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A [2,3]-Wittig Rearrangement that Requires Severe Deformation from a Stable 6-Membered Ring Chair Structure and Its Application to Synthesize 1,3-*anti*-3,5-*anti*-1,3,5-Trimethylated Carbon Chain Compounds

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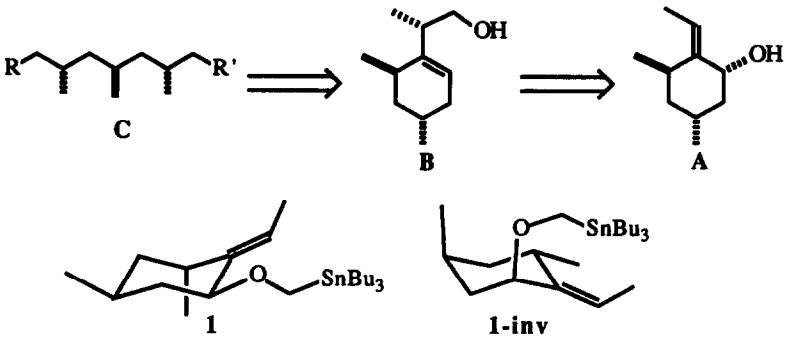
Abstract: A [2,3]-Wittig rearrangement was accomplished overcoming severe six-membered ring deformation barrier and utilized as a key step in a highly stereoselective synthesis of the title compounds.

[2,3]-Wittig rearrangement is a versatile synthetic tool for carbon-carbon bond formation. Due to the nature of a five-membered ring transition state, it provides a regiospecific and stereoselective process which has found widespread applications.[1] Recently, both theoretical[2] and experimental[3] studies have shown that the lithium-bearing terminus of the rearranging system undergoes inversion of configuration. The orbital interaction for an allyl lithiomethyl ether can be described graphically as shown below, its concerted reaction requires the overlap of the terminal olefinic p-orbital with the back lobe of sp^3 orbital used for bonding with the lithium, and the overlap between the breaking C-O bond and the second olefinic p-orbital.

A question arises, in the case of a rigid system whose stable conformation forbids such orbital overlap, as to whether it can overcome the serious deformation barrier, meet the overlap requirement and proceed with the rearrangement. We were confronted by this issue during our methodology studies to synthesize 1,3,5-trimethylated carbon chain compounds. These trimethylated chains are found as side chains or segments in a number of natural products such as pectinatone,[4] siphonarienedione[5] and lardolure.[6] One of our approaches toward these acyclic compounds and their stereoisomers hinged on the potential of alcohol A[7] as the starting material leading to 1,3-*anti*-3,5-*anti*-1,3,5-trimethylated chains (C). This strategy is conceptually similar to our group's previous study for synthesis of vitamin E side chains[8] and requires a [2,3]-Wittig rearrangement of lithiomethyl ether of A to afford alcohol B. Ring opening at the carbon-carbon double bond of B followed by

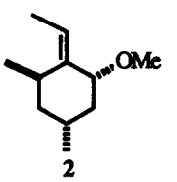
deoxygenation would then yield the target chain C. The starting material for the [2,3]-Wittig rearrangement, tributylstannymethyl ether[9] of alcohol A could be easily prepared by deprotonation of A (KH/THF, -20 °C) followed by addition of tributylstannymethyl mesylate[10] (-20 to 20 °C, 95%). The confidence in a successful rearrangement, however, was not strong due to the realization that the C-O bond to be broken lies nearly in the olefin plane. This allyl ether (**1**) was thought to be a quite rigid chair system because the inverted chair (**1-inv**) encounters a severe 1,3-allylic ($A^{1,3}$) interaction[11] between the two methyls. But the rearrangement would have to occur from the inverted chair or some other high energy conformers.



Treatment of the tin species **1** with *n*-BuLi (10 equiv., THF) gave the results summarized in the following table. At low temperatures (-78 to -65 °C), the desired [2,3] process proceeded only sluggishly and upon quenching with water, the allyloxymethyl anion was protonated to yield methyl ether **2**. At 0 °C, while the major product was homoallylic alcohol **B**, an unexpected compound **A** which could be generated from the α-elimination[12] of the carbanion, was also produced in substantial amount. Only when the temperature was moderately low (-45 to -25 °C), could **B** be obtained in high yield. Interestingly, there was no detectable [1,2]-Wittig rearrangement product.

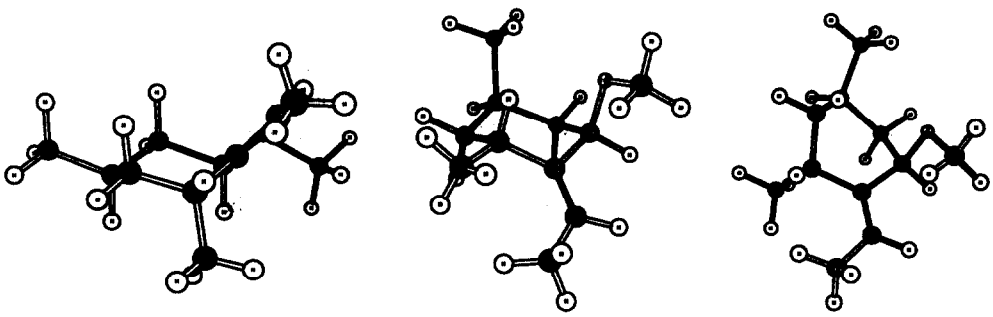
temp(°C)	time	B	2	A
-78 to -65	3 h	5%	57%*	5%
-45 to -25	3 h	90%		4%
0	1 h	65%		20%

*This ether is volatile and substantial loss of it during rotary evaporation is expected



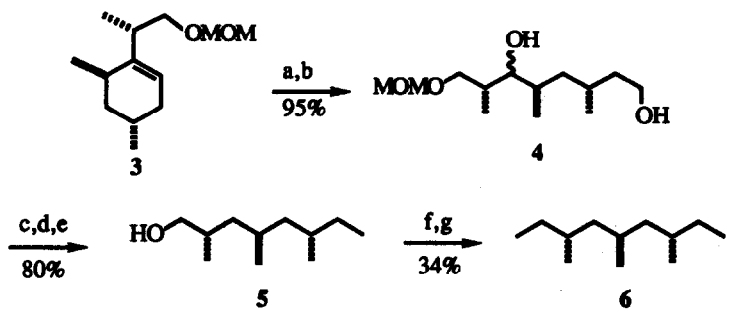
These results demonstrate that at moderate temperatures, our system can substantially change its conformation so that the orbital overlap requirement can be met. The conformation change could result in a chair-like geometry for the six-membered ring as in **1-inv**, another possibility would be a boat-like structure. Methyl ether **2** was used as a model in MacroModel calculations[13] with MM2 force field, and some of the results are shown below. The lowest energy conformer was found to be **chair** which obviously does not allow the concerted process. As expected, the inverted chair (**chair-inv**) was higher in energy than **chair** by approximately 4 kcal/mol. Although the twisted boat (**boat**) was also less stable than **chair**, it showed an

increased stability over **chair-inv** presumably due to the much diminished Me-Me $A^{1,3}$ interaction in **boat**. Whatever the geometry of the transition state is, a considerable barrier resulting from the severe deformation from the stable chair conformation must add difficulty to the rearrangement reaction. This should help to explain the moderate temperature required for our successful rearrangement. Thus our reaction gives an interesting example to show the power of the [2,3]-rearrangement in overcoming unfavorable geometries.



chair (0 kcal/mol) **chair-inv** (3.9 kcal/mol) **boat** (2.3 kcal/mol)

The transformation process toward the 1,3-*anti*-3,5-*anti*-1,3,5-trimethylated chains was quite straight forward. Homoallylic ether **3** was obtained by treatment of alcohol **B** with MOMCl/(*i*-pr)$_2$NEt/CH_2Cl_2 in high yield (95%). Ozonolysis of **3** followed by reduction with $NaBH_4$[14] provided an epimeric mixture of diols **4** which should allow easy functionalization at both ends of the chain. Thus, the 1,3-*anti*-3,5-*anti* relationship among the three methyls has been established. In combination with our previous work,[7] we have synthesized this type of trimethylated chain compounds from 5-methylcyclohex-2-en-1-one in an overall stereoselectivity of > 96:4. This strategy provides an alternative to Oppolzer's methodology of camphorsulphonamide-based asymmetric 1,4-additions.[15]



(a) O_3, MeOH/CH_2Cl_2, -78 °C. (b) $NaBH_4$ (excess), -78 °C for 1 h. & 0 °C for 30 min. (c) MsCl (10 eq.), pyr., 0 to 20 °C, 3 h. (d) LAH (excess), THF, reflux, 5 h. (e) THF, 10% HCl, reflux, 10 h. (f) *p*-TsCl (1.5 eq.), pyr., 36 h. (g) Me_2CuLi (1.5 molar eq.), ether, 0 °C, 30 min.

Although we were confident of the stereochemical outcome of the [2,3]-rearrangement in creating a new chiral center, the relative stereochemical assignment of the three chiral centers had to be unequivocally substantiated. NMR elucidation of an appropriate derivative with certain symmetry would help in this cause. Thus diol **4** was converted to hydrocarbon **6** in five steps. Dimesylation of **4** and LAH reduction[16] followed by removal of the MOM group with HCl afforded alcohol **5**. Tosylation of **5** and methyl-displacement reaction with methyl cuprate then yielded **6**. The low yield (34%) reflects the fact that most of the product **6** was lost during purification due to its volatility. The relative stereochemistry of the three methyls of the hydrocarbon chain has to be either 1,3-*anti*-3,5-*anti* or 1,3-*syn*-3,5-*anti*. The latter is an asymmetric compound and the former a symmetric one. NMR studies showed that hydrocarbon **6** is symmetric since it gave only seven carbon peaks (^{13}C NMR) and three different methyls (^{1}H NMR), therefore it has the structure shown.

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