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A CONTRATHERMODYNAMIC EPIMERIZATION OF A 2,3-TRANS-DISUBSTITUTED BUTYROLACTONE: INTERMEDIATES FOR CHIRAL POLYPROPIONATE UNITS.

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ABSTRACT: A method is described which produces the less thermodynamically stable cis-2,3-disubstituted lactone 8 from its more stable epimer 6. These substances are complementary to aldol and crotyl organometallics in the construction of chiral polypropionate residues.

Previous reports from this Laboratory have revealed that the Claisen rearrangement of S-3-methylbutyrolactone (as its diethyl ortholactone) with R-(E)-2-octen-4-ol affords the antipode of 2 (ent-1 → ent-2) with the exclusion of ent-4 (Scheme I).[1] The rearrangement establishes two new centers of asymmetry, which permit the formation of four possible diastereomers. These diastereomers are the outgrowth of the four possible permutations of olefin facial selectivity in the rearrangement of the ketene acetal. The requirement that the butyl group must occupy an equatorial position in either chair or boat transition state reduces the number of possible diastereomers to two for a given combination of enantiomeric lactone and enantiomeric alcohol and results in the exclusive formation of E-olefins.

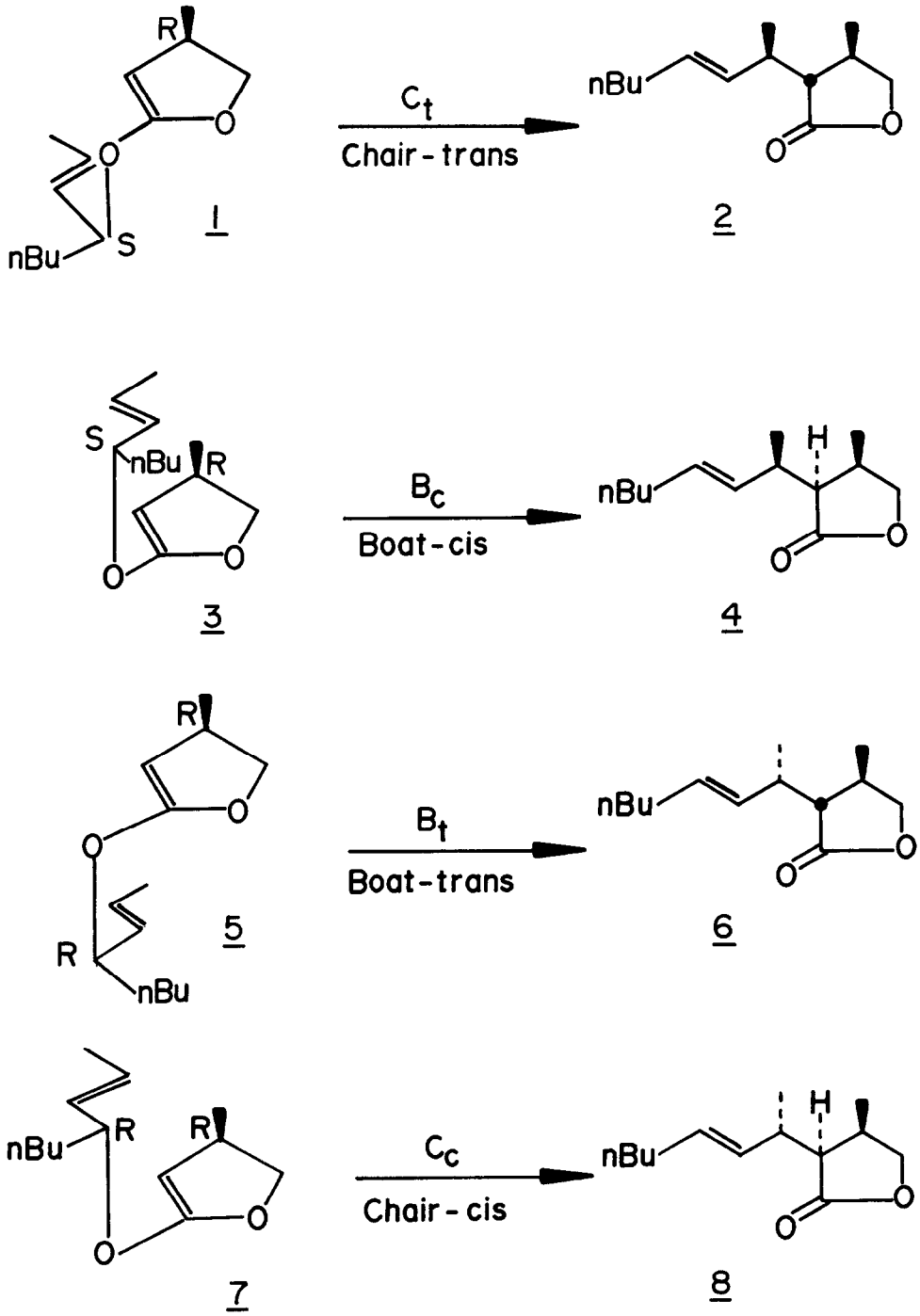
The rearrangement of 1 ($R_{lact}S_{alc}$) or its antipode, ent-1 ($S_{lact}R_{alc}$), proceeds through the lower energy chair (C) transition state[2] with C-C bond formation occurring on the less hindered face (trans (t) to the methyl) of the heterocyclic ring. The alternative transition state (3 → 4), boat-cis (B_c), is too high in energy to compete with the C_t transition state.

What is the course of the rearrangement of the diasteromeric keteneacetal ($R_{lact}R_{alc}$)?

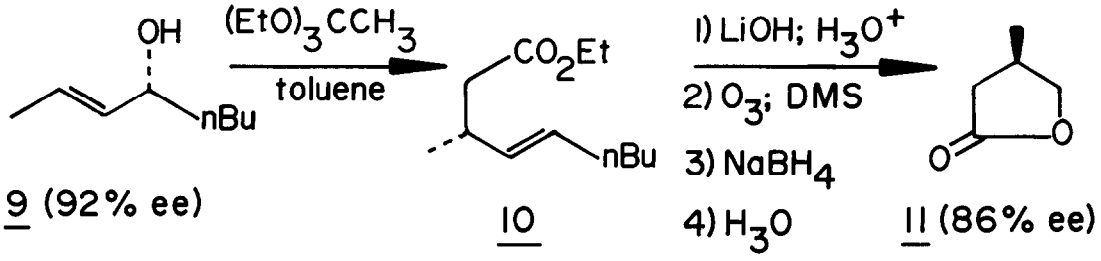
R-3-Methylbutyrolactone was prepared from R-(E)-2-octen-4-ol[3] as outlined in Scheme II.[4,5] Rearrangement of lactone 11 as its ortholactone with a sample of alcohol 9 (> 98% ee) provided lactones 6 (B_t), 8 (Cc), and ent-2[6] in 94% yield as a mixture (51/42/6). The two major components of the mixture result from the opposing effects of the boat-trans and chair-cis transition states. The small excess of the B_t over the C_c isomer indicates that the effect of the methyl substituent slightly overrides the chair vs. boat effect.

Epimerization of the mixture (t-BuOK/t-BuOH, 25°C) afforded the thermodynamically

Scheme I


R
O
O
nBu
S
1
C_t
Chair-trans
nBu
O
O
2
S
nBu
R
O
O
3
B_c
Boat-cis
nBu
H
O
O
4
R
O
O
R
nBu
5
B_t
Boat-trans
nBu
O
O
6
nBu
R
R
O
O
7
C_c
Chair-cis
nBu
H
O
O
8

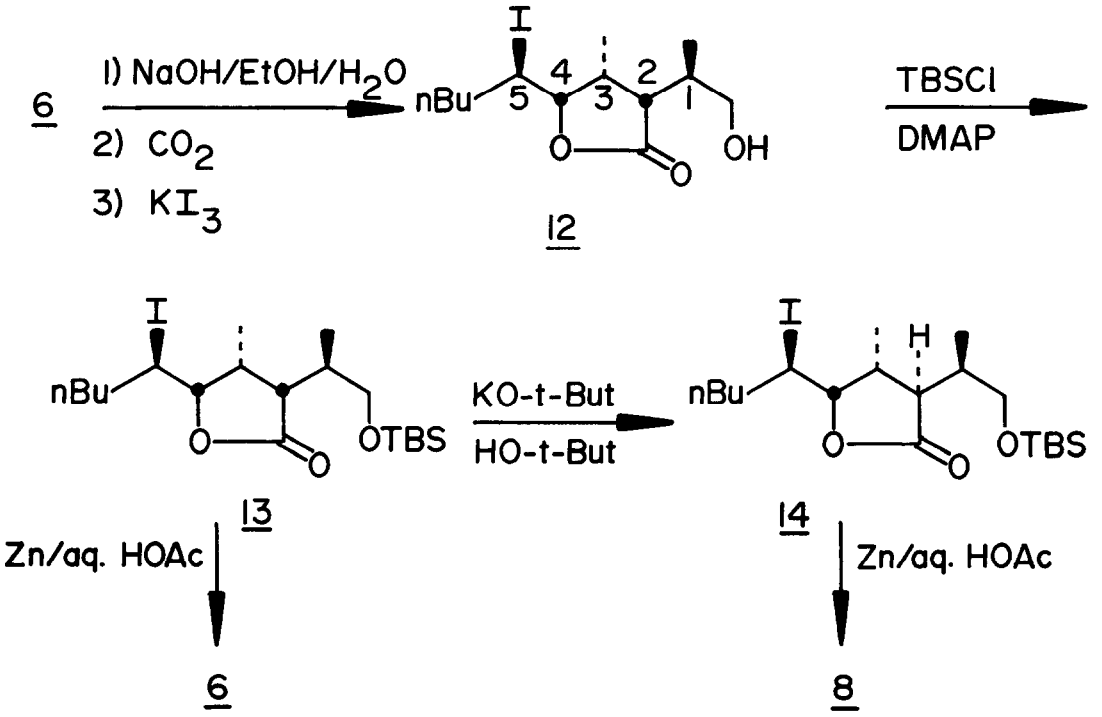
Scheme II



9 (92% ee) 10 11 (86% ee)

more stable trans-substituted lactone 6. The stereoselective formation of the less stable epimer 8 was accomplished as outlined in Scheme III. Because the methyl groups of 2,3-trans-disubstituted lactone 6 have a pseudo-C_2-symmetry axis, saponification and subsequent iodolactonization produce a 2,3-cis-disubstituted iodolactone 12 as a consequence of the lactone transposition. The relative stereochemistry of C_3-C_4 was

Scheme III



12 13 14 6 8

assigned on the basis of NMR coupling constants ($J_{1,2}$ = 10.0 Hz, $J_{2,3}$ = 6.1 Hz, $J_{3,4}$ = 3.0 Hz, $J_{4,5}$ = 10.0 Hz) and is in accord with the product of kinetic iodolactonization.[7] The hydroxyl group of cis-iodolactone 12 was protected as its TBS ether to avoid possible lactone exchange during subsequent epimerization. Reduction of iodolactone 13 with Zn/aq. HOAc provided the starting trans-lactone 6, thereby demonstrating the efficacy of the reductive elimination-relactonization procedure. Controlled epimerization ($\sim 10^{-3}$ M base, 1 equiv., 25°C, 36h) converted cis-iodolactone 13 into trans-iodolactone 14 without elimination. Reductive elimination and relactonization provided cis-2,3-disubstituted lactone 8 in 88% yield, thereby completing the "contrathermodynamic epimerization."

The ability to prepare lactones 2, 6, and 8 and their enantiomers from allylic alcohols 9 and ent-9, coupled with the ability to effect formal Baeyer-Villiger oxidation of these lactones,[1b,8] provides a useful method for constructing terminal, differentially functionalized, chiral bis-propionate chains.

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