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STEREOSELECTIVE SYNTHESIS OF 2-(2'-CYCLOALKENYL)GLYCINATES VIA ESTER-ENOLATE CLAISEN REARRANGEMENT

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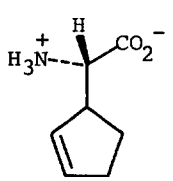
Ester-enolate Claisen rearrangement of 2-cycloalkenyl N-t-Boc-glycinates leads to the biologically active RS,SR-diastereomers selectively.

γ,δ-Unsaturated α-amino acids are of interest as atypical, naturally-occurring amino acids,[1] as enzyme inhibitors,[2] and as synthetic precursors to other derivatives.[3] The recent isolation of 2-(2'-cyclopentenyl)glycine 1 from a natural source[1a] and the stereochemical elucidation of this material[4a] and the 2-cyclohexenyl analog 2[4b] prompt us to report our work on the stereoselective synthesis of these compounds.

As indicated in the preceding communication,[3] the ester-enolate Claisen rearrangement is useful for the diastereoselective construction of γ,δ-unsaturated isoleucine derivatives. To study its application to the synthesis of 1 and 2, we prepared the 2-cyclopentenyl and 2-cyclohexenyl esters 3a,b and 4a,b.[5,6]

Rearrangement of the hippuryl esters 3a and 4a as described in the preceding report[3] proceeds non-diastereoselectively and in poor to fair yields: the cyclopentenyl isomers 5a:6a are formed in 1:1 ratio and 45% yield; the cyclohexenyl



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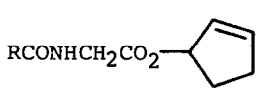

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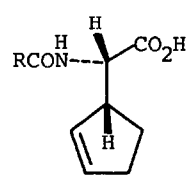

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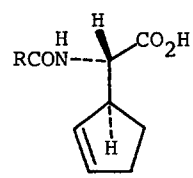

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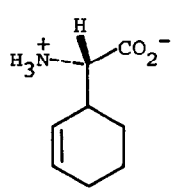

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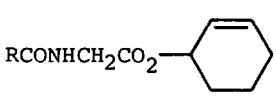

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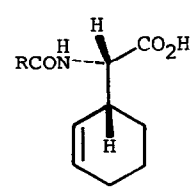
a: R = Ph b: R = Me_3CO

c: R = Me



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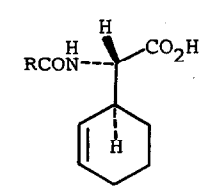


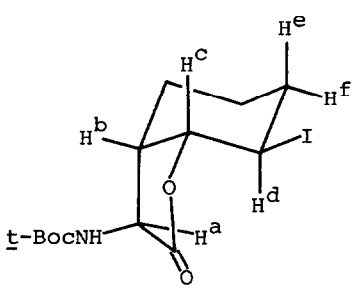
8

analogs 7a:8a in 2:1 ratio and 22% yield. In view of the results obtained on ester-enolate Claisen rearrangement of other cyclic esters[7] and with the analogous crotyl ester,[3] the absence of stereoselectivity is somewhat surprising. Whether this is inherent in the rearrangement or the result of subsequent epimerization is not clear.[8]

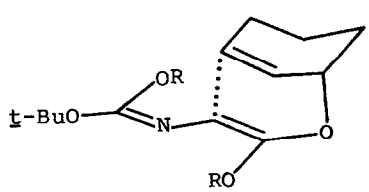
On the other hand, the N-t-Boc-protected ester 3b and 4b rearrange in significantly better yield and with higher stereoselectivity: in the cyclopentenyl case, the diastereomers 5b:6b are obtained in a ratio of 3:1 and a yield of 73%. Cleavage of the t-Boc protecting group and acetylation enabled us to assign the stereochemistry by comparison with the reported ^{1}H-NMR properties for the two diastereomers 5c and 6c.[4a,9] It should be noted that the reported acetylation conditions (acetic anhydride in pyridine at 60°C for 2 hours)[4a] lead to significant epimerization, presumably via the oxazolone. Acetylation without epimerization can be accomplished with acetic anhydride in aqueous $NaHCO_3$.

Although the yield on rearrangement of the cyclohexenyl ester 4b is a modest 40%, the reaction proceeds almost stereospecifically to provide RS,SR diastereomer 7b (ratio of 7b:8b = 25:1 by ^{1}H-NMR of the N-acetyl methyl esters). We determined the structure of this material by conversion to the iodolactone 9,[10] which was shown by ^{1}H-NMR to have the stereochemistry indicated, in analogy to the related methyl-[7] and hydroxy-substituted[11] analogs. Subsequent to this work, the report by Trowitzsch and coworkers on the X-ray analysis of 8c appeared,[4b] and we were able to confirm our stereochemical assignment by NMR, as discussed above for the cyclopentenyl analog.[12]

The formation of the RS,SR-diastereomers 5b and 7b as the major Claisen rearrangement products is consistent with the predominant generation of the E-enolate and subsequent rearrangement via the boat-like transition state 10b. The cis-selectivity for dianions such as 10a appears to be a general phenomenon



J_{ab} = 12.7 Hz
J_{bc} = 7.5 Hz
J_{cd} = 10.0 Hz
J_{de} = 13.0 Hz
J_{df} = 4.0 Hz



10a: R = Li

10b: R = $SiMe_3$

for a variety of amino acid derivatives, as revealed by their Claisen rearrangement selectivities.[3,13] Moreover, the occurrence of the boat-like transition state in the Claisen rearrangement of *cyclic* allylic esters is well-established.[7,14]

Although we performed these experiments using racemic material, the suprafacial nature of the Claisen rearrangement ensures that the 2-(2'-cycloalkenyl)-glycines would be available in optically active form from optically active 2-cycloalkenols. It is of further interest to note that it is only the 2S,1'R diastereomers of 1 and 2 that show biological activity,[4] and that this relative stereochemistry is the one produced selectively by the ester-enolate Claisen rearrangement process.

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6. All new compounds were characterized spectroscopically and by elemental analysis.

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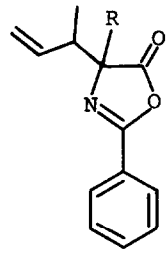
8. In unpublished work, we have observed the intermediacy of oxazolones such as i in the rearrangement of more highly substituted amino acid esters. Rapid epimerization of a glycine analog would be expected.



i

9. Recrystallization of the 3:1 mixture of 5c:6c from methanol afforded material of mp 172-174°C (lit.[4a] 156-158°C for a 1:1 mixture of 5c:6c (racemic); 171-172°C for 5c as a single enantiomer).

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12. Recrystallization of 7c from methanol afforded material of mp 196-198°C (lit.[4b] 184°C for a 1:1 mixture of 7c:8c (racemic); 204-205°C for 7c as a single enantiomer).

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