Adventures with Acetylenes: A Personal Odyssey from Wyerone and Crepenyenic Acid to Enediynes, Acetylenic Cyclophanes, and Propargyl Alcohols

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This Account is dedicated to the late Professors Peter Yates, Ewart (Tim) R. H. Jones, and Raymond (Ray) U. Lemieux for their guidance, inspiration and our friendships. Also to Wanda, Graham, and Dawn for their love, patience, and encouragement.

Abstract: This account provides an overview, in varying depth, of our research into diverse aspects of acetylene chemistry over the last three decades. Initial studies with acetylenic natural products (Wyerone, Crepenyenic Acid) were followed several years later with synthetically oriented projects. These involved enediyne mimics of natural products (Taxamycins) and unusual selenium dioxide oxidations of σ-alkynyl ethers. Helical acetylenic cyclophanes (Revolvenynes) were synthesized by sequential palladium- and copper-mediated reactions, which set the precedent for later research. Related cyclophanes as potential intermediates for buckminsterfullerene (C60) are discussed. Helical carbocyclic liquid crystalline and heterocyclic (copper-free and complexed) cyclophanes were also prepared. A very strained 153.5° triple bond was discovered which reacted with cyclohexadiene to form the bicyclic adduct in situ and extruded ethylene to generate a new cyclophane with an anulated benzene ring attached. In situ desilylation–dimerization sequences are described and a table is presented for guidance to predict the preferred product from competing intra- and intermolecular copper-mediated coupling pathways. The synthetic details for two different helical, σ-stacked C60 cyclophane families with para and meta bonded caps and different structural motifs are presented (Scheme 13 and Scheme 14) for comparison with Scheme 1. These concepts are being extended to the synthesis of allenoacyclophanes. A brief discussion of a π-extended boron–azulene complex is followed by a summary of magnesiun-mediated carbometallations of propargyl alcohols. A final comment reexamines our cyclophane-based approach to buckminsterfullerene.

1 Acetylenic Natural Products (Wyerone, Crepenyenic Acid)
Life is full of coincidence and unexpected events that play a role in our careers. We may reflect on the ‘road not taken’ but in my case the chemical and personal opportunities that have presented themselves have continued to be extremely fortunate and beneficial. The invitation from Peter Vollhardt in the summer of 2003 to write this account recommended an article that would be ‘laced with a personal flair’ and caused me to reflect on some of our research.1 We have had a long association with pericyclic reactions, related tandem-sequential, and multiple bond forming sequences, due to their synthetic efficiency and the stereocntrol they provide. This would have been a suitable topic but we have written accounts on these and related areas previously.2

Fate intervened a few weeks later when I was writing lecture notes for a course on the biosynthesis of medicinal natural products: I consulted the book by Dewick, and two old friends jumped off the page.3 These were the compounds Wyerone and Crepenyenic Acid, acetylenic natural products I had investigated as a postdoctoral fellow at Oxford (Figure 1). In view of our current interest in triple bonds, both for their synthetic versatility and assembly of large cyclic arrays, a change in the subject matter of this account was clearly indicated.

This decision requires the proper historical context. Prior to completing my Ph.D. with Peter Yates at Toronto, we discussed the advantages of postdoctoral research in another country. Despite his British ancestry and education, he strongly urged me to go to the United States. He also emphasized that postdoctoral experience was essential if I had aspirations of an academic career, as I knew. This was sound advice; however, ancestral ties and an interest in history compelled me to cross the Atlantic by boat. Consequently, I wrote to the late Franz Sondheimer at Cambridge to explore the possibility of a postdoctoral position in his laboratory to work on either of his current interests, annulenes or cardenolides. I used an annulene problem for my NRC Postdoctoral Fellowship Application (now NSERC) but in a subsequent letter he said he would be moving to University College and was uncertain if he would have funds for a stipend if my scholarship application was unsuccessful.4

2 Enediynes (Taxamycins)
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This prompted a rapid series of fresh letters and by return mail, the late Sir Ewart Jones at Oxford offered me a position with a modest salary. Fortunately, the NRC fellowship was awarded and it was a simple matter, and ethically correct, to have it transferred to Oxford. Jones lectured at Toronto before my degree was complete and during our discussion I was led to believe that I would work on a steroid problem once I arrived in England. This is not what I had expected from our previous correspondence. In addition, I felt the acetylene problems were both more interesting and more significant. However, upon arrival in Oxford I was presented with a single sheet of paper, which unexpectedly contained some alkene-acetylenes for me to synthesize. A trip to the library revealed the first compound was already known, which surprised me, particularly as my new research colleagues seemed unaware of this, although they were pursuing related research!

![Figure 1](image)

Wyerone is an antifungal acetylenic furanoid keto-ester isolated from the shoots of the broad bean (*Vicia faba L.*, Fam. Papilionaceae). The bean seedlings were grown on damp paper towel for various time periods (ca. 8 days) to establish the maximum yield of the compound. The natural product was isolated by solvent extraction and purified by chromatography. The structure was confirmed by total synthesis and thus with my collaborators represented my first natural product isolation, structure determination, and total synthesis in one package! It should be noted that, before the days of ChemDraw and related drawing programs, structures were drawn by hand and typewriter manipulation. Would current readers recognize the equivalent furan formula (Figure 1) while turning pages or scanning the Web?

The next more significant problem we wished to investigate involved a simple question but potentially a complex answer. How does nature introduce triple bonds into natural products, particularly in the phospholipid oleate-18:2 into an 18:1 fatty acid? For example, by what mechanism was linoleic acid converted to its dehydrogenated product, crepenylic acid [(9Z)-octadeca-9-en-12-ynoic acid; Figure 1]. It was also not clear at what stage the triple bond was introduced into Wyerone. Was the precursor an allylic alcohol or cis-enone or neither? It has been suggested that the furan ring may originate from oxygenation of a conjugated diyne.

Over the past three decades the advances in the synthetic methods applied to the manipulation of acetylenes and alkenes have exceeded all our expectations. The diversity, ease of use, and utility of the metal-based protocols for coupling unsaturated compounds continues to expand. Together the imaginative use of organometallic intermediates, the best of which are catalytic, has allowed us to design routes and synthesize molecules, both natural and unnatural products whose synthesis could never have been achieved with the methodology available in the 1960’s. Thus, early in their careers young organic chemists are already familiar with the following representative...

**Biographical Sketch**

Alex G. Fallis was born in Toronto, Canada, and received his B.Sc. Hon. (1963), M.A. (1964) and Ph.D. (1967) degrees from the University of Toronto with the late Professor Peter Yates. After a National Research Council of Canada Postdoctoral Fellowship (now NSERC) at Oxford University with the late Professor Ewart R. H. Jones, he joined the Department of Chemistry at Memorial University of Newfoundland in 1969. In 1988 he was appointed Professor in the Department of Chemistry at the University of Ottawa and was Director of the Ottawa-Carleton Chemistry Institute (now NSERC) at Ottawa University with the late Professor Ewart R. H. Jones, he joined the Department of Chemistry at Memorial University of Newfoundland in 1969. In 1988 he was appointed Professor in the Department of Chemistry at the University of Ottawa and was Director of the Ottawa-Carleton Chemistry Institute. He was a Visiting Professor at the California Institute of Technology (1977), the Institute de Chimie des Substances Naturelles (1994), and the Australian National University (2001). Awards include the Basic Research Award of the Ottawa Life Sciences Council, Saunders-Matthey Foundation Award for Breast Cancer Research and in 1998 the Alfred Bader Award of the Canadian Society for Chemistry. His diverse research interests encompass synthetic, medicinal and functional organic chemistry. Particularly investigations involving pericyclic reactions, synthesis of natural products with medicinal potential, organometallic methods, acetylenic cyclophanes and molecules for organic thin film electronics.
list of elements and their applications (Al, B, Cu, Co, Cr, Cs, Fe, Li, Mg, Ni, Pd, Pt, Rh, Ru, Si, Sn, Ti, Zn). In this context, examination of the synthesis of 10 (Scheme 1) will reveal the roots from which later discoveries have evolved and help us measure how far we have progressed.

The Wittig salt 1 (Scheme 1) was selected as a stable intermediate to introduce the requisite ‘skipped’ methylene into the C16 to C18 enyne esters related to 10, and for the synthesis of compounds containing the 1-ene-4,6-diynes moiety with more highly unsaturated chromophores.6 Treatment of the aldehyde 2 with this salt in THF–DMSO at 0 °C for 35 hours afforded the desired olefin 3 (80%, 95% cis). The desilylated ester 4 could not be converted into the bromo-acetylene 5 with sodium hypobromate and gave low yields when coupled with bromopentyne in the presence of cuprous chloride. Exposure to silver nitrate cleaved the silyl group in 3 and precipitated the silver acetylide 6. This was converted in situ to the iodo-ester 7 upon treatment with iodine. It was important to remove any excess silver nitrate prior to adding iodine to prevent formation of the nitrate ester 8.

Scheme 1

The addition of iodonium nitrate to cyclohexane had been observed previously.7 In retrospect, the fact that 8 was the only isomer implied an opportunity may have been missed by not investigating the potential of this addition–elimination sequence. The yields improved in the copper(I)-mediated coupling between the iodo-ester 7 and 9. This was a pleasing result, particularly as at the time iodoacylene Cadiot–Chodkiewicz couplings had not been reported. It was assumed iodoacylenes were too reactive and would perform poorly due to their ability to act as strong oxidizing agents towards copper(I) ion. Consequently, dimerization would be strongly favored.9 Perhaps an early lesson, that one should not be overly constrained by current dogma. It is important to be rationally optimistic and try experiments regardless of the literature precedent or personal bias.

Despite the synthesis of labeled compounds (3H and 14C) we were unable to answer our biosynthetic question unambiguously. It is only very recently that the fatty acid acetylenase of Crepis alpina has been investigated. In the presence of this enzyme crepenynic acid is synthesized in two discrete steps from the oxidation of linoleate by hydrogen atom abstraction at C12 of a linoleoyl substrate.9

2 Enediyynes (Taxamycins)

With the exception of the occasional use of dimethyl acetylenedicarboxylate we seldom used acetylene-based chemistry in our research for the next twenty years. Two natural product families reawakened our interest in triple bonds. The taxoids and the enediyne antibiotics of which Taxol® and Calicheamicin/Esperamicin are representative (Figure 2). They shared common structural similarities, bridgehead double bonds, allylic oxygenation, and different yet novel modes of action in their biological activity that had not been encountered previously. These involved tubulin binding and cycloaromatization diradical-mediated DNA strand cleavage, respectively. Independently, these compounds appeared in the late 1980’s and early 1990’s to have the potential to become useful drugs and also presented significant synthetic challenges.

Figure 2

Our initial approach to the taxane skeleton was based on the premise that a cyclohexene A ring would act as a handle to facilitate the intramolecular cycloaddition between suitably functionalized appendages. An acetylenic ketone
11 was selected as the dienophile to reduce the conformations available in the transition state. Thermal cyclization (microwave oven, sealed tube, toluene) of 11 afforded the desired cyclohexadiene adduct 12, which upon treatment with DDQ aromatized as expected to give 13 (Scheme 2).10

We were aware from the literature there was growing interest in taxoid analogues, including aromatic taxanes,11 particularly those that might have improved therapeutic potential. This area is still receiving attention.12

Scheme 2

One afternoon at the blackboard we shared a 'eureka moment' of unexpected excitement. Of course this was simply a different way of looking at something that was obvious. In rapid fashion we sketched on the black board enediyne–taxoid hybrids, which we anticipated could have a twofold purpose. They should afford an interesting, relatively short route to aromatic taxanes via cycloaromatization. In addition, incorporation of a suitable trigger mechanism would create a two-pronged warhead. These compounds might disrupt cancer cell mitosis by tubulin binding and free radical initiated DNA cleavage by hydrogen abstraction. We named these mimics Taxamycins to reflect their components and anticipated biological activity. This was based on the expectation that sufficient functionality could be installed to facilitate binding and a cycloaromatization trigger. We envisioned a family of taxamycin-10, 11, and 12 ring systems (where the number represents the size of the ring containing the enediyne unit; Figure 3).

These structures were approached by a common building block approach the enediyne synthon 14 in which advantage was taken of the relative rates of cleavage of the TMS and TIPS groups to facilitate selective carbonyl additions.13 The preparation of this enediyne moiety was to have a profound effect on a major portion of our research over the next decade, that continues to this day, although we had no inkling of this at the time.

The model 11- and 12-membered ring systems were assembled as outlined (Scheme 3) from the appropriate masked cyclohexene dialdehydes 15 and converted to the iodoacetylenes 16 and 24. A variety of options were available for the final ring-closure with an acetylenic anion or equivalent. Several of these were investigated with mixed results. We developed a reliable method for these intramolecular cyclizations in which the reagent of choice was the tetrahydrofuran–chromium dichloride complex in excess, in the presence of approximately half an equivalent of nickel chloride.14 This was adapted from the extension developed by Crevisy and Beau,15 for these cyclizations of iodoacetylenes with aldehydes based on the Nozaki–Kishi coupling of iodoalkenes.16 Microwave assisted thermolysis of 17 in a sealed tube follow by pyridinium dichromate oxidation afforded a low yield of the ketone 13. This result was not surprising as the terminal triple bond separation (c–d) is ca. 3.8 Å considerably more than the ca. 3.2 Å distance observed for spontaneous separation. The 10-membered ring value found in the natural products is ca. 3.5 Å. Consequently, a cyclodecadiyne model was considered a more promising target, particularly if a suitable trigger mechanism could be introduced to initiate the cycloaromatization, and the requisite C13 side chain was present.

Figure 3

We often think our knowledge of established reactions is well advanced. However, when we obtain an unexpected result it is usually only after the fact that we can rationalize what actually happened. Chromium trioxide and pyridinium chlorochromate failed to introduce the desired allylic ketone into the cyclohexene ring to give 19 and only starting material was recovered. In contrast, selenium dioxide oxidation of the acetate 18 was also expected to lead to the ketone 19 but instead the ether group had disappeared and the C2 position had been oxidized to a ketone to afford 20 as the exclusive product (89%). Initially, it appeared that the acidity of the reaction had resulted in the hydrolysis of the MOM ether followed by oxidation of the resulting alcohol. However, this was not the case as the parallel oxidation of the methyl ether 26 also gave the corresponding C2 ketone (not illustrated). Consistent with the accepted mechanism of selenium dioxide oxidations these reactions likely proceeded via an ene reaction (21) to form the allene intermediate 22, followed by sigmatropic rearrangement to 23, and subsequent hydrolysis to the ketone 20 upon aqueous workup. The bridgehead double

bond in these cyclohexene rings is hindered by both the enediyne bridge on one face and by the sterically demanding gem dimethyl group on the other. This interpretation was confirmed below from the behavior of the nor-methyl 10-membered ring compound 28 upon exposure to selenium dioxide.

The cyclodecadienyne family (Scheme 4) was prepared by a parallel route to those above. Cyclization of 27 and allylic oxidation of the cyclized skeleton 28 with selenium dioxide afforded the exo-allylic alcohol (not illustrated) as a single diastereomer (60%). Subsequent treatment with pyridinium chlorochromate provided the ketone 29. Reduction from the top face due to the steric hindrance of the enediyne bridge afforded the epimeric endo-alcohol 30. The Taxotere® side chain was installed via the Commercon protocol17 to afford the 10-membered ring analogue 31 with the Taxotere® side chain attached. 18 The natural enantiomer was isolated and tested. Unfortunately, 31 displayed negligible effects on tubulin polymerization and weak cytotoxicity compared to Taxol®.

Undeterred, we turned our attention to the unsaturated ketone 29 in order to develop an aromatization trigger mechanism based on the analogy with the conjugate addition preformed so easily by intramolecular sulfide addition in nature. We had hoped that in a biological system glutathione might induce the Michael addition but 29 was inert to treatment with KSMe. Molecular models implied that if we could generate the 5-membered ring represented in 32 that the acetylene termini would be close enough to cause cyclization to the desired benzylene radical 33 and ultimately provide the aromatic compound 34 (Scheme 4).

Our attempts to accomplish this with the xanthate type anion 35, the enolate anion derived from 36, the intramolecular Diels–Alder reaction of 37, or photochemically induced [2+2] cycloaddition of 38 all failed. In addition, the 11,12 double bond was inert to hydrogenation. However, nature knows best. Clearly for this type of conjugate addition the approach of the anion must mimic the natural products so it is delivered at the correct angle to the alkene π-orbitals for conjugate addition to be successful. This can only be accomplished from delivery of the anion from the methylene bridge and not from an adjacent exo-substituent at C10.

These results were certainly disappointing but we had not yet given up. A different preparation of 11- and 12-membered rings 42 was accomplished via an intramolecular pinacol coupling of the dialdehydes 39 to the diol 40 followed by thermolysis of the thiocarbonates 41 to complement the methods above (Scheme 5).

An additional 10-membered, ring single enantiomer, target 44, was also designed.19 The tartaric derivative 43 was treated with enediyne 15 to afford the hydroxy-ether 44 after iodoacetylene cyclization. It was anticipated that hydrolysis of the acetal in 44 would release the strain inherent in the trans-acetal component of the highly unsaturated 10-membered ring system and generate the aromatic triol 46. No such luck. A multitude of acid treatments failed to generate the diol. In contrast, heating 44 at ca. 100 °C afforded 45, which hydrolyzed readily in aqueous acid! Undoubtedly, the use of a more readily cleavable group such as a carbonate would be more amenable to hydrolysis but the conversation described below elicited a new opportunity and it was prudent to move forward.
3 Acetylenic Cyclophanes

3.1 Revolvenynes

The exhilaration that arises from random discussions with members of your research group can have a significant impact. This is especially true when these conversations lead to new ideas or insights. In the best scenarios, these sessions can launch a new research project or a new train of thought that was not previously considered. One afternoon, students on adjacent benches were investigating the preparation of the bis-triflate 47 and another student was scaling up our preparation of the enediyne 14. In conversation they wondered if we could make an aromatic ‘basket’ by combining 47 and 14 (Figure 4). We immediately recognized the bond lengths, bond angles, and carbon skeleton would be horrendously strained. Therefore, synthesizing this molecule was improbable. However, excited by this idea, we were soon drawing structures with various combinations of alkene–alkyne bridges attached to phenyl rings. We realized these molecules possessed interesting features. The cyclophanes 48 and 49 were two of the attractive molecules that resulted from our deliberations. It was clear that a combination of modern palladium- and copper-mediated reactions should generate these ring systems. Perhaps less obvious, these ring systems are

Scheme 4

Scheme 5
not flat as drawn but are helical and thus chiral by virtue of twist. In addition, if one builds a Dreiding model and you tap the benzene cap with your finger it rotates freely in the cavity. Consequently, we named the compounds Revolvenynes.\textsuperscript{20} We also anticipated that by cooling a sample in an NMR experiment we could lower the rate of this rotation to measure the through space interactions. Unfortunately, we could not cool the solution sufficiently to observe these phenomena. Substituted aromatic rings with non-bonded interactions that restrict the rotation should accomplish this.

These cyclophanes are similar to related D\textsubscript{2h}-symmetric cyclophanes. The strain present in 48 and 49 is relieved by rotation of one benzene ring with respect to the other about an axis that passes through the center of both caps. This gyrochiral property implies that at suitable temperatures the enantiomers with appropriate substituents may be resolvable. However, these structures are not locked and thus at room temperature the two enantiomers interconvert. This equilibrium between the R and S helical conformations is depicted in Figure 4. With a single triple bond in each bridge the transition state intermediate related to 48 is quite strained with the benzene caps superimposed on each other. Indeed, I thought I was going to break my Dreiding models the first time I interconverted the R and S forms! The extra triple bonds in 49 relieve a significant amount of the strain present in 48. These molecules possess accordion-like flexibility yet the rigid nature of the bridges presents a cavity for complexation (inclusion) with extra functionality and appropriate substrates.

Given the widespread use of liquid crystal displays in 2004 it may be hard to appreciate that 10 years ago they were much less developed. We realized at that time the best ferroelectric liquid crystals tended to have an aromatic core and a chiral center as close as possible to the core. There were no examples in which the chirality was also supplied by the aromatic component. This appeared to be a good topic for a research proposal within the mandate of Canada’s strategic grant program.\textsuperscript{21} The referees were not convinced and stated ‘this was interesting, innovative research but it was too fundamental and too far from the market place’. I agree it was miles from the market place but can research at a university be too fundamental? This slowed us down but because we were intrigued by these structures and could see potential uses for organic electronics and materials, etc., we have continued these investigations. Our fourth grant application to this program is pending. Naturally, we hope it will finally be funded. Especially as in the interim we have completed the research described below.

Cyclophanes in these families can be designed with the different bonding motifs summarized in Figure 5. The para capped compounds have the general structure 48 observed above, but bonding to the meta position results in a ‘flat’ type of structure. Flat is a misnomer, as discussed below, because the molecules are still twisted with the capping groups in two different planes superimposed on one another with a separation of ca. 3.5 Å. It is unlikely that the compound 50 can be prepared due the steric hindrance introduced by the para-hydrogens, which protrude into the shielding cone of the opposite rings.

3.2 Enediynes for C\textsubscript{60}?

The discovery of fullerenes and nanotubes continues to stimulate worldwide interest in this growing family of molecules. It is amusing to realize that each time we have used a Bunsen burner we have probably generated a few molecules of C\textsubscript{60}, however this does not constitute a total synthesis!

We felt that the knowledge gained above could be turned to advantage in an attractive retrosynthetic ‘paper’ approach to buckminsterfullerene (55) as outlined in Figure 6. We intended to trimerize the triyne 51 to afford
52, which after copper-catalyzed dimerization (in an ideal world) would generate 53. In principle, the styrenyl bonds would react with bromine and after elimination of hydrogen bromide give the very strained 60 carbon species 54. It was anticipated this polyyne would rearrange to the less strained buckyball (55; AM1 calculations suggest each carbon atom in the acetylene isomer 54 contains 9.4 kcal/mol higher strain energy than 55).22

Unfortunately, 51 was unstable at temperatures above 40 °C and despite considerable effort to find mild conditions with various cobalt, nickel and palladium catalysts trimerization was not observed in acceptable yields. Other related precursors, which had the potential to orient the acetylene appendages in the same direction to encourage dimerization were also not promising due to our failure to make the chromium complex 56 and the bicyclic system 57.

3.3 Carbocycles

In parallel with the studies above we next examined the extension of the revolvenyne concept by replacing the corner double bonds with benzene rings. We anticipated that copper-mediated dimerization of 58 would parallel the reaction we had utilized to generate 49 and thus afford 60 after exposure to cupric acetate, but we were again surprised.

Compound 58 was treated with copper acetate in pyridine–diethyl ether at reflux to provide a single product in 90% yield that differed from what was expected. The structure was established by X-ray analysis of a carboxylic acid derivative. This confirmed the product was 59, which had resulted from intramolecular cyclization (Scheme 6). In contrast, three days at room temperature afforded a separable mixture in which the monomer was still the major product in a 2:1 ratio accompanied by the intermolecular macrocycle 60.23

X-ray analysis of 60 (Figure 7) revealed that the central benzene rings are aligned in a slightly offset overlapping manner so that π-stacking can still occur. This cyclophane co-crystallized with dichloromethane (2:1 ratio) in a helical arrangement. The ‘outer’ rings created two ‘arms’ in the ‘pincer’ like structure illustrated. This stereochemical arrangement implies, that with appropriate heteroatom caps self-association with small molecules should be possible, but this potential remains to be investigated.

![Figure 6](image-url)

![Scheme 6](image-url)

![Figure 7](image-url)
The X-ray side view of 62 in Figure 8 clearly shows the helical framework we sought. Preparation of an actual liquid crystal required a couple of different attempts and design of a modified route with the appropriate tails attached. This was achieved from the oxidative cyclization of 63 into 64 (Scheme 8). This cyclophane melted from 48 °C to 66 °C to provide a gray opaque solution typical of liquid crystal behavior.24

However, this was not the first liquid crystal compound with a novel helical core in which the aromatic core also provided the chirality. We were too tardy and Katz et al. constructed both racemic and chiral non-racemic helicenes ahead of us. These compounds 64 possessed long alkyl chains, which form a liquid crystalline phase and assembled in solution to form helical columns.25

We continue to have a latent interest in C60 molecules and potential approaches to their construction. Carbon rich species with cavities based on acetylenic cyclophanes have interesting potential in this regard. We thought an attractive approach to a C60 cavity could arise from the oxidative dimerization of 66 (Scheme 9). Our bias told us that if we didn’t form a polymer that the likely product was 69. The strain inherent in the diyne structure 67 seemed excessive and should have precluded its formation. Nature had a different preference and the exclusive product was indeed the unusual, excessively strained, intramolecular coupled product 67.26 We were not alone in this assessment, after our work was completed, I was discussing our results with a distinguished organic chemist in my office. His response was ‘You’re kidding, there is no dimer’?

There is considerable interest in strained cycloalkenes and bent polyynes. In these molecules, the normal linear geometry for the C-CC bond is often severely distorted (ca. 165–158°) from planarity. However, previous studies have confirmed that large deviations from the idealized bond angle of 180° can be tolerated, and consequently these bonds are significantly more flexible than their C-C=C and C-C-C counterparts. X-ray analysis of the bromine derivative 68 confirmed that one triple bond was significantly distorted, 26.6° from the normal 180° bond angle. The actual acetylene bond angle in 68 between C(13)-C(14)-C(15) was 153.5°. Perhaps this is close to a world record. In contrast, the second butadiyne triple bond C(15)-C(16)-C(17) was 164.6°, a standard value for a strained butadiyne.

We speculated that the most strained triple bond should show enhanced reactivity. Not exactly a risky conjecture! In most circumstances, very reactive inverse demand dienes such as cyclopentadienones are required to effect [4+2] cycloadditions with diphenylacetylene and 1,4-diphenyl-butadiynes. In the case of the cyclic butadiyne-system 68, the very strained nature of the butadiyne bridge was confirmed via uncatalyzed thermal Diels–Alder reactions with cyclopentadiene and 1,3-cyclohexadiene
The cyclophane 68 underwent cycloaddition with cyclopentadiene (sealed tube, 120 °C) to give the bicyclic adduct 70. Of greater interest the reaction with 1,3-cyclohexadiene did not stop at the bicyclo[2.2.2]octadiene adduct 71 but instead after the initial cycloaddition with 1,3-cyclohexadiene, a retro-Diels–Alder reaction ensued with the expulsion of ethylene to give the interesting annulated acetylenic-tetraphenyl product 72. These results further established the ‘olefinic nature’ of this distorted triple bond and its rare dienophilic characteristics.26

Scheme 10

Often the acetylene building blocks required for our investigations have limited stability. Thus, procedures where they may be handled and generated under mild conditions are particularly desirable. In addition, it is widely recognized that linear arrays of polyynes are of interest for their electronic properties, spectra, and capacity to act as molecular wires. The most common synthetic method for the assembly of polyynes involves bond formation between two acetylenes via oxidative coupling as exemplified above. The instability of some polyynes is a major challenge in their preparation and phenylbutadiynes are particularly sensitive to decomposition or polymerization. Two students frustrated by these complications decided ‘enough of this, we need a better method’. Recently, others have also developed different protocols for the in situ desilylation–dimerization of acetylenes.27 We have made frequent use of triisopropylsilyl (TIPS) protected phenylbutadiyne units as building blocks for more complex structures. Deprotection and isolation of the terminal acetylenes was not possible in several cases, as the products rapidly decomposed before oxidative coupling could occur. Consequently, we chose to develop an alternative desilylation–dimerization protocol using a fluoride source to effect desilylation of both TIPS and TMS protected acetylenes. The general scheme and two representative examples are presented in Scheme 11.28

Scheme 11

3.4 Heterocycles

Despite our progress with this research we were still dealing with racemates and wanted to change this. The next family that we investigated was helical 1,10-phenanthroline capped cyclophanes. These heterocyclic cyclophanes held potential for complexation of various metals. Substituted phenanthrolines are also of interest due to their spectral characteristics.29 We hoped that the copper complexed cyclophane might retard the helical isomerization sufficiently at room temperature to allow isolation of the individual enantiomers.

The palladium mediated combination of two equivalents of 73 (X = Br) with the dibromophenanthroline 74 afforded the bis-acetylene compound 75 in an efficient manner (Scheme 12). Careful experimentation revealed the oxidative coupling was influenced by the nature of the copper–phenanthroline complex formed initially in the reaction mixture. Template-directed formation of the dimer 78 was achieved via the initial intermediate complex 76 in which the acetylene substituents were oriented in a favorable direction for diyne bond formation. This knowledge led to a very direct extension of our in situ coupling protocol above. Thus, the TIPS protected diamine 75 was treated sequentially with half an equivalent of copper acetate, followed by tetrabutylammonium fluoride, excess copper acetate, and finally with potassium cyanide to yield the free phenanthroline cyclophane 77.30

Variable temperature 13C NMR analysis of the copper complex 78 indicated the barrier to helical isomerization was 13.6 kcal/mol, an increase of 4 kcal/mol relative to the uncomplexed cyclophane. Unfortunately, this was insufficient to stop the room temperature isomerization. Shortly after this paper was published we received an interesting query from a European chemist. Stated politely, he asked, ‘were we sure we had not measured the nitrogen inversion rather than the helical isomerization?’ Well yes, we were confident our experiments were reliable but this raised a question for which we lacked unambiguous experimental data. In addition, typical inversion barriers for substituted anilines range from 12 kcal/mol to 17 kcal/mol.30 We all know that excellent students are worth their
weight in palladium and platinum combined. Commencing the next day and through the Christmas holidays my co-author completed the synthesis of the iso-propylphenanthroline cyclophanes 79 and 80. The iso-propyl methyl groups in 79 were enantiotopic while in the copper complex 80 they were diastereotopic. He determined that the helical isomerization barrier had increased to 16.2 kcal/mol. Consistent with our expectations these variable temperature NMR experiments confirmed our published results.31

3.5 C60 Carbocycles

Recently, we have synthesized large C60 acetylenic cyclophanes that possess different molecular conformations and variable through-space interactions. These are significantly larger molecules than the parent compounds 48 and 50 in Figure 5. Cyclophane 86 possesses a para-(1,4) bridged benzene skeleton while cyclophane 92 is composed of meta-(1,3) bridged benzene caps. Due to the frequent insolubility of these large unsaturated hydrocarbons, others and we have circumvented this difficulty by introducing alkyl or alkyl amine groups. Consequently, we decided to synthesize and investigate the properties of the more soluble amine-substituted cyclophanes 86 and 92 in order to gain further understanding of various features, including their helical geometry, through-space interactions, and preferred conformations from various molecular folding pathways. The reaction details have been kept to a minimum in the majority of the discussions above. However, it is instructive to provide two more detailed synthetic Schemes (Scheme 13 and Scheme 14) for comparison with Scheme 1 in order to appreciate the progress organic chemists have achieved in this area over the past 35 years.32

A step-wise approach to the C60 cyclophane core with early assembly of the tetracyne moiety was investigated. Iodide 73 (X = I) underwent a Negishi coupling with the organozincate derived from cis-4-chloro-1-trimethylsilylbut-3-en-1-yne (81) upon treatment with n-BuLi (2 equiv), and quenching with ZnBr2 to give 82. Subsequent one-pot desilylation–coupling with K2CO3 and Cu(OAc)2 in pyridine–methanol (1:1) led to tetracyne 83 in 92% yield. Exposure to tetrabutylammonium fluoride afforded chromatographically (SiO2) unstable acetylene 84 that was reacted directly with 1-bromo-4-iodobenzene [2 equiv, Pd(PPh3)2Cl2, CuI, Et3N] to give the desired dibromide 85. This compound also decomposed during chromatography. Therefore, the coupling with 1-bromo-4-iodobenzene was repeated and its disappearance was monitored. Once all of the iodobenzene was consumed, Pd(PhCN)2Cl2 and P(t-Bu)3 were added and the reaction...
was heated to reflux. Dropwise addition of a second equivalent of 85 led to cyclophane 86 as desired. Proton and carbon NMR spectra plus molecular modeling revealed that 86 adopted a highly symmetrical C$_{2v}$-conformation in solution. In contrast to our experience with related cyclophanes above, cyclophane 86 was conformationally stable at room temperature. This is expected since isomerization requires the adoption of a strained, planar, rectangular-like intermediate.

Figure 9 summarizes our previous observations regarding the competition between copper-mediated acetylenic intramolecular and intermolecular reactions. These calculations revealed the favored reaction pathway was dictated, as expected by the termini separation. The intramolecular alternative was inhibited when the reactive acetylenic termini were separated by more than 7.5 Å. Consequently, the dimerization strategy towards 92 was particularly attractive as the termini separation was approximately 13.7 Å. This cyclophane was synthesized by our established dimerization protocol (Scheme 14). Unfortunately, iodide 73 (X = I) failed to undergo a direct Sonogashira coupling reaction with trimethylsilylacetylene under a variety of reaction conditions. In order to overcome this challenge, the iodide was converted to aldehyde 87 by halogen–metal exchange with t-BuLi (2 equiv) and quenching with dimethylformamide (DMF). This aldehyde was then treated with Ohira’s reagent 88 and K$_2$CO$_3$ in MeOH to yield acetylene 89. A Cadiot–Chodkiewicz alkyne cross-coupling reaction of 89 with dibromide 90 gave the amino substituted C30 precursor 91 for the dimerization experiment. This hexyne was then transformed by our in situ disilylation–coupling protocol with TBAF and Cu(OAc)$_2$ to afford two new molecules (15% yield) that were consistent with the generic cyclophane structure 92. However, this flat cyclic representation of 92 does not accurately reflect the actual conformation of these molecules. The two isomers of cyclophane 92 were separated via size-exclusion semi-prep HPLC. The major isomer 92a displayed higher symmetry than the minor isomer 92b (3:1) based on their proton and carbon NMR spectra. Computer-based molecular modeling revealed that the two different isomeric conformers were possible. These were the symmetrical isomer ‘bowtie-like’ and ‘butterfly-like’ structures, 92a and 92b, respectively. Cyclophane conformer 92a possessed C$_{2v}$-symmetry, while cyclophane 92b belonged to the lower symmetry C$_{2}$ point group. This created an environment in which the aromatic π-π-stacking interactions between the benzene caps in each structure were quite similar despite their pictorial appearance. The inter-planar separations for the superimposed aromatic rings in 92a and 92b are 3.55 Å and 3.52 Å, respectively. These ‘sandwich-like’ arrangements are clearly evident with values similar to theoretical numbers calculated for the parallel dimer of benzene itself. These two cyclophanes constitute a pair of atropisomers due to their restricted rotation. They are both conformationally and configurationally stable even upon heating to 100 °C. Interconversion of 92a to 92b involves a significant energy barrier, which requires one of the capping benzene rings to undergo a ‘skipping rope’ type rotation through the other cyclophane macrocycle ring en route to the second isomer.

The helical stereochemistry in the two novel C60 cyclophanes in Scheme 13 and Scheme 15 is governed by the para-(1,4) or meta-(1,3) substitution of the benzene caps. Both series are geometrically distinct, but adopt helical conformations in which the benzenoid caps π-stack. The meta isomer follows a different molecular folding pathway during the macrocyclization reaction to generate the two atropisomers 92a and 92b. These acetylenic, shape-persistent, π-stacked C60 cyclophanes with modified functional groups possess interesting potential for different types of ferroelectric liquid crystals and thin film electronic devices.

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**Scheme 13**

3.6 Termini Separation

The schemes above suggest that for Cu-mediated oxidative coupling of acetylenes, there exists an optimal distance where intermolecular coupling becomes the preferred reaction pathway.

Similarly, there appears to exist a ‘grey-zone’, in which intra- and intermolecular coupling may be competitive. Obviously, the intramolecular coupling product will predominate when the substrate can adopt a conformation in which the two acetylene termini are closely juxtaposed. Can acetylene termini separation be used as a predictive tool for intra- vs. intermolecular coupling of α,ω-diacetylenes? Figure 9 lists the results of molecular modeling calculations in an effort to answer this question. Density functional theory (DFT) calculations were performed on substrates from our own laboratory and one example from the literature. A ND basis set was used to find the lowest energy conformation of the dimerization precursors (modeled compounds are illustrated). In most cases, the lowest energy substrate conformation was not useful as the triple bonds were oriented in the wrong direction with large separations. Consequently, appropriate conformations were selected in which the terminal acetylenes were in close proximity to one another to mimic the transition state geometry. These conformations were energetically minimized and used for the calculations. The intramolecular coupling product was obtained for each substrate with a terminal acetylene distance (r) of less than 7 Å. If the value of (r) was between 7–8 Å, a mixture of the monomer and dimer products were observed. Separation distances, (r) greater than 9 Å afforded intermolecular coupling products exclusively. These values provide a useful guide for the design and successful synthesis of new more complex macrocycles.

4 Allenophanes

Allenophanes have received little attention and the one reported example gave a mixture of isomers. In our initial experiments 93 was reacted with methyl magnesium bromide to provide the alcohol 94 which was protected as the acetate 95 (Scheme 15). A second treatment with methyl magnesium bromide afforded the allene 96. Under copper mediated conditions this tetrayne 96 generated an unstable product, which decomposed on silica gel and could not be fully characterized. We believe this is the intramolecular cyclic product 97 as there was no trace of the dimer. This experiment will be repeated as it appears 97 is the first member of a new family of allenyl-ethynyl-phenyl cyclophanes. A parallel series of reactions commencing with a shortened acetylene bridge chain length 93 (n = 1) generated the cyclophane 102 from the coupling of the two allene components 99 and 100. This sequence is now being modified to afford the corresponding cyclophane as a chiral non-racemic macrocycle.
Scheme 15
There is growing interest in a new class of highly fluorescent, extended \( \pi \)-electron boranes. These compounds frequently feature a triduryl (1,2,4,5-tetramethylphenyl) core which is sufficiently bulky to offer steric protection of the central boron atom.\(^{40}\) The addition of three functionalized arylethynyl groups results in a significant extension of the \( \pi \)-conjugation, as evidenced by the long wavelength absorption and emission bands. The suitable choice of ethynyl-aryl groups, directs the flow of electrons from the outside edges towards the empty \( \pi \)-orbital of the boron. This push–pull or donor–acceptor combination forms the basis of non-linear optical materials and this new class of compounds may find application in this area.\(^{41}\)

Tris(azulene-yliduryl)borane (103) was synthesized and is a green solid which dissolves to yield a beautiful blue-green solution (Figure 10). The UV/Vis absorption spectrum in THF displayed \( \lambda_{\text{max}} \) 421 nm with a second weak signal at 613 nm but there was negligible fluorescence.\(^{41}\) On the same platform phenanthroline substituents were attached in the expectation that both copper-complexed and copper-free compounds could be prepared. We obtained a yellow solid which we believe is 103 (103 with phenanthroline attached), this material did not dissolve in any common organic or aqueous acid solvents. Consequently, it could not be properly characterized. Possibly repetition of this chemistry with butyl amine functionality or alkyl chains would overcome this difficulty. In place of durene, both 1,2,4,5-tetramethoxy benzene and 1,4-dimethoxy-2,5-dimethylbenzene were examined in order to alter the electron density in the core. The tetra-methoxybenzene component was too sterically encumbered to undergo the requisite palladium coupling reactions. A fate that was not experienced with the dimethoxy compound and the triamine 105 was prepared. This amino aryl borane displayed \( \lambda_{\text{max}} \) 367 nm and fluorescence at \( \lambda_{\text{max}} \) 511 nm in THF.

6 Propargyl Alcohols (Magnesium-Mediated Carbometallation)

Earlier we required halodienes with defined stereo- and regiochemistry for our taxoid synthesis and initially developed a five step sequence to these components.\(^{13}\) We felt there had to be a better way and were attracted to earlier research in which allyl Grignard reagents were added to propargyl alcohols.\(^{42}\) Initially in our hands, the addition of vinyl magnesium chloride to the various propargyl alcohols we required for these dienes had a rough start, all the reactions failed. A postdoctoral fellow spent several weeks (too long) trying this reaction with no progress! We have all experienced this situation with a reaction that doesn’t succeed the first few times. Ultimately, one has to decide how long to continue these experiments. When I was younger, I thought this decision to abandon a set of experiments would get easier with experience. However, time has dictated otherwise, as on several occasions perseverance has paid off and a new door has opened from which we have reaped subsequent dividends. Approximately a year and a half elapsed and a new postdoctoral fellow was persuaded to have another look at this magnesium carbometallation reaction. This time we decided to limit this reinvestigation to a short time interval. In fact, this wasn’t necessary he worked out the initial experimental conditions in two days! Sadly, he has given up chemistry, now lives in a monastery, and will certainly not read this account.

We have improved the conditions and now have a versatile protocol using the magnesium mediated carbometallation of propargyl alcohols to assemble several diverse compounds generated in a single reaction, for a variety of objectives.\(^{43}\) The synthesis of differentially substituted furans 107 in which five bonds are assembled in a one-pot, four component coupling is representative. This experiment illustrates the common theme for this procedure.
via the magnesium chelate 106 illustrated in Scheme 16. In addition, to furans, endiynes 108, butenolides 109, halodienes 110 and 111, and taxoid intermediates 112 can be prepared by this protocol. Recently, this chemistry has been extended to a versatile procedure for the regio- and stereospecific one-pot palladium(0) cross-coupling of aryl- and alkenyl halides from the intermediate chelate 106 to give a variety of tetrasubstituted alkenes and dienes (Scheme 17). Skipped dienes 113 and 114 were generated with allyl substituents. In these cases the allyl or phenyl functionality may be introduced as either the magnesium or palladium component. Fully substituted dienes 115 may be synthesized and vinylsilanes 116 allow further transformations. This protocol has also been extended to a direct synthesis of (Z)-Tamoxifen from the reaction of the propargyl alcohol 118 with phenyl magnesium chloride followed by chain extension of the primary alcohol 119.\(^{44}\)

We are currently developing a new annulation procedure to attach substituted benzene rings to cyclic ketones (Scheme 18). We intend to apply this protocol to a variety of interrelated objectives. This method employs a vinyl triflate A (or halide) which is coupled in the presence of palladium(0) with a propargyl alcohol to give B. Addition of vinyl magnesium chloride generates the magnesium chelate C, in situ reaction with an electrophile such as iodide (Y = I) affords a triene of type D. In the case of some bicyclic ketones this triene undergoes spontaneous electrocyclic cyclization to E. Oxidation with MnO\(_2\) or DDQ affords an iodo-benzaldehyde F. However, various substitution patterns may be generated for different objectives as outlined below.

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Scheme 16

Scheme 17

Scheme 18
This protocol was used to convert (+)-camphor (120) into its triflate 121, palladium-mediated coupling with the propargyl alcohol to form 122, and then via chelate 123 to various compounds (Scheme 19). Quenching with boron trimethyletherate and treatment with DDQ afforded 130 whose properties as a chiral Lewis acid will be investigated. In a similar fashion will be examined as a chiral auxiliary. Treatment of 123 sequentially with iodine and manganese dioxide gave the aldehyde 129. A second oxidation with buffered sodium chlorite provided the camphor-iodobenzoic acid 128.

Conversion to the chiral IBX oxidant 127 and the Dess–Martin (DMP) oxidant 126 will allow the potential of these reagents for the asymmetric oxidation of sulfides and the investigation of their effectiveness for kinetic resolutions of racemic alcohols to be assessed.

7 Buckminsterfullerene (Revisited)

Some final thoughts on buckminsterfullerene. The trimerization outlined in Scheme 6 failed because of the instability of the triacetylene precursor 51 and the harsh conditions required (above room temperature!). Is it possible to modify our carbometallation protocol to generate this hexabenzene precursor under mild conditions and thus revisit its trimerization to 52 and dimerization to 53? Matsuura and Komatsu have demonstrated that exposure of diiodide 131 to n-butyllithium at –78 °C, followed by sequential addition of cuprous iodide and cupric chloride afforded tris[bicyclo[2.1.1]hexeno]-benzene (133) via the alkyne intermediate 132 after warming to room temperature. This suggests that the following sequential combination may be feasible. Initial palladium coupling of 81 (Scheme 13) with propargyl alcohol, followed by addition of Grignard reagent 134, also derived from 81, should generate the iodo-alcohol 135 (R = CH2OH). Oxidation to the corresponding carboxylic acid and conversion to a Barton ester would allow the low temperature photolysis to introduce an iodide or bromine (135, R = I or Br) for examination of the Komatsu copper-mediated trimerization. However, the preferred outcome in the presence of copper salts, envisages formation of the initial radical and expulsion of the iodine radical directly without isolation of the dihalide (Scheme 20).

This will temporarily generate the requisite triple bond in 136 (i.e., 51, Figure 6) required for trimerization to 52. An additional advantage of this approach is the potential to use different silyl groups to influence the geometric orientation of the enyne substituents in the hexa-substituted benzene ring for improved control of the coupling step(s). Palladium-catalyzed alkyne homocoupling reactions provide an alternative to the copper-mediated oxidations above for control of these reactions. For an experiment that may fail completely, a brave, risk-oriented co-worker is awaited.

8 Conclusion

I had no inkling when I synthesized my first useful acetylene compound three decades ago that this fascinating research area would become an obsession. Although I already knew, as illustrated by the material above, that...
organic chemistry would continue to provide both pleasure and pain. Fortunately, the former commodity arises in greater abundance. Indeed the love affair with organic chemistry that many of us share can be likened to a demanding chemical mistress who is always in our thoughts. Years ago I thought this was an original concept but C. Djerassi expressed the same idea in an interview last century! Indeed, few ideas are completely new, novel, and significant in one package. We all stand on the shoulders of our predecessors. Several essential ingredients are required for success in academic research. One requires funding but this is wasted if you are not privileged to have talented, dedicated students with a creative flare, and a willingness to work diligently. Their enthusiasm and insights have made this account possible.

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References

(1) I have taken Peter at his word and this account is not a comprehensive review but a personal journey through the forest of organic chemistry. I apologize for only passing credit to the chemical literature and the discoveries of others that made our work possible.


(4) I later learned that his wife apparently preferred the bustle and bright lights of London to the pastoral scholarly life of Cambridge!


(21) Canada has a strategic grant program to support research in collaboration with an industrial partner, provided there is applied potential that will benefit society.


(36) Universal Force Field (UFF) calculations were obtained using the Cerius®-Dmol® molecular modeling suite from Molecular Simulations Inc. San Diego, 1999. We thank S. Drouin and D. Fogg (University of Ottawa) for assistance.


(39) Clay, M. D. unpublished results.


(48) After submission of this manuscript for review, a current group member volunteered to examine this idea. The Grignard could not be generated from 81 with magnesium turnings, but with Reike® magnesium it acted as a base and the chloride was eliminated to generate the triple bond (Scheme 13); consequently, commencing with a halobenzene is more prudent.