27th NATIONAL ORGANIC CHEMISTRY SYMPOSIUM

THE AMERICAN CHEMICAL SOCIETY

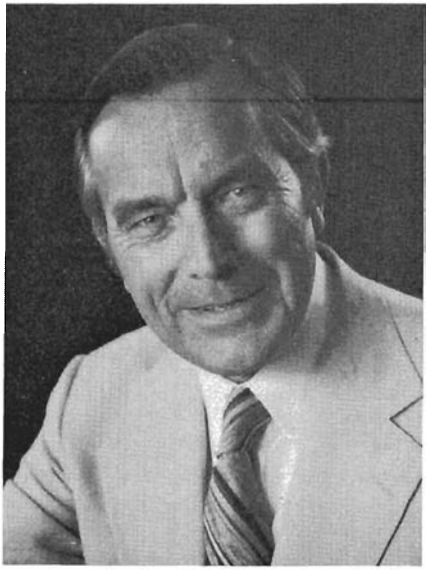
Under the auspices of the
Division of Organic Chemistry &
Vanderbilt University
June 21-25, 1981
Nashville, Tennessee

The Roger Adams Award in Organic Chemistry

The Roger Adams Award in Organic Chemistry has been established with joint sponsorship by the American Chemical Society, Organic Reactions, Inc., and Organic Syntheses, Inc. 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. The presentation of the award is made at the biennial National Organic Chemistry Symposium of the Division of Organic Chemistry of the American Chemical Society, and the recipient delivers a lecture as part of the program of the Symposium.

The award recognizes the distinguished career of Roger Adams, who played such a vital role in each of the three organizations sponsoring the award, having been Chairman of the Board of Directors as well as President of the American Chemical Society and cofounder of Organic Syntheses and Organic Reactions.

The recipient of this year's award is Professor Nelson J. Leonard of the Department of Chemistry of the University of Illinois. His award address is entitled "Organic Syntheses: Bio-functional Interactions."

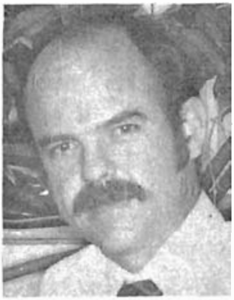


Nelson J. Leonard

Speakers


O. Chapman


S. Hanessian


K.N. Houk


H. House


A. Kende


J.C. Martin


L. Paquette


W. Clark Still


B.M. Trost

Organizing Committees

The plans and program for the 27th National Organic Chemistry Symposium have been developed by the members of the Executive Committee of the Division of Organic Chemistry who have served during the past two years.

	1979-80	1980-81
Chairman	R. Ireland	P.G. Gassman
Chairman-elect	P.G. Gassman	A.I. Meyers
Secretary-Treasurer	P.Beak	P. Beak
Secretary-Treasurer-elect		W.S. Trahanovsky
National Symposium Executive Officer	L. Mandell	L. Mandell
Executive Committee	R.M. Coates D.A. Evans A.S. Kende J.A. Marshall L.A. Paquette E. Wasserman	R.M. Coates D.A. Evans K. Nakanishi L.A. Paquette M.F. Semmelhack E. Wasserman Edward M. Burgess Michael Cava Norman A. LeBel Ernest Wenkert Albert Padwa Stuart Staley Jacob Szmuszkovicz

This program was produced by the Office of Publications, Emory University, Atlanta, Georgia.

Program

SUNDAY, JUNE 21

2-5pm	Registration

MONDAY, JUNE 22

8-9am	Registration
9:30-11am	H. HOUSE, "Unsaturated Carbonyl Compounds with Distorted Double Bonds"
11am-12:30pm	A. KENDE, "New Tactics in Organic Synthesis: Regiospecific Condensations of Enolates with Polyhaloolefins"
7:30-9pm	O. CHAPMAN, "Organic Chemistry Beyond Van't Hoff and LeBel"

TUESDAY, JUNE 23

9-10:30am	L. PAQUETTE, "The Dodecahedrane Story"
10:30am-12noon	B. TROST, "New Aspects for Selectivity in Organic Synthesis"
7:30-9pm	N. LEONARD, "Organic Synthesis: Bio-functional Interactions"

WEDNESDAY, JUNE 24

8:30-10am	S. HANESSIAN, "Strategies in Natural Products Synthesis from Carbohydrates. Target: Boromycin"
10-11:30am	C. STILL, "New Methods for the Synthesis of Natural Products"
9-10:30pm	J.C. MARTIN, "The Coordination Chemistry of Nonmetallic Elements--Pentavalent Carbon and Related Species"

PROGRAM, continued

THURSDAY, JUNE 25

9-10:30am	C. HEATHCOCK, "Applications of Stereoselective Aldol Condensations in Natural Products Synthesis
10:30am-12noon	K. HOUK, "Molecular Distortions and Transition State Conformational Analysis"

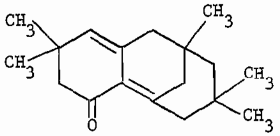
Contents

UNSATURATED CARBONYL COMPOUNDS WITH DISTORTED DOUBLE BONDS

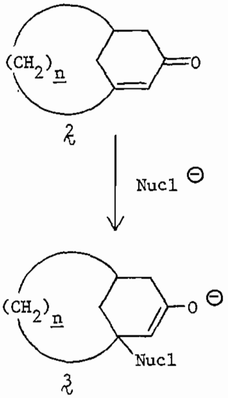
Herbert O. House

Georgia Institute of Technology
Atlanta, Georgia

An earlier study[1] of the structure and genesis of a trimeric substance from isophorone and base led us to conclude that the dienone 1 was a reaction intermediate. This dienone 1 shares with enones of the type 2 the property of allowing effective conjugation between the C=O and C=C groups and yet having significant distortion about the C=C bond. Such enones 2 should be highly reactive Michael acceptors since formation of a Michael adduct 3 is accompanied by relief of distortion. These enones 2 can be contrasted with other, more thoroughly studied[2] enones with bridgehead double bonds such as 4 and 5 that do not have effective conjugation between the C=O and C=C groups. This latter group of enones are not reactive Michael acceptors because formation of a Michael adduct (e.g., 6) does not remove distortion. Prior to our studies, the only reported examples of enones 2 were relatively unstrained compounds with large methylene bridges (n = 6 and 9 in structure 2).[3]

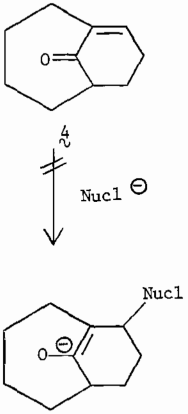


1



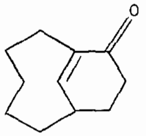
2

3



4

6



5

Both studies of molecular models and force field calculations[4] indicate the major distortion in the bridgehead enones 2 is at the C=C bond with the bond being twisted (T = twist angle) and the C=C substituents being distorted from planarity (P_1 and P_2 = pyramidal distortion angles). The overall strain in the various enones can be estimated from force field calculations as an inherent strain value (in kcal/mol).[4] Alternatively, the strain associated with the distorted C=C may be estimated[5] using the twist

NEW TACTICS IN ORGANIC SYNTHESIS:
REGIOSPECIFIC CONDENSATIONS OF ENOLATES WITH POLYHALOOLEFINS

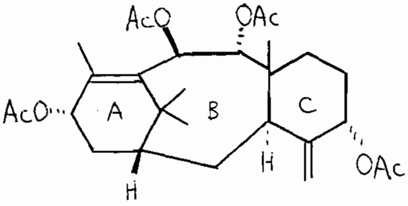
Andrew S. Kende, Michel Benechie, John H. Hill and
Pawel Fludzinski

University of Rochester
Rochester, New York

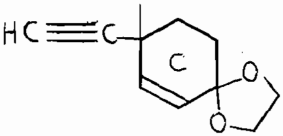
NEW TACTICS IN ORGANIC SYNTHESIS:
REGIOSPECIFIC CONDENSATIONS OF ENOLATES WITH POLYHALOOLEFINS

Andrew S. Kende, Michel Benechie, John H. Hill and
Pawel Fludzinski
Department of Chemistry, University of Rochester,
Rochester, New York 14627

In the course of a synthetic route to the taxane diterpenes (e.g., taxusin, I) we required the preparation of the C-ring synthon II. After some difficulties, the 4-ethynylcyclohexenone equivalent II was prepared in high yield by a hitherto unknown reaction: the uncatalyzed condensation of an enolate with trichloroethylene.



I



II

We have found that the uncatalyzed condensation of highly reactive enolates with polyhaloolefins is frequently a useful and regiospecific route to a variety of ethynyl, ω-haloethynyl and dihalovinyl derivatives of carbonyl compounds. In addition, hexachlorobutadiene has been found to condense with one or with two

ORGANIC CHEMISTRY BEYOND VAN'T HOFF AND LEBEL

O.L. Chapman

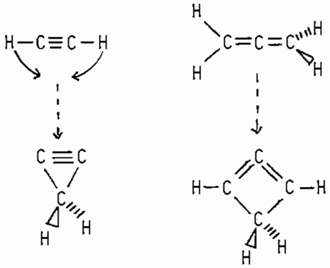
University of California/Los Angeles
Los Angeles, California

Organic Chemistry Beyond
Van't Hoff and LeBel

O.L. Chapman
Department of Chemistry
University of California Los Angeles
405 Hilgard Avenue
Los Angeles, Ca. 90024

The deduction of the tetrahedral carbon atom by Van't Hoff and by Le Bel in 1874 provided the structural basis of our science. It is, in fact, the most successful theory in science. The concept of the tetrahedral carbon and the digonal carbon have sufficed to represent all of organic chemistry including the development of molecular genetics, and indeed, all of molecular biology. It is with a deep sense of reverence that we have sought the limits of this remarkable structural theory. In the present work, we have at long last gone beyond the domain bounded by the theory of Van't Hoff and LeBel. In doing so, we have revealed a small part of our own bias--the bias that limits progress in science. The bias from which Van't Hoff and LeBel suffered much.

The aspects of our research which are of immediate interest began with the concept of systematically deforming bond angles in acetylenes and allenes. Deformation of each system can be accomplished by inclusion in increasingly smaller rings. The ultimate systems are cyclopropyne and cyclobuta-1,2-diene. The chemistry of severely strained acetylenes encountered in these studies has been quite striking--in many cases rather similar to that of metals. The chemistry of 1,2-dienes has proved no less remarkable than that of the acetylenes. It is replete with rearrangements, even incredible rearrangements, which have led us to postulate and to synthesize molecules for which the Van't Hoff and LeBel structures have no real meaning. This fundamental turning point in our research has led us to contemplate new possibilities in mechanism and new synthetic challenges. It has led to an understanding of problems in existing industrial processes, and it has led to the design of a new industrial process. The transition from research on matrix isolated molecules at 10K to the billion pound per year plant is fraught with pitfalls, but the present study provides a cogent response to critics in government (and elsewhere) in the contention that University research is not translated to technological innovation in the United States.



THE DODECAHEDRANE STORY

Leo A. Paquette

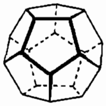
The Ohio State University
Columbus, Ohio

THE DODECAHEDRANE STORY

Leo A. Paquette

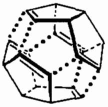
Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

① TARGET MOLECULE

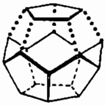


---

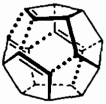
② UNSUCCESSFUL (TO DATE) CONVERGENT APPROACHES



WOODWARD



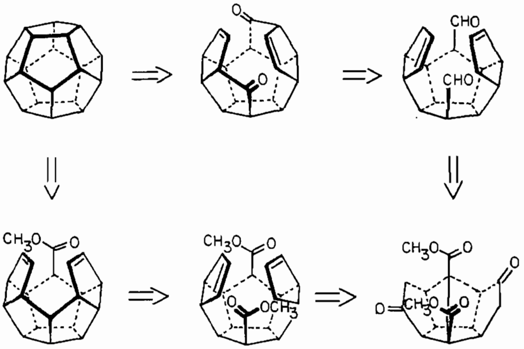
EATON



PAQUETTE

---

③ RETROGRADE ANALYSIS OF SERIAL SYNTHESES INVOLVING $\underline{C}_2$- OR $\underline{C}_s$ SYMMETRIC INTERMEDIATES



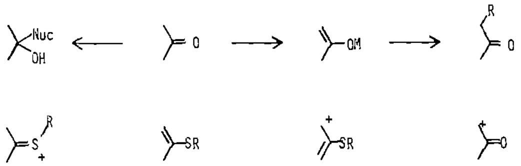
NEW ASPECTS FOR SELECTIVITY IN ORGANIC SYNTHESIS

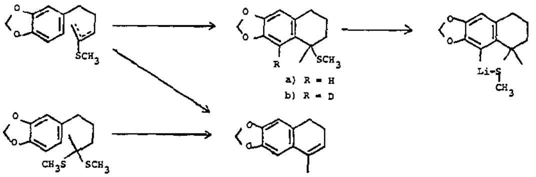
Barry M. Trost

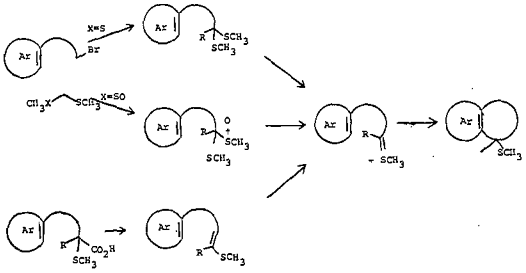
University of Wisconsin
Madison, Wisconsin

NEW ASPECTS FOR SELECTIVITY IN ORGANIC SYNTHESIS

Barry M. Trost
McElvain Laboratories of Organic Chemistry
Department of Chemistry
University of Wisconsin
Madison, Wisconsin 53706







ROGER ADAMS AWARD ADDRESS:
ORGANIC SYNTHESIS: BIO-FUNCTIONAL INTERACTIONS

Nelson J. Leonard

University of Illinois
Urbana, Illinois

ORGANIC SYNTHESIS: BIO-FUNCTIONAL INTERACTIONS

Nelson J. Leonard
Roger Adams Laboratory
University of Illinois
Urbana, IL 61801

The study of intramolecular and intermolecular associations in biological systems may follow two routes. One, the careful and appropriate spectroscopic examination of the system or natural entity itself, is open to all who can isolate and purify, beg, or buy the material. The other, which includes initially synthesis, then examination, of meaningful models, is a less-traveled route to answers that may prove to be more definitive and less descriptive.

We first prepared analogues of dinucleotides or dinucleoside phosphates in which the nucleic acid bases were connected by polymethylene chains, particularly a trimethylene chain. These compounds, $B-(CH_2)_3-B'$, in which B and B' are 9-substituted adenine or guanine or 1-substituted cytosine, thymine, or uracil residues, are free from the complicating factors associated with hydrogen bonding and carbohydrate and phosphodiester conformations, yet the trimethylene bridge allows them to assume conformations in which the rings are in close proximity, or near-parallel coplanarity. In aqueous solution, at concentrations low enough to preclude formation of intermolecular complexes, perturbations associated with the 1:1 interaction (stacking) of a pair of bases can be characterized by percent hypochromism in the UV that depends upon the relative orientation of the transition moments in the ordered array. Intramolecular interaction between the bases in $B-(CH_2)_3-B'$ in 1:1 ethylene glycol-water glass at 77° K can also be demonstrated by the broadened and red-shifted fluorescence emission spectra compared with those of the monomeric bases. A complex between B in the singlet excited state and B' in the ground state is thus implicated. Triplet energy transfer is also an efficient mechanism in these molecules at 77° K, since the phosphorescence emission from all the neutral dinucleotide analogues is characteristic of the base with the lower lying triplet state. The influence of ethanol, an effective denaturing agent for DNA and single-stranded poly(A), on $Ade^9-C_3-Ade^9$ and $Thy^1-C_3-Thy^1$ is shown by the absence of detectable base-base interaction in this solvent.

The successful application of the spectroscopic methodology to these simple models led us to synthesize other series in order to answer additional questions concerning intramolecular interactions, such as: 1) the effect of synthetic spacer length on percent hypochromism at 25° C for the series $Ade^9-C_n-Ade^9$; 2) variation in interaction between two adenine rings as a function of positions of attachment as in $Ade^x-C_3-Ade^y$; 3) the positional dependence of the internal photodimerization of two thymine rings held together by a trimethylene bridge, which leads, in appropriate models, to respective *syn-cis*, *syn-trans* (solid-state irradiation), *anti-cis*, and *anti-trans* photoproducts.

Among the specific stacking interactions that may contribute to the positioning of protein with respect to nucleic acid, interaction between

STRATEGIES IN NATURAL PRODUCTS SYNTHESIS FROM CARBOHYDRATES

TARGET: BOROMYCIN

Stephen Hanessian, Peter Tyler, Gilles Demailly, Daniel Delorme
and Yves Chapeur

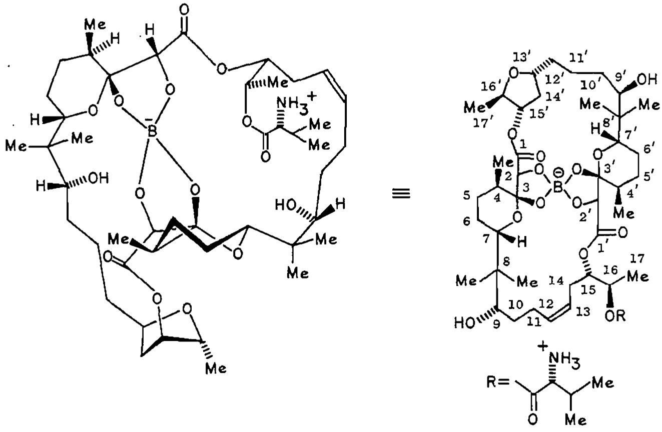
University of Montreal
Montreal, Quebec

STRATEGIES IN NATURAL PRODUCTS SYNTHESIS FROM CARBOHYDRATES.
TARGET: BOROMYCIN.

Stephen Hanessian, Peter Tyler, Gilles Demailly, Daniel Delorme and Yves Chapleur.

Department of Chemistry, University of Montreal, Montreal, Quebec H3C 3V1 CANADA.

Boromycin, $C_{45}H_{74}BNO_{15}$ is a unique boron-containing antibiotic produced by a strain of Streptomyces antibioticus. By a combination of limited degradative studies and an X-ray analysis, it was shown by Prelog, Dunitz and coworkers in 1974[1] to be a boric acid Böeseken complex of a novel macrodiolide containing a D-valine ester as the cationic moiety. Desvalino boromycin obtained by mild alkaline hydrolysis forms crystalline cesium and rubidium salts. The overall molecular shape is that of a lipophilic spherical surface and a cleft lined with oxygen atoms. The cation is coordinated by some of the oxygen atoms in an irregular arrangement. The constitutional structure of boromycin is depicted below in two perspectives one of which approximates its three dimensional X-ray structure. It is of interest that the neopentyl type hydroxyl functions at C-9 and 9' have S and R configurations respectively. Also of note is the open-chain segment C-10—C-17, which if visualized in a cyclized tetrahydrofuran ring form (between O-16 and C-13) would produce a molecule with C-2 symmetry (except for C-9, 9'). In fact, a recently isolated second boron-containing antibiotic, aplasmomycin,[2] has such a structure except for the presence of E double bonds at C-11—C-12 and C-11'—C-12' and R stereochemistry at C-9,9'.



Boromycin

NEW METHODS FOR THE SYNTHESIS OF NATURAL PRODUCTS

W. Clark Still

Columbia University
New York, New York

NEW METHODS FOR THE SYNTHESIS OF NATURAL PRODUCTS

W. Clark Still
Department of Chemistry
Columbia University
New York, NY

In recent years, my research group has been involved with the synthesis of various complex acyclic and macrocyclic natural products including pheromones, macrolides and polyether antibiotics. Although current methodology allows such molecules to be prepared, the difficulties associated with such endeavors indicate that satisfactory solutions may evolve only through the development of strategically new methodology. Many of the current difficulties involve the general problem of effective and efficient control of stereochemistry in conformationally flexible systems. Over the past few years, my research group has been involved more and more with certain simple chemical reactions which produce one or more asymmetric centers with stereochemical control by a preexisting center of asymmetry. Such reactions are inherently economical in their application to stereoselective synthesis but gain special significance from our recent observations that macrocyclic intermediates and transition states allow asymmetric induction to be effectively transmitted over a considerable molecular distance (at present up to 11 carbon atoms). I believe that the remote direction of stereochemistry is an exceedingly powerful approach to the synthesis of complex acyclic and macrocyclic molecules and will describe new results as well as the background in this area.

THE COORDINATION CHEMISTRY OF NONMETALLIC ELEMENTS--PENTAVALENT (10-C-5) CARBON AND RELATED SPECIES

J.C. Martin

University of Illinois
Urbana, Illinois

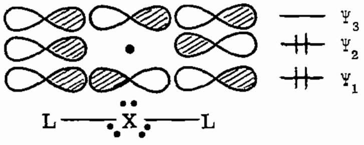
THE COORDINATION CHEMISTRY OF NONMETALLIC ELEMENTS--PENTAVALENT (10-C-5) CARBON AND RELATED SPECIES

J. C. Martin
Roger Adams Laboratory
University of Illinois
Urbana, IL 61801

Much attention has been devoted over the years to the design of ligands for transition metal species which accentuate desired reactivity patterns or impart desired physical or chemical properties to these organometallic compounds. Relatively little attention has been paid, however, to the systematic design of ligands for the nonmetallic elements, the area which we could call organoNONmetallic chemistry. Our research has recently been directed toward the synthesis of compounds containing new organic functional groups which owe their existence to their incorporation of ligands specifically designed to provide stability to the higher coordination states of nonmetals. Our goal has been to isolate, or to observe directly, species in which formal expansion of the valence octet of a central nonmetallic atom is accompanied by expansion of the coordination sphere, compounds with the sort of electron-rich multicenter bonding which has been called hypervalent.[1]

Figure 1 provides a partial periodic table of hypervalent organononmetallic species, arranged in a systematic manner to highlight the relationships between them which will be discussed in this lecture. Each species is given an N-X-L designation,[2] where N is the number of valence-shell electrons formally assignable to the valence shell of the central atom X, either as unshared pairs of electrons or as pairs of electrons in the L sigma bonds joining ligands to the X.

A cursory examination of the types of compounds listed in Figure 1 can serve to remind one of the fact that the first reported examples of many of these species contained, like XeF_2, fluorine atom ligands to the central nonmetal. The electronegativity of fluorine makes it very effective in stabilizing many of these species, particularly when it occupies the apical positions of one of these pseudo trigonal bipyramidal (TBP) molecules. (We may consider electron pairs to occupy equatorial positions in a pseudo TBP geometry.) All of the examples of species from Figure 1 which are to be discussed in this lecture have slightly distorted TBP geometry. Of the several compounds for which X-ray crystal structures have been determined, none has an angle between the two apical bonds which deviates by more than 18° from the ideal 180°. We can therefore describe these species in terms of the approximate hypervalent bonding theory for three-center four-electron bonds,[1] a molecular orbital description which uses only atomic p-orbitals of the central atom (X) and the ligands (L) to construct the molecular orbitals of the three-center bond.



APPLICATIONS OF STEREOSELECTIVE ALDOL CONDENSATIONS IN NATURAL PRODUCTS SYNTHESIS

Clayton H. Heathcock

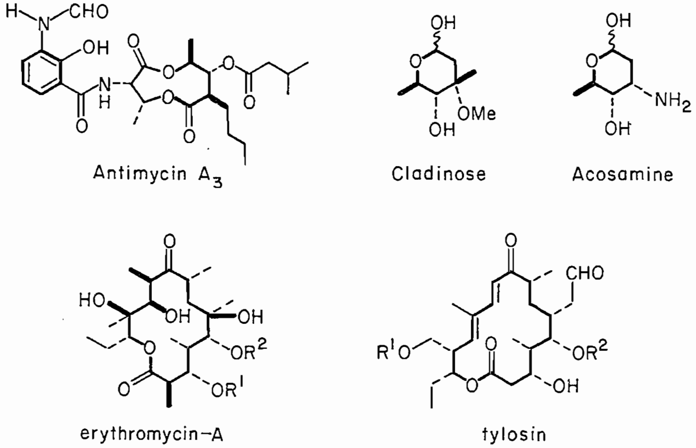
University of California
Berkeley, California

APPLICATIONS OF STEREOSELECTIVE ALDOL CONDENSATIONS IN NATURAL PRODUCTS SYNTHESIS

Clayton H. Heathcock

Department of Chemistry, University of California
Berkeley, California 94720

Organic chemistry is currently immersed in a "reaction selectivity" phase. Much of the current research which is going on is directed toward the development of new methods for achieving regioselective, chemoselective, and stereoselective transformations. At Berkeley, we have for several years been exploring the aldol condensation as a method for realizing stereocontrol in the synthesis of acyclic molecules having two or more asymmetric carbons. A selection of natural products in which control of relative stereochemistry is a major synthetic problem is depicted in Figure 1.



Antimycin A_3 Cladinose Acosamine

erythromycin-A tylosin

Figure 1. Some β-Hydroxycarbonyl Natural Products

Our basic thesis in this project is that we can learn to control the stereochemistry of this venerable reaction (the aldol condensation was first reported in 1838) to the extent that it becomes a valuable method for the synthesis of complex materials such as erythromycin (Figure 2). There are two different stereochemical problems which must be solved in this regard. When one creates a new carbon-carbon bond by the aldol condensation, two new asymmetric carbons may be formed. These may have either the *erythro* or the *threo* relative configuration, as shown in Figure 3.

MOLECULAR DISTORTIONS AND TRANSITION STATE CONFORMATIONAL ANALYSIS

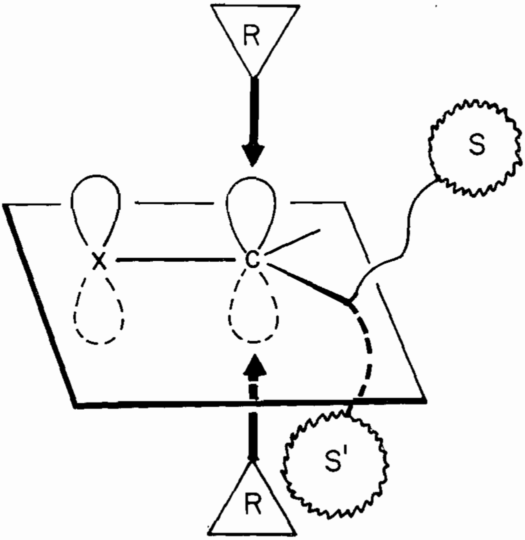
K.N. Houk

University of Pittsburgh
Pittsburgh, Pennsylvania

MOLECULAR DISTORTIONS AND TRANSITION STATE CONFORMATIONAL ANALYSIS

In unsaturated molecules with diastereotopic faces, the rates of attack of various reagents on the two faces of the π bond are unequal.[1] We refer to this selectivity as "π-facial stereoselectivity".

π-Facial Stereoselectivity



Interest in π-facial stereoselectivity is at an all-time high due to the importance of asymmetric induction in the stereospecific synthesis of natural products,[2] particularly polyether antibiotics.[3] Because the successful design of stereospecific synthesis depends upon the reliability of models used to predict π-facial stereoselectivity, and because the electronic factors governing stereoselectivity are the subject of some debate, we have turned our attention to this fascinating area of organic chemistry.

In this lecture, I will describe two recently discovered phenomena which we believe are the keys to understanding π-facial stereoselectivity.

First, we have found that alkenes and carbonyls which lack a plane of symmetry pyramidalize so as to produce partial staggering of the trigonal carbon with respect to allylic bonds. While generally small,