Table I. Stability Constants, Log K_S (±0.2), for Anion Binding by the Polyammonium Macrocycles 1-6H$^+$, 2-8H$^+$, and 3-6H$^+$ in Aqueous Solution[14]

anion	macrocyclic ligand[a] 1-6H$^+$	2-8H$^+$	3-6H$^+$
sulfate^{2-}	4.0	4.0	4.5
oxalate^{2-}	3.8	3.7	4.7
malonate^{2-}	3.3	3.9	3.8
succinate^{2-}	2.4	3.6	2.8
tartrate^{2-}	2.5		2.9
maleate^{2-}	3.7	4.1	4.0
fumarate^{2-}	2.2	2.9	2.6
squarate^{2-}	3.2	3.6	3.4
citrate^{3-}	4.7	7.6	5.8
1,3,5-benzenetricarboxylate^{3-}	3.5	6.1	3.8
$Co(CN)_6^{3-}$	3.9	6.0	3.3
$Fe(CN)_6^{4-}$	6.9	8.9	6.3
AMP^{2-}	3.4	4.1 (7.2)[b]	4.7
ADP^{3-}	6.5	7.5 (10.2)[b]	7.7
ATP^{4-}	8.9	8.5 (12.8)[b]	9.1

[a] The following pK_a values (±0.1) were determined for the three ligands: 10.45, 10.35, 9.05, 7.90, 7.15, 6.60 for 1; 10.70, 10.45, 9.65, 9.00, 8.05, 7.50, 6.95, 6.45 for 2; 9.65, 9.15, 8.45, 6.80, 5.80, 5.70 for 3; aqueous solution, 0.1 M NMe_4Cl. [b] Log K_S values calculated for formation of 1/2 ligand/substrate complexes (see text).

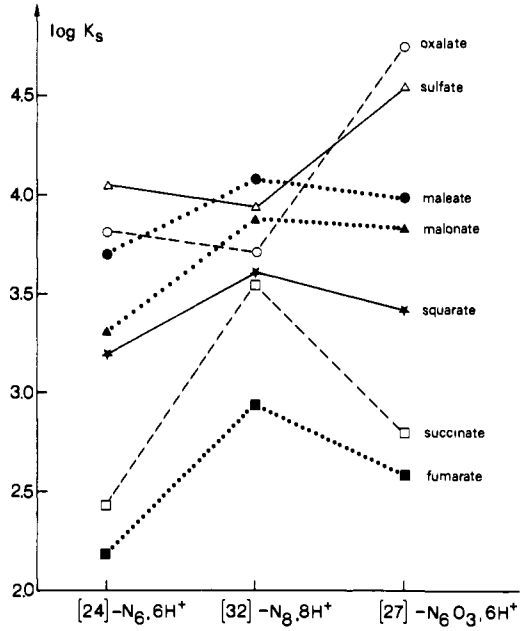


Figure 1. Graphical representation of the stability constants (log K_s) of the complexes formed by the polyammonium macrocycles 1-6H$^+$, 2-8H$^+$, and 3-6H$^+$ with various molecular anions (see also Table I).

(3) The complexation of AMP, ADP, and ATP has also been studied by following the changes in ^{31}P NMR chemical shifts on addition of ligand to a solution of substrate anion at pH 6.5. The smaller macrocycle ([24]N_6, 6H$^+$) forms a 1/1 complex with ATP, whereas for ADP both 1/1 and 1/2 species are detected. The larger ring system ([32]N_8, 8H$^+$) binds two substrate molecules in all three cases.

(4) *Electrostatic interactions* play a major role in both strength and selectivity of anion binding. Thus, for a given receptor molecule, the anions most strongly complexed are usually the smallest and most highly charged ones, i.e., those of highest charge density (see for instance the sequence oxalate > malonate > succinate and maleate > fumarate).

(5) *Structural effects* are observed in the trends represented in Figure 1. The larger dianions, like squarate, fumarate, and especially succinate, form more stable complexes with the larger [32] macrocycle, 2-8H$^+$, than with the [24] macrocycle, 1-6H$^+$; this is not the case for the smaller sulfate and oxalate anions. Ligand 3-6H$^+$ binds sulfate and oxalate more strongly than the smaller cycle 1-6H$^+$ of same charge; this may be due to a higher local charge density in an ethylenediammonium group than in a propylenediammonium group. Large polyanions like citrate, 1,3,5-benzenetricarboxylate, $Co(CN)_6^{3-}$, and $Fe(CN)_6^{4-}$, form very strong complexes with the large and highly charged 2-8H$^+$ receptor.

(6) In terms of *structural complementarity* between the anionic substrate and the macrocyclic receptor, 1-6H$^+$ and 3-6H$^+$ correspond to substrates of threefold symmetry and 2-8H$^+$ to substrates of fourfold symmetry. Molecular models show that indeed planar XO_3^{n-} or tetrahedral XO_4^{n-} anions fit well into the cavity of 1-6H$^+$, forming hydrogen bonds with all six ammonium sites. On the other hand, squarate dianion and the square-planar structural fragment in the equatorial plane of the octahedral $M(CN)_6^{n-}$ complex anions fit into the 2-8H$^+$ macrocycle in an eightfold hydrogen-bonding pattern.[15] This apparently agrees with the particularly high stabilities displayed by $Co(CN)_6^{3-}$ and $Fe(CN)_6^{4-}$ with 2-8H$^+$.

(7) The binding of anions like $Fe(CN)_6^{4-}$, $Co(CN)_6^{3-}$, or other complex anions of transition metals yield species which may be considered as *complexes of complexes*: the central cation is complexed by cyanide anions and the resulting species is in turn bound by the polyammonium macrocycle.[16] Such complexation may permit regulation of the physical properties of the substrate. Indeed, electrochemical measurements show that $Fe(CN)_6^{4-}$ forms 1/1 complexes with 1-6H$^+$ and 2-8H$^+$, resulting in a strong shift of its redox potential toward more positive values.[18]

In conclusion, the macrocyclic polyammonium cations 1-6H$^+$, 2-8H$^+$, and 3-6H$^+$ are *anion receptor molecules* forming strong and selective complexes with a variety of molecular anions. Since the selectivity of complexation depends both on electrostatic and structural effects, modification of size and shape of the macrocyclic system should allow controlling the selectivity sequence. More accurate structural control should be achievable in macropolycyclic systems which may be expected to yield even stronger and more selective complexes (see for instance ref 4). The selective complexation of biologically important anions (like AMP, ADP, ATP, citrate, and other carboxylates) is of particular interest, especially if, by attachment of hydrocarbon chains, the ligands are converted into selective *anion carriers*. Binding of anionic functional groups may result in *catalysis*. Finally, applications in the areas of analytical chemistry (for instance anion selective electrodes) and separation science may be envisaged. Various extensions of the present work along these lines are being studied.[19]

(15) It has not yet been possible to produce crystals suitable for X-ray structure determination. A crystalline complex of 2-8H$^+$ with $Pt(CN)_4^{2-}$ having the composition 2-8H$^+$/4 $Pt(CN)_4^{2-}$ has been isolated.

(16) Complexation of anionic clusters may also be envisaged. Conversely, the binding of cationic transition-metal complexes to a hexacarboxylate macrocyclic polyether[17] has been detected: Vierling, P., unpublished observations.

(17) Lehn, J. M.; Vierling, P.; Hayward, R. C. *J. Chem. Soc., Chem. Commun.* **1979**, 296–298.

(18) Peter, F.; Gross, M., unpublished results.

(19) The macrocyclic polyamines 1, 2, and 3 also form complexes with transition-metal cations (work in progress).

A Highly Stereoselective Synthesis of Trans Epoxides via Arsonium Ylides[1]

W. Clark Still* and Vance J. Novack

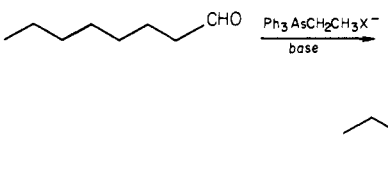
Department of Chemistry, Columbia University
New York, New York 10027

Received December 22, 1980

We wish to report a useful new method for the direct epoxidation of carbonyl compounds. The procedure involves the

0002-7863/81/1503-1283$01.25/0

Table I

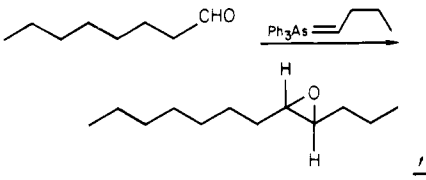


base	solvent	X^-	trans:cis[8] (yield)[9]
$KN(Me_3Si)_2$	THF + 10% HMPA	BF_4^-	100:1 (80%)
$KN(Me_3Si)_2$	THF	BF_4^-	33:1 (73%)
BuLi	THF + 10% HMPA	BF_4^-	3:1 (62%)
$KN(Me_3Si)_2$	THF + 10% HMPA	I^-	12:1 (74%)
BuLi	THF + 10% HMPA	I^-	<10:1 (53%)

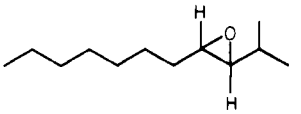
reaction of an unstabilized[2] arsonium ylide with an aldehyde or ketone to perform an operation which is mechanistically analogous to the well-known sulfur ylide[3] epoxidations. Unlike previous methods, however, the arsonium ylide route from aldehydes to epoxides proceeds with a high degree of stereochemical control. In this regard, the epoxidation described here is closely related to the isostructural Wittig reaction, since both reactions display almost identical diastereoselection for the erythro betaine-like product.[4] Thus most aldehydes react cleanly with arsonium ylides to yield trans epoxides with stereoselectivity ≥50:1.

The reaction of triphenylarsonium ethylide with octanal to produce largely (*E*)-2-decene oxide is representative of the type of transformation we have studied most thoroughly. The orange ylide is best prepared by deprotonation of the ethyltriphenylarsonium fluoroborate[5] (1.4 equiv) with 0.5 M $KN(Me_3Si)_2$ (1.2 equiv) in 10% HMPA–THF at −40 °C (10 min).[6] On chilling the mixture to −78 °C, the aldehyde (1.0 equiv) is added and the reaction mixture is allowed to warm slowly to room temperature. Aqueous workup and chromatography[7] give the product. In the case of octanal, the isolated yield of pure epoxide is 80% and the stereochemistry (capillary VPC) is 99% trans. Other conditions were less effective, as seen in Table I. It is interesting that optimum selection for the trans product is observed under the same "salt-free" conditions used to give cis olefination in the Wittig reaction.[10] The dependence of stereochemistry on the arsonium salt counterion is particularly striking. Whether this effect is a reflection of the low solubility of KBF_4 in THF (20 mg/L at 25 °C) relative to KI (120 mg/L) or is due to some more specific effect associated with the anion is not clear at this time.

A survey of variously substituted ylides and carbonyl compounds shows that the scope of the reaction is quite broad and that high stereoselection for the trans epoxide is always observed under the standard conditions described above. Thus the ylide may be elaborated by one or two additional substituents. The aldehyde

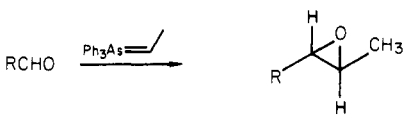


98% *E* (76%)

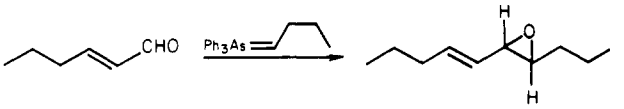


>99% *E* (72%)

may be further substituted or may be α,β unsaturated. Aromatic aldehydes, however, give relatively poor results. Finally, simple

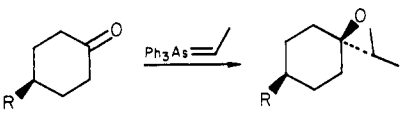


R = cyclohexyl, >99% *E* (84%)
R = phenyl, 83% *E* (61%)



98% *E*[11] (75%)

ketones give acceptable yields of trisubstituted epoxides.



R = H (78%)
R = *t*-Bu (66%)[12]

Toxicity considerations aside,[13] the method has the minor drawback that triphenylarsine is less nucleophilic than the corresponding phosphine, and thus simple nucleophilic substitution of alkyl halides does not provide a general route to arsonium salts. While ethyltriphenylarsonium fluoroborate is prepared simply from triphenylarsine and triethyloxonium fluoroborate,[5] more complex salts require two- or three-step preparations. Primary salts without

(1) This work was described at the Gordon Research Conference on Natural Products in New Hampton, NH, July 25, 1980.

(2) Although semistabilized (e.g., benzylic), arsonium ylides have been noted previously to react with carbonyl compounds to give olefins or epoxides depending on the system and the reaction medium; unstabilized arsonium ylides have received relatively little investigation. M. C. Henry and G. Wittig, *J. Am. Chem. Soc.*, **82**, 563 (1960); A. W. Johnson, "Ylide Chemistry", Academic Press, New York, 1966, pp 288–299; S. Trippett and M. A. Walker, *J. Chem. Soc.* C, 1114 (1971); P. S. Kendurkar and R. S. Tewari, *J. Organomet. Chem.*, **60**, 247 (1973); **85**, 173 (1975); N. Kumari, P. S. Kendurkar, and R. S. Tewari, *ibid.*, **108**, 175 (1976); R. S. Tewari and S. C. Chaturvedi, *Tetrahedron Lett.*, 3843 (1977); I. Gosney, T. J. Lillie, and D. Loyd, *Angew. Chem., Int. Ed. Engl.*, **16**, 487 (1977); D. G. Allen, N. K. Roberts, and S. B. Wild, *J. Chem. Soc., Chem. Commun.*, 364 (1978).

(3) Review: B. M. Trost, "Sulfur Ylides: Emerging Synthetic Intermediates", Academic Press, New York, 1975.

(4) For a recent review of the Wittig reaction, see I. Gosney and A. G. Rowley in "Organophosphorus Reagents in Organic Synthesis", J. I. G. Cadogan, Ed., Academic Press, New York, 1979, pp 17–153.

(5) M. C. Henry and G. Wittig, *J. Am. Chem. Soc.*, **82**, 563 (1960).

(6) Above −20 °C ylide decomposition yielding triphenylarsine becomes rapid. The *tert*-butyldiphenyl ylides described later in this paper appear even more disposed to decomposition and must be prepared at −78 °C [0.5 M $KN(Me_3Si)_2$, 5 min).

(7) Simple flash chromotography [W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978)] allows easy recovery of triphenylarsine during isolation of the epoxide.

(8) All stereoisomer ratios were determined by digitally integrated capillary VPC (25-∞m Carbowax 20 M) with conformation by ^1H NMR. Authentic samples of the cis and trans epoxides were prepared by peracid epoxidations (MCPBA, CH_2Cl_2) of the corresponding cis and trans olefins.

(9) All yields are based on carbonyl compounds and refer to pure epoxides isolated by chromatography.

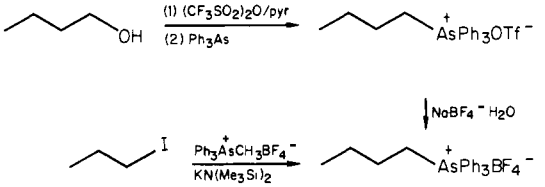
(10) For a related study of conditions for the Wittig reaction, see C. Sreekumar, K. P. Darst, and W. C. Still, *J. Org. Chem.*, **45**, 4260 (1980).

(11) Authentic materials for comparison were not prepared in this reaction. The structure assignment follows from a 2-Hz ^1H NMR coupling constant across the epoxide [^1H NMR (CCl_4) δ 5.70 (1 H, dt, J = 6, 16 Hz), 5.03 (1 H, br dd, J = 8, 16 Hz), 2.80 (1 H, dd, J = 2, 8 Hz), 2.54 (1 H, m), 1.96 (2 H, br q, J = 7 Hz), 1.40 (6 H, br m), 0.88 (6 H, br t, J = 7 Hz)]. This trans epoxide was the only isomer detectable by ^1H NMR spectroscopy. Capillary VPC analysis (25-m Carbowax 20 M) showed the major product to be in excess of any other to the extent of at least 40:1.

(12) In the case of 4-*tert*-butylcyclohexanone, the ylide added equatorially to the extent of >100:1 (capillary VPC analysis with standardization by authentic materials).

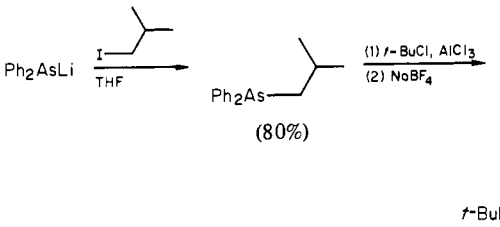
(13) The arsenic compounds described here should be handled with caution. Although triphenylarsine has been used for years as a ligand by inorganic chemists and seems to have only moderate acute toxicity, repeated exposure should be avoided by working with care in an efficient hood. Since the compounds described in this paper are largely nonvolatile, actual danger is minimal. Toxicity data on inorganic arsenic compounds includes an acute LD_{50} for As_2O_3 of 45 mg/kg. Volatile arsenic compounds like AsH_3 are more of a problem and exposure by inhalation to levels of 0.5 ppm is considered to be dangerous.

α branching turn out to be readily accessible by nucleophilic substitution of an alkyl triflate (CH_2Cl_2, 25 °C, 2–3 days) followed by fluoroborate exchange (100 equiv $NaBF_4/H_2O$ and extraction into CH_2Cl_2) or alkylation of an arsonium methylide (THF, −78–0 °C). Salts having α branches cannot be efficiently prepared by



mp 138–141 °C (87%)

using either of the two methods above due to competitive rearrangement or elimination. For these systems, highly nucleophilic lithiodiphenylarsine (from Ph_3As and Li/THF)[14] is reacted with the appropriate primary iodide (THF, −78 °C) and the resulting diphenylarsine is quaternized (*t*-BuCl, CH_2Cl_2, $AlCl_3$, or Et_2AlCl; 25 °C) and fluoroborate exchanged ($NaBF_4/H_2O$).



mp 135–138 °C (72%)

These sequences are of considerable generality and proceed in good overall yield to produce the required arsonium tetrafluoroborates as stable, crystalline products. Experimental details are available as supplementary material.

Due to the unique capacity of unstabilized arsonium ylides to react with aldehydes to yield trans epoxides cleanly, it is expected that the above described reaction will find considerable application to the synthesis of acyclic molecules having adjacent chiral centers. Furthermore, we believe that the synthetic chemistry of the ylides will prove at least as rich as that associated with phosphorus ylides. Further work in this area will be reported in due course.[15]

Supplementary Material Available: Experimental details (6 pages). Ordering information is given on any current masthead page.

(14) A. M. Aguviar and T. G. Archibald, *J. Org. Chem.*, **32**, 2627 (1967); P. W. Clark, *Org. Prep. Proced. Int.*, **11**, 103 (1979).

(15) This work was supported by grants from NSF (CHE7801769) and NIH (R01 HL25634).

On the Nonconcertedness of Allylic Cation Promoted π-Cyclization Reactions[1]

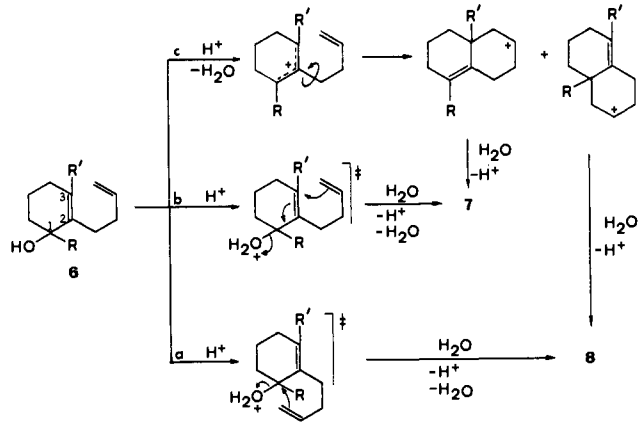
Mladen Ladika,† Ivo Bregovec, and Dionis E. Sunko*

Department of Chemistry
Faculty of Natural Sciences and Mathematics
University of Zagreb, 41000 Zagreb
Croatia, Yugoslavia

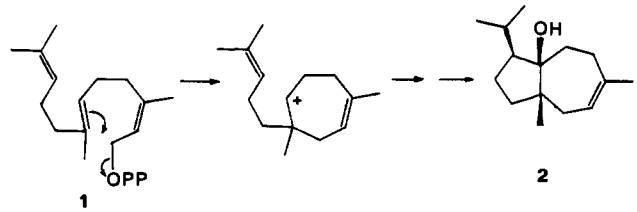
Received July 15, 1980

Allylic cations play a significant role in a number of biochemically important cyclization and condensation reactions. Thus, the biosynthesis of carotal (**2**) is thought to involve an anti-

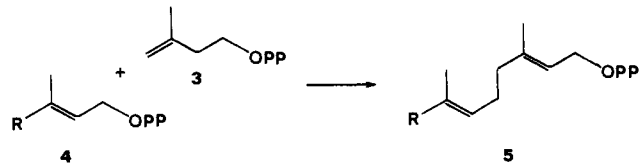
Scheme I



Markovnikov cyclization of the central double bond of *cis,trans*-farnesyl pyrophosphate[2] (**1**).



The prenyl transferase catalyzed 1′,4 coupling reaction between isopentenyl pyrophosphate (**3**) and an allylic pyrophosphate (**4**) is also known to include cationic intermediates.[3]



Recent synthetic applications of biomimetic polyene cyclizations[4] sustained the interest in the elucidation of mechanistic details in these reactions.[5] The important question regarding the stepwise or concerted nature of cation-induced cyclizations still remains to be answered.[4,6]

Poulter et al.[7] presented compelling evidence that reaction **3** + **4** → **5** proceeds by an ionization–condensation–elimination mechanism, but it is not at all certain that this mechanism also applies to cases such as **1** → **2** where the allylic moiety and the double bond are parts of the same molecule.[8] Here the remote double bond could directly assist the departure of the leaving group without intervention of the allylic π system. We addressed ourselves to this problem by studying the formic acid catalyzed cyclization of cyclohexenol derivatives **6a,b**.

Deuterium labeling introduces a convenient perturbation of symmetry, and the mechanistic implications of investigating the course of this well-known reaction[9] by means of labeled substrates are the following (Scheme I): (a) direct displacement of the leaving group by the double bond (π participation) should afford

† Department of Chemistry, The University of Utah, Salt Lake City, UT 84112.

(1) This investigation was supported by research grants from the Research Council of Croatia and the National Institutes of Health (02-011-1/PL 480).

(2) Souček, M *Collect. Czech. Chem. Commun.* **1962**, *27*, 2929.
(3) Poulter, C. D.; Rilling, H. C. *Acc. Chem. Res.* **1978**, *11*, 307.
(4) (a) Johnson, W. S. *Angew. Chem., Int. Ed., Engl.* **1976**, *15*, 9. (b) Amupitan, J.; Sutherland, J. K. *J. Chem. Soc. Chem. Commun.* **1980**, 398.
(5) Garst, M. E.; Cheung, Y-F.; Johnson, W. S. *J. Am. Chem. Soc.* **1979**, *101*, 4404.
(6) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.
(7) Poulter, C. D.; Satterwhite, D. M.; Rilling, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 3376. Poulter, C. D.; Argyle, J. C.; Marsh, E. A. *J. Biol. Chem.* **1978**, *253*, 7227.
(8) For other examples, see: Coates, R. M. *Prog. Chem. Org. Nat. Prod.* **1976**, *33*, 73.
(9) (a) Johnson, W. S.; Lunn, W. H.; Fitzi, K. *J. Am. Chem. Soc.* **1964**, *86*, 1972. See also: Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*,1. (b) Marshall, J. A.; Cohen, N. *J. Am. Chem. Soc.* **1965**, *87*, 2773. Marshall, J. A.; Cohen, N.; Hochstetler, A. R. *Ibid.* **1966**, *88*, 3408.

0002-7863/81/1503-1285$01.25/0