Aldrichimica Acta

Volume 19, Number 1, 1986

Dedicated to Professor Ralph Alexander Raphael on his sixty-fifth birthday

chemists helping chemists in research & industry

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Aldrichimica Acta

Volume 19, Number 1, 1986
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About Our Cover:

This portrait of an old man (oil on panel, 52 × 42cm) leaves you with an unforgettable image of wisdom in old age. Our chemist-collector recently purchased this from a Hungarian nobleman; it had been in the well known Esterhazy collection where, of course, it had been attributed to Rembrandt. It is, in fact, by one of Rembrandt's students, Solomon Koninck, signed and dated 164....

In the nineteenth century such paintings were generally called "Portrait of a Rabbi," but how can you tell? Look, for instance, at Rembrandt's portrait of Johannes Uyttenbogaert. If we did not know that he was a well known Protestant preacher of the time, we might call it, too, "Portrait of a Jew" or of a rabbi.

In any case, the old man depicted on our cover is almost ethereal, wise and kind, his mind as much in the world to come as in this one. What a fitting work to grace the cover of the *Acta* dedicated to Professor Ralph A. Raphael who, until age 16, had considered becoming a rabbi. Now, at age 65, he must know that he has taught, guided and helped many people even though he chose a different path.

Pictures from the Age of Rembrandt

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

Reprints of Aldrich Catalog Covers

Eight beautiful 14 x 11 inches, full-color reproductions of paintings on our catalog covers are available, ready for framing, to add beauty to your laboratory.

Selections from the Aldrichimica Acta, 1968-1982

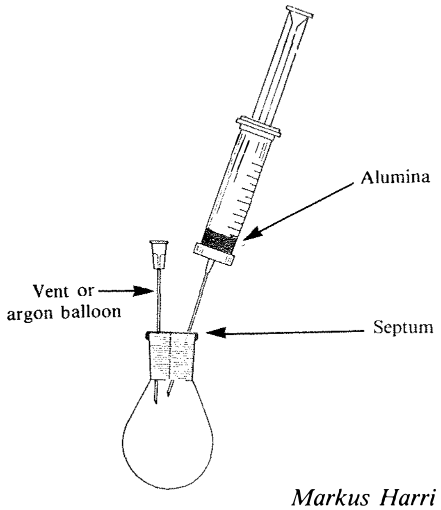
Because of the ever-increasing demand for earlier issues of the *Acta*, we now offer a collection of articles from volumes 1-15. We chose those articles which we believe are still of interest to our readers — 354 pages of great review articles, in one beautiful hardbound volume.

Lab Notes

We have found a convenient improved technique to dry solvents on a small scale by filtration through alumina (or molecular sieves). Instead of glass chromatography columns, we use a 10-ml disposable plastic syringe.

A plug of cotton wool is poked into the narrow needle part of the syringe barrel followed by *ca.* 2ml of alumina (or molecular sieves). The barrel is filled with solvent. Reinsertion of the piston causes the first milliliter or two to be expelled through the needle. The needle can then be inserted through the septum and a measured amount of solvent squirted into the reaction vessel. (For large amounts of solvent, we have attached a needle to a chromatography column with an Aldrich needle-tubing connector.)

The advantage of this method is that the inert gas atmosphere of the reaction vessel is not disturbed during the procedure and there is no water condensing as the solvent evaporates from the tip of the dispenser.



Markus Harri
Ciba-Geigy Ltd.
4002 Basle
Switzerland

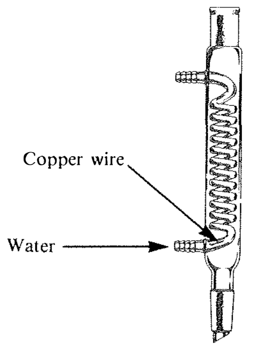
Editor's note: Aldrich carries a full line of anhydrous solvents. Check the equipment section of our Catalog/Handbook for disposable syringes and needle-tubing connectors.

The deterioration of partly used lithium reagents is a common problem, in spite of efforts to prevent hydrolysis and oxidation by means of Sure/Seal™ caps. We have found, however, that a few simple precautions can prolong the life of lithium alkyls significantly.

The bottle is secured by a clamp and the Sure/Seal pierced with a 16-gauge hypodermic needle connected to a nitrogen supply, which is maintained at a slight overpressure. The lithium alkyl solution is withdrawn by piercing the seal again with a gas-tight syringe; only little suction may be necessary if the nitrogen overpressure is high enough (*ca.* 50mm Hg). Syringe and gas supply are then removed and the holes in the cap immediately sealed by applying a small dab of silicon grease which is squeezed tight with the screw cap. (A small round piece of silicone rubber *ca.* 1mm thick may serve the same purpose.) The bottle is then stored in a freezer at -10 °C. The grease is wiped off prior to the next withdrawal to avoid contamination of the reagent. When *n*-butyllithium was handled in this way we found that the reduction in the lithium alkyl concentration was 10% or less over a period of approximately twelve months.

Manfred Bochmann
School of Chemical Sciences
University of East Anglia
Norwich NR4 7TJ

The growth of algae in the condensers of rotary evaporators or any permanent distillation set-up is greatly inhibited by copper wire (*ca.* 5cm long) placed in the coils of the condensers.



J.B. Fisher, III
Aldrich Chemical Co., Inc.

Intractable emulsions are often encountered in workup of phase-transfer reactions. We have noticed that small trapped air bubbles appear to stabilize the emulsions. Application of aspirator vacuum to the afflicted separatory funnel rapidly removes these bubbles, speeding the separation of the phases. **Naturally, a separatory funnel of appropriate strength must be selected when this technique is used.**

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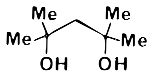
Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt**. *We reserve the right to retain all entries for consideration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

"Please Bother Us."

by Alfred Bader.

Professor E.J. Corey at Harvard University suggested that we offer 2,4-dimethyl-2,4-pentanediol. Just catalytic amounts of the Cr(VI) ester of this ditertiary 1,3-diol are needed for the high-yield peroxyacetic acid oxidation of secondary alcohols to ketones.[1] The chromate ester is easily prepared *in situ*.



As chromium reagents are environmental hazards and, also, large quantities complicate product isolation, this catalytic use of the chromium ester is clearly advantageous.

Naturally we made the diol.

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

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[1] Corey, E.J.; Barrette, E.P.; Magriotis, P.A. *Tetrahedron Lett.* **1985**, *26*, 5855.

Ralph Alexander Raphael: A Lover of Acetylenes at 65

Dudley H. Williams
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England

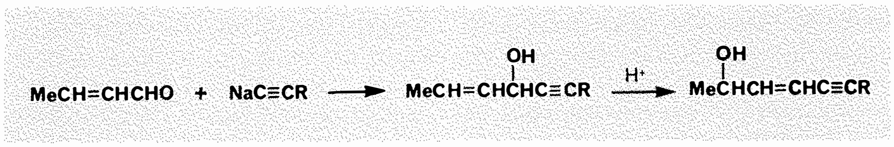
A few years ago, Professor Ralph Alexander Raphael[1] was attending a university committee meeting at which issues affecting the future of scientific departments were being discussed. During the meeting, he proposed a strategy which he believed would lead to a favourable outcome for those departments. The plan was opposed by an individual who regarded the proposal as less than 100% altruistic. Ralph paused briefly and then intoned, "Well, if you wish to pursue the politics of Byzantium in decline...." I think this statement encapsulates that mixture of pragmatic yet civilised behaviour which has made him one of the most successful Heads of Organic Chemistry Departments that the United Kingdom has known.

Ralph was born on New Year's Day in 1921, and attended school at Wesley College, Dublin and Tottenham, London. By 1941, he had graduated in Chemistry from Imperial College with First Class Honours, and also had run off with the Hofmann Prize. But the bland facts do not convey the realities of the time. The winter of 1940-1941 was a tough time to be living in London — air raids were almost continuous from September 1940 until May 1941, and thousands were killed. In the midst of the carnage, life went on, and Ralph took half of the final papers in February 1941 and the other half in June. He was one of five who obtained a First Class degree and, by courtesy of his then (and later) mentor, Sir Ewart Jones, I am now able to disclose his marks (%) for public scrutiny: Inorganic, 78; General and Physical, 62; Physical, 68; Course Work, 82; Organic, 78; Practical Organic, 83 and Analytical, 85.

His outstanding performance in analytical chemistry may account for his present group's ability to absorb vast numbers of NMR and mass spectra; and his similar performance in practical organic may explain his jaundiced eye when he once saw me attempt to pick up a test tube. His weaker performance in physical chemistry will explain the Raphael hypothesis which states, "The melting point of a compound is equal to its molecular weight."[2] He would have been top of the class, but was narrowly beaten by one Geoffrey Wilkinson.[3] His undergraduate studies were followed by postgraduate research, also at Imperial College, and he was awarded his Ph.D. in 1943.

Of course, there had to be time for some sport, and the he-man image we see in Fig. 1 may have played a significant role in the wooing of his future wife, Prudence.

RAR's first paper, coauthored with Sir Ian Heilbron and (now) Sir Ewart Jones, stems from this period, and appeared in the *Journal of the Chemical Society* in 1943. It reported the following reactions:



$$\mathrm{MeCH{=}CHCHO + NaC{\equiv}CR \longrightarrow MeCH{=}CH\overset{OH}{C}HC{\equiv}CR \xrightarrow{H^+} Me\overset{OH}{C}HCH{=}CHC{\equiv}CR}$$

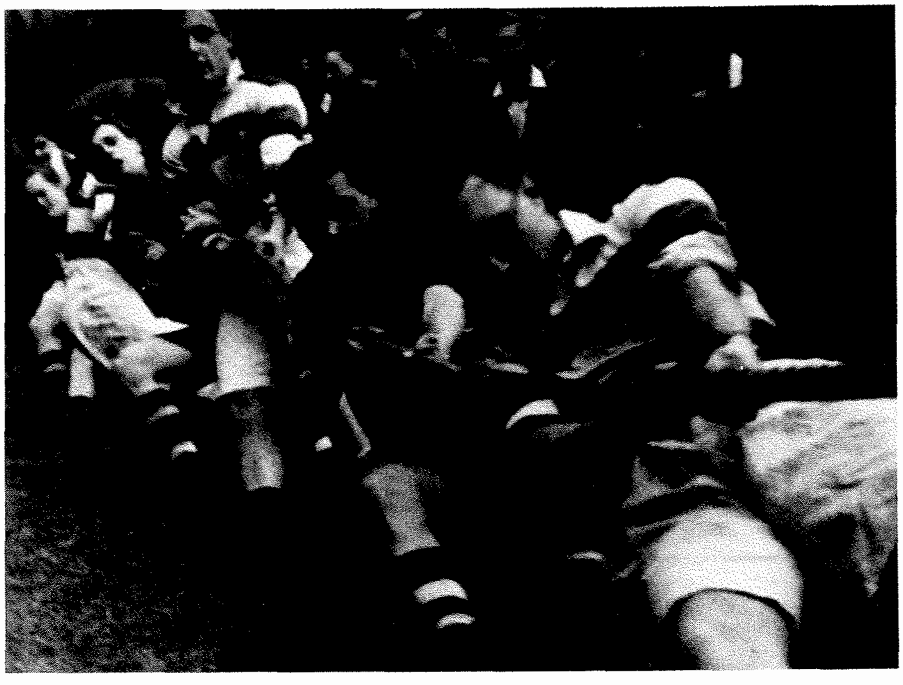


Fig. 1 - Imperial College tug-of-war team, 1942 (RAR in front). Prudence Raphael informs me that this was the first photograph of himself that Ralph ever gave her. Readers must draw their own conclusions!

The work, the long-term goal of which was the synthesis of polyene alcohols related to vitamin A, makes interesting reading today. Imperial College was justly proud of its UV spectrometer, and large pictures of the spectra grace the pages. The young Raphael not only meticulously prepared crystalline 3,5-dinitrobenzoates and α-naphthylurethanes of his alcohols, and semicarbazones of his carbonyl compounds, but also showed that his alcohols really had one OH per molecule by measuring the volume of methane evolved in the Zerewitinoff determination. The seeds of a life-long interest in acetylene chemistry had already been sown.

At the ripe old age of 22, Ralph moved to May and Baker to head the chemotherapeutic research unit, working on the chemistry and synthesis of penicillin. Despite the rather grandiose title, there was still some time to work at the bench and, on at least one occasion, with well documented catastrophic results. Ralph was in the process of isolating a carboxylic acid by the time-honoured procedure of acidifying an aqueous solution of the sodium salt in dilute sodium carbonate, and then extracting the liberated acid into ether. He gave the separatory funnel a couple of good shakes and was left holding the stopper whilst the funnel shot upwards and burst against the wall of the laboratory, precisely above the swing door through which the Assistant Director was entering. The poor man was drenched with its contents and, relatedly or not, Ralph left May and Baker in 1946.


Fig. 2 - At an Oxford conference, 1949. Left to right: J. Cymerman Craig, T.L. Jacobs, RAR and B.C.L. Weedon.

The enticement which took him from May and Baker was an ICI Fellowship at..... you've guessed it..... Imperial College. Do not conclude that the young Raphael was narrow but rather that Imperial was an obvious centre of excellence in his chosen field at that time. Ralph's days (1946-1949) as an ICI Research Fellow were happy days (Fig. 2) of great chemical activity, recognised in his receipt of the Meldola Medal of the Royal Institute of Chemistry in 1948. Basil Weedon recalls of the Imperial College days that RAR did some of the preliminary work which he later took over — this was the development of the reaction which is now generally known as the 'Jones oxidation'. He also recounts that following Ralph's marriage to Prudence, it was not uncommon to enter the departmental library and find Ralph surrounded by journals, but at the same time minding their baby in a pram. He adds that "this does not sound very significant these days, but I can assure you it made quite an impact on that male-dominated community at that time." In this period, Ralph also formed a close friendship with Franz Sondheimer (Fig. 3a). Their first joint paper appeared in *Nature* in 1949, and was followed by no less than four others in the next year. By a curious quirk of fate, I was also to form a close friendship with Franz when we arrived in Cambridge simultaneously in 1964. Having known this warm, gentle and sensitive man, himself a great acetylene chemist, it is easy to understand Ralph's great sense of loss upon Franz's untimely death a few years ago.

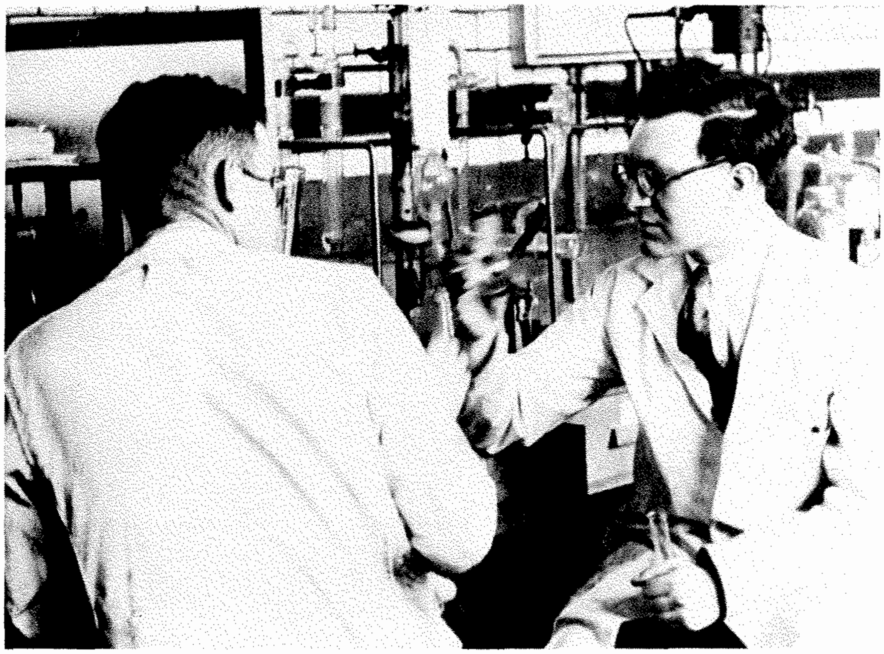


Fig. 3a - RAR with Franz Sondheimer at Imperial College ca. 1946 - searching for crystals.

In 1949, Ralph accepted the position of lecturer at Glasgow University. His colleagues from those days recall his phenomenal powers of concentration; he could sit and read in a noisy room. Perhaps "concentration" explains the incident when, on a wet day, he was found walking along one of the department's long corridors still

Fig. 3b - RAR alone ca. 1959 - searching for natural products.

holding his umbrella over his head. His colleagues knew then he soon would be Professor Raphael. The tenure of his Glasgow lectureship (1949-1954) proved to be one of the most productive periods of his life, and included such notable achievements as the synthesis of tropolones and the synthesis of carbohydrates and histamine from acetylenic precursors. Among his students was one A.I. Scott.

But he did something which could have seriously hindered his progress — he delivered spoof lectures. One on the synthesis of catenanes began with serious chemistry and gradually — imperceptibly — became less credible; it culminated in the description of their absorption spectra in the audible region. Since he was promoted to become the first Professor of Organic Chemistry at Queen's University, Belfast, in 1954, one can only conclude either that (i) his mentors swallowed it hook, line and sinker or (ii) he was just good.

His stay in Belfast was to prove relatively short (1954-1957), and in 1957 he returned to Glasgow, this time as Regius Professor of Chemistry. He was to remain there for fifteen years. The story is told that his promotion had been so rapid that initially he was observed to knock at his new office door and wait for his predecessor to ask him in.

As always with Ralph, "non-chemical" memories abound along with the science. When he appeared on the bowling green during a departmental outing, he had to be warned for "body-line" bowling, and remains on the record books as the only person who ever managed to bounce a bowl right across the green, over the ditch, across the path, and into the neighbouring bowling green. The affection with which he was held in the department is conveyed by a depiction of him as Santa Claus on the departmental organic bulletin in Fig. 4, whereas Fig. 5 shows him with the first two of his research students to be appointed to chairs.

The happy image of the department spread throughout the world, not least through the mouths of peripatetic Scots whom I met in various parts of the world. The stories that they would invent about their professors after imbibing a few glasses of malt whiskey are so scurrilous that I can only tell the mild ones and attribute them to Glasgow Professors X, Y and Z:

Long-standing Professor X: *That tie looks vaguely familiar.*
Student: *Yes, it's the tie of the Glasgow Chemical Society.*

Professor Y: *Have I met you before?*
Student: *No, I'm one of your final-year research students.*

Professor Z: *Was I going up or down these steps prior to our conversation?*
Student: *Up.*
Professor Z: *Ah, in that case, I have had my lunch.*

But no matter how much those former students may like their images of dreamy professors, Ralph fits the image only rarely. Much more commonly, he is the master of the economical and appropriate phrase. In Glasgow, a well known manufacturer of expensive instruments had been leading the department a dance over a period of months in relation to the malfunction of a relatively new machine. Patience having passed breaking point, Ralph's letter to the managing director opened: "Like the Bourbons, Nameless Ltd. have experienced everything and learnt nothing." Students were treated with the same open manner as the instrument manufacturer. When senior university officials visited the Chemistry Department, some over-active students attempted to douse them. The method was to empty the contents of buckets of water from the roof of the building as the officials were trying to enter the building. Ralph was not amused, and the students were duly carpeted. "Well," he enquired, "which of you missed the Vice-Chancellor?"

Fig. 4 - Santa Raphael

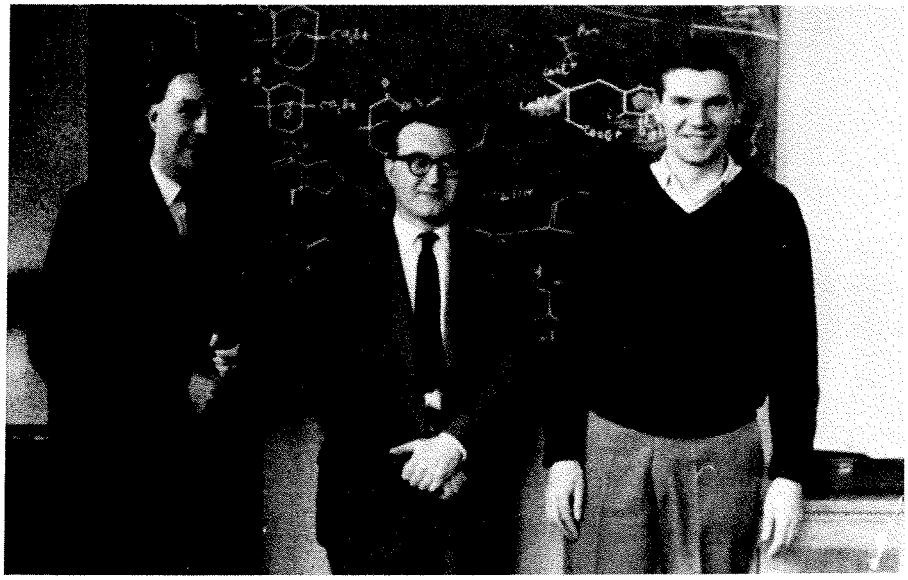


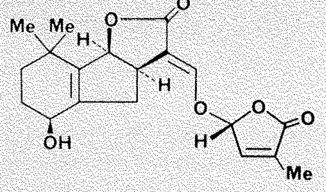
Fig. 5 - RAR with Ian Scott (left) and Willie Parker (right), prior to the appointment of Willie to his position at Stirling University.

During this second period in Glasgow, the science blossomed as before. In 1959, he published with Parker and Wilkinson the structure and synthesis of bullatenone; in 1960, a stereospecific synthesis of D-(-)-shikimic acid (with McCrindle and Overton); and in 1961, a new synthesis (with Kennedy and McCorkindale) of queen bee substance, a compound secreted by the queen honeybee to inhibit ovary development in the worker bees and further queen rearing within the colony. In recognition of this and much other outstanding synthetic work, he was the Tilden Lecturer of the Chemical Society in 1960, and was elected a Fellow of the Royal Society in 1962. His wider services to the chemical community in this period were also expressed through his membership of the Chemistry Committee of the Science Research Council, and in his role as Vice-President (1963-1966) and Council Member of the Chemical Society.

It was perhaps inevitable that his combination of scientific and administrative talents would lead other institutions to try to entice him to move on. In 1973, he moved to Cambridge to his present appointment as Professor of Organic Chemistry and Head of Department of Organic and Inorganic Chemistry. Folklore has it that Cambridge professors only die when they finally wobble off their bicycles at the age of 90 on an idyllic summer's day. Whatever the truth of the matter, the previous occupants of Ralph's present position had not taken to short terms of office. He has had only three predecessors in 124 years: G.D. Liveing (1861-1908), Sir William Pope (1908-1939) and Lord Todd (1944-1971). Although, as in the case of Lord Todd, modern rules demand that he will have to retire from his position as a youngster, his fifteen years in the job to date have been handled with equanimity, typified by RAR's characteristic role in the following story.

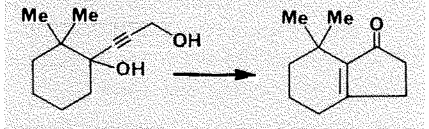
A young American chemist was visiting the U.K. and his first port of call was Oxford. In the office of the Professor of Organic Chemistry, he spied a large red telephone and on enquiring what it was for, he was told it was a hot line directly upstairs for solving difficult chemical problems. He was invited to use this telephone, and after a two-minute conversation was charged £1000, which he thought was good value for the money. His next visit was to RAR in Cambridge, and here again he saw a large red telephone. This time his problem took 15 minutes to solve, but Professor Raphael wanted only £1 for the call. On asking why there should be this big difference between Oxford and Cambridge, Ralph replied that it was a local call from Cambridge. I personally doubt the veracity of this story. Knowing Ralph, it is much more likely that all calls from Oxford on the red telephone are answered by him, and that the charges are an appropriate way to increase Cambridge's budget at the expense of Oxford.

RAR's time in Cambridge has resulted in more elegant synthetic work and to illustrate this, I have chosen points from his syntheses of strigol, steganacin, and pseudomonic acid. Strigol is the germination stimulant of witchweed, a troublesome semi-parasitic plant which damages corn, rice and sugarcane crops. The seeds of the witchweed can lie dormant in the soil for many years; their germination is triggered by contact with the stimulant strigol (**1**), exuded from the roots of the growing "victim" plant. Since, in principle, a synthetic substitute for natural strigol would render witchweed seed germination possible in the absence of standing crops, the synthesis of strigol was an important goal.



1

The synthesis[4] epitomises Ralph's love of acetylene chemistry, and the vigour with which he was attacking synthesis in the early 70's. It is economic, as can be illustrated by the one-pot conversion of the acetylenic diol **2** into the bicylic enone **3**. The conversion is concisely summarised in the paper as one "which blends the Newman mechanism for the Rupe rearrangement with a consequent Nazarov-type conrotatory electrocyclisation."

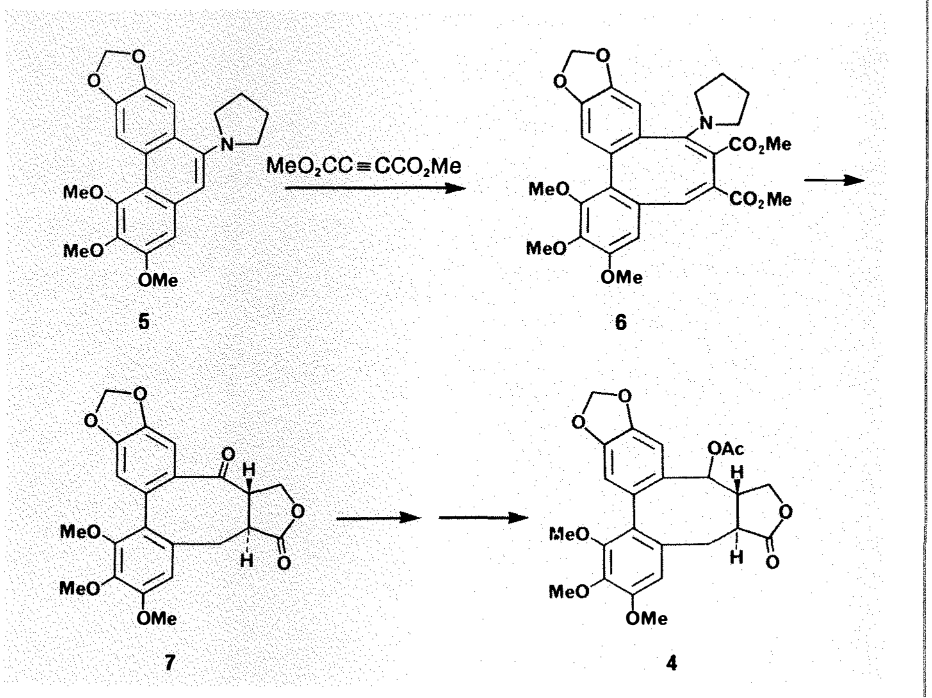


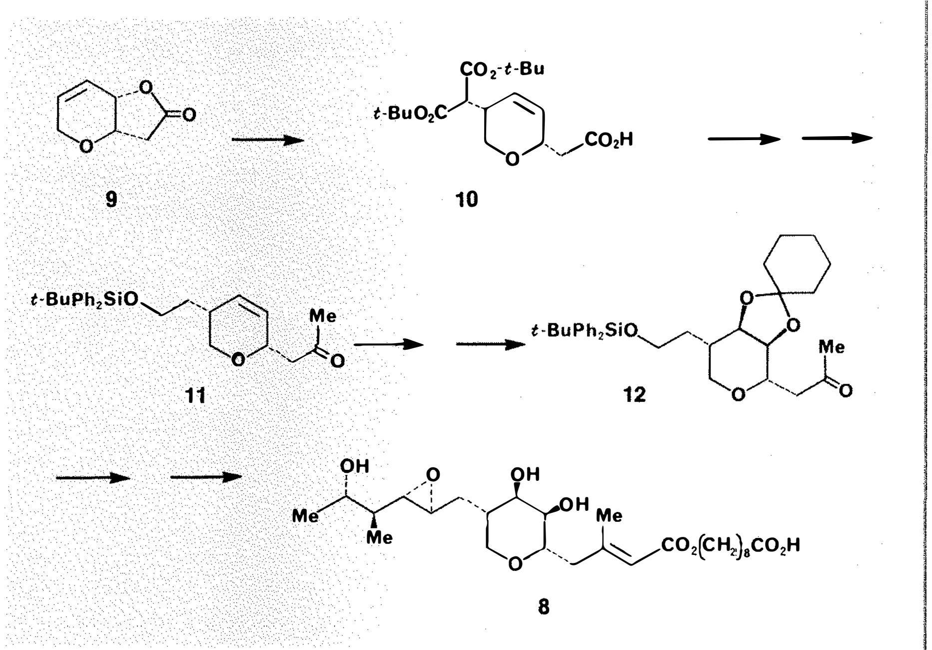
2 **3**

Steganacin (**4**) is a compound of significant antileukaemic activity; and efficiency is once more the keyword in the Raphael synthesis.[5] The enamine **5** was synthesised by relatively conventional methods, and the desired 8-membered ring of the target then elegantly produced by treating this with dimethyl but-2-ynedioate. The product **6** was converted in 5 further steps, *via* (±)-steganone (**7**), to (±)-steganacin (**4**). The overall yield of (±)-steganone in the ten-step synthesis was 23%, corresponding to an average yield of almost 90% per step.

His total synthesis of (±)-pseudomonic acids (*e.g.*, acid A, **8**) was achieved relatively recently and with a characteristic elegance of strategy.[6] The lactone **9** was treated with di-*t*-butyl sodiomalonate in the presence of bis(dibenzylidenacetonato)palladium(0) and 1,2-bis(diphenylphosphino)ethane, resulting in allylic displacement of the internal carboxylate with double inversion to give the pyranylacetic acid **10**. Having ensured the *cis* stereochemistry of the 2- and 5-substituents, **10** was converted in several steps to **11** which was then *cis*-dihydroxylated from the face opposite to the 2- and 5-sidechains using *N*-methylmorpholine *N*-oxide and a catalytic amount of osmium tetroxide. The cyclohexylidene acetal **12** of this diol has been converted to the pseudomonic acids (*e.g.*, **8**) in the hands of others.

What of RAR's teaching in Cambridge? It is a well known fact, and the source of much humour, that a sizeable minority of university teachers do not teach well. W.H. Auden had it that a professor is one who talks in someone else's sleep. Worse still, the story is told of a famous European professor who had such a propensity to confuse the issue that in one of his lectures a student rose to ask, "Excuse me, Professor, would you mind repeating that? It is not yet totally unclear to me." Ralph has no such problems. His lectures are not only clear, but laced with sufficient humour and enough examples of the relevance of synthesis to society, that even the most sleepy students are stimulated. Most undergraduates are aware of Murphy's Law, one statement of which is, "What can go wrong, will." But Ralph frequently makes them sit up in puzzlement with O'Brien's Law (sometimes also known as O'Reilly's Corollary), concisely stated as "Murphy was an optimist."





The humour which is demonstrated in the lecture theatre also carries over into his daily life, and particularly to the dinner table. Here, either as an after-dinner speaker on more formal occasions (Fig. 6), or as a story-teller at informal parties, he is a formidable raconteur. My favourite memory of him in the latter role dates to an occasion about four years ago. Dinner was almost finished at Ralph and Prudence's house, and I was in a relaxed and mellow mood having taken liberally to the excellent wines and Prudence's superb French cuisine. A twinkle appeared in Ralph's eye, which I would have done well to have noted. He commenced a story which told of the procedure which occurs upon entrance to heaven. One is welcomed by St. Peter, and informed that those who have led a life of which God approves will be rewarded by being paired with a partner of the opposite sex of great physical attraction. Conversely, those who conducted themselves on Earth in a manner which God judged to be reprehensible will be punished by being paired with an extremely ugly partner of the opposite sex. The ground rules laid, Ralph told of his personal disappointment upon being paired with an old crone upon his arrival in heaven. However, he appreciated that even the Head of a Cambridge University department should not quarrel with the heavenly rules (at least, not until he had assessed the local personalities), and dutifully walked away, arm in arm, with the crone. After walking about 100 metres, he turned around to regard once more the pearly gates. The sight which greeted his eyes turned his disappointment to anger. Dudley Williams had just arrived and was in the process of being paired with a female of exquisite physical beauty. At this stage in the story, I dreamily savoured a few more drops of wine, a self-satisfied smile upon my face; my chest puffed out perceptibly. After a pregnant pause to allow the assembled company to perceive my smug reaction, Ralph continued, "I went back to St. Peter and enquired why I had been

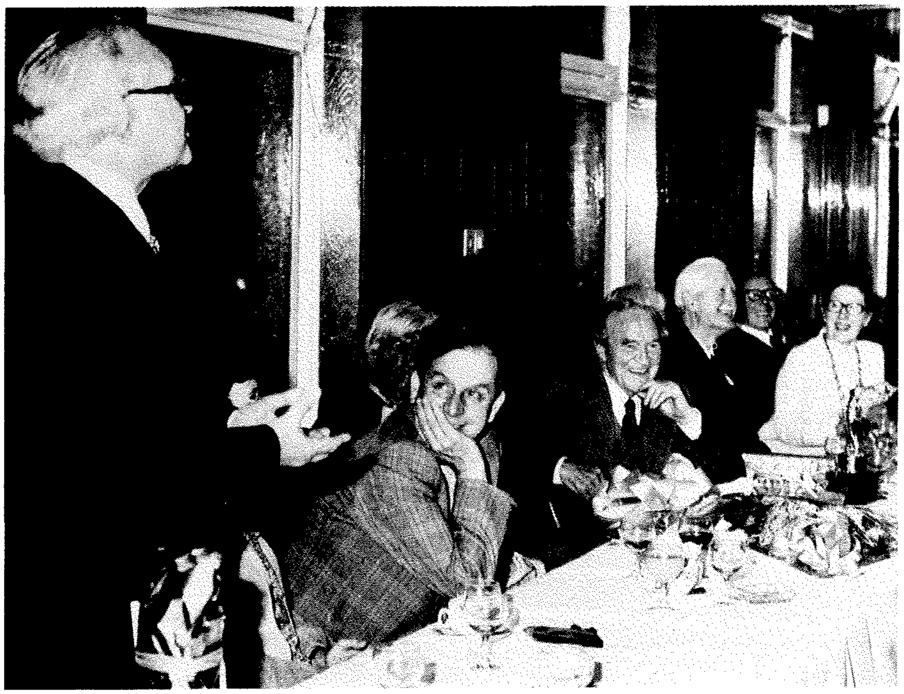


Fig. 6 - In characteristic pose and eliciting admiring and amused glances from Durward Cruickshank and James Monteath Robertson (with elbows on table), and Prudence Raphael.

A new experience on coming to Cambridge was to be a Fellow of a Cambridge College. This experience can be rewarding, educational, frustrating, and pleasurable; and gives exposure to the eccentricities that occasionally go with long-established tradition. Upon election to a Fellowship at Christ's College he found himself, although a senior member of the University, the most junior Fellow of the College. As such, he was "Mr. Nib", with the duty to pour after-dinner drinks for other Fellows of the College and their guests. This can be an exacting task; the great statistician R.A. Fisher, when at Caius College, would raise a quizzical eyebrow if his glass was not filled within a few millimetres of the top; the signal meant "carry on pouring." I have a feeling that with Ralph, he might have soon needed a new suit, with a consequent consideration by Fisher of the probability of error as a function of the size of the error. In any event, he seems to have performed his duties with a suitably traditional style, for the entry in Christ's Wine-Book for 26 June, 1972, reads: "Professor Raphael presented a bottle of Sauterne to celebrate the first occasion he had occupied

paired with an old crone, yet Dudley Williams had received this sex goddess. 'Ah', replied St. Peter, 'do not draw hasty conclusions. Dudley Williams is her punishment.' "

Doing research, lecturing and maintaining a sense of humour, are but a small part of Ralph's present Cambridge position. The department is a big one, and therefore a large fraction of his time is inevitably spent in administration. Not only has he coped with this almost single-handedly, but he has also lent his broad shoulders to other institutions in either formative or mature years. He has sat on sufficient professional appointment committees to become affectionately known as "the Godfather" in some institutions.

Since coming to Cambridge, his talents have been tapped as a Member of the Council of the Royal Society, President of the Organic Chemistry Division of the Royal Society of Chemistry, and U.S. Pacific Coast Lecturer. Additionally, he was a Pedler Lecturer of the Chemical Society in 1973, received their Ciba-Geigy Award for Synthetic Chemistry in 1975, and was Davy Medallist of the Royal Society in 1981. All his services to chemistry were recognised when he received the CBE (Commander of the Order of the British Empire) in the Queen's Birthday Honours List in 1982 (Fig. 7).

Fig. 7 - At Buckingham Palace with Prudence upon receiving his CBE in 1982.

Mr. Nib's chair, and to express his appreciation of the friendly forebearance of the Room."

There was a time when Cambridge professors did not have to retire, and went on well into their dotage (and often beyond). A popular story concerns one lecturer informing another, "Professor Smith is dead." "Oh," came the mildly interested reply, "and how did they know?" Unfortunately for us, Ralph will have to retire, and the department will know. It will know it has lost a distinguished synthetic chemist, and an outstanding Head of Department who has kept Cambridge chemistry vigourous through difficult times. When that time comes, the world of organic chemistry will be much the poorer, and his numerous friends hope that he will still keep his contacts with the worldwide chemical community.

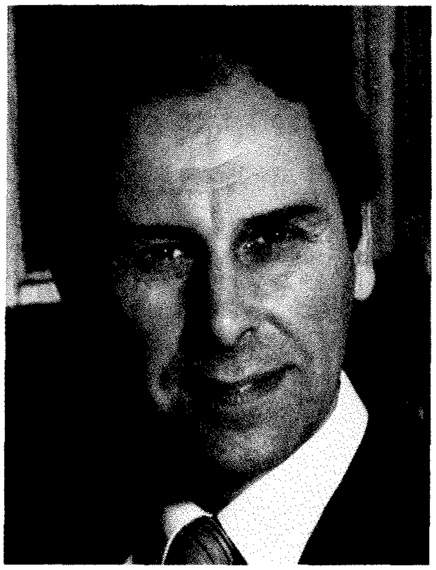
Acknowledgments

The author wishes to thank George Buchanan, Joe Connolly, Jim Roberts, Tim Jones, Andy Holmes, Basil Weedon, and Karl Overton for details of Ralph Raphael's career. Though all could not be published, all were appreciated!

References and notes:

1) RAR is the third professor of organic chemistry to whom an issue of *Aldrichimica Acta* has been dedicated. The other two were Robert Burns Woodward (Vol. 10, No. 1, 1977) and Gilbert Stork (Vol. 15, No.1, 1982). The author hopes that the article, often light-hearted and then serious, as in the other cases, will be taken as an affectionate look at both the RAR personality and the chemist.
2) This holds beautifully for benzoic acid, but unfortunately most other compounds behave exceptionally.
3) Wilkinson appears to have disappeared without a trace. If anyone can find evidence of any significant achievements by him in chemistry (*e.g.,* discovery of a catalyst, receipt of a Nobel Prize), the author would be grateful to receive details.

4) MacAlpine, G.A.; Raphael, R.A.; Shaw, A.; Taylor, A.W.; Wild, H.J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 410.
5) Becker, D.; Hughes, L.R.; Raphael, R.A. *ibid.* **1977**, 1674; for a later modification of the synthesis to make it suitable for large-scale work, see Larson, E.R.; Raphael, R.A. *Tetrahedron Lett.* **1979**, 5041.
6) Jackson, R.F.W.; Raphael, R.A.; Stibbard, J.H.A.; Tidbury, R.C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2159.



About the Author

Dudley Williams obtained his Ph.D. degree from the University of Leeds in 1961 with Basil Lythgoe, and spent three years as a post-doctoral fellow with Carl Djerassi at Stanford University. Since 1964, he has carried out research and taught at Cambridge University, where he is now Reader in Organic Chemistry and a Fellow of Churchill College.

The Synthesis of Labeled Compounds *via* Organoboranes

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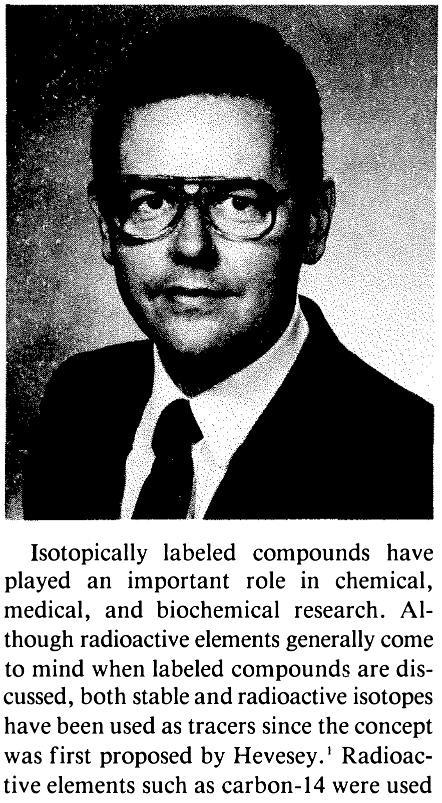


Isotopically labeled compounds have played an important role in chemical, medical, and biochemical research. Although radioactive elements generally come to mind when labeled compounds are discussed, both stable and radioactive isotopes have been used as tracers since the concept was first proposed by Hevesey.[1] Radioactive elements such as carbon-14 were used more extensively than their stable counterparts, *e.g.*, carbon-13, during the first half of this century because available detection techniques were capable of measuring small quantities of these elements quite accurately. Indeed, the use of radioisotopes has continued to increase at a rapid rate because of the ready availability of a variety of radioactive elements.[2] In recent years, the area has received renewed attention due to the development of relatively inexpensive medical cyclotrons which are capable of producing a selection of useful isotopes. These cyclotrons make it possible to generate radionuclides such as carbon-11 and nitrogen-13, which are easily detected using modern scintillation cameras but which place increased demands on the synthetic chemist due to their short half-lives (20 minutes and 10 minutes, respectively).

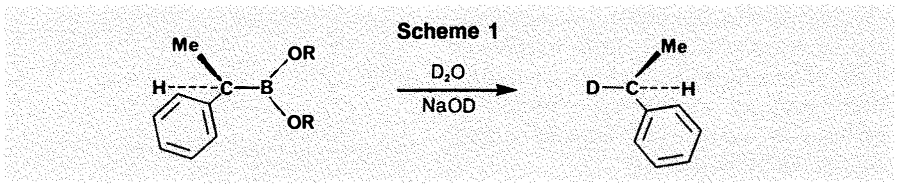
The role of stable isotopes in chemistry and medicine has grown even more rapidly than that of radioisotopes. A number of factors have contributed to this phenomenon: availability of a variety of useful isotopes, development of high-resolution gas chromatography-mass spectrometry systems, and rapid advances in Fourier-transform, multinuclear magnetic resonance instruments including the new whole-body magnetic resonance imaging instruments.[4]

Syntheses of isotopically labeled compounds normally involve the use of small, rather stable, isotopically labeled materials, such as carbon dioxide, water, nitric oxide or halide salts because they can be readily obtained from cyclotrons and reactors or they are more amenable to cryogenic distillation, a common source of a number of stable isotopes. As might be expected, these simple starting materials limit the number of synthetic routes available to chemists.[5] The problems are magnified in synthetic routes involving short-lived isotopes such as carbon-11 ($t_{1/2} = 20$ minutes) since the isotopes will disappear if the synthesis time exceeds the half-life by more than a factor of five.

Surprisingly, the use of organometallic reagents for the synthesis of isotopically labeled compounds has not been extensively developed; the Grignard reaction is the only exception. The role of organoboranes in isotopic labeling reactions is representative of this phenomenon. In spite of the proven utility of organoboranes in organic synthesis,[6] boranes were virtually ignored as potential precursors to a variety of useful labeled compounds. With the exception of hydrogen isotopes, the first report of the use of organoboranes in the synthesis of labeled compounds appeared in 1978.[7] The development of organoborane-isotope incorporation methodology has been rapid since that time and is the subject of this review.

HYDROGEN ISOTOPES

As noted above, hydrogen isotopes had been utilized in early borane research efforts. Indeed, the reports of deuterium-[8] and tritium-labeled[9] boranes began to appear shortly after the first convenient preparation of diborane was reported by Schlesinger and Brown.[10] However, the early studies involving boranes focused on the mechanism of the hydrolysis,[11] oxidation,[12] and substitution reactions[13] of borane complexes rather than on the synthesis of labeled organic molecules. If labeled compounds were synthesized, they were generally by-products in studies which focused on the mechanism of organoborane transformations. As an example, Davies and his co-workers synthesized optically active α-deuteroethylbenzene (Scheme 1), which demonstrated that the basic hydrolysis of alkylboronic acids proceeds with inversion of configuration at carbon.[14]



Scheme 1

Deuterated boranes have been used to elucidate the regiochemistry and stereochemistry of a variety of organoborane transformations. Brown and his co-workers determined the regiochemistry of the hydroboration-protonolysis sequence for rigid alkenes utilizing deuterated reagents,[15] as illustrated in Scheme 2. We carried out an NMR analysis of the hydroboration-protonolysis sequence utilizing nonrigid systems and reached the same conclusion, *i.e.*, that the sequence results in the *syn* addition of H_2 (HD) to an alkene.[16]

The hydroboration-oxidation reaction sequence has also been investigated utilizing deuterated boranes.[17] The experiments indicate that the sequence results in the *syn* hydration of alkenes as shown in Scheme 3.

Interestingly, the stereochemistry of the hydroboration reaction had been inferred from the products of protonolysis and oxidation sequences. Only recently has evidence been presented which clearly demonstrated that the hydroboration reaction involves the *syn* addition of the boron-hydrogen moiety to the carbon-carbon double bond[18] (Scheme 4).

Deuteroboration has also been utilized to confirm the stereo- and regiochemistry of the hydroboration of alkynes as well as the protonolysis of the vinylborane intermediates[19] (Scheme 5).

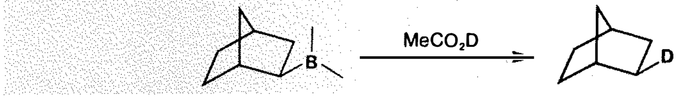
Deuterated boranes were also used to investigate the reduction of carbonyl compounds.[20] Among the more interesting deuterated boranes are those involving optically active reagents[21] (Scheme 6).

Of course, the reagents can be utilized to reduce derivatives of carbonyl reagents as illustrated in Scheme 7, which outlines a mild alternative to the Wolff-Kishner sequence.[22]

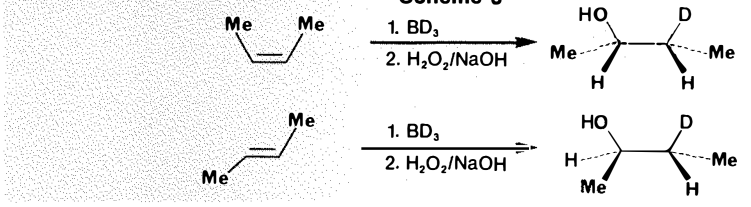
CARBON ISOTOPES

Isotopes of carbon have played a significant role in chemical and medical research studies since Ruben, Hassid and Kamen first used carbon-11 as a tracer.[23] Carbon-14 soon replaced carbon-11 in tracer studies due to its significantly longer half-life ($t_{1/2}$ = 5740 years). The ready reaction of organoboranes with simple carbon precursors such as carbon monoxide[24] and cyanide salts[25] would appear to make these reactions ideal routes for carbon isotope incorporation. As noted earlier, we reported the first use of organoborane chemistry for the incorporation of isotopic carbon in 1978.[7] The carbonylation reaction has since been used to incorporate carbon-14[26] (Scheme 8), carbon-13[27] (Scheme 9) and carbon-11[28] (Scheme 10).

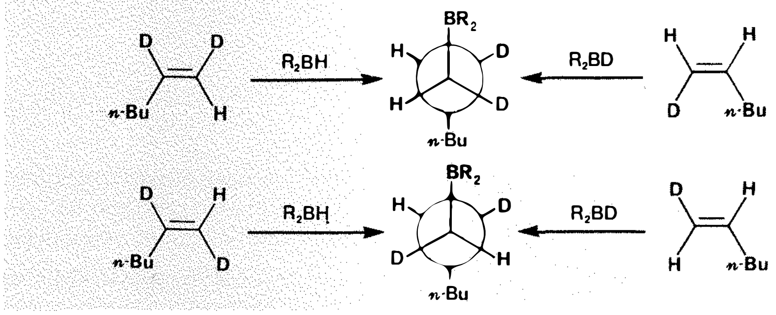
Scheme 2



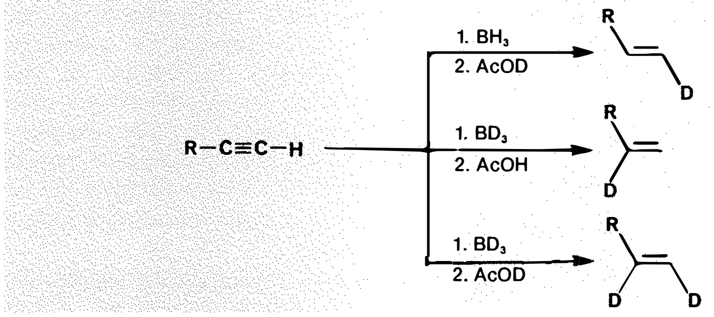
Scheme 3



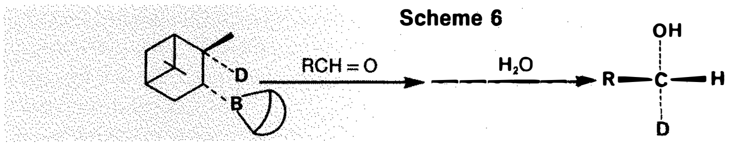
Scheme 4



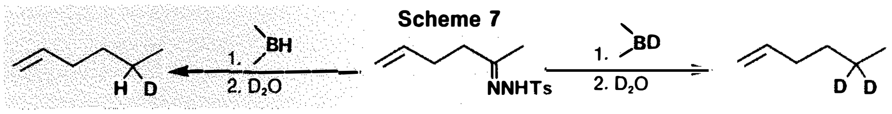
Scheme 5



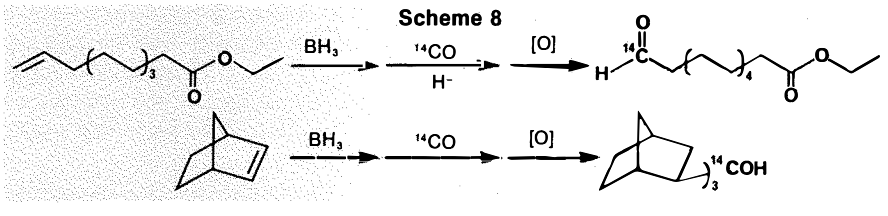
Scheme 6



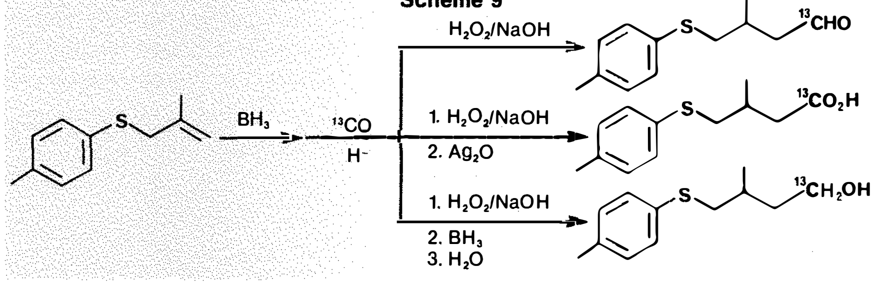
Scheme 7



Scheme 8



Scheme 9

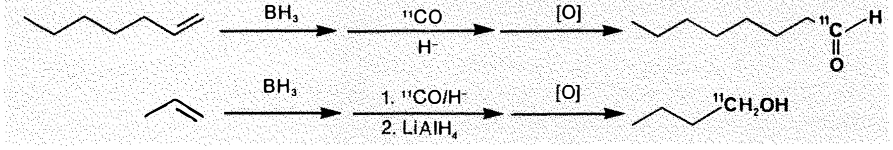


The hydroboration-carbonylation sequence can be accomplished in the presence of a variety of functional groups, which makes it particularly valuable in the radiopharmaceutical area, since it is the functional groups which impart physiological activity to the target molecules. A further advantage which is not immediately obvious is that, consequently, the isotope can be incorporated into the molecule in the final stages of the synthesis, a significant advantage when the isotope is either expensive or has a short half-life, *e.g.*, the 10-minute half-life of nitrogen-13.

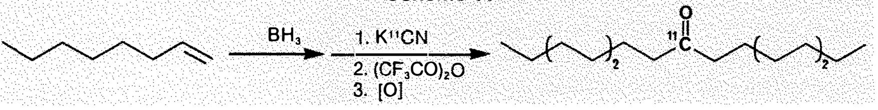
It was this latter consideration which led to the development of the cyanidation procedure as a method for incorporating carbon isotopes. Early on, it was found that the carbonylation procedure could only be utilized to synthesize molecules labeled in the terminal position because only the hydride-catalyzed carbonylation reaction was sufficiently rapid to be used in carbon-11 sequences. (As a rule of thumb, the total synthesis time should not exceed three half-lives of the isotope utilized, *e.g.*, it should not exceed one hour for carbon-11 syntheses.) This fact limited the utility of the carbonylation sequence and, consequently, other organoborane reactions were investigated.

It was found that the cyanidation procedure could be utilized to incorporate carbon-14[29] and carbon-13,[30] which permitted the synthesis of more complex molecules. More recently, it was found that the reaction can be utilized to successfully incorporate carbon-11 into secondary alcohols and ketones[31] (Scheme 11). The syntheses of carbon-14-labeled indanone and phenanthrone systems[29] (Scheme 12) are part of an extended investigation focused on the syntheses of estradiol and related hormones labeled with short-lived isotopes for use in evaluation of breast tumors.

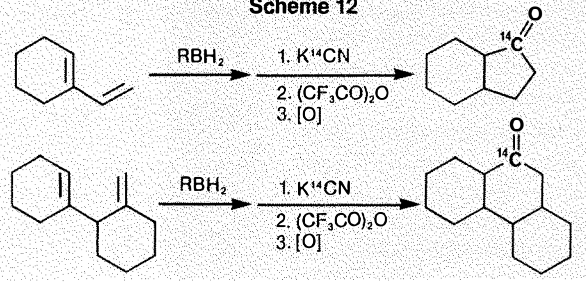
Scheme 10



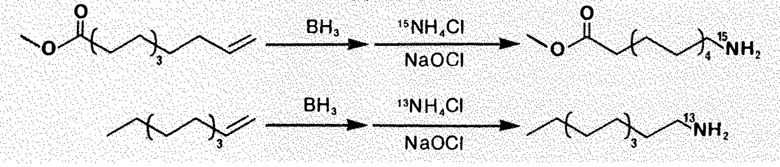
Scheme 11



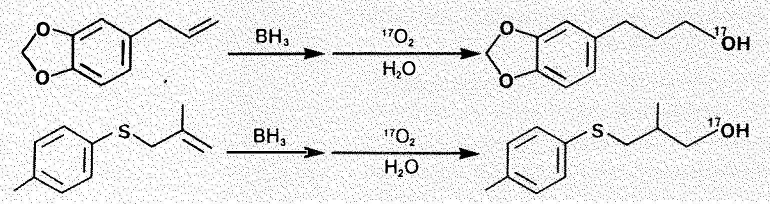
Scheme 12



Scheme 13



Scheme 14



Scheme 15

$$(MeCH_2CH_2CH_2)_3B \xrightarrow{^{15}O_2} MeCH_2CH_2CH_2{}^{15}OH$$

NITROGEN ISOTOPES

The utility of nitrogen isotopes in agricultural chemistry is well documented. The development of modern gas chromatographic-mass spectrometry systems as well as multinuclear magnetic resonance instrumentation, including the recently developed whole-body machines, has insured that the need for nitrogen-15-labeled compounds will increase dramatically. In addition, the very recent development of small medical cyclotrons promises to provide a user group for nitrogen-13-labeled compounds. The fact that organoboranes were known to react with chloramine and hydroxylamine-*O*-sulfonic acid[32] made them ideal candidates for use in syntheses of labeled compounds containing nitrogen isotopes. The development of a rapid, one-pot amination sequence which tolerated a wide variety of functional groups was the key to the success of this approach.[33] The synthesis centers on the use of labeled ammonium chloride, which is one of the most convenient sources of isotopically labeled nitrogen. The sequence has been utilized to prepare a variety of nitrogen-15-[34] and nitrogen-13-labeled amines[35] (Scheme 13).

OXYGEN ISOTOPES

Organoboranes react readily with a variety of oxidizing agents to produce alcohols, peroxides, acids and various carbonyl compounds. The direct reaction of oxygen with organoboranes, first reported in 1862[36] and then later developed into a useful synthetic procedure,[37] appeared to be the most promising for isotope-incorporation studies since oxygen isotopes are readily available as oxygen gas. The reaction has been utilized to prepare a number of oxygen-17-labeled alcohols in excellent yields[38] (Scheme 14).

More recently, the direct reaction of oxygen-15-labeled oxygen gas has been utilized to prepare the first oxygen-15-labeled organic compound, oxygen-15-labeled butanol[39] (Scheme 15). The synthesis of this material was particularly difficult because oxygen-15 has a half-life of only 2.0 minutes! The value of oxygen-15-labeled butanol lies in the fact that it can be used to measure cerebral blood flow employing modern nuclear medicine detection methodology (PET scanning). Such procedures may be carried out prior to other nuclear medicine procedures since the ^{15}O-labeled material will decay completely in 10 minutes.

HALOGEN ISOTOPES

The radiohalogens, especially the iodine isotopes, have a long history in nuclear medicine.[4a] In fact, radioiodine was the first isotope to be used routinely in therapeutic nuclear medicine. Not surprisingly, the synthesis of radiohalogenated compounds has been focused on radioiodination techniques, a situation which is not likely to change because of the variety of useful iodine isotopes which are currently available. Iodine-123, a single-photon-emitting isotope with a half-life of 13.3 hours, has recently become commercially available and is gaining popularity in the medical community because of its nearly ideal decay characteristics. A number of iodine-123-labeled agents such as *N*-isopropyl-*p*-iodoamphetamine **(1)**,[41] *m*-iodobenzylguanidine **(2)**[42] and iodoheptadecanoic acid **(3)**[43] have proven to be quite effective in clinical investigations (Scheme 16).

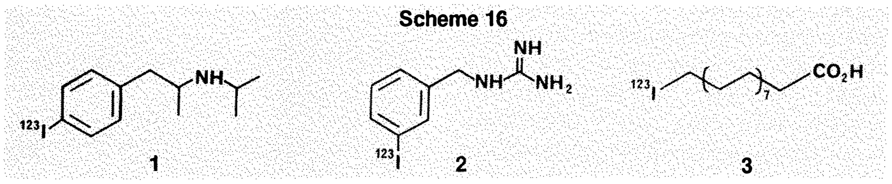
The reaction of organoboranes with molecular iodine in the presence of base had been effectively developed by Brown and his coworkers[44] and appeared to be an ideal method for incorporating isotopes of iodine. On closer inspection, the reaction sequence possessed a number of problems for use as an isotope-incorporation route. The two most troublesome aspects were the necessity of using sodium methoxide, which could be deleterious to desired functionality, and the requirement for molecular iodine, which is a particularly inconvenient and expensive chemical form for iodine isotopes (radioiodine is normally available in the halide form).

We carried out an extensive investigation of the iodination reaction in an effort to develop a methodology more suitable to radioiodination sequences. An important discovery was that the iodination reaction involved the electrophilic attack of iodine on an electron-rich organoborane complex.[45] This resulted in an inversion of configuration of the carbon attached to the boron and, more importantly, revealed that any electrophilic form of iodine could be utilized in the reaction.[46] The new iodine methodology had additional advantages in that it required only a mild base, sodium acetate, and resulted in excellent yields of radiolabeled products[47] (Scheme 17).

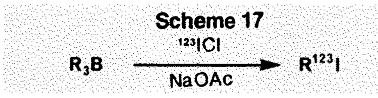
Even though radioiodinated iodine monochloride is readily available, it is not stable over a period of weeks and consequently, we turned our attention to developing a more satisfactory radioiodination procedure. The most convenient procedure involves the *in-situ* oxidation of sodium iodide by mild oxidants such as chloramine-T in the presence of an organoborane[48] (Scheme 18).

The method is a simple one: radiolabeled iodide is added to the organoborane in THF and then chloramine-T or *N*-chlorosuccinimide is added; after a few minutes, the product is isolated *via* HPLC, column chromatography or TLC. Excellent yields of the desired radioiodinated products are generally obtained[49] (Scheme 19).

Scheme 16

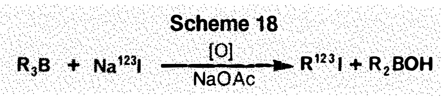


Scheme 17



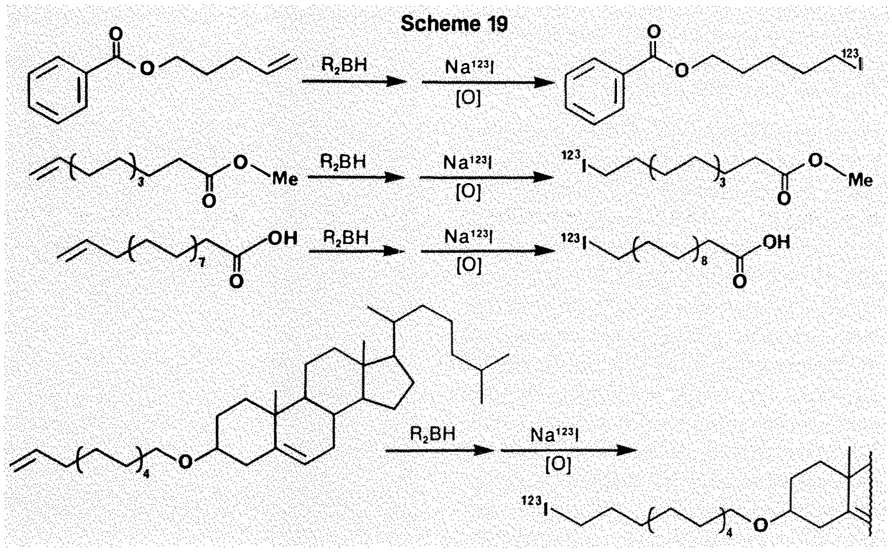
$$R_3B \xrightarrow[\text{NaOAc}]{^{123}\text{ICl}} R^{123}I$$

Scheme 18

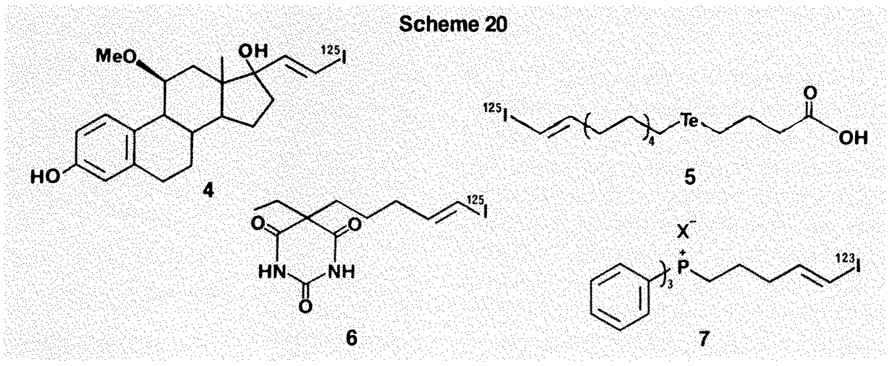


$$R_3B + Na^{123}I \xrightarrow[\text{NaOAc}]{[O]} R^{123}I + R_2BOH$$

Scheme 19



Scheme 20



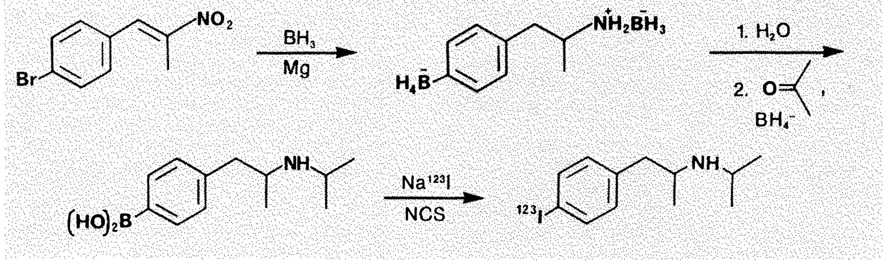
A significant aspect of the *in-situ* iodination methodology is that the radioiodinations can be carried out on a "no-carrier-added" basis.[50] This is important because it insures that the quantity of labeled agent is kept well below pharmacological dosages in nuclear medicine procedures. Traditional routes to iodine-labeled materials often involve substitution reactions which can lead to dilution of the desired product by nonlabeled starting materials. Recently, it was reported that no-carrier-added iodinations could be achieved on TLC plates using molecular oxygen in the atmosphere as the oxidizing agent![51]

The *in-situ* radioiodination of vinylboranes has made a significant impact in the radiopharmaceutical arena. Prior to our report in 1982,[52,53] it had been assumed that vinyl halides would be metabolically labile and thus, unsuitable for radiopharmaceutical studies. It has since been demonstrated that radioiodinated iodovinyl derivatives have a remarkably long half-life *in vivo* and a number of materials have been developed, including iodovinyl steroids[53] **(4)**, fatty acids of varying types[54] **(5)**, barbiturates[55] **(6)** and phosphonium halides[56] **(7)** (Scheme 20).

The syntheses of the radioiodinated vinyl iodides involve the *in-situ* oxidation of sodium iodide in the presence of a vinylboronic acid,[57] which are based on earlier iodination reactions involving molecular iodine.[58] The reactions possess an advantage over a number of other synthetic routes due to the inherent stability of the prerequisite vinylboronic acids, which are normally crystalline, air-stable solids.

Aromatic iodides are under renewed investigation in the radiopharmaceutical literature because they are more stable toward metabolic decomposition than alkyl iodide derivatives.[59] We have investigated the iodination of aromatic rings *via* the direct reaction of the corresponding arylboronic acid with labeled sodium iodide in the presence of a mild oxidizing agent.[52,60] The reaction is effective but is somewhat limited due to the modest variety of arylboronic acids which can be readily prepared. The situation has improved with the recent development of transmetallation reactions which will make arylboronic acids more readily available.[61] The synthesis of "no-carrier-added" iodine-123-labeled *N*-isopropyl-*p*-iodoamphetamine is representative of the versatility of these new reactions[62] (Scheme 21).

Scheme 21

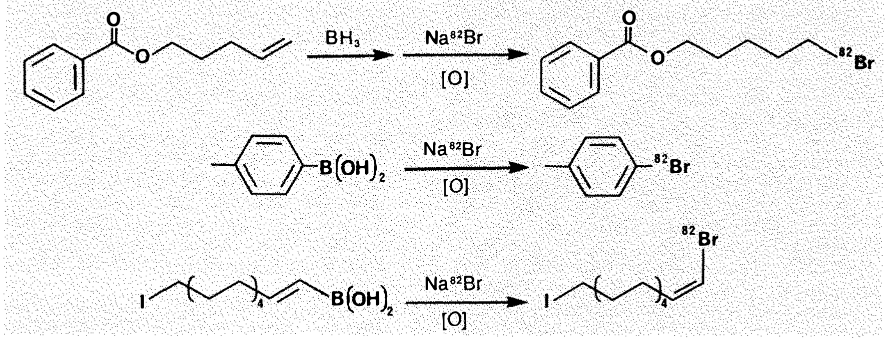


Fluorine-18, bromine-77 and chlorine-34m are isotopes of interest in the nuclear medicine field. We have found that modest yields of fluoroxysulfate materials can be obtained *via* the reaction of reagents such as acetyl hypofluorite, xenon difluoride and cesium fluoroxysulfate with trialkylborane reagents. However, the reactions are not efficient enough to be currently useful for incorporating fluorine-18 into agents of interest to scientists involved in radiopharmaceutical research.

A number of chlorination reactions involving organoboranes have been reported.[63] A few of the reactions appear suitable for use in radiochlorination sequences[64] but no syntheses have been reported to date.

An *in-situ* synthesis for preparing radiobrominated derivatives of alkyl, vinyl and aryl bromides has been reported, however, and is suitable for synthesizing a variety of radiobrominated agents[65] (Scheme 22).

Scheme 22



Although the role of organoboranes in syntheses involving isotope incorporation is relatively new, it is clear that these reagents will be utilized with ever-increasing frequency because of the ease with which a variety of functionally substituted organoboranes can be prepared, as well as their subsequent ready reactions with a wide variety of isotopically labeled precursors.

Acknowledgement. Dr. Kabalka's research in radiopharmaceutical synthesis is supported by the Office of Health and Environmental Research of the U.S. Department of Energy.

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About the Author

Professor George W. Kabalka received the B.Sc. degree from the University of Michigan in 1965 and the Ph.D. degree from Purdue University in 1970 under the guidance of Prof. Herbert C. Brown. After a short postdoctoral stay with Prof. Brown, he became Assistant Professor of Chemistry at the University of Tennessee in 1970 and was named Professor in 1981. Since 1984, he has held a joint appointment as Professor in the Radiology Department of the University of Tennessee Memorial Research Hospital where he serves as Head of Basic Science Research.

Dr. Kabalka was named a University of Tennessee Chancellor's Research Scholar in 1984. He is an active member of the American Chemical Society and currently serves as Alternate Councilor for the East Tennessee Section of the ACS. He has served as a consultant to Oak Ridge National Laboratory since 1974 and to a number of companies.

He has published nearly 150 scientific research papers, many of them on the use of organoboranes in organic and radiopharmaceutical syntheses. He is also interested in the elucidation of organometallic reaction mechanisms and the design of agents for use in nuclear medicine and magnetic resonance imaging.

NEXT SLIDE, PLEASE

there was no question that the reaction worked
but transient colors were seen
in the slurry of sodium methoxide in dichloromethane
and we got a whole lot of products
for which we can't sort out the kinetics
the next slide will show
the most important part
very rapidly
within two minutes
and I forgot to say on further warming
we get in fact the ketone
you can't read it on the slides
but I refer to the structure you saw before
the low temperature infrared spectrum
as I say
gives very direct evidence
so does the NMR
we calculated it
throwing away the geminal coupling
which is of course wrong
there is a difference of 0.9 parts per million
and it is a singlet
and sharp
which means two things
either
you're doing this NMR in excess methoxide
and it's exchanging
or
I would hazard a guess
that certainly in these nucleophilic conditions
there could well be
an alternative path
to the enone you see there
it's difficult to see
you could monitor this quite well in the infrared
I'm sorry, in the NMR
my time is up I see
well this is a brief summary of our work
not all of which
I've had time to go into
in as much detail as I wanted
today.

Roald Hoffmann
Cornell University
Ithaca, New York

Rare Sugars of Biochemical Interest

Alkylation of **2-acetamido-2-deoxy-1-thio-β-D-glucopyranose-3,4,6-triacetate** affords an alternative route[1] to thioglycosides of *N*-acetylglucosamine, ligands binding β-*N*-acetylglucosaminidase[2] and, possibly, proteins of similar specificity.

Recent intense interest in the chemistry and biology of heparin[3] gives special value to related monosaccharides. Availability of **L-iditol hexaacetate** provides a GLC standard for component analyses of carboxyl-reduced[4] heparins. Oxidation of **L-iditol** gives L-idaric acid and its lactone, a specific inhibitor of α-L-iduronidase.[5] Syrupy L-idose can be derived[6] from the relatively stable **1,2-*O*-isopropylidene-β-L-idofuranose,** also a starting point for preparing idosides and iduronides.[7] **2,5-Anhydro-D-mannitol** is the monosaccharide moiety produced in the nitrous acid degradation of heparin.[8]

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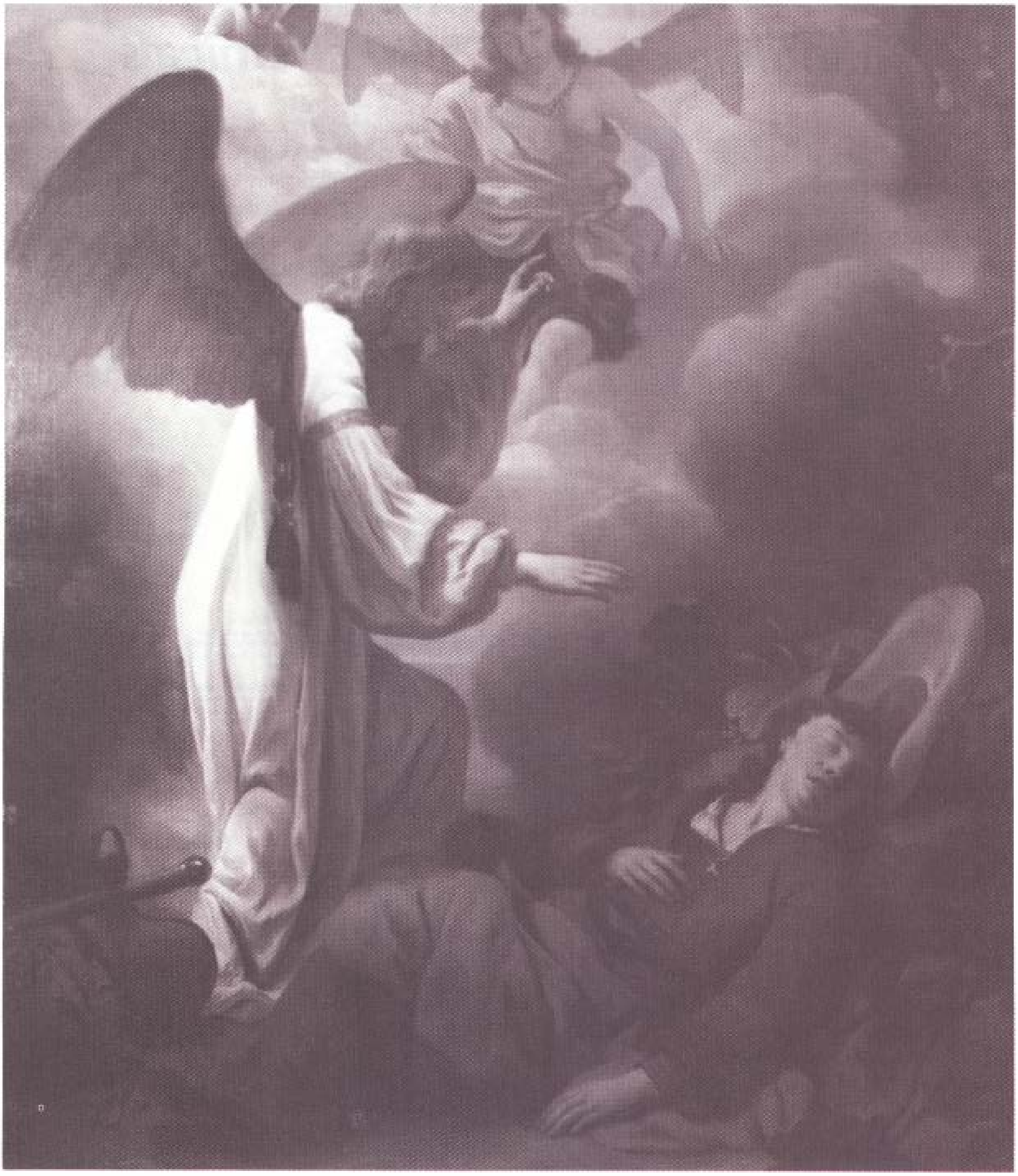

Guidelines for Handling Air-Sensitive Compounds

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About Our Cover:

Readers of the *Acta* will remember that *Jacob's Dream* is one of the favorite subjects of baroque artists — "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 is also such a favorite of our chemist-collector that three have appeared on our covers: Vol. 8, No. 4; Vol. 12, No. 3 and Vol. 15, No. 1. You may also remember that Gerbrand van den Eeckhout, Rembrandt's best friend, is one of our chemist-collector's favorite artists. His works have graced two previous covers: Vol. 8, No. 2 and Vol. 17, No. 2; the latter, the *Rest on The Flight to Egypt*, is perhaps Eeckhout's finest work. We had so many requests that we had color reproductions made. And so our readers will not be surprised at yet another Eeckhout, of *Jacob's Dream* (oil on canvas, 121 x 103cm) on our cover.

Eeckhout must have thought about this subject a good deal, since he painted it several times. The earliest version (Fig. 1), of 1642, is in Warsaw and another (Fig. 2), of 1669, is in Dresden. Our version is one of Eeckhout's last works, dated 1672. Two of the preparatory drawings (Figs. 3 and 4) he made for this painting are in Schwerin and in the Albertina in Vienna.

Fig. 1

Fig. 3

Fig. 2

Fig. 4

As we wrote previously: "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."

Lab Notes

I wish to point out that red (or clear) silicone rubber tubing possesses many advantages over common rubber or plastic tubing. Because of its self-lubricating quality, it slips easily over glass tubulations that would never permit the same size rubber tubing; thus only 2 sizes (¼in. i.d. x ⅛in. wall and 3/16in. i.d. x 3/64in. wall) accommodate most glassware. The larger size slips easily over even ⅜in. tubulation and does not collapse under vacuum. Furthermore, it will not melt on accidental contact with heating mantles nor will it lose flexibility when connected to a steam bath. From a safety standpoint, its use with glass tubing can certainly be recommended in a teaching laboratory. The higher cost of silicone rubber tubing can be offset by its longer life.

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We have found a solution to the problem of storing NMR samples at low temperatures and anhydrous conditions (for following reactions in NMR tubes over a number of days) by using inexpensive "Zip-Loc" bags (4 to 6mil) containing a small amount of desiccant. Capped but unsealed NMR samples stored for up to two weeks in a freezer showed no evidence of hydrolysis from atmospheric moisture. We have also found "Zip-Loc" bags to be effective miniature desiccators for short-term storage of moisture-sensitive materials.

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In Lab Notes, *Aldrichim. Acta,* Vol. 17, No. 2, p. 30, 1984, a hydrogenation procedure was described in which a balloon was used as a reservoir for hydrogen. A common variation is the use of an argon-filled balloon to maintain an inert atmosphere during a reaction. Thus, a good-quality rubber balloon is attached to a ~2-in. section of pressure tubing (¼in. i.d., ⅜in. o.d.) with a rubber band. The balloon is inflated and deflated 6-8 times with argon. It is inflated once more (to ~5-in. diameter for a 7-in. maximum diameter balloon) and attached to a hose-to-needle adapter (*e.g.,* Aldrich Z10,116-8) fitted with a ~1-in., 20-gauge needle. Some gas is allowed to escape *via* the needle. The needle is then used to attach the balloon to a previously argon-purged reaction vessel equipped with a rubber septum. Reagents and/or solvents can then be introduced *via* syringe or cannula. The balloon expands to accommodate the volume change.

An argon-filled balloon can also make the removal of air- or moisture-sensitive reagents from a septum-capped vessel (*e.g.,* a Sure/Seal™ bottle) more convenient. The septum is first pierced with a 20-gauge needle furnished as above with an argon-filled balloon. An oven-dried syringe is equipped with a lightly greased stainless steel syringe stopcock (*e.g.,* Aldrich Z10,235-0). A needle (20-gauge, except for viscous solutions like Red-Al® in toluene which require an 18- or even a 16-gauge needle) is attached and the needle is passed through the vessel's septum. The syringe stopcock is opened and the reagent is withdrawn. The syringe is then raised to allow withdrawal of some argon (clearing the needle of reagent and allowing accurate measurement of the volume of reagent). The stopcock is closed and the syringe needle can then be safely removed from the vessel. This procedure is recommended particularly for pyrophoric liquid reagents.

Dr. R. Thomas Swann
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Buffalo, NY 14260

Editor's note: Aldrich now lists balloons suitable for the manipulations discussed above. See page 50 of this *Acta* issue.

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Visualization of compounds on TLC plates with iodine is usually a slow process. We have found that the time for development can be shortened by blowing iodine gas directly on the surface of the plate. The device that we have used is a disposable Pasteur pipette with a few iodine crystals held between two glass-wool wads. In the hood, the iodine gas is blown gently over the dried plate by passing air through the pipette (*via* a compressed-air line or rubber bulb). The visualization is best achieved by using a movement that follows the expected path of the sample. The spots are then preserved by placing a glass plate or plastic tape on the plate.

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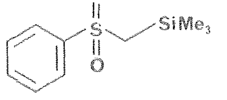
Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt**. *We reserve the right to retain all entries for consideration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

"Please Bother Us."

by Alfred Bader.

Mr. Donald Craig and Professor Steven V. Ley at Imperial College in London suggested that we offer phenyl trimethylsilylmethyl sulfone for the conversion[1] of aldehydes and ketones to the corresponding vinyl sulfones *via* a modified Peterson olefination.[2]

Naturally, we made it.



1) Craig, D.; Ley, S.V.; Simpkins, N.S.; Whitham, G.H.; Prior, M.J. *J. Chem. Soc., Perkin Trans.1* **1985**, 1949.
2) Peterson, D.J. *J. Org. Chem.* **1968**, *33*, 780.

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

Guidelines for Handling Air-Sensitive Compounds

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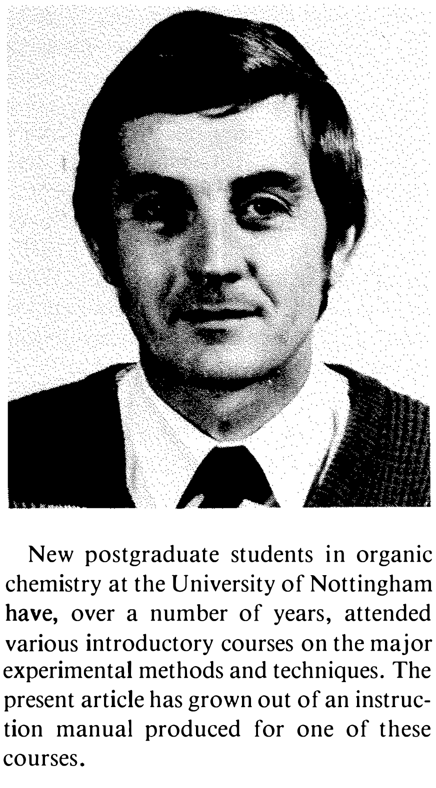
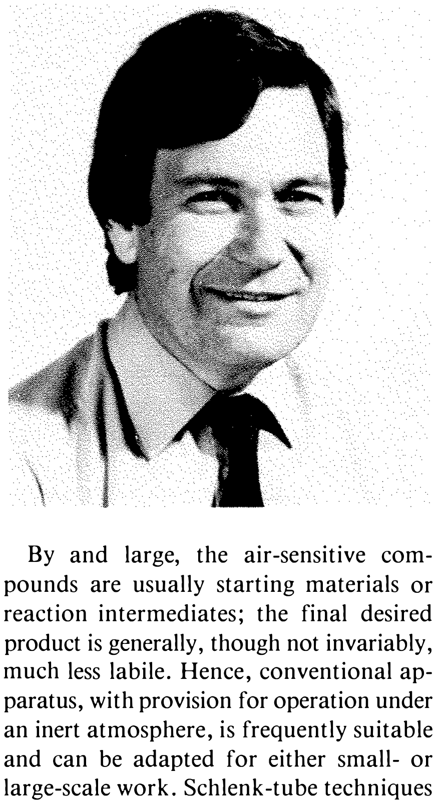




New postgraduate students in organic chemistry at the University of Nottingham have, over a number of years, attended various introductory courses on the major experimental methods and techniques. The present article has grown out of an instruction manual produced for one of these courses.

1. INTRODUCTION

The practice of organic chemistry sooner or later brings the organic-laboratory worker face to face with the practical problems of handling air-sensitive materials. Most commonly, the decomposition occurs on exposure to oxygen and/or water; however, reaction with CO_2 is a frequent occurrence, and even N_2 is not inert to all chemical reagents. This article summarizes the main methods adopted for the manipulation of such materials. These notes are only guidelines; there is no substitute for careful analysis of the problems of each experiment, and for individual ingenuity. The inexperienced should always seek practical help from those familiar with these problems.

By and large, the air-sensitive compounds are usually starting materials or reaction intermediates; the final desired product is generally, though not invariably, much less labile. Hence, conventional apparatus, with provision for operation under an inert atmosphere, is frequently suitable and can be adapted for either small- or large-scale work. Schlenk-tube techniques may also be employed, but are relatively unpopular with organic chemists. They are invaluable for the preparation and isolation of labile products. Vacuum-line methods, which are much beloved by inorganic chemists, are rather cumbersome for most organic preparative requirements. Nevertheless, simplified versions may be valuable for certain purposes.

Air sensitivity is usually associated with the decomposition of the substance with stoichiometric quantities of O_2, H_2O or CO_2. Fortunately, catalytic decomposition is fairly rare. Ease of decomposition is affected by the physical state of the material, and finely divided solids, dilute solutions, and vapors are the most susceptible.

Table 1 lists some common reagents (most of them commercially available) that need protection to varying degrees.

There are four main problems associated with handling compounds of the types listed below:

- how to use them efficiently and safely for their intended purpose
- how to avoid deterioration of the bulk sample once the bottle has been opened
- how to store these materials for long periods
- how to dispose of unwanted residual material.

Table 1

Class of Reagent	**Examples**
Free metals	Li, Na, K
Metal hydrides	$LiAlH_4$, R_2BH, R_2AlH, NaH, KH
Metal alkyls	RLi, RMgBr, R_3Al
Lewis acids	BF_3, BBr_3, $AlCl_3$, $TiCl_4$, R_2AlCl
Strong bases	$LiNR_2$, *t*-BuOK, NaOEt
Various oxides and anhydrides	OsO_4, $(CF_3SO_2)_2O$
Zerovalent metal complexes	
Hygroscopic solvents and solutions	
Organic compounds susceptible to nucleophilic attack	Acid halides, anhydrides, α-haloethers, isocyanates, diimides, imidazoles
Compounds susceptible to autoxidation	

Solutions to these problems are discussed in the relevant sections below. Additional information is available in the book by Shriver,[1] the review by Kramer, Levy and Midland,[2] and Aldrich Technical Information Bulletins.[3] These references are most important sources of practical detail.

One final general point deserves specific mention, and that is the question of reaction scale. Small-scale reactions are easier to perform and safer to handle. The reduction in apparatus size usually leads to a reduction in size of standard-taper (₸) ground-glass joints and rubber septa; this is beneficial since both types of union are less prone to leaks because of the reduction in surface area of contact. However, for a spherical flask, where volume/surface area = r/3, capacity reduces more rapidly with decreasing radius than does surface area. Hence, for small flasks, the glass surfaces need to be much drier. Additionally, relatively more solvent is employed per mmol. of reactants for small-scale work than for large-scale work; therefore solvents need to be drier. Finally, the O_2/H_2O content of the inert gas assumes a greater importance in small-scale work, and the small losses that occur on a 1-mol. or 100-mmol. scale may not be tolerable on a 1-mmol. scale. It follows that small-scale work requires much more care and attention to detail.

2. ESSENTIAL TECHNIQUES

A. Decontamination of the apparatus

Glassware, syringes, stirrers, etc. can be freed of surface moisture by drying at 125 °C overnight, or at 140 °C for 4 hours. Teflon® softens appreciably at these temperatures and should not be oven-dried. The apparatus should be assembled while hot and allowed to cool under a flow of inert gas. For short-term reactions (<3 hours), the use of grease is often avoided to prevent contamination of the reaction product. A minimum of grease, or a Teflon sleeve, is required for proper sealing or to prevent jamming (beware especially of joints subject to refluxing solvent or those which become warm in a vacuum apparatus). If positive pressures of inert gas are used, then joints need to be secured with, for example, spring clips.

The apparatus can be dried by flaming while flushing with inert gas. Cold pockets usually remain in which moisture may condense. This can be avoided by flaming the apparatus while it is connected to an oil-pump vacuum line. When particularly stringent precautions are necessary, dry the apparatus at 140 °C (>4 hours), assemble while hot, connect to an oil-pump vacuum line, flame the reaction flask, then allow it to cool *in vacuo*. The apparatus can be filled with inert gas by use of a suitable manifold (Fig. 1) or a Firestone valve (Fig. 2). Removal of oxygen from the apparatus is best achieved by alternate evacuation and inert gas-flushing cycles; three such cycles should suffice.

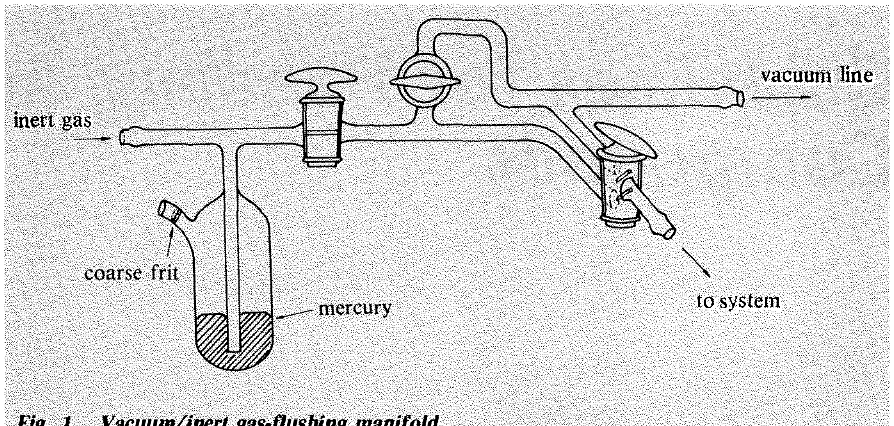


Fig. 1. **Vacuum/inert gas-flushing manifold.**

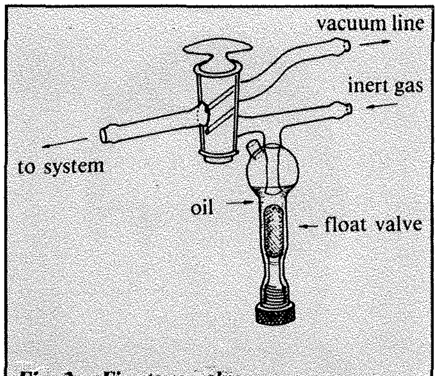


Fig. 2. **Firestone valve.**

B. Decontamination of solvents

This topic is discussed in several reference books[2,4-6] and in a series of papers.[7] Solvents may require drying in two stages: first with a high-capacity agent of medium efficiency, then with a high-efficiency agent. The solvent should be finally distilled under an inert atmosphere; reduced pressure is necessary with some aprotic solvents to prevent decomposition.

A few tests for dryness are available. For example, water content can be estimated by Karl Fischer titrations.[8] Alternatively, benzophenone ketyl (*e.g.*, $Ph_2CO + Na \rightarrow Ph_2CONa$) can be employed; its purple color is discharged by both water and oxygen.[5] The efficiency of the drying process can also be checked in a highly sensitive assay by use of tritium-labeled water.[7]

Ether and hydrocarbon solvents are especially popular for work with air-sensitive materials. Lithium aluminum hydride is often used for the final drying. A common mistake is the use of a large excess of this reagent — *ca.* 1% should be enough. The hydride can ignite on rubbing (use a plastic spatula) and reacts with ether solvents at elevated temperatures (explosively with THF and glyme >160 °C). ***Do not distill to, or near to, dryness!*** Even dry solvents bubble with fresh $LiAlH_4$ because of the high heat of solvation. When dry the solvent will dissolve some of the hydride and a little of the *solution* will react violently with water.

If there is a regular need for a particular dry solvent, then it is more convenient and effective to use a custom-made solvent still (Fig. 3). The solvent is refluxed in the presence of the high-efficiency drying agent (*e.g.*, $LiAlH_4$) and preferably under an inert atmosphere which serves to remove oxygen and prevent autoxidation. This part of the procedure is performed with Teflon valves A and D open. Once the solvent is dry and is required for use, tap A is closed so that material collects in the central bulb which, for convenience, should be graduated. Withdrawal of dry, deoxygenated solvent can be made by inserting a syringe needle through the septum of valve C (opened). If, however, the nature of the work requires >10-20ml of solvent on a regular basis, this port should be situated at C′ so that solvent can be drained directly into the reaction flask. For safety reasons, some thought should be given to the position of the still. The reflux should be stopped at the end of each working day (maintain the inert gas bleed); otherwise, provision should be made for automatic shut-down should the water supply fail.

Dried and deoxygenated solvents are invariably best when freshly prepared. However, many can be stored satisfactorily for later use. The containers should be

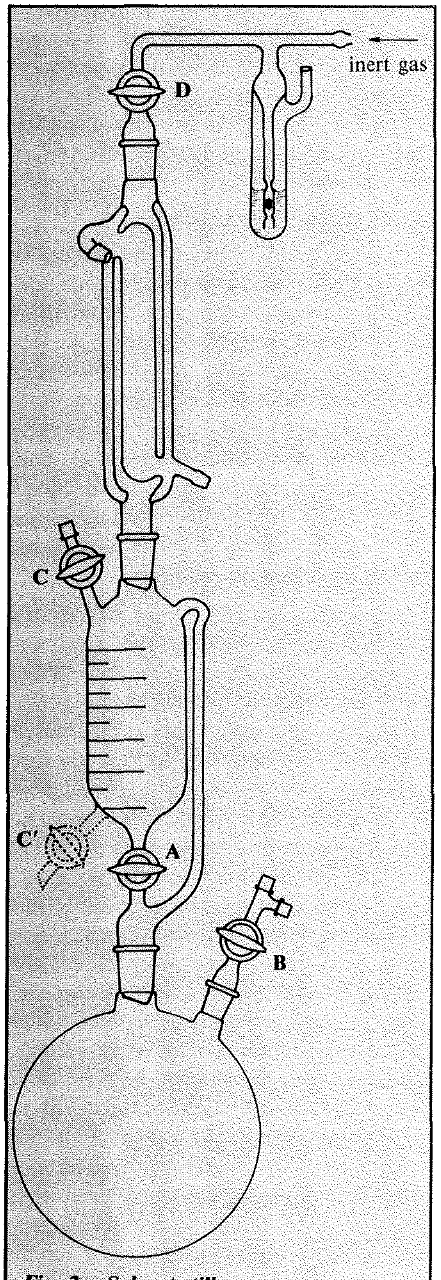
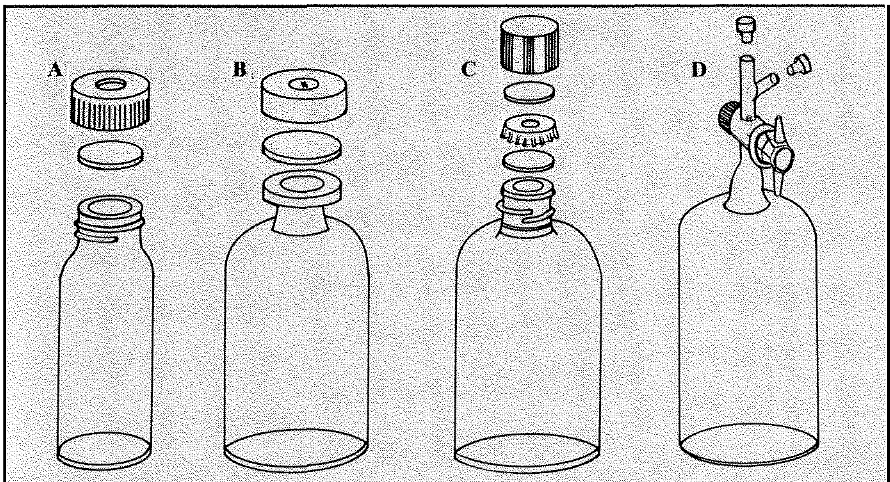


Fig. 3. Solvent still.

thoroughly baked out, as above, and allowed to cool under an inert gas flow. The dry solvent is transferred under an inert atmosphere (see below for basic techniques) and the container closed to the atmosphere with an adequate seal, *e.g.*, a Teflon-faced septum, a Teflon gasket or a Teflon valve. Ordinary reagent bottles may be used, but more secure sealing is obtained with Aldrich Sure/Seal™ bottles, aluminum-capped septum vials or similar equipment (Fig. 4). Storage should be at *ca.* 20 °C, and solvent is removed by syringe as required (see below). When the presence of oxygen is permissible and autoxidation is not a problem, then a simple predried reagent bottle which is securely sealed in air may be employed. Since transfers are then conducted in air, it is usual to store the solvent over a suitable granular desiccant of high efficiency (*e.g.*, molecular sieves) to prevent deterioration.



A. Septum vial with screw cap. B. Septum vial with aluminum cap (crimped). C. Aldrich Sure/Seal™ system. D. Storage bottle with Teflon valve.

Fig. 4. Liquid containers that allow sampling without opening (items are not drawn to the same scale).

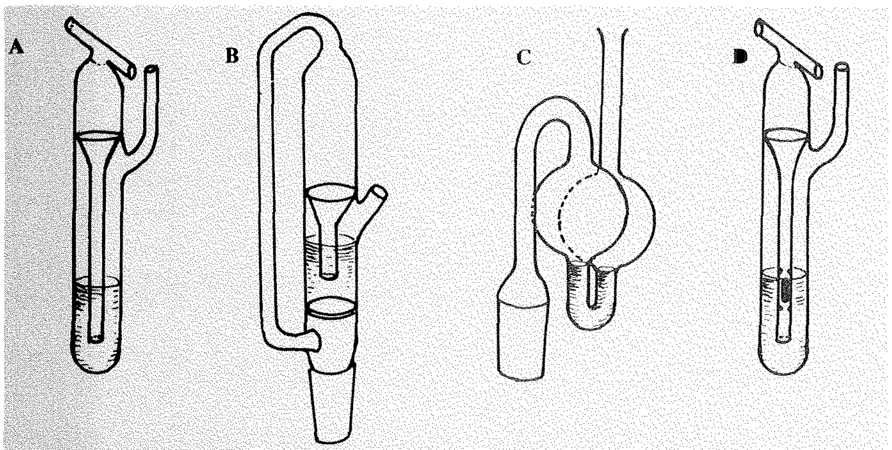
C. Inert atmosphere

Inert gases used for this purpose are N_2, Ar or He. The last is only employed in special cases where a light gas is needed to displace air downwards. Nitrogen is the most popular, largely on the grounds of cost, and needs only be avoided where metallic Li is being handled. Argon gives better protection since it is heavier than air and diffuses more slowly than nitrogen. It is to be preferred when particularly stringent precautions are required, as in the handling of pyrophoric materials. Specifications for industrial inert gases have improved greatly over the last 20 years, and various grades based on purity are readily available. The most expensive are the research-grade materials which, typically, contain less than 0.5 ppm CO_2, 1 ppm O_2, and 0.5-1 ppm H_2O. For routine chemical work, most laboratories buy the somewhat cheaper high-purity grade of gases: the impurity levels are usually less than 0.5 ppm CO_2, 2-3 ppm O_2, and 1-2 ppm H_2O. Gases of lower quality are not recommended unless it is intended to purify the gas stream.

We routinely use high-purity-grade gases without further purification since it is easier to *contaminate* the gas than to purify it further. The use of aqueous solutions for O_2 absorption (*e.g.*, chromous sulfate, Fieser's solution, etc.) is misguided since these introduce massive quantities of H_2O vapor, and any subsequent desiccant must then be fast-acting, of high capacity, and of high efficiency. Additionally, the purification train inevitably introduces a number of glass-to-glass joints and lengths of flexible tubing which are permeable to both O_2 and H_2O.[1] Shriver[1] discusses the merits of various purification methods, and some excellent (if expensive) commercial equipment is available. However, unless one has the facilities for checking the impurity levels in the "purified" gas, there seems little point in attempting to improve the specification of the high-purity-grade material since simple calculations indicate that these efforts are often counter-productive. It is much better to ensure that the apparatus is leak-free and that the shortest possible length of rubber or plastic tubing is employed between the apparatus and the gas cylinder. Copper piping should be used for long runs.

The exit to the apparatus should contain a gas bubbler filled with a hydrocarbon oil (Fig. 5); bubblers serve to monitor flow rate and prevent back-diffusion. Guard tubes (drying tubes) of silica gel or calcium chloride serve no purpose, for they remove little water and no oxygen and are inefficient baffles.

An inflated balloon can be used to maintain an inert atmosphere for a short time. The set-up shown in Fig. 6 is particularly convenient; when attached to the apparatus, the two-way Y-neck allows evacuation, balloon inflation and connection of the balloon ballast to the reaction flask. Since the apparatus is pressurized, joints should be held together with spring clips. The inflated balloon gives a false sense of security, since it would appear inconceivable for O_2, CO_2 or H_2O to diffuse into the system against the internal pressure. However, the rates of permeation



A and B. Aldrich models. C. Simple "wine-type" bubbler suitable for a wide range of joint sizes and for mounting off-vertical. D. Bubbler with check valve.

Fig. 5. Various designs for gas bubblers.

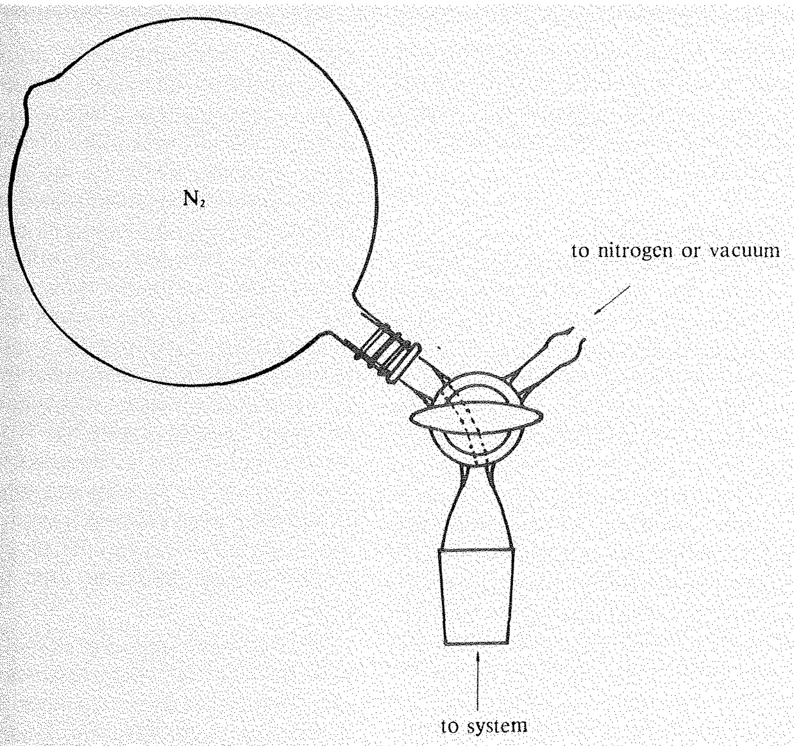


***Fig. 6. A convenient nitrogen-filled balloon** set-up.*

of these gases through the *ca.* 0.013-cm balloon membrane depends upon the difference in their partial pressures on the two sides of the membrane. The internal pressure exerted by the inert gas is irrelevant. Simple calculation using standard permeability data[1] will provide an estimate for the extent of the intrusion for a given system. Be prepared for an answer indicating several hundred ppm contamination in an hour or so! Hence, balloons are best reserved for various 5-min. tasks, some of which are more readily expedited if the balloon is attached (*via* a stopcock) to a hypodermic needle. These tasks include slightly pressurizing a reagent bottle prior to sampling the contents by syringe, providing a suitable ballast during the rapid force-cooling of a reaction vessel (*Note:* with "live" gas, suck-back at the bubbler tends to occur), or providing an inert atmosphere for a rapid reaction or one that is essentially complete but must be left for a while. The use of balloons is certainly better than taking no precautions at all, and in many cases better water exclusion is probably achieved than by the use of a drying tube filled with silica gel or calcium chloride.

When a cylinder of inert gas nears exhaustion, the drop in internal pressure causes H_2O to desorb from the metallic surface, increasing the impurity level in the gas stream. For nitrogen especially, the cost of the gas is relatively small in comparison with the cylinder rental charges, and it makes sense to change cylinders before they are completely empty.

D. Syringe-and-septum methods

Properly used, syringes and pierceable septa which reseal after use provide simple and convenient methods for handling air-sensitive liquids. Various syringes, syringe valves and single- and double-ended needles are available. The correct methods for filling and cleaning syringes and for conducting liquid transfers have been fully described in a review,[2] in an earlier *Aldrichimica Acta* article[3a] and in several Technical Information Bulletins.[3b] These articles are essential reading.

Certain reagents (*e.g.*, R_3Al, R_2AlCl and $TiCl_4$) on exposure to O_2 or moist air form a heavy solid residue (*i.e.*, Al_2O_3 or TiO_2) which may plug the syringe needle or jam the syringe stopcock. Lubricating the syringe with a little of the dry solvent may help to provide a temporary air-tight seal prior to filling with the reagent. The subsequent transfer should be conducted as rapidly as possible. The same syringe should not be used for multiple transfers without cleaning, since a blockage then becomes highly likely. It is better to be prepared for this contingency by having available duplicate syringes. Similar problems arise in the use of a catheter (double-ended needle) for the batchwise transfer of such reagents into a number of separate flasks or bottles under an inert atmosphere (see below). Exposure of the needle tip to the atmosphere is inevitable in changing from one receiver to the next in the batch and a blockage may well result. Although this can be readily cleared with a cleaning wire, the pressure of inert gas (which is used to provide the force for the transfer) must meanwhile be relieved in the stock bottle.

Various types of septa are available for sealing reagent bottles or vials, standard-taper joints, and standard-wall tubing. Elastomer-based septa reseal the best after being punctured, but are prone to chemical attack and solvent absorption which cause them to swell. Other materials are more inert but reseal less well; Teflon offers the best resistance to chemical attack but does not reseal. Hence, septa on stock bottles should be periodically replaced under inert atmosphere (see below). With certain reagents, we prefer either to buy in small quantities on a regular basis (rather than one large bottle) or to split the bulk reagent into several bottles (*e.g.*, see Figs. 4 and 9), the aim in each case being to minimize exposure by having a rapid turn-over. The caps of bottles containing corrosive reagents such as $SnCl_4$ or $TiCl_4$ should be inspected regularly and replaced with a fresh cap and Teflon liner if any deterioration is apparent.

E. Glove bags, glove boxes and related equipment

Glove bags and boxes are simple in concept, but present many difficulties which are discussed by Shriver.[1] In addition to use for O_2- and H_2O- "free" work, they are valuable for containing poisonous and noxious vapors when vented to a good fume hood. If pyrophoric materials are being handled, it is essential that a second person be present in case of mishap since gloves can be very difficult to remove in a hurry.

The effectiveness of glove boxes is roughly proportional to their cost, the best being the most expensive. The initial filling of the box with inert gas is best done by inflating a slightly over-sized weather balloon *in situ* to displace all of the air. Subsequent leakage of O_2 and H_2O through the seals and gloves presents a formidable obstacle to maintaining an inert atmosphere in the box, and an efficient high-capacity purification apparatus is essential for recirculating the inert gas (commercial equipment is available). A constant influx of inert gas is also required from the cylinder, and use of the integral gloves causes inert gas to be expelled. An anti-suck-back device is also required to counter the effects of removal of the hands from the gloves. Static electricity can build up in a glove box and can prevent balances from registering correct weights; anti-static devices should be used. Back-diffusion is considerable with a plastic glove bag, and only operations which can be conducted in <1 hour are easily managed. It is essential to wear double gloves and work quickly (rehearse!) to complete the transfers in *ca.* 0.5 hour. Fortunately, this is an adequate time for most applications, such as the transfer of sensitive solids, replacing septa, etc. Various sizes of glove bags are available commercially. The equipment is loaded in air and the bag is then sealed and evacuated to allow it to collapse around the apparatus. It is then inflated with high-purity nitrogen or argon (the latter is preferred); the evacuation/refilling process should be repeated about three times and the bag finally inflated to *ca.* 0.5 atmosphere pressure.

Simpler protective equipment is sometimes more appropriate (see Section 3B).

F. Schlenk tubes

Schlenk tubes are basically normal items of glassware with standard taper joints but are fitted with additional necks to permit connection to a vacuum/nitrogen manifold. Thus, each item can be easily filled with inert gas, and subsequent operations are carried out by unstoppering the tubes, joining different tubes together, adding reagents, etc. *while maintaining a brisk flow of N_2 out of the neck of the tube to prevent entry of air.* An inert atmosphere can be maintained during manipulations involving medium to large quantities. The basic techniques are thoroughly discussed by Shriver.[1] Commercial apparatus is available, but standard glassware is readily modified by the glassblower, or items can be made. The basic principle — that an apparatus can be opened if an *outflow* of inert gas is maintained — can be applied in many situations, including filtration. One of the most useful applications is the addition of a sensitive solid to a reaction using a Schlenk tube filled in a dry bag (see Fig. 12).

G. Vacuum lines

The principles of a simple vacuum line are described by Shriver.[1] The best protection from moist air can be achieved using such a system, but various technical problems make vacuum-line methods inappropriate for most organic preparations. They are especially useful for the transfer of condensable gases such as BF_3, bulb-to-bulb distillation of liquids, degassing reagents in Carius tubes prior to sealing, preparation of clean samples of alkali metals, etc. The addition of break-seal ampules and sample bulbs (using magnetic hammers) allows solid samples to be introduced. Some small-scale dry reactions, especially those involving noxious or radioactive materials, can only be run in miniature vacuum lines which are usually custom-built.

3. LABORATORY OPERATIONS

A. Choice of method

The method chosen as appropriate in a particular case depends upon a number of factors:

- the sensitivity of the reactants
- the reaction scale
- the time length of the experiment
- the temperature of the experiment
- the cost of the reagent.

Clearly, if the reagent is particularly sensitive (*e.g.,* a pyrophoric material such as *sec*-BuLi or Me_3Al), then stringent precautions should be taken to exclude both O_2 and H_2O for *every* such experiment. In this case, the first consideration is the most important. If, however, the reagent is fairly insensitive (*e.g.,* an acid chloride) or only moderately sensitive (*e.g.,* a Grignard reagent), then the questions of scale, time, temperature, and cost assume a much greater importance. Obviously, a reaction run below 0 °C (beware of condensation) for many hours and with regular monitoring by sample removal, requires better control of moist air than a 10-min. room-temperature reaction on the same scale with the same reagent. Small-scale reactions demand much greater care than their medium-scale counterparts.

Cost, in its widest sense, is also relevant since time is money, especially in industrial laboratories. If a reagent is cheap and readily available, then it is not always cost-effective to take maximum precautions to avoid waste. **Safety considerations, however, should not be overlooked** nor should the subsequent purification of the desired product. It makes little sense to save time in performing a reaction by taking minimum precautions if side reactions, which have not been minimized, make the subsequent purification a lengthy and tedious process.

B. Storing and dispensing reagents

Many reagents are supplied by manufacturers in containers designed for bulk protection of the sample as cheaply as possible. Cans, plastic bags in cans, plastic-sealed bottles, and thick-walled glass ampules are common. These packages often do not suit the user, who needs to be able to remove samples and reseal the package without destruction or deterioration of the remainder. Exceptions are the Sure/Seal bottles and Sure/Pac™ cylinders in which Aldrich supplies sensitive solutions; these can be sampled by syringe.

Anyone intending to purchase an air-sensitive material should bear in mind not only how the material is packaged, but also its shelf life, assuming proper storage. Some reagents have limited shelf-lives. For the commonly used organolithium reagents, the loss in activity with time depends somewhat on the temperature of storage;[9] the figures in Table 2 are only approximations.

Branched-chain alkyllithiums are the most labile. However, storage at -20 °C (freezer) is not recommended for we have experienced bottles fracturing at these temperatures! ***It should be standard practice to store bottles of pyrophoric materials inside sealed cans.*** An additional margin of safety is provided by placing a layer of desiccant in the can and flushing out with argon before sealing.

Table 2
Loss in activity with time of some organolithium reagents

Reagent	Storage at 25 °C	Storage at 0 °C
1.6*M* *n*-BuLi in *n*-hexane	5%/1 year	0%/1 year
2.5*M* *n*-BuLi in *n*-hexane	1-2%/3 months	0%/1 year
s-BuLi in cyclohexane	1%/week	0%/6 months
t-BuLi in *n*-pentane	2%/month	0%/6 months
MeLi in ether	1-2%/3 months	0%/1 year
PhLi in ether/cyclohexane	1%/month	0%/1 year

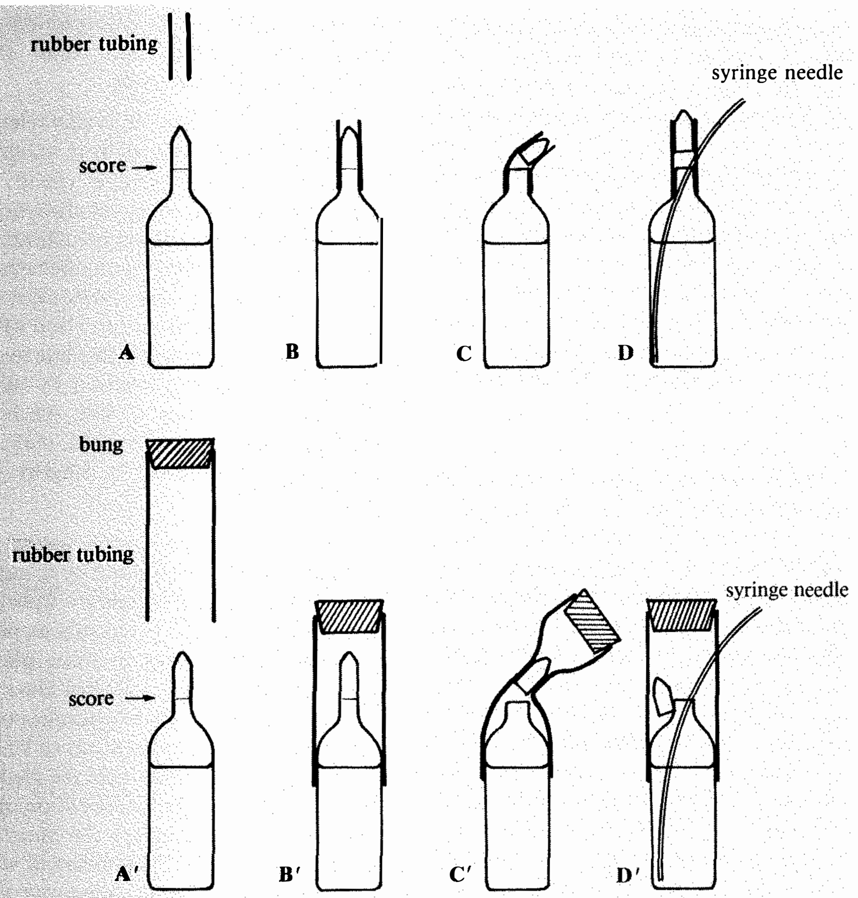


Fig. 7. ***Two methods for sampling an ampule; the sequence of operations is A, B, C, D in each case.***

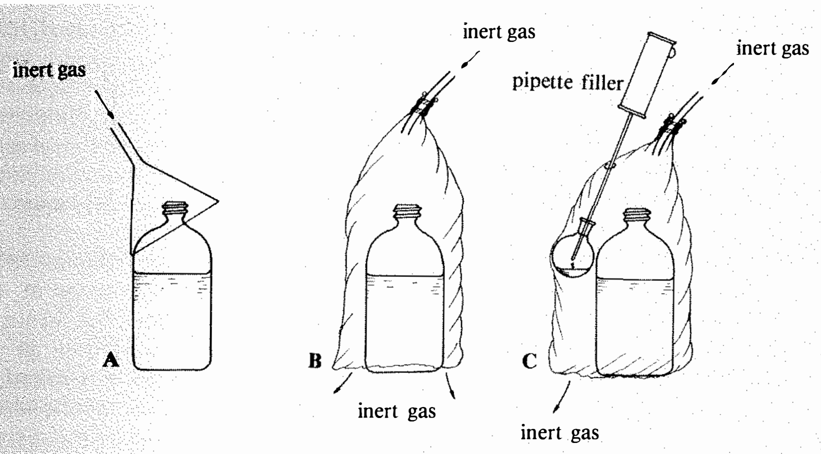


Fig. 8. ***Various ways of providing an inert-gas blanket. A. Inverted funnel. B. Polythene bag. C. One method of dispensing reagents under an inert-gas blanket.***

The following check-list is suggested for all who intend to purchase air-sensitive material.

- How often will the reagent be used?
- Will it be used up quickly?
- Will it be sampled often (*i.e.,* in many small or a few large doses)?
- For how long must it be stored?
- What are the difficulties in disposing of unwanted reagent?
- In light of the above, is it more sensible to purchase small quantities of reagent fairly frequently, or a large container once in a while?

Some containers will have to be opened in a dry bag or other device for supplying a blanket of inert gas (see below). The tops of bottles containing solids can be sealed with parafilm or hot wax. Storage of the bottle in a desiccator filled with argon provides additional long-term protection. Ampules which can be scored and cracked open can be protected from the atmosphere by use of a dry bag. The ampule can then be fitted with a septum, or the contents transferred to a more convenient container. Smaller ampules can be opened and their contents sampled by employing rubber tubing in the manner indicated in Fig.7.[2]

Liquids that are supplied in regular reagent bottles or cans (*i.e.,* without a fitted septum) may be opened under an inert gas blanket supplied by way of an inverted funnel (Fig. 8A) or a suitably robust polythene bag set up as shown in Fig. 8B. Better exclusion of moist air is provided by the latter (or a dry bag), and its flexibility allows manipulations to be performed more rapidly and safely. Corrosive acidic reagents such as $SnCl_4$ or $TiCl_4$ are probably best stored in simple reagent bottles, using a Teflon gasket to avoid destruction of the cap. These reagents can be sampled while protected as in Fig. 8B. As an example, Fig. 8C shows the use of a graduated pipette and mechanical filler to effect transfer to a reaction flask. Since both $SnCl_4$ and $TiCl_4$ have an appreciable vapor pressure at room temperature, some fuming will occur at the opening of the polythene bag (*Note*: operations must be performed in a fume hood). There should be no fumes around the neck of the container or pipette if moisture is rigorously excluded, but with $TiCl_4$ (which is very sensitive to trace water) a thin "smoke" may be difficult to avoid. With other reagents (*e.g.,* Me_3Al in hexane), it is often appropriate to plug the neck of the vessel with a tightly-fitting Suba•Seal septum; this should be "wired-on" for extra security. Such a septum will provide adequate protection and enables the material to be rebottled as detailed below. Septa unprotected by a layer of Teflon or an intervening Teflon stopcock are subject to chemical attack, and may swell on contact with solvent vapors.

It is often sensible to rebottle the material into more convenient packages, especially if it is to be used frequently. It may be better to divide the sample into small portions which can be sealed and used entirely as required. For solids, this can be accomplished readily by use of a dry bag, whereas for *solutions* the double-ended-needle technique is particularly convenient. Manufacturer's instructions should be followed for the dispensing and storing of neat liquids or solutions that are supplied in cylinders or pressure bottles.

Fig. 9 illustrates a suitable set-up for the rebottling of an air-sensitive material contained in stock bottle A. The receivers B (Sure/Seal bottles or simpler septum vials; the contents of the latter should be used up rapidly once the septum has been pierced) are oven-dried, allowed to cool in a vacuum desiccator equipped with an inert-gas bleed, and then fitted with tightly fitting Suba•-Seal septa. The septa need not be unused, but must be in good condition. The various needles should also be oven-dried; narrow-bore needles should be avoided, especially if the reagent has an appreciable vapor pressure and forms a solid residue on contact with moist air (*e.g.,* Me_3Al and Et_2AlCl). Nevertheless, ensure that a cleaning wire is close at hand. All connections involving flexible plastic or rubber tubing must be wired on.

Briefly, the basic transfer procedure is as follows:

1. Ensure that the bulk reagent is at room temperature. Clamp the container A securely but loosely; the same should be done with receiver B. Flush bubbler D with argon, then use its needle to pierce the septum of the stock bottle to vent any internal pressure.

2. Purge assembly E with argon with stopcock F open. Fit needle G to bottle A; close stopcock F to vent argon through D and reduce gas flow to a minimum.

3. Equip the receiving bottle with bubbler C. Insert the longer needle of assembly E so that it reaches near the bottom of bottle B. Increase argon flow and open stopcock F to expel argon through C. Remove bubbler D but keep it close at hand; it can be used to vent pressure in A if needle blockage should occur.

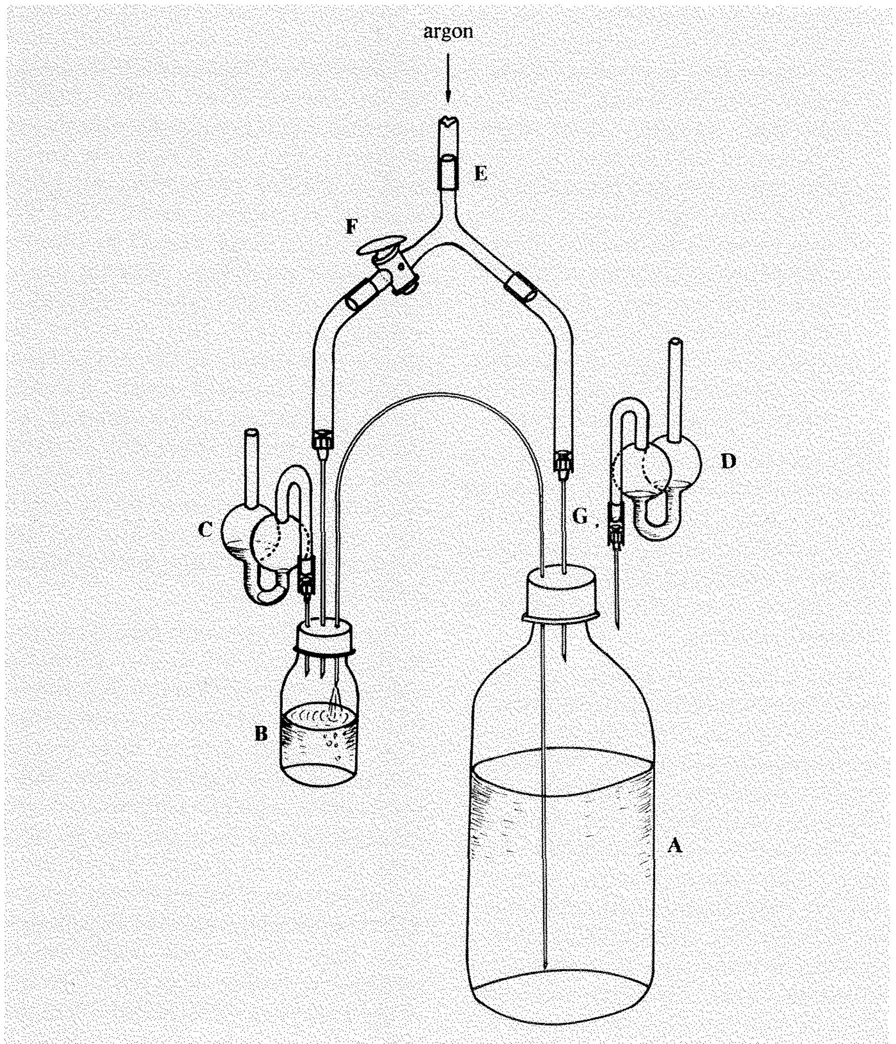


Fig. 9. Set-up for rebottling liquid reagents under inert atmosphere.

4. Allow B to be purged for approximately 2 min., then ease up the needle connecting F to the position shown in Fig. 9. Insert the shorter arm of the double-ended needle into bottle B. This may interrupt gas flow through C as the needle is purged. After a short period, insert the longer arm through the septum of A stopping short of the liquid surface. Argon should issue from C, even when stopcock F is temporarily closed. Open stopcock F.

5. Push the double-ended needle below the liquid surface in A and close stopcock F; liquid should be delivered into B if sufficient argon pressure is being applied. If there is no flow, open stopcock F and remove the U-needle and unblock it, then proceed as in Step 4.

6. Just before the desired volume has collected in B, carefully raise the U-needle above the liquid in A; allow the needle to drain and purge, then reduce the argon flow. Detach bottle B by removing, in this order, the needle connecting F, the U-needle, and finally outlet C. Open stopcock F and temporarily plug the U-needle by inserting its free end into a rubber stopper.

7. Clamp a fresh receiver B in position and proceed as in Steps 3-6. With practice, the whole operation can be conducted smoothly and without incurring any blockage. The design of the apparatus allows for easy location of any blockage, should one occur, and for venting pressure from A by opening F. If a blockage is suspected but not located, then decrease argon flow and reattach vent D to the stock bottle A; this allows a more leisurely examination of the system.

8. Replace the punctured septum of bottle B with a Teflon-faced septum. A dry bag or the apparatus shown in Fig. 8B is suitable for this purpose. Small bottles such as this are best stored in a sealed can under argon, as noted above. We have successfully stored

> 25% (w/w) solutions of Me_3Al, Et_2AlCl and $EtAlCl_2$ in hexane in simple septum vials in this way for *ca.* 2 years without any deterioration. Once punctured, however, these single-Teflon-faced septa do not afford adequate protection, and the contents of the vial should be used up within *ca.* 7 days. In any event, it is then prudent to afford secondary protection by fitting a rubber cap (*e.g.,* upside down Suba•Seal) over the punctured septum; paraffin wax film may also be used. Alternatively, Sure/Seal containers afford better long-term protection.

The various types of storage vessels that are commercially available, or that can be made, are shown in Fig. 4. The vessels fitted with Teflon stopcocks (closed during storage) are equipped with two septa to allow purging of the head space with N_2 or Ar *before* sampling.

Some thought must be given to choosing the location and storage temperature of the various air-sensitive reagents in use in modern organic laboratories. We store the pyrophoric reagents in an explosion-proof refrigerator in a fireproof room. Corrosive or toxic materials require storage in a fume hood. In the interest of safety, many air-sensitive compounds should not be stored on work benches. Refrigeration causes a reduction in pressure in the dead space of the storage vessel, which may cause moist air to be sucked in through an imperfect seal (*e.g.,* a punctured septum). Hence, those reagents that do not deteriorate at room temperature, or decompose only very slowly, should not be refrigerated without considering other factors such as expected storage time and effectiveness of the seals. Materials that have been refrigerated should be allowed to warm up to room temperature before opening; otherwise, the condensation of atmospheric moisture may occur.

C. Running reactions

The apparatus and solvents are dried as described previously. Solutions and solvents are conveniently handled with the syringes which are used to sample the septum-capped container, and are injected through the septum of the reaction vessel. In medium- to large-scale work, it is better to use the double-ended-needle method to effect the transfer from the stock bottle to the reaction flask, pressure-equalizing dropping funnel, or measuring cylinder, as appropriate. These methods are fully described in the Aldrich Technical Information Bulletins.[3b]

Solids can be transferred under an argon blanket or in a glove bag. If possible, they are dissolved in an appropriate dry solvent for convenience before further transfer; otherwise they may be loaded directly into the reaction flask or a Schlenk tube (for the gradual addition of the solid during the course of the reaction, see Fig. 12) which is then fitted to a side neck of the reaction flask under argon flow. Whereas precise quantities of liquids can be dispensed by volume provided that densities are known,[10] solids must be weighed (using an argon-filled stoppered vessel). Although precise weights are easily established, obtaining the *desired* weight will clearly involve several transfers, increasing the risk of exposure. It is better to obtain near to the desired quantity in one or two weighings, and then scale all other reaction quantities accordingly.

The reaction apparatus itself is most efficiently purged of air by alternately evacuating (oil pump) and filling with inert gas using a manifold or Firestone valve (Figs. 1 and 2); two or three evacuation/purging cycles should suffice. When less stringent precautions are required, simple flushing with inert gas may be sufficient. One method for achieving this, which is especially useful for small-scale work or when the reaction vessel has only one neck, is to use a hypodermic needle pushed through the septum as an inlet. The vent to the apparatus must be connected to a bubbler filled with mineral oil to prevent back-diffusion of air and to monitor gas flow (Fig. 5). If the bubbler is equipped with a septum-sealed sidearm on its inlet side, it can also function as a convenient source of inert gas for filling syringes. Some bubblers are equipped with float valves to prevent accidental suck-back of air. Mercury may be used as the fluid if it is necessary to slightly pressurize the reaction flask. It is best not to continually pass inert gas over the surface of volatile reaction solvents or reagents, for solvent evaporation or reagent fuming (at the exit bubbler) will occur. A gas inlet close to the exit bubbler is adequate to maintain an inert atmosphere, provided the apparatus is leak-free. Alternatively, the atmosphere may be maintained for short periods by using a nitrogen-filled balloon; the shortcomings of this method were discussed in Section 2C.

Some typical reaction assemblies are shown in Figs. 10-12; they can be modified simply to suit a variety of requirements. The glands of mechanical stirrers are a weak point; the majority leak when the system is evacuated, which makes the displacement of all oxygen and water vapor more difficult than if magnetic stirring is employed. Some glands have a screw fitting which allows tightening of the seals around the stirrer shaft during evacuation. After purging, the pressure on the seals must be relieved in order that stirring may

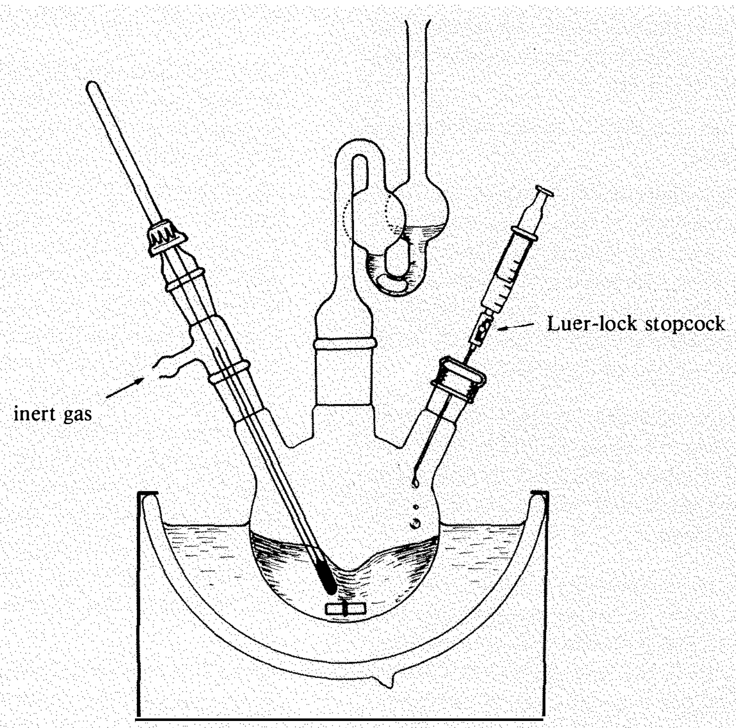


Fig. 10. Low-temperature reaction with liquid addition and magnetic stirring.

proceed. Oil- and mercury-filled stirrer glands will not withstand even partial evacuation of the apparatus, and are therefore unsuitable for reflux reactions because appreciable condensation of solvent occurs in the oil.

"Sealed-tube" reactions can be employed with advantage for many small-scale processes. Reacti-Vials™ (Fig. 13A), which are sealed with Teflon-faced septa, are popular for this use and will withstand moderate pressures without leaking provided that the septum has not been punctured. We tend to prefer modified Schlenk tubes which use high-vacuum Teflon screw valves joined to heavy-wall tubing (Fig. 13B). These are leak-free even under fair internal pressures, and the inert atmosphere can be maintained almost indefinitely. Both systems are suitable for magnetic stirring, and can be heated in a metal block or oil bath (in which case safety screens must be used). Solids are preloaded into these vessels (using dry bag, etc.); solvents or solutions can be injected *via* the septum or added against a counter-flow of argon, as appropriate.

Few organic *products* are so sensitive to air that they will not tolerate brief exposure to it; thus, product isolation under air-free conditions is seldom required. If the product is labile, then it is necessary to design the reaction so that nonaqueous isolation is possible. Distillation, solvent extraction, crystallization and filtration may all be effected under inert gas, if necessary.[1,2] For sensitive solid products, Schlenk-tube techniques are particularly convenient. If it is desired merely to remove solvent (or other volatiles) from a dissolved solid product (*e.g.*, a carbanion salt), then passage of inert gas over the surface may be successful. Clearly, this will take a long time at low temperatures, and reduced pressure may be necessary. Insoluble solid products may be freed from liquid contaminants by filtration in a Schlenk apparatus followed by rinsing with a suitable volatile, dry and degassed solvent.

4. SAFETY ASPECTS

Several points concerning safety have already been made in relation to handling pyrophoric materials, using sealed-tube reactions, anticipating blockages in hypodermic needles, the positioning of solvent stills, and storing reagents. Such precautions are common sense and the wary should not allow the potential hazards to dissuade them from handling these materials. In our experience, accidents are *less* common with such compounds *because* the various problems have been carefully

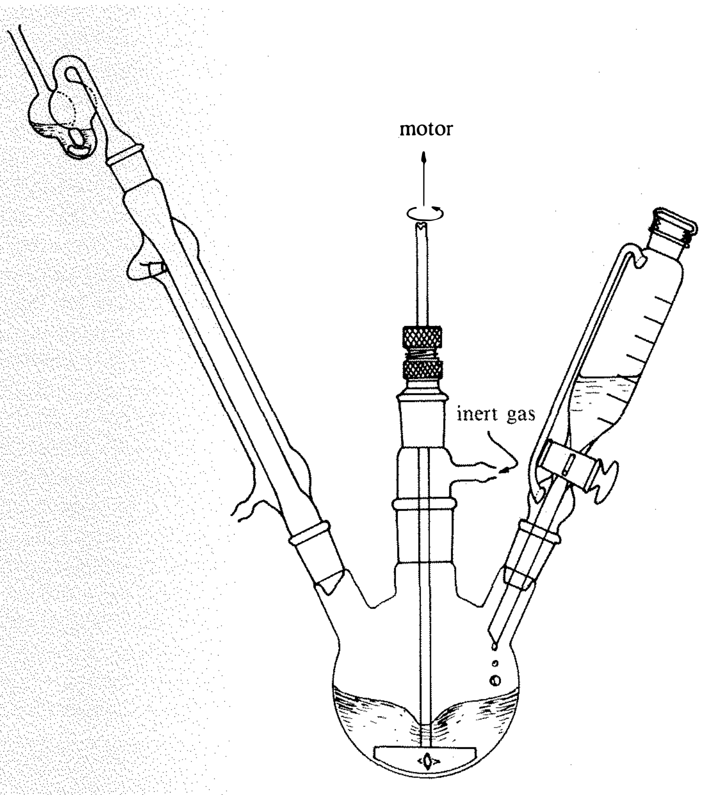


Fig. 11. ***Liquid addition and mechanical stirring (for viscous products) with reflux, if necessary.***

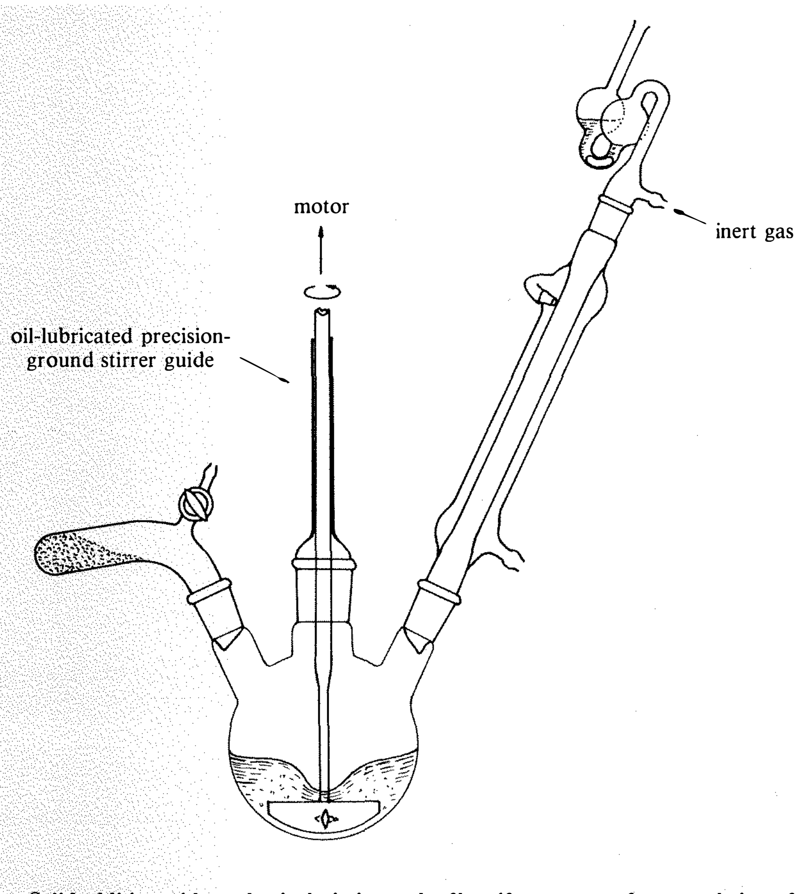


Fig. 12. ***Solid addition with mechanical stirring and reflux, if necessary, after completion of addition.***

analyzed *before* starting work. It is not possible to cover all other contingencies here, and the following are simply some of our further thoughts on these matters.

Acetone/dry ice (solid CO_2) cooling baths are commonly employed in this area to provide a temperature of -78 °C, but they do introduce the risk of fire. It is important therefore to avoid the accidental discharge of a pyrophoric solution from a syringe in the vicinity of such a cooling bath. Luer-lock syringe stopcocks or a needle-tip vial (Fig. 14) can be employed to prevent such an accident. The vial is flushed with argon, butted up to the septum of the reagent bottle, and the syringe needle inserted through the three septa into the stock solution; the needle of the filled syringe is then withdrawn until the tip is located between the two septa of the vial. Injection into the reaction flask is then made by piercing the septa of the vial and of the reaction vessel.

In busy laboratories it is extremely easy to lose track of the quantity of potentially hazardous materials that is in-house at a given time (especially if there are several autonomous research groups), or to identify the owner and age of a bottle of material found "lying around". It is the duty of those using such compounds not to expose others to unnecessary dangers. For these reasons, we purchase air-sensitive reagents such as organoboron, -aluminum and -lithium reagents for communal use, and store them in a fireproof room. This not only avoids proliferation, but ensures a rapid turn-over of labile materials. The label of each bottle is marked (using permanent felt-tip ink) with a code containing the initials of the *staff member* and the month and year of purchase (*e.g.*, ABC/10/85). Establishing ownership is important when the time comes for disposing of unwanted or decomposed compounds!

The disposal of unwanted reagents presents a thorny problem, which is why the optimum use of all chemicals should be given a high priority. Recommendations for disposal are given by Aldrich for all of the chemicals in the Aldrich Catalog/Handbook and in the *Sigma-Aldrich Library of Chemical Safety Data* and these publications can be used for quick reference. The person who is generally best equipped to deactivate or detoxify a given chemical is its user for he *should* be familiar with its reactivity and chemical properties. Water-sensitive compounds, for example, are usually *added slowly* (under inert atmosphere, if necessary) *to* stirred solvents with which they react much less violently (*e.g.*, ethyl acetate for $LiAlH_4$ and *n*-butanol for *n*-BuLi or Me_3Al solutions). Transfers can be made by the methods already discussed. However, it is more difficult to decide how to handle a solution that has decomposed to give a "mush" of solid and liquid; this can arise, for example, with alkyllithiums that have been stored incorrectly, for too long, or in a leaky container. It is not safe to assume that a pyrophoric reagent has thus become deactivated, nor can the material be removed by syringe for dropwise addition to, for example, *n*-butanol. If, literally, only residue remains in the bottle, then we usually introduce a small leak in the septum by piercing it with a short hypodermic needle or by slitting. The container is left undisturbed for about a week; the septum is then removed and exposure to the atmosphere continued for a day or so. It is usually perfectly safe then to drench the residue in 2-propanol. If, however, the above-mentioned "mush" or badly deteriorated solution represents a substantial quantity of material, we dispose of it by breaking the bottle from a remote distance on a hazardous waste site (as approved by local regulations); after a while, the residues are drenched with water. The alkali metal hydroxides thus formed are soon converted to carbonates in the atmosphere. The broken glass is removed after a day or two. Extra precautions are necessary if there is pedestrian or other traffic in the area. ***Only qualified personnel should dispose of large quantities of hazardous material.***

Disposal procedures for chemical waste, however, are very much a matter for individual laboratories and institutions, for local facilities and conditions vary widely. In some cases (*e.g.*, substantial quantities of partially hydrolyzed $SnCl_4$), it is easier to *recover by purification* (*e.g.*, distillation under N_2) than to effect disposal. ***Regardless of the material or the method of disposal, all federal, state and local laws should be observed.***

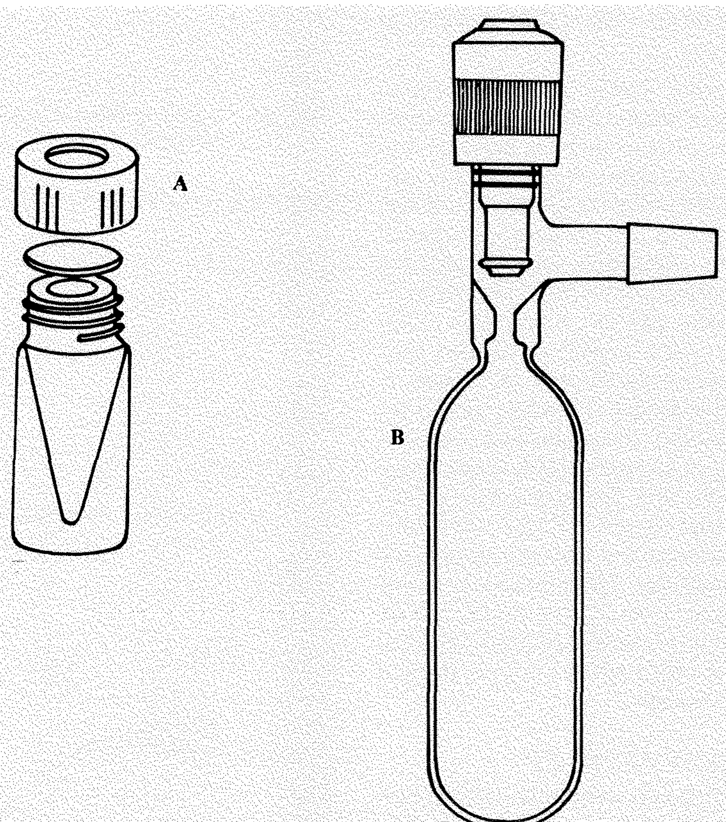


Fig. 13. Sealed reaction vessels. A. Reacti-Vial™ B. Schlenk-type tube in heavy-wall glass and fitted with a high-vacuum Teflon screw valve.

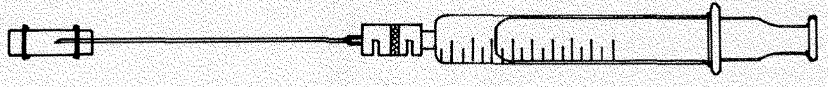


Fig. 14. Needle-tip vial constructed from glass tubing, fitted with septa, and purged with inert gas.

These guidelines are intended for use by technically skilled persons. We do not guarantee favorable results and we assume no liability in connection with their use. This information is not intended as a license to operate under, or a recommendation to infringe, any patent covering any material or use.

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1) Shriver, D. F. "The Manipulation of Air-Sensitive Compounds"; McGraw-Hill: New York, 1969.
2) Kramer, G.W.; Levy, A.B.; Midland, M.M.; Brown H.C. Laboratory Operations in "Organic Syntheses *via* Boranes"; John Wiley & Sons, Inc.: New York, 1975; Chapter 9.
3) a) Lane, C.F. *Aldrichim. Acta* **1977**, *10*(1), 11.
b) Aldrich offers a fine series of comprehensive Technical Information Bulletins dealing with packaging, equipment, handling and storage of air-sensitive reagents:
   - AL-134 – *Handling Air-Sensitive Reagents*
   - AL-135 – *Equipment for Handling Air-Sensitive Reagents*
   - AL-136 – *The Aldrich Sure/Pac™ Cylinder Packaging System and Recommended Transfer Procedures*
   - AL-137 – *The Aldrich HPLC Solvent Sure/-Seal™ System*
   - AL-149 – *Aldrich Kilo-Lab™ Cylinder Packaging System and Recommended Transfer Procedures*
   - AL-150 – *Equipment for Transfer of Liquids from Aldrich Kilo-Lab™ Cylinders*
4) Organic Solvents: Physical Properties and Methods of Purification. Riddick, J.A.; Banger, W.B. in "Techniques of Chemistry", 3rd ed.; Wiley-Interscience: New York, 1971; Vol. 2.
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7) Burfield, D.R.; Smithers, R.H.; Tan, A.S.C. *J. Org. Chem.* **1981**, *46*, 629 and references cited therein; Burfield, D.R. *ibid.* **1982**, *47*, 3281; Burfield, D.R.; Smithers, R.H. *J. Chem. Educ.* **1982**, *59*, 703.
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9) Smith, R.W. Aldrich Chemical Co., Ltd., personal communication.
10) Some manufacturers still supply solutions with compositions given as a w/w percentage, but without density data. This is useless to the organic chemist handling air-sensitive material, and it is hoped that all will quote compositions as molarities in the future.

About the Authors

Dr. Bryon Gill received the B.Sc. (1959) and Ph.D. (1963) degrees from the University of London, moving from King's College to Birkbeck College in 1960 with his supervisor, Dr. Gareth Williams. His doctoral research concentrated on the mechanisms of the radical decompositions of organic peroxides. After one year (1962-1963) on a DSIR/NATO Fellowship for work on alkyl and fluoroalkyl radicals from alkylmercury iodide photolyses, he took an assistant lectureship at the University of Nottingham, where he is now senior lecturer in organic chemistry. His research interests have included mechanistic and synthetic aspects of free-radical reactions, intramolecular rearrangements in alicyclic systems, pericyclic reactions (especially ene reactions), organometallic chemistry and, more recently, allene chemistry, butenolide synthesis, and halogen-exchange processes.

Dr. Don Whiting received the B.Sc. (1958) and Ph.D. (1961) degrees from King's College, London. After holding a Shell Research Fellowship in London for a year, he took up an assistant lectureship at University College, Cardiff, in 1962, and moved to Nottingham University in 1969 where he is now Reader in Organic Chemistry. He was awarded the D.Sc. degree by the University of London in 1974. His research interests are broadly based on the chemistry of natural products of biological importance and include synthetic studies on blockers of electron transport, antifungal and antitumor compounds and enzyme inhibitors. He is engaged in structural research on new plant and microbial insecticides and fungicides, and in biosynthetic studies involving phenols and terpenes from higher plants, including work with new plant enzymes.

Reagents and equipment related to the preceding article.

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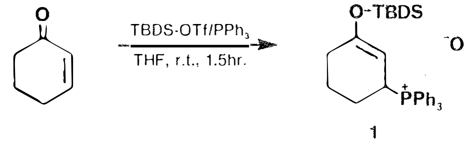
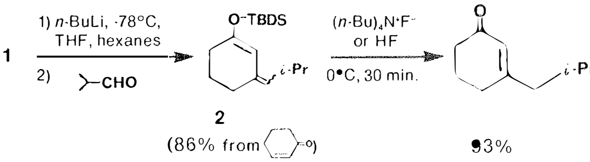
New applications for proven reagents

Professor Alan Kozikowski at the University of Pittsburgh recently reported that cyclic enones undergo phosphoniosilylation on reaction with *tert*-butyldimethylsilyl triflate (TBDS-OTf)/triphenylphosphine.[1] A typical example is shown in eq. 1.



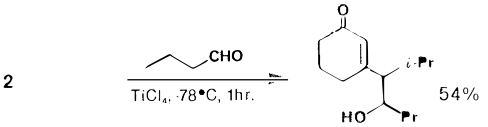
(eq. 1)

The phosphonium salt **1** provides facile access to β-substituted enones in good yields (eq. 2) and affords an alternative route to sometimes cumbersome methodology involving organocuprate conjugate addition, enolate trapping and subsequent oxidation.[2,3]



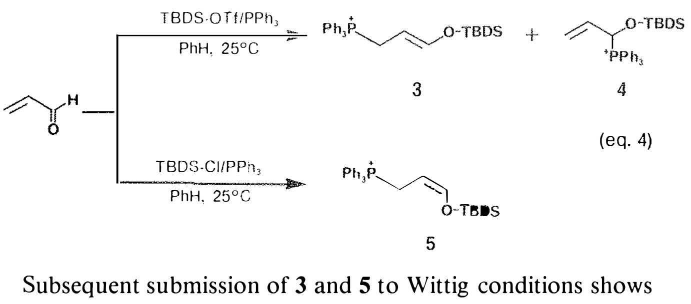
(eq. 2)

Silyl dienol ethers, such as **2**, are not limited to simple protodesilylation. In eq. 3, kinetically controlled electrophilic attack is observed at the γ-position;[4-7] other electrophiles are possible.[1]



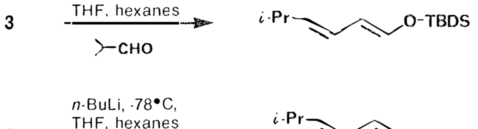
(eq. 3)

The reaction of TBDS-OTf/PPh$_3$ with acyclic enones[1] is markedly different from that of the TBDS-Cl/PPh$_3$ reagent employed by Evans *et al.*[8-11] The silyl triflate reagent reacts with acrolein to afford the *E*-phosphonium salt **3** along with some 1,2-addition product **4**. The silyl chloride reagent yields the *Z*-isomer **5** exclusively (eq. 4).

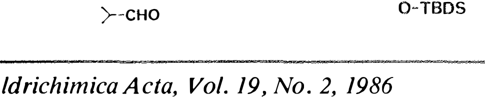


(eq. 4)

Subsequent submission of **3** and **5** to Wittig conditions shows that the stereochemistry about the silyl enol ether double bonds remains intact while the newly formed double bonds are of indiscriminate stereochemistry (eqs. 5 and 6).

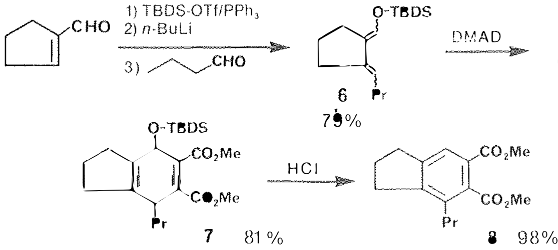


(eq. 5)



(eq. 6)

The phosphoniosilylation method has been used to prepare exocyclic 1,3-dienes, such as **6**. The reaction of **6** with dimethyl acetylenedicarboxylate (DMAD) afforded the O-protected 1,4-cyclohexadienol, **7**, which was subsequently aromatized to **8** with HCl (eq. 7).[1] This method may provide a simple and efficient benzannulation route.[12-14]



(eq. 7)

Aldrich offers all the reagents shown in the above examples and welcomes your ideas and suggestions in this promising area. Please send for a free computer printout of all of the organosilicon and organophosphorus reagents available from Aldrich.

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Some Useful Synthetic Applications of Gold's Reagent

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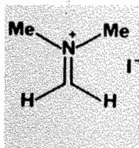
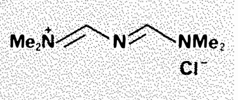
Introduction

While looking for some appropriate research projects, I had been impressed by and interested in the work of Danishefsky[1] and others[2] regarding the use of "Eschenmoser's salt" (**1**). During the course of a literature search on an industrial project, we came across an article by Gold,[3] which described the preparation of a rather interesting vinylogous iminium salt (**2**). The name assigned to this compound was [3-(dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride. This terminology seemed a little cumbersome for routine discussions so we adopted the name "Gold's Reagent" for compound 2. Although the reagent had been prepared[3] in 1960, very little research[4] had been performed on this substance in the intervening years. We therefore decided to begin an exhaustive study to delineate and define what, if any, useful synthetic chemistry could be developed from Gold's Reagent.



1

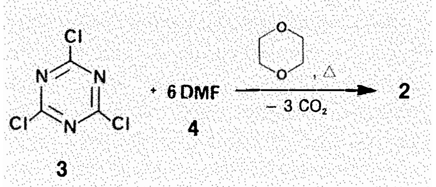


2

Preparation and properties

Gold's Reagent is easily prepared[5] in nearly quantitative yield by treating one equivalent of cyanuric chloride (**3**) with six equivalents of *N,N*-dimethylformamide (**4**) in an inert solvent such as dioxane (Scheme 1). After heating the mixture for approximately 30-40 minutes, an exothermic reaction ensues[6] evolving three equivalents of carbon dioxide over a 1- to 2-hour period. On cooling the dark solution to room temperature, a tan to dark-brown solid (**2**) rapidly forms. This material is isolated by either 1) rapid filtration and washing with acetone or 2) removal of solvents *in vacuo*, and then drying under vacuum. This tan to brown solid is very hygroscopic but can be stored indefinitely in a dry environment. Gold's Reagent is soluble in water and chloroform but is not soluble in any of the normal, nonpolar organic solvents. Based on its NMR spectrum,[5] it is assumed to have the W-configuration.

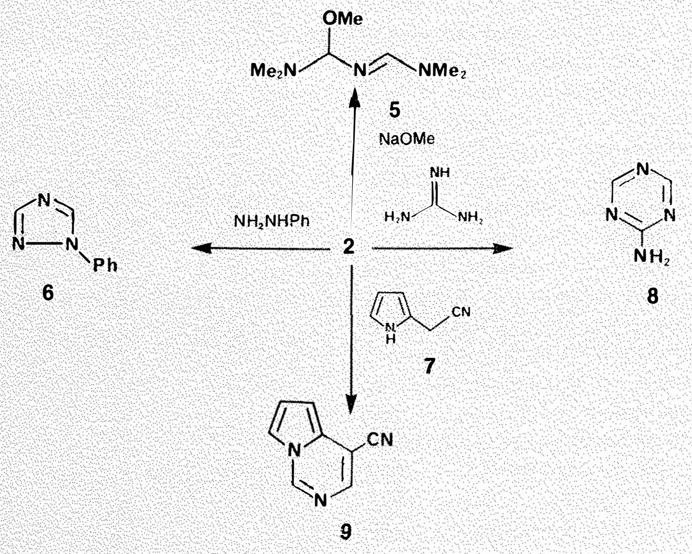
Scheme 1



Initial work by Gold and others

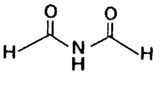
In his initial report,[3] Gold demonstrated that this vinylogous iminium system would react with alkoxide ion, guanidine and phenylhydrazine (Scheme 2). In 1974 Jutz[4] and coworkers studied the reaction of 2 with 2-cyanomethylpyrrole (**7**). In all cases which had been studied up to this point, it appeared that the CH = N-CH unit of Gold's Reagent had been incorporated into the reaction product with the loss of two equivalents of dimethylamine.

Scheme 2



Recent work

Gold's Reagent can be viewed formally as a 3-azavinamidinium salt[7] and can be represented by the contributing resonance structures shown in Scheme 3. Interestingly, Gold's Reagent, as well as other vinamidinium compounds can also be viewed as a masked 1,3-dicarbonyl system. The vinamidinium system possesses some advantages over analogous 1,3-dicarbonyl compounds in reactions with nucleophiles, since deprotonation of N-H cannot occur.



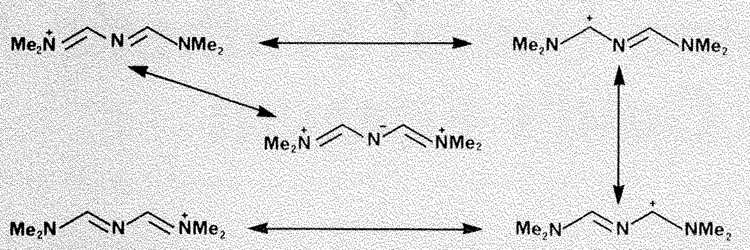
10

Since some dinucleophiles had already been investigated by Gold[3] and Jutz,[4] we decided initially to study[8] some simple mononucleophiles such as amines, and anions derived from aryl methyl ketones and benzamides (Scheme 4). All these reactions proceed cleanly and in good yield to produce amidines, acylamidines and enaminones which are useful and important materials in their own right.[9] Under these conditions, which normally employ $NaOCH_3/CH_3OH$, Gold's Reagent is functioning as a β-dimethylaminomethylenating agent. Apparently, what is happening in this situation is attack of a nucleophilic species at positions 1 or 3 of the reagent to form a tetrahedral intermediate which subsequently eliminates *N,N*-dimethylformamidine (Scheme 5).

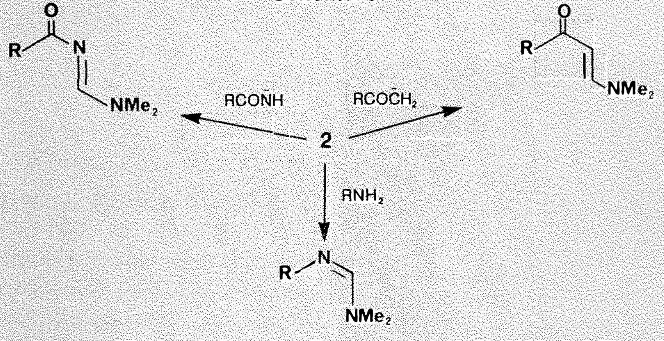
Danishefsky suggested that we follow up this study with a further investigation into the reaction of **2** with unsymmetrical ketones. Upon carrying out this work, we were surprised to learn that the reaction proceeded with complete regioselectivity to produce the least substituted enaminone (Scheme 6).[10] We believe that the high degree of regioselectivity results from a chair-like transition state in which gauche-type steric effects play a major factor. Since enaminones are important intermediates, this regioselective reaction may well prove useful to synthetic chemists.

In order to further extend the synthetic utility of Gold's Reagent, we decided to next examine anions derived from esters, lactones and *o*- or *p*-nitrotoluenes (Scheme 7).[11] These reactions also proved interesting since β-dimethylaminomethylenation was achieved. In addition, they are significant in that enamino lactones can be converted to α-methylene lactones,[12] and *o*-nitrophenylenamines can be converted to indoles.[13]

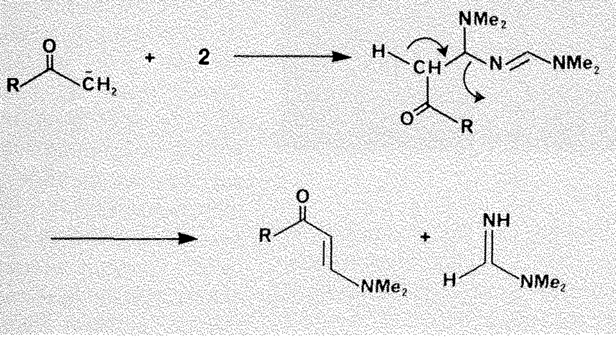
Scheme 3



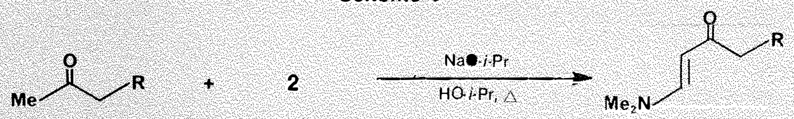
Scheme 4



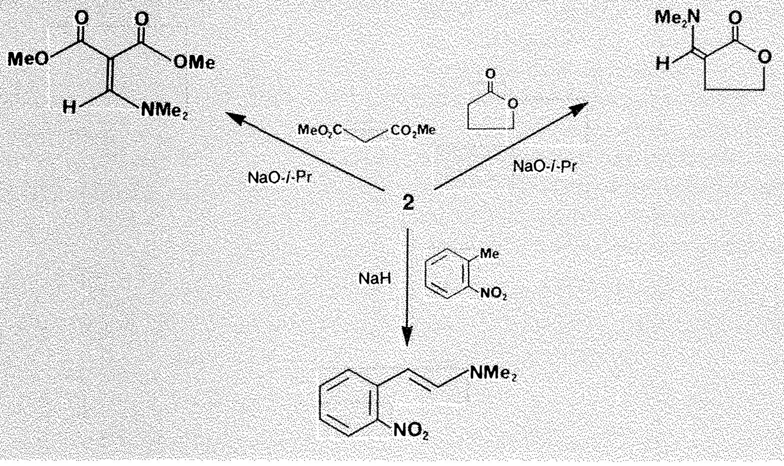
Scheme 5



Scheme 6



Scheme 7



Grignard reagents[14] were then treated with **2** to produce one-carbon-homologated aldehydes upon acid hydrolysis of the intermediates (Scheme 8). This method is general for aryl, benzyl and alkyl Grignard reagents and may well be the best method for the formylation of such carbanions. The reaction can be rationalized by the mechanism shown in Scheme 9.

More recently, we decided to extend our study of **2** beyond simple monofunctional nucleophiles to 1,4- and 1,5-dinucleophiles[15] which had not been previously examined by Gold (Scheme 10). In the reaction with *o*-phenylenediamines, *o*-aminophenols and *o*-hydroxyacetophenones, Gold's Reagent was found to function as a "one-atom lynchpin", whereas, in a similar reaction with anthranilic acid, **2** was found to function as a "two-atom lynchpin" to produce quinazolinones. The results are rationalized in Schemes 11 and 12.

Gold's Reagent has recently been used in the preparation of a chiral formamidine from L-valinol *tert*-butyl ether. Reports of the use of this chiral auxiliary in the asymmetric syntheses of indole,[16,17] isoquinoline[18-20] and pyrrolidine[21] alkaloids have appeared.

Conclusion

Although there are other reagents, such as the DMF acetals[22] and chloromethylene iminium salts,[23] which (in some cases) accomplish similar functions, Gold's Reagent has some distinct advantages. It is a well defined, stable and preformed salt which reacts with a variety of nucleophiles cleanly under slightly basic to basic conditions with significant regioselective control. We therefore consider Gold's Reagent to be an efficient, economical and clean alternative to analogous reagents. We believe that we have only begun to scratch the surface of synthetic methodology available through the reactions of this interesting substance.

Acknowledgements

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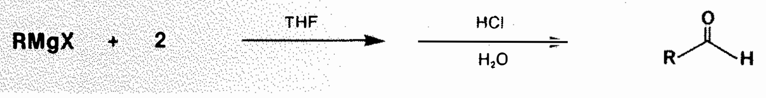
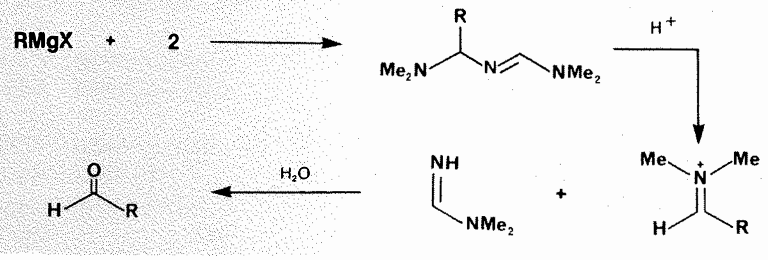
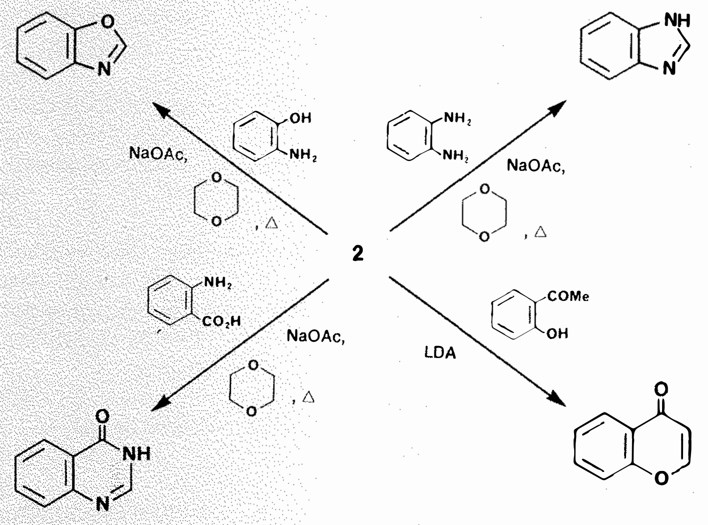
Scheme 8



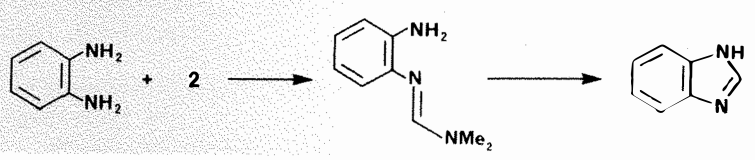
Scheme 9



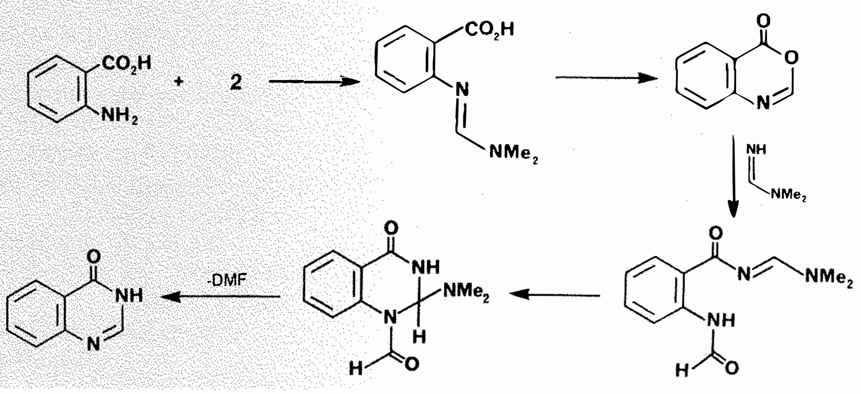
Scheme 10



Scheme 11



Scheme 12



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About the Author

John Gupton received the B.Sc. degree from the Virginia Military Institute in 1967 and the M.S. degree from Georgia Tech. in 1969. After a 3-year tour of service in the U.S. Air Force he received his Ph.D. degree from Georgia Tech. in 1975 under the direction of Dr. Drury Caine. He spent 3½ years in the Agricultural Division of CIBA-GEIGY Corporation prior to joining the University of Central Florida in 1978. His research interests include new synthetic applications of vinylogous iminium salts, new methods for the incorporation of fluoroalkyl groups into organic molecules and novel reactions of HMPA.

Organometallics

$$(Ph_3P{=})_2N^+\ X^-$$

Bis(triphenylphosphoranylidene)ammonium acetate (PPN acetate) catalyzes the monosubstitution of triruthenium dodecacarbonyl with triphenylphosphine.[1] It also reacts with triruthenium dodecacarbonyl to form a trinuclear cluster.[2]

Bis(triphenylphosphoranylidene)ammonium nitrite (PPN nitrite) converts metal carbonyls to nitrosyl carbonyl complexes, in high yields with no side products.[3]

1) Lavigne, G.; Kaesz, H.D. *J. Am. Chem. Soc.* **1984**, *106*, 4647.
2) Darensbourg, D.J.; Pala, M.; Waller, J. *Organometallics* **1983**, *2*, 1285.
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Versatile Silver Salts

$CF_3CF_2CF_2CO_2Ag$

1

CF_3CO_2Ag

2

$AgBF_4$

3

Silver heptafluorobutyrate (**1**) and **silver trifluoroacetate** (**2**) are both used for the preparation of heptafluoro-2-nitrosopropane and 1-chlorohexafluoro-2-nitrosopropane, avoiding the use of nitrosyl fluoride.[1] They also react with halobis(trifluoromethyl)phosphine to give the corresponding carboxylatobis(trifluoromethyl)phosphines.[2]

Silver heptafluorobutyrate and **silver tetrafluoroborate** (**3**) catalyze the formation of tricyclanone from 3-diazocamphor.[3]

Mixtures of **1** and lanthanide $(fod)_3$'s act as binuclear shift reagents for alkenes.[4]

1) Banks, R.E.; Dickinson, N.; Morrissey, A.P.; Richards, A. *J. Fluorine Chem.* **1984**, *26*, 87.
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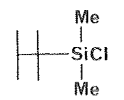
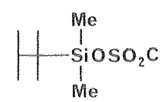
Dimethylthexylsilyl Compounds

New Protecting Reagents

Dimethylthexylsilyl chloride (**1**) and **dimethylthexylsilyl trifluoromethanesulfonate** (**2**) are useful reagents for the protection of alcohols.[1]


1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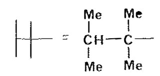
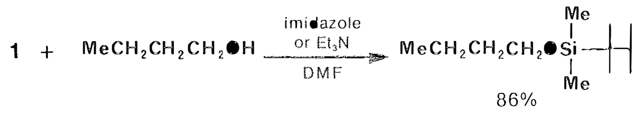
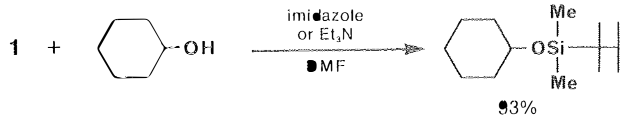
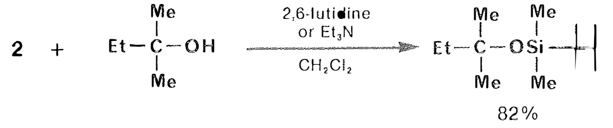

(thexyl)

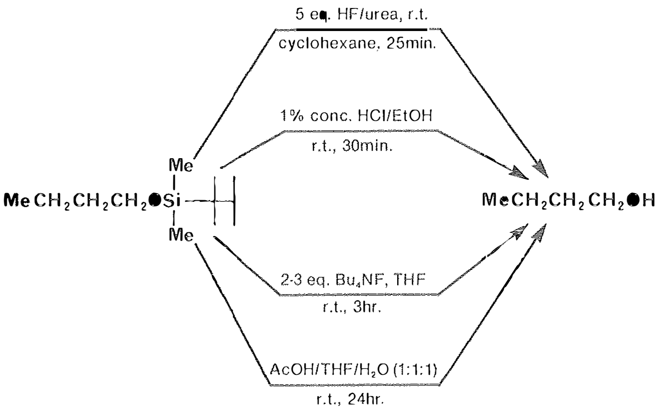
Primary and secondary alcohols, including phenols, are readily converted to the corresponding silyl ethers by reaction with **1**, while tertiary alcohols require the more reactive **2**.



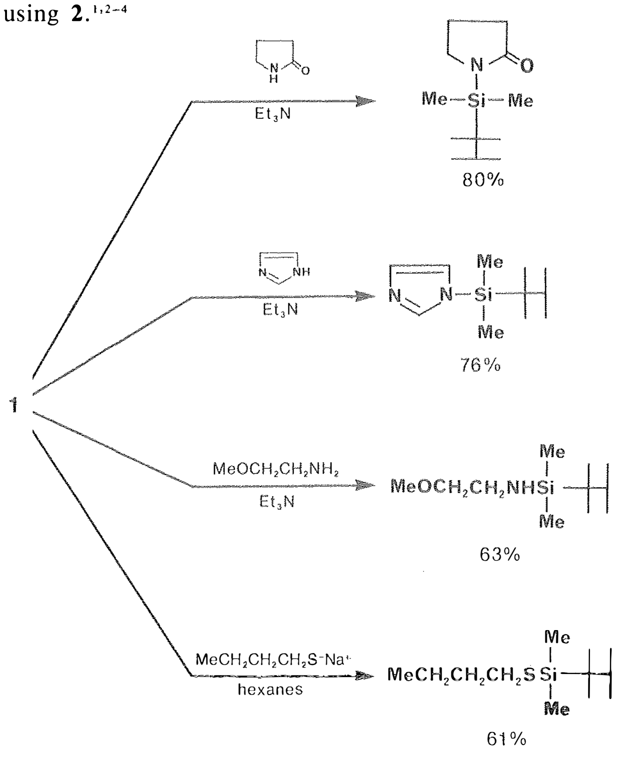


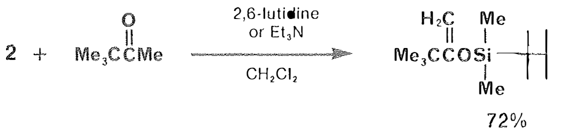


The synthetic utility of *tert*-butyldimethylsilyl chloride is well established.[2-4] **Dimethylthexylsilyl chloride (1)** provides a useful alternative. It is a clear, colorless liquid which is not moisture-sensitive and which is much easier to handle than the solid *tert*-butyldimethylsilyl chloride. The resulting dimethylthexylsilyl ethers are more stable toward hydrolysis than the corresponding *tert*-butyldimethylsilyl ethers, yet they can be readily cleaved (deprotected) under a variety of conditions:



Compound **1** may also be used to protect a number of other functional groups, including amides, amines, mercaptans and carboxylic acids; dimethylthexylsilyl enol ethers can be prepared using **2**.[1,2-4]





As we continue to expand our line of organosilicon reagents, we invite your suggestions and inquiries. Please send for a free computer printout of all the organosilicon reagents available from Aldrich.

References:
1) Wetter, H.; Oertle, K. *Tetrahedron Lett.* **1985**, *26*, 5515.
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The Use of the Aldrich-Nicolet IR Peak-Search and Retrieval Programs in Introductory Chemical Instrumentation*

Instrumental analysis is one of the key areas of chemical technology. It is important from the points of view of product development, product analysis and pollution analysis. One of the most widely used pieces of instrumentation is the infrared spectrometer, ranking third in academia and fifth in industry.[1] Traditionally, the IR spectrometer is used to identify the presence (or absence) of functional groups, thus establishing the class to which an unknown compound belongs. In conjunction with other methods of instrumentation (NMR spectroscopy, mass spectroscopy, etc.), compound identification can be established. There is a wealth of information in the so-called "fingerprint region" of the IR spectrum, but from the standpoint of the routine user, this information is not readily interpretable.[2]

At Merrimack College, a two-semester sequence in Instrumental Analysis has been offered since the mid-1960's. The theory and use of infrared spectroscopy have always been a fundamental part of these courses in the above-mentioned traditional manner. The rapid pace of advancement of new instrumental techniques led us to establish a course in "Chemical Instrumentation for Professionals".[3] People trained in chemistry prior to 1965 have little or no exposure to even basic techniques in this area. Those graduating more recently may have had little exposure to instrumentation due to the "reserving" of the instruments for the graduate students.

The Aldrich-Nicolet Peak Search Personal Computer Software[4] and ***The Aldrich Library of FT-IR Spectra***[5] were incorporated into both our undergraduate Instrumental Analysis course and our professional program. This development was met with great enthusiasm on the part of course participants.

Infrared instruction was presented in the following manner. The students were first given basic theory on the interpretation of infrared spectra. In the laboratory, the spectra of representative compounds containing various functional groups were run on a dispersive infrared spectrometer. After calibration of the spectra using polystyrene film as a reference, the peak locations were entered into the computer using ***Aldrich-Nicolet IR Peak-Search Software***. A departmental Apple® II Plus computer was used.

The students were directed to first choose the most differentiating peak of the spectrum (*e.g.*, absorbances in the range of 3050-3600cm^{-1} or 1650-2900cm^{-1}, if any), and enter it as 30cm^{-1} window. For example, a peak at 1750cm^{-1} would be entered at the window 1735-1765cm^{-1}. This window width is necessary due to the limited precision of the dispersive instrument's peak frequency. If one were using FT-IR, a much narrower window could be used (5-10cm^{-1}). The program then determines the sumber of compounds containing peaks within this spectral window. The subset is saved and additional peaks are entered and merged with the original subset. Searching can also be done "in reverse". If one is confident that no peak is present at a location, all compounds with that peak can be eliminated. When sufficient peak data have been entered to reduce the number of compounds in the subset to fewer than ten, the spectral code numbers (referring to location in the Aldrich Library) are then listed. The spectra are then looked up in ***The Aldrich Library of FT-IR Spectra*** and compared to the experimental spectrum. In this manner, identification is effected.

The entire process, from the running of the experimental spectrum to the identification of the unknown, takes about twenty minutes. The program is quite accurate, provided that the selected compound has a reasonable number of definitive peaks. In certain cases where a group of compounds have similar spectra (*e.g.*, the *n*-alkanes), it may be impossible to narrow the subset to a single compound. Instead, a group of spectra is obtained. In one student's words, "We may not always converge on the intended compound, but we always, at least, hit a first cousin." The program also contains prompts, so that too wide or too narrow a window isn't used, or that nujol mull peaks are not entered.

The students found the program easy to assimilate. Standard laboratory compounds were not the only ones investigated. Several students brought in samples from their workplace for analysis. These samples were industrial organic chemicals, mainly fuel oils and perhalogenated hydrocarbons. In all cases, we were able to establish identity of the sample components. The students were surprised at the ease and rapidity with which an unknown could be identified with confirmation from published data. At this point, the standard question concerned cost. Most were pleased to learn that the inclusive cost of the Library and the IR Peak-Search program was under $700.

It seems obvious to the authors, based on our experience, that most undergraduate instrumentation courses and most industrial concerns would greatly benefit from the inclusion of spectral searching techniques in their training and/or research programs. The method is fast, easily taught and very instructive.

Acknowledgements

We would like to acknowledge the financial support of the Bay State Skills Corporation in the funding of the "Chemical Instrumentation for Professionals" course.

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4) *The Aldrich-Nicolet Peak-Search Personal Computer Software*, for the Apple® II, IIc, IIe and II Plus computers, Catalog No. Z12,774-4, $295.00; for the IBM PC, PC-XT and PC-AT computers, Z12,776-0, $295.00.
5) Pouchert, C.J. *The Aldrich Library of FT-IR Spectra*; Aldrich Chemical Company, Inc.: Milwaukee, 1985. Catalog No. Z12,700-0, $375.00.

*See the insert at page 42 of this issue of the *Acta* for details on the library and computer software.

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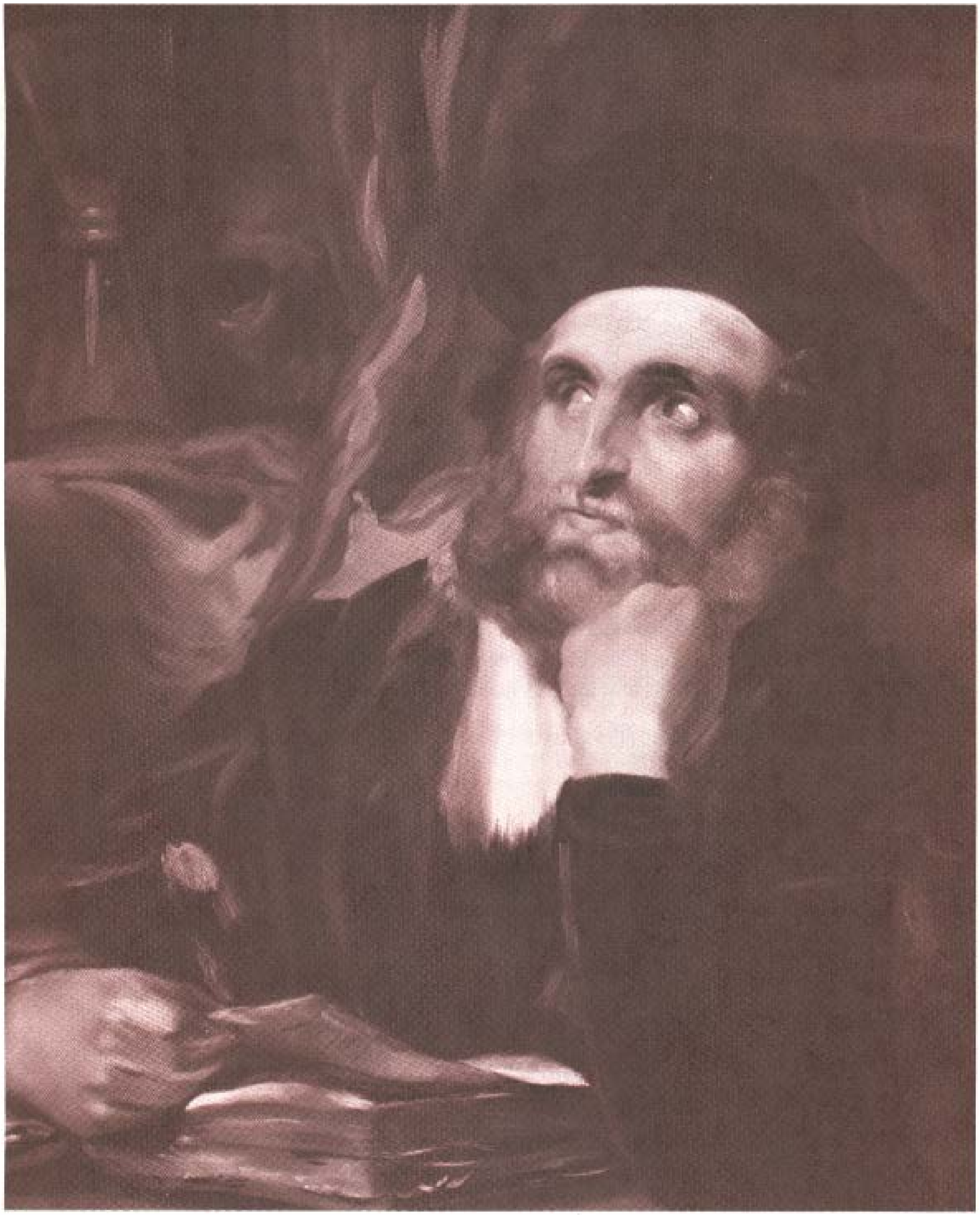

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Our chemist-collector loves puzzles both of iconography and authorship, and is doubly delighted when these coincide in a painting. The previous owner, one of London's most sensitive and honest dealers, believed that this painting (oil on canvas, 28¾ x 23¼ inches), then filthy dirty, was by a late 17th-century Dutch artist, and that it might depict a specific cabalistic rabbi who had lived in Frankfurt and Amsterdam. Recent cleaning shows this to be untenable. It was painted about 1820, probably in England, by a most painterly artist, a great colorist who used such rich reds in the curtains — someone like Sir David Wilkie.

Is it a portrait of a rabbi, or of an actor, or of a figure from literature or history? In any case, this painting, done with such bravura, seems most fitting for the *Acta* with Professor Danishefsky's masterly essay.

Rembrandt and the Bible - in Japan

We are offering a limited number of a 174-page catalog of an exhibition in Japan, the first of its kind there, on Rembrandt and the Bible. The scholarly essays in Dutch, English, German and Japanese deal with works by Rembrandt and his students — 38 paintings, 7 drawings and 44 etchings, all beautifully illustrated. Thirteen of the paintings, all in full color, have appeared on covers of the *Acta*. The works are fully described in English and Japanese. An unusual and wonderful buy for lovers of art and the Bible!

Pictures from the Age of Rembrandt

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

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Eight beautiful 14 x 11 inches, full-color reproductions of paintings on our catalog covers are available, ready for framing, to add beauty to your laboratory.

Selections from the Aldrichimica Acta, 1968-1982

Because of the ever-increasing demand for earlier issues of the *Acta*, we now offer a collection of articles from volumes 1-15. We chose those articles which we believe are still of interest to our readers — 354 pages of great review articles, in one beautiful hardbound volume.

Lab Notes

Independent communications by Dawson and Harwood [*Aldrichim. Acta* **1985,** *18*(1)] on improved procedures for flash column chromatography prompt me to report a method which we have been using in these laboratories for the past three years.

The procedure was developed to eliminate the loading problems encountered when the sample to be purified is not readily soluble in the eluant mixture. We call this procedure "*dry flash*" column chromatography to indicate that it is a hybrid between normal dry column and flash column chromatography as reported by Still.[1]

Selection and packing of the column are according to Still's procedure. The sample is dissolved in a low-boiling organic solvent or solvent mixture and the solution is used to prepare a slurry with silica gel (ratio of sample to adsorbent *ca.* 1:7, by weight). The solvent is allowed to evaporate at room temperature while the mixture is stirred manually with a spatula. The dry sample-containing silica gel is placed as a thin, even band at the top of the column and covered with *ca.* 2in of sand. Expulsion of the air and final packing of the column are done by passing the least polar solvent of the mixture through the column. At this point the flow rate can also be regulated. The purification is initiated by adding the chosen eluant.

We have found that mixtures of Skellysolve B/acetone, ethyl ether/Skellysolve B and benzene/acetone give best results. A further advantage in using these solvent mixtures is that often compounds crystallize upon concentration of the fractions.

Column lengths may vary from 8in for complex mixtures to 4in for simple purifications. We have used this method to purify mixtures of 3-350mg.

1) Still, W.C.; Kalin, M.; Mitra, A. *J. Org. Chem.* **1978,** *43*, 2923.

Luis Manuel Pena-Rodriguez
Graduate Student
Department of Chemistry
The University of Alberta
Edmonton, Alberta
Canada T6C 2G2

Traditional procedures for the purification of chlorotrimethylsilane are objectionable since the methods for removal of residual hydrogen chloride are either very tedious or provide material of varied quality. Recently we have developed a new procedure for purification of chlorotrimethylsilane. Commercial material is stirred with calcium hydride overnight and distilled under an inert atmosphere through a dry short-path distillation apparatus into a *ca.* 100-ml bottle *previously charged with a ½-inch layer of cross-linked poly(4-vinylpyridine).* The bottle is then sealed under an inert atmosphere with a septum. The material obtained is often initially very cloudy due to the fact that traces of hydrogen chloride are still being scavenged by the polymer. The material is allowed to sit 2-3 days at room temperature, after which all polymer settles to the bottom of the container and the supernatant chlorotrimethylsilane is crystal clear. The material so obtained contains very little hydrogen chloride and is completely suitable for use with lithium dimethylcuprate and other proton-sensitive organometallic reagents on a submillimole scale. The chlorotrimethylsilane purified in this manner can be stored at room temperature for at least one month prior to redistillation.

D. K. Hutchinson
Department of Chemistry
Purdue University
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I would like to report a simple solution to the problem of removal of volatile solvent from an organic solution contained in a small test tube or ampule.

Instead of flushing it with dry nitrogen and/or heating it with a heat gun, we placed the tube into a round-bottom flask (with ground-glass joint) of appropriate height. The tube must stand in the flask. The evaporation is then conducted under reduced pressure in a rotary film evaporator.

This nontedious method affords a deposit of the sample in the bottom of the ampule, making sealing it easier.

Darío Doller
Departamento de Química Orgánica y UMYMFOR
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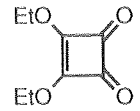
Buenos Aires, Argentina

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 **Pictures from the Age of Rembrandt.** *We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Alfred Bader.



Professor Lanny S. Liebeskind at Emory University suggested that we offer diethyl squarate. 3,4-Disubstituted 3-cyclobutene-1,2-diones of this type have been shown recently[1,2] to be useful starting materials for the general synthesis of highly substituted quinones.

Naturally, we made diethyl squarate.

1) Liebeskind, L.S.; Iyer, S.; Jewell, C.F., Jr. *J. Org. Chem.* **1986,** *51*, 3065.
2) Perri, S.T.; Foland, L.D.; Decker, O.H.W.; Moore, H.W. *ibid.* **1986,** *51*, 3067.

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

Reflections on Organic Synthesis: The Evolution of a General Strategy for the Stereoselective Construction of Polyoxygenated Natural Products

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1. Introduction

It is nearly fifty years since an expedition into the total synthesis of equilenin was launched by the Bachmann group at the University of Michigan.[1] That successful effort was a milestone in the emergence of natural-product total synthesis as an identifiably serious endeavor. Many of the themes of that program have recurred. Equilenin was a well defined target system. The challenges associated with its total synthesis provided sharply etched criteria for success or failure. Success would be possible only through the highest of experimental and intellectual achievement. It would be necessary to draw from the "state of the art" of the existing arsenal of organic chemistry and mobilize it into action.

Indeed, the rewards of success were high. The total synthesis of equilenin was eventually followed by highly efficient total syntheses of rather more complicated and more important steroids. A creative collaboration between organic chemistry, biology and medicine began to emerge in the field of steroidal hormones. The ability of organic chemistry to play a pivotal role in this consortium arose, to a considerable extent, from a series of total syntheses which started with equilenin.

It is well to consider some of the factors which have been responsible for the durability and growth of total synthesis during the intervening half-century. High on the list must be the continuing appearance of target systems of provocative structure and promising biological activity. Dramatic advances in three cognate fields, *i.e.*, separation science, spectroscopy and X-ray crystallography, assure a reliable supply of such challenging structures. Greatly improved biological screening protocols and ever more sophisticated techniques for relating gross activity to biological mechanisms at the molecular level, will undoubtedly identify many of these targets as being worthy of particular attention.

Even as the outlook for finding new and important natural products is increasingly favorable, changes in emphasis for total synthesis are likely to emerge. The field will continue to draw inspiration from the intrinsic challenge posed by the structures. There is no denying (nor should there be a need to deny!) that the sheer sense of challenge posed by a complex molecular target serves to stimulate the creative impulses of the synthetic chemist. However, the purely "mountain climbing" dimension might well become less central. The intellectual and experimental foundations of organic chemistry are sufficiently formidable, and the recorded triumphs are sufficiently impressive, such as to imply that, in principle, virtually any natural product can be synthesized.

To offer this observation is not to be unmindful of the extraordinary difficulties which still beset the total synthesis of a multifunctional goal, or one with a complicated ring system. Only those lacking firsthand familiarity with the subject can fail to appreciate the mix of experimental virtuosity, courage and intellectual creativity that is required to reach such targets. No special farsightedness is required to perceive how the attributes which go into a successful effort in total synthesis can be applied to the solution of other problems.

Nonetheless, it seems likely that greater

Professor Samuel J. Danishefsky (left) receiving the A.C.S. Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich, from Dr. Irwin Klundt, Vice-President, Aldrich Chemical Co., Inc.

scrutiny will properly be directed to why certain "mountains" are being selected for climbing, to the efficiency with which these mountains are being climbed, and *to the implications of the climbing exercise itself for organic chemistry and for allied fields.* The triumphs which the next half-century will bring cannot now even be perceived. However, it can safely be predicted that increased sensitivity to the kinds of issues implied above will foster ever more exciting opportunities for accomplishment. These opportunities will continue to engage the wit, the resourcefulness, the courage and, above all, the creativity of bright young people who respond to the clarion call of total synthesis.

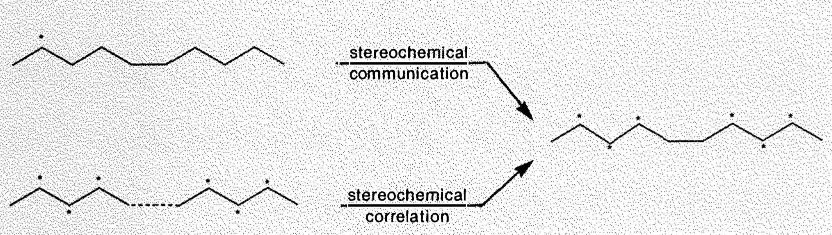
2. Stereochemical Communication and Correlation

Conciseness has always been a general striving in synthesis. Even beyond issues of economics, conciseness to the synthetic organic chemist has artistic implications. In a subject as sensitive to the esthetic dimension as in total synthesis, such matters are of no small moment. The goal which served to focus and to unify the research described here is that of achieving conciseness and stereoselectivity in the synthesis of polyoxygenated natural products.

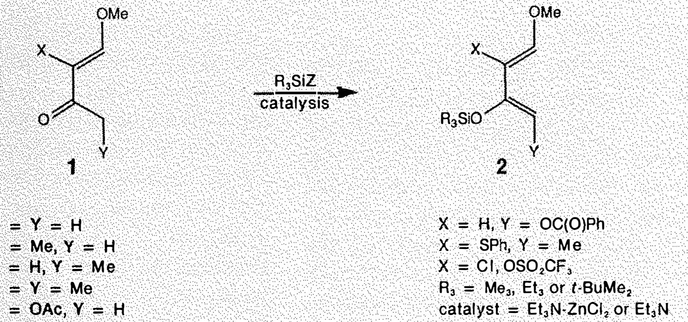
The emphasis of our approach, as matters transpired, was on "stereochemical communication". Our research led us to seek new ways by which dissymmetric imprints present within a substrate or within a reaction ensemble could be conveyed, in a serial fashion, to influence the emergence of new dissymmetric elements as the synthesis progressed.

This outlook can be distinguished from an alternate discipline, *i.e.,* that of "stereochemical correlation". In the latter activity, two properly correlated dissymmetric subcomponents are joined. In some instances, the very act of coupling might entail the creation of new stereochemistry, but the management of the relationship of the preexisting dissymmetry elements is an exercise in correlation. Scheme 1 attempts to capture the distinction between "communication" and "correlation".

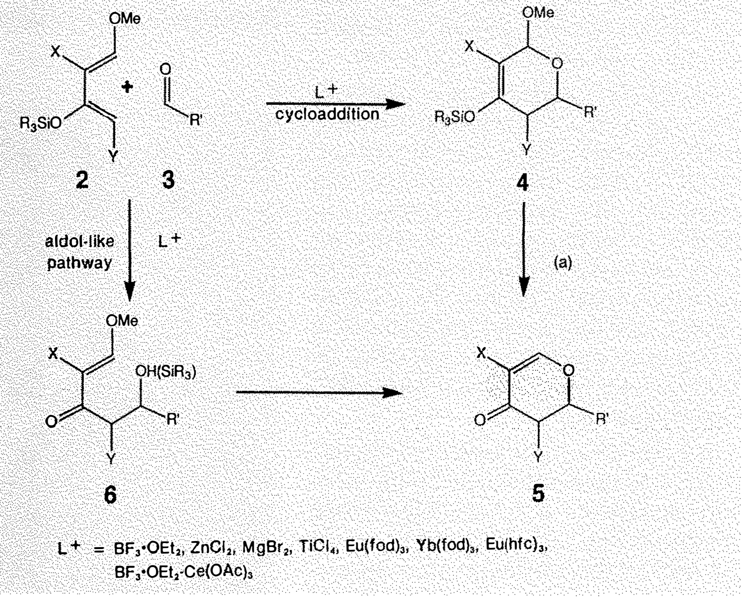
Scheme 1



Scheme 2



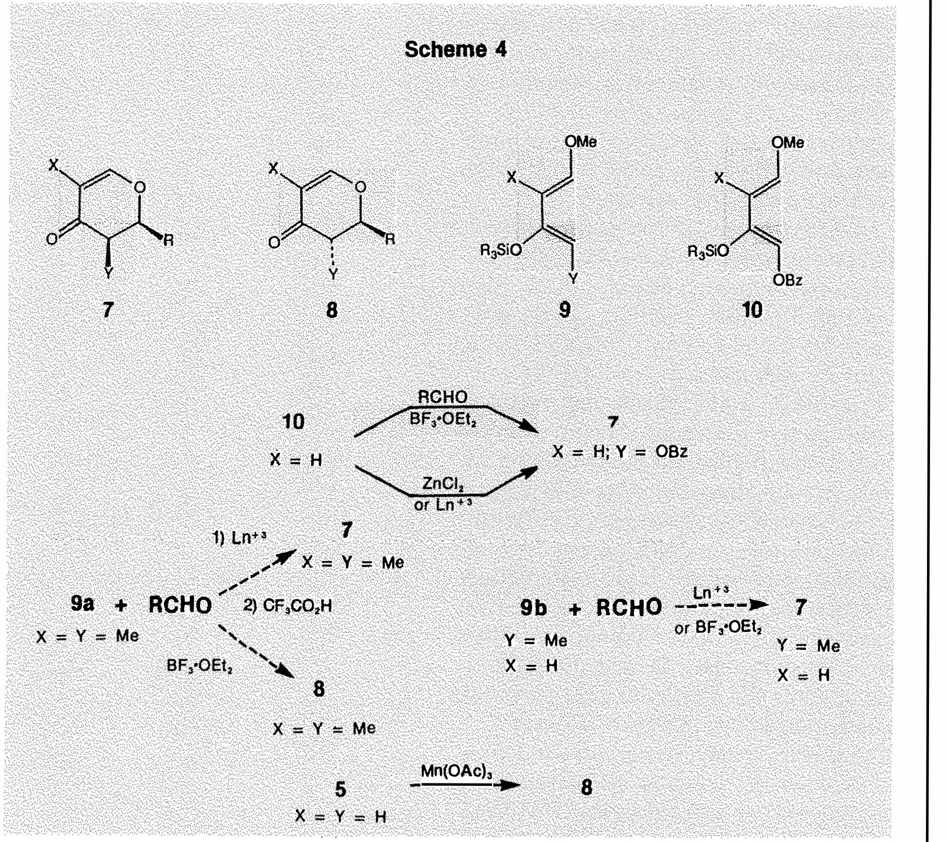
Scheme 3



The coupling of two amino acids to provide a dipeptide is a powerful, if sometimes overlooked, instance of "stereochemical correlation". The coupling of two monosaccharides to give rise to a disaccharide is an important exercise in combining stereochemical correlation with stereochemical communication. The relative relationship at all but the glycosidic bond is achieved by correlation. The configuration at the glycosidic bond is attained by communication from one (or both) of the monosaccharide components. General pronouncements on the relative merits of stereochemical communication *vs.* stereochemical correlation are not useful. The synthetic chemist, more concerned with results than with doctrinal consistency, will evaluate each new problem on its own practicalities. Nonetheless, it is worthwhile to take note of the existence of these two styles in attempting to transact stereochemical relationships.

3. Some Early Discoveries

The approach taken in our laboratory stemmed from a long-term interest in the chemistry and synthetic utility of siloxydienes.[2] Our explorations toward the goal structures, to be discussed below, began from this context. It is well known that siloxydienes can be prepared by the enol silylation of α,β-unsaturated ketones. In


Scheme 4

1974, Dr. Takeshi Kitahara discovered that enol silylation could be extended to β-alkoxyketones (*i.e.*, vinylogous esters) of the type **1**.[3] Dr. Kitahara used a two-component catalyst system (zinc chloride-triethylamine) to effect the reaction. Trialkylsilyl chlorides were the silylating agents. Recently, the advent of trialkylsilyl triflates[4] has rendered enol silylation a particularly facile process. In Scheme 2 we record some examples of vinylogous-ester types which have been converted to their corresponding siloxydienes. Particular note should be taken of the opportunities for incorporating diverse functionality into the dienes.

Our initial investigations into the applications of activated dienes of the type **2** were directed to their use in the classical all-carbon Diels-Alder reaction.[2] In 1980 James Kerwin recorded some exciting observations in his laboratory notebook.[5] Through the use of Lewis acid catalysts, siloxydienes of type **2** undergo reactions with virtually any aldehyde. Indeed, all of the diene permutants indicated in Scheme 2 have, in fact, undergone reactions with a range of aldehydes. Thus, we had available a broadly applicable reaction covering two readily available classes of functional groups, *i.e.*, aldehydes and siloxydienes. A list of the principal Lewis acid catalysts which have been employed is included in Scheme 3.

Not surprisingly in such a widely applicable reaction, a range of mechanisms and related pathways has been identified.[6] The situation is summarized in Scheme 3. The cycloaddition route exhibits the salient characteristics of a Diels-Alder reaction (suprafaciality in the diene, endo addition of the aldehyde).[7] When the primary product **4** is isolated, the evidence for cycloaddition seems to be secure. Failure to obtain a type **4** compound certainly does not rule out cycloaddition, since such compounds are extremely vulnerable to acidic unraveling to afford dihydropyrones of the type **5**. An alternate pathway starts with an aldol-like addition of the siloxydiene **2** to the aldehyde **3**.[8] This might or might not be accompanied by an O → O silicon migration (see structure **6**). Heterocyclization of such aldol-like intermediates (usually through the action of trifluoroacetic acid) provides an alternate route to the dihydropyrone **5**.

Extensive investigations have revealed a relationship between the Lewis acid catalyst and the mechanistic pathway.[6,9] The precise nature of the aldehyde and the diene is also of relevance in determining the pathway which is followed. We have used the descriptor "cyclocondensation" as a term which focuses on the overall result rather than on the reaction mechanism.

We next turn to the stereochemical features of the reaction and to the opportunities for stereoselective operations on its products. Progress on these fronts was central if the findings indicated above were to be marshalled into an effective program for synthesis.

4. On the Stereochemistry of the Cyclocondensation Reaction

Even with the parent diene **2** (X = Y = H), a stereochemical question concerning the relationship of the anomeric center (C_2) with C_6 arises in cycloadduct **4**. More commonly, the unraveling product **5** is obtained. In this case, two stereoisomeric dihydropyrones, **7** (cis) and **8** (trans), can be obtained. We refer to this as a question of topography.[6] In a near-concerted mechanism, the topographic question is analyzed in terms of endo *vs.* exo cycloaddition. In an "aldol" or "siloxonium" pathway, the paradigm is discussed in terms of chair *vs.* boat transition states, synclinal *vs.* antiperiplanar ensembles and erythro *vs.* threo acyclic products.

The two major diene systems where this question has been pertinent are **9** and **10**. With diene **9a** (X = Me) or **9b** (X = H), it has been found that catalysis by lanthanide systems such as $Eu(fod)_3$, $Eu(hfc)_3$, $Yb(fod)_3$ or by zinc chloride favors formation of cis product through an apparent endo-like transition state.[6-8] Similarly, diene type **10**[10] affords primarily cis-type products with such catalysts.

With BF_3•etherate as the catalyst, a more complicated situation applies. With diene **9a**, substantial preference for the trans isomer **8** can be realized through careful optimization of solvent and of silyl ligand. However, with diene type **9b**, *where C_2 is unsubstituted,* even BF_3 catalysis is selective in favor of cis dihydropyrone **7**.[6] Also, with diene type **10**, BF_3•etherate catalysis is selective in favor of cis product type **7**.[10]

The remarkable sensitivity of the trans (**8**): cis (**7**) ratio as a function of the degree of substitution on the diene (*i.e.*, on the nature of X in **9**) is not understood at present. Also, it will be necessary to accumulate more data in the case of trioxygenated dienes (*cf.* **10**) to ascertain whether the cis selectivity is a special function of the benzoyloxy group or is primarily a consequence of the trisubstituted character of the diene (*i.e.*, **10**, X = H; *cf.* **9b**, X = H).

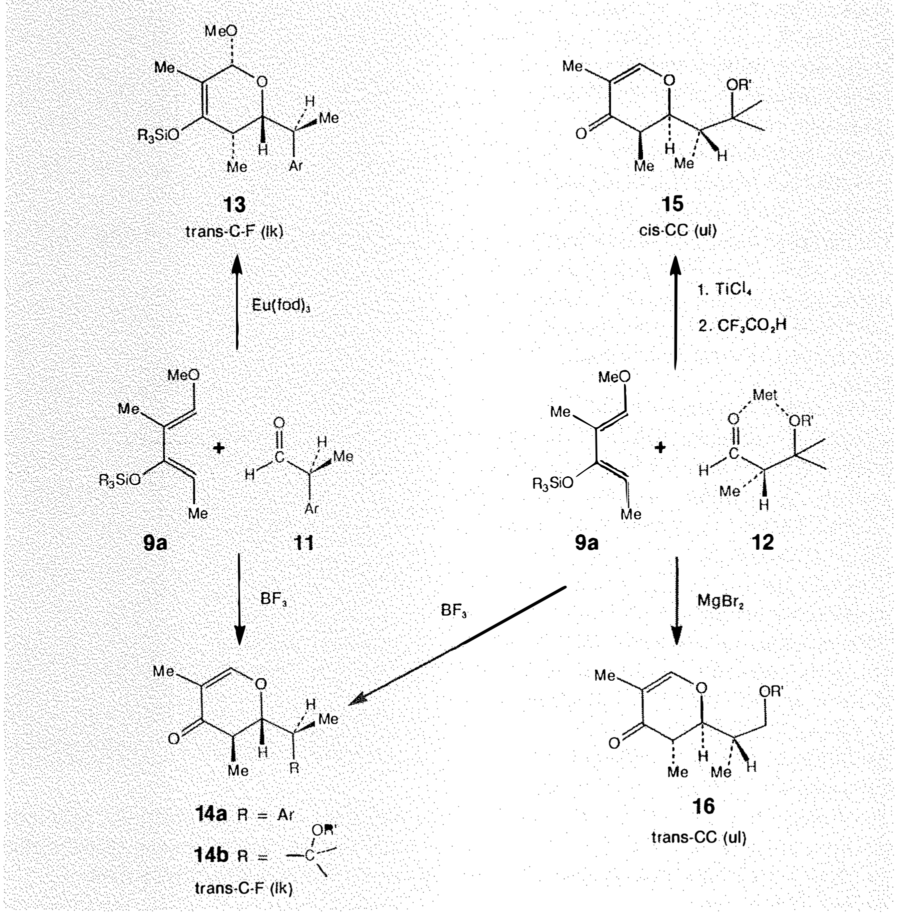
Two solutions were developed to provide stereoselective access to trans dihydropyrones of the type **8** where X = H, Y = OBz. One of these paths was developed in the context of a total synthesis to which this capability was crucial (see Scheme 9, transformation **37** → **38**, and Scheme 14, transformation **55** → **56**, for the synthetic route to hikosamine). Another type of entry (see Scheme 4) for pyrone **8** (X = H, Y = acyloxy) was achieved *via* oxidation of the unsubstituted compound **5** (X = Y = H) with manganese(III) acetate.[11,12]

A different issue, that of diastereofacial directivity, arises when the aldehyde contains stereogenic centers. For the cyclocondensation reaction to be synthetically useful in such a situation, there must be a connectivity between the configurational sense of the emerging pyranoid structure and the already present dissymmetry. It is particularly instructive to investigate situations where the topographic and diastereofacial issues were confronted simultaneously. In studying this type of problem *vis-à-vis* the cyclocondensation reaction, two important discoveries were realized. The first finding was that aldehydes of types **11** and **12** show a remarkably high fidelity to diastereofacial control in the Cram-Felkin (C-F) sense.[13-17] *The selectivity goes far beyond that which is achieved by addition of conventional nucleophiles to such aldehydes.* This near-diastereofacial specificity is surely related to the Lewis acid-catalyzed nature of the reaction and has been so interpreted on a theoretical basis.[18] The second finding was that through the use of chelating catalysts, particularly magnesium bromide or titanium tetrachloride, α- and β-oxygenated aldehydes afford highly selective cyclocondensation reactions whose diastereofacial sense is opposite to that which occurs in the absence of such groups. The outcome of these reactions seems to be controlled by chelation (CC).[16]

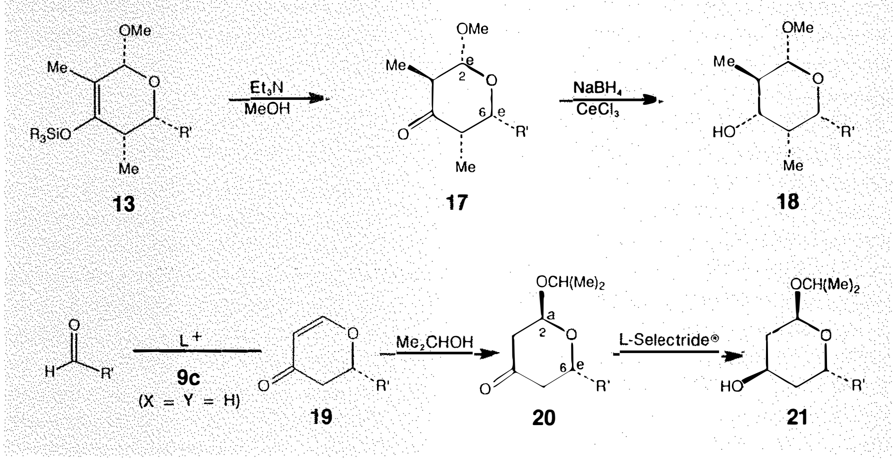
Scheme **5** demonstrates the crucial role of the Lewis acid catalyst in the concurrent control of diastereofacial and topographic stereoselection. Elsewhere, we have referred to this capability as metal-tunable asymmetric induction.[19] The use of lanthanide catalysis [Eu(fod)$_3$ or Eu(hfc)$_3$] with diene type **9a** and aldehyde type **11** strongly favors cycloaddition in the endo/C-F sense, leading to product **13**. Four stereogenic centers have been defined in a single operation in adduct **13**. With BF$_3$•etherate as the catalyst, aldehyde **11** still exhibits virtual C-F specificity. The topography of the reaction is threo-like in the aldol or siloxonium sense, leading to product **14a**. Similarly, aldehyde type **12** shows a strong threo/C-F selectivity, thus providing access to system **14b** *via* cyclocondensation with diene **9a**.

The cyclocondensation of aldehyde type **12** with either titanium tetrachloride or magnesium bromide catalysis occurs in the opposite diastereofacial sense. In each case the pyranoid ring is formed under apparent chelation control (CC) as implied in structure **12**. With anhydrous magnesium bromide as the catalyst, the process is one of cycloaddition in the exo sense, leading to product type **16**. The relationship between chelation control and exo topography will be elaborated below. With titanium tetrachloride, chelation control is coupled to erythro topography in an aldol-like process.[20]

Scheme 5



Scheme 6



The reader is referred to the original literature to share more fully the finer interpretive arguments regarding these stereochemical issues. For the present, we emphasize the application of these findings for synthetic progress. Of course, the obvious point is that three stereogenic centers (four in the case of compound type **13**) have been related in one operation with high selectivity through readily accessible reagents. However, the implications run much deeper, since the pyran ring provides a reliable framework to control the installation of additional stereo elements. In this way, the configurational selectivity achieved in the cyclocondensation reaction is "leveraged" to provide larger domains susceptible to stereochemical communication. It is to such opportunities that we now turn.

5. Stereochemical Manipulation in the Pyran Matrix

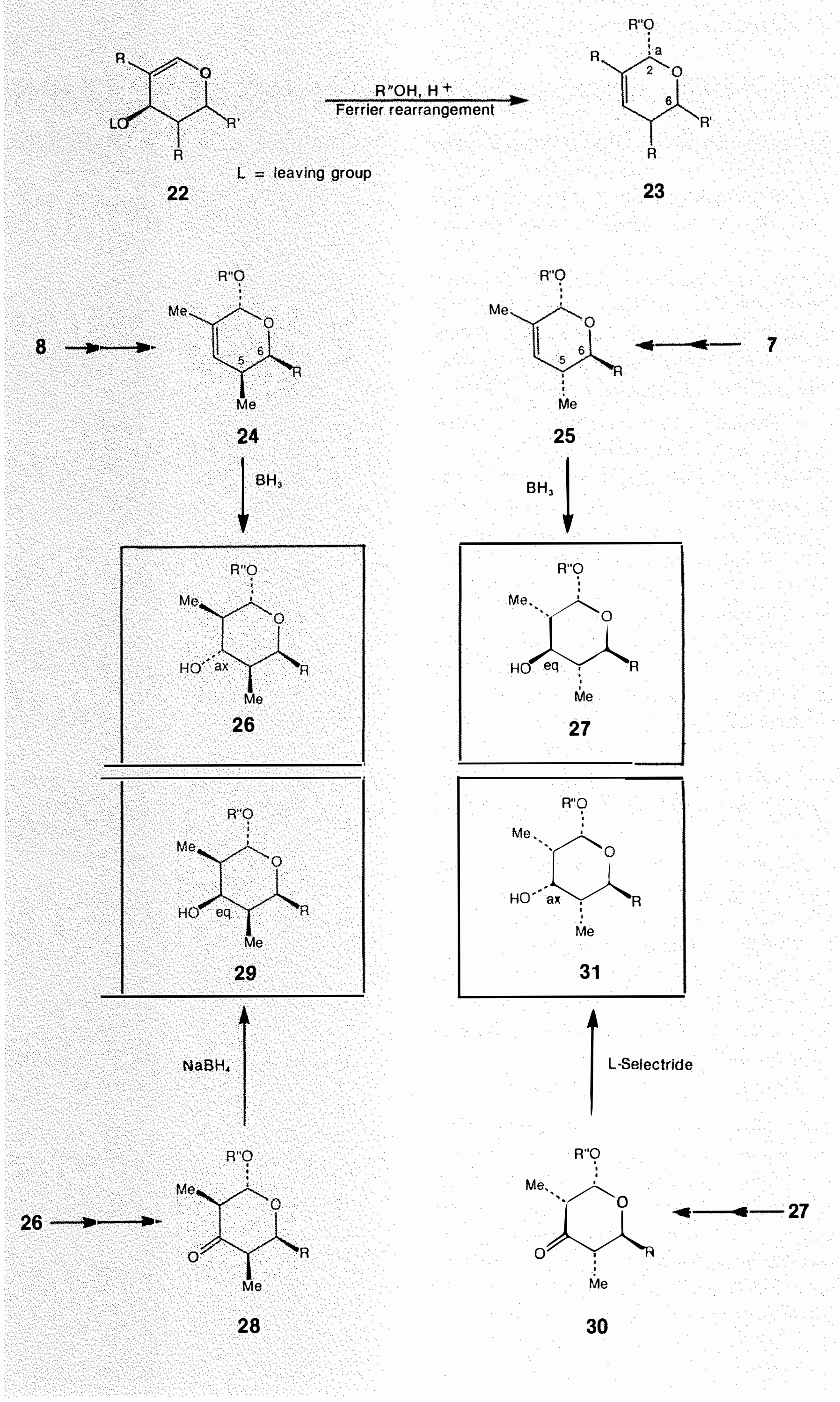
Treatment of cycloadduct **13** with triethylamine in methanol leads to apparent axial protonation, resulting in the formation of pyranone **17**.[7] In these 2,6-cis compounds, the anomeric methoxy group is equatorial. Reduction of such products with sodium borohydride affords a highly specific route to equatorial alcohols (*cf.* **18**).[21] The preference for equatorial alcohol formation in this anomeric series extends even to the use of Selectride® reagents (K and L), well known for their proclivity to produce axial alcohols *via* hydride delivery from an equatorial direction.

The axial anomer series is reached from our chemistry by two routes. In one permutation, Michael-like addition of alcohol to dihydropyrone **19** is employed to afford **20**. Reduction of the ketone with L-Selectride® in the axial anomer series proceeds normally (equatorial hydride delivery) to afford axial alcohol **21** (Scheme 6).[5,21]

A more general route to the axial anomer series involves a Ferrier rearrangement.[22] The reaction is carried out on the glycal system such as **22**, and gives rise to **23**. We have used such displacements in both the cis-5,6 and trans-5,6 series and have thus gained access to compounds such as **24** and **25**. An important finding was made concerning the hydroboration of such unsaturated branched pyran derivatives.[23] The reaction is highly sensitive to the stereochemistry at C_5. Hydroboration occurs anti to the C_5 methyl group in both series with high selectivity. Accordingly, compound types **26** and **27** become available from **24** and **25**, respectively.

It is also possible to obtain the epimeric alcohols. Oxidation of **26** affords ketone **28** which, upon reduction with sodium borohydride, affords equatorial alcohol **29**. Similarly, oxidation of alcohol **27** provides ketone **30**. In the axial-alkoxy-anomer series, Selectride® reductions occur in the normal sense, affording axial alcohols. This had been demonstrated previously with ketone type **20**. Reduction of **20** with L-Selectride® gives rise to **21** which corresponds in stereochemistry to the pyranone segment of compactin.[5] Similarly, the reduction of branched pyranone **30** affords axial alcohol **31** (see Scheme 7).[23]

Scheme 7



Stereoselective adjustment reactions have also been worked out for the non-branched pyranone series. It will be recalled (see Scheme 4) that cyclocondensation of diene type **10** with either BF_3 or zinc chloride leads preferentially to the cis dihydropyrone **7**. Reduction of **7** with sodium borohydride/cerium(III) chloride affords

32.[24] Acylation of **32** followed by treatment of **33** with MCPBA affords **34** with galactose stereochemistry. On the other hand, if oxidation is carried out on the free alcohol **32**, the product **35** has the talose stereochemistry.[5]

A similar flexibility is available from the glucal-like series **36**. This series is available by reduction of dihydropyrone type **8** with sodium borohydride/cerium(III) chloride. Access to system **8** through our chemistry is provided by two routes. One entails oxidation of desoxy system **5** by manganese(III) acetate[12] (see **5** → **8**, Scheme 4). An alternate approach which is now considered involves a significant variation of the cyclocondensation itself.

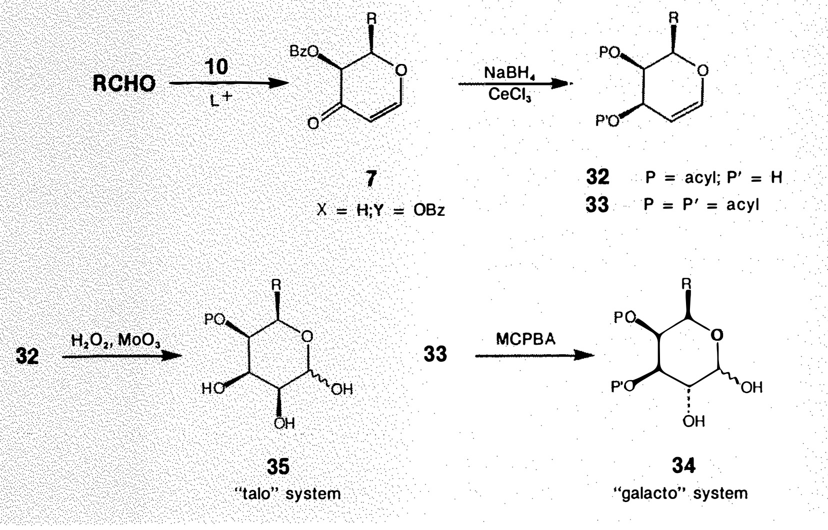
In analyzing the relationship of topographic and diastereofacial control, it seemed likely that chelation control at the diastereofacial level would impose an exo topography on the cycloaddition reaction.[19] This notion is captured in the ensemble of **10** + aldehyde type **37** → the trans dihydropyrone **38**. The reader is referred to the original literature for a more detailed analysis of the reasons for endo addition in the general case[6,9] (see, for instance, transformation **9** → **7**, Scheme 4) in contrast to exo addition in the case of chelation control (see transformation **12** → **16**, Scheme 5, as well as **37** → **38**, Scheme 9).[19,25]

The double bond of the glucal system **36** can be subjected to stereocontrolled functionalization. Thus, epoxidation of the free alcohol (P′ = H) leads to the mannose-like system **39**.[26a] Conversely, hydroxylation of the acylated form of **36** (P′ = acyl) with osmium tetroxide leads smoothly to the gluco system **40**.[26b]

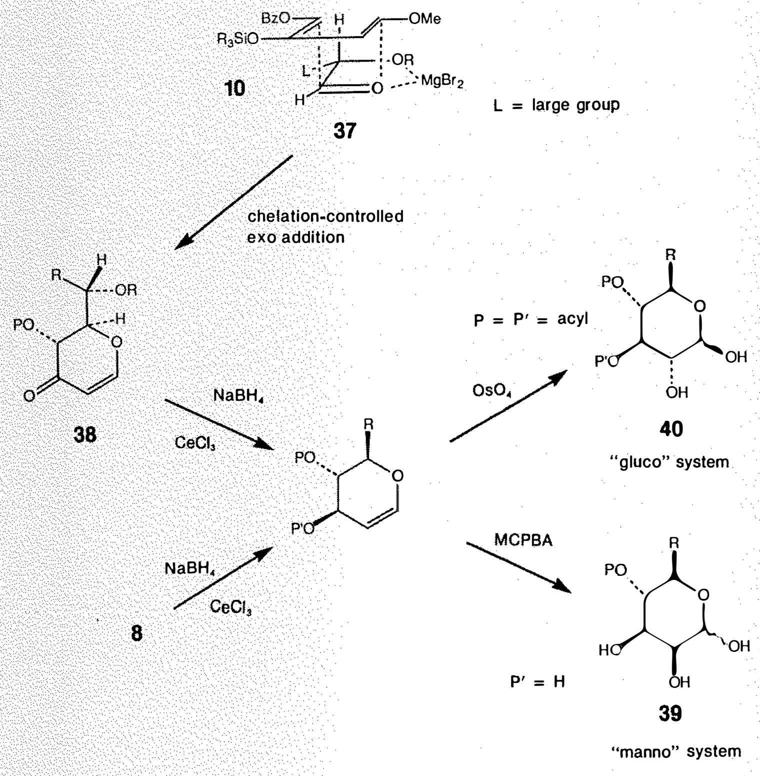
6. Reiterative Cyclocondensations

The capacity for control of topographic and facial stereoselection in the cyclocondensation reaction with simple substrates emboldened us to reiterate the process with more elaborate aldehydes[27] which themselves would have been fashioned through the chemistry described above. *The reiterative option allows for rapid access to long networks containing a multiplicity of stereogenic centers.* Two possibilities for reiteration suggested themselves. These are described in Scheme 10 (see structures **41** and **43**).

Scheme 8



Scheme 9



In one situation, option A, an aldehyde linkage is generated in the sidechain of a pyran. The reiterative cyclocondensation reaction generates a bis-pyranoid structure **42**. This formulation allows for disconnection of either the matrix ring (cleavage of "a" bond) or the derived ring (cleavage of "b" bond). An alternative approach, option B, involves dismantling the "first" pyran obtained from the first cyclocondensation reaction and using the anomeric carbon to generate the "second" aldehyde (**43**). After reiteration of the cyclocondensation reaction, a pyran connected to an acyclic dissymmetric domain is produced (**44**).

7. Extension of the Chiral Biases of the Pyranose Ring

In addition to the capacities of construction, elaboration and orderly dismantling of pyranoid rings, it is necessary to acquire one additional capability, *i.e.*, that of extending the chiral biases of the pyranoid system. This goal is generalized in the transformation **45** → **46**. The ability to transmit the ring dissymmetry to the sidechain is a crucial element of the reiterative cyclocondensation (see Scheme 10), since it allows for systematic introduction of stereogenic centers between the initial pyran and the second aldehyde [see (C_n) in structure **41**]. Furthermore, there are a great many polyoxygenated natural products which contain stereogenic centers on the periphery of C_2 and C_6 of a pyran structure (*cf.* structure **47**). In many instances, it would be awkward to accommodate both dissymmetric sectors as part of the dynamics of the cyclocondensation reaction. In such a situation, chirality extension might be more feasible. We have, in fact, developed an extensive collection of selective reactions which address such goals. The reader is referred to the original literature on this matter.[28] Two examples are shown in Scheme 11.

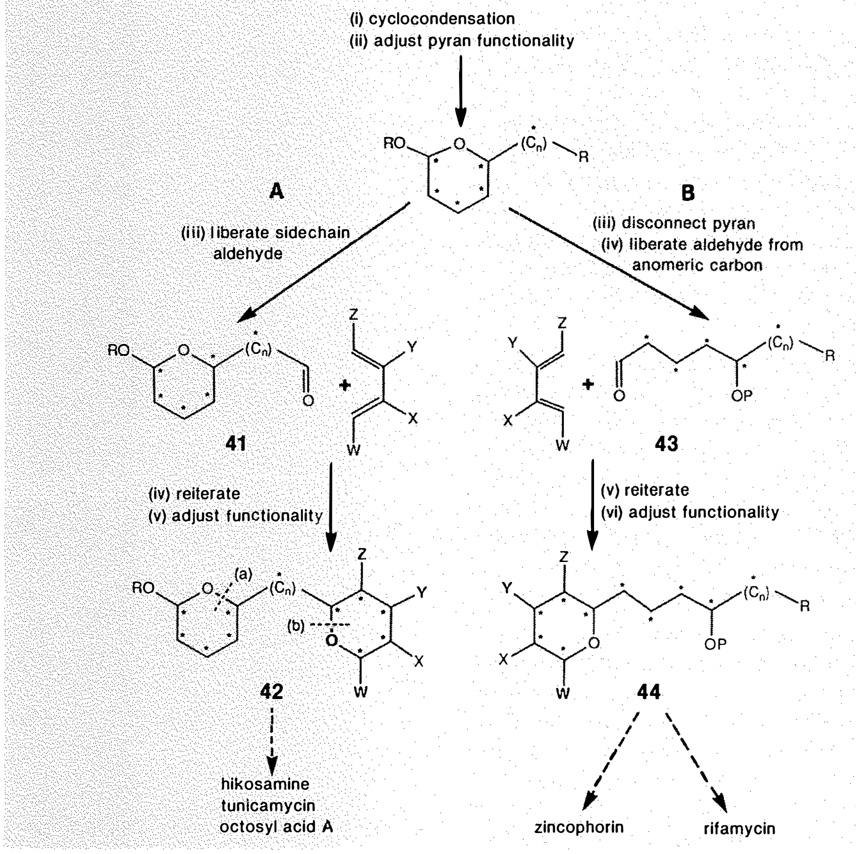
The first involves nucleophilic addition of allyltrimethylsilane to an aldoseulose (*cf.* structure **48**). This is another instance of metal-tunable asymmetric induction. With BF_3•etherate as the catalyst, the diastereofacial outcome of the reaction is quite selective for the C-F sense[13,15] (see product **49**). Conversely, through the use of titanium tetrachloride, the reaction is under apparent CC control[13,16] (see product **50**). This chirality-extending reaction has many interesting potential applications. Such a stereocontrolled Sakurai reaction was very helpful in the synthesis of α-methylhikosaminide (see Scheme **14**).

More recently, we have uncovered a promising new route to type **47** systems based on the reactions of *E*- and *Z*-crotyl silanes with activated glycals (*cf.* **51**). This chemistry is still undergoing development, but two examples can already be disclosed[29] (see transformation **51** → **52** or **53**). This form of chirality extension was used in our synthesis of zincophorin[30] (see transformation **69** → **70** in Scheme 16) and is an important component of our strategy to achieve the total synthesis of the avermectins.[31]

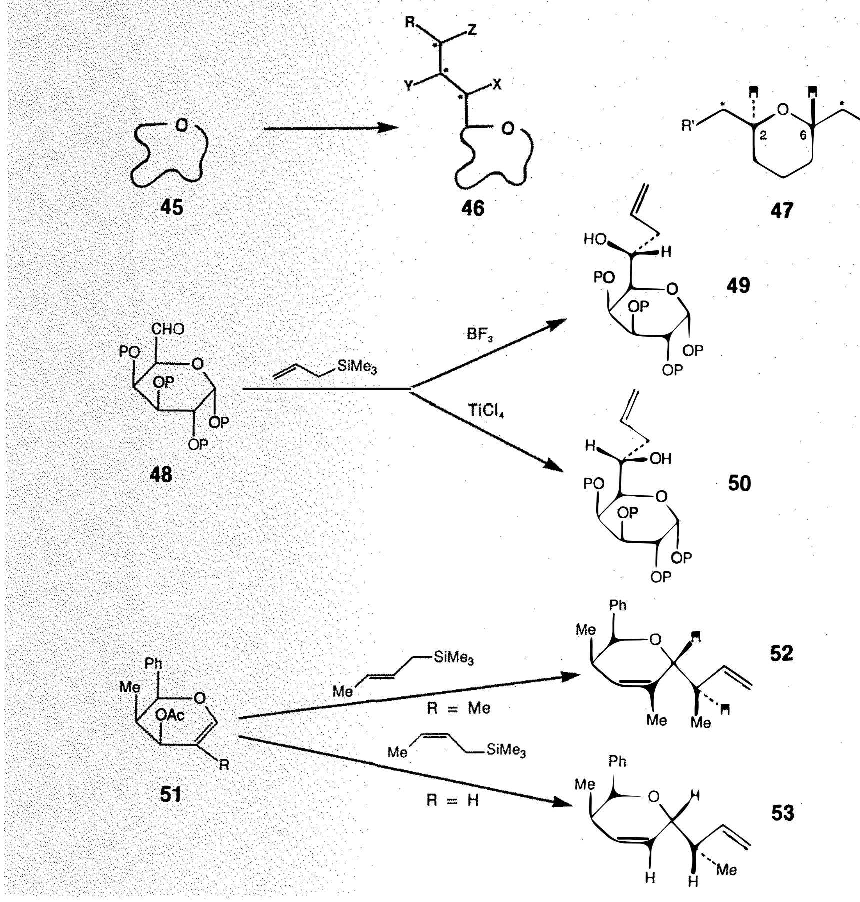
8. Some Observations on the Interactivity between Synthetic Strategy and Reaction Development

In analyzing the feasibility of a plan for the synthesis of a target system, one is implicitly obliged to think hard about the state of the art of existing methodology. Quite often this examination will reveal that the corpus of known reactions can support the strategy. The intellectual contribution of such a synthesis lies in the cognition that a particular problem in fact falls within the

Scheme 10



Scheme 11



scope of known chemistry. This type of advance is not to be belittled. Given the mass of information which is, in principle, relevant, and given the multitude of plausible ways of looking at a problem of even moderate complexity, the achievement of relating a problem to manageable terms is not trivial. Evidence in support of this view is gathered by contemplating the generally uninteresting solutions to complex synthetic problems which have been provided thus far by computers. (Clearly this will change in time!)

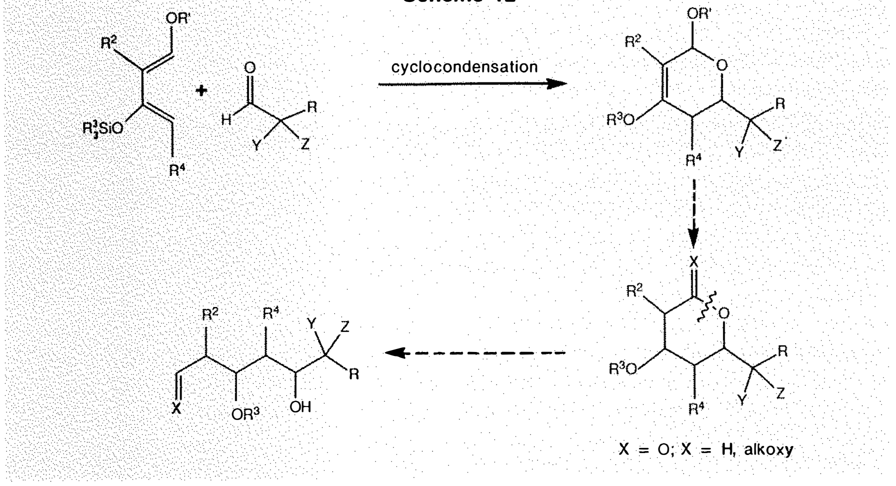
This said, we would assert our judgment that one of the most important consequences of abstract synthetic conjecture is that it serves to identify lacunae and even major shortcomings in existing methodology and capability. *The desire to translate a strategy to a reality can serve as a powerful impulse to explore new chemistry to close the gaps identified by the analysis.*

One need hardly emphasize the value of studies into synthetic methodology even in the absence of an overarching goal-oriented framework. It is to be ardently hoped that the increasing sophistication of organic chemistry will not serve to quench or even dampen such curiosity and will not discourage experiments driven by the sheer joy of learning. To turn off this type of knowledge source is to rob a discipline of its capacity for spontaneity and much of its excitement.

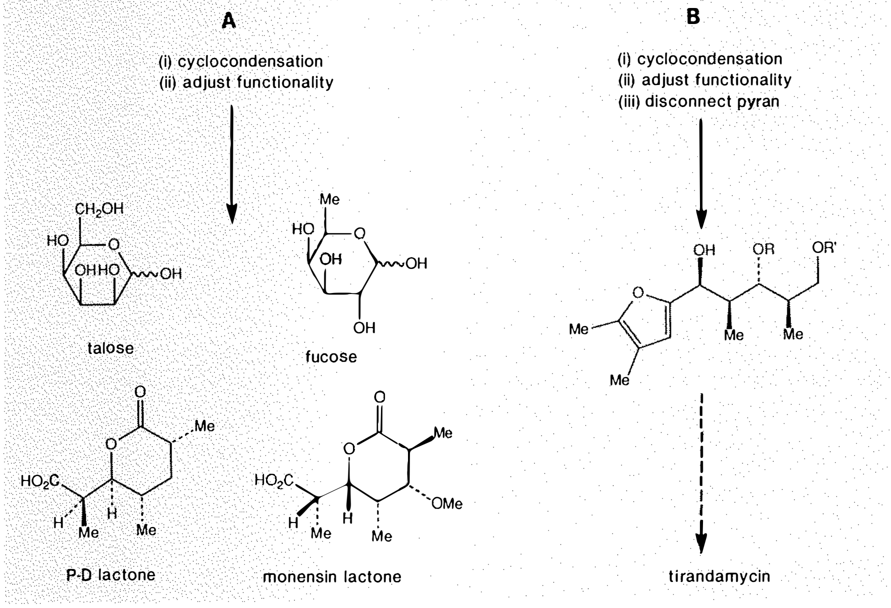
However, the reaction-development work described above was carried out with the ulterior motive of total synthesis. The notion was that the pyran ring might be a valuable matrix for controlling stereochemistry. The pyran could be dismantled and its chiral imprint conveyed to an acyclic fragment. The general logic implied in Scheme 12 formed the core element of our projected route to polyoxygenated natural products. We saw in this chemistry the potential for a broad-ranging strategy which would encompass cyclic as well as acyclic arrays.

In Scheme 13 we identify two relatively simple types of applications. In situation **A**, the target structure was, in fact, a pyran derivative such as the Prelog-Djerassi lactone,[32] the monensin lactone,[33] and various hexose systems (*e.g.*, talose[5] and fucose[24]). Our synthesis of these systems involved cyclocondensation and pyranoid modification. In situation **B**, the target structure (or substructure) is an acyclic fragment. This exercise is fundamentally similar to exercise **A**. Once again, we start with a cyclocondensation reaction. Once again, the stereochemistry of the pyran is adjusted

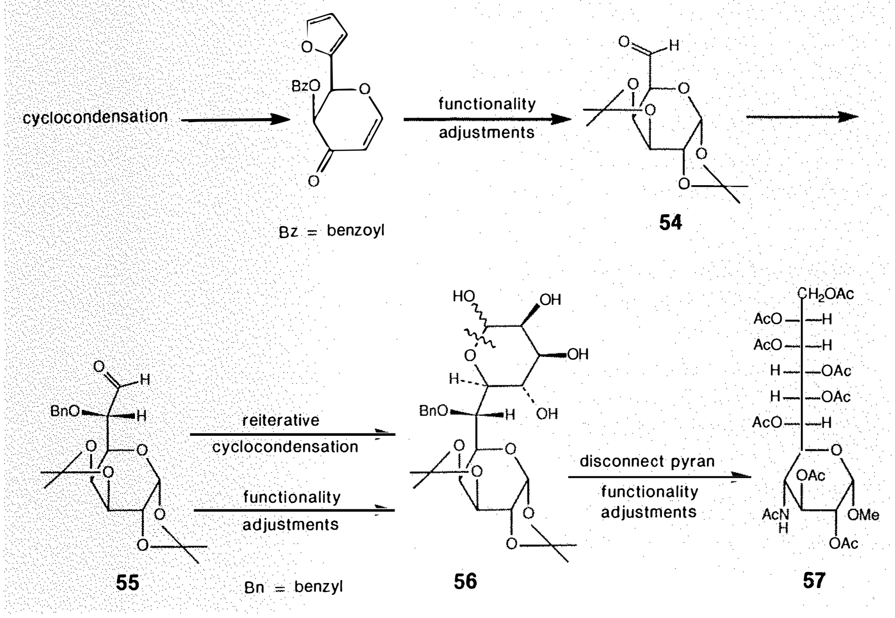
Scheme 12



Scheme 13



Scheme 14



using methodology developed above. At a strategic point, the ring is disassembled and the stereochemistry is expressed in an acyclic product. Our route to the chiral array of tirandamycin[33] was built on such a premise.

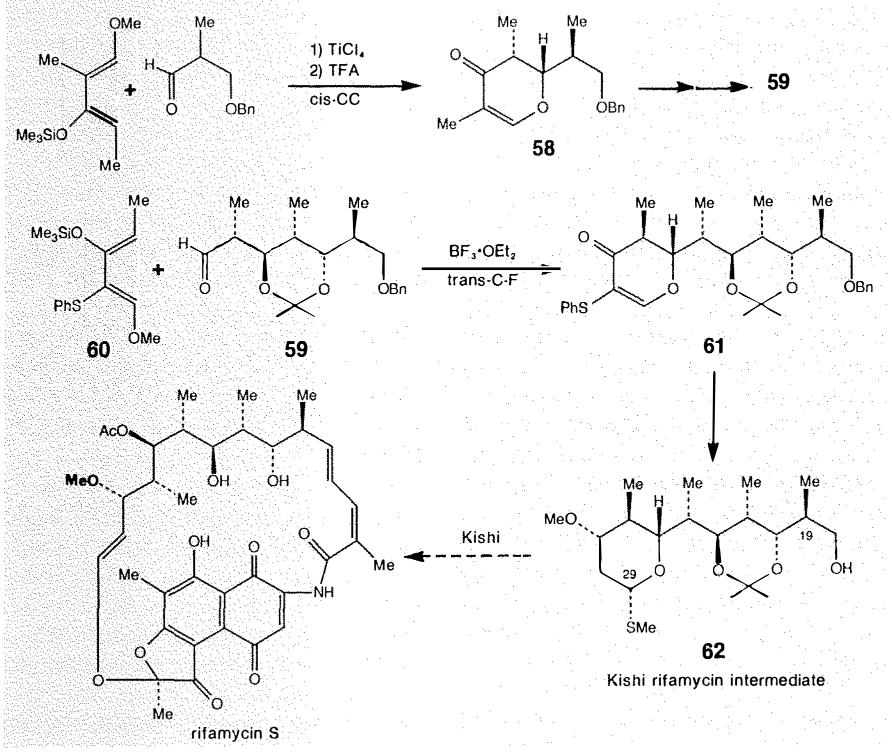
9. Applications to Total Synthesis

Three examples serve to illustrate the applicability of the strategy to the synthesis of more elaborate polyoxygenated targets. Stereochemical relationships in these long domains are established by "communication" (see Scheme 1). The synthesis of α-methylhikosaminide derivative **57** demonstrates the blending of many of the capabilities.[26a] The principal stages of the synthesis (Scheme 14) are cyclocondensation, followed by adjustment of pyranoid functionality (structure **54**). Extension of the pyranoid dissymmetry *via* allylsilane chemistry[28a,b] (see Scheme 11) leads to aldehyde **55**. Reiterative cyclocondensation (see Scheme 10) with diene **10** under the guidance of magnesium bromide occurs, with chelation control, in the expected[19] trans topography.

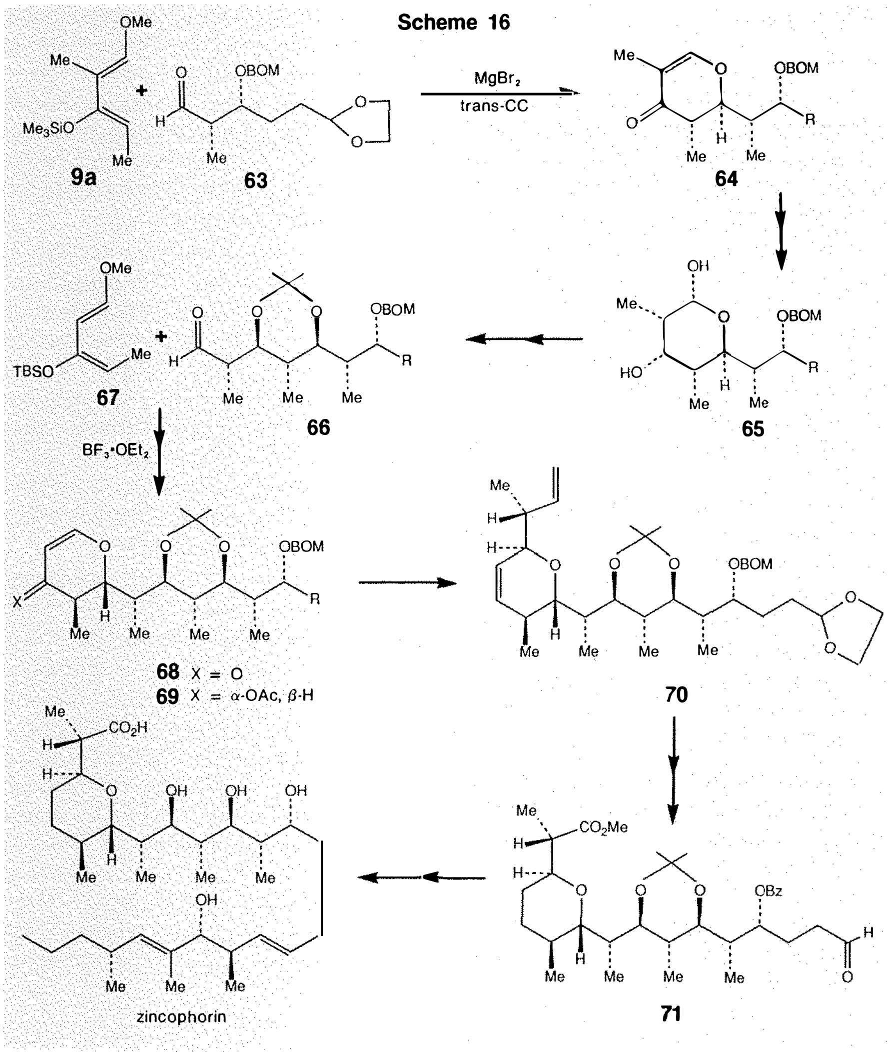
The hikosaminide effort demonstrated the applicability of this chemistry to control nine contiguous stereogenic centers all bearing hetero substituents. The program also accomplished differentiation of the carbon atom bearing the unique acetamido group.

The synthesis of the Kishi intermediate comprising C_{19}-C_{29} of rifamycin establishes the adaptability of the chemistry to complex polypropionates. Scheme 15 provides a brief rendering of the highlights of that synthesis. All carbon-carbon bonds are established through the two cyclocondensation reactions. Proper choice of Lewis acid catalysts and aldehydo substrates provides topographic and diastereofacial guidance to the two reactions. The first cyclocondensation occurs *via* an initial chelation-controlled erythro aldol process under guidance by $TiCl_4$[19] leading to structure **58**. Functional-group adjustments of the type described in Scheme 7 followed by pyran-ring disconnection and unmasking of an aldehyde afforded **59**. The reiterative cyclocondensation (see Scheme 10) in this instance utilized the novel diene **60**. The reaction was mediated by BF_3•etherate. The purpose of the thiophenyl group was to serve as a disposable "dummy" group which would favor trans pyrone formation.[34] These ends were admirably served and pyrone **61** was obtained. Eventual transformation to the Kishi intermediate[35] was accomplished shortly thereafter.

Scheme 15



Scheme 16



Finally, we describe our recently completed total synthesis of the novel zinc-sequestering ionophore, zincophorin[36] (see Scheme 16). An intermediate in our synthesis was the aldehyde ester **71**. The route to **70** started with a magnesium bromide-mediated cyclocondensation reaction between aldehyde **63** and diene **9a** under chelation control in the expected trans topography. The resultant dihydropyrone **64** was converted through the agency of the tetrahydropyran **65** to acyclic aldehyde **66.** To achieve trans selectivity in the next cyclocondensation reaction, it was necessary to use the difficultly accessible[6] diene **67**. In the event, dihydropyrone **68** was selectively obtained. The face selectivity in this reaction was essentially total, but the topographic preference was 4.5:1. Its derived activated glycal **69**, upon reaction with *E*-trimethylcrotylsilane, afforded dihydropyran **70**. Again the selectivity in favor of β-face attack by the silane was extremely high. The topographic preferences in the range of 20-40:1 have been developed.[29] Compound **71** was eventually converted through a Julia coupling to zincophorin.

10. Future Prospects

The chemistry described above provides a framework by which a large number of polyoxygenated natural products, or major segments thereof, can be synthesized in a concise fashion. Remarkably, the diastereofacial selectivity which we can obtain is greater than the topographic control. Certainly, in this latter area, some significant room for improvement remains. Current efforts are addressed to 6a-deoxyerythronolide B and avermectin. Major progress has already been achieved and these targets could well fall before very long. The key element which enabled our progress to date has been the remarkable responsiveness of the stereochemistry of these reactions to simple changes in Lewis acid catalyst, in solvent, and even in the ligands on the silyl group. There are some major opportunities within reach if one can gain more reliable understanding of the way in which these often delicate changes influence the reaction outcome.

I would close this somewhat rambling account by offering a few observations on future directions for organic synthesis in general and for its subspecialty, total synthesis. One major opportunity would appear to lie in developing new chemistry and new strategies which are germane to the real world of process chemistry. In many instances, there is enormous difficulty in translating the technology which goes into a sophisticated total synthesis to the harsh realities "out there" where serious amounts of materials must be furnished by rather specific deadlines. From the perspective of process chemistry, many of the solutions which were adequate to achieve a complex total synthesis are inappropriate. If I might be forgiven for pressing the "mountain climbing" analogy further, I would note that the tactics by which one hardy sportsman survived a precarious journey to the top might not be relevant to moving a brigade, let alone a division, to the summit. Far from being depressed by the magnitude of many of these problems, the truly creative practitioner will rise to the challenge.

Another major area of opportunity would seem to lie in applying those insights gained in a total-synthesis effort toward a better understanding of the natural product itself. It should be the case that the completion of an exercise of total synthesis would signal an inflection point rather than a termination of a program. In these terms, total synthesis would be viewed as an important element in a multifaceted study of a natural product rather than as an isolated exercise. In a total synthesis, there can be revealed unique insights into the chemical and even the biological personality of the target. The perspective gained through the synthesis of a highly unstable material can provide original perceptions not available through other means.

In short, the challenges, at least in outline form, are clear. The synthetic effort should seek to develop new chemical insights as it goes along. It should identify major gaps in the state of the art. It should turn these gaps into creative opportunities for growth. The synthesis should at least strive to provide solutions which can be useful to the larger community of chemists including those manning the often lonely barricades of process research.

Moreover, the ideal total-synthesis program would be one which helps to clarify the nature and *even the mode of action* of the natural product it seeks to synthesize. It is well within the scope of belief that such clarifications might find important applications in biology and perhaps in medicine. The capacity to develop increasingly vibrant and inciteful collaborations with allied biological disciplines is likely to emerge as one of the new frontiers of organic synthesis. The only limits which I would place on the ultimate reach of such collaborations are the limits of nerve and imagination.

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13) The descriptor C-F is used to designate those products formed under diastereofacial guidance which would have been predicted from either the acyclic Cram Rule (15a) or the Felkin analyses (15b). Although the premises are totally different, the actual predictions in almost all cases converge. The descriptor CC is used to designate a product formed under chelation control.[16]
14) We also use a complementary system of nomenclature to deal with the relationship of the preexisting stereogenic center and the face of the aldehyde which is attacked. The cis or trans substitution of the pyrone is explicitly stated for simplicity and the lk and ul designators[17] are reserved only to define the diastereofacial sense of the reaction.
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Dedication

This paper is dedicated to the Process Research Group at Merck & Co., Inc. for its brilliant and practical total synthesis of thienamycin.

Acknowledgements

I wish to thank the National Institutes of Health for its support of this research. At several important stages of this effort, additional and valuable support from Merck & Co., Inc. was crucial to the progress of the programs.

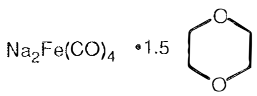
Most of all, I want to express my appreciation to my co-workers on these projects. Their names are cited in the references. It is their intellectual creativity and experimental virtuosity that made these successes possible.

About the Author

Samuel Danishefsky was born and raised in Bayonne, New Jersey. He received his undergraduate education at Yeshiva University in New York and his graduate education at Harvard University where he received the Ph.D. degree under Professor Peter Yates. He pursued his research as an NIH-sponsored Postdoctoral Fellow in the laboratories of Professor Gilbert Stork at Columbia University. From 1964-1980 he served on the Faculty of the University of Pittsburgh, rising to the rank of Full Professor in 1979. He moved to Yale University in January 1980, and was named Eugene Higgins Professor of Chemistry in 1984. He has served as Chairman of the Yale Chemistry Department since July 1981.

Dr. Danishefsky received the 1986 American Chemical Society Award for Creative Work in Synthetic Organic Chemistry sponsored by Aldrich Chemical Co., Inc. He was elected to the American Academy of Arts and Sciences in 1984. In 1986 he was elected to the National Academy of Sciences, was elected a Fellow of the American Association for the Advancement of Science and was named an Arthur C. Cope Scholar. He serves on the Editorial Boards of the *Journal of the American Chemical Society, Chemical Reviews, Carbohydrate Research* and the *Journal of Carbohydrate Chemistry.* He has been a named lecturer at many universities, including Bachmann Lecturer at the University of Michigan. He is currently a consultant for Merck Sharp & Dohme Laboratories and for the General Electric Corporation.

Collman's Reagent



For several years, Aldrich has offered Collman's Reagent, a complex of 1,4-dioxane and disodium tetracarbonylferrate. The reagent has been employed in a variety of synthetically useful transformations.[1] It is unreactive toward esters, amides, nitriles, isolated carbon-carbon double bonds and many other functional groups.

Some interesting synthetic applications include:

carbonylations to aldehydes and ketones [2]
hemifluorinated-ketone synthesis [3]
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cyclizations [5]
selective reductions [6]
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hydroacylation of Michael acceptors [8]
thioester formations. [9]

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1) Collman, J.P. *Acc. Chem. Res.* **1975,** *8,* 342.
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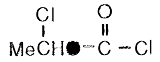
1-Chloroethyl Chloroformate



$$\mathrm{Me}\overset{\mathrm{Cl}}{\overset{|}{\mathrm{CH}}}\bullet-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{Cl}$$

This compound has been shown to be an efficient reagent for the selective N-dealkylation of tertiary amines in high yields.

Olofson, R.A. *et al. J. Org. Chem.* **1984,** *49,* 2081.
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A Tribute to PROFESSOR MAX TISHLER *on the Occasion of His Eightieth Birthday*

When I was first asked to capture the essence of Professor Max Tishler in a few words, I hardly knew where to start! Upon thinking back, however, one incident from my days at Wesleyan immediately came to mind. It had nothing to do with Max as the eminent scientist, leader of industry, inspiring teacher, humanist, or devoted family man that so many of us have been privileged to know.

The incident took place during the winter of 1975 in a rather wicked New England blizzard. Max had just bought a new, bright red Cordoba, and it had the audacity to become stuck in snow right in front of his office on Lawn Avenue.

With Max already at the helm and his graduate students Bill Jacobs, Ann Jakubowski, and Elaine Wyszkowski at their places about to start pushing, I ran up to Max's open window. "Where would you like me to stand, Professor Tishler?", I asked dutifully.

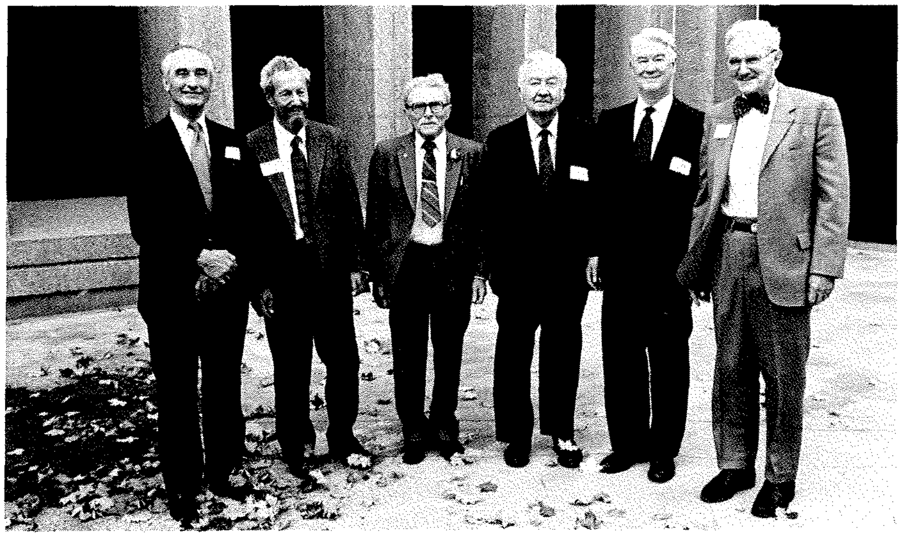
Replied The Boss in a mildly irritated tone, ***"Don't stand on ceremony, just push...!"***

With apologies for taking his words out of context, I believe these same words best describe Max Tishler's approach to life!

Happy Birthday, Max, with much respect and affection.

Bill Szabo

Editor's Note: Dr. Szabo did postdoctoral work with Professor Tishler at Wesleyan University from 1974 to 1976, when he joined Aldrich. He is currently Aldrich's Manager of Production.



Max Tishler Day at Wesleyan University, October 23, 1986. From left to right: Dr. Lewis H. Sarett, Prof. Frank H. Westheimer, Prof. Tishler, Prof. John C. Sheehan, Mr. John J. Horan and Prof. Donald J. Cram.

About Max Tishler

Max Tishler was born on October 30, 1906. He received the B.S. degree (1928) from Tufts College and the M.A. (1933) and Ph.D. (Organic Chemistry, 1934) degrees from Harvard University. After an instructorship at Harvard (1936-1937), he moved to Merck & Co., Inc., in 1937, at the persuasion of George Merck, son of the founder. He became President of Merck Sharp & Dohme Research Laboratories in 1956 and Senior Vice President for Research and Development of the parent company, Merck & Co., in 1969. Many important drugs (*e.g.*, cortisone, streptomycin, penicillin G, indomethacin, chlorothiazide, riboflavin, amitriptyline and vitamins B_{12}, K_1, and C) were introduced under his direction.

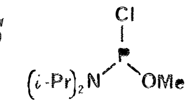
Upon retiring from Merck he joined Wesleyan University as Professor of Chemistry in 1970, was named University Professor of the Sciences in 1973 and attained emeritus status in 1975. He continues to lead an active role in research, teaching, and departmental leadership at Wesleyan.

Max Tishler's many professional activities and honors include Editor-in-Chief, *Organic Syntheses* (1959), Priestley Medal of the American Chemical Society (1970), President of the American Chemical Society (1972), election to the National Academy of Sciences (1953), American Academy of Arts and Sciences (1965), and National Inventors' Hall of Fame (1982), and the Chester Stock Award of the Sloan Kettering Institute for Cancer Research for Pioneering Contributions and Outstanding Leadership in Chemotherapy (1984). He holds 9 honorary doctorate degrees, has authored or coauthored over 130 papers in the areas of drug and natural product syntheses, and is listed as inventor on over 100 U.S. patents.

Max Tishler's warmth and dedication continue to be an inspiration to all whose lives he has touched.

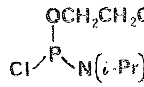
Phosphoramidite Reagents

for DNA Synthesis



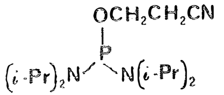
$(i\text{-Pr})_2N\text{-}P(Cl)\text{-}OMe$

1



$Cl\text{-}P(OCH_2CH_2CN)\text{-}N(i\text{-Pr})_2$

2



$(i\text{-Pr})_2N\text{-}P(OCH_2CH_2CN)\text{-}N(i\text{-Pr})_2$

3

Until very recently, the most popular method of DNA synthesis has been based on nucleoside phosphoramidites prepared with reagent **1**.[1] This method produces oligonucleotide intermediates with phosphotriester groups protected by a methyl group.

Of growing importance is a new technology recently described by Köster[2] based on 2-cyanoethyl protection using nucleoside phosphoramidites prepared with reagent **2**. The cyanoethyl protecting group is removed during the extremely mild reaction (aqueous ammonia, 50 °C) used for deprotection of the heterocyclic bases,[2] eliminating the need for the harsher conditions used for the cleavage of methyl protecting groups.[1,2] Cyanoethyl protection also prevents a potentially serious side reaction, the methylation of thymine bases by internucleotidic methyl phosphate.[3] Alkylation of base residues by internucleotidic cyanoethyl phosphate is usually insignificant.[4]

Very recently, **2** has been employed successfully in the phosphitylation of the anomeric hydroxyl function of sugar derivatives in the preparation of biologically important glycosyl derivatives.[5]

We have recently added another phosphoramidite reagent, **2-cyanoethyl** *N,N,-N',N'*-**tetraisopropylphosphorodiamidite (3)**.

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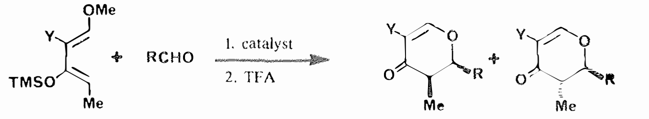
Award-Winning Chemistry — 1986
Professor Samuel J. Danishefsky

Samuel J. Danishefsky, Professor of Chemistry at Yale University, is the recipient of the 1986 ACS Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich. We extend our congratulations to Professor Danishefsky, and herein acknowledge some of his significant contributions to the fields of glycoside and alkaloid synthesis.

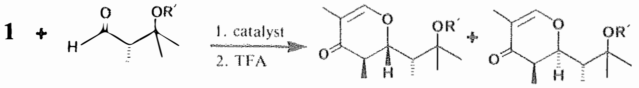
His investigation of the cyclocondensation reactions with activated dienes has provided a stereocontrolled method for construction of a wide variety of substituted pyrans.[1] This elegant work has paved the way for the synthesis of saccharide targets such as tunicaminyluracil, vineomycinone B_2, 3-deoxy-D-manno-2-octulopyranosate (KDO), lincosamine, daunosamine, fucose and chalcose.[2] The use of novel amino-annulation methodologies in the alkaloid field has led to the synthesis of mitomycin C, quinocarcinol, pretazettine, δ-coniceine and renierone.[3]

Cyclocondensation reaction

The cyclocondensation reaction, so named to denote its overall result rather that its mechanistic pathway, has shown two general modes of stereochemical versatility in extensive studies by Danishefsky and coworkers. First, reaction of dienes **1** (Y = Me, H) with aldehydes, when catalyzed by zinc chloride or lanthanide reagents, *e.g.*, $Eu(fod)_3$, afforded predominantly cis pyrones (**2**) (5:1, 15:1 for Y = Me, H, respectively) indicating an endo-like transition state.[2e] Conversely, catalysis of this transformation with $BF_3 \cdot Et_2O$ (only when Y = H) yielded trans pyrones (**3**) preferentially.[4] Also, when the C_5 methyl was replaced by OBz, the respective analog of cisoid **2** was the major observed product.[2c] Secondly, reaction of diene **1** (Y = Me) with aldehydes such as **4** was diastereofacially controlled in a Cram-Felkin sense to give predominantly pyrone **5** with $BF_3 \cdot Et_2O$ catalysis, or in a chelation-controlled manner to afford primarily pyrone **6** with $TiCl_4$ catalysis.[5] The advantage of these processes is that three stereocenters can be controlled in a single operation.



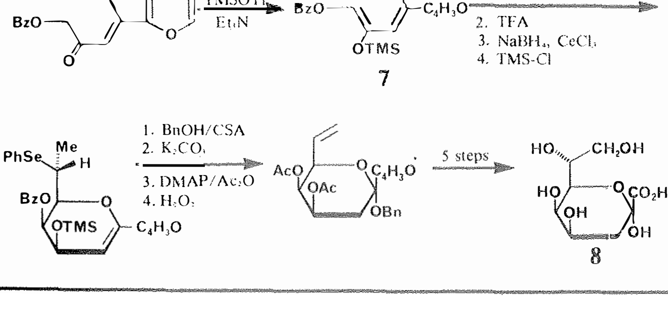
1 **2** **3**



4 **5** **6**

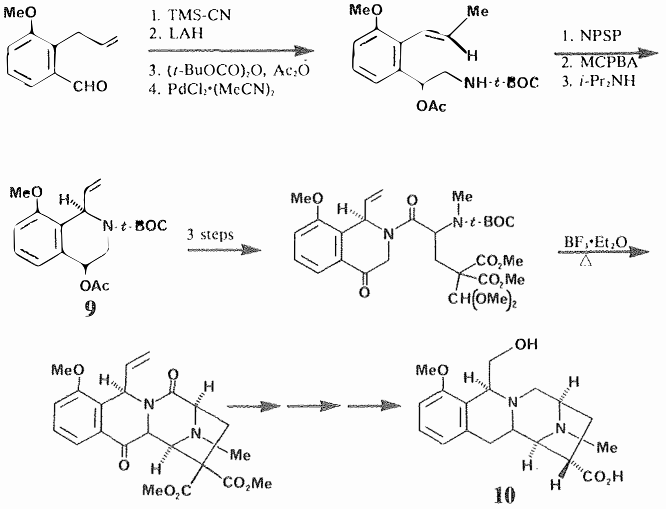
KDO synthesis

Professor Danishefsky's use of the cyclocondensation reaction in the synthesis of KDO typifies the strategy employed in his preparation of polyoxygenated natural products. The synthesis of an activated furan-substituted diene (**7**) (for a general method, see the Danishefsky diene preparation[6]) and diastereofacial-selective $BF_3 \cdot Et_2O$-catalyzed cyclocondensation (2.4:1 cis preference) with a chiral aldehyde afforded a pyran system which was readily converted to the gram-negative bacteria cell component KDO (**8**).



Quinocarcinol synthesis

One key step in the synthesis of the tetracyclic antitumor antibiotic quinocarcinol utilized *N*-(phenylseleno)phthalimide (NPSP) to effect aminocyclization to a bicyclic intermediate (**9**). Tandem $BF_3 \cdot Et_2O$-mediated annulations to a tetracyclic precursor and a few subsequent transformations gave quinocarcinol (**10**).



References:

(Professor Danishefsky is the senior author in all cases.)

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2) (a) *J. Am. Chem. Soc.* **1985**, *107*, 7761. (b) *ibid.* **1985**, *107*, 1285. (c) *ibid.* **1985**, *107*, 1280. (d) *ibid.* **1985**, *107*, 1274. (e) *ibid.* **1985**, *107*, 1269. (f) *J. Org. Chem.* **1982**, *47*, 1597.
3) (a) *J. Am. Chem. Soc.* **1985**, *107*, 3891. (b) *ibid.* **1985**, *107*, 1421. (c) *ibid.* **1982**, *104*, 7591. (d) *Tetrahedron Lett.* **1983**, *24*, 11. (e) *ibid.* **1980**, *21*, 4819.
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6) *Org. Synth.* **1983**, *61*, 147.

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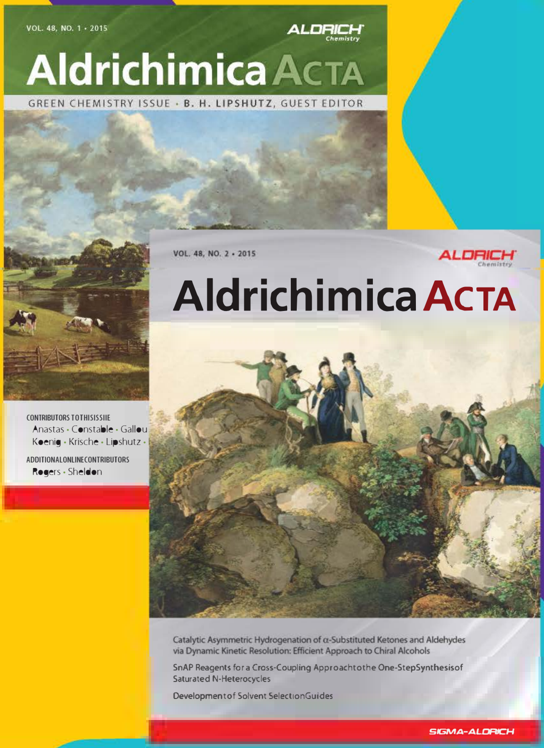

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