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Electrochemistry in Organic Synthesis

The Ireland-Claisen Rearrangement

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About Our Cover:

This painting (oil on canvas, 17⅞ x 27³⁄₁₆ in.) from the collection of The Saint Louis Art Museum is entitled *The Dovecote* and was painted in 1758 by the French artist Francois Boucher (1703-1770). Few artists were ever so completely in sympathy with the tastes and values of their patrons as Francois Boucher. A delightful landscape painted at the height of his career, this painting is just the sort of confection that made him the favorite of Louis XIV's mistress Madame de Pompadour and her fashionable circle. The dovecote tower and other elements of the composition are based perhaps on sketches made from life, but this is no record of a particular place. Instead, Boucher has conjured up an enchanted garden as charming as it is unreal. The idealized conception of country life expressed in this painting was shared by Boucher's patrons, who, to amuse themselves, would sometimes don rustic costumes and play at milking cows or tending sheep.

Color is a key ingredient in creating the painting's delectable illusion, from the deep blue-green foliage against the frosted blue sky to the touches of pale pink and bright coral. Boucher's masterful manipulation of light and shadow and the undulating curves that animate the sky, the trees, and even the rickety bridge bespeak the plausibility of this impossible world, so fluently rendered in short strokes of thickly applied paint.

Enthusiasm for charming yet highly artificial works like this one was not universal among Boucher's contemporaries. To the philosophers of the Enlightenment, such bonbons were symptomatic of the moral and intellectual flabbiness of the French ruling class.

Lab Notes

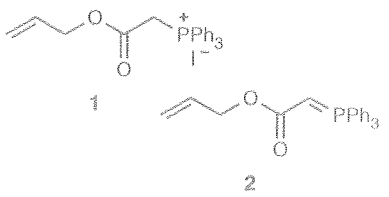
Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to: Aldrich (attn: Lab Notes, Aldrichimica Acta).

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



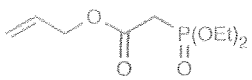
1

2

Dr. David Dean of Smith Kline Beecham Pharmaceuticals (U.K.) suggested that we offer the phosphonium salt **1** and its ylide **2**. The allyl ester group of the α,β-unsaturated esters (resulting from the Wittig reaction of aldehydes and ketones with **2**) can be readily removed using standard palladium or rhodium chemistry.

Naturally, we added these products to our listings.

Vyplel, H. et al. *J. Med. Chem.* **1991**, *34*, 2759.

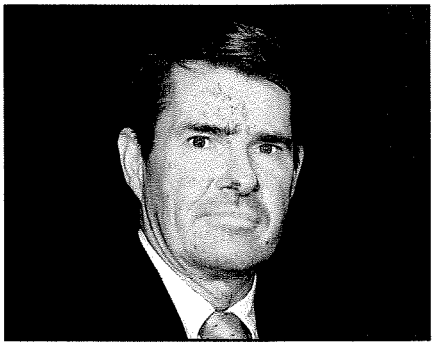


The phosphonoester analogs of Wittig reagents frequently expand the scope of Wittig reactions by offering different E/Z-selectivity and modified workup conditions (i.e., easier removal of by-products). Thus, we took Dr. Dean's suggestion one step further and have added allyldiethylphosphonoacetate as a new Aldrich product as well.

Hoffman, R.W. et al. *Liebigs Ann. Chem.* **1990**, 23.

Electrochemistry in Organic Synthesis

Albert J. Fry
Department of Chemistry
Wesleyan University
Middletown, Connecticut 06457



After many years as an exotic branch of organic chemistry, electrochemistry has become an important organic synthetic tool in recent years. This is primarily a result of advances made in the last decade or so, as well as increasing availability of electrochemical equipment. Many processes are now known which can be carried out more cleanly, quickly, cheaply, or in higher yield using electrochemistry than with other methods, and some reactions are known which can only be carried out electrochemically. There is a large organic electrochemical literature. For this review I have selected a number of examples from that literature to illustrate the kinds of reactions which can be carried out electrochemically. Unfortunately, many useful reactions could not be included because of space limitations. There are however a number of books and reviews on organic electrochemistry which can be consulted for further information.[1]

Electrochemistry deals with oxidation and reduction, depending on whether the reaction of interest takes place at the anode or the cathode of the cell, respectively. However, its scope is actually considerably broader: many reagents, including acids, bases, halogens, reactive metals and metal ions, etc., can themselves be made electrochemically for use *in situ*.[1] Electrochemical generation of reagents can be of considerable value when the reagent is expensive, hazardous or otherwise difficult to work with in large quantities, produces toxic by-products, or must be added to the medium at high dilution. One can, for example, easily produce reagents at steady-state concentrations as low as $10^{-5}M$ or less, simply by controlling the amount of current passing through the cell.[2] This review will primarily cover processes which occur by direct electrochemical reaction. There are a number of extensive reviews on processes in which a substance produced electrochemically is the actual reagent in the overall transformation.[1,3]

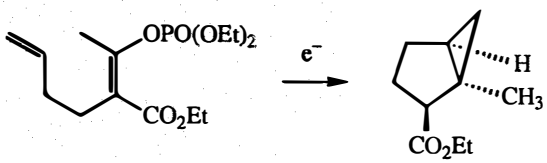
Electrochemical Reductive Cleavage of Single Bonds

Probably the simplest electrochemical reaction is the cleavage of a carbon-heteroatom bond. Most studies have involved alkyl halides, but the reaction is more general (eq 1). Although radicals are short-lived intermediates in such reductions[4] and radical derived products are occasionally isolated (eq 2),[5] in most cases the radical is usually immediately reduced to a carbanion. Equation 1 therefore constitutes a mild, neutral, and very general method for generating carbanions. The latter can react intramolecularly to form cyclized products (eqs 3-5)[6-9] or can be trapped by added electrophiles, including CO_2, aldehydes, ketones, acid anhydrides, acid chlorides, imines, trialkylsilyl and stannyl halides, and activated alkenes (eq 6).[10] Reduction in the presence of D_2O or T_2O allows regioselective

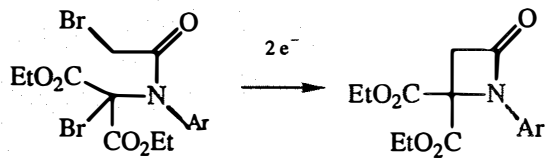
$$\text{R-X} + 2\,e^- \longrightarrow \text{R}^- + \text{X}^-$$

$$\text{X} = \text{Cl, Br, I, OSO}_2\text{R', SO}_2\text{R', SR', NR}_3\text{, etc.}$$

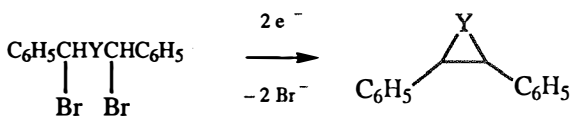
(eq 1)



(eq 2)

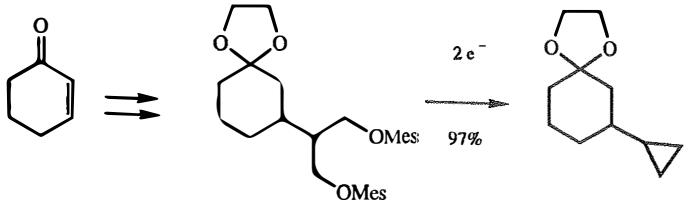


(eq 3)

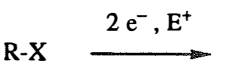


$$\text{Y} = \text{CH}_2,\ \text{CO},\ \text{S},\ \text{SO},\ \text{SO}_2,\ \text{P(O)(OCH}_3)_2$$

(eq 4)

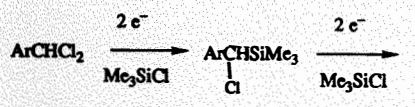


(eq 5)

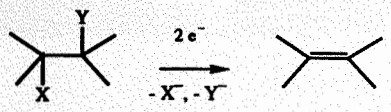


(eq 6)

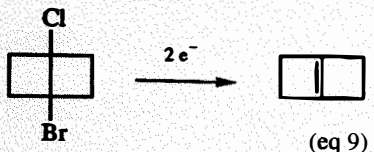
introduction of deuterium or tritium.[11] Metal ion catalysis frequently improves the efficiency of electrophilic trapping.[12] Stepwise introduction of trialkylsilyl groups can be effected by reduction of a geminal dihalide in the presence of a silyl halide (eq 7).[13] Alkenes can be prepared by reductive elimination of vicinal dihalides and other β-substituted alkyl halides (eq 8). The reaction has been used for synthesis of strained alkenes (eqs 9-10)[14,15] and in schemes for protection and deprotection



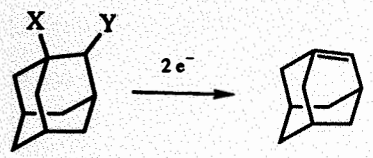
(eq 7)



(eq 8)

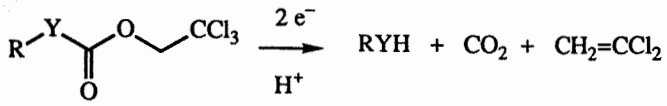


(eq 9)

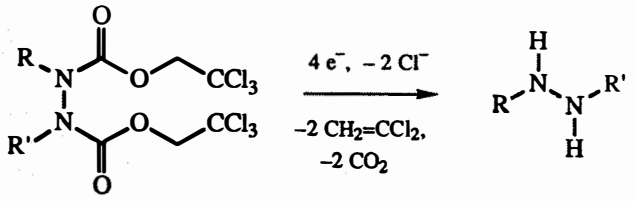


(eq 10)

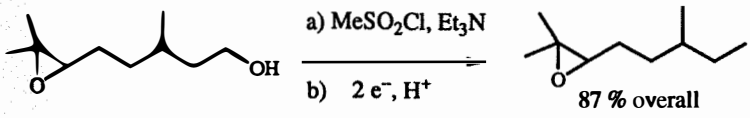
of alcohols, thiols, amines, carboxylic acids, hydrazines, and alkenes (eqs 11-12).[16-18] In a protic medium the carbanion is protonated. One can take advantage of the high selectivity associated with such cleavages to remove functional groups in the presence of sensitive functionality (eqs 13-14).[19,20] Fry and co-workers carried out an extensive study of the electrochemical reduction of α,α'-dibromoketones (**1**) in protic media.[21] The initial intermediate is a 2-oxyallyl bromide, which immediately ionizes and is protonated to afford a hydroxylallyl cation (**2**) which then reacts with a nucleophile in the medium providing an α-substituted ketone (**Scheme 1**). Reduction in the absence of nucleophiles affords an α-methylene ketone.[22] Reduction of α,α-dibromoketones, on the other hand, affords products which appear to derive from a zwitterion (**3**) or its diradical equivalent (**Scheme 2**).[23] Reduction of α,ω-dihalides in the presence of activated alkenes yields cyclized materials (eq 15).[24]



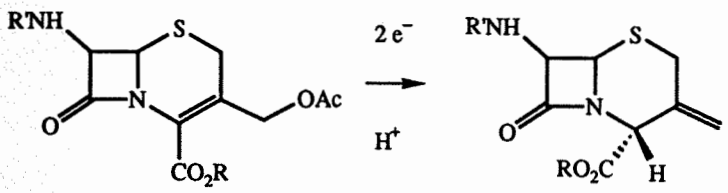
R = an alkyl or acyl group; Y = O, S, or NR' (eq 11)



(eq 12)

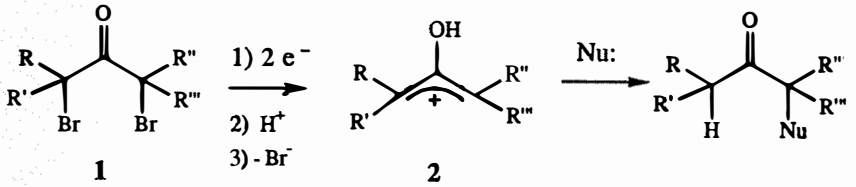


(eq 13)

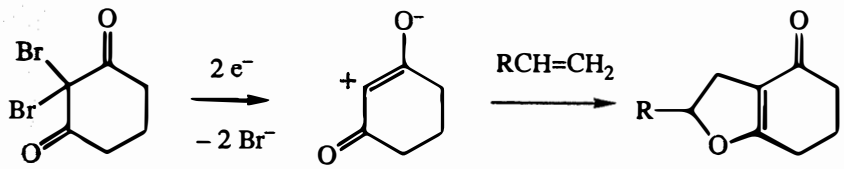


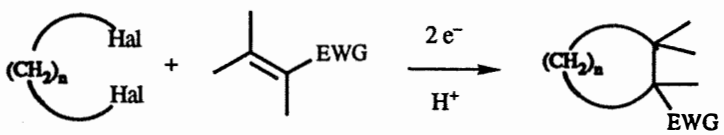
(eq 14)

Scheme 1



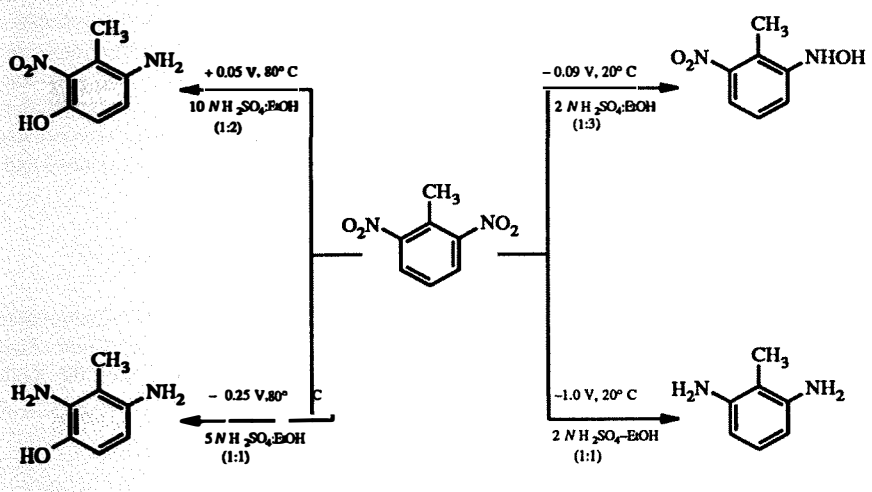
Scheme 2



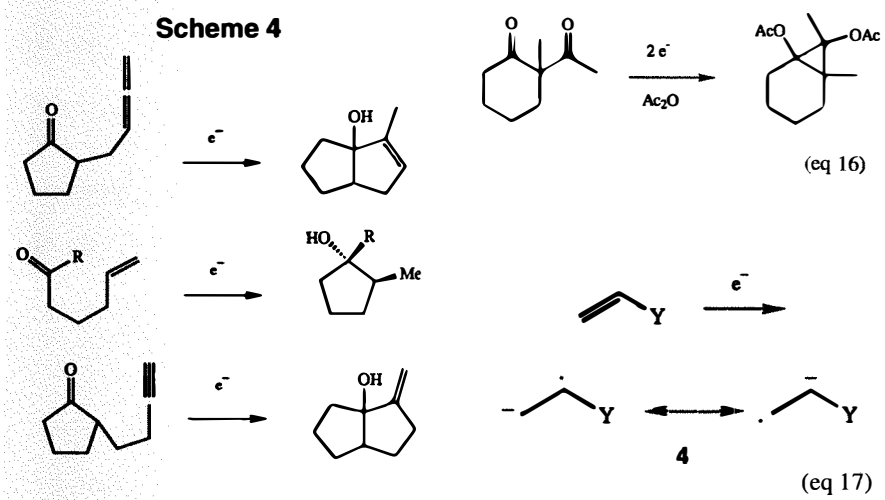


(eq 15)

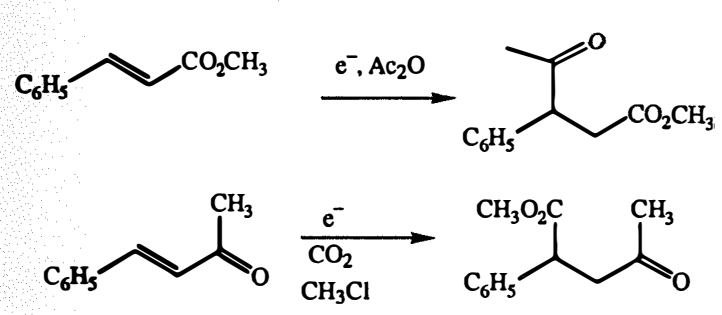
Scheme 3



Scheme 4



Scheme 5



Electrochemical Modification of Functional Groups

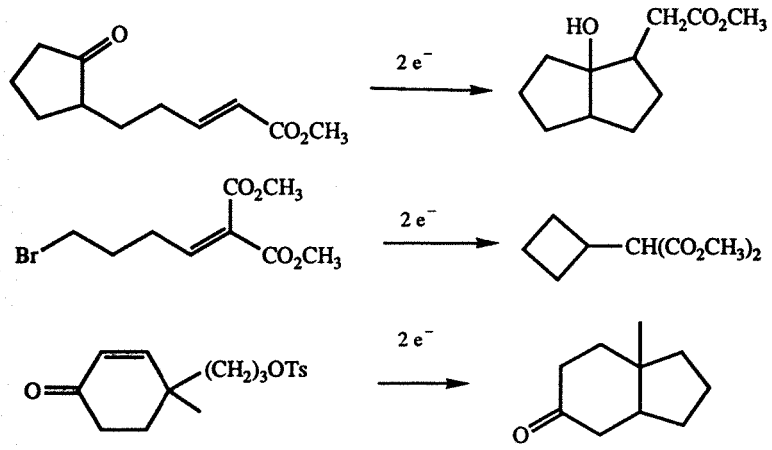
A variety of organic functional groups, including carbonyl, thiocarbonyl, imine, azo, nitroso, nitro, and diazonium, can be reduced electrochemically.[1,25] Furthermore a given functional group can frequently be converted electrochemically into several different products depending upon conditions. For example, a nitrobenzene may be converted into an aniline, phenylhydroxylamine, *p*-aminophenol, azoxybenzene, azobenzene, hydrazobenzene, or benzidine by proper control of the reduction potential, pH and temperature (**Scheme 3**).[26]

One does have to keep a sense of perspective here. Electrochemistry may not be the method of choice when a chemical reductant is already available to effect a desired conversion. For example, it would be absurd to use electrochemistry to reduce an aldehyde or ketone to the corresponding alcohol when the same conversion can be done easily using a metal hydride. Similarly, there are a number of good chemical and catalytic methods for converting nitro compounds into amines. Electrochemistry can be competitive when high selectivity is needed or when the necessary reagent is expensive or less effective. For example, electrochemical reduction of nitro compounds to hydroxylamines can be carried out easily in a simple apparatus,[1,25a] whereas catalytic reduction is prone to over-reduction, and chemical reduction to the hydroxylamine stage requires the expensive reagent SmI_2.[27a] (For those applications which do require SmI_2, it is much cheaper to prepare *in situ* electrochemically than to use the preformed material).[27b] Electrochemical reduction is also useful when one wishes to trap reactive intermediates: electrolytic reduction of carbonyl compounds in aprotic media affords ketyls, which can be trapped intramolecularly by nearby sites of unsaturation (**Scheme 4**).[28] Similarly, electrochemical reduction of 1,3-diketones in the presence of acetic anhydride affords 1,2-cyclopropanediol derivatives (eq 16).[29]

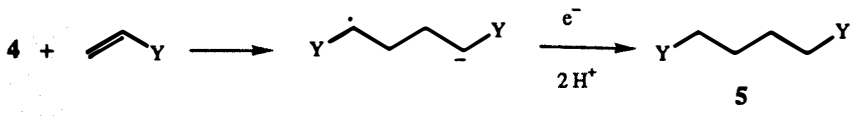
Eletrochemical Reductions of Conjugated Systems

Electrochemical reduction of activated alkenes has proven to be a versatile synthetic process, particularly in non-aqueous media, where the initial intermediate is a radical anion (**4**) (eq 17), which carries negative charge at the β-carbon and can undergo reaction at that site with electrophiles (**Scheme 5**).[30] Little and Baizer, among others, have reported a number of intramolecular variants on this process (**Scheme 6**).[31-33] The propensity of species **4** to afford dimeric products by Michael-type attack upon the starting material to give so-called "hydrodimers" (**5**)

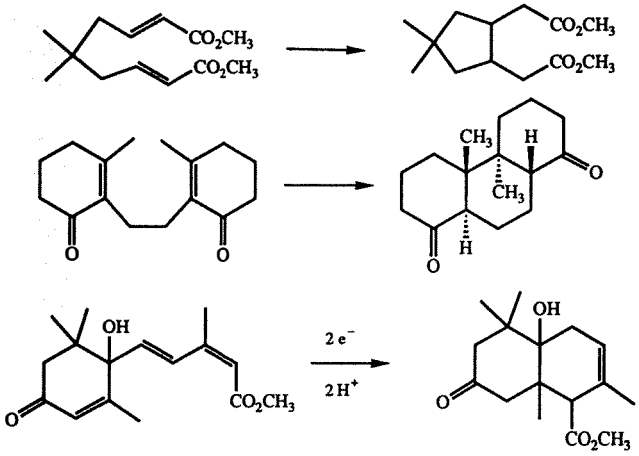
Scheme 6



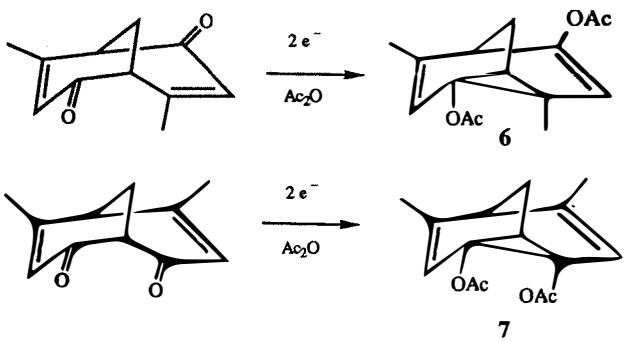
Scheme 7



Scheme 8



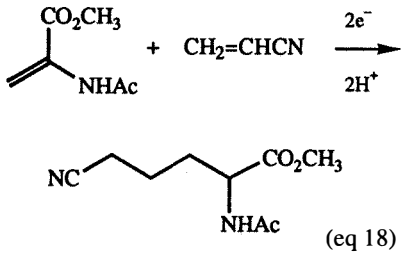
Scheme 9



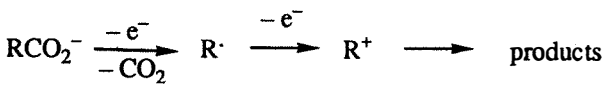
(**Scheme 7**) is of considerable interest.[1,34] The reaction can be carried out intramolecularly (**Scheme 8**) and between unlike components to afford mixed hydrodimers; one such reaction is the key step in a short synthesis of lysine (eq 18).[35] Although hydrodimerization usually occurs "tail-to-tail' so as to connect the two β-carbons, head-to-tail and head-to-head dimers have occasionally been isolated, as in the synthesis of the barbaralanes **6** and **7** (**Scheme 9**).[36]

Electrochemical Oxidation of Carboxylic Acids

One of the oldest reactions of organic chemistry is the electrochemical oxidation of carboxylates to afford dimers, i.e., the Kolbe reaction (eq 19). Most functional groups are

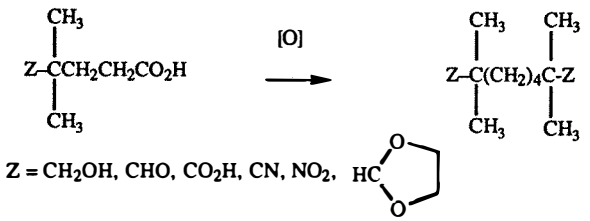


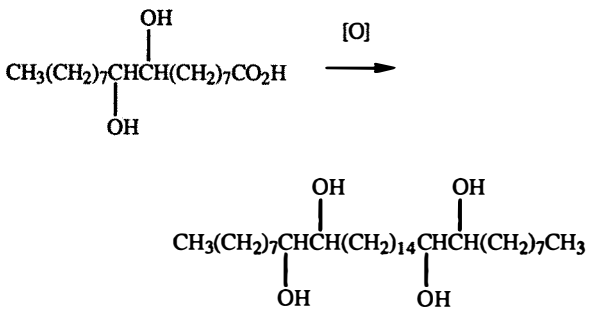
(eq 18)



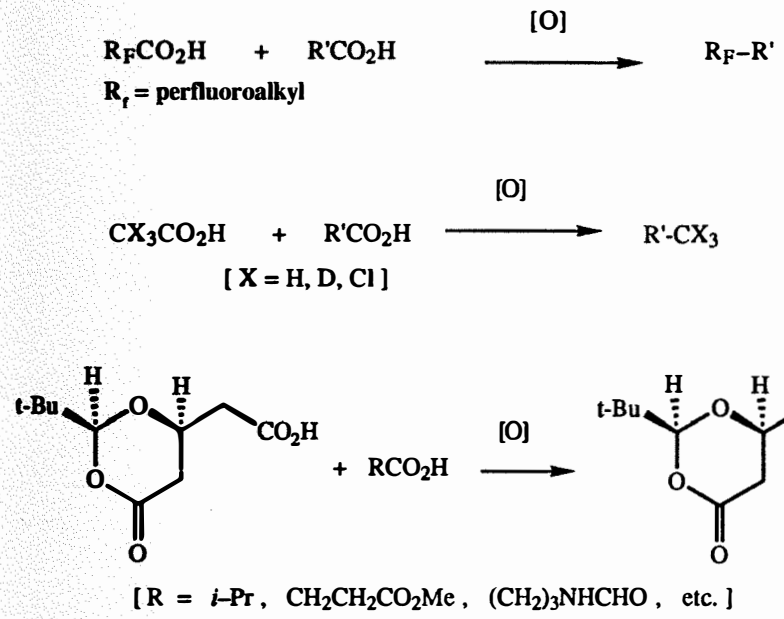
(eq 19)

Scheme 10



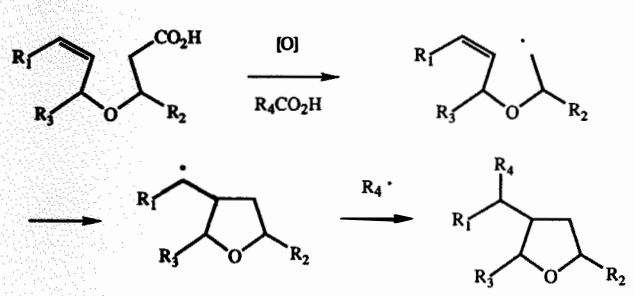


Scheme 11

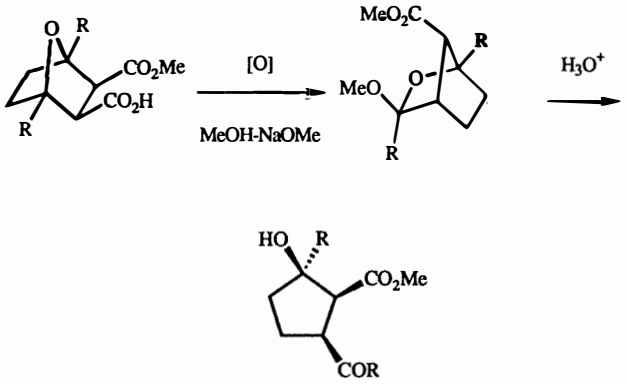


stable under Kolbe conditions[37] (**Scheme 10**) and mixed Kolbe reactions can be carried out between two carboxylic acids (**Scheme 11**).[38] A statistical mixture of all possible dimers is produced, hence such "crossed Kolbe" reactions are most useful where one of the components is cheaper than the other. Schäfer has reported crossed Kolbe reactions in which the radical intermediate from anodic oxidation of an unsaturated acid cyclizes before coupling (**Scheme 12**) and has used this sequence to synthesize complex tetrahydrofurans and pyrrolidines.[39] Under certain experimental conditions (high applied voltage, carbon anode) and especially when the intermediate radical carries one or more electron-supplying groups, further oxidation to a carbocation takes place. A variety of reactions depending upon this feature have been reported (**Scheme 13**).[40] Oxanorbornane half-acid esters undergo stereoselective conversion to highly substituted cyclopentane derivatives (**Scheme 14**).[41] Vicinal dicarboxylic acids can be anodically bis-decarboxylated to alkenes (**Scheme 15**).[42b] Bloomfield has reported especially efficacious conditions for anodic bis-decarboxylation.[42b]

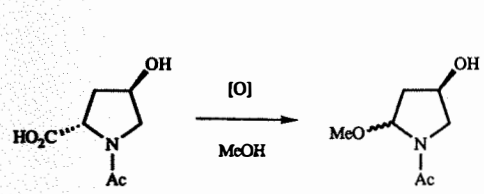
Scheme 12

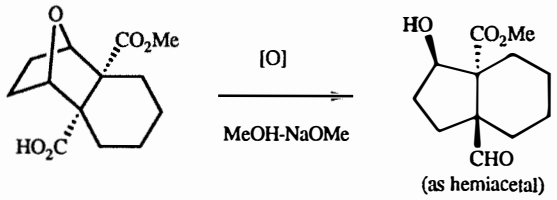


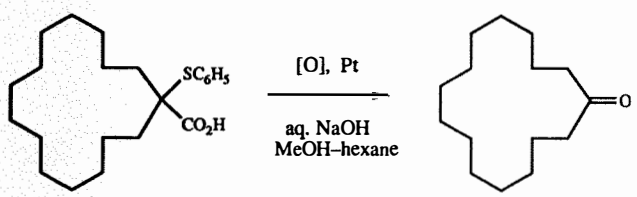
Scheme 14

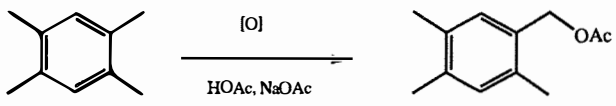


Scheme 13







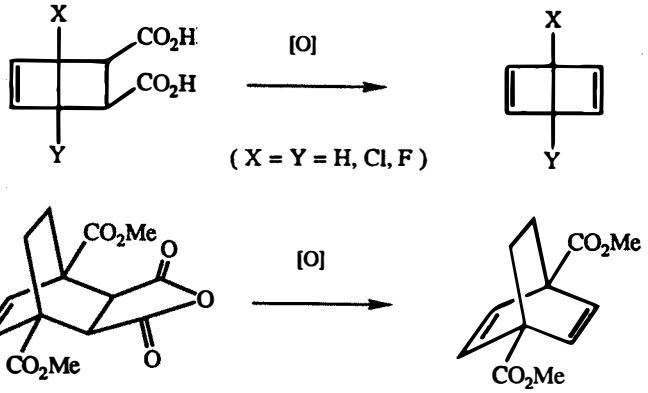


(eq 20)

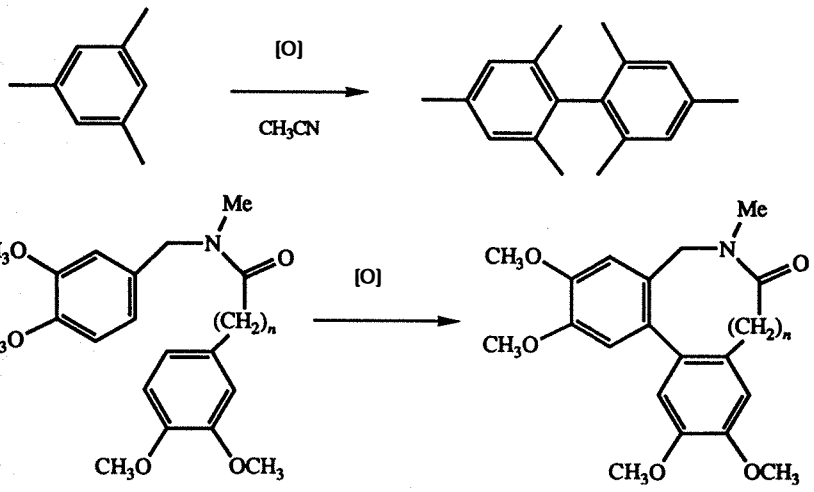
Electrochemical Oxidation of Aromatic Compounds

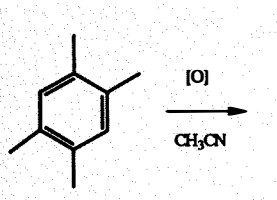
Aromatic hydrocarbons, phenol ethers, and aromatic amines undergo a diverse range of reactions under acidic conditions, including side-chain substitution (eq 20),[43] ring-to-ring coupling (**Scheme 16**),[44] and side chain-to-ring coupling (eq 21).[45] Which path a given substrate takes depends upon its structure and the experimental conditions.[1a] Oxidation of phenols affords species such as **8** which undergo nucleophilic attack at the position *para* to the phenol oxygen atom (**Scheme 17**).[46] Yamamura has applied this reaction in elegant fashion to the formation of polycyclic intermediates for natural product synthesis (**Scheme 18**).[47] Moeller has recently studied an analogous anodic reaction of enol ethers, in which a cationic intermediate cyclizes intramolecularly onto a nucleophilic alkene moiety (eq 22).[48] Anodic oxidation of hydroquinone mono and dialkyl ethers in alkaline methanol affords quinone mono- and bis- ketals, respectively (**Scheme 17** and eq 23).[46,49] Swenton has developed a large number of useful applications based upon this reaction, including preparation of a number of key intermediates in natural product synthesis.[50] Pirrung has recently shown that species **9** are converted photochemically to substituted cyclopentenones (**Scheme 19**).[51]

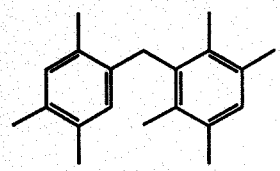
Scheme 15



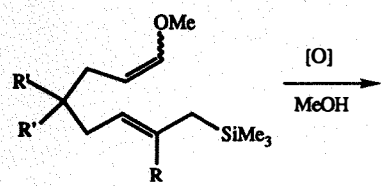
Scheme 16

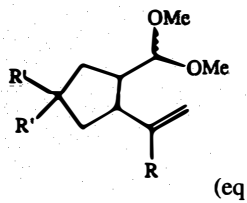






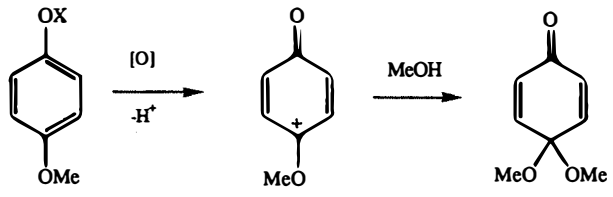
(eq 21)





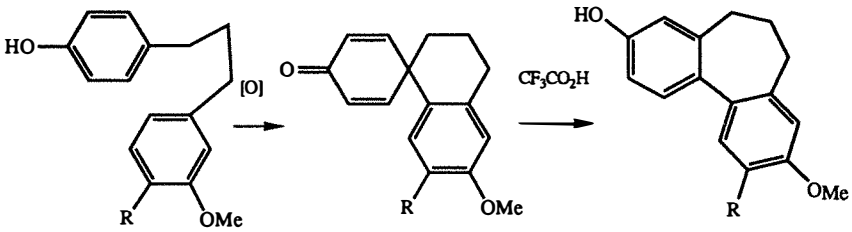
(eq 22)

Scheme 17

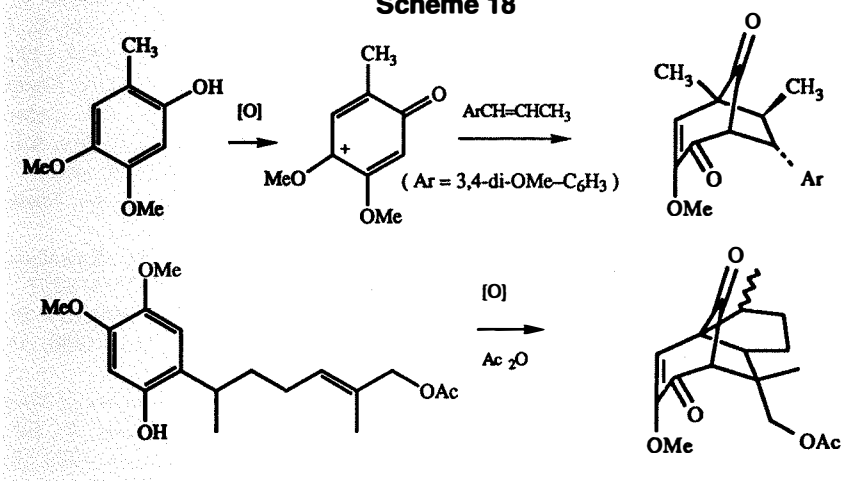


8

X = H, Me_3Si, *t*-$BuMe_2Si$, $MeOCH_2$



Scheme 18



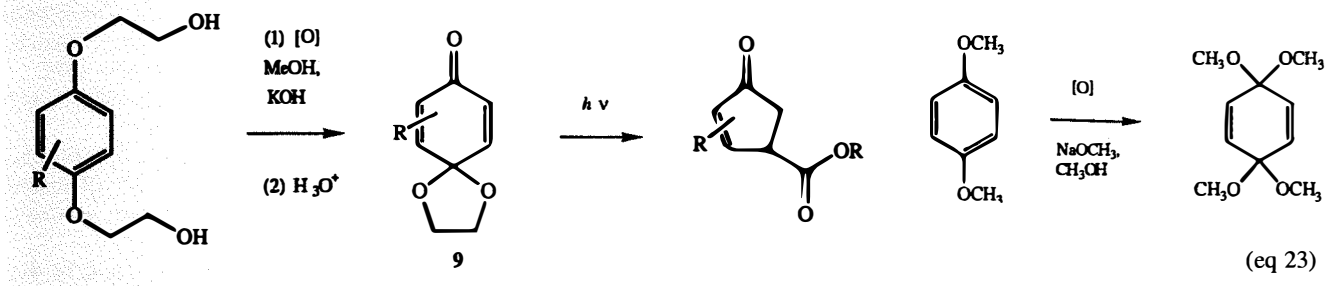
Functionalization Alpha to Heteroatoms

A new, important, and very general anodic process has been discovered in recent years in the electrochemical oxidation of nitrogen, sulfur, and oxygen compounds. This process, the so-called α-functionalization reaction (**Scheme 20**), has been intensively studied in a number of variations upon the process, including applications to the synthesis of heterocycles, e.g., a number of piperidine, pyrrolizidine, and indolizidine alkaloids (**Scheme 21**).[52a]

Experimental Aspects

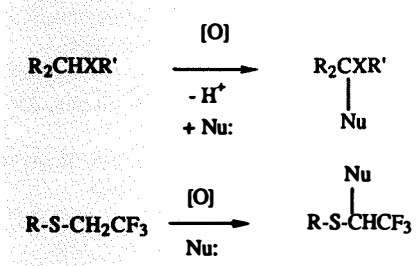
Every synthetic organic laboratory should have electrochemical equipment. The equipment is simple, inexpensive and versatile, i.e., it can be used for a wide variety of electrolytic processes. One inhibiting factor

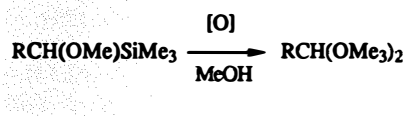
Scheme 19

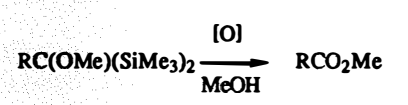


(eq 23)

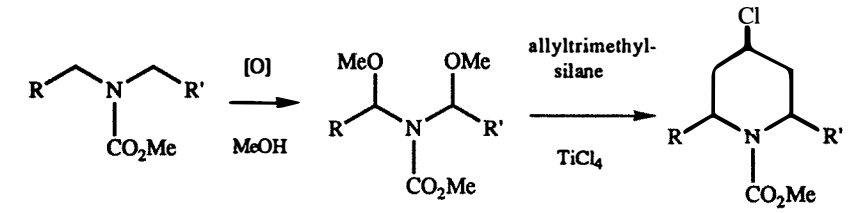
Scheme 20

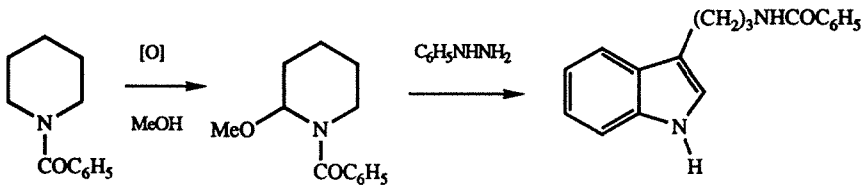


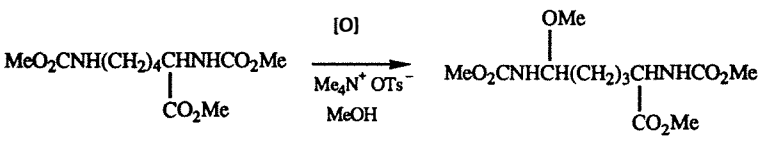




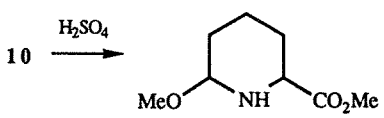
Scheme 21







10



in the past was the availability of equipment. One had to obtain each component of the experiment from a separate source, and generally even had to have the cell constructed by a glassblower. [Imagine what organic synthesis would be like if we had to have our three-necked flasks made to order in the glassblower's shop!] Fortunately, these days the situation is much improved. There are companies which offer a wide variety of electrochemical supplies,[53] and one such company[54] sells a complete kit containing all of the components needed to carry out an electrolysis (power supply, cell, electrodes, and step-by-step directions). There is not sufficient space available in this review, nor is this the proper place, for a detailed discussion of experimental details. My advice is rather to first learn what electrochemistry can do for you— if after examining the examples and references in this article you want to try an electrolysis, there are a number of good references available which discuss the theory and experimental details and which are written with the organic chemist in mind.[1] Companies in the field are generally eager to offer advice.[53,54]

Scale and Scale Up

The largest single factor governing the scale on which one can carry out a given electrochemical process is the electrical resistance of the solvent system, because heating effects become serious in high-resistance solvents at high currents. Although solvents as nonpolar as tetrahydrofuran can be used for small scale work,[13] it is more common to use a fairly polar organic solvent or an aqueous-organic mixture. Kadish has tabulated the resistance of a variety of common organic solvents.[55]

In general, using a reasonably polar organic solvent system, it is not difficult to prepare up to 20 grams or so of a desired substance electrochemically. Larger amounts can be prepared with some modification of the experimental equipment used; frequently this will involve changing from batch to flow cell operation.[1a] Successful scaleup to greater than laboratory-scale quantities requires careful attention to experimental design, but there are no intrinsic barriers to large-scale electrolysis: commercial organic electrochemical syntheses producing more than 100,000lb/year are known.

Acknowledgements

The hospitality and helpfulness of the faculty and staff of the University of California at Santa Barbara, especially Professor R. Daniel Little, during a sabbatical leave from Wesleyan University during which this article was written, are gratefully acknowledged. The National Science Foundation and the State of Connecticut provided financial support for those aspects of the work discussed herein which were carried out at Wesleyan University.

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About the Author

Albert J. Fry was born in Philadelphia, Pennsylvania. He received the B.S. degree in chemistry from the University of Michigan in 1958 and the Ph.D. degree in organic chemistry from the University of Wisconsin in 1963 for work with Professor David Lemal on the synthesis of novel carbenes and carbene precursors. After a year of postdoctoral research in organic photochemistry with Professor George Hammond at the California Institute of Technology, he joined the faculty of Wesleyan University. He has been Professor of Chemistry since 1977 and has served several terms as departmental chairman during his tenure.

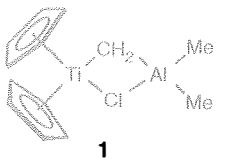
Professor Fry has carried on research in the mechanistic and synthetic aspects of organic electrochemistry for over 25 years. His interests include the mechanism, stereochemistry, and applications of the electrohemical reduction of alkyl halides, the electrochemical behavior of aromatic and non-benzenoid aromatic hydrocarbons, and the application of quantitative techniques of linear sweep and cyclic voltammetry to mechanistic analysis. Recently, he has begun a collaboration with Professors Susan Sobolov of Wesleyan University and James Fenton of the University of Connecticut, directed toward the use of enzyme-modified electrodes in large scale synthesis.

Prof. Fry is the author of *Synthetic Organic Electrochemistry*, 2nd ed. (Wiley, 1989) and the co-editor of *Topics in Organic Electrochemistry* (Plenum, 1986) with Dr. Wayne E. Britton, a former student. He has had a long-time interest in encouraging organic chemists to explore the use of electrochemistry in synthesis, and to that end started The Electrochemicals Company to supply electrochemical equipment, instruction, and advice in this exciting new area.

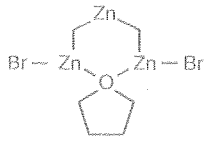
Methylenation Reagents

The conversion of a carbonyl group into an exocyclic vinyl group (methylenation) is an important synthetic transformation. Thus, methylenation reagents are valuable synthetic tools for the organic chemist and biochemist. Through judicious selection of the precise reagent and reaction conditions, high selectivities and yields can be achieved on a wide variety of substrates.

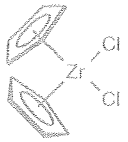
The Wittig reaction is a time-honored process for preparing terminal alkenes from simple ketones and aldehydes,[1-5] and we list a variety of reagents (phosphoranes, phosphonates, phosphonium salts, and salts admixed with a strong base) for this method. However, the Wittig reaction is limited to aldehydes and ketones with minimal steric hindrance that do not readily enolize.[1,3,6] The following newer methylenation reagents are offered as an alternative for such substrates.



1
Tebbe



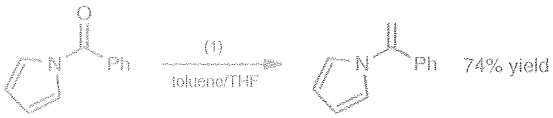
2
Nysted



3
Zirconocene Dichloride

The Tebbe Reaction

The "transition metal ylide" (**1**), known as the Tebbe reagent, readily methylenates ketones,[6a] aldehydes,[7] esters,[8] lactones,[8] and amides[9] without the limitations imposed by base-sensitive functionalities or sterically-hindered substrates. This example from the literature illustrates the utility and efficiency of this reagent.

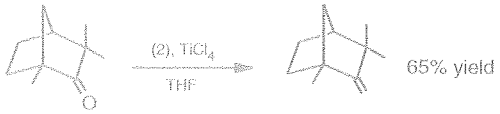


General Procedure[10]

To the N-acyl heterocycle in toluene/THF at 0°C is added dropwise a 0.5M toluene solution of the Tebbe Reagent (two-fold excess). After stirring at room temperature, the reaction is quenched at 0°C with methanol. When gas evolution has ceased, the mixture is diluted with ether, dried, filtered, and the crude product isolated by solvent removal.

The Nysted Reaction

The Nysted reagent (**2**) has been used in the conversion of keto-steroids to the corresponding methylene derivatives.[11] For sterically hindered ketones where Wittig methylenation fails and use of the Tebbe reagent gives very low yields, the Nysted reagent offers another possible route to the desired alkene.

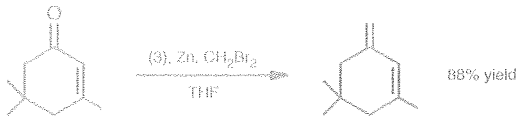


General Procedure[12]

A nitrogen-purged round-bottomed flask equipped with a stirrer, thermometer, condenser, and addition funnel is charged with a 30% excess of the Nysted reagent and cooled to -78°C. The desired ketone is added, followed by an equimolar amount of $TiCl_4$ while maintaining the temperature below -50°C. After warming to 25°C, the mixture is refluxed for 24 hours. The mixture is cooled, quenched with water, and the product isolated by ether extraction.

Zirconium-Promoted Methylenation

Recently, a zirconocene dichloride (**3**) promoted methylenation procedure has been found useful for cases when the more Lewis acidic titanium-based reagents give poor results.[13] Using **3** with dibromomethane and zinc allows the rapid methylenation of aldehydes, ketones and enones at room temperature in high yields.



General Procedure[13]

A nitrogen-flushed flask is charged with zinc, zirconocene dichloride, ketone, THF and dibromomethane. After stirring for 3 hours the mixture is quenched with water. The product is isolated by extraction.

References:

(1) Maercker, A. *Org. React.* **1965**, *14*, 270. (2) House, H.O. *Modern Synthetic Reactions*; Benjamin: Menlo Park, CA, 1972, pp 709-862. (3) *Organophosphorous Reagents in Organic Synthesis*; Cadogan, J.I.G., Ed.; Academic: New York, 1979. (4) Bestman, H.J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, *109*, 65. (5) Kulkarni, Y.S. *Aldrichim. Acta* **1990**, *23*, 39. (6)a) Pine, S.H. etal. *Synthesis* **1991**, *2*, 165. b) Sowerby, R.L. et al. *J. Am. Chem. Soc.* **1972**, *94*, 4558. c) Fieser, M.; Fieser, L.F. *Reagents for Organic Synthesis*; Wiley: New York, 1975; Vol. 5, pp 458,527. d) McMurry, J.E. et al. *Tetrahedron Lett.* **1980**, *21*, 2477. e) Boeckman, R.K., Jr. et al. *ibid.* **1973**, *36*, 3497. (7) Tebbe, F.N. et al. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (8) Pine, S.H. etal. *ibid.* **1980**, *102*, 3270. (9) Pine, S.H. etal. *J. Org. Chem.* **1985**, *50*, 1212. (10) Wattanasin, S.; Kathawala, F.G. *Synth. Commun.* **1989**, *19*, 2659. (11)a) Nysted, L.N. US Patent 3 865 848, 1975; *Chem. Abstr.* **1975**, *83*, 10406q. b) Nysted, L.N. US Patent 3 960 904, 1976; *Chem. Abstr.* **1976**, *85*, 94618n. (12) Unpublished results, Aldrich Chemical Company, Inc. (13) Tour, J.M. et al. *Tetrahedron Lett.* **1989**, *30*, 3927.

The Aldrich Library of FT-NMR Spectra

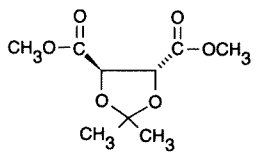
A

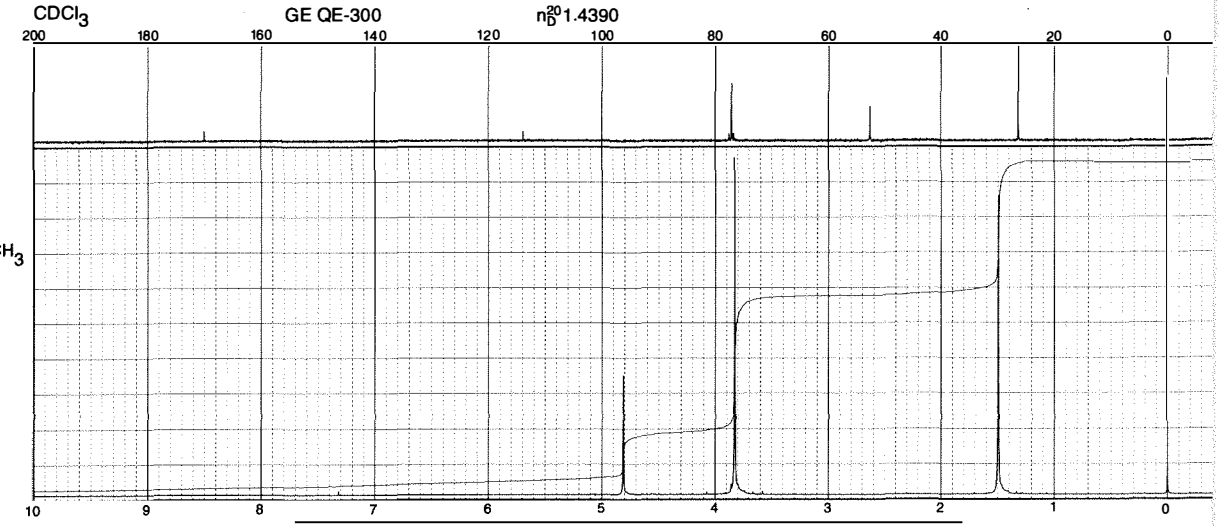
Aldrich 35,906-8 *CAS [37031-29-1]*

(4*R*,5*R*)-(-)-Dimethyl 2,3-*O*-Isopropylidene-l-tartrate

$C_9H_{14}O_6$ Fp >230°F
FW 218.21
bp 150°C (19 mm)
d 1.188
n_D^{20} 1.4390

$CDCl_3$ GE QE-300





B

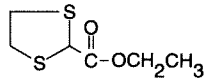
Aldrich 22,630-0 *CAS [20461-99-8]*

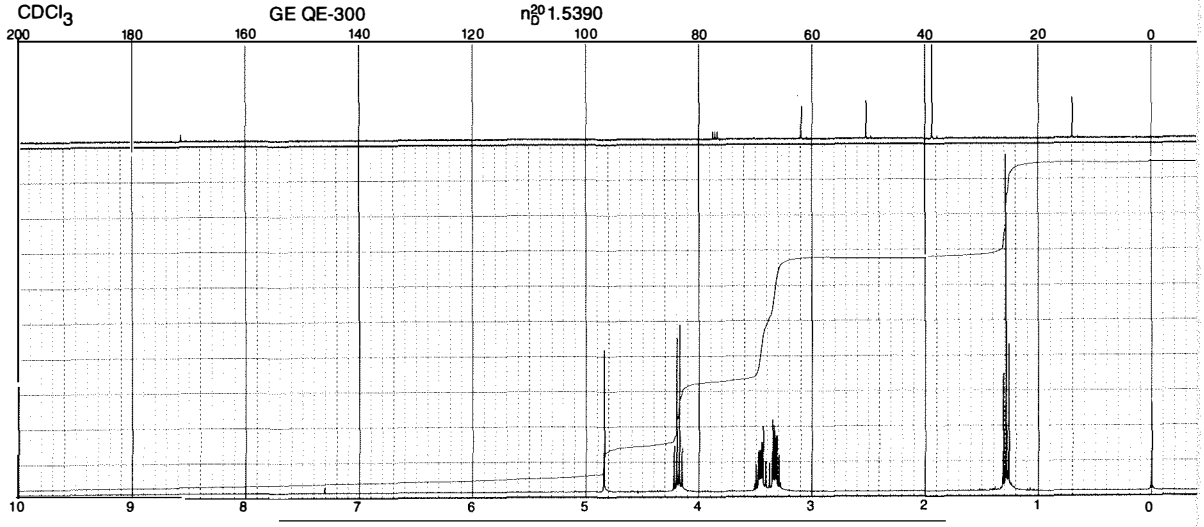
Ethyl 1,3-dithiolane-2-carboxylate

$C_6H_{10}O_2S_2$ Fp >230°F
FW 178.27
bp 85°C
d 1.249
n_D^{20} 1.5390

60 MHz: ***1***, 566A
FT-IR: ***1***, 676B
VP-FT-IR: ***3***, 739C

$CDCl_3$ GE QE-300





C

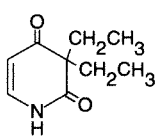
Aldrich 21,010-2 *CAS [77-04-3]*

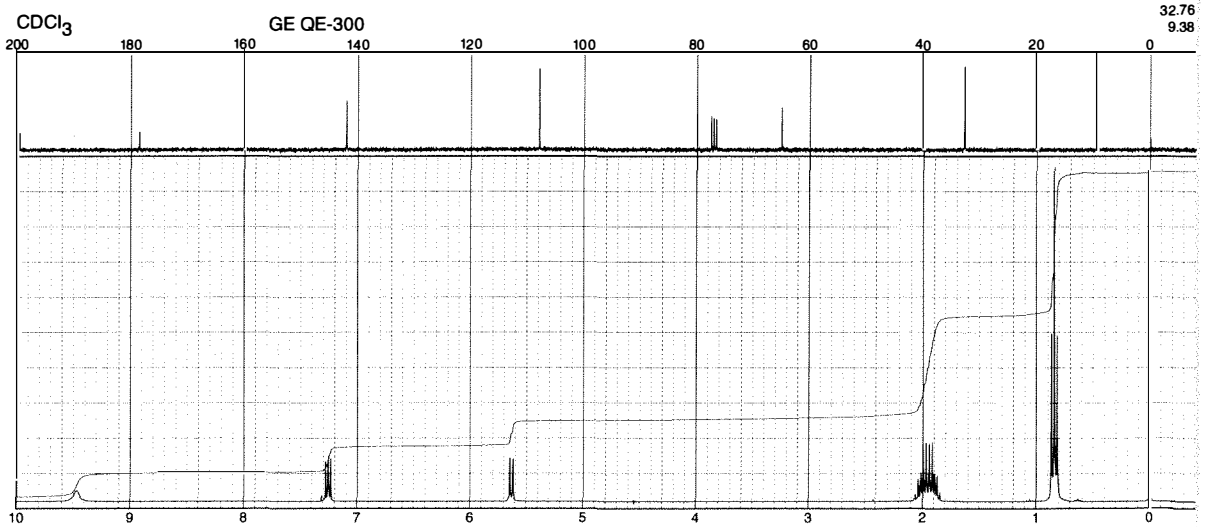
Pyrithyldione

$C_9H_{13}NO_2$
FW 167.21
bp 188°C (14 mm)

60 MHz: ***2***, 679A
FT-IR: ***1***, 794D

$CDCl_3$ GE QE-300





A

ldrich C550-5 *CAS [3731-16-6]*

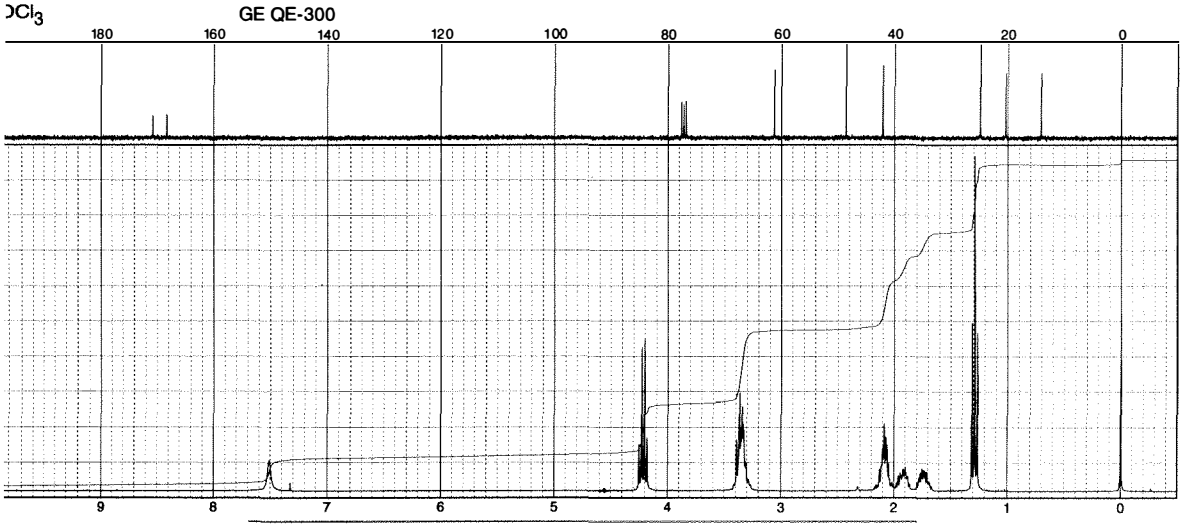
Carbethoxy-2-piperidone

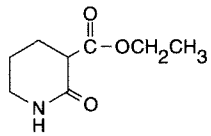
$C_8H_{13}NO_3$
FW 171.20
mp 81°C

60 MHz: *1*, 665A
FT-IR: *1*, 795B

170.79	42.06
168.28	24.86
61.27	20.36
48.60*	14.12*

DCl_3 GE QE-300





B

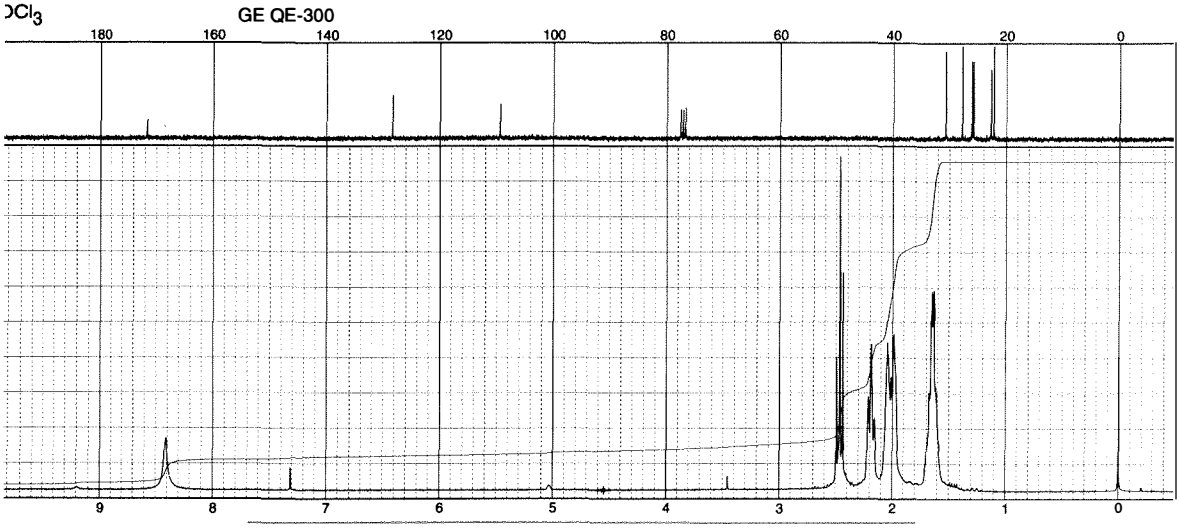
ldrich 29,964-2 *CAS [10333-11-6]*

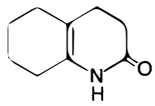
4,5,6,7,8-Hexahydro-2(1*h*)-quinolinone

$C_9H_{13}NO$
FW 151.21
mp 145°C

171.62	26.14
128.36	25.83
109.43	22.73
30.71	22.22
27.84	

DCl_3 GE QE-300





C

ldrich 33,423-5 *CAS [98203-44-2]*

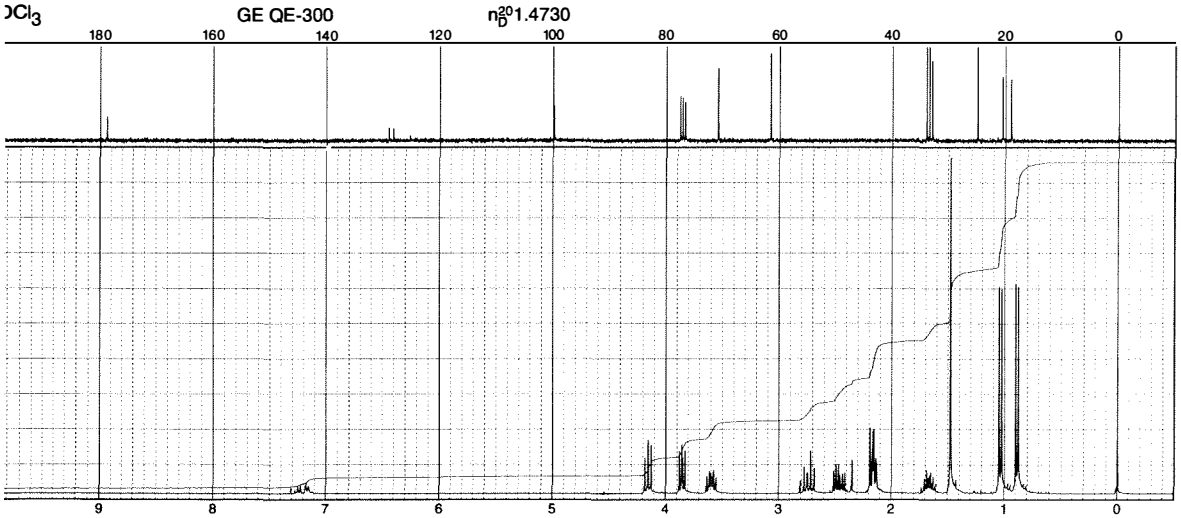
)-3-Isopropyl-7a-methyltetrahydro
rrolo(2,1-*b*)oxazol-5(6*h*)-one

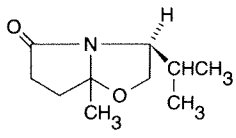
$C_{10}H_{17}NO_2$
FW 183.25
bp 70°C
d 1.027
n_D^{20}1.4730

Fp 137°F

178.80	33.45*
99.83	32.96
70.89	24.94*
61.62*	20.52*
33.93	19.01*

DCl_3 GE QE-300





ALDRICH

The Ireland-Claisen Rearrangement

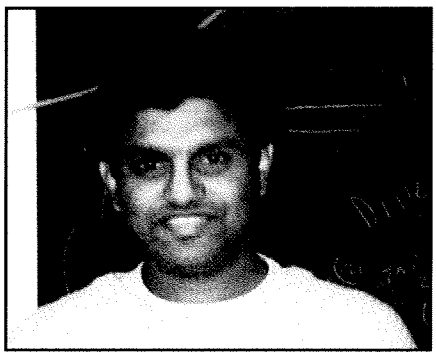
*Schubert Pereira and Morris Srebnik**
Department of Chemistry
University of Toledo
Toledo, OH 43606.

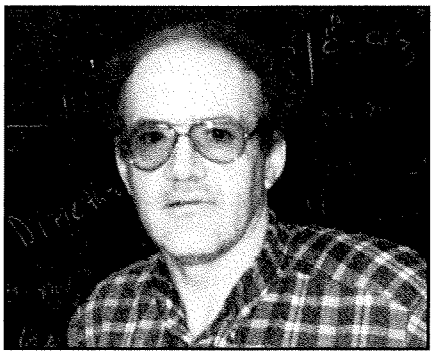
Introduction

The Ireland-Claisen rearrangement, first reported in 1972,[1] has developed over the ensuing years to become a powerful tool in organic synthesis. The importance of this rearrangement derives from the flexibility it provides the synthetic organic chemist to control the diastereoselectivity of two newly generated stereocenters as well as the predictability of product stereochemistry. This review covers the development of this reaction from its inception to its current role in synthetic methodology.

The Ireland-Claisen rearrangement refers to the [3,3]-sigmatropic rearrangement of allylic esters (**1**) as ester enolates (**2**) to give 3,4-unsaturated acids (**3**)(**Scheme 1**).[1] The rearrangement is a suprafacial, concerted, non-synchronous, pericyclic process. When the sp^2-hybridized C_1 and C_6 positions of the allyl vinyl ether are substituted, the rearrangement can proceed via two achiral transition states to give two racemic diastereomers, bearing two centers of asymmetry at C_2 and C_3 of the product.

Prior to the development of Ireland's modification, other popular variants of the aliphatic Claisen rearrangement included the vinyl ether[2], the Johnson orthoester[3] and the amidcacetal rearrangements.[4] Base-catalyzed reactions of allylic esters were also reported, but employed harsh conditions and gave low yields.[5] The major advantage of the Ireland modification over these base-catalyzed rearrangements is the ease of preparation and subsequent facile rearrangement of allyl vinyl ethers as their lithium enolates.



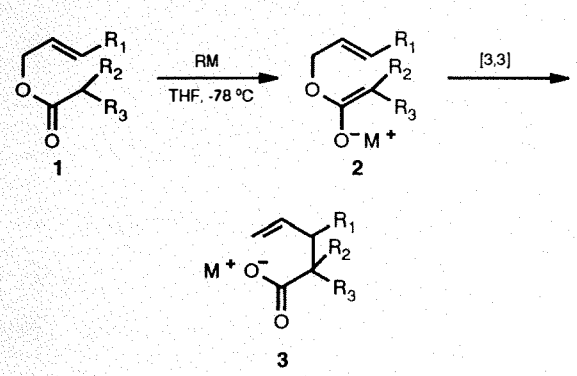


Generation of Ester Enolates

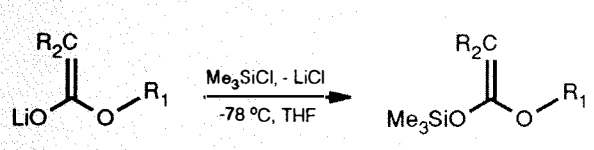
Theoretically, alpha allyloxy enolates can undergo either [3,3]-sigmatropic or competing [2,3]-Wittig type rearrangements. Surprisingly, ester enolates, especially silyl ketene acetals, do not undergo a [2,3]-Wittig rearrangement.[6]

In his initial work, Ireland employed lithium esterenolates generated by the method of Rathke,[7] but these proved unsatisfactory as they rearranged to give unwanted aldol condensation side products.[1] However, the lithium enolates, when silylated by TMSCl, afford trimethylsilyl ketene acetals (**Scheme 2**) which in turn rearrange readily to give 3,4-unsaturated acids. One problem with this approach is the formation of 2-6% C-silylated product.[1] This was overcome by using *tert*-butyldimethylchlorosilane (TBSCl) as the silylation reagent which provides predominantly the O-silylated ketene acetal.[8]

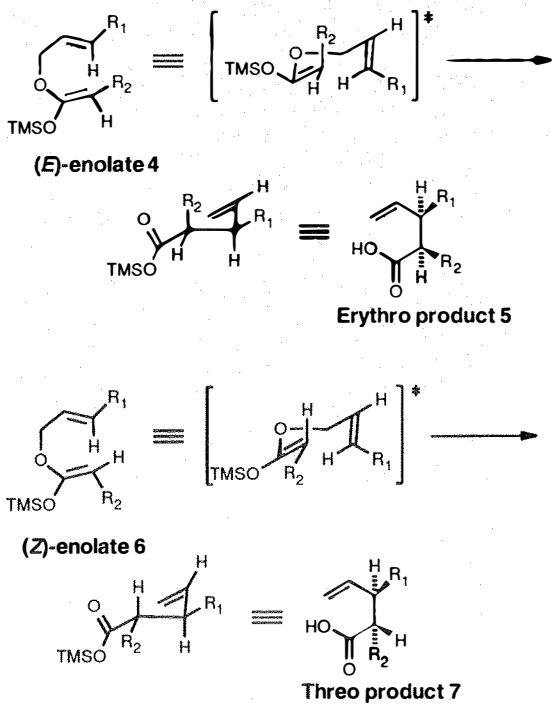
Scheme 1



Scheme 2



Scheme 3



Stereoselective Generation of Ester-Enolates

The geometry of the products of the Ireland-Claisen rearrangement can be predicted by the stereochemistry of the double bonds involved in the ketene acetal rearrangement. The (*E*)-enolate (**4**) gives predominantly an erythro product (**5**), while the (*Z*)-enolate (**6**) gives a threo compound (**7**) as the main product (**Scheme 3**).[9] The rearrangement is proposed to proceed through a four centered "chairlike" transition state as shown, thus allowing stereoselection of the products.[9,10]

The geometry of the silyl ketene acetal can be controlled during the ester enolization process by varying the solvent system. The formation of (*Z*)-enolates is favored by THF as the solvent, while the use of 23% HMPA/THF favors the formation of the (*E*)-enolate (lithium enolate). Regardless of the allylic bond configuration (*cis* or *trans*), the stereochemistry is retained on silylation and the two compounds give predominantly the erythro and threo isomers, respectively, on rearrangement (**Scheme 4**).[9]

Mechanism of Ester-Enolate Control - Thermodynamic or Kinetic?

It was initially proposed that the *E*:*Z* ratio of the enolate esters was kinetically determined, regardless whether THF or a mixture of HMPA/THF was used.[9,11] The two possible transition states **1** and **2** are shown in **Figure 1**. In the absence of HMPA, the lithium atom is strongly coordinated to the carbonyl oxygen leading to an unfavorable interaction between R and R_1. In the presence of HMPA, the lithium atom is highly solvated. In this case, favorable steric interactions between R and R_1 lead preferentially to (*Z*)-enolate formation. Note that these steric considerations had initially been used to explain ketone enolate selectivity and can also be used to explain ester enolate selectivity.

Corey's studies on enolate selectivity led to the conclusion that the use of hindered bulky bases like lithium *tert*-octyl butyl amide (LOBA) gave superior selectivity to (*E*)-enolates as compared to LDA (**Table 1**).[12] He argued that the stereochemical outcome in the presence of HMPA was not a kinetic effect, but was due to equilibration to the more thermodynamically stable (*Z*)-enolate. Corey's conclusion was based on his experiments using TMSCl as an internal quenching agent during the enolization with a lithium base (**Table 2**). The investigations of Rathke also support this conclusion (**Scheme 5**).[13]

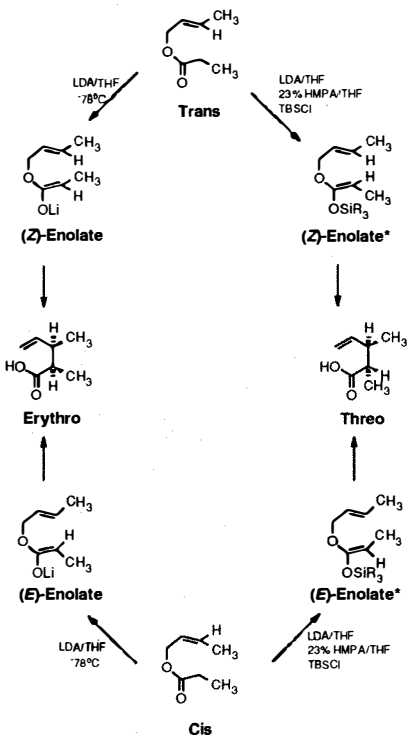
The addition of 1-4 equivalents of HMPA or TMEDA did not change the *E*:*Z* ratio, but the addition of 0.2 equivalent of 3-pentanone caused rapid isomerization to an equilibrium mixture of enolates with an *E*:*Z* ratio of 16:84. Rathke suggested the reverse aldol condensation isomerization mechanism illustrated in **Scheme 6**.[13] It was possible to control the deprotonation of 3-pentanone in THF solution so as to produce predominantly the (*E*)-isomer (**8**) by addition of the ketone to 10% excess lithium 2,2,6,6-tetramethyl piperidide (LiTMP) at 0° C (*E*:*Z* ratio 87:13), or to produce predominantly the (*Z*)-isomer (**9**) by addition of the ketone to a slight deficiency of LiTMP (*E*:*Z* ratio 16:84). He concluded that the formation of the (*E*)-enolate could be the result of kinetically controlled deprotonation, but the formation of the (*Z*)-enolate is thermodynamically favored.

To thoroughly examine the aspects of selectivity in ketene acetal formation, Ireland conducted a number of experiments, varying different parameters and using ethyl propionate as the ester.[14]

Solvent Effects

The effect of solvent on the stereoselectivity of silyl ketene acetal formation of ethyl propionate with LDA is indicated in **Table 3**. The addition of metal-chelating solvents such as HMPA, TMEDA and DMPU reversed the selectivity in favor of the (*Z*)-isomer, as opposed to the predominant formation of the (*E*)-isomer in pure THF. The best selectivity was attained by increasing the amount of DMPU to 45%. However, when the amount of TMEDA is increased, the yield decreases substantially.

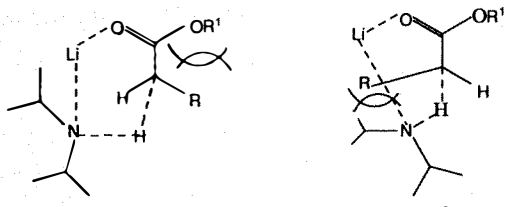
Scheme 4



* Note that configurations are opposite due to priority of Si over Li.

Figure 1

Possible configurations of the T.S. of the of the Li ester-enolate with THF as the solvent



Favored in absence of HMPA

Favored in presence of HMPA

Table 1. ENOLATE SELECTIVITY WITH DIFFERENT BASES

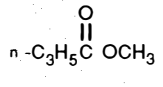
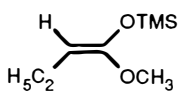
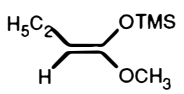
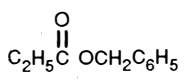
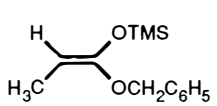
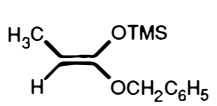
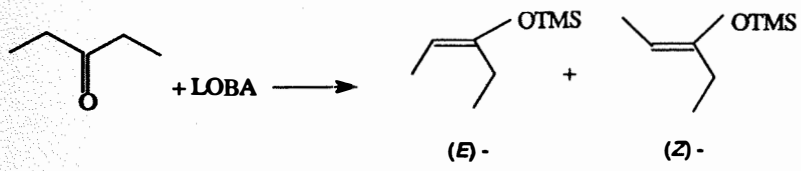
Substrate	TMS Ketene Acetal		*E*:*Z*	
	E	*Z*	LDA	LOBA
			91:9	95:5
			80:20	95:5

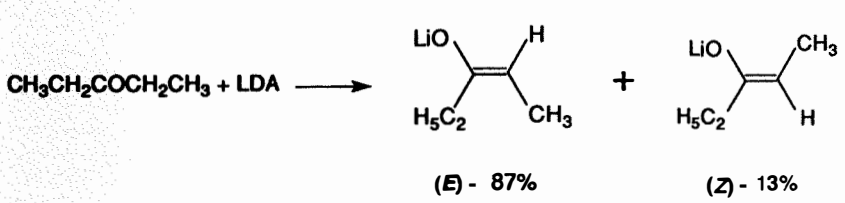
Table 2. Enolate selectivity with Corey's internal quench experiments



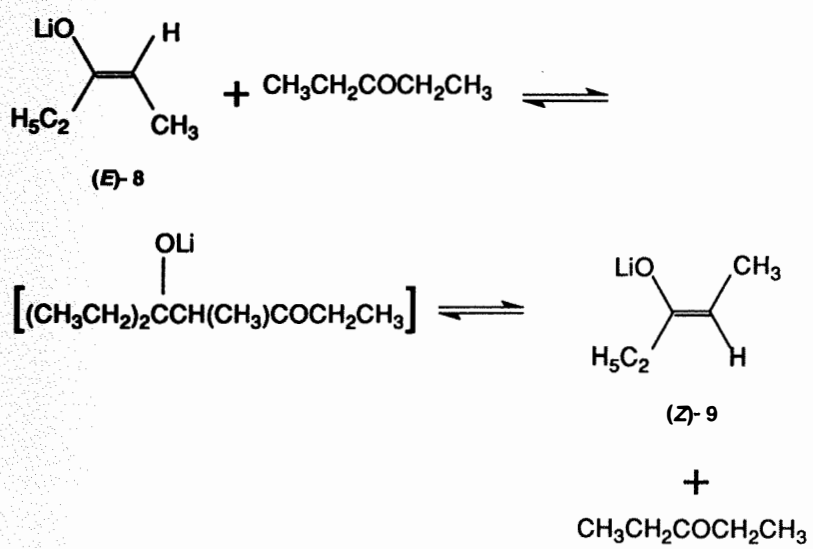
Method	Solvent	(E)-		(Z)-
internal quench	THF	98	:	2
internal quench (8 equiv. TMSCl)	HMPA/THF	37	:	63
internal quench (17 equivs. TMSCl)	HMPA/THF	46	:	54
two step procedure*	HMPA/THF	18	:	82

*slow addition of ketone to LDA followed by silylation

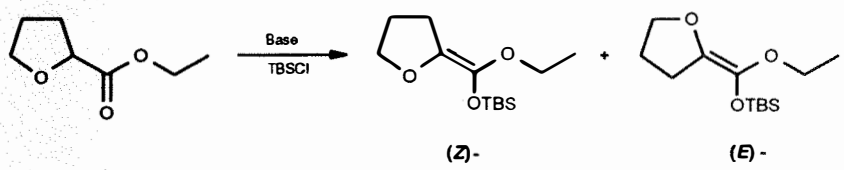
Scheme 5



Scheme 6



Scheme 7



Ester to Base Ratio

Table 4 summarizes Ireland's ester to base ratio experiments. In THF, a decrease in the ester to base ratio from 1:1 to 0.6:1 does not change the selectivity or yield. However, an increase in that ratio from 1:1 to 1:4 drastically reduces the yield from 90% to 5%. A decrease in the ester to base ratio in the mixed THF/chelating solvent system lowers the (*Z*)-selectivity and decreases the yield. Conversely, a slight increase in the ester to base ratio leads to an increase in (*Z*)-selectivity, accompanied by a drop in yield. Thus, increased (*Z*)-silylketene acetal selectivity can be obtained by adding a slight excess of the ester solution. It is also pertinent that addition of small amounts of a polar solvent like DMSO after enolization also increases the (*Z*)-selectivity.[14]

Effect of the Base

The comparison of LDA with a slightly bulkier base, i.e. lithium hexamethyl disilazide (LHMDS), showed that LHMDS is slightly more efficient for (*E*)-selective enolate formation than LDA in 23% HMPA/THF solvent mixture.[14]

Effect of an Alpha Oxygen Substituent on the (Z)-Enolate

The formation of the (*Z*)-enolate predominates due to chelation with an alpha O-atom as shown in **Scheme 7**. When the solvent is THF, the *Z*:*E* ratio is 90:10, whereas when 23% HMPA/THF is used the ratio drops to 63:37 with the (*Z*)-isomer still favored.

Ireland pointed out that the conclusions of Rathke and Corey were based on ketone enolates and not directly applicable to ester enolates. An aldol type equilibrium would be too slow and irreversible with acid derivatives such as esters and amides. To support his claim Ireland set up an analogous experiment with ethyl propionate in THF and TMSCl. After enolization of one equivalent of the ester by one equivalent of LDA, addition of 30% DMPU led to a *Z*:*E* silyl ketene acetal ratio of only 1:4. Furthermore, addition of 0.1 equivalents of ester to 2 equivalents of a preformed 60:40 mixture of (*E*)- to (*Z*)-lithium ester enolates led to only a small change in ratio to 69:31 (**Scheme 8**).

These observations suggest a kinetic resolution process. A preformed ratio of (*Z*)- and (*E*)- ester enolates can be altered by addition of a small amount of trapping agent that reacts at different rates with the two isomers, thus making it possible to carry out the reaction with the more reactive enolate. Ireland then set up a series of experiments using competitive trapping of the more reactive enolate with TBSCl (**Scheme 9; Table 5**).

The change in ratios is due to a competition for silylation between the two enolates (competition constant, K=k*Z*/k*E*, of 2.6 with DMPU and 1.4 with HMPA). It was concluded that "...kinetically controlled enolization in combination with a kinetic resolution process accounts for the selective

formation of (*E*)- and (*Z*)- silyl ketene acetals in THF and THF/dipolar solvent systems with bases such as LDA, LHMDS, and KHMDS."[14] Ireland's experiments thus shift the evidence in favor of a kinetic resolution process in the case of ester enolates, but do not account for the observations made by Rathke and Corey on the mechanism of enolate formation from ketones (3-pentanone).

Chelation Control of Enolate Selectivity

The lithium enolates' preference for the *Z*-conformer is well established. Investigations by Bartlett,[15] Fujisawa[16] and Burke[17] showed that in the case of a heteroatom substituent that can undergo chelation with the lithium atom, the major isomer formed is the *E*-conformer (**Scheme 10**). Although the ratio of the isomers was not measured, it could be determined from the ratio of the final products. This coordination effect has been utilized in stereoselective syntheses, wherein control of the prostereogenic sp^2 sites is achieved by an allylic oxygen substituent.[18]

Yet another method for enolate control has been developed by Corey and Kim.[19] A chiral boron reagent (**Figure 2**) has been used to promote enantioselective aldol reactions of achiral propionate esters to give either syn or anti aldol products with excellent enantioselectivity and diastereoselectivity.

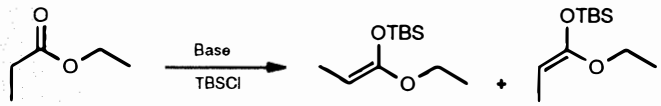
The enolate of choice can easily be controlled by use of the proper solvent:base combinations. When the chiral boron reagent [R_2BBr] and TEA in a toluene/hexane/CH_2Cl_2 solvent is used with *tert*-butyl propionate at -78°C, the transoid boron enolate is formed (O-B and methyl are *trans* to each other; *Z*-isomer by priority group nomenclature). These enolates react with aldehydes to give the expected anti aldol products in 90-97% e.e. However, when the base is the sterically demanding diisopropylethylamine and the solvent the more polar CH_2Cl_2, the cisoid enolate is formed to give the syn aldol product in 83-97% e.e.

The Transition State - Chair or Boat?

Prior investigations of [3,3]-sigmatropic rearrangements showed that unhindered 1,5-diene systems undergo rearrangement via a chair transition state.[20] Later evidence suggested the possibility of a chair, boat, twist helix or twist plane transition state for the closely related Claisen rearrangement.[21] Since Ireland's variant takes place at moderately low temperatures, the twist configurations are not likely. Further transition state studies of the Cope rearrangement led to the conclusion that substituents on the 1,5-hexadiene play a major role. In fact, a boat transition state is favored due to the nature of the substituents on certain ester enolates.[21]

From previous studies on the Cope[22,23] and Claisen[24,25] rearrangements, it was generally

Table 3. Effect of solvent on ester enolate selectivity



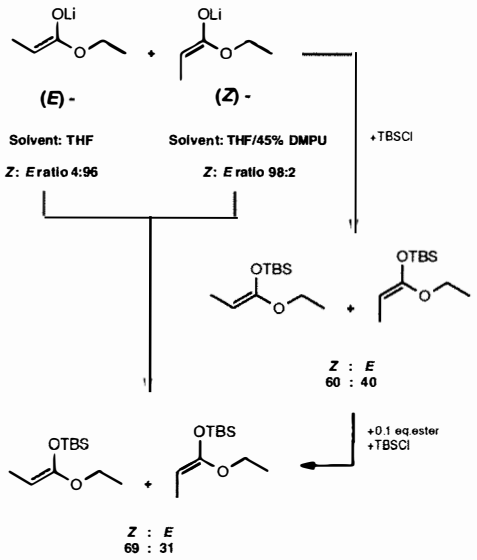
ENTRY	SOLVENT	ESTER:BASE	*Z*:*E*	YIELD
1	THF	1:1	6:94	90
2	THF/25%TMEDA	1:1	60:40	50
3	THF/50%TMEDA	1:1	--	0
4	THF/15%DMPU*	1:1	37:63	90
5	THF/30%DMPU	1:1	69:31	85
6	THF/45%DMPU	1:1	93:7	90
7	THF/23%HMPA	1:1	85:15	90

*DMPU=N,N'-dimethyl-N,N'-propylene urea

Table 4. Effect of ester to base ratio on the stereoselectivity in silyl ketene acetal formation of ethyl propionate with LDA

ENTRY	SOLVENT	ESTER:BASE	*Z*:*E*	YIELD
1	THF	1.4:1	1:1	5
2	THF	1.2:1	20:80	35
3	THF	1.1:1	6:94	90
4	THF	0.6:1	6:94	90
5	THF/30%DMPU	1.2:1	98:2	70
6	THF/30%DMPU	0.95:1	67:33	90
7	THF/30%DMPU	0.8:1	68:32	85
8	THF/30%DMPU	0.5:1	60:40	95

Scheme 8



Scheme 9

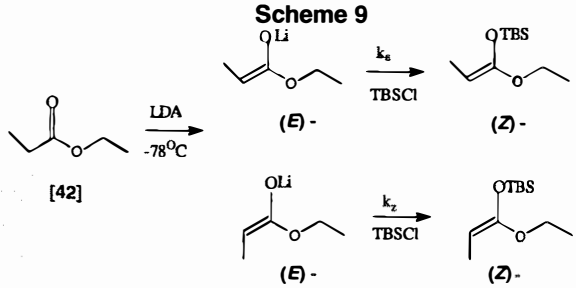
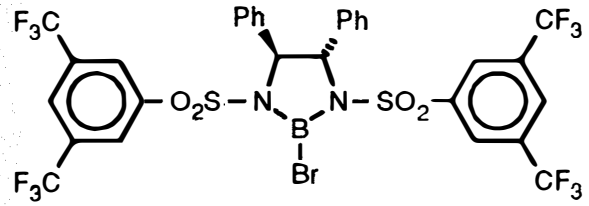


Table 5. Results of competitive trapping of the enolate with TBSCl

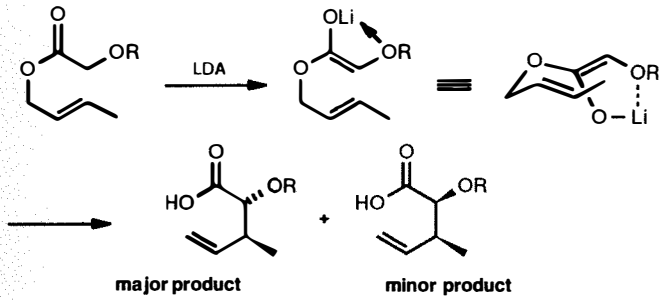
ENTRY	SOLVENT	ESTER:BASE	TBSCl	*Z:E*
1	THF/15%DMPU	0.8:1	0.9	30:70
2	THF/15%DMPU	0.8:1	0.08	14:86
3	THF/23%DMPU	0.8:1	0.9	73:27
4	THF/23%DMPU	0.8:1	0.08	66:34
5	THF	1:1	1.1	94:6
6	THF	1:1	0.9	4:96

Figure 2



Chiral Boron Reagent

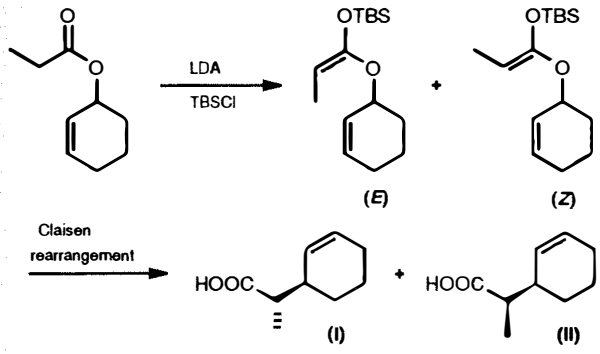
Scheme 10



R=	MAJOR:MINOR	YIELD
-Me	10.2:1	65
-CH_2Ph	9.6:1	77
MEM*	7.2:1	70
H	2.4:1	38

*(2-methoxyethoxy)methoxy

Scheme 11



SOLVENT	*E:Z*	(I):(II)	%YIELD	FAVORED T.S.
THF	83:17	84:16	79	chair
THF/45%DMPU	4:96	72:28	91	boat
THF/23%HMPA	14:86	73:27	60	boat

found that in cyclic systems a boat transition state is preferred. Another interesting observation was made by Bartlett in his studies of the ester enolate rearrangement of cyclohexenal propanoate.[26] The (*E*)-silyl ketene acetal rearranged via a chair transition state, while the (*Z*)-silyl ketene acetal rearranged via a boat transition state. Bartlett explained his observations by considering the transition states involving the chair and boat forms (**Figure 3**).

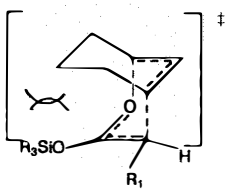
In the case of the (*Z*)-isomer there is an unfavorable interaction between the -$OSiR_3$ group and the methylene proton of the cyclohexene ring if the transition state proceeds through chair form **1**. Thus, the boat form is favored. However, the boat transition state of the (*E*)-isomer has greater steric interaction between the R group and the cyclohexene ring as in **2** (**Figure 3**), thus favoring the chair form.

Ireland carried out a systematic investigation of the effects of various cyclic and acyclic systems on the rearrangement to determine the underlying factors leading to stabilization of either the chair or boat transition state.[27]

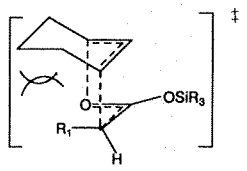
Cyclohexene and Pyranoid Derivatives

Ireland's results with cyclohexenyl propionate were identical to those of Bartlett's. Though diastereoselectivity was observed with both the (*E*)- and the (*Z*)-silyl ketene acetals, the (*E*)-isomer rearranged via a chair transition state while the (*Z*)-silyl ketene acetals rearranged via a boat transition state (**Scheme 11**). The rearrangement employing a pyranoid derivative involved a boat transition state for either (*E*)- or (*Z*)- silyl ketene acetals (**Scheme 12**). These results suggest that the ring oxygen atom can contribute between 1.0 kcal/mol (*Z*-silyl ketene acetal) and 2.2 kcal/mol (*E*-silyl ketene acetal) to the relative stabilization of a boat over a chair transition state. Since both the cyclohexene and the pyranoid rings are sterically similar, the stabilization of the boat transition state is, most likely, due to stereoelectronic rather than steric factors.

Figure 3



Transition State 1 (*Z*)-



Transition State 2 (*E*)-

A more useful picture of the rearrangement can be obtained by considering the chair and boat forms of the transition states of both (*E*)- and (*Z*)- conformers of the enolate (**Figure 4**).

Cyclopentene and Furanoid Derivatives

In the case of a cyclopentene derivative both the (*E*)- and the (*Z*)- isomers rearrange by a chair transition state (**Scheme 13**). However, the furanoid derivative rearranged by a boat transition state for both the ketene acetal configurations, thereby supporting the results of the pyranoid-cyclohexene series. The O-atom leads to relative stabilization of the boat form of the transition state over the chair form on the order of 1.4 kcal/mol (*E*-conformer) and 1.9 kcal/mol (*Z*-conformer).

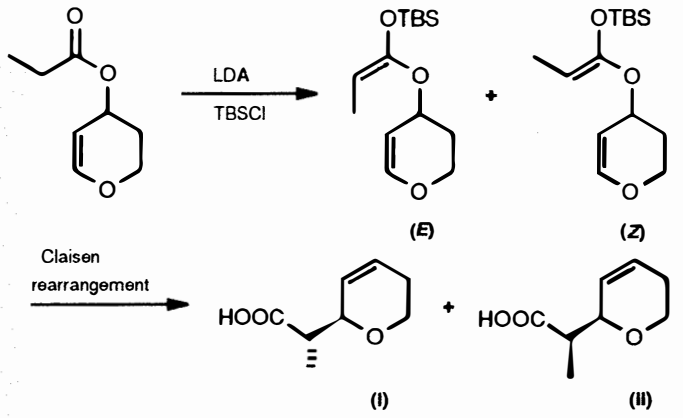
The chair and boat forms of the transition states of the (*E*)- and (*Z*)-enolates of cyclopentene-furanoid glycal derivatives are depicted in **Figure 5**.

Methoxy Allyl Propionate Derivative

The (*E*)- and (*Z*)-silyl ketene acetals of methoxy allyl propionate gave a mixture of carboxylic acids with a preference for the isomer expected via the chair transition state. Thus, in the acyclic series, the effect of the O-atom is not as important as it is in the cyclic series for stabilizing the boat transition state.

Using alpha-secondary deuterium isotope effects, Gajewski proposed that the transition state of the aliphatic Claisen rearrangement resembles an oxoallyl radical-allyl radical pair, rather than a 2-oxocyclohexane-1,4-diyl (**Scheme 14**).[28] This results in a transition state with much more advanced

Scheme 12



SOLVENT	(I):(II)	%YIELD	FAVORED T.S.
THF	29:71	77	boat
THF/45%DMPU	86:14	35	boat

Scheme 13

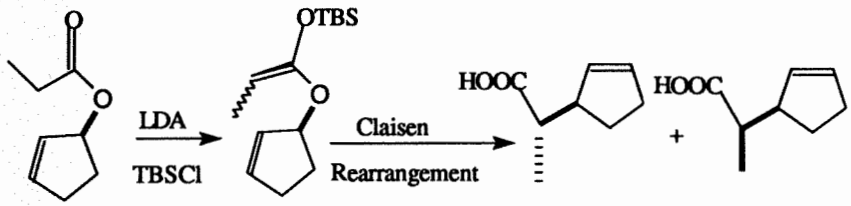


Figure 4. Transition states of cyclohexene-pyranoid glycal derivatives

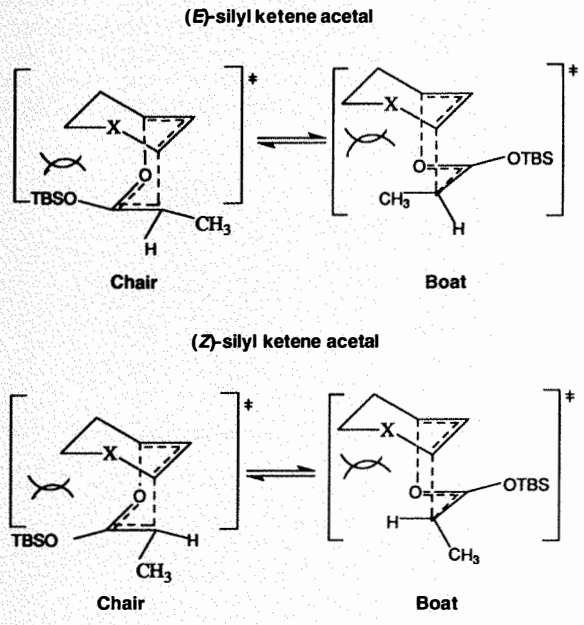
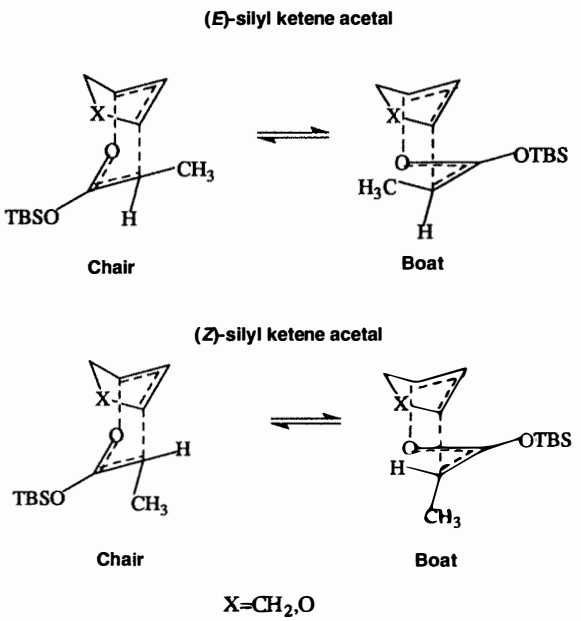
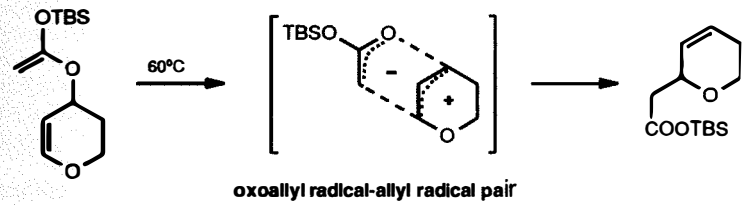


Figure 5

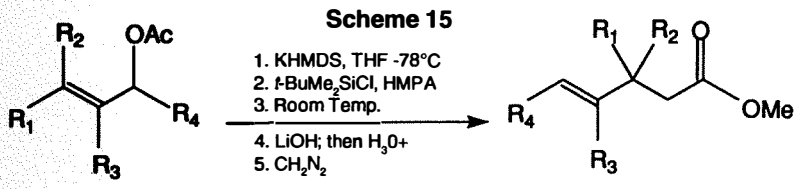


Scheme 14



oxoallyl radical-allyl radical pair

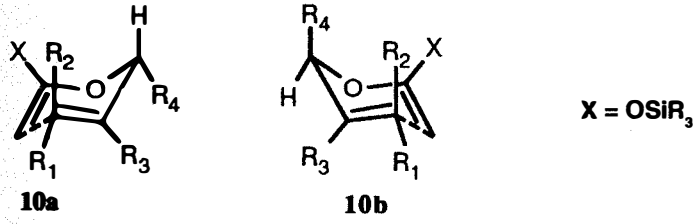
Scheme 15



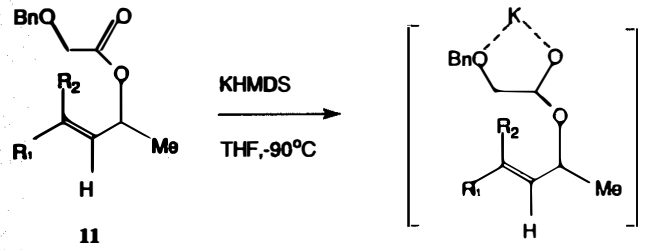
8 [a-c] **9 [a-c]**

ESTER	R1	R2	R3	R4	%YIELD
8a&9a	Me	H	H	$SnBu_3$	60
8b&9b	Me	Me	H	$SnBu_3$	62
8c&9c	$SnBu_3$	H	H	Me	54

Figure 6. Possible Transition States of the Enolate

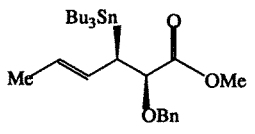


Scheme 16

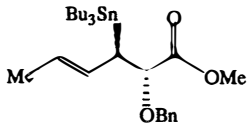


Config.	R_1	R_2
11 (*E*)-	$SnBu_3$	H
11 (*Z*)-	H	$SnBu_3$

1. TMSCl (excess) THF, -90°C heat to RT
2. H_3O^+
3. CH2N2



13 syn



14 anti

O(3)-C(4) bond breaking than in the parent unsubstituted system. Thus, one would expect a rate enhancement effect from a C(6)-donor substituent to be especially effective in glycal systems.

Ireland concluded that there is a definite stereoelectronic effect which stabilizes the boat over the chair form. The energy differences between the chair and the boat forms in the transition state are small and hence tend to be influenced by substituent interactions. In the absence of steric interactions, the pyranoid and furanoid systems will rearrange by a boat transition state. A simple acyclic substituent with a C(6)- oxygen atom will not rearrange via the chair form.

Variations of the Ireland-Claisen Rearrangement

An interesting variation of the Ireland-Claisen rearrangement developed by Ritter uses an organotin ester and the chelation effect of the counterion to produce primarily the (*Z*)-enolate from the O-protected butenyl stannane (**8**). This rearrangement gives a high diastereoselectivity ratio (**Scheme 15**).[29]

The chair transition state (**10a**), with R_4 in the pseudoequatorial position, is energetically favored over (**10b**), with R_4 in the pseudoaxial position, resulting in the exclusive formation of the (*E*)-isomers (**9a - c**). The (*E*)-tributylstannylbutenol reacted six times faster than the (*Z*)-isomer, reflecting the energy difference between the transition states with the tributyltin moiety in a pseudoequatorial (**10a**) or pseudoaxial (**10b**) position (**Figure 6**).

Ritter also investigated the chelation effect of the counterion to form predominantly the (*E*)-enolate from O-protected butenyl glycolates. The rearrangement of (*Z*)- or (*E*)-4-tributylstannyl-3-buten-2-yl (benzyloxy)acetate (**11**) (**Scheme 16**), through intermediate **12**, gave (*E*)-2-benzyloxy-3-tributylstannyl-4-hexenoic acid methyl ester in a 92% yield.

Due to the chelation control of enolate geometry, the syn ester (**13**) is the main product (syn:anti ratio 39:1) from the glycolate ester (**11**) (*E*). The glycolate ester (**11**) (*Z*) rearranges to give an anti:syn ester ratio of 40:1, thus emphasizing the utility of the rearrangement of organotin compounds to afford diastereoselective products.

Brown and co-workers recently reported a useful method for controlling enolate geometry through the use of dialkylboron reagents of the type R_2BX (X = Cl, OTF) in the presence of tertiary amines.[30] They found that the formation of the (*E*)-enol borinate is favored by the following:

(i) use of R_2BCl instead of R_2BOTF;
(ii) use of Et_3N instead of *i*-Pr_2EtN;
(iii) use of a dialkylboron group with a larger steric requirement (i.e. dicyclohexylboron instead of 9-BBN).

A recent publication by Corey extends this work to the highly enantioselective and

diastereoselective Ireland-Claisen rearrangement of achiral allylic esters.[31] The rearrangement utilizes a recyclable chiral boron reagent (**Scheme 17**), resulting in greater than 97% e.e. in some cases.

The (*E*)- or (*Z*)-enolate is selected using the specific solvent combinations along with the chiral catalyst as shown in **Tables 6 and 7**. The (*E*)-isomer rearranged to give predominantly threo products while the (*Z*)-isomer rearranged to form mainly the erythro carboxylic acids. The diastereoselectivity of the rearrangements is consistent with the assigned geometry of the boron enolate and the expectation of the preferred chair geometry of the transition state.

Applications of the Ireland-Claisen Rearrangement

The rearrangement has been used in the synthesis of polyether antibiotics,[21,32] sesquiterpenes,[33] steroids,[34] iridoids,[35] tetronates,[36] marine natural products,[37] amino acids,[38] C-glycosides,[39] large carbocycles[40] and chiral stannanes[29] and silanes.[41] Recent applications include the synthesis of long chain or large ring molecules and demonstrate the utility of this rearrangement in controlling stereocenters.

A clever strategy utilizing a boron mediated aldol condensation in tandem with the Ireland-Claisen rearrangement provided a synthetic route to ebelactone-A, an esterase inhibitor.[42] Furthermore, a general method for the synthesis of unsaturated diesters with a high degree of stereocontrol at four chiral centers as well as two trisubstituted double bonds was devised (**Scheme 18**). Interestingly, the rearrangement could be carried out without protection of the keto group at C_7.

After the rearrangement of the diester **16A**, the resulting diacid was esterified to give the desired meso all syn diester **18A** (63% yield, 86% d.s.). The unsymmetrical diester **18B** is obtained in 53% yield and 95% d.s. from **16B**. An important aspect is that the electrophilic ketone carbonyl group is not attacked and there is no epimerization at the adjacent stereocenters. This is probably due to the flanking methyl groups which protect it from the sterically hindered base LDA and also blocks intramolecular aldol condensation. This synthesis demonstrates the use of a "double" Ireland-Claisen rearrangement to create two contiguous stereocenters.

A new, high yield synthesis of coumarin derivatives employing the rearrangement was reported by Collado and is shown in **Scheme 19**.[43] The rearrangement does not occur unless the phenolic hydroxyls are protected as, for example, their benzyl ethers.

Curran and co-workers have used the Ireland-Claisen rearrangement in a stereoselective synthesis of chiral iridoid aglycones (**Scheme 20**).[44] The iridoids are a family of natural products which have an oxygenated fused cyclopentapyran ring system possessing anti-microbial to anti-leukemic properties.

The best stereoselectivity was obtained by the generation of the (*E*)-silyl ketene acetal. This proceeded with good diastereoselectivity by a chair transition state to give **23** and its diastereomer in a 5:1 ratio. The rearrangement of the (*Z*)-silyl ketene acetal also gave **23** as the major product in a 3:2 ratio, but this time via the boat transition state, a result in keeping with the findings of Bartlett and Ireland.

Schreiber and co-workers have described the asymmetric synthesis of the cyclohexyl moiety of FK-506, a macrolide antibiotic with potent immunosuppressive properties (**Scheme 21**).[45] The rearrangement from **27** to **28** proceeded in 71% overall yield via the boat transition state. Wang has also used this rearrangement in the synthesis of the C_{10}-C_{24} fragment of FK-506.[46]

Jasperse and Curran have used the rearrangement to form two contiguous quater-

Scheme 17

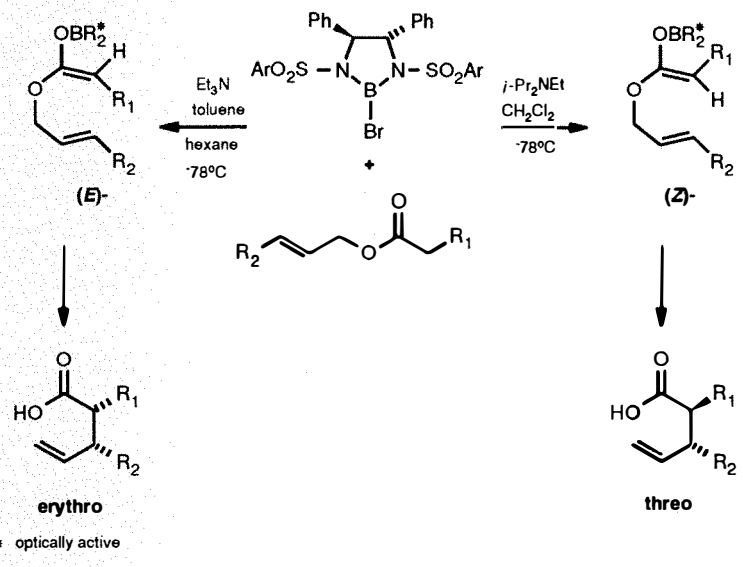


Table 6. Enantioselective rearrangement in CH_2Cl_2 via the (*E*)-boron enolate

ENTRY	R1	R2	%YIELD	THREO: ERYTHRO	e.e.%
1	Me	Me	75	99:1	<97
2	Et	Me	79	98:2	95
3	Me	Me	75	91:9	>97
4	Et	Ph	72	91:9	>97
5	Ph	Ph	100	23:77	>97
6	SPh	Me	52	39:61	>97
7	CH_2Ph	H	70	---	82
8	CH_2-1-naphthyl	H	48	---	77

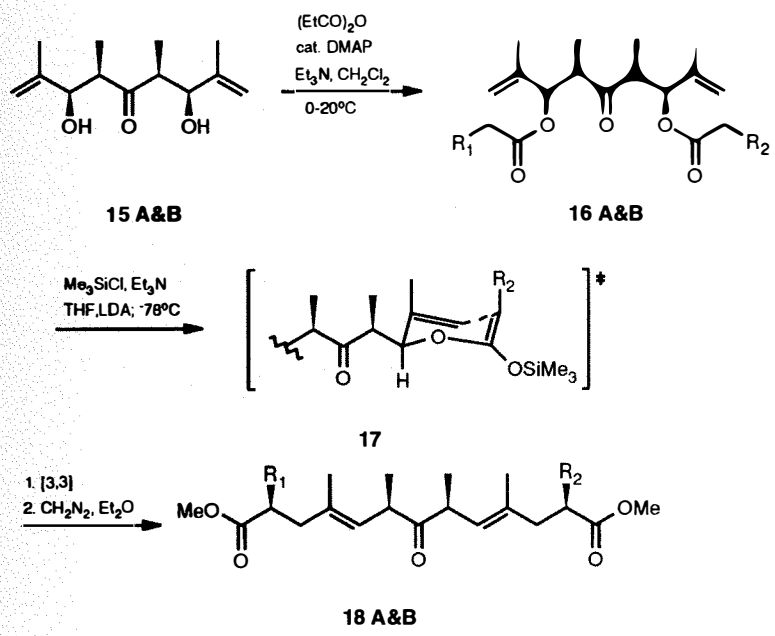
Diastereomeric ratios were determined by GC analysis of benzyl or methyl esters. e.e. values were determined by HPLC analysis of methyl esters using a Diacel OJ column.

Table 7. Enantioselective rearrangement in toluene-hexane via the (*E*)-boron enolate

ENTRY	R1	R2	%YIELD	THREO: ERYTHRO	e.e.%
1	Me	Me	65	90:10	96
2	Et	Me	79	89:11	>97
3	Me	Ph	88	96:4	>97
4	Et	Ph	69	95:5	>97
5	Ph	Ph	100	98:2	>97
6	SPh	Me	56	95:5	>97
7	SPh	Ph	45	91:9	>97
8	CH_2Ph	H	57	---	84
9	CH_2-1-naphthyl	H	63	---	79

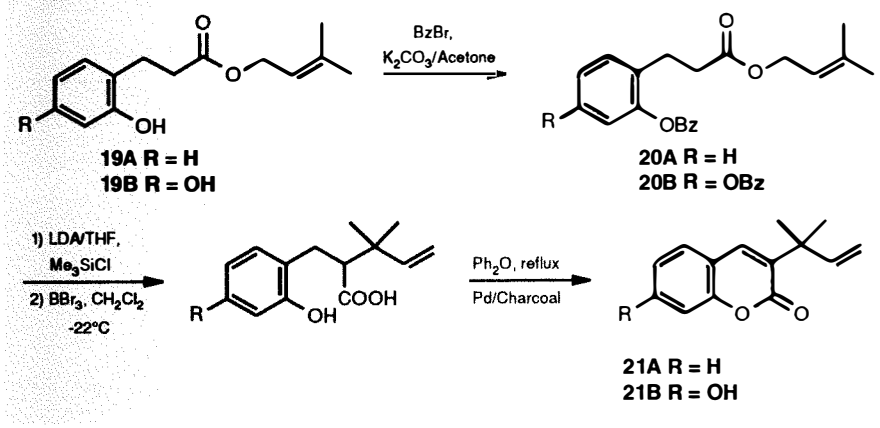
Diastereomeric ratios were determined by GC analysis of benzyl or methyl esters. e.e. values were determined by HPLC analysis of methyl esters using a Diacel OJ column.

Scheme 18

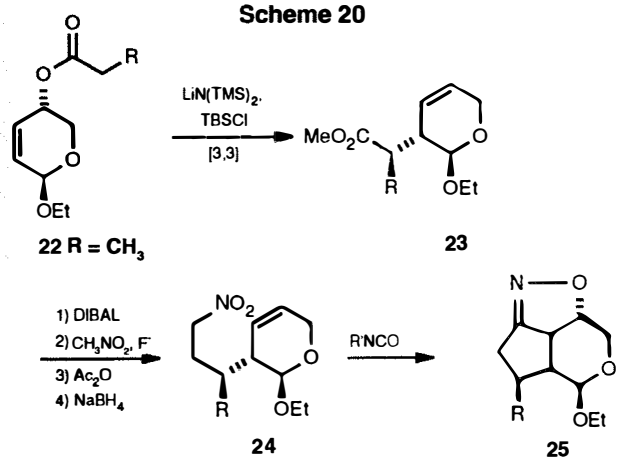


[A] R1 = R2 = Me
[B] R1 = Me; R2 = Et

Scheme 19



Scheme 20



nary centers needed for the intermediate in their synthesis of modhephene in 50% yield (**Scheme 22**).[47]

Intermediates to polyoxins which are structurally related to nucleoside peptide antibiotics were prepared by Duthaler.[48] As shown in **Scheme 23** the (*Z*)-allyl ester rearranges in a highly stereoselective manner to give predominantly the *trans*-substituted lactone, while the (*E*)-allyl ester rearranges to give mainly the *cis*-lactone.

The rearrangement was evaluated for application to the synthesis of macrocyclic lactones. Brunner and Borschberg investigated the potential synthesis of (R,S)-muscone (**37**) as shown in **Scheme 24**.[49] On rearrangement, **33** gave a mixture of **34**, **35** and **36**. The stereoselectivity of this rearrangement is rather low compared to that of acyclic systems. While of no consequence to the synthesis of the target molecule, this result highlights the fact that C-silylation may still be a problem in the case of large molecules. These findings supplement the model studies on the synthesis of medium and large carbocycles using the Ireland-Claisen rearrangement carried out by Knight, where a lack of stereospecificity was reported, and by Danishefsky.[49]

Burke has used the reaction to prepare the hydropyran subunit in his synthesis of macrodiolide and macrotriolide ionophores. He was able to effect the rearrangement of **38** to **39** in 76% yield (**Scheme 25**).[50]

In their paper titled "Stereocontrolled Synthesis of a Polyether Fragment", Bartlett describes the use of the Ireland-Claisen rearrangement to synthesize a tetrahydropyran lactone with several chiral centers.[51] The stereoselective step using the rearrangement is shown in **Scheme 26**.

The ratio of **40** to **41** is 10:1 since the use of HMPA favors the formation of the (*Z*)-enolate-ester, which in turn gives **10**.

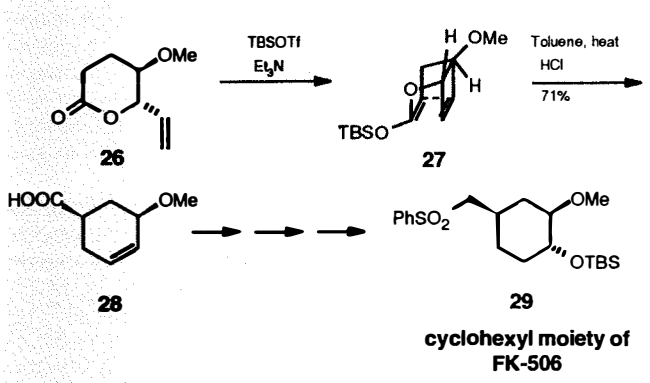
Cane and co-workers have used the rearrangement in the synthesis of chain elongation intermediates of the Monensin biosynthetic pathway.[52] They have been able to prepare **43** from **42** in 50-75% yield (Scheme 27).

Danishefsky has ingeniously used the Ireland-Claisen rearrangement to merge awkwardly positioned chiral centers in his synthesis of the C_{28}- C_{49} unit of Rapamycin, a metabolite of *Streptomyces hygroscopicus*, an antibiotic with immunosupressive properties (**Scheme 28**).[53]

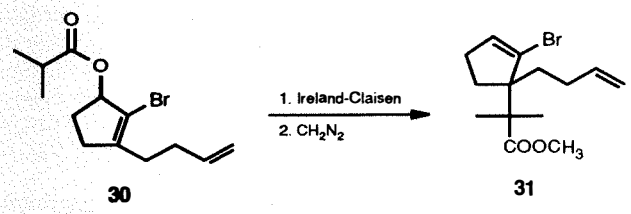
After preparing alcohol **44** and acid **45** separately, esterification in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDCI) and DMAP gave **46** which, in turn, after rearrangement of the silyl enol ether furnished **47**.

The rearrangement of lactones to carbocycles has also been carried out by Danishefsky in his synthesis of the *Fusarium* toxin equisetin.[54] Keto-lactone **48** was converted to its bisilyl derivative **49** and subsequently rearranged to yield ester **50** in 52% yield (**Scheme 29**).

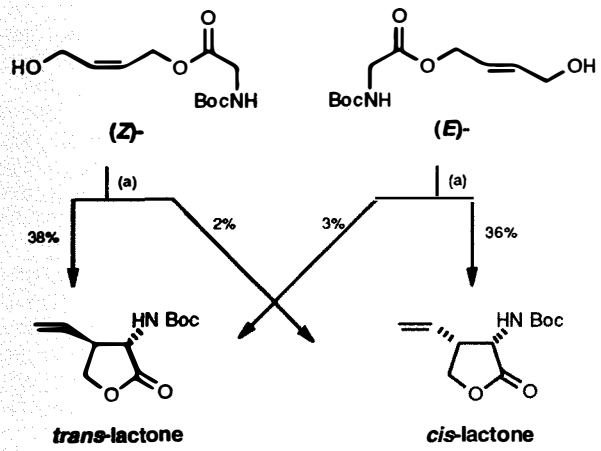
Scheme 21



Scheme 22

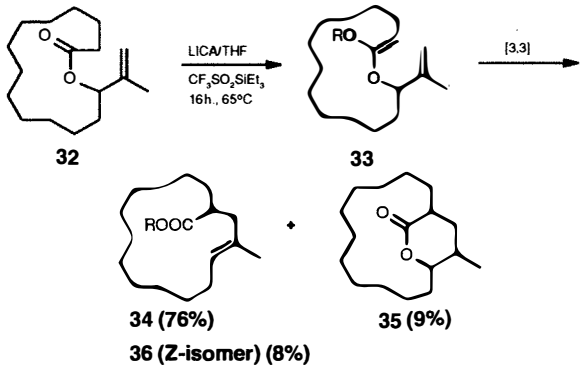


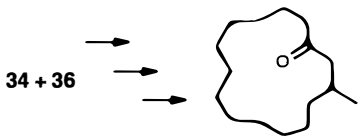
Scheme 23



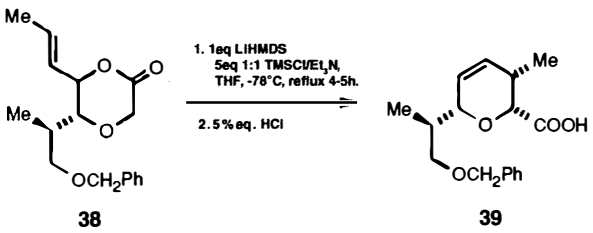
(a): 1. hexamethyldisilazane/reflux
2. LICA/THF/-76°C
3. TMSCl/-78°C to reflux

Scheme 24

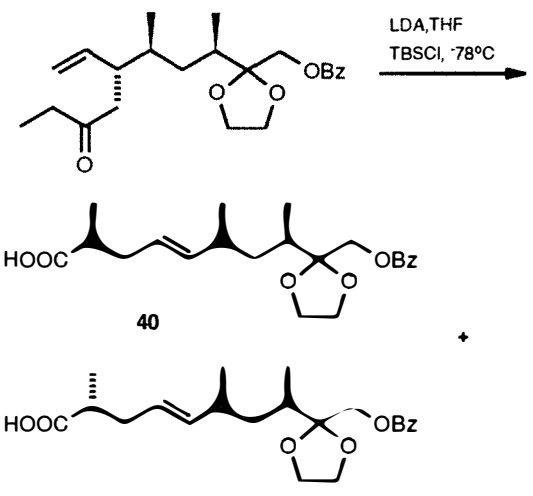




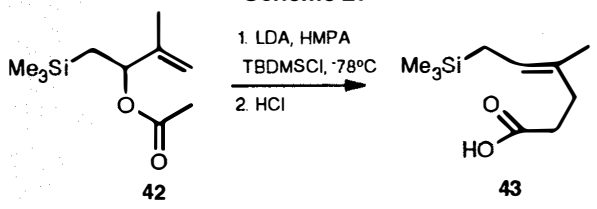
Scheme 25



Scheme 26

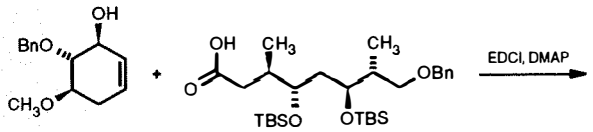


Scheme 27

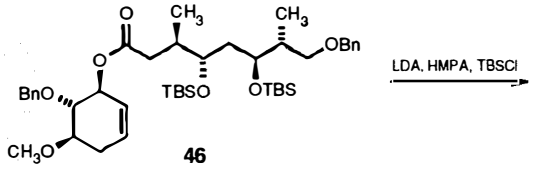


42 43

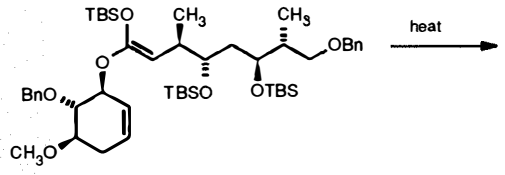
Scheme 28

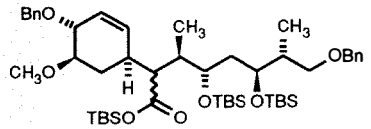


44 45



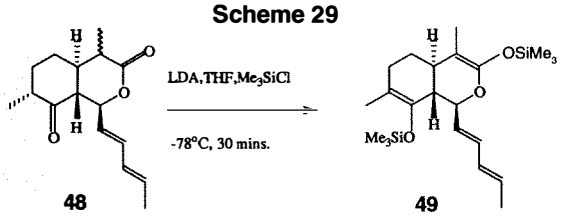
46



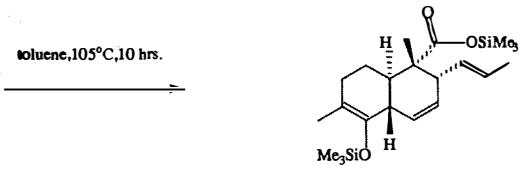


47

Scheme 29



48 49



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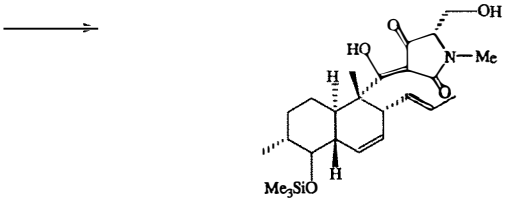
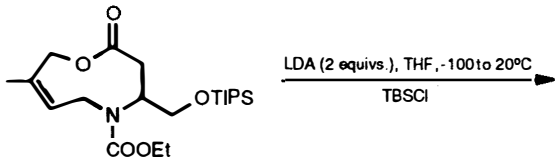
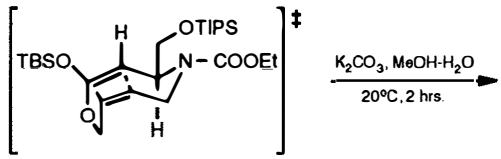


Equisetin

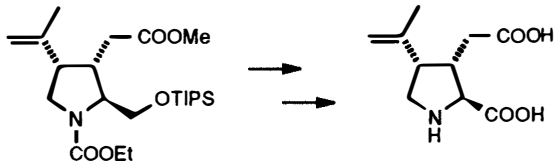
Scheme 30



51

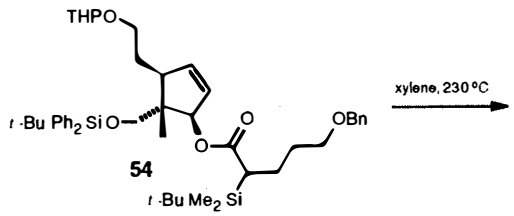


52

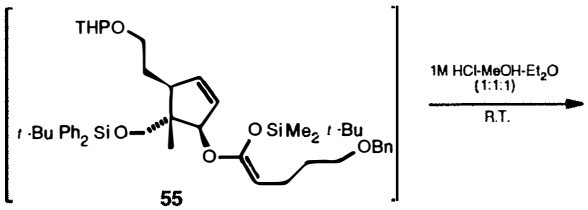


53 Kainic acid

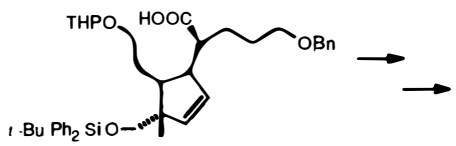
Scheme 31



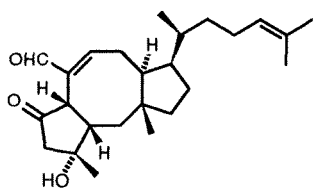
54



55



56



Ophiobolin C

The Ireland-Claisen rearrangement has also been used in syntheses involving the ring contraction of lactones (Claisen contraction). For example, Knight and co-workers have devised a strategy for the enantiospecific total synthesis of(-)-α-kainic acid using ring contraction of lactone (**51**) to pyrrolidinedicarboxylic acid (**53**) in 55% overall yield (**Scheme 30**).[55] The silyl ketene acetal **52** was proposed to rearrange through a boat transition state.

Another excellent example of Claisen ring contraction was reported by Funk for the preparation of the in,out-bicyclo[4.4.1] undecan-7-one core of the potent tumor promoter ingenol G49.[56]

In Kishi's total synthesis of ophiobolin C the silyl ketene acetal **55** prepared from **54** rearranged to stereoisomer **56** in 72% overall yield and 6:1 diastereoselectivity (**Scheme 31**).[37]

Conclusion

Over the years the discipline of synthetic organic chemistry has seen a trend towards the catalyzed stereoselective synthesis of natural products. These natural products often contain large carbocyclic rings and polyether fragments of well defined stereochemistry. The Claisen rearrangement,[57] reported more than 80 years ago, has remained an important synthetic tool.[58] The Ireland modification of this rearrangement enables the chemist to have better control over diastereoselectivity and to apply it to unsaturated esters. The Ireland-Claisen rearrangement has often been used to synthesize large carbocyclic structures with complex stereochemistry and will continue to be an important synthetic strategy in this class of compounds. The discovery that the Claisen rearrangement is routinely used by nature in the synthesis of aromatic amino acids via the shikimic acid pathway emphasizes the importance of the rearrangement in the synthetic preparation of these chiral natural products and others.[58]

Recent developments involving the use of organotin and organoboron chemistry have given excellent enantioselectivities (ca. 98% e.e.). In an age where high enantiomeric excesses and stereoselectivity are the order of the day, the rearrangements with organotin and organoboron reagents will be used more frequently in the future.

However, there are several areas that still have not been actively researched. Synthetic work involving the Claisen rearrangement (though not the Ireland-Claisen rearrangement) has already been investigated using organoaluminum as the diastereoselective agent, and has shown great promise for higher diastereoselectivity.[59] These, as well as other organometallic agents, should be utilized in the Ireland-Claisen rearrangements and may well enhance the diastereomeric selectivity currently achieved.

The effect of electron withdrawing substituents on the allylic ester is also significant. Welch and co-workers have studied the ester enolate rearrangement of allyl α-fluoroacetates and propanoates and demonstrated these rearrangements to be fairly selective.[60]

The aspect of diastereoselective synthesis of large carbocycles also leaves ample room for improvement of the rearrangement. For example, this topic has not been systematically investigated with the use of organometallic or lanthanide catalysts/ diastereoselective agents which are now known to exert a significant chelation effect. The "double" Ireland-Claisen rearrangement described earlier could well be investigated for various chain lengths and cyclic compounds.

Another area which has received considerable attention is that of biochemical catalysis. A recent publication reports a highly stereospecific Claisen rearrangement catalyzed by an antibody.[61]

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About the Authors

Schubert Pereira was born in Bombay, India in 1967. He received his BSc and MSc from the Bombay University in 1987 and 1989 respectively. After working in the cosmetics R & D industry in India for a few years, he joined the University of Toledo's doctoral program in chemistry where he is engaged in the synthesis of siderophores for magnetic resonance imaging.

Professor Morris Srebnik received his PhD from the Hebrew University in Jerusalem in 1984, under the direction of Raphael Mechoulam. In 1985/86 he went to Purdue University on a Lady Davis Fellowship where he worked with Professor H.C. Brown on the asymmetric chemistry of organoboranes. Except for a sojourn during 1986/87 at the Aldrich Chemical Company, he remained at Purdue until 1990 when he moved to the Department of Chemistry at the University of Toledo. His research group, consisting of MSc, PhD and undergraduate students, is exploring the chemistry of organozincs, organoboranes, transmetallations and asymmetric catalysis.

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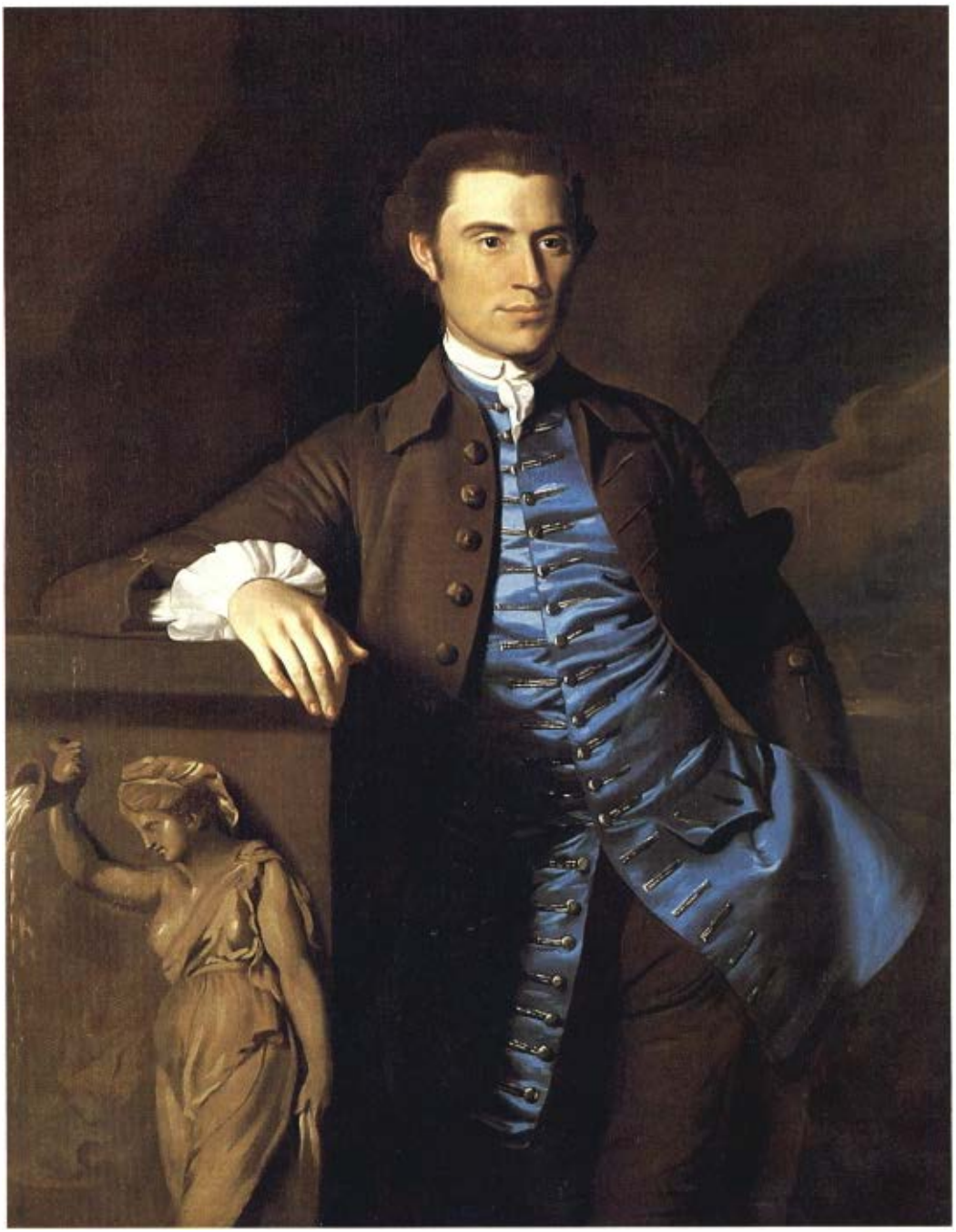

Oxidation Reactions Using Magnesium Monoperphthalate and Urea Hydrogen Peroxide

Modern Methods for the Monofluorination of Aliphatic Organic Compounds

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About Our Cover:

The painting that graces our cover is a portrait of **Thaddeus Burr** (oil on canvas, 50 x 39 in., 1758-1760). With its companion painting, a portrait of Burr's wife, Eunice Dennie Burr, these paintings represent the high point of American colonial portraiture, a field that was dominated by John Singleton Copley during the period between 1753 and 1774 when Copley left for England. Copley was virtually a self-taught artist since eighteenth-century Boston offered few masters to serve as artistic models. His first works were completed when he was only fifteen, and by the late 1750's Copley had achieved a style of compelling naturalism and sumptuous surface texture.

Thaddeus Burr was a Fairfield, Connecticut landholder and a graduate of Princeton. He was a close friend of John Hancock, and was one of two Fairfield delegates to the convention in Hartford to ratify the Constitution of 1788. Burr's hip-shot pose and clean chiseled features reflect the rational ideology of the eighteenth century. His stance looks to America's political future: leaning against a classical relief, the allegorical figure of abundance makes reference both to his position as landholder as well as the Greek democratic ideals which soon would shape the ideologies of the American and French revolutions. In 1759 he married Eunice Dennie; their marriage may have been the occasion for the commission of these portraits.

Both paintings are in the collection of The Saint Louis Art Museum.

Lab Notes

We have found a very convenient and practical way of generating free bases from salts of compounds having secondary or tertiary amines in their molecules. Generally, the free bases of such salts are liberated by dissolving them in water and then treating them with a strong base and extracting with the appropriate solvent. Recovery of the free base is frequently not quantitative. In our method the appropriate salt is placed on top of a short bed of a neutral alumina column and then eluted with a solvent containing 10% methanol in chloroform or an appropriate eluent. After removing the solvent the free base can be recovered in quantitative yield.

Shiv D. Kumar, Ph.D.
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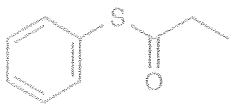
Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to Aldrich (attn: Lab Notes, Aldrichimica Acta). For submitting your idea, you will receive a complimentary, laminated periodic table poster (Cat. No. Z15,000-2, $9.90 value). 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



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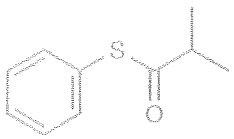

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Professor James S. Nowick of the University of California-Irvine suggested that we make these thiol esters which are efficient acyl transfer reagents[1] and ketone synthons.[2] More recently these thiol esters have been used by Danheiser and Nowick in an efficient and general synthesis of β-lactones through condensation of their enolates with aldehydes and ketones. Since β-lactones are known to decarboxylate stereospecifically to the corresponding olefins this method also constitutes a convenient approach to the synthesis of a variety of substituted alkenes.[3]

(1) Ahmad, S.; Igbal, J. *Tetrahedron Lett.* **1986**, *27*, 3791. (2) Cardellicchio, C.; Finandanese, V.; Marchene, G.; Ronzini, L. *ibid.* **1985**, *26*, 3595. Fehr, C.; Galindo, J. *J. Org. Chem.* **1988**, *53*, 1830. (3) Danheiser, R.L.; Nowick, J.S. *ibid.* **1991**, *56*, 1176.

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

Oxidation Reactions Using Magnesium Monoperphthalate and Urea Hydrogen Peroxide

Harry Heaney
Department of Chemistry
Loughborough University of Technology,
Leicestershire
LE11 3TU, U.K.

Chemists have long been interested in using reagents derived from hydrogen peroxide (peroxidic reagents) but some of these reagents are either hazardous (see note 1a), not widely available, or both. In this brief review I will discuss recent work involving new, relatively safe peroxidic reagents that have been developed to overcome some, but not all, of the problems associated with materials that are now no longer in favour. I will also comment on other workers' results using the reagents that my co-workers and I have been involved with and also, where appropriate, draw comparisons with other peroxygen reagents, especially m-chloroperoxybenzoic acid (MCPBA). Many workers continue to use MCPBA successfully.

INTRODUCTION

A number of oxidations that have been reported in the past have used the so-called *'hightest'* (**>85%**) aqueous hydrogen peroxide in order to generate, for example, **trifluoroperoxyacetic** acid. But perhaps the most widely reported peroxidic reagent in the past twenty-five years or so has been **MCPBA.** The reluctance of suppliers to **transport** the 'rocket fuel' high test hydrogen **peroxide** needs no explanation, and regulations with respect to the **transportation** of pure **MCPBA** have also made the search for safe alternatives a sensible goal. Pure **MCPBA** is both shock-sensitive and potentially explosive in the condensed phase as indicated by a positive result of 30 ms for **MCPBA** upon evaluation by the standard time/pressure test for products that are capable of deflagration.[1b] The usual contaminant that is present in commercial MCPBA is *m*-chlorobenzoic acid which may be removed by washing with a phosphate buffer of pH 7.5 and drying the residue under reduced pressure.[2] The presence of *m*-chlorobenzoic acid does lead to some reduction in the hazardous nature of commercial MCPBA, but it is still shock-sensitive and capable of deflagration.

By comparison, magnesium monoperoxyphthalate hexahydrate (MMPP) (**1**), a recently developed peroxygen product,[3] is both non-shock-sensitive and non-deflagrating. It is available both as a laboratory and as a bulk chemical.[4]

Our early investigations showed that MMPP can be used to carry out a wide variety of oxidation reactions, some of which we reported a few years ago.[5] We were also attracted to the possibility of using hydrogen bonded adducts of hydrogen peroxide by the report of the use of DABCO-diperhydrate as an alternative to anhydrous hydrogen peroxide in the preparation of bis(trimethylsilyl) peroxide.[6] We looked at a number of perhydrates including DABCO-di-*N*-oxide-diperhydrate (**2**),[7] triphenylphosphine oxide-perhydrate,[8] and urea-hydrogen peroxide (UHP) (**3**).

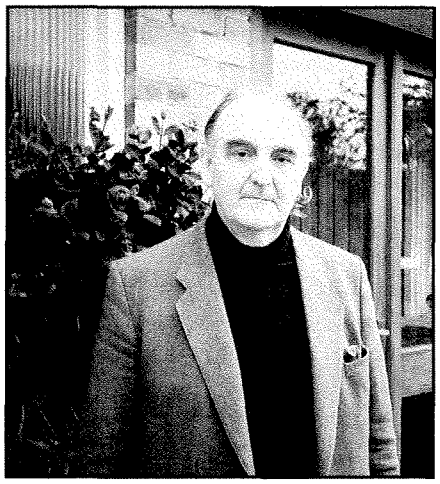
The hydrogen bonded urea adduct UHP is a white crystalline solid formed when urea is recrystallised from aqueous hydrogen peroxide.[9] Its use was investigated in detail for a number of reasons, including ease of preparation and commercial availability.

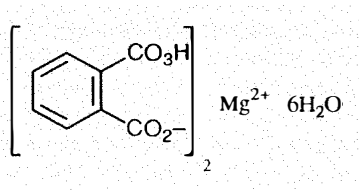
Infrared evidence favours structure **3** in which hydrogen bonding occurs between a peroxide oxygen and one of the urea hydrogen atoms.[10] It is of interest to note that the complex that is formed between hydrogen peroxide and biuret is an inclusion complex that apparently does not involve strong hydrogen bonding of the type found in UHP. However, preliminary investigations suggest that biuret-H_2O_2 will be less useful.[11]

The relatively high proportion of hydrogen peroxide in the UHP adduct (36.2%) was another feature that attracted us. The anhydrous material is hygroscopic and is best stored at low temperatures due to the possibility of thermal decomposition. The high percentage of hydrogen peroxide places it within the range of organic-hydrogen peroxide mixtures which are explosive and, in a sufficiently forcing test, it can be made to explode. The thermal decomposition has been studied and is acceleratory above 355 K (82°C).[12]

The commercial material, which we use, typically has an available oxygen content of about 90% of the theoretical value. It may be stored at room temperature over long periods of time (ca. 1 year) without a significant loss of available oxygen. This material is reasonably stable as judged by negative impact and pressure-time tests on small samples.

We have published a preliminary account of the use of UHP in a range of typical





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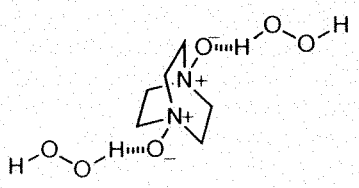

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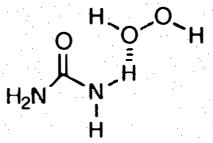

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oxidations,[13] and the details of a new procedure for the preparation of bis(trimethylsilyl)peroxide (eq 1), involving the use of UHP, were also published simultaneously.[14] It is worth noting at this point that DABCO-diperhydrate has been found to be very unstable, decomposing violently in the presence of trace amounts of transition metal salts which are sometimes present on 'clean' glassware and stirrer bars.

Some of the early uses[15] of MCPBA indicate the initial objectives that one would consider when evaluating new potential substitutes. The epoxidation of alkenes such as 1-octene (eq 2) and ethyl crotonate (eq 3), as well as the epoxidation of enol ethers followed by cleavage (eq 4)[16] are illustrative. Baeyer-Villiger oxidation reactions, such as the oxidation of a 20-ketosteroid which afforded the 17-β-hydroxysteroid after hydrolysis of the ester,[15] and the formation of *N*-oxides (eq 5)[17] also serve as early examples. Of course, many colleagues still prefer to use MCPBA. However, as will be evident from this article, MMPP in particular is gaining acceptance as an MCPBA substitute and now appears in a well known undergraduate textbook[18] and a practical text.[19]

EPOXIDATION REACTIONS

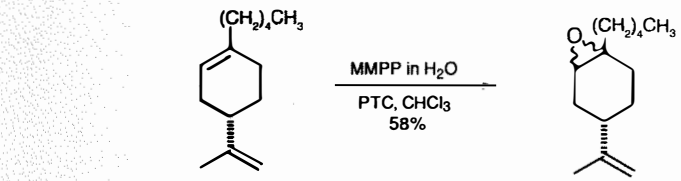
The majority of successful examples of epoxidation reactions using MMPP have been carried out using a hydroxylic solvent to dissolve the reagent. This solvent has usually been a low molecular weight alcohol or, where the substrate to be epoxidised is insoluble in such a solvent, water has been used together with a phase transfer catalyst to carry the monoperphthalate anion into an organic solvent such as chloroform or dichloromethane. It may be noted in this connection that the epoxidation of cholesterol proceeds very efficiently in the absence of a phase transfer catalyst. 2-Methylbut-2-ene (eq 6) and cyclohexene were both epoxidised in high yield using aqueous isopropanol as the solvent.[5] The epoxidation of 4,7-dihydroindane (eq 7) and 1,2-dimethylcyclohexa-1,4-diene with MMPP in ethanol[20] should be compared with the latter reaction using MCPBA.[21]

The oxidation of the allylic alcohol shown in equation 8 was achieved in excellent yield when carried out in a mixture of isopropanol and water, affording an approximate 4:1 mixture of the diastereomeric epoxides.[22] It was assumed that hydrogen bonding of the peracid with the hydroxyl group led to the preferential formation of the α-epoxide. Diastereoselectivity in the epoxidation of allylic alcohols using either vanadium(V)/*tert*-butylhydroperoxide or MCPBA was discussed briefly in an earlier article,[23] and additional examples continue to appear some of which report very high de's.[24,25] Another interesting recent example concerns the formation of the mono-epoxide from [$^2H_6$]buta-1,4-diene which was carried out by having one atmosphere of the diene over an aqueous solution of MMPP.[26]

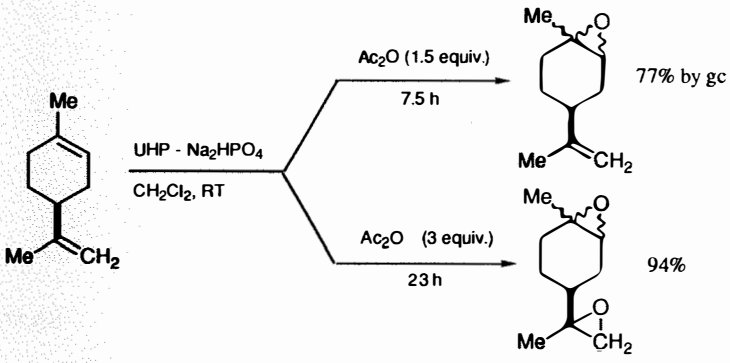
Other examples of epoxidation reactions involving dienes using MMPP result, similarly to MCPBA, in reaction at the more electron rich double bond. The example shown in equation 9 is one of the steps in a synthesis of the quinone antibiotic frenolicin and used MCPBA in the presence of 5% aqueous sodium hydrogen carbonate.[27] Limonene affords a mixture of diastereomeric 1-methyl-4-(1-methylethenyl)epoxycyclohexanes using MMPP and phase transfer reaction conditions. Similarly, epoxidation of the terpene-derived diene shown in equation 10 using MMPP gave the epoxides shown in a reasonable yield.[28]

Because presently available procedures based on UHP use an excess of the oxidising agent, reactions involving dienes make efficient isolation of monoepoxides difficult. This point is indicated by the examples using UHP shown in equation 11. However, it is worth noting that as expected, geranyl acetate can be converted into 6,7-epoxygeranyl acetate.

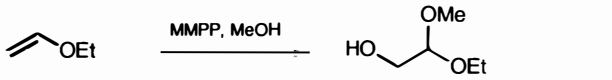
The epoxidation of enol ethers can be carried out successfully using a variety of reagents including MCPBA, peroxyimidic



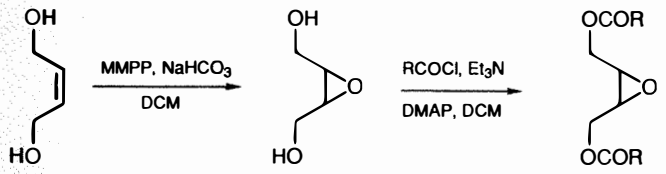
(eq 10)



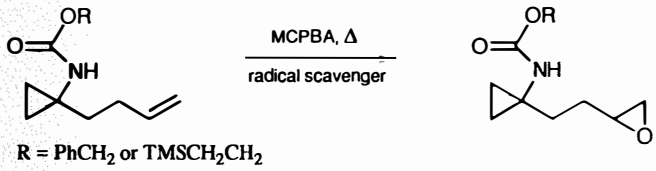
(eq 11)



(eq 12)

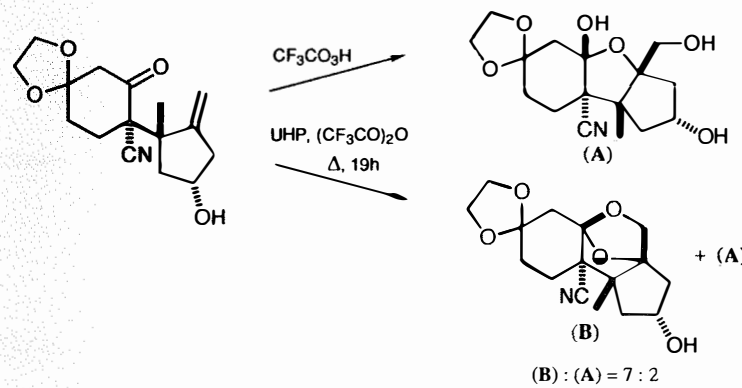


(eq 13)



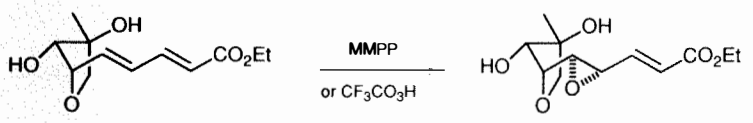
(eq 14)

R = $PhCH_2$ or $TMSCH_2CH_2$



(B) : (A) = 7 : 2

(eq 15)



(eq 16)

acids, and MMPP. A comparison of the reactions of ethyl vinyl ether (eq 12) has been reported,[29] as also has the sequence from *cis*-but-2-ene-1,4-diol to the corresponding epoxyesters (eq 13).[30]

There have been examples reported where the attempted epoxidation of alkenes has failed in the presence of MMPP (for example, terminal olefins of the type shown in equation 14.) However, epoxidation was successful using MCPBA employing Kishi's high temperature method[31] in which a radical inhibitor 4,4'-thiobis(6-*tert*-butyl-3-methylphenol) was employed.[32] The decomposition of peroxycarboxylic acids at high temperatures presumably occurs by radical processes. It may well be that some apparent failures using MMPP result from very slow rates of reaction at room temperature. On the other hand, MMPP has been used successfully together with 5,10,15,20-tetraphenyl-2,6-dichlorophenylporphinatomanganese(III) acetate in oxygenation reactions that mimic cytochrome P-450 enzymes.[33] The addition of pyridine or 4-methylpyridine improves the rate of epoxidation and even electron depleted alkenes such as isobutyl 3-butenoate are efficiently epoxidised under mild reaction conditions.

Selectivity in epoxidation reactions frequently depends on the reagent and reaction conditions chosen. For example, the epoxidation of the homoallylic alcohol shown in equation 15 proved to be difficult when using trifluoroperoxyacetic acid generated conventionally and afforded only the hemiacetal (**A**).[34] When the reaction was carried out using the UHP procedure, although the hemiacetal was still an isolable product, the spiroacetal was obtained as the major product.[35] The diene ester shown in equation 16 surprisingly gave no epoxide on treatment with MCPBA. However, MMPP and trifluoroperoxyacetic acid, generated from the anhydride and 85% hydrogen peroxide, both gave the α-epoxide exclusively. Also, 3,5-dinitroperoxybenzoic acid gave a mixture of α- and β-epoxides (3:1).[36] The epoxidation of cholesterol using a range of peroxycarboxylic acids, including MMPP, gives a mixture in which the α-epoxide predominates over the β-epoxide by about 4:1 (**Scheme 1**).

On the other hand, using trifluoroperoxyacetic acid generated by the UHP procedure[11] one obtains mainly the 3-β-trifluoroacetoxy-5,6-α-epoxide. The epoxidation of cholesteryl benzoate using MMPP gave a ratio of α- to β-epoxide of 5.5:1 and using trifluoroperoxyacetic acid an α:β-epoxide of ca. 3:1 was indicated by the ^1H NMR spectrum. It is of interest to note that the epoxidation of cholesteryl benzoate using the catalytic system shown in equation

17 gave an α:β ratio of ca. 3:7.[37] When $Mn(II)(dpm)_2$ was used the α:β ratio was ca. 1:4.5.[38] Presumably, long lived radical intermediates are involved in these reactions as indicated by the fact that *Z*-oct-2-ene gave a mixture of *cis*- and *trans*- epoxides in an almost 1:1 ratio. The results obtained in the reactions with cholesteryl benzoate are reminiscent of those obtained in reactions of steroidal alkenes with dioxiranes. Cholesteryl acetate reacts with dimethyldioxirane to afford a mixture of epoxides in which the β-isomer is present in larger amounts than is normally the case when using a peroxycarboxylic acid.[39]

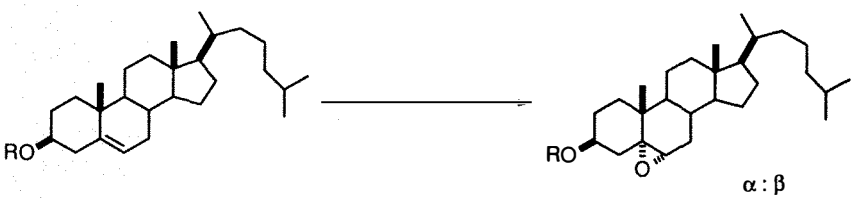
Selectivity in the epoxidation of dienes where the two alkene residues are of widely differing nucleophilicities is not difficult to achieve and we will return to this point later in this review. However, it is worth pointing out that quite good diastereofacial selectivity was reported in the epoxidation shown in equation 18, part of a total synthesis of (+)-altholactone. The epoxidation step using MCPBA proceeded with poor selectivity whereas MMPP gave predominant attack on the β-face and a 3.5:1 mixture of the substituted tetrahydrofuran derivatives resulted after acid-catalysed cyclisation.[40]

Epoxidation reactions using UHP as the source of hydrogen peroxide require that the anhydride and other reactions conditions are chosen carefully. For particularly nucleophilic alkenes our best procedure uses acetic anhydride and disodium hydrogen phosphate at room temperature. In this way we were able to obtain α-methylstyrene oxide in a 75% yield and the epoxide derived from α-pinene in 79% yield as shown in equation 19. Other workers have shown that a styrene derivative may be converted into a diol (eq 20) by ring opening the epoxide formed.[41]

With relatively non-nucleophilic and non-volatile terminal alkenes, for example 1-octene, we have generated peroxytrifluoroacetic acid in the presence of disodium hydrogen phosphate and heated the mixture under reflux for a brief period. In this way we were able to obtain a high yield of 1,2-epoxyoctane as indicated in equation 21. Other examples of the use of these and other procedures are given in **Table 1** (see p. 40).

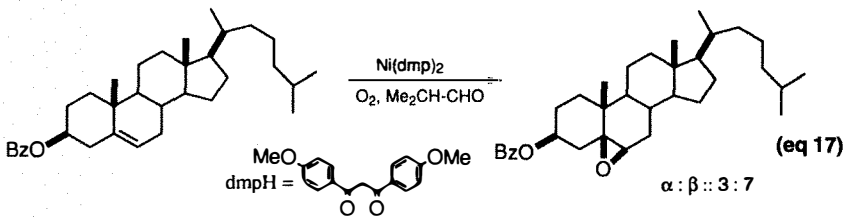
The epoxidation of electron deficient alkenes such as methyl methacrylate has also been carried out using reaction conditions similar to those shown in equation 21. With α,β-unsaturated ketones alkaline hydrogen peroxide has been generated from UHP and affords good yields of epoxides. For example, pulegone gave a 50% yield of the epoxide, and the result obtained with isophorone is shown in equation 22.

The epoxidation of nitroalkenes such as β-methyl-β-nitrostyrene has been reported

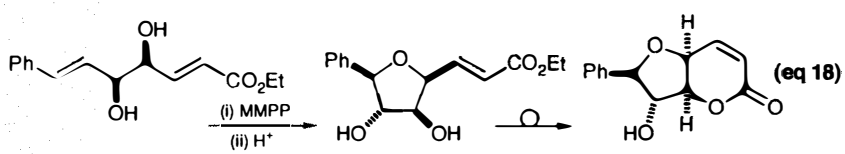


			α : β
R = H	MMPP, $CHCl_3$, H_2O	R = H 88%	4 : 1
R = H	UHP-$(CF_3CO)_2O$, Na_2HPO_4 at RT 16 h	R = CF_3CO 62%	4 : 1
R = PhCO	MMPP, $CHCl_3$, H_2O	R = PhCO	5.5 : 1
R = PhCO	UHP-$(CF_3CO)_2O$, Na_2HPO_4 at RT 16 h	R = PhCO 51%	3 : 1

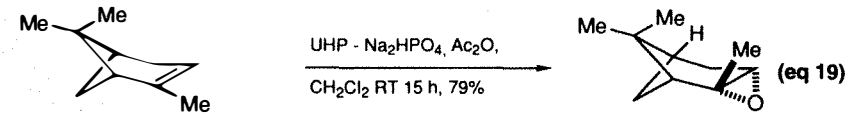
Scheme 1



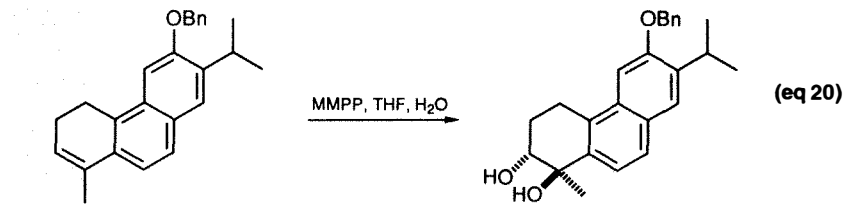
(eq 17)



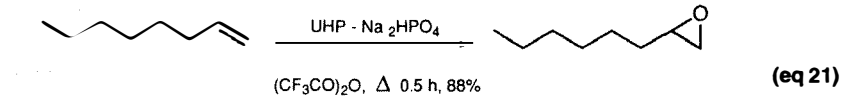
(eq 18)



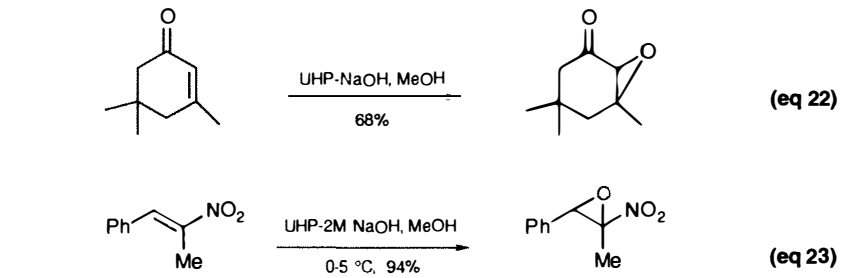
(eq 19)



(eq 20)

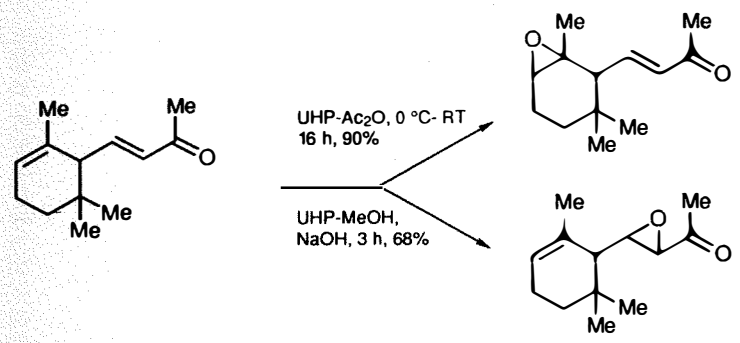


(eq 21)

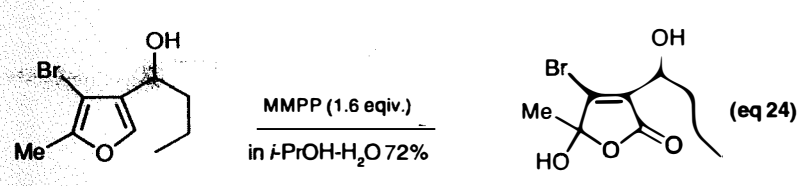


(eq 22)

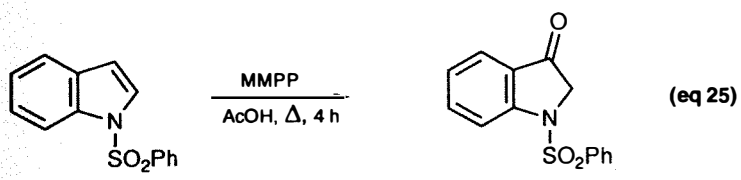
(eq 23)



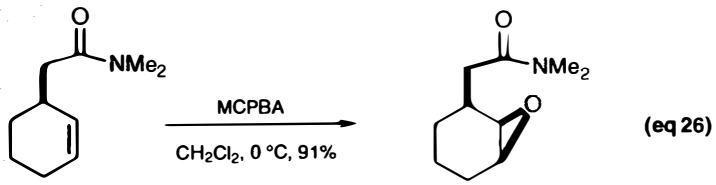
Scheme 2



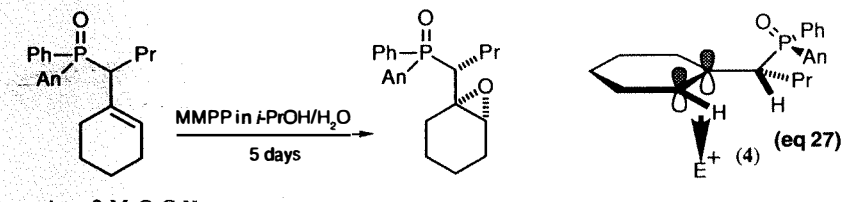
(eq 24)



(eq 25)

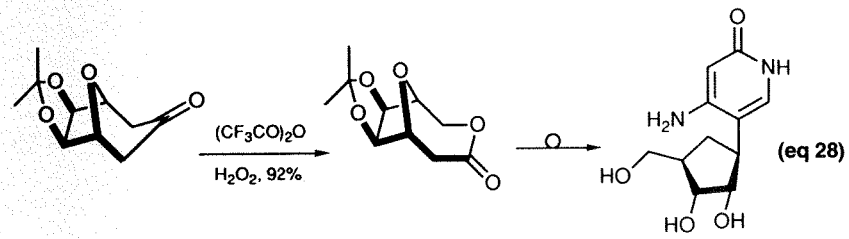


(eq 26)

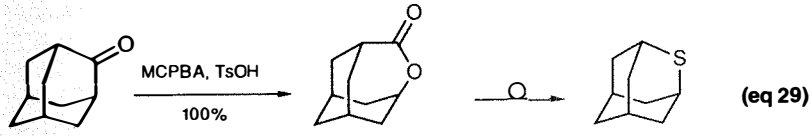


(eq 27)

An = 2-MeO-C_6H_4



(eq 28)



(eq 29)

using alkaline hydrogen peroxide.[42] The epoxide shown in equation 23 was obtained in an almost quantitative yield when we used UHP in methanol-aqueous sodium hydroxide at low temperatures. At higher temperatures and in the presence of stronger than 2*M* sodium hydroxide we obtained mixtures of benzaldehyde and benzoic acid, products resulting from hydroxide ion-induced fragmentation of the epoxide and further oxidation. As expected, the epoxidation of α-ionone can be carried out using different procedures in order to functionalise the two different double bonds (**Scheme 2**).

We mentioned earlier the epoxidation of geranyl acetate using the UHP method. Conventional epoxidation of geraniol using MCPBA results in the formation of a 2:1 mixture of the 6,7-epoxide and the 2,3-isomer despite the reduction in electron density at the 2,3-position caused by the allylic hydroxyl group.[43] In this connection it is interesting to note that the 2,3-epoxide is formed in a 93% yield by using an emulsion technique in which the 6,7-double bond is kept away from the MCPBA in a hydrocarbon phase.[44]

The oxidation of some heteroaromatic compounds using MMPP have been reported. Some of the products clearly result from initial epoxidation. The reaction shown in equation 24 was used in the synthesis of bromobeckerelide, a product isolated from a marine red alga.[45] Other furan derivatives that carry electron releasing groups in the 2- and 5-positions afford ring opened dienones using either MCPBA or MMPP. In the latter case the reactions were carried out in aqueous ethanol and gave very good yields.[46] The oxidation of 1-benzenesulfonylindole using MMPP results in the formation of the corresponding indoxyl by way of initial epoxidation as shown in equation 25.[47]

Before leaving the subject of epoxidation reactions we should make brief return to the question of the control of stereochemistry involving the use of neighbouring functional groups. The reaction shown in equation 26 is a recently published example involving the use of MCPBA.[48] High diastereofacial selectivity has also been observed in epoxidation reactions using MMPP. Both of the diastereomers of the phosphine oxides (eq 27) are epoxidised with stereoselectivities in excess of 95:5.[49] Reactions using compounds which retained the chiral phosphorus centre gave very low selectivities showing that the stereoselectivity is dominated by the effect of the chiral carbon centre.

It was assumed that the stereochemical control resulted from Houk[50] selectivity as illustrated by **4**. Similar arguments have been adduced in connection with a number of reactions of allyl silanes, including epoxidation reactions.[51] The osmium tetrox-

ide catalysed hydroxylation of *E*-γ-hydroxy-α,β-unsaturated esters using *N*-methylmorpholine-*N*-oxide and aqueous acetone has also been explained in terms of a conformation resulting from favourable interactions between the p-orbitals of the double bond and an unshared electron pair on the γ-oxygen.[52]

BAEYER-VILLIGER AND RELATED REACTIONS

The facility with which the Baeyer-Villiger oxidation of aldehydes and ketones can be effected is related to the strength of the conjugate acid of the leaving group. The stronger the acid the more powerful is the peroxyacid in its oxidation reactions. Not surprisingly, the more commonly available peroxyacids are the most frequently used. In this respect MCPBA has been, until recently, the most widely used.

Trifluoroperoxyacetic acid is a remarkably powerful reagent for use in Baeyer-Villiger reactions.[53] However, this reagent was prepared by the reaction of trifluoroacetic anhydride with 85-92% hydrogen peroxide and thus its use is severely limited by the lack of availability and hazardous nature of that reagent. On the other hand there have been examples reported where lower strength hydrogen peroxide has been used successfully.[54]

Two recent examples of the conversion of ketones into lactones using trifluoroperoxyacetic acid or MCPBA are shown in equations 28 and 29. In the first case (eq 28) the Baeyer-Villiger reaction was used as part of a stereocontrolled general synthesis of C-nucleosides.[55] The second example is concerned with a route from adamantanone to thiaadamantane (eq 29).[56]

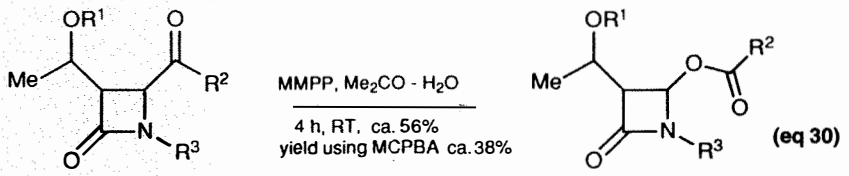
In our preliminary account on the use of MMPP we mentioned two examples where Baeyer-Villiger reactions had been carried out satisfactorily.[5] Cyclohexanone and 3,3-dimethylbutanone were converted into caprolactone and *tert*-butyl acetate respectively in good yields. There have been a few other reports of this use of MMPP. The reactions of the β-lactams shown in equation 30 are reported to proceed efficiently using MMPP.[57] These results may be compared with those obtained using oxygen and an aldehyde in the presence of an iron(III) catalyst.[58] Although the cubane derivative shown in equation 31 undergoes the tris-Baeyer-Villiger reaction in good yield using MCPBA, an attempted reaction using MMPP failed. When the UHP-trifluoroacetic anhydride method was tried a satisfactory result was obtained and the expected product was isolated in 80% yield.[59] There have been a number of other reports where MMPP has either shown no advantage over more established methods or has given unsatisfactory results in attempted Baeyer-Villiger reactions.[60] The major reason is probably related to the requirement to dissolve the MMPP in a hydroxylic solvent.

The Baeyer-Villiger oxidative rearrangement of menthone was one of the first examples reported using Caro's acid (i.e., H_2SO_5). Baeyer-Villiger reactions of cycloalkanones (eq 32) using trifluoroperoxyacetic acid (generated by the interaction of UHP with trifluoroacetic anhydride in dichloromethane in the presence of disodium hydrogen phosphate as a buffer) result

Table 1 Epoxidation Reactions Using Urea-Hydrogen Peroxide (UHP)

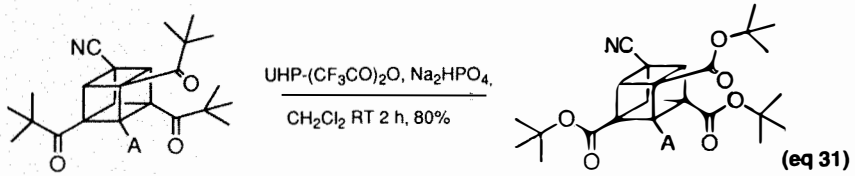
Substrate	Product	Method	Yield [%]
styrene	styrene oxide	(1)	60
α-methylstyrene	1-phenyl-1-methyloxirane	(1)	83
β-methylstyrene	1-phenyl-2-methyloxirane	(1)	86
trans-stilbene	1,2-diphenylepoxyethane	(1)	47
2,3-dimethylbut-2-ene	2,3-dimethyl-2,3-epoxybutane	(1)	51
hex-1-ene	1,2-epoxyhexane	(2)	53
oct-1-ene	1,2-epoxyoctane	(3)	88
cyclohexene	epoxycyclohexane	(1)	74
1-methylcyclohexene	1-methylepoxycyclohexane	(1)	56
3-methylcyclohexene	3-methylepoxycyclohexane	(1)	58
limonene	limonene diepoxide	(1)	94
α-pinene	1,2-α-epoxypinane	(1)	79
α-ionone	1,1,3-trimethyl-2-(3-oxo-but-1-enyl)-3,4-epoxycyclohexane	(1)	90
cyclooctene	epoxycyclooctane	(3)	60
phenyl allyl ether	1,2-epoxy-3-phenoxypropane	(2)	51
linalool	2-methyl-5-(2'-propyl-2'-hydroxy)-2-vinyl-tetrahydrofuran†	(2)	64
geraniol	geranioldiepoxide	(1)	66
geranyl acetate	6,7-epoxygeranyl acetate	(1)	82
cholesterol	3-β-hydroxy-5,6-α-epoxycholestane and 3-β-hydroxy-5,6-β-epoxycholestane	(1)	65 28
cholesterol	3-β-trifluoroacetoxy-5,6-α-epoxy cholestane	(2)	62
cholesteryl benzoate	3-β-benzyloxy-5,6-α-epoxy cholestane*	(2)	53
isophorone	3,5,5-trimethyl-2,3-epoxycyclohexanone	(4)	68
pulegone	pulegonepoxide	(4)	50
α-ionone	1,1,3-trimethyl-2-(3-oxo-1,2-epoxybutyl)cyclohex-3-ene	(4)	68
β-methyl-β-nitrostyrene	2-nitro-3-phenyl-2,3-epoxypropane	(4)	94
methylmethacrylate	methyl 2-methyl-2,3-epoxypropanoate	(3)	56

† major product; * ratio α :β 5:2;
methods: (1) UHP-Ac_2O-Na_2HPO_4, 0° to RT; (2) UHP-$(CF_3CO)_2O$-Na_2HPO_4, RT; (3) UHP-$(CF_3CO)_2O$-Na_2HPO_4, reflux; (4) UHP-NaOH/MeOH.



(eq 30)

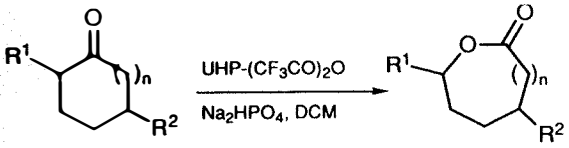
R^1 = H, TMS, or TBDMS
R^2 = H, $PhCH_2$, or 4-$MeOC_6H_4CH_2$
R^3 = Ph or Me



(eq 31)

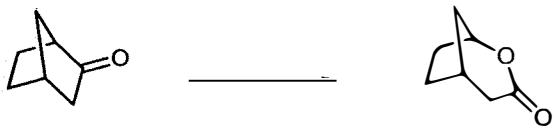
A = C(OH)Me *t*-Bu

A = C(OH)Me *t*-Bu



(eq 32)

n = 0, $R^1 = R^2 = H$	53%
n = 1, $R^1 = R^2 = H$	61%
n = 1, R^1 = Me, R^2 = H	63%
n = 1, R^1 = *i*-Pr, R^2 = Me	98%
n = 2, $R = R^2 = H$	85%



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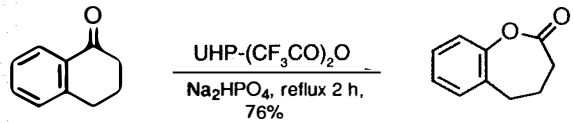
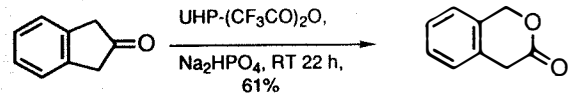
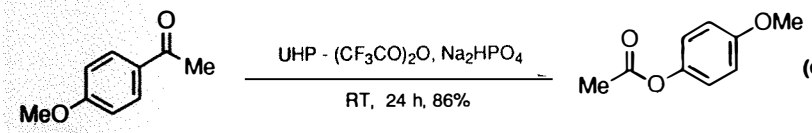


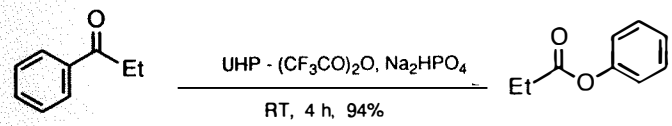
(eq 34)



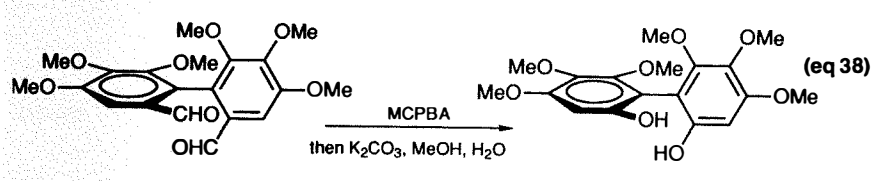
(eq 35)



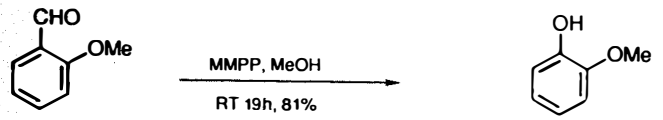
(eq 36)



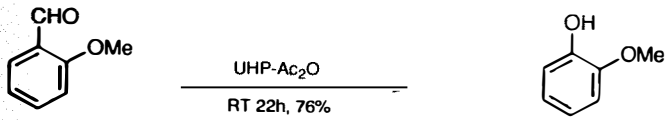
(eq 37)



(eq 38)



(eq 39)



(eq 40)

in the formation of the expected lactones in good to excellent yields. The exclusive formation of 7-methylcaprolactone from 2-methylcyclohexanone illustrates the generalisation that secondary alkyl groups have a higher migratory aptitude than primary alkyl groups. The isolation of a single product in an almost quantitative yield from menthone also testifies to the effectiveness of this method. The procedure also works well for bicyclic ketones such as norcamphor (eq 33) and acyclic ketones such as 3,3-dimethylbutanone. The method also works efficiently with benzocycloalkanones and is exemplified by the reactions of α-tetralone (eq 34) and 2-indanone (eq 35). The anticipated Baeyer-Villiger reactions of simple aralkyl ketones in which the oxidative rearrangement occurs with aryl migration are shown in equations 36 and 37.

The oxidation of aromatic aldehydes to phenols via the corresponding aryl formates is known as the Dakin reaction and is evidently related to the Baeyer-Villiger oxidation of ketones. The use of MCPBA is well known,[61] and new examples continue to be reported (eq 38).[62] The successful use of MMPP and UHP-acetic anhydride in these reactions (eq 39 and 40) can be achieved with aldehydes that have electron releasing substituents in an *ortho* - or *para* - position. In the absence of a suitable electron releasing substituent, hydrogen migration occurs and the product is a carboxylic acid. In fact the use of UHP and methanolic sodium hydroxide allows a wide range of aromatic aldehydes to be oxidised to the corresponding carboxylic acid in good yields as indicated by the examples shown in equation 41.

HETEROATOM OXIDATION REACTIONS

The Oxidation of Sulfur

The oxidation of sulfides to sulfoxides or sulfones depends on the reaction conditions used. Hydrogen peroxide and *tert*-butyl hydroperoxide have both been used as have a variety of peroxycarboxylic acids. Since all the peroxycarboxylic acids are stronger oxidants than hydrogen peroxide, milder conditions may be used when carrying out the oxidation of sulfides to sulfoxides with a reagent such as MCPBA. In the example shown in equation 42 the diastereomeric sulfoxides were obtained in good yields.[63]

Oxaziridines are also useful oxidants for the conversion of sulfides into sulfoxides and good enantioselectivity has been achieved using chiral oxaziridines.[64] In our preliminary investigations, we showed that tetrahydrothiophene could be oxidised by MMPP either to the sulfoxide or to the sulfone.[5] The use of UHP led to the sulfone

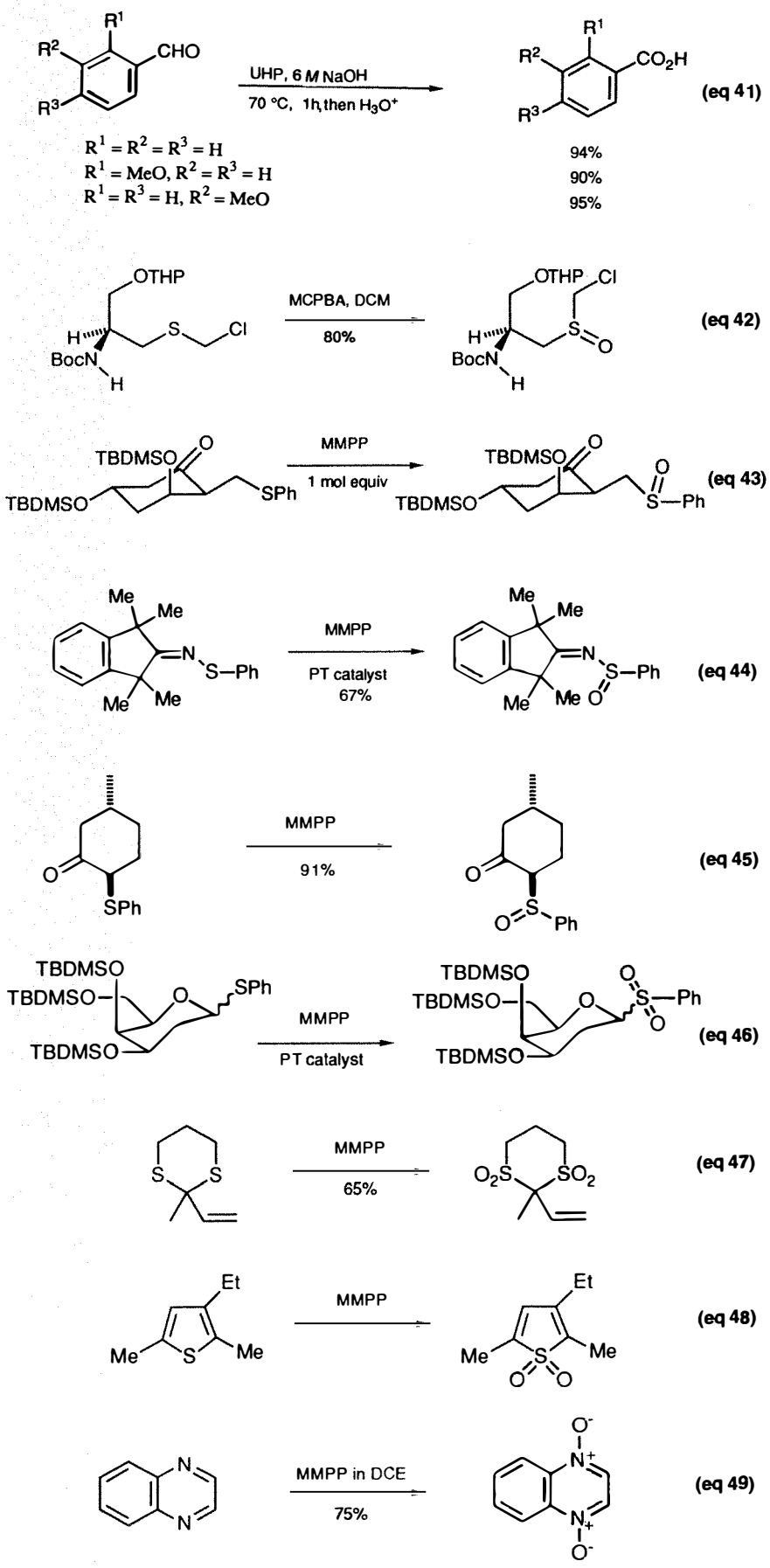
exclusively, presumably due to using an excess of the reagent.[13] Careful control of reaction conditions using MMPP allows sulfoxides to be isolated (eq 43).[65] The related conversion shown in equation 44 gave a good yield after a brief reaction period,[66] and the conversion shown in equation 45 was used in a synthesis of artemisinin.[67] By using an excess of MMPP good yields of sulfones have been reported by a number of resesarch groups[68-71] and are indicated in equations 46,[68] 47,[69] and 48.[70]

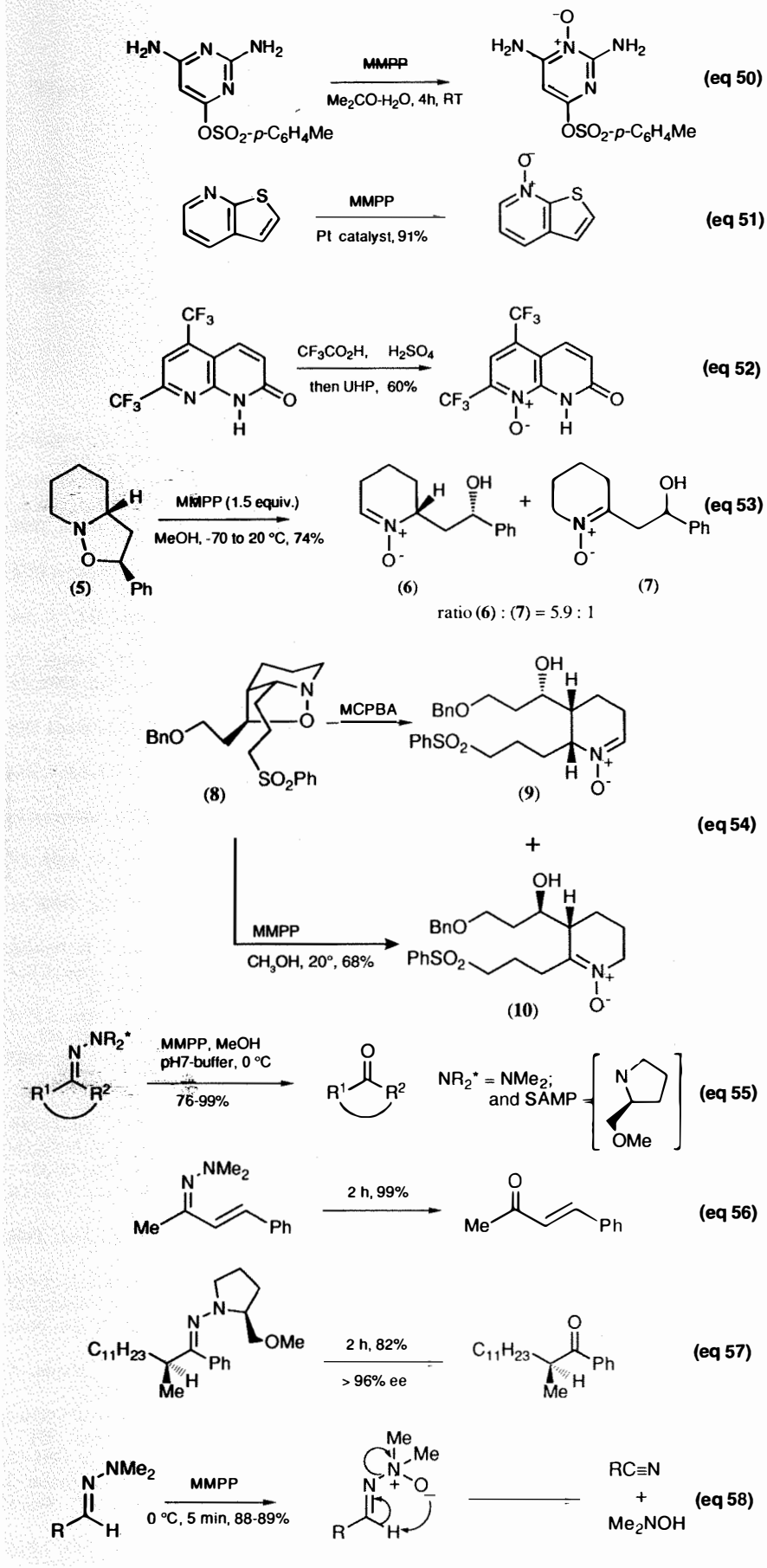
The oxidative conversion of a phosphothionate group to a phosphate (thionate to oxon), an important biochemical process, has been studied with a wide variety of reagents. It was shown that MMPP was better than MCPBA, the next best reagent in the oxidation of malathion to malaoxon. MMPP gave the best result with respect to yield and diastereoselectivity.[72]

The Oxidation of Nitrogen

Pyridine, 2-methylpyridine, and 2-chloropyridine can all be oxidised to the corresponding *N*-oxides using MMPP in acetic acid.[5] In our more recent work we also showed that the UHP-trifluoroacetic anhydride method also gave a moderate yield of quinoxaline di-*N*-oxide.[11] It is likely that isolation difficulties were a major problem in the latter case. The oxidation of quinoxaline in dichloroethane using MMPP proceeds in high yield (eq 49) and there are no difficulties in isolating the product. High yields of the *N*-oxides shown in the equations 50[73] and 51[74] were reported using MMPP, and in a modification of our UHP method, phthalic anhydride was used in the oxidation of 4-*tert*-butylpyridine to the *N*-oxide in 93% yield.[75] When we started our study of the use of MMPP and UHP we were not aware of the report of the use of UHP as a substitute for 90% hydrogen peroxide in *N*-oxidations.[76] The reaction involving the naphthyridine derivative (eq 52) indicates the value of that system.

The preparation of tetrahydropyridine-*N*-oxides by means of the oxidative cleavage of suitable bicyclic isoxazolidines has been studied in connection with projected syntheses of indolizidine alkaloids.[77] The oxidation of the compound **5** gave a mixture of the nitrones **6** and **7** in which **6** was slightly favoured using MCPBA. On the other hand, MMPP gave more useful yields of the nitrone **6**, particularly when the reaction was carried out at low temperatures (eq 53). The isoxazolidine **8** gave nitrones **9** and **10** in which the product **9** predominated when using MCPBA. In contrast, the regiochemical control was superior when using MMPP and afforded nitrone **10** as the only product in 68% yield (eq 54).





One of the potentially most valuable uses of MMPP that has been developed is the oxidative regeneration of ketones from hydrazones. *N,N* -Dimethylhydrazones are easily metallated and these derivatives are thus valuable enolate equivalents. As is well known, the methodology has been extended to the RAMP- and SAMP- hydrazone procedures which allow high regio-, diastereo-, and enantioselective electrophilic substitution reactions α- to the original carbonyl group.[78] A number of methods are available for the cleavage of *N,N*-dimethylhydrazones including the use of sodium perborate.[79] Very good yields have been reported for the oxidative regeneration of ketones from *N,N*-dimethylhydrazones and SAMP-hydrazones using MMPP, in the latter case with no racemization of the chiral centre α- to the carbonyl group.[80] A generalised scheme is shown in equation 55 and two examples in equations 56 and 57.

In our own work we have compared the efficiency of the UHP and MMPP systems in the cleavage of phenyl- and *N,N*-dimethylhydrazones. In the latter case we observed that the MMPP method is normally better but the reverse was usually the case when cleaving phenylhydrazones. Cleavage reactions of *N,N*-dimethylhydrazones derived from aldehydes have also been reported.[81] High yields of nitriles were obtained in rapid reactions carried out with MMPP and again the integrity of the chiral centre next to the original formyl group is maintained. A suggested mechanism is shown in equation 58 and an example in equation 59.

In further studies we have also investigated the use of the UHP-trifluoroacetic anhydride system to oxidise aromatic amines to nitro compounds. In the aliphatic series a number of aldoximes have been oxidised to the corresponding nitro compounds using the same methodology.[82] As expected, configurational integrity is maintained at neighbouring chiral centres (eq 60).

I hope that this brief survey of the uses of MMPP and UHP has shown that it is possible to develop new reagent systems that overcome the perceived deficiencies and difficulties with other methods. Although the reagents described have been used with complete safety it is important to stress that risks must not be taken with peroxidic reagents. Appropriate safety shields must be used at all times and the absence of peroxides, especially diacylperoxides when using the UHP methods, must be confirmed before work-up.

Other workers are beginning to find some advantages to the use of UHP.[83-85] For example, a UHP method has been used in a survey of the epoxidation methods that were required in the synthesis of the brassinolide

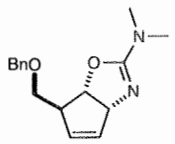
side chain,[84] and in a GoAgg[II] reaction as an alternative to anhydrous hydrogen peroxide.[85] There are still problems to be resolved but it may be anticipated that further progress in devising new procedures for the control of oxidative processes will be achieved in the next few years.

ACKNOWLEDGMENTS

It is a pleasure to record my thanks to Amanda Newbold and David Williams, a number of their results that are unpublished are mentioned in this account. It is also a pleasure to be able to thank my friends at Interox (Widnes) for their support, especially Paul Brougham, David Cummerson, Bill Sanderson, and Phil Sankey.

REFERENCES AND NOTES

(1) (a) A recent report of a "small explosion" reemphasizes potential dangers when using peroxidic materials. The explosion resulted when the neat alkene (**A**) was treated with trifluoroperoxyacetic acid generated by the interaction of 90% hydrogen peroxide with trifluoroacetic anhydride. It is possible that the presence of a small amount of the highly explosive diacylperoxide [bis(trifluoroacetyl)peroxide], which could have formed, was responsible for the explosion. See Trost, B.M.; Vanuranken, D.L. *J. Am. Chem. Soc.*, **1993**, *115*, 444



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(b) UN test method, Test 2 (b) (iii) -ST/AG/AC 10/11.

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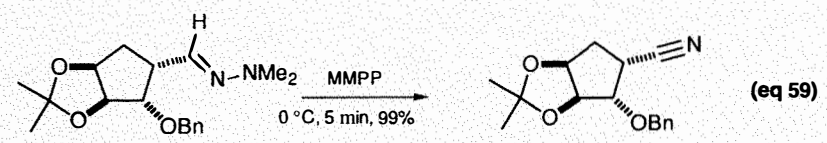
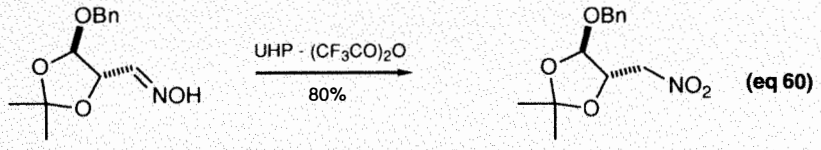


(eq 59)

one pot procedure from aldehyde 84% yield



(eq 60)

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ABOUT THE AUTHOR

Harry Heaney was born in 1931 in Salford, England. He received his Bachelor degree from the University of Keele in 1954 and his Ph.D. from the University of Manchester in 1957 working with Drs. I.T. Millar and G.F. Smith. He was awarded the degree of DSc in 1972 by the University of Keele.

After a period of teaching, he joined the staff at what was to become Bradford University and moved to the Department of Chemistry at Loughborough University of Technology in 1965. He has remained a member of that department, first as a senior lecturer, then as reader (1968), and since 1990 as a professor of organic chemistry. He has acted as a member of various committees, including the primary journals committee of what is now The Royal Society of Chemistry and has acted as an advisor for The British Council.

Professor Heaney has directed research in a number of areas, almost always connected with electrophilic reagents and systems. His early work was concerned with benzyne chemistry during the period from the beginning of the 1960's. More recently he has been interested in developing new reagents (including oxidising agents) and in the simplification of methods, in particular in connection with the control of stereochemistry in carbon-carbon bond forming reactions.

Modern Methods for the Monofluorination of Aliphatic Organic Compounds

Nucleophilic Fluoride Transfer Reagents

Oreste A. Mascaretti
Instituto de Química Orgánica de Síntesis
CONICET-Universidad Nacional de Rosario
Casilla de Correo 991
2000 Rosario, Argentina

INTRODUCTION

The replacement of a hydrogen atom, hydroxyl group or halogen (Cl, Br, I) by a fluorine atom (isosteric replacement) is one of the simplest structural modifications that can be made which, in turn, alters the chemical and biological activities of organic compounds.[1] Although the size of a fluorine atom is very similar to that of hydrogen (van der Waals' radius of 1.35 A vs 1.10 A, respectively) resulting in negligible effects due to steric difference, its electronegativity is much higher (4.0 vs 2.1). This results in a pronounced effect on the electron distribution in a molecule. Moreover, the large ionization energy of the carbon-fluorine bond (403.3 Kcal/g atom) implies that species involving electron deficient fluorine would be less likely than those involving hydrogen (315.0 Kcal/g atom) or chlorine (300.3 Kcal/g atom).[2]

The fluorine atom in a carbon-fluorine bond thus resembles both a hydrogen atom since it has a similar shape and a hydroxyl group in that it is electron-rich and potentially can participate in hydrogen bonding.

Its inductive effect can have a pronounced influence on the acidity of a geminal hydrogen atom with resultant enhanced binding to a hydrogen bond acceptor. Fluorine is also a moderately good leaving group and thus capable of displacement by other nucleophiles.

The need for selective fluorination procedures, especially with regard to complex biomolecules, is thus apparent. Selective incorporation of fluorine into these complex species has led to the development of several new medicinal agents and biologically active molecules and is the subject of several recent reviews.[2-10]

This review will attempt to provide an update of new nucleophilic fluorinating agents for the introduction of a single fluorine atom into aliphatic organic molecules, with representative applications taken from the recent literature (1982 to 1993). It is beyond the scope of this review to discuss in detail the uses of diethylaminosulfur trifluoride (DAST) and analogs,[11] tris(diethylamino)sulfonium difluorotrimethylsilicate (TAS-F),[12] and complexes of hydrogen fluoride with organic bases.[13] However, some examples involving these reagents are included. A number of excellent reviews on these reagents have been published.[11b, 13] Recently, one review has appeared which describes advances in the selective formation of the C-F bond.[14]

NUCLEOPHILIC FLUORIDE TRANSFER REAGENTS

1.1 Quaternary Onium Fluorides

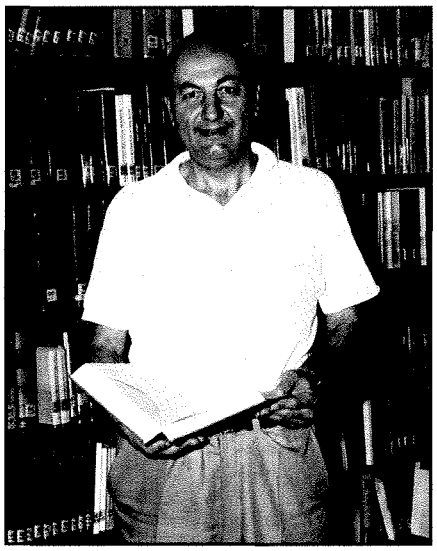
Quaternary onium fluorides such as tetrabutylammoniumfluoride (TBAF),[15] -hydrogen bifluoride (TBABF)[16] and -dihydrogen trifluoride (TBATF)[17] are the reagents of choice for carrying out carbon-fluorine bond forming reactions in aprotic solvents (e.g., THF, CH_2Cl_2, $CHCl_3$, DMF, HMPT, CH_3CN, benzene). In these solvents, the onium salts form loose ion pairs in which the fluoride (F^-), hydrogen bifluoride (HF_2^-) and dihydrogen trifluoride ($H_2F_3^-$) anions are considered "naked". Note, however, the only organic unsolvated ("naked") fluoride salts that have proven reliable are tetramethylammonium fluoride[18] and phosphazenium fluoride.[19]

The reported molecular structures of these anions[20] (**Figure 1**) show that the hydrogen bifluoride anion **1** is linear, with the hydrogen atom placed symmetrically between the fluorine atoms, and has $D_{\infty h}$ symmetry. The dihydrogen trifluoride anion **2** has a bond angle (FHFHF) of 130°-139° and C_{2v} symmetry.

A quantitative study of how the intrinsic reactivity (nucleophilicity and basicity) of these anions is affected in solvents of low polarity by specific solvation with protic solvents, such as water, has recently been reported.[21] Landini and co-workers found that these anions displayed different sensitivities to specific hydration, decreasing in the order: $F^- >> H_2F_2^- > H_2F_3^-$. On the basis of their charges and sizes, their "hardness" can be expected to decrease in the same order.[22] Thus, when a soft base or nucleophile is needed, the HF_2^- and $H_2F_3^-$ anions should be considered.[10a]

The tetraalkyl and tetraphenylphosphonium fluorides, such as tetrabutylphosphoniumfluoride (TBPF)[23] and -hydrogen bifluoride (TBPBF),[23,24] tributylmethylphosphonium fluoride (TBMPF)[25] and tetraphenylphosphonium hydrogen bifluoride (TPPBF),[26] are also useful reagents for nucleophilic fluorination in non-polar solvents.

Most applications of these nucleophilic fluoride transfer reagents involve substitution at a saturated carbon[27] and halofluorination of olefins (i.e., addition of fluoride and a halonium ion across a carbon-carbon double bond).



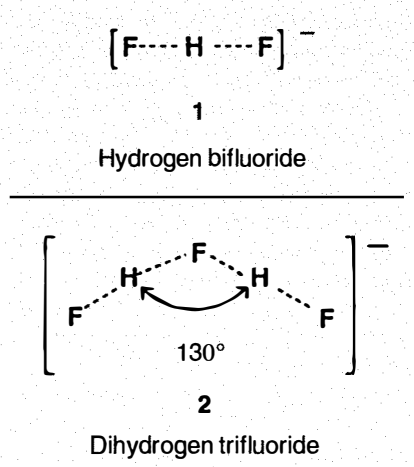


Figure 1

1.2 Nucleophilic Substitution at Saturated Carbon Atoms

Nucleophilic substitution of halides and sulfonates by fluoride ion is one of the most widely employed methods for the introduction of fluorine into aliphatic compounds.

These nucleophilic substitutions have also been effectively carried out by metal fluoride reagents such as KF/18-crown-6,[28] "spray-dried" KF,[29] polymer supported fluoride [Amberlyst A-26 (F^-)],[30] silver fluoride supported on calcium fluoride,[31] calcium fluoride supported on alkali metal fluorides,[32,33] Cu_2O-HF-organic base,[34] and KF/PEG 400.[35]

A number of useful examples involving the onium fluorides TBAF, TBABF and TBATF are illustrated in **Schemes 1-3** and discussed below.

1.2a TBAF

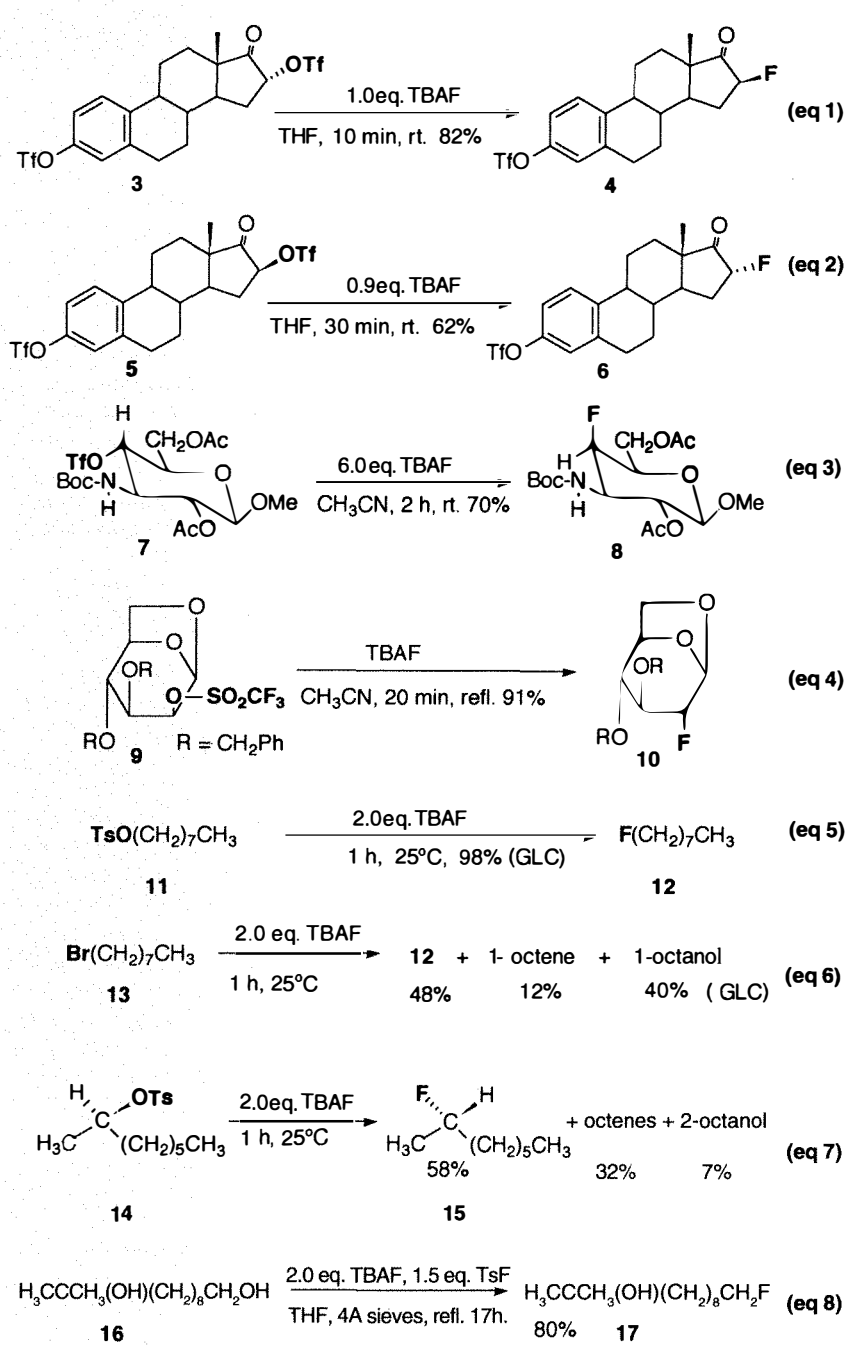
Fluoroestrones **4** and **6** were prepared by fluoride ion displacement on the corresponding epimeric estrone trifluoromethanesulfonates (triflates) by an S_N2 mechanism (**Scheme 1,** eq 1 and 2).[36]

Similarly, the 4-*O*-trifyl group of monosaccharide, **7**, undergoes substitution by fluoride ion with inversion of configuration.[37] The reaction of 1,6-anhydro-3,4-di-*O*-benzyl-2-*O*-(trifluoromethanesulfonyl)-β-D-mannopyranose **(9)** with TBAF provides a rapid and high-yield approach to 2-deoxy-2-fluoro-D-glucose (eq 4).[38] In contrast, it was reported that the use of cesium fluoride in DMF led to extensive decomposition of **9**.

Recently, Cox and co-workers reported a study of the reactivity of "anhydrous" TBAF with a range of halo- or tosyl-substituted compounds containing allylic, benzylic, primary, secondary and tertiary sp^3 centers.[15c] This study demonstrated that "naked" fluoride can act as either a nucleophile or a base. Benzyl bromide reacts rapidly to produce benzyl fluoride. Primary tosylates and halides give exclusively or predominantly primary fluorides (eq 5 and 6), whereas secondary halides such as 2-bromooctane give predominantly olefinic products. Reaction of "anhydrous" TBAF with (*R*)-(-)-2-octyltosylate **(14)** gives (*S*)-(+)-2-fluorooctane **(15)** indicating that fluoride substitution proceeds solely by an S_N2 process. Elimination of TsOH is the dominant side reaction (eq 7).

Chemoselective fluorination of primary alcohols in the presence of secondary or tertiary hydroxyl groups or olefins, ketones, esters and ethers, via an in situ formation of their corresponding triflates or mesylates was described by Shimizu and co-workers.[39] The selectivity of this methodology was explained in terms of the sulfonylating reaction: the reaction is faster for primary alcohols than for secondary ones, and practically no reaction occurs with tertiary hydroxyl groups.

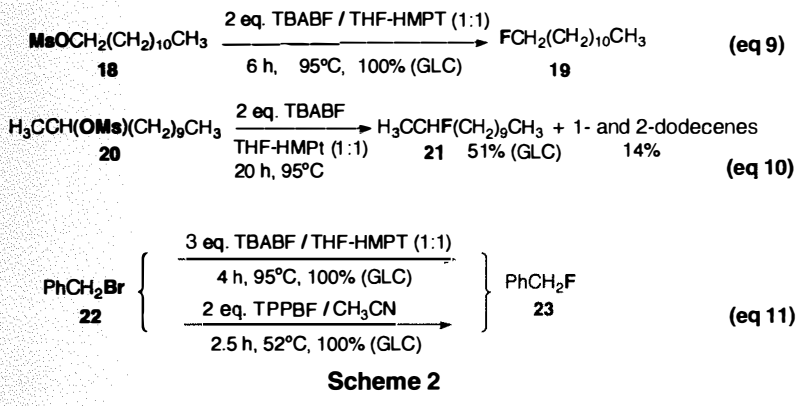
The utility of this methodology is illustrated by the conversion of 2-methyldodecane-2,11-diol **(16)** into 11-fluoro-2-hydroxy-2-methyldodecane **(17)** (eq 8).



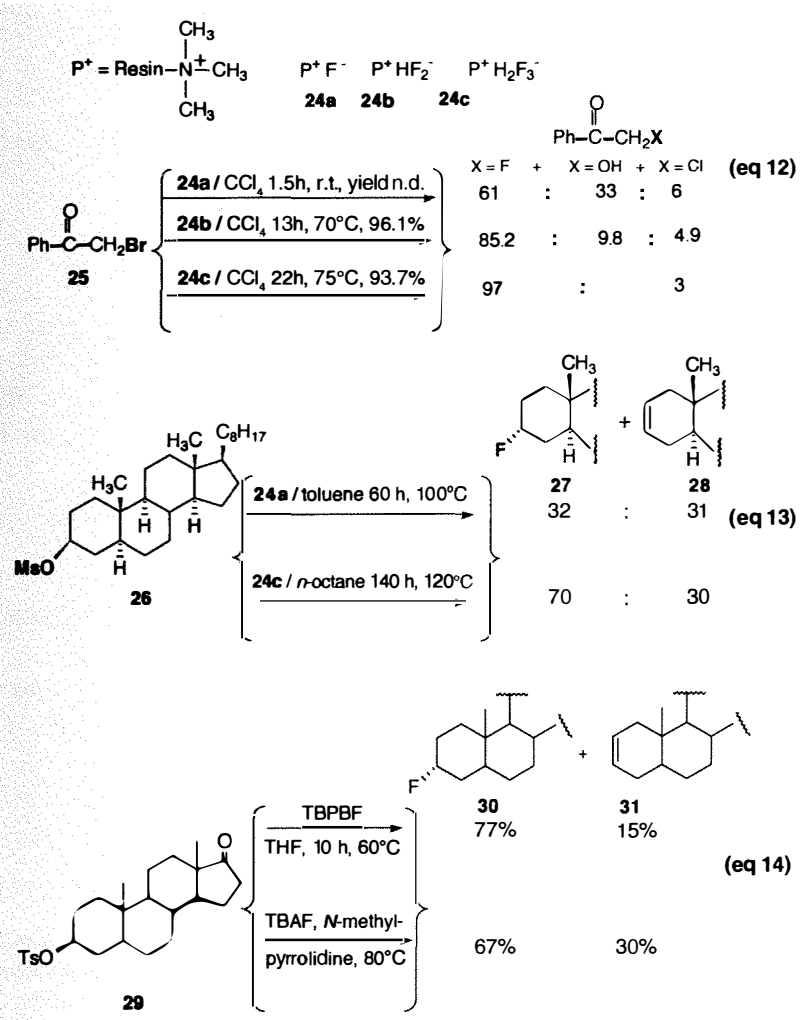
Scheme 1

1.2b TBABF

The use of tetrabutylammonium hydrogen bifluoride as a stable, readily available source of fluoride ions in nucleophilic substitution processes was reported by Guerrero and co-workers (**Scheme 2**).[16] These authors found that TBABF is useful for the conversion of primary alcohols into the corresponding fluorides through the intermediate tosylates and mesylates (eq 9), whereas reaction with mesylates of secondary alcohols, such as 2-dodecanol, led to the formation of isomeric olefins and other side products (eq 10). On the other hand, the same authors reported that reaction of aliphatic and benzyl halides (eq 11) gave comparable or better yields than with "anhydrous" TBAF[15c] and other methods of nucleophilic fluorination.



Scheme 2



Scheme 3

1.2c TBATF/Amberlyst A-26

Cousseau and Albert recently reported[40] that polymer supported dihydrogen trifluoride $P^+H_2F_3^-$ (P^+ is the cationic part of a macroreticular basic anion-exchange resin; for example, Amberlyst A-26 or Amberlite IRA 900) can act as a good source of nucleophilic fluoride. In this study they compared the nucleophilic power of the F^-, HF_2^- and $H_2F_3^-$ anions by testing the reactivities of the polymer supported reagents P^+F^-, $P^+HF_2^-$ and $P^+H_2F_3^-$ with three model bromoketones and with secondary non-activated mesylates and halides.

From the results with bromoketones (eq 12), the authors concluded that the reagents **24a** and **24b**, unlike **24c**, retain a small but significant amount of water which leads to undesired hydrolysis byproducts. Thus, although the overall reactivities can be ranked in the order **24a** > **24b** ≅ **24c**, the best yield of fluoro substitution is provided by **24c**.

With 3β-OMs-5α-cholestane (**26**) the authors compared their results with those reported by Colonna.[30b] The products are mixtures of 3α–fluoro-5α-cholestane (**27**) and 2-cholestene (**28**) (eq 13). This indicates that under the conditions used, namely high temperatures and extended reaction times, **24a** and **24c** may act as either a nucleophile (substitution) or a base (elimination).

1.2d TBPF, TBPBF and TBPTF

The tetrabutylphosphonium fluorides (e.g., TBPF, TBPBF, TBPTF) and several other lipophilic onium fluorides, bifluorides and trifluorides were prepared by Landini and coworkers using an ion exchange resin in a two-phase system.[23]

Yoshioka recently reported[24] the preparation of anhydrous TBPBF and TBPTF (from tetrabutylphosphonium hydroxide and aqueous HF), and TBPF (from TBPBF and *n*-BuLi). These authors also describe their utility in the selective nucleophilic fluorination of oxiranes, alkyl halides and sulfonates of aliphatic and steroidal alcohols. TBPBF was found to be a more selective reagent than TBAF for the fluorination of 3β-toluenesulfonyloxyandrostan-17-one(eq 14). TBPBF and TBPTF also were found useful for the nucleophilic fluorination of aromatic substrates containing chlorine, or bromine atom(s) or a nitro group.[41]

1.2e TBMPF

In 1980 Leroy and co-workers reported[25] the preparation and use of tri(*n*-butyl)methylphosphonium fluoride (*n*-Bu_3MePF) for the nucleophilic substitution of sulfonates and activated alkyl halides under mild conditions in non-polar solvents.

1.2f TPPBF

Tetraphenylphosphonium hydrogen bifluoride (Ph_4PHF_2) has been used for the fluorination of organic halides with good success (eq 11).[31] Clark and Brown first reported that this onium fluoride showed excellent solubility in polar aprotic solvents such as CH_3CN, DMSO and $CHCl_3$ and is easily prepared and dried.[26,42] This reagent picks up small quantities of atmospheric moisture only over extended periods of time, and displays good thermal stability. In their paper the authors studied the rate of production of $PhCH_2F$ from $PhCH_2Br$ in CH_3CN at 52° C using two mole equivalents of (a) Ph_4PHF_2 and (b) $Ph_4PHF_2{\cdot}H_2O$ and found that less product results with the hydrate.

1.2g TBAFPS

In 1991 Gingras reported[43] the preparation and the use of tetrabutylammonium difluorotriphenylstannate (**32**, TBAFPS), the first hypervalent complex of tin acting as a fluorinating agent. The *trans* stereochemistry of the trigonal bipyrimidal structure (**Figure 2**) of this anion was also determined by Gingras.[44] This new fluorinating agent is soluble in many organic solvents (CH_2Cl_2, $CHCl_3$, THF and most polar solvents). TBAFPS is a very promising fluoride ion source that is potentially useful in many areas of organic chemistry.

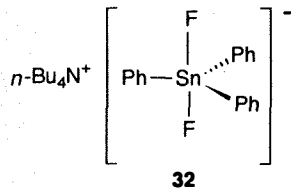


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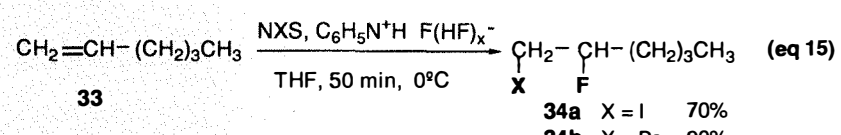
Figure 2

1.2h Scope and Limitations

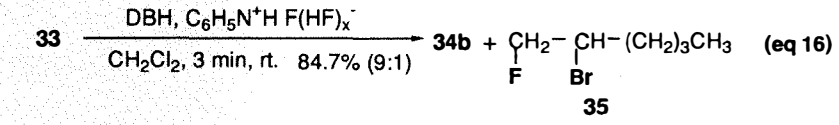
Two of the most important and straightforward strategies for the introduction of fluorine into a target molecule are the conversion of a hydroxyl group into its corresponding sulfonate and subsequent displacement by nucleophilic fluoride and halogen-exchange fluorination of aliphatic halides. In these two methods it is important to balance the nucleophilicity and protophilicity of the fluoride source in order to control the competitive reactions of substitution versus elimination.

Diethylaminosulfur trifluoride (DAST) can be used for the direct conversion of a hydroxyl group to a fluoride atom. It is noteworthy that the stereochemical consequences of using the direct versus the indirect substitution by fluorine with chiral alcohols may be quite different. Substitution of a good nucleofugal group by fluoride normally occurs through an S_N2 mechanism (**Schemes 1-3**), whereas the use of DAST can lead to either retention by an S_Ni mechanism (intimate ion pair)[10a] or inversion by an S_N2 mechanism.[2]

One of the most promising reagents for the transformation of primary, secondary or tertiary achiral aliphatic halides into fluoroalkanes appears to be the Cu_2O-HF^- organic base reagent reported by Yoneda.[34] It was proposed that the reaction involved the initial formation of cuprous halide to form an alkyl cation R^+, which readily reacts with fluoride providing the fluoroalkane without rearrangement of the carbon skeleton.



33 **34a** X = I 70%; **34b** X = Br 90%; **34c** X = Cl 40%



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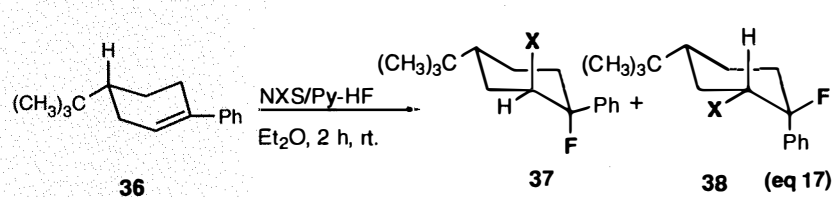
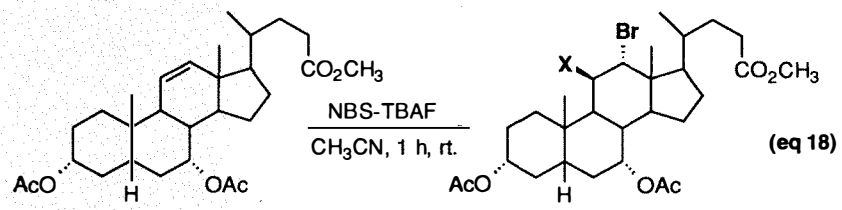


36 **37** **38**

X = Br 64% 36%
X = Cl 60% 40%



39 **40** X = F 87%; **41** X = OH 11%

Scheme 4

1.3 Halofluorination of Alkenes

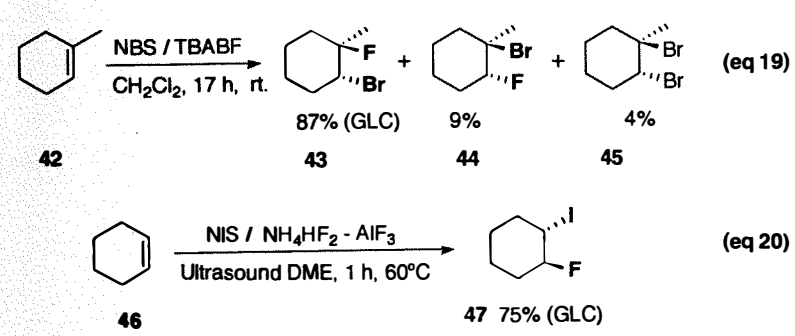
Halofluorination of olefins is one of the most important reactions for the synthesis of monofluoro aliphatic compounds via electrophilic and nucleophilic substitution reactions.

This reaction is usually carried out with a halonium fluoride XF (X = Cl, Br, I), either as such or generated in situ with a combined reagent system.[45] Such a system consists of a fluoride source [e.g., $Bu_4N^+F^-$, Bu_4N^+ HF_2^-, Bu_4N^+ $H_2F_3^-$, NH_4^+ HF_2^-•AlF_3, $C_6H_5NH^+$-$F(HF)_xF^-$, $[(C_2H_5)_3N \cdot 3HF]$, BF_3, P^+F^- (P^+ is poly(styrene-co-4-vinylpyridine) complex), or SiF_4] and a halonium ion source [e.g., *N*-halosuccinimides, *N*-haloacetamides or 1,3-dibromo-5,5-dimethyl hydantoin (DBH)]. Since fluorine is the most electronegative element, it will always be the nucleophilic partner and other halogens the electrophilic partner.

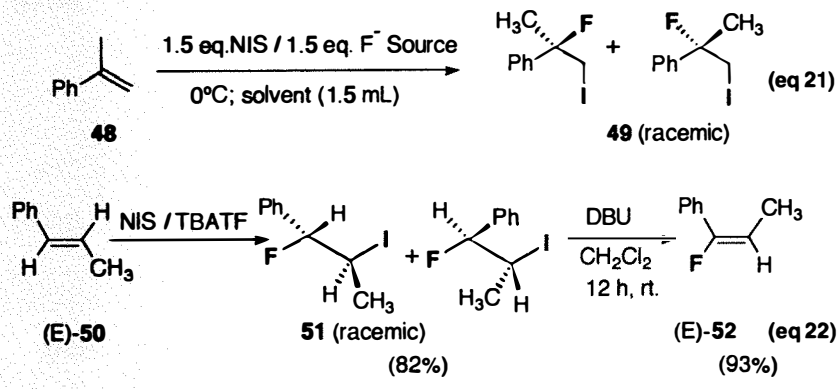
Olah and co-workers reported[46] halofluorination of alkenes using *N*-halosuccinimides in conjunction with HF-pyridine complex. Iodo- and bromofluorination of alkenes are also effected using bromine or iodine with an equivalent amount of silver nitrate in pyridinium poly(hydrogen fluoride) solution. One example of halofluorination using NBS, NCS and NIS is shown in equation 15. The addition products follow Markovnikov orientation, which means that fluorine is introduced at the more substituted olefinic carbon.

An interesting application of this kind of process is the preparation of vicinal difluorides from the corresponding alkenes without isolation of the intermediate halofluorinated compounds. This is simply carried out by adding silver fluoride to the solutions of 1,2-haloalkanes, thus effecting the halogen-exchange fluorination in situ.

Katzenellenbogen and co-workers[47] have studied the bromofluorination of model olefins (e.g., allylbenzene, 1-hexene and



Scheme 5



Scheme 6

Table 1. Iodofluorination of 2-phenylpropene

Entry	F^- Source	Solvent	Time (h)	Isolated Yield%
1	$Bu_4NH_2F_3$	CH_2Cl_2	1	92
2	$Bu_4NH_2F_3$	$(CH_2Cl_2)_2$	1	90
3	$Bu_4NH_2F_3$	$CHCl_3$	1.5	90
4	$Bu_4NH_2F_3$	CH_3CN	5	87
5	$Bu_4NH_2F_3$	$(MeOCH_2)_2$	5	83
6	Bu_4NHF_2	$(CH_2Cl)_2$	5; rt. 13	83
7	Bu_4NF	$(CH_2Cl)_2$	5; rt. 13	11

propene) using DBH in conjunction with HF-pyridine complex, or metal fluorides with acid in dichloromethane. Thus, bromofluorination of 1-hexene (**33**) proceeds rapidly (3 min.) and efficiently (85% yield) at room temperature. The Markovnikov and anti-Markovnikov products, **34b** and **35**, were obtained in a ratio 9:1.(eq 16).

The halofluorinated product can be reduced by a tin hydride reagent to give the fluoroalkane product resulting from Markovnikov addition of HF, with the advantage that the net addition of HF by halofluorination-reduction can be done under milder and safer conditions. A plausible explanation of why halofluorination proceeds under milder conditions than hydrofluorination, based on the relative hard-soft acid-base characteristics of the interacting species, is given.[47] The halofluorinated product can also undergo base promoted elimination to afford vinyl fluorides. This publication also pointed out an interesting application of the olefin halofluorination reaction as a method for labeling molecules with the positron-emitting radionuclide fluorine-18.[47]

Zupan and Gregorcic[48] studied the stereochemistry of bromo- and chlorofluorination of 1-phenyl-4-*tert*-butylcyclohexene (**36**) using *N*-bromo- or *N*-chlorosuccinimide in the presence of HF-pyridine complex and found that the addition followed Markovnikov-type regioselectivity and proceeded stereospecifically *anti*, thus forming two pairs of vicinal halofluorides **37** and **38** (eq 17). They also reported the bromofluorination of various phenyl-1-substitutedolefins with NBS in the presence of polymer supported HF in dichloromethane.[49]

Boron trifluoride-etherate in combination with *N*-haloamides, *N*-haloimides and *N*-haloamines has also been used to promote the vicinal halofluorination of alkenes.[50]

Over the past few years there has been increasing interest in the use of TBAF, TBABF and TBATF for the generation of halogen fluorides. These reagents and triethylamine trihydrofluoride are a highly versatile source of fluoride ions, for halofluorination. They are easy to handle and permit the use of normal glass apparatus.

1.3a *N*-Haloimides and TBAF

The combination of *N*-bromosuccinimide and TBAF for the vicinal bromofluorination of alkenes was first described by Maeda and co-workers.[51] Bromofluorination of 4-*tert*-butyl-1-methyl-cyclohexene gave a mixture of the two bromofluorides. The results indicated that the reaction follows Markovnikov orientation and proceeds with *anti* stereoselectivity, in accord with previously reported results.[48]

Similar treatment of methyl 3α,7α-diacetoxy-5β-chol-11-ene-24-carboxylate, (**39**) afforded the 12α-bromo-11β-fluorosteroid (**40**)(eq 18). The formation of this product was explained through an initial approach of electrophilic bromine cation to the C_{11}- C_{12} double bond from the α-face followed by a fluoride anion attack from the β-face ("anti-parallel pathway"). The authors explained that the formation of the side product 12α-bromo-11β-hydroxysteroid (**41**) indicated that water was present in the TBAF reagent.

1.3b *N*-Haloimides and TBABF

The halofluorination reaction of a variety of acyclic and alicyclic olefins by using TBABF in the presence of *N*-halosuccinimide has been reported by Guerrero and co-workers.[52] This process occurs stereospecifically to afford *anti* addition products, and with unsymmetrical olefins a marked Markovnikov-type regioselectivity. A representative example is given in **Scheme 5** (eq 19).

Using NBS and NCS, the formation of variable amounts of the corresponding vicinal dibromo or dichloro derivatives was reported. A free-radical mechanism was postulated to explain this side reaction.

The vicinal halofluorination of alkenes was also achieved under solid-liquid biphasic conditions with ammonium hydrogen bifluoride and porous aluminum fluoride (NH_4^+ HF_2^- • AlF_3), *N*-halosuccinimide and ultrasound in dimethoxyethane or 1,2-dichloroethane. These solvents are useful for iodofluorination, whereas diethyl or

diisopropyl ether are more useful for bromofluorination.[53] The porous aluminum fluoride was shown to accelerate the reaction and increase the yield. A mechanism involving activation of HF_2^- salts by both porous aluminum fluoride and ultrasound was proposed. The structure of the intermediate ammonium hexafluoroaluminate $[(NH_4)_3AlF_6]$ was determined by powder X-ray diffraction.

For example, the heterogenous mixture of cyclohexene(**46**), NIS and $NH_4HF_2 \cdot AlF_3$ subjected to ultrasonic irradiation at 60°C for one hour afforded the desired *trans*-1-fluoro-2-iodocyclohexane **47** in 75% yield (eq 20). The stereoselectivity of this process is *anti*, however the regioselectivity with unsymmetrical alkenes was not as high in some reactions. In the case of the bromofluorination reaction, the formation of a 1,2-dibromo side-product in about 20% yield was also reported.

1.3c *N*-Iodosuccinimide or DBH and TBATF

In 1991 Kuroboshi and Hiyama[54] described the use of the combination of TBATF and NIS or DBH for the iodo- or bromofluorination of a variety of alkenes having alkyl and/or aryl substituents. They also reported that under similar conditions, chlorofluorination with *N*-chloro-succinimide did not occur at all with complete recovery of the starting alkenes.

Optimization of the reaction conditions by employing the combinations of NIS with TBAF, TBABF and TBATF in the solvents CH_2Cl_2, $CHCl_3$, $ClCH_2CH_2Cl$, CH_3CN or DME using 2-phenylpropene (**48**) were reported (eq 21)(**Table 1**). The results indicated that reactions were complete within two hours in chlorinated hydrocarbon solvents (entries 1-3) whereas those conducted in acetonitrile or DME required longer reaction times (entries 4 and 5). TBABF used as the fluoride ion source in 1,2-dichloroethane gave the same product as with TBATF, in a comparable yield, but required warming to room temperature and a longer reaction time (entry 6). TBAF was found to be much less effective (entry 7).

The best reaction conditions found were NIS or DBH (1.5 mmol) and TBATF (1.5 mmol) in CH_2Cl_2 (1.5 mL).

It is noteworthy that under these conditions and at 0°C for two hours, olefins bearing an oxirane group have been iodofluorinated chemoselectively.

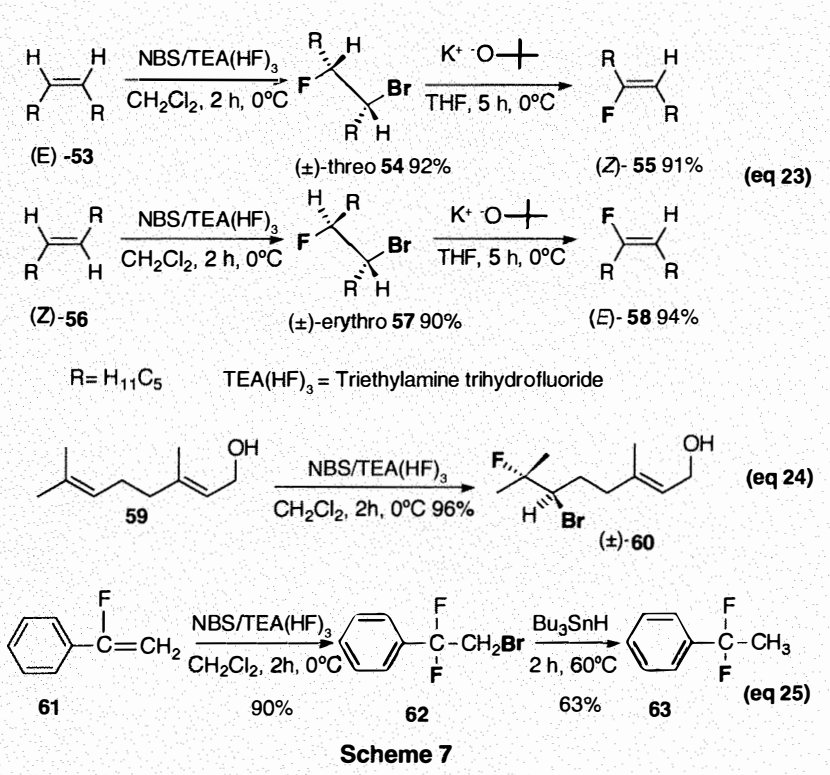
The authors reported that the stereochemistry of the addition of F-I was *anti* with all the olefins tested and followed Markovnikov-type regioselectivity.

When the 1,2-iodofluorinated alkanes thus obtained were treated with DBU in CH_2Cl_2, dehydroiodination readily occurred at room temperature to give vinyl fluorides in excellent yield. As both F-I addition and H-I elimination proceeded in an *anti* fashion, (*E*)-1-phenylpropene (**50**) was converted into (*E*)-1-fluoro-1-phenylpropene (**52**) by a two step procedure (eq 22).

In a more recent paper,[55] Kuroboshi and Hiyama observed that the iodofluorination of olefins is readily effected in a two-phase system using dilute hydrofluoric acid, NIS, TBAF and KHF_2, and suggested that the active fluoride ion is $H_2F_3^-$ rather than HF_2^- or F^-. Indeed, this suggestion is highly predictable since the reported procedure for the preparation of TBATF[56] employed HF-KHF_2 and TBAF. The authors have simply generated the anion $H_2F_3^-$ in situ.

In 1991 Landini and co-workers reported[57] the use of stoichiometric amounts of TBATF and an excess of *N*-halosuccinimide for the halofluorination of alkenes. The reaction products obtained show predominant Markovnikov regiochemistry. Olefins containing hydroxy, epoxy, acetoxy and alkoxy groups do not undergo side reactions under these conditions.

A number of other reagents for the halofluorination of alkenes have been introduced during the past 10 years. The most versatile of these are: a) various modified forms of $py(HF)_x$ complex as a fluoride ion source[58-61], b) DBH in conjunction with silicon tetrafluoride[62], and c) bis(pyridine)-[63] and bis(*sym*-collidine)iodonium(I) tetrafluoroborate.[64]



Scheme 7

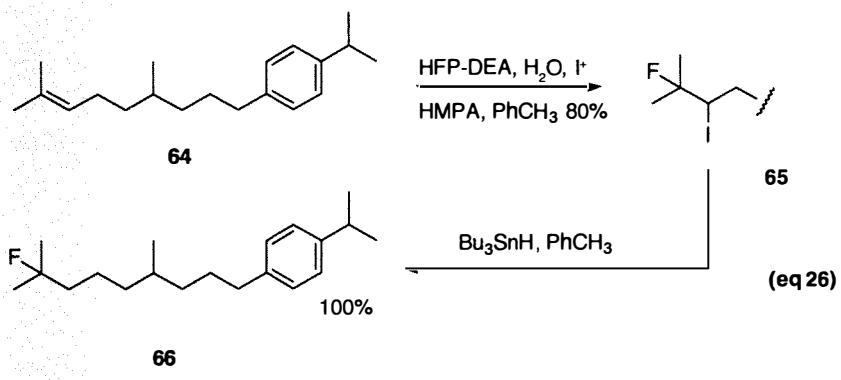
1.3d Halosuccinimides and Triethylamine Trihydrofluoride

Laurent and co-workers reported[58] the use of *N*-halosuccinimide and triethylamine trihydrofluoride $[(C_2H_5)_3N \cdot 3HF]$ as a convenient and effective reagent for the halofluorination of alkenes. The reaction proceeded stereospecifically *anti*. In the case of unsymmetrical alkenes, the main products again result from Markovnikov selectivity.

A more recent application of this method is the bromofluorination of allylic alcohols to afford vicinal fluorobromohydrins. Treatment of the formed fluorobromohydrins with aqueous sodium hydroxide gave epifluorohydrins.[59]

Schlosser and co-workers reported[60] another application of this combination. Representative examples are presented in **Scheme 7.** *Cis*- or *trans*-6-dodecene (**53**) and (**56**) gave (±)*threo*- and (±)*erythro*-6-bromo-7-fluorododecane (**54**) and (**57**), respectively, in almost quantitative yield. Dehydrobromination with potassium *tert*-butoxide in THF at 0°C afforded (*Z*)- and (*E*)-6-fluoro-6-dodecene, (**55**) and (**58**), respectively. Geraniol (**59**) was quantitatively converted to (*E*)-6-bromo-7-fluoro-3,7-dimethyl-2-octen-1-ol (**60**) as indicated in equation 24.

A salient feature of this work was the demonstration that the presence of a fluorine atom in the olefin, as in 2-fluoro-1-alkenes, enhanced both the reactivity and the regiocontrol in the electrophilic addition process. The observed stereospecificity was ascribed to stabilization of the initially formed



(eq 26)

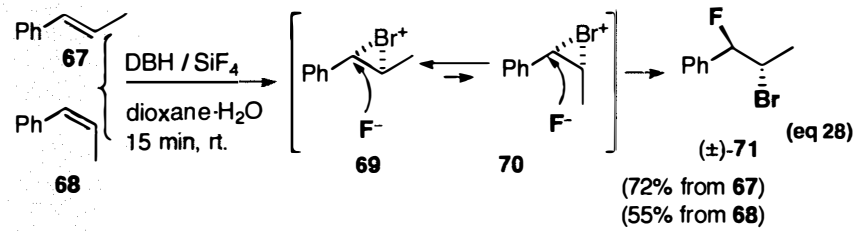
$$Et_2NCF_2CHFCF_3 + H_2O \longrightarrow Et_2NCOCHFCF_3 + 2\,HF$$

$$HF + X^+ \longrightarrow XF + H^+$$

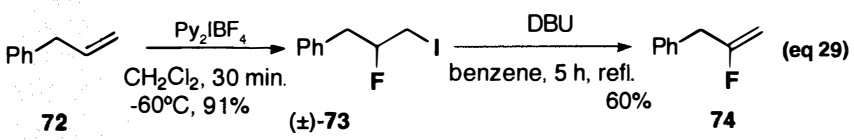
(eq 27)

X = I from NIS and X = Br from DBH

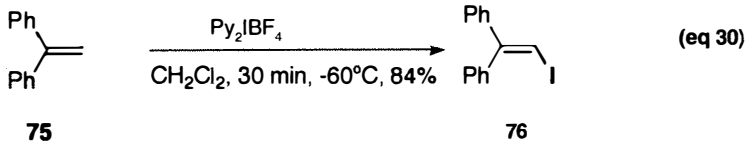
Scheme 8



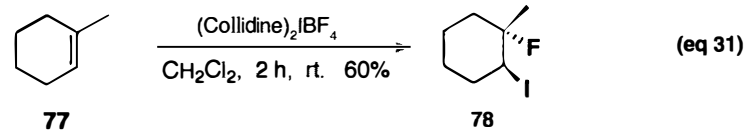
(eq 28)



(eq 29)



(eq 30)



(eq 31)

Scheme 9

carbenium ion by the electron donating resonance effect of fluorine. The reaction of 1-fluoro-1-phenylethylene (**61**) illustrated this point (eq 25). Reduction of 2-bromo-1,1-difluoro-1-phenylethane (**62**) with tributyltin hydride lead to 1,1-difluoro-1-phenylethane, (**63**).

1.3e *N*-Bromosuccinimide and PVPHF

The polymeric fluorinating reagent poly(4-vinylpyridinium)poly(hydrogen fluoride) (PVPHF), first reported by Olah,[61] is useful for hydrofluorination, the fluorination of alcohols and, with the co-reagent NBS, for bromofluorination of alkenes and alkynes. Advantages of this reagent include ease of handling and convenient work-up.

In 1991 Fujisawa and co-workers described[65] the use of hexafluoropropene-diethylamine complex (HFP-DEA) and *N*-haloimides for the halofluorination of olefins with high regio- and stereoselectivities.

One representative application of this reaction is in the synthesis of a fluorine analogue of juvenile hormone MV-678 (**Scheme 8**, eq 26). The authors suggested that these reactions proceed most probably via generation of a limited amount of hydrogen fluoride from HFP-DEA complex and water, followed by formation of the XF species (eq 27).

1.3f DBH and Silicon Tetrafluoride

Recently, Shimizu and co-workers described[62] a convenient method of bromofluorination of olefins with DBH-SiF_4. The combination of NIS- or NCS-SiF_4 was not successful. From the various solvents used only 1,4-dioxane gave satisfactory results. No side products are formed in the presence of water.

Aliphatic, aromatic and alicyclic alkenes underwent bromofluorination to give the adducts in good to excellent yields. DBH-SiF_4 is a convenient combination which does not affect acid sensitive functionalities.

The stereochemical outcome of aryl-subsituted alkenes is noteworthy. Both (*E*)- and (*Z*)-1-phenylpropene (**67**) and (**68**) gave *anti*-2-bromo-1-fluoro-1-phenylpropane (**71**) exclusively and in good yield. This result was explained in terms of the involvement of a pair of bridged bromonium ions, **69** and **70**, that are stabilized by 1,4-dioxane and isomerized to the more thermodynamically stable intermediate **69**.

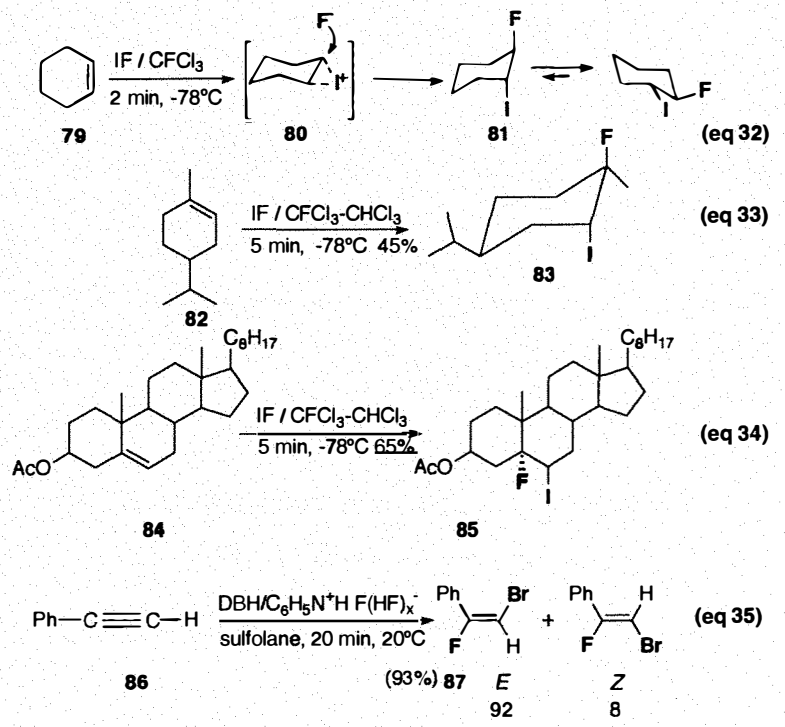
1.3g Bis(pyridine)iodonium(I) tetrafluoroborate and Bis(γ,γ-collidine)-iodonium(I) tetrafluoroborate

These complexes can be classified as 2-coordinate halogen(I) species and can be described as containing a central halogen that is hypervalent.[66]

In 1985 Barluenga and co-workers reported[63a] that when cyclohexene was treated with bis(pyridine)iodonium(I) tetrafluoroborate (py_2IBF_4) in the presence of fluoroboric acid at -30°C in CH_2Cl_2, *trans*-1-fluoro-2-iodocyclohexane was obtained in 67% yield. In 1991 the same author reported[63b] the generality of, and optimal conditions for, the reaction of iodofluorination of alkenes using py_2IBF_4. The reaction is quite general, irrespective of the structure of the starting alkene. Nevertheless, in the case of acrylates, it required a modified experimental approach. In general, these reactions are very clean and fast at -60°C. The reaction takes place regio- and stereoselectively. Equation 29 illustrates the iodofluorination of 3-phenylpropene (**72**) using py_2IBF_4 yielding exclusively 2-fluoro-1-iodo-3-phenylpropane (**73**) as expected. The stereoselectivity of the addition was found to be *anti* as is usually the case. Compound **73** was dehydroiodinated in the presence of DBU in benzene at reflux providing **74** in 60% yield.

Another interesting application of this reagent is the iodofunctionalization of olefins with substituents attached to the carbon-carbon double bond that are able to strongly stabilize a positive charge. 1,1-Diphenylethylene (**75**) was used to demonstrate this application (eq 30).

The method using the analogous reagent (*s*-collidine)$_2$IBF$_4$ is illustrated in equation 31.



Scheme 10

2.1 Fluorine Interhalogens

2.1a Halofluorination of Olefins

The most convenient method for the preparation of halogen monofluorides is direct synthesis from molecular fluorine with other halogens. A good review of this synthesis has been recently published by Boguslavskaya and Chuvatkin.[67]

The in situ generation of IF and BrF from the reaction of 10% fluorine in a nitrogen stream with iodine or bromine in CCl_3F at -75°C and its application to the halofluorination of alkenes has been recently reported.[46] The results of this work are summarized in **Scheme 10**.

Indeed, the rather low thermal stability of these interhalogens (ClF, BrF, IF) and lack of commercial availability has prevented a rapid expansion in their use.

Over the past ten years there has been increasing interest in the use of a source of positive halogen (I^+, Br^+ and Cl^+) and a source of nucleophilic fluoride. Such reactions are indicated by the notation [XF] or "XF" meaning that these elements are eventually added across a double bond but not necessarily through the employment of the XF molecule itself. The mechanism proposed by Rozen and Brand for iodine monofluoride and bromine monofluoride addition to a carbon-carbon double bond involves the initial electrophilic addition of iodine or bromine to form a cyclic halonium ion intermediate (eq 32). The fluorine is transformed into a "nucleophilic species" which then attacks in an *anti* fashion on the carbon which corresponds to the more stable carbenium ion. In the case of BrF these authors used EtOH or *i*-PrOH as a proton donor to enhance the polarizability of the Br-F bond. This ionic mechanism is often invoked for these two consecutive reactions. A similar mechanism has been proposed for the complexes of positive iodine of the type bis(pyridine)iodonium(I)[63] and bis-(collidine)iodonium(I)[64] with the tetrafluoroborate counteranion acting as a source of fluoride.

The major drawbacks of using ethanol or isopropanol as proton donors is the formation of vicinal bromoethers resulting from nucleophilic attack by the alcohol on the cyclic bromonium ion intermediate.

2.1b Halofluorination of Alkynes

Recently Eddarir[68] reported the bromofluorination of alkynes by using the combination of DBH and pyridine-HF to afford a mixture of (*Z*)- and (*E*)-1-bromo-2-fluoroalkenes. The reaction was regioselective leading to the bromine atom on the unsubstituted side of the carbon-carbon triple bond and giving the *E*-isomer with good stereoselectivity. Sulfolane was used as the solvent and an example is shown in **Scheme 10** (eq 35).

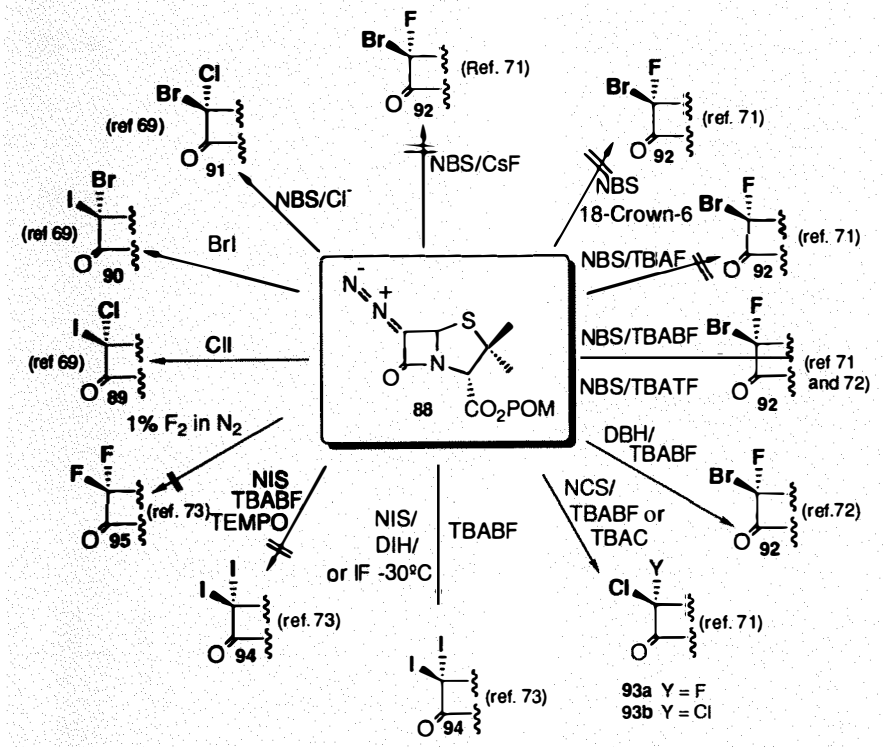
2.1c Geminal Halofluorination of Diazo Compounds

In 1979 Olah[46] described the *geminal*-halofluorination and -hydrofluorination of α-diazo ketones and diazoalkanes with the combination of *N*-halosuccinimide and pyridinium poly(hydrogen fluoride) (PPHF) solution.

This paper inspired me to carry out a broader study on the stereochemistry, generality and optimal conditions for the *geminal* dihalogenation reaction of interhalogens, halofluorides and fluorine with 6-diazopenicillanate esters. This reaction involved electrophilic and nucleophilic substitutions using a combined reagent system consisting of a halonium and a fluoride source, or halonium fluoride generated in situ, paralleling the reported reaction with alkenes (**Scheme 11**).

The (pivaloyloxymethyl)-6,6-heterodihalopenicillanates **89**, **90** and **91** have been stereoselectively prepared from the reaction of (pivaloyloxymethyl)-6-diazopenicillanate (**88**), with either *N*-halosuccinimide/halide or the interhalogens XI (X= Cl, Br). Their configuration was determined by single crystal X-ray analysis. These reactions proceed stereoselectively with the electrophilic halogen being placed in a β-orientation and the nucleophilic halide atom in an α-orientation in agreement with the proposed two-step S_N2 mechanism for the displacement reaction.[69]

The conversion of 6-diazopenicillanates into 6-bromo-6-fluoropenicillanates using *N*-



Scheme 11

bromosuccinimide and pyridine-HF was reported.[70] In our hands the use of this procedure was unsatisfactory when applied to the POM ester **88**, giving rise to a complex mixture of products.[71] We also investigated the use of mixtures of NBS and a range of other fluorides including KF/18-crown-6 complex, CsF and TBAF without success. However, after considerable experimentation the combination of NBS and TBABF in CH_2Cl_2 was found to be more reliable and gave the desired POM 6β-bromo-6α-fluoropenicillanate **(92)** in 40% yield. Extension of this procedure to include the synthesis of benzyl 6β-bromo-6α-fluoropenicillanate with NBS-TBABF, DBH-TBABF and NBS-TBATF was also successful.[72]

POM 6β-chloro-6α-fluoropenicillanate, **(93a)** was synthesized by using NCS and TBABF in 25% yield. In addition, the regioselective introduction of two chlorine atoms at C-6 of the penam nucleus of **88** was achieved using a combination of NCS and tetrabutylammonium chloride (TBAC), affording **93b**. However, attempts to convert **88** into the corresponding 6β-iodo-6α-fluoropenicillanate employing NIS or 1,3-diiodo-5,5-dimethyl hydantoin (DIH) and TBABF under the same conditions led only to 6,6-diiodopenicillanate in excellent yield. The same result was obtained when **88** was treated with IF in $CFCl_3$ at -30°C. At -60°C no reaction occurred. The same reaction at -30°C in the presence of TEMPO, a free radical scavenger, completely suppressed the formation of compound **94**. This total inhibition of the formation of **94** might induce one to consider the occurrence of a free radical process in this iodofluorination reaction, which competes with the ionic pathway. The low temperature used ruled out the well-known possibility of the formation of molecular iodine from the disproportionation of IF.[73]

Our attempts[73] to synthesize POM 6,6-difluoropenicillanate (**95**) from 6-diazo penicillanate (**88**) by using 1% F_2 in a nitrogen stream under several experimental conditions, including those reported by Rozen and Brand[74] to promote ionic addition of F_2, led only to an intractable mixture of products.

2.1d Addition of HF to Activated Carbon-Carbon Triple Bonds

Tetrabutylammonium and polymer supported dihydrogen trifluoride was first introduced in organic synthesis by Albert and Cousseau in 1985.[75] In this communication the authors described the addition of HF to carbon-carbon triple bonds activated by electron withdrawing groups such as nitrile, ester, ketone or aldehyde, affording the *Z* -and *E*- isomers of the corresponding fluoroalkenes. A full account of this work reported in 1986 best represents the current state of the art, providing numerous examples of addition to the carbon-carbon triple bond.[76]

The use of polymer-supported dihydrogen trifluoride as a nucleophilic reagent for the substitution of a leaving group on a saturated carbon was reported by the same authors in 1989.[40] (For a description of this work see the corresponding subject in this review.)

Returning to the addition of HF to an activated acetylenic bond, TBATF and its analog, polymer supported $P^+H_2F_3^-$, allow the addition of HF under mild conditions to mono- and bis-activated carbon-carbon triple bonds (**Scheme 12**). Interestingly, unactivated acetylenic compounds do not add HF when they are treated with these reagents. In all cases studied the addition stops at the ethylenic stage, generally leading to a mixture of the *Z*- and *E*-fluoroolefins in good yield. Comparative experiments performed with TBABF indicated that it reacts very little, and neither pyridine-HF complex nor $[Et_3N{\cdot}3HF]$ induces the expected addition. Some examples of this reaction using TBATF are depicted in **Scheme 12**; Rozen and coworkers also describe examples using $P^+H_2F_3^-$.[74]

In the same paper the authors comment on the role played by the $H_2F_3^-$ ion in the addition of HF to activated carbon-carbon triple bonds which is likely initiated by a nucleophilic attack of fluoride ion. This proposal was supported by the lack of reaction observed with pyridine-HF, since the latter reagent has been reported to be a good electrophile and a very weak nucleophile.[46] Otherwise, as expected, the high stability of the HF_2^- ion does not allow the addition to readily occur with TBABF. Finally, the authors pointed out that only the $H_2F_3^-$ ion possesses the required properties: good nucleophilic power associated with good ability to provide HF due to the relatively weak H-F hydrogen bonds.

2.1e Conversion of Epoxides to Fluorohydrins

In the last four years much interest has been shown in the ring opening reaction of epoxides to give fluorohydrins as a method for the introduction of fluorine into organic molecules.

In 1988, Poulter and Muehlbacher[77] demonstrated that treatment of benzyl ether derivatives of simple aliphatic epoxides with diisopropylamine trihydrofluoride gave mixtures of the corresponding fluorohydrins in good yields.

Shimizu and Yoshioka[78] first demonstrated the utility of employing silicon tetrafluoride in conjunction with Hunig's base

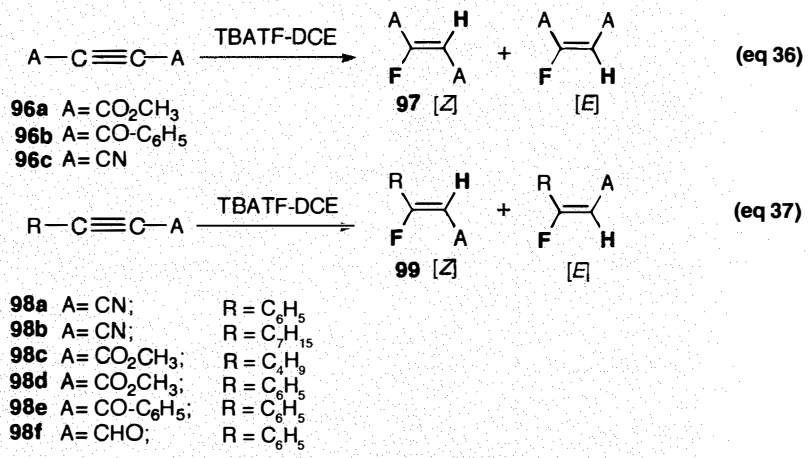
(diisopropylethylamine), or TBAF, or water for the transformation of epoxides to fluorohydrins. The authors suggested that hypervalent fluorosilane (SiF_5^- or SiF_6^{2-}) formed from SiF_4 and $(n\text{-}Bu)_4NF$ or SiF_4 and H_2O would increase the nucleophilicity of fluoride anion and facilitate the opening of epoxides. In the case of 1-methylcyclohexene oxide (**100**) (**Scheme 13**), SiF_4/*i*-Pr_2NEt treatment gave no fluorohydrin. In the presence of water, this same reaction gave (±)-*trans*-2-fluoro-2-methylcyclohexanol (**102**) in 71% yield. It was assumed that the *trans*-opening of **100** was caused by the activation of the oxirane ring with SiF_4 or R_3NHSiF_5 to form the intermediate **101**, which is then attacked by hypervalent fluorosilanes (eq 38). The fluorine atom was regiospecifically introduced at the more substituted carbon. In other examples the chemoselectivity is also noteworthy. Olefins and ethers were unaffected under the same reaction conditions.

In 1989, Ichichara and Hanafusa[79] reported that the combination of potassium (or sodium) hydrogen bifluoride and porous aluminum fluoride is a stable and efficient solid reagent for promoting the ring-opening reaction of simple aliphatic oxiranes to give the fluorohydrins under sonication.

The typical solid-liquid biphasic reaction was carried out in a Pyrex test tube with a Teflon-coated screw cap as follows: to well dried KHF_2 (5 mmol) and porous AlF_3 (15 mmol) in DME (4 mL) was added cyclohexene oxide (2 mmol). The heterogeneous reaction mixture was subjected to ultrasonic irradiation at 55°C. The ring-opening reaction proceeded smoothly to afford a 60% yield of the corresponding fluorohydrin with complete disappearance of the substrate within two hours. The solid material was filtered off and washed with CH_2Cl_2. After evaporation of the solvent, purification of the crude oil was accomplished by column chromatography (silica gel; pentane : ether :: 5:1) yielding (±)-*trans*-2-fluorocyclohexanol (**104**) in 49% yield (eq 39).

The authors demonstrated that reaction between KHF_2 and AlF_3 produces K_3AlF_6. They also propose that "HF" is generated in low concentration with strong complexation of the fluoride anion with the aluminum cation. The resulting "HF" on the surface of the solid AlF_3 attacks the epoxide immediately to give the corresponding fluorohydrin. Ultrasound accelerates both the solid phase inorganic reaction and the subsequent organic reaction, resulting in a reduction of the reaction time and an increase in the product yield.

In 1990, Landini and Penso[80] reported that the conversion of epoxides to the corresponding fluorohydrins can be successfully accomplished using KHF_2 in the presence of



Scheme 12

Table 2. Hydrofluorination of alkynes with TBATF

Acetylenic compound	Reaction temp. (°C)	Reaction time (h)	Product	Overall yield (%)	[Z] (%)	[E] (%)
96a	60	9	**97a** $H_3CO_2C\text{-}CF{=}CH\text{-}CO_2CH_3$	90	100	0
96b	60	24	**97b** $C_6H_5\text{-}CO\text{-}CF{=}CH\text{-}CO\text{-}C_6H_5$	57	100	0
96c	25	3	**97c** $NC\text{-}CF{=}CH\text{-}CN$	—	65	35
98a	110	7	**99a** $C_7H_{15}\text{-}CF{=}CH\text{-}CN$	95	70	30
98b	110	8	**99b** $C_6H_5\text{-}CF{=}CH\text{-}CN$	80	80	20
98c	120	24	**99c** $C_4H_9\text{-}CF{=}CH\text{-}CO_2CH_3$	90	42	52
98d	120	21	**99d** $C_6H_5\text{-}CF{=}CH\text{-}CO_2CH_3$	75	95	5
98e	110	50	**99e** $C_6H_5\text{-}CF{=}CH\text{-}CO\text{-}C_6H_5$	53	100	0
98f	110	4.5	**99f** $C_6H_5\text{-}CF{=}CH\text{-}CHO$	75	91	9

catalytic amounts of TBATF under phase-transfer catalysis conditions. One example of this methodology is illustrated in **Scheme 13**. 3β-hydroxy-5α,6α-epoxycholestane (**105**) gave 3β-5α-dihydroxy-6β-fluorocholestane (**106**) in 47% yield. The observed regio- and stereochemistries indicate the reaction proceeds through an S_N2 mechanism, wherein nucleophilic attack by fluoride at the less substituted carbon atom of the oxirane ring is electrophilically assisted by a proton. TBATF provides the HF required by the stoichiometry of the reaction, and the solid KHF_2 regenerates the quaternary salt, TBATF (eq 41).

Schlosser and co-workers reported[81] that terminal epoxides preferentially gave 2-fluoro-1-alkanols (e.g., **108**) with pyridine-hydrogen fluoride in toluene. In contrast, 1-fluoro-2-alkanols (e.g., **109**) are the major products of the reaction with the hydrogen fluoride/*N*-ethyldiisopropylamine adduct. A mechanism was proposed to rationalize the regiochemical outcome of the hydrogen fluoride addition to oxiranes. When treated with potassium *tert*-butoxide in THF, the *p*-toluenesulfonates derived from fluorohydrins afforded *Z*- and *E*- fluoroolefins in high yields. The reaction of 1,2-epoxydecane represents one example of this work (eq 42).

Finally, the regiospecific ring opening of 1,2-epoxysilanes with SiF_4 in the presence of diisopropylethylamine and water to give selectively 1-fluoro-2-silylalcohols, and their subsequent olefination with potassium hexamethyldisilazide to afford fluoroalkenes in good yield, was recently reported by Shimizu and Yoshioka.[82]

2.1f Scope and Limitations

Whatever strategy is chosen for the nucleophilic introduction of a fluorine atom into an organic molecule, the reported nucleophilicity scale[21] $F^- >> F^- \text{-} H_2O > HF_2^- > H_2F_3^-$ has to be seriously considered along with the chemical properties of each reagent. For example:

1) pyridinium poly(hydrogen fluoride) is a slightly acidic reagent;[46]

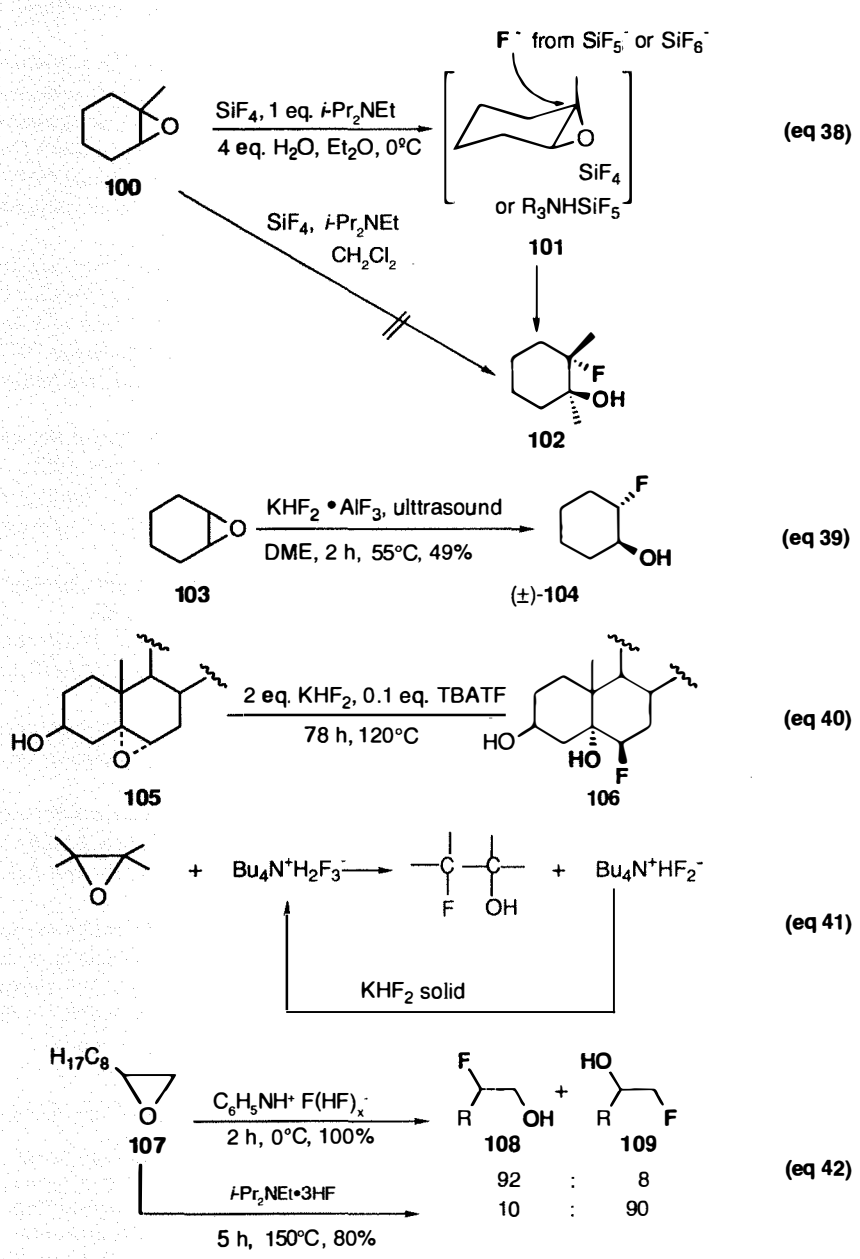
2) "naked" F^- is a very strong base

3) F^- is a hard base, whereas HF_2^- and $H_2F_3^-$ are softer bases;

4) SiF_4 reportedly is a reagent which does not affect acid sensitive functionalities;

5) and reactions where rigorously anhydrous conditions are needed, TBABF can be considered one of the reagents of choice.

To avoid the drawbacks of a proton donor and enhance the polarizability of Br-F or



(eq 38) (eq 39) (eq 40) (eq 41) (eq 42)

Scheme 13

other interhalogens, it seems reasonable to consider the use of catalytic amounts of a Lewis acid. Boron trifluoride will be able to polarize the X—F bond (X = Br, Cl or F) and at the same time the BF_4^- formed will provide the F^- and regenerate BF_3 for a new cycle of activation.

CONCLUSION

This review has concentrated on tried and tested methodologies, for the nucleophilic introduction of fluorine into aliphatic compounds, with an emphasis on recent developments.

During the last ten years several new reagents have been developed, which hold considerable promise as an F^- source. Most of these can be handled safely and easily in standard laboratory glassware and react under mild experimental conditions. Particularly useful for their applications in organic synthesis are those reagents which are very soluble in polar aprotic solvents. Polymer supported fluoride reagents as well as solid supported and ones used under phase-transfer catalytic conditions are also very promising and convenient sources of "F^-".

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ABOUT THE AUTHOR

Oreste A. Mascaretti holds the position of Full Professor of Medicinal Chemistry at the Universidadde Rosario and Senior Researcher at the Institute of Organic Synthesis of Consejo Nacional de Investigaciones Cientificas y Técnias (CONICET).

Prior to his current position he was Assistant Professor of Organic Chemistry at Buenos Aires University (1975-1983). During a leave of absence from Buenos Aires he was Visiting Assistant Professor of Medicinal Chemistry and an NIH Research Fellow at Purdue University (Fogarty Center).

Professor Mascaretti was born, raised, and received most of his formal education in Argentina obtaining the Doctorate of Pharmacy from Buenos Aires University in 1975.

He has held several international fellowships including:

- Research Fellow of the Royal Society (London) June-July 1988 and July 1991.
- Research Fellow of Deutsche Forschungsgemeinschaft (DFG) Germany, August 1988.
- Visiting Professor at Ruhr University (Bochum-Germany) August 1988.
- Research Fellow of Deutscher Akademischer Austauschdienst (DAAD) Germany, August 1991.
- Visiting Professor at Max-Planck institute für Strahlenchemie (Muelheim-Germany) August 1991.

In 1987 he received the Research Prize of the Academic Award Foundation, Faculty of Pharmacy and Biochemistry, Buenos Aires University.

Professor Mascaretti is the author of over 30 scientific papers, and is a member of the Organic Chemistry Research Association (Argentina) and an Associate Fellow of the Royal Society of Chemistry (London).

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Riedstrasse 2, D-7924 Steinheim
Telephone: 497329870
FAX: 49732987139/239

Holland
Aldrich Chemie
Telephone: 3238991301
FAX: 3238991311

India
Aldrich-India
B4/158 Safdarjung Enclave
New Delhi 110 029
Telephone: 91116886872
FAX: 91116886873

Italy
Aldrich Chimica
Via Gallarate, 154
20151 Milano
Telephone: 39233417340
FAX: 39238010737

Japan
Aldrich Japan
Kyodo Bldg. Shinkanda
10 Kanda-Mikuracho
Chiyoda-Ku, Tokyo
Telephone: 81332580155
FAX: 81332580157

Spain
Aldrich Quimica
Apt. de Correos, 161
28100 Alcobendas, Madrid
Telephone: 3416619977
FAX: 3416619642

Switzerland
Aldrich Chemie
Industriestrasse 25
CH-9470 Buchs
Telephone: 41817552723
FAX: 41817567420

United Kingdom
Aldrich Chemical Co. Ltd.
The Old Brickyard, New Road
Gillingham, Dorset SP8 4JL
Telephone: 44747822211
FAX: 44747823779

About Our Cover:

This alluring masterpiece entitled *Portrait of a Lady* (oil on canvas, 80.7 x 65.2 cm) was painted by Jean-Marc Nattier in 1738 at the threshold of a very successful career as a portraitist of ladies of the court of Louis XV. His portraits included the King's wife, daughters, and various mistresses. In the Salon exhibition of that year Nattier exhibited three portraits: one of the Chevalier d'Orléans; one of Mlle de Canisy, wife of the Marquis d'Antin; and one of Mlle de Rohan which has not been located. Nattier was fond of painting his female sitters in mythological guises. Mlle de Rohan was represented as Hebe, the goddess of youth, usually shown with an eagle and cup. Whoever the lady in this portrait is, she is represented as Flora, goddess of flowers — a flattering device often used for the portraits of attractive women. Another Flora-figure by Nattier, still not identified, was shown in the Salon of 1746.

It was only a year before *Portrait of a Lady* was painted that Nattier had shown his first portrait in a Salon. An Academician since 1718, he had been a history painter, making drawings for engravings of Rubens' *Life of Marie de Médici* series, and admiring the work of Rubens and LeBrun. In 1717 in the Netherlands he had painted a *Battle of Poltava* for Peter the Great of Russia as well as portraits of Peter and his wife Catherine. Financial considerations probably caused him to abandon his history painting for portraiture — a genre in which he was most successful, endowing his sitters with beguiling grace and charm.

The painting is in the collection of The Saint Louis Art Museum.

Lab Notes

Hints for NMR Sample Preparation

We offer a number of deuterated NMR solvents in a variety of packages for our customers. Because of the solvents high chemical and isotopic purities as well as their hygroscopic nature, relatively small amounts of contaminants can result in unusually large impurity signals. The following suggestions should help you get the best results from deuterated solvents.

Drying all glassware at ca. 150°C for 24 hours and cooling under an inert atmosphere will ensure moisture-free surfaces. For less demanding applications, a nitrogen blanket during sample preparation may be adequate.

Use of clean, dry glassware and Teflon® accessories (e.g., NMR tube caps) will help reduce chemical impurity problems that generally arise from the leaching of chemicals from rubber or plastic surfaces (e.g., NMR tube caps). Use of a vortex mixer will eliminate the need to shake the tube contents vertically and the resultant contamination from NMR tube caps. Residual chemical vapor from equipment can also be a source of impurities, residual acetone in pipette bulbs being the most common example.

Protonated solvent residues are often effectively removed by co-evaporation with a small quantity of the desired deuterated solvent, brief (ca. 5-10 min.) high vacuum drying and then preparing the NMR sample. Some solvents such as chloroform-*d*, benzene-d_6, and toluene-d_8 will also remove residual water azeotropically.

Use of solvent from a freshly opened 0.5 or 1mL single-use ampule or from septum bottles employing a syringe-needle technique will also help.

—Aldrich Stable Isotopes Department
—NMR Laboratory Staff

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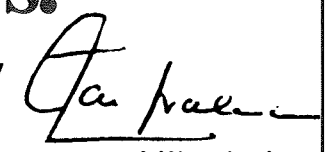
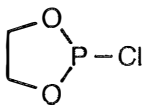
Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to Aldrich (attn: Lab Notes, Aldrichimica Acta). For submitting your idea, you will receive a complimentary, laminated periodic table poster (Cat. No. Z15,000-2, $9.90 value). 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



Professor Dimitris S. Argyropoulos of the Pulp and Paper Research Centre at McGill University (Montreal) kindly suggested that we offer this dioxaphospholanyl chloride which is a useful derivatization reagent for ^{31}P NMR analysis of soluble lignocellulosic substances. The technique involves selective phosphitylation in the presence of pyridine of a variety of functional groups present in lignins and carbohydrates (e.g., ArOH, 1°,2°,3°-OH, RCOOH, etc.) followed by examination of the decoupled ^{31}P NMR spectrum. Signals arising from the three principal forms of phenolic hydroxyls present in lignin structures (i.e., *p*-hydroxyphenyl, guaiacyl and syringyl), the erythro and threo forms of arylglycerol-β-aryl ethers and labile protons in carbohydrates can be unambiguously assigned.

Argyropoulos, D.S.; Bolker, H.I.; Heitner, C.; Archipov, Y. *J. Wood Chem. Technol.* **1993**, *13*, 187. Archipov, Y.; Argyropoulos, D.S.; Bolker, H.I.; Heitner, C. *Carbohydrate Res.* **1991**, *220*, 49.

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

New Synthetic Methods and Strategies and Total Synthesis of Natural Products[1]

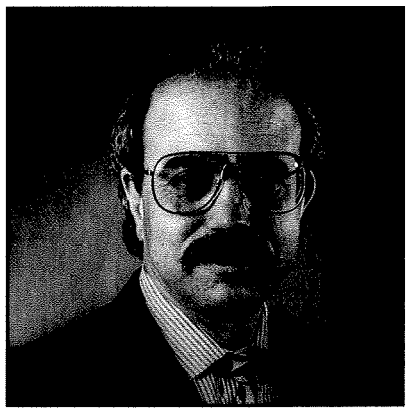
K.C. Nicolaou
Department of Chemistry
The Scripps Research Institute
10666 N. Torrey Pines Road
La Jolla, California 92037

Department of Chemistry
University of California, San Diego
9500 Gilman Drive
La Jolla, California 92093

INTRODUCTION

Natural products have always been favorite challenges to synthetic organic chemists, for they provide strictly defined and often formidable molecular targets. Such synthetic challenges test the state of the art of organic synthesis and stimulate the invention of new reactions and strategies.

As we move forward into the next decade, molecular design of new compounds becomes increasingly important, particularly in the search for new substances of specific biological action as well as for new materials for advanced technology. Here too, the synthetic chemist is challenged. However, the challenge is often lessened by intentional structural compromises in the designed molecules to fit existing synthetic methods. It is this distinction that makes natural products the ultimate challenge in synthesis since no compromises can be made in terms of the structure of the target molecule which is strictly defined by Nature. It is also this uncompromising condition that forces the daring synthetic chemist into new territories of synthetic technologies and strategies, for he cannot escape the original challenge by redefining the target. The opportunities for the invention of new reactions and synthetic strategies are thus maximized by targeting architecturally novel and challenging natural products.



Recipient of 1993 ACS Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich.

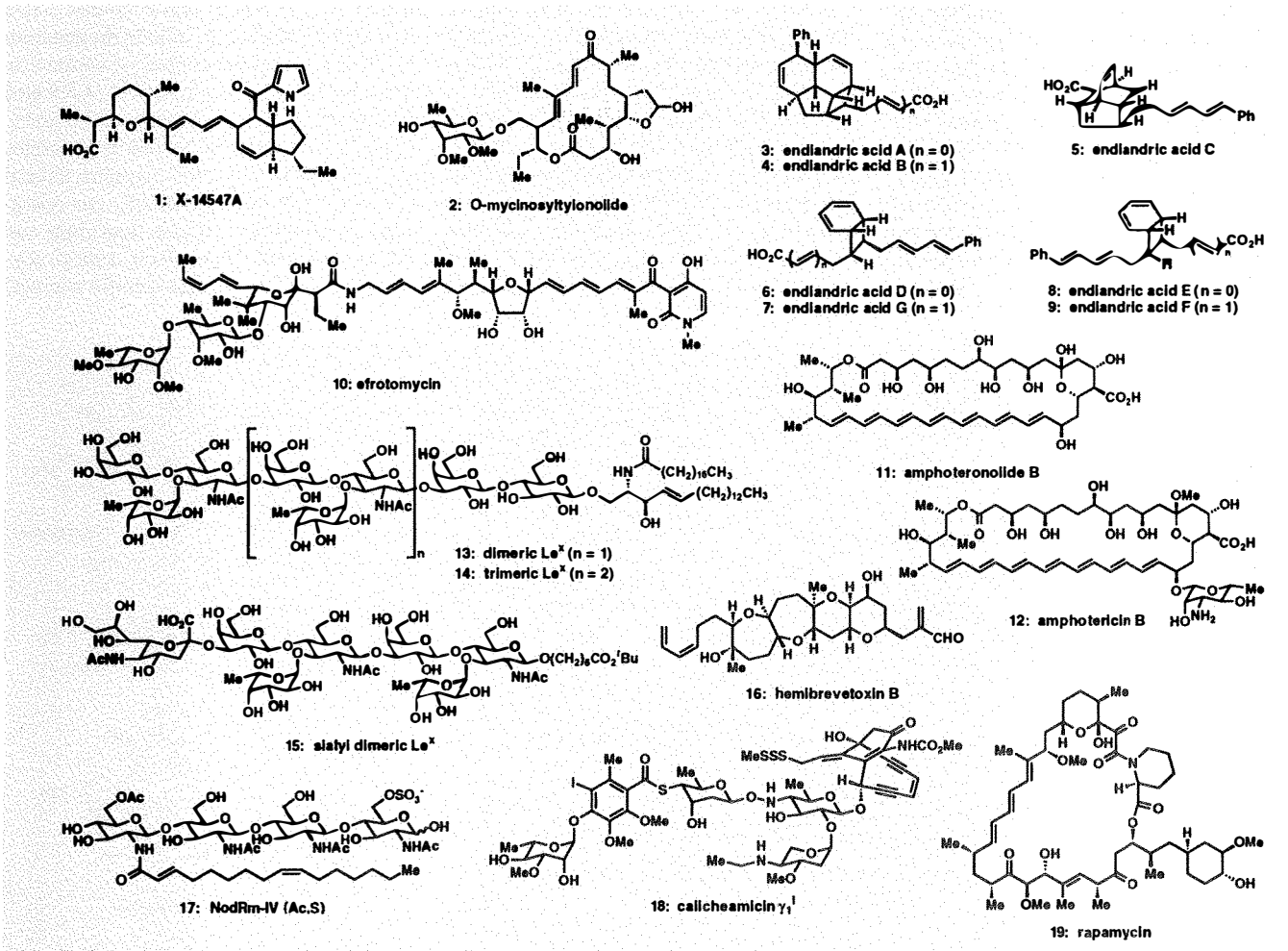


Figure 1. Selected targets synthesized over the last decade or so by the Nicolaou group.

On the other hand, the combination of the arts of molecular design and chemical synthesis has its own advantages, in that it often leads to materials with highly desirable biological or physical properties. This practice is also distinguished for its added value in terms of creating new entities rather than making a known substance of natural origin.

Recognizing the importance of both endeavors, our group has been engaged over the last few years in the total synthesis of natural products and the molecular design and chemical synthesis of new molecules of theoretical and biological interest. In this article, highlights of our studies in natural product synthesis will be discussed with particular emphasis on target selection, development of new synthetic technologies and total synthesis. The natural products shown in **Figure 1**[2] are representative examples of those molecules synthesized in our laboratories over the last decade.

Antibiotic X-14547A (Indinamycin)

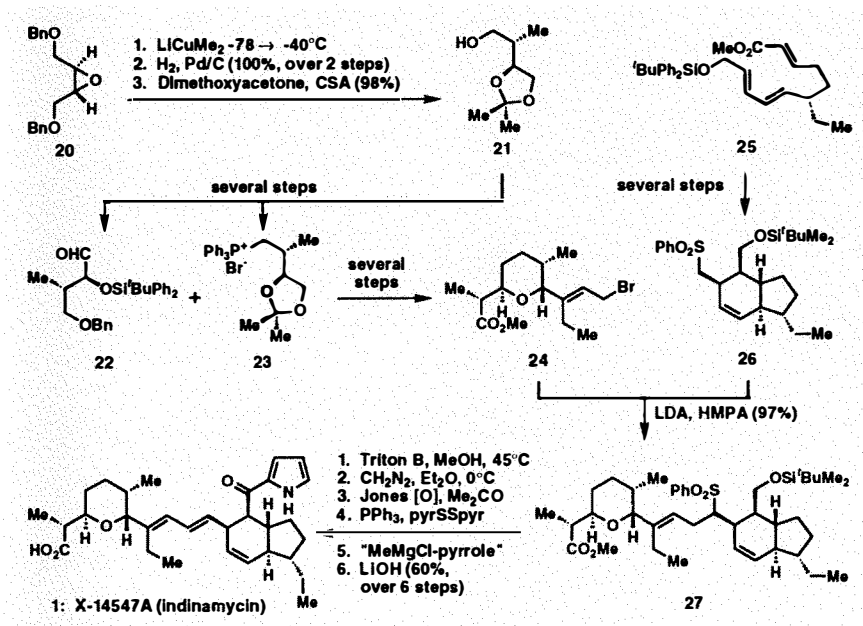
At the time of its structural elucidation (1978), antibiotic X-14547A (indinamycin, **1, Scheme 1**) looked highly appealing and challenging to the synthetic chemist. Its tetrahydropyran, tetrahydroindan, and ketopyrrole ring systems appeared particularly intriguing and, like several other groups, we became interested in its total synthesis. Our strategy[3] was based on the recognition that the tetrahydropyran system contained certain subtle symmetry elements and that the tetrahydroindan system could be derived from an acyclic precursor via an intramolecular Diels-Alder reaction. Finally, a Julia coupling reaction followed by further elaboration was to be used for the completion of the synthesis. Thus, epoxide **20 (Scheme 1)** derived from (-)-diethyl D-tartrate was converted, via intermediates **21-23**, to allylic bromide **24**. The latter compound was coupled with the bicyclic phenylsulfone **26**, derived from **25**, to afford compound **27**. Elimination of the sulfone to afford the conjugated diene system, followed by installation of a 2-pyridinethiol ester and reaction with a pyrrole-Grignard reagent[4] and ester hydrolysis gave the natural product **1** in high overall yield. This convergent synthesis was particularly pleasing, not only because it was the first for X-14547A, but also because it allowed the demonstration and exploitation of the above mentioned principles and reactions.

O-Mycinosyltylonolide

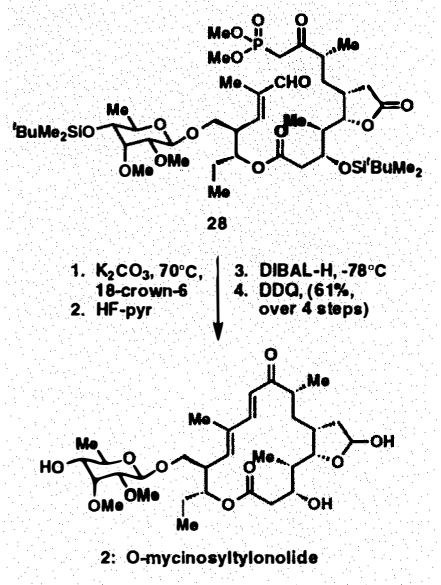
O-Mycinosyltylonolide (**2, Scheme 2**), a degradation product of the macrolide antibiotic tylosin, was targeted for total synthesis in the early 1980's for its architectural novelty and to test the state of the art at that time with respect to a number of concepts and new reactions. At the heart of this synthesis[5] lie: (a) the successful utilization of carbohydrates as starting materials for total synthesis; (b) a new glycoside bond forming reaction utilizing phenylthioglycosides and *N*-bromosuccinimide[6]; and (c) the utilization of an intramolecular ketophosphonate-aldehyde condensation to form the macrocyclic dienone system of the target molecule (**28→2, Scheme 2**). The chemistry developed in this project was instrumental to further advances in subsequent programs involving oligosaccharides and polyene macrolide antibiotics (*vide infra*).

Endiandric Acids A-G

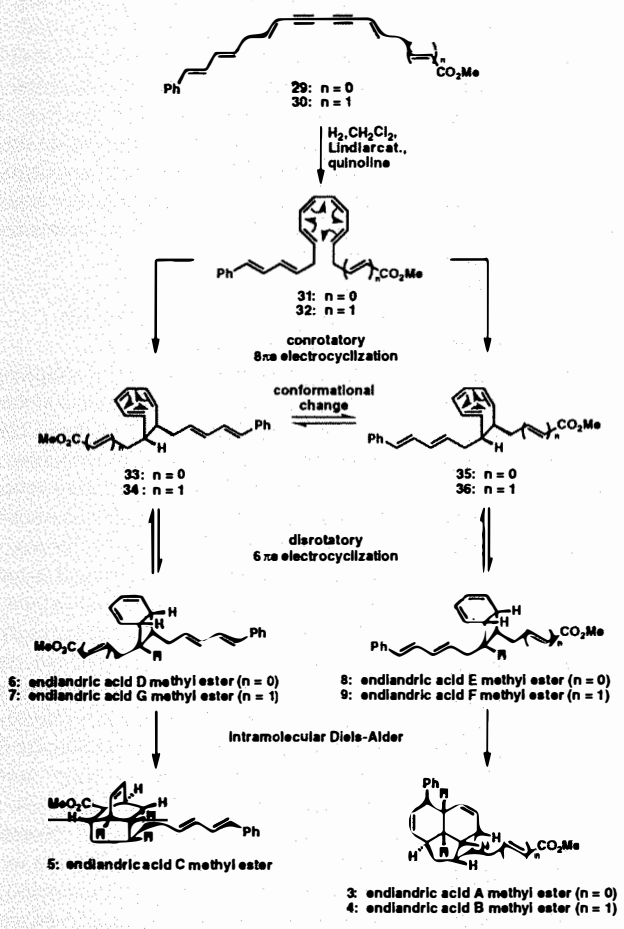
The endiandric acids A-G (**Scheme 3**) appeared on the scene in 1980 as racemic mixtures, despite their natural origin and eight stereogenic centers. This unusual phenomenon taken together with their co-occurrence in the same plant species led to an intriguing hypothesis[7] for their "biogenetic" origin involving achiral precursors and non-enzymatic reactions. In order to verify this attractive hypothesis, and relying on some relatively unexplored electrocyclizations which are thermally allowed by the Woodward-Hoffman rules,[8] we designed[9] both a stepwise strategy and a one-operation approach to this series of compounds. **Scheme 3** outlines our one-operation, "biomimetic" synthesis of endiandric acids A-G methyl esters (**3-9**) starting with the polyunsaturated precursors **29** and **30**. Thus, mild hydrogenation of diacetylenic compound **29** using Lindlar catalyst and quinoline at 25°C followed by chromatographic purification led to endiandric acids A,D and E methyl esters (**3,6 and 8**). Similarly, mild hydrogenation of **30** led to the generation of endiandric acids B,C,F and G methyl esters (**4,5,9 and 7, Scheme 3**). The endiandric acid B and C cascade is remarkable in that it generates two seemingly unrelated complex natural product structures in essentially one operation, creating, in each case, four rings and eight stereogenic centers from achiral, acyclic precursors in a stereospecific manner!



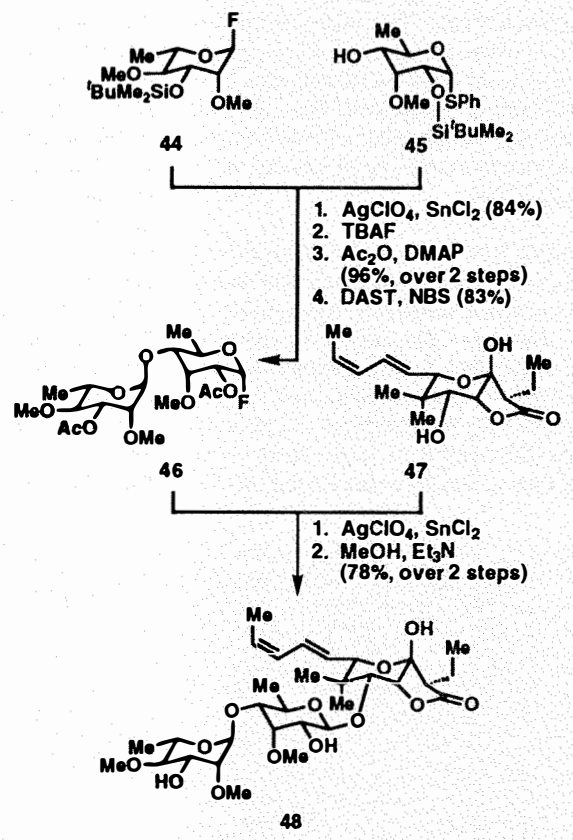
Scheme 1. Total synthesis of antibiotic X-14547A (indinamycin, 1).



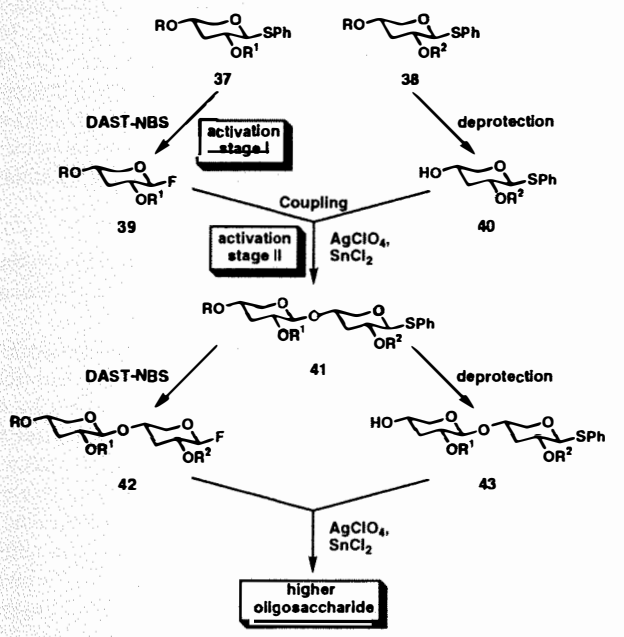
Scheme 2. Total synthesis of O-mycinosyltylonolide (2).



Scheme 3. "Biomimetic" synthesis of endiandric acids A-G (3-9) via electrocyclization reactions.



Scheme 5. Construction of efrotomycin oligosaccharide (48) by the two-stage activation procedure of oligosaccharide synthesis.



Scheme 4. The two-stage activation procedure for the synthesis of oligosaccharides.

Oligosaccharide Synthesis by the Two-Stage Activation Procedure

The challenge of complex oligosaccharides[10] prompted us to develop a mild and efficient method for their construction. This strategy of combining thioglycoside with glycosyl fluoride derivatives for the synthesis of oligosaccharides became commonly known as the two-stage activation procedure.[11] Shown in **Scheme 4**, and utilizing phenylthioglycosides as stable starting materials, this method has already found several applications in synthesis. One of the earliest total syntheses in which this method features prominently is that of efrotomycin (**10**) discussed below. Other applications of the two-stage activation procedure in the construction of oligosaccharides will follow later in this article.

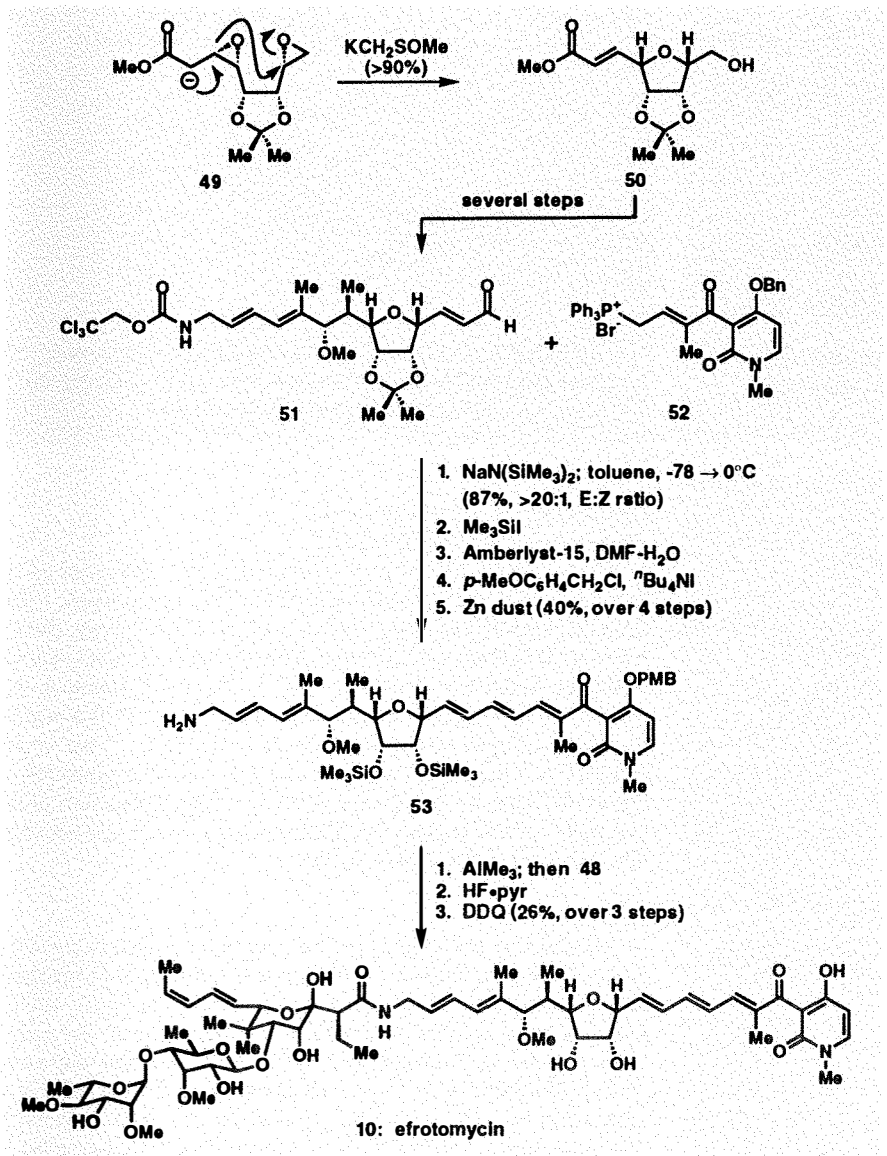
Efrotomycin

Efrotomycin (**10, Scheme 6**) is the most prominent member of the elfamycin class of antibiotics. This, as well as its novel architecture, prompted our interest in its total synthesis in the early 1980's. Focusing on a convergent synthesis,[12] we decided on the amide linkage as the key strategic bond for the final coupling, and compounds **48** (**Scheme 5**) and **53** (**Scheme 6**) as the key advanced intermediates. The tetracyclic system **48** was stereoselectively constructed from glycosyl fluoride **44** and phenylthioglycoside **45** using the two-stage activation procedure as shown in **Scheme 5**. On the other hand the synthesis of the allyl amine **53** featured a novel anionic diepoxide opening (**49** ➤ **50, Scheme 6**) and a Wittig-type

coupling (**51+52, Scheme 6**). Finally, trimethylaluminum-assisted coupling of **48** and **53** followed by further elaboration led to efrotomycin (**10**). The regio-and stereoselective diepoxide opening utilized in this synthesis to construct the challenging all-*cis* tetrasubstituted tetrahydrofuran system was one of the first examples of such cascade reactions leading to complex systems of the polyether type.

Amphoteronolide B and Amphotericin B

As one of the most complex and widely used macrolide antibiotics, amphotericin B (**12, Scheme 8**) and its aglycon, amphoteronolide B (**11, Scheme 7**), presented the synthetic strategist with a formidable and attractive challenge. In the early 1980's we decided to tackle these target molecules in search of opportunities to discover, create, and test new chemistry and synthetic strategies. Questions such as: could one construct such a large macrocyclic ring carrying the sensitive functionality of the amphotericin molecule and, could the nitrogen-containing carbohydrate moiety be attached efficiently and stereoselectively onto the amphoteronolide skeleton to afford the complete amphotericin framework, were pointing to the risky, but also intriguing nature of the venture. By the end of 1986 both amphoteronolide B (**11**) and amphotericin B (**12**) had been synthesized. Final success was realized when the chemistry highlighted in **Schemes 7** and **8** was utilized.[13] Most notable in these constructions was the intramolecular ketophospho-nate-aldehyde condensation by which the acyclic precursor **56ab** was converted to the 36-membered ring heptaenone **57ab** in 70% yield (**Scheme 7**). Further chemistry and stereoselective reduction of the carbonyl group in **58** followed by deprotections led to amphoteronolide B (**11**). The conversion of the precursor heptaenone **57a** to amphotericin B (**12**) required the stereoselective attachment of the azido sugar **52a** to compound **59**, followed by appropriate stereochemical and functional group adjustments (intermediates **60-63**) as summarized in **Scheme 8**.



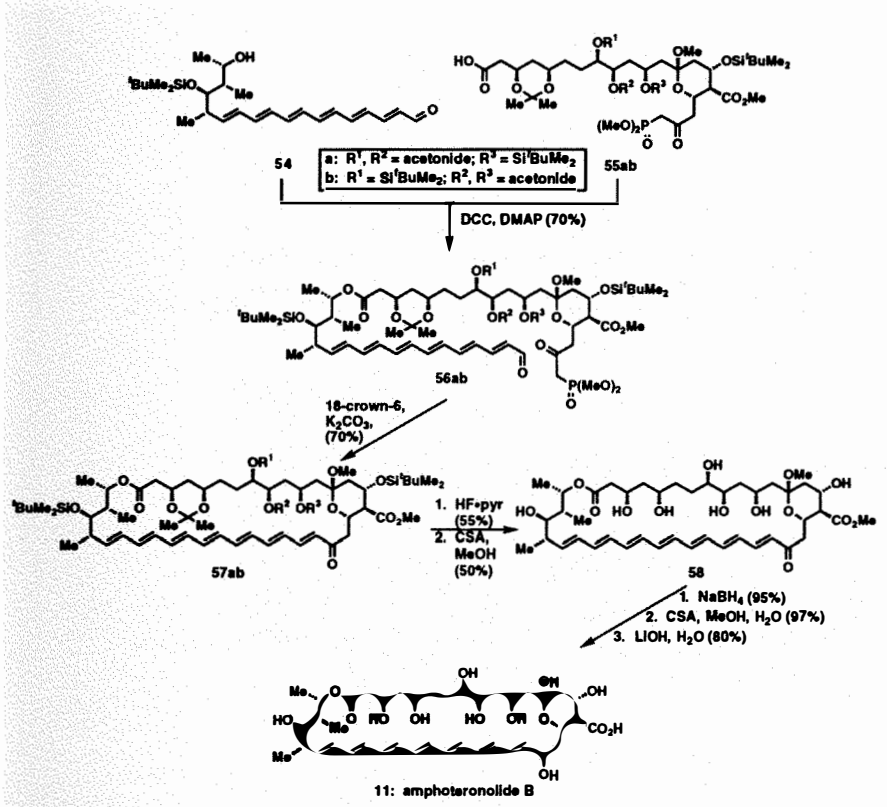
Scheme 6. Total synthesis of efrotomycin (10).

Glycosphingolipids: Dimeric and Trimeric Lewis^x Antigens

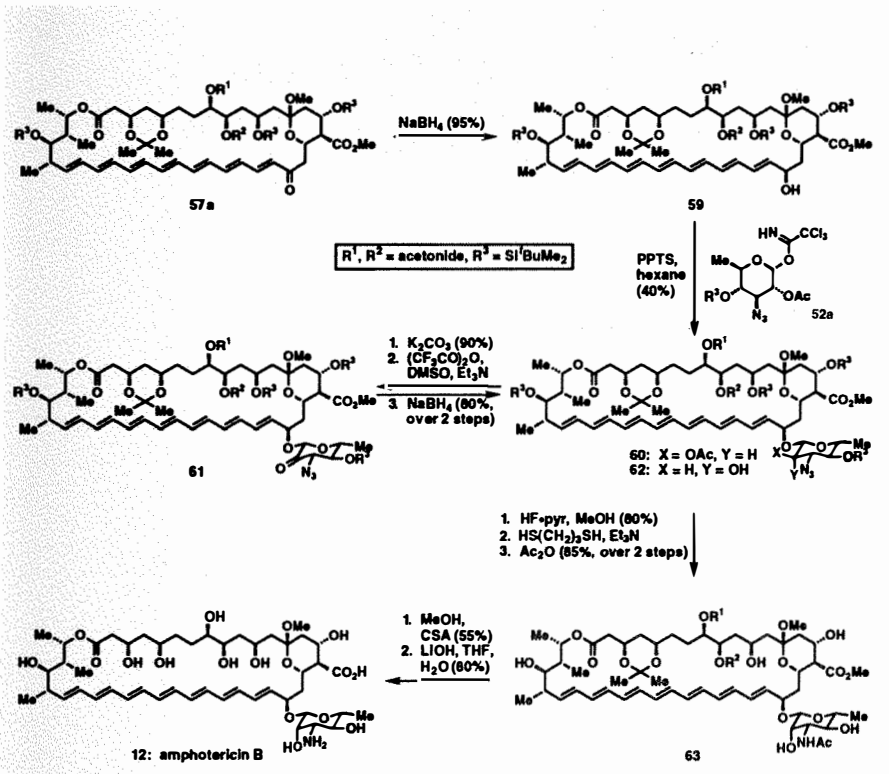
The glycosphingolipids are a ubiquitous class of biomolecules usually found embedded in cell membranes. They have been recognized as the fundamental mediators of cell-cell recognition and communication, cell-growth regulation, cell immune response, and oncogenic transformation.[10] Because of their important biological roles and natural scarcity as well as their structural complexity, these molecules were targeted for chemical synthesis. Our strategy included construction and utilization of an optically active sphingosine equivalent and application of our two-stage activation procedure for the attachment of the carbohydrate units. Glycosphingolipids with 1,2,3,5,8, and 11 sugar residues were synthesized.[14] **Scheme 9** outlines the construction of the two most complex, dimeric Le^x (**13**) and trimeric Le^x (**14**) antigens. Thus, compounds **64-66** were appropriately combined employing coupling operations and standard functional group manipulations to afford compounds **67** and **68**. Complete acetylation, followed by reduction of the azide and attachment of the second lipid chain led, after a series of standard steps, to the targeted glycosphingolipids **13** and **14** via **69** and **70** respectively. Notable in these syntheses are: (a) the regioselective reaction of glycosyl donors at the 3-equatorial position of the glycosyl acceptors; and (b) the stereoselective glycosidation directed by the 2-phthalimido group.

Stereospecific 1,2-Migrations in Carbohydrates. Stereocontrolled Synthesis of α- and β-2-Deoxyglycosides

During our ventures into carbohydrate chemistry we discovered[15] the interesting 1,2-migration reactions exemplified by the conversion of **71** to **72** shown in **Scheme 10**. These DAST-induced migrations allow a number of important objectives to be reached, including:(a) the introduction of fluorine at C-1; (b) the installment of oxygen, sulfur, and nitrogen substituents at C-2; (c) inversion of configuration at C-2; (d) deoxygenation at C-2; and (e) stereocontrolled construction of α- and β-glycoside bonds, including the challenging 2-deoxy-β-glyco-



Scheme 7. Total synthesis of amphoteronolide B (11).



Scheme 8. Total synthesis of amphotericin B (12).

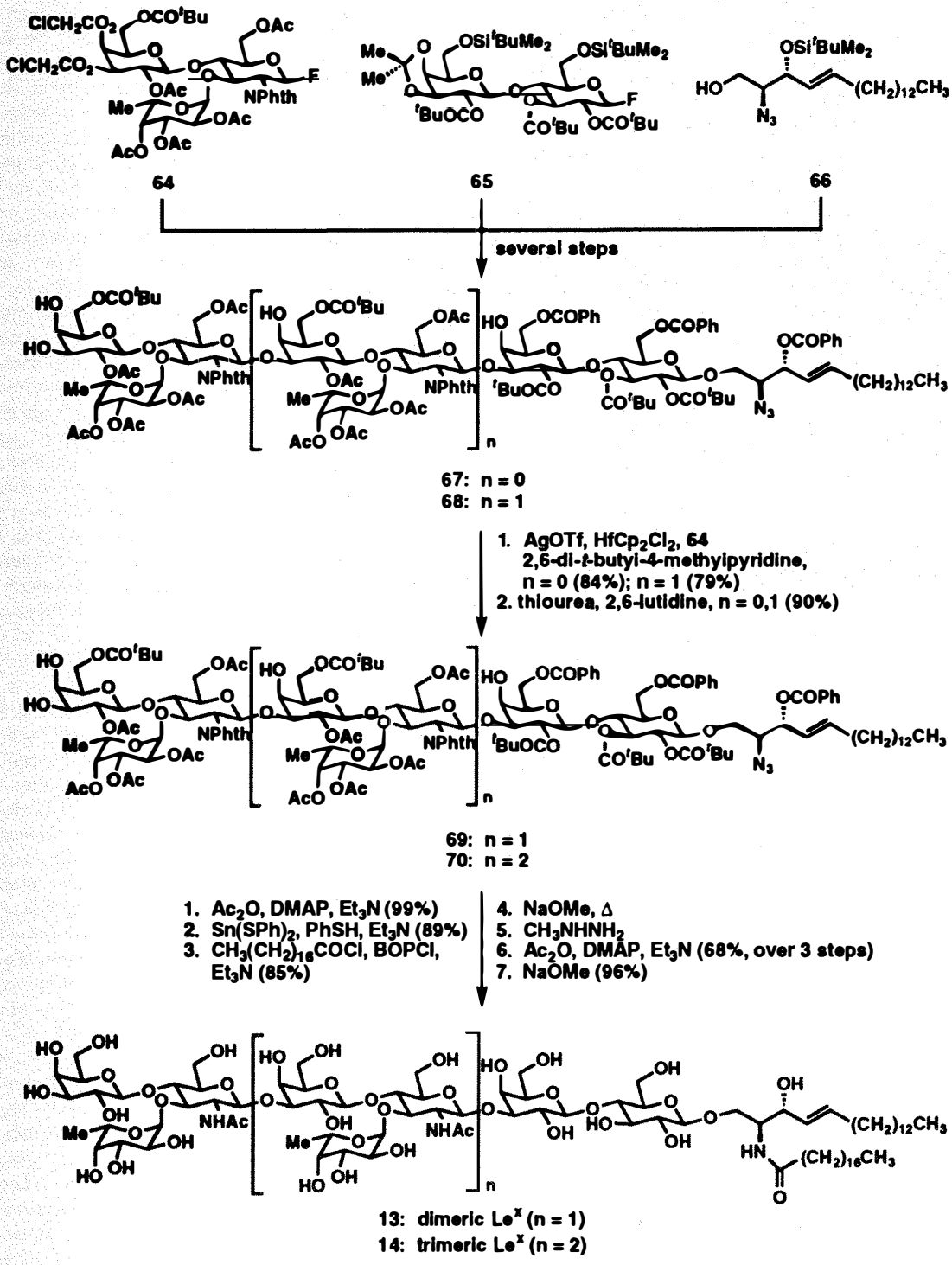
side linkage. **Scheme 10** outlines this chemistry and summarizes its application to the synthesis of α- and β-2-deoxyglycosides (**77** and **78**).

Monomeric and Dimeric Sialyl Lewis^x

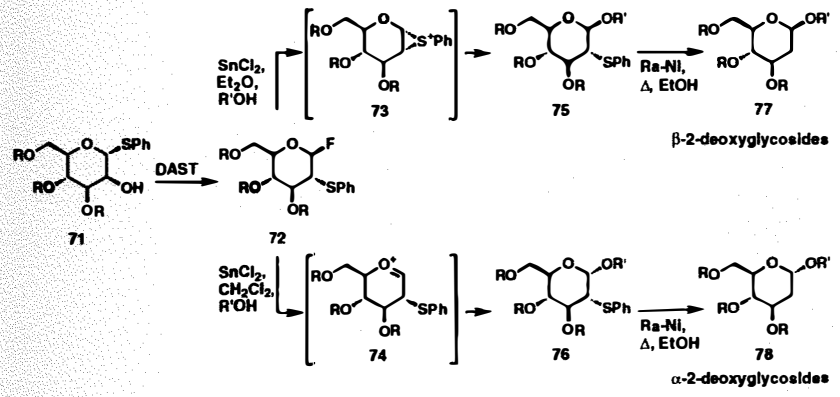
Sialyl Lewis^x-type molecules such as **82** and **15** (**Scheme 11**) have been identified as ligands to the selectins, receptor molecules which have been implicated in leukocyte migration and inflammation. As such, these compounds and their potential biological mimics became prime targets for synthesis. Applying the two-stage activation procedure[11] and our method[15] for the stereocontrolled construction of β-2-deoxyglycosides discussed above, we synthesized both monomeric[16] and dimeric[17] sialyl Le^x type molecules as indicated in **Scheme 11**. Regioselective coupling of fragments **79b** and **80** led to the tetrasaccharide **81b** which served as a precursor to monomeric sialyl Le^x (**82**). While the completion of the monomeric compound proceeded via a few conventional steps, the synthesis of the dimeric sialyl Le^x (**15**) required activation of the reducing end of tetrasaccharide **81a** (obtained from **79a** and **80**) and attachment of a second Lewis^x fragment (**84**), followed by the steps summarized in **Scheme 11**. Again, excellent regio- and stereoselectivity and high efficiency characterize these synthetic sequences.

Brevetoxins A and B

Upon their appearance in the chemical literature, the brevetoxins [A, **90**, **Fig. 2** and B, **93**, **Fig. 3**] with their beautiful and challenging molecular structures, immediately caught our attention. Coupled with their fascinating molecular architecture, their potent neurotoxic properties and association with the "red tide" catastrophes elevated them to the top of our agenda as opportunistic synthetic targets. What was needed first, however, was the invention of new reactions and the development of new strategies for their construction. To this end, several new approaches to cyclic ethers were developed, including: (a) ring-selective constructions of tetrahydropyran, tetrahydrofuran, and oxepane systems via hydroxy epoxide openings (**Scheme 12**)[18]; (b) hydroxydithioketal cyclizations (**Scheme 13**)[19]; (c) bridging of macrocycles to bicycles (**Scheme 14**)[20]; (d) photoinduced oxepane formations (**Schemes 15**[21] and **16**[22]); (e) nucleophilic additions to thionolactones (**Scheme 17**)[23]; and (f) reductive hydroxy ketone cyclizations (**Scheme 18**)[24]. Particularly pleasing were the bridging reactions and the isolation and X-ray crystallographic characterization of the first stable 1,2-dithietane system, dithiatopazine (**106**, **Scheme 15**).



Scheme 9. Total synthesis of dimeric Le^x (13) and trimeric Le^x (14).



Scheme 10. Synthesis of α-2- and β-2-deoxyglycosides.

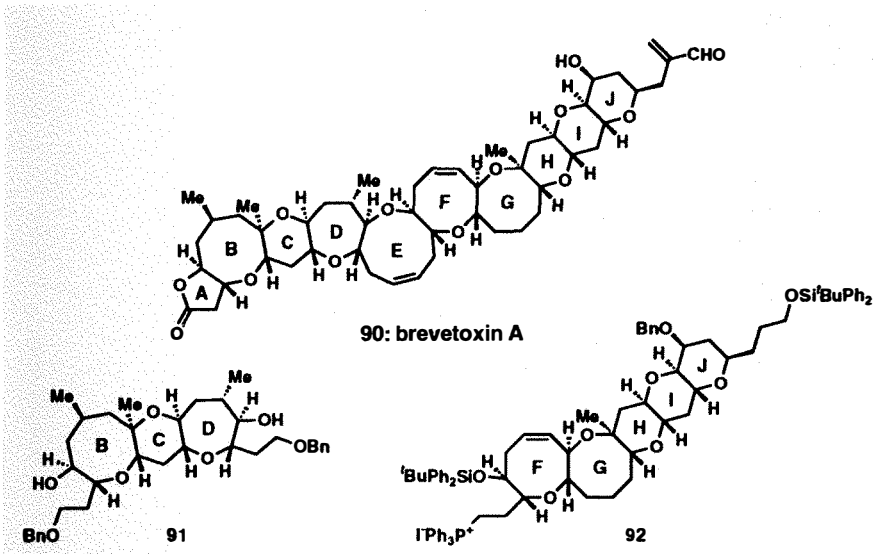


Figure 2. Brevetoxin A (90) and synthesized fragments (91,92).

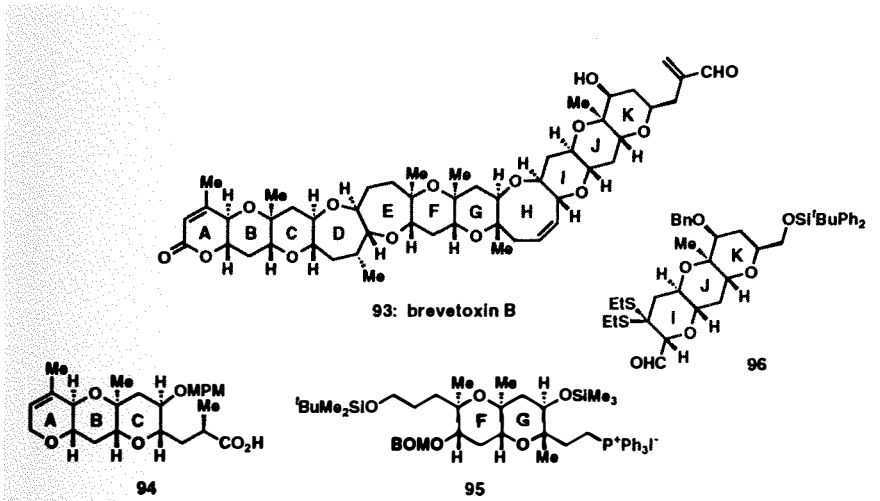


Figure 3. Brevetoxin B (93) and synthesized fragments (94-96).

Application of these new synthetic technologies and strategies to the synthetic problems presented by the brevetoxins A (**90**) and B (**93**) led to the efficient construction of advanced intermediates **91**[25] and **92**[26] (**Fig. 2**) and **94**[27,28], **95**[28,29], and **96**[28,30] (**Fig. 3**).

Hemibrevetoxin B

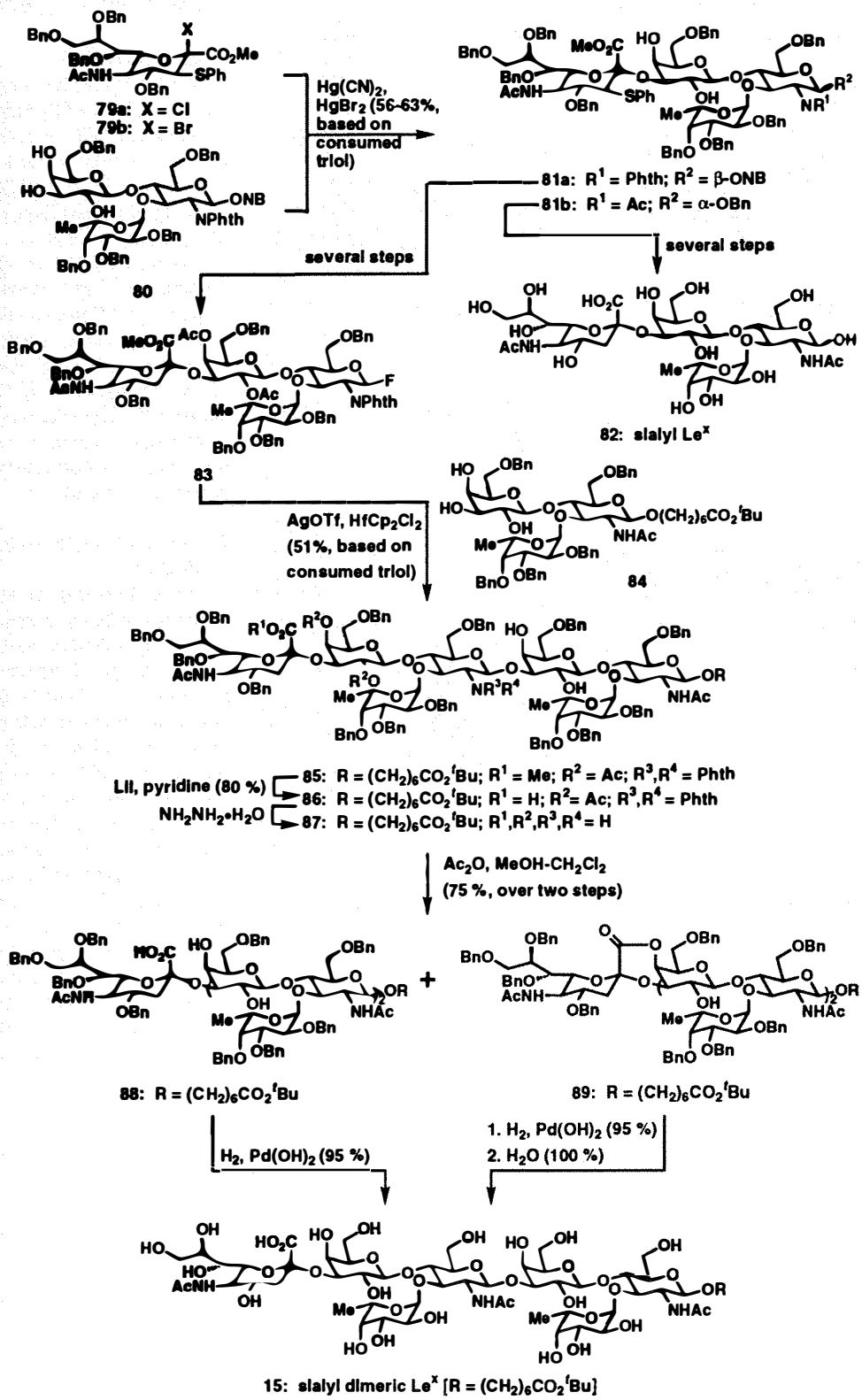
Being one of the simplest brevetoxins, hemibrevetoxin B (**16, Scheme 19**) was synthetically reached[31] in a relatively short time after its isolation and structural elucidation. In realizing this goal (**Scheme 19**), we utilized chemistry developed for the synthesis of tetrahydropyrans (regio- and stereocontrolled hydroxy epoxide openings), (**Scheme 12**)[18] and oxepanes (nucleophilic additions to thionolactones, **Scheme 17**),[23] as well as a number of other selective transformations. The total synthesis proceeded via intermediates **116-123** as summarized in **Scheme 19**. This success represents the first synthesis of any of the brevetoxins, although any conquest of brevetoxins A or B is expected to overshadow it.

Rhizobium Nodulation Signals: NodRm-IV Factors

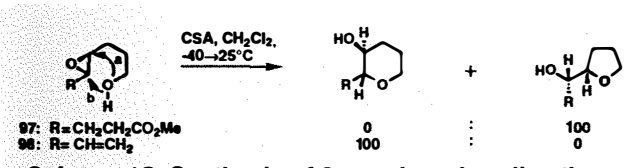
Recent studies of the Rhizobium-legume symbiosis on the molecular level revealed a series of lipo-oligosaccharides of which NodRm-IV (Ac,S) (**17, Scheme 20**) is a prominent example. These fascinating molecules behave as crucial signals from the microorganism to the plant, eliciting nitrogen-fixing root nodules and root hair deformation on specific legume host species. Their important biological function coupled with their natural scarcity and unique molecular architecture prompted us to target them for chemical synthesis.[32] The two-stage activation procedure[11] and the directing effect of the 2-phthalimido group played important roles in their successful construction. **Scheme 20** outlines the sequence leading to **17**. These studies open the way for extensive biological studies in this area, including the possible isolation of the NodRm-IV receptors.

Calicheamicin γ_1^I

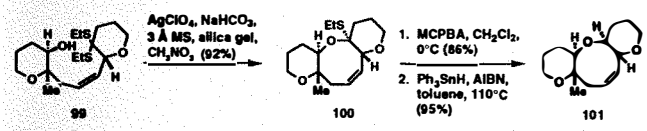
As a synthetic challenge, calicheamicin γ_1^I (**18, Scheme 23**) is very hard to surpass. Its architectural complexity initially appeared to us both appealing and awesome. On the one hand, one is confronted with a unique opportunity to create and discover, but on the other hand, the final goal may not be attained. While at first, this molecular structure appeared beyond reach, if not unlikely, upon further reflection we found the courage to embark on a program directed toward its possible total synthesis. Aside from the gratification of successfully executing a total synthesis of this magnitude, there was the



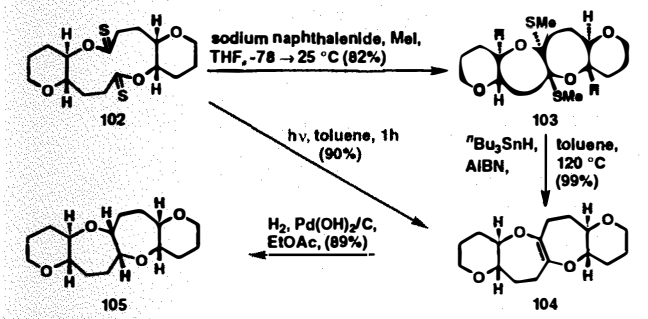
Scheme 11. Total synthesis of sialyl Le^x (82) and dimeric sialyl Le^x (15).



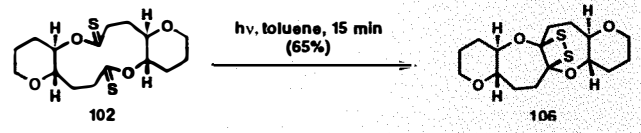
Scheme 12. Synthesis of 6-membered cyclic ethers.



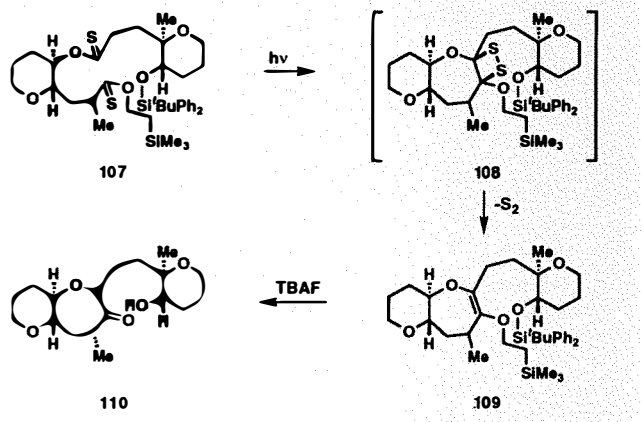
Scheme 13. Synthesis of oxocene ring systems.



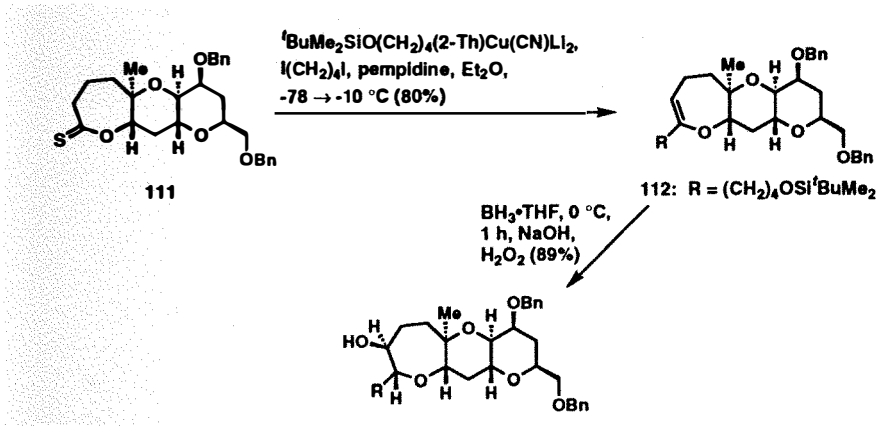
Scheme 14. Bridging of macrodithionolactones: construction of polycyclic ethers.



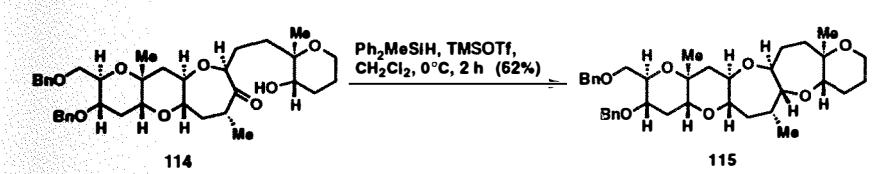
Scheme 15. Bridging of macrodithionolactones: the first stable 1,2-dithietane.



Scheme 16. Bridging of dithionoesters: construction of cyclic ethers.



Scheme 17. Nucleophilic additions to thionolactones: construction of cyclic ethers.

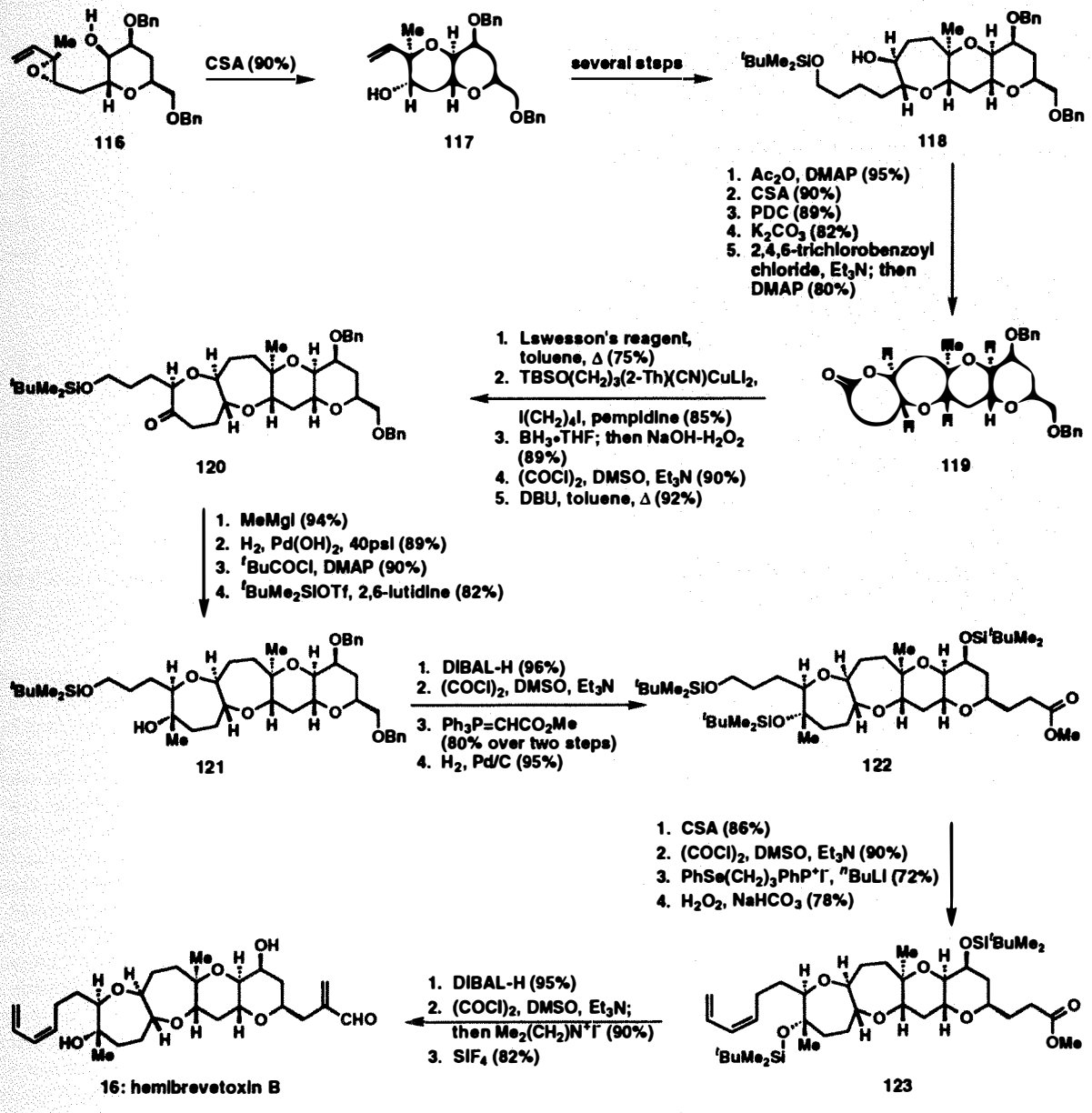


Scheme 18. Cyclization of hydroxy ketones: construction of oxepanes.

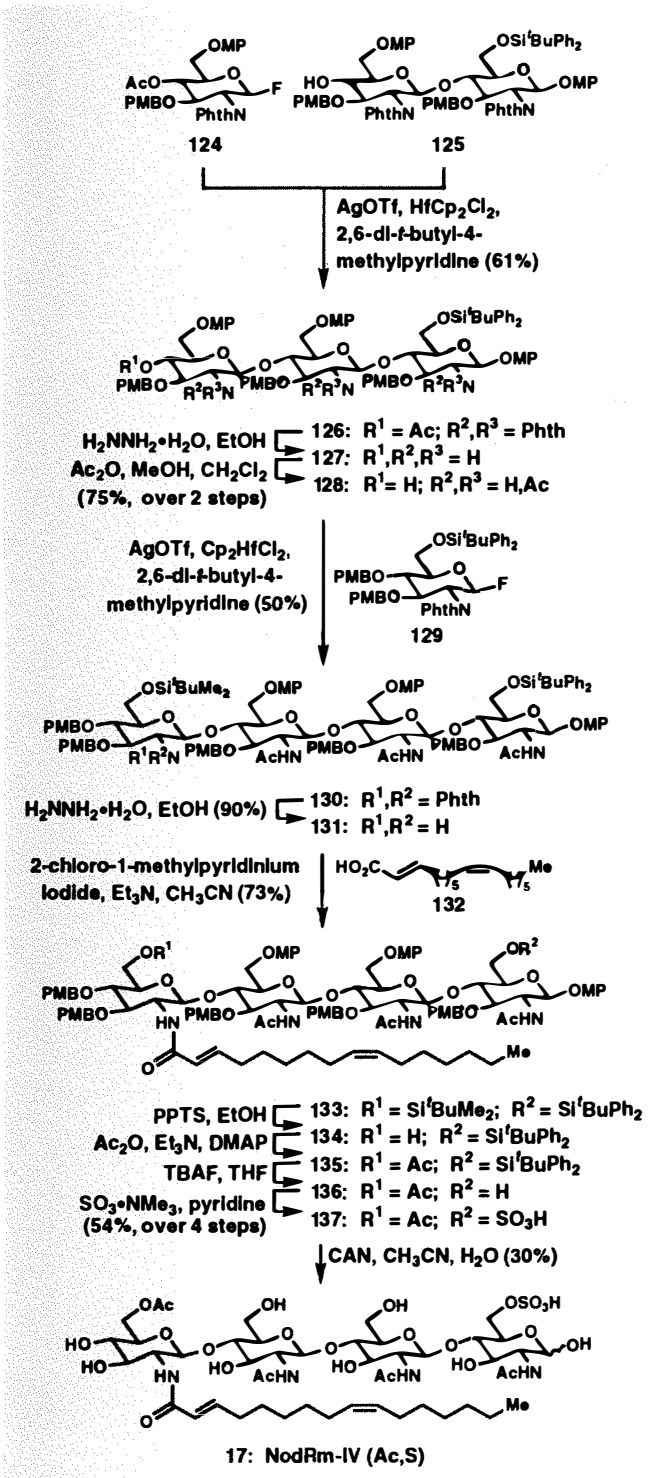
distinct opportunity to develop new synthetic methods and strategies as well as to design and synthesize interesting biological mimics of this fascinating class of antitumor antibiotics, known today as the enediynes.[33]

From the strategic point of view the total synthesis of calicheamicin γ_1^I required the construction of appropriately functionalized intermediates representing its oligosaccharide domain and aglycon fragment. Routes to such systems were, therefore, sought during the first phase of the project. The trichloroacetimidate **148** (**Scheme 21**) was successfully constructed[34] by properly assembling the individual ring systems. Initial glycosidation using the two-stage activation procedure[11] of suitable ring A and E equivalents led to disaccharide **138** which was further elaborated to ketone **139**. Oxime formation between **139** and **140** furnished trisaccharide **141** which was elaborated to thionoimidazolide **144** via intermediates **142** and **143**. A [3,3]-sigmatropic rearrangement of **144** afforded **145**, which was then converted to **146**. Coupling with **147** via a thioester linkage and further manipulations led to the aryl oligosaccharide **148**.

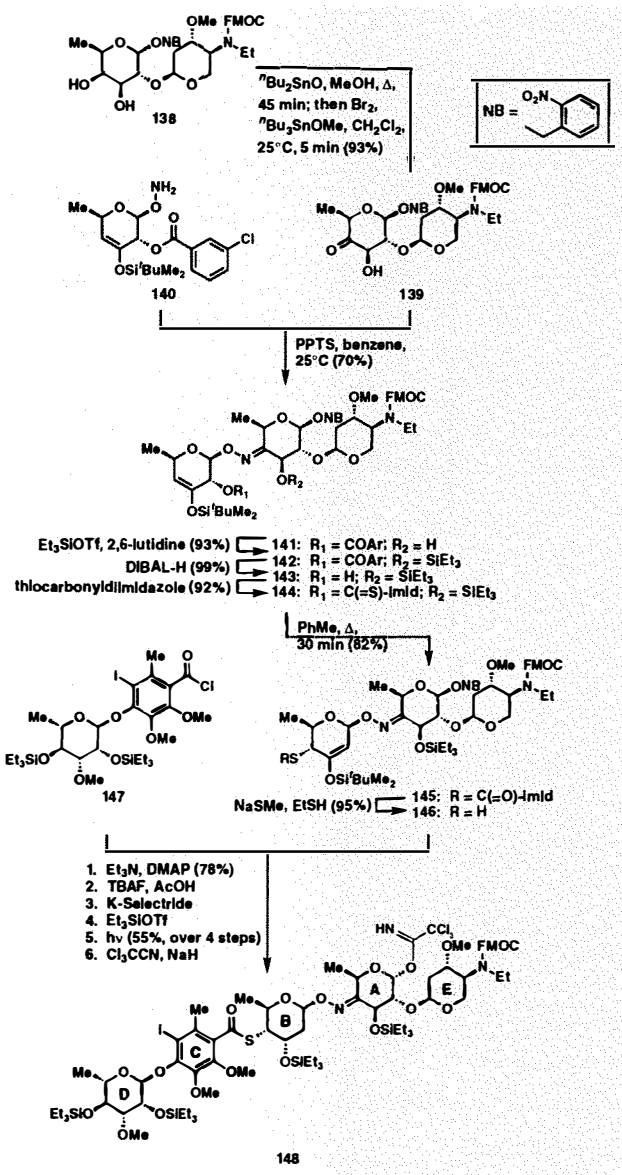
After several abortive attempts to construct the unusual skeleton of calicheamicinone (the aglycon portion of



Scheme 19. Total synthesis of hemibrevetoxin B (16).



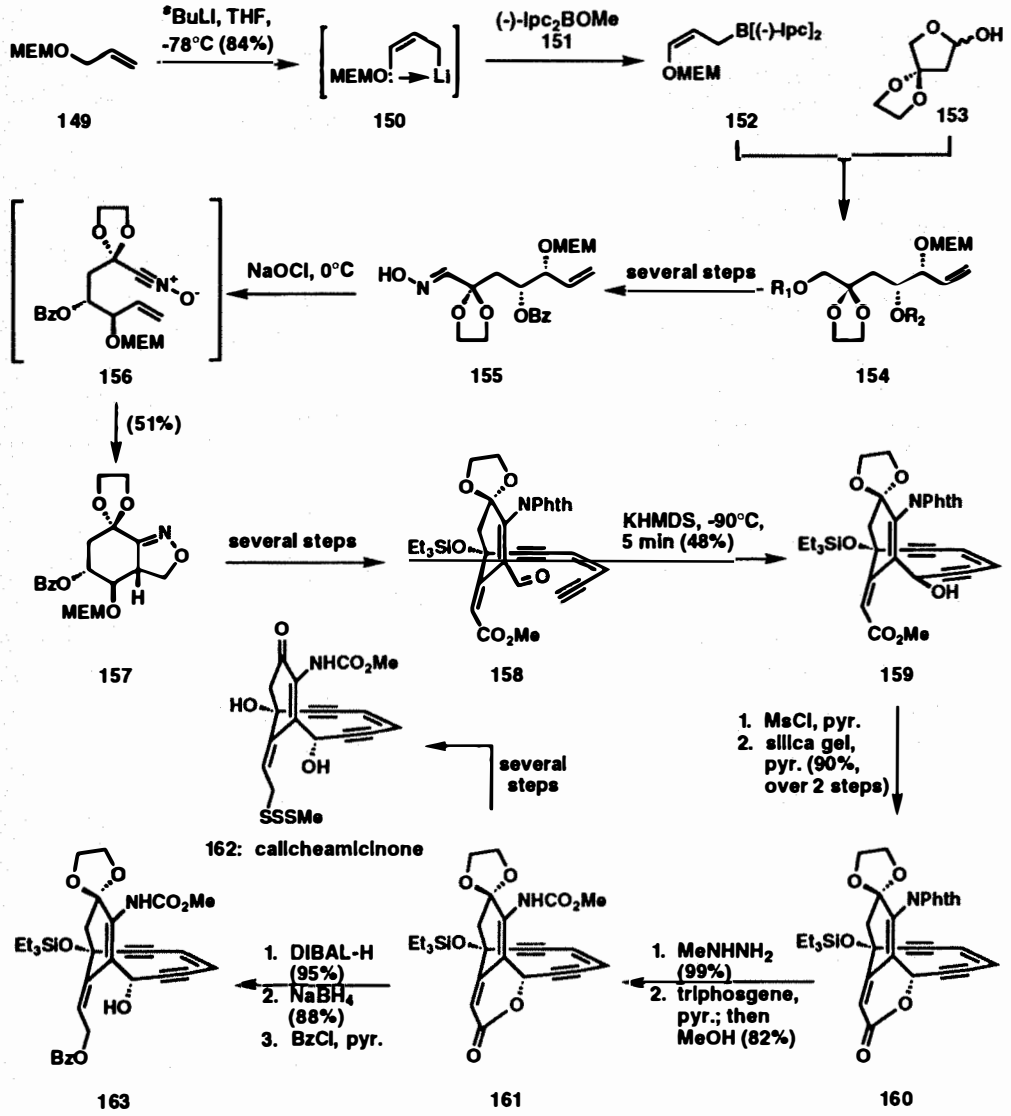
Scheme 20. Total synthesis of NodRm-IV (Ac,S) (17).



Scheme 21. Synthesis of the oligosaccharide portion (148) of calicheamicin γ_1^I.

calicheamicin γ_1^I), a successful synthesis[35] emerged when we adopted a strategy based on an intramolecular [3+2]-nitrile oxide/olefin cycloaddition reaction. This synthesis (**Scheme 22**), which delivered optically active compounds, began with addition of the chiral boron reagent **152** to lactol **153** (derived from tetronic acid) to afford, in 95% ee, compound **154**. Elaboration of **154** through a multistep sequence involving oxime **155** led to nitrile oxide **156**. The latter intermediate closed spontaneously upon formation, leading to the heterocyclic system **157** containing the six-membered ring of calicheamicinone with all the necessary groups to deliver the ultimate functionalities of the target, including the urethane nitrogen. Sequential conversion of **157** to intermediates **158-161** allowed the generation of both calicheamicinone (**162**) and the requisite key intermediate **163** (**Scheme 22**).

With key intermediates **148** and **163** at hand, and in reasonable quantities, the final coupling and completion of the total synthesis became possible (**Scheme 23**). Stereoselective glycosidation[36] of **163** with **148** was promoted by $BF_3•Et_2O$, yielding the coupling product **164** which was converted to the thioacetate **167** by deprotection of the allylic position followed by Mitsunobu reaction (AcSH) and desilylation (intermediates **165** and **166**). Reduction of the oxime bond in **167** generated the desired hyroxylamine derivative **168** as the major product which was taken via intermediate **169** to the thiol **170** by silylation and deprotection. Finally, installment of the trisulfide unit using PhthNSSMe, followed by final deprotection gave, via intermediates **171-173**, synthetic calicheamicin γ_1^I (**18**), identical in all respects with the naturally occurring compound. The total synthesis of calicheamicin γ_1^I[37] not only proved its originally proposed molecular structure, but also made possible the synthesis of a



Scheme 22. Synthesis of calicheamicinone (162) and intermediate (163).

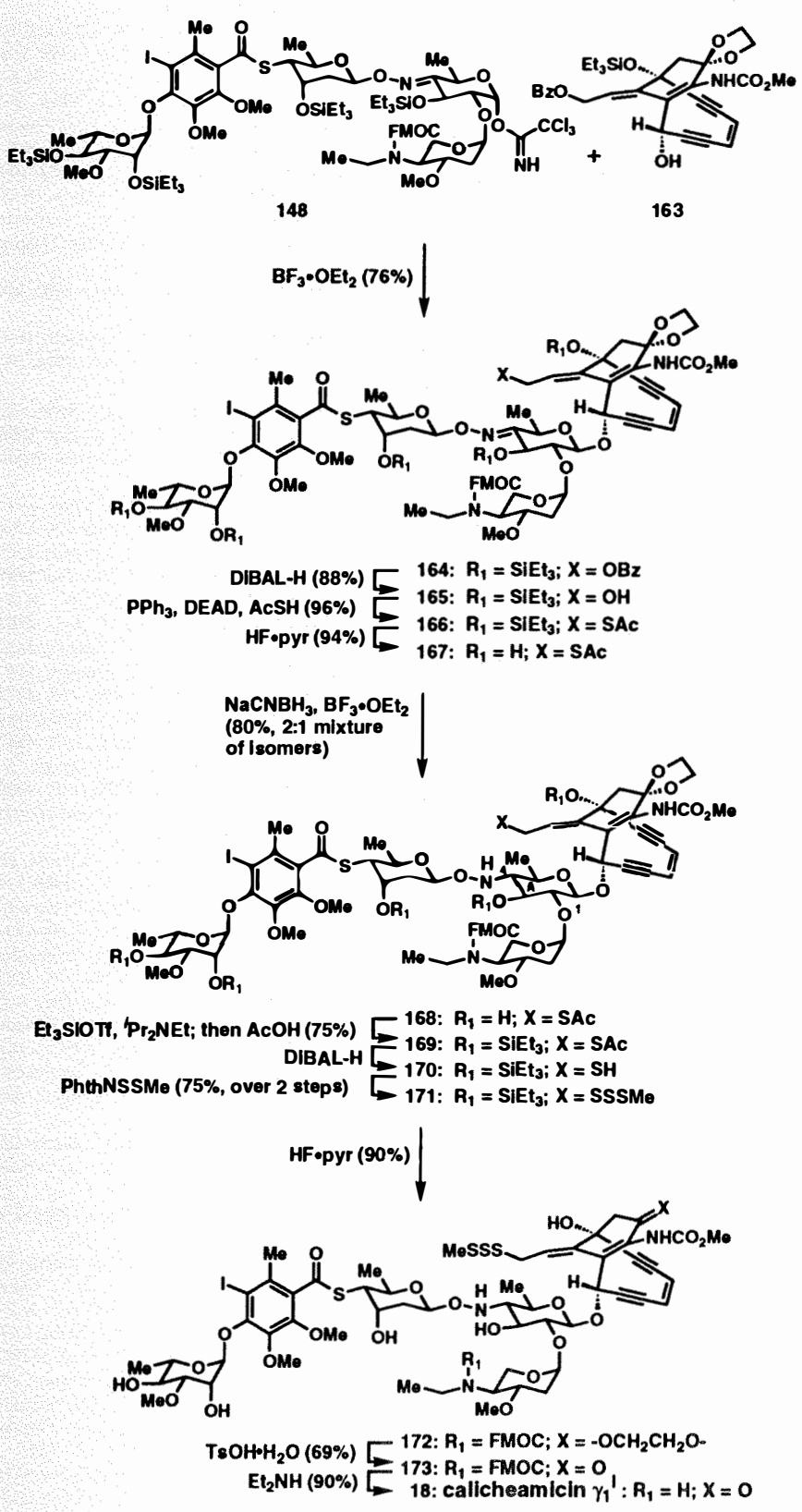
series of novel analogs for biological investigation. The sheer pleasure derived from the final outcome by those of us who had the good fortune to be there at the moment of glory can only be fully appreciated by those who have been there, at similar heights, before us!

Rapamycin

Rapamycin's powerful immunosuppressant properties coupled with its novel and challenging molecular structure rapidly attracted the attention of synthetic organic chemists. Our approach[38] towards rapamycin (**19**, **Scheme 24**) postulated a rather daring operation as the final step to complete the synthesis. A stitching-macrocyclization process as shown in **Scheme 24** was projected as a new strategy to macrocycle formation. Indeed, the completely functionalized and deprotected precursor **175** was successfully converted to rapamycin (**19**) by incorporation of the missing olefinic linkage via reaction with distannane **174** under Stille coupling conditions. This synthesis represents not only the first for this target molecule, but also a new strategy for the construction of polyene macrocyclic systems.

CONCLUSION

With the above examples, an attempt was made to demonstrate the identification and pursuit of synthetic targets from the natural products field. As highlighted in the discussion, the criteria for the selection of the synthetic problems often included novelty in molecular architecture and important biological activity as well as fascinating and



Scheme 23. Total synthesis of calicheamicin γ_1^I (18).

intriguing mode of action and biogenesis. Such criteria ensure the positioning of the practitioner at the center of opportunity arenas to discover, create, and develop new "science" and make significant contributions to the peripheral disciplines of biology and medicine.

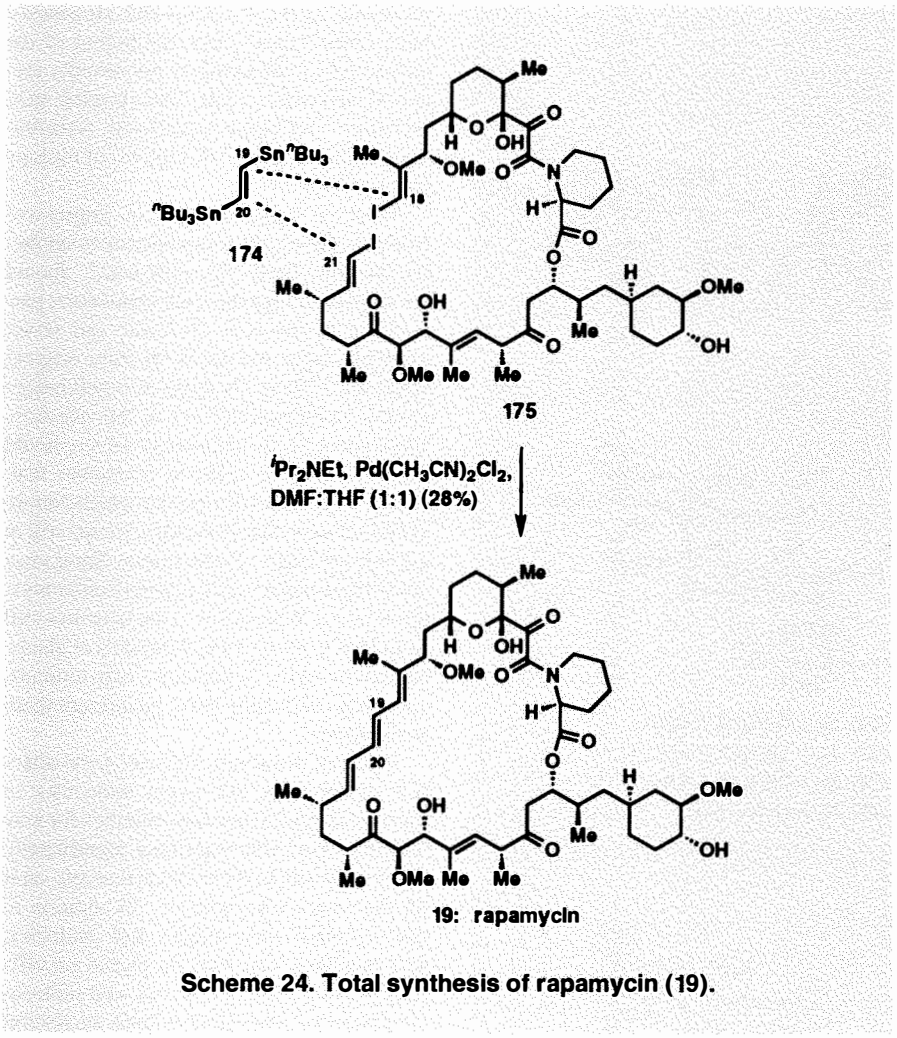
After so many decades of impressive strides in the area of natural products synthesis, one may fairly ask, what next? Should we continue to pursue such endeavors, particularly in the face of fewer and fewer available target molecules of truly original structures? There are those who will hasten to offer an unqualified "no" to this question. The prudent and firm answer, however, should be "yes", for we ought to remember that, compared to the efficiency by which Nature synthesizes its own molecules, we are still in a primitive stage. Furthermore, Nature has not yet finished revealing its molecular mysteries to us. Who knows what treasures still lie hidden in the molecular libraries of plants, bacteria, marine organisms, and animals, and what will Nature teach us through them in the future.

We must be careful, however, to be selective in choosing our target molecules in order to maximize our opportunities for new "science" that will contribute significantly to our field and to those fields that rely on it for their own advancement. In addition to new synthetic technologies and strategies, new emphasis may now be placed on efficiency, environmental control, and molecular design on biological mimics of natural products. Testing the state of the art of organic synthesis could often be complemented by dimensions included to test biogenetic pathways and mechanistic concepts associated with the natural products involved.

In short, we must be much more demanding in our pursuits of natural products synthesis, whether we do it for the complexity and challenge of the target, in search of new chemical reactions and synthetic strategies, for its value in biomedical research, or for sheer excitement!

ACKNOWLEDGMENTS

I would like to take this opportunity to express my many thanks and admiration to my present and past students and postdoctoral fellows who were involved in the work described in this article. The successes of this group are primarily due to their dedication and intellectual and experimental contributions. My assistants Vicky Nielsen and Janise Petrey also deserve my thanks for keeping the group together and for their patience and diligence in dealing with the manuscript and with all of us. I would also like to thank all my colleagues at the Univer-



Scheme 24. Total synthesis of rapamycin (19).

sity of Pennsylvania, the University of California, San Diego, and The Scripps Research Institute for their support and for stimulating discussions over the last few years.

Many thanks and gratitude are also due to my friends from industry who constantly and generously supported our research programs and at the same time contributing to the education and training of my students.

To my teachers, the late Professor F. Sondheimer, Peter J. Garratt, Tom J. Katz, and E.J. Corey, I am grateful for their guidance, valuable teachings, and support. To my friends Madeleine M. Joullié, Ralph F. Hirschmann, and Sam J. Danishefsky I owe much for their constant support and encouragement and to my family, Georgette, Collette, Alex, Chris and Paul, I owe everything for being there all the time, even though I was often absent!

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ABOUT THE AUTHOR

K.C. Nicolaou was born on July 5, 1946, in Cyprus where he grew up and went to school until the age of 18. In 1964 he went to England where he spent two years learning English and preparing to enter the University. He studied chemistry at the University of London (B.Sc., 1969, Bedford College; Ph. D. 1972, University College, with Professors F. Sondheimer and P.J. Garratt). In 1972 he moved to the United States and, after postdoctoral appointments at Columbia University (1972-1973, Professor T.J. Katz) and Harvard University (1973-1976, Professor E.J. Corey), he joined the faculty at the University of Pennsylvania where he rose through the ranks to become the Rhodes-Thompson Professor of Chemistry. In 1989, he accepted joint appointments at the University of California, San Diego, where he is Professor of Chemistry, and The Scripps Research Institute where he is the Darlene Shiley Professor of Chemistry and Chairman of the Department of Chemistry. His awards and honors include an A.P. Sloan Fellowship (1984), a Camille and Henry Dreyfuss Teacher-Scholar Award (1980), the American Chemical Society, Philadelphia Section Award (1983), a Guggenheim Fellowship (1984), Humbolt Foundation US Senior Scientist Award (1987), an A.C. Cope Scholar Award from the American Chemical Society (1987), the Japan Society for the Promotion of Science Award (1988), the Alan R. Day Award by the Philadelphia Organic Chemists' Club (1993) and the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry (1993). K.C. Nicolaou's research interests focus on chemical synthesis, molecular design and molecular recognition, and the biological actions of organic molecules.

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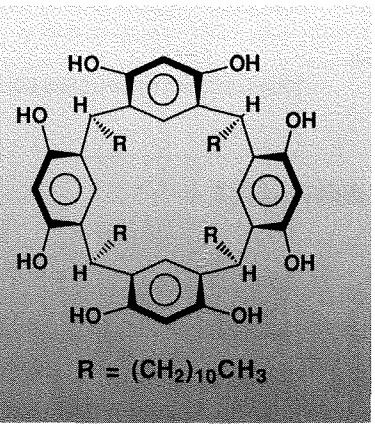

The Reagent:

C-Undecylcalix[4]resorcinarene is a macrocyclic, bowl-shaped compound having unprecedented properties. It is a lipophilic host forming stable complexes with polar oxygen-functionalized guests. By complex formation water, glycerol, carbohydrates and other polyols as well as carboxylic acids and esters are solubilized in aprotic, organic solvents[1]. The eight hydroxy groups which constitute the hydrophilic rim of the bowl-shaped compound form four independent sites for the hydrogen-bonding of guests[1]. Polyols and dicarboxylic acids undergo very selective complexation depending on the number of functional groups, their spatial arrangement and stereochemistry[2,3]. Thus carbohydrates are very selectively complexed (ribose > fructose > glucose)[4-6]. The bowl-shaped aromatic cavity leads to a considerable upfield shift of ^{1}H-NMR signals of a complexed guest[7] and to an induced circular dichroism with a chiral guest[8]. This novel host can be used as an ^{1}H-NMR-shift reagent and also as a reagent for determining the absolute configuration of a chiral guest (exciton chirality induction).

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[1] Y. Aoyama, Y. Tanaka, H. Ogoshi, J. Am. Chem. Soc. **110**, 634 (1988).
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[8] Y. Kikuchi, K. Kobayashi, Y. Aoyama, J. Am. Chem. Soc. **114**, 1351 (1992).

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The Fluka Prize:

Since 1987, the Fluka Prize "Reagent of the Year" has been awarded anually to a research project, in which a new compound has been shown to be a reagent of prime importance, useful in organic chemistry, biochemistry or analytical chemistry. The winner will be awarded the sum of sFr. 10'000.-. He will be free of any obligations whatsoever. Full details regarding the Fluka Prize are available upon request.

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Aldrichimica Acta

Volume 26, Number 4, 1993

Starburst™/Cascade Dendrimers: Fundamental Building Blocks for a New Nanoscopic Chemistry Set

Probing the Specificity of Synthetically Useful Enzymes

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Aldrichimica Acta

Volume 26, Number 4, 1993
A publication of the ALDRICH CHEMICAL COMPANY

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Telephone: 41817552723
FAX: 41817567420

United Kingdom
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The Old Brickyard, New Road
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Telephone: 44747822211
FAX: 44747823779

About Our Cover:

A nostalgic glimpse of a hundred years ago entitled **New Bedford: The View Across to Fairhaven from Center Street in 1884** (oil on canvas, 18 x 24 in.) was painted by the contemporary marine artist, John Stobart. This view of Center Street, New Bedford, is almost exactly the same today as it was in this painting. If it were not for the main highway crossing the foot of the street, one would still be able to walk right into this view and down onto the wharf, which is still in commercial use. The churches across the river in Fairhaven are still there. All that is gone, and gone forever, are the whaleships that so characterized this New England harbor when it was home port to so many of the vessels between 1845 and the turn of the century.

In this painting showing Central Wharf in 1884, the brig Isabella, is at anchor in the Acushnet River. Down on the wharf to the left of the little shack that seems to be in almost all photographs ever taken of New Bedford, an older bark has been stripped down to her lower masts prior to undergoing renovation. As a form of dedication, the artist has used the names of two gentlemen on advertising signs: his good friends Richard Kugler, curator of the New Bedford Whaling Museum, and Richard Fitton, M.D., whom Stobart has immortalized as proprietor of the ship chandlery on the right.

The painting is in the collection of the artist.

Stobart: The Rediscovery of America's Maritime Heritage

J. Stobart and R.P. Davis, E.P. Dutton, New York, NY, 1985, 208pp.
Contains over 60 paintings in full-color and numerous drawings by the popular marine artist, John Stobart. In this volume Stobart re-creates a bygone era — "where ships were ships and not tin pots" — transporting the reader aboard clipper ships, packets, brigs, whalers, etc. and to America's famous and colorful coastal and inland river ports.

American Maritime Paintings of John Stobart

J. Stobart and R.P. Davis, Penguin Books, New York, NY, 1991, 237pp.
This second volume of John Stobart's maritime art contains over 70 paintings in full-color with numerous halftones and drawings. As in his earlier book (see above) the paintings are grouped by ports and the vessels associated with them. Each painting is accompanied by an informative account of the history surrounding the port and vessel.

Lab Notes

A common problem chemists have when chromatographing milligram quantities using a pipette column is the lack of reservoir space for the eluant. A remedy to this problem is to use a disposable 10-ml syringe as the solvent reservoir.

The pipette column is connected to a carrier gas line using silicone tubing. The needle is inserted through the tubing into the top of the pipette. This allows the constant addition of eluant to the column simply by pushing the syringe barrel when needed. No longer do you have to remove the carrier gas line, collect one fraction and repeat the process due to an empty solvent reservoir.

Dale Krolikowski
Scientist II
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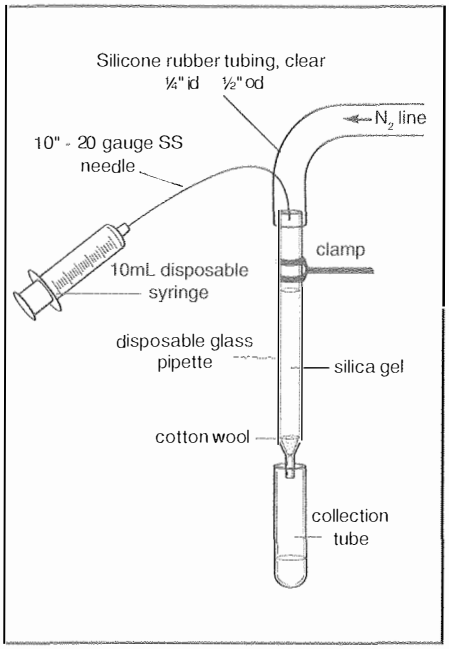

Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to Aldrich (attn: Lab Notes, Aldrichimica Acta). For submitting your idea, you will receive a complimentary, laminated periodic table poster (Cat. No. Z15,000-2). If we publish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

"Please Bother Us."

by Jai Nagarkatti

Jai Nagarkatti, President

1 R = H
2 R = Cl

Professor Daniel L. Comins of North Carolina State University kindly suggested that we manufacture these pyridine based triflating reagents. They are stable, white crystalline solids and are much more reactive than *N*-phenyltriflimide (Aldrich Cat. No. 29,597-3) allowing preparation of most vinyl triflates at -78°C in 2 - 4 hours.

Chromatographic purification (silica gel; EtOAc/hexane) of the product vinyl triflates is also much easier — another advantage over *N*-phenyltriflimide.

Naturally, we made these two interesting reagents.

Comins, D.L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

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

Starburst™/Cascade Dendrimers: Fundamental Building Blocks for a New Nanoscopic Chemistry Set[1]

Donald A. Tomalia
Nanoscopic Chemistry and Architecture
Michigan Molecular Institute
1910 W. St. Andrews Road
Midland, Michigan 48640

Chemistry is not just a science involving the study of electron movement to rearrange and connect atoms. It is a philosophy, a way of thinking about the world, about how matter is constructed, organized, and how it functions throughout the dimensional hierarchy of the universe, from the simplest atoms to the most complex phenomena — namely life itself. The adventure I would like to present in this paper evolved from just such a philosophical perspective. It deals to a large extent with the *analysis and interpretation of some simple but pervasive patterns observed in Nature.*

Historically, the origin of our "first chemistry set," that based on atomic building blocks, dates back to the publication of "The Elements of Chemistry" in 1789 by Antoine Lavoisier (1743-1794). At that time, the 23 building blocks were defined empirically as the "actual terms whereat chemical analysis had arrived." This new science described a totally different vision of compound materials which were characterized by constant, well defined elementary compositions, as opposed to physical mixtures of indefinite composition. The objectives of its disciples were to prepare new substances and materials with new properties. These new building blocks taken two at a time might yield hundreds of new compounds, or combined three at a time would give thousands, while the possibility of combining four different building blocks ran into the millions.

The notion of fixed building blocks of matter that exhibit certain "pervasive patterns" was basic to the atomic theory of John Dalton (1766-1844) as he published his "New System of Chemical Philosophy" in 1808. This theory postulated that each chemical element is a homogeneous assembly of atoms which differ in relative weight, number per unit volume, and in combining number (valency) or set of combining numbers from the atoms of other elements. In fact, without the benefit of understanding quantum mechanics or electronic theory, the operational parameters of our first chemistry set became fairly well defined throughout the 19th century. These parameters, derived from simple logic, were clearly based on experimental

The First Chemistry Set (Based on Atomic Building Blocks)

Pervasive Patterns Supported by Experimental Observations	Discovering Scientist	Contributions
I. Atoms form chemical bonds	Antoine Lavoisier (1743 - 1794)	"Traite Elementaire de Chimie" (1789)
II. Atoms (elements) possess well defined masses relative to each other (combining weights).	Joseph L. Proust (1754 - 1844)	"Law of Definite Proportions" (1797)
III. Atoms (elements) form chemical bonds with well defined valency.	John Dalton (1766-1844)	"Law of Multiple Proportions" "New System of Chemical Philosophy" (1808)
IV. Atoms (the elements) exhibit periodicity in their reactivity and emerging properties.	Dmitri Mendeleev (1834 - 1907)	Periodic Table of the Elements (1869)
	J. Lothar Meyer (1830 - 1895)	(1870)
V. Atoms (elements) exhibit well defined directionality in the formation of chemical bonds.	Louis Pasteur (1822 - 1895)	Spatial Chemistry
	Joseph-Achille LeBel (1847 - 1930)	Tetrahedral Nature of Carbon (1874)
	Jacobus V'ant Hoff (1852 - 1911)	Tetrahedral Nature of Carbon (1874)

Table 1. Five key criteria (patterns) that were observed and analyzed by 18th-19th century scientists to define our "atomic level chemistry set" before the advent of quantum mechanics and electronic theory.

observations and generally involved the interpretation of pervasive patterns. In summary, they include the five critical criteria (I-V) listed in **Table 1** and the scientists associated with their discovery.

Throughout this past decade of research on dendrimer systems we have observed essentially all of the same patterns noted by these 19th century scientists for atomic building blocks (**Table 1**). Now that we have obtained substantial experimental evidence to define, support, and describe these five "pervasive patterns" common to each system, it is appropriate to relate the rich analogies shared by the organized matter of our well known picoscopic/subnanoscopic (atomic) systems and the ordered complexity of the new dendrimeric (nanoscopic) systems.

Before we begin this discussion, let us briefly review some of the inspirational parameters, both philosophical and experimental, that led to this dendrimeric concept for organizing matter. Based on my formal training as a synthetic/physical-organic chemist and my informal training as a polymer chemist in the Dow Research Laboratories, I had many opportunities to traverse the boundaries of these formalized disciplines. Most of my career prior to the early 1980's had been devoted to the synthesis and characterization of new organic structures. In some cases, new monomers were synthesized which were polymerized into macromolecular products, usually with broad statistical distributions of molecular weight. As an organic chemist, these products tended to violate my appreciation for articulate, well defined structures in pure isolable forms. As a polymer chemist, it is perfectly acceptable to deal with these products as statistical mixtures of common composition, but definitely not as singular products of well defined molecular weight. This has been the practice since Staudinger introduced the world to polymer chemistry in the 1930's. Somehow, throughout all of these experiences, the notion evolved of progressing from these precise sub-nanoscopic monomers to precise macromolecular structures with a systematic strategy that would give total structural control and thereby make macromolecules more articulate and "user friendly" to synthetic organic chemists.

There is no doubt that the dendritic patterns encountered as a hobbyist nurseryman/tree grower for the past 31 years had a profound influence on my choice of strategies. In fact, the subconscious desire to mimic these macroscopic tree branching patterns with chemical structures became somewhat of a preoccupation for me during the 1970's. Analysis of the parameters involved in synthetically mimicking these pervasive branching patterns, found also in coral

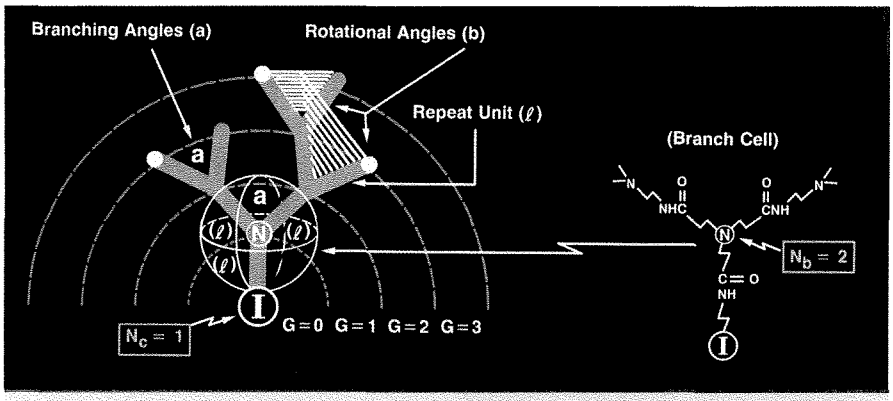

Figure 1. Construction parameters controlling macroscopic space in a tree or critical molecular design parameters in a nanoscopic dendron.

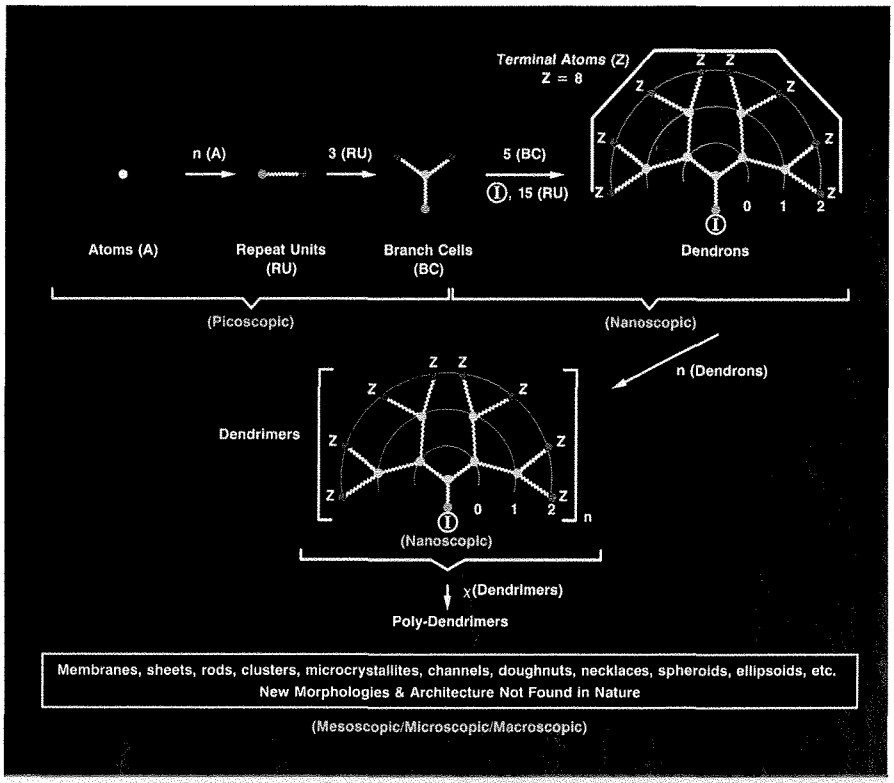

Figure 2. Atomic and molecular aufbau leading to dendrimers and dendrimer assemblies.

and physiological structures, included the following considerations (**Figure 1**);

1. Construction and control of branch cell repeat unit lengths (l).
2. Control and development of branch cell multiplicities (N_b) and core multiplicities (N_c).
3. Development of high yield reiterative growth processes which would allow concentric, radial construction of branches upon branches around an initiator core Ⓘ, which specifies the direction of growth.

The branch cell segments (l) are determined by the choice of monomers, the branch angles ($\angle$a) are determined by the nature (geometry) of the branch juncture, whereas the rotational angles ($\angle$b) are influenced by secondary structure parameters such as steric effects and hydrogen bonding. These parameters contribute significantly to the development of excluded volume around the branch juncture. Reiteration of these branching patterns in an ideal tiered manner (G = 0, 1, 2, 3...) leads to highly ordered macromolecular domains ("nanodomains"). The ultimate interplay of all these parameters gives nearly total control over critical molecular design parameters (CMDP's) such as size (mass), shape, and disposition of chemical moieties, both in the interior and on the exterior surface of these nanodomains.

This strategy for these molecular constructions (aufbau) involves, first, the as-

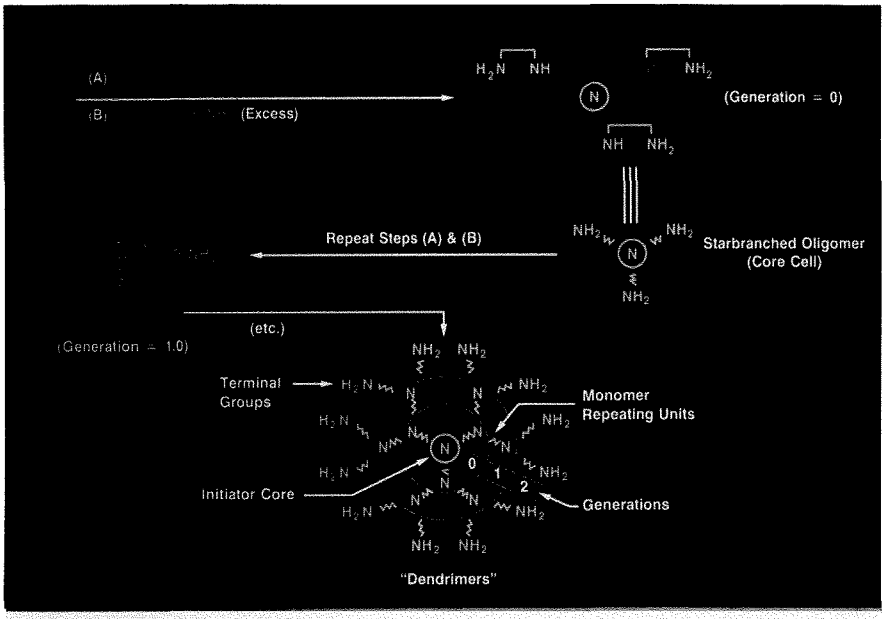

Figure 3. Reaction scheme for synthesis of Starburst™ (cascade) poly(amidoamines) PAMAM's.

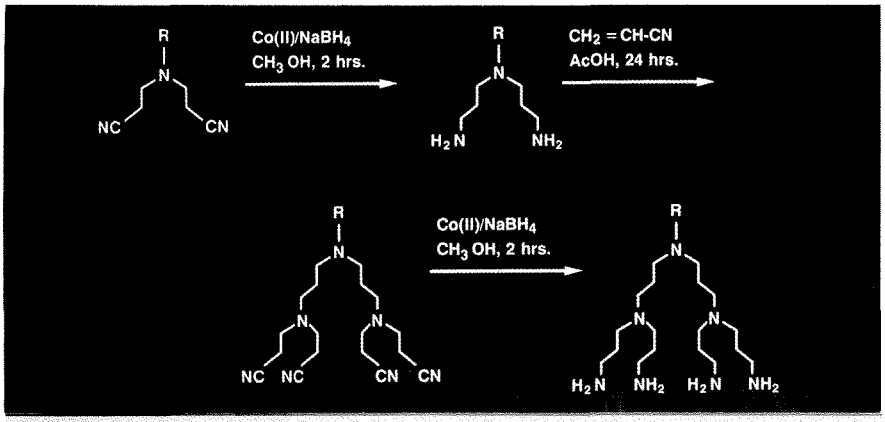

Figure 4. Vögtle synthesis of "cascade molecules."

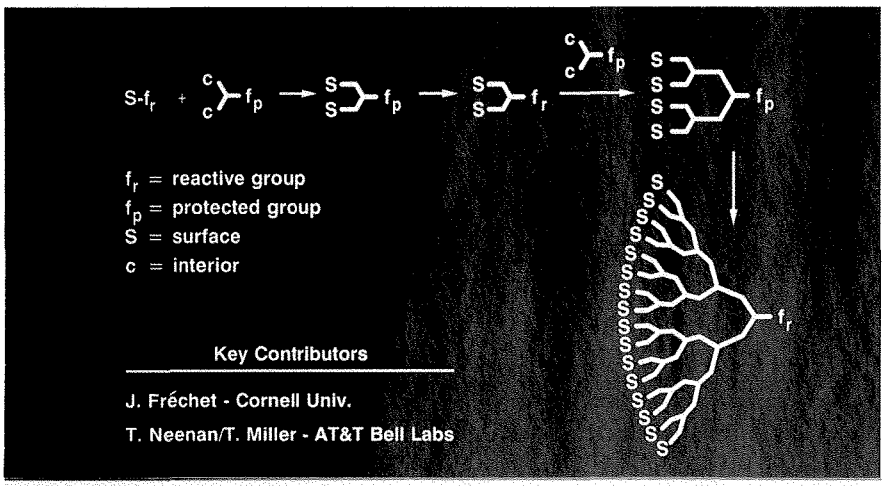

Figure 5. Fréchet/Hawker and Miller/Neenan convergent synthesis strategy.

sembly of three picoscopic/sub-nanoscopic sized repeat units (RU) possessing a monovalent terminus (**1**) which is reactive with a divalent terminus (*) to produce a branch cell (BC) containing a branch juncture (⟨). Attaching this first branch cell to the reference point (Ⓘ) yields a labeled branch cell with a valency of four which is referred to as generation = 0. Stepwise attachment of RU's, usually using protection/deprotection schemes, produces the next generation = 1, with a valency of eight. Reiteration gives generation = 2, resembling a cascade assembly consisting of 5 BC's, 15 RU's, and 8 terminal surface atoms.

This single-trunked, two-dimensional projection resembling a tree is referred to as a *dendron* (Greek word for tree). These dendrons can be viewed as "Lego type" components that may be assembled in multiples around cores (Ⓘ) to produce *dendrimers* with n(dendrons) (**Figure 2**). These operations allow one to advance from picoscopic to nanoscopic dimensions by systematically organizing atoms according to these branching rules.

Using these dendrimers as reactive building blocks, one can assemble x(dendrimers), where x = small numbers, to produce "*nanoscopic compounds.*" Alternatively, by connecting large multiples of dendrimers by chemical bonding or non-bonding association, super- or supramolecular structures and architecture of micro-/macroscopic proportions not found in Nature can be produced.

We have grown dendrons simultaneously around a functionalized core such as ammonia (**Figure 3**), wherein the core multiplicity (N_c=3) and the branch cell multiplicity (N_b=2) give a tri-dendron poly(amidoamine) dendrimer family. These reiterations could be continued with approximately 1nm (10Å) increases in diameter/generation until a desired molecular size was reached. However, according to predictions made in 1983, a so-called "de Gennes dense packed" stage is reached at generation = 10 for this dendrimer family, wherein reaction rates decrease by an order of magnitude and catastrophic levels of defects are observed.[2,7] These syntheses were accomplished in our laboratory during the period 1979-1981, almost coincidental with the publication by Vögtle (1978)[3] of the first synthesis of lower molecular weight polyamine dendritic systems referred to as "cascade molecules" (**Figure 4**).

This synthetic approach to dendron and dendrimer synthesis is now referred to as the *divergent method.* The method emerged during the period 1978-1987 with key contributions coming from Denkewalter,[4] Newkome,[5a-c] and our laboratory.[6a-i] To date, successful divergent methods[7,15] have involved either (a) *in situ* construction of branch cells around an initiator core, or (b) coupling of preformed branch cells (derived from branch cell reagents) around such an attractor. A wide variety of dendrimer families have been synthesized by these divergent methods and include poly(amidoamines),[6a-i,8] poly(ethers),[6f] poly(siloxanes),[9a-c] poly(thioethers),[10] poly(amidoalcohol),[5a-c] poly-

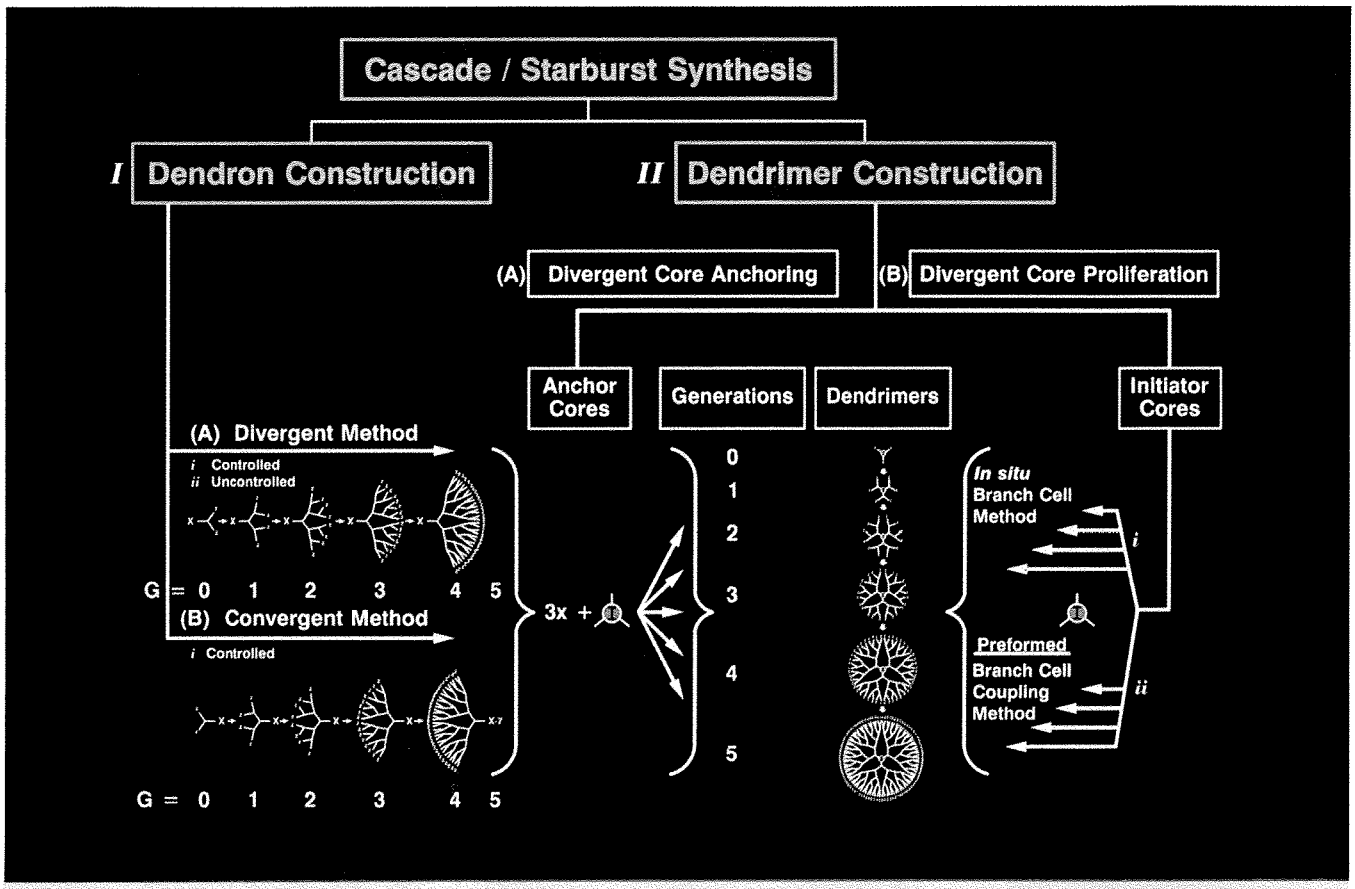

Figure 6. Overview of all known synthesis strategies to dendrimers.

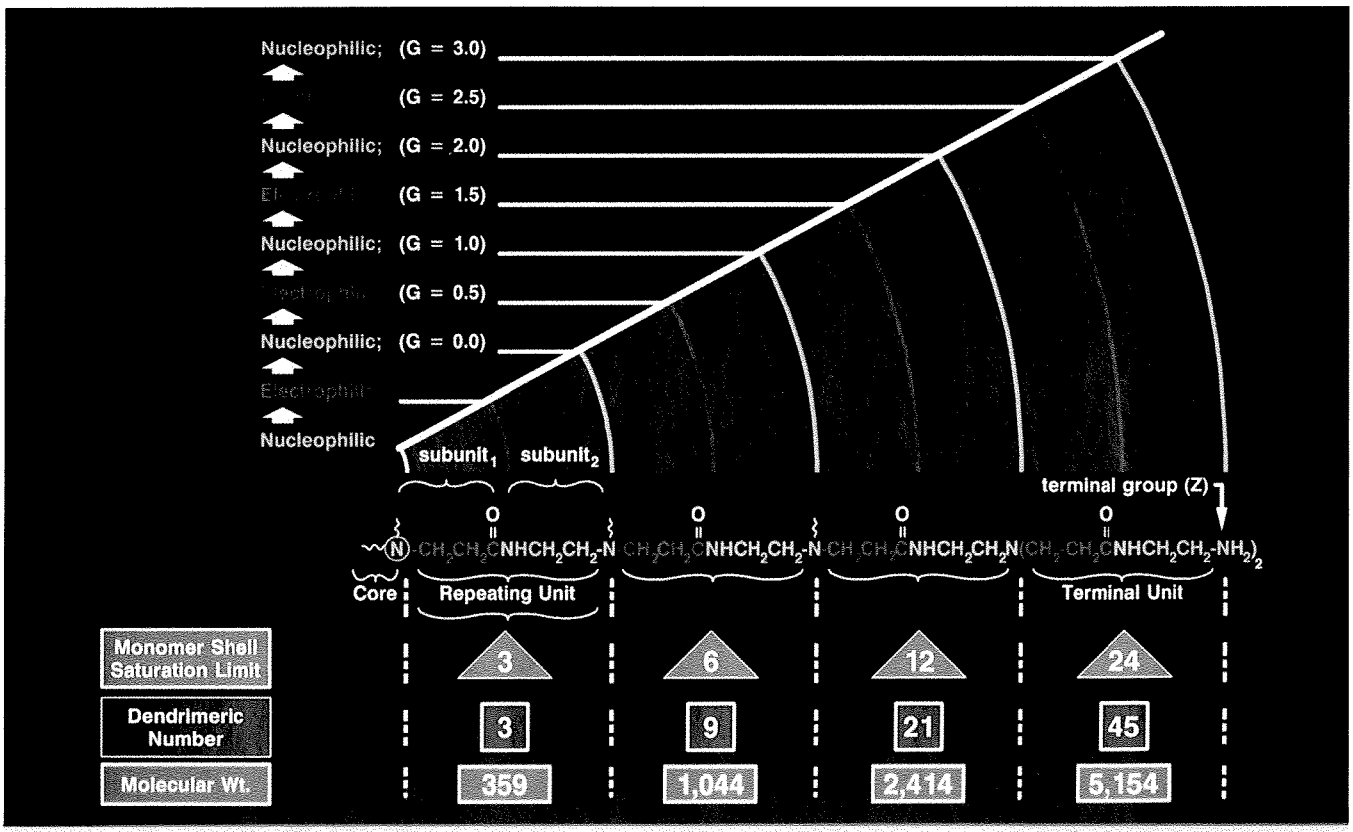

Figure 7. Cross-sectional view of PAMAM dendron (generation = 3.0) illustrating core, repeating unit, terminal units and electronic nature of the dendron surface as a function of generation.

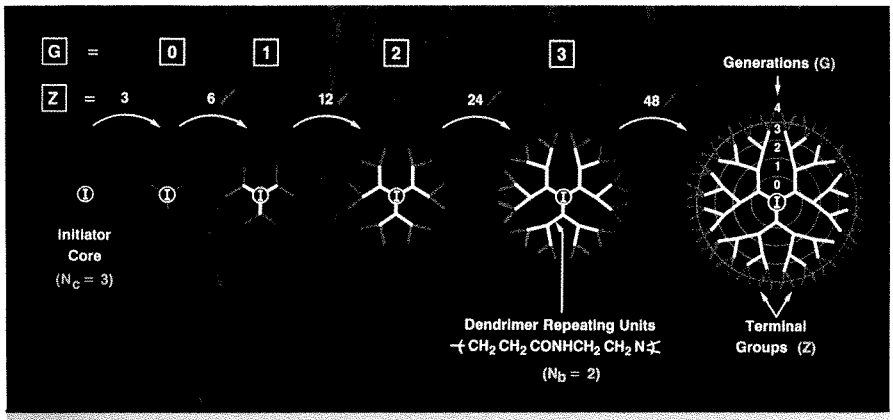

Figure 8. Time sequenced molecular level aufbau around ① to give a poly(amidoamine) (PAMAM) dendrimer; G = 4.0, N_c = 3, N_b = 2. Magic numbers [Z] indicate number of monomer units required to saturate monomer shell at the respective generation levels [G].

(amines),[7] poly(phosphonium),[11a-c] poly(alkanes),[12a-c] poly(nucleic acids),[13a-c, 27] and more recently poly(organometallic) types.[14a,b] Comprehensive reviews covering much of this chemistry have been published.[7,15-20]

An interesting alternative approach to dendron/dendrimer syntheses has been reported independently by Hawker and Fréchet[21a-c] and by Miller and Neenan.[22a,b] This method is referred to as the *convergent method* and involves two stages: a reiterative coupling of protected/deprotected branch cells to produce a focal point functionalized dendron (**Figure 5**), followed by divergent core anchoring to produce various multidendron dendrimers (as shown in the overview of dendron/dendrimer synthesis, **Figure 6**). This convergent dendron/divergent core anchoring method, as well as the divergent dendron/divergent core anchoring method developed in our laboratory,[24] has the unique advantage of allowing one to differentiate dendron sectors as a function of branch cell chemical composition as well as surface functionality. By these means, *directionality reactivity* can be designed into the surface features of the final dendrimer structure. This is an important feature when using these nanoscopic dendrimers as "atom analogues" for the construction of well defined "nanoscopic compounds." This issue will be discussed later.

In all dendrimer syntheses, a reiterative branch cell assembly scheme is necessary for developing concentric (shells) generations and advancing the Starburst (cascade) architecture to various levels. These covalent bond forming schemes are usually driven by alternating the reactivity of the dendrimer surface from generation to generation. In the case of the Starburst (cascade) poly(amidoamines), PAMAM's, the first step involves Michael addition of three moles of methyl acrylate to the nucleophilic ammonia core. This operation leads to an electrophilic carbomethoxy surface which is then allowed to react with an excess of ethylenediamine to give a nucleophilic surface at generation = 0 (**Figure 7**). Reiteration of these two steps first involves addition of six moles of methyl acrylate to give G = 0.5 (electrophilic, carbomethoxy surface), followed by amidation to a nucleophilic surface at G = 1.0.

As a result of these reiterative branch cell assembly operations, these constructions follow systematic branching rules (geometric progressions) if the assembly is near ideal. This allows one to predict the number of repeat units assembled (N_{RU}; degree of polymerization), the number of surface groups (valency, Z), and calculate dendrimer theoretical molecular weights as a function of initiator core multiplicity(N_c), branch cell multiplicity (N_b), and generations (G), according to the following relationships:

$$\bullet\ DP = \boxed{N_{RU}} = N_c\left[\frac{N_b^{G+1} - 1}{N_b - 1}\right]$$

$$\bullet\bullet\ \boxed{MW} = M_c + N_c\left[M_{RU}\left(\frac{N_b^{G+1} - 1}{N_b - 1}\right) + M_c N_b^{G+1}\right]$$

$$\bullet\bullet\bullet\ \boxed{\text{Valency}}\ (Z) = N_c N_b^{G}$$

For example, **Figure 8** illustrates the time sequenced molecular level aufbau of monomer units around an initiator core with a multiplicity (N_c = 3), designed to produce *in situ* branch cells with multiplicities of N_b = 2. This step-wise poly(amidoamine) dendrimer growth gives N_{RU} values of 3, 9, 21, 45, and 93 and Z values of 3, 6, 12, 24, and 48 for generations 0, 1, 2, 3, and 4, respectively. These Z values (magic numbers) represent the saturation limit wherein no additional monomer units can be added to that particular generation (shell).

Upon saturation of a particular generation, the dendrimer becomes essentially inert toward further reaction and reminds one of inert gas configurations which we are all familiar with at the atomic level. If one imagines monomer units as analogues of electrons and initiator cores as nuclei analogues architecturally, this "molecular level aufbau" becomes reminiscent of the electron filling events usually associated with atomic aufbau. The major differences are that electrons fill shells around atomic nuclei due to charge neutralization and occupy space around the nuclei as a function of quantum mechanical rules. In contrast, monomer units fill shells around initiator cores in dendrimers driven by chemical bond formation and occupy space around these attractors as a function of steric requirements and other considerations.

Since discovering that we could organize monomer units in precise numbers (geometric progression) as a function of concentric shells around a core (nucleus) and occupy three dimensional space in a very predictable fashion, the notion of mimicking atomic architecture at the molecular level became an intriguing concept. The initial two-dimensional projections of dendrimers (e.g., N_c = 3; N_b = 2) had this haunting similarity to Bohr atoms, yet we were well aware of the fact that these molecular level organizations of atoms could not holistically harbor the same quantum mechanical properties and implications that are associated with atoms. In fact, during this past decade, there were many critics who asked, "Why do we want to make such an outrageous comparison — such a stretch for this analogy?" I must confess there were a few moments when I did not have good answers for these comments.

However, as "hard data" accumulated on the nearly two dozen dendrimer families and one hundred surface modifications that have been documented in our laboratory and elsewhere, it has become more and more difficult to ignore the pervasive patterns and combining properties that picoscopic (1-6Å) atomic building blocks have in common with nanoscopic (10-1000Å) dendrimeric building blocks.

In systems that are constructed from discrete components under well defined rules, geometric or arithmetic patterns usually develop. These may involve various symmetries or repetitive structures, with or without scaling, or regular sequences of numbers describing quantities of the components. Being aesthetically pleasing, these "magic patterns" or "magic numbers" often serve both as memory aids and predictive tools for the understanding of ordered systems.

Such a system familiar to all organic chemists is the 4n+2 π-electron rule for aromaticity defined by Hückel. Without an understanding of molecular orbital theory, he derived this relationship by observing the patterns of molecular formulae of known aromatics. This relationship led to the discovery of additional aromatic materials with larger or smaller rings than the common benzenoid aromatics, such as [18]-annulene, or with charges that complete aromaticity, such as the cyclopentadienyl anion and the cycloheptatrienyl cation.

The sequence of electron orbital filling of the elements is another example of patterns resulting from the organization of discrete components according to well-defined rules, namely, the principles of quantum mechanics. It is well recognized that organization patterns for electrons in the elements of the periodic table are defined with such "magic numbers" as principal quantum numbers (i.e., n = 1, 2, 3, 4) associated with saturated electron shells leading to the stable inert gas configurations (i.e., 2, 8, 8, 18, 18, 32, etc.). As an operational definition, it was unnecessary to know the quantum mechanical origin of these magic numbers. Chemists of the 19th century simply recognized and used these patterns to predict reactivity, valency, combining masses, bonding directionality, and other elemental properties as described in **Table 1**. Theoretical explanation of the precise nature of these "atomic magic numbers" had to wait for the development of the quantum theory in the 1920-30's.

Noting the concentric monomer shell construction, the mathematical predictability of monomer shell filling, and the reactivity found in dendrimers, we were prompted to make a comparison with the electron shell filling and the reactivity of atomic entities. In order to analyze these similarities, one must think of the monomer units or branch cells in dendrimers as architectural analogues to electrons as they exist in atoms. In each case they occupy space in predictable numbers around an attractor (nucleus core) according to very well defined, but different mathematical rules. Electrons and monomer units have well defined lower and upper limits of proximity to their respective attractors. In the case of atoms, these relationships are derived from charge neutralization and are quantum mechanically driven; whereas with dendrimers, these relationships are Newtonian and are determined by bonding connectivity to the core and the space actually occupied by the atoms involved in the dendrimeric organization. With this in mind, it should be noted that another major difference between atomic and dendrimeric architecture is that most of the mass in atoms is located at the nucleus (core), whereas in

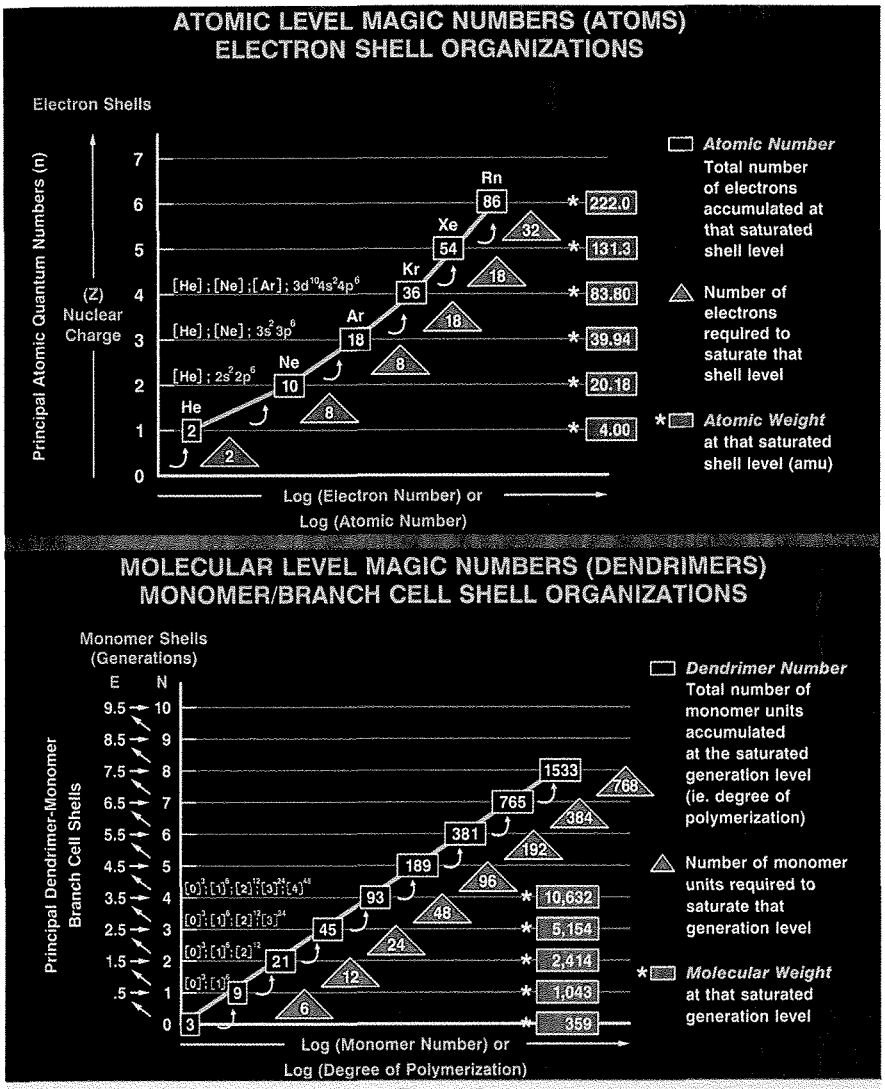

Figure 9

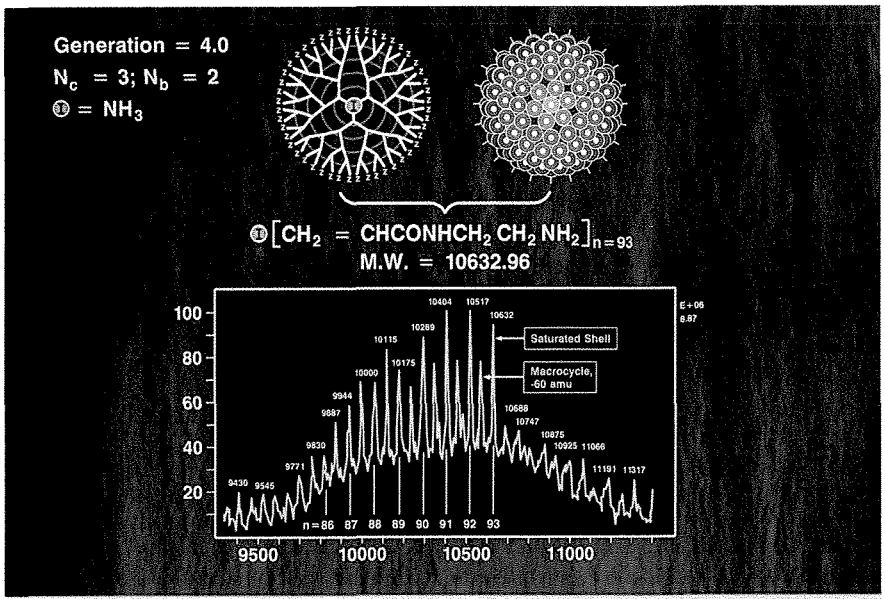

Figure 10. Electrospray Ionization Mass Spectrum (deconvoluted) of Starburst (PAMAM) dendrimer: generation = 4; NH_3 core; N_c = 3; N_b = 2; D.P. = 93 and theoretical MW = 10,633.

dendrimers it resides with the monomers in the functional shells (generations) surrounding the core.

Yet in spite of these differences, there still remain very rich parallelisms that cannot be ignored. Just as mathematical formalisms of quantum mechanics set the maximum number of electrons that may reside in a given shell, the geometric progressions that result from the influence of core (N_c) and branch multiplicities (N_b) in dendrimers determine the maximum number of monomer units or branch cells that may reside in a given dendrimer shell. Thus, atomic orbitals fill with electrons in the "magic number" sequence of 2, 8, 8, 18, 18, 32, etc.; whereas, the shells of dendrimers (N_c = 3, and N_b = 2) fill with repeat units in the sequence 3, 6, 12, 24, 48, etc. (**Figure 9**). It should be emphasized that, in each case, mathematics determine the maximum occupancy of respective shells. In atoms, partially filled shells have unfilled orbitals that will readily accept electrons, which become the basis for chemical reactivity involving ionization or bonding. A filled shell is seen as a satisfied valency which requires more extreme conditions to elicit further chemical reactivity.

Therefore, reactivity of the atomic (picoscopic/sub-nanoscopic) chemistry set is usually associated with the atomic building blocks preceding the inert gas configurations in the respective periods. The inert gas configurations possessing filled shells are generally not considered highly reactive. It has been recognized since Wöhler (1828) that elements in the second period (carbon in particular) may combine with first period elements (hydrogen), second period elements (oxygen, nitrogen, boron), and third period elements (sulfur, selenium, etc.) to produce nearly all the compounds we classify today as organic. Essentially all other combinations we refer to as inorganic. Without the benefit of quantum mechanics or electronic theory, 19th century chemists determined that an atom's reactivity was associated with electron occupancies residing between these "magic numbers." Furthermore, these elements combined with precise valencies to give compounds with predictable combining masses, as illustrated in **Figure 9**.

In a similar fashion, dendrimers possessing unfilled monomer shells are found to be very reactive. They may proceed to nanoscopic compounds by inter-dendrimer reactions or simply combine intra-molecularly to produce macrocyclic sites. In contrast, dendrimer species possessing saturated monomer shells commensurate with the "magic numbers" (**Figure 9**) are not reactive with each other or reagents possessing common surface functionality (i.e., either nucleophilic or electrophilic moieties, respectively).

Electrospray mass spectroscopy, gel electrophoresis, and capillary electrophoresis have proven very effective for monitoring the formation of saturated monomer shell species (perfect structure) and unfilled monomer shell species (defective structure) residing between the "magic number" species illustrated in **Figure 9**.

For example, if a shell in a dendrimer is not completely filled to the "magic number" at the half generation acrylate addition stage,

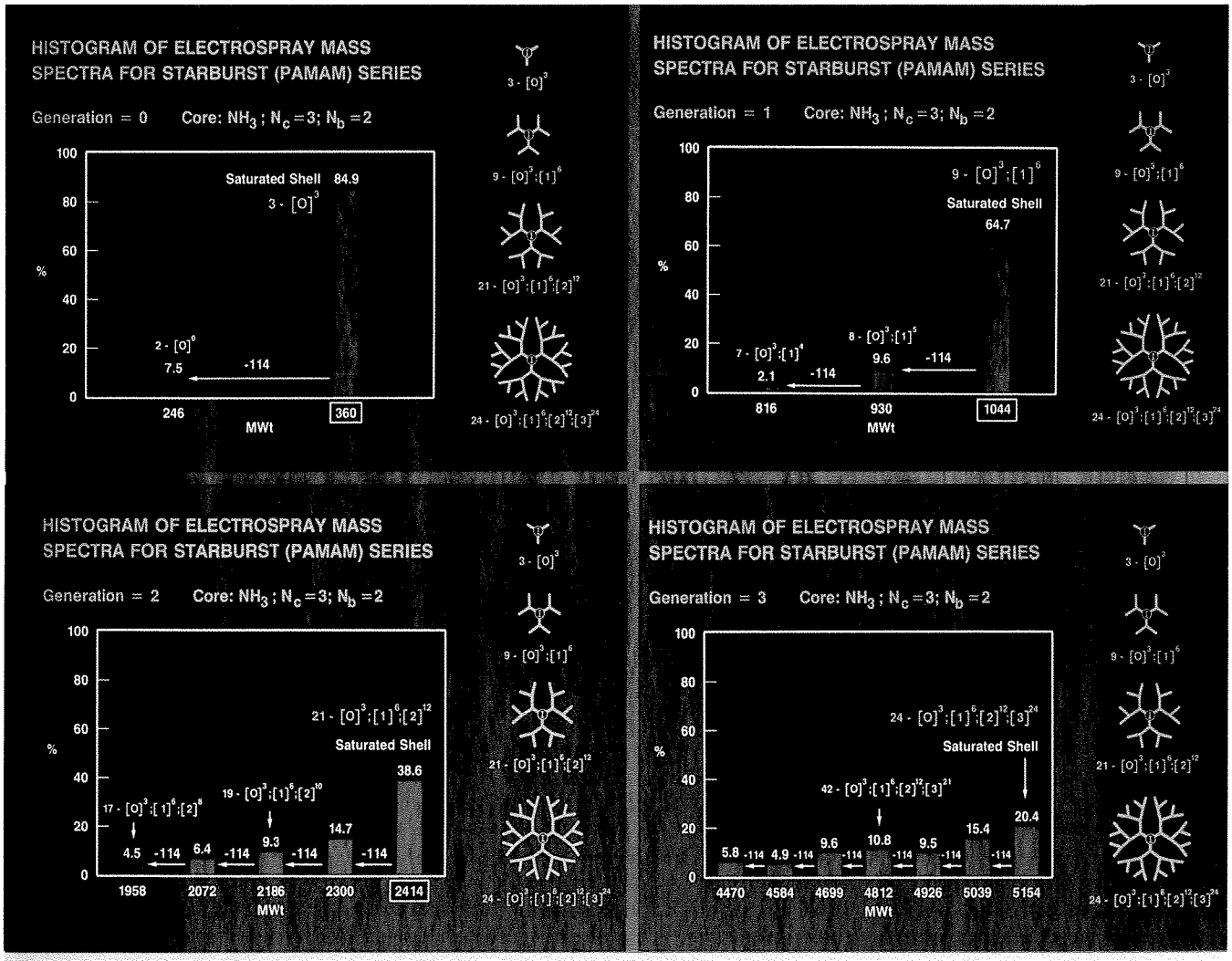

Figure 11. Histograms of electrospray mass spectra for Starburst (PAMAM) series; generation = 0, 1, 2, and 3.

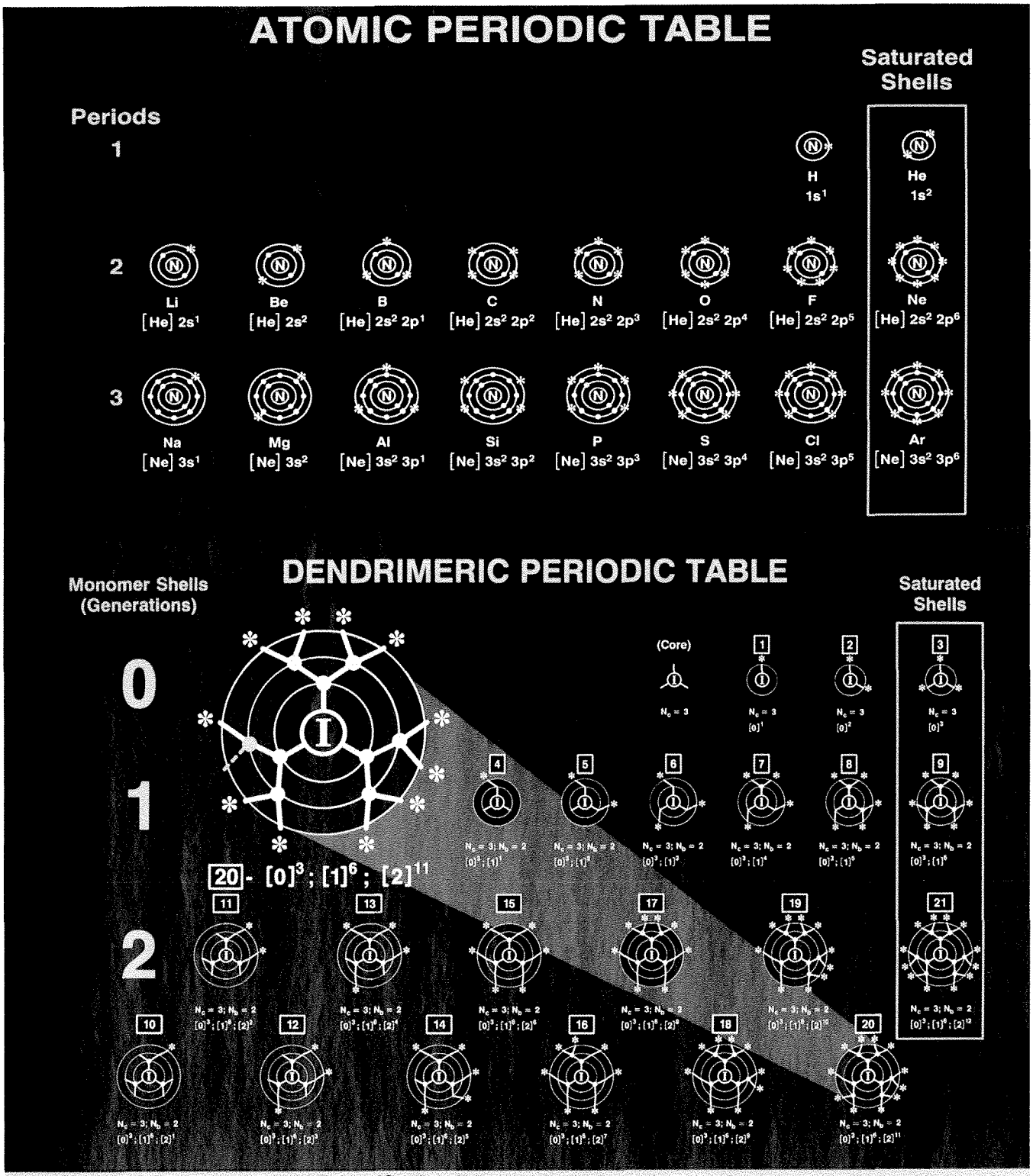

Figure 12. Atomic and Dendrimeric Periodic Tables

subsequent amidation with ethylenediamine leaves that monomer shell deficient by a corresponding number of 2-(aminoethyl)-acrylamide monomer units (i.e., 114 amu/monomer). Experimental evidence for the efficiency of shell filling in dendrimer synthesis has been found in the mass spectra of these materials. For example, the mass spectrum of a fourth generation poly(amidoamine) dendrimer has shown a narrow spread of masses (M_w/M_n = 1.0005) starting at the theoretical maximum (10,632 daltons) and decreasing through a series of masses corresponding to unfilled shell and macrocyclic modified structures with masses 10,632 - x(114) amu and [10,632 - x(114) - x(60) amu (where x = 1-7).[23] Comparison of the relative abundances of the various species (**Figure 10**) with a statistical model of dendrimer growth, including the filling of the vacancies described above, shows that each cycle of the dendrimer synthesis (**Figure 3**) incorporates the maximum possible number of repeat units. The x(114) mass unit deficiencies below the saturated dendrimer shell

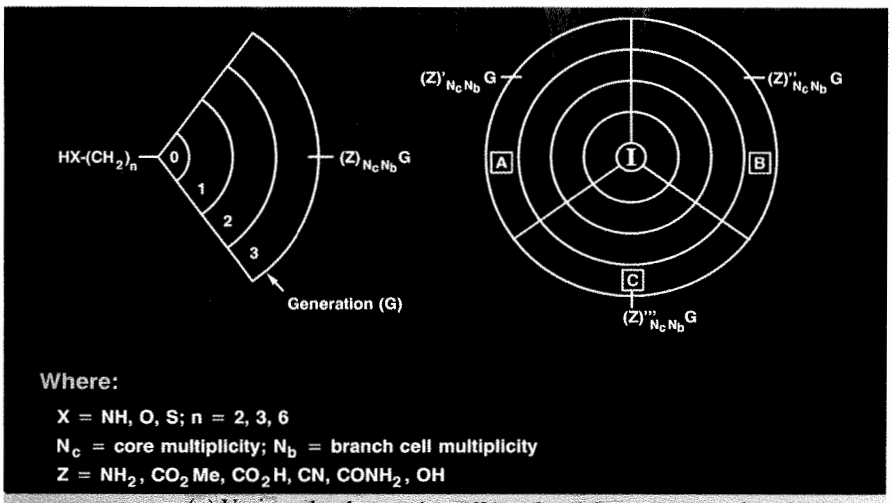

Figure 13. (a) Various dendrons with differentiated focal points and surfaces. (b) Tri-dendron dendrimer with differentiated surface sectors.

(a) n = 93; $[3]^3$; $[6]^6$; $[12]^{12}$; $[24]^{24}$; $[48]^{48}$ -(NH_2)

(b) n = 93; $[3]^3$; $[6]^6$; $[12]^{12}$; $[24]^{24}$; $[48]^{48}$ -(CO_2Me)

(c) n = 86-92; $[3]^3$; $[6]^6$; $[12]^{12}$; $[24]^{24}$; $[48]^{41-47}$ -(NH_2)

(d) n = 86-92; $[3]^3$; $[6]^6$; $[12]^{12}$; $[24]^{24}$; $[48]^{41-47}$ -(CO_2Me)

Nanoscopic dimers, trimers, clusters, etc.

Where: n = degree of polymerization as shown in Figure 10.

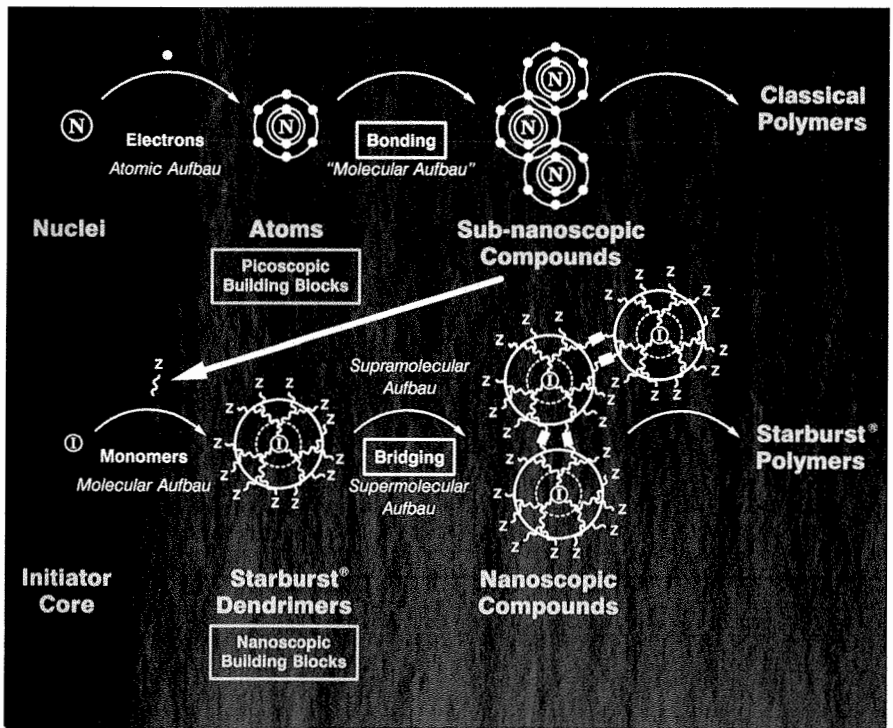

Figure 14. Analogies between nanoscopic dendrimer assemblies and the assembly of subatomic particles into picoscopic atoms and sub-nanoscopic molecules.

values leave unreacted secondary amine functions in the respective dendrimer shells and, in fact, mimic the deficiencies of electrons relative to saturated shell levels in atomic systems. In these reaction media, these species are reactive entities compared to the saturated "inert gas type configurations."

Therefore, by analogy to electronic configurations, we designate the perfect structure, generation = 4, saturated shell species with mass 10,632 and n = 93 as $[3]^3$; $[6]^6$; $[12]^{12}$; $[24]^{24}$; $[48]^{48}$ (N). The (N) denotes this outer shell is nucleophilic, whereas (E) would indicate the outer shell was electrophilic, thus placing it at the precursor generation = 3.5 (carbomethoxy stage in this dendrimer construction, **Figures 3** and **7**). The perfect structure (saturated shell mass)-60 and other x(60) deficient masses are believed to be due to intra-dendrimer amidation leading to macrocyclic sites. Other products believed to be derived from these unsaturated shell reactive species include dimer, trimer and higher covalently bridged clusters, identified and characterized by electrophoresis and mass spectroscopy. Possible reaction schemes leading to these products may involve the combinations and permutations illustrated at left (**a-d**).

Histograms (**Figure 11**) of electrospray mass spectra similar to **Figure 10** were obtained for generations 0, 1, 2, and 3 of the Starburst (cascade) PAMAM series. For simplicity, macrocyclic defects were deleted to show relative amounts of saturated shell and unfilled shell species that are present in typical samples after workup. Monomeric configurations are included for further reference to two-dimensional projections (**Figure 12**). In this illustration, one can compare the first three periods of the "atomic chemistry set" to the first three generations of the "dendrimeric chemistry set," noting the relationship of saturated shell and unfilled shell species in each case. Just as certain predictions about reactivity, morphological changes, dimensions, physical properties, etc. can be made by vertical and horizontal inspection of the atomic periodic table, so can one make similar predictions about such emerging properties within the dendrimeric periodic table.[7] It should be noted that although we can have only one atomic periodic table with a present limit of seven periods, the number of dendrimeric periodic tables will be determined by the number of different dendrimer families. The number of periods within each periodic table will be determined by the de Gennes dense packing stages for each dendrimer family.[2]

The only atomic feature remaining to be mimicked by the dendrimeric systems, according to **Table 1**, is the ability to control

directionality in bond formation. Considerable progress has been made in this area, both in Fréchet's laboratory[25,26] and in our laboratory.[7,24] In this regard, differentiated dendrons were synthesized via the *Divergent Controlled Method A* (**Figure 6**) using the reiterative scheme in **Figure 3**. While protecting the dendron focal group, various surface groups were introduced with regioselective reactions using standard methods. Deprotection of the focal group followed by anchoring to various cores produced dendrimers with differentiated sectors A, B or C, wherein Z' ≠ Z" ≠ Z"' or Z' = Z" ≠ Z"'. In addition, the interior structures of sectors A, B, and C could be varied by changing the monomer (branch cell) compositions or by anchoring dendrons at various generational levels (i.e., G = 1-4).

Whereas most chemical reactions between atoms to form compounds involve surface electrons, so it is also the case with the terminal monomer functionality in dendrimers. Over one hundred different stoichiometric reactions have been documented between dendrimer surfaces and sub-nanoscopic reagents.[15] In general, these reactions merely modify dendrimer surfaces and effect the dimensions of the dendrimers incrementally. However, when nucleophilic dendrimers are allowed to react with dendrimers possessing electrophilic surfaces, the resulting products are dramatically enhanced in dimensions (i.e., 1-100nm) and are referred to as *nanoscopic compounds, clusters, and polymers*. **Figure 13** illustrates this concept. Unlike classical picoscopic/sub-nanoscopic compounds derived from atomic building blocks, these nanoscopic *supermolecular compounds*, clusters, and assemblies are large enough to be observed directly by electron microscopy. In some instances suitable dendrimer surfaces have led to entirely new *supramolecular assemblies* never before observed in Nature.

In conclusion, what does all of this mean to the organic chemist? First, we have intentionally sought to follow the logic used by our 19th century predecessors while defining the "atomic chemistry set." Applying this logic to our present system, we believe the ability to precisely control mass, surface valency, and surface directionality in these dendrimer structures clearly validates their proposed roles as fundamental building blocks possessing architecture and function analogous to atoms, albeit, with nanoscopic dimensions (i.e., 1-100nm) (**Figure 14**). Secondly, with this new "nanoscopic chemistry set," it should be possible to systematically examine many of the classical issues of organic chemistry that have been the focal point of interest and analysis since the days of Wöhler. In the context of these higher dimensional building blocks, such new issues as: *nanoscopic steric effects, nanoscopic chirality, new nanoscopic architecture, nanoreactors, and nanoscopic recognition*, just to mention a few, will require further understanding. These studies will undoubtedly involve the evolution of new rules and concepts which may have a direct impact on our insights to the behavior and characteristics of the many biological nano-structures that are so intimately involved in creating and sustaining life.

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Starburst is a trademark of the Michigan Molecular Institute.

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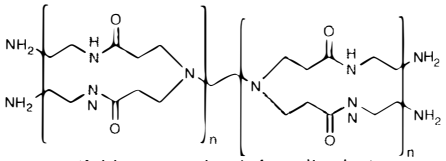


(Initiator core is ethylene diamine)

ABOUT THE AUTHOR

Dr. Tomalia received his B.A. in chemistry from the University of Michigan in 1961 and his Ph.D. in physical-organic chemistry from Michigan State University in 1968. His major activities from 1965 to 1975 were in the area of synthetic polymers; his discovery of the cationic polymerization of 2-oxazolines led to international industrial research awards for creative research in 1978 and 1986. Presently, he is Research Professor/Director of Nanoscopic Chemistry and Architecture at the Michigan Molecular Institute, and Scientific Advisor and Director of Dendritech, Inc.

Dr. Tomalia is a member of the American Chemical Society, Sigma Xi, and the American Association for the Advancement of Science. He has received numerous awards and honors including the Midland Section ACS Award for Outstanding Achievement and Promotion of the Chemical Sciences (1992), three Research and Development - 100 Awards (1978, 1986, 1991), NEDO (MITI) Global Project Award, Japan (1988), Sigma Xi Award (1987), Distinguished Lecture Awards, The Society of Polymer Science, Japan (1984). He holds 83 U.S. patents and has published more than 60 papers and chapters.

His research interests include molecular recognition, genealogically directed design/synthesis of precisely defined macromolecules, and controlled/targeted delivery systems.

Probing the Specificity of Synthetically Useful Enzymes[1]

J. Bryan Jones
Department of Chemistry
University of Toronto
Toronto, Ontario
Canada M5S 1A1

Enzymes are now widely accepted as useful catalysts for a broad range of organic syntheses, with their capacities for inducing asymmetric transformations being the most exploited.[2] However, despite the widespread uses of both enzymes and microorganisms in asymmetric synthesis, relatively little is known of the factors that determine the structural specificity and stereospecificity of enzymes.

In view of the increasingly broad spectrum of new and unnatural substrate structures that synthetically useful enzymes are being called on to accommodate, it is becoming more and more essential to delineate the enzyme-substrate interactions that regulate and control enzyme specificity. This will then permit the selection of enzymes that are best suited for any given chiral synthon preparation. It will also facilitate the development of active site models capable of accurately forecasting whether an enzyme will accept a new structure as a substrate, and of reliably predicting what the stereochemical outcome of the reaction will be. Knowledge of the factors determining specificity will also facilitate the rational tailoring of enzyme specificity by the site-directed mutagenesis techniques of protein engineering.

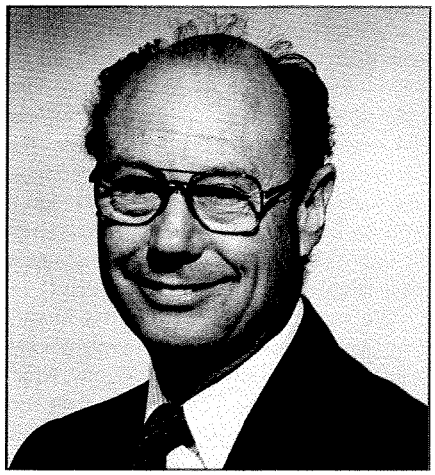
The classes of enzymes most widely applied are the hydrolases and the oxidoreductases. This paper will focus on probing the specificity of representative, synthetically useful members of both of these groups.

HYDROLASES

An Active Site Model for Pig Liver Esterase.

Hydrolases are currently the enzyme group receiving the most attention. Within this group, the esterase that has seen the most extensive utilization is pig liver esterase (PLE, EC 3.1.1.1).[3] PLE is a serine protease that catalyzes the hydrolysis of a broad range of carboxylic acid esters. It is capable of enantiomeric and enantiotopic group specificity. PLE has been widely employed for resolving racemic esters and for producing chiral acid-ester synthons from prochiral diester substrates. Despite its proven value in asymmetric synthesis, organic chemists became somewhat uneasy in their continued use of PLE because of some uncertainty about the fidelity of its stereospecificity.

For an enzyme to receive universal approval as a routine catalyst for synthetic applications, it is important that its stereospecificity be unwavering in its absolute configuration preferences from one substrate to another. In this regard, PLE posed a dilemma in that its stereochemistry appeared to be somewhat fickle towards certain substrate groups. For example, within the homologous series of monocyclic *meso* diesters **1**-**3**, the stereoselectivity of PLE hydrolysis reverses itself. For the cyclobutane diester **1**, the *S*-ester is hydrolyzed to give **4**, while for the cyclohexane substrate **3**, the



acid-ester **6** from *R*-ester cleavage is formed. Both **4** and **6** are enantiomerically pure. The cyclopentane substrate **2** represents the change-over point, with the acid-ester **5** being virtually racemic.[4a] This behaviour turned out to be general, with similar stereospecificity reversals being observed in other substrate series.[4b]

Initially we felt that the apparent variability of PLE's stereospecificity was due to the fact that the commercially available material was a melange of similar proteins, with some having *R*, and others *S*, stereospecificity preferences, and that separating the mixture into its components would provide us with enzymes of both *R*- and *S*-types. Separation of PLE into its components by

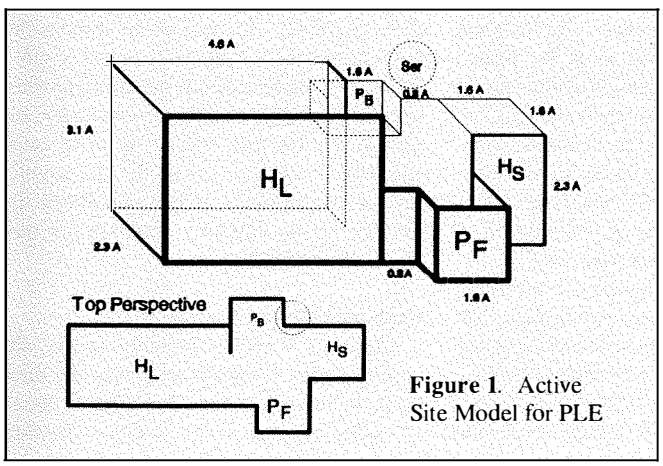
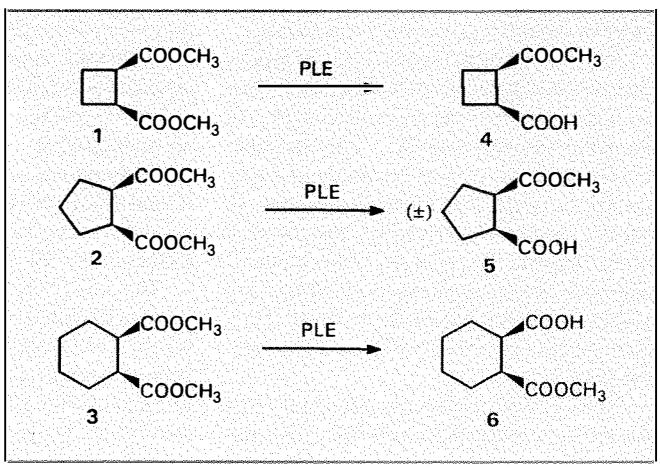


Figure 1. Active Site Model for PLE



isoelectric focussing gave six distinct fractions of different isoelectric points. However, when each of these fractions was employed to hydrolyze diesters such as **1-3**, the stereospecificity results were unchanged.[5] This demonstrated that, although commercial PLE is a mixture, it behaves as if it is a single species. Thus, the stereospecificity reversal patterns observed are a fundamental attribute of PLE's active site. This stimulated us to create an active site model that would permit all PLE's specificity characteristics to be interpreted.

As with other active site model proposals,[6] the lack of an X-ray structure dictated an empirical approach. We surveyed all the known literature substrates and, using computer graphics, overlaid them to determine the active site volumes and orientations that permitted each substrate to be accommodated satisfactorily in steric terms, and in accord with the experimentally observed stereospecificities. The picture that emerged was surprisingly simple[7] and is depicted in **Figure 1**.

The model is comprised of five binding loci. The boundaries of the binding pockets represent the physical restrictions which amino acids of the enzyme place on substrates binding in the active site and, with the exceptions noted below, substrates may not penetrate them. The catalytically essential region is that of the serine residue that initiates hydrolysis by its attack of the carbonyl group of the susceptible ester function. The binding regions controlling specificity are composed of four pockets, of which two are hydrophobic. Two others are more polar in character.

The two hydrophobic zones, which interact with the aliphatic or aromatic hydrocarbon portions of a substrate, are designated $H_{L(arge)}$ and $H_{S(mall)}$. The larger of the two, H_L, has a volume of approximately 33 Å^3, while the smaller H_S pocket has a volume of roughly 5.5 Å^3. Polar groups (such as hydroxyl, amino, carbonyl, nitro, etc.) are excluded from these areas. However, the hydrophobic pockets can accommodate less polar heteroatom functions (such as halogen, and ether or ketal oxygen atoms) if necessary.

The remaining two sectors accept groups that are more polar (P) or hydrophilic. They are located at the front (P_F) and back (P_B) of the active site, respectively. Unlike the other binding regions, the rear boundary of the P_B pocket is open, and hydrogen-bonding or similar groups may extend beyond the back of this region. The area above the model is also open and is completely accessible to any substrate moiety that needs to locate there. Such groups may extend in this direction without restriction.

This model reveals the structural basis for the stereospecificity reversals. For homologous series of substrates (such as **1-3**), small hydrophobic groups bind in H_S until they become too large to do so. At this point the substrate orientation must be turned around to place the larger hydrophobic group in the H_L pocket, where there is room to accommodate it. It is this "turning over" requirement that is responsible for the *S*-to-*R* (and vice versa) switches observed experimentally. The situation is exemplified in **Figure 2** for the **1-3** substrate series.[7]

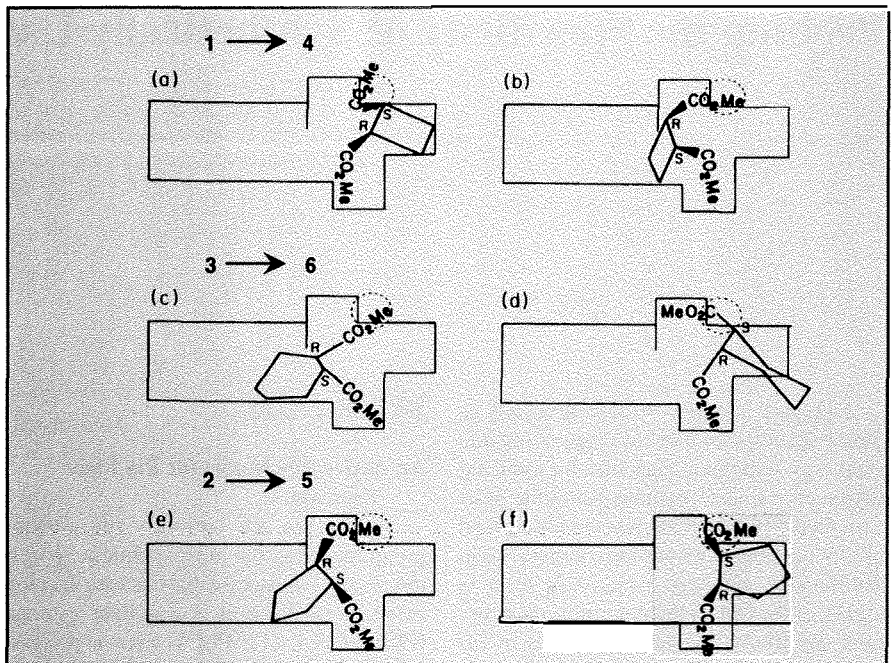


Figure 2. Top-perspective view of the active site model is used to illustrate the binding mode selections for diesters **1-3**. Hydrolysis of an ester group can only occur when it locates within the spherical locus of the catalytically active serine function. **Dimethyl cyclobutane-1,2-dicarboxylate (1).** The *S*-center ester hydrolysis orientation shown in (a) permits all substrate groups to be accommodated in the active site binding pockets, with the cyclobutane ring fitting cleanly into, and filling, the H_S pocket. The alternative binding mode required for hydrolysis of the *R*-center ester would place a portion of the cyclobutyl ring in the H_L pocket, (b). Since binding of hydrophobic groups must occur in the H_S rather than the H_L site if sterically possible, substrate-binding as in (a) is preferred, in accord with the observed formation of the 2*S*-acid product **4**. **Dimethyl cyclohexane-1,2-dicarboxylate (3).** The binding depicted in (c) shows the preferred ES-complex for hydrolysis of the *R*-center ester to the 2*R*-acid **6**, with the cyclohexane ring bound in the large hydrophobic pocket. Hydrolysis of the *S*-ester would require the orientation shown in (d). This is clearly precluded since the H_S pocket is clearly too small to accept the six-membered ring. **Dimethyl cyclopentane-1,2-dicarboxylate (2).** In this instance, both *R*- and *S*-center ester functions can be acceptably located in the serine sphere, as shown in **(e)** and **(f)** respectively. The cyclopentyl group is marginally too large for optimum fit into H_S, ensuing in a slight preference for hydrolysis via **(e)** that results in a 17% ee of the corresponding 2*R*-acid **5**.

The pocket sizes represented in the initial model (**Figure 1**) represent minimum volumes. Their actual sizes have subsequently been systematically probed with substrates of varying steric requirements.[8] The dimensions of H_S, P_B, and P_F have been confirmed as originally identified, but H_L's capacity for large groups turned out to be greater than first specified. Its maximum dimensions have now been established[9] as 6.1 x 4.6 x 3.1Å. To the best of our knowledge, when applied correctly,[7] this final model now permits all known PLE specificity to be satisfactorily interpreted. The model also enables the stereospecificity of PLE-catalyzed hydrolysis to be correctly forecast for new substrate structures.

Probing Enzyme Specificity

Because of their simplicity, active site specifications of the Figure 1-type are presently the models of choice of organic chemists using enzymes synthetically, even when

X-ray structures are available. However, they do not provide the understanding of enzyme specificity that in the long term is essential for identifying the range of substrate structures any synthetically useful enzyme can accept, and for selecting the most appropriate enzyme for transforming a given substrate structure into a desired synthon.

Accordingly, in order to gain insight into the factors that control and determine enzyme specificity, we have begun to probe the nature of enzyme-substrate interactions in a systematic manner. This involves studying only synthetically useful enzymes for which good X-ray structures are available, using graphics analyses to select substrate or inhibitor structures that address a particular specificity question most appropriately and, after kinetic studies on the selected structures, analyzing the experimental data with the aid of graphics and molecular modelling methods. The eventual goal of this approach is to maximize the synthetic potential of each enzyme.

However, no natural enzyme can be expected to handle the ever increasing range of substrate structures imposed by the chiral synthon demands of asymmetric synthesis. An important corollary of this strategy is thus its potential for identifying unfavourable amino acid residues at an active site that preclude conversion of a synthetically desirable substrate structure. This opens up the possibility of using the site-directed mutagenesis techniques of protein engineering to correct unsuitable amino acid positions, and eventually to tailor an enzyme's specificity so that any given structural requirement will be accommodated.

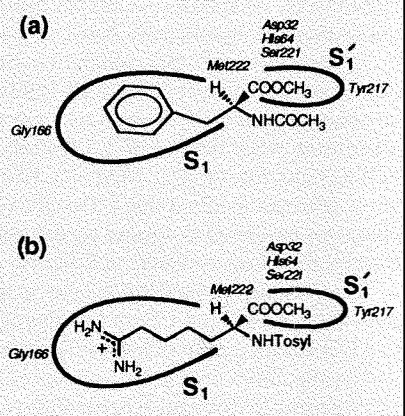


Figure 3. Schematic representation of the active site of subtilisin BPN'. In **(a)** the non-polar benzyl group of NAPME binds well in the hydrophobic S_1 pocket, which has a Gly166 located at its end. The S_1' region that accommodates the leaving group is not very large, being blocked off at the end by Tyr217. S_1' also contains the serine residue of the catalytically vital Ser221-His64-Asp32 serine protease triad. In **(b)** TAME is depicted in an orientation that site-directed mutagenesis of Gly166 to Asn or Ser should promote by creating a favourable hydrogen bonding environment for the guanidinium function, thereby ameliorating the inhospitality of the hydrophobic milieu of S_1 towards polar groups.

Probing the Structural Specificity of Hydrolases

The target enzymes selected as being representative of synthetically useful hydrolases were subtilisin BPN' (SBPN, EC 3.4.21.14), subtilisin Carlsberg (SC, EC 3.4.21.14), and α-chymotrypsin (CT, EC 3.4.21.1). These serine proteases favour ester substrates possessing hydrophobic groups that bind well into the S_1 active site pocket, as represented schematically in **Figure 3(a)** for the ES-complex formed by SBPN and its excellent substrate *N*-acetyl-L-phenylalanine methyl ester (NAPME). In this ES-complex, the hydrophobic benzyl group of NAPME fits nicely into the S_1 pocket, which in this case provides an appropriate environment as a result of the hydrophobic amino acid residues that form it. However, the unnatural substrates that SBPN may in the future be called on to hydrolyze could well include polar residues, towards which the natural S_1 environment would be hostile. We therefore decided to see if the S_1 pocket of the wild-type (WT) enzyme could be protein engineered to be more accommodating of polar groups.

N-Tosyl-L-arginine methyl ester (TAME) was selected as a substrate structure whose positively charged side chain was much more polar than that of NAPME. A poor interaction was anticipated between the substrate's guanidinium group and the hydrophobic S_1-environment of WT-SBPN if binding in the **Figure 3(b)** manner took place. We therefore explored the prospect of making the S_1 trough more receptive to TAME-like side chains by changing the Gly166 residue at the bottom of S_1 to amino acids, such as Asn or Ser, whose side chains are capable of hydrogen bonding to polar groups such as guanidinium.

The results obtained supported the validity of this strategy, with the effectiveness of TAME binding being increased by up to 2.4-fold. This is reflected by the improvement in K_m from 34 mM for WT-SBPN to 21 mM and 14 mM for the Gly166Asn and Gly166Ser mutants, respectively. The G166S enzyme was the most effective catalyst of this series for TAME hydrolysis, and graphics analysis indicated it to be the optimum 166 mutant for this substrate.[10]

The S_1' site is also an important region in terms of specificity control. It is the zone in which the leaving groups of amide and ester substrates locate prior to, and during, the acylation step. In SBPN, the S_1' site is not very large, having at its end a bulky hydroxybenzyl side chain of Tyr217 (**Figure 3**) with the potential to restrict its ability to accept large leaving groups. In such situations, replacement of the relatively large Tyr217 at the end of the S_1' region of SBPN by the smaller Leu residue (as present in subtilisin Carlsberg) should increase the space available for accommodating leaving groups. This was confirmed for the Tyr217Leu mutant, prepared by the Genencor International group,[11] using the tetrapeptide substrates **7a,b**.

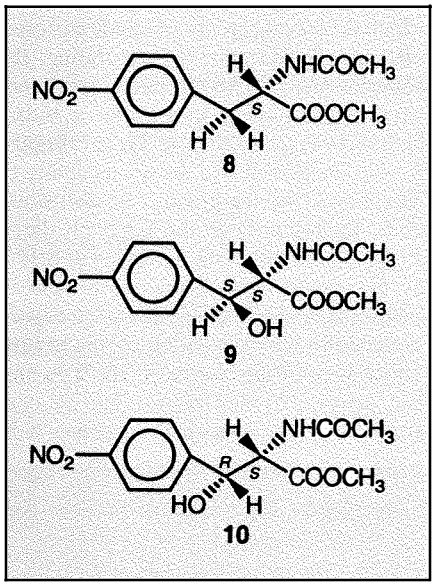
Succinyl-L-Ala-L-Ala-L-Pro-L-Phe-X

7a, X = *p*-nitroanilide
7b, X = thiobenzyl

For **7a**, the *p*-nitroanilide leaving group is still present in the rate-determining acylation step. The catalytic constant k_{cat} is increased by a factor of 5.6 when the volume of S_1' is increased by substituting the smaller Leu side chain for that of Tyr217 of the WT-SBPN. In contrast, for the ester substrates such as TAME or **7b**, for which leaving groups have already departed prior to the deacylation rate-determining step, the k_{cat} values for the Tyr217Leu and WT enzymes are virtually identical, as expected. The differences in size between the thiobenzyl and methoxy functions have no effect on the catalytic constant.[10]

Mutation of Met222 to Phe represents the converse situation in that the volume of S_1' is markedly reduced by the substitution of the benzyl side chain for that of methionine. The rate of hydrolysis of the amide substrate **7a**, with its medium-sized leaving moiety, is now reduced by this mutation. The k_{cat} value observed for hydrolysis of **7a** with the Met222Phe is 14-fold lower than for the WT-enzyme. Again as expected, because deacylation is rate-determining for esters, the k_{cat}'s for WT- and Met222Phe-catalyzed hydrolyses of TAME and **7b** are unaffected. While reducing catalytic effectiveness is seldom a worthwhile goal, in this case the combination of the sharply reduced amide hydrolysis efficiency and unchanged esterase activity of SBPN Met222Phe is of particular synthetic interest. This mutant should be an excellent catalyst for the preparation of

peptides by the coupling of amino acid ester components in that the ester-to-acyl enzyme steps will proceed normally, but little subsequent hydrolysis of the newly formed peptide bond can occur. The potential thus



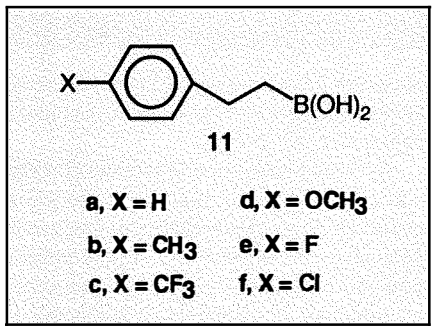
exists for practical peptide synthesis in aqueous solution.

Probing Hydrolase Stereospecificity

So far, with some exceptions, the use of enzymes in asymmetric synthesis has been largely confined to the creation of chiral synthons with only one stereocentre. However, the large chiral environments provided by enzymes have the capacity to discriminate and control many stereocentres concurrently, potentially providing access to any multiple-stereocentre combination desired in syntheses of chiral targets. We have begun to explore this prospect with the two-stereocentre substrates **9** and **10**, in which the natural L (*S*)-configuration preferred by esterases is maintained at the α-amino position, but with either an *S*- (**9**) or *R*- (**10**) configuration at C-3. These *p*-nitro compounds were selected because of their synthetic potential as chloramphenicol precursors.[12] The question was: will serine proteases such as subtilisin Carlsberg (SC) or α-chymotrypsin (CT) discriminate the second, C-3 centre?

The kinetic results, together with those on the *p*-nitrophenylalanyl parent **8** of **9** and **10**, showed that the replacement of either the pro-*R* or pro-*S* C-3-H by an OH-group caused a $>10^4$-fold reduction in the hydrolysis rates, as reflected by the specificity constants, k_{cat}/K_M, for both SC- and CT-catalyzed reactions. While the rates of SC and CT hydrolyses of **9** and **10** were low, they remained preparatively viable. However, for SC, the hydrolysis rates of **9** and **10** were about the same, being 126 and 360 $M^{-1}s^{-1}$, respectively. This shows that the enzyme did not distinguish significantly between a C-3 *S*- or *R*-centre and that separation of a diastereomeric mixture of **9** and **10** could not be achieved using SC hydrolysis. On the other hand, while the rate of CT hydrolysis of **9** was also low (k_{cat}/K_M 70 $M^{-1}s^{-1}$), **10** was not a substrate at all so that CT could very effectively be applied to separate the individual diastereomers from a mixture of **9** and **10**.

The reasons for the dramatic rate reductions for both SC and CT on introducing a C-3 OH substituent of either configuration, and for the differences in the abilities of the two enzymes to distinguish between the two C-3 configurations, were revealed by molecular modelling. The acyl enzyme intermediates derived from the *p*-nitrophenylalanyl parent compound **8** for each of SC and CT were minimized by molecular mechanics and molecular dynamics using the BioSym *Discover* program. For the SC-complex, the C-3 hydrogens of **8** were located in the bottom of the S_1 pocket in environments of about equal steric constraints that are large enough to accept either an *S*- or *R*-centre hydroxyl group, but not without engendering some unfavourable steric interactions (specifically with Ala152 and Asn155 for an *S*-OH and with Ser 125 for an *R*-OH). Thus the consequences of replacing either the C-3 pro-*S* or pro-*R* hydrogens by hydroxyl, as in **9** or **10** respectively, both result in reduced hydrolysis rates, and to approximately the same degree. On the other hand, while the situation for the pro-*S* C-3-H of **9** in the CT-complex parallels closely that of the SC situation, the pro-*R* C-3-H of **10** is already in van der Waals contact with Cys191, Met192, Gly193, and Asp194, and this site cannot accommodate anything bigger than hydrogen. Thus, when the pro-*R* C-3-H is replaced by OH, as in **10**, formation of an acyl enzyme is precluded and the *S*,*R*-diastereomer **10** is a non-substrate. In fact, **10** does not bind at all to CT, as demonstrated by its ineffectiveness (K_I > 150 mM) as a competitive inhibitor.



Exploiting Electrostatic Contributions to Binding

When the electrostatic potential surfaces of SC and CT are calculated using the BioSym *Delphi* program, the patterns for the two enzymes are very different. We wondered if such electrostatic differences could be exploited to improve the strength or selectivity of binding to enzymes for appropriately designed substrates or inhibitors. For example, the calculations showed that, at the bottom of the S_1 pocket of SC, there was a region of positive potential which could contribute to increased binding strength of a substrate or inhibitor possessing a group of negative potential capable of interacting with this positive enzyme locus. The initial evalua-

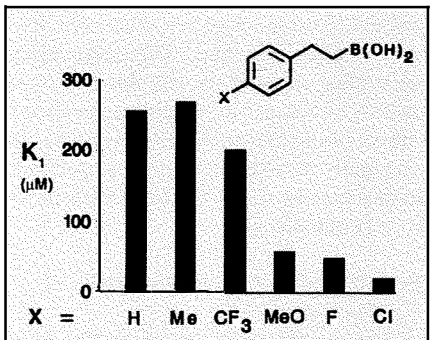


Figure 5. *Para*-substituent effects on phenylboronic acid inhibitors of Subtilisin Carlsberg.

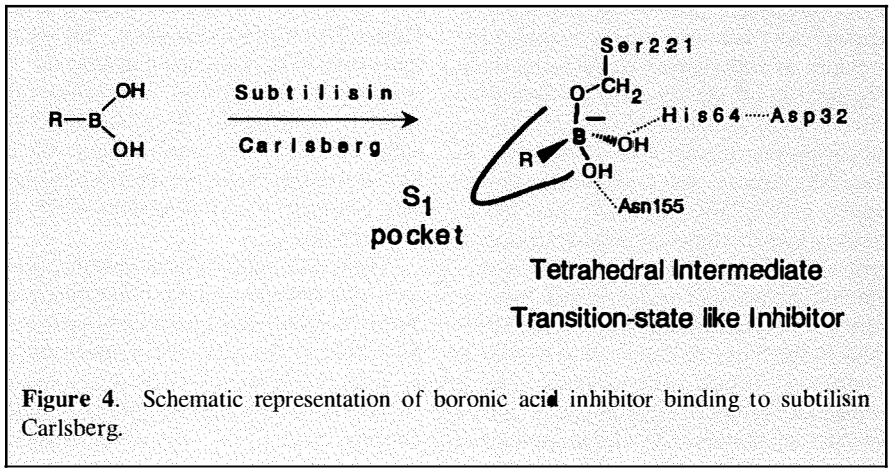
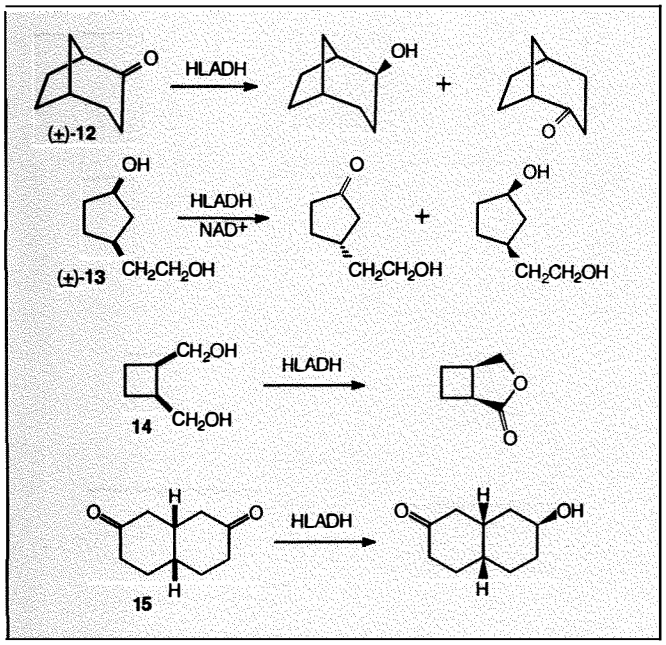


Figure 4. Schematic representation of boronic acid inhibitor binding to subtilisin Carlsberg.



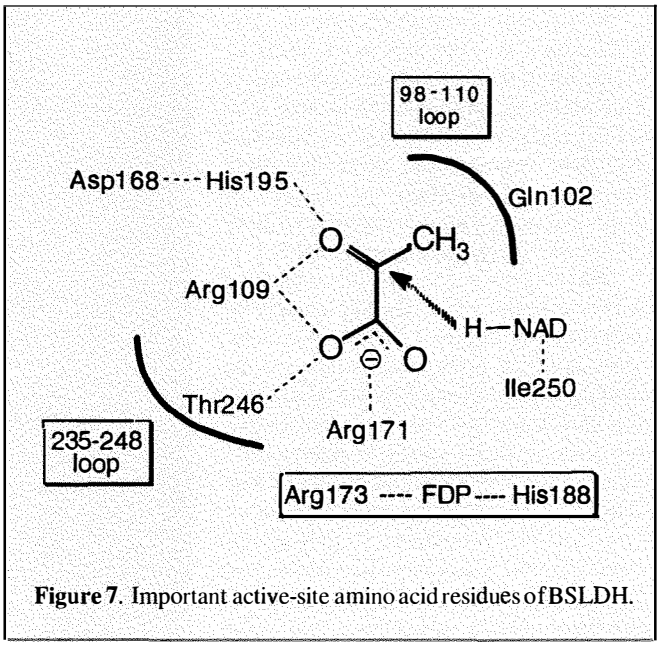


Figure 7. Important active-site amino acid residues of BSLDH.

tions of this concept were carried out with the boronic acid inhibitors **11**. When bound to serine proteases, boronic acids of this type are transition state inhibitors that form EI-complexes of the type represented in **Figure 4**, in which the aromatic group binds in S_1.

In such orientations, the *para*-substituents should then project into the positive region at the base of S_1. The results observed with the series of inhibitors **11a-f** support this concept (**Figure 5**) with the strength of binding increasing, as reflected by the decreasing K_I values, as the negative potential character of the *para*-substituent increases.[13] For the *p*-chloro-inhibitor **11f**, with the most negative *para*-group and thus the greatest electrostatic attraction with the base of S_1, binding is 13.5-fold stronger than for the parent compound **11a**. The possibility that the observed trends simply reflected desolvation energy differences between the inhibitors on forming the respective EI-complexes was excluded by calculations and from literature tabulations of experimental solvation data.

OXIDOREDUCTASES

Oxidoreductases, such as horse liver alcohol dehydrogenase (HLADH), have proven of considerable value in asymmetric synthesis. Illustrative examples of HLADH use include resolution, combined with diastereotopic face selectivity, of racemic ketones such as **12**, and additionally of regioselectivity, as in the oxidation of **13**, and of the enantiotopic group and face distinctions involved in the conversions of **14** and **15**.[2c]

With the potential of a broad specificity oxidoreductase like HLADH well documented, we decided to examine an enzyme of this group with narrower specificity with the intent of probing the factors determining structural and stereospecificity. The oxidoreductase selected was the L-lactate dehydrogenase of *Bacillus stearothermophilus* (BSLDH). BSLDH is an excellent candidate for such exploratory studies since it is a very stable, thermophilic enzyme of known protein sequence. Its properties have already been the subject of several studies.[14] Also, its gene has been cloned and the protein very efficiently overexpressed, thereby enabling large quantities of BSLDH to be produced inexpensively from small fermentation volumes.[15] Furthermore, the feasibility of altering the specificity of the native enzyme by site-directed mutagenesis of key active-site amino acid residues has been established.[14]

On the Structural Specificity of BSLDH

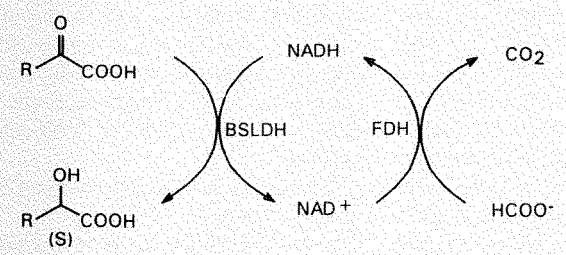
BSLDH is an NAD/H-coenzyme dependent, fructose-1,6-diphosphate (FDP) activated enzyme whose *in vivo* function is to catalyze pyruvate ⇌ L-lactate oxido-reductions of the type:

RCOCOOH + NADH + H^+ ⇌

16

RCH(OH)COOH + NAD

17



R	Rel. Rate	%Yield	% ee
CH_3	++++		
CH_3CH_2	+++	88	>99
$CH_3(CH_2)_2$	+	89	>99
H_3C, CH_3	<+	88	>99
cyclopropyl	+	89	>99
CH_2-phenyl	++	90	>99

Figure 6. Preparative-scale BSLDH-catalyzed reductions.

While strongly favouring pyruvate (**16**, R=Me) as a substrate due to its small R-group, BSLDH will accept a broad range of α-ketoacids as substrates, albeit with substantial rate penalties for large or branched R-groups. Nevertheless, preparative-scale reactions to produce a range of enantiomerically pure L-α-hydroxyacids **17** are feasible, as illustrated in **Figure 6**.[14]

Much is known about the structure of the active site of BSLDH.[16] The key features are represented in **Figure 7**. The narrow substrate specificity is due, at least in part, to the fact that the 98-110 and 235-248 loops close over the ketoacid substrate during the formation of the active ES-complex, thereby leaving only a restricted volume for the R-side chains. Graphics analyses revealed that, in the productive ES-complex, large R-groups would engender a bad steric interaction with the loop residue Gln102. They also indicated that these adverse interactions with bulky (especially branched-chain, substrates) could be diminished by reducing the size of the 102-position amino acid side chain.

The validity of this analysis was tested by using site-directed mutagenesis to replace Gln102 by Asn, an amino acid of similar hydrophobicity but having one fewer CH_2-group in its side chain (thus providing more room for bigger side chains). The results obtained supported the application of such protein engineering approaches to expand the structural specificity of enzymes, with the Gln102Asn mutant now being a better enzyme than WT-BSLDH for substrates such as **16**, with large R-groups [R = $CH_3(CH_2)_{2\text{-}5}$-, $(CH_3)_2CH$-, $(CH_3)_2CHCH_2$-, $CH_3CH_2CH(CH_3)$-, and C_6H_5-].[17]

Probing BSLDH Stereospecificity

The stereospecificity of enzymes is their most important property for asymmetric synthetic applications. However, as noted already, little is known about the factors that determine and control enzyme stereospecificity. With L-LDH's being so committed to *Re*-face carbonyl attack to give (*S*)-α-hydroxyacids, BSLDH provides an excellent instrument for beginning to identify and understand important stereospecificity determinants, initially of oxidoreductases, but eventually of all enzymes.

Among the methods of probing the factors controlling enzyme stereospecificity, evaluating how effectively an enzyme resists attempts to change this capability is potentially one of the most powerful. The natural L-stereospecificity of BSLDH is determined by the orientation of 2-ketoacids, such as pyruvate (**16**, R = CH_3), in the ES-complex such that the hydride-equivalent from NADH is delivered to the *Re*-face of the carbonyl group. This is depicted schematically in **Figure 8(a)**. An important interaction helping to maintain this pyruvate orientation is that between the substrate's COO^- and Arg171.

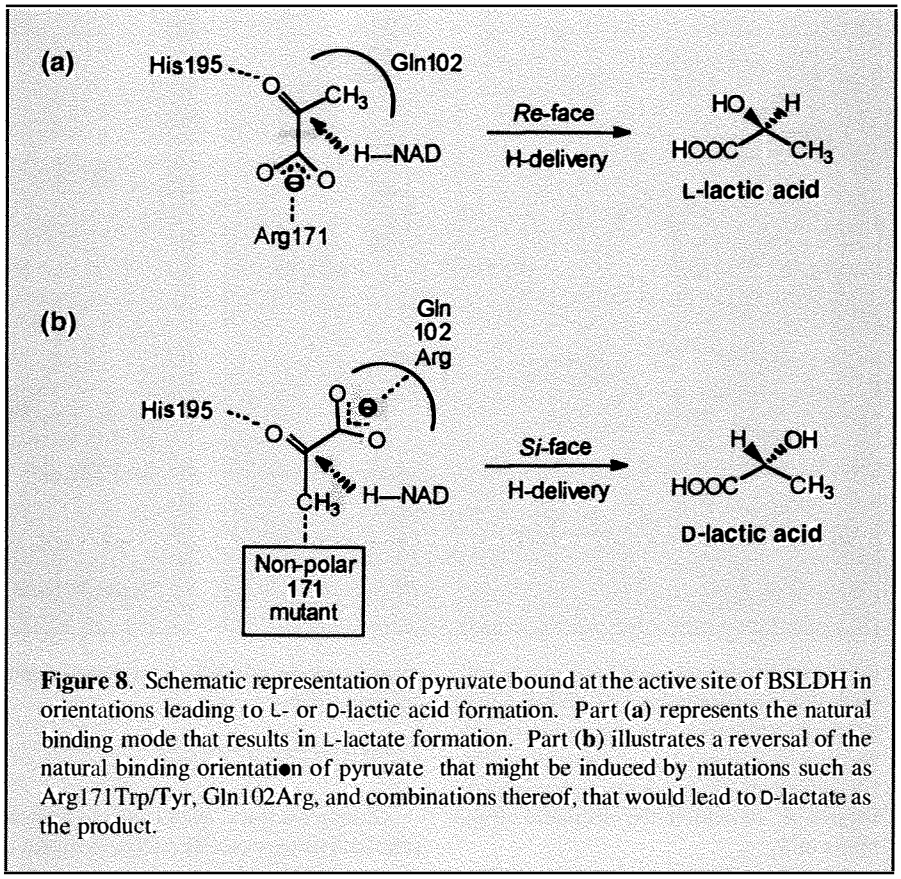


Figure 8. Schematic representation of pyruvate bound at the active site of BSLDH in orientations leading to L- or D-lactic acid formation. Part (**a**) represents the natural binding mode that results in L-lactate formation. Part (**b**) illustrates a reversal of the natural binding orientation of pyruvate that might be induced by mutations such as Arg171Trp/Tyr, Gln102Arg, and combinations thereof, that would lead to D-lactate as the product.

As one measure of BSLDH's commitment to the L-pathway, we elected to evaluate its resistance to being induced to catalyze D-lactate formation. Reduction of pyruvate to D-lactate requires delivery of the NADH-"hydride" to the *Si*-face of pyruvate. One of the ways that can be envisaged of inducing this *Si*-face attack would be via an ES complex in which the orientation of pyruvate was reversed, as illustrated in **Figure 8(b)**.

Towards this goal, Arg171 was replaced by Tyr and Trp. Despite the elimination of the key Arg171-COO^--binding orientation, the Arg171Trp/Tyr mutants were still completely L-stereoselective.[18] In a subsequent study, the WT-Arg171 was retained but a second COO^--binding Arg residue was introduced in place of Gln102, thereby providing a competitive possibility between the **Figure 8(a)** and **8(b)** pyruvate orientations and the prospect of formation of racemic products. As expected,[19] the best substrates for this mutant were dicarboxylic α-ketoacids that concurrently exploit both the Arg171 and 102Arg binding sites. However, once again, this Gln102Arg mutation did not disturb the L-proclivity of BSLDH in any preparatively significant way, with only L-α-hydroxyacids being produced in preparative scale reactions. Nevertheless, this mutant provided the first indication that it was possible to disturb the natural L-stereospecificity of BSLDH in that, in contrast to the WT-situation (for which oxidation of L-malate was much faster than for the D-enantiomer), the rates of oxidation of L- and D-malate for the Gln102Arg mutant had become approximately equal.[14]

In more recent experiments, the 171Trp/Tyr and 102Arg mutations were combined in order to eliminate any prospect of the natural Arg171-COO^- interaction and at the same time to provide the opportunity for a reversal of pyruvate orientation via 102Arg-COO^--binding. Furthermore, the formation of the natural, Arg171-directed, **Figure 8(a)** type complex is clearly impossible for the Arg171Trp/Tyr;Gln102Arg double mutants. Despite the binding constraints designed into these double mutants, their fidelity with respect to L-stereospecificity remained dominant, with preparative- scale reductions of α-ketoacids affording L-hydroxyacids, within the limits of detection of the NMR analytical methods used.[20]

The question of how the above BSLDH-mutants maintain their control of L-stereospecificity is thus an intriguing one. The X-ray structure of the 171Trp/102Arg/97Gly triple mutant that is now being refined should provide new insights into these questions. Already it is clear that Arg171Trp replace-

ment is not wholly benign and that the 171Trp side chain shifts out of the active site.[21]

Because none of the 171 or 102 mutations disturbs the natural stereospecificity of BSLDH, it is evident that there must be fail-safe, L-directing interactions that take over when Arg171 is not present. One such fail-safe candidate is Thr246. Other X-ray data[16] indicate that the Thr246 side chain is close enough to the substrate carboxylate function for effective hydrogen bonding (**Figure 7**), although explaining how such a secondary, hydrogen-bonding interaction could override carboxylate binding to 102Arg-containing mutants in the productive ES-complexes remains a quandary. This is particularly true for small substrates such as pyruvate for which, other than the carbonyl group being reduced, the carboxylate group is the only function capable of binding strongly to the enzyme.

We have started to investigate the role of Thr246 by studying the catalytic properties of several 246 mutants, including Thr246Ala/Val/Leu/Ser. Although none of the mutants was as effective an oxidoreductase as WT-BSLDH, they did exhibit some interesting catalytic properties with respect to substrate inhibition.

Substrate inhibition is a common phenomenon in enzyme-catalyzed reactions and can be a major problem in preparative-scale applications because of the very high substrate concentrations that are employed in large-scale transformations. In fact, substrate inhibition can be very serious for BSLDH, particularly with pyruvate as substrate, and can result in reductions being brought to a virtual standstill. However, when no hydroxyl group is present in the 246 side chain, as for Thr246Val/Ala, substrate inhibition is virtually eliminated. This is shown by the constant V_{max} values at high [S] for these two mutants (**Figure 9**). Substrate inhibition of BSLDH arises from the strong complexation of pyruvate with the E.NAD$^+$ complex in the catalytic cycle. This does not occur with Thr246Val/Ala because pyruvate no longer binds effectively to E.NAD$^+$, as reflected by the dramatic increases in apparent K_I for pyruvate for this step for these two mutants (**Figure 10**).[22]

The effect is especially evident for the smaller 246Ala side chain where, with a K_I(app) of almost 800 mM, pyruvate is clearly not binding at all to E.NAD$^+$. Also, for WT-BSLDH, the rate determining step ($k = 250\ s^{-1}$)[15] for pyruvate reduction is closure of the 98-110 loop. Mutation of Thr246 to Ala slows the loop closure rate such that the hydride transfer process becomes at least partially rate limiting, as reflected by the k_H/k_D kinetic isotope effect of 2.4.

Although the Arg171 and Gln102 mutations did not disturb the stereospecificity of the enzyme, there were serendipitous benefits to these changes. The thermal stability of BSLDH was further increased, dramatically so for the Arg171Tyr enzyme, for which the T_m(app) was increased by 9.4°C over that of WT-BSLDH. The greatest increase in T_m(app) was 10.7°C for Arg171Tyr, Gln102Arg.

At high ionic strength, even higher thermal stabilization was manifest. Notably, in the presence of 100 mM K_2SO_4, the Arg171Tyr, Gln102Arg mutant retains 30% activity even after heating for 30 minutes at 100°C, conditions under which the already moderately thermostable WT-enzyme is completely inactivated in less than 2 minutes.[21] This has considerable potential synthetic benefits since preparative-scale BSLDH-catalyzed reactions at temperatures of up to 100°C can now be contemplated, subject to NAD-coenzyme survival for sufficient time.

The reason for the increased thermal stabilizations on replacing the Arg171 by hydrophobic residues such as Trp seems due to more favourable hydrophobic subunit contacts. This view is supported by preliminary X-ray structural evidence for a mutant BSLDH containing tryptophan in 171-position. In this structure, the 171W-side chain is rotated around the C_a—C_b-bond, relative to the wild-type arginine side chain. The mutant indolyl-group is thus located completely outside of the active site, and it projects into the space occupied by the other subunit in the BSLDH-dimer in a manner that increases the hydrophobic subunit interface area.[23]

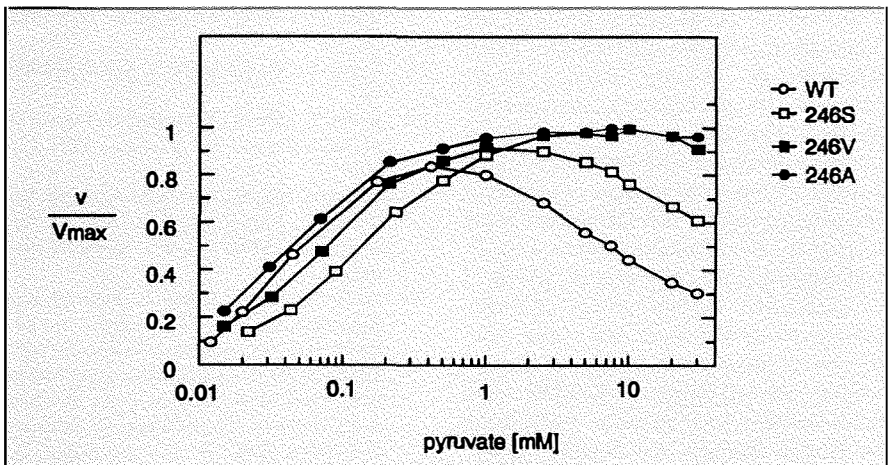


Figure 9. Elimination of substrate inhibition by pyruvate by T246V/A mutations.

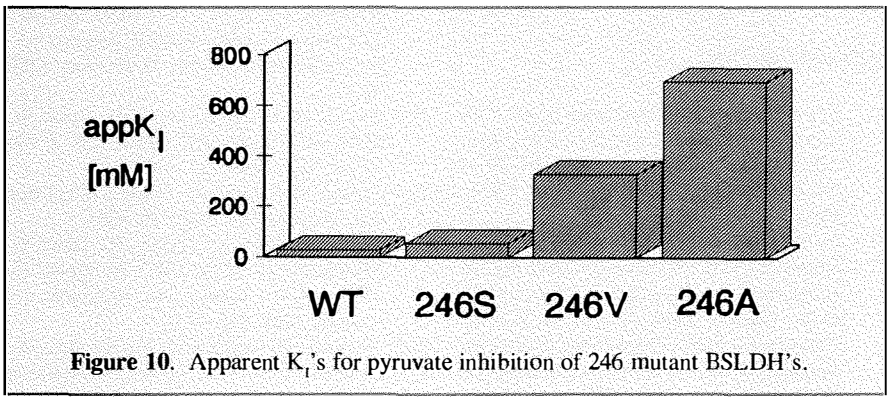


Figure 10. Apparent K_I's for pyruvate inhibition of 246 mutant BSLDH's.

While the data presented in this lecture represent a beginning towards identifying the factors that determine enzyme specificity, it is evident that much needs to be done before enzymes and substrates can be tailored with confidence to permit optimum results in all asymmetric synthetic applications, and to maximize their performance and stability as catalysts. However, in view of the tremendous progress now being made in protein research, many exciting new insights into enzyme catalysis and specificity can be anticipated in the next few years.

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ABOUT THE AUTHOR

Professor Jones was born in North Wales and obtained his Ph.D. in alkaloid chemistry with A.R. Pinder at the University College of Wales, Cardiff. He then did postdoctoral work, and a D.Phil., at Oxford on polyacetylene synthesis with Sir Ewart Jones. After further postdoctoral studies at MIT with A.C. Cope, and then at Caltech where he first started on enzymes with C. Niemann, he returned to Oxford as ICI Fellow. In 1963 he joined the University of Toronto where he has been Professor of Chemistry since 1974. He is a Fellow of the Royal Society of Canada and of the Chemical Institute of Canada, and has been a Killam Fellow of the Canada Council. He has received the Perlman Award of the American Chemical Society, the Charmian Medal of the Royal Society of Chemistry, and the Labatt Award, and most recently the Bader Award, of the Canadian Society for Chemistry.

Professor Jones has been a pioneer in the application of enzymes as practical catalysts for organic synthesis. The results obtained by his research group have demonstrated the unique benefits that the use of enzymes can bring to the production of chiral synthons of broad applicability, including key intermediates for antibiotics, insecticides, and pheromones. In contrast to the almost complete absence of synthetic exploitations of enzymes when he began his work, the field is now a large, well established, and dynamic one, with multiple applications in academic and industrial research and processes. More recently, he has begun to address the next frontier of the field — to identify the factors determining and controlling the catalytic activities and specificities of the enzymes of asymetric synthetic value, using molecular graphics, molecular dynamics, and site-specific mutagenesis approaches. The same strategy is being applied in designing and synthesizing compounds that can act as drugs by inhibiting medicinally important enzymes.

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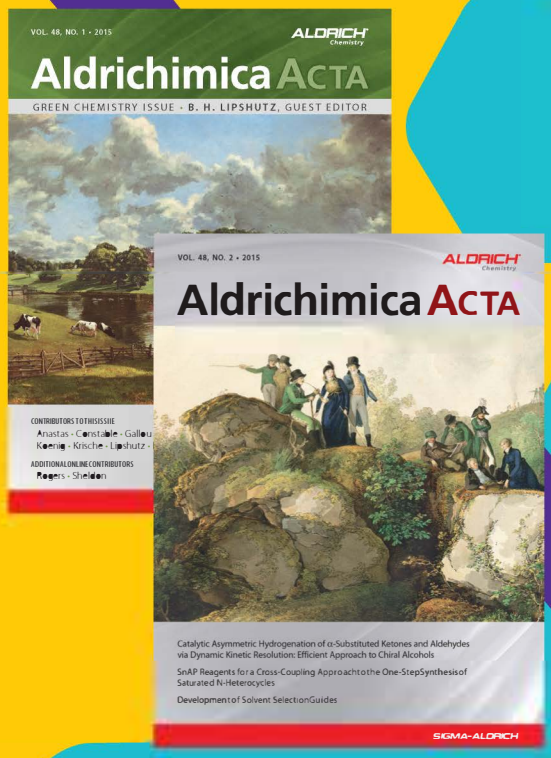

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