Ring-Enlarging Cyclohexane Annulations

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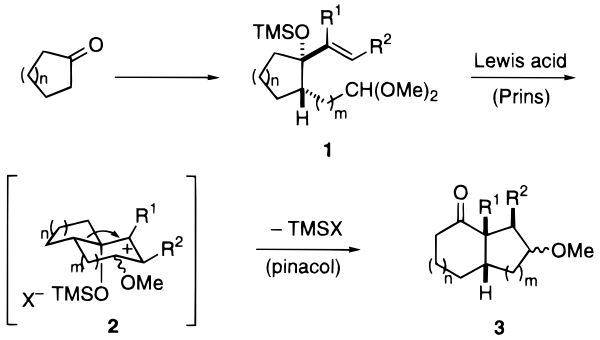
A Prins−pinacol rearrangement is the key step in a new method for synthesizing *cis*-bicyclo[*n*.4.0]alkanones. The alkenyl acetal rearrangement substrates **1** are assembled from cycloalkanone precursors in four steps (Table 1). Prins−pinacol rearrangement to form *cis*-bicyclo[*n*.4.0]alkanones **3** is best accomplished by exposure of **1** to 1 equiv of TMSOTf and a proton scavenger (2,6-di-*tert*-butyl-4-methylpyridine) at −78 °C → rt.

One of the strategies that we have found particularly effective in the design of new processes for ring construction is to employ pinacol rearrangements to terminate cationic cyclization reactions.[1] Ring-forming processes of this type have been employed for the synthesis of both carbocycles and heterocycles.[2] In 1989 we reported a novel construction of carbocycles in which a cyclopentane annulation is coupled with one-carbon ring expansion of a starting ketone (Scheme 1, $m = 1$).[3] The conversion of **1** → **3** is believed to occur by a Prins cyclization−pinacol rearrangement sequence.[4] The high levels of stereocontrol that are hallmarks of this ring-forming method arise from both steps occurring by highly ordered 6-membered transition structures, as illustrated in the conversion of **2** → **3**.

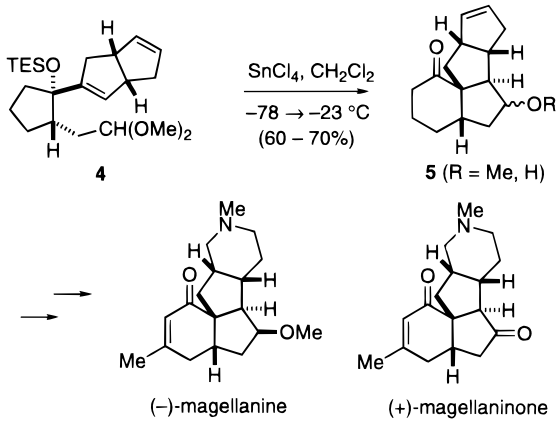
The Prins−pinacol construction of cyclopentane-containing carbocycles is particularly powerful when R^1 and R^2 comprise a ring, since this reaction then delivers angularly-fused ring systems. The conversion of **4** → **5**, the central step in our recent synthesis of (−)-magellanine and (+)-magellaninone, provides a good illustration (Scheme 2).[5]

The utility of the cyclization−pinacol approach to carbocycle construction would be significantly expanded if the intermediate formed in the Prins cyclization could also be 7-membered, since a cyclohexane annulation would then result. The successful development of ring-enlarging cyclohexane annulations (Scheme 1, $m = 2$) is the subject of this report.

Scheme 1



Scheme 2



Results

Preparation of Cyclization Substrates. Rearrangement substrates were assembled by the sequence summarized in Scheme 3. Imines **6**−**8** were initially deprotonated with lithium diethylamide in THF at −78 → 0 °C, and the resulting lithio enamines were alkylated with 1-bromo-3,3-dimethoxypropane.[6] Selective hydrolysis of the imine functionality of the alkylation products with NH_4Cl in THF−H_2O at reflux provided **9**−**11** in high overall yields. Reaction of keto acetals **9**−**11** with a representative group of alkenyllithium reagents (−78 °C)[7,8] or alkenyl Grignard reagents (23 °C) followed by

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(1) For brief reviews, see: (a) Overman, L. E. *Aldrichimica Acta* **1995**, *28*, 107. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352. (c) Overman, L. E. In *Selectivities in Lewis Acid-Promoted Reactions*; NATO ASSI Series 289; Schinzer, D., Ed.; Kluwer Academic: Dordrecht, The Netherlands, 1989; pp 1−20.

(2) For our most recent application of this strategy in the construction of polycyclic ethers, see: MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391.

(3) Hirst, G. C.; Howard, P. N.; Overman, L. E. *J. Am. Chem. Soc.* **1989**, *111*, 1514.

(4) For related ring-enlarging cyclopentene annulations, see: Johnson, T. O., Jr.; Overman, L. E. *Tetrahedron Lett.* **1991**, *32*, 7361.

(5) Hirst, G. C.; Johnson, T. O., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992.

(6) (a) Stork, G.; Benaim, J. *J. Am. Chem. Soc.* **1971**, *93*, 5938. (b) Battersby, A. R.; Buckley, D. G.; Staunton, J.; Williams, P. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2550. (c) Larchevêque, M.; Valette, G.; Cuvigny, T. *Tetrahedron* **1979**, *35*, 1745. (d) Imine **6** is prone to polymerization upon prolonged heating and was distilled in small batches.

(7) (a) Maitte, P. *Bull. Soc. Chim. Fr.* **1959**, 499. (b) Ndebeka, G.; Raynal, S.; Caubére, P.; Bartsch, R. A. *J. Org. Chem.* **1980**, *45*, 5394.

(8) An improved synthesis of α-lithiostyrene and α-lithio-3,4-(methylenedioxy)styrene was developed: A solution of DBU (1.4 equiv) and (1,2-dibromoethyl)benzene or 1-(1,2-dibromoethyl)-3,4-(methylenedioxy)-benzene in pentane−CH_2Cl_2 (5:1) was stirred at rt for 5 h. The reaction mixture was then washed with saturated aqueous NH_4Cl and H_2O, dried (Na_2SO_4), and concentrated. The crude styrenyl bromide was distilled under reduced pressure. The freshly distilled bromide (1.5−2.0 M) in THF was then added over 45 min to *n*-BuLi or *s*-BuLi (0.7 M) at −78 °C. See also: Newman, M. S.; Dhawan, B.; Hashem, M. M; Khanna, V. K.; Springer, J. M. *J. Org. Chem.* **1976**, *41*, 3925.

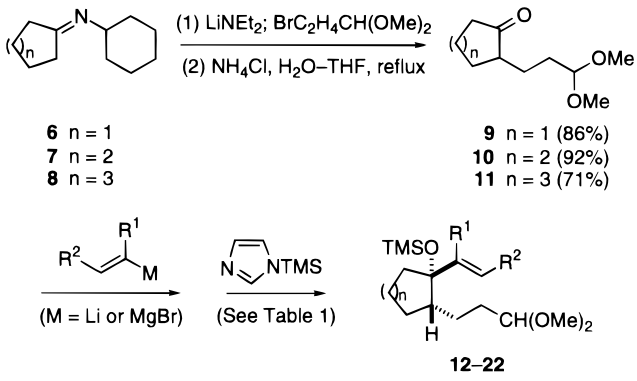
S0022-3263(97)00399-X CCC: $14.00

Table 1. Preparation of Rearrangement Substrate 12−22 from Keto Acetals 9−11

keto acetal			alkenyl organometallic			cyclization substrate		
entry	compd	*n*	R^1	R^2	M	compd	yield, %[a]	ds[b],[c]
1	**9**	1	H	H	MgBr	**12**	83	83:17
2	**9**	1	Me	H	Li	**13**	88	90:10[d]
3	**9**	1	Me	H	MgBr	**13**	70	>95:5[e]
4	**10**	2	Me	H	MgBr	**14**	84	>95:5[e]
5	**11**	3	Me	H	MgBr	**15**	77	>95:5[e]
6	**9**	1	$(CH_2)_3$		Li	**16**	71	75:25
7	**10**	2	$(CH_2)_3$		Li	**17**	79	95:5
8	**9**	1	$(CH_2)_4$		Li	**18**	72	95:5
9	**9**	1	Ph	H	Li	**19**	72	>95:5[e]
10	**10**	2	Ph	H	Li	**20**	93	>95:5[e]
11	**11**	3	Ph	H	Li	**21**	74	>95:5[e]
12	**10**	2	MDP[f]	H	Li	**22**	83	>95:5[e]

[a] Mixture of diastereomers after purification by column or radial chromatography (see text). [b] The major diastereomer is shown in Scheme 3. [c] Ratio was determined by ^{1}H NMR analysis. [d] Ratio was determined by GLC analysis. [e] Only one diastereomer was observed by ^{1}H NMR analysis. [f] MDP = 3,4-(methylenedioxy)phenyl.

Scheme 3

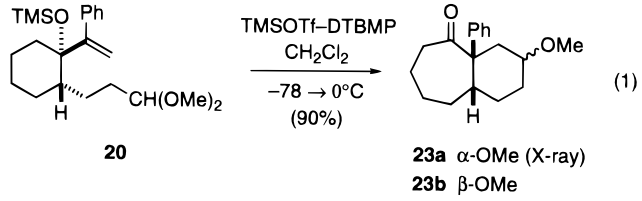


silylation provided cyclization substrates **12**−**22** in 70−93% overall yield (Table 1).

Only a single diastereomer was observed by ^{1}H and ^{13}C NMR analysis for the cycloheptyl products **15** and **21**, for the cyclohexyl products **14**, **20**, and **22**, and for the cyclopentyl product **19**. Alkenylcyclopentane acetal **13** was also formed as a single diastereomer when 2-propenylmagnesium bromide was used (entry 3, Table 1). The other products (entries 1−2 and 6−8 of Table 1) were formed as mixtures of stereoisomers (3:1−19:1). Silylation of the intermediate allylic alcohols could be accomplished at 23 °C under standard conditions (TMSCl/imidazole, TMSOTf/2,6-lutidine, or *N*-(trimethylsilyl)imidazole)[9,10] with the exception of the significantly less reactive styrenyl alcohols (entries 9−12). Attempted silylation of the styrenyl alcohols with the first two reagents required elevated temperatures and led to the formation of complex product mixtures.[11] However, silylation of these substrates could be efficiently accomplished with *N*-(trimethylsilyl)imidazole at 100 °C.[9] For styrenyl substrates **19**−**22** it was advantageous to purify the crude allylic alcohol product on neutral alumina prior to silylation.

The major isomer of **12**−**22** is believed to have a trans relationship of the alkenyl and 3,3-dimethoxypropyl side chains (as depicted in Scheme 3). These stereochemical assignments follow by analogy with the stereoselection observed in the addition of lithium and Grignard reagents to other 2-substituted cyclopentanones,[12] cyclohexanones,[13] and cycloheptanones.[14]

Ring-Enlarging Cyclohexane Annulations. Rearrangement of styrenyl acetal **20** was investigated in detail. A variety of Lewis acids [$SnCl_4$, Et_2AlCl, BF_3·Et_2O, *i*-Bu_2AlOMs,[15] TMSOTf, TMSOTf/2,6-di-*tert*-butyl-4-methylpyridine (DTBMP[16]), and methylbis(4-bromo-2,6-di-*tert*-butylphenoxy)aluminum (MABR[17])] and rearrangement temperatures (−78 → 23 °C) were surveyed. No reaction was observed when **20** was exposed to excess BF_3·OEt_2 at −78 °C or *i*-Bu_2AlOMs at −78 → 23 °C, while exposure to excess TMSOTf at −78 °C in the absence of a protic acid scavenger provided a complex reaction mixture. The product **23** of ring-enlarging cyclohexane annulation was obtained in moderate to good yields when **20** was treated with excess $SnCl_4$ at −78 → −23 °C, Et_2AlCl at −78 °C, or MABR at −20 °C. Best results were obtained when TMSOTf (1.0 equiv) was premixed with 2.0 equiv of DTBMP in CH_2Cl_2 and added to a CH_2Cl_2 solution of **20** at −78 °C. After allowing the reaction to warm to 0 °C, bicyclo[5.4.0]undecanone **23** was obtained in 90% yield as a 2:1 mixture of methoxy epimers (eq 1). The stereochemistry of the minor α-epimer **23a** was secured by single-crystal X-ray analysis.[18] Additionally, the ring junction stereochemistries of both epimers could be assigned on the basis of the substantial ^{1}H NOE (6−9%) observed between the ortho aryl hydrogens and the angular hydrogen.



(1)

Results obtained when alkenyl siloxy acetals **13**−**22** were treated with TMSOTf/DTBMP, and selected other Lewis acids, are summarized in Table 2. Cyclopentyl and cylohexyl substrates **13** and **14** containing 2-propenyl substituents (entries 1−5, Table 2) cyclized in the presence of $SnCl_4$, TMSOTf/DTBMP, or TBDMSOTf/DTBMP to afford *cis*-decalone **24** (as a 1.1:1−1.7:1 ratio of epimers) and *cis*-bicyclo[5.4.0]undecanone **25** (as a 1.1−

(9) Heathcock, C. H.; Jennings, R. A.; von Geldern, T. W. *J. Org. Chem.* **1983**, *48*, 3428.

(10) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 2nd ed.; John Wiley: New York, 1991; Chapter 2.

(11) Bicyclic acetals (diagnostic ^{1}H NMR signals at δ 4.2−4.5 for the acetal methine hydrogen) were typically components of this complex mixture.

(12) (a) Avasthi, K.; Salomon, R. G. *J. Org. Chem.* **1986**, *51*, 2556. (b) Battioni, J. P.; Capmau, M.-L.; Chodkiewicz, W. *Bull. Soc. Chim. Fr.* **1969**, 976.

(13) For a review, see: Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521.

(14) (a) Condroski, K. R.; Ando, K.; Houk, K. N.; Wu, Y.-D.; Ly, S. K.; Overman, L. E., submitted for publication. (b) Ly, S. K. Honors B.S. Thesis, University of California, Irvine, 1993.

(15) Hoppe, D.; Lichtenberg, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 239.

(16) For the preparation of DTBMP and its use as a protic acid scavenger in Lewis acid-promoted reactions, see: (a) Anderson, A. G.; Stang, P. J. *Org. Synth.* **1981**, *60*, 34 and references cited therein. (b) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570. (c) Cho, C. G.; Feit, B. A.; Webster, O. W. *Macromolecules* **1992**, *25*, 2081.

(17) Ooi, T.; Maruoka, K.; Yamamoto, H. *Org. Synth.* **1993**, *72*, 95.

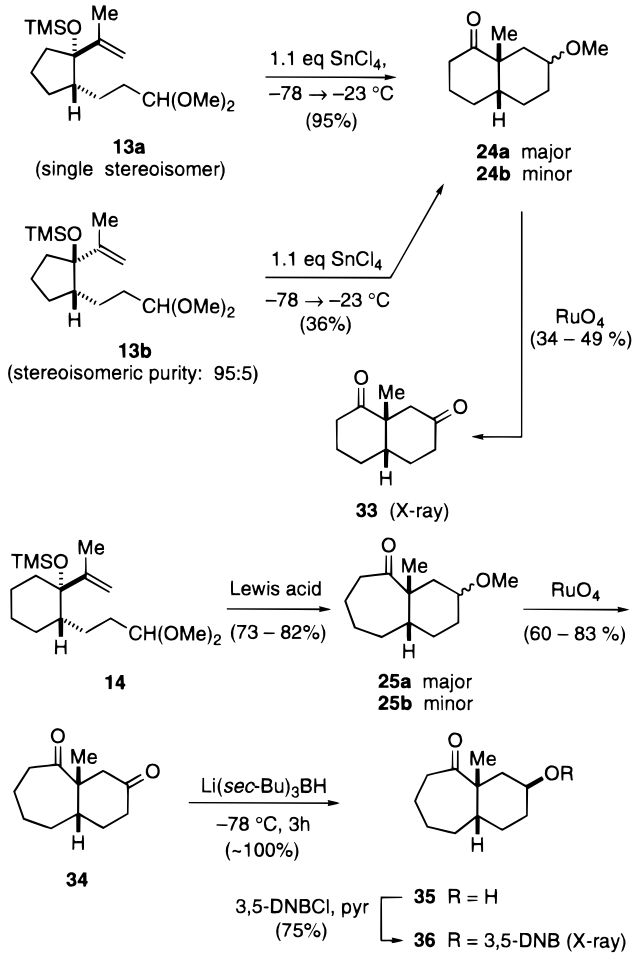
(18) The authors have deposited atomic coordinates for this compound with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Table 2. Ring-Enlarging Cyclohexane Annulations

allylic acetal						reaction conditions		product	
entry	compd	*n*	R^1	R^2	ratio[a]	Lewis acid (equiv)	temp (°C)	compd[b]	yield, %[c]
1	**13**	1	Me	H	90:10	$SnCl_4$ (1.1)	−78 → −23	**24**	83
2	**13**	1	Me	H	>95:5[d]	TMSOTf (0.5)[e]	rt	**24**	87
3	**13**	1	Me	H	>95:5[d]	TBDMSOTf (0.5)[e]	rt	**24**	80
4	**14**	2	Me	H	95:5	$SnCl_4$ (1.1)	−78 → −23	**25**	82
5	**14**	2	Me	H	>95:5[d]	TMSOTf (0.5)[e]	rt	**25**	73
6	**15**	3	Me	H	>95:5[d]	$SnCl_4$ (1.1)	−78 → −23	**26** + **37**	68[f,g]
7	**15**	3	Me	H	>95:5[d]	TMSOTf (0.5)[e]	rt	**26** + **37**	79[f,h]
8	**16**	1	$(CH_2)_3$		75:25	TMSOTf (1.0)[e]	rt	**27**	33
9	**16**	1	$(CH_2)_3$		83:17	$TiCl_4$ (1.1)	−78 → −23	**27**	61
10	**17**	2	$(CH_2)_3$		>95:5[d]	$TiCl_4$ (1.1)	−78 → −23	**28**	43
11	**18**	1	$(CH_2)_4$		95:5	$SnCl_4$ (1.1)	−78 → −23	**29**	40[h,i]
12	**19**	1	Ph	H	>95:5[d]	$SnCl_4$ (1.1)	−78 → −23	**30**	74
13	**19**	1	Ph	H	>95:5[d]	TMSOTf (1.0)[e]	−78 → 0	**30**	82
14	**20**	2	Ph	H	>95:5[d]	$SnCl_4$ (1.1)	−78 → −23	**23**	84
15	**20**	2	Ph	H	>95:5[d]	TMSOTf (1.0)[e]	−78 → 0	**23**	90
16	**21**	3	Ph	H	>95:5[d]	$SnCl_4$ (1.1)	−78 → −23	**31**	58
17	**21**	3	Ph	H	>95:5[d]	TBDMSOTf (1.0)[e]	−78 → 0	**31**	84
18	**21**	3	Ph	H	>95:5[d]	TMSOTf (1.0)[e]	−78 → 0	**31**	92
19[j]	**22**	2	MDP	H	>95:5[d]	$SnCl_4$ (1.1)	−78 → −23	**32**	79
20[j]	**22**	2	MDP	H	>95:5[d]	TMSOTf (1.0)[e]	−78 → 0	**32**	56

[a] Stereoisomeric purity was determined by ^{1}H NMR analysis with the exception of entry 1 (GLC analysis). [b] In all cases as mixtures of methoxy epimers. Epimer ratios and stereochemical assignments are discussed in the text and in Schemes 5−8. [c] After purification by column or radial chromatography. [d] Only one diastereomer was detected by ^{1}H NMR analysis. [e] 2.0 equiv of DTBMP per equiv of triflate was employed. [f] A mixture of *cis*-bicyclo[6.4.0]dodecan-2-one (**26**) and bicyclo[5.4.1]dodecan-12-one (**37**) was obtained. [g] Isomer ratio = 23:13:46:18. [h] Isomer ratio was not determined. [i] Spirocycle **29** was obtained (see Scheme 7). [j] MDP = 3,4-(methylenedioxy)phenyl.

Scheme 4



1.2:1 ratio of epimers), respectively, in high yields (Scheme 4). With these reactive substrates, as little as 0.5 equiv of silyl triflate could be employed (entries 2, 3, 5, and 7, Table 2). Although this reaction, in principle, should be catalytic in TMSOTf, use of <0.5 equiv resulted in lower yields of the bicyclic products.

Cyclopentyl stereoisomer **13a**, which has the 2-propenyl and 3,3-dimethoxypropyl substituents trans, and the minor stereoisomer **13b** having these groups cis both afforded *cis*-decalone **24** as the exclusive product of Prins−pinacol reaction. However, the yield of **24** was low from cis precursor **13b**.

The two decalin methoxy epimers **24a**,**b** were independently oxidized with RuO_4[19] to *cis*-decalindione **33**. The stereostructure of this product was secured by single-crystal X-ray analysis.[18] The epimeric *cis*-bicyclo[5.4.0]-undecalones **25a**,**b** were also oxidized independently with RuO_4 to give a single dione (**34**). The less hindered cyclohexane carbonyl group of this intermediate could be selectively reduced with Li(*s*-Bu)$_3$BH at −78 °C to provide alcohol **35** in essentially quantitative yield. The 3,5-dinitrobenzoate derivative **36** provided X-ray quality crystals, thus allowing unambiguous confirmation of stereochemistry.[18]

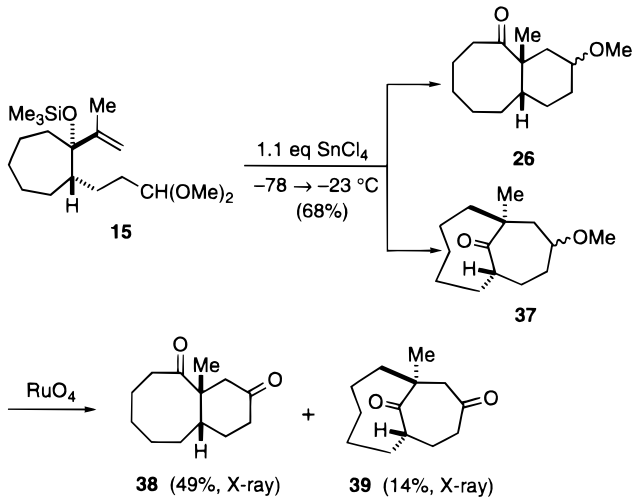
Rearrangement of the cycloheptyl 2-propenyl substrate **15** (entries 6 and 7 of Table 2 and Scheme 5) provided a mixture of two bicyclic products (**26** and **37**), each as a mixture of methoxy epimers (^{1}H NMR analysis) in a combined yield of 68%. Chromatography provided one epimer of **26** in 12% yield and a fraction containing an inseparable mixture of the other isomers (56%). Consequently, the crude product mixture was oxidized with RuO_4 to provide a separable 3:1 mixture of two diketones **38** and **39**. Both diketones provided X-ray quality crystals that allowed the cis stereochemistry of bicyclo-[6.4.0]dodecanone **38** to be confirmed and the "inside−outside" bicyclo[5.4.1]dodecanedione structure of **39** to be definitively established.[18]

In marked contrast to the 2-propenyl substrates **13**−**15**, siloxy acetal **12** containing a terminal vinyl group failed to undergo ring-enlarging cyclohexane annulation when exposed to either $SnCl_4$ or TMSOTf/DTBMP.

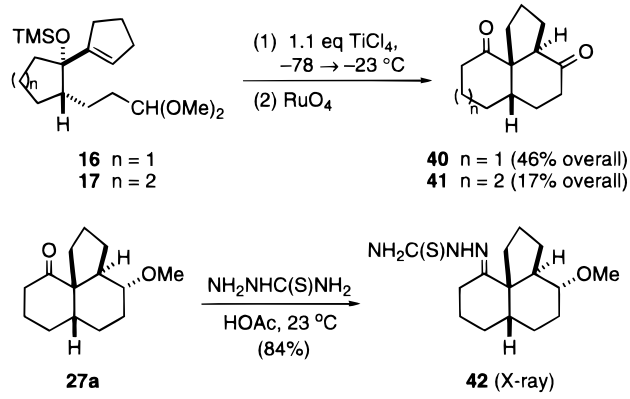
A number of Lewis acids (BF_3·OEt_2, Et_2AlCl, TMSOTf, and $EtAlCl_2$) promoted rearrangement of cyclopentyl

(19) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

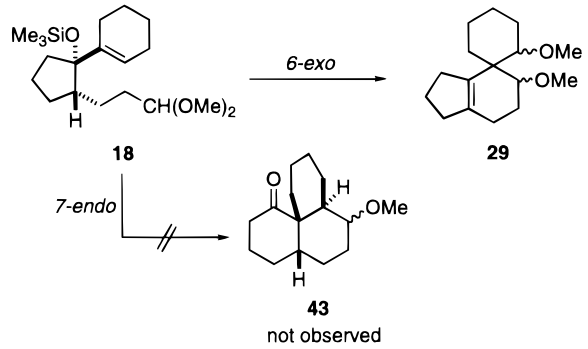
Scheme 5



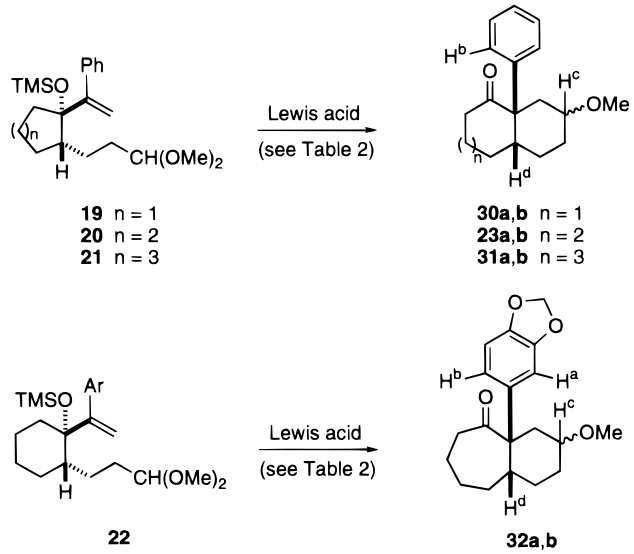
Scheme 6



Scheme 7



Scheme 8



siloxy acetal **16** to give the angular tricyclic product **27** in moderate yield (entries 8−11 of Table 2 and Scheme 6). The optimal promoter was $TiCl_4$ (entry 9, Table 2), which provided **27** in 61% yield as a 1.9:1 mixture of methoxy epimers. For the related cyclohexyl substrate **17**, $TiCl_4$ once again was optimal (entry 10, Table 2) and gave **28**, a 1.7:1 mixture of methoxy epimers, in 43% yield. That the products obtained in each case were methoxy epimers was established by oxidizing the crude product mixtures with RuO_4 to yield diketones **40** and **41** (Scheme 6). Conversion of **27a** to the crystalline thiosemicarbazone derivative **42** allowed the rigorous assignment of the ring fusion stereochemistry.[18]

Attempted rearrangement of cyclopentyl siloxy acetal **18** containing a cyclohexenyl π participant did not lead to the expected product **43** of ring-enlarging cyclohexane annulation. Exposure of **18** to $SnCl_4$ at −78 → −23 °C (entry 11, Table 2) gave spirotricyclic alkene **29** in 40% yield (Scheme 7). This product showed diagnostic spectroscopic signals for a tetrasubstituted double bond and two methoxy groups, while carbonyl and siloxy groups were conspicuously absent. Tricyclic alkene **29** could arise by 6-exo Prins cyclization of **18**, followed by trapping of the spirotricyclic cation by methanol and elimination of the tertiary siloxy substituent.

Styrenyl substrates **19**−**21** (entries 12−18 of Table 2, Scheme 8) gave the corresponding *cis*-decalin (**30**), *cis*-bicyclo[5.4.0]undecanone (**23**), and *cis*-bicyclo[6.4.0]dodecanone (**31**) Prins−pinacol products in high yields (82−92%) when exposed to TMSOTf at −78 → 0 °C. These products (1.2−2.9:1 mixtures of methoxy epimers) were also formed in the presence of $SnCl_4$; however, yields were somewhat lower (58−84%). Cyclization of (methylenedioxy)phenyl substrate **22** under similar conditions (entries 19 and 20, Table 2) gave *cis*-bicyclo[5.4.0]undecanone **32** in moderate to good yields (56−79%) as a 2:1 mixture of epimers.

Isomerically pure samples of the methoxy epimers of **30**−**32** were obtained by preparative TLC. Extensive NMR investigations, in particular the diagnostic ^1H NOE's summarized in Table 3, confirmed the cis stereochemistry of the ring junction for each pair of isomers. In the case of **31**, the stereochemistry of the methoxy epimers also followed unambiguously from ^1H NOE data.[20]

Discussion

Synthetic Aspects. The chemistry reported here allows fused bicyclic ketones to be constructed with complete cis stereoselectivity in five steps and good overall yields from cycloalkanone precursors (eq 2). Although the ring-enlarging cyclohexane annulation was demonstrated for cyclopentanone, cyclohexanone, and cycloheptanone precursors only, it will likely be successful

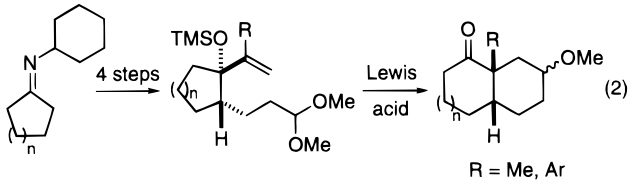
(20) Substantial enhancements were observed between the ortho aryl hydrogens (H^a and H^b) and the angular hydrogens (H^d) of **30** and **32** (4−9%), establishing a *cis*-ring fusion (Table 3). Since an enhancement was not observed between H^b and H^d of **31a**, this assignment was made by relaying the following enhancements: H^d to H^c, H^c to H^f, and H^f to H^b. A large enhancement was observed between H^c and H^d (4%) of **31a**, indicating that the cyclohexane ring of **31a** exists largely in a twist boat conformation. A small (<1%) was observed

Table 3. ^{1}H NMR Signals and ^{1}H DNOE Results for 23 and 30−32

	^{1}H NMR, δ (J)[a]				^{1}H DNOE[b]	
compd	H^a	H^b	H^c	H^d	Hx/Hy	%
30a		7.04 (d, 8.7)	3.72 (tt, 11.0, 4.5)	2.34 (m)	H^b/H^d	4
30b		7.32 (d, 8.7)	3.20 (tt, 6.5, 4.0,)	2.37 (m)	H^b/H^d	8
23a		7.20 (d, 8.0)	3.59 (tt, 7.5, 4.0)	2.34 (m)	H^b/H^d	6
23b		7.45 (d, 8.1)	2.83 (tt, 11.5, 4.0)	2.46 (m)	H^b/H^d	9
31a		7.43 (app s)	3.39 (app t, 10.0)	2.96 (m)	H^b/H^d	0
31b		7.51 (d, 8.8)	3.11 (app t, 10.0)	2.97 (tt 10.5, 1.0)	H^b/H^d	0
32a	6.59 (s)	6.87 (m)	3.56 (m)	2.19 (m)	H^a/H^d	4
32b	6.78 (s)	7.05 (d, 2.6)	2.84 (tt, 11.8, 4.0)	2.11 (m)	H^a/H^d	5

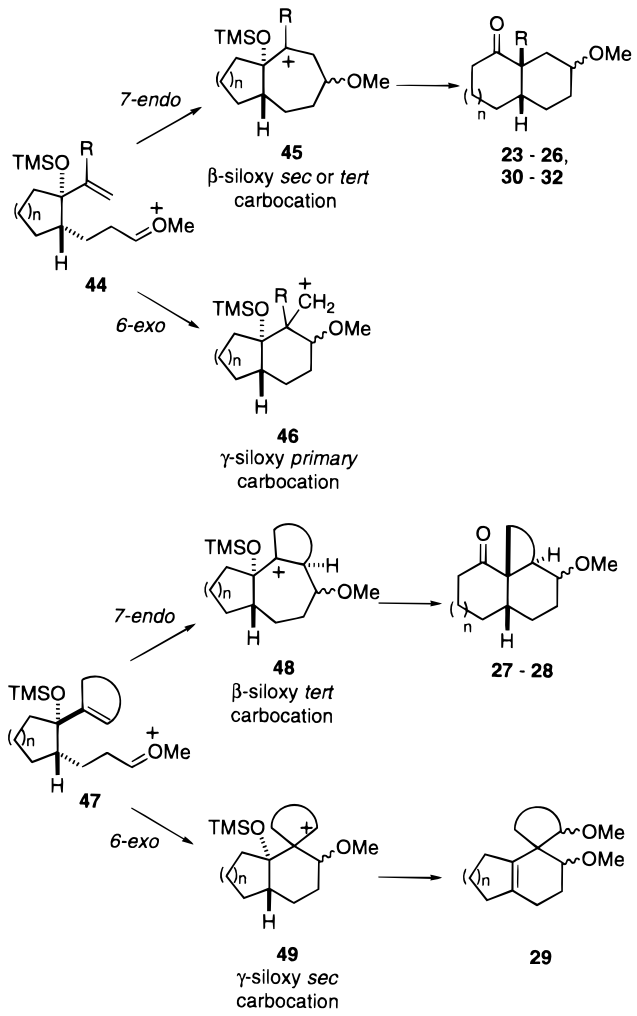
[a] Coupling constants in parentheses are in hertz. [b] ^{1}H DNOE analyses were run in C_6D_6 (500 MHz).

with many cyclic ketones. Key features of this method for preparing *cis*-fused carbocycles are the ability to directly incorporate angular substituents adjacent to the carbonyl group and to utilize starting materials having one less carbon than is found in the final ketone-containing ring. Two major limitations emerge from our exploration of ring-enlarging cyclohexane annulations: (1) only alkenes more nucleophilic than terminal vinyl (R ≠ H) can be employed and (2) angularly-fused tricyclic products cannot yet be synthesized in good yields since the efficiency of the Prins−pinacol conversion is low with cycloalkenyl substrates.



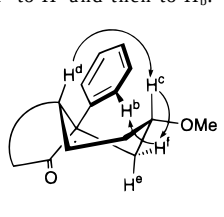
Mechanistic and Stereochemical Issues. As noted previously, Prins−pinacol ring-enlarging cyclohexane annulations fail with terminal vinyl π participants and proceed inefficiently when the π participant is a cycloalkene. In marked contrast, these limitations are not seen in related ring-enlarging cyclopentane annulations.[3,5] The principal reason for this disparity derives from the initial Prins cyclization step, which is particularly favorable in ring-enlarging cyclopentane annulations since a 6-membered ring is formed.[21] Successful ring-enlarging cyclohexane annulations require the Prins cyclization to occur in a less favorable 7-endo sense (Scheme 9). 2-Propenyl and styrenyl substrates represent best case scenarios in as much as 7-endo cyclization generates a tertiary (or tertiary benzylic) cation **45** (R = Me or Ar), while competing 6-exo cyclization produces an unstable primary carbenium ion **46**. With a terminal vinyl substrate, the Prins cyclization is less biased since a secondary cycloheptyl carbocation (**45**, R = H) results from 7-endo cyclization. Apparently the slower rate of cyclization to form a 7-membered (rather than a 6-membered) secondary cation is responsible for the failure of terminal vinyl substrates to participate in ring-enlarging cyclohexane annulations.

Scheme 9

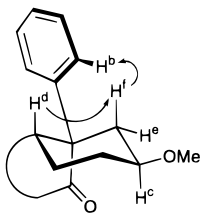


What is responsible for the poor efficiency of the Prins-pinacol transformation with cycloalkenyl substrates? The possibility that this result derives from inherent lower reactivity of the cycloalkenyl π-nucleophiles is untenable, since Mayr and co-workers have shown that anisylphenylcarbenium ion reacts 20 times faster with 1-methylcyclopentene than with isobutylene, while 1-methylcyclohexene reacts only slightly slower than isobutylene with this electrophile.[22] The poor performance of the cycloal-

between H^b and H^d for compound **31b**. The assignment of the *cis*-ring junction for this product was established by relaying enhancements from H^d to H^f and then to H_b.



31a

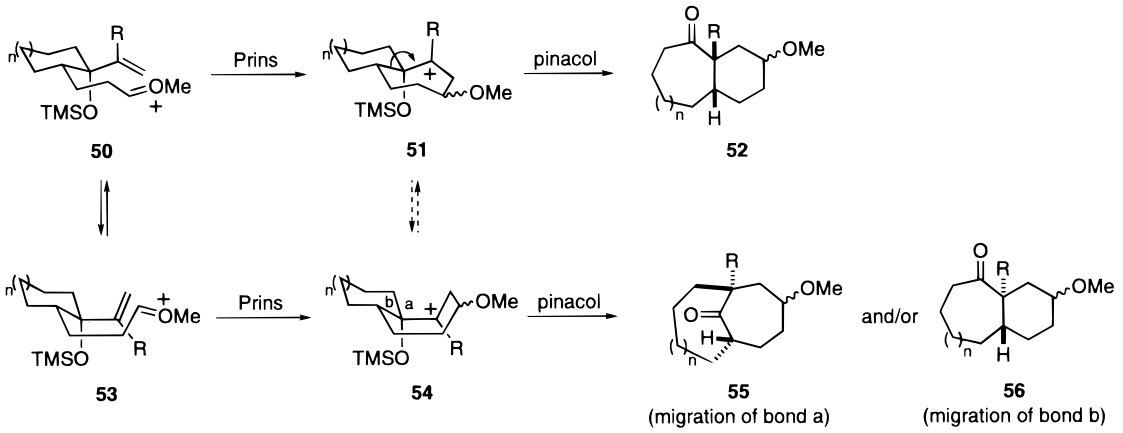


31b

(21) The particular facility of 6-endo cationic cyclizations underpins the powerful polyene cyclization approaches to terpenes and steroids. For a recent review, see: Sutherland, J. K. In *Comprehenive Organic Synthesis*; Trost, B. M., Fleming, I., Ed.; Pergamon: Oxford, 1991; Vol. 3, p 341.

(22) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938.

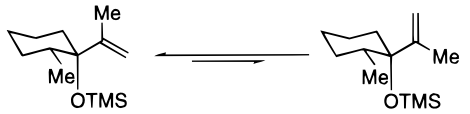
Scheme 10



kenyl substrates likely arises from competitive 6-exo cyclization of these substrates. As illustrated in Scheme 9, 6-exo cyclization of **47** forms a γ-siloxy secondary cation (**49**) while 7-endo cyclization generates β-siloxy tertiary cation **48**. Inductive electron withdrawal by the β-siloxy group apparently erodes the stability of the developing tertiary cation **48** to such an extent that 6-exo cyclization occurs competitively.[23] The isolation of spirotricyclic alkene **29** from attempted Prins−pinacol rearrangement of **18** (Scheme 7) is consistent with this analysis.

The exclusive formation of *cis*-fused products from the ring-enlarging cyclohexane annulation reactions of cyclopentyl and cyclohexyl substrates requires that pinacol rearrangement occurs only from bicyclic cation **51** (n = 0, 1) as depicted in Scheme 10. If pinacol rearrangement were faster than equilibration of carbenium ion conformers **51** and **54**, the observed cis stereoselectivity would derive from a preference for Prins cyclization by the **50** → **51** pathway.[24] Such a scenario is likely, in light of our recent observation that pinacol rearrangement is faster than conformational equilibration of 9-decalyl cations generated by Prins cyclization.[25] The proclivity for cyclization via conformation **50** likely derives from simple conformational preferences about the allylic bond. A molecular mechanics study of a model allylic silyl ether (eq 3) finds that the lowest energy conformation has a dihedral angle of 151° between the C−Me and C−O σ-bonds (represented by **57**).[26] All minima within 1.9 kcal/mol of the global minimum had dihedral angles greater than 145° between these bonds, while the lowest lying conformer having a syn relationship of the Me and OTMS groups (analogous to cyclization conformer **53**) was 3.6 kcal/mol above the global minimum.

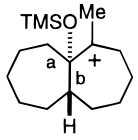
Competitive pinacol rearrangement via conformer **54** was seen only in the cycloheptyl series (n = 2) and in this case took place with exclusive migration of the methylene group (bond a). Clearly formation of an



(3)

57

inside−outside bicyclic product would be disfavored with the cyclopentyl and cyclohexyl substrates due to the considerable strain energy of "in−out" bicyclo[4.3.1]decane and bicyclo[4.4.1]undecane ring systems.[27] To pursue why the minor pathway in the cycloheptyl series involved exclusive migration of the methylene group of **54**, we examined the model bicyclo[5.5.0]dodecyl cation intermediate **58** by molecular mechanics calculations.[26] Many low-energy conformations of **58** (within 2.4−3.7 kcal/mol of the global minimum) having good overlap (dihedral angles of <30°) between bonds a or b and the vacant p orbital and leading to either "in−out" bicyclo[5.4.1]dodecane or *cis*-bicyclo[6.4.0]dodecane products were found. In contrast, no conformation of **58** that would generate a *trans*-bicyclo[6.4.0]dodecane upon pinacol rearrangement was within 5 kcal/mol of the global minimum.



58

Conclusion

The ring-enlarging cyclohexane annulation reaction reported here broadens the scope of the Prins−pinacol construction of carbocycles. Although this sequence is not as general as the related cyclopentane annulation reaction,[3,5] this chemistry provides an efficient new route to *cis*-bicyclo[n.4.0]alkanones having angular alkyl or aryl substituents (eq 2).

Experimental Section[28]

General Procedure for the Preparation of 2-(3,3-Dimethoxypropyl)cycloalkanones 9 and 11.[6c] A

(23) For example, the rate of carbocation formation is estimated to be 50 times faster from *t*-BuOH than from pinacol and 40 times faster from 2-butanol than from 1,2-propanediol: Herlihy, K. P. *Aust. J. Chem.* **1981**, *34*, 107.

(24) Stereoelectronically favorable 1,2-shifts of carbocations can have very low activation barriers, see: Shubin, V. G. *Top. Curr. Chem.* **1984**, *116/117*, 267.

(25) Minor, K. P.; Overman, L. E. *Tetrahedron*, **1997**, *53*, 8927.

(26) Monte Carlo conformational searches were done using Macromodel version 5.5 and the MM2* forcefield, see: Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. Saunders, M.; Houk, K. N.; Wu, Y.-D.; Still, W. C.; Lipton, M.; Chang, G.; Guida, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 1419.

(27) Alder, R. W.; East, S. P. *Chem. Rev.* **1996**, *96*, 2097.

(28) The procedure we employed to purify THF, CH_2Cl_2 and toluene has been described: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics*, **1996**, *15*, 1518. TMSOTf was distilled from poly(4-vinylpyridine) prior to use and hexanes were distilled from CaH_2. HPLC separations were performed using Waters Nova Silica, 6 μm, 19 mm × 300 mm, 8:1 hexane−EtOAc, 5 mL/min flow rate. Other general experimental details have been described: Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.

THF solution of imine **6**−**8**[6a] (0.5 M) was deprotonated with $LiNEt_2$ (1.05 equiv, 1 M) at −78 °C.[6a] The reaction was allowed to warm to 0 °C, and after 2 h, 1-bromo-3,3-dimethoxypropane[6b] (1.1 equiv) was added dropwise at −78 °C.[6b] After the solution was allowed to warm to rt overnight, a mixture of NH_4Cl (saturated aqueous) was added and the resulting mixture was heated at reflux (65−70 °C) for 5 h. After cooling to rt, the mixture was extracted with Et_2O (3 × 20 mL) and the ether extracts were washed with H_2O (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the residue was purified by vacuum distillation.

2-(3,3-Dimethoxypropyl)cyclopentanone (9): 71% as a colorless liquid; bp 92−93 °C (1.3 mm); ^{1}H NMR (300 MHz, C_6D_6) δ 4.20 (t, J = 6.0 Hz, 1H), 3.10 (s, 6H), 1.99−1.87 (m, 1H), 1.78−1.03 (m, 10H); ^{13}C NMR (75 MHz, C_6D_6) δ 218.4, 104.5, 52.3, 52.2, 48.5, 37.8, 30.6, 29.6, 25.1, 20.7; IR (film) 1736 cm^{-1}; MS (CI, isobutane) m/z 155 (M − MeO). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.36; H, 9.78.

2-(3,3-Dimethoxypropyl)cycloheptanone (11): 82% as a colorless liquid; bp 140−145 °C (3.8 mm); ^{1}H NMR (300 MHz, C_6D_6) δ 4.20 (t, J = 7.0 Hz, 1H), 3.11 (s, 3H), 3.09 (s, 3H), 2.30−2.17 (m, 3H), 1.76−1.64 (m, 1H), 1.54−1.46 (m, 6H), 1.35−1.20 (m, 2H), 1.12−0.98 (m, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 213.4, 104.6, 52.4, 52.0, 51.6, 42.8, 31.9, 30.5, 29.6, 28.9, 27.7, 24.5; IR (film) 1702 cm^{-1}; MS (CI, isobutane) m/z 183 (M − MeO). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.18; H, 10.34.

(2*S,1*R**/*S**)-2-(3,3-Dimethoxypropyl)-1-ethenyl-1-(trimethylsiloxy)cyclopentane (12).** A solution of keto acetal **9** (500 mg, 2.7 mmol) and THF (8 mL) was added dropwise to vinylmagnesium bromide (1.0 M in THF, 5.4 mL, 5.4 mmol) at 0 °C; then the cooling bath was removed. After 2 h, ice cold saturated NH_4Cl (10 mL) was added. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with H_2O (1 × 10 mL), dried (K_2CO_3), and concentrated. The crude alcohol was dissolved in *N*-(trimethylsilyl)imidazole (0.8 mL, 5.5 mmol) at rt. After 18 h, the resulting brown solution was cooled to 0 °C, and MeOH (5 mL) was carefully added to quench excess silylating agent; then Et_2O (10 mL) was added and the resulting solution was washed with H_2O (2 × 15 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by radial chromatography (4 mm thickness, SiO_2, 20:1 hexanes−EtOAc, 1% Et_3N), followed by bulb-to-bulb distillation to afford a 4.9:1 stereoisomeric mixture of **12** (636 mg, 83%): bp 105 °C (0.4 mm, bulb-to-bulb distillation); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dd, J = 17.3, 10.7 Hz, 1H), 5.13 (dd, J = 17.3, 1.6 Hz, 1H), 5.02 (dd, J = 10.7, 1.6 Hz, 1H), 4.33 (t, J = 5.6 Hz, 1H), 3.30 (s, 3H), 3.29 (s, 3H), 1.90−1.15 (m, 11H), 0.09 (s, 9H, TMS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 112.3, 104.9, 104.8, 85.1, 52.4, 50.6, 38.7, 31.4, 29.5, 23.1, 21.2, 2.14; IR (film) 3048, 1631 cm^{-1}; MS (CI, isobutane) m/z 255 (M − MeO). Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 63.00; H, 10.58.

General Procedure for Preparing Cyclization Precursors 13−15. A solution of keto acetal **9**−**11** and THF was added dropwise at rt to a solution of 2-propenylmagnesium bromide [1 M in THF, from 2-bromopropene (2.0 equiv) and Mg (2.4 equiv)]. After 2 h, ice cold saturated NH_4Cl and then Et_2O and H_2O were added. The organic layer was dried (Na_2SO_4) and concentrated, and the crude alcohol product was dissolved in *N*-(trimethylsilyl)imidazole (5.0 equiv). After 18 h at rt, the resulting brown solution was cooled to 0 °C and MeOH was carefully added to quench excess silylating agent. Et_2O was then added, the resulting solution was washed with H_2O and dried (Na_2SO_4), and the crude product was purified by radial chromatography (4 mm thickness, SiO_2, 20:1 hexanes−EtOAc, 1% Et_3N).

(2*S,1*R**/*S**)-2-(3,3-Dimethoxypropyl)-1-(2-propenyl)-1-(trimethylsiloxy)cyclopentane (13).** Following the general procedure, keto acetal **9** (1.0 g, 5.37 mmol) afforded **13** (1.13 g, 70%) as a single diastereomer after radial chromatography (4 mm thickness, SiO_2, 20:1 hexanes−EtOAc, 1% Et_3N). Using 2-propenyllithium, the same procedure provided **13** (88%) as a 9:1 mixture (GLC analysis) of stereoisomers. The diastereomers were separated by HPLC.[27] Major diastereomer **13**: bp 115 °C (0.6 mm, bulb-to-bulb distillation); ^{1}H NMR (300 MHz, C_6D_6) δ 4.98 (d, J = 2.0 Hz, 1H), 4.85 (d, J = 2.0 Hz, 1H), 4.32 (t, J = 5.8 Hz, 1H), 3.30 (s, 3H), 3.29 (s, 3H), 2.05−1.97 (m, 1H), 1.83−1.67 (m, 5H), 1.65−1.35 (m, 7H), 1.22−1.13 (m, 1H), 0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 111.2, 104.9, 87.7, 52.4, 48.1, 37.1, 31.3, 29.6, 23.2, 21.7, 19.9, 2.0; IR (film) 3040, 1643 cm^{-1}; MS (CI, isobutane) m/z 301 (MH). Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 64.06; H, 10.74.

Details of the preparation of **14** and **15** are found in the Supporting Information.

General Procedure for Preparing Cyclization Precursors 16−22. A 1 M solution of keto acetal **9**−**11** and THF was added dropwise over 15 min at −78 °C to a THF solution (0.5−0.8 M) of an alkenyllithium [from *s*-BuLi (1.2 M in cyclohexane, 2.0 equiv) or *n*-BuLi (2.2 M in hexanes, 2.0 equiv) and the freshly distilled alkenyl bromide[7,8] (2.0 equiv)]. After 3 h at −78 °C, MeOH was added, followed by ice cold saturated NH_4Cl. The resulting mixture was extracted with Et_2O, and the combined organic layers were washed with H_2O, dried (K_2CO_3), and concentrated. The crude alcohol product was purified by column chromatography (Al_2O_3, neutral, activity I) and then dissolved in *N*-(trimethylsilyl)imidazole (13.5 equiv). The solution was heated at 100 °C overnight, then cooled to 0 °C, and MeOH was carefully added to quench excess silylating agent. This solution was partitioned between Et_2O and H_2O, and the organic layer was washed with H_2O, dried (Na_2SO_4), and concentrated. The crude product was purified by radial chromatography (4 mm or 2 mm thickness, SiO_2, 10:1 hexanes−EtOAc, 1% Et_3N).

(1*R/*S**,2*S**)-2-(3,3-Dimethoxypropyl)-1-(cyclopenten-1-yl)-1-(trimethylsiloxy)cyclopentane (16).** Following the general procedure, keto acetal **9** (376 mg, 2.0 mmol) and 1-bromocyclopentene[7a] (594 mg, 4.0 mmol) afforded **16** (470 mg, 71%) as a 3:1 mixture of stereoisomers after radial chromatography (4 mm thickness, SiO_2, 10:1 hexanes−EtOAc, 1% Et_3N): bp 140 °C (0.7 mm, bulb-to-bulb distillation); ^{1}H NMR (500 MHz, C_6D_6) δ 5.63 (t, J = 2.1 Hz, 1H, major), 5.42 (t, J = 1.8 Hz, 1H, minor), 4.35 (t, J = 5.4 Hz, 1H, major), 4.30 (t, J = 5.4 Hz, 1H, minor), 3.15 (s, 3H, major), 3.14 (s, 3H, minor), 3.12 (s, 3H, minor), 3.11 (s, 3H, minor), 2.57−0.81 (m, 34H), 0.16 (s, 9H, major), 0.15 (s, 9H, minor); ^{13}C NMR (125 MHz, $CDCl_3$, major isomer) δ 152.6, 148.7, 125.6, 124.8, 105.3, 104.9, 85.2, 82.8, 52.4, 51.4, 50.2, 48.7, 37.9, 35.1, 32.8, 32.6, 32.4, 32.3, 31.3, 31.1, 29.5, 27.8, 25.9, 24.0, 23.6, 23.5, 21.4, 20.6, 2.1, 1.8; IR (film) 3029, 1429 cm^{-1}; MS (CI, isobutane) m/z 327 (MH). Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.49. Found: C, 66.02; H, 10.46.

Details of the preparation of **17**−**22** are found in the Supporting Information.

General Procedures for Ring-Enlarging Cyclohexane Annulations. Procedure A ($SnCl_4$). A solution of a Lewis acid (1.0 M, 1.1 equiv) and CH_2Cl_2 was added to a solution of cyclization substrate (0.05 M) and CH_2Cl_2 at −78 °C, and the resulting solution was allowed to warm to −23 °C. After 5 min, excess Et_3N was added, followed by excess MeOH. EtOAc and HCl (1.0 M) were then added, and the organic layer was separated, washed with brine, dried (MgSO4), and concentrated. The residue was purified by radial chromatography and/or bulb-to-bulb distillation. **Procedure B (R_3SiOTf).** A solution of freshly purified TMSOTf or TBDMSOTf (0.5−1.0 equiv, approximately 0.5 M), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 1−2 equiv), and CH_2Cl_2 was added dropwise to a 0.1 M CH_2Cl_2 solution of the styrenyl cyclization substrates **19**−**22** at −78 °C; then the cooling bath was removed. After 15−30 min, the reaction was quenched by adding saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with Et_2O (3 × 10 mL), dried, and concentrated. The crude product was purified by radial chromatography and/or bulb-to-bulb distillation. Aliphatic analogs **13**−**16** were cyclized at rt.

(1*R,7*S**,10*R**/*S**)-10-Methoxy-1-phenylbicyclo[5.4.0]undecan-2-one (23a/23b).** Following procedure A, **20** (426 mg, 1.09 mmol) was cyclized in the presence of $SnCl_4$ to give **23** (249 mg, 84%) as a 2.9:1 mixture of epimers after radial chromatography (2 mm thickness, SiO_2, 10:1 hexanes−EtOAc). Following procedure B, **20** (81 mg, 0.22 mmol) afforded **23** (54 mg, 90%) as a 2.2:1 mixture of epimers. The epimers were separated by preparative TLC (1 mm thickness, SiO_2, 20:1 hexanes−EtOAc). Minor α-epimer (**23a**):[18] mp 101−103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 7.3 Hz, 2H), 7.35 (t, J = 7.3 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 3.26 (s, 3H), 2.96−2.93 (m, 1H), 2.84−2.78 (m, 2H), 2.64−2.59 (m, 1H), 2.01−1.97 (m, 1H), 1.96−1.83 (m, 3H), 1.82−1.74 (m, 1H), 1.68−1.43 (m, 6H), 1.23−1.15 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 212.6, 138.8, 128.9, 128.3, 126.9, 76.4, 59.2, 55.4, 38.9, 36.1, 35.2, 32.9, 30.6, 28.6, 28.3, 27.2; IR (film) 1691 cm^{-1}; HRMS (CI, isobutane) m/z 272.1772 (M, 272.1776 calcd for $C_{18}H_{24}O_2$). Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.36; H, 8.89. Found: C, 79.35; H, 8.95. Major β-epimer (**23b**): ^{1}H NMR (500 MHz, C_7D_8, 95 °C) δ 7.15−7.05 (m, 4H), 6.98−6.92 (m, 1H), 3.49 (m, 1H), 2.99 (s, 3H), 2.44−2.35 (m, 2H), 2.35−2.28 (m, 1H), 2.03−1.95 (m, 1H), 1.79−1.71 (m, 2H), 1.71−1.61 (m, 2H), 1.43−1.88 (m, 7H); ^{13}C NMR (125 MHz, C_7D_8, 95 °C) δ 211.8, 143.8, 137.6, 127.0, 126.6, 76.2, 60.7, 55.5, 42.1, 38.9, 31.5, 30.4, 27.2, 26.3, 24.8, 20.5; IR (film) 1698 cm^{-1}; HRMS (CI, isobutane) m/z 272.1764 (M, 272.1776 calcd for $C_{18}H_{24}O_2$).

Details of the preparation of **24**−**32** and **37** are found in the Supporting Information.

General Procedure for Oxidation of Bicyclic Keto Ethers 24−**28.** Following procedure A, aliphatic precursors **13**−**17** were cyclized with $SnCl_4$. The resulting crude carbocyclic products were then oxidized with RuO_4 according to a procedure by Sharpless.[19]

(1*R,6*S**)-1-Methylbicyclo[4.4.0]decane-2,9-dione (33).** Oxidation of **24** gave diketone **33** (47%) as a colorless solid after purification by column chromatography (SiO_2, 1.5:1 hexanes−EtOAc): mp 63−64 °C;[18] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.83 (dd, J = 14.5, 1.5 Hz, 1H), 2.52 (ddd, J = 14.7, 9.2, 6.0 Hz, 1H), 2.43−2.32 (m, 2H), 2.26 (dddd, J = 14.9, 9.1, 5.8, 1.3 Hz, 1H), 2.15−2.05 (m, 2H), 2.05−1.94 (m, 1H), 1.92−1.78 (m, 4H), 1.78−1.71 (m, 1H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 208.6, 52.7, 47.3, 43.5, 39.2, 37.0, 28.0, 25.7, 24.0, 23.6; IR (KBr) 1714, 1698 cm^{-1}; MS (EI, 70 eV) m/z 180 (M). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.38, H, 8.97.

Details of the preparation of **38**−**41** are found in the Supporting Information.

(1*R,7*S**,10*S**)-10-((3,5-Dinitrobenzoyl)oxy)-1-methylbicyclo[5.4.0]undecan-2-one (36).** Oxidation of **25** gave dione **34** (52%) as a colorless solid after purification by column chromatography (SiO_2, 4:1 hexanes−EtOAc): bp 135 °C (0.8 mm, bulb-to-bulb distillation); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.79 (dt, J = 11.4, 3.2 Hz, 1H), 2.48 (d, J = 14.9 Hz, 1H), 2.35−2.25 (m, 3H), 2.18−2.12 (m, 1H), 2.07−1.95 (m, 3H), 1.86−1.78 (m, 2H), 1.75−1.71 (m, 1H), 1.60−1.45 (m, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.6, 210.9, 54.5, 46.0, 40.1, 39.3, 37.1, 32.5, 29.4, 29.0, 27.5, 23.8; IR (film) 1712, 1710 cm^{-1}; MS (EI, 70 eV) m/z 194 (M). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.00; H, 9.29.

A solution of Li(*s*-Bu)$_3$BH (1.0 M, 1.1 mL) and THF was added dropwise to a solution of diketone **34** (200 mg, 1.0 mmol) and THF (5.0 mL) at −78 °C. After 2 h, additional Li(*s*-Bu)$_3$BH (0.5 mL, 0.5 mmol) was added at −78 °C. After 1 h, MeOH (3.0 mL), 1 N aqueous NaOH (3.0 mL), and H_2O_2 (30% aqueous solution, 3.0 mL) were then added sequentially and the reaction was allowed to warm to rt over 15−20 min. The aqueous was separated and extracted with EtOAc (4 × 20 mL), and the resulting organic layer was washed with brine (2 × 20 mL), dried (Na_2SO_4), and concentrated to give **35** (215 mg).

A portion of this crude alcohol (115 mg, 0.53 mmol) and pyridine (51 mg, 0.64 mmol) were dissolved in Et_2O (1 mL). 3,5-Dinitrobenzoyl chloride (145 mg, 0.63 mmol) was added, and the mixture was heated at reflux overnight and then cooled and diluted with EtOAc (20 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layer was washed with H_2O (10 mL), 10% aqueous HCl (10 mL), H_2O (10 mL) and saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$), and concentrated. After recrystallization from benzene, **36** was obtained (187 mg, 75%) as a 1:1 complex with benzene from which single crystals were obtained:[18] mp 81−83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (t, J = 2.0 Hz, 1H), 9.12 (m, 2H), 5.39−5.37 (m, 1H), 2.87−2.82 (m, 1H), 2.34−2.30 (m, 1H), 2.16 (dd, J = 14.4, 2.9 Hz, 1H), 2.05−1.96 (m, 1H), 1.93−1.72 (m, 7H), 1.67−1.47 (m, 4H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.5, 161.7, 148.6, 134.5, 129.3, 122.2, 73.4, 50.1, 41.3, 40.4, 36.0, 31.8, 28.0, 26.9, 26.5, 25.5, 25.3; IR ($CHCl_3$) 1728, 1697 cm^{-1}; MS (CI, isobutane) m/z 391 (MH). Anal. Calcd for $C_{19}H_{22}N_2O_7 \cdot C_6H_6$: C, 64.09; H, 6.02; N, 5.98. Found: C, 64.07; H, 6.02; N, 5.99.

(1*R,6*R**,9*S**,10*S**)-9-Methoxytricyclo[4.4.0.3^{1,10}]tridecan-2-one Thiosemicarbazone (42).** Tricyclic ketone **27** (30 mg, 0.14 mmol) and thiosemicarbazide (49 mg, 0.54 mmol) were dissolved in glacial HOAc (1.4 mL), and after 18 h at rt, HOAc was removed azeotropically with toluene (2 × 10 mL). The residue was purified by column chromatography (SiO_2, 2:1 hexanes−EtOAc) to afford **42** (32 mg, 84%) as a colorless solid. Single crystals were obtained by recrystallization from acetonitrile:[18] mp 189−190 °C; ^{1}H NMR (500 MHz, CD_4OD) δ 3.31 (s, 4H), 3.28 (s, 3H), 2.80−2.76 (m, 1H), 2.63 (dt, J = 14.5, 5.0 Hz, 1H), 2.17−2.06 (m, 2H), 1.96−1.90 (m, 1H), 1.82−1.57 (m, 12H), 1.34−1.29 (m, 1H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 118.1, 81.0, 56.5, 54.7, 48.5, 45.1, 40.0, 37.9, 29.7, 28.9, 25.9, 25.6, 24.9, 23.0; IR (film) 1481, 1382 cm^{-1}; HRMS (FAB) *m/z* 295.1713 (295.1718 calcd for $C_{14}H_{25}N_3SO$).

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Supporting Information Available: Experimental procedures and characterization data for the preparation of **14**, **15**, **17**−**22**, **24**−**32**, and **37**−**41** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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