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Aldrichimica Acta

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About Our Cover:

Our chemist-collector loves puzzles — puzzles of authorship and iconography. So he purchased the painting (oil on panel, 18 $^1/_2$ x 24 $^3/_4$ inches) shown on our cover, knowing it involved two puzzles.

It is signed 'de Gelder f.' Aert de Gelder was one of Rembrandt's last students, and is one of our collector's favorite artists. Yet this painting does not look like any work of de Gelder that our collector has ever seen, and so he wonders whether he misreads the signature, or whether it is an early work of de Gelder before the artist came under Rembrandt's influence.

The other puzzle involves the scene depicted. It has been called *Esther before Ahasuerus*, specifically when Esther comes before the King knowing her life depends on his stretching out his scepter. In many Dutch depictions of this subject, Esther faints, a detail taken from the apocryphal rather than the Biblical Book of Esther. Here, the beautiful, young Esther is as self-assured as could be, in delightful contrast to the King. But is it really Esther? Or could it be the King's first wife, Vashti, refusing to dance before the King? Or perhaps even a non-Biblical subject?

Our chemist dislikes the Book of Esther more than any other book of the Bible, because one of the two villains of the story, Ahasuerus, that gluttonous King, without whose acquiescence Haman would never have succeeded in the first place, not only goes scot-free but is rewarded by marriage to Esther. Why then, we asked our chemist, did he buy another painting of Esther? Well, he replied, beauty, in this case particularly of color, comes first, and perhaps what has happened with the first painting of 'Esther' illustrated on the *Aldrichimica Acta*, Vol. 7, No. 1 (1974) will happen again: that work by Leonard Bramer was shown later to be of the *Queen of Sheba before King Solomon* rather than Esther before Ahasuerus. The Lions of Judah in the throne, the gifts in the left foreground and the absence of the King's scepter are proof that it depicts the Ethiopian Queen rather than Esther.

Are you interested in our Acta Covers? *Selections from the Bader Collection*, with 30 duotone reproductions, many of previous Acta covers, and an introduction by the late Professor Wolfgang Stechow is now available to all chemist art-lovers.

Z10,118-4 $6.00

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

At last! a responsible, expert source for biological stains and dyes

Meet Dr. Floyd Green, member of and consultant to the Board of Trustees of the Biological Stains Commission and a fourteen-year member of the ACS Analytical Reagents Committee.

Dr. Green is the quiet, capable man heading the Aldrich Chemical Company's growing new Stain and Dye Division that, with good reason, bears his name. When he joined Aldrich in the fall of '77, it was expressly for the purpose of establishing and directing the new division which was being created to fill the void caused by legislation and economic conditions that had strangled many commercial dye sources. To take on this task, Dr. Green gave up his own business — Aristo Custom Chemicals, Inc., Cincinnati, Ohio.

Today, he deserves world-wide respect for his record as a manufacturing chemist and for his comprehensive knowledge in the area of stains and dyes.

In college, Green had been leaning originally toward a career in medicine. He received his baccalaureate in biology from Maryville College in Maryville, Tennessee, but then World War II came. He joined the Navy which sent him to the Naval Medical School in Bethesda, Maryland. His training there centered on malaria and epidemiology. Subsequently, he was sent to the Pacific theater where he spent the next 26 months obtaining epidemiological profiles on the native population. It was there that he had his first exposure to stains, having had to prepare and analyze thousands of blood smears daily.

When the war ended, Green went to work as an assistant to one of the U.S. pioneers in biological stains, Arthur Coleman, who was one of the entrepreneurs in the field (Coleman and Bell). Green worked directly with Coleman for five years. The work was difficult. It was then that he became aware of the lack of reliable published information on stains and dyes.

All in all, Green invested 27 years with MCB, though he found time to attain the M.S. in chemistry from the University of Cincinnati in 1950. He also received an M.S. in biochemistry and chemistry in 1967 and a Ph.D. in 1969 from St. Thomas Institute of Advanced Studies. His thesis for the latter was based on work he had done with a University of Illinois pathologist. Their months of work together — alternate weekends in Illinois and Ohio — were directed toward cross-linking agents relative to stabilizing and preserving badly decayed teeth. Their initial work sought to use Procion dyes to stabilize collagen in teeth pulp, and it evolved into the development of colorless cross-linking agents to replace the Procions. Consequently, papers were presented to the Dental Research Institute and 13 patents were issued.

During his years with MCB and after, Green did additional graduate work at St. Xavier and M.I.T.

Dr. Green and the Floyd Green Stain and Dye Division of the Aldrich Chemical Company, Inc. have these objectives.

The first is to provide a reliable source of consistently pure stains and dyes for biological and scientific research. To this end, the Division will be fully operational this Spring.

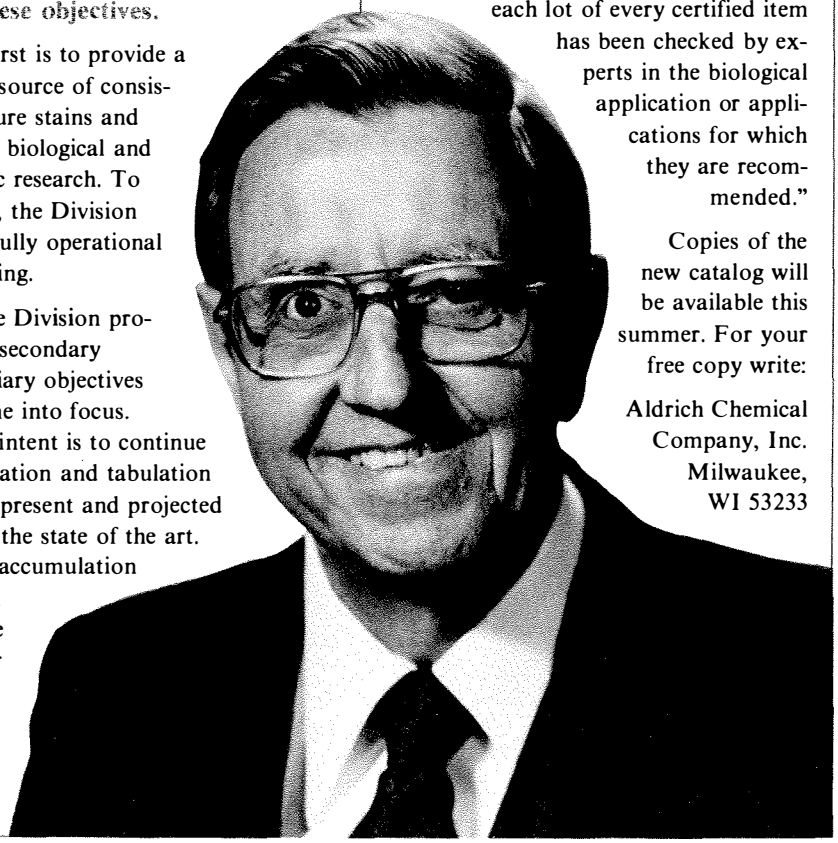
As the Division progresses, secondary and tertiary objectives will come into focus. Green's intent is to continue accumulation and tabulation of past, present and projected data on the state of the art. It's this accumulation that will form the basis for what, in fact, might be this country's, if not the world's, first library of stains and dyes; and following this development, the Division could well become a center for consultation within the industry.

As Green puts it in the foreword to the Division's first catalog: "This manufacturing division is dedicated to providing quality products whether well known or only recently described in the literature. The scope of the manufacturing capability of this division sets it apart from most other domestic sources of biological stains and chemical indicators, and the uniqueness does not stop there. Indeed, traditional quality-control methods have been supplemented with cross checks wherever appropriate. For example, uv-visible and wet-method dye-concentration determinations are routinely correlated to C, H and N determinations.

"Items that are on the Biological Stain Commission list of certified stains are submitted to the Commission for certification. Thus, you can be assured that each lot of every certified item has been checked by experts in the biological application or applications for which they are recommended."

Copies of the new catalog will be available this summer. For your free copy write:

Aldrich Chemical Company, Inc.
Milwaukee, WI 53233



A Status Report on Biological Stains

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Milwaukee, Wisconsin 53233

INTRODUCTION:

The use of stains (dyes) as colorants for biological substrates has closely paralleled the use of dyes in the textile industry. In fact, microbiologists began using synthetic dyes shortly after Perkin's revolutionary discovery of a synthetic route to "mauve" in 1856. In less than twenty years some significant staining techniques had been developed, notably by Ehrlich.

While textile manufacturers were concerned with dyes strictly from an aesthetic standpoint, biologists were interested primarily in gaining information on the structure and function of tissues, cells, and subcell components. This is not to say that differentially stained biological specimens cannot be strikingly beautiful.

With the advent of synthetic dyes, microbiologists were provided a new tool to assist them in their quest to release some of the secrets held captive in the cell. In fact, this was the first significant advance in the art since its inception in the 17th century when Leewenhoek opened up the startling new world of "animalcules" (tiny animals) with his invention and development of the microscope. (It should be noted that natural products such as saffron and carminic acid were used within their limits as biological stains prior to the development of synthetic dyes and some, including the two mentioned, are still used.) For the first time tissue and cell components could be differentially colored effectively to provide contrasts heretofore unattained. (The basis of differential or selective staining of biological materials lies in the chemical and physical heterogeneity of tissue, cells and subcell components.) Thus, the geometry and chemical affinity of tissue, cells and subcell structures could be more readily observed and studied by utilizing skillfully tailored staining techniques.

FIXATIVES:

Unlike textiles, many biological substrates are water soluble. In addition, they are rendered useless for subsequent microscopic observation by temperatures commonly used in textile dying. They are also susceptible to degradation by bacteria and their own hydrolytic enzymes. These are a few of the problems that must be overcome before a biological substrate can be stained effectively and observed under a microscope. Therefore, the substrate must undergo a prestaining conditioning which frequently is quite elaborate. Denaturants known as fixatives are used to stabilize the substrate matrix. These vary with the substrate and the application. Organic solvents, reactive compounds (*e.g.*, aldehydes, osmium tetroxide and chlorotriazines), and heat are among the fixatives commonly used. Obviously, it is impossible to observe the substrate *in vivo* after fixation. The goal is to treat it as gently as possible in the stabilization process so as to minimize the resulting distortion.

A monocellular layer of substrate will afford the most information on cell detail to a microscopist. To approach this end, thin layers of cell suspensions are smeared on a slide or tissue blocks are sliced thinly by a specialized slicing device known as a microtome. These tissue blocks must be made rigid prior to cutting, and this is accomplished by freezing or embedding with media such as warm paraffin "wax," which solidifies on cooling, or plastic monomers, thus providing the necessary support to the tissue to minimize mechanical distortion during the cutting operation.

DYE ATTACHMENT:

In order for a chromophore to be of value as a colorant, it must become attached with some permanence to the substance being dyed. To a large degree, this holds true for biological stains. However, some staining techniques require stains that will respond to selective destaining.

The tenacity of the dye's attachment to the substrate and the concomitant color depth achieved varies, not only with the bonding mode in effect, but with chemical affinity, density, and permeability of the substrate.

There are several bonding modes or forces that can come into play when a chromophore becomes attached to a biological substrate. These, of course, vary with the dye and substrate. The ionic bond appears to be one of the most prevalent means of attachment. However, other linkages occur in addition to ionic bonding. These include the covalent bond, hydrogen bond, van der Waals forces, hydrophobic bond and mordants. A combination of two or more of these forces, depending on the nature of the dye and the substrate, participate in the attachment.

IONIC BONDS:

The ionic bond formed between appropriately matched dyes and biological substrates is basically no different from the ionic bond demonstrated in other dye applications. The linkage occurs as the result of the Coulombic force initiated

when a cation and an anion come into close proximity of each other. In other words, basic dyes (cations) are attracted to anionic sites in the substrate while acid dyes (anions) are attracted to cationic sites.

The ionic bonding mode plays a large role in linkages demonstrated by the Romanowsky-type blood stains (Fig. 1). Although the ionic bond should not be considered as the only type of bond that exists when these dye mixtures are utilized, it is certainly a major linking force in this application. Methylene Blue and its oxidation products (the azur dyes) serve as the basic dyes in these blends while Eosin Y (yellowish) serves as the acid dye counterpart. These mixtures, containing both acid and basic dyes, stain thin blood films differentially from an "acid" bath. The optimum pH of the bath varies from 6.4-6.7 depending on the technique used. There are three different types of dry stain blends: (1) A mixture of dry powders of the acid dye Eosin Y and basic dyes (*e.g.* Methylene Blue or Azur A). (2) Eosinates (Eosin Y ionically linked to a basic dye such as Methylene Blue or one of the azurs) which are prepared by adding an aqueous solution of Eosin Y to an aqueous solution of the basic dye. The resulting precipitates are alcohol-soluble and water-insoluble. (3) A combination of 1 and 2. Methanolic solutions (0.3%) of any of the three dye blends will stain a fixed thin blood film satisfactorily, if not optimally, when diluted with an equal volume of buffer solution of pH 6.4. The resulting differentially stained blood film demonstrates that each dye component seeks out its ionic counterpart in the subcell structures of the blood cell milieu. Thus, regardless of whether the solution is prepared from dye blend 1,2, or 3, the component dyes respond ionically in an aqueous system.

COVALENT BONDS:

Covalently bonded dyes, of course, offer the ultimate when permanence is desired since a dye linked in this manner becomes an integral part of the substrate with which it is linked. Naturally there are inherent disadvantages when these dyes are used in biological applications.

Dyes formed *in situ* from "colorless" components are important and useful representatives of the covalent bonding mode. These dyes are generally formed as a result of a coupling reaction between a diazonium salt and a phenolic or naphthoic protein moiety. Stable diazonium salts (zinc double salts) which are commercially available are frequently used in this application. Also, diazonium salts can be coupled to "colorless" naphthoic disulfides which have been linked *via* a disulfide bond to an amino acid site such as cystine in the substrate (Fig. 2C). This is another specific application.

Reactive dyes such as the Procion and Remazol dyes form covalent bonds with cellulosic and proteinaceous substrate entities and are quite effective in textile and other commercial dying. However, they have not proven to be very useful as biological stains due to their lack of selectivity since the reactive chlorines on the cyanuric chloride moiety of the Procion dyes will react readily with, among other functions, primary and secondary amino, hydroxyl, carboxyl and sulfhydryl groups to form covalent bonds *via* condensation reactions.

The diazo chloromercury-type reactive dyes (Fig. 2B) are more suited to biological applications because they are more selective than the Procions and Remazols in their functional group attachment to proteins.

OTHER BONDING FORCES:

While there is less evidence to support hydrogen bonding, hydrophobic bonding and van der Waals forces as major linking modes, these forces certainly can act in supportive or reinforcing roles after a major linking mode is in progress. Indeed, it is conceivable that they initiate link-ups under proper conditions.

Hydrogen bonding is frequently suggested as a linking mode when the evidence does not suggest other forces. A plausible position can be established for an attraction between peptide hydrogens of tissue protein and amino-group hydrogens of the dye molecule.

Van der Waals attractions and hydrophobic bonding play somewhat competing roles in dye bonding and are difficult to quantitate. For this reason it is assumed that they generally play minor bonding roles. However, these bonding forces undoubtedly come into play in involved staining procedures where the solvent system is switched from water to an organic solvent medium such as alcohol, DMF, or DMSO. The relative contribution of these two

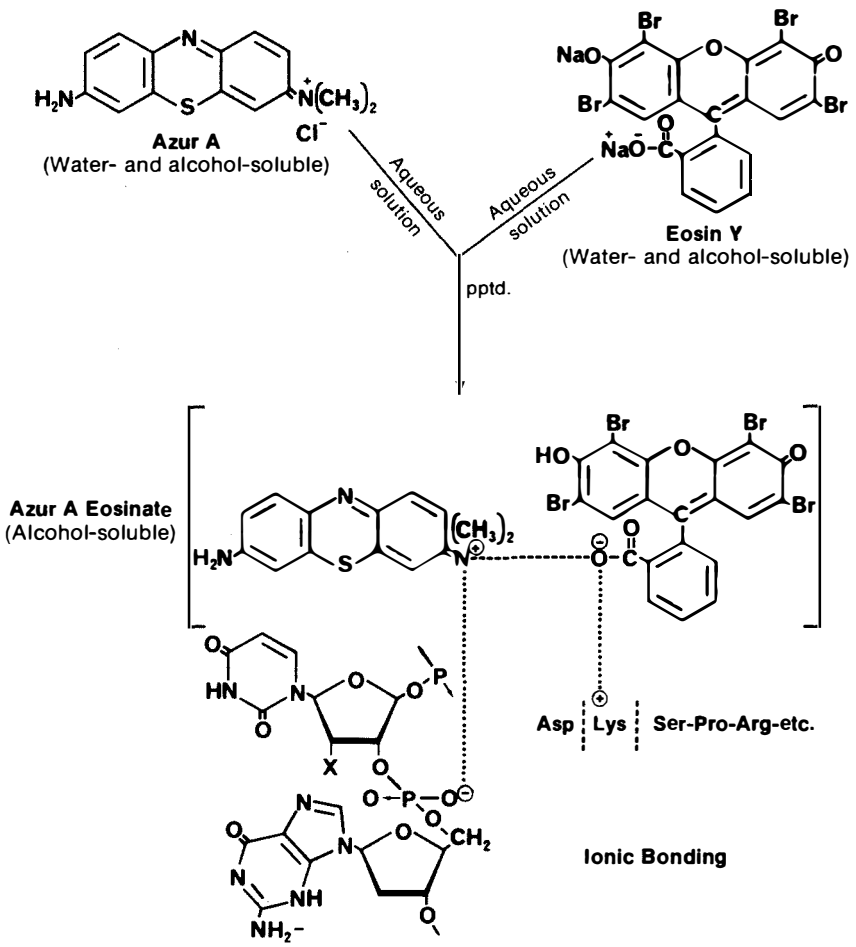


Fig. 1 Anionic dye (Eosin Y bonded ionically with basic amino acid in hypothetical polypeptide chain.)
Cationic dye (Azur A bonded through ionic bond with hypothetical section of nucleotide chain.)

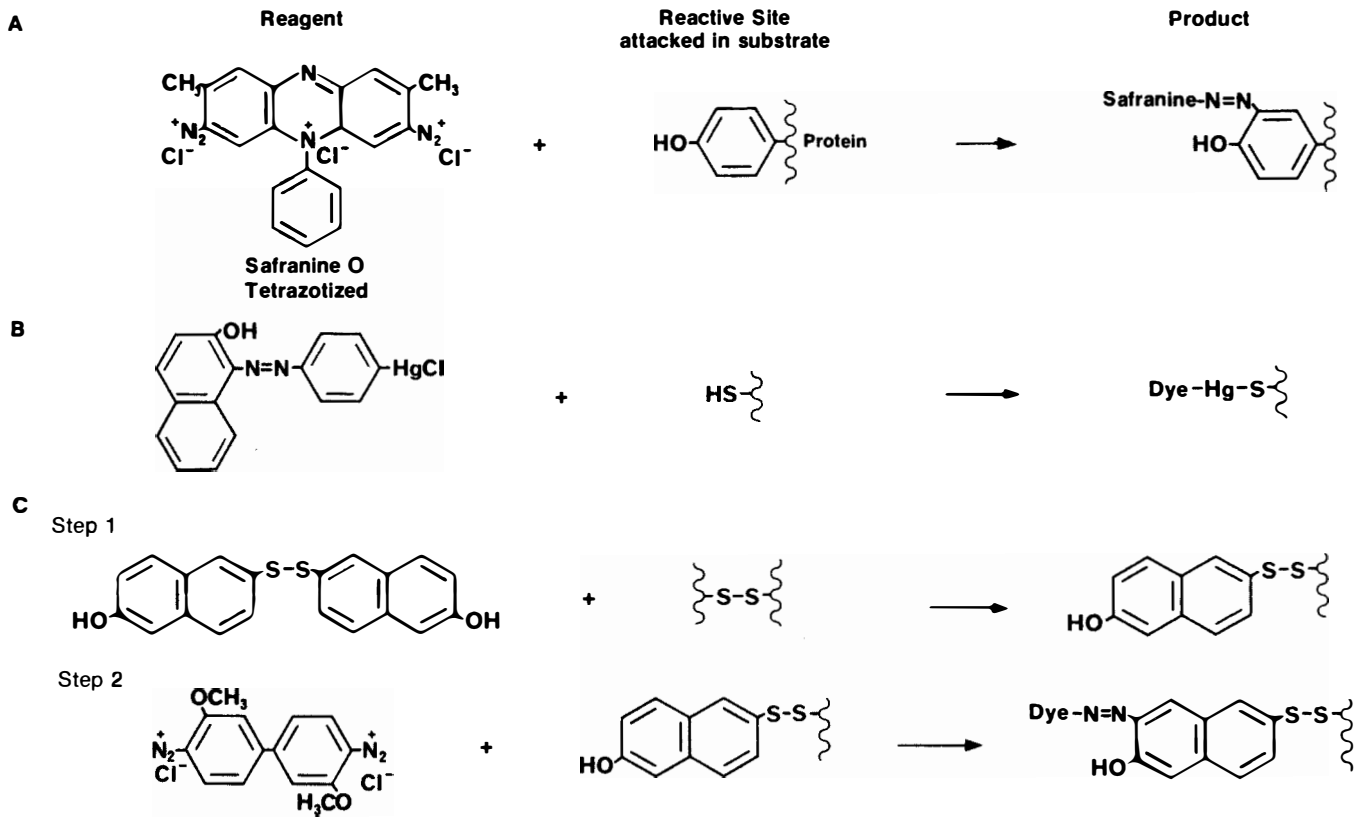


Fig. 2 Examples of Covalent Bonding Between Dye and Substrate

forces to the bonding in effect varies with the molecular size and polarity of the dye and the solvent system utilized.

The so-called instant Wright blood stain (staining time, 10 seconds) which utilizes one of the dry stain mixtures mentioned earlier demonstrates how the movement of the dye from bath to substrate can be accelerated by increased system entropy. This can be accomplished by adding approximately 5-10% of a polar solvent such as DMF or DMSO to the methanol normally used as the solvent. Advantage is also taken of the greater solubility of these polar dyes in the highly polar solvents mentioned. Thus, the dye concentration may be increased two- to three-fold.

METACHROMASIA:

Certain pure dyes (free of related dyes or dyes formed by degradation), usually basic dyes, produce different colors with different tissue components. This phenomenon is termed metachromasia.

A substrate stained normally (without an absorbance shift) is said to be stained orthochromatically (orthochromasis) while a substrate causing an absorbance shift, usually hypsochromic, is said to be stained metachromatically. Current evidence indicates that this color shift is due to a dye-dye interaction which varies with the substrate site. In other words, the intensity of the bonding affinity between the dye molecule and the site will dictate the ability of the bonded dye molecule to interact with other dye molecules and conceivably form dimers or polymers. Basic dyes comprise the bulk of the metachromatic dyes known and, in all cases, these molecules contain either primary or secondary amino group or groups. Dye molecules containing only tertiary amino functions are not metachromatic. However, it should be emphasized that not all basic dyes containing a primary or secondary amine are metachromatic. While the absorbance maximum shift of basic metachromatic dyes is normally hypsochromic, the few acid dyes (usually azo dyes such as Congo Rubin) that demonstrate metachromasia display a bathochromic shift.

Some unstable dye solutions stain a given substrate more than one color. However, this phenomenon, unlike metachromasia, is due to a new dye formed as the result of the degradation of the initial dye. For example, an aqueous solution of Nile Blue A (Fig. 3) can form a new dye molecule on standing. This new oxazone dye, Nile Red, stains neutral fat and alkylated fat sites red, while fatty acid-rich sites are stained blue by the unchanged dye portion. This phenomenon, involving two distinct dye molecules, is known as allochromasia.

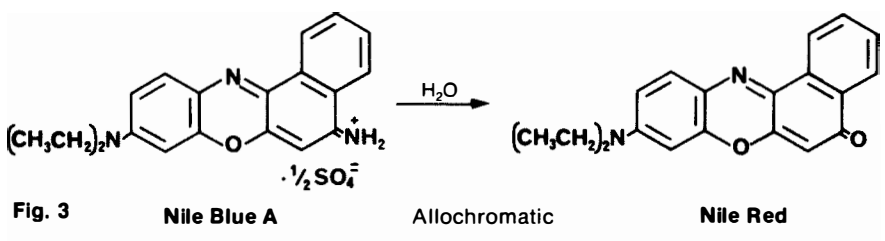
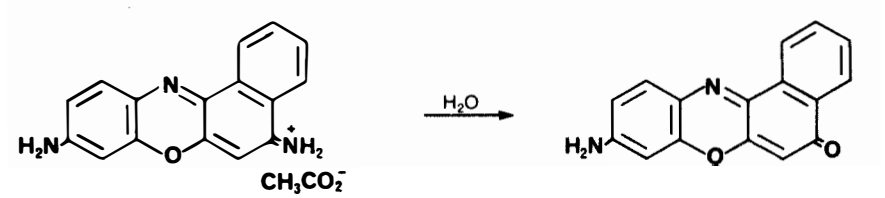


Fig. 3 **Nile Blue A** Allochromatic **Nile Red**



Cresyl Violet Acetate Allochromatic, Orthochromatic and Metachromatic **Cresyl Red**

Fig. 4

Knaysi found that this phenomenon is not limited to the oxazine family of dyes, which Nile Blue A represents. Indeed, Neutral Red, an azine dye, and the thiazine dye, Methylene Blue. are specifically cited.

Cresyl Violet Acetate (Fig. 4), another oxazine dye, can act orthochromatically, metachromatically and allochromatically if enough of the oxazone impurity is present to function as the allochromic form. Normally, there is plenty of the oxazone present if the product is formed by the classic oxazine synthetic route. In fact, when used as a laser dye, Cresyl Violet has to be purified routinely by liquid-liquid extraction (H_2O and toluene) to eliminate the oxazone impurity.

CONCLUSION:

As noted earlier, biologists have been dependent upon commercial dye sources (dye manufactured primarily for the paper, textile and leather trades) directly or indirectly since Perkin launched the industry.

Some of the early suppliers, such as the renowned Dr. Grübler and his successor, Dr. Hollborn, apparently selected dyes suitable for biological purposes from commercial dye lots while early American entrepreneurs in the biological stain industry, such as Arthur Coleman, William Bell and Milton Hartman, got more involved in purifying suitable commercial dye products and synthesizing products not available from commercial sources. Their enterprises were started about the same time as The Biological Stain Commission which was founded in Geneva, N.Y. in 1922 by Dr. Harold J. Conn *et al.* The Commission was established to test and certify the suitability of dye lots for biological purposes. This organization has been and continues to be at the forefront of the struggle to provide quality stains for biological applications.

Today, the struggle to keep quality stains available intensifies as the biologists' reliance on commercial sources may have reached an impasse and their dependence on this industry is no longer assured. Technical problems have become secondary as the impact of recent legislation has emerged as the primary impediment to the availability of quality stains at prices confined to the general economy's inflationary spiral.

Indeed, within the last year, domestic commercial manufacturers curtailed or discontinued manufacture of four dyes of importance to biologists for three quarters of a century. Methylene Blue Chloride, Pararosaniline, Rosaniline and Safranine O have all but disappeared from commercial sources, putting an increased burden on the small dye manufacturers who, in the past, have produced special dyes solely for the biological market to supplement those available from textile sources.

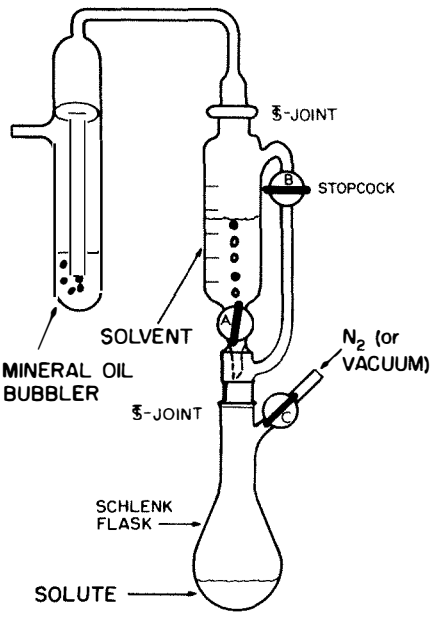
Suggested Reading Material:

1) J.R. Baker, "The Principles of Biological Microtechnique," Methuen and Co., Ltd., London, 1958.
2) F.J. Green, *Stain Technol.*, **41,** 115 (1966).
3) F.J. Green, *ibid.*, **41,** 223 (1966).
4) R.W. Harbin, *J. Soc. Dyers Colour.*, **91,** 4 (1975).
5) J. Thompson, "Selected Histochemical and Histopathological Methods," Thomas, Springfield, IL, 1966.
6) A.G.E. Pearse, "Histochemistry, Theoretical and Applied," Vol. I and II, Little, Brown and Co., Boston, MA, 1953.
7) K. Ventakataraman, "The Chemistry of Synthetic Dyes," Vol. I, II, III and IV, Academic Press, New York, NY, 1952 and 1973.
8) T. Vickerstaff, "The Physical Chemistry of Dyeing," 2nd ed, Oliver and Boyd, London, 1954.
9) H.J. Conn, "Biological Stains," 9th ed, R.D. Lillie, Ed., The Williams and Wilkins Co., Baltimore, MD, 1977.
10) R.D. Lillie and H.M. Fullmer, "Histopathologic Technique and Practical Histochemistry," 4th ed, McGraw-Hill and Co., New York, NY, 1976.
11) J. Knaysi, *J. Bacteriol.*, **42,** 587(1941).
12) J. Knaysi, *Dairy Sci.*, **25,** 585 (1942).

Lab Notes

A convenient method for deoxygenating solvents for bench-top inert-atmosphere reactions has been used routinely with excellent results, particularly in cases where a second solvent or solution must be added to the initial solution or reaction mixture. It is useful to have available a small manifold equipped with a series of two-way stopcocks to which is attached a source of inert gas (*e.g.*, N_2) at slight positive pressure and a source of vacuum. The following steps are carried out with reference to the figure:

1) The solute or reactants are placed in a Schlenk-type flask, which is capped, evacuated, and filled with nitrogen through stopcock **C**.
2) With a nitrogen flush through the flask, the cap is replaced with a graduated addition funnel containing solvent (stopcock **A** closed, **B** open). After 10-15 sec, stopcock **B** is closed and **A** is opened,



allowing nitrogen to bubble through the solvent in the funnel. (Note: stopcock A should be grease-free, *e.g.*, Teflon.)
3) A mineral oil bubbler is connected to the top of the addition funnel *via* a standard-taper joint (other options for preventing back-flow of air can also be used.)
4) After 5-10min of nitrogen flow, a measurable quantity of deoxygenated solvent can then be added to the flask by closing stopcock **A**, opening stopcock **B**, capping the top of the funnel, and reopening stopcock **A** (**C** remaining open throughout).
5) After the solvent is added, the funnel can be removed or a second solvent or solution can be added by repeating steps 2 - 4.

The above procedure is less complex than it would at first appear and can be carried out quite rapidly with practice.

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The complete removal of selenium by-product from a reaction mixture is a problem well known to any chemist who has performed oxidations with selenium dioxide; this "headache" is especially pronounced in the case of the red, colloidal modification of selenium. Fieser and Fieser[1] have also taken note of the lack of a general solution to this problem.

We wish to report that red colloidal selenium, occluded in organic reaction mixtures, can be readily converted to the black, granular, easily filtrable form by briefly heating the mixture in DMF. Black selenium, which appears to be far less soluble in DMF than the red colloidal form, spontaneously precipitates from solution in a few minutes. Extended periods of reflux or chromatography on silver-impregnated alumina columns are unnecessary in this procedure, and the simplification thus achieved recommends it highly. Solubility of the organic reaction mixture in DMF, reasonable thermal stability, and chemical inertness to DMF are the only prerequisites to insure success in utilizing the technique.

Our laboratory has employed this method extensively during the preparation and purification of numerous arylglyoxals *via* the Riley Reaction.[2]

Stanley R. Milstein, Ph.D.
Eugene A. Coats, Ph.D.
College of Pharmacy
University of Cincinnati Medical Center
Cincinnati, Ohio 45267

References:
1) L.F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Vol. 1, John Wiley and Sons, Inc., 1967, p 992-993.
2) H.A. Riley and A.R. Gray, *Org. Syn., Coll. Vol. 2*, 509 (1943).

It is often difficult to accomplish the complete removal of a high-boiling solvent from a reaction product or other solute. The following procedure is recommended: (a) Mix the solution in a beaker with sufficient filter aid to give a free-flowing powder. (b) Transfer this powder to a round-bottom flask, apply oil-pump vacuum and heat gently. (c) When constant weight is achieved, recover the solute by elution with a low-boiling solvent.

This procedure is particularly advantageous when working on a small scale or when the solute is non-crystalline.

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Raleigh, NC 27607

Any interesting shortcut or laboratory hint you'd like to share with ACTA readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome red and white ceramic Aldrich coffee mug as well as a copy of **Selections from the Bader Collection** (see "About Our Cover"). We reserve the right to retain all entries for consideration for future publications.

"Please Bother Us."

by Alfred Bader.

Occasionally, a reagent is of such versatility that many chemists suggest that we make it available. Such was the case with **iodotrimethylsilane** (trimethylsilyl iodide) which is an efficient reagent for the cleavage of ethers and esters under neutral conditions, for the conversion of ketals to ketones, sulfoxides to sulfides, alkyl carbamates to amines (M.E. Jung and M.A. Lyster, submitted to *Chem. Commun.*) and even for the synthesis of the important medicinal building block, dibenzocyclooctadienone (M.E. Jung, A.B. Mossman, and M.A. Lyster, submitted to *J. Org. Chem.*).

Naturally, with a reagent of such importance, we worked hard to scale-up its preparation to fill the need which is bound to develop. We have been successful, and have even been able to reduce the price.

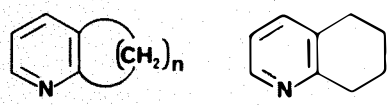
It was no bother at all, just a pleasure to be able to help.

Chemical Reactions of 2,3-Cycloalkenopyridines

Helmut Beschke
Degussa

INTRODUCTION

In the last decades pyridine derivatives have gained importance, particularly in the production of herbicides and medicinals. The only 2,3-cycloalkenopyridines (**1**, n = 3-13) of any importance have been 5,6,7,8-



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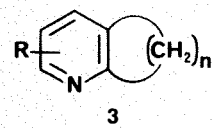

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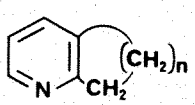
tetrahydroquinoline (**2**) and its alkyl derivatives. The syntheses known for **1** did not enable the technical utilization of these compounds, although derivatives of **2** are accessible through hydrogenation of the corresponding quinolines.[1] A new synthesis of 2,3-cycloalkenopyridines (**3**, n = 3-13; R = H, CH_3) involving a heterocatalytic gas-phase reaction of cycloalkanones with alkenones and ammonia,[2] makes such pyridines accessible. From acrolein and the ketones cyclohexanone, cyclopentanone, cycloheptanone and cyclododecanone, one obtains 5,6,7,8-tetrahydroquinoline, 2,3-cyclopentenopyridine, 2,3-cycloheptenopyridine and 2,3-cyclododecenopyridine respectively in yields of 60-90%. Methyl vinyl ketone yields 2-methyl derivatives, whereas methacrolein and crotonaldehydes lead to 3-methyl- and 4-methyl derivatives. Since these compounds can now be made so easily, their applications have become of special interest. The purpose of this review is to summarize the reactions of these 2,3-cycloalkenopyridines.

CHEMICAL TRANSFORMATIONS WITH 2,3-CYCLOALKENOPYRIDINES

Chemical reactions of 2,3-cycloalkenopyridines can be most easily classified according to the initial chemical reaction of the cycloalkenopyridine, *i.e.*, N-oxidation, hydrogenation of the pyridine ring, dehydrogenation of the aliphatic ring, metallation of the reactive CH_2 group attached to the α-position of the pyridine ring, and the reaction of this reactive group with carbonyl compounds.

As this reactive methylene group is especially important in many reactions, these 2,3-cycloalkenopyridines will be depicted as **4**.



4

Most of the reactions in the literature involve 5,6,7,8-tetrahydroquinoline (**4**, n = 3) or its methyl derivatives, 2,3-cyclopentenopyridine (**4**, n = 2) and 2,3-cycloheptenopyridine (**4**, n = 4). Methyl substitution, particularly common in the 3-position of 5,6,7,8-tetrahydroquinoline, will not be referred to specifically, because it does not affect the reaction schemes.

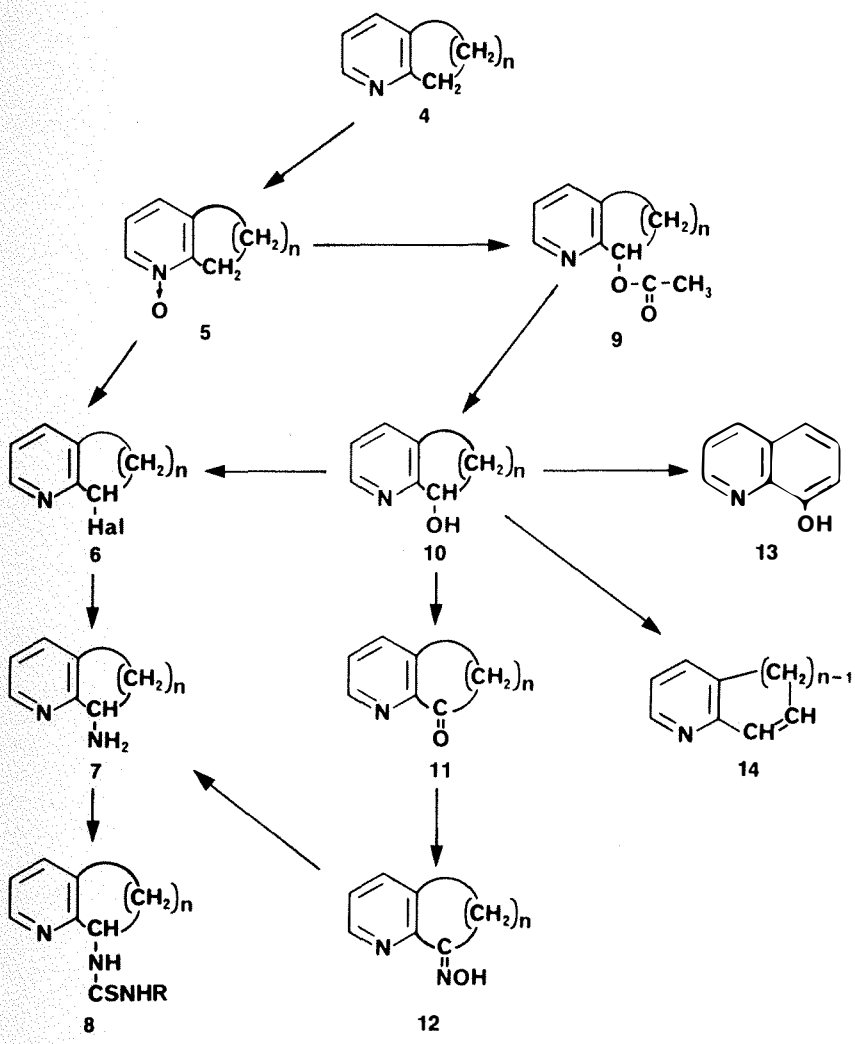
N-Oxidation and Subsequent Reactions (Scheme I)

The N-oxidation of various 2,3-cycloalkenopyridines with H_2O_2 in acetic acid has been described.[3-7] Reaction of the *N*-oxide **5** with methanesulfonyl chloride yields the α-chloro compound **6**,[5,6] which is transformed to the α-amino compound **7** by treatment with methanolic ammonia at 80° for 24 hours.[5,6] Reaction with isothiocyanates affords the corresponding 8-thiocarbamoylamino derivative **8**,[5] *e.g.*, **7** reacts with methyl isothiocyanate in acetonitrile to yield the 8-methylthiocarbamoylamino compound, and with benzoyl isothiocyanate in acetone to give the 8-benzoylthiocarbamoylamino compound. The latter is hydrolyzed with alkali to the 8-thiocarbamoylamino compound.[5]

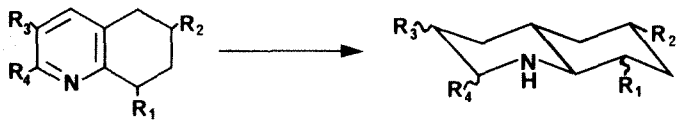
The Boekelheide rearrangement converts the *N*-oxide **5** (with acetic anhydride) to the acetate **9**, which undergoes saponification with alkali or hydrochloric acid to the carbinol **10**.[9]

8-Hydroxy-5,6,7,8-tetrahydroquinoline (**10**, n = 3) was dehydrogenated with palladium on charcoal in diisopropylbenzene to 8-hydroxyquinoline **13**[9] and it was dehydrated (by heating with polyphosphoric acid) to 5,6-dihydroquinoline (**14**, n = 3).[10] The analogous dehydration of 7-hydroxypyrindan to 5,6-dihydropyrin-

Scheme I



Scheme II



a: $R_1 = R_2 = R_3 = R_4 = H$
b: $R_1 = R_2 = R_3 = H$; $R_4 = CH_3$ (α, β)
c: $R_1 = R_2 = R_4 = H$; $R_3 = CH_3$ (α, β)
d: $R_1 = R_3 = R_4 = H$; $R_2 = CH_3$ (only α)
e: $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$ (α, β)

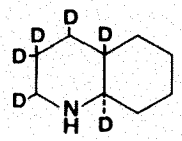
dan (**14**, n = 2) has also been described.[10]

The carbinol **10** can be oxidized with manganese dioxide in methylene chloride[5,7] or with chromium trioxide in dilute sulfuric acid[9] to the ketone **11** which has been converted to the oxime **12**[5,7] followed by hydrogenation with Raney nickel to the amine **7**.[5] Finally, **10** has been converted to the chloro compound **6** with thionyl chloride[5,6] and to the corresponding bromide with PBr_3.[11] The preparation of various guanidines from the amine **7** has also been described.[12]

Hydrogenation of the Pyridine Ring (Scheme II)

The hydrogenation of 5,6,7,8-tetrahydroquinoline and its methyl derivatives **15a-e** with sodium in ethanol leads to the corresponding *trans*-decahydroquinolines **16** in better than 90% yields.[13] The methyl derivatives **15b, c** and **e** yield two diastereoisomers, α and β, whereas **15d** yields only the α-isomer in which the methyl group is equatorial.

Hydrogenation of 5,6,7,8-tetrahydroquinoline in ethan(ol-*d*) yields predominantly the *trans*-decahydroquinoline-2,3,3,4,9,10-d_6, **17**.[13]



The synthesis of the corresponding *trans*-diastereoisomers by reduction with sodium in ethanol has been described for cycloheptano-2,3-piperidine[14] and cyclopentadecano-2,3-piperidine.[15] In contrast, the hydrogenation with platinum and acetic acid yields the *cis*-diastereoisomers, *e.g.*, *cis*-cyclopentadecano-2,3-piperidine.[15]

Dehydrogenation of the Aliphatic Ring

The dehydrogenation of the aliphatic ring of 2,3-cycloalkenopyridines succeeds only in the case of 5,6,7,8-tetrahydroquinolines: by heating with palladium at 300°C, the expected quinoline is formed.[16] This dehydrogenation fails with compounds such as 2,3-cyclopentenopyridine in which no aromatic ring can be formed, and which are unchanged by palladium or selenium at elevated temperatures.[16]

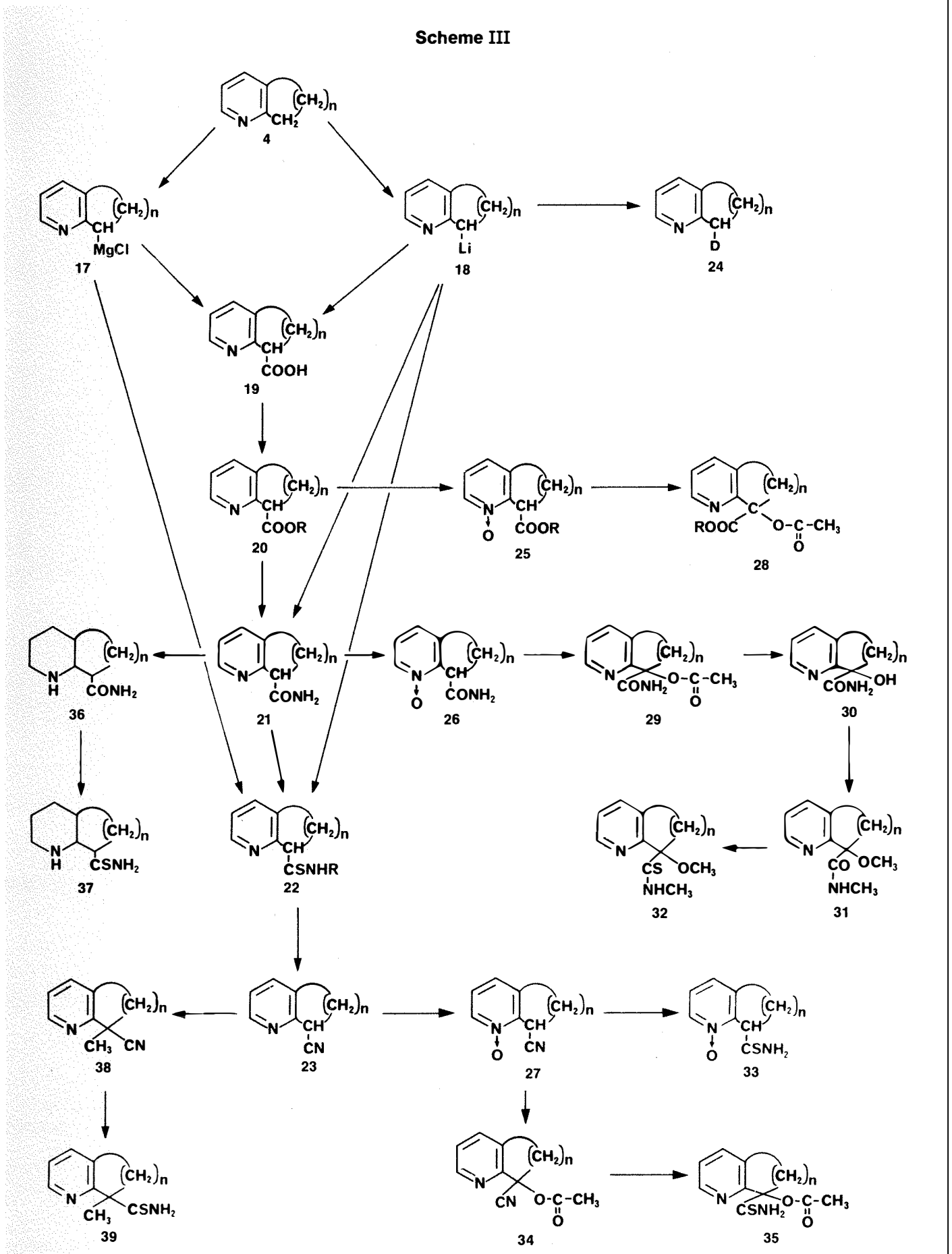
Metallation of the Reactive CH_2 Group (Scheme III)

Numerous compounds can be synthesized from 2,3-cycloalkenopyridines *via* the metallation of the reactive CH_2 group. These compounds can undergo further reaction, *e.g.*, N-oxidation or hydrogenation. It is even possible for the N-oxides to rearrange with acetic anhydride to form acyloxy compounds, yielding cycloalkenopyridines with two different substituents on the α-methylene carbon atom.

Metallation can be effected with either Grignard reagents to form **17**[17,18,20] or, better, with organolithium compounds to yield **18**.[17,18,21,22] As expected, the carboxylic acids **19**,[20-22] esters **20**,[20-22] amides **21**,[18-20,22] thioamides **22**,[17,18,21,22] and nitriles **23**[18] were formed. The deuterated derivative **24** has also been made.[21]

The *N*-oxides **25**, **26** and **27** made from the esters, amides and nitriles have been described.[23,24] Rearrangement of the ester *N*-oxide **25** yields the acetoxy ester **28**.[23] The corresponding amide **26** was converted in four steps *via* the acetoxycarboxamide **29**, the hydroxycarboxamide **30** and the methoxy-*N*-methylcarboxamide **31**, into the methoxy-*N*-methylthiocarboxamide **32**.[23,24] The cyano-*N*-oxide **27** was converted to the thiocarboxamide-*N*-oxide **33**, and also, by rearrangement to the acetoxycarbonitrile **34**, to the acetoxycarbothioamide **35**.[23]

Scheme III



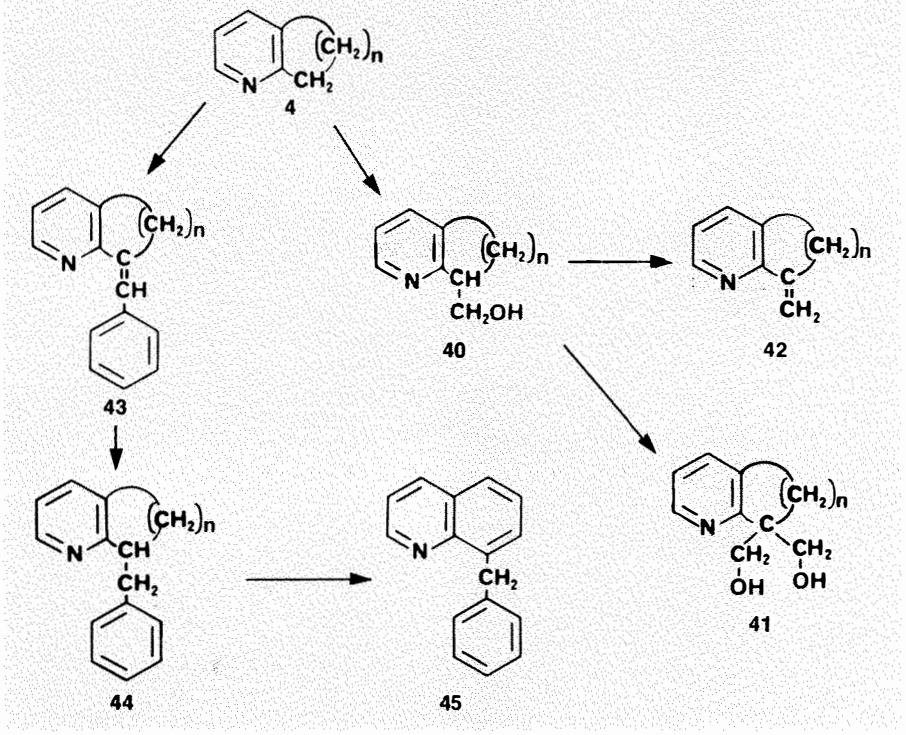
As already mentioned, one can hydrogenate substituted 2,3-cycloalkenopyridines to the corresponding piperidines. For example, the carboxamide **21** can be reduced to the decahydro-3-methylquinoline-8-carboxamide **36**, which can then be converted to the thioamide 37.[24]

The 8-cyano-5,6,7,8-tetrahydro-3-methylquinoline, **23**, was metallated further and reacted with methyl iodide to produce the compound with a methyl group on the reactive carbon atom. The product, 8-cyano-5,6,7,8-tetrahydro-3,8-dimethylquinoline, **38**, was then converted to the corresponding thioamide **39** with H_2S.[24]

Reactions with Carbonyl Compounds (Scheme IV)

2,3-Cycloalkenopyridines **4** react with formaldehyde to yield the hydroxymethyl derivatives **40** at 110-120° and the bis(hydroxymethyl) derivatives **41** at 150-160°.[3] The hydroxymethyl derivatives can be dehydrated to the "styrenes" **42** with polyphosphoric acid.[11] Reaction with benzaldehyde,[25,26] methoxybenzaldehydes[25] and *m*-nitrobenzaldehyde[26] yields the benzylidene derivatives **43**. Some of these were hydrogenated to the benzyl derivatives **44**[25] and, where n = 3, the 8-benzylquinoline **45** was obtained by dehydrogenation.

Scheme IV



CONCLUSION

It is surprising that many compounds have been made from the relatively few 2,3-cycloalkenopyridines that were known prior to Degussa's work.[2] About half of the published work came from one group [12,24] that has been interested in antiulcer therapeutic agents. Considering the ease and specificity with which one can chemically modify the 2,3-cycloalkenopyridines, these versatile intermediates offer the synthetic and medicinal chemist a fresh area for exploration, bounded only by the imagination.

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About the Author

Helmut Beschke, born in 1919 in Unseburg near Magdeburg, began his chemical studies in Jena in 1941. He joined Degussa in 1955 working in medicinal chemistry. He has been involved in the synthesis of pyridine derivatives since 1970.

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About Our Cover:

As we have mentioned before, our chemist-collector likes nothing better than to determine the meaning and authorship of old paintings. Some years ago he bought the wild and colorful painting (oil on canvas, 29 x 46 inches) reproduced here, at an auction in Lucerne. It was attributed then to Aert de Gelder and was called *The Counting of the Children in Bethlehem*. De Gelder is one of our chemist's favorite artists, and he is convinced that that attribution was as wrong as the title — in fact, no counting of the children in Bethlehem is recorded in the Bible. At first our chemist thought that it might depict the judgment of Solomon or, perhaps, Elisha with the widow of Obadiah (II Kings *4*), but now he is convinced that it is really *Joseph Selling Food to the Egyptians*. Pharaoh had "arrayed Joseph in vestures of fine linen, and put a gold chain about his neck" (Genesis *41*, 42). The scene is based on the 47th chapter of Genesis, when the Egyptians had become desperate and were selling themselves and their families to Pharaoh.

Our chemist believes that this painting is by a greatly underrated Amsterdam mid-seventeenth century painter, Jan van Noordt, who, from this painting, appears as a link between Rembrandt and the Venetian masters of the 18th century. The girl on the left looking at us seems to have walked right out of Rembrandt's *Nightwatch*; yet the whole atmosphere and, particularly, the bright colors, blue, gold and pink, remind us more of Tiepolo and his followers, or — in the draftsmanship of the social realism on the left — even of Daumier!

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Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

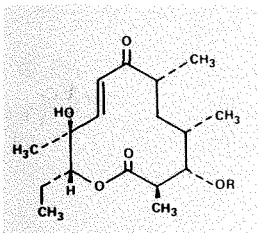
Recent Progress in Macrolide Synthesis

Award Address
presented by
Professor Satoru Masamune
Department of Chemistry
University of Alberta
Edmonton, Canada
at the
ACS Award Symposium
held on March 14, 1978
in Anaheim, California

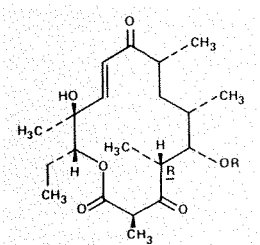
The recent history of organic chemistry is adorned with an impressive list of synthetic achievements of numerous complex molecules. Most of these compounds, however, incorporate 5- and 6-membered-ring systems where conformational analysis displays its power. In contrast, the synthesis of acyclic systems has received less attention in the past and there remains much to be explored in order to enhance synthetic expertise in this area. The structures of macrolides are basically acyclic, uniquely and regularly oxygenated, and rich in chirality. Thus, the synthesis of macrolides obviously demands new methodologies fundamentally important to organic chemistry, and further, there is good reason to believe that a deeper understanding of several basic reactions may enrich our knowledge of biochemical processes involved in the early stages of lipid synthesis. We are now witnessing a surge of effort underway in many laboratories, directed toward these objectives. It is my pleasure to present some of our contributions in this lecture.

The macrolide family includes more than one hundred physiologically active metabolites,[1] and approximately a half of these compounds are subgrouped as polyoxo macrolides, represented by the five antibiotics shown below [methymycin (**1**), pikromycin (**2**), erythromycin (**3**), leucomycin A_1 (**4**), and tylosin (**5**)]. They are twelve-, fourteen-, and sixteen-membered lactones with numerous substituents on the ring, and one or more hydroxy groups are glycosidated with sugars. It is clear from the structures that these compounds are biosynthesized from acetate and propionate, and in the case of 16-membered macrolides such as **4** and **5**, one butyrate unit is incorporated. This lecture concerns mainly the progress that has been made in this area since our methymycin synthesis, and particular emphasis is placed on pikromycin, the first macrolide antibiotic discovered.[2] The arrangement of substituents attached to the lactone framework is remarkably systematic and all follow what is now called Celmer's model (**6**),[3] expressed by the Fischer projection formula (Figure 1), and the antibiotics differ mainly in the degree of oxidation. The conformation of macrolides has received much attention and indeed there have appeared numerous papers concerning this subject.[4] In short, the majority of 14-membered macrolides, represented by erythronolide B (**7**), prefer a conformation similar to that shown by the bold line indicated in the diamond model I. Conformer **7a** is further modified in order to eliminate *syn*-periplanar interactions between the two methyl groups indicated by the arrow and also in order to enhance

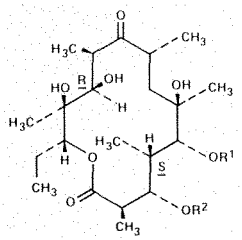
Professor Satoru Masamune (right) receiving the ACS Award for Creative Work in Synthetic Organic Chemistry sponsored by Aldrich, from Dr. Irwin Klundt, vice-president of Aldrich.



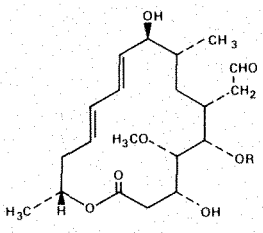
Methymycin (1)
R=desosaminyl



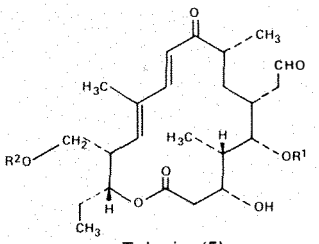
Pikromycin (**2**)
R=desosaminyl



Erythromycin A (**3**)
R^1=desosaminyl
R^2=cladinosyl



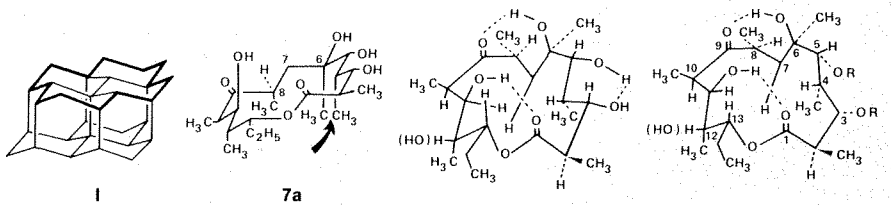
Leucomycin A_1 (**4**)
R=mycarosyl-mycaminosyl



Tylosin (**5**)
R^1=mycarosyl-mycaminosyl
R^2=mycinosyl

the hydrogen bonding interaction in the molecule. This provides what we now call Perrin's conformer **7b** or **7c**, which turned out to be almost the same as that of the crystal structure elucidated by X-ray analysis.[5] Two comments are in order. First, it is clear that the molecule does not have much conformational freedom even in solution; thus, the molecule is very rigid. This rigidity can be clearly indicated by space-filling models such as CPK models, and one is led to believe that even the seco-acid derived from the macrolide may possess a high degree of rigidity except for one or two freely rotating carbon-carbon single bonds. This consideration was important in selecting a synthetic scheme for a macrolide, and we were led to believe that the seco-acid might cyclize under proper conditions much more readily than one would normally expect. Another interesting feature of the molecule is that virtually all of the hydroxy groups are oriented on one side and most of the methyl groups lie below the ring framework, a structural feature likely having an important bearing on the microbial activity of the antibiotic.

Let me review briefly two major, obvious problems associated with the macrolide synthesis. The first one is the construction of a medium- or large-sized lactone and the second involves the incorporation of the substituents in a stereochemically controlled manner. It is natural to devise a methodology for lactone formation first, and then to test its applicability to more complex molecules. This has been the practice in many recent cases. Some representative approaches are illustrated by equations 1-3. Borowitz disclosed a clever idea of the fused bond rupture of a bicyclo[m.n.o] system to obtain the corresponding keto-lactone,[6] and Vedejs

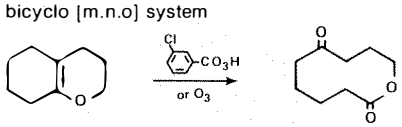


I 7a 7b 7c

Conformation of Erythronolide B

utilized a 2,3-sigmatropic rearrangement by which the original ring system was expanded by three carbon atoms.[7] This ring-growing reaction is repeatable; therefore, consecutive applications of this sequence would lead, in principle, to the construction of a desired ring system. The approaches represented by these two examples, however, must solve difficult stereochemical problems of a medium-sized ring system at each step. Several cyclizations of acyclic precursors have been reported, and one of the most recent involves the aldol condensation of an aldehydic bromo ester.[8]

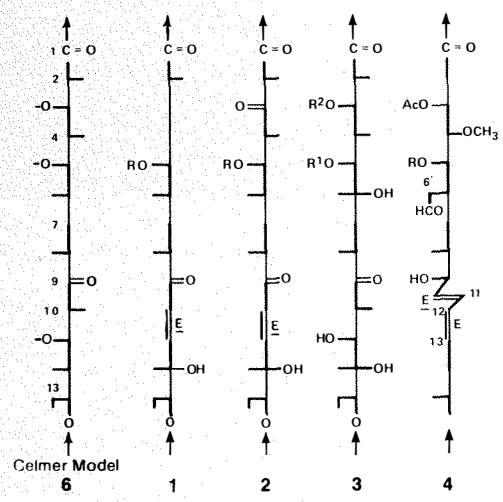
The fused bond rupture of a bicyclo [m.n.o] system



Borowitz[6] **(eq. 1)**

It is appropriate at this point to consider the feasibility of the direct lactonization of the seco-acid corresponding to a natural macrolide. This is obviously a most naive way to analyze the synthesis of a macrolide, and it is rather surprising that this method has not been utilized until recently. There was one reason for it. Stoll's classical work on the acid-catalyzed lactonization of ω-hydroxycarboxylic acids (eq. 4) was indeed discouraging for the purpose of preparing the corresponding monolactone, and even the use of a dilute solution of the carboxylic acid (**8**) led to none of compound **9** and the majority of the product consisted of the dimer **10** or oligomer.[9] This reaction, in essence, is the competition between the first order versus second order reaction; therefore, in an infinitely dilute solution of **8** the lactone **9** should be the sole product. This high dilution technique can be effected in practice, if one can devise an efficient method for the reaction. Suppose you add slowly a solution of compound **11** (eq. 5) to dimethyl sulfoxide containing potassium carbonate.[10] Since the lactonization proceeds very rapidly, the first drop of compound **11** completes its reaction before the second drop is added to the solution; thus, at any given time the concentration of **11** is extremely small. Galli and Mandolini report that the ratio of **9** to **12** is 89:9.[10] Another important consideration in this connection is concerned with the conformational rigidity of the seco-acid which may favor the lactonization rather than intermolecular ester formation. These two encouraging, nonetheless very risky predictions led us to examine direct lactonization of the seco-acid for the synthesis of methymycin, and fortunately we were able to complete the first synthesis of this polyoxo macrolide.[11] Since then the lactonization of seco-acids has become the standard ap-

Figure 1



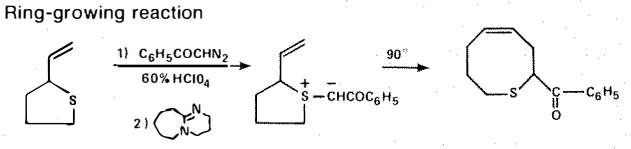
Celmer Model

6 **1** **2** **3** **4**

1: Methymycin 3: Erythromycin A

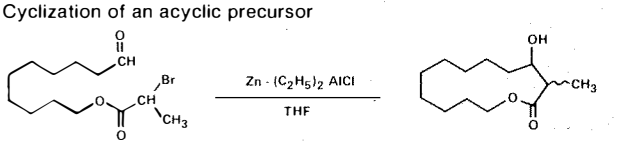
2: Pikromycin 4: Leucomycin

Ring-growing reaction

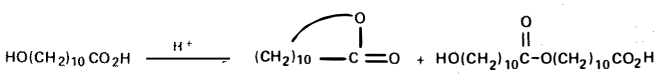


Vedejs[7] **(eq. 2)**

Cyclization of an acyclic precursor

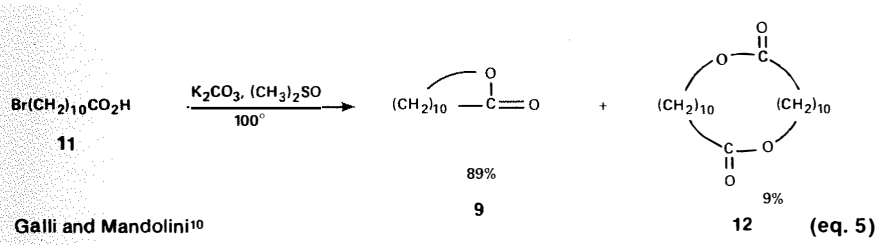


Nozaki[8] **(eq. 3)**



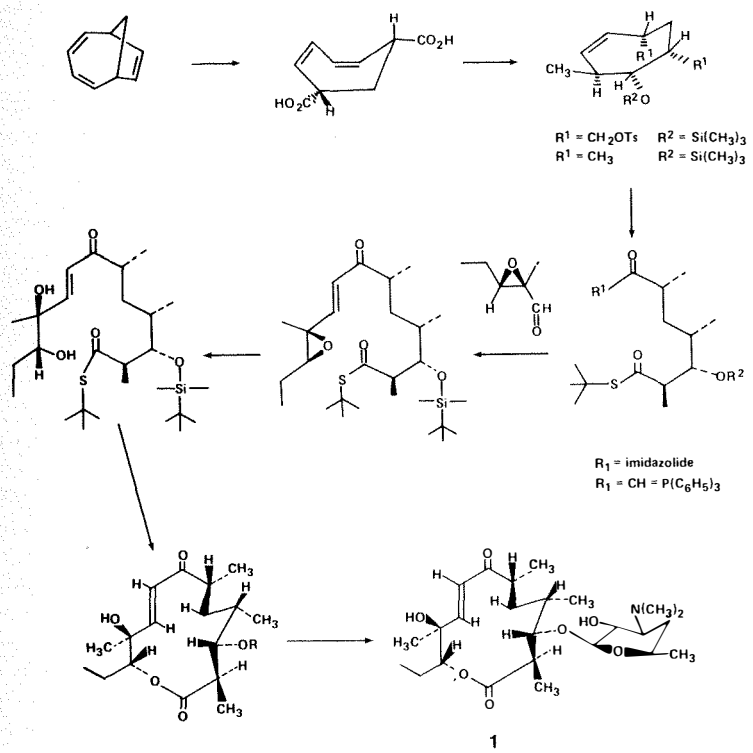
8 **9** **10**

Stoll[9] **(eq. 4)**



Galli and Mandolini[10] (eq. 5)

Scheme I



1

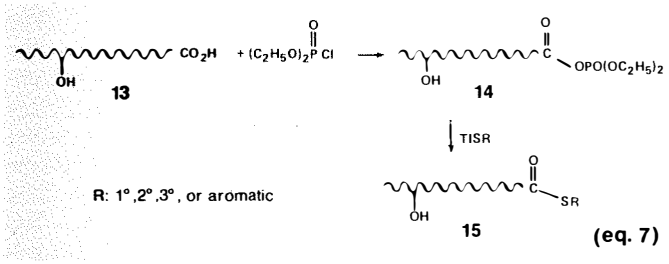
proach to the synthesis of macrolide molecules.

Scheme I outlines the synthesis of methymycin (**1**)[11] which appears to represent a major part of the citation for the Award. I am not going into details of each step but wish to draw your attention to the process of lactonization. The use of thiol esters for this purpose is obviously hinted at by a similar process likely taking place in the biological system, and a considerable effort has been made since the completion of the methymycin synthesis in order to widen the scope and define the limitations.

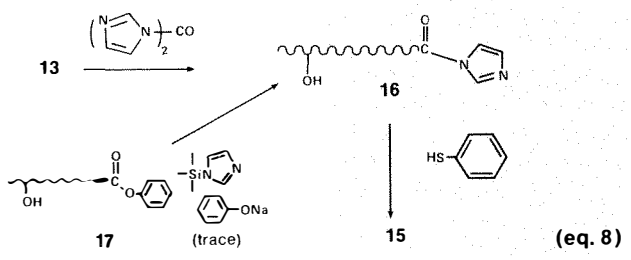
In view of the enormous amount of sulfur chemistry accumulated over a century, I was surprised to find at the outset of this work that there had not been much chemistry done which was useful and applicable to our case. The synthesis of thiol esters was one of them. Thus, our work began with this apparently simple preparative method. The standard method to prepare thiol esters using an acid chloride and sodium thiolate does not proceed well when both R and R[1] are bulky and this problem was quickly solved by replacing sodium with thallium (eq. 6).[12] Another problem which one faces very often in the macrolide synthesis is selective functionalization of the carboxylic acid in the presence of hydroxy groups in the same molecule. The examination of the behavior of diethyl chlorophosphate has suggested that it might distinguish between the two groups. Indeed, use of this reagent converted compound **13** into the anhydride (**14**) of compound **13** and phosphoric acid which in turn produced the desired thiol ester (**15**) upon treatment with thallium thiolate (eq. 7). This reaction is quite general and R can be primary, secondary, tertiary aliphatic, or aromatic.[13] A similar selectivity was also attained with carbonyldiimidazole and the intervening acid imidazolide (**16**) was converted into its benzenethiol ester (**15**) (eq. 8).[14] This last reaction appears to require protonation of imidazole; therefore, a less acidic alkanethiol does not react readily with this intermediate. Very often the direct conversion of an ester into the corresponding thiol ester is desirable, and this has been achieved by reacting a phenyl ester (**17**) with trimethylsilylimidazole in the presence of trace amounts of sodium phenoxide.[15] Reactive thiol esters such as pyridinethiol esters (**18**) can be prepared by Mukaiyama's procedure[16] using triphenylphosphine and the corresponding disulfide (eq. 9).

Several satisfactory procedures are now available for the preparation of thiol esters, and the next step involves conversion of the thiol esters to the corresponding lactones or O-esters through thiol activation. Three efficient techniques for this conversion were disclosed almost simultaneously by three research groups and became available for use three years ago. Our method utilizes thiophilic mercury(II) salts to activate alkanethiol esters (eq. 10).[17] The reaction proceeds, in general, almost instantaneously at room temperature or below to provide a near-quantitative yield of compound **19**. Corey's procedure is patterned after Mukaiyama's peptide synthesis using pyri-

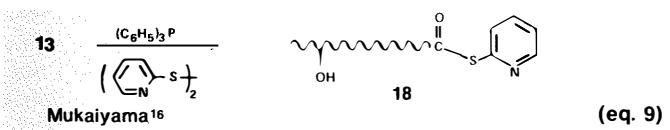
RCOCl + TISR[1] ⟶ RCOSR[1] (eq. 6)
(R,R[1]: Bulky)



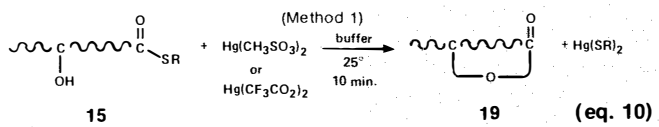
(eq. 7)



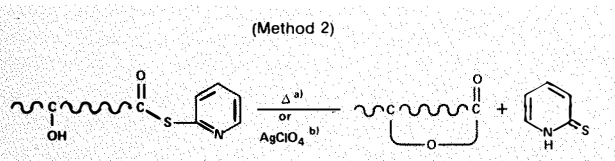
(eq. 8)



(eq. 9)



(eq. 10)



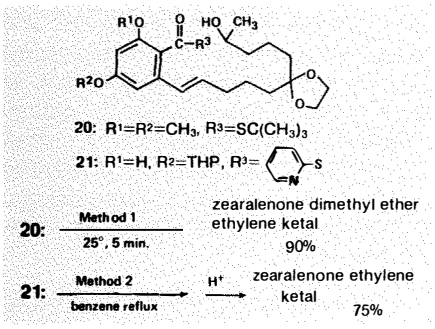
equation 11a Corey[18]
equation 11b Gerlach[19]

(eq. 11)

Table 1

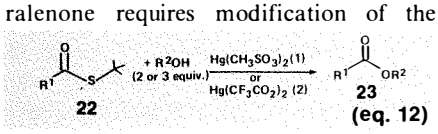
Entry	R^1	R^2	Reagent	Buffer	Yield(%)
1			1 or 2	Na_2HSO_4 (or none)	100%
2			1		90%
3			1 or 2		85%
4				Na_2HPO_4	

dinethiol esters (**18**) for the S→O conversion (eq. 11).[18] Since the hydroxy group is not a particularly good nucleophile toward thiol esters as compared with the amino group, this conversion requires refluxing of a xylene or toluene solution of compound **18** for a prolonged period of time (eq. 11a). Gerlach found that the same reaction was enormously accelerated by the addition of silver perchlorate and was completed within one hour at room temperature (eq. 11b).[19] The superiority of the newer methods as compared with the earlier,



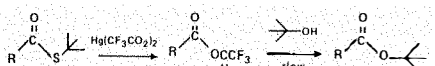
classical techniques was evident. For instance, the lactonization of a zearalenone seco-acid derivative (**20** with R^3=OH) by means of the mixed anhydride method published in 1968, proceeded in low yield,[20] whereas use of the thiol esters (**20** and **21**) with or without a catalyst brought about quite acceptable results.

The application of equation 10 to macrolides other than methymycin and zearalenone requires modification of the

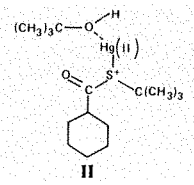


(eq. 12)

original procedure and progress has been made to this end.[21] First, it should be pointed out that 2-methylpropane-2-thiol esters (**22**) are as stable toward acid and base as O-esters and survive many synthetic operations. Second, the S→O conversion (eq. 12) proceeds smoothly even if both R^1 and R^2 are very bulky (Table 1). The pivalic thiol ester provides a 90% yield of its O-*tert*-butyl ester (**23**) upon this treatment (entry 2). The double bond conjugation does not suppress the efficiency of this reaction (entry 3). This result almost excludes the intermediacy of the ketene during this reaction and the retention of the α-deuterium during the same reaction (entry 4) further corroborates this conclusion. Expectedly, in the absence of an alcohol, Hg(II) trifluoroacetate converts thiol esters (**22**) into the mixed anhydride (**24**) which only slowly reacts with *tert*-butyl alcohol, approximately ten times more slowly than the above S→O conversion (eq. 13). Therefore, we conclude that the major course of the direct conversion involves an intermediate complex similar to that shown as II. In this intermediate, the soft-



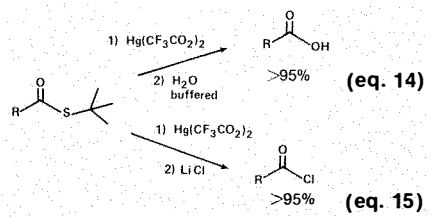
(eq. 13)



II

soft interaction between the sulfur and Hg(II) and the hard-hard combination of the hydroxy and acyl groups ideally satisfy Saville's rule[22] and effect the desired reaction smoothly. There arises no problem in the hydrolysis of thiol esters and their conversion into the acid chlorides also proceeds without difficulty (eqs. 14 and 15).[23] These two operations are executed under neutral or near neutral conditions, so that sensitive functional and protective groups remain intact.

Needless to say, this Hg(II)-assisted activation of thiol esters is not free from disadvantageous side reactions, which are mainly caused by the soft-soft interaction of Hg(II) with other functional groups. Thus, the metal cation reacts with an electron-rich double bond to bring about the well known hydroxymercuration although α,β-unsaturated ketones and esters very



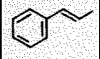
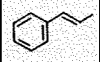
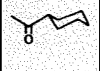
(eq. 14)

(eq. 15)

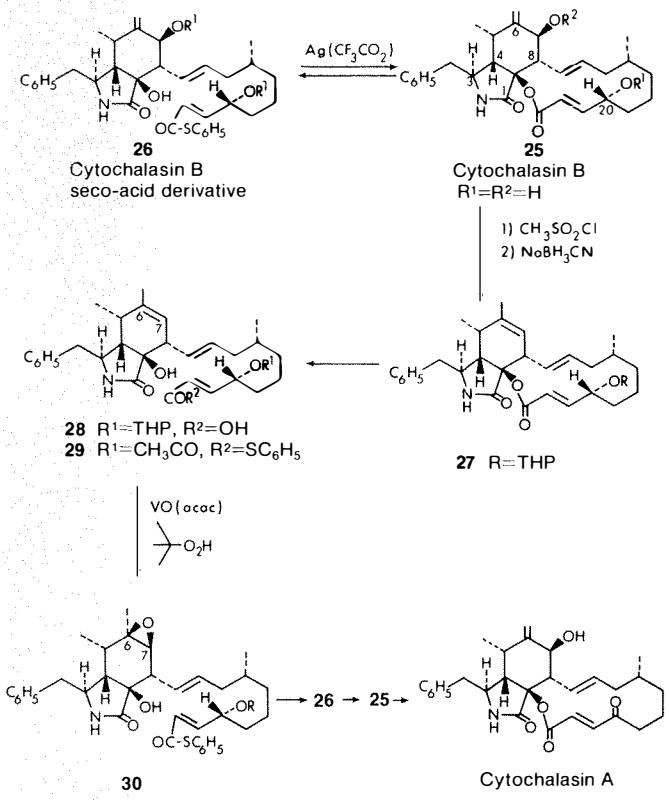
often found in macrolides are inert to this reagent. How can we overcome this difficulty when a reactive double bond is present in the substrate? Note that in the S→O conversion reaction there are four variables to manipulate: S, R^2, M, and X (eq. 16). All that has to be done is to find a combination of reactivity-matching pairs for the reaction. Since selenol esters are found to offer no obvious advantages and indeed suffer from several other serious side reactions, we decided to concentrate our investigation on the behavior of thiol esters. Known soft or thiophilic cations other than Hg(II), and chemically inert to ordinary double bonds are Ag(I), Cu(I), and Cu(II), and the reactivity of these cations toward thiol esters was first tested. Interestingly, *S-tert*-butyl cyclohexylmethanethioate was completely inert to $Ag(I)CF_3CO_2$ and $Ag(I)CF_3SO_3$ even if a tetrahydrofuran reaction mixture was refluxed for a prolonged period of time (entry 1 in Table 2). This result suggested a need for modification of R^2 in order to match the reactivity of S with Ag(I). Thus, replacement of the *tert*-butyl group with the phenyl or benzothiazole group brought about very rewarding results (entries 2 and 3). The three entries (4, 5, and 6) deal with the model experiment for a synthesis of cytochalasin, and the last three examples (entries 7, 8, and 9) provide some assurance that pikromycin seco-acid which has a β-keto moiety would cyclize with the combination of the 2-methylpropane-2-thiol ester and $Cu(I)CF_3CO_2$ or the benzenethiol ester and $Ag(I)CF_3CO_2$.

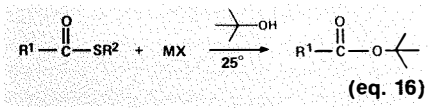
Cytochalasins have attracted much attention in recent years because of their unique cytostatic activity (see Scheme II). The structure of the B species (**25**) shows, in a rather straightforward manner, that a simple retrosynthesis dissects the molecule into three sub-units because of the stereochemistry of the ring juncture and also the presence of functional groups, providing the seco-acid can be lactonized at a late stage of the synthesis. This assumption is rather "shaky" because of the tertiary nature of the hydroxy group and the extreme crowdedness of the reaction center as well as the presence of some sensitive functional groups in its neighborhood. Therefore the

Table 2

Entry	R¹	R²	MX	Solvent	Time	Yield
1			$Ag(CF_3CO_2)$ $Ag(CF_3SO_3)$	THF THF	18 hr. 18 hr.	0 0
2			$Ag(CF_3CO_2)$	C_6H_6/THF	3 hr.	95%
3			$Ag(CF_3CO_2)$	C_6H_6	10 min.	100%
4			$Cu(CF_3SO_3)$	C_6H_6/THF	5 hr	80%
5			$Cu(CF_3SO_3)_2$ $Ag(CF_3CO_2)$ $AgBF_4$ $Ag(CF_3SO_3)$	CH_3CN C_6H_6 (Δ) C_6H_6 (Δ) C_6H_6 (Δ)	1.5 hr. 1.5 hr. 1 hr. 1 hr.	24% 100% 5% 5%
6			$Ag(CF_3CO_2)$ $Cu(CF_3SO_3)$ $Cu(CF_3SO_3)_2$	C_6H_6 (Δ) C_6H_6/THF CH_3CN	1.5 hr. 5 hr. 30 min.	100% 90% 100%
7			$Hg(CF_3CO_2)_2$ $Ag(CF_3CO_2)$ $Cu(CF_3SO_3)$	CH_3CN THF C_6H_6	0.5 hr. 18 hr. 2 hr.	0 recover 100%
8			$Cu(CF_3CO_2)$	CH_2Cl_2	2 hr.	100%
9			$Hg(CF_3CO_2)_2$ $Ag(CF_3CO_2)$	CH_3CN THF	0.5 hr. 2 hr.	0 95%

Scheme II



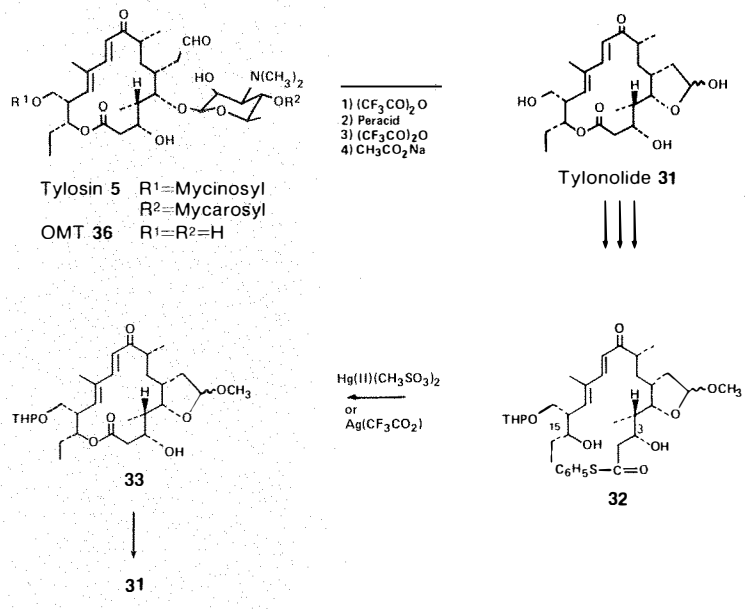


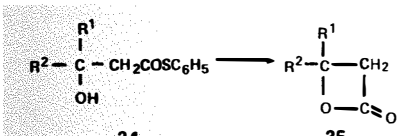
(eq. 16)

feasibility of the lactonization should be examined before attempting the construction of the seco-acid. None of the then existing methods was applicable to this lactonization and the Hg(II) activation simply destroyed cytochalasin B very readily. Indeed it was this failure that had motivated us to modify the original procedure and broaden the scope of the S→O conversion reaction that has been discussed. Ag(I) forms a complex with cytochalasin but is inert chemically, and eventually turned out to be a reagent of choice. The benzenethiol ester (**26**) of the diacetylcytochalasin seco-acid derived from the natural metabolite underwent smooth cyclization in the desired manner,[21] and therefore the presumed last step of the synthesis is now secured. Additional conversions of **25** have been made.[21] Reductive isomerization of the allylic system *via* the mesylate (**25**→**27**) followed by lactone opening provided **28** which was converted to **29** and then epoxidized by Sharpless' procedure. The acid treatment of **30** afforded cytochalasin B seco-acid **26**. The utility of compound **28** as a relay compound is thus evident. The stereochemistry of this ring juncture is such that the Diels-Alder reaction of two appropriate components (diene and ene) does lead to the correct stereochemistry as shown by Weinreb,[24] and substantial progress toward the synthesis of **28** has already been made.

Another interesting observation is worth mentioning. Tylonolide (**31**), the aglycone of a 16-membered macrolide antibiotic, tylosin (**5**), has been converted into the corresponding seco-acid derivative (**32**) through three steps (Scheme III). Treatment of the compound with Hg(II)-$(CH_3SO_3)_2$ or better with Ag(I)CF_3CO_2 effected formation of the 16-membered lactone system.[25] It is rather surprising to note that the 15-hydroxy group had to compete with the hydroxy group located at the 3-position for lactonization, yet the macrocyclic ring (**33**) has formed. We were aware that the benzenethiol ester of a β-hydroxycarboxylic acid (**34**) produces, under the same conditions, the corresponding β-lactone (**35**) in good yield (eq. 17) and that the β-lactone corresponding to **32** is not an intermediate of the lactonization of **32** to **33**. There must be some strong conformational preference as is suggested

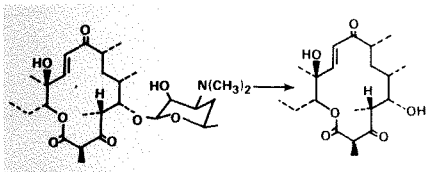
Scheme III





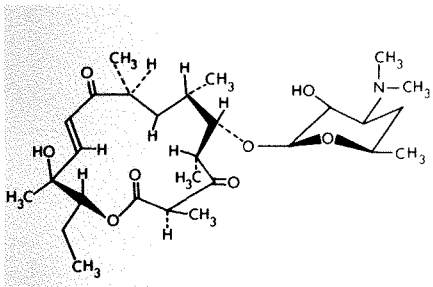
34 35

(eq. 17)



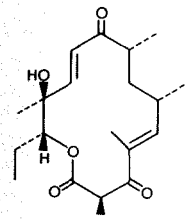
Pikromycin Pikronolide (37)

(eq. 18)



2a
Pikromycin

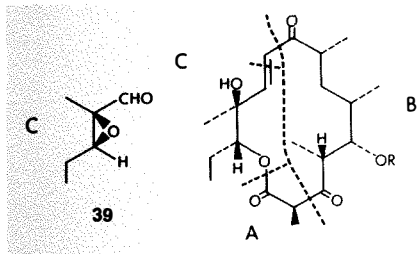
pH 6.5
100°



38

Kromycin

(eq. 19)



39 37
Pikronolide (R=H)

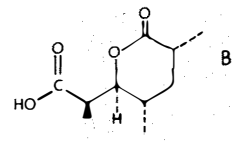
(+)-C + rac.B + A → (+)-C—(+)-B—A + (+)-C—(-)-B—A

from the CPK atomic model. No appreciable non-bonded interaction is expected to be present inside the ring system in contrast to the situation of 12-membered methymycin. Tylosin also provided us with the unique opportunity to devise a procedure to remove an acid-resistant amino sugar from an antibiotic under mild conditions in order to secure an intact aglycone — a general problem inherent to macrolide antibiotics that required a solution. Obviously, direct acid hydrolysis of the glycoside linkage present in tylosin leads to partial or total destruction of the aglycone tylonolide. Application of the Polonovski reaction to OMT (**36**) involving the conversion of the amine to its amine oxide and ensuing acylation offered a smooth pathway to tylonolide. This technique is also found to be applicable to pikromycin (**2**) (eq. 18), which is unusually prone to eliminate water as is evident from its structure.

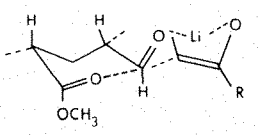
The rest of this lecture describes our effort directed toward the synthesis of pikromycin. We are no longer worried about the success of lactonization, but our main attention has been directed toward two unique aspects of this molecule: the presence of the β-keto ester moiety which has indeed caused many problems during the synthesis, and facile elimination of water from the β-hydroxy ketone fragment. Brockmann, as early as 1950, noted this elimination and his attempt at preparing pikronolide (**37**), the intact aglycone, invariably led to the formation of kromycin (**38**) (eq. 19). The correct structure and a likely conformation of this antibiotic are now known, and the facile elimination which occurs even at pH 6.5 (an observation by Brockmann) is explained by the *anti*-periplanar disposition of the hydroxy and glycosidic linkages as shown in **2a**. The retrosynthetic dissection of the molecule was patterned after our earlier synthesis of methymycin and consists of three fragments A, B, and C.

The enolate or its equivalent derived from propionic thiol ester (propanethioate) serves as fragment A and the aldehyde **39** which has already been available in optically pure form can be utilized to construct the C unit. Fragment B is a modified representation of the so-called Prelog-Djerassi lactonic acid (**40**), which was prepared from the cycloheptene derivative (**41**) as described in the methymycin synthesis.[11] Recently lactonic acid **40** has been more conveniently obtained from aldehyde **42** using Heathcock's procedure (eq. 20).[26] Reaction of this readily obtainable aldehyde (**42**) with enolate **43** afforded the aldol product **44** in as high as 50% yield (eq. 21). This result is rather surprising because Cram's rule does not apply to this case. A tentative explanation may be offered by invoking some weak interaction of the rather remote carbomethoxy group with the aldehydic group. The β-side approach of the enolate as shown in **III** is thus disfavored and the now preferred conformation similar to **IV** leads to the formation of **44**. Recent studies in our laboratory demonstrate that boron enolates also undergo stereoselective aldol condensations and appear to solve several fundamental problems exemplified here by the conversion of **42** into **44**. Hopefully the progress of this investigation will soon reach a stage that the results may be disclosed.

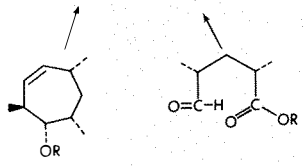
We planned to combine the optically pure C fragment with racemic B+A to give a diastereoisomeric mixture of (+)-C-(+)-B-A and (+)-C-(-)-B-A. Our expectation was that the wrong isomer might fail to cyclize as judged from inspection of CPK



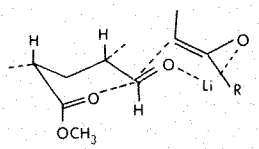
40
Prelog-Djerassi lactonic acid



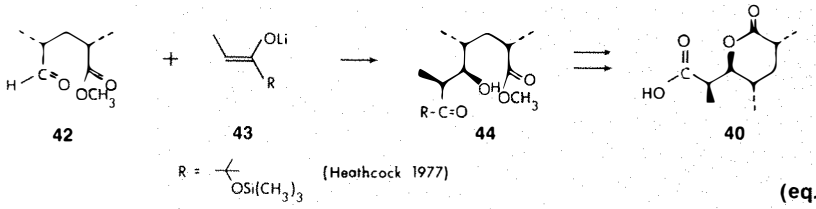
III



41 42 (eq. 20)



IV



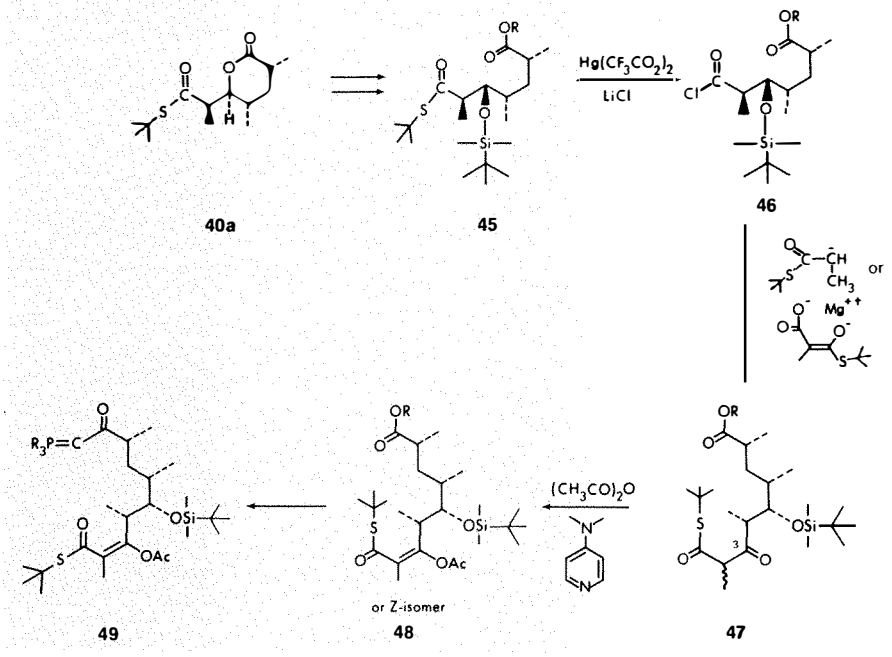
42 43 44 40

R = $-O-Si(CH_3)_3$ (Heathcock 1977)

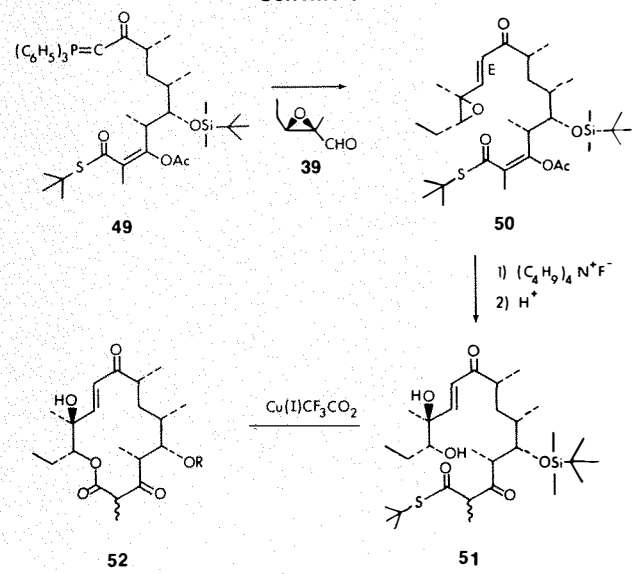
(eq. 21)

models, and thus, separation would be facilitated after the lactonization. There are two sequences for combination of the three fragments: A+B+C (counter clockwise) and C+B+A (clockwise). The A+B+C sequence was examined first and is briefly summarized in Scheme IV. The facile ring opening of the δ-lactone **40a** which proceeds *ca.* 100 times as fast as the alkaline hydrolysis of normal esters leads to the hydroxy acid salt which is then converted *via* two steps to the silyl ether (**45**) with R = C_6H_5 or Cl_3C-CH_2. The acid chloride **46** is now readily obtainable from the thiol ester and treated at -70°C with a standard acylating reagent without causing epimerization of the chiral centers to provide compound **47**. In order to suppress the facile dehydration of **47**, there was a need for deactivation of the 3-keto group which was attained by means of acetylation. Conversion of **48** into the (neutral) Wittig reagent (**49**) followed the procedure previously utilized for the methymycin synthesis.

Scheme IV



Scheme V



The Wittig reagent **49** with the aldehyde **39** proceeded in the expected manner to afford **50** with an *E* double bond and the next operation involved the removal of an O-protecting group (Scheme V). The two protecting groups were originally chosen because the generation of the O^- anion at the 5-position by means of the F^- anion should induce the acyl migration from the C-3 enol position. What actually occurred in the system was that the silyl group brought in its vicinity the F^- anion which subsequently attacked the C-3 acetyl group rather than the C-5 silyl protecting group. We realized the seriousness of this result, nonetheless proceeded with the next cyclization which provided the 14-membered lactone **52** in acceptable yield. Compound **52** turned out to be, as we were afraid, a dead-end product and all the attempts at removing the silyl group resulted in either recovery of **52** or destruction of the system. For example, the F^- anion, a specific reagent for cleavage of the O-Si bond, in this case caused enolate formation at C-2,3 and the silyl ether remained intact. This unusual stability of the O-Si$(CH_3)_2$(*tert*-C_4H_9) group toward the F^- anion may be due to the presence of the electronegative O-group in the vicinity of the silyl group repelling the approach of a second anion of F^-. Also mild acid treatment of **52** led to complete recovery of starting material under conditions normally used to liberate the hydroxy group of a silyl ether. This result may be due to the extremely crowded environment of the silyl ether at C-5.

Clearly there was a need for the invention of a new OH-protecting group or reexamination of older ones to replace the *tert*-butyldimethylsilyl group. We have also considered the alternative C+B+A, clockwise approach rather than the A+B+C that has just been presented. While the latter approach requires two protecting groups, the former needs only one for the 5-OH group, but demands a mild acylation technique, disallowing the use of the normal, basic conditions generally used for this reaction. Thus, if one adopts the C+B+A approach, there are two problems: (1) use of a proper OH-protecting group which satisfies several conditions and (2) realization of non-basic acylation.

The requirement for the OH-protecting groups in the present case is described as follows. The same group must be attached to both the hydroxy and carboxy group and be selectively removed to regenerate the latter. Because the hydroxycarboxylic acid (**45** without Si protection) derived from Prelog-Djerassi's lactone (**40a**) relactonizes with extreme ease, the attachment of the protective group to OH must proceed with high efficiency. The protected hydroxy group then should survive a variety of conditions tabulated below and be removed selectively under mild conditions. Our choice, after many trials, has turned out to be the old methoxymethyl group, which has not enjoyed popularity in the

Stability of R-OCH_2OCH_3

survive:

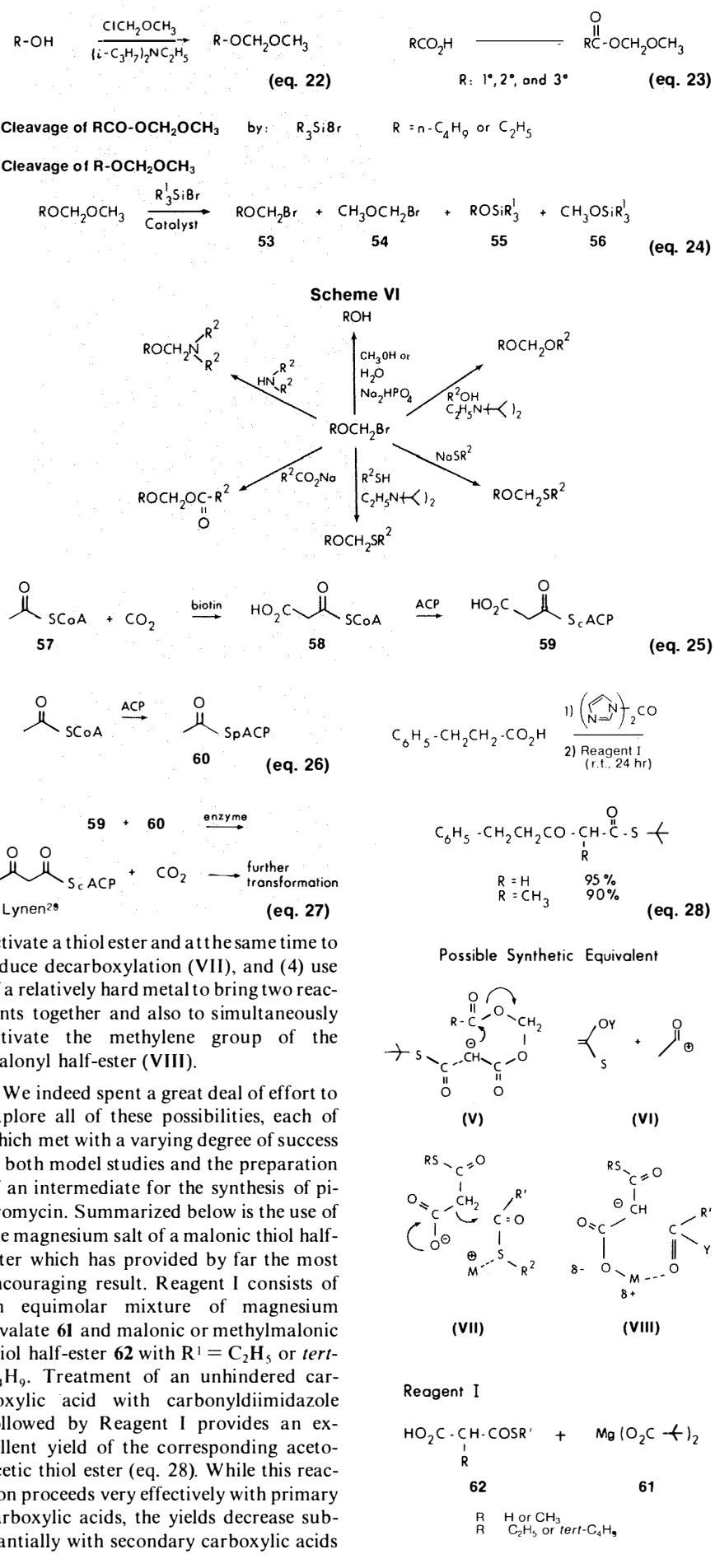
1N H_2SO_4 in THF, 16 hr
$ZnBr_2$, $MgBr_2$
$(CH_3)_3C$-S^- in DMF or THF
Hg(II), Cu(I)
$(n$-$C_4H_9)_4N^+F^-$

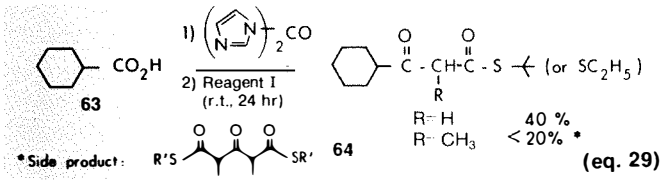
past, partly because the removal requires somewhat drastic conditions or hydride abstraction.[27] The deficiencies have now been remedied. First, primary, secondary, and tertiary hydroxy groups as well as carboxylic acids are protected efficiently (eqs. 22 and 23). The stability of $R\text{-}OCH_2OCH_3$ appeared quite adequate for its use in the sequence and provided a promising outlook.

Selective cleavage of methoxymethyl esters in the presence of methoxymethyl ethers can easily be effected by bromotributylsilane and a trace amount of methanol,[28] followed by near-neutral hydrolysis. In contrast, cleavage of methoxymethyl ethers is somewhat complex. Some phosphorus impurities which had fortuitously been introduced into the silyl reagents in our earlier preparations, and whose exact composition is still unknown to us, were found to catalyze the reaction (eq. 24). With small R^1, the reaction of a methoxymethyl ether with bromosilanes leads initially to a kinetically controlled distribution of four possible products (**53**, **54**, **55** and **56**) which equilibrate to a thermodynamically controlled mixture. However, when both R and R^1 are bulky (*e.g.*, *i*-C_4H_9) as in the present case, there is no equilibration and the formation of $ROCH_2Br$ proceeds in excellent yields. Thus, removal of the methoxymethyl protecting group or its conversion into other protecting groups appropriate for the ensuing operation has become feasible as shown (Scheme **VI**).

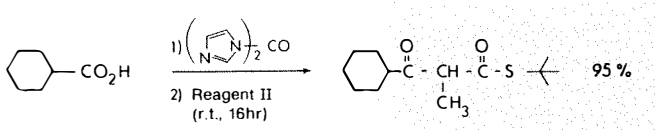
The methoxymethyl protecting group having met the requirements, our attention was focused on the development of a facile non-basic acyl-transfer reaction. A brief description of the acetoacetic acid biosynthesis is an appropriate introduction to this subject.[29] One molecule of acetyl CoA (**57**) is transformed, with the aid of biotin, into malonyl CoA (**58**) which is properly attached to an acyl carrier protein (ACP) through a so-called central SH, as indicated in **59** (eq. 25). Another molecule of acetyl CoA, after being linked with a peripheral SH in ACP, moves into the active site of an enzyme and acts as an acceptor of malonyl CoA (eq. 26), and then the condensation takes place with concurrent evolution of CO_2 (eq. 27). Probably organic chemists can conceive several reaction systems that mimic this biosynthetic process and bring about a non-enzymatic, efficient acetoacetic acid condensation. Four such reaction systems are: (1) intramolecular acylation, using malonyl thiol half-ester as an enolate source (V), (2) neutral generation of an acyl cation in the presence of a ketene hemithioacetal (VI), (3) use of a thiophilic metal [*e.g.*, Cu(I)] to activate a thiol ester and at the same time to induce decarboxylation (VII), and (4) use of a relatively hard metal to bring two reactants together and also to simultaneously activate the methylene group of the malonyl half-ester (VIII).

We indeed spent a great deal of effort to explore all of these possibilities, each of which met with a varying degree of success in both model studies and the preparation of an intermediate for the synthesis of pikromycin. Summarized below is the use of the magnesium salt of a malonic thiol half-ester which has provided by far the most encouraging result. Reagent I consists of an equimolar mixture of magnesium pivalate **61** and malonic or methylmalonic thiol half-ester **62** with $R^1 = C_2H_5$ or *tert*-C_4H_9. Treatment of an unhindered carboxylic acid with carbonyldiimidazole followed by Reagent I provides an excellent yield of the corresponding acetoacetic thiol ester (eq. 28). While this reaction proceeds very effectively with primary carboxylic acids, the yields decrease substantially with secondary carboxylic acids

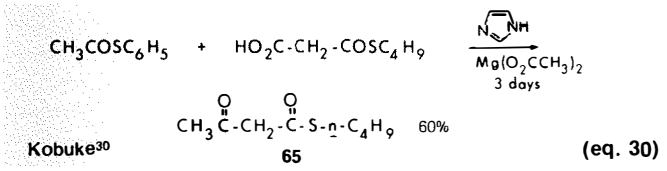




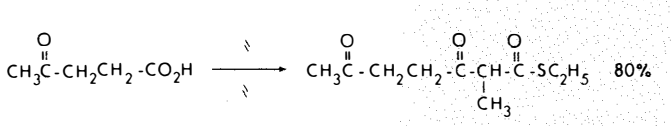
(eq. 29)



(eq. 32)

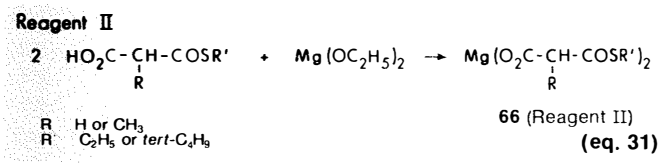


(eq. 30)

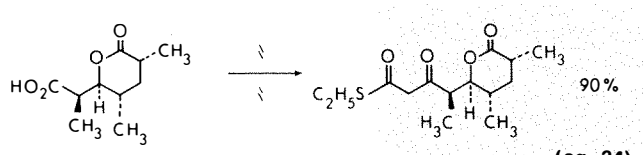


(eq. 33)

Reagent II



(eq. 31)

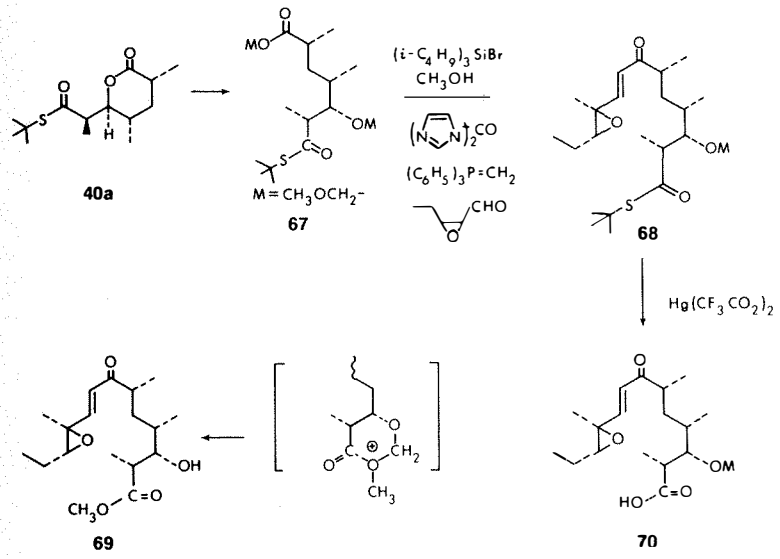


(eq. 34)

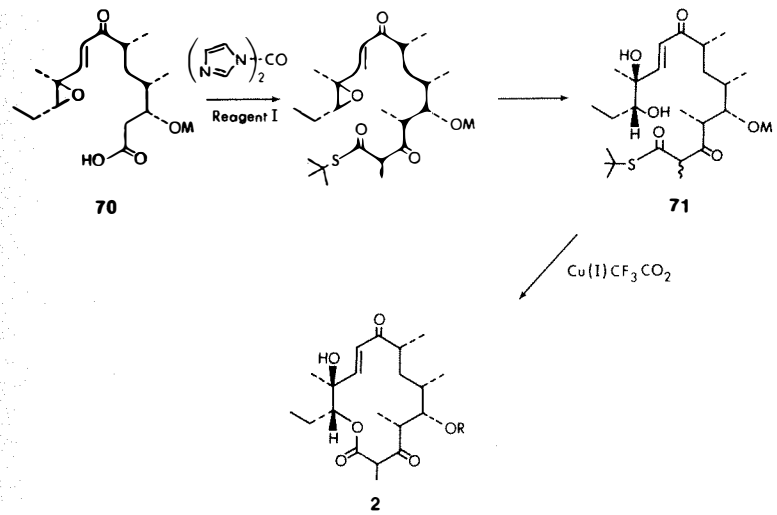
such as cyclohexanecarboxylic acid **63** and the formation of dimethylacetonedicarboxylic thiol ester **64** becomes a major reaction course (eq. 29). Other salts thus far tested include Zn(II), Cu(II), Co(II), $Ag(I)CF_3CO_2$, $Mg(II)(CF_3CO_2)_2$, and these were found to be less effective than Mg(II) pivalate **61**. Before a newer version (Reagent II) of Reagent I is discussed, a recent report by Kobuke and Yoshida should be mentioned, which describes the formation of an acetoacetic thiol ester **65** from the benzenethiol ester of acetic acid and a malonic half-thiol ester in the presence of imidazole and magnesium acetate (eq. 30).[30]

Reagent II, the magnesium salt of malonic or alkylmalonic thiol half-ester **66** (eq. 31), is much more effective than Reagent I and provides a wide scope of this reaction. Note that Reagent II is a neutral, crystalline salt, and that the acylation proceeds under *near-neutral conditions with sensitive functional groups being kept intact*, an achievement significant to organic synthesis. Three selected examples clearly demonstrate the superiority of this reaction (eqs. 32-34).

Scheme VII



Scheme VIII



We were now ready to utilize the new acylation reaction for the synthesis of pikromycin **2**. The thiol ester (**40a**) of the Prelog-Djerassi lactone was converted to its open form with the methoxymethyl protective group as shown in **67** (Scheme VII) and then was connected with the left-hand fragment C to provide **68** in a manner similar to that described earlier. The reaction of **68** with $Hg(CF_3CO_2)_2$ under the standard conditions took a rather abnormal course to give **69** because of the unexpected participation of the methoxymethyl group in the reaction, but this difficulty was soon overcome by a modified procedure.

The next crucial step, acylation of **70**, (Scheme VIII) proceeded rather ironically even with Reagent I, which is normally less efficient than Reagent II, despite the steric congestion around the carboxylic acid. As was noted earlier in the Hg(II) treatment of **68**, this anomalous behavior appears to be again attributable to the methoxymethyl participation which leads to the activation of the acid imidazolide intermediate which reacts with Reagent I. We now have the pikronolide seco-acid precursor **70** with the

properly protected functional groups, and from previous experience we do not anticipate any major problem in executing the lactonization of **71**.

I have outlined the current status of our work in this area. I may conclude that the problems associated with the formation of medium- and large-sized lactones have found satisfactory solutions. This completes phase I of macrolide syntheses and we and others have now entered the second stage of the project that concerns the acyl and aldol condensations. I am pleased to learn at this meeting that some important progress has been made and am sure that the next few years will witness the major breakthrough in this challenging problem.

No account of this work would be complete without mention of the devotion and expertise of my co-workers. I wish to express my particular appreciation to Dr. G.S. Bates and Mr. D.W. Brooks who have made the progress in the pikromycin synthesis, and also to Drs. Y. Hayase and W.-K. Chan who have executed numerous delicate experiments on cytochalasin and tylosin.

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ABOUT THE AUTHOR

Professor Satoru Masamune, the recipient of the 1978 ACS Award for Creative Work in Synthetic Organic Chemistry, currently holds a joint appointment with the University of Alberta and the Massachusetts Institute of Technology.

Professor Masamune was born in Fukuoka, Japan, and received his undergraduate training at Tohoku University, an A.B. being conferred in 1952. In 1953, he came to the United States as one of the first Fulbright exchange students at the University of California at Berkeley and obtained his Ph.D. in 1957. From 1956 until 1961 he held a research appointment with the University of Wisconsin, first as a postdoctoral fellow, then as lecturer. For the next three years, he was a Fellow of the Mellon Institute in Pittsburgh before joining the staff of the University of Alberta in 1964. He was promoted to full professor in 1967. His appointment with MIT was initiated on July 1, 1978. In 1975, he was elected a Fellow of the Royal Society of Canada and has been on the editorial board of Organic Syntheses since 1970, and of Chemical Intermediates since 1976. He is in demand as a seminar speaker and recent major lectureships include the 2nd IUPAC meeting on Non-benzenoid Aromatic Compounds held in Lindau, West Germany in 1974, the 4th International Symposium on Syntheses in Organic Chemistry at Cambridge, England in 1975, the 1975-76 Purves lectureship at McGill University, the 1976-77 distinguished visiting professorship at the University of Texas, Austin, the Karl Pfister visiting professorship at MIT in 1977, and the 10th National Symposium on Non-benzenoid Aromatic Chemistry sponsored by the Chemical Society of Japan in 1977.

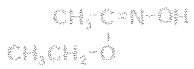
Professor Masamune has made many significant contributions to two broad areas of organic chemistry, the synthesis of natural products and the chemistry of small ring systems. His well known synthetic achievements which have resulted in international acclaim are the diterpene alkaloids, the indole alkaloids, ajmaline, and the macrolide antibiotic, methymycin. The first successful synthesis of the polyoxomacrolide was indeed remarkable in that it required solution of two formidable problems, 1) the construction of a medium-sized lactone ring and 2) the introduction of chiral centers into a straight-chain aliphatic acid. His work on small ring systems has included both cyclic π-electron and strained systems. Important results which have enriched the knowledge of the cyclic π-electron system have emerged from his work on cyclobutadiene and cyclodecapentaene. His contributions to the chemistry of strained systems have opened a new dimension in carbocation chemistry and have provided invaluable experimental evidence to evaluate recent theoretical treatments of organic molecules.

"Please Bother Us."

by Aldrich Boaders.

While visiting the Chemistry Department at Notre Dame recently, Professor Marvin Miller suggested that we make ethyl *N*-hydroxyacetimidate (frequently erroneously called ethyl acetohydroxamate in the literature), a starting material for many unusual O-substituted hydroxylamines. (Y. Tamura, J. Minamikawa and M. Ikeda, *Synthesis*, 1 (1977); M.J. Miller and G.M. Loudon, *J. Am. Chem. Soc.*, **97**, 5295 (1975); M.J. Miller, F.E. DeBons, and G.M. Loudon, *J. Org. Chem.*, **42**, 1750 (1977).

Naturally, we made this very interesting building block.



It was no bother at all, just a pleasure to be able to help.

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Selenium Reagents. See Page 43.

Organic Sulfur Compounds in Organic Synthesis. See Page 51.

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About Our Cover:

Some time ago, our chemist-collector was invited to speak to the New Orleans section of the ACS, and there he saw, in an elegant furniture store, this beautiful painting of a church interior (oil on canvas, 36 x 42$^1/_2$ inches). The painting was nameless, rather dirty and hung so high that it was difficult to see; yet our chemist was so struck by its beauty and particularly by the subtle handling of light, that he bought it.

He now believes that it was painted by one of the able mid-seventeenth century Dutch painters, Job Berckheyde, and that it depicts a Protestant church — perhaps real, perhaps imaginary. If any of our Dutch readers knows the specific church, please let our collector know.

Our chemist is a Jew, and we asked him whether he had any qualms about buying a painting of a church. He replied, "Of course not. Whenever I am in a beautiful church or see a fine painting of one, I realize with what devotion it was built or painted, and I think of Jacob's exclamation at Bethel — 'This is none other but the house of God, and this is the gate to heaven.' "

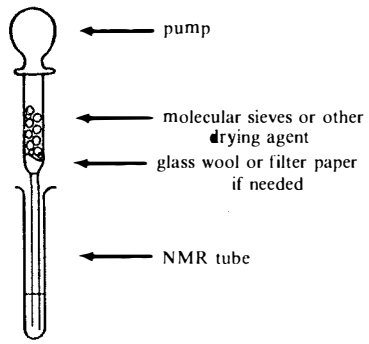
Are you interested in our Acta Covers? *Selections from the Bader Collection*, with 30 duotone reproductions, many of previous Acta covers, and an introduction by Professor Wolfgang Stechow is available to all chemist art-lovers.

Also, many paintings reproduced on our Acta covers were shown at the Milwaukee Art Center in an exhibition, "The Bible Through Dutch Eyes," arranged by Dr. Bader in 1976. The fully illustrated catalog with 66 black-and-white and 4 full-color reproductions contains many art historical and Biblical comments.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

Lab Notes

I would like to report a convenient method of drying a small amount of sample inside an NMR tube.



Often, after obtaining a spectrum, we found that the sample contained moisture. Here is a good way to dry a sample. Fill a disposable pipet (which can be made from glass tubing to desired length) with molecular sieves and any other drying agent, then pump the sample solution through a few times. The solution will be thoroughly dry, and the drying agent can be washed with a small amount of solvent.

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Sintered glass filter funnels are often difficult to clean. The following procedure works quite well. Place the funnel in a beaker or other suitable container. Add concentrated H_2SO_4 to completely cover the bottom of the funnel. *Carefully* add 5-6 drops of 30% H_2O_2 down the side of the funnel. Mixture will effervesce and froth while cleaning the glass frit. After emptying the acid, run water through the filter to rinse out the acid.

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Rapid elimination of water and ethanol from chloroform

Chloroform always contains water and ethanol (*ca.* 0.5% w/w, added as stabilizer); however, for some syntheses (*e.g.*, Schotten-Baumann reactions) it is preferable to use a solvent free of hydroxyl-containing impurities.

For an expedient purification of a desired quantity, phosphorus pentoxide is poured into chloroform; anhydrous solvent is recovered by vacuum distillation on a rotating evaporator. (Note: an efficient dessicant guard tube should be placed between the evaporator and the water aspirator!)

The solvent is stable for some days in dark bottles, as checked by the absence of the 1809 cm^{-1} absorption (C = O vibration of phosgene) in its IR spectrum.

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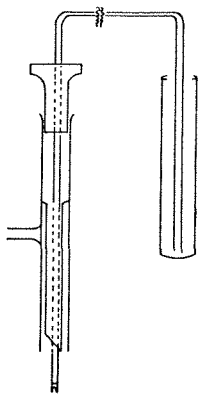
For those who routinely use fraction collectors, the transfer of fractions from test tubes to some larger vessel is very tedious, not to mention the possibility of spilled fractions and broken test tubes.

In our laboratories, we have solved these problems in a very simple manner. Shown below is a diagram of a vacuum-transfer apparatus. It consists of a vacuum adapter with 14/20 ground-glass joints, a 14 x 18-mm rubber septum and 1-m length of 1.55-mm i.d. Teflon tubing. The septum is placed on the top joint and the Teflon-tubing inserted to 1-2cm beyond the drip spout.



When vacuum is applied, the free end of the tubing is immersed into the fraction tube. All the solvent is then drawn into the collection flask. After rinsing twice, the test tube is ready for reuse without having been removed from the fraction collector. Of course, this process does not eliminate periodic cleaning of all the test tubes.

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"Please Bother Us."

by Ofira Bader.

For many years the Fieser molecular models were the best models and by far the least expensive on the market. Then their production stopped and they became collector items. As a Fieser student, I really missed them and was just so happy when I was able to arrange for their production recently. We decided to offer them in research kits containing 30 carbon atoms, enough that one could build a steroid model.

Many professors then called and wrote, suggesting that there was real need for these models for undergraduates also, but that students would not want to spend $18.00 for a research kit. We had several choices, *e.g.*, offer a smaller kit at $8.00 to $10.00, or offer the models so inexpensively to chemistry department storerooms, that the models could be resold individually to students at very low prices. We chose the latter, and offer the models in lots of 100. Thus, storerooms can now offer, say, six carbon atoms, one oxygen and one nitrogen model for under $4.00.

It was no bother at all, just a pleasure to be able to help.

Any interesting shortcut or laboratory hint you'd like to share with ACTA readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome red and white ceramic Aldrich coffee mug as well as a copy of **Selections from the Bader Collection** *(see "About Our Cover"). We reserve the right to retain all entries for consideration for future publication.*

Selenium Reagents for Organic Synthesis

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During the last few years the rapid development of selenium chemistry has provided organic synthesis with a number of very useful procedures.[1] Selenium metal is, of course, the starting point for all of these developments but it is convenient to summarize the new work by describing the main transformations that can be done with commercially available reagents or with materials easily made from them.

1. Preparation of α,β-unsaturated carbonyl compounds

One of the major applications of organoselenium chemistry is based on the fact[2] that phenyl alkyl selenides can be converted into olefins under very mild conditions (eq. 1).

The intermediate selenoxide fragments by a *syn*[2d] elimination as shown and the process is usually both rapid and efficient at room temperature. It constitutes a standard method for making α,β-unsaturated carbonyl compounds (eq. 2) and is carried out *formally* in three steps: (a) introduction of a benzeneseleno group (PhSe-) *alpha* to the carbonyl, (b) oxidation of the resulting selenide to the selenoxide level and (c) fragmentation of the selenoxide.

The usual method for introducing the PhSe- group is by way of a lithium enolate generated at a low temperature in tetrahydrofuran and then allowed to react with PhSe-SePh, PhSeCl, or PhSeBr* (eq. 3). This method has not been used with *aldehydes* but it works for ketones,[3] esters,[4] lactones,[3,4c,5] nitriles[6] and lactams.[7]

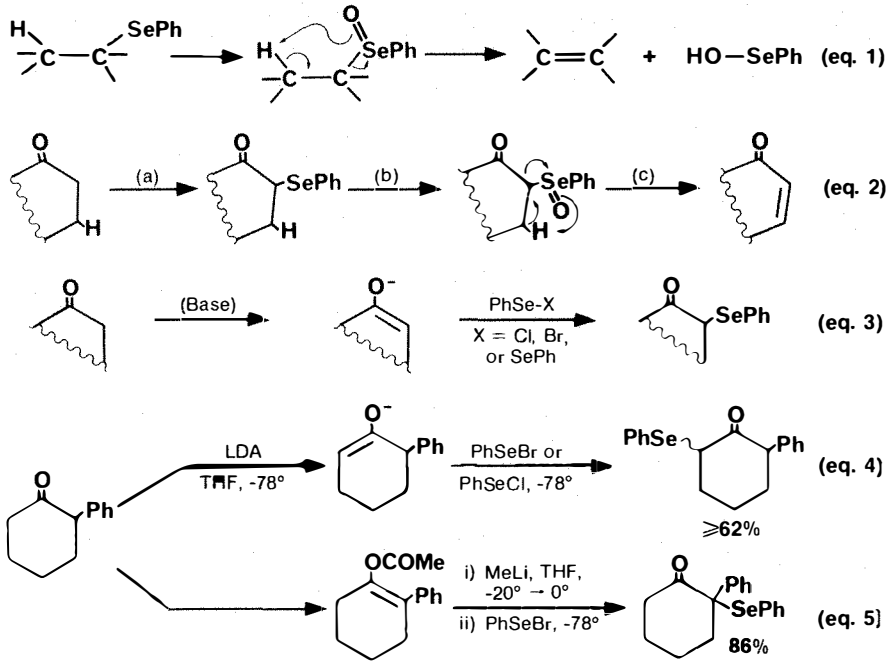
In the case of unsymmetrical ketones (eqs. 4 and 5) the kinetic enolate can be generated using LDA while the isomeric enolate is accessible *via* the enol acetate.[8] These enolates react very rapidly[3] with PhSeCl and PhSeBr, but PhSe-SePh is not suitable as a selenenylating agent for ketones.[3] It can be used, however, with the enolates of esters, lactones, and nitriles. Lactams have been studied only with PhSeCl.[7] Equations 6 → 9 are representative examples and two special points should be noted. First, the selenenylation of enolates sometimes requires the presence of HMPA to proceed well, and, secondly, *two* equivalents of base are needed for the monoselenenylation of nitriles and lactams. PhSeCl and PhSeBr can probably be used interchangeably.

The enolates of multifunctional compounds such as β-keto-esters, β-keto-sulfoxides, and β-diketones are also selenenylated by treatment with PhSeCl or PhSeBr.[3]

The selenenylation of aldehydes[4c] (and ketones) may be carried out by direct treatment with PhSeCl (*not* PhSeBr) (eq. 10). The process is accelerated by addition of a little concentrated hydrochloric acid but all mineral acid — both that added deliberately and that generated in the reaction — must be removed before oxidation of the selenide.

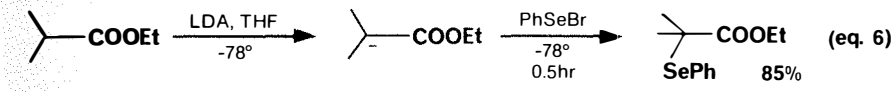
Finally, it is possible to introduce the PhSe- group in the absence of a strong base by using certain enol derivatives (eqs. 11 and 12).

With the α-selenenylated carbonyl compound in hand, the next stage involves oxidation followed by fragmentation of the resulting selenoxide. A variety of methods is available for these processes. Sodium periodate, peracids (usually *m*-chloroper-



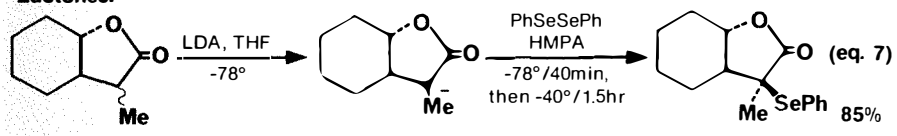
*Of these, only PhSeBr is not commercially available. It is made by adding Br_2 (1 equiv.) in dry CCl_4 to a solution of PhSe-SePh in the same solvent. Removal of CCl_4 after 30 minutes leaves a maroon, crystalline residue of PhSeBr.

Esters:[4a]



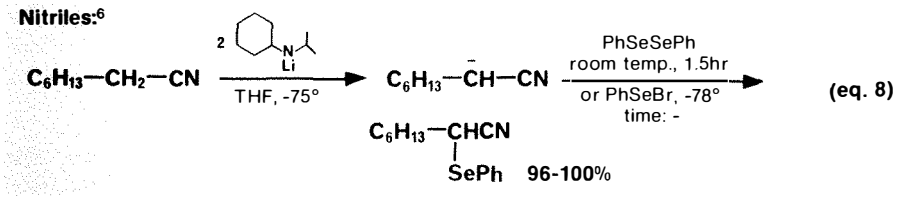
(eq. 6)

Lactones:[5b]



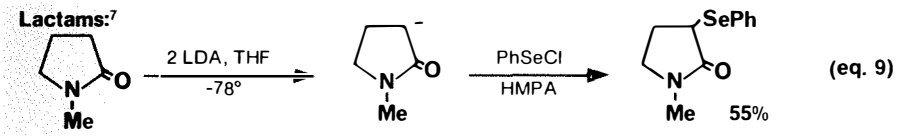
(eq. 7)

Nitriles:[6]

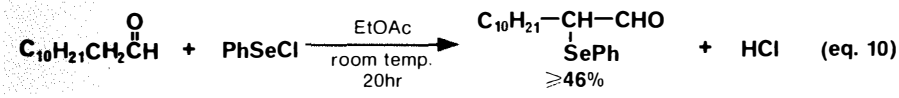


(eq. 8)

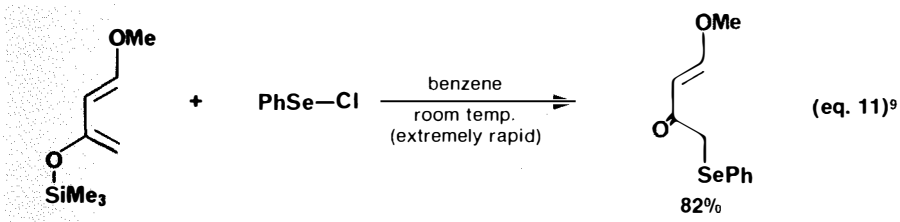
Lactams:[7]



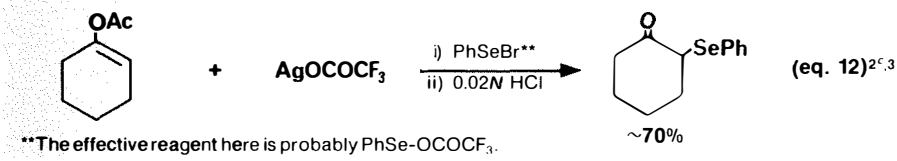
(eq. 9)



(eq. 10)

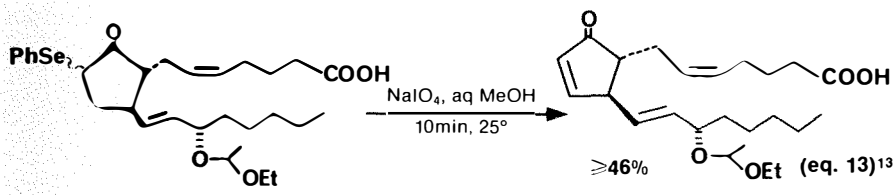


(eq. 11)[9]

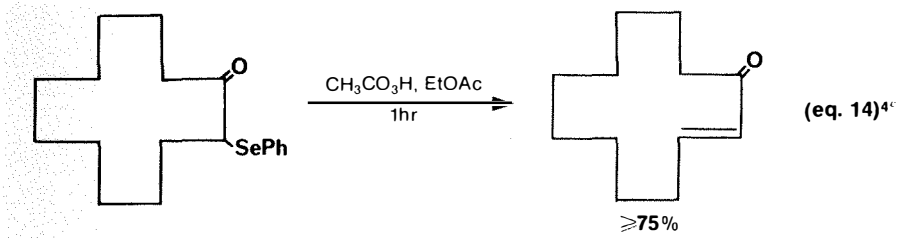


(eq. 12)[2c,3]

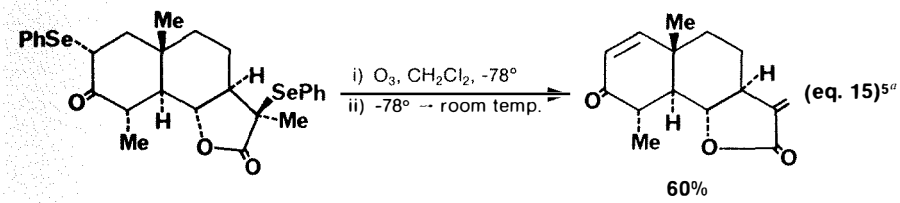
**The effective reagent here is probably PhSe-OCOCF$_3$.



(eq. 13)[13]



(eq. 14)[4c]



(eq. 15)[5a]

benzoic acid), ozone, and hydrogen peroxide are the most common reagents and it is often advisable to purify the α-selenenylated carbonyl compound — especially to free it of unselenenylated material.

The choice of reagent is guided[10] by several factors. Other functionalities in the molecule must, of course, be inert and, where an excess of oxidant is used, the sensitivity of the fragmentation product is a factor to be considered. One of the products of selenoxide fragmentation is PhSe-OH, which can disproportionate to PhSe-SePh, PhSe(O)OH, and H_2O.[3] Sometimes, however, unless special precautions are taken, the PhSe-OH is oxidized by residual selenoxide so that the eventual yield of unsaturated compound is lowered.[11]

With $NaIO_4$ general practice calls for an aqueous organic solvent and at least sufficient oxidant to react with the selenide and the PhSeOH. Under these conditions oxidation and fragmentation are complete at room temperature. Occasionally, it is an advantage to buffer the reaction mixture with sodium bicarbonate.

Peracids are generally used in an organic solvent and are employed in stoichiometric amounts (1 mole per mole of selenide) at low temperature. If the fragmentation product is inert to peracid, a sufficient amount is used to oxidize the PhSeOH formed, and the reaction is run in the temperature range of 0° to 25°.

It is usual to employ ozone at -78° (if possible) in CH_2Cl_2, Et_2O, or CCl_4. (The reagent attacks THF.)

The selenoxide (from peracid or ozone treatment) can be allowed to fragment by warming the cold selenoxide solution to room temperature. (Occasionally, pyridine is added to suppress certain side reactions.[3]) Alternatively, the cold (-78°) selenoxide solution is added to refluxing CH_2Cl_2 or CCl_4 and a useful variation of this procedure is to mix *i*-Pr_2NH with the selenoxide initially. The presence of the amine again results in improved yields.

Hydrogen peroxide (typically 30-50% w/w) is one of the most frequently used oxidants and a sufficient quantity is employed to quench the PhSeOH resulting from the fragmentation. THF is the usual solvent and careful temperature control (0° to room temperature) is necessary because the oxidation is strongly exothermic. Hydrogen peroxide converts[12] PhSe(O)OH into PhSe(O)OOH, and this compound has sometimes caused problems by epoxidizing double bonds or causing ketones to undergo the Baeyer-Villiger reaction.[12] Products sensitive to basic H_2O_2 can be protected by addition of a trace of acetic

acid.

Often, best results with H_2O_2 are obtained with the following two-phase system: a CH_2Cl_2 solution of the selenide and, usually, two equivalents of pyridine are stirred with an excess of H_2O_2. Oxidation and fragmentation are usually complete within about 15 minutes.[3]

The selenium method for making α,β-unsaturated carbonyl compounds has proved very effective in natural-product synthesis. A few of many[10] published examples of the method are shown below (eqs. 13 → 16).

2. *Preparation of olefins by using aryl selenide anions and aryl selenocyanates*

Aryl selenide anions ($ArSe^-$) are strong nucleophiles and this property can be used to attach the arylseleno group to a carbon skeleton and then by selenoxide fragmentation, to introduce a carbon-carbon double bond under mild conditions.

$PhSe^-Na^+$ is generated[14] (as a BH_3 complex) by addition of $NaBH_4$ to an ethanol solution of PhSe-SePh. The selenium ion attacks epoxides, halides and sulfonates (eqs. 17 → 19). Aryl-substituted selenide anions have been used with halides and sulfonates (eq. 20). The anion shown (see eq. 20) is generated by treating the selenocyanate with $NaBH_4$. (Both EtOH and DMF[16] have been used as solvents for this reduction.)

Selenide anions are also involved, mechanistically, in an efficient method (eqs. 21 and 22) for converting primary alcohols and aldehydes into selenides.

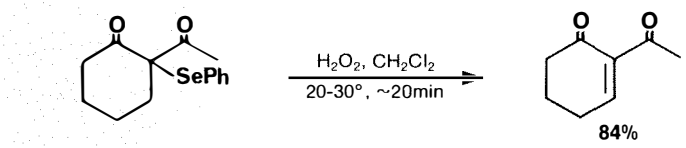
A phenyl selenide anion with enhanced nucleophilic properties can be generated by heating sodium with PhSe-SePh in THF.[14b] The uncomplexed salt, $PhSe^-Na^+$, formed in this way, and solubilized by addition of HMPA or 18-crown-6, opens lactones. $PhSe^-Na^+$ generated in DMF by $NaBH_4$ reduction of PhSe-SePh[19] reacts similarly at 110-120° (eq. 23).

Each of the selenides (see eqs. 17 → 23) can be converted into an olefin by oxidation under appropriate conditions (*e.g.*, eqs. 24 → 28).

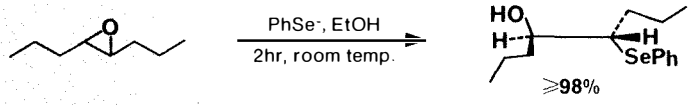
Several points emerge from these and many other related experiments:

(i) Conformational freedom permitting, disubstituted olefins are formed with ***trans*** stereochemistry, except in the case of α,β-unsaturated nitriles which give both *cis* and ***trans*** isomers.

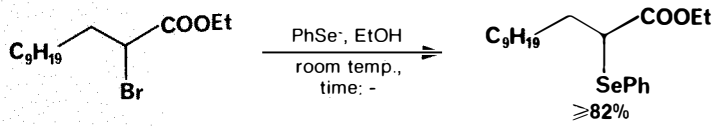
(ii) When adjacent oxygen substituents are present (see eq. 24) elimination is strictly away from the oxygen-bearing carbon to give an allylic alcohol.



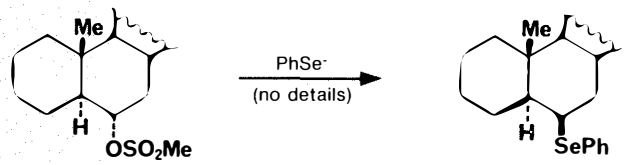
(eq. 16)[3]



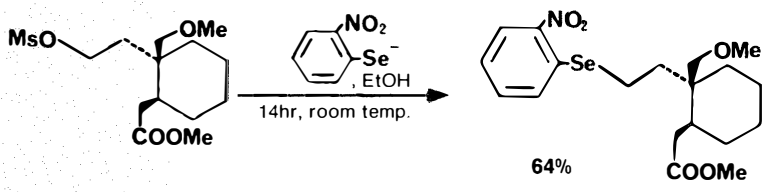
(eq. 17)[14a]



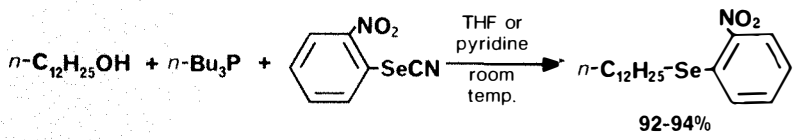
(eq. 18)[4c]



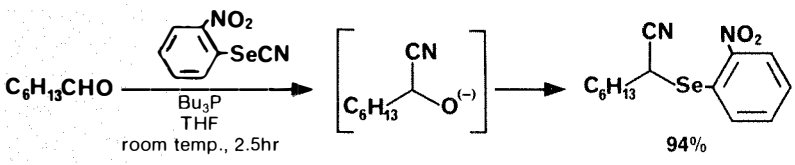
(eq. 19)[2a]



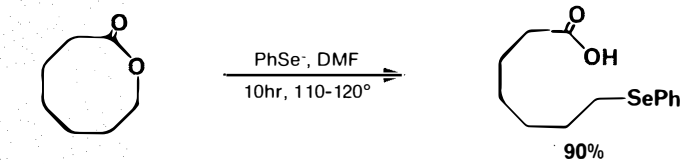
(eq. 20)[15]



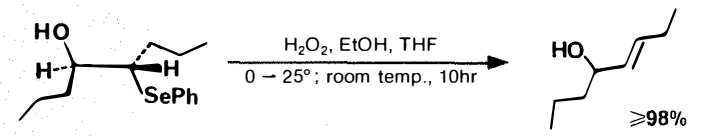
(eq. 21)[17]



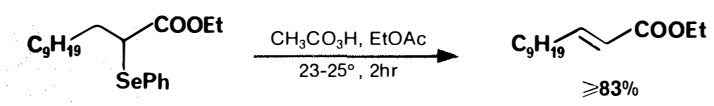
(eq. 22)[18]



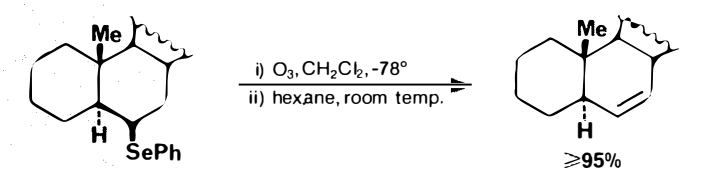
(eq. 23)[19]



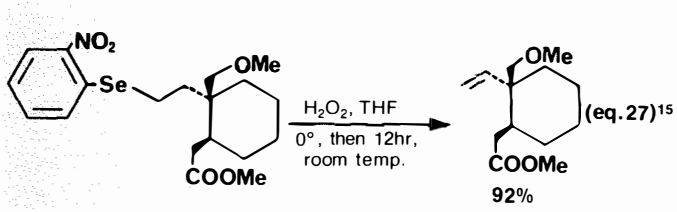
(eq. 24)[14a]

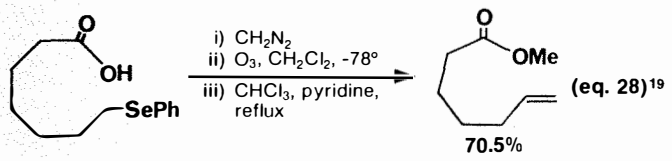


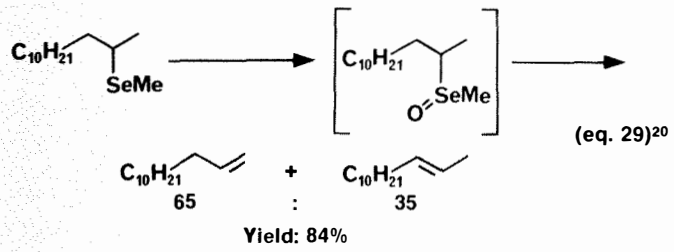
(eq. 25)[4c]

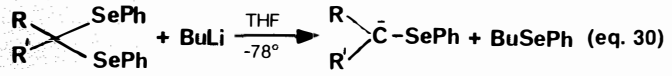


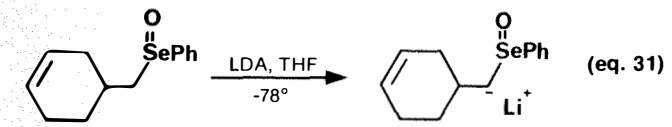
(eq. 26)[2a]

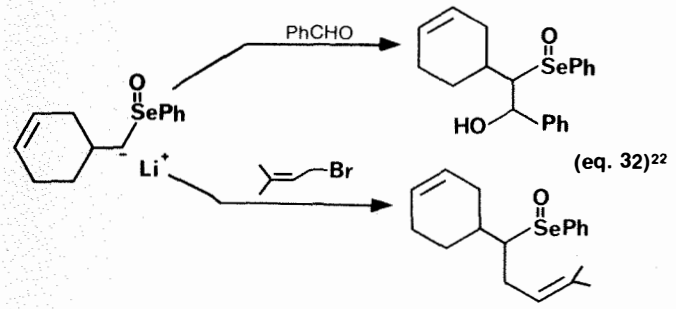


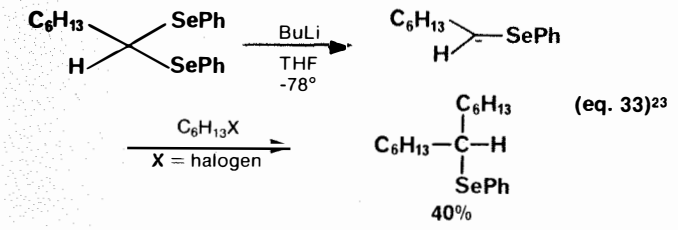


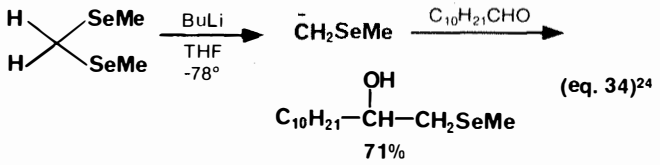


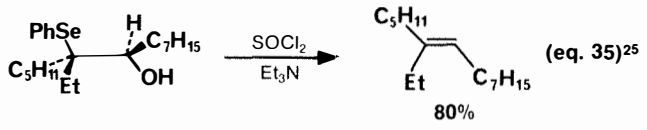


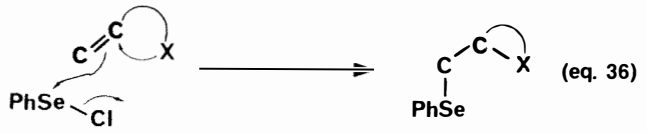


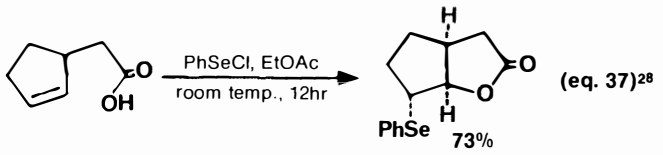


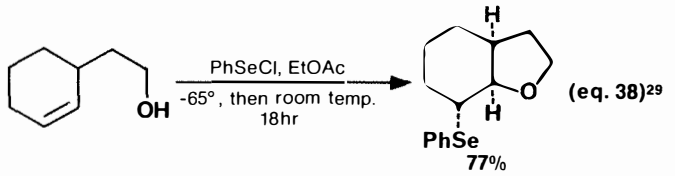


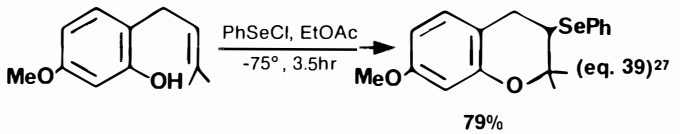


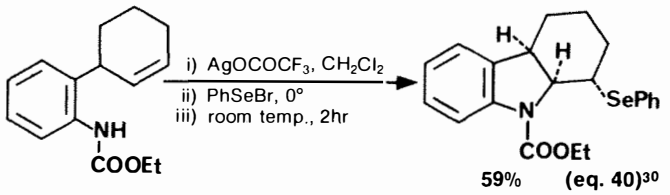


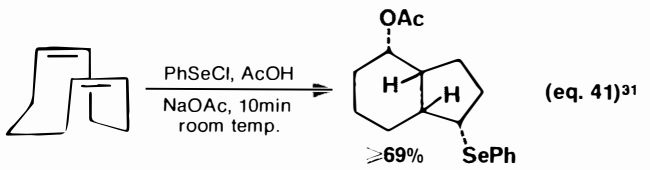












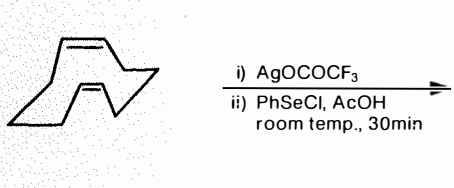
(iii) The preparation of terminal olefins — using the oxidation-fragmentation methods already described — often proceeds poorly unless (a) specially substituted aryl selenides are used (eq. 27) or (b) the selenoxide is made to collapse by heating[3] in the presence of a base (eq. 28). However, a very promising alternative procedure is being developed. The selenide is warmed (55°) in THF containing suspended alumina and an excess of *t*-BuOOH. Under these conditions terminal (unsubstituted) phenyl selenoxides and even methyl alkyl selenoxides[10] fragment readily (eq. 29).

3. Formation of carbon-carbon double bonds by using selenium-containing synthons

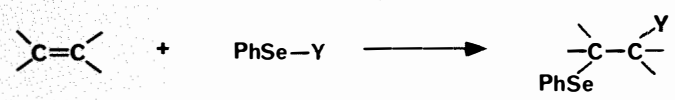
A methodology more advanced than the attachment of the benzeneseleno group to an existing carbon framework is one that uses synthons already containing this group. Such procedures are made possible in part by the fact that selenoacetals can be converted[21] into carbanions (eq. 30) and in part by the fact that selenoxides (kept at a low temperature) can be deprotonated[22] (eq. 31). Both selenium-stabilized and selenoxide-stabilized anions react with alkyl halides and with carbonyl compounds. The following are typical examples (eqs. 32 → 34).

The products of these reactions are suitable for a variety of transformations:

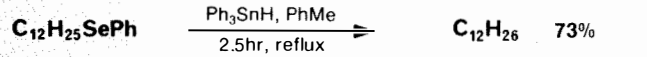
(i) Selenides (*e.g.*, from the process of eq. 33) can be oxidized and allowed to fragment, or the resulting selenoxide can be deprotonated and treated with an alkyl



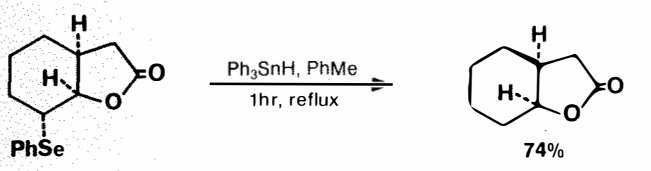
(eq. 42)[32]



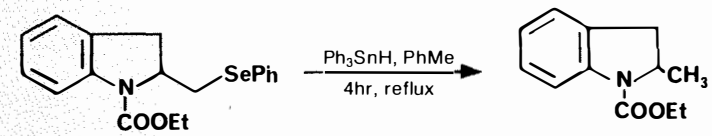
(eq. 43)



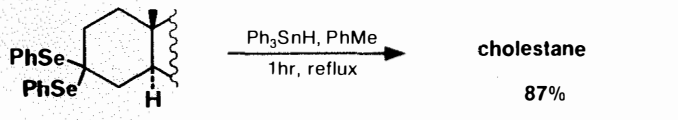
(eq. 44)



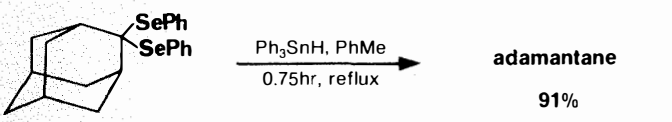
(eq. 45)



(eq. 46)



(eq. 47)



(eq. 48)

halide or a carbonyl compound.

(ii) Selenoxides (*e.g.*, from the process of eq. 32) can be permitted to fragment or they can be reduced ($NaHSO_3$ or KI) to the Se(II) level. In the case of β-hydroxyselenides, conversion of the -OH to a good leaving group affords an olefin (eq. 35).

Several reagents are available for this purpose[24,25,26] [$(CF_3CO)_2O + Et_3N$; TsOH; $HClO_4$; $SOCl_2 + Et_3N$; $MeSO_2Cl + Et_3N$] and β-hydroxyselenides, which are usually made by processes of the type shown in eq. 34, are useful precursors to olefins. Removal of the $PhSe^-$ and OH^- groups occurs in a ***trans*** fashion.

4. Cyclofunctionalization with selenenyl reagents

Cyclofunctionalization[27] is an intramolecular ring-forming process in which one end of the double bond involved in the cyclization becomes attached to a group — such as PhSe — that allows further transformations at that site (eq. 36). Typical examples are shown in eqs. 37 → 42. The reactions, which occur under the conditions indicated, proceed in a clearly defined stereochemical fashion and the utility of these processes has been demonstrated in natural-products work.[33]

Olefins not properly constituted for cyclofunctionalizations react with selenenyl reagents as shown in eq. 43, where Y can be Cl, Br, $OCOCH_3$, $OCOCF_3$, OMe, OEt, O-*i*-Pr depending on the reaction conditions.[34]

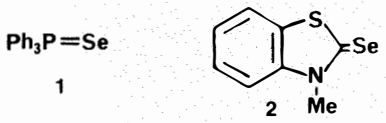
5. Deoxygenation reactions using selenium chemistry

Raney nickel can be used to hydrogenolize monoselenides and selenoacetals[23] but both compound classes are reduced smoothly by tin hydrides[35] (eqs. 44 → 48).

This tin hydride reduction, which works in the presence of a range of functionality is, of course, suitable for making labelled compounds by use of Ph_3SnD.

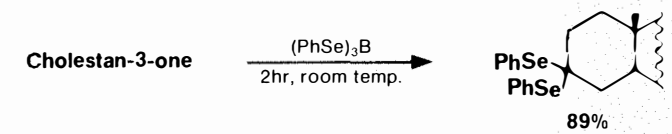
The selenoacetals needed for the reduction can be generated from aldehydes and ketones by treatment with PhSeH in the presence of sulfuric acid or zinc chloride.[36] Selenoacetals are also formed by treating carbonyl compounds with $(PhSe)_3B$ (eqs. 49 and 50). This reagent is a crystalline carrier for the very air-sensitive PhSeH. In using the boron reagent[37] it is sometimes advantageous or necessary to add to the reaction mixture a small amount (~10 mole %) of trifluoroacetic acid. Some preliminary results are given in the equations.

A second type of deoxygenation is the conversion of epoxides into olefins (eq. 51) by Reagents **1**[38] and **2**.[39] Both react with epoxides in the presence of one equivalent of trifluoroacetic acid and the olefin is generated without disturbing the relative stereochemistry about the carbon-carbon bond of the epoxide.

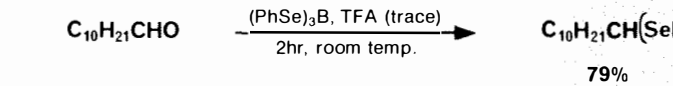


6. Catalytic uses of selenium

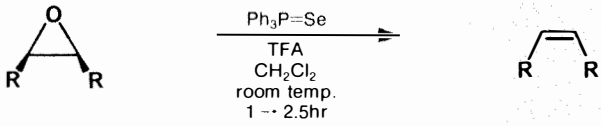
Metallic selenium can be used — frequently in a catalytic manner — to generate carbonyl selenide, which reacts with nucleophiles to give species of the type



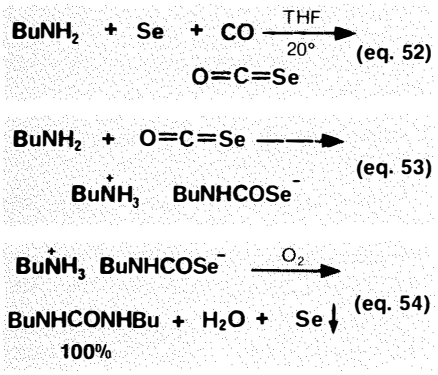
(eq. 49)



(eq. 50)



(eq. 51)

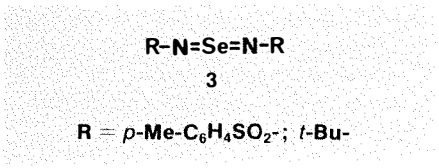


X-C(=O)-Y where X and Y are heteroatoms.

For example, when CO is passed into a THF solution of $BuNH_2$ containing a small portion of selenium, the metal dissolves as it is converted into COSe (eq. 52). The latter reacts with the amine (eq. 53) and, if a controlled amount of oxygen is now added to the CO stream, the salt (see eq. 53) is converted into a urea (eq. 54). The selenium metal generated in the latter process is recycled. Therefore, production of the urea is catalytic in selenium.[40] Equations 55 → 59 summarize analogous processes that have been reported.

7. *Selenium dioxide*

Substantial insight has been obtained into the mechanism of action of SeO_2[46] and a few aza-analogs, *e.g.*, 3, are now available.



These species aminate olefins (eq. 60).

Selenium dioxide can also be used to convert semicarbazones into 1,2,3-selenadiazoles[48] (eq. 61).

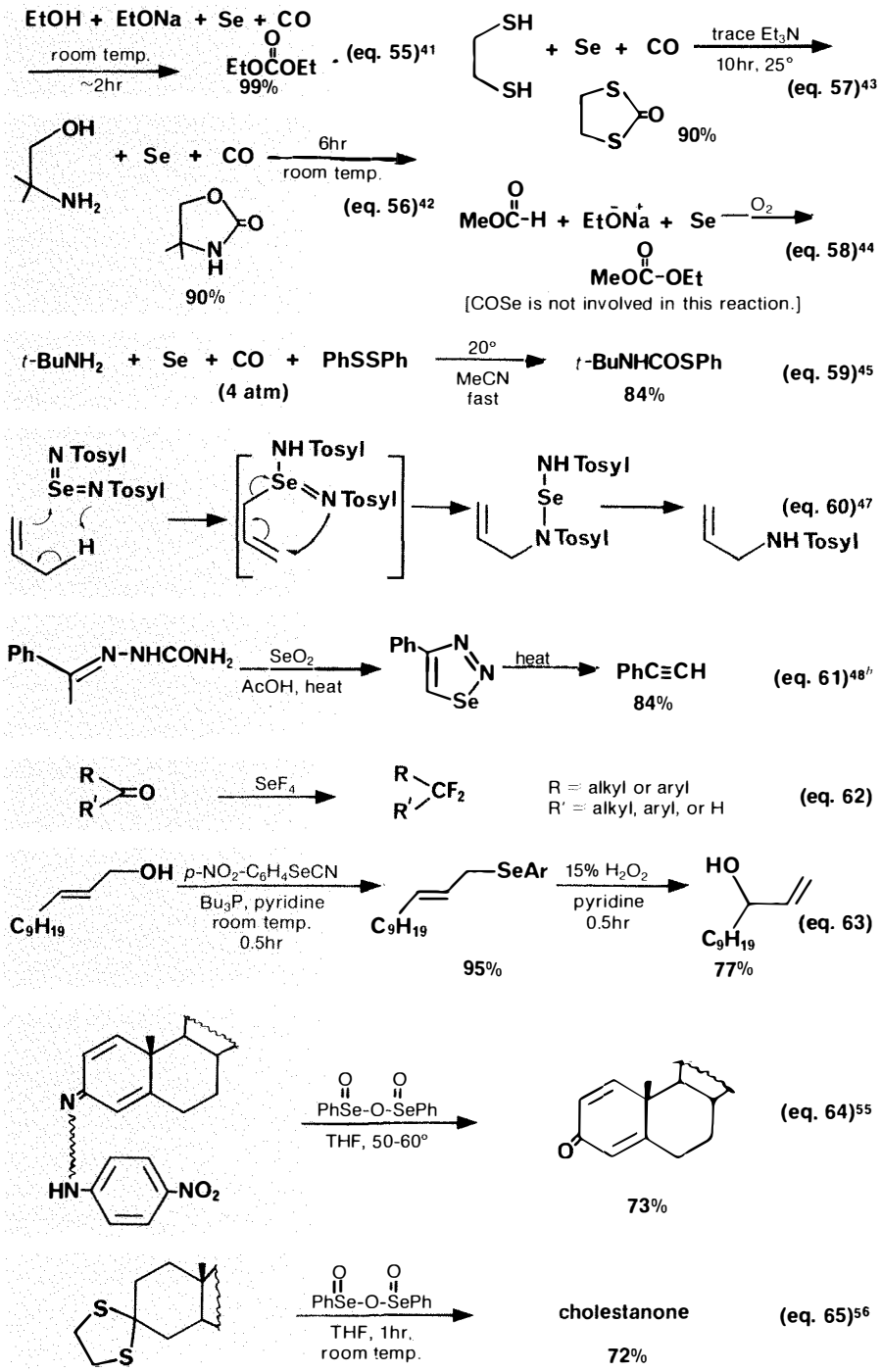
These heterocycles decompose — usually between 160 and 220° — to afford acetylenes. Although thermally severe conditions are needed the yields of simple acetylenes are frequently excellent.

8. *Preparation of fluoro-compounds*

Dissolution of selenium pellets in ClF_3 affords SeF_4 which converts ketones and aldehydes into *gem*-difluorides[49] at, or below, room temperature (eq. 62) in yields of 65-100%. Alcohols are converted into alkyl fluorides and carboxylic acids (as well as their anhydrides) into acyl fluorides.[49] Reactions with hydroxylic substrates are best done in the presence of an equivalent of pyridine to quench the HF that is evolved.

9. *1,3-Transposition of allylic alcohols*

1,3-Transposition of primary allylic alcohols can be achieved[50] by the sequence



summarized in eq. 63. The intermediate allylic selenoxide rearranges and the resulting selenenic ester is hydrolyzed *in situ*. Both of these stages occur spontaneously in the reaction medium.[51]

10. *Applications of benzeneseleninic anhydride*

Benzeneseleninic anhydride oxidizes certain amines to the ketone level[52] and can be used to hydroxylate[53] or aminate[54] phenols. The reagent has a general application in synthesis for releasing carbonyl compounds from hydrazones, oximes, semicarbazones, and thioacetals (eqs. 64 and 65).

11. *Miscellaneous reactions*

(i) Benzeneselenol reduces diazonium salts to arylhydrazines.[57]

(ii) $PhCH_2Se^-Na^+$, in refluxing DMF, demethylates phenolic ethers.[58]

(iii) Selenoxides can be used as weak oxidizing agents.[59]

12. *Acknowledgements*

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University of Alberta selenium chemists (left to right): seated, Dr. D. Clive, Dr. Gim Chittattu; standing, Dr. Wong, Neville Curtis, William Kiel, Steve Menchen.

About the Author

Dr. Clive was educated at Imperial College, London and received his Ph.D. from that Institute for research work in Sir Derek Barton's group. Postdoctoral studies followed, under the supervision of Professor Woodward at Harvard. Dr. Clive then became an I.C.I. fellow at Imperial College and is now on the staff of the Chemistry Department at the University of Alberta.

The purpose of the experimental work in Clive's laboratory is the invention of new reagents and methods that can be applied in the synthesis of natural products and pharmaceuticals. His group has found that organic selenium and tellurium chemistry is a very fertile area in this respect.

Organic Sulfur Compounds in Organic Synthesis: Some Recent Advances

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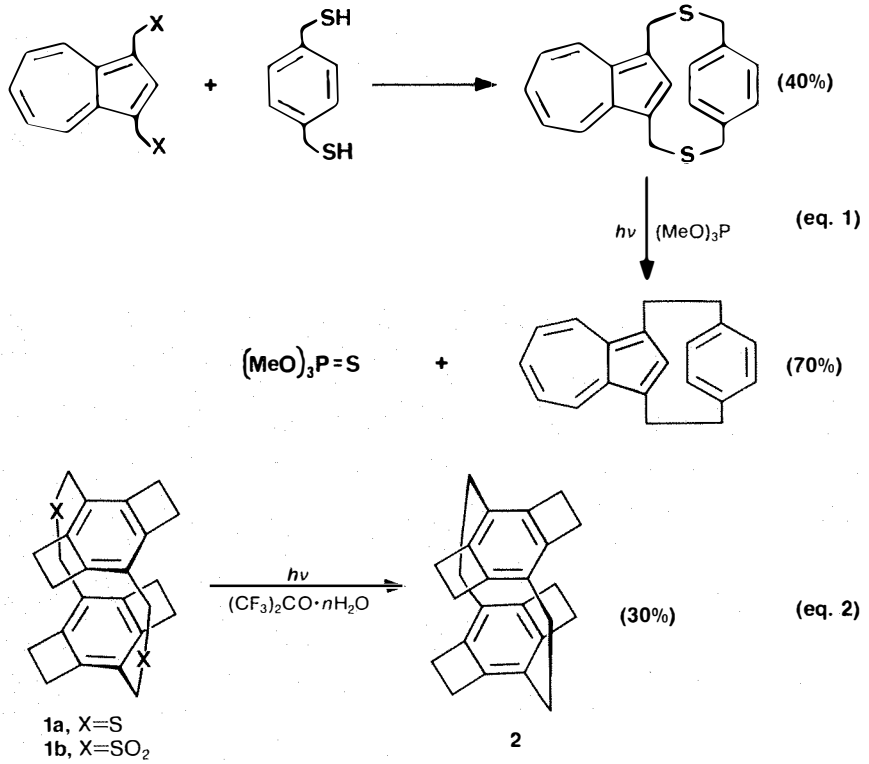
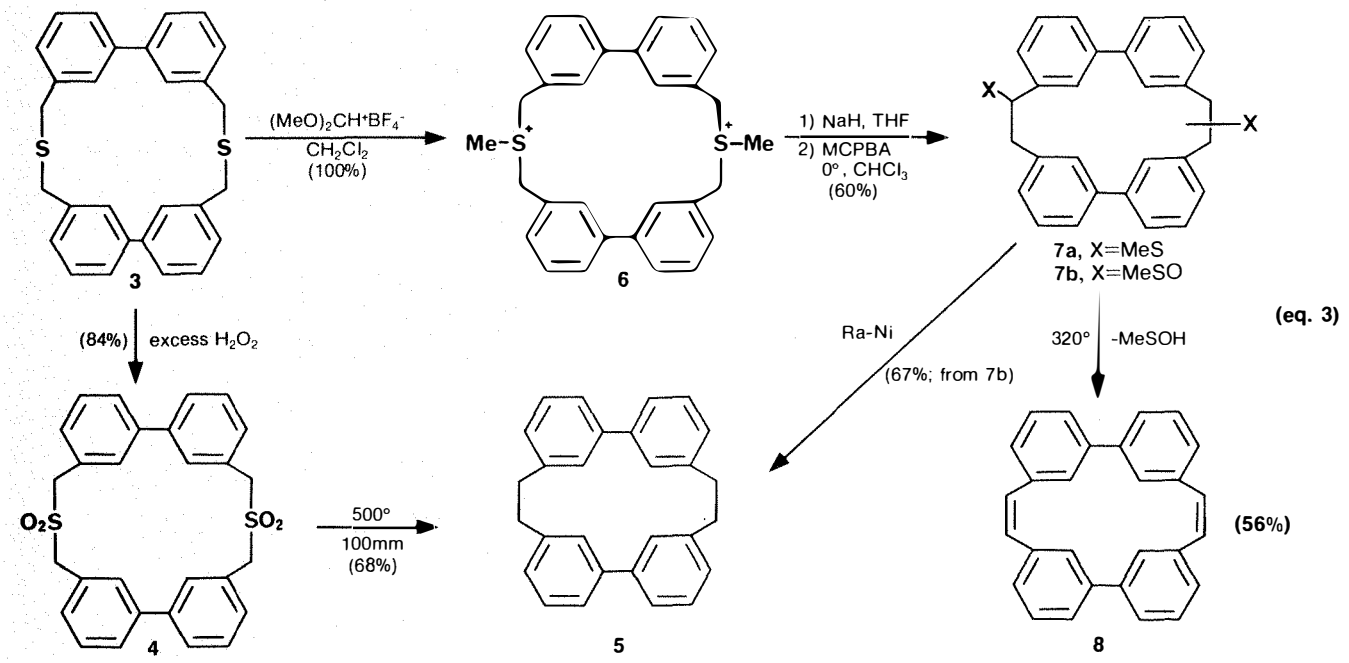
"We may judge, with great accuracy, of the commercial prosperity of a country from the amount of sulfuric acid it consumes." This often repeated observation by the great German chemist Justus von Liebig[1] is as true today as it was in 1851, for sulfuric acid annually tops the list, in tonnage, of all synthetic chemicals. Since most sulfuric acid is made from elemental sulfur it is fair to say that sulfur is the chemical industry's most widely used raw material. While dwarfed in importance by their inorganic counterparts, organic sulfur compounds have nonetheless become increasingly useful and important in organic synthesis. This essay will briefly outline some of the transformations which can be effected with sulfur-containing reagents, using examples selected from the recent literature. More detailed consideration of the reactions described herein and of the basic chemistry of organosulfur compounds is to be found in a recently published book by this author.[2]

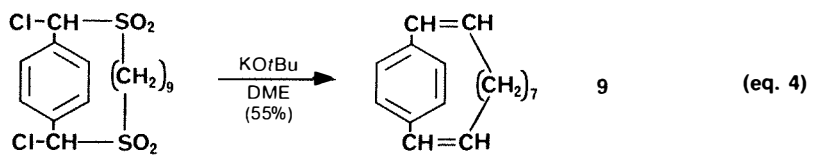
The range of reactions available for organosulfur compounds is aptly illustrated by examples chosen from syntheses of cyclophanes, strained molecules with interesting properties due to transannular π-electron interaction between the facing aromatic rings. An important synthetic approach to these structures involves coupling a bis-thiol with a bis-halide (or related derivative) under high dilution conditions and then extruding the sulfur with concomitant carbon-carbon bond formation. In eq. 1,[3] carbon-carbon bond formation is achieved by photodesulfurization in trimethyl phosphite, a procedure discovered by Corey and Block.[4] Photodesulfonylation of sulfone **1b**, prepared in quantitative yield by *m*-chloroperbenzoic acid (MCPBA) oxidation of sulfide **1a**, has been employed in the synthesis of novel cyclophane **2**.[5] Pyrolytic methods are also very useful in cleanly removing sulfur. For example, [2.2](3,3')biphenylophane, **5**, may be synthesized in good yield by pyrolysis (at 500°) of sulfone **4**.[6] Sulfur dioxide is, of course, an excellent leaving group in pyrolysis reactions. Sulfenic acids (RSOH) are also readily produced, efficient leaving groups as illustrated by the conversion of dithiacyclophane **3** to [2.2](3,3')biphenylophane-1,15-diene, **8**, through a sequence involving methylation of **3** with dimethoxycarbonium tetrafluoroborate, double Stevens rearrangement of the bis-sulfonium salt **6**, oxidation of bis-sulfide **7a** to the bis-sulfoxide **7b** with MCPBA at 0°, and finally elimination of CH_3SOH at 320°C. Bis-sulfoxide **7b** may also be desulfurized to **5** with Raney nickel in refluxing ethanol.



Several additional points should be made regarding the reactions in eq. 3. The ability to oxidize sulfide sulfur to the sulfoxide or sulfone level selectively, often in the presence of other sensitive functionalities, is critical in realizing the full synthetic potential of sulfur. Generally, the oxidation can be stopped at the sulfoxide stage as the second oxidation (to sulfone) is slower than the first. Reagents are available, however, which will transform sulfoxides to sulfones in the presence of sulfides without affecting the latter.[7] Pyrolysis of sulfoxides represents a very useful means of introducing unsaturation. Often the elimination reaction is combined with an alkylation sequence involving α-sulfinyl or α-sulfenyl carbanions as will be discussed below. Pyrolysis of sulfoxides also represents a useful means of synthesizing sulfenic acids which themselves are interesting compounds whose basic structure has been only recently determined.[8] An alternative to the Stevens/sulfenic acid

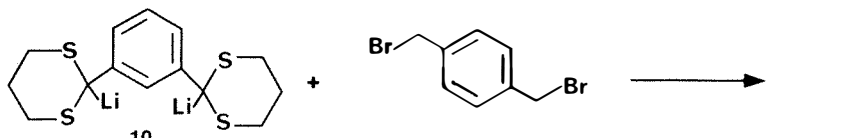


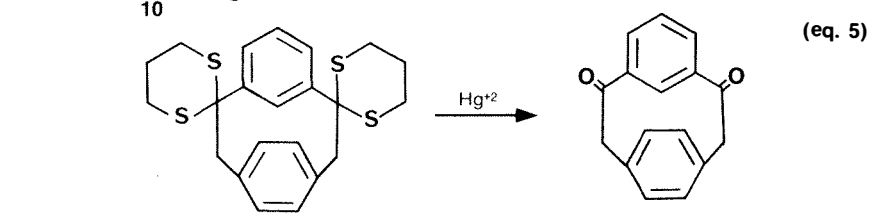
elimination route to unsaturated cyclophanes is the Ramberg-Bäcklund reaction, illustrated by the preparation of **9**.[9] Cyclophanediones may be generated by a sequence employing alkylation of bis-dithianyl derivative **10**.[10] Both of these latter routes will be discussed further.

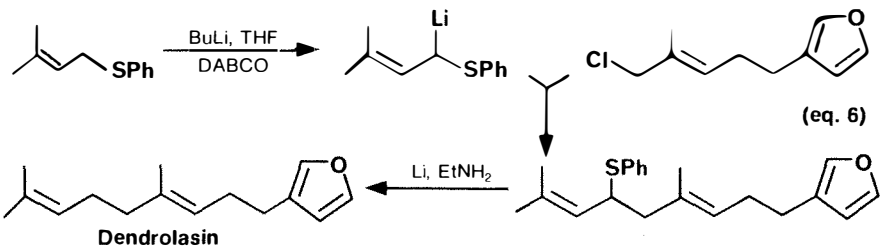


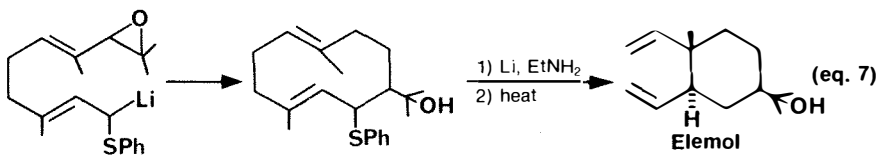
C - C from C - X

The controlled formation of C - C bonds is often a critical step in organic syntheses. Organosulfur carbanions have proven to be extremely useful in this process. In eq. 5, carbon-carbon bond formation is achieved by displacement on an alkyl halide by a lithio dithiane. Allylic groups can be coupled *via* allylic thiocarbanions in a process termed **Biellmann alkylation.**[11] In the dendrolasin synthesis (eq. 6),[12] the thiophenyl group is removed with lithium-ethylamine.[7] Elemol has been synthesized by an intramolecular variant of the Biellmann alkylation process (eq. 7).[13] Alkylation of **α-sulfinyl carbanions** followed by sulfenic acid elimination has been employed in a triene synthesis (eq. 8)[14] and in the synthesis of muscone (eq. 9).[15] (±)-**N**uciferal has been prepared by alkylation of an α-sulfonyl carbanion followed by elimination of sulfinate anion (eq. 10).[16]



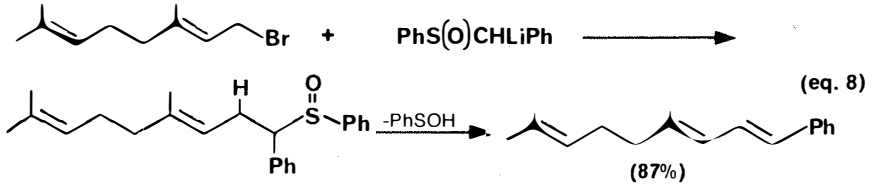


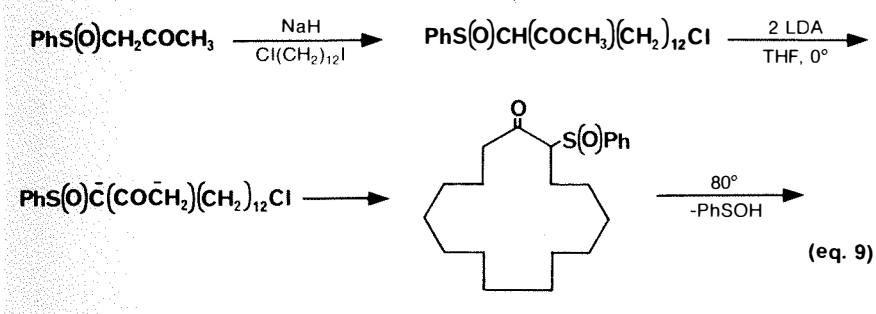




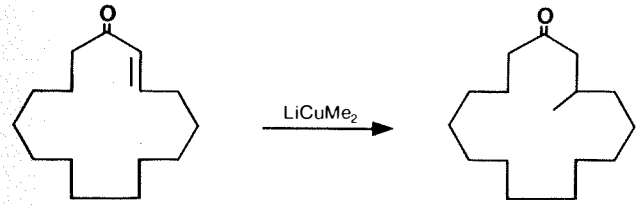
C - C from C = O
O

While phosphorus ylides react with carbonyl compounds giving olefins *via* the well known Wittig reaction, sulfur ylides afford epoxides under analogous conditions, *e.g.*, **11** (eq. 11).[17] In view of the importance of epoxides as synthetic intermediates and the ready availability of

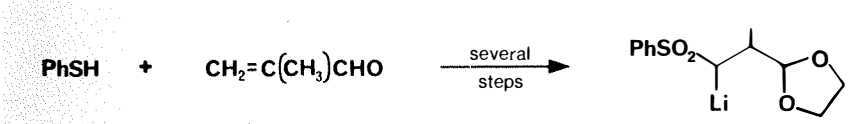


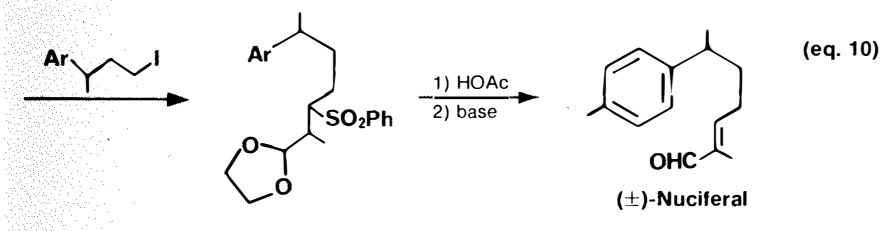


(eq. 9)



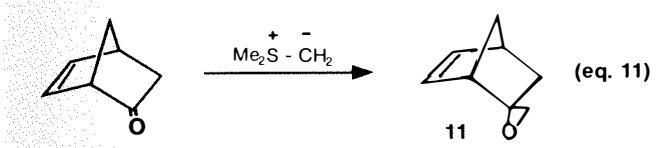
d/-**Muscone**





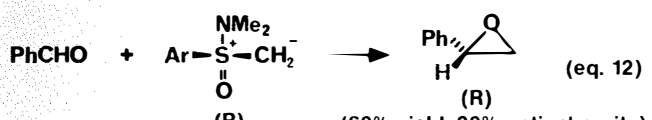
(±)-**Nuciferal**

(eq. 10)



11

(eq. 11)

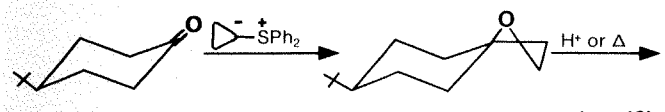


(R)

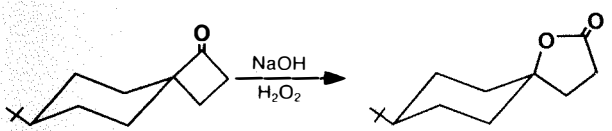
(R)

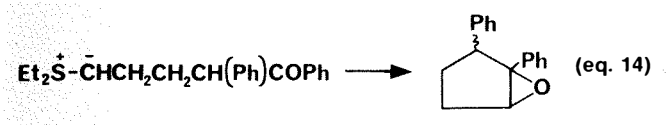
(60% yield, 20% optical purity)

(eq. 12)



(eq. 13)





(eq. 14)

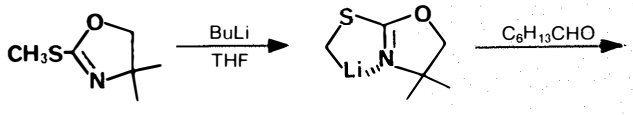
carbonyl compounds, epoxide formation using sulfur ylides is a very useful procedure that has been studied in great detail both from a mechanistic and a preparative standpoint. The generality of the reaction is demonstrated by the lack of interference from enol ethers, acetals, amides, nitriles, divalent sulfur, and in some cases, esters, hydroxyl groups and amino groups.[18] Asymmetric syntheses of epoxides may be realized using optically active sulfur ylides (eq. 12).[19] The use of cyclopropyl sulfur ylides is the basis for the novel process of "spiroannelation" (eq.13).[18] An instance of intramolecular epoxide formation has been published recently (eq. 14).[20]

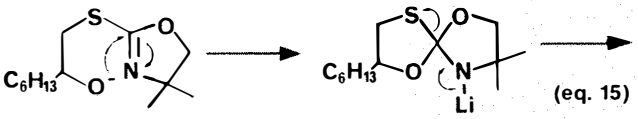
C - C from C = O

Ketones and aldehydes may be converted into thiiranes using lithio derivatives of 2-(thiomethyl)-Δ^2-oxazolines as shown in eq. 15.[21] Through the use of ^{13}C-labeled methyl iodide, ^{13}C-labeled thiiranes may be prepared. These compounds have been employed in mechanistic studies of the thermal rearrangement of allene episulfide (eq. 16).[22]

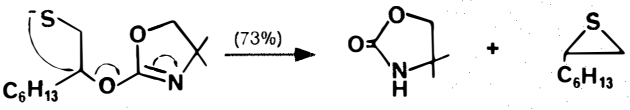
C - C from C = C

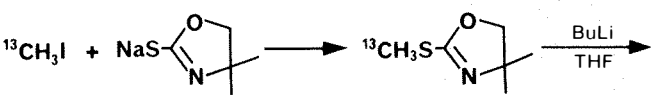
Sulfonium and sulfoxonium ylides readily add to such Michael acceptors as α,β-unsaturated ketones, esters, nitriles, isonitriles, sulfones, sulfoxides, sulfonamides, sulfonates, and nitro compounds to afford cyclopropanes,[18] *e.g.*, eq.

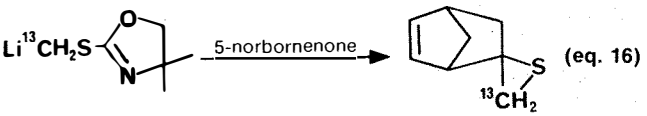




(eq. 15)







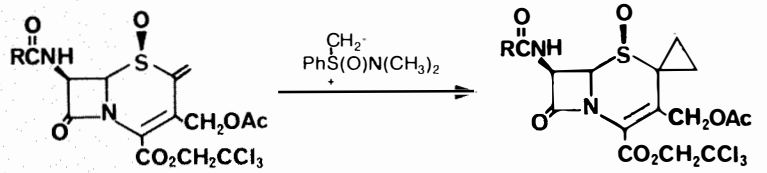
(eq. 16)

17.[23] These reactions are all nucleophilic cyclopropanations which proceed best with electron deficient olefins. While sulfonium ylides such as diphenyl sulfonium methylide are normally unreactive toward olefins such as *cis*- and *trans*-2-octene, it has been discovered that cyclopropanation does occur in the presence of copper salts and that these reactions are stereospecific with retention (eq. 18).[24]

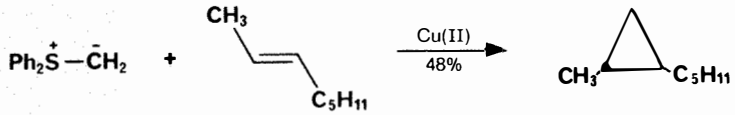
C = O from CHOH

A useful procedure for the selective oxidation of alcohols to aldehydes or ketones involves treatment of the alcohols with dimethyl sulfoxide (DMSO) and a coreagent such as dicyclohexylcarbodiimide (DCC)-pyridinium trifluoroacetate (Pfitzner-Moffatt oxidations, eq. 19),[25] acetic anhydride, methanesulfonic anhydride, trifluoroacetic anhydride, oxalyl chloride or pyridine-sulfur trioxide (the latter three coreagents are compared in eq. 20).[26] All of these reactions involve α,β'-elimination of an intermediate oxysulfonium ylide.[2] A number of sulfonium and sulfoxonium reagents of the type $R_2\overset{+}{S}X$ and $R_2\overset{+}{S}(O)X$ have also proven useful in alcohol oxidations as indicated by the reactions in eqs. 21[27] and 22.[28] The latter reaction is significant in that a vicinal diol is oxidized without complications from C - C bond cleavage (the case with most other oxidants!).

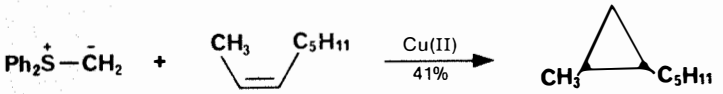
A variety of organosulfur compounds that have the same level of oxidation as aldehydes and ketones (*e.g.*, **12-15**) or carboxylic acids (*e.g.*, **16**) and which are readily converted into the carbonyl equivalents by hydrolysis is known. Thioacetals and thioketals, of course, have long been used as protecting groups for the carbonyl function. By taking advantage of the carbanion-forming capacity of these organosulfur carbonyl equivalents, it becomes possible to achieve *nucleophilic acylation,* as illustrated for the 1,3-dithianyl group in eq. 23. In effect, the normal direction of polarity of the carbonyl group has been temporarily reversed, transforming the normally electrophilic carbonyl carbon into a nucleophilic center (termed *Umpolung* or *dipole inversion*). This procedure is of obvious great synthetic importance since the whole range of reactions characteristic of carbanions can now be conducted with these nucleophilic carbonyl equivalents. Following the original publications by Corey and Seebach, reports of other useful organosulfur (and sulfur-free) nucleophilic acylating agents have appeared frequently in the chemical literature. Certain of these newer methods are claimed to offer advantages over the dithiane method because of

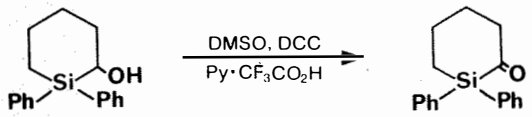


(eq. 17)



(eq. 18)

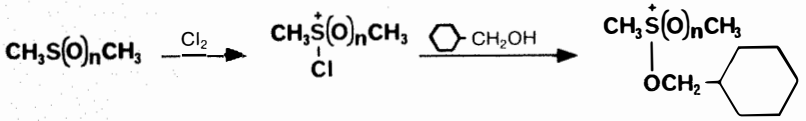




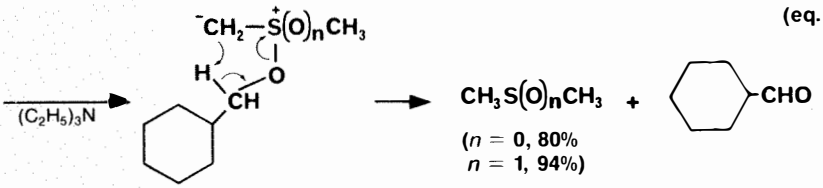
(eq. 19)

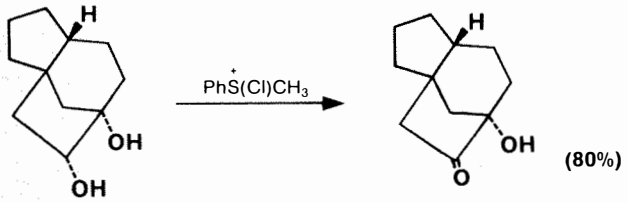
System	Yield
DMSO, $(COCl)_2$	97%
DMSO, TFAA, *i*-Pr_2NEt	85%
DMSO, Py-SO_3	42%

(eq. 20)



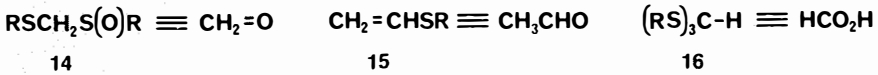
(eq. 21)



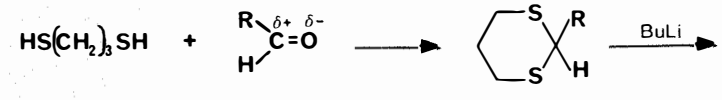


(eq. 22)

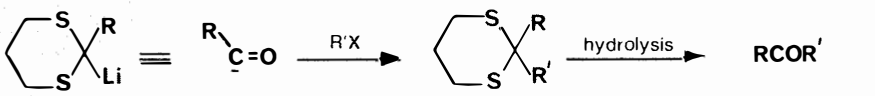
12 13



14 15 16



(eq. 23)



greater ease of hydrolysis to carbonyl compounds or greater availability of starting materials. One example of the use of a dithianyl reagent has already been given (eq. 5); other examples are the preparation of L-streptose (eq. 24),[29] alnusone dimethyl ether (eq. 25),[30] and the Δ^1-cannabinoid derivative **17** (eq. 26).[31] Examples of other nucleophilic acylating agents are given in eqs. 27[32] and 28.[33] Extensive reviews of nucleophilic acylation and *Umpolung* employing organosulfur reagents have been published.[34]

E, R C - NH_2 from RCH - NH_2

A method has recently been reported for the *Umpolung* of reactivity of amino carbons. As illustrated in eq. 29,[35] transformation of primary amines to *N*-sulfinylamines followed by treatment with base affords the equivalent of α-amino carbanions which may then be converted into α-alkylated amines.

ortho-Alkylation of aromatic amines can be realized through application of the Sommelet-Hauser rearrangement of ylides (a [2,3]-sigmatropic process) derived from azasulfonium salts as shown in eq. 30 and Scheme I.[36]

O - C - C_n - C = O from HO - C - C_n - COOH

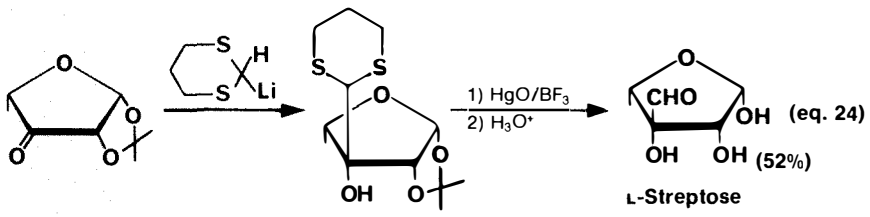
A valuable method for lactonization consists of the treatment of ω-hydroxy-*S*-2-pyridyl carbothioates with silver perchlorate as illustrated by the conversion of ricinoleic acid, **18**, to ricinoleic acid lactone, **19** (eq. 31).[37] An additional feature of this synthesis is the *cis* to *trans* isomerization of **18** through irradiation in the presence of diphenyl disulfide. The lactonization process is thought to be promoted by coordination of the silver ion.[38] In some instances, cyclization can be achieved without the silver salt although higher temperatures are required.[39]

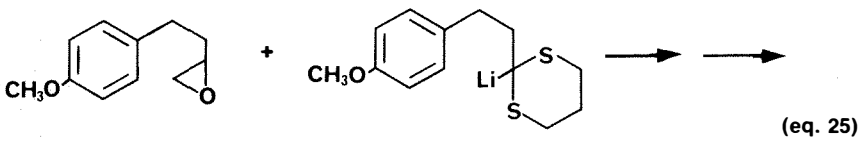
C - Hal from C - O

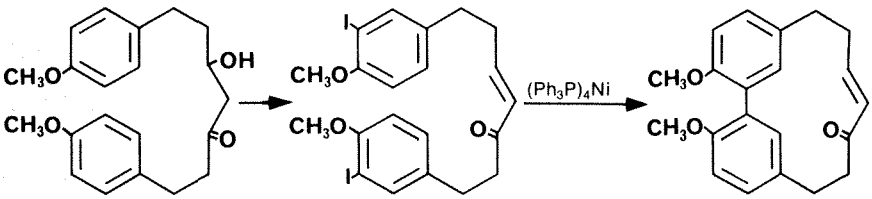
Allylic hydroxyl functions can be selectively replaced by chloride in the presence on nonallylic alcohol units. (eq. 32.).[40]

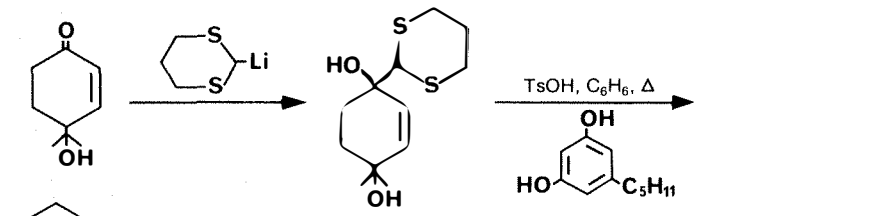
C - CH_2I from C - I

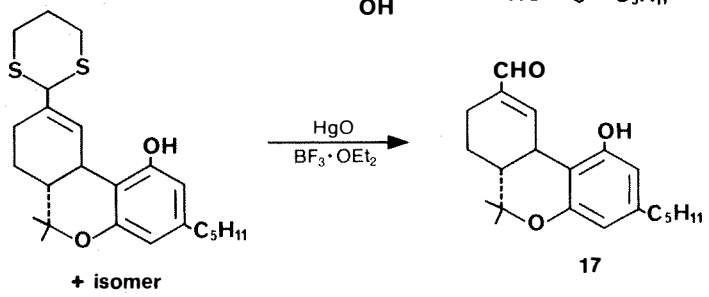
Polymeric phenylthiomethyllithium is a reusable reagent for homologation of alkyl iodides (eq. 33).[41]

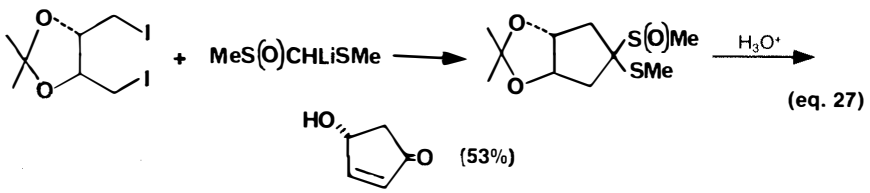


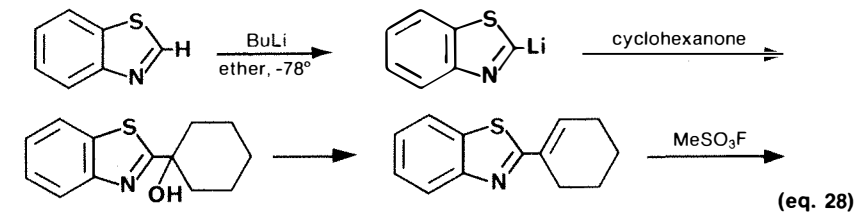


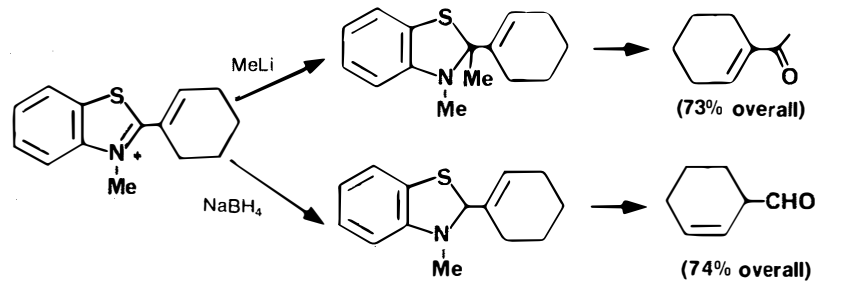


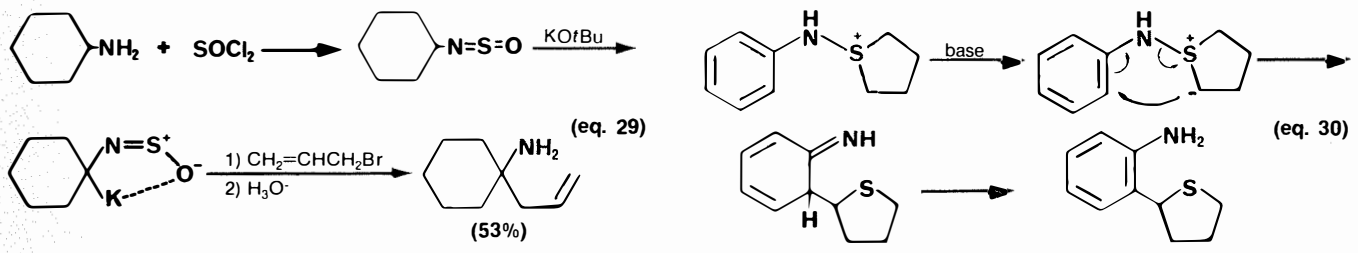




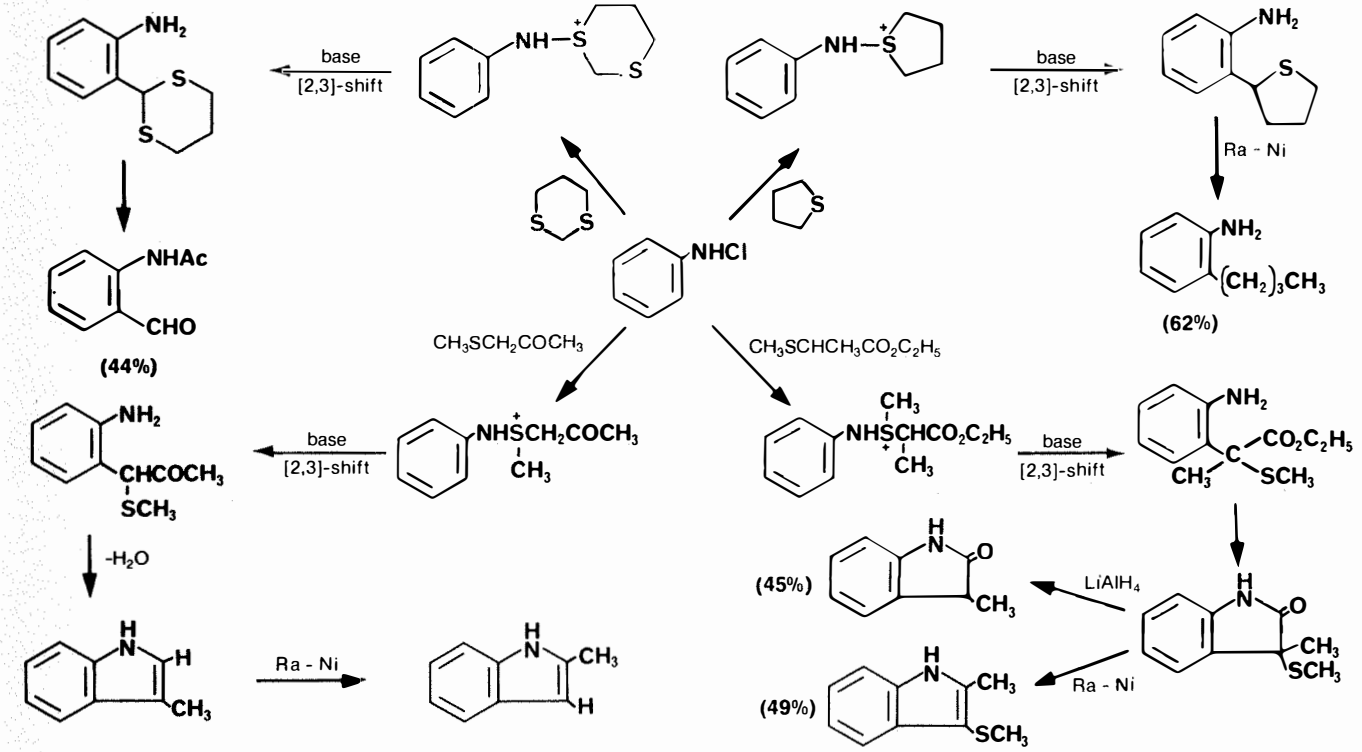


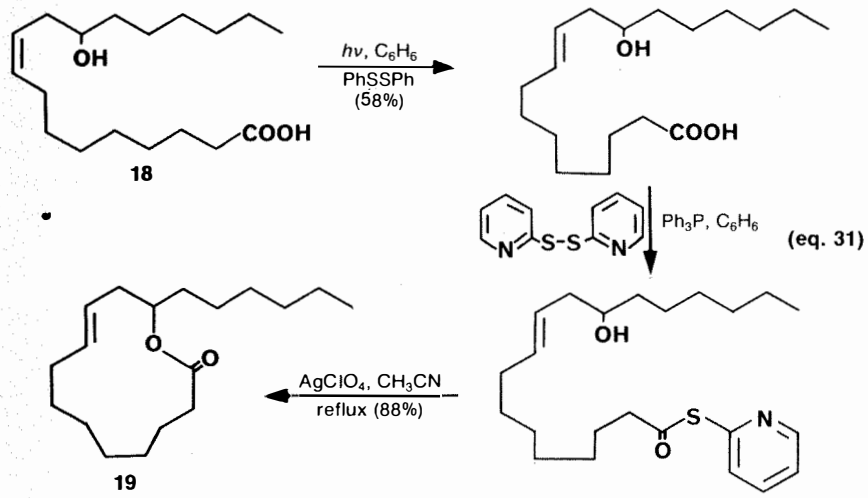


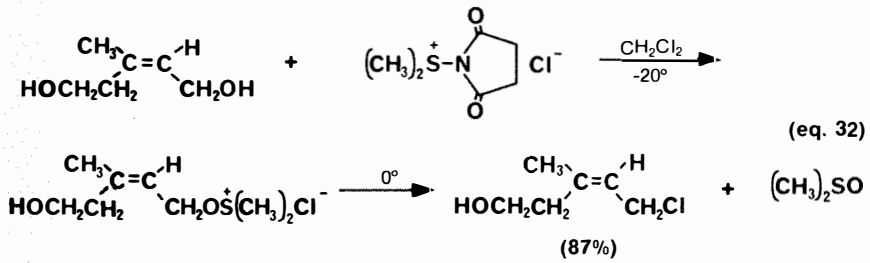




Scheme I. Azasulfonium Route to Substituted Anilines and N-Heterocycles







O⁻ from C - O

The high nucleophilicity of RS^- is exploited in the splitting of *O*-methyl bonds in esters (eq. 34)[42] and ethers (eq. 35).[43]

C - NH_2 from C - OH

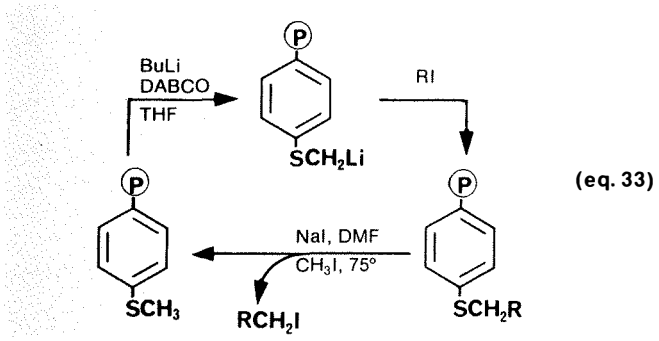
Lithium bisbenzenesulfenimide is employed in a variant of the Gabriel synthesis of primary amines. The N-S bonds are easily cleaved with acid (eq. 36).[44]

C - H from C - NH_2

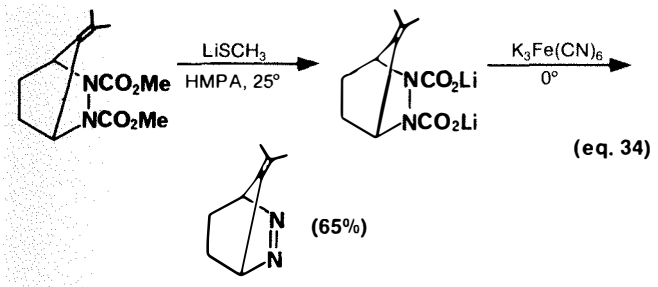
Reductive deamination of primary amines is achieved *via* borohydride reduction of *N,N*-disulfonamides (eq.37).[45]

C - H from C - OH

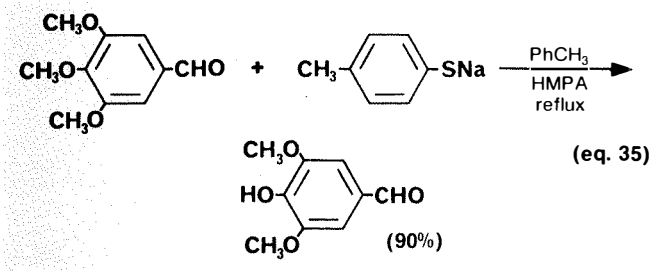
Barton has devised a new method for the replacement of a hydroxyl function by hydrogen involving conversion of the hydroxyl group to a xanthate ester followed by treatment with tributyltin hydride (eq. 38).[46a] Using tributyltin deuteride, stereoselective synthesis of certain deoxydeuterio systems is possible.[46b]



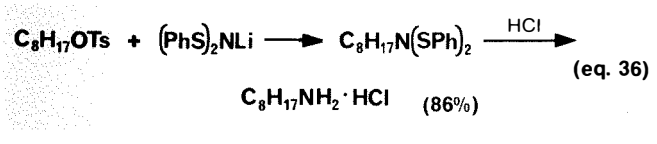
(eq. 33)



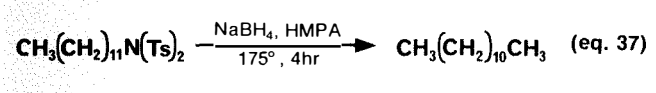
(eq. 34)



(eq. 35)

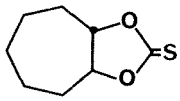
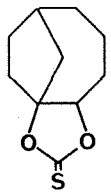
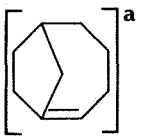
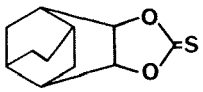
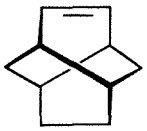
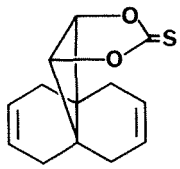
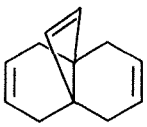
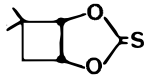
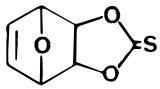
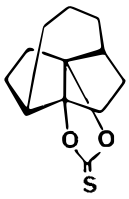
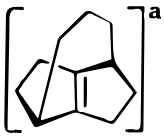


(eq. 36)

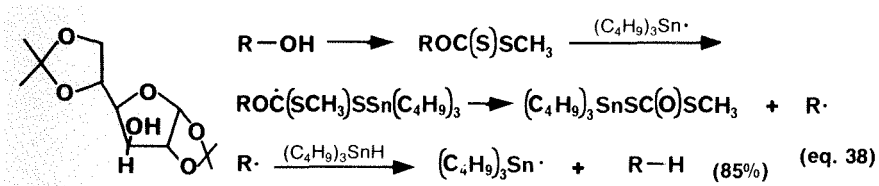


(eq. 37)

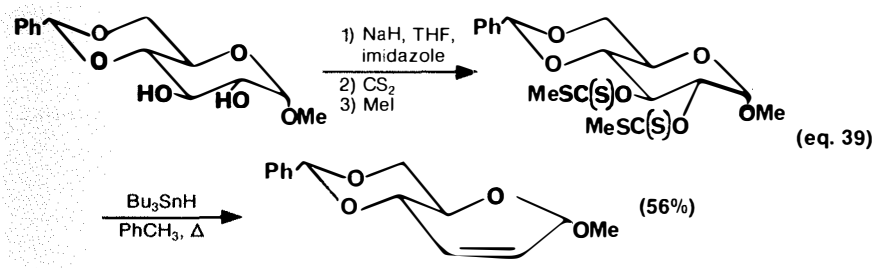
Table I. The Corey-Winter Olefin Synthesis

Entry	Substrate	Product	Yield (%)	Ref.
1		 [a]	—	48a
2		 [a]	62	48b
3			50	48c
4			54	48d
5			71	48e
6			60	48f
7		 [a]	85	48g

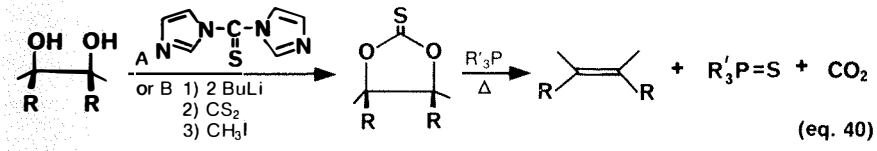
[a] As 2,5-diphenyl-3,4-isobenzofuran adduct



(eq. 38)



(eq. 39)



(eq. 40)

C = C from C(OH)C(OH)

A procedure related to that shown in eq. 38 enables the conversion of vicinal diols to olefins (eq. 39).[47] This same type of conversion can be accomplished stereospecifically through the Corey-Winter olefin synthesis which involves conversion of the diol to a cyclic thiocarbonate followed by heating with a tervalent phosphorus compound (eq. 40).[2] Applications of the Corey-Winter olefin synthesis are summarized in Table I.[2]

C = C from 2 C = O

Barton (and independently, Kellogg) has developed a "two-fold extrusion" approach to olefin synthesis which involves pyrolysis of Δ^3-1,3,4-thiadiazolines (available in good yields from ketones or thioketones as shown in eq. 41) in the presence of phosphines, reagents known to extrude sulfur from episulfides.[49] Applications of this reaction appear in Table II.

C = C from 2 C - X

The Ramberg-Bäcklund reaction, the sulfur analog of the Favorskii rearrangement, is general for molecules containing the structural elements of a sulfonyl group, an α-halogen (or other suitable leaving group), and at least one α'-hydrogen atom and, with few exceptions, enables the clean replacement of a sulfonyl group by a double bond (see eq. 42)[2,51] The required α-halogen atom may be introduced by treatment of the corresponding α-sulfonyl carbanion with a source of X^+ ($BrCN$, I_2 and Cl_3CSO_2Cl are convenient sources of Br^+, I^+, and Cl^+, respectively).[52] A particularly useful modification of the Ramberg-Bäcklund reaction has been developed by Meyers[53] whereby sulfones may be taken directly to olefin without the isolation of α-halosulfones (carbon tetrachloride serves as the halogen source). A variety of synthetic applications of the Ramberg-Bäcklund reaction and the Meyers modification of this reaction is listed in Table III (also see eq. 4). An additional related reaction sequence in which an episulfone is produced by oxidation of an α,α'-sulfonyl dicarbanion is shown in eq. 43.[55]

ACKNOWLEDGMENT

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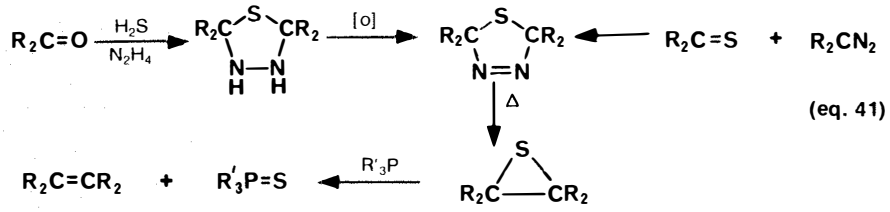
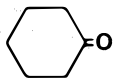
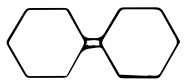
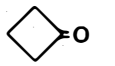
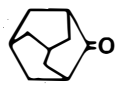
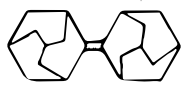
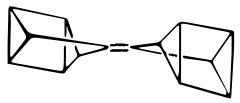
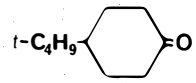
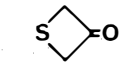
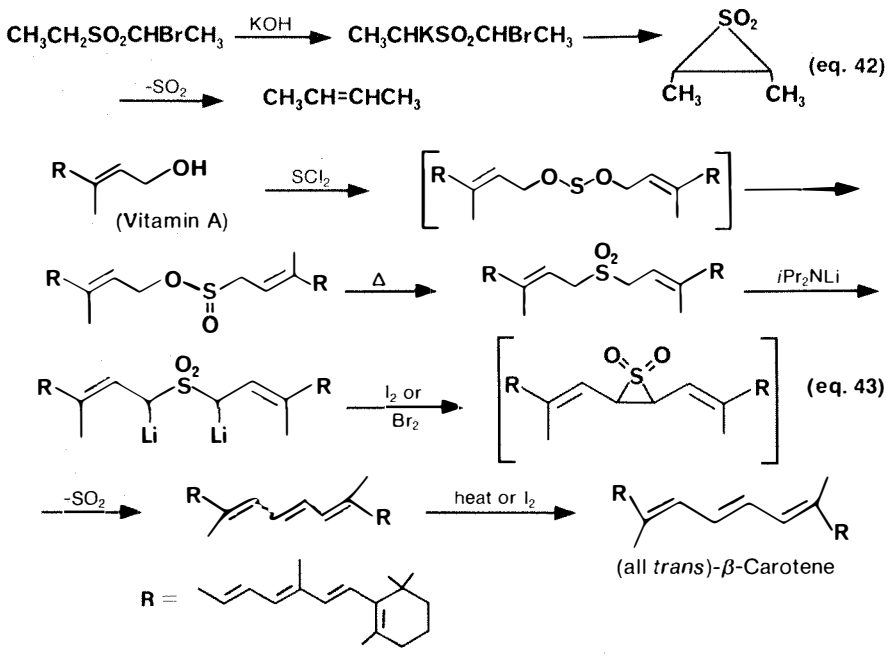


Table II. Olefin Synthesis *via* Two-fold Extrusion

Ketone (or thioketone)	Olefin product	Overall yield (%)	Reference
		42	49
		69	50a
		65	50b
		20	50c
$(t\text{-}C_4H_9)_2C{=}S$[a]	$(t\text{-}C_4H_9)_2C{=}CPh_2$	68[b]	49
		90[b]	50d
		50	50e

[a] Coreactant is diphenyldiazomethane.
[b] From *cis*-Δ^3-1,3,4-thiadiazoline.



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11) See, for example, J.F. Biellmann and J.B. Ducep, *Tetrahedron*, **27**, 5861 (1971) and references therein.
12) K. Kondo and M. Matsumoto, *Tetrahedron Lett.*, 391 (1976).
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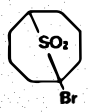
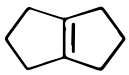
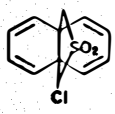
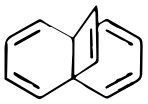
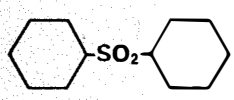
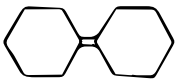
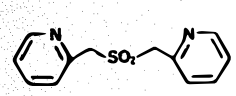
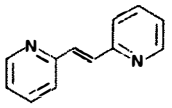
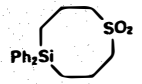
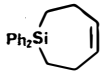
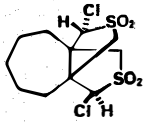
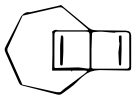
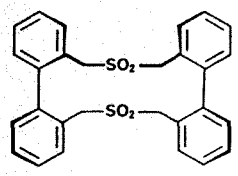
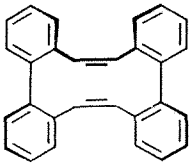
22) E. Block, R.E. Penn, M.D. Ennis, T.A. Owens, and S.L. Yu, *J. Am. Chem. Soc.*, in press.
23) D.O. Spry, *Tetrahedron Lett.*, 2413 (1973).

Table III. Some Synthetic Applications of the Ramberg-Bäcklund Reaction

Sulfone	Product	Yield (%)	Reference
		81	52
		14	54a
		68	54b
		32	53
		—	54c
		40	54d
		12	54e
		65	54f

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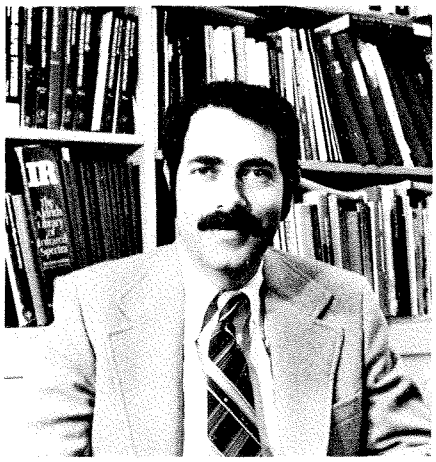

About the Author

Dr. Eric Block is Associate Professor of Chemistry at the University of Missouri-St. Louis. He received his B.S. degree from Queens College of the City University of New York (1962) and his M.S. (1965) and Ph.D. (1967) from Harvard University. He has served as visiting professor at the University of Illinois (summer 1973) and Harvard University (1974), and, under the NATO Research Grants Programme, at the University of Frankfurt (1978). Professor Block is a Reporter for the British Chemical Society's Specialist Periodical Reports on "Organic Compounds of Sulphur, Selenium, and Tellurium" and is the author of the recent monograph "Reactions of Organosulfur Compounds" (Academic Press, 1978) and over 30 other publications in the areas of organic sulfur chemistry, flash-vacuum pyrolysis, applications of microwave spectroscopy in organic chemistry, small-ring chemistry and mechanistic organic chemistry.

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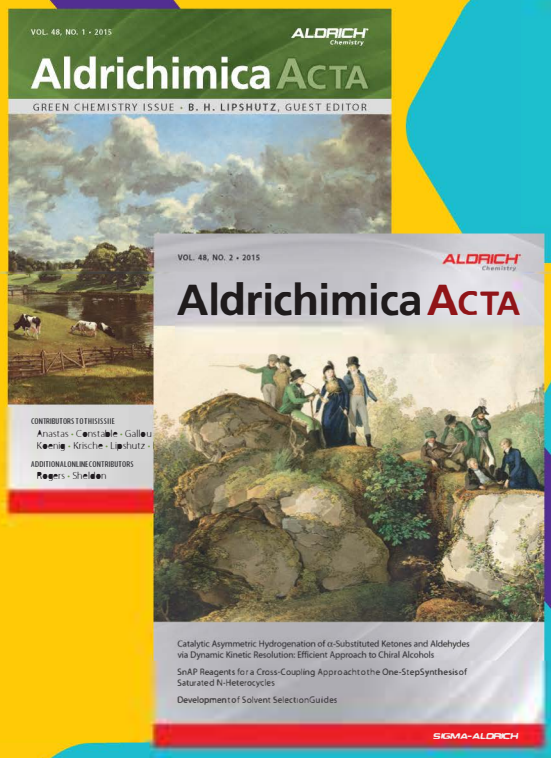

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