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Vol. 15, Number 1, 1982

Dedicated to Professor Gilbert Stork in celebration of 35 years in research and teaching.

Aldrichimica Acta

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About Our Cover:

When we asked our chemist-collector to allow us to reproduce his finest recent acquisition in the *Acta* dedicated to Professor Stork, he pointed to the painting (oil on panel, 23½ × 17½ inches) reproduced on our cover. "Not *another* Jacob's Dream!" Our first reaction subsided quickly when we saw the quality of the painting — truly a dream in every sense of the word.

When it came up for sale in April of 1980, it was so covered by layers of dirty varnish (Fig. 1) that Christie's in London, who operate two auction galleries — one on King Street for better works and the other in Kensington for minor works — put it into the Kensington sale. It was attributed to one of the Carraccis, an artist family in Bologna early in the 17th century. Cleaning revealed that the painting is in excellent condition and is by Domenico Fetti, an artist who also worked early in that century in Rome, Mantua and Venice. Fetti often produced several versions of his compositions, and his best-known of this subject (Fig. 2) is in Vienna.

The painting had been sent to Christie's by its former owner in Weymouth, Dorset, who had inherited it from his grandfather. Nothing is known of its previous history, although it must have belonged to a collector whose seal (Fig. 3) is burnt three times into the back of the panel. Our collector has not yet determined the identity of the seal, and would be most grateful for help from any reader who recognizes it.

Fig. 1 (far left)

Fig. 2

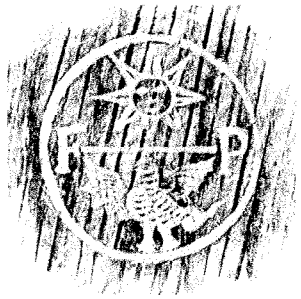

Fig. 3

We are reminded of what we have written about this wonderful subject, in Vol. 8, No. 4 and Vol. 12, No. 3, of the *Acta*: "The Bible is the book of dreams, par excellence: dreams of individuals, dreams of a people, dreams of all mankind. It is surely no accident that the very first well known dream in the Bible is not that of a king or of a general but of a man at the lowest point in his life — homeless and hunted, yearning for God's promise that He would return him to his country.

"The vision of a ladder with angels going up and down on it is unique in Biblical imagery, and so *Jacob's Dream* has aroused artists' imaginations for centuries."

It seems a particularly fitting subject for the cover of this *Acta*, because Professor Stork — like Jacob — escaped from his homeland. We, in America, are lucky that Professor Stork did not return to France, but stayed with us and became one of our greatest chemists and teachers.

Lab Notes

The Aldrich Sure/Seal™ system of packaging sensitive reagents is so effective that we wanted to use it on our own samples. We saved the bottles, obtained a set of teflon septa and steel crown caps, Aldrich Cat. Nos. Z10,215-6 and Z10,214-8, and then discovered that there was no way of applying a cap to a bottle without using a capping device, available, for example, from Sears. Since it was not immediately apparent in our laboratory that such devices are available, we'd like to share this knowledge with other chemists to facilitate their use of this excellent system.

Jeanne Hoftiezer Marvin J. Hoard
Warner Lambert Co.
Pharmaceutical Research Division
Ann Arbor, MI 48105

Editor's note:
Aldrich now offers the following capping devices:

)

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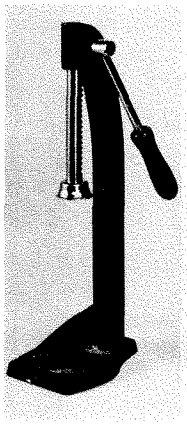
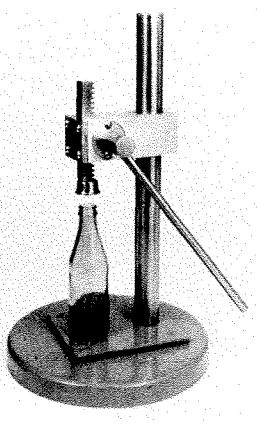


Z11,296-8



Z11,297-6

Ethyl acetimidate hydrochloride, prepared by the method of Dox (*Org. Syn. Col. Vol. 1*, p 5) is a solid mass which must be broken up for removal from the flask. Since it is hygroscopic and readily hydrolyzed, atmospheric moisture must be excluded. This could be accomplished conveniently by attaching a drying tube to the sidearm of the reaction flask and placing a glass rod or spatula in the flask with the handle protruding into the finger of a rubber glove secured around the neck of the flask with a rubber band. The rod or spatula may be manipulated almost as easily as if the glove were not present, and the arrangement, besides excluding moisture, protects the manipulator from HCl fumes.

This technique may be applied conveniently in many operations requiring manual stirring or crushing under anhydrous conditions. It is equally useful with multi-neck round-bottom flasks, and, by the attachment of an appropriate nitrogen inlet in place of the drying tube, may be applied in operations requiring an inert atmosphere.

John F. Hansen
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Normal, IL 61761

A recent *Lab Note* described a qualitative air-flow monitor for a fume hood (*Aldrichimica Acta* **1981**, *14*, 22). In our laboratory the same function has been fulfilled for many years by what we believe is a much simpler and more convenient device. Thus, a disposable paper wiper was clamped by its narrow side, with a metal clip, to the lower edge of the hood window. In an efficient hood, when the window is half-way down, the free end of the tissue is sucked inside reaching an almost horizontal position. Obviously, in the absence of airflow the tissue hangs in a vertical position.

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In trace-level analytical methods, it is necessary to minimize background levels. When quenching fluorinated acid anhydride derivatization reactions using aqueous phosphate buffer solutions, we have found that pre-extracting the buffer with a suitable immiscible solvent, *e.g.*, benzene, removes residues that could interfere with subsequent electron-capture gas-chromatographic assays. Also, the traces of benzene that remain in the buffer solution prevent the growth of mold. This treatment can also be applied to deionized water and NaOH solutions (inhibits carbonate formation) not only to minimize background, but to enhance stability on storage.

Charles Nony
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Jefferson, AR 72079

Preparation of dilute polymer solutions in 100-ml volumetric flasks is a routine task in our lab and wet resin invariably forms lumps, sometimes sticking to the wall of the flask.

While the use of a tiny magnetic stirring bar is common practice, we have found that its efficiency is notably increased when the flask is placed *on its side*. With the flask in this position the speed of mixing can be increased greatly without having the bar fly all over the flask. The vortex is deep and smooth. Finally, the liquid moves vigorously through the neck of the flask where stray resin often adheres.

When a large number of samples are involved this technique can speed up the entire process appreciably.

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Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Selections from the Bader Collection**. *We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Ayira Bader.

Last December Dr. John Frost at Harvard suggested that solid tetrabutylammonium fluoride trihydrate would be even more useful than the THF solution we have been selling, simply because a solid is so much more convenient to handle. The solution can corrode syringes, and sometimes solvents other than THF are needed. We had thought that the solution would be more convenient, but of course we are happy to offer the solid also.

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

Gilbert Stork
A Celebration of 35 Years in Research & Teaching

Frances Hoffman
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Thirty-five years spent in research and teaching is not a special milestone, but for friends of Gilbert Stork, it provides a welcome focus to think back on our happy associations with him as well as to look forward to the continued sharing in his creative life. One of Gilbert's most remarkable qualities is his willingness to share time and energy with those who seek his counsel. His involvement could range from an in-depth discussion of the enamine reaction with a starting graduate student to whether a distinguished colleague should accept a position as president of a major academic institution or an industrial concern. In every situation, not only does he project complete attention, he gives it. At the end of a discussion with Gilbert, one certainly knows a lot more about chemistry and life, and, equally important, one's self-confidence grows as a result of his generous encouragement and recognition. He always gives more than he receives. Although he is one of chemistry's superstars, he is a warm human being.

It is no surprise that the graduate students and postdoctoral research fellows who have been associated with Gilbert are among the most productive and influential academic and industrial chemists in the world today. The deep loyalty felt by this group prompted the creation of an informal organization known as "The Stork Group." In Gilbert's Cope Award address in 1980, he presented, as his last slide, a list of the members of the Stork Group who presently hold positions in academia throughout the world. The slide listed over 110 names, an impressive number — indeed a possible world record for a single research professor. The names on the slide belong to distinguished chemists and Gilbert must feel proud of this remarkable list — a superb testimony to him.

Gilbert Stork's birthday is celebrated by everyone throughout the world, for he was born on New Year's Eve in 1921 in Brussels, Belgium. Shortly afterward, his parents, Jacques and Simone Weil Stork, moved to Paris where he spent his childhood.

Certain of Gilbert's well recognized characteristics were evident in his youth. For example, his rigorous testing of reality began at an early age. One day his nurse took him to the park and carefully explained that he should under no circumstances go near a pond which was completely covered with water lilies. Since he found it difficult to believe that there could be any danger with what appeared to be a solid flower garden, he ran over to test the nurse's story. When he was pulled out of the pool with his felt hat still firmly fastened under his chin, he believed her; but the poor nurse lost her job.

Gilbert's qualities for leadership were evident quite early, for as a Boy Scout he was elected head of the choir in spite of being completely tone-deaf. This small group, under his command, was propelled to greater feats than music. With visions of Napoleon at Austerlitz, he conceived an adventure which would have taken his group into the woods of St. Cloud to emerge proudly from the wilderness by marching smartly down the main street in full view of the proud citizenry of Garches, a small suburb of Paris. Unfortunately, his leadership ran afoul with his lack of sense of direction and the group became completely lost in the woods. The adventure ended with a "Waterloo-like atmosphere" consisting of bedraggled Boy Scouts and hysterical parents.

His creative solutions to difficult problems also surfaced early. Gilbert's favorite occupation during his summers at Ostend was going for pony rides on the beach. Unfortunately, he often had to wait fifteen to twenty minutes because of the long lines. One weekend, Gilbert was left in the care of his favorite Uncle Alex. Gilbert explained his problem to his uncle and proposed that the way to solve it was to have a pony of his own. His uncle found this to be a good solution, but when the pony appeared on the grounds of his home, considerable rumblings from the neighbors mounted to a volcanic eruption when Gilbert's parents returned.

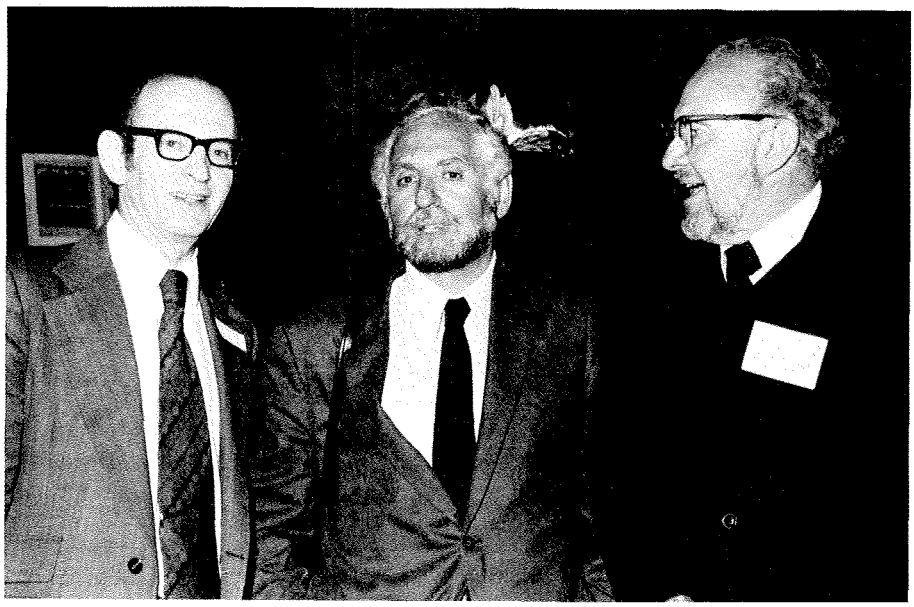
Gilbert's interest in chemistry was sparked by an excellent teacher at the Lycée Janson de Sailly (other graduates we know are Jacques Barzun and Giscard d'Estaing). By the time his family came to the United States at the beginning of World War II, his course had been set. But Gilbert was in

a new country, did not speak English and was familiar only with the French educational system where, if one wished to attend a university, one simply showed up on the first day of classes. Consequently, there was a slight detour in his path toward the study of chemistry. He decided that the best way to select a university was to read everything published by the Office of Higher Education available in the New York Public Library. After two weeks of study, he concluded that the University of North Carolina was the best school for chemistry so he immediately boarded a bus for Chapel Hill. Unfortunately, the University did not expect him, was on a quarter system and furthermore, it was very cold in North Carolina at that time. After a brief and unsatisfactory interview, he got back on the bus, headed further south to St. Petersburg, Florida, still speaking no English and still not realizing that one had to apply for admission to a university. The details were sorted out eventually, and he was admitted to the University of Florida at Gainesville, in those days an all-male school with an enrollment of 3,000 students.

During the six weeks Gilbert had to wait for the semester to start, he enrolled in English and Speech courses in St. Petersburg. It was in those classes that he met Winifred Stewart whom he later married. Winifred has been his life's partner and they now have four grown children. It is difficult to imagine that Gilbert could be the person he is today, had he not married Winifred.

Problems of American procedures continued to plague Gilbert at Gainesville. For example, he thought it unnecessary to attend chemistry laboratory classes if he knew the answers to the questions in the laboratory notebook. Instead, he spent his time in the chemistry library where he read an extraordinary paper by Paul Rabe published in the 1930's on the synthesis of dihydroquinine. Quinine had become an important national problem, and after reading Rabe's paper, Gilbert devised a synthesis of quinine. On the basis of this synthesis, he was given his own laboratory. The grumble on his non-attendance of laboratory courses lowered considerably. The starting material for his synthesis was bis(2-chloroethyl)methylamine which he prepared in large quantities. During the preparation, his left hand became a red, swollen glob with fingers no longer visible. Some time later, it was learned that this compound was a lethal nerve gas - we are lucky to have Gilbert to write about today. He graduated in two-and-a-half years from the University of Florida, in part, because of the many credits he received for having taken Greek in France, and obviously, because he was a rather special student.

His chemical interests had been aroused by pyridine and piperidine compounds, so Gilbert decided to do graduate work with either Professor Roger Adams at the University of Illinois or Professor S.L. McElvain at Wisconsin. Again, he boarded a bus, this time for Urbana, Illinois, but he was told that Professor Adams could not see him that day. Gilbert therefore continued his bus trip to Madison, Wisconsin. He saw Professor McElvain and gave him his projected synthesis of quinine to think about overnight. Professor McElvain was so impressed with the synthesis that Gilbert started working in the laboratory the following day. This work on *cis*-3,4-disubstituted piperidines inspired his life-long interest in the stereochemical control of reactions. In 1946 he devised a synthesis of 6-methoxy-α-tetralone, which he probably wishes he had patented, for it is still the method used to make starting material for aromatic steroids such as estrone.



The Three Musketeers.

It was at Wisconsin that Gilbert had his first experience with formal teaching. At first, he supported himself by analyzing for nitrogen and phosphorus in fertilizer but he was later promoted to the lofty position of teaching assistant. His section was composed of Army recruits who had the lowest grade-point averages in chemistry and were less than competent in the laboratory. Remembering how he had learned English by the use of flash cards, Gilbert devised a set of chemistry cards. He went to the barracks where his students copied them and studied from them. On the next examination, his group received the highest grades on the exam and, instead of being praised, Gilbert was accused of giving his students the answers to the questions on the examination. The *coup de grace* came, however, when some of his students climbed out a laboratory window to beat the lunch crowd at the student union. This heinous crime was discovered by the major domo of the laboratory and Gilbert was asked to give the students' names. He refused in the name of honor. The fact is that he had not remembered their names and did not know who had skipped out. As a result of this incident, he was summarily fired as a teaching assistant and was told that he was an incompetent teacher and should plan on doing something else with his life. The dark cloud had a silver lining, for the next day he received a university fellowship which permitted him to devote full time to research.

Two of his closest life-long friendships developed while he was at Wisconsin. Carl Djerassi was a fellow graduate student and William S. Johnson was a member of the staff. Gilbert's friendship with Carl was cemented by such episodes as sharing living quarters in Mexico City for three days during a complete shut-off of the city's water supply.

After receiving his degree from Wisconsin, he joined Lakeside Laboratories in Milwaukee as the only senior research chemist in the company. By day he worked as a medicinal chemist; by night he worked on his own ideas.

Bill Johnson was responsible for encouraging Gilbert to apply for an independent fellowship at Harvard. Part of the application was an original research proposal

on the synthesis of estrone. Professor Paul Bartlett, then Chairman of the Department, called and offered him an instructorship at Harvard. Gilbert promptly accepted.

Harvard was an incredibly exciting and fun place to be when Gilbert was there. Many still remember the colloquia he presented during those years, especially one on the stereochemistry of polyene cyclization in which he proposed what is now known as the "Stork-Eschenmoser Hypothesis." Notable achievements during the Harvard years include the total synthesis of cantharidin, a significant accomplishment since no entirely stereospecific synthesis of a natural product had yet been reported. The synthesis was completed at 4:00 a.m. on July 4, 1951 while Albert Burgstahler, the graduate student working on the problem, alternated between working-up the last step and singing Gregorian chants on the roof of the chemistry building. The determination of the structure of cedrene was also completed during the Harvard period. At the same time, Carl Djerassi arranged for Gilbert to be a consultant at Syntex. His contribution to the introduction of an 11-oxygen function into sterols unsubstituted in ring C led not only to an important industrial method, but also to Gilbert's and Carl's appearance in a *Life* magazine photograph.

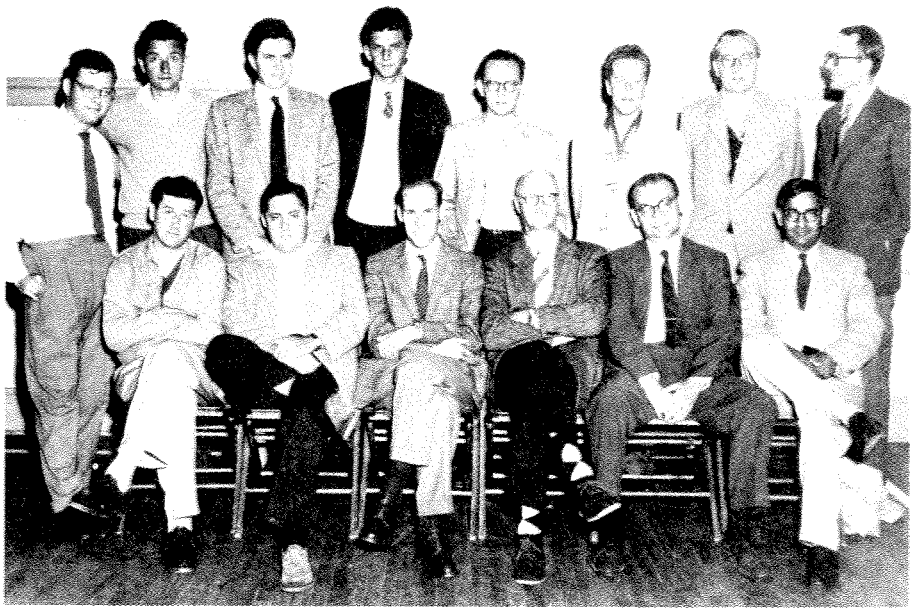
A novel aspect of chemistry.

At the urging of Professor Louis Hammett, Gilbert joined the Department of Chemistry of Columbia University in 1953 as an Associate Professor. Columbia was a far cry from what it is today, both physically and academically. I remember the alchemical nature of the laboratories, heightened by the dimness of the light, the effort it took to pull open the cast-iron laboratory drawers while trying desperately not to break the glass contents, the thick white line painted across the sixth-floor corridor which was meant to keep organic chemists from crossing into Professor Victor K. La Mer's territory, and Gilbert's office, which would have made a rather spacious closet. This closet had had a distinguished history since it had served as the office of Professor Arthur C. Cope and Professor William E. von Doering.

The inner sanctum at Columbia, 1953.

A distinguished event occurred there when Linus Pauling came to discuss the possibility of Gilbert's moving to Cal Tech. At that time, the Columbia Chemistry Department had a regular table at the Faculty Club and Gilbert remembers, with mischievous pleasure, that he took Pauling to lunch making certain that he and Pauling could be seen from the Chemistry table. The physical chemists, not knowing of the Cal Tech offer, could not understand why the great physical chemist, Pauling, would choose to discuss scientific matters with Gilbert rather than with them.

Gilbert has had a distinct elegance and style in all his endeavors — from playing table tennis to working in the laboratory where he resembles a Grand Prix racing driver. An example is the synthesis of bicyclo[4.1.0]octanone from *m*-hydroxybenzoic acid. It was calculated to take eight steps and Gilbert asserted that it would



How many of these "distinguished looking" chemists can you identify? See page 10.

take only two days to prepare. The rest of us roared with laughter at this unrealistic suggestion and the substantial bet of $100 was made that he could not do it in two days. The race began on Saturday morning and by 7:00 on Sunday evening, the compound was ready to be sent for analysis. I will always remember paying off part of the bet.

There is one aspect of Gilbert's life that has bewildered me. How can such an intelligent man insist on buying cars which, without fail, are incapacitated at least fifty percent of the time? One of these "treasures" was a sporty, white Simca with red, leather seats. After spending a good amount of money transporting it from France, a small fortune to adapt it to New Jersey requirements and further fortunes to keep it running, the engine blew up as he was driving to Yale to present the Treat B. Johnson lectures. With the usual Storkian luck, the car was on an incline which terminated in front of a gas station. Gilbert arranged for the car to be fixed and took a train to New Haven. He retrieved the car on the way back after contributing Yale's honorarium to the garage mechanic. While on the Merritt Parkway, the engine exploded again. This was the end of Gilbert's endurance and he decided to abandon the car then and there. While he was removing the license plates, a state trooper stopped to check on the strange situation. With characteristic aplomb, Gilbert struck a bargain — the state trooper could have the car in exchange for a ride to the nearest railway station. I have often wondered who made out best on that one.

Then, there was the elegant, British-racing-green Jaguar with its impeccable styling. It was nursed through frequent nervous breakdowns by a mechanic complete with French beret and eyes which projected megabucks. The demise of this thoroughbred was spectacular. One wet evening Gilbert was crossing the George Washington Bridge when the car lurched to a stop. Concurrently, a series of collisions occurred on the opposite side of the bridge. The bridge patrol was baffled by the number of simultaneous accidents until a wheel was spotted careening back and forth, between and over the cars like a volley ball. This was Gilbert's wheel which eventually plunged into the Hudson River. Shaken by these six accidents, Gilbert and the Jaguar parted company the next day.

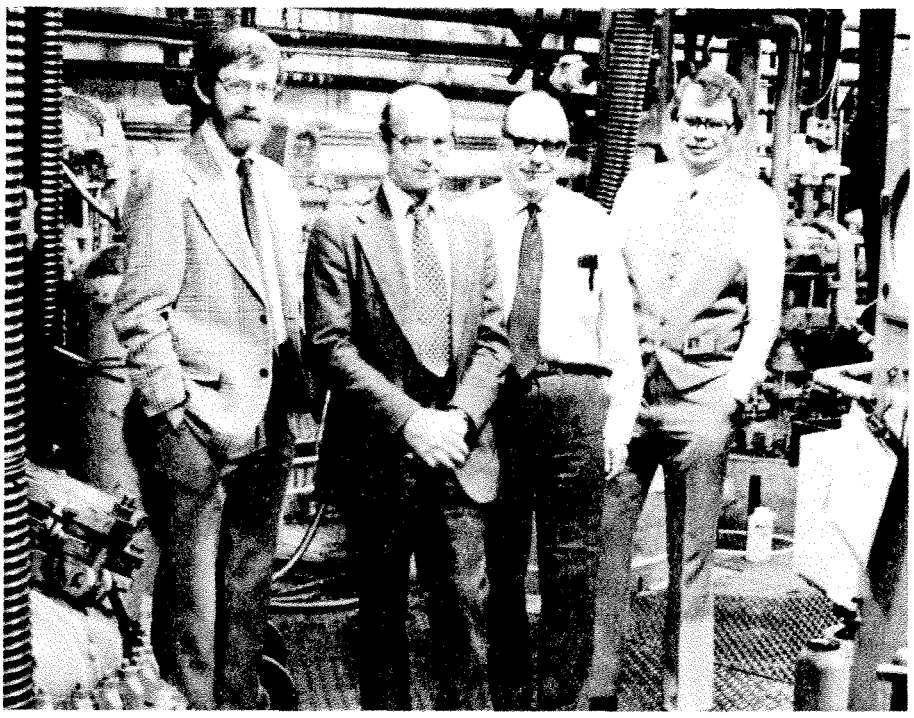
At present, his "true love" is a 1957, silver, two-seater Thunderbird. What marvelous shape! But don't step too firmly on the floorboards or your feet will hit the pavement.

An unpublished Stork original construction.

Stork has been the master architect of Columbia's organic group. The emergence of this faculty from relative obscurity in 1952 to its present position of eminence would not have taken place without his remarkable intuition and judgment. Because of his ability to recognize young people of outstanding talent and to persuade them to join Columbia, the building of the organic group was accomplished (with one exception) with appointments at the non-tenure level. Perhaps one of the most striking attributes of the Columbia organic faculty is its ability to combine a passionate involvement in chemistry with a relaxed and friendly attitude. Gilbert has had much to do with this feeling which extends to the graduate students of all the organic research groups.

The core of Gilbert Stork's life has been his creative research in organic chemistry. Since I do not have the expertise to give a summary of his glittering scientific achievements, I wish to express my thanks to those who have contributed the material for this section.

Stork's achievements fall into three "naturally occurring" areas: the total synthesis of complex natural products; the creation of new synthetic methods; and, finally, the investigation of reaction mech-



On the occasion of a reunion at Aldrich.

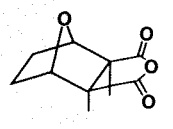
anisms. To separate synthesis from the creation of new reactions is totally arbitrary because of the strong interplay between these two areas. It has been Stork's philosophy that the purpose of a total synthesis must be more than a demonstration of the brilliance of the molecular architect in the clever orchestration of known synthetic methods. In his search for new reactions he has concentrated his efforts in seeking new and controlled methods of forming carbon-carbon bonds, the foundation of organic synthesis.

A. TOTAL SYNTHESIS

From the very first, Stork's syntheses were designed to be stereospecific. The importance of achieving a stereoselective synthesis had not been considered or recognized before Stork. This principle, now universally appreciated and used, was already a factor in his design of the synthesis of cincholoipon (1946), a *cis*-3,4-disubstituted piperidine related to hydroquinine; and in the totally stereospecific synthesis of cantharidin in 1951. It is of historical interest, with respect to the development of stereocontrolled syntheses, that his very first paper (1945), a communication (of which he is sole author), reported the synthesis of a 3,4-diaminofuran, the starting material for a planned stereospecific synthesis of biotin. The correct stereochemistry was to follow from catalytic hydrogenation of a 2,3,4-trisubstituted furan followed by further stereo-controlled transformation of oxabiotin to biotin itself.

Many of these total syntheses served as the focus for the development of new reactions. The stereospecific synthesis of the pentacyclic triterpene lupeol is a showcase of the power of the regiospecific formation and trapping of enolates. In this molecule a system of ten asymmetric centers was put in place with complete stereochemical control. Regiospecific formation and trapping of enolates was also used to simplify markedly the building of such diverse molecules as the prostaglandins, lycopodine and some of the steroids.

It would be surprising if enamines had not found an important use in a variety of these total syntheses: it will suffice to mention the construction of yohimbine and aspidospermine. Even seemingly small synthetic contributions have had considerable impact: the synthesis of 6-methoxy-α-tetralone, the previously mentioned starting material for the aromatic steroids, was based on Stork's discovery that the catalytic hydrogenation of substituted naphthalenes could be made to take place in the unsubstituted ring.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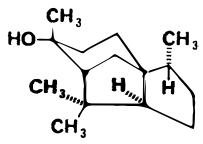
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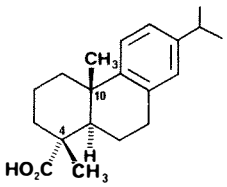
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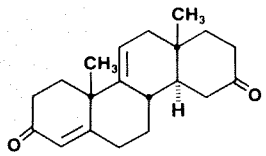
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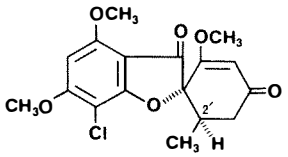
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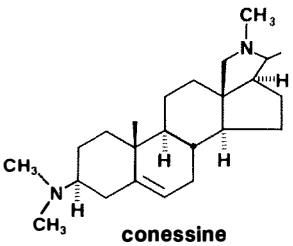
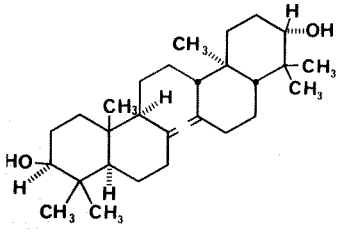
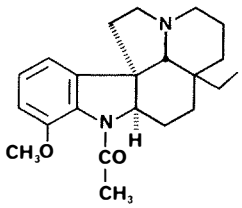
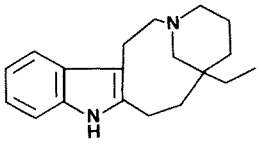
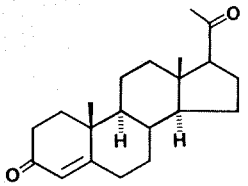
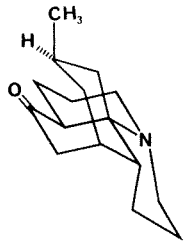

conessine


α-onocerin


aspidospermine


quebrachamine


progesterone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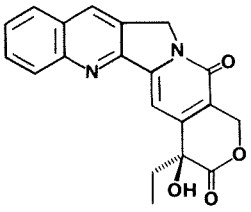
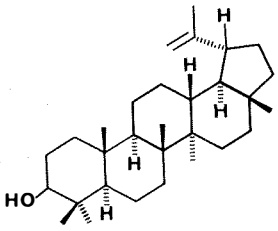
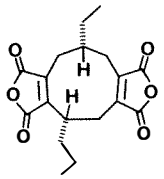
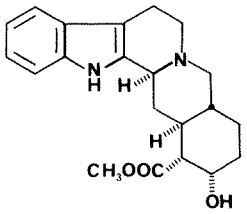
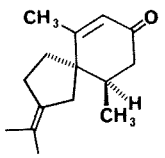
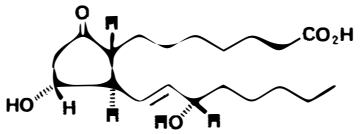

camptothecin

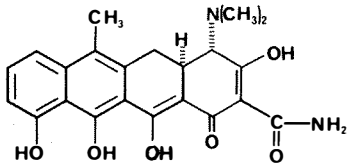

lupeol

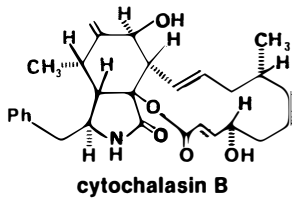

byssochlamic acid

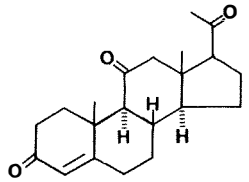

yohimbine

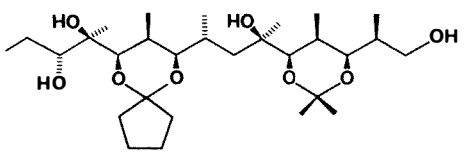

β-vetivone


prostaglandins


anhydrodeoxytetracycline


cytochalasin B


corticosteroids

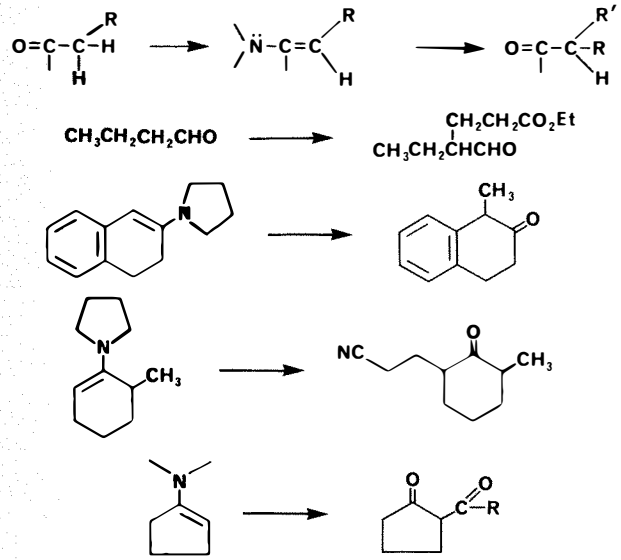

chiral erythronolide sequence

B. SELECTED SYNTHETIC METHODS

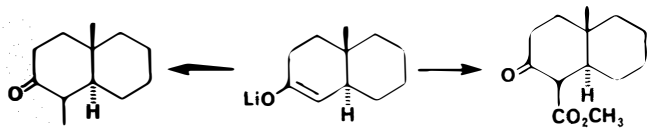
It is the creation of new synthetic methods rather than the area of total synthesis which Stork believes will be his most valuable contribution to organic chemistry. These methods can be divided conveniently into three parts.

The first, and perhaps foremost, concerns the regiospecific formation of carbon-carbon bonds *alpha* to a carbonyl group. To understand what impact this has had on modern chemistry, it must be recalled that, prior to this work, it was impossible to achieve such a fundamental operation as the alkylation of an *aldehyde* with an alkyl halide or with an electrophilic olefin, or the *regiospecific* (the word did not even exist) formation of a carbon-carbon bond on one or the other side of a ketone carbonyl. Gilbert Stork created many important synthetic transformations which contributed greatly to the explosive development of organic synthesis. His creative brilliance can be judged by the following work:

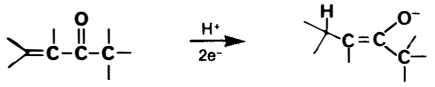
1) Formation of carbon-carbon bonds by the monoalkylation of ketones and aldehydes with alkyl halides, aldehydes, acylating agents and electrophilic olefins: "The Enamine Alkylation and Acylation" (1954, 1956, 1959, 1961, 1963).



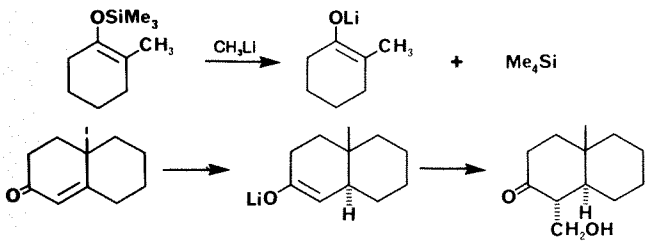
2) Demonstration that *lithium* enolates can be alkylated and carbonated without loss of any built-in regiospecificity (1961; 1965).



3) First and most widely used method for the specific formation of a ***lithium*** anion on either side of a ketone carbonyl (1961; 1965).

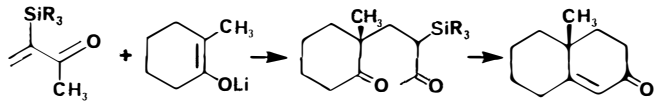


4) Generation of specific lithium enolates by cleavage of silyl enol ethers with lithium alkyls (1968).

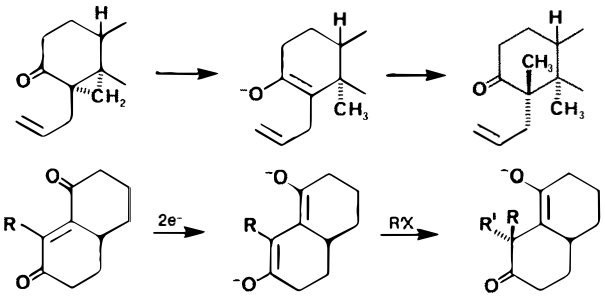


Two friends in search of a treasure on the sixth floor of Chandler.

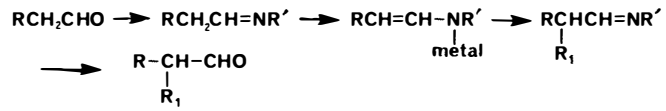
5) Extension of the regiospecific lithium enolate alkylation reaction to aldol condensations (1974), and to the first general solution to the problem of trapping these enolates with Michael acceptors (*via* α-silylated vinyl ketones, esters . . .) (1973, 1974).



6) Extension of the regiocontrolled enolate processes to cyclopropyl ketones (1971) and to enediones (1980).

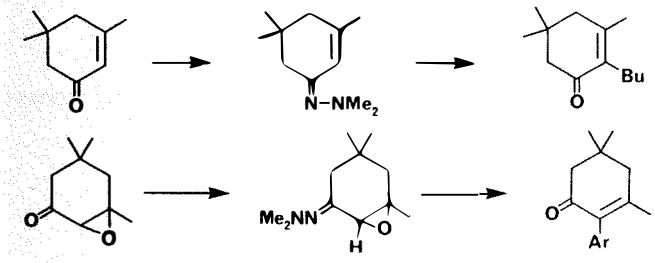


7) First demonstration that imines can be deprotonated to imine anions ("metalloenamines") thus leading to a general method for the monoalkylation of ketones (saturated and conjugated) and aldehydes with a wide variety of halides (1963).



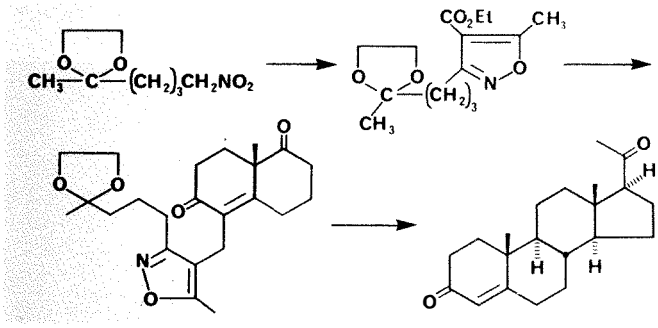
8) First extension of the process to *N,N*-dimethylhydrazones (1971). Further extension to regiospecific arylation *via* the *N,N*-dimethylhydrazones of epoxyketones (1978). These processes have seen numerous applications by many groups in recent years,

especially in the area of asymmetric induction using chiral imines and related substances.

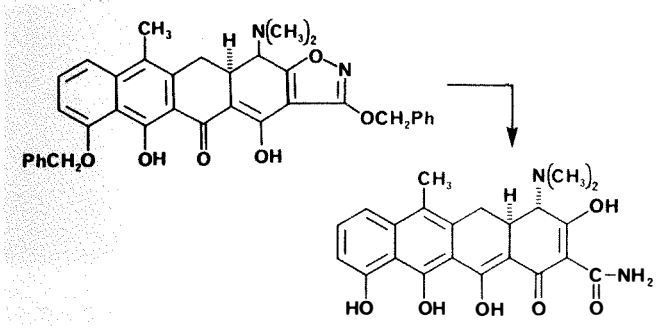


A variety of novel systems have been designed which allow the storage of reactive carbonyl systems in relatively stable forms until needed (*cf.* 9-13):

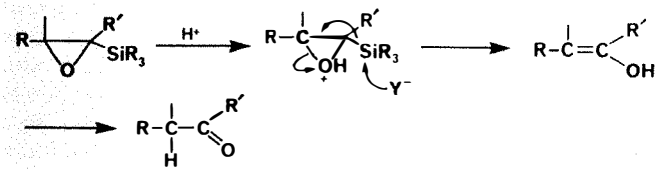
9) The isoxazole annelation, as illustrated in a total synthesis of progesterone (1967).



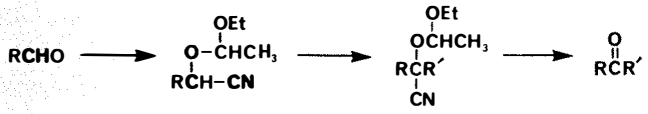
10) Another form of isoxazole annelation as exemplified by the construction of the most characteristic ring of the tetracyclines **(1979).**



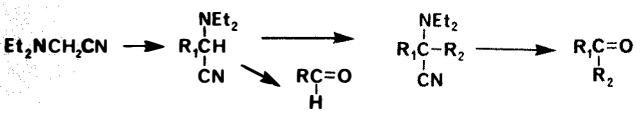
11) Introduction of the vinylsilane moiety as an enol (*i.e.*, latent ketone or aldehyde) precursor (1971).



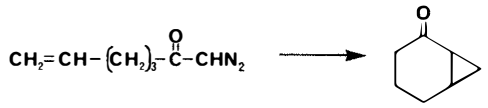
12) Protected cyanohydrins (1971, 1974, 1975) as acyl carbanion equivalents in the formation of cyclic and acyclic ketones.



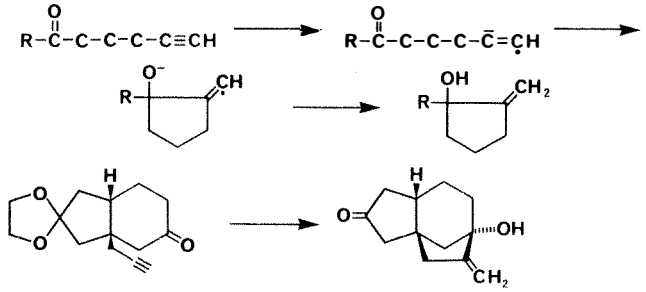
13) The α-dialkylaminoacetonitrile system as a carbonyl dianion equivalent (1978, 1979).



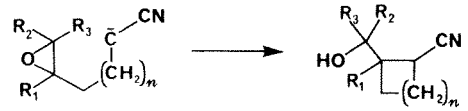
14) Cyclization of unsaturated α-diazoketones (1961).



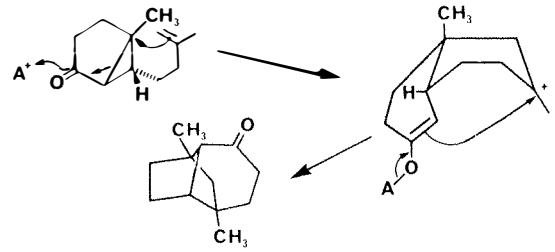
15) Reductive cyclization of unsaturated (*e.g.*, acetylenic) ketones (1965).



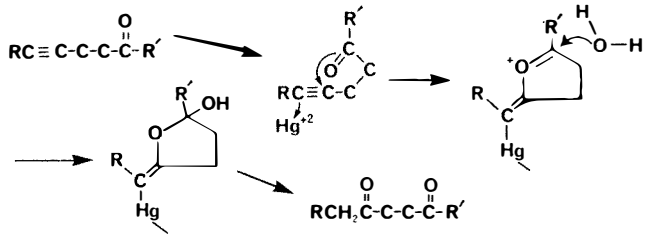
16) Formation of various-size rings by intramolecular opening of epoxynitriles. This leads, *inter alia,* to one of the few non-photochemical syntheses of functionally substituted cyclobutanes (1974).



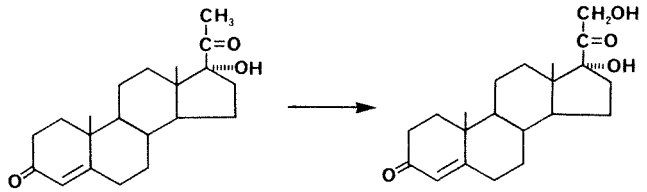
17) Generation of polycyclic and bridged systems from olefinic acylcyclopropanes (1969, 1971).



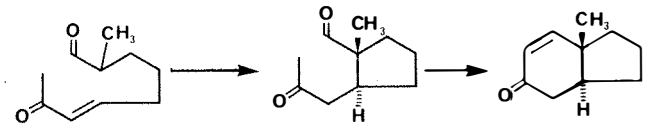
18) General synthesis of 1,4- and 1,5-diketones by carbonyl-assisted hydration of acetylenes (1964).



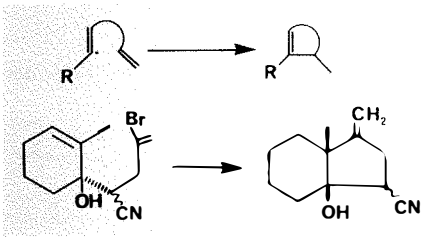
19) Direct C-21 hydroxylation in the construction of the dihydroxyacetone side chain of corticoids (1957).



20) Stereocontrol in vicinally substituted rings and *trans* hydrindanes by internal Michael addition (1982).



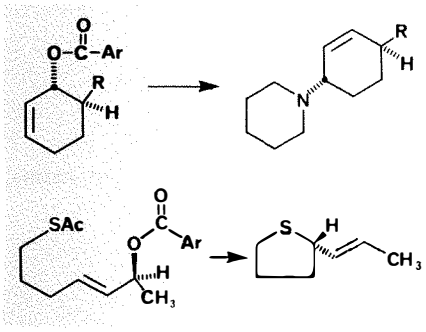
21) Functionally substituted rings *via* the cyclization of olefinic vinyl radicals (1982).



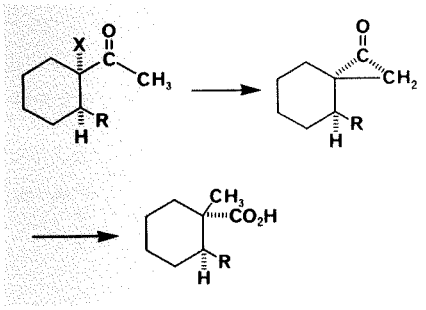
C. MECHANISTIC AND STEREOCHEMICAL STUDIES

These studies were conducted not so much for their own sake as for their potential in leading to controlled synthetic processes.

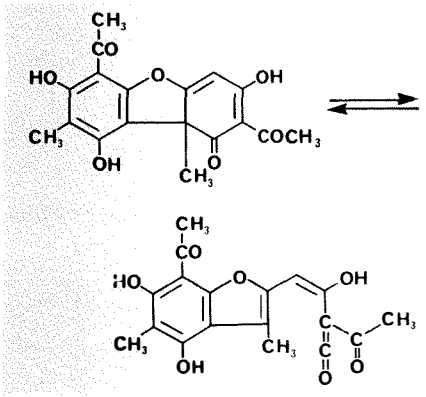
1) Investigation of the stereochemistry of the S_N2' reaction (1956, 1977).



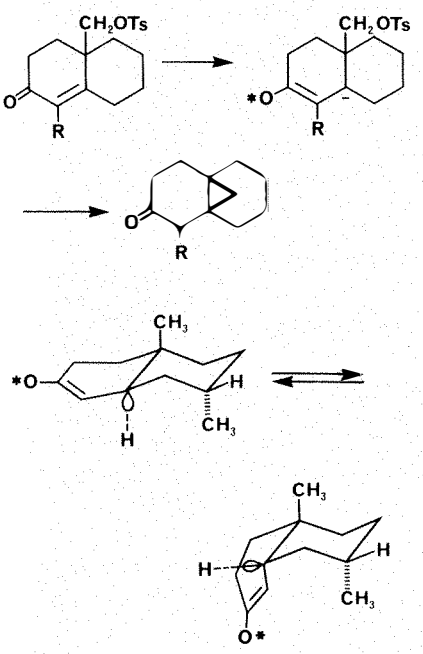
2) Stereochemistry of the Favorskii rearrangement of α-haloketones (1960).



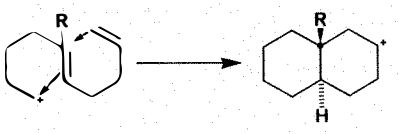
3) The mechanism of the racemization of usnic acid. This problem had long baffled the chemical community and was explained as a reversible electrocyclic reaction (1955).



4) Intermediates and stereochemistry in the metal-ammonia reduction of enones (1960, 1961, 1964).



5) We end by referring to the Stork-Eschenmoser hypothesis. The conclusion that the stereochemistry of a bicyclic cation made by a *concerted* reaction from an acyclic triene must be a *trans* bicyclic system was advanced in 1950. The possibility was then raised that this theoretical conclusion might well be the explanation of the *trans-anti-trans* arrangement so prevalent in polyterpenes and steroids. This has been amply confirmed, biogenetically as well as by the superb synthetic work of W. S. Johnson.



Not many people have had greater impact on modern organic chemistry than Gilbert Stork. He certainly has left his imprint on those who have had the good fortune to be associated with him.

HONORS AND AWARDS

Award in Pure Chemistry of the American Chemical Society (1957)
Baekeland Medal (1961)
D.Sc. (Hon.) Lawrence University (1961)
Elected to the National Academy of Sciences (1961)
Elected to the American Academy of Arts and Sciences (1962)
Harrison Howe Award (1962)
Edward Curtis Franklin Memorial Award, Stanford University (1966)
American Chemical Society Award for Creative Work in Synthetic Organic Chemistry (1967)
SOCMA Gold Medal (1973)
Roussel Prize, Paris (1978)
D.Sc., Honoris Causa, Université Pierre et Marie Curie of Paris, (1979)
Nichols Medal (1980)
Arthur C. Cope Award (1980)
Edgar Fahs Smith Award (1982)
Willard Gibbs Medal (1982)
National Academy of Sciences Award in Chemical Sciences (1982)

Note: The picture of the "distinguished looking" chemists was taken in the mid '50's at a conference in the Grand Manan Island, Nova Scotia. Back row, left to right: H. Conroy, K. Wiesner, E. Wasserman, Z. Valenta, G. Stork, P. Belleau, D.H.R. Barton, and B. Witkop. Front row: J. Fried, C. Djerassi, F. Anet, F. Toole, M. Kupchan, and H.G. Khorana.

About the Author

Frances Hoffman has been a friend of Gilbert Stork for over thirty years.

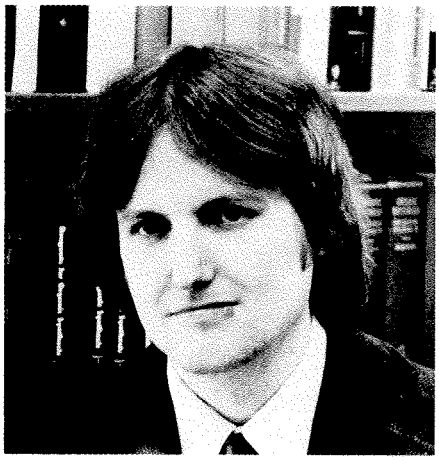
After graduating from Mount Holyoke College, she obtained a position with Carl Djerassi at Ciba. When he left to join Syntex in Mexico, she went to work with Gilbert in the Department of Chemistry at Harvard and in 1953 moved to Columbia's Department of Chemistry with the Stork group.

From 1954 to 1961 she was a member of Lewis H. Sarett's research department at Merck and Company where she did research in the field of steroid chemistry.

In 1961 she returned to the Department of Chemistry of Columbia University as Director of Chemical Laboratories. For the past twenty years she has contributed to the growth and development of that department. At present, she is deeply involved in the development of plans for a new chemistry building.

Recent Applications of Homogeneous Catalysis to Organic Synthesis

T. Howard Black
Aldrich Chemical Company



INTRODUCTION

Transition metal-assisted organic synthesis has enjoyed explosive growth and exploitation in the past decade.[1] One of the most exciting advances is the adaptation of stoichiometric homogeneous reactions to catalytic reactions, largely decreasing the amount of noble metal needed.

Nearly everyone is familiar with heterogeneous catalysis, usually as applied to hydrogenations. Actually, these catalysts can be used in the synthetic applications to be discussed, but are extremely inefficient compared to their solubilized counterparts. Homogeneous catalysis embodies several important advantages:

1) Each expensive metal atom is an "active site", as opposed to just those on a surface.
2) Each atom is in an identical environment, increasing reaction specificity.
3) Selectivity can be "fined-tuned" by the judicious choice of ligands, solvents, and other variables.
4) Heat is more efficiently dissipated, and reaction conditions are generally milder.
5) Mechanistic studies are easier, allowing better understanding and thus greater control of reactions.

The sheer vastness of this expanding field precludes in-depth treatment of any particular aspect in this survey. The aim is, rather, to provide the reader with an overview of the very diverse, useful, and intriguing reactions made possible by homogeneous catalysis. Specifically omitted are hydrogenation reactions[2] and those employing chiral ligands.[3]

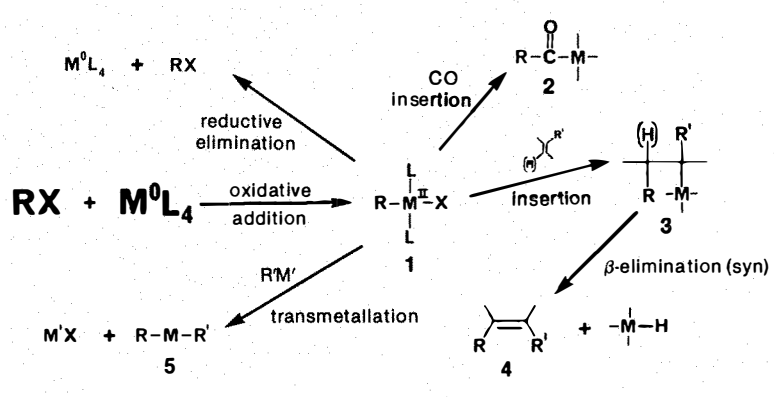
MECHANISTIC CONSIDERATIONS[4]

Transition metals undergo reaction pathways impossible for organic molecules, thus, complexation of a functional group to a metal usually drastically alters its normal chemistry. In order to aid in the planning and execution of a catalytic reaction, a short summary of pertinent organometallic reactions will be presented. In this review, the term "metal" (M) will always refer to a Group VIII metal.

Both σ- and π-organometallic complexes are involved in catalysis. σ-Complexes usually arise from the oxidative addition of a metal to an organic halide. Since the metal loses two electrons in the process, ligands which increase electron density facilitate the reaction while electron-withdrawing ligands impede it. Thus, phosphines (strong σ-donors) aid oxidative addition while carbonyls (strong π-acceptors) retard it.

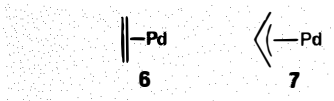
σ-Complexes (*e.g.*, **1**) undergo five major reactions, summarized in Scheme I. Reductive elimination is the reverse of oxidative addition, and often constitutes the last step of a catalytic reaction. Insertion of carbon monoxide affords a metallated acyl species (**2**), while alkenes insert to give complexes such as **3**. If a β-hydrogen is present, (*syn*) β-elimination of metal hydride yields an alkene, **4** (of course, this can also

Scheme I



occur in **1** if R contains a β-hydrogen). Finally, transmetallation with another organometallic species affords σ-complex **5**.

Electrophilic attack by metal on an alkene can result in the formation of either a π-olefin (**6**) or a π-allyl (**7**) complex. The most important consequence of such interaction is activation of the involved carbon atoms toward nucleophilic attack.



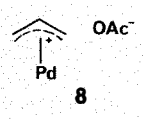
6 **7**

LIGAND ABBREVIATIONS

A great many ligands are employed in transition-metal chemistry. Throughout this survey standard abbreviations are employed: acac = acetylacetonate; DIPHOS = 1,2-bis(diphenylphosphino)ethane; dba = dibenzylideneacetone; COD = 1,5-cyclooctadiene; NBD = norbornadiene; dppf = 1,1′-bis(diphenylphosphino)ferrocene.

ALLYLIC ALKYLATION[1d,5,6]

The nucleophilic alkylation of allylic systems constitutes one of the most thoroughly studied aspects of transition-metal-catalyzed reactions. Basically, a metal (usually Pd) induces ionization of an allylic unit (often an acetate) which is then attacked by a nucleophile. Studies on the racemization of optically active allylic lactones implicate a symmetrical π-allylpalladium intermediate (*e.g.*, **8**),[7] although recent evidence[8] indicates that other species may be involved.

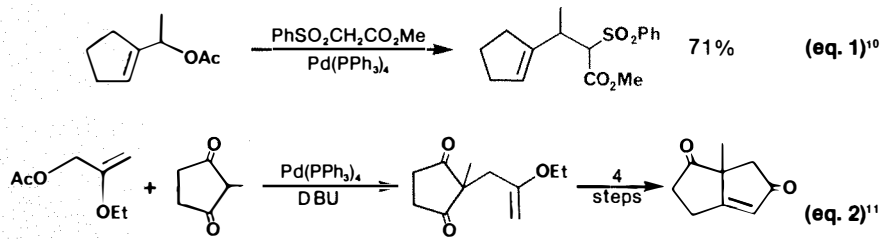


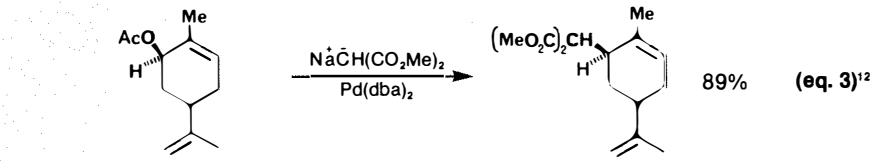
8

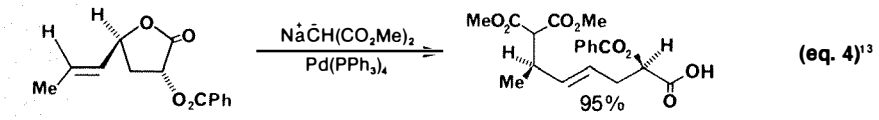
Many nucleophiles participate in this reaction. The regiochemical outcome is highly dependent upon the nature of the nucleophile, the allylic substituents, and the ligands on the metal.[9]

1,3-Diketones are favorite alkylating agents, although alkyl α-sulfonylacetates are often more synthetically useful due to the variety of possible further manipulations. The nucleophile can be used directly (eqs. 1,2) or is sometimes first deprotonated (eqs. 3,4). Since the leaving group departs and the nucleophile enters *trans* to the metal, retention of configuration is observed (eq. 3). Scheme II outlines a short synthesis of phoracantholide J,[14] in which the penultimate step involves an intramolecular alkylation. (±)-Recifeiolide has also been prepared *via* this approach.[15]

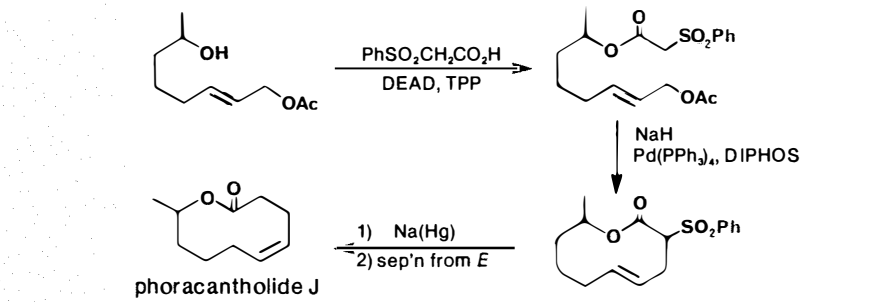
Other nucleophiles recently applied to this reaction include enamines (eq. 5), alcohols (eq. 6), and amines (eq. 7). The latter

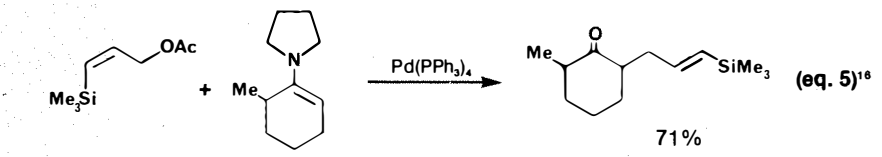


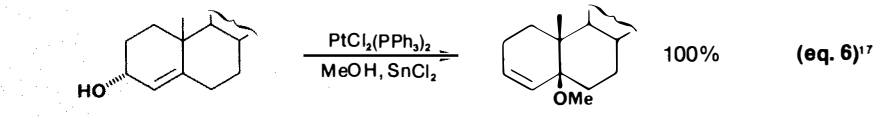


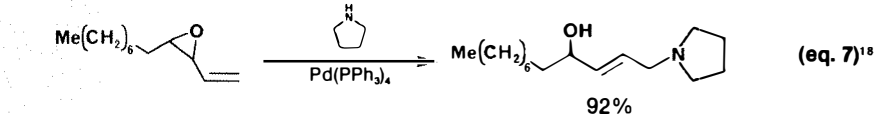


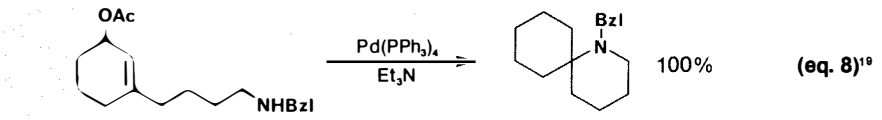
Scheme II

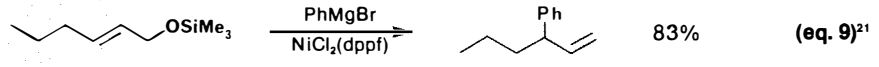


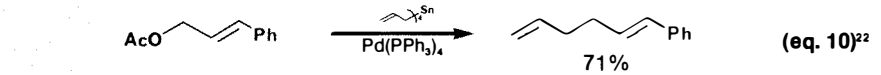












are particularly useful intramolecularly (eq. 8) and have enabled the facile construction of N-heterocycles (*e.g.*, isoquinuclidine).[20]

Organometallic species also serve well; compounds of magnesium (eq. 9), tin (eq. 10, or tin enolates[23]), zirconium,[24] aluminum,[25] and others have been employed successfully.

ALLYLIC TRANSPOSITIONS; REARRANGEMENTS

In the absence of added nucleophiles, allylic acetates can undergo 1,3-transposition, usually toward the less hindered allylic terminus. The *E* isomer generally predominates (eqs. 11 and 12). Since the acetate departs and enters *trans* to palladium (as noted previously), efficient transfer of chirality is possible (eq. 13).

A general furan synthesis involves rearrangement of an acetylated cyanohydrin followed by ester saponification, nitrile reduction, and acid-catalyzed cyclization (eq. 14).

Various Pd species also catalyze sigmatropic rearrangements, usually of the [3,3] variety involving heteroatoms. Of particular note is the propensity for S→N migration (eqs. 15 and 16). A potentially very useful reaction employs a Pd(0)-catalyzed allyl vinyl ether shift to construct prostaglandin precursors (eq. 17).

ISOMERIZATIONS

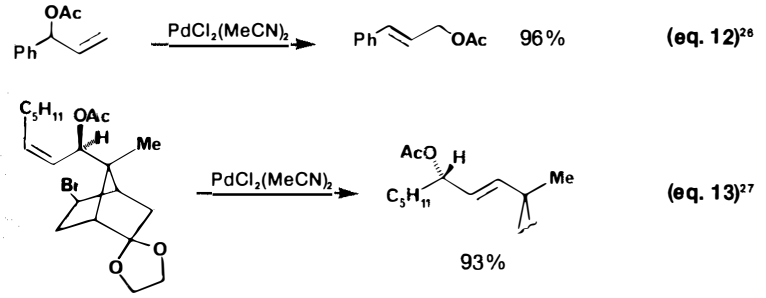
Although valence isomerizations have been observed (*e.g.*, eq. 18), positional isomerization of alkenes is most often the purpose of metal catalysis. Usually the thermodynamically more stable isomer is produced, as noted in a new synthesis of hydroquinones (eq. 19).

A useful facet of ruthenium catalysis is the tendency for isomerization of allyl to vinyl ethers, allowing the preparation of enol ethers from allylic alcohols (eq. 20). A short, general tetrahydrofurancarboxaldehyde synthesis exploits this phenomenon (Scheme III).[35]

Enol ethers also result from rearrangement of alkoxycyclopropanes (eq. 21).

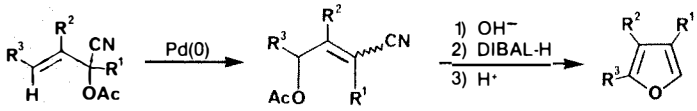
OLEFIN DIMERIZATIONS; ADDITIONS

Metal-catalyzed oligomerization of butadienes has been known for many years.[37] Often, dimerization of the olefin is followed by attack of a nucleophile, resulting in the net attachment of a 2,7-octadiene fragment (eq. 22). Additionally, methylenecyclopropane codimerizes with CO_2 or certain olefins to afford some interesting products; $Pd(dba)_2$ is used for these transformations (Scheme IV).

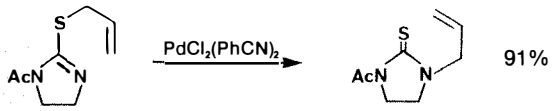


(eq. 12)[26]

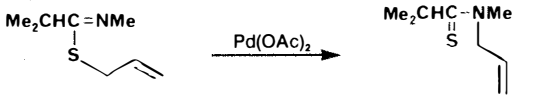
(eq. 13)[27]



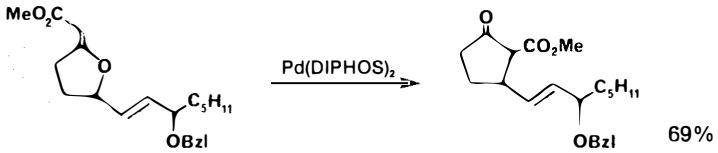
(eq. 14)[28]



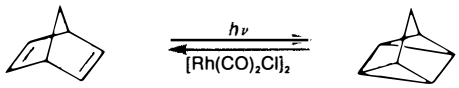
(eq. 15)[29]



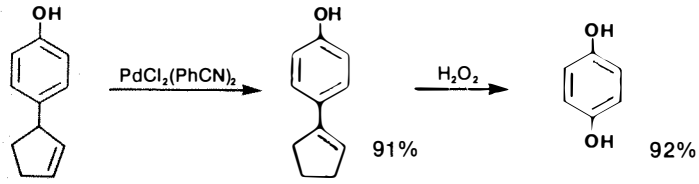
(eq. 16)[30]



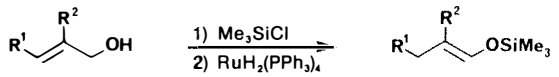
(eq. 17)[31]



(eq. 18)[32]



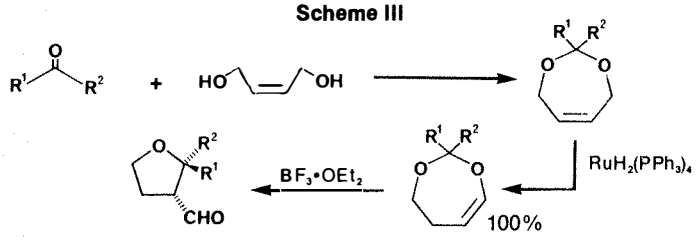
(eq. 19)[33]

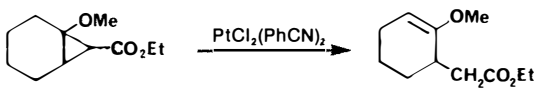


R¹,R² = H,Me — >90% (mainly *Z*)

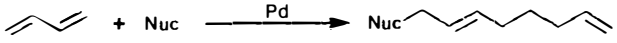
(eq. 20)[34]

Scheme III





(eq. 21)[36]



(eq. 22)

Nuc = NH_3[38]; HOAc[39]; acyloins[40]; acylamino ketones[41] (exclusive C-allylation)

Olefins also undergo electrophilic addition of halogenated compounds,[45] as seen in a novel, one-step γ-lactone synthesis (eq. 23). If the olefin possesses two allylic hydrogens, elimination to form 4-alkylidene-but-2-enolides is possible (eq. 24). The reaction also works well with silyl carboxylates.[47]

Trimethylenemethane, a Diels-Alder diene equivalent,[49] can be generated *in situ* to react with a variety of dienophiles in a unique three-carbon annulation technique (eq. 25).

CYCLIZATIONS

Many 1,5- and 1,6-dienes are cyclized in the presence of palladium. Although ring size can be governed by the oxidation state of the catalyst (eq. 26), five-membered rings usually are formed. Functionalized cyclopentenes[52] and γ-methylenebutyrolactones[53] have been constructed in this way.

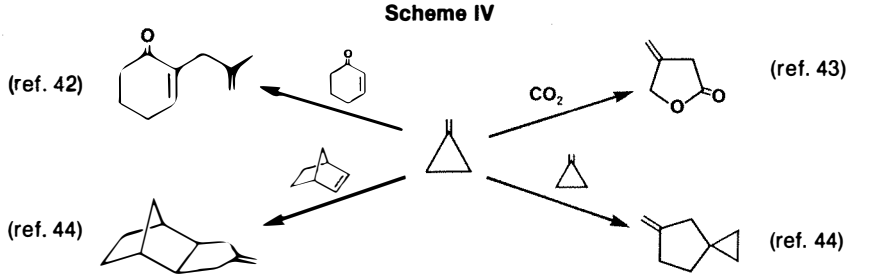
Miscellaneous cyclizations which have appeared recently include the formation of N-heterocycles from α,ω-diamines (related to the disproportionation of primary amines),[54] and the one-step synthesis of quinolines[55] and chromans[56] from monocyclic precursors.

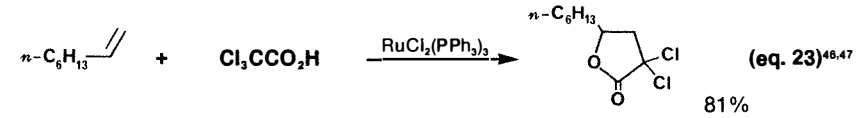
THE HECK REACTION[57]

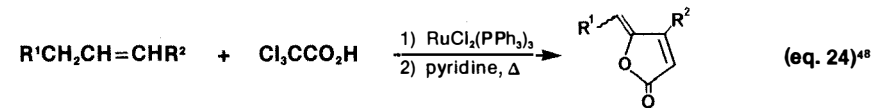
One of the most general and useful applications of homogeneous catalysis is the Heck reaction, in which organic halides are coupled with olefins under palladium catalysis (eq. 27). The reaction is remarkably selective, and almost any functional group can be present in either reactant. Generally, the halide prefers the less-substituted carbon of the olefin, whose stereochemistry is *retained* consistent with the *syn* addition of an RPdX species followed by *syn* β-elimination of palladium hydride. Typically, $Pd(OAc)_2$ is used in conjunction with tri-*o*-tolylphosphine; triethylamine is added to scavenge the HX produced. Scheme V outlines some representative examples with aromatic bromides.[57a,58] Note that allylic alcohols (or their trimethylsilyl ethers[59]) afford carbonyls; these arise from vinylic alcohols created in the elimination step. A recent synthesis of curcumone makes use of this transformation.[60]

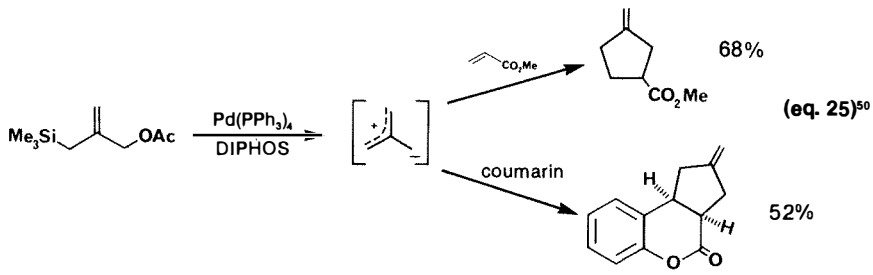
Aryl iodide-palladium complexes require no phosphines for stabilization; thus, selective reactions (*e.g.*, eq. 28) are possible. *o*-Iodoanilines are cyclized with dimethyl maleate to 2-quinolines in one step.[62] The aryl component can also be organometallic (*e.g.*, boron[63] and mercury[64]) or a diazonium salt.[65] Very recently, N-substituted anilines have been shown to be equally effective,[66] affording β-amino enones.

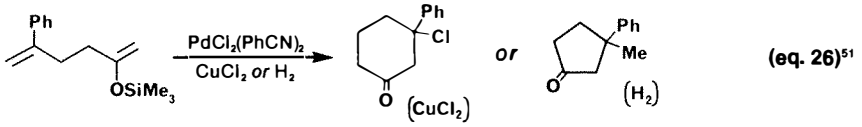
Scheme IV

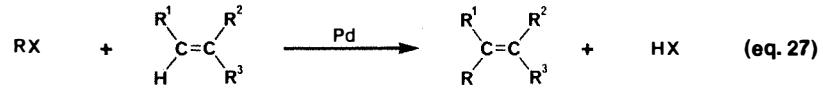






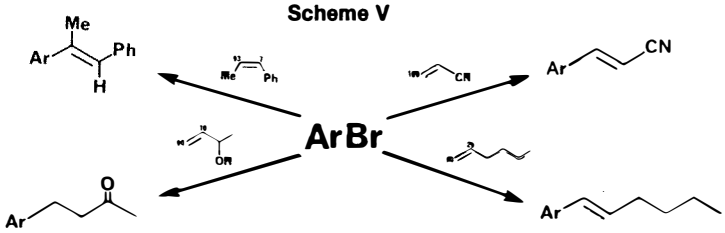




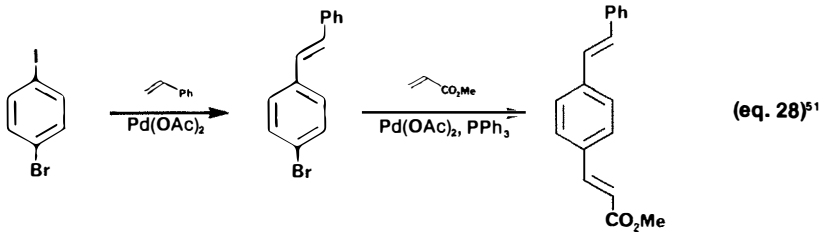


R = aryl; vinyl (no β-H)

Scheme V



(numbers refer to % attack at that position)



Vinyl halides also couple smoothly, exhibiting the same high stereoselectivity and generality, as indicated in eqs. 29 and 30.

CONJUGATE ADDITIONS

Many 1,4-additions are expedited by metal catalysis. The nucleophilic species is usually organometallic, although amines can often be effective.[69] Arylmercurials are commonly employed (eq. 31), although tin and many other metals also add; the choice is mainly one of synthetic convenience.

Alkenylzirconiums, easily prepared from alkynes, smoothly add to both enones and dienones (eq. 32) under Ni(0) catalysis; prostaglandin precursors have been prepared *via* this route.[73] Alkynylalanes also pose no problem (eq. 33).

COUPLING REACTIONS

A species such as **5** (Scheme I), formed *via* transmetallation, often undergoes reductive elimination to complete a very useful coupling reaction. A host of metals and halides can participate; as before, their choice is usually one of synthetic expediency. Thus, magnesium[76] (eq. 34) and boron[77] (eq. 35) compounds are commonly used, although tin,[79] silicon,[80] zirconium,[81] zinc,[82] aluminum,[83] lithium,[84] and others[85] are effective. The halides involved include aromatic, alkenyl, benzyl, propargyl, and allenyl derivatives. The major asset of this method is the retention of olefin geometry resulting in products of exceptional isomeric purity.

Acyl halides can couple with organometallics to afford ketones in high yield. Benzoyl chloride has been coupled with vinyl,[86] trimethylsilyl,[87] benzyl,[88] aryl,[86] and alkyl[89] groups.

Aryl and vinyl halides couple with acetylenes in the presence of Pd(II) and Cu(I) (eq. 36); even sensitive iodouracils are compatible.[91]

A related reaction allows the displacement of enol ethers by Grignard reagents to afford alkenes (eqs. 37 and 38). Interestingly, enol phosphates are displaced preferentially to enol thioethers.[94]

CARBONYLATION

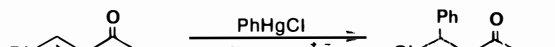
Metallated carbonyls (*e.g.*, **2**, Scheme I) which arise from CO insertion react with an array of nucleophiles to afford ketones. Scheme VI illustrates the diversity of this reaction. Intramolecular transformations include the synthesis of lactones from *o*-iodobenzyl alcohols,[97] indolines from *o*-allyl amines,[99] and berbines from papaverines.[100]

When carbonylated in the presence of carboxylates, aryldiazonium species afford mixed anhydrides which thermally

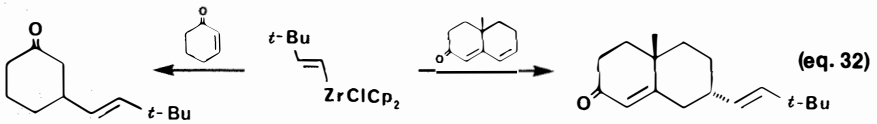
(eq. 29)[67]

(eq. 30)

X = CO_2Me[61b], $CH(OMe)_2$[68], CH_2-N-succinimide[61b]

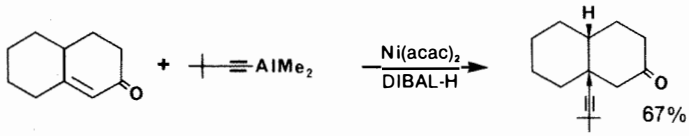


(eq. 31)[70]

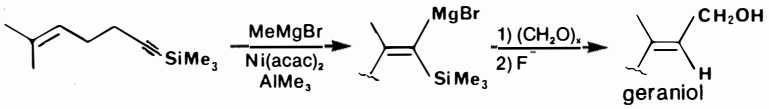


(eq. 32)

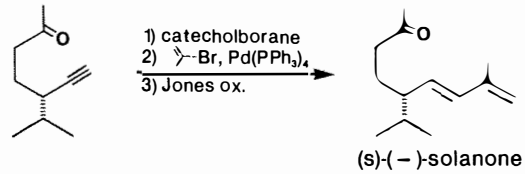
[71] [72]



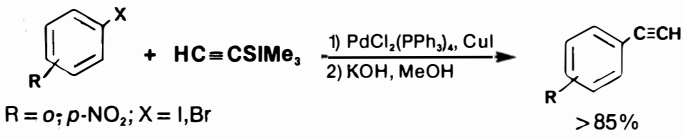
(eq. 33)[74]



(eq. 34)[75]

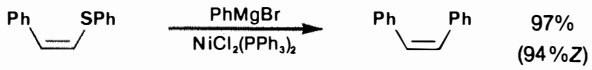


(eq. 35)[78]

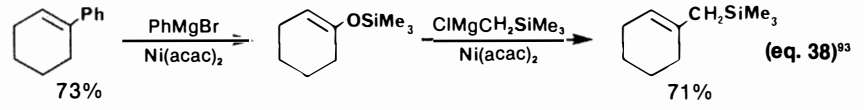


(eq. 36)[90]

R = *o*; *p*-NO_2; X = I,Br

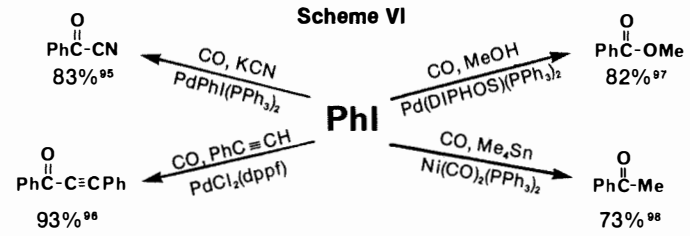


(eq. 37)[92]



(eq. 38)[93]

Scheme VI



(eq. 39)[101]

rearrange into symmetrical aryl anhydrides (eq. 39).

Alkenylboranes readily carbonylate in methanol to give α,β-unsaturated esters.[102] In the absence of added nucleophiles, alkenylmercury compounds dimerize onto CO to produce divinyl ketones (eq. 40), previously very difficult to prepare. Intramolecular alkene carbonylations have enabled the one-step construction of substituted 2(5*H*)-furanones[104] and α-methylene-γ-lactones.[105]

Small-ring heterocycles also insert CO, as in the preparation of α-phenylpropiolactone from styrene oxide[106] or of fused β-lactams from aziridines (eq. 41). The latter process would appear to have great potential for antibiotic synthesis.

In the presence of allyl or benzyl chlorides and a palladium catalyst, cyclic ethers open to form ω-chloro ethers (eq. 42).

DECARBOXYLATION

In the presence of base, allylic acetates can be oxidatively eliminated to afford olefins. The reaction is most facile when an aromatic (*e.g.*, eq. 43) or conjugated system results; the latter was exploited in a recent homoazulene synthesis.[110] α-Carboxylic acids depart as easily as protons (*e.g.*, eq. 44); a vitamin A precursor was constructed in this manner.[112]

Allyl esters decarboxylate in a new carbon-carbon bond-forming reaction (eq. 45) which also allows the preparation of ethers from carbonates.[114]

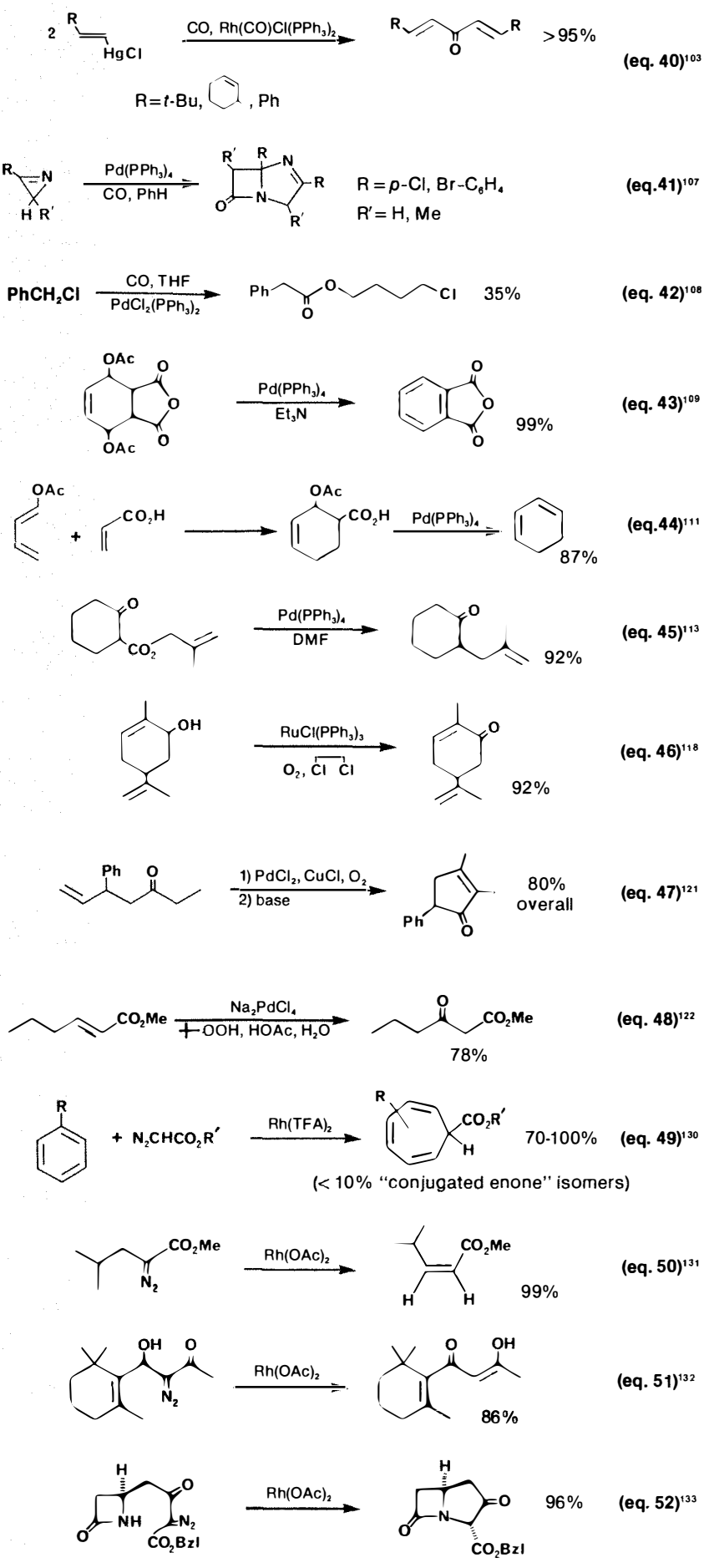
OXIDATIONS

Transition-metal catalysis enables mild, selective oxidations under neutral or basic conditions. Under Ru catalysis, alcohols are oxidized to either aldehydes or acids depending on the oxidant [PhIO *vs.* $PhI(OAc)_2$].[115] Other oxidants include CCl_4,[116] aryl bromides,[117] and oxygen (specific for allylic alcohols, eq. 46). Such methods offer an attractive alternative to the acidic chromium systems.

Terminal olefins are oxidized to methyl ketones under Pd(II) catalysis in an extension of the industrially important Wacker process.[119] The transformation involves a formal addition of H_2O; the added oxidant (even air![120]) serves to re-oxidize extruded Pd(0). Eq. 47 illustrates a two-step cyclopentenone synthesis based on this conversion, which has recently been shown to apply to enone systems (eq. 48).

REDUCTIONS

Metals catalyze many useful reductions besides hydrogenations. In the presence of Ru complexes, ketones are reduced to alcohols in high yield by formic acid[123] or



trialkoxysilanes.[124] Interestingly, the former effects the 1,4-reduction of chalcone to yield the saturated ketone.[125]

Aryl ketones are smoothly reduced to methylenes by a $NaBH_4/PdCl_2$ system in a mild, neutral alternative to Wolff-Kishner or Clemmensen chemistry.[126] Imines are easily reduced to amines by isopropanol under rhodium catalysis.[127] Finally, $Li(t\text{-}BuO)_3AlH$ can be replaced by $n\text{-}Bu_3SnH/Pd(0)$ for the preparation of aldehydes from acid chlorides.[128]

DIAZO CHEMISTRY

α-Diazoketones are valuable precursors to reactive carbenoid species.[129] Classically effected by copper, the decomposition of α-diazoketones proceeds in high yield in the presence of Rh(II) carboxylates (commonly acetate). Cycloheptatrienes can be prepared from substituted benzenes in high chemical and stereochemical yield using alkyl diazoacetates (eq. 49).

Z-α,β-Unsaturated esters result from treating α-diazoesters with $Rh(OAc)_2$ (eq. 50). The key step in an elegant synthesis of α-damascone involved the conversion shown in eq. 51; this mild oxidation avoids the partial retro-aldol reaction which always accompanies the acid treatment of α-diazo-β-hydroxy ketones.[132]

A recently developed intramolecular carbene addition allows easy entry into the 1-carbapenam ring system from diazo precursors (eq. 52). Yields are high, and rarely is more than one isomer produced. The generality of this method is indicated by its recent application in the syntheses of Antibiotic PS-5[134] and epithienamycin.[135]

CONCLUSION

Space limitations have prohibited the coverage of many useful miscellaneous reactions mediated by homogeneous catalysts, among them N-[136] and C-alkylations,[137] epoxide openings,[138] desulfurizations,[139] and Wittig-type olefinations.[140] It is hoped, however, that this short survey has instilled in the reader an appreciation of homogeneous catalysis as a rich and diverse methodology not to be neglected in planning a synthetic strategy. Many of the transformations covered in this review simply have no one-step synthetic alternative. Hopefully, broader awareness of this exciting field and its tremendous potential will result in greater application in organic synthesis.

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About the Author

After undergraduate work at Ohio Wesleyan University, Dr. Howard Black received the M.S. degree in 1977 from Central Michigan University, where he worked in the area of organic photochemistry. He obtained the Ph.D. degree in 1980 from Northwestern University, where he prepared and studied strained bicyclic alkenes under the direction of Professor James A. Marshall. Dr. Black is currently the Principal Investigator of Aldrich's preparative contract with the National Cancer Institute; his interests include the chemistry of strained and/or optically active hydrocarbons, synthetic applications of photochemistry, and homogeneous catalysis as applied to organic synthesis.

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Studies in Asymmetric Synthesis. The Development of Practical Chiral Enolate Synthons

A Compilation of References on R-Functional Acyl Anion Synthons, RCO^-

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About Our Cover:

The painting (oil on canvas, 44½ × 35½ inches) reproduced on our cover has been auctioned twice at Christie's — once in London in 1969, then believed to be by Barent Fabritius, and again last year in New York as by Jan Victors, both Rembrandt students. It is, in fact, an early work by one of Rembrandt's ablest students, Nicolaes Maes. Several drawings for it exist; the best known (Fig. 1) is in the Victoria and Albert Museum.

The very human face of the angel portrays one of Nicolaes Maes' friends, probably the artist Barent Fabritius, whose face we meet again on the far left of Maes' most famous work, *Jesus Blessing the Children* (Fig. 2, detail in Fig. 3), now in the National Gallery in London.

Fig. 1

Fig. 2

Fig. 3

Abraham's Sacrifice was a favorite subject among Dutch artists. To quote *The Bible Through Dutch Eyes*: "It is probably significant that, of all the many sacrifices detailed in the Five Books of Moses, this is the only one that specifically mentions the use of a knife — to heighten our revulsion toward human sacrifice. The word used here for knife in Hebrew, Maacheleth, occurs only here in the entire Five Books of Moses. Abraham's sacrifice is one of the most difficult events in the Bible to understand. Why did God demand that of Abraham? It cannot have been to show God how obedient Abraham was, because God knew what would happen. The only plausible explanation is that God wanted us to see that Abraham and Isaac were willing to do at God's command what must have been the most abhorrent act possible to them."

Maes must have been fascinated by this story which shows a trust in God we find hard to understand and could not match, and so he was challenged to portray this moment of complete obedience.

Are you interested in our Acta covers? *Selections from the Bader Collection*, with 30 duotone reproductions, many of previous Acta covers, and an introduction by Professor Wolfgang Stechow is available to all chemist art-lovers.

Also, many paintings reproduced on our Acta covers were shown at the Milwaukee Art Center in an exhibition, "The Bible Through Dutch Eyes," arranged by Dr. Bader in 1976. The fully illustrated catalog with 66 black-and-white and 4 full-color reproductions contains many art historical and Biblical comments.

Lab Notes

The attachment of rubber tubing to glassware (condensers, etc.) is often difficult unless grease, oil, silicone or water is used. Recently, I wished to attach an air condenser to the top of a micro Snyder column; a collar of 4-mm-i.d. latex tubing would not fit over the 8.5-mm-o.d. column and it was desirable not to use the usual lubricants since contamination and hydrous conditions had to be avoided.

When silanizing glassware to reduce adsorption of a diamine, the glassware becomes "slippery". This phenomenon was used to facilitate attachment of the above latex tubing. The glassware was wiped with or dipped into the silanization reagent, dichlorodimethylsilane (99%, Aldrich D6,082-6), and air-dried.

Brian L. Worobey
Sir Frederick Banting Research Centre
Tunney's Pasture
Ottawa, Ontario K1A 0L2

To facilitate manipulations in a controlled-atmosphere bag, the gloves can be replaced by a pair of "rubber" gloves. These are easily connected to the arm openings with 4-in. embroidery hoops.

I have used Playtex gloves for several years, but use of your Viton gloves would allow safe handling of toxic materials which readily penetrate other gloves.

Robert Gotts
Research Laboratory
Muskatatuck State Hospital
and Training Center
Butlerville, IN 47223

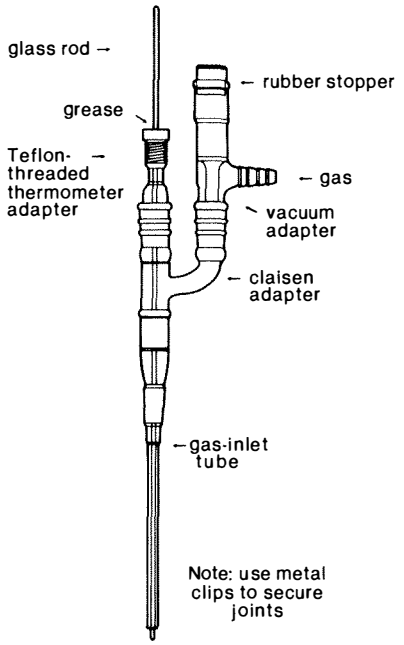
Editor's note: Aldrich now offers a gloveless AtmosBag™ which is provided with two glove rings (3½-in. diam., 1½in. wide) made of high-density polyethylene to which desired gloves can be taped.

™Trademark of Aldrich Chemical Company, Inc.

We have found a simple and inexpensive solution to the problem of large graduated cylinders with broken bases. Simply place the broken cylinder in a shallow dish made from the bottom of a plastic bottle (bleach bottles work well) and fill with clear casting resin. Upon hardening, the cylinder is equipped with a broader, more stable, shatterproof base. Careless handling of certain solvents may shorten the life of the base, but we have used this method to salvage 1- to 4-liter cylinders satisfactorily for several years.

Roger Nash and JoAnn Garner
Crown City Plating Co.
4350 Temple City Blvd.
El Monte, CA 91731

Often during reactions involving gas addition, the formation of solids causes the gas inlet tube to become plugged. It is a nuisance to have to shut off the gas and remove the tube to unplug it, especially when working with toxic or corrosive gases. Aggravation can be avoided by using the following setup which consists of common glassware.



By using the glass rod as a plunger, solids in the inlet tube can be dislodged without interrupting the gas addition. Not only is this method convenient, it is safe since the rubber-stoppered neck will serve as a pressure-relief outlet should the tube become plugged.

Jeff Reimer
Aldrich Chemical Co.

We purchase 95% and absolute ethanol in unmarked gallon bottles, which are distinguished only by the labels on the boxes in which they arrive. Occasionally someone will remove a bottle from the box without labeling it, causing a potentially time-consuming identity problem. A quick way to distinguish 95% ethanol from absolute or denatured ethanol is to mix one part (by volume) of the alcohol with two parts of petroleum ether; 95% ethanol forms a separate layer while the other alcohols are miscible.

John W. Lehman
Assoc. Professor of Chemistry
Lake Superior State College
Sault Ste. Marie, MI 49783

Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Selections from the Bader Collection** *(see "About Our Cover"). We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Ofira Bader.

Recently a young chemist in San Francisco, Steven Gill, interested and very knowledgeable in chemiluminescence, expressed his surprise that we could offer TKDE so inexpensively. He inquired whether we might also be able to offer 6,13-pentacenequinone — the bis(phenylethynyl)pentacene made from it would be an interesting red fluorescer.

We do not know much about chemiluminescence but offer hundreds of quinones (mainly through our ABC Library of Rare Chemicals) and many intermediates for chemiluminescents (such as phenylacetylene). So we made the pentacenequinone.

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

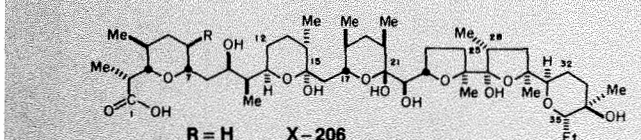
Studies in Asymmetric Synthesis. The Development of Practical Chiral Enolate Synthons.[1]

David A. Evans
Laboratories of Chemistry
California Institute of Technology
Pasadena, California 91125

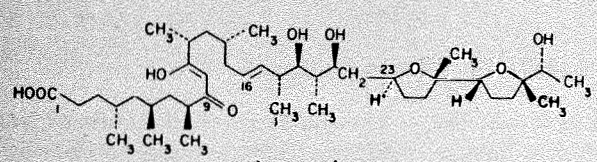
During the last decade, impressive progress has been made by organic chemists in further advancing the science of chemical synthesis. Within this discipline, one of the major ongoing objectives has been associated with the discovery and development of highly stereoselective bond construction reactions. With the recognition of macrolide and polyether antibiotics as potentially viable targets for total synthesis came the realization that "state-of-the-art" reaction methodology left much to be desired when applied to these architecturally complex molecules. One need only survey the stereochemical complexity of the ionophores, such as ionomycin (14 asymmetric centers) and alborixin (23 asymmetric centers), or the macrocyclic antibiotics, such as erythronolide or tylosin, to realize that highly stereoselective chemical reactions are an absolute necessity for such synthesis ventures (Scheme I). By inspection, one can readily perceive an acyclic carbon backbone in each of the illustrated target molecules which contains a center of asymmetry at nearly every carbon. Conventional wisdom has dictated that such acyclic stereochemical exercises may be addressed by interlocking sets of asymmetric centers

Professor David A. Evans (right) receiving the A.C.S. Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich, from Dr. Irwin Klundt, vice-president of Aldrich.

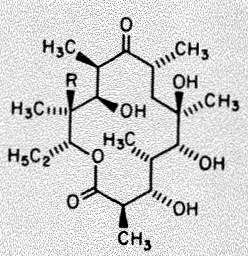
Scheme I



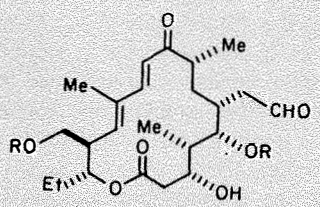
R = H X-206
R = Me Alborixin



Ionomycin



R = OH, Erythronolide A
R = H, Erythronolide B

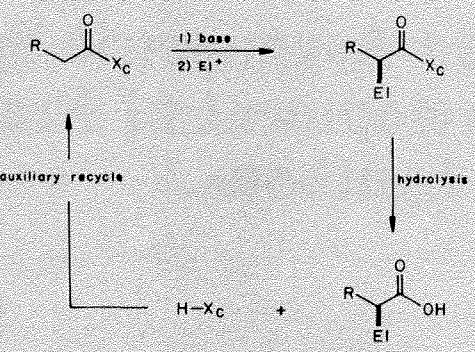


Tylosin

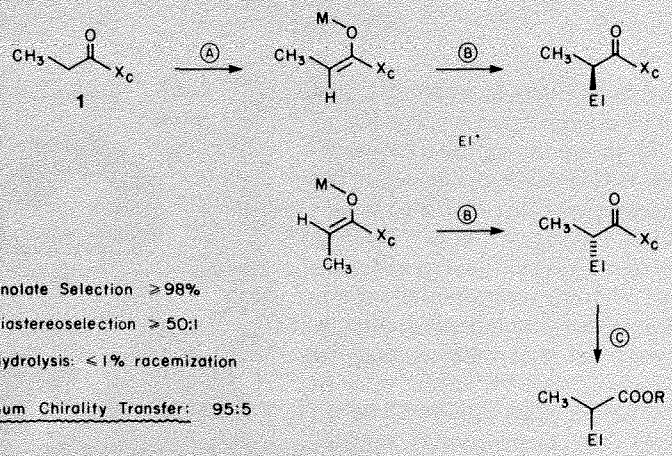
via the agency of temporarily formed rings wherein remote asymmetric induction from one center to another may be achieved in a predictable fashion with the aid of ring conformational analysis. Two elegant syntheses of erythromycin employing this "cycle strategy" for chirality transfer have been reported in recent years.[2,3]

Our own approach to the architectural problems presented by these classes of molecules has been to focus on the development of efficient asymmetric C—C bond constructions which are relevant to the synthesis of polyketide-derived natural products. Our first objectives in this area have been directed toward the development of chiral enolate-derived reactions such as alkylations, aldol additions and acylations wherein the chiral auxiliary (X_C) is both readily obtained and easily recoverable after the desired bond construction has been achieved (Scheme II). The major obstacles presented by this overall objective are threefold in nature (Scheme III): Given the carbonyl derivative **1**, the chiral auxiliary X_C must provide a strong bias for a highly selective enolization process (A); it must also provide a strong topological bias for enolate diastereoface selection in the bond construction (B); and finally its nondestructive removal (C) must be carried out with minimal racemization under mild conditions. For the reasons outlined in a previous review, we have chosen to develop chiral amide and imide enolates.[4] Several important aspects associated with these systems are illustrated below. With respect to the question of enolization stereoselectivity, we reasoned that *Z*-enolates should be strongly preferred if one considers transition state allylic strain conformational control elements (Scheme IV). This same conformational control element in the enolization process also assumes an important role in preventing product racemization (*via* enolization) in the bond-construction process. This important point will become strikingly evident later in this discussion (*vide infra*). Given the assumption that *Z*-enolates will be produced during the enolization process, the derived chiral amide enolates (Scheme V) require an additional organizational feature which locks the chiral auxiliary, X_C, in either the W- or U-conformation to ensure a pronounced enolate diastereofacial bias during the bond construction (Scheme V). Early in our studies, chiral amide enolates possessing fixed chirality disposition in both the W- and U-geometries were explored. The prolinol-derived amide enolates **2** and the imide enolates **3** developed in this laboratory have both proven to be exceptionally versatile chiral nucleophiles. In numerous instances, the two systems have been quite complementary in nature. The general utility of these systems in both alkylation and aldol addition reactions becomes apparent from the following data.

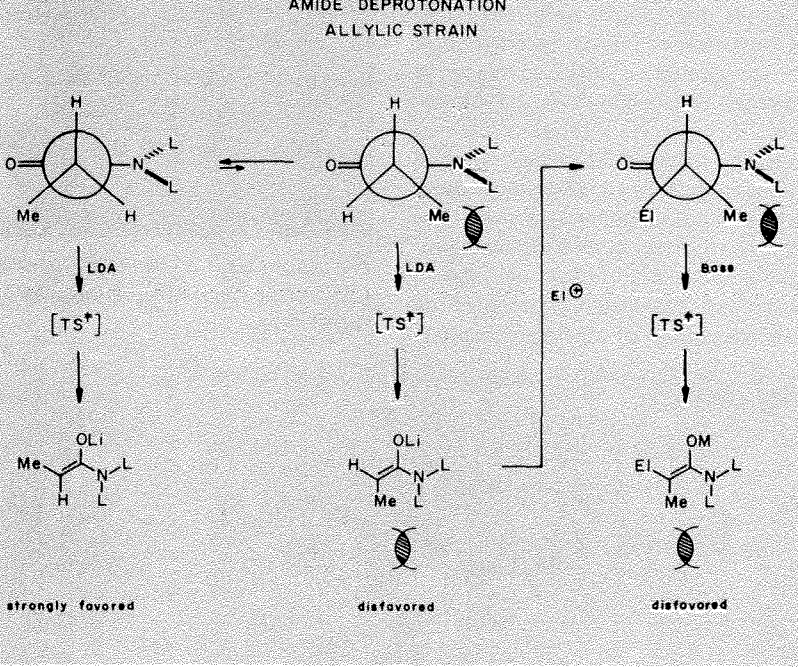
Scheme II



Scheme III

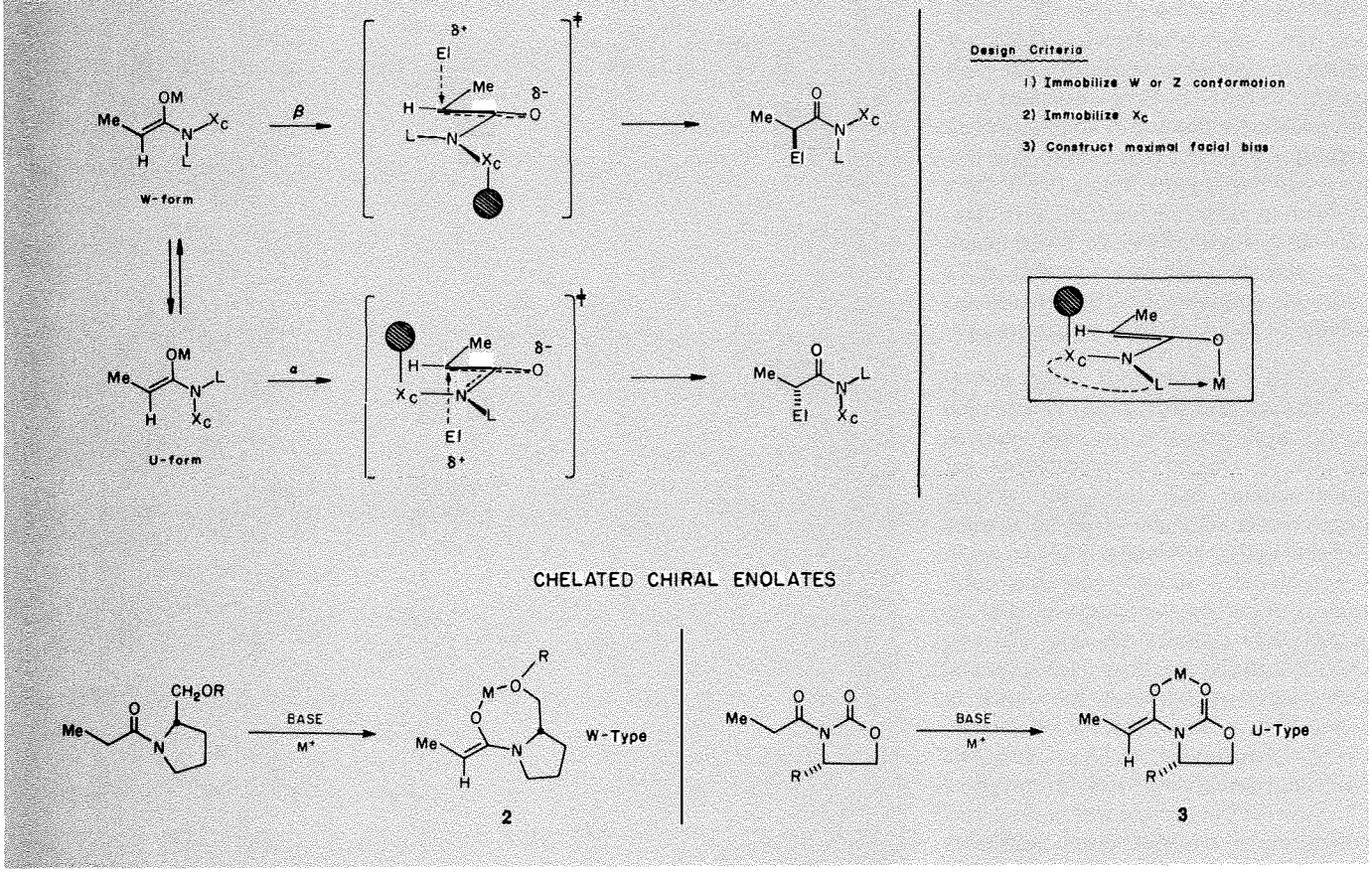


Scheme IV

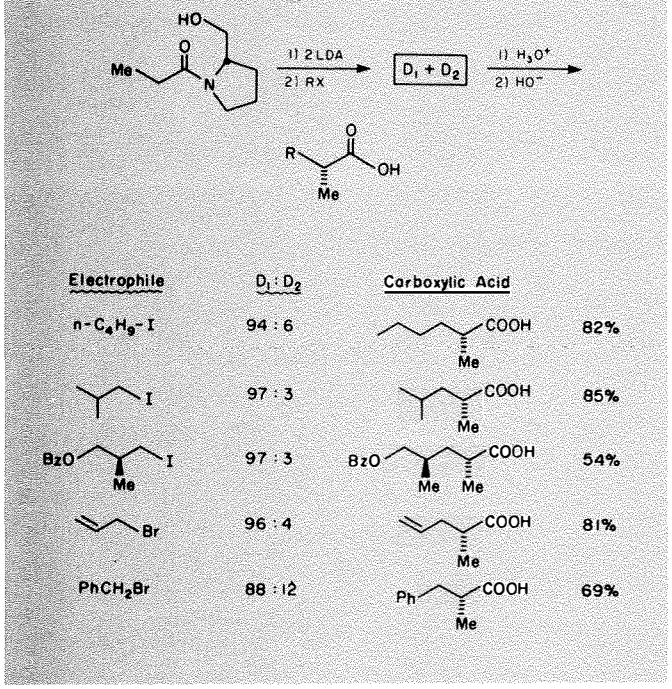


The alkylation studies summarized in Scheme VI for the highly nucleophilic prolinol amide enolate **2** lead to the conclusion that excellent si-face enolate diastereoface

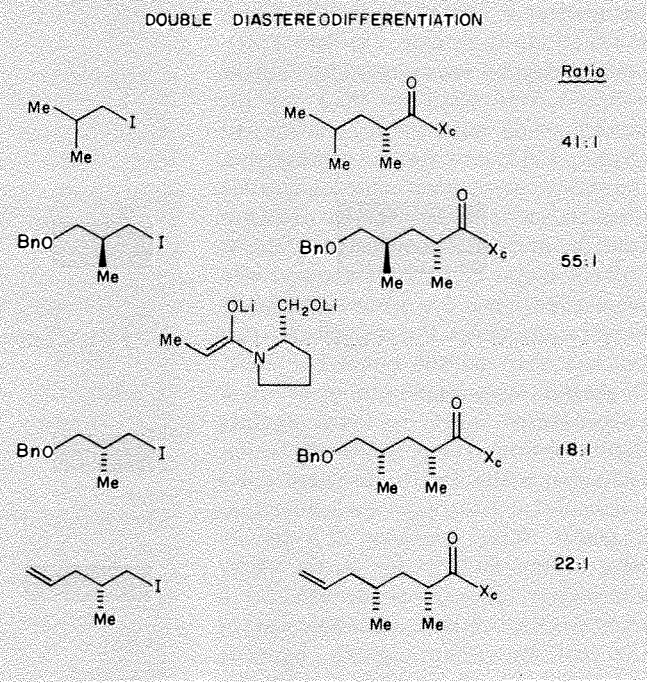
Scheme V



Scheme VI



Scheme VII



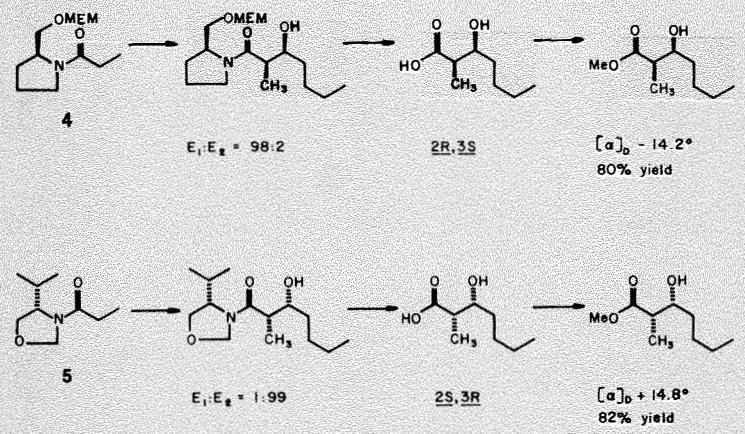
selection is observed for a range of alkyl halides.[5] We have also studied the influence of chirality in the alkylating agent with this enolate (Scheme VII). Under individually optimized reaction conditions, the illustrated chiral alkyl iodides were found to exhibit alkylation diastereoselection ranging from 18 to 55:1.[6]

Not surprisingly, the aldol addition reactions of the lithium enolates derived from these systems proved to be unsatisfactory; however, the derived zirconium enolates in these and related systems have proven to be exceptional.[7,8] Several examples which illustrate the utility of the zirconium metal center in providing stereoregulation in amide enolate aldol additions are illustrated in Scheme VIII. The amides

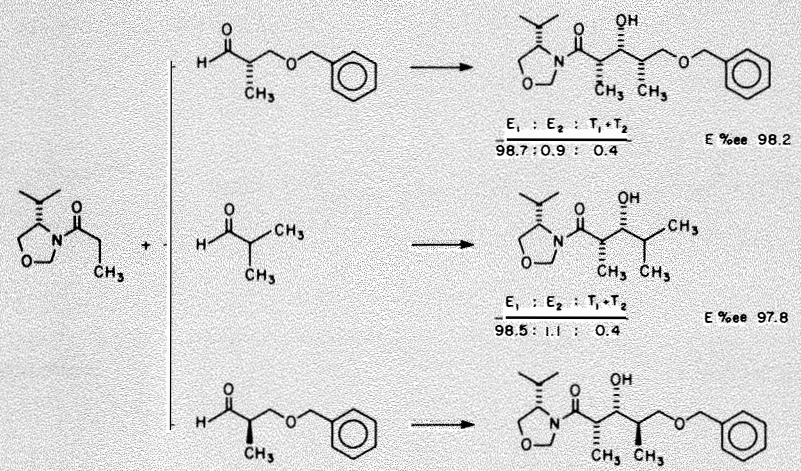
4 and **5**, each of which is readily derived from *S*-proline and *S*-valine respectively, exhibit good *erythro* diastereoface selection with a range of aldehydes. The major limitation that we have noted with these systems to date has been associated with the acidic conditions that are required to hydrolyze these chiral amides to their derived carboxylic acids. While this is not a problem in simple systems, in more complex cases where acid-labile functionality (*e.g.*, protecting groups) is present, these hydrolytic conditions have proven to greatly limit the utility of these enolate systems.

Due to the limitations noted above, several years ago we turned our attention to the exploration of the imide-derived enolates **3**. Our initial expectations for these systems were that good enolate diastereoface selection would be possible and that the derived imides might be readily hydrolyzed or reduced under mild conditions required for the construction of architecturally complex systems. The two chiral 2-oxazolidones chosen for study and their respective syntheses are shown in Scheme IX. As illustrated, the *S*-valine-derived heterocycle **6** (X_V) and the 1*S*,2*R*-norephedrine-derived heterocycle **7** (X_N) are readily prepared from inexpensive commercially available chiral precursors whose optical purities exceed 99%. The preparation of the derived imides and their respective alkylation reactions are summarized in Schemes X and XI.[9] As is evident from these data, excellent diastereofaceselection was observed for both the valine-derived auxiliary (X_V) and the corresponding norephedrine counterpart (X_N). In full accord with our expectations, the sense of asymmetric induction noted in these alkylation studies was that predicted from the chelated *Z*-enolate **3** (*c.f.* Scheme V). The major limitation associated with these imides is that they are not particularly potent nucleophiles. For example, no reaction was observed with isobutyl bromide. In general, these reactions must be run at temperatures $\leq 0°C$ to avoid enolate decomposition. The counterpoint to this restriction is the superb alkylation selectivity noted with these systems in numerous instances. When questions of reactivity have become an issue for us, the highly nucleophilic prolinol amide enolates **2** (Schemes VI, VII) serve admirably. One of the real, but unanticipated, benefits associated with the oxazolidone auxiliaries is in the area of diastereomer resolution. Invaribly, we have found that the diastereomeric alkylation products (*c.f.* Scheme X, XI) are easily separated by either column chromatography or recrystallization. It should be noted that the iso-

Scheme VIII

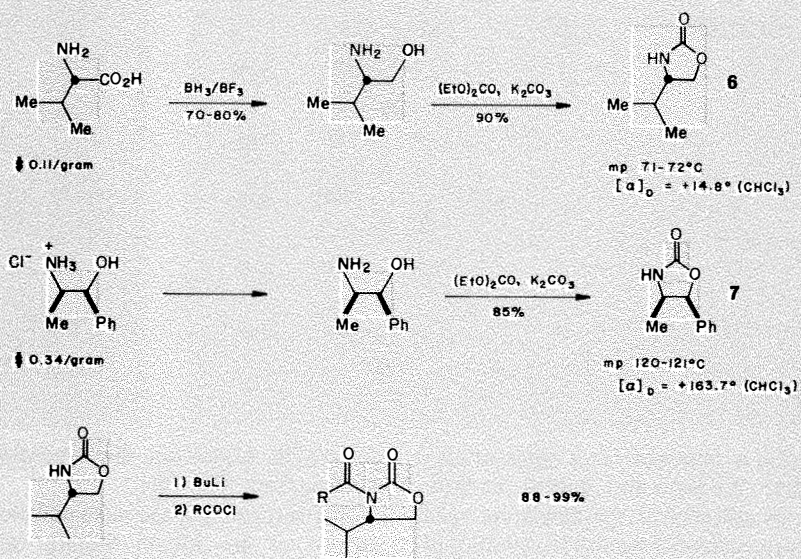


DOUBLE DIASTEREOSELECTION
via Zirconium Enolates



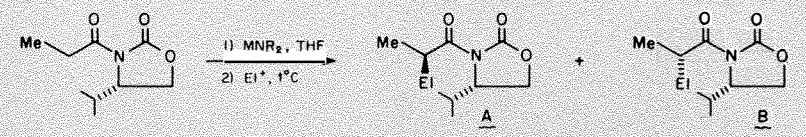
Scheme IX

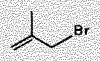
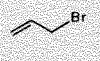
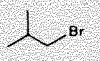
CHIRAL AUXILIARY SYNTHESIS



lated yields cited in these alkylation studies refer to diastereomerically "pure" (A:B ≥ 99:1) adducts. With regard to the influence of chiral auxiliary structure versus enolate diastereoselection, we have carried out a series of enolate methylations on a variety of substituted N-acyl-2-oxazolidones (Scheme XII).[10] As anticipated from the presumed chelated *Z*-enolate structure **8**, the C_5-substituent (R_2) is not involved in the creation of the enolate diastereofacial bias. More surprisingly, our own preconception that the "size" of the C_4-substituent (R_1) would be an important consideration in asymmetric induction is strikingly refuted. The data in Scheme XII indicate that a broad range of β-amino alcohol-derived oxazolidone auxiliaries can be employed with nearly equal success. This being the case, other factors such as product crystallinity can become the major criteria associated with the selection of a specific chiral oxazolidone for a given application.

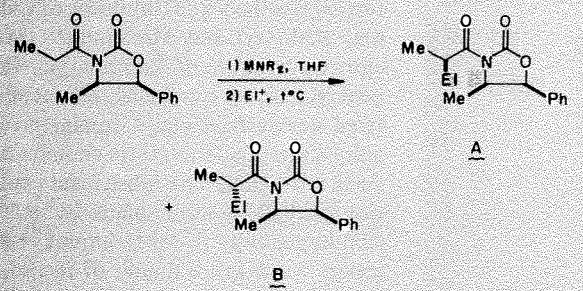
Scheme X

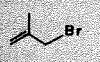


Electrophile	Metal	Temp	Ratio	Yield*
$PhCH_2Br$	Li	0°C	120:1	75%
	Li	0°C	98:2	62%
	Li	0°C	98:2	71%
	Na	-78°C	99:1	
CH_3CH_2I	Li	0°C	96:4	36%
$PhCH_2OCH_2Br$	Li	-30°C	98:2	77%
	No reaction			

*A:B ≥ 99:1

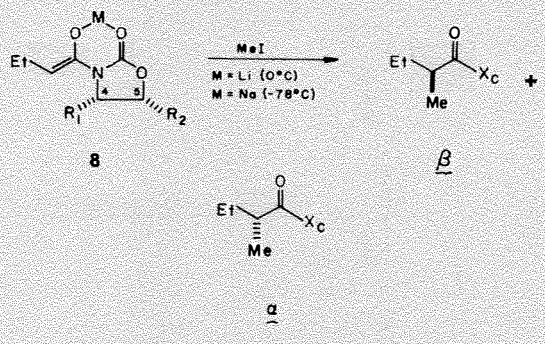
Scheme XI



Electrophile	Metal	Temp	Ratio	Yield*
$PhCH_2Br$	Li	0°	2:98	75%
	Li	0°	3:97	73%
	Li	0°	2:98	75%
CH_3CH_2I	Li	-78°	6:94	
$PhCH_2OCH_2Br$	Li	-30°	2:98	70%

*B:A ≥ 99:1

Scheme XII



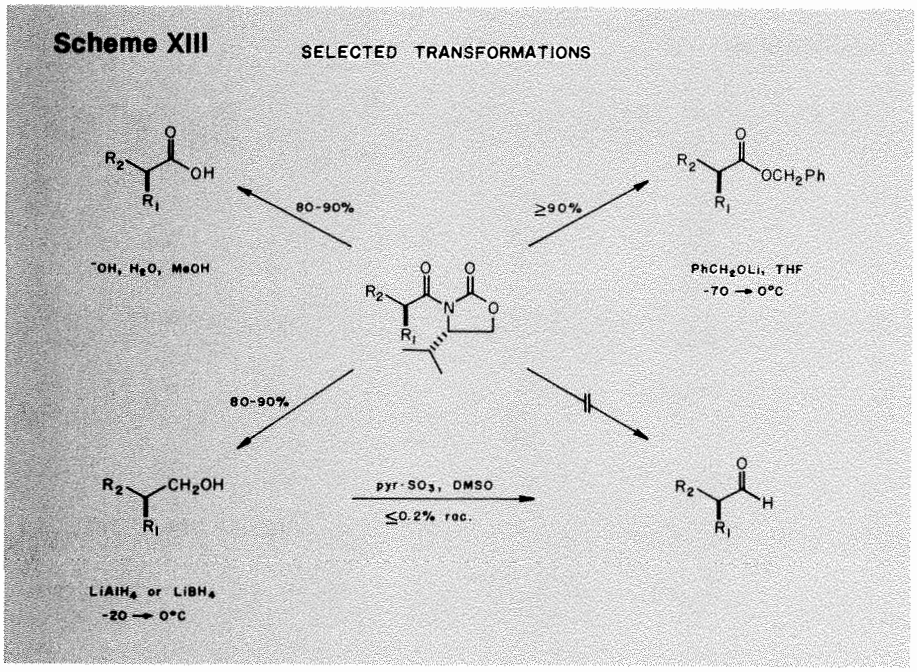
R_1	R_2	β:α Ratio (Li)	β:α Ratio (Na)
$i\text{-}C_3H_7$	H	90:10	91:9
C_6H_5	H	81:19	87:13
CH_3	H	86:14	92:8
CH_3	Ph	87:13	93:7

Conclusion: R_2-substituent plays no role dictating degree of diastereoface selectivity.

To date, we have examined a series of transformations that result in the mild, nondestructive removal of the oxazolidone auxiliaries (Scheme XIII).[9] Basic hydrolysis, transesterification and reduction are all viable chemical operations in these systems; however, some system dependence associated with the success of these reactions has been noted. Specifically, the major side reaction, which becomes significant as the steric requirements of R_1 and R_2 increase, is competitive nucleophile attack at the oxazolidone carbonyl center. Surprisingly, the noted transesterification process has been the most system-independent transformation yet discovered. Overall, these chiral imide enolates have provided us with an exceptionally useful class of optically pure, dioxygenated synthons (Scheme XIV) in either enantiomeric series which are currently being employed in a range of ongoing projects. One particularly relevant example is shown in Scheme XV. The chiral alcohol **11**[11] has proven to be exceptionally valuable in the synthesis of polyether antibiotics.[12] We routinely prepare optically pure *R*- or *S*-**11** in good overall yield from the diastereomerically pure precursor imides **10** or **9** respectively.

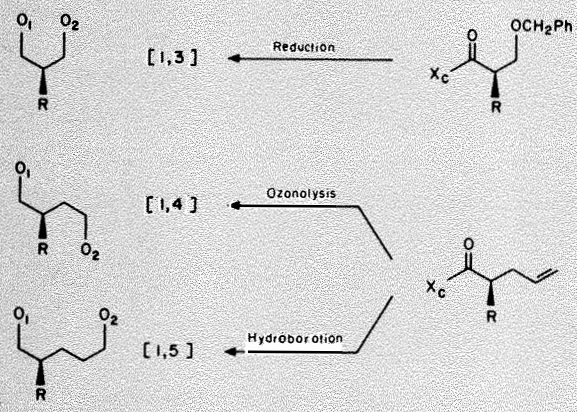
To date, the full range of electrophiles has not yet been explored with these imide enolate systems; nevertheless, we have already made a number of striking observations which should considerably extend the general utility of these reagents. One such case is the acylation reaction illustrated in

Scheme XIII SELECTED TRANSFORMATIONS

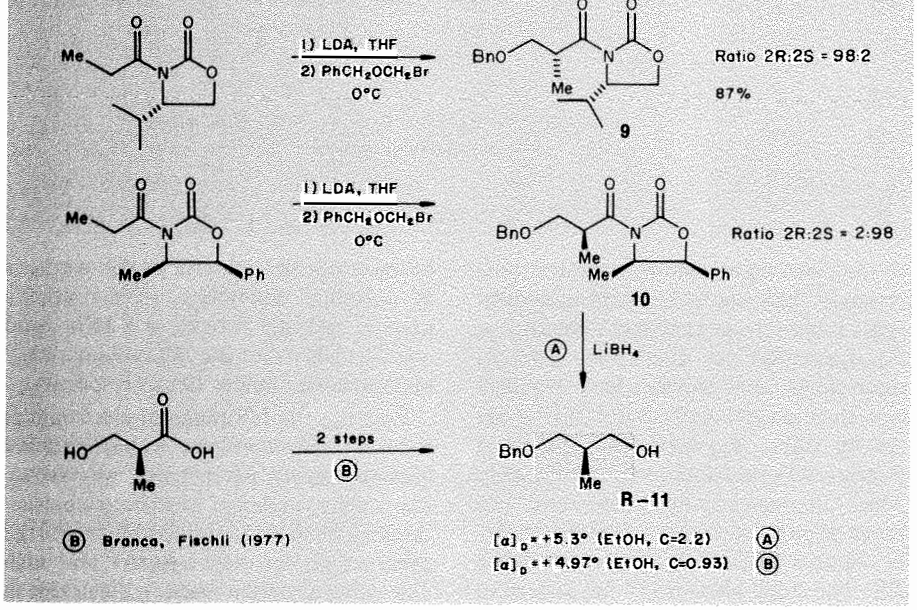


Scheme XIV

CHIRAL DI-OXYGENATED SYNTHONS



Scheme XV

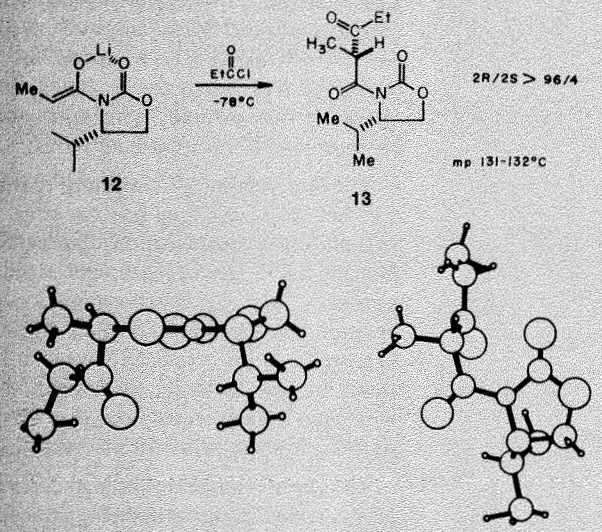


Scheme XVI.[13] Acylation of enolate **12** with propionyl chloride afforded the chiral β-keto imide **13** (95% yield) which was found to be remarkably resistant to racemization *via* enolization. An examination of its X-ray structure reveals that the allylic strain concepts earlier delineated (*c.f.* Scheme IV) destabilize that conformation of the molecule wherein both carbonyl π-systems are co-planar with the C_2-hydrogen. This unprecedented observation provides an entry into an exceptionally interesting class of chiral substances. The full details of these reactions await a more detailed examination.

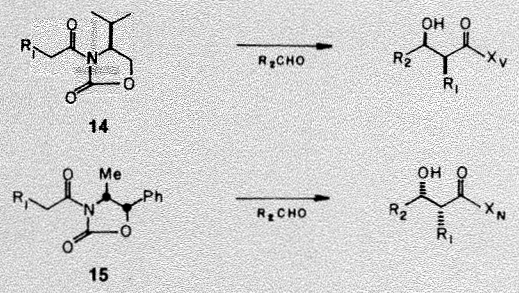
The aldol process has occupied a great deal of our attention over the last few years.[7,8,14] This reaction is of paramount importance in devising efficient approaches to the synthesis of polyketide natural products. Understandably, a number of research groups have addressed this problem over the last five-year period, and remarkable strides have been made in this area,[15] particularly from the laboratories of Professors Heathcock[16] (University of California, Berkeley) and Masamune[17] (Massachusetts Institute of Technology). In our own studies, we concluded that metal-centered steric effects play a dominant role in aldol stereoregulation from enolates of defined structures. The subsequent exploitation of dialkylboryl enolates by us,[14] and simultaneously by the Masamune research group,[17] are now a matter of record, and the application of this technology to the aldol addition reactions of the previously developed chiral imides has led to some of the most stereoselective bond constructions yet revealed (Scheme XVII). From the illustrated valinol and norephedrine imides **14** and **15**, the derived dibutylboryl enolates undergo condensation with a broad range of aldehydes in greater than 99% asymmetric induction for both newly formed asymmetric centers. We have found that a wide range of enolate substituents, R_1, may be tolerated without loss of reaction stereoselectivity.[18] With regard to condensations with chiral α-substituted aldehydes, the chiral propionimides illustrated in Scheme XVIII perform with equal facility.[19] In these cases, resident enolate chirality strongly overrides chirality in the aldehyde condensation partner. This point is further emphasized in the addition reactions of enolate **18** (R = OMe, Me) with the optically pure aldehydes **16** and **17** (Scheme XIX). In both examples the illustrated adducts were obtained in good yield and in high diastereomeric purity.[20]

One additional set of aldol addition reactions which we have not yet reported is illustrated in Scheme XX.[21] We have found

Scheme XVI



Scheme XVII



Conditions

$(n\text{-Bu})_2B\text{-}OSCF_3$

Et_3N or $EtN(i\text{-}C_3H_7)_2$

CH_2Cl_2 ≤0°C

Permutations on R_1

$-CH_3$ and n-alkyl

$-CH_2CO_2Me$

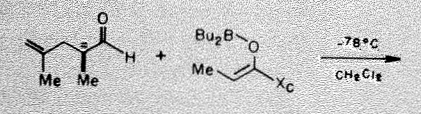
$-CH{=}CH_2$

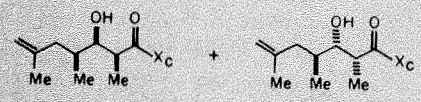
$-OMe$, OCH_2Ph

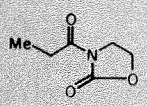
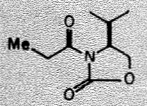
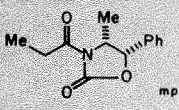
$-SMe$

Erythro Diastereoselection: >99%

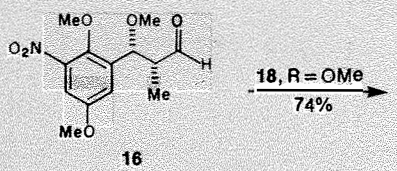
Scheme XVIII

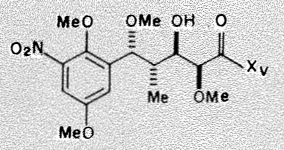


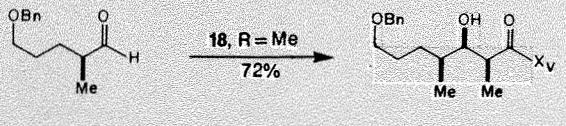


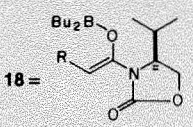
Substrate	(2S,3R):(2R,3S)	Yield
	36 : 64	—
	≥400 : 1	73%
 mp 110-111°C	< 1 : 500	86%

Scheme XIX



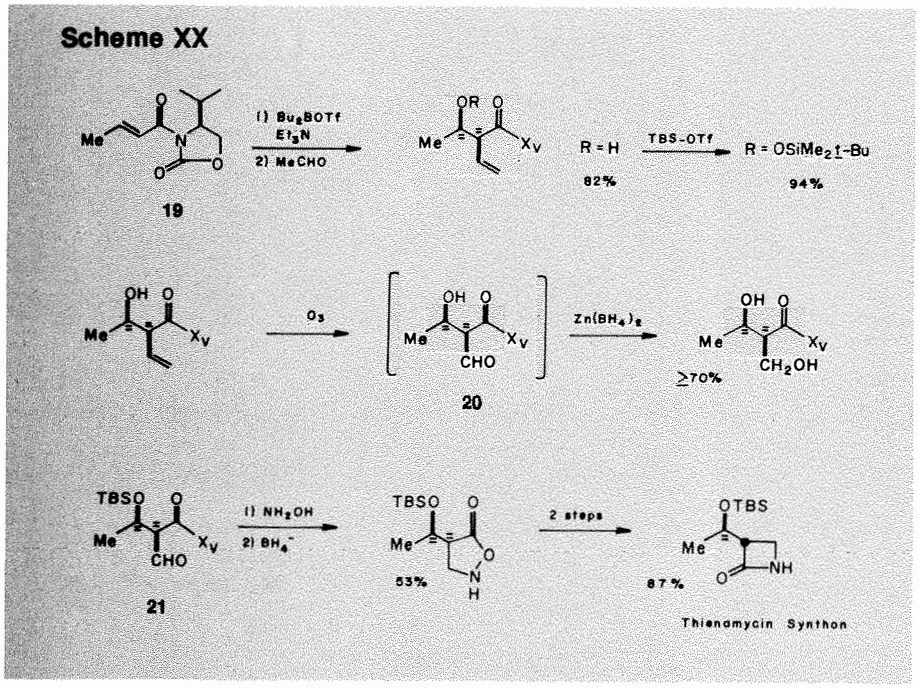


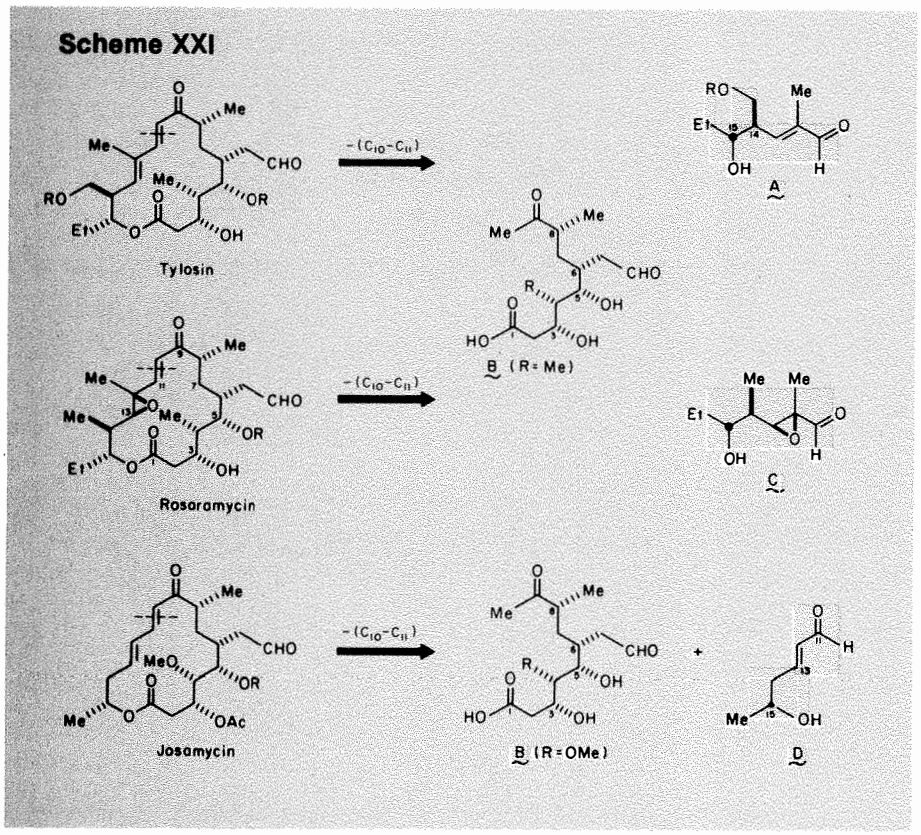




that chiral crotonate imides such as **19** also undergo the analogous aldol condensations with equal facility. The diastereomerically pure adducts provide a facile entry to the chiral α-formyl imides **20** and **21** *via* ozonolysis. Based upon our earlier discussion on the low kinetic acidity of the dipropionyl imide **13** (*c.f.* Scheme XVI), it is no longer quite so surprising that both **20** and **21** can be chemically manipulated *via* either reduction or oxime formation without racemizing the potentially labile center of asymmetry.

From the preceding discussion, one may now begin to address a number of architectural exercises wherein chiral enolate-derived bond constructions may be effectively exploited. One such project area currently under study here at Caltech is a general approach to the macrolides tylosin, rosaramycin, and josamycin. The derived aglycones for these three structures may be disconnected into a C_1-C_{10} synthon **B** (R = Me, R = OMe) and three smaller fragments containing the C_{11}-C_{15} moieties of the individual macrocycles. In approaching the construction of the C_1-C_{10} synthon, it is apparent from the previous studies that all of the asymmetry in this fragment may be derived from a single source, the (1*S*,2*R*)-





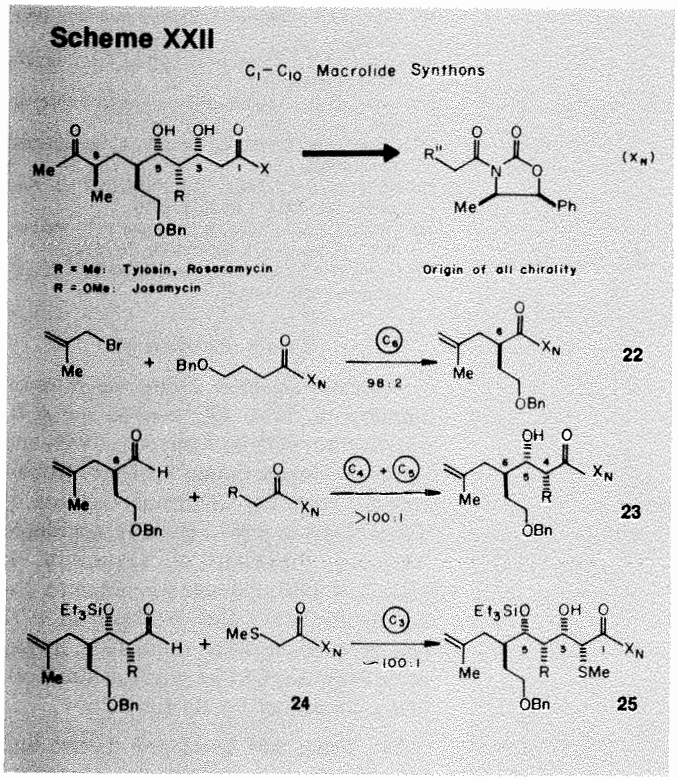
norephedrine-derived 2-oxazolidone chiral auxiliary, X_N (Scheme XXII). In recently completed studies, we have demonstrated that the C_6-stereocenter may be constructed with 50:1 diastereoselection *via* the illustrated alkylation process while the C_4 (R = Me)- and C_5-asymmetric centers are efficiently established *via* the previously developed boron enolate aldol technology.[22] The C_3-asymmetric center was also established *via* the same aldol process wherein the chiral thiomethyl acetate **24** is required as a chiral acetate enolate synthon.[18] The C_8-asymmetric center in the C_1-C_{10} macrolide synthon may be stereoselectively introduced at a variety of points in the synthesis *via* hydroboration. Prior studies from our laboratory have revealed that the 1,3-asymmetric induction noted for this hydroboration process is rather general in nature (Scheme XXIII), and an example of this process was noted in our recently published Prelog-Djerassi lactonic acid synthesis (*c.f.* Scheme XXIV).[19] Consequently, we have observed that the required C_8-asymmetric center for tylosin and related macrolides may be introduced *via* the hydroboration of either **23** or **25** but not **22** (Scheme XXII). Nicolaou and coworkers have recently noted related observations in their own successful approach to the synthesis of the tylosin aglycone.[23]

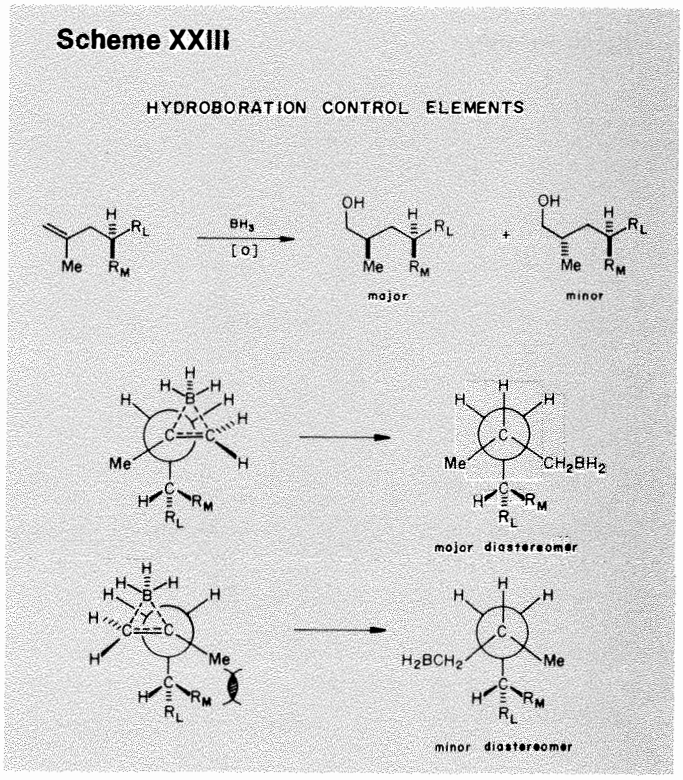
The remaining C_{11}-C_{15} subunit required for the tylosin aglycone and our basic approach for its construction is illustrated in Scheme XXV. The establishment of the desired C_{14}- and C_{15}-stereocenters for this synthon has been accomplished *via* the illustrated aldol process. The five-step synthesis of this molecule (Scheme XXVI), which has been executed in an overall yield of 64%, is noteworthy for its brevity.

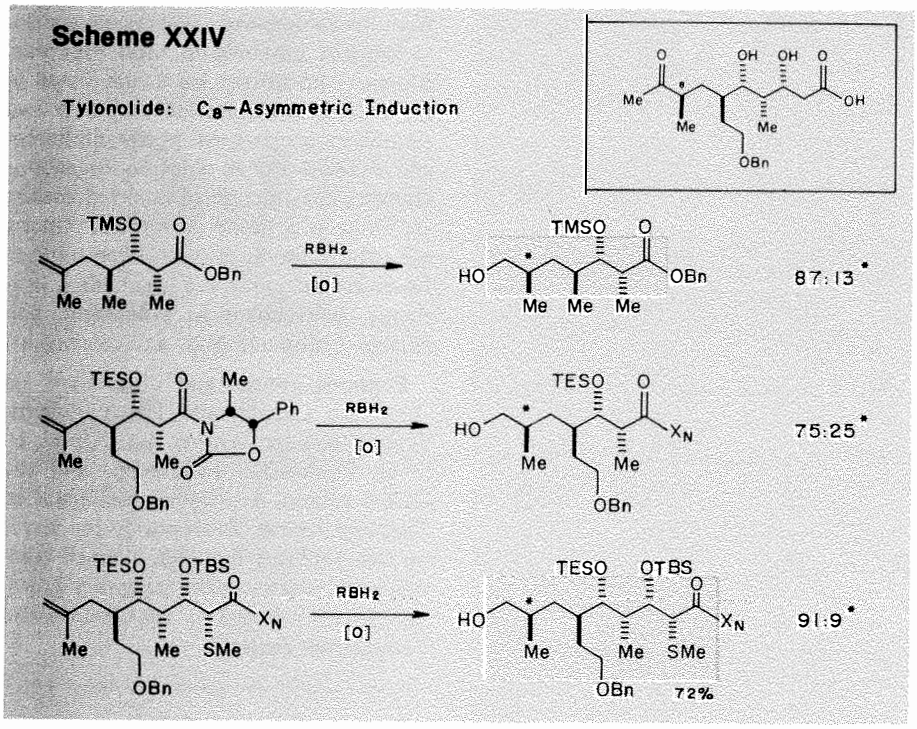
The chiral enolate technology described in this review is currently being applied to architectural exercises in the polyether antibiotics field as well. One such project, which is nearing completion, is the synthesis of the calcium-selective ionophore ionomycin (Scheme XXVII).[24] The basic approach being followed has focused on the synthesis of the four illustrated subunits (**A** → **D**). The basic protocol for absolute stereochemical control in this project is identical to that previously described for the tylosin synthesis. All asymmetry is being derived from the chiral oxazolidone auxiliaries highlighted in this review. At the present time we have already accomplished the synthesis of all four of the illustrated ionomycin synthons (**A-D**) in optically pure form.[25]

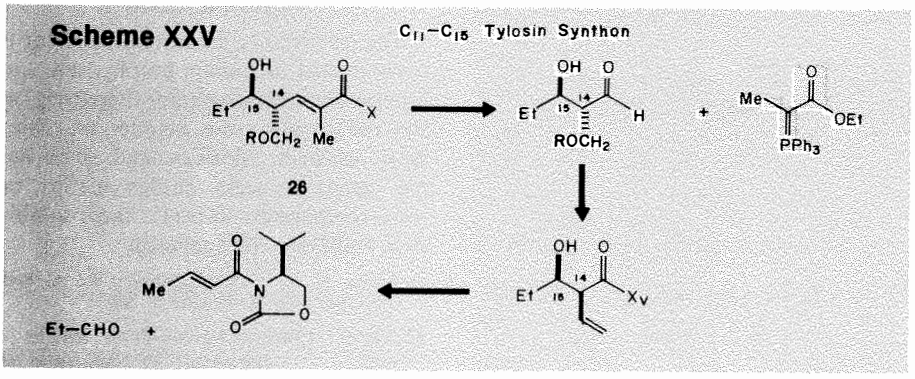
In summary, there are several well recognized approaches that are currently being followed for the production of chiral substances. These include chemical resolution, the chemical modification of chiral natural products (*e.g.*, carbohydrates), and asymmetric synthesis. Until recently, organic chemists have not enjoyed a great deal of success in this latter venture. This has been particularly true in the area of asymmetric carbon-carbon bond construction. It is my firm conviction that we will witness spectacular advances in this field over the next few years.

I feel exceptionally fortunate to have been associated with a number of outstanding colleagues, both graduate students and postdoctoral associates, who have contributed the experimental expertise and a great deal of the intellectual input contained in this research effort. Finally, I wish to acknowledge financial support from the National Science Foundation (CHE-81-01742), the National Institutes of Health (CA-29187-02, GM-27111-07) and the Eli Lilly Company.









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14) For a full account of our studies on aldol stereoregulation *via* boron enolates, see: Evans, D.A.; Nelson, J.V.; Vogel, E.; Taber, T.R. *J. Am. Chem. Soc.* **1981**, *103*, 3099 and earlier references cited therein.
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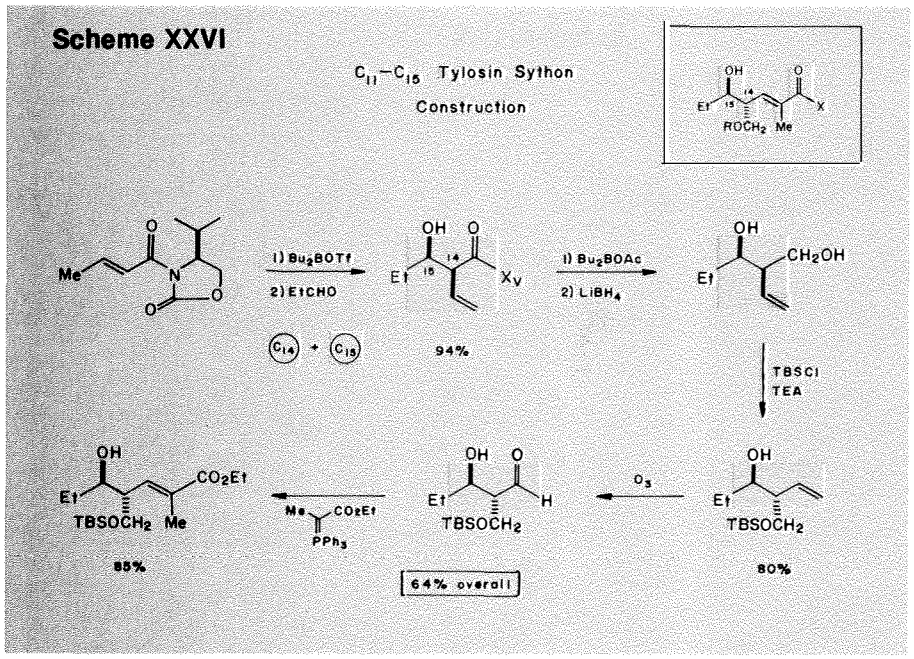

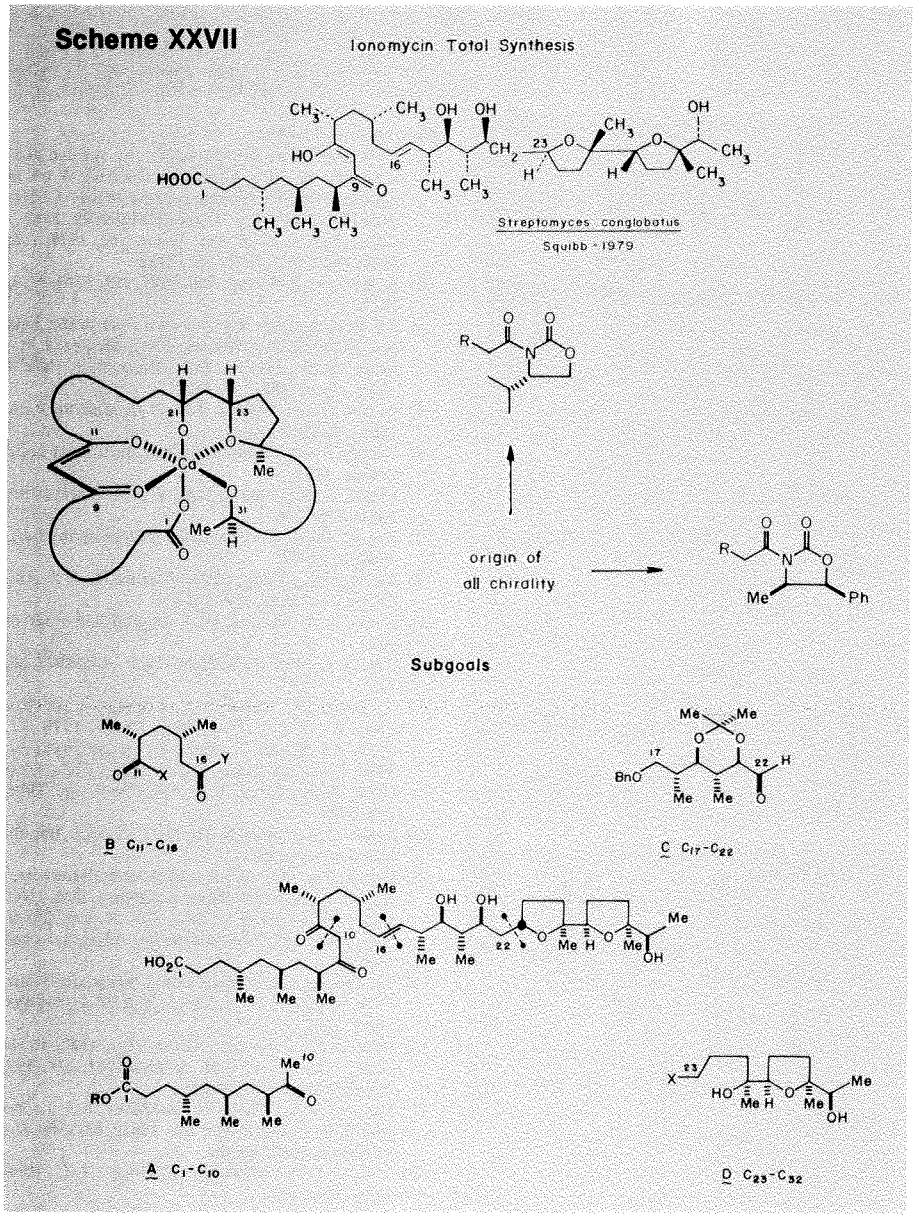

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About the Author

Professor David A. Evans was born on January 11, 1941. He received the A.B. degree from Oberlin College in 1963, and the Ph.D. degree (under Professor Robert Ireland) from the California Institute of Technology in 1967. He was appointed Assistant Professor of Chemistry at UCLA in 1967 and was promoted to Associate Professor and Professor in 1972 and 1974, respectively. Since 1974, he has been Professor of Chemistry at Cal Tech and a consultant for Eli Lilly Co.

Dr. Evans has developed diverse and valuable synthetic methodologies ranging from the anionic oxy-Cope rearrangement to blocked quinones in total synthesis. Recently, his efforts have culminated in the successful application of boron and zirconium enolates to highly diastereo- and enantioselective aldol condensations allowing construction of complex carbon skeletons in optically pure form. Among the natural products synthesized by Professor Evans' group are hasubanan, luciduline, bakkenolide-A, β-dolabrin, colchicine, histrionicotoxin, and calcimycin.

Previous awards and distinctions include the Camille and Henry Dreyfus Teacher-Scholar Award, an Alfred P. Sloan Foundation Fellowship, and the UCLA Alumni Association Distinguished Teaching Award. Professor Evans serves on two National Research Council committees as well as on the Honorary Editorial Advisory Board of *Tetrahedron* and *Tetrahedron Letters*.

Reducing Agent

The reactivity of lithium borohydride is between that of sodium borohydride and lithium aluminum hydride; therefore, $LiBH_4$ reduces aldehydes, ketones, acid chlorides, lactones, epoxides, and esters but not carboxylic acids, nitriles, olefins, or nitro compounds.[1] It is also more soluble than $NaBH_4$ in ether solvents.

1) Brown, H. C. "Hydroboration"; W. A. Benjamin, Inc.: New York, 1962; p. 245.

A Compilation of References on R-Functional Acyl Anion Synthons, RCO^-

Tapio A. Hase and Jorma K. Koskimies
University of Helsinki, Department of Chemistry
Vuorikatu 20, Helsinki 10
Finland

R-Functional RCO^- Synthons

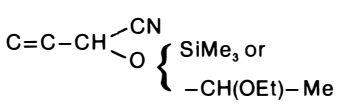
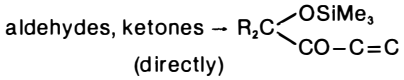
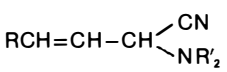
Functionality in R:

1) C=C Unsaturation
   a) Protected β,γ-unsaturated cyanohydrins and analogs
   b) Allylic or ketene dithioacetals
   c) Allenic ethers, thioethers, and analogs
2) Carbonyl
3) Carboxylic acid, ester, nitrile, etc.
4) Hydroxyalkyl, alkoxyalkyl, aminoalkyl, etc.
5) C-Cationic or additional C-anionic center elsewhere in chain

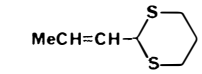
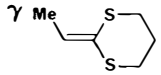
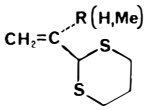
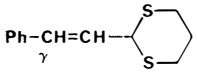
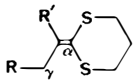
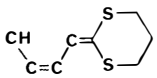
Note that many of the acyl anion synthons (RCO^-, $ArCO^-$) listed previously (*Aldrichimica Acta* **1981**, *14*, 73) presumably can accommodate functionality (*e.g.*, unsaturation, ether groups, etc.) in R (or Ar), although the original papers may not have given specific examples of such cases. Within the present group, conjugated enone acyl anion synthons (Subgroup 1) constitute a special case as they may react at the α- ($C=C-\dot{C}O^-$) and/or the γ-site ($^-\dot{C}-C-COOH$) irrespective of the original location of the double bond. This is especially true of Subgroup 1b synthons (allylic or ketene dithioacetals). Synthons in which the γ-reactivity mode is dominant will be presented in a forthcoming installment. For studies on the effect of solvent, temperature, counterion, etc. on the α/γ reactivity of ketene dithioacetal anions, see references 1-7. In view of the importance of allylic or ketene dithioacetal anions in this context, we include here a concise survey of some of the more recent routes to such compounds (for references to earlier work, see ref. 8). "Trivial" routes involving the γ-alkylation of ketene dithioacetals belong to the group of $^-C-C-COOH$ synthons. Also, the obvious route to allylic dithioacetals from 2-enals is omitted here.

Again, expressions such as C=C–CO are used to imply generality in regard to double-bond substitution. A direct carbonyl as opposed to Michael addition to such species is indicated by "1,2-" or "1,4-", respectively, in parentheses. Individual substitution patterns (*e.g.*, CH_3-$COCO^-$) are only shown when generality is lacking or was not reported. In Subgroup 5, the electrophiles and/or nucleophiles which are known to react at the sites shown are indicated separately.

1a) Protected β,γ-unsaturated cyanohydrins and analogs.

Equivalence	Reagent	Electrophile	Ref.
$C=C-CO^-$		RBr, RI, ROTs	9-11
		aldehydes, ketones →  (directly)	12,13
		C=C–COR (1,2-)	12
$RCH=CHCO^-$		ketones	14

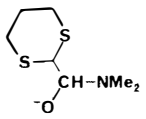
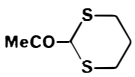
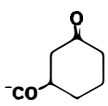
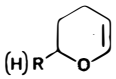
1b) Allylic or ketene dithioacetals

Equivalence	Reagent	Electrophile	Ref.
$MeCH{=}CH{-}CO^-$ (*E*)		$ArCH_2Br$	2
$CH_2{=}CH{-}CO^-$		cyclobutanone and cyclopentanone only; aldehydes and other ketones give γ products	1
$CH_2{=}C(R(H,Me))CO^-$		cyclic C=C–COR (1,4-)	3
$PhCH{=}CH{-}CO^-$ (*E*)		RX, Me_2SO_4, Me_3SiCl ($PhCH_2Br$ gives γ product)	2
$RCH{=}CR'{-}CO^-$		RX; aldehydes and ketones give α/γ mixtures RCH_2I, allylic and benzylic Br, Me_2S_2	15 16
$C{=}C{-}C{=}C{-}CO^-$		MeI	15

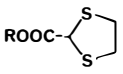
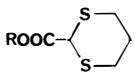
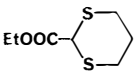
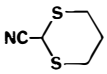
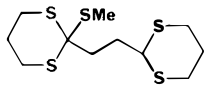
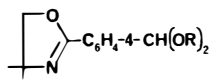
1c) Allenic ethers, thioethers and related compounds

$CH_2{=}CH{-}CO^-$	$(RO)_2PO{-}NMe{-}CH{=}C{=}CH_2$	MeI, $PhCH_2Br$	17
$MeCH{=}CH{-}CO^-$ (*E*)	$CH_2{=}CH{-}CH{=}CH{-}OMe$	PhCHO	18
$CH_2{=}CH{-}CO^-$	$BuOCH{=}CH{-}CH_2OBu$	RBr, RI	19
$RCH{=}CH{-}CO^-$	$RCH{=}C{=}CH{-}SR'$	aldehydes, ketones	20
$RCH{=}CH{-}CO^-$	$RCH_2C{\equiv}C{-}SEt$	RBr	21
$CH_2{=}CH{-}CO^-$	$CH_2{=}C{=}CH{-}OR$ (or $HC{\equiv}C{-}CH_2OR$)	aldehydes, ketones, Me_2S_2 RX (primary only)	22 23

2) Aldehyde or ketone functionality in R

Equivalence	Reagent	Electrophile	Ref.
$OHC{-}CO^-$	 (from 2-lithio-1,3-dithiane + DMF; *in situ* alkylation)	allylic Br	24
$OHC{-}CO^-$	$(EtO)_2CH{-}CHO$	thiazolium salt-catalyzed addition to C=C–CO (1,4-)	25
$MeCOCO^-$ [and $CH_2{=}C(OMe){-}CO^-$]	$CH_2{=}C(OMe)CH(CN){-}OSiMe_3$	RI, $PhCH_2Br$	11
$MeCOCO^-$ ($MeOCOCH_2CH_2CH_2CO{-}CO^-$ similarly)		RI, allyl Br, $PhCH_2Br$	26
$RCOCO^-$ (or $ArCOCO^-$)	$RCOCH_2SEt$ (or $ArCOCH_2SEt$)	RI, $PhCH_2Br$, ArCHO, oxiranes	27
$OHC{-}CH_2{-}CO^-$	$MeSC{\equiv}C{-}CH_2OMe$	RX	28
$RCO{-}CH_2{-}CO^-$	$MeS{-}CR{=}C{=}CH{-}OMe$ (from $MeSC{\equiv}C{-}CH_2OMe$)	ketones	28
$RCOCH_2CH_2CO^-$		RCH_2Br aldehydes, ketones, esters	29 30
	$(MeS)_2CH{-}SnR_3$ + 2-cyclohexenone	MeI	31
$(H^-)\ R{-}CO(CH_2)_3CO^-$		RCH_2I, allylic Br, ketones	32

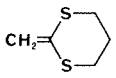
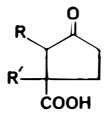
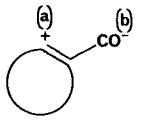
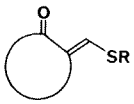
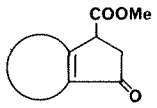
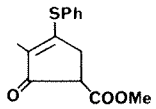
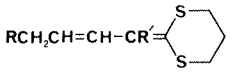
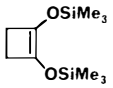
3) Carboxylic acid or derived functionality in R

Equivalence	Reagent	Electrophile	Ref.
(H) ROOC–CO⁻ [and ROOC–C⁻(OMe)₂]	(H) $ROOCCH_2SEt$	RI, $PhCH_2Br$, ArCHO, oxiranes	27
ROOC–CO⁻	$ROOC-CHCl_2$	RBr, aldehydes	33
ROOC–CO⁻ [and ROOC–C⁻(OR′)₂]	$ROOC-CH(OR')_2$	RI (primary, secondary), RBr (primary, allylic, benzylic), $MeOCH_2Cl$	34
		aldehydes, ketones; 2-cyclohexenone (1,2-)	35
		butenolides (1,4-)	36
HOOC–CO⁻	$HOOC-CH(SR)_2$	RI, RBr, $PhCH_2Cl$, ROTs, oxiranes, N-Ts-aziridine	37,38
ROOC–CO⁻	$ROOC-CH(SEt)_2$	$C=C-CO\{^{R}_{OR}$ (1,4-)	39
ROOC–CO⁻		$C=C-CO\{^{R}_{OR}$ (1,4-)	40
ROOC–CO⁻		RBr (primary, secondary), $PhCH_2Cl$	41
EtOOC–CO⁻	 (Li or Mg enolate)	aldehydes (using Mg enolate), 2-enals (1,2- with Mg enolate but 1,4- with Li enolate)	42
NC–CO⁻		RBr, $PhCOCH_2Br$	43
$HOOC-CH_2CO^-$	$HOOC-C\equiv CH$	oxiranes	44
$EtOOC-CH_2CO^-$	$(EtO)_2CH-C\equiv C-SMe$	RCH_2X	45
$R_2NCO-CH_2CO^-$	$R_2NCO-CH=CH-NR'_2$	RI, ArCOOR″	46
MeOOC–CHMe–CO⁻	MeOOC–CMe=CH–SPh	aldehydes, acyl Cl; 2-enoic esters (1,4-); 2-enals (can be made to react either 1,2- or 1,4-)	47
R′OOC–CHR–CH_2CO^-	R′OOC–CHR–CH_2CH(SMe)–SOMe [from R′OOC–C⁻HR + CH_2=C(SMe)–SOMe]	MeI, allylic Br	48
ROOC–$CH_2CH_2CO^-$		RX	49
p-HOOC–$C_6H_4CO^-$		RI, allylic X, acyl Cl, aldehydes	50

4) Hydroxyalkyl, alkoxyalkyl, aminoalkyl or similar functionality in R

Equivalence	Reagent	Electrophile	Ref.
$HOCH_2CO^-$	CH_2=CHOMe	ketones	51
$RSCH_2CO^-$	RS–CH=CH–SR (*Z*)	FSO_3Me, aldehydes, Me_2S_2	52
$HOCH_2(CH_2)_nCO^-$ (n = 2 or 3)		RCH_2I, allylic Br, ketones	32
Ph_3C-, RCO–, BOC– } $NH(CH_2)_n$-CHRCO⁻	BOC–$NH(CH_2)_n$CHR–CONH–CH(*i*-Pr)–COOH (n = 0, 1 or 9)	CH_2=CHCOOEt, CH_2=CHCN (1,4-)	53
RCO⁻; R = $ROCH_2$-, 2- or 3-THP-yl, or 2-(Δ^3 or Δ^4-DHP)yl	RCHO	thiazolium salt-catalyzed addition to 2-enones (1,4-)	54

5) C-cationic or additional C-anionic center elsewhere in chain

Equivalence	Reagent	Electrophile	Ref.
(a) (b) $^{+}CH_2CO^{-}$		(a) RLi (b) MeI	55
(a) (b) $^{+}CH_2CO^{-}$	$CH_2=C(SR)-SOR$	(a) ester enolate (b) MeI, allyl Br	56
(a) (b) $^{+}CH_2CO^{-}$	$CH_2=C(Y)-SiMe_3$; Y = SMe or $SiMe_3$	(a) RLi (excl. MeLi, PhLi, RMgX) (b) RCHO (~ RCH_2^{+})	55
(a) (b) $^{+}CH_2CO^{-}$	$CH_2=C(CN)-NMe-Ph$	(a) *t*-BuLi, allyl Li, ArLi (b) RI, $PhCH_2Br$	57
(a) (b) $RC^{+}H-CO^{-}$	$RCH=C(SMe)-SOMe$	(a) imine α-anion (b) MeI	58
(a) (b) $^{+}CH_2CH_2CO^{-}$		(a) + (b) β-keto ester enolate, → 	59
		(a) + (b) $CH_2=CHCOOMe$, → 	60
(a) (b) $^{+}CO-CHMe-CO^{-}$	$PhS-CLi=CMe-COOMe$	(a) + (b) $CH_2=CHCOOMe$, → 	61
(a) (b) $RC^{+}HCH=CR'-CO^{-}$		(a) RLi (b) MeI	55
(a) (b) $^{+}COCH_2CH_2CO^{-}$		(a) MeMgI (b) acetals, then oxidation, → $MeCOCH_2CH_2CO-CRR'-OMe$	62
(a) (b) $^{-}CH_2CO^{-}$	Me-CSSEt	(a) aldehydes (b) CO_2, aldehydes, 2-enals (1,2-), R_2NCHO	63
(a) (b) $^{-}COCH_2CO^{-}$	$MeS-C\equiv C-CH_2OMe$	(a) RX (b) ketones	28
(a) (b) $^{-}CH=CH-CO^{-}$	$(RO)_2PO-NMe-CH=C=CH_2$	(a) MeI, $PhCH_2Br$ (b) $PhCH_2Br$	17
(a) (b) $R-C^{-}=CH-CO^{-}$	$RC\equiv C-CH_2OMe$	(a) R_2SO_4, Me_3SiCl (b) RBr, R_2SO_4, Me_3SiCl	64
(a) (b) $Ph-C^{-}=CH-CO^{-}$	$PhC\equiv C-CH_2OMe$	(a), (b) RCH_2Br, Me_2SO_4, Me_3SiCl	65
$Me_3SiC^{-}=CH-CO^{-}$ (a) (b)	$Me_3SiC\equiv C-CH_2OBu$	(a) MeI, Me_3SiCl (b) MeI, Me_3SiCl, ketones	66
(a) (b) $^{-}CH=C(SePh)-CO^{-}$	$PhSeCH_2C\equiv CH$	(a) RCH_2Br, RI (secondary) (b) MeI, Me_3SiCl, aldehydes, ketones	67,68
(a) $^{-}CH=CH-CH=CH-CO^{-}$ (*E*,*E*) (b)	$CH_2=CHCH_2CH_2-CSSR$	(a) aldehydes, ketones (b) RI	69

Routes to allylic or ketene dithioacetals

1) By chain extension of ketene dithioacetals, excluding alkylation of γ-anion
2) Dehydrogenation of saturated dithioacetals
3) *Via* alkanethionocarboxylic acids and related compounds
4) Wittig- or Peterson-type olefinations
5) Other

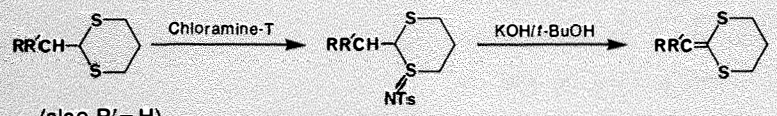
1) Chain extension of ketene dithioacetals

Ref. 70

$RCO-CR=C(SMe)_2 \xrightarrow{Ph_3P=CH_2} CH_2=CR-CR'=C(SMe)_2$ — 71

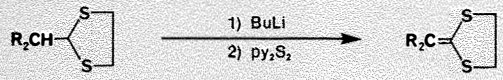
$RCH_2CO-CR'=C(SMe)_2 \xrightarrow[ZnCl_2]{Me_3SiCl/Et_3N} RCH=C(OSiMe_3)-CR'=C(SMe)_2$ — 71

2) Dehydrogenation of saturated dithioacetals



72

(also R' = H)



73

(or dithiane)

3) From alkanethionocarboxylic acids and related compounds

$RR'CH-CSSMe \xrightarrow[2)\ Me_3SiCl]{1)\ LDA} RR'C=C(SMe)-SSiMe_3$ — 74

(also R' = H)

$MeSCS-NHNHTs + RCH=CR'-CH_2X \longrightarrow TsNHN=C(SMe)-SCH_2CR'=CHR$ — 75

1) NaH
2) [2,3]- rearr.
3) MeI

$(MeS)_2C=CR-CR'=CH_2$

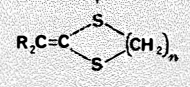
$CH_2=CHCH_2CH_2CSS\text{-}i\text{-}Pr \xrightarrow[2)\ RCOR\ 3)\ MeI]{1)\ base} R_2C(OH)CH_2CH=CH-CH=C(SMe)-S\text{-}i\text{-}Pr$ — 69

$RR'CH-CSSH \xrightarrow[2)\ R''X]{1)\ LDA} RR'C=C(SR'')_2$ — 76

(R, R' = H or alkyl)

$RCH_2-CSSR' \xrightarrow{^-OH/MeI} RCH=C(SMe)-SR'$ (also monoxide) — 58

$R_2CHMgX + CS_2 + Cl(CH_2)_nBr \longrightarrow R_2CH-CSS(CH_2)_nCl$ — 77



n = 1-4 (not for n = 1 when $R_2 = H_2$ or H + Me)

$MeMgCl \xrightarrow[3)\ Me_2SO_4]{1)\ CS_2\ \ 2)\ LDA} CH_2=C(SMe)_2$ (also monoxide) — 78

$RCH_2MgX \xrightarrow[3)\ R'X]{1)\ CS_2\ \ 2)\ LDA} RCH=C(SR')_2\ \ [R_2C=C(SR')_2]$ similarly — 79

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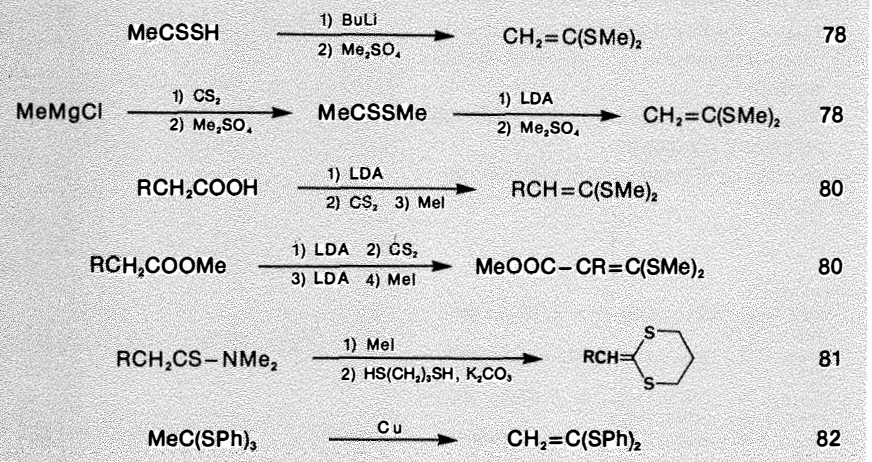
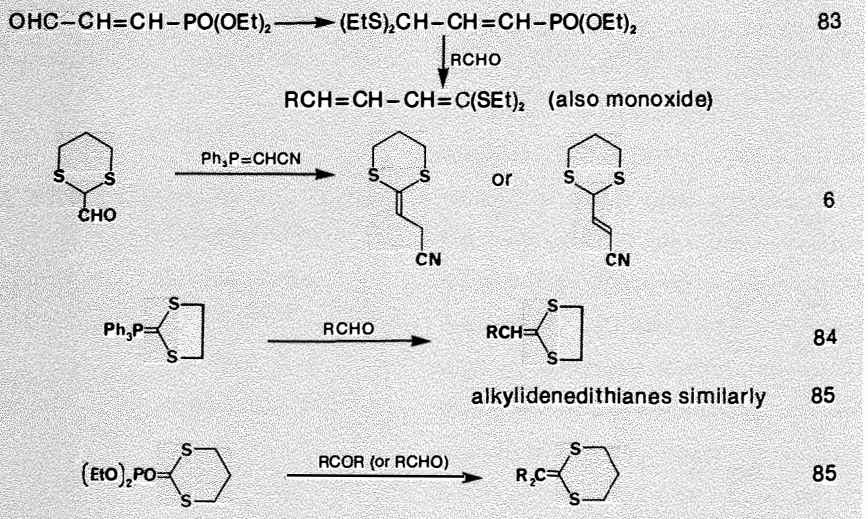
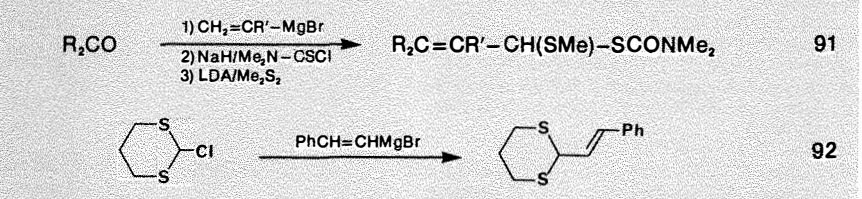
3) From alkanethionocarboxylic acids and related compounds (continued)



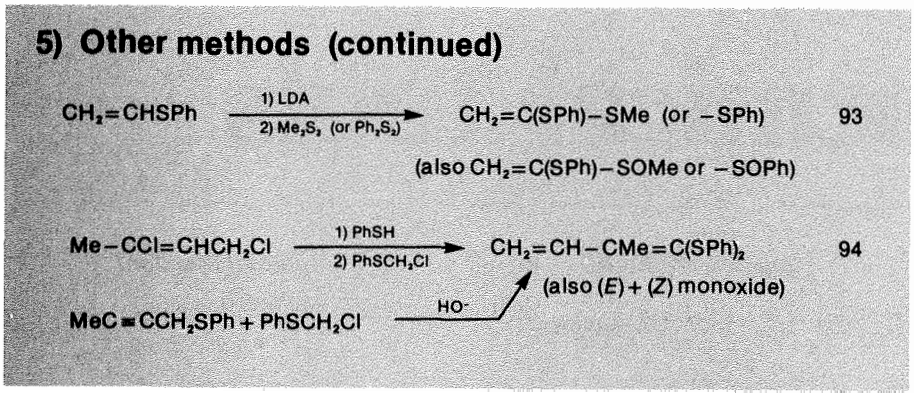
4) Wittig- or Peterson-type olefinations



5) Other methods



5) Other methods (continued)



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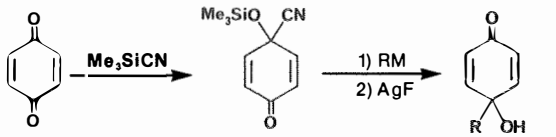
Award-Winning Chemistry

1982 - Professor David Evans

The work of Professor David Evans, recipient of the 1982 ACS Award for Creative Work in Synthetic Organic Chemistry, is characterized by a detailed mechanistic approach to practical synthetic problems. The result has been the successful development of a variety of important methodologies whose impact on synthetic chemistry continues to grow. For example, the anionic oxy-Cope rearrangement, pioneered by Professor Evans, is now a commonly employed method for the highly stereoselective construction of cyclic carbon frameworks.[1] His most recent endeavors center on the use of masked quinones in synthesis and on developing stereoselective aldol condensations *via* different metal enolates.

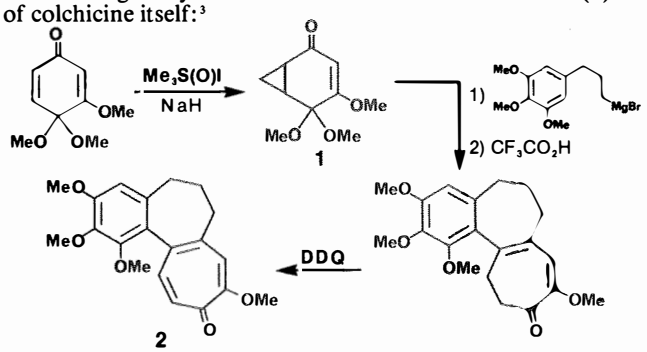
Quinone Methodology

Blocked quinones function effectively as aryl cation equivalents. The redox-related side reactions associated with adding nucleophiles to quinones are avoided by employing **trimethylsilyl cyanide**; the resulting silylated cyanohydrin is easily cleaved:[2]



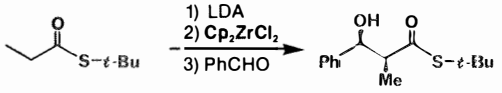
RM = organolithium, Grignard reagents

The ability of **1** to function as a tropolone dication equivalent enabled elegant syntheses of desacetamidoisocolchicine **(2)** and of colchicine itself:[3]



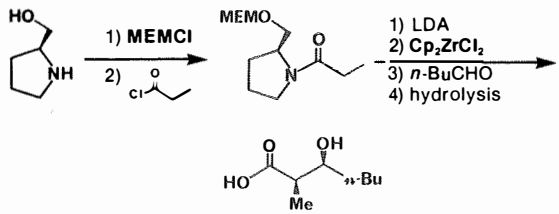
Stereoselective Aldol Condensations[4]

The bulk of Professor Evans' recent work has been directed toward developing chiral carboxylic acid enolate synthons.[5] Initial work indicated that zirconium enolates exhibited excellent *erythro* diastereoselection:



(ref. 6)

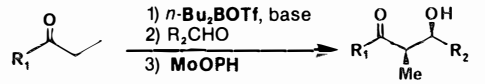
erythrolthreo = 93/7



(ref. 7)

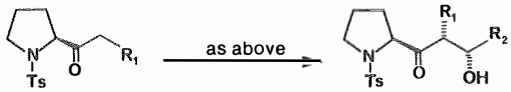
erythrolthreo = 96/4

Boron enolates also exhibit high *erythro* selectivity:



(ref. 8)

R_1	R_2	*erythrolthreo*
Et	*i*-Pr	>97/3
Ph	Ph	>97/3

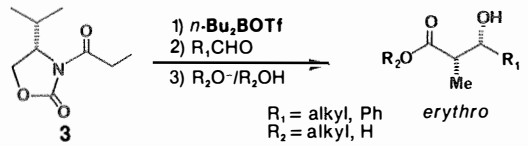


(ref. 9)

(from L-proline) R_1 = H, Me; R_2 = *i*-Pr, Ph

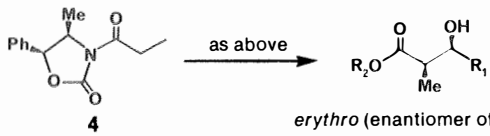
erythrolthreo = 83/17 (R_1 = H, R_2 = Ph)

Perhaps most impressive to date is the introduction of oxazolidinones **3** and **4** (prepared from ***S*-valinol** and **1*S*,2*R*-norephedrine**, respectively) as *recyclable* chiral auxiliaries allowing access to β-hydroxy acids or esters with extraordinary enantio- and diastereoselectivity: GC analysis of the crude reaction mixture (after silylation with **Et_2NSiMe_3**) indicated ratios as high as 500:1![10]



R_1 = alkyl, Ph; R_2 = alkyl, H — *erythro*

3



4

erythro (enantiomer of above)

See Professor Evans' review in this issue of *Aldrichimica Acta* for a detailed summary of his outstanding work in the field of chiral enolate design.

References (Professor Evans is the senior author in all cases):
(1) *J. Am. Chem. Soc.* **1980**, *102*, 774. (2) *Pure Appl. Chem.* **1979**, *51*, 1285. (3) *J. Am. Chem. Soc.* **1981**, *103*, 5813. (4) For a recent comprehensive review, see *Top. Stereochem.* **1982**, *13*, 1. (5) *Pure Appl. Chem.* **1981**, *53*, 1109. (6) *Tetrahedron Lett.* **1980**, *21*, 3975. (7) *J. Am. Chem. Soc.* **1981**, *103*, 2876. (8) *Ibid.* **1981**, *103*, 3099. (9) *Tetrahedron Lett.* **1980**, *21*, 4675. (10) *J. Am. Chem. Soc.* **1981**, *103*, 2127.

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Aldrichimica Acta

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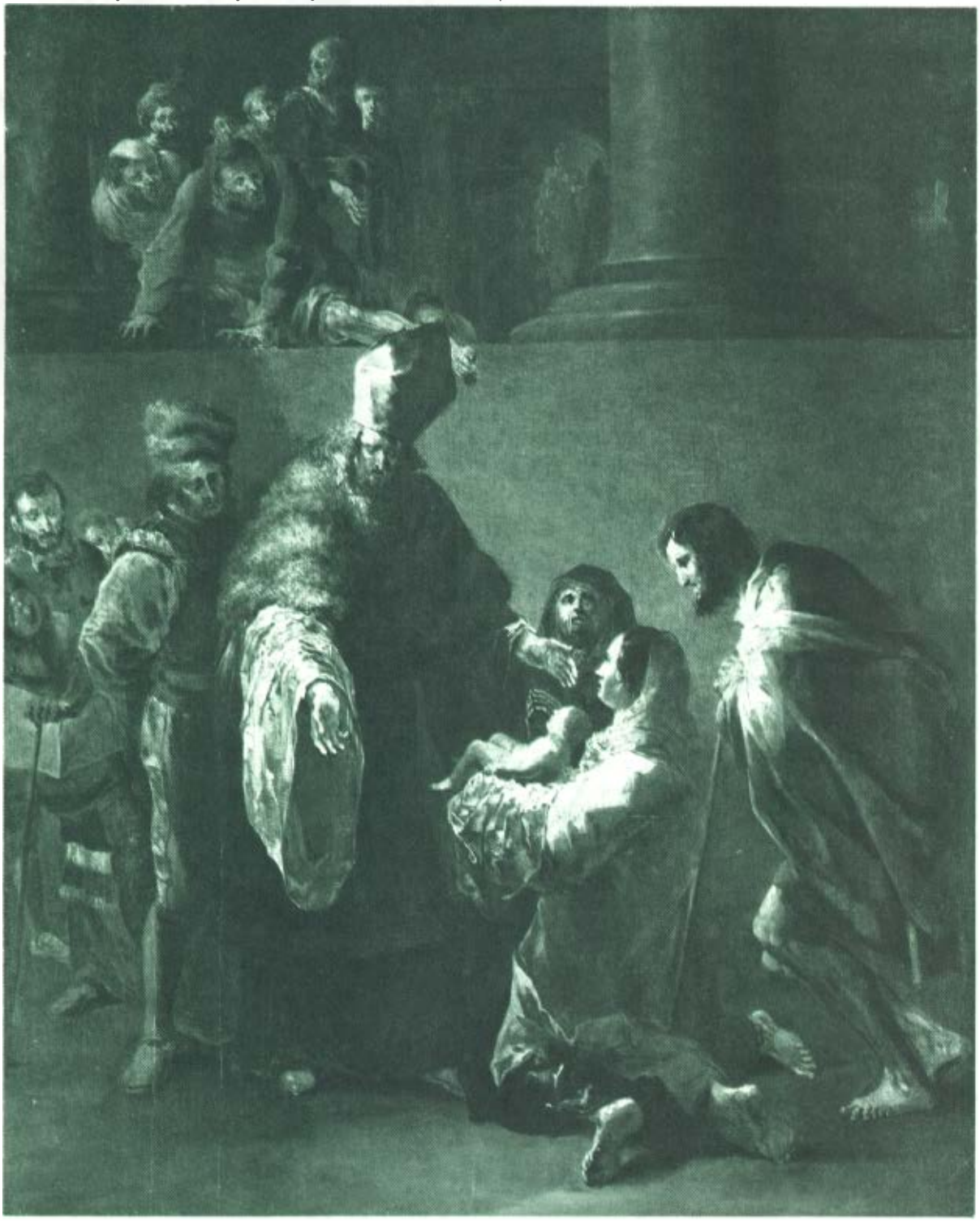

Advances in Stereochemical Control. The 1,2- and 1,3-Diol Systems.

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About Our Cover:

As you know, our chemist-collector buys paintings for all sorts of reasons: puzzles of authorship or iconography, and often for the sheer beauty of the work.

We have sometimes wondered whether there were many great old masters whose names are now almost unknown. Our chemist-collector believes that Leonard Bramer is one of these little-known painters whose works are greatly undervalued.

Readers of the *Aldrichimica Acta* may remember the "Queen of Sheba Visiting King Solomon," a painting by Bramer which appears on the cover of Vol. 7, No. 1, 1974. This issue's cover, "The Presentation in the Temple" (oil on panel, 27¼ × 21½ inches) is another work of Bramer so beautiful in composition, coloring and light that it immediately appealed to our collector.

Though Bramer was 10 years older than Rembrandt, his works show the influence of both Rembrandt and the Italians, and provide an important link between Rembrandt and 18th-century Italians like Magnasco.

This painting has an interesting history. It belonged to Thomas Jefferson Bryan, one of America's first serious collectors of old master paintings. He was born in Philadelphia in 1802, graduated from Harvard in 1823, and after twenty years in Europe returned to New York. In 1867 he gave his large collection to the New York Historical Society which sold 113 of his paintings, this one among them, at auction at Sotheby Parke Bernet in New York in 1980.

Are you interested in our *Acta* covers? Selections from the Bader Collection, with 30 duotone reproductions, many of previous *Acta* covers, and an introduction by Professor Wolfgang Stechow is available to all chemist art-lovers.

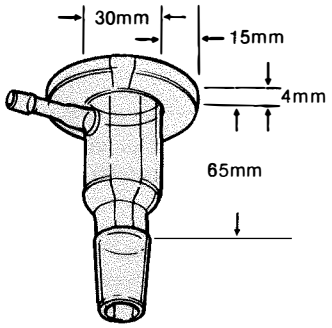
Also, many paintings reproduced on our *Acta* covers were shown at the Milwaukee Art Center in an exhibition, "The Bible Through Dutch Eyes," arranged by Dr. Bader in 1976. The fully illustrated catalog with 66 black-and-white and 4 full-color reproductions contains many art historical and Biblical comments.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

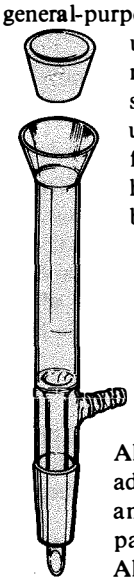
Lab Notes

The most common sequence of operations in preparative organic chemistry is probably aqueous extraction, drying over a desiccant, filtration and rotary evaporation. Generally, one filters into a filter flask and then transfers into an evaporating flask.

We have found that a simple adapter with a rubber collar is useful for filtering directly into an evaporating flask.



The dimensions given are those for a general-purpose adapter, which may be used with small Hirsch funnels or sinters. Particularly small funnels or filter columns may be mounted *via* a flat block of rubber with a hole in the middle (*e.g.*, a bung sliced in half).



Dr. David R. Kelly
Dyson Perrins Laboratory
Oxford University
England

Editor's note:

For the same purpose, Aldrich offers three sizes of the adapter shown at left. For size and price information, see page 1335 of the 1982-1983 Aldrich Catalog/Handbook.

Like most synthetic chemists, we are perpetually faced with the problem of removing small amounts of product from large reaction flasks. Scraping with spatulas usually only leads to a smearing of the product into an even finer coating on the sides of the flask.

To overcome this problem of material loss we use the following process. The product is loosened from the walls of the flask by scraping with a spatula and then a small amount of liquid nitrogen is added to the flask. The liquid nitrogen is swirled around for a few seconds and then left to settle at the bottom of the flask. The product becomes suspended in the liquid nitrogen, and as the nitrogen evaporates, it leaves a pellet of product which can be simply removed with a spatula. Water condensation is prevented by blowing a nitrogen stream through the flask during evaporation.

John R. Thornback
Department of Chemistry
Loughborough University of Technology
Loughborough, Leicestershire LE11 3TU
England

In our laboratory, heat-sensitive chemicals are stored in a regular refrigerator modified with an external thermostat, and with the internal light and defroster disconnected to prevent sparking and the possibility of an explosion.

We have found that the inevitable slow leakage from the containers causes an accumulation of obnoxious and potentially dangerous vapors. The simple solution was the installation of a vent in the refrigerator. A hole was carefully drilled through one wall just below the freezer compartment, another in the bottom of the door. The holes were fitted with two short pieces of glass tubing and a flexible sealant. A long, thin drying tube (1cm × 75cm) filled with Drierite®, to retard frost accumulation, was fastened onto the door and connected to the tube there. The other vent was attached to the house vacuum (an equivalent source of vacuum would also serve). A slow, continuous flow rate essentially eliminated the odors. The rate of consumption of the drying agent was quite slow (less than 15cm/-month).

Werner Fritz
Department of Chemistry
The University of Manitoba
Winnipeg, Manitoba R3T 2N2

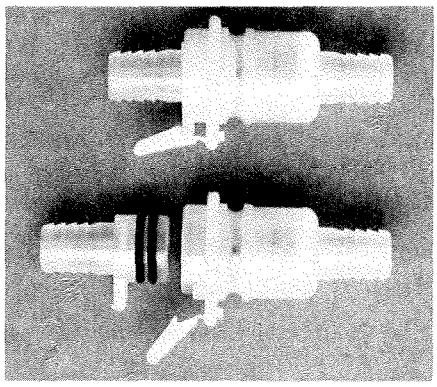
Quick connectors in cooling water lines make the assembly of lab glassware fast and convenient. Unfortunately, accidental separation of quick connectors can result in lab floods — particularly in the case of unattended equipment.

A simple, lightweight retaining clip for quick connectors can be readily constructed from sheet metal. In one useful design, a 7/8″ strip of 20-gauge cold-rolled steel is formed into the shape of a "U" and slots are cut into the sides of the end pieces. For one brand of quick connector (Mallinckrodt QD Size 1), the base of the "U" is 1-1/8″ with 7/8″ square end pieces and 7/16″ × 5/8″ slots. This design yields an effective retaining clip weighing less than 9g.

Paul E. Eckler
International Minerals & Chemical Corp.
P.O. Box 207
Terre Haute, IN 47808

Editor's note:

In response to Mr. Eckler's lab note, we now offer two "lockable quick disconnects" shown in the picture below. We hope to make a retaining clip available to our customers soon.



Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Selections from the Bader Collection.** *We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Ayra Bader.

When I visited Oxford University recently, I received many good suggestions for new products. One of them, from Dr. Carl Ziegler, was for 3-(phenylsulfonyl)-propionic acid, an elegant tool for 3-carbon homologation.[1]

Naturally, we made it.

1) Iwai, K. *et al. Synth. Commun.* **1976**, *6*, 357.

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

Advances in Stereochemical Control: The 1,2- and 1,3-Diol Systems[1]

Satoru Masamune* and William Choy
Department of Chemistry
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1. Introduction and Background

In recent years natural-product synthesis has placed heavy emphasis on asymmetric synthesis.[2] This trend has been brought about not only for the elucidation of fundamental processes involved in asymmetric synthesis, but by the structural requirement of some target molecules. The pre-1970 literature records many elegant total syntheses of steroids, alkaloids, terpenes, and others in **racemic** form. In addition to those polycyclic compounds, numerous other natural products are of a different structural type, **basically acyclic** in nature, as exemplified by macrolide and ionophore antibiotics. Structural analysis of this last group of compounds readily reveals that coupling of two chiral fragments A and B be incorporated as a logical step in their syntheses.[3] With *d*-A—*d*-B representing the structure of a natural product, this assembly can be executed in three ways: (1) connection of the optically pure fragments both in *d*-form (eq. 1), (2) reaction of *d*-A with the racemate of B (eq. 2) normally leading to a mixture of two compounds *d*-A—*d*-B and *d*-A—*l*-B, which are diastereomeric and hence potentially separable, and (3) pairing of the two racemates (eq. 3) usually resulting in the formation of two A-B racemates in nearly equal quantities,

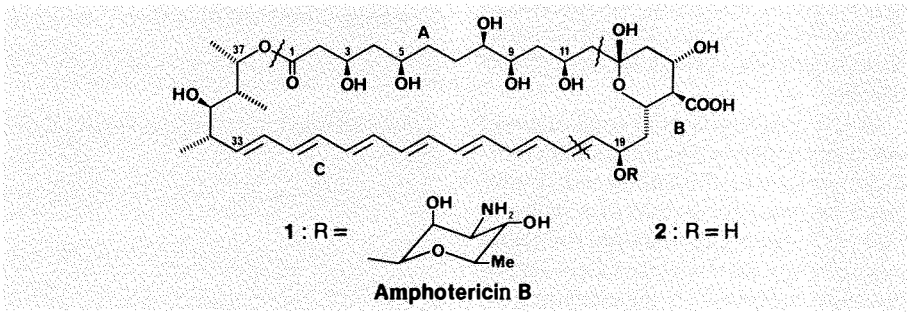
d-A + *d*-B ⟶ *d*-A—*d*-B (eq. 1)

d-A + *dl*-B ⟶ *d*-A—*d*-B + *d*-A—*l*-B (eq. 2)

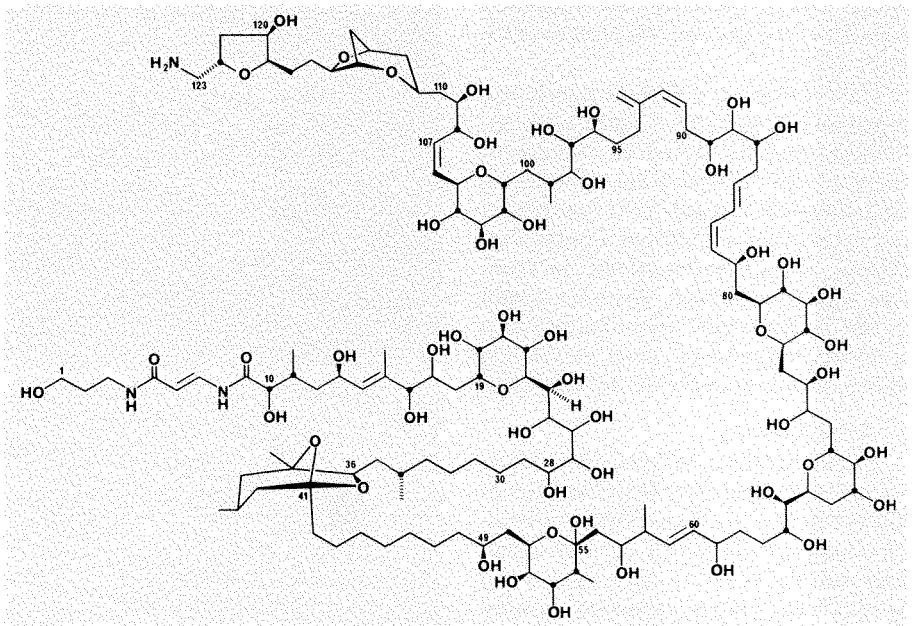
dl-A + *dl*-B ⟶ *d*-A—*d*-B + *l*-A—*l*-B + (*d*-A—*l*-B + *l*-A—*d*-B) (eq. 3)

unless, on rare occasions, the reaction is carried out under ideal conditions of kinetic resolution. While reactions 2 and 3 must be followed by separation of the diastereoisomers, a normally tedious process of optical resolution is further required in the latter case in order to complete the synthesis of the target molecule *d*-A—*d*-B. Thus, the method of choice is obviously reaction 1, for which *enantiomerically pure A and B fragments are required*. The role of asymmetric synthesis is self-evident and will become even more significant as this Account unfolds.

As an illustration, let us examine the structure of amphotericin B (**1**)[4] which represents the large family of macrolides of acetate and propionate origin.[3] One logical retrosynthesis of its aglycone (**2**) (the non-sugar portion of **1**) dissects, as indicated by the wavy lines in **2**, the 38-membered lactone into chiral fragments A, B, and C which feature the presence of one 1,2-diol and several 1,3-diol structural units. In fact, these dihydroxyl units are ubiquitous in numerous polyketide natural products of biological significance, as exemplified in a dramatic manner by palytoxin (**3**), a potent toxin of marine origin having a molecular formula of $C_{129}H_{223}N_3O_{54}$, 64 asymmetric centers, and eight double



Amphotericin B



3 Palytoxin

$C_{129}H_{223}N_3O_{54}$, 64 asymmetric centers, 8 double bonds

bonds.[5] Thus, an approach or approaches to the construction of these basic diol units become a necessity. Once efficient methodologies are established, one can contemplate a logical synthetic scheme even for palytoxin, although in this particular instance, one will be inevitably bogged down with repetitious operations as well as technical problems associated with the handling of large molecules such as peptides.

Approximately three years ago at M.I.T., we launched a project aimed at the efficient synthesis of several representative macrolide antibiotics of medium complexity, with the prime objective of establishing the methodology for the sequential construction of the 1,3- and 1,2-diol systems. Although seemingly severe at the time, our requirements for a successful methodology were (a) a stereoselection of, at minimum, 15:1, (b) a chemical yield of greater than 80%, and (c) functional groups in the product so chosen that they can be easily and mildly transformed into a substrate for the next stereoselective reaction of the sequence. For these objectives, two synthetic transformations were selected: (1) the asymmetric aldol reaction for the 1,3-diols (eq. 4) and (2) a sequence of reactions involving Wittig reaction, asymmetric epoxidation, and ring opening for the 1,2-diols (eq. 5).

Five or fewer consecutive applications of eqs. 4 and 5 together with additional functional-group transformations will be adequate for the construction of a molecule with ten or fewer chiral centers, the degree of stereochemical complexity possessed by the target molecules. If the conditions set above are met, the overall stereoselection for all the reactions will still exceed a gratifying 72%.

In this article we outline the mainstream of our own research developments, and deliberately limit the citation of other contributors to only those pertinent to the discussion. Emphasis is placed on the analysis of the stereochemical problems and the conceptual development in solving the problems that have emerged. There is a wealth of new findings in the fields of asymmetric aldol reaction and asymmetric epoxidation and excellent review articles already exist.[6]

2. Aldol Reaction

2.1. Stereochemical Descriptors.[7] Before we unfold a rather complicated account of aldol chemistry, the nomenclature to be used throughout this article must be unambiguously defined. The aldol reaction (eq. 6) is a carbon-carbon bond-forming reaction which involves an aldehyde (4) and an enolate (5) and, in general, creates two chiral centers in the product (6). Thus, if 4 is an enantiomerically pure 2-methyl-substituted aldehyde and 5 is an enolate derived from an ethyl ketone, the reaction products that may result from this reaction are four diastereoisomers, **6a-6d**. For the reasons detailed elsewhere,[7] the stereochemistry of these isomers is now expressed in this article by the zigzag main-chain formula, and the descriptors "*syn*" and "*anti*" are used, as shown in eq. 6, to describe two (non-hydrogen) substituents on the same side and those on the opposite sides of the plane defined by this chain, respectively. The proposal of an additional set of descriptors also appears to be appropriate. The two lithium enolates **7a** and **7b** are designated *Z* and *E*. Since very often we are concerned with the relative disposition of the OLi and methyl groups with respect to the double bond, and in fact both enolates **7a** and **7b** induce the same stereochemical consequence, it is preferred to assign the same descriptors to both of them. We propose the use of *Z*(O), indicating that top priority is conferred on the element in the bracket in this special case.[7] *E*(O) is defined in the same manner. These two sets of stereochemical descriptors eliminate the ambiguity that unfortunately has appeared in the recent aldol literature, and this proposed nomenclature hopefully will receive universal acceptance in the future.

2.2. Models for the Aldol Reaction. Any condensed-phase reaction which involves an organometallic reagent (including metal enolates) takes an extremely complicated course, and our understanding of it is still at the infant stage. Even in cases where the degree of aggregation of the reagent in solution was known, *e.g.*, a lithium enolate[8] and cuprate,[9] the actual species reacting with a substrate had not been determined. Moreover, reactions of the same type have been performed under a variety of experimental conditions, *i.e.*, the aldol condensation may have been effected with various Lewis acids or bases, and thus, the conformation of the transition state has varied from case to case.[6a-d] For these reasons we are concerned only with aldol reactions (eq. 7) using a cation M^+ (M in 8: a Group I, II, or III metal) and the model of our selection is one which best rationalizes the experimental results.

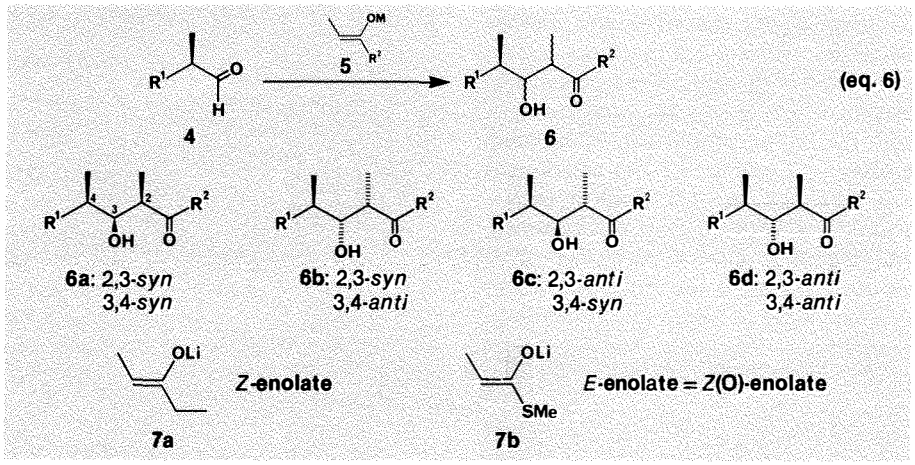
Some time ago Zimmerman and Traxler proposed, for the Ivanov reaction, the chair-type pericyclic intermediate[10] (al-

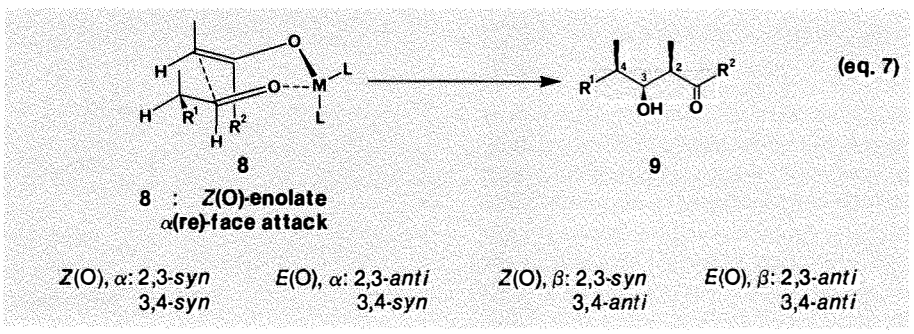
Asymmetric Aldol Reaction (eq. 4)

$$^{*}R\text{-}CHO \longrightarrow {}^{*}R\text{-}{}^{*}CH(OH)\text{-}{}^{*}CH(Me)\text{-}CHO$$

Asymmetric Epoxidation and Ring Opening (eq. 5)

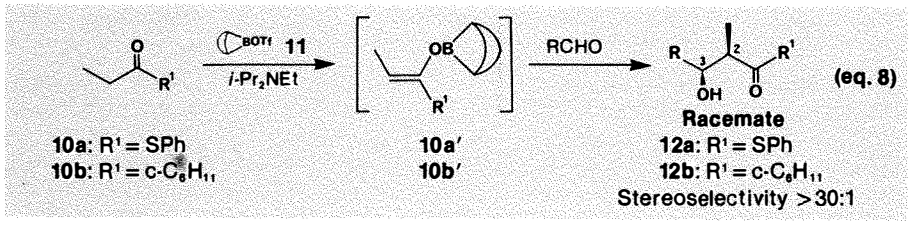
$$^{*}R\text{-}CH{=}CH\text{-}CH_2OH \longrightarrow {}^{*}R\text{-}{}^{*}CH\text{-}{}^{*}CH\text{-}CH_2OH \longrightarrow {}^{*}R\text{-}{}^{*}CH(OR)\text{-}{}^{*}CH(OR)\text{-}CHO$$

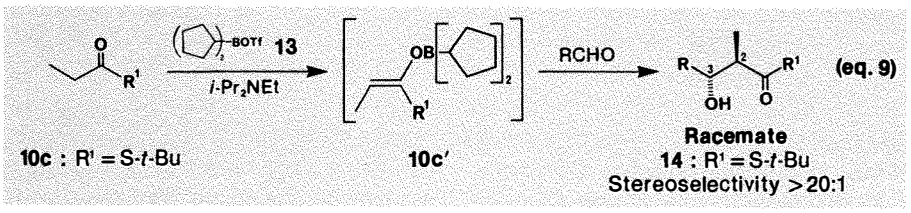


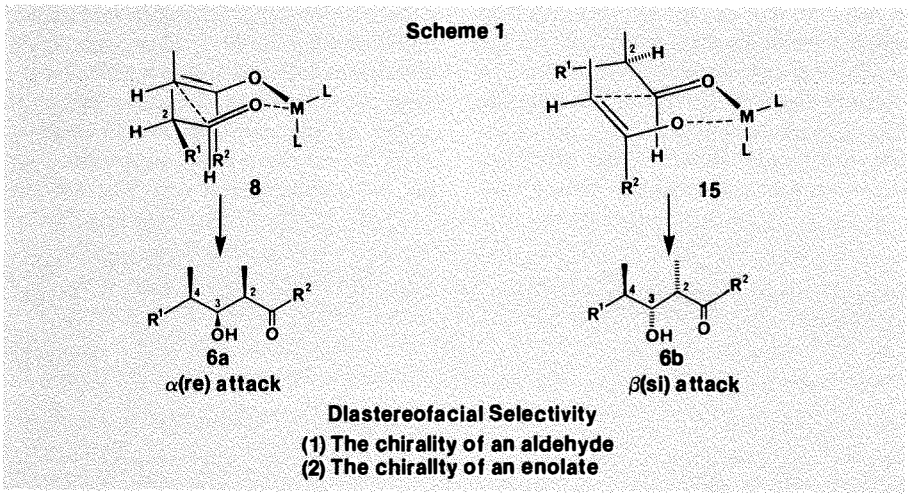


most the same as shown in **8**) which, prior to our initiation of this project, had already proven useful in explaining the stereochemical course of several aldol-type reactions.[6a-d]

The outcome of the reaction proceeding through **8** which delineates the case of the *Z*(O) enolate approaching the α(re)-face of the aldehyde is straightforward: the aldol product **9** should have the 2,3-*syn*, 3,4-*syn* stereochemistry. The other combinations for the assembly of the enolate and aldehyde are: *E*(O) enolate approaching the α-face of the aldehyde; *Z*(O) enolate, β(si)-face, and lastly *E*(O) enolate, β-face. The stereochemistry of the product in each case is tabulated. It is clear that (1) the *Z*(O) and *E*(O) geometries of the enolate are translated into the 2,3-*syn* and 2,3-*anti* stereochemistry of the aldol product, respectively and (2) the enolate's approach to the aldehyde (from the α- or β-face) determines the absolute configuration of the C-3 hydroxyl group created in the reaction. (The α- and β-face selections correspond to the β- and α-absolute configurations of the C-3 hydroxyl group of the product, respectively.) Since the β-absolute configuration of the C-4 methyl group in **9** is "handed over" from the aldehyde, the 3,4-stereochemistry of **9** is *syn* in this case. Therefore, the stereochemical problem in the aldol reaction consists of two parts: how to control the 2,3- and 3,4-stereochemistry.







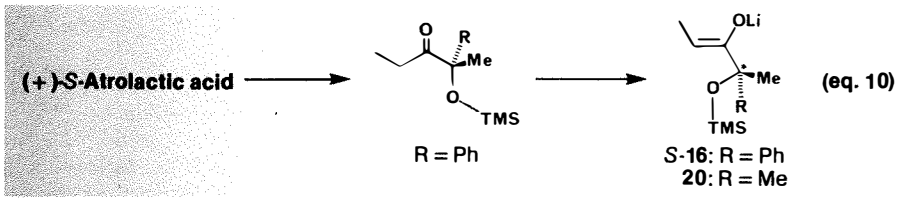
2.3. **2,3-Stereochemistry.**[11] One simplistic conformational analysis of the transition state **8** (coupled with some serendipity) has led to an expeditious solution of this problem. The relatively short O—B and C—B bondlengths as well as the strong affinity of boron toward an oxygen lone pair would "tighten" the transition state; at the same time a bulky ligand attached to the boron atom would exert a steric demand in the lower space of the chair ring. These factors would thus force the orientation of the aldehyde in the manner shown in **8**. This prediction has indeed been realized and, in a way, validates the Zimmerman-Traxler model, particularly in the case of the boron-mediated aldol condensation.[12]

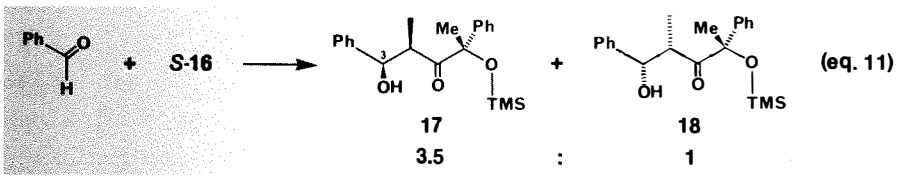
The experimental results are briefly summarized in eqs. 8 and 9.[11] Treatment of *S*-phenyl propionate (**10a**) and ethyl cyclohexyl ketone (**10b**) with **9-borabicyclo-[3.3.1]nonyl** trifluoromethanesulfonate (triflate) (**11**) effects the stereoselective formation of the corresponding *Z*(O) boron enolates **10a'** and **10b'**, respectively, which react with many aldehydes of various structural types to provide the racemic 2,3-*syn*-3-hydroxy-2-methylcarbonyl compounds **12a** and **12b** with a stereoselection of at least 30:1. On the other hand, **dicyclopentylborinyl** triflate (**13**) converts *S*-**tert-butyl** propionate (**10c**) to its *E*(O) enolate **10c'**, which is capable of producing 2,3-*anti* aldol products (**14**), again with excellent stereoselection (>20:1). The majority of the above results have been confirmed independently by Evans and coworkers.[13] Although a number of methods for the stereoselective synthesis of **racemic** 2,3-*syn*- and *anti*-3-hydroxy-2-methylcarbonyl compounds are now available, the boron-enolate aldol reaction remains the method of choice in terms of overall selectivity, yield, and operational simplicity.

2.4. 3,4-Stereochemistry. While the 2,3-problem quickly came to a successful end, the 3,4-problem consumed a great deal of our effort. The issue in question was this: how to force the enolate into either the α (see **8**) or the β (see **15**) side of an aldehyde.

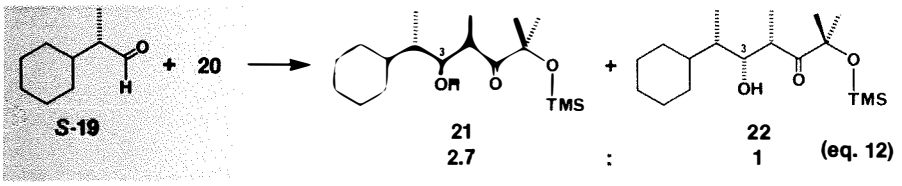
The aldehyde (with a trigonal carbon) has two faces: re and si (α and β, respectively) as shown in Scheme 1. These faces (or environments) are equivalent when the aldehyde is achiral, *i.e.*, R' = H or Me. In the case of R' ≠ H or Me, these faces are diastereotopic.[14] Thus, when an **achiral** reagent (a nucleophile in the aldol reaction) approaches the aldehyde, the reagent, in principle, exhibits a varying degree of preference for one face over the other. The degree of this preference normally shown in the product ratio is defined as **diastereofacial selectivity**.[15] The same argument also applies to the reagent. Thus, an **achiral** aldehyde approaching a **chiral** enolate "senses" the difference between the two faces of the enolate, and the latter becomes diastereoface-selective. Furthermore, the chirality of the ligands (L) attached to the metal (M) will also contribute to choosing between **8** and **15**. Although in actual synthesis the aldehyde is normally preselected, the enolate, metal, and its ligands can be varied, providing a means of controlling the 3,4-stereochemistry. Diastereofacial selectivity of the aldehyde has been extensively investigated both experimentally[2,16] and theoretically[17] and is often referred to as the Cram/anti-Cram selectivity.

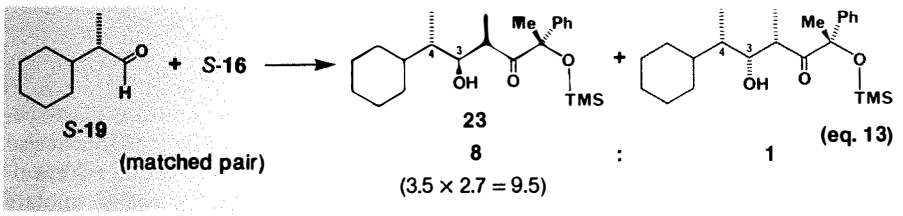
The concept of diastereofacial selection is not new.[14] However, our appreciation of the concept, which was clearly recognized in the process of solving the entire 2-, 3-, and 4-stereochemical problem, justifies a somewhat elaborate illustration.[7a] The chiral lithium enolate *S*-**16** has been readily prepared from (+)-*S*-atrolactic acid (eq. 10). The reaction of benzaldehyde with *S*-**16** leads to the formation of two aldol products, **17** and **18**, in a 3.5:1 ratio (eq. 11) which can be equated to the diastereofacial selectivity of *S*-**16**. As indicated by the β absolute configuration of the C-3 hydroxyl

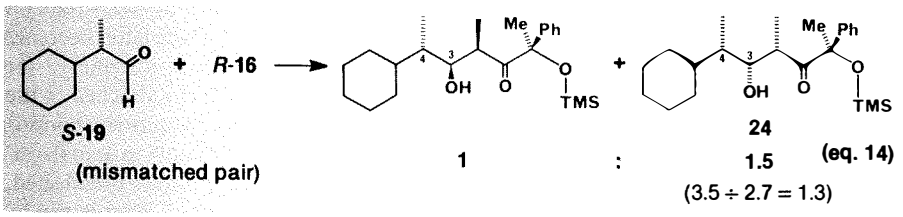




group of the major product **17** (section 2.2), the transition state of type **8** is more stable than that of type **15**, and thus *S*-**16** enolate exhibits a slight preference for the α-face of the aldehyde in the reaction. The diastereofacial selectivity of an aldehyde has also been evaluated. Thus, *S*-2-cyclohexylpropionaldehyde (*S*-**19**) provides, upon treatment with achiral lithium enolate **20** (R = Me), a 2.7:1 ratio of aldol products **21** and **22** (eq. 12), favoring its α-diastereoface for the approach of the external nucleophile **20**.[18a] Then, upon combination of *S*-**19** and *S*-**16** (a matched pair), both the aldehyde and enolate favor the α-face of the aldehyde in the reaction which would result in the enhancement of the 3,4-stereoselection (eq. 13). On the other hand, the reaction of *S*-**19** with *R*-**16** (a mismatched pair) would lead to inferior stereoselection (eq. 14). These predictions are confirmed by the results shown (8:1 in favor of **23** for the matched pair, and 1.5:1 in favor of **24** for the mismatched counterparts).[7a,19] Note that the absolute configuration of the hydroxyl groups in **23** and **24** are β and α, respectively.

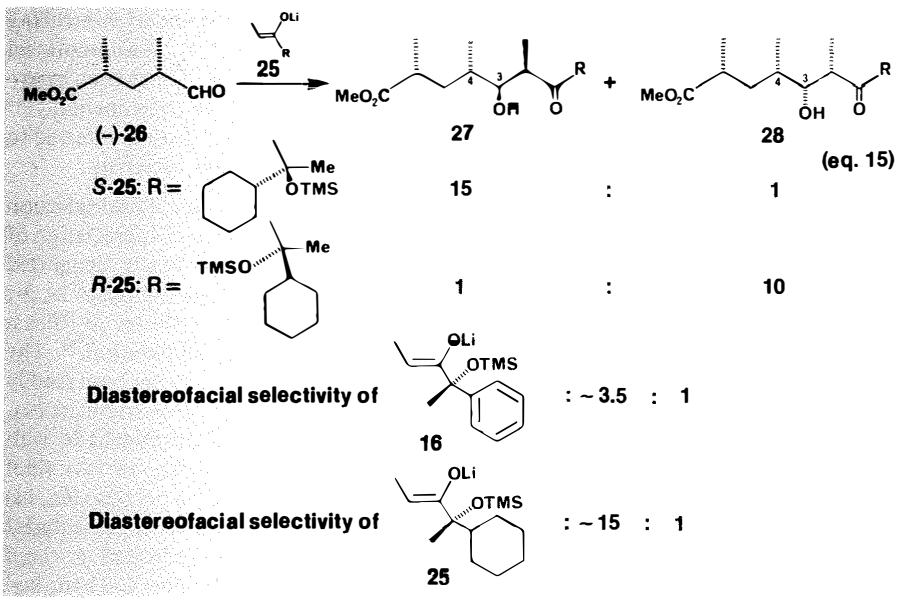






A judicious choice of a pair, reagent and substrate, may succeed in achieving the highly selective construction of 3,4-stereochemistry of *one kind* (*e.g.*, 3,4-*anti* as in **23**). Unfortunately, this methodology is bound to fail in preparing the other 3,4-stereoisomer (*e.g.* , **24**) in an equally selective manner. Therefore, stereochemical **control** has not been achieved. However, there emerges an important corollary: if one can prepare a chiral enolate reagent which possesses sufficiently high diastereofacial selectivity (*i.e.*, > 100:1), the normally small (Cram/anti-Cram) selectivity of aldehydes (ranging 1:1 to 4:1)[11] can be easily outweighed to the extent that either the 3,4-*syn* or the 3,4-*anti* isomer can be prepared as the (nearly) exclusive product. The first step we took toward this aim was the use of reagent **25** (eq. 15), the hexahydro derivative of **16**, which was found to have a diastereofacial selectivity of approximately 15:1.

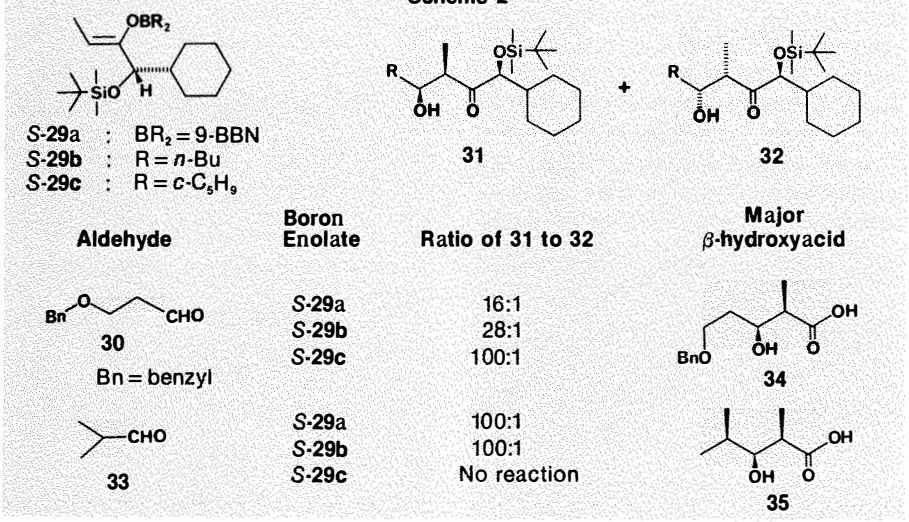
The reaction of semi-aldehyde (−)-**26** with the chiral lithium enolate reagent *S*-**25** provides a 15:1 ratio of **27** (3,4-*anti*) and **28** (3,4-*syn*). Use of the *R*-reagent reverses the ratio to 1:10.[7a] This was the **first important demonstration of 3,4-control** in aldol chemistry, although admittedly, the ratios are marginally acceptable and the diastereofacial selectivity of **26** is only in the neighborhood of 3:2.



2.4.1. Chiral *Z*(O) Boron Enolate Reagent (2,3-*syn*-Selective).[20] An immediate goal was clear at this stage: we must prepare a chiral enolate reagent with a diastereofacial selectivity of 100:1 or greater. Eliminating the details of the long road leading to this goal as well as abbreviating a mechanistic rationale for its high selectivity, we show in Scheme 2 the structure of the reagent(s) which are now used routinely for the synthesis of complex molecules (see Section 3). The *S*(or *R*)-boron enolates [*S*(*R*)-**29a,b,c**] are prepared from optically active mandelic acids through routine operations (see Experimental Part). The reactivity and selectivity of **29** in the aldol reaction can be adjusted with the selection of a proper boron substituent as shown (a-c). For instance, aldehyde **30**, a primary aldehyde chosen from many examples tested, undergoes aldol reaction with *S*-**29c**, the most stereoselective (but least reactive) to

provide a 100:1 mixture of two diastereoisomers **31** and **32** (R = $PhCH_2O-CH_2-CH_2$-). In the case of **33**, an α-branched aldehyde, the stereoselectivity of the reaction is very high [>100:1 of **31** to **32** (R = Me_2CH-)] even with the least selective (but most reactive) ***S*-29a**.[21] Successive treatments of a mixture of **31** and **32** with hydrogen fluoride (or fluoride anion) followed by sodium metaperiodate provide the corresponding 2,3-*syn*-3-hydroxy-2-methylcarboxylic acid (**34** or **35**) with an enantiomeric excess higher than 98%! These results meet the standards set for the project. The capability of these reagents to control the 3,4-stereochemistry in the reaction with chiral aldehydes will be examined in the total syntheses that are described in Section 3.

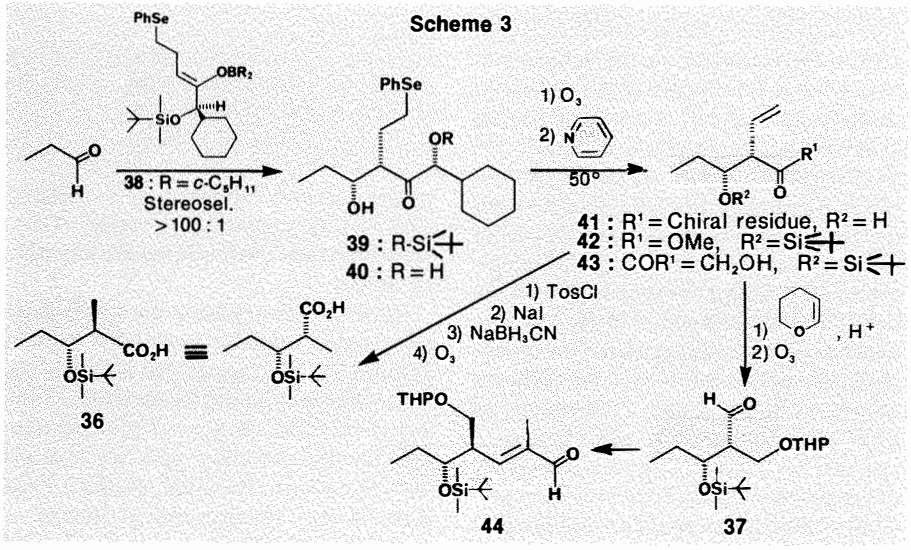
Scheme 2



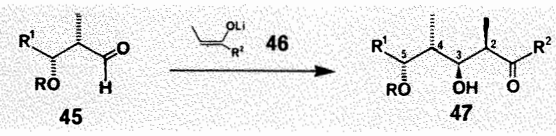
2.4.2. **Enantioselective Synthesis of the 2,3-*anti*-3-Hydroxy-2-methylcarbonyl Compounds *via* an Indirect Route.**[7b] Since the aldol reaction with the *Z*(O) boron enolate **29a-c** provides a means of synthesizing 2,3-*syn* compounds enantioselectively, this general approach should be extended to the use of chiral *E*(O) enolates. From the above discussions, these *E*(O) enolates are expected to give rise to optically active 2,3-*anti* isomers (*e.g.*, **36**). Unfortunately, many attempts made thus far by us and others at devising such *E*(O) reagents (with diastereofacial selection comparable to that of **29a-c**) have met with only partial success.[22] Enolate precursors (Et-COR) which have a bulky chiral auxiliary (R) are prone to form the corresponding *Z*(O) enolate even with reagents normally used to generate *E*(O)-isomers (Section 2.3). This tendency is mainly responsible for the lack of a highly diastereofaceselective *E*(O) reagent at present. An indirect and somewhat circuitous solution which we have found for this 2,3-*anti* problem is outlined below. This tentative solution also happens to provide a route to the systems having two hydroxyl groups at the β and β′ positions to a carbonyl group (*e.g.*, **37**), another structural unit commonly found in natural products (Sections 3.3 and 5), but difficult to construct otherwise.

Syntheses of the optically pure 2,3-*anti*-3-*tert*-butyldimethylsilyloxy-2-methylpentanoic acid (**36**, Scheme 3) and the corresponding 2-hydroxymethyl aldehyde **37** illustrate the case. The reaction of propionaldehyde with the new chiral selenium-containing reagent **38**, modified slightly in structure from **29c**, proceeds in the expected manner (diastereoselection >100:1) to provide **39** which, after removal of the silyloxy protecting group (see **40**), is subjected to standard conditions for the elimination of the PhSeOH group (O_3 and then warming at 50° with pyridine). Successive treatments of the resulting vinyl compound **41** with sodium metaperiodate, diazomethane, and *tert*-butyldimethylsilyl triflate provide a key intermediate (**42**), which possesses two different functional groups, an olefin and an ester. Both groups can be readily modified to reach **36** and **37**. First, diisobutylaluminum hydride (DIBAL-H) reduction converts **42** into **43**. Transformations of **43** into **36** and **37** are straightforward (see Scheme 3). Compound **37** has been used to prepare the right-hand portion (**44**) of tylonolide (Section 3.3) through a Wittig reaction with ethoxycarbonylethylidenetriphenylphosphorane, DIBAL-H reduction, and Collins oxidation. Another application of this methodology appears in Section 5. It is apparent that the right-hand end of the main chain and the 2-substituent of the key intermediate **42** are interchanged in **36** and **37** in order to construct the 2,3-*anti* stereochemistry. Thus, overall, a chiral *Z*(O) enolate provides a highly selective synthesis of an optically active 2,3-*anti* aldol product as well.

Scheme 3

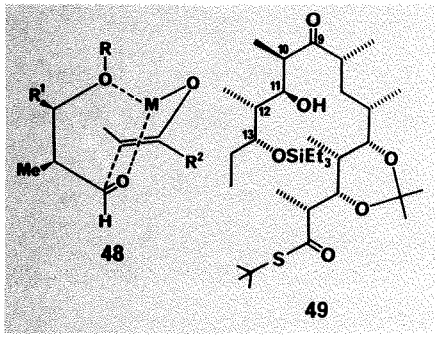


2.4.3. **Coordination of the Lithium Cation with an Alkoxy Substituent: Construction of the 2,3-*syn*-3,4-*anti*-4,5-*syn*-3,5-Dihydroxy-2,4-dimethylcarbonyl System.**[23] Lithium and magnesium enolates used in aldol reactions, in contrast to boron enolates, exhibit distinct propensity for coordination with oxygenated functional groups present in either the enolate itself or the reacting aldehyde. The stereochemical consequence resulting from this coordination has been delineated by Cram's cyclic (coordination) model,[24] as illustrated by the reaction of a 2,3-*syn*-3-alkoxy-2-methylcarboxaldehyde (**45**) with a lithium *Z*(O) enolate (**46**, eq. 16).

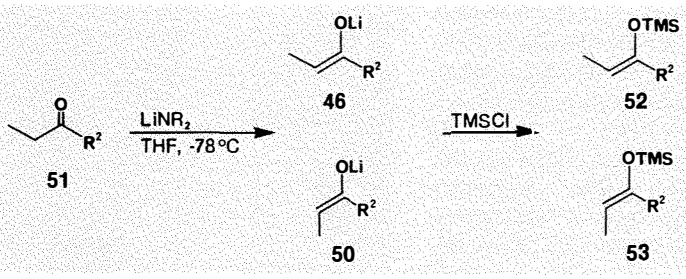


(eq. 16)

In a Cram-type transition state (**48**) the lithium cation is coordinated with three oxygen atoms including one of the 3-alkoxy group. The enolate **46** is assumed to approach the aldehyde **45** from the α (re) face of **45** in order to minimize the interaction between **46** (carrying the substituent R^2) and the two substituents at the 3- and 2-positions of **45**. Transition state **48** should



lead to the formation of the 2,3-*syn*-3,4-***anti***-4,5-***syn***-3,5-dihydroxy-2,4-dimethylcarbonyl derivative **47**, a structural feature in several natural products such as C-9—C-13 fragment (**49**) of 6-deoxyerythronolide B. Obviously, the difference between the two transition states [emerging from the re (shown in **48**) and si (not shown) approaches] is likely to depend in part on the size of both R^1 in **45** and R^2 in **46**. Also prerequisite for the construction of the stereochemistry embedded in **47** is the exclusive generation of the lithium *Z*(O)-enolate **46** from the corresponding ethyl ketone, a task that has demanded an extensive survey of lithium bases. [Compare with the generation of *Z*(O) boron enolate which is under nearly perfect control (Section 2.3).] In general the *Z*:*E* ratio of the two geometrically differing enolates **46** and **50** (eq. 17) derived from an ethyl ketone **51** with a lithium amide depends largely on the size of the R^2 group in **51** as well as the basicity and steric bulk of the base used. Thus, while treatment of a 2,2-dimethylpentan-3-one (**51** with a bulky R^2) with lithium diisopropylamide provides its *Z*-enolate (**46**:$R^2 = t$-Bu) quantitatively, the direct, exclusive generation of the *Z*-lithium enolate from a ketone with a less bulky R^2 such as ethyl had not been realized prior to our investigation. Table 1 summarizes some selected results. Pentan-3-one (**51a**) and ethyl cyclohexyl ketone (**51b**), chosen as representative ethyl ketones having a small and a medium R^2 group, respectively, provide varying *Z*:*E* ratios (**46** versus **50**), as analyzed by the corresponding trimethylsilyl ethers (**52** and **53**) obtained from their lithium enolates. Clearly, in both cases, the ratio is significantly enhanced as the size of the substituents of the disilazide increases; in particular, the use of lithium 1,1,3,3-tetramethyl-1,3-diphenyldisilazide (**54**) leads



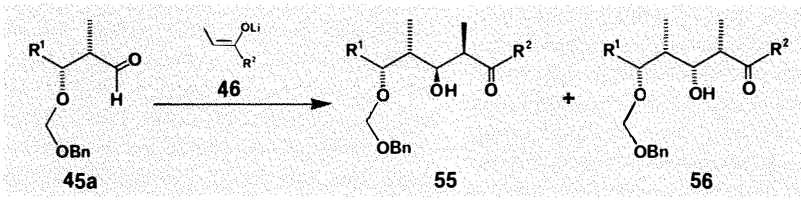
(eq. 17)

Table 1
The *Z*:*E* Ratio of the Enolates derived from Ethyl Ketones.

R^2 in 51	Base	Z:E Ratio
Et (**51a**)	*i*-Pr_2NLi	30:70
Et (**51a**)	$(Me_3Si)_2NLi$	70:30
Et (**51a**)	$(Me_2PhSi)_2NLi$ (**54**)	>100:1
Et (**51a**)	$(Et_3Si)_2NLi$	99:1
Cyclohexyl (**51b**)	*i*-Pr_2NLi	61:39
Cyclohexyl (**51b**)	$(Me_3Si)_2NLi$	85:15
Cyclohexyl (**51b**)	$(Me_2PhSi)_2NLi$ (**54**)	99:1
Cyclohexyl (**51b**)	$(Et_3Si)_2NLi$	94:6

to the exclusive formation of *Z*-enolates. This finding is general for a variety of simple ketones and obviously has great synthetic utility.

With the geometrically pure *Z*-enolates now readily available from ethyl ketones **51a** and **51b**, the factors that influence the stereoselectivity in the construction of the 2,3-*syn*-3,4-*anti*-4,5-*syn*-3,5-dihydroxy-2,4-dimethylcarbonyl system (see **55** or **47**) may be defined. The aldol reaction of **45a** with **46** (eq. 18) proceeds efficiently at -78 °C to provide two major products **55** and **56** (see Table 2), in addition to minor amounts of the 2,3-*anti*-stereoisomers corresponding to **55** and **56**. (Amounts of these 2,3-*anti*-3,4-*syn*-isomers are significantly smaller than those observed in the aldol reaction with an aldehyde carrying no β-alkoxyl substituent.) This is consistent with the view that the reaction of **45a** proceeds through the transition state **48**. The β-alkoxyl substituent organizes, in **48**, a rigid framework with the lithium cation which steers the reaction to create the 2,3-*syn* stereochemistry. The interaction between the enolate with R^2 and the two groups of the aldehyde, methyl and in particular R^1, are indeed important, as anticipated. With a small interaction (entries 1-3, Table 2) the ratio ranges between 3.5:1 to 5:1 and increases to approximately 10:1 when R^1 is primary or secondary alkyl and R^2 is secondary alkyl (entries 4, 6, 8). Most significantly, when R^1 carries an additional ethereal substituent, and thus creating yet



(eq. 18)

Table 2

Entry	R^1 in 45a	R^2 in 46	Ratio of 55 : 56	Combined Yield (%) of 55 and 56
1	H	Et	4:1	87
2	H	Cyclohexyl	3.6:1	79
3	Et	Et	5:1	81
4	Et	Cyclohexyl	9:1	79
5	$PhCD_2$-	Et	5.5:1	71
6	$PhCD_2$-	Cyclohexyl	9:1	70
7	*i*-Pr	Et	6.9:1	75
8	*i*-Pr	Cyclohexyl	11.5:1	68
9	*t*-$BuMe_2SiOCH_2CH_2$-	Et	13:1	82
10	*t*-$BuMe_2SiOCH_2CH_2$-	Cyclohexyl	19:1	79

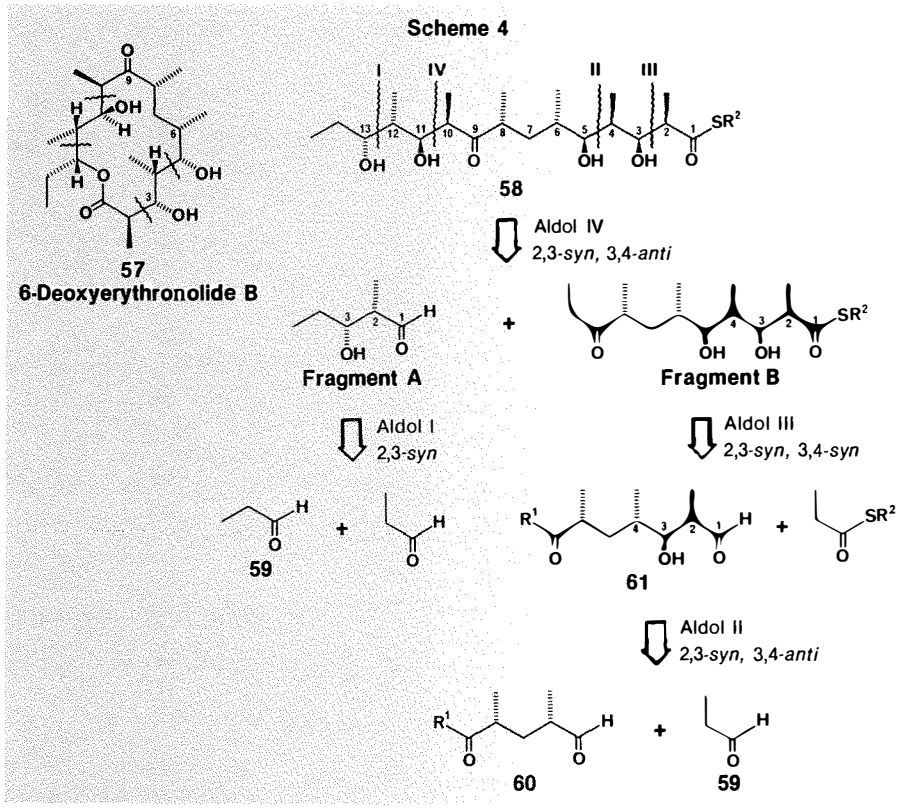
another ligand to coordinate the lithium cation, the observed selectivities (entries 9, 10) now exceed 10:1.

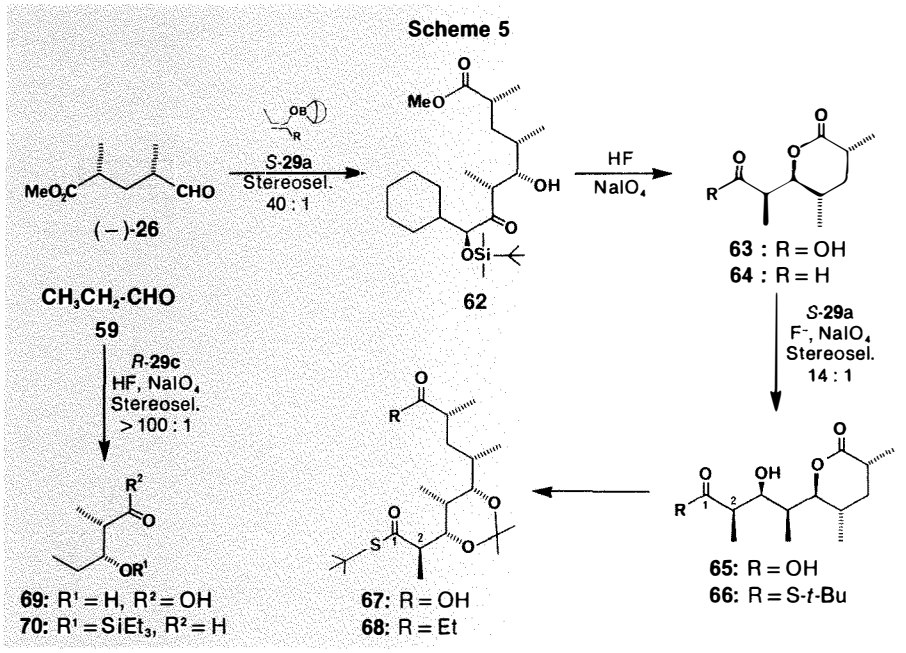
3. Macrolide Synthesis *via* Aldol-Type Reactions

Stereocontrol described in the preceding sections is sufficient for most of the crucial synthetic transformations in the total syntheses of the selected macrolides: 6-deoxyerythronolide B, rifamycin S, and tylonolide. All the synthetic designs follow the simple and now established "seco-acid aldol approach" (in which a seco-acid is, in a final stage, lactonized to the corresponding macrolide).[3] The central issue is the creation of the chiral centers embedded in the carbon skeleton, and this challenge has been resolved by means of the aldol methodology with remarkable overall efficiency in terms of both yield and stereoselection.

3.1. **6-Deoxyerythronolide B.**[25] This metabolite **57** is biosynthesized exclusively from propionates (one propionyl CoA and six methylmalonyl CoA's) and leads to all the erythromycins presently known. Once the seco-acid aldol approach is adopted, designing a synthetic scheme is straightforward. Splitting the seco-acid derivative **(58)**, drawn in a zigzag fashion, into fragments A and B immediately suggests the order of the aldol reactions to be utilized in the synthesis (Scheme 4). Aldol I (involving propanal **59** and its equivalent) produces fragment A, while aldols II (**59** and **60**) and III (**61** and an equivalent of **59**) complete a synthesis of fragment B. Finally, both fragments are combined *via* aldol IV. Note that aldols I, II, and III all concern the creation of **2,3-*syn*** stereochemistry, the task that can be readily achieved with the chiral boron enolates **29a,b,c** described earlier (Section 2.4.1).

3.1.1. **Seco-Acid.** The reaction of (−)-aldehyde **26** with the *S*-chiral reagent **29a** (Scheme 5) proceeds smoothly (stereoselection 40:1) to provide an aldol product **62**[18] which, after removal of the chiral auxiliary (HF and then $NaIO_4$), is converted quantitatively into the Prelog-Djerassi lactonic acid **63**. A key intermediate in the syntheses of several natural products such as methymycin[26] and narbonolide,[27] **63** is readily available in multigram quantities and in optically pure form (>98% e.e.). Addition of the C-1, C-2 fragment to **63** again uses the *S*-chiral reagent **29a**. Aldol reaction of the aldehyde **64** derived from **63** provides (with 14:1 stereoselection) the major product which, upon standard treatment (*e.g.*, **62** to **63**), is transformed to the carboxylic acid **65** and then to its thiol ester **66**. After modification of the functional groups of **66** through a series of routine reactions, the resulting carboxylic acid **67** is further converted to the corresponding ethyl ketone **68**, which is an equivalent of fragment B.





The enantioselective synthesis (selectivity >100:1) of the hydroxy acid **69** corresponding to fragment A (Scheme 5) is readily achieved using propionaldehyde (**59**) and the *R*-chiral reagent **29c**. A sequence of standard operations converts **69** into aldehyde **70** which is ready for coupling with **68**.

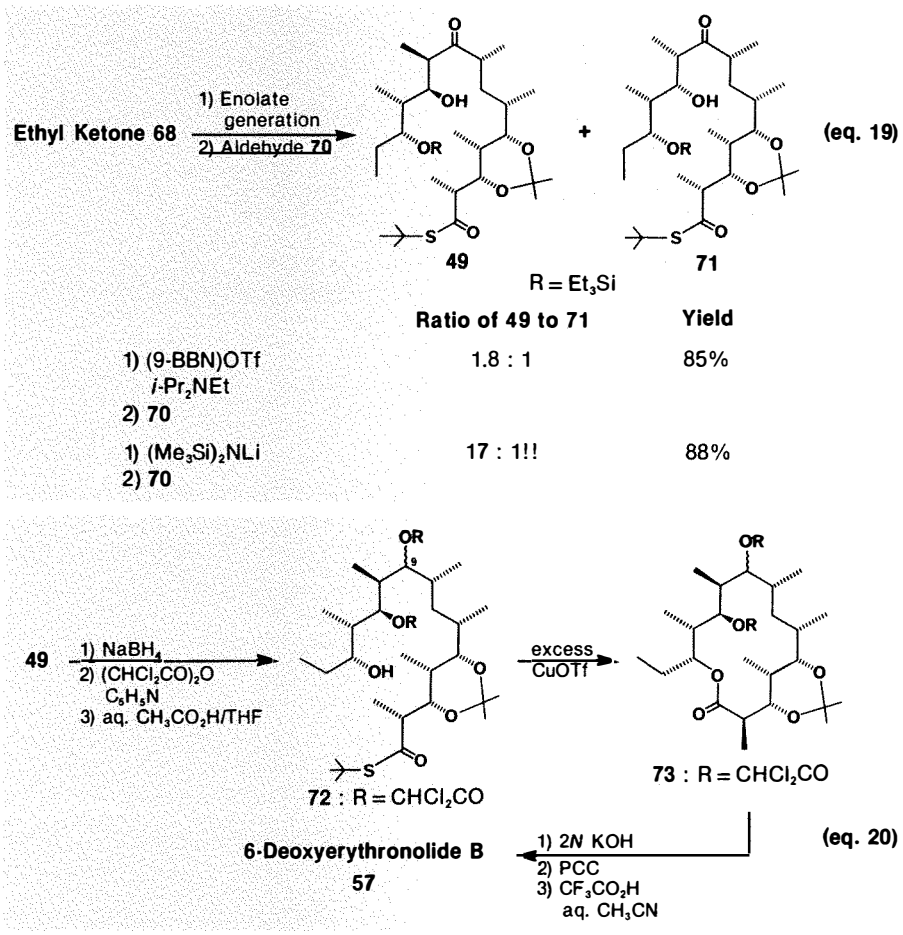
The final aldol coupling of **70** and **68** (eq. 19) is different from those described above in that both the aldehyde and enolate (ethyl ketone) are set and a diastereofacial-selective reagent (such as **29**) cannot be used to advantage. What is displayed in this final carbon-carbon bond formation is the strong coordinating power of the lithium cation with the ethereal oxygen atom attached to the β-carbon of aldehyde **70**, as already outlined in Section 2.4.3. Treatment of **68** with lithium hexamethyldisilazide* at -78 °C followed by addition of **70**

*The use of **54** is unnecessary to achieve the exclusive formation of the *Z*-enolate in this case because the effective bulk of the C-8—C-1 fragment of this ethyl ketone **68** is considerably larger than that of **51a** or **51b**.

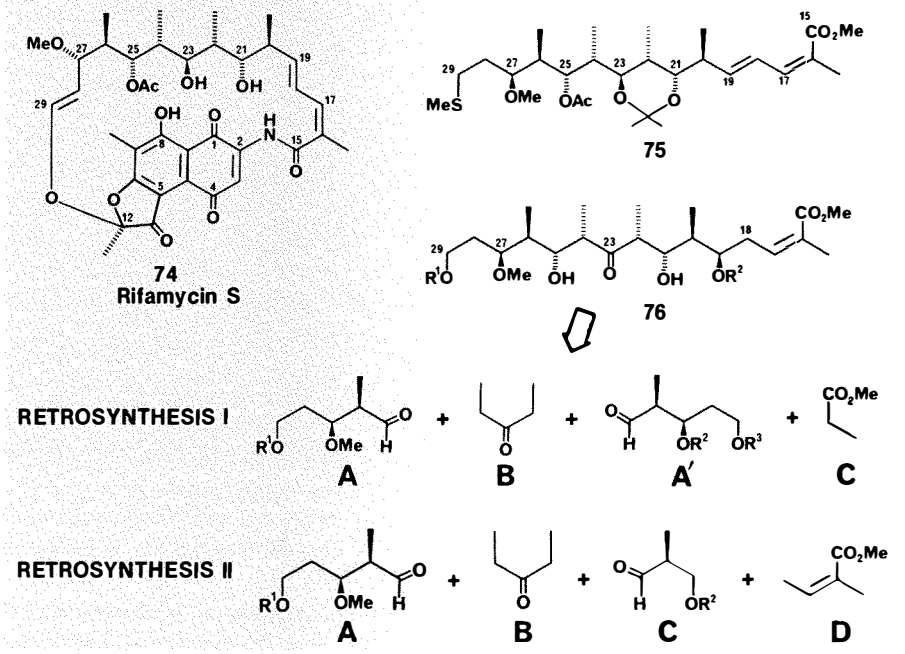
gives rise to the desired **49** and its diastereoisomer **71** at a diastereoselection of 17:1, a highly gratifying result in view of the low selectivity (1.8:1) observed in the boron-mediated aldol reaction. The synthesis of the seco-acid **49** containing 10 chiral centers thus proceeds in 11% overall yield based on (-)-aldehyde **26** and propanal **59** used and an overall stereoselection of 85% for the four aldol reactions.

3.1.2. **Lactonization.** The conclusion of the 6-deoxyerythronolide B synthesis is briefly summarized below, as this is not the main subject of this article. A sequence of reactions (eq. 20), (1) reduction of **49** with $NaBH_4$, (2) bisdichloroacetylation of the resulting dihydroxyl compounds, and (3) desilylation, provides epimeric (9α and 9β) 13-hydroxy thiol ester **72** which is lactonized with excess copper(I) trifluoromethanesulfonate[25] in benzene containing 2 equiv. of diisopropylethylamine. After the successful execution of this crucial lactonization step, the subsequent transformation of **73** proceeds in a straightforward manner. Removal of the dichloroacetate protecting group, followed by selective oxidation of the C-9 hydroxyl group and finally hydrolysis of the acetonide group with mild acid completes the synthesis of the target molecule **57**.

3.2. **The Ansa Chain of Rifamycin S.**[26] Rifamycin S (**74**) is a well known antibiotic belonging to the ansamycin family (see Scheme 6).[28] The structure of this compound is uniquely characterized by the naphthoquinone moiety bridged at the 2 and 12 positions by the "ansa" chain (**75**). The symmetry element which is present in **75** becomes all the more evident with two retrosynthetic operations: (1) oxidation of the C-23 hydroxyl group to the ketone, and (2) hydration of the double bond as indicated in **76**. The C-18—C-28 fragment incorporating all the chiral centers in **76** now has C_s symmetry (if R^2 = Me). Dissection of **76** leads to a set of four units, A, B, A′, C (retrosynthesis I) or another set, A, B, C, D (retrosynthesis II), the former (I) being more symmetrical than the latter. Note that (1) units A and A′ are enantiomeric and are readily available in >98% optical purity (see Section 2.4.1) and that (2) each half (C-18—C-23 and C-23—C-28) of **76** constitutes a 2,3-*syn*-3,4-*anti*-4,5-*syn*-2,4-dihydroxy-3,5-dimethylcarbonyl system (numbering starts with the carbonyl group), whose stereoselective construction can be achieved by a single aldol reaction (see Section 2.4.3). The aldol approach to the synthesis of **75** is, thus, extremely attractive. The synthesis described below is based on retrosynthesis II rather than I, as II offers the advantage of confirming the stereochemistry of a synthetic intermediate halfway in the entire sequence. Even with this less symmetrical design, the 18-step synthesis proceeds in 30% overall yield and with 80% overall stereoselectivity.[29]



Scheme 6



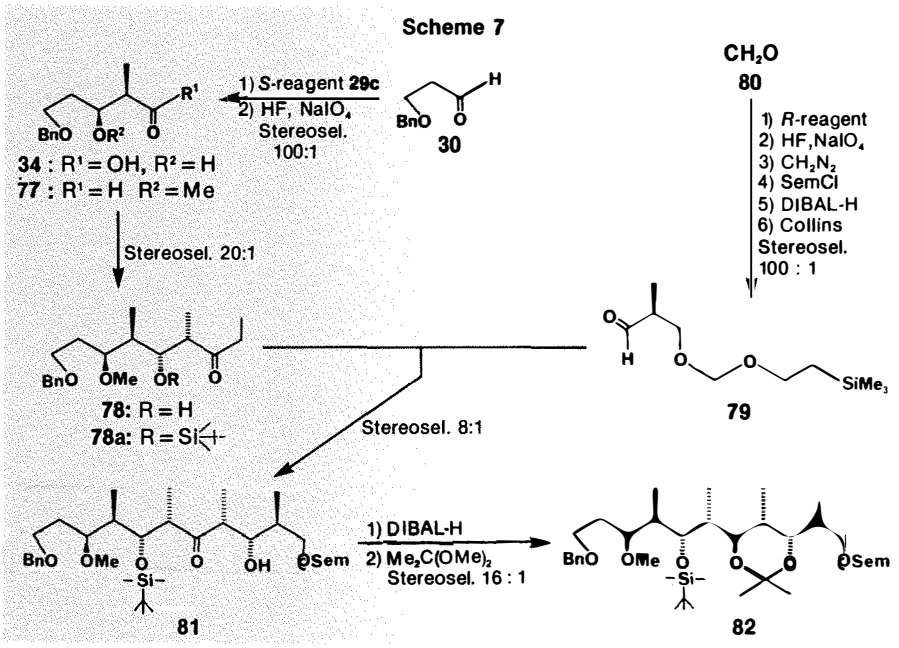
3.2.1. **The C-19—C-29 Fragment.** The synthesis (Scheme 7) starts with (-)-3-hydroxy-2-methylcarboxylic acid (**34**) which is readily prepared enantioselectively (99% e.e.) from **30** (see Section 2.4.1). A sequence of standard reactions converts **34** into **77** which is ready for the aldol reaction with the *Z*-enolate generated from pentan-3-one with lithium 1,1,3,3-tetramethyl-1,3-diphenyldisilazide (Section 2.4.3). The reaction proceeds smoothly to provide the

ethyl ketone **78** in >95% yield and with 20:1 stereoselection. The C-25 hydroxyl group of **78** is then protected with a ***bulky*** group (*t*-BuMe$_2$Si). The silylated ketone **(78a)** is converted to the corresponding lithium *Z*-enolate for the final aldol reaction with aldehyde **79**, prepared from formaldehyde **(80)**[30a] or, directly, from enzymatically derived *S*-3-hydroxyisobutyric acid.[30b] With the bulky substituent at the C-25 position of the enolate (derived from **78a**), the **intramolecular** coordination of the lithium cation is suppressed and the intermolecular coordination with the ethereal oxygen of **79** is maximized.[31] Yet, as expected from the structure of **79**, having the primary Sem-O substituent (Section 2.4.3), the diastereoselectivity of this aldol reaction is only modest (3:1) and is enhanced to 8:1 only with the addition of bis(cyclopentadienyl)-zirconium dichloride to the lithium enolate[32] prior to the reaction with **79**. This ratio is expected to be further enhanced if the synthesis is based on the symmetrical retrosynthesis I (see Section 2.4.3).

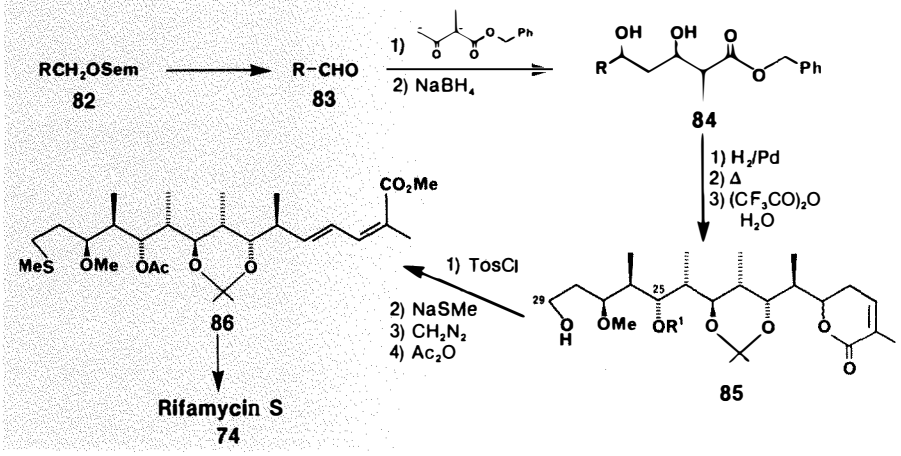
The reduction of **81** with DIBAL-H proceeds with a stereoselection of 16:1 as expected, and the resulting diol is converted to its acetonide **82**, which is correlated with a degradation product of the antibiotic **74** to confirm its stereochemistry. Thus, **the seven-step sequence** converts **34** into **82** which incorporates all the 8 chiral centers present in the ansa chain.

3.2.2. Ansa Chain. The addition of a five-carbon (C-15—C-18) unit to the C-19—C-29 fragment to construct a *Z*:*E*-dienoic acid system is patterned after the methodology originally developed for the synthesis of monomethyl *Z*,*E*-muconate by Linstead and coworkers.[33] Thus, aldehyde **83** (derived from **82**, Scheme 8) is treated with the lithium dianion of benzyl 2-methylacetoacetate to yield the expected β-keto ester which is reduced with NaBH$_4$ to yield the diol isomers **84**. The number of diastereoisomers (eight) is irrelevant, since all will be converted to a single final product. Hydrogenolysis followed by heating causes complete lactonization; treatment with trifluoroacetic anhydride and then water provides the α,β-unsaturated δ-lactones **85** (R^1 = CF$_3$CO). The C-29 primary hydroxyl group of **85** is then tosylated. The ensuing step is efficient; reaction of the tosylate of **85** with excess sodium methanethiolate effects three transformations: (1) substitution of the tosyl group, (2) liberation of the C-25 hydroxyl group, and (3) the desired lactone ring opening to yield the *Z*,*E*-dienoic acid (80%) without double-bond isomerization. Esterification and acetylation completes the synthesis of **86**, which was earlier converted to rifamycin S.[29]

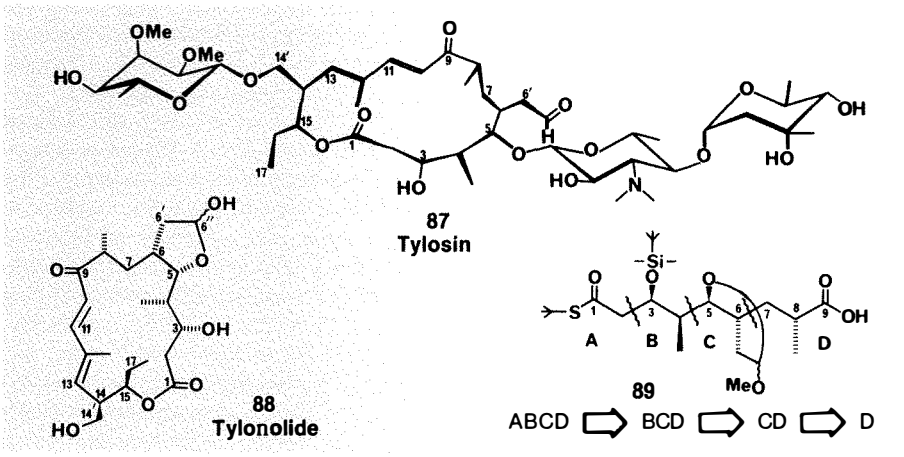
Scheme 7



Scheme 8



3.3. Tylonolide, the Aglycone of Tylosin.[15] The antibiotic tylosin **(87)** represents the well known family of 16-membered polyoxomacrolide antibiotics.[15] The structure of its aglycone, tylonolide **(88)**, reveals the unique C-13—C-15 unit with an *anti*-14-hydroxymethyl-15-acyloxy stereochemistry, a structural and stereochemical feature absent in 6-deoxyerythronolide B **(57)** and rifamycin S **(74)**. With the methodology developed for the construction of this unit (Section 2.4.2), the seco-acid aldol approach to the synthesis of **88** is now feasible. A retrosynthetic analysis of **88** which is similar to that applied to **57** dissects the 16-membered ring into three fragments: the left-hand (C-11—C-17, **44**), C-10, and the right-hand (C-1—C-9, **89**). The last



fragment is further split into four subunits in the manner, ABCD→BCD→CD→D.[34] The synthesis of **89** features the asymmetric aldol reaction and asymmetric hydroboration. In addition there emerges a new problem of constructing the 3-hydroxycarbonyl (-*CHOH-CH_2-CO-) system (in contrast with 3-hydroxy-2-methyl system discussed repeatedly above).

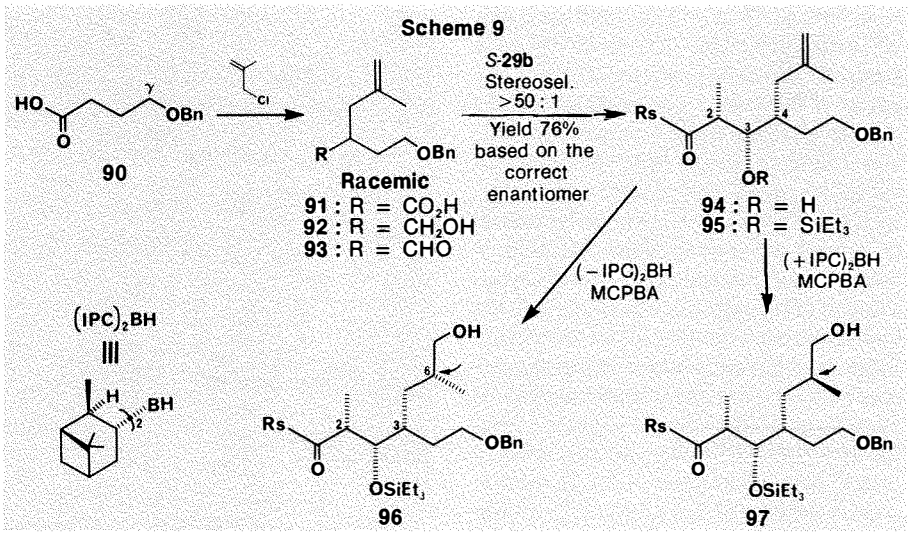
3.3.1. **Preparation of Subunit BCD (C-3—C-9) in 89.** Reaction of the lithium dianion derived from 4-benzyloxybutyric acid (**90**) with methallyl chloride (Scheme 9) provides the racemic monoalkylated carboxylic acid **91**, which is converted into the corresponding aldehyde **93** through the hydroxyl compound **92**. The *S*-enantiomer of **93**, which is of no avail in the synthesis, is most conveniently removed in the subsequent step.

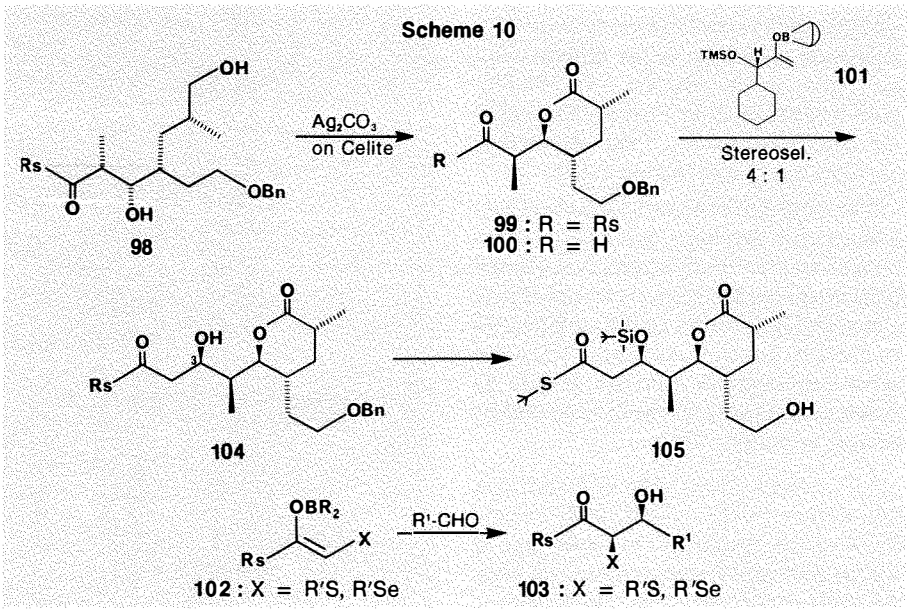
The construction of three chiral centers (C-2, C-3, and C-6 in **96** corresponding to C-4, C-5, and C-8 in **88** or **89**) is achieved with an excellent overall stereoselection of >25:1. Thus, aldol reaction of **93** with 1.7 equiv. of the *S*-boron enolate reagent (**29b**) proceeds with the dominating diastereofacial selectivity inherent in the reagent, converting the *R*-enantiomer of **93** exclusively to **94** and the *S*-enantiomer of **93** (see above) to the C-4 epimer of **94**. The two diastereomeric products are separated (Section 1). Hydroboration of **95**, the triethylsilylated derivative of **94**, with (−)- and (+)-bis(isopinocampheyl)borane [$(IPC)_2$-BH] results in the exclusive formation of **96** and **97**, respectively. This remarkably high stereoselectivity (>50:1) is normally not expected for the reaction of the methallyl system with these reagents.[35] Compound **95** behaves in a unique manner and, apparently, the chirality existing in **95** hardly influences the overall steric course of the reaction.

3.3.2. **Preparation of the Right-Hand Fragment 86: Problems Concerning the Acetate Addition.** The dihydroxyl compound **98** (Scheme 10) that results from selective deprotection of the C-3 hydroxyl group of **96** is oxidized with Fetizon's reagent to provide directly the lactone **99**, which, after desilylation, borane-ammonia reduction, and sodium metaperiodate oxidation, is converted to aldehyde **100**. Thus, we arrive at the last stage of the sequence leading to **89**, which involves a stereoselective addition of an acetate unit to aldehyde **100**. This two-carbon extension is indeed a fundamental process in the synthesis of acetate-derived natural products for which a general method has been sought.

Many examples have already been quoted above to demonstrate the large diastereofacial selectivity of boron enolates derived from the corresponding *ethyl* ketones, *e.g.*, **29a,b,c**. In contrast, an aldol reaction using an analogous enolate [*e.g.*, **101a** (TBDMS instead of TMS in **101**)] prepared from the *methyl* ketone and an achiral aldehyde proceeds virtually nonselectively. Although the sulfur reagent (**102** with X = SMe or SPh) similar to that described by Evans *et al.*[21] regenerates the high selectivity, experiments in our laboratories have shown that removal of the thiol group from aldol products (**103** with X = RS) involves rather serious problems [such as low yields (35-40%)]. Extensive investigation has been carried out to explore the reaction involving selenium reagents in combination with a variety of hindered bases (including 2,6-di-*tert*-butyl-4-methylpyridine) to generate the corresponding enolates (**102** with X = MeSe, *c*-C_6H_{11}Se, *i*-PrSe, PhSe) in high yield.[36] After the completion of an aldol reaction, the selenyl group is readily and quantitatively eliminated from **103** (X = R'Se) by washing with a K_2HPO_4-buffered solution containing benzenethiol.[37] The overall selectivity of the aldol reaction with primary aldehydes, followed by removal of the selenyl group, ranges between 20-50:1 with a 50-80% yield. However, the reaction with secondary aldehydes (which are model substrates pertinent to the present case) is extremely sluggish and results in an unacceptable yield of the product.[36]

After all this, we concluded that at the time, the aldol reaction of **100** with **101** served as the best available solution in terms of yield, stereoselectivity, and operational simplicity. Using the chiral boron enolate **101** in the standard boron-mediated aldol reaction with 9-BBN(OTf), **100** provides a 4:1 mixture of aldol products, **104** and its C-3 epimer, in 88% yield. While both **100** and **101** exhibit small but apparently "matched" diastereofacial selectivities, thus bringing about the above modest ratio, this selectivity certainly falls short of the standards originally set for the project.





Indeed, this result catalyzed our exploration of eq. 5 involving asymmetric epoxidation, mentioned at the beginning of this article and to be elaborated in Sections 4 and 5.

Compound **104** is converted to **105** *via* a sequence of six reactions: (1) removal of the chiral auxiliary, (2) catalytic hydrogenolysis, (3) silylation, (4) hydrolysis of the silyl ester, (5) conversion into the thiol ester, and finally, (6) selective hydrolysis of the primary silyl ether.

3.3.3. **Preparation of the Seco-acid Derivatives and Their Lactonization.** With all of the chiral centers embedded in tylonolide **88** having been constructed, the remaining tasks were to join the right- and left-hand fragments and then to lactonize the resulting seco-acid derivative whose functional groups were properly protected. These transformations have been achieved in a manner similar to that of the narbonolide synthesis.[27]

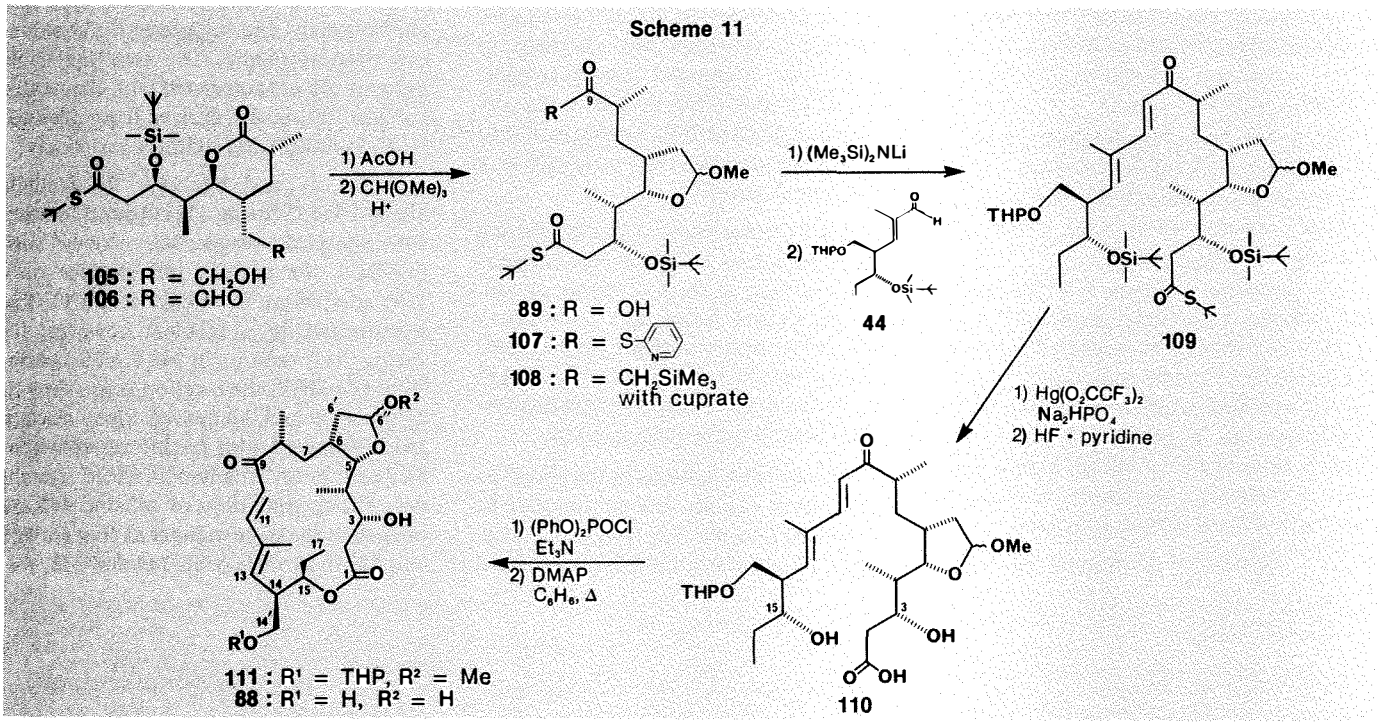
The aldehyde **106** derived from **105** (Scheme 11) undergoes an acid-catalyzed rearrangement of the δ-lactone into the γ-lactol, which is protected to give **89**. This C-9 carboxylic acid is converted through **107** to the corresponding trimethylsilylmethyl ketone (**108**), the lithium anion of which is condensed with the left-hand aldehyde **44** to complete the construction of the seco-acid skeleton (**109**). Partial deprotection of the functional groups attached to **109** leads to seco-acid **110**, which is then macrolactonized through a phosphate intermediate. Acid treatment of the resulting lactone **111** produces tylonolide **88**.

4. Asymmetric Epoxidation — Ring Opening Sequences[6,9]

As shown in the preceding sections, the excellent stereoselective addition of a propionate unit to an aldehyde (**A**) can be applied effectively in the preparation of any of the stereoisomerically possible 3-hydroxy-2-methylaldehydes (**B**, reaction 4, Scheme 12), whereas the aldol reaction for transforming **A** to **C**, formally an addition of an acetate unit, proceeds with only marginal stereoselection. For the latter transformation, a route involving epoxidation and reductive ring opening was considered highly promising. Thanks to Sharpless' discovery, the versatile epoxide functionality can be introduced into the allylic system of various structural types with his titanium reagent which possesses an impressively high diastereofacial selectivity (50-100:1).[38] It soon became apparent that this general route, with some modification, would bring about another important transformation, **A** to **D** (reaction sequence 5), thus creating two chiral hydroxymethylene (-*CHOH-) centers in one sequence.

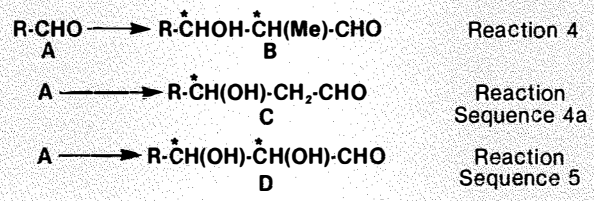
Reaction sequences 4a and 5 (Scheme 13)

Scheme 11

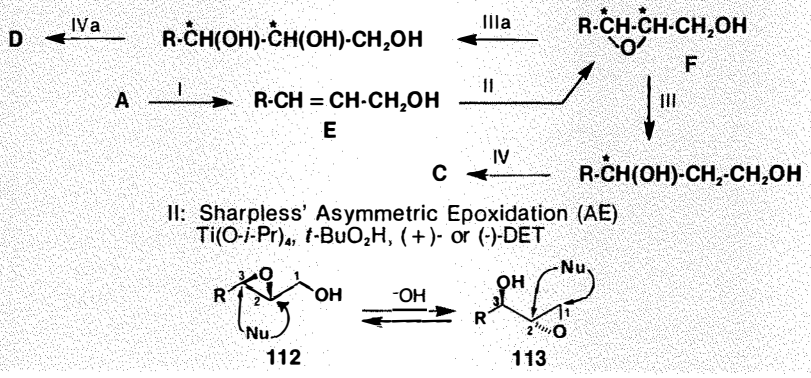


Scheme 12

Work in collaboration with Professor Sharpless' group.



Scheme 13



are formulated as follows: The first step (I) consists of the construction of an *E*- or *Z*-allylic alcohol (**E** or its precursor) *via* a Wittig reaction. In the next step (II) the asymmetric epoxidation (AE) using titanium tetraisopropoxide and *tert*-butyl hydroperoxide with (−)- and (+)-diethyl tartrate (DET) or diisopropyl tartrate (DIPT) plays a key role. While these first two steps are obvious choices for the overall conversions of **A** to **C** and **A** to **D**, the subsequent steps, III and IV, and IIIa and IVa involve little known transformations of epoxy alcohols **F**; *e.g.*, **112** which are rearranged to the isomeric alcohols **113** with base (Payne rearrangement).[39] Thus, all of the C-1, C-2, and C-3 positions of **F** can be sites for nucleophilic attack.

The approach outlined above is best illustrated by the exploratory work which has been most effectively carried out through collaboration with Professor Sharpless' research group.

4.1. **Reaction Sequence 5.**[40] The scope and limitations of reaction sequence 5, **A** to **D**, (Scheme 12) can be evaluated through the synthesis of model compounds, tetritols and pentitols, which may lead to the establishment of a general, iterative approach to a wide variety of higher and more complicated saccharides and other polyhydroxylated natural products.

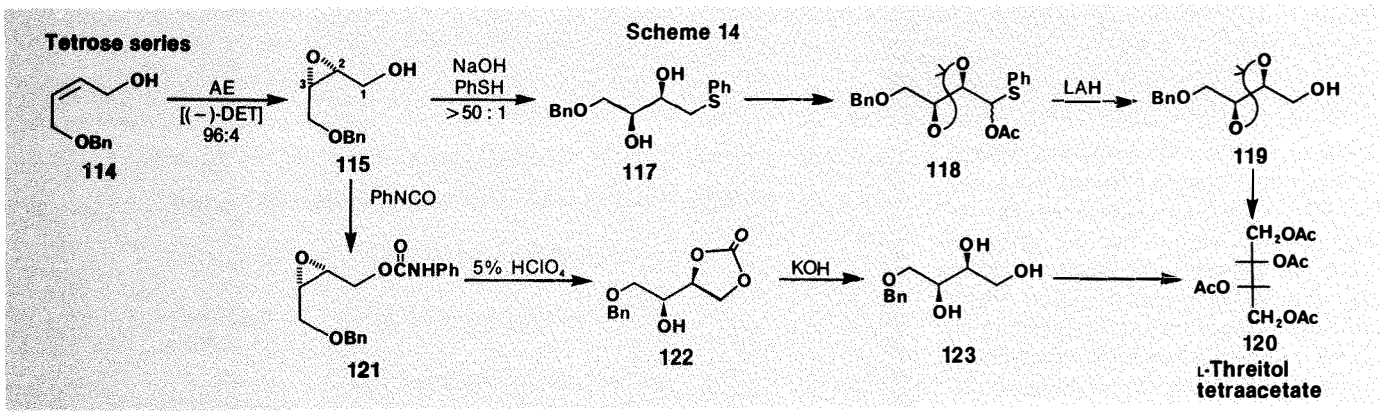
4.1.1. **Tetritols.**[40] Because of the ready availability of the monobenzyl ether **114** (Scheme 14), this series omits step I. The asymmetric epoxidation proceeds satisfactorily to yield **115**. The exposure of **115** to sodium benzenethiolate and sodium hydroxide in a protic solvent leads, through the Payne rearrangement of the epoxy alcohol moiety, to exclusive attack of benzenethiolate at the C-1 position, yielding *threo* diol **117** (the stereochemical descriptors in Section 4 conform to the convention of sugar chemistry). This mode of epoxide opening is discussed in some depth at the end of Section 4.1.2. Compound **117** provides for protection of the two newly generated hydroxyl groups and sets the stage for a facile Pummerer rearrangement. Thus, **117** is converted *via* **118** to the corresponding alcohol **119**; its conversion to L-threitol tetraacetate **120** proceeds in a conventional manner.

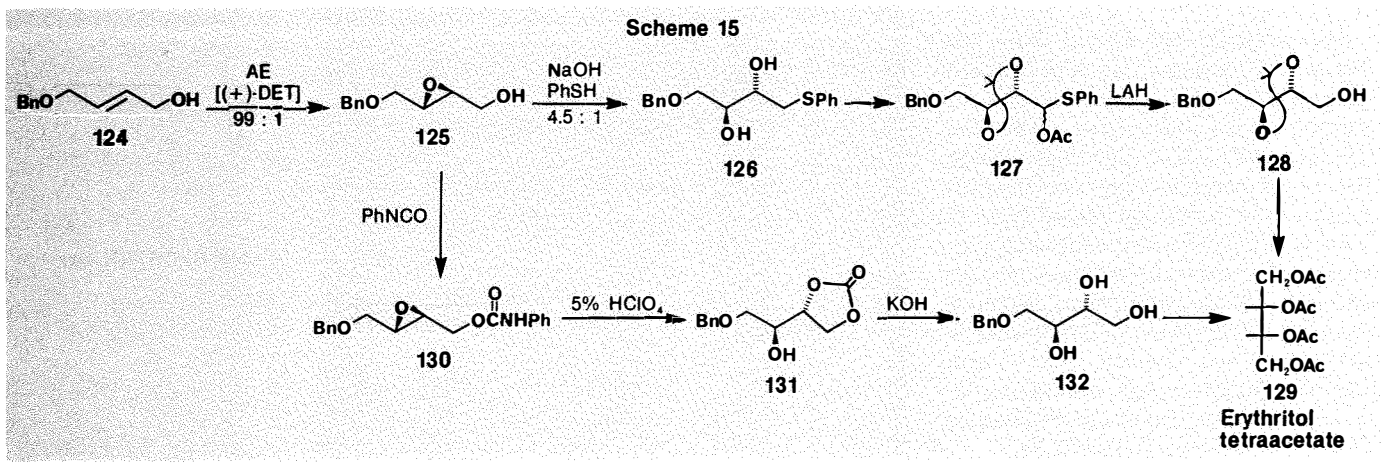
Another stereoselective epoxide opening employs attack by an intramolecular oxygen nucleophile at the C-2 center of **115**. The phenylurethane **121** undergoes smooth ring opening with the aid of an acid catalyst,[41] and the resulting carbonate **122** is converted to **123** with potassium hydroxide and then to the tetraacetate **120**.

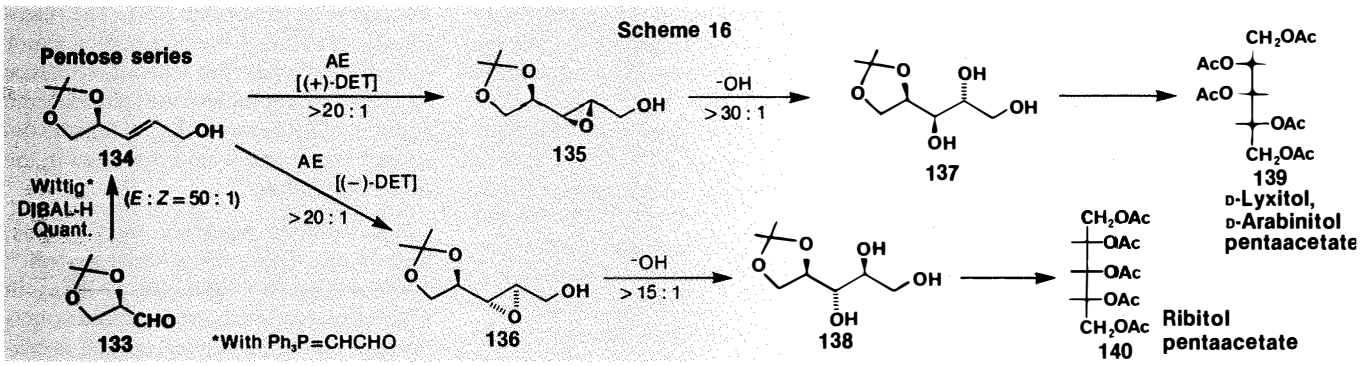
All the transformations in the above sequence apply equally well to the *E*-allylic alcohol **124** (Scheme 15). The epoxy alcohol **125**, obtained from **124**, is transformed through two sets of intermediates **126-128** and **130-132** to the final tetraacetate **129** of erythritol.

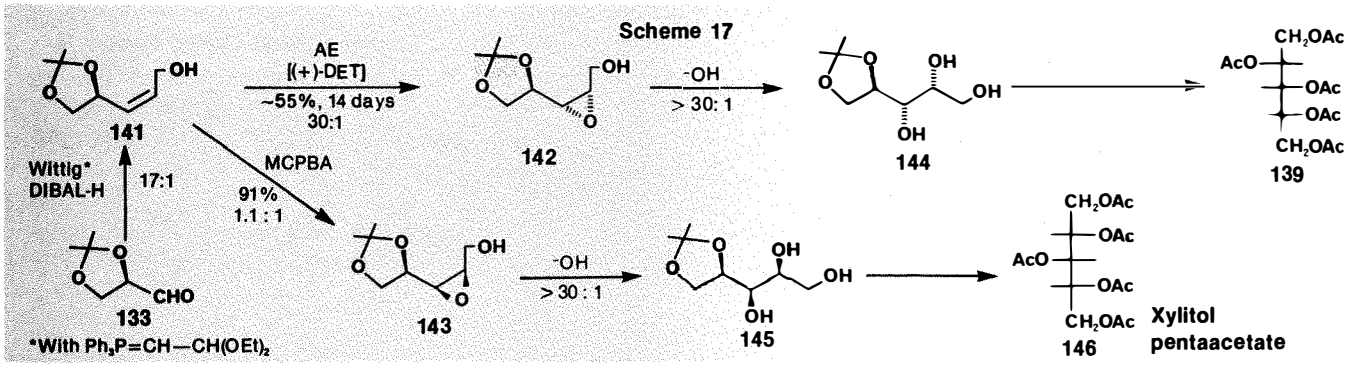
4.1.2. **Pentitols.**[40] The Wittig reaction of the known D-glyceraldehyde acetonide **133** with triphenylformylmethylenephosphorane followed by DIBAL-H reduction yields the *E*-allylic alcohol **134** (Scheme 16). The asymmetric epoxidation of **134** proceeds in the normal fashion with both (+)- and (−)-DET to epoxy alcohols **135** and **136**, respectively. The hydroxide ion attack provides both **135** and **136** exclusively, which constitutes yet a third variation on the stereo- and regioselective epoxide-ring-opening theme. The resulting triols **137** and **138** are correlated with the pentaacetates **139** and **140** derived from D-lyxitol (= D-arabinitol) and ribitol, respectively.

So far, so good. However, the *Z*-allylic alcohol **141** (Scheme 17) is found to react with Sharpless' reagent very slowly: with (+)-DET the epoxidation reaches only 55% completion in 14 days at -20 °C. The stereoselectivity is excellent however, favoring the formation of **142** in a 30:1 ratio. With (−)-DET, the reaction is too slow to be practical and the desired epoxy alcohol **143** is prepared with *m*-chloroperoxybenzoic acid in a virtually non-selective manner. The epoxide rings of **142** and **143** are opened in the same manner as that for **135** and **136** to provide triols **144** and **145**, res-



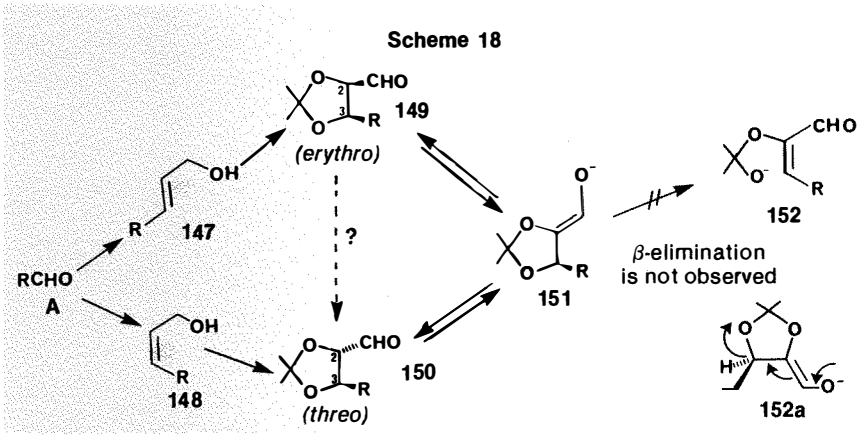


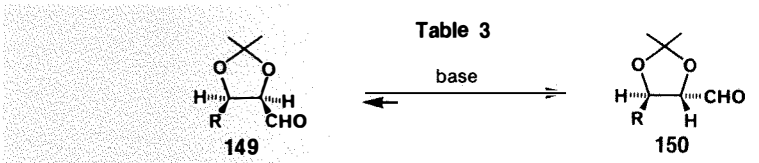




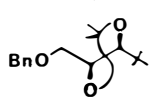
pectively, which are further converted to D-arabitol pentaacetate (**139**) and xylitol pentaacetate (**146**).

The above preliminary examination of the reaction sequence **5** as applied to the synthesis of the pentitols and other similar compounds reveals that (1) in all cases examined, the sequence (Scheme 18) leading to the **2,3-*erythro*** products **149** (such as **137** and **138**) *via* the *E*-isomer **147** (such as **134**) is satisfactory, and (2) in contrast, the AE of the *Z*-isomer **147** (such as **141**) in the **2,3-*threo*** series **150** (such as **144** and **145**), when **R** is chiral, often proceeds intolerably slowly and/or with low stereoselection. This latter deficiency is now remedied by a simple but highly effective modification, and the overall transformation is now executed in a unified manner as summarized below.[42]





BASE-CATALYZED EPIMERIZATION OF ERYTHRO (149) TO THREO (150) ACETONIDES

ERYTHRO ISOMER	THREO ISOMER	R IN 149 AND 150	EQUILIBRIUM RATIO OF 150:149
149a	150a	$PhCH_2OCH_2$	97:3
149b	150b		98:2
149c	150c		95:5

In compounds **149** and **150** the proton at C-2 is α to the aldehyde group and thus epimerizable. From the expected stability of **150** relative to **149**, the latter which is readily obtainable, can be equilibrated to give a mixture enriched in **150**, which has been up to now of limited access (see above). The acetonide chosen as a protecting group apparently suppresses the potential complication of a β-elimination (**151** to **152**) as the acetonide group helps maintain orthogonality between the enolate π system and the β-alkoxy substituent (see **152a**). Thus, treatment of **149a-c** with potassium carbonate in methanol at 25 °C effects smooth isomerization (>20:1) as summarized in Table 3. These examples represent the tetrose, pentose, and hexose series. Incorporation of this critical epimerization technique in our general approach leads to the satisfactory synthesis of all possible stereoisomers derived through reaction sequence 5.

Our final version is shown in Scheme 19, using the pentoses as illustration (**A** = **133**). The epoxy alcohol **136** undergoes ring opening to provide **153** which is converted to the acetonide **154** through kinetically

controlled acetonation followed by oxidation and acetylation. Reaction of **154** with DIBAL-H provides, virtually without epimerization, a product **(155)** which proves to be a ribose derivative. Compound **154** can also be converted to the C-2 epimer of **155**. Thus, treatment of **154** with potassium carbonate in methanol (see above) causes hydrolysis of the acetoxythioacetal group and epimerization at the C-2 center to give a mixture of **156** and **155** in a 98:2 ratio. Compound **156** has the arabinose configuration. The acetonides **(159** and **160)** of xylose and lyxose are prepared in exactly the same manner. The key intermediate **158** obtained from **135** *via* **157** provides **159** and **160** in a manner indicated in the scheme. In this way a highly efficient route from the same intermediate **134** to either the *erythro*- or the *threo*-2,3-dihydroxy aldehydes has been established.

It is obvious that the success of the above scheme depends heavily upon high asymmetric induction realized by the titanium-catalyzed epoxidation with (+)- or (−)-tartrates. The diastereofacial selectivity of this reagent outweighs the influence of the pre-existing chirality in the allylic alcohol. Now that **efficient, practical** routes from a chiral or achiral aldehyde to all the four possible bishomologated aldehydes have been established, these final products are ready for a second two-carbon extension. Indeed, the synthesis of all the possible hexoses has now been completed,[43] although a detailed discussion of the synthesis is abbreviated in this article.

A brief comment appears appropriate at this point on the ring opening of epoxy alcohols which have been proven to be extremely versatile synthetic intermediates. As described earlier, the known, facile base-catalyzed equilibration of 2,3- and 1,2-epoxy alcohols (*i.e.*, **112** and **113)** has been exploited to draw out a subtle mode of reactivity, and both epoxides possess two potential sites for nucleophilic attack. It is now evident that in the carbohydrate context, C-1 of compound **135** (Scheme 20), for instance, is by far the most reactive electrophilic site for a range of nucleophiles including the thiolate and hydroxide ions. Thus, the attack at C-1 of **161** leads to **162**, as exemplified by the predominant formation of **137** and **157**. Under proper conditions it is also possible to direct nucleophiles selectively to either C-2 or C-3. For example, reaction of **135** with the azide ion provides compound **163** as the major product.[44] The most interesting example by far is reduction at C-2 with metal hydrides, in particular, sodium bis(methoxyethoxy)-aluminum hydride (Red-Al®). The regiospecificity of this reduction plays a major role in developing the reaction sequence 4a, which would achieve the stereospecific addition of an acetate unit to aldehydes described earlier and is now discussed in the following section.

4.2. Reaction Sequence 4a, Construction of the 3-Hydroxycarbonyl System.[45]

Table 4 lists two examples of many in which Red-Al reduction of epoxy alcohols proceeds smoothly under normal conditions (THF solvent) to provide a single

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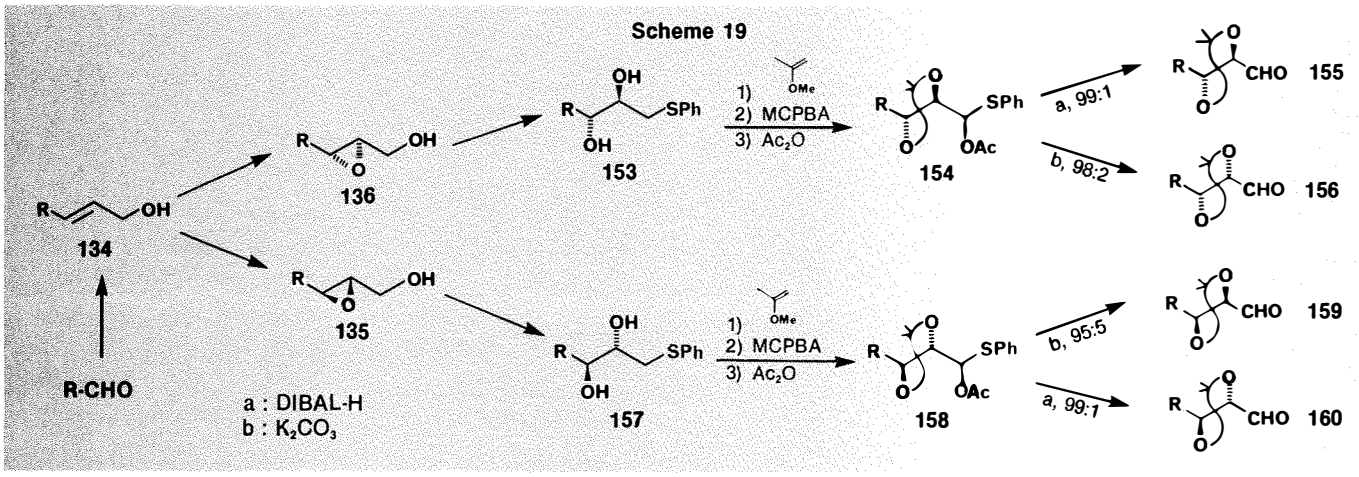
Scheme 19



Scheme 20

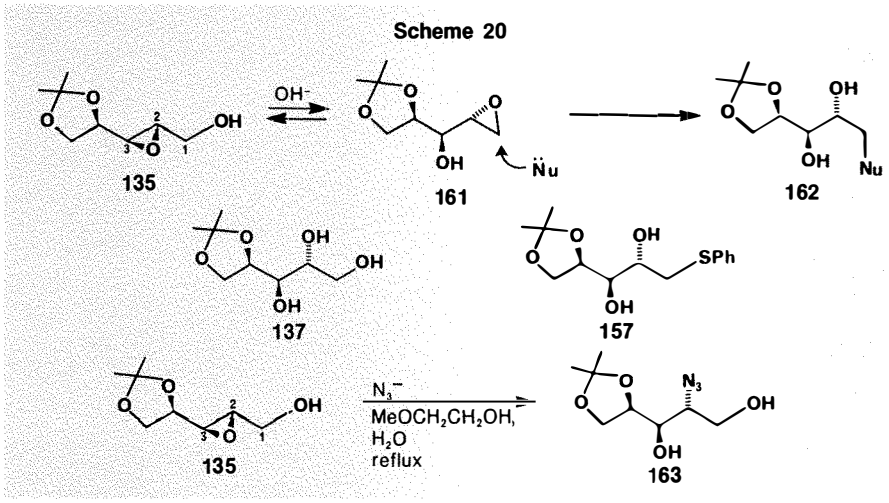
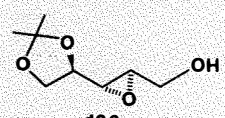
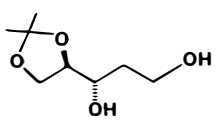
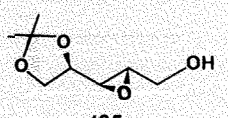
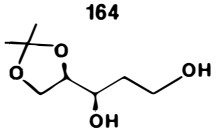


Table 4

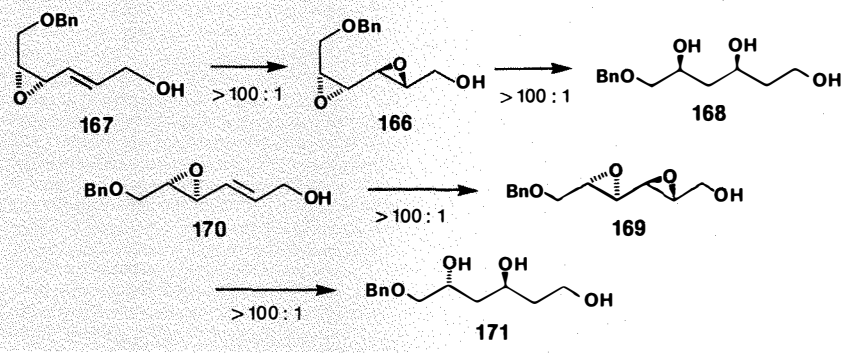
Epoxyalcohol	Reductant (Reaction temperature, °C)	Ratio	Yield (%)	Structure of the major diol
	Red-Al (0)	>100 : 1	78	
	Red-Al (0)	>100 : 1	82	

product, a 1,3-diol. The regioselectivity is uniformly high and in many cases no traces of the corresponding 1,2-diols are found. A more impressive demonstration of this selectivity includes the reduction of 2,3:4,5-diepoxy alcohol with the same reductant. Thus, compound **166** (prepared from **167** through AE) undergoes clean double-ring opening to provide only one product, 1,3,5-triol **168** with the indicated stereochemistry (Scheme 21). Similarly, Red-Al reduction of **169** (obtained from **170**) provides **171** exclusively. These findings, in particular the simultaneous creation of two new hydroxylated chiral centers of 1,3-relationship, are important and bring us to the synthesis of amphotericin B (**1**), the polyenemacrolide described in the introduction of this article.

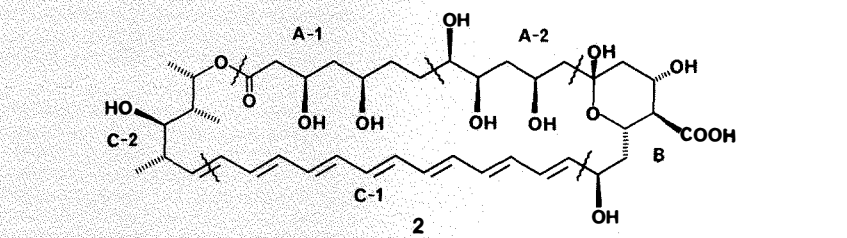
5. Studies Toward the Synthesis of Amphotericin B

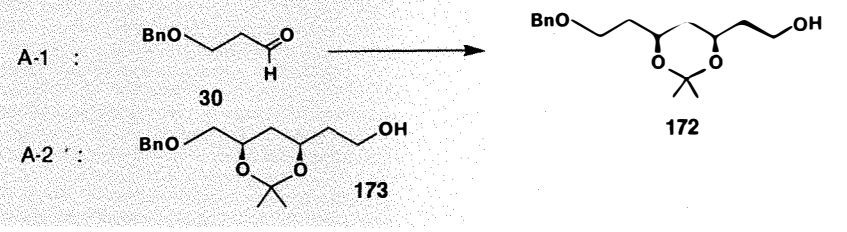
As indicated earlier, the retrosynthetic dissection of **2**, the aglycone of the antibiotic, leads to fragments A, B, and C (Scheme 22), two of which may be further split into smaller sub-fragments: A into A-1 and A-2 and C into C-1 and C-2. Both A-1 and A-2 can be readily derived from **30** and the enantiomer of **168**, respectively, and have indeed been prepared in substantial quantities. The construction of the polyene (C-1) and the propionate (C-2) moieties should not present serious problems. As we are equipped with adequate methodologies (Section **2**), these two fragments are also in our hands. The only fragment that remained to be prepared was B. The methodology for the synthesis of **43** discussed in Section 2.4.2 is now applied in this instance. The 2-vinylcarboxylic acid ester **174** (Scheme 23) obtained from **30** (see Sections 2.4.1 and 2.4.2) is reduced with DIBAL-H. The resulting hydroxy compound is oxidized with Collins' reagent to yield (without isomerization of the double bond or epimerization of the C-2 center of **174**) the corresponding aldehyde, which is then treated with a Wittig reagent followed by DIBAL-H reduction to provide **175**. A sequence of four now standard reactions indicated in the Scheme converts **175** into the carboxylic acid **176**, which, after methylation and hydrolysis of the primary silyloxy ether leads to **177**, an immediate precursor of fragment B. The assembly of all these fragments to synthesize **2** is in progress and will hopefully be completed shortly.

Scheme 21

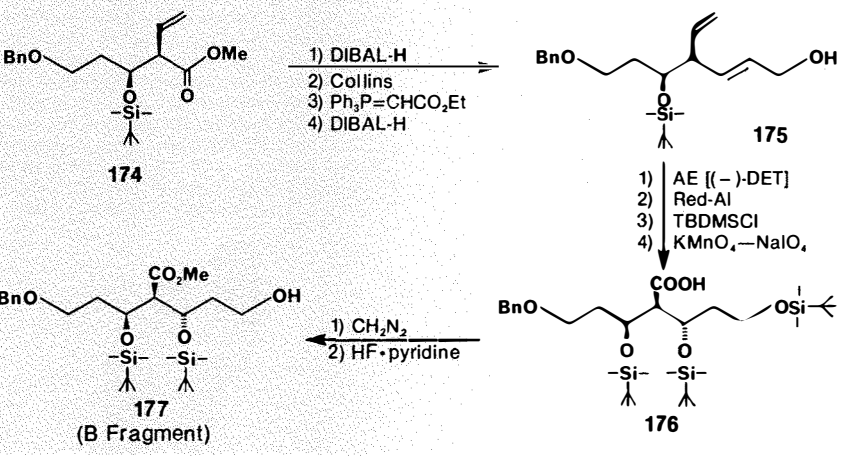


Scheme 22





Scheme 23



Evans (Pasadena) — mainly because of space limitations. This article attempts to present the chronological and conceptual development of our research in this area.

The initial investigation dealt mainly with the control of the 2,3-stereochemistry of aldol products. It soon entered the second generation through the modest but important demonstration of the 3,4-stereochemical control using chiral enolate reagents derived from the enantiomers of atrolactic acid. With the advent of highly diastereoselective enolate reagents, as well as a clearer understanding of the influence of metal coordination, one can now draw efficient and reasonably short synthetic schemes for most of the macrolide antibiotics of polypropionate origin. The aldol methodology offers one distinct advantage: stereoselective creation of two new chiral centers *in one step*. Moreover, the chiral auxiliaries contained in our reagents (*e.g.*, **29**), after the aldol reaction, can be removed quantitatively and under virtually neutral conditions to provide intermediates ready for the next sequence or a final product, a technical aspect which is extremely important in executing the synthe-

6. Concluding Remarks.

The authors must apologize for the deletion in the above discussion of numerous contributions made by other groups — in particular, those led by Professors Heathcock (Berkeley) and

sis of the acid- and base-sensitive polyhydroxyl compounds.

Natural products or their fragments which are of **polyacetate** origin are also amenable to synthesis. In the asymmetric epoxidation process developed by Sharpless, the diastereofacial selectivity of the reagent is, at least, as high as that of **29** and thus overrides, in many cases, the stereochemical complications arising from a chiral substrate used in the reaction. With these two asymmetric reactions, aldol and epoxidation, we can now achieve many synthetic tasks which were regarded as unattainable even as recently as three years ago.

What has been learned about organic synthesis? Previously, stereochemical control in the synthesis of (poly)cyclic compounds, as witnessed in numerous classical examples, usually took advantage of the **large** diastereofacial selectivity of reacting substrates through the ingenious design of synthetic intermediates which were cyclic. This advantage no longer exists in **acyclic** stereoselection, as the Cram/anti-Cram selectivity is small and either does or does not favor the construction of a desired stereoisomer (Section 2.4). However, with the invention of highly diastereoface-selective chiral reagents, as well as a better understanding of the stereochemical interaction between reagent and substrate, we can now create any new required chiral center or centers (C_n^*) in a highly diastereoselective manner as shown in equation 1′: *d*-**A** + *d*-**B** → *d*-**A**′-(C_n^*)-*d*-**B**′ . Normally this can be achieved only with a combination of enantiomerically pure **A** and **B**. The clear recognition of this last precept underlying asymmetric synthesis is perhaps the most important outcome of the entire work.

Acknowledgments. With great pleasure we thank our major contributors in several areas of the chemistry discussed herein: exploration of the aldol strategy, Mr. J. Ellingboe; 6-deoxyerythronolide B, Drs. M. Hirama, S. Mori, Sk.A. Ali, and D.S. Garvey; rifamycin S, Ms. B. Imperiali; tylosin, Drs. W. Jackson, L. Lu, T. Toyoda, and Mr. T. Kaiho; amphotericin B, Messrs. P. Ma and T. Sakai. It has also been a memorable and gratifying experience for us to have collaborated with Professor K.B. Sharpless in the carbohydrate research which involved Drs. T. Katsuki, A. Lee, V. Martin, D. Tuddenham, and F. Walker, and Messrs. P. Ma and S. Viti. The work and this writing have been supported by grants from the National Institutes of Health, the National Science Foundation, as well as Hoffmann-La Roche (Nutley, N.J.) and Yoshitomi Pharmaceutical Industries (Japan).

Experimental Part:

The preparation of *R*- or *S*-1-cyclohexyl-1-*tert*-butyldimethylsilyloxybutan-2-one, the precursor for the *R*- or *S*-chiral enolate

(A) *R*- or *S*-Hexahydromandelic Acid. A 500-ml Parr hydrogenator bottle is charged with 19.78g of either *R*-or *S*-mandelic acid (130mmol), 115ml of methanol, 1.25ml of acetic acid, and 5g of 5% rhodium on alumina. The bottle is connected to a Parr pressure hydrogenation apparatus and charged to a pressure of 45psi. The bottle is shaken until absorption of hydrogen ceases. After disconnection from the apparatus the reaction mixture is filtered through a 2.5-cm pad of Celite. The solid residue is washed with a further 150ml of methanol. The combined filtrates are evaporated (rotary evaporator) to afford a white solid which is then powdered and further dried under high vacuum. Recrystallization from 50ml of acetone at -20°C affords 13.4-14.2g (65-69%) of optically pure hexahydromandelic acid, m.p. 128-129°. Optically pure *R*-hexahydromandelic acid should have $[\alpha]_D^{22} = -22.8°$ (c = 1.10, CH_3CO_2H); the *S*-enantiomer should have $[\alpha]_D^{22} = +23.0°$ (c = 1.065, CH_3CO_2H). NMR: δ[$(CD_3)_2CO$] 1.10-2.10 (11 H, m), 3.95 (1 H, d, J = 3Hz), and 6.57 (2 H, br s, D_2O ex).

(B) *R*- or *S*-1-Cyclohexyl-1-hydroxybutan-2-one. A dry 1-liter three-neck round-bottom flask fitted with a magnetic stirring bar, a jacketed dropping funnel (Fig. 1), an argon inlet, and a condenser is charged with 12.66g of *R*- or *S*-hexahydromandelic acid (80mmol) and 200ml of diethyl ether. The dropping funnel which has been precooled to -23 °C (carbon tetrachloride/dry-ice) is charged with 276ml of 1.1*M* ethyllithium and the reaction vessel is cooled to -78°. The ethyllithium is added dropwise over two hours to the stirred reaction mixture. The mixture is then allowed to stir for 3 hours at 0°C and then overnight (15 hours) at room temperature. The reaction mixture is *carefully* poured onto 1 liter of 1*N* HCl in a 3-liter beaker, which is moderately stirred with a stirring bar. The mixture is transferred to a 2-liter separatory funnel and the aqueous phase is extracted twice with 200ml of diethyl ether. The combined ether extracts are washed with 500ml of a saturated sodium bicarbonate solution followed by 500ml of distilled water. After drying over anhydrous sodium sulfate the solvent is removed by rotary evaporation to afford an oil which is distilled to give 9.4-11.4g (69-84%) of *R*- or *S*-1-cyclohexyl-1-hydroxybutan-2-one, b.p. 63-64° (0.3 mm). The crude ethyl ketone should be distilled soon after removing the solvent. The ketone becomes yellow on exposure to light and cannot be fully purified by distillation. Similarly, the distilled material should be used in the next reaction as soon as possible to avoid the same problem. For the *R*-enantiomer, $[\alpha]_D^{22} = -128.0°$ (c = 1.45, $CHCl_3$) and for the *S*-enantiomer, $[\alpha]_D^{22} = +128.5°$ (c = 1.26, $CHCl_3$). NMR: δ($CDCl_3$) 1.10 (3 H, t, J = 7Hz), 1.30-2.10 (11 H, m), 2.52 (2 H, q, J = 7Hz), 3.53 (1H, s), and 4.05 (1 H, d, J = 2Hz).

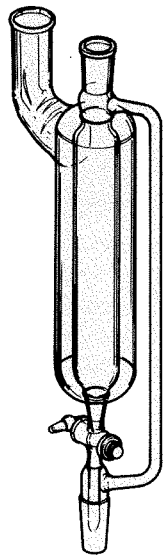


Fig. 1
Jacketed Dropping Funnel, 250ml, §24/40
(Aldrich Catalog No. Z11,742-0, $189.00)

(C) *R*- or *S*-1-Cyclohexyl-1-*tert*-butyldimethylsilyloxybutan-2-one. A 250-ml round-bottom flask, fitted with a magnetic stirring bar, a condenser, and an argon inlet is charged with 6.12g of *R*- or *S*-1-cyclohexyl-1-hydroxybutan-2-one (36mmol), 10.9g of *tert*-butyldimethylsilyl chloride (72mmol), 9.8g of imidazole (140mmol), 0.1g of 4-dimethylaminopyridine, and 150ml of tetrahydrofuran. The mixture is stirred at reflux for 18 hours. After cooling to room temperature, the mixture is poured into 1 liter of distilled water and the products are extracted three times with 200ml of petroleum ether (b.p. 30-60°). The combined petroleum ether extracts are washed with 200ml of 1*N* hydrochloric acid followed by 200ml of distilled water. The solution is dried over anhydrous sodium sulfate, filtered, and the solvent removed by rotary evaporation. The resulting oil is warmed (50°C, water bath) under high vacuum until the weight is about 10.5g. The residue is distilled to give 8.5-9.5g (83-95%) of *R*-or *S*-1-cyclohexyl-1-*tert*-butyldimethylsilyloxybutan-2-one, b.p. 112-114° (1.5mm). For the *R*-enantiomer, $[\alpha]_D^{23} = +59.8°$ (c = 1.24, $CHCl_3$); for the *S*-enantiomer, $[\alpha]_D^{22} = -61.0°$ (c = 1.14, $CHCl_3$). NMR: δ($CDCl_3$) 0.04 (3 H, s), 0.06 (3 H, s), 1.10 (9 H, s), 1.17 (3 H, t, J = 7Hz), 1.30-2.00 (11 H, m), 2.33 (2 H, m), and 3.73 (1 H, d, J = 5Hz).

Preparation of ethyllithium.

A 2-liter three-neck, round bottom flask, fitted with a mechanical stirrer, a 250-ml pressure-equalized dropping funnel and a condenser with an argon inlet is charged with 17g of chopped lithium wire (2.45mol) and 200ml of diethyl ether. A solution of 134g of ethyl bromide (1.23mol) (distilled from phosphorus pentoxide immediately before use) in 260ml of diethyl ether is added to the cooled (-30 ± 5°C, CH_3CN/dry ice), stirred mixture over a period of 3 hours. The volume of solution requires that the addition funnel be charged twice. After the addition is complete, 340ml of diethyl ether is added to dilute the mixture and the temperature is raised to 0°C, with an ice bath (under argon and with the aid of a cannula). The mixture is filtered through a Schlenck frit containing 1cm of Celite, and the receiver is cooled in a bath of acetone/dry ice. The product should be stored in a freezer (-25 to -30°C) and used within one week after preparation. The concentration of ethyllithium is determined by titration. The amount of the reagent is sufficient for at least two reactions on the scale described. All solvents used in this and experiments B and C must be dried in the usual manner prior to use.

References and Notes:

1) This article is based mainly on the 24th Bachmann Memorial lecture presented by S. Masamune at the University of Michigan on April 15 and 16, 1982.
2) This phrase is used in the article in the sense originally defined by (a) W. Marckwald (*Ber.* **1904**, *37*, 1368): "those reactions which produce *optically active* substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical processes." For a broader definition, see (b) Morrison, J.D.; Mosher, H.S. "Asymmetric Organic Reactions"; American Chemical Society: Washington D.C., 1976; p 4.
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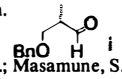

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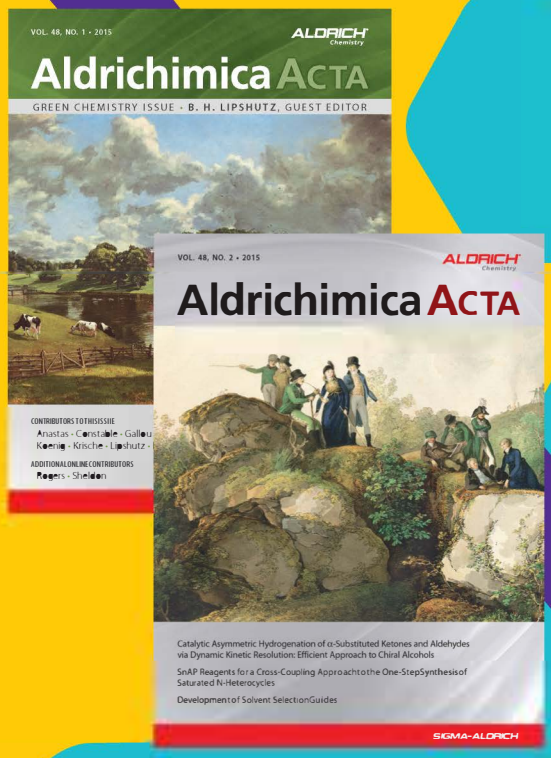

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