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# HIGH DIASTEREOSELECTION IN THE CLAISEN REARRANGEMENT OF ENANTIOMERICALLY PURE BUTYROLACTONES

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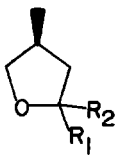
*Abstract: The Claisen rearrangement permits the stereoselective formation of butyrolactone 5b,c or 13b,c through the utilization of enantiomeric lactone 1a and enantiomeric alcohols 2b, ent-2b, 2c, and ent-2c.*

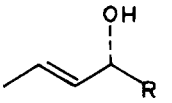
Macrolides and ionophores have prompted interest in the development of methods for the control of stereochemistry in acyclic systems.[1] The principal methods which have been employed are the aldol condensation,[2] the stereocontrolled opening of epoxyalcohols[3] and hydroboration of olefinic alcohols,[4] and variations on the Claisen rearrangement.[5] In this Letter, we report a method which addresses this problem through the judicious control of preferred Claisen rearrangement transition states.

When an equimolar solution of ortholactone *rac*-1b,[6,7] derived from the lactone *rac*-1a,[8] and butenol 2a (propionic acid (cat.), toluene, 93%) was refluxed, a mixture of three isomeric butyrolactones, *rac*-5a (68%), *rac*-7a (18%), and *rac*-9a (14%), was formed. Epimerization of cis isomer *rac*-9a (KO-t-But, HO-t-But, 25°C) afforded trans isomer, *rac*-7a. A similar experiment employing S-ortholactone 1b[9] provided the same distribution of enantiomeric lactones.

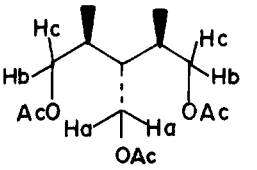
The structure of the major component, *rac*-5a, was confirmed by sequential ozonolysis, reduction of the intermediate aldehydolactone with $LiAlH_4$, and acetylation to provide triacetate 3. The $^1H$ nmr spectrum of 3 displayed two pairs of non-equivalent methylene protons ($2H_b$, δ 3.90, dd, J=11.0, 7.3Hz; $2H_c$, δ 4.14, dd, J=11.4, 4.8Hz) and one pair of equivalent methylene protons ($2H_a$, δ 4.15, d, J=4.8Hz). The decoupled $^{13}C$ nmr spectrum revealed seven lines. These data require triacetate 3 to be a meso compound and derived from *rac*-5a. The



1a, $R_1, R_2 = O$
b, $R_1 = R_2 = OC_2H_5$



2a, R=H
b, $R=CH_3$
c, $R=n\text{-}C_4H_9$
d, $R=C_6H_{11}$

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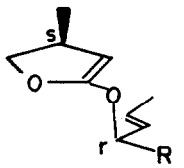

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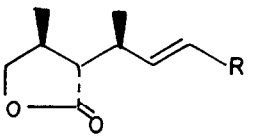
Ct R(eq)



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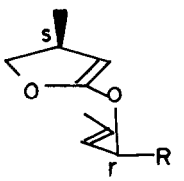

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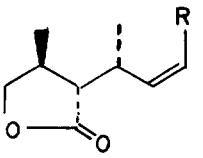
Bt R(ax)



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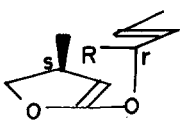

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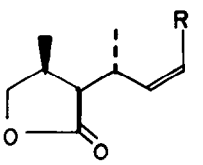
Cc R(ax)



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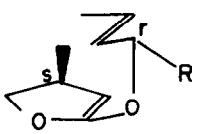

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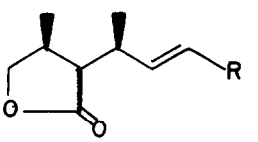
Bc R(eq)



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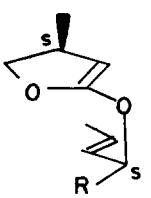

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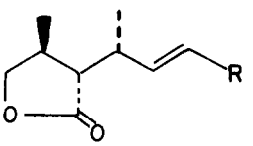
Bt R(eq)



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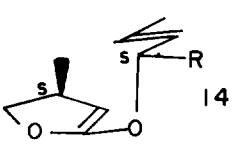

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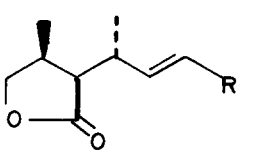
Cc R(eq)



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a, R=H, b, $R=CH_3$ c, $R=n\text{-}C_4H_9$

alternative meso structure would have had to be derived from *rac*-11a, a cis isomer, which would have been expected to undergo base catalyzed epimerization as was observed for *rac*-9a.

The major isomers, *rac*-5a and 5a, arise through a chairlike transition state[10] (C) with carbon-carbon bond formation occurring trans (t) to the methyl group of the ring. Lythgoe has observed that the orthoester of valerolactone and *rac*-2b, when subjected to Claisen rearrangement, afford two diastereomeric lactones in an 88/12 (chair/boat) ratio, both of which contain E-olefins. This observation requires the non-vinylic methyl group to be equatorially disposed in the transition state. Thus, rearrangement of the Claisen intermediate derived from 1b and 2b (R-alcohol) would be expected to proceed through transition state 4b, while 6b and 8b would be excluded because of the axial methyl group. Transition state 10b, although containing an equatorial methyl group, would be inoperative since rearrangement did not occur with 10a. This analysis was found to be correct. Claisen rearrangement of 1b and 2b[11] provided lactone 5b as the sole product. In a similar fashion, alcohol 2c afforded 5c; alcohol 2d did not undergo rearrangement under the reaction conditions.

Rearrangement of 1b with one equivalent of *rac*-2b afforded 50% of 5b, derived necessarily from 2b, while *ent*-2b provided 13b (28%) and 15b (22%). The S-alcohol generates transition states 12b and 14b having the methyl (or n-butyl) substituent equatorial, wherein the Bt transition state is slightly preferred over the Cc transition state. Utilization of *ent*-2b, coupled with epimerization, must necessarily generate 13b.

Since transition state 4b is predictably lower in energy than 12b or 14b, a kinetic resolution of *rac*-2b (3 equivalents) was attempted with ortholactone 1b. However, the distribution of products was the same as was obtained with one equivalent of *rac*-2b. This result requires the rate of rearrangement of 4b, 12b, and 14b to be faster than alcohol exchange.

This method permits clean control of side chain stereochemistry to provide enantiomerically pure butyrolactones with high diastereoselection.

The manipulation of the butyrolactone ring to afford acyclic systems is currently under investigation.

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6. All chiral structures are the enantiomers shown, unless otherwise specified.
7. Prepared as described for 1b.
8. Prepared from 2a: a) $CH_3C(OC_2H_5)_3$, pivalic acid, $\Delta$, b) $O_3$, DMS, c) $NaBH_4$.
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10. For the sake of clarity, transition states are represented as ground state conformations.
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