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HIGHLY STEREOSELECTIVE CLAISEN REARRANGEMENT OF VINYL ETHER OF 1-(1-HYDROXYETHYL)-2-METHYL-3-ALKYLCYCLOPENTENE. A ROUTE TO *CIS*- AND *TRANS*(1*E*)-ETHYLIDENE-8-METHYLHYDRINDAN-5-ONE.

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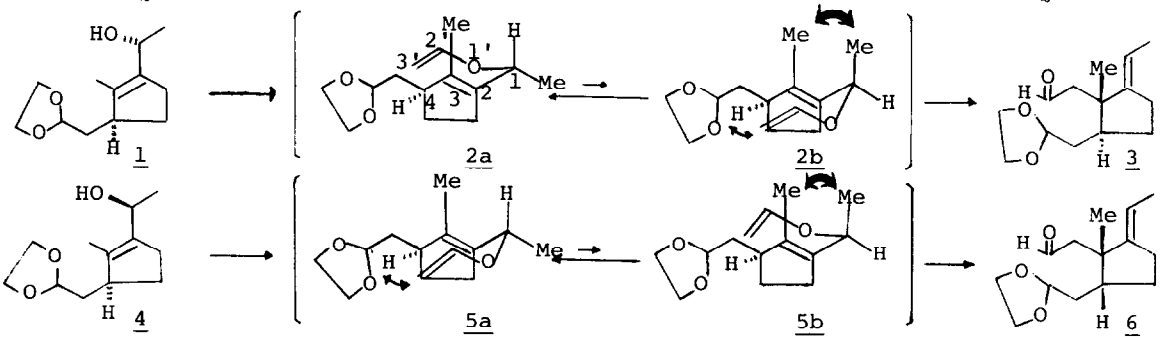
Summary: The highly stereoselective Claisen rearrangement of the α-isomer of vinyl ether of 1-(1-hydroxyethyl)-2-methyl-3-alkylcyclopentene introduces the trans stereochemistry between C(8)methyl and C(9)hydrogen and the geometry of *E*-olefin, necessary for a synthetic precursor of various steroids. The β-isomer gives the cis stereochemistry.

The Claisen rearrangement is a useful synthetic reaction[1] and extensive studies on its stereo- and regio-selectivity have been carried out. However, the reaction is carried out mostly with acyclic systems or cyclic systems containing both double bond and allylic alcohol as part of a ring system. Few detailed stereochemical studies on systems which contain the double bond in a ring and the allylic alcohol outside of the ring have been reported.[2] We have examined here the stereoselectivity of Claisen rearrangements on allylic alcohols 1 and 4. The latter rearranged to give the *cis*-stereochemistry between methyl and hydrogen, while the former provided the *trans*-stereochemistry. These highly stereoselective Claisen rearrangements are potentially useful for the synthesis of steroid CD ring, since one of the major difficulties in the synthesis of steroids is the stereoselective introduction of *trans*-stereochemistry between C(13) methyl and C(14) hydrogen (steroid numbering). Furthermore these stereoselective Claisen rearrangements have following characteristic features: (1) The newly formed *E*-olefin can be converted to various steroid chains[3] or can be used as a protecting group of carbonyl group at C(17). (2) The control of the thermal reaction is, particularly on a large scale, easier than previous methods.[4]

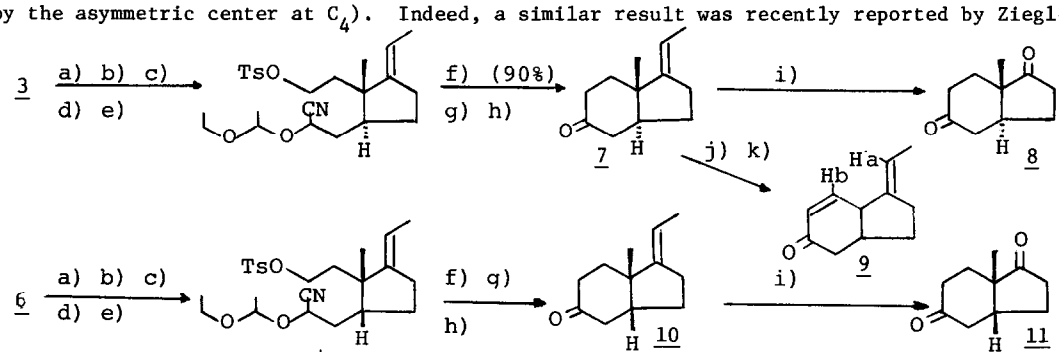
Allylic alcohols 1 and 4 were prepared either from the butadiene telomer[5] or 2-methylcyclopentenone.[3] Thermal treatment (1 h, at 160°C in collidine under nitrogen) of the vinyl ether 2, prepared from 1[6] and 10 equiv. of ethyl vinyl ether in the presence of $Hg(OAc)_2$, provided only the aldehyde 3[7] in quantitative yield. In contrast the thermolysis of the vinyl ether 5, prepared from



Scheme-1

4,[6] at the same temperature gave the aldehyde 6[7] in 95% yield. No diastereomeric isomer was detected in both cases by careful examinations (NMR, HPLC). The stereochemistry between the methyl and hydrogen in both 3 and 6 was estabilised by transformations of the aldehyde 3 into the diketone 8[8] and the aldehyde 6 into 11[8] as shown in the scheme 2. The *E*-olefin configulation of the aldehyde 3 was confirmed by conversion of the ketone 7 into the enone 9 and by its Nuclear Overhauser Effect (NOE) study. The irradiation of the proton Hb increased the intensity of Ha (41%).

These results and mechanistic considerations indicate that the rearrangement proceeds, respectively, through transition states 2a and 5a with selectivity more than 98%. The transition states 2b and 5b are not favorable, because there is great 1.3-diaxial interaction between two methyl groups as shown scheme 1. Thus, it is concluded that when the allylic alcohol is the secondary, the face-selection of the five-membered ring is controlled by the asymmetric center at C_1 but not by that at C_4. If the allylic alcohol is the primary, the Claisen rearrangement might proceed through the less hindered face of the five-membered ring (the face-selection might be controlled by the asymmetric center at C_4). Indeed, a similar result was recently reported by Ziegler.[2b]



a) $NaBH_4$ b) TsCl/Py. c) H^+ d) NaCN/$NaHSO_4$ e)  f) $NaN(SiMe_3)_2$ g) H^+ h) ^-OH
i) O_3/Me_2S j) LDA/PhSeBr k) $NaIO_4$

Scheme-2

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