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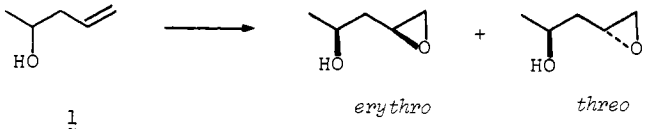
"Phosphate Extension". A Strategem for the Stereoselective Functionalization of Acyclic Homoallylic Alcohols

Sir:

Configurational control in the introduction of chiral centers is one of the paramount considerations in the design of a natural product synthesis. While chemists have developed many versatile methods for the stereocontrolled synthesis of rigid or conformationally well-defined molecules, stereochemical control in the elaboration of acyclic or conformationally heterogeneous systems remains an elusive goal. Attention is now being directed toward the synthesis of compounds, such as the macrocyclic natural products, whose construction will require such methodology, and the need for appropriate stereoselective transformations is becoming increasingly important.[1]

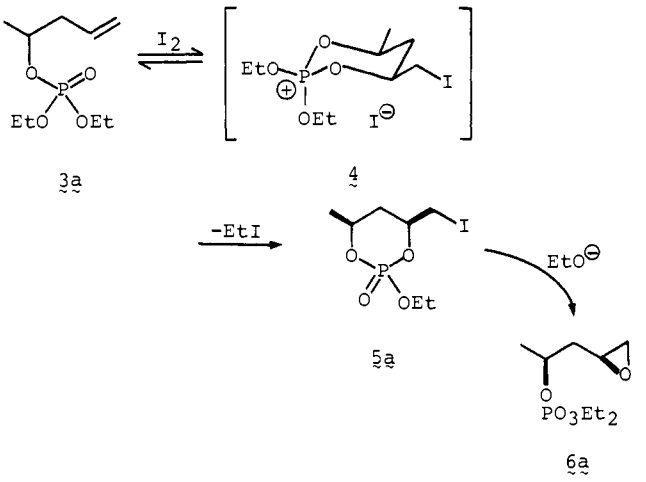
In spite of considerable work in this area,[2] reactions which exhibit high 1,2- or 1,3-asymmetric induction in the generation of chiral centers in acyclic systems are relatively rare. Among the more consistently successful in this regard are reactions of chiral alcohols and amines in which the heteroatom is intimately involved in the transition state, either by coordinating and directing the incoming reagent or by stabilizing a particular conformation of the substrate.[2b,c,3] For example, both epoxidation of allylic alcohols[3] and the addition of organometallic reagents to α-hydroxy or α-amino ketones[2b] proceed with high stereoselectivity in many acyclic cases.

Stereocontrolled epoxidation[4] of a double bond promises to be a useful transformation in the construction of conformationally mobile systems,[5] because it generates one or two asymmetric centers and facilitates further stereospecific carbon–carbon bond-forming reactions. We have investigated a variety of methods for effecting 1,3-asymmetric induction in the epoxidation of homoallylic alcohols, and initially focused our attention on 4-penten-2-ol (**1**).[6] In view of the simplicity of the structure and the distance of the chiral center from the double bond, it is not surprising that only low asymmetric induction is observed in the direct epoxidation of **1** (reagent, conditions, ratio of **2e**/**2t**):[7] *m*-chloroperbenzoic acid, chloroform at 25 °C, 1.2; *t*-BuOOH–$VO(acac)_2$, benzene at 25 °C, 2.0; *t*-BuOOH–$Mo(CO)_6$, benzene at reflux, 0.8. Although the vanadium and molybdenum catalysts show opposite selectivities, the diastereomer ratios clearly are not synthetically useful.

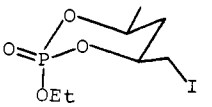


1 2e 2t

Williams and co-workers have shown that the rate of attack of electrophilic halogen species on a double bond is significantly increased by concomitant attack by an appropriately positioned nucleophile.[9] We sought to extend the nucleophilic character of the hydroxyl group of 4-penten-2-ol so that it could assist electrophilic attack on the double bond and involve the chiral center in a more predictable fashion.[10] To this end, we prepared the diethyl phosphate **3a** and studied its reaction with iodine. We felt that formation of the cyclic tetraalkoxyphosphonium ion (**4**), by addition of iodine and the phosphoryl oxygen to the double bond, would be readily reversible and would heavily favor the cis diastereomer. Dealkylation of this intermediate would then furnish a cyclic phosphate (**5a**) which would be amenable to further transformation.



Treatment of the homoallylic phosphate **3a** with 2.2 equiv of iodine in acetonitrile at 25 °C for 2 days affords an 87% yield of the desired cyclic phosphate **5a,** which is predominantly (>90%) one isomer by VPC and by ^{13}C NMR. The long-range couplings of 2.0 and 2.3 Hz between phosphorus and the iodomethyl and methyl protons,[11] respectively, and an IR absorption of 1305 cm^{-1} for the P→O group[12] indicate that it is the anticipated most stable isomer **7a.** This compound rapidly reverts to acyclic olefinic material on treatment with bromotrimethylsilane in chloroform,[13] which is consistent with our prediction of ready reversibility in the formation of **4.** At present it is not clear whether the high selectivity for the axial ethoxy configuration results from selective dealkylation of **4** or from subsequent equilibration of **5a** by adventitiously produced hydrogen iodine. Treatment of the cyclic phosphate mixture (**5a**) with 1 equiv of sodium ethoxide in tetrahydrofuran at 0 °C gives the dialkyl phosphate of the erythro epoxide (**6a**) in 75% yield, contaminated with <2% isomeric material by ^{13}C NMR analysis. The cyclic phosphates **5a** must therefore be epimeric at phosphorus, because only this chiral center is lost on conversion to the epoxide.

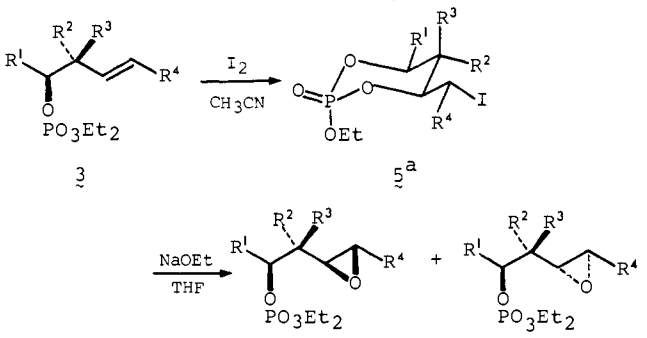


7a

We have explored the generality of this strategy with a variety of acyclic homoallylic alcohols, as shown in Table I. Of particular interest are the results obtained with the diastereomeric 3-methyl-4-penten-2-ol derivatives **3c** and **3d,**[14] which demonstrate that 1,3-asymmetric induction takes precedence over the 1,2 effect. Although the acyclic methyl is forced into an axial position in **5d,** the stereoselectivity in the epoxidation of **3d** is still exceptionally high for 1,3-asymmetric induction.[2] Stereochemical control by the asymmetric carbon more remote from the site of reaction thus appears to be a useful aspect of this strategy.

The introduction of two chiral centers by epoxidation of a disubstituted olefin was studied with the diethylphosphate of *trans*-5-hepten-3-ol (**3e**). While the stereoselectivity of the epoxidation sequence is still excellent, the iodocyclization of this material has proceeded only in low yield so far. The cy-

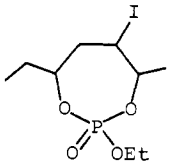
Table I. Epoxidation of Homoallylic Phosphates

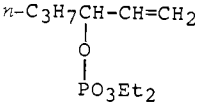


Series	Substituents	% yield of 7[b]	% yield of 6 + 8[c]	Ratio, 6/8[d]
a	$R^1 = CH_3$; $R^2 = R^3 = R^4 = H$	87	75	>98:2
b	$R^1 = n\text{-}C_3H_7$; $R^2 = R^3 = R^4 = H$	85	75	>98:2
c	$R^1 = R^2 = CH_3$; $R^3 = R^4 = H$	80	72	95:5
d	$R^1 = R^3 = CH_3$; $R^2 = R^4 = H$	76	82	80:20
e	$R^1 = C_2H_5$; $R^2 = R^3 = H$; $R^4 = CH_3$	30	77	95:5

[a] Only the major isomer is depicted. [b] 2.2 equiv of I_2 in CH_3CN, 25 °C. [c] 1 equiv of NaOEt in THF, 0 °C. [d] Determined by ^{13}C NMR.

clization is still under investigation; however, preliminary evidence indicates that the seven-membered 1,3,2-dioxaphosphepane (**9**), a conceivable by-product,[10a,15] is not formed. An attempt to apply this strategy to epoxidation of the allylic phosphate **10** was not successful; treatment of this material with iodine in a variety of solvents failed to give any characterizable cyclic product.





Intramolecular participation of an appropriately placed nucleophile promises to be a useful strategy in the stereocontrolled synthesis of acyclic systems, because it is an effective way to reduce the conformational mobility and to increase the free-energy difference of diastereomeric transition states. In this overall epoxidation sequence, the phosphoryl group serves two purposes: it extends the nucleophilic character of the hydroxyl group in a useful manner and it is a bulky, achiral unit which maximizes the steric constraints on the cyclic intermediate. As a result, this derivative of the homoallylic alcohols can be epoxidized with 1,3-asymmetric induction with selectivities which are unprecedented for such acyclic substrates.

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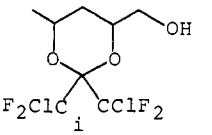

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(15) Satisfactory analytical and spectral characterization was obtained for all new compounds.

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Trialkylammonium-2,2,3,3,4,4-hexafluorocyclobutane Ylides.[1] Preparation and Isolation of an Unusually Stable Fluorinated Carbanion

Sir:

The first reported example of a stable polyhalogenated phosphonium ylide was 2,2,3,3,4,4-hexafluoro(triphenylphosphoranylidene)cyclobutane (**I**), which was obtained from the reaction of hexafluorocyclobutene (**II**) with triphenylphosphine.[2,3] Ylide (**I**) is a rare example of an isolable fluorinated carbanion. The remarkable stability of **I** was attributed to the overlap of the phosphorus d orbitals with the ylide carbon p orbitals and the strong inductive effect of the adjacent difluoromethylene groups.[6] However, in this case it was difficult to assess the relative importance of the inductive effect of the