28th NATIONAL ORGANIC CHEMISTRY SYMPOSIUM

THE AMERICAN CHEMICAL SOCIETY

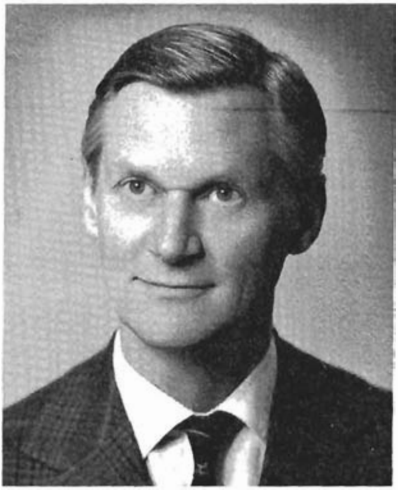
Under the auspices of the
Division of Organic Chemistry &
Montana State University
June 19-23, 1983
Bozeman, Montana

The Roger Adams Award in Organic Chemistry

The Roger Adams Award in Organic Chemistry is sponsored jointly by the American Chemical Society, Organic Reactions, Inc., and Organic Synthesis, Inc. The award recognizes the distinguished career of Roger Adams who played a vital role in each of these three organizations. He was Chairman of the Board of Directors as well as President of the American Chemical Society, and he co-founded Organic Synthesis and Organic Reactions.

The award is made biennially to an individual, without regard to nationality, for outstanding contributions to research in organic chemistry. The award consists of a medal and an honorarium of ten thousand dollars. It is presented at the biennial National Organic Chemistry Symposium of the Division of Organic Chemistry of the American Chemical Society. The awardee is a featured lecturer in the program of the Symposium.

The recipient of this year's Roger Adams Award is Professor Alan R. Battersby of Cambridge University. His award address is entitled "Vitamin B_{12}".



Alan R. Battersby

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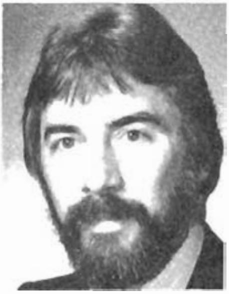
PAUL WENDER


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BERT FRASER-REID


HAROLD HART

AMOS SMITH III

ALBERT PADWA

GARY SCHUSTER

K. BARRY SHARPLESS

ROBERT GRUBBS

Program

SUNDAY, JUNE 19

2-5 PM	Registration

MONDAY, JUNE 20

8:30 AM	Welcome, Response, and Announcements
9:00 AM	P.A. WENDER, Recent Advances in Arene Olefin Photocycloadditions
10:30 AM	J.F. BUNNETT, Chemical Events During Mixing of Solvated Electrons with Organic Halogen Compounds
7:30 PM	K.B. WIBERG, Inverted Tetrahedral Carbons

TUESDAY, JUNE 21

9:00 AM	B. FRASER-REID, Carbohydrate Derivatives in the Asymmetric Synthesis of Natural Products
10:30 AM	H. HART, Polysubstituted Aromatics and the Use of Diaryne Equivalents in Synthesis
7:30 PM	A.R. BATTERSBY, Vitamin B_{12}

WEDNESDAY, JUNE 22

8:30 AM	A.B. SMITH III, Synthetic Studies in the Milbemycin-Avermectin Area: A New Generation of Insecticides
10:00 AM	A. PADWA, Strain, Reactivity and Microcycles
11:15 AM	G.B. SCHUSTER, Chemical Properties of Short-lived Reactive Organic Intermediates

THURSDAY, JUNE 23

9:00 AM	K.B. SHARPLESS, Recent Advances in Asymmetric Synthesis
10:30 AM	R.H. GRUBBS, The Organic and Organometallic Chemistry of $Cp_2Ti=CH_2$
12 NOON	Closing Remarks

Contents

RECENT ADVANCES IN ARENE OLEFIN PHOTOCYCLOADDITIONS

Paul A. Wender

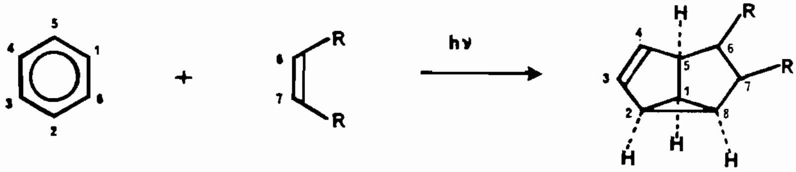
Stanford University
Stanford, California

RECENT ADVANCES IN ARENE OLEFIN PHOTOCYCLOADDITIONS

P. A. Wender
Department of Chemistry
Stanford University
Stanford, California 94305

The arene olefin meta photocycloaddition[1,2] (eq.1)

EQUATION 1



represents a particularly powerful process for the synthesis of a range of commonly encountered natural and non-natural skelta. It proceeds from readily available compounds under mild conditions with the development of three new rings and up to six stereocenters. Cleavage of the labile cyclopropane bonds of the cycloadduct allows easy access to 5 and 7-membered rings as well as bicyclo [3.2.1] octanes and [3.3.0] octanes, rich in stereochemical detail (Scheme I).

The intramolecular variant of the meta cycloaddition[1b,c,2] holds particular promise for polycycle synthesis. Its utility is coupled, however, to the control which can be exercised over mode selectivity, regioselectivity, endo/exo selectivity and stereoinduction. In order to explore these issues and the utility of this reaction in complex molecule synthesis, we recently investigated the application of this reaction to the synthesis of cedrene[2a] (Scheme II). In the course of this work, it was established that the intramolecular reaction, involving an excited state ortho-substituted anisole tethered by a three carbon link to a trisubstituted alkene, proceeds via the meta mode of addition, a characteristic mode preference for arenes and alkenes whose ionization potentials are similar[1]. It was also

CHEMICAL EVENTS DURING MIXING OF SOLVATED ELECTRONS WITH ORGANIC HALOGEN COMPOUNDS

Joseph F. Bunnett

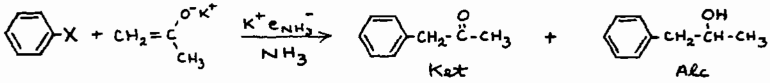
University of California
Santa Cruz, California

CHEMICAL EVENTS DURING MIXING OF SOLVATED ELECTRONS WITH ORGANIC HALOGEN COMPOUNDS

Joseph F. Bunnett

University of California
Santa Cruz, California 95064

First, some experimental data:



X	Yield, % Ket	Yield, % Alc	PhH	Ket/Alc
I	66	10	4	7
Br	78	11	6	7
Cl	20	37	18	0.6
F	12	42	29	0.3

R.R. Bard, J.F. Bunnett, X. Creary & M.J. Tremelling,
JACS <u>102</u>, 2852 (1980)

These reactions were conducted by adding potassium metal, either as bits or dissolved in ammonia, to an ammonia solution of a halobenzene and potassium acetone enolate. Whatever the addition protocol, the product distribution is strongly dependent on the identity of the halogen: with iodine, a high ketone/alcohol ratio and little benzene, but with fluorine a low ketone/alcohol ratio and much benzene, with PhBr & PhCl falling between.

These reactions are believed to occur by the $S_{RN}1$ mechanism:

INVERTED TETRAHEDRAL CARBONS

Kenneth B. Wiberg

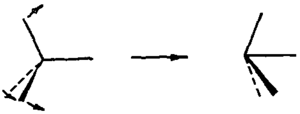
Yale University
New Haven, Connecticut

INVERTED TETRAHEDRAL CARBONS

Kenneth B. Wiberg

Department of Chemistry, Yale University

Some years ago, we considered the possible modes by which a tetrahedral carbon might be deformed. One of these, the "umbrella mode," retains one of the three-fold axes of symmetry, and leads to an "inverted" geometry at carbon:



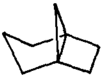
The small-ring propellanes consititute a group of compounds which contain this structural element. Examples of compounds which have been studied include:

1

2

3

4

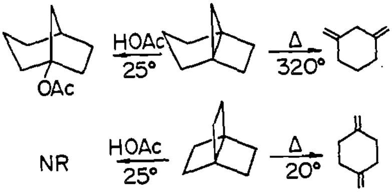


5

6

We prepared a derivative of [3.2.1]propellane in 1968,[1] and the hydrocarbon itself (5) was prepared by us[2] and by Gassman, Topp and Keller[3] in 1969. A derivative of [2.2.2]propellane (4) was prepared by Eaton and Temme in 1973.[4] An X-ray structure determination demonstrated that 5 did have an inverted geometry at the bridgeheads.[5] The properties of 4 and 5 present an interesting contrast in reactivity:

Ring Opening Reactions



CARBOHYDRATE DERIVATIVES IN THE ASYMMETRIC SYNTHESIS OF NATURAL PRODUCTS

Bert Fraser-Reid

Duke University
Durham, North Carolina

CARBOHYDRATE DERIVATIVES IN THE ASYMMETRIC SYNTHESIS OF NATURAL PRODUCTS

PYRANOSIDIC HOMOLOGATION - A SOLUTION FOR MULTICHIRAL CONCATENATIONS

Bert Fraser - Reid*[a], Leon Magdzinski[b], Bruce Molino[b] and
Bruce Cweiber[b,c]

Departments of Chemistry
[b]University of Maryland
College Park, MD 20742 and
[a]Duke University
Durham, N.C. 27706
[c]undergraduate collaborator

In 1975[1] we drew attention to the fact that although carbohydrates represented a vast resource of accessible, tractable, and well-researched substances, synthetic organic chemists were by and large totally innocent of their existence. At that time synthetic methodology applicable to non-carbohydrate targets had not received any concentrated attention, although Miljkovic had announced his intention of synthesizing erythronolide from sugars (1974)[2], and Stork's prostaglandin synthesis was then underway[3]. This latter work, in addition to our synthesis of avenaciolide (1975)[4], and Hanessian's approach to erythronolide (1977)[5] were early consciousness-raisers, and the vitality of this "idea whose time has come" is manifested by the fact that for the FIFTH IUPAC Conference on Organic Synthesis (Freiburg, 1984), one of the four topics will be "Carbohydrates in Organic Synthesis".

The burgeoning literature reveals the remarkable versatility of these simple substances; but their impact has been strongest on synthetic approaches to macrolides and ionophores. The literature shows that the idea of utilizing sugars for these endeavours was first expressed by Miljkovic[2], although the greatest advances were by Hanessian's group[5]. That early connection was logical since the seco-acid of erythronolide, 1, may be classified as a higher-carbon sugar - an aldonic acid to be precise[6]. It is therefore appropriate to regard these substances as "pseudo" long-chain sugars.

The current trendy glamour of macrolides and ionophores should not be allowed to detract from the fact that there are many authentic long-chain sugars which are components of important antibiotics. A sampling of these is also shown in

POLYSUBSTITUTED AROMATICS AND THE USE OF DIARYNE EQUIVALENTS IN SYNTHESIS

Harold Hart

Michigan State University
East Lansing, Michigan

POLYSUBSTITUTED AROMATICS AND THE USE OF DIARYNE EQUIVALENTS IN SYNTHESIS

Some years ago, during studies on electrophilic aromatic hydroxylation,[1] we discovered that hexamethylbenzene and other highly substituted arenes could be oxidized to cyclohexadienones in good yield (*e.g.* 1 → 2[2]). These highly substituted dienones, unlike less substituted analogs, did not undergo Diels-Alder dimerization and proved to be useful synthetic intermediates. Some of the remarkable chemistry derived from 2 is shown in Chart I. The facile equilibration

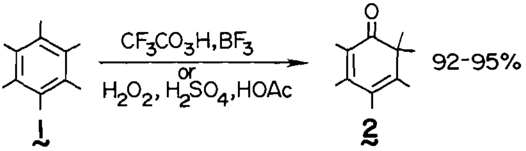
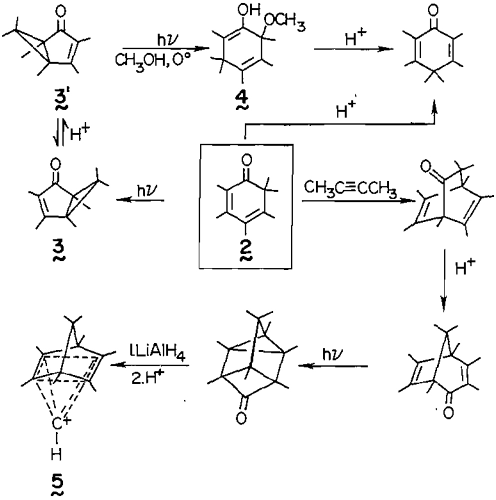


CHART I



VITAMIN B_{12}

Alan R. Battersby

University Chemical Laboratory
Cambridge, England

VITAMIN B_{12}

The complex molecule of vitamin B_{12} (1) is both fascinating and biologically very efficient. Two major problems concerning this vitamin have been brilliantly solved, namely, structure determination and total synthesis. Two more remain, which are mode of action and biosynthesis. One of the major interests of my group at Cambridge over the past 15 years has been concerned with this last problem of biosynthesis.

At the heart of the structure of vitamin B_{12} is the corrin macrocycle which comprises four pyrrole-derived rings linked by three one-carbon bridges, there being a direct link between rings A and D. The periphery of the macrocycle is highly chiral as a result of extensive C-methylation. The aim of our work is to discover, and to determine the structure of, all the intermediates on the entire pathway as, step-by-step, the various methyl groups are introduced and other modifications, e.g. decarboxylation, occur. Success in this phase then opens up challenging opportunities for total syntheses of the novel macrocycles which have been revealed. The lecture will cover the synthetic as well as the biosynthetic aspects of the researches.

The first macrocycle formed on the pathway to vitamin B_{12} (1) is the colourless uroporphyrinogen-III (2), usually shortened to uro'gen-III. The way in which this surprising structure is constructed in living systems was one of the major puzzles in biosynthesis. However, the progress made since 1968 has been striking and most features of the pathway have been discovered. This chemistry in its broadest sweep will be surveyed including synthetic, spectroscopic, kinetic and enzymatic aspects.

Macrocycles of prime interest for the biosynthetic story beyond uro'gen-III (2) are shown as (3), (4), (5), (6) and (7). These all retain the one-carbon bridge between rings A and D which has been eliminated by the time vitamin B_{12} (1) has been built. In what form is the fragment extruded and at what oxidation level? These questions raised special problems but it will be seen that their nature is such that they are attackable using the strength and approaches of organic chemistry.

SYNTHETIC STUDIES IN THE MILBEMYCIN-AVERMECTIN AREA: A NEW GENERATION OF INSECTICIDES

Amos B. Smith III

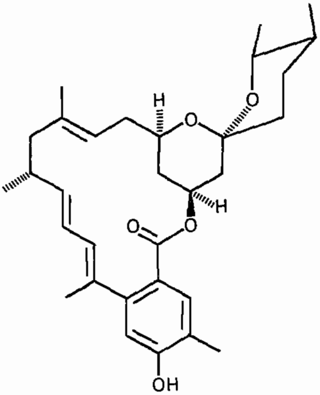
The University of Pennsylvania
Philadelphia, Pennsylvania

SYNTHETIC STUDIES IN THE MILBEMYCIN-AVERMECTIN AREA: A NEW GENERATION OF INSECTICIDES

Amos B. Smith, III

Department of Chemistry, The Monel Chemical Senses Center and
The Laboratory for Research on the Structure of Matter
The University of Pennsylvania, Philadelphia, Pennsylvania 19104

In this presentation we describe the first total synthesis of milbemycin β_3 and its epimer, epimilbemycin β_3, the simplest members of a family of some thirteen architecturally novel macrolide antibiotics structurally related to the avermectins, and known to possess remarkably potent pesticidal activity against a host of agricultural pests. Our approach to this class of antibiotics is short (longest linear sequence, sixteen steps), convergent and for the most part, stereocontrolled. Milbemycin β_3 is the first member of the milbemycin-avermectin class of macrolide antibiotics to yield to total synthesis [A. B. Smith, III, *et al., J. Amer. Chem. Soc.,* **104**, 4015 (1982)].



MILBEMYCIN β_3

STRAIN, REACTIVITY AND MICROCYCLES

Albert Padwa

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STRAIN, REACTIVITY AND MICROCYCLES

Albert Padwa

Department of Chemistry, Emory University
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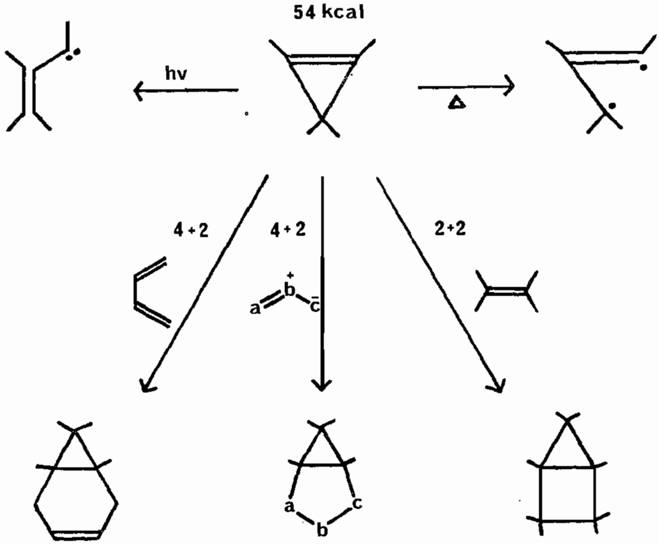
Small ring hydrocarbons are particularly interesting compounds because their high energy content, relative to the acyclic isomers, often endows them with unusual reactivity. Cyclopropene is one of the simplest of such molecules in terms of chemical composition and at the same time perhaps the most strained of the compounds hitherto known, if strain is calculated per carbon atom. The strain energy in cyclopropene is approximately 54 kcal/mol and is primarily due to the strain present in the σ-framework. The relief of ring strain combined with resonance stabilization of the corresponding ring-opened species accounts for the relatively facile ring-opening reaction of this molecule. Addition across the double bond in cyclopropene also proceeds quite readily since it reduces ring strain by 26 kcal/mol.



Cycloaddition reactions have figured prominently in both synthetic and mechanistic organic chemistry. Current understanding of the underlying principles in this area has grown

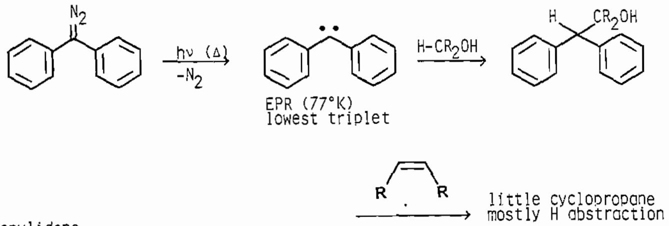
CHEMICAL PROPERTIES OF SHORT-LIVED REACTIVE ORGANIC INTERMEDIATES

Gary B. Schuster

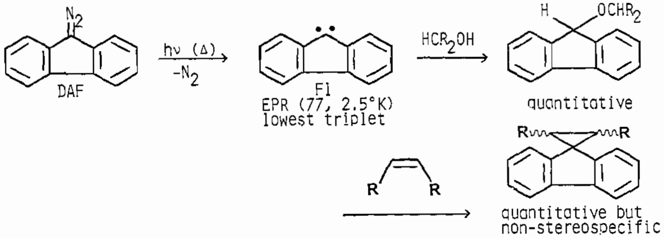
University of Illinois
Urbana, Illinois

Substituted Carbenes - Two Examples

Diphenylmethylene:



Fluorenylidene:



RECENT ADVANCES IN ASYMMETRIC SYNTHESIS

K. Barry Sharpless

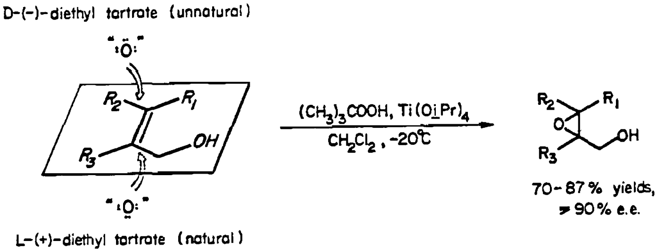
Massachusetts Institute of Technology
Cambridge, Massachusetts

RECENT ADVANCES IN ASYMMETRIC SYNTHESIS

K. Barry Sharpless

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts, 02139

In the three years since it first appeared in literature the titanium-catalyzed asymmetric epoxidation process has become a popular means of obtaining enantiomerically pure compounds. In this lecture I wish to present several new asymmetric processes which have emerged from our research during the past year. These include a method for kinetic resolution of β-hydroxyamines, a method for asymmetric chlorohydroxylation of alkenes, and a method for the asymmetric reduction of ketones to chiral secondary alcohols.



THE ORGANIC AND ORGANOMETALLIC CHEMISTRY OF $Cp_2Ti{=}CH_2$

Robert H. Grubbs

California Institute of Technology
Pasadena, California

THE ORGANIC AND ORGANOMETALLIC CHEMISTRY OF $Cp_2Ti{=}CH_2$

**D. A. Straus, W. Finch, K. C. Ott, S.
Buchwald and R. H. Grubbs**

Department of Chemistry
California Institute of Technology
Pasadena, California 91125

The reactive 16 e^- species $Cp_2Ti{=}CH_2$ can be generated from precursors of the type $Cp_2Ti(CH_2)L$, where L = olefin (metallacyclobutane) and phosphine complexes, at temperatures between -20°C and 60°C in the presence of a desired reactant. These complexes (L = olefin) are metathesis catalysts and have been studied to elucidate the mechanism of this important reaction. Reaction products and mechanisms for its reaction with benzyl, main group and transition metal halides have been examined. The evidence to date suggests that these reactions proceed through a halogenation abstraction reaction. The reaction with transition metal halides provide bridging bimetallic methylene complexes of a new type. Of particular interest is the reaction of these species with CO to form ketene complexes. Alternate sources of the same ketene complex will also be described. The reactions of Cp_2TiCH_2 result in a number of useful organic transformations. Some of the useful transformations which can be accomplished using this chemistry are: