Stereochemical Control in the Claisen Rearrangement: Influence of an Adjacent Chiral Centre

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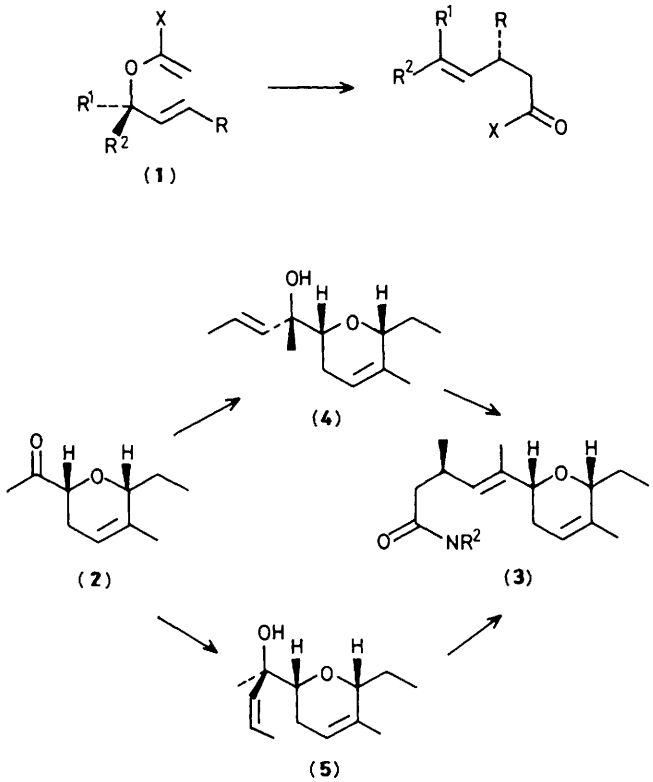
In the Claisen rearrangement of a series of diastereoisomeric tertiary allylic alcohols the stereoselectivity is found to be dependent upon the chiral centre adjacent to the allylic alcohol.

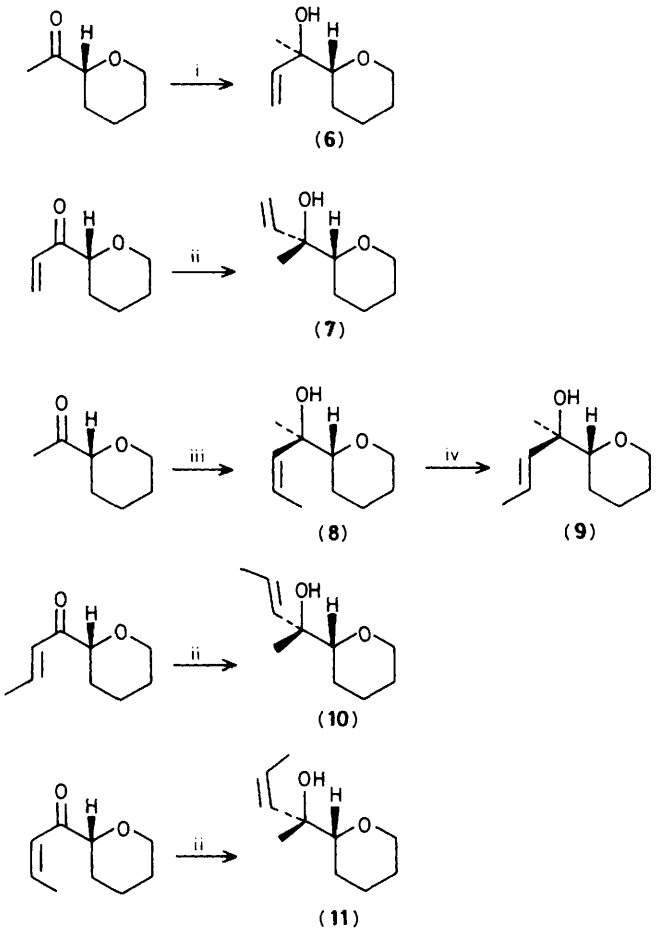
The Claisen rearrangement of secondary allylic alcohols (**1**, R^1 = H, R^2 = alkyl) is a valuable synthetic transformation since it forms (*E*) double bonds selectively and transfers chirality efficiently.[1] In the case of Claisen rearrangement of tertiary allylic alchols (**1**, R^1, R^2 = alkyl), where the steric difference between the substituents is smaller, mixtures of isomers are usually obtained and the reaction has therefore not been used widely in organic synthesis.[2] In connection with our work on ambruticin[3] we required a method for the conversion of ketone (**2**) into amide (**3**). The most straightforward approach to (**3**) would be *via* a Meerwein–Eschenmoser Claisen rearrangement[4] of tertiary alcohols (**4**) or (**5**), but clearly we might be faced with a lack of stereoselectivity in this reaction. We nevertheless decided to study this approach in simpler systems as we considered that the stereoselectivity might be affected by the oxygen substituent on the adjacent chiral centre.

The alcohols (**6**)—(**11**) were prepared in a stereoselective manner by chelation controlled addition of Grignard reagents to the tetrahydropyranyl ketones[5] (Scheme 1). The relative stereochemistry of the allylic alcohols is based on the expected direction of attack.[5] The stereoselectivity for addition of vinyl- or propenyl- magnesium bromide was 6:1 whereas for the addition of methylmagnesium bromide it was 4:1. The rearrangements were carried out by heating the allyl alcohols with dimethylacetamide dimethylacetal at 120 °C in the absence of solvent and the products analysed by high field ^1H and ^{13}C n.m.r. spectroscopy.† The stereochemical integrity of

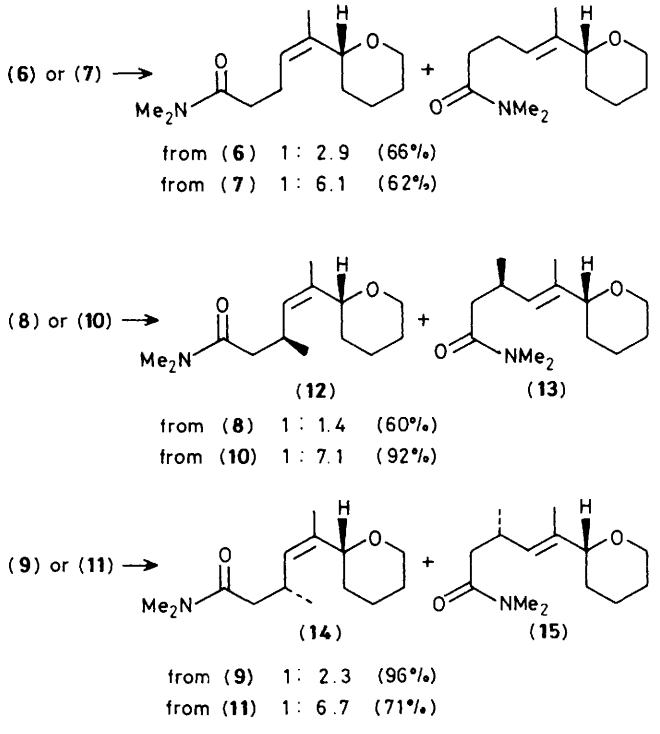


† By stopping the reaction before completion we were able to confirm that the ratio of products and the stereochemistry of the starting material did not alter under the reaction conditions.

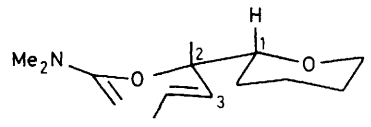
the Claisen reaction was confirmed by the observation that both (**8**) and (**10**) gave the same products, namely (**12**) and



Scheme 1. *Reagents:* i, CH_2=CHMgBr; ii, MeMgBr; iii, (*Z*)-MeCH=CHMgBr; iv, *hν*, PhCOMe.



Scheme 2



(16)

(13) and similarly both (9) and (11) gave the same products (14) and (15). None of (14) or (15) was detected in the rearrangement of (8) or (10) nor was any of (12) or (13) detected in the rearrangement of (9) or (11).

In the compounds studied the (*R**,*R**) diastereoisomers (6), (8), and (9) all rearranged with poor selectivity giving an (*E*):(*Z*) ratio of *ca.* 2 : 1 in each case. However, the (*R**,*S**) diastereoisomers (7), (10), and (11) showed a much higher selectivity of *ca.* 7 : 1 (Scheme 2). The origin of the enhanced selectivity for the (*R**,*S**) diastereoisomers is not clear. It could be a simple steric effect or it could be due to the presence of the oxygen atom adjacent to the tertiary centre. The C–O bond at C-1 may have to adopt a particular orientation with respect to the breaking C–O bond at C-2 or the forming double bond at C-2–C-3, (16). The effect of adjacent oxygen atoms on the stereochemistry of Claisen rearrangements[6] and other pericyclic reactions[7] has previously been reported.

In conclusion, whatever the origin of this effect it is clear that in systems such as these good stereoselectivity can be achieved by choosing the correct combination of diastereoisomer and olefin geometry. Hence Claisen rearrangements of tertiary allylic alcohols could prove to be of value in organic synthesis.

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