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THE DIANION CLAISEN REARRANGEMENT OF β-HYDROXY ESTERS

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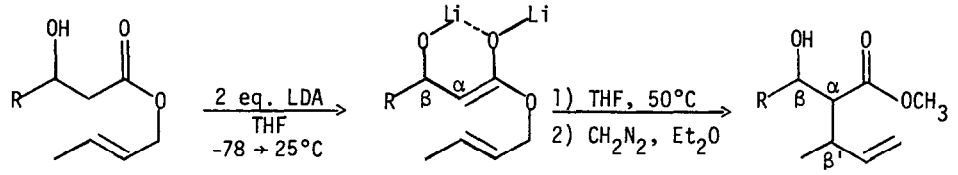
Abstract: Claisen rearrangement of β-hydroxy allylic ester dianions provides stereocontrolled access to three contiguous chiral centers on an acyclic framework; an unambiguous method has been developed for assessing diastereoselectivity.

The Claisen rearrangement is well established as an important method for the stereoselective construction of acyclic systems.[1] However, Claisen protocols which utilize the "remote" chirality[2] of an auxiliary group to induce asymmetry at the pro-chiral termini of the rearranging 1,5-diene have received little attention. The Ziegler/Thottathil orthobutyrolactone procedure[3] and our *N*-allylketene *N,O*-acetal rearrangement[4] are two examples where an auxiliary chiral center affords "remote" stereocontrol. We reasoned that this approach to asymmetric induction could be extended to the β-hydroxy ester dianion Claisen rearrangement 1 → 3. The "remote" chiral center C-β in 2 was envisioned to impart stereoselectivity in the ensuing dianion Claisen rearrangement. Several examples of α-alkoxy ester enolate[5] and α-hydroxy ester dianion[6] Claisen rearrangements have been reported. Herein we describe our preliminary results delineating the preparation of dianion 2, its Claisen rearrangement, and the development of a reliable method of determining diastereoselectivity for this rearrangement.



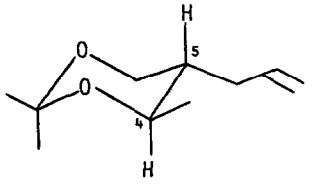
1a; R = CH_3 2a; R = CH_3 3a; R = CH_3

1b; R = $CH(CH_3)_2$ 2b; R = $CH(CH_3)_2$ 3b; R = $CH(CH_3)_2$

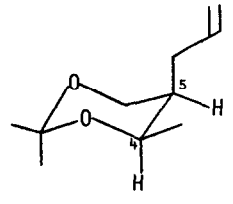
Starting β-hydroxy crotyl esters 1a and 1b were prepared by aldol condensation of (*E*)-crotyl acetate[7] with the appropriate aldehyde ($LiN(SiMe_3)_2$, THF, -78°C; RCHO, -78°C; H_3O^+). Treatment of 1a with lithium diisopropylamide followed by warming to 50°C (2 eq. LDA, THF,

-78°C; -78°C → 25°C, 6h; 50°C, 6h) gave the rearranged carboxylic acid. Diazomethane esterification followed by silica gel medium-pressure liquid chromatography (MPLC; 1:1::*n*-hexane:EtOAc) afforded an inseparable 81:19 mixture[8] of two diastereomers of ester 3a in 39% overall yield from 1a. Similarly, the isopropyl analog 1b was rearranged to an inseparable (MPLC; 1:1::*n*-hexane:EtOAc) 84:16 mixture[8] of 3b diastereomers in 37% overall yield.

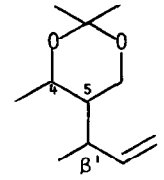
Erythro-threo stereochemical assignments in hydrogen-bonded β-hydroxy ester systems can often be made based on the magnitude of the vicinal coupling constant $J_{\alpha,\beta}$.[9] In the present examples, $J_{\alpha,\beta}$ for our major diastereomer in both 3a ($J_{\alpha\ \beta}$ = 4.4Hz) and 3b ($J_{\alpha,\beta}$ = 3.2Hz) falls within the "normal" erythro range ($J_{\alpha,\beta}$ = 3 to 6Hz). Erythro assignments for these major Claisen diastereomers would require that in the kinetically preferred transition-state, σ-bond formation occurs from the diastereoface which includes the C_β methyl (2a) or C_β isopropyl (2b) group. Clearly this would be an unexpected result. Therefore, we developed the following 1,3-dioxane based method for clarifying this apparent ambiguity. Relative to the β-hydroxy esters, the reduced conformational mobility of the dioxane ring was anticipated to facilitate stereochemical assignments.[10] Therefore, model 1,3-dioxanes 4-*trans* and 4-*cis* were prepared as a 2:3 mixture from methyl acetoacetate by a sequence involving allylation (NaH, Aliquat 336, allyl bromide, benzene)[11], reduction ($LiAlH_4$, Et_2O, 25°C), and acetalization with 2,2-dimethoxypropane (PTSA, benzene, 4Å molecular sieves). The relative configurations of these diastereomers were easily deduced from the magnitude of the vicinal coupling constant $J_{4,5}$ (360-MHz ^1H NMR). Dioxane 4-*trans* displayed $J_{4,5}$ = 9.6Hz, a value compatible with a 1,2-diaxial relationship between H_4 and H_5. In contrast, an axial-equatorial coupling constant of $J_{4,5}$ = 2.0Hz was observed in 4-*cis*, thus verifying the potential of this method. When applied to dioxanes with three contiguous stereocenters as in 5, this ^1H NMR technique is anticipated to clearly distinguish between *cis* and *trans* dioxane configurations. On the other hand, acyclic stereochemistry in the C_5 appendage (Cβ') would not be defined. However, since only two diastereomeric products were produced in each dianion Claisen rearrangement of 2, this assessment technique was anticipated to clearly delineate which diastereomers were formed.



4-*trans*



4-*cis*



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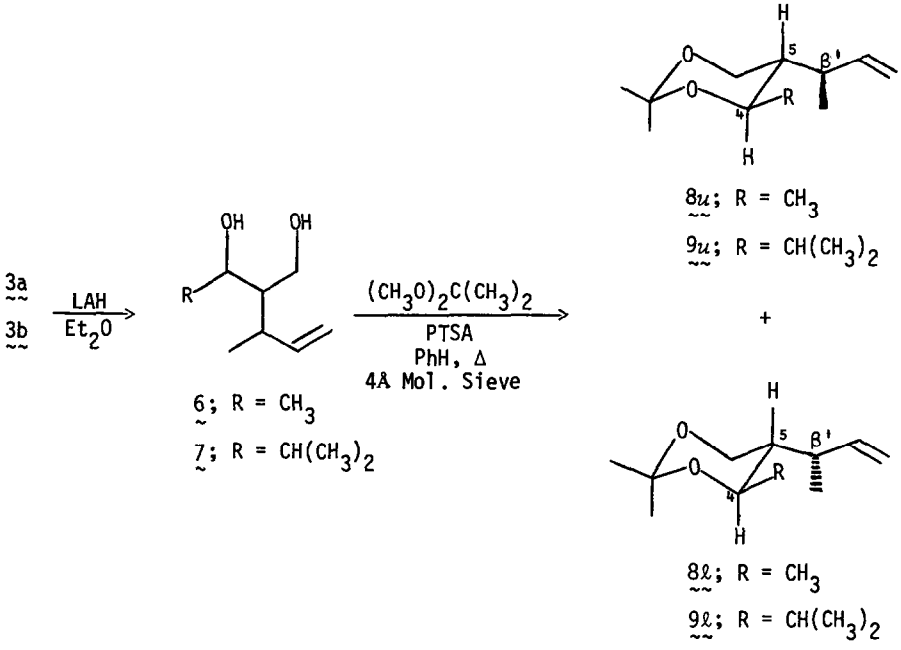
This technique was applied to the question of 2 → 3 Claisen selectivity as follows. Lithium aluminum hydride reduction of ester 3a (81:19 diastereomeric mixture) gave diol 6. Acetalization of this crude diol afforded a 4:1 mixture of dioxanes which proved inseparable by preparative GC (5% SE-30, 3/8" x5', 120°C). Analysis of this mixture by 360-MHz ^1H NMR

revealed $J_{4,5}$ vicinal coupling constants of 9.9Hz for each diastereomer. As in 4-*trans*, the magnitude of these coupling constants are consistent with a diequatorial arrangement of the C_4,C_5 dioxane appendages. Consequently the Claisen diastereomers from 2a are shown to be epimeric at Cβ', the acyclic stereocenter, and structures 8*u* and 8*l* can be assigned. Similarly, the two diastereomers of ester 3b produced an inseparable (preparative GC) 5:1 mixture of dioxanes, each with $J_{4,5}$ vicinal coupling constants of 9.9Hz. Therefore, these diastereomeric dioxanes can be assigned structures 9*u* and 9*l*. These dioxane results suggest that gauche interactions in β-hydroxy ester 3 invalidate $J_{\alpha,\beta}$ based erythro-threo stereochemical assignments.



Since only threo Cα,Cβ diastereomers of 3 were detected, the observed 4 or 5:1 product ratios indicate moderate chair-boat selectivity in these rearrangements.[12] An assumed chair transition-state preference[1] in the rearrangement of 2 implicates the stereochemical assignments depicted in 8*u* and 9*u* for the major Claisen diastereomer of 2a and 2b, respectively. Experiments are currently underway to verify this working hypothesis,[13] improve the product selectivity of these Claisen rearrangements, and further delineate the synthetic potential of this reaction.

Acknowledgement

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7. The crotyl alcohol used was 99:1::*E*:*Z* and the Claisen diastereoselectivities we report are uncorrected.
8. Ratio determined by 360-MHz ^{1}H NMR of 3.
9. Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* 1982, *13*, 1-115.
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13. Application of this dianion Claisen rearrangement in a synthesis of the antibiotic botryodiplodin is in progress. Theses results will unambiguously define the relative stereochemistry at Cβ'.

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