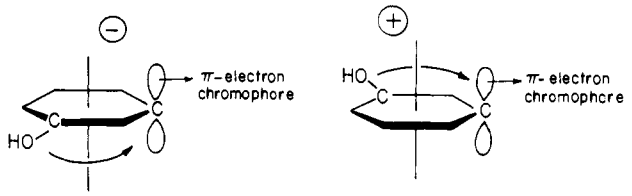

Figure 3. Relation between the substitution pattern of monohydroxylated secosteroids and steroids (β-side pointing upward) and the sign of the intermolecular exciton effect.

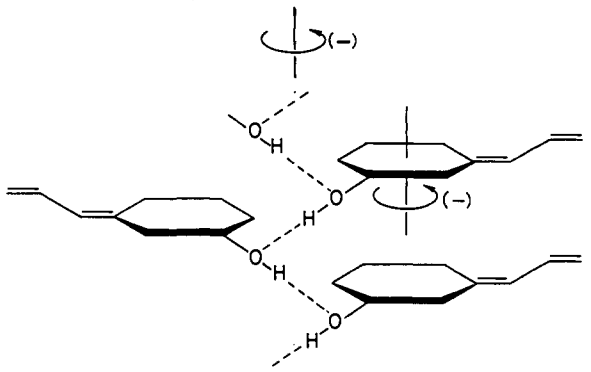

Figure 4. Schematic representation of the assemblies of hydrogen-bonded dienes **1** possessing negative helicity (β-side of the secosteroid pointing upward).

sign of the intermolecular exciton effect: when the shortest direction going from C bearing OH to C bearing the chromophore, relative to an axis perpendicular to the steroidal plane with its β-side pointing upward, is clockwise or counterclockwise, the sign of the exciton effect will be positive or negative, respectively (Figures 3 and 4).

Low-temperature exciton coupling effect was also observed in the steroidal dienol **6**, in IP/MCH solution ($\Delta\epsilon_{232}$ = −21; −175 °C, *c* 0.7 × 10^{-3} M), whose negative sign is in accordance with the above deduction.

It is reasonable to assume a stepwise concentration-dependent self-association of OH groups, resulting in dimers and oligomers. However, the formation of the energetically more favored helical organization of the oligomers which predominate at low temperatures is determined not only by H bonding but also by intermolecular interaction between molecular surfaces. Chiral patterns of packing occur in crystals of steroids possessing an OH function.[6] This may be exemplified by vitamin D_3 crystals, which are composed of molecules packed in infinite coils, in which OH are H bonded and the trans-diene functions form a positive helix.[7] Positive helical arrangement of the chromophores also exists in vitamin D_3 aggregates, as evidenced by the positive intermolecular exciton effect observed at low temperatures and in hydrocarbon solvents.

Formation of H-bonded oligomers could also be detected in hydrocarbon solution of monoesters of cholestane-1,2-diols **7**, in which OH and the ester function are in close proximity. Thus, cholestane-2α,3α-diol 3-monoanisate (**7a**) exhibits, at low temperatures, a positive exciton effect whose intensity increases with higher concentration and lowered temperature ($\Delta\epsilon_{262}$ = +28; −125 °C, *c* 1.5 × 10^{-3} M). The positive sign of the effect in **7a** was not changed either by altering the chromophore (**7b**: $\Delta\epsilon_{278}$ = +15; −125 °C, *c* 7.0 × 10^{-3} M) or its configuration and conformation (**7c**: $\Delta\epsilon_{262}$ = +14; −125 °C, *c* 1.2 × 10^{-3} M) but was reversed on interchanging both substituents (**7d**: $\Delta\epsilon_{262}$ = +16; −150 °C, *c* 1.0 × 10^{-3} M). Also in these cases, the relation between the signs of exciton effects and their substitution pattern is in accord with the deduction proposed above for the dienols and trienols.

We have shown that hydroxylated steroids and secosteroids form, in hydrocarbon solvents at low temperature, H-bonded oligomers with a favored helical organization whose chirality can be determined by circular dichroic spectroscopy.

(6) (a) Duax, W. L.; Weeks, C. M.; Rohrer, D. C. *Top. Stereochem.* **1976**, *9*, 289–294. (b) Motherwell, W. D. S.; Riva di Sanseverino, L.; Kennard, O. Abstracts, First European Crystallographic Conference, Bordeaux, France, 1973, Group B6.

(7) Trinh-Toan; DeLuca, H. F.; Dahl, L. F. *J. Org. Chem.* **1976**, *41*, 3476.

Substituent Effects on the Claisen Rearrangement. The Accelerating Effect of a 6-Donor Substituent

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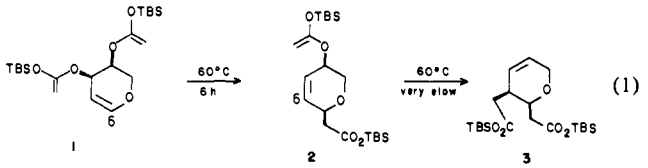
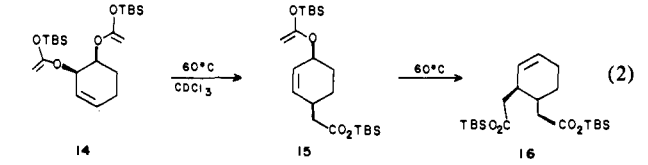
The Claisen rearrangement has emerged as one of the most important carbon–carbon bond-forming reactions in organic synthesis by virtue of its simplicity and selectivity.[2] Despite this, relatively little is known about the effect of various substituents on the rate of the reaction.[3] During the development of a synthetic approach toward pseudomonic acid antibiotics, we recently observed a dramatic example of the synthetic utility of rate differences in Claisen rearrangements (eq 1).[4] We now present



(1)

experimental evidence indicating that this rate difference is the result of an unrecognized accelerating substituent effect. Furthermore, this effect contradicts theoretical predictions based upon Hückel π-electron energies, and we will offer an alternate rational based on the "vinylogously anomeric" nature of the system.

For the factors responsible for the success of the mono-Claisen rearrangement in eq 1 to be elucidated, a series of rate studies was undertaken.[5] As expected, all substrates showed first-order rate behavior. These are collected in Chart I. Also of interest is the cyclohexene analogue (**14**) to the double rearrangement (eq 2). Here accurate rates could not be obtained since both rearrangements proceed at roughly similar rates. For example, after



(2)

16 h at 60 °C, the reaction consisted of **14** (14%), **15** (46%), and **16** (40%). The results indicate that (1) the origin of selectivity

(1) Recipient of a Camille amd Henry Dreyfus Award for New Faculty in Chemistry 1981–1986.

(2) Reviews: (a) Bennett, G. B. *Synthesis* **1977**, 589. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (c) Rhoads, S. J.; Raulins, N. R.; *Org. React. (N.Y.)* **1975**, *22*, 1. (d) Rhoads, S. J. In "Molecular Rearrangements"; deMayo, P., Ed.; Wiley-Interscience, New York, 1963; Part I, 655. (e) Tarbell, D. S. *Org. React. (N.Y.)*, *2*, 1. (f) Tarbell, D. S. *Chem. Rev.* **1940**, *27*, 495.

(3) Electron-donating substituents in the 2-position are well-known to accelerate the Claisen rearrangement. (a) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030. (b) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 741. (c) Denmark, S. E.; Harmata, M. A. *Ibid.* **1982**, *104*, 4972. See also ref 5. For quantitative studies on the effect of a cyano group at each position, see: Carpenter, B. K.; Burrows, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 6983.

(4) Curran, D. P. *Tetrahedron Lett.* **1982**, *23*, 4309. Curran, D. P.; Suh, Y.-G. *Tetrahedron Lett.*, in press.

(5) All rearrangements were conducted following the general Ireland procedure. (a) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48. (b) Ireland, R. E.; Muller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (c) Ireland R. E.; Wilcox, C. S. *Tetrahedron Lett.* **1977**, 2839.

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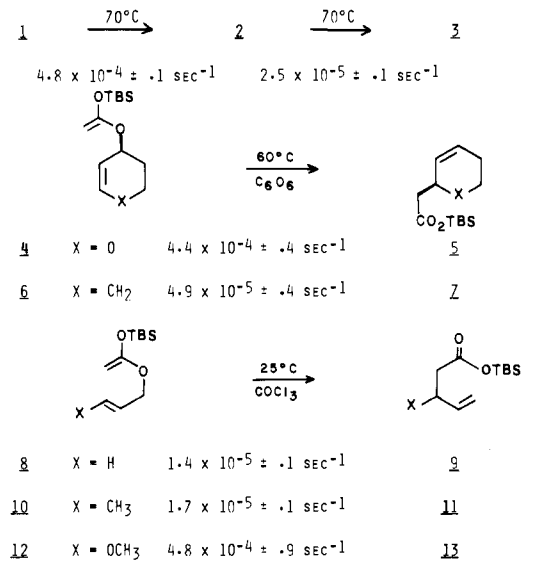
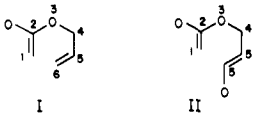
Chart I. Claisen Rate Studies



(eq 1) is due to a rate acceleration of the first Claisen rearrangement (**1** → **2**) rather than a deceleration of the second (**2** → **3**) and that (2) this acceleration is not primarily a consequence of steric[6] and/or conformational effects. In particular, ^{1}H NMR coupling constant studies readily indicate that each of the substrates **1**, **2**, **4**, and **6** exists in a conformation with the migrating group preferentially axial, as required. Thus, there is no inherent conformational bias. While these cyclic examples likely proceed via a boat transition state, the acyclic examples (**8**, **10**, **12**) rearrange via a chair transition state.[7] Again, this does not affect the general trend.

In each case, the example possessing oxygen in the γ-allylic position rearranges 10 to 25 times faster than its counterpart. We conclude that a substituent effect is operating; that is, an electron-donating substituent (O) in the 6-position (see II) can accelerate the Claisen rearrangement relative to its unsubstituted counterpart (I).[8,10] Compare this with the Carpenter model[9] for

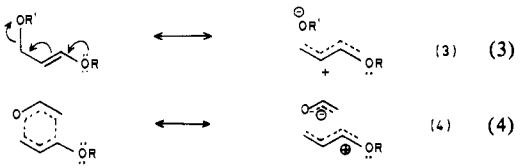


I II

the effect of a substituent on the rates of pericyclic reactions. This theoretical approach calculates the difference in Hückel π-electron energy between suitable reactant models and an aromatic (or other suitably conjugated) model of the transition state. Rate acceleration (deceleration) is determined solely by the gain (loss) of resonance energy in proceeding from the reactant model to the transition-state model. Despite its simplicity,[9] the Carpenter resonance energy approach has proved to be an excellent qualitative model for the prediction of the effect of substituents on a variety of pericyclic reactions.[3] It correctly predicts the accelerating effect of a 2-electron donor. However, the Carpenter model predicts a rate deceleration by an electron donor in the 6-position.[9b] It seems that the model is valid, i.e., there is some loss of resonance energy in proceeding from the reactant to the transition state. Some other factor(s) must override this effect.[10]

It is of interest to evaluate the nature of the 6-electron donor substituted system (II). The O_3–C_4 bond in this system may be considered to be vinylogously anomeric.[11] By analogy to the anomeric effect,[12] a molecular orbital rationalization may be provided by a $\pi \rightarrow \sigma^*$ stabilization from the vinyl ether.[13] Again borrowing from the anomeric effect, two consequences can be advanced. These are (1) an axial preference for a "vinylogously anomeric" C–O bond,[13,14] in order to provide the optimium geometry for orbital interaction, and (2) a weakening of this C–O bond due to population of an antibonding orbital.

Bearing in mind that the "vinylogous anomeric effect" is a manifestation of a more fundamental stereoelectronic preference,[12] we propose that the observed rate acceleration of the Claisen rearrangement by a 6-donor substituent is a chemical consequence of this effect. Although a molecular orbital rational may also be invoked, consider a standard "double-bond–no-bond" resonance interpretation of the vinylogous anomeric effect (eq 3). Now



consider an analogous approach to the transition state of the Claisen rearrangement (eq 4). Excellent experimental evidence indicates that the Claisen rearrangement has an early transition state with bond breaking well advanced with respect to bond making.[15] It is readily seen that the 6-oxygen substituent should lower the energy of the transition state (hence, accelerate the reaction) by facilitating the cleavage of the weakened O_3–C_4 bond. This interpretation emphasizes the importance of consideration of bond-breaking (and bond making) energies with respect to substituent effects on 3,3-sigmatropic shifts.[16] In the case at hand, any resonance energy loss incurred in proceeding from the reactants to the transition state is more than offset by the facilitation of bond cleavage.

In conclusion, we have demonstrated a novel accelerating substituent effect on the Claisen rearrangement and rationalized this in terms of the "vinylogously anomeric" nature of the cleaving C–O bond. The experimental evidence indicates that evaluation of substituent effects on the Claisen rearrangement should include consideration of resonance energy changes as well as bond-making and bond-breaking energies. While the variable nature[16b–d] of the transition state of the Claisen rearrangement makes predictions difficult, some evaluations can be made. When resonance-energy considerations and bond-breaking energies work in concert, an

(6) In conversion of **2** → **3**, the equatorially oriented β-$CH_2CO_2SiR_3$ group provides little hindrance for the axially entering group. This is evidenced by the results of eq 2 as well as the relative rate of **4** vs. **6**.

(7) For an evaluation of boat vs. chair transition states and other references, see: (a) Bartlett, P. A.; Pizzo, C. F. *J. Org. Chem.* **1981**, *46*, 3896. (b) Ireland, R. E.; Vevert, J.-P. *Ibid.* **1980**, *45*, 4259.

(8) In fact, the acceleration provided by the methoxy group in the acyclic system is clear from Ireland's $t_{1/2}$ studies though **8** and **10**[5b] were rearranged at a slightly different temperature from **12**[5c] in separate studies. This accelerating trend has also been recognized in other systems (C. Wilcox, personal communication).

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

(10) It is important to note that there are two substituent effects involved. In each pair of rearrangements, both substrates possess a strongly accelerating 2-donor substituent while only one possesses the 6-donor substituent. Thus, we have not yet determined the effect of an isolated 6-donor and although nonadditive combination effects may be operative (see ref 9), it does not seem likely that these would reverse the effect of the 6-donor.

(11) The term "vinylogous anomeric effect" has recently been independently introducted to identify the conformational preferences in related systems. See ref 14f.

(12) Kirby, A. J. "The Anomeric and Related Stereoelectronic Effects at Oxygen"; Springer-Verlag: New York, 1983.

(13) For a related molecular orbital rational, see: Tronchet, J. M. J.; Xuan, T. N. *Carbohydr. Res.* **1978**, *67*, 469.

(14) (a) Mico, M.; Santoro, J. *Org. Magn. Reson.* **1976**, *8*, 49. (b) Lessard, L.; Phan Viet, M. T.; Martino, R.; Saunders, J. K. *Can. J. Chem.* **1977**, *55*, 1015. (c) Burfitt, A. I. R.; Guthrie, R. D.; Irvine, R. W. Aust. *J. Chem.* **1977**, *30*, 1037. (d) Lessard, J.; Saunders, J. K.;Phan Viet, M. T. *Tetrahedron Lett.* **1982**, *23*, 2059. (e) Ishiyama, J.; Senda, Y.; Imaizumi, S. *J. Chem. Soc., Perkin Trans. 2* **1982**, 71. (f) Denmark, S. E.; Dappen, M. S. *J. Org. Chem.* **1984**, *49*, 798.

(15) (a) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 2747. (b) McMichael, K. D.; Korver, G. L. *Ibid.* **1979**, *101*, 2746.

(16) Previous theoretical studies have recognized the importance of these effects. (a) Delbecq, F.; Anh, N. T. *Nouv. J. Chim.* **1983**, 505. (b) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 6693. (c) Gajewski, J. J. *Acc. Chem. Res.* **1980**, *13*, 142. (d) Gajewski, J. J.; Gilbert, K. E. *J. Org. Chem.* **1984**, *49*, 11. (e) Steigerwald, M. L.; Goddard, W. A.; III; Evans, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 1994. (f) Rozeboom, M. D.; Kiplinger, J. P.; Bartmess, J. E. *Ibid.* **1984**, *106*, 1025.

unusually facile rearrangement can be expected. This should be the case when an electron-donating substituent is placed on C_4, and indeed there is evidence that such a rearrangement will proceed with ease.[17]

Acknowledgment. We thank Professor K. N. Houk for numerous helpful discussions. We also thank Professor B. K. Carpenter for communication of unpublished results.

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Unprecedented Regio- and Stereochemical Control in the Addition of Organoaluminum Reagents to Chiral α,β-Unsaturated Acetals

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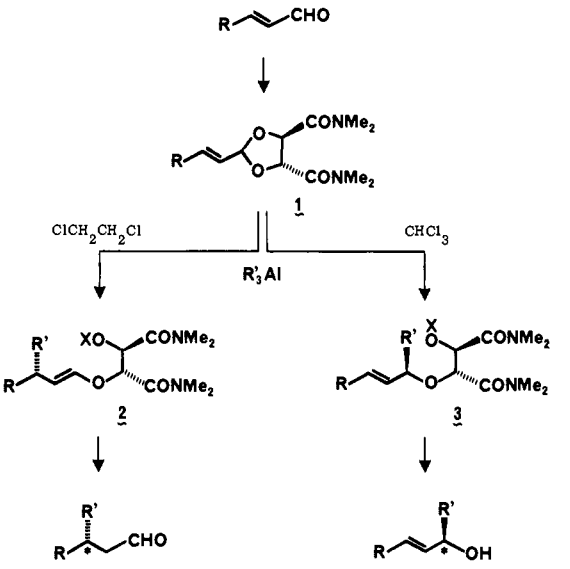
A highly effective method for the synthesis of optically active alcohols has been recently developed based on a strategy of utilizing a chiral protecting group that is subjected to activation by electrophiles[1] or nucleophiles.[2] Here we wish to report either the nucleophilic 1,4- or 1,2-addition of organoaluminum reagents to chiral α,β-unsaturated acetals with remarkably high asymmetric induction, thus providing an easy access to β-substituted aldehydes or allylic alcohols, respectively, in optically active forms (Scheme I).[3,4]

Chiral α,β-unsaturated acetal **1** was readily accessible by transacetalization of α,β-unsaturated aldehyde diethyl acetal with (*R,R*)-(+)-*N,N,N',N'*-tetramethyltartaric acid diamide[5] in quantitative yield.

The course of the reaction appeared to be highly dependent on the nature of substrates, solvents, and temperature as revealed in Table I. A typical experimental procedure is exemplified by the 1,4-addition of Me_3Al to the acetal **1** (R = *n*-Pr; entry 1). To a solution of the acetal **1** (R = *n*-Pr; 0.5 mmol; $[\alpha]^{18}_D$ −42.69° (*c* 2.15, MeOH)) in 1,2-dichloroethane (10 mL) was added a 2

Scheme I



M hexane solution of Me_3Al (2.5 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 12 h. The mixture was poured into 10% NaOH and extracted with CH_2Cl_2. The combined extracts were concentrated in vacuo to give the crude oil, which was acetylated by using Ac_2O–Py in the presence of catalytic 4-(dimethylamino)pyridine at room temperature for 1 h.[6] Evaporation of excess Ac_2O–Py followed by silica gel column chromatography (MeOH–AcOEt as eluant) of the residue afforded 1,4-adduct **2** (R = *n*-Pr, R' = Me, X = Ac) preferentially in 84% yield accompanied by 13% of 1,2-adduct **3**.[7] The optical purity of the 1,4-adduct **2** was substantiated by GC analysis after converting to the acetal of (−)-2(*R*),4(*R*)-pentanediol (catalytic TsOH, toluene reflux, 2 h; 93%).[8,9] In sharp contrast, however, the use of $CHCl_3$ as sovlent under the comparable conditions gave rise to 1,2-adduct **3** (R = *n*-Pr, R' = Me, X = H) exclusively in 85% yield (entry 7). Cleavage of the 1,2-adduct **3** with potassium *tert*-butoxide in isopropyl alcohol produced (*R*)-(+)-hepten-2-ol, $[\alpha]^{19}_D$ +10.68° (*c* 3.58, $CHCl_3$)[10] in 57% yield, the optical purity of which was determined by GC analysis of the (*S*)-(−)-MTPA ester.[11]

In connection with regio- and stereochemical control, the characteristic features observed in the 1,4-addition of Me_3Al to **1** (R = *n*-Pr) follow (entries 1–7):[12,13] (1) By manipulating the solvents, either addition mode appears feasible. (2) Nonpolar solvents such as toluene produced higher diastereofacial selectivity at the expense of regiocontrol than polar solvents such as 1,2-dichloroethane. (3) The high optical yield (~95% ee) was ob-

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(6) The 1,4- and 1,2-adducts were converted into the corresponding acetates because of their easy separation by column chromatography and the efficient acetalization of the 1,4-adduct with (−)-2(*R*),4(*R*)-pentanediol.

(7) The reaction gave entirely the trans isomers **2** and **3** as judged by 200-MHz ^{1}H NMR spectroscopy.

(8) Optically active (−)-2(*R*),4(*R*)-pentanediol is available from Aldrich Chemical Co. and Wako Pure Chemical Industries, Ltd., and its $[\alpha]_D$ value should be checked before use.

(9) For determination of enantiomeric purity by using chiral acetals, see: (a) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183. (b) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S. K.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081. See also: (c) Eliel, E. L.; Ko, K.-Y. *Tetrahedron Lett.* **1983**, *24*, 3547. (d) Meyers, A. I.; White, S. K.; Fuentes, L. M. *Ibid.* **1983**, *24*, 3551.

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(12) Attempted reaction of α,β-unsaturated acetal derived from (−)-2(*R*),4(*R*)-pentanediol with Me_3Al resulted in formation of 1,2-adduct exclusively with loss of diastereoselectivity.

(13) Treatment of the cis isomer of **1** (R = *n*-Pr) with Me_3Al in toluene furnished a mixture of 1,4- and 1,2-adducts in 23% yield (ratio, 4:1). The optical purity of the 1,4-adduct was found to be 77% ee with the *R* configuration.

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