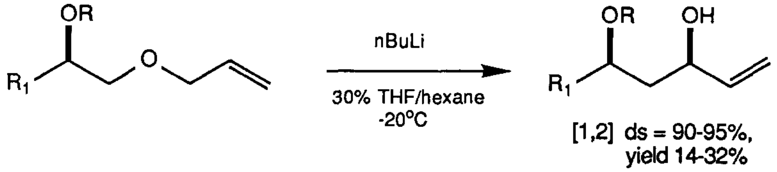
Tetrahedron Letters,Vol.28,No.10,pp 1043-1046,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

STEREOCHEMISTRY OF THE 1,2-WITTIG REARRANGEMENT: A SYNTHESIS OF SYN-1,3-DIOL MONOETHERS

Stuart L. Schreiber and Mark T. Goulet*
Sterling Chemistry Laboratory, Yale University
New Haven, Connecticut 06511

Abstract The [1,2] Wittig rearrangement of β-alkoxyalkyl allyl ethers has been studied and found to provide *syn*-1,3-diol derivatives in 14-32% yield and with useful levels of diastereoselection.

The rearrangement of α-metalated ethers (Wittig rearrangement) has been of interest to investigators since its discovery in 1928, in part due to the mechanistic questions it has provoked.[1] In recent years the [2,3] Wittig rearrangement has proved to be an important synthetic method, allowing for the stereoselective formation of homo-allylic alcohols from the corresponding α-metalated allyl ethers.[2] The [1,2] Wittig rearrangement, in contrast, has not prospered in a similar manner presumably due to the lower yields associated with this reaction.[3] In accordance with the general observations that have been made on this reaction, we have found the [1,2] rearrangement products of *β-alkoxyalkyl allyl ethers* are obtained in ca. 20-30% yield. However, a feature of these reactions that increases their attractiveness concerns the reaction diastereoselectivity: *syn*-1,3-diol derivatives are formed preferentially.[4] Herein, we report on our investigations of this reaction class.



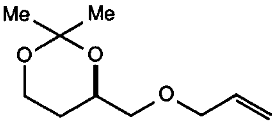
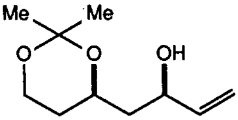
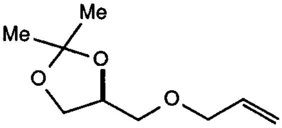
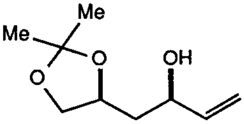
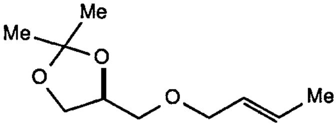
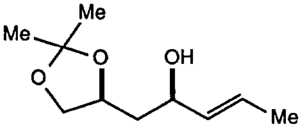
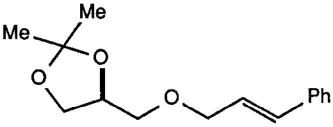
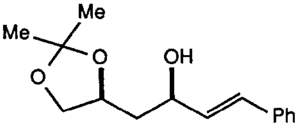
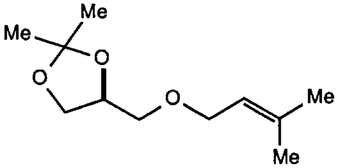
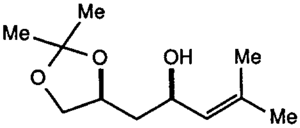
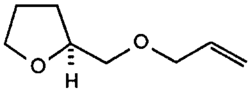
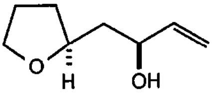
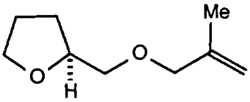
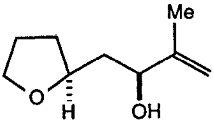
and [1,4] rearrangement product

eq 1

An interest in the synthesis of *syn*-1,3-polyols prompted an investigation into a [1,2] Wittig rearrangement wherein a carbon-carbon bond is constructed concommitant to the formation of a 1,3-diol monoether. For this purpose, the Wittig rearrangement of a variety of β-alkoxyalkyl allyl ethers was conducted as depicted in equation I. Deprotonation of the allyl ether with n-butyllithium in a 30% THF/hexane solution at -20°C resulted in a rapid reaction that provided both the [1,2] and [1,4] rearrangement products.[5] In all cases, the major [1,2] rearrangement product was found to possess a *syn*-relationship of the two secondary alkoxyl substituents (Table 1). The easily separable [1,4] product was found to predominate under these conditions, the extent of its formation being markedly dependent on reaction temperature and solvent polarity. At elevated temperatures (0°C) the [1,2]/[1,4] ratio can increase to as high as 2:1, however, the absolute yield of [1,2] product remains approximately the same.[6]

The determination of *syn* -stereoselectivity was accomplished by synthetic means (Scheme 1). The allyl ether of D-glycerol acetonide **1** was prepared and subjected to the normal rearrangement protocol (entry 2) to provide a 12:1 mixture of diasteromeric products **2**. The identity of the major diasteromer was secured by its conversion to the optically inactive tetraacetate **3a**,[8] a result that is consistent with *syn* -stereoselectivity in the [1,2] Wittig rearrangement reaction. The versatile allylic alcohol **2** was also used in a short synthesis of the 3-deoxypentose D-cordycepose according to the reaction

Table Wittig Rearrangements[a]

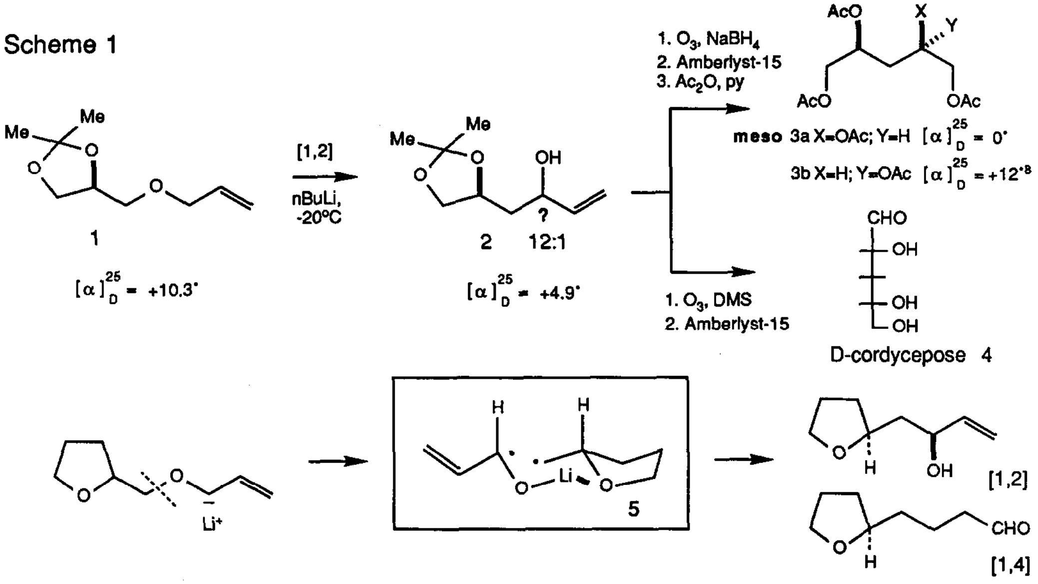
entry	allyl ether[b]	[1,2] product	ratio[c]	yield
1			12:1	32%
2			12:1	32%
3			10:1	30%
4			9:1	25%
5			9:1	14%
6			10:1	30%
7			17:1	28%

---

[a] Reactions were conducted in 30% THF/hexane solutions by addition of 1.5 eq. n-BuLi at -78°C followed by warming to -20°C for 30 min. [b] Ethers were prepared by allylation of the corresponding alcohols. [c] Syn:anti ratios determined by capillary glc analysis.

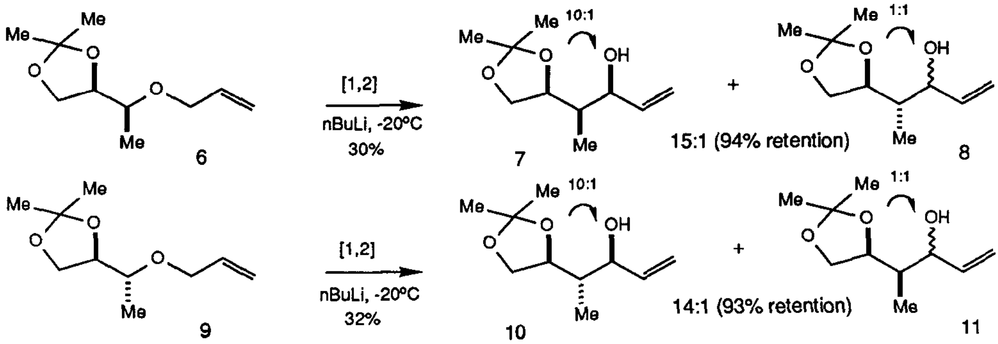
transformations depicted in Scheme 1.[7] The stereochemistry of the remaining products in the Table was assigned by analogy to this precedent, however, other examples of this reaction have been determined to proceed with *syn*-selectivity by unambiguous means (X-ray, synthesis; unpublished results from these laboratories).

Scheme 1



To account for the stereoselectivity of this reaction, we propose the following model based on the radical pair cleavage-recombination mechanism advanced by Lansbury.[9] Deprotonation of the allyl ether results in a lowering of the bond dissociation energy of the adjacent carbon-oxygen bond[10]. Homolytic cleavage, according to the Lansbury mechanism, ensues to provide the radical pair. If the ether oxygen were to coordinate to the lithium counterion of the acrolein ketyl, a complex with a minimum of non-bonded interactions (such as **5**) would be favored. Radical coupling *via* this lithium template would result in the formation of the *syn*-product. A surprising feature of this reaction is the unprecedented degree of retention obtained at the migrating center of secondary alkyl ethers (Scheme 2).[11] The rearrangement of **6** and **9**[12] proceeded with 94% retention (12% racemization) while maintaining *syn* -selectivity in the major product (**7** and **10**,

Scheme 2



respectively). This high degree of retention indicates that the rate of recombination of the radical pair is large relative to that of C_2-C_3 bond rotation. Interestingly, the minor (inverted) products **8** and **11** are formed as a 1:1 diastereomeric mixture which may indicate that their origin is from recombination outside of the primary cage.[13]

In conclusion, the Wittig rearrangement of β-alkoxyalkyl allyl ethers results in the selective formation of *syn*-1,3-diol monoethers. To increase the value of this reaction in synthesis, the discovery of conditions that result in an increase in the yield of 1,2-rearrangement product is required. Further investigations of this reaction and applications to the synthesis of *syn*-1,3-polyols are underway.

Acknowledgements These investigations were supported by the NIH, NSF (Presidential Investigator Award), Alfred P. Sloan Foundation (1985-87), and The Camille and Henry Dreyfus Foundation, Inc. (Teacher/Scholar Award 1984-89) to whom we are grateful. Matching funds for the NSF-PYI Award were generously provided by American Cyanamid, the Upjohn Co., and Pfizer, Inc.

References and Footnotes

1. Wittig rearrangement (a) discovery: Schlenk, W.; Bergmann, E. Liebigs Ann. Chem. **1928**, 464, 22; Wittig, G.; Lohmann, L. ibid. **1942**, 550, 260. (b) for a leading review on this subject see: Schollkopf, U. Angew. Chem. Int. Ed. Engl.**1970**, 9, 763; also Rautenstrauch,V. J. Chem. Soc., Chem. Commun. **1970**, 4; Baldwin, J.E.; Patrick, J.E. J. Am. Chem. Soc. **1971**, 93, 3556; Garst, J.F.; Smith,C.D. J. Am. Chem. Soc. **1976**, 78, 1526; Felkin, H.; Frajerman,C. Tetrahedron Lett. **1977**, 3485; Nakai, T.; Mikami, K. Chem. Rev. **1986**, 86, 885.
2. (a) Schulte-Elte, K.H.; Rautenstrauch, V.; Ohloff, G. Helv. Chim. Acta **1971**, 54, 1805; (b) Cazes, B.; Julia, S. Bull. Soc. Chim. Fr.**1977**, 925.; (c) Wada, M.; Fukui, A.; Nakamura, H.; Takei, H. Chem. Lett. **1977**, 557; (d) Still, W.C.; Mitra, A. J. Am. Chem. Soc. **1978**, 100, 1927; (b) Still, W.C.; McDonald, J.H.; Collum, D.B.; Mitra, A. Tetrahedron Lett. **1979**, 593; (e) Mikami, K.; Kimura, Y; Kishi, N.; Nakai, T. J. Org. Chem. **1983**, 48, 279 and ref. therein. (f) Midland, M.M.; Kwon, Y.C. Tetrahedron Lett. **1985**, 26, 5013 and ref. therein; (g) Mikami, K.; Kishi, N.; Nakai, T.; Fujita, Y. Tetrahedron **1986**, 42, 2911.
3. (a) Rautenstrauch, V.; Buchi, G.; Wuest, H. J. Am. Chem. Soc. **1974**, 96, 2576; (b) Lee, B.H.; Biswas, A.; Miller, M.J. J. Org. Chem. **1986**, 51, 106.
4. For other *syn*-1,3-diol syntheses, see: (a) Narasaka, K.; Pai, H.C. Chem. Lett. **1980**, 1415; (b) Floyd, D.M.; Fritz, A.W. Tetrahedron Lett. **1981**, 22, 2847; (c) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. J. Chem. Soc.Chem. Commun. **1981**, 465; (d) Bartlett, P.A.; Meadows, J.D.; Brown, E.G.; Morimoto, A.; Jernstedt, K.K. J. Org. Chem. **1982**, 47, 4013 and ref. therein; (e) Ma, P.; Martin, V.S.; Masamune, S.; Sharpless, K.B.; Viti, S.M. J. Org. Chem., **1982**, 47, 1378; (f) Nicolaou, K.C.; Uenishi, J. J. Chem. Soc., Chem. Commun. **1982**, 1292; (g) Finan, J.M.; Kishi, Y. Tetrahedron Lett. **1982**, 23, 2719; (h) Stork, G.; Paterson, I.; Lee, F.K.C. J. Am. Chem. Soc. **1982**, 104, 4686; (i) Hirama , M.; Uei, M. Tetrahedron Lett.**1982**, 23, 5307; (j) Nakata, T.; Takao, S.; Fukui, M.; Tanaka, T. Oishi, T. Tetrahedron Lett. **1983**, 23, 3873; (k) Lipshutz, B.H.; Kozlowski, J.A. J. Org. Chem., **1984**, 49, 1147; (l) Kiyooka, S.; Sasaoka, H.; Fujiyama, R.; Heathcock, C.H. Tetrahedron Lett. **1984**, 25, 5331; (m) Kiyooka, S.; Kuroda, H.; Shimasaki, Y. Tetrahedron Lett. **1986**, 27, 3009; (n) Feldman, K.S.; Simpson, R.E.; Parvez, M. J. Am. Chem. Soc. **1986**, 108, 1328. (o) Kathawala, F.G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M.J.; Stabler, R.S.; Widler, L. Helv. Chim. Acta. **1986**, 69, 803. (p) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. J. Am. Chem. Soc.**1986**, 108, 6090.
5. Felkin, H.; Tambute, A. Tetrahedron Lett. **1969**, 821.
6. For a previous observation and explanation of this phenomenon, see: Baldwin, J.E.; DeBernardis, J.; Patrick, J.E. Tetrahedron Lett. **1970**, 353.
7. Kaczka, E.A.; Trenner, N.R.; Ariso, B.; Walker, R.W.; Folkers, K. Biochem. Biophys. Res. Commun. **1964**, 14, 456 for syntheses of cordycepose, see: Hansske, F.; Robins, M.J. Tetrahedron Lett. **1985**, 26, 4295 and ref. therein.
8. Ritchie, R.G.S.; Vyas, D.M.; Szarek, W.A. Can. J. Chem. **1978**, 56, 794.
9. Lansbury, P.T.; Pattison, V.A.; Sidler, J.D.; Bieber, J.B. J. Am. Chem. Soc. **1966**, 88, 78.
10. Evans, D.A.; Baillargeon, D.J. Tetrahedron Lett. **1978**, 3315, 3319.
11. For earlier racemization studies, see: Schollkopf, U.; Schafer, H. Liebigs Ann. Chem.**1963**, 663, 22 and ref. cited therein.
12. Ethers **6** and **9** were synthesized by allylation of the known alcohols, see: Mulzer, J.; Angermann, A. Tetrahedron Lett. **1983**, 24, 2843.
13. The stereochemical outcome of these reactions was determined by comparison of the spectral and chromatographic properties of the products with materials prepared by alternative and unambiguous syntheses.

(Received in USA 2 December 1986)