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Stereoselection in the Prins-Pinacol Synthesis of Acyltetrahydrofurans

Frederick Cohen, David W. C. MacMillan,[†] Larry E. Overman,* and Alex Romero[‡]

Department of Chemistry, 516 Rowland Hall, University of California, Irvine, California 92697-2025

leoverma@uci.edu

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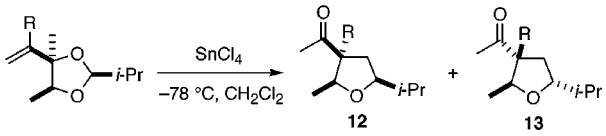
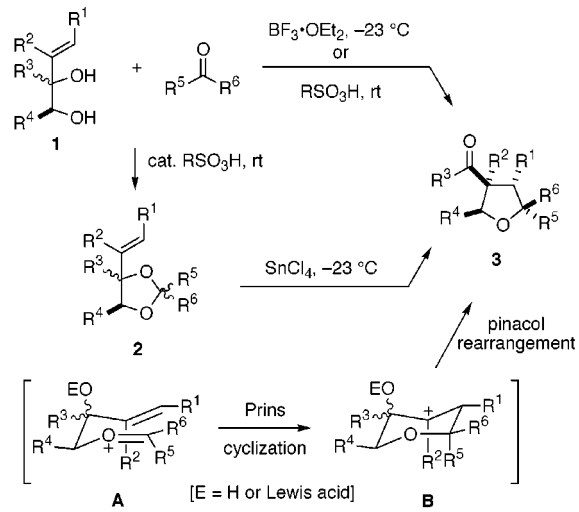
ABSTRACT



Depending upon the nature of the alkene and allylic substituents, acid-promoted rearrangements of acetals derived from anti allylic diols give 12 or stereoisomeric acyltetrahydrofurans 13. Stereoelectronic effects of the allylic substituents and the extent of bonding in the Prins cyclization transition state are central features of a proposed new model for predicting stereoselection in the Prins-pinacol synthesis of acyltetrahydrofurans.

A wide variety of polysubstituted tetrahydrofurans and complex ring systems containing a tetrahydrofuran fragment have been prepared by acid-promoted reaction of allylic diols with aldehydes and ketones (Scheme 1).[1−3] This powerful transformation has served as the cornerstone of stereocontrolled total syntheses of several oxacyclic natural products families.[4] Although mixtures of allylic diol epimers were used in most instances, one tetrahydrofuran stereoisomer was generated with high selectivity when the reaction was accomplished under the "standard" conditions depicted in Scheme 1.[1,2,4] The high stereoselectivity observed in these reactions has been rationalized by a stereochemistry-determining Prins cyclization, **A** → **B**,[5−7] in which the oxocarbenium ion (α-alkoxycarbenium ion) adopts the more stable *E* configuration and the R^4 substituent is quasiequatorial in a chair transition state assembly.[8] In all cases examined, the R^3 substituent was small (hydrogen, methyl, or methylene), and therefore configuration at the allylic stereogenic center was believed not to influence the distribution of products.

Scheme 1



[†] Current address: Department of Chemistry, Mail Code 164-30, California Institute of Technology, Pasadena, CA 91125.

[‡] Current address: Optimer Pharmaceuticals, Inc., 10130 Sorrento Valley Road, Suite D, San Diego, CA 92121.

(1) For brief reviews, see: (a) Overman L. E. *Acc. Chem. Res.* **1992**, *25*, 352−359. (b) Overman L. E. *Aldrichimica Acta* **1995**, *28*, 107−120.

(2) Representative examples include (a) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354−5365. (b) Brown, M. J.; Harrison, T.; Herrinton, P. M.; Hopkins, M. H.; Hutchinson, K. D.; Mishra, P.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5365−5378. (c) Overman, L. E.; Rishton, G. M. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. IX, pp 4−9.

(3) For the discovery of this route to tetrahydrofurans, see: Martinet, P.; Mousset, G. *Bull. Soc. Chim. Fr.* **1970**, 1071−1076.

(4) (a) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378−5384. (b) Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468−2477. (c) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391−10392. (d) Hanaki, N.; Link, J. T.; MacMillan, D. W. C.; Overman, L. E.; Trankle, W. G.; Wurster, J. A. *Org. Lett.* **2000**, *2*, 223−226. (e) Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683−2686.

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In this communication, we report the first detailed investigation of the Prins-pinacol synthesis of acyltetrahydrofurans using isomerically pure allylic diols. In the anti series, the stereochemical outcome was discovered to depend dramatically on the nucleophilicity of the alkene and the size of the allylic substituent R^3; in contrast, in the syn series a single tetrahydrofuran stereoisomer is formed preferentially with all substrates investigated. A new model for predicting stereochemistry in Prins-pinacol syntheses of tetrahydrofurans is advanced.

The substrates examined in this investigation are summarized in Figure 1. Mixtures of diol stereoisomers enriched

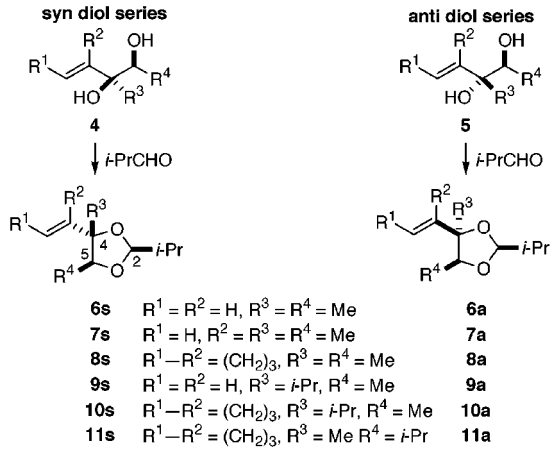
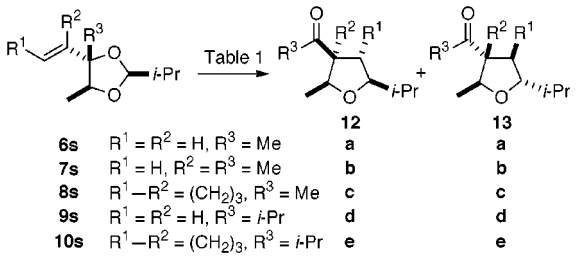


Figure 1. Acetal substrates.

in either the syn or anti stereoisomer[9,10] were condensed with 10 equiv of isobutryaldehyde (0.1 equiv of *p*-toluenesulfonic acid, excess $MgSO_4$, CH_2Cl_2, rt), and the major acetal stereoisomer thus produced was isolated by medium-pressure liquid chromatography or preparative HPLC.[11,12] Consistent with previous studies by Eliel and co-workers,[13] the predominant acetal epimer in both stereoisomeric series had a cis relationship of the C2 and C5 substituents. Stereochemical assignments for **6s**−**11s** and **6a**−**11a** were made by ^{1}H NMR NOE studies.[12]

Prins-pinacol rearrangements were carried out under identical conditions at −78 °C in the presence of either 1.1 equiv of $SnCl_4$ or 3 equiv of triflic acid.[14] Syn acetals **6s**−**10s** rearranged with high stereoselectivity to give acyltetrahydrofurans **12a**−**e** having a cis relationship of the acyl group and the C2 and C5 substituents (Table 1). Only in the case of acetal **10s** having an isopropyl substituent at the allylic position was diastereoselection less than 24:1.[15] To our surprise, acetal **11s** bearing an isopropyl substituent at the homoallylic position decomposed without forming any detectable acetyltetrahydrofuran.

Table 1. Rearrangements of Syn Acetals **6s**−**10s**[a]



entry	acetal	acid	time, h	% conv	**12**:**13**[b]
1	**6s**	$SnCl_4$	14	31[c]	>99:1
2	**6s**	TfOH	14	90[d]	>99:1
3	**7s**	$SnCl_4$	14	94	97:3
4	**7s**	TfOH	14	88	97:3
5	**8s**	$SnCl_4$	6	80	>99:1
6	**9s**	$SnCl_4$	17	67[e]	>99:1
7	**9s**	TfOH	16	98	96:4
8	**10s**	TfOH	14	82[d]	90:10

[a] Reactions were conducted in CH_2Cl_2 at −78 °C in the presence of 1.1 equiv of $SnCl_4$ or 3 equiv of TfOH with acetals of >97% diastereomeric purity. The acetal concentration was 0.01 M. [b] Product ratios were determined by capillary GLC analysis. [c] **6s** was recovered in 65% yield. [d] Isolated yield. [e] **9s** was recovered in 28% yield.

In marked contrast, substrate-dependent stereoselectivity was observed in rearrangements of anti acetals **6a**−**10a** under

(5) In the absence of stereoelectronic constraints, pinacol rearrangements have extremely low activation barriers,[6] and thus conformational dynamics of the initially formed cyclic cation should not affect stereochemical outcome.[7]

(6) (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, 1991; Vol. 3, pp 721−732.

(7) Minor, K. P.; Overman, L. E. *Tetrahedron* **1997**, *53*, 8927−8940.

(8) (a) Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc.* **1985**, *107*, 2435−2441. (b) Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006−5017.

(9) Syn allylic diols **4** were prepared from the reaction of vinyl Grignard reagents and α-hydroxy or α-benzyloxy ketones,[10a] whereas anti allylic diols **5** were derived from condensation of vinyllithium reagents and α-(*tert*-butyldiphenylsiloxy)ketones.[10b]

(10) (a) Still, W. C.; MacDonald, J. H., III. *Tetrahedron Lett.* **1980**, *21*, 1031−1034. (b) Overman, L. E.; Rishton, G. M. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. IX, pp 139−142.

(11) In 94−99% isomeric purity by capillary GLC analysis.

(12) Romero, A. Ph.D. Dissertation, University of California, Irvine, 1998.

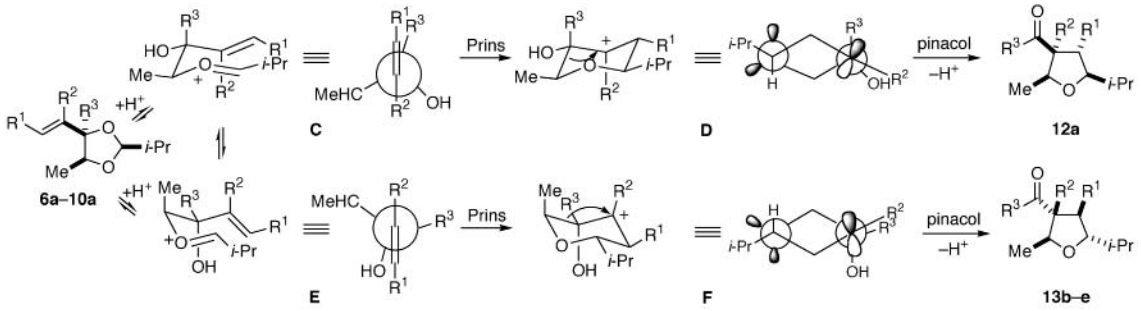
(13) Eliel, E. L.; Binsh, G.; Willey, W. J. *J. Am. Chem. Soc.* **1970**, *92*, 5394−5402.

(14) When $SnCl_4$-promoted rearrangements of **6s**−**8s** were attempted in the presence of 1.0 equiv of 2,6-di-*tert*-butyl-4-methylpyridine, starting acetals were recovered unchanged. These experiments suggest that a complex protic acid formed by the reaction of $SnCl_4$ with adventitious water is the likely promoter of the reaction. Consistent with this suggestion, rigorous exclusion of H_2O from $SnCl_4$-promoted reactions led to lower reaction rates.

(15) Isomer ratios were determined by capillary GLC analysis and are mean values of 2−4 experiments. When the minor isomer was not detected, the ratio is shown as >99:1.

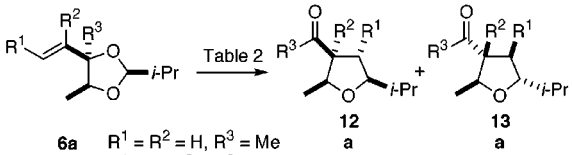
(16) (a) Epimers at the acetal carbon were formed to a minor extent (<10%). At higher temperatures, acetal **8a** partially epimerized to acetal **8s**, presumably by way of an allyl cation intermediate. (b) A 1:1 mixture of **7s** and **7a** was rearranged in the presence of 1.0 equiv of $SnCl_4$ for 4 min at −78 °C, and the reaction was then quenched at this temperature by adding excess Et_3N. Acyltetrahydrofurans **12b** and **13b** were isolated in a 1.2:1 ratio and 61% combined yield, and acetals **7s** and **7a** were recovered in a 1.6:1 ratio (31% combined yield). This result demonstrates that the anti stereoisomer reacts slightly faster and confirms that **7s** would have been detected, if epimerization of **7a** → **7s** had been occurring under the rearrangement conditions (Table 2, entry 4).

Scheme 2. Model for Stereoselection in the Anti Diol Series



identical conditions (Table 2). Consistent with an earlier observation,[2a,c] acetal **6a** containing a terminal vinyl group rearranged to provide the all-cis tetrahydrofuran **12a** as the predominant product (entries 1 and 2). However, acetal **7a** in which the π nucleophile is an isopropenyl group gave stereoisomeric tetrahydrofuran **13b** with high selectivity: 1:6 (TfOH) to 1:11 ($SnCl_4$). Acetal **8a** having a 1-cyclopentenyl group as the π nucleophile generated tetrahydrofuran **13c** with similar stereoselectivity (entries 6 and 7). Rearrangements of acetals **9a** and **10a** having an isopropyl group at the allylic site also yielded tetrahydrofurans **13d** and **13e** preferentially, with stereoselectivity being >99:1 in the case of the 1-cyclopentenyl substrate **10a**. As with the related syn acetal harboring an isopropyl substituent at the homoallylic position, **11a** decomposed upon attempted rearrangement.

Table 2. Rearrangements of Anti Acetals **6a**−**10a**[a]



6a	$R^1 = R^2 = H$, $R^3 = Me$	**a**	**a**
7a	$R^1 = H$, $R^2 = R^3 = Me$	**b**	**b**
8a	R^1—$R^2 = (CH_2)_3$, $R^3 = Me$	**c**	**c**
9a	$R^1 = R^2 = H$, $R^3 = i$-Pr	**d**	**d**
10a	R^1—$R^2 = (CH_2)_3$, $R^3 = i$-Pr	**e**	**e**

entry	acetal	acid	time, h	% conv	**12**:**13**[b]
1	**6a**	$SnCl_4$	14	47[c]	94:6
2	**6a**	TfOH	14	97	95:5
3	**7a**	$SnCl_4$	17	99	8:92
4	**7a**	$SnCl_4$	0.1	37[d]	8:92
5	**7a**	TfOH	15	96[e]	14:86
6	**8a**	$SnCl_4$	6	60[e]	9:91
7	**8a**	TfOH	6	74	14:86
8	**9a**	$SnCl_4$	16	36[f]	9:91
9	**9a**	TfOH	16	90	7:93
10	**10a**	$SnCl_4$	0.5	90	1:99
11	**10a**	TfOH	12	96[e]	1:99

[a] Unless noted otherwise, reactions were conducted in CH_2Cl_2 at −78 °C in the presence of 1.1 equiv of $SnCl_4$ or 3 equiv of TfOH with acetals of >97% diastereomeric purity. Acetal concentration was 0.01 M. [b] Product ratios were determined by capillary GLC analysis. [c] **6a** was recovered in 50% yield. [d] **7a** was recovered in 61% yield. [e] Isolated yield. [f] **9a** was recovered in 28% yield.

Two additional aspects of these rearrangements merit note. In experiments reported in Tables 1 and 2 in which the starting acetal was recovered, no isomerization of the recovered acetal was detected (by capillary GLC or ^{1}H NMR analysis).[16] To pursue whether product ratios were kinetically controlled, tetrahydrofurans **12a**, **13c**, and **13d** were independently resubmitted to the $SnCl_4$-promoted reaction conditions for 48 h at room temperature. In each case, the starting acyltetrahydrofuran was recovered in high yield and with unchanged isomeric purity.

Stereostructures of acyltetrahydrofurans **12a**−**e** and **13a**−**e** were determined by ^{1}H NMR NOE studies. Details of these experiments are provided in Supporting Information.[17]

Two salient trends are readily recognized: (1) The nature of the alkene and the size of the C3 substituent have little effect on stereoselection in rearrangements of acetals derived from syn allylic alcohols (Table 1). (2) In the anti series, acyltetrahydrofurans **12** are the major products only when the C3 substituent is small and the π nucleophile is a terminal vinyl group; with other substrates, tetrahydrofuran **13** is formed preferentially (Table 2). Particularly striking is the reversal in stereoselection in the anti series as the alkene component is varied from terminal vinyl (**12**:**13** = 16:1) to isopropenyl or 1-cyclopentenyl (**12**:**13** = 1:11).

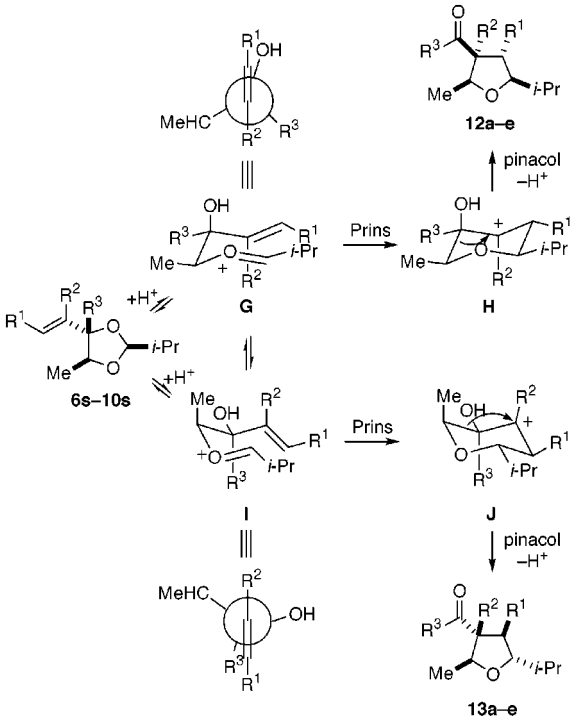
We have considered a number of mechanistic scenarios to rationalize these observations, including those involving changes in the mechanism and stereochemistry-determining step.[12] Although such possibilities cannot be excluded, we offer a simpler explanation for consideration. As depicted in Scheme 2, acid-promoted rearrangements of anti acetals **6a**−**10a** could proceed by two chair cyclization conformers having *E* oxocarbenium ion units,[8] **C** and **E**. If stereochemistry were determined in the cyclization step,[5] the **C** → **D** pathway would lead to **12**, whereas the **E** → **F** pathway would deliver **13**. Examination of the Prins cyclization step reveals an important stereoelectronic aspect. In conformer

(17) (a) Additional evidence for the cis relationship of the acetyl and C2 methyl groups of **12a** was obtained by exposing **12a** to methanolic KOH at room temperature for 24 h to give **12a** and its C3 acetyl epimer in a ratio of 8:92. Similar treatment of **13d** provided an 84:16 ratio **13d** and its C3 epimer under identical conditions, consistent with the acetyl and C2 substituents being trans in **13d**. (b) The stereostructure of the major acyltetrahydrofuran product formed from a congener of **13c** was secured by single-crystal X-ray analysis of the thiosemicarbazone derivative; see: MacMillan, D. W. C. Ph.D. Dissertation, University of California, Irvine, 1996.

E overlap of the hydroxy σ^*_{C-O} and alkene π_{C-C} is attenuated and hyperconjugative interaction between π^*_{C-C} and σ_{C-R}[3] increases nucleophilicity, whereas the situation is reversed in **C** where overlap of the low-lying hydroxy σ^*_{C-O} and alkene π_{C-C} decreases nucleophilicity.[18] However, as **E** evolves to chair hydropyranyl cation **F**, the stabilizing interaction between the vacant p orbital and σ_{C-R}[3] progressively decreases as the destabilizing interaction between the σ_{C-O} and the vacant p orbital increases. The situation is reversed in the **C** → **D** pathway where increasing bonding between the termini leads to increasing overlap between σ_{C-R}[3] and the developing vacant p orbital. These electronic effects would be superimposed upon steric preferences for the larger substituents to be equatorial. Because the Prins cyclization step should have a later transition state when the alkene component is less nucleophilic,[19,20,21] the observed propensity for rearrangement of **6a** ($R^1 = R^2 = H$, $R^3 =$ Me) to proceed by the **C** → **D** pathway is in accord with both steric and electronic considerations. The preferential generation of **13** when the alkene unit is a more nucleophilic isopropenyl or 1-cycloalkenyl group[21] would be consistent with the earlier transition state for these Prins cyclizations, if the electronic preference for the allylic OH substituent to be eclipsed with the alkene is worth more energetically than steric destabilization resulting from having a quasiaxial homoallylic methyl group. When the allylic substituent is a bulky isopropyl group, the **E** → **F** pathway could reasonably be favored irrespective of alkene nucleophilicity.

The related analysis of the Prins-pinacol pathway in the syn diol series is shown in Scheme 3. In this case, cyclization conformer **G** having a favored eclipsed orientation of the alkene and allylic hydroxyl group is also favored by placing the R^3 and homoallylic methyl substituents in quasiequatorial positions. Thus, it is apparent why substrates having strongly nucleophilic π bonds or bulky R^3 substituents would lead to **12**. To rationalize preferential formation of **12a** from the terminal vinyl substrate **6s** ($R^1 = R^2 = H$, $R^3 =$ Me) one only has to propose that the steric preference for the methyl substituent to be quasiequatorial overrides any electronic

Scheme 3. Model for Stereoselection in the Syn Diol Series



destabilization associated with generating hydropyranyl cation **H** via a late transition state.

In summary, acid-promoted rearrangements of allylic acetals derived from syn allylic diols lead with high stereoselectivity (90:10 to >99:1) to 3-acyltetrahydrofurans **12** having a cis relationship of the acyl group and the C2 and C5 substituents. Similar rearrangements of acetals prepared from anti allylic diols lead with useful levels of stereocontrol to **12** or stereoisomeric acyltetrahydrofurans **13** depending upon the nature of the alkene and allylic substituent. A distinctive stereoelectronic feature of cationic cyclizations that generate six-membered products is identified: An eclipsed allylic substituent in a reactant, whose σ bond has no or poor overlap with the adjacent π bond, evolves to an axial position in the six-membered ring product having good overlap of its allylic σ bond with the adjacent vacant p orbital. A model to rationalize stereoselection in Prins-pinacol syntheses of tetrahydrofurans that incorporates this apparently previously unrecognized stereoelectronic peculiarity is proposed.

Acknowledgment. This research was supported by a Javits Neuroscience Investigator Award from NIH NINDS (NS-12389). Merck, Pfizer, Roche Biosciences, and Smith-Kline Beecham provided additional support. NMR and mass spectra were determined using instruments acquired with the assistance of NSF and NIH shared instrumentation grants.

Supporting Information Available: Representative experimental procedures and characterization data and ^{1}H NOE data for **12** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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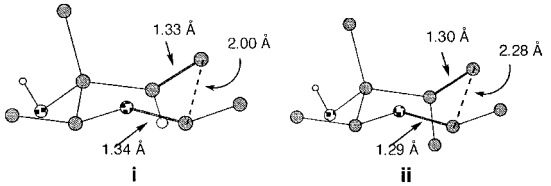
(18) For reviews, see: (a) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y. D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108−1117. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370. (c) For an alternate analysis, see: Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650−663.

(19) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334−338.

(20) Transition states found at the 6-31G* level are consistent with the transition state of the Prins cyclization being later in the vinyl **i** than the propenyl **ii** series (black = carbon, dotted = oxygen, clear = hydrogen; only the internal hydrogen of the vinyl group is shown). The dihedral angle between the developing p orbital and the σ bond to the methyl group at the original allylic carbon is 43.1° in **i** and 47.9° in **ii**.



(21) In bimolecular additions to diaryl carbenium ions, 1,1-disubstituted alkenes react >10^4 faster than 1-substituted alkenes; see: Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938−957.