

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

Alex G. Fallis*

Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, K1N 6N5, Canada

Fax +1(613)5625170; E-mail: afallis@science.uottawa.ca

Received 5 June 2004

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, Crepenynic Acid) were followed several years later with synthetically oriented projects. These involved enediyne mimics of natural products (Taxamycins) and unusual selenium dioxide oxidations of α -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 annulated 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, π -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 allenocyclophanes. A brief discussion of a π -extended boron–azulene complex is followed by a summary of magnesium-mediated carbometallations of propargyl alcohols. A final comment reexamines our cyclophane-based approach to buckminsterfullerene.

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Key words: enediyne, acetylene, palladium, copper, cyclophanes, propargyl alcohols, magnesium, C60

1 Acetylenic Natural Products (Wyerone, Crepenynic 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 stereocontrol 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 Crepenynic 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

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!

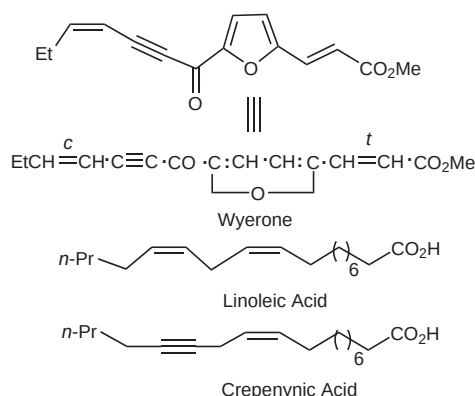


Figure 1

Wyerone is an antifungal acetylenic furanoid keto-ester isolated from the shoots of the broad bean (*Vicia faba* L, Fam. Papilionaceae).⁵ 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-linoleate-crepenynate cascade? For example, by what mechanism was linoleic acid converted to its dehydrogenated product, crepenynic acid [(9*Z*)-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.³

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



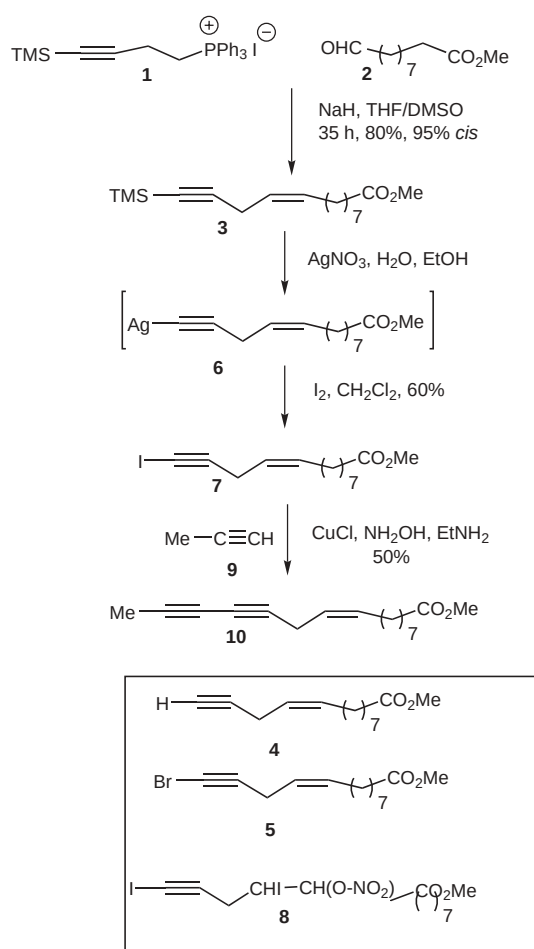
Alex G. Fallis was born in Toronto, Canada, and received his B.Sc. Hon. (1963), M.A. (1964) and Ph.D. (1967) degrees from the University of Toronto with the late Professor Peter Yates. After a National Research Council of Canada Postdoctoral Fellowship (now NSERC) at Oxford University with the late Professor Ewart R. H. Jones, he joined the Department of Chemistry at Memorial University of Newfoundland in 1969. In 1988 he was ap-

pointed Professor in the Department of Chemistry at the University of Ottawa and was Director of the Ottawa-Carleton Chemistry Institute from 1990–1993. He was a Visiting Professor at the California Institute of Technology (1977), the Institut 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-diyne 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 iodoacetylene Cadot–Chodkiewicz couplings had not been reported. It was assumed iodoacetylenes 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.⁸ 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 Enediynes (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.

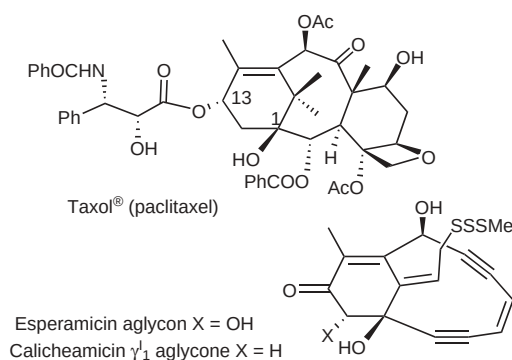
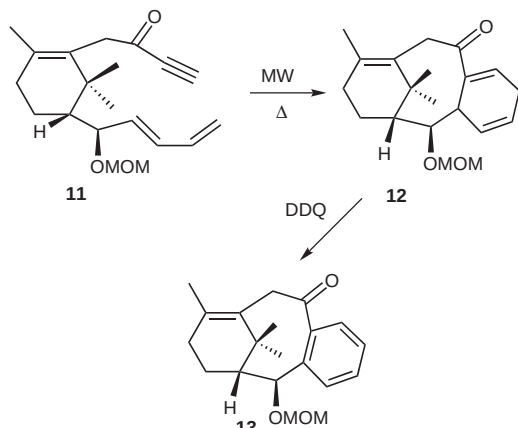


Figure 2

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 followed 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 cyclodecadienyne 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.

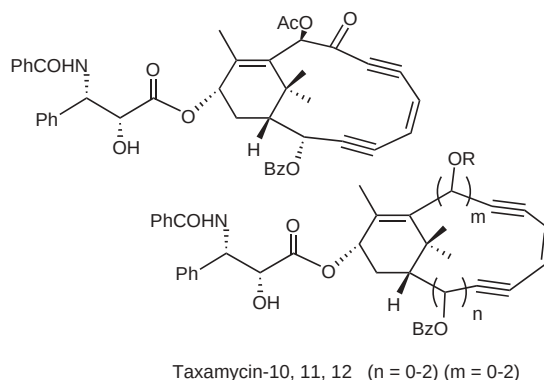


Figure 3

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.

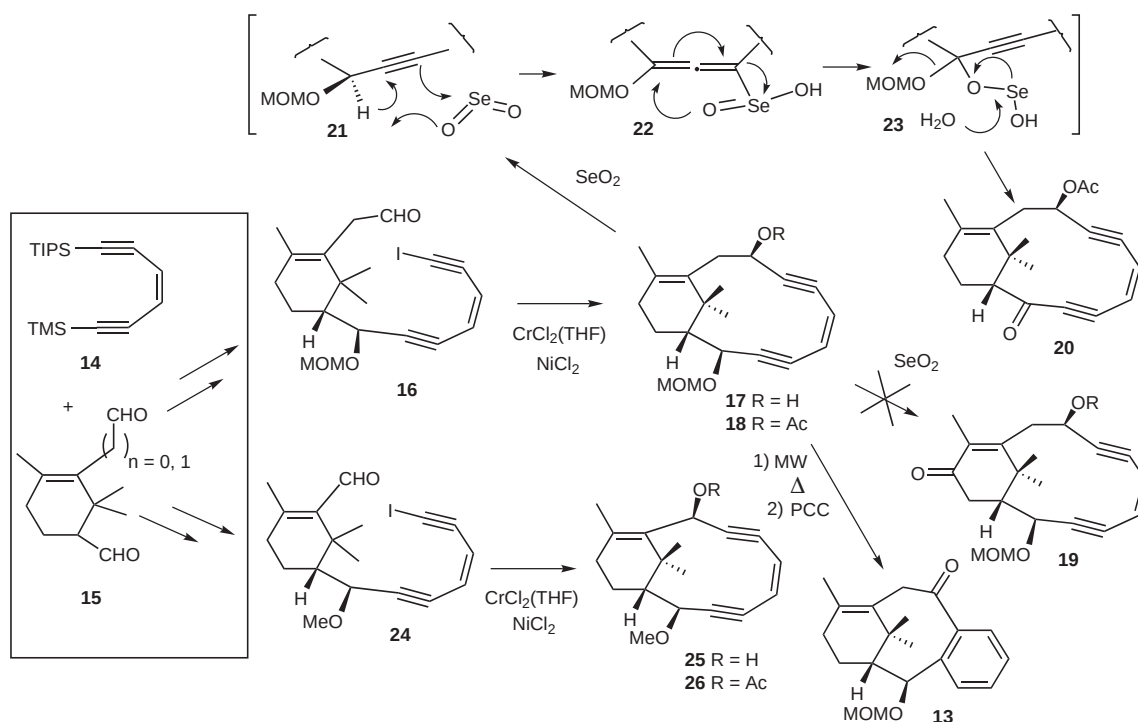
The cyclodecadienyne family (Scheme 4) was prepared by a parallel route to those above. Cyclization of **27** and allylic oxidation of the cyclized skeleton **28** with selenium dioxide afforded the *exo*-allylic alcohol (not illustrated) as a single diastereomer (60%). Subsequent treatment with pyridinium 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[®].

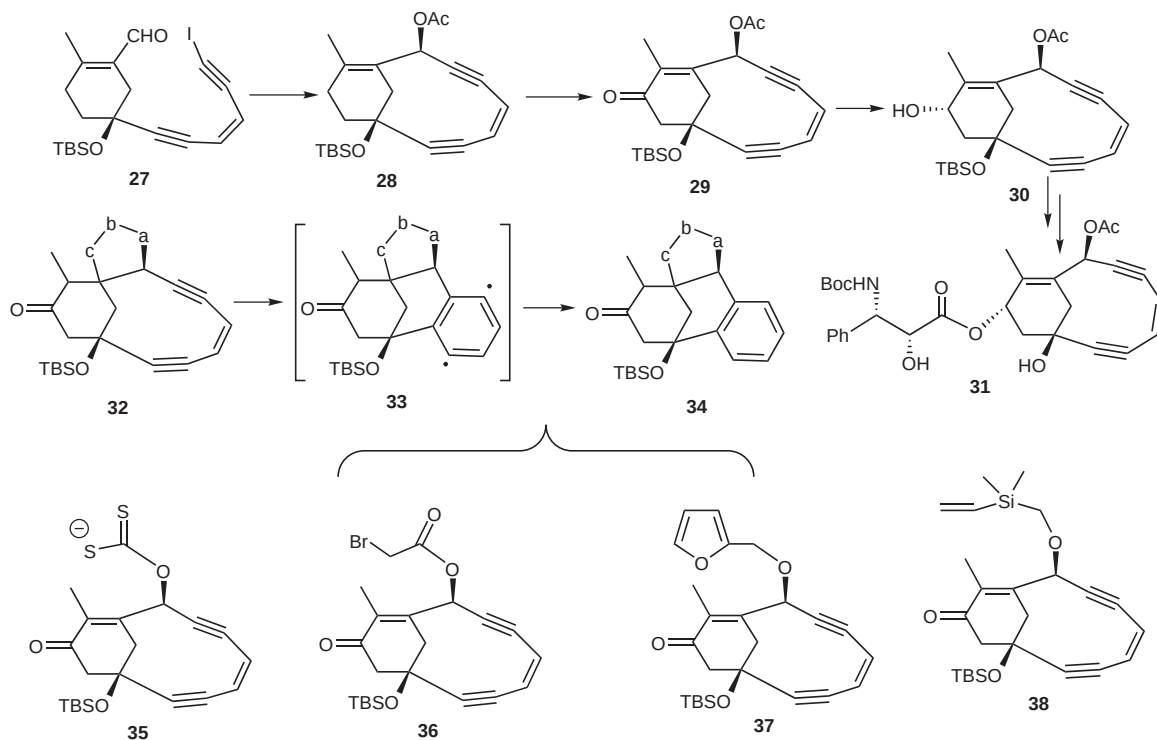
Undeterred, we turned our attention to the unsaturated ketone **29** in order to develop an aromatization trigger mechanism based on the analogy with the conjugate addition preformed so easily by intramolecular sulfide addition in nature. We had hoped that in a biological system glutathione might induce the Michael addition but **29** was inert to treatment with KSMc. 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 benzyne 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.

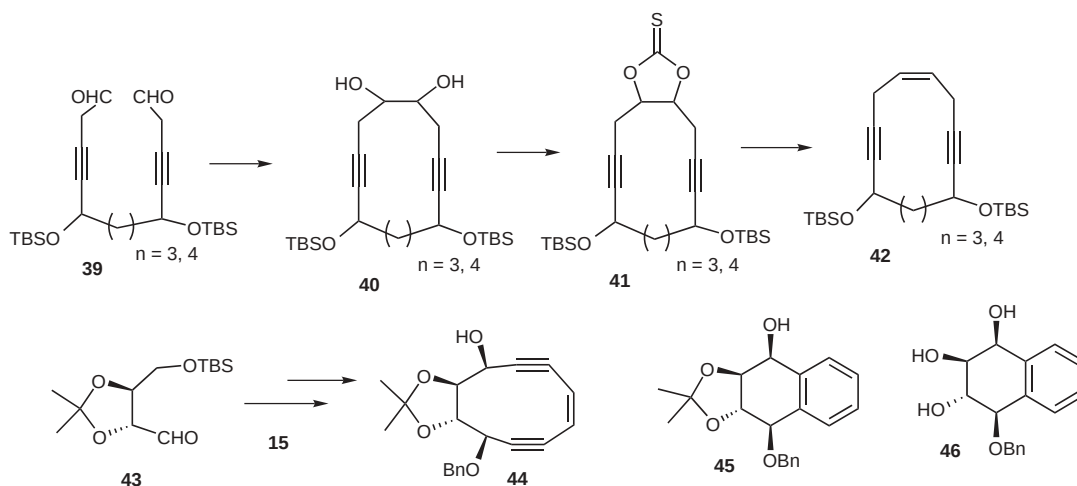
These results were certainly disappointing but we had not yet given up. A different preparation of 11- and 12-membered rings **42** was accomplished via an intramolecular pinacol coupling of the dialdehydes **39** to the diol **40** followed by thermolysis of the thiocarbonates **41** to complement the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





Scheme 4



Scheme 5

3 Acetylenic Cyclophanes

3.1 Revolvernynes

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 conver-

sation 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

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 Revolvynes.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.

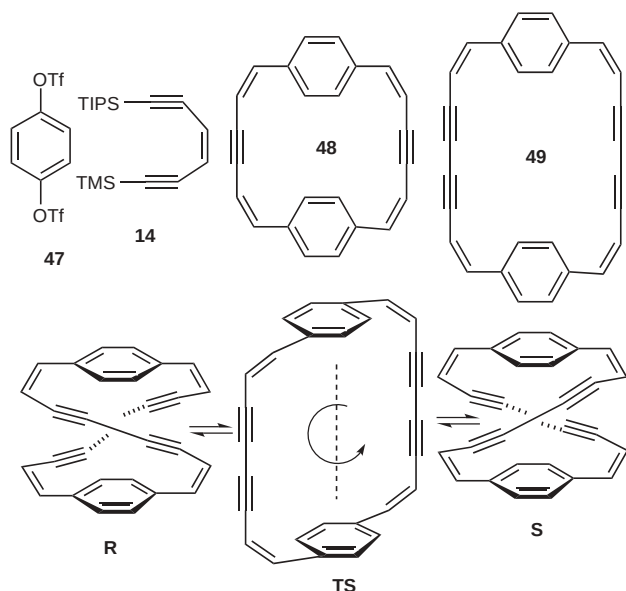


Figure 4

These cyclophanes are similar to related D_2 -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.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.

Design Criteria for Chiral Helical Cyclophanes

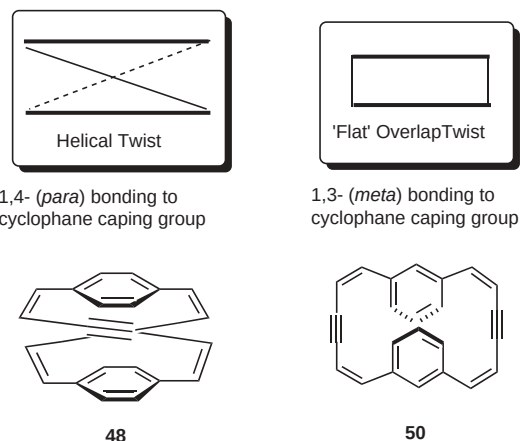


Figure 5

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 C60?

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 C60, 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

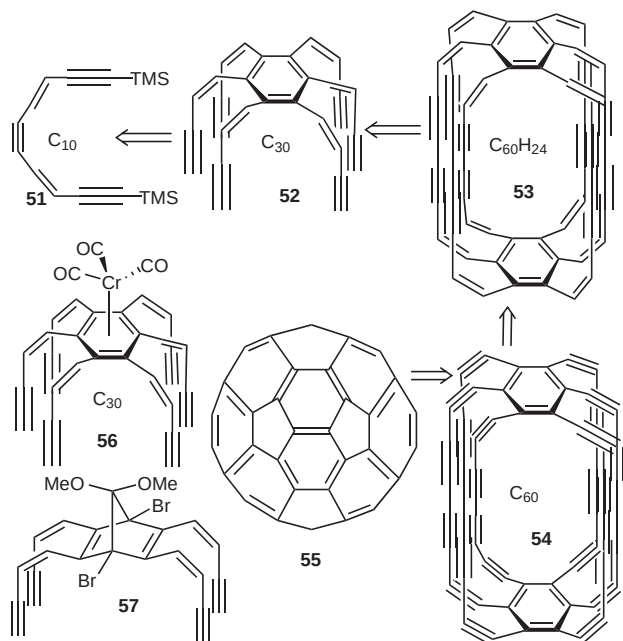


Figure 6

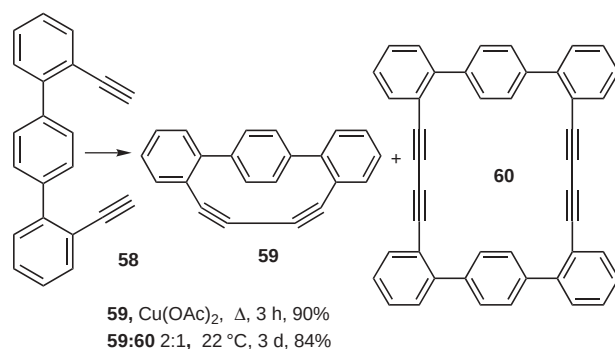
Unfortunately, **51** was unstable at temperatures above 40 °C and despite considerable effort to find mild conditions with various cobalt, nickel and palladium catalysts trimerization was not observed in acceptable yields. Other related precursors, which had the potential to orient the acetylene appendages 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 revolvynene 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



Scheme 6

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.

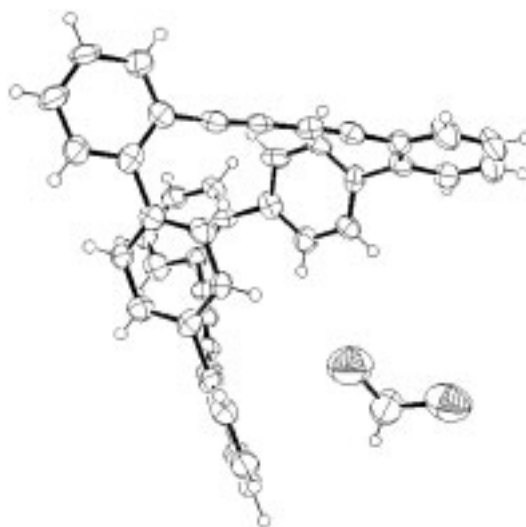
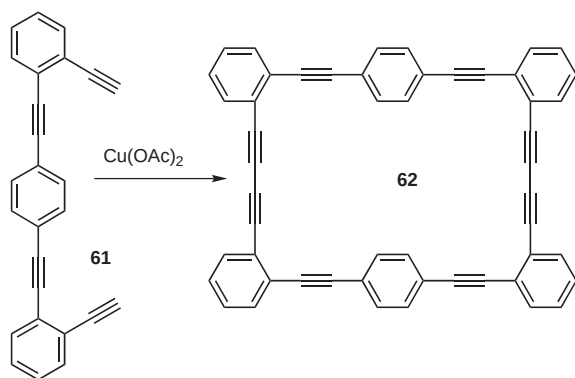


Figure 7

One afternoon in my office, after a further grant rejection, a student looked at our submission and reports. He was not overly discouraged like I, but rather displayed the confidence and determination we hope we can instill in all our co-workers. He declared ‘I am going to make us a liquid crystal’. I was delighted, as we could then prove our faith in these helical structures was warranted. The candidate D_2 -symmetric core structure **62** was selected and this cyclophane was synthesized from the dimerization of **61** (Scheme 7).



Scheme 7

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

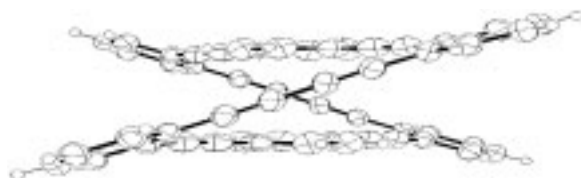
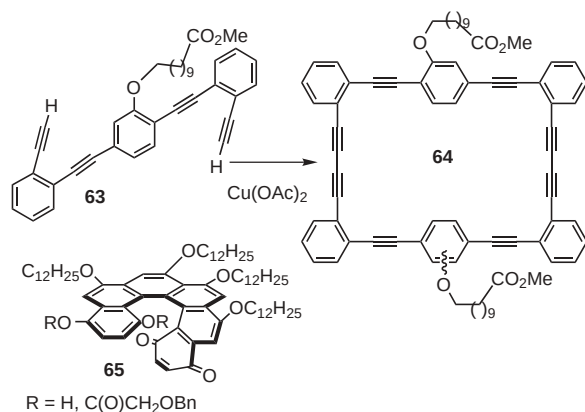


Figure 8

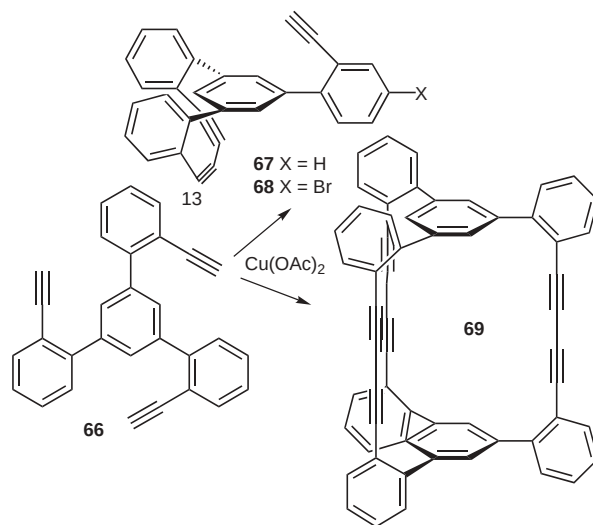
However, this was not the first liquid crystal compound with a novel helical core in which the aromatic core also provided the chirality. We were too tardy and Katz et al. constructed both racemic and chiral non-racemic heli-cenes ahead of us. These compounds **64** possessed long alkyl chains, which 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



Scheme 8

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'?

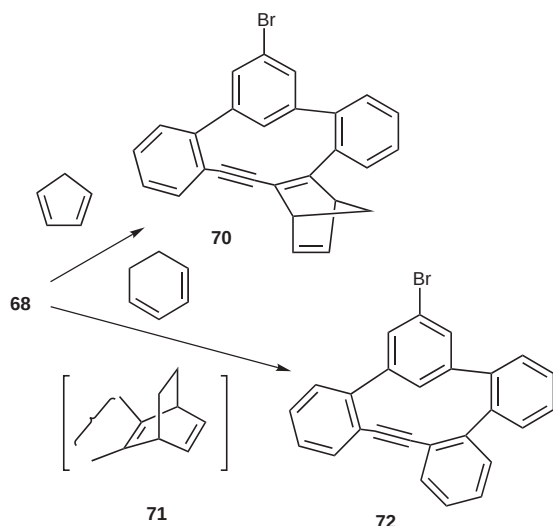


Scheme 9

There is considerable interest in strained cycloalkenes and bent polynes. 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.

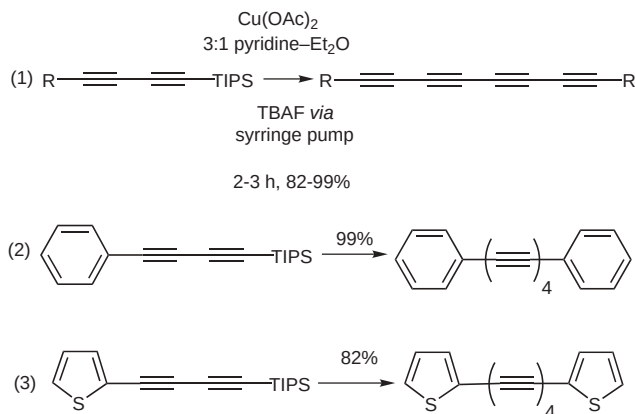
We speculated that the most strained triple bond should show enhanced reactivity. Not exactly a risky conjecture! In most circumstances, very reactive inverse demand dienes such as cyclopentadieneones are required to effect [4+2] cycloadditions with diphenylacetylene and 1,4-diphenyl-butadiynes. In the 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

(Scheme 10). 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 polyyenes are of interest for their electronic properties, spectra, and capacity to act as molecular wires. The most common synthetic method for the assembly of polyyenes involves bond formation between two acetylenes via oxidative coupling as exemplified above. The instability of some polyyenes 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 one pot 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

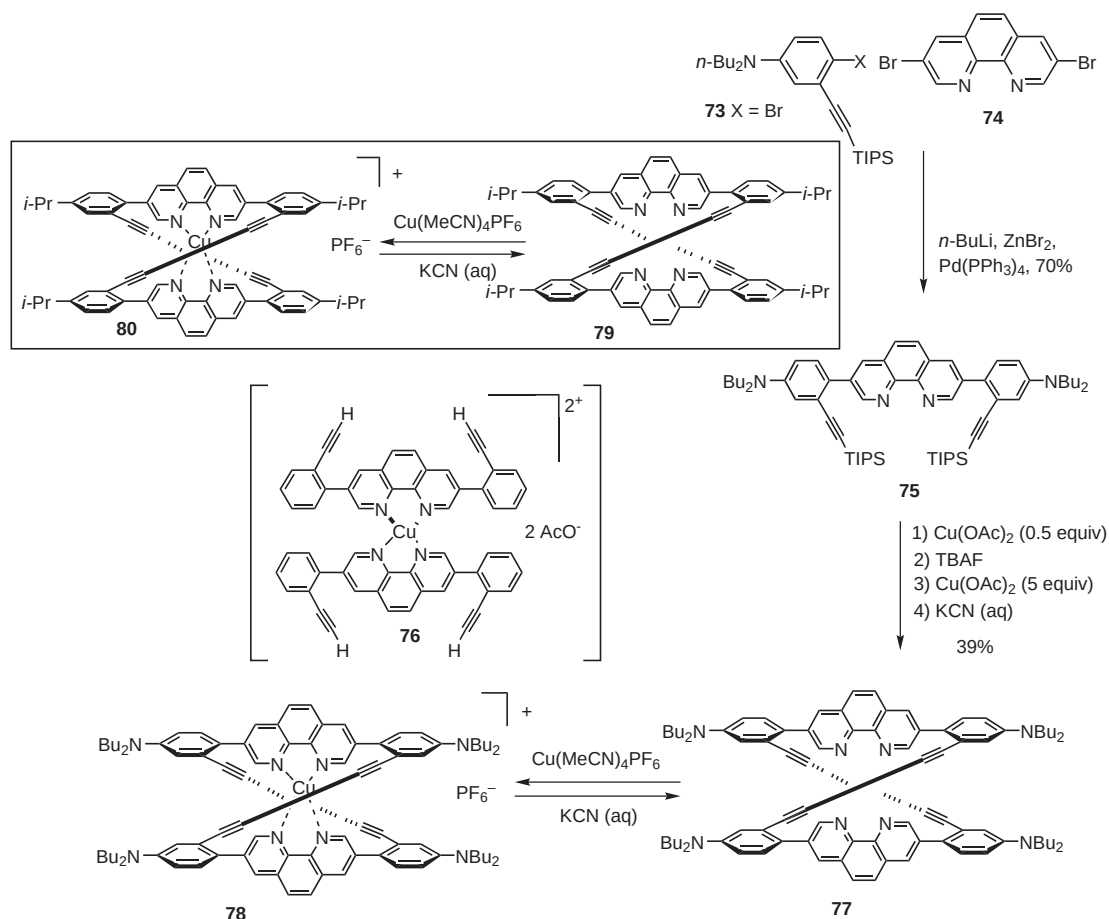
3.4 Heterocycles

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



Scheme 12

weight in palladium and platinum combined. Commencing the next day and through the Christmas holidays my co-author completed the synthesis of the isopropylphenanthroline cyclophanes **79** and **80**. The isopropyl 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, in-

cluding 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 tetrayne 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**)¹³ 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 tetrayne **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.³³

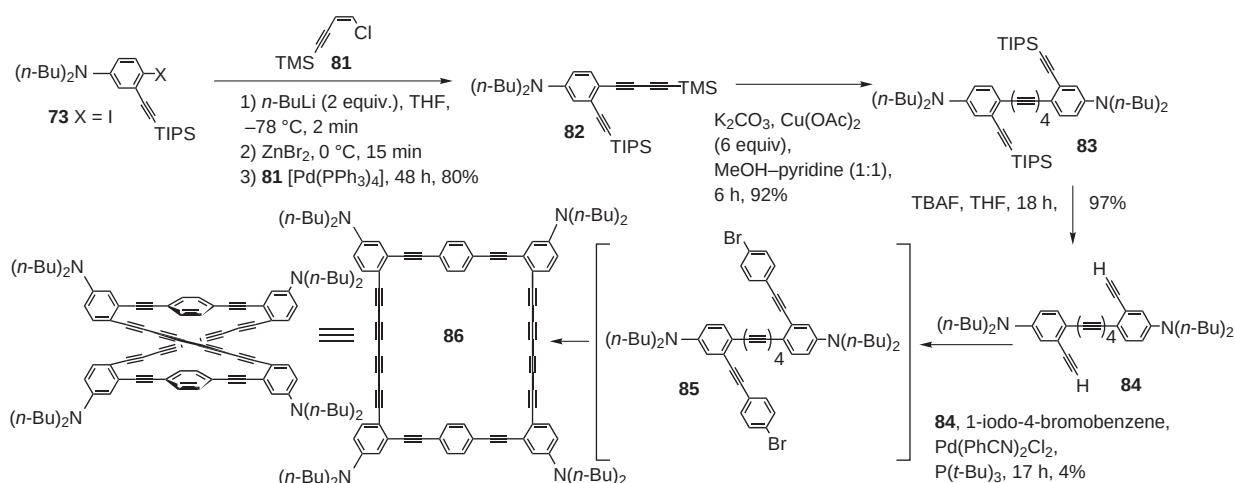
Proton and carbon NMR spectra plus molecular modeling revealed that **86** adopted a highly symmetrical C_2 -conformation in solution. In contrast to our experience with related cyclophanes above, cyclophane **86** was conformationally stable at room temperature. This is expected since isomerization 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.

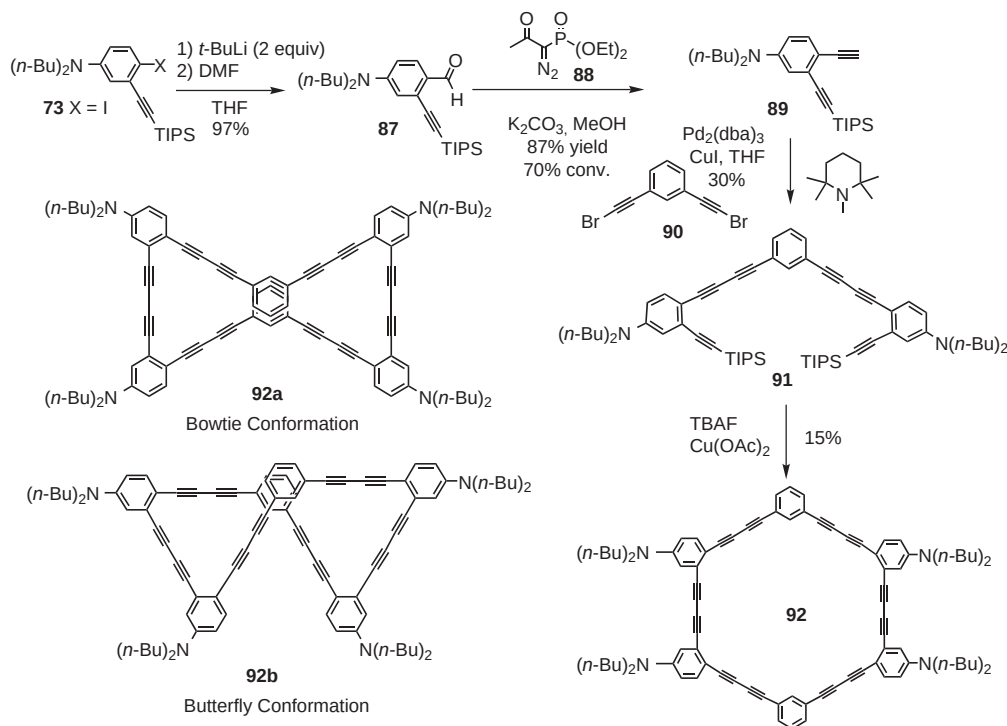
Consequently, the dimerization strategy towards **92** was particularly attractive as the termini separation was approximately 13.7 Å. This cyclophane was synthesized by our established dimerization protocol (Scheme 14). Unfortunately, iodide **73** ($X = I$) failed to undergo a direct Sonogashira coupling 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 reagent³⁴ **88** and K_2CO_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** required 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 cy-

clophane **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 isomeric 'bowtie-like' and 'butterfly-like' structures, **92a** and **92b**, respectively. Cyclophane conformer **92a** possessed C_{2h} -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.³⁵ 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.



Scheme 13



Scheme 14

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 performed³⁶ on substrates from our own laboratory and one example from the literature.²² A ND basis set was used to find the lowest energy conformation of the dimerization precursors (minimized structures constitute a large data set thus simplified 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.³⁷ 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.³⁸ 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.³⁹

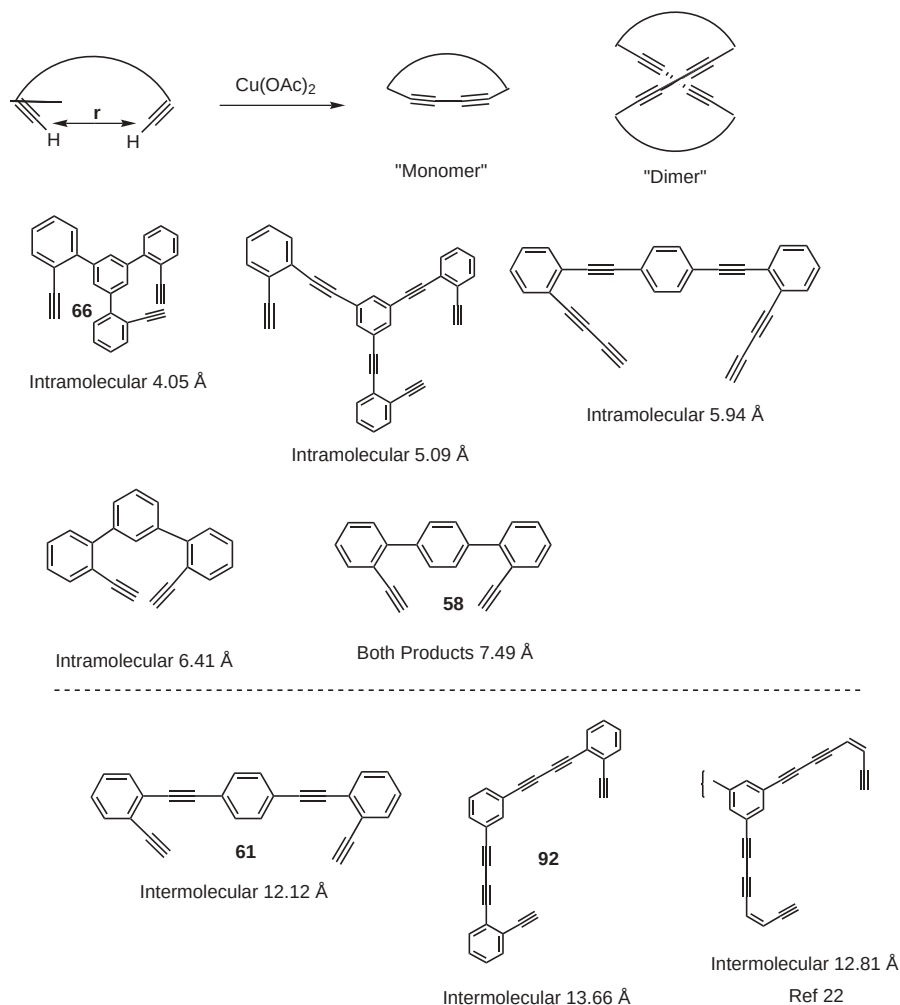
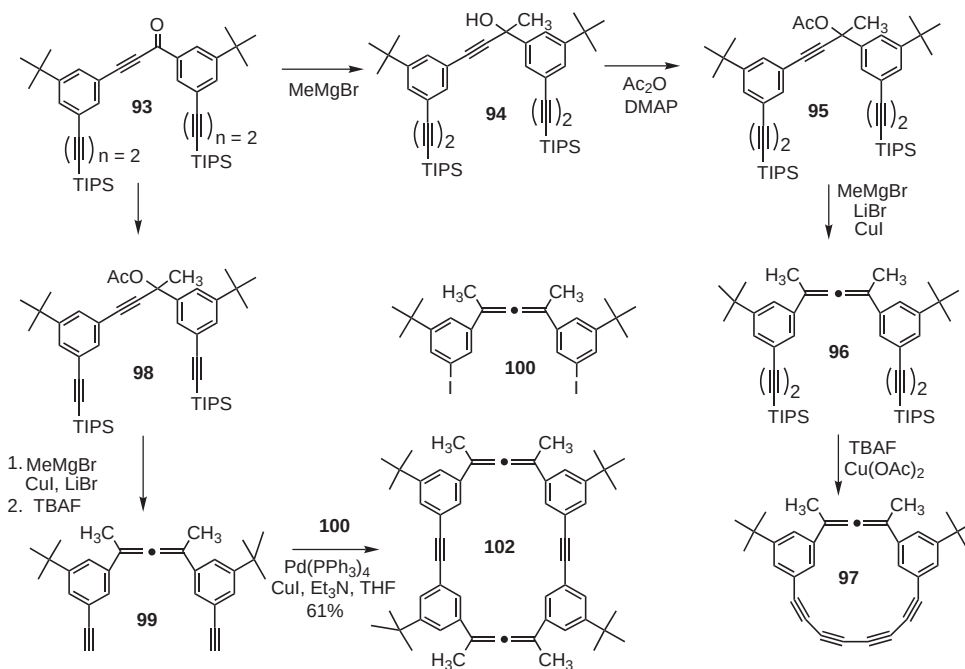


Figure 9



Scheme 15

5 π -Conjugated Boranes

There is growing interest in a new class of highly fluorescent, extended π -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 π -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 π -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. *Tris*(azulethynyl)duryl)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 λ_{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 λ_{max} 367 nm and fluorescence at λ_{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

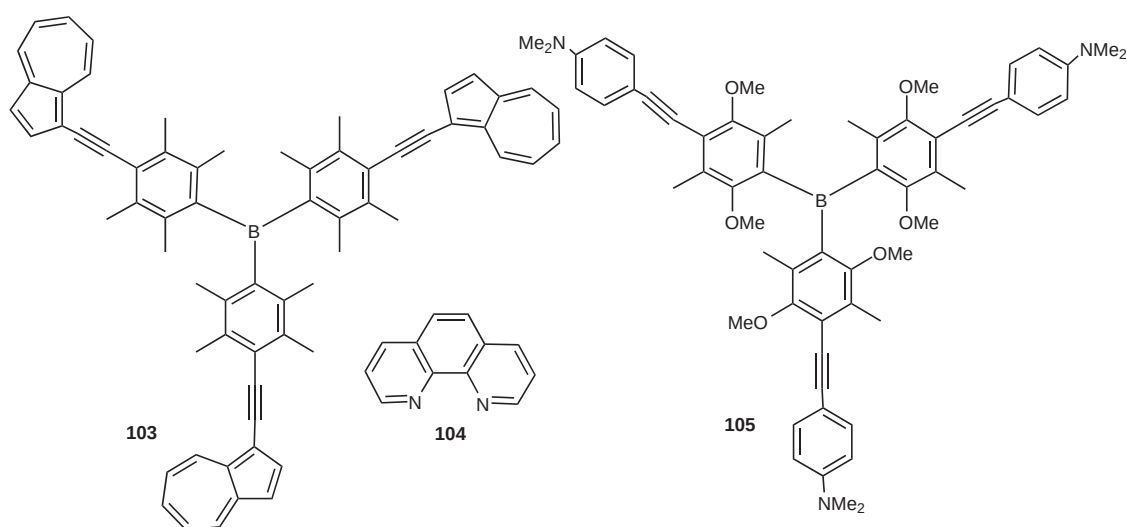
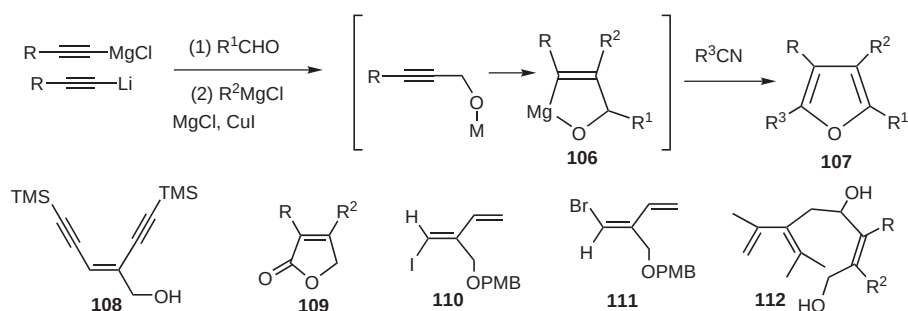


Figure 10

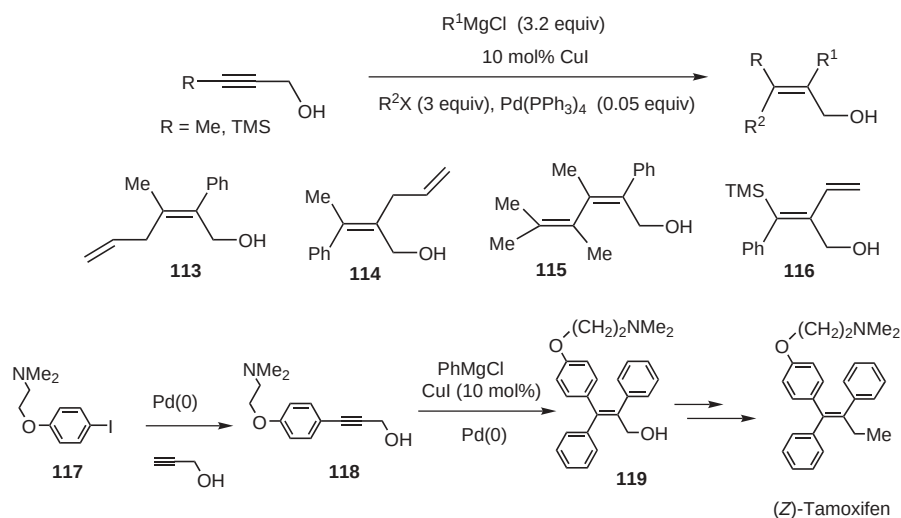
via the magnesium chelate **106** illustrated in Scheme 16. In addition, to furans, endiynes **108**, butenolides **109**, halodienes **110** and **111**, and taxoid intermediates **112** can be prepared by this protocol. Recently, this chemistry has been extended to a versatile procedure for the regio- 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

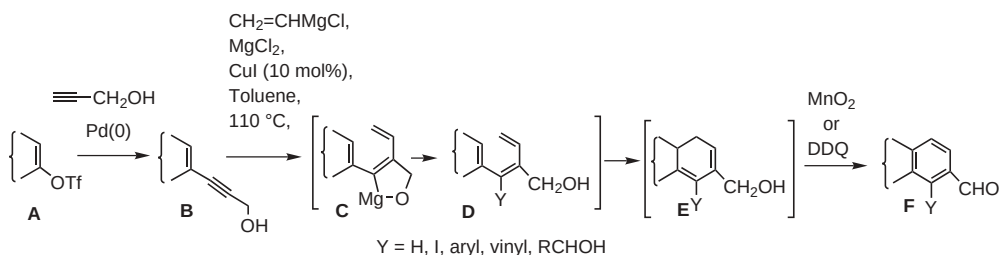
We are currently developing a new annulation procedure to attach substituted benzene rings to cyclic ketones (Scheme 18). We intend to apply this protocol to a variety of interrelated objectives. This method employs a vinyl triflate **A** (or halide) which is coupled in the presence of palladium(0) with 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.



Scheme 16



Scheme 17



Scheme 18

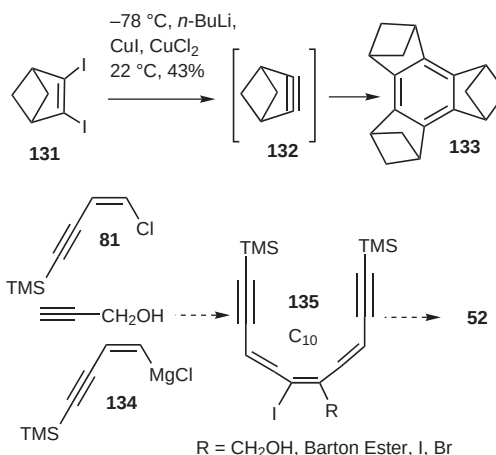
This protocol was used to convert (+)-camphor (**120**) into its triflate **121**, palladium-mediated coupling with the propargyl alcohol to form **122**, and then via chelate **123** to various compounds (Scheme 19).⁴⁵ Quenching with boron trimethyletherate and treatment with DDQ afforded **130** whose properties as a chiral Lewis acid will be investigated. In a similar fashion **125** 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.⁴⁶ 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** ($\text{R} = \text{CH}_2\text{OH}$). 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**, $\text{R} = \text{I}$ 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).

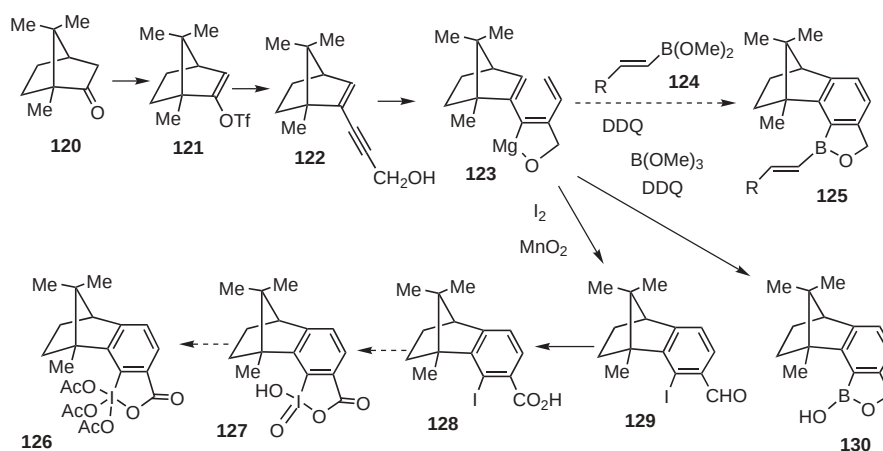


Scheme 20

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.⁴⁷ For an experiment that may fail completely, a brave, risk-oriented co-worker is awaited!⁴⁸

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



Scheme 19

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.

Acknowledgment

The majority of my financial support has come from the various programs administered by NSERC (Natural Sciences and Research Council of Canada). Their Discovery Grants, as the name implies, allows one to follow one's nose and deviate from the proposed research when something more significant attracts your attention. The research above is a direct consequence of this freedom. However, we have also benefited from collaboration with industry on topics with applied potential and it is a pleasure to acknowledge funding from the following companies: Merck-Frosst, Rhone-Poulenc Rorer (now Adventis), Torcan (now Avecia), BioChem Pharma (now Shire) and Aegera (formerly Apoptogen) for diverse projects. These interactions have enriched my chemical life and also provided careers for my collaborators.

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- (48) After submission of this manuscript for review, a current group member volunteered to examine this idea. The Grignard **134** 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.