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Nucleophilic Additions to Fused Bicyclic Five-Membered Ring Oxocarbenium Ions: Evidence for Preferential Attack on the Inside Face

Deborah M. Smith, Michelle B. Tran, and K. A. Woerpel*

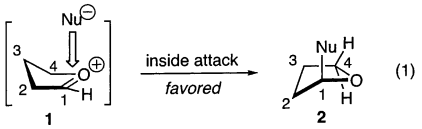
Contribution from the Department of Chemistry, University of California, Irvine, California 92697-2025

Received July 24, 2003; E-mail: kwoerpel@uci.edu

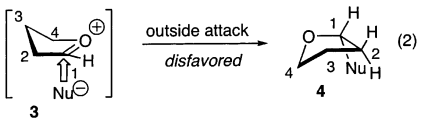
Abstract: Evidence is provided that nucleophilic attack on five-membered ring oxocarbenium ions occurs from the inside face of the envelope. An eight-five fused-bicyclic system in which two substituents are constrained to pseudoequatorial positions underwent nucleophilic addition with selectivity that was comparable to an unconstrained monocyclic system. On the other hand, a bicyclic six-five analogue underwent reaction with low selectivity. This observation indicates that minimization of eclipsing interactions by attacking inside the envelope is not enough to control selectivity, but that the changes in the overall three-dimensional structure of the ring must be favorable as well. In the bicyclic six-five series, the six-membered ring is accommodated in the cation, but it destabilizes the transition state structure leading to the first-formed product of inside attack.

Introduction

The stereoselective addition of carbon nucleophiles to oxocarbenium ions has proven to be a useful method for the functionalization of tetrahydrofuran rings.[1−3] We recently reported a model to explain the diastereoselective reactions of substituted five-membered ring oxocarbenium ions.[4] This model stipulates that when a nucleophile attacks a five-membered ring oxocarbenium ion in the envelope conformation, it attacks preferentially from the inside face of the envelope (eq 1).[5] Attack from the outside face is disfavored, because eclipsing interactions between the substituents at C-1 and C-2 develop in the transition structure leading to the first-formed product **4** (eq 2). In recognizing that staggered transition structures are lower in energy than eclipsed ones, our model shares features with the analysis reported by Reissig.[6−8]



(1)



(2)

The outside attack product **4** (eq 2) is not only differentiated from the inside attack product **2** (eq 1) by eclipsing interactions. The two modes of attack provide the products in different conformations. Upon nucleophilic attack, the oxocarbenium ion carbon undergoes rehybridization from trigonal planar[9] to tetrahedral. This rehybridization significantly alters the entire three-dimensional structure of the five-membered ring. The consequence of this rehybridization upon the conformation of the product is a fundamental tenet of the accepted model used to understand nucleophilic additions to six-membered ring iminium and oxocarbenium ions.[10−12] In those cases, rehybridization and torsional angle changes are favored for a chairlike transition structure instead of a twistlike structure.

In this paper, we provide further evidence that nucleophilic attack on five-membered ring oxocarbenium ions occurs from inside the envelope according to eq 1. In addition, these studies indicate that the impetus to minimize eclipsing interactions is not the only factor that governs selectivity, but that the overall three-dimensional structure of the ring must be favorable as well.

Experiment Design

While the inside attack model was useful for analyzing a number of reactions of five-membered ring oxocarbenium ions,[4] observations such as the highly stereoselective reaction of

(1) For a review that includes nucleophilic substitution on five-membered ring acetals, see: Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711−1754.
(2) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Tarrytown, NY, 1995; Vol. 13.
(3) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, FL, 1995.
(4) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209.
(5) Five-membered ring iminium ions are believed to undergo nucleophilic attack by transition structures similar to those for oxocarbenium ions: Bur, S. K.; Martin, S. F. *Org. Lett.* **2000**, *2*, 3445−3447.
(6) Schmitt, A.; Reissig, H.-U. *Synlett* **1990**, 40−42.
(7) Schmitt, A.; Reissig, H.-U. *Chem. Ber.* **1995**, *128*, 871−876.
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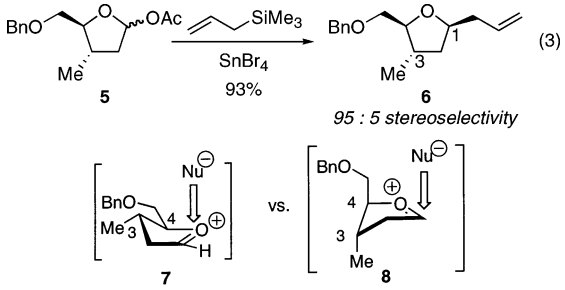
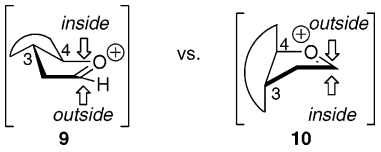
(9) Dudley, T. J.; Smoliakova, I. P.; Hoffmann, M. R. *J. Org. Chem.* **1999**, *64*, 1247−1253.
(10) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032−7035.
(11) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289−296.
(12) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 209−221.

disubstituted acetal **5** (eq 3)[4,13,14] could be reinterpreted. We proposed that the major product was formed by inside attack on the diequatorial oxocarbenium ion **7**.[4] Alternatively, the major product could arise from outside attack on the higher energy diaxial conformer **8**.[15] Because both conformers would be accessible, the conformer undergoing reaction (**7** or **8**) could not be unambiguously determined. While reasonable assumptions could be made about which conformer predominated, it was possible that the more reactive conformer of the oxocarbenium ion may not be the more populated one, in accord with the Curtin−Hammett principle.[16,17] If the cation could be locked into only one conformation, the diastereoselectivity of the nucleophilic substitution would reveal the inherent stereoelectronic preference for inside versus outside attack.

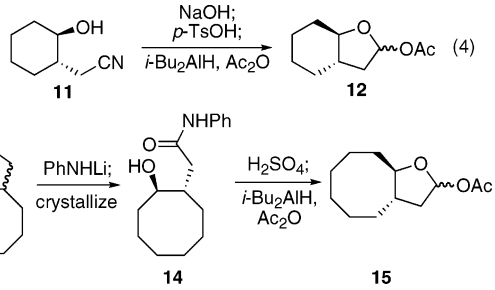


A bicyclic acetal related to acetal **5** would provide the appropriately constrained analogue.[18] If the two substituents at C-3 and C-4 were tethered together with a chain of a relatively short length, only the diequatorial oxocarbenium ion **9** would be accessible. The diaxial oxocarbenium ion **10** would be severely strained, because this conformer requires a 180° dihedral angle within the fused ring. With only a diequatorial conformer available, the inherent stereoelectronic preference for inside attack versus outside attack would be revealed because neither trajectory for approach is disfavored for steric reasons.



Synthesis of Substrates

The required acetate substrates **12** and **15** were prepared as shown in eqs 4 and 5. Nitrile **11**, prepared in one step from cyclohexene oxide,[19] was cyclized to the lactone[20] which was reductively acylated[21,22] to afford acetate **12** (eq 4).[23] A mixture of cis- and trans-lactones **13**, which was prepared in one step from cyclooctene,[23] was converted to a mixture of anilides,[24] from which the diastereomerically pure trans isomer **14** could be obtained by crystallization. Cyclization under acidic conditions[25] provided the trans lactone, which upon reductive acylation[21,22] yielded the required acetate **15** (eq 5).



Nucleophilic Substitutions

With the acetal substrates in hand, attention turned to the nucleophilic substitution reactions, which likely proceed via oxocarbenium ion intermediates.[26,27] The nucleophile allyltrimethylsilane was employed because attack by this nucleophile onto a carbocation should be irreversible,[28,29] and because this small nucleophile is relatively insensitive to steric effects upon approach to the cation.[30]

The nucleophilic substitution reactions of the six-five ring system are shown in eq 6 and Table 1. Regardless of the solvent

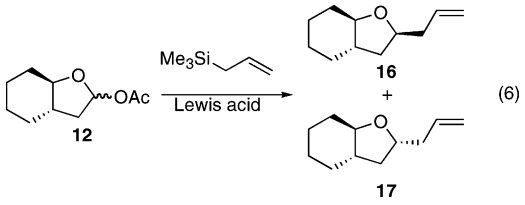


Table 1. Stereoselectivity of Nucleophilic Substitution of Six-Five Bicyclic Acetate **12** (eq 6)

entry	Lewis acid	solvent	**16**:**17**[a]	yield[b] (%)
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	73:27	76
2	$SnBr_4$	CH_2Cl_2	69:31	82
3	Me_3SiOTf	CH_2Cl_2	71:29	74
4	Me_2AlCl	CH_2Cl_2	65:35	67
5	$MeAlCl_2$	CH_2Cl_2	68:32	76
6	$TiCl_4$	CH_2Cl_2	—[c]	—[c]
7	$BF_3{\cdot}OEt_2$	$C_6H_5CH_3$	73:27	76
8	$BF_3{\cdot}OEt_2$	Et_2O	56:44	50
9	$BF_3{\cdot}OEt_2$	$CHCl_3$	73:27	55
10	$BF_3{\cdot}OEt_2$	CH_3CN	73:27	61

[a] Diastereoselectivity determined by gas chromatography and confirmed by ^1H NMR spectroscopy. [b] Yield of product after flash chromatography. [c] No product was isolated, but starting material was consumed.

and the Lewis acid, the selectivities were low.[31] The configurations of the products were determined by analysis of NOE data.

(13) Ishihara, J.; Miyakawa, J.; Tsujimoto, T.; Murai, A. *Synlett* **1997**, 1417−1419.
(14) Yang, J.; Cohn, S. T.; Romo, D. *Org. Lett.* **2000**, *2*, 763−766.
(15) Similarly, the minor product could arise from either outside attack on the diequatorial oxocarbenium ion **7** or inside attack on the diaxial cation **8**.
(16) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134.
(17) Seeman, J. I. *J. Chem. Educ.* **1986**, *63*, 42−48.
(18) For a recent example that compares the stereoselectivity of constrained versus unconstrained five-membered ring oxocarbenium ions, see: Crich, D.; Hao, X. *J. Org. Chem.* **1999**, *64*, 4016−4024.
(19) Bartlett, P. A.; Ting, P. C. *J. Org. Chem.* **1986**, *51*, 2230−2240.
(20) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1980**, *45*, 4111−4117.
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(22) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191−198.
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(24) Ooi, T.; Tayama, E.; Yamada, M.; Maruoka, K. *Synlett* **1999**, 729−730.
(25) Askin, D.; Volante, R. P.; Ryan, K. M. *Tetrahedron Lett.* **1988**, *29*, 4245−4248.
(26) See, for example: (a) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915−7916. (b) Matsutani, H.; Ichikawa, S.; Yaruva, J.; Kusumoto, T.; Hiyama, T. *J. Am. Chem. Soc.* **1997**, *119*, 4541−4542. Other reactions of acetals do not appear to involve free cations: (c) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089−8110.
(27) In our experiments with both tetrahydrofuran and tetrahydropyran acetals, the stereochemistry of nucleophilic substitution was independent of the anomer ratios of the starting acetates: (a) ref 4. (b) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168−169.
(28) Burfeindt, J.; Patz, M.; Müller, M.; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 3629−3634.
(29) Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954−4961.

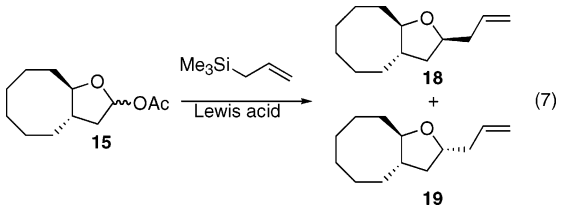


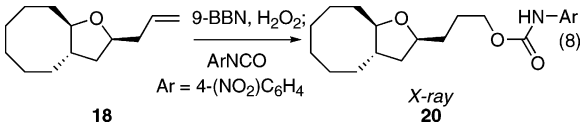
Table 2. Stereoselectivity of Nucleophilic Substitution of Eight-Five Bicyclic Acetate **15** (eq 7)

entry	Lewis acid	solvent	**18**:**19**[a]	yield[b] (%)
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	93:7	83
2	$SnBr_4$	CH_2Cl_2	93:7	82
3	Me_3SiOTf	CH_2Cl_2	93:7	85
4	Me_2AlCl	CH_2Cl_2	92:8	64
5	$MeAlCl_2$	CH_2Cl_2	92:8	81
6	$TiCl_4$	CH_2Cl_2	—[c]	—[c]
7	$SnBr_4$	$C_6H_5CH_3$	96:4	80
8	$SnBr_4$	Et_2O	91:9	82
9	$SnBr_4$	$CHCl_3$	92:8	81
10	$SnBr_4$	CH_3CN	91:9	74

[a] Diastereoselectivity determined by gas chromatography and confirmed by ^{1}H NMR spectroscopy. [b] Yield of product after flash chromatography. [c] No product was isolated, but starting material was consumed.

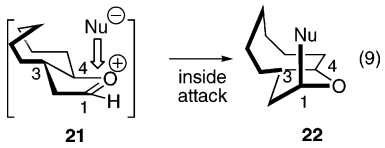
The sense of stereoselectivity corresponds to that exhibited by the unconstrained acetate **5** (eq 3), although the unconstrained system showed markedly higher selectivity (about 10-fold higher).

In contrast to the observations of the six-five ring system (eq 6 and Table 1), nucleophilic substitution reactions with the bicyclic eight-five ring system proceeded with high selectivity. As shown in eq 7 and Table 2, the diastereoselectivities of these reactions matched the selectivities observed for the unconstrained system, and these selectivities were independent of the solvent and the Lewis acid.[27,31,32] The configuration of the major product was assigned by conversion of the alkene to the carbamate **20** (eq 8), whose structure was determined by X-ray crystallography.[33]



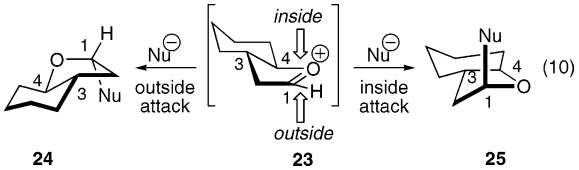
Discussion

The highly stereoselective reactions of the fused eight-five bicyclic system **15** (eq 7 and Table 2) provide evidence that a five-membered ring oxocarbenium ion undergoes nucleophilic attack with a stereoelectronic preference for inside attack. Because of the constraints imposed by the trans ring fusion and the short tether, only a diequatorially substituted conformer of the five-membered ring should be accessible (i.e., **21**).[34] Under all conditions examined, the product that was obtained with >90% selectivity arose from nucleophilic attack on the cation from the inside face of the envelope (eq 9). Because the outside approach of the nucleophile does not appear to be sterically disfavored, the preference for inside attack must be a result of steric interactions that form within the ring during outside attack (minimizing eclipsing interactions, vide supra). Because the stereoselectivity observed for the bicyclic system matches the selectivity observed for the unconstrained acetal **5** (eq 3), the selectivity of the unconstrained system most likely results from inside attack on the diequatorially substituted cation **7** (vide supra).



The contrast between the results with the eight-five and the six-five systems (cf., Tables 1 and 2) is meaningful. The low selectivity observed for the six-five fused acetal **12** (eq 6, Table 1) indicates that the preference for inside attack of the nucleophile in this system is diminished. If the minimization of eclipsing interactions were all that were important to define stereoselectivity, then the two fused systems must behave similarly. Therefore, any analysis that considers only eclipsing interactions in transition structures cannot accommodate these results.

The inside attack model accounts for the low selectivity of nucleophilic attack exhibited by the six-five fused ring oxocarbenium ion. The five-membered ring of oxocarbenium ion **23** adopts an envelope conformation,[35] and the dihedral angles within this ring accommodate the optimal chair conformer of the six-membered ring. According to the inside attack model, the envelope would undergo an overall ring flip upon nucleophilic attack from the inside face, leading to the first-formed product **25** (eq 10). This overall change in the conformation of the five-membered ring would modify the conformation of the six-membered ring, because the dihedral angles around the C3−C4 bond are different in product **25** than in oxocarbenium ion **23**.[35] The six-membered ring of product **25** would be distorted from the ideal chair structure, so the transition state leading to product **25** would be destabilized.[35] On the other hand, attack on the outside of the envelope would proceed by a transition structure that would maintain the chair conformation of the six-membered ring. As product **24** is formed, however, unfavorable eclipsing interactions would develop in the five-membered ring. Consequently, the two pathways for reaction of oxocarbenium ion **23** (inside and outside attack) each involve destabilized transition structures, resulting in a reaction with low stereoselectivity.



(30) Bear, T. J.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **2002**, *67*, 2056−2064.
(31) With each Lewis acid, the counterion for the oxocarbenium ion is different, but the selectivity is independent of this counterion. In addition, because the selectivities are insensitive to the solvent, ion pairing is not evidently important.
(32) The diastereoselectivity of this nucleophilic substitution is independent of the ratio of anomeric acetates, consistent with the intermediacy of oxocarbenium ions (details of these experiments are provided as Supporting Information).
(33) Additional details are provided as Supporting Information.
(34) While other conformations of the eight-membered ring may be relatively close in energy, it is the conformation of the five-membered ring that is important in controlling stereoselectivity. Oxocarbenium ion **21** and the product **22** are shown with the eight-membered ring in a boat-chair conformation, because the eight-membered rings of trans-fused eight-five ring systems adopt boat-chair forms: Umehara, M.; Hosomi, H.; Ohba, S. *Acta Crystallogr., Sect. C* **1999**, *55*, 1721−1725.

Conclusion

These experiments with fused-ring acetals provide additional support that the reactions of five-membered ring oxocarbenium ions with nucleophiles are strongly influenced by stereoelectronic effects. The preference for attack from inside the envelope was observed for the eight-five ring system, in which the five-membered ring is constrained to an envelope conformer with the eight-membered ring spanning two equatorial positions. The different behavior of the six-five and eight-five ring systems illuminates that, upon nucleophilic attack, the five-membered ring undergoes a significant change in its overall three-dimensional structure, and that this change must not engender too much strain elsewhere if high selectivity is to be observed.

Experimental Section[33]

General Procedure for Allylation of γ-Lactol Acetates. A solution of acetate in CH_2Cl_2 (0.10 M) was treated with allyltrimethylsilane (4 equiv) and then cooled to −78 °C. After treatment with Lewis acid (1.1 equiv), the reaction mixture was warmed to 22 °C over 2 h. The reaction mixture was treated with saturated aqueous Na_2HPO_4 (1 mL per mmol of acetate). The aqueous layer was then extracted three times with CH_2Cl_2 (1 mL per mmol of acetate), and the organic phases were dried (Na_2SO_4) and concentrated in vacuo.

Six-Five Bicyclic Alkene (16 and 17). The standard allylation procedure was followed with acetate **12** (0.051 g, 0.28 mmol) and $BF_3{\cdot}OEt_2$ (0.4 mL, 0.3 mmol). GC and ^{1}H NMR spectroscopic analysis of the unpurified product showed a pair of diastereomers in a 73:27 ratio of 1,3-trans:cis diastereomers. Purification by flash chromatography (2:98 Et_2O/pentane) provided the product as a clear oil (0.035 g, 76%). The major isomer **16** was isolated as a pure sample, while the minor isomer **17** was isolated as a mixture of **16** and **17**. IR and mass spectrometry data were obtained for **16** and **17** as a mixture of diastereomers. IR (thin film): 2932, 2857, 1641, 1072 cm^{-1}. HRMS (EI) *m/z* calcd for $C_8H_{13}O$ $(M - C_3H_5)^+$ 125.0966, found 125.0969.

Major Isomer 16. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 (ddt, J = 17.2, 10.3, 6.9, 1H), 5.09 (m, 1H), 5.06 (m, 1H), 4.12 (m, 1H), 3.08 (td, J = 10.1, 3.7, 1H), 2.40 (m, 1H), 2.29 (m, 1H), 2.16 (m, 1H), 1.90 (m, 1H), 1.81 (m, 1H), 1.71 (m, 2H), 1.60 (td, J = 11.7, 9.1, 1H), 1.15−1.35 (m, 4H), 1.07 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.5, 117.3, 84.2, 77.2, 44.7, 41.7, 35.9, 31.8, 29.6, 26.4, 24.8.

Minor Isomer 17. ^{1}H NMR (500 MHz, $CDCl_3$, distinctive peaks): δ 3.15 (td, J = 10.3, 3.7, 1H), 1.42 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, distinctive peaks): δ 82.9, 78.2, 46.7, 41.6, 40.0, 31.9, 29.5, 26.2, 24.8.

Eight-Five Bicyclic Alkene (18). The standard allylation procedure was followed with acetate **15** (0.050 g, 0.24 mmol) and $BF_3{\cdot}OEt_2$ (0.04 mL, 0.3 mmol). GC and ^{1}H NMR spectroscopic analysis of the unpurified product showed a pair of diastereomers in a 93:7 ratio of 1,3-trans:cis diastereomers. Purification by flash chromatography (2:98 EtOAc/hexanes) provided the product as a colorless oil (0.038 g, 83%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 (ddt, J = 17.2, 10.2, 7.0, 1H), 5.05 (m, 2H), 3.82 (quintet, J = 6.7, 1H), 3.66 (td, J = 8.5, 4.0, 1H), 2.33 (m, 1H), 2.17 (m, 1H), 2.04 (m, 2H), 1.83 (m, 2H), 1.69 (m, 4H), 1.60 (m, 1H), 1.33−1.46 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.6, 117.0, 85.4, 76.5, 42.9, 41.3, 40.7, 35.5, 34.9, 28.2, 27.4, 25.5, 23.6. IR (thin film): 3075, 2922, 2853, 1641 cm^{-1}. HRMS (EI) *m/z* calcd for $C_{13}H_{23}O$ $(M + H)^+$ 195.1749, found 195.1748. Anal. Calcd for $C_{13}H_{22}O$: C, 80.36; H, 11.41. Found: C, 80.53; H, 11.55.

Acknowledgment. This research was supported by the National Institutes of Health, National Institute of General Medical Science (GM-61066), and by Johnson & Johnson. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. D.M.S. thanks Johnson & Johnson for a graduate research fellowship. K.A.W. thanks Merck Research Laboratories, Johnson & Johnson, and the Sloan Foundation for awards to support research. We thank Ms. Catharine Larsen for carrying out some preliminary experiments, Dr. Brian Ridgway for helpful discussions, Dr. John Greaves and Dr. John Mudd for mass spectrometric data, and Dr. Joe Ziller for the X-ray crystallographic analysis.

Supporting Information Available: Complete experimental procedures, product characterization, stereochemical proofs, X-ray crystallographic data for carbamate **20**, and GC and spectral data for selected compounds (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(35) The dihedral angle between C3 and C4 within the five-membered ring of structure **25** is about 25° smaller than that for the chair conformation of cyclohexane. Consequently, the six-membered ring of **25** should be distorted from a chair conformation by a comparable angle. For a review of five-membered ring conformational analysis, see: Fuchs, B. *Top. Stereochem.* **1978**, *10*, 1−94.