Construction of Trans-Fused Polycyclic Ethers: Methodology for the Brevetoxins

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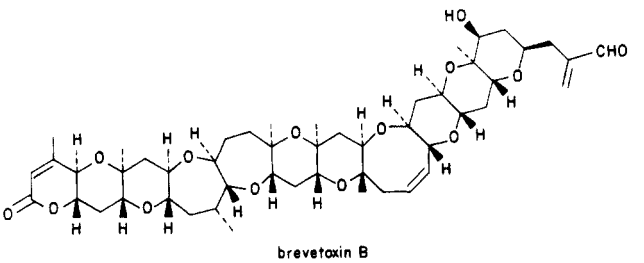
A strategy for the synthesis of trans-syn-trans-fused polyethers of the type found in the brevetoxins is described. Iodocyclization of an alkenyl-substituted cyclohexanol or tetrahydropyranol derivative leads to a bicyclic 6,6- or 6,5-system, depending on the substitution pattern and the conditions of the reaction (e.g., **8** → **9** or **10**). Silver ion induced solvolysis of these iodo ethers takes place with retention of configuration, by way of an oxiranium ion intermediate, and furnishes either the fused tetrahydropyran (**11**) or ring-contracted tetrahydrofuran (**12**), depending on the directing effect of the substituents and the inherent torsional bias of the bicyclic system. With appropriate choice of substituents, an angular methyl group can be placed at either of the ether centers which are generated in the course of the reaction. The iterative nature of the strategy is demonstrated by synthesis of the tricyclic diether **40**. The method can also be extended to construction of the homologous oxepane moiety. Compound **34**, with the desired trans-syn-trans stereochemistry, is generated on solvolysis of the axial iodide **31**; however, the latter compound is formed as the minor product of iodocyclization.

Seldom are new classes of natural products identified with structures as radically different from the norm as the brevetoxins.[1] Some six members of this class of toxins have been isolated from the dinoflagellate *Gymnodinium breve*; five of them have been shown to have the undecacyclic framework of trans-syn-trans-fused oxane, oxepane, and oxocane rings represented by brevetoxin B. They are potent neuro- and cardiotoxins that exert their effect by locking sodium channels in the open form,[2] in contrast to other shellfish poisons such as saxitoxin and tetrodotoxin that block these channels. Virtually all of the stereocenters in the brevetoxins are contained in vicinally oxygenated carbons, which suggests that stereocontrolled functionalization of a polyolefin precursor may be be involved in their biosynthesis, as has been proposed for the catenated polyethers such as monensin.[3] Such a sequence involving epoxide intermediates is also being explored as a strategy for synthesis of the brevetoxins.[4] Relatively few methods have been reported for construction of the pyranopyran ring system,[5] and only those reported recently by Kozikowski and Ghosh[6] and Nicolaou et al.[4] are readily adapted to the fusion of additional ether rings. We now present a sequence involving electrophilic olefin cyclization as a strategy for the iterative and stereocontrolled formation of trans-syn-trans-fused ethers of the brevetoxin type.

We recently reported a strategy for construction of trans-2,5-disubstituted tetrahydrofurans by the cyclization/ring contraction sequence **1** →→ **3** → **4**.[7] We reasoned that the oxiranium interemediate **3** could serve equally well as a precursor to a 2-hydroxytetrahydropyran (**3** → **5**) with appropriate electronic or geometric direction in the solvolysis process. Indeed, the elements of this strategy were demonstrated by using thallium(III) as the electrophile.[8] From intermediate **5** an iterative process for the sequential introduction of trans-syn-trans-fused ether rings can be envisaged (**5** →→ **6** →→ **7** ...) (Scheme I).



brevetoxin B

Results

(Note: preparation of the 2-alkenylcyclohexanol substrates will be described at the end of the Dicussion section).

Formation of the 6,6-Ring System. We reasoned that two structural aspects of the oxiranium intermediate **3** would be crucial in controlling the ring size of its solvolysis product: substituents which exert a Markovnikov-type orientational effect and torsional or geometric constraints that favor formation of one over the other ring system. To explore these effects, we chose the *trans*-2-(2-alkenyl)-cyclohexanols **8** as model substrates, by using the cyclohexane ring to represent the preceding ether in an iterative sequence. The trisubstituted alkene **8a** is discussed first, since the orientational effects in this case are quite straightforward (Scheme II).

Iodocyclization of alkenol **8a** under thermodynamically controlled conditions (I_2/acetonitrile) gives the 6,6-iodide **9a**, albeit in poor yield. In contrast, the products of both stereoelectronic[9] and Markovnikov control, the 6,5-isomers **10a** (10:1 stereoisomer ratio), are produced in 80% yield with *N*-iodosuccinimide in dichloromethane at 0 °C. Treatment of this isomer mixture with silver tetrafluoro-

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(4) Nicolaou, K. C.; Duggan, M. E.; Ladduwahetty, T. *Tetrahedron Lett.* **1984**, *25*, 2069-72. Nicolaou, K. C.; Duggan, M. E.; Hwang, C. K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359-62.

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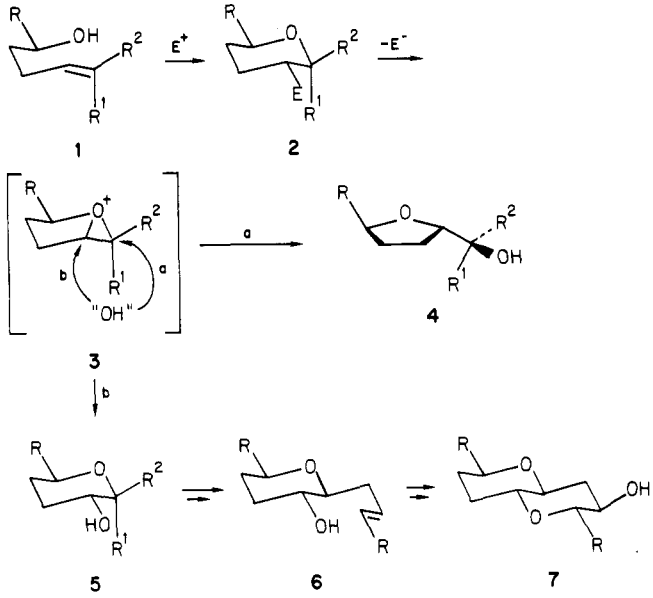
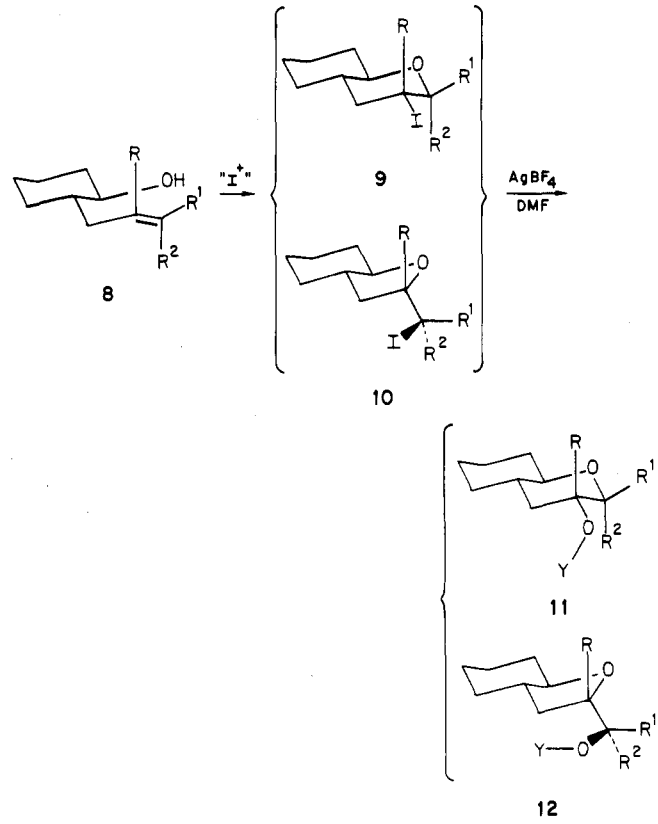
(9) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. Baldwin, J. E.; Kruse, L. I. *Ibid.* **1977**, 233.

0022-3263/86/1951-2230$01.50/0

Scheme I



Scheme II



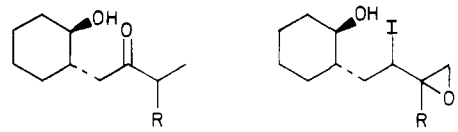
borate in dimethylformamide, followed by aqueous work-up leads to the ring-expanded 6,6-formate **11a-F** in 60% yield. This isomer is the expected product from solvolysis of the oxiranium ion intermediate by attack at the tertiary center, i.e., "Markovnikov-type" orientation. No formate or alcohol with the 6,5-skeleton was observed in the product; nor was any material identified as arising from reaction of the minor stereoisomer of **10b**, the solvolysis of which would require a boat-like oxiranium ion. As we reported previously, the acetate ester **11a-A** can be produced directly from **8a** in 50% yield on treatment with thallium triacetate in acetic acid.[7]

The disubstituted alkenol **8b** lacks any electronic bias to the regiochemical outcome of the cyclization/ring expansion sequence; hence, it provides an indication of the degree to which the transition state for solvolysis of the oxiranium ion reflects the greater stability of trans-fused decalin- over hydrindan-type systems. In this instance, the optimal cyclization conditions proved to be iodine in acetonitrile, which give the thermodynamically favored trans-fused 6,6-iodide **9b** in 90% yield. Solvolysis of this iodide ($AgBF_4$/DMF, then H_2O) leads to alcohol **11b-H** and its formate ester **11b-F** in a combined yield of 72%. That the iodide in **9b** is replaced with retention of configuration, i.e., double inversion, is evidence for the intermediacy of the oxiranium ion. It is interesting to note that the opening of this oxiranium intermediate is directed toward the thermodynamically favored product isomer, even in the absence of Markovnikov effects. In this instance, the direct thallium-induced cyclization of **8b** is considerably less efficient, affording a 4:1 mixture of the acetates **11b-A**:**12b-A**, respectively, with the hydroxy ketone **13** as the major product.[7]

The more highly functionalized, disubstituted alkenol **8c** was also studied. Either the 6,5-iodide **10c** (6.5:1 ratio of stereoisomers, 80% yield) or the 6,6-isomer **9c** (54% yield) can be prepared selectively, depending upon whether sodium carbonate is included (kinetic control) or excluded (thermodynamic control) from the reaction mixture (iodine/acetonitrile). In the latter case, iodo epoxide **14** is a side product produced on formation of **9c**. The isomeric iodo ethers **9c** and **10c** give the same major products on solvolysis, the 6,6-formate **11c-F** and -alcohol **11c-H**. The conversion of 6,6-iodide **9c** to **11c** (66% combined yield) is considerably more efficient than solvolysis of the 6,5-isomer **10c**, which furnishes the regioisomeric 6,5-alcohol

a, R = R^1 = Me; R^2 = H
b, R = R^2 = H; R^1 = Me
c, R = R^2 = H; R^1 = CH_2OCH_2Ph
d, R = H; R^1 = R^2 = Me
e, R = H; R^1 = CH_2OCH_2Ph; R^2 = Me
f, R = H; R^1 = CH_2OCH_2-2,4-$Cl_2C_6H_3$; R^2 = Me
g, R = H; R^1 = CH_2O_2C-2,4-$Cl_2C_6H_3$; R^2 = Me
-H, Y = H
-F, Y = CHO
-A, Y = $COCH_3$

12c-H in 11% yield along with only 22% of the desired 6,6-products. The different product distribution in the two solvolyses indicates that they do not proceed through the same oxiranium ion.

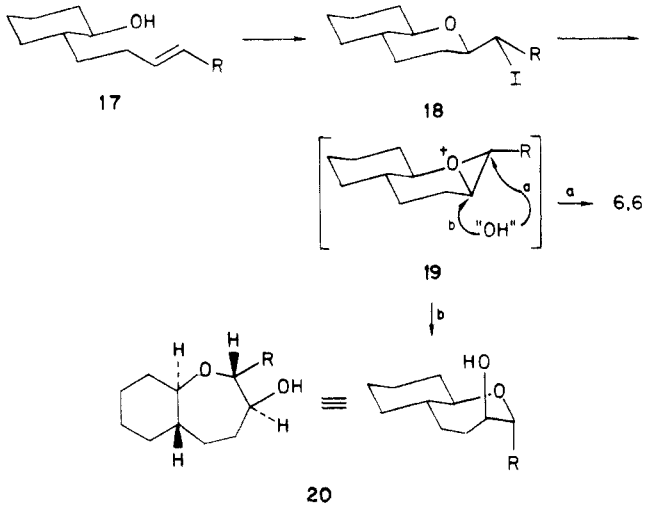


13, R = H
15, R = Me

14, R = H
16, R = Me

In cyclization/solvolysis of the alternative trisubstituted olefin **8d**, the electronic and torsional orienting effects are opposed. *N*-iodosuccinimide induced cyclization affords the 6,6-iodide **9d** in 74% yield; however, solvolysis leads to a mixture of formates in which the ring-contracted 6,5-isomer **12d-F** predominates over the 6,6-compound **11d-F** (37% and 14%, respectively). A major side product in this solvolysis is the hydroxy ketone **15** (10% yield), arising from hydride migration from the oxiranium ion. Reaction of **8d** in the presence of thallium acetate proceeds more cleanly to give a 4.5:1 mixture of **12d-A**:**11d-A** in 70% yield. With the trisubstitution pattern of **8d**, it is clear that the electronic effects are stronger that the torsional ones. We, therefore, investigated some allylically substituted derivatives of this material in order to tip the balance in the other direction.

Scheme III

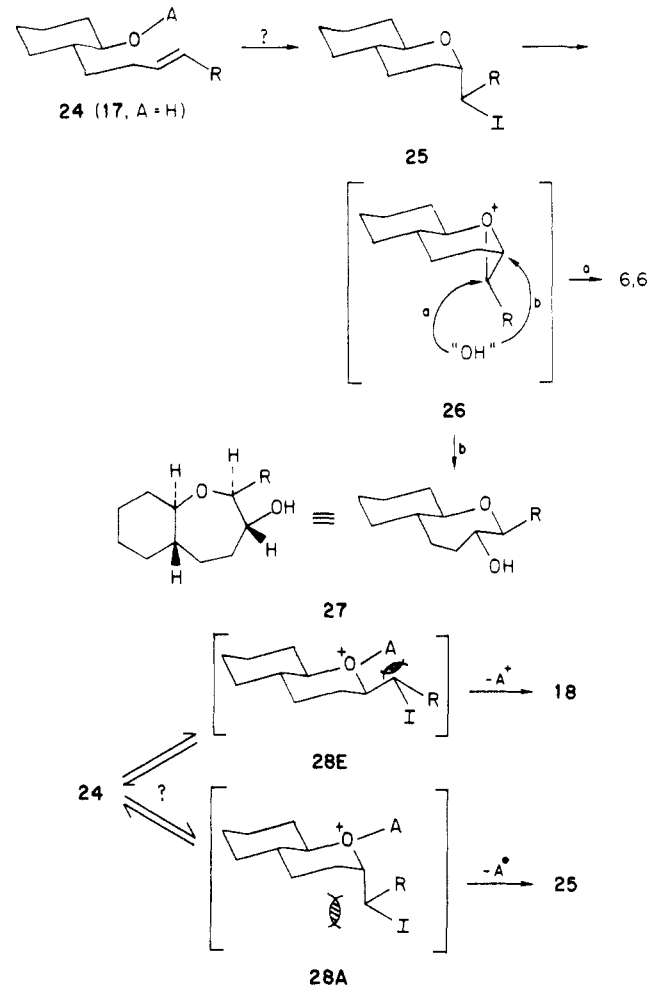


The first such substrate to be investigated was the simple benzyl ether **8e**; however, iodocyclization of this material produces a significant amount of the iodo epoxide (45% of **9e** vs. 22% of **16**). Use of the 2,6-dichlorobenzyl ether **8f** avoids this problem, affording a 6,6-iodide **9f** which undergoes solvolysis to a 2:1 ratio of 6,6:6,5-formates **11f-F**:**12f-F** (55% yield). Even higher selectivity for the desired 6,6-isomer can be obtained by using the more electron-withdrawing 2,4-dichlorobenzoate ester **8g**: the 6,6-iodide **9g** affords a 14:1 mixture of formates **11g-F** and **12g-F** (62% yield), accompanied by some of the corresponding alcohols **11g-H** and **12g-H** (10% yield as 1.3:1 ratio). It is therefore clear that with proper derivatization, an angular methyl group can be introduced at either position of the cyclization site.

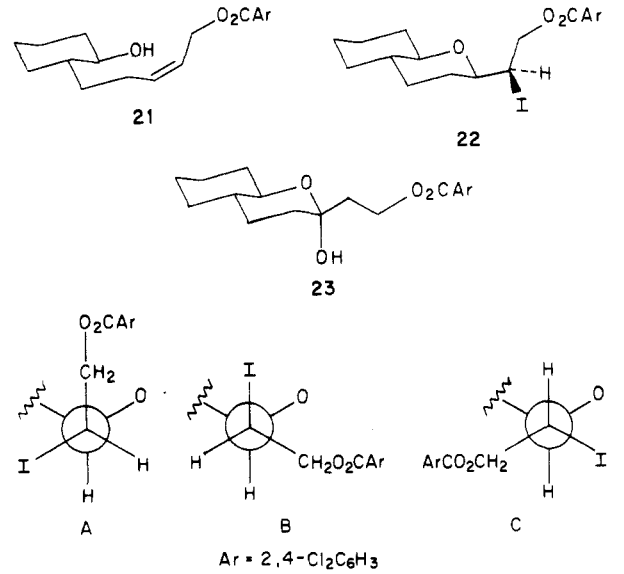
Formation of the 6,7-Ring System. In principle, analogous compounds incorporating a seven-membered ether ring could be generated by cyclization/ring expansion of a chain-extended substrate (Scheme III). Examination of this sequence from the point of view of stereochemistry indicates that the undesired trans-anti-trans product **20** would be generated in the expected course of events, namely cyclization to give the equatorially substituted 6,6-ether **18** followed by ring expansion via oxiranium intermediate **19**. One approach that we investigated to circumvent this problem involves cyclization of the cis isomer of olefin **17** (interchange of H and R in structure **20**). This strategy would generate the desired configuration α to the ether; the oxygen substituent at the β-position could be inverted subsequently.

We chose ester **21** as the model substrate, incorporating the allylic 2,4-dichlorobenzoate group as the directing moiety for ring expansion. This material undergoes cyclization in the anticipated sense with iodine in acetonitrile at 0 °C, buffered with solid $NaHCO_3$, to give the equatorial 6,6-iodo ether **22** in 80% yield. On treatment under the normal conditions for solvolysis of iodides **9** or **10** ($AgBF_4$ in DMF, then H_2O), compound **22** affords the hemiketal **23** as the major product (54% yield); none of the expected 6,6- or 6,7-formates are discernible. Formation of the ketal rather than the desired ring-expansion product can be explained with reference to the Newman projections A, B, and C which depict the staggered conformations around the side chain bond. By virtue of gauche interactions between the (acyloxy)methyl group and the tetrahydropyran ring, ground-state conformation A is the least stable, yet it is the one from which the desired oxiranium ion would be formed. The most stable conformation is likely to be B, from which the observed hydride migration or

Scheme IV

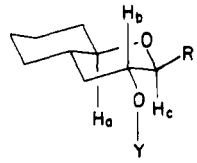


proton loss (and subsequent readdition) is easily rationalized.



An alternative solution to the stereochemical problem posed by the 6,7-ring system would be to drive the cyclization of trans alkene **17** toward the less stable axial product **25** (Scheme IV). Ring expansion of this isomer via oxiranium ion **26** would then lead directly to the desired configuration at both the new stereocenters (**27**). The challenge in this approach clearly is to overcome the driving force leading to formation of the equatorial product

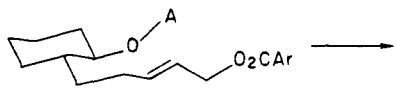
Table I. Selected ^1H NMR Chemical Shifts for Bicyclic 6,6-Esters



compd	δ (mult, J) H_a (ddd)	H_b	H_c
11a-F	2.98 (4, 10, 10)	–	3.58 (q, 6.4)
11a-A	2.97 (4, 10, 10)	–	3.54 (q, 6.4)
11b-F	2.95 (4.6, 10, 10)	4.61 (ddd, 5, 10, 10)	3.44 (dq, 9.5, 6.2)
11c-F	2.96 (4, 10, 10)	4.90 (ddd, 5, 10, 10)	3.57 (m)
11d-F	3.15 (3, 10, 10)	4.80 (dd, 5, 8.5)	–
11d-A	3.16 (m)	4.67 (dd, 4.6, 11)	–
11f-F	3.17 (m)	5.06 (dd, 5, 11)	–
11g-F	3.22 (3.7, 10, 10)	5.19 (dd, 4.8, 10.6)	–
37	2.94 (3.8, 10, 10)	–	3.38 (dd, 2.3, 10)
40	–	4.69 (ddd, 5.3, 10, 10)	3.59 (ddd, 2.1, 9.6, 9.6)

in the initial cyclization reaction. To do this we resorted to a tactic used with success in a method we had devised for the synthesis of cis-2,5-substituted tetrahydrofurans,[10] namely incorporation of a "steric auxiliary". We reasoned that cyclization of an ether such as **24** would lead initially to oxonium ions **28** in which the $A^{1,3}$-type interaction encountered in the equatorial isomer **28E** could counter the steric congestion of the axial isomer **28A**. The stereoselectivity of the cyclization process would then depend on the relative importance of these competing effects and the opportunity for equilibration of the oxonium ion prior to loss of the steric auxiliary.

Cyclization of the benzyl ether **29a** with iodine in acetonitrile affords a 1:2.1 ratio of the axial (**31**) and equatorial (**30**) isomers in 90% yield. The ratio is improved to 1:1.6 on cyclization of the 4-bromobenzyl ether **29b** (85% yield). With the analogous 2,4-dichlorobenzyl derivative **29c** the cyclization is impeded to the extent that no iodo ether is obtained, and with the bulkier dichlorobenzhydryl ether **29d**, the selectivity in favor of the equatorial isomer is increased to 1:4. These latter two examples indicate that the electronic characteristics of the ether substituent are critical: if loss of this group as the cation is either too slow or too fast, the cyclization does not occur or the desired stereoselectivity is not manifested.



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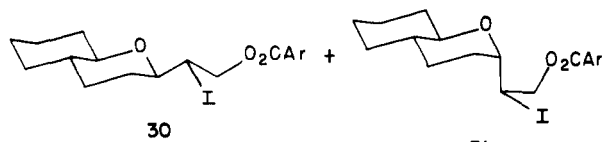
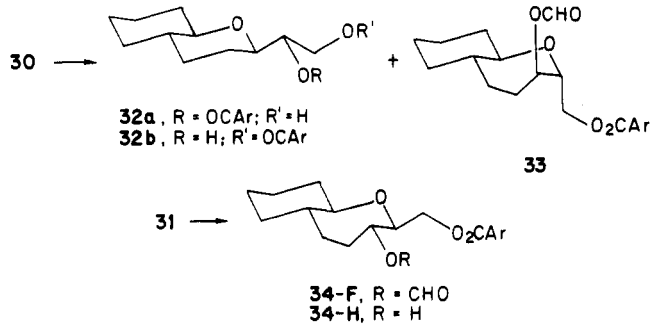


30 31

a, A = $CH_2OCH_2C_6H_5$
b, A = CH_2OCH_2-4-BrC_6H_4
c, A = CH_2OCH_2-2,4-$Cl_2C_6H_3$
d, A = $CH_2OCH(4\text{-}ClC_6H_4)_2$

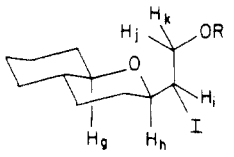
Ar = 2,4-$Cl_2C_6H_3$

From solvolysis of the equatorial isomer **30** under the standard conditions we isolated only three products: the 6,6-alcohols **32a** and **32b** in 23% and 6% yield, respectively, and the anticipated *trans-anti-trans*-6,7-formate **33** in only 4% yield. The gross structures of these materials were readily discerned by ^1H NMR; however, the assignment of stereochemistry rests on the presumed mechanism of their formation. The isomeric 6,6-products probably arise from participation of the ester carbonyl in attack on the oxiranium ion, with subsequent hydrolysis by attack at the benzylic position. In contrast, solvolysis of the axial isomer **31** affords only two products of significance: the desired *trans-syn-trans*-6,7-formate **34-F** and -alcohol **34-H** in a combined yield of 42%. These compounds were correlated chemically, and the gross and stereostructure of the formate was demonstrated by two-dimensional ^1H COSY and NOESY experiments as described below. Although we have not investigated this approach to the 6,7-system fully or obtained a preponderance of the desired isomer, the basic premise of our strategy appears to be valid.



Formation of a Tricyclic Model by Sequential Ring Formation. To demonstrate the iterative nature of this strategy, we investigated the sequential cyclization/solvolysis of 2-(alkadienyl)cyclohexanol **35**. This particular substitution pattern was chosen to allow us to explore the cyclization of a tertiary alcohol as well. In analogy to the behavior of the lower homologue **8**, cyclization of **35** with *N*-iodosuccinimide affords the 6,5-iodide **36** (12:1 isomer ratio) in 96% yield. Solvolysis as usual with $AgBF_4$ in DMF gives the desired 6,6-formate **37** in 54% yield. Saponification of the formate and treatment of the tertiary alcohol **38** with iodine in acetonitrile lead in turn to the 6,6,6-iodide **39** as the only characterizable product (64% yield). Finally, solvolysis of this compound provides the *all-trans,syn*-fused tricyclic target **40**. Although this compound is the major product, it is accompanied by the 6,6,5-isomer **41** as a minor component (3:1 ratio of **40**:**41**, combined yield 55%). It is not immediately clear why the presence of the angular methyl group would diminish the selectivity of this solvolysis (in comparison to the analogous transformation of **9b**), especially in view of the predomi-

(10) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963–4.



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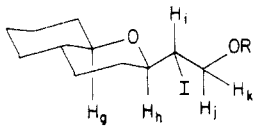

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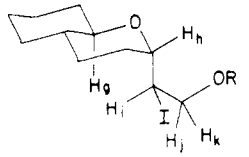
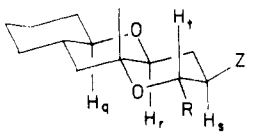
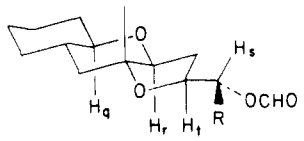


H	22	30	31
H_g (ddd)	3.01 (3.5, 9.5, 9.5)	2.96 (4.0, 10, 10)	3.13 (m)
H_h (ddd)	3.09 (3, 3, 10.3)	3.46 (2.0, 7.3, 10.7)	4.25 (ddd, <1, 5.6, 11.1)
H_i (ddd)	4.30 (3.4, 7, 7)	4.28 (app q, J = 6)	4.88 (3.5, 7.2, 10.9)
H_j (dd)	4.65 (6.5, 11.7)	4.69 (d, 2 H, 5.8)	4.57 (7.0, 12.2)
H_k (d)	4.71 (7.0, 11.6)	*a*	4.77 (3.3, 12.2)

[a] H_j and H_k are coincident.



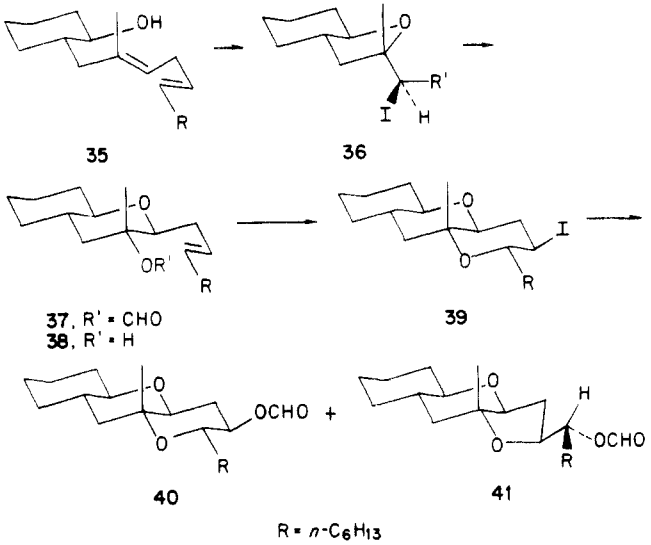
39, Z = I
40 Z = OCHO



41

H	39	40	41
H_q (ddd)	2.99 (3.8, 10, 10)	3.00 (3.9, 10, 10)	3.04 (3.8, 10, 10)
H_r (dd)	3.06 (4.0, 12.1)	3.15 (3.9, 12.6)	3.50 (4.4, 12.5)
H_s (ddd)	3.85 (4.7, 11, 11)	4.69 (5.3, 10, 10)	5.18 (br s, J < 6.5 Hz)
H_t (ddd)	3.77 (2.3, 11, 11)	3.59 (2.1, 10, 10)	3.74 (br ddd, <3, 5, 5)

nance of the tetrahydropyran isomer under the thermodynamically controlled conditions which lead to iodo ether **39**.



35 36

37, R' = CHO
38, R' = H

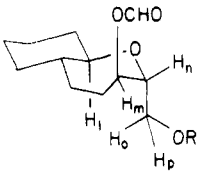
39

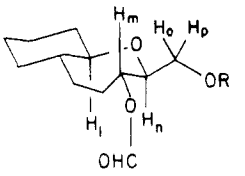
40 41

R = *n*-C_6H_{13}

Structural and Stereochemical Assignments of Ether Intermediates. The primary key to unraveling the structures of the cyclization/solvolysis products was analysis of the formate esters: the downfield shift induced in the carbinol proton by the ester moiety indicated which carbon it was attached to. Tables I and II list the relevant ^1H NMR data for the bicyclic 6,6- and 6,5-esters. The stereochemistry of the 6,6-compounds was in turn revealed by the trans-diaxial coupling constants between H_b and H_c (when relevant) and their neighboring protons; the indicated stereochemistry for the 6,5-isomers was inferred from the presumed mechanism of the solvolyses.

Iodocyclization of the homologues **21** and **29** leads unambigously to the bicyclic 6,6-iodo ethers **22** and **30** and **31**, respectively. The configuration of the latter isomers was assigned straightforwardly by ^1H NMR: compound **30** shows coupling constants of 2.0 and 10.7 Hz between H_h and the adjacent, endocyclic hydrogens; the corresponding coupling constants for the axial isomer **31** are <1 and 5.6 Hz. As indicated above, solvolysis of the equatorial isomer **30** leads to a mixture of the 6,6-hydroxy esters **32** and the trans-anti-trans-6,7-formate **33**. These isomers were readily distinguished and assigned by ^1H as well (data recorded in Experimental Section). NMR comparison of the bicyclic 6,7-formates **33** and **34-F** produced on solvo-





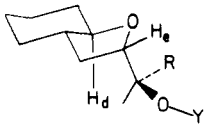
H	33	34-F
H_l	2.94 (m)	3.05 (ddd, 3.9, 10, 10)
H_m	3.67 (ddd, 3, 3, 7.7)	3.90 (app q, 6.0)
H_n	5.36 (ddd, 3, 3, 7)	5.21 (ddd, 3.6, 7, 7)
H_o	4.51 (dd, 7.7, 12.1)	4.35 (d, 2 H, 5.5)
H_p	4.63 (dd, 3.3, 12.1)	*a*

[a] H_o and H_p are coincident.

lysis of the equatorial and axial isomers **30** and **31**, respectively, reveals a number of subtle differences; however, there is no firm basis for stereochemical assignment. That isomer **34-F** had the desired trans-syn-trans stereostructure shown was demonstrated unambiguously by 2D NMR. The COSY spectrum revealed the connectivity: H_m (ddd, δ 5.21) ← (J = 6.0 Hz) → H_n (dt, δ 3.90) ← (J = 5.5 Hz) → H_o, H_p (d, δ 4.35) (magnetically equivalent). Assignment of the syn relationship between H_l and H_n was supported by a strong cross peak in the NOESY spectrum between their resonances (δ 3.90 (dt) and 3.05 (ddd), respectively) and by the absence of a cross peak between those for H_m (δ 5.21 (ddd)) and H_l.

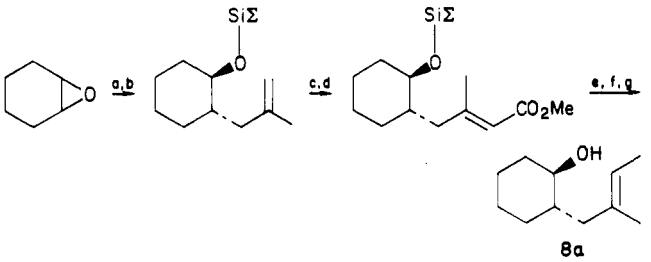
Assignment of stereochemistry of the intermediates in construction of the tricyclic system **40** was straightforward,

Table II. Selected ^1H NMR Chemical Shifts for Bicyclic 6,5-Esters



compd	δ (mult, J) H_d (ddd)	H_e
12d-A	3.15 (3.6, 10, 10)	4.06 (dd, 6.4, 9.5)
12f-F	3.08 (3.8, 10, 10)	4.22 (dd, 6.4, 9.6)
12g-F	3.16 (m)	4.40 (dd, 6.9, 9.4)
41	–	3.74 (dd, 5.5, 5.5)

Scheme V[a,b]



[a] Σ = *t*-BuMe$_2$Si. [b] (a) ClMgCH$_2$C(CH$_3$)=CH$_2$, CuI, Et$_2$O, 94%; (b) ∑SiCl, TEA, DMAP, THF–DMF, Δ, 80%; (c) O$_3$, MeOH, –60 °C; Me$_2$S, 88%; (d) Et$_2$O$_3$PCH$_2$CO$_2$Me, NaH, THF, Δ, 87%; (e) Dibal, –78 → 0 °C, Et$_2$O; HPLC, 54% of (*E*), 14% of (*Z*); (f) Pyr-SO$_3$, THF; LiAlH$_4$, 67%; (g) 48% aqueous HF, MeCN, 0 °C, 97%.

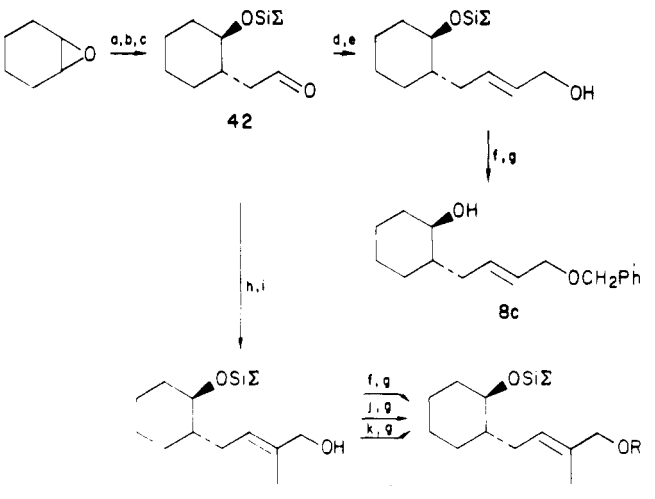
based on analogy with the simpler compounds. The bicyclic ether **37**, for example, shows NMR shifts and coupling constants for the hydrogens α to the ether oxygen similar to those for compounds **11a-F** and **-A** (see Table I). Most diagnostic for the trans-syn-trans 6,6,6-compounds **39** and **40** is the fact that the coupling patterns for all of the hydrogens on oxygenated carbons reveal clear trans-diaxial relationships. In contrast, the minor isomer from the final solvolysis shows smaller coupling constants for H_s and H_t indicating that the terminal ring is five-membered.

Synthesis of Cyclization Substrates. Trisubstituted isomer **8a** was generated as shown in Scheme V. Little comment is necessary except to note that the Wadsworth–Emmons condensation produces a 7:1 mixture of *E*:*Z* isomers which are not separated until after reduction to the allylic alcohols.

The di- and trisubstituted olefins **8b** and **8d** have been produced by the copper-catalyzed addition of the appropriate Grignard reagents to cyclohexene,[11,12] although we synthesized both **8c** and **8d** from the acetaldehyde derivative **42**. As shown in Scheme VI, we used **42** as a key intermediate in the preparation of compounds **8c–g**.

Derivatives of the homologous propionaldehyde **43** were the key intermediates for synthesis of the cyclization substrates leading to the 6,7-systems (Scheme VII). Condensation of the silyl ether with methyl bis(trifluoroethyl) phosphonacetate according to Still and Gennari[13] provded the cis acrylate with high selectivity; the analogous trans isomer was produced with the conventional Wittig reagent. A combination of reduction and appropriate acylation, alkylation, and deprotection steps then furnished the cyclization substrates **21** and **29a–e**.

Scheme VI[a]



8e, R = CH_2Ph
8f, R = CH_2-2,6-$Cl_2C_6H_3$
8g, R = CO-2,4-$Cl_2C_6H_3$

[a] (a) LiCH$_2$CN, THF, 0 °C, 78%; (b) ∑SiCl, TEA, DMAP, THF–DMF, 88%; (c) Dibal, PhCH$_3$, –78 → 0 °C, 86%; (d) Ph$_3$P=CHCO$_2$Me, CHCl$_3$, Δ, 86%; (e) Dibal, –78 → 0 °C, PhCH$_3$, 85%; (f) KH, PhCH$_2$Br, THF, DMF, >90%; (g) 48% aqueous HF, MeCN, 0 °C, >90%; (h) Ph$_3$P=CHCO$_2$Me, CHCl$_3$, Δ, 90% (12:1 *E*:*Z*); (i) Dibal, –78 → 0 °C, PhCH$_3$, 94%; (j) KH, PhCH$_2$Br, THF, DMF, 100%; (k) 2,4-Cl$_2$-PhCOCl, TEA, DMAP, CH$_2$Cl$_2$, 90%.

A number of routes were explored for formation of the (*E*,*E*)-alkadienyl derivative **35** (Scheme VIII), starting with the protected derivative of the known alcohol **44**.[14] This material undergoes carbometalation with high regioselectivity according to the procedure of Van Horn and Negishi,[15] as shown by iodination or protonation. Neither the alanate **46c** derived from the vinyldimethylalane intermediate **46a** nor the vinyllithium **46d** or cuprate **46e** produced on transmetalation of the iodide **46b** could be induced to couple with a propargylic or crotyl halide in good yield. In contrast, the reaction between cyanocuprate **46f** and the allenyl bromide **47**[16] affords enyne **48** in 72% yield. Lithium in ammonia reduction followed by deprotection then give the (*E*,*E*)-diene **35** stereospecifically.

Experimental Section

General Methods. Unless otherwise indicated, NMR spectra were obtained in $CDCl_3$ solution at 250 MHz; spectral data are presented as follows: chemical shift (relative to internal tetramethylsilane as 0 ppm) (multiplicity, number of protons, coupling constants in hertz). IR spectra were also obtained in $CDCl_3$ solution. Unless otherwise indicated, all reaction workups culminated in washing the organic layer with brine, drying over $MgSO_4$, and evaporating under reduced pressure on a rotary evaporator. Preparative chromatography was performed on silica gel according to the method of Still.[17] Thin-layer chromatography was performed on E. Merck silica gel-60 F-254 plates of 250-μ thickness.

General Cyclization Procedure A: (1*R,3*S**,4*R**,6*S**)-4-Iodo-3-methyl-2-oxabicyclo[4.4.0]decane (9b).** To 300 mg (1.94 mmol) of alcohol **8b** in 10 mL of dry acetonitrile cooled to 0 °C under nitrogen was added 1.23 g (4.86 mmol) of iodine. After being stirred in the dark at 0 °C for 3 h, the reaction mixture was diluted with 40 mL of ether, washed with 25 mL of saturated $Na_2S_2O_3$, and worked up, and the crude product was purified by

(11) Felkin, H.; Frajerman, C.; Roussi, G. *Bull. Soc. Chim. Fr.* **1970**, 3704.
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(15) Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252. Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.
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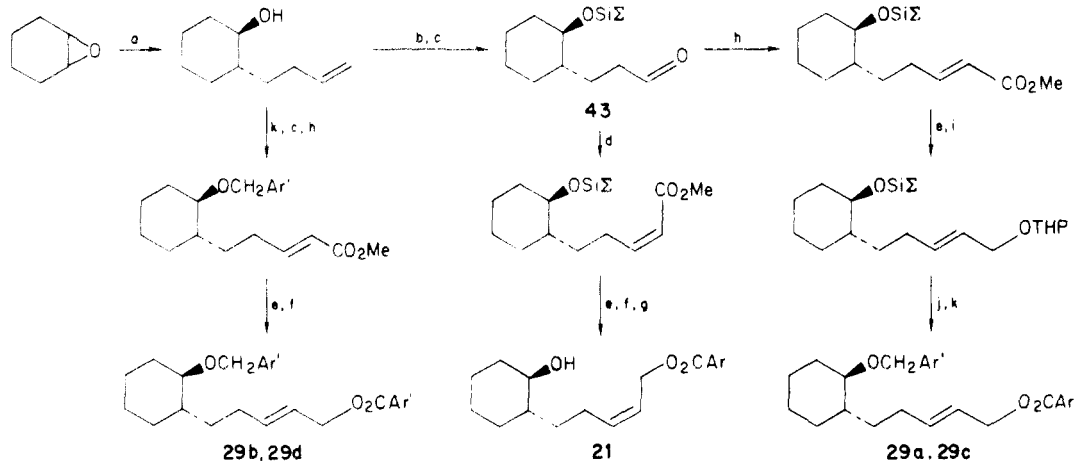
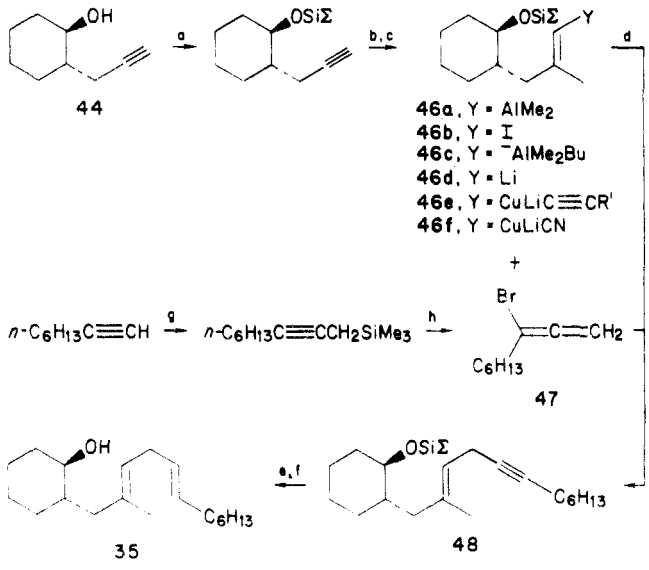
(17) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Scheme VII[a]



[a] (a) $BrMgCH_2CH_2CH{=}CH_2$, CuI, Et_2O, 66%; (b) ΣSiCl, TEA, DMAP, THF–DMF, Δ, 75%; (c) O_3, MeOH, −60 °C; Me_2S, >50%; (d) $(CF_3CH_2)_2O_3PCH_2CO_2Me$, $KN(Me_4Si)_2$, THF, 18-C-6, 56%; (e) Dibal, Et_2O, −78 → 0 °C, >95%; (f) 2,4-$Cl_2C_6H_3COCl$, TEA, DMAP, CH_2Cl_2, >90%; (g) 48% aqueous HF, MeCN, 0 °C, >85%; (h) $Ph_3P{=}CHCO_2Me$, $CHCl_3$, Δ, >90%; (i) DHP, PPTS, CH_2Cl_2, 93%; (j) Nu_4NF, TEA, THF, Δ, 90%; (k) Ar'CH_2Br, $KN(Me_4Si)_2$, THF–DMF, >75%; (l) PPTS, EtOH, Δ or AcOH, aqueous THF, Δ, >85%.

Scheme VIII[a]



[a] (a) ΣSiCl, TEA, DMAP, THF–DMF, Δ, 90%; (b) Cp_2ZrCl_2, 3 equiv Me_3Al, CH_2Cl_2; (c) **46a** → **46b**: I_2, Et_2O, 92%; (d) **46b** → **48**: *sec*-BuLi, THF, −78 °C; CuCN; **47**, 72%; (e) Li, NH_3, THF, 2 equiv $(NH_4)_2SO_4$, 5 equiv *t*-BuOH, −40 °C, 72%; (f) *n*-Bu_4NF, TEA, THF, 88%; (g) *n*-BuLi, THF, HMPA, $CF_3SO_3CH_2SiMe_3$, −78 °C, 76%; (h) Br_2, CH_2Cl_2, −78 °C, 41%.

chromatography (5% ether–hexane) to give 485 mg (89% yield) of **9b** as a white solid: mp 35–37 °C; R_f 0.48 in 10% ethyl acetate–hexane; IR 2940, 1450, 1145, 1080 cm^{-1}; ^1H NMR δ 0.87–1.13 (m, 1), 1.13–1.54 (m, 4), 1.44 (d, 3, J = 6.1), 1.54–1.73 (m, 2), 1.73–2.00 (m, 3), 2.42 (ddd, 1, J = 3.9, 3.9, 13.0), 3.05 (ddd, 1, J = 4.1, 9.9, 9.9), 3.66 (dq, 1, J = 6.0, 11.1), 3.90 (ddd, 1, J = 4.4, 10.9, 10.9). Anal. Calcd for $C_{10}H_{17}IO$: C, 42.87; H, 6.13; I, 45.29. Found: C, 43.12; H, 6.11; I, 44.98.

(1*R,3*S**,4*R**,6*S**)-3-((Benzyloxy)methyl)-4-iodo-2-oxabicyclo[4.4.0]decane (9c) and (1*R**,2*S**)-2-(3,4-Epoxy-2-iodobutyl)cyclohexan-1-ol.** According to general cyclization B (see below), 102 mg (0.392 mmol) of alcohol **8c** was converted to 81 mg (54% yield) of iodo ether **9c** as a light yellow solid and 17 mg (15% yield) of epoxide as a yellow liquid. Iodo ether **9c**: mp 76–78 °C; R_f 0.44 in 20% EtOAc–hexane; IR 2950, 1460, 1070 cm^{-1}; ^1H NMR δ 0.83–1.51 (m, 6), 1.51–2.03 (m, 4), 2.47 (ddd, 1, J = 4.4, 4.4, 12.8), 3.05 (ddd, 1, J = 3.9, 10.0, 10.0), 3.68 (ddd, 1, J = 1.9, 4.2, 10.4), 3.81 (dd, 1, J = 4.2, 10.8), 3.88 (dd, 1, J = 1.8, 10.8), 4.26 (ddd, 1, J = 4.4, 11.7, 11.7), 4.55 (d, 1, J = 12.2), 4.65 (d, 1, J = 12.2), 7.33 (m, 5); ^{13}C NMR δ 24.62, 25.16, 26.98, 30.86, 32.03, 45.10, 45.20, 72.19, 73.49, 82.18, 82.33, 127.47, 127.84, 128.18, 138.12. Anal. Calcd for $C_{17}H_{23}IO_2$: C, 52.85; H, 6.01; I, 32.85. Found: C, 53.10; H, 6.17, I, 32.68. Epoxide: R_f 0.15 in 20% EtOAc–hexane; IR 3600, 2960, 1460, 1090, 1060 cm^{-1}; ^1H NMR δ 0.83–1.48 (m, 5), 1.48–2.14 (m, 6), 2.45 (ddd, 1, J = 4.0, 4.0, 12.9), 3.11 (ddd, 1, J = 4.5, 9.9, 9.9), 3.64 (m, 1), 3.74 (dd, 1, J = 5.7, 11.4), 4.08 (m, 2).

(1*R,4*R**,6*S**)-3,3-Dimethyl-4-iodo-2-oxabicyclo[4.4.0]decane (9d).** According to general cyclization procedure B described below, 300 mg (1.78 mmol) of alcohol **8d** was converted to 391 mg (74% yield) of iodo ether **9d** as a white solid: mp 48.5–50.0 °C; R_f 0.26 in 10% EtOAc–hexane; IR 2940, 1450, 1140, 1070 cm^{-1}; ^1H NMR δ 0.95–1.35 (m, 6), 1.40 (s, 3), 1.49 (s, 3), 1.52–1.70 (m, 1), 1.70–1.86 (m, 2), 2.03 (ddd, 1, J = 12.4, 12.4, 12.4), 2.23 (ddd, 1, J = 4.1, 4.1, 13.2), 3.25 (ddd, 1, J = 3.3, 9.9, 9.9), 4.18 (dd, 1, J = 4.3, 12.7). Anal. Calcd for $C_{11}H_{19}IO$: C, 44.90; H, 6.52; I, 43.13. Found: C, 45.09; H, 6.39; I, 43.25.

(1*R,3*S**,4*R**,6*S**)-3-(((2,6-Dichlorobenzyl)oxy)methyl)-4-iodo-3-methyl-2-oxabicyclo[4.4.0]decane (9f).** According to general cyclization procedure A described above, 400 mg (1.17 mmol) of alcohol **8f** was converted to 299 mg (55% yield) of iodo ether **9f** as a yellow oil: R_f 0.54 in 20% EtOAc–hexane; IR 2940, 1440, 1110, 1070 cm^{-1}; ^1H NMR δ 0.90–1.49 (m, 5), 1.40 (s, 3), 1.49–1.70 (m, 2), 1.70–1.87 (m, 2), 2.03 (ddd, 1, J = 12.6, 12.6, 12.6), 2.26 (ddd, 1, J = 4.1, 4.1, 12.9), 3.27 (ddd, 1, J = 3.6, 10.1, 10.1), 3.60 (d, 1, J = 11.0), 3.65 (d, 1, J = 9.0), 4.67 (dd, 1, J = 4.5, 13.0), 4.80 (d, 1, J = 11.1), 5.00 (d, 1, J = 11.1), 7.17 (dd, 1, J = 7.1, 8.9), 7.28 (d, 1, J = 8.2), 7.31 (dd, 1, J = 1.1, 8.0); MS, m/e (relative intensity) 469 (0.00), 413 (0.01), 341 (3.48), 279 (3.44), 152 (4.87); HRMS calcd for $C_{18}H_{23}Cl_2O_2$ (M − I) 341.1077, found 341.1071.

(1*R,3*S**,4*R**,6*S**)-3-(((2,4-Dichlorobenzoyl)oxy)methyl)-4-iodo-3-methyl-2-oxabicyclo[4.4.0]decane (9g).** According to general cyclization procedure A described above, 350 mg (0.980 mmol) of alcohol **8g** was converted to 253 mg (54% yield) of iodo ether **9g** as a colorless oil: R_f 0.50 in 20% EtOAc–hexane; IR 2940, 1735, 1590, 1450, 1380, 1290, 1110, 1050 cm^{-1}; ^1H NMR δ 0.95–1.44 (m, 5), 1.54–1.70 (m, 2), 1.56 (s, 3), 1.70–1.83 (m, 2), 2.09 (ddd, 1, J = 12.4, 12.4, 12.4), 2.30 (ddd, 1, J = 4.1, 4.1, 13.0), 3.31 (ddd, 1, J = 3.3, 9.9, 9.9), 4.37 (d, 1, J = 11.7), 4.48 (d, 1, J = 11.7), 4.56 (dd, 1, J = 4.4, 12.8), 7.32 (dd, 1, J = 2.0, 8.4), 7.48 (d, 1, J = 2.0), 7.84 (d, 1, J = 8.5); MS, m/e (relative intensity) 355 (1.69), 279 (1.43), 173 (5.20), 165 (5.91); HRMS calcd for $C_{18}H_{21}Cl_2O_3$ (M − I) 355.0869, found 355.0858.

General Iodocyclization Procedure B: (1*R,6*S**,8*R**)-8-((1*S**)-1-Iodoethyl)-8-methyl-7-oxabicyclo[4.3.0]nonane (10a).** To 300 mg (1.78 mmol) of alcohol **8a** dissolved in 8 mL of dry dichloromethane cooled to 0 °C under nitrogen in the dark was added 441 mg (1.96 mmol) of *N*-iodosuccinimide. The resulting solution was allowed to stir at 0 °C for 3.5 h. The reaction

mixture was diluted with 40 mL of CH_2Cl_2, washed with 25 mL of saturated $Na_2S_2O_3$ and 25 mL of 1 N NaOH, and worked up, and the crude product was purified by chromatography (5% ether–hexane) to give 426 mg (81% yield) of **10a** as a colorless liquid: R_f 0.41 in 10% EtOAc–hexane; IR 2950, 1450, 1140, 1060 cm^{-1}; ^1H NMR δ 1.03–1.70 (m, 6), 1.39 (s, 3), 1.70–2.13 (m, 5), 1.93 (d, 3, J = 7.0), 3.25 (ddd, 1, J = 3.6, 10.0, 10.0), 4.23 (q, 1, J = 6.9); ^{13}C NMR δ 22.64, 23.99, 24.15, 25.56, 28.71, 31.64, 39.98, 45.47 and 45.62 at 10:1 ratio for trans:cis isomers, 46.15, 83.17 and 83.35 at 10:1 ratio, 84.08. Anal. Calcd for $C_{11}H_{19}IO$: C, 44.90; H, 6.52; I, 43.13. Found: C, 44.98; H, 6.29; I, 43.32.

(1*R,6*S**,8*R**)-8-((1*S**)-2-(Benzyloxy)-1-iodoethyl)-7-oxabicyclo[4.3.0]nonane (10c) and the 1*R**,6*S**,8*S**(1*R**) Isomer.** According to general cyclization procedure A described above, modified by the inclusion of powdered Na_2CO_3 in the reaction mixture, 30 mg (0.115 mmol) of alcohol **8c** was converted to 36 mg (80% yield) of iodo ether **10c** as a white solid: mp 81–83 °C; R_f 0.38 in 20% EtOAc–hexane; IR 2960, 2880, 1460, 1120, 1050 cm^{-1}; ^1H NMR δ 1.03–1.60 (m, 6), 1.60–2.16 (m, 4), 2.29 (m, 1), 3.11 (ddd, 1, J = 3.5, 6.9, 6.9) and 3.27 (ddd, 1, J = 4.0, 9.8, 9.8) at ratio 1:6.5, 3.76 (dd, 1, J = 6.7, 10.8), 3.83 (dd, 1, J = 5.2, 10.9), 4.13 (m, 1), 4.30 (m, 1), 4.56 (d, 1, J = 12.1), 4.62 (d, 1, J = 12.1), 7.33 (m, 5), Anal. Calcd for $C_{17}H_{23}IO_2$: C, 52.85; H, 6.01; I, 32.85. Found: C, 53.07; H, 5.97; I, 32.74.

(1*R,3*S**,4*R**,6*S**)-3,4-Dimethyl-2-oxabicyclo[4.4.0]dec-4-yl Formate (11a-F).** According to the general solvolysis procedure described below, 313 mg (1.06 mmol) of iodide **10a** was converted to 137 mg (61% yield) of formate **11a-F** as a colorless liquid: R_f 0.59 in 20% EtOAc–hexane; IR 2940, 1720, 1455, 1205, 1110 cm^{-1}; ^1H NMR δ 0.86–1.10 (m, 1), 1.10–1.43 (m, 4), 1.17 (d, 3, J = 6.4), 1.43–1.70 (m, 3), 1.54 (s, 3), 1.81 (m, 1), 1.92 (m, 1), 2.57 (dd, 1, J = 3.3, 12.1), 2.98 (ddd, 1, J = 4.2, 10.0, 10.0), 3.58 (q, 1, J = 6.4), 8.00 (s, 1); ^{13}C NMR δ 14.14, 17.27, 24.33, 24.88, 30.88, 31.46, 39.53, 42.12, 76.03, 81.60, 81.89, 159.38. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.88; H, 9.51. Found: C, 67.92; H, 9.44.

General Solvolysis Procedure: (1*R,3*S**,4*R**,6*S**)-3-Methyl-2-oxabicyclo[4.4.0]dec-4-yl Formate (11b-F) and (1*R**,3*S**,4*R**,6*S**)-3-Methyl-2-oxabicyclo[4.4.0]decan-4-ol (11b-H).** To 200 mg (0.714 mmol) of iodide **9b** in 3 mL of dry DMF under nitrogen was added 208 mg (1.07 mmol) of silver tetrafluoroborate, and the resulting solution was heated in a 70 °C oil bath for 10 h. The reaction mixture was cooled to 21 °C, and the silver iodide was removed by filtering through glass wool and washed with 25 mL of ether. The filtrate was washed with 15 mL of 1 N HCl and with 15 mL of saturated $NaHCO_3$ and worked up. The crude product was purified by chromatography (7% EtOAc–hexane then 30% EtOAc–hexane) to give 89 mg (63% yield) of **11b-F** as a white solid and 11 mg (9% yield) of **11b-H** as a white solid. **11b-F**: mp 46–47.5 °C; R_f 0.46 in 20% EtOAc–hexane; IR 2940, 1720, 1450, 1220 cm^{-1}; ^1H NMR δ 0.92–1.44 (m, 6), 1.21 (d, 3, J = 6.2), 1.54–1.73 (m, 2), 1.73–1.86 (m, 1), 1.86–2.00 (m, 1), 2.10 (ddd, 1, J = 2.7, 4.5, 11.2), 2.95 (ddd, 1, J = 4.5, 9.6, 9.6), 3.44 (dq, 1, J = 6.2, 9.5), 4.61 (ddd, 1, J = 4.8, 9.8, 9.8), 8.06 (d, 1, J = 0.9); ^{13}C NMR δ 18.11, 24.75, 25.21, 31.14, 31.80, 36.31, 40.83, 73.75, 75.19, 81.25, 160.21. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.62; H, 9.17. Found: C, 66.66; H, 9.12. **11b-H**: mp 67–69 °C; R_f 0.18 in 20% EtOAc–hexane; IR 3640, 3450, 2940, 1450, 1090 cm^{-1}; ^1H NMR δ 0.89–1.43 (m, 6), 1.30 (d, 3, J = 5.80), 1.43–1.73 (m, 3), 1.73–2.06 (m, 3), 2.90 (ddd, 1, J = 4.5, 9.8, 9.8), 3.21 (m, 1), 3.30 (ddd, 1, J = 4.6, 9.0, 9.0). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.53; H, 10.68. Found: C, 70.72; H, 10.49.

(1*R,3*S**,4*R**,6*S**)-3-((Benzyloxy)methyl)-2-oxabicyclo-[4.4.0]dec-4-yl Formate (11c-F) and (1*R**,3*S**,4*R**,6*S**)-3-Methyl-2-oxabicyclo[4.4.0]decan-4-ol (11c-H).** According to the general solvolysis procedure described above, 545 mg (1.41 mmol) of iodide **9c** was converted to 228 mg (53% yield) of formate **11c-F** as a colorless liquid and 51 mg (13% yield) of alcohol **11c-H** as a colorless liquid. Formate **11c-F**: R_f 0.40 in 20% EtOAc–hexane; IR 2940, 2870, 1720, 1455, 1190, 1070 cm^{-1}; ^1H NMR δ 1.13–1.51 (m, 6), 1.67 (m, 2), 1.83 (m, 1), 2.00 (m, 1), 2.17 (ddd, 1, J = 4.0, 4.0, 11.7), 2.96 (ddd, 1, J = 3.9, 9.9, 9.9), 3.57 (m, 3), 4.50 (d, 1, J = 12.3), 4.61 (d, 1, J = 12.3), 4.90 (ddd, 1, J = 4.8, 9.6, 10.6), 7.32 (m, 5), 7.93 (s, 1). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.01; H, 7.96. Found: C, 71.11; H, 7.95. Alcohol **11c-H**: R_f 0.17 in 20% EtOAc–hexane; IR 3500, 2940, 1450, 1090 cm^{-1}; ^1H NMR δ 0.95–1.41 (m, 6), 1.57–2.06 (m, 5), 2.92 (m, 2), 3.37 (m, 1), 3.71 (m, 2), 3.76 (dd, 1, J = 4.7, 9.5), 4.56 (d, 1, J = 12.5), 4.61 (d, 1, J = 13.8), 7.33 (m, 5); ^1H NMR (benzene-d_6) δ 0.65–1.63 (m, 9), 1.94 (m, 2), 2.71 (ddd, 1, J = 4.1, 10.0, 10.0), 2.79 (s, 1) 3.39 (ddd, 1 J = 5.5, 9.2, 9.2), 3.64 (m, 1), 3.66 (dd, 1, J = 6.1, 9.5), 3.76 (dd, 1, J = 4.9, 9.6), 4.28 (s, 2), 7.13 (m, 5); ^{13}C NMR δ 24.75, 25.22, 31.21, 31.72, 38.96, 40.40, 69.41, 71.89, 73.50, 79.25, 81.16, 127.64, 128.27, 137.52. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.86; H, 8.77. Found: C, 74.19; H, 8.73.

(1*R,4*R**,6*S**)-3,3-Dimethyl-2-oxabicyclo[4.4.0]dec-4-yl Acetate (11d-A) and 1-Methyl-1-((1*R**,6*S**,8*R**)-7-oxabicyclo[4.4.0]dec-4-yl)ethyl Acetate (12d-A).** To 50 mg (0.297 mmol) of alcohol **8d** in 1.5 mL of a 1:1 acetic acid/acetic anhydride solvent system was added 146 mg (0.356 mmol) of thallium acetate trihydrate. The resulting solution was allowed to stir at 21 °C under nitrogen for 1 h. Saturated NaCl (3 mL) was added in order to precipitate the thallium(I) salts, which were removed by filtration through glass wool and washed with 25 mL of EtOAc. The filtrate was washed with 15 mL of 1 N NaOH and worked up, and the crude product was purified by chromatography (10% EtOAc–hexane) to give 47 mg (70% yield) of a 1:4.5 mixture of **11d-A**, **12d-A** as a colorless liquid: R_f 0.40 in 20% EtOAc–hexane; IR 2940, 1730, 1450, 1370, 1270, 1140, 1060 cm^{-1}; ^1H NMR δ 1.02–2.21 (m, 11), 1.19 (s, 3) and 1.23 (s, 3) for **11d-A** and 1.47 (s, 3) and 1.50 (s, 3) for **12d-A** at ratio 1.0:4.5, 2.00 (s, 3) and 2.04 (s, 3) at ratio 4.5:1.0, 3.16 (m, 1), 4.10 (dd, 1, J = 6.5, 9.3), and 4.67 (dd, 1, J = 4.8, 11.3) at ratio 4.5:1.0. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.98, H, 9.82. Found: C, 68.97; H, 9.78.

(1*R,3*S**,4*R**,6*S**)-3-(((2,4-Dichlorobenzoyl)oxy)-methyl)-3-methyl-2-oxabicyclo[4.4.0]decan-4-ol (11g-H) and Formate Ester (11g-F).** According to the general solvolysis procedure described above, 182 mg (0.377 mmol) of iodide **9g** was converted to 93 mg (62% yield) of formate **11g-F** as a colorless oil and 14 mg (10% yield) of alcohol **11g-H** as a light yellow oil. Formate **11g-F**: R_f 0.31 in 20% EtOAc–hexane; IR 2940, 1730, 1590, 1290, 1180, 1050 cm^{-1}; ^1H NMR δ 1.00–1.57 (m, 5), 1.34 (s, 3), 1.57–1.76 (m, 3), 1.76–1.92 (m, 2), 1.92–2.16 (m, 1), 3.16 (m, 1), and 3.22 (ddd, 1, J = 3.7, 9.8, 9.8) at ratio 1.0:13.8 for [4.3.0]:[4.4.0] ring systems, 4.20 (d, 1, J = 11.7), 4.27 (d, 1, J = 11.7), 4.40 (dd, 1, J = 6.4, 9.4) and 5.19 (dd, 1, J = 4.8, 10.6) at ratio 1.0:13.8, 7.31 (dd, 1, J = 2.0, 8.4), 7.47 (d, 1, J = 2.0), 7.85 (d, 1, J = 8.5), 8.02 (d, 1, J = 0.9) and 8.17 (s, 1) at ratio 13.8:1.0. Anal. Calcd for $C_{19}H_{22}Cl_2O_5$: C, 56.86; H, 5.54; Cl, 17.67. Found: C, 57.01; H, 5.62; Cl, 17.54. Alcohol **11g-H** R_f 0.15 in 20% EtOAc–hexane; IR 3600, 3500, 2940, 1730, 1590, 1290, 1130 cm^{-1}; ^1H NMR δ 1.00–1.51 (m, 5), 1.26 (s, 3), 1.51–1.92 (m, 6), 1.92–2.35 (m, 1), 3.15 (m, 1), 3.74 (dd, 1, J = 4.8, 11.2) and 4.07 (dd, 1, J = 6.3, 9.6) at ratio 1.3:1.0 for [4.4.0]:[4.3.0] ring systems, 4.29 (d, 1, J = 11.3) and 4.35 (d, 1, J = 11.3) vs. 4.52 (d, 1, J = 11.7) and 4.59 (s, 1) at ratio 1.0:1.3, 7.32 (dd, 1, J = 2.0, 8.4), 7.49 (d, 1, J = 2.0), 7.85 (d, 1, J = 8.5).

(1*R,3*R**,6*S**)-3-((1*R**)-2-(((2,4-Dichlorobenzoyl)oxy)-methyl)-1-iodoethyl)-2-oxabicyclo[4.4.0]decane (22).** To 50 mg (0.140 mmol) of alcohol **21** dissolved in 0.75 mL of dry CH_2Cl_2 cooled to 0 °C under nitrogen in the dark was added 29 mg (0.350 mmol) of $NaHCO_3$ and 89 mg (0.350 mmol) of iodine. The resulting mixture was allowed to stir at 0 °C for 1.5 h and then was diluted with 25 mL of EtOAc. The organic solution was washed with 15 mL of saturated $Na_2S_2O_3$ and worked up. The crude product was purified by chromatography (10% ether–hexane) to give 55 mg (81% yield) of **22** as a colorless liquid: R_f 0.59 in 20% EtOAc–hexane; IR 2940, 1735, 1585, 1290, 1240, 1100 cm^{-1}; ^1H NMR δ 0.89–1.06 (m, 1), 1.06–1.44 (m, 5) 1.52–1.95 (m, 7), 3.01 (ddd, 1, J = 3.5, 9.5, 9.5), 3.09 (dt, 1, J = 10.3, 3.0), 4.30 (ddd, 1, J = 3.4, 6.7, 6.7), 4.65 (dd, 1, J = 6.5, 11.7), 4.71 (dd, 1, J = 7.0, 11.6), 7.33 (dd, 1, J = 2.0, 8.5), 7.49 (d, 1, J = 2.0), 7.89 (d, 1, J = 8.4); MS, m/e (relative intensity) 373 (0.04), 355 (1.06), 190 (0.65), 165 (2.01), 131 (3.38); HRMS calcd for $C_{18}H_{21}Cl_2O_3$ 355.0869, found 355.0871.

(1*R,3*S**,6*S**)-3-(2-((2,4-Dichlorobenzoyl)oxy)ethyl)-2-oxabicyclo[4.4.0]decan-3-ol (23).** To 326 mg (0.675 mmol) of iodide **22** dissolved in 3 mL of dry DMF under nitrogen was added 396 mg (2.02 mmol) of silver tetrafluoroborate. The resulting solution was allowed to stir at 21 °C for 2 days, and then 1 mL of saturated NaCl was added in order to precipitate the excess silver tetrafluoroborate. The silver salts were removed by filtration through Celite and were washed with 25 mL of EtOAc. The

filtrate was washed with 15 mL each of 1 N HCl and saturated $NaHCO_3$ and worked up. The crude product was purified by chromatography (20% EtOAc–hexane) to give 135 mg (54% yield) of **23** as a colorless oil: R_f 0.23 in 20% EtOAc–hexane; IR 3600, 2940, 1730, 1590, 1290, 1250, 1100 cm^{-1}; ^1H NMR δ 0.81–0.95 (m, 1), 0.95–1.41 (m, 6), 1.48–1.89 (m, 6), 2.08 (m, 2), 2.73 (s, 1), 3.50 (ddd, 1, J = 3.5, 9.9, 9.9), 4.49 (dt, 1, J = 11.9, 6.3), 4.64 (dt, 1, J = 11.5, 6.1), 7.30 (dd, 1, J = 2.0, 8.5), 7.47 (d, 1, J = 2.0), 7.80 (d, 1, J = 8.4); ^{13}C NMR δ 25.03, 25.73, 26.00, 31.41, 32.29, 34.40, 41.34, 41.36, 61.57, 74.10, 95.80, 126.97, 128.23, 130.94, 132.62, 134.77, 138.32, 164.95. Anal. Calcd for $C_{18}H_{22}Cl_2O_4$: C, 57.91; H, 5.95; Cl, 18.99. Found: C, 58.15; H, 6.10; Cl, 18.77.

(1*R,3*R**,6*S**)-3-((1*S**)-2-((2,4-Dichlorobenzoyl)oxy)-1-iodoethyl)-2-oxabicyclo[4.4.0]decane (30) and the 1*R**,3*S**,6*S**,(1*R**) Isomer (31).** To 1.50 g (2.84 mmol) of 4-bromobenzyl ether **29b** dissolved in 15 mL of dry acetonitrile cooled to 0 °C under nitrogen in the dark was added 2.16 g (8.52 mmol) of iodine. The resulting purple solution was allowed to stir at 0 °C for 21 h and was quenched with 50 mL of saturated $Na_2S_2O_3$. The aqueous solution was extracted twice with 50 mL of EtOAc, and the organic layer was washed once with 50 mL of saturated $NaHCO_3$ and worked up. The crude product was purified by chromatography (3% ether–hexane) to give 723 mg (53% yield) of the equatorial isomer **30** and 440 mg (32% yield) of the axial isomer **31** as colorless liquids. Equatorial **30**: R_f 0.31 in 10% EtOAc–hexane; IR 2940, 1740, 1590, 1300, 1250, 1110 cm^{-1}; ^1H NMR δ 0.95 (m, 1), 1.06–1.54 (m, 6), 1.54–1.95 (m, 5), 2.12 (dd, 1, J = 2.4, 12.5), 2.96 (ddd, 1, J = 4.0, 10.2, 10.2), 3.46 (ddd, 1, J = 2.0, 7.3, 10.7), 4.28 (q, 1, J = 5.9), 4.69 (d, 2, J = 5.8), 7.33 (dd, 1, J = 2.0, 8.4), 7.49 (d, 1, J = 2.0), 7.91 (d, 1, J = 8.4); MS, *m/e* (relative intensity) 375 (0.03), 373 (0.04), 357 (1.33), 355 (1.80), 175 (3.14), 173 (3.48), 165 (4.44), 147 (2.98), 139 (3.48), 131 (2.73), 121 (3.55); HRMS calcd for $C_{18}H_{21}Cl_2O_3$ 355.0869, found 355.0881. Axial **31**: R_f 0.24 in 10% EtOAc–hexane; IR 2940, 1740, 1590, 1300, 1250, 1110 cm^{-1}; ^1H NMR δ 0.83–1.13 (m, 1), 1.13–1.35 (m, 5), 1.48–1.70 (m, 3), 1.70–1.86 (m, 2), 1.86–2.03 (m, 1), 2.40 (d, 1, J = 14.0), 3.13 (m, 1), 4.25 (dd, 1, J = 5.6, 11.1), 4.57 (dd, 1, J = 7.0, 12.2), 4.77 (dd, 1, J = 3.3, 12.2), 4.88 (ddd, 1, J = 3.5, 7.2, 10.9), 7.33 (dd, 1, J = 2.1, 8.5), 7.50 (d, 1, J = 2.0), 7.97 (d, 1, J = 8.5); MS, *m/e* (relative intensity) 357 (0.27), 355 (0.41), 343 (0.06), 341 (0.08), 291 (0.08), 175 (3.53), 173 (3.99), 165 (4.21), 139 (5.19), 121 (5.14); HRMS calcd for $C_{18}H_{21}Cl_2O_3$ 355.0869, found 355.0861.

(1*R,3*R**,4*S**,7*S**)-3-(((2,4-Dichlorobenzoyl)oxy)-methyl)-4-(formyloxy)-2-oxabicyclo[5.4.0]undecane (33), (1*R**,3*R**,6*S**)-3-[(1*S**)-2-((2,4-Dichlorobenzoyl)oxy)-1-hydroxyethyl]-2-oxabicyclo[4.4.0]decane (32a), and (1*R**,3*R**,6*S**)-3-[(1*S**)-1-((2,4-Dichlorobenzoyl)oxy)-2-hydroxyethyl]-2-oxabicyclo[4.4.0]decane (32b).** To a solution of 229 mg (0.474 mmol) of iodide **30** in 2 mL of dry DMF under nitrogen was added 138 mg (0.711 mmol) of silver tetrafluoroborate. The resulting solution was kept at 65 °C for 12 h and then cooled to 21 °C. Saturated NaCl was added in order to precipitate the excess silver ion. The silver salts were removed by filtration through Celite and washed with 25 mL of EtOAc. The filtrate was washed with 10 mL each of 1 N HCl and saturated $NaHCO_3$ and worked up. The crude product was purified by chromatography (10% EtOAc–hexane then 20% EtOAc–hexane) to give 8 mg (4% yield) of formate **33** as a colorless oil, 41 mg (23% yield) of alcohol **32a** as a colorless oil, and 11 mg (6% yield) of alcohol **32b** as a colorless oil. Formate **33**: R_f 0.34 in 20% EtOAc–hexane; IR ($CDCl_3$) 2950, 1740, 1590, 1290, 1250, 1190, 1110 cm^{-1}; ^1H NMR δ 0.83–1.10 (m, 1), 1.10–1.44 (m, 5), 1.44–1.97 (m, 7), 2.95 (m, 1), 3.67 (ddd, 1, J = 3.3, 3.3, 10.7), 4.51 (dd, 1, J = 7.7, 12.1), 4.63 (dd, 1, J = 3.3, 12.1), 5.36 (ddd, 1, J = 3.3, 3.3, 6.9), 7.30 (dd, 1, J = 2.0, 8.4), 7.47 (d, 1, J = 2.0), 7.79 (d, 1, J = 8.5), 8.19 (s, 1). Alcohol **32a**: R_f 0.15 in 20% EtOAc–hexane; IR ($CDCl_3$) 3580, 2950, 1735, 1590, 1290, 1250, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83–1.06 (m, 1), 1.06–1.41 (m, 5), 1.48–1.97 (m, 7), 2.78 (d, 1, J = 5.0), 2.98 (ddd, 1, J = 4.0, 10.5, 10.5), 3.49 (ddd, 1, J = 5.2, 5.2, 10.0), 3.79 (dddd, 1, J = 5.3, 5.3, 5.3, 5.3), 4.39 (dd, 1, J = 5.7, 11.6), 4.45 (dd, 1, J = 4.3, 11.7), 7.31 (dd, 1, J = 2.0, 8.5), 7.48 (d, 1, J = 2.0), 7.84 (d, 1, J = 8.4). Alcohol **32b**: R_f = 0.12 in 20% EtOAc–hexane; IR ($CDCl_3$) 3610, 3500, 2940, 1730, 1590, 1290, 1250, 1110 cm^{-1}; ^1H NMR δ 0.83–1.10 (m, 1), 1.10–1.44 (m, 5), 1.44–1.95 (m, 7), 2.82 (t, 1, J = 5.8), 2.99 (ddd, 1, J = 3.9, 9.8, 9.8), 3.82 (ddd, 1, J = 4.3, 4.3, 9.7), 3.97 (m, 2), 5.12 (ddd, 1, J = 4.1, 4.1, 4.1), 7.32 (dd, 1, J = 2.0, 8.4), 7.48 (d, 1, J = 2.0), 7.86 (d, 1, J = 8.4).

(1*R,3*S**,4*R**,7*S**)-3-(((2,4-Dichlorobenzoyl)oxy)-methyl)-2-oxabicyclo[5.4.0]undecan-4-ol (34-H) and the Formate Ester (34-F).** To 434 mg (0.898 mmol) of iodide **31** dissolved in 4 mL of dry DMF under nitrogen was added 262 mg (1.35 mmol) of silver tetrafluoroborate. The resulting solution was heated at 60 °C for 26.5 h and then cooled to 21 °C. Saturated NaCl (2 mL) was added in order to precipitate the excess silver tetrafluoroborate. The silver salts were removed by filtration through Celite and washed with 50 mL of EtOAc. The organic solution was washed with 25 mL each of 1 N HCl and saturated $NaHCO_3$ and worked up. The crude product was purified by chromatography (10% EtOAc–hexane then 20% EtOAc–hexane) to give 105 mg (29% yield) of **34-F** as a white solid and 42 mg (13% yield) of **34-H** as a white solid. Both formate and alcohol can be recrystallized from EtOAc–hexane. Formate **34-F**: mp 65–67 °C; R_f 0.37 in 20% EtOAc–hexane; IR 2940, 1730, 1590, 1290, 1250, 1190, 1110 cm^{-1}; ^1H NMR δ 0.95–1.41 (m, 5), 1.51–1.92 (m, 5), 1.92–2.06 (m, 3), 3.05 (ddd, 1, J = 3.9, 10.1, 10.1), 3.90 (q, 1, J = 6.0), 4.35 (d, 2, J = 5.5), 5.21 (ddd, 1, J = 3.6, 3.6, 6.6), 7.31 (dd, 1, J = 2.1, 8.4), 7.48 (d, 1, J = 2.0), 7.82 (d, 1, J = 8.5), 8.06 (s, 1). Anal. Calcd for $C_{19}H_{22}Cl_2O_5$: C, 56.86; H, 5.54; Cl, 17.67. Found: C, 56.78; H, 5.55; Cl, 17.54. Alcohol **34-H**: mp 104–105 °C; R_f 0.19 in 20% EtOAc–hexane; IR 3610, 3500, 2940, 1740, 1590, 1300, 1250, 1110, 1060 cm^{-1}; ^1H NMR δ 0.86–1.44 (m, 6), 1.44–2.10 (m, 8), 3.02 (ddd, 1, J = 3.7, 10.2, 10.2), 3.69 (ddd, 1, J = 4.6, 6.6, 6.6), 3.92 (m, 1), 4.43 (d, 2, J = 4.4), 7.31 (dd, 1, J = 2.1, 8.4), 7.48 (d, 1, J = 2.0), 7.83 (d, 1, J = 8.4). Anal. Calcd for $C_{18}H_{22}Cl_2O_4$: C, 57.91; H, 5.95; Cl, 18.99. Found: C, 58.15; H, 5.97; Cl, 18.86.

(1*R,2*S**,(2*E*,5*E*))-2-(2-Methyldodeca-2,5-dienyl)cyclohexan-1-ol (35).** An oven-dried 200-mL, three-necked, round-bottomed flask with a dry ice condenser was charged with a solution of 1.50 g (3.84 mmol) of alkyne **48** (see below) in 25 mL of dry THF under nitrogen. $(NH_4)_2SO_4$ (1.01 g, 7.68 mmol) and 1.8 mL (19.19 mmol) of dry *tert*-butyl alcohol were added. The reaction mixture was cooled to −40 °C, and the dry ice condenser was cooled to −78 °C. Approximately 100 mL of ammonia (dried with sodium) was distilled into the reaction mixture to give a cloudy white solution. Lithium (213 mg, 30.71 mmol) was washed first in methanol and then in hexane and added in 10–15-mg pieces over 9.5 h to the reaction mixture in order to keep it blue in color. The reaction mixture was quenched with solid NH_4Cl, and warmed to 21 °C in order to allow the ammonia to evaporate. The resulting solution was diluted with 100 mL of ether, washed once with 50 mL of saturated NH_4Cl, and worked up to give 1.52 g of colorless liquid. The crude product was purified by chromatography (hexane, 5% ether–hexane, then 10% ether–hexane) to give 1.08 g (72% yield) of the diene as a colorless liquid: R_f 0.32 in hexane; IR 2940, 1460, 1250, 1090 cm^{-1}; ^1H NMR δ 0.04 (s, 6), 0.89 (s, 9), 0.63–1.00 (m, 3), 1.00–1.67 (m, 15), 1.56 (s, 3), 1.67–1.83 (m, 2), 1.83–1.92 (m, 1), 1.92–2.10 (m, 2), 2.60 (d, 1, J = 12.2), 2.69 (m, 2), 3.17 (ddd, 1, J = 3.7, 8.8, 8.8), 5.09 (t, 1, J = 7.1), 5.39 (m, 2). Anal. Calcd for $C_{25}H_{48}OSi$: C, 76.43; H, 12.34. Found: C, 76.56; H, 12.46.

To 1.56 g (3.97 mmol) of the above silyl ether dissolved in 12 mL of dry THF under nitrogen was added 0.55 mL (402 mg, 3.97 mmol) of triethylamine and 7.9 mL (7.94 mmol) of 1 M tetra-*n*-butylammonium fluoride in THF. The resulting soltuion was allowed to stir at 21 °C for 25 h. The reaction mixture was diluted with 100 mL of EtOAc, washed with 50 mL each of 1 N HCl and saturated $NaHCO_3$, and worked up. The crude product was purified by chromatography (15% EtOAc–hexane) to give 977 mg (88% yield) of **35** as a light yellow liquid: R_f 0.30 in 20% EtOAc–hexane; IR 3540, 2940, 1450, 1220 cm^{-1}; ^1H NMR δ 0.76–0.95 (m, 4), 1.10–1.51 (m, 12), 1.51–2.06 (m, 8), 1.64 (s, 3), 2.40 (dd, 1, J = 6.1, 13.3), 2.69 (t, 2, J = 5.9), 3.29 (m, 1), 5.24 (t, 1, J = 7.2), 5.38 (m, 2). Anal. Calcd for $C_{19}H_{34}O$: C, 81.93; H, 12.33. Found: C, 81.77; H, 12.33.

(1*R,6*S**,8*R**)-8-((1*S**,3*E*)-1-Iodo-3-decenyl)-8-methyl-7-oxabicyclo[4.3.0]nonane (36).** To 968 mg (3.48 mmol) of alcohol **35** dissolved in 20 mL of CH_2Cl_2 under nitrogen cooled to 0 °C in the dark was added 860 mg (3.83 mmol) of *N*-iodosuccinimide. The resulting solution was allowed to stir for 3 h and then diluted with 100 mL of CH_2Cl_2. The organic solution was washed with

50 mL each of saturated $Na_2S_2O_3$ and saturated $NaHCO_3$ and worked up to give 1.6 g of yellow liquid. The crude product was purified by chromatography (5% ether–hexane) to give 1.35 g (96% yield) of **36** as a colorless liquid: R_f 0.38 in 5% EtOAc–hexane; IR 2940, 1450, 1380, 1060 cm^{-1}; ^1H NMR δ 0.88 (t, 3, J = 6.6), 1.00–1.63 (m, 13), 1.41 (s, 3), 1.63–1.95 (m, 3), 1.95–2.16 (m, 3), 2.43 (ddd, 1, J = 7.0, 11.2, 15.0), 2.77 (dd, 1, J = 4.4, 15.0), 3.23 (ddd, 1, J = 3.5, 10.1, 10.1), 3.95 (dd, 1, J = 2.4, 11.4), 5.42 (dt, 1, J = 15.2, 5.8), 5.50 (dt, 1, J = 15.3, 6.4); ^{13}C NMR δ 14.11, 22.62, 23.13, 24.15, 25.55, 28.73, 28.79, 29.23, 31.63, 31.69, 32.53, 38.50, 45.25, 47.24, 50.21, 83.26, 84.06, 128.36 and 128.79 at ratio 13:1, 133.30 and 133.39 at ratio 12:1. Anal. Calcd for $C_{19}H_{33}IO$: C, 56.42; H, 8.24; I, 31.38. Found: C, 56.54; H, 8.30; I, 31.34.

(1*R,3*S**,4*R**,6*S**)-3-((2*E*)-2-Nonenyl)-4-methyl-2-oxabicyclo[4.4.0]dec-4-yl Formate (37).** To 1.34 g (3.31 mmol) of iodide **36** dissolved in 15 mL of dry DMF under nitrogen in the dark was added 0.774 g (3.98 mmol) of silver tetrafluoroborate. The resulting solution was allowed to stir at 21 °C for 23 h as silver iodide precipitated. Saturated NaCl (3 mL) was added in order to precipitate the excess silver ion. The silver salts were removed by filtration through Celite and washed with 150 mL of ether. The filtrate was washed with 50 mL each of water and saturated $NaHCO_3$ and worked up to give 1.05 g of a colorless liquid. The crude product was purified by chromatography (3% ether–hexane, 5% ether–hexane, then 10% ether–hexane) to give 571 mg (53% yield) of **37** as a colorless liquid: R_f 0.57 in 20% EtOAc–hexane; IR 2940, 1715, 1210 cm^{-1}; ^1H NMR δ 0.88 (t, 3, J = 6.6), 0.83–1.06 (m, 1), 1.06–1.41 (m, 14), 1.41–1.73 (m, 1), 1.54 (s, 3), 1.73–1.89 (m, 1), 1.89–2.16 (m, 4), 2.32 (dd, 1, J = 3.2, 16.1), 2.55 (dd, 1, J = 3.3, 11.9), 2.94 (ddd, 1, J = 3.8, 10.1, 10.1), 3.38 (dd, 1, J = 2.3, 10.0), 5.51 (m, 2), 8.00 (s, 1); ^{13}C NMR δ 14.06, 18.26, 22.62, 24.81, 25.39, 28.75, 29.39, 31.38, 31.72, 31.89, 32.08, 32.60, 40.02, 42.85, 82.15, 82.25, 82.53, 126.81, 132.30, 159.89. Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.47; H, 10.65. Found: C, 74.81; H, 10.87.

(1*R,3*S**,4*R**,6*S**)-3-((2*E*)-2-Nonenyl)-4-methyl-2-oxabicyclo[4.4.0]decan-4-ol (38).** To 570 mg (1.77 mmol) of formate **37** dissolved in 5 mL of THF was added 5 mL of water and 141 mg (3.54 mmol) of NaOH. The resulting solution was allowed to stir at 21 °C for 13 h. The reaction mixture was neutralized with 3.5 mL of 1 N HCl and 20 mL of saturated NH_4Cl and extracted twice with 25 mL of EtOAc. The combined organic solution was worked up to give 550 mg of crude product which was purified by chromatography (15% EtOAc–hexane) to give 499 mg (96% yield) of **38** as a colorless liquid: R_f 0.31 in 20% EtOAc–hexane; IR 3610, 2940, 1450, 1380, 1070 cm^{-1}; ^1H NMR δ 0.79–1.10 (m, 5), 1.25 (s, 3), 1.10–1.41 (m, 13), 1.54–1.70 (m, 2), 1.70–1.86 (m, 2), 1.86–2.06 (m, 3), 2.06–2.22 (m, 1), 2.32–2.44 (m, 1), 2.89 (m, 1), 3.17 (dd, 1, J = 4.6, 8.3), 5.53 (br singlet, 1); ^{13}C NMR δ 14.09, 21.29, 22.62, 24.94, 25.44, 28.81, 29.41, 31.48, 31.70, 31.98, 32.61, 32.89, 40.55, 47.01, 70.99, 82.45, 84.28, 127.36, 132.54. Anal. Calcd for $C_{19}H_{34}O_2$: C, 77.48; H, 11.66. Found: C, 77.37; H, 11.73.

(1*R,3*S**,5*R**,6*S**,8*R**,10*S**)-6-Hexyl-5-iodo-8-methyl-2,7-dioxatricyclo[8.4.0.0^{3,8}]tetradecane (39).** To 378 mg (1.28 mmol) of alcohol **38** dissolved in 7 mL of dry acetonitrile cooled to 0 °C in the dark under nitrogen was added 814 mg (3.21 mmol) of iodine. The resulting purple solution was allowed to stir at 0 °C for 3.5 h. The reaction mixture was diluted with 50 mL of ether, washed with 25 mL each of saturated $Na_2S_2O_3$ and saturated $NaHCO_3$, and worked up to give 545 mg of a yellow liquid. The crude product was purified by chromatography (5% ether–hexane) to give 346 mg (64% yield) of **39** as a colorless liquid: R_f 0.57 in 10% EtOAc–hexane; IR 2940, 1460, 1150, 1080 cm^{-1}; ^1H NMR δ 0.88 (t, 3, J = 6.5), 1.26 (s, 3), 1.13–1.54 (m, 15), 1.54–1.69 (m, 2), 1.69 (dd, 1, J = 3.6, 11.8), 1.80 (m, 1), 1.86–2.06 (m, 2), 2.27 (ddd, 1, J = 12.1, 12.1, 12.1), 2.46 (ddd, 1, J = 4.1, 4.1, 12.3), 2.99 (ddd, 1, J = 3.8, 10.1, 10.1), 3.06 (dd, 1, J = 4.0, 12.1), 3.77 (ddd, 1, J = 2.3, 10.6, 10.6), 3.85 (ddd, 1, J = 4.7, 10.7, 10.7); ^{13}C NMR δ 14.08, 15.43, 22.60, 24.98, 25.24, 25.55, 28.96, 29.07, 31.63, 31.75, 31.99, 34.27, 39.16, 40.62, 44.73, 73.15, 74.26, 81.15, 83.84. Anal. Calcd for $C_{19}H_{33}IO_2$: C, 54.28; H, 7.93; I, 30.18. Found: C, 54.13; H, 8.01; I, 30.27.

(1*R,3*S**,5*R**,6*S**,8*R**,10*S**)-6-Hexyl-8-methyl-2,7-dioxatricyclo[8.4.0.0^{3,8}]tetradec-5-yl Formate (40) and (1*R**,3*S**,5*R**,7*R**,9*S**)-5-((1*R**)-1-((Formyloxy)heptyl))-7-methyl-2,6-dioxatricyclo[7.4.0.0^{3,7}]tridecane (41).** To 143 mg (0.340 mmol) of iodide **39** dissolved in 1.5 mL of dry DMF was added 79 mg (0.408 mmol) of silver tetrafluoroborate. The resulting solution was heated at 75 °C for 27 h under nitrogen and then cooled to 21 °C. Saturated NaCl (2 mL) was added in order to precipitate the excess silver ion. The silver salts were removed by filtration through Celite and washed with 25 mL of ether. The filtrate was washed with 15 mL each of 1 N HCl and saturated $NaHCO_3$ and worked up to give 109 mg of a light yellow liquid. The crude product was purified by chromatography (5% EtOAc–hexane) to give 63 mg (55% yield) of **40,41** as a colorless liquid: R_f 0.23 in 10% EtOAc–hexane; IR 2940, 1725, 1455, 1190, 1150, 1000 cm^{-1}; ^1H NMR δ 0.87 (t, 3, J = 6.0), 0.95–1.57 (m, 18), 1.57–2.06 (m, 7), 2.23 (ddd, 1, J = 4.2, 5.0, 11.5) for major **40**, 3.00 (ddd, 1, J = 3.9, 10.1, 10.1) and 3.04 (ddd, 1, J = 3.8, 9.8, 9.8) at ratio 2.9:1.0 for **40:41**, 3.15 (dd, 1, J = 3.9, 12.6) and 3.50 (dd, 1, J = 4.4, 12.5) at ratio 2.9:1.0, 3.59 (dt, 1, J = 2.1, 9.6) and 3.74 (t, 1, J = 5.5) at ratio 2.9:1.0, 4.69 (ddd, 1, J = 5.3, 10.2, 10.2) and 5.18 (br s, 1) at ratio 2.9:1.0, and 8.04 (d, 1, J = 0.8) and 8.13 (d, 1, J = 0.4) at ratio 2.9:1.0; ^{13}C NMR δ (resonances for minor **41** in parentheses) 13.99 (14.70), 15.32, 22.52, 24.95, 25.04, 25.52 (25.42), 29.11 (29.03), 30.77 (30.18), 30.99, 31.57, 31.68, 31.97, 40.59 (40.78), 44.51, 70.67 (70.16), 71.52, 72.49 (73.12), 78.38 (76.14), 83.87 (84.01), 159.88 (160.23). Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.95; H, 10.14. Found: C, 71.23; H, 10.25.

(1*R,2*S**,(2*E*))-1-((*tert*-Butyldimethylsilyl)oxy)-2-(3-iodo-2-methyl-2-propenyl)cyclohexane (46b). (1*R**,2*S**)-1-((*tert*-Butyldimethylsilyl)oxy)-2-(2-propynyl)cyclohexane.** To a solution of 2.50 g (18.09 mmol) of *trans*-2-(2-propynyl)-1-cyclohexanol[13] in 70 mL of dry THF and 30 mL of dry DMF was added 2.29 g (3.2 mL, 22.61 mmol) of triethylamine, 442 mg (3.62 mmol) of 4-(dimethylamino)pyridine, and 3.00 g (19.89 mmol) of *tert*-butyldimethylsilyl chloride. The resulting solution was allowed to reflux under nitrogen for 24 h, and triethylamine hydrochloride was precipitated. The reaction mixture was cooled to 21 °C, and the solvent was removed by rotary evaporator. The liquid residue was diluted in 300 mL of ether, washed with 150 mL each of 1 N HCl and saturated $NaHCO_3$ and worked up to give 4.6 g of an orange liquid. The crude product was purified by chromatography (2% ether–hexane) to give 4.10 g (90% yield) of the product as a colorless liquid: R_f 0.23 in 20% EtOAc–hexane; IR 3310, 2940, 1250, 1090 cm^{-1}; ^1H NMR δ 0.06 (s, 3), 0.07 (s, 3), 0.89 (s, 9), 1.22 (m, 4), 1.44 (m, 1), 1.70 (m, 2), 1.89 (m, 2), 1.94 (t, 1, J = 2.7), 2.22 (ddd, 1, J = 2.7, 7.3, 16.6), 2.43 (ddd, 1, J = 2.9, 3.6, 16.6), 3.34 (ddd, 1, J = 4.5, 9.4, 9.4). Anal. Calcd for $C_{15}H_{28}OSi$: C, 71.34; H, 11.20. Found: C, 71.50; H, 11.35.

An oven-dried, three-necked, 100-mL, round-bottomed flask equipped with an addition funnel and flushed with argon was charged with 2.55 g (8.71 mmol) of bis(cyclopentadienyl)zirconium dichloride which was suspended in 12 mL of dry CH_2Cl_2. Trimethylaluminum (11.9 mL, 23.77 mmol, 2 M in toluene) was added via gas-tight syringe. The bis(cyclopentadienyl)zirconium dichloride dissolved to give a clear yellow solution which was allowed to stir at 21 °C for 15 min. A solution of the above alkyne (2.00 g, 7.92 mmol) dissolved in 8 mL of dry CH_2Cl_2 was added dropwise via addition funnel. The resulting mixture was allowed to stir at 21 °C for 6 h and then cooled to 0 °C. A solution of iodine (3.02 g, 11.88 mmol) dissolved in 10 mL of dry THF was added dropwise via addition funnel. The purple iodine color was discharged immediately. The reaction mixture was allowed to stir at 0 °C for another 20 min and then carefully quenched with 75 mL of 1 N HCl and enough concentrated HCl to dissolve all of the aluminum salts. The solvent was removed by rotary evaporator, and the aqueous solution was extracted twice with 100 mL of ether. The combined organic layers were washed with 100 mL each of saturated $Na_2S_2O_3$ and saturated $NaHCO_3$ and worked up to give 3.1 g of a light yellow liquid. The crude product was purified by chromatography (2% ether–hexane) to give 2.87 g (92% yield, including 5% of protonated product) of **46b** as a colorless liquid: R_f 0.32 in hexane; IR 2940, 1250, 1090 cm^{-1}; ^1H NMR δ 0.04 (s, 3), 0.05 (s, 3), 0.76 (m, 1), 0.89 (s, 9), 1.03–1.51 (m, 4), 1.51–1.95 (m, 5), 1.80 (s, 3), 2.77 (d, 1, J = 13.5), 3.16 (ddd, 1, J = 4.1, 9.5, 9.5), 5.78 (s, 1); MS, m/e (relative intensity) 379 (0.09), 338 (1.33), 337 (3.54), 212 (1.67), 211 (4.05), 169 (2.66); HRMS calcd for $C_{16}H_{31}IOSi$ 379.0955; Found 379.0958.

(1*R,2*S**,(2*E*))-1-((*tert*-Butyldimethylsilyl)oxy)-2-(2-methyldodec-1-en-5-ynyl)cyclohexane (48).** An oven-dried,

2-necked, 100-mL, round-bottomed flask flushed with argon was charged with a solution of 4.54 g (11.52 mmol) of vinyl iodide **46b** in 35 mL of dry THF and cooled to −78 °C. *sec*-Butyllithium (16.6 mL, 23.04 mmol, 1.39 M in cyclohexane) was added via gas-tight syringe, and the resulting solution was allowed to stir at −78 °C for 1 h to give a cloudy orange solution. The reaction mixture was warmed to −40 °C, and transferred by cannula under nitrogen pressure into an oven-dried, 100-mL, round-bottom flask charged with 1.13 g (12.67 mmol) of CuCN. The resulting solution was allowed to stir at −40 °C for 2 h, during which time it became brown and then black in color. Bromoallene **47**[16] (2.34 g, 11.52 mmol) was added, and the reaction mixture was warmed to −20 °C and stirred for 27 h. The reaction mixture was quenched with 100 mL of 4:1 saturated NH_4Cl:NH_4OH, the blue aqueous solution was extracted 3 times with 100 mL of ether, and the organic solution was worked up to give 5.2 g of brown liquid. The crude product was purified by chromatography (hexane then 5% ether–hexane) to give 3.25 g (72% yield) of **48** as a colorless liquid: R_f 0.20 in hexane; IR 2940, 1460, 1250, 1090 cm^{-1}; ^1H NMR δ 0.04 (s, 6), 0.89 (s, 9), 0.67–1.06 (m, 3), 1.06–1.79 (m, 19), 1.57 (s, 3), 1.79–1.95 (m, 1), 2.16 (m, 1), 2.60 (d, 1, J = 12.0), 2.87 (d, 1, J = 5.8), 3.16 (ddd, 1, J = 3.6, 8.9, 8.9), 5.14 (t, 1, J = 6.7); MS, m/e (relative intensity) 333 (0.06), 255 (0.36), 225 (0.34), 213 (2.63), 195 (1.61), 185 (0.38), 169 (1.24); HRMS calcd for $C_{25}H_{46}OSi$ 333.2615, found 333.2615.

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Registry No. **8** (R = R^2 = CH_3, R^1 = CH_2OH) (silyl ether), 101859-23-8; **8** (R = R^1 = H, R^2 = CO_2Me) (silyl ether), 101859-28-3; **8** (R = R^2 = H, R^1 = CO_2Me) (silyl ether), 101976-92-5; **8** (R = H, R^2 = CH_3, R^1 = CH_2OCH_2Ph) (silyl ether), 101859-32-9; **8** (R = CH_3, R^1 = R^2 = H), 101859-19-2; **8** (R = CH_3, R^1 = R^2 = H) (silyl ether), 101859-20-5; **8** (R = H, R^2 = CH_3, R^1 = CO_2Me) (silyl ether), 101859-22-7; **8** (R = H, R^1 = CH_2OCH_2-2,6-$Cl_2C_6H_3$, R^2 = CH_3) (silyl ether), 101859-33-0; **8a**, 101859-25-0; **8a** (silyl ether), 101859-24-9; **8b**, 101858-79-1; **8c**, 101858-81-5; **8c** (silyl ether), 101859-30-7; **8d**, 54363-09-6; **8e**, 101859-57-8; **8f**, 101858-84-8; **8g**, 96502-30-6; **8g** (silyl ether), 101859-34-1; **9b**, 101858-80-4; **9c**, 101858-82-6; **9d**, 101858-83-7; **9f**, 101858-85-9; **9g**, 101858-86-0; **10a**, 101858-87-1; **10c** (isomer 1), 101858-88-2; **10c** (isomer 2), 101858-89-3; **11a-F**, 101858-90-6; **11b-F**, 101858-91-7; **11b-H**, 101858-92-8; **11c-F**, 101858-93-9; **11c-H**, 101858-94-0; **11d-A**, 101858-95-1; **11g-F**, 101858-96-2; **11g-H**, 101858-97-3; **12d-A**, 101915-77-9; **17** (R = H), 3392-93-6; **17** (R = H) (silyl ether), 101859-35-2; **17** (R = H) (*p*-bromobenzyl ether), 101859-45-4; (*Z*)-**17** (R = CO_2Me) (silyl ether), 101859-37-4; (*Z*)-**17** (R = CO_2Me) (*p*-bromobenzyl ether), 101859-47-6; (*E*)-**17** (R = CO_2Me) (silyl ether), 101976-93-6; (*E*)-**17** (R = CH_2OTHP) (silyl ether), 101859-40-9; (*E*)-**17** (R = CH_2OTHP), 101859-41-0; (*E*)-**17** (R = CH_2OTHP) (benzyl ether), 101859-42-1; (*E*)-**17** (R = CH_2OTHP) (2,4-$Cl_2C_6H_3CH_2$ ether), 101859-49-8; **21**, 101858-98-4; **21** (silyl ether), 101859-38-5; **22**, 101858-99-5; **23**, 101859-00-1; **24** (R = CH_2OH) (A = 2,4-$Cl_2C_6H_3CH_2$, 101859-50-1; **24** (R = H) (A = $CH(p\text{-}ClC_6H_4)2$), 101859-52-3; (*Z*)-**24** (R = CO_2Me) (A = $CH(p\text{-}ClC_6H_4)_2$), 101859-54-5; (*Z*)-**24** (R = CH_2OH) (A = Si(Bu-*t*)Me_2), 101976-95-8; (*E*)-**24** (R = CH_2OH) (A = Si(Bu-*t*)Me_2), 101859-39-6; (*E*)-**24** (R = CH_2OH) (A = CH_2Ph), 101859-43-2; (*E*)-**24** (R = CH_2OH) (A = *p*-$BrC_6H_4CH_2$), 101859-48-7; (*E*)-**24** (R = CH_2OH) (A = $CH(p\text{-}ClC_6H_4)_2$), 101859-55-6; (*E*)-**24** (R = CO_2Me) (A = $CH(p\text{-}ClC_6H_4)_2$), 101976-94-7; (*E*)-**24** (R = CO_2Me) (A = *p*-$BrC_6H_4CH_2$), 101976-96-9; **29a**, 101859-44-3; **29b**, 101859-01-2; **29c**, 101859-51-2; **29d**, 101859-56-7; **30**, 101859-02-3; **31**, 101859-03-4; **32a**, 101859-05-6; **32b**, 101859-06-7; **33**, 101859-04-5; **34-F**, 101976-90-3; **34-H**, 101859-07-8; **35**, 101859-10-3; **35** (silyl ether), 101859-09-0; **36**, 101915-78-0; **37**, 101859-11-4; **38**, 101859-12-5; **39**, 101859-13-6; **40**, 101859-14-7; **41**, 101859-15-8; **42**, 101859-27-2; **43**, 101859-36-3; **43** (bromobenzyl ether), 101859-46-5; **43** (bis(chlorophenyl)methyl ether), 101859-53-4; **44**, 101859-16-9; **44** (silyl ether), 101859-17-0; **46b**, 101859-18-1; **47**, 75101-95-0; **48**, 101859-08-9; $Ph_3P{=}CHCO_2Me$, 2605-67-6; $Ph_3P{=}CHCH_2CO_2Me$, 40955-14-4; $(F_3CCH_2)_2O_3PCH_2CO_2Me$, 88738-78-7; bis(4-chlorophenyl)methyl bromide, 6306-46-3; 3-chloro-2-methyl-1-propene, 563-47-3; cyclohexene oxide, 286-20-4; 1-((1*R**,2*S**)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-2-propanone, 101859-21-6; (1*R**,2*S**)-2-hydroxycyclohexane acetonitrile, 101976-91-4; (1*R**,2*S**)-((2-*tert*-butyldimethylsilyl)-oxy)cyclohexaneacetonitrile, 101859-26-1; (2E,1(1*R**,2*S**))-4-(2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-2-buten-4-ol, 101859-29-4; (1*R**,2*S**,(2*E*))-2-((*tert*-butyldimethylsilyl)oxy)cyclohexane-3-methyl-2-buten-4-ol, 101859-31-8; 2,6-dichlorobenzyl bromide, 20443-98-5; 2,4-dichlorobenzoyl bromide, 89-75-8; 4-bromobutene, 5162-44-7; brevetoxin B, 79580-28-2.

Supplementary Material Available: Experimental details for the synthesis and characterization of the cyclization substrates (23 pages). Ordering information is given on any current masthead page.

Metalloporphyrin-Catalyzed Decomposition of Cyclic Diperoxides (1,2,4,5-Tetraoxanes)

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Cyclic diperoxides of type **1** (**a**, R = H; **b**, R = Ph; **c**, R = *n*-Bu; **d**, R = Me) were found to be very stable (E_a = 42–48 kcal/mol, log A = 17–19). Decomposition of **1** was greatly promoted by addition of ZnTPP or CoTPP, leading to formation of ketone PhCOR and ester (or acid) $PhCO_2R$ as the major products. In the presence of Ph_2S or Ph_2SO as oxygen acceptor, the oxygen transfer reaction occurred and the production of $PhCO_2R$ (= $PhCO_2Bu$) was completely suppressed in the case of **1c**, while it (the production of $PhCO_2H$) was not measurably suppressed in the case of **1a**. Chemiluminescence (CL) that is due to singlet ZnTPP formation was detected from the reaction of ZnTPP with **1a** but not with **1c**. The observed first-order decay rate of CL for the reaction of **1a** with ZnTPP and its para-substituted derivatives Zn(*p*-X)TPP increased with the increase in electron-donating nature of the substituents (CN < Cl < H < CH_3 < OCH_3). A tentative mechanism for this ZnTPP-catalyzed decomposition reaction, which takes the different behaviors of **1a** and **1c** into account, is proposed.

Decomposition of valerophenone diperoxide (**1c**) has previously been performed thermally and photochemically under a nitrogen atmosphere (eq 1).[1,2] The primary reaction observed was the formation of (a) valerophenone

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