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Origin of Stereocontrol in the Construction of the 12-Oxatricyclo[6.3.1.0^{2,7}]dodecane Ring System by Prins−Pinacol Reactions

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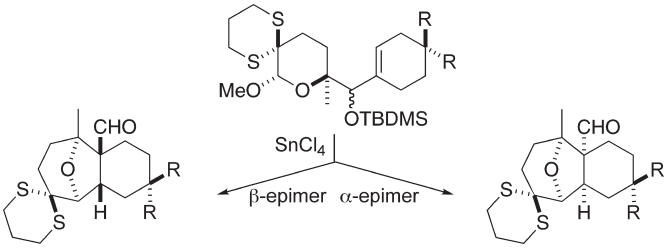

Polycyclic products containing the 12-oxatricyclo[6.3.1.0^{2,7}]dodecane moiety having either the trans (**8a**−**e**) or cis (**9a**−**e**) relative configuration of the oxacyclic bridge and the cis angular substituents are formed stereospecifically by Prins−pinacol cyclizations of unsaturated α-dithianyl acetals **14a**−**e** or **15a**−**e**. These results show that the topography (boat or chair) of the Prins cyclization of the sulfur-stabilized oxocarbenium ions generated from acetals **14a**−**e** or **15a**−**e** is controlled by the stereoelectronic influence of the allylic substituents, with steric effects playing a minor role. A complex molecular rearrangement that is terminated by a thio-Prins−pinacol reaction is also identified.

Introduction

The efficient construction of complex molecular structures from simple materials is one of the primary goals of synthetic organic chemistry. A particularly expeditious way to build complexity is to combine two or more distinct steps into a single transformation.[1] One such process, the Prins−pinacol cascade reaction wherein the carbocation produced by a Prins cyclization is terminated by a pinacol shift,[2] has proven to be useful in the stereoselective synthesis of complex carbocyclic and heterocyclic structures.[3]

We described in 2001 a stereoelectronic model that allowed the prediction of the stereochemical outcome of Prins−pinacol syntheses of substituted tetrahydrofurans.[4] Stereoselectivity in the synthesis of carbocycles has been explained with similar models.[5] However, these models have only been applied to Prins−pinacol reactions occurring by generally favored chairlike transition structures,[6] with the caveat that steric interactions could

(1) For selected recent reviews, see: (a) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley−VCH: Weinheim, Germany, 2006. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (c) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619–1665. (d) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143–2173. (e) Müller, T. J. J., Ed. Metal Catalyzed Cascade Reactions. In *Topics in Organometallic Chemistry*; Springer-Verlag: Berlin, Germany, 2006; Vol 19. (f) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1–21. (g) Enders, D.; Grondal, C.; Huettl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581. (h) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477–1489. (i) Miyabe, H.; Takemoto, Y. *Chem.—Eur. J.* **2007**, *13*, 7280–7286. (j) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341–5378. (k) Kirsch, S. F. *Synthesis* **2008**, 3183–3204. (l) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037–2046.

(2) (a) Martinet, P.; Mousset, G.; Michel, M. C. R. *Acad. Sci. Paris, Ser. C* **1969**, *268*, 1303–1306. (b) Martinet, P.; Mousset, G. *Bull. Soc. Chim. Fr.* **1970**, 1071–1076.

(3) For recent reviews, see: (a) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143–7157. (b) Overman, L. E. *Tetrahedron* **2009**, *65*, 6432–6446.

(4) Cohen, F.; MacMillan, D. W. C.; Overman, L. E.; Romero, A. *Org. Lett.* **2001**, *3*, 1225–1228.

(5) Gahman, T. C.; Overman, L. E. *Tetrahedron* **2002**, *58*, 6473–6483.

(6) For reviews, see: (a) Snider, B. B. In *The Prins Reaction and Carbonyl Ene Reactions*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 527−561. (b) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2007**, *11*, 925–957.

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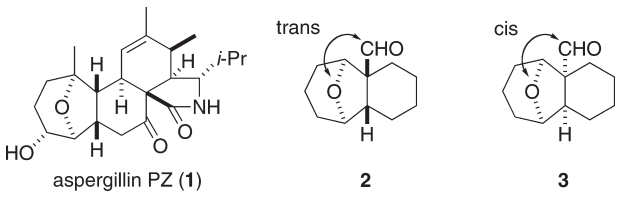
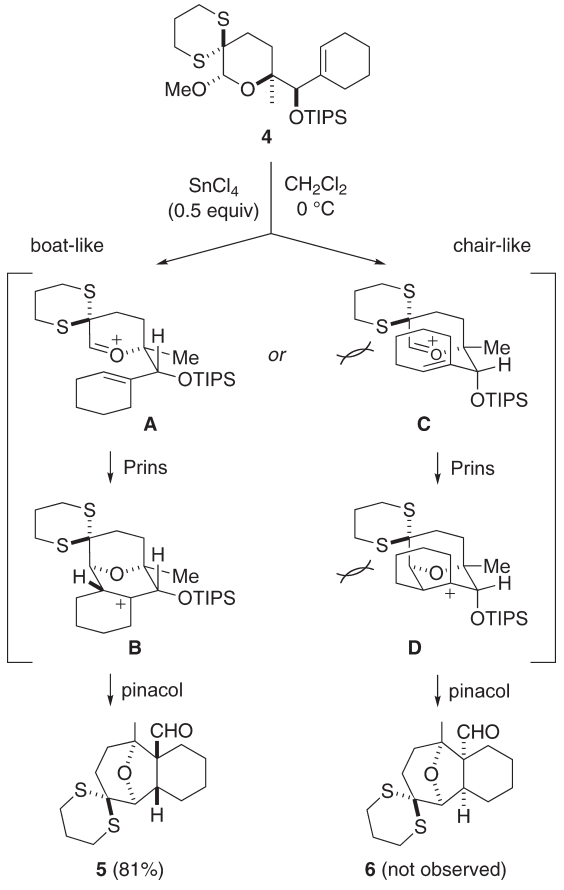


FIGURE 1. 12-Oxatricyclo[6.3.1.0^{2,7}]dodecanes.

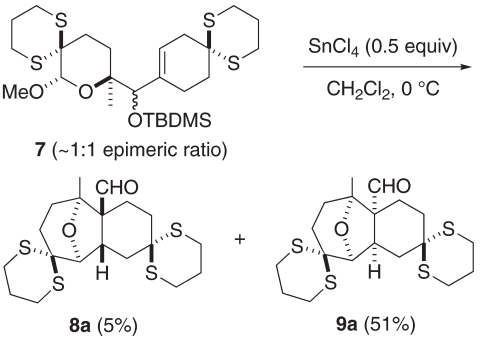
potentially override the typically dominant stereoelectronic effects.

In preliminary scouting experiments carried out in the context of a projected total synthesis of the structurally novel fungal metabolite aspergillin PZ (**1**),[7] we reported that 12-oxatricyclo[6.3.1.0^{2,7}]dodecanes having either a trans or cis relative configuration of the oxacyclic bridge and the cis angular substituents could be constructed by Prins−pinacol reactions (**2** or **3**, Figure 1).[8,9] In that report, we concluded that stereocontrol in the Prins−pinacol reaction hinged upon steric factors. It was specifically proposed that the steric bulk of the 1,3-dithiane carbonyl protecting group in cyclization precursor **4** was responsible for sufficiently destabilizing the typically favored chair cyclization/rearrangement sequence (**C** → **D** → **6**) that the boatlike pathway (**A** → **B** → **5**) was favored (Scheme 1). The siloxy epimer of **4** was reported to form an intractable mixture of products under identical conditions.

SCHEME 1. Steric Rationale for Prins−Pinacol Stereoselectivity[8]



Although the results depicted in Scheme 1 were attributed initially to steric effects, further experimentation revealed that additional factors must be operative. If steric factors were of paramount importance, it was expected that incorporating additional bulky substituents on the cyclohexene ring of the cyclization precursor would further increase the steric clash depicted in structures **C** and **D**, increasing the energy of the chair-like pathway. However, submission of a mixture of epimers of bis-dithiane acetal **7** to standard Prins−pinacol cyclization conditions ($SnCl_4$, CH_2Cl_2, 0 °C) resulted in the predominant formation of product **9a**, which would arise from a chair topography pathway (eq 1).[10] Replacement of $SnCl_4$ with the monodentate Lewis acid $BF_3 \cdot OEt_2$ yielded similar results, ruling out chelation between the two dithiane rings as the cause of this unexpected preference for the formation of pentacyclic product **9a**.



(1)

To enhance our understanding of the factors that control stereoselection in Prins−pinacol reactions, additional experimental studies were undertaken. This article reports the results of such an investigation that highlights once again the importance of stereoelectronic factors in dictating the outcome of Prins−pinacol processes. Additionally, a new skeletal rearrangement/thio-Prins−pinacol cascade reaction is described.

Results

Preparation of Prins−Pinacol Substrates. To help identify which structural features are important in determining stereoselection in Prins−pinacol reactions of the type depicted in eq 1, a series of cyclization precursors that differ at a single position of the cyclohexene ring were prepared (Scheme 2). In a straightforward sequence, cyclohexenyl iodides **10a**−**e**[11] were treated individually with 1.8 equiv of *tert*-butyllithium, and the resulting alkenyllithium species were coupled at −78 °C in THF with racemic aldehyde **11**[8] to provide a 1.6−2.0:1 mixture of secondary alcohol epimers **12a**−**e** (*S**,*R** relative

(7) Zhang, Y.; Wang, T.; Pei, Y.; Hua, H.; Feng, B. *J. Antibiot.* **2002**, *55*, 693–695.

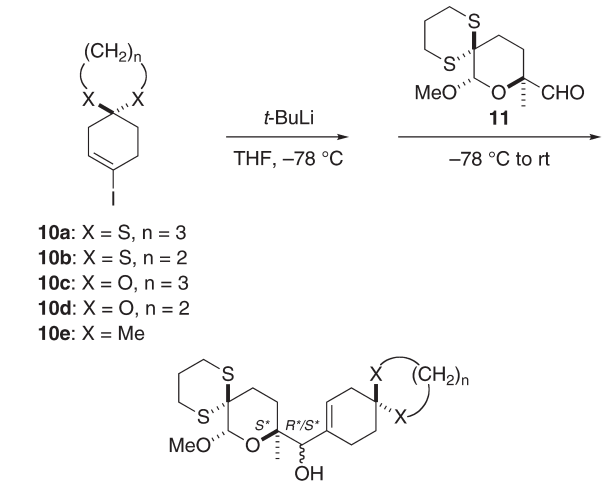
(8) Overman, L. E.; Velthuisen, E. J. *Org. Lett.* **2004**, *6*, 3853–3856.

(9) For a quite different approach to the construction of the trans variant of this oxatricyclic ring system, see: Molander, G. A.; Czakó, B.; St. Jean, D. J., Jr. *J. Org. Chem.* **2006**, *71*, 1172–1180.

(10) Velthuisen, E. J. Ph.D. Dissertation, University of California, Irvine, 2005.

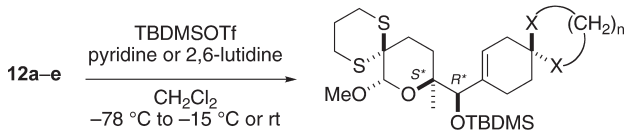
(11) The preparation of cyclohexenyl iodides **10a**−**e** is described in the Supporting Information.

SCHEME 2. Preparation of Prins–Pinacol Substrates 14a–e and 15a–e

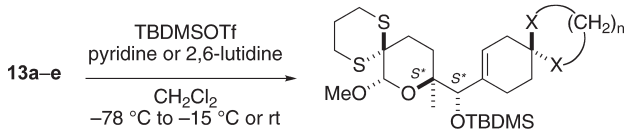


10a: X = S, n = 3
10b: X = S, n = 2
10c: X = O, n = 3
10d: X = O, n = 2
10e: X = Me

12a (*S*, R**), **13a** (*S*, S**): X = S, n = 3; 52% (1.6:1)
12b (*S*, R**), **13b** (*S*, S**): X = S, n = 2; 75% (1.6:1)
12c (*S*, R**), **13c** (*S*, S**): X = O, n = 3; 57% (1.6:1)
12d (*S*, R**), **13d** (*S*, S**): X = O, n = 2; 62% (1.6:1)
12e (*S*, R**), **13e** (*S*, S**): X = Me; 68% (2.0:1)



14a: X = S, n = 3; 80%
14b: X = S, n = 2; 86%
14c: X = O, n = 3; 84%
14d: X = O, n = 2; 89%
14e: X = Me; 84%

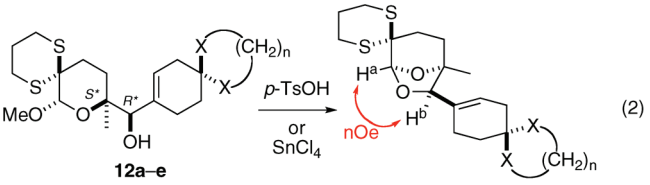


15a: X = S, n = 3; 87%
15b: X = S, n = 2; 87%
15c: X = O, n = 3; 84%
15d: X = O, n = 2; 97%
15e: X = Me; 78%

configuration of the vicinal stereocenters) and **13a–e** (*S**, *S** relative configuration of the vicinal stereocenters), respectively. These mixtures of alcohol epimers were separated by HPLC, and samples of isomerically pure (>97:3 dr) alcohols were silylated to yield the *S**,*R** cyclization substrates **14a–e** and their *S**,*S** siloxy epimers **15a–e** in good overall yields.

The relative configurations of alcohols **12a–e** and **13a–e** were verified by their individual transformation upon exposure to *p*-toluenesulfonic acid or stannic chloride to cyclic acetals **16a–e** (eq 2) and **17a–e** (eq 3). The presence or absence of NOESY crosspeaks between the signals for the dioxolane methine hydrogens H^a and H^b allowed the relative configuration of the secondary alcohol stereocenters of the precursors to be specified.

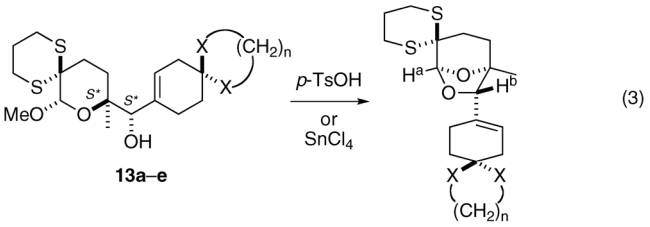
Prins–Pinacol Reactions. Prins–pinacol precursors **14a–e** and **15a–e** were chosen to allow both the size and electronic properties of the C4 substituents of the cyclohexene ring to be varied. Substrates **14c** and **15c** contain a spiro-1,3-dioxane group in which the oxygen substituents will be more electron withdrawing than the sulfur substituents of substrates **14a** and **15a**.[12] 1,3-Dithiolane substrates **14b** and **15b** and 1,3-dioxolane substrates **14d** and **15d** are sterically smaller than their 1,3-dithiane and 1,3-dioxane congeners, but maintain similar electronic profiles. Geminal dimethyl substrates **14e** and **15e** provide an additional set of reactants in which only the steric size of the C4 substituents is varied.



12a–e

(2)

16a: X = S, n = 3; 86%
16b: X = S, n = 2; 85%
16c: X = O, n = 3; 19%
16d: X = O, n = 2; 50%
16e: X = Me; 99%



13a–e

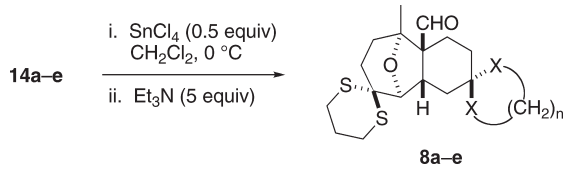
(3)

17a: X = S, n = 3; 97%
17b: X = S, n = 2; 94%
17c: X = O, n = 3; 25%
17d: X = O, n = 2; 49%
17e: X = Me; 94%

All substrates reacted within 30 min upon exposure to 0.5 equiv of $SnCl_4$ in CH_2Cl_2 at 0 °C. Precursors having the *S**, *R** relative configuration of the vicinal stereocenters (**14a–e**) cyclized to provide Prins–pinacol products **8a–e** having a trans relationship between the oxygen bridge and the angular substituents (Table 1). Depending upon the substituents on the cyclohexene ring, the yields of product **8** varied greatly. Prins–pinacol products **8a** and **8b** were formed in very low yield from the dithiane and dithiolane substrates, with many other unidentified products being produced. The low yield (7%) of Prins–pinacol product **8a** produced from the *S**,*R** precursor **14a** is consistent with the results observed earlier in reactions of a mixture of siloxy epimers (eq 1).[10] However, the alternative Prins–pinacol products **9a–e** having the epimeric configuration of the cis angular substituents were not observed in the ^1H NMR spectra of the crude reaction mixtures. The relative configuration of Prins–pinacol products **8a–e** followed from the diagnostic small (<1 Hz) coupling constants observed between the vicinal methine hydrogens H^a and H^b, consistent with a dihedral angle of nearly 90° between these hydrogen atoms (Figure 2).[13]

(12) The revised Pauling electronegativity of sulfur is 2.58 (similar to carbon, 2.55), whereas for oxygen it is 3.44: Allred, A. L. *J. Inorg. Nucl. Chem.* **1961**, *17*, 215–221.
(13) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870–2871.

TABLE 1. Prins−Pinacol Cyclizations of *S,*R** Substrates 14a−e**



precursor			product	
compd	X	*n*	compd	yield,[a] %
14a	S	3	**8a**	7[b]
14b	S	2	**8b**	18
14c	O	3	**8c**	54
14d	O	2	**8d**	72
14e	Me		**8e**	43

[a]Mean yield of pure product from duplicate experiments. [b]Yield was determined by ^{1}H NMR spectroscopy, using 1-chloro-4-nitrobenzene as an internal standard.

Substrates **15a−e** having the *S**,*S** relative configuration of the vicinal stereocenters cyclized to form two major products: the Prins−pinacol products **9a−e** and a byproduct **18a−e** (Table 2). The relative configuration of products **9a−e** was signaled by the ∼7.5 Hz coupling constant observed for H^a and H^b, as would be expected from the small dihedral angle between these hydrogens (Figure 2).[13] In all reactions, the alternate Prins−pinacol products **8a−e** were not detected by ^{1}H NMR analysis of crude reaction mixtures.

Aldehydes **18a−e** are the only significant byproducts produced in the Prins−pinacol cyclizations of substrates **15a−e**. The most striking spectroscopic feature of these products is the chemical shift of the aldehyde hydrogen in the ^{1}H NMR spectrum, which at δ ∼10.5 ppm is downfield of the normal range for aliphatic aldehydes.[14] Single-crystal X-ray diffraction analysis confirmed the identity of product **18b**,[15] with products **18a**,**c**,**d**,**e** being assigned in analogous fashion on the basis of their distinctive aldehyde chemical shifts. Byproducts **18a−e** contain a unique pentacyclic ring system in which the former 1,3-dithiane ring is expanded to a seven-membered 1,4-dithiepane ring. The oxo bridge spanning the carbocyclic seven-membered ring of these byproducts is also displaced by one carbon from its position in Prins−pinacol products **8** and **9**, with the ring junction between the carbocyclic seven- and six-membered rings being trans rather than cis.

Discussion

Among the trends apparent in the results of the Prins−pinacol reactions summarized in Tables 1 and 2, one stands out: the configuration of the allylic silyl ether determines the stereochemical outcome of the Prins−pinacol reaction. Substrates **14a−e** with the *S**,*R** relative configuration of the vicinal stereocenters cyclize to give **8a−e**

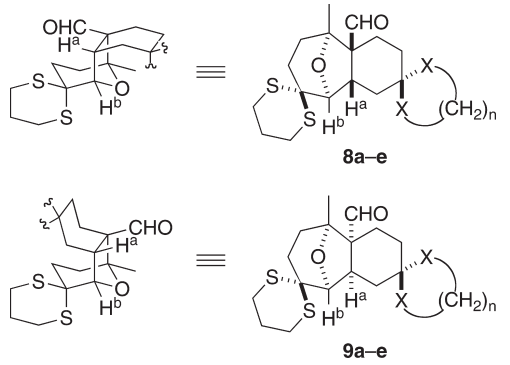
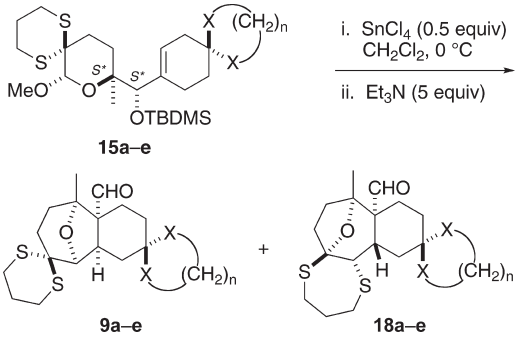


FIGURE 2. Conformations of Prins−pinacol products **8** and **9**.

TABLE 2. Prins−Pinacol Cyclizations of *S,*S** Substrates 15a−e**



unsaturated acetal			products			
compd	X	*n*	compd	yield,[a] %	compd	yield,[a] %
15a	S	3	**9a**	73	**18a**	5[b]
15b	S	2	**9b**	46	**18b**	11
15c	O	3	**9c**	39	**18c**	26
15d	O	2	**9d**	31	**18d**	36
15e	Me		**9e**	68	**18e**	12

[a]Mean yield of pure product from duplicate experiments. [b]Yield was determined by ^{1}H NMR spectroscopy from the ratio of the integrals of the aldehyde signals of **9** and **18**.

having a trans relationship between the oxygen bridge and the angular substituents, whereas substrates **15a−e** having the *S**,*S** relative configuration lead to **9a−e** in which this relationship is cis. In contrast, no clear relationship between stereoselection and the size of the cyclohexene C4 substituents is observed.

In our earlier studies,[3−5] we found that stereoselection in Prins−pinacol reactions can be rationalized by the topography of the Prins cyclization step,[16] consistent with the very low activation barriers typically observed for pinacol rearrangements.[17,18] The transformation of the oxocarbenium

(14) Pretsch, E.; Bühlmann, P.; Affolter, C. *Structure Determination of Organic Compounds*; Springer−Verlag: Berlin, Germany, 2000; pp 12 and 218.

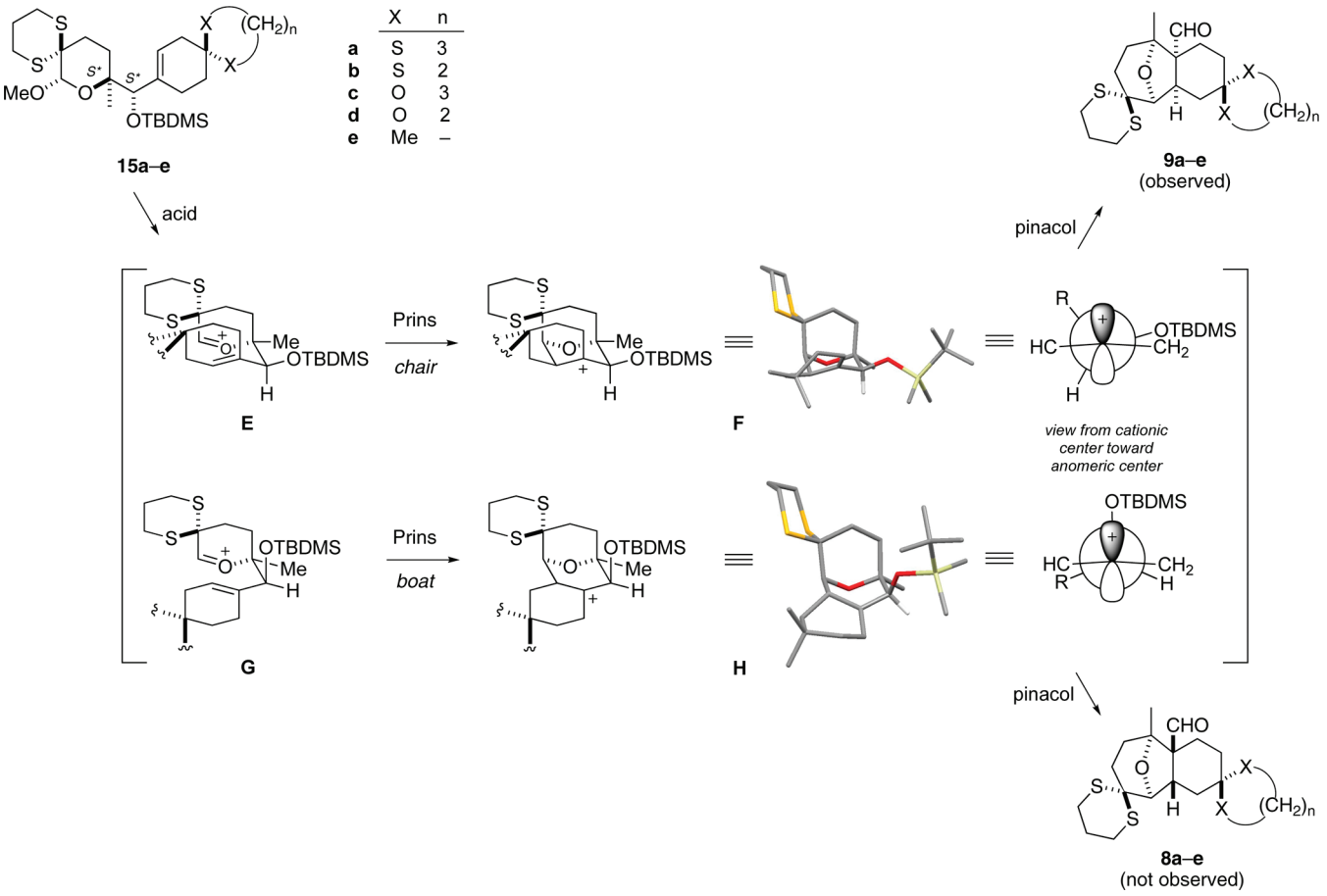
(15) Crystallographic data for this compound were deposited at the Cambridge Crystallographic Data Centre: CCDC 753122. An ORTEP diagram of compound **18b** may be found in the Supporting Information. As is evident in this diagram, the aldehyde hydrogen atom projects close to the oxo bridge and directly into the cavity of the molecule.

(16) An alternate explanation for the stereoselection observed in Prins−pinacol reactions that has not yet been probed thoroughly is the possibility that the cyclization and rearrangement steps occur with some degree of concert. Computational studies to evaluate this possibility are underway.

(17) In the absence of stereoelectronic constraints, pinacol rearrangements have low activation barriers, see: (a) Bartok, M.; Molnar, A. In *Chemistry of Ethers, Crown Ethers, Hydroxyl Compounds and Their Sulfur Analogues*; Patai, S., Ed.; Wiley: New York, 1980; Part 2, pp 722−732. (b) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 3, pp 721−732.

(18) For a particularly revealing example, see: Minor, K. P.; Overman, L. E. *Tetrahedron* **1997**, *53*, 8927–8940.

SCHEME 3



ion derived from unsaturated acetals **15a**−**e** by either a chair or boat Prins−pinacol pathway is analyzed in Scheme 3.[19] The initially generated oxocarbenium ion should be stabilized by hyperconjugative electron release from the adjacent axial C−S σ-bond.[20,21] As a result, we assume that the transition state for the Prins cyclization will be late and resemble the 4-hydropyranyl carbenium ion intermediate.[4] The orientation of the vacant p-orbital and the adjacent siloxy substituent and geminal hydrogen are quite different in carbenium ion intermediates **F** and **H** that would arise from chair or boat topography Prins cyclizations, respectively. In the case of the chair hydropyranyl carbenium ion **F**, the hyperconjugative donor C−H σ-bond has good overlap, whereas the analogous bond in the boat carbenium ion intermediate **H** is nearly orthogonal to the vacant p-orbital. Likewise, the poor hyperconjugative donor C−O σ-bond has poor overlap with the empty p-orbital in chair carbenium ion **F**, whereas this bond has good overlap in boat carbenium ion **H**. Thus, stereoelectronic factors favor the formation of chair hydropyranyl carbenium ion intermediate **F**. Apparent also in three-dimensional models for intermediate **F** is the lack of destabilizing steric interactions between the dithiane substituent of the hydropyranyl ring and the cyclohexane ring.

Since our initial stereoelectronic analysis of Prins−pinacol cyclizations to form tetrahydrofurans was disclosed in 2001,[4] Alder and co-workers published a high-level computational study of the Prins cyclization of 2-oxonia-1,5-hexadiene to form the 4-hydropyranyl carbenium ion.[22] This study highlighted the delocalized character and special stability of the chair 4-hydropyranyl carbenium ion. In this parent series, the boat analogue of the 4-hydropyranyl cation was calculated to be more than 12 kcal/mol less stable. In the *S**,*S** series, both the stereoelectronic influence of the allylic substituents and the delocalized nature of a chair 4-hydropyranyl carbenium favor the chair Prins−pinacol pathway.[23]

A similar analysis of the Prins−pinacol reaction of precursors **14a**−**e** is presented in Scheme 4. With these

(19) The three-dimensional models shown in Schemes 3 and 4 were generated by the analysis of 15−20 low-energy conformers using MMFF conformational searches (Spartan '08 for Macintosh; Wavefunction, Inc.; Irvine, CA, 2008) on cations derived from Prins cyclization of dimethyl substrates **14e** and **15e**, followed by DFT geometry optimization at the B3LYP/6-31G* level. Minima containing strong deformation of the carbocationic center toward a sulfur atom of the dithiane substituent or ones that could not be formed directly by the Prins reaction were disregarded.

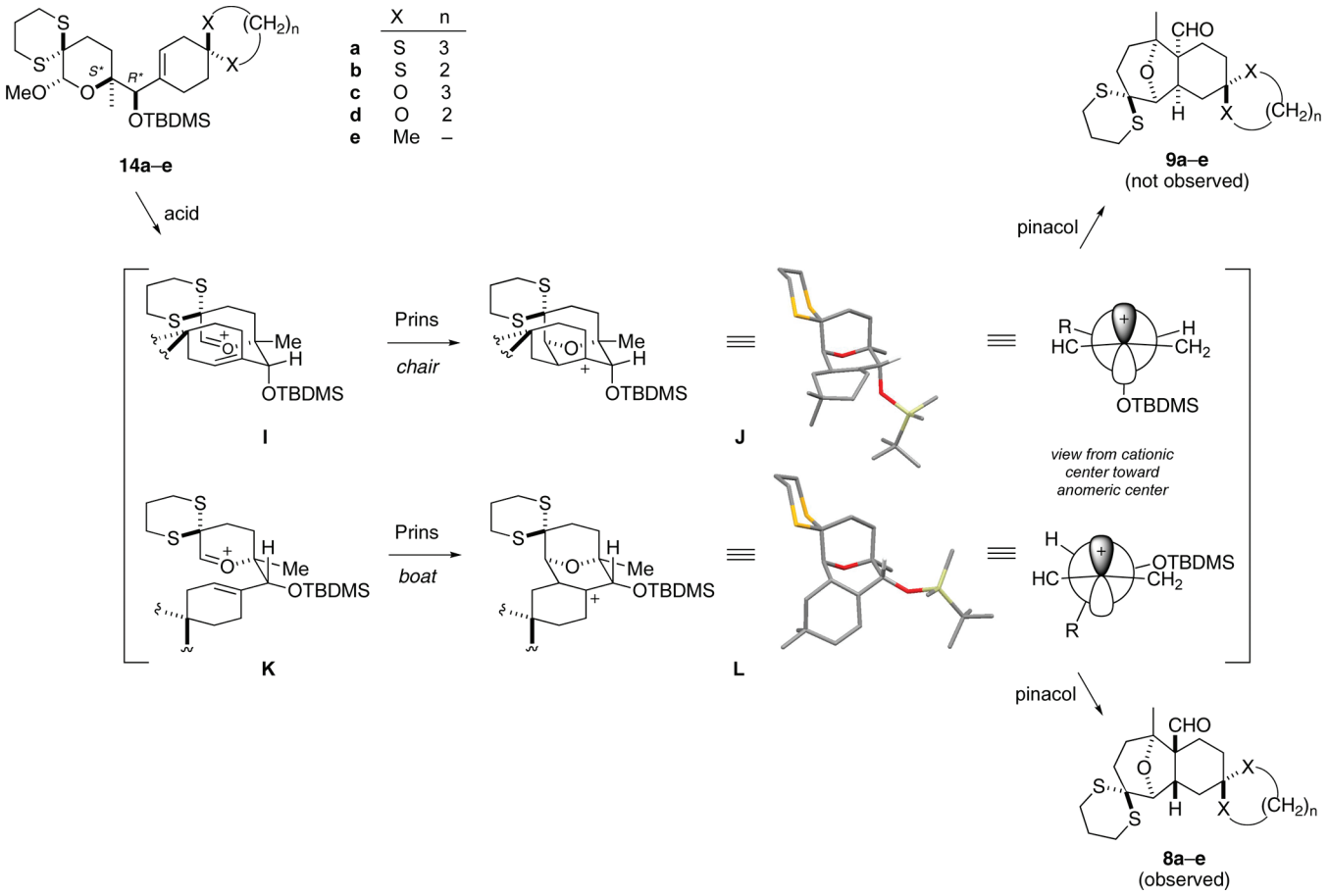
(20) For an incisive analysis of the structure of oxocarbenium ions bearing proximal heteroatoms, and evidence against bridging from an adjacent sulfur atom to form a stable episulfonium ion intermediate, see: Beaver, M. G.; Billings, S. B.; Woerpel, K. A. *Eur. J. Org. Chem.* **2008**, 771–781.

(21) (a) Dudley, T. J.; Smoliakova, I. P.; Hoffmann, M. R. *J. Org. Chem.* **1999**, *64*, 1247–1253. (b) Alabugin, I. V.; Manoharan, M. *J. Org. Chem.* **2004**, *69*, 9011–9024.

(22) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960–4961.

(23) A similar chair preference was seen in the Prins−pinacol reaction of the configurationally analogous, structurally less elaborate, precursor (compound **16** in our earlier study).[8]

SCHEME 4

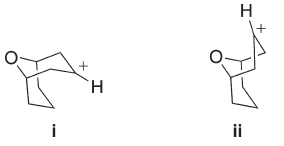


substrates, the observed product arises from the boat topography pathway (**14** → **K** → **L** → **8**). In this series, the electron-releasing C−H σ-bond geminal to the siloxy substituent has poor overlap with the adjacent p-orbital in chair hydropyranyl cation intermediate **J** and better overlap in the corresponding boat intermediate **L**, whereas the opposite is the case for the C−O σ-bond. As a result, stereoelectronic factors favor formation of the boat 4-hydropyranyl carbenium ion intermediate. If this effect is responsible for the preferential formation of Prins−pinacol products **8a**−**e**, the stability provided by the greater hyperconjugative stabilization in boat hydropyranyl carbenium ion intermediate **L** must be quite significant.[24,25]

It merits note that molecular models suggest that the stereoelectronically favored carbenium ions **F** (Scheme 3) and **L** (Scheme 4) have good overlap between the vacant p-orbital and the C−C σ-bond that migrates in the pinacol rearrangement, whereas this orbital overlap is poor in the alternative carbenium ions **H** and **J**. This stereoelectronic factor would be important if the Prins−pinacol reactions took place by a concerted pathway, a possibility that merits further consideration.[16]

Byproducts **18a**−**e** produced from $SnCl_4$-promoted reaction of the *S**,*S** precursors **15a**−**e** are the result of extensive structural rearrangement. The 1,4-dithiepin and thioacetal fragments present in these products suggest that both 1,2-sulfur and 1,2-oxygen migrations are involved in their genesis. One plausible sequence is suggested in Scheme 5. Lewis acid-promoted ionization of acetals **15** would generate oxocarbenium ion **M**. From recent studies of Woerpel and co-workers, the 1,3-dithiane would be expected to stabilize this cation and likely facilitate its formation by hyperconjugation of the axial C−S σ-bond, rather than by bridging to form episulfonium ion intermediate **N**.[20,26] 1,2-Migration of this axial sulfur atom via **N** (presumably a high-energy intermediate or transition state) would generate the tetrasubstituted thiocarbenium ion **O**.[27] This ring expansion sequence has close precedent in the synthesis of 5,6-dihydro-1,4-dithiepins and 2-alkylidene-1,4-dithiepanes from

(24) DFT (Spartan 08, B3LYP/6-31G*) calculations on chair and boat conformers of the 9-oxobicyclo[3.3.1]nonanyl carbenium ions **i** and **ii** show that the preference for chair structure **i** (10.7 kcal/mol) is somewhat less than that for the parent 4-hydropyranyl carbenium ion (12.6 kcal/mol)[22] (see the Supporting Information for details).



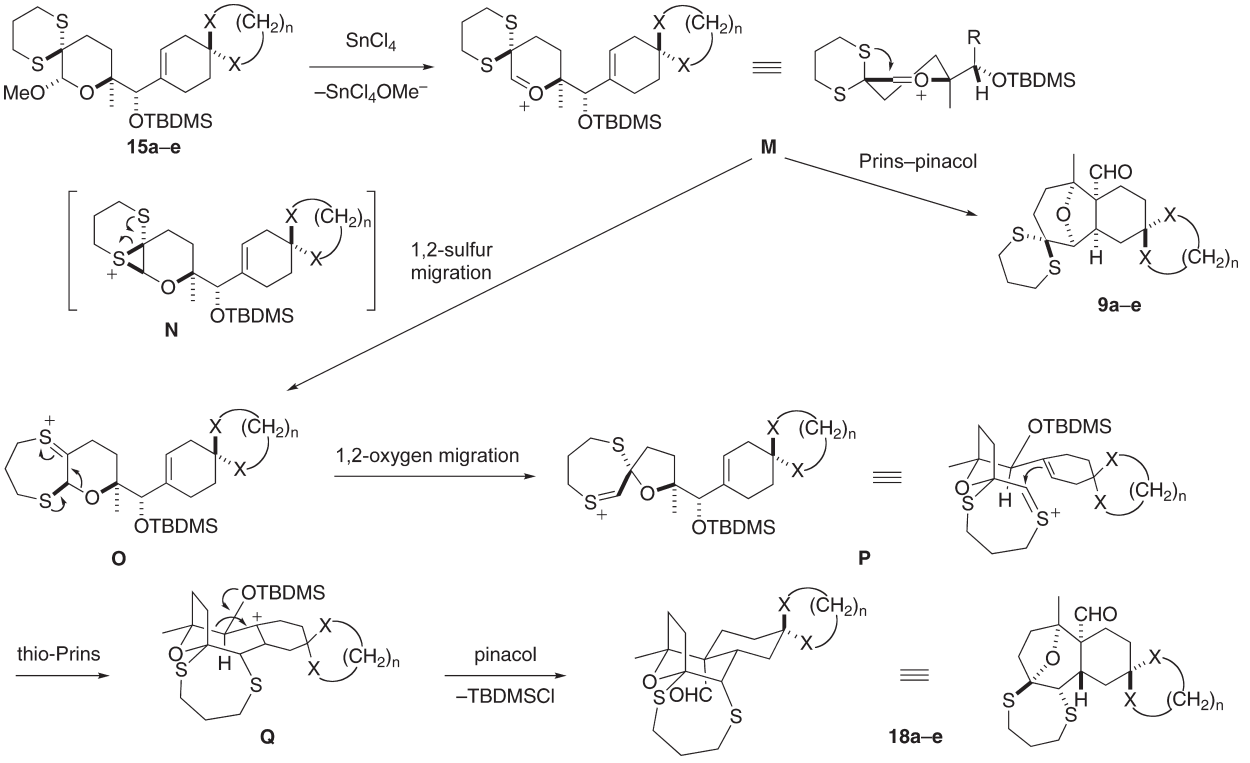
i **ii**

(25) For a recent computational study and detailed discussion of the donor ability of C−H bonds to adjacent vacant p-orbitals, see ref 21b.

(26) Billings, S. B.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 5171–5178.

(27) For reviews of 1,2-sulfur migrations, see: (a) Fox, D. J.; House, D.; Warren, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2462–2482. (b) Sromek, A. W.; Gevorgyan, V. *Top. Curr. Chem.* **2007**, *274*, 77–124.

SCHEME 5. Possible Mechanism of Formation of Byproducts 18a−e



dithiane precursors.[28] In the present case, rather than losing an adjacent hydrogen, intermediate **O** is poised for a 1,2-oxygen shift to form thiocarbenium ion **P**. This electrophilic intermediate is then positioned for capture by the adjacent cyclohexene π-bond, initiating a thio-Prins−pinacol reaction sequence. If the thio-Prins cyclization occurred by a topography in which the bulky *tert*-butyldimethylsilyl substituent is oriented in a quasiequatorial fashion (**P** → **Q**), the observed products **18a−e** would result.[29]

The yield of the thio-Prins−pinacol byproduct **18** was higher in reactions of the 1,3-dioxane and 1,3-dioxolane precursors **15c**,**d** (Table 2). Because of inductive electron withdrawal by the oxygen substituents, the alkene π-bond in these acetal precursors would be expected to be less nucleophilic. Thus, the higher yields of the thio-Prins−pinacol byproducts **18c**,**d** suggest that oxocarbenium ion **M** partitions between Prins cyclization to eventually generate Prins−pinacol products **9** and 1,2-sulfur migration to generate thiocarbenium ion **O** and ultimately thio-Prins−pinacol products **18**.

Conclusions

Stereoelectronic effects, not steric factors, are responsible for the stereoselectivity observed in Prins−pinacol reactions employed by us previously[8] and in the present study to assemble polycyclic products containing the 12-oxatricyclo-[6.3.1.0^{2,7}]dodecane moiety. The observation that siloxy epimers **14** and **15** are transformed stereoselectively to two different products **8** and **9**, respectively, provides a dramatic demonstration of the importance of allylic stereoelectronic effects in determining the outcome of Prins−pinacol reactions. Depending upon the configuration of this single stereocenter, the Prins−pinacol reaction occurs by either a boat- or chairlike sequence.

A new molecular reorganization was identified that yields products **18** that contain a previously unknown oxygen-bridged 2,6-dithiabicyclo[5.5.0]dodecane ring system. A complex cascade sequence that involves oxocarbenium ion formation, followed by sequential 1,2-sulfur and 1,2-oxygen migrations and eventually a thio-Prins−pinacol reaction, is suggested to explain the formation of these products.

Experimental Section[30]

***rel*-(*R*)-(1,4-Dithiaspiro[4.5]dec-7-en-8-yl)(*rel*-(7*S*,9*S*)-7-methoxy-9-methyl-8-oxa-1,5-dithiaspiro[5.5]undecan-9-yl)methanol (12b) and *rel*-(*S*)-(1,4-Dithiaspiro[4.5]dec-7-en-8-yl)(*rel*-(7*S*,9*S*)-7-methoxy-9-methyl-8-oxa-1,5-dithiaspiro[5.5]undecan-9-yl)methanol (13b).** To a stirring solution of *t*-BuLi (10.9 mL, 1.05 M in pentane) in THF (64 mL) at −78 °C was added a solution of vinyl iodide **10b** (1.90 g, 6.37 mmol) in THF (8 mL) dropwise by syringe over 5 min. After 15 min, a solution of aldehyde **11** (1.52 g, 5.74 mmol) in THF (8 mL) was added in similar fashion. After 1 h, the cooling bath was removed and the reaction was allowed to warm to rt and was maintained at rt for 1 h. The reaction mixture was treated with saturated aqueous NH_4Cl (60 mL), and the layers were separated. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried

(28) (a) Saigo, K.; Hashimoto, Y.; Fang, L.; Hasegawa, M. *Heterocycles* **1989**, *29*, 2079–2082. (b) Afonso, C. A. M.; Barros, M. T.; Godinho, L. S.; Maycock, C. D. *Synthesis* **1991**, 575–580 and references cited therein.

(29) The formation of products **18** is the first example of a thio-Prins−pinacol sequence in which the initial thio-Prins cyclization generates a seven-membered ring.

(30) Representative experimental procedures for preparing a cyclization substrate and its rearrangement upon reaction with $SnCl_4$. General experimental details, experimental procedures, and characterization for other new compounds can be found in the Supporting Information.

over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash chromatography (25:73:2−30:68:2 ethyl acetate−hexanes−Et_3N) to yield a 1.6:1 mixture of **12b** and **13b**, respectively, as an off-white solid (1.89 g, 75%): R_f 0.1 (20:80 ethyl acetate−hexanes).

The mixture was separated by HPLC (35:65 ethyl acetate−hexanes isocratic, 40 mL/min; Peeke KromaSpher 80, 5 μm silica, 300 × 50 mm i.d., λ = 254 nm) to give pure samples of the alcohol epimers: **12b**: t_R = 25 min; colorless solid; mp 121−122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (br s, 1H), 4.73 (s, 1H), 3.95 (s, 1H), 3.48 (s, 3H), 3.39−3.28 (m, 4H), 2.88 (ddd, J = 14.3, 9.9, 3.3 Hz, 1H), 2.82−2.72 (m, 4H), 2.71−2.64 (m, 1H), 2.57−2.50 (m, 1H), 2.50 (td, J = 13.1, 4.9 Hz, 1H), 2.34 (td, J = 13.6, 4.0 Hz, 1H), 2.31−2.18 (m, 2H), 2.15−1.98 (m, 3H), 1.95−1.85 (m, 1H), 1.37−1.31 (m, 1H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5 (C), 126.4 (CH), 102.7 (CH), 82.3 (CH), 78.8 (C), 65.7 (C), 56.6 (CH_3), 52.3 (C), 42.6 (CH_2), 39.0 (CH_2), 38.8 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 25.3 (CH_2), 23.4 (CH_3); IR (film) 3531, 2927, 1424, 1142 cm^{-1}; HRMS (ES) m/z calcd for $C_{19}H_{30}NaO_3S_4$ (M + Na)$^+$ 457.0976, found 457.0977. **13b**: t_R = 28 min; colorless solid; mp 129−132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (br s, 1H), 4.72 (s, 1H), 3.73 (s, 1H), 3.50 (s, 3H), 3.38−3.27 (m, 4H), 2.88−2.72 (m, 6H), 2.67−2.61 (m, 1H), 2.50−2.30 (m, 3H), 2.32 (td, J = 11.7, 3.9 Hz, 1H), 2.22 (dt, J = 13.7, 4.5 Hz, 1H), 2.16−1.87 (m, 4H), 1.38 (dt, J = 13.6, 3.9 Hz, 1H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0 (C), 125.4 (CH), 103.0 (CH), 81.1 (CH), 77.9 (C), 65.8 (C), 56.8 (CH_3), 51.6 (C), 42.7 (CH_2), 39.0 (CH_2), 38.9 (CH_2), 38.7 (CH_2), 28.6 (CH_2), 27.7 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 25.33 (CH_2), 25.29 (CH_2), 22.9 (CH_3); IR (film) 3531, 2927, 1425 cm^{-1}; HRMS (ES) m/z calcd for $C_{19}H_{30}NaO_3S_4$ (M + Na)$^+$ 457.0976, found 457.0977.

***rel*-(1*S*,5*R*,7*R*)-1-Methyl-7-(1,4-dithiaspiro[4.5]dec-7-en-8-yl)-6,8-dioxaspiro[bicyclo[3.2.1]octane-4,2′-[1,3]dithiane] (16b).** To a stirring solution of allylic alcohol **12b** (30 mg, 0.070 mmol) in CH_2Cl_2 (1.0 mL) at rt was added p-TsOH·H_2O (1.0 mg, 0.0053 mmol). After 45 min, Et_3N (300 μL) and H_2O (1.0 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (20:80 ethyl acetate−hexanes) to yield **16b** as a colorless oil (24 mg, 85%): R_f 0.4 (30:70 ethyl acetate−hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (br s, 1H), 5.54 (s, 1H), 4.04 (s, 1H), 3.42−3.25 (m, 4H), 2.97 (dd, J = 8.0, 5.3 Hz, 1H), 2.90−2.63 (m, 5H), 2.37−2.23 (m, 2H), 2.20−2.03 (m, 3H), 2.00−1.85 (m, 4H), 1.65−1.55 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.9 (C), 122.8 (CH), 101.4 (CH), 86.3 (CH), 80.8 (C), 65.6 (C), 51.9 (C), 42.0 (CH_2), 39.0 (CH_2), 38.9 (CH_2), 38.4 (CH_2), 31.1 (CH_2), 29.0 (CH_2), 26.4 (CH_2), 26.2 (CH_2), 25.8 (CH_2), 24.9 (CH_2), 23.8 (CH_3); IR (film) 2917, 2842, 1424 cm^{-1}; HRMS (ES) m/z calcd for $C_{18}H_{26}NaO_2S_4$ (M + Na)$^+$ 425.0714, found 425.0713.

***rel*-(1*S*,5*R*,7*S*)-1-Methyl-7-(1,4-dithiaspiro[4.5]dec-7-en-8-yl)-6,8-dioxaspiro[bicyclo[3.2.1]octane-4,2′-[1,3]dithiane] (17b).** In a similar fashion, a solution of allylic alcohol **13b** (32 mg, 0.074 mmol) in CH_2Cl_2 (1.0 mL) was treated with p-TsOH·H_2O (2.0 mg, 0.010 mmol), and the crude product was purified by silica gel flash chromatography (20:80 ethyl acetate−hexanes) to yield **17b** as a colorless oil (28 mg, 94%): R_f 0.35 (30:70 ethyl acetate−hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (s, 1H), 5.55 (br s, 1H), 4.27 (s, 1H), 3.37−3.27 (m, 4H), 2.99 (ddd, J = 14.6, 8.9, 4.8 Hz, 1H), 2.86−2.61 (m, 5H), 2.41−2.33 (m, 1H), 2.24−1.90 (m, 8H), 1.53−1.46 (m, 1H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7 (C), 124.7 (CH), 102.5 (CH), 85.1 (CH), 81.9 (C), 65.4 (C), 52.0 (C), 42.3 (CH_2), 39.04 (CH_2), 39.02 (CH_2), 38.5 (CH_2), 33.5 (CH_2), 31.2 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 25.2 (CH_2), 24.8 (CH_2), 20.9 (CH_3); IR (film) 2919, 1445, 1424 cm^{-1}; HRMS (ES) m/z calcd for $C_{18}H_{26}NaO_2S_4$ (M + Na)$^+$ 425.0714, found 425.0725.

***tert*-Butyl(*rel*-(*R*)-(1,4-dithiaspiro[4.5]dec-7-en-8-yl)(*rel*-(7*S*,9*S*)-7-methoxy-9-methyl-8-oxa-1,5-dithiaspiro[5.5]undecan-9-yl)methoxy)dimethylsilane (14b).** To a stirring solution of allylic alcohol **12b** (280 mg, 0.63 mmol), *N*,*N*-dimethyl-4-aminopyridine (5.0 mg, 0.041 mmol), and pyridine (260 μL, 3.2 mmol) in CH_2Cl_2 (6.3 mL) at −78 °C was added TBDMSOTf (290 μL, 1.3 mmol) dropwise by syringe over 2 min. After a further 10 min, the cooling bath was removed and the reaction was allowed to warm to rt and was maintained at rt for 18 h. Water (8 mL) was then added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dry-loaded onto silica gel and purified by silica gel flash chromatography (15:84:1 ethyl acetate−hexanes−Et_3N) to yield **14b** as a colorless foam (320 mg, 86%): R_f 0.4 (20:80 ethyl acetate−hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (br s, 1H), 4.68 (s, 1H), 4.01 (s, 1H), 3.46 (s, 3H), 3.38−3.26 (m, 4H), 3.07−2.97 (m, 2H), 2.79−2.64 (m, 4H), 2.56−2.48 (m, 1H), 2.36−2.27 (m, 1H), 2.15 (ddd, J = 13.9, 8.4, 4.2 Hz, 1H), 2.12−1.90 (m, 6H), 1.60 (ddd, J = 13.9, 8.4, 4.2 Hz, 1H), 1.28 (s, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9 (C), 124.5 (CH), 104.3 (CH), 79.3 (CH), 78.3 (C), 65.6 (C), 56.7 (CH_3), 50.9 (C), 42.6 (CH_2), 39.3 (CH_2), 39.2 (CH_2), 39.0 (CH_2), 30.3 (CH_2), 29.4 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.7 (CH_2), 26.1 (CH_3), 25.6 (CH_2), 22.5 (CH_3), 18.3 (C), −4.1 (CH_3), −4.9 (CH_3); IR (film) 2952, 2856, 1472 cm^{-1}; HRMS (ES) m/z calcd for $C_{25}H_{44}NaO_3S_4Si$ (M + Na)$^+$ 571.1840, found 571.1838.

***tert*-Butyl(*rel*-(*S*)-(1,4-dithiaspiro[4.5]dec-7-en-8-yl)(*rel*-(7*S*,9*S*)-7-methoxy-9-methyl-8-oxa-1,5-dithiaspiro[5.5]undecan-9-yl)methoxy)dimethylsilane (15b).** In a similar fashion, allylic alcohol **13b** (140 mg, 0.63 mmol) was silylated, and the crude product was purified by silica gel flash chromatography (10:90 ethyl acetate−hexanes) to yield **15b** as a colorless solid (150 mg, 87%): mp 51−54 °C; R_f 0.4 (20:80 ethyl acetate−hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (br s, 1H), 4.91 (s, 1H), 3.91 (s, 1H), 3.52 (s, 3H), 3.40−3.28 (m, 4H), 3.06 (ddd, J = 13.9, 8.4, 3.7 Hz, 1H), 2.97 (ddd, J = 14.2, 8.7, 3.7 Hz, 1H), 2.78−2.63 (m, 4H), 2.45 (br s, 2H), 2.22−2.08 (m, 3H), 2.05−1.90 (m, 4H), 1.47 (ddd, J = 13.9, 7.3, 4.2 Hz, 1H), 1.28 (s, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0 (C), 125.2 (CH), 105.5 (CH), 83.7 (CH), 78.3 (C), 65.7 (C), 56.9 (CH_3), 51.0 (C), 42.7 (CH_2), 39.10 (CH_2), 39.05 (CH_2), 38.96 (CH_2), 30.9 (CH_2), 28.8 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.2 (CH_3), 25.9 (CH_2), 25.6 (CH_2), 24.0 (CH_3), 18.4 (C), −4.2 (CH_3), −4.9 (CH_3); IR (film) 2952, 2856, 1472 cm^{-1}; HRMS (ES) m/z calcd for $C_{25}H_{44}NaO_3S_4Si$ (M + Na)$^+$ 571.1840, found 571.1843.

Prins−Pinacol Reaction of Unsaturated Acetal 14b with Stannic Chloride. Preparation of *rel*-(1*S*,2*S*,7*S*,8*R*)-2-Formyl-1-methyl-12-oxabispiro[tricyclo[6.3.1.0^{2,7}]dodecane-9,2′-[1,3]dithiane-5,2′-[1,3]dithiolane] (8b). To a stirring solution of TBDMS ether **14b** (104 mg, 0.189 mmol) in CH_2Cl_2 (3.8 mL) at 0 °C was added $SnCl_4$ (190 μL, 0.095 mmol, 0.5 M in CH_2Cl_2) dropwise by syringe over 20 s. After a further 30 min, Et_3N (130 μL, 0.95 mmol) was added. After an additional 5 min, the mixture was poured into saturated aqueous $NaHCO_3$ (8 mL) that was precooled in ice/water and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (15:85 ethyl acetate−hexanes) to yield **8b** as a colorless solid (13 mg, 17%): mp 156−158 °C; R_f 0.3 (30:70 ethyl acetate−hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 4.21 (br s, 1H), 3.40−3.28 (m, 5H), 2.93 (ddd, J = 14.2, 9.4, 3.9 Hz, 1H), 2.88 (ddd, J = 14.6, 8.2, 3.9

Hz, 1H), 2.77 (ddd, J = 14.6, 7.3, 3.9 Hz, 1H), 2.72 (ddd, J = 14.2, 6.2, 3.9 Hz, 1H), 2.40−2.30 (m, 1H), 2.28 (dd, J = 13.7, 6.2 Hz, 1H), 2.20 (dd, J = 13.7, 9.8 Hz, 1H), 2.12−1.94 (m, 6H), 1.90−1.80 (m, 2H), 1.44 (dd, J = 13.3, 5.9 Hz, 1H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6 (CH), 85.1 (C), 84.4 (CH), 63.6 (C), 60.0 (C), 51.6 (C), 42.6 (CH_2), 41.7 (CH), 39.8 (CH_2), 39.6 (CH_2), 37.8 (CH_2), 32.0 (CH_2), 31.5 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 25.3 (CH_2), 24.7 (CH_2), 21.9 (CH_3); IR (film) 2935, 2829, 2711, 1715, 1424 cm^{-1}; HRMS (ES) m/z calcd for $C_{18}H_{26}NaO_2S_4$ $(M + Na)^+$ 425.0714, found 425.0709.

Prins−Pinacol Reaction of Unsaturated Acetal 15b with Stannic Chloride. Preparation of *rel*-(1*S*,2*R*,7*R*,8*R*)-2-Formyl-1-methyl-12-oxabispiro[tricyclo[6.3.1.0^{2,7}]dodecane-9,2′-[1,3]dithiane-5,2-[1,3]dithiolane] (9b) and *rel*-(1*S*,7*S*,8*S*,13*R*,14*S*)-13-Formyl-14-methyl-17-oxa-2,6-dithispiro[tetracyclo[12.2.1.0^{1,7}.0^{8,13}]heptadecane-10,2′-[1,3]dithiolane] (18b). With use of a procedure identical with that employed for the Prins−pinacol reaction of **14b**, unsaturated acetal **15b** (104 mg, 0.189 mmol) was exposed to $SnCl_4$ (190 μL, 0.095 mmol, 0.5 M in CH_2Cl_2) at 0 °C, and the crude product was purified by silica gel flash chromatography (15:85 ethyl acetate−hexanes) to yield the following fractions: **9b**: 37 mg (48%) as a colorless solid after recrystallization from CH_2Cl_2, mp 175−176 °C; R_f 0.25 (30:70 ethyl acetate−hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.46 (d, J = 1.9 Hz, 1H), 4.62 (dd, J = 7.4, 2.0 Hz, 1H), 3.42−3.21 (m, 5H), 2.90−2.84 (m, 2H), 2.84−2.74 (m, 2H), 2.53 (dd, J = 13.7, 13.5 Hz, 1H), 2.45 (ddd, J = 15.7, 7.4, 1.1 Hz, 1H), 2.35−2.23 (m, 3H), 2.17 (ddd, J = 14.7, 12.7, 5.8 Hz, 1H), 2.07−1.90 (m, 4H), 1.66−1.55 (m, 2H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0 (CH), 85.2 (C), 81.6 (CH), 65.3 (C), 57.1 (C), 53.2 (C), 44.5 (CH), 39.7 (CH_2), 39.1 (CH_2), 38.7 (CH_2), 36.5 (CH_2), 32.7 (CH_2), 31.4 (CH_2), 26.6 (CH_2), 25.7 (CH_2), 24.8 (CH_2), 23.0 (CH_3), 20.0 (CH_2); IR (film) 2935, 2821, 2709, 1717, 1463 cm^{-1}; HRMS (ES) m/z calcd for $C_{18}H_{26}NaO_2S_4$ $(M + Na)^+$ 425.0714, found 425.0726. **18b**: 11% by integration in the ^{1}H NMR spectrum of the crude reaction mixture, via a ratio with the integration values from isolated product **9b**;[31] colorless crystals, mp 99−101 °C; R_f 0.5 (50% ethyl acetate−hexanes) ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.55 (d, J = 2.1 Hz, 1H), 3.84 (ddd, J = 15.4, 11.3, 6.4 Hz, 1H), 3.35−3.25 (m, 4H), 3.16 (d, J = 5.4 Hz, 1H), 3.08 (ddd, J = 15.4, 5.4, 1.1 Hz, 1H), 2.99 (ddd, J = 14.9, 11.4, 6.4 Hz, 1H), 2.79−2.72 (m, 1H), 2.68 (ddd, J = 12.4, 5.4, 2.7 Hz, 1H), 2.41 (td, J = 13.5, 4.5 Hz, 1H), 2.29−2.15 (m, 3H), 2.04 (dd, J = 13.5, 12.7 Hz, 1H), 2.04−1.90 (m, 4H), 1.86 (dt, J = 13.5, 2.5 Hz, 1H), 1.80−1.72 (m, 1H), 1.29−1.21 (m, 1H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.0 (CH), 91.4 (C), 88.6 (C), 69.1 (C), 62.9 (CH), 55.2 (C), 44.3 (CH_2), 42.0 (CH), 40.2 (CH_2), 39.1 (CH_2), 38.6 (CH_2), 38.1 (CH_2), 34.2 (CH_2), 33.3 (CH_2), 30.3 (CH_2), 28.2 (CH_2), 27.3 (CH_2), 22.5 (CH_3); IR (film) 2923, 2856, 2769, 1708 cm^{-1}; HRMS (ES) m/z calcd for $C_{18}H_{26}NaO_2S_4$ $(M + Na)^+$ 425.0714, found 425.0706.

(31) Byproduct **18b** is highly crystalline, and after crystallization is difficult to redissolve in standard chromatography solvents. As a result, some product was lost during purification.

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Supporting Information Available: Experimental procedures, tabulated characterization data, optimized structures, and relative energies and Cartesian coordinates from DFT calculations on 9-oxobicyclo[3.3.1]nonanyl carbenium ions **i**, **ii**, and other conformational isomers, and copies of ^{1}H and ^{13}C NMR spectra for new compounds not previously reported, CIF file for X-ray structure of **18b**, and PDB files of the models of intermediates **F**, **H**, **J**, and **L**. This material is available free of charge via the Internet at http://pubs.acs.org.