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ENHANCEMENT OF DIASTEREOSELECTIVITY IN THE CLAISEN REARRANGEMENT INDUCED BY REMOTE STEREOCENTERS VIA USE OF STERICALLY DEMANDING LEWIS ACID CATALYSTS.

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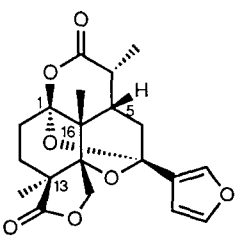
Summary: *Several cases of significant enhancement in the diastereoselectivity of acyclic Claisen rearrangement of cyclohexenyl allyl ethers governed principally by remote asymmetric center(s) have been observed when Lewis acid catalysts are employed rather than the usual thermal rearrangement conditions.*

The Claisen rearrangement is an invaluable tool in synthetic chemistry owing to its usually predictable and highly stereoselective formation of carbon-carbon bonds.[1] This [3,3] sigmatropic rearrangement often requires relatively high temperatures which can limit its utility, but recently a substantial effort has been focused on overcoming this limitation by means of catalysis.[2] Thus, several groups have established that the desired [3,3] rearrangement proceeds at ambient temperatures or below when conducted in the presence of either aluminum[3] or transition metal Lewis acids.[4]

In the case of chiral allyl vinyl ethers, the diastereofacial selectivity of both thermal and catalyzed reactions is usually governed by the strong preference for substituents on the sp^3 carbon of the hetero 1,5 dienes to occupy a pseudoequatorial environment in the normally more favorable chair-like transition state.[5] It has also been shown that diastereofacial selectivity can be moderately influenced by chiral centers remote to the reacting centers in the 1,5 diene.[6] However, Yamamoto has elegantly shown that the aforementioned preference for these proximal substituents to occupy a psuedoequatorial environment in the chair-like transition state can be overridden by the use of a sufficiently bulky Lewis acid catalyst.[7] We wish to report herein several cases of substantial enhancement in stereoselectivity of a thermal acyclic Claisen rearrangement when Lewis acids are employed as catalysts. In these rearrangements, the stereoselectivity is governed only by one or more remote asymmetric centers and proximal substituents which usually control the choice of diastereomeric transition states are absent.



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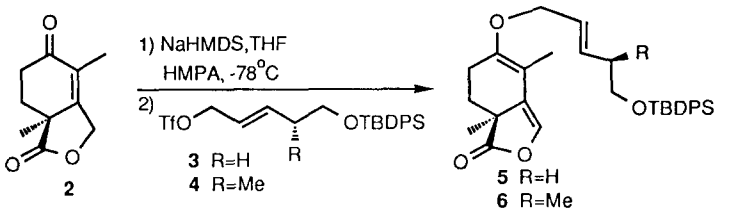
In the course of developing a synthetic route to the naturally occurring hypoglycemic agent saudin (**1**),[8] we had occasion to examine the Claisen rearrangement of cyclohexenyl allyl ether substrates such as **5**-**6** (Equation 1) to establish two key stereocenters C_5 and C_{16} (saudin numbering), wherein the required diastereoselectivity would be

induced by the preexisting remote stereocenter at C_{13}.

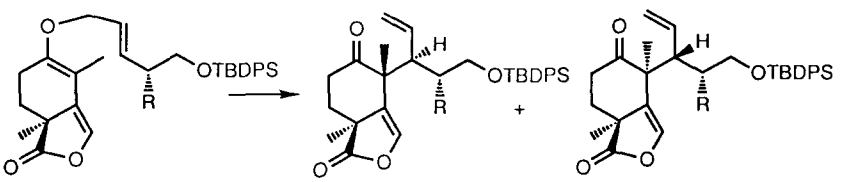
The required enantiomerically pure cyclohexenyl allyl ethers **5**-**6** were prepared from the enantiomerically pure enone lactone **2**[9] and allylic triflates **3** and enantiomerically pure **4** (Equation 1). The thermodynamically favored



(1)

extended enolate was generated from lactone **2** upon treatment with NaHMDS (1 equiv, 1.0M in THF) slowly dropwise at -78°C (checked by silylation). Addition of anh HMPA (~20% by volume) to increase the propensity for O-alkylation followed by the freshly prepared allylic triflates **3** or **4** (allylic alcohol, *n*BuLi, Tf_2O, -78°C) afforded the required cyclohexenyl allyl ethers **5** and **6** in ≥90% yield after purification by flash chromatography.

Table 1



5, R=H
6, R=CH_3

7 R=H
9 R=CH_3

8 R=H
10 R=CH_3

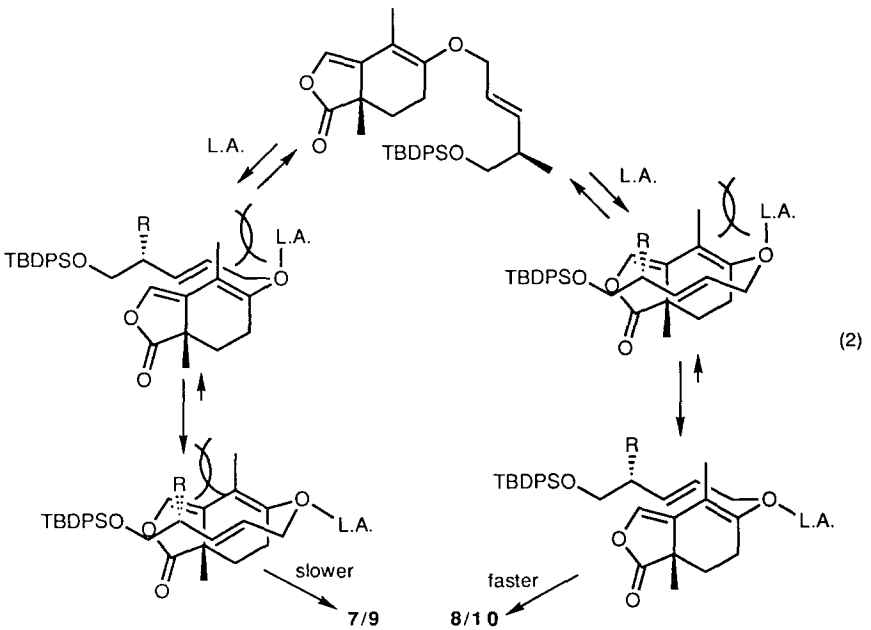
Entry	R	Lewis acid(equiv)	time(h)	temp (°C)	7/9:8/10 (%yield)[a]
1	H		2	105	1:1 (81%)
2	H	*i*Bu$_3$Al (2.0)	18	25	1:2 (33%)[b]
3	H	(CH$_3$)$_3$Al (2.0)	0.9	25	1:3 (90%)
4	H	MAD[7] (4.0)	2	25	1:2.5 (88%)
5	H	Et$_2$AlCl-Ph$_3$P (2.0)	1.5	-50	1:4 (57%)[c]
6	H	Et$_2$AlCl-Ph$_3$P (2.0)	0.5	25	1:5 (94%)
7	CH_3		2	125	1:3 (76%)
8	CH_3	(CH$_3$)$_3$Al (2.0)	0.2	45	1:24 (60%)[d]
9	CH_3	MAD[7] (4.0)	2	25	1:24 (43%)[d]
10	CH_3	Et$_2$AlCl-Ph$_3$P (2.0)	0.5	25	1:24 (39%)[d]

a) Total yield of isolated chromatographically pure materials.
b) Yield adjusted for conversion of 67%.
c) Yield adjusted for conversion of 30%.
d) Yields unoptimized for these cases.

Thermal rearrangement of **5** and **6** in toluene at 105°-125°C provided the expected rearrangement products **7/9-8/10** as a mixture of diastereomers in good yield (Table 1). However, the diastereoselectivity of the rearrangement was disappointingly low, ranging from 1:1-3 (**7/9**:**8/10**). The stereochemistry of the major products **8/10** was assigned utilizing ^{1}H NMR spectroscopy, and subsequently confirmed by single crystal X-ray analysis of a derivative in both cases.[10] In an effort to modulate and enhance the level of the diastereoselection in these rearrangements, use of Lewis acid catalysis was investigated.[7] Thus, treatment of **5** and **6** with various Lewis acids again smoothly afforded the expected diastereomeric Claisen products **7/9-8/10** in moderate to excellent chemical yields (not all optimized). Furthermore, the overall diastereoselectivity was significantly enhanced (5-8 fold) with respect to the thermal rearrangement, in spite of the fact that the diastereoselectivity is apparently influenced principally by the remote stereocenters at C_4 and C_{13} with respect to the atoms of the 3-oxa-1,5- diene unit undergoing rearrangement.

The optimal Lewis acid for rearrangement of **5-6** was found to be the 1:1 complex of Et_2AlCl and Ph_3P which provided high yields and clean products at room temperature.[3] The stereoselectivity in the rearrangement of **5** appears to increase both with increasing steric bulk of the ligands on the Lewis acid, and with increasing electron deficiency of the Lewis acidic center. Under optimal conditions, using $Et_2AlCl \bullet PPh_3$, the selectivity rises to 1:5 (**7/8**). In the case of **6** the synergism of the two asymmetric centers overwhelms the magnitude of the effects owing to the nature of the Lewis acid which affords a remarkable enhancement from 1:3 to 1:24 (**9/10**) in all cases. In energetic terms, the observed level of enhancement for the catalyzed rearrangement relative to the related thermal rearrangement corresponds to a $\Delta\Delta G^{\ddagger}$ of ~1 Kcal/mole for **5** and a $\Delta\Delta G^{\ddagger}$ of ~1.75 Kcal/mole for **6**.

It is difficult to establish unequivocally a mechanistic model for the observed enhancement of stereoselectivity. Upon complexation with the Lewis acid (Equation 2), the oxygen becomes chiral and the Lewis acid becomes a substituent which can occupy an equatorial-like or axial-like environment in the subsequent chair-like transition state



(2)

structures. The Lewis acid complexation can be clearly seen to raise significantly the energy of 2 of the 4 possible transition state structures as a result of allylic strain owing to interaction with the vinyl methyl group. Thus, product formation is expected to occur only by way of the two remaining transition state structures in which the Lewis acid occupies an equatorial-like environment. The enhanced preference in the catalyzed rearrangement for those transition state structures leading to **8/10** in which the allyl sidechain approaches the bicyclic ring system from the face *anti* to the angular methyl group arises from a combination of two factors: 1) an earlier reactant-like transition state for the catalyzed rearrangement in which the interactions with the angular methyl group are more fully developed in the transition state leading to **7/9** relative to the interactions with the concave bicyclic enol lactone ring system and the eventual 1,3-diaxial methyl-methyl interaction developing in the reactant-like transition state leading to **8/10**, and 2) the additional steric interactions found in the transition state leading to **9** arising from interactions with the secondary methyl and/or silyloxymethyl group with the angular methyl group.

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10. Details of the single crystal X-ray analysis of the derivatives of **7/9** will be published as part of a full account of these studies.

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