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On the Stereochemistry of Vicinal Nucleophilic Substitution of β-(Phosphatoxy)alkyl Radicals

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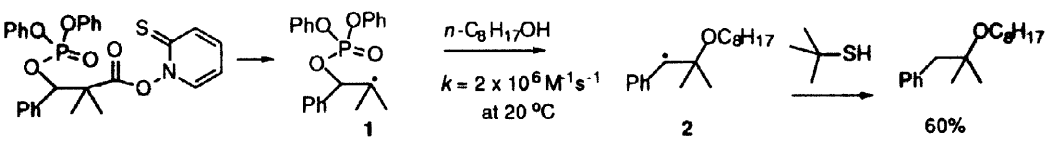
Abstract. It is demonstrated by means of diastereomeric probes that the vicinal nucleophilic displacement of a diethylphosphate group from a β-(phosphatoxy)alkyl radical may take place by backside or frontside attack depending on steric constraints

Keywords: Radicals and radical reactions; phosphoric acid and derivatives; stereoselection

In recent years, and contrary to popular opinion, it has become obvious that derived β-hydroxyalkyl radicals, such as the β-(phosphatoxy)alkyl and β-(acyloxy)alkyl radicals have a rich and increasingly varied chemistry.[1] Rate constants for the rearrangement of such radicals can, depending on the substituent pattern, range as high as 1 x 10^7 s^{-1} at 80 °C[2,3] which is more than competitive with the type of 5-hexenyl radical rearrangement frequently encountered in synthetic schemes. Arguably, the best synthesis of 2-deoxy sugars has a β-(acyloxy)alkyl migration as its key step.[4] Recently, we described the first example of a new reaction type, the bimolecular, vicinal substitution of a β-(phosphatoxy)alkyl radical (**1**) by an alcohol giving a transposed β-(alkoxy)alkyl radical (**2**) (Scheme 1).[5] Here, we describe the results of a preliminary investigation into the stereochemistry of this intriguing process.



1 2

Scheme 1

Although, to our knowledge, the example described in Scheme 1 represents the first actual example of this reaction type we note that Zipse, in putting forward his methylenology principle, had predicted the existence of the general class.[6-8] Calculations were conducted by Zipse on the vicinal substitution of the β-chloroethyl radical by chloride anion and predicted a transition state (Fig. 1) resulting from backside attack.[6,7]

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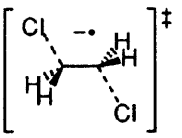
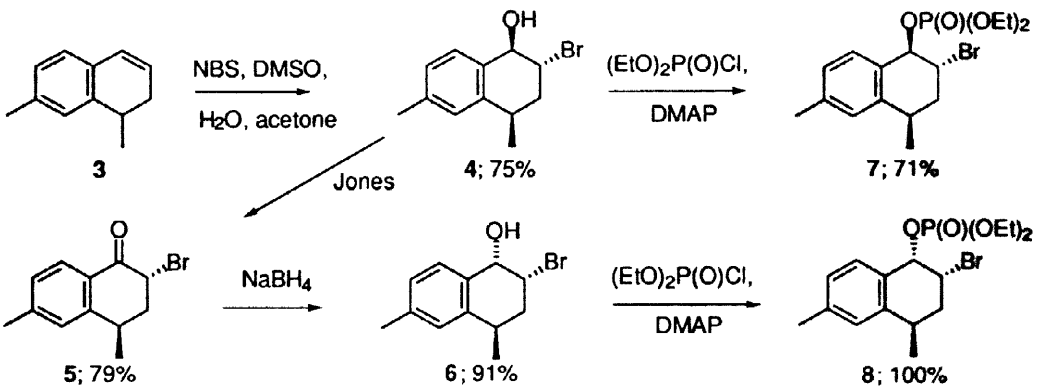


Fig. 1

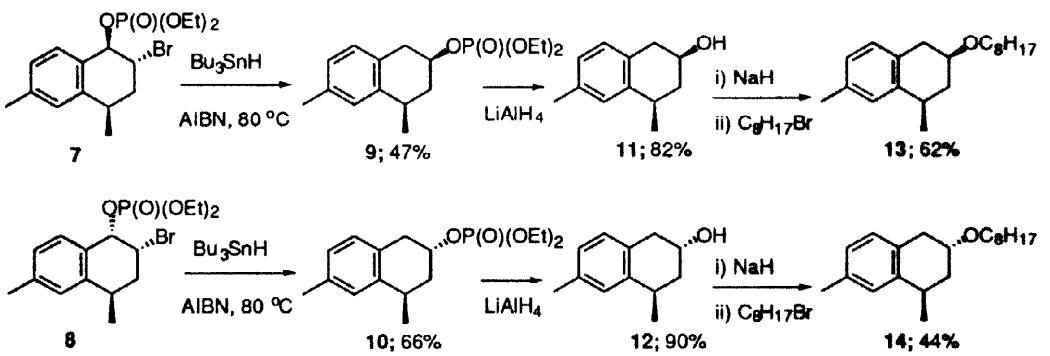
The methylenology principle states that this type of substitution process is the one electron equivalent of the two electron allylic substitution (S_N2') reaction which, for heteroatom nucleophiles but not cuprates, usually occurs preferentially in syn-facial manner.[9] A knowledge of the true stereochemistry of this new reaction type is therefore of interest for numerous reasons pertaining to the mechanism of the reaction and its potential for eventual use in stereoselective processes.

Two diastereomeric bromophosphates **7** and **8** were prepared, as outlined in Scheme 2, from the dihydronaphthalene **3**, which itself was readily available by reduction and dehydration of 4,6-dimethyltetralone.



Scheme 2

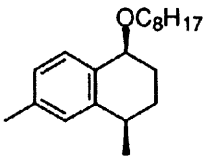
Treatment of **7** and **8** with Bu_3SnH and catalytic AIBN in benzene at reflux provided, stereospecifically, the rearranged products **9** and **10**, respectively, which were converted to the octyl ethers **13** and **14**, respectively, as indicated in Scheme 3.



Scheme 3

Dropwise addition of Bu_3SnH and AIBN to a solution of **7** (0.1 M) in 43:57 benzene/octanol at 80 °C resulted in the formation of the rearrangement product **9**, and the substitution products **13-15** in the ratios

indicated, as determined by GC (Table 1). The comparable reaction of diastereomer **8** with Bu_3SnH in benzene/octanol gave only three products (Table 1) resulting from rearrangement (**10**) and vicinal substitution (**13** and **14**) (Table 1).



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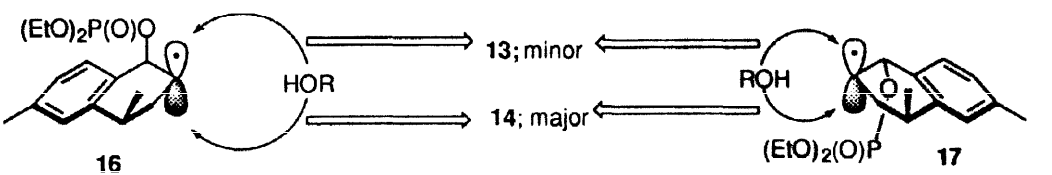
An authentic sample of the benzyl ether **15**, of which only a single diastereomer was identified, was prepared by Bu_3SnH reduction of **4** followed by etherification with NaH and octyl bromide. That **15** was only formed from diastereomer **7** suggests that it arose not from a radical process but rather by competing collapse of the *trans*-bromophosphate **7** to a cyclic bromonium ion with subsequent opening by octanol and eventual debromination with Bu_3SnH. Indeed, this was subsequently confirmed by the obvious control experiments.

Table 1. Reactions of Bromophosphates with Bu_3SnH and Octanol[10]

Substrate	Products (Ratio)	Ratio **13**:**14**
7	**9**:**13**:**14**:**15** (14:6:10:70)	0.6
8	**10**:**13**:**14** (40:11:49)	0.22

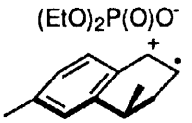
It is readily apparent from Table 1 that the methyl group used as a stereochemical marker influences the outcome of the reactions. Thus, with both **7** and **8** the preponderence of the substitution occurs anti to the methyl group. However, it is also clear from the ratios of **13**:**14** that the extent of the influence of the marker is different in the two cases, from which we conclude that a common intermediate, i.e. a diffusively free radical cation arising from elimination of phosphate from the initial radicals, is not involved. The results may be explained by a mechanism involving attack of the alcohol on either lobe of the singly occupied orbital in the diastereomeric radicals **16** and **17** (Scheme 4) with the methyl group more effectively shielding one face in the latter stereoisomer. This type of bimolecular transition state is in accord with the kinetics of the example of Scheme 1.



Scheme 4

Unfortunately, it is not possible at this stage to conclusively exclude a mechanism based on nucleophilic attack on tight, caged ion pairs such as **18** and **19**. Whatever the precise details of the mechanism,

it is already apparent that this type of vicinal nucleophilic substitution of β-(phosphatoxy)alkyl and related radicals is not restricted to backside attack.



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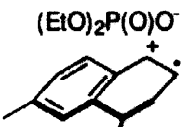

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Further work on the stereochemistry and mechanism of this novel reaction type will be described in due course.

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References

1. Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. *Chem. Rev.* **1997**, *97*, 3273-3312.
2. Crich, D.; Jiao, X.-Y. *J. Am. Chem. Soc.* **1996**, *118*, 6666-6670.
3. Choi, S.-Y.; Crich, D.; Horner, J. H.; Huang, X.; Newcomb, M.; Whitted, P. O. *Tetrahedron* **1998**, *54*, in press.
4. Giese, B.; Groninger, K. S. *Org. Synth Coll . Vol.* **1993**, *VIII*, 583-586.
5. Choi, S.-Y.; Crich, D.; Horner, J. H.; Huang, X.; Martinez, F. N.; Newcomb, M.; Wink, D. J.; Yao, Q. *J. Am. Chem. Soc.* **1998**, *120*, 211-212.
6. Zipse, H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2691-2697.
7. Zipse, H. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1985-1988.
8. Zipse[6,7] has called this type of reaction $S_{RN}2'$.
9. Magid, R. M. *Tetrahedron* **1980**, *36*, 1901-1930.
10. Both reactions gave reproducible results to within a few percent over the course of several runs.