Stereochemical Control in the Ester Enolate Claisen Rearrangement. 2. Chairlike vs Boatlike Transition-State Selection[1a]

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The preference for chair- and boatlike transition-state geometries in the ester enolate Claisen rearrangement of straight chain, carbocyclic, and heterocyclic propanoates was investigated. A novel stereoelectronic effect in pyranoid and furanoid glycal systems leads to a significant relative stabilization of the boatlike vs the chairlike TS*. The preferred transition state in six- and five-membered carbocyclic systems is highly dependent on steric factors, as the energy difference between chair- and boatlike TS* tends to be small. With straight-chain substrates, a significant contribution of the boatlike TS* to the rearrangement product mixture is only expected in bis-donor substituted allylic esters.

Introduction

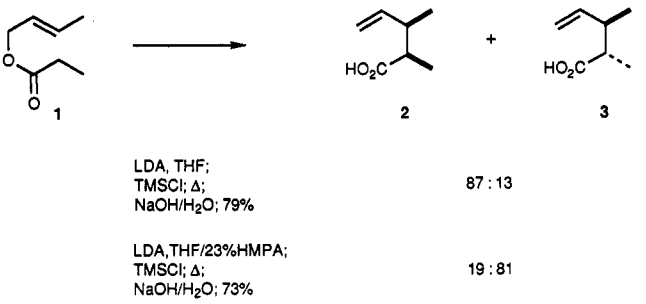
The aliphatic Claisen rearrangement of allyl enol ethers has developed into an extremely valuable tool for the stereocontrolled C-C bond formation.[2] Among the available procedures,[3] the silyl ketene acetal variant of the Claisen rearrangement allows a predictable transfer of stereochemistry from starting material to product under exceptionally mild reaction conditions (Scheme I).[4]

In part 1 of this report, factors influencing the stereoselectivity in silyl ketene acetal formation were described.[5] For the correct prediction of product stereochemistry and therefore the proper choice of enolization conditions, it is nevertheless crucial to know the preference for chair- or boatlike transition state (TS*) in the actual [3,3]-sigmatropic shift (Scheme II).

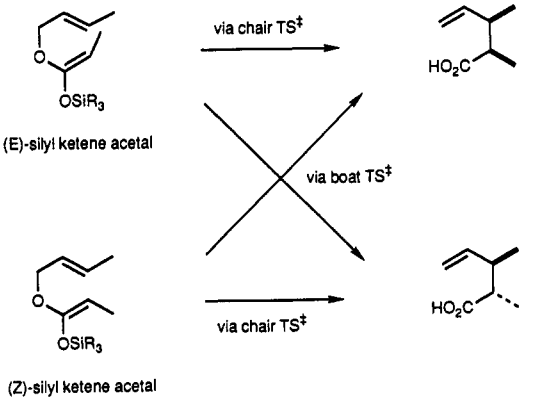
According to the Woodward-Hoffmann rules,[6] four concerted transition states are possible for the Claisen as well as the closely related Cope rearrangements: chair, boat, twist, and plane.[7] Only the chair and boat TS* have to be considered, as twist and plane are antarafacial-antarafacial processes and require highly elevated temperatures.[8]

In acyclic systems, Claisen rearrangements show a well-established preference for chairlike transition states. With crotyl propenyl ether the chair selectivity amounts of 97-98% at 142 °C, which corresponds to a ca. 3 kcal/mol difference between the free energy of activation ($\Delta\Delta G^*$) of chair and boat TS*.[9] The prefernece for a chairlike geometry in the TS* is even more pronounced in the Cope rearrangement: 99.7% of the 3,4-dimethylhexa-1,5-diene rearranges at 225 °C via a chairlike TS*, corresponding to a $\Delta\Delta G^*_{\text{chair-boat}}$ of -5.7 kcal/mol.[9a,10] The latter result

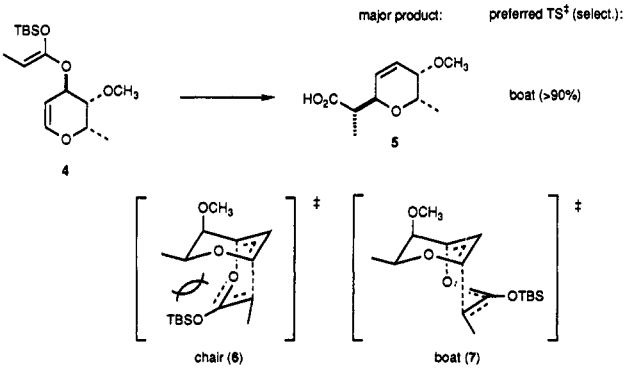
Scheme I



Scheme II



Scheme III



(1) (a) Grateful acknowledgment is made for support of this investigation by a grant from the NIH (GM-39998). (b) Present address: University of Pittsburgh, Department of Chemistry, Pittsburgh, PA 15260.

(2) For recent reviews, see: (a) Wipf, P. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.2. (b) Blechert, S. *Synthesis* **1989**, 71. (c) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

(3) (a) Carroll, M. F. *J. Chem. Soc.* **1940**, 1266. (b) Arnold, R. T.; Searles, S., Jr. *J. Am. Chem. Soc.* **1949**, *71*, 1150. (c) Steen, K.; Felix, D.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425. (d) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

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(5) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650.

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(8) Gajewski, J. J.; Benner, C. W.; Hawkins, C. M. *J. Org. Chem.* **1987**, *52*, 5198.

(9) (a) Vittorelli, P.; Winkler, T.; Hansen, H. J.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1457. (b) Vittorelli, P.; Hansen, H. J.; Schmid, H. *Ibid.* **1975**, *58*, 1293. (c) Vance, R. L.; Rondan, N. G.; Houk, K. N.; Jensen, F.; Borden, W. T.; Komornicki, A.; Wimmer, E. *J. Am. Chem. Soc.* **1988**, *110*, 2314.

(10) (a) Doering, W. von E.; Roth, W. R. *Angew. Chem.* **1963**, *75*, 27. (b) Brown, A.; Dewar, M. J. S.; Schoeller, W. *J. Am. Chem. Soc.* **1970**, *92*, 5517. (c) Shea, K. J.; Phillips, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 3156.

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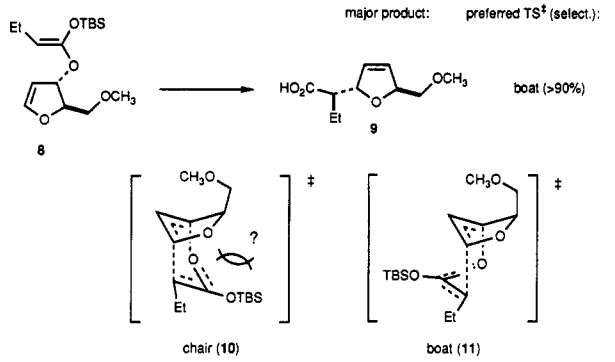
Scheme IV

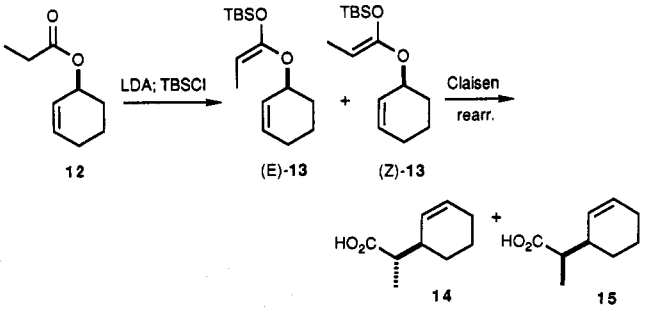


closely parallels the difference in energy of the chair and boat conformations of cyclohexane (5–6 kcal/mol).[11]

In cyclic systems, however, conformational constraints can override the inherent preference for chairlike transition states in Cope[12] as well as Claisen[13,14] rearrangements and lead to a partial involvement if not a dominance of boatlike TS‡ structures. In fact, numerous examples of ester enolate Claisen rearrangements have established the general rule that in cyclic systems a boat TS‡ is strongly preferred.[15,16] This experimentally established difference between cyclic and acyclic systems is presumably due to destabilizing steric interactions of the silyloxy substituent and the ring atoms in chairlike TS‡ such as the pyranoid glycal 6 (Scheme III[17]).[4,13]

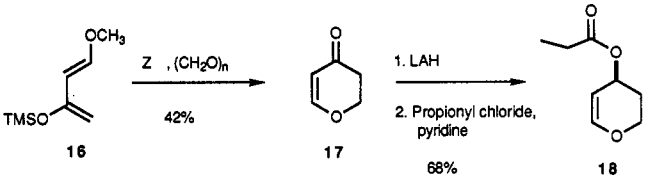
In furanoid glycal systems, the destabilizing interaction between the silyloxy substituent and the ring carbons in the chairlike TS‡ should be considerably diminished. However, there is still a strong preference for boatlike TS‡ geometries (Scheme IV[17]). Interestingly, Bartlett and Pizzo reported in 1981 the occurrence of a chairlike TS‡ in the ester enolate rearrangement of the (*E*)-silyl ketene acetal of cyclohexenyl propanoate **12**.[18,19] The corresponding (*Z*)-silyl ketene acetal still rearranged predominantly via a boatlike TS‡. The reason for the partly different TS‡ geometry preferences of propionates **12** and **4** remained unclear.

Scheme V

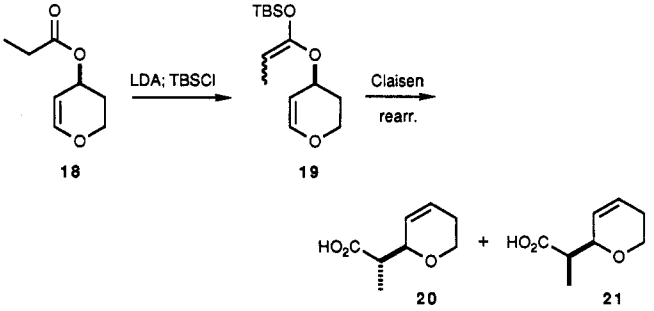


solvent	(*E*)-13:(*Z*)-13	14:15	% yield	favored TS‡
THF	83:17	84:16	79	chair
THF/45% DMPU	4:96	72:28	91	boat
THF/23% HMPA	14:86	73:27	60	boat

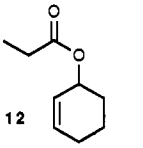
Scheme VI



Scheme VII



solvent	20:21	% yield	favored TS‡
THF	29:71	77	boat
THF/45% DMPU	86:14	35	boat



In order to gain more insight into the mechanisms that lead to a relative stabilization of either chair- or boatlike TS‡ structures in ester enolate Claisen rearrangements of cyclic substrates, possible ambiguities caused by steric or conformational influences of ring substituents were avoided by a systematic investigation of the parent glycal and carbocyclic systems.

Results

Claisen Rearrangement of Cyclohexene and Pyranoid Glycal Derivatives. The formation of diastereomeric products in the ester enolate Claisen rearrangement can be attributed to either the geometric integrity of the silyl ketene acetals or the selectivity of the chairlike vs the boatlike TS‡. We therefore determined the amount of (*E*)- and (*Z*)-silyl ketene acetals obtained by the various en-

(11) Johnson, W. S.; Bauer, V. J.; Margrave, J. L.; Frisch, M. A.; Dreger, L. H.; Hubbard, W. N. *J. Am. Chem. Soc.* **1961**, *83*, 606.

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(13) (a) Chapleo, C. B.; Hallett, P.; Lythgoe, B.; Waterhouse, I.; Wright, P. W. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 1211. (b) Cave, R. J.; Lythgoe, B.; Metcalfe, D. A.; Waterhouse, I. *Ibid.* **1977**, 1218. (c) Büchi, G.; Powell, J. E., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 3126.

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(15) (a) Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S.; Vanier, N. R. *Can. J. Chem.* **1979**, *57*, 1743. (b) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48. (c) Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155. (d) Ireland, R. E.; Vevert, J. P. *J. Org. Chem.* **1980**, *45*, 4259. (e) Ireland, R. E.; Vevert, J. P. *Can. J. Chem.* **1981**, *59*, 572. (f) Ireland, R. E.; Wutz, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205. (g) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479. (h) Ireland, R. E.; Godfrey, J. D.; Thaisrivongs, S. *J. Am. Chem. Soc.* **1981**, *103*, 2446.

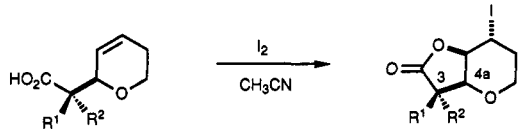
(16) (a) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988. (b) Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285. (c) Ireland, R. E.; Häbich, D.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3271. (d) Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279. (e) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635. (f) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854.

(17) Only the rearrangements of (*Z*)-silyl ketene acetals are shown; the corresponding (*E*)-silyl ketene acetals exhibit closely similar preferences for TS‡ geometries.

(18) Bartlett, P. A.; Pizzo, C. F. *J. Org. Chem.* **1981**, *46*, 3896.

(19) A combination of bicyclic chair- and boatlike transition states in the Claisen rearrangement of propanoates of cyclic allylic alcohols has also been observed by Curran and co-workers: Kim, B. H.; Jacobs, P. B.; Elliott, R. L.; Curran, D. P. *Tetrahedron* **1988**, *44*, 3079. Erroneously, the geometry of the silyl ketene acetal obtained by ester enolization with $LiN(TMS)_2$ was assigned as *E* in this report.

Scheme VIII



20, R^1=H, R^2=CH_3 22, R^1=H, R^2=CH_3; 83%

21, R^1=CH_3, R^2=H 23, R^1=CH_3, R^2=H; 80%

olization procedures[5] and reinvestigated the [3,3]-shift of 2-cyclohexenyl propanoate (12) (Scheme V).

Our results with propanoate 12 clearly confirm Bartlett and Pizzo's findings; after Claisen rearrangement at 60 °C and hydrolysis of the silyl ester, an 83:17 mixture of (*E*)- and (*Z*)-silyl ketene acetals (*E*)-13 and (*Z*)-13 led in 79% yield to a 84:16 mixture of C(2) isomeric acids 14 and 15.[20] The (*Z*)-silyl ketene acetal (*Z*)-13 was obtained in high selectivity by enolization of ester 12 in THF/45% DMPU,[5] and led, analogously, to a 72:28 mixture of the isomeric acids 14 and 15 to 91% yield. Accordingly, the (*E*)-silyl ketene acetal (*E*)-13 undergoes a [3,3]-sigmatropic shift with a ca. 6.1:1 preference for the chairlike over the boatlike TS‡, which corresponds to a $\Delta\Delta G^{\ddagger}_{\text{chair-boat}}$ of −1.2 kcal/mol.[21] The difference in activation energies for boat- and chairlike TS‡ for the (*Z*)-silyl ketene acetal can be calculated as ca. 0.60 kcal/mol ($\Delta\Delta G^{\ddagger}_{\text{chair-boat}}$) in favor of the boat.

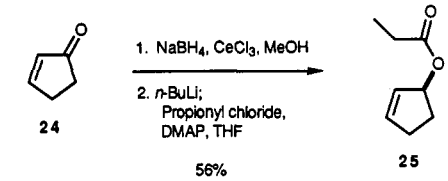
The pyranoid glycal 18 was prepared through hetero-Diels–Alder cycloaddition of 1-methoxy-3-((trimethylsilyl)oxy)buta-1,3-diene with formaldehyde,[22] reduction with LAH, and subsequent acylation with propionyl chloride (Scheme VI).

Enolization and rearrangement of glycal 18 under the conditions used for propanoate 12 led to a mixture of diastereomeric acids. Rather surprisingly, the predominant isomer was formed via a boatlike TS‡ in the rearrangement of both the (*E*)- and the (*Z*)-silyl ketene acetals (Scheme VII)!

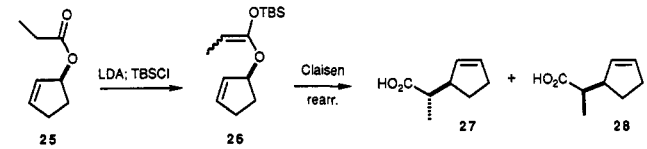
The relative stereochemistry of the pyranoid acids was established by ^{1}H NMR analysis of the corresponding iodo lactones (Scheme VIII). ^{1}H NMR chemical shifts and coupling constants for iodo lactones 22 and 23 were assigned by a series of double resonance experiments. The preferred conformation of both bicyclic ring systems—a trans diaxial orientation of lactone oxygen and iodide—was indicated by C(7)-H–C(7a)-H coupling constants of 1.5 Hz (for lactone 22) and 2.5 Hz (for lactone 23) and by molecular mechanics calculations.[23] The C(3)-H–C(4a)-H coupling constants of 0 Hz for the α-methyl isomer 22 (dihedral angle of 90° between C(3)-H and C(4a)-H) and 3.9 Hz for β-methyl isomer 23 (dihedral angle of 42° between C(3)-H and C(4a)-H) allowed an unambiguous assignment of the product stereochemistry and therefore the favored transition states for the sigmatropic rearrangement.

Assuming a similar ratio of (*E*)- and (*Z*)-silyl ketene acetals as observed in the carbocyclic series (Scheme V),[24] the $\Delta\Delta G^{\ddagger}_{\text{chair-boat}}$ for the (*E*)-silyl ketene acetal in the glycal series can be calculated to be ca. 1.0 kcal/mol in favor of a boatlike TS‡. For the (*Z*)-silyl ketene acetal $\Delta\Delta G^{\ddagger}_{\text{chair-boat}}$ amounts to 1.6 kcal/mol. Accordingly, the change from a methylene substituent at the allylic ether portion of the Claisen system to an oxygen atom can be roughly estimated to contribute between 1.0 kcal/mol ((*Z*)-silyl ketene acetals) and 2.2 kcal/mol ((*E*)-silyl ketene acetals) to a relative stabilization of the boatlike over the chairlike TS‡ in the [3,3]-rearrangement. The pyranoid glycal/cyclohexene system is therefore the first striking example of a

Scheme IX

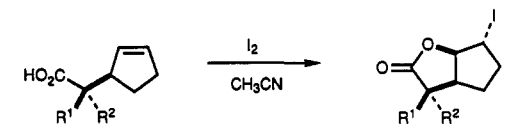


Scheme X



solvent	27:28	% yield	favored TS‡
THF	75:25	48	chair
THF/23% HMPA	40:60	63	chair

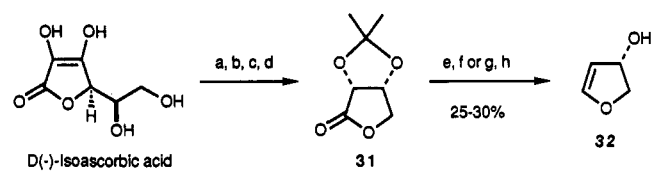
Scheme XI



27, R^1=H, R^2=CH_3 29, R^1=H, R^2=CH_3; 85%

28, R^1=CH_3, R^2=H 30, R^1=CH_3, R^2=H; 70%

Scheme XII[a]



[a] (a) Na_2CO_3, H_2O; (b) 30% H_2O_2; (c) 6 N HCl; (d) acetone, $(CH_3)_2C(OMe)_2$, TsOH; (e) DIBAL, ether; (f) PPh_3, CCl_4, THF; (g) HMPT, CCl_4, THF; (h) Li/NH_3(l).

(20) The configuration on C(2) was assigned according to ref 18.

(21) $\Delta\Delta G^{\ddagger}_{\text{chair-boat}}$ were calculated from RT in (ratio of chair to boat selectivity). As this ratio depends on the relative ratio of (*Z*)- and (*E*)-silyl ketene acetals in the reaction mixture and is not equal to the observed product ratio, the following string of equations has to be solved:

$$\frac{aS_{EC} + bS_{ZB}}{aS_{EB} + bS_{ZC}} = \alpha \qquad S_{EC} + S_{EB} = 1$$

$$\frac{cS_{EC} + dS_{ZB}}{cS_{EB} + dS_{ZC}} = \beta \qquad S_{ZC} + S_{ZB} = 1$$

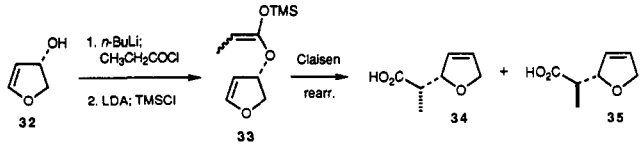
The percentage of (*E*)- and (*Z*)-silyl ketene acetal is expressed as *a* and *b*, respectively, in the first enolization mixture, and *c* and *d*, respectively, in the second solvent system. The observed product ratios are expressed as α and β. The desired chair and boat selectivities of (*E*)- and (*Z*)-silyl ketene acetals are expressed as S_{EC}, S_{EB}, S_{ZC}, and S_{ZB}, respectively. Therefore, as a first approximation the same rearrangement selectivities are used for both solvent mixtures. This seems reasonable, as dipolar solvents are also added after enolization with LDA in THF to enhance the rate of silylation. The rearrangement temperatures are recorded in the Experimental Section.

(22) Danishefsky, S.; Webb, R. R. *J. Org. Chem.* 1984, *49*, 1955.

(23) Molecular mechanics calculations were performed with an extended MM2 parametrization of the Chem3D Plus program (Cambridge Scientific Computing, Inc.) on a Macintosh II. For detailed information, see the supplementary material.

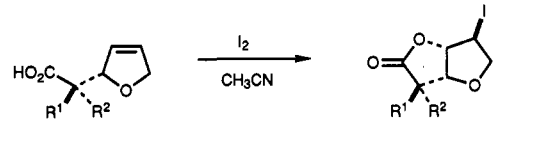
(24) The spectroscopic analysis of the actual ratio of (*E*)- to (*Z*)-silyl ketene acetals was complicated by the sensitivity of these derivatives in the glycal series. With more highly substituted glycals, however, a good correlation of the silyl ketene acetal ratios to the ratios in the carbocyclic series were observed. For a detailed analysis of *E*/*Z* ratios as a function of enolization conditions, see ref 5.

Scheme XIII



solvent	34:35	% yield	favored TS‡
THF	57:43	44	boat
THF/23% HMPA	20:80	40	boat

Scheme XIV



34, R^1=H, R^2=CH_3

35, R^1=CH_3, R^2=H

36, R^1=H, R^2=CH_3; 70%

37, R^1=CH_3, R^2=H; 81%

shift from a preference of chairlike to boatlike transition states in the ester enolate Claisen rearrangement that is a consequence of a disparate stereoelectronic stabilization of the two TS‡ geometries rather than being based on steric factors.

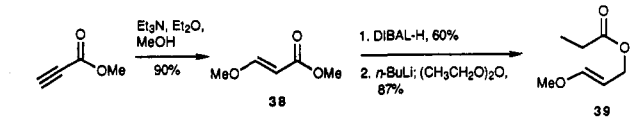
Claisen Rearrangement of Cyclopentene and Furanoid Glycal Derivatives. Encouraged by the remarkable effect of the oxygen substituent on the relative stabilities of chair- and boatlike transition states in the six-membered ring series, attention was turned toward the corresponding cyclopentene and furanoid glycal derivatives. Cyclopentenyl propanoate **25** was prepared in 56% yield by a Luche reduction[25] of 2-cyclopentenone followed by acylation of the allylic alcohol with propionyl chloride (Scheme IX).

Propanoate **25** was enolized with LDA in THF and silylated with TBSCl to give predominantly the (*E*)-silyl ketene acetal (*E*)-**26**. Subsequent Claisen rearrangement and basic hydrolysis of the resulting silyl ester led in 48% yield to a 75:25 ratio of carboxylic acids **27** and **28** (Scheme X). The (*Z*)-silyl ketene acetal (*Z*)-**26** was prepared in THF/23% HMPA and rearranged in 63% yield to a 40:60 ratio of acids **27** and **28**. With both (*E*)- and (*Z*)-silyl ketene acetals the major isomer was therefore formed via a chairlike TS‡.

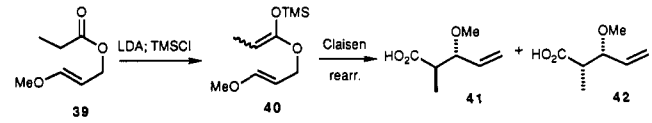
The relative stereochemistry at C(2) of the rearrangement products **27** and **28** was again determined by analysis of the coupling constants of the corresponding iodo lactones that were obtained in 85% and 70% yield by treatment of the acids with iodine in acetonitrile (Scheme XI).[26]

The furanoid glycal system was obtained from D-(−)-isoascorbic acid by the procedure outlined in Scheme XII.[27] Acylation an in situ [3,3]-rearrangement of glycal **32** through the (*E*)-silyl ketene acetal (*E*)-**33** was followed by hydrolysis with HCl/H_2O and led in 44% yield to a 57:43 mixture of acids **34** and **35**. The major isomer **34** was formed through a boatlike TS‡ geometry. The corresponding (*Z*)-silyl ketene acetal (*Z*)-**33** was formed in THF/23% HMPA and led to a 20:80 ratio of isomeric acids, again predominantly by a boatlike TS‡ (Scheme XIII).

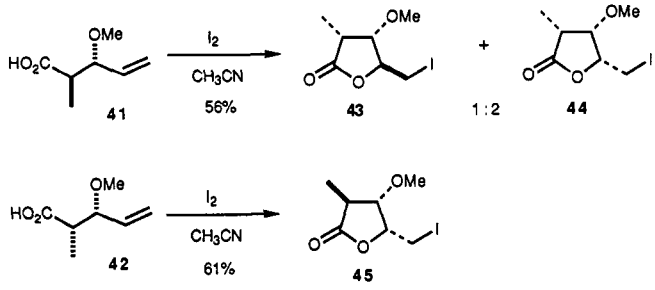
Scheme XV



Scheme XVI



Scheme XVII



The analysis of the coupling constants of the iodocyclization products **36** and **37** allowed a straightforward assignment of the relative stereochemistry at C(2) of the Claisen rearrangement products from which their preferred transition states were assigned (Scheme XIV).[26] In accordance with the results obtained in the cyclohexene/pyranoid glycal series, the exchange of the ring methylene substituent at the allyl portion of the Claisen system with an oxygen atom leads to a high relative stabilization of the boatlike over the chairlike TS‡ in the [3,3]-rearrangement of ketene acetals **26** and **33**. This relative increase of stabilization ($\Delta\Delta G^{\ddagger}_{chair-boat}$) in the cyclopentene/furanoid glycal system amounts to 1.4 kcal/mol for the (*E*)- and 1.9 kcal/mol for the (*Z*)-silyl ketene acetal.[28]

Claisen Rearrangement of Methoxyallyl Propionate. The surprising magnitude of the effect of a carbon–oxygen exchange at C(6) of the Claisen system on the relative energies of chair- and boatlike TS‡ ($\Delta\Delta G^{\ddagger}_{chair-boat}$) in the six- as well as in the five-membered ring systems led to the consideration of the acyclic enolether proponate **39**. This and related acyclic systems had already been investigated earlier, but at that time the relative stereochemistry of the products was based on the assumption of a chairlike TS‡ and was not rigorously investigated.[29]

In a modification of the original procedure,[29,30] methanol was added to methyl propiolate with triethylamine catalysis to give methyl (*E*)-methoxyacrylate (**38**) in 90% yield. No (*Z*)-isomer could be detected under these reaction conditions. Reduction with DIBAL-H in ether followed by acylation with propionic anhydride led in high yield to the desired propanoate **39** (Scheme XV). Subsequently silyl ester enolate Claisen rearrangement of the (*E*)-silyl ketene acetal led to a 87:13 mixture of carboxylic acids **41** and **42**. A 25:75 mixture of the same acids was isolated upon rearrangement of the corresponding (*Z*)-silyl ketene acetal (Scheme XVI).

The relative stereochemistry of the C(2)-methyl group could again be derived from the analysis of the coupling

(25) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2227.

(26) See supplementary material for a detailed analysis of coupling constants and conformational energy minimization data.

(27) (a) Cohen, N.; Banner, B. L.; Laurenzano, A. J.; Carozzo, L. *Org. Synth.* **1985**, *63*, 127. (b) Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S. *J. Org. Chem.* **1978**, *43*, 786.

(28) This $\Delta\Delta G^{\ddagger}$ value is based on a 86:14 mixture of (*E*)- to (*Z*)-silyl ketene acetals for the ester enolization/silylation in THF and a 18:82 mixture of (*E*)- to (*Z*)-silyl ketene acetals for the ester enolization/silylation in THF/23% HMPA, cf. ref 5.

(29) Ireland, R. E.; Wilcox, C. S. *Tetrahedron Lett.* **1977**, *33*, 2839.

(30) Winterfeldt, E.; Preuss, H. *Chem. Ber.* **1966**, *99*, 450.

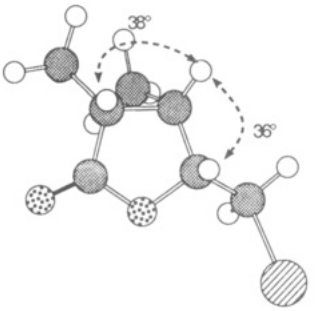


Figure 1. X-ray structure of iodo lactone **44**.

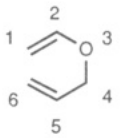


Figure 2.

constants of the corresponding monocyclic iodo lactones. Thermodynamic iodolactonization[31] of the carboxylic acid **41** led to a 1:2 mixture of iodo lactones **43** and **44** (Scheme XVII).

The syn orientation of the methyl and the methoxy substituents on lactones **43** and **44** was indicated by 6.3- and 4.8-Hz coupling constant between C(3)-H and C(4)-H. In isomer **43**, a small 1.2-Hz coupling between C(4)-H and C(5)-H was the basis of the assignment of an anti orientation between the C(4)-methoxy substituent and the C(5)-iodomethylene group. In isomer **44** this coupling constant amounted to 3.3 Hz and thus indicated a syn orientation. Additionally, the ^{1}H NMR and molecular mechanics based assignments for the relative configuration and conformation of these two lactones **43** and **44** were confirmed by an X-ray structural analysis of the major isomer **44**, which unambiguously established the all syn stereochemical relationship for the substituents on the lactone ring (Figure 1).[26,32] With coupling constants of 1.2 Hz between C(3)-H and C(4)-H and 4.5 Hz between C(4)-H and C(5)-H, the ^{1}H NMR analysis of the product from rearrangement of the (*Z*)-silyl ketene acetal (*Z*)-**40**—iodo lactone **45**—was in full accordance with an anti–syn relationship of the substituents on the lactone ring.[33]

The relative configuration of the products of the silyl ester enolate Claisen rearrangement of (*E*)-methoxyallyl propanoate (**39**) is therefore in accordance with a preference for the chairlike TS‡ in approximately the same magnitude as observed with crotyl propanoate (Scheme I). In the acyclic series, the effect of the oxygen substituent at the allylic ether portion of the Claisen system on the relative energy of the two possible transition states is therefore markedly smaller than the effect detected in the cyclic series.

Discussion

The influence of donor and acceptor substituents on the *rates* of the Claisen and other sigmatropic rearrangements has been widely investigated.[4,34-37] A theoretical model

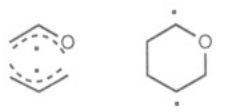
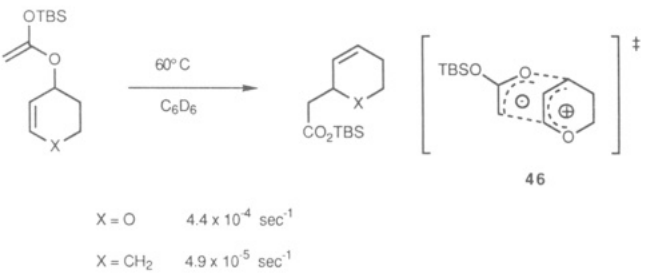


Figure 3.

Scheme XVIII



by Carpenter and Burrows predicts, based on HMO calculations, an accelerating effect of donor groups at positions 1, 2, and 4 of the Claisen system while donor groups at positions 5 and 6 should have the opposite influence (Figure 2).[38,39] Based on secondary deuterium kinetic isotope studies, Gajewski and co-workers concluded that the TS‡ of the aliphatic Claisen rearrangement more resembles an oxaallyl radical–allyl radical pair than a 2-oxacyclohexane-1,4-diyl (Figure 3).[40,41] Stabilization of the TS‡ by resonance interactions is therefore considered to be an important factor.[42] Accordingly, the ease of the silyl ester enolate Claisen reaction (the free energy of activation is reduced by roughly 9 kcal/mol relative to allyl vinyl ether itself)[4] is mainly due to the stabilization of the π-bond of the oxaallyl species by the 2-((trialkylsilyl)oxy) substituent.[43] This results in a TS‡ structure with much more advanced O(3)–C(4) bond breaking than in the parent, unsubstituted rearrangement system.[40-42,44] Not surprisingly, a C(6)-donor substituent exerts a similar

(31) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.

(32) See the supplementary material for the X-ray structural analysis.

(33) Besides lactone **45**, small amounts of isomers **43** and **44** from diastereomeric acid **41** could be detected in the crude iodolactonization mixture of acid **42**. However, no C(5)-epimer of **45** was found, indicating a higher than 10:1 selectivity in the cyclofunctionalization of the carbocyclic acid **42**. This selectivity is probably based on the matched combination of the anti directing influence of the methyl substituent at C(2) and the syn directing effect of the methyl ether at C(3), cf. ref 31.

(34) Claisen rearrangements: (a) Gajewski, J. J.; Emrani, J. *J. Am. Chem. Soc.* **1984**, *106*, 5733. (b) Welch, J. T.; Eswarakrishnan, S. *J. Org. Chem.* **1985**, *50*, 5909. (c) Denmark, S. E.; Harmata, M. A. *Tetrahedron Lett.* **1984**, *25*, 1543. (d) Ponaras, A. A. *J. Org. Chem.* **1983**, *48*, 3866. (e) Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5572. (f) Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1427. (g) Normant, J. F.; Reboul, O.; Sauvêtre, R.; Deshays, H.; Masure, D.; Villieras, J. *Bull. Chem. Soc. Fr.* **1974**, 2072. (h) Welch, J. T.; Samartino, J. S. *J. Org. Chem.* **1985**, *50*, 3663. (i) Kahn, S. D.; Hehre, W. J. *J. Org. Chem.* **1988**, *53*, 301. (j) Gajewski, J. J.; Gee, K. R.; Jurayj, J. *J. Org. Chem.* **1990**, *55*, 1813. (k) Wilcox, C. S.; Babston, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 6636.

(35) Cope rearrangements: (a) Berson, J. A.; Walsh, E. J., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 4730. (b) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765. (c) Evans D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774.

(36) [1,3]-sigmatropic rearrangements: (a) Simpson, J. M.; Richey, H. G., Jr. *Tetrahedron Lett.* **1973**, 2545. (b) Trost, B. M.; Scudder, P. H. *J. Org. Chem.* **1981**, *46*, 506. (c) Paquette, L. A.; Wells, G. J.; Horn, K. A.; Yau, T. H. *Tetrahedron* **1983**, *39*, 913. (d) Scheidt, F.; Kirmse, W. *J. Chem. Soc., Chem. Commun.* **1972**, 716. (e) Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943. (f) Franzus, B.; Scheinbaum, M. L.; Waters, D. L.; Bowlin, H. B. *J. Am. Chem. Soc.* **1976**, *98*, 1241.

(37) (a) Curran, D. P.; Suh, Y. G. *J. Am. Chem. Soc.* **1984**, *106*, 5002. (b) Curran, D. P.; Suh, Y. G. *Carbohydr. Res.* **1987**, *171*, 161. (c) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160.

(38) (a) Carpenter, B. K. *Tetrahedron* **1978**, *34*, 1877. (b) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983, 6984.

(39) Dewar, M. J. S.; Healy, E. F. *J. Am. Chem. Soc.* **1984**, *106*, 7127.

(40) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 6693.

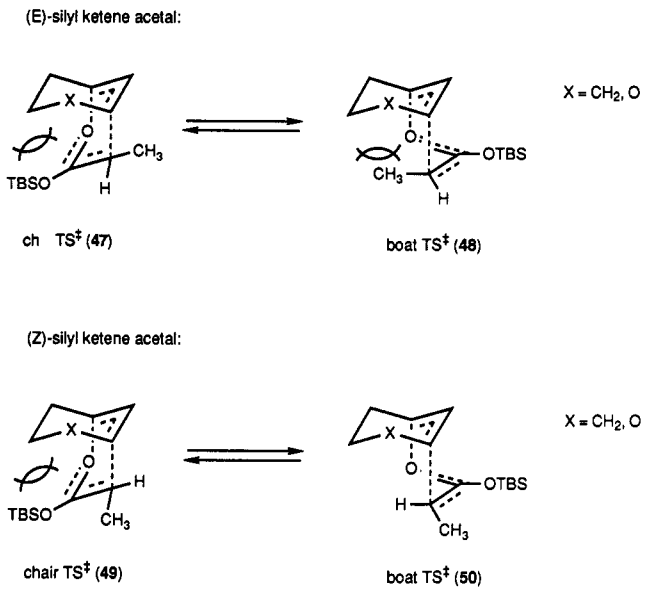
(41) (a) Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 2915. (b) Gajewski, J. J.; Jurayi, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170.

(42) (a) Gajewski, J. J. *Acc. Chem. Res.* **1980**, *13*, 142. (b) Gajewski, J. J.; Gilbert, K. E. *J. Org. Chem.* **1984**, *49*, 11.

(43) Gajewski, J. J.; Emrani, J. *J. Am. Chem. Soc.* **1984**, *106*, 5733.

(44) McMichael, K. D.; Korver, G. L. *J. Am. Chem. Soc.* **1979**, *101*, 2746.

Scheme XIX



enhancing effect on the rate of the Claisen rearrangement, though somehow less pronounced than the rate accelerating effect of the 2-silyloxy substituent (ca. 1.4 kcal/mol).[37] As Curran and Coates reported, this vinylogous anomeric effect[45] of the C(6)-donor substituent is especially effective in glycal systems. The energy of the TS‡ is decreased by an assist in the cleavage of the O(3)–C(4) bond, which results in a ca. 10-fold acceleration of the rearrangement (Scheme XVIII).[37]

The combined accelerating effect of the 2- and 6-oxygen substituents most certainly leads to an increased dipolar character of the TS‡ for the silyl enolate Claisen rearrangement,[46] with bond breaking substantially more advanced than bond formation (cf. structure **46**). It seemed therefore reasonable to consider a vinylogous anomeric effect as a possible explanation for the striking differences in stereoselectivity between the carbocyclic and glycal systems in the context of a different stabilization of boat- vs. chairlike transition states.

Analysis of the Six-Membered Ring Series. The transition states for the [3,3]-sigmatropic rearrangement of the cyclohexyl (X = CH_2) and the pyranoid glycal (X = O) systems are shown in Scheme XIX.

In the chairlike TS‡ **47** and **49** there is an unfavorable interaction between the silyloxy group and the X-CH_2 portion of the six-membered ring that should lead to a general slight preference for boatlike TS‡ **48** and **50**. However, in the (*E*)-silyl ketene acetal the boat conformation **48** is also destabilized by an eclipsing interaction between the allylic methyl and the ring proton, resulting in an overall preference for the chairlike TS‡ in this case. The change in two steeocontrolling factors (silyl ketene acetal geometry and TS‡ geometry) leads, as observed, to the formation of the same major isomer for both (*E*)- and (*Z*)-silyl ketene acetals in the cyclohexene series (Scheme V).

Sterically and conformationally there are only minor differences between the cyclohexene and the corresponding glycal series (Scheme XIX, X = CH_2 or O). Correspondingly, the same steric effects mentioned above should lead to a pronounced preference for a chairlike TS‡ for the (*E*)-silyl ketene acetal and a slight preference for a boatlike TS‡ for the (*Z*)-silyl ketene acetal for the pyranoid glycals. As experimentally determined, however, there is a strong preference for the boatlike TS‡ for both silyl ketene acetal isomers; in fact, the boatlike TS‡ is stabilized by 1–2 kcal/mol relative to the chairlike TS‡ by the introduction of the oxygen substituent at C(6) of the Claisen system (Table I).

Table I. Summary of $\Delta\Delta G^{\ddagger}_{\text{chair-boat}}$ for the Six-Membered Ring Series[21]

cyclohexene:	(*E*)-silyl ketene acetal:	$\Delta\Delta G^{\ddagger}_{\text{chair-boat}}$ = −1.2 kcal/mol
(12)	(*Z*)-silyl ketene acetal:	$\Delta\Delta G^{\ddagger}_{\text{chair-boat}}$ = 0.6 kcal/mol
pyranoid glycal:	(*E*)-silyl ketene acetal:	$\Delta\Delta G^{\ddagger}_{\text{chair-boat}}$ = 1.0 kcal/mol
(18)	(*Z*)-silyl ketene acetal:	$\Delta\Delta G^{\ddagger}_{\text{chair-boat}}$ = 1.6 kcal/mol
	$\Delta\Delta G^{\ddagger}_{\text{chair-boat}}(O) - \Delta\Delta G^{\ddagger}_{\text{chair-boat}}(CH_2)$ = 1.0–2.2 kcal/mol	

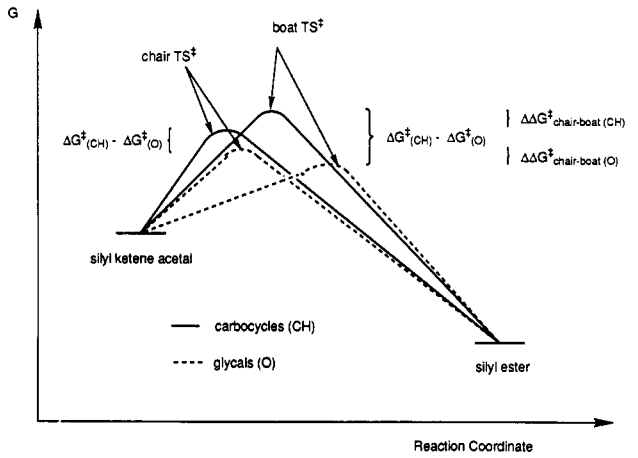


Figure 4. Effect of the C(6) substituent on the relative energies of the ester enolate Claisen rearrangement.

Figure 5.

Two possible explanations for the striking, obviously not sterically based, difference between the carbocyclic and the glycal system are proposed.[47] First, the boatlike TS‡ in the [3,3]-sigmatropic shift presumably has a more productlike, "looser" geometry than the chairlike TS‡, resulting in a higher degree of O(3)–C(4) bond cleavage.[48] The resonance stabilization by the C(6)-oxygen in the glycal ring is therefore expected to be more significant for the more dissociated boatlike TS‡. Any extension of the C(3)–O(4) bond leads to a further reduction of the boat-destabilizing steric interactions between the allylic methyl group and the ring atoms observed for the (*E*)-silyl ketene acetal TS‡ **48**. As a consequence, whereas both chairlike and boatlike TS‡ are energetically stabilized by the C-(6)-donor substituent, the boatlike TS‡ is expected to be significantly more affected by these changes in the elec-

(45) For introduction of the term vinylogous anomeric effect, see: Denmark, S. E.; Dappen, M. S. *J. Org. Chem.* **1984**, *49*, 798.

(46) The rate enhancement observed with polar solvents corresponds well with a dipolar transition state in the Claisen rearrangement: (a) Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5008. (b) Brandes, E.; Grieco, P. A.; Gajewski, J. J. *J. Org. Chem.* **1989**, *54*, 515. (c) Grieco, P. A.; Brandes, E. B.; McCann, S.; Clark, J. D. *J. Org. Chem.* **1989**, *54*, 5848.

(47) Conformational effects can be neglected, as in both the cyclohexene and the glycal derivative the 2-((trialkylsilyl)oxy)oxaallyl substituent has to assume an axial orientation in order to provide for optimum geometry for orbital interaction.

(48) Gajewski, J. J.; Jimenez, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 468.

Scheme XX

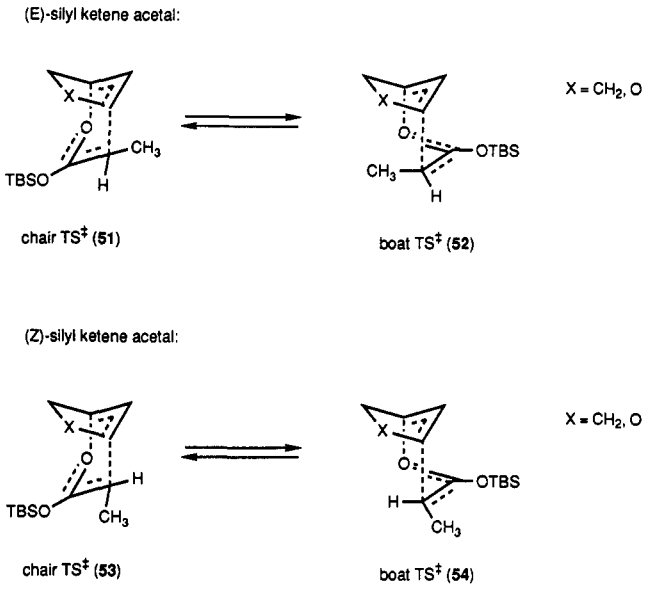


Table II. Summary of $\Delta\Delta G^{\ddagger}_{chair-boat}$ for the Five-Membered Ring Series[21]

cyclopentene:	(*E*)-silyl ketene acetal:	$\Delta\Delta G^{\ddagger}_{chair-boat}$ = −1.0 kcal/mol
(25)	(*Z*)-silyl ketene acetal:	$\Delta\Delta G^{\ddagger}_{chair-boat}$ = −0.5 kcal/mol
furanoid glycal:	(*E*)-silyl ketene acetal:	$\Delta\Delta G^{\ddagger}_{chair-boat}$ = 0.4 kcal/mol
(from 32)	(*Z*)-silyl ketene acetal:	$\Delta\Delta G^{\ddagger}_{chair-boat}$ = 1.4 kcal/mol
	$\Delta\Delta G^{\ddagger}_{chair-boat}(O) - \Delta\Delta G^{\ddagger}_{chair-boat}(CH_2)$ = 1.4–1.9 kcal/mol	

tronic nature of the C(6)-substituent (Figure 4).

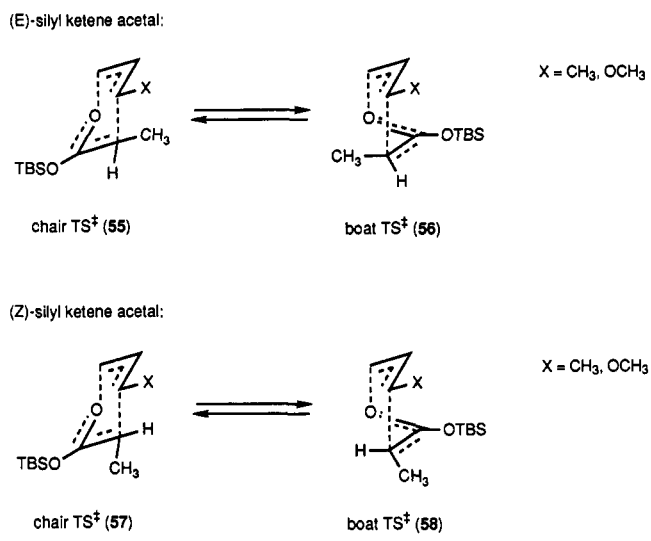
Second, the vinylogous anomeric effect in the glycal system leads to an increase in the dipolar character of the TS‡, as already mentioned above. The Coulombic attraction between the two ends of the dipole is greater in the endo type boatlike TS‡ that allows for a six atom overlap than in the exo type chairlike TS‡, which only provides for a four atom overlap, again resulting in an increased net stabilization of the boatlike TS‡ (Figure 5).

The sum of these factors can easily account for the 1–2 kcal/mol increase in relative stabilization of the boatlike over the chairlike TS‡ that is observed in the transition from the cyclohexene to the pyranoid glycal system.

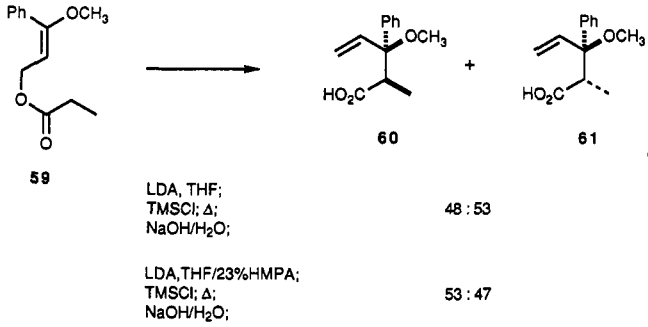
Analysis of the Five-Membered Ring Series. The transition states for the five-membered ring systems are shown in Scheme XX. For both sets of TS‡ geometries, the steric interactions between the silyloxy and allylic methyl and the ring atoms are reduced in the five-membered ring series. In the carboxylic ring systems, therefore, both the (*E*)- and the (*Z*)-silyl ketene acetals are expected to undergo a [3,3]-rearrangement via the chairlike TS‡ **51** and **53**, as experimentally observed (Scheme X).

In the furanoid glycal series, a similar relative stabilization of the boatlike vs the chairlike TS‡ as observed in the pyranoid glycal case is expected. In fact, both the (*E*)- and the (*Z*)-silyl ketene acetal of the furanoid glycal rearrange predominantly via the boat TS‡ **52** and **54** (Scheme XIII). The increase in relative stabilization of the boatlike vs the chairlike TS‡ from the carbocyclic to the heterocyclic systems can again be estimated at ca. 1.2–1.5 kcal/mol (Table II). The shift from a preference of chairlike to boatlike transition states in the ester enolate Claisen rearrangement found in the six-membered systems is therefore reproduced in the five-membered glycals.

Scheme XXI



Scheme XXII

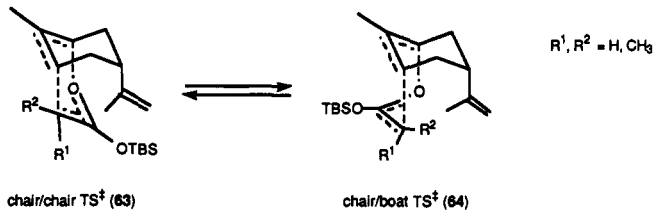


Analysis of the Acyclic Series. The transition states for the acyclic systems are shown in Scheme XXI. With regard to interactions between substituents, all TS‡ structures are now essentially strain-free. Due to the inherently lower energy of the chairlike TS‡, the crotyl derivative (X = CH_3) rearranges predominantly through chair TS‡ **55** or **57**. The observed ratio of diastereomeric acids (Scheme I) indicates a higher than 95% selectivity for the rearrangement through these chair TS‡. This high chair selectivity is clearly diminished in the methoxyallyl derivatives (X = OCH_3, Scheme XVI). However, due to the inherently high energy difference between chair- and boatlike TS‡ in the acyclic series (ca. >2 kcal/mol), the additional relative stabilization of the boatlike TS‡ by the methoxy substituent falls short in overriding the clear chair preference. Additionally, the stabilization of the Claisen TS‡ by the C(6)-methoxy group must be smaller than the stabilization observed in the glycal systems, as in the glycal systems the lone pairs of the ring oxygen are stereoelectronically locked to provide for an optimal vinylogous anomeric effect, whereas in the acyclic series the C(6)–O-CH_3 bond rotation reduces this orbital interaction.[49] Hence the dipolar character of the TS‡ in the methoxyallyl series should be reduced compared to the glycal series. Quite reasonably, the decrease in selectivity for a chairlike TS‡ is therefore only moderate.[50] However, it may be noted that through the introduction of two stabilizing substituents at C(6), such as phenyl and methoxy groups, the chair selectivity is further reduced by an additional

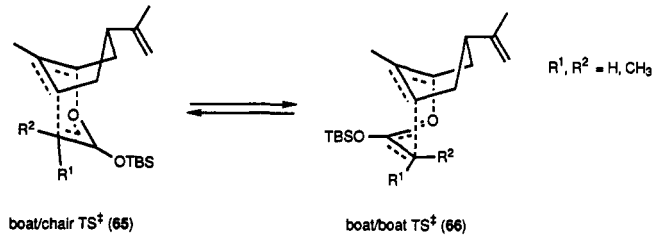
(49) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983.

(50) Significantly, the rate increase for the Claisen rearrangement of methoxyallyl propionate is only about a factor 3 over the parent crotyl system, compared to a factor 10 for the pyranoic glycals, cf. ref 36.

Scheme XXIII



Scheme XXIV



relative stabilization of the boatlike TS‡ geometry (Scheme XXII).[29]

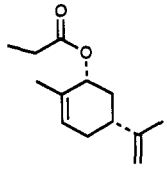
The energy difference between the boatlike and the chairlike TS‡ in (*E*)- and (*Z*)-silyl ketene acetals of propanoate **59** is close to zero, as both rearrange to a ca. 1:1 ratio of diastereomeric acids **60** and **61**.

Conclusions

In summary, a novel stereoelectronic effect of the C-(6)-oxygen substituent on the relative stabilities of chairlike and boatlike TS‡ in the silyl ester enolate Claisen rearrangement has been demonstrated. This effect is especially pronounced in glycal systems and is apparently based on an increase in the dipolar character of the boatlike TS‡. A vinylogous anomeric effect of the C(6)-oxygen leads to an increased relative stabilization of the more loosely organized endo type boat TS‡ on the order of 1–2 kcal/mol. In the absence of exceptional steric effects, pyranoid and furanoid glycal systems can be expected to undergo [3,3]-rearrangement preferentially via boatlike transition states. The corresponding six- and five-membered carbocyclic systems are much more susceptible to steric influence by substituent interactions, as the energy difference between chair- and boatlike TS‡ tends to be small. Especially with cyclohexene derivatives both chair- and boatlike TS‡ have to be expected depending on the size and position of the substituents on the ring and the geometry of the silyl ketene acetals. Five-membered carbocyclic ring systems demonstrate an increased preference for the "normal" chairlike TS‡ due to a somewhat reduced steric interaction between the ring and the silyl ketene acetal portion.

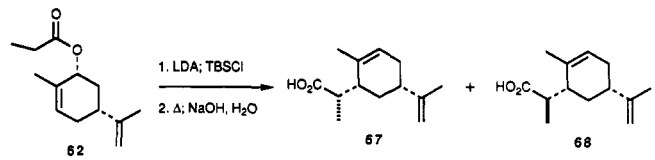
Generally, with or without C(6)-oxygen substituents, silyl ester enolates of acyclic precursors rearrange highly preferentially through chairlike transition states. A significant contribution of the boatlike TS‡ to the rearrangement product mixture can only be expected in 6,6-bis-donor substituted systems such as **59**.

An application of these principles is illustrated in the analysis of the ester enolate Claisen rearrangement of carvyl propanoate **62**. A consideration of the possible

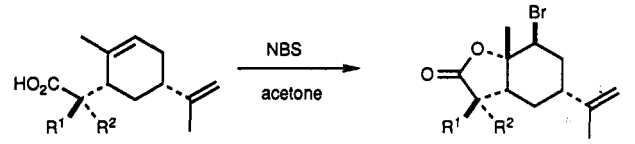


62

Scheme XXV



solvent	67:68	% yield	favored TS‡
THF	25:75	56	chair
THF/45% DMPU	98:2	60	chair
THF/23% HMPA	90:10	70	chair



67, R^1=H, R^2=CH_3 **69**, R^1=H, R^2=CH_3; 83%

68, R^1=CH_3, R^2=H **70**, R^1=CH_3, R^2=H; 80%

Figure 6.

transition states for the [3,3]-shift of propanoate **62** leads to the conclusion that both the chair- and the boatlike transition states shown in Scheme XXIII are strongly destabilized due to the severe interaction of the axially oriented isopropenyl ring substituent with the vinyl ether portion. However, an alternative set of TS‡, where the cyclohexene ring adopts a boat conformation, avoids these destabilizing interactions (Scheme XXIV).

Based upon the currently observed preference for the chairlike TS‡ in carbocycles in the absence of destabilizing steric factors, product formation through boat/chair TS‡ **65** has to be expected for both (*E*)- and (*Z*)-silyl ketene acetal geometries. In fact, enolization and subsequent Claisen rearrangement of propanoate **62** in THF led to a 25:75 ratio of carboxylic acids **67** and **68**, favoring a chairlike TS‡ geometry (Scheme XXV).

In THF/45% DMPU the (*Z*)-silyl ketene acetal of ester **62** was formed predominantly and carboxylic acid **67** was isolated in greater than 96% diastereomeric excess. The ratio of acids **67** and **68** obtained in THF/23% HMPA was only 90:10, due to a lower selectivity in the enolization step.[5] Again the chairlike TS‡ is predominant. The stereochemistry at C(2) of the rearrangement products was assigned after analysis of the coupling constants of the corresponding bromolactones **69** and **70** (Figure 6).[26] Additionally, the configuration at C(2) of acid **68** was confirmed by an X-ray analysis of a derivative.[51]

Both (*Z*)- and (*E*)-silyl ketene acetals of carvyl propanoate **62** rearrange predominantly through a chair TS‡. Earlier, the stereochemistry of the major rearrangement product in THF/23% HMPA was wrongly assigned as **68**,[52] according to an assumed boatlike TS‡ and based upon results obtained in substituent-wise closely related glycal systems.[16,17] Propanoate **62** thus provides another striking example of the different electronic nature of the TS‡ of carbocyclic and sterically closely related glycal systems.

The dominating effect of the electronic characteristics of substituents on the regio- and stereochemistry of pericyclic reactions such as Diels–Alder and 1,3-dipolar cycloadditions has long been recognized. The experimental material presented in this report gives conclusive evidence that in the Claisen and very likely in other sigmatropic

(51) Xiang, J. N.; Ph.D. thesis, University of Virginia, 1990.
(52) Ireland, R. E.; Maienfisch, P. *J. Org. Chem.* **1988**, *53*, 640.

rearrangements there is a crucial electronic effect of substituents on the relative TS* energies and thus the product stereochemistry. Further applications of enolization and TS* control in the silyl ester enolate Claisen rearrangement will be reported in due course.

Experimental Section

General. See ref 5. 2-Cyclohexenyl propanoate (**12**) was prepared by acylation of 2-cyclohexenol (Aldrich).[18] 2,3-Dihydro-4*H*-pyran-4-one (**17**) was prepared by $ZnCl_2$–cat. heter-Diels–Alder addition of 1-methoxy-3-((trimethylsilyl)oxy)buta-1,3-diene (Aldrich) with formaldehyde.[22] (3*S*)-3-Hydroxy-4,5-dihyrofuran (**32**) was prepared from D-(−)-isoascorbic acid (Aldrich) according to published procedures.[27] Carvyl propanoate (**62**) was prepared from (−)-carvone (Aldrich).[52]

(2*SR*)-2-[(1*RS*)-2-Cyclohexenyl]propanoic Acid (14) and (2*RS*)-2-[(1*RS*)-2-Cyclohexenyl]propanoic Acid (15) by Deprotonation in THF. A solution of 1.11 g (10 mmol) of diisopropylamine in 10 mL of THF was cooled to 0 °C, and 4 mL of a 2.5 M solution of *n*-BuLi in hexanes was added. This mixture was stirred for 3 min at 0 °C and subsequently cooled to −78 °C. A solution of 1.54 g (10 mmol) of 2-cyclohexenyl propanoate (**12**) in 10 mL of THF was added over a 2-min time period under intensive stirring. After 20 min, 7.1 mL (11 mmol) of a 1.56 M solution of TBSCl in hexanes was added, followed by 8 mL of DMPU.[53] The reaction mixture was stirred for an additional 5 min at −78 °C and subsequently allowed to warm up to room temperature. An aliquot was removed and a 83:17 ratio of silyl ketene acetals (*E*)-**13** and (*Z*)-**13** was determined by integration of the characteristic resonances at 82.2 ppm (for (*E*)-**13**) and 72.8 ppm (for (*Z*)-**13**) in ^{13}C NMR.[5] The solution of the silyl ketene acetals was heated at reflux for 3 h, treated with 10 mL of 2 N NaOH, stirred at room temperature for 15 min, and extracted with 2 N NaOH (2×). The combined aqueous layers were acidified with 6 N HCl and extracted with ether (3×). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give 1.20 g (78%) of a 84:16 mixture of acids **14** and **15**. For spectral data, see ref 18.

Deprotonation in THF/45% DMPU. A solution of 1.11 g (10 mmol) of diisopropylamine in 6 mL of THF was cooled to 0 °C, and 4 mL of a 2.5 M solution of *n*-BuLi in hexanes was added. This mixture was stirred for 3 min at 0 °C, cooled to −78 °C and 14 mL of DMPU were added. A solution of 1.54 g (10 mmol) of 2-cyclohexenyl propanoate (**12**) in 10 mL of THF was added over a 2-min time period under intensive stirring. After 20 min, 7.1 mL (11 mmol) of a 1.56 M solution of TBSCl in hexanes was added, and the reaction mixture was stirred for an additional 5 min at −78 °C and allowed to warm up to room temperature. Subsequent manipulations were performed as described above and led through a 4:96 mixture of silyl ketene acetals (*E*)-**13** to (*Z*)-**13** to a 72:28 ratio of acids **14** and **15** in 91% yield.

Deprotonation in THF/23% HMPA. A solution of 1.11 g (10 mmol) of diisopropylamine in 10 mL of THF was cooled to 0 °C, and 4 mL of a 2.5 M solution of *n*-BuLi in hexanes was added slowly. This mixture was stirred for 3 min at 0 °C, cooled to −78 °C, and 7 mL of HMPA was added. Subsequently manipulations were performed as described above and led through a 14:86 mixture of silyl ketene acetals (*E*)-**13** to (*Z*)-**13** to a 73:27 ratio of acids **14** and **15** in 60% yield.[54]

(4*SR*)-2,3-Dihydro-4*H*-pyran-4-yl Propanoate (18). A solution of 5.00 g (51.0 mmol) of 2,3-dihydro-4*H*-pyran-4-one (**17**) in 30 mL of ether was slowly added at 0 °C to a suspension of 2.20 g (58.0 mmol) of LAH in 70 mL of ether. The reaction mixture was stirred for 15 min at room temperature, quenched with H_2O and aqueous 15% NaOH solution, filtered, and concentrated under reduced pressure. The oily residue was dissolved in 150 mL of CH_2Cl_2 and treated at 0 °C with 16.0 (202 mmol, 4 equiv) of pyridine, 5.09 g (55 mmol) of freshly distilled propionyl chloride, and 50 mg (0.4 mmol) of 4-(dimethylamino)pyridine. The reaction mixture was stirred at 0 °C for 5 h and extracted with H_2O (4×). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed[55] (ethyl acetate/hexane, 1:3) to give 5.4 g (68%) of unstable ester **18** that was immediately used in the Claisen rearrangement.

(2*SR*)-2-[(2*RS*)-5,6-Dihydro-2*H*-pyranyl]propanoic Acid (20) and (2*RS*)-2-[(2*RS*)-5,6-Dihydro-2*H*-pyranyl]propanoic Acid (21) by Deprotonation in THF. (4*RS*)-2,3-Dihydro-4*H*-pyran-4-yl propanoate (**18**) was enolized in THF as described above for propanoate **12**. Subsequent Claisen rearrangement led to a 29:71 mixture of acids **20** and **21** in 77% yield: ^1H NMR δ 0.95, 0.97 (2 d, 3, *J* = 7), 2.05 (m, 1), 2.30–2.50 (m, 2), 3.45 (m, 1), 3.75 (m, 1), 4.18 (m, 1), 5.50 (m, 1), 5.70 (m, 1).

2*SR* Isomer **20**: ^{13}C NMR δ (discernible from mixture) 11.5, 25.3, 44.3, 63.7, 75.0, 127.2, 127.8, 176.5.

2*SR* Isomer **21**: ^{13}C NMR δ (discernible from mixture) 12.3, 25.4, 44.4, 63.8, 75.2, 127.2, 127.8, 176.6.

The acids **20** and **21** were characterized as the following iodo lactones **22** and **23**.

Deprotonation in THF/45% DMPU. (4*RS*)-2,3-Dihydro-4*H*-pyran-4-yl propanoate (**18**) was enolized in THF/45% DMPU as described above for propanoate **12**. Subsequent Claisen rearrangement led to an 86:14 mixture of acids **20** and **21** in 77% yield.

(3*SR*,3a*SR*,7*RS*,7a*RS*)-3,3a,5,6,7,7a-Hexahydro-7-iodo-3-methyl-1,4-dioxa-2*H*-inden-2-one (22) and (3*RS*,3a*SR*,7*RS*,7a*RS*)-3,3a,5,6,7,7a-Hexahydro-7-iodo-3-methyl-1,4-dioxa-2*H*-inden-2-one (23). A solution of 200 mg (1.28 mmol) of a 86:14 mixture of acids **20** and **21** and 650 mg (2.56 mmol) of I_2 in 4 mL of CH_3CN was stirred in the dark for 24 h at room temperature. After addition of ether and extraction with a saturated aqueous solution of Na_2SO_3 (2×) and a saturated aqueous solution of $NaHCO_3$ (2×), the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to yield 300 mg (83%) of iodo lactones **22** and **23**. Recrystallization of the crude mixture from CH_2Cl_2/hexane gave lactone **22** as the major isomer: mp 90–91 °C; IR 3000, 1767, 1202, 1171, 1061, 919, 725 (br) cm^{-1}; ^1H NMR δ 1.18 (d, 3, *J* = 7.8), 1.81 (m, 1, *J* = 15, 3, 1.2), 2.15 (m, 1, *J* = 15, 8, 3.6, 1.5), 2.60 (q, 1, *J* = 7.8), 3.7–3.8 (m, 2), 4.24 (d, 1, *J* = 1.8), 4.58 (dd, 1, *J* = 2.5, 1.8), 4.70 (ddd, 1, *J* = 3.6, 3.0, 2.5);[56] ^{13}C NMR δ 12.2, 23.6, 29.5, 45.1, 62.5, 75.6, 78.5, 178.9. Anal. Calcd for $C_8H_{11}O_3I$: C, 34.06; H, 3.93. Found: C, 34.14; H, 3.91.

Analogous iodolactonization of a 29:71 mixture of acids **20** and **21** gave lactones **22** and **23** in 80% yield. Recrystallization of the crude mixture from CH_2Cl_2/hexane gave **23** as the major isomer: mp 116–117 °C; IR 3000, 1768, 1216, 1193, 1152, 1129, 1061, 977 cm^{-1}; ^1H NMR δ 1.23 (d, 3, *J* = 7.2), 1.83 (m, 1, *J* = 15.3, 1.5), 2.21 (m, 1, *J* = 15.3, 8.7, 4.2, 1.5), 2.68 (dq, 1, *J* = 7.2, 3.9), 3.84 (m, 2), 4.44 (dd, 1, *J* = 1.5, 1.5), 4.49 (dd, 1, *J* = 3.9, 1.5), 4.76 (ddd, 1, *J* = 4.2, 1.5, 1.5);[56] ^{13}C NMR δ 8.1, 24.0, 29.3, 43.6, 62.4, 72.3, 78.4, 178.4. Anal. Calcd for $C_8H_{11}O_3I$: C, 34.06; H, 3.93. Found: C, 34.12; H, 3.82.

2-Cyclopentenyl Propanoate (25). A solution of 4.04 g (49.3 mmol) of 2-cyclopentenone and 9.10 g (24.4 mmol) of $CeCl_3 \cdot 7H_2O$ in 60 mL of methanol was treated at 0 °C with 1.86 g (49.3 mmol) of $NaBH_4$. The reaction mixture was stirred for 3 h at room temperature, quenched with water, and extracted with ether (3×). The combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure to yield crude 2-cyclopentenol: ^1H NMR δ 1.80–2.50 (m, 5), 4.83 (m, 1 H), 5.81 (dd, 1, *J* = 5.3, 2.0), 5.96 (m, 1); ^{13}C NMR δ 31.4, 33.7, 77.9, 133.7, 135.4.

A solution of crude 2-cyclopentenol, 50 mg of 4-(dimethylamino)pyridine, and 10 mg of 1,10-phenanthroline in 80 mL of THF was treated at −78 °C with 23 mL of a 2.5 M solution of *n*-BuLi in hexane. After 10 min, 5.00 g (54.2 mmol) propionyl chloride was added. The reaction mixture was stirred for 1.5 h at room temperature, quenched with water, and extracted with ether (2×). The combined organic extracts were washed with 50 mL of a saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed[53] (*n*-hexane/ether, 15:1) to give 3.85 g (56% from 2-cyclopentenone)

(53) DMPU: Seebach, D.; Mukhopadhyay, T. *Helv. Chim. Acta* **1982**, *65*, 385.

(54) We thank Dr. J. D. Armstrong for performing this experiment.

(55) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(56) Coupling constants of multiplets were identified by extensive double resonance experiments.

of propanoate **25** as a liquid: R_f = 0.44 (*n*-hexane/ether, 15:1); bp 70 °C (35 mmHg); IR (neat) 2920, 1720, 1280, 1140, 1030 cm^{-1}; ^1H NMR δ 1.11 (t, 3, J = 7.5), 2.28 (q, 2, J = 7.5), 5.69 (m, 1), 5.80 (dd, 1, J = 5.7, 2.4), 6.07 (m, 1); ^{13}C NMR δ 9.5, 28.2, 30.2, 31.5, 80.7, 129.8, 137.8, 174.9. Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.59; H, 8.59.

(2*SR*)-2-[(1*RS*)-2-Cyclopentenyl]propanoic Acid (27) and (2*RS*)-2-[(1*RS*)-2-Cyclopentenyl]propanoic Acid (28) by Deprotonation in THF. By use of the procedure described for the preparation of acids **14** and **15**, 800 mg (5.70 mmol) of 2-cyclopentenyl propanoate (**25**) was deprotonated in THF, silylated, and rearranged to give 382 mg (48%) of a 75:25 mixture of acids **27** and **28**.[57]

2*SR* Isomer **27**: ^1H NMR δ (discernible from mixture) 1.14 (d, 3, J = 7.2), 5.63 (m, 1).

2*SR* Isomer **28**: ^1H NMR δ (discernible from mixture) 1.18 (d, 3, J = 6.9), 5.70 (m, 1).

Deprotonation in THF/23% HMPA. By use of the procedure described for the preparation of acids **14** and **15**, 2-cyclopentenyl propanoate (**25**) was deprotonated in THF/23% HMPA, silylated, and rearranged to give 63% of a 40:60 mixture of acids **27** and **28**.

(3*SR*,3a*SR*,6*RS*,6a*RS*)-1,2,3,3a,4,5,6,6a-Octahydro-6-iodo-3-methyl-1-oxapentalen-2-one (29) and (3*SR*,3a*SR*,6*RS*,6a*RS*)-1,2,3,3a,4,5,6,6a-Octahydro-6-iodo-3-methyl-1-oxapentalen-2-one (30). By use of the procedure described for the preparation of iodo lactones **22** and **23**, a 75:25 mixture of acids **27** and **28** was cyclized to give 85% of iodo lactones **29** and **30**. Anal. Calcd for $C_8H_{11}O_2I$: C, 36.11; H, 4.17. Found: C, 36.14; H, 4.03.

The major isomer, lactone **29**: R_f = 0.50 (pentane/ether, 4:1); IR (neat) 2970, 1760, 1435, 1360, 1150, 975 cm^{-1}; ^1H NMR δ 1.31 (d, 3, J = 7.2), 1.58 (m, 1), 2.07 (m, 2), 2.45 (m, 2), 2.78 (m, 1), 4.41 (d, 2, J = 4.2), 5.17 (d, 1, J = 6.3); ^{13}C NMR δ 18.2, 29.6, 31.9, 35.2, 43.3, 45.1, 91.2, 180.1.

A 40:60 mixture of acids **27** and **28** was cyclized to give 70% of iodo lactones **29** and **30**. The major isomer, lactone **30**: R_f = 0.49 (pentane/ether, 4:1); IR (neat) 2970, 1760, 1430, 1365, 1150, 970 cm^{-1}; ^1H NMR δ 1.20 (d, 3, J = 7.2), 1.64 (m, 1), 2.07 (m 2), 2.86 (qd, 1, J = 7.2, 5.4), 3.17 (m, 1), 4.41 (d, 1, J = 4.2), 5.05 (d, 1, J = 5.4); ^{13}C NMR δ 11.8, 23.9, 29.3, 35.8, 38.3, 42.0, 90.7, 180.1.

(2*S*)-2-[(2*S*)-2,5-Dihydrofuranyl]propanoic Acid (34) and (2*R*)-2-[(2*S*)-2,5-Dihydrofuranyl]propanoic Acid (35) by Deprotonation in THF. A solution of 290 mg (3.37 mmol) of the glycal **32**, 10 mg of 4-(dimethylamino)pyridine, and 5 mg of 1,10-phenanthroline in 8 mL of THF was treated at −78 °C with 1.35 mL of a 2.5 M solution of *n*-BuLi in hexane until the solution turned brown (1.35 mL). After 5 min, 0.35 mL (3.37 mmol) of propionyl chloride was added. The mixture was stirred for 5 min at −78 °C, warmed up to 0 °C, and then transferred to a cold (−78 °C) solution of 5.06 mmol of LDA in THF. After 10 min, 2 mL of a mixture of TMSCl and Et_3N (3:1, v/v) was added rapidly. The reaction mixture was stirred for 10 min at −78 °C, 20 min at room temperature, and 30 min at 40 °C. The reaction was quenched with 15 mL of a 1% aqueous solution of HCl and diluted with 35 mL of ether. After the mixture was stirred for 30 min at room temperature, the organic phase was separated and extracted with 2 N NaOH (2×). The combined basic aqueous extracts were washed with ether (2×), acidified with concd HCl to pH 2, and extracted with ether (3×). The combined organic layers were washed with a saturated aqueous solution of NaCl, dried ($MgSO_4$), and concentrated under reduced pressure to give 158 mg (44%) of a 57:43 mixture of acids **34** and **35**: R_f = 0.17 (1:1 ether/*n*-hexane); bp 80 °C (0.1 mmHg); IR (neat) 3540, 3400, 1760, 1345, 660 cm^{-1}. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 58.87; H, 7.18.

2*S* Isomer **34**: ^1H NMR δ (discernible from mixture) 1.17 (d, 3, J = 7.8), 2.67 (qd, 1, J = 7.2, 6.9), 4.66 (m, 2), 5.05 (m, 1), 5.85 (dd, 1, J = 3.9, 1.5); ^{13}C NMR δ 12.5, 45.5, 76.1, 87.3, 127.1, 128.9, 179.4.

2*R* Isomer **35**: ^1H NMR δ (discernible from mixture) 1.21 (d, 3, J = 7.2), 2.44 (m, 1), 4.70 (m, 2), 5.15 (m, 1), 5.80 (m, 1), 6.01 (m, 1); ^{13}C NMR δ 11.6, 45.0, 76.5, 87.1, 127.5, 128.7, 174.2.

(57) Beilstein 9 III 172f.

Deprotonation in THF/23% HMPA. Using the procedure outlined above, glycal **32** was acylated, deprotonated in THF/23% HMPA, silylated, and rearranged to give a 20:80 mixture of acids **34** and **35** in 40% yield.

(3*S*,3a*R*,6*S*,6a*S*)-2,3,3a,5,6,6a-Hexahydro-6-iodo-3-methyl-1,4-dioxapentalen-2-one (36) and (3*R*,3a*R*,6*S*,6a*S*)-2,3,3a,5,6,6a-Hexahydro-6-iodo-3-methyl-1,4-dioxapentalen-2-one (37). By use of the procedure described for the preparation of iodo lactones **22** and **23**, a 57:43 mixture of acids **34** and **35** was cyclized to give 70% of iodo lactones **36** and **37**. Anal. Calcd for $C_7H_9O_3I$: C, 31.37; H, 3.38. Found: C, 31.45; H, 3.42.

The major isomer, lactone **36**: R_f = 0.45 (*n*-hexane/ethyl acetate, 3:1); IR (neat) 2960, 2920, 2840, 1720, 1360, 1160, 980 cm^{-1}; ^1H NMR δ 1.29 (d, 3, J = 7.2), 2.68 (qd, 1, J = 7.2, 5.7), 4.18 (dd, 1, J = 11.1, 1.5), 4.28 (dd, 1, J = 11.1, 4.2), 4.41 (bd, 1, J = 3.9), 4.95 (dd, 1, J = 5.7, 3.6), 5.14 (d, 1, J = 3.6); ^{13}C NMR δ 9.5, 22.6, 39.9, 76.6, 80.1, 88.4, 164.0.

A 20:80 mixture of acids **34** and **35** was cyclized to give 81% of iodo lactones **36** and **37**. The major isomer, lactone **37**: R_f = 0.40 (*n*-hexane/ethyl acetate, 3:1); IR (neat) 2960, 2840, 1720, 1360, 1160, 980 cm^{-1}; ^1H NMR δ 1.28 (d, 3, J = 7.8), 2.76 (q, 1, J = 7.8), 4.16 (dd, 1, J = 11.1, 1.5), 4.34 (dd, 1, J = 11.1, 4.2), 4.41 (bd, 1, J = 3.9), 4.67 (d, 1, J = 3.9), 5.22 (d, 1, J = 3.9); ^{13}C NMR δ 22.2, 42.5, 76.4, 84.2, 89.0, 15.0, 163.1.

Methyl (*E*)-3-Methoxyacrylate (38). To a solution of 10.0 g (118.9 mmol) of methyl propiolate in 200 mL of ether was added 16.5 mL (118.9 mmol) of Et_3N. The mixture was stirred for 5 min at room temperature, and 4.80 mL (118.94 mmol) of CH_3OH was added dropwise. The resulting reaction mixture was stirred overnight and concentrated under reduced pressure. Distillation of the residue at 61 °C (16 mmHg) afforded 12.1 g (90%) of ester **38** as a colorless liquid:[28,29] ^1H NMR δ 3.65 (s, 3), 3.66 (s, 3), 5.16 (d, 1, J = 12.6), 7.59 (d, 1, J = 12.6); ^{13}C NMR δ 51.5, 57.7, 96.0, 163.6, 168.5.

(*E*)-3-Methoxyallyl Propanoate (39). A solution of 5.50 g (48.63 mmol) of ester **38** in 150 mL of ether was treated at −78 °C dropwise with 107 mL (107 mmol) of a 1 M solution of DIBAL-H in hexane. The reaction mixture was stirred for 50 min, quenched with 200 mL of a 0.5 M solution of Na^+,K^+ tartrate, and stirred at room temperature until two clear phases formed. The organic layer was washed with 200 mL of a saturated aqueous solution of NaCl, dried ($MgSO_4$), and concentrated under reduced pressure to give 2.53 g (59%) of (*E*)-3-methoxyallyl alcohol: ^1H NMR δ 3.56 (s, 3), 4.06 (d, 2, J = 7.2), 5.01 (dt, 1, J = 12.6, 7.2), 6.57 (d, 1, J = 12.6); ^{13}C NMR δ 56.4, 61.1, 102.3, 151.5.

To a solution of 2.50 g (28.38 mmol) of (*E*)-3-methoxyallyl alcohol in 80 mL of THF at −78 °C was added 11.4 mL of a 2.5 M solution of *n*-BuLi in hexane. After 5 min, 3.1 mL (28.38 mmol) of propanoic anhydride was added, and the resulting mixture was stirred for 5 h at room temperature. The reaction was quenched with 150 mL of water and extracted with ether (2×), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give 3.55 g (87%) of propanoate **39** as a colorless liquid:[28,29] ^1H NMR δ 1.12 (t, 3, J = 7.8), 2.30 (q, 2, J = 7.8), 3.56 (s, 3), 4.49 (d, 2, J = 7.5), 4.91 (dt, 1, J = 12.6, 7.5), 6.60 (d, 1, J = 12.6); ^{13}C NMR δ 9.5, 28.1, 56.5, 62.9, 97.5, 153.6, 174.8.

(2*RS*,3*RS*)-3-Methoxy-2-methyl-4-pentenoic Acid (41) and (2*SR*,3*RS*)-3-Methoxy-2-methyl-4-pentenoic Acid (42) by Deprotonation in THF. To a solution of 3.87 mmol of LDA in 5 mL of THF was added at −78 °C 345 mg (2.39 mmol) of ester **39**. After 10 min, 1 mL of a mixture of TMSCl and Et_3N (3:1, v/v) was added rapidly, and the resulting mixture was stirred for 3 min at −78 °C, 20 min at 20 °C, and 30 min at 30 °C. The reaction was quenched with 20 mL of a 2% aqueous solution of HCl and diluted with ether. The organic layer was washed with water and then extracted with 2 N NaOH (2×). The combined basic aqueous extracts were washed with ether, acidified to pH 2 with concd HCl, and extracted with ether (2×), and the combined organic extracts were washed with 20 mL of saturated aqueous NaCl and then dried ($MgSO_4$). The solvent was removed under reduced pressure to give 232 mg (67%) of a 87:13 mixture of acids **41** and **42**.[28,29]

2*RS* Isomer **41**: ^{1}H NMR δ (discernible from mixture) 1.10 (d, 3, J = 7.2), 2.59 (m, 1), 3.27 (s, 3), 3.70 (t, 1, J = 8.4), 5.2-5.7 (m, 3).

Deprotonation in THF/23% HMPA. By use of the procedure outlined above, ester **39** was deprotonated in THF/23% HMPA, silylated, and rearranged to give 67% of a 25:75 mixture of acids **41** and **42**.[28,29]

2*SR* Isomer **42**: ^{1}H NMR δ (discernible from mixture) 1.18 (d, 3, J = 7.2), 2.67 (m, 1), 3.31 (s, 3), 3.84 (dd, 1, J = 7.2, 5.6), 5.2-5.8 (m, 3).

(2*RS*,3*SR*,4*SR*)-4-(Iodomethyl)-3-methoxy-2-methyl-γ-butyrolactone (43) and (2*RS*,3*SR*,4*RS*)-4-(Iodomethyl)-3-methoxy-2-methyl-γ-butyrolactone (44). By use of the procedure described for the preparation of iodo lactones **22** and **23**, a 87:13 mixture of acids **41** and **42** was cyclized to give a 56% yield of iodo lactones **43** and **44** that were separated by silica gel chromatography[53] (pentane/ether, 2:1). The major isomer, lactone **44**, was recrystallized from ether/pentane: mp 85 °C; IR 2980, 1750, 1200, 750, 650 cm^{-1}; R_f = 0.40 (pentane/ether, 3:1); ^{1}H NMR δ 1.31 (d, 3, J = 7.2), 2.74 (qd, 1, J = 7.2, 4.8), 3.41 (dd, 1, J = 8.7, 8.1), 3.43 (dd, 1, J = 8.7, 4.6), 3.56 (s, 3), 4.06 (dd, 1, J = 4.8, 3.3), 4.52 (ddd, 1, J = 8.1, 4.6, 3.3); ^{13}C NMR δ -1.1, 8.9, 42.8, 62.0, 80.1, 82.0, 177.7. Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.11. Found: C, 31.21; H, 4.18.

The minor isomer, lactone **43**: R_f = 0.35 (pentane/ether, 3:1); IR (neat) 2920, 2820, 1700, 1420, 1280, 1030 cm^{-1}; ^{1}H NMR δ 1.25 (d, 3, J = 7.2), 2.82 (qd, 1, J = 7.2, 6.3), 3.15 (dd, 1, J = 10.5, 8.1), 3.38 (dd, 1, J = 10.5, 3.9), 3.44 (s, 3), 3.94 (dd, 1, J = 6.3, 1.2), 4.49 (ddd, 1, J = 8.1, 3.0, 1.2); ^{13}C NMR δ 3.4, 8.8, 38.5, 58.0, 81.5, 81.7, 177.6. Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.11. Found: C, 31.23; H, 4.18.

(2*SR*,3*SR*,4*RS*)-4-(Iodomethyl)-3-methoxy-2-methyl-γ-butyrolactone (45). By use of the procedure described for the preparation of iodo lactones **22** and **23**, a 25:75 mixture of acids **41** and **42** was cyclized to give a 61% yield of an unseparable mixture of iodo lactones **43**, **44**, and **45**. The major isomer, lactone **45**: R_f = 0.45 (pentane/ether, 2:1); IR (neat) 2970, 2920, 2820, 1775, 1280, 1040 cm^{-1}; ^{1}H NMR δ 1.31 (d, 3, J = 7.5), 2.80 (qd, 1, J = 7.5, 1.2), 3.30-3.50 (m, 2), 3.39 (s, 3), 3.76 (dd, 1, J = 4.5, 1.2), 4.71 (ddd, 1, J = 7.2, 6.3, 1.2); ^{13}C NMR δ -0.7, 14.2, 41.6, 58.2, 81.1, 83.2, 177.9. Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.11. Found: C, 31.05; H, 4.20.

(2*S*)-[2-Methyl-5(*R*)-(2-propenyl)-2-cyclohexen-1(*R*)-yl]propionic Acid (67) and (2*R*)-[2-Methyl-5(*R*)-(2-propenyl)-2-cyclohexen-1(*R*)-yl]propionic Acid (68) by Deprotonation in THF. Carvyl propanoate (**62**) was enolized in THF as described above for propanoate **12**. Subsequent Claisen rearrangement led to a 25:75 mixture of acids **67** and **68** in 56% yield.

2*R* Isomer **68**: R_f = 0.20 (1:1 ether/*n*-hexane); bp 120 °C (0.1 mmHg); IR (neat) 3030, 2900, 1680, 1225, 875 cm^{-1}; ^{1}H NMR δ 0.96 (d, 3, J = 6.9), 1.65 (s, 3), 1.70 (s, 3), 2.92 (m, 2), 4.69 (bs, 2 H), 5.59 (t, 1, J = 2.1), 10.80 (bs, 1); ^{13}C NMR δ 9.6, 21.1, 21.3, 29.1, 31.5, 40.1, 41.6, 42.5, 109.2, 126.1, 133.7, 150.1, 183.0. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.90; H, 9.71.

Deprotonation in THF/45% DMPU. Carvyl propanoate (**62**) was enolized in THF/45% DMPU as described above for propanoate **12**. Subsequent Claisen rearrangement led to a >98:2 mixture of acids **67** and **68** in 60% yield.

2*S* Isomer **67**: ^{13}C NMR δ 13.2, 21.2, 21.9, 31.4, 32.2, 41.3, 42.1, 44.0, 109.1, 125.2, 134.7, 150.2, 182.4. For additional data, see ref 52.

Deprotonation in THF/23% HMPA. See ref 52.

(3*S*,3a*R*,5*R*,7*S*,7a*S*)-2,3,3a,4,5,6,7,7a-Octahydro-7-bromo-3,7a-dimethyl-5-(2-propenyl)-1-oxainden-2-one (69) and (3*R*,3a*R*,5*R*,7*S*,7a*S*)-2,3,3a,4,5,5,7,7a-Octahydro-7-bromo-3,7a-dimethyl-5-(2-propenyl)-1-oxainden-2-one (70). For the experimental procedure, see ref 52.

Isomer **70**: R_f = 0.25 (pentane/ether, 5:1); $[\alpha]^{25}_D$ +13.86° (*c* 0.94, $CHCl_3$); IR 2910, 1705, 1430, 1365, 1210, 1090, 1040 cm^{-1}; ^{1}H NMR δ 1.26 (d, 3, J = 7.2), 1.62 (s, 3), 1.77 (s, 3), 1.96 (m, 2), 2.15 (m, 2), 2.46 (m, 2), 2.66 (dq, 1, J = 11.1, 7.2), 4.38 (dd, 1, J = 12.5, 5.4), 4.82 (s, 1), 4.88 (s, 1); ^{13}C NMR δ 15.3, 22.0, 23.4, 26.9, 36.9, 39.8, 40.1, 50.6, 54.3, 84.9, 111.1, 146.6, 178.0. Anal. Calcd for $C_{13}H_{19}O_2Br$: C, 54.37; H, 6.67. Found: C, 54.12; H, 6.51.

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Supplementary Material Available: Tables of coupling constants and MMX minimized geometries of halo lactones; X-ray data for lactone **44** (16 pages). Ordering information is given on any current masthead page.

Stereoselective Synthesis and Thermal Rearrangement of the First Analogue of (7*Z*)-Vitamin D[1,2]

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The first (7*Z*)-vitamin D analogue, **15**, was synthesized stereoselectively using, as the key step, Wittig-Horner coupling between an allylphosphine oxide anion and a α-benzoyloxy ketone. Compound **15** has the same triene system as the putative 7*Z* intermediate of the mechanism postulated by Okamura and co-workers for thermally induced [1,5]-sigmatropic hydrogen shifts in vinylallenes. Okamura's hypothesis is supported by the identity of the products of thermally induced [1,7]-sigmatropic hydrogen shifts in **15**.

Introduction

Vitamin D_3 (cholecalciferol, **1a**), the well-known calcium homeostatic prohormone,[3] is unique among the steroid hormones in lacking the steroid B ring, which is replaced by a conjugated $\Delta^{5,7,10(19)}$ triene. The presence of this structural feature gives rise to a plethora of thermal[4] and photochemical[5] rearrangements which have attracted a great deal of attention from physical organic chemists for more than two decades. Concurrently, the purely medi-

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(2) This paper was presented in part at the 7th Workshop on Vitamin D (Rancho Mirage, CA, April 1988).

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