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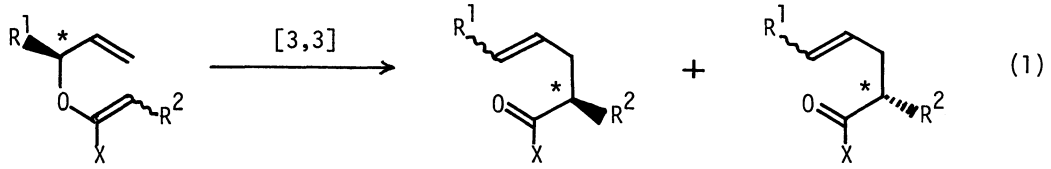
1,4-CHIRALITY TRANSFER VIA THE ESTER ENOLATE CLAISEN REARRANGEMENT

Masako NAGATSUMA, Fumiyuki SHIRAI, Noboru SAYO, and Takeshi NAKAI*
Department of Chemical Technology,
Tokyo Institute of Technology, Meguro-ku, Tokyo 152

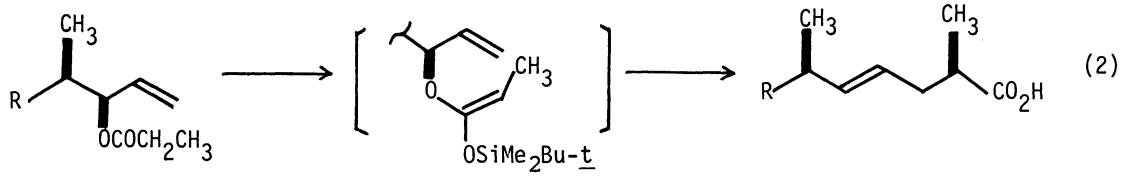
The Claisen rearrangement of (S)-1-buten-3-yl propanoate via the (E)- and (Z)-silylketene acetal has been shown to proceed with 96-100% of 1,4-chirality transfer to afford (E,R)- and (E,S)-2-methyl-4-hexenoic acid, respectively. The variation in sense and degree with solvent and silylating agent is discussed on mechanistic grounds.

In a continuing study on chirality transfer via sigmatropic rearrangements,[1] we have now investigated the 1,4-chirality transfer via the Claisen rearrangement (Eq. 1), where the substrate chirality could specifically be transmitted across the newly created carbon-carbon bond.[2] In order to effect the chirality transfer to a synthetically useful extent, extremely high degrees of stereocontrol over both the enol ether involved and the double bond formed in product are essential.



(1)

Recently the two groups[3] have reported essentially 100% of 1,4-chirality transfer in the Ireland-Claisen processes[4] using diastereomerically-defined substrates within the context of natural product syntheses (Eq. 2). Their results

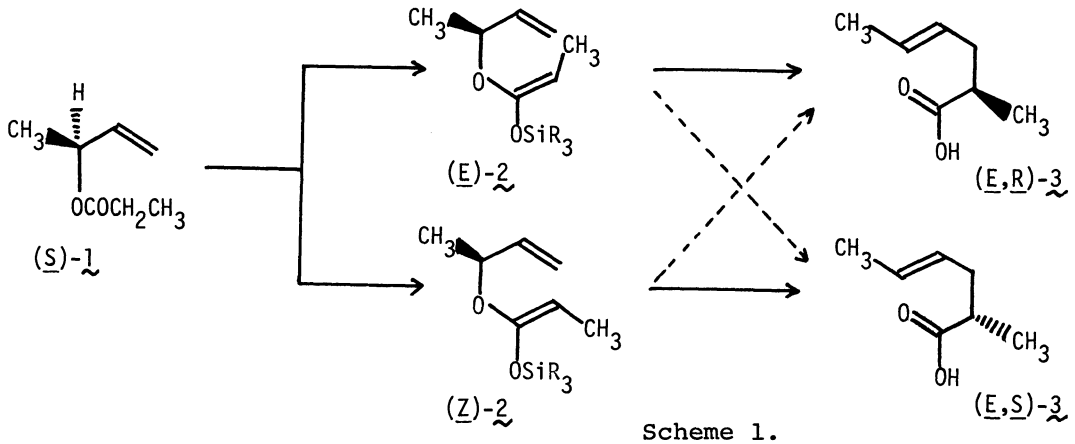


(2)

were surprising to us since the complete transfer of chirality means at least the complete control over the enolate geometry which seemed impossible in practice.[4] Thus, our effort has now been directed toward a detailed study using enantiomerically-defined substrates which permits more accurate evaluations of the sense and degree of the chirality transfer. We now report our observation on the enolate Claisen process of (S)-1-buten-3-yl propanoate (1) and the methoxyacetate (4).

Chiral substrates, (S)-1 and -4, were derived from an optically-resolved[5] 1-buten-3-ol. First, we carried out the rearrangement of (S)-1 (90% ee) according to Ireland's procedure (Scheme 1)[4] which involves the enolization with lithium diisopropylamide(LDA) in either THF or 23 vol% hexamethylphosphoramide(HMPA)-THF at -85 °C

followed by silylation with either trimethylchlorosilane or t-butyldimethylchlorosilane at that temperature. The resulting silylketene acetal (2) was allowed to rearrange at room temperature for one day followed by treatment with an aqueous sodium hydroxide to afford, after usual workup, a stereoisomeric mixture of the acid 3 in 75-85% of isolated yields. Table 1 summarizes some of the stereochemical results thus obtained.



Scheme 1.

Several significant trends are evident from the data in Table 1. (1) As expected, the enolization in THF leading to the selective formation of (E)-2 ultimately results in the preferential formation of (E,R)-3, whereas the enolization in HMPA-THF takes an alternative course to (Z)-2 and (E,S)-3 predominates.[6] (2) The use of t-$BuMe_2SiCl$ leads to a remarkably higher degree of chirality transfer than that of Me_3SiCl. This observation is very surprising in view of the fact that the degree of control over the enolate geometry should be independent of the silylating agent employed.[4] (3) The rearrangement via enolization in THF is more sensitive to the factor exerted by the silyl group as compared to the counterpart via enolization in HMPA-THF.

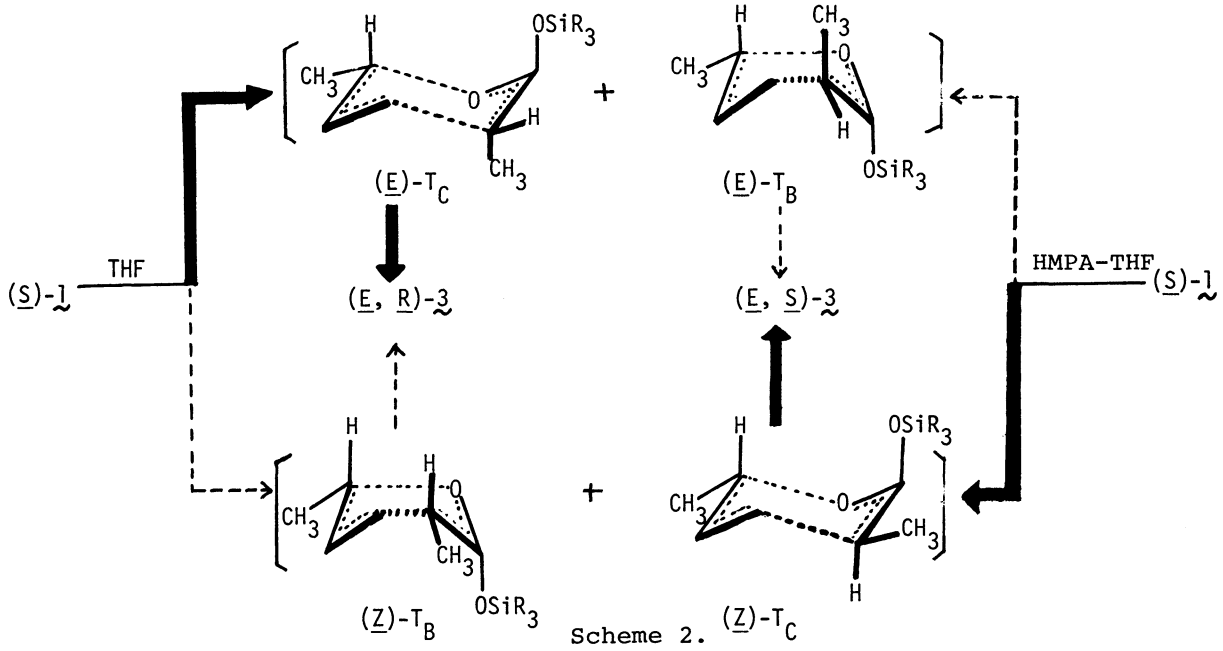
While these trends impart considerable stereochemical predictability to this methodology, let us discuss them on mechanistic grounds. Scheme 2 depicts the four possible transition states which all lead to the (E)-double bond in 3 as actually observed. Given the reasonable postulate that the rearrangement proceeds via the chair conformation (T_C), one might anticipate that (E)- and (Z)-2 afford (E,R)- and (E,S)-3, respectively, the degree of enantiospecificity depending solely upon the degree of control over the enolate geometry. The expectation is consistent with the observed sense, but not fully with the observed variation in degree, indicating that the enolate geometry is not the sole factor in dictating the degree of 1,4-chirality transfer.

The observed variation in degree with silylating agent suggests that the changeover in enantiospecificity might occur in the rearrangement step via the boat conformation (T_B) to some extents, depending on the steric parameter exerted by the silyl group. For example, (E)-T_B might be destabilized relative to (E)-T_C by changing R_3Si from Me_3Si to t-$BuMe_2Si$, thus leading to an enhanced degree as actually observed. Accordingly, our observations reveal that the overall degree of 1,4-chirality transfer is dictated by a combination of the two factors, i.e.,

Table 1. The Claisen Rearrangement of (S)-1 (90% ee)

Entry	Solvent[a]	R_3SiCl	Geometric purity of 3[b]	%ee of 3[c] (Config.)[d]	Chirality transfer / %[e]
1	THF	Me_3SiCl	>95% E	48 (R)	53
2[f]	THF	Me_3SiCl	>95% E	59 (R)	66
3	THF	t-$BuMe_2SiCl$	>95% E	86[g] (R)	96
4	HMPA-THF	Me_3SiCl	>95% E	76 (S)	85
5	HMPA-THF	t-$BuMe_2SiCl$	>95% E	90[h] (S)	100

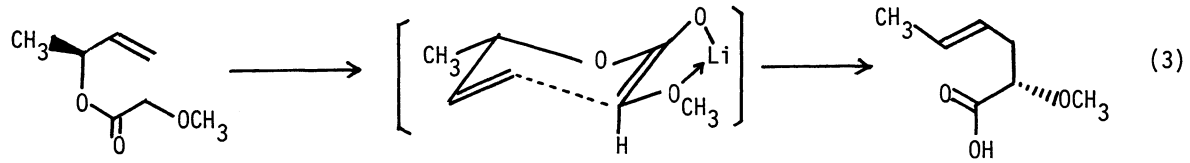
a) THF = 100% THF; HMPA-THF =23 vol% HMPA-THF. b) Determined by ^{13}C NMR assay. No signal due to the (Z)-methyl was detected. c) Determined by NMR analysis of the methyl ester of 3 using the chiral shift reagent, (+)-$Pr(DPPM)_3$, which was kindly provided by Prof. N. Ishikawa of our Department. In entries 1,2 and 4 the %ee was determined from the $[\alpha]_D$-values for 3. d) The (R)-configuration of (-)-3 was assigned through the (R)-configuration of (-)-2-methylhexanoic acid (3') derived from (-)-3 via hydrogenation, which was assigned on the basis of the reported configuration of (-)-(R)-3' ($[\alpha]_D$= -9.5° (Et_2O)): P. A. Levene and L. W. Bass, J. Biol. Chem., 70, 211 (1926). e) Refers to the %ee of 3 relative to 1 (90% ee). The data was not greatly reproducible (±5%) due to the complexities of this process. f) Instead of LDA, $LiN(SiMe_3)_2$ was used. g) $[\alpha]_D$= -8.81° (c 0.99, Et_2O). h) $[\alpha]_D$= +9.28 (c 1.02, Et_2O).



Scheme 2.

the degree of control over the enolate geometry and the relative heats of formation of the chair- and boat-like transition states from an enolate of defined geometry. Furthermore, it should be pointed out that the use of t-$BuMe_2SiCl$ is essential for minimizing the unfavorable changeover in enantiospecificity.

Finally, we also studied the enolate Claisen rearrangement of the chiral methoxyacetate (S)-4 (Eq. 3), where a highly selective formation of the metal-chelated (Z)-enolate (5) is expected.[7] Thus, the rearrangement of (S)-4 (72% ee) was carried out in THF in the same manners as described above except that the silylation step was omitted. We found that the rearrangement afforded (E,S)-6 (68% ee)[8] with 94% of chirality transfer and greater than 95% of (E)-selectivity. This observation is readily explained in terms of a combination of the expected high (Z)-selectivity in the enolization and the selective adoption of the chair-like transition state in the rearrangement. A notable feature of this particular variant is that a relatively high transfer of chirality is achieved without the assistance by t-$BuMe_2Si$ group as mentioned above.



(S)-4 (Z)-5 (E,S)-6 (3)

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2) While this type of chirality transfer remains largely unexplored, the 1,3-chirality transfer along the allylic array has been amply precedented. For reviews: F. E. Ziegler, Acc. Chem. Res., 10, 227 (1977); P. A. Bartlett, Tetrahedron, 36, 2 (1980); T. Nakai, K. Mikami, and N. Sayo, J. Synth. Org. Chem., Jpn., 41, 100 (1983).
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6) For a detailed discussion of the dramatic solvent effect on the stereoselectivity in the kinetic enolization, see Ref. 4.
7) S. D. Burke, W. F. Fobare, and G. J. Pacofsky, J. Org. Chem., 48, 5221 (1983); J. Kallmerten and T. J. Gould, Tetrahedron Lett., 24, 5177 (1983).
8) The optical purity was determined by the NMR analysis of the methyl ester using (+)-$Pr(DPPM)_3$ as chiral shift reagent (see footnote c), Table 1) and the geometric purity was determined by ^{13}C NMR assay. The (S)-configuration was assigned by the similarity of the methyl ester in shifts using the chiral shift reagent to methyl (S)-2-methoxy-3-pentenoate obtained from our separate work. Note that this assignment is fully consistent with the mechanistic considerations.

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