mixture (3.5:1) of the adducts **23** and **24** in 92% combined yield. It is interesting to note that **22** added to the C(21) aldehyde function of **21** predominantly via the desired Felkin–Anh (Cram) mode in contrast to that observed in a closely related addition performed by Kallmerten.[5b] The structure of **23** was unequivocally established by its conversion [(a) KH, THF, MeI, 0 °C; (b) TBAF, THF; (c) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2; (d) TFA, aqueous THF] in 87% overall yield into **25**, which was identical (^1H and ^{13}C NMR) with an authentic sample.[20]

Since **25** was an advanced intermediate in Baker's asymmetric synthesis of macbecin I (**1**),[5a] its preparation by the route outline above constitutes a formal synthesis of **1**. However, we are presently exploring more convergent approaches for the synthesis of **23**, more direct methods for conversion of **23** and related compounds into macbecin I, and several strategies for the total synthesis of herbimycin A from the key intermediate **17**. Moreover, we are examining several stragegies for the total synthesis of herbimycin A from the key intermediate **17**. These results will be revealed in due course.

Acknowledgment. We wish to thank the Robert A. Welch Foundation and the National Institutes of Health (CA 50991) for generous support of this research.

Supplementary Material Available: Complete experimental details for all new compounds (20 pages). Ordering information is given on any current masthead page.

---

(18) We thank Professor James Kallmerten for providing details for the synthesis of **22**. See also: Guay, V.; Brassard, P. *Heterocyclic Chem.* **1987**, *24*, 1649.

(19) For another account of a similar reaction, see: Plaumann, D. E.; Fitzsimmons, B. J.; Ritchie, B. M.; Fraser-Reid, B. *J. Org. Chem.* **1982**, *47*, 941.

(20) We thank Dr. Raymond Baker for providing an authentic sample of **25** for comparison.

Inversion of Configuration in the Displacement of Lithium by Hydrogen during a Transannular 1,4-Hydrogen Transfer Accompanying a [1,2]-Wittig Rearrangement

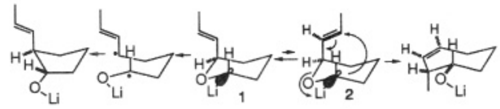
Erik J. Verner and Theodore Cohen*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

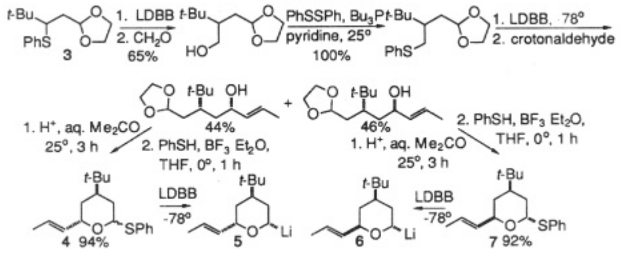
Received November 13, 1991

Summary: The presence of a 4-*tert*-butyl group on 2-lithio-6-(*trans*-1-propenyl)tetrahydropyran dramatically changes the rearrangement behavior, inhibiting the formation of [2,3]-Wittig rearrangement product and leading to a 1,4-transannular H-transfer to the lithium-bearing carbon atom with inversion of configuration.

Scheme I

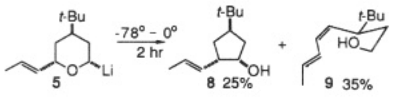


Scheme II



Herein we elucidate the intimate stereochemical course of a rare, if not unique, transannular 1,4-hydrogen transfer that occurs only in the presence of a remote *tert*-butyl group. Recently, we have provided evidence that both the [1,2]- and [2,3]-Wittig rearrangements of **1** occur with inversion of configuration at the lithium-bearing carbon atom by the mechanisms shown in Scheme I.[1] Substrate **1** was generated by reductive lithiation of *trans*-2-(phenylthio)-6-(*trans*-1-propenyl)tetrahydropyran by lithium 4,4′-di-*tert*-butylbiphenylide[2] (LDBB), a reaction the proximate product of which is the other chair conformer of **1** in which the C–Li bond is axial;[3] the rearrangements are believed to require an equatorial C–Li bond which is anti periplanar to the C–O bond that cleaves. The present work was designed to study the rearrangements of **5** and **6** in which stable chair forms containing equatorial C–Li bonds can not be attained.

The syntheses of **5** and **6** are shown in Scheme II.[4,5] Since it has been demonstrated[3] that the proximate product of reductive lithiation of a 2-(phenylthio)tetrahydropyran has an axial C–Li bond, **4** and **7** are expected to yield, respectively, **5** and **6**, the configurations of which were verified by ^1H NMR spectroscopic examination of the products of quenching with CH_3OD.[3,6]



(1)

The results of warming **5** and **6** to 0 °C are shown in eqs 1 and 2.[7] The absence of [2,3]-rearrangement (ring expanded) product from **5** and the trace from **6** are quite significant and in accord with the mechanism in Scheme I. **5** is incapable of attaining a stable conformation (possessing an equatorial *tert*-butyl group) in which C2 and C6 are arranged as in **2**, and only one of the stable boat conformations of **6** (along with the related twist confor-

---

(1) Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.*, in press.

(2) Freeman, P.; Hutchinson, L. *J. Org. Chem.* **1980**, *45*, 1924.

(3) (a) Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130. (b) Lancelin, J.-M.; Morin-Allory, L.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1984**, 355.

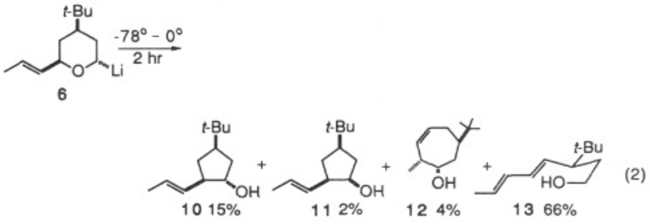
(4) Reductive lithiation of phenyl thioethers as a route to organolithiums: Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152. A general route to homoenolate equivalents (e.g., that from **3**) by this method: Cherkauskas, J. P.; Cohen, T. *J. Org. Chem.*, in press.

(5) Yields reported in this paper are of isolated and purified material.

(6) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.

(7) Other products either remained at the base line during TLC or appeared to be generated during chromatography of the dienes; thus, it is likely that they are polymers or other transformation products of the dienes.

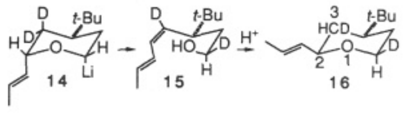
0022-3263/92/1957-1072$03.00/0



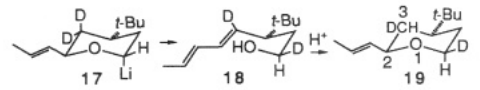
(2)

mations) is capable of attaining the proper orientation for this rearrangement. The [1,2]-rearrangement can proceed from any of the stable boat or twist-boat conformations possessing an equatorial C–Li bond.

A feature of these reactions that differs dramatically from that of **1**,**2** is the stereospecific formation of dienes **9** and **13** as the major products from **5** and **6**, respectively. The course of this elimination was elucidated by allowing the doubly deuterated versions, **14** and **17**, prepared as in Scheme II by using CD_2O, to rearrange to carbinol-labeled dienols **15** and **18**. The configurations of the latter were assigned by performing an acid-catalyzed ring closure to yield isolable quantities of **16** and **19**, which differ from each other only in the configuration of the deuterium atom at the 3-position. In **16** and **19** the anomeric deuterium atom is cis to the *tert*-butyl substituent whereas the lithium atoms in **14** and **17** are trans to this substituent. Thus, the displacement of the Li by H has occurred with inversion of configuration. An alternative possibility, that epimerization[3a] of the lithium-bearing carbon atom occurs prior to H-transfer and that the transfer thus occurs with retention, is untenable since such epimerization in the case of **5** would lead to a species that would undergo a rapid [2,3]-Wittig rearrangement[1] which does not occur to a detectable extent.



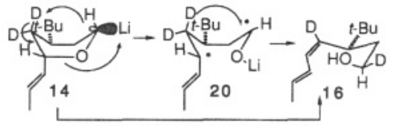
(3)



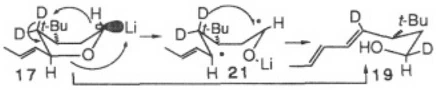
(4)

Such "α',β-eliminations" have been noted previously in α-metallo ethers and they have been studied fairly extensively, although these are the first examples in such cyclic systems.[8] However, none of the previous studies was capable of determining the stereochemistry of displacement of the metal. This inversion of configuration is in sharp contrast to the retention that is observed when Li is exchanged for H during the treatment of α-lithioethers with methanol.[3,6]

Why are these dienes produced only in the presence of the *tert*-butyl group and why is the Li replaced by H with inversion? In the absence of this substituent, the two types of Wittig rearrangement can occur readily after the proximate product of reductive lithiation undergoes a ring inversion to yield the chair conformer bearing the required equatorial C–Li bond. However, in the presence of the *tert*-butyl group the molecule must attain less favorable boat or twist-boat conformations in order for the C–Li bond to become equatorial. Due to the reluctance of the *tert*-butyl group to assume an axial orientation, there is only a limited number of such conformations of **14** and **17**. One such boat conformation of **14** and one of **17**, shown in eqs 5 and 6, are arranged so that C6, which bears the Li, is close to the axial H or D atom on C3. It is readily seen from molecular models that, with a minimum of molecular motion, the axial C3 hydrogen atom can be transferred to the back side of C6. This may be a concerted process, as shown by the arrows in **14** and **17** of eqs 5 and 6, or it may be a 1,4-hydrogen atom transfer proceeding from the diradical (**20** or **21**) which can also be an intermediate[8a] in the 1,2-Wittig rearrangement. Both mechanisms have been suggested for the eliminations accompanying Wittig rearrangements[8] and distinguishing between them is extremely difficult.[9] In the concerted process, as the hydrogen being transferred approaches C2, the bond connecting it to C5 approaches syn periplanarity with the C–O bond that breaks. Such a $({}_\pi 2_s + {}_\sigma 2_a + {}_\sigma 2_a)$ transformation would belong to the same symmetry class as the [2,3]-Wittig rearrangement that occurs in the absence of the *tert*-butyl group.[1] In the diradical mechanism, a 1,4-hydrogen atom transfer is required; these are quite rare, but among the several that are known[10] is an intramolecular quenching of a diradical.[11]



(5)



(6)

At least two questions are raised by this work. 1. Are the purported β-eliminations[8b,12] that occur upon treatment of oxepane and 2-methylated tetrahydrofurans and tetrahydropyrans with strong bases actually instead α-deprotonations followed by α',β-eliminations? If so, contrary to current beliefs, the first step in the reaction of these heterocycles and of tetrahydrofuran[12] with strong base is identical. This would constitute a welcome unification of reaction pathways. 2. Is the inversion that accompanies the replacement of Li by H peculiar to this type of system or would it be found to be common if the stereochemistry of processes such as organolithium-induced eliminations were examined more closely?

Acknowledgment. We thank the National Institutes of Health for financial support. We also thank Steven Norton for helpful suggestions.

Supplementary Material Available: Experimental procedures and spectral data (6 pages). Ordering information is given on any current masthead page.

---

[8] (a) Lansbury, P. T.; Pattison, V. A.; Sidler, J. D.; Bieber, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 78 and references cited therein. (b) Maercker, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 972. (c) Schlosser, M.; Strunk, S. *Tetrahedron* **1989**, *45*, 2649. d'Orchymont, H.; Goeldner, M. P.; Biellmann, J. F. *Tetrahedron Lett.* **1982**, *23*, 1727. Brière, R.; Chérest, M.; Felkin, H.; Frajerman, C. *Tetrahedron Lett.* **1977**, 3489–3492.

[9] Borden, W. T.; Loncharich, R. J.; Houk, K. N. *Ann Rev. Phys. Chem.* **1988**, *39*, 213.

[10] Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; deMayo, P., Ed.; Academic Press: New York, 1980; p 161.

[11] Wagner, P. J.; Chiu, C. *J. Am. Chem. Soc.* **1979**, *101*, 7134.

[12] Bates, R. B.; Kroposki, L. M.; Potter, D. E. *J. Org. Chem.* **1972**, *37*, 560.