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Volume 25, Number 1, 1992

A Methionine Salvage Pathway

Asymmetric Syntheses of α-Amino Acids

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Aldrichimica Acta

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About Our Cover:

Just ten years ago we had a painting of Rembrandt's old, and almost blind, father on the cover of our Catalog/Handbook. And so, it seems fitting now to show a study of Rembrandt's mother, done the same year, in 1629, by Rembrandt's fellow artist, Jan Lievens, who may have shared a studio with Rembrandt in Leiden.

This is one of our chemist collector's favorite works—the marvelous, delicate transparency of the headscarf with its subtle play of color provides such a foil for the face of this plain old woman—almost as if the artist wanted the scarf as a symbol of her inner goodness.

What we said about Rembrandt's father in the 1981-1982 Catalog applies equally to Rembrandt's mother: "The overpowering emotion one feels when viewing this study is that of the care of one human being for another."

If you would like to have a reproduction of this painting, please do not tear off this cover; we will be happy to send you a full color print of the painting suitable for framing (Cat. No. Z23,135-5, $2.10, postpaid).

The Detective's Eye: Investigating the Old Masters

Twenty-four paintings that have been reproduced on our *Aldrichimica Acta* covers, and five that have been on our catalog covers, were among some seventy works in an exhibit at the Milwaukee Art Museum (January 19 through March 19, 1989) for which Isabel and Alfred Bader were guest curators.

If you relish detective work and puzzles about Old Master paintings, you will find much to enjoy in this illustrated catalog, and you will learn something about our chemist collector's interest in art and connoisseurship as well.

Telling Images—Images Révélatrices

Large, 150-page catalog of thirty-six Old Master paintings in an exhibition that toured Canada. All were given by the Baders to Queen's University.

The catalog illustrates all thirty-six paintings, thirteen of them in color. The extensive scholarly text written by Professor David McTavish is in English and French.

From Dura to Rembrandt—Studies in the History of Art

A collection of nineteen papers, seventeen in English and two in German, by Rachel Wischnitzer (1885-1989). The content ranges from synagogue architecture to the iconography of works by Rembrandt. Includes this remarkable woman's life story (written by Professor Bezalel Narkiss, director of the Center for Jewish Art at the Hebrew University).

Lab Notes

I would like to suggest some modifications to your mercury manostats (Z14,799-0/ Z15,236-6).

1. The constriction in the tube between the chambers prevents the Hg from "thumping" back and forth when the vacuum level is changed. By slowing the flow of the Hg down, it prevents the Hg from shooting down the pumping line.

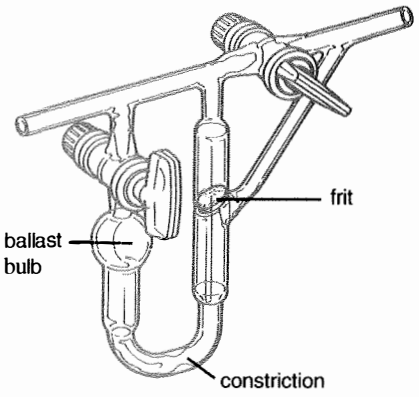
2. The smaller chamber diameters with the bulb on the trapped-air side decrease the amount of Hg needed to control the system while allowing a larger amount of ballast gas to remain in the trapped side. The Hg still can cover the frit without having to use large quantities of Hg to compensate for the larger amount of gas. This system should be able to function well with 10-12mL of Hg in the manostat.

Less Hg means less weight, less possibility of breakage, and less severe clean-up problems.

Please let me know what your glassblowers think.

Steven L. Gatton
Organic Laboratory Coordinator
Department of Chemistry
Bowling Green State University
Bowling Green, Ohio 43403-0213

Editor's Note: The improved design (based on Mr. Gatton's suggestions) offers safe and accurate automatic control of vacuum pressure. It is now available to our customers, as shown below.

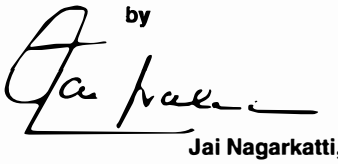


Aldrich mini manostats
Frit porosity

Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to Aldrich (attn: Lab Notes, Aldrichimica Acta). For submitting your idea, you will receive a complimentary, laminated periodic table poster (Cat. No. Z15,000-2, $9.90 value). If we publish your *Lab Note*, you will also receive **The Detective's Eye: Investigating the Old Masters** (see previous page). We reserve the right to retain all entries for consideration for future publication.

"Please Bother Us."

by



Jai Nagarkatti, President

Dr. James P. Demers of the R.W. Johnson Pharmaceutical Research Institute (Raritan, New Jersey) suggested that we offer a solution of phosphorus pentoxide in methanesulfonic acid, better known as "Eaton's Reagent".[1] This solution is an excellent alternative to polyphosphoric acid in cyclodehydration reactions leading to cyclopentenones,[2] butenolides[3] and polycyclic aromatics.[4]

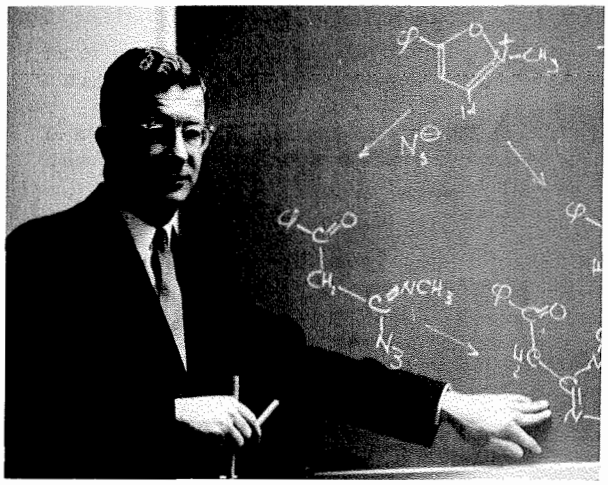
Naturally, we made this reagent.

(1) Eaton, P.E.; Carlson, G.R.; Lee, J.T. *J. Org. Chem.* **1973**, *35*, 4071. (2) Eaton, P.E. et al. *J. Am. Chem. Soc.* **1977**, *99*, 2751. (3) Schultz, A.G.; Yee, Y.K. *J. Org. Chem.* **1976**, *41*, 561. (4) Axon, B.W.; Davis, B.R.; Woodgate, P.D. *J. Chem. Soc., Perkin Trans. I* **1981**, 2956.

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

Working with R. B. Woodward

Professor Robert Burns Woodward of Harvard University was one of the world's greatest organic chemists. Former students, co-workers and friends gathered at the Beckman Center for the History of Chemistry in Philadelphia April 10-11, 1992, the 75th anniversary of R.B.W.'s birth, at the opening of a scholarly exhibition detailing his life and work.



Z23,407-9 *Working with R. B. Woodward* by Prof. Dr. Helmut Vorbrüggen

This travelling exhibition is most important because it teaches young chemists of the enormous impact one man can have.

One of the many former co-workers of R.B.W., Dr. Helmut Vorbrüggen of Schering AG, 1000 Berlin 65, Germany, has written a touching and human description of his time with R.B.W. It is available from Aldrich at no charge when requested with any order.

Attention Sharpless Asymmetric Epoxidation (AE) users:

Aldrich offers two grades of anhydrous TBHP in isooctane: 3 molar and 5.5 molar. Only the 5.5 molar solution is compatible with the AE. The titanium tartrate catalyst is destroyed by hydrocarbon solvents and can tolerate only a small amount (such as that introduced with the 5.5 molar grade of TBHP) in the total solvent mixture for the reaction. Professor Sharpless has informed us that a great many chemists have inadvertently been using the 3 molar grade which introduces too much isooctane, thereby crippling the catalyst and usually leading to dramatic attrition in both enantiomeric excess and yield. Thus for the Sharpless Asymmetric Epoxidation NEVER USE the 3 molar TBHP in isooctane. The 5.5 molar grade is the only one to use, as it was specifically formulated for this reaction.

A Methionine Salvage Pathway

Robert H. Abeles
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Brandeis University
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Waltham, MA 02254-9110

5'-*S*-Methyl-5'-thioadenosine (MTA, Fig. 1) is a product of several reactions involving *S*-adenosylmethionine which, in turn, is derived from the reaction of ATP and methionine.

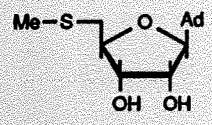
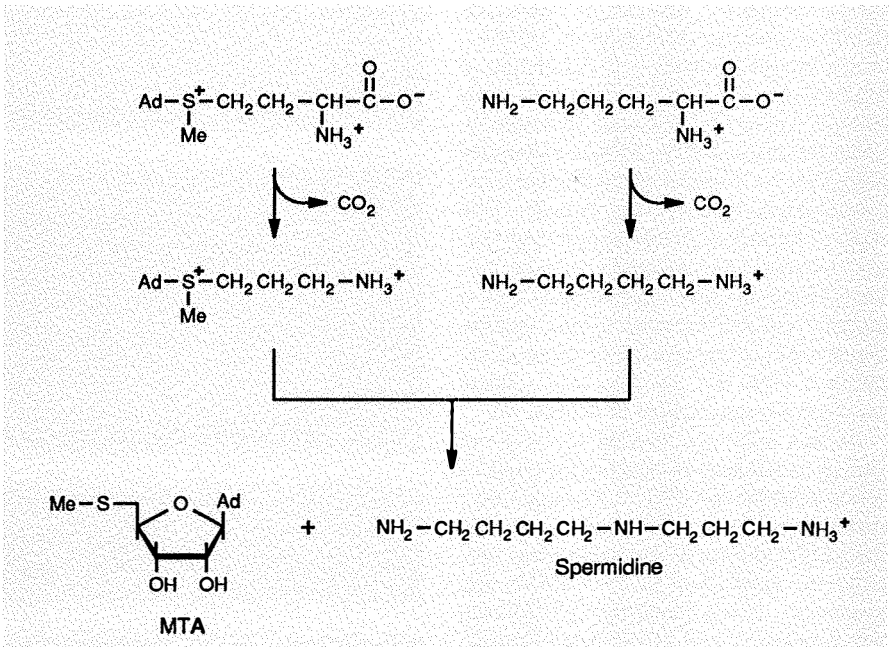


Figure 1: MTA

In mammalian systems, MTA is generated in the production of polyamines,[1,2] as shown in Scheme I. In plants, it is generated in the course of ethylene production,[3-5] as illustrated in Scheme II. In this reaction, *S*-adenosylmethionine is converted to 1-aminocyclopropane-1-carboxylic acid and MTA. It has been known for some time that MTA is converted to methionine in mammals,[6-10] microorganisms,[11-14] and plants.[15-17] The conversion of MTA to methionine is thus a salvage pathway. This pathway may be of particular importance in plants, since plants have to synthesize all amino acids. When mammalian cells are grown in culture in the absence of methionine, MTA can replace methionine.[10] MTA is more effective than methionine in the growth of *Ochromonas malhamensis*.[18]



Scheme I: Biosynthesis of Polyamines and Formation of MTA

The reaction sequence whereby MTA is converted to methionine is not obvious and we, therefore, investigated this transformation. It was known that in mammals,[19,20] in plants,[21,17] and in microorganisms,[11-14] 1-phospho-5-*S*-methylthio-D-ribofuranoside (1-PMTR) is an intermediate in the reaction pathway. The next intermediate identified in mammalian and bacterial systems was 2-keto-4-(methylthio)butyrate.[7,9,22] This keto acid is converted to methionine by transamination. Additionally, we established that formate is also produced.[9] The information available at this point is summarized in Scheme III.

Next, the metabolic fate of 1-PMTR was investigated in *Klebsiella pneumoniae*.[22] We established that 1-PMTR is converted to 1-phospho-5-*S*-methylthioribulose (1-PMT-Ru). This reaction is related to aldose/ketose isomerizations that proceed as shown in eq 1. This isomerization requires a free aldehyde. Therefore, it is very likely that, in an early

Dr. Robert H. Abeles being presented with the Alfred Bader ACS Award for Biochemistry by Dr. Stephen J. Branca, Director of Research and Development, Aldrich Chemical Company, Inc.

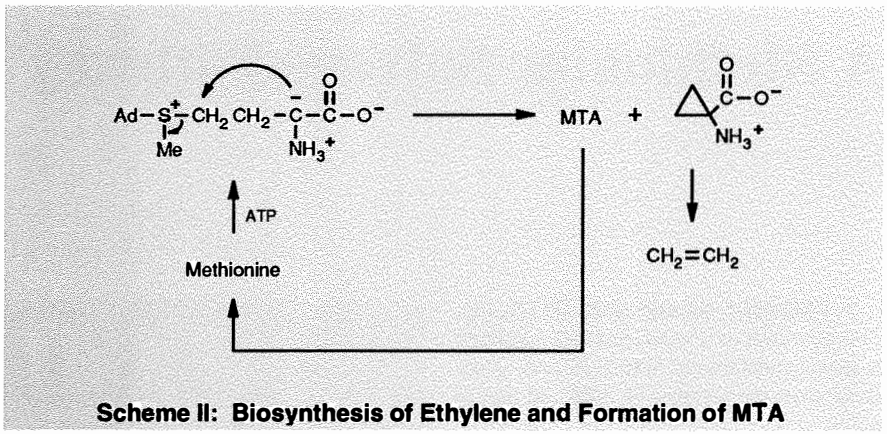
stage of the reaction, the phosphoryl group of PMTR is transferred either to the enzyme or the adjacent OH group so that the aldehyde function becomes available. Thereafter, the reaction proceeds as do other aldose/ketose isomerizations. A speculative mechanism is shown in Scheme IV. In this mechanism we propose that the phosphoryl group is transferred to the adjacent OH group.

The next step in the metabolic pathway is the conversion of 1-PMTRu to 1-phospho-2,3-diketo-5-*S*-methylthiopentose (PDK).[22] A mechanism involving α,β elimination of H_2O is shown in Scheme V. This leads to the formation of an enol that, upon ketonization, yields the diketone PDK. PDK is oxidatively converted to 2-keto-4-methylthiobutyrate, 3-methylthiopropionate, and formate. One mole of formate is formed per mole of keto acid and two moles of formate per mole of 3-methylthiopropionate. Experiments with a partially purified bacterial extract indicate that at least one unstable intermediate occurs between PDK and the keto acid. These reactions are summarized in Scheme VI.

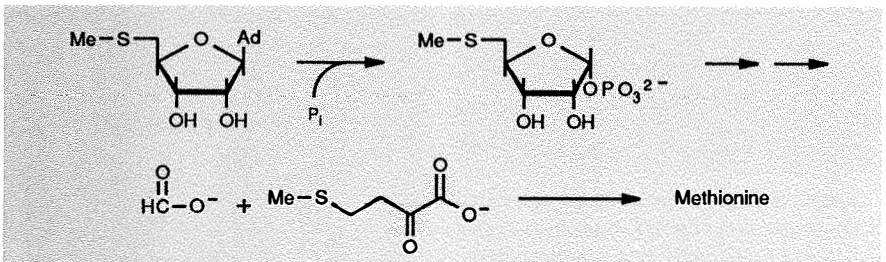
At this point we decided to carry out isotope experiments to establish the origin of formate and the fate of O_2.[23] We employed a partially purified bacterial extract that converts MTR to formate and methionine. Initially the metabolism of [1-^{13}C]MTR was examined. It was found that [^{13}C]formate was formed, as well as unlabeled formate. Formate arises from C-1 of MTR, as well as from another carbon. When the reaction was carried out in the presence of ^{18}O, it was found that methionine and [^{13}C]formate contained ^{18}O. The data suggested that a dioxygenase is involved. We propose the mechanism shown in Scheme VII for the action of the dioxygenase.

Next, we turned to the purification of the enzyme(s) that oxidatively convert PDK to the keto acid. Up to this point, PDK was synthesized enzymatically, starting with PMTR. Only inadequate amounts of material could be obtained by this procedure. We, therefore, decided to consider an alternate substrate and, thus, synthesized a PDK analog (**I**, Scheme VIII).

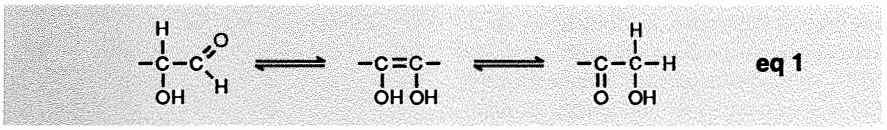
If **I** is metabolized through the same pathway as PDK, we would expect α-ketopentanoate, formate, and butyrate (Scheme VIII). When **I** was added to a partially purified bacterial extract, O_2 was consumed, and formate and α-ketopentanoate were formed. No attempt was made to detect butyrate. We then proceeded to purify an enzyme activity that oxidatively produced formate from **I**. We obtained a homogeneous enzyme that oxidatively converts **I** to formate and α-ketopentanoate as major products, with glyoxylate and butyrate as minor products.[24] This enzyme will be referred to



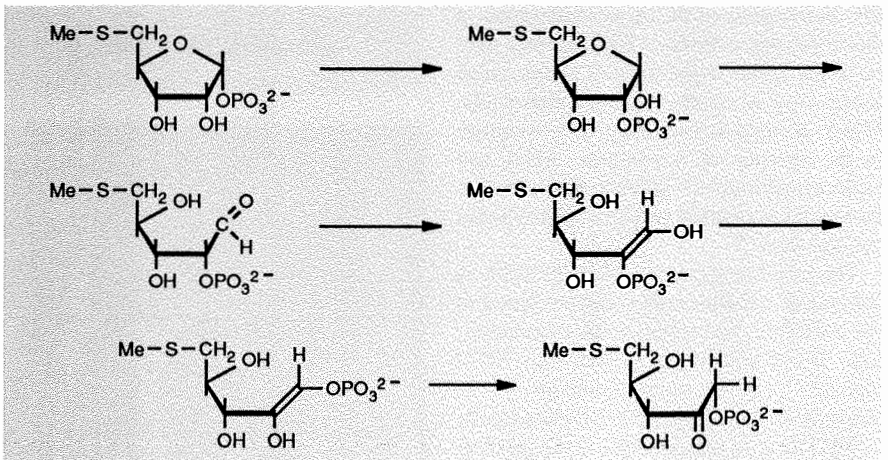
Scheme II: Biosynthesis of Ethylene and Formation of MTA



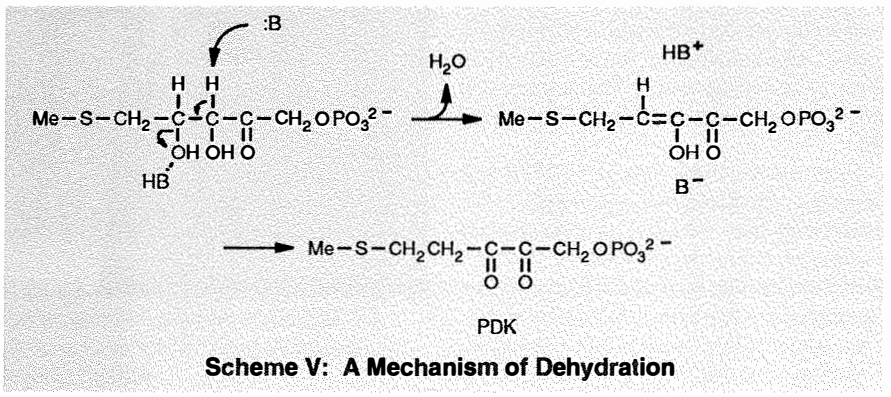
Scheme III: Conversion of MTA to Methionine and Formate



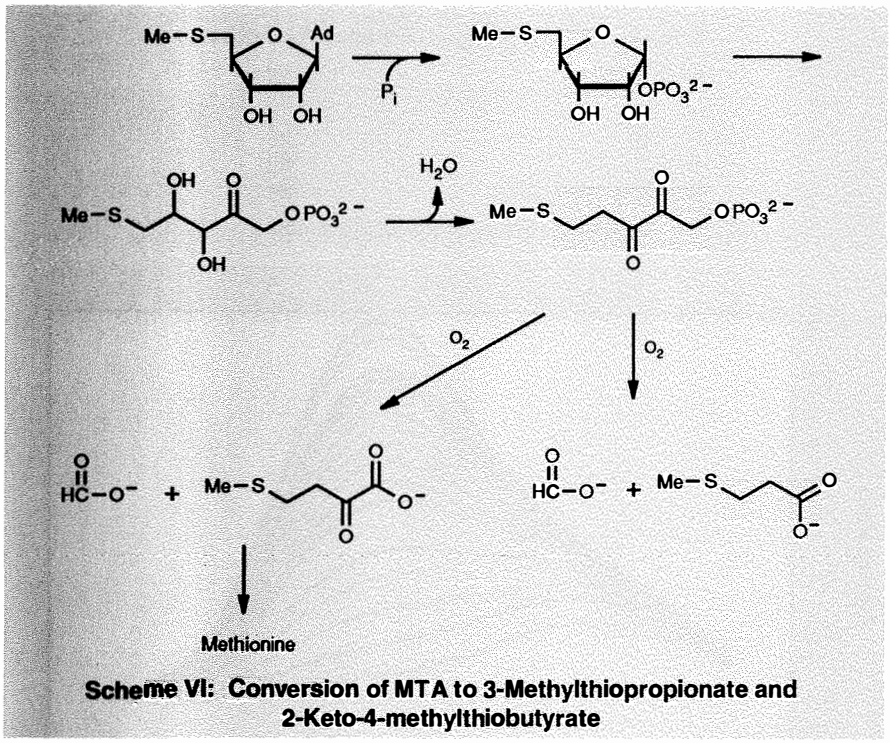
eq 1



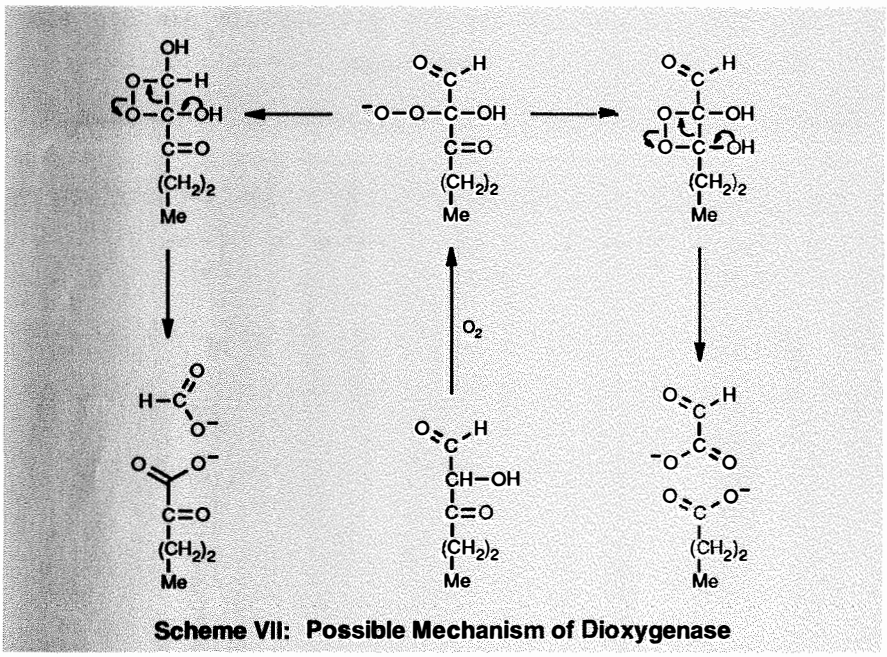
Scheme IV: Possible Mechanism for Isomerization of 1-PMTR



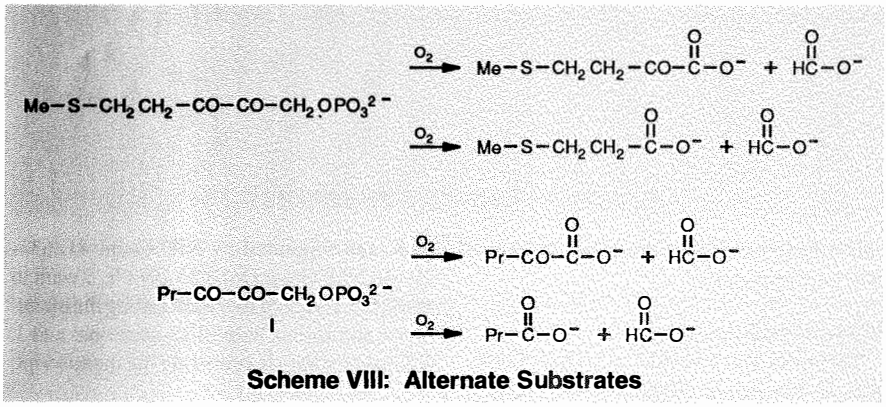
Scheme V: A Mechanism of Dehydration



Scheme VI: Conversion of MTA to 3-Methylthiopropionate and 2-Keto-4-methylthiobutyrate



Scheme VII: Possible Mechanism of Dioxygenase



Scheme VIII: Alternate Substrates

as E_1. The stoichiometry of the reaction catalyzed by E_1 is shown in Table I.

During the course of action of E_1 upon **I**, formation of chromophores was detected, as shown in Figure 2. Upon addition of enzyme to **I** under anaerobic conditions, an absorption maximum at 270 nm appears, and then gradually disappears. A new maximum at 340 nm develops. Admission of air results in the disappearance of the 340 nm peaks. The structures of the two compounds were determined by UV, ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectroscopy. The reaction catalyzed by E_1 is shown in Scheme IX.[24]

The enzyme appears to catalyze several reactions. It catalyzes the conversion of **I** to **II**, an enolization. The second reaction is the dephosphorylation of **II** to produce **III,** and the final reaction is the oxidative conversion of **III** to formate, α-ketopentanoate, and minor products. The question arises as to whether all of these reactions are enzyme-catalyzed. Compounds **I** and **II** are stable compounds; therefore, the conversions of **I** to **II** and **II** to **III** is enzyme-catalyzed. The reaction of **III** with O_2 to produce formate and α-ketopentanoate is not enzyme catalyzed since the rate of oxidation of **III** is not dependent on the concentration of E_1.

The conversions of **I** to **II** and **II** to **III** are catalyzed by a single protein. E_1 is homogeneous, as evidenced by electrophoresis, end group analysis, and amino acid sequence determination. Furthermore, the ratio of the two activities is constant throughout the protein peak eluted from a mono-Q column. The phosphatase activity of E_1 is highly selective. We have not found any other phosphate ester that is hydrolyzed. Is free **II** on the reaction pathway? Upon addition of **I** to E_1, a peak at 270 nm forms rapidly. This peak gradually decreases and is converted to **III** (340 nm). The amount of **II** formed initially far exceeds the amount of enzyme present. Additionally, the rate of conversion of **I** to **III** is not a linear function of enzyme concentration. This would be expected if the reaction proceeds through free **II**. The rate of conversion of **I** to **II** and **II** to **III** is linearly dependent on enzyme concentration.

It is surprising that an unstable intermediate in the conversion of **I** to **III** is released into solution. It should be kept in mind that, in the reaction described here, an analog of the natural substrate is used. Possibly, the conversion of **II** to **III** is much slower than the corresponding reaction with the natural substrate. With the natural substrate, little or none of the natural compound corresponding to **II** might be released.

It was also possible to obtain compounds **II** and **III** without the use of E_1.[24] When **I** is heated at 100 °C for 7 min at pH 7.4, a new compound is formed with NMR and UV

spectra identical to that of **II** produced with E_1. Treatment of this compound with alkaline phosphatase results in a compound with UV and NMR spectra identical with that of **III**. The compound formed with alkaline phosphatase treatment reacts with O_2 at the same rate as **III** and forms the same products.

We had previously obtained evidence for the existence of an unstable precursor of formate and α-keto-γ-methylthiobutyrate, as well as 3-methylthiopropionate.[21] Presumably, **III** is the analog of this unstable compound. An enzyme probably exists that converts **III** to formate and α-ketobutyrate, as well as another enzyme that converts **III** to formate and butyrate. We, therefore, undertook a search for these enzymes. This search was facilitated by the following observation: the rate of O_2 consumption by **I** in the presence of E_1 is greatly decreased by catalase. No catalase effect is observed in a partially purified bacterial extract. It is likely that catalase reduces the rate of the nonenzymic oxidation of **III**. Presumably, the oxidation of **III** in the partially purified system is enzyme-catalyzed and not subject to inhibition by catalase. We, therefore, searched for a protein fraction that, upon addition to E_1, would abolish the catalase effect on the oxidation of **III**. Such a fraction (PF_1) was found.[25] Addition of this fraction to E_1 greatly accelerated the oxidation of **I**, and the rate of O_2 uptake was not inhibited by catalase. In the presence of PF_1 and E_1, no α-ketobutyrate was produced from **I**; instead, butyrate and formate were produced. Purification of this protein fraction is now in progress.

The reaction sequence, as currently known, for the conversion of MTA to methionine is shown in Scheme X. All enzymes have been identified, except the enzyme that produces α-keto-γ-methylthiobutyrate from its immediate precursor.

The reaction sequence whereby PMTA is converted to 1-PMTR differs in mammals and microorganisms (Scheme X). In mammals, direct phosphorylation occurs. In microorganisms, MTA is first hydrolyzed and the resulting *S*-methylthioribose is phosphorylated by a kinase. This kinase is absent in mammals and, therefore, *S*-methylribose cannot be converted to 1-PMTR. This difference was utilized[26] to develop a compound, *S*-ethylthioribose, that is toxic to microorganisms, but nontoxic to mammals. It occurred to us that this selective toxicity is due to the ability of microorganisms to convert *S*-ethylthioribose to ethionine, a known toxic compound. Mammals cannot carry out this conversion since they lack the kinase. We verified this proposal by showing that an extract from *Klebsiella pneumoniae* efficiently converts *S*-ethylthioribose to ethionine.

Table I: Stoichiometry of Product Formation

Product	nmoles
O_2	72
HCO_2H	42
$RC(O)CO_2^-$	45
butyrate, glyoxylate	nd

Substrate initially present: 72 nmoles

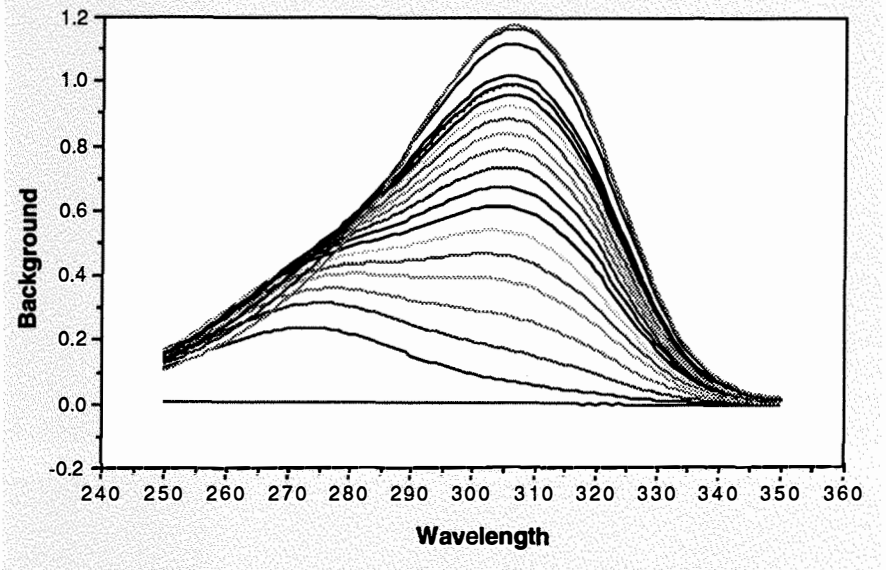
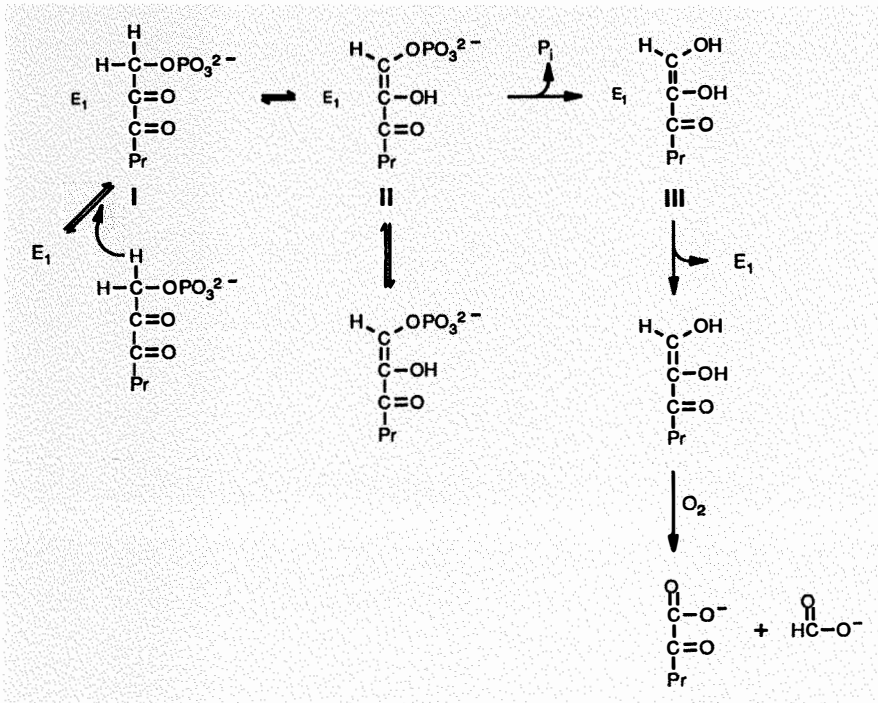


Figure 2: Spectral Changes During the Conversion of I to II (anaerobic)

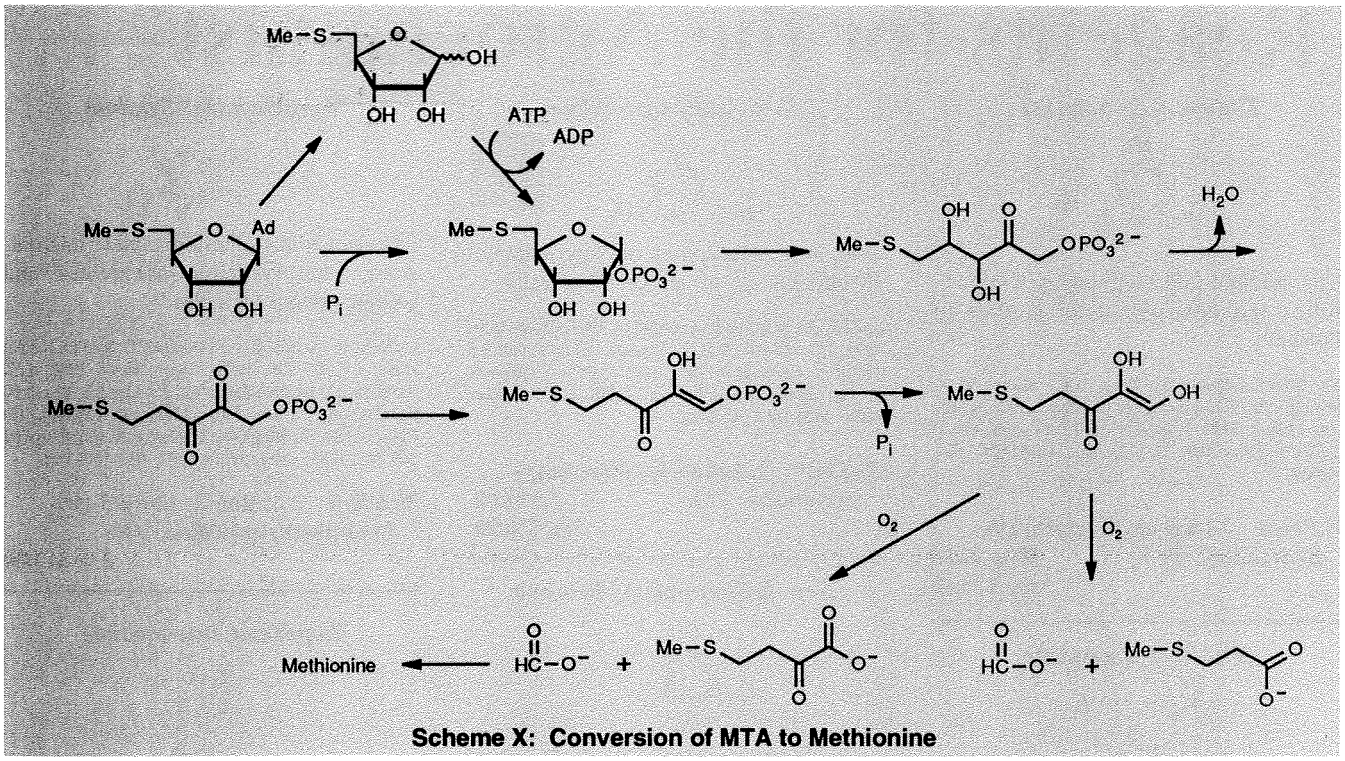


Scheme IX: Reaction Catalyzed by E_1

This conversion did not occur in fortified rat liver homogenates.[23]

Acknowledgements

This work was carried out by P.C. Trackman, E. Furfine, R. Myers, J. Wray, and S. Fish, and supported by NIH Grant #12633-29 and NSF Grant DMB 85-05498. I want to thank Dr. T. Alston for proofreading the manuscript and for his helpful suggestions; and J. Johnson for help in preparing the manuscript.



Scheme X: Conversion of MTA to Methionine

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About the Author

Robert Abeles received his Ph.D. from the Department of Biochemistry at the University of Colorado in 1955. His Ph.D. dissertation concerned the oxidative conversion of *N*-methylglycine to glycine and formaldehyde. During two postdoctoral years spent under Professor Westheimer at Harvard University, he investigated NAD model systems. Prof. Abeles discovered one of the first systems in which NADH nonenzymatically reduced a thioketone. His first academic position (1956-1960) was at Ohio State University in the Chemistry Department. The next four years were spent in the Biochemistry Department of the University of Michigan. From there Prof. Abeles moved to the Biochemistry Department at Brandeis University, his current position. He was chairman of the department from 1973 to 1987. He is a member of the American Academy of Arts and Sciences and the National Academy of Sciences.

Research interests fall into two general categories: investigation of enzyme mechanisms and the rational design of enzyme inhibitors and inactivators. Enzyme mechanism studies include the investigation of the mechanism of action of B_{12} coenzyme. In this investigation, positional isotope exchange was used, for the first time, to demonstrate the intermediate participation in hydrogen transfer of the methyl group of 5'-deoxyadenosine. Studies of the mechanism of action of proline reductase led to the identification of pyruvate at the active site of that enzyme. Dehydroalanine was found at the active site of histidine deaminase. These are the first examples of nonamino acid residues at the active site of enzymes. Abeles' laboratory played a major role in the development of suicide inactivators, which were synthesized for flavoproteins, pyridoxal-phosphate dependent enzymes, and, most recently, serine proteases. Highly effective reversible inhibitors, based on trifluoroketones, have been synthesized for serine proteinases and other proteinases.

The Molecular Basis of Biological Order and Amide-Amide Hydrogen Bonds—An Addendum

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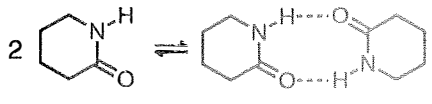
In a recent article in *Aldrichimica Acta*,[1] an approach to the molecular basis of biological order in aqueous solution was outlined. In the approach, which builds on the earlier work of others, the observed free energy of binding (ΔG kJ mol^{-1}) of **A** to **B** to give **A•B** was factorized into the following four terms (for the idealized case of good complementarity between **A** and **B** and the absence of conformational strain in **A•B**): the adverse free energy (ΔG_{t+r}, largely entropic) of a bimolecular association, the adverse free energy (ΔG_r) of restricting any internal rotations in the binding process, the favorable free energy of the hydrophobic effect (ΔG_h), and the favorable free energy (ΔG_p) of interaction between complementary pairs of polar functional groups (generated in **A•B**) and summed over all such pairs of interactions (to give $\Sigma\Delta G_p$).

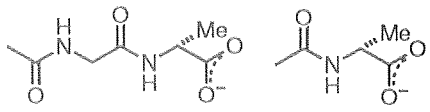
$$\Delta G = \Delta G_{t+r} + \Delta G_r + \Delta G_h + \Sigma\Delta G_p \qquad \text{eq 1}$$

It was noted that published data for the formation of assumed[2] hydrogen-bonded dimers of several small molecules (urea, diketopiperazine, valerolactam) can be used to obtain ΔG_p values for the amide-amide hydrogen bond. In broad terms, the dimerization constants reported for these small molecules in aqueous solution are close to 10^{-1} M^{-1}. Thus, for the formation of the dimer **1**, with loss of the rotational and translational entropy of one component (adverse by ca. 10^{-9} M^{-1}), the data indicate that dimerization is promoted by the formation of the amide-amide hydrogen bonds by ca. 10^8 M^{-1}. Hence, the conclusion[1,3] that such hydrogen bonds promote dimerization by ca. 10^4 M^{-1} (ΔG_p = -23 kJ mol^{-1}) per bond. Note that this method of accounting credits the favorable entropy associated with this hydrogen bond to ΔG_p. The favorable entropy is expected to be large since the formation of two hydrogen bonds allows much residual motion in the dimer **1**. This is a legitimate way of accounting, and leads to the conclusion that the hydrogen bonds are strong. If, on the other hand, the relative translation and rotation that exists between the two halves of the dimer is regarded as translational and rotational entropy of the separate components that was never lost, then the hydrogen bonds are concluded to be much weaker.[2,3]



1

The value of ΔG_p = -23 kJ mol^{-1}, deduced above, is close to the value reported[4] for the extra amide-amide hydrogen bond formed when *N*-Ac-Gly-D-Ala (**2**), rather than *N*-Ac-D-Ala (**3**) binds to the vancomycin group antibiotics. The article[1] assumed that this agreement lent support to the idea that such amide-amide hydrogen bonds are indeed stronger than hitherto supposed. However, this is an erroneous analysis since the values should, in fact, be different. When the increase in binding constant of **2** over **3** to the antibiotics is analyzed, account must be taken of the likelihood that residual motions of ligand relative to antibiotic in both these complexes are similar.



2 **3**

The ΔG_p values for the amide-amide hydrogen bond, deduced from the antibiotic data, should therefore be smaller (since they will not be credited with the favorable entropy of residual motions). The originally estimated[4] ΔG_p value (-24 kJ mol^{-1}) assumed no significant difference in hydrophobic effects between the binding of **2** and **3**, since the acetyl methyl group of **2** points out of the binding site. However, it is now appreciated that the antibiotic binding cleft is deep enough for this methyl group to be involved in a hydrophobic effect (ΔG_h), and additional hydrophobic effects are generated when hydrocarbon-containing portions of the antibiotic abut against the acetyl amide extension of **2** (relative to **3**). Accounting for such effects, and other subtle effects in methods of accounting related to residual motion, gives ΔG_p = -(10 to 13) kJ mol^{-1} for the amide-amide hydrogen bond formed by the acetyl carbonyl of **2** to the antibiotics, and ΔG_p = -(4 to 7) kJ mol^{-1} for the amide-amide hydrogen bond formed by **3** to the antibiotics.

From enzyme engineering experiments, hydrogen-bond strengths between uncharged entities have been concluded to be in the range -2 to -7.5 kJ mol^{-1}.[5] These values should bear comparison with the values derived from the above antibiotic work, since, in both cases, residual local motions should be similar before and after deletion of the hydrogen bond under investigation.[6] Indeed, given the uncertainty in proportioning the free energy changes between the various parameters in equation 1 and experimental ΔG values, amide-amide hydrogen bonds (derived of the benefit of the residual motions they allow) cannot be concluded to be stronger than hitherto believed. This is contrary to the original conclusion.[1] Further consequences are (i) there is currently no good evidence that amide-amide hydrogen bonds, or amide-hydroxyl hydrogen bonds, are stronger than hydroxyl-hydroxyl bonds,[8] (ii) nor is there evidence that rotor restrictions may have free energy costs as high as 20 kJ mol^{-1} per residue in long peptide chains. Thus, the entropically favorable release of water from the amide functionality when it forms a hydrogen bond is currently an unnecessary hypothesis;[1,4,8] and in the promotion of protein folding, the formation of intramolecular hydrogen bonds is seen to have a smaller or comparable[7] influence relative to the hydrophobic effect (and not a larger influence[1]).

The interpretation of the thermodynamic data for the formation of single- and double-stranded RNA and DNA structures remains an enigma. A plausible case can be made that in single-strand formation, the average entropic cost (in terms of $T\Delta S$ at 300K) of restricting a rotor in the sugar phosphate backbone is indeed high (ca. 8 kJ mol^{-1});[1] but, perhaps, some additional, and currently unappreciated adverse entropic effect, is involved in single-strand formation. Since it is concluded above that there is not good evidence that the amide-amide hydrogen bond is stronger than previously thought, it may be that the chemically similar hydrogen bonds in DNA are not stronger than originally concluded.[9] But the anomaly that two sugar phosphate backbones can be ordered with a similar entropic cost to ordering one remains; and it remains true that in estimating the strengths of these bonds in double helices, the entropic costs of rotor restrictions have been neglected.

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Asymmetric Syntheses of α-Amino Acids

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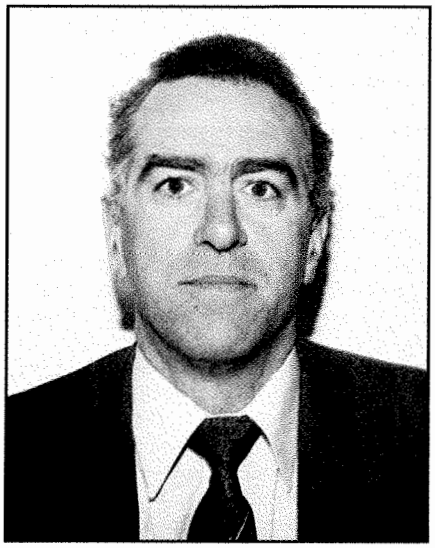
Introduction

α-Amino acids,[1] being the fundamental constituents of proteins, serve a central role in biology and chemistry. They also serve as mediators of nitrogen metabolism and provide the raw materials from which a large number of biologically important primary and secondary metabolites are constructed.[2] In addition, the relatively abundant proteinogenic amino acids have served as useful chiral, nonracemic reagents for a variety of synthetic applications.[3] The number of naturally occurring nonproteinogenic amino acids is rapidly approaching 1000; many of these substances possess important biological properties. With the advent of a variety of sophisticated spectroscopic and computational methods to elucidate the relationships between amino acid sequence, protein conformation, and corresponding chemical, physical, and biological properties, a tremendous level of interest has been generated in the *de novo* design and synthesis of unnatural amino acids for the purposes of imparting enzyme-inhibitory, antimetabolite, protease resistance, and unique conformational-inducing properties to peptides and derivatives. In addition, techniques have recently been developed[4] to incorporate unnatural amino acids into proteins that have shown promise in probing and altering enzymatic mechanism and function. As a consequence, the development of versatile new methodology for the preparation of proteinogenic, natural, and unnatural amino acids in optically pure form has emerged as a highly significant and challenging synthetic endeavor. The diverse nature of functional groups found or desired in the amino acid α-substituent (*R*) and the obligate importance of accessing either the L (*S*) or D (*R*) absolute configuration (**Figure 1**) requires the conception and development of numerous strategic solutions to this problem. Several extensive reviews on this subject have recently appeared.[1,5]

The established methods for the asymmetric synthesis of amino acids can be divided roughly into six categories.[1,5] (1) The highly stereoselective hydrogenation of chiral, nonracemic dehydro amino acid derivatives or the asymmetric hydrogenation of prochiral dehydro amino acid derivatives. (2) Chiral glycine equivalents serve as useful α-amino acid templates undergoing homologation via carbon-carbon bond formation at the α-position through nucleophilic carbanion alkylation or (3) electrophilic carbocation substitution. In addition, both (4) nucleophilic amination and (5) electrophilic amination of optically active carbonyl derivatives have recently been developed. (6) Enzymatic and whole cell-based syntheses have recently become more attractive in terms of substrate versatility, cost, and scale. All of these methods have their relative strengths and weaknesses; the optimum method for each individual application must still be considered on a case by case basis with respect to functionality, quantity desired, cost, and time. This account describes the development and utility of chiral glycine templates that permit the elaboration of structurally diverse α-amino acids in either the L- or D-configurations. The glycine framework is ideally situated for performing a variety of different C-C bond-forming reaction strategies owing to the capacity of the α-carbon to stabilize the formation of carbanionic, cationic, and radical character through resonance and dipolar interactions with the flanking nitrogen atom and carbonyl group (**Figure 2**).

At the time we initiated this work at Colorado State University, there were several reports in the literature concerning the preparation of α-amino acids through enolate alkylation of chiral glycine equivalents.[6] It was felt that a complementary chiral glycine cation equivalent would be valuable to access functionality not readily available by the enolate approach. Although numerous glycine cation equivalents producing racemic amino acids were known,[7] there were no reports prior to 1985 on asymmetric versions of this strategy.[8] The investigations that prompted our work were the electrophilic glycine anhydride derivatives (**1, Scheme 1**) that were developed to access the difficult branched and oxidized isoleucine moiety of the bridging framework of the antibiotic bicyclomycin (**3**).[9] It was felt that a similar, rigid six-membered ring glycinate should be adaptable to an asymmetric version.

After examining several moderately successful systems, we turned our attention to a single report by Kagan and associates in 1968[10] who reported the condensation of *erythro*-1,2-diphenylethanolamine (**4, Scheme 2**) with dimethyl acetylenedicarboxylate to yield the α,β-dehydrolactone **6**. Hydrogenation of this substance on Raney nickel followed by catalytic hydrogenation on a palladium catalyst furnished β-methyl aspartate in 98% optical purity. The clean, quantitative hydrogenolysis of the Raney nickel reduction product promised that a glycinate system based on this heterocycle would be an ideal candidate.



Dr. Robert M. Williams

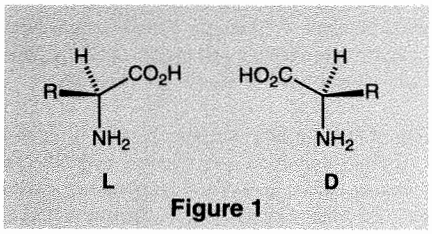


Figure 1

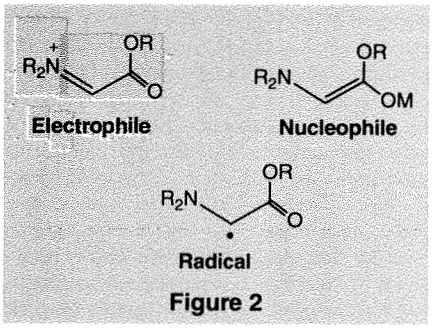
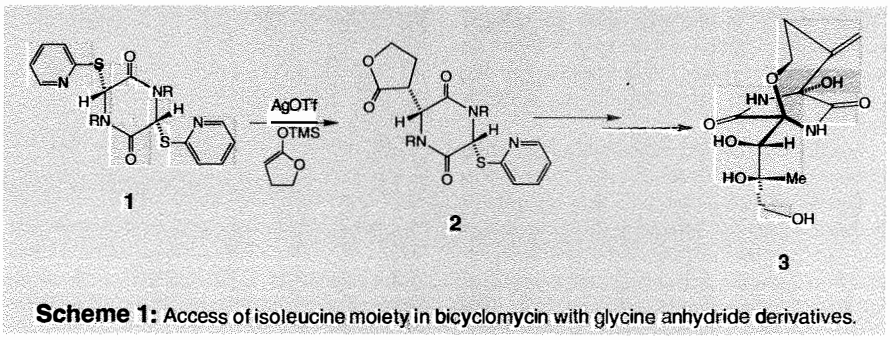


Figure 2



Scheme 1: Access of isoleucine moiety in bicyclomycin with glycine anhydride derivatives.

Preparation of Optically Active Glycinates

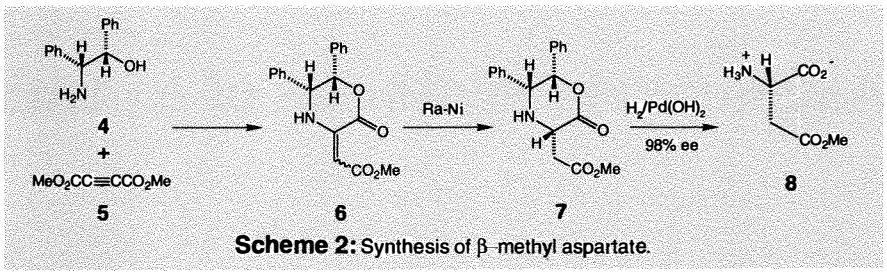
Inexpensive benzoin is converted into the oxime (**9, Scheme 3**) and stereospecifically hydrogenated to the racemic *erythro*-amino alcohols **4**; these are subsequently resolved through the derived L-glutamate salts on a large scale, according to Tishler et al.,[11] providing each optical isomer **4a** and **4b** of >98% ee. These amino alcohols are now commercially available from Aldrich.[12] Each isomer is then separately alkylated with ethyl bromoacetate, acylated with either benzyl chloroformate or di-*t*-butyl dicarbonate, and, finally, lactonized with catalytic *p*-TsOH in hot benzene or toluene to afford the crystalline lactones **10/11** in ~65% overall yield from the amino alcohols. The entire sequence from benzoin is accomplished without any chromatographic separations. All four isomers, **10a/10b, 11a/11b,** as well as the corresponding racemic substances, are now commercially available from Aldrich.[13] The benefit of the resolution is manifested in providing access to either D- or L-configured amino acids in a predictable manner. The lactones are readily soluble in most organic solvents (THF, dioxane, CCl_4, etc.) and possess excellent shelf-life storage properties.

Recently, Sharpless[14] reported an alternative, direct asymmetric synthesis[15] of the amino alcohols **4a/4b** utilizing the asymmetric dihydroxylation of *trans*-stilbene (**Scheme 4**). Thus, *trans*-stilbene can be asymmetrically dihydroxylated in 80-84% yield (optically pure following crystallization) to afford the stilbene diols **15a/15b**. Conversion to the cyclic sulfates (**16**), followed by S_N2 opening with azide, furnishes the corresponding *erythro*-azido alcohols. These are in turn reduced by catalytic hydrogenation giving the optically pure amino alcohols **4a/4b** in good overall yield.

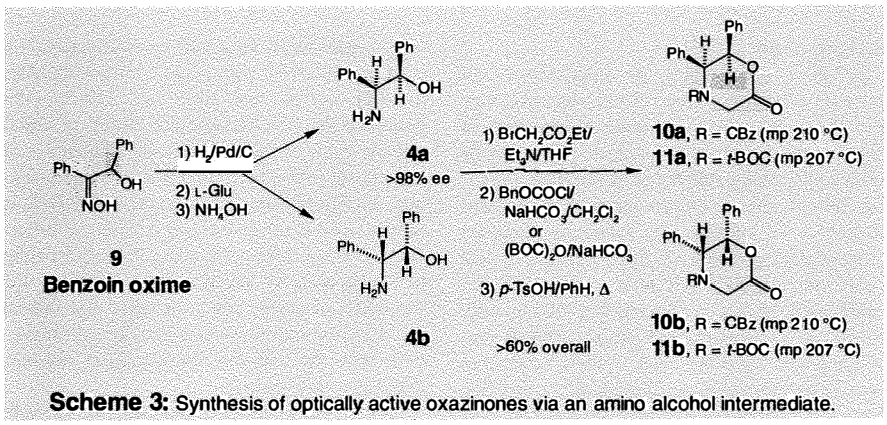
Electrophilic Glycinates

Bromination of these oxazinones with NBS in refluxing carbon tetrachloride proceeds in essentially quantitative yield.[16] The experimental protocol simply involves cooling the solution after the reaction is complete (ca. 60-90 min, reflux), precipitating the insoluble succinimide that is filtered off leaving, after evaporation, a white amorphous powder of the corresponding bromides (**17/18, Scheme 5**). The bromides are unstable to silica gel purification and are used directly (crude) for the subsequent coupling reactions. The relative stereochemistry of the bromide is *anti*- and only a single diastereomer is observed from the bromination reaction. The corresponding chloride can be obtained by chlorination with *t*-butyl hypochlorite, but apparently offers few advantages over the bromides. Reaction of the bromides with various organometallic reagents in the presence of zinc chloride results in displacement of the halogen providing the homologated oxazinones **19/20**. In most cases, the relative stereochemistry of the coupling reactions proceeds with net *retention* providing *anti*-**19/20**.

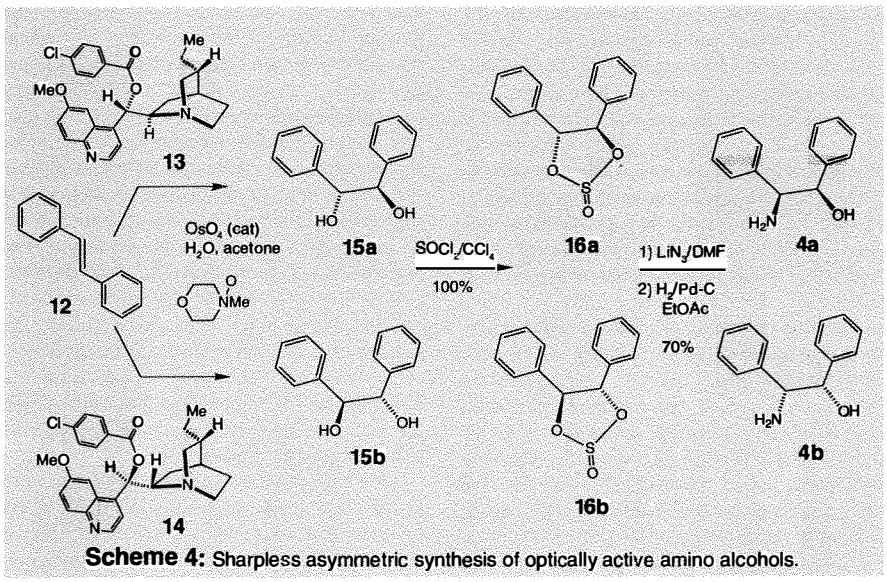
Based on the observed stereochemical outcomes, it can be speculated that the zinc(II) salt coordinates to the halogen, ultimately providing the reactive iminium species (**23, Scheme 6**). Since the phenyl rings are *cis*, the sterically least encumbered approach is from the face *anti*- to the two phenyl substituents (shown). Depending on which type of BOC protecting group is employed, two different types of reductive protocol have been devised. In the case of the *N*-CBz systems, either catalytic hydrogenation on a Pd^0 catalyst or dissolving metal reduction directly provides the free zwitterionic amino acids **21**. In the corresponding *N*-*t*-BOC systems, dissolving metal reduction directly provides the *N*-*t*-BOC-protected amino acids, **22**. **Table 1** lists the results of surveying a variety of coupling reactions with **17/18**, the coupling conditions, the reduction method, the amino acid



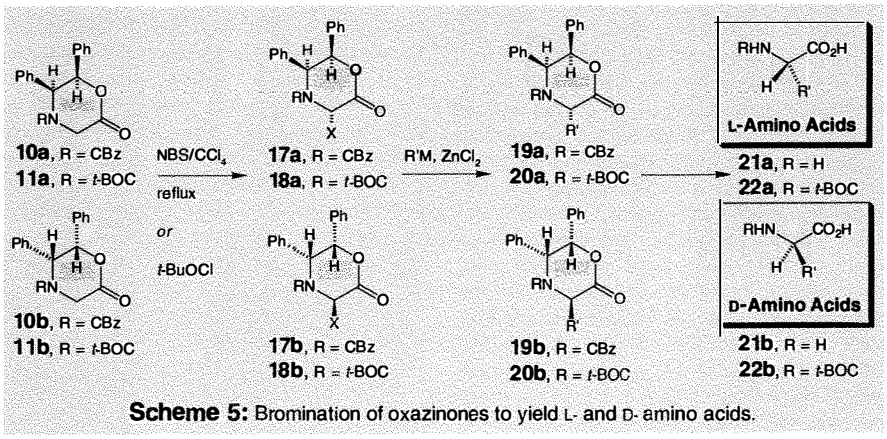
Scheme 2: Synthesis of β-methyl aspartate.



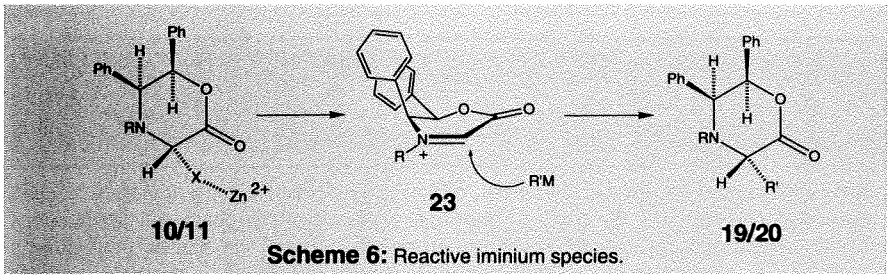
Scheme 3: Synthesis of optically active oxazinones via an amino alcohol intermediate.



Scheme 4: Sharpless asymmetric synthesis of optically active amino alcohols.

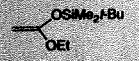
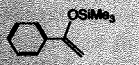
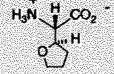


Scheme 5: Bromination of oxazinones to yield L- and D- amino acids.



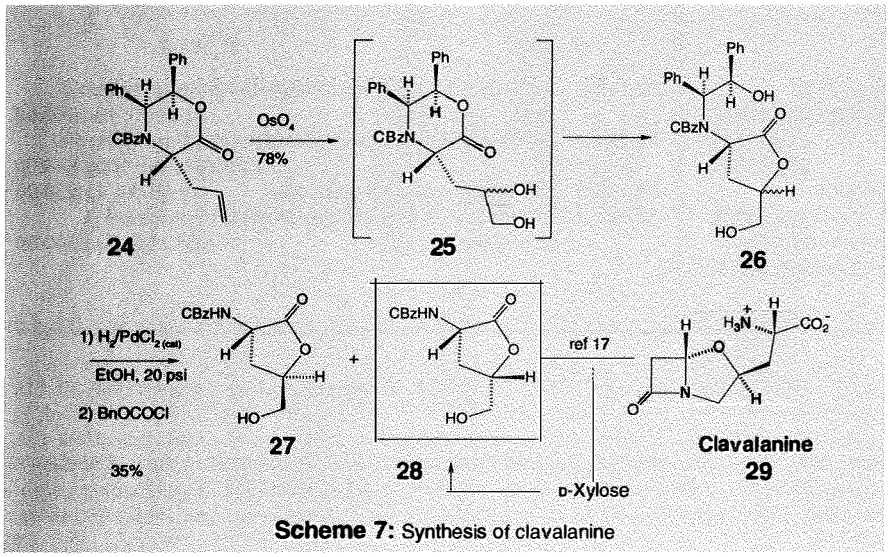
Scheme 6: Reactive iminium species.

Table 1: Survey of a variety of coupling reactions.

Nucleophile	Reaction Conditions	Yield of 19	Deprotection Method	Yield of Amino Acid	% ee
	$ZnCl_2$/THF 25 °C	74%	$H_2/PdCl_{2\ (cat)}$ EtOH, 20 psi	85% **Ethyl aspartate**	>96%
	$ZnCl_2$/THF 25 °C	66%	$H_2/PdCl_{2\ (cat)}$ EtOH, 20 psi	93% **Norvaline**	>98%
	$ZnCl_2$/THF	66% 25 °C	Li^0/NH_3/ EtOH	90% **Allylglycine**	>91%
H_3CZnCl	THF	46% -78 °C	$H_2/PdCl_{2\ (cat)}$ EtOH, 20 psi	100% **Alanine**	>96%
$Bu_2Cu(CN)$	THF/Et_2O	48% -78 °C	$H_2/PdCl_{2\ (cat)}$ EtOH, 20 psi	52% **Norleucine**	>99%
	$ZnCl_{2\ (cat)}$/MECN	72% 25 °C	$H_2/PdCl_{2\ (cat)}$ EtOH, 20 psi	91% **Homophenylalanine**	>96%
	$ZnCl_2$/THF	82% 25 °C	$H_2/PdCl_{2\ (cat)}$ EtOH, 20 psi	91% **Cyclopentylglycine**	>96%
	$ZnCl_2$/THF	82% 25 °C	Li^0/NH_3/ EtOH	94% **Cyclopentenylglycine**	>96%
	$ZnCl_2$/THF	64% 25 °C	$H_2/PdCl_{2\ (cat)}$ EtOH, 20 psi	89% 	>96%
	$ZnCl_2$/THF	66% 25 °C	$H_2/PdCl_{2\ (cat)}$ EtOH, 20 psi	89% **Dihydrofuranomycin**	not det.

***N*-*t*-BOC Amino Acids from *N*-*t*-BOC Lactones 11**

	$ZnCl_2$/THF 25 °C	63%	Li^0/NH_3/ EtOH	85% **Ethyl aspartate**	>96%
	$ZnCl_2$/THF 25 °C	59%	Li^0/NH_3/ EtOH	85% **Ethyl aspartate**	>96%



Scheme 7: Synthesis of clavalanine

produced in each case, and the % ee. The chemical yields for **19/20** reflect the two-step conversion of the oxazinones **10/11** into the bromides and, hence, to **19/20**. It should be noted that, with richly basic reagents such as methylzinc chloride or the cuprates, relatively modest yields result when compared to the 'neutral', electron-rich nucleophiles. This is due to a competing reduction of the halides back to the starting oxazinones and is interpreted as involving an electron transfer radical-radical coupling mechanism in these cases. The % ee's are excellent, typically exceeding 96% ee. Full experimental details accompany this work.[16]

The crystalline allylated substance **24** (**Scheme 7**) was osmylated to provide the γ-butyrolactone **26** as a 1:1 diastereomeric mixture in 78% yield. The initially formed diol **25** spontaneously rearranges to the thermodynamically more stable γ-butyrolactone isomer under the reaction conditions. Reductive removal of the chiral auxiliary, followed by acylation with benzyl chloroformate, provided **27** and **28,** which were separated by silica gel chromatography. Isomer **28** was previously converted into the unusual β-lactam antibiotic clavalanine (**29**) by a Hoffmann-La Roche group.[17]

Scheme 8 details an extremely short and convenient synthesis of chiral glycine derivatives.[18] The bromide **17a** is simply reduced with tritium carrier gas on Pd^0 at 1 atmosphere in tritiated water/THF. Ion-exchange isolation provided **30** in ~31-38% chemical yields that was 88-93% optically pure and had a specific activity of 0.78 Ci/mmol. The authors note[18b] that the material obtained by this procedure contained less than 1% of the corresponding di-tritiated material **31** that is found as a major contaminant in the classical enzymatic exchanges with serine hydroxymethyl transferase and glutamic-pyruvic transaminase. The contamination of **31** produced by the enzymatic exchange protocol precluded the use of this material for the Alberta group[18b] that was studying the stereospecific abstraction of the α-methine protons of terminal glycine amides by the enzyme peptidyl α-amidating monooxygenase (PAM). The corresponding α-deuterioglycines were obtained[18a] by hydrogenating **17a** or **17b** on a Pd^0 catalyst in D_2O giving material of 84-90% isotopic purity, 77-82% ee and 54% yield. It should be noted that if D_2O is not employed, the Pd catalyst exchanges protons from the solvent giving material of reduced *isotopic* purity. The Alberta group notes that, at 1 atm pressure which is required for tritium reactions, a full molar equivalent of $PdCl_2$ must be employed to obtain reasonable yields. On the other hand, the deuterium reduction can be carried out with catalytic amounts of $PdCl_2$ at 20-40 psi. The primary advantage of this synthesis is the overall simplicity (two steps from commercially available **10**), the high isotopic purity, and the introduction of the isotopic atom in the last step. This contrasts to alternate chemical syntheses of chiral glycine that are often multistep and carry the isotope through many manipulations.

Scheme 9 details an asymmetric synthesis[19] of the recently discovered amino acid β-carboxy aspartic acid (Asa, **33**) that was obtained from ribosomal protein hydrolysates by Koch, et. al. Asa is a notoriously unstable amino acid that is sensitive to decarboxylation under acidic conditions and

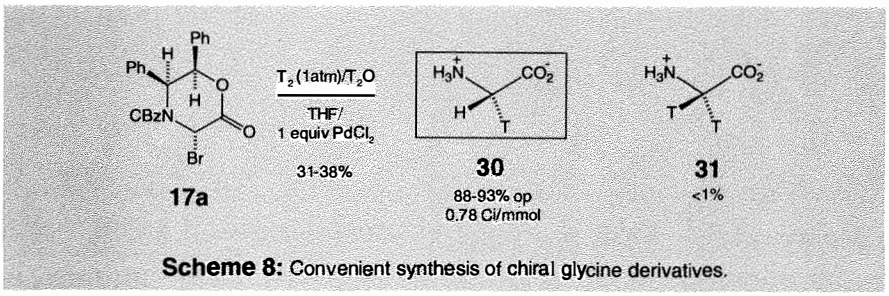
continued on page 15

continued from page 13

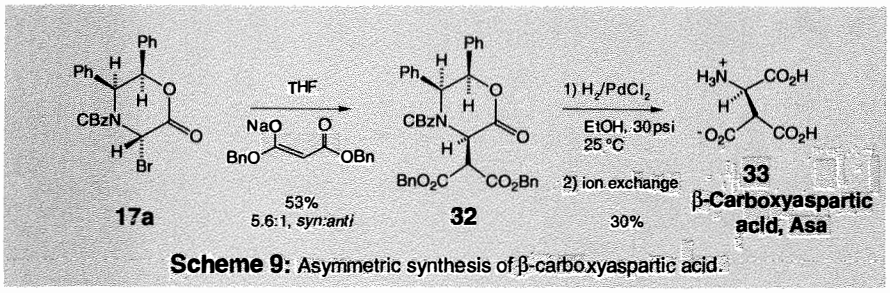
elimination of ammonia under basic conditions. The inherent lability of Asa is sufficiently problematic that the harsh conditions employed in conventional peptide-sequencing techniques (resulting in production of Asp in most cases) have limited the detection of Asa in natural systems. Coupling of **17a** with sodium dibenzyl malonate in THF furnished, in 53% yield, the malonate **32** as a 5.6:1, *syn:anti* mixture of diastereomers that was separated by chromatography. As discussed below, the highly nucleophilic malonate anion suffers primarily S_N2 displacement of the bromide providing *syn*-**32** as the major product. Reduction of all five benzylic residues over a Pd^0 catalyst provided Asa (**33**) as a 4:1 mixture with Asp. These were easily separated by acidic ion exchange chromatography which allows Asa (pKa = 0.8) to pass freely off the column. The small amount of Asp produced in the reduction presumably results from the small amount of HCl produced from the $PdCl_2$ and reflects the sensitive nature of this difficult amino acid. The pure Asa is obtained in 30% yield from **32** and >98% ee. The % ee was determined by decarboxylation to Asp and Mosher amide formation.

We have devised a straightforward and practical experimental protocol for directly preparing the zwitterionic amino acids in a pure form as shown in **Scheme 10**. In the case of saturated "R" groups (i.e., stable to catalytic hydrogenation), the Kagan-type[10a] reductive cleavage is typically chosen. The substrate (e.g., **34**) is dissolved in ethanol and hydrogenated over a catalytic amount of $PdCl_2$ at room temperature at 20-50 psi for 1-2 days in a glass hydrogenation bottle. The reaction is purged with nitrogen, the catalyst filtered off, and the ethanol evaporated leaving an oily residue. This residue is then triturated several times with ether or pentane to remove the bibenzyl (**35**) produced in the reductive cleavage of the chiral auxiliary. The remaining water-soluble residue becomes solid during the trituration and is subsequently dissolved in water, filtered through cotton, and concentrated to afford essentially pure amino acid (e.g., **36**). A small amount of HCl from the $PdCl_2$ accompanies the crude amino acid that may be easily removed by exposure to a quick ion exchange filtration.[20] For most applications where the amino acid will be transformed into an ester or urethane for peptide coupling, the crude materials are sufficiently pure to utilize directly without further purification.

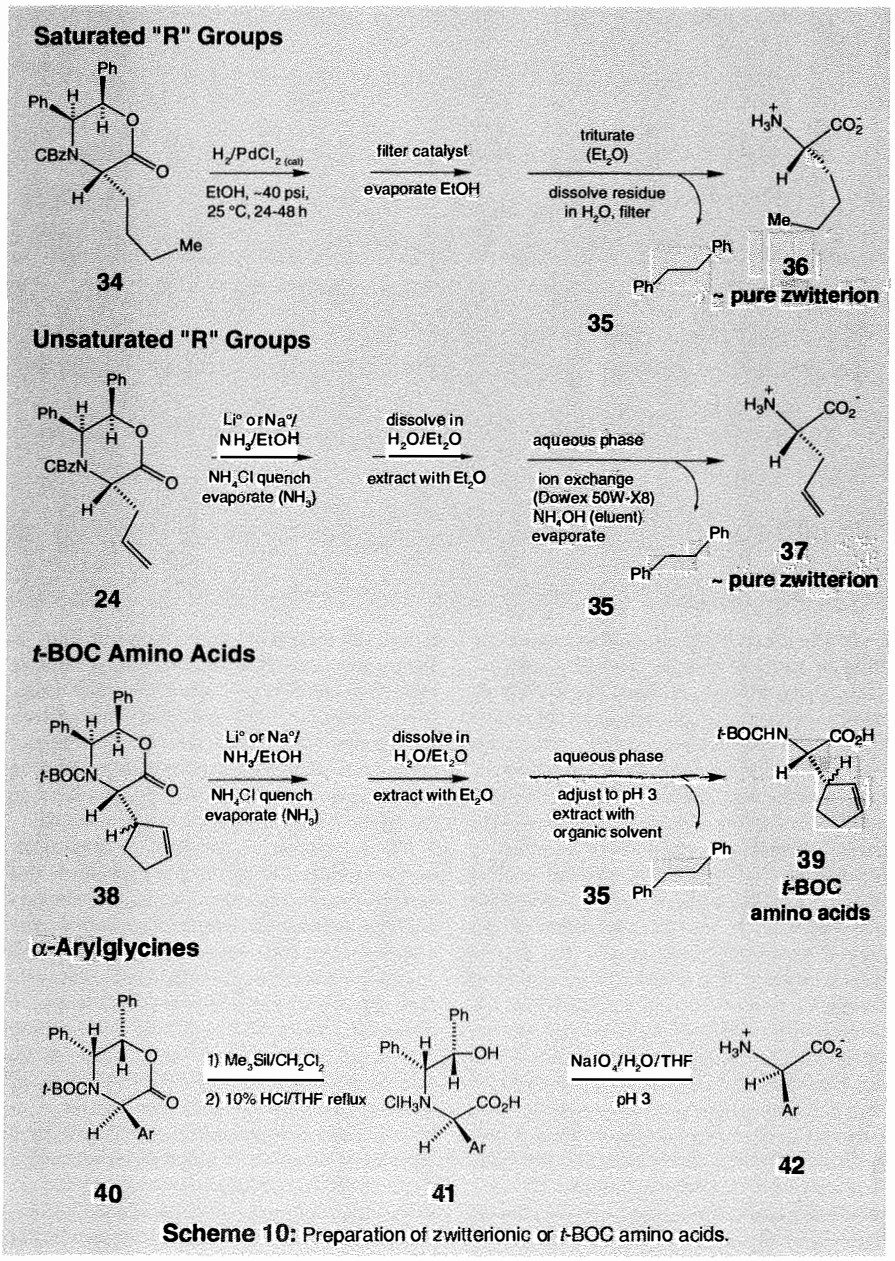
In the case of unsaturated or hydrogenolizable "R" groups, the dissolving metal protocol is employed. The substrate (e.g., **24**) is dissolved in liquid ammonia containing ethanol at -33 °C and either lithium or sodium metal is added to the reaction mixture. The metal is added until the blue color persists for ca. 1 min and is then quenched with solid ammonium chloride. The ammonia is allowed to evaporate and the ethanolic residue partitioned between water and ether in a separatory funnel. Extraction with ether again removes the bibenzyl (**35**) leaving the pure amino acid in the aqueous phase. The aqueous phase is then filtered through an ion-exchange resin affording essentially pure zwitterionic unsaturated amino acids (e.g., **37**). In the case of the dissolving metal reduction of the *t*-BOC substances (**38** to **39**) the same protocol is followed, except that the aqueous phase is acidified to pH 3 after the organic extrac-



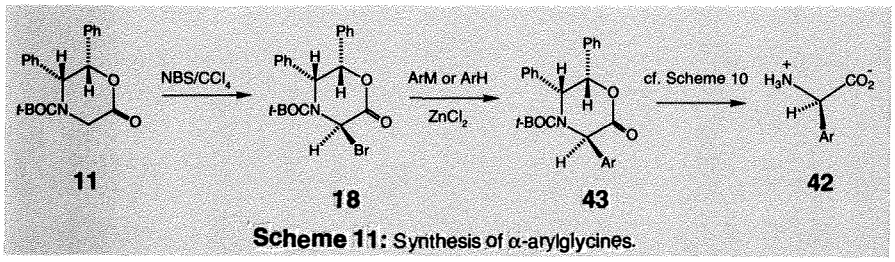
Scheme 8: Convenient synthesis of chiral glycine derivatives.



Scheme 9: Asymmetric synthesis of β-carboxyaspartic acid.



Scheme 10: Preparation of zwitterionic or *t*-BOC amino acids.

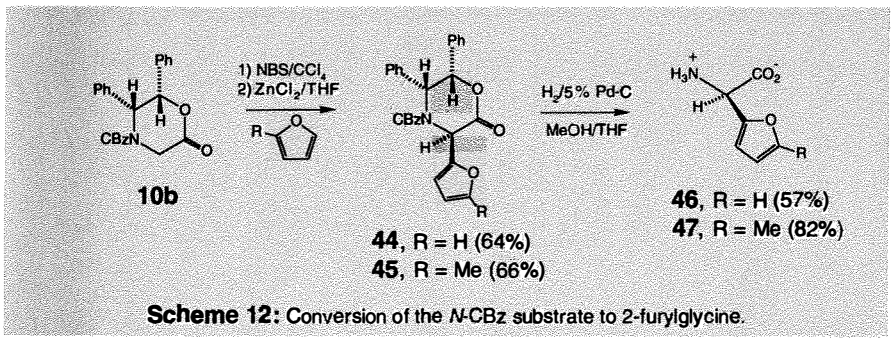


Scheme 11: Synthesis of α-arylglycines.

Table 2: α-Arylglycines.

ArM / ArH	Conditions	Yield % 43	Yield % 42[a]	% ee 42
$(C_6H_5)_2CuLi$	Et_2O/THF	56	52	82
$(C_{10}H_7)_2CuLi$	Et_2O/THF -78 °C, 1.5 h	55	29	94
1,3-dimethoxybenzene	$ZnCl_2$/THF 25 °C, 4.5 h	83[b]	62	91
furan	$ZnCl_2$/THF 25 °C, 5.5 h 4Å molecular sieves	50	26	90
2-methylfuran	$ZnCl_2$/MeCN 25 °C, 4 h 4Å molecular sieves	39	73	93

a) Yield for three steps. b) Two-step yield for the lactone after TMSI removal of the *t*-BOC group.



Scheme 12: Conversion of the *N*-CBz substrate to 2-furylglycine.

tion of **35** and extracted with ethyl acetate, etc., to afford the pure *t*-BOC amino acids (e.g., **39**).

In applying these glycine templates to the problem of arylglycines, an alternate means of removing the chiral auxiliary needed to be devised that would selectively cleave the C-O and C-N benzylic residues of the auxiliary and not cleave the C-N benzylic bond of the arylglycine unit itself. The standard protocol discussed above for effecting reductive removal of the chiral auxiliary involves either a dissolving metal reduction or a catalytic hydrogenation. It was anticipated that neither reaction condition would achieve the desired chemoselectivity. The Strecker-based method of Weinges[21] proceeds through a related 3-aryl-5-phenyl-6-hydroxymethyloxazinone and was reported to be disassembled using either oxidation with periodate or reduction on a Raney-nickel catalyst. It seemed reasonable that periodate should selectively remove two molar equivalents of benzaldehyde from the hydroxy acids (**41**) providing the arylglycines in a similar fashion. We have found[22] that application of the oxidative protocol employed by Weinges provides the desired selectivity on the present substrates. Removal of the *t*-BOC group from **40**, with trimethylsilyl iodide in methylene chloride, proceeds cleanly and the resulting lactones are then subjected to hot aqueous HCl to afford the hydroxy acids **41**. Treatment of these crude substances with sodium periodate in (pH 3) aqueous THF, followed by ion-exchange purification, furnishes the free amino acids **42**.

It must be added that, although the chiral auxiliary is sacrificed in the final deprotections, this system offers an important advantage over numerous other amino acid syntheses that require expensive, time-consuming chromatographic separations, recovery and 'recycling' of chiral auxiliaries (rarely done in practice), and hydrolyses of esters, etc., to obtain the amino acids themselves. In the present case, the chiral auxiliaries are polar, water-soluble substances that, even if it were possible to recover, would require a difficult separation from the products. Thus, the destruction of the chiral auxiliary in this case turns out to be a significant advantage, since the final processing converts the chiral auxiliary into an innocuous substance of greatly different solubility properties than the amino acids or *t*-BOC amino acids and is easily removed by trituration or extraction. The raw cost of the amino alcohols **4**, of course, precludes the application of this chemistry to large, multi-kilo industrial scale syntheses. As with virtually all of the (non-catalytic) wholly 'organic' amino acid syntheses, this system is most appropriate for the basic research chemist who needs rapid and predictable access to a large number of structurally diverse amino acids in optically active form.

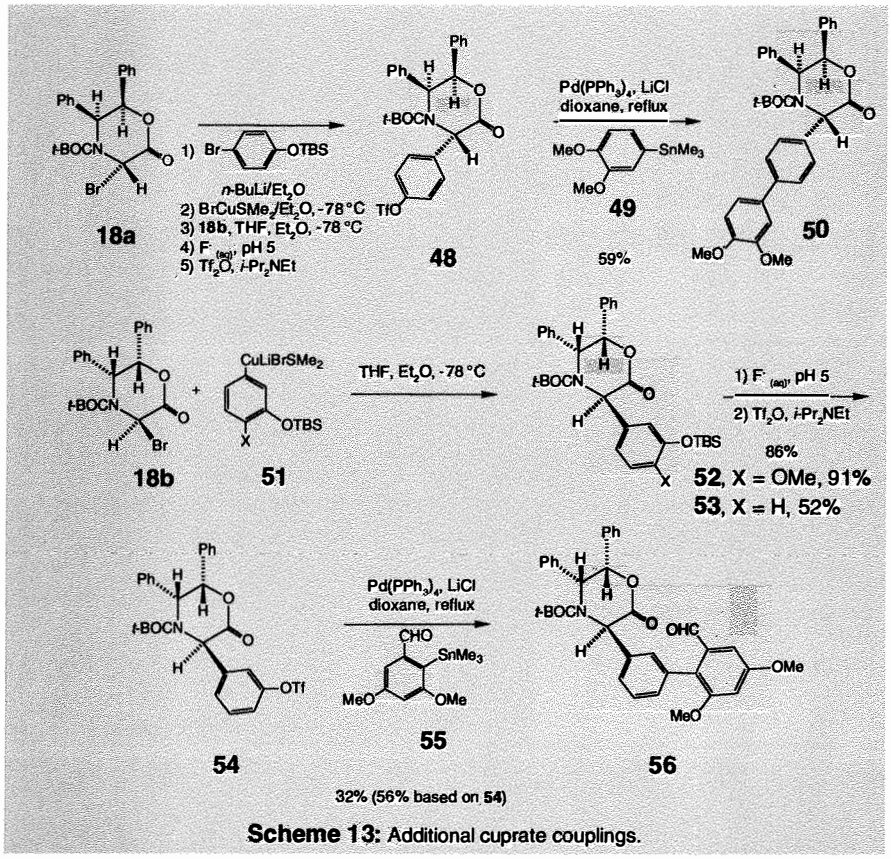
The arylglycines constitute an important class of nonproteinogenic α-aminoacids. Numerous other, highly functionalized arylglycines are found in numerous peptide and glycopeptide antibiotics such as the vancomycins. The apparent simplicity of the arylglycine structure is complicated by the ease of base-catalyzed racemization of the α-methine proton rendering these substances challenging synthetic targets to obtain in optically pure form. As illustrated in **Scheme 11**, glycinate **11** is brominated, as described above, to furnish the bromide **18**. Reaction of this material with either an arylcuprate or electron-rich aromatic under Friedel-Crafts conditions provides the *anti*-arylated substances **40 (Scheme 10)**.[22] Cleavage of the auxiliary as described above furnishes the α-arylglycines **42** (**Table 2**). Varying amounts of partial racemization accompany the final deprotection as diastereochemically homogeneous materials (**43**) are obtained from the couplings to **18**.

We have also found that the *N*-CBz substrate **10b** (**Scheme 12**) could be converted into 2-furylglycine (**46**) by a selective three-step method involving: (1) selective removal of the *N*-CBz group with 5% Pd-C/H_2 at atmospheric pressure; (2) ring-opening of the lactone; and (3) periodate cleavage. It is noteworthy that the furan ring is not saturated in the first step, nor oxidized in the last step. In one remarkable instance, we found that the furan adducts **44** and **45** could be cleanly hydrogenated to the corresponding amino acids **46** and **47** in 57% and 82% yield, respectively. This reaction is noteworthy in that the furan ring is not saturated nor is the "benzylic" C-N moiety of the amino acid cleaved under these conditions. Based on extensive experience hydrogenating these types of oxazinones to the amino acids, we know that the *N*-CBz group is cleaved first, followed by the lactone C-O benzylic bond, and lastly, the C-N residue. We have been able to isolate these stepwise reduction products by carefully varying the pressure and loading of the catalyst. It would seem reasonable that the *anti*-stereochemistry of **44/45** and the relative sluggishness of reducing the furan C-N benzylic residue relative to that of the benzyl C-N bond contribute to the observed selectivity in these two cases. At higher pressure on a Pd• catalyst, substrates **44** and **45** suffer clean conversion to the corresponding 2-tetrahydrofuranylglycine derivatives.[16] We have examined the direct hydrogenation of other α-aryl-*N*-CBz substrates corresponding to **44**, but with only limited success. In most cases, small amounts (~10%) of the arylglycine can be obtained under 1 atm of H_2/Pd-C conditions, but a myriad of other products are produced. The furan substrates would seem to be an unusual (but reproducible) exception. The oxidative periodate protocol is consistently successful for all of the aryl substitutions we have examined.

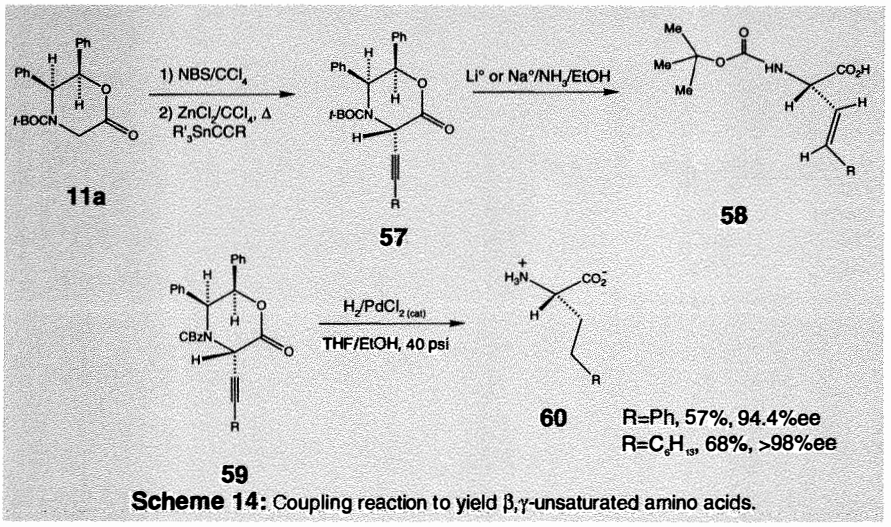
Scheme 13 illustrates some additional cuprate couplings that were part of an investigation to access bis-arylglycines such as those found in the glycopeptide antibiotics exemplified by vancomycin. The cuprate couplings are compatible with silyl-protected phenolic groups, and the resultant α-arylated lactones can be further manipulated with no detectable loss of stereochemical integrity. Thus, aryl cuprate coupling to **18** with siloxy aromatics produces the *anti*-homologation products in 52-91% yields. These can subsequently be converted into the corresponding triflates (**48**; **54**) and subjected to Stille biaryl couplings.[23,24]

The β,γ-unsaturated amino acids constitute a challenging and biologically active class of amino acids. Some members of this class have been shown to exhibit neuroexcitatory, antimicrobial, and enzyme inhibitory properties.[25] Like the arylglycines discussed above, the β,γ-unsaturated amino acids are prone to racemization and rearrangement to the conjugated α,β-dehydro isomers. This inherent lability renders their asymmetric synthesis quite difficult. A new coupling reaction has been developed to access the β,γ-unsaturated amino acids as shown in **Scheme 14**. The oxazinones are brominated in the usual way and then condensed with trialkyltin acetylides[26] in the presence of zinc chloride in warm carbon tetrachloride to afford the crystalline alkynes **57** as single diastereomers (*anti*). Dissolving metal reduction directly provides exclusively the (*E*)-vinylglycine derivatives **58** in good chemical yields and good to excellent % ee (**Table 3**). The partial racemization that occurs in several cases must attend either the reduction step, the subsequent work-up, or the % ee determination (involving removal of the BOC group and Mosher amide formation) since the alkynes **57** are stereochemically pure (>99% de and >99% ee). This method provides the first stereocontrolled, asymmetric synthesis of γ-substituted vinyl amino acids.[27] It is also possible to effect complete saturation of the alkynes[28] (**59**) by catalytic hydrogenolysis to the free amino acids **60**.

To study the mechanism of coupling to the bromides, a solvent/Lewis acid study[16] was undertaken as shown in **Schemes 15-17**. When **17** is condensed with the ketene silyl acetal of ethyl acetate in methylene chloride, using zinc chloride as the Lewis acid, the *syn* isomer (**62**) is produced as the major product to the extent of at least 45:1, *syn:anti* (**62**:**61**). When a more polar solvent is used, such as THF, the selectivity decreases giving as little as 14:1, *syn:anti*. When a very powerful Lewis acid (AgOTf) is used, the ratio decreases to 2:1, *syn:anti*. These results indicate that in the nonpolar solvent, methylene chloride, and with a weak Lewis acid, zinc chloride, the electron-rich ketene silyl acetal effects a clean S_N2 displacement of the bromide. When the conditions are changed to encourage formation of the iminium species **23** (see Scheme 6, more polar solvent, strong halophile), more of the S_N1 product (*anti*) begins to appear. When a slightly less electron-rich nucleophile is employed, such as the silyl enol ether of acetophenone (**Scheme 16**), a predominance of the *syn*- isomer (**64**) is produced, but in a poorer ratio (3.4:1, *syn:anti*) than the above system under identical conditions. As the reaction conditions are changed toward a more polar solvent and a more powerful Lewis acid, the selectivity completely reverses giving as high as a 24.5:1, *anti:syn* ratio of **63**:**64**. When an electron-releasing substituent is added to increase the nucleophilicity of the silyl enol ether (**Scheme 17**), intermediate behavior (expressed as selectivity) between the



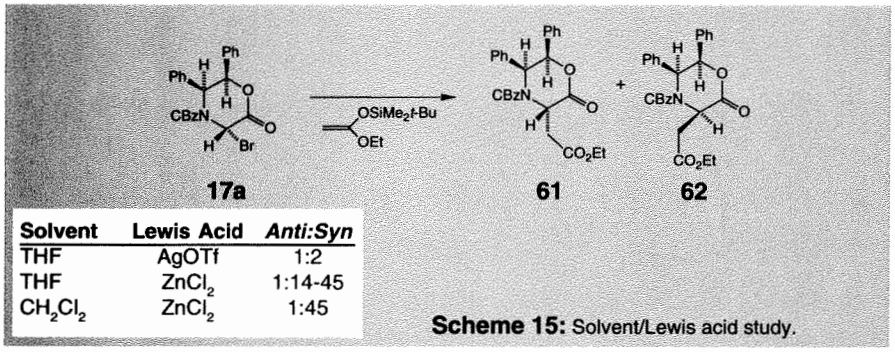
Scheme 13: Additional cuprate couplings.



Scheme 14: Coupling reaction to yield β,γ-unsaturated amino acids.

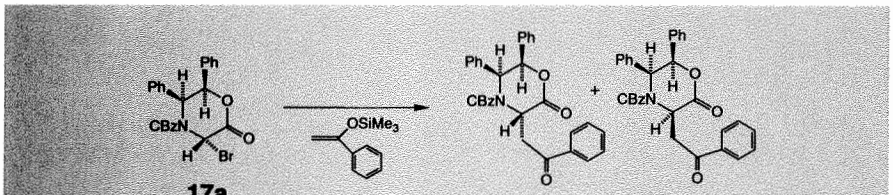
Table 3: (*E*)-Vinylglycine derivatives.

R	R'	BOC	%57a	%58 via Na°	%ee via Na°	%58 via Li°	%ee via Li°
-Me	*n*-Bu	*t*-BOC	99	79	64	18-80	80->98
-*n*-C_3H_7	*n*-Bu		70	80	61	20	72
-*n*-C_6H_{13}	*n*-Bu		61	74	56	16	65
-$(CH_2)_2OSiMe_2$*t*-Bu	*n*-Bu		71	71	68	—	—
-C_6H_5	*n*-Bu		99				
-$SiMe_3$	Me		69				
-CH_2OSiMe_2*t*-Bu	*n*-Bu		99				
-$(CH_2)_2OSiMe_2$*t*-Bu	Me	CBz	74				
-*n*-C_6H_{13}	*n*-Bu		53				
-C_6H_5	*n*-Bu		55				
Me	*n*-Bu		70				



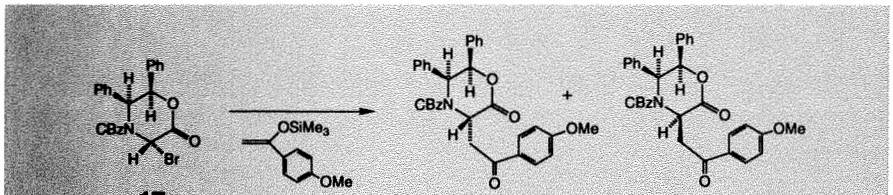
Solvent	Lewis Acid	*Anti:Syn*
THF	AgOTf	1:2
THF	$ZnCl_2$	1:14-45
CH_2Cl_2	$ZnCl_2$	1:45

Scheme 15: Solvent/Lewis acid study.



Solvent	Lewis Acid	*Anti:Syn*
THF	AgOTf	24.5:1
MeCN	$ZnCl_2$	14.5:1
THF	$ZnCl_2$	7:1
CH_2Cl_2	$ZnCl_2$	1:34

Scheme 16: Solvent/Lewis acid study.



Solvent	Lewis Acid	*Anti:Syn*
THF	AgOTf	5.9:1
MeCN	$ZnCl_2$	2.9:1
THF	$ZnCl_2$	1:1.6
CH_2Cl_2	$ZnCl_2$	1:11.2

Scheme 17: Solvent/Lewis acid study.

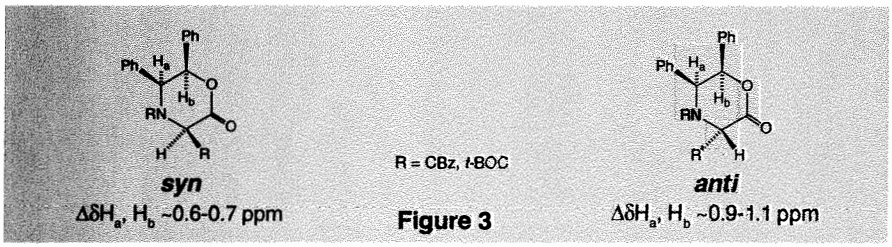


Figure 3

above two extremes is displayed as expected. We must caution workers to be cognizant of the relative nucleophilicity of the specific reagent under consideration since the reaction conditions can be modified to favor either the S_N2 or S_N1 pathways. The best selectivities are obtained with very weak 'neutral' carbon nucleophiles, such as the allylic silanes and the tin acetylides which typically give exclusive formation of the S_N1 (*anti*) products.

The *syn*- and *anti*-oxazinones from a given coupling reaction are readily distinguishable by examination of the Δδ of the benzylic methine protons (H_a and H_b) of the lactone ring in the proton NMR. The *anti*- isomers consistently display a larger Δδ for H_a/H_b than the corresponding *syn*-isomers (**Figure 3**). We also note that the NMR spectra of these substances must be recorded at ~398 K to obviate the line-broadening induced by slow conformational exchange of the urethane moiety.

Furthermore, the *anti*-isomers have consistently proven to be crystalline substances and the corresponding *syn*-isomers tend to be oily. It can be noted that, if the selectivity of a given coupling reaction is modest, the general difference in the physical properties of the two diastereomers permits simple crystallization of the *anti*-isomers (generally the major products) consistently resulting in >96-99% de of the homologated lactones and a correspondingly high % ee for the final amino acids.

Asymmetric Synthesis of 1-Aminocyclopropane-1-Carboxylic Acids

The 1-aminocyclopropane-1-carboxylic acids (ACC) are of tremendous interest because of their biological activity, potential use in conformationally restricted peptides, and as biosynthetic and mechanistic probes.[29] For example, ACC has been found to be the biosynthetic precursor to the plant hormone ethylene[30] and is a substrate to the PLP-linked enzyme ACPC deaminase, which converts ACC to ammonia and 2-ketobutyrate.[31] It has also been shown that allonorcoronamic acid is a substrate and the strongest known competitive inhibitor of the ethylene forming enzyme (EFE) in mung bean hypocotyls.[32] Our approach[33] to this class of amino acids begins with the conversion of the bromolactones into the corresponding phosphonates (**67**) as shown in **Scheme 18**.

The crude bromide (**18**) was immediately dissolved in THF and gently refluxed with a slight excess of trimethyl phosphite to provide the white crystalline phosphonate ester (**67**) in 86% overall yield. Subsequent treatment of **67** with base and an aldehyde provided the (*E*)-α,β-dehydrolactone adducts (**68**) in generally high yields (**Table 4**). The assignment of the (*E*)-stereochemistry was firmly established for **68b** and **68f** by x-ray crystallographic analysis. Since all of the final amino acids have a *cis* orientation of the carboxyl and "R" groups (*vida infra*), it follows that **68c-e** and **68g** also possess the (*E*)-stereochemistry.

After examining several cyclopropanating reagents, we found that (diethylamino)-phenyloxosulfonium methylides, first prepared by Johnson and coworkers,[34] gave excellent diastereoselectivities (**Table 5** compares the results of diazomethane and dimethylsulfoxonium methylide reactions with **68**). Cyclopropanation of **68a** with (diethylamino)phenyloxosulfonium methylide provided cyclopropanes **73** and **74** in 94% yield (as a 9.6:1 ratio). In addition, it was observed that by simply running the latter reaction at approximately 18 °C (freezing point of DMSO) followed by slow thawing, the ratio could be increased to 11:1 (**Scheme 19**). Utilizing the same freeze-thaw technique, adducts **68b-f** gave excellent yields of the corresponding cyclopropanes, and, furthermore, only a single diastereomer was isolated in each case (**Table 5**). Assignment of the diastereochemical ratios could be determined by observing the C-5 and C-6 benzylic methine protons of the lactone by ^1H NMR.

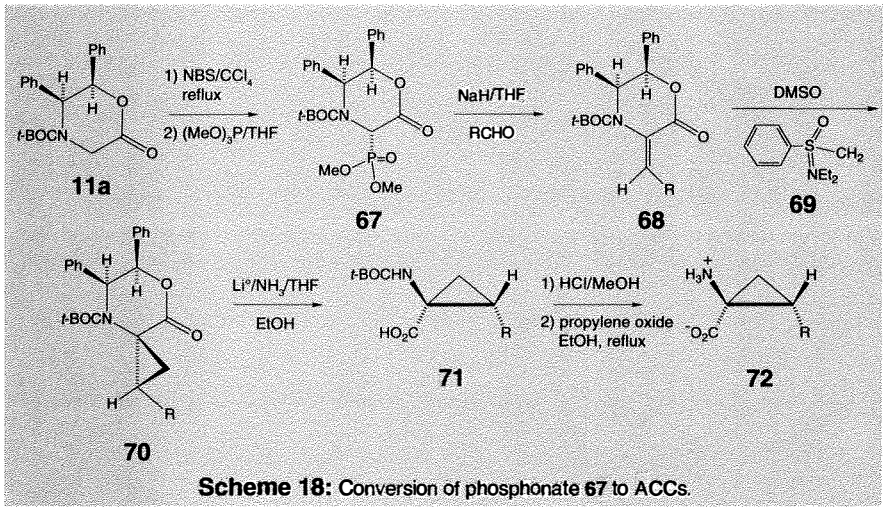
Conversion of the cyclopropyl adducts into the corresponding *N*-*t*-BOC amino acids and free zwitterions was accomplished by the dissolving metal reduction protocol. Thus, treatment of cyclopropanes **70b-d** (and **73/74**) with Li^0 in liquid NH_3 (**Scheme 18 and 19**) provided the *N*-*t*-BOC-protected amino acids (**71b-d, 75**) in good yields (**Table 6**). To remove the *t*-BOC protecting group, compounds **71b-d**, and **75** were treated with 40 molar equivalents of anhydrous 1*N* HCl in MeOH, produced in situ from acetyl chloride and methanol. The hydrochloride salts of (**72b-d, 76**) were obtained quantitatively and immediately treated for 20 min with a refluxing mixture of excess propylene oxide in EtOH to produce, in essentially quantitative yield, the free amino acids coronamic acid (**72c**), norcoronamic acid (**72b**), **72d** and **76** (**Table 6**). This procedure works extremely well and obviates the need for ion-

exchange chromatography.

To confirm the absolute stereochemistry of the final cyclopropane amino acids, assignments were made, in part, by comparing the optical rotations of coronamic acid (**72c**) and norcoronamic acid (**72b**) with those reported in the literature. In addition, the relative stereochemistry of the cyclopropyl lactone **70c** was rigorously determined by x-ray analysis of the *N*-*p*-bromobenzoyl derivative. This structure clearly shows that both the alkene geometry is preserved and that sulfoximine attack on the lactone proceeds from the top (β) face of the double bond (**Scheme 20**).

Several interesting stereochemical points need to be mentioned. The stereoselectivity of the olefination reactions (**67→68**, **Scheme 18**) is unusual both in the sense of stereochemistry, (*E*)-selectivity, and the complete absence of the (*Z*)-isomer. This stereochemical outcome is probably a direct result of the steric interaction between the aldehyde R group and the bulky *t*-BOC protecting group experienced by the two diastereomeric betaine transition states.[35] Generally, it has been observed that condensations involving dialkoxyphosphorylglycine derivatives and aldehydes result in the formation of (*E*)/(*Z*)-alkene isomer mixtures with the (*Z*)-stereochemistry being predominant.[36] Recently, Seebach reported the preparation of an (*E*)-α,β-dehydroamino acid derivative via the phosphoryl condensation approach.[35b] Due to the propensity of most phosphorylglycine olefinations to produce the (*Z*)-isomers, cyclopropanations of these substrates also produce, as major products, the (*Z*)-substituted cyclopropanes. The methodology described herein, which selectively delivers the (*E*)-isomers, therefore, nicely complements the existing approaches to this class of amino acids.

Other types of π-facial selective additions to **68**, including Diels-Alder reactions, [1,3]-dipolar cycloadditons, [2+2] photochemical reactions, and Michael-type conjugate addition reactions, are under investigation for accessing additional classes of highly functionalized amino acids.



Scheme 18: Conversion of phosphonate **67** to ACCs.

Table 4: (*E*)-α,β-Dehydrolactone adducts.

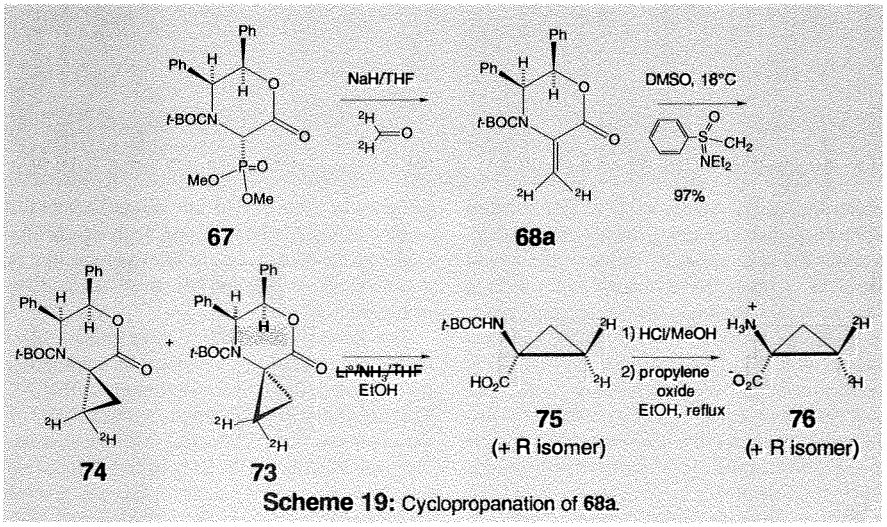
Aldehyde	Reaction Conditions	68, % Yield[a]	H =, R =
$H_2CO(^2H_2CO)$	NaH/THF, 25 °C	**68a**, quant.	^2H,^2H (H,H)
acetaldehyde	LDA/THF, 0 °C to RT	**68b**, 92.8	H, Me
propionaldehyde	LDA/THF, 0 °C to RT	**68c**, 91.5	H, Et
butyraldehyde	LDA/THF, 0 °C to RT	**68d**, 81.8	H, *n*-Pr
isobutyraldehyde	LDA/THF, 0 °C to RT	**68e**, 18.8	H, *i*-Pr
benzaldehyde	NaH/φH, RT to 80 °C	**68f**, 96.4	H, Ph
p-nitrobenzaldehyde	NaH/φH, RT to 80 °C	**68g**, 84.0	H, *p*-NO_2Ph

a) The (*E*) stereochemistry of the olefin was obtained exclusively for compounds where R = alkyl or aryl. This was confirmed, in part, by x-ray crystallographic analysis of **68b** and **68f**.

Table 5: Diazomethane and sulfoxonium methylide reactions.

Substrate	"CH_2:" Reagent	Conditions	70, (% yield)	Diast. Ratio
68a	$(CH_3)_2S^+O(CH_3)I^-$	NaH/DMSO, RT	**73/74**, 98%	3-3:1
68b	$(CH_3)_2S^+O(CH_3)I^-$	NaH/DMSO, RT	**70b**, 77%	2-3:1
68a	CH_2N_2[b]	Et_2O, -78 °C to RT	**73/74**, 100%	1: 2-3
68b	CH_2N_2[b]	Et_2O, -78 °C to RT	**70b**, 91%	1: 1.6
68a	(±)$Ph(Et_2N)S^+O(CH_3)BF_4^-$	NaH/DMSO, 18 °C to RT	**73/74**, 97.1%	11:1
68a	(±)$Ph(Et_2N)S^+O(CH_3)BF_4^-$	NaH/DMSO, 18 °C to RT	**70b**, 82%	1:0[a]
68c	(±)$Ph(Et_2N)S^+O(CH_3)BF_4^-$	NaH/DMSO, 18 °C to RT	**70c**, 79.3%	1:0[a]
68d	(±)$Ph(Et_2N)S^+O(CH_3)BF_4^-$	NaH/DMSO, 18 °C to RT	**70d**, 88.2%	1:0[a]
68f	(±)$Ph(Et_2N)S^+O(CH_3)BF_4^-$	NaH/DMSO, 18 °C to RT	**70f**, 96.4%	1:0[a]

a) Ratios determined by ^1H NMR analysis. b) Diazomethane prepared from 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) and 5*N* NaOH (aq) at -15 °C.



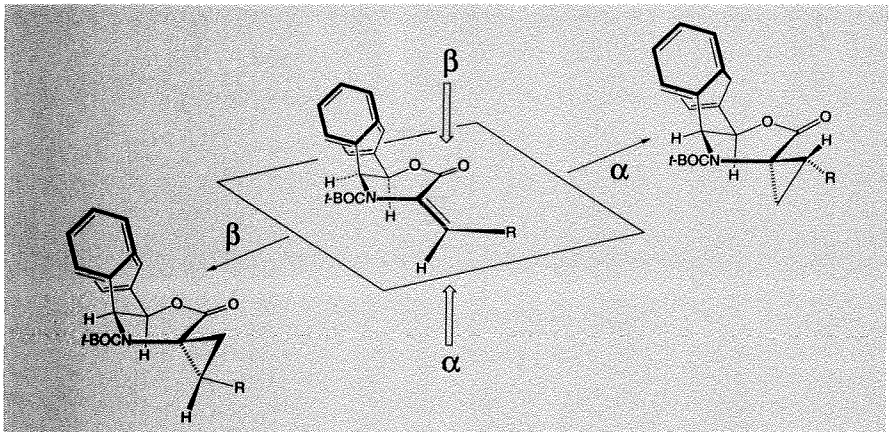
Scheme 19: Cyclopropanation of **68a**.

Glycine Enolates

More recently, the enolate alkylation chemistry of the glycinates **10** and **11** has been examined (**Schemes 21 and 22**).[37,38] Addition of the enolate repertoire to these systems greatly expands the scope and versatility of these templates for accessing complex amino acid functionality. Generation of the enolate with lithium or sodium hexamethyldisilylamide for 30-40 min in THF at low temperature, followed by addition of an alkyl halide, results in the formation of highly diastereoselective (typically >**99**% de) crystalline *trans*-alkylation products **77** and **80**. This protocol is effective for alkylations with activated alkyl halides, such as benzylic bromides, allyl halides, and methyl iodide. With unactivated alkyl halides, such as *n*-propyl iodide, unreacted starting material or substantial decomposition was observed under the same conditions. Raising the reaction temperature or admixing good solvating agents, such as HMPA, promoted decomposition of the enolate as evidenced by lower recovery of starting material. In the case of the activated alkylating agents, we observed significant amounts of the disubstituted products (**81** or **83** where $R_1 = R_2$) if more than one equivalent of base was employed. If the reaction conditions are not carefully controlled, as described below, the dialkylated products could be detected, along with unreacted starting material (even when one molar equivalent of base was employed in the case of dimethallyl, allyl, and benzyl alkylations). A simple and reliable protocol that obviates these problems involves the addition of lithium or sodium

Table 6: Yields of free amino acids.

Substrate	*t*-BOC-Amino Acids (% yield)	Free Amino Acids (% yield)	% ee
73/74	75 (65.4)	76 (100)	83.3
70b	71b (63.2)	72b (100)	>99
70c	71c (64.4)	72c (100)	>99
70d	71d (60.9)	72d (98.6)	>99



Scheme 20: Illustration of top (β) face.

Table 7: Comparison of Methods A and B.

Oxazinone Substrate	77/80 Yield %	RX	Method[a]	Base (equiv)	Amino Acid Yield	% ee
1a	20	CH_2=$CHCH_2Br$	A	$LiN(SiMe_3)_2$ (1)		
1a	71(12)[b]	CH_2=$CHCH_2Br$	A	$LiN(SiMe_3)_2$ (2)		
1a	48(21)[c]	CH_2=$CHCH_2Br$	A	$NaN(SiMe_3)_2$ (1)		
1a	86(5)[c]	CH_2=$CHCH_2I$	B	$LiN(SiMe_3)_2$ (1.2)	50-70	98
2a	82	CH_2=$CHCH_2I$	B	$LiN(SiMe_3)_2$ (1.2)		
1a	91	MeI	A	$NaN(SiMe_3)_2$ (1.1)	54	97
2a	88	MeI	B	$NaN(SiMe_3)_2$ (1.5)		
1a	70(9)[c]	$PhCH_2Br$	A	$NaN(SiMe_3)_2$ (1)	76	98
2b	77(6)[b]	$PhCH_2Br$	B	$NaN(SiMe_3)_2$ (1.2)	93	>99
1a	68(20)[c]	Me_2C=$CHCH_2Br$	A	$NaN(SiMe_3)_2$ (1)		
1a	84(2)[b]	Me_2C=$CHCH_2Br$	B	$NaN(SiMe_3)_2$ (1.1)	52	>99
1a	64	$BrCH_2CO_2Et$	A	$NaN(SiMe_3)_2$ (1.1)		
1b	61(20)[c]	$BrCH_2CO_2Et$	A	$NaN(SiMe_3)_2$ (1)	71	96
1a	0	n-C_3H_7I	A	$NaN(SiMe_3)_2$ (1.2)		
1a	77(12)[b]	n-C_3H_7I	B	$NaN(SiMe_3)_2$ (1.5)		
2a	76(3)[c]	n-C_3H_7I	B	$NaN(SiMe_3)_2$ (1.5)		
2a	79	$I(CH_2)_4I$	B	$LiN(SiMe_3)_2$ (1.5)		
2b	61	$I(CH_2)_4I$	B	$LiN(SiMe_3)_2$ (1.5)		
2b	47	ICH_2CH_2CH=CH_2	B	$LiN(SiMe_3)_2$ (1.8)		
1b	72	$I(CH_2)_3Cl$	B	$LiN(SiMe_3)_2$ (1.5)		
1b	86	$I(CH_2)_3I$	B	$LiN(SiMe_3)_2$ (1.5)		

(a) Method A involves addition of the base to the oxazinone at -80 °C followed by addition of the electrophile; Method B involves addition of the base to a -80 °C mixture of the oxazinone containing the electrophile. (b) Denotes dialkylated product. (c) Denotes recovered starting material.

hexamethyldisilylamide to a -80 °C THF solution of the oxazinone containing the alkylating agent. In this way, high chemical yields of the monoalkylation products can be obtained with very high diastereoselectivities with little or no contaminating dialkylated material. For the unactivated alkyl halides, addition of HMPA (THF:HMPA, 10:1) significantly improves the chemical yields. We have examined a variety of bases and find that either lithium or sodium hexamethyldisilylamide gives the best results. In no case have we been able to obtain satisfactory alkylation results with LDA or other strong bases (*n*-BuLi, *t*-BuLi, NaH). In addition, potassium hexamethyldisilylamide seems to be too reactive for the monoalkylations, giving decomposition and disubstituted alkylation products. The results of these alkylation reactions are collected in Table 7. The free amino acids or the corresponding *N*-*t*-BOC amino acids can be obtained by the reductive or oxidative processing as described above (**Scheme 10**). In all cases, the % ee exceeded 95%.

The diastereoselectivity of these enolate alkylations can be readily rationalized by considering the expected twist boat conformation (cf. **23**, **Scheme 6**) that disposes the phenyl ring at C-5 of the oxazinone in a pseudoaxial orientation, creating steric shielding of the C-3 position of the same face from electrophilic attack. The *anti*-relative stereochemistry of these alkylation products was secured for R = methyl, allyl, benzyl, and ethoxycarbonylmethyl by comparing the absolute configurations of the final synthetic amino acids to known amino acids. In all other cases, the relative stereochemistry was established by comparison of the $\Delta\delta$ for the methine protons at C-5 and C-6 of the oxazinones (**77** and **80**). The alkylations observed all proceed with very high levels of diastereoselectivity, giving the *anti*-oxazinones.

To access the α-disubstituted α-amino acids,[39] we first examined the enolate alkylation of α-methyl substituted oxazinone **77a** (R = Me) by employing method A (i.e., enolate generation followed by electrophilic quench). Unfortunately, the homologated products **81a** were not detected. Even when potassium bis(trimethylsilyl)amide and allyl iodide were used, none of the desired product **81a** could be detected; only decomposition of the starting material was observed. By employing the protocol described above (method B, involving addition of the base to a mixture of oxazinone containing the electrophile), the enolate alkylations of the α-methyl substituted oxazinone **77a** were realized, as shown in **Scheme 22**. First, sodium bis(trimethylsilyl)amide was examined to determine whether it was reactive enough for the second alkylation. To a solution of **77a** (R = Me) and allyl iodide in THF-HMPA was added sodium bis(trimethylsilyl)amide at -78 °C. The homologated oxazinone **81a** (R_1 = Me, R_2 = allyl) was detected only in trace amounts by TLC. The same procedure was performed by using potassium bis(trimethylsilyl)amide instead of sodium bis(trimethylsilyl)amide. After standard aqueous work-up, the α-methyl-α-allyloxazinone **81a** was produced in 57% yield. This substance proved to be one diastereomer by ^{1}H NMR analysis. If the solvating reagent HMPA is not used as cosolvent, the yield is significantly enhanced (57% to 87%). It is presumed that the employment of HMPA is not effective for the more reactive potassium enolates and only promotes decomposition. Oxazinone **77a** smoothly underwent coupling with dimethallyl bromide in the presence of potassium bis(trimethylsilyl)amide to afford the α-methyl-α-dimethallyloxazinone in 80% yield as a single diastereomer. The results of couplings with allyl iodide, dimethallyl bromide, benzyl bromide, and cinnamyl bromide are presented in Table 8. In all cases, we observed the production of a single diastereomer in good to excellent chemical yields.

The dialkylation of these oxazinones with less reactive alkyl halides (relative to allyl iodide) was studied by employing the protocol described above. Thus, addition of two equivalents of potassium bis(trimethylsilyl)amide to a THF solution of the oxazinone (**77** or **80**) containing benzyl bromide or methyl iodide at -78 °C, then quenching with H_2O after 30-40 min, did not furnish the desired products. In all of the cases presented above, the enolate alkylations were performed by using two equivalents of potassium bis(trimethylsilyl)amide. We were surprised to find that the employment of additional excess base for the dialkylation of hindered oxazinones solved this problem. Thus, the allyl lactone **80a** was alkylated efficiently with benzyl bromide in the presence of three equivalents of potassium bis(trimethylsilyl)amide to furnish the α-allyl-α-benzyloxazinone **83a** in 84% yield (**Table 8**, entry 10). The enolate alkylation of **80a** (R = *n*-propyl) required five equivalents of potassium bis(trimethylsilyl)amide (compare entries 7-9, **Table 8**).

The enantiomeric excess of each amino acid was determined using the same protocol as that em-

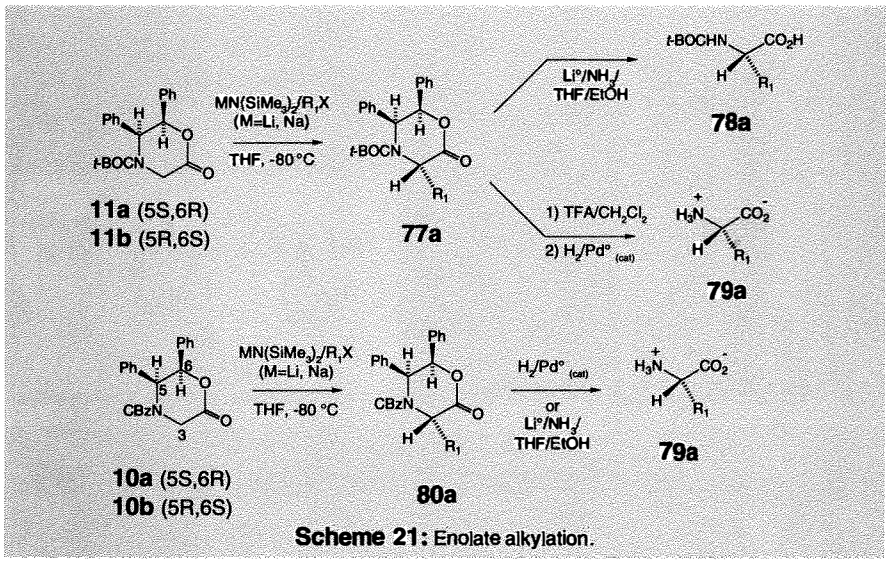
ployed for the monosubstituted amino acids. However, formation of the methyl esters of the dialkylated amino acids did not take place in refluxing 1*N* methanolic hydrochloride solution. The employment of more drastic conditions (~5*N* HCl-MeOH, refluxing) led to complex reaction mixtures. A method to prepare the methyl esters of the hindered dialkylated amino acids involves refluxing the free amino acids (**84**) in methanolic thionyl chloride solution.

As expected, the second alkylation proceeded *anti*- to the two phenyl rings of the oxazinone. A parallel conformational analysis to that discussed above of the incipient enolate derived from **10/11** can be invoked. A single crystal x-ray analysis of **83a** (where R_1 = Me and R_2 = benzyl) further corroborated this assignment. This result clearly shows that the attack of the second electrophile (in this case, benzyl bromide) to the enolate occurs from the less hindered face of the oxazinone enolate. The direct method to prepare *N-t*-BOC protected disubstituted amino acids, which are in a suitable form for direct peptide coupling, is very advantageous because acylating α,α-dialkylated amino acids is often difficult to achieve due to steric hindrance.

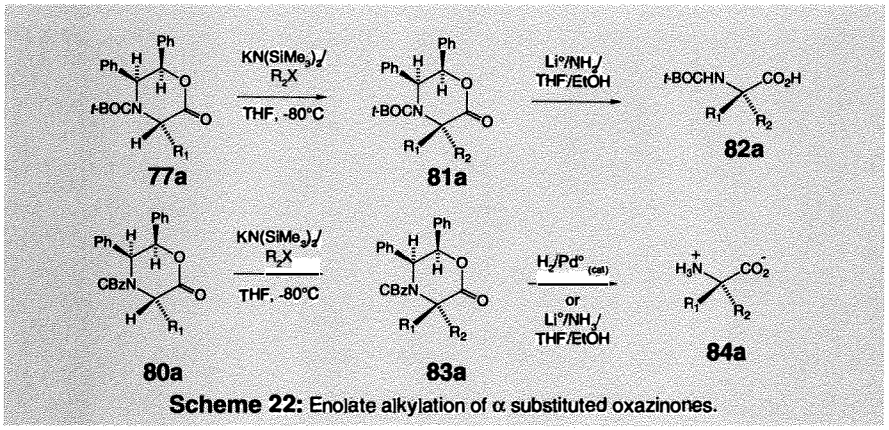
Aldol condensation reactions have also been studied by Miller[35a] and subsequently by us.[40] Reaction of **10a** with di-*n*-butylboron triflate in the presence of triethylamine in methylene chloride at 0 °C produces the boron enolate (**85**, **Scheme 23**). Condensation with several aldehydes afforded the *anti*-β-hydroxy adducts (**86, Table 9**). In one instance (R = Me), the major adduct was reduced to afford *allo*-threonine (**87**). This stereochemical outcome has been rationalized[35a] as arising via a Zimmerman-Traxler chair-type transition state where the aldehyde approaches the (fixed) (*E*)-enolate from the least hindered face of the lactone.

We have utilized a combination of the enolate-based coupling reactions and the aldol condensation conditions disclosed by Miller[35a] to construct the naturally derived amino acid *N*-2,6-diamino-6-hydroxymethylpimelic acid (**97, Scheme 24**). This substance is the only functionalized, naturally occurring member of the diaminopimelic acid family of "bis"-amino acids. Diaminopimelic acid (DAP) is an important amino acid biosynthesized in bacteria and higher plants.[41-43] L,L- and *meso*-DAP serve as the penultimate biosynthetic precursor of the essential amino acid L-lysine. *meso*-DAP functions as a cross-linking constituent of virtually all Gram-negative and some Gram-positive bacterial peptidoglycans and also serves to anchor various membrane-associated macromolecules, such as lipoproteins, to the cell wall. Since mammals lack the diaminopimelate pathway and require L-lysine in their diet, specific inhibitors of the enzymes along this route are potential antimicrobial or herbicidal agents that should display low mammalian toxicity. Despite the apparent simplicity of this amino acid, there exist no stereochemically unambiguous chemical syntheses of *meso*-DAP nor asymmetric syntheses of L,L-DAP. Two very recent exceptions are the syntheses of β-fluoro-DAP by Vederas and Gelb[44a] and β-hydroxy-DAP by Bold and associates.[44b]

N-(2,6-Diamino-6-hydroxymethylpimelyl)-L-alanine (**98, Figure 4**) was isolated from the culture



Scheme 21: Enolate alkylation.



Scheme 22: Enolate alkylation of α substituted oxazinones.

Table 8: Coupling results of oxazinone substrates.

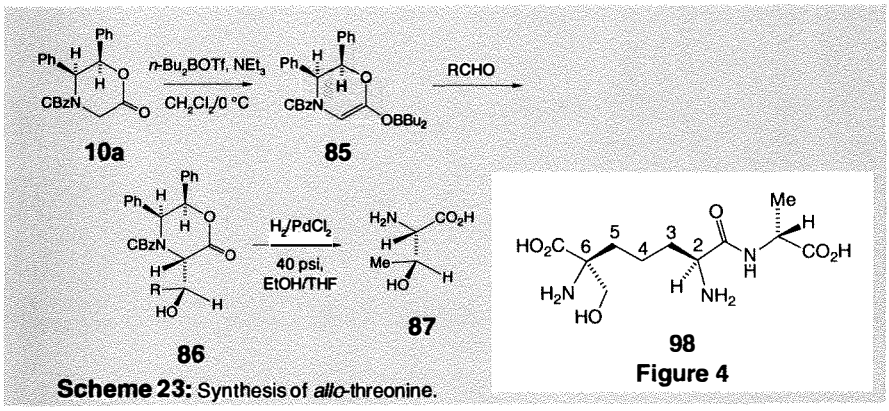
Oxazinone Substrate	R_1	Yield	R_2X	Base (Equivalent)	Amino Yield	Acid %ee
77a	Me	trace	CH_2=$CHCH_2I$	$NaN(SiMe_3)_2$ (2)		
77a	Me	87	CH_2=$CHCH_2I$	$KN(SiMe_3)_2$ (2)	70	~100
77a	Me	80	Me_2C=$CHCH_2Br$	$KN(SiMe_3)_2$ (2)	65	~100
77a	*n*-C_3H_7	90	CH_2=$CHCH_2I$	$KN(SiMe_3)_2$ (2)	60	~100
80a	Me	84	$PhCH_2Br$	$KN(SiMe_3)_2$ (2)	93	~100
80a	Me	80	PhCH=$CHCH_2Br$	$KN(SiMe_3)_2$ (2)	95	~100
80a	*n*-C_3H_7	0	$PhCH_2Br$	$KN(SiMe_3)_2$ (2)		
80a	*n*-C_3H_7	38	$PhCH_2Br$	$KN(SiMe_3)_2$ (4)		
80a	*n*-C_3H_7	85	$PhCH_2Br$	$KN(SiMe_3)_2$ (5)		
80a	allyl	84	$PhCH_2Br$	$KN(SiMe_3)_2$ (3)		

Entries 1-2: HMPA-THF (10:1) was used as solvent.
Entries 3-10: THF was used as solvent.

extracts of a microorganism identified as *Micromonospora chalcea* by the Shionogi Co. in Japan.[45] The stereochemistry at C-2 of the natural dipeptide was determined by chemical degradation to be L; the stereochemistry of the quaternary center (C-6) was unknown. We unambiguously synthesized the 2*S*,6*S*-**97** and the corresponding 2*S*,6*R*-stereoisomer and showed that the natural dipeptide possessed the 2*S*,6*S* absolute stereochemistry (**Scheme 24**).[40,46] The key coupling of aldehyde **90** and the boron enolate (**85**) gave the *anti*-β-hydroxy aldol **91** as the major product along with a minor diastereomer **92** (25:1 ratio). The Barton deoxygenation reaction[47] proved to be quite troublesome due to competing elimination reactions of the activated thionocarbonate **93**. The modest yield (38%) of the esterification process on this substrate reflects the difficulty associated with activating this hindered alcohol in the presence of base that mediates the subsequent competing elimination. After tin hydride reduction, the major bis-lactone (**94**) was cleanly hydrogenated in nearly quantitative yield to **96**. Cleavage of the methyl ether in concentrated HBr gave the 2*S*,6*S*-amino acid **97**. This same strategy[48] has also been applied to the asymmetric synthesis of L,L- and D,D-DAP; the preparation of L,L-DAP is detailed in Scheme 25.

Asymmetric [1,3]-Dipolar Cycloadditions

A variety of important natural products contain highly substituted pyrrolidinecarboxylic acid ring



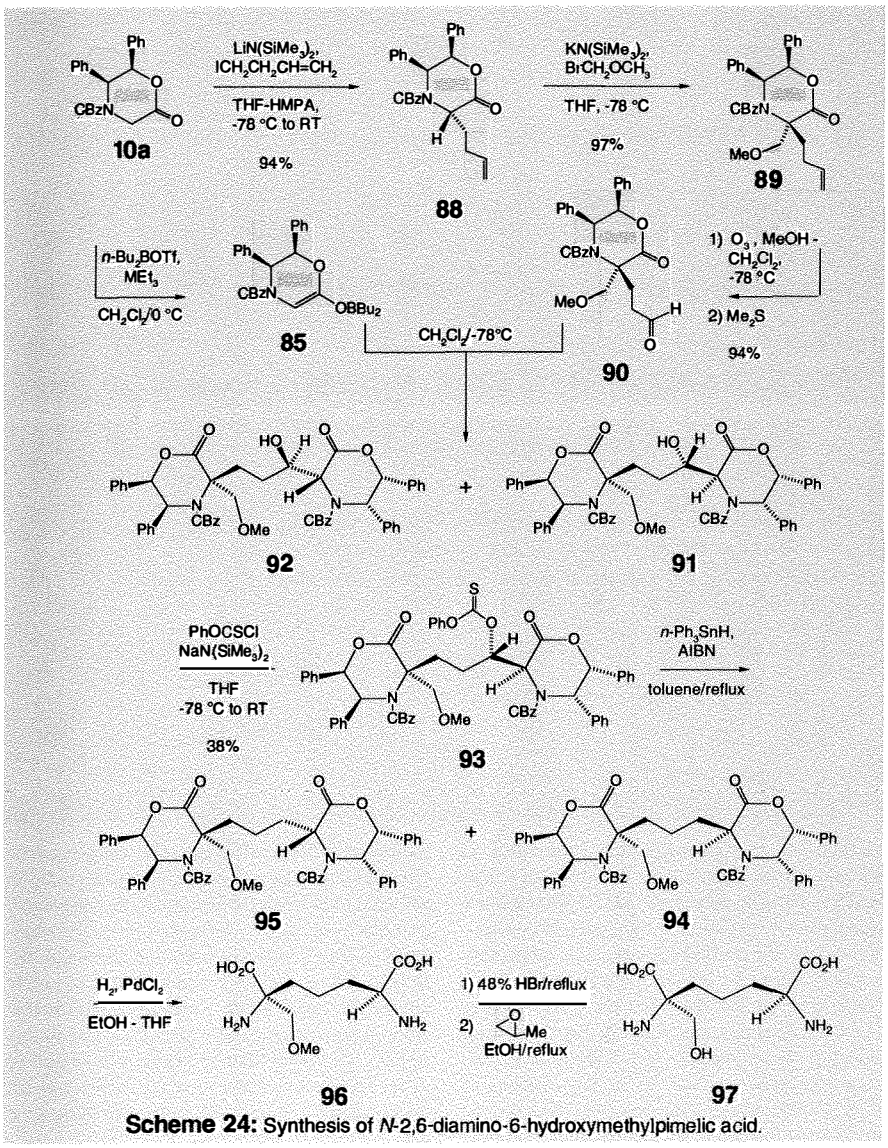
Scheme 23: Synthesis of *allo*-threonine.

98

Figure 4

Table 9: *anti*-β-Hydroxy adducts.

Aldehyde	Ratio of Diastereomers	Recrystallized Yield of Major Isomer (86)
acetaldehyde	17 : 3 : 1	57%
butanal	5:1	38%
2-methylpropanal	5:1	42%



Scheme 24: Synthesis of *N*-2,6-diamino-6-hydroxymethylpimelic acid.

systems, the kainic acids and domoic acids being examples. We have conducted a preliminary investigation[49] of asymmetric [1,3]-dipolar cycloadditon reactions on the glycinate templates, as illustrated in **Scheme 26**. Removal of the *t*-BOC group from **11a** with either trimethylsilyl iodide or TFA furnishes the secondary amine **104**. Reaction of this substance with an aldehyde (e.g., benzaldehyde) in the presence of acid and dimethyl maleate furnishes the bicyclic substances **105** and **106** in 70% combined yield. An x-ray stereostructure for the major isomer (**106**) secured the relative stereochemistry and NOE experiments on **105** secured the relative stereochemistry shown. Both products are the result of *endo*-addition to the ylide. Alternatively, condensation of **104** with chloromethyl methyl ether furnishes the labile hemi-aminal that is directly treated with acid and dimethyl maleate, as above, to furnish a single stereoisomeric adduct **107**; again, an x-ray structure firmly secured the relative stereochemistry. Reduction of **107** affords the 3,4-di-(carbomethoxy)proline (**108**) in quantitative yield. Alternatively, the lactones can be opened with base, esterified with diazomethane and cleared with $Pb(OAc)_4$. This protocol is necessary for the R = aromatic adducts. The relative stereochemistries of the dipolar cycloaddition adducts indicate that the ylide **109** that is generated in situ suffers exclusively *endo* attack by the olefin from the least hindered face (**110**, shown). The epimeric mixture in the case of **105/106** merely reflects the *E*:*Z* ratio of the incipient ylides; complete *endo*-selectivity is observed in both systems. A variety of aromatic and aliphatic aldehydes participate in this reaction giving exclusively the *endo* adducts (**111**, **Table 10**). Additional examples of this strategy employing ketones and unsymmetrical dipolarophiles are in progress. This asymmetric version of the well-known [1,3]-dipolar cycloadditions of amino acid derivatives should find numerous applications in the preparation of optically active, substituted pyrrolidines and prolines.

Summary

We have exploited the rich chemistry of the glycine framework to carry out a variety of useful homologation reactions at the α-position of the simplest amino acid building block. This has resulted in the practical synthesis of a large structural array of amino acids in optically active form. The rigid geometry of the six-membered ring glycinate templates allows for both diastereocontrolled C-C bond-forming processes and convenient spectroscopic determinations of relative and absolute configurations and diastereochemical ratios of the homologated products. These properties render these glycinates predictable and powerful tools for accessing a rich functional array of amino acids in either the D- or L-configurations. The *N*-*t*-BOC substrates, in particular, offer the peptide chemist a convenient manifold for directly obtaining nonproteinogenic amino acids in a form suitable for immediate peptide coupling. For the research chemist interested in quickly assembling a new amino acid for further manipulation, these templates offer operational advantages over other related glycine-derived templates, since the chiral auxiliary and the target amino acid are typically separated by a mere extraction. The relative configurations of the homologated lactones are readily determined and ensure an unambiguous method to assign the absolute configuration to a new, synthetic amino acid. Many additional, challenging functionalities desired in the α-R substituent remain to be conquered and will continue to provide an impetus for refining and developing new approaches to the synthesis of amino acids.

Acknowledgements

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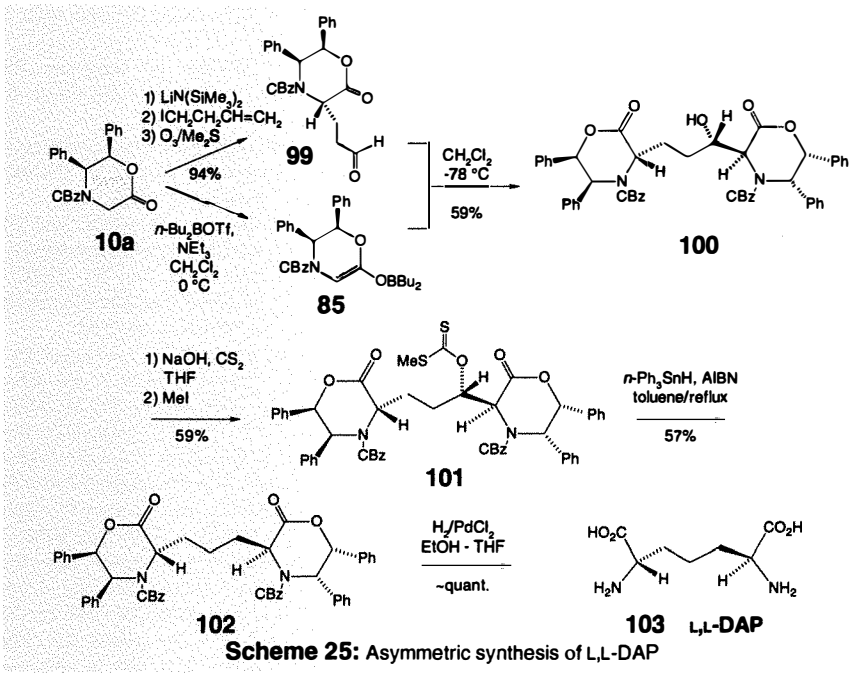
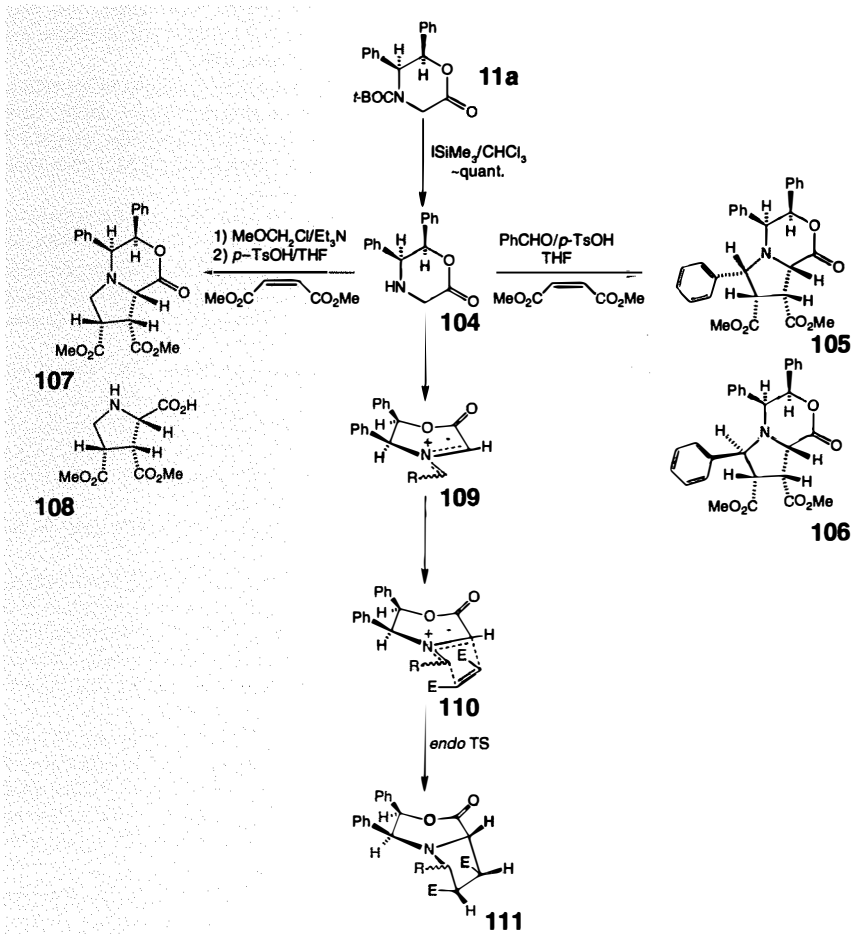


Scheme 25: Asymmetric synthesis of L,L-DAP



Scheme 26: Investigation of asymmetric [1,3]-dipolar cycloaddition reactions.

Table 10: Pathways to *endo* adducts.

R	E	Ratio (C-3')	Yield % 111	R	E	Ratio (C-3')	Yield % 111
H	CO_2Me	—	73	Ph	CO_2Me	1.7:1	70
Et	CO_2Me	1:1	37	*p*-MeOPh	CO_2Me	1:1	76
i-Pr	CO_2Me	1:0	50	*p*-NO_2Ph	CO_2Me	1:1	83
				2-furyl	CO_2Me	1:1	68

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About Our Cover:

fig. 1

The problems posed by this painting (oil on canvas, 38½ x 32½ in.) of Hendrickje Stoffels as *Venus with Cupid* are described in detail in entry No. 34 of *The Detective's Eye* (see below). The painting was sold at an auction in New York in 1988, described as a copy after a painting (fig. 1) in the Louvre that had been attributed to Rembrandt. Cleaning revealed our painting to be of high quality—superior, our chemist collector believes, to the painting in Paris. Neither is by Rembrandt, and so a key question is whether there ever was a Rembrandt original. When this painting was sold in an auction in Berlin in 1933, it had a signature that the catalog described as "hard to read". By the time it appeared in the New York sale in 1988, the painting had been cut down and the signature lost. It looks close to the works of one of Rembrandt's ablest students, Willem Drost.

Rembrandt scholars believe that several paintings long attributed to Rembrandt, for instance, the *Polish Rider*, are really by Drost. His works will surely be studied in great detail, and in time these puzzles will be solved.

From Private Collection To Corporate Identity

Selections from the Collection of Dr. and Mrs. Alfred Bader. In honor of Nobel Laureate, Herbert C. Brown's 80th birthday. Softcover, 31pp.

The Detective's Eye: Investigating the Old Masters

Twenty-four paintings that have been reproduced on our *Aldrichimica Acta* covers, and five that have been on our catalog covers, were among some seventy works in an exhibit at the Milwaukee Art Museum (January 19 through March 19, 1989) for which Isabel and Alfred Bader were guest curators.

If you relish detective work and puzzles about Old Master paintings, you will find much to enjoy in this illustrated catalog, and you will learn something about our chemist collector's interest in art and connoisseurship as well.

Art in Organic Synthesis, 2nd ed.

Documents important synthetic achievements, 427pp.

Selections from the Aldrichimica Acta, 1968-1982

Contains 49 articles published in Aldrichimica Acta from 1968-1982, 354pp.

Lab Notes

Various lubricants have been used in the laboratory for years. Stopcock grease is still used by some, even for ground glass joints. Molybdenum sulfide grease or Teflon• tape is often used to prevent galling of metal threads on fittings and screw attachments. I detest the various oils and greases, as they seem to permeate the lab, and make their way into the background spectra and chromatograms of almost any system. A nice substitute, I have found, is dry Teflon• spray. Easier to use than Teflon• tape, it can be applied to threads as a very thin coat, especially useful for gas regulators or HPLC fittings. It should not be used around a GC system employing an electron capture detector, but other than that, it appears to be a nice alternative to any other lubricant.

Doug Wittmer (CT)
Millipore Corporation
34 Maple Street
Milford, MA 01757

It is often critical when conducting an exploratory synthetic investigation to know something concerning the thermal stabilities of both starting materials, as well as desired products under the contemplated reaction conditions.

We have found what we believe to be a convenient, rapid and reliable solution to this problem, which could have fairly wide applicability.

The procedure consists of the following steps:

1) Filling a number of melting point capillaries with the samples to be studied, to a height of about 1.5cm.
2) The melting point bath is then heated to the desired temperature of the study.
3) When the desired temperature has been attained (and is stabilized) the sample-containing capillaries are all placed in the bath at the same time.
4) Successive samples are removed at predetermined intervals (e.g., 0.5 hr, 1.0 hr, etc.)
5) The tubes are carefully cleaned (to remove bath oil) and placed in small containers (e.g., 75mm test tubes). The lower portions of the tubes, which contain the samples, are crushed with a clean glass rod and are extracted with a small amount of a suitable solvent.
6) The extracts thus obtained are analyzed by TLC and compared with unheated standards.
7) The data obtained by this means should furnish the desired thermal-stability data.

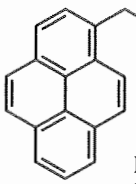
David H. Steinberg, Ph.D.
CIBA-GEIGY Corp.
Additives Research
Ardsley, NY 10502

We offer pyrex test tubes in a variety of sizes. Please see page 1922 of our current Catalog/Handbook for a complete listing.

Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to Aldrich (attn: Lab Notes, Aldrichimica Acta). For submitting your idea, you will receive a complimentary, laminated periodic table poster (Cat. No. Z15,000-2, $9.90 value). If we publish your *Lab Note*, you will also receive **The Detective's Eye: Investigating the Old Masters** (see previous page). We reserve the right to retain all entries for consideration for future publication.

"Please Bother Us."

by Jai Nagarkatti



Jai Nagarkatti, President

Professor Tapio A. Hase of the Department of Organic Chemistry at the University of Helsinki, Finland, suggested that we offer pyrenylacetic acid, a new reagent for the titration of organolithiums and Grignard reagents.[1] An intense red dianion of this compound unmistakably identifies the titration end point.

Naturally, we made it.

(1) Kiljunen, H.; Hase. T.A. *J. Org. Chem.* **1991**, *56*, 6950.

BUILDING BLOCKS FOR DENDRITIC MACROMOLECULES

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Abstract: *The ready availability of novel, branched building blocks (monomers) and initiator cores is critical to the development and advancement of new dendritic macromolecules. The structural features of these building blocks and cores were "designed" to circumvent the synthetic problems experienced with the creation of our initial work on arborols and to afford rapid easy access to specifically designed polymers. Utilization of these monomers for the preparation of dendritic macromolecules is presented.*

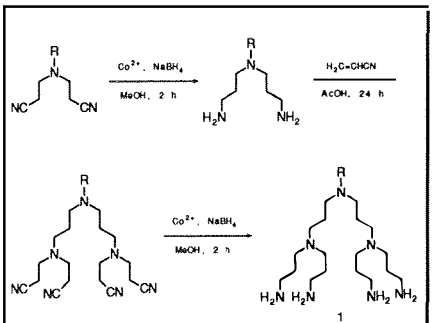
Introduction

Today, the field of "cascade" (dendritic) polymer chemistry is expanding the traditional synthetic limits into the meso/macromolecular frontier. These polymers are based upon the application of mathematical progressions to organic synthesis, and thus possess a well-defined molecular topology. These unique polymeric structures were initially derived from an architectural model[1] for trees and provide new methods for the construction of specific micellar molecules. This review will present our approaches to the design and construction of new monomers, whose combinations can generate cascade molecules and polymers with diverse internal or external functionality.

In the early forties, Flory[2] published a classic series of papers that provided both experimental and theoretical evidence for the formation of branched-chain, three-dimensional macromolecules. He included methods for determining their molecular size distributions, and demonstrated statistically that these structures appeared only after the reaction had proceeded to a certain extent. Subsequently, Stockmayer[3] developed not only formulas for determining the size distribution of branched-chain polymers but also an equation to ascertain when a gel (or three-dimensional network) should appear.

By the late forties, Flory delineated[4] "scaling" properties and demonstrated[5] that highly branched polymers could be synthesized without gelation by using a trifunctional monomer possessing two distinct functional groups. Flory noted: "Conceivably, one might separate a small fraction of very high molecular weight from such a polymer and thereby secure a sample which is highly branched, or cross-linked. The breadth of the distribution coupled with the impossibility of selectively fractionating 'branching' and 'molecular weight' separately make this approach impractical. Attempts to investigate 'branching' by such means consequently have been notably 'fruitless'. His monumental work was nearly four decades ahead of the synthetic and instrumental techniques necessary to enter the supramolecular regime.

It was not until Vögtle et al. first reported the preparation of a "cascade" molecule,[6] that Flory's noted limitations were circumvented. Thus, Michael-type addition of an amine to acrylonitrile permitted the attachment of the initial two arms, or branches (**Scheme 1**). Subsequent reduction of the nitriles gave the desired diamine, which was subjected to the same synthetic sequence to afford 4-cascade:benzylamine[2-*N*,*N*]:(1-aza-butylidene):propylamine[7] (second generation, **1**). Difficulties associated with nitrile reduction limited the continued growth of this cascade.[8] Polyamine **1** possesses several salient features, including branching from trigonal *N*-centers, and three methylenes between branching centers. For the first time, Vögtle's synthesis provided *(cascade)*



Scheme 1

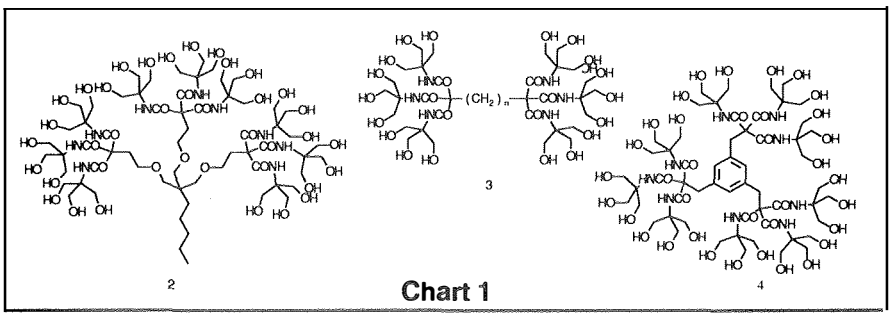


Chart 1

polymeric intermediates, which were isolated, purified, and fully characterized; thus, technological advances were in place to circumvent past obstacles at least with the small members of this class of polymer.

By 1985, two synthetic groups, ours[9] and Tomalia's,[10] published their progress toward cascade syntheses. Each utilized different strategies and building blocks toward divergent polymer construction; however, both sought to prepare and investigate the properties of high molecular weight, polyfunctional substances, and likened the topology of the resultant macromolecules to that of trees. Since the resultant topology of our molecules possessed terminal hydroxyl moieties and a branching pattern analogous to the Leeuwenberg model for tropical trees, we thus designated these tree-like structures by the Latin term *arbor-ols*.[11]

Arborols and Silvanols

We have used the term "directionality" to define the number of branched arms attached to the initiator core. Thus, a *one-directional* cascade would describe our initial arborol **2**, which was prepared in 6 steps. This methodology was subsequently used to prepare two- (**3**),[12,13] three- (**4**) (**Chart 1**),[14] and four-(**5**)[15,16] (**Scheme 2**) directional cascades.

Initially attempted arborols used pentaerythrityl bromide (**6**) and its homolog **7** (**Chart 2**).[17] Due to the documented[18] chemical inertness of **6** and the sluggish reactivity of **7** with triethyl methanetricarboxylate[19] (TEM) under moderate conditions, bromide **8** was prepared[16] and readily reacted with TEM to give dodecaester, **9**. Treatment of ester **9** with TRIS (**Scheme 2**) gave the spherical arborol **5** possessing 36 surface hydroxyl moieties.[15]

Since calixarenes[20] ([1$_n$]metacyclophanes) are practically insoluble in water, attachment of polar functionalities[21] or "growth" of an arborol surface to generate a molecular "saikei" or silvanol[22] can circumvent this drawback. Known calixarenes[23] were readily converted[24] into the [36]- (**10**) and [72]-silvanols (**11**) via similar procedures (**Chart 3**). These silvanols were directly imaged via electron microscopy at high magnification (350,000×) to verify the molecular dimensions and investigate aggregate formation.

Design and Synthesis of Novel Dendritic Building Blocks

In our quest for an all-carbon, spherical unimolecular micelle,[25,26,27] a new series of molecular building blocks possessing polyfunctional terminal groups attached to a central quaternary *C*-core was created.

Monomers

Earlier problems associated with conversion of terminal, neopentyl-type hydroxymethyl groups were bypassed by the introduction of spacer groups. Although these transformations proved successful, they added several steps to the iterative process. Thus, "Bishomotris" (**12**) was prepared[28,29] to directly incorporate the necessary 3-atom spacer. Exhaustive Michael-type addition of $MeNO_2$ to acrylonitrile afforded the trisnitrile **13**, which was subsequently quantitatively transformed to the trisacid **14** (**Scheme 3**). Alternatively, trisacid **14** was obtained via Michael-type addition of $MeNO_2$ to methyl acrylate and subsequent saponification of trisester **15**. Generally, **15** was obtained in higher yield and was easier to purify than trisnitrile **13**. Smooth reduction of the acid moieties with BH_3·THF gave excellent yields of the nitrotriol **16**. Further reduction with T-1 Raney Ni[30] yielded the desired aminotriol **12**.

The nitrotriol **16** became a pivotal reagent for the preparation of new monomers: acetylation with Ac_2O gave **17**, which was subsequently reduced to give aminotriacetate **18**; and benzylation gave trisether **19**, which afforded entrance to polyfunctionalized neopentane cores (**Scheme 4**). Cascade synthesis was subsequently accomplished[31,32] by coupling of amine **18** with a (poly)acid, followed by saponification and oxidation to generate the next tier of polyacids. This approach was improved by preparation of *tert*-butyl ester **20**, which was readily re-

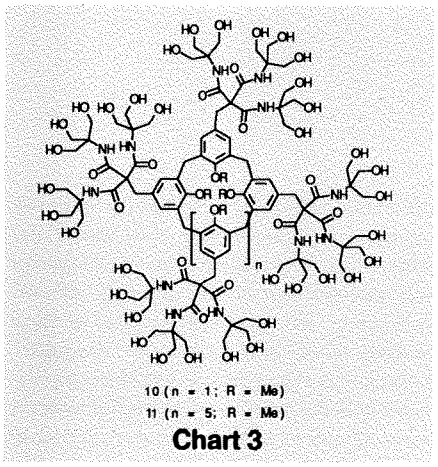
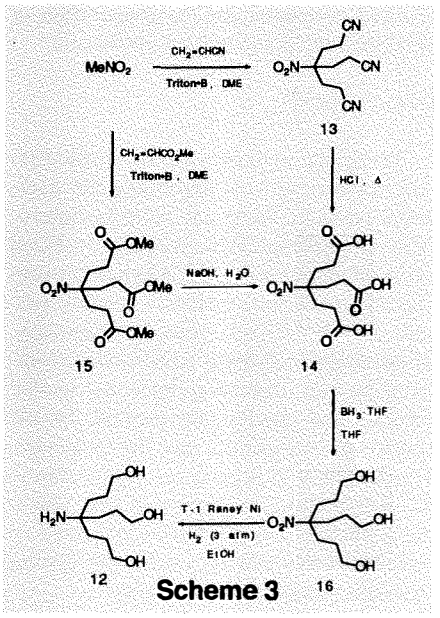


Chart 3



Scheme 3

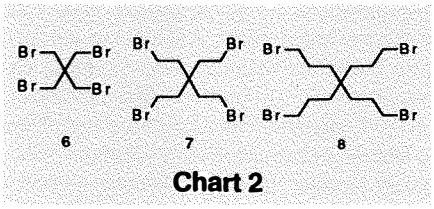
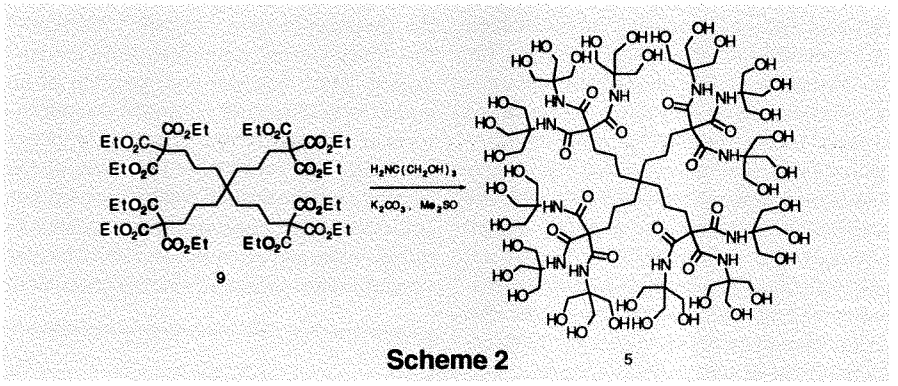
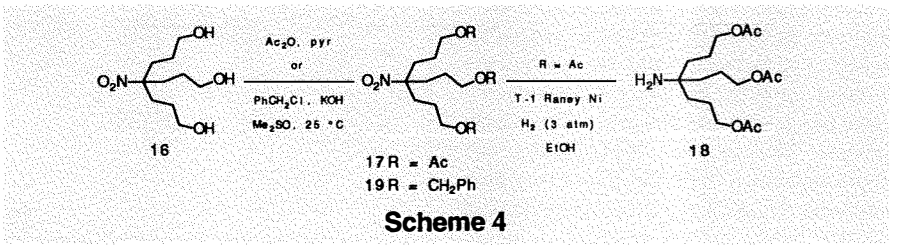


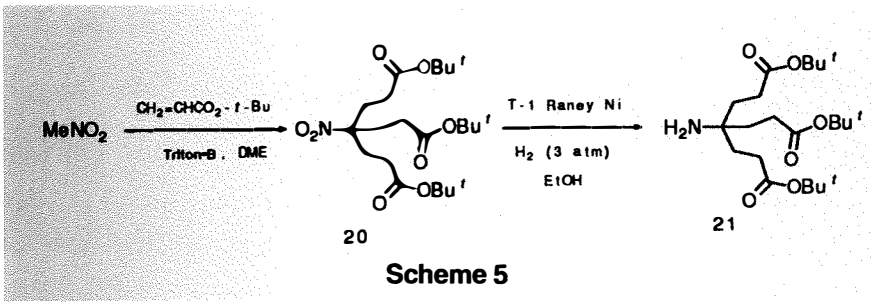
Chart 2



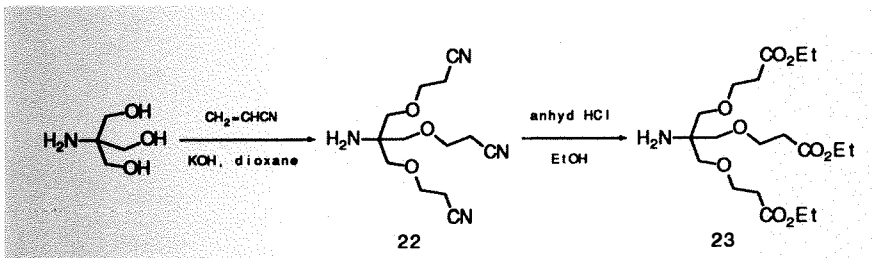
Scheme 2



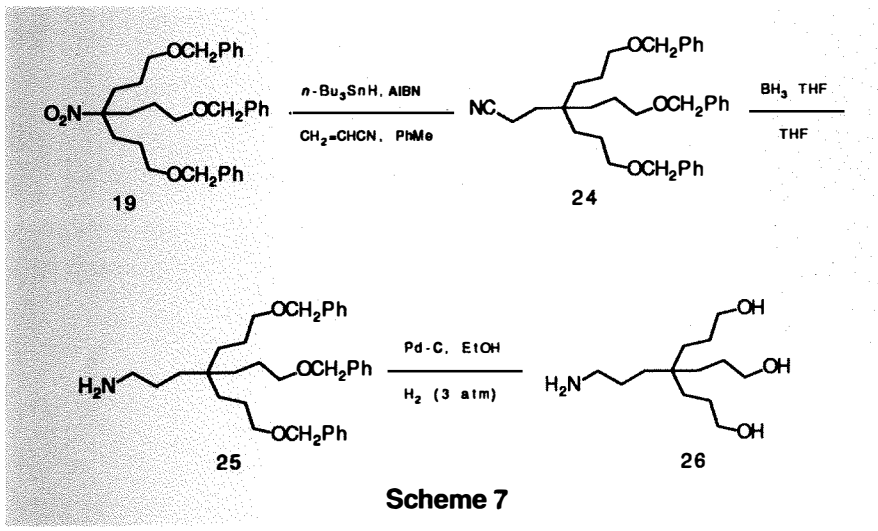
Scheme 4



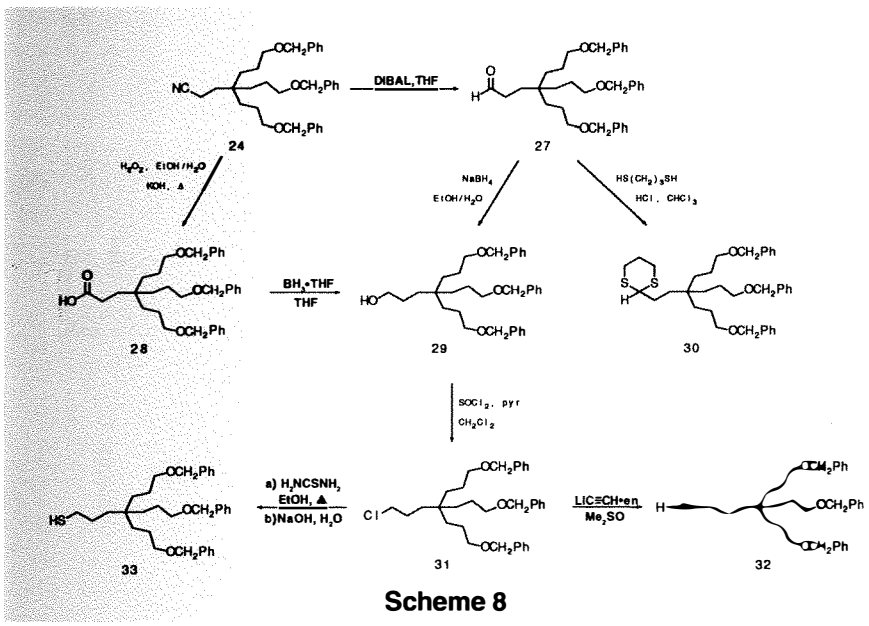
Scheme 5



Scheme 6



Scheme 7



Scheme 8

duced to give the desired amine **21**[33] (**Scheme 5**). The bulky *tert*-butyl ester is required to prevent lactam formation during reduction.[34] Trisester **21** thus shortens the cascade synthesis to: amide formation, hydrolysis with formic acid, and repetition of the sequence.

Alternatively, an ethereal analogue of **21** was prepared by treatment of TRIS with acrylonitrile to afford the trinitrile **22**, followed by ethanolysis to give amine **23** (**Scheme 6**). Utilization of **23** in a cascade synthesis provided ether-amido functionalized dendrimers.[35]

Although the monomers described above provided several pathways for the preparation of amide based dendrimers; derivatization of key nitro precursors afforded access to a novel family of monomers and a perfect methane core. Replacement of the nitro moiety of benzyl ether **19** by denitration-cyanoethylation (**Scheme 7**) via the method of Ono[36] gave mononitrile **24**. Reduction of **24** with BH_3·THF gave amine **25**; subsequent catalytic reduction of the ethers gave "trishomobishomotris" **26**.

Ether protected nitrile **24** was easily converted (**Scheme 8**) to either aldehyde **27** (via reduction with DIBAL), or acid **28** (via basic hydrolysis). Reduction of either **27** or **28** gave alcohol **29**, whereas treatment of aldehyde **27** with 1,3-propanedithiol gave dithiane **30**, whose carbanion provides an entrance to hydrocarbon (all *C*-) based dendrimers.

An alternate route to *C*-based dendritic polymers was provided by treatment of **29** with $SOCl_2$ to quantitatively generate chloride **31**, which upon treatment with lithium acetylide afforded alkyne **32**. Thioether based dendrimers are also readily accessible from chloride **31** by treatment with thiourea, and subsequent basic hydrolysis to give thiol **33**.

Nitro moieties attached to tertiary carbon atoms are known to undergo radical anionic displacements.[37] Thus, reaction of the sodium salt of nitromethane with **13** via the method of Kornblum[37] gave homolog **34** (**Scheme 9**).[38] Subsequent transformations[39] of the -CH_2NO_2 moiety gave nitriles **35** and **36**, aldehyde **37**, or acid **38**. This methodology has recently been applied to nitrotrisether **19** and nitrotriester **20**.[40] Thus, homologation of **19** gave **39**, which was cyanoethylated to give nitrile **40** (**Scheme 10**). The pendant nitro moiety of **40** was easily removed by treatment with $(n\text{-Bu})_3SnH$ to afford nitrile **41**, a *homolog* of nitrile **24**. Either **40** or **41** can be derivativized, as described above for nitrile **24**, and utilized for the preparation of *C*-based cascades. Cascade synthesis with an alkyne derivative of **40** will provide a cascade possessing pendent nitro moieties that can be reduced to amines; these amines may be used for the synthesis (or attachment) of desired functionality (e.g., imi-

dazole, pyridine, ...) along the interior of the cascade polymer. Nitromethylation of the tris(*tert*-butyl)ester **20** gave the homologated triester **42**; subsequent reduction afforded the amine building block **43** (**Scheme 11**). When used in conjunction with amine **21** for cascade construction, the additional atom (methylene) should permit fine-tuning of the resultant cascade properties (e.g., molecular diameter), and delay the onset of dense-packing.

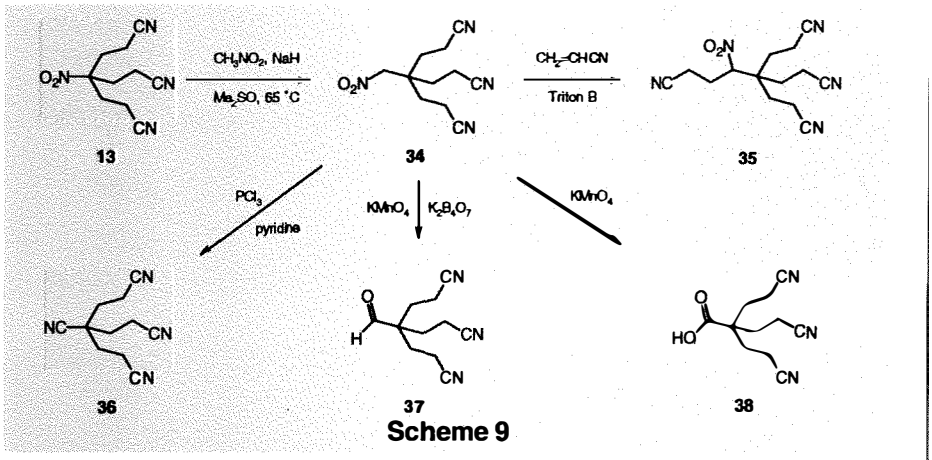
Other recent developments in our laboratories include the preparation of building block monomers that, after attachment and deprotection, will give amine or pyridine terminated cascades. Reduction of trinitrile **13** with BH_3·THF gave triamine **44** (**Scheme 12**). The amino moieties were protected by treatment with methyl chloroformate to give **45**; the nitro moiety was reduced with T-1 Raney nickel to give aminotriscarbamate **46**.[41] Coupling of a polyacid cascade with amine **46** and subsequent hydrolysis of the carbamate moieties affords the desired amine terminated cascade.

Michael additions are possible with 2- and 4-vinylpyridines;[42] thus, exhaustive Michael-type addition of $MeNO_2$ to 4-vinylpyridine in the presence of Triton B afforded trispyridine **47**, which was smoothly reduced to amine **48** (**Scheme 13**).[43] Dicyclohexylcarbodiimide mediated coupling of **48** to an acid terminated cascade gives a pyridine terminated cascade and provides a means for the formation of transition metal complexes on the surface of these dendritic polymers.

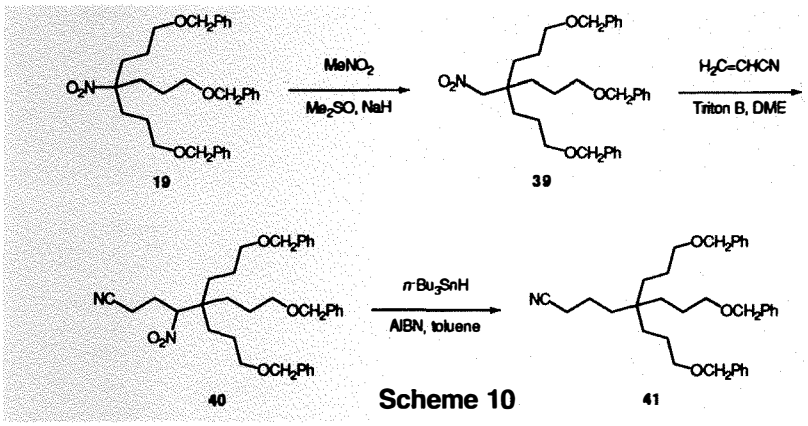
Initiator Cores

We focused on tetrabromide **8** as the ideal initiator core for the preparation of a hydrocarbon-based dendrimer, since the terminal functionalities were deemed sufficiently removed from the steric retardation of nucleophilic substitution caused by the neopentyl core. Since tetraalkyl substituted methanes are not easily prepared, especially symmetrical ones[44] (i.e., **7**[45] and **8**[46]), improved syntheses were sought. Hydrogenolysis of benzyl ether **29** gave tetraol **49** (a useful core for preparation of ether-based dendrimers), which upon treatment with HBr gave **8**. Alternatively, nitrotriol **16** was reacted with MeI and base to give triether **50**, whose pendant nitro moiety was transformed via the method of Ono,[36] to give ester **51**. Reduction of ester **51** with $LiAlH_4$ gave hydroxy ether **52**, which was directly converted to tetrabromide **8**. Tetraacid **53** (an acyl-based initiator core) was cleanly prepared via oxidation[47] of tetraol **49** (**Scheme 14**).

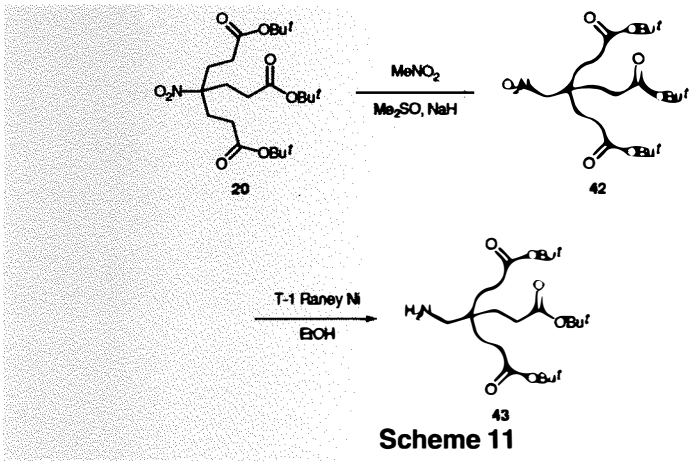
The related ethereal tetraacid **54** was easily prepared in two steps (**Scheme 15**) from



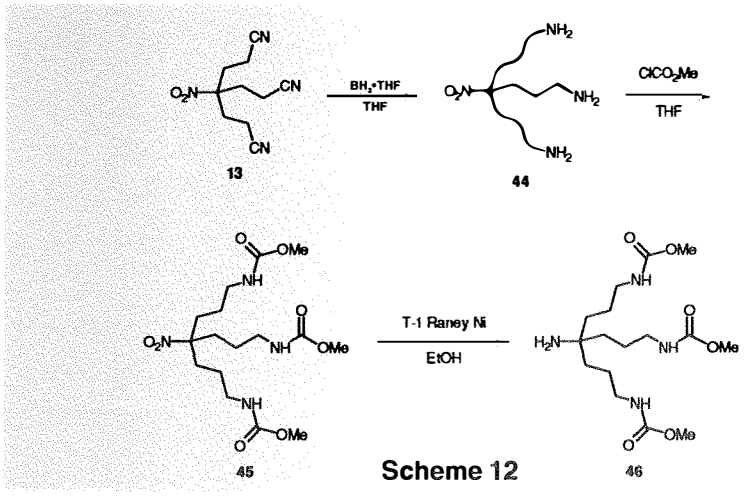
Scheme 9



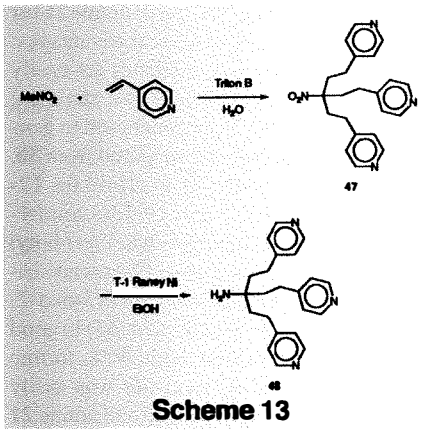
Scheme 10



Scheme 11



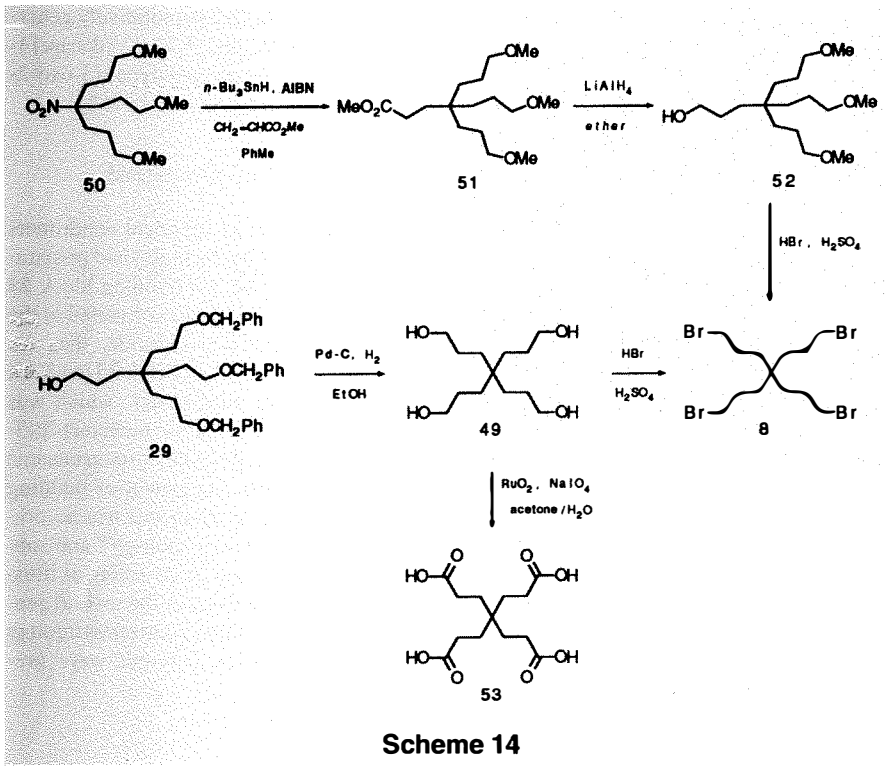
Scheme 12



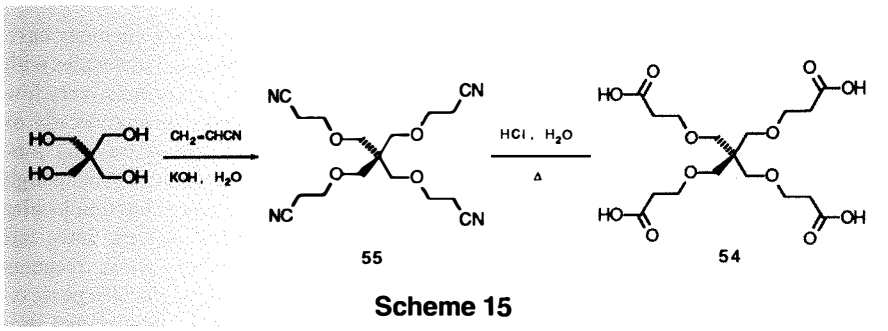
Scheme 13

pentaerythritol. Tetra(cyanoethoxymethyl)-methane (**55**) was prepared via Bruson's method,[48] then hydrolyzed to afford **54**. Thus, the readily available tetraacid **54** was transformed to dendritic polymers possessing central ethereal functionalities and 6 atoms between the central quaternary carbon and the first branch point.

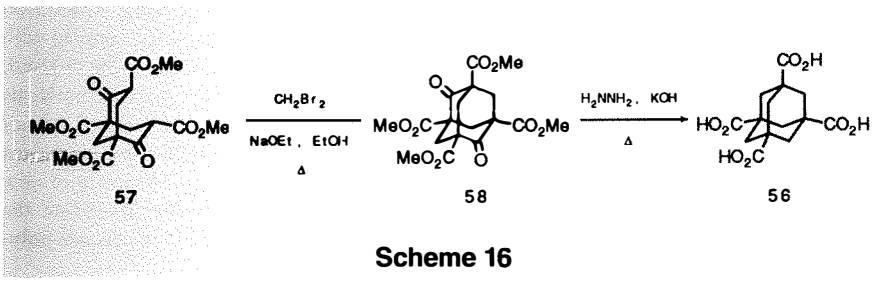
An improved 3-step preparation of 1,3,5,7-adamantanetetracarboxylic acid (**56**) was devised (**Scheme 16**) to provide a tetraacid possessing a rigid tetrahedral arrangement. Thus, reaction of dimethyl malonate and aqueous formaldehyde in the presence of diethylamine *instead of* piperidine gave Meerwein's ester **57**,[49] which cyclized to the dione tetraester **58** upon treatment with dibromomethane and sodium ethoxide.[50] Reduction of **58** by hydrazine in a steel bomb gave the crystalline tetraacid **56**.



Scheme 14



Scheme 15



Scheme 16

Examples of Dendritic Polymer Synthesis

Construction of cascade polymers possessing diverse internal functionality and porosity was previously hindered by the *availability* of appropriate core molecules and suitably functionalized monomers. Combinations of the above cores and building blocks opened the door to new macromolecular structures. Surface modifications,[51] coatings with metal ions,[52] and bioactive moieties[53] have been demonstrated.

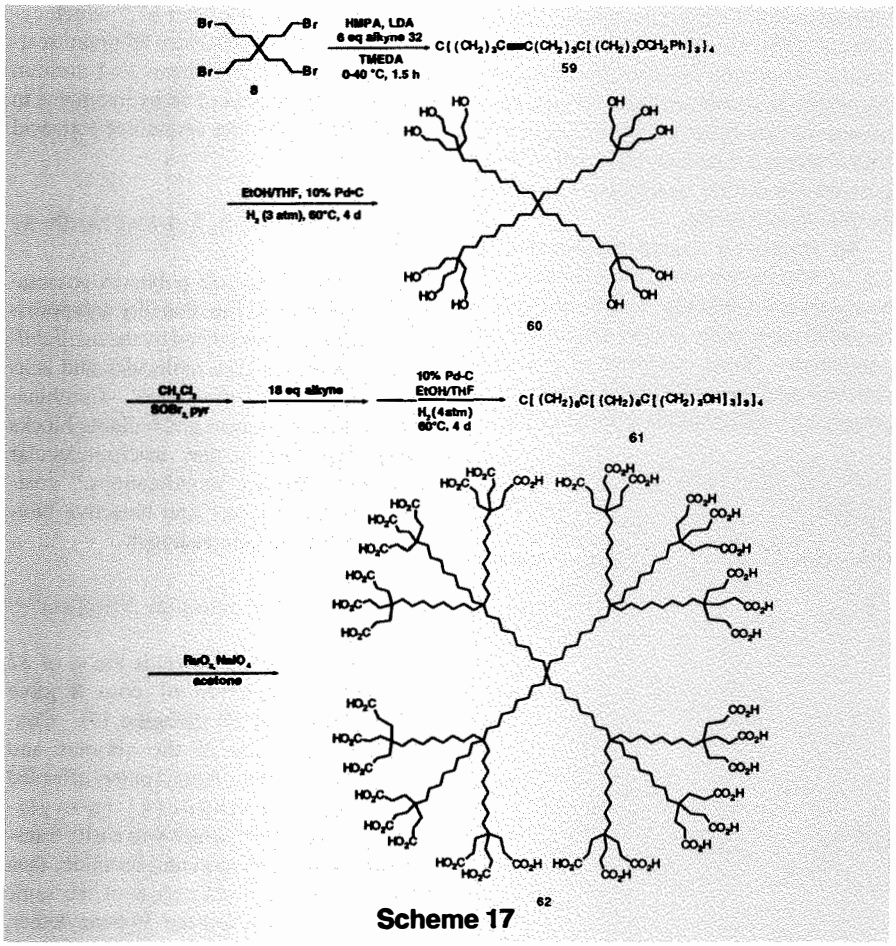
Micellanes™ (Unimolecular Micelles)[25,26]

Generation of the alkynide anion of **32** followed by addition of core **8** gave dodecabenzylether **59** (**Scheme 17**). Concomitant reduction of the alkynes and hydrogenolysis of the benzyl ethers afforded 12-cascade:methane[4]:(nonylidyne):propanol (**60**), which was easily transformed to the corresponding bromide, then treatment with a slight excess of the same alkynide anion yielded the 36-benzylether, which upon reduction and hydrogenolysis gave 36-cascade:methane[4]:(nonylidyne)^2-:propanol (**61**).

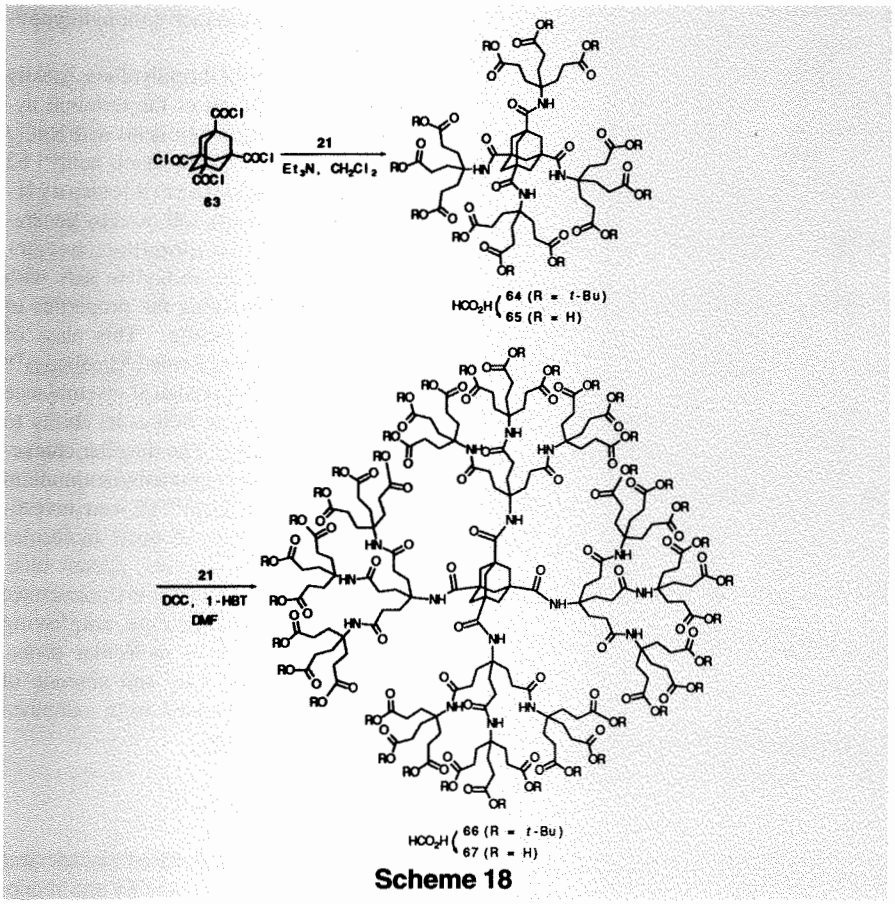
Water solubility of the polyol was greatly enhanced by oxidation of the terminal hydroxyl groups to carboxylic acids with RuO_2/$NaIO_4$ to afford [8^2·3]Micellanoic acid™ **62** (36-cascade:methane[4]:(nonylidyne)^2:propanoic acid), followed by generation of the corresponding polytetramethylammoniumcarboxylate salt with the objective of studying the properties of this *unimolecular* micelle. This class of cascade polymers was termed Micellanes™ due to the obvious topological resemblance to globular micelles as well as its ability to function as a micelle. The micellar characteristics of the polytetramethylammonium salt of [8^2·3]Micellanoate™ **62** were investigated via UV analysis of guest molecules such as pinacyanol chloride, phenol blue, and naphthalene combined with fluorescence lifetime decay experiments employing diphenylhexatriene as a molecular probe. The monodispersity, size, and absence of intermolecular aggregation were examined by electron microscopy.

Amide Functionalized

An exemplary amide-based cascade was easily constructed from core **56** and mono-



Scheme 17



Scheme 18

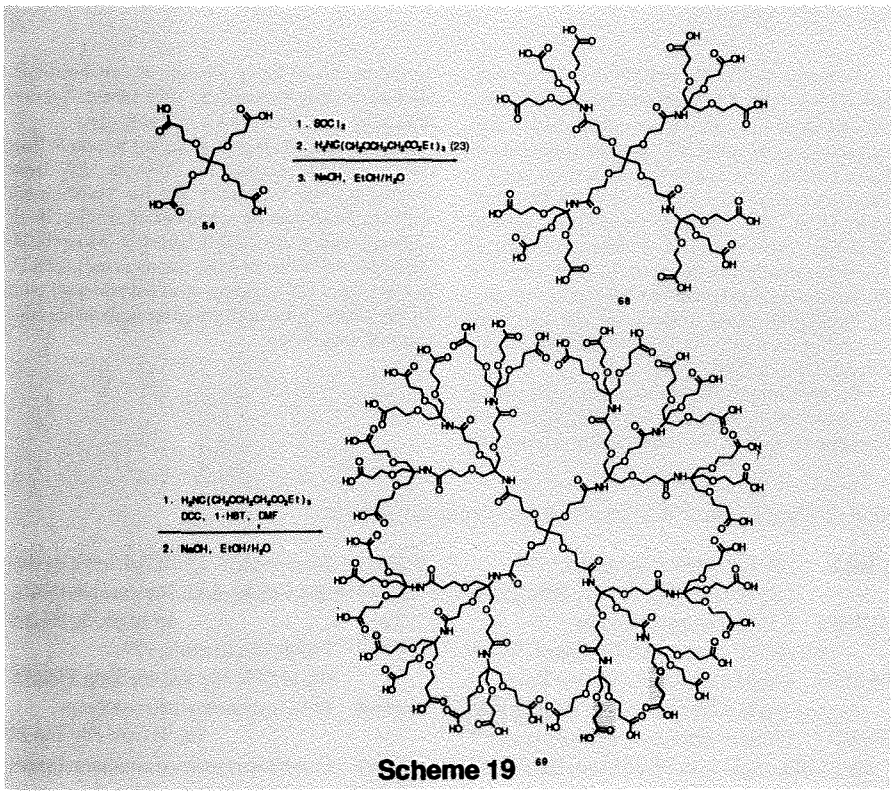
mer **21** (**Scheme 18**). The use of amine **21** for cascade synthesis offers several advantages: (a) the *t*-butyl ester intermediates are easily purified solids, and (b) only two steps are required to progress from generation to generation. Acid chloride **63**, prepared from **56**, was treated with amine **21** to afford the 12-cascade:tricyclo[3.3.1.1^{3,7}]decane[4-1,3,5,7]:(3-oxo-2-azapropylidyne):*tert*-butyl propanoate (**64**), which gave 12-cascade:tricyclo[3.3.1.1^{3,7}]decane[4-1,3,5,7]:(3-oxo-2-azapropylidyne):propanoic acid (**65**) in good yield when hydrolyzed with 96% formic acid. Addition of the next tier was easily realized by coupling of acid **65** and amine **21** with DCC and 1-HBT to afford ester **66**, which upon hydrolysis quantitatively generated 36-cascade:tricyclo[3.3.1.1^{3,7}]decane[4-1,3,5,7]:(3-oxo-2-azapropylidyne):(3-oxo-2-azapentylidyne):propanoic acid (**67**).

Ether-Amide Functionalized

Rapid synthesis of spherical dendrimers was accomplished by the high yield preparation of ether core **54** and building block **23** (**Scheme 19**). Acid **54** was converted to the corresponding tetraacid chloride, then reacted with amine building block **23** to afford the corresponding dodecaester, which was saponified to give 12-cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne):4-oxopentanoic acid (**68**). Iterative attachment of building blocks to the growing dendrimer was accomplished via peptide methodology[54] and subsequent saponification of the esters as illustrated for the preparation of the second generation acid **69**. Ultimately, cascades through the fourth generation polymer were prepared.[55]

Conclusions

For nearly two centuries chemists have created millions of unnatural molecules with specific composition. Amazingly, very few combinations of reagents have given rise to single organic molecules possessing molecular weights >2000 Daltons, even though the majority of biomolecules have molecular weights starting where chemists have left off. Combinations of the above reagents have given rise to macromolecules possessing nearly 3000 surface moieties and molecular weights approaching 1,000,000 Daltons. Thus, these reagents, coupled with others in the literature or yet to be devised, will expand the chemists' synthetic horizons to include the creation of tailored meso/macromolecules. The application of recent bio-techniques and the development of new instrumentation will further accelerate the growth of the budding field of cascade polymers.



Scheme 19

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$$Z\text{-}cascade{:}\underset{unit}{core}\ [N_c]{:}(\underset{repeat\ unit}{intermediate_c})^{I}{:}\underset{unit}{terminal}$$

where Z is the number of terminal moieties; N_c is the multiplicity of branching from the central core; and I is the number of layers of repeated units (i.e., number of generations (G) in this case).

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(56) We wish to thank the National Science Foundation for partial support of this work.

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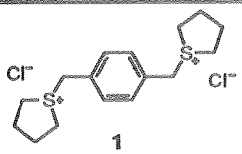
Professor George R. Newkome is Vice President for Research, Distinguished Research Professor, and Director of the Center for Molecular Design and Recognition (CMDR) at the University of South Florida. He began his research in organic chemistry at Kent State University where he earned his Ph.D. in 1966. He spent the next two years at Princeton University on a National Institutes of Health Postdoctoral Fellowship. In 1968, he joined the faculty at Louisiana State University, advancing through the ranks to Professor and Executive Director of the Center for Energy Studies, until his move to USF in 1986.

Dr. Newkome has published over 220 papers and numerous books in the areas of organic and inorganic chemistry. He has served as advisor and on the boards of many prestigious organizations. He was recently awarded the 1991 Florida Section Award by the American Chemical Society.

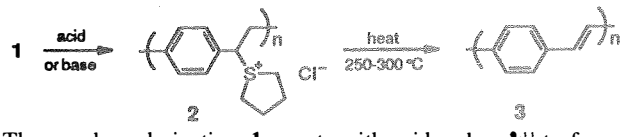
Dr. Gregory R. Baker, Assistant Research Professor, CMDR, received his Ph.D. in 1989 from Louisiana State University and has collaborated with Dr. Newkome on a number of articles, book chapters, and grants. Dr. Charles N. Moorefield, Post-doctoral Research Assistant, received his Ph.D. in 1991 from USF, and has also collaborated with Dr. Newkome's research group throughout his educational experience.

Poly(p-phenylene vinylene) Precursor



1

Poly(*p*-phenylene vinylene), **3**, is a rigid conjugated polymer with applications in sensors,[1] batteries,[2] Langmuir-Blodgett films,[3] nonlinear optics,[4] organic conductors,[5] graphite precursors,[6] and light-emitting diodes.[7] The lack of efficient processing methods to synthesize products of desired size and shape has seriously hindered the commercial development of this and other rigid polymers.[8]



2 **3**

The *p*-xylene derivative, **1**, reacts with acid or base[9-11] to form a soluble polymer, **2**, which can be easily cast,[9] spin-coated,[6] blended with other polymers,[2] or gel-spun[12] into the needed form. Polymer **2** can be readily converted to poly(*p*-phenylene vinylene) by thermal treatment in solution[13] or solid phase[7,8] thereby allowing access to this rigid polymer in the form and size needed.

Aldrich offers an extensive array of polymers and monomers in our Catalog/Handbook. If you don't find what you are looking for, please call our Technical Services Department at (800) 231-8327 with your suggestions.

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THE SYNTHESIS OF POLYQUINANES AND POLYQUINENES *VIA* THE WEISS REACTION

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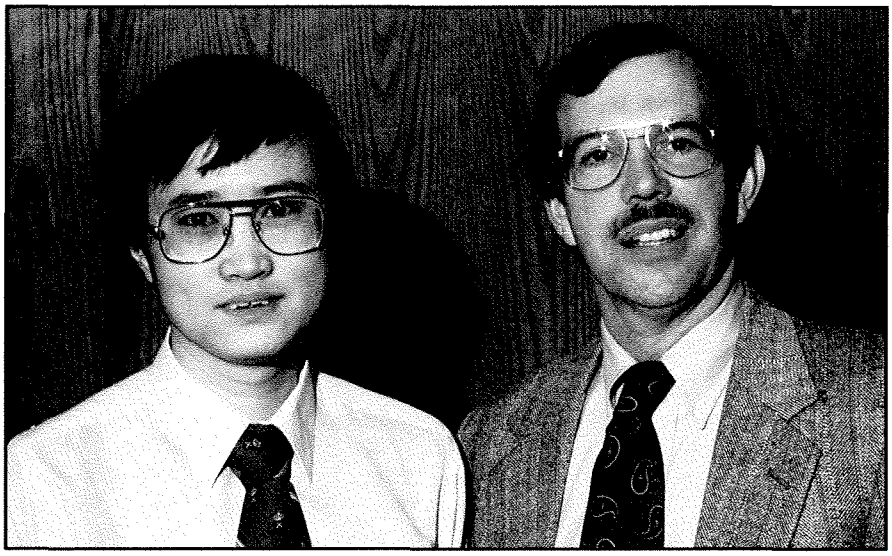
I. INTRODUCTION

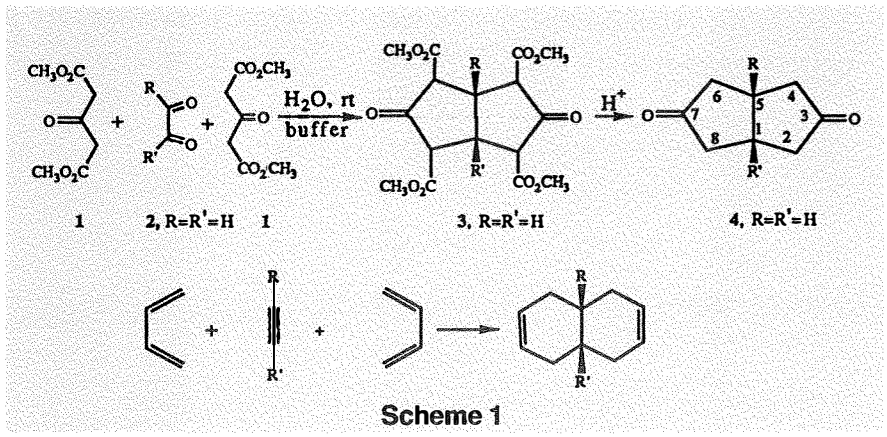


The reaction[1] of two molecules of dimethyl 3-oxoglutarate **1** with one molecule of glyoxal **2** in aqueous acidic solution to provide modest and repeatable yields of tetramethyl *cis*-bicyclo[3.3.0]octane-3,7-dione-2,4,6,8-tetracarboxylate **3**, a result which had been obtained previously by a much more involved procedure,[2] was discovered by Weiss and Edwards. Acid-catalyzed hydrolysis of **3** followed by spontaneous decarboxylation of the β-ketoacid functions which resulted gave *cis*-bicyclo-[3.3.0]octane-3,7-dione **4** (**Scheme 1**).

In a synthetic (not mechanistic) sense, the generation of two five-membered rings from the Weiss reaction parallels the generation of two six membered rings in the Diels-Alder reaction, as illustrated at the bottom of **Scheme 1**. Consequently, this facile formation of two cyclopentanoid rings from aliphatic precursors, albeit in relatively low yield, prompted the investigation of this condensation under a variety of conditions to explore the potential of this process.[3]

Characterization of several other β-ketoesters produced from **1** and **2** under acidic conditions by Weiss, Rice, *et al.*[4] provided the first clues as to the low yield of **3** in earlier work. Apparently, dimethyl 3-oxoglutarate **1** and glyoxal **2** were present in equilibrium with **3** in the reaction medium, which eventually resulted in the formation of tricyclic and tetracyclic byproducts. However, the potential of this condensation was greatly increased when the reaction of **1** with **2** was carried out in an aqueous alkaline medium.[4e,5] Under these conditions, the 1:2 adduct **3** precipitated from the reaction solution, and dramatically decreased the side reactions of **3** with both **1** and **2**. Additionally, the aqueous alkaline conditions also increased the reaction rate. This modified procedure furnished the *cis*-bicyclo[3.3.0]-octane-3,7-dione system **3** in excellent yield and as the sole reaction product.[5]

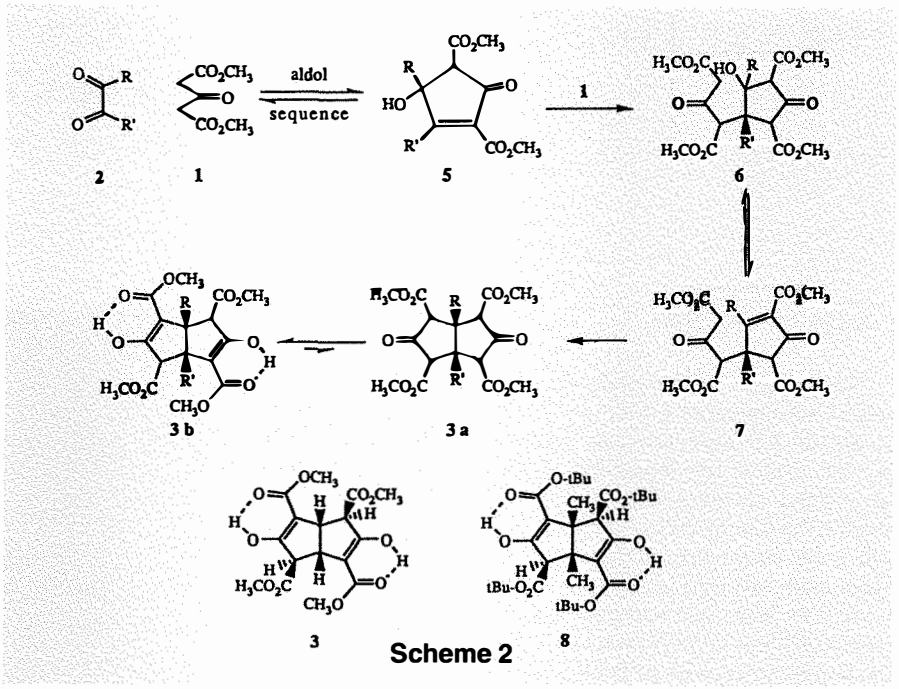
The mechanism of the Weiss reaction has been studied and is outlined in **Scheme 2**.[3c,4f] The aldol condensation of one molecule of α-dicarbonyl compound **2** with one molecule of dimethyl 3-oxoglutarate **1** generates a β-hydroxyketone. This intermediate undergoes an intramolecular aldol reaction followed by dehydration to form the α,β-unsaturated ketone **5** as a 1:1 adduct. The Michael reaction of enone **5** with another molecule of oxoglutarate **1**, followed by dehydration of the β-hydroxyketone **6** that resulted, produced enone **7**. This enone was set up for a second Michael addition that proceeded in an intramolecular fashion. The *cis*-bicyclo[3.3.0]octane-3,7-dione system was generated by this cyclization, as shown in **Scheme 2**. The tetramethyl ester **3a** that resulted usually exists as the bisenol tautomer **3b** which is stabilized by intramolecular hydrogen bonding.[6] The sequence from dimethyl 3-oxoglutarate **1** with 1,2-dione **2** has the merit of complete stereospecificity, and it results in the *cis*-fused bicyclo[3.3.0]octane system in each case investigated to date. Since the transition state for the intramolecular attack of the enol carbon atom of β-ketoester **7** at the Michael acceptor double bond is favored when attack occurs from the bottom face of the enone, the *cis* stereochemistry observed in the Weiss reaction is not surprising. In addition, in the bicyclo[3.3.0]octane system, the *cis* hydrocarbon has been shown to be more stable than the *trans* hydrocarbon by 6-7 kcal/mol,[7] which favors the generation of the *cis*-fused molecule based also on thermodynamic grounds. It has been shown by NMR spectroscopy and X-ray crystallography[4e,8,9] that the methyl carboxylate functions at positions C-4 and C-8 in the bisenol forms of tetraesters **3** and **8**, respectively, exist with the *exo* stereochemistry.



Scheme 1

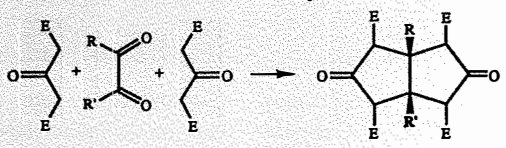
The reaction of 3-oxoglutarate **1** with 1,2-dicarbonyl compounds other than **2** established the generality of this process.[4f-11] For example, pyruvaldehyde and biacetyl gave the 1-monomethyl and 1,5-dimethyl analogs of **3**, respectively, while the use of alicyclic α-dicarbonyl compounds provided a simple one-pot procedure for the preparation of [n.3.3]propellane derivatives such as **11** and **12** (**Scheme 3**). Since large alicyclic 1,2-dicarbonyl compounds exhibit limited solubility in aqueous media, Ginsburg developed the preparation of the [22.3.3]propellanedione by a modification of the Weiss conditions in non-aqueous solution. He and Sukenik employed methanolic potassium hydroxide and benzene to extend the series to include the [38.3.3]propellanedione.[12] This successful modification to include water insoluble substances further increased the versatility of this condensation.

The influence of steric and electronic effects on the success of the Weiss reaction has been studied by varying the nature of the



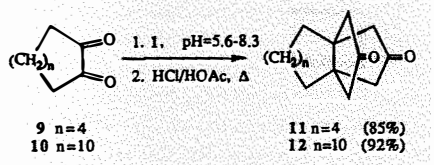
Scheme 2

Table 1. The Preparation of Aliphatic Substituted 2,4,6,8-Tetramethyl *cis*-bicyclo[3.3.0]octane-3,7-dione tetracarboxylates *via* the Weiss Reaction.



Dicarbonyl Compound	R,R'	Conditions	pH	Yield of 1:2 Adduct	References
Glyoxal	H,H	Aq. Buffer	5.3	15-30%	1,9
		Aq. Buffer	8.3	77%	5
		NaOH/MeOH,Δ	>12	60-75%	5,9
Methyl glyoxal	Me,H	Aq. Buffer	5.0	52%	1
		Aq. Buffer	8.4	80%	5
Biacetyl	Me,Me	Aq. Buffer	5.0	60%	1
		Aq. Buffer	8.3	70-90%	5
1,4-Dibromo-2,3-butanedione	CH_2Br,CH_2Br	Aq. Buffer	5.6	0%	10
		Aq. Buffer	8.3	0%	10
2,3-Pentanedione	Et,Me	Aq. Buffer	8.3	75%	10
2,3-Hexanedione	Pr,Me	Aq. Buffer	8.3	70%	10
4,5-Dioxopentanoic acid	$CH_2CH_2CO_2H$,H	Aq. Buffer	6.8	80%	5c
4,5-Dioxohexanoic acid	$CH_2CH_2CO_2H$,Me	Aq. Buffer	6.8	84%	25
Ethyl 4,5-dioxo-hexanoate	$CH_2CH_2CO_2Et$,Me	Aq. Buffer	6.8	80%	25b
Methyl 2,3-dioxobutanoate	CO_2Me, Me	Aq. Buffer	6.8	18%[a]	6b
Ethyl 3-(ethoxy carbonylmethyl)-4,5-dioxopentanoate	$CH(CH_2CO_2Et)_2$,H	Aq. Buffer	8.3	51%	3c
3-Allyl-1,2-dioxo-5-hexene	$CH(CH_2CH{=}CH_2)_2$,H	Aq. Buffer	8.3	30%	10
1-(3'-Cyclopentenyl)-1,2-ethanedione	C_5H_7,H	Aq. Buffer	5.6	78%	3c
		Aq. Buffer	8.3	83-90%	3c
1-(4'-Cycloheptenyl)-1,2-ethanedione	C_7H_{11},H	Aq. Buffer	8.3	70%	3c
Biscyclopentyl-1,2-ethanedione	C_5H_9,C_5H_9	NaOH/MeOH,Δ	>12	12	10
Biscyclohexyl-1,2-ethanedione	C_6H_{11},C_6H_{11}	NaOH/MeOH,Δ	>12	0%	13
Bis-3'-cyclopentyl-1,2-ethanedione	C_5H_7,C_5H_7	NaOH/MeOH,Δ	>12	10	10
1-Phenyl-1,2-ethanedione	C_6H_5,H	Aq. Buffer	8.3	66%	5
1-Phenyl-1,2-propanedione	C_6H_5,CH_3	Aq. Buffer	8.3	68%	10
		NaOH/MeOH,D	>12	50%	10

[a] The reported yield is of the hydrolysis product of the 1:2 adduct tetraester.



Scheme 3

1,2-dicarbonyl component.[13,14] It has been found that the yield of the reaction decreased as the size of the R and R' substituents of the dione **2** increased. For instance, when the substituents were R=R'=cyclohexyl in **2**, only the 1:1 adduct **5** was isolated. This result is due in large part to the increased steric hindrance in the intermediate 1:1 adduct **5** which inhibits attack by a second molecule of **2**. In the case of aliphatic α-dicarbonyl compounds, only those 1,2-diones with substituents (R and R') that occupy a molecular volume equal to or less than a cyclopentane unit have been successfully converted into 1:2 adducts in good yields.[3a]

With regard to the construction of the *cis*-bicyclo[3.3.0]octane ring system, analysis of the Weiss reaction using graph theory indicated that it was comparable to the Diels-Alder reaction for the rapid generation of molecular complexity in a single step.[15] The Weiss reaction has been described by Posner as a 3-component (3+2+3) coupling reaction, and an overall yield of 90% in the reaction can be viewed as an average yield of 97.5% for each of the new carbon-carbon bonds so formed.[16]

It is clear that the most obvious attribute of this reaction is the facile generation of the *cis*-bicyclo[3.3.0]octane ring system. How-

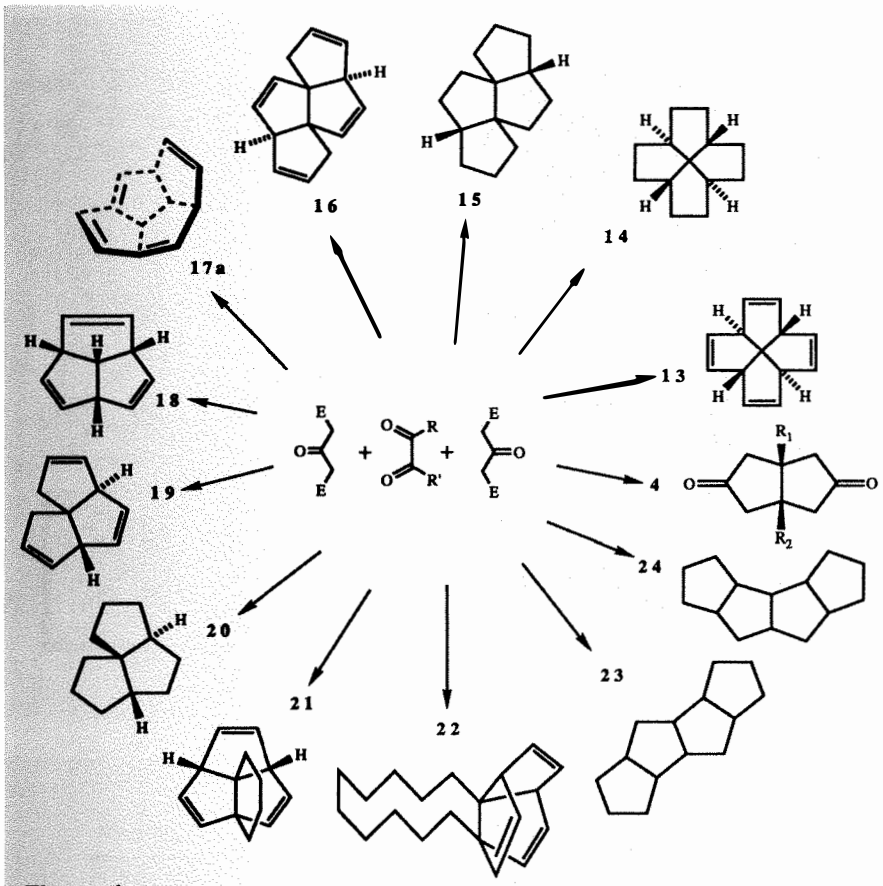


Figure 1. Polyquinanes and Polyquinenes Synthesized *via* the Weiss Reaction.

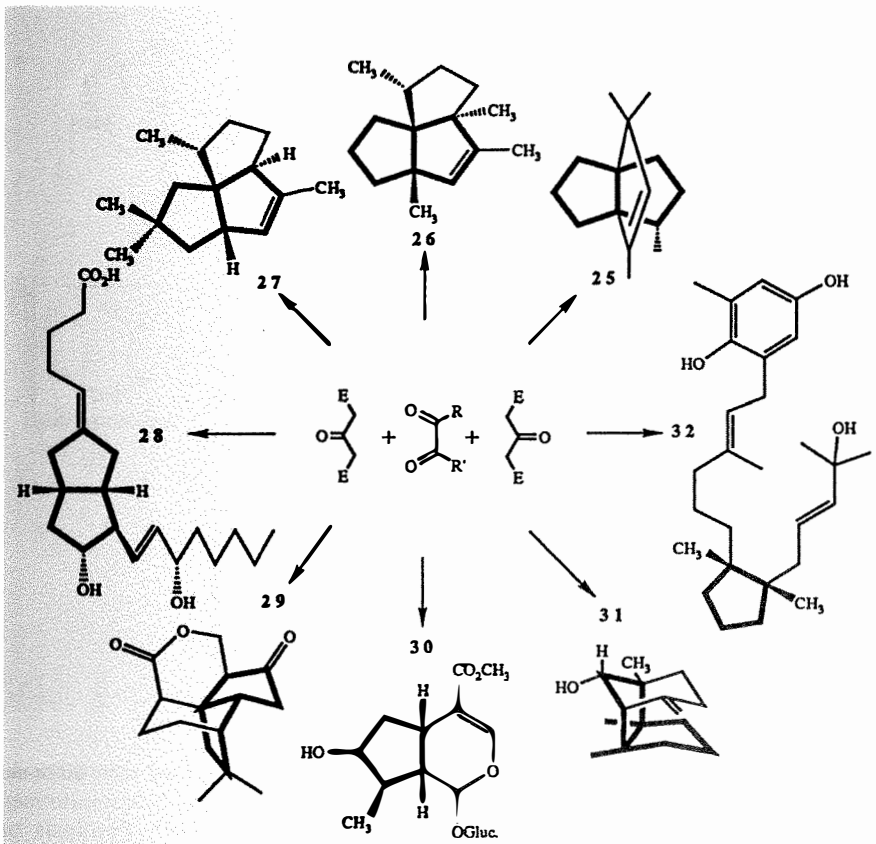


Figure 2. Polyquinane Natural Products Synthesized *via* the Weiss Reaction.

ever, more importantly from a synthetic point of view, this condensation is particularly suited to the rapid construction of higher polyquinane natural and non-natural products. At least one retrosynthetic pathway in this series of compounds will always involve a *cis*-bicyclo[3.3.0]octane system. The versatility of this process permits the simple and facile construction of monosubstituted and 1,5-disubstituted *cis*-bicyclo[3.3.0]octane-3,7-diones based upon the choice of the dicarbonyl starting material. Both the tetraester and its hydrolysis product can be alkylated by standard procedures to introduce substituents at positions C-2, C-4, C-6 and C-8. The carbonyl groups at positions C-3 and C-7 also provide a means for the construction of more complex polyquinenes. Following this approach, a number of polyquinanes and polyquinenes have been prepared in our laboratories and include (**Figure 1**): staurane-2,5,8,11-tetraene **13**[17] and the corresponding [5.5.5.5]fenestrane staurane **14**; tetracyclo[6.6.0.0^{1,5}.0^{8,12}]-tetradecane **15** and the corresponding -3,6,-10,13-tetraene **16**;[18] *cis*-tetracyclo[7.2.1.0^{4,11}-.0^{6,10}]dodeca-3,5,7,9-tetraene **17a**;[19] triquinacene **18**,[20] the related triquinane triene **19**,[36] and the parent hydrocarbon **20**; tetracyclo[5.5.2.0^{1,8}.0^{4,8}]tetradecane-2,5,13-triene **21**;[21] tetracyclo[11.5.2.0^{2,13}-.0^{2,16}]eicosa-14,17,19-triene **22**;[22] and the perhydrodicyclopenta[*a,e*]pentalene **23** and perhydrodicyclopenta[*a,d*]pentalene **24** systems.[23] This method has also been employed for the synthesis of several polyquinane natural products including (**Figure 2**): modhephene **25**,[24] isocomene **26**,[25] pentalenene **27**,[26] 6a-carbaprostaglandin-I$_2$ **28**,[27] quadrone **29**,[28] loganin **30**,[29] gymnomitrol **31**[30] and bifurcarenone **32**.[31]

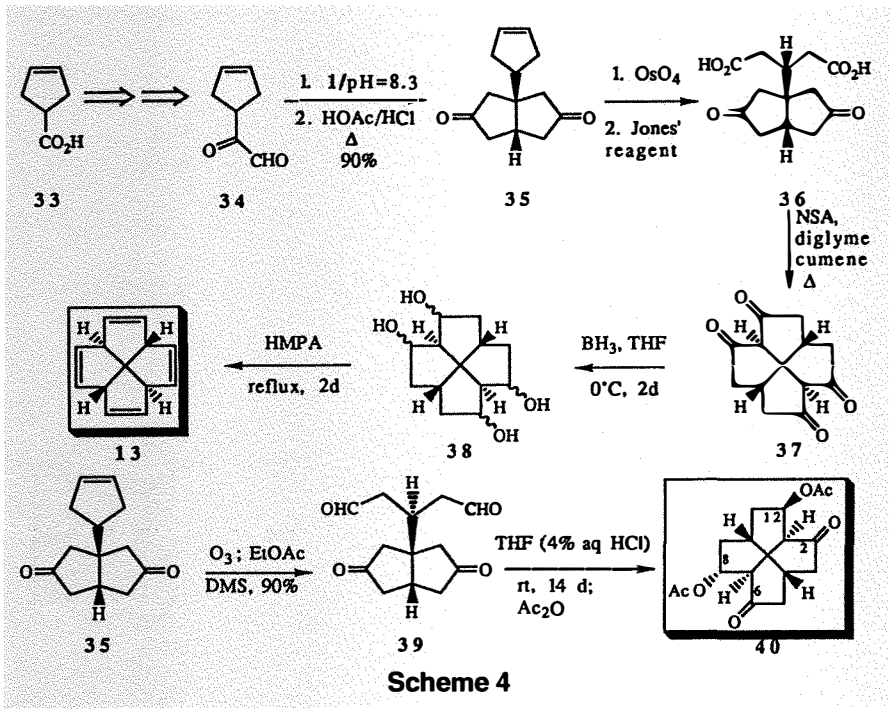
II. APPLICATION TO THE SYNTHESES OF NON-NATURAL POLYQUINENES

1. Synthesis of staurane-2,5,8,11-tetraene 13.

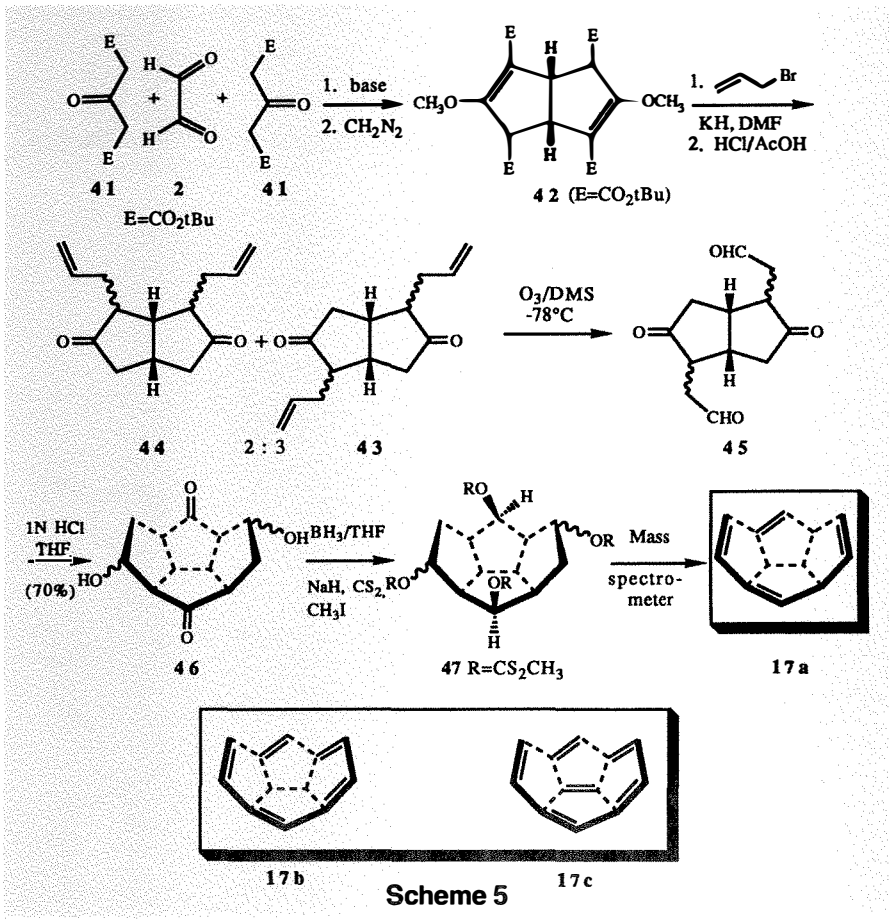
The potential deviation of tetracoordinate carbon from tetrahedral to square planar geometry has intrigued scientists for many years.[32-35] Since Hoffmann's landmark paper[32] in the early 1970's on tetracoordinate planar carbon, a number of molecular candidates to house such a carbon atom have been proposed for synthetic exploration. Of these, staurane hexaene has been of particular interest in both a computational and synthetic sense.[10,35,36] Several syntheses of the [5.5.5.5]fenestrane system have been reported by Mitschka *et al.*[3,11c] and Keese *et al.*[36] Outlined in **Scheme 4** is the synthesis[11c,17,37] of staurane-2,5,8,11-tetraene **13** *via* the Weiss reaction.

Cyclopentene-3-carboxylic acid **33** was prepared in good yield on kilogram scale from the reaction of diethyl malonate with *trans*-1,4-dichloro-2-butene, followed by a pericyclic vinylcyclopropane rearrangement. The acid **33** was then converted into cyclopentene-3-glyoxal **34** *via* the method of Bestmann[38] in excellent yield. The cyclopentene substituted *cis*-bicyclo[3.3.0]octane-3,7-dione tetraester was obtained in 95% yield by the Weiss reaction of dimethyl 3-oxoglutarate **1** with 1,2-glyoxal **34**, and this was followed by hydrolysis and decarboxylation to provide the 1-substituted *cis*-bicyclo[3.3.0]octane-3,7-dione **35** (90% yield). The diketoolefin **35** was transformed *via* diacid **36** into staurane tetraone **37** by an acid-catalyzed bisacylation sequence. Lewis acid-mediated (BH_3/THF) reduction of **37** to the corresponding tetrol in high yield, and subsequent HMPA-mediated dehydration furnished staurane tetraene **13** accompanied by a small amount of the bridgehead isomer. The latter olefin was converted into the more stable tetraene **13** by a *p*-TSA-catalyzed isomerization.[17]

In another approach, cleavage of the olefinic bond of diketoolefin **35** *via* ozonolysis afforded the dialdehyde **39** in high yield. The aldol cyclization of bisaldehyde **39** was carried out under conditions of thermodynamic equilibrium to provide the [5.5.5.5]fenestrane diketodiacetate **40**,[37] which can be converted into staurane tetraene **13** using known methods.[18] Studies with regard to the transformation of **13** into its corresponding pentaene and/or hexaene are underway.



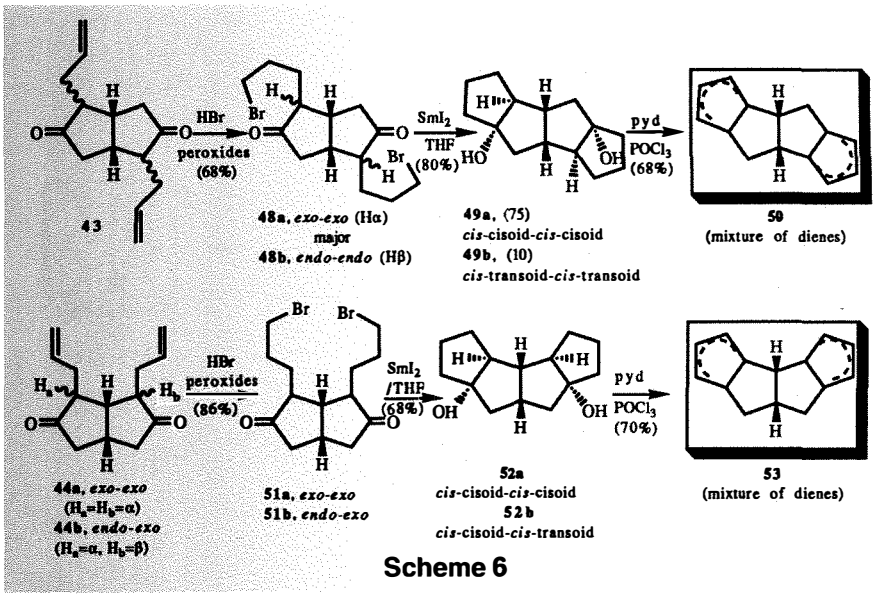
Scheme 4



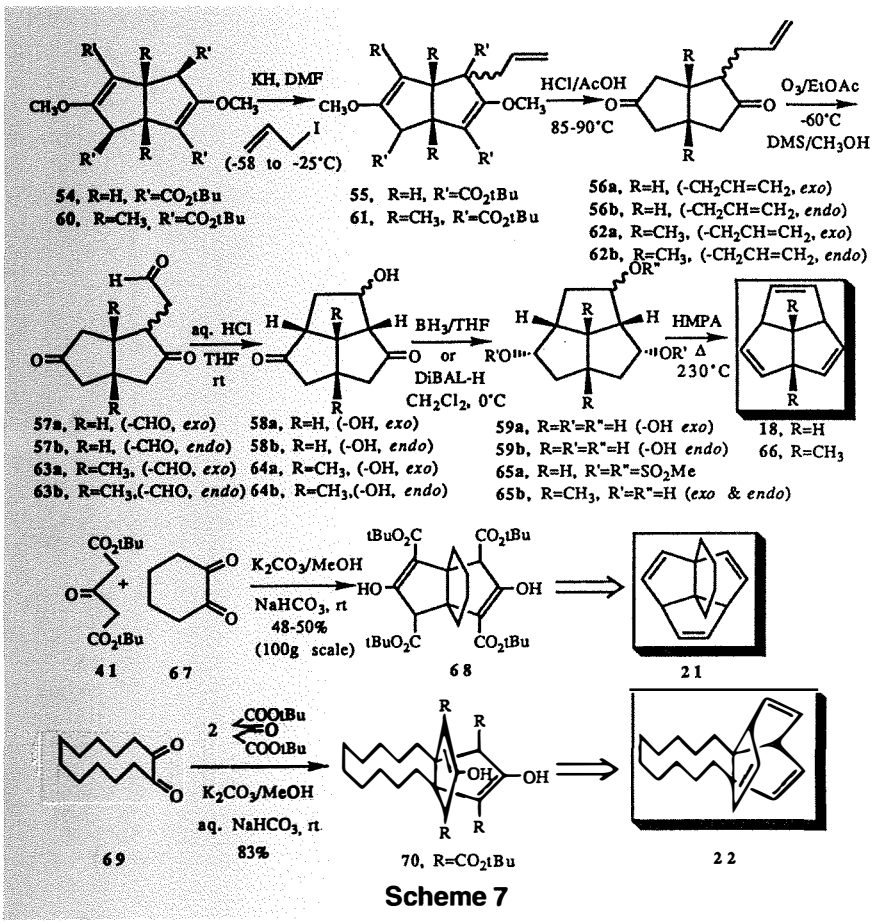
Scheme 5

2. Studies directed toward the synthesis of *cis*-tetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]-dodeca-3,5,7,9-tetraene 17a.

A number of computational studies have been performed to determine the stability and resonance energy of cyclopentapentalenes **17b** and **17c**. Moreover, MNDO[19] and MM2[39] calculations have been employed recently to describe the substantial increase in strain energy for the transition from dihydrodicyclopenta[*cd,gh*]-pentalene (pentaene) **17b** to dicyclopenta[*cd,gh*]pentalene (hexaene) **17c**. Depicted in **Scheme 5** are efforts directed toward the synthesis of tetraene **17a** *via* the Weiss reaction, which ultimately resulted in the synthesis and observation of this molecule **17a** as a transient intermediate. The important steps in the synthesis of dicyclopenta[*cd,gh*]tetraene **17a** were the bisalkylation of bisenol ether **42** to provide the 2,6- and 2,8-diallyl diones **43** and **44** in a 3:2 ratio, and the aldol cyclization of bisaldehyde **45** to generate the tetracyclic diol **46** in 70% yield. The desired 2,6-bisaldehyde **45** was prepared by ozone-mediated cleavage of the olefinic bonds of 2,6-diallyl-*cis*-bicyclo[3.3.0]octane-3,7-dione **43**. Lewis-acid mediated reduction of the diketodiol **46** was executed with diborane and the tetrol which resulted was transformed into the tetraxanthate **47**. Pyrolysis of tetraxanthate **47** in the mass spectrometer indicated the presence of the desired tetraene



Scheme 6



Scheme 7

17a. However, in the laboratory, pyrolysis of **47** with or without the addition of diphenylisobenzofuran (DPIBF) provided only black polymeric material from which **17a** was not isolated.

Observation of the tetraene **17a** under high vacuum in the mass spectrometer, but failure to isolate or trap the compound, illustrates the instability of this highly reactive cyclopentapentalene olefinic system. Even if π delocalization in the 10π annulene **17a** were to occur, the resonance energy (<36kcal/mol) gained from the overlap would not be enough to offset the increase in energy in going from **17a** to **17b**, and the hexaene **17c** would likely be even more unstable.[19]

The two bisalkylated intermediate 2,6- and 2,8-diallyl diones **43** and **44** described above (Scheme 5) were also employed in the synthesis of the perhydrodicyclo-penta[*a,e*]-pentalene **23** and the perhydrodicyclopenta[*a,d*]pentalene **24**, respectively.[23] The corresponding 14π tetracyclic pentalenes have stimulated much study due to the interest in the aromaticity, antiaromaticity and resonance energy of such Hückel systems.[40-42]

The anti-Markovnikov addition of hydrogen bromide to 2,6-regioisomer **43** gave 2,6-bis(3-bromopropyl)-*cis*-bicyclo[3.3.0]-octane-3,7-dione **48** as a mixture of diastereomers in 68% yield. The mixture of epimeric dibromides **48** was then converted into the desired tetracyclic diol **49** with samarium diiodide,[23] as depicted in **Scheme 6**. Treatment of diol **49** with $POCl_3$ generated the tetracyclic intermediate **50** as a mixture of dienes. In a similar approach,[23] a mixture of dienes (see diene **53**) in the dicyclopenta[*a,d*]pentalene system was obtained from the regioisomeric 2,8-diallyl dione **43**, as illustrated in **Scheme 6**.

3. Synthesis of centrosubstituted triquinacenes.

The synthesis and chemistry of triquinacene **18** have been a topic of continuous interest since the molecule was first prepared by Woodward *et al.* in 1964.[43] A number of routes to this triquinene have been devised as part of an approach toward dodecahedrane.[20,43,44] Recently, Serratosa *et al.*[45] have proposed an "aldol approach" to the synthesis of dodecahedrane related to the pericyclic (concerted) route originally proposed for this molecule by Woodward,[43] Müller[46] and Jacobson.[44] Difficulties encountered in the reaction of the two triquinene units in the desired fashion *via* the concave versus the convex faces have hampered previous attempts to execute this convergent reflexive synthesis.[47] However, the unique topography of the centrosubstituted triquinacenes, especially the tetracycles **21** and **22** with [4.3.3] and [10.3.3]propellane molecular structures, may prove to be useful in the pericyclic and aldol approaches to the spherically shaped dodecahedrane. The six or twelve membered rings of **21** and **22**, respectively, should prohibit dimerization *via* the convex face of the triquinacene skeleton in favor of reaction between the two concave faces.

A general approach for the synthesis of these centrosubstituted triquinacenes based on the Weiss reaction has been developed and is depicted in **Scheme 7**. The key steps consisted of the highly selective monoallylation of bisenol tetra-*t*-butyl esters such as **54**, and the acid-catalyzed regio and stereospecific intramolecular aldol condensation of aldehydes represented as **57** to provide the diketo monol **58**. Lewis acid-mediated reduction of **58** with BH_3/THF provided

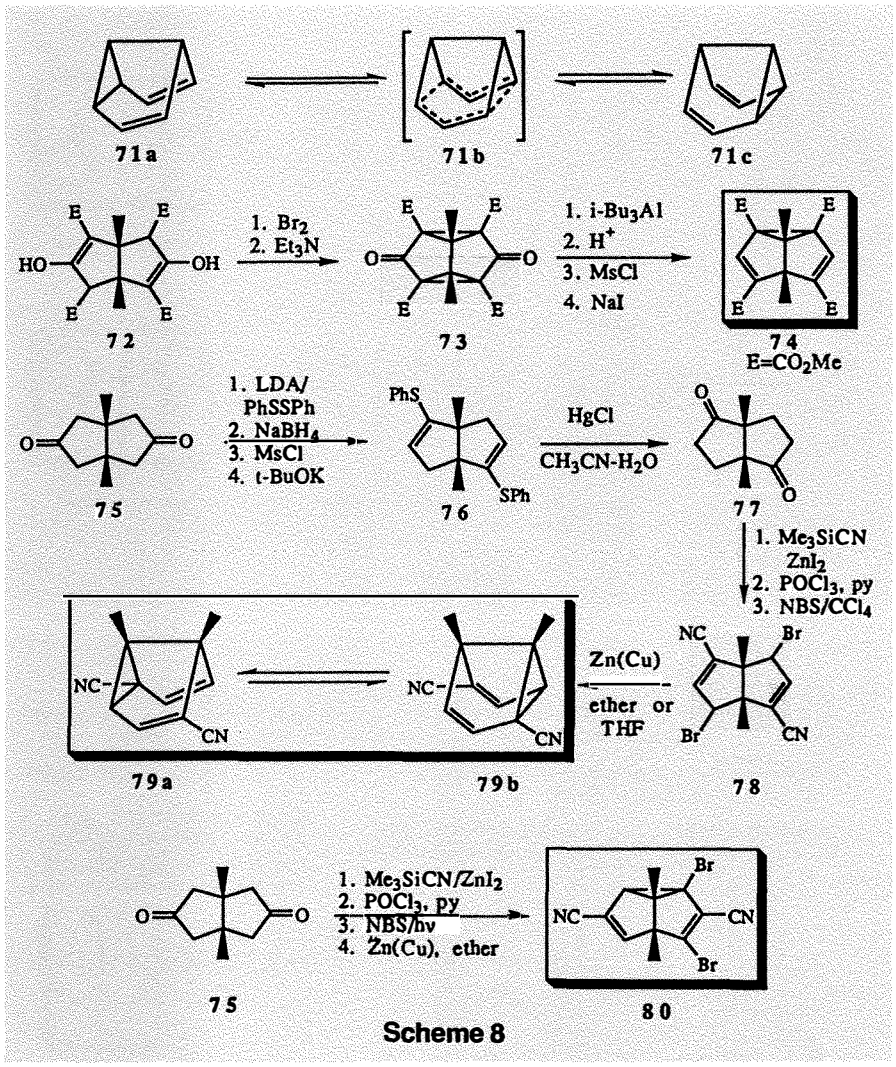
a mixture of stereoisomeric triols which were dehydrated to **18** by an HMPA-mediated sequence.[20] Triquinacene **18** was accompanied by a small amount of the bridgehead olefinic isomer which was easily converted into the thermodynamically more stable triene **18** by acid (*p*TSA)-catalyzed isomerization in methylene chloride-pentane solution.[48]

The versatility of the Weiss reaction has permitted a highly efficient synthesis of other centrosubstituted triquinacenes. Substitution of biacetyl for glyoxal in the condensation provided 1,10-dimethyltriquinacene **66** in excellent yield. Replacement of glyoxal in the process with cyclohexane-1,2-dione **67** provided a simple route to 1,10-cyclohexanotriquinacene **21**,[21] while cyclododecane-1,2-dione **69** was smoothly converted into ellacene **22**.[22]

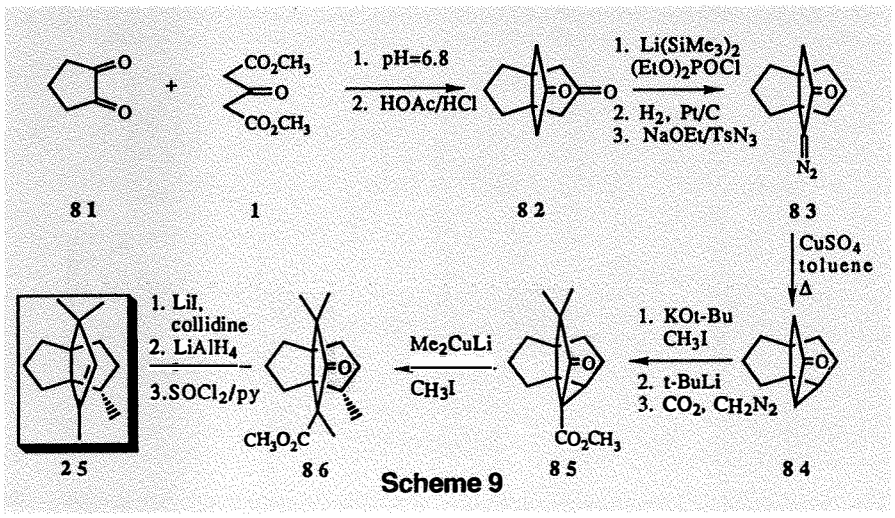
In the case of ellacene, the HMPA-mediated dehydration sequence provided triene **22**, accompanied by several byproducts that contained ether linkages.[22] This problem was circumvented by conversion of the triol into the trisxanthate, which was subsequently heated in HMPA (230 °C) to provide ellacene in 90% yield.[22]

4. Synthesis of semibullvalenes.

Semibullvalene **71** was first prepared by Zimmerman in 1966,[49] and has been studied computationally with regard to a facile Cope rearrangement (**71a** <=> **71c**). This rearrangement has been proposed to proceed through the homoaromatic species **71**b as a transition state, and semibullvalenes provide candidates for potential neutral homoaromaticity.[50] Experimental results[49] have indicated that the activation energy barrier for this Cope rearrangement is as low as 4.8 kcal/mol. It has been suggested that appropriate substitution of the semibullvalene nucleus would lead to a decrease in the activation energy for this process.[51] This interest has fostered many syntheses of substituted semibullvalenes, and indeed the activation energy barrier has been lowered in some cases.[52] Substitution at positions C-1 and C-5 of the *cis*-bicyclo[3.3.0]octane-3,7-dione system derived from the Weiss reaction has functioned as an appropriate starting point for the synthesis of substituted semibullvalenes. Some examples of this approach are included in **Scheme 8**.



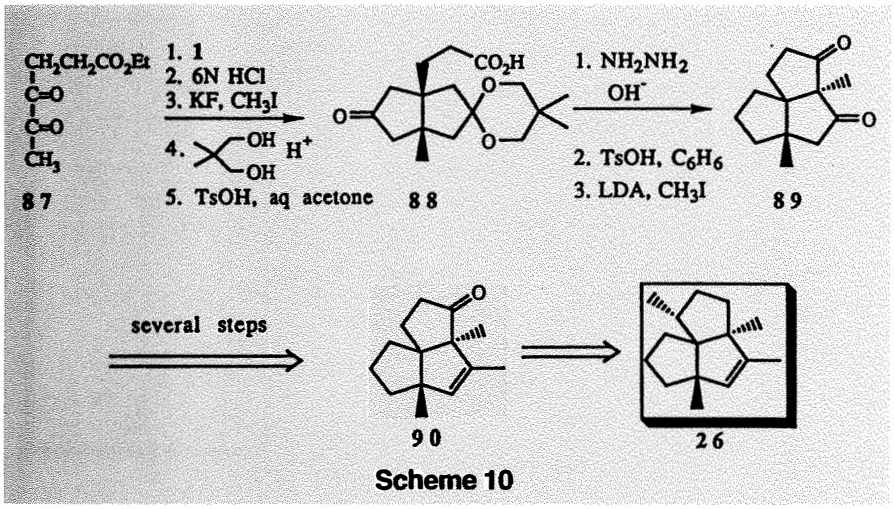
Scheme 8



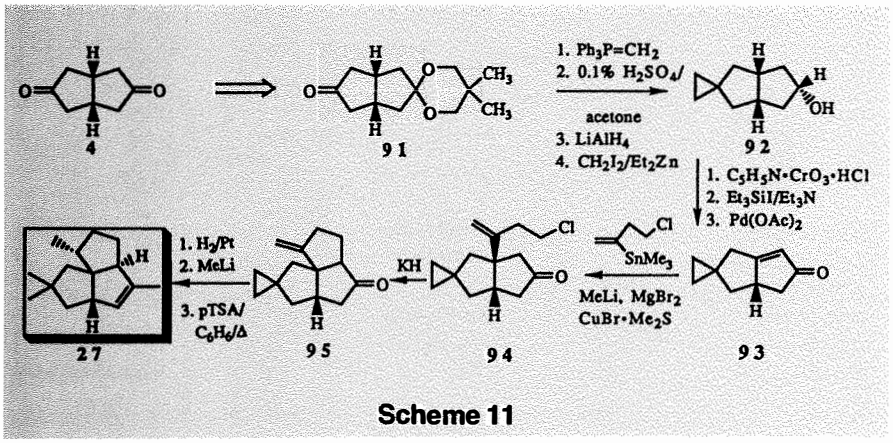
Scheme 9

The synthesis of the novel bisdimethyl semibullvalene tetramethyl ester **74** was reported by Miller, Grohmann *et al.*[52a] in 1981. The preparation began with the *cis*-1,5-dimethylbicyclo[3.3.0]octane-3,7-dione system **72** which underwent bisbromination and base-mediated cyclization to provide the bisketone **73**. The bisketone **73** was then converted into the desired semibullvalene derivative **74**, as illustrated in **Scheme 8**.

The 2,6-dicyano-1,5-dimethylsemibullvalene **79** has been synthesized by Quast *et al.*[52c] from the starting 1,5-dimethyl *cis*-bicyclo[3.3.0]octane-3,7-dione **75**. The key intermediate **77** was obtained from dione **75** *via* several standard transformations. Nucleophilic addition of cyanide anion to bisketone **77** was followed by dehydration of the resulting cyanohydrin intermediate and bisbromination (NBS) to furnish dibromodiene **78** with cyano groups at the desired 2,6-positions. The substituted semibullvalene **79** obtained from diene **78**, was also found to undergo a Cope rearrangement (**79a** <=> **79**b) with a lower activation energy than



Scheme 10



Scheme 11

semibullvalene.[52b,c] However, when the dibromo dicyano derivative **80** was prepared in a similar fashion from **75**,[52d] it was found to undergo the Cope rearrangement with an activation energy higher than the parent semibullvalene.

III. SYNTHESIS OF POLYQUINANE NATURAL PRODUCTS

1. Modhephene.

Modhephene **25**, the first carbocyclic propellane obtained from a natural source, was isolated from *Isocoma wrightii* by Zalkow in 1978[53] and soon attracted considerable interest.[54] A successful stereocontrolled synthesis of racemic modhephene *via* the Weiss reaction was executed and is summarized in **Scheme 9**.[24] The [3.3.3]propellane dione system **82** was prepared by the Weiss condensation of cyclopentane-1,2-dione **81** with dimethyl 3-oxoglutarate **1**. It was converted in 75% yield into the monoketone derivative *via* the enolphosphonate method of Coates,[30a] and was subsequently transformed into the diazoketone **83.** The preparation of the strained, monoactivated cyclopropyl ketone **84** was achieved by heating the diazoketone **83** in toluene in the presence of copper(II) sulfate. This ultimately permitted regiospecific incorporation of the *gem*-dimethyl group into the molecule. The flanking *gem*-dimethyl groups protected the carbonyl function from the usual addition of alkyllithiums. Instead, *t*-butyllithium abstracted the bridgehead proton alpha to the carbonyl group, and the bridgehead anion was transformed into the methyl ester **85**. Cuprate [dimethylcopper(I)lithium] addition to the cyclopropane ester **85** occurred with complete stereospecificity to provide the modhephene skeleton **86** in 85% yield. The tetramethyl derivative **86** was then converted into modhephene **25** in high yield in three routine steps.

2. Isocomene.

The sesquiterpene isocomene **26** is a representative member of a growing class of compounds isolated from natural sources which possess the tricyclo-[6.3.0.0^{1,5}]undecane skeleton. It was isolated[55] independently by Zalkow from *Isocoma wrightii* and Bohlmann from *Berkheya radula*. Of the several synthetic strategies directed toward isocomene,[56] the Weiss reaction[57] appeared best suited for the synthesis of this molecule through the parent 1,5-disubstituted diquinane ring system. This synthesis has been carried out by Dauben and Walker[25] (**Scheme 10**). The approach began with the condensation of the α-dicarbonyl ethyl ester **87** with dimethyl 3-oxoglutarate **1**, followed by hydrolysis to provide the diketoacid derivative. The two carbonyls of the diketo ester intermediate were differentiated from each other by formation of the bisketal, followed by partial hydrolysis to afford the monoketal **88** in good yield. The keto acid intermediate was obtained by Wolff-Kishner reduction of monoketal **88** and subsequent acidic hydrolysis of the protecting ketal function. The acid and base sensitive tricyclic diketone system was then obtained in 88% yield by *p*TSA-catalyzed cyclization in refluxing benzene, according to the method of Oehldrich.[57] Diketone **89** was transformed by standard means into monoketone **90**, which was efficiently carried on to isocomene. This route is of general interest for the preparation of tricyclo[6.3.0.0^{1,5}]undecane ring systems.

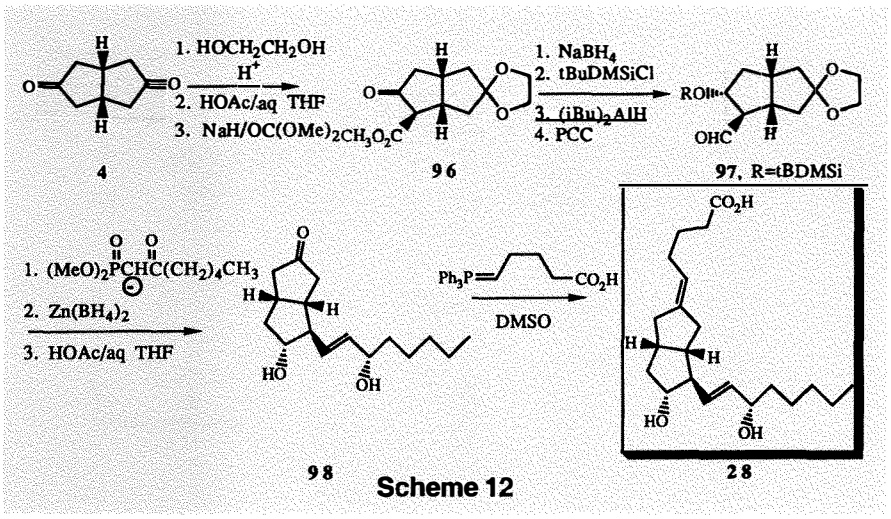
3. Pentalenene.

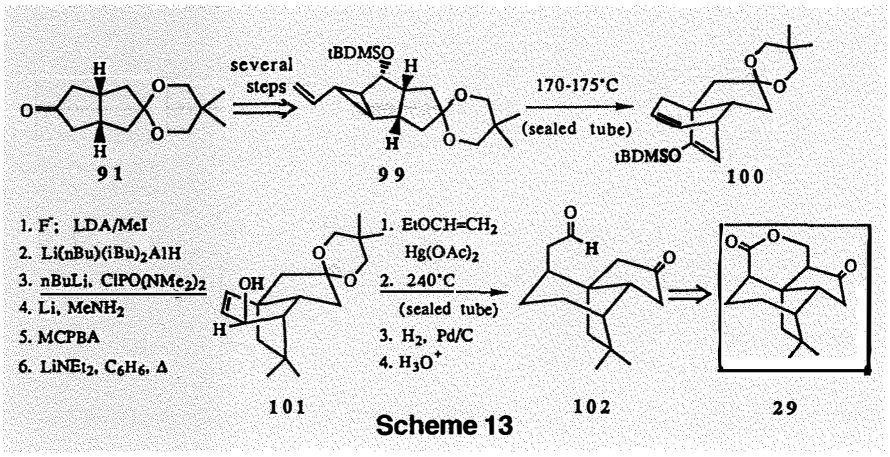
Pentalenene **27**, isolated from *Streptomyces griseochromogenes*,[58] represents the parent carbon skeleton of the pentalenolactone family of sesquiterpene antibiotics. It has been demonstrated by Cane *et al.*[59i] that oxidative catabolism of pentalenene generates pentalenic acid, pentalenolactone and other members of the pentalenolactone family of natural products. The synthesis[59] of pentalenene *via* the Weiss reaction has been reported by Piers *et al.*[26] (**Scheme 11**). The monoketal **91** formed from *cis*-bicyclo[3.3.0]octane-3,7-dione **4** was converted into the cyclopropyl bicyclo-[3.3.0]octane monol **92** using standard Wittig/Simmons-Smith conditions. Oxidation of the hydroxyl function of **92** to a ketone and conversion of this material into an enol ether was followed by oxidation with Pd(OAc)2 to furnish the key intermediate enone **93**. A cuprate directed conjugate addition of the bifunctional Grignard reagent 4-chloro-2-trimethylstannylbut-1-ene to enone **93** generated the chloroketone **94**. This material was then subjected to a base-mediated intramolecular alkylation to furnish the tricyclic skeleton of **95**. Reduction of the double bond and hydrogenolysis of the cyclopropane ring of **95** was effected under conditions of catalytic hydrogenation to provide a mixture of diastereomeric isomers. Treatment of the carbonyl functions which remained in the diastereomeric isomers with methyllithium and dehydration of the tertiary alcohol which resulted provided (±)-pentalenene **27**, accompanied by another stereoisomer.[26]

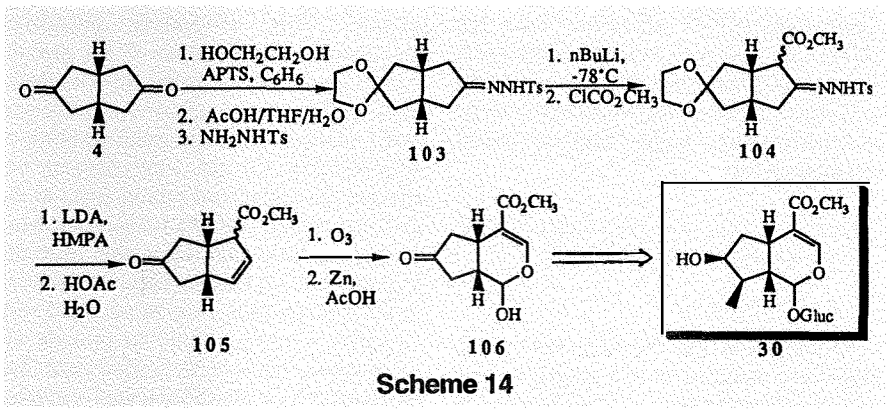
4. 6a-Carbaprostaglandin-I_2.

Prostacyclin, a substance of biological importance in the prevention of stroke, thrombosis, and heart attack, is very unstable due to the presence of a labile enol ether linkage in the molecule. The preparation of a chemically stable analogue with therapeutic potential provided the impetus to search for a derivative of this molecule by Nicolaou[27] and others.[60] A synthesis of this target, 6a-carbaprostaglandin-I_2 **28** is depicted in **Scheme 12**.

The *cis*-bicyclo[3.3.0]octane ring system comprises the basic skeleton of the alicyclic analog **28**. Ready access to diquinane **28** has been gained using the Weiss reaction by Nicolaou. Monoketalization of **4** and introduction of a formyl group into the ring system at C-6 *via* methyl ester **96** furnished aldehyde **97** by standard procedures as illustrated. The aldehyde **97** was then subjected to a Horner-Wadsworth-Emmons olefination to introduce the side chain at C-6. Reduction of the carbonyl function in the side chain with $Zn(BH_4)_2$ and hydrolysis of the ketal protecting group generated the carbonyl compound **98** with the correct stereochemistry at the side chain. A Wittig reaction of the ketodiol **98** with 4-carboxybutyl(triphenyl)-phosphorane dissolved in DMSO provided a mixture of olefinic isomers rich in 6a-carbaprostaglandin-I_2 **28**.[28]







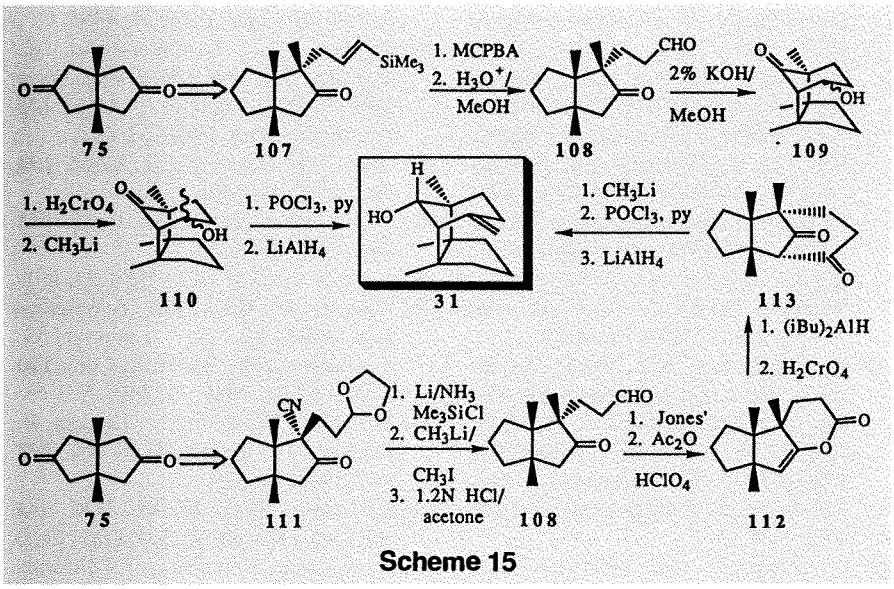
5. Quadrone.

Interest in the total synthesis of the polyquinane quadrone isolated from the fungus *Aspergillus terreus*[61] has been stimulated by its cytotoxic activity, as well as a unique carbon skeleton. The preparation was first reported by Danishefsky *et al.*,[62a] and since then at least seventeen other syntheses of racemic quadrone have been reported.[28,62] The synthesis of naturally occurring (-)-quadrone and its enantiomer has recently been accomplished by Smith *et al.*[62c]

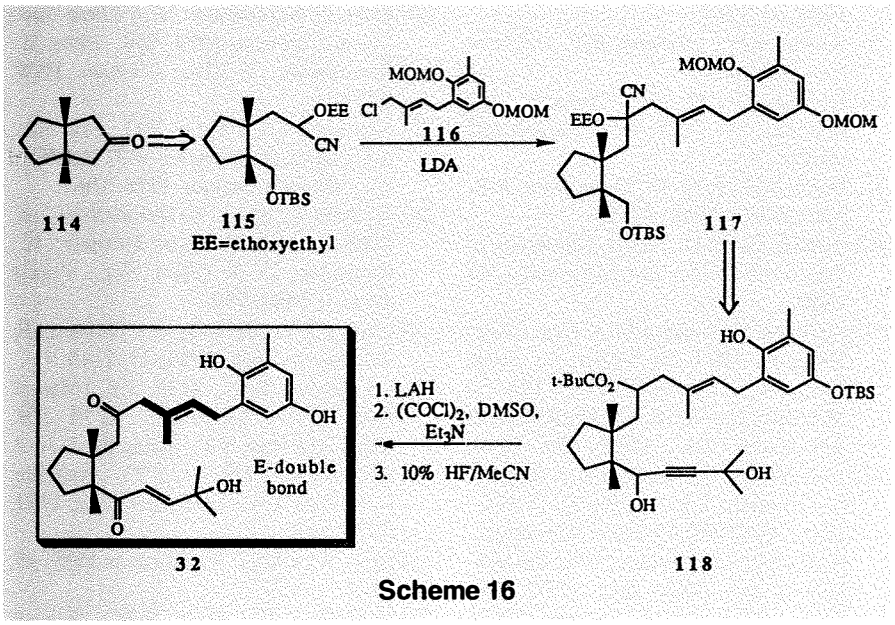
An approach to quadrone *via* the Weiss reaction has been developed by Piers and Moss[28a] and is outlined in **Scheme 13**. The pivotal step of this synthesis involved a thermal (Cope) rearrangement of the highly functionalized vinylcyclopropane derivative **99**, which had been obtained from the monoketal **91** of *cis*-bicyclo[3.3.0]octane-3,7-dione **4**. The tricyclic intermediate **100** was then converted into the ketoaldehyde **102** *via* the homoallylic alcohol **101** in ten steps, as illustrated in **Scheme 13**. The ketoaldehyde **102** was also employed as an intermediate in the total synthesis of quadrone by Burke *et al.*[62c] In addition the Weiss reaction has been utilized in another synthesis of the quadrone skeleton by Cooper *et al.*[28b]

6. Loganin.

The glucoside loganin **30** was first isolated from *Strychnos nux vomica*,[63a] and is a widely distributed product of secondary plant metabolism. It has proven to be an important monoterpene in plant biochemistry due to the role this intermediate plays in the biosynthesis of monoterpene indole alkaloids and other natural products.[63] Structurally, loganin cannot be classified as a polyquinane; however, a precursor of loganin has been synthesized by Caille *et al.*[29] starting from the *cis*-bicyclo[3.3.0]octane-3,7-dione **4**, as depicted in Scheme **14**. It is important to note that the stereochemistry of the *cis*-ring junction of **4** is transformed into the *cis*-ring junction of loganin (see **30**). A regioselective Shapiro reaction was employed to convert hydrazone **104** *via* **103** into the β,γ-unsaturated ester **105**. Hemiacetal **106** was obtained from unsaturated ester **105** by ozonolytic cleavage of the double bond, which was followed by spontaneous cyclization of the resulting dialdehyde and dehydration to form the key α,β-unsaturated ester system of **106**. This hemiacetal **106** had been transformed earlier into loganin **30** by Büchi *et al.*[63b] in 1973.



Scheme 15



Scheme 16

7. Gymnomitrol.

Gymnomitrol **31**, a tricyclic sesquiterpene, was first isolated from the liverwort *Gymnomitrion obtusum* (L.) Pears as a major metabolite by Connolly and coworkers.[64] The 4,8-methanoazulene carbon skeleton which contained five adjacent chiral centers, three of which were quaternary, attracted the attention of Coates,[30a] Paquette[30b] and others[65] due to its molecular complexity. Both of the syntheses[30] of **31** by Coates and Paquette began with *cis*-1,5-dimethyl bicyclo[3.3.0]octane-3,7-dione **75** which was readily available on large scale[5b] from the Weiss reaction.[1] Both of these syntheses, as depicted in **Scheme 15**, proceeded through a common ketoaldehyde intermediate **108** which was prepared by independent routes. The key reaction involved in the synthesis of the bicyclic ketoaldehyde **108** by Coates *et al.* proceeded with the alkylation of a ketonitrile intermediate generated from *cis*-dimethylbicyclo[3.3.0]octane-3,7-dione **75** *via* the cyanoketone **111**. This was followed by a reductive methylation with methyllithium and hydrolysis of the acetal protecting group. Paquette and coworkers, on the other hand, converted **75** into an α-methylene carbonyl compound, and then carried out a cuprate-mediated 1,4-addition of the required Grignard reagent (vinyl silane) to provide an α-ketocarbanion. This anion was alkylated from the convex face of the bicyclo[3.3.0]octane system to provide **107** with the required stereochemistry. The vinyl silane **107** was then oxidized to the ketoaldehyde **108** and subsequently underwent transannular aldolization (base-catalyzed) to furnish monol **109.** Oxidation of the hydroxyl group followed by regioselective addition of methyllithium to the carbonyl which resulted generated the gymnomitrol precursor **110**. This material underwent dehydration and reduction to provide **31**, as shown in **Scheme 15**. In the Coates route, however, the third ring of **31** was generated through enol lactone **112** to provide the transannular dione **113**. The remaining steps were similar to those of Paquette as illustrated (**Scheme 15**).

8. Bifurcarenone.

Bifurcarenone **32**, an inhibitor of mitotic cell division, was isolated from *Bifurcaria galapagensis* by Fenical *et al.*[66] in 1980. This natural product contains a structurally unique monocyclic diterpenoid moiety in combination with a hydroquinone C7-unit. Additionally, the structure for bifurcarenone proposed originally possessed a trisubstituted double bond with the thermodynamically less stable *Z*-configuration. These molecular features attracted the interest of synthetic chemists. Use of the Weiss reaction permitted the incorporation of the 1,2-*cis*-fused dimethyl functions into the synthetic route from the beginning, as reported by Mori and Uno.[31] The *cis*-1,5-dimethylbicyclo[3.3.0]octane-3,7-dione **75** was converted into the monoketone **114** *via* standard procedures.[31] This retention of configuration from dione **75** has provided a route to bifurcarenone **32** relatively free of other stereochemical constraints. The carbonyl group of monoketone **114** was cleaved and the intermediate which resulted was converted into cyanoether **115**. Alkylation with allylic chloride **116** provided cyanoether **117**. The stereochemistry of the remaining *E*-double bond of the side chain was controlled by alkylation and then reduction of the triple bond of acetylene derivative **118**, as shown in **Scheme 16**. The same reaction sequence which employed an aromatic C7-unit and a *Z*-double bond was also executed to generate an olefin with the same structure as that originally proposed for the natural product, a trisubstituted double bond of the *Z*-configuration. However, the synthetic material *via* this route was not identical in all respects to the natural **32**. Consequently, the structure of bifurcarenone with a *Z*-configuration was revised to that with the *E*-configuration depicted in **32**. At this point, the physical and spectral properties of synthetic **32** were found to be identical to those of bifurcarenone in all respects.[31]

IV. CONCLUSION

The interest in molecules which contain polyquinane (cyclopentanoid) ring systems

has been well documented in recent years.[3a,60,67] In addition, the isolation of cyclopentanoid natural products which contain novel structural features and/or important biological activities has stimulated further interest in this area of research. The synthesis of these molecules has formed one of the most active areas of study in the past few years. A number of new reactions and new synthetic methods for the preparation of cyclopentanoid compounds have consequently been developed.[67] Among them, the Weiss reaction has been shown to be a versatile approach for the synthesis of both non-natural polyquinenes (part II) and polycyclopentanoid natural products (part III). The use of an alkaline medium (pH = 8.3) for the Weiss reaction has greatly increased the yields, reduced the byproducts to a minimum and permitted large-scale preparations without difficulty.[3a,5b] The modified conditions of Ginsburg have increased the effectiveness of this process with regard to the reaction of α-dicarbonyl compounds which are only sparingly soluble in water.[12b] It has been shown that the Weiss condensation is the simplest route for the preparation of both mono and 1,5-disubstituted *cis*-bicyclo[3.3.0]octane systems.[3a] Furthermore, the presence of two carbonyl moieties at positions C-3 and C-7 of the carbon skeleton has rendered this process a facile route to polyquinenes.[3a] The *cis* ring junction is of importance in the synthesis of natural products since it simplifies the route to such complex structures, especially in regard to stereochemistry. It is reasonable to anticipate that this synthetic method will be applied to the construction of many more polyquinanes and polyquinenes of complex structure in the future.[68]

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68) This paper is dedicated to the memory of Dr. Ulrich Weiss whose interest in the synthesis of cyclopentanoid compounds provided the impetus for this review.

About the Authors

Xiaoyong Fu

Xiaoyong Fu received his B.S. degree in 1982 in pharmacy from Hunan College of Traditional Chinese Medicine and his M.S. degree in pharmaceutical chemistry in 1985 from the National Institute for the Control of Pharmaceutical and Biological Products (P.R. China). He then worked as a research associate in the same institute. Under Professor Guoshi Tu, while in China, he worked on the isolation, structure elucidation and quantitative determination of isoquinoline alkaloids from *Corydalis* species that have been widely used as analgesics in Chinese medicine. He came to the University of Wisconsin-Milwaukee in 1987 and joined Professor Cook's group as a research assistant. While in Milwaukee he has been involved in the synthesis of strained polyquinenes *via* the Weiss reaction, as well as completing a preparation of the centrosubstituted triquinacene, ellacene. Attempts to dimerize this triene to provide a substituted dodecahedrane were also carried out. He has also worked on an approach to the synthesis of [5.5.6.6]fenestranes with regard to the preparation of molecules which may house a planar tetracoordinate carbon atom. Recently, he has achieved an enantiospecific total synthesis of the ajmaline-related alkaloids, (-)-suaveoline, (-)-raumacline and (-)-N_b-methyl-raumacline. He received his Ph.D. degree in organic chemistry in 1992 from the University of Wisconsin-Milwaukee.

James M. Cook

Professor James Cook received his B.S. degree in Chemistry, with honors, in 1967 from West Virginia University and his Ph.D. in 1971 from the University of Michigan. While at Michigan, he worked on the isolation and structure determination of monomeric and antihypertensive bisindole alkaloids from *Alstonia* species. During 1972-73, he was a National Institutes of Health Postdoctoral Fellow at the University of British Columbia working on the synthesis of the antitumor alkaloids vincristine and vinblastine. He joined the faculty of the University of Wisconsin at Milwaukee in 1973 and has been Professor since 1986. An organic chemist by training, Professor Cook's interests include synthetic organic and natural products chemistry, as well as medicinal chemistry. His current research interests include the use of the chirally controlled Pictet-Spengler reaction for the total synthesis of antileukemic, antitumor, and antihypertensive indole alkaloids as well as the chemistry of reserpine, quinidine, and quinine in relation to their biological activity. This has culminated recently in an enantiospecific synthesis of the sarpagine and ajmaline-related alkaloids, alstonerine, suaveoline, and raumacline. His group has recently carried out seminal studies on the use of the Weiss reaction for the synthesis of polyquinanes and is currently investigating this reaction as a source of strained polyquinenes to study bonding character in organic chemistry. The major thrust of his interest in medicinal chemistry is directed toward investigation of the structure, topology, and function of the benzodiazepine (Valium) receptor. β-Carbolines and diindoles which have been prepared in this study are important tools for studying anxiety, convulsions, sleep, and memory-learning, as well as reversal of the effects of Valium-alcohol or barbituate-alcohol overdose.

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How We Stumbled into Peptide Chemistry

A Curiosity Driven Search for New Chemical Reactions

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About Our Cover:

This painting (oil on canvas, 20 x 27in.) from the collection of The Saint Louis Art Museum (St. Louis, MO) is entitled **Capriccio: An Island in the Lagoon with a Pavilion and a Church**. The Italian artist, Antonio Canal, known as Canaletto (1697-1768), specialized in views of Venice and the Venetian countryside. The English in particular coveted images of the views and ruins they had admired on their visits to Italy. Sometimes, these scenes were inspired by but not faithful to the topographical details they purported to document. They were imaginary combinations of landscape and landmarks, known by the Italian term *capricci*. The seemingly precise line of Canaletto's architecture often denies these scenes a sense of fanciful invention; they masquerade as recorded fact.

In the St. Louis painting, the artist has combined the Venetian lagoon with some buildings from nearby Padua and a campanile from yet another source to produce a grouping of simple structure and subtle balance. The light, as always in Canaletto's work, is an important element of the painting. It bathes the buildings in radiant tones and confers upon the whole an almost unnaturalistic clarity. Human figures are secondary players in this carefully contrived arrangement. Their casual poses as they pursue various tasks belie their careful placement in the structural logic of the whole; at times they even echo the larger architectural forms. The virtuoso handling of paint, the warmth and clarity of the light, and the mastery of composition make Canaletto's paintings as appealing today as they were to his eighteenth-century clients.

This painting was one of a pair of imaginary views; its pendant included a middle ground column surmounted by a crouching figure and a domed church. The paintings were purchased by Lord Boston (1707-1775) and remained in the family until they were sold at auction in 1942.

Lab Notes

We have found a very simple method for the accurate delivery of ozone, even in submilligram amounts, into reaction mixtures.[1] Upon describing this method to many other chemists we were surprised that none had heard of this being done and are thus presenting it to your readers so that they may use it. The method consists of drawing a sample of the ozone-oxygen gas mixture from the effluent stream of an ozonizer into a 50 or 100ml syringe fitted with a small diameter Teflon® tube, measuring the ozone content, and delivering a measured amount of the gas into the reaction mixture. We measure the ozone concentration, typically 1mg/50ml when the ozonizer is set to deliver 15mg of ozone per minute, by injecting a measured portion of the sample into a solution of excess 2,3-dimethyl-2-butene in CD_3OD in an NMR tube. The ^1H NMR spectrum of the resulting reaction mixture contains three singlets due to alkene, acetone, and the CD_3OD adduct of acetone carbonyl oxide. Integration of the spectrum allows one to calculate the ozone content of the gas. The ozone content does not change upon storage of the gas in the syringe for an eight hour period.

(1) Kopecky, K.R.; Molina, J.; Rico, R. *Can. J. Chem.* **1988**, *66*, 2234.

Karl R. Kopecky
Professor of Chemistry

University of Alberta
Edmonton, Alberta
Canada T6G 2G2

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See page 69 for information on the new Aldrich Library of ^{13}C and ^1H FT-NMR Spectra.

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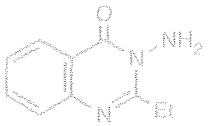
"Please Bother Us."

by



Professor Robert Atkinson of the University of Leicester, Leicester, UK, suggested we offer this amino quinazolinone. Dr. Atkinson discovered that the *N*-acetoxy derivative of this amine (generated by lead tetraacetate oxidation) allows oxidative addition of nitrogen to alkenes. This method opens up a convenient pathway to aziridines![1] A stable (-20°C) solution of the derived reagent is not only useful for the aziridination of simple alkenes, but gives *syn* stereoselectivity with cyclohex-2-enols and *anti* stereoselectivity with the corresponding acetates.[2] Reaction with vinylsilanes and vinylstannanes gives silyl or stannyl substituted aziridines,[3] while enol ethers and silyl ketene acetals lead eventually to α-amino carbonyl products.[4]

Naturally, we added this product to our listings.

(1) Atkinson, R.S.; Kelly, B.J. *Tetrahedron* **1989**, *45*, 2875. (2) Idem *J. Chem. Soc., Perkin Trans. 1* **1989**, 1515. (3) Idem *J. Chem. Soc., Chem. Commun.* **1989**, 836. (4) Atkinson, R.S.; Kelly, B.J.; Williams, J. *ibid.* **1992**, 373.

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

How We Stumbled Into Peptide Chemistry

Dieter Seebach
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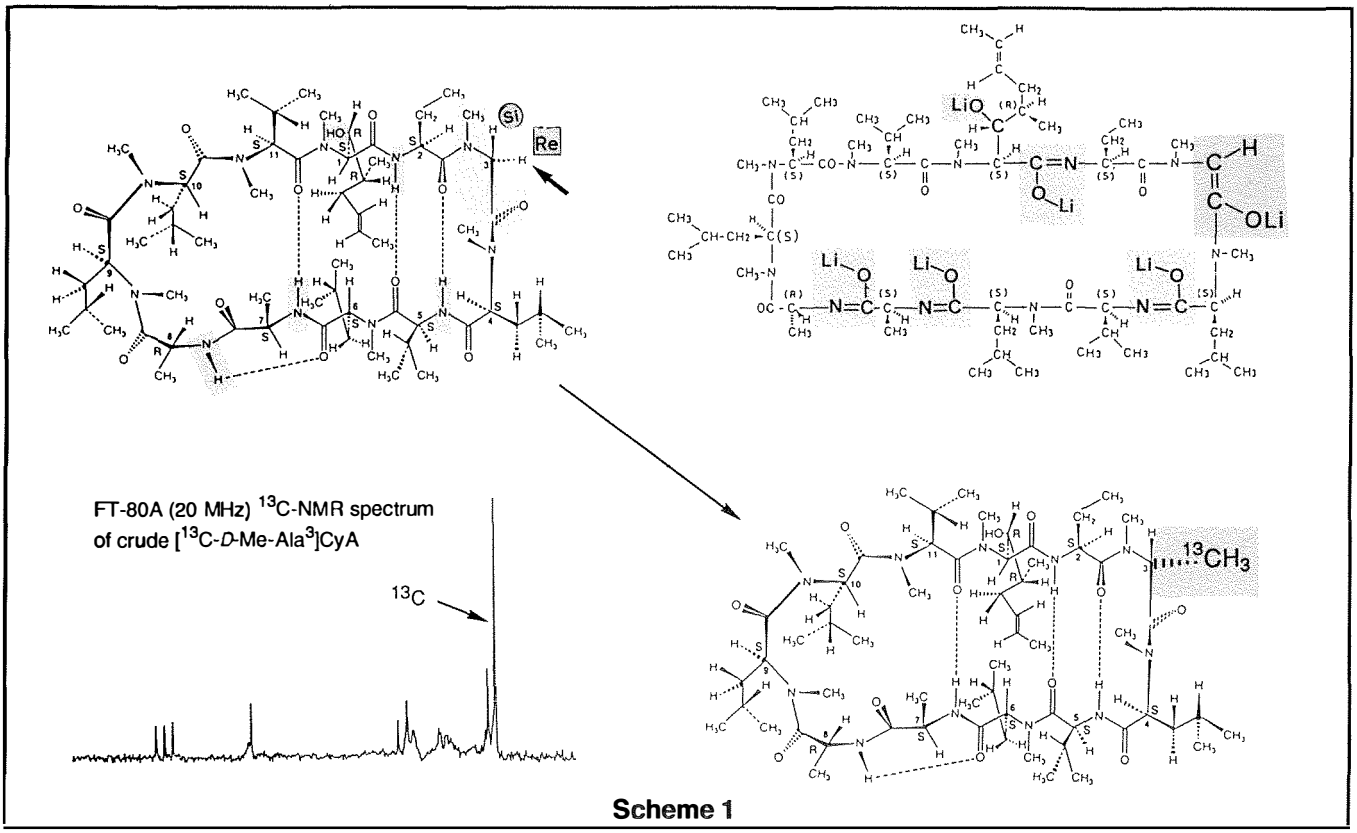
In the fall of 1983 I returned to Zürich from a consulting visit in Basel with a bottle full of cyclosporin A (CyA), the immunosuppressive cyclic undecapeptide used so successfully to fight rejection of transplanted organs. The sample of CyA was given to me, in kind of a mocking mood, after I had proposed to generate an enolate of the peptide and thus derivatize it. I gave the compound to Reto Naef, who had finished his thesis work and was ready to defend his dissertation and to go to the USA for a postdoctoral position. I persuaded Reto, a gifted experimentalist and enthusiastic chemist, to treat a solution of the peptide in THF with excess LDA and try to alkylate it with $^{13}CH_3I$ - for ready detection of any products by ^{13}C-NMR spectroscopy. The result is outlined in **Scheme 1.** Apparently through a hexalithio derivative H^{Re} of the one and only sarcosine moiety in the peptide was replaced by a CH_3 group with a selectivity of *ca.* 7 : 1, as shown by comparison with authentic samples of the CyA analogs containing (*R*)-

Professor Dr. Dieter Seebach (right) receiving the 1992 American Chemical Society Award for Creative Work in Synthetic Organic Chemistry from Dr. Stephen J. Branca, Director, New Products.



Scheme 1

or (*S*)-MeAla instead of Sar at position 3 of the peptide.[1] In the meantime, this our first encounter with the chemistry of peptides has led to the establishment of a highly active sub-group in our laboratory and to a series of publications.[2-12]

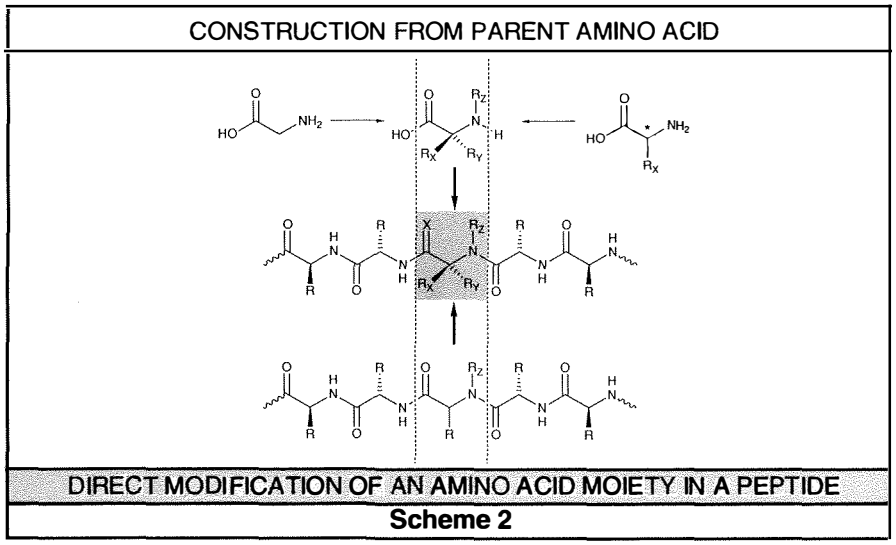
INTRODUCTION

Modification *vs.* Synthesis of Peptides

Inspired by the alkylation of CyA we decided to look for general methods which would allow us to modify a given peptide and thus to prepare analogs more economically than by the usual synthetic route in which the desired amino acid unit is incorporated in the course of the peptide construction from building blocks (**Scheme 2**). It is trivial, of course, and more or less well established to modify a peptide by reaction of a side chain functional group as present in the proteinogenic amino acids Arg, Asp, Cys, Glu, His, Lys, Met, Ser, Thr, Trp and Tyr. What we decided to try were modifications of the peptide backbone itself. The journey turned out to be a quest of solubility (of peptides and their derivatives in organic solvents); eventually effects were discovered which could be exploited for such mundane procedures as solid phase machine synthesis or HPLC separation and purification of peptides.

Thionation, Serine Dehydration, and Electrolysis with Peptides - merely *cosmetic* alterations?

Incorporation of a C=S in place of a C=O group in a peptide is normally achieved by preparing a thiono-dipeptide which is then further elaborated to the desired product. We used Lawesson's reagent, the standard method for C=O to C=S conversion, directly on the undecapeptide CyA (again!) to find that of the eleven C=O groups only those which are not part of an N-methyl amide react. Depending on the conditions up to four sulfurs were introduced, and nine different sulfur derivatives of CyA were isolated in pure form.[3] Of the many surprising properties of these analogs, we found the conformations of [$^1\Psi^2$,CS-NH]CyA most intriguing (**Figure 1**). In addition to conformer A, which is essentially identical to that of CyA in organic solvents, the $CDCl_3$ solution of CyA with a thiocarbonyl group on MeBmt (amino acid No. 1) contains a second conformer B having a *cis*-peptide bond on the Sar moiety in position 3. Since A and B are present in almost equal amounts, new NMR techniques had to be developed to tackle the problem of structure determination.[3] Those engaged with modelling and molecular dy-



Scheme 2

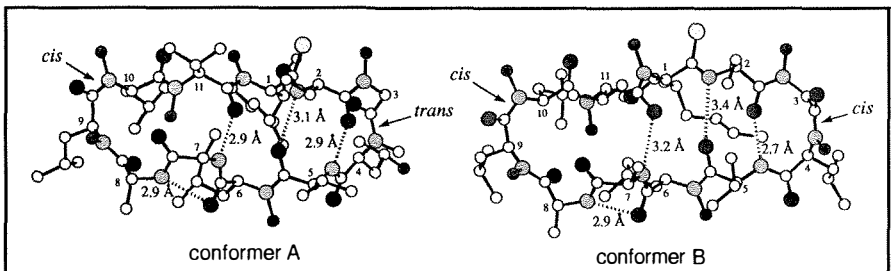
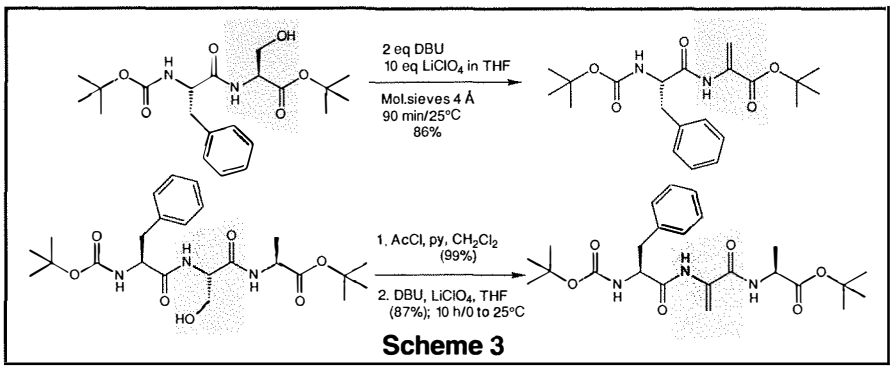
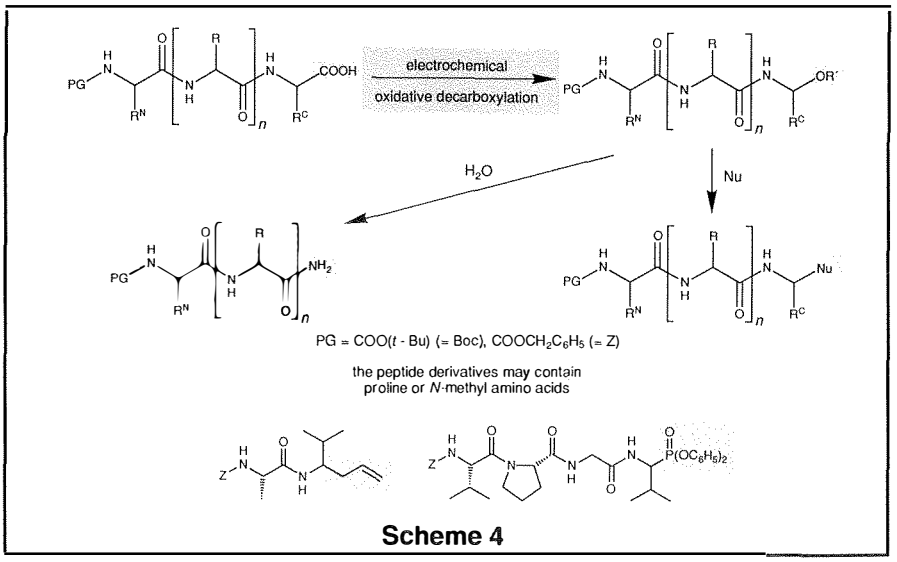


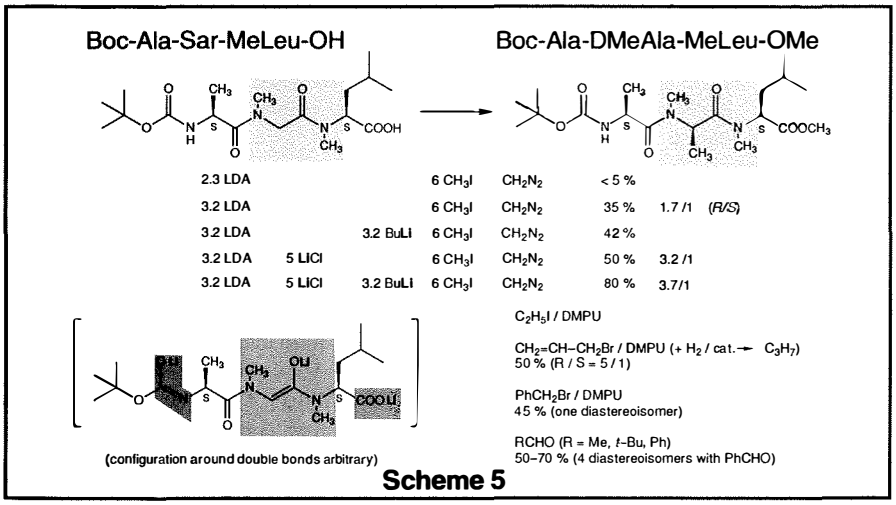
Figure 1. *Conformers of Thio-Cyclosporin ([$^1\Psi^2$,CS-NH]CyA) in $CDCl_3$ determined by NMR spectroscopy.[3] Colorcode: C in chain white, CH_3N grey, N blue, O red, S yellow.*



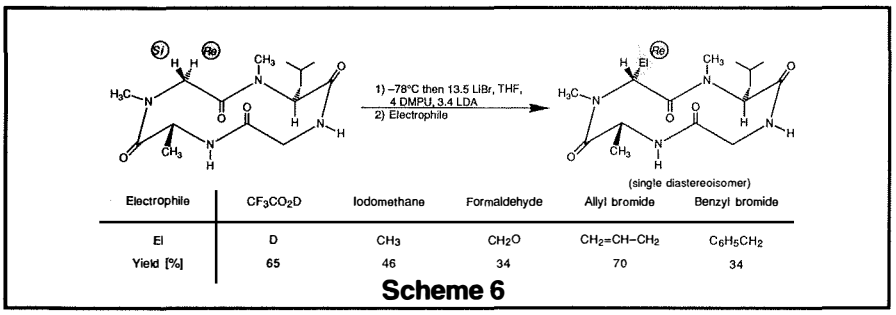
Scheme 3



Scheme 4

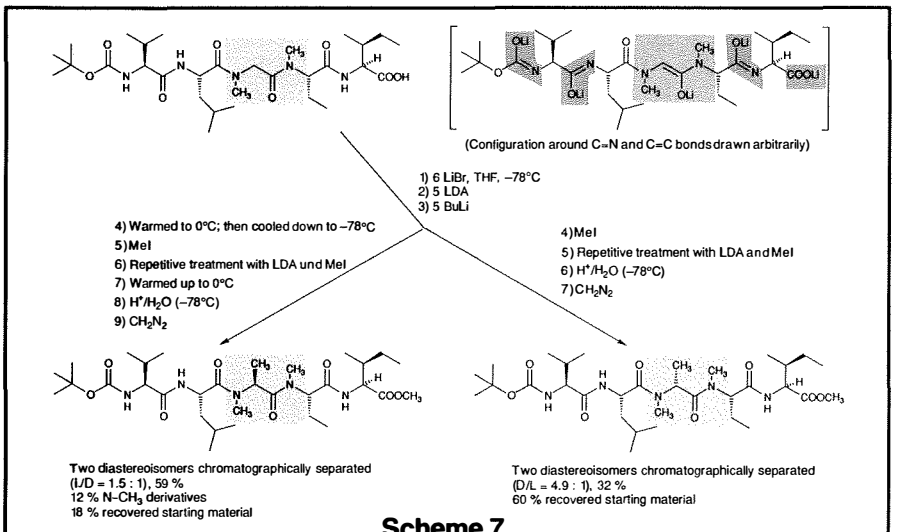


Scheme 5



Electrophile	CF_3CO_2D	Iodomethane	Formaldehyde	Allyl bromide	Benzyl bromide
El	D	CH_3	CH_2O	CH_2=CH–CH_2	$C_6H_5CH_2$
Yield [%]	65	46	34	70	34

Scheme 6



Scheme 7

namics of peptides are called upon to reproduce the rather dramatic remote structural change caused by O/S-substitution!

Another peptide alteration, achieved at the site of a serine, was discovered in the course of tests carried out in connection with our work on solid phase synthesis (*vide infra*). As outlined in **Scheme 3**, the serine moiety can be dehydrated directly or in a two-step sequence, using DBU/$LiClO_4$ as a base in THF.[12b,c] The didehydro alanine containing peptides thus available are known to undergo Michael additions leading[13] - in the overall process - to peptides in which the serine C-OH bond has been replaced by a C-C bond.

Finally, we have subjected oligopeptides to anodic oxidation (**Scheme 4**).[4] As with other α-heterosubstituted carboxylic acids, no coupling (Kolbe electrolysis) but double oxidation (Hofer-Moest reaction) occurs, with formation of acetal derivatives (**Scheme 4**). These can be used as intermediates leading to a peptide C-terminal amide (by hydrolysis), to a peptide containing a phosphonate instead of the carboxylate end group (by a Michaelis-Arbuzov substitution), or to peptide analogs with a lipophilic aliphatic carbon chain in place of the carboxyl group (for instance by reaction with allyl silanes/$TiCl_4$).[4] So far, we have not found conditions applicable for preparative electrolyses of peptides containing more than ten amino acids.

In the reactions of peptides discussed in this section solubility is not a problem: CyA is more soluble in organic media than in water, the peptides used for serine dehydrations are soluble under the conditions specified, and the electrolyses are preferably done in the polar protic solvents acetic acid or methanol in which simple oligopeptides are usually soluble.

Enolates of Peptides and Backbone Alkylations

Solubility *raises its ugly head*[14] when polylithiated peptides are generated in attempts to form the enolates of glycine moieties within peptides. Probably aggregation of lithiated sites leads to large molecular assemblies comparable to cross-linked polymers. We have found that in many cases clear and readily stirrable solutions of polydeprotonated compounds in THF can be obtained, even at low temperatures, in the presence of excess of LiX additives (normally, we use LiCl, LiBr or $LiNR_2$). We assume that the added salts form mixed aggregates with the polylithiated species, and thus solubilize them.[1a,6] Another effect is that, depending on the type of Li salt used the regio- and stereoselectivity of the reaction may change.[1a,5] Full accounts on alkylations of linear tri- and hexapeptides[6a] and of cyclic tetrapeptides[6b] have been published; for two examples see **Schemes 5** and **6.** Often addition of the cosolvent DMPU, a cyclic urea and a non-toxic substitute for HMPA,[15] leads to better results. Recently, we noticed that the stereochemical course of these reactions can be reversed by a simple change of conditions: the penta-lithio derivative of a pentapeptide containing a sarcosine enolate gave rise to a product with an (*R*)-MeAla component (selectivity 4.9 : 1) when the reaction mixture was kept at dry-ice temperature throughout, while the newly formed stereogenic center had the (*S*)-configuration (ratio 1.5 : 1) when the temperature was allowed to rise to 0°C (**Scheme 7**).[12a] In all these reactions a peptide containing stereogenic centers in α-carbonyl positions is treated with very strong bases. Still we do not observe epimerizations, or racemizations of the amino acid components as proved by acidic hydrolysis, derivatization of the amino acids and GC analysis on a chiral column.[16] This is understandable upon inspection of the *formulae* of the polylithiated species in **Schemes 5** and **7**: the stereogenic centers are all adjacent to Li aza-enolate or carboxylate centers which strongly reduce the acidity of the hydrogens bonded to them. Also, all peptides which we have so far

successfully alkylated contain a sarcosine unit with a second N-methyl amino acid attached to it (**Schemes 5 - 7**), so that the CH_2 group to be deprotonated is not deactivated.

In summary, the outcome of the reactions depends not only upon structural features of the peptide but also upon the nature of the LiX additive, the presence of cosolvents and of secondary amines (coproducts of the deprotonation with $LiNR_2$) and the choice of the reaction temperature.

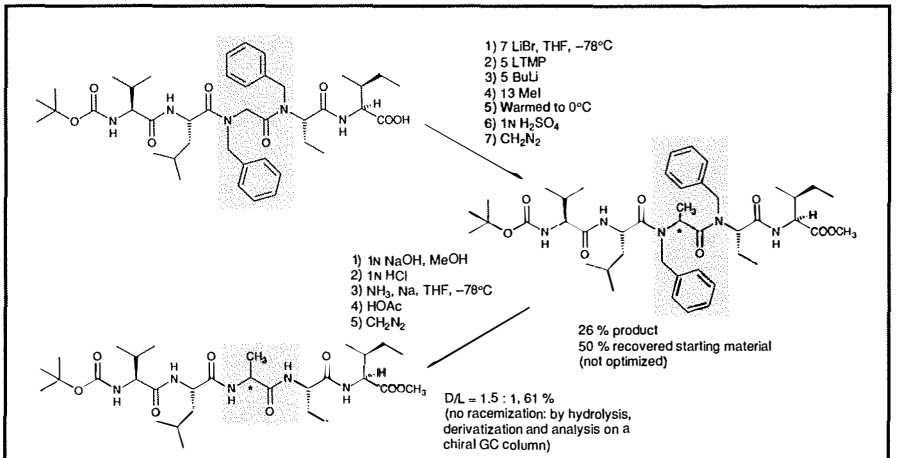
To those not familiar with the many facets of the structures and dynamics of Li derivatives[1a,17] this complexity must be confusing - just look at the crystal structures of Li enolates[10] and aza-enolates (**Figure 2**)[11] derived from carboxylic acid amides, and you are prepared to accept *any* kind of strange behaviour of a polylithiated peptide!?

In order to overcome the restriction that only sarcosine units can be alkylated we have tested the possibility of using peptides bearing two N-benzyl groups instead of N-methyl on and adjacent to a glycine. These can be obtained by synthesis from the corresponding N-benzyl amino acids or by direct benzylation of a peptide with KF on alumina as a base in acetonitrile.[12a,18] Deprotection of the N-benzyl amide or peptide groups is not possible by hydrogenolysis, but can be readily accomplished under dissolving metal conditions.[19] Preliminary results on the methylation of Boc-Val-Leu-BnGly-BnAbu-Ile-OH are described in **Scheme 8**. The yield of the reaction is still low, and it occurs without any diastereoselectivity to speak of, however the entire procedure can be carried out[12a] without epimerization[16b] on the four stereogenic centers present in the starting material.

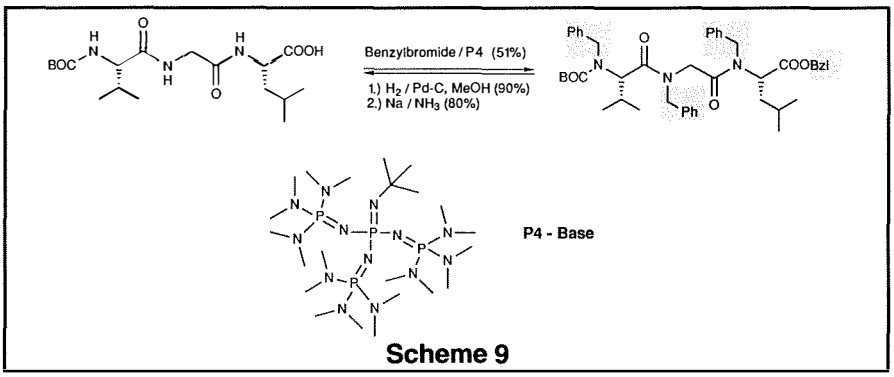
Finally, we have found that the new phosphazene **P4** superbase (Schwesinger base)[20,21] can be used for perbenzylations of peptides.[7] For an example see **Scheme 9.** All acidic **XH** protons of various linear and cyclic oligopeptides can be replaced by benzyl groups with this method. The OBn on the C-terminus is removable hydrogenolytically, and the N-Bn groups by sodium/liquid ammonia in THF. Again the basic conditions of both introduction and cleavage of the benzyl groups do not lead to epimerization of the stereogenic centers[16b] in the peptides tested so far. Luckily, the peptides to be benzylated in this way (THF, -100 to 20°C) need not be soluble to begin with. They dissolve in the course of the reaction. Thus the new procedure[7a] may be considered a protection *and* a solubilization of the peptide in organic solvents; some of the prepared derivatives are readily soluble in pentane. Glycine and sarcosine containing peptides have been found to be C-benzylated under these conditions[7a], so that it appears feasible to do enolate chemistry with peptides in salt-free media and without solubility problems!

Solubilization of Peptides in Organic Solvents Containing Inorganic Salts - Applications to Solid Phase Peptide Synthesis

When preparing for a multiple peptide deprotonation in the presence of LiCl, Adrian Thaler weighed samples of LiCl and Boc-Ala-Gly-Gly-Gly-OH, a compound of great solubility in water but very poor in THF, into



Scheme 8



Scheme 9

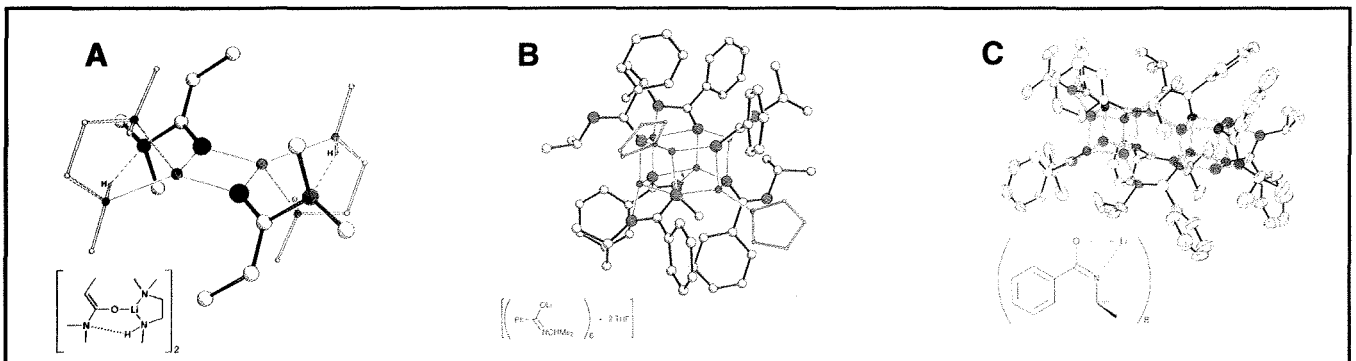
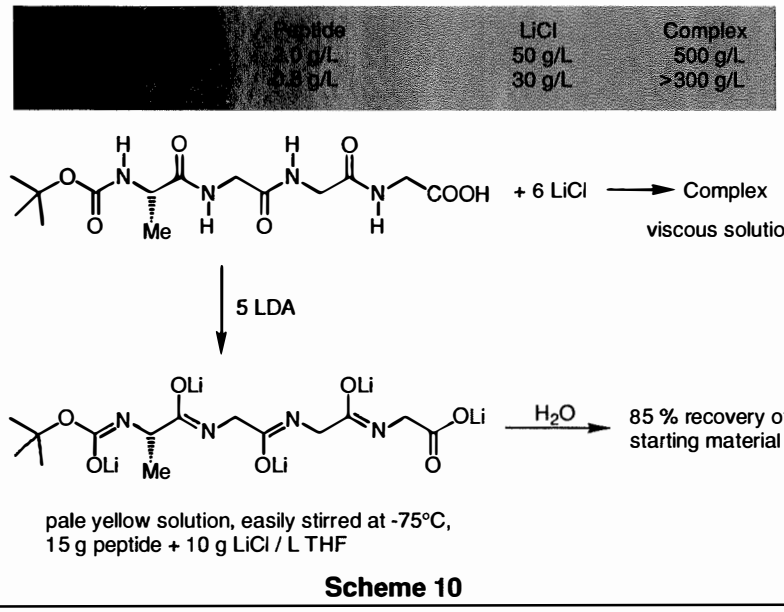
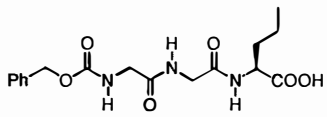


Figure 2. *Structures of Lithiated Carboxylic Acid Amides.* A) Tri-MEDA complex of the Li enolate of N,N-dimethyl propionamide.[10c] B) Hexamer of the Li aza-enolate from N-i-propyl benzamide containing four *E*- and two *Z*-imino groups.[11a] C) Octamer of the same Li aza enolate as in B, containing E-imino groups only.[11b]



Scheme 10

Z-Gly-Gly-Nva-OH



[mg/ml THF]

Temp. [°C]	Eq. LiX	Peptide initial	Peptide after evap.	Complex
-78°C	0.0	5.1		
room temp.	0.0	27		
	3.0 LiCl	> 200	> 500	> 700
	6.0	> 50	> 130	> 230
	3.6 LiBr	> 80	> 470	> 860
	2.9 LiI	> 310	> 420	> 860
	3.0 $LiBF_4$	> 130	> 360	> 640
	3.0 $LiClO_4$	> 200	> 340	> 640

[mg/ml solvent]

Added metal derivative Formula	Mol.-equiv.	Solvent	Peptide initial	Peptide after evap.
none		THF	27	
NaI	3.3	THF	>50	>80
$MgBr_2$	2.0	THF	>90	
$CaBr_2$	1.9	THF	34	
$Ti(OEt)_4$	3.0	THF	>260	>510
$Ti(OCHMe_2)_4$	3.0	THF	>70	>440
none		DIOX	28	
LiCl	3.1	DIOX	20	
none		DME	10	
$LiClO_4$	3.2	DME	>145	

[mg/ml THF]

other peptides	no LiX	Complex	eq. LiX
Boc-Gly-Gly-Nva-OH	27	> 840	2.9 LiBr
Boc-Ala-Gly-Gly-Gly-OH	2.0	> 500	5.9 LiCl
Z-Ile-Gly-Gly-OH	23	> 440	2.8
NH_2-Asp(OBzl)-Val-Tyr-OBzl HCl	1.5	> 620	2.9
NH_2-Lys(Z)-Asp(OBzl)-Val-Tyr-OBzl HCl	3.8	> 480	6.8
Z-Arg-Lys(Z)-Asp(OBzl)-Val-Tyr-OBzl HCl	0.7	> 210	3.5
NH_2-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala-OH		> 310	20 LiBr

Table 1. *Solubilization of Peptides in Ether Solvents by Inorganic Salts.* Typically, the peptide and the salt are suspended in the corresponding dry solvent. With stirring further solvent is added in portions over several hours until dissolution is reached ("*initial*" concentration). Solvent removal gives rise to the isolation of often fluffy and flaky solids which in turn dissolve in a much smaller volume of solvent than the one they had been obtained from (concentration "*after evaporation*").[8a,12c] The example of the nonapeptide with lipophilic side chains/LiBr is taken from the work of Peter Lansbury, Jr.[23] DIOX = dioxane; DME = dimethoxy ethane.

a flask, and added THF under an inert atmosphere. To his surprise, a clear solution was formed containing more than 100-fold the amount of peptide which would be soluble in the absence of LiCl. In fact, the two compounds solubilize each other; see the data given in **Scheme 10**. The somewhat viscous solution is stable for long periods of time without crystallization ensuing. Somewhat less concentrated solutions are stirrable even at dry-ice temperature, and the penta-lithio derivative can be generated, and is likewise soluble in THF (**Scheme 10**).[8a] We found that the salt effect[22] on peptide solubility in ether solvents is quite general. In **Table 1** some examples are collected in which different peptides, solvents, and salts were used.[8a,12c] While the effect is especially strong with various Li salts, $MgBr_2$, $ZnCl_2$, and, notably, titanates can also be employed (usually one equivalent of salt per amino acid). The concentrations in THF are in many cases so high that it would be appropriate to speak of molten complexes of the peptide with the inorganic salt, containing a few solvate ether molecules.

There is a striking contrast between the solubilizing effect of excess salt on peptides in ether solvents and the precipitation from water of linear oligopeptides as 1 : 1 complexes with alkali halides (Pfeiffer effect,[24a] see **Figure 3**). In our case, the intermolecular interactions and crystal packing forces of both the peptide and the salt must be overridden by complex formation and by solvation with THF. In Pfeiffer's case the large energy of solvation in water of both the peptide and the salt must be overcompensated by the mainly Coulombic packing forces (Li^+ is neutralized by COO^- groups, the Br^- ions are near the NH_3^+ peptide termini in the structure depicted in **Figure 3**).

The interaction between Li salts and amides is well known. Thus, the barrier to rotation around the CO-N bond of DMF increases by several kcal/ mole in the presence of Li salts (NMR measurement in aprotic solvent; see discussion in reference 8a).[25] From NMR measurements in d_8-THF the formation of new conformers (or rotamers) of peptides in the presence of LiCl is evident; at room temperature these conformers interconvert slowly on the NMR time scale.[8a] For detailed information about the solution structure of the complex formed between LiCl and CyA a collaborative effort with Horst Kessler, one of the peptide NMR *supermen* was necessary (just like in the case of the two thio-CyA conformers mentioned above). The resulting structure[9] is pictured and compared with that of CyA itself in **Figure 4.** As can be seen, dramatic changes have occurred: the *cis* peptide bond of CyA between amino

acid 9 and 10 has rotated to become *trans* and the shape of the molecule has been altered in such a way that all intramolecular hydrogen bonds have disappeared. Although we do not know the positions of the lithiums, it looks as if the carbonyl oxygens previously engaged in β-sheet-type hydrogen bonding have moved outwards to become available for complexation with Li. It is intriguing to note that the same fundamental changes occur when CyA docks to its binding protein cyclophilin, also shown in **Figure 4**. Thus, the cyclosporin structure is highly flexible and can adjust itself to the needs of its binding partners, be they as simple as Li ions or as complicated as a 172-amino acid protein.

As predicted in our original paper about the solubilizing effect of Li salts on peptides,[8a] unnatural conformers of peptides can be generated as Li complexes and their properties studied. This was also demonstrated in a recent investigation by Daniel Rich.[26]

As synthetic organic chemists we, of course, looked for synthetic applications of the solubilizing effect we had discovered. We learned that the poor yields in solid phase peptide synthesis of sequences containing mainly amino acids with aliphatic substituents is due to aggregation of the growing chains (β-sheet formation, poor solvation, "resin shrinking"). In fact, when an Ala_5-chain is coupled seven times with alanine (using N-Fmoc-Pfp- ester on a so-called PS resin, see **Figure 5**)[8c] there is an appreciable amount of Ala_5 left which has survived seven coupling cycles untouched! We therefore chose the Ala_5 to Ala_6 step as a model to test whether addition of LiCl to the solvent leads to an improvement of the situation. Indeed, the yields climbed above the magic 95 *plus* percent on both resins used when LiCl was present in the solvents dimethyl formamide/CH_2Cl_2, N-methyl-pyrrolidone, and dimethyl propylene urea (**Figure 6**).[8c] Ironically, the yields dropped upon addition of LiCl when THF was used, the solvent in which we had first observed the solubilizing effect of Li salts! At first sight it appears to be surprising that LiCl causes an improvement of the coupling yield in amide and urea solvents which contain the same functional group as the peptide to be solublized. Polymer chemists would disagree: it is known that LiCl in N,N-dimethyl acetamide is a unique solvent system for certain synthetic polyamides which can be spun to fibers from the corresponding solutions.[27] Thus, we may have been of help by just filling an information gap between peptide machine synthesizers and polymer chemists!

Serendipity was involved when we discovered a highly efficient method of

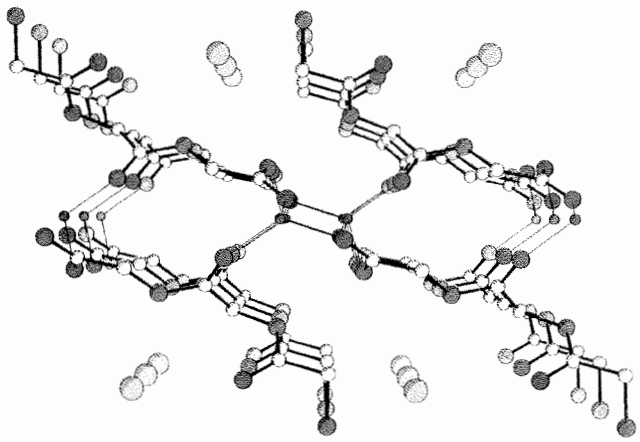


Figure 3. *Solid-State Structure of [(Gly-Gly-Gly)-LiBr] Determined by X-Ray Diffraction.*[24b] The complex crystallizes from water.[24a] It looks like there could be ion conductivity along the axis of projection shown here. Beautiful large single crystals of this and other Pfeiffer complexes have recently been grown by us.[12e,d] The color code is: Li blue, O red, N green, Br yellow, C white.

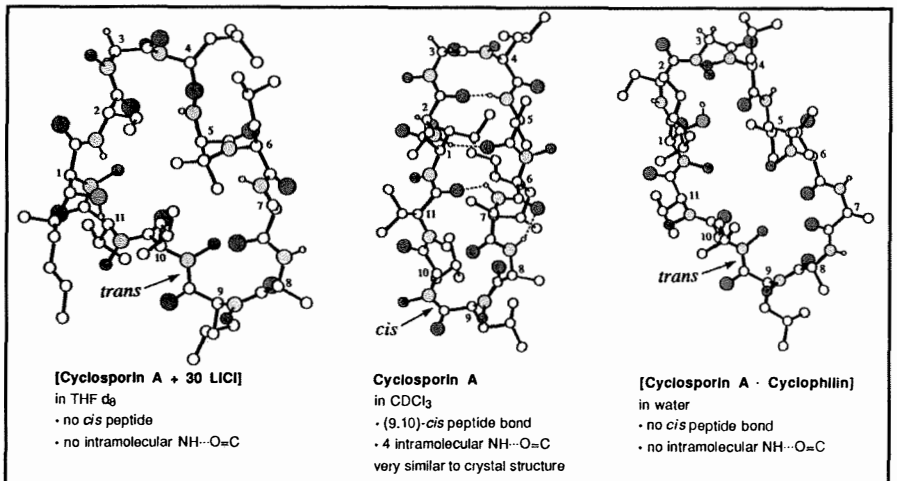


Figure 4. *A Comparison of the NMR Solution Structures of CyA+LiCl in (d_8-THF), CyA in ($CDCl_3$), and CyA·Cyclophilin in (water).* For leading references see[9b].

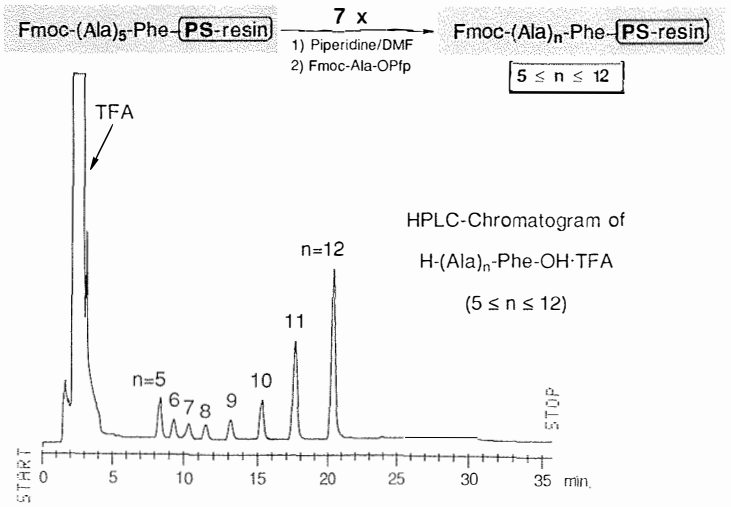


Figure 5. *Composition of the Peptide "Cocktail" Resulting from an Ala_5 Chain by Seven Coupling Steps with Alanine.* HPLC Analysis of the peptide trifluoroacetate mixture obtained by detachment from the resin.[8c]

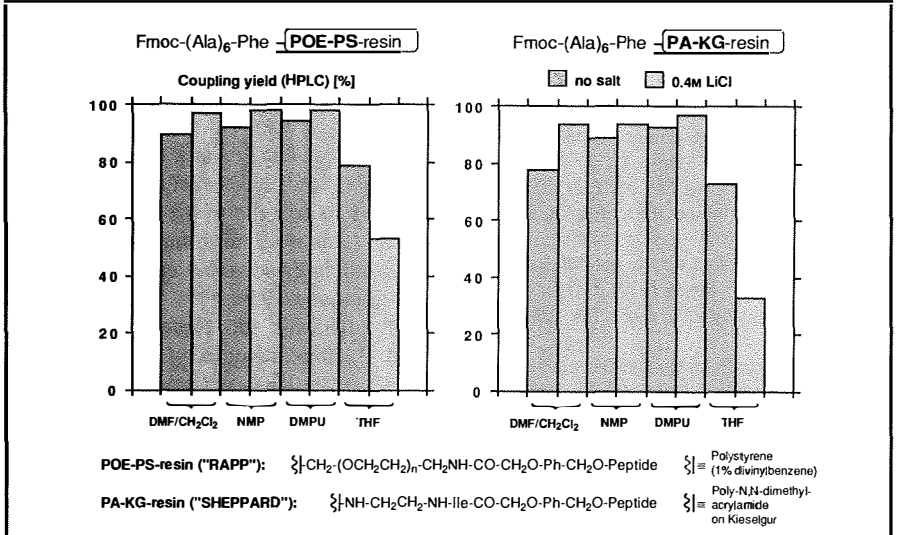
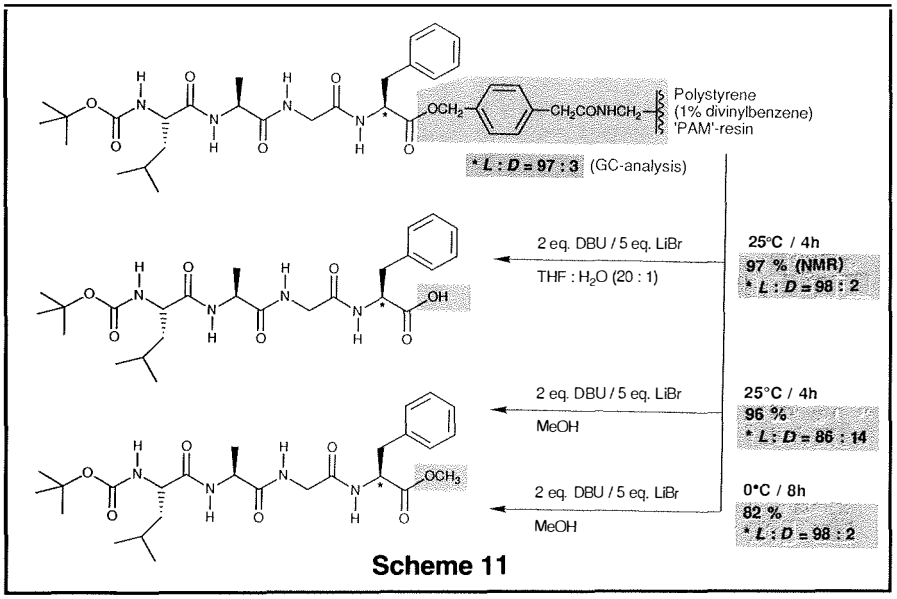


Figure 6. *Ala_5 to Ala_6 Coupling Using the Fmoc Technique on a POE Polystyrene (Merrifield) and on a Polyacrylamide/SiO_2 Resin (Sheppard) in Different Solvents with and without Addition of LiCl.* The coupling yield was determined by detachment of the peptide from the resin, followed by HPLC analysis of the resulting Ala_5/Ala_6 mixture.[8c]



Scheme 11

transesterification, also and especially well suited for peptide solid phase synthesis. We had noticed[28] that traces of water in the solvent (THF) used for a Wittig-Horner olefination with DBU/LiBr, a very special base for this reaction,[29] caused the phosphonate diester to be hydrolyzed. DBU/LiBr turned out to be a mixture for mediating hydrolyses and transesterifications of esters with incredibly high rates.[8d] These conditions could be used for detachment of peptides from resins (**Scheme 11**) - normally done with HF. If the reaction is carried out at 0°C, even peptides with the epimerization-prone phenyl alanine C-terminal amino acid could be liberated from the resin, without simultaneous removal of the acid labile protecting groups.[8d]

We hope that our excursion into peptide chemistry may at least cause others to think about possible non-conventional methods in the synthesis of this important class of compounds.

Acknowledgements

The collaboration of a group of enthusiastic graduate students and postdoctoral fellows is gratefully acknowledged; their names appear in the list of references. I am also grateful to Hans G. Bossler, Thomas Pietzonka, Albert K. Beck, Dietmar A. Plattner and Silvia Sigrist for their help in preparing the manuscript and the originals for schemes, figures, and tables. The Swiss National Science Foundation and Sandoz AG (Basel) have generously supported our peptide project.

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About the Author:

Professor Dr. Dieter Seebach was born, raised and educated in Karlsruhe, Germany. After secondary school he studied chemistry at the University of Karlsruhe (TH) receiving his master's degree in 1961 and Ph.D. degree in 1964 with a thesis on small-ring compounds and peroxides under the supervision of Professor Criegee.

Following positions as a postdoctoral fellow with Professor E.J. Corey (Li-dithiane chemistry) and as Lecturer on Chemistry at Harvard (1965/1966) he returned to the University of Karlsruhe to do independent research. This work on sulfur- and selenium-stabilized carbanions and carbenes led to a Habilitation in 1969.

He attained a full professorship at the Justus Liebig-Universität Giessen in 1971 and six years later relocated to his current position as Professor of Chemistry at the Eidgenössische Technische Hochschule in Zürich.

Dr. Seebach's main areas of research include the development of new synthetic methods (e.g., umpolung of reactivity, enantioselective reactions, self-regeneration of stereogenic centers), natural product synthesis (e.g., macrolides, amino acids), mechanistic studies (e.g., stability of carbenoids, aggregation of Li-compounds) and structure determination (Li- and Mg-derivatives, NMR, X-ray diffraction).

Dr. Seebach has held visiting professorships at the Universities of Wisconsin and Strasbourg, and at Caltech. He has been Karl Ziegler-Professor at the Max Planck-Institut (Mülheim), Walter Hieber-Professor at the Technische Universität (München) and JSPS visitor in Japan.

He has held several distinguished lectureships such as the Kharasch (Chicago), the Bachmann (Ann Arbor), the Barré (Montréal), the Hirschman (Wisconsin), the Büchi (MIT), the Firth (Sheffield) and the Max Tishler Prize Lecture at Harvard, among others.

Dr. Seebach has received numerous awards and prizes in recognition of his research such as the Dozentenpreis (Germany), the Havinga Medal (Leiden), the Karl Ziegler-Preis (GDCH), the Fluka Reagent of the Year (1987) and the current ACS Award for Creative Work in Organic Synthesis.

Dr. Seebach also holds an honorary Ph. D. degree (Dr. h.c.) from the University of Montpellier, France (1989), is a member of several prestigious international chemical societies and has published over 450 research papers.

A Curiosity Driven Search For New Chemical Reactions

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1. INTRODUCTION

The traditional approach of the synthetic organic chemist is undoubtedly influenced by his early mechanistic training in the use of the two electron 'curly arrow' and is therefore essentially ionic in nature. For the past eight years at Imperial College, however, we have adopted a deliberate policy of concentrating on those reactive intermediates which are less commonly used. The end result, as illustrated by some of the reactions[1-5] in **Scheme 1**, is a somewhat diverse range of topics, which is essentially driven by a simple yet fundamental curiosity about the various factors which control the timing of bond breaking and bond making processes. Overlaying this, in selecting areas of research, is the realisation that the modern chemical industry provides an invaluable source of challenges for the synthetic chemist. Finally as the writing of this article too inevitably convinced me, the introduction of unplanned "leitmotifs" can often intrude, as in a demonstrable weakness for the chemistry of cyclopropanes (vide infra). Our hope, simply stated, but much more difficult to achieve, is therefore to develop practical reactions and to prepare molecules which other chemists may actually wish to use. The present article continues to highlight these themes by concentrating on some problems of current interest.

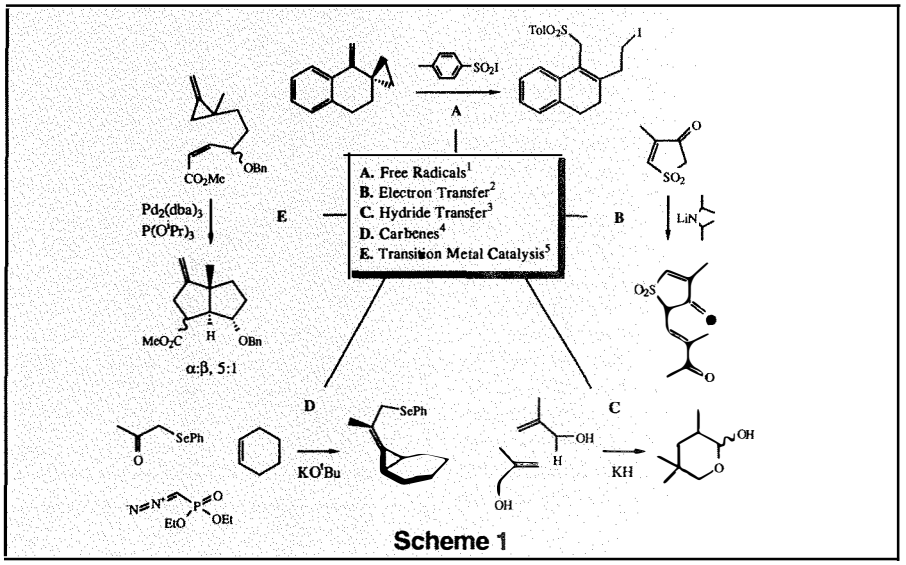
2. FREE RADICAL CHAIN REACTIONS

It has been a great source of pleasure over the last twenty years to be associated with the increasing number of organic chemists who have come to appreciate the beauty of a well designed free radical chain reaction. Growth in this area has almost certainly been stimulated by the advent of a range of mild methods for the generation of carbon centred free radicals.[6] Unlike their ionic counterparts, these reactive intermediates possess the inherent advantage of neutrality and, hence, essentially unencumbered by solvation effects, can operate in highly hindered and polar molecular environments. Our particular interest in recent times has been to focus on the design of controlled rearrangement reactions for carbon-carbon bond formation, as exemplified by the two themes shown below.

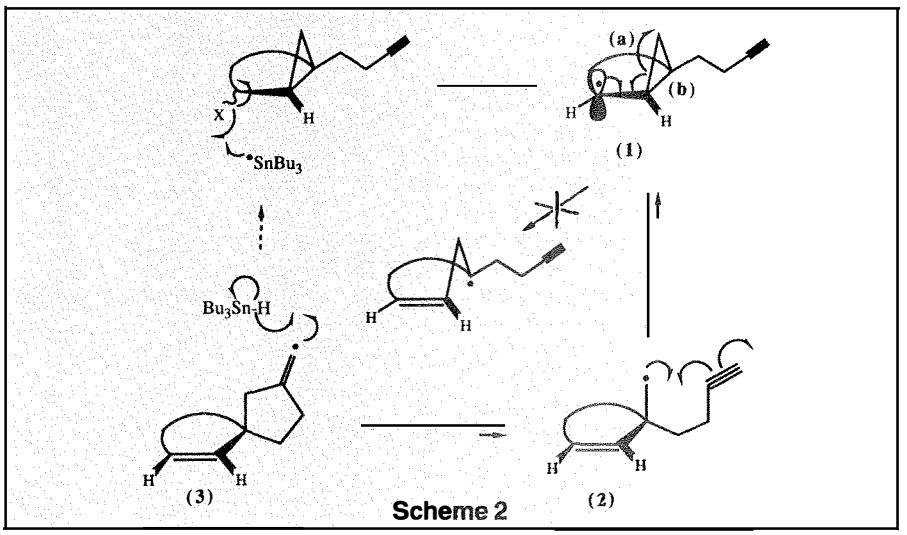
2.1 The Construction of Bicyclic Systems via a Tandem Cyclopropylcarbinyl Rearrangement - Cyclisation Strategy.

The essential planning features of this system, as illustrated for the particular case of a spiro-fused exomethylene cyclopentane (**Scheme 2**), were initially based on kinetic considerations. These suggested that, at low concentrations of stannane, the formation of the first carbon centred radical (**1**) would be followed by a rapid radical cascade via (**2**) without competing hydrogen atom abstraction until radical (**3**) had been formed. A second factor of equal importance was the selection of the rigid bicyclo[x.1.0] framework which ensured that stereoelectronically controlled cleavage of the exocyclic bond (bond a) of the cyclopropane would predominate over the thermodynamic alternative (bond b).

The foregoing analysis was supported by the study shown in **Scheme 3**.[7] Model precursors (**5**) and (**6**) were readily constructed in stereospecific



Scheme 1



Scheme 2

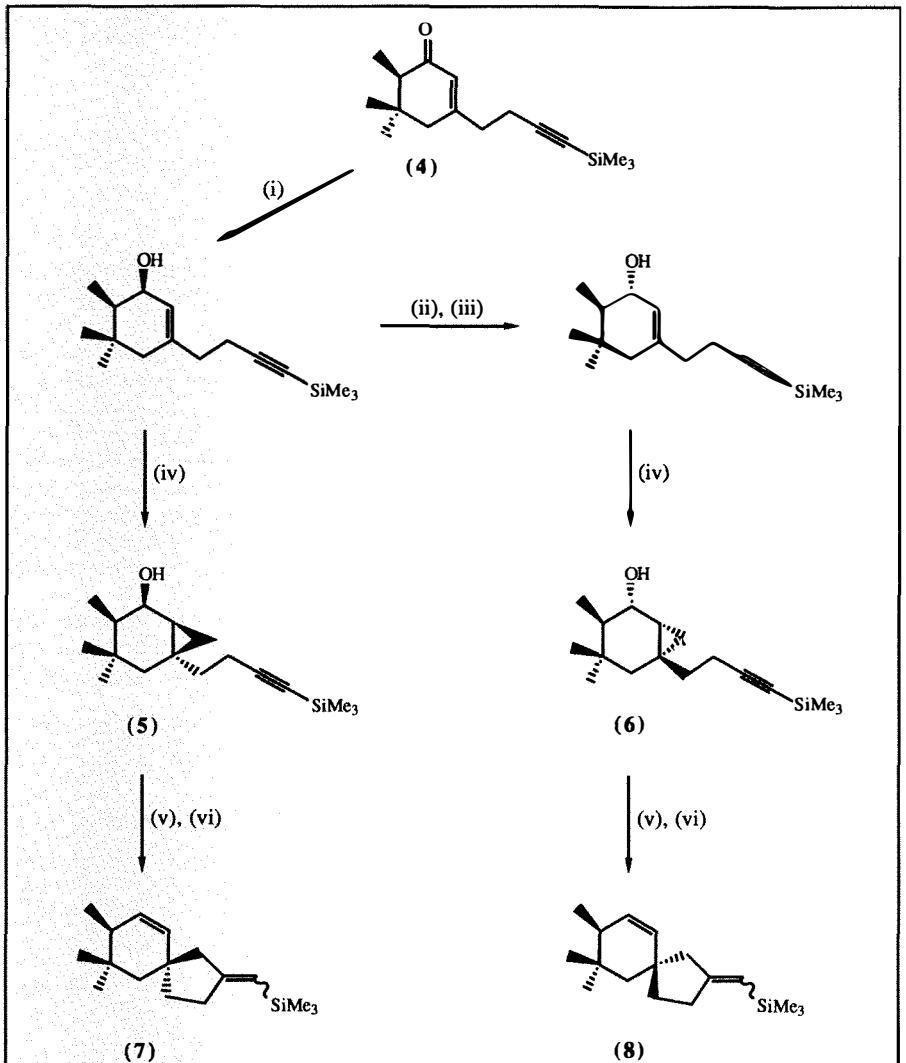
fashion from the common enone (**4**) by selecting the appropriate combination of Mitsunobu inversion protocol and the excellent hydroxyl directed Simmons-Smith cyclopropanation sequence to set the quaternary centre. Conversion of the alcohols to their derived thiocarbonylimidazolides as a suitable radical trigger followed by tri-n-butylstannane reduction then afforded spirocycles (**7**) and (**8**) which differ only in the relative orientation of the vinylsilane moiety with respect to the methyl group marker. The absence of any stereochemical crossover in the two parallel series provides firm evidence that cleavage of the endocyclic cyclopropyl bond to give a common radical intermediate is not occurring at any time during the reaction.

A variety of connectivity patterns may be used in this tandem rearrangement - cyclisation strategy. Two of these are shown in **Scheme 4** and provide access to a range of bicyclic (and even tricyclic!) skeletons.[8] The wealth of kinetic data available for free radical reactions meant that the above sequence, both in prospect and in retrospect, was a reaction realised by conception.

A further ramification of this approach, as illustrated in equation 1 (**Scheme 5**), was the realisation that the single electron transfer induced ring opening reaction of bicyclic cyclopropyl ketones would lead to a particularly attractive intermediate (**9**), featuring both a regiospecific enolate and a carbon centred radical for further elaboration. In the event, the problem was not to induce single electron transfer but to prevent further formation of strongly basic dianions! Samarium(II) iodide/DMPU in tetrahydrofuran eventually proved to be the reagent of choice, by permitting the carbon centred radical either to participate in further cyclisations or to undergo hydrogen atom abstraction from solvent.[9] The regiochemical stability and reactivity of the resultant samarium enolates could also be exploited through formation of either enolic derivatives or carbonalkylated products by addition of a suitable electrophilic quench. Some selected examples of this approach are shown in **Scheme 5.**

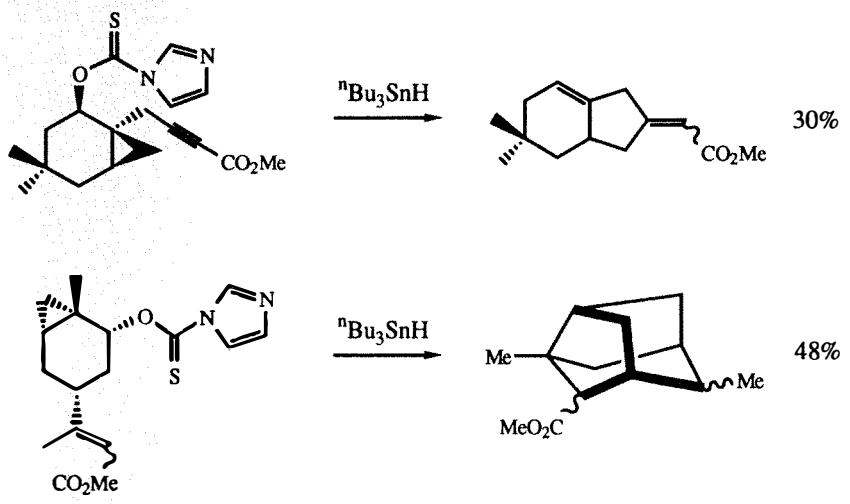
2.2. Intramolecular Free Radical Ipso Substitution.

The biaryl unit is often encountered as a central core in a very large number of natural product families. Faced by the problem of developing a flexible approach to such systems, which would tolerate both hindered environments and a wide variety of functional groups of differing electronic character, we decided to adopt an approach based on intramolecular free radical ipso substitution of a suitably constituted sulphonyl substituted aromatic derivative by a second ortho substituted aryl radical (**Scheme 6**). The essential requirement was, of course, to discover the number and electronic nature of the atom or atoms (X) in the tethering chain such that formation of a spirocyclic intermediate (**10**), capable of rearomatisation and sulphur dioxide extrusion, would be favoured over the direct addition process.

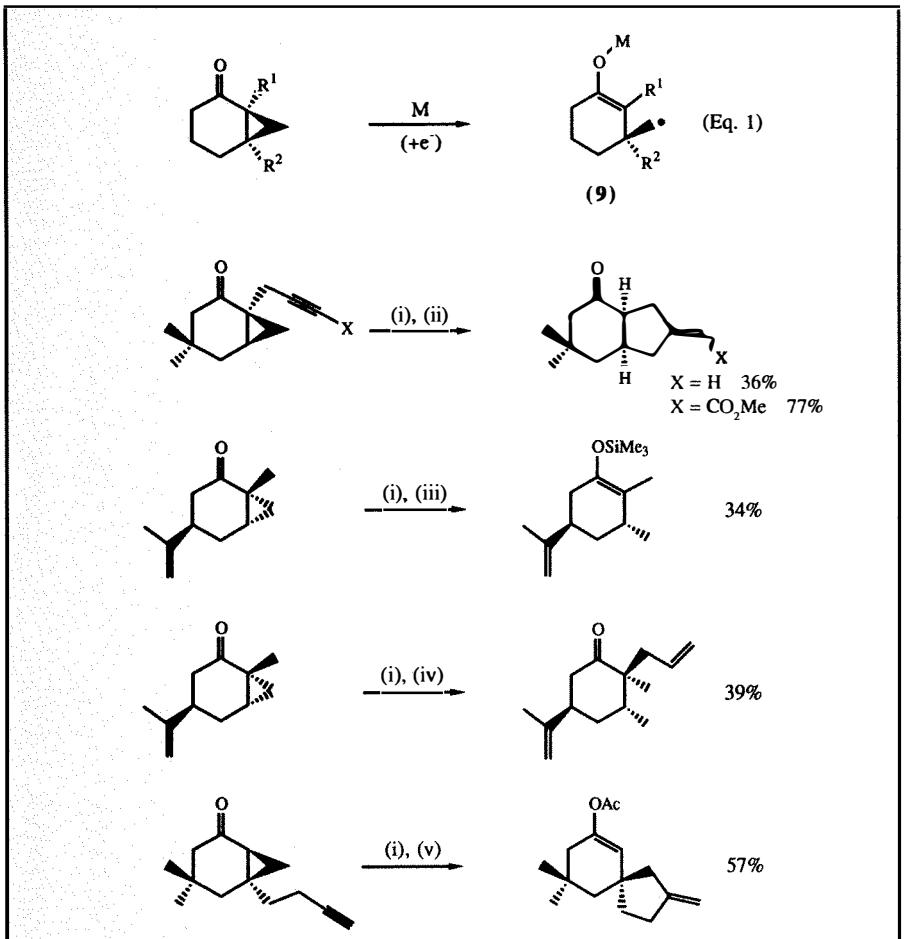


Reagents: (i) L-Selectride (65%); (ii) Ph_3P, EtO_2C-N=NCO_2Et, $PhCO_2H$ (65%); (iii) $Ti(O^iPr)_4$, propan-2-ol (60%); (iv) Zn/Ag, CH_2I_2 [(5) in 74% yield, (6) in 84% yield]; (v) thiocarbonyldiimidazole (100%); (vi) Bu_3SnH [(7) in 79%, (8) in 81% yield].

Scheme 3



Scheme 4



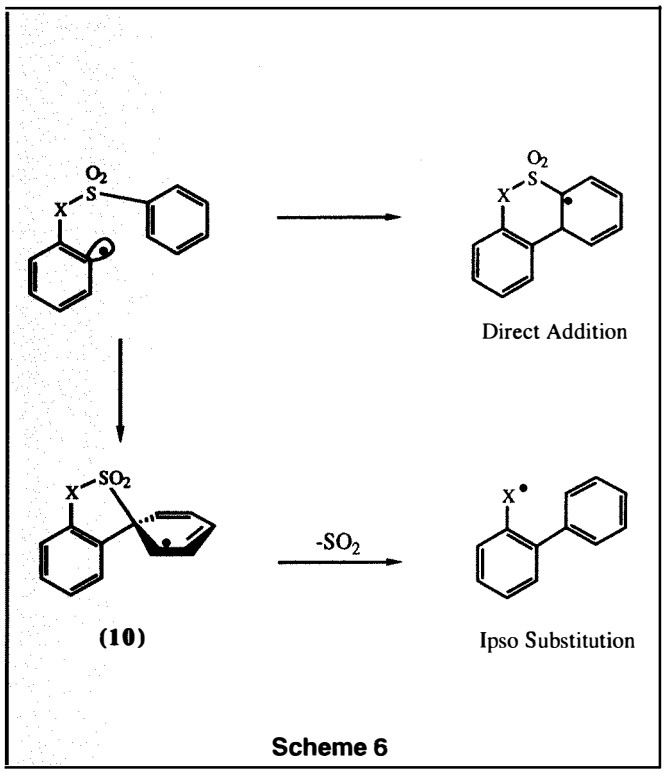
Scheme 5

Some of our results to date (**Scheme 7**) show that readily prepared sulphonyl derivatives of ortho halo phenols, anilines, and carboxylic acids may be successfully used.[10] In terms of substituent effects, however, this simple system has proved to be a frustratingly subtle probe for electronic effects in radical reactions, and although, as hoped, both electron donating and withdrawing groups may be used on the sulphonyl substituted aromatic acceptor, we have yet to attain sufficiently high levels of predictive power for the outcome of these reactions.

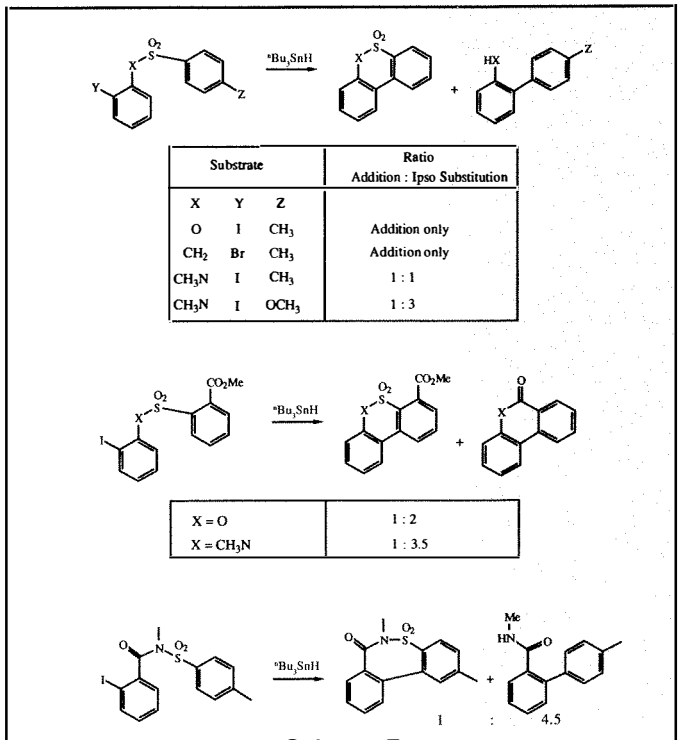
The concept of intramolecular free radical ipso substitution need not, of course, be restricted to biaryl formation, but can also be applied to other carbon centred free radicals. An initial study of the addition of vinyl radicals, generated by reversible addition of tri-n-butylstannyl radicals to homopropargyl arenesulphonates did, however, produce an unexpected surprise.[11] As outlined in **Scheme 8**, while the initial [1,6] ipso substitution proceeded as expected, the loss of sulphur dioxide from intermediate (**11**) was sufficiently slow to permit an alternative 6-endo proximal addition elimination sequence, with expulsion of a potentially catalytic tri-n-butylstannyl radical as the chain carrier. The overall result provided a general route to unusual 4-aryl-5,6-dihydro-1,2-oxathiin-2,2-dioxides.

3. NEW REACTIONS AND REAGENTS FOR SELECTIVE FLUORINATION.

Our interest in this branch of chemistry was certainly not based on any previous personal scientific experience, but arose in almost accidental fashion by contact with colleagues in the



Scheme 6



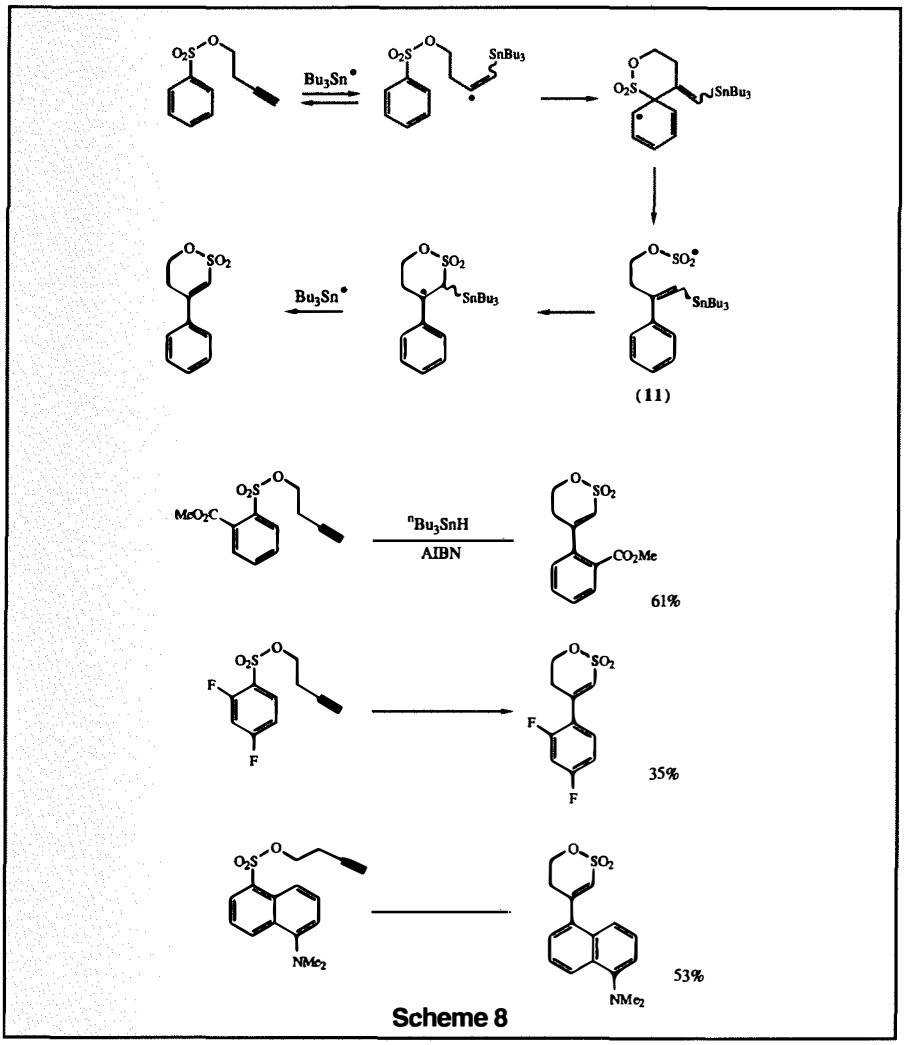
Scheme 7

pharmaceutical industry who indicated that there were many interesting challenges to be tackled. Thus far, two distinct themes have emerged, one concerned with the development of iodoarene difluorides as reagents for selective functional group manipulation, and the other based on the chemical reactivity of a gem difluoroenol ether unit.

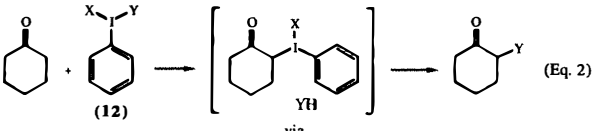
3.1 Hypervalent Iodoarene Difluorides.

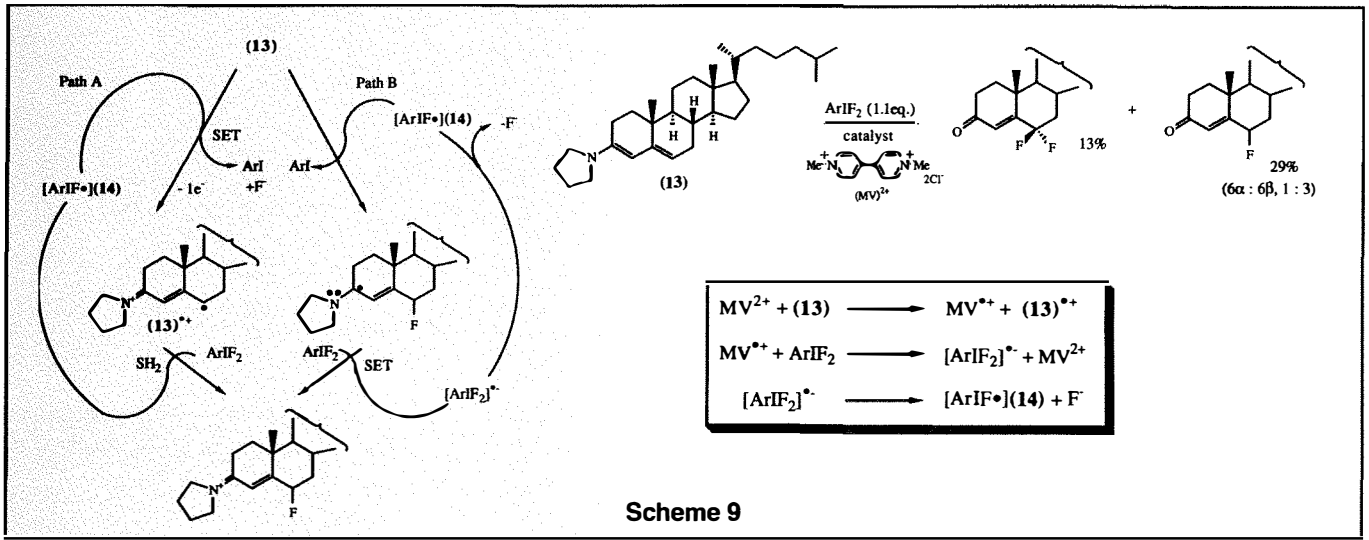
Work on this class of compounds began with the idle speculation (Equation 2) that if Koser's reagent[12] **(12)** (X = OH, Y = OTs) could function as a formal source of "electrophilic tosylate", then the corresponding iodoarene difluorides (X = Y = F) might well function by a similar double displacement mechanism and hence achieve "pretence electrophilic fluorination". Although we were unaware of it at the time, a Japanese friend, Dr. Tadahiko Tsuchima, had in fact demonstrated the viability of this concept in the reaction of silyl enol ethers with para chloro iodobenzene difluoride.[13] An attractive feature of these reagents is that they are easily prepared by simple halogen exchange from the corresponding dichlorides using a cocktail of aqueous hydrofluoric acid and mercuric oxide. Appropriately, an experimental "trick" in this reaction decrees that the mixture be shaken and not stirred! Furthermore, the para tolyl and para-t-butyl derivatives are crystalline solids which are readily soluble in organic solvents.

Our own studies commenced however with an investigation of the reaction of the steroidal dienamine **(13)** with para-t-butyl iodobenzene difluoride[14] **(Scheme 9)**. Although we were able to demonstrate that selective introduction of a fluorine atom occurred at the 6-position, yields were low; it was only after several months of extensive experimentation that we realised that the double displacement hypothesis was entirely wrong in this instance. We had, in fact, uncovered a novel electron transfer chain mechanism which was eventually improved by the addition of methylviologen $(MV)^{2+}$ as a catalyst in order

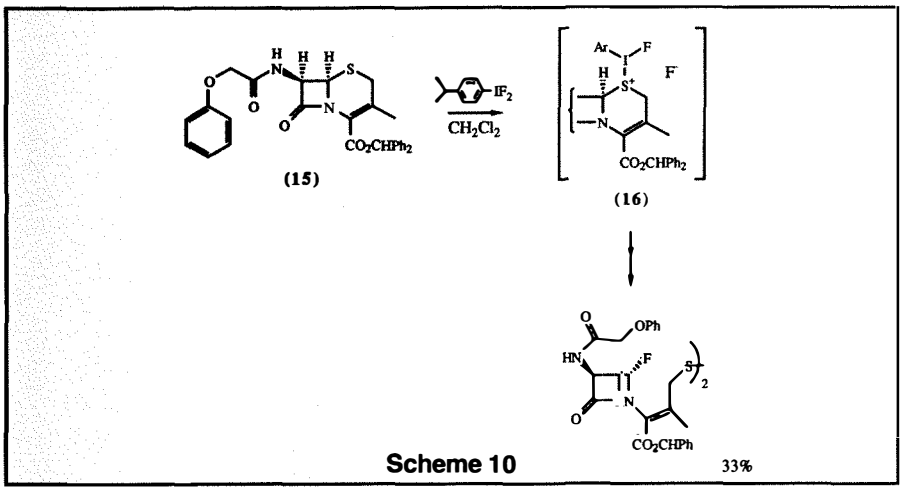


Scheme 8

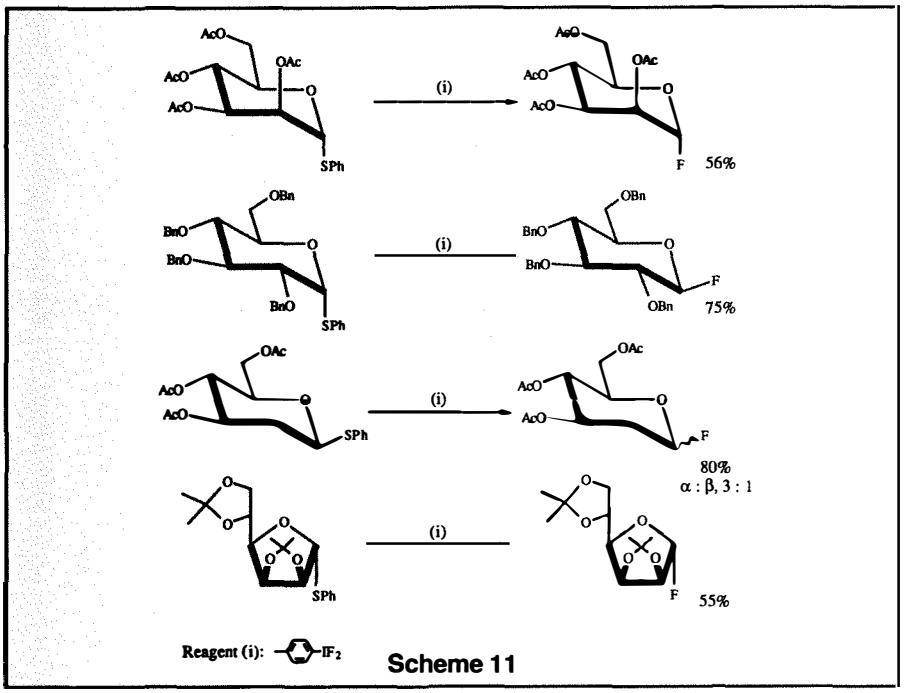




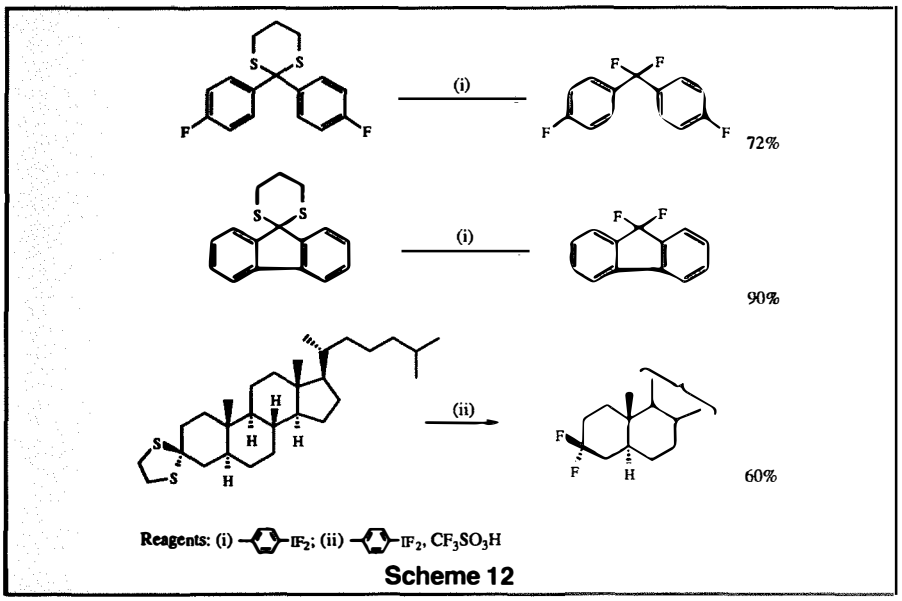
Scheme 9



Scheme 10



Scheme 11



Scheme 12

to generate the monofluoroiodoarene radical (**14**) as a key intermediate which could then function either as a one electron oxidant (path A) or as an electrophilic radical (path B). This, in retrospect, is therefore an example of a reaction discovered by misconception.

In similar vein, a study of the cephalosporin ester (**15**) in the search for a possible fluoro - Pummererreaction via intermediate (**16**) (**Scheme 10**), proved very useful in demonstrating the high affinity of these reagents for sulphur.[15] This, in turn, then led by a more predictable direct analogy to the development of useful methods for the preparation of glycosyl fluorides (**Scheme 11**)[16] and certain gem difluoromethylene compounds from thioketals (**Scheme 12**).[17]

3.2. The Chemistry of Exocyclic Carbohydrate Difluoroenol Ethers.

A request to achieve regiospecific replacement of the anomeric oxygen atom in glycoside derivatives by a difluoromethylene group led us to consider the possibility that carbohydrate gem difluoroenol ethers should be accessible from their derived lactones by a Wittig-like strategy and would prove to be versatile building blocks. Our interest increased when examination of the literature revealed that only a single non-carbohydrate example of this functional group had been described.[18] In simple electronic terms, it was amusing to contemplate that while three electronegative atoms were attached to the σ–framework of the carbon-carbon double bond, no less than eighteen electrons were involved in the π-system and associated oxygen and fluorine lone pairs. A series of AMI molecular orbital calculations on simpler systems revealed that whilst the HOMO energies are very similar to those of the corresponding methylene analogues, the LUMO energies are relatively lowered, and hence more accessible.

In the event, as shown in **Scheme 13**, these derivatives were readily prepared from commonly available γ- and δ - lactones using a combination of dibromodifluoromethane, tris(dimethylamino)phosphine and zinc dust.[19] Significantly, our only failure in this series was the initial non carbohydrate derivative (**17**), which underwent particularly facile [2+2] addition to give the dimers (**18**), thereby providing an appropriate comment on the use of model compounds!

Some reactions of typical ethers are set out in **Scheme 14**. While simple catalytic hydrogenation (Equations 3 and 4) provides an effective route to gem-difluoromethyl C-glycosides, we could not resist the temptation to explore the use of such substrates in preparative free radical chain reactions.[20] In the first instance, we chose to examine the use of such alkenes as radical traps for both electrophilic (Equation 5) and nucleophilic (Equation 6) carbon centred radicals. The regiospecific nature of the addition at the least hindered diifluoromethylene terminus then allowed us to prepare the first example of a difluoromethylene linked disaccharide derivative (Equation 7) . A second complementary

radical strategy for carbon-carbon bond formation was also possible via the AIBN initiated addition of thiophenol. These derivatives, in turn, served as apposite precursors of difluoroalkyl radicals in chain reactions with allylstannanes (Equations 8 and 9).

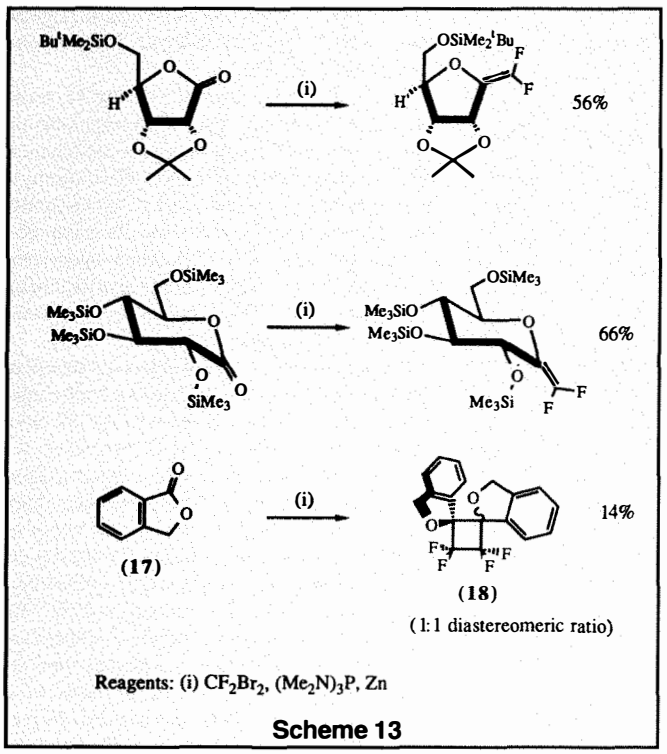
4. ORGANOMETALLIC INTERMEDIATES

Of all research areas, the concept of using a transition metal complex to achieve a chemical transformation, particularly at the highest level as a catalyst, is certainly one of the most aesthetically attractive and of potential use to industry. Yet again, we have approached this subject as novices, and our learning curve has been relatively slow as we begin to appreciate some of the more subtle characteristics of reagent design. Within the scope of the present article, we will consider both a catalytic isomerisation process for allylic alkoxides, and a stoichiometric "Grignard - like" formation of organozinc carbenoids from carbonyl compounds.

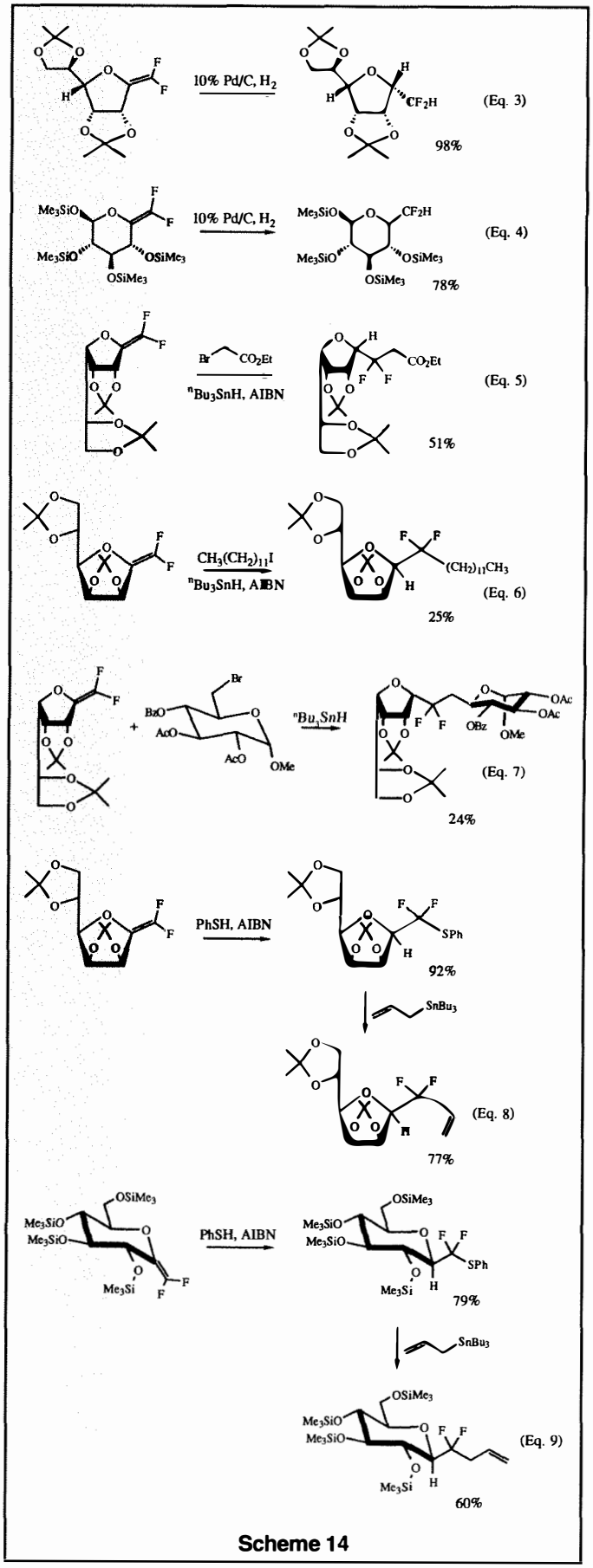
4.1 A New Route to Enolate Anion Chemistry.

The constraints of modern day Organic Synthesis require that the traditional approach to enolate anion generation involving deprotonation of the corresponding carbonyl compound is not only regiospecific but also stereospecific. Some four years ago, however, inspired by the elegant studies of Noyori,[21] we conceived the simple idea (**Scheme 15**) that controlled isomerisation of a preformed trisubstituted allylic metal alkoxide using a chiral transition metal complex could afford a chiral enolate anion of defined geometry. To date, we have yet to carry out this experiment! In the interim, our first task has been to establish that such an approach is viable and that, in certain cases, it may offer some possible advantages over existing methods.

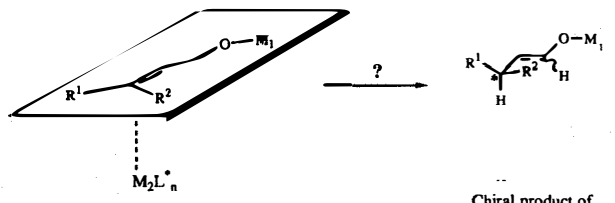
Although a wide variety of more unusual metal alkoxides could have been selected, our early experiments have concentrated on the formation of well documented lithium enolates and covalent boronate complexes. As shown in **Scheme 16** efficient isomerisation was achieved using the cationic rhodium complex $[Rh(dppe)(thf)_2]^+ ClO_4^-$.[22] Moreover, a distinct preference for formation of the Z enolate was noted in these reactions, as demonstrated by a subsequent aldol reaction under kinetically controlled conditions.



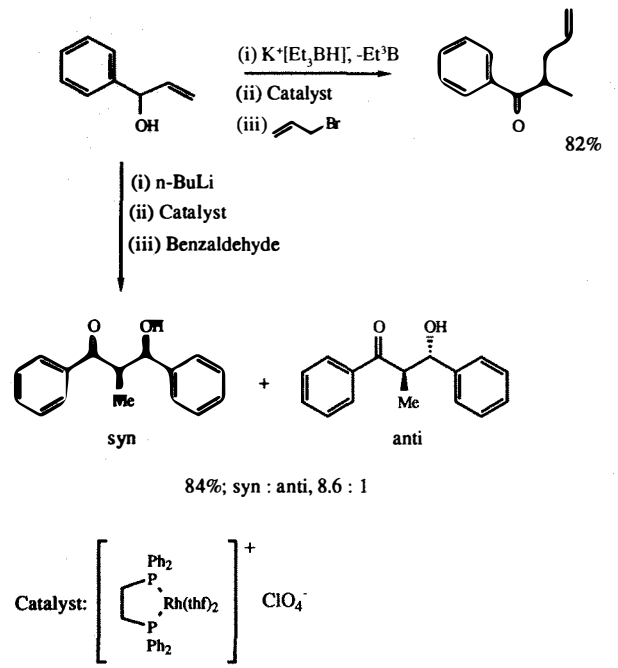
Scheme 13



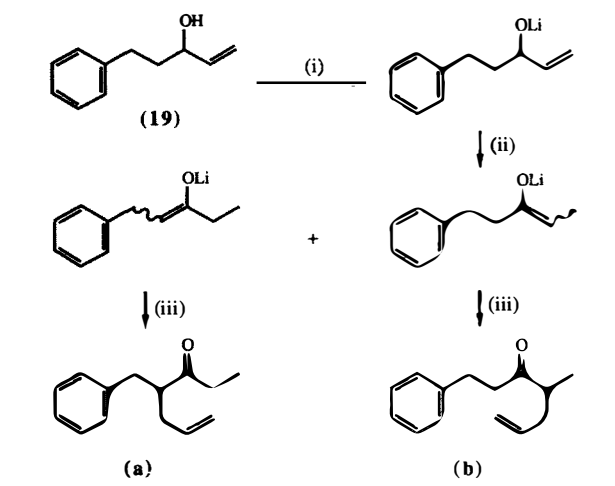
Scheme 14



Scheme 15



Scheme 16



CATALYST	YIELD	(a) : (b)
$[Rh(dppe)(thf)_2]ClO_4$	79%	1 : 1.2
$(Cy_3P)_2NiCl_2$	78%	15 : 1

Scheme 17

In recent studies directed towards extending the range of this approach, a disastrous problem of regiochemical control arose on attempted isomerisation of substrate **(19)** (**Scheme 17**). The use of a nickel catalyst system based on $(Cy_3P)_2NiCl_2$ proved, however, to be successful, and also allowed the application of this approach to more highly substituted alkenes and cyclic systems in which rhodium was ineffective (**Scheme 18**).[23]

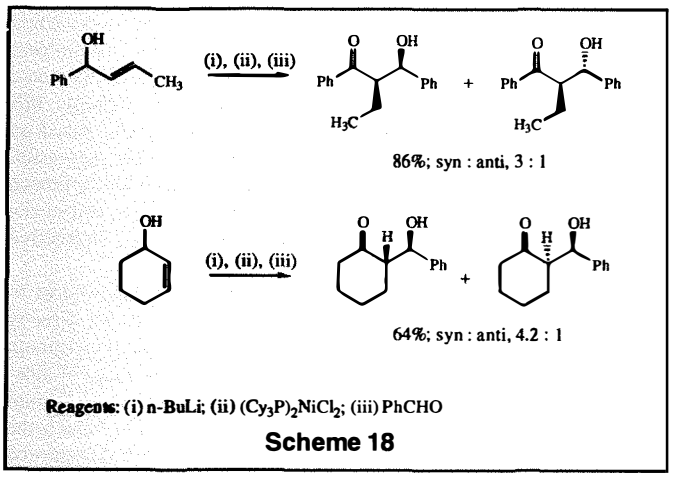
This simple concept has also allowed us to tackle some problems which are not directly soluble using the chemistry of the carbonyl group, as in the formation of lithium enolates of aldehydes, (Equation 10) where use of lithium diisopropylamide leads to reduction,[24] and in the stereoselective formation of tetrasubstituted enolates of defined geometry. (Equation 11).[25] For the synthetic chemist our hope is that an allylic alcohol will become not merely a latent but a direct synthon for entry into enolate anion chemistry.

4.2 From Carbonyl Compounds to Organozinc Carbenoids.

The direct deoxygenation of alicyclic ketones to alkenes (Equation 12) using chlorotrimethylsilane and zinc was the first paper in which, as an independent investigator, I was required to be the author of my own experimental work.[26] Looking back, almost twenty years later, it is horrifying to note that I was apparently so "inebriated by the lugubrious use of polysyllabic verbosity" that not a single structure or visual scheme appears in the text! This, in retrospect, was a blessing in disguise, since the communication went largely unnoticed by the chemical community and we were therefore allowed to return to this area some years later on completion of my apprenticeship.

In mechanistic terms, the essence of the reaction is most readily appreciated as a simple variant of the more familiar Clemmensen reduction, in which the proton has been replaced by a silicon electrophile (**Scheme 19**). The major difference, of course, is that the key organozinc carbenoid (**20**), whether it be regarded as a homogeneous Simmons-Smith like entity or as attached to the zinc surface, does not evolve to a geminal disilane, but undergoes reactions which are typically carbenoid in nature, as in the alkene formation shown above or in the formation of bicyclo [3.3.0] octane from cyclooctane by transannular insertion (Equation 13).[26]

Within the last three years, our efforts have focused on the development of intermolecular reactions of aryl and α, β-unsaturated carbonyl compounds. Such substrates are particularly prone to undergo pinacolic coupling or dimerisation at the softer β-carbon atom as a result of single electron transfer. Our first requirement was therefore to improve the efficiency of carbenoid generation. Since the formation of these species requires two silicon electrophiles, the simple selection of 1,2-bis(chlorodimethylsilyl)ethane, which can cater for intramolecular delivery of

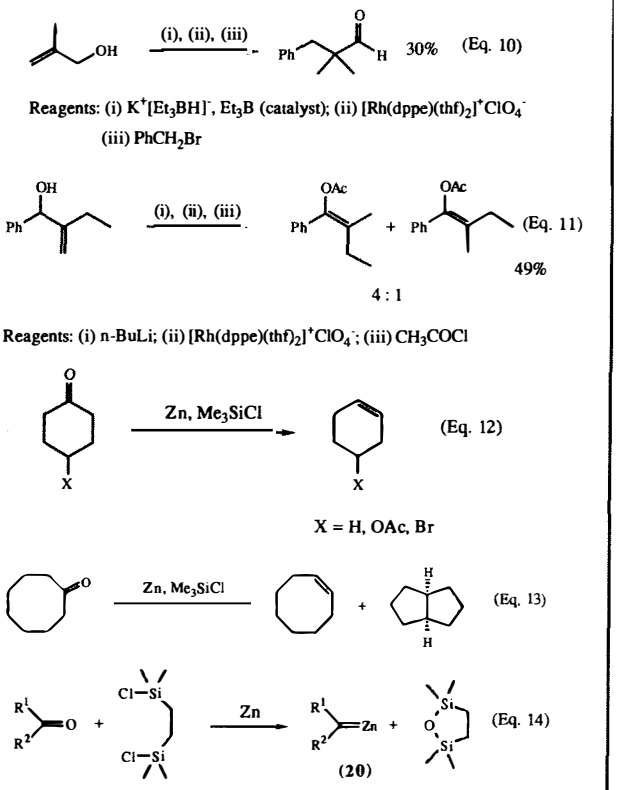


Scheme 18

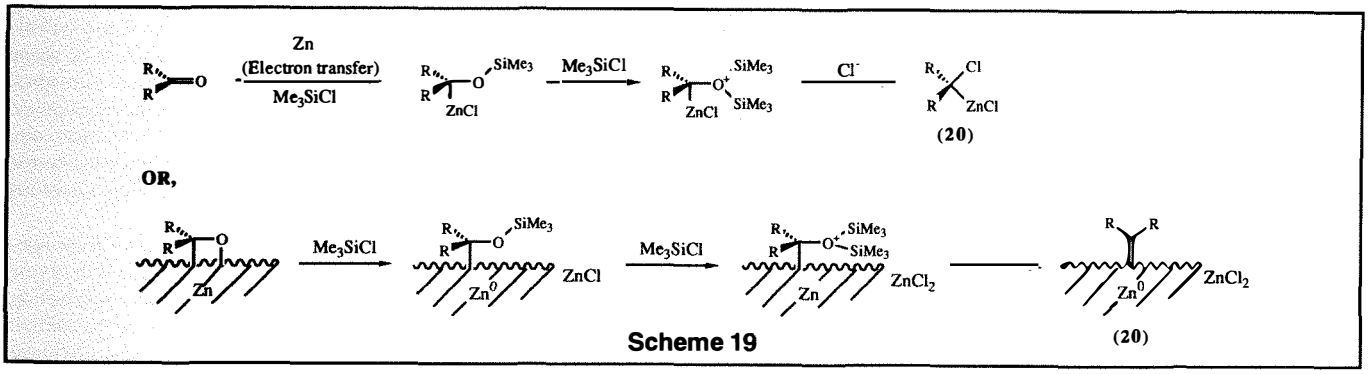
the second silicon atom, seemed to offer a convenient solution (Equation 14).

In this way, we were able to improve the yields in a symmetrical dicarbonyl coupling reaction which we had discovered some time earlier.[27] Some representative examples of stilbene derivatives and highly hindered trienes which can be prepared are shown in **Scheme 20**.[28]

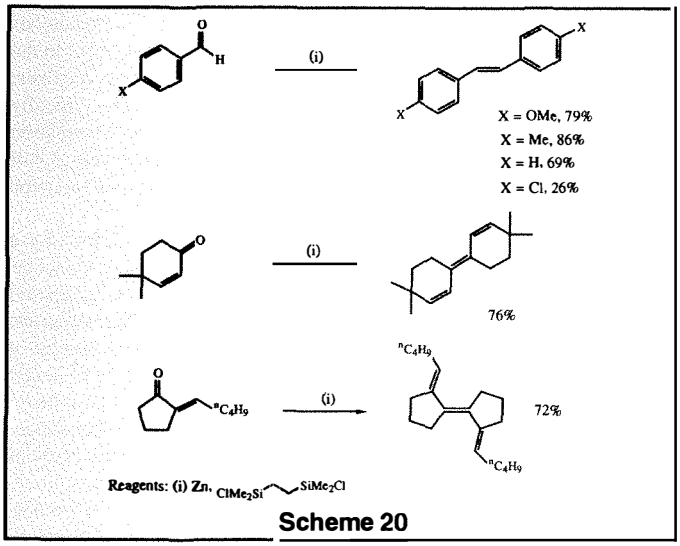
Unlike the McMurry reaction, vicinal diols or their derived silyl ethers are inert, and the most probable mechanism at the present time involves trapping of the organozinc carbenoid by a second molecule of carbonyl compound to give a carbonyl ylide followed by subsequent deoxygenation of the resultant epoxide (**Scheme 21**). Some evidence for this pathway comes from an attempted intramolecular coupling of (**21**) (**Scheme 22**) in which epoxide formation is retarded by a combination of electronic effects and ring strain and the reaction pathway is therefore diverted to the enol



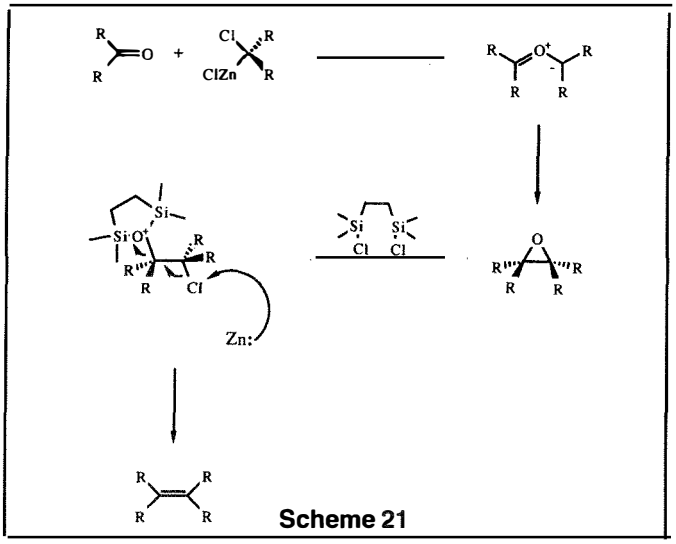
Equations 10 - 14



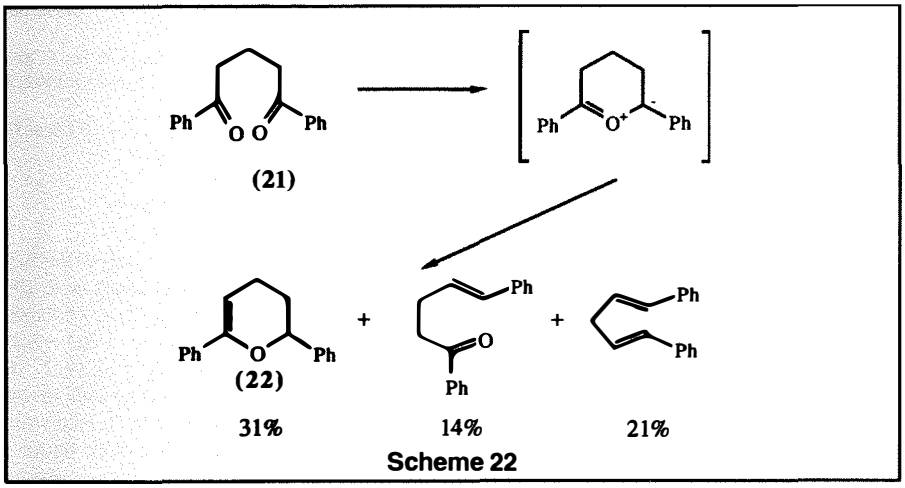
Scheme 19



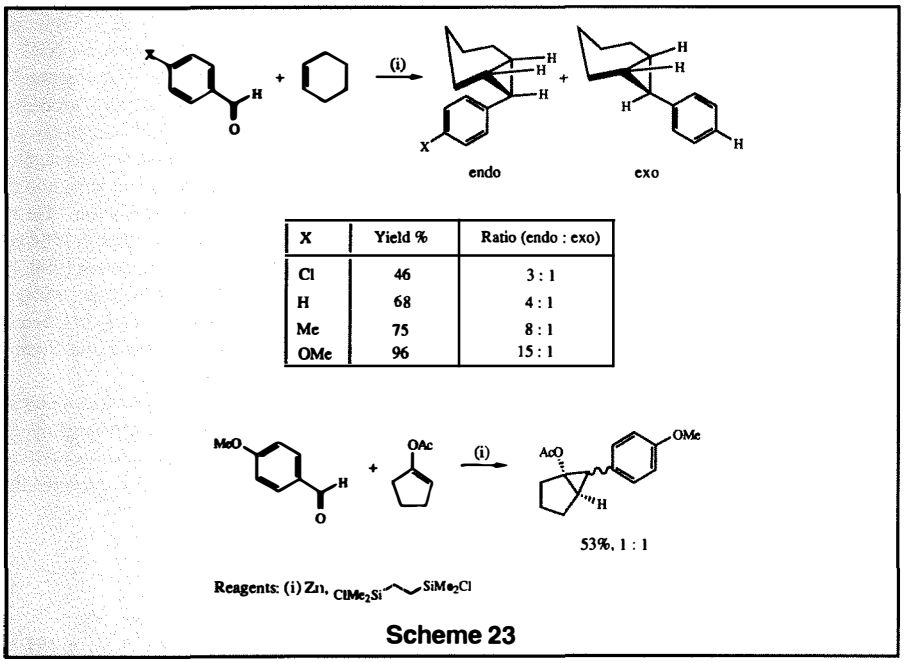
Scheme 20



Scheme 21

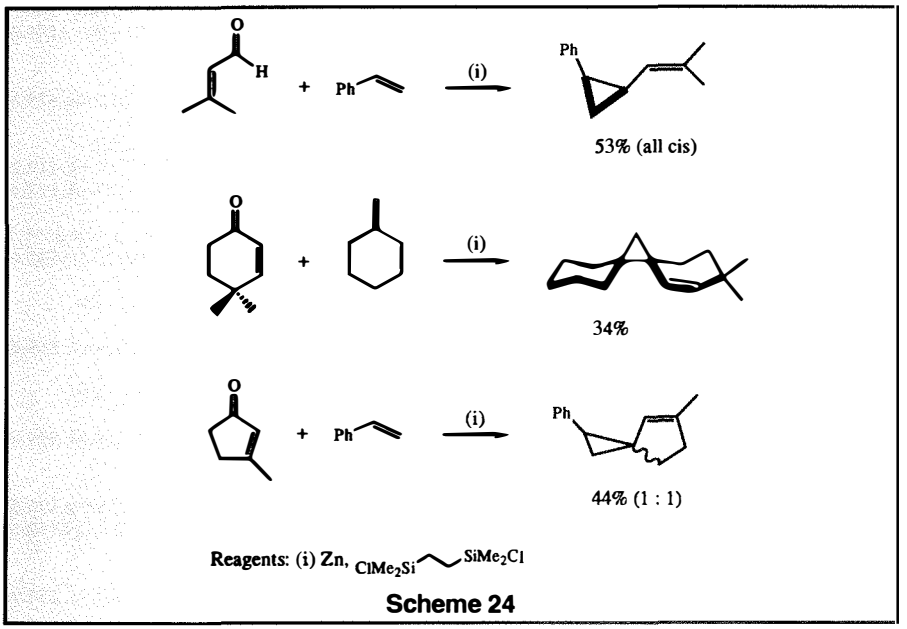


Scheme 22



X	Yield %	Ratio (endo : exo)
Cl	46	3 : 1
H	68	4 : 1
Me	75	8 : 1
OMe	96	15 : 1

Scheme 23



Scheme 24

ether (**22**). The formation of a variety of ylide species using organozinc carbenoids is, of course, an interesting prospect.

The simplest, and most potentially useful intermolecular reaction of an organozinc carbenoid, would be for the cyclopropanation of alkenes in a fashion reminiscent of the Simmons-Smith reaction, but without the necessity for preparation and handling of the diazo or gem dihalo precursors which are required for other metallocarbenoids. Moreover, in view of the fact that we have spent a considerable time breaking cyclopropane bonds, it seemed only appropriate that we should contribute to their preparation. The preliminary experiment using benzaldehyde, cyclohexene, zinc and chlorotrimethylsilane may be found in my 1973 lab notebook!

The results for a series of aromatic aldehydes are shown in **Scheme 23**.[29] The trapping of the organozinc carbenoid derived from para methoxybenzyaldehyde using only 2.0 molar equivalents of cyclohexene is particularly striking both in terms of yield and stereoselectivity. Curiously, however, with other substrates, although the isolated yields parallel those of the Clemmensen reduction, this is also mirrored by a decrease in stereoselection.

We have also found that the vinylidene carbenoids from a variety of acyclic and alicyclic α,β-unsaturated carbonyl compounds can also be usefully trapped in a reaction which is of considerable potential for natural product synthesis (**Scheme 24**). It would appear however that some degree of steric crowding or alkyl branching around the β-terminus of the enone unit is necessary for efficient generation and trapping of this class of substrate, since simpler substrates such as cyclohexenone and cyclopentene-1-carboxaldehyde fail to yield adducts.

Although the above discussion has centred on the generation of organozinc carbenoids, it is important to recognise that, in principle, any metal surface or organometallic anion capable of delivering two electrons to a carbonyl group may, in the presence of two silicon electrophiles, provide a general route to metallocarbenoids.

5. CONCLUSIONS

Within the last twenty years, spectacular advances have been made in synthetic organic chemistry. Unfortunately, however, in terms of their relationship with colleagues in other scientific disciplines, these achievements have often been understated by the very practioners of the art themselves. It is perhaps time to reverse this trend. As every bench chemist knows, curiosity driven research is only possible because our level of fundamental understanding of the subject is such that there is still no substitute for careful experimentation. In our own brief experience, our predictive power, as measured by response to the simple question "What if ....?", only convinces us that most of the useful reactions have yet to be discovered.

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Most of all, however, it has been my joy and privilege to be associated with those postgraduate students and postdoctoral fellows in our group, a very special Imperial College breed; without their commitment, determination, perseverance and enthusiasm our joint curiosity could not even begin to be assuaged.

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About the Author

Dr. William B. Motherwell received the B.Sc. degree from the University of Glasgow in 1969 and, as the holder of a Carnegie Trust scholarship under the supervision of Dr. James S. Roberts, the Ph.D. from the same institution in 1972. He subsequently worked as an independent investigator under the auspices of an I.C.I. Fellowship, prior to joining Professor Sir Derek Barton at Imperial College as a Schering-Plough postdoctoral fellow in 1975. Research was then transferred in 1977 to the Institut de Chimie des Substances Naturelles of the French CNRS in Gif-sur-Yvette where, as Chargé de Recherche, he continued to collaborate with Professor Barton during a highly creative period which saw the initiation of studies on organobismuth reagents, acylthiohydroxamate radical precursors, and the Gif system for hydrocarbon oxidation. He returned to Imperial College as lecturer in 1984 and became Reader in Organic Chemistry in 1990. He was the recipient of the 1983 Corday Morgan Medal and Prize of the Royal Society of Chemistry and most recently in 1991, the Royal Society of Chemistry Bader Award.

His current research interests centre around the development of new reactions and reagents for organic synthesis, particularly focusing on those which involve free radical and organometallic intermediates.

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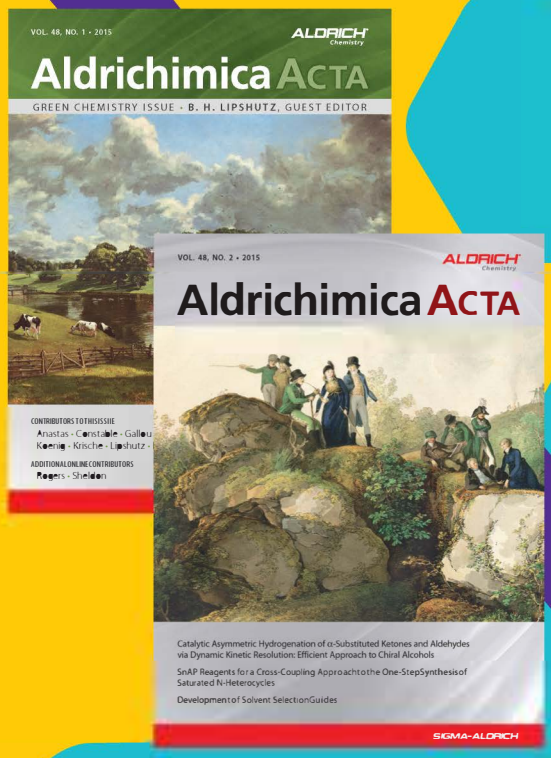

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