the shielding cone of the carbonyl group. This difference appears to be a useful and consistent means of assigning stereochemistry for this class of cycloadducts.

The structure elucidation of **50** was less straightforward. The ^1H NMR contained a total of 26 protons including an olefinic proton at 5.50 ppm as a singlet. A one-proton singlet at 4.11 ppm suggested an oxygenated carbon, and a broad, one-proton signal at 2.38 ppm was indicative of a hydroxy group. The ^{13}C NMR spectrum had signals for two olefinic carbons at 141.9 and 124.9 ppm and a signal at 115.1 ppm, suggestive of a ketal-like carbon. No carbonyl group was evident. The IR spectrum had strong bands at 3374 and 1068 cm^{-1}, indicative of the alcohol and ether functionalities assumed present in the structure. The structure and stereochemistry were confirmed by X-ray analysis.[37]

The formation of **50** clearly indicates a stepwise reaction with the intermediacy of an allylic carbocation as shown in Scheme 4. The precise mechanism of the carbon−oxygen bond-forming and dealkylation steps is not known, and other pathways to the product are certainly viable.

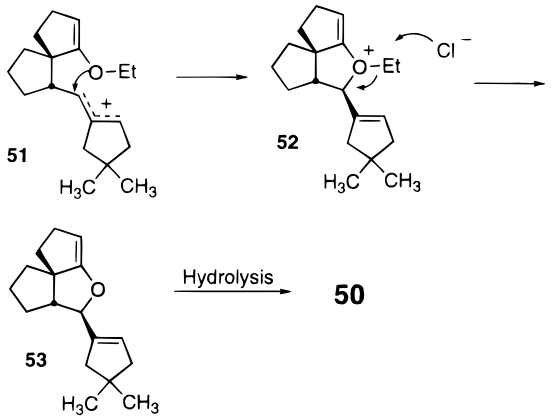
Concerned about the apparent lack of generality involving cycloadditions based on alkoxyallylic sulfones, we decided to prepare a substrate which would possess a less reactive dienophile. To that end ketone **54** was prepared and chlorinated.



(14)

The resulting α-chloroketone was dissolved in a solution of sodium trifluoroethoxide in trifluoroethanol. This led to a 1:1 mixture of **49a**,**b** in 61% yield. The scope of this process, which leads rapidly to a 5−8−5 fused ring system, remains to be determined.

Scheme 4



Conclusion

In summary, we have shown that the intramolecular 4 + 3 cycloaddition of cyclic oxyallylic cations gives rise to cycloadducts stereoselectively and in fair to good yields. On the basis of the assumption of a concerted cycloaddition, the following conclusions can be drawn. Five-, six-, seven-, and eight-membered ring oxyallylic cations are U-shaped and react preferentially via exo transtion states, except for the cyclopentenyl case, in which the endo mode is preferred. The cyclodecenyl oxyallylic cation is apparently exclusively sickle-shaped in accord with Hoffmann's analysis.[8c] The cyclododecenyl cation derived from **20e** is also mostly sickle-shaped, with a small amount of W-shaped cation contributing to product formation. Some progress has been made in the study of cycloadditions to substituted butadienes, and both alkoxyallylic and oxyallylic cations show promise in this area. Side products formed with alkoxyallylic cations suggest that a stepwise reaction involving cationic intermediates may be involved in the formation of certain cycloadducts.

It is clear that much mechanistic and methodological work remains to be done. These studies and the application of these results to total synthesis are in progress and will be reported in due course.

Experimental Section

General Information. All air- or moisture-sensitive reactions were carried out in oven-dried (at 120 °C) or flame-dried glassware under a nitrogen atmosphere. Moisture-sensitive and hydroscopic solid materials were added to the reaction vessels in a glovebag in a nitrogen atmosphere. HMPA was distilled from CaH_2 and was stored over activated molecular sieves. DMF was used as received from the supplier unless indicated otherwise. 2,2,2-Trifluoroethanol was dried over $CaSO_4$ and distilled. Sulfone **38** was prepared according to a procedure (unpublished at the time) that was provided to us by Professor Funk of Pennsylvania State University.[30] Cyclodecanone was prepared according to a literature procedure.[38] Flash chromatography was performed as described by Still and co-workers on 230−400 mesh silica gel with technical grade solvents that were distilled prior to use.[39] Gas chromatographic analyses were done with a SPB-5 fused silica capillary column (length 15 m, 0.25 mm i.d.) and a flame ionization detector. Melting points are uncorrected. Boiling points are the distilling temperatures for vacuum distillation at the indicated reduced pressures using Kugelrohr distillation apparatus. Infrared spectra were obtained

(37) Data on **50**: space group $P21/n$; a = 10.1970(20) Å, b = 15.2430-(20) Å, c = 10.1480(20) Å, b = 95.196(9)°; V = 1570.9(5) $Å^3$; Z = 4; $F(000)$ = 576; D_{calcd} = 1.109 $g\cdot cm^{-3}$; m = 0.23 mm^{-1}; radiation = Mo Kα (λ = 0.709 30) Å; temperature = 23/−1°; final R = 0.059 for 1686 reflections with $I > 2\sigma(I)$.

(38) Burpitt, R. D.; Thweatt, J. G. In *Organic Syntheses Collective Volume 5*; Baumgarten, H. E., Ed.; Wiley: New York, 1973; pp 277−80.

(39) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

as a neat liquid or as a KBr pellet. ^{1}H NMR spectra were recorded on a 250 or 500 MHz spectrometer with tetramethylsilane as the internal standard as $CDCl_3$ solutions unless otherwise stated. ^{13}C spectra were obtained using the same instruments at 62.9 or at 125.8 MHz, respectively. Low-resolution mass spectra were obtained with a capillary GC interfaced with a mass selective detector at an ionization voltage of 70 eV. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ.

General Alkylation Procedure for Methyl 2-Oxocyclopentanecarboxylate: Preparation of (±)-Methyl 2-Oxo-1-[3-(2-furanyl)propyl]cyclopentanecarboxylate (10a). In an oven-dried two-necked flask equipped with a stirring bar and a reflux condenser under an inert nitrogen atmosphere, sodium hydride (390 mg, 16.2 mmol; 1.15 mmol of NaH/1.0 mmol of keto ester) was suspended in freshly distilled THF (42 mL; 3 mL/1.0 mmol of keto ester). Sodium hydride was used as supplied (60% suspension in mineral oil). The suspension was cooled to 0 °C. Methyl 2-oxocyclopentanecarboxylate (2.9 g, 14.1 mmol) dissolved in dry THF (28 mL; 2 mL/mmol of ester) was added to the suspension dropwise via a syringe. When the addition of the keto ester was completed, the mixture was allowed to continue stirring at 0 °C until the grayish color of the suspension disappeared. The cold bath was then removed and the alkylating halide (4.4 g, 18.3 mmol, 1.3 equiv) was added via a syringe. The reaction mixture was then refluxed for 48−72 h while the progress of the reaction was monitored by TLC. Analytical thin layer chromatography was performed on silica gel plates (0.25 mm thickness) with F254 indicator. Detection was accomplished by visualization under UV (254 nm) lamp and or by developing in iodine, vanillin solution (prepared by dissolving 6 g of vanillin in a solution of 1.5 mL of concentrated H_2SO_4 and 100 mL of absolute ethanol), or phosphomolybdic acid (PMA) solution (prepared by dissolving 32 g of PMA in 320 mL of absolute ethanol) followed by heating on a hot plate. Upon completion of the reaction, the reaction mixture was allowed to cool to room temperature followed by quenching with water and extraction in ether. The organic extracts were dried over anhydrous $MgSO_4$ or Na_2SO_4. Filtration and removal of the solvent under reduced pressure on a rotary evaporator gave the products as yellow residues that were purified by column chromatography on silica gel. The crude product was purified by flash column chromatography and eluted with 10% ethyl acetate in hexanes (R_f 0.28). The pure product was obtained as a colorless oil (bp 134−136 °C/0.2 mmHg by Kugelrohr distillation) in 86−92% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 (d, 1H, J = 1.0 Hz), 6.26 (dd, 1H, J = 1.0, 3.0 Hz), 5.98 (d, 1H, J = 3.0 Hz), 3.70 (s, 3H), 2.67−2.60 (m, 2H), 2.58−2.51 (m, 1H), 2.43−2.37 (m, 1H), 2.28−2.21 (m, 1H), 2.04−1.95 (m, 2H), 1.94−1.85 (m, 2H), 1.73−1.52 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.54, 171.27, 155.23, 140.75, 109.96, 104.93, 60.26, 52.41, 37.78, 33.25, 32.63, 27.98, 23.34, 19.48; IR (neat) 2955 (s), 1746 (s), 1726 (s), 1147 (s) cm^{-1}; MS (70 eV) 232 (M^+ − 18, 16), 173 (73), 162 (52), 108 (32), 94 (97), 81 (100). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.93; H, 7.09.

Krapcho Decarboalkoxylation of β-Keto Esters: Preparation of (±)-2-[3-(2-Furanyl)propyl]cyclopentanone (11a).[15] Substrate **10a** (2.5 g, 10 mmol) was dissolved in DMF (20 mL; 2.0 mL/1 mmol of keto ester) in a reaction flask equipped with a stirring bar and refluxing condenser. To the solution were added H_2O (360 mg, 20 mmol; 2 mmol/1 mmol of keto ester) and LiCl (850 mg, 20 mmol; 2.0 mmol/1 mmol of keto ester). The reaction solution was then refluxed for 12−36 h while the progress of the reaction was monitored by TLC. Upon reaction completion, the mixture was allowed to cool down to room temperature and then diluted with pentane (100 mL; 10.0 mL/1.0 mmol of keto ester) in a separatory funnel and worked up (standard aqueous workup). The resulting crude brown oils were purified by column chromatography. Purification of the crude residue by flash column chromatography (eluting with 10% ethyl acetate in hexanes, R_f 0.26) gave the product as a colorless oil (bp 99−101 °C/0.5 mmHg) in 69−73% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, 1H, J = 1.6 Hz), 6.25 (dd, 1H, J = 1.6, 2.6 Hz), 5.9 (d, 1H, J = 2.6 Hz), 2.75−2.57 (m, 2H), 2.30−2.19 (m, 2H), 2.12−1.91 (m, 3H), 1.84−1.65 (m, 4H), 1.60−1.47 (m, 1H), 1.34−1.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 220.55, 155.68, 140.57, 109.90, 104.69, 48.69, 37.86, 29.41, 29.10, 27.81, 25.93, 20.55; IR (neat) 2959 (s), 2870 (s), 1737 (s), 1148 (s) cm^{-1}; MS (70 eV) 192 (M^+, 24), 108 (33), 95 (59), 81 (100). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.16; H, 8.31.

General 4 + 3 Cycloaddition Procedures for Cyclic α-Chloroketones. Preparation of (±)-(3aα,6α,7β,9aβ)-2,3,6,7,8,9-Hexahydro-3a,6-epoxy-7,9a-methano-1*H*-cyclopentacycloocten-10-one (12a). To a solution of diisopropylamine (290 mg, 2.85 mmol; 1.1 mmol/1.0 mmol of ketone) in freshly distilled THF (6.55 mL; 2.5 mL/1.0 mmol of ketone) was added *n*-BuLi (1.04 mL of 2.5 M solution; 1.0 equiv) at −78 °C. After the mixture was stirred for 15 min at −78 °C, the ketone **11a** (500 mg, 2.6 mmol) in dry THF (6.5 mL; 2.5 mL/1.0 mmol of ketone) was added dropwise via a syringe with stirring over 10 min period. The reaction mixture was then stirred for an additional 30 min, and trifluoromethanesulfonyl chloride (526 mg, 3.1 mmol; 1.2 mmol/mmol of ketone) was added. The reaction mixture was stirred for 5−10 min and then removed from the cold bath and quenched with water. The reaction mixture was diluted with ether (5 mL/1 mmol of ketone) and worked up. The resulting crude α-chloroketone was cyclized without purification by one of two methods.

Method A: The crude chloroketone was dissolved in freshly distilled ether (26 mL; 10 mL/1 mmol of ketone). Anhydrous $LiClO_4$ (8.3 g, 78 mmol; to make 3.0 M solution in $LiClO_4$) and freshly distilled (from CaH_2) triethylamine (790 mg, 7.8 mmol; 3 equiv) were added. The mixture was allowed to stir at room temperature for 12−48 h while the progress of the reaction was monitored by TLC.

Method B: In a flame-dried reaction flask equipped with a stir bar and rubber septum, thin shavings of sodium metal (5 mmol/mmol of ketone) were dissolved in dry 2,2,2-trifluroethanol (8 mL/mmol of ketone) at 0 °C. A TFE solution (2 mL/mmol of ketone) of the crude chloroketone was then added to the sodium trifluoroethoxide solution dropwise. The solution was stirred at room temperature, and the reaction progress was monitored by TLC. Although refluxing was not necessary, the reaction proceeded much faster when refluxed. In either method, when the reaction was completed the mixture was diluted with ether (10 mL/1 mmol of ketone) in a separatory funnel and standard aqueous workup was performed. The crude products were purified by flash column chromatography or by MPLC. Cycloadduct **12a** was prepared via method A. Silica gel flash column chromatography of the crude reaction mixture (12% ethyl acetate in hexanes, R_f 0.11) gave the cycloadduct as a mixture of two isomers in the ratio of 14.5−16:1 in favor of the endo product in a combined yield of 53−56%. Attempts to obtain the minor product in its pure form were unsuccessful. The major isomer was obtained as a white solid substance (from hexanes, mp 83 °C): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.28 (br d, 1H, J = 5.7 Hz), 6.09 (d, 1H, J = 5.8 Hz), 4.69 (dd, 1H, J = 1.5, 3.4 Hz), 2.41 (dd, 1H, J = 4.0, 5.6 Hz), 2.17−2.12 (m, 1H), 2.08−1.99 (m, 3H), 1.94−1.69 (m, 4H), 1.5−1.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.42, 135.05, 133.42, 97.10, 83.95, 64.21, 50.26, 29.40, 28. 21, 23.22, 21.03, 20.31; IR (KBr pellet) 1743 (s), 1099 (m), 981 (s) cm^{-1}; MS (70 eV) 190 (M^+, 69), 162 (61), 135 (50), 134 (62), 91 (54), 81 (100), 55 (68). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.63; H, 7.42. Found: C, 75.57; H, 7.31.

(±)-(3aα,6α,7β,9aβ)-2,3,6,7,8,9-Hexahydro-7-chloro-3a,6-epoxy-7,9a-methano-1*H*-cyclopentacycloocten-10-one (14a). This chlorinated adduct was produced in 4−7% yield from the cyclization of **11a** via method A. It was isolated as a white solid (from hexanes, mp 91−93 °C): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.39 (br d, 1H, J = 5.8 Hz), 6.23 (br d, 1H, J = 5.8 Hz), 4.70 (d, 1H, J = 1.5 Hz), 2.53−2.42 (m, 1H), 2.33−1.80 (m, 7H), 1.71−1.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 62 MHz) δ 202.00, 137.00, 132.55, 97.84, 88.63, 74.71, 63.85, 31.50, 30.46, 27.80, 24.10, 20.94; IR (KBr) 1763 (s) cm^{-1}; MS (70 eV) 226 (M^+ + 2, 7), 224 (M^+, 26), 196 (100), 91 (51), 81 (88). Anal. Calcd for $C_{12}H_{13}O_2Cl$: C, 64.15; H, 5.83. Found: C, 64.25; H, 6.03.

2-[3-(2-Furanyl)propyl]cyclopent-2-en-1-one (15a). This product was obtained in 14−17% yield as a byproduct from the cyclization process of precursor **11a** via method A. It was separated from the cycloadduct by MPLC chromatography (12% ethyl acetate in hexanes). It was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31−7.29 (m, 1H), 7.27 (dd, 1H, J = 0.7, 1.9 Hz), 6.25 (dd, 1H, J = 1.9, 3.0 Hz), 5.97 (dd, 1H, J = 0.7, 3.0 Hz), 2.62 (t, 2H, J = 7.5 Hz), 2.60−2.53 (m, 2H), 2.38−2.36(m, 2H), 2.23−2.20 (m, 2H), 1.8 (pentet, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.75, 157.57, 155.55, 145.67, 140.70, 109.99, 104.91, 34.45, 27.52, 26.38, 25.95,

24.20; IR (neat) 2927 (s), 2884 (m), 1699 (s), 1004 (s) cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.68; H, 7.18.

(±)-(3aα,6α,7β,9aβ)-2,3,6,7,8,9-Hexahydro-6-methyl-3a,6-epoxy-7,9a-methano-1*H*-cyclopentacycloocten-10-one (12b). Prepared from the cyclization of the cyclopentanone derivative **11b** (1 g, 4.85 mmol) via cycloaddition method A. Purification of the reaction mixture by MPLC chromatography (10% ethyl acetate in hexanes) afforded the cycloadduct as a single stereoisomer in 56% (65% based on recovered **11b**). The product was isolated as a white solid (from hexanes, mp 91−92 °C): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.11 (d, 1H, J = 5.7 Hz), 6.04 (d, 1H, J = 5.7 Hz), 2.22 (d, 1H, J = 6.0 Hz), 2.08−2.00 (m, 4H), 1.97−1.73 (m, 4H), 1.50−1.37 (m, 8H; including singlet at 1.43 for 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.02, 136.94, 135.08, 96.84, 89.21, 61.91, 54.74, 28.25, 28.21, 22.93, 20.34, 19.77, 19.26; IR (KBr) 2972 (s), 1734 (s), 1135 (m) cm^{-1}; MS (70 eV) 204 (M^+, 75), 133 (53), 95 (100). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.61; H, 7.79.

2-[3-(5-Methyl-2-furanyl)propyl]cyclopent-2-en-1-one (15b). This elimination product was produced in 13−16% as a side product in the cycloaddition process of ketone **11b** discussed above: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33−7.30 (m, 1H), 5.85−5.82 (m, 2H), 2.61−2.53 (m, 4H), 2.41−2.37 (m, 2H), 2.24−2.20 (m, 5H), 1.87−1.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.74, 157.46, 153.73, 150.13, 145.82, 105.72, 105.15, 34.48, 27.64, 26.40, 26.11, 24.24, 13.40; IR (neat) 1701 (s) cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_2$: C, 75.76; H, 7.42. Found: C, 75.50; H, 7.60.

(±)-(4aα,7α,8α,10aα)-1,2,3,4,7,8,9,10-Octahydro-4a,7-epoxy-8,10a-methanobenzocycloocten-11-one (12c). Cyclization of the cyclopentanone derivative **11c** (1.25 g, 6.1 mmol) via cycloaddition method A followed by silica gel column chromatography (15% ethyl acetate in hexanes) gave **12c** mixed with elimination product. Separation of this mixture was accomplished by flash column chromatography using a 9:10:1 solution mixture of benzene−hexanes−ethyl acetate as an eluting solvent. The cycloadduct was obtained as a white solid (from hexane, mp 65−66 °C) in 38−42% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.29 (d, 1H, J = 5.9 Hz), 6.26 (dd, 1H, J = 1.5, 5.9 Hz), 4.67 (dd, 1H, J = 1.5, 4.1 Hz), 2.48 (dd, 1H, J = 4.1, 6.0 Hz), 2.29 (ddd, 1H, J = 4.2, 1.5, 9.5 Hz), 1.93−1.75 (m, 5H), 1.72−1.69 (m, 1H), 1.60 (dt, 1H, J = 4.0, 14.0 Hz), ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 (dd, 1H, J = 0.7, 1.9 Hz), 6.26 (dd, 1H, J = 1.9, 3.0 Hz), 1.47 (dq, 1H, J = 3.3, 14.4 Hz), 1.42−1.24 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.22, 134.54, 133.18, 89.79, 81.82, 56.88, 50.89, 28.98, 27.55, 27.08, 23.98, 22.33, 21.10; IR (KBr) 2963 (s), 1745 (s), 945 (s) cm^{-1}; MS (70 eV) 204 (M^+, 100), 176 (62), 135 (55), 81 (73). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.63; H, 7.81.

(±)-(4aα,7α,8α,10aα)-1,2,3,4,7,8,9,10-Octahydro-8-chloro-4a,7-epoxy-8,10a-methanobenzocycloocten-11-one (14c). This chlorinated cycloadduct was obtained in 7% yield as a side product from the cycloaddition of **11c** above. It was isolated as a crystalline solid (from hexane, mp 77 °C): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.78 (d, 1H, J = 5.9 Hz), 6.32 (dd, 1H, J = 5.9, 1.6 Hz), 4.67 (d, 1H, J = 1.6 Hz), 2.46 (ddd, 1H, J = 4.0, 11.0, 11.7 Hz), 2.35 (ddd, 1H, J = 4.0, 11.7, 12 Hz), 1.96−1.80 (m, 4H), 1.75−1.66 (m, 2H), 1.60−1.56 (m, 1H), 1.50 (ddd, 1H, J = 4.0, 11.4, 12 Hz), 1.40−1.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.27, 136.57, 132.03, 90.15, 86.70, 74.14, 56.52, 31.64, 28.80, 28.47, 27.66, 23.68, 21.48; IR (KBr) 2941 (s), 1762 (s), 967 (s) cm^{-1}; MS (70 eV) 238 (M^+, 22), 95 (55), 81 (100). Anal. Calcd for $C_{13}H_{15}OCl$: C, 65.41; H, 6.33. Found: C, 65.64; H, 6.24.

2-[4-(2-Furanyl)butyl]cyclopent-2-en-1-one (15c). This compound was produced in a competing elimination process during the cycloaddition of ketone **11c**. It was obtained as a colorless oil in 36% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49−7.23 (m, 2H), 6.27 (dd, 1H, J = 2.0, 3.0 Hz), 5.98 (d, 1H, J = 3.0 Hz), 2.64 (t, 2H, J = 7.4 Hz), 2.57−2.55 (m, 2H), 2.41−2.39 (m, 2H), 2.23−2.20 (m, 2H), 1.70−1.64 (m, 2H), 1.56−1.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.87, 157.41, 156.00, 146.03, 140.63, 109.96, 104.67, 34.50, 27.69, 27.61, 27.10, 26.36, 24.41; IR (neat) 1700 (s) cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.40; H, 7.96.

(±)-(3aα,6α,7β,9aβ)-2,3,4,5,6,7,8,9-Octahydro-3a,6-epoxy-7,9a-methano-1*H*-cyclopentacycloocten-10-one (16a). Two hundred mg (1.05 mmol) of **12a** and 30 mg of 10% palladium on carbon (2.5 mol % Pd) were dissolved in 20 mL of ethyl acetate in a hydrogenation flask. The reaction flask was affixed to a hydrogenation apparatus at 40 psi of hydrogen gas for 4 h. TLC indicated completion of the hydrogenation, and the reaction solution was filtered through Celite. The filtrate was concentrated under reduced pressure, and the resulting solid residue was further purified by recrystallization from hexanes to afford the desired product as white crystals (mp 68−69 °C) in 98% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.35 (dd, 1H, J = 4.2, 5.8 Hz), 2.30−2.21 (m, 3H), 2.14−2.08 (m, 1H), 1.99−1.83 (m, 4H), 1.77−1.42 (m, 5H), 1.40−1.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.93, 95.77, 83.63, 61.07, 52.68, 33.16, 31.51, 29.12, 28.60, 22.70, 20.03, 19.13; IR (KBr) 1743 (s), 1065 (s) cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.93. Found: C, 75.04; H, 8.33.

General Procedure for the Alkylation of Cyclic Ketones: Preparation of (±)-2-[3-(2-Furanyl)propyl]cyclohexanone (20a). To a freshly distilled diisopropylamine (1.18 g, 11.7 mmol; 1.15 mmol/1.0 mmol of ketone) dissolved in freshly distilled THF (35 mL; 2.5 mL/1.0 mmol of ketone) was added *n*-BuLi (4.5 mL of 2.5 M solution; 1.1 equiv) at −78 °C under an inert nitrogen atmosphere. After the mixture was allowed to stir for 20−30 min at −78 °C, the ketone (cyclohexanone, 1 g, 10.2 mmol) dissolved in dry THF (10 mL; 1 mL/1.0 mmol of ketone) was added dropwise via a syringe over 10 min period. The reaction mixture was then stirred at −78 °C for 60 min, and 2-(3-iodopropyl)furan (3.1 g, 13.3 mmol, 1.3 equiv) was added. The reaction was allowed to warm up slowly to room temperature while stirring, and stirring continued for 6−12 h. Upon completion, the mixture was transferred to a separatory funnel and worked up. The ether extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude reaction mixture by flash column chromatography using ethyl acetate−benzene−hexane (1:9:10) as an eluent gave the monoalkylation product along with the dialkylation product in 49−53% and 14−17% yields, respectively. The desired monoalkylation product was obtained as a colorless oil (bp 96−98 °C, 0.35 mmHg): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, 1H, J = 2.0 Hz), 6.25 (dd, 1H, J = 2.0, 3.0 Hz), 5.98 (d, 1H, J = 3.0 Hz), 2.65−2.56 (m, 2H), 2.38−2.34 (m, 1H), 2.30−2.24 (m, 2H), 2.11−1.97 (m, 2H), 1.88−1.79 (m, 2H), 1.75−1.59 (m, 4H), 1.49−1.33 (m, 1H), 1.28−1.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.91, 155.96, 140.53, 109.92, 104.61, 50.37, 41.88, 33.80, 28.87, 27.97, 27.89, 25.53, 24.79; IR (neat) 2936 (s), 1709 (s) cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.60; H, 9.01.

(±)-(3aα,6α,7α,10aα)-2,3,6,7,8,9-Hexahydro-3a,6-epoxy-7,10a-methano-1*H*,10*H*-cyclopentacyclononen-11-one (21b). Produced by subjecting the cyclization precursor **20a** (500 mg, 2.4 mmol) to the 4 + 3 cycloaddition process via method A. The crude reaction residue was purified by flash chromatography (12% ethyl acetate in hexanes) to give an inseparable mixture of two 4 + 3 cycloadducts in combined yield of 56% (61% based on recovered ketone **20a**) in a ratio of 2.6:1 as was determined by ^{1}H NMR of the isolated mixture. Separation of the mixture was accomplished by MPLC (12% ethyl acetate in hexanes, R_f 0.15 for the major isomer **21b**). The minor isomer was never isolated in its pure form. The major adduct **21b** was further recrystallized from hexanes to give a crystalline solid (from hexanes, mp 47−48 °C) whose X-ray structure revealed the syn relationship between the oxygen and carbonyl bridges: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.64 (dd, 1H, J = 2.1, 5.8 Hz), 6.46 (d, 1H, J = 5.8 Hz), 5.02 (dd, 1H, J = 2.1, 8.7 Hz), 3.02−2.99 (m, 1H), 2.69−2.58 (m, 1H), 2.19−2.08 (M, 1H), 1.99−1.91 (m, 3H), 1.9−1.84 (m, 1H), 1.82−1.72 (m, 2H), 1.69−1.61 (m, 2H), 1.37−1.26 (m, 1H), 1.10−1.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.83, 137.95, 136.47, 96.52, 80.32, 63.92, 49.05, 36.60, 36.11, 33.21, 28.75, 24.28, 17.78; IR (KBr) 2953 (s), 1716 (s), 989 (s) cm^{-1}; MS (70 eV) 204 (M^+, 6), 147 (73), 117 (100), 94 (64). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.66; H, 7.75.

(±)-(3aα,6α,7α,11aα)-2,3,6,7,8,9,10,11-Octahydro-3a,6-epoxy-7,11a-methano-1*H*-cyclopentacyclodecen-12-one (22b). Cyclization of precursor **20b** (550 mg, 2.5 mmol) via method A followed by purification on silica gel (15% ethyl acetate in hexane, R_f 0.22 for the major isomer) gave a 7.3:1 isomeric mixture (^{1}H NMR ratio) of two 4 + 3 cycloaddition products in combined yield of 56% (64% based on recovered ketone **20b**). The stereochemical relationships for the major adduct were established by X-ray analysis (from hexane, mp 97−98 °C): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.54 (dd, 1H, J = 1.9, 5.8 Hz), 6.40 (d, 1H, J = 5.8 Hz), 4.95 (dd, 1H, 1.9, 8.6 Hz), 3.2 (t, 1H, J =

8.6 Hz), 2.77−2.72 (m, 1H), 2.00−1.59 (m, 8H), 1.43−1.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.10, 137.83, 136.10, 95.38, 80.06, 66.01, 49.72, 37.54, 36.30, 35.82, 26.16, 25.33, 24.25, 23.50; IR (KBr) 2957 (s), 1708 (s) cm^{-1}; MS (70 eV) 218 (M^+, 3), 131 (100). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.07; H, 8.29. Found: C, 77.18; H, 8.20.

(±)-(3aα,6α,7α,12aα)-2,3,6,7,8,9,10,11,12-Octahydro-3a,6-epoxy-7,12a-methano-1*H*,6*H*-cyclopentacycloundecen-13-one (23b). Cycloadditon of **20c** (400 mg, 1.7 mmol) via method A followed by purification (15% ethyl acetate in hexanes) gave the product as a mixture of two stereoisomers in 14−17% yield in a ratio of 9.5:1 as determined by ^{1}H NMR. The syn isomer **23b** was the major adduct. Chlorination of 240 mg (1 mmol) of **20c** and cycloaddition via method B proceeded smoothly to give the cycloaddition products. Purification by column chromatography on silica gel (15% ethyl acetate in hexanes) afforded the same mixture of the two adducts obtained in method A in 61% yield (69% corrected) in 10:1 ratio (by ^{1}H NMR) favoring the syn adduct. The minor adduct was produced in small amounts and was never obtained in its pure form. The major isomer was obtained as a white solid (from pentane, mp 40−41 °C): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.49 (dd, 1H, J = 2.1, 5.9 Hz), 6.37 (d, 1H, J = 5.9 Hz), 4.94 (dd, 1H, J = 2.1, 8.0 Hz), 2.89 (q, 1H, J = 8.2 Hz), 2.48−2.38 (m, 1H), 2.09−1.99 (m, 2H), 1.92−1.87 (m, 1H), 1.72−1.68 (m, 6H), 1.64−1.32 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 215.05, 137.54, 134.29, 95.86, 80.54, 65.83, 50.88, 37.59, 36.35, 35.44, 29.98, 28.97, 24.85, 24.30, 23.02; IR (KBr) 1700 (s) cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.47; H, 8.49.

(±)-(3a*R,6*S**,7*S**,14a*R**)-2,3,7,8,9,10,11,12,13,14-Decahydro-1*H*,6*H*-3a,6-epoxy-7,14a-methanocyclopentacyclotridecen-15-one (29a)**. Chlorination and cyclization of ketone **20d** (580 mg, 2.2 mmol) via method A gave a 19:1 (^{1}H NMR) mixture of two adducts in 59% yield (67% yield based on the recovered ketone **20d**). Column chromatography (10% ethyl acetate in hexanes) gave the major isomer as a white solid (from hexanes, mp 53−54 °C) whose stereochemistry was established by crystallographic analysis (the minor adduct was not produced in enough quantity to be isolated in its pure form): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.69 (dd, 1H, J = 1.8, 5.8 Hz), 6.16 (d, 1H, J = 5.8 Hz), 4.43 (br t, 1H, J = 2.2 Hz), 3.38 (dt, 1H, J = 2.7, 12.6 Hz), 2.82 (ddd, 1H, J = 3.5, 6.4, 12.6 Hz), 2.29−2.22 (m, 1H), 2.10 (ddd, 1H, J = 2.7, 9.3, 16.6 Hz), 1.92−1.84 (m, 3H), 1.79−1.68 (m, 2H), 1.52−1.20 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.57, 138.36, 133.45, 98.65, 83.67, 69.94, 46.76, 35.18, 33.60, 30.02, 26.41, 26.10, 24.90, 24.62, 23.34, 23.15, 21.66; IR (KBr) 2957 (s), 1714 (s) cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.66; H, 9.27.

(±)-(3a*R,6*S**,7*S**,16a*R**)-2,3,7,8,9,10,11,12,13,14,15,16-Dodecahydro-3a,6-epoxy-7,14a-methano-1*H*,6*H*-cyclopentacyclopentadecen-17-one (33a).** Reaction of ketone **20e** (500 mg, 1.7 mmol) via cycloaddition method A followed by chromatography (12% ethyl acetate in hexanes) gave a 7.3:1:1 mixture of three 4 + 3 adducts (**33a**:**33b**:**33c**) in combined yield of 68% (71% corrected yield). The major adduct (white solid, mp 99−100 °C) was recrystallized from hexanes and a single X-ray structure indicated the shown stereochemical relationship: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.64 (dd, 1H, J = 1.95, 5.8 Hz), 6.16 (d, 1H, J = 5.8 Hz), 4.42 (t, 1H, J = 2.0 Hz), 2.84 (dt, 1H, J = 2.4, 12.0 Hz), 2.66−2.60 (m, 1H), 2.21−2.14(m, 1H), 1.95−1.85 (m, 2H), 1.75−1.60 (m, 3H), 1.56−1.48 (m, 1H), 1.46−1.32 (m, 5H), 1.30−1.16 (m, 6H), 1.15−0.96 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.23, 137.07, 133.75, 97.42, 83.98, 68.86, 44.40, 35.28, 33.33, 30.12, 27.36, 26.42, 26.28, 24.16, 22.64, 22.31, 22.12, 21.48, 19.93; IR (KBr) 2951 (s), 1712 (s), 1469 (s), 997 (s) cm^{-1}. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.80. Found: C, 78.83; H, 9.69. Adducts **33b** and **33c**: ^{1}H NMR (1:1 mixture, $CDCl_3$, 250 MHz) δ 6.42 (dd, 1H (**33c**), J = 2.1, 5.9 Hz), 6.28 (d, 1H (**33c**), J = 5.9 Hz), 6.23 (dd, 1H (**33b**), J = 1.8, 5.8 hz), 6.07 (d, 1H (**33b**), J = 5.8 Hz), 4.90 (dd, 1H (**33c**), J = 2.1, 7.9 Hz), 4.68 (dd, 1H (**33b**), J = 1.8, 3.6 Hz), 3.33 (dt, 1H (**33b**), J = 2.8, 11.0 Hz), 2.72−2.62 (m, 1H (**33c**)), 2.30−2.24 (m, 2H), 2.13−1.95 (m, 2H), 1.88−1.80 (m, 2H), 1.78−0.94 (m, 43H); ^{13}C NMR (1:1 mixture of **33b**:**33c**, $CDCl_3$, 62 MHz) δ 212.40, 210.8, 137.31, 136.53, 133.5, 95.73, 94.51, 85.20, 80.34, 71.10, 66.67, 65.65, 51.76, 48.02, 34.52, 33.52, 32.86, 28.23, 27.44, 26.82, 26.25, 26.10, 25.36, 24.87, 23.90, 23.71, 23.37, 23.10, 22.84, 22.22, 22.11, 22.00, 21.22, 20.70, 20.11, 18.60, 17.77.

General Procedure for Alkylation of 2-Ethoxy-3-(phenylsulfonyl)cyclopentene 38. Preparation of (±)-[[2-Ethoxy-1-[3-(2-furanyl)propyl]-2-cyclopentenyl]sulfonyl]benzene (7). To a solution of **38** (1.19 g, 4.36 mmol) in freshly distilled THF (22 mL; 5 mL/1 mmol of sulfone) was added dry HMPA (1.6 g, 8.9 mmol; 2 mmol/1 mmol of sulfone), and the solution was cooled to −78 °C. After the mixture was stirred for several min at −78 °C, *n*-BuLi (1.92 mL of a 2.5 M solution, 1.1 equiv) was added dropwise via a gas-tight syringe. After the addition of *n*-BuLi was complete, the mixture was allowed to stir at −78 °C for an additional 30 min followed by quenching of the resulting anion with 2-(3-iodopropyl)furan (1.34 g, 5.7 mmol; 1.3 equiv). The reaction mixture was then allowed to warm gradually to room temperature and continued to stir for 30−60 min. The mixture was diluted with ether in a separatory funnel, and standard aqueous workup was performed. The crude products were purified by column chromatography in the presence of 0.5% Et_3N in the eluting solvent to prevent the hydrolysis of the enol ether functionality. Purification of the crude product by flash column chromatography on silica gel (30% ethyl acetate in hexanes, R_f 0.32) afforded the product as a white solid (from *tert*-butyl methyl ether, mp 78 °C) in 92% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84 (dd, 2H, J = 1.1, 7.3 Hz), 7.6 (br t, 1H, J = 7.4 Hz), 7. 47 (br t, 2H, J = 8.0 Hz), 2.27 (br d, 1H, J = 1.0 Hz), 6.25 (dd, 1H, J = 1.0, 3.0 Hz), 5.96 (d, 1H, J = 3.0 Hz), 4.66 (t, 1H, J = 2.0 Hz), 3.69−3.64 (m, 2H), 2.69−2.62 (m, 3H), 2.16−2.02 (m, 4H), 1.93 (dt, 1H, J = 4.5, 10.0 Hz), 1.74−1.65 (m, 1H), 1.57−1.44 (m, 1H), 1.14 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.45, 153.36, 140.84, 137.51, 133.25, 130.13, 128.14, 110.04, 105.00, 102.40, 78.58, 65.20, 29.69, 28.17, 28.02, 26.06, 22.62, 14.22; IR (KBr) 1645 (s), 1445 (s), 1341 (s), 1285 (s), 1245 (s), 1097 (s) cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.71. Found: C, 66.50; H, 6.61.

General 4 + 3 Cycloaddition Procedure from Cyclic Alkoxyallylic Sulfones: Preparation of (±)-(3aα,6α,9a*β*)-1,2,3,4,5,6,7,9a-Octahydro-3a,6-methano-3a*H*-cyclopentacycloocten-10-one (41a). To a stirring solution of the cyclic alkoxyallylic sulfone derivative **40** (350 mg, 1 mmol) in freshly distilled methylene chloride (10 mL; 10 mL/1 mmol of substrate) at −78 °C was added neat $TiCl_4$ (210 mg, 1.1 mmol, 1.1 equiv) dropwise via a gas-tight syringe. When the addition of $TiCl_4$ was complete, the reaction mixture was allowed to stir for additional 2−3 min. Then, the flask was removed from the cold bath and the reaction was quenched with water. The mixture was diluted with methylene chloride (10 mL/1 mmol of starting substrate) and washed three times with water and once with saturated sodium chloride. All aqueous washes were back extracted with methylene chloride, and the organic layers were combined and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude products were purified by chromatography (4% ethyl acetate in hexanes) to afford an inseparable mixture of two cycloaddition products in 78−81% yield in a ratio of 2.4:1 by GC analysis. The major adduct (R_f 0.23) was obtained as a sweet smelling colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.65 (d finely split, 1H, J = 12.9 Hz), 5.34 (d finely split, 1H, J = 12.8 Hz), 2.56 (dddd, 1H, J = 3 × 4.8, 9.6 Hz), 2.41 (ddq, 1H, J = 2.7, 4.8 18 Hz), 2.30−2.22 (m, 2H), 2.15−2.03 (m, 2H), 1.95−1.72 (m, 5H), 1.63−1.48 (m, 2H), 1.28−1.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 220.82, 130.64, 122.48, 58.68, 50.65, 43.67, 35.65, 35.12, 32.77, 31.75, 23.89, 23.31; IR (neat) 1733 (s) cm^{-1}; MS (70 eV) 176 (m^+, 75), 108 (100), 91 (84). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.60; H, 8.91.

(±)-(3aα,6α,9a*β*)-Decahydro-3a,6-methano-3a*H*-cyclopentacycloocten-1-one. One hundred ten mg (0.62 mmol) of cycloadduct **41a** and 25 mg of 10% palladium on activated carbon (4.6 mol % of palladium) were dissolved in 25 mL of ethyl acetate in a hydrogenating flask. The flask was affixed to a hydrogenation apparatus at 48 psi of H_2 for 5 h. TLC indicated completion of the hydrogenation, and the mixture was filtered through Celite. Concentration of the filtrate under reduced pressure and purification of the resulting residue by column chromatography (5% ethyl acetate in hexanes; R_f 0.24) gave the hydrogenated product as a colorless oil in 99% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.47 (dddd, 1H, J = 3 × 4.3, 8.9 Hz), 2.18 (ddd, 1H, J = 6.6, 11.1, 12.7 Hz), 2.04−1.85 (m, 1H), 1.30−1.67 (m, 2H), 1.65−1.48 (m, 10H), 1.42−1.34 (m, 1H), 1.16−1.10 (m, 1H), 0.98−0.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 221.67, 58.28, 50.25, 45.51, 37.38, 36.51, 34.22, 32.95, 30.70, 26.49, 23.37, 19.07; IR (neat) 1734

(s) cm^{-1}; MS (70 eV) 178 (M^+, 49), 79 (100). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.73; H, 10.33.

(±)-(3aα,6α,9aα)-Heptahydro-2*H*,7*H*-3,9a-ethanocyclopent[*b*]-oxocin-2-one (42). The above ketone (75 mg, 0.4 mmol) and technical (80−85%) 3-chloroperoxybenzoic acid (145 mg, 0.8 mmol; 2 mmol/1 mmol of ketone) were dissolved in freshly distilled methylene chloride (2 mL/1 mmol of ketone). The solution was then cooled to 0 °C and kept under inert atmosphere of nitrogen. Then, trifluoroacetic acid (48 mg, 0.4 mmol; 1 mmol/1 mmol of ketone) was added dropwise at 0 °C over 5 min period while stirring.[32] The reaction was protected from light by wrapping the flask with aluminum foil. The mixture was allowed to warm slowly to room temperature while stirring, and then stirring continued until completion. Reaction progress was monitored by TLC. Once the reaction was complete, the reaction mixture was diluted with methylene chloride (2 mL; 5 mL/1 mmol of starting ketone) and transferred to a separatory funnel. The mixture was then washed once with 10% aqueous Na_2SO_3 (1 mL; 2 mL/1 mmol), once with saturated aqueous K_2CO_3 (2 mL/1 mmol), and twice with water (2 mL; 5 mL/1 mmol). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure on a rotary evaporator. Purification on silica gel (10% ethyl acetate in hexanes; R_f 0.18) gave a colorless soft solid substance in 77% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.88−2.84 (m, 1H), 2.13−2.03 (m, 2H), 2.00−1.93 (m, 2H), 1.92−1.71 (m, 9H), 1.65−1.42 (m, 3H), 1.25−1.14 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.22, 90.44, 52.61, 44.03, 35.77, 34.68, 33.85, 30.92, 28.10, 13.62, 21.80, 19.10; IR (thin film) 2931 (s), 1724 (s) cm^{-1}; MS (70 eV) 194 (M^+, 15), 122 (100), 79 (66), 55 (82). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.97; H, 9.23.

(±)-(3aα,6α,9a*β*)-Decahydro-3a-hydroxy-1*H*-cyclopentacyclooctene-6-methanol: A suspension of $LiAlH_4$ (11 mg, 0.28 mmol; 1.1 mmol/1 mmol of lactone) in freshly distilled THF (0.5 mL; 2.5 mL of THF/1 mmol of lactone) was cooled to 0 °C. To the suspension was added dropwise the lactone **42** (50 mg, 0.26 mmol) dissolved in dry THF (2.5 mL/1 mmol of lactone) under an inert environment of nitrogen. After the addition of the lactone was completed, the cold bath was removed and the reaction mixture was allowed to stir at room temperature until the reaction was complete. The progress of the reaction was followed by TLC. When completed, the reaction was worked up by slow addition of crystalline sodium sulfate decahydrate ($Na_2SO_4 \cdot 10H_2O$) to the reaction mixture while stirring until the grayish color of the solution disappeared. The mixture was then allowed to stand for 15−20 min to give a colorless liquid layer and a white precipitate. The liquid layer was separated from the precipitate by filtration. The filtrate was dried over $MgSO_4$, filtered, and concentrated. The crude solid residue was purified by recrystallization from 5% ethyl acetate in hexanes. The pure diol (mp 86 °C) was obtained in 87% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.48−3.39 (m, 2H), 2.09−2.04 (m, 1H), 1.89−1.84 (m, 1H), 1.74−1.63 (m, 4H), 1.58−1.53 (m, 5H), 1.51−1.31 (m, 7H), 1.24−1.19 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 83.48, 68.98, 48.28, 43.99, 41.55, 36.18, 35.90, 30.58, 28.20, 27.29, 26.56, 22.19; IR (KBr) 3347s (br), 2951 (s), 1458 (s) cm^{-1}; MS (70 eV) 180 ($(M - H_2O)^+$, 28), 134 (45), 91 (63), 79 (100). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.80; H, 10.98.

(±)-(3aα,6α,9a*β*)-Decahydro-3a-hydroxy-α-benzoxy-1*H*-cyclopentacyclooctene-6-methanol (43): Thirty mg (0.15 mmol) of the above diol, 37 mg (0.30 mmol) of DMAP, and 50 mg (0.23 mmol) of benzoic anhydride were all dissolved at the same time in freshly distilled methylene chloride (1.5 mL). The reaction mixture was allowed to stir at room temperature for 28 h (without monitoring). TLC indicated reaction completion, and the mixture was diluted with 5 mL of ether in a separatory funnel. The mixture was washed once with saturated aqueous potassium carbonate (5 mL), twice with water (5 mL each), and once with brine. All aqueous rinses were back-extracted in 5 mL of ether, and the two ether extracts were combined and dried over $MgSO_4$. Filtration and removal of the solvent on a rotary evaporator followed by chromatography (15% ethyl acetate in hexanes (R_f 0.23) gave the benzoate ester as a white solid (from hexanes, mp 88 °C) in 91% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (dd, 2H, J = 7.75, 1.2 Hz), 7.55 (t, 1H, J = 7.44 Hz), 7.44 (t, 2H, J = 7.75 Hz), 4.19−4.13 (m, 2H), 2.07−2.00 (m, 2H), 1.99−1.52 (m, 10H), 1.50−1.41 (m, 6H), 1.15 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.65, 132.82, 130.47, 129.51, 128.33, 80.45, 69.60, 46.00, 43.95, 38.31, 38.24, 33.99, 28.11, 27.33, 24.33, 24.06, 20.48; IR (KBr) 3523 (s), 1699 (s), 1317 (s), 1123 (s) cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.23; H, 8.54.

(±)-(3aα,6α,9a*β*)-1,2,3,4,5,6,7,9a-Octahydro-9-ethyl-3a,6-methano-3a*H*-cyclopentacycloocten-10-one (45a). This compound was prepared by cyclization of **44** (250 mg, 0.67 mmol) according to the procedure for **41a**. Purification of resulting reaction residue by flash chromatography (8% ethyl acetate in hexanes) gave a mixture of two 4 + 3 adducts in 56−59% yield in a ratio of 2.35:1. The major isomer (R_f 0.32) was obtained in 41% yield as a colorless oil with a sweet odor: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.20 (d finely split, 1H, J = 6.3 Hz), 2.53 (app. sextet, 1H, J = 4.4 Hz), 2.35 (ddddd, 1H, J = 17.6, 2 × 4.0, 2 × 2.0 Hz), 2.20−2.14 (m, 2H), 2.11−2.04 (m, 3H), 2.03−1.90 (m, 3H), 1.88−1.80 (m, 2H), 1.76−1.68 (m, 1H), 1.66−1.50 (m, 2H), 1.22 (m, 1H, J = 2 × 9.3, 2 × 12.6 Hz), 1.03 (t, 3H, J = 4.1); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 222.67, 142.70, 117.39, 57.95, 53.56, 44.75, 33.40, 33.26, 33.22, 32.20, 31.88, 22.60, 22.14, 14.05; IR (neat) 2999 (s), 1735 (s) cm^{-1}; MS (70 eV) 204 (m^+, 10), 124 (91), 95 (100), 79 (89). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.50; H, 10.00.

(±)-(3aα,6α,9aα)-1,2,3,4,5,6,7,9a-Octahydro-9-ethyl-3a,6-methano-3a*H*-cyclopentacycloocten-10-one (45b). The compound was produced as the minor isomer (R_f 0.29) from the cycloaddition of sulfone **44** (discussed above). It was obtained in 17% yield as a colorless oil with a sweet odor: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.56−5.54 (m, 1H), 2.54−2.51 (m, 1H), 2.40−2.35 (m, 1H), 2.32−2.26 (m, 1H), 2.14−2.00 (m, 5H), 1.94−1.80 (m, 2H), 1.75−1.59 (m, 3H), 1.56−1.40 (m, 3H), 1.01 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 224.33, 143.18, 120.75, 58.05, 52.71, 47.04, 33.58, 32.26, 32.02, 30.96, 29.35, 23.34, 22.65, 13.94; IR (neat) 2959 (s), 1734 (s) cm^{-1}. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.21; H, 9.87.

(5*R,6*S**)-6-(3-Chloro-1-ethyl-1-propenyl)spiro[4.4]nonan-1-one (46).** This compound was produced as a side product during the cyclization of sulfone **44**. It was obtained as a colorless oil in 19−21% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.47 (t, 1H, J = 8.0 Hz), 4.15−4.07 (m, 2H), 2.98 (dd, 1H, J = 10.3, 6.8 Hz), 2.36−2.31 (m, 1H), 2.25−2.17 (m, 1H), 2.15−2.04 (m, 1H), 1.91−1.80 (m, 3H), 1.78−1.69 (m, 4H), 1.67−1.51 (m, 4H), 0.97 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 223.72, 148.07, 121.64, 59.16, 50.47, 40.51, 38.92, 37.71, 33.16, 30.63, 24.10, 23.36, 19.16, 13.75; IR (neat) 2979 (s), 1731 (s) cm^{-1}; MS (79 eV) 240 (M^+, 14), 204 (100), 175 (55), 97 (58). Anal. Calcd for $C_{14}H_{21}OCl$: C, 69.84; H, 8.79. Found: C, 70.00; H, 8.80.

(5*R,6*S**)-6-[3-(4-Bromobenzoxy)-1-ethyl-1-propenyl]spiro[4.4]-nonan-1-one (47).** An oven-dried 25 mL flask equipped with a stir bar and septum was charged with 38 mg of NaH (64 mg of 60% NaH in oil, 1.6 mmol). The oil was removed by rinsing several times with dry THF under nitrogen. The NaH was suspended in 2 mL of dry THF. 4-Bromobenzoic acid (318 mg, 1.6 mmol) dissolved in 2 mL of dry THF was added dropwise under nitrogen. The resulting milky solution was allowed to stir at room temperature for 30 min. The solvent was removed under reduced pressure on a rotary evaporator to yield a white solid which was dried under vacuum. The salt was suspended in 2 mL of dry DMF, and **46** (38 mg, 0.16 mmol) in 1 mL of dry DMF was added. The reaction mixture was heated to reflux for several min, but the salt did not dissolve. Dry HMPA (2 mL) was added and reflux resumed. After 1.5 h, TLC indicated reaction completion. The greenish solution was cooled and standard aqueous workup gave a residue which was purified by flash chromatography and recrystallized from ethanol (mp 76−78 °C) to give 53 mg of **47** (83%). This compound was characterized by X-ray analysis.[34]

(±)-(3a*β*,4α,6aα,9a*β*)-1,2,3,3a,4,5,6,6a,7,8,9,9a-Dodecahydro-2,2-dimethyl-4a,6-methanodicyclopenta[*a*,*d*]cycloocten-11-one (49a). This compound was prepared from **48** (350 mg, 0.85 mmol) by the method described for the synthesis of **41a** or from **54** (500 mg, 2 mmol) by the method described for the synthesis of **12a** (method B). The crude mixture was purified by column chromatography to give a 1:1 mixture of adducts in 61% yield (67% yield based on recovered ketone **48**). The two isomers were separated by flash column chromatography (gradient: 0%, 0.65%, 1.25%, 1.75%, 2.5%, and 3.25% ethyl acetate in hexanes). The stereochemistry of the adducts was established on the basis of ^{1}H NMR comparison with other cycloaddition products.

Adduct **49a** was obtained as a colorless soft solid which melts at room temperature: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.23 (t, 1H, J = 1.9 Hz), 2.58 −2.54 (m, 1H), 2.25−2.44 (m, 1H), 2.40−2.34 (m, 1H), 2.26−2.18 (m, 2H), 2.16−2.15 (m, 1H), 2.11−1.92 (m, 3H), 1.87−1.66 (m, 4H), 1.62−1.47 (m, 2H), 1.41−1.33 (m, 2H), 1.01 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 217.64, 143.71, 124.05, 60.51, 51.12, 49.60, 48.18, 47.60, 47.30, 36.98, 36.84, 34.99, 32.83, 30.04, 29.63, 26.95, 25.55; IR (neat) 2950 (s), 1735 (s) cm^{-1}. Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.36; H, 9.91.

(±)-(3aα,4α,6aα,9aα)-1,2,3,3a,4,5,6,6a,7,8,9,9a-Dodecahydro-2,2-dimethyl-4a,6-methanodicyclopenta[*a*,*d*]cycloocten-11-one (49b). This compound was produced by the cyclization procedures described for the preparation of **49a** above. This stereoisomer was obtained as white crystals (from hexanes, mp 94−95 °C): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.57 (br s, 1H), 2.56−2.53 (m, 1H), 2.40−2.32 (m, 2H), 2.26−2.24 (m, 1H), 2.15−2.00 (m, 2H), 1.99−1.97 (m, 1H), 1.92 (ddd, 1H, J = 4.7, 12.3, 14.5 Hz), 1.78−1.63 (m, 4H), 1.60−1.45 (m, 2H), 1.42−1.27 (m, 3H), 1.08 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 224.20, 146.40, 123.52, 59.26, 51.42, 51.08, 50.05, 46.83, 45.29, 37.37, 33.03, 32.44, 31.08, 28.66, 26.64, 22.59, 19.63; IR (KBr) 2957 (s), 1724 (s) cm^{-1}. Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.69; H, 10.14.

(1*R,3*R**,4*R**,8*R**)-1-Hydroxy-3-(4,4-dimethylcyclopent-1-enyl)-2-oxatricyclo[6.3.0.0^{4,8}]undecane (50).** This compound was produced as the major product (27−32% yield) during the cyclization reaction of sulfone **48**. It was obtained as a white solid (from hexanes, mp 96−99 °C): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.50 (br s, 1H), 4.11 (d, 1H, J = 9.2 Hz), 2.38 (br s, 1H), 2.19−2.03 (m, 6H), 2.02 (d, 1H, J = 5.6 Hz), 1.78−1.48 (m, 8H), 1.23−1.14 (m, 2H), 1.08 (s, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.94, 124.90, 115.06, 81.75, 62.19, 58.38, 47.25, 45.77, 41.40, 38.29, 36.05, 29.76, 29.74, 29.24, 26.34, 22.81; IR (KBr) 3374 (s), 2956 (s), 1013 (s) cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_2C$, 77.82; H, 9.99. Found: C, 77.84; H, 10.01.

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Supporting Information Available: Crystallographic data for **12c**, **21b**, **22b**, **33a**, **47**, and **50**, spectral and analytical data for **10b**,**c**, **11b**,**c**, **20b**−**e**, **40**, **44**, **48**, and **54** (and its precursor), and procedures for the synthesis of the dienyl iodides involved in the synthesis of **44** and **48** (61 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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