Aldrichimica Acta

Volume 24, Number 1, 1991

Simple, Novel Methods for the Synthesis of Carbonyl Compounds Using Metal Complexes as Catalysts

Samarium(II) Iodide in Organic Synthesis

chemists helping chemists in research & industry

aldrich chemical company, inc.

Aldrichimica Acta

Volume 24, Number 1, 1991
A publication of the ALDRICH CHEMICAL COMPANY

Aldrich Chemical Co., Inc.
1001 West Saint Paul Avenue
Milwaukee, Wisconsin 53233 USA

To Place Orders

Telephone	800-558-9160 (USA/Canada)
	414-273-3850
TWX	910-262-3052 Aldrichem MI
TELEX	26 843 Aldrich MI
FAX	800-962-9591
	414-273-4979
Mail	P.O. Box 2060
	Milwaukee, WI 53201 USA

Customer Service

Customer Inquiries	800-558-9160
Technical Information	800-231-8327
Bulk Sales	800-255-3756
Custom Synthesis	800-255-3756
Flavors & Fragrances	800-227-4563

General Correspondence
P.O. Box 355, Milwaukee, WI 53201 USA

Belgium
Aldrich Chemie
Bd. Lambermontlaan, 140 b6
B-1030 Bruxelles/Brussel
Telephone: 32 (0)2 242 8750
(local) 114747
Telex: 62302 Alchem B
FAX: 022428216

France
Aldrich-Chimie S.a.r.l.
BP 234
67006 Strasbourg Cedex
Telephone: 88327010
Telex: 890076 Aldrich F
FAX: 88751283

Germany
Aldrich-Chemie GmbH & Co. KG
D-7924 Steinheim
Telephone: 07329870
For orders: 0732987110
Telex: 714838 Aldri D
FAX: 0732987139/239

Holland
Aldrich Chemie
Lambermont 140 b6
B-1030 Brussel
Telephone: 32 (0)2 242 8750
(local) 060224748
Telex: 62302 Alchem B
FAX: 022428216

Italy
Aldrich Chimica
Via Pietro Toselli, 4
20127 Milano
Telephone: 022613689
Telex: 330862 Aldrch I
FAX: 022896301

Japan
Aldrich Japan
Kyodo Bldg. Shinkanda
10 Kanda-Mikuracho
Chiyoda-Ku, Tokyo
Telephone: 032580155
FAX: 032580157

Spain
Aldrich Quimica
Apt. de Correos 161
28100 Alcobendas (Madrid)
Telephone: 6619977
Telex: 22189 SAQS-E
FAX: 6618084

United Kingdom
Aldrich Chemical Co. Ltd.
The Old Brickyard, New Road
Gillingham, Dorset SP8 4JL
Telephone: 0747822211
For orders: 0747824414
Telex: 417238 Aldrch G
FAX: 0747823779

About Our Cover:

Fig. 1

The Bible is the world's most diverse book: what stories of true love and unmitigated hatred, of ecstasy and depression!

When we worry about the Middle East, as we do so much right now, we can find encouragement in the story of the love of a "Jordanian" woman, Ruth, a woman who became the ancestor of David and hence of the Messiah, for her "Israeli" mother-in-law, Naomi. This is one of the most heart-warming stories.

In contrast, one of the strangest stories is illustrated on our cover, which could be called "Don't Kill the Messenger."

At first our chemist collector did not know its subject, but a good friend, Dr. Volker Manuth, explained that Willem de Poorter, a Rembrandt student, has here illustrated a story very rarely depicted in the 17th century. The first chapter of the second book of Samuel tells of the arrival of a young Amalekite before David. He has brought Saul's crown and news of the death of Jonathan and Saul on Mount Gilboa. David was stricken with grief at the news and ordered the messenger to be killed.

Why did David have him killed? Surely not only because he had brought such tragic news and had helped Saul in his suicide. It was probably also because he was an Amalekite.

During the Exodus from Egypt these wild nomads attacked the Israelites (Exodus 17:8-16), striking the hindmost, the weakest first. Moses commanded the Israelites (Deuteronomy 25:17-19), "Remember what Amalek did unto you. . .you shall blot out the remembrance of Amalek from under heaven, you shall not forget." King Saul forgot and spared the life of Agag, King of Amalek (I Samuel 15:1-35) and that led to Samuel's leaving Saul and eventually to Saul's suicide.

Dr. Manuth explained that de Poorter used a Bible illustration (Fig. 1) by Hans Holbein, the Younger, clearly showing David's deep grief and the relationship between David and the messenger.

The Amalekites have disappeared, but the spirit of terrorism has not. The kind of love that Ruth shared with Naomi must still exist, but a Ruth of today might fear her own people. How can we encourage people to think of each other as individuals, rather than as stereotypes — Amalekites or Arabs or Jews?

The Detective's Eye: Investigating the Old Masters

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

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

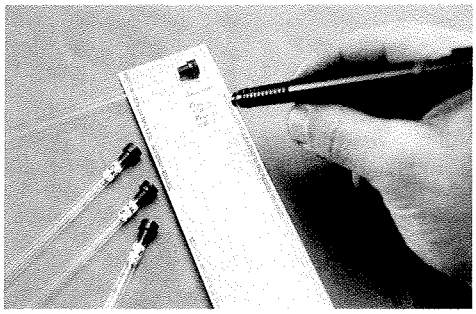
Lab Notes

In a recent issue of *Aldrichimica Acta* (Vol. 23, No. 2), the use of the perforated edge of a chart paper was proposed as a convenient method to label 5-mm NMR tubes. We have found that small adhesive labels (37 x 9 mm) used in the electrical industry to label electrical wires are an ideal method to label any NMR tube regardless of size. The labels have an opaque, white section suitable for writing on with ball-point pen, and they retain their adhesive power in both high- and low-temperature regimes (at least -100 to +160°C). We recommend the use of these labels for the universal labelling of NMR samples.

P.S. Farley
MRPRA
Brickendonbury
Hertford, SG13 8NL
England

Dr. H. Parkes
Department of Chemistry
Birkbeck College
Gordon House
29 Gordon Square
London, WC1H 0PP
England

Editor's Note: Aldrich now carries the NMR tube labels shown here.



NMR tube labels
Self-laminating vinyl labels (8.7 x 38 mm) resist oil, water, and, solvent. Usable temperature range is -40 to 150°F (-40 to 66°C). Supplied in a package of 25 cards (26 labels/card).

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, *at no cost*, a laminated periodic table poster. 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

Professor M.F. Lappert of the School of Chemistry and Molecular Sciences at the University of Sussex and Professor Philip Power of the Department of Chemistry at the University of California at Davis suggested that we offer bis(trimethylsilyl)-chloromethane. Use of the bis(trimethylsilyl)-methyl ligand has permitted the isolation of several transition-metal and main-group compounds. The most common method for the introduction of the bis(trimethylsilyl)methyl ligand is by treatment of $(Me_3Si)_2CHLi$ with an active halide. The precursor for the preparation of the lithium derivative is the chloride, $(Me_3Si)_2CHCl$.

Naturally, we made this compound.

Lappert, M.F. *Adv. Chem. Ser.* **1976**, *150*, 256. Hitchcock, P.B.; Lappert, M.F.; Leung, W.P.; Buttrus, N.H. *J. Organomet. Chem.* **1990**, *394*, 57 and references therein.

$(Me_3Si)_2CHCl$

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

Simple, Novel Methods for the Synthesis of Carbonyl Compounds Using Metal Complexes as Catalysts

Howard Alper
Department of Chemistry
University of Ottawa
Ottawa, Ontario, Canada K1N 6N5

The past twenty years have witnessed a significant increase in the utilization of transition-metal complexes as catalysts for a variety of oxidation, reduction, and carbon-carbon bond-forming reactions. One example of the latter class is carbonylation reactions in which carbon monoxide is the source of one of the carbon atoms participating in the coupling process. The purpose of this article is to provide an account of recent developments at Ottawa on synthetic methods which are of considerable potential. Several different synthetic approaches will be described, including the net addition of formaldehyde, formic acid, or ester to an unsaturated organic substrate and the "stitching" of one or two carbon monoxide units into a small ring to construct a larger cyclic system.

Hydrocarboxylation and Hydroesterification Reactions

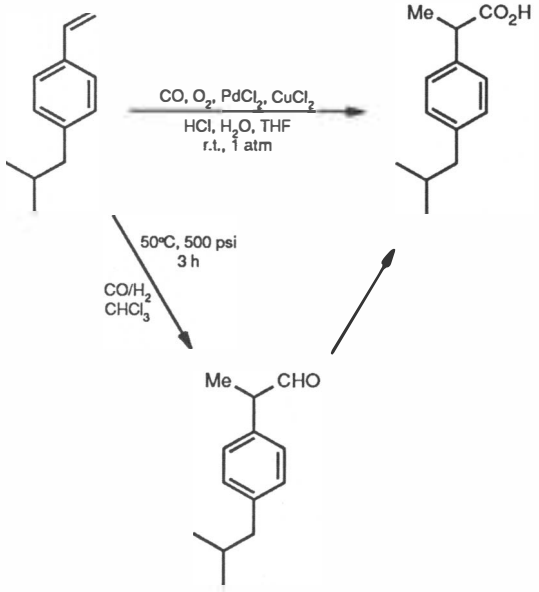
The regiospecific hydroesterification of olefins to branched-chain carboxylic esters can be effected under exceptionally mild conditions, affording products in high yields by the use of carbon monoxide and oxygen in acidic alcohol, and catalytic quantities of palladium and copper chlorides (eq. 1).[1] Overall, this reaction involves Markovnikov addition of a formate ester to a double bond. One can synthesize the carboxylic acid rather than the corresponding ester by simply using water in tetrahydrofuran instead of alcohol as the reaction solvent.[2] Of particular note is the application of this reaction to the preparation of nonsteroidal anti-inflammatory agents including ibuprofen (Scheme 1) and naproxen. Repetition of the hydrocarboxylation reaction in the presence of (*R*)-(-)- or (*S*)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate gave optically active acids in high enantiomeric excess.[3]

Lactones can be prepared from unsaturated alcohols by an intramolecular version of the hydroesterification reaction. Five- and six-membered ring lactones have been synthesized by this method.[4,5] Asymmetric induction can be attained, in up to 61% ee, by the use of poly-L-leucine (MW ~21,700) as an added chiral ligand (eq. 2).[6] The intramolecular addition of palladium hydride to the coordinated double bond of a five-coordinate palladium(II) complex intermediate (Fig. 1) is the probable chiral discrimination step in the asymmetric induction process.

Recipient of the Canadian Alfred Bader Award in 1990.

$$RCH{=}CH_2 + CO + R'OH \xrightarrow[HCl,\ r.t.,\ 1\ atm]{O_2,\ PdCl_2,\ CuCl_2} RCH(CO_2R')Me \qquad \text{(eq. 1)}$$

Scheme 1



$$MeCH{=}CHCH_2OH + CO \xrightarrow[HCl,\ THF,\ poly\text{-}L\text{-}leucine\ r.t.,\ 1\ atm]{O_2,\ PdCl_2,\ CuCl_2} \text{(R), 61\% ee} \qquad \text{(eq. 2)}$$

Hydroformylation

An alternate route to ibuprofen and other anti-inflammatory agents is via the hydroformylation of olefins to aldehydes, and subsequent oxidation.[7] Although numerous publications have appeared on olefin hydroformylation, few have reported highly regioselective or regiospecific routes to branched chain aldehydes. We have found that the zwitterionic complex **1** (Fig. 2), easily prepared from rhodium chloride, sodium tetraphenylborate, and 1,5-cyclooctadiene, catalyzes the conversion of monosubstituted styrenes (Scheme 1) or vinyl ethers (eq. 3) to branched chain aldehydes in excellent yield and regioselectivity. The process is also regiospecific for 1,1-disubstituted olefins such a α-methylstyrene, but the product formed has the aldehyde unit attached to the least substituted carbon atom of the double bond (eq. 4).[8] The reaction is not useful for simple aliphatic monosubstituted olefins, since it lacks any regiocontrol. However, the presence of a bulky group (e.g., *t*-Bu) results in the formation of the linear aldehyde in a regiospecific process.

Metal Catalyzed Carbonylation—Ring Expansion Reactions

Three-membered ring heterocycles undergo carbonylation and ring expansion in the presence of different metal catalysts. For example, 2-arylaziridines can be converted to β-lactams in excellent yield, using rhodium(I) complexes as catalysts.[9] Insertion of carbon monoxide into the aryl bearing carbon-nitrogen bond occurs with retention of configuration (eq. 5). Use of *d*- or *l*-menthol as a chiral ligand in the carbonylation of racemic aziridines enables one to achieve the synthesis of β-lactams in high optical purity by kinetic resolution. It is conceivable that binuclear rhodium complexes, containing bridging menthoxy ligands, are primarily responsible for the observed chiral discrimination. α-Lactams also experience carbon monoxide incorporation into the saturated ring carbon-nitrogen bond affording azetidine-2,4-diones (eq. 6).[10] However, insertion into the weak nitrogen-nitrogen bond, rather than the carbon-nitrogen bond, occurs when diaziridines are employed as substrates in the presence of palladium or cobalt complexes (eq. 7).[11] Finally, palladium compounds catalyze the conversion of methyleneaziridines to α-methylene-β-lactams with coordination of the nitrogen lone pair and the π-electrons of the double bond to palladium fixing the site of incorporation of carbon monoxide (eq. 8).[12]

Metallocycles may play an important role in the ring expansion of three- to four-membered heterocycles with, for instance,

Figure 1

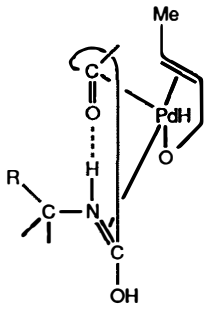
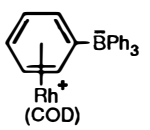
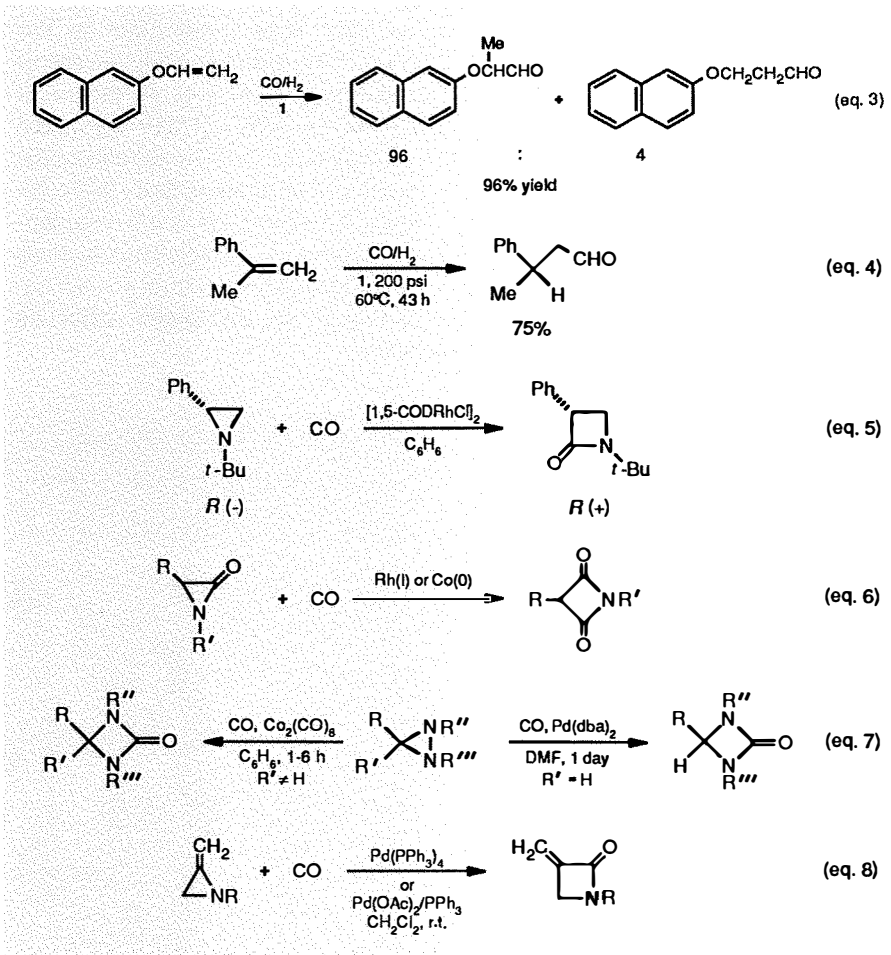


Figure 2



1



(eq. 3)

(eq. 4)

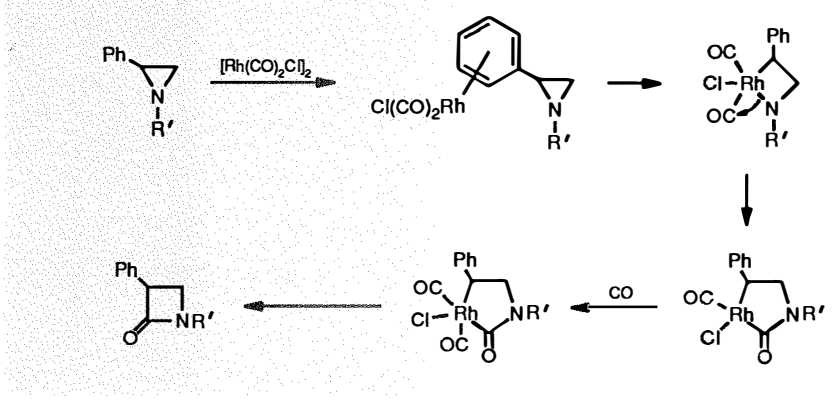
(eq. 5)

(eq. 6)

(eq. 7)

(eq. 8)

Scheme 2



coordination of the 2-substituent of an arylaziridine directing oxidative addition of the metal into the ring carbon-nitrogen bond to give an azametallacyclobutane (Scheme 2). An azairidacyclobutane has been isolated and characterized.[13]

A question which needs to be addressed concerns the scope of the carbonylation ring expansion process in terms of the ring size of the reactant. In other words, is the noted process limited to strained ring systems, and if not, are the regio- and stereochemical features in accord with those found in the case of aziridines?

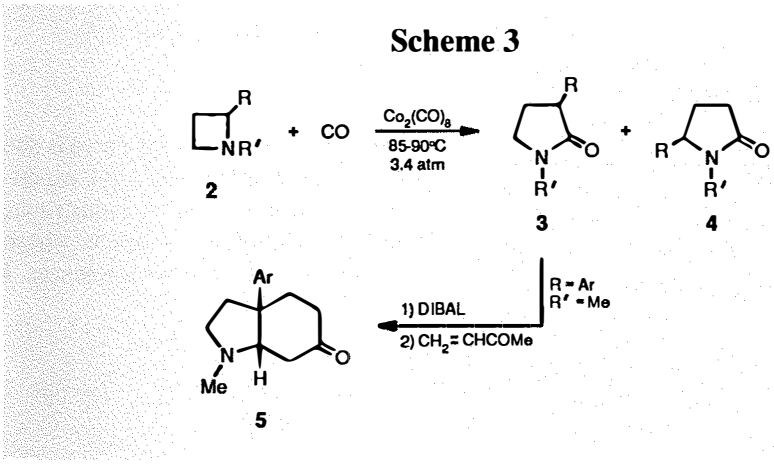
The four-membered ring compound, 1-methyl-2-phenylazetidine (Scheme 3; **2**, R=Ph, R'=Me), reacts with carbon monoxide in the presence of catalytic amounts of cobalt carbonyl to form 1-methyl-3-phenylpyrrolidin-2-one, **3**, in 90% isolated yield, with only traces of isomeric **4**.[14] [Although rhodium (I) complexes can be used, product yields are significantly less than when compared with cobalt.] Therefore, carbonyl insertion occurs, almost exclusively, into the substituted ring carbon-nitrogen bond, analogous to the results obtained with 2-arylaziridines. This reaction provides a facile entry to the mesembrine alkaloids, **5**, several of which exhibit CNS activity.[15] While 2-alkylaziridines do not undergo carbonylation and ring expansion under the usual conditions, 2-alkylazetidines are carbonylated to the five-membered ring lactam. Furthermore, the regiochemistry is opposite to that found for 2-phenylazetidine, with the 1-substituted-5-alkylpyrrolidin-2-one, **4**, isolated as the only product in all cases. Both **3** and **4** (with **4** as the major product) were formed when 1-*tert*-butyl-2-(methoxycarbonyl)-azetidine was employed as the reactant.

A novel expansion of four- to seven-membered ring heterocycles occurred for 2-vinylazetidines leading to tetrahydroazepinones. This new reaction may be occuring via a cationic π-allylcobalt complex (Scheme 4). This intramolecular cyclization-carbonylation reaction is of considerable potential for the preparation of a variety of azepinones.

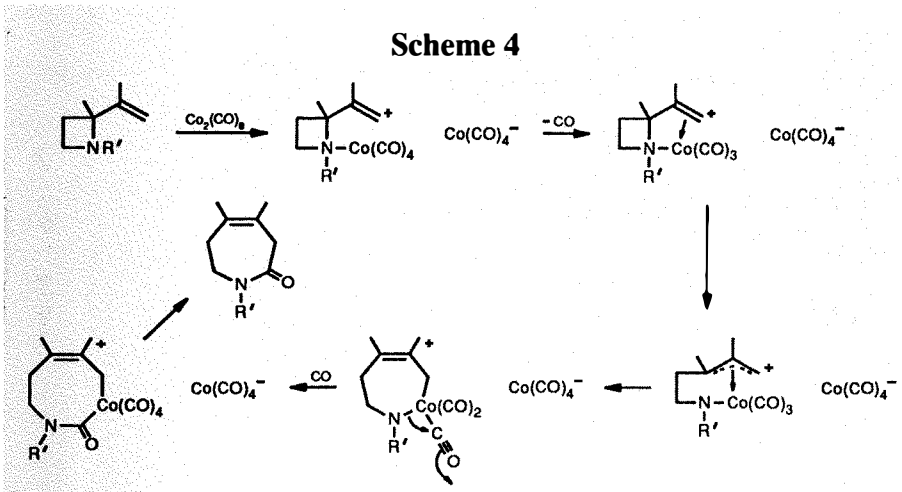
γ-Butyrolactones and γ-thiobutyrolactones (eq. 9) are formed in excellent yields by regiospecific carbonylation of oxetanes and thietanes, respectively, using catalytic quantities of cobalt and ruthenium carbonyls [20:1:1 ratio of heterocycle: $Co_2(CO)_8$:$Ru_3(CO)_{12}$]. While either metal carbonyl alone can catalyze this reaction, superior product yields were realized using a mixture of both metal catalysts.[16] An attractive feature of the reactions of all three classes of four-membered ring heterocycles is the observed stereospecificity, and consequently this methodology is of value for the construction of five-membered ring lactams, lactones or thiolactones, with stereochemically defined substituents (eq. 10).

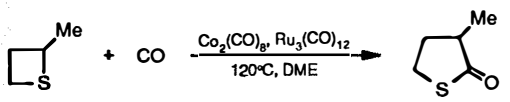
The ring expansion process is also

Scheme 3

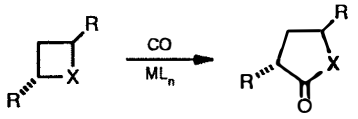


Scheme 4

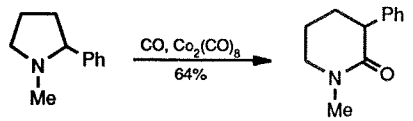




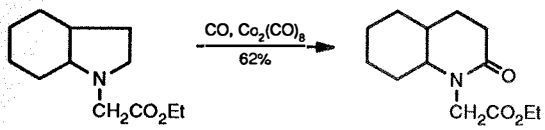
(eq. 9)



(eq. 10)



(eq. 11)



(eq. 12)

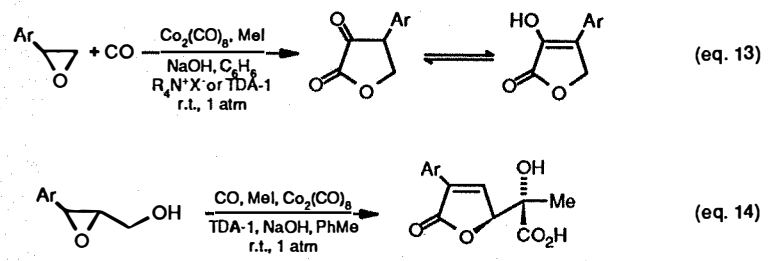
applicable to five-membered ring compounds with the regiochemistry mimicking that of the four-membered ring heterocycles (eq. 11, 12).[17] These processes can also be used for five-membered ring heterocycles having two heteroatoms (e.g., oxazolidines).

Double and Triple Carbonylation Reactions

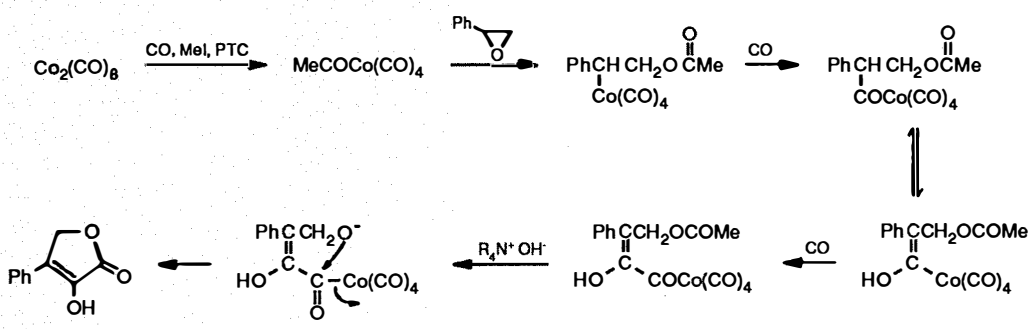
Double carbonylation processes can be defined as reactions involving the incorporation of two carbon monoxide units at adjacent sites. This area has attracted widespread interest in recent years.[18] Most studies have focused on the palladium- or cobalt-catalyzed conversion of halides to α-keto acids, esters, or amides. In the case of a halodiene, a methylene α-keto lactone was isolated using nickel cyanide as the catalyst under phase-transfer condition.[19] α-Keto lactones (or the enol tautomer) were also formed by phase-transfer-catalyzed reaction of epoxides with carbon monoxide and methyl iodide in the presence of catalytic amounts of cobalt carbonyl and either a quaternary ammonium salt[20] or TDA-1 as the phase-transfer catalyst (eq. 13). A possible mechanism for this reaction is depicted in Scheme 5 (illustrated for styrene oxide). In order to secure evidence for this pathway, the reaction of β-epoxy alcohols with carbon monoxide was examined, since it was reasoned that the hydroxymethyl group in intermediate **6** (Scheme 6) could intercept the acylcobalt portion of the complex to ultimately produce 2,5-dihydro-2-oxo-3-phenylfuran, **7**. While **7** is formed from 3-phenylglycidol, it is the minor product, the major one (42% yield) being 2-*C*-(2,5-dihydro-2-oxo-3-phenylfur-5-yl)lactic acid, obtained as the *anti*-diastereomer. The conversion of 3-phenylglycidol and other β-epoxy alcohols to 2-*C*-lactic acids is a diastereospecific process, and constitutes the first example of a net triple carbonylation reaction (eq. 14).[21] Careful work has demonstrated that sequential mono- and double carbonylation reactions are occurring in this overall process, with the 2,5-dihydro-2-oxofuran as the key organic intermediate. Indeed, treatment of **7** or its analogs with carbon monoxide, methyl iodide, and cobalt carbonyl under identical phase-transfer conditions to those used for β-epoxy alcohols afford the 2-*C*-lactic acids in good yields. As in the previously described double carbonylation reaction of epoxides to α-keto lactones, enol cobalt complexes may participate in the conversion of 2,5-dihydro-2-oxofurans to 2-*C*-lactic acid derivatives (Scheme 7).

Acknowledgments

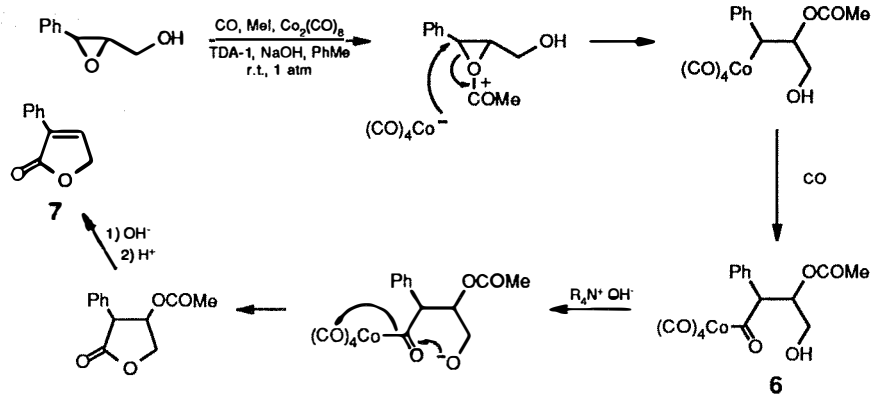
The research summarized above is due to the splendid intellectual and experimental contributions of an industrious, enthusiastic group of co-workers whose names are mentioned in the references. I



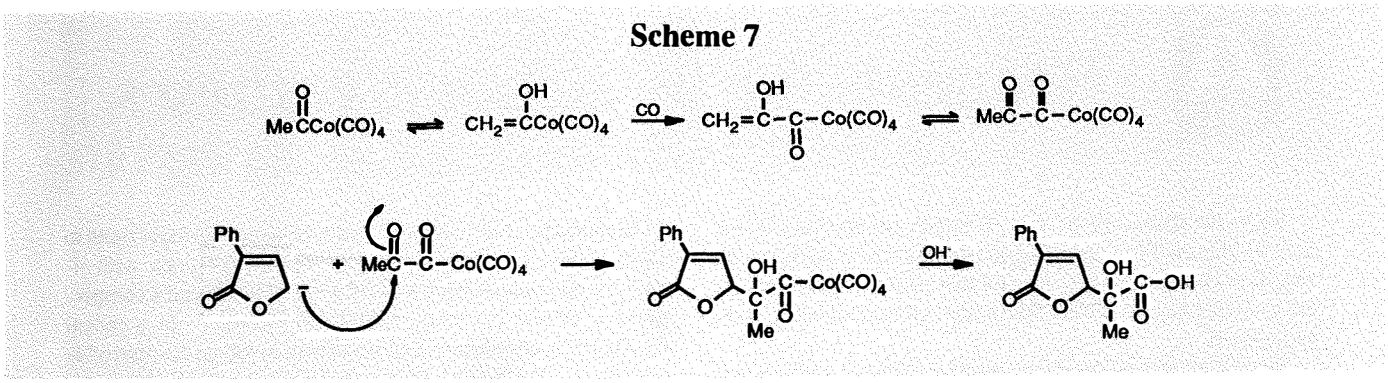
Scheme 5



Scheme 6



Scheme 7



have indeed been privileged to have had such a first-class group of associates. I am also indebted to NSERC, British Petroleum, and the Merck-Frosst Centre for Therapeutic Research, for support of this work.

References:

1) Despeyroux, B.; Alper, H. *Ann. N.Y. Acad. Sci.* **1983**, *415*, 148.
2) Alper, H.; Woell, J.B.; Despeyroux, B.; Smith, D.J.H. *J. Chem. Soc., Chem. Commun.* **1983**, 1270.
3) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803.
4) Alper, H.; Leonard, D. *J. Chem. Soc., Chem. Commun.* **1985**, 511.
5) *Idem Tetrahedron Lett.* **1985**, *26*, 5639.
6) Alper, H.; Hamel, N. *J. Chem. Soc., Chem. Commun.* **1990**, 135.
7) Parrinello, G.; Stille, J.K. *J. Am. Chem. Soc.* **1987**, *109*, 7122.
8) Amer, I.; Alper, H. *ibid.* **1990**, *112*, 3674.
9) Calet, S.; Urso, F.; Alper, H. *ibid.* **1989**, *111*, 931.
10) Roberto, D.; Alper, H. *Organometallics* **1984**, *3*, 1767.
11) Alper, H.; Delledonne, D.; Kameyama, M.; Roberto, D. *ibid.* **1990**, *9*, 762.
12) Alper, H.; Hamel, N. *Tetrahedron Lett.* **1987**, *28*, 3237.
13) Klein, D.P.; Hayes, J.C.; Bergman, R.G. *J. Am. Chem. Soc.* **1988**, *110*, 3704.
14) Roberto, D.; Alper, H. *ibid.* **1989**, *111*, 7539.
15) Kochbar, K.S.; Pinnik, H.W. *Tetrahedron Lett.* **1983**, *23*, 4785.
16) Wang, M.D.; Calet, S.; Alper, H. *J. Org. Chem.* **1989**, *54*, 20.
17) Wang, M.D.; Alper, H., unpublished results.
18) Collin, J. *Bull. Soc. Chim. Fr.* **1988**, 976.
19) Alper, H.; Vasapollo, G. *Tetrahedron Lett.* **1989**, *30*, 2617.
20) Alper, H.; Arzoumanian, H.; Petrignani, J.F.; Saldana-Maldonado, M. *J. Chem. Soc., Chem. Commun.* **1985**, 340.
21) Alper, H.; Eisenstat, A.; Satyanarayana, N. *J. Am. Chem. Soc.* **1990**, *112*, 7060.

About the Author

Professor Howard Alper was born in Montréal, Canada in 1941. He received a B.Sc. (Honors Chemistry) in 1963 from Sir George Williams University and a Ph. D. degree in 1967 with Jack Edward at McGill University. Following a year spent as a NATO postdoctoral fellow with Paul Schleyer at Princeton, he joined the faculty of the State University of New York at Binghamton in 1968. He returned to Canada at the end of 1974, assuming the position of Associate Professor of Chemistry at the University of Ottawa. He served as Chairman of the Department of Chemistry during 1982-85 and again from 1988-91.

The research interests of Professor Alper are wide-ranging, including the development of new synthetic methods in oxidation, reduction, and carbonylation reactions, by the use of homogeneous and phase-transfer catalysis; novel organometallic complexes; and the chemistry of metal-metal multiple bonds. He was an E.W.R. Steacie Fellow of the Natural Sciences and Engineering Research Council (NSERC) of Canada during 1980-82, a J.S. Guggenheim Fellow in 1985-86, and a Killam Research Fellow (Canada Council) during 1986-88. He received the Catalysis Award of the Chemical Institute of Canada in 1984 and the Alcan Award in Inorganic Chemistry in 1980. He was elected as a Fellow of the Royal Society of Canada in 1984.

Professor Alper has served on the NSERC Chemistry Grants Selection Committee during 1984-87 and as Group Chairman during 1987-90 representing Chemistry on the Committee on the Research Base. The latter committee advises NSERC on policy matters, allocation of resources, etc. He served on the Committee on the Reorganization of the Academy of Sciences of the Royal Society of Canada (1988-89) and as Convenor of the Chemistry Committee of the same society. He is also Chairman of the Council of Canadian University Chemistry Chairs.

He has served as a member of the Editorial Board of several journals (e.g., *Organometallics*) and has presented numerous invited research lectures, including Japan Society for Promotion of Science Lecturer in 1983 and 1990. Finally, Professor Alper has also presented lectures on the chemistry of chocolate, an area where he has significant expertise, both in assessment and consumption.

Samarium(II) Iodide in Organic Synthesis

John A. Soderquist
Department of Chemistry
University of Puerto Rico
Rio Piedras, PR 00931

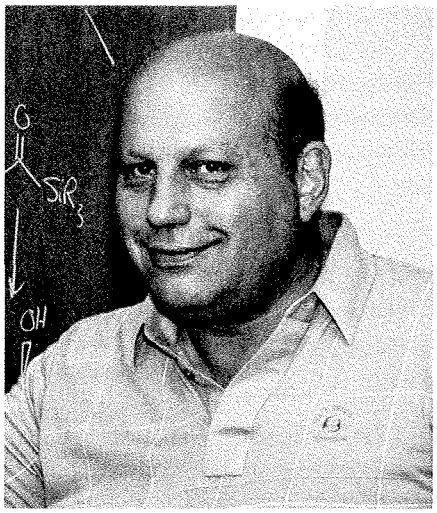
First introduced by Kagan and coworkers as a reagent for organic synthesis,[1] samarium(II) iodide, **1**, continues to provide chemists with an ever-increasing variety of useful transformations.[2] To demonstrate the broad scope of its applications to organic synthesis, representative examples of the conversions which have employed this reagent are highlighted in this review.

Samarium(II) iodide, **1**, can be prepared in tetrahydrofuran (THF) as an approximately 0.1 *M* solution from samarium metal through its oxidation with 1,2-diiodoethane,[3] molecular iodine,[4] or mercuric iodide (Scheme 1).[5] The reaction gives SmI_3 initially, but this is subsequently reduced by samarium to form a beautiful blue solution of SmI_2.

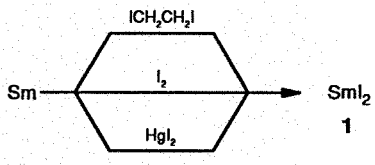
A powerful reducing agent [E^o_{aq} (Sm^{+2}/Sm^{+3}) = -1.55 V], SmI_2 initiates a variety of selective coupling reactions and functional group conversions with halogen- and oxygen-containing substrates.[2] These transformations can be either radical or carbanionic in nature. Many of the latter transformations can be viewed as occurring through stepwise processes involving two equivalents of SmI_2 which ultimately results in a net two-electron reduction accompanied by the formation of Sm(III) by-products.[1] This reactivity can be effectively utilized for the deoxygenation of organoheteroatom oxides.[1,6] Employing hexamethylphosphoric triamide (HMPA) as a cosolvent enhances the reduction of sulfoxides and is essential for the deoxygenation of sulfones, phosphine oxides and organotin oxides (Scheme 2).[7]

In several cases, isoxazoles, **2**, are reductively cleaved with SmI_2 in THF to provide the corresponding β-amino enones, **3** (eq. 1).[8] This process is compatible with ester, acetal and alkene functionalities. However, the presence of halogen or aldehydic groups in these substrates leads to coupling and reduction coproducts.

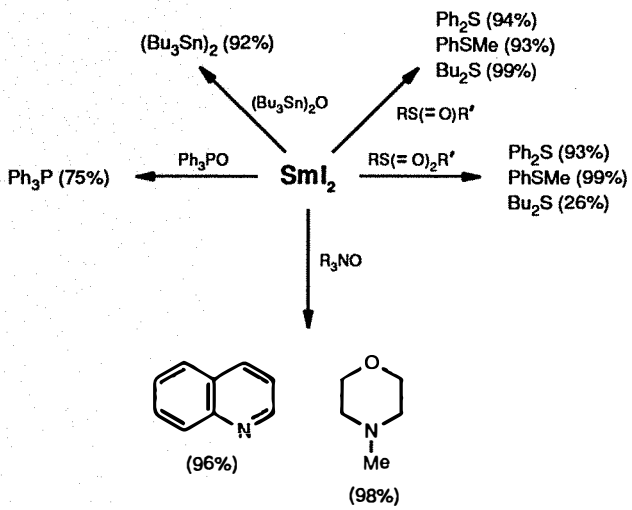
Initial studies by Kagan[1] revealed that SmI_2 in THF gave coupled products from benzylic halides while their alkyl counterparts were reduced to the parent hydrocarbon. Molander found that SmI_2, in the presence of methanol as a proton source, efficiently reduces α-heterosub-

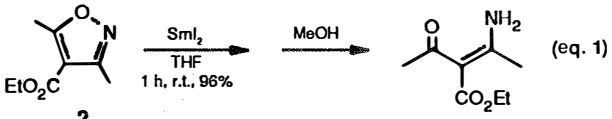


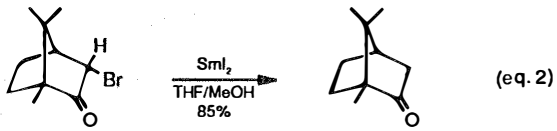
Scheme 1

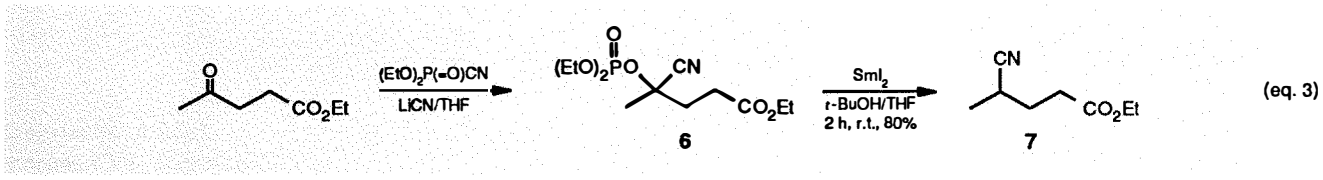


Scheme 2







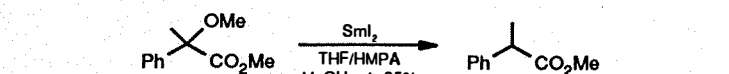


(eq. 3)

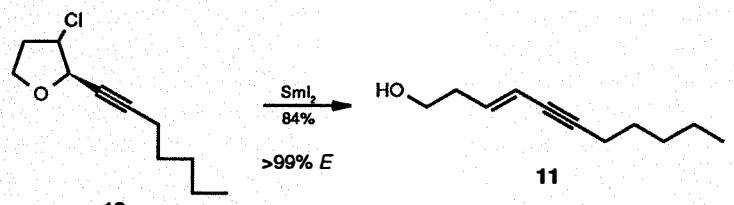
stituted ketones at low temperature (i.e., -78°C).[9] As illustrated for 3-bromocamphor, **4** (eq. 2), a wide variety of sulfur- and oxygen-containing α-substituents can also be reductively cleaved to provide the corresponding ketones in excellent yields. The dehydroxylation of acyloins, while less efficient than for substrates with better leaving groups, is enhanced by the addition of acetic anhydride prior to reduction with SmI_2.[9]

Recently, this methodology has been developed into a convenient protocol for the reductive cyanation of aldehydes and ketones through cyanophosphate intermediates (eq. 3).[10] The approach is quite general for both aliphatic and aromatic substrates as well as for α,β-unsaturated aldehydes and ketones.

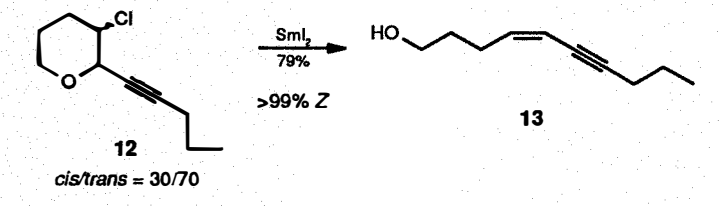
Although α-bromo esters were efficiently debrominated at -78°C with SmI_2 in THF, α-acetoxy esters were not reduced under these conditions.[9] However, Inanaga has recently reported that by employing a THF-HMPA solvent system, SmI_2 effects the clean reduction of α-oxygenated (e.g., OAc, OMe, OTHP, OH) esters at room temperature, as is represented for **8** (eq. 4).[11] While alcohols were satisfactory proton sources for the deoxygenation of acetoxy and alkoxy derivatives, pivalic acid proved to be superior for the reduction of α-hydroxy esters.



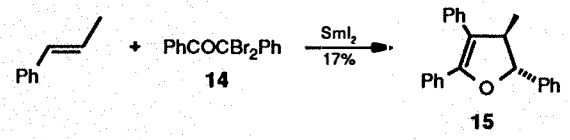
(eq. 4)



(eq. 5)



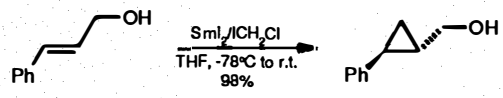
(eq. 6)



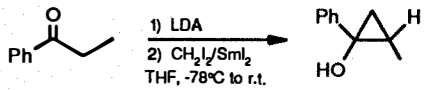
(eq. 7)

Reductive 1,2-eliminations are observed with SmI_2 for 3-chloro furans and pyrans.[12] Furans provide alkenes with high (>95%) *E*-selectivity. Pyrans normally exhibit a modest *trans* selectivity for 2-alkyl derivatives, but with 2-alkynyl-3-chloropyrans (e.g., **12**), a remarkable *Z*-selectivity is observed (eq. 6). When combined with the high *E*-selectivity of the related furanyl system, **10** (eq. 5), these processes provide very useful entries into either *cis* or *trans* enynes which also contain the versatile alcohol functionality.

Dihydrofurans, **15**, are produced from the reduction of α,α-dibromodeoxybenzoin, **14**, with SmI_2 in the presence of styrenes or 1,3-butadienes (eq. 7).[13] This conversion gives results similar to those obtained from the reduction of **14** with zinc[14] and is believed to proceed through a ketocarbene or carbenoid intermediate. The observation of C-H insertion by-products in the case of α-methylstyrene is consistent with such a mechanistic pathway.



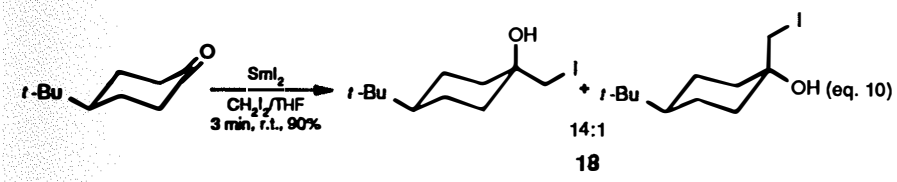
(eq. 8)



(eq. 9)

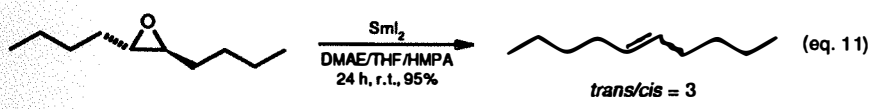
The samarium-based Simmons-Smith reaction is thought to form carbenoids from samarium metal and diiodomethane by analogy to the iodomethylzinc intermediates from the standard protocol.[15] Unlike zinc reagents, however, these intermediates selectively cyclopropanate allylic alcohols to the complete exclusion of reaction at isolated alkene centers.[16] Similar chemistry, possibly involving Sm(III) carbenoids, is observed for SmI_2, ICH_2Cl and allylic alcohol substrates (eq. 8). Imamoto had shown earlier that SmI_2 and diiodomethane could effectively cyclopropanate lithium enolates under very mild conditions, providing a convenient route to cyclopropanols, **17** (eq. 9).[17] These mild conditions, together with the change from zinc to samarium, evidently provide stable intermediate cyclopropylates which do not form the α-methylated ketones observed with the Simmons-Smith methodology.[18]

Reaction of the SmI_2/CH_2I_2 system with aldehydes or ketones leads to isolable iodohydrins, **18** (eq. 10).[19] The precise nature of this process is not understood, but it was established that if epoxides were formed as intermediates, these would

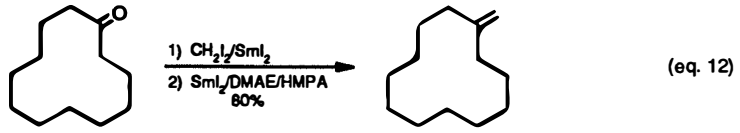


(eq. 10)

18

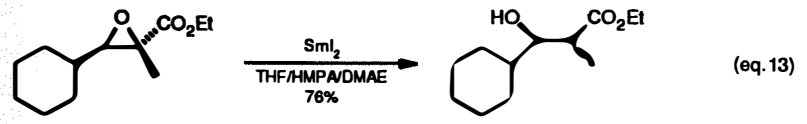


(eq. 11)



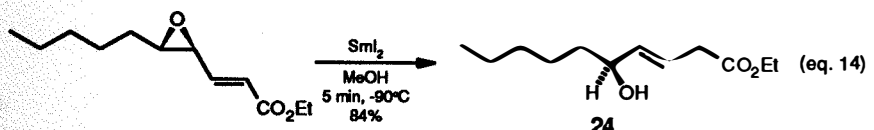
(eq. 12)

19 20



(eq. 13)

21 22

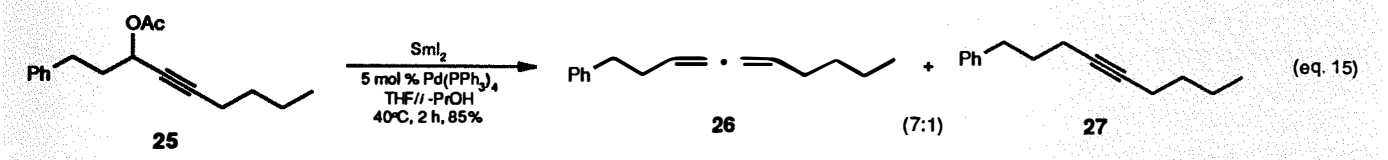


(eq. 14)

23 24

undergo ring-opening with SmI_3 to give the observed iodohydrin product. From the pioneering studies of Kagan, SmI_2 is known to efficiently deoxygenate epoxides in the presence of a proton source such as *t*-butyl alcohol.[1] The reaction takes several days at room temperature and gives *E*/*Z* mixtures. However, in many cases, excellent conversions to alkenes are obtained free of either alcohol or ketone by-products. Reasoning that trace quantities of Sm(III) could initiate this deoxygenation through β-iodoalkoxysamarium(III) intermediates, Inanaga[20] developed a very rapid and efficient procedure for this conversion employing HMPA and *N*,*N*-dimethylaminoethanol (DMAE) additives (eq. 11). He also combined this with his iodomethylation methodology to result in a new one-pot olefination of carbonyl compounds (eq. 12). The Simmons-Smith procedure, which gives both olefination and cyclopropanes from carbonyl compounds,[18] may follow a similar pathway. However, the mild conditions and relative inertness of isolated alkenes toward cyclopropanation with Sm(III) carbenoids, may account for the fact that these latter products are not observed with the samarium-based methodology.

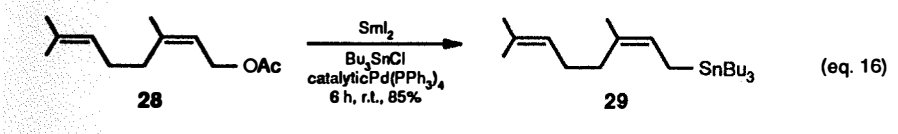
The selective reduction of α,β-epoxy



(eq. 15)

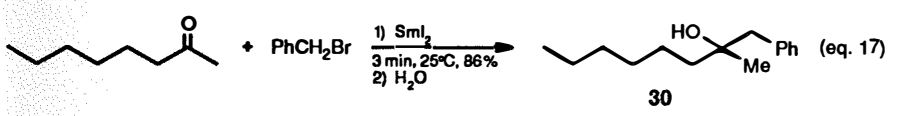
25 26 (7:1) 27

ketones[21] and esters[22] can be induced by SmI_2 to provide a convenient route to the corresponding β-hydroxy carbonyl compounds (eq. 13). Molander has also extended this reaction to vinylogous systems to provide an elegant approach to the synthesis of optically active *trans* allylic alcohols (eq. 14).[23]



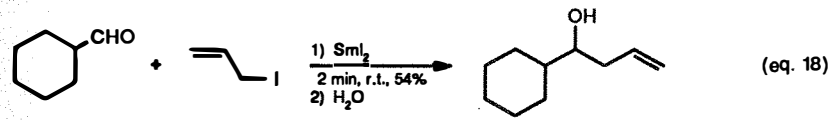
(eq. 16)

28 29



(eq. 17)

30

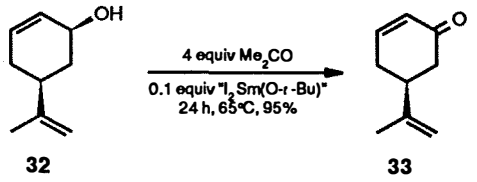


(eq. 18)

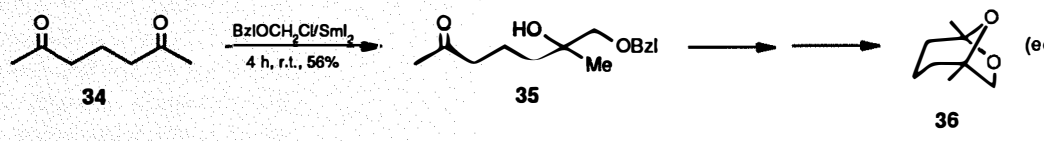
31

The Pd-catalyzed reduction of both allylic and propargylic acetates can be effected with SmI_2 (eq. 15).[2b,24,25] For the latter case, the relative amount of allene (i.e., **26**) can be increased to 20:1 employing very hindered alcohols as proton sources [e.g., $(i\text{-Pr})_2CHOH$].[25] When these alcohols are replaced with carbonyl compounds and other electrophiles, good yields of the corresponding cross-coupled products are obtained (eq. 16).[2b,26]

Kagan discovered that SmI_2 induces a Barbier-type reaction of alkyl halides with ketones to provide tertiary alcohols such as **30** (eq. 17).[1] Benzylic halides or allylic halides,[27] acetates[2b] and phosphates[28] are sufficiently reactive to permit this coupling with aldehydes to give secondary alcohols (e.g., **31**) in good yields (eq. 18). Aldehydes with SmI_2, in the presence of less reactive halides, can either undergo pinacolic coupling or be reduced to the corresponding primary alcohols. The reductive properties of the secondary alkoxysamarium(III) adducts formed in this reaction were found to be responsible for this latter process. These same intermediates, generated from other sources, were found to function as effective catalysts in a novel samarium-based Meerwein-Ponndorf-Verley-Oppenauer protocol.[29] Aldehydes and ketones are reduced under these reversible conditions by employing an excess of 2-propanol. Alternatively, alcohols can be oxidized by acetone to provide the corresponding carbonyl compounds in good to excellent yields (e.g., **33**) (eq. 19).



32 **33** (eq. 19)

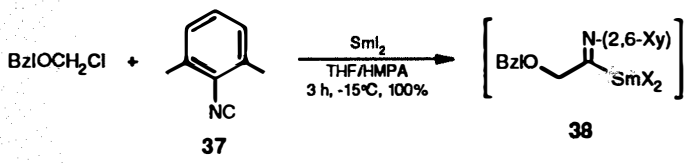


34 **35** **36** (eq. 20)

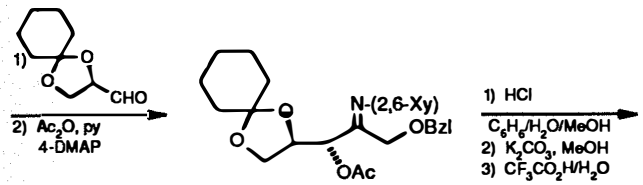
The hydroxymethylation of aldehydes and ketones via a samarium-based Barbier reaction was described by Imamoto and co-workers.[30] Aldehydes required tetraethylene glycol ethers as cosolvents to suppress pinacol formation. The resultant monobenzylated diols were hydrogenated under standard conditions (Pd/C) to obtain the deprotected 1,2-diols. Other chloromethyl ethers were also successfully coupled to ketones. The utility of this methodology was demonstrated by its application in the synthesis of racemic frontalin, **36**, through **35** (eq. 20).

Very recently, SmI_2 provided a very useful α-hydroxyacetyl anion equivalent, **38**, by its reaction with benzyl chloromethyl ether in the presence of 2,6-xylyl isocyanide, **37**, and HMPA.[31] The reagent efficiently adds to aldehydes and ketones. At -30°C, reaction of **38** with protected D-glyceraldehyde was complete

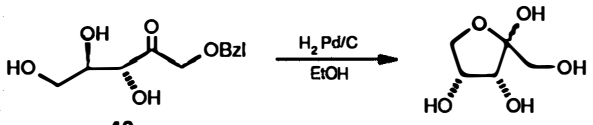
Scheme 3



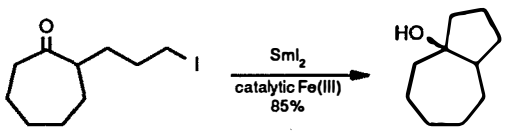
37 **38**



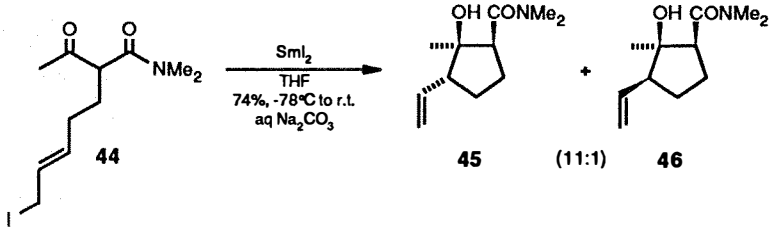
39
anti/syn = 10



40 **41**



42 **43** (eq. 21)
cis/trans = 2



44 **45** (11:1) **46** (eq. 22)

in 14 hours, and after acetylation, the coupled product, **39**, was obtained in quantitative yield with high *anti* selectivity. Hydrolysis and reduction gave D-ribulose, **41** (Scheme 3).

Molander and Etter first demonstrated the utility of SmI_2 in a Barbier-type intramolecular alkylation of cyclic ketones.[32] This operation provides a variety of bicyclic alcohols in excellent yields. The products are normally obtained as *cis/trans* mixtures (eq. 21), but excellent *cis* selectivity (>99.5%) is observed for bicyclo[3.3.0]octan-1-ol. More recently, it was found that metal chelation employing β-oxo amides and esters as substrates could provide excellent diastereoselective control in these intramolecular cyclizations.[33] The highly substituted cyclopentanes obtained (e.g., **45**, **46**) contained three new asymmetric centers, epimeric only at the C-3 position (eq. 22).

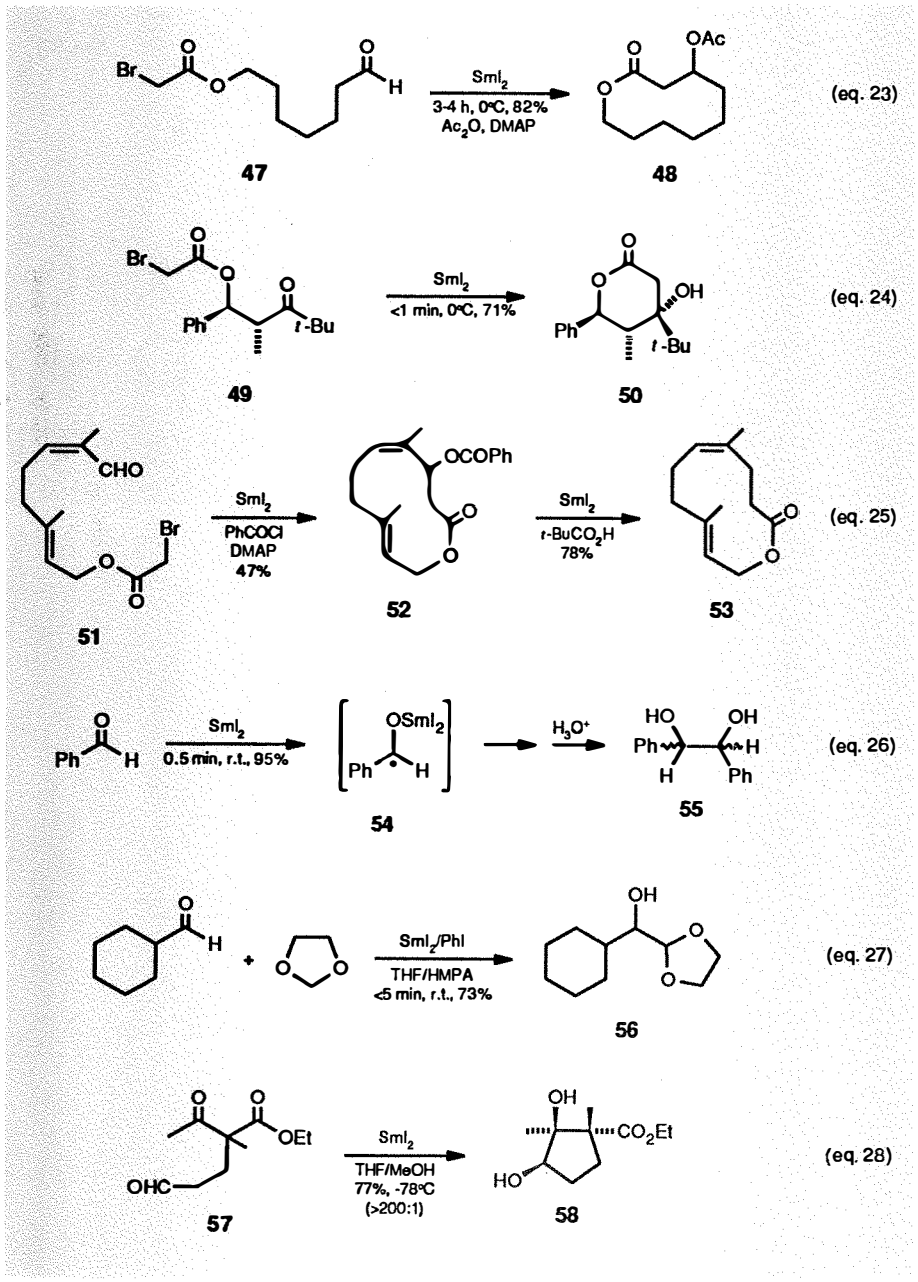
Inanaga[34] demonstrated that α-bromo esters could be utilized in an intramolecular Reformatsky-type process to provide an efficient synthesis of medium- and large-ring lactones (eq. 23). Performed under dilute conditions, the reaction showed little diastereoselectivity for examples which employed substitution *alpha* to bromine. By contrast, Molander found that extremely high selectivities could be obtained in his synthesis of β-hydroxy-δ-valerolactones, particularly for reactants which contained substituents *beta* to the ketone functionality (eq. 24).[35] The transition state leading to **50** with a *cis*-1,3-diequatorial relationship of the substituents at the β and δ positions in **50** is highly favored over its diastereomeric alternative in a reaction which is believed to proceed through a samarium enolate-carbonyl chelate.

Recently, Inanaga[36] demonstrated that the insect pheromone, ferrulactone, **53**, was available in four steps from geraniol via two applications of the reductive properties of SmI_2 (eq. 25). This samarium-mediated cyclization provided the desired macrolide ring skeleton and the reduction of the derived allylic benzoate with the SmI_2/THF/HMPA system in the presence of pivalic acid afforded the natural product.

The intermolecular coupling of aldehydes or ketones to give high yields of the corresponding pinacols, **55**, can be achieved with SmI_2 (eq. 26).[37] A number of functional groups (i.e., NO_2, CO_2H, CN, OMe, NMe_2) in the *para* position of aromatic aldehydes were found to survive this coupling intact. Essentially no diastereoselectivity was observed in the reaction (e.g., **55**: *dl/meso* = 56:44), which is thought to proceed via a ketyl intermediate, **54**. Except for acetaldehyde, good to excellent yields (66-95%) of **55** are obtained for aromatic and aliphatic aldehydes as well as for methyl ketones.

Inanaga found that the intermediate phenyl radicals generated from SmI_2 and iodobenzene could readily abstract a hydrogen atom from 1,3-dioxolane to provide a clever masked formylation of aldehydes and ketones (eq. 27).[38] While the precise nature of the process is not fully understood, the 1,3-dioxolanyl radical is apparently involved and is either further reduced to the anion which adds to the carbonyl compound or couples with a ketyl to give **56**.

The intramolecular pinacolic coupling induced by SmI_2, unlike the above-mentioned intermolecular examples, can provide diols in a very stereoselective manner (eq. 28).[39] It was suggested that the preferred chelation leading to this coupling may occur between the samarium(III) ketyl and the ketone which accounts for the dominant *cis* diol stereochemistry observed in **58**. The absence of this chelation for the carboethoxy moiety



apparently results in an electronically-based preference for the formation of these products having an unusual *trans* relationship between this group and its adjacent hydroxyl.[40]

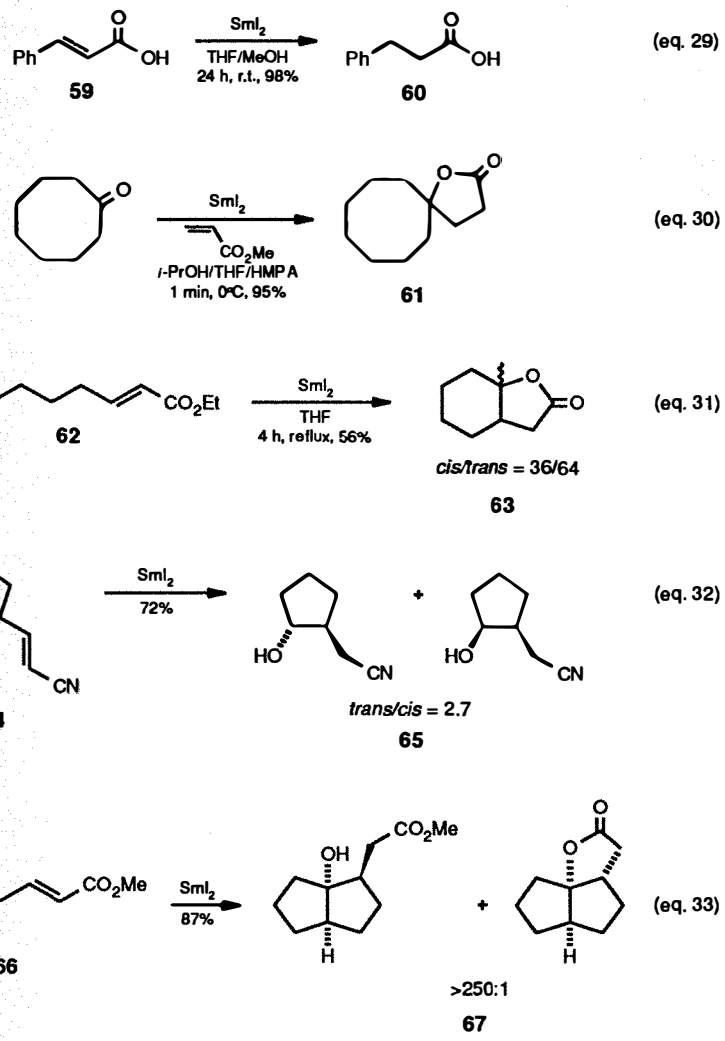
The reduction of α,β-unsaturated acids and esters with SmI_2 in the presence of alcohols provides very high yields of the corresponding saturated acid (eq. 29).[1]

The above process can be avoided when more reactive substrates are present to accept electrons from SmI_2. For example, the coupling of aldehydes or ketones with α,β-unsaturated esters via SmI_2,[41] provides a very convenient route to γ-lactones including spiro derivatives (e.g., **61**) (eq. 30). The reaction is very rapid in the presence of added HMPA. Fukuzawa et al. showed that this methodology could be utilized in an intramolecular sense for the preparation of bicyclic lactones (eq. 31).[42]

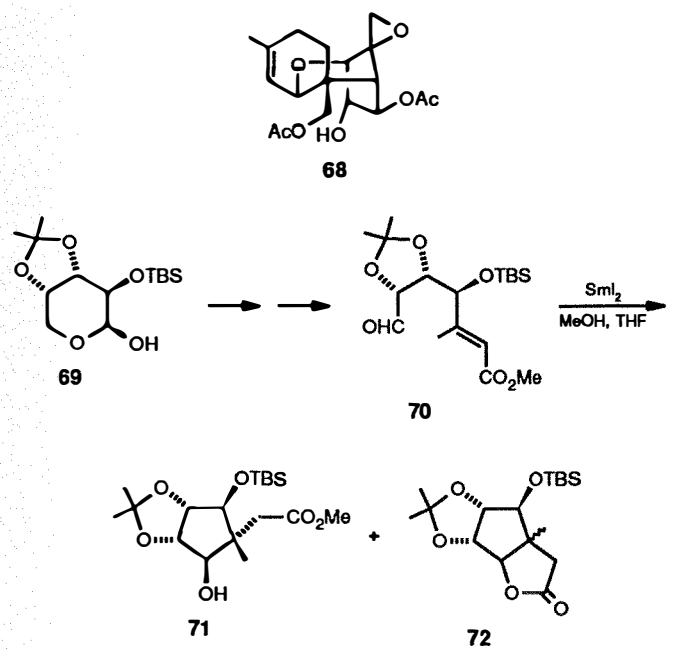
Very recently, Enholm and co-workers[43] have examined this process with a variety of conjugated olefins containing a δ-aldehyde functionality. This procedure results in a modest *trans* selectivity in the cyclopentanes formed (e.g., **65**) regardless of the alkene substitution (i.e., Ph, CN, CO_2Me) (eq. 32). However, for ring closures to cycloalkanones, the *trans* substitution pattern about the olefin portion of the molecule in **66** is essential to achieve the high *trans* selectivity observed for the appendant groups on the newly formed C-C bond in **67** (eq. 33). This approach was employed in the synthesis of the C-ring precursor to the fungal metabolite, anguidine, **68** (Scheme 4).[44] At -78°C, SmI_2 effected the cyclization to afford **71** and **72** with a 5:1 selectivity. Isolated in 65% yield, **71** was subsequently converted to the desired precursor of **68**.

Inanaga has recently demonstrated that ketones can be coupled to alkenes which contain a variety of activating substituents (e.g., OAc, $SiMe_3$, CH_2OAc, Ph, and vinylic).[45] Coupling to 2-trimethylsiloxy-1,3-butadiene, **73**, takes place at the 4 position selectively to provide a novel entry to γ-hydroxyketones (e.g., **74**) (eq. 34).

Some time ago, β-keto esters and amides containing the simple alkene functionality were demonstrated to undergo smooth intramolecular coupling with SmI_2

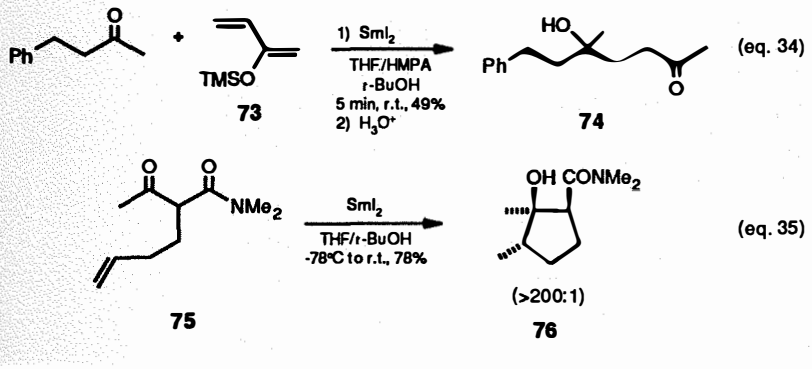


Scheme 4

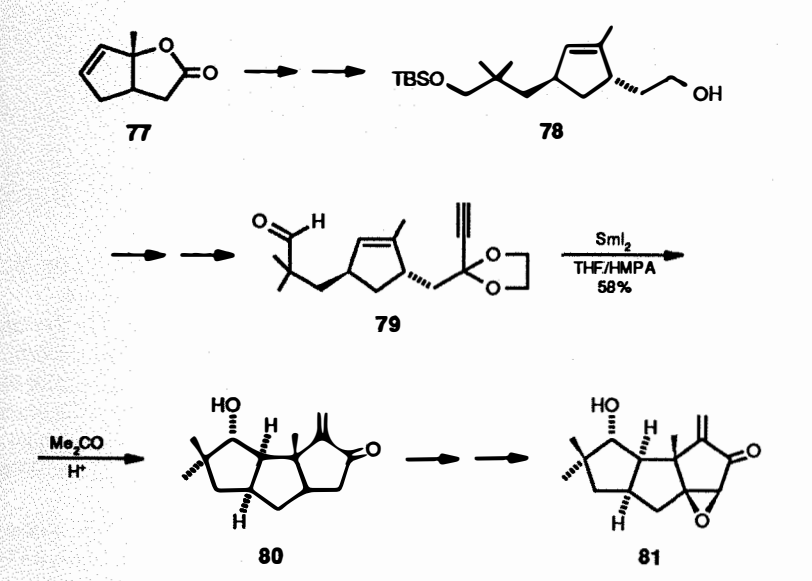


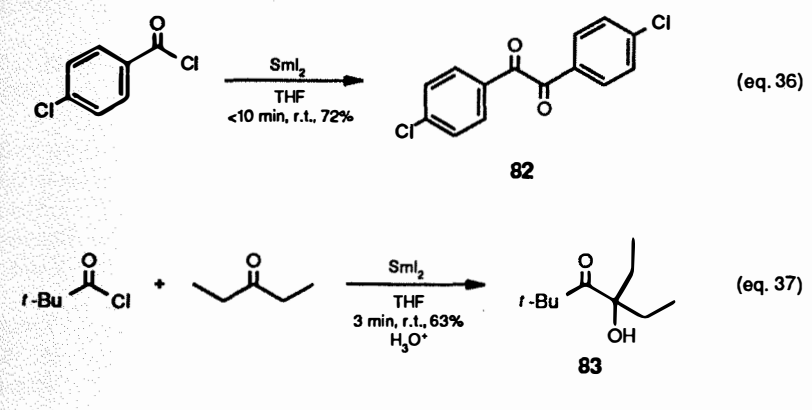
to provide highly substituted cyclopentyl systems in a very selective manner (eq. 35).[46] This olefin-ketone coupling overcomes the difficulties encountered with potential secondary halide precursors to **71** which give retro aldol products. More extensive studies have been reported recently wherein the origin of the high stereoselectivity observed in these cyclizations is discussed in detail.[40]

It is possible for SmI_2 to induce a tandem radical cyclization resulting in the stereoselective formation of natural polycyclic ring systems such as those found in the triquinane series of sesquiterpenes. This scenario was most elegantly demonstrated by Curran and coworkers[47] in their total synthesis of (±)-hypnophilin, **81** (Scheme 5), a sequence which also constitutes a formal synthesis of (±)-coriolin. The tandem cyclization was established to be a radical process with less than two equivalents of SmI_2 being required for the complete reaction of **79**. Also, no deuterium was incorporated into **80** upon quenching with D_2O.



Scheme 5





The pioneering studies of Kagan established that SmI_2 effectively coupled acid chlorides to form α-diketones (e.g., **82**) (eq. 36).[48] The reaction is most amenable to aryl derivatives, but aliphatic acid chlorides can also be coupled with lower efficiency. When an equimolar mixture of an acid chloride and an aldehyde or ketone is added to SmI_2 in THF at room temperature, good yields of the corresponding ketols (e.g., **83**) are obtained after an aqueous work-up (eq. 37).[49] In an attempt to trap acyl radicals or acylsamarium intermediates, both thought to be intermediates in these reactions, acid chlorides were prepared with a proximate allyl ether functionality. A double cyclization occurs with the formation of cyclopropanols (*cf.*, **85**) (Scheme 6).[50] While several mechanistic pathways are possible to account for the formation of these cyclopropanols, the most probable would appear to involve the addition of an acyl radical to the double bond with resulting formation of radical **86**. This species is not unlike those implicated in intramolecular olefin-ketone couplings.[40,46] Such intermediate radicals could also be formed in Imamoto's cyclopropanation of lithium enolates with SmI_2 and CH_2I_2 to give related products.[17] An alternative pathway involving an acylsamarium species, **87**, which rearranges to an oxycarbene, **88**, was also considered plausible for this conversion.

In addition to the above coupling reactions, the formation of an acylsamarium(III) intermediate can account for the cyclization of an acid chloride to give the acyliridium complex, **90**, (eq. 38)[51] which was found to require two equivalents of SmI_2.

In conclusion, it is apparent that the chemistry of samarium(II) iodide is both diverse and fascinating. With the powerful reducing capability of this soluble reagent, many highly useful transformations can be conveniently accomplished. Clearly,

unraveling the mechanistic subtleties of the reductive processes involving polyfunctional compounds will be particularly challenging. Undoubtedly, many new synthetic applications for samarium(II) iodide will be forthcoming.

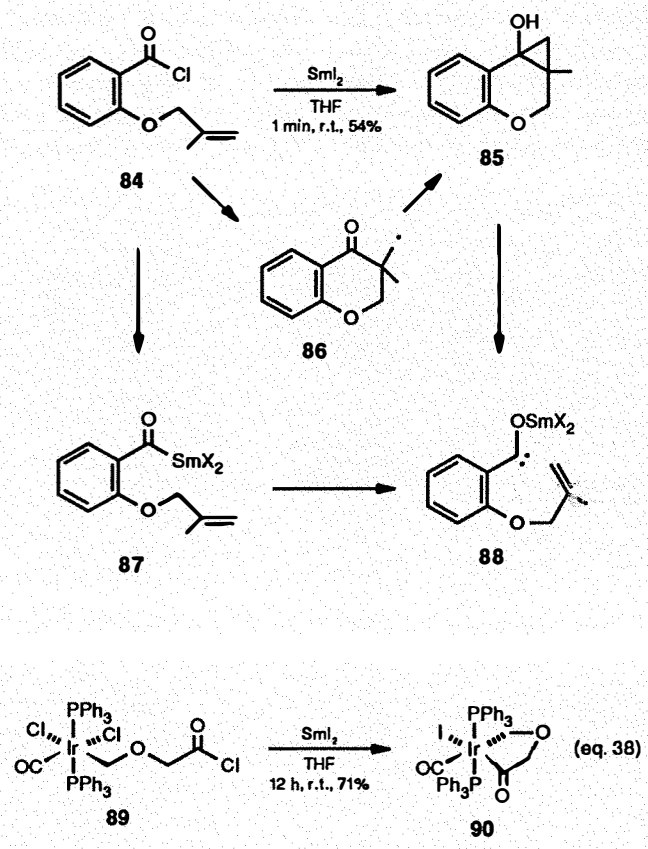
Acknowledgment

The author would like to thank Mr. Tom Benson of Aldrich Chemical Co., Inc. for his help in the preparation of this manuscript and Professor Gary A. Molander of the University of Colorado for helpful discussions regarding this work.

References

1) Girard, P.; Namy, J.L.; Kagan, H.B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.
2) a)Kagan, H.B.; Namy, J.L. *Tetrahedron* **1986**, *42*, 6573. b)Inanaga, J. *Yuki Gosei Kagaku Kyokaishi (Japan)* **1989**, *47*, 200. c)Kagan, H.B. *New J. Chem.* **1990**, *14*, 453. d)Huang, X. *Huaxue Shiji* **1990**, *12*, 86, 117.
3) Namy, J.L.; Girard, P.; Kagan, H.B.; Caro, P.E. *Nouv. J. Chim.* **1981**, *5*, 479.
4) Imamoto, T.; Ono, M. *Chem. Lett.* **1987**, 501.
5) Deacon, G.B.; Forsyth, C.M. *ibid.* **1989**, 837.
6) Zhang, Y.; Lin, R. *Synth. Commun.* **1987**, *17*, 329.
7) Handa, Y.; Inanaga, J.; Yamaguchi, M. *J. Chem. Soc., Chem. Commun.* **1989**, 298.
8) Natale, N.R. *Tetrahedron Lett.* **1982**, *23*, 5009.
9) Molander, G.A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.
10) Yoneda, R.; Harusawa, S.; Kurihara, T. *Tetrahedron Lett.* **1989**, *30*, 3681.
11) Kusuda, K.; Inanaga, J.; Yamaguchi, M. *ibid.* **1989**, *30*, 2945.
12) Crombie, L.; Rainbow, L.J. *ibid.* **1988**, *29*, 6517.
13) Fukuzawa, S.-I.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1987**, 920. For 1,2-additions, see: Ma, S.; Lu, X. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2031; *Idem Tetrahedron* **1990**, *46*, 357.
14) Scott, L.T.; Cotton, W.D. *J. Am. Chem. Soc.* **1973**, *95*, 2708.
15) Molander, G.A.; Etter, J.B. *J. Org. Chem.* **1987**, *52*, 3942.
16) Molander, G.A.; Harring, L.S. *ibid.* **1989**, *54*, 3525.
17) Imamoto, T.; Takeyama, T. *Tetrahedron Lett.* **1987**, *28*, 1307.
18) Simmons, H.E.; Cairns, T.L.; Vladuchick, S.A.; Hoiness, C.M. *Org. React.* **1973**, *20*, 1.

Scheme 6



19) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3891.
20) Matsukawa, M.; Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 2101.
21) Molander, G.A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596.
22) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4437.
23) Molander, G.A.; La Belle, B.E.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 5259.
24) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 601.
25) *Idem ibid.* **1986**, *27*, 5237.
26) *Idem ibid.* **1987**, *28*, 215. See also: Hanzawa, Y.; Ishizawa, S.; Kobayashi, Y.; Taguchi, T. *Chem. Pharm. Bull.* **1990**, *38*, 1104.
27) Souppe, J.; Namy, J.L.; Kagan, H.B. *Tetrahedron Lett.* **1982**, *23*, 3497.
28) Araki, S.; Hatano, M.; Ito, H.; Butsugan, Y. *J. Organomet. Chem.* **1987**, *333*, 329.
29) Namy, J.L.; Souppe, J.; Collin, J.; Kagan, H.B. *J. Org. Chem.* **1984**, *49*, 2045. For a recent example of a highly *anti*-selective Sm(III)-catalyzed Tischenko reduction of β-hydroxy ketones, see: Evans, D.A.; Hoveyda, A.H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.
30) Imamoto, T.; Takeyama, T.; Yokoyama, M. *Tetrahedron Lett.* **1984**, *25*, 3225.
31) Murakami, M.; Kawano, T.; Ito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2437.
32) Molander, G.A.; Etter, J.B. *Tetrahedron Lett.* **1984**, *25*, 3281. For a recent SmI_2-initiated radical cyclization prior to intermolecular addition of alkylsamarium intermediates to ketones, see: Molander, G.A.; Harring, L.S. *J. Org. Chem.* **1990**, *55*, 6171.
33) Molander, G.A.; Etter, J.B.; Zinke, P.W. *J. Am. Chem. Soc.* **1987**, *109*, 453.
34) Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889.
35) Molander, G.A.; Etter, J.B. *J. Am. Chem. Soc.* **1987**, *109*, 6556.
36) Moriya, T.; Handa, Y.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1988**, *29*, 6947.
37) Namy, J.L.; Souppe, J.; Kagan, H.B. *ibid.* **1983**, *24*, 765. For the analogous coupling of imines, see: Imamoto, T.; Nishimura, S. *Chem. Lett.* **1990**, 1141; Enholm, E.J.; Forbes, D.C.; Holub, D.P. *Synth. Commun.* **1990**, *20*, 981.
38) Matsukawa, M.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 5877.
39) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1988**, *53*, 2132.

40) *Idem J. Am. Chem. Soc.* **1989**, *111*, 8236.
41) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763.
42) Fukuzawa, S.-I.; Iida, M.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1987**, 920.
43) Enholm, E.J.; Trivellas, A. *Tetrahedron Lett.* **1989**, *30*, 1063.
44) Enholm, E.J.; Satici, H.; Trivellas, A. *J. Org. Chem.* **1989**, *54*, 5841.
45) Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2837.
46) Molander, G.A.; Kenny, C. *ibid.* **1987**, *28*, 4367. For the related coupling of alkynes with carbonyl compounds, see: Shim, S.C.; Hwang, J.T. *ibid.* **1990**, *31*, 4765.
47) Fevig, T.L.; Elliot, R.L.; Curran, D.P. *J. Am. Chem. Soc.* **1988**, *110*, 5064.
48) Souppe, J.; Namy, J.L.; Kagan, H.B. *Tetrahedron Lett.* **1981**, *22*, 3959.
49) *Idem ibid.* **1984**, *25*, 2869.
50) Sasaki, M.; Collin, J.; Kagan, H.B. *ibid.* **1988**, *29*, 6105.
51) Zizelman, P.M.; Stryker, J.M. *Organometallics* **1990**, *9*, 1713.

About the Author

Professor John A. Soderquist was born in Iowa in 1944. After receiving the B.S. degree in chemistry from Iowa State University in 1966, he taught high school chemistry and received the M.S. degree from Bowling Green State University under Professor T.H. Kinstle. He obtained the Ph.D. degree in 1977 from the University of Colorado under the direction of Professor A. Hassner. After postdoctoral studies at Purdue University with Professor H.C. Brown from 1977-79, he joined the faculty of the University of San Francisco, where, after promotion to associate professor, he served as Department Chairman (1982-83). In 1983, he moved to the University of Puerto Rico, becoming a full professor in 1988. He spent the past academic year at Aldrich as Manager of Laboratories in Sheboygan, Wisconsin.

Professor Soderquist is the recipient of the Scholarly Productivity Award, NSF-EPSCoR of Puerto Rico (1988, 1989, 1990); the Distinguished Research Award, University of San Francisco (1983); the Conoco Fellowship, University of Colorado (1974-1975); and the Ted Gilman Award for Outstanding Teaching of Freshman Chemistry, University of Colorado (1973). He and his group are currently involved with research in the area of silicon-, germanium- and tin-mediated chemical synthesis, principally through organoborane chemistry.

Page intentially blank

Aldrichimica Acta

Volume 24, Number 2, 1991

Fluoroheterocyclic Compounds:
Synthesis, Reactions, and Commercial Applications

Transannular Diels-Alder Reaction on Macrocycles:
A General Strategy for the Synthesis of Polycyclic Compounds

chemists helping chemists in research & industry

aldrich chemical company, inc.

Aldrichimica Acta

Volume 24, Number 2, 1991
A publication of the ALDRICH CHEMICAL COMPANY

Aldrich Chemical Co., Inc.
1001 West Saint Paul Avenue
Milwaukee, Wisconsin 53233 USA

To Place Orders

Telephone	800-558-9160 (USA/Canada)
	414-273-3850
TWX	910-262-3052 Aldrichem MI
TELEX	26 843 Aldrich MI
FAX	800-962-9591
	414-273-4979
Mail	P.O. Box 2060
	Milwaukee, WI 53201 USA

Customer Service

Customer Inquiries	800-558-9160
Technical Information	800-231-8327
Bulk Sales	800-255-3756
Custom Synthesis	800-255-3756
Flavors & Fragrances	800-227-4563

General Correspondence
P.O. Box 355, Milwaukee, WI 53201 USA

Belgium
Aldrich Chemie
Bd. Lambermontlaan, 140 B6
B-1030 Bruxelles/Brussel
Telephone: 02 242 87 50
(local) 11 47 47
Telex: 62302 Alchem B
FAX: 02 242 82 16

France
Aldrich-Chimie S.a.r.l.
BP 234
67006 Strasbourg Cedex
Telephone: 88 32 70 10
Telex: 890076 Aldrich F
FAX: 88 75 12 83

Germany
Aldrich-Chemie GmbH & Co. KG
D-7924 Steinheim
Telephone: (0) 7329 87 - 0
For orders: (0) 7329 87 110
Telex: 714838 Aldri D
FAX: (0) 7329 87 - 139/239

Holland
Aldrich Chemie
Telephone: 32 (0)2 242 87 50
(local) 06 022 47 48
Telex: 62302 Alchem B
FAX: 32 (0)2 242 82 16

Italy
Aldrich Chimica
Via Pietro Toselli, 4
20127 Milano
Telephone: 02/261 36 89
Telex: 330862 Aldrch I
FAX: 02/289 63 01

Japan
Aldrich Japan
Kyodo Bldg. Shinkanda
10 Kanda-Mikuracho
Chiyoda-Ku, Tokyo
Telephone: 03-3258-0155
FAX: 03-3258-0157

Spain
Aldrich Quimica
Apt. de Correos, 161
28100 Alcobendas (Madrid)
Telephone: (9)1-661 99 77
Telex: 22189 SAQS E
FAX: (9)1-661 80 84

United Kingdom
Aldrich Chemical Co. Ltd
The Old Brickyard, New Road
Gillingham, Dorset SP8 4JL
Telephone: (0747) 822211
For orders: 0800 71 71 81
Telex: 417238 Aldrch G
FAX: (0747) 823779

About Our Cover:

Our chemist collector loves to buy problem paintings — those with problems of attribution or with the subject in doubt. This painting (oil on canvas, 34 x 25 inches) obviously depicts Tobias catching the fish — the seventh Tobias on our *Aldrichimica Acta* covers. It is fully signed Jan van de Venne, but who was this artist? Our chemist collector knows of only one other painting with this signature, a winter landscape dated 1670, which belonged to the museum in Darmstadt but which was burnt during the last war. However, surely an artist who painted so well must have produced other works. Dealers have often erased signatures to be able to attribute works to better known and, hence, more valued painters. We don't even know whether this artist was Flemish or Dutch. Perhaps our cover will lead to other paintings, resulting in a clearer understanding of this painter's work.

The Detective's Eye: Investigating the Old Masters

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

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

Telling Images—Images Révélatrices

Large, 150-page catalog of thirty-six Old Master paintings now in a travelling exhibition touring Canada. All were given by the Baders to Queen's University.

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

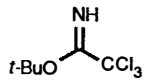
Pictures from the Age of Rembrandt

Twenty-eight paintings that have been reproduced on our *Acta* covers, and seven that have been on our catalog covers were among the thirty-six paintings in an exhibition of Dutch paintings at Queen's University in Kingston, Ontario. The fully illustrated catalog written by Professor David McTavish contains a wealth of art-historical information — enough for several evenings of relaxed enjoyment — probably the best value in art-history anywhere.

"Please Bother Us."

by Yfra Baan.

Dr. R.F.W. Jackson at the University of Newcastle and Mr. D.J. Wadsworth, working with Professor S.V. Ley at Imperial College, suggested this interesting reagent for the preparation of *tert*-butyl ethers and esters.



Naturally, we made this compound.

Wessel, H.-P.; Iversen, T.; Bundle, D.R. *J. Chem. Soc., Perkin Trans. 1* **1985,** 2247. Armstrong, A.; Brackenridge, I.; Jackson, R.F.W.; Kirk, J.M. *Tetrahedron Lett.* **1988,** *29,* 2483.

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

Interested in Alchemy?

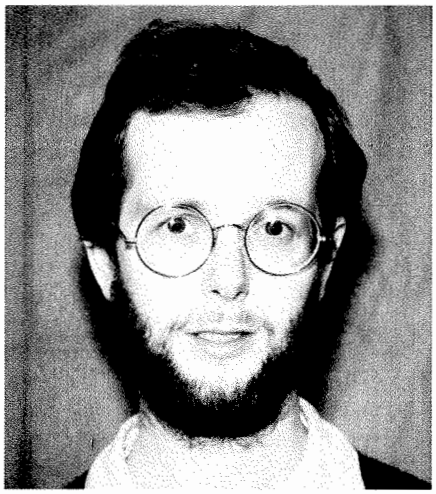
In February 1931, one of the greatest chemists of this century, Professor Tadeus Reichstein, presented a lecture on the true meaning of alchemy at the ETH in Zürich.

With any order of Aldrich products, you can now obtain, *at no charge*, a printed English version or a photocopy of the original German manuscript.

Z22,319-0 The Meaning of Alchemy
Z22,320-4 Der Sinn der Alchemie

Fluoroheterocyclic Compounds:
Synthesis, Reactions, and Commercial Applications

Michael J. Silvester
Aldrich Chemical Co. Ltd.
Bristol Organics Division
Sharpness Docks
Berkeley
Gloucestershire
GL13 9UG
England



INTRODUCTION

In a previous article,[1] we discussed the benefits of having fluorine in a molecule and, in general terms, the chemistry of fluoroaromatic compounds. Heterocyclic compounds offer many opportunities for the synthetic organic chemist, and the challenges offered by the presence of fluorine are just as exciting. Fluoroheterocyclic compounds are important in both academic and industrial fields and will continue to be of significant interest. In order to introduce this area, we shall consider the synthesis, reactions, and commercial applications of those compounds containing five- or six-membered heterocyclic rings substituted with either fluorine or a polyfluoroalkyl group. Heteroatoms will be limited to O, N, and S. Reviews are available on polyfluoroheteroaromatic chemistry[2-4] and general fluoroheterocyclic chemistry.[5]

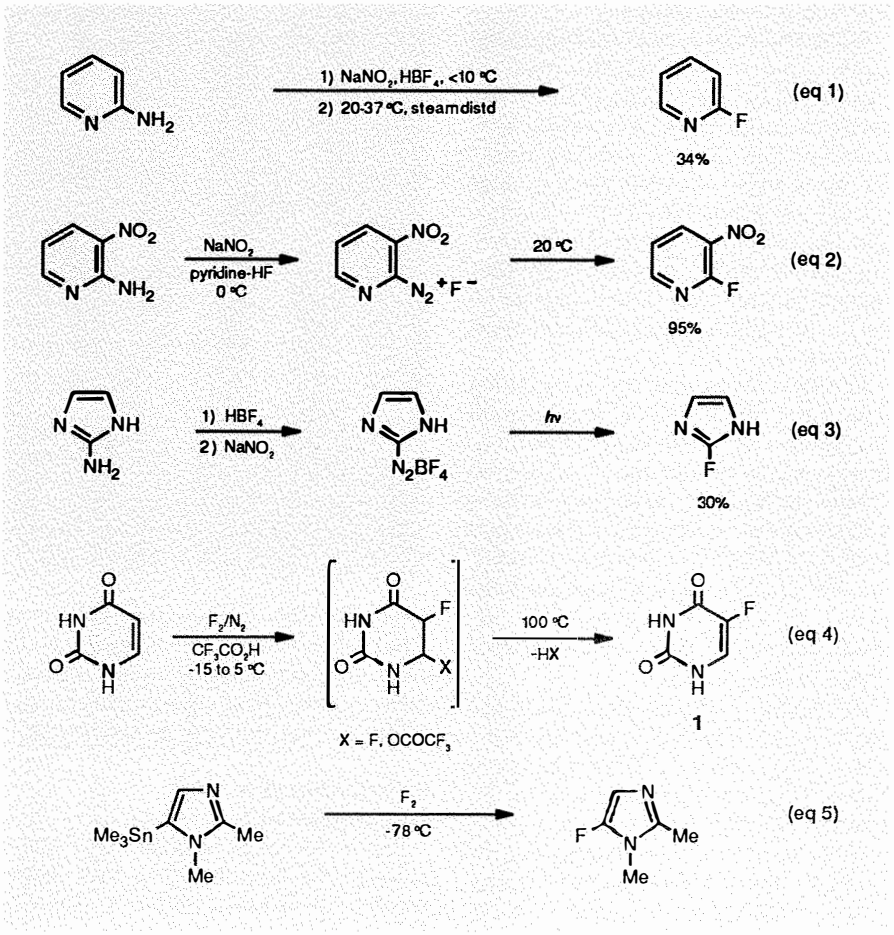
SYNTHESIS

Introduction of Fluorine into a Heterocycle

Partially fluorinated heteroaromatics can readily be obtained by the conversion of $-NH_2$ to -F using the Balz-Schiemann[6] and related reactions. The intermediate tetrafluoroborate salt can be decomposed by pyrolysis,[7] as can the diazonium fluoride.[8] Salts that are too soluble in aqueous medium for isolation can be decomposed in situ. Photochemical decomposition is a useful technique in this instance and is of great interest in the development of antiviral compounds.[9] Transformation of $-NH_2$ to -F can also be achieved using *tert*-butyl nitrite in pyridine-HF, the concentration of HF being critical.[10] (eq 1-3)[11-13]

Introduction of elemental fluorine into a heterocycle can be achieved by the use of fluorine or an electrophilic fluorinating reagent. Direct fluorination was once notorious for being unpredictable and nonselective; however, extensive work has gone into developing new approaches to overcome these problems.[14-16] By careful choice of conditions, selective or total fluorination is possible. Direct fluorination of uracil enabled the large scale production of 5-fluorouracil (**1**, eq 4),[17] and this has been extended to other nucleosides.[18] Introduction of an organometal site enables fluorination to occur selectively (eq 5).[19] On the other hand, highly branched *N*-heterocycles can be perfluorinated.[20]

There is increasing literature on the use of electrophilic fluorinating (F^+) reagents, especially in the synthesis of bioactive molecules where selectivity and mild reaction conditions are important considerations. Examples include trifluoromethyl hypofluorite (CF_3OF),[21] which converts cytosine to 5-fluorocytosine in 85% yield,[22] and cesium fluoroxysulfate ($CsSO_4F$),[23] which reacts with uracil to give 5-fluorouracil.[24]



Acetyl hypofluorite ($MeCO_2F$) has been used to fluorinate bimane derivatives.[25]

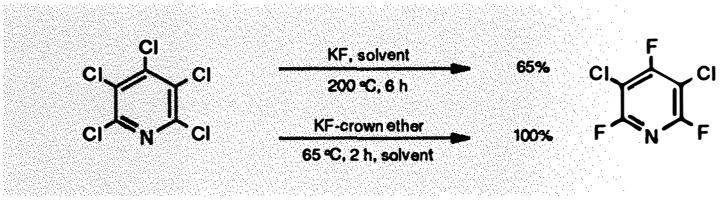
Extensive fluorination of heterocycles can be achieved by the use of halogen exchange methods,[26] high-valency metal fluorides,[27] and electrochemical methods.[28]

Halogen exchange methods are of major importance in the synthesis of polyfluoroazaaromatics, with the activating influence of the ring nitrogen having a major effect on the ease of substitution of chlorine by fluorine. This has enabled a general approach to be developed whereby the hydrocarbon analog is polychlorinated, followed by halogen replacement with potassium fluoride. As with fluoroaromatics, the conditions and source of fluoride ion can be varied depending on the reactivity of the precursor and the product desired. This process is widely applicable and has enabled the synthesis of, for example, pentafluoropyridine,[29] perfluoroquinoline and -isoquinoline,[30] and perfluoropyrimidine.[31] Although potassium fluoride is the most common source of fluoride ion, sodium fluoride can be used with highly activated compounds such as 1,3,5-trichlorotriazine.[32] Halogen exchange is also possible at highly activated sites using KHF_2.[33] Crown ethers and tetraalkylammonium salts can be used to enhance reactivity (eq 6).[34,35] Electrophilic halogen exchange is also possible with HF[36] and antimony fluorides.[37]

While fluorination-defluorination/dehydrofluorination is a useful route to fluoroaromatics, the yields are very low for fluoroazaaromatics. In contrast, however, fluorinated furans[38] and thiophenes[39] can be obtained in good yield by high valency metal fluoride (HVMF) fluorination and subsequent dehydrofluorination. This allows access to compounds that, being π-electron rich, are not suitable for the nucleophilic halogen exchange route (Scheme 1).

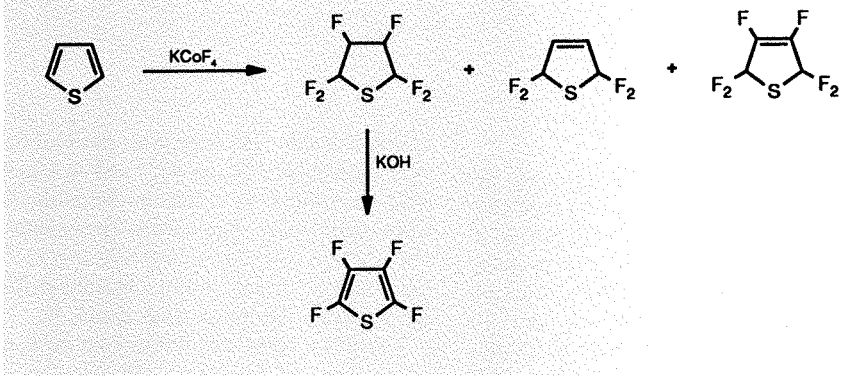
Complex mixtures can arise during HVMF fluorination, but it has been found that the introduction of a polyfluoroalkyl group greatly enhances stability. This has allowed a methodology to develop whereby a fluoroalkene is added by a free radical reaction to an ether, followed by fluorination with the HVMF to give the perfluoro analog in excellent yield (eq 7).[40] Recently this has been extended to electrochemical fluorination.[41]

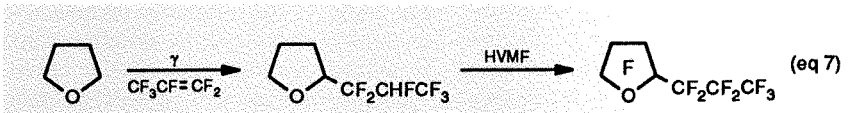
Electrochemical fluorination is the process whereby an organic compound is electrolyzed in HF, usually with KF to improve conductivity, and at potentials below that at which fluorine is evolved. Saturation occurs together with perfluorination; for example, pyridine yields perfluoropiperidine.[42] Perfluorocyclic ethers can be obtained directly, as mentioned before, or from straight chain esters that can undergo cyclization. Cyclic tertiary amines, such as derivatives of morpholine and piperidine, are similarly perfluorinated.[43]



(eq 6)

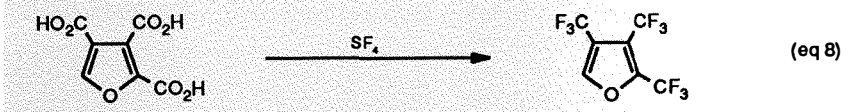
Scheme 1



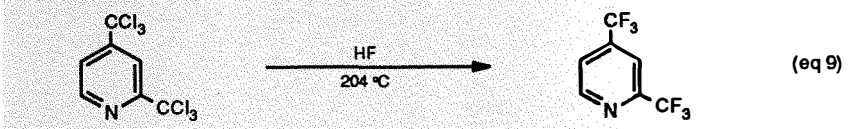


(eq 7)

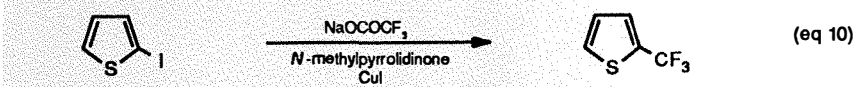
Note: An F in the center of a ring implies that all unassigned positions are attached to fluorine.



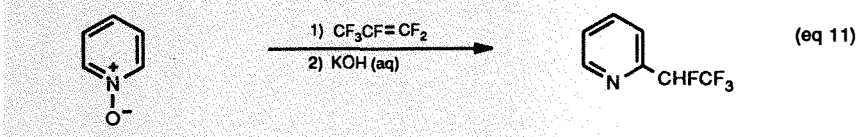
(eq 8)



(eq 9)



(eq 10)



(eq 11)

2

Introduction of a Polyfluorinated Side Chain

The trifluoromethyl group is the most important polyfluorinated side chain. Sulfur tetrafluoride converts $-CO_2H$ to $-CF_3$ (eq 8)[44,45] and enables, for example, trifluoromethylated pyridines to be obtained in 70-75% yield.[46] Trifluoromethylated thiophenes can be obtained similarly,[47] and the reaction is quite general. The transformation of $-CCl_3$ to $-CF_3$ can be carried out using HF[48] either on its own or with antimony pentafluoride (eq 9).

Both of these methods have disadvantages related to reaction conditions, toxicity, and difficulty of handling; therefore,

there is an increasing search for new methods for directly introducing -CF_3. Trifluoromethyl iodide will trifluoromethylate bromo- and iodoheterocycles in the presence of copper.[49] The reaction is believed to proceed via a complex involving [CF_3Cu][50] and this has led to an interest in preforming it; a review on the preparation of [CF_3Cu] is available.[51] Trifluoromethylation of bioactive molecules, such as halouracils,[52] is possible. Burton's reagent (Cu, CF_2Br_2, $AcNMe_2$) allows direct trifluoromethylation of 2-chloropyridine.[53] Other methods involving an intermediate copper complex include the copper(I) iodide assisted decomposition of sodium trifluoroacetate (eq 10).[54,55]

Other sources of the trifluoromethyl group include electrolysis of trifluoroacetic acid;[56] bis(trifluoroacetyl) peroxide,[57] which trifluoromethylates thiophene in good yield via an electron-transfer mechanism; and $CF_3N(NO)SO_2CF_3$, which introduces the CF_3 group into uridine.[58]

Longer perfluoroalkyl chains may be introduced by reaction of the perfluoroalkyl copper reagent with a bromoheterocycle.[59] Photochemical perfluoroalkylation of sodium imidazolide with perfluoro-*n*-alkyl iodides yields 4-fluoroalkylated compounds.[60] Groups such as -CF_2CF_3 and -$CF(CF_3)_2$ can be introduced into activated heteroaromatics via the respective carbanions. This area will be discussed in the Reactions section. A novel route enables the introduction of -$CHFCF_3$ by nucleophilic attack of **2** on $CF_3CF{=}CF_2$ (eq 11).[61]

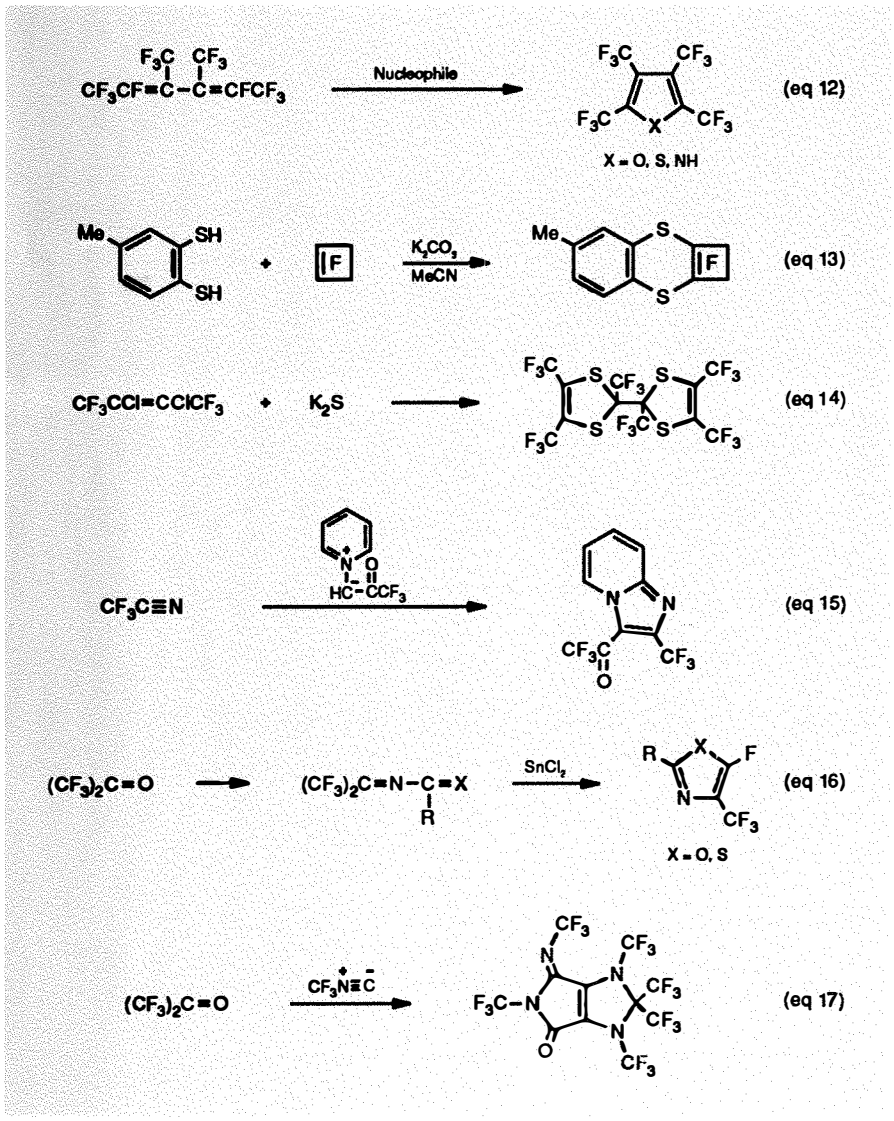
Formation of a Heterocyclic Ring from Fluorinated Precursors

There are many approaches to the synthesis of heterocyclic rings from fluorinated precursors. As expected, nucleophilic substitution plays an important role, although sometimes the distinction between nucleophilic attack and cycloaddition, as in the case of 1,3-dipoles, is rather arbitrary.[62] Reaction of 1,3-dipoles with fluoroalkenes and alkynes is a tremendously important area with many intriguing ring structures being obtained and rearrangements leading to further interesting derivatives.

Conversely, fluorinated 1,3-dipoles, such as $CF_3C{\equiv}N^+{-}O^-$ and $CF_3C{\equiv}N^+{-}C^-HAr$, may be used as synthons for trifluoromethyl azoles.[63] Cycloaddition reactions allow access to a wide range of heterocycles, for example, the [4π + 2π] addition of nitriles to perfluorocyclohexa-1,3-diene yields 2-substituted tetrafluoropyridines,[64] which are otherwise not readily accessible. Condensation reactions using classical methods offer another possible approach.[65]

The use of hexafluoroacetone as a means of synthesizing heterocycles containing the CF_3 group has been reviewed.[66] Oxazoles, thiazoles, and imidazoles are potential end-products (eq 16),[67] and also allow access to CF_3-substituted α-amino and α-hydroxy acids.[68] Other fluorinated building blocks include $(CF_3)_2C{=}C{=}S$ in cycloaddition reactions;[69] trifluoropyruvic acid hydrate for trifluoromethylated benzoxazine, thiazine, and oxazoles;[70] and trifluoropyruvaldehyde in the synthesis of CF_3-pyrazines.[71]

A few examples of the tremendous number of reactions and fluorinated compounds are illustrated in equations 12-17.[72-76]



REACTIONS

Highly fluorinated azaaromatics react with a wide range of nucleophiles with reactivity increasing along the series perfluoropyridine, -pyrimidine, and -*s*-triazine. A substantial amount of work has gone into understanding the factors that influence the reactivity and orientation of substitution.[77] The ring nitrogen has a dominant influence with *o*- and *m*-fluorines being strongly activating.[78] Perfluoroazaaromatics are considerably weaker bases than their hydrocarbon analogs; however, protonation with Lewis or proton acids can occur. Subsequent reaction with nucleophiles leads to a different pattern of substitution.[79]

A wealth of chemistry is based around polyfluoroalkylation reactions involving perfluorocarbanions (R_F^-) and perfluoroazaaromatics. The reaction sequence can be likened to an inverse demand Friedel-Crafts.[80] As in the Friedel-Crafts reaction, rearrangements can occur, with factors such as carbanion stability being important. With polysubstitution, the R_F groups may begin to control the site of further attack, steric effects may become important, and some of the reactions can be reversible. Competition between kinetic and thermodynamic control can result, and this area has considerable

significance for mechanistic chemistry (Scheme 2).[80] Recent developments include an investigation into the chemistry of the nitrogen anion **3**. This anion is observable on the NMR time scale and can be trapped with various electrophiles,[81] as well as fluoroazaaromatics (Scheme 3).[82]

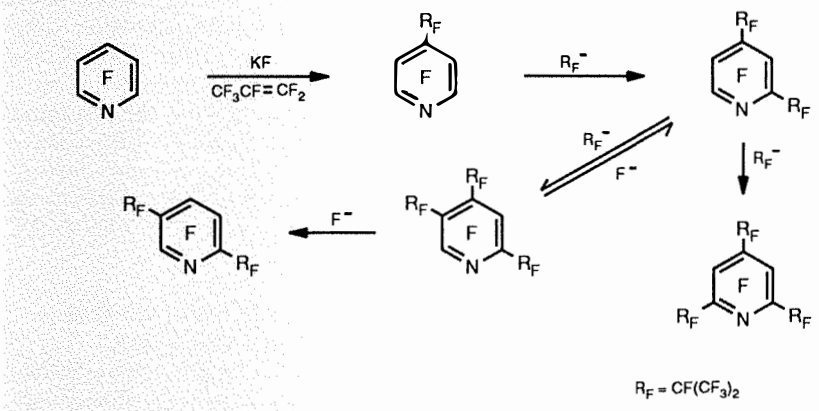
The thermal and photolytic chemistry of perfluoroalkylated azaaromatics is a rich area of study. The striking thermal stability of perfluoroalkyl-substituted strained rings, thought to be a kinetic phenomenon,[83] has enabled many unusual compounds to be isolated. Photochemical transformation of perfluoroalkyl pyridines allows access to valence isomers of surprising stability. For example, **4** is unchanged after six months at room temperature (eq 18).[84] Fluorine or R_F groups are useful in monitoring skeletal rearrangements, because side reactions are kept to a minimum. Different R_F groups on the same ring allow insight into the mechanism, and ^{19}F-NMR is very useful in structural determination. Fluorinated thiophenes[85] and furans[86] can undergo similar photochemical transformations.

Photochemical decomposition of fluorinated 1,2,3-triazine derivatives leads to interesting structures and there is evidence for the generation, trapping, and direct observation of an azete (eq 19).[87] Thermal rearrangement of fluorinated pyridazines gives predominantly pyrimidines in a radical process that is complicated by the fact that one compound promotes the rearrangement of the other (eq 20).[88] High-valency metal fluoride fluorination of perfluoroalkylated azaaromatics can lead to cyclic azaolefins via a radical cation mechanism.[89] In some instances, the products themselves undergo photochemical conversions to cyclobutenes by a rare example of a photochemically induced retro-Diels-Alder reaction.[90]

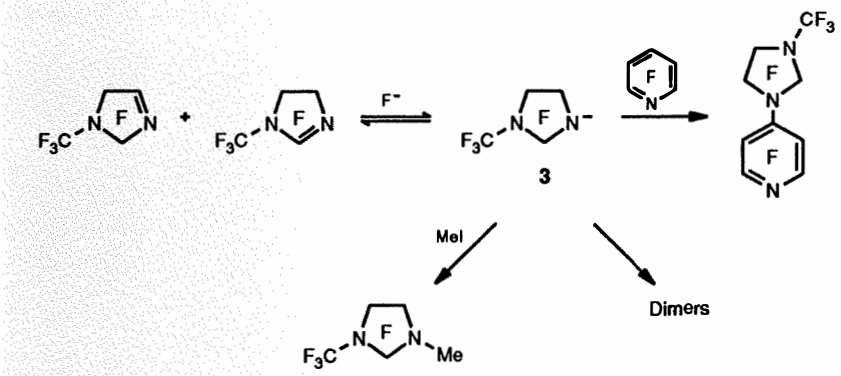
Pentafluoropyridine can be reduced electrochemically via a radical anion to the 4,4'-bipyridyl **5**.[91] An alternative would be the usual copper coupling reaction,[92] and indeed, much standard chemistry can be carried out on fluoroheterocycles (Scheme 4). Selective chlorination of tetrafluoropyrimidine with anhydrous hydrogen chloride offers a new route to 5-fluorouracil.[93] Organometallic compounds can be obtained, but they are relatively unstable and their chemistry is not as well developed as the chemistry of fluoroaromatics.[2]

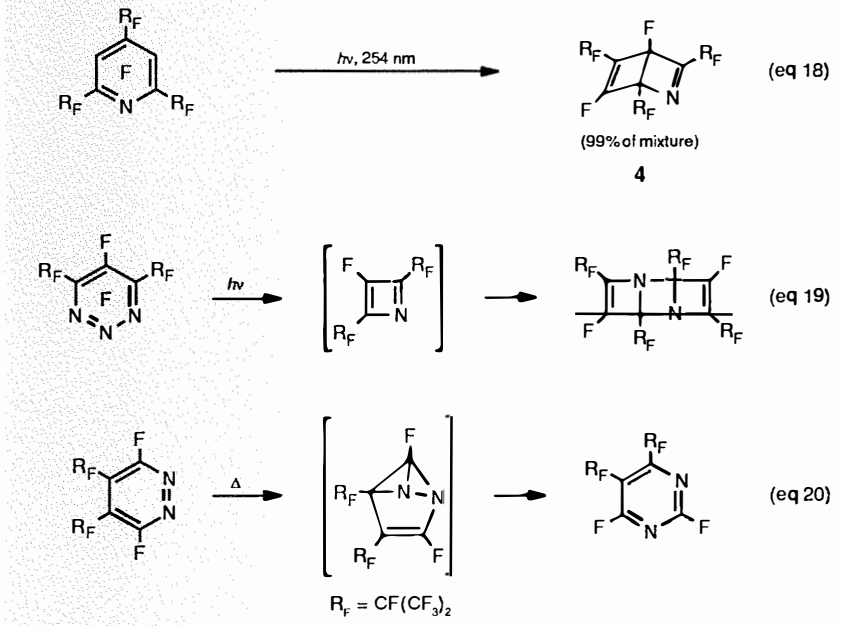
For many fluoroheterocyclic compounds, the chemistry available is standard and will not be discussed. With perfluorinated cyclic ethers and amines, the lack of reactivity is their main feature, although treatment of perfluoro(*N*-alkyl-cyclic amines) with oleum yields perfluorolactams.[94]

Scheme 2



Scheme 3





COMMERCIAL APPLICATIONS

The uses of fluoroheterocycles are as many as they are varied; therefore, only general areas with examples will be described here. The interested reader is directed toward two volumes on industrial organofluorine chemistry.[95,96]

Agrochemicals and pharmaceuticals are major areas of interest. In both cases, the presence of fluorine either imparts some useful property to the end-product or is important as an activating or leaving group in a complex synthesis. Agrochemical intermediates[97] include **6** (eq 21)[98] and **7** (eq 22).[99] Trifluoromethylated pyridines, such as **8**, are of continuing interest,[100] but the overall complexity of types is illustrated by two herbicides (**9** and **10**).

The antitumor activity of 5-fluorouracil (5-FU) is well known,[101] but there is a continual search for new and more efficacious compounds.[102] Developments include *N'*-tetrahydrofuranyl uracils. Ftorafur[103] is a source of in vitro 5-fluorouracil and is claimed to be more effective and less toxic than 5-FU. 5-Fluorocytosine is an orally active antifungal agent. The importance of investigating all isomers for bioactivity is well illustrated by the fact that 2-fluorohistidine, an antiviral agent, shows a wide spectrum of activity while 4-fluorohistidine is devoid of activity.[104] Fluorinated cyclic ethers have been considered as inhalation anesthetics (e.g., **11**, Figure 2).[105] Replacement of hydrogen with fluorine reduces flammability but can lead to instability toward alkali scrubbers, and incomplete substitution is necessary for good anesthesia. A balance between hydrogen and fluorine has to be struck.

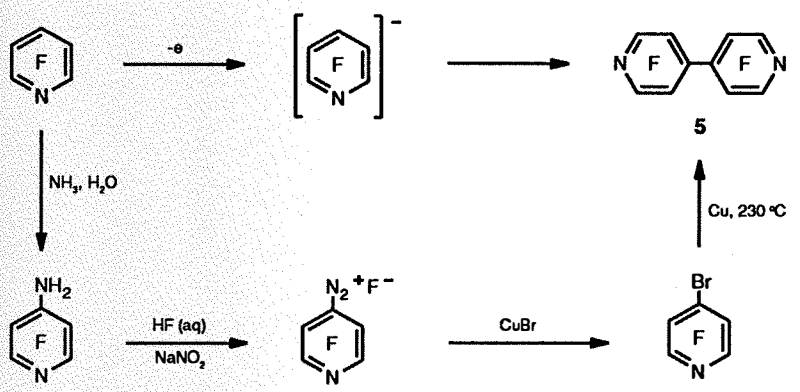
Mefloquine was developed as an antimalarial agent to overcome the increasing resistance toward other agents and illustrates how a complex molecule can be constructed from a simple building block.[106] In many cases, fluorine can be used as an activating or leaving group in a synthetic chain. For example, enoxacin, a potent antibacterial agent, can be prepared from fluoronictonic acid derivatives, while **12** is an intermediate for others.[107] Fluoroquinolones are tremendously important antibacterials.

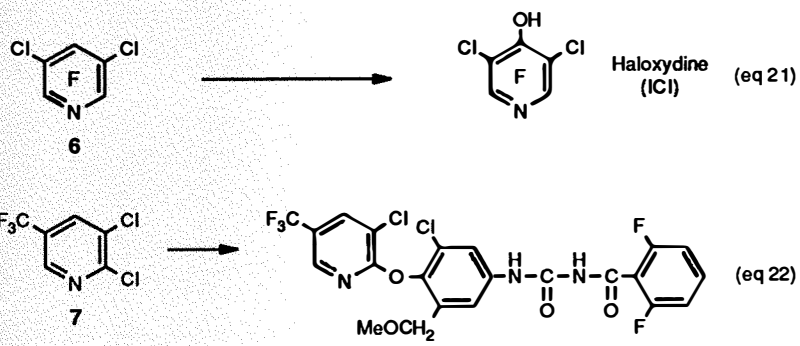
A great deal of interest has been expressed in perfluorosaturated compounds as potential blood substitutes, where their physical and chemical properties are of great value.[108] Residence time in the body, toxicity, emulsification properties, and solubility of both oxygen and carbon dioxide are just some of the many factors that have to be considered. Perfluoronitrogen and -oxygen heterocycles such as **13** are potential candidates.

The inertness of saturated fluorinated heterocycles has encouraged investigation into their use as hydraulic and heat pump fluids.[109] They have electrical properties that make them useful as electrical insulating oils (e.g., **14**).[110] Perfluoroalkylated-*s*-triazines are also useful as high-temperature lubricants and hydraulic fluids[111] and as elastomers.[65]

Polyfluoroazaaromatics are important precursors to fiber-reactive dyes.[112] Reactive dyes based on fluoropyrimidines have been on the market since 1970, with 5-chloro-2,4,6-trifluoropyrimidine being the principal intermediate. In all cases, it is the activation of the compound toward nucleophilic substitution that is important (eq 23). There is continued interest in development of dyes based on triazines or containing a

Scheme 4

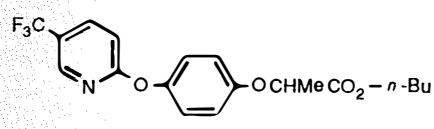




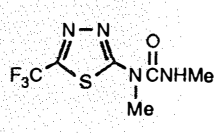
6

7

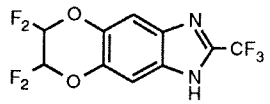
Figure 1



8
Fluazifop-butyl



9
Thiazafluron



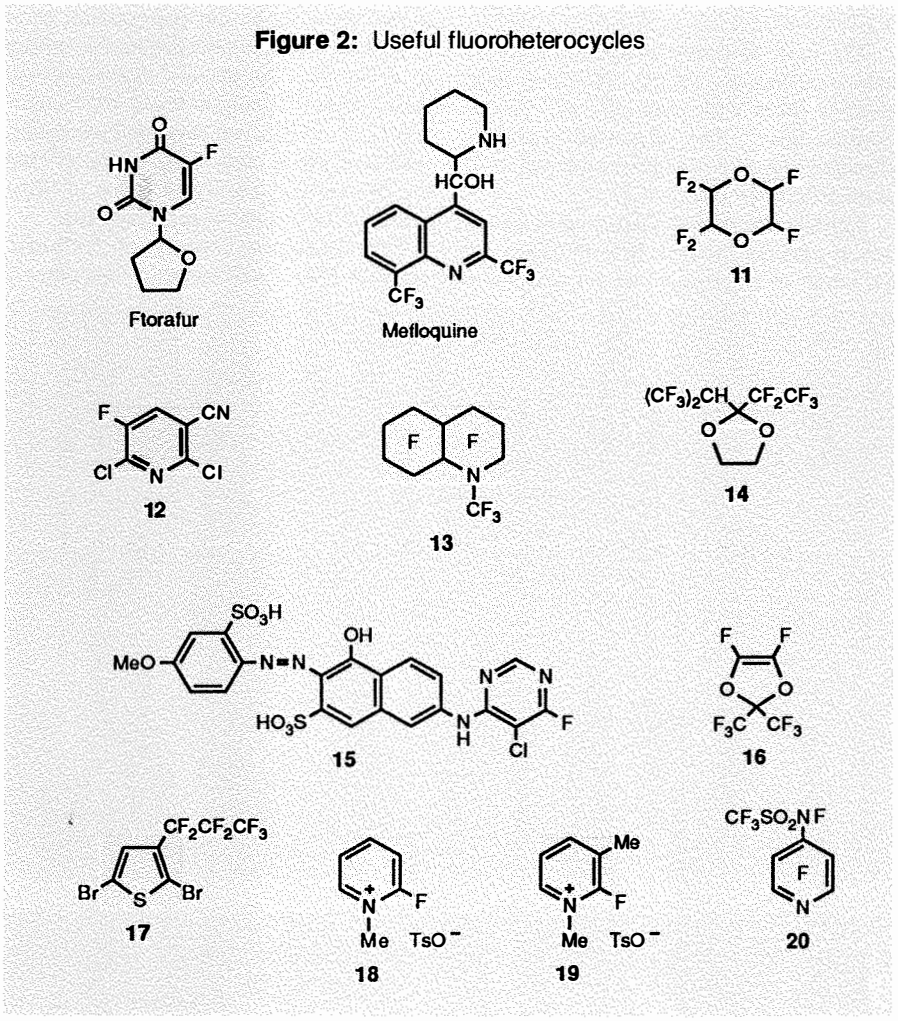
10

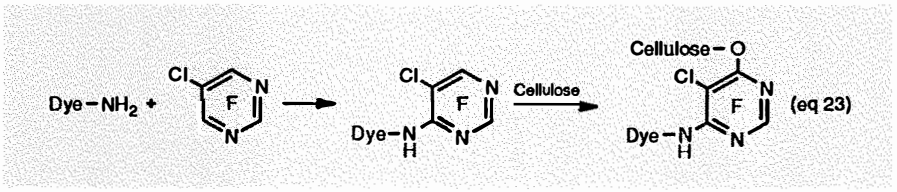
broad range of chromophores. Reduction in waste and improvement of fastness are also of concern. A typical example of a fiber-reactive dye is **15**.[113]

Fluoroheterocyclics find diverse applications in polymers. An example of the use of fluorine as a leaving group is illustrated by 2,6-difluoropyridine, an intermediate for aromatic polyether synthesis.[114] Compound **16** forms the basis of a new family of polymers (Teflon AF - DuPont) which, together with the usual properties of fluoropolymers, also has a very high glass transition temperature and excellent optical clarity.[115] For example, electrical conducting materials can be obtained from, for example, **17**.[116]

Finally, fluorinated heterocycles are used in analysis and as reagents. 2-Fluoro-1-methylpyridinium *p*-toluenesulfonate (**18**) activates hydroxyl groups on polysaccharide gels.[117] Pentafluoropyridine selectively protects phenolic and alcoholic functions in steroids.[118] Perfluoroalkyl-*s*-triazines can be used as markers in mass spectrometry. 2-Fluoro-1,3-dimethylpyridinium tosylate (**19**) is an unusual fluorinating agent,[119] while **20** is an example of the ever increasing number of sources of electrophilic fluorine.[120]

Figure 2: Useful fluoroheterocycles





References:

1) Hewitt, C.D.; Silvester, M.J. *Aldrichim. Acta* **1988,** *21,* 3.
2) Chambers, R.D.; Sargent, C.R. *Adv. in Het. Chem.* **1981,** *28,* 1.
3) Yakobson, G.G.; Petrova, T.D.; Kobrina, L.S. *Fluorine Chem. Rev.* **1974,** *7,* 115.
4) *Gmelin Handbuch der Anorganischen Chemie, Perfluorohalogeno organo Verbindungen der Hauptgruppen-elemente,* Parts 1-6; Springer-Verlag: Berlin and New York, 1973-1978.
5) *Fluorocarbon and Related Chemistry,* Vols 1-3; Banks, R.E.; Barlow, M.G., Eds.; Chemical Society: London, 1971, 1974, 1976.
6) Suschitzky, H. *Adv. Fluorine Chem.* **1965,** *4,* 1.
7) Lyle, J.L.; Taft, R.W. *J. Heterocycl. Chem.* **1972,** *9,* 745.
8) Boudakian, M.M. U.S. Patent 3 703 521, 1972; *Chem. Abstr.* **1973,** *78,* 29635g. Boudakian, M.M.; Chiras, S.J. U.S. Patent 3 798 228, 1974; *Chem. Abstr.* **1974,** *80,* 146026m.
9) Reepmeyer, J.C.; Kirk, K.L.; Cohen, L.A. *Tetrahedron Lett.* **1975,** 4107.
10) Robbins, M.J.; Uznanski, B. *Can. J. Chem.* **1981,** *59,* 2608.
11) Roe, A.; Hawkins, G.F. *J. Am. Chem. Soc.* **1947,** *69,* 2443.
12) Fukuhara, T.; Yoneda, N.; Suzuki, A. *J. Fluorine Chem.* **1988,** *38,* 435.
13) Kirk, K.L.; Cohen, L.A. *J. Am. Chem. Soc.* **1971,** *93,* 3060.
14) Purrington, S.T.; Kagen, B.S.; Patrick, T.B. *Chem. Rev.* **1986,** *86,* 997.
15) Lagow, R.; Margrave, J.L. *Proc. Inorg. Chem.* **1979,** *26,* 162.
16) *New Fluorinating Agents in Organic Synthesis;* German, L.S.; Zemskov, S.V., Eds.; Springer-Verlag: Berlin-Heidelberg, 1989.
17) Schuman, P.D.; Tarrant, P.; Warner, D.A.; Westmoreland, G. Can. Patent 985 681, 1976; *Chem. Abstr.* **1976,** *85,* 46738e. Misaki, S.; Furutaka, Y. Jpn. Patent 149 287, 1976; *Chem. Abstr.* **1977,** *87,* 135378w.
18) Cech, D.; Beerbaum, H.; Holy, A. *Collect. Czech. Chem. Commun.* **1977,** *42,* 2694. Cech, D.; Heerman, G.; Holy, A. *Nucleic Acid Res.* **1977,** *4,* 3259. Cech D.; Meinert, H.; Etzold, G.; Langen, P. *J. Prakt. Chem.* **1973,** *149,* 315.
19) Bryce, M.R.; Chambers, R.D.; Mullins, S.T.; Parkin, A. *Bull. Soc. Chim. Fr.* **1986,** 930.
20) Lin, W.-H.; Lagow, R.J. *J. Fluorine Chem.* **1990,** *50,* 15.
21) For a review on CF_3OF, see: Kollonitsch, J. *Isr. J. Chem.* **1978,** *17,* 53.
22) Robins M.J.; MacCoss, M.; Naik, S.R.; Ramani, G. *J. Am. Chem. Soc.* **1976,** *98,* 7381.
23) For a general review, see: Zupan, M. *Vestn. Slov. Kem. Drus.* **1984,** *31,* 151; *Chem. Abstr.* **1984,** *101,* 229451z.
24) Stavber, S.; Zupan, M. *J. Chem. Soc., Chem. Commun.* **1983,** 563.

25) Kosower, E.M.; Hebel, D.; Rozen, S.; Radkowski, A. *J. Org. Chem.* **1985,** *50,* 4152.
26) For a review, see: Dolby-Glover, L. *Chem. and Ind.* **1986,** 518.
27) For a general review, see: Stacey, M.; Tatlow, J.C. *Adv. Fluorine Chem.* **1960,** *1,* 166.
28) For a general review, see: Nagase, S. *Fluorine Chem. Rev.* **1967,** *1,* 77.
29) Chambers, R.D.; Hutchinson, J.; Musgrave, W.K.R. *Proc. Chem. Soc.* **1964,** 83. *Idem J. Chem. Soc.* **1964,** 3573.
30) Chambers, R.D.; Hole, M.; Iddon, B.; Musgrave, W.K.R.; Storey, R.A. *J. Chem. Soc. (C)* **1966,** 2328.
31) Banks, R.E.; Field, D.S.; Haszeldine, R.N. *ibid.* **1967,** 1822.
32) Tullock, C.W.; Coffman, D.D. *J. Org. Chem.* **1960,** *25,* 2016.
33) Wielgat, J. *Rocz. Chem.* **1971,** *45,* 931; *Chem. Abstr.* **1971,** *75,* 98411f.
34) Banks, R.E.; Haszeldine, R.N.; Latham, J.V.; Young, I.M. *J. Chem. Soc.* **1965,** 594.
35) Akhmetova, N.E.; Vlasov, V.M.; Yakobson, G.G. *Bull. Acad. Sci. USSR* **1978,** *27,* 823.
36) Kysela, E.; Klauke, E.; Schwarz, H. Ger. Patent 2 729 762, 1979; *Chem. Abstr.* **1979,** *90,* 168649a.
37) Maxwell, A.F.; Fry, J.S.; Bigelow, L.A. *J. Am. Chem. Soc.* **1958,** *80,* 548.
38) Burdon, J.; Chivers, G.E.; Tatlow, J.C. *J. Chem. Soc. (C)* **1969,** 2585. *Idem ibid.* **1970,** 2146.
39) Burdon, J.; Parsons, I.W.; Tatlow, J.C. *ibid.* **1971,** 346. Burdon, J.; Campbell, J.G.; Parsons, I.W.; Tatlow, J.C. *ibid.* **1971,** 352.
40) Chambers, R.D.; Grievson, B.; Drakesmith, F.G.; Powell, R.L. *J. Fluorine Chem.* **1985,** *29,* 323.
41) Chambers, R.D. et al. *ibid.* **1990,** *49,* 409.
42) Banks, R.E.; Cheng, W.M.; Haszeldine, R.N. *J. Chem. Soc.* **1962,** 3407.
43) Meinert, H. et al. *J. Fluorine Chem.* **1991,** *51,* 53.
44) For a general review, see: Boswell, G.A.; Ripka, W.C.; Scribner, R.M.; Tullock, C.W. *Org. React.* **1974,** *1,* 21.
45) Lyalin, B.V.; Grigorash, A.V.; Alekseeva, L.A.; Yagulpol'skii, L.M. *Zh. Org. Khim.* **1975,** *11,* 460.
46) Kobayashi, Y.; Chinen, E. *Chem. Pharm. Bull. Tokyo* **1967,** *15,* 1896.
47) Nishida, M. et al. *J. Fluorine Chem.* **1990,** *46,* 445.
48) McBee, E.T.; Haas, H.B.; Hodnett, E.M. *Ind. Eng. Chem.* **1947,** *39,* 389.
49) Kobayashi, Y.; Kumadaki, I. *Tetrahedron Lett.* **1969,** 4095. Kobayashi, Y. et al. *Chem. Pharm. Bull.* **1970,** *18,* 2334.
50) Kobayashi, Y.; Kumadaki, I.; Hanzawa, Y. *ibid.* **1977,** *25,* 3009.
51) Burton, D.J. *Actual Chim.* **1987,** 142.
52) Polishchuk, V.R.; Bekker, G.Ya.; Avetisyan, E.A.; German, L.S. *Zh. Vses. Khim. O-va* **1976,** *21,* 222. Cech, D.; Wohlfeil, R.; Etzold, G. *Nucleic Acid Res.* **1975,** *2,* 2183.
53) Clark, J.H.; McClinton, M.A.; Blade, R.J. *J. Chem. Soc., Chem. Commun.* **1988,** 638.
54) Carr, G.E.; Chambers, R.D.; Holmes, T.F.; Parker, D.G. *J. Chem. Soc., Perkin Trans. 1* **1988,** 921.
55) Matsui, K.; Tobita, E.; Ando, M.; Kondo, K. *Chem. Lett.* **1981,** 1719.
56) Hein, L.; Cech, D. *Z. Chem.* **1977,** *17,* 415.
57) Sawada, H. et al. *J. Fluorine Chem.* **1990,** *46,* 423.
58) Umemoto, T.; Ando, A. *Bull. Chem. Soc. Jpn.* **1986,** *59,* 447.
59) Chen, G.J.; Tamborski, C. *J. Fluorine Chem.* **1990,** *46,* 137.
60) Chen, Q.; Qiu, Z. *J. Chem. Soc., Chem. Commun.* **1987,** 1240.
61) Mailey, E.A.; Ocone, L.R. U.S. Patent 3 534 056, 1970; *Chem. Abstr.* **1971,** *74,* 87835a. Mailey, E.A.; Ocone, L.R. *J. Org. Chem.* **1968,** *33,* 3343.
62) Bryce, M.R.; Chambers, R.D.; Taylor, G. *J. Chem. Soc., Perkin Trans. 1* **1984,** 509.
63) Tanaka, T.; Mitsuhashi, K. *Yukei Gosei Kagaku Kyokaishi* **1987,** *45,* 269; *Chem. Abstr.* **1987,** *107,* 134137m.
64) Anderson, L.P.; Feast, W.J.; Musgrave, W.K.R. *J. Chem. Soc. (C)* **1969,** 2559.
65) For a general discussion of those involving N, see: Young, J.A. *Fluoropolymers;* Wall, L.A., Ed.; Wiley Interscience: New York, 1972; Chapter 9.
66) Burger, K. *Actual Chem.* **1987,** 168.
67) Burger, K.; Geith, K.; Sewald, N. *J. Fluorine Chem.* **1990,** *46,* 105. Burger, K.; Geith, K.; Huebl, D. *Synthesis* **1988,** 189.
68) Burger, K.; Gaa, K.; Geith, K.; Schierlinger, C. *Synthesis* **1989,** 850.
69) England, D.C.; Krespan, C.G. *J. Org. Chem.* **1970,** *35,* 3322.
70) Mustafa, M.E.-S.; Takaoka, A.; Ishikawa, N. *Heterocycles* **1986,** *24,* 593.
71) Cushman, M.; Patel, H.; McKenzie, A. *J. Org. Chem.* **1988,** *53,* 5088.
72) Briscoe, M.W. et al. *J. Chem. Soc., Chem. Commun.* **1990,** 1127.
73) Bayliff, A.E.; Bryce, M.R.; Chambers, R.D. *J. Chem. Soc., Perkin Trans. 1* **1987,** 763.
74) Krespan, C.G.; England, D.C. *J. Org. Chem.* **1968,** *33,* 1850.
75) Banks, R.E.; Mohialdin, S.N. *J. Fluorine Chem.* **1986,** *34,* 275.
76) Lenz, D.; Bruedgam, I.; Hartl, H. *Angew. Chem.* **1987,** *99,* 951.
77) Chambers, R.D.; Close, D.; Williams, D.L.H. *J. Chem. Soc., Perkin Trans. 2* **1980,** 778 and references therein.
78) For a review on nucleophilic substitution, see: Rodionov, P.P.; Furin, G.G. *J. Fluorine Chem.* **1990,** *47,* 361.
79) Chambers, R.D.; McBride, J.A.H.; Musgrave, W.K.R. *J. Chem. Soc. (C)* **1968,** 2989.
80) For a more detailed discussion, see: reference 2 and Chambers, R.D. *Fluorine in Organic Chemistry;* Wiley-Interscience: New York, 1973.
81) Barnes, R.N. et al. *J. Chem. Soc., Perkin Trans. 1* **1985,** 53.
82) Chambers, R.D.; Hewitt, C.D.; Silvester, M.J.; Klauke, E. *J. Fluorine Chem.* **1984,** *24,* 211.
83) Greenberg, A.; Liebman, J.F.; Van Vechten, D. *Tetrahedron* **1980,** *36,* 1161.
84) Chambers, R.D.; Middleton, R. *J. Chem. Soc., Chem. Commun.* **1977,** 154.
85) Wiebe, H.; Bravlavsky, S.; Heicklen, J. *Can. J. Chem.* **1972,** *50,* 2721. Kobayashi, Y.; Kumadaki, I.; Ohsawa, A.; Sekine, Y. *Tetrahedron Lett.* **1974,** 2841.
86) Chambers, R.D.; Lindley, A.A.; Fielding, H.C. *J. Fluorine Chem.* **1978,** *12,* 337.
87) Chambers, R.D.; Tamura, M.; Shepherd, T.; Ludman, C.J. *J. Chem. Soc., Chem. Commun.* **1987,** 1699.
88) Chambers, R.D.; Musgrave, W.K.R.; Sargent, C.R. *J. Chem. Soc., Perkin Trans. 1* **1981,** 1071.
89) Chambers, R.D. et al. *ibid.* **1974,** 114. Chambers, R.D.; Hercliffe, R.D.; Musgrave, W.K.R. *J. Chem. Soc., Chem. Commun.* **1978,** 304.
90) Barnes, R.N.; Chambers, R.D.; Hercliffe, R.D.; Middleton, R. *J. Chem. Soc., Perkin Trans. 1* **1981,** 3289.
91) Chambers, R.D.; Sargent, C.R.; Drakesmith, F.G. *Tetrahedron Lett.* **1979,** 1917.

92) Banks, R.E.; Burgess, J.E.; Cheng, W.M.; Haszeldine, R.N. *J. Chem. Soc.* **1965,** 575. Chambers, R.D.; Hutchinson, J.; Musgrave, W.K.R. *ibid.* **1965,** 5040.
93) Baasner, B.; Klauke, E. *J. Fluorine Chem.* **1989,** *45,* 417.
94) Hayashi, E.; Abe, T.; Nagase, S. *J. Fluorine Chem.* **1988,** *41,* 213.
95) *Organofluorine Chemicals and Their Industrial Applications;* Banks, R.E., Ed.; Ellis Horwood: Chichester, UK, 1979.
96) *Preparation, Properties, and Industrial Applications of Organofluorine Compounds;* Banks, R.E., Ed.; Ellis Horwood: Chichester, UK, 1982.
97) Newbold, G.T. In reference 95, Chapter 8.
98) Slater, J.W. *Weed Res.* **1968,** *8,* 149.
99) Haga, T. et al. Jpn. Patent 62 155 249, 1987; *Chem. Abstr.* **1988,** *108,* 131310x.
100) Haga, T. et al. *Heterocycles* **1984,** *22,* 117.
101) Heidelberger, C. In *Carbon-Fluorine Compounds: Chemistry, Biochemistry, and Biological Activities;* A Ciba Foundation Symposium; Elsevier-Excerpta Medica: Amsterdam, 1972.
102) Hoshi, A. *Fluoropyrimidines in Cancer Therapy;* Kimura, K.; Fujii, S.; Ogawa, M.; Bodey, G.P.; Alberto, P., Eds.; Elsevier Science: Amsterdam, 1984.
103) Kobayashi, Y. et al. *Jpn. Kokai Tokyo* **1977,** *59,* 152; *Chem. Abstr.* **1977,** *87,* 168080w.
104) Kirk, K.L.; Cohen, L.A. In *Biochemistry Involving Carbon-Fluorine Bonds;* Filler, R., Ed.; ACS Symposium Series 28; American Chemical Society: Washington, DC, 1976.
105) Jones, W.G.M. In reference 95.
106) Ohnmacht, C.J.; Patel, A.R.; Lutz, R.E. *J. Med. Chem.* **1971,** *14,* 926.
107) Miyamoto, T.; Egawa, H.; Matsumoto, J. *Chem. Pharm. Bull.* **1987,** *35,* 2280. Miyamoto, T. et al. *J. Heterocycl. Chem.* **1987,** *24,* 1333.
108) Riess, J.G.; Le Blanc, M. *Angew. Chem., Int. Ed. Engl.* **1978,** *17,* 621. Riess, J.G. *Artif. Organs* **1984,** *8,* 44. Gollan, F.; Clark, L.C. *Physiologist* **1966,** *9,* 191.
109) Powell, R.L. Eur. Patent 127 365, 1984; *Chem. Abstr.* **1985,** *102,* 65005z.
110) Sugasawa, K.; Nakayama, N.; Shimizu, H.; Nemoto, F. Jpn. Patent 61 183 281, 1986; *Chem. Abstr.* **1987,** *106,* 33074n.
111) Schuman, P.D.; Stump, E.C. U.S. Patent 3 888 854, 1975; *Chem. Abstr.* **1975,** *83,* 193398f.
112) Harms, W. In reference 95, Chapter 9.
113) Schuendehette, K.H.; Stoehr, F.M. Ger. Patent 3 900 182, 1990; *Chem. Abstr.* **1990,** *113,* 233337g.
114) Kricheldorf, H.R.; Schwarz, G.; Erxleben, J. *Makromol. Chem.* **1988,** *189,* 2255.
115) Resnick, P.R. *J. Fluorine Chem.* **1989,** *45,* 100.
116) Sawada, H.; Nakayama, N. Int. Patent 08 792, 1990; *Chem. Abstr.* **1991,** *114,* 7475q.
117) Ngo, T.T. *Biotechnology* **1986,** *4,* 134.
118) Jarman, M.; McCague, R. *J. Chem. Soc., Chem. Commun.* **1984,** 125. *Idem. J. Chem. Res. (S)* **1985,** 114.
119) Mukaiyama, T.; Tanaka, T. *Chem. Lett.* **1976,** 303.
120) Banks, R.E.; Khazaei, A. *J. Fluorine Chem.* **1990,** *46,* 297.

About the Author

Dr. Michael J. Silvester received his B.Sc. from the University of Durham in 1977. In 1981, he was awarded a Ph.D. for investigations into the electro-organic chemistry of organofluorine compounds, under the supervision of Professor Richard D. Chambers.

After continuing his career as a Senior Research Assistant at Durham, he joined Aldrich Chemical Co. Ltd. (Bristol Organics Division) as a Senior Production Chemist in 1986. He also assists in new product development and the introduction of new fluorine technologies.

Transannular Diels-Alder Reaction on Macrocycles: A General Strategy for the Synthesis of Polycyclic Compounds

Professor Pierre Deslongchamps
Laboratoire de synthèse organique
Département de Chimie
Université de Sherbrooke
Sherbrooke, Québec, Canada J1K 2R1

The great contribution of R.B. Woodward and his contemporaries to the field of organic synthesis was the demonstration that organic chemists were capable of synthesizing highly complex organic substances in the laboratory. In their days, it was known that synthesis had to be carried out with functional groups. Since chemical reactivity was poorly understood, the synthetic planning had to be very general in nature, and each step had to be discovered along the way by studying the reactivity of each intermediate. Later, the reactivity of functional groups became better understood, and it became possible to put more logic into synthetic planning. It is on this basis that E.J. Corey and his contemporaries were able to demonstrate the value of the principle of retrosynthetic analysis, which is based on the chemical reactivity of functional groups.

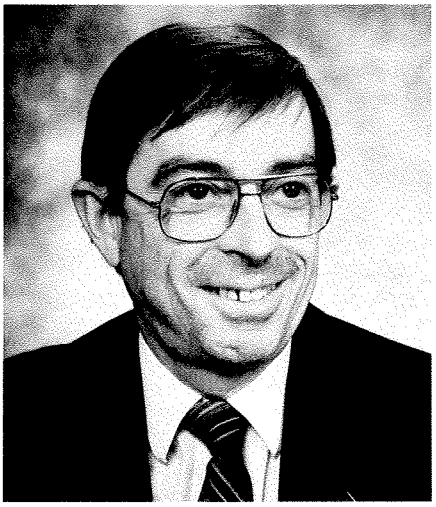
Progress in organic synthesis is presently achieved through the discovery of new chemical reactions (methods, etc.), new reaction conditions with an emphasis on asymmetric synthesis, and new synthetic strategies. It is recognized that a good synthetic plan should have a high degree of control on the chemical reactivity (chemoselectivity), regioselectivity, and stereoselectivity (enantio- and diastereoselectivity). Furthermore, a good plan should be simple, minimizing bond-forming processes as much as possible, especially functional-group manipulations (transformation, activation, protection, and deprotection).

Returning to synthetic strategy, it is also recognized that a chemical process can be classified in three different categories. It can either be intermolecular or intramolecular in nature, and the latter can be subdivided to formation of a bond via a simple cyclization reaction or via a transannular process. In 1984, we briefly discussed the merits of these different approaches in another *Aldrichimica Acta* article.[1] It was mentioned that transannular processes ought to be very powerful synthetically. Indeed, being carried out on macrocycles, there is a high degree of conformational restriction. As a result, proximity effects become operative, and very often these effects will increase the rate of one reaction and slow down others that are normally competing. The total synthesis of ryanodol[2] was described as one of the rare examples where transannular processes are used as key steps. In this synthesis, the formation of the required macrocycles for one of the transannular processes was produced indirectly via the cleavage of a small ring.

It was also noted that transannular processes had not been used frequently in synthesis, because this approach requires the use of macrocycles. It was pointed out that if direct methods for the formation of large rings would become available, synthetic chemists would be in a position to develop new, innovative strategies of molecular construction. We also suggested that it should be relatively easy to construct macrocycles using a simple and direct method of cyclization. However, one condition had to be respected; namely, the acyclic precursor should have some unsaturation appropriately located along the chain in order to cut down the degrees of freedom while eliminating, at the same time, most of the transannular steric repulsion during the cyclization step.

We concluded that article by reporting some preliminary results[3] showing that a ten-membered ring could be produced under medium dilution conditions via the direct displacement of an allylic or propargylic chloride by a malonate anion. A ten-membered ring being one of the most difficult medium rings to construct directly, it should be relatively easy to construct various larger rings. We became convinced that there was a real future for the development of new powerful synthetic strategies based on transannular reactions on macrocarbocycles. The remainder of this article reports the progress we have made in this direction.

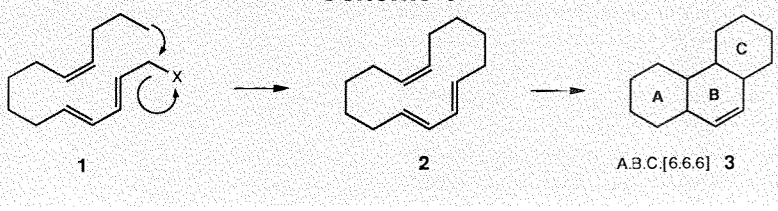
The transannular Diels-Alder reaction on macrocyclic trienes was selected as our first objective. This reaction is generally recognized as the most powerful synthetic method for the construction of carbocycles. It is also well suited for a transannular process, because the two reacting species, the diene and the dienophile, are neutral (not positively or negatively charged), requiring, in principle, only heat to undergo the Diels-Alder cycloaddition process. This study was also attractive from a synthetic point of view. In two steps from an acyclic triene (**1** → **2** → **3**), it appeared possible to construct a tricyclic compound having four stereogenic centers and one functional group in ring B (Scheme 1).



Recipient of the Canadian Alfred Bader Award in 1991.

Our first two attempts in this direction met with failure because we could not induce the desired macrocyclization.[4] In the first case, we constructed *trans-trans-trans* (TTT) β-keto ester **4** (Scheme 2) having an allylic chloride but could not induce its conversion into macrocycle **5**. This result was rationalized by the fact that the chain is probably too rigid due to conjugation, preventing cyclization. TTT β-Keto ester **6**, which lacks the aromatic ring, was then constructed, and again, the desired macrocycle **7** could not be obtained. The enolate salt of **6** is still too

Scheme 1



highly conjugated, and the two ends of the chain cannot easily reach each other to induce the macrocyclization. We therefore decided to try the macrocyclization step on precursors that were less conjugated and registered our first successes.

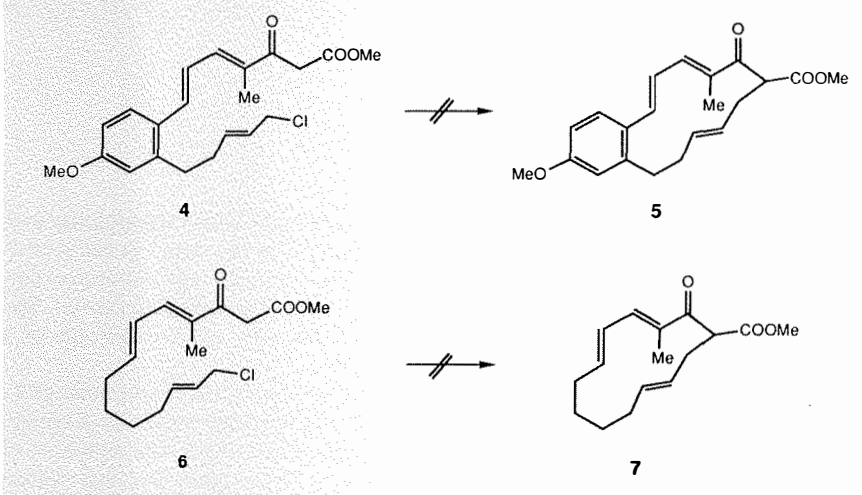
The acyclic β-keto ester **8** (Scheme 3) having a *trans-trans* olefin geometry was prepared, and it produced (K_2CO_3, NaI, acetone) the desired macrocycle **9** in 77% yield.[5] This product was then converted into the macrocyclic trienone **10** having a cis-trans-trans (CTT) geometry. Similarly, the other *trans-cis* acyclic β-keto ester **16**[5] was prepared and converted into macrocycle **17** (74%), which, in turn, was transformed into the TCC macrocyclic trienone **18**. We were then ready to attempt our first transannular Diels-Alder reactions.

On heating at 300 °C, CTT macrocyclic trienone **10** gave a mixture of three Diels-Alder products (**13**, **14,** and **15**; 1.8:2:1) in 90% yield. The result was more complex than anticipated, but this could be readily explained. We had observed the formation of the expected product **13**, having a cis-anti-cis (CAC) geometry, but molecular models revealed that this is a sterically hindered process. When the diene takes the cisoid geometry required for the Diels-Alder reaction (*cf.* **11**), there is severe steric repulsion between the methyl group and the C_{-6} methylene group in the transition state. As a consequence, a competitive process took place, starting with a 1,5 sigmatropic hydrogen migration producing a new macrocyclic trienone **12** with TCT geometry. This can then easily undergo a Diels-Alder reaction, relatively free of steric interaction, producing a tricyclic ketone **14** with CAC geometry and a secondary methyl group. At the reaction temperature, tricyclic ketone **14** was then thermally equilibrated with the isomeric ketone **15** via their corresponding enol intermediate.

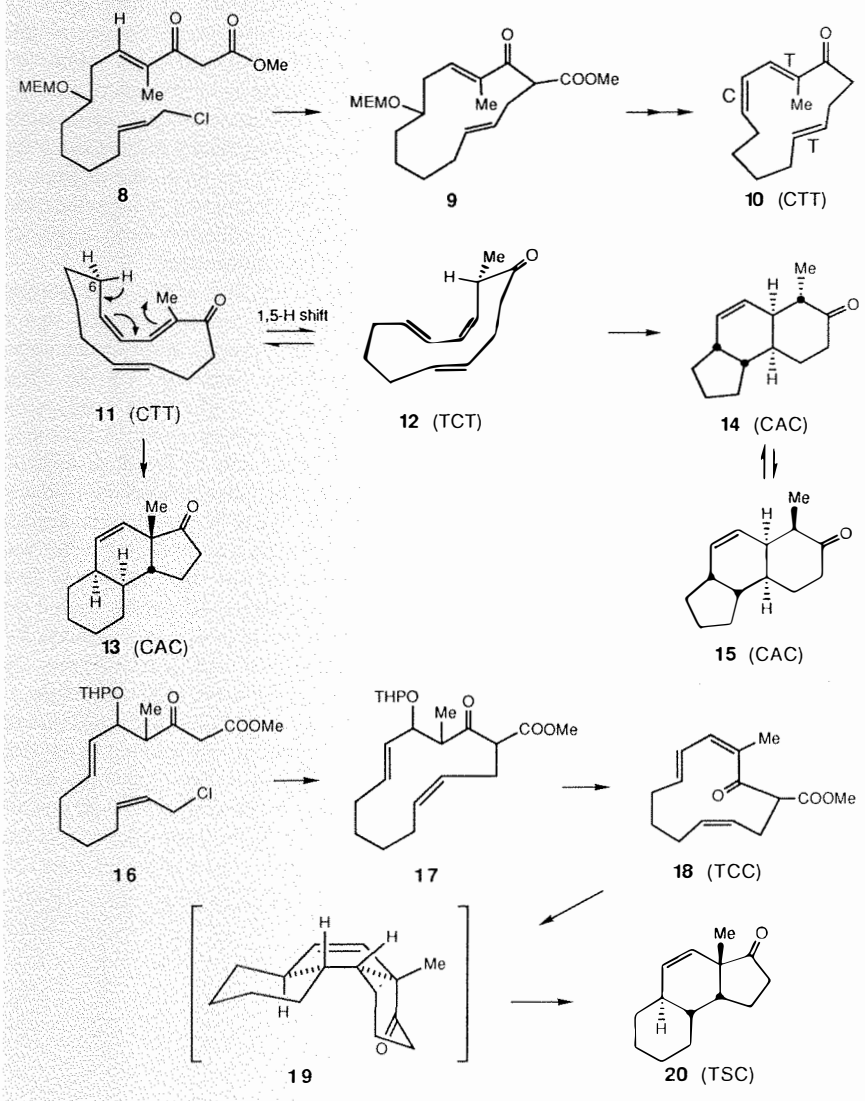
Study of the other macrocycle **18** gave better results. On heating at 300 °C, TCC macrocycle **18** was cleanly transformed (90%) into the tricyclic ketone **20** by transannular Diels-Alder with concomitant decarbomethoxylation. In this case, only one product was observed because there is only one Diels-Alder reaction that can take place without severe steric hindrance at the transition-state level (*cf.* **19**) to produce tricyclic ketone **20** having the trans-syn-cis (TSC) geometry.

While this work was progressing, we also carried out a systematic study on direct macrocyclization affording 11- to 14-membered rings containing two sites of unsaturation (triple or double bond, cis or trans) using the displacement of allylic and propargylic chloride with a malonate. This work[6] clearly

Scheme 2



Scheme 3



showed that the desired macrocycle is the predominant product, formed in good yield in most cases. The next step was to verify that macrocyclization could be induced directly from an acyclic triene using the intramolecular alkylation of a malonate with an allylic chloride.

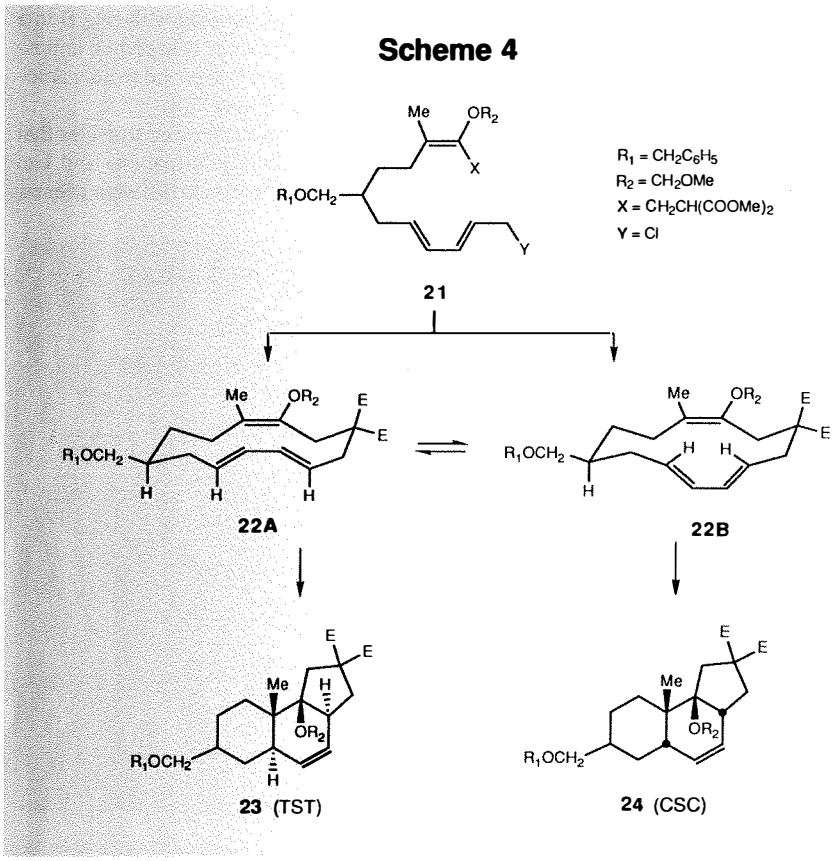
The acyclic precursor **21** (Scheme 4) contains a tetrasubstituted enol ether as a dienophile, a *trans-trans* diene, a malonate ester, and an allylic chloride. It was synthesized and submitted to macrocyclization conditions (slow addition to a suspension of sodium hydride in THF-DMF at 70 °C). To our surprise, this experiment[7] directly gave two tricyclic products having the TST and the CSC structures **23** and **24**, respectively, in a 2:1 ratio. Thus, the anticipated 13-membered *trans-trans-cis* macrocyclic triene **22** could not be isolated, as it directly underwent the Diels-Alder reaction. Formation of the two products results from the fact that the diene and the dienophile can react in two different manners (*cf.* **22A** and **22B**). In this case, the cisoid conformation of the *trans-trans* diene is essentially sterically free, facilitating the Diels-Alder reaction (*vide infra*), but it was felt that proximity effects due to the 13-membered ring must be the main driving force for this very facile cycloaddition. This was demonstrated by comparing the reactivity of acyclic triene **21** (X = CO_2Me) with macrocyclic triene **22**. Compound **21** (X = CO_2Me) should be more reactive because its dienophile is now conjugated by an ester function; however, it was found to be unreactive even when heated at 210 °C for 10 h. Clearly, this indicated that the transannular Diels-Alder reaction represents a definite synthetic advantage, as it can greatly enhance the chemical reactivity of dienes and dienophiles. As a result, the Diels-Alder reaction becomes a more general process when carried out in a transannular fashion.

Having shown that a macrocyclic triene can be constructed directly from an acyclic triene precursor, we decided to modify our general approach for the study of the synthetic potential of the transannular Diels-Alder reaction. The methods used so far for the preparation of the acyclic triene, being linear in nature, were lengthy and cumbersome. We wanted more flexibility in our approach and decided to adopt a highly convergent method using prefabricated building blocks. This method was already developed for our general study on the macrocyclization of 10- to 14-membered ring dienes. This approach is summarized in Scheme 5 and consists of assembling four different building blocks: a diene and a dienophile, each having two potential leaving groups, and two connectors.

The assembling of the macrocyclic triene is carried out in the following order. One connector is first reacted with the dienophile via a displacement reaction of a homoallylic leaving group (Y_1 = mesylate). This is then followed by an allylic coupling reaction with the diene compound (displacement of X_1). The homoallylic functional group in the resulting product is then converted into a good leaving group (Y_2 = mesylate) and reacted with the second connector, producing the acyclic triene precursor **25**. The remaining allylic functional group is then activated (X is converted to an allylic chloride) in order to undergo the desired macrocyclization.

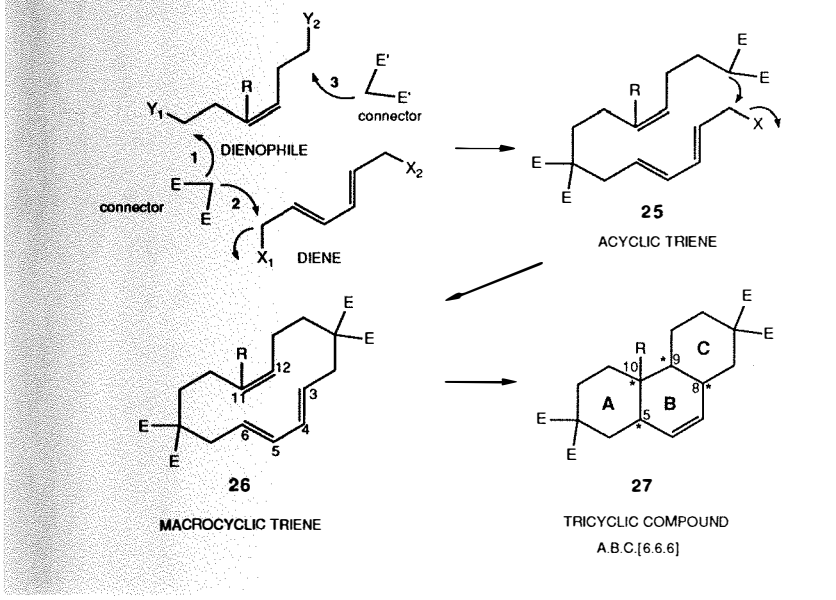
There are several advantages to this highly convergent approach. Several dienes and dienophiles having various geometries and

Scheme 4



Scheme 5

CONVERGENT GENERAL STRATEGY



substituents can be readily prepared and quickly assembled with the help of all sorts of connectors, producing a large variety of macrocyclic trienes. The use of connectors has the additional advantage that they can play a role as substituents at the Diels-Alder stage and, more importantly, can become useful functional groups later. This approach provides tricyclic compounds, having a functional group in each ring, that can be useful for further elaboration. In principle, the connectors can also be chiral in nature, and this provides an opportunity (*vide infra*) for the induction of chirality at the Diels-Alder step, yielding optically active tricyclic compounds. Thus, these connectors, which can be very useful in the preparation of macrocycles, can also serve later as functional groups or as devices for the control of stereoselectivity (diastereo- and enantioselectivity) during the formation of tricyclic compounds.

In our general preliminary study, it was important to choose a connector that would not create additional chiral centers. Dimethyl malonate was chosen for both connectors. This is a versatile symmetrical connector that can be alkylated under mild conditions, yet it can be easily converted into a stereogenic center if necessary.

The next step in this project was the consideration of the relationship between geometrical isomerism of the macrocyclic triene and stereochemistry in the resulting tricycle.[8] A diene can have four different configurations (TT, TC, CT, or CC) and the dienophile can have two (C or T). The corresponding macrocyclic triene **26** can therefore have eight different configurations. For example, a TC diene with a T dienophile corresponds to a TCT configuration, where the three letters refer to the unsaturations at C_5, C_3, and C_{11}, respectively (*cf.* **26**). Tricycle **27**, which has four chiral centers (C_5 and $C_{8\text{-}10}$, steroid numbering), can exist in eight different racemic diastereoisomeric configurations (e.g., CAC, TST, etc.), as indicated in Table 1.

On first analysis, each triene configuration can theoretically lead to two different tricyclic diastereoisomers (and their respective enantiomer). For example, triene CTT can give either tricycles TAT or CAC. However, as indicated in Table 1, it can be predicted that several transannular Diels-Alder reactions cannot take place. This is due to the fact that the Diels-Alder reaction must take place via a boat-like transition state, producing an A.B.C.[6.6.6] tricycle in which the middle ring must be in a boat conformation. Indeed, molecular models showed that because of this restriction, which is stereoelectronic in nature, it is sterically impossible, in some cases, to reach the required chair-boat-chair transition states. For instance, due to steric reasons, tricycle TAT cannot take a conformation with ring B in a boat form. As a result, it becomes impossible to produce this compound from macrocyclic trienes CTT and TCT.

On the other hand, there are tricycles that can take two such conformations and can thus be produced from two different trienes.

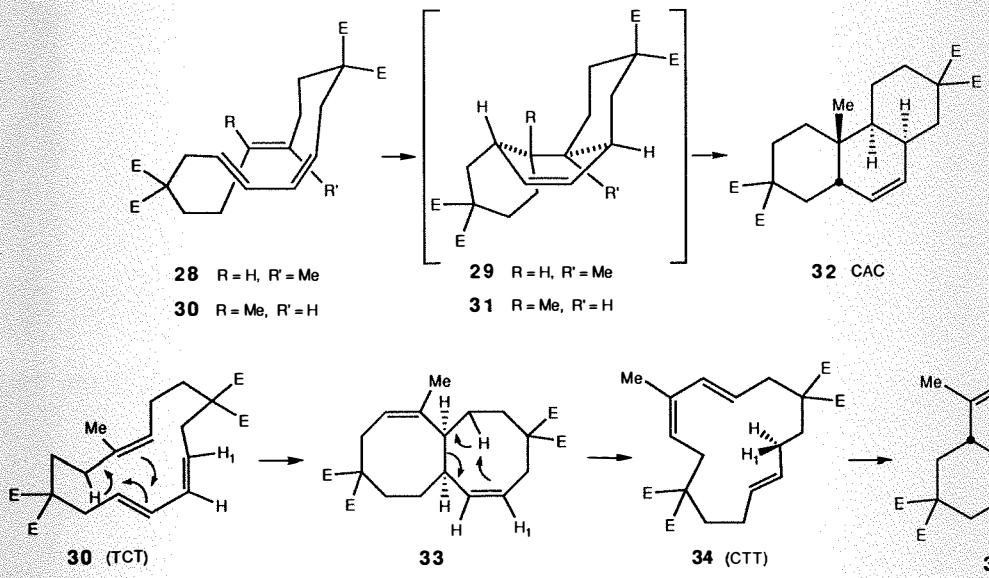
Table 1. Predictions for the Transannular Diels-Alder

Entry	Tricycle Stereochemistry		Triene Geometry		Tricycle Stereochemistry
(1)	TAT	←X—	CTT	→	CAC
(2)	TAT	←X—	TCT	→	CAC
(3)	TAC	←X—	CCT	—X→	CAT
(4)	TAC	←	TTT	→	CAT
(5)	TSC	←X—	CTC	→	CST
(6)	TSC	←	TCC	—X→	CST
(7)	TST	←X—	CCC	→	CSC
(8)	TST	←	TTC	→	CSC

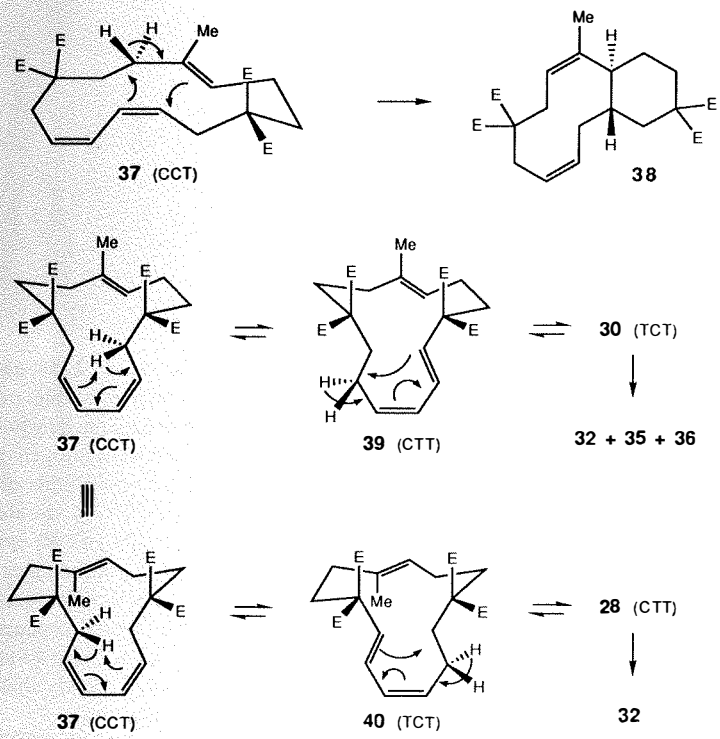
Table 2. Macrocyclization and Transannular Diels-Alder Reaction

Entry	Macrocycle geometry (yield)	Diels-Alder temp	time	Tricycle stereochemistry	Ratio	Yield
1	CTT (87%)	300°C	2 h	**32** (CAC)	—	91%
2	TCT (30%)	350°C	1 h	**32** (CAC) + **36** + **37**	2:3:1	>90%
3	CCT (66%)	300°C	3 h	**38** + **32** (CAC) + (**36** + **37**)	6.4:1.4:1.7	>90%
4	TTT (not isolated)	80°C	—	**56** (CAT) + **57** (TAC)	1:2	65%
5	CTC (81%)	300°C	2.75 h	**43** (CST)	—	89%
6	TCC (88%)	300°C	2 h	**46** (TSC)	—	100%
7	CCC (72%)	365°C	30 min	**43** (CST) + **46** (TSC)	1:1	95%
8	TTC (not isolated)	80°C	—	**62** (TST)	—	53%

Scheme 6



Scheme 7

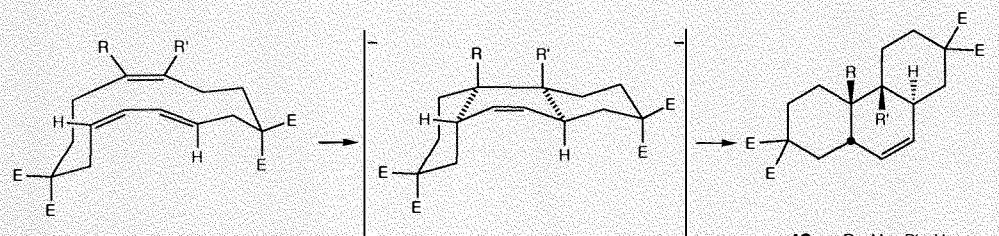


This is the case for tricycle CAC, which can be formed from either a CTT or a TCT macrocyclic triene. There are other situations where the tricycle can take only one conformation with ring B in a boat form. These tricycles can therefore be produced from only one macrocyclic triene. For instance, TSC can be produced from triene TCC, but not from triene CTC. Also, if the triene cannot take a conformation leading to a boat-like transition state as required for the transannular Diels-Alder, then this reaction should not take place. This is the case for triene CCT.

In summary, the predictions for the eight triene configurations are the following: one triene (CCT) cannot undergo the transannular Diels-Alder, five trienes (CTT, TCT, CTC, TCC, and CCC) can give only one racemic diastereoisomer, and two trienes (TTT and TTC) can each give, theoretically, two racemic diastereoisomers. Also, only one (TAT) of the eight diastereoisomeric tricycles cannot be produced directly by a transannular Diels-Alder reaction. It is also interesting to mention that *syn* and *anti* tricyclic compounds are derived from *cis* and *trans* dienophiles, respectively.

The next stage in our investigation was to submit these predictions to experimental verification.[9] The required four dienes and two dienophiles were synthesized and assembled using dimethyl malonate to produce the eight acyclic trienes. Macrocyclization was carried out by slow addition of the acyclic trienes **25** to a solution of cesium carbonate in THF-DMF (1:1) at 80 °C. The results obtained at the macrocyclization step and at the Diels-Alder stage are summarized in Table 2. Macrocycles were isolated in six cases (entries 1-3 and 5-7). In the remaining cases (TTT and TTC), tricyclic compounds rather than the expected macrocycles were directly isolated, indicating that the Diels-Alder reactions took place at the temperature of macrocyclization (80 °C). The mild reaction conditions for these Diels-Alder cycloadditions can be explained by the fact that, in the TTT and the TTC macrocycles, the TT diene can take the required cisoid conformation that is devoid of steric repulsion. The other macrocycles were heated at high temperature (>300 °C) in order to observe a complete thermal conversion. This indicates a severe steric hindrance prevent-

Scheme 8

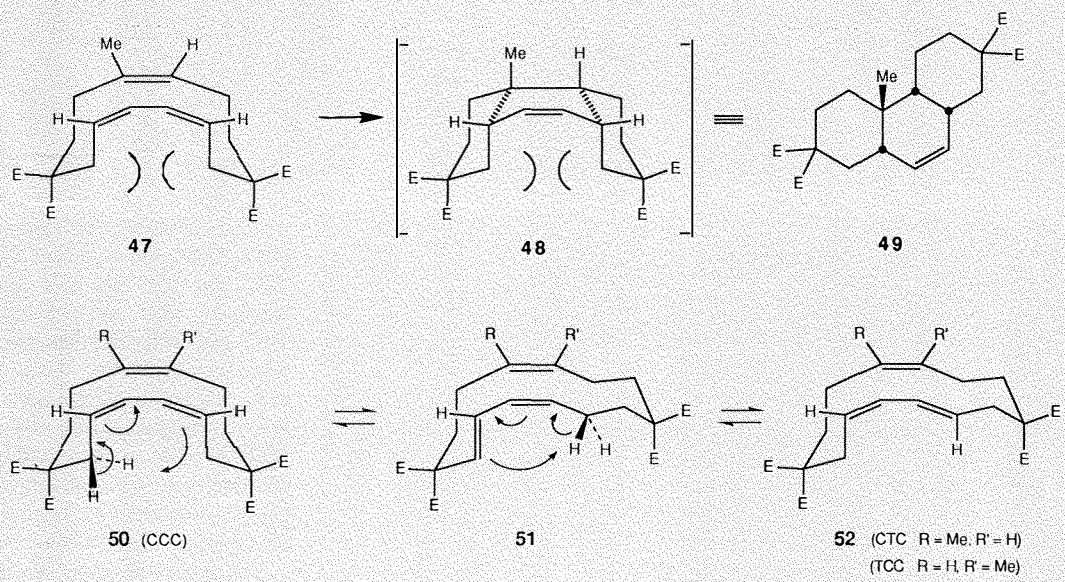


41 (CTC) R = Me, R' = H
44 (TCC) R = H, R' = Me

42 R = Me, R' = H
45 R = H, R' = Me

43 R = Me, R' = H
46 R = H, R' = Me

Scheme 9



47

48

49

50 (CCC)

51

52 (CTC R = Me, R' = H)
(TCC R = H, R' = Me)

ing the cisoid conformation when the diene has a CT or CC geometry.

Macrocycle CTT **28** (Scheme 6) gave the expected CAC tricycle **32** at 300 °C. The same tricycle **32** was also obtained from macrocycle TCT **30** at 350 °C but as a mixture with two other components (**35** and **36**; 2:3:1). Compound **35** was shown to have an unexpected CAC tricyclic structure having the methyl group on the double bond. (**36** could not be isolated pure, and its structure is unknown.) The above results can be rationalized in the following way. Assuming that the Diels-Alder reaction takes place via a chair-boat-chair-like transition state, molecular models clearly indicate that the methyl group creates much more steric hindrance in the CAC transition state from TCT (*cf.* **31**) than that from CTT (*cf.* **29**). As a consequence, the reaction **28** → **29** → **32** is quantitative, but reaction **30** → **31** → **32** is not. The formation of the unexpected tricycle **35** from macrocycle **30** can be explained by a competing transannular ene reaction producing **33,** which can in turn give TCT macrocycle **34**. This compound is then easily transformed into tricycle CAC **35,** because the Diels-Alder reaction is no longer sterically hindered by the presence of the methyl group. Interestingly, the process **30** → **33** → **34** is an oxido-reduction process where the dienophile and the diene have been mutually interconverted.

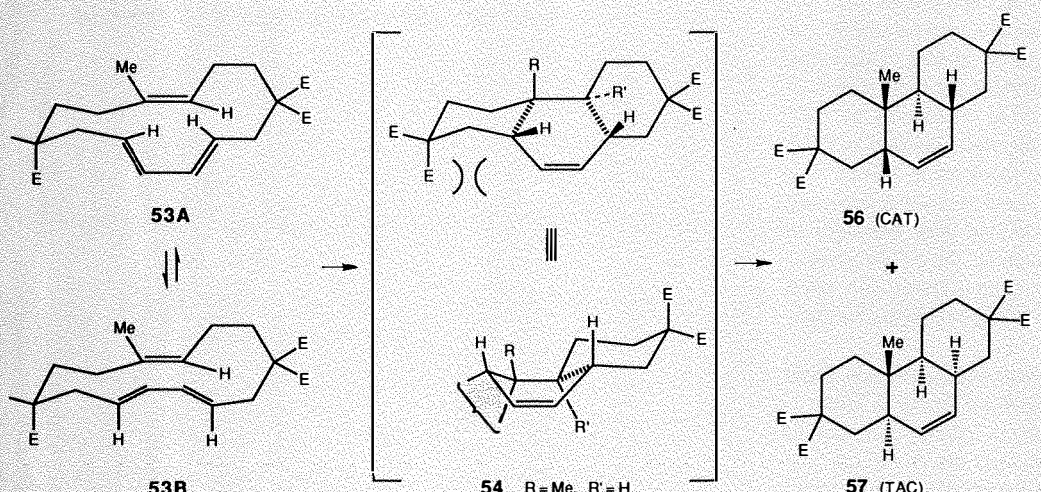
The prediction that the macrocyclic triene CCT **37** (Scheme 7) is not allowed to directly produce a tricyclic compound was supported experimentally. On heating at 300 °C, triene **37** gave ten-membered bicycle **38** (64%) along with a mixture of the three products (**32, 35,** and **36**) previously obtained from macrocyclic trienes TCT **30** and CTT **28**.

The major bicyclic product (**38**) is formed from **37** by a transannular ene reaction. Since we know that TCT **30** gives **32** + **35** + **36**, while CTT **28** gives **32**, it is reasonable to assume that macrocycle CCT **37** must have partly isomerized into a mixture of macrocyclic trienes CTT **28** and TCT **30** in order to produce the mixture of **32, 35,** and **36**. The thermal isomerization of the macrocyclic triene CCT can be explained by two consecutive 1,5 sigmatropic hydrogen migrations from **37**, which can yield either macrocyclic triene TCT **30** or CTT **28** via the CTT and TCT intermediates **39** and **40,** respectively. It is interesting that intermediates **39** and **40** do not undergo a Diels-Alder reaction, probably because they would produce tricycles having an A.B.C.[5.6.7] ring structure. This formation must be sterically disfavored by the seven-membered ring.

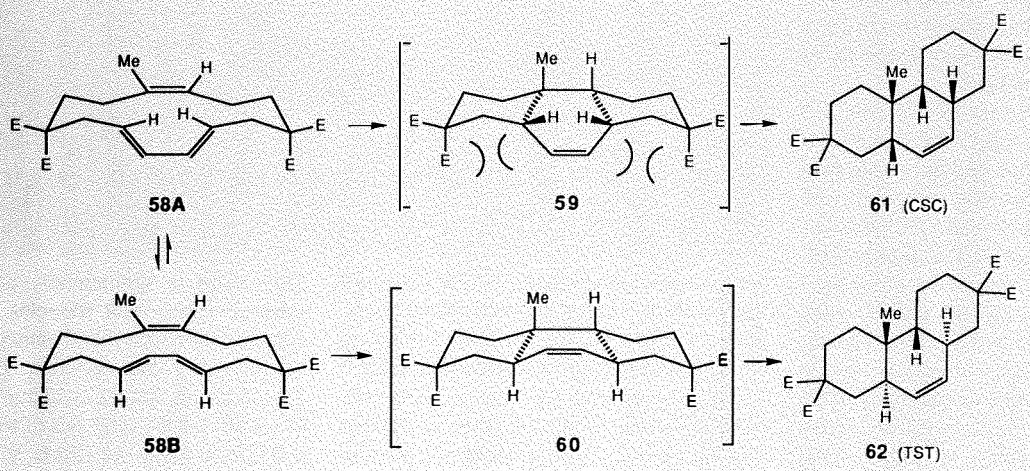
The Diels-Alder reaction of CTC and TCC macrocyclic trienes **41** and **44** (Scheme 8) produced the corresponding CST and TSC stereoisomers **43** and **46**, respectively, as predicted, in excellent yield. This is readily explained, since both processes can take place via chair-boat-chair-like transition states devoid of severe steric repulsion, as indicated in structures **42** and **45**.

CCC Macrocyclic triene **47** (Scheme 9) was predicted to give only CSC tricycle **49**

Scheme 10



Scheme 11



via transition state **48,** which appears to be quite sterically crowded. This situation results from the fact that the *cis-cis* diene is severely sterically congested when it takes the cisoid geometry required for the Diels-Alder reaction. Not surprisingly, on heating at 365 °C, none of the predicted CSC tricycle **49** was isolated; rather, it produces an approximately 1:1 mixture of tricycles CST **43** and TSC **46**. Clearly, this indicates that the process **47** → **48** → **49** is too costly energetically, and CCC macrocycle **47** instead undergoes thermal isomerization to give a mixture of CTC and TCC macrocycles **41** and **44**, which are then converted into tricycle CST **43** and TSC **46**, respectively. Again, the thermal conversion of **47** into **41** and **44** can take place by two consecutive 1,5 sigmatropic hydrogen migrations (*cf.* **50-52**).

As previously mentioned, the remaining macrocyclic trienes TTT and TTC were not isolated, as they underwent the Diels-Alder reaction at the temperature of macrocyclization. The TTT macrocycle **53** (Scheme 10) gave a 1:2 mixture of tricycles CAT **56** and TAC **57**. This is in accord with the original prediction, since the TTT macrocycle can react via conformations **53A** and **53B** to yield tricycles CAT and TAC, respectively. The two competing pathways can be best compared by examining their respective transition states, **54** and **55**. Using this method of comparison, it can be seen that the only difference between the two competing transition states is the location of the methyl group. Molecular models show that the methyl group is sterically more crowded in transition state **55**, which leads to the TAC tricycle **57**. The difference does not appear to be very large; a mixture is therefore expected. What is surprising, however, is that this analysis predicts a ratio where the CAT tricycle **56** would be predominating. This is in contradiction with the experimental ratio, and this topic will be discussed again later.

The TTC macrocyclic triene gave only the TST tricycle **62** (Scheme 11) rather than the predicted mixture of CSC and TST tricycles **61** and **62**. This experimental result can be readily explained by consideration of the relative steric effect played by the ester functions. The TTC macrocycle can either react via conformation **58A** or **58B** leading to tricycles CSC **61** and TST **62,** respectively. Analysis with molecular models reveals that, in the transition state **59,** which leads to tricycle CSC **61**, there are two 1,3-

diaxial-type steric interactions between each pseudo-axial ester function and the CH atoms of the olefin of the final product (*cf.* **59**). There are no equivalent interactions in the competing transition state **60**. This steric effect would therefore be the main discriminating factor favoring formation of TST tricycle **62**. The macrocyclization of TTC acyclic triene was repeated at lower temperature (45 °C), and the corresponding macrocycle was isolated pure although in low yield. As anticipated, the TTC macrocyclic triene **58** was quantitatively converted into TST tricycle **62** upon reflux in benzene.[10]

In general, the results summarized in Table 2 confirm the predictions made in Table 1. The anomalous results (entries 2, 7, and 8) are readily rationalized on the basis of a simple analysis at the transition-state level. The results demonstrate the power of transannular Diels-Alder reactions on macrocyclic trienes for the construction of tricyclic compounds. Indeed, so far six of the eight possible diastereoisomers can be obtained and the degree of stereochemical control is remarkable. The next step in this project was the evaluation of the potential of this strategy as a general method for the synthesis of polycyclic natural products.

For instance, triterpene **69** (Scheme 12) can be viewed as an A.B.C.D.E.[6.6.6.6.5]-pentacyclic system that can be constructed from one of the three key tricycles: **66** (A.B.C.[6.6.6]8-Me,10-Me), **67** (B.C.D.-[6.6.6]8-Me,14-Me), or **68** (C.D.E.[6.6.5]14-Me). These tricycles can, in turn, come from the macrocyclic trienes **63**, **64**, and **65**, which vary in their ring size (13- and 14-membered) and in the degree of substitution on the diene and dienophile components. This type of retrosynthetic analysis can be carried out with most diterpenes, triterpenes, and steroids. As a result, it can be foreseen that transannular Diels-Alder reaction on macrocycles is potentially a general method for the synthesis of most natural products belonging to these classes. In fact, this synthetic method is even more general in nature, since it leads not only to natural products, but also to polycyclic products having either varied stereochemistry for the skeleton or all sorts of substituents. Most terpenes and steroids are classified in two books.[11,12] Using this source of information, we have estimated that there are more than 4000 natural products that could be constructed from about 50 types of key tricyclic intermediates. Table 3 shows the number of natural products that can be made from the 20 most important tricycles.

The next objective of our investigation was clear. We had to verify that the Diels-Alder reaction would remain the predominant pathway when the diene and the dienophile are diversely substituted. We first studied the macrocyclization and subsequent Diels-Alder reaction on macrocycles having no substituents on the diene and the dienophile.[13] The macrocycles having a *cis-cis* diene were not considered, as they are prone to undergo thermal isomerization and lead to a mixture of products. Four macrocycles were studied, and the predicted tricyclic isomer was obtained in each case (CTT → CAC, TTT → CAT, CTC → TSC, and TTC → TST). No side products were observed because the energy barrier for the Diels-Alder reaction has not been unduly raised by the presence of alkyl substituents. Due to symmetry reasons, the TTT tricycle can only yield one isomer since the CAT and TAC stereoisomer are identical substances. The same reasoning applies for CTC (TSC = CST).

We then examined macrocycles having a tetrasubstituted, unactivated dienophile bearing two methyl groups (*cf.* **64** → **67**).[14] Again, four macrocycles were studied, and specific formation of one stereoisomer was observed in each case (CTT → CAC, TTT → CAT, TTC → TST, and CTC → CST). It was remarkable to observe that the TTT macrocyclic triene was not isolated, as it went directly to the CAT tricycle (CAT = TAC). This result is synthetically attractive because it shows that tricycles having two adjacent stereocontrolled quaternary centers can be easily constructed by this strategy. This indicates that the synthetic route (**64** → **67** → **69**) for the synthesis of triterpenes via a B.C.D.[6.6.6]8-Me,10-Me tricyclic intermediate should be taken seriously into account. Indeed, this could lead to a rather simple synthesis of complex triterpenoids.

There are several natural products having alkyl groups at C_8 and C_{10} (*cf.* A.B.C.[6.6.6]8-R,10-R, Table 3). Therefore, macrocyclization and the Diels-Alder reaction were undertaken with dienes and dienophiles each having one methyl group. Six different macrocycles (**63**) were studied,[15] and it is worth noting that all macrocyclizations were carried out in good yield (57-93%). In this series, it was possible to isolate the macrocycles having a TT diene because the presence of a methyl group on the diene generates enough steric hindrance to prevent the formation of the cisoid conformation at the temperature of macrocyclization. Three macrocycles (TCC, TTT, and TCT) gave only one stereoisomer while the others (CTT, CTC, and TTC) led to mixtures. The TCC macrocycle gave, as predicted, only the cor-

Scheme 12

SYNTHETIC STRATEGIES FOR A TRITERPENE

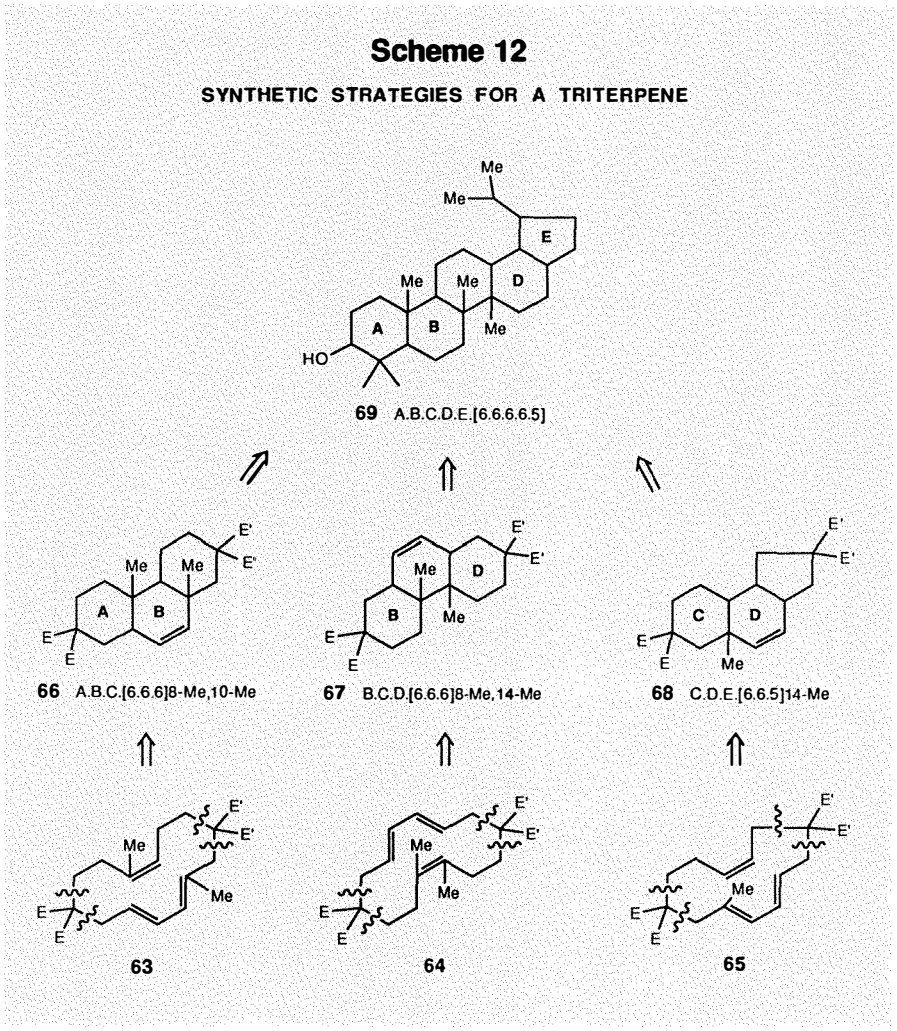
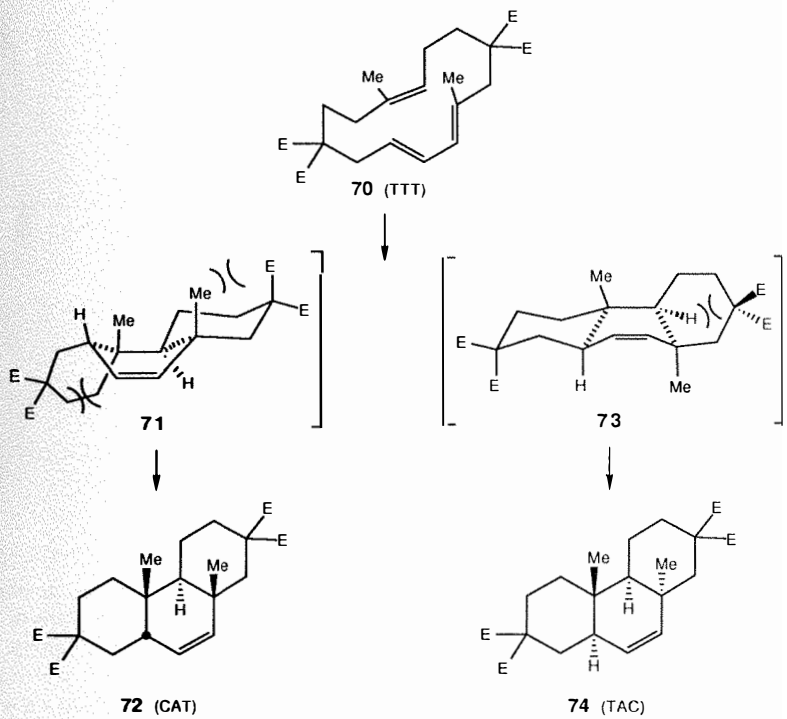


Table 3. Key Tricyclic Structures Recognized in Various Natural Products

Key tricycles (position of substituents) (steroid numbering)	Number of natural products	Key tricycles	Number of natural products
A.B.C.[6.6.6]		**B.C.D.[6.6.5]**	
5R,10R	70	8R,13R	70
8R,10R	700	8R,14R	76
9R	40	9R,13R,14R	30
13R	1350	13R	570
		13R,14R	550
A.B.C.[6.6.5]			
9R,10R	25	**C.D.E.[6.6.6]**	
10R	17	13R,14R,17R	30
14-oxa,8R,10R	25	14R,17R	200
B.C.D.[6.6.6]		**C.D.E.[6.6.5]**	
8R,13R	32	14R,17R	41
8R,14R	280	14R,18R	17
8R,13R,14R	18		
17-oxa,8R,13R	33		

Scheme 13



responding TSC tricycle. This is readily explained on the basis of a chair-boat-chair transition state devoid of severe steric repulsion (similar to **44** → **45** → **46**). The TTT macrocycle **70** (Scheme 13) underwent the Diels-Alder reaction at 200 °C producing only TAC tricycle **74**. In this case, the CAT tricycle **72** was not observed because there is one additional severe steric interaction in the corresponding transition state **71** when compared with **73**, which leads to **74**. The TCT macrocycle gave a CAC tricycle, which was found to have a methyl group on the olefin, as well as a secondary methyl group in ring C.[15a] Thus, a process similar to the one previously described for TCT macrocycle **30** (**30** → **33** → **34** → **35**, where H_1 = Me) is again taking place, with the exception that it is the major transformation. In this case, the transient formation of an intermediate equivalent to bicycle **33**, having an additional methyl group (**33**, H_1 = Me), could be detected by NMR spectroscopy. The other three macrocycles (CTT, CTC, and TTC) gave complex mixtures of tricycles. These mixtures were obtained because the methyl group on the diene creates additional steric interaction in the required cisoid conformation, and as a result, competing isomerization processes of the macrocyclic dienes took place prior to the Diels-Alder reaction. In summary, these results are understood, but details are omitted in this article.

Several studies were also carried out with 13-membered macrocyclic trienes (**75**, Scheme 14) that can lead to B.C.D.[6.6.5] tricycles (**76**).[16] Again, it would be too lengthy to discuss these results in detail. Suffice it to say that the Diels-Alder reaction gave results similar to those observed with 14-membered rings; however, yields of macrocyclization were generally lower. Study of 15-membered macrocyclic trienes, which can produce A.B.C.[6.6.7] tricycles, was also carried out.[10,17] The case of the TTT macrocycle **77** turned out to be quite interesting, because this macrocycle, in which the cisoid conformation is sterically free, was stable at room temperature. The Diels-Alder reaction that gave the expected TAC and CAT tricyclic isomers **78** and **79** had to be carried out at 200 °C. Thus, one extra methylene group makes a significant difference, since the corresponding Diels-Alder reaction in the 14-membered series took place at less than 80 °C. This is a clear indication that proximity effects play an important role in the case of the transannular Diels-Alder reaction. Those proximity effects are further substantiated by the fact that the corresponding TTT acyclic triene does not undergo the corresponding Diels-Alder reaction when heated at 200 °C for 20 h.[10]

It can be concluded from the above study that transannular Diels-Alder reaction on

macrocycles is a general process where ring size and alkyl sustituents can be varied. It is certainly worth exploring from a synthetic point of view. The next step in the elaboration of this new general synthetic method was to start working with another variable, the connectors, in order to see if they can be used as a device for the control of the relative, as well as the absolute, stereochemistry of tricycles.

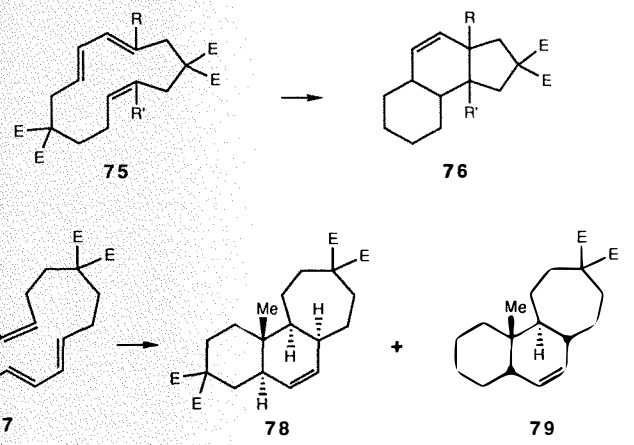
The first case studied was the TCC macrocycle **80** (Scheme 15), which has three ester functions and produced via **81** and **83**, respectively, a 63:37 mixture of racemic TSC tricycles **82** and **84**, isomeric at C_3.[18] This result is explained by the steric effect played by the monoester function at the transition-state level. This group is equatorially oriented in **82** and axially oriented in **84**. Upon basic equilibration with sodium methoxide, an 84:16 ratio of **82** and **84** was obtained. This indicates that, at the transition-state level, the axial steric interaction (*cf.* **83**) must be slightly less important, because the C_5-C_{10} bond is not yet completely formed.

We then carried out a similar study with CTT macrocyclic triester **85**.[19] Based on an analysis similar to the one just described, we expected the formation of only CAC stereoisomer **89**, because in this case, the formation of the other stereoisomer requires a rather severe pseudo-1,3-diaxial steric interaction that is developing between the olefinic CH atoms and the ester function (*cf.* **86**) at the transition-state level. However, contrary to our expectation, we found out that macrocycles **85** gave a 1:4 mixture of CAC isomers **87** and **89**. This result came as a surprise, because it was thought that the difference in steric effects between the two processes (*cf.* **86** and **88**) would be sufficient to completely eliminate the minor one. It was also a disappointment, because the attempt to use a chiral connector as a device to obtain complete control of stereochemistry of the tricycle was compromised.

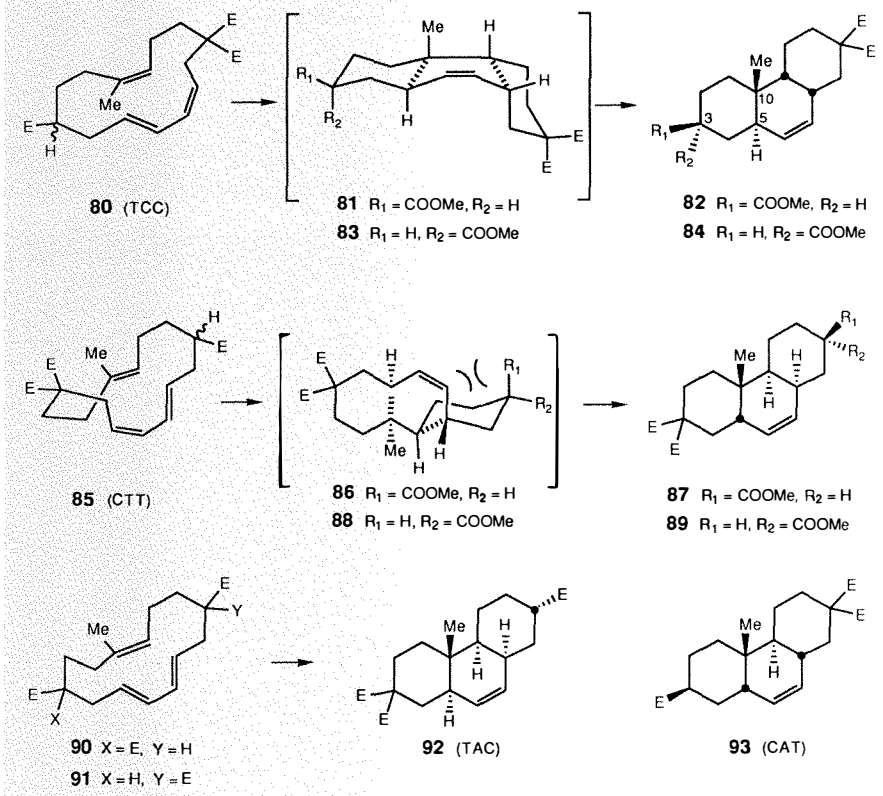
We were also hoping to use the connectors for controlling the CAT/TAC ratio in the Diels-Alder reaction of TTT macrocycles. This goal was important synthetically since there are several natural products that have either the CAT or the TAC stereochemistry. Again, the results obtained were not completely satisfactory.[20] The predicted product was always the major isomer (~80%), but the other possible stereoisomers were always present to some extent. For instance, **90** gave mainly the TAC stereoisomer **92** as predicted, while **91** gave mainly the CAT stereoisomer **93**. However, to be useful synthetically, 100% stereochemical control is required!

At this stage, we realized that there were several results that could not be explained completely, and we started to seriously question the validity of our theoretical model, which was based on the assumption that the Diels-Alder reaction always takes place via a chair-boat-chair-like transition state. For instance, why did our theoretical model predict the preferential formation of CAT tricycle **56**, while the experiments produced a 2:1 ratio in favor of the TAC isomer **57** from TTT macrocycle **53** (Scheme 10)? It does not appear possible to invoke the influence of stereoelectronic effects since the only substituent is a methyl group. This led us to assume that the formation of tricycles CAT and TAC might take place via a boat-boat-chair rather than the normally more appealing chair-boat-chair transition states **54** and **55**. In transition states **54** and **55**, there is a severe 1,3-diaxial steric interaction between one ester function and the olefinic

Scheme 14



Scheme 15

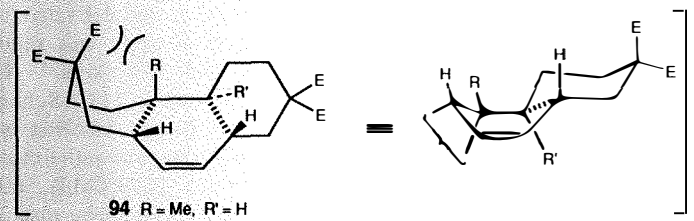


CH group. This interaction occurs in ring A for CAT (*cf.* **54**) and in ring C for TAC (*cf.* **55**). These steric interactions can be eliminated if the formation of CAT and TAC **56** and **57** takes place from boat-boat-chair transition states **94** and **95**, respectively (Scheme 16). Moreover, these two new transition states are quite appealing because the relative ratio of the TAC and CAT tricycles **56** and **57** can be readily explained. Indeed, in **94** the methyl group is in a boat-like conformation creating more steric hindrance than in **95** where the methyl group is in a chair-like orientation. On that basis, transition state **95** is of lower energy than **94**, and this explains why the TAC tricycle is obtained as the major isomer.

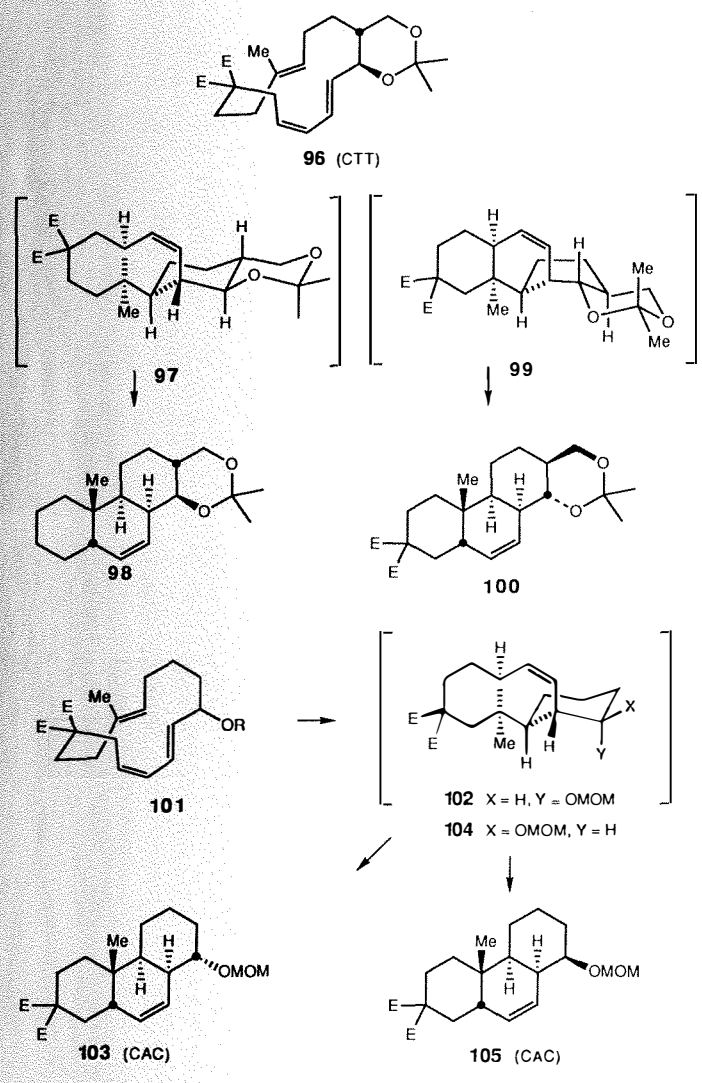
It is important to rigorously establish the preferred conformation of the Diels-Alder transition states, not only in order to explain the results obtained so far, but also because this new knowledge is a prerequisite for the conception of synthetic routes with complete control of the relative and absolute stereochemistry. Demonstration that a boat-boat-chair can compete with a chair-boat-chair transition state was realized by the study of the Diels-Alder reaction of CTT macrocyclic triene **96**, which contains an additional acetonide ring with a trans junction (Scheme 17).[21] Racemic macrocycle **96** gave a 7:3 mixture of tetracycles **98** and **100**. Molecular models indicate that tetracycles **98** and **100** are formed from chair-boat-chair-chair and chair-boat-boat-chair transition states **97** and **99**, respectively. In this case, transition state **97** does not suffer from severe 1,3-diaxial steric interaction. It is therefore surprising to observe that transition state **99** can compete with **97**. However, this situation occurs because of a stereoelectronic effect related to the presence of the C-O bond, which raised unduly the energy level of transition state **97**. This stereoelectronic effect was first observed by studying the Diels-Alder reaction of CTT macrocyclic triene **101**, which has an OR group (R = methoxymethyl).[22] This compound gave CAC tricyclic isomers **103** and **105** in 63:37 ratio, indicating that the transition state **102**, with an axially oriented OR group, is of lower energy than that of **104**, with an equatorially oriented OR group. This result is surprising, as it is contrasteric in nature. However, it indicates that a stereoelectronic effect raising the energy of **104** must be occurring. We are suggesting that in **104**, the OR group, being equatorial, is antiperiplanar to the C-C bond, which is in the process of formation. Overlap of the C-OR antibonding orbital with this electron-poor C-C bond at the transition state must be destabilizing. As a result, the predominant formation of CAC tricycle **103** via **102** was observed. These results further indicate that the study of the transannular Diels-Alder reaction is also interesting from a mechanistic point of view, because it provides experimental information not readily available either from intermolecular or simple intramolecular studies. This is because the transannular Diels-Alder reaction provides much better information on the precise conformation of transition states.

It was mentioned at the beginning of this article that the TAT tricycle cannot be obtained directly from a transannular Diels-Alder reaction. Since a vast number of natural products contain this relative stereochemistry, it was of interest to demonstrate that the TAT tricycle can be readily obtained from the isomerization of another tricycle. At the same time, it was also interesting to

Scheme 16



Scheme 17



show that one chiral center on the macrocycle could induce the control of the absolute configuration of tricycles. Both of these aspects were examined by the study of the optically active TCC macrocyclic triene **107** (Figure 18).[23]

The optically active *cis* dienophile, having a *p*-methoxybenzyl group, was prepared from L-(*S*)-glyceraldehyde acetonide.[24] Further coupling with dimethyl malonate and the *trans-cis* diene, following the general method described in Scheme 5, gave TCC allylic chloride **106**, which was cyclized under the usual conditions to yield crystalline TCC macrocyclic triene **107** in 80% yield. The TCC macrocycle **107**, when heated at 270 °C (3 h), led to the formation of optically active TSC tricycle **108** in 85% yield after chromatography. Removal of the *p*-methoxybenzyl protecting group with DDQ, followed by oxidation (PCC) of the resulting alcohol, gave a TSC tricyclic ketone that was converted by isomerization (Na_2CO_3, MeOH) to the more stable TAT tricyclic ketone **109**.

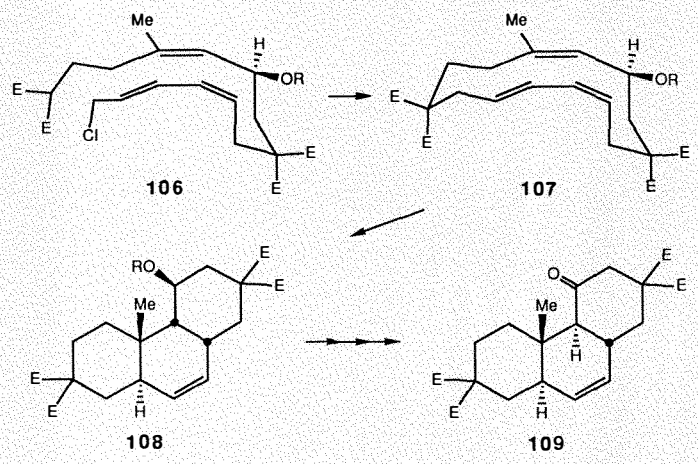
We have also studied several macrocycles where the diene and dienophile were first assembled by an aldol reaction. Only the most interesting cases are reported here.[22] On attempted macrocyclization at 80 °C, the TTT acyclic triene **110** (Scheme 19), having a bis-sulfone (E = SO_2Ph) as a connector, gave exclusively the TAC tricycle **113** in an overall yield of 90% with none of the normally competing CAT tricycle being observed. A similar result[25] was obtained with TTT acyclic triene **110**, having a bis-malonate connector (E = CO_2Me), which again gave only **113** but in a lower overall yield (70%).

In these two cases, the Diels-Alder reaction of the transient macrocycle **111** can take place via chair-boat-chair transition state **112**, which is devoid of destabilizing effects due to the appropriate orientation of the two functional groups in the newly formed ring C. Thus, the presence of these two substituents disfavors the occurrence of the chair-boat-boat competing transition state previously observed in other situations. This approach is quite interesting synthetically, because the use of an asymmetric aldol coupling methodology can, of course, lead to optically active tricycles with complete control of the relative and the absolute configuration. This approach is also quite appealing for future elaboration of ring C, because the problem of regioselectivity is, in principle, solved. Indeed, having two functional groups in this ring should facilitate the direct introduction of other substituents or rings.

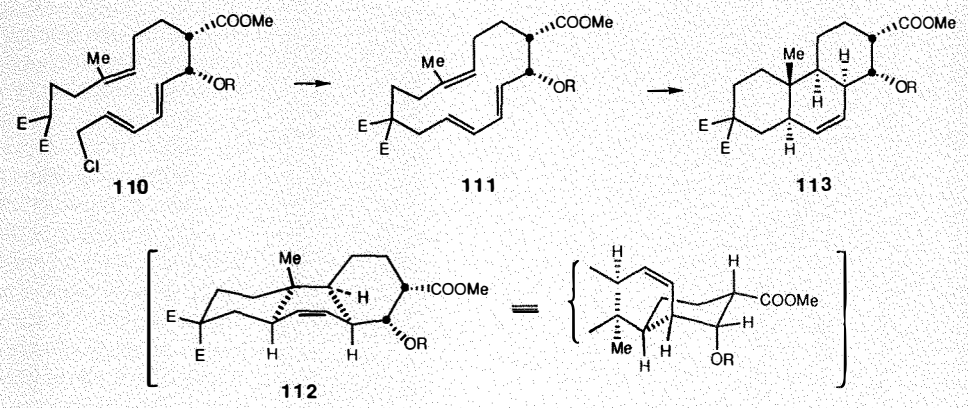
These last experiments indicate the general direction our laboratory is taking. Problems needing to be addressed and presently under investigation are the following: (a) new methods of macrocyclization, (b) discovery of connectors that would be more amenable (including the problem of regioselectivity) to further synthetic transformation once the tricycle has been produced, (c) dienophiles conjugated with a functional group to facilitate the Diels-Alder reaction and to obtain diastereoisomeric control from the endo rule, and (d) new solutions concerning the control of relative and absolute configuration. The most important operation is to find appropriate target molecules to be constructed in order to demonstrate the power of the transannular Diels-Alder reaction on macrocycles.

In the course of our general study, a total synthesis of a steroid derivative using the transannular strategy was reported by Takahashi and co-workers.[26] The TTT acyclic precursor **114** (Scheme 20), containing a D-ring, was first assembled and cyclized using ethoxyethyl cyanohydrin as a connector [$LiN(TMS)_2$, 80 °C] to produce the corresponding macrocycle in 75% yield. The cyanohydrin ether was then hydrolyzed under acid conditions to produce the TTT macrocyclic ketone **115**. Upon

Scheme 18



Scheme 19

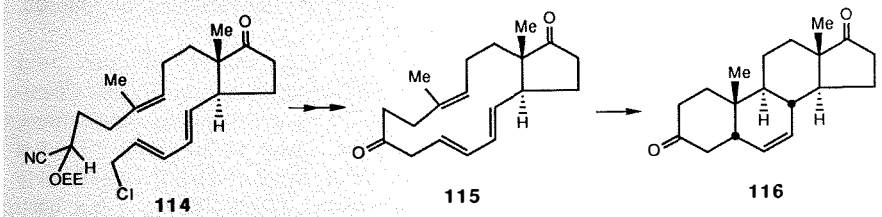


heating at 180 °C, **115** was converted into the steroid **116** (84%), having a CAT stereochemistry for the newly formed A.B.C. rings. In this case, the trans junction between the macrocycle and the cyclopentanone ring sterically inhibits the formation of other stereoisomers having a TAC stereochemistry.

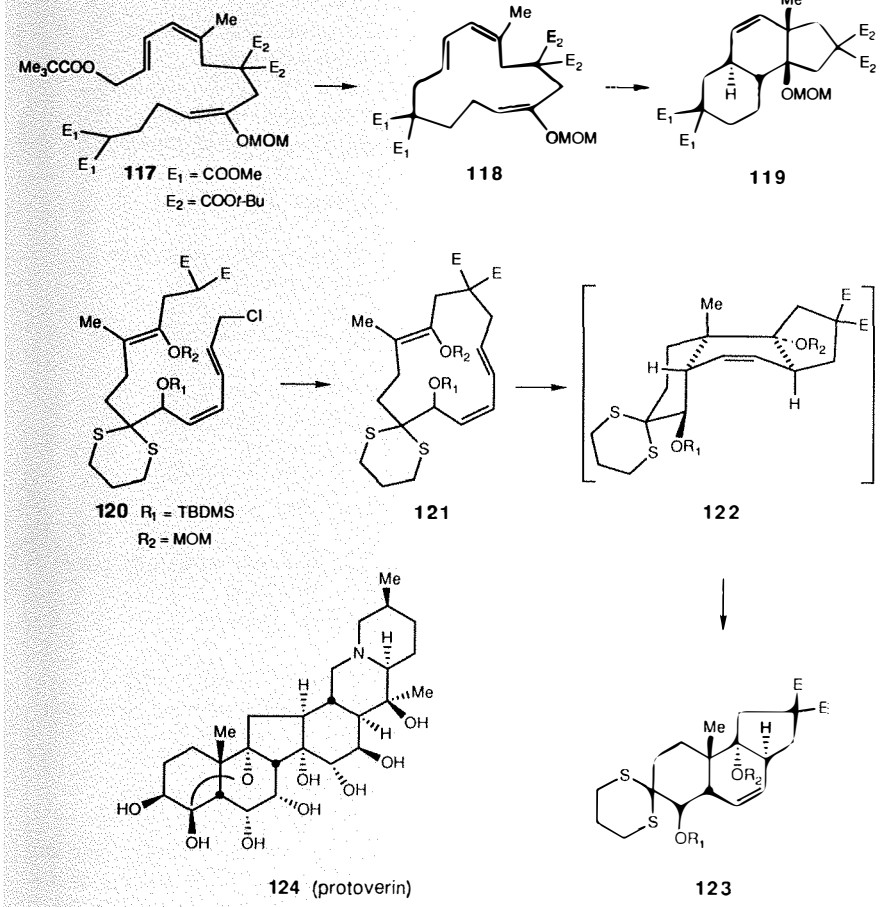
We are concluding this article by reporting two model studies that were carried out while having a specific target in mind. The first case[25] concerns the TCC acyclic triene **117** (Scheme 21). This contains an allylic pivalate that can be converted into TCC macrocyclic triene **118** in 80% yield using a palladium catalyst [*O*,*N*-bis(trimethylsilyl)-acetamide, $(Ph_3P)_4P$, $Ph_2PCH_2CH_2PPh_2$, THF].[27] Heating **118** at 180 °C gave TSC tricycle **119** with a B.C.D. stereochemistry corresponding to that found in 14β-hydroxysteroids. Appropriate modification of this model series should, therefore, lead to an interesting synthesis of cardioactive steroids. In the second case,[28] the CTT acyclic triene **120** was cyclized to give CTT macrocyclic triene **121** in 75% yield. Heating **121** at 220 °C provided, via transition state **122**, CAC tricycle **123** in 76% yield after chromatography. This A.B.C.[6.6.5] tricycle can be viewed as an interesting key intermediate for the synthesis of the complex veratrum alkaloids, **124**. Indeed, it has the correct ring size and functionalities required for the first three rings, and only one chiral center (C_8) need be corrected in order to serve as a useful key intermediate for the synthesis of this complex family of steroidal-alkaloids.

Work on the development of a general, rationally designed method for the synthesis of several classes of diterpenes, triterpenes and steroids, and closely related products is presently in progress in our laboratory.

Scheme 20



Scheme 21



Acknowledgment

This work was carried out experimentally by my collaborators cited in the references. Each of them worked with dedication, and it is with pleasure that I acknowledge their excellent contributions. This work was supported financially by the Natural Sciences and Engineering Research Council of Canada (NSERCC) and by the Ministère de la Science et de la Technologie du Québec. Financial assistance from a University-Industry grant from NSERCC and Merck Frosst Center for Therapeutic Research is also acknowledged.

References

1) Deslongchamps, P. *Aldrichim. Acta* **1984,** *17,* 59. Deslongchamps, P. *Bull. Soc. Chim. Fr. II* **1984,** *9,* 349.
2) Bélanger, A. et al. *Can. J. Chem.* **1979,** *57,* 3348. Deslongchamps, P. et al. *ibid.* **1990,** *68,* 115, 127, 153, 186.
3) Deslongchamps, P.; Lamothe, S.; Lin, H.-S. *ibid.* **1984,** *62,* 2395. *Idem ibid.* **1987,** *65,* 1298.
4) Baettig, K; Pitteloud, R., unpublished results.
5) Baettig, K.; Dallaire, C.; Pitteloud, R.; Deslongchamps, P. *Tetrahedron Lett.* **1987,** *28,* 5249. Baettig, K.; Marinier, A.; Pitteloud, R.; Deslongchamps, P. *ibid.* **1987,** *28,* 5253. Marinier, A.; Baettig, K.; Dallaire, C.; Pitteloud, R.; Deslongchamps, P. *Can. J. Chem.* **1989,** *67,* 1609.
6) Brillon, D.; Deslongchamps, P. *Tetrahedron Lett.* **1986,** *27,* 1131. *Idem Can. J. Chem.* **1987,** *65,* 43, 56.
7) Bérubé, G.; Deslongchamps, P. *Tetrahedron Lett.* **1987,** *28,* 5255. *Idem Can. J. Chem.* **1990,** *68,* 404.
8) Lamothe, S.; Ndibwami, A.; Deslongchamps, P. *Tetrahedron Lett.* **1988,** *29,* 1639.
9) *Idem ibid.* **1988,** *29,* 1641.
10) Lamothe, S. Ph.D. Thesis, Université de Sherbrooke, 1990.
11) Devon, T.K.; Scott, A.I. *Handbook of Naturally Occurring Compounds, Vol. II: Terpenes;* Academic Press: New York, 1972.

12) *Heterocycles,* Supplement no. 2; Kametani, T., Ed.; The Sendai Institute of Heterocyclic Chemistry: Sendai, Japan, 1983.
13) Cantin, M.; Xu, Y.-C.; Deslongchamps, P. *Can. J. Chem.* **1990,** *68,* 2144.
14) Roberge, J. M.Sc. Thesis, Université de Sherbrooke, 1988. Giguère, P., unpublished results.
15) a) Roughton, A. M.Sc. Thesis, Université de Sherbrooke, 1988. b) Plante, R.; Xu, Y.-C., unpublished results.
16) Soucy, P.; Hildenbrand, C., unpublished results.
17) Müller, R., unpublished results.
18) Ndibwami, A. Ph.D. Thesis, Université de Sherbrooke, 1988.
19) Berthiaume, S. M.Sc. Thesis, Université de Sherbrooke, 1989. Giguère, P., unpublished results.
20) Soucy, P.; Grimley, F., unpublished results.
21) Ouellet, C., unpublished results.
22) Dory, Y., unpublished results.
23) Marinier, A. Ph.D. Thesis, Université de Sherbrooke, 1990.
24) Maloneyhluss, K.E. *Synth. Commun.* **1986,** *15,* 273. Hubschwerlen, C. *Synthesis* **1986,** 962.
25) Soucy, P., unpublished results.
26) Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J.; Fukazawa, Y. *J. Am. Chem. Soc.* **1988,** *110,* 2674.
27) Trost, B.M.; Brickner, S.J. *ibid.* **1983,** *105,* 568. Trost, B.M. *Science* **1983,** *219,* 245. Marshall, J.A.; Andrews, R.C.; Lebioda, L. *J. Org. Chem.* **1987,** *52,* 2378.
28) Quimpère, M. Ph.D. Thesis, Université de Sherbrooke, 1990.

About the Author

Professor Pierre Deslongchamps received the B.Sc. degree from the University of Montreal in 1959 and the Ph.D. degree from the University of New Brunswick in 1964. He did postdoctoral work with Prof. R.B. Woodward at Harvard University in 1965. He has been a member of the faculty of the Université de Sherbrooke since 1967, attaining the ranks of Associate Professor in 1968 and Professor of Chemistry in 1972.

Dr. Deslongchamps was named a Fellow of the Alfred P. Sloan Foundation in 1970, of the Guggenheim Memorial Foundation in 1979, of the Royal Society of Canada in 1980, of the Royal Society of London in 1983, and of the American Association for the Advancement of Science in 1988. He has been awarded honorary doctorates from Université Pierre et Marie Curie (Paris), Bishop's University (Québec), the University of Montreal, Laval University (Québec), and the University of New Brunswick.

He has received numerous other awards including the Scientific Prize of Québec (1971), the E.W.R. Steacie Prize (Natural Sciences, 1974), the Médaille Vincent de l'ACFAS (1975), the Merck, Sharp, and Dohme Lectures Award (1976), the Médaille Pariseau de l'ACFAS (1979), and the Marie-Victorin Prize (Government of Québec, 1987).

He is the author of the text "Stereoelectronic Effects in Organic Chemistry" and over 125 scientific publications, with eight patents to his credit. He has served as President of the Canadian Society for Chemistry (1990-1991) and has been elected an Officer of the "Order of Canada".

Page intentially blank

Aldrichimica Acta

Volume 24, Number 3, 1991 *(Last issue in 1991)*

Organic Chemistry in Unconventional Solvents

The Molecular Basis of Biological Order

chemists helping chemists in research & industry

aldrich chemical company, inc.

Aldrichimica Acta

Volume 24, Number 3, 1991 *(Last issue in 1991)*
A publication of the ALDRICH CHEMICAL COMPANY

Aldrich Chemical Co., Inc.
1001 West Saint Paul Ave., Milwaukee, Wisconsin 53233 USA

To Place Orders

Telephone	800-558-9160 (USA/Canada)
	414-273-3850
TWX	910-262-3052 Aldrichem MI
TELEX	26 843 Aldrich MI
FAX	800-962-9591 or 414-273-4979
Mail	P.O. Box 2060, Milwaukee, WI 53201 USA

Customer Service

Customer Inquiries	800-558-9160
Technical Information	800-231-8327
SAF Bulk Chemicals	800-336-9719
Custom Synthesis	800-255-3756
Flavors & Fragrances	800-227-4563

General Correspondence
P.O. Box 355, Milwaukee, WI 53201 USA

Belgium
Aldrich Chemie
Bd. Lambermontlaan, 140 B6
B-1030 Bruxelles/Brussel
Telephone: 02 242 87 50
(local) 11 47 47
Telex: 62302 Alchem B
FAX: 02 242 82 16

France
Aldrich-Chimie S.a.r.l.
BP 234
67006 Strasbourg Cedex
Telephone: 88 32 70 10
Telex: 890076 Aldrich F
FAX: 88 75 12 83

Germany
Aldrich-Chemie GmbH & Co. KG
D-7924 Steinheim
Telephone: (0) 7329 87 - 0
For orders: (0) 7329 87 110
Telex: 714838 Aldri D
FAX: (0) 7329 87 - 139/239

Holland
Aldrich Chemie
Telephone: 32 (0)2 242 87 50
(local) 06 022 47 48
Telex: 62302 Alchem B
FAX: 32 (0)2 242 82 16

Italy
Aldrich Chimica
Via Pietro Toselli, 4
20127 Milano
Telephone: 02/261 36 89
Telex: 330862 Aldrch I
FAX: 02/289 63 01

Japan
Aldrich Japan
Kyodo Bldg. Shinkanda
10 Kanda-Mikuracho
Chiyoda-Ku, Tokyo
Telephone: 03-3258-0155
FAX: 03-3258-0157

Spain
Aldrich Quimica
Apt. de Correos, 161
28100 Alcobendas (Madrid)
Telephone: (9)1-661 99 77
Telex: 22189 SAQS E
FAX: (9)1-661 80 84

United Kingdom
Aldrich Chemical Co. Ltd
The Old Brickyard, New Road
Gillingham, Dorset SP8 4JL
Telephone: (0747) 822211
For orders: 0800 71 71 81
Telex: 417238 Aldrch G
FAX: (0747) 823779

About Our Cover:

Readers of the *Aldrichimica Acta* have known for twenty-four years that our chemist collector prefers Dutch 17th century paintings, preferably of Biblical subjects by Rembrandt students. But occasionally he just cannot resist buying more modern paintings. So it was with this large family portrait (oil on canvas, 59 x 91 inches), which he first saw in the basement of a Paris dealer. The clothing suggests that it was painted about 1815, but where and by whom? Is the ring on the middle finger of the mother's left hand a clue to the country and denomination? The desk looks New England of the period, but there may have been desks just like this in Scandinavia. The family Bible is open at "Acts", in English.

The raw canvas was exported from England by the London firm of Jesse Middleton which supplied canvases to Rembrandt Peale and Gilbert Stuart, but probably also to European artists. The sylvestris pine of the heavy stretcher could have grown in North America or northern Europe. Prof. R. B. Hoadley and his students at the University of Massachusetts at Amherst have developed a method[1] to distinguish between them, which involves measurements of fusiform ray heights. Unfortunately, there is a range where one cannot distinguish between North American red pine and northern European Scots pine, and values obtained from this stretcher fall into that range.

What is most enchanting is the depiction of the personalities: the stern father (a minister?), the mother, concerned mainly with the welfare of the family, and each of the children, alike in some ways, yet so different. And don't overlook the dog and cat.

Our hope is that descendants of this family will recognize their ancestors and so point to where this was painted and perhaps even to the artist.

Some years ago, in *Aldrichimica Acta 11*, 3 (1978), we depicted a Dutch church, and several readers identified the church through its distinctive organ. Perhaps readers will be able to help us with this, also.

The quality of this painting makes it a fitting cover for the *Acta* with the truly exciting papers of Prof. Grieco and Dr. Williams.

1) "The Use of Fusiform Rays as a Basis for Distinguishing the Woods of *P. sylvestris* and *P. resinosa*," Zarifan, S.A. M.Sc. Thesis, University of Massachusetts at Amherst, Department of Forestry and Wildlife Management, May, 1987.

The Detective's Eye: Investigating the Old Masters

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

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

Lab Notes

I was surprised to find that one type of flask which has been made by German and Czech glassblowers for at least 50 years was not available in the U.S. Since this flask with the round bottom, the "Apollo" flask, is so useful to the organic chemist, I suggest that Aldrich might like to offer it.

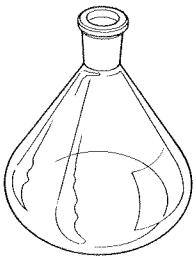
It has properties similar to the Apollo space ship; when dropped on water it has two stable positions. In most cases it will stand on a bench in a stable position without a ring, and it can float on a liquid surface, even in a very unstable position, keeping the neck up. It will float in a stable position upside down in a liquid. This means that if a filled flask drops from the rotavap, most of the solution remains inside the flask. Simply close the neck with a stopper and remove it from the bath. A further advantage of the Apollo flask is that it has a larger inner volume than the round-bottom flask for the evaporation of foaming liquids, and the inner surface of the flask is easily reached with a spatula.

Dr. Pavel Drasar
Institute of Organic Chemistry
and Biochemistry
Czechoslovak Academy of Sciences
Flemingovo 2
CS-166 10 Praha 6
Czechoslovakia

Apollo Flasks

Low profile flasks for easy access with a spatula. Inner shape of the flask is best for the controlled evaporation of foaming solvents, such as toluene or xylene, on a rotovap.

Editor's Note: Aldrich now offers five volumes of Apollo flasks in both ₹14/20 and ₹14/23 joint sizes. These are listed below. For more information, contact our Technical Services Department at 800-231-8327.



"Please Bother Us."

by Ian O'Neil

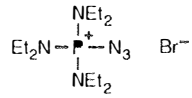
Dr. Ian O'Neil of the University of Liverpool kindly suggested that we offer a reversed phase silica gel for column chromatography. Using chromatography methods, compounds such as organic stannanes,[1] amino-acids, nucleosides, carboxylic acids, and sulfonic acids may be readily separated.[2]

Naturally, we made this material.

(1) Farina, V. *J. Org. Chem.* **1991**, *56*, 4985. (2) O'Neil, I.A. *Synlett.* **1991**, 661.

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

New Diazo Transfer Reagent



This new reagent, suggested by Prof. Ralph Raphael of Cambridge University, bears a strongly basic phosphorimine nitrogen (allowing basic autocatalysis), generates a neutral leaving group (hexaethylphosphoramidic triamide, easily removed as its hydrobromide salt), and is reportedly exceptionally stable against shock, friction, and rapid heating.

McGuiness, M.; Shechter, H. *Tetrahedron Lett.* **1990**, *31*, 4987.

Organic Chemistry in Unconventional Solvents

Paul A. Grieco
Department of Chemistry
Indiana University
Bloomington, Indiana 47405

Introduction

The use of water as a solvent in organic chemistry has, for the most part, been nonexistent despite the fact that many biochemical processes occur in the presence of water at ambient temperature. Whereas Mother Nature discovered the secrets of water millions of years ago, the organic chemist has only recently come to appreciate the enormous potential water holds for those engaged in synthetic organic chemistry.

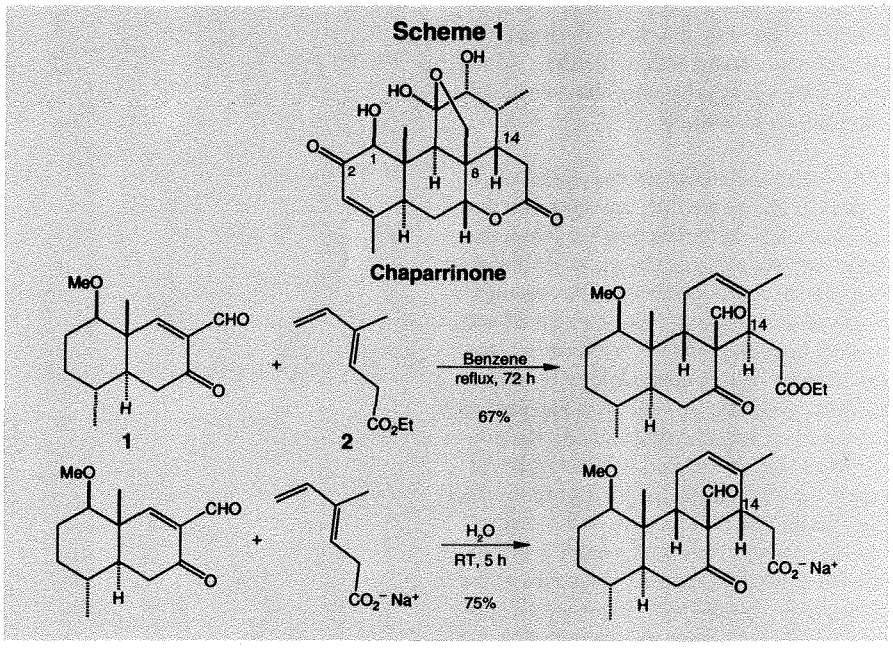
Our own realization that water can have a profound effect on the way one does organic chemistry goes back a few years to our early work on the quassinoids. In fact, it was over ten years ago that we embarked on a total synthesis of the highly oxygenated quassinoid, chaparrinone, employing a Diels-Alder approach (Scheme 1). The strategy that we adopted was a modification of the [4+2] cycloaddition chemistry we had developed in conjunction with the first successful synthesis of the parent quassinoid, quassin.[1]

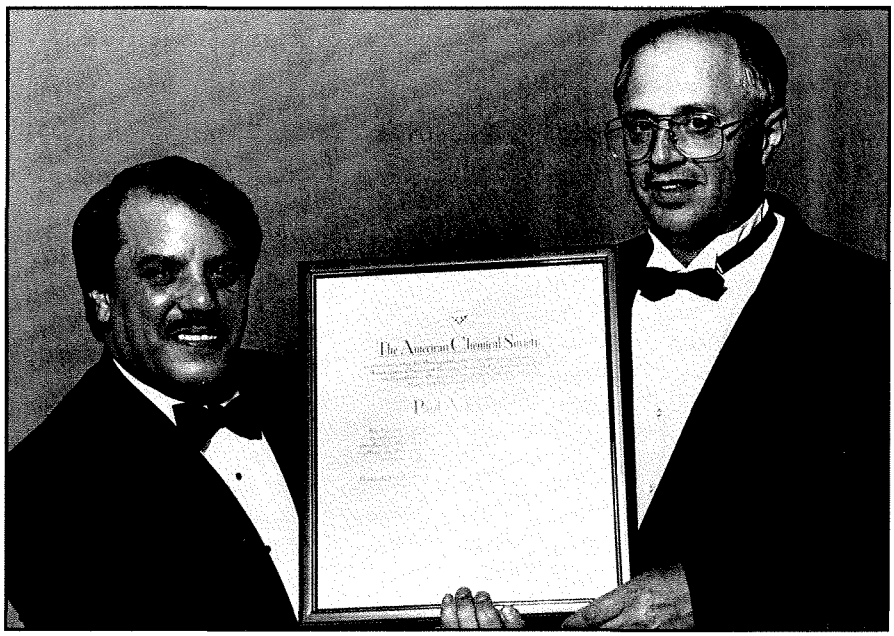
There are, in principle, four possible Diels-Alder adducts that can arise from cycloaddition of **1** and **2**: two adducts from the β-face of the dienophile and two from the α-face, all via endo transition states. In reality, only two of the four possible adducts were anticipated since the presence of the angular methyl group in the dienophile precludes approach of the diene from the β-face. Proceeding along conventional lines, the diene and dienophile (Scheme 1) were dissolved in benzene and allowed to reflux over an extended period of time. One major product that possessed the incorrect configuration at C(14) was isolated.

The problem of reversing the selectivity in the Diels-Alder reaction proved to be a formidable challenge. However, after extensive experimentation, the desired reversal in selectivity could be achieved by conducting the Diels-Alder reaction in water and employing the sodium salt of 4-methyl (*E*)-3,5-hexadienoic acid as the diene.[2] Equally noteworthy was the fact that, in water, the rate of the reaction was dramatically accelerated. Best results were obtained when the reaction was conducted with a five-fold excess of diene carboxylate (2.0 *M* in water).

Several features of this reaction warrant comment. The reaction rate is dramatically slowed upon lowering the concentration of diene below 1.0 *M*. Furthermore, upon addition of organic solvents (e.g., dioxane, methanol, tetrahydrofuran) to help solubilize the dienophile, the reaction rate, once again, is dramatically slowed. The above observations strongly suggest that aggregation of the diene carboxylate plays a critical role in helping to solubilize the dienophile. However, the observed rate acceleration, along with the reversal in selectivity, is attributed

Scheme 1





Dr. Stephen Branca, Aldrich Chemical, presenting Dr. Paul A. Grieco wth the 1991 ACS Award for Creative Work in Synthetic Organic Chemistry.

to the hydrophobic effect (the entropy driven association of nonpolar species in water that minimizes their exposure to water). When several transition states are possible, the more compact transition state, occupying the smallest volume, should be favored. Examination of the transition state leading to the desired C(14) β-H adduct reveals a compact, ball-like structure, whereas the transition state leading to the undesired isomer is bulky and cumbersome.

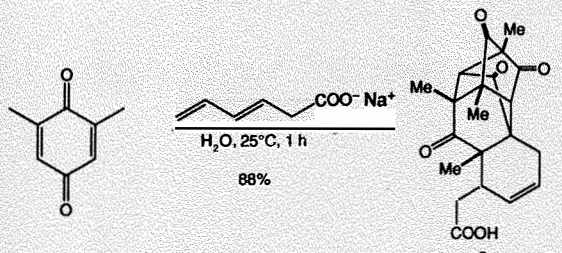
The enhanced reaction rate and reversal in selectivity observed above led us to investigate further the scope of water and other unconventional solvents for the Diels-Alder reaction. I would be remiss at this point if I did not mention the pioneering work of Breslow who was the first to report the hydrophobic acceleration of the Diels-Alder reaction between cyclopentadiene and methyl vinyl ketone in water.[3,4]

Diels-Alder Reactions in Aqueous Medium

During the course of our study on the aqueous Diels-Alder reaction, we found that diene carboxylates react in water at ambient temperature with a wide range of dienophiles.[5] Much of this work has been published and will not be reviewed here; however, several applications of this methodology to natural products synthesis, as well as an application to a novel carbocyclic ring forming reaction, are deserving of mention. In the latter category, we were particularly intrigued to find that, during the examination of the reaction of diene carboxylates with a number of substituted benzoquinones, we obtained a novel pentacyclic compound.[6] Exposure of 2,6-dimethylbenzoquinone to 1.5 equiv of a 1.0 *M* solution of sodium (*E*)-3,5-hexadienoate in water containing a catalytic amount of sodium hydroxide gave rise to carboxylic acid **3** (Scheme 2). The anticipated Diels-Alder adduct is obtained in the absence of base. The formation of **3** arises via deprotonation of the Diels-Alder adduct followed by two sequential 1,4-Michael addition reactions (Scheme 3). Similar results were obtained with sodium (*E*)-4,6-heptadienoate. Other substituted benzoquinones (e.g., 2,5-dimethylbenzoquinone) behave similarly.

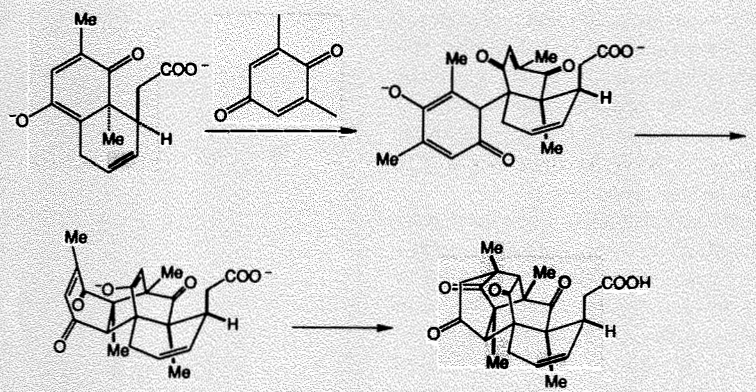
Two examples serve to illustrate the applicability of the aqueous Diels-Alder strategy to the synthesis of natural products. The synthesis of the bicyclic lactone **6**, which constitutes the basic AB ring system of the sesquiterpene lactone, vernolepin, was readily realized via a one pot procedure (Scheme 4).[7] Cycloaddition of sodium (*E*)-3,5-hexadienoate with the α-substituted acrolein **4** in water followed by direct reduction of the intermediate Diels-Alder adduct **5**, without workup, gave rise, upon acidification, to **6** in excellent yield.

Scheme 2



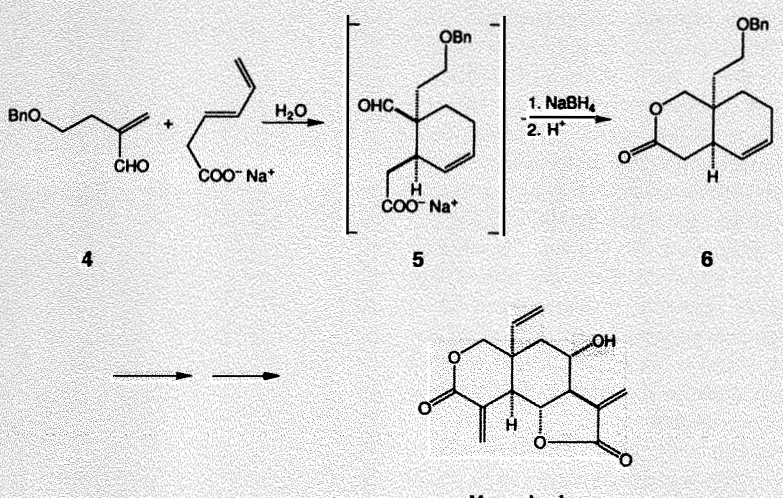
3

Scheme 3



3

Scheme 4

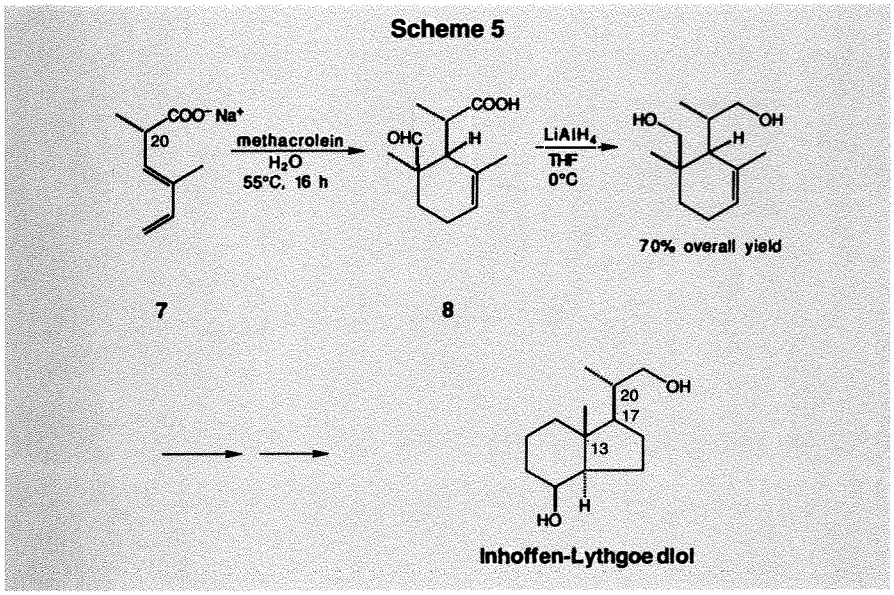


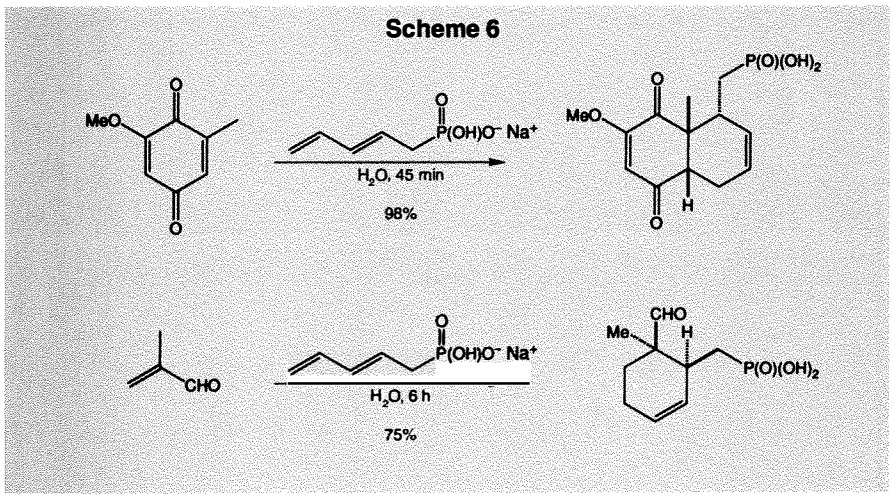
4 5 6

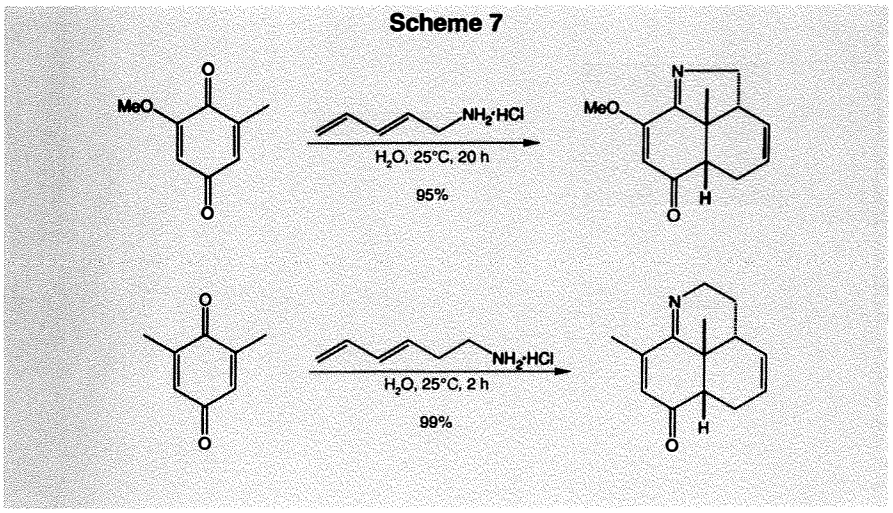
Vernolepin

In connection with synthesizing the Inhoffen-Lythgoe diol (Scheme 5), a novel intermolecular Diels-Alder strategy in water was employed, wherein an intact C(20) stereocenter, as part of a diene unit, was used to elaborate directly the stereocenters of the latent C/D trans-fused hydrindane ring system at C(13) and C(17).[8] Remarkably, condensation of methacrolein with the sodium salt of chiral diene **7** proceeded in water, giving rise to carboxylic acid **8**. Approximately 15% of the other diastereoisomer could be isolated. In contrast to the high degree of diastereoselection observed above, the corresponding reaction employing the methyl ester of **7** gave no diastereoselectivity in the absence of water.

The aqueous Diels-Alder methodology can be extended to dienes bearing other water solubilizing groups. In this regard, we have examined the sodium salt of (*E*)-2,4-pentadienylphosphonic acid (Scheme 6)[9] and the dienyl ammonium chloride salts (Scheme 7)[10] derived from (*E*)-2,4-pentadienyl-







amine and (*E*)-3,5-hexadienylamine. The Diels-Alder reactions were conducted along the lines delineated above, employing a five-fold excess of diene, generally 1.0 - 2.0 *M* in water. In all cases, the Diels-Alder adducts were derived from endo transition states with ortho regiochemistry. With respect to the dienyl ammonium salts, the Diels-Alder adducts underwent subsequent internal imine formation. Uncyclized free amino compounds could not be detected upon workup. The (*E*)-2,4-pentadienylphosphonic acid used in connection with the above study was prepared, in straightforward fashion, by an Arbuzov reaction between (*E*)-2,4-pentadienyl bromide and tris(trimethylsilyl) phosphite, followed by exposure of the resultant bis(trimethylsilyl) (*E*)-2,4-pentadienylphosphonate to methanol.

Water as a Solvent for the Claisen Rearrangement

In the midst of our study on aqueous Diels-Alder chemistry, we became intrigued by the possibility of promoting Claisen rearrangements in water. There was ample precedent in the literature to suggest that water should have an accelerating influence. In fact, a number of research groups had independently demonstrated that polar solvents accelerate Claisen rearrangements.[11]

In a preliminary, qualitative study, allyl vinyl ether **9** was shown to undergo [3,3]-sigmatropic rearrangement in water at 60°C, giving rise to aldehyde **10** (Scheme 8). Rearrangement of the corresponding ester **11** in water is equally facile and efficient at 60°C despite the fact that the reaction medium is heterogeneous. In contrast, the rearrangement of **11** proceeds very slowly in benzene (Scheme 8). A solvent polarity study on the rate of the rearrangement of allyl vinyl ether **9** has been conducted in solvent systems ranging from pure methanol to water at 60°C.[12] The first order rate constant for the rearrangement of **9** in water is 18 x $10^{-5}s^{-1}$, compared to 0.79 x $10^{-5}s^{-1}$ in pure methanol.

The accelerating influence of water as a solvent on the rate of the Claisen rearrangement has been demonstrated on a number of substrates, which clearly illustrates the enormous potential it holds for those engaged in the synthesis of natural and unnatural products.[13] Notable, among the many cases that have been examined, is the rearrangement of allyl vinyl ether **12** (Scheme 9), which proceeds at 80°C. During his total synthesis of aphidicolin, McMurry found that the Claisen rearrangement of **12**, wherein the 1,3-diol unit was protected, required temperatures in excess of 200°C and was plagued by the elimination of acetaldehyde.[14]

Equally remarkable is the effect of water on the rearrangement of allyl vinyl ether **13** (R = Na; Scheme 10), a key intermediate in a synthesis of the Inhoffen-Lythgoe diol. The rearrangement of **13** (R = Na), which presumably occurs via a boat transition state, proceeds at 95°C. The corresponding ester **13** (R = Me) led only to recovered starting material upon prolonged heating in decalin at 95°C.

In an attempt to probe further the potential of water as a solvent for the Claisen rearrangement, we set out to study the rearrangement of the [4.5.5.5]-fenestrene derivatives **14** and **16** (Scheme 11), which, as a direct consequence of the [3,3]-sigmatropic process, would impart significant torsional strain

to the novel functionalized fenestrenes **15** and **17**. Note that fenestrene **17** possesses a trans ring fusion between the two five-membered rings common to the acetaldehyde unit.

Claisen rearrangement of allyl vinyl ether **14** proceeded at 90°C, affording aldehyde **15**. The structure of **15** was unambiguously established by single-crystal X-ray analysis of the corresponding carboxylic acid. The transformation of **16** into **17** was surprisingly facile. It is particularly interesting to note that all previous attempts to employ Claisen rearrangements within the carbon framework of a fenestrane system, as well as efforts to synthesize a fenestrane possessing a trans ring fusion, have been unsuccessful.

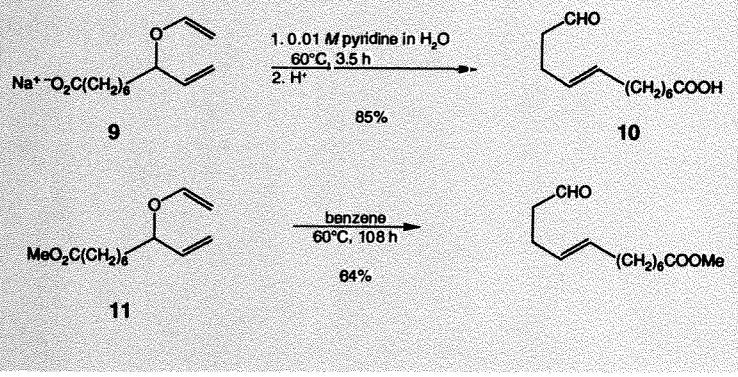
Lithium Perchlorate in Diethyl Ether — A Unique Medium for Accelerating the [1,3]-Sigmatropic Rearrangement of Allyl Vinyl Ethers

The rate accelerations recorded above have been attributed, in part, to stabilization of a polar transition state by water. We were particularly intrigued with the idea of using other, more polar media to lower further the barrier for the Claisen rearrangement. In view of the fact that lithium perchlorate solutions in diethyl ether have previously been employed to accelerate reactions with polarized transition states, we set out to examine the effect of lithium perchlorate-diethyl ether on the rate of the Claisen rearrangement. Over thirty years ago, Winstein[15] demonstrated that the ionization rate of *p*-methoxyneophyl *p*-toluenesulphonate in 0.1 *M* $LiClO_4$-Et_2O increased by a factor of 10^5. Similarly, Pocker[16] has observed that 5.0 *M* $LiClO_4$-Et_2O increases the rate of ionization of trityl chloride by 7.0×10^9.

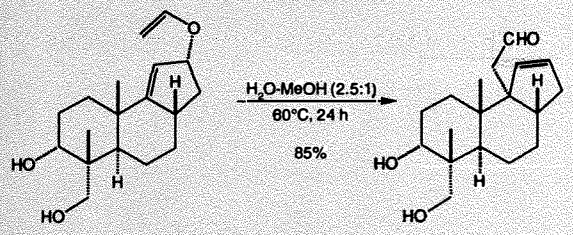
In order to probe the effect of lithium perchlorate in diethyl ether on a number of simple allyl vinyl ethers, a number of substrates (e.g., **18**; Scheme 12) were initially exposed to 0.1 *M* $LiClO_4$-Et_2O. After several hours at ambient temperature, no reaction was observed. However, exposure of **18** to 1.0 *M* $LiClO_4$-Et_2O over 24 h resulted in the disappearance of the starting allyl vinyl ether and the formation of one major product, which was not the product of the anticipated [3,3]-sigmatropic rearrangement, but instead the result of an exclusive [1,3]-sigmatropic rearrangement (Scheme 12). The rearrangement of **18** is best performed in 3.0 *M* $LiClO_4$-Et_2O. The intervention of the [1,3]-sigmatropic rearrangement during the course of a Claisen rearrangement is a rare event, witnessed previously in only a very few special cases where the normal [3,3]-process is either energetically or sterically unfavorable, or both.

The above procedure, utilizing 3.0 *M* $LiClO_4$-Et_2O to promote [1,3]-rearrangement

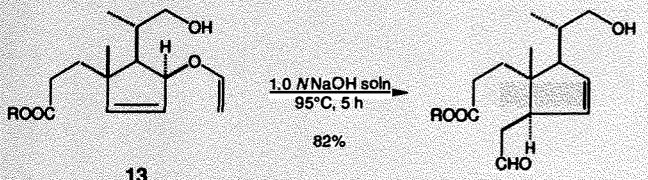
Scheme 8



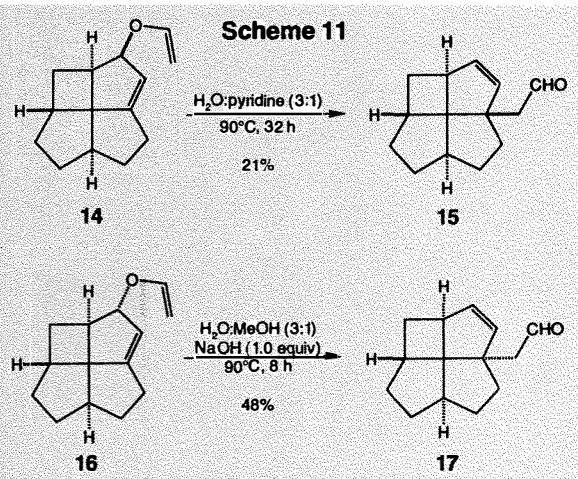
Scheme 9



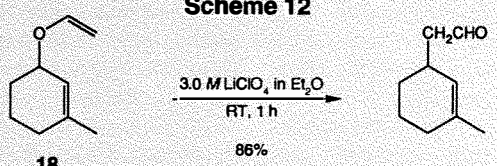
Scheme 10



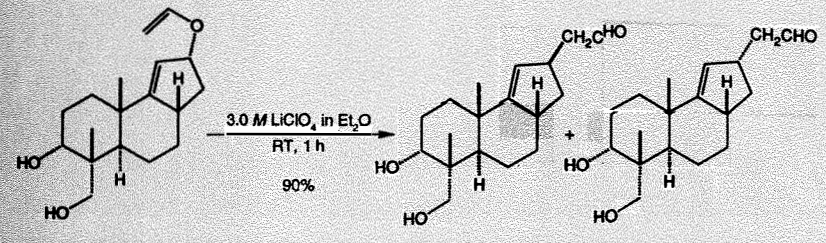
Scheme 11



Scheme 12

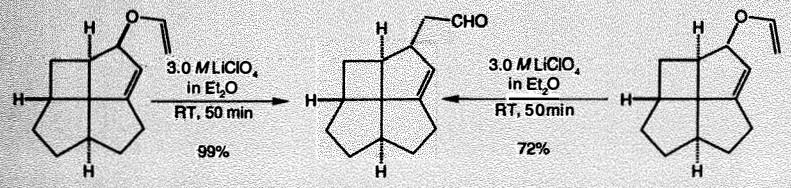


Scheme 13



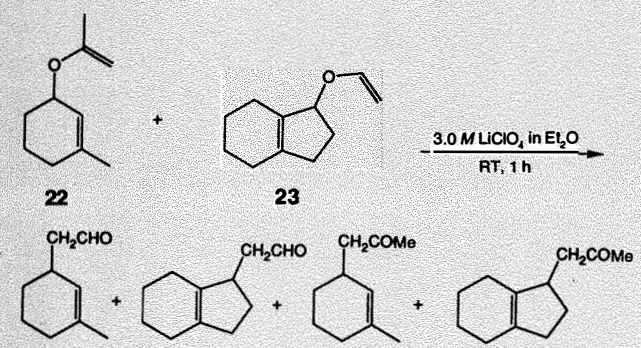
12 19 20

Scheme 14



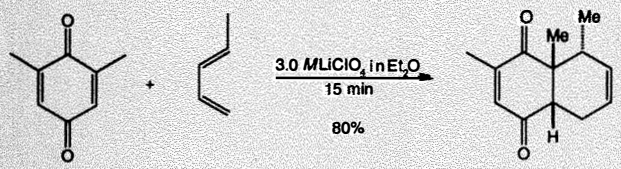
14 21 16

Scheme 15

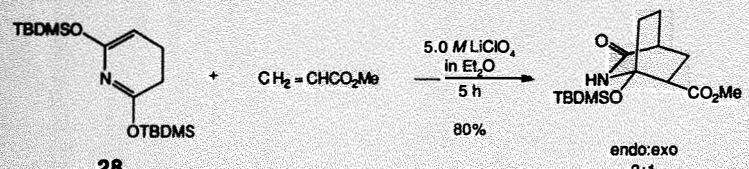


22 23 24 25 26 27

Scheme 16



Scheme 17



28

of allyl vinyl ethers, is applicable to a variety of substrates.[17] For example, a 0.2 *M* solution of allyl vinyl ether **12** (Scheme 13) in 3.0 *M* $LiClO_4$-Et_2O underwent exclusive [1,3]-rearrangement within 1 h at ambient temperature, giving rise to **19** and **20** in a ratio of 5:1. Use of 5.0 *M* $LiClO_4$-Et_2O afforded **19** and **20** in the same ratio within a few minutes. Interestingly, exposure of the corresponding C(12) epimeric allyl vinyl ether to 3.0 *M* $LiClO_4$-Et_2O gave rise, within 1 h, to a 94% yield of **19** and **20** in a 5:1 ratio.

We were surprised to find that the fenestrene-derived allyl vinyl ethers **14** and **16**, employed above in conjunction with the aqueous Claisen rearrangement study, also underwent [1,3]-sigmatropic rearrangement, giving rise to the same aldehyde **21** (Scheme 14), suggesting, as did the data from the rearrangement of allyl vinyl ether **12**, that the observed [1,3]-rearrangement products may arise via dissociated ions, followed by recombination. In order to determine the extent of ionization of allyl vinyl ethers in 3.0 *M* $LiClO_4$-Et_2O, allyl vinyl ethers **22** and **23** (Scheme 15) were subjected to a crossover experiment. In a separate set of experiments, prior to the crossover study, it was established that both **22** and **23** (each 0.1 *M* in 3.0 *M* $LiClO_4$-Et_2O) undergo smooth transformation within one hour to their respective [1,3]-rearrangement products **26** and **25,** in excellent yields. Upon admixture of **22** and **23**, a mixture of aldehydes **24** and **25**, and ketones **26** and **27** was obtained in a ratio of 1.0:1.8:1.5:1.6, suggesting that dissociated ions are involved. We also established, via kinetics, that the reaction rate for the [1,3]-rearrangement of substrate **18** is dependent upon the concentration of lithium ion; however, additional factors may be operational.

Acceleration of Diels-Alder Reactions in 5.0 *M* Lithium Perchlorate-Diethyl Ether

Our longstanding interest in the Diels-Alder reaction led us to examine lithium perchlorate in diethyl ether as a medium for effecting [4+2]-cycloadditions, despite the general view that the rate of the Diels-Alder reaction is essentially independent of solvent polarity. This consensus is not surprising since, for years, the Diels-Alder reaction has been thought of as proceeding via a highly ordered, relatively nonpolar transition state. However, contrary to this widely held view, we have seen that a polar solvent, such as water, can have a profound effect on the rate of a Diels-Alder reaction. Unfortunately, there are limitations associated with water as a solvent: the vast majority of organic compounds are insoluble in water and water precludes the use of moisture-sensitive substrates.

Our findings in this area clearly reveal that 5.0 *M* lithium perchlorate in diethyl ether is

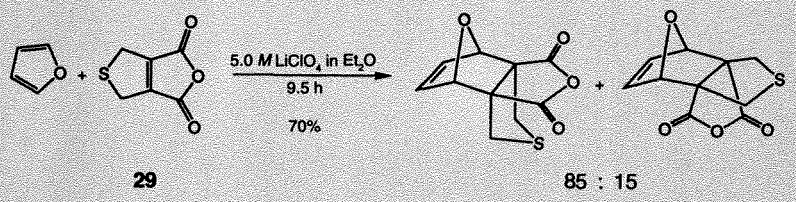
a powerful medium for facilitating [4+2]-cycloadditions.[18,19] A few representative examples serve to illustrate the effect. Whereas the reaction of *trans*-piperylene with 2,6-dimethylbenzoquinone in 5.0 *M* $LiClO_4$-Et_2O is complete within a few minutes (Scheme 16), the corresponding reaction in water is extremely sluggish. In the case of the sensitive diene **28**, reaction with methyl acrylate (Scheme 17) was complete in a few hours. In contrast, the reaction of **28** with methyl acrylate in benzene required 72 h at 60°C in order to go to completion.[20]

Diels-Alder adducts that hitherto were not accessible via conventional means can now be realized in 5.0 *M* lithium perchlorate in diethyl ether. For instance, furan is known to be a poor diene in the Diels-Alder reaction because of its aromaticity. In addition, the high temperatures required are not compatible with the furan cycloaddition products that cyclorevert at high temperatures. To circumvent the above difficulties, ultrahigh pressure has been employed to effect furan Diels-Alder chemistry. In his classic synthesis of cantharidin, Dauben found that reaction of furan with dienophile **29** required 15 kbar of pressure in order to realize reaction.[21] In striking contrast, the Diels-Alder reaction between furan and **29** proceeds smoothly in 5.0 *M* $LiClO_4$-Et_2O at ambient temperature and pressure (Scheme 18).

During the course of our study with dienophile **29**, we found that ethyl acetate and acetone can be employed in place of diethyl ether. For example, reaction of furan with **29** in 5.0 *M* lithium perchlorate in ethyl acetate proceeds at a reaction rate that is comparable to the rate in diethyl ether and gives rise to the Diels-Alder adducts shown in Scheme 18 in improved yield. Also effective was the use of 5.0 *M* lithium perchlorate in acetone. In contrast, the reaction rate was slowed considerably when tetrahydrofuran was employed.

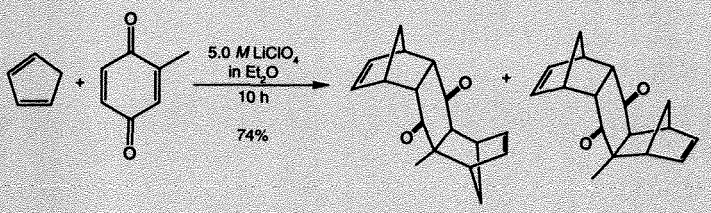
Equally fascinating and informative was the observation detailed in Scheme 19, wherein methylbenzoquinone was exposed to excess cyclopentadiene in 5.0 *M* lithium perchlorate in diethyl ether. The formation of Diels-Alder adducts, such as **30** and **31**, normally requires ultrahigh pressure and is accompanied by copious amounts of dicyclopentadiene, a result that is not surprising since reaction rates for all Diels-Alder reactions should be increased under pressure due to the fact that all [4+2]-cycloaddition reactions proceed with a highly negative volume of activation. Interestingly, during the formation of **30** and **31** in 5.0 *M* lithium perchlorate-diethyl ether, the rate of dimerization of cyclopentadiene is not affected. A similar discovery was made recently by Forman and Dailey[22] who observed that the reaction rate for the Diels-

Scheme 18



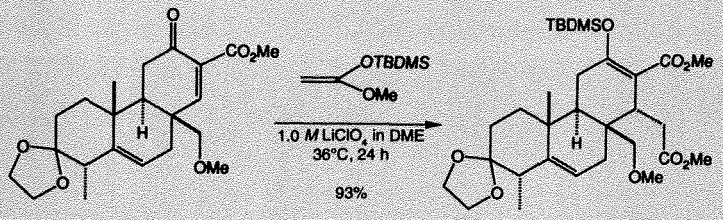
29 85 : 15

Scheme 19



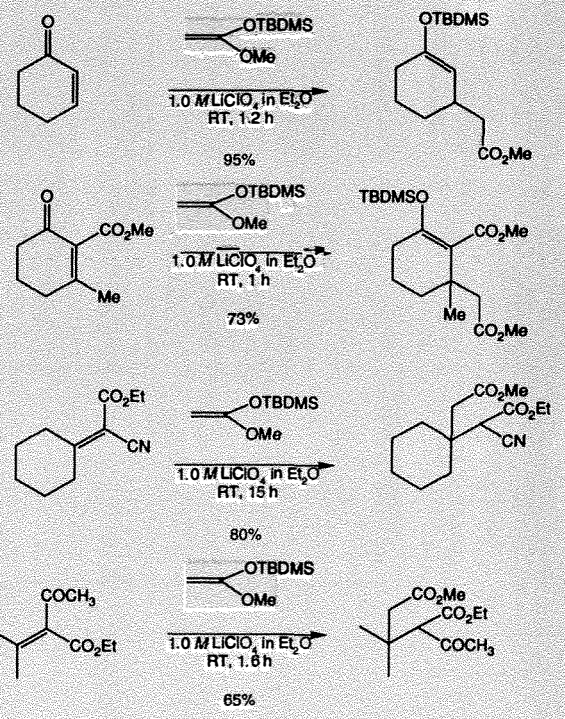
30 **31**

Scheme 20



32 **33**

Scheme 21



Alder reaction between styrene and 1,3-diphenylisobenzofuran is unaffected by lithium perchlorate in diethyl ether.[22] In this same report, Forman and Dailey present evidence indicating that the rate accelerations observed in lithium perchlorate-diethyl ether are consistent with lithium ion catalysis.

Lithium Perchlorate Catalyzed Conjugate Addition of Silyl Ketene Acetals to α,β-Unsaturated Carbonyl Compounds

Several years ago, in conjunction with an approach to bruceantin, we were unable to carry out the 1,4-conjugate addition of a silyl ketene acetal to activated enone **32** (Scheme 20) either thermally or under conventional Lewis acid catalysis (e.g., titanium tetrachloride or a 1:1 mixture of titanium tetrachloride and titanium tetraisopropoxide in methylene chloride). We have found that lithium ion catalysis will promote the conjugate addition of silyl ketene acetals to highly functionalized, hindered α,β-unsaturated carbonyl systems.[23] For example, treatment of a 0.1 *M* solution of activated enone **32** in 1.0 *M* lithium perchlorate in dimethoxyethane with 1-methoxy-1-(*t*-butyldimethylsiloxy)-ethylene gave rise, in excellent yield, to a single 1,4-addition product, **33,** possessing the C(14) α stereochemistry (Scheme 20). Use of 1.0 *M* lithium perchlorate in diethyl ether gave rise to considerable amounts of the 1,2-addition product. It is of interest to note that previously, in those instances where the thermal Michael reaction has failed due to steric congestion, or in cases where conventional Lewis acids are not compatible with existing functionality, ultrahigh pressure has been used to promote conjugate addition reactions.[24]

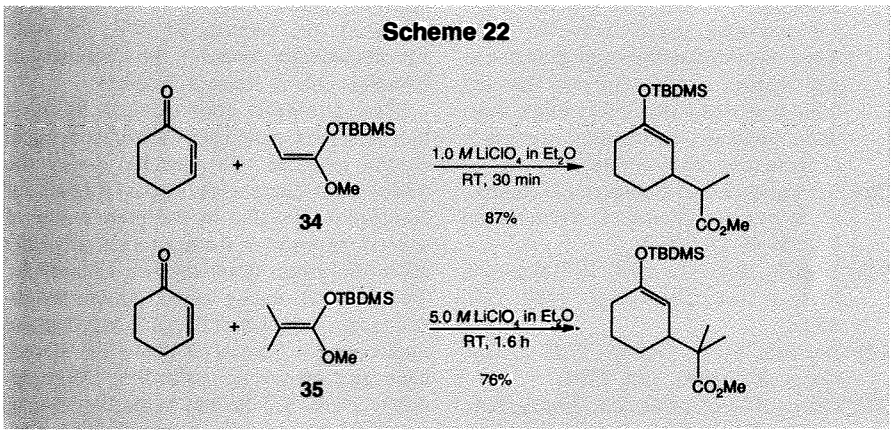
The lithium perchlorate catalyzed Michael reaction has been conducted on a number of substrates, including sterically demanding, β,β-disubstituted, unsaturated carbonyl compounds (Scheme 21). In the majority of cases examined, 1.0 *M* lithium perchlorate in diethyl ether appears to be the solvent of choice; however, more demanding situations may require increasing the concentration of lithium ion. Whereas silyl ketene acetal **34** undergoes smooth 1,4-addition to cyclohexenone in 1.0 *M* lithium perchlorate-diethyl ether at ambient temperature and pressure, the more demanding silyl ketene acetal **35** required the use of 5.0 *M* lithium perchlorate in diethyl ether (Scheme 22). No reaction was observed using 1.0 *M* lithium perchlorate in diethyl ether.

Lithium perchlorate has also been employed to catalyze the 1,4-addition of silyl ketene acetals to α,β-unsaturated δ-lactones. Reactions involving unsaturated lactones are best carried out in 2.5 *M* lithium perchlorate in diethyl ether. For example, treatment of a 0.1 *M* solution of δ-lactone **36** in 2.5 *M* lithium perchlorate in diethyl ether at ambient temperature and pressure with 1-methoxy-1-(*t*-butyldimethylsiloxy)ethylene afforded, within a few minutes, an excellent yield of lactone **37** (Scheme 23). Similarly, unsaturated lactone **38** was transformed into lactone **39**, a key intermediate in a recently completed synthesis of the cytotoxic natural product sesbanimide A (Scheme 24).[25]

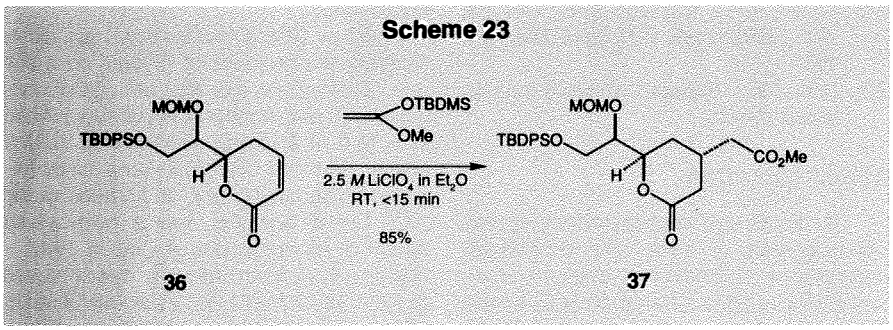
Acknowledgements

It is a pleasure for me to express my sincere appreciation to the dedicated, hardworking, skillful efforts of my graduate students and postdoctoral associates whose names appear in the references cited. To them I will forever remain deeply indebted. I am grateful to the National Institutes of Health and the National Science Foundation for the generous support that made this research possible.

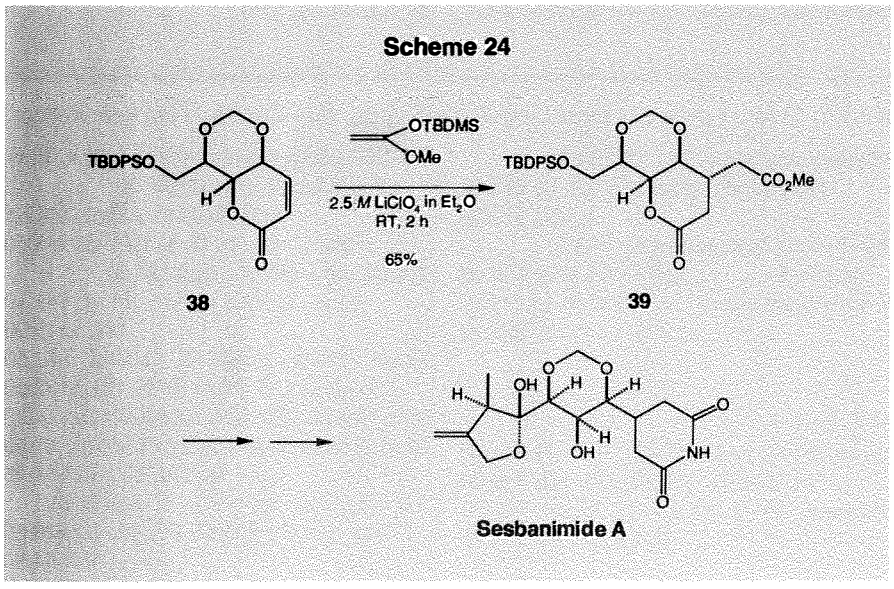
Scheme 22



Scheme 23



Scheme 24



References:

1) Grieco, P.A.; Ferrino, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586. Vidari, G.; Ferrino, S.; Grieco, P.A. *ibid.* **1984**, *106*, 3539.
2) Grieco, P.A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897.
3) Rideout, D.C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.
4) Also see, Lubineau, A.; Queneau, Y. *Tetrahedron Lett.* **1985**, *26*, 2653. *Idem J. Org. Chem.* **1987**, *52*, 1001.
5) Grieco, P.A.; Yoshida, K.; Garner, P. *ibid.* **1983**, *48*, 3137. Grieco, P.A.; Yoshida, K.; He, Z. *Tetrahedron Lett.* **1984**, *25*, 5715. Yoshida, K.; Grieco, P.A. *Chem. Lett.* **1985**, 155. Larsen, S.D.; Grieco, P.A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. Drewes, S.E.; Grieco, P.A.; Huffman, J.C. *J. Org. Chem.* **1985**, *50*, 1309.
6) Grieco, P.A.; Garner, P.; Yoshida, K.; Huffman, J.C. *Tetrahedron Lett.* **1983**, *24*, 3807.
7) Yoshida, K.; Grieco, P.A. *J. Org. Chem.* **1984**, *49*, 5257.
8) Grieco, P.A.; Brandes, E.B.; Garner, P. *J. Chem. Soc., Chem. Commun.* **1988**, 500.
9) He, Z.; Lentz, N.L. Indiana University, unpublished results.
10) Grieco, P.A.; Galatsis, P.; Spohn, R.F. *Tetrahedron Symposia in Print* **1986**, *42*, 2847.
11) Gajewski, J.J.; Jurayj, J.; Kimbrough, D.R.; Gande, M.E.; Ganem, B.; Carpenter, B.K. *J. Am. Chem. Soc.* **1987**, *109*, 1170. Copley, S.D.; Knowles, J.R. *ibid.* **1987**, *109*, 5008. Coates, R.M.; Rogers, B.D.; Hobbs, S.J.; Peck, D.R.; Curran, D.P. *ibid.* **1987**, *109*, 1160. Ponaras, A.A. *J. Org. Chem.* **1983**, *48*, 3866.
12) Brandes, E.B.; Grieco, P.A.; Gajewski, J.J. *ibid.* **1989**, *54*, 515.
13) Grieco, P.A.; Brandes, E.B.; McCann, S.; Clark, J.D. *ibid.* **1989**, *54*, 5849.
14) McMurry, J.E.; Andrus, A.; Ksander, G.M.; Musser, J.H.; Johnson, M.A. *Tetrahedron* **1981**, *37* (Supplement No. 1), 319.
15) Winstein, S.; Smith, S.; Darwish, D. *J. Am. Chem. Soc.* **1959**, *81*, 5511.
16) Pocker, Y.; Buchholz, R.F. *ibid.* **1970**, *92*, 2075.
17) Grieco, P.A.; Clark, J.D.; Jagoe, C.T. *ibid.* **1991**, *113*, 5488.
18) Grieco, P.A.; Nunes, J.J.; Gaul, M.D. *ibid.* **1990**, *112*, 4595.
19) After the completion of our study, we became aware of a report in the literature [Braun, R.; Sauer, J. *Chem. Ber.* **1986**, *119*, 1269] that described the enhanced endo selectivity for the Diels-Alder reaction between cyclopentadiene and methyl acrylate in concentrated lithium perchlorate-diethyl ether solutions; however, no mention was made of increased reaction rates.
20) Rivera, M.; Lamy-Schalkens, H.; Sainte, F.; Mbiya, K.; Ghosez. L. *Tetrahedron Lett.* **1988**, *29*, 4573.
21) Dauben, W.G.; Kessal, C.R.; Takemura, K.H. *J. Am. Chem. Soc.* **1980**, *102*, 6893.
22) Forman, M.A.; Dailey, W.P. *J. Am. Chem. Soc.* **1991**, *113*, 2761.
23) Grieco, P.A.; Cooke, R.J.; Henry, K.J.; Vander Roest, J.M. *Tetrahedron Lett.* **1991**, *32*, 4665.
24) Bunce, R.A.; Schlecht, M.F.; Dauben, W.G.; Heathcock, C.H. *ibid.* **1983**, *24*, 4943.
25) Henry, K.J. Indiana University, unpublished results.

About the Author

Paul A. Grieco was born in Framingham, Massachusetts, in 1944. He received his undergraduate education at Boston University and his graduate education at Columbia University where he obtained the Ph.D. degree under Professor Gilbert Stork. He was an NSF Postdoctoral Fellow with Professor E. J. Corey at Harvard University. In 1971 he joined the faculty at the University of Pittsburgh, rising to the rank of Full Professor in 1977. He moved to Indiana University in 1980 as Professor, and was named the Earl Blough Professor of Chemistry in 1985. He has served as Chairman of the Department of Chemistry at Indiana since July 1988.

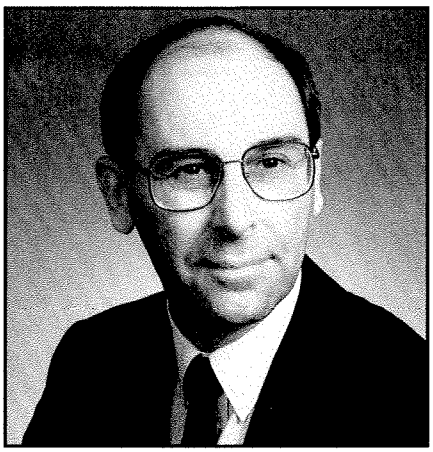
The synthesis of terpenoids by Grieco in the 1970s led to the successful syntheses of a range of sesquiterpene lactones—syntheses that are pivotal to current developments in natural product synthesis. Key to many of these syntheses is the use of a bicyclo[2.2.1]heptane nucleus as a stereochemical control vehicle. In recognition of this work, he received, in 1981, the ACS Ernest Guenther Award in the Chemistry of Essential Oils & Related Products.

This strategic approach of using a bicycloheptane nucleus as a stereochemical control template was extended during the 1980s in Grieco's classic synthesis of compactin and also in the preparation of several members of the macrolide/polyether antibiotic group (methynolide, calcimycin, and tylonide, among others) where stereochemical data built into the bicycloheptane nucleus were transformed into the stereochemistry of acyclic molecules. More recently, he has led the way in the synthesis of complex quassinoids, accomplishing syntheses of quassin, chaparrinone, and klaineanone.

Professor Grieco has also been engaged in studying the behavior of organic reactions (e.g., Diels-Alder, Claisen) in aqueous media as well as in ambient temperature molten salts (5.0 *M* lithium perchlorate in diethyl ether). Professor Grieco has been the recipient of numerous honors. In addition to the ACS Ernest Guenther Award, he received the ACS Akron Section Award in 1982, a National Cancer Institute NIH Merit Award in 1988, an Arthur C. Cope Scholar Award in 1990, and the ACS Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich, in 1991.

The Molecular Basis of Biological Order

Dudley H. Williams
University Chemical Laboratory
University of Cambridge
Lensfield Road
Cambridge CB2 1EW, U.K.



An essential feature of many biological interactions is reversibility. For example, the DNA double helix must form when a second complementary strand is built from a template strand, but sections of a double helix must come apart in order to expose a template strand during transcription. Additionally, small globular proteins unfold readily and reversibly, and their net stability (typically 20 to 80 kJ mol^{-1}) is shown, in this article, to correspond to about 1 to 5 amide-amide hydrogen bonds. When these polymeric molecules involve enormous numbers of hydrogen bonds, shown in this article to be much stronger than hitherto thought, how is such low net stability achieved? This article argues that a key element in determining this low net stability is the number of rotors that must be restricted in passing from a random coil to a highly ordered structure. Thus, reversibility in biology will frequently be associated with organized structures formed from flexible molecules. It is shown that the formation of the most common neutral-neutral hydrogen bonds in biologically important molecules [other than ROH...O(H)R] is favored entropically, due to the release of water molecules from the polar functionalities that form the hydrogen bonds. Natural selection has utilized functionalities that release an amount of water (favorable entropically) sufficient to restrict a few rotations (unfavorable entropically) as part of a strategy to yield functional molecules and complexes of small net stability.

Specifically, we have recently measured the intrinsic binding energy of the amide-amide hydrogen bond in aqueous solution as -20 ±7 kJ mol^{-1}. We conclude that this free energy of binding is largely entropy driven, and find its origin in the disordering of water molecules released from the amide CO and NH groups involved in hydrogen bond formation. The free energy of binding corresponds to a factor of at least 1000 in selectivity. A factor greater than the specificity of 2 to 20 hitherto accepted for individual uncharged hydrogen bonds. The free energy of binding of the amide-amide hydrogen bond, the most prevalent hydrogen bond in a folded protein, has repercussions for views of the free energy changes involved in protein folding. We show that the favorable entropy change associated with amide-amide hydrogen bond formation closely balances the unfavorable entropy change associated with the ordering of the peptide backbone. Thus, there is a relatively small overall entropy change upon protein folding. It is shown that similar factors are involved in RNA duplex formation, where the hydrogen bonds between base pairs are again concluded to be stronger than previously thought.

An equation for the estimation of association constants (either intramolecular or intermolecular) in aqueous or nonpolar media is presented. This equation may prove useful, in some cases, for estimating rough optimal binding constants for drugs to receptors, and possibly for substrates to enzymes.

Introduction

If the question, "What is the most important hydrogen bond in biology?" is posed, there might be some consensus for the answer, "the amide-amide bond" (Figure 1). For after all, it occurs on the order of 100 times even in the smallest of proteins. Surprisingly, there is still uncertainty with regard to the strength of this bond when formed in aqueous solution. And yet it is clear that the subject of molecular recognition might develop into a mature scientific discipline (i.e., one capable of making predictions) when this, and related interactions, have been at least approximately quantified.

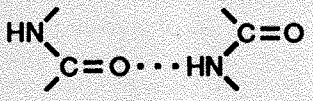


Figure 1. The amide-amide bond.

To make the necessary semi-quantitative determinations, either theory or experiment, or a combination of both, could be used. Computational approaches are having some success, but, in my own group, we have used an approach that uses some theory, but relies heavily on experiment. The theory used to analyze the experimental data is simple and approximate, and was established by others many years ago. It is outlined first, with the principles being illustrated by the binding of the antibiotic ristocetin A to the cell wall peptide analogue N-Ac-D-Ala-D-Ala to give the complex in Figure 2.

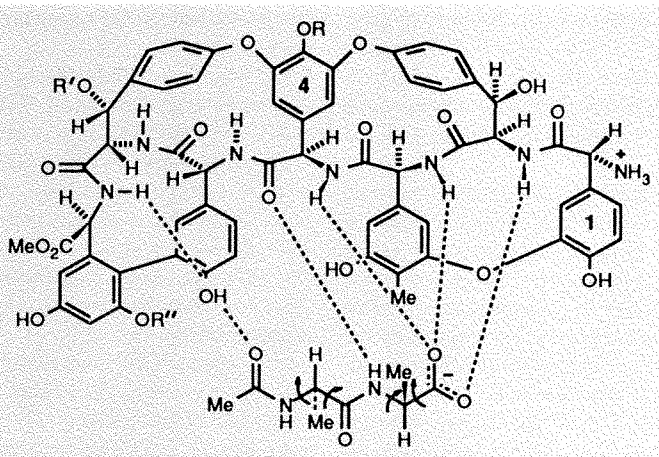


Figure 2. The complex resulting from the binding of the antibiotic ristocetin A to the cell wall peptide analogue N-Ac-D-Ala-D-Ala.

An Approximate Partition of the Free Energy of Binding: Equations for the Estimation of Binding Constants

We use four factors for the free energy of binding. The consideration of only four factors is justified only if the ligand and receptor show good van der Waals complementarity, and if the conformations of the bound components correspond closely to conformational energy minima in the separated states.[1,2] The first factor is the low probability of "catching" the ligand on the receptor in the absence of intermolecular forces. The second is the adverse free energy change (largely entropic) associated with the restriction of any internal rotations of either component upon complex formation. The third is the promotion of binding if hydrocarbon fragments can be removed from exposure to water upon complex formation, and the the fourth factor is the promotion of binding due to favorable interactions of polar functional groups in the complex. These four factors are now enumerated and elaborated.

(1) Any bimolecular binding process is entropically unfavorable due to the formation of a single molecule of complex, which occurs with loss of translational and rotational entropy. When allowance is also made for the small intrinsic exothermicity of such a process (due to the release of the kinetic energy associated with the loss of three degrees of rotational freedom and three degrees of translational freedom), the unfavorable free energy of association (ΔG_{t+r}, kJ mol^{-1}) as a function of the molecular weight of a ligand binding to a larger receptor is given in Figure 3.[1] As with all other free energy changes given in this account, it can be converted to an effect on $\log_{10}K$ by dividing by 5.7 (for room temperature binding). This scale is given on the right hand side of Figure 3. We find that within 4 kJ mol^{-1}, the same values apply for any molecular shape (rod, disc, or sphere) of a given molecular weight binding to any receptor of molecular mass 1,200 or greater.[1] Thus, for example, ΔG_{t+r} is adverse to binding by a factor of 10^{10} for a ligand of molecular weight 150, where the molecular weight includes bound solvent molecules, which can be regarded as translating and rotating with the ligand.

(2) Following Page and Jencks,[3] we note that binding is adversely affected by approximately 5 to 6 kJ mol^{-1} (ΔG_r) for each rotation restricted upon association. In the case of the complex in Figure 2, we approximate that no rotations of the antibiotic are stopped by the binding process (its peptide backbone is already relatively rigid due to the cross-linking of all the amino acid sidechains), whereas four rotations of N-Ac-D-Ala-D-Ala (see arrows in Figure 2) are restricted upon association. Thus, these rotational restrictions are adverse to binding by ca. 10^4. We note later that, for long chains with correspondingly larger moments of inertia of groups attached to the bond where rotation is to be restricted, the free energy cost of restricting a rotor may rise to 8 or 9 kJ mol^{-1}. Taking generalized values for the free energy cost of restricting rotations is, of course, an oversimplified approach, but is justified on the grounds that in many cases it works well. A more sophisticated approach would involve a knowledge of the free energy of rotation over 360° in the free state, and of the residual torsion in the bound state.

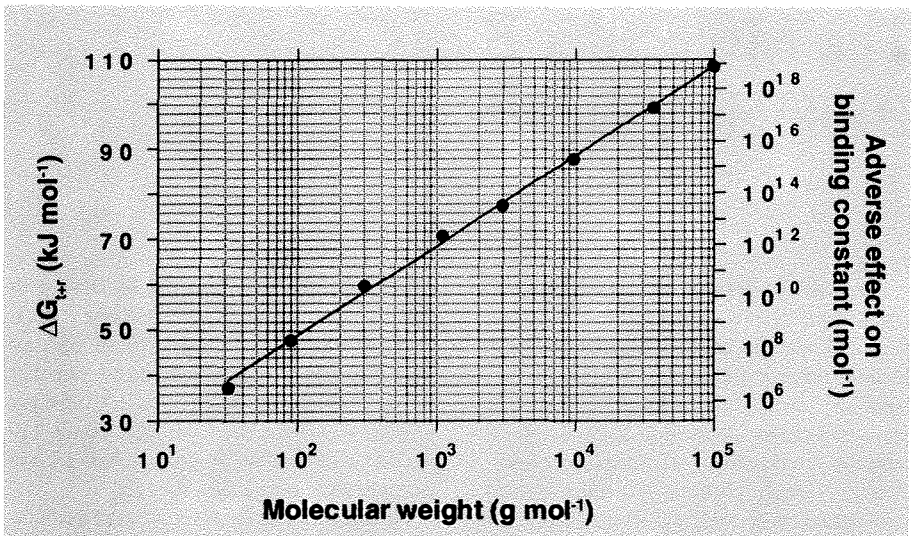


Figure 3. An estimate of the intrinsic adverse effect on binding constant due to a bimolecular association in aqueous solution when a molecule of given molecular weight binds to a receptor. For association in a nonpolar medium, add one power of 10 to the aqueous value, e.g., for a molecular weight of 1000, the adverse effect on bimolecular association from the graph is 10^{12} mol^{-1} (aqueous solution), and 10^{13} mol^{-1} (nonpolar medium).[1]

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

$$\Delta G = \Delta G_{t+r} + \Delta G_r + \Delta G_h + \Sigma \Delta G_p + \Delta G_{conf} + \Delta G_{vdW} \quad \text{(eq 2)}$$

$$-\Delta G = 10.5 + 11 + 3 \text{ kJ mol}^{-1} \quad \text{(eq 3)}$$

(3) For every square angstrom (Å^2) of hydrocarbon fragments removed from exposure to water by the binding process, we assume the binding energy to be increased by 0.19 kJ mol^{-1}.[4,5] This value is based on thermodynamic measurements of the solubility of simple hydrocarbons in water, which indicate that this hydrophobic effect is essentially entropy driven at room temperature. Thus, if the area of hydrocarbon buried is xÅ^2, then the free energy change (ΔG_h) due to the hydrophobic effect is taken as 0.19x kJ mol^{-1}.

(4) The bringing together of the two binding entities is accounted for in factors 1 and 2. Thus, the free energy of binding that results from the interaction of any pair of functional groups (ΔG_p) is the same if the process occurs either intramolecularly or bimolecularly. Although such values, "intrinsic binding energies" when they occur with optimum geometry for binding,[6] have the potential to be fundamental and usefully constant numbers, it will remain for future experiment to establish or refute this potential. We will show that the binding energy of the amide-amide hydrogen bond is similar at two sites within an antibiotic complex, and assume that other values, which have been determined for the interactions of specified functional groups, will behave similarly.

In summary, the free energy (ΔG, kJ mol^{-1}) of a bimolecular association, following the above specifications, is approximated by equation 1, where $\Sigma \Delta G_p$ represents the free energies of binding for each set of interacting functional groups summed over all such sets of interactions.

For the more general case where ΔG_{conf} represents the total conformational strain energy produced upon binding, and ΔG_{vdW} represents the change in van der Waals energy between free and bound states (due, for example, to the existence of van der Waals repulsions or cavities in the complex), then equation 2 results.[1]

The Application of Equation 1: The Intrinsic Binding Energy of the Amide-Amide Bond

The thermodynamic parameters for the binding of the ligand N-Ac-Gly-D-Ala to ristocetin A and to the related antibiotic vancomycin, are available, as are those for the binding of N-Ac-D-Ala to the same antibiotics.[7] In passing from the former to the latter ligand, the leftmost amide-amide hydrogen bond in Figure 2 is deleted. The resultant reduction in the binding energy is 10.5 kJ mol^{-1} (mean value for the two antibiotics). But, as shown in equation 3, we must correct for the fact that the larger ligand is more difficult to catch (by 3 kJ mol^{-1},[1] factor 1), and for the fact that two more rotors are restricted in the binding of the larger ligand (10 to 12 kJ mol^{-1}, mean value of 11 kJ mol^{-1}, factor 2).

We conclude[1] that the intrinsic binding energy of this particular hydrogen bond is -24 ±7 kJ mol^{-1} (eq 3). An analysis[1] of the thermodynamics of formation of a second amide-amide hydrogen bond in Figure 2 to the carbonyl group of the amino acid associated with ring 4 gives ΔG_p = -18 ±7 kJ mol^{-1}. Taking the mean value of all the antibiotic data for this biologically crucial hydrogen bond gives ΔG_p = -20 ±7 kJ mol^{-1}, a selectivity in binding of ca. 10^2 to 10^4—much greater than has previously been appreciated, as will be discussed later. Moreover, the thermodynamic data[7] show that the difference in the binding energy of the two ligands is essentially completely entropy driven. The favorable free energy of binding of amide-amide hydrogen bond formation in water is almost all entropic in origin. What is the physical explanation for the experimental result?

The overall change occurring upon formation of the amide-amide hydrogen bond in aqueous solution is given in Scheme 1. Consider first the enthalpy change on passing from left to right in Scheme 1. The change involves making two hydrogen bonds and breaking two hydrogen bonds.[8] In terms of electrostatic binding energy (enthalpy), all of these hydrogen bonds may be of different or similar strengths. For example, it could plausibly be proposed that the order of exothermicities would be **C > A ≃ B > D**. But, even if this were so, it seems likely that the mean strength of **A + B** would be similar to the mean strength of **C + D**. Thus, the overall enthalpy change (ΔH) would be near zero, as found experimentally.

What is the physical origin of the large favorable entropy of binding? In the equations for binding (equations 1 and 2), the losses, in rotational and translational entropy and in entropy due to the restriction of internal rotations, in making bond C have been factored out. Thus, a favorable entropy change on passing from left to right in Scheme 1 arises because water is much more ordered by the NH and CO groups of the two amide groups participating in hydrogen bond formation than is water by bulk water. It is the release of water from the participating amide functionalities that provides much of the favorable free energy change. This last conclusion provides support for the postulate that the exothermicities for the formation of the hydrogen bonds is **C > A ≃ B > D**. It is probably because the electrostatic interactions of the amide groups with water molecules are stronger than those of water with water that the amide groups order water more effectively than bulk solvent.

Is the Approach a Useful Approximation and of General Applicability?

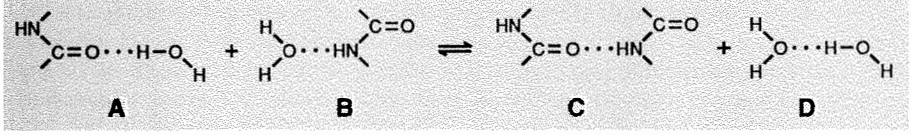
It should be noted that, in the above determination of the amide-amide hydrogen bond strength, the binding of one slightly truncated ligand (N-Ac-D-Ala) was compared with another (N-Ac-D-Gly-D-Ala). The term ΔG_{t+r} is very similar for these two ligands, and roughly independent of the broad assumptions made in determining this parameter (Figure 3). A test of the reliability of the ΔG_{t+r} parameter would, therefore, be to determine the same thermodynamic amide-amide hydrogen bond parameters by a method that uses the estimated absolute value of ΔG_{t+r}. This has been done[9] by considering the data of others for the dimerization of urea,[10] and of the cyclic lactams δ-valerolactam[11] and diketopiperazine[12] in aqueous solution. The values we obtain[9] per amide-amide hydrogen bond are ΔG_p = -27 kJ mol^{-1} for urea, ΔG_p = -27 kJ mol^{-1} for δ-valerolactam, and ΔG_p = -25 kJ mol^{-1} for diketopiperazine. If these values are broken down into ΔH and TΔS terms (at room temperature), then from the urea data ΔH = 0kJ mol^{-1} and TΔS = 27 kJ mol^{-1}, from the δ-valerolactam data ΔH = -8 kJ mol^{-1} and TΔS = 19 kJ mol^{-1}, and from the diketopiperazine data ΔH = -5 kJ mol^{-1} and TΔS = 20 kJ mol^{-1}. These values merit comment.

First, the ΔG_p values for the amide-amide hydrogen bonds formed to the antibiotics and in the dimers are in gross terms similar, and both are much larger than previously believed for these bonds in water. However, the values obtained for the dimers are, on average, about 6 kJ mol^{-1} more negative than for the antibiotics. This might partly reflect greater vibrational motion per hydrogen bond associated with the two hydrogen bonds of the dimers relative to the vibrational motion in the more extensive set of hydrogen bonds in the antibiotic complexes. The difference may also reflect inadequacies in the estimation of ΔG_{t+r},[9] or variations in CO to NH bond angle between the two cases. The finding of ΔG_p values for amide-amide hydrogen bond formation much larger than hitherto believed and self-consistent within one to two orders in magnitude in binding constant, by two different methods, argues well for their utility. But will ΔG_p values be usefully constant in the general case?

Intuitively, it might be anticipated that ΔG_p values for an interaction X...Y would change as Y makes progressively more interactions with X. For example, if X is the electron acceptor, then its affinity for electrons should be less after binding the electron donor Y than before, assuming Y to be a better electron donor than the displaced solvent molecule. Therefore, when the second Y binds to X, to give Y...X...Y, the ΔG_p value for the second interaction is anticipated to be less than for the first. There is experimental evidence that this is indeed the case, but the effects are not necessarily large, and can, in any case, be allowed for if the appropriate experimental data are available. Thus, when successive ammonia molecules (1 to 6 molecules) associate with Ni^{2+} in aqueous solution, the association constants are 468, 132, 41, 12, 4, and 0.8 M^{-1},[13,14] That is, the mean decrease in the intrinsic binding constant of the $(n+1)^{th}$ ammonia over the n^{th} ammonia is a factor of 3.6 M^{-1}, and the mean decrease of the intrinsic binding energy is only 3 kJ mol^{-1}. Specifically, we estimate that the first ammonia molecule binds with an intrinsic binding free energy of about -55 kJ mol^{-1}, the second one with an intrinsic binding energy of about -52 kJ mol^{-1}, the third with an intrinsic binding energy of -49 kJ mol^{-1}, and so on. In summary, ΔG_p values may decrease somewhat if one of the functionalities involved is already participating in other favorable interactions, but the effect may not be large.

Second, as for amide-amide hydrogen bond formation to the antibiotics (Figure 2, reminiscent of the formation of a ß-sheet), amide-amide hydrogen bond formation in the dimers described above is largely entropy driven. Once more, it is the release of water from the amide functionalities that largely provides the favorable free energy change (with an additional contribution due to residual mo-

Scheme 1



tions associated with the amide-amide hydrogen bonds).

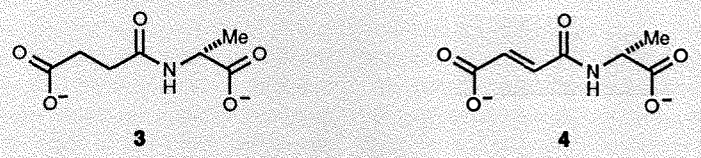
Having made a case that ΔG_{t+r} may be reasonably well estimated, and that ΔG_p values may not show large variations for specified functional group interactions, how useful is the generalization that ΔG_r=5 to 6 kJ mol^{-1}? Certainly, this value may tend to increase with an increase in the moments of inertia of the end groups whose rotational motion is restricted by the "freezing out" of the rotation. (It is later concluded that ΔG_r may be, on average, near 8 to 9 kJ mol^{-1} for freezing out N-C_α and C_α-CO rotors of a long peptide backbone, such as those found in a protein.) Additionally, it will tend to be decreased by an increased rotational barrier for this same rotation. If necessary, these variables can be accommodated in a subsequent, more sophisticated approach. But, in the meantime, we have tested the usefulness of the simple approximation, in one case, by comparing the binding constants of **3** and **4** to the antibiotic ristocetin A (Figure 4).[15]

The former binds with a binding constant of 12,000 M^{-1} (ΔG = -23 kJ mol^{-1}), and the latter with a binding constant of 120,000 M^{-1} (ΔG = -29 kJ mol^{-1}). The presence of the double bond in the latter freezes out a rotation present in the former, leading, on the basis of the simple approach, to a predicted increase in the binding energy of 5 to 6 kJ mol^{-1}, in excellent agreement with the experimental value of 6 kJ mol^{-1}. A more sophisticated approach, allowing for a small difference in hydrophobic effect between the two ligands and also for the increased barriers to rotation about the bonds between the C=C double bond of **4** and its carbonyl groups (due to conjugation), predicted an increase in binding energy of 8 kJ mol^{-1}, still in good agreement with experiment.

The above considerations, with the justifications of the values of the parameters used, take care of all the principles involved in the approach. It appears that the approach may be of general utility, and some consequences for systems of wide interest are now presented.

Consequences for Drug/Receptor and Enzyme/Substrate Interactions

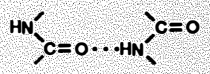
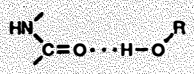
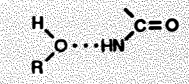
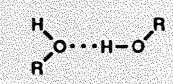
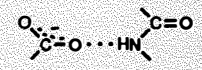
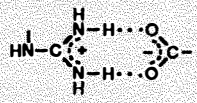
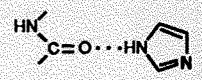
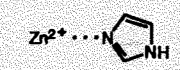
For the interaction of a drug at a complementary receptor, or for the interaction of a substrate with an enzyme, equation 1 can be used (given the appropriate values of ΔG_p) to estimate *roughly* the maximum possible binding constant.[16a] The utility of the equation depends upon the availability of ΔG_p values for a wide variety of functional group interactions that are commonly found in drug/receptor and enzyme/substrate interactions.[16b] Table 1 gives values that we have determined so far, although they may, of course, require adjustments as a consequence of subsequent experiments and numerical refinement of the approach. Clearly, an enormous number of important values remain to be determined, but some important principles can already be illustrated with this limited set of provisional values.



3 4

Figure 4. **3** binds with a binding constant of 12,000 M^{-1} (ΔG = -23 kJ mol^{-1}) and **4** binds with a binding constant of 120,000 M^{-1} (ΔG = -29kJ mol^{-1}).

Table 1
ΔG_p Values (kJ mol^{-1}, in aqueous solution) for Some Common Functional Group Interactions of Biological Importance[a]

Interaction	ΔG_p	Interaction	ΔG_p
	-20		-12
	-12[b]		~0[b]
	-28		-51
	-24		-65

[a]Estimated errors in these values are ±30%.
[b]Inferred on the basis of theoretical arguments.[17]

First, it is clear from a consideration of equation 1 (in conjunction with Figure 3, the cost of restricting rotors, the limited benefits of hydrophobic effects for association, and Table 1), that a small linear peptide can never bind strongly to another small linear peptide in aqueous solution through formation of an isolated element of ß-sheet (Figure 5). The formation of one amide-amide bond (-20 ±7 kJ mol^{-1}, taking the mean of the antibiotic-derived values as being more reliable than those for dimerization) per two residues (repeat unit of Figure 5) can, at best, counter the unfavorable free energy change of restricting four backbone rotations (probably 20 to 24 kJ mol^{-1}), but is not sufficient to also overcome the unfavorable loss of rotational and translational free energy for a bimolecular association (Figure 3). It is for this reason that the antibiotics of the vancomycin group must have cross-linked sidechains in order to work. Through this crosslinking (Figure 2), the rotation of the antibiotic backbone is restricted, and physiologically useful binding of a small unconstrained peptide becomes possible. (The ordering of the peptide backbone of small globular proteins is covered subsequently.) Second, as would be expected, intrinsic bind-

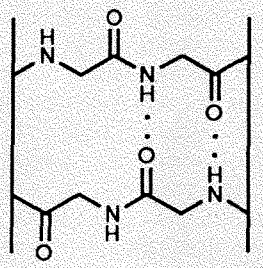


Figure 5. An isolated element of a β-sheet.

ing constants of polar groups to multiply-charged metal ions will be large (e.g., Table 1). Interactions to multiply-charged ions are important for productive binding of ligands otherwise capable of forming only weak or few hydrogen bonds (e.g., of ethanol to alcohol dehydrogenase, carbon dioxide to carbonic anhydrase, and oxygen to hemoglobin).

Why Do Different Types of Uncharged Hydrogen Bonds Vary Greatly in Free Energy of Formation?

It is evident from the data given in Table 1 that different types of uncharged hydrogen bonds vary greatly in their free energy of formation in aqueous solution—from the large value for the amide-amide hydrogen bond (ca. -20 kJ mol^{-1}),[1,9] to the very small value for the hydroxyl-hydroxyl hydrogen bond (-2 kJ mol^{-1}).[8] It is postulated that both ends of an amide dipole organize coordinated H_2O more than H_2O is organized in bulk water, and that release of H_2O from the amide functionalities, therefore, provides a major part of the favorable entropy change observed for amide-amide hydrogen bond formation. Let us now estimate the free energy of formation of the amide-hydroxyl bond (NHCO...HOR, Scheme 2) from a theoretical analysis.

If ROH...OH_2, where ROH is a phenol (as in tyrosine) or an alcohol (as in serine), and H_2O...H_2O hydrogen bonds are assumed to have similar electrostatic (ΔH) strengths, then the water molecules associated with ROH will be ordered to about the same extent as those in bulk water. There will be no significant net entropy change associated with the release of water from ROH. Thus, the intrinsic binding free energy of the NHCO...HOR interaction will be derived essentially from the entropically favorable release of the relatively highly ordered water molecules associated to the amide carbonyl group. If we make the reasonable postulate that each end of the amide dipole (NH or CO) organizes coordinated H_2O to about the same extent, then the favorable entropy of formation of NHCO...NHCO will be about twice that of NHCO...HOR, as is found experimentally (Table 1).[17]

These concepts are further strengthened by extending the arguments to the intrinsic binding free energy of the hydroxyl-hydroxyl interaction (Scheme 3). Since the hydroxyl group is assumed to organize coordinated water, through hydrogen bond formation, to about the same extent irrespective of whether the hydroxyl group is part of a phenol, alcohol, or water, the entropy change associated with this interaction is postulated to be near zero. The enthalpy change is also, of course, near zero (Scheme 3), and, hence, so is the intrinsic binding free energy (Table 1). Indeed, small values (e.g., -2 kJ mol^{-1}) for deletion of a hydroxyl-hydroxyl interaction are found experimentally.[8] Since these experimental values are based on protein engineering experiments, there are several possible reasons why they might be small and negative rather than zero from the analysis associated with Scheme 3. For example, in the mutation of L-tyrosine to phenylalanine, the analysis is more complicated than indicated in Scheme 3, for several possible reasons. Thus, the deletion of a hydroxyl group results in a cavity, a partially or totally collapsed cavity (with an associated cost in free energy of reorganization), or a cavity accommodated by a water molecule (but in a space that has evolved to be somewhat smaller than is required for a water molecule).[8]

Consequences for Protein Folding

Creighton has recently reviewed[18] our understanding of the physical basis of the stability of the folded conformations of proteins, and noted that, "currently there appears to be an unprecedented degree of confusion in the literature." He notes contradictory statements by different authors, such as "stability is maintained only by...van der Waals and hydrogen bonding" and "hydrogen bonding opposes folding". In this section, it is proposed that the concepts developed and the parameters presented in earlier sections may clarify the situation.

1. Organization of the Peptide Backbone

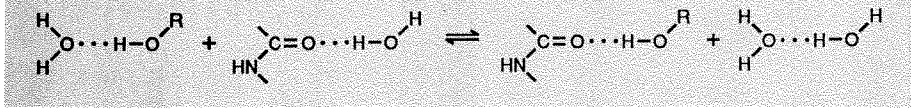
As noted in the introduction, by far the most common hydrogen bond in a protein is the amide-amide hydrogen bond—about 60 to 70 in a typical 100-residue protein.[19] It is clear that the physical basis of protein folding cannot be analyzed until an approximate free energy of this hydrogen bond is defined. We have now measured this value (-20 ±7 kJ mol^{-1}).[1] Physically, this value corresponds to the answer to the question, "What is the free energy change upon making the amide-amide hydrogen bond in aqueous solution, when the unfavorable free energy change associated with bringing the amide functionalities into the bonding geometry has been factored out?" Thus, it is a general parameter for this interaction, appropriate to both unimolecular (protein folding) and bimolecular (substrate/receptor) interactions.

There are two important points to note about this value. First, it is much larger than the values previously accepted for uncharged hydrogen bonds (in the range of 0 to -7.5 kJ mol^{-1}, giving a factor of 0 to 20 to selectivity),[8] and specifically much larger than the value accepted for the amide-amide hydrogen bond as involved in protein folding.[20-23] As we have already seen, the amide-amide hydrogen bond gives a factor of 10^2 to 10^4 to selectivity. Second, it is associated with a very small enthalpy change, being almost completely entropy driven. In summary, it is suggested that the amide-amide hydrogen bond is a major entropy driven, free energy change in promoting protein folding.

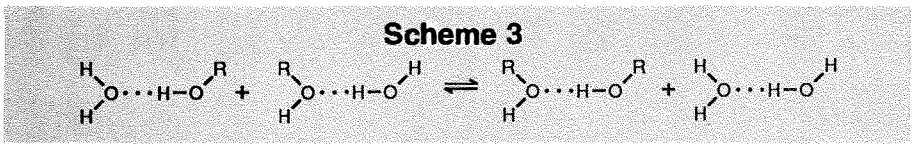
To illustrate the important consequences for the understanding of protein folding of the above conclusion, we apply the Gibbs equation, $\Delta G = \Delta H - T\Delta S$, where a negative ΔH indicates heat given out in a change, and a negative value of $T\Delta S$ indicates an overall increase in order in a change occurring at a temperature, T (degrees K). In the globular proteins that have been studied calorimetrically, it is clear that at room temperature both ΔH and $T\Delta S$ of folding are remarkably small (given the very large number of interactions involved).[24] A small $T\Delta S$ for folding immediately poses the question, "How can this be so, since a folded protein clearly has a much more ordered peptide backbone than does the unfolded state from which it is formed?"

It is evident from the study of model peptides that many α-helices of moderate length (i.e., 15 to 50 residues) are formed with ΔG not far from zero in aqueous solution at physiological temperatures.[25] Additionally, ΔH per residue for helix formation is relatively small (-3.8 to -5.5 kJ mol^{-1} per residue).[25] It follows that $T\Delta S$ for isolated helix formation (Figure 6) is similarly negative, but, most importantly, similarly small (compared to the favorable and large value of $T\Delta S$ for amide-amide hydrogen bond formation). Since there is good evidence that the small ΔH value for helix formation is not critically dependent on the nature of the amino acid sidechains,[25] the small value of $T\Delta S$ must be a property of the changes involving the peptide backbone. In making a long helix, these changes are: one amide-amide hydrogen bond is made per resi-

Scheme 2



Scheme 3



due, and two rotors (N to C_α and C_α to C=O) per residue are restricted. There may also be a small effect due to further restriction of an already limited amide bond rotation. We have already concluded that the cost of restricting a rotor in a long chain will be greater than the 5 to 6 kJ mol^{-1} taken for a terminal amino acid. Since a consensus set of thermodynamic parameters for the amide-amide bond from our work[1,9] (weighting more those derived using the more reliable ΔG_r parameter than those derived using absolute values of ΔG_{t+r}) is ΔG = -20 kJ mol^{-1}, ΔH = -2 kJ mol^{-1}, and $T\Delta S$ = 18 kJ mol^{-1}, then the value of ΔG to freeze out the backbone rotations of one amino acid residue must be ca. 20 kJ mol^{-1}. Since the experimental exothermicity of helix formation (-3.8 to -5.5 kJ mol^{-1} per residue) is close to the exothermicity of hydrogen bond formation and restriction of two rotations,[26] the ΔG value for stopping the rotations of one amino acid residue finds its origins essentially completely in $T\Delta S$ (ca. -22 kJ mol^{-1}, Table 2). That is, it is largely an adverse entropy change due to the organization of the peptide backbone, as demanded by any physically plausible interpretation.

The value of ΔG of about 20 kJ mol^{-1} to restrict the rotations of one amino acid residue at room temperature is an entirely reasonable value—8 to 9 kJ mol^{-1} per N-C_α and C-C(O) rotor in a long chain, with perhaps an additional marginally unfavorable increment due to very limited restriction of sidechain α-ß rotation (alanine excepted). Amino acid sidechains are, of course, important in the "fine-tuning" of helix stability, but it is argued that the large and opposing effects are mainly properties of amide-amide bond formation and of the restriction of peptide backbone rotations.

Similar conclusions apply to ß-sheet formation. In the formation of an extended ß-sheet, the central parts of the sheet form one amide-amide hydrogen bond per residue (Figure 7). As in the case of helix formation, the peptide backbone of one amino acid in the protein has to be restricted for every amide-amide hydrogen bond that is made. Assuming that ß-sheet formation involves an intramolecular strain and hydrophobic effect of the backbone that is not much different to that for α-helix formation, then again the entropic advantage of amide-amide hydrogen bond formation will be about equal and opposite to the entropic disadvantage of organizing the peptide backbone of one amino acid residue. As in the case of α-helix formation, formation of an infinitely extended ß-sheet will occur with ΔG near to zero per residue (excluding "fine-tuning").

Since ΔG is near zero for formation of extended sheets and helices, both can be populated reversibly at room temperature. The "permanent" population of such structures (i.e., in folded proteins) would then be dependent on additional favorable free energies of "fine tuning". These "fine tuning" factors would include the nature of the amino acids sidechains, and the ability of two transiently stable amphiphilic helical or sheet structures to stabilize each other via hydrophobic inter-

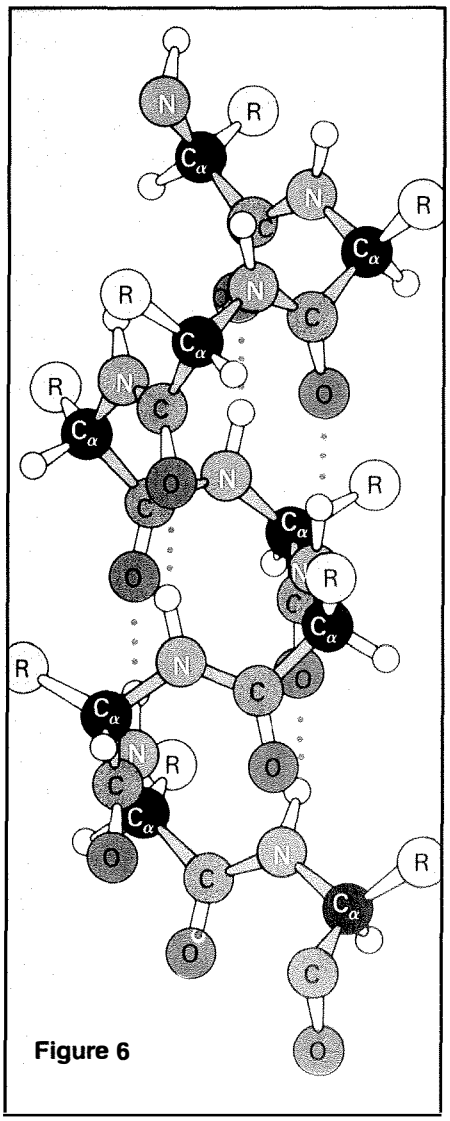


Figure 6

Table 2
Approximate Thermodynamic Parameters (kJ mol^{-1} per residue) for Peptide Backbone Organization in α-Helix Formation

	ΔG	ΔH	TΔS
Generalization from experiment	0	-4	-4
Amide-amide bond formation	-20	-2	18
Restriction of backbone rotors	20	-2	-22

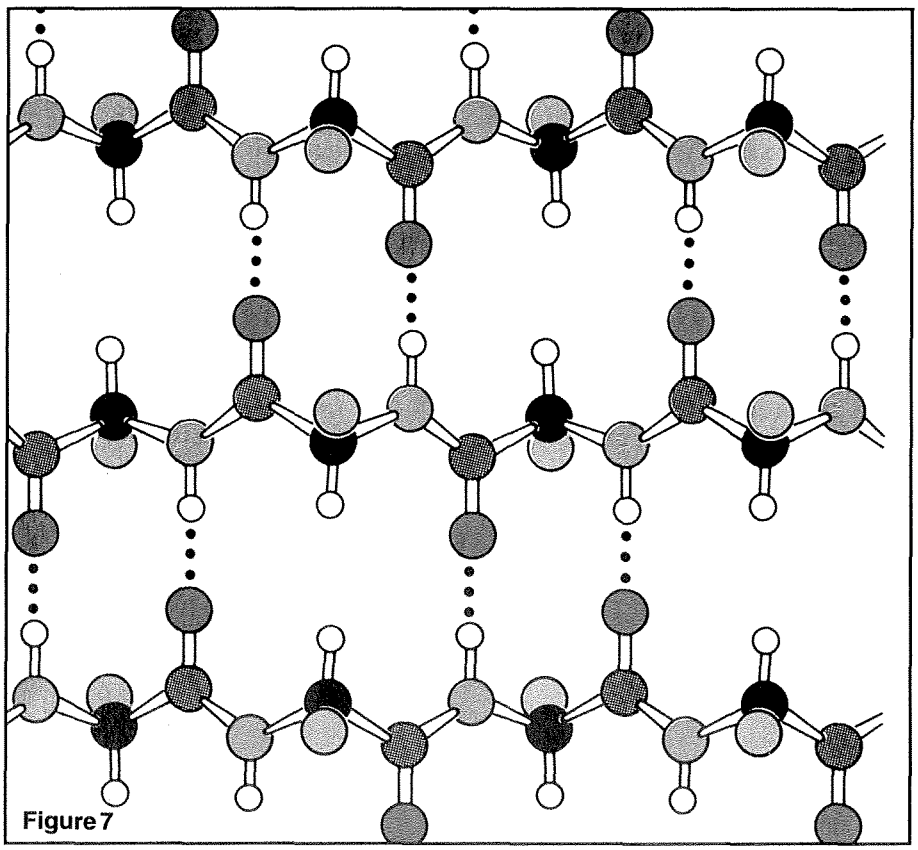


Figure 7

actions between the helices, sheets, or sheet and helix. The requirement of ΔG near zero for extended elements of sheet and helix, and evidenced by much prior experimental work, seems inescapable. If ΔG were large and negative for such structural elements, then almost any such element could be formed with a low probability of reversal, and hence mistakes would be common in folding pathways. If, on the other hand, ΔG were large and positive for such elements, then their populations would be insignificant, and protein folding would be too slow. The similar intrinsic stabilities of sheets and helices is evidenced not only by the fact that the difference in preferences of specific amino acids to occur in either unit is not large,[27] but also by the fact that pentapeptides of the same sequence can occur either in sheet or helix.[28] Additionally, O'Neil and DeGrado have shown[29] that the relative thermodynamic stabilities of each of the 20 commonly occurring amino acids in the α-helical versus random coil states varies by only 3.2 kJ mol^{-1} from the most favorable, alanine, to (excluding proline) the least favorable, glycine. Marginal helix and sheet stability in the absence of tertiary interactions is largely, but not exclusively, a property of the thermodynamic characteristics of the peptide backbone defined above.

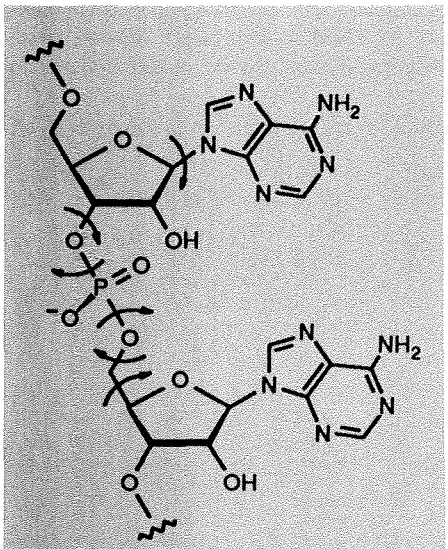


Figure 8. Illustration of the 6 rotors which must be restricted (arrows) for formation of an additional base stack.

2. A View of the Balance of Free Energies, Enthalpies, and Entropies Involved in Protein Folding

The large favorable free energy of amide-amide hydrogen bond formation means that the balance of free energy changes responsible for protein folding must be reconsidered. Since the hydrophobic core of a protein has packing close to that of a solid, and the unfolded state does not, there is net van der Waals stabilization of the folded state. From the structures of a number of relatively small, water soluble, globular proteins, the number of hydrogen bonds, magnitude of the hydrophobic effect, and van der Waals stabilization of an average protein of 100 residues (one lacking crosslinks and cofactors) can be estimated.[30] The data and associated conclusions are presented in Table 3.

By far the most reliable number in Table 3 is the total ΔG, but it is also reliably known that ΔH and TΔS of folding are both small.[24] Since amide-amide hydrogen bonds predominate over all others, hydrogen bond formation is enormously favorable entropically, and to an extent that the most probable value is about double that for the hydrophobic effect. Since the overall entropy of folding is small, it follows that the disordering associated with the release of water from polar and hydrocarbon groups closely balances the ordering of both the peptide backbone and the sidechains (restriction of internal rotations, Table 3).[30] Additionally, since ΔH of folding is also remarkably small (near -1 kJ mol^{-1} per residue), it follows that the significant release of heat due to efficient packing of the hydrocarbon core, small exothermicity of hydrogen bond formation, and restriction of internal rotations,[26] must be balanced by an opposing endothermic process. This presumably reflects strain in the folded structure, and indeed the crude strain value estimated in this way (Table 3) is consistent with the strain estimate cited by Creighton.[31]

In summary, the numbers given in Table 3 are crude, but what is important and new is the very large influence of water release from amides in aiding the restriction of bond rotations upon folding. The free energy change associated with the hydrophobic interaction is too small to organize the peptide backbone; amide-amide hydrogen bond formation is the major free energy change necessary to bring this about. Finally, it should be noted that the large binding energy (-51 kJ mol^{-1}) for the guanidinium-carboxylate interaction (Table 1) is not inconsistent with the weak binding energies (i.e., ΔG = 0 to -5 kJ mol^{-1}) found experimentally for salt bridges at the surface of proteins.[32,33] The cost of rotor restrictions in the sidechains of amino acids that can form such bridges (arginine or lysine with aspartic acid or glutamic acid) is comparable to, but opposite in sign to, the large intrinsic binding free energies associated with ion-pair interactions.[33,34] Additionally, the surface salt bridges found in proteins may not form the ideal geometry indicated in Table 1.

Table 3
Factorization of the Thermodynamics of Folding an "Average" Protein of 100 Residues (kJ mol^{-1}) at 298K

Factor	ΔG	ΔH	TΔS
Strain in folded state	750 ±500	750 ±500	
Hydrophobic effect	-900 ±300		-900 ±300
Van der Waals effects	-350 ±100	-350 ±100	
Hydrogen bond	-2000 ±700	-200 ±300	1800 ±700
Internal rotations	2500 ±800	-300 ±300	-2800 ±800
Total	**-50 ±30**	**-100 ±200**	**-100 ±200**

Consequences for the Formation of RNA and DNA Helices

The formation of RNA and DNA helical structures from random coil single strand structures can be analyzed at three levels:[35]

(1) in the increment of ΔG for extension of single strand helices by an additional base, which involves only the restriction of 6 rotors (Figure 8) to be balanced against the formation of an extra stack of one base or another (Figure 9A);

(2) in the increment of ΔG for each base pair added to a double helix; this involves the restriction of 12 rotors of the two sugar phosphate backbones (the restrictions shown in Figure 8 occuring twice), the formation of 2 base pair stacks, and the formation of 2 hydrogen bonds for A-T (or A-U) base pairs, or 3 hydrogen bonds for G-C base pairs (Figure 9B); and

(3) in the formation of double helical structures of short duplexes from random coil single strands. This process involves all the changes listed under (2), but also involves the loss of rotational and translational free energy when the bimolecular association of two strands to give a duplex occurs.

Thermodynamic parameters are available for all these changes.

1. Single and Double Helix Extension

The mean values of thermodynamic parameters for single strand helix formation (per added single stack, from 10 sets of published data, Figure 9A), and for double helix formation (per added double stack, from 6 sets of published data, Figure 9B) are summarized in Table 4.[36] A striking feature of the data presented in Table 4 is the close similarity of the parameters for formation of the two

structures. The exothermicities must be associated mainly with base stacking, and are almost the same, despite the fact that only one stack is formed in single strand formation, and two stacks are formed in double strand formation. It must be concluded that, per stack formed, stacking is enthalpically more favorable in single strand structures than in double strand structures. This is, of course, physically reasonable since, in single strand formation, stacking has to be compatible only with rotor restriction; whereas, in double strand formation, stacking has to be simultaneously compatible with both rotor restriction and hydrogen bond formation (i.e., the geometrical restraints are much more demanding in the latter situation). The key point is that, despite this much smaller favorable exothermicity per base stack in the double strand case, the extension of a double strand by one base pair has a favorable free energy of a magnitude comparable to that for extension of a single strand by one base (Table 4). This is despite the fact that the formation of the double strand structure involves the restriction of 12 rotations, whereas the formation of the single strand structure involves the restriction of only 6 rotations.[35]

In other words, the entropy changes involved in the two very different types of structural extensions are essentially the same (Table 4). Therefore, the entropic cost of restricting the extra 6 rotations necessary for extension of the double strand structure must be comparable to the entropic benefit of a structural feature unique to double strand formation (i.e., to the entropic benefit of forming two hydrogen bonds, since the data in Table 4 refers to the formation of A-U and A-T base pairs).

The hydrophobic effect per added base pair to a duplex is similar to the hydrophobic effect per added base pair to a single strand[35] (at least in part due to the poorer base/base overlaps on average in double-stranded compared to single-stranded structures, see above), and is ca. 12 kJ mol^{-1}. Thus, from the entropy data for single strand formation in Table 4, if y is the value of TΔS for restricting 6 rotations at 300K:

$$-116 \times 300 \times 10^{-3} = y + 12$$
$$\text{i.e., } y = -47 \text{ kJ mol}^{-1}.$$

In light of the physically similar rotor restrictions occurring twice over in duplex formation, and using the entropy data for duplex formation from Table 4, then if z is the value of TΔS for formation of the two hydrogen bonds of the duplex:

$$-110 \times 300 \times 10^{-3} = z + 12 + (-47 \times 2) + (-5)$$
$$\text{i.e., } z = 54 \text{ kJ mol}^{-1}$$

where the last term on the right hand side of the equation (-5 kJ mol^{-1}) is a small factor to allow for the adverse TΔS for restriction of rotation of the adenine amino group upon hydrogen bond formation (Figure 10). Thus, the favorable TΔS per hydrogen bond is ca. 27 kJ mol^{-1}. Strikingly, the entropy change is large and favorable, as is that derived earlier in this article for the chemically similar amide-amide bond (ca. 18 kJ mol^{-1}, Table 2). The large favorable entropy term is again assumed to find its origin to an important extent in the release of water from the polar functional groups involved in hydrogen bond formation (Figure 10). On the basis of a hydrogen bond inventory,[8] hydrogen bond formation in RNA and DNA duplexes should be approximately isoenthalpic, since there are the same number of hydrogen bonds on both sides of the equilibrium (Figure 10). Thus, it is concluded that in duplex formation, the free energy of formation of a hydrogen bond is in the vicinity of -27 kJ mol^{-1}. As for the amide-amide hydrogen bond formed in the folding of proteins, the conclusion is that the hydrogen bonds formed between bases in the generation of nucleic acid double helices are stronger than hitherto thought. Turner et al.,[37] derived a strength of -2 to -8 kJ mol^{-1} (specificity of 2 to 20), whereas the *lower* limit obtained here, assuming an error limit of ±25%, corresponds to a selectivity of about 3,500.

2. Double Helix Formation

Given the thermodynamic parameters for extension of a preformed double helix by one base pair (Table 4), then formation of a short $(A.U)_n$ double helix from single strands of A_n and U_n will, in addition, be determined by the change in translational plus rotational free energy (ΔG_{t+r}) for the bimolecular association of two strands to give one of duplex. Indeed, the melting temperatures reported[38] for a number of short A.U duplexes can be reproduced by using thermodynamic parameters derived from Table 4 in conjunction with ΔG_{t+r} taken as 70-85% of the value read off from Figure 3.[35b] These results indicate how experimental data for associations can be used to reduce uncertainties in the approach.

Uncertainties in the Approach

The experimental parameters used in this article fall into two classes. First, those that are directly determined on the system of interest, e.g., binding constants. Second, those that are determined on model systems to

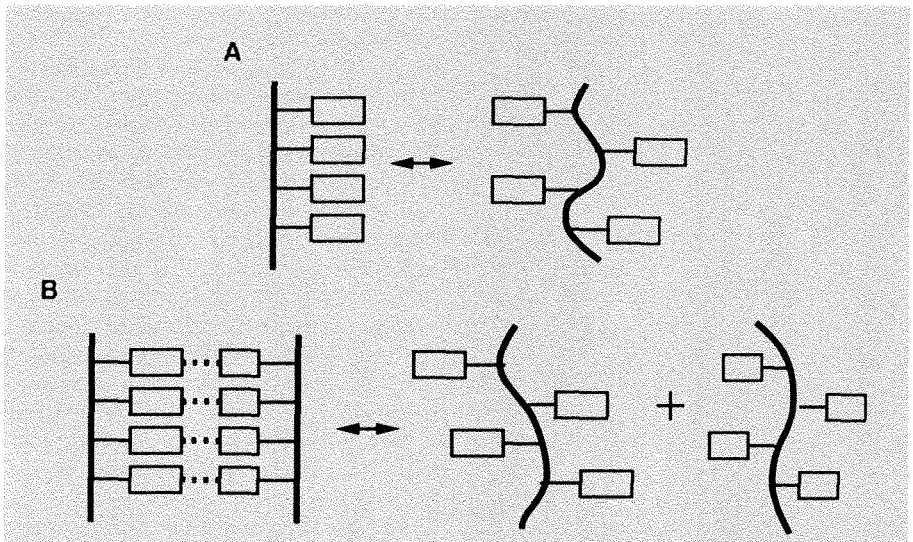


Figure 9. Schematic illustration of base stacking in the formation of a single strand helix (A) and a double strand helix (B).

Table 4
Thermodynamic Parameters for Single Strand and Double Strand Helix Formation[a]

Structure	ΔG (kJ mol^{-1})	ΔH (kJ mol^{-1})	ΔS (J mol^{-1} K^{-1})
Single	-2.2 ±2.7	-37 ±4	-116 ±17
Double	-5.3 ±3.9	-38 ±8	-110 ±16

[a]The data for double strand helix formation are all for the formation of A-U or A-T base pairs.

allow the separation of variables relevant to the system of interest, e.g., parameters for the hydrophobic effect (ΔG_h), for the change in rotational and translational free energy upon bimolecular association (ΔG_{t+r}) , and for the free energy change in restricting internal rotations (ΔG_r). It is in this second class of parameters that the main uncertainties lie. All that can be said about them is that values corresponding to the currently accepted numbers in the literature have been used. The values used for ΔG_{t+r} are consistent with the relative rates of many unimolecular versus, otherwise analogous, bimolecular reactions, and those used for ΔG_r are, for example, from experimental rotor restrictions occurring upon cyclization reactions (and, in one case, from a system of direct interest, see **3** versus **4**). Nevertheless, uncertainties in these parameters remain because the degree of residual motion in biologically important aggregates is, itself, uncertain. However, even though the approach will doubtless evolve and the parameters be refined, the fact remains that in evaluation of the strengths of some of the most important hydrogen bonds in biology, long established principles regarding entropy changes have been ignored, and the bonds appear to be stronger than conventional wisdom would have us believe.

Conclusion

Solution binding constants determine whether a particular ordered structure, perhaps important for biological function, will be highly populated. A difficult task in the crude estimation of solution binding constants is the estimation of strain and van der Waals repulsion energies. Although these can, in principle, be allowed for (equation 2), it seems simplest to first examine structures in which such strains and repulsions might be minimal. It is argued, in this article, that some of the interactions honed by natural selection may satisfy this criterion, and thereby allow, to a useful approximation, the application of equation 1. In these cases, rough optimal binding constants can potentially be estimated by reading off the low probability of "catching" one molecule upon another from Figure 3 (or a modified version of it, see, for example, the comment on nucleic acid double helix formation), allowing for the number of rotations restricted in the binding process, estimating the hydrophobic effect from the area of hydrocarbon buried (for associations occuring in aqueous solution), and allowing for the binding free energies associated with each interaction of polar functional groups (e.g., Table 1). If the approach proves to be of general utility, the measurement of a large number of intrinsic binding free energies[6,8] will be necessary in the future. The parameters suggested in this article may need subsequent refinement since they represent early work. However, the principles involved seem to be well based, and the initial conclusions physically plausible. In particular, hydrogen bonds formed in aqueous solution between uncharged groups are concluded to vary in strength. The hydrogen bonds in nucleic acid duplexes, and the main hydrogen bonds in proteins, amide-amide, are concluded to be stronger than hitherto believed.[39]

Rotor restrictions that occur upon association are seen as a powerful factor opposing binding. This point may bear on the frequent occurrence of polycyclic secondary metabolites, in which 5- and 6-membered rings are common. Polycyclization, to form small rings, generates a large amount of order in a small molecule. The common presence of this order supports the concept that secondary metabolites (defined as products without a role in the internal economy of the producer) have evolved under the pressures of natural selection to bind to selected targets in organisms that compete with, or have competed with, the producer.[40] It is a further consequence of this idea that control of the extent of ring formation will allow subtle control of binding, and, hence, of physiological function.

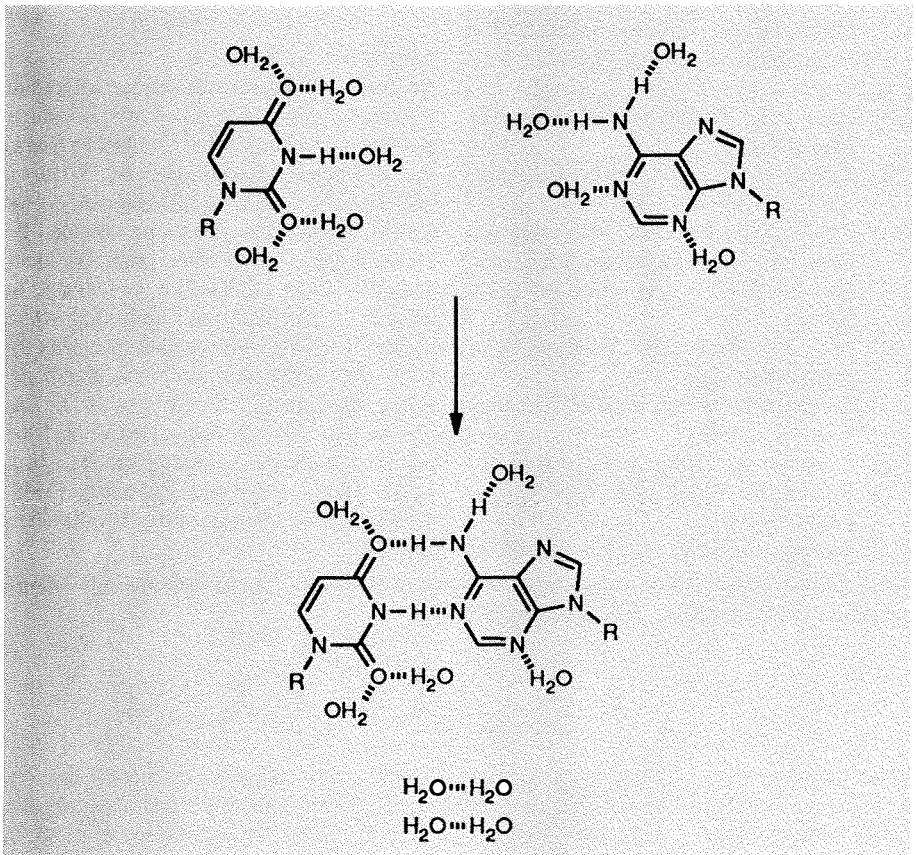


Figure 10. Illustration of the entropically favorable release of water associated with the formation of hydrogen bonds between base pairs.

Acknowledgements

I wish to thank all my colleagues named in references 1 and 35 for their efforts in making this work possible. In particular, special thanks are due to Andrew Doig for his insight in semi-quantitatively determining many aspects of the theoretical approach. SERC (UK), Smith Kline Beecham, and the Upjohn Company are thanked for financial support. Contributions from Eli Lilly, ICI, Roussel Uclaf, Pfizer, and Schering towards specific parts of the program are also gratefully acknowledged.

References

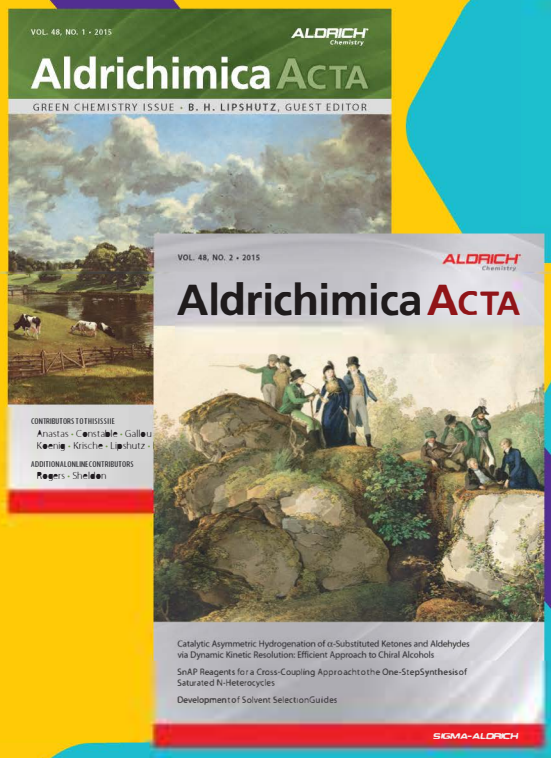
1) Williams, D.H.; Cox, J.P.L.; Doig, A.J.; Gardner, M.; Gerhard, U.; Kaye, P.T.; Lal, A.R.; Nicholls, I.A.; Salter, C.J.; Mitchell, R.C. *J. Am. Chem. Soc.* **1991**, *113*, 7020.
2) For prior and similar partitioning of the free energy of binding (but, necessarily, largely carried out without knowledge of the receptor sites involved), see Andrews, P.R.; Craik, D.J.; Martin, J.L. *J. Med. Chem.* **1984**, *27*, 1648.
3) Page, M.I.; Jencks, W.P. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1678.
4) Kauzmann, W. *Adv. Protein Chem.* **1959**, *14*, 1. Chothia, C.; Janin, J. *Nature* **1975**, *256*, 705.

5) This value is ca. 50% larger than that used in our previous work (ref 1). The value used previously is based directly on the experimentally determined solubilities of selected hydrocarbons in water. In such experiments, one side of the equilibrium involves separate hydrocarbon and water phases, each restricted to a specified volume of the container. In contrast, in the molecular recognition processes under study, all species have access to the total volume of the solution. Thus, the values obtained from the water solubility of hydrocarbons include a favorable entropy of mixing (Sharp, K.A.; Nicholls, I.A.; Fine, R.F.; Honig, B. *Science* **1991**, *252*, 106). When a correction has been made for this factor, the value of 0.19 kJ $mol^{-1}/Å^2$ is obtained.
6) Jencks, W.P. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4046.
7) Rodriguez-Tebar, A.; Vasquez, D.; Perez-Valazquez, J.L.; Laynez, J.; Wadso, I.J. *J. Antibiotics* **1986**, *39*, 1587.
8) Fersht, A.R.; Shi, J.-P.; Knill-Jones, J.; Lowe, D.M.; Wilkinson, A.J.; Blow, D.M.; Brick, P.; Carter, P.; Waye, M.M.Y.; Winter, G. *Nature* **1985**, *314*, 235. Fersht, A.R. *Trends in Biochem. Sci.* **1987**, *12*, 301.
9) Doig, A.J.; Williams, D.H. *J. Am. Chem. Soc.* , in press.
10) Schellman, J.A. *C.R. Trav. Lab. Carlsberg. Ser. Chim.* **1955**, *29*, 230.
11) Susi, S.; Timasheff, S.M.; Ard, J.S. *J. Biol. Chem.* **1964**, *239*, 3051.
12) Gill, S.J.; Noll, L.J. *J. Phys. Chem.* **1972**, *76*, 3065.
13) The Chemical Society (London), Special Publication 17, 1964.
14) The Chemical Society (London), Special Publication 25, 1971.
15) Gerhard, U.; Willliams, D.H., University of Cambridge, unpublished work.
16) (a) This follows since ΔG_{conf} (equation 2) will, in general, be positive. (b) Where an enzyme/substrate interaction involves strain, so that the transition state for reaction can be bound more strongly than the substrate (thus aiding catalysis), the binding energy will tend to be less than that estimated by equation 1.
17) Cox, J.P.L.; Nicholls, I.A.; Williams, D.H. *J. Chem. Soc., Chem. Commun.* **1991**, 1295.
18) Creighton, T.E. *Current Opinion in Structural Biology* **1991**, *1*, 5.
19) Baker, E.N.; Hubbard, R.E. *Prog. Biophys. Mol. Biol.* **1984**, *44*, *97*.
20) Baldwin, R.L. *Trends in Biochem. Sci.* **1989**, *14*, 291.
21) Dill, K.A. *Biochemistry* **1990**, *29*, 7133.
22) Pace, C.N.; Heinemann, U.; Hahn, U.; Saenger, W. *Angew. Chem.* **1991**, *30*, 343.
23) Murphy, K.P.; Gill, S.J. *Thermochim. Acta* **1990**, *172*, 11.
24) Privalov, P.L.; Gill, S.J. *Adv. Protein Chem.* **1988**, *39*, 191.
25) Scholtz, J.M.; Marqusee, S.; Baldwin R.L.; York, E.J.; Stewart, J.M.; Santoro, M.; Bolen D.W. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 2854.
26) Guided by the work of Pitzer (Pitzer, K.S. *Quantum Chemistry* Constable: London, 1953), we estimate an exothermicity of 2.5 kJ mol^{-1} for the restriction of each rotation. When allowance is made for retention of approximately half this quantity as kinetic energy of the torsion remaining after rotor restriction, then the net exothermicity for each rotor restriction is slightly in excess of 1 kJ mol^{-1}.
27) Chou, P.Y.; Fasman, G.D. *Biochemistry* **1974**, *13*, 222.
28) Kabsch, W.; Sander, C. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 1075.
29) O'Neil, K.T.; DeGrado, W.F. *Science* **1990**, *250*, 646. Lehrman, S.R.; Tuls, J.L.; Lund M. *Biochemistry* **1990**, *29*, 5590.
30) Doig, A.J.; Gardner, M.; Williams, D.H., unpublished work.
31) Creighton, T.E. *Proteins* W.H. Freeman: New York, 1984.
32) Horovitz, A.; Serrano, L.; Avron B.; Bycroft, M; Fersht, A.R. *J. Mol. Biol.* **1990**, *30*, 1031.
33) Dao-pin, S.; Sauer, U.; Nicholson, H.; Matthews, B.W. *Biochemistry* **1991**, *30*, 7142.
34) Searle, M.S.; Doig, A.J.; Williams, D.H., submitted for publication.
35) (a) Searle, M.S.; Williams, D.H., submitted for publication. (b) Searle, M.S.;Williams, D.H.; Doig, A.J., in preparation.
36) At the melting temperatures of the RNA and DNA duplexes, the population of the single strand helical structures is considered and accounted for as a minor correction.
37) Turner, D.H.; Sugimoto, N.; Kierzak, R.; Dreiker, S.D. *J. Am. Chem. Soc.* **1987**, *109*, 3783.
38) Porshke, D. *Biopolymers* **1971**, *10*, 1989.
39) The selectivities of the hydrogen bonds cited in this article are those for the case in which the separated functional groups are solvated by water. The removal of a hydrogen bond can give larger selectivities, if the removal gives rise to a cavity, such that the functional group remaining in the cavity is prevented from hydrogen bonding to the solvent (Wolfenden, R.; Kati, W.M. *Acc. Chem. Res.*. **1991**, *24*, 209).
40) Williams, D.H.; Stone, M.J.; Hauck, P.R.; Rahman, P.R. *J. Nat. Prod.* **1989**, *52*, 1189.

About the Author:

Dr. Dudley Williams is a Reader in Organic Chemistry at the University of Cambridge, and Deputy Director of the Cambridge Center for Molecular Recognition. Dr. Williams began his research in organic chemistry at the University of Leeds, where he obtained his Ph.D. in 1961. After three years as a postdoctoral fellow at Stanford University, he went to the University of Cambridge, where he has carried out work on mass spectrometry, NMR, natural products, and molecular recognition phenomena. For this work, he has received the Meldola Medal, the Corday Morgan Medal, the Tilden Medal, and the Alfred Bader Award in Organic Chemistry (1991) He was elected a Fellow of the Royal Society in 1983.

Acta Archive Indexes



The Acta Archive Indexes document provides easy access to all of the Acta content; 1968 to the present.

The volumes, issues, and content are sorted as follows:

- Chronological
- Authors
- Titles
- Affiliations
- Painting Clues (by volume)

From this index, you can jump directly to a particular volume. Using the sorted sections, you can locate reviews by various authors or author affiliation. Additionally, the content is fully searchable, allowing you to look for a particular key word from the various data available.

To access the index, **click here**.

2017-02521
02/17