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Treasures old and new: what we can learn regarding the macrocyclic problem from past and present efforts in natural product total synthesis

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In this review the strategies leading to successful macrocyclization, in the context of total synthesis are discussed. These synthetic endeavors will be discussed paying particular attention to the methods employed, and including the type of reactive intermediates that could play a key role in key cyclization steps. In many cases "simple" macrocyclization methods were found to be inadequate, and alternative creative approaches were required. For example, we describe Boger's imaginative development of the intramolecular version of the Larock annulation which yielded the chloropeptin 1 DEF macrocycle. Peptide coupling approaches were unsuccessful. In another example, a key macrocyclic domain within diazonamide was beautifully installed (Nicolaou, *et al.*) by single electron oxidation/reduction (Witkop reaction), thereby establishing a crucial biaryl functionality. In contrast, oxidative methodologies failed to deliver the distorted biaryl found in haouamine, and Baran, *et al.* subsequently exploited a spectacular pyrone *N*-butyne intramolecular Diels–Alder reaction to install this biaryl moiety. Other unexpected and mechanistically intriguing observations will be described throughout the review.

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1. Introduction

The construction of macrocycles can present formidable synthetic challenges. The improvement in cyclisation efficiency at the expense of intermolecular reactions is a crucial goal in macrocyclisations that was tackled traditionally by high dilution and/or slow addition of one or more reagents. In the process of macrocyclization, the entropic consequences of ring/chain equilibrium must be carefully considered. Where the transformation involves a macrocyclization catalyst, selecting reaction conditions that facilitate separation of the catalyst from the substrate is an important consideration. Recently James and co-workers[1] have employed the parameter Emac (efficiency of macrocyclization) where the relationship between calculated and experimentally determined yields can be exploited to compare different macrocyclization protocols. Another area of study that is becoming more important in the synthesis of macrocyclic peptides is the concept of pre-organization, described by Yudin, *et al.*,[1] in which hydrogen bonding in linear precursors prior to or even during macrocyclization[1,2] plays a critical role. This review examines several total syntheses with a view to describing the particular reactions by which the macrocyclic entity was constructed (or the key ring closure realized). Even rates of addition can have profound effects on macrocyclization outcomes. For example, in the course of this synthesis of bielschowsky model systems, Nicolaou found that when specific furan ketoester precursors where exposed to ceric ammonium nitrate, introduced by syringe addition at 0 °C, intramolecular cyclisation occurred, but if the reagent was added in one portion at 0 °C, intermolecular reactions occurred, followed by macrocyclisation resulting in even large macrocycles.

Macrocyclic entities have increased in importance due to recorded anticancer, antifungal and immunosuppressive activities and because more than 100 marketed macrocyclic drugs isolated from natural products are known.[3–6] The diversity-oriented synthesis of natural product-based libraries as part of drug discovery programmes has increased the focus on macrocycles in part because the conformational restriction inherent in macrocyclic structures seems to enhance binding affinity[6–8] and bioavailability when compared to drug like molecules of more "conventional" structure.[9]

In the 1970's and in more recent developments,[10,11] the highly original methodology exploiting, for example, 2,2-dipyridyl disulphide by Corey and Nicolaou, subsequently named after these inventors, solved several macrolactonisation problems in circumstances where other macrolactonisation

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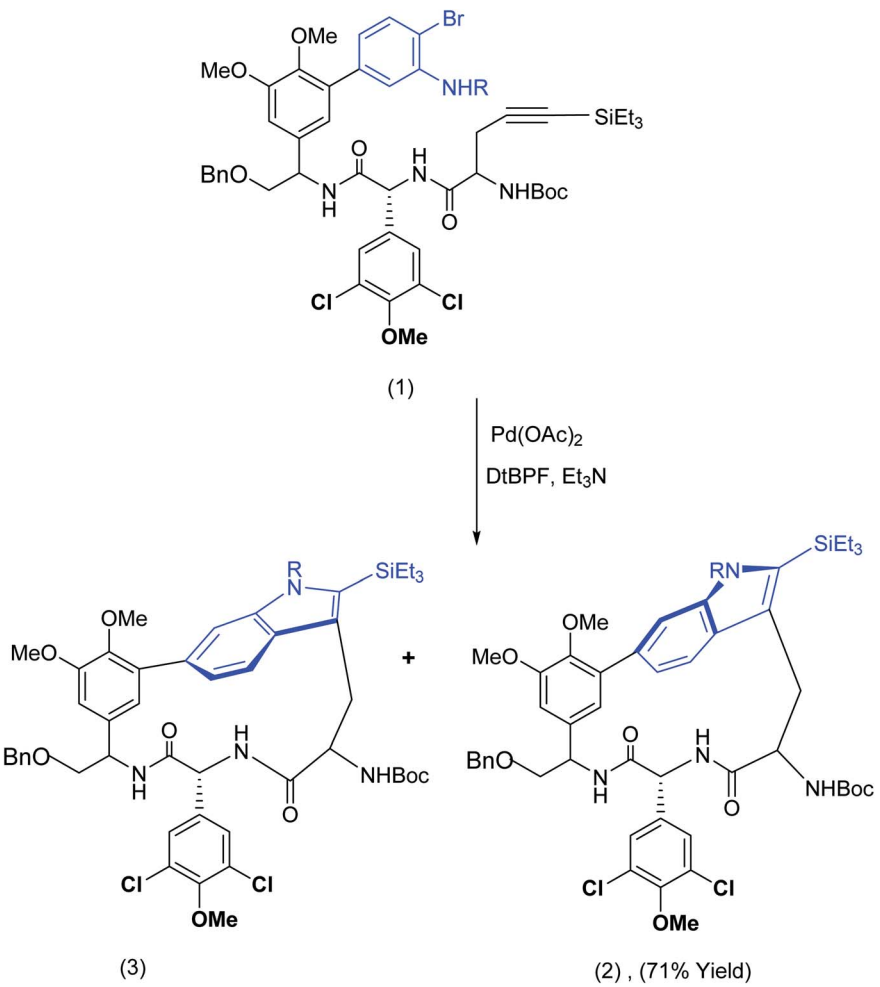
protocols failed.[12–14] On the other hand, conventional methods, *e.g.* intramolecular amide construction (peptide coupling), may fail rather unexpectedly in certain situations. For example, during Boger's synthesis of the chloropeptin 1 DEF macrocycle,[15] he discovered that conventional peptide coupling (and free radical protocols) were unsuccessful. The macrocyclization problem was solved by an imaginative exploitation of Larock annulation (Scheme 1). The intriguing observation that free radical protocols failed to deliver the macrocycles that were the target of Boger's investigations raises the question as to whether radical cation protocols might offer unique advantages (*vide infra*). The macrocyclic Larock annulation[16] described by Boger proceeded with good atropodiastereoselectivity and rivals in efficiency the better known Stille[17] and Suzuki[18,19] cross-coupling reactions. In this process, oxidative insertion, palladium ligand exchange, carbopalladation *etc.* are key mechanistic events.[20] For selected papers related to the original Larock annulation the following papers should be consulted Larock,[21–24] Cacchi,[25,26] Gribble[27] and Poli.[28]

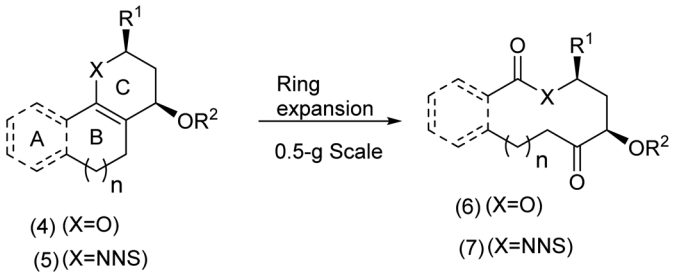
In the first part of this review, although we examine an interesting oxidative cleavage process, we wish to highlight mainly electron transfer processes involving oxidative and/or reductive protocols. At specific points we will include carbon centred radical protocols exemplified by the use of tributyltin hydride for comparison. Although such examples will be presented as possible alternatives to intramolecular peptide coupling, lactamisation and lactonization methods, these latter methods will be discussed in situations where the use of these "more conventional" methods has been singularly instructive and efficient. In the second part, we will attempt to examine other strategies for macrocyclic construction more broadly. This will include exploitation of the Tsuji–Trost reaction, Rh(III) catalyzed processes, HATU catalyzed macrolactamisation, Witkop processes and imaginative applications of the intramolecular Diels Alder reaction to list only a few examples. Occasionally, we include a few non – macrocyclic syntheses where these have a bearing on mechanistic questions (for example the chemistry in Scheme 14).

1.1. Macrocycles accessed by means of ring cleavage/expansion protocols

Tan *et al.*[9] has developed an approach in which polycyclic enol ethers and enamines were exposed to $RuCl_3$ and $NaIO_4$. The process resulting in novel macrocycles is illustrated in Scheme 2.



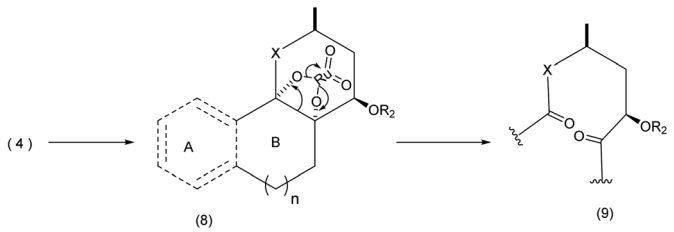
Scheme 1 Efficient macrocyclisation achieved by the Larock annulation.[15]



Scheme 2 Tan's oxidative ring cleavage expansion approach.[29]

For certain substrates, oxone based systems proved very effective. The mechanism most likely involves a cyclic ruthenium complex (Scheme 3).[30]

This method implies a creative alternative to macrocyclic lactonization and lactamisation approaches. For further examples of ring expansion reactions creatively applied to the macrocyclic problem, including non-oxidative variants, the review by Unsworth is highly informative and thought provoking.[31] Having examined an oxidation cleavage process exemplified by the Tan chemistry, we now turn to a single electron transfer oxidative cyclisation developed by the Nicolaou group[32] during their investigation of the synthesis of complex furanocembranoids.



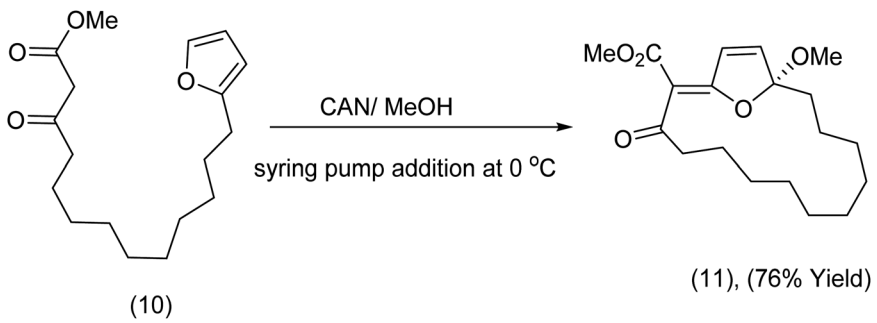
Scheme 3 The oxidative cleavage-ring expansion mechanism.[9]

1.2. Exploitation of CAN (ceric ammonium nitrate) promoted single electron oxidation in macrocyclic synthesis

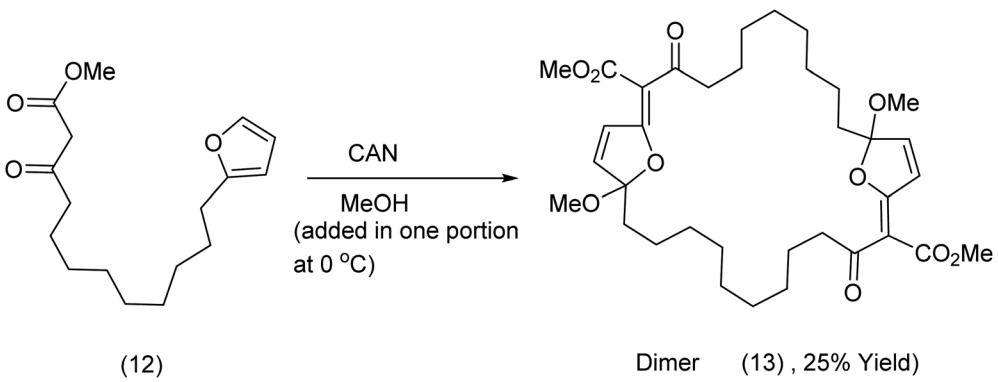
The furanocembranoids are marine diterpenoids possessing a C_{14} cembrane skeleton. Examples of such structures are found in the publications of Baran,[33] Rodriguez[34] and Stonik.[35] In the course of synthetic studies related to the bielschowskysin model system, Nicolaou *et al.*, discovered that when furans tethered to β-ketoesters are exposed to ceric ammonium nitrate, oxidation of the active methylene gave rise to radicals that subsequently attacked the furan moiety. For example, substrate (**10**) produced (**11**) when exposed to CAN (Scheme 4).

In contrast to methods yielding the monomeric product (**11**), the addition of the reagent to the substrate at a concentration of 0.05 M produced the dimeric product (**13**). Addition of the reagent in one portion at 0 °C was crucial to a successful outcome (Scheme 5).

A typical example of this methodological differentiation is shown below:



Scheme 4 Exploitation of tethered β-ketoesters and furans in macrocyclic synthesis.[36]



Scheme 5 A 27 membered macrocycle produced by CAN oxidation of a tethered furan/ester.[32]

The Nicolaou group[32,33,36,37] described several examples of macrocycles exemplified by (**11**) and (**13**) prepared in good to excellent yields. It is interesting to note that other reagents were tried by Nicolaou *et al.*, such as manganese(III), iron(III) and cobalt(II) complexes but the results were disappointing. It may be that the furan ring is not an efficient acceptor of the radical under these conditions. The "hardness" or "softness" of the radical may well depend of the oxidizing agent employed. Nicolaou[38] proposed the following mechanism for the transformations in (Schemes 4 and 6).

In is interesting to observe that α-methylene radicals generated by means of $Mn(OAc)_3$ are efficiently trapped by indole rings as Kerr *et al.*[39] has demonstrated (Scheme 7), although macrocycles were not the intended targets.

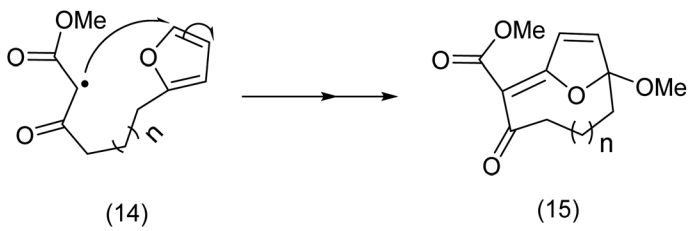
Nishino *et al.*[40] has developed a macrocyclization procedure that exploits tethered bis ketoesters and tethered terminal alkenes which react in the presence of $Mn(OAc)_3$/AcOH at 100 °C in an argon atmosphere (Scheme 8). Remarkably this was an intermolecular process with a spectacular outcome. For further examples and applications of related chemistry from the Nishino group (see ref. 41–51).

From a mechanistic standpoint, a ketoenolate Mn^{III} complex ((**23**) Scheme 9) is formed by reaction of the $Mn(OAc)_3$ with the keto ester moiety. The complex breaks down to yield the methylene radical (**24**) which then attacks the olefin to yield doubly stabilized radical. We have previously invoked such Mn^{III} keto enolates to explain the regioselective lactonization of stilbenes appropriately substituted.[52]

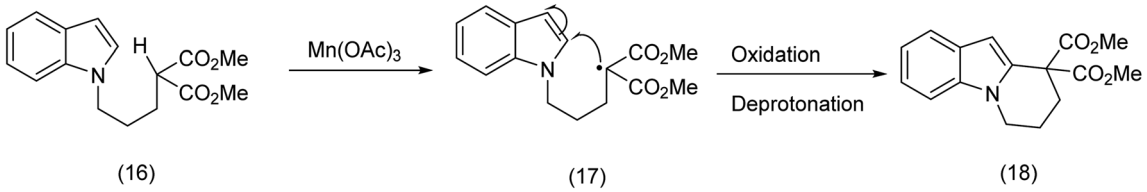
For articles related to manganese triacetate promoted reactions more generally, the reviews by Snider[53–59] should be consulted.

1.3. Reductive radical generation protocols for macrocyclic construction

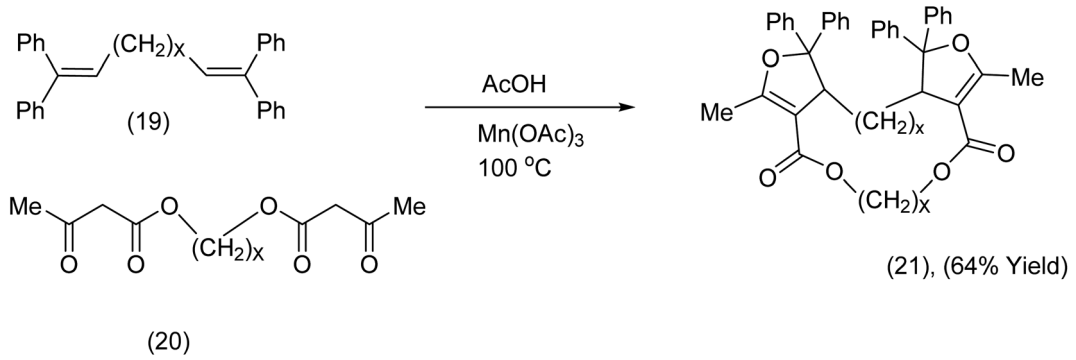
In contrast to the addition of oxidatively generated radicals to furans as a creative entry to macrocycles (see the Nicolaou chemistry (Scheme 4)), we now turn to reductive generation of the radical and its synthetic utility. The Pattenden group[60] had for a number of years studied radical mediated macrocyclisation–transannulation.[61–64] Later they reported the addition of vinylic radicals to furans resulting in a cascade culminating in the tetracyclic diketone (**33**) (Scheme 10). It is



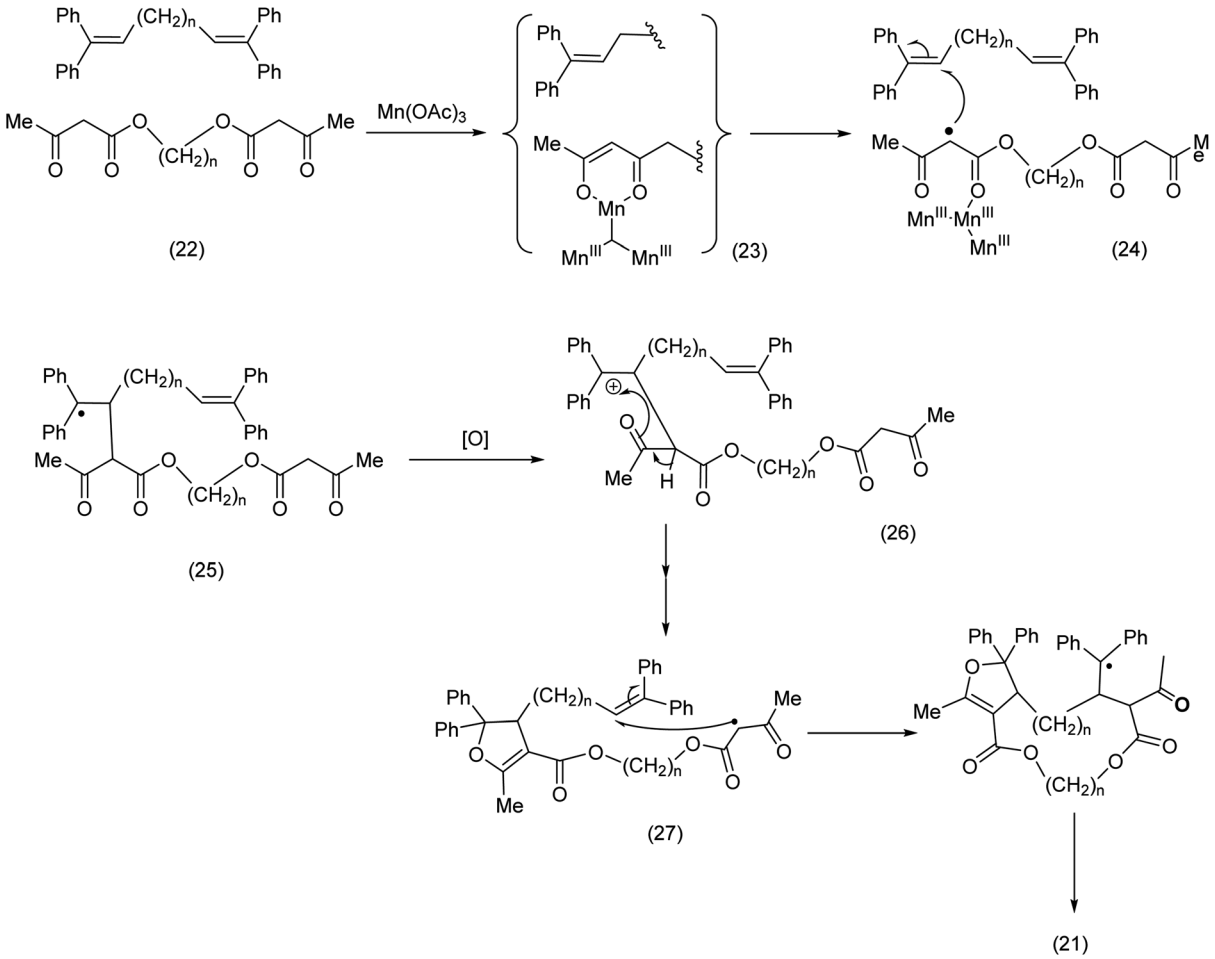
Scheme 6 Furan trapping of a doubly activated carbon radical.[37]



Scheme 7 Indole trapping of a beta ketoester (malonyl) – carbon radical.[39]

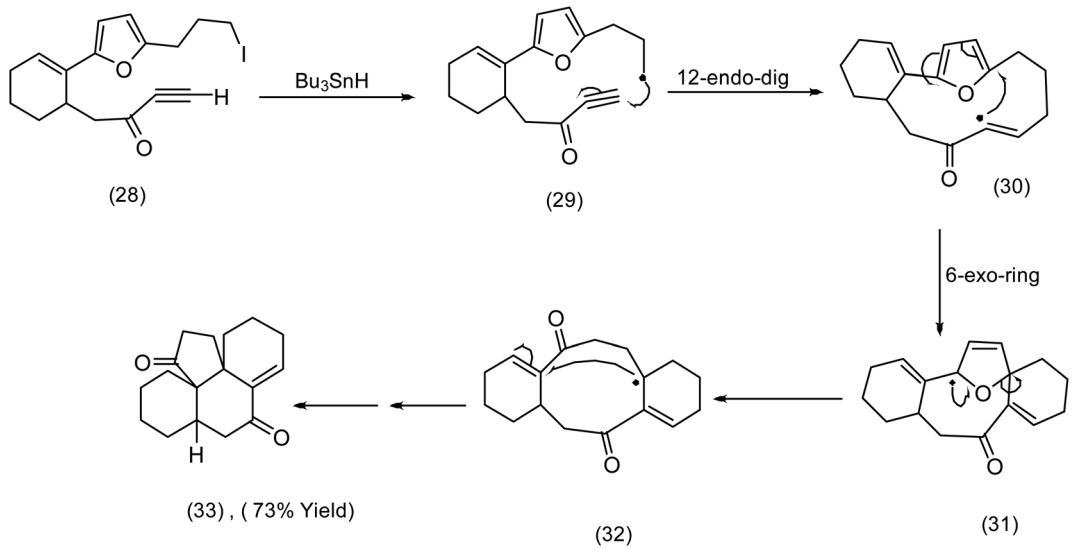


Scheme 8 Manganese triacetate promoted of a bisdihydrofuran-diester macrocycle.[46]

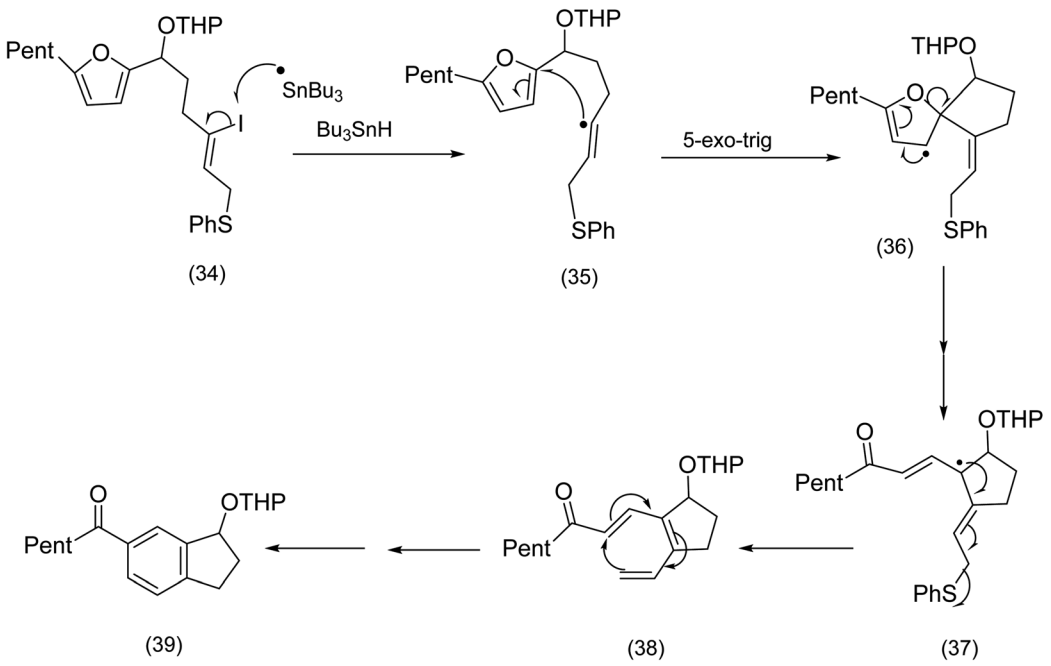


Scheme 9 Intermolecular trapping in the course of an active methylene radical-pathway.[51]

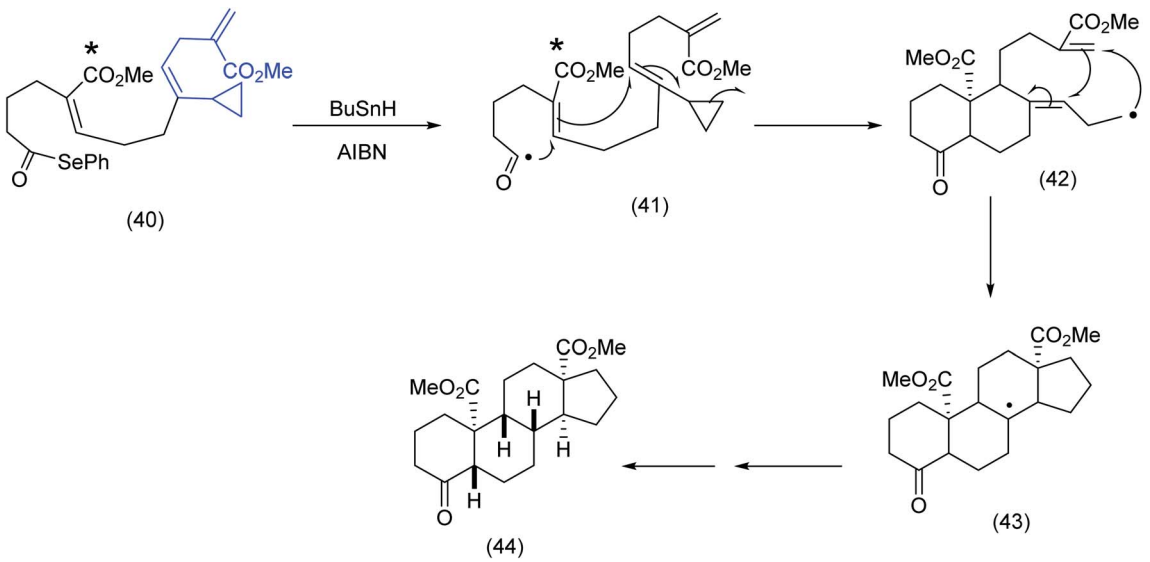
instructive to compare this sequence with Parson's furan iodovinyl to indole construction (Scheme 11), in which vinyl radical addition to the furan resulted in a spirodihydrofuran (compare (**36**) Scheme 11 with (**31**) Scheme 10) electrocyclic cascade. Although Parson's chemistry was not directed at macrocyclisation, it is nonetheless mechanistically significant.



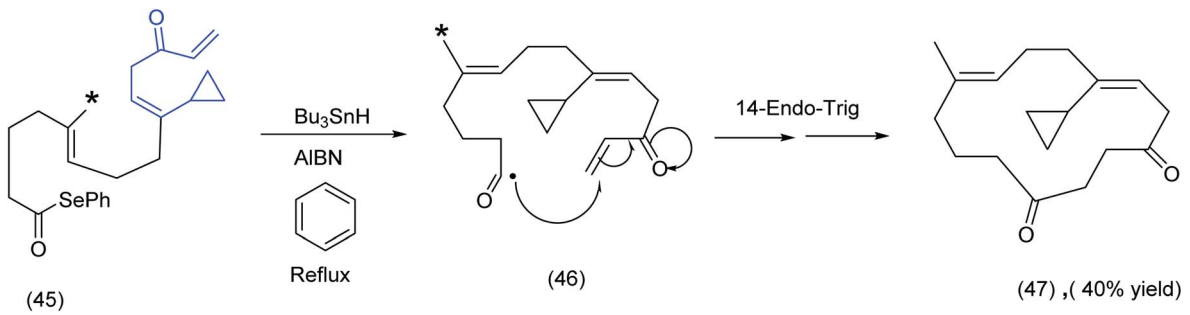
Scheme 10 Pattenden's elegant reductive radical generation – cascade cyclisation.[64]



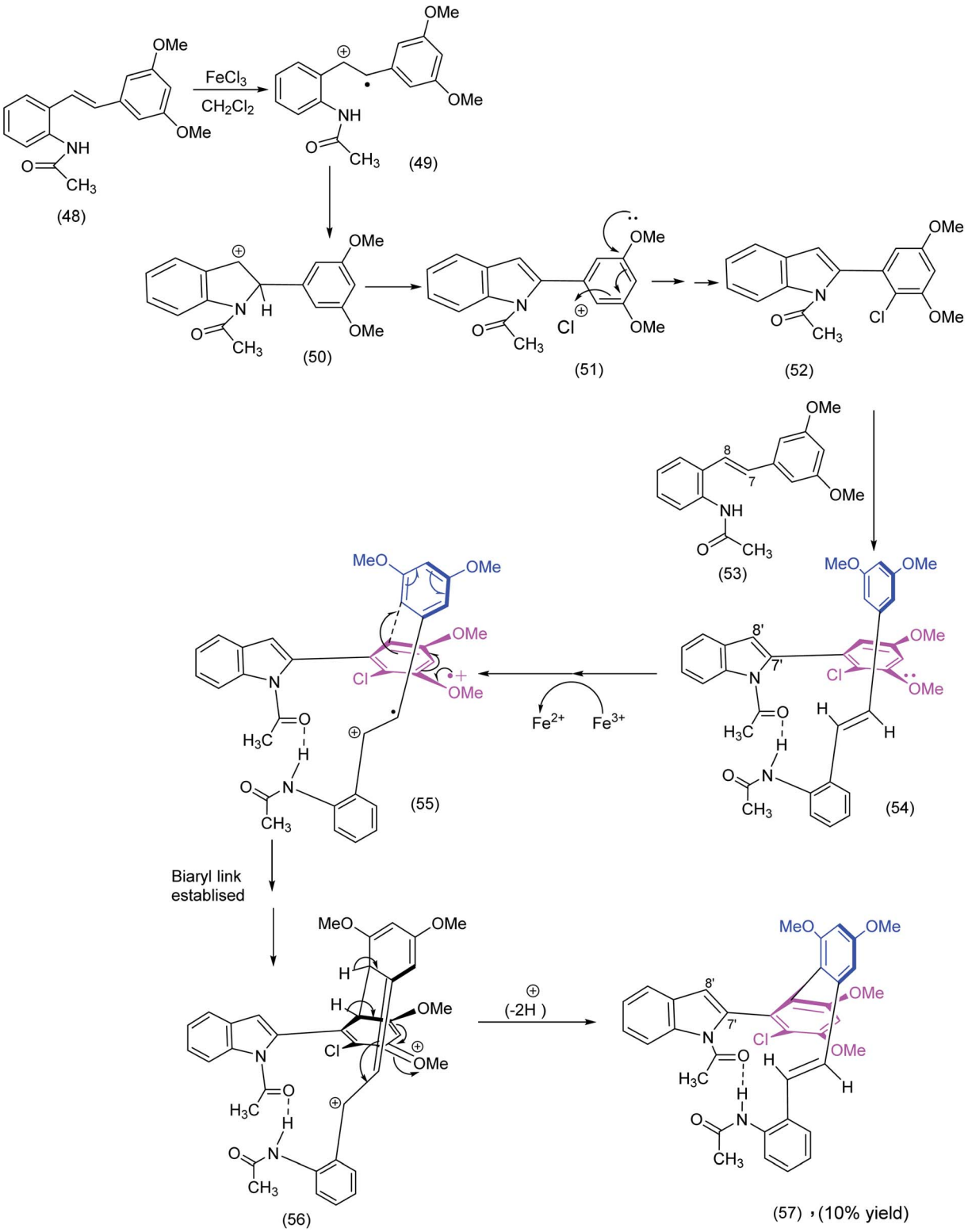
Scheme 11 Parson's reductive radical generation/cyclisation (non – macrocyclic)[64]



Scheme 12 Radical cascade differentiation: acyl radicals to steroids.[64]



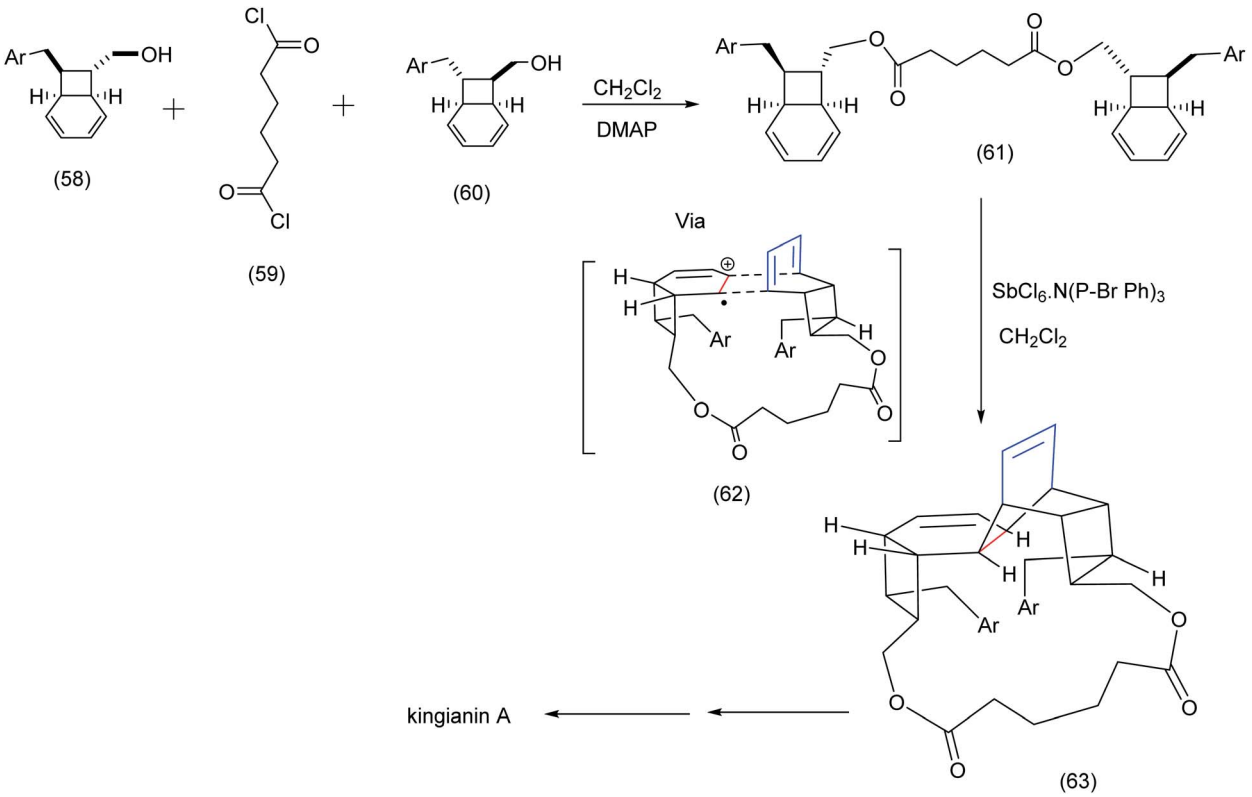
Scheme 13 Radical cascade differentiation: acyl radicals to macrocyclic diketones.[65]



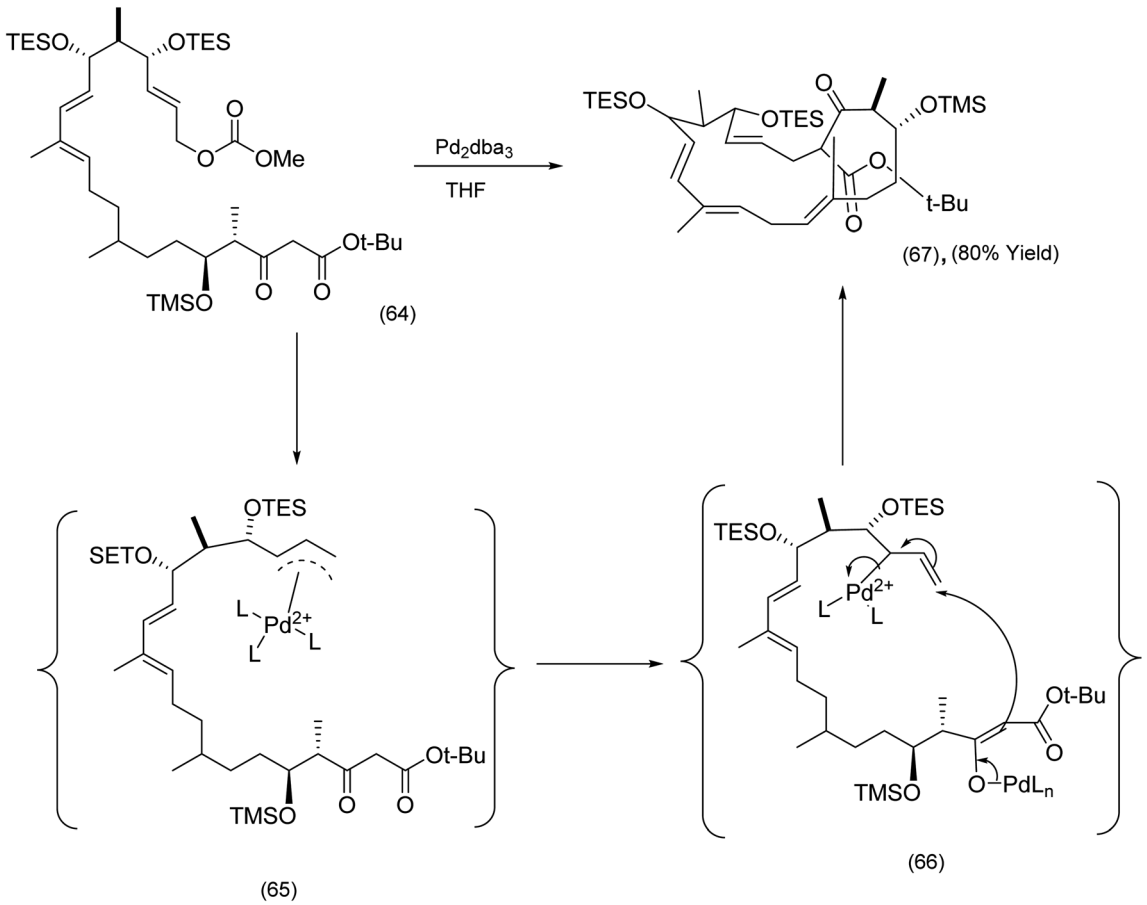
Scheme 14 A radical cation mediated construction of a biaryl system in an unusual indolostilbene (57) synthesis.[66]

In both sequences the vinylic radical was generated differently, Pattenden exploited a 12 endo diagonal ring closure of a methylene radical[60] obtained by exposure of an iodomethyl moiety to tributyltin hydride. Parsons subjected a vinyl iodide to tributyl hydride to generate his vinyl radical.

In a fascinating example of the subtle interplay of electronic and conformational factors influencing macrocyclization, Pattenden examined two acyclic trienone systems incorporating seleno ester and vinyl cyclopropane moieties. The close proximity of the acyl radical to the α,β unsaturated ester was clearly



Scheme 15 Parker's radical cation mediated macrocyclization exploiting a diester tether.[67]



Scheme 16 Utilization of the intramolecular Trost–Tsuji reaction enolate to FR182877.[78]

critical to the initial 6-endo trigonal ring closure and the ensuing cascade sequence that produced the steroid skeleton (Scheme 12).

In comparing (**40**), Scheme 12 with (**45**), Scheme 13, the ester group (note asterisk) has now been replaced by a methyl group (see the asterisked carbon). The original 6-endotrigonal cascade (**40**) to (**41**) (Scheme 12), has now been suppressed and replaced by the sequence (**46**) to (**47**), Scheme 13. The juxtaposition of α,β unsaturated ketone in relation to the cyclopropane in (**45**) is a likely contributing factor in the very different course the reaction has taken.

1.4. Oxidative generation of radical cations in pseudomacrocyclic and macrocyclic synthesis

Our own unexpected synthesis of a pseudomacrocycle resulted[66] from exposure of an apparently "innocuous" stilbene to ferric chloride. In contrast to other stilbene derivatives, the 3,5-dimethoxy-10-acetamido stilbene, when exposed to ferric chloride hexahydrate, gave rise to four products, one of which was the pseudomacrocyclic indolo-stilbene atropodiasteroisomer ((**56**) Scheme 14), for which we proposed the following cascade sequence below:

We recognize of course that the sequence depicted in Scheme 14 does not end in a true macrocycle, the function of the scheme is nevertheless threefold.

(1) The intramolecular hydrogen bonding (see intermediates (**54**) to (**57**)) have conformational implications and brings to mind the kind of pre organization well known in the synthesis of cyclic peptides (Fig. 1 in the Yudin review[1]).

(2) The establishment of the biaryl link *via* oxidative coupling (radical cations as reactive intermediates) – structure (**55**) – Scheme 14 brings to mind an intriguing biaryl coupling (Witkop cyclisation) exploited with profit by Nicolaou *et al.* (Scheme 19) in his diazonamide synthesis.

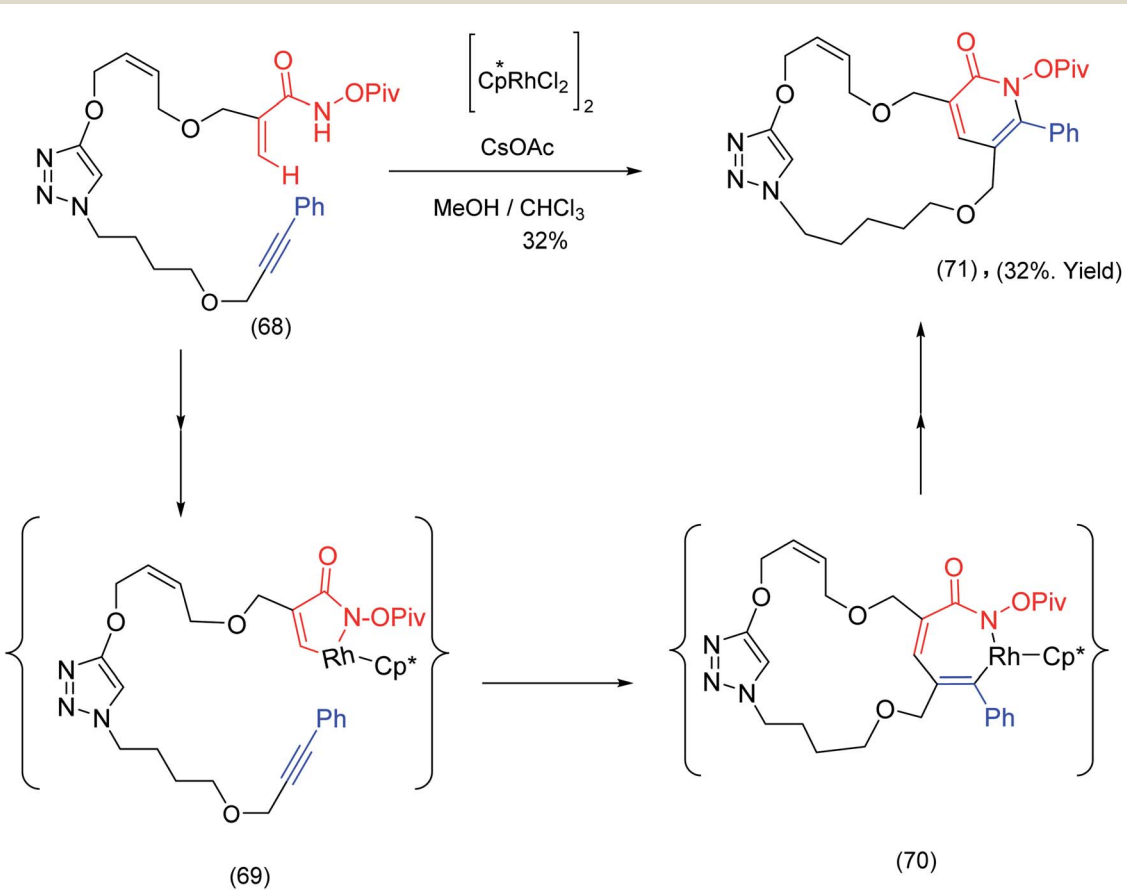
(3) Both of the syntheses described above are in stark contrast to a brilliant non-oxidative solution to a unique biaryl system in Baran's haouamine synthesis (Scheme 31).

Parker *et al.*[67] devised an imaginative radical cation Diels Alder approach that resulted in the macrocyclic intermediate (**63**) leading ultimately to kingianin A.

For additional examples of the radical cation Diels–Alder reaction see the work of Bauld,[68,69] Lin,[70,71] Yoon,[72] MacMillan,[73] and Wiest.[74] For major critical reviews on transition metal photocatalysis in relation to radical cation generation and the utility of visible light photocatalysis the publications of Yoon[75–77] must be consulted.

1.5. Synthetic utility of π allyl complexes and C–H activation in macrocyclic synthesis: the roles of palladium and rhodium

The next sub section describes macrocyclizations in which π-allyl complexes and C–H activation (metal catalyzed) play



Scheme 17 Rh(III) catalyzed intramolecular pyridones formation – a macrocycle forming transformation.[79]

a critical role. With regard to the former, the Sorensen chemistry described below is instructive. The key macrocyclization step in the synthesis of the potent microtubule stabilizing agent FR182877 by the Sorensen[78] group was a beautifully executed and chemoselective Trost–Tsuji reaction (Scheme 16). Nucleophilic attack by the enolate (**66**) on an electrophilic π-allyl complex is the key step leading to the advanced intermediate (**67**).

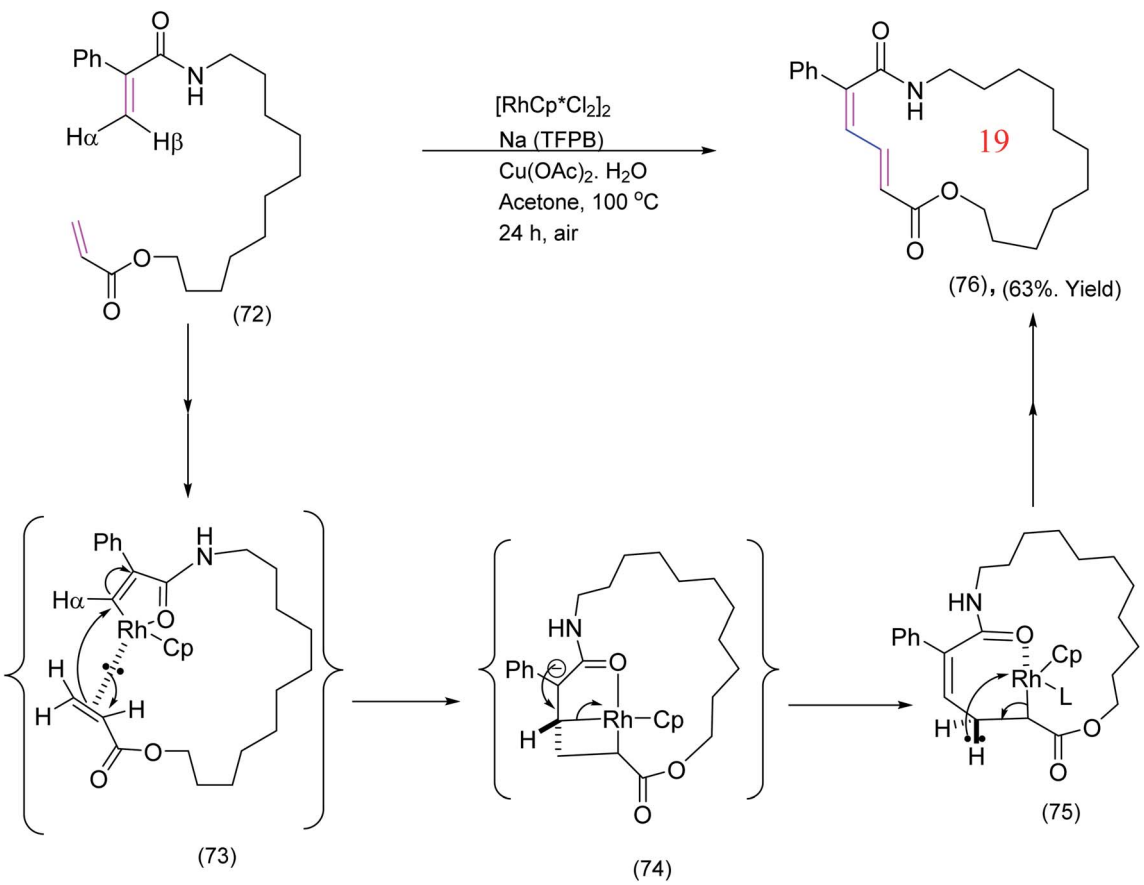
Cossy *et al.*,[79] has exploited Rh(III) catalyzed activation for the construction of macrocyclic pyridones. The precursor, incorporating both terminal α,β unsaturated amides and alkynes, was exposed to $[Cp^*RhCl_2]_2$/CsOAc leading to wide range of macrocyclic pyridones *e.g.* (**71**). Mechanistically the reaction proceeds through 5 and 7 membered ring rhodium lactam complexes (**69**) and (**70**), (rhodacyclic enamide species) see Scheme 17.

Jiang *et al.*,[80] has also reported a rather different Rh catalyzed macrocyclization *via* oxidative cross coupling of the olefinic moieties. This highly efficient cross coupling is illustrated by the example below (Scheme 18). The mechanism presented below is slightly different from the mechanism proposed by Jiang *et al.*[80]

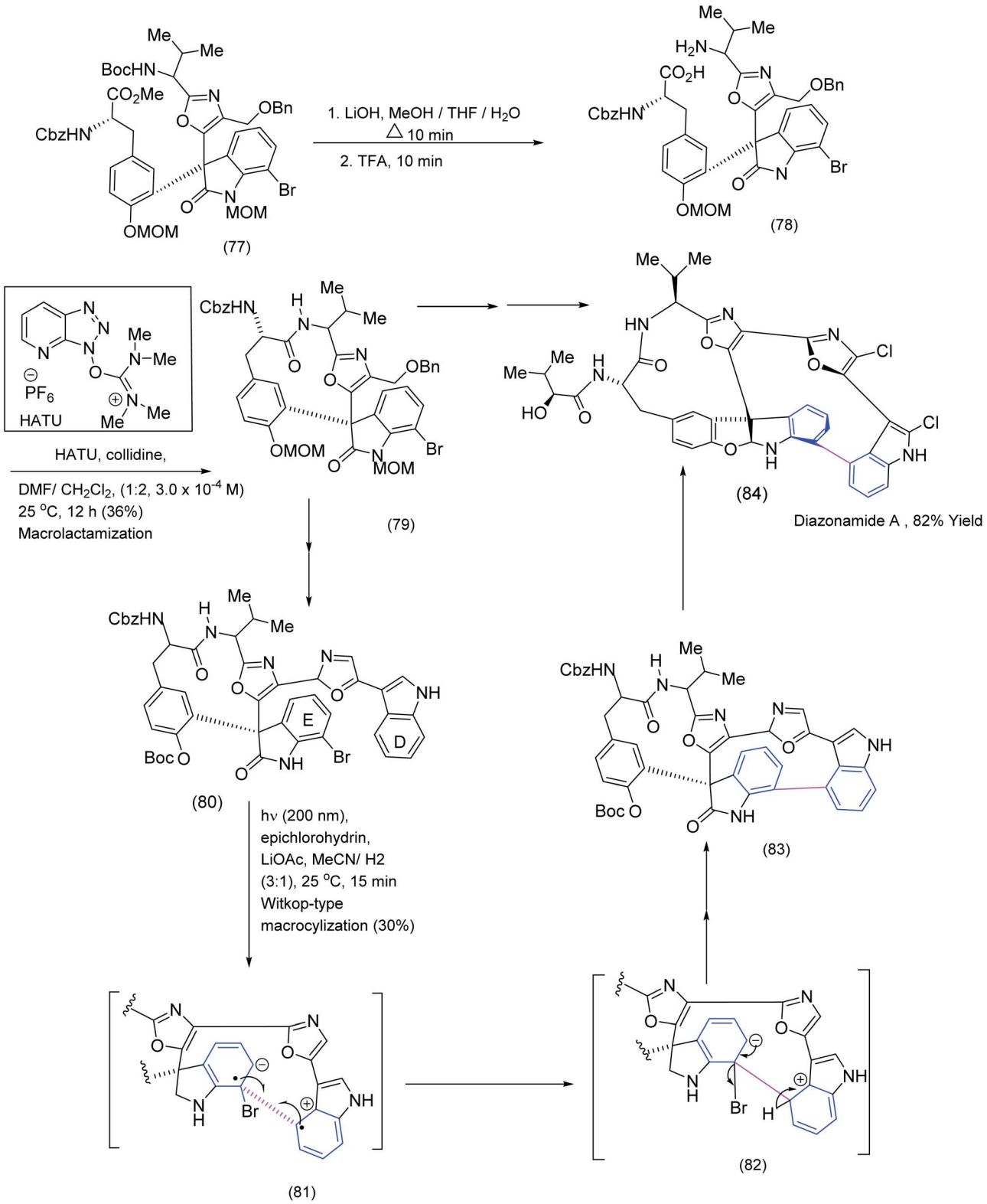
As a result of kinetic isotope effect (KIE) studies,[80] it was proposed that the active catalyst [Cp*Rh (OAc)][BARF] coordinates to the enamide moiety by oxidative insertion (removal) of the syn-hydrogen (syn to the amide carbonyl *i.e.* H_β) to yield (**73**). The next step could be viewed as a migratory insertion of the Rh into α-CH bond of the αβ-unsaturated ester. Alternatively, one may envisage the process as a 1,4-type addition to the enamide followed by fragmentation of the rhodium-complex [(**73**) to (**74**) to (**75**)] but this is not certain and other pathways are possible. Decomplexation *via* β-hydride elimination which does not preclude other possibilities completes the formation of the desired product. Reductive elimination and reoxidation regenerates the active catalyst.

1.6. Distinctive macrocyclic domains and the most appropriate methodology: HATU/amidation and the Witkop coupling

The following example of macrocyclisation from the Nicolaou group is instructive because the target molecule, diazonamide A, possesses two distinctive macrocyclic domains, each constructed by a different method, one of which involved an intriguing biaryl coupling. The total synthesis of diazonamide by the Nicolaou group[81] was challenging and provided an excellent opportunity to test various macrocyclization protocols (Scheme 19). In a molecule consisting of two macrocyclic submits, the selective deprotection of terminal BOC amide and methyl ester moieties (TFA and LiOH treatment (**77**) to (**78**)) lead to an intermediate which underwent smooth



Scheme 18 Rhodium catalyzed olefin cross coupling providing access to macrocyclic dienamides.[80]



Scheme 19 Exploitation of HATU and Witkop cyclisations to install the two distinctive macrocyclic domains in diazonamide.[82]

macrolactamisation by means of the HATU/collidine procedure under carefully controlled conditions. Thus one of the two macrocyclic submits was successfully installed. The installation of the second macrocyclic domain within diazonamide A exploited the rarely used Witkop cyclisation. This is a photochemically induced process that involves both a single electron oxidation and a single electron reduction producing a radical cation and radical anion ((**89**) to (**84**) (Scheme 19)).

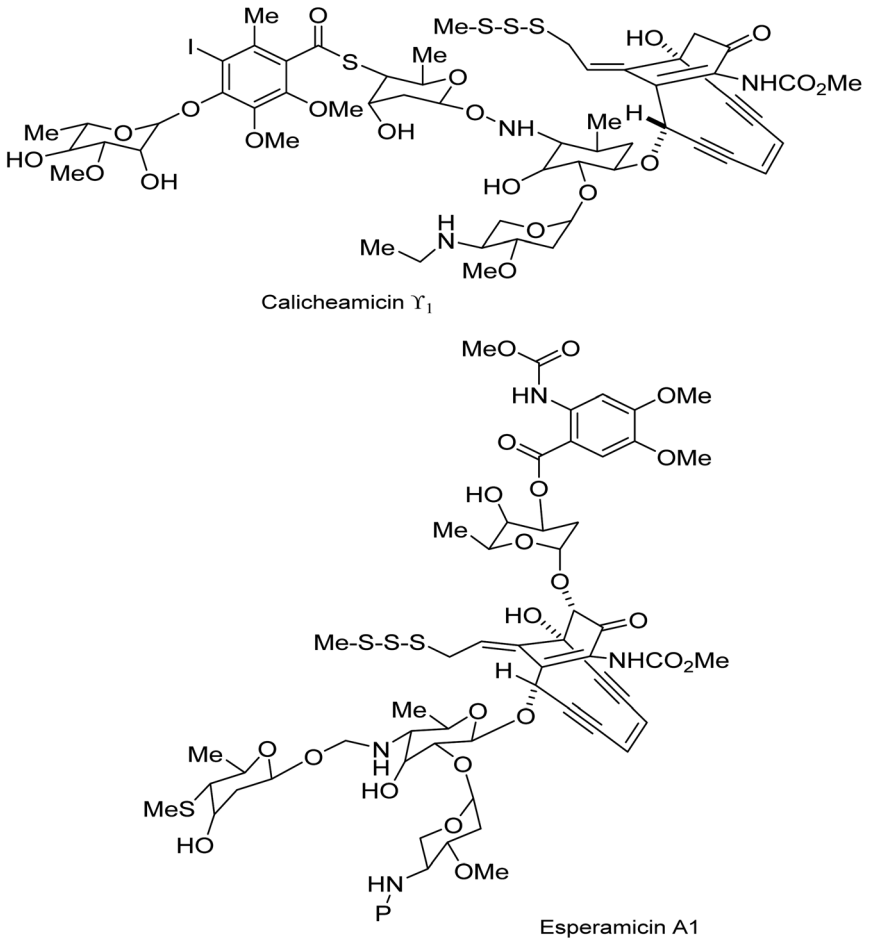
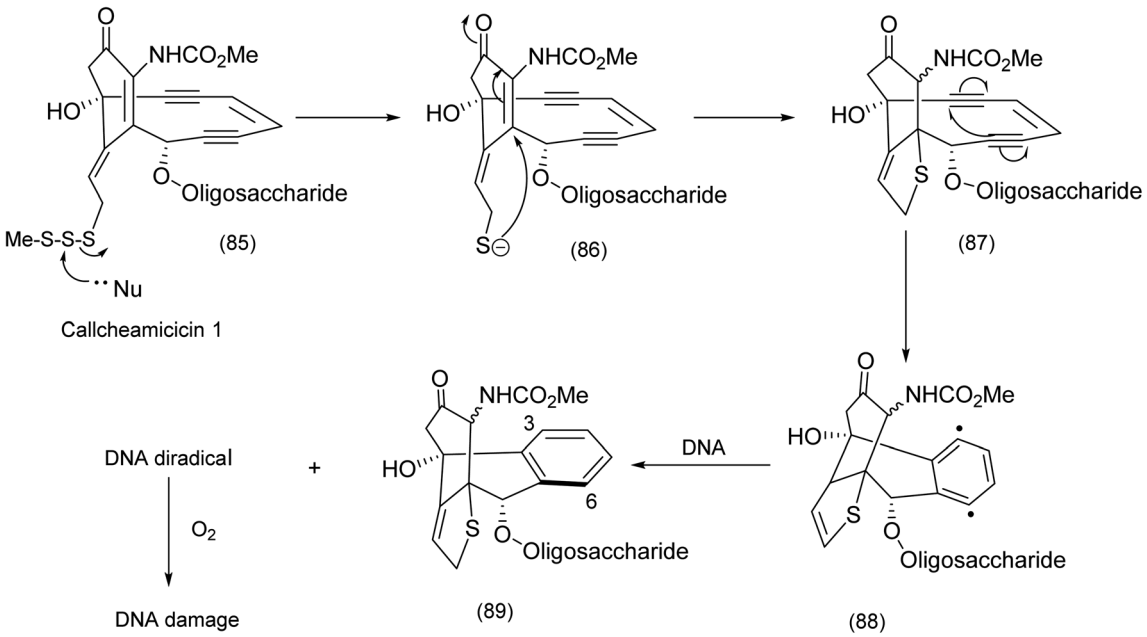


Fig. 1 Structure of calicheamicin Υ_1 and esperamicin A1 anticancer agents.[85]



Scheme 20 Biochemical intramolecular conjugate addition – Bergman cyclization diradical formation.[85]

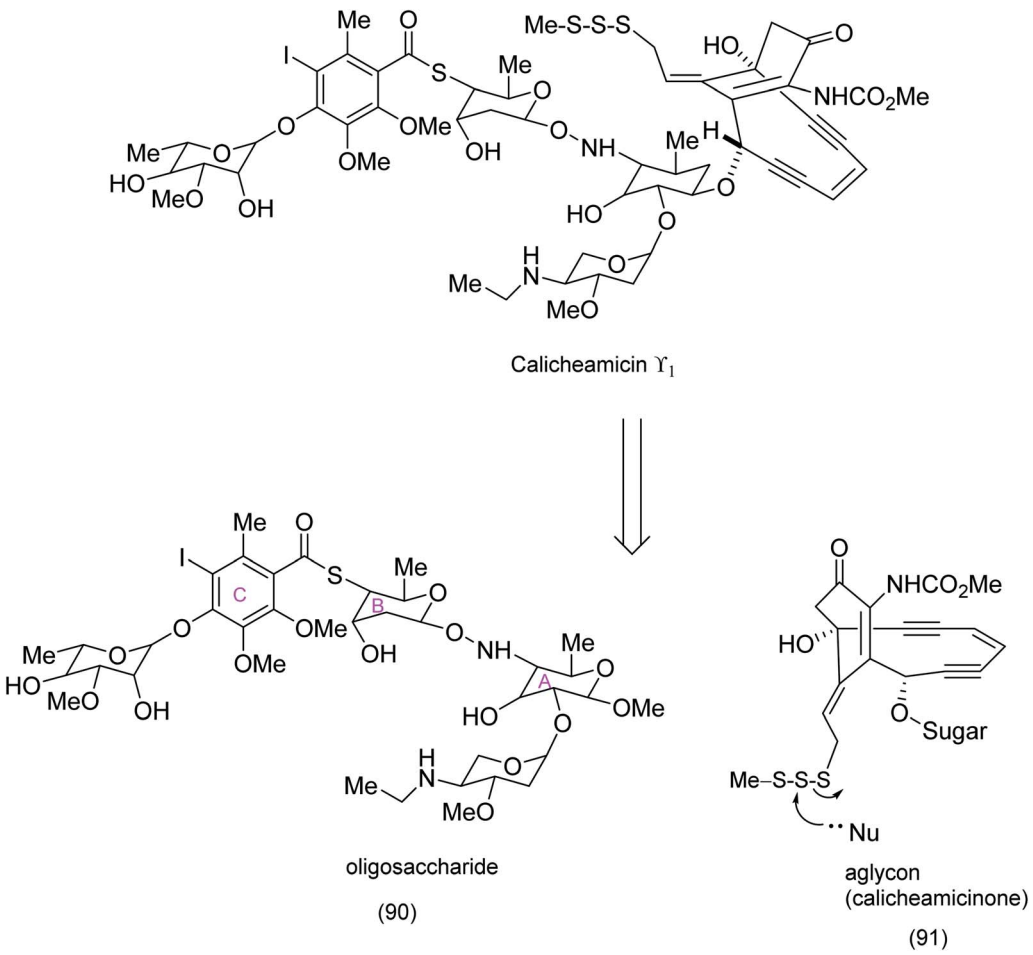
1.7. The contributions of Nicolaou, Schreiber, Baran and Kishi: enediyne macrocycles, bent biaryls and the Diels Alder reaction

The revisiting of the calicheamicin Υ_1/esperamicin (Fig. 1) story allows us to compare two conceptually different but equally fascinating approaches to the elaboration of calicheamicinone (or its analogue) – incorporating the remarkable enediyne moiety. This remarkable class of molecule demonstrates a high potency against tumour cells by a mechanism that involves intramolecular conjugate addition and Bergman cyclization/aromatization leading to the formation of diradicals which induce double strand cuts in DNA[83–85] (Schemes 20 and 21).

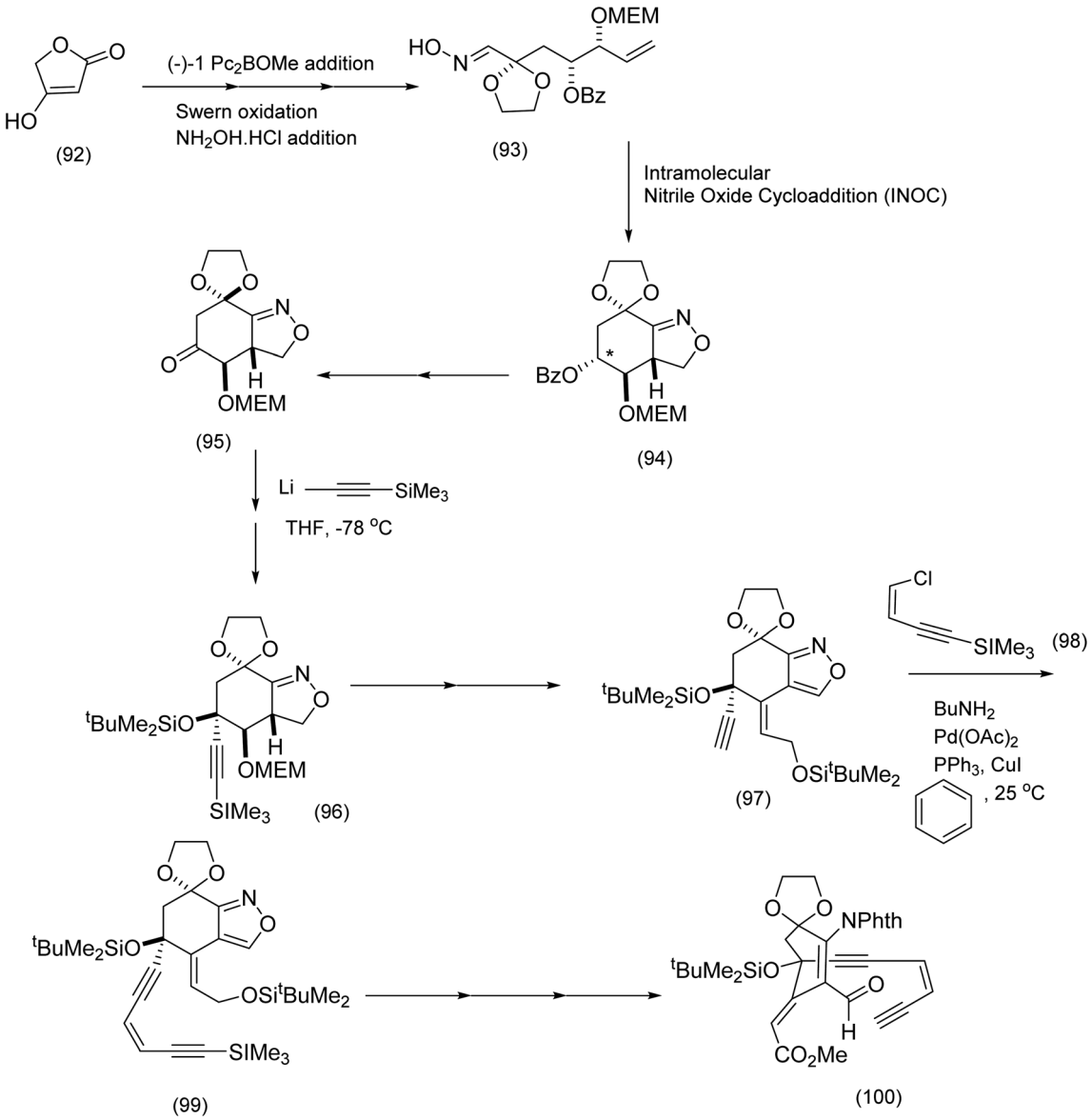
Both calicheamicin and the related esperamicin incorporate a strained enediyne and a α-carbamato cyclohexenone. Nicolaou's approach to calicheamicinone (Scheme 22), depended critically on the choice of tetronic acid (**96**) as a starting material, the application of H. C. Brown's (*Z*)-diisopinocamphenyl allyl borane/aldehyde coupling – a nucleophilic addition that has been shown to produce syndiols of high enantiomeric purity and an intramolecular nitrile oxide cycloaddition (INOC). This chemistry yields a bicyclic isooxazoline (**94**) which is a masked α-carbamato cyclohexenone characteristic of calicheamicinone (*i.e.* (**103**) to be unmasked later).

From the product of the intramolecular nitrile oxide cycloaddition (**94**), the completion of the installation of the enediyne moiety (Nicolaou *et al.*[86]) necessitated at least two key steps: addition of lithium acetylide to the functionalized cyclohexanone (**95**) to produce (**96**), and palladium/CuI catalyzed coupling of the *Z*-enyne (**98**) to the ethynyl *t*-butylsilyl ether (**97**) to produce (**99**) (Scheme 22). Further transformations including isoxazole cleavage produced the intermediate from which the corresponding ethynyl anion (**101**) was generated (after desilylation of (**99**)) by exposure to potassium hexamethyl disilazide (KHMDS) prior to intramolecular attack on the aldehyde (**101**) to set up elegantly, the macrocyclic enediyne core of calicheamicinone (**103**) (Scheme 23).[84]

An alternative approach to a molecule closely related to calicheamicinone was reported by the Schreiber group. This chemistry, beautiful in conception, is described below[87] (Scheme 24). Schreiber developed a sequence of reactions leading to an endiyne tethered diene and α,β unsaturated ester moieties. An intramolecular Diels Alder reaction would deliver (it was assumed, not unreasonably) the bridged bicyclic core of a calicheamicinone analogue in a single reaction.[87] The *Z*-dichloroethene (**104**) was transformed by successive Castro Stevens cross couplings to produce the protected enediyne (**105**). Acetal deprotecting and metalation of 1-methoxy-3-



Scheme 21 Identification of calicheamicinone as a key intermediate *enroute* to the synthesis of calicheamicin Υ_1.[85]



Scheme 22 Generation of the functionalized bicyclic oxazoline (**94**) and incorporation of the endiyne moiety.[86]

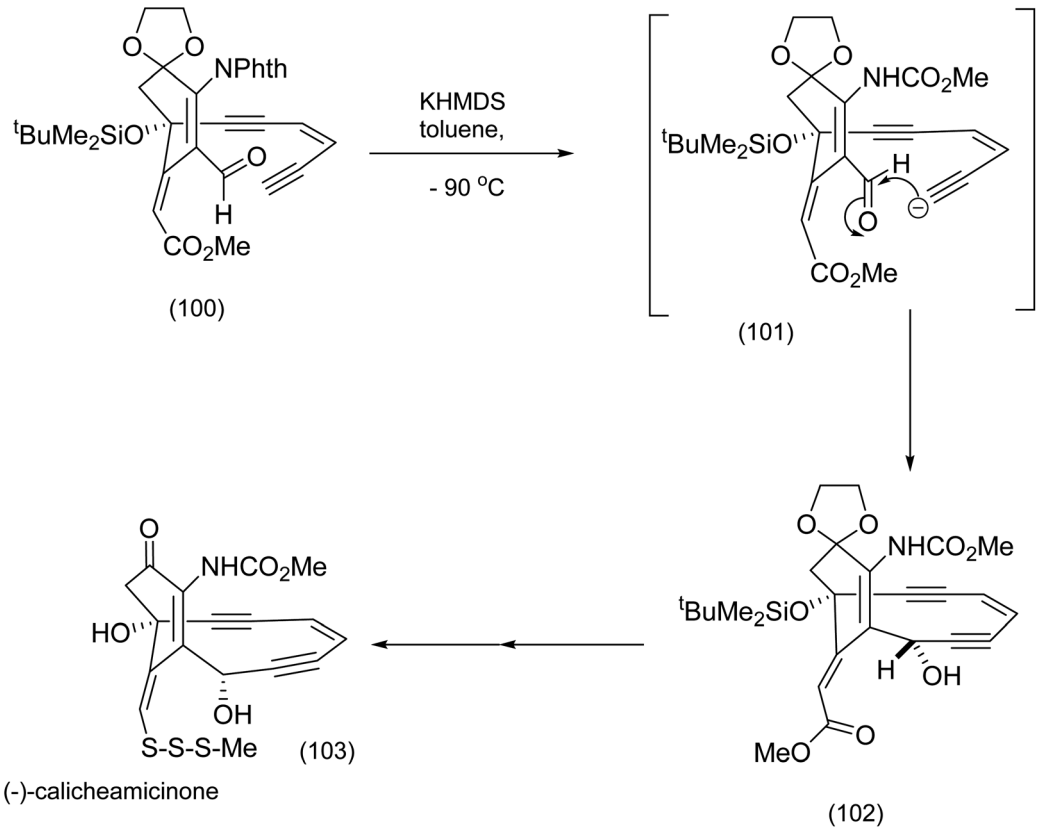
bromo-1,3-butadiene with *n*-butyllithium and subsequent addition resulted in intermediate (**106**). Further Castro Stevens coupling produced the desired diene and dienophile moieties separated by the enediyne tether (**106**) to (**107**).[87]

After protection of the secondary alcohol, exposure of the product to Kish's radical inhibitor (as a precaution) and heating in benzene at 80 °C effected a remarkable Diels Alder reaction believed at the time to have resulted in the desired bridged bicycle (**109**) (Scheme 25).

The Schreiber group adopted a similar strategy for the synthesis of (**110**) which was efficiently transformed into the bridged enone (**111**),[87] (Scheme 26).

After the work above was published, further investigations of the presumed structure (**111**) and the critical observation that it failed to undergo the Bergman cyclisation, led to the conclusion that the Diels–Alder reaction depicted in scheme (**25**) had followed a different course leading to the alternative regioisomer. In short structure (**109**) was incorrect. The actual path the Diels–Alder reaction had followed is shown in Scheme 27.

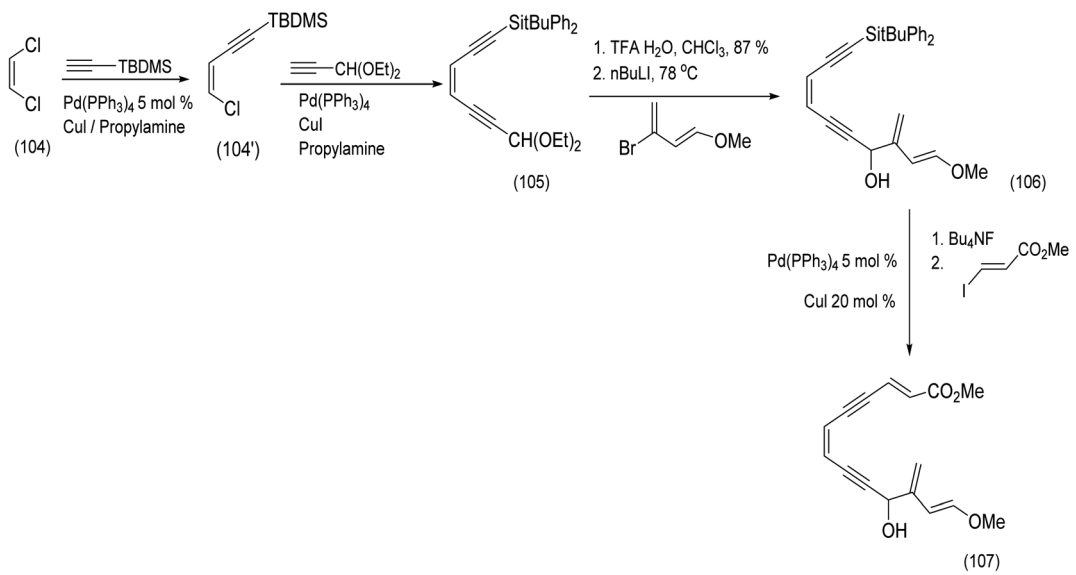
The judicious selection of reactions that revealed the original structural misassignment was insightfully described in a paper by Schreiber *et al.*[88] The same authors pondered the possibility of carefully manipulating the Diels–Alder reaction conditions with a view to generating the correct regiochemistry. As it turned out the breathtakingly ingenious solution to the problem depended on the application of the Tsuchihashi pinacol rearrangement.[89] Schreiber generated a modified version of his tethered diene and dienophile by means of the following sequence of reactions. Coupling of the readily available aldehyde (**114**) to the vinyl lithium species (**112**), (obtained by treatment of the vinyl stannane with butyl lithium) gave the diene-endiyne (**116**). A palladium catalysed coupling of the



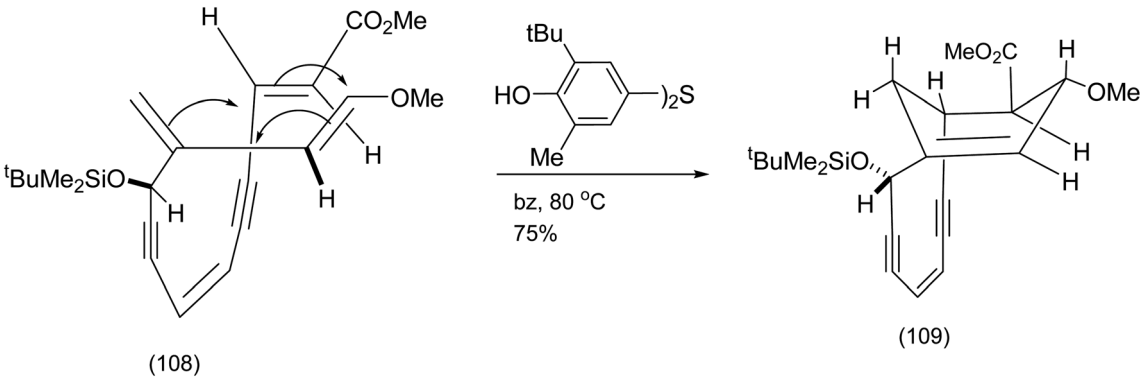
Scheme 23 Final stages in (−)-calicheamicinone construction.[86]

bromovinylene carbonate (**118**) to (**117**)[89] gave the crucial Diels–Alder precursor (**119**). Subjection of (**119**) to the Diels Alder first conditions shown in Scheme 27 produced in good yield the cyclisation product ((**120**) Scheme 28).

The selective base promoted cleavage of the cyclic enecarbonate and selective mesylation of the axial hydroxy group probably proceeds by the following mechanism ((**121**) to (**123**) Scheme 29).

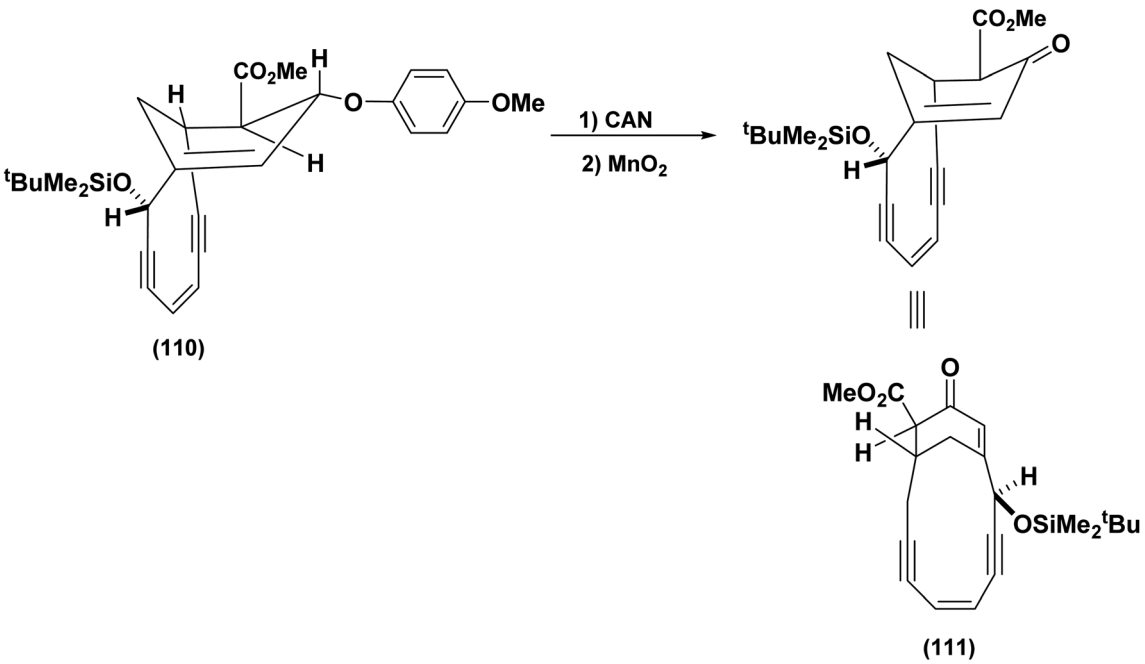


Scheme 24 Application of the Castro Steven's coupling to enediyne construction.[87]



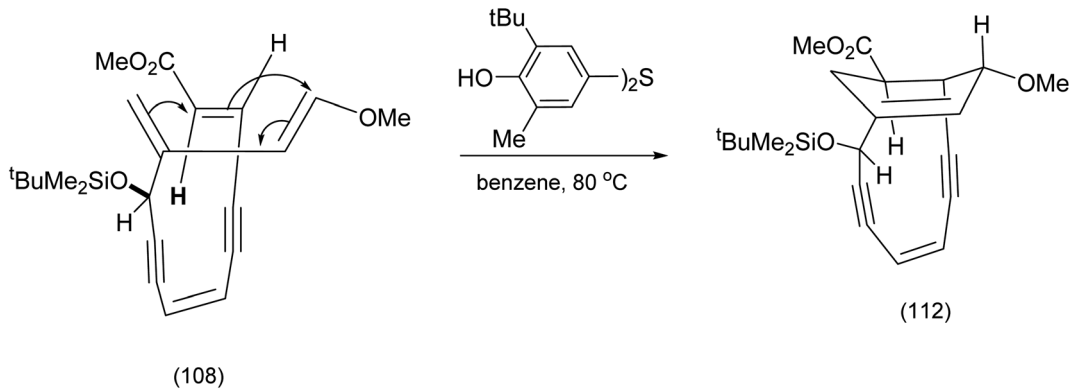
(108) (109)

Scheme 25 The first attempted 4 + 2 cycloaddition of tethered endiyne.[87]



(110) (111)

Scheme 26 Deprotection/oxidation to generate the bicyclic enone.[88]



(108) (112)

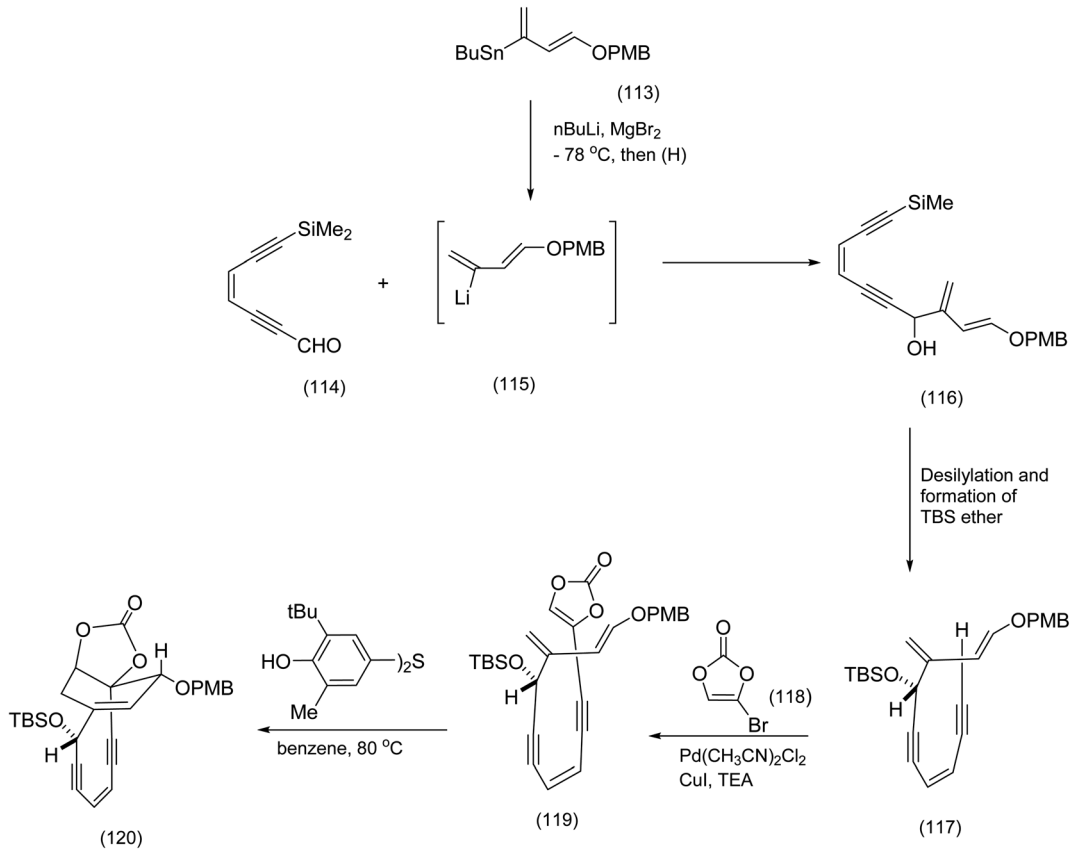
Scheme 27 Recognition of the unexpected regiochemical outcome for the intramolecular endiyne tethered Diels Alder reaction.[88]

Treatment of with (**123**) six equivalents of diethyl aluminum chloride gave rise to the desired bridged enone (**128**) *via* the mechanism described below.[89] The combination of an imaginative type II Diels Alder reaction and an ingenious pinacol rearrangement have combined to make this a memorable achievement (Scheme 30).

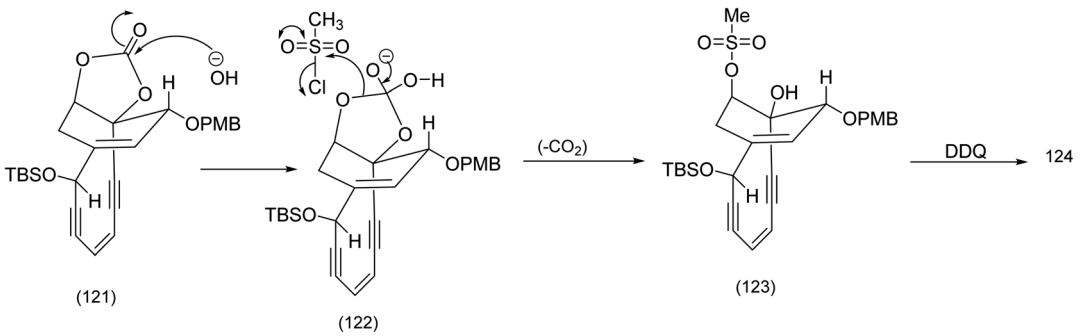
This type of pinacol rearrangement was first reported on different system by Tsuchihashi.[90]

The next macrocyclic construction, culminating in the molecule Haouamine, gave us pause as we could not quite decide where in this account to insert it. On the one hand, the presence of the biaryl moiety in Haouamine suggested that Baran's synthesis could have been discussed after Nicolaou's Diazonamide synthesis in which the installation of the biaryl was achieved by a single electron oxidation/reduction. On the other hand, Baran's solution to the problem of the strained biaryl moiety within Haouamine involved such an ingenious use of Diels Alder chemistry, that it seemed appropriate to discuss this innovation after Schreiber's[91] exhilarating Diels Alder accomplishment.[90]

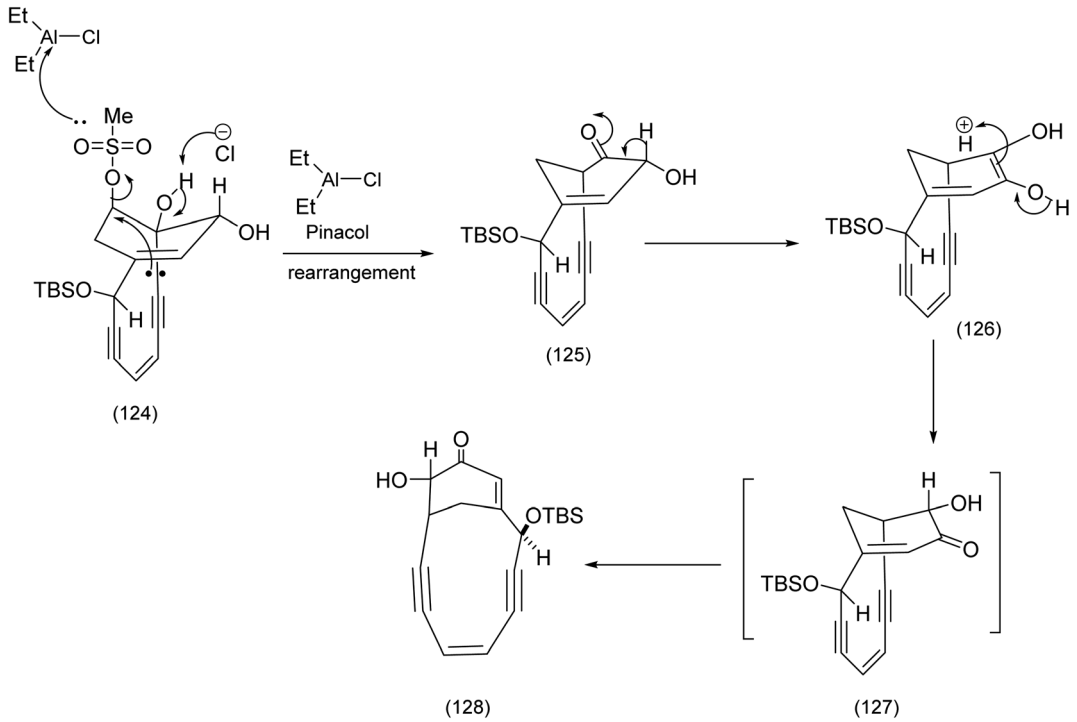
Haouamine A is a structurally unique alkaloid. The most outstanding feature of this alkaloid is the 11 membered ring



Scheme 28 Installation of the cyclic enecarbonate into the endiyne tethered.[88]



Scheme 29 Selective installation of the axial mesylate set up for the Tsuchihashi rearrangement.[90]



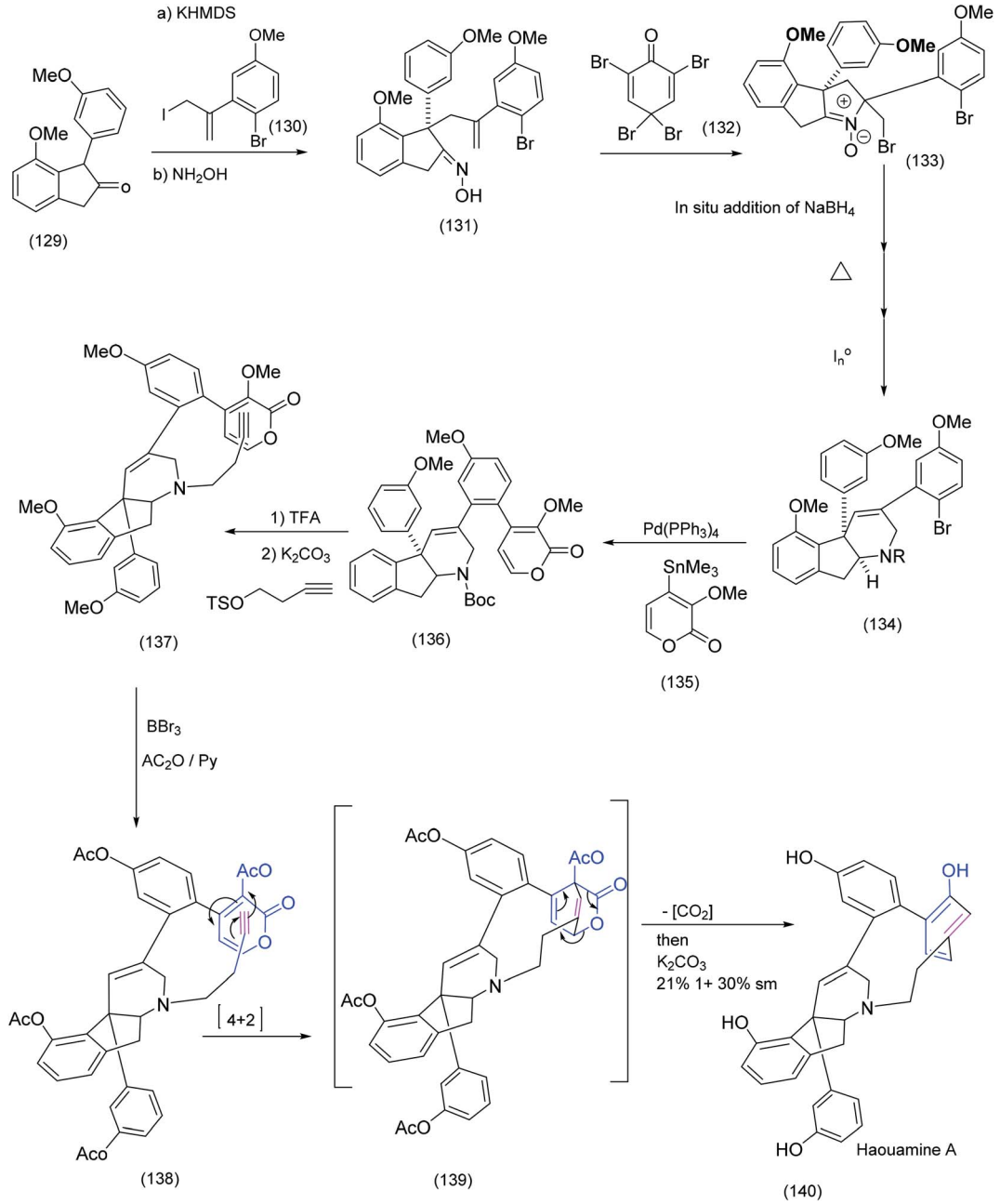
Scheme 30 The Tsuchihashi pinacol rearrangement and the effective regioisomeric correction.[90]

that links an indeno-tetrahydropyridine and a strained biaryl moiety (an aza-paracyclophane) in which one of the benzene rings of the biaryl system is in the boat conformation. The Baran group[92] rose to the challenge of this unusual system. Oxidative coupling (single electron oxidation) has proven to be effective in the synthesis of a number of bicyclic systems (see our own endeavours in the area, as depicted in scheme (**14**), in which a $FeCl_3$ promoted biaryl construction leading to a unique chloindolostilbene hybrid is described). Suzuki and Stille couplings have also been successfully employed in biaryl synthesis and, as we previously described, the Witkop cyclisation was exploited with profit in Nicolaou's Diazonamide construction resulting in the successful installation of the biaryl system. Nevertheless Baran *et al.*[92] reported that more conventional methods failed to achieve the successful construction of the strained biaryl in Haouamine. The creative solution to this problem was found in the pyrone-alkyne Diels–Alder reaction that delivers, at least initially, a cyclohexadiene in the boat conformation. The sequence of steps in this approach is described below.

Coupling of tricyclic ketone (**129**) with allylic iodide (**130**) proceeded smoothly to yield the intermediate tetracyclic oxime (**131**). A series of transformations that included bromination/nucleophilic attack by the oxime, $NaBH_4$ addition, then heat followed by chemoselective N–O bond reduction produced advanced intermediate (**134**) which underwent Stille coupling to the pyrone (**135**) to give (**136**) which, on further treatment with TFA followed by *N*-alkylation, successfully installed the terminal ethynyl dienophile (**137**). Demethylation produce the tetraol which was subsequently acetylated to produce (**138**). At this point, the moment of truth – the pyrone alkyne Diels Alder reaction – had arrived. Heating of (**138**) proceeded as expected to yield the tetra acetylated Diels Alder adduct (complete with the strained aza-paracyclophane) which on treatment with K_2CO_3 gave Haouamine. The last two synthesis we have examined from the groups of Schreiber and Baran were beautiful but contrasting examples of the use of the Diels Alder reaction in macrocyclic construction. In this next example Kishi *et al.*[86] successfully effected a remarkably stereoselective late stage intramolecular Diels Alder reaction to yield an advanced intermediate ultimately transformed to the formidable target molecule, pinnatoxin A (Scheme 32).

1.8. The vinblastine story according to Fukuyama: macrocycles as synthetic intermediates (a second example see Scheme 15)

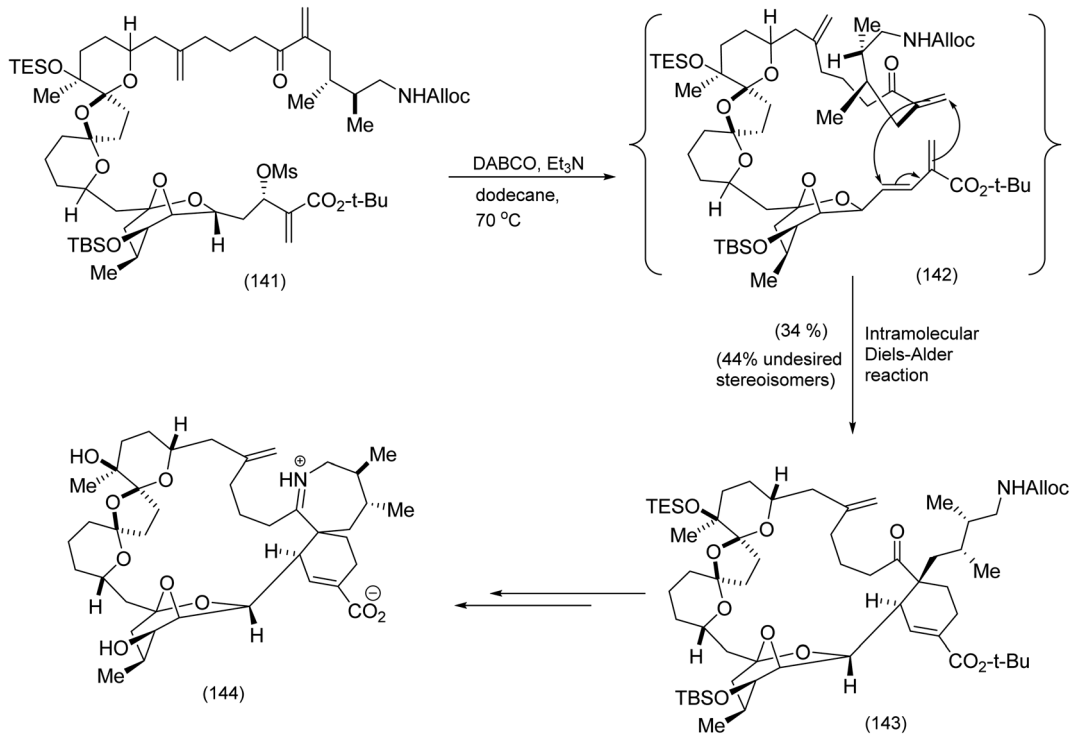
In this final example we have chosen, the medium-sized ring was generated in elegant fashion by an intramolecular nucleophilic attack of a nitrobenzenesulphonamide on an epoxide to yield the 11 membered ring. Fukuyama exploited this intermediate in the course of an efficient synthesis of vinblastine. Thus the medium-size ring was not an end itself but a lightly creative means to a significant end. We have previously seen another example of the exploitation of macrocycles as invaluable intermediates in Parker's syntheses that involved a radical cation Diels–Alder transformation (compound **62**, Scheme 15). Fukuyama recognised the role played by 11-membered ring indolic macrocycles for the generation of medium-sized ring azabenzfulvenes, which are highly electrophilic species. Prior to



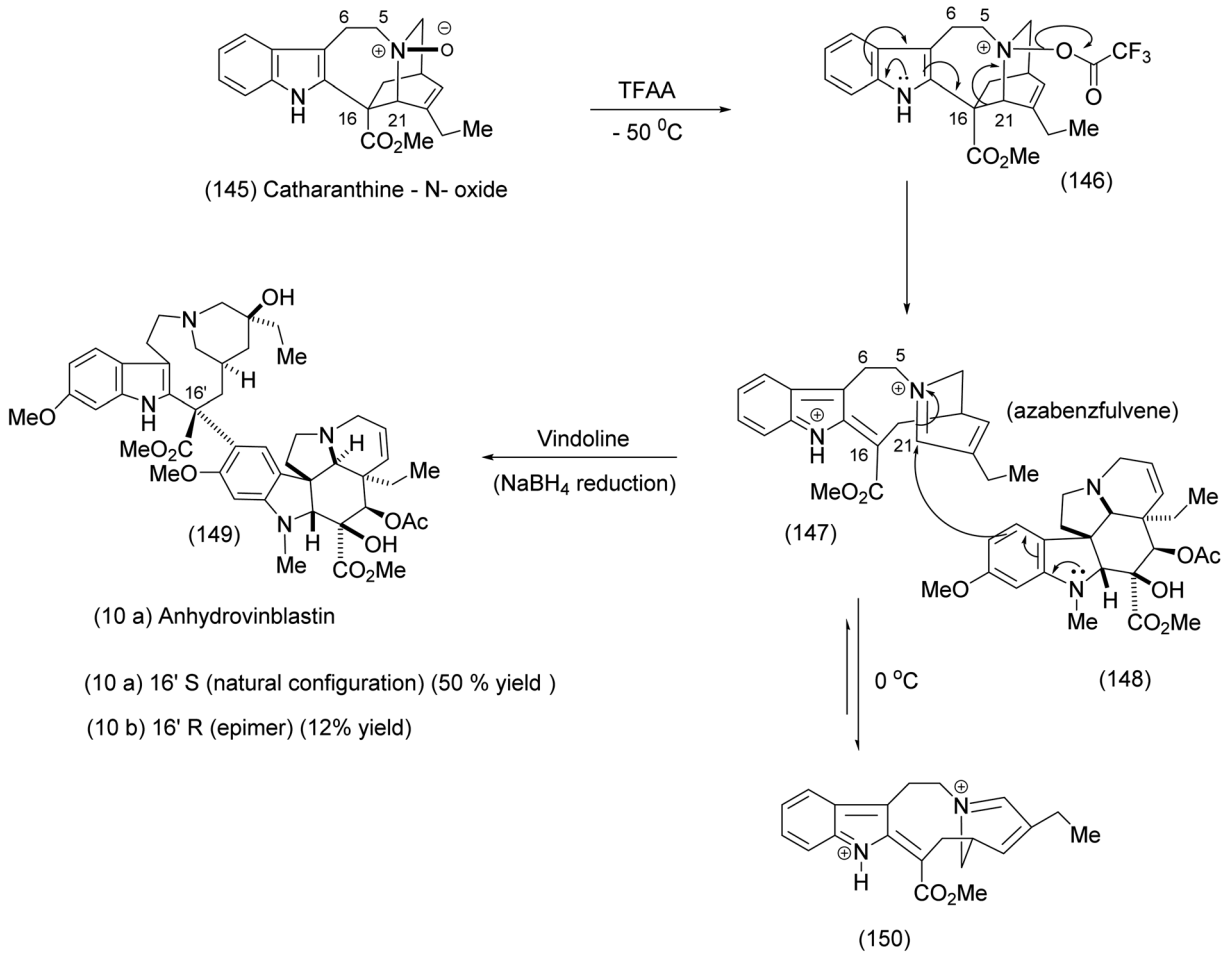
Scheme 31 Key steps in Baran's synthesis of the tricyclic azabutyne/pyrone intermediate, reaction and the subsequent macrocyclising Diels Alder.[92]

Fukuyama's synthesis,[93,94] Potier had effected the fragmentation of catharanthine – *N*-oxide by means of a trifluoroacetic anhydride leading to the macrocyclic azabenzfulvene (**147**), which was subsequently attacked by vindoline to yield anhydrovinblastine (**149**) after $NaBH_4$ reduction (Scheme 33).[93,95,96]

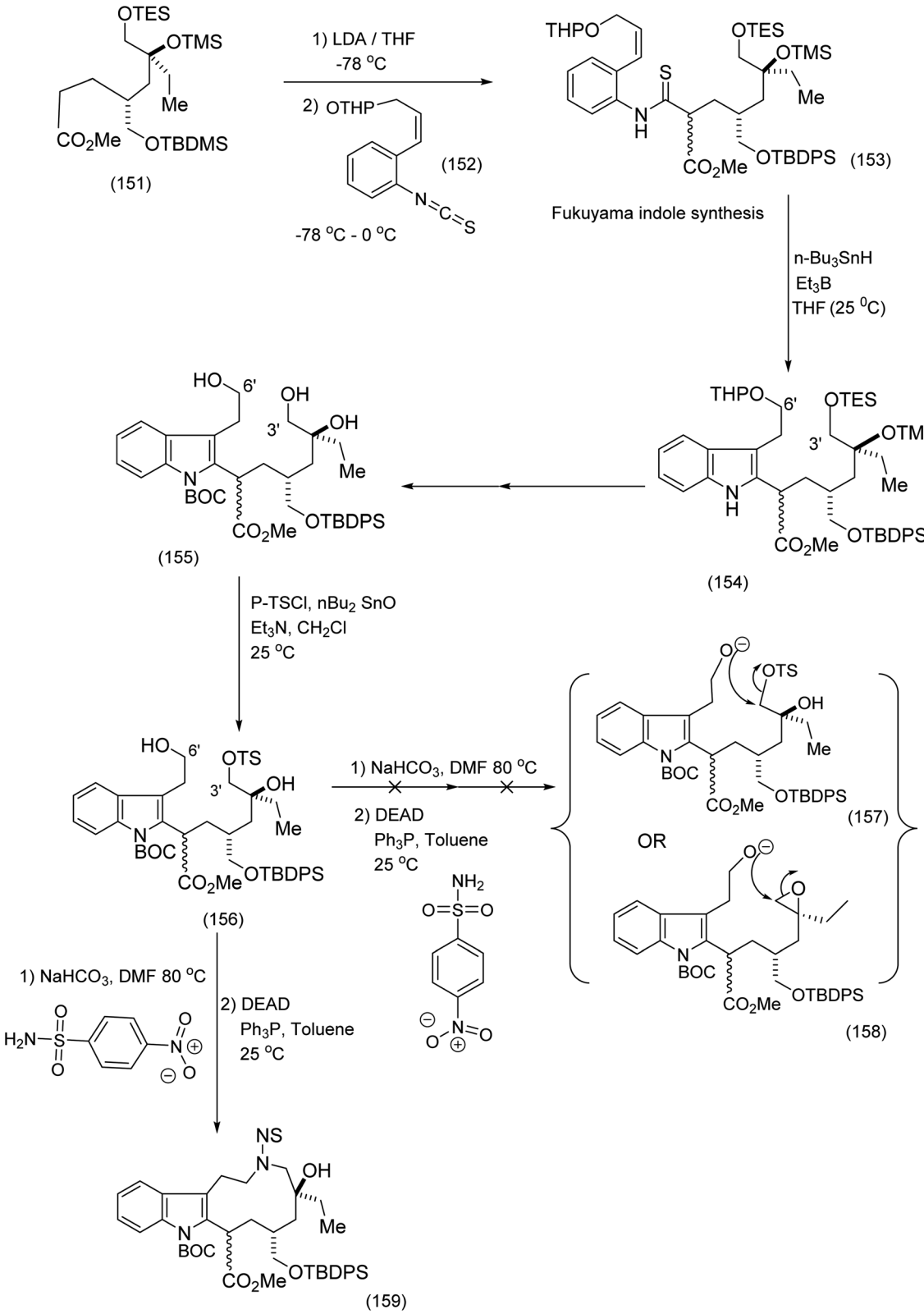
Fukuyama's synthesis commenced with the treatment of the functionalised octanoate easter (**151**) with LDA, THF-78 °C followed by isothiocyanate (**152**) to generate thioamide (**153**) which was transformed by means of tributyl tin hydride/triethylborane to yield the corresponding functionalised indole (**153**) in 67% yield (the Fukuyama indole synthesis). Further functional group manipulations produced the triol (**155**). Selective C (3′)-tosylation was efficiently performed by means of the five membered tin acetal to yield (**154** and **156**). The nitrobenzene sulphonamide was then introduced at C (6′) by the Mitsunobu procedure, whose intriguing mechanism is depicted (see (**160**) to (**163**)). It is noteworthy that in the presence of $NaHCO_3$/DMF, (**169**) (Scheme 35) was obtained *via* the epoxide (**164**) (see Scheme 35 for full mechanistic details). Alternative pathways *via* intermediates (**157**) or (**158**) were suppressed (Scheme 34), thus enabiliting installation of the nitrobenzene sulphonamide ((**162**), Scheme 35) by the



Scheme 32 A spectacular intramolecular Diels Alder reaction (Diels Alder based self construction) *enroute* to pinnatoxin.[86]

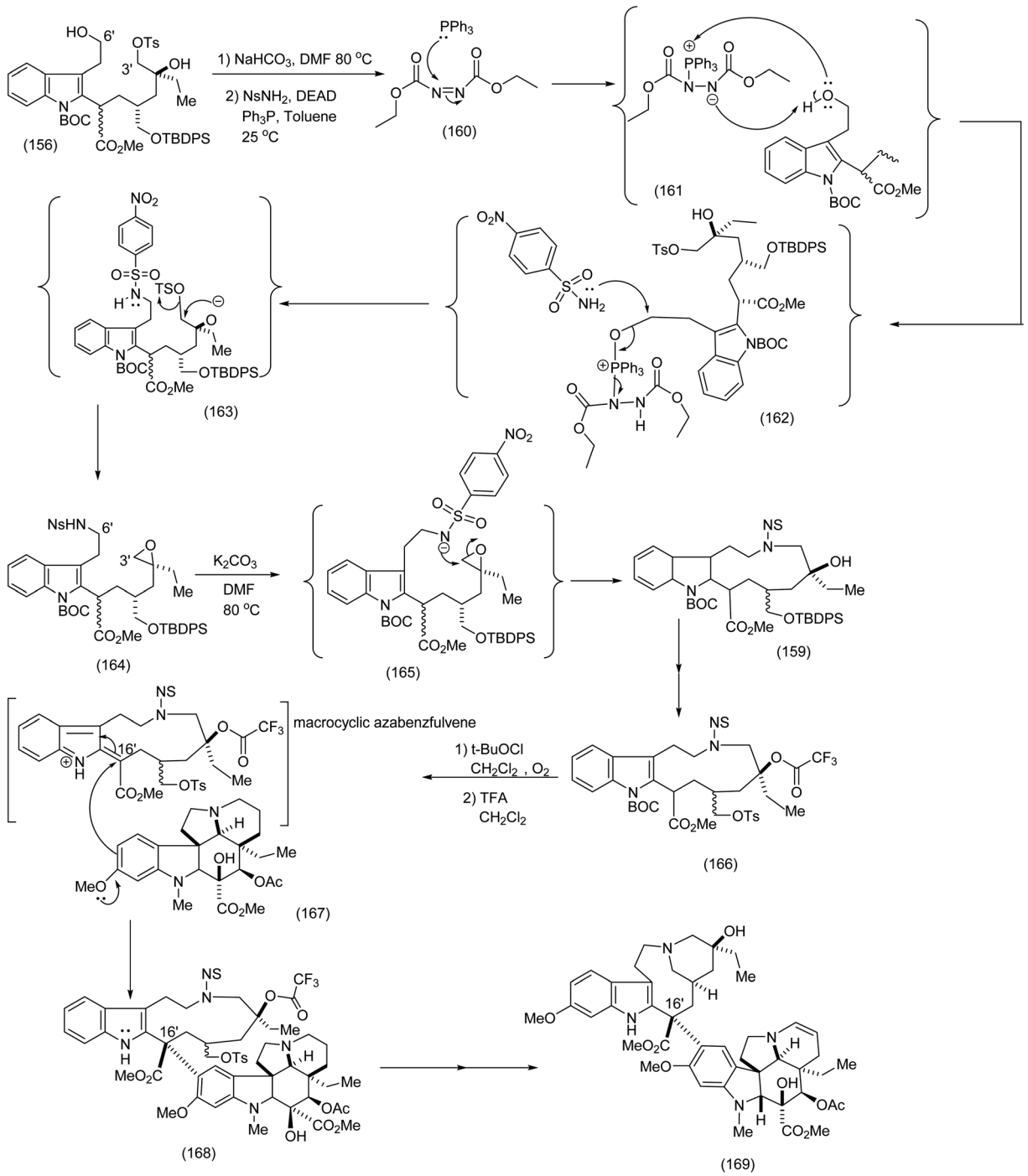


Scheme 33 The Potier TFAA fragmentation of catharanthine – *N*-oxide.[93]



Scheme 34 Key steps in the construction of the indolic macrocyclic intermediate[93] (**159**).

Mitsunobu protocol. Treatment of epoxide (**164**) with K_2CO_3 in DMF at 80 °C proceeded smoothy to produce the desired macrocycle (**159**). As a demonstration of the value of electrophilic macrocyclic reactive intermediates in complex alkaloid synthesis, (**166**) was exposed to tertiary butyl hypochlorite. This gave rise to the azabenzfulvene (**167**) which on



Scheme 35 The critical chemoselective installation of the nitrobenzene sulphonamide (Mitsunobu reaction) and final steps leading to vinblastine.[93]

further exposure to vindoline to gave rise to vinblastine (**169**) after judicious functional group manipulations (Scheme 35).

2. Conclusion

This review has acknowledged more recent solutions to macrocylic syntheses problems. On the one hand the elegant exploitation of Rh(III) complexes in macrocyclisation from the work of Loh and independently Cossy is detailed. On the other, the older literature has not been ignored as the description of Schreiber's application of pinacol rearrangement to enediyne problem demonstrates. The biaryl coupling in macrocyclic construction highlights the work of Nicolaou and Baran on different targets.

Conflicts of interest

There are no conflicts.

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