DIASTEREOSELECTIVE [2,3] WITTIG REARRANGEMENT OF TERTIARY α -LITHIO ETHERS

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Summary: Tertiary allylic methyl(tri-n-butylstannyl) ethers undergo transmetallation and subsequent diastereoselectve [2,3] Wittig rearrangement, wherein chirality transfer and olefin selectivity for the [2,3] signatropic event is mediated by a stereogenic center external to the signatropic framework.

The [2,3] Wittig rearrangement has become an increasingly important tool for the stereorational construction of highly-functionalized acyclic and macrocyclic systems as details of the accompanying stereochemical transfer and diastereoselection have emerged.^{1,2} Recently we reported the diastereoselective rearrangement of α -allyloxy anions derived from tertiary ethers **1**, which offers a stereocontrolled sigmatropic entry to remotely-functionalized trisubstituted olefins **2**.³ Of considerable interest is the observation that a stereogenic center outside the sigmatropic framework directs the stereochemical outcome of the electrocyclic event for these tertiary substrates.⁴ Thus, ethers **1a**, derived from <u>anti</u> diols, rearrange with exclusive diastereoselectivity while the <u>syn</u> ethers **1b** afford mixtures of <u>E</u> and <u>Z</u> products, a result which is consistent with rearrangement through a conformation involving participation of the vicinal α -alkoxy group in a multidentate coordination³ of the reaction cation. As part of our program to define the scope of this novel stereocontrol, we have examined the [2,3] Wittig rearrangement of α -lithio ethers **3b**, obtained from transmetallation of the corresponding methyl trialkylstanyl ethers **3a**.⁵ We now report that the [2,3] Wittig rearrangement of these systems exhibits a stereochemical divergence similar to that observed for oxazoline-substituted tertiary ethers.



The series of tertiary methyl(tri-n-butylstannyl) ethers 5 and 6 were prepared from the optically active alcohols^{2d} using a modification of Still's original procedure.^{5a,b} Transmetallation with n-BuLi (THF, -78°C) resulted in rapid [2,3] sigmatropic rearrangement to trisubstituted olefins <u>7-10</u>. As shown in Figure 1, rearrangement of α -lithio ethers derived from **Z**-5 and **E**-5 afforded, as the only isolated products, the epimeric alcohols <u>7</u> and <u>8</u> respectively.⁶ In contrast, rearrangement of the lithiated ether derived from alcohol <u>E-6</u> resulted

Figure 1



in a 1.5:1 mixture^{6b} of **8** and the \underline{Z} olefinic product **2**. Interestingly, the isomeric \underline{Z} - $\underline{6}$ exhibited significantly greater olefin selectivity, yielding a 13:1 mixture of \underline{E} and \underline{Z} olefins **7** and **10**. No C₂ epimers were detected in these examples, indicating that stereochemical transfer for the [2,3] signatropic reaction is high, an observation consistent with Midland's assessment of chirality transfer for the analogous secondary ethers.^{5c}

Olefin geometries for rearrangement products **7-10** were assigned based on the results of NOE difference studies.³ Configurations of the remote stereogenic centers were defined by the conversion of **8** and **9** to the known lactones **12** and **14**. Thus, directed hydrogenation of **9** using the Evans protocol⁷ afforded the saturated alcohol **13** as the only isolated product. Deprotection and oxidation yielded (-)-invictolide **14**, a component of the queen recognition mixture of the imported red fire ant.^{8,9} Similarly, olefin **8** was transformed to (-)-2-epi-invictolide **12**, which exhibited physical and spectroscopic properties in accord with those described previously.^{8a}

The chirality transfer and olefin selectivity observed for the [2,3] sigmatropic rearrangement of tertiary α lithio ethers parallels that of oxazoline-stabilized tertiary substrates,³ and suggests that the configuration of the vicinal stereogenic center bearing the α -benzyloxymethyl group serves a critical function in establishing the stereochemical course of the rearrangement. The exclusive diastereoselectivity observed for the rearrangement of

Figure 2



 α -lithio ethers derived from $\underline{5}$ is consistent with a transition state geometry approximating the chairlike conformation A, involving chelation of the reaction counterion with the vicinal benzyloxymethyl substituent. For α -allyloxy ethers $\underline{6}$, rearrangement must occur through two or more reactive conformations of approximatly equal energy. We suggest that the stereochemical divergence observed for this series is accomodated by rearrangement through conformations resembling B and C, in which rotation of the olefin across the plane of the chelate would allow addition to either olefin face. This model additionally accounts for the diminished stereoselectivity observed for \underline{E} - $\underline{6}$ relative to the \underline{Z} isomer, where such a rotation would give rise to severe non-bonded interactions.



The one-carbon homologation of tertiary allylic alcohols to generate stereochemically defined, remotely functionalized trisubstituted olefins such as \mathbf{Z} represents a direct and versatile entry to highly-functionalized acyclic intermediates which complements existing convergent approaches to these systems. The relevance of this procedure to the preparation of polyketide-derived natural products is demonstrated in a short synthesis of racemic Prelog-Djerassi lactonic ester (\pm) -20.¹⁰ Alkylation of tertiary alcohol 15³, followed by transmetallation and subsequent [2,3] signatropic rearrangement yielded a 2.5:1 mixture of 17 and the \mathbf{Z} olefin 18. Directed hydrogenation of $\mathbf{17}$ was accompanied by internal ketalization to give 19, which was further transformed to (\pm) -20 using reported conditions.^{10b,c} Further application of the tertiary [2,3] Wittig protocol to the stereocontrolled construction of highly-oxygenated acyclic and macrocyclic targets will be the subject of future reports.



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