Tandem Reactions in Organic Synthesis: Novel Strategies for Natural Product Elaboration and the Development of New Synthetic Methodology

Philip J. Parsons,* Clive S. Penkett, and Adrian J. Shell

School of Chemistry and Molecular Sciences, University of Sussex, Falmer, Brighton BN1 9QH, U.K.

Received July 6, 1995 (Revised Manuscript Received September 14, 1995)

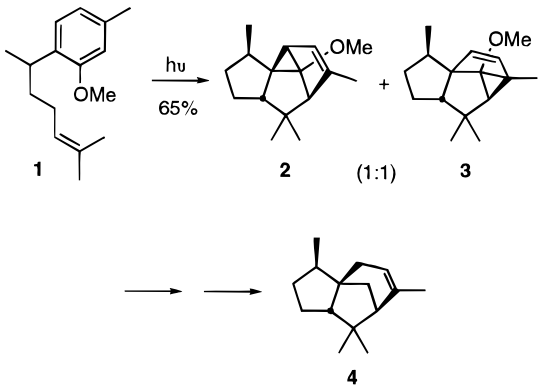
Contents

I. Introduction

This review is not intended to provide an in-depth coverage of every cascade reaction, but will highlight relevant reactions where appropriate. General references to excellent earlier reviews in the area of cascade reactions will provide the reader with supplementary material. We will endeavor to recognize major contributions from other groups; however, it is not possible in the scope of this review to include all relevant work.

Modern synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of complexity.[1] The disconnection approach[2] to synthesis design offers an analysis of complexity change corresponding to each bond disconnection. The result of breaking a bond or bonds leading to the greatest decrease in structural complexity usually defines the shortest synthetic route. An excellent example of one reaction which maximizes complexity with maximum efficiency is the arene/alkene photoaddition discovered simultaneously by Bryce-Smith, Gilbert, and Orger at Reading and Wilzbach and Kaplan at Chicago in 1966.[3] Paul Wender and his colleagues at Stanford[4] have developed the intramolecular variant of this reaction in an exceedingly elegant fashion (Scheme 1) and in

Scheme 1



very few steps converted the photoadducts **2** and **3** into (±)-α-cedrene (**4**). In the key photoaddition step one observes a dramatic increase in molecular complexity.

A cascade sequence can also lead to an increase in molecular complexity by combining a series of reactions in one synthetic operation.[5,6] The possibility of designing a "one-pot" sequence for the construction of highly complex molecules is a major driving force for our research program. This review compiles our findings in the general area of cascade reactions together with relevant work from other laboratories. The plan here will be to highlight areas of brevity in organic synthesis concentrating on useful methodology for the construction of biologically important natural substances. We will also highlight our unexpected chemical findings and discuss solutions to synthetic problems when the tandem reactions failed.

II. Cycloaddition Sequences to Selected Natural Products

(With reference to radical and anionic methods in relevant cases)

A. Morphine

The alkaloid morphine (**5**) was isolated in 1805 by Sertürner,[7] and the first total synthesis was completed in 1955 by Gates and Tschudi.[8] Since then interest in the development of new and clean analgesics[9] led us to consider novel ways of constructing morphine and its analogues.

0009-2665/96/0796-0195$25.00/0

Philip J. Parsons was born in Southampton in 1952. He received his B.Sc (CNAA) in 1974, M.Phil (Aston, 1975), and his Ph.D. in 1978 with Professor R. C. Cookson FRS at Southampton University. Following a period (1978–1979) at Columbia University as a postdoctoral fellow with Professor G. Stork, he returned to the University of Southampton to a lectureship and then senior lectureship (1988) in organic chemistry. In 1990 he was appointed Professor of Organic Chemistry at the University of Reading and recently (1995) has been appointed Professor of Organic Chemistry at the University of Sussex. He has authored or co-authored over 80 publications and his research interests include the novel synthesis of biologically important natural products (morphine, avermectins, galbonolides, rapamycin, frog toxins, Taxol). His research group now comprises 20 students some of whom are developing novel products for the management of memory disorders.

Clive S. Penkett was born in Oxford in 1969. He received a First Class Honours Degree in Chemistry at the University of Southampton in 1990, and moved to Reading in 1990 with Professor Philip Parsons, where he obtained his Ph.D. in 1993. After a year at the University of Pennsylvania, as a postdoctoral fellow with Professor J. D. Winkler, he returned to Reading in 1994 as a senior research fellow. In 1995 he will begin a lectureship at the University of Sussex.

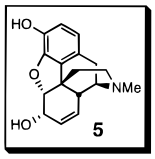
Our program of novel strategy and chemical methodology began in the late 1970s, under the direction of Malcolm Chandler[10] and was subsequently continued by Ian Matthews,[11] Grant Spoors,[12] Charles Ellwood[13] and Adrian Shell.[14]

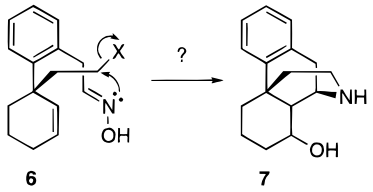
The initial plan relied on a tandem oxime alkylation/cycloaddition sequence as shown in Scheme 2.

Our idea was to alkylate the oxime (**6**), thus forming a nitrone which would perform an intramolecular [2 + 3] dipolar cycloaddition in "one pot" to give the basic morphinan skeleton (**7**). Although the original idea failed this strategy led to a concise synthetic plan for the construction of morphine (**5**) (Scheme 3).[10−13]

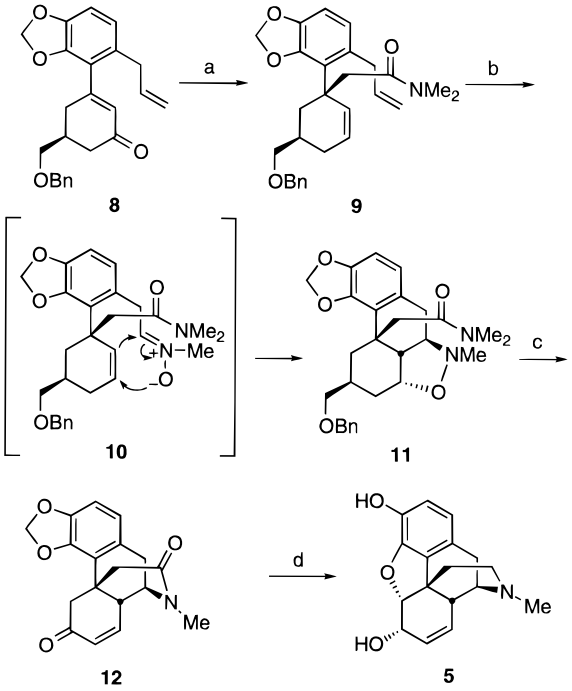
Adrian J. Shell was born in Exeter in 1966. He received his First Class Honours Degree in Chemistry in 1992 at the University of Reading, where he remained for his Ph.D. For his Ph.D. he studied intumescent pyrotechnics under the supervision of Dr. F. J. Davis, and with Professor P. J. Parsons he studied a synthesis of a fragment of FK506 and the chemistry of novel memory enhancing agents.

Scheme 2





Scheme 3

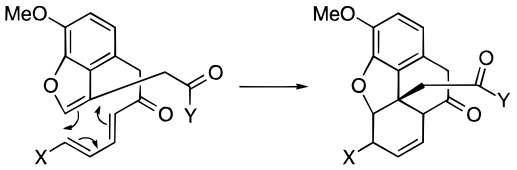


(a) (i) $NaBH_4$ / $CeCl_3$; (ii) $MeC(OMe)_2NMe_2$, 49% overall; (b) (i) OsO_4; (ii) $NaIO_4$; (iii) MeNHOH, 30% overall from **9** to **11**; (c) (i) H_2, $PdCl_2$; (ii) HCl, heat in vacuum; (iii) p-$NO_2C_6H_4SeCN$, Bu_3P, then H_2O_2; (iv) O_3, Ph_3P; (d) (i) $CuBr_2$, MeCN, then $KOBu^t$; (ii) $LiAlH_4$, 6% overall from **11**.

The enone **8**, obtained by Grignard methodology, was reduced under Luche conditions, and the resulting allylic alcohol was subjected to an Eschenmoser−Claisen rearrangement.[15] This rapidly assembled the key quaternary center in **9** for our synthesis of morphine. Oxidative cleavage of the monosubstituted double bond, followed by treatment with *N*-methylhydroxylamine formed the nitrone **10**, which spontaneously cyclized to give the isoxazolidine **11**. Hydrogenation of **11** resulted in cleavage of the N−O bond and the benzyl group to give an amino diol. The HCl salt of the amino diol cyclized in vacuo to give a cyclic amide, which on treatment with nitrophenylselenyl cyanide and tributylphosphine gave an intermediate selenide which was not isolated, but was oxidized in situ to give the enone **12**. A carbene-mediated cyclization followed by reduction gave **5** albeit in low yield.

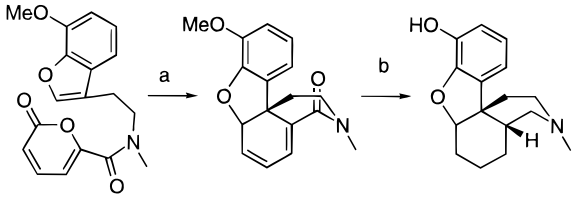
An alternative scheme involved the use of an intramolecular Diels−Alder[16] reaction as a key step (Scheme 4).

Scheme 4



This mirrors the work of Ciganek,[17] who investigated a tandem Diels−Alder/retro-Diels−Alder strategy for the construction of morphine analogues (Scheme 5).

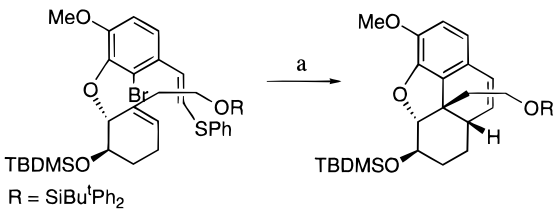
Scheme 5



(a) 215 °C, 53%; (b) (i) H_2 / Pd / C, THF; (ii) $BH_3.SMe_2$; (iii) PrSK, DMF, 86% overall.

Other tandem approaches to morphine include the work of Parker[18] and Fuchs.[19] Parker[18] (Scheme 6)

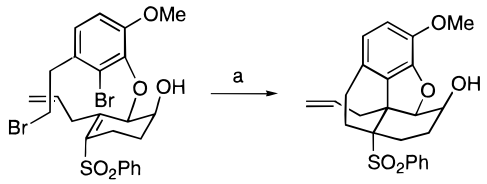
Scheme 6



(a) Bu_3SnH, AIBN, Benzene, reflux, 35%.

demonstrates the elegance of tandem radical cyclization reactions and in one step creates two rings. Fuchs[19] published a related strategy, based on a tandem anionic sequence which again formed two rings in one simple operation (Scheme 7).

Scheme 7

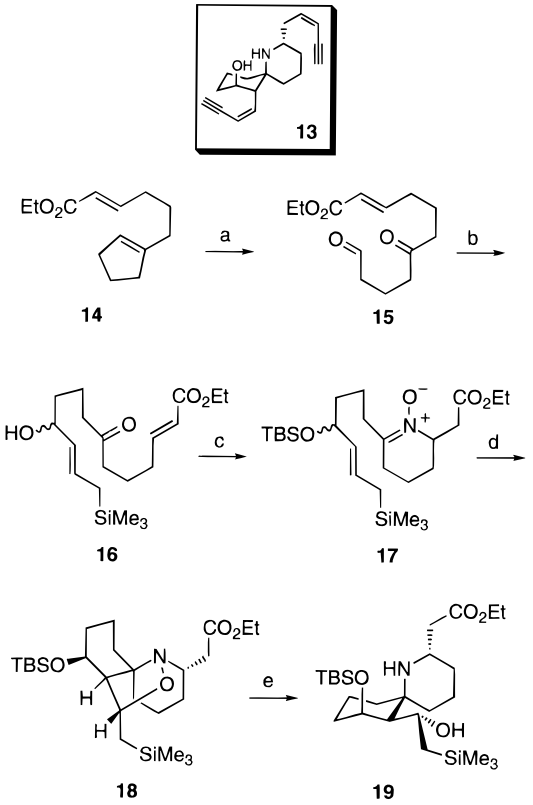


(a) n-BuLi, THF, -78 to 4°C, 63%.

B. Histrionicotoxin

Continuing our interest in tandem cycloaddition reactions, we developed a novel sequence for the construction of the potent neurotoxin histrionicotoxin (**13**). Elizabeth Tyrrell's[20] original work (outlined in Scheme 8) was extended by Richard Angell[21] and Alan Cornell[22] with a view to completing a total synthesis of the natural product.

Scheme 8



(a) (i) MCPBA; (ii) HIO_4, 56% overall; (b) 1-Bromo-3-trimethylsilylpropene, $CrCl_2$, DMF, 72%; (c) (i) TBDMSCl, imidazole, DMAP, DMF, 71%; (ii) EtOH, NH_2OH, 100%; (d) PhMe, Δ, 27%; (e) H_2 / Pd / C, 70%.

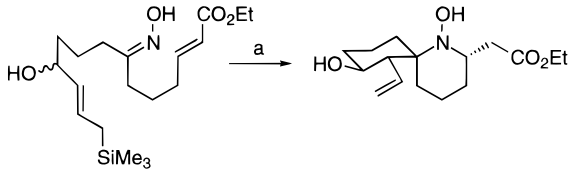
The key step involves the addition of an oxime to an electron-poor double bond; a reaction which has been extensively studied.[23,24]

Selective cleavage of the cyclopentenyl double bond in the unsaturated ester **14** provided the ketoaldehyde **15**, which underwent a chromium-mediated selective nucleophilic addition to the aldehyde carbonyl giving the cyclization precursor **16**. Reaction of **16** with hydroxylamine-initiated a tandem cascade sequence involving an addition/cyclization reaction which resulted in the formation of the isoxazolidine **18**. Although **18** was only formed in 25% yield, the efficiency of bond formation was high with four new

bonds formed in one pot. Reductive cleavage of the isoxazolidine ring produced the histrionicotoxin skeleton (**19**).

If the key cyclization reaction was performed using the unprotected secondary alcohol **20**, a one-step Michael addition/cyclization/fragmentation reaction occurred; the first example of such a tandem sequence (Scheme 9).

Scheme 9



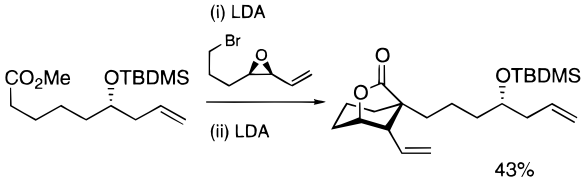
20 **21**

(a) Toluene, Δ, 40%.

The dual role of silicon to direct regiochemistry in the nitrone addition and to act as a feeble proton was pivotal in this tandem sequence.

Two total syntheses of histrionicotoxin have been reported by Kishi[25] and Stork.[26] Stork's enantioselective synthesis[26] (Scheme 10) incorporates a tandem

Scheme 10

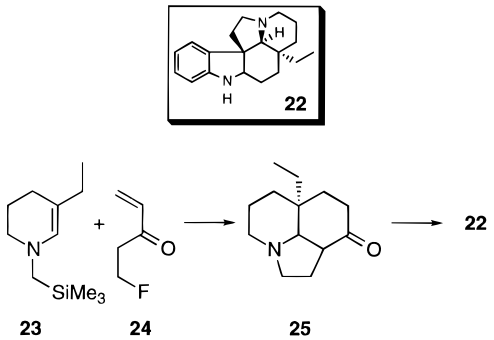


anionic sequence in the formation of one of the spirocyclic rings. The chiral lactone generated is beautifully set up for nitrogen incorporation utilizing Curtius methodology.

C. Aspidospermidine

We embarked on a synthesis of aspidospermidine (**22**) with Andrew Sharpe[27] using a strategy which involved a tandem Michael addition/elimination/cycloaddition sequence for the construction of the tricyclic ketone **25**. Our intention was to elaborate **25** to aspidospermidine (**22**) using a Fischer indole sequence [28] (Scheme 11).

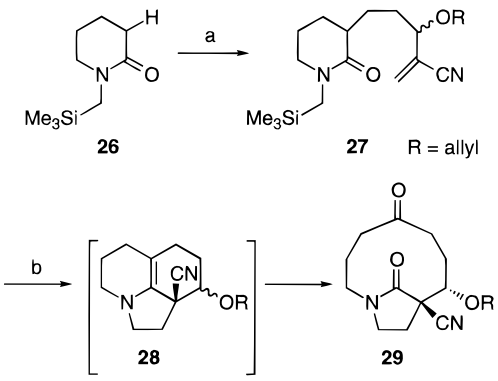
Scheme 11



23 **24** **25**

All attempts at the "one-pot" tandem sequence failed to produce the required tricyclic ketone. However, the desired cyclization was observed indirectly by employing an alkylation procedure (Scheme 12).

Scheme 12



(a) (i) LDA, $Me_3SiO(CH_2)_3Br$; (ii) Na_2CO_3 / Swern; (iii) acrylonitrile, DABCO; (iv) Allyl bromide, Ag_2O, 57% overall; (b) (i) Me_3OBF_4; (ii) Δ, CsF, DME,10%.

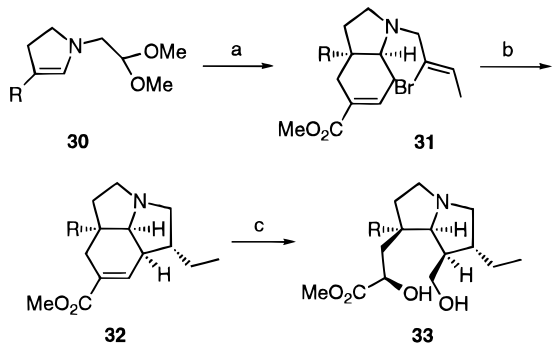
The silylated lactam **26** was converted into the unsaturated cyanide **27** using the Bayliss-Hillman[29] methodology. Treatment of **27** with Meerwein's salt followed by cesium fluoride in DME[30] gave the ketoamide **29**, which we assume is formed by oxidative cleavage of the double bond in the intermediate **28**. This offers a new and useful method for the formation of macrocyclic ketones.

III. Tandem Radical Reactions

A. Hydrogen Atom Abstraction/Cyclization Processes

In an approach to highly substituted pyrrolizidine alkaloids we envisaged a tandem hydrogen atom abstraction/cyclization sequence.[31] In 1982 David Lathbury[32] was able to demonstrate the feasibility of this reaction, and the work was subsequently continued by Ivan Pinto[33] (Scheme 13).

Scheme 13



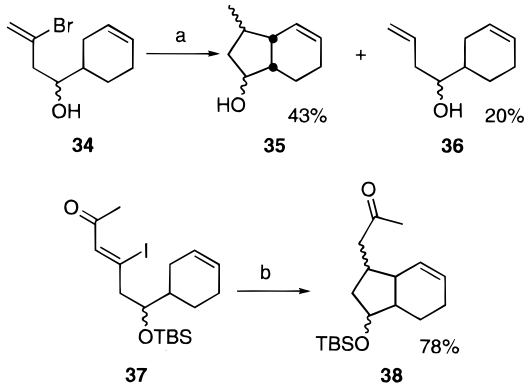
R= Ph or SPh

(a) (i) 3-carbomethoxydihydrothiophene-1,1-dioxide; (ii) $(CO_2H)_2$; (iii) PhNHOH, (iii) $MeCH{=}C(Br)CH_2Br$, K_2CO_3, 86% overall; (b) Bu_3SnH, AIBN, PhH, hv, 85%; (c) (i) HCl; (ii) O_3, $NaBH_4$, overall 56%.

The enamine **30** (prepared by a Cloke rearrangement[34]) was converted to the unsaturated ester **31** using an inverse electron demand Diels−Alder reaction followed by a deprotection and an alkylation sequence. Treatment of **31** with tri-*n*-butyltin hydride gave the tricyclic intermediate **32** which resulted from a tandem hydrogen atom abstraction/cyclization sequence. The intermediate **32** was then further elaborated to give a range of pyrrolizidines **33**.

Steven Caddick[35] extended these findings to the formation of carbocyclic rings (Scheme 14).

Scheme 14

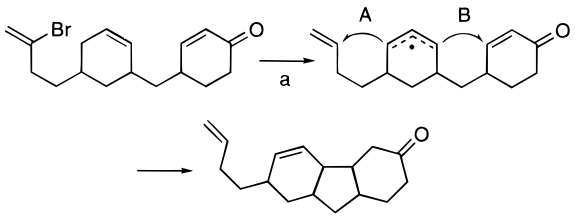


(a) 10% Bu_3SnCl, $NaCNBH_3$, AIBN, t-BuOH, reflux, 3 days; (b) Bu_3SnH, AIBN, Benzene, reflux, 0.5 hours.

Generation of the alkenyl radical from **34** under Stork's[36] catalytic tin conditions gave the cyclized product (**35**), resulting from a tandem hydrogen atom abstraction/cyclization sequence. The yield of the desired product (**35**) was low due to an electronically unfavorable cyclization step. In order to increase the yield of the cyclization product the radical precursor **37** was synthesized;[35] the radical acceptor double bond being electron poor allowed a more facile cyclization to occur.

Peter Duff[37] performed a competition experiment (Scheme 15) which demonstrated that electron-rich allylic radicals will preferentially react with electron-poor double bonds (route B) rather than electron-rich double bonds (route A).

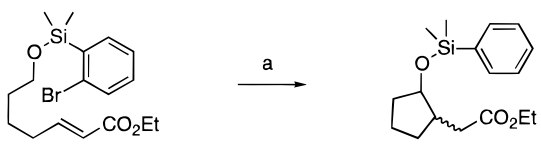
Scheme 15



(a) Bu_3SnH, AIBN, PhH, reflux, 85%.

Shortly after our original publication,[33] Curran and his co-workers[38] published other spectacular examples of hydrogen atom abstraction reactions (Scheme 16).

Scheme 16

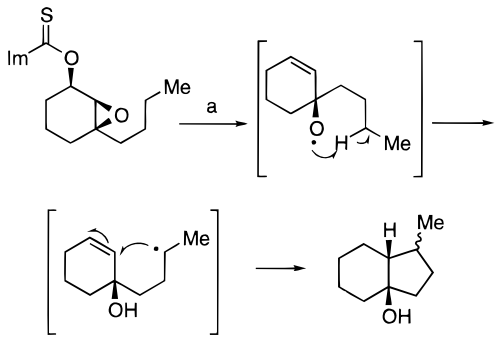


(a) 10% Bu_3SnCl, $NaCNBH_3$, AIBN, t-BuOH, reflux, 61%.

Other groups have shown the utility of hydrogen atom abstraction sequences in synthesis, including those of Rawal,[39] Murphy,[40] and Simpkins.[41]

Rawal[39] demonstrated an interesting radical-induced epoxide opening/1,5-hydrogen atom abstraction/cyclization sequence (Scheme 17).

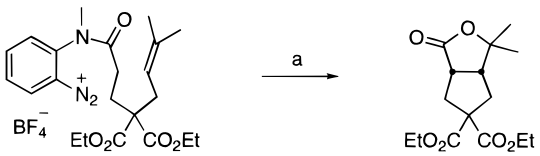
Scheme 17



(a) Bu_3SnH, AIBN, Benzene, reflux, 68%.

In a different approach Murphy[40] utilized tetrathiafulvalene to induce aryl radical formation from a diazoaromatic species which then underwent a hydrogen atom abstraction/tandem cyclization procedure to form a fused lactone (Scheme 18).

Scheme 18



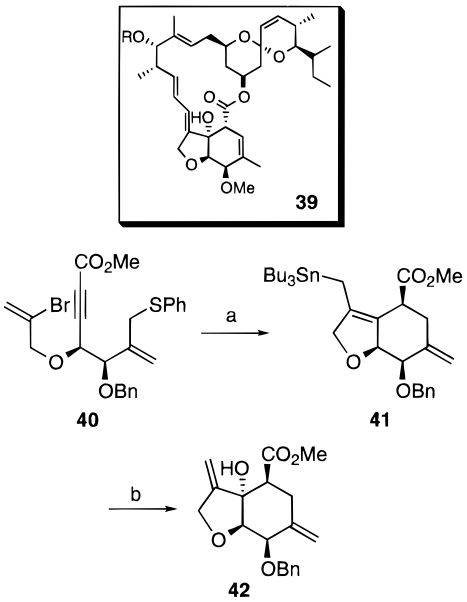
(a) Tetrathiafulvalene, 45%.

B. The Avermectins

(An excursion into organopalladium chemistry and novel cascade sequences)

The avermectins (**39**) are an important class of antiparasitic agents. Paul Willis[42,43] investigated a model for the construction of the hexahydrobenzofuran fragment of these molecules (Scheme 19).

Scheme 19



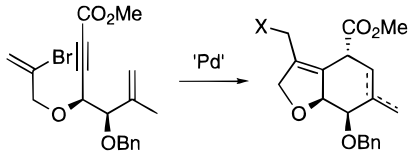
(a) Bu_3SnH, AIBN, PhH, reflux, 52%; (b) MCPBA, 30%.

The acyclic radical precursor **40** was synthesised[42] using titanium-mediated alkylation chemistry. When the bromoalkene **40** was treated with 2 equiv of tri-

n-butyltin hydride the desired tandem intramolecular cyclization/intermolecular addition of tri-*n*-butyltin radicals occurred, giving the allylstannane **41** in 52% yield. Oxidation of **41** with peracid gave the desired product **42**.

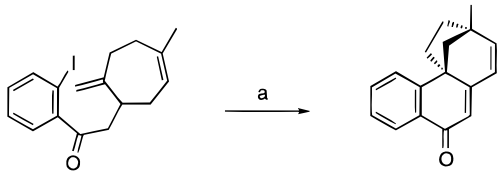
We considered the use of a palladium cascade reaction to perform the desired cyclization sequence in our hexahydrobenzofuran synthesis (Scheme 20).

Scheme 20



An important feature of these reactions is the reductive elimination of palladium to provide a synthetically useful double bond. The literature contains a wealth of examples of palladium-mediated cyclization reactions. Overman[44] has demonstrated the use of this reaction in the synthesis of scopadulcic acid B (Scheme 21).

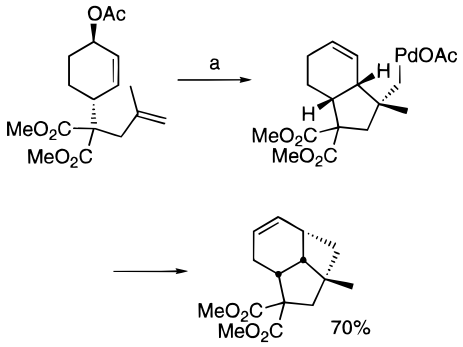
Scheme 21



(a) (i) 5% $Pd(OAc)_2$-Ph_3P (1:2), MeCN, 80°C, 85%; (ii) DDQ, PhCl, reflux, 63%.

Grigg[45] has published a tandem palladium cascade sequence for the production of polycyclic ring systems (Scheme 22).

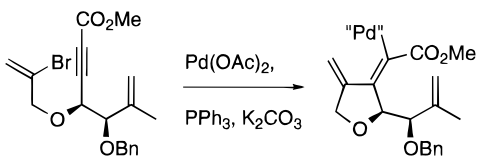
Scheme 22



(a) $Pd(OAc)_2$, PPh_3, anisole, sodium formate, 110°C.

Paul Willis attempted the intramolecular Heck reaction, but was unable to isomerize the organopalladium intermediate **46** in order to complete the final cyclization[42] (Scheme 23).

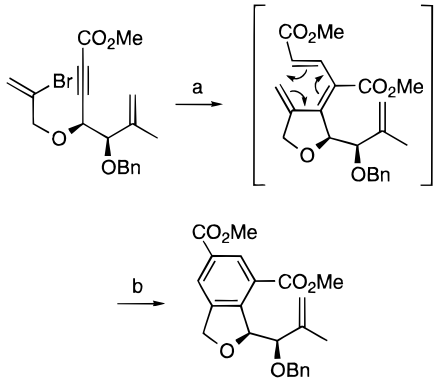
Scheme 23



45 **46**

We found, however, that the organopalladium intermediate could be trapped with a variety of alkenes resulting in a tandem cyclization/electrocyclic ring closure sequence (Scheme 24).

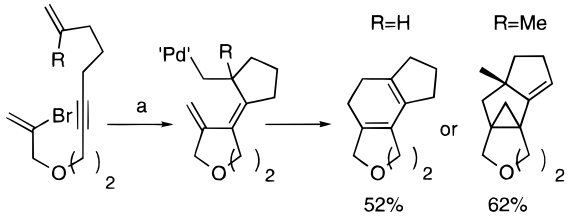
Scheme 24



(a) $Pd(OAc)_2$, Ph_3P, K_2CO_3, Methyl acrylate; (b) O_2, 56% overall.

Marijan Stefinovic and Frank Meyer[46] extended these findings to intramolecular systems (Scheme 25). These findings have been further developed by

Scheme 25

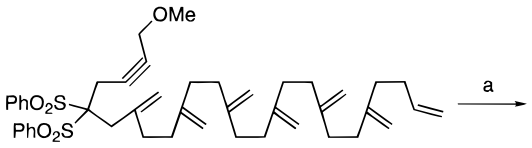


(a) $Pd(OAc)_2$, Ph_3P, Ag_2CO_3.

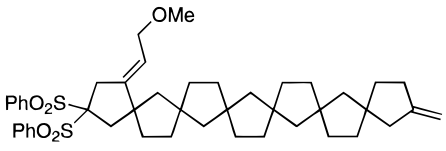
the de Meijere group.[47] We are currently exploring the use of this chemistry for the facile construction of pseudopterosin[48] and the potent anticancer agent camptothecin.[49]

The increase in molecular complexity here is dramatic and many bonds are formed in "one pot". Two spectacular examples of multi-bond-forming reactions have been published by Trost[50] and Negishi.[51] In the construction of a heptaspirane ring system **44** Trost[50] and his co-workers treated the heptaeneyne (**43**) with a palladium catalyst. The

Scheme 26



43



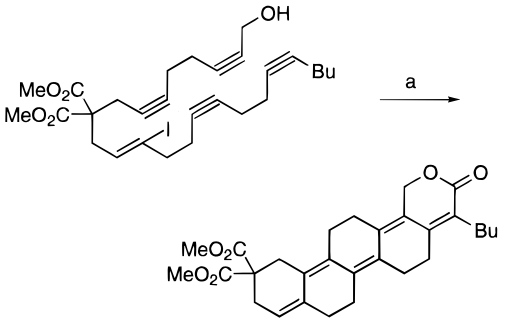
44

(a) HOAc, $Pd_2(dba)_3.CHCl_3$, $AsPh_3$, benzene, reflux, 77%.

resulting zipper reaction shows the dramatic increase in molecular complexity and the power of such a tandem cascade sequence (Scheme 26).

The impressive example by Negishi[51] of a tandem sequence with incorporation of carbon monoxide in the final step demonstrates the developments that are currently taking place in the field of palladium cascade chemistry (Scheme 27).

Scheme 27

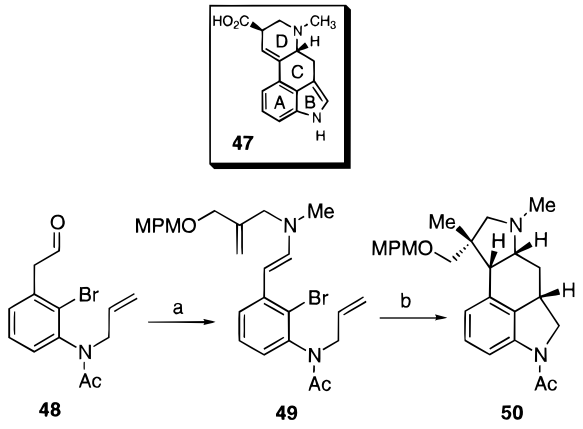


(a) $Cl_2Pd(PPh_3)_2$, CO, NEt_3, MeOH, 70°C, 66%.

C. Indole Alkaloids and Cascade Processes

We examined the possibility of using aryl radicals for the construction of various indole alkaloids. A simple synthesis of lysergic acid (**47**) was proposed which resulted in a novel approach to the natural product and its analogues. The initial work by David Cladingboel[52] is shown in Scheme 28.

Scheme 28

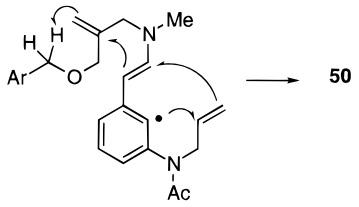


(a) $MPMOCH_2C(CH_2NHMe)=CH_2$, mol. sieves, 100%;
(b) Bu_3SnH, AIBN, PhH, reflux, 70%.

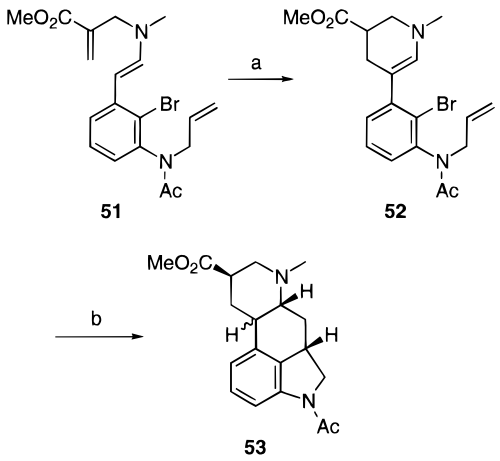
The readily available aldehyde **48** was converted into enamine **49** and subjected to a tri-*n*-butyltin hydride-mediated radical cascade cyclization to give the skeleton of lysergic acid. Unfortunately the tandem cyclization resulted in the D ring contracted analogue of lysergic acid (**50**) in high yield. The radical cascade reaction involved a 5-*exo*-*trig*-6-*endo*-*trig*-5-*exo*-*trig* cyclization/hydrogen atom abstraction sequence (Scheme 29).

In a continuation of this work, Yusuf Özlü[53] constructed the six-membered D ring of lysergic acid prior to radical cyclization. This led to a successful synthesis[54] of the lysergic acid analogue **53** (Scheme 30).

Scheme 29



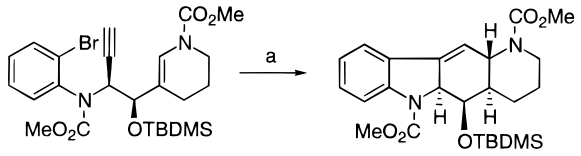
Scheme 30



(a) PhMe, reflux, 5 hours; (b) Bu_3SnH, AIBN, PhMe, reflux, 75% overall.

Further research utilizing aryl radicals[55] was performed by Julian Jenkinson[56] for the formation of a key intermediate toward the synthesis of ajmaline (Scheme 31).

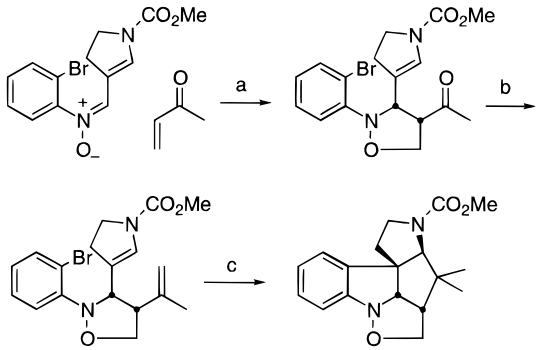
Scheme 31



(a) Bu_3SnH, AIBN, PhH, reflux, 48%.

A similar disconnection was utilized by Clive Penkett[57] in an approach to the pseudocopsinine skeleton (Scheme 32).

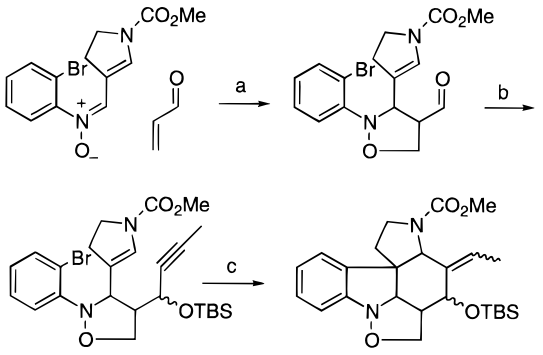
Scheme 32



(a) Sealed, tube, 105°C, 39%; (b) $Ph_3P=CH_2$, THF, -78C, 83%; (c) Bu_3SnH, AIBN, benzene, reflux, 22%.

The use of a different dipolarophile in the nitrone cycloaddition step allowed a facile entry into the aspidosperma alkaloid framework[57] (Scheme 33).

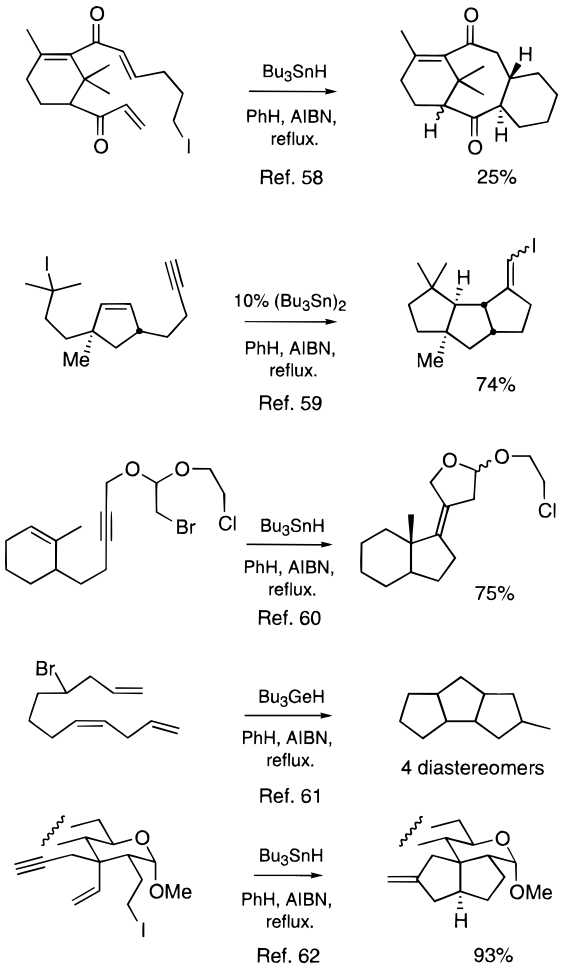
Scheme 33



(a) Sealed tube, 105°C, 100%; (b) (i) Propynyllithium, THF, -78°C, 75%; (ii) Imidazole, TBDMSCl, DMF, 95%; (c) 10% Bu_3SnCl , AIBN, $NaCNBH_3$, t-BuOH, reflux, 6%.

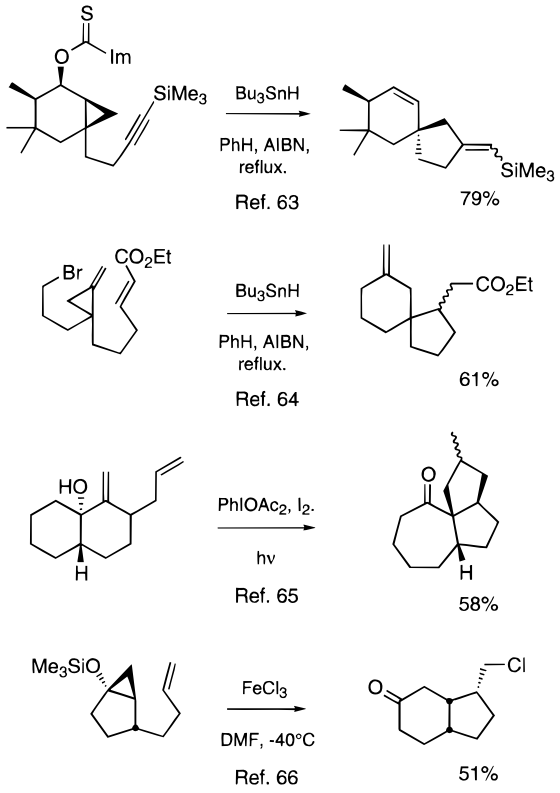
Key contributions to the field of tandem radical cyclization processes for the construction of natural products have emerged from several groups. Schemes 34 and 35 demonstrate the vast diversity of radical reactions reported to date. Scheme 34 details ex-

Scheme 34



amples of radical cyclizations by Pattenden,[58] Curran,[59] Stork,[60] Beckwith,[61] and Fraser-Reid.[62] Scheme 35 demonstrates how radical fragmentation/cyclization reactions have been used by the groups of Motherwell,[63] Kilburn,[64] Pattenden,[65] and Booker-Milburn[66] for the synthesis of highly complex molecules.

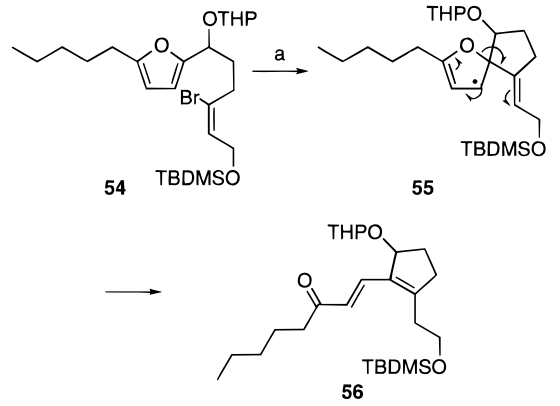
Scheme 35



D. Carbocyclic Rings via Radical Addition/ Fragmentation Sequences

Max Penverne has investigated the intramolecular addition of alkenyl radicals to furans.[67] This chemistry provides a novel entry into highly functionalized cyclopentenes (Scheme 36).

Scheme 36

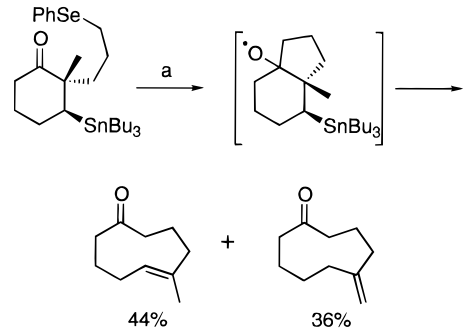


(a) Bu_3SnH, AIBN, PhMe, reflux, 40%.

Intramolecular alkenyl radical addition to the furan moiety (**54**) gave an allylic radical intermediate (**55**) which fragmented to give the highly functionalized five-membered ring (**56**). Aydin Demircan[68] has continued our work in this area with a view to the synthesis of prostanoids[2] and their analogues.

Radical addition/fragmentation processes can also be used for ring expansion reactions, as demonstrated by Baldwin[69] and Dowd.[70] Baldwin reported[69] an elegant process for the construction of medium-sized rings by a radical addition/fragmentation/elimination sequence (Scheme 37).

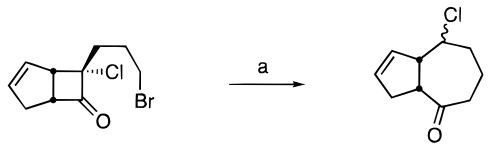
Scheme 37



(a) Bu_3SnH, AIBN, PhH, reflux.

Dowd[70] has published a flexible ring expansion sequence (Scheme 38). By altering the length of the alkyl halide chain, the cyclobutanone ring can be expanded by 3 or 4 carbons (Scheme 38).

Scheme 38



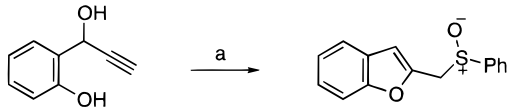
(a) Bu_3SnH, AIBN, PhH, reflux, 80%.

IV. Tandem Anionic Processes

A. Formation of Carbocyclic and Heterocyclic Rings

On the basis of our earlier work on the inter- and intramolecular addition of alcohols to allene sulfoxides,[71−73] Matthew Gray[74] developed a tandem sequence for the construction of highly substituted benzofurans (Scheme 39).

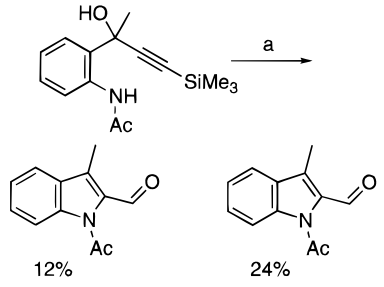
Scheme 39



(a) PhSCl, Et_3N, -23°C, Et_2O, 98%.

The chemistry outlined in Scheme 39 was further developed for the synthesis of indoles. A tandem [2,3]-sigmatropic shift/Michael addition/sila-Pummerer rearrangement was observed as a "one-pot" sequence. We are directing this chemistry to the synthesis of complex indole alkaloids (Scheme 40).

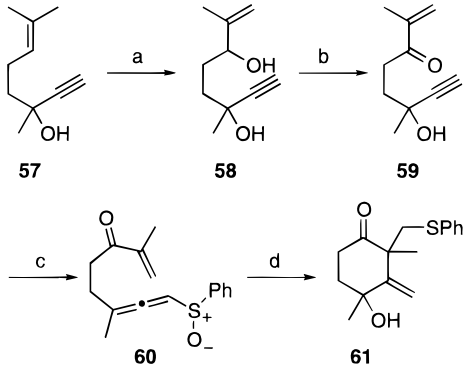
Scheme 40



(a) (i) PhSCl, Et_3N, Et_2O, -23°C;
(ii) $HgCl_2$, H_2O, -23°C.

A further extension of the above chemistry for the construction of all-carbon ring systems was investigated by Marijan Stefinovic[75] (Scheme 41).

Scheme 41

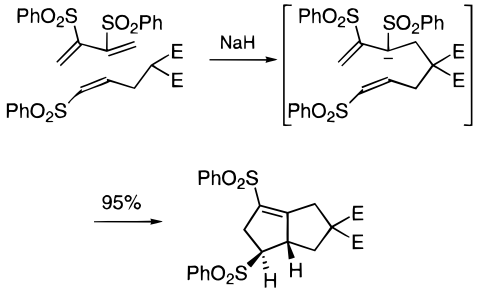


(a) (i) O_3, CH_2Cl_2, -78°C, then Zn / HOAc; (ii) isopropenylmagnesium bromide, THF, 70%; (b) DMSO, SO_3.py, NEt_3, 56%; (c) PhSCl, Et_2O, NEt_3, -20°C, 70%; (d) PhSLi, THF, 0°C.

From dehydrolinalool (**57**) the allenyl sulfoxide **60** was prepared in three steps. Addition of lithium thiophenoxide to **60** led to the isolation of a highly substituted cyclohexane ring **61**. A tandem double Michael addition/[2,3]-sigmatropic shift occurred providing a precursor of the taxol A ring in one synthetic operation.

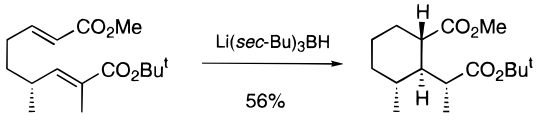
Other tandem anionic approaches toward the synthesis of carbocyclic rings have been published by Padwa[76] and Yoshii.[77] Padwa[76] reported the elegant use of a tandem Michael sequence for the construction of fused rings (Scheme 42).

Scheme 42



Yoshii[77] demonstrated the use of a sequential Michael addition sequence for the formation of a carbocyclic ring with a high degree of stereocontrol (Scheme 43).

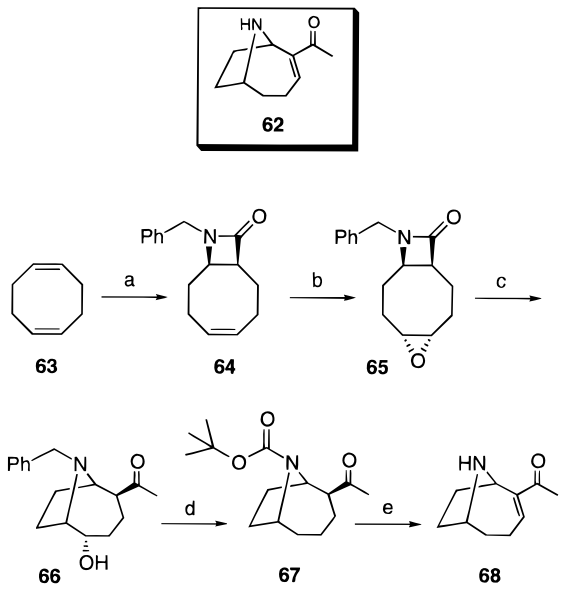
Scheme 43



B. Tandem Ring Opening/Cyclization Cascade Sequences: A Total Synthesis of Anatoxin

The blue-green algae *Anabaena flos aqua* produces a toxin which is known as "very fast death factor" or anatoxin A (**62**).[78] The toxin has proved fatal to livestock, waterfowl and fish as it mimics the neurotransmitter acetylcholine and acts as a potent agonist for the nicotinic acetylcholine receptor

Scheme 44

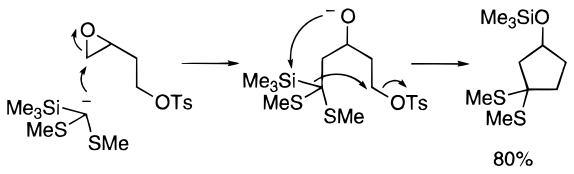


(a) (i) $ClSO_2NCO$, CH_2Cl_2, 48%; (ii) $NaOH_{(aq)}$, CH_2Cl_2, Bu_4NHSO_4, BnBr, 95%; (b) MCPBA, CH_2Cl_2, 84%; (c) MeLi, THF, -25°C, 40%; (d) (i) H_2, 10% Pd / C, MeOH, Boc_2O, 84%; (ii) Ph_3P, I_2, imidazole, CH_2Cl_2, 85%; (iii) Bu_3SnH, AIBN, PhMe, reflux, 86%; (e) (i) NaH, TBDMSCl; (ii) PhSeCl; (iii) MCPBA; (iv) TFA, 86% from **67** to **68**.

(nAChR). In our approach to anatoxin we envisaged a tandem β-lactam ring opening/epoxide ring opening sequence to give in one synthetic operation the anatoxin skeleton (Scheme 44). Mark Underwood[72] carried out the model studies and Nick Camp completed the synthesis.[79]

Treatment of cyclooctadiene (**63**) with chlorosulfonyl isocyanate followed by epoxidation with MCPBA yielded the lactam-epoxide **65**. Reaction of the lactam epoxide **65** with methyllithium results in a tandem β-lactam ring opening/intramolecular cyclization to give the alcohol **66** which was readily converted to anatoxin by known methods.[80] Other tandem anionic processes have also been utilized by Fuchs[19] (Scheme 7), Stork[28] (Scheme 10), and Schaumann[81] (Scheme 45).

Scheme 45



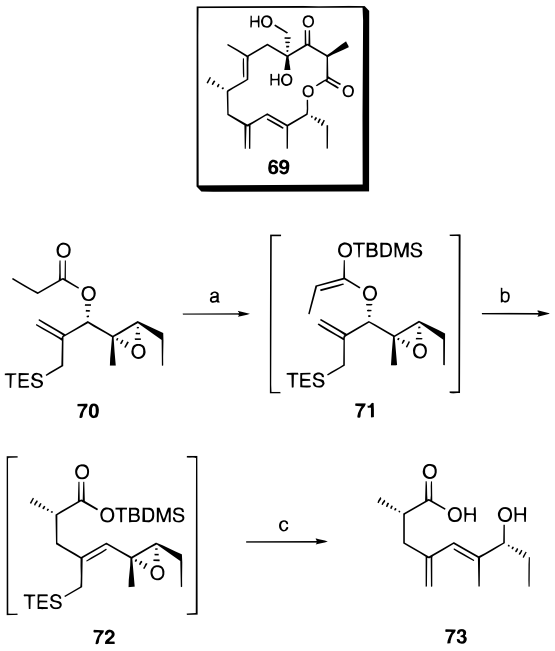
V. Rearrangement/Fragmentation Routes

The galbonolides have been shown to have a broad range of activity against fungi that are pathogenic to man.[82] Our synthesis toward galbonolide B (**69**) involves as a key step, a tandem "Ireland–Claisen[83]/silyl-mediated epoxide opening" reaction, to set up the stereochemistry of the lower fragment. James Eshelby's work[84] is shown in Scheme 46.

An Ireland–Claisen[83] rearrangement of the acetal **71** yielded the silyl ester **72**, which upon acid workup rearranged to the alcohol **73**.

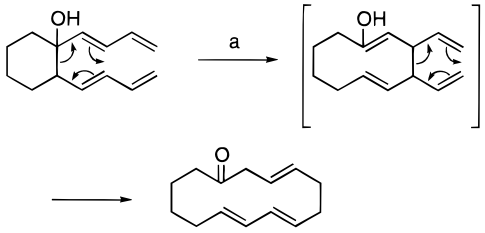
Other examples representative of this theme have been reported by Wender[85] and Overman.[86] Wender[85] published a tandem Cope–Cope rearrangement to form a 14-membered macrocycle in one pot (Scheme 47). Overman assembled the skeleton of strychnine[86] utilizing an aza-Cope–Mannich sequence (Scheme 48).

Scheme 46



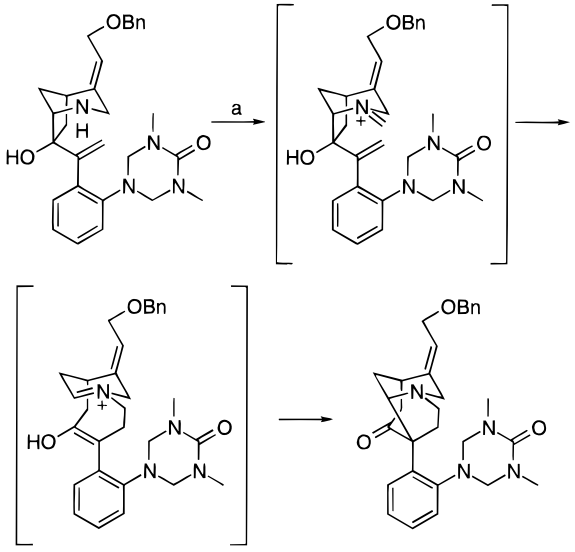
(a) LDA, TBDMSCl, DMPU, THF, -78°C; (b) reflux; (c) (i) $NH_4Cl_{(aq)}$; (ii) dil.HCl, 90% overall.

Scheme 47



(a) KH, THF, reflux, 90%.

Scheme 48



(a) $(CH_2O)_n$, Na_2SO_4, MeCN, 98%.

VI. Conclusion

This short review covers recent aspects of tandem methodology and its use for the construction of highly functional molecules. The future of organic synthesis lies in efficient methodology and the discovery of new processes for controlling the formation of homochiral centers as well as building up complex chemical architecture using simple techniques. Brevity in organic synthesis is of paramount importance for industry and over the next few years we will see dramatic improvements in this subject and the development of novel catalysts for achieving tandem reactions. Such processes will minimize waste and costs will be kept to a minimum thus increasing efficiency.

Organic synthesis remains the key training ground for organic chemists and underpins the economy of this country. We owe much of the modern discoveries in chemistry to the polymer chemists, who were the forerunners of cascade reaction processes.

VII. Acknowledgments

We wish to thank the Parsons group past and present for their enthusiasm and dedication to organic chemistry over the years and in particular those students who were brave enough to tackle the more speculative projects. One of us (P.J.P.) wishes to thank Professors Richard C. Cookson and Gilbert Stork for their continued support and encouragement.

VIII. References

(1) (1) Trost, B. M. *Science* **1991**, *254*, 1471. N. Hall, *Science* **1994**, *266*, 32.
(2) Corey, E. J.: Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley Interscience: New York, 1989.
(3) Bryce-Smith, D.; Gilbert, A.; Orger, B. H. *J. Chem. Soc., Chem. Commun.* **1966**, 512. Wilzbach, K. E.; Kaplan, L. *J. Am. Chem. Soc.* **1966**, *88*, 2066.
(4) Wender, P. A.; Howbert, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 688.
(5) Ho, T. L. *Tandem Reactions in Organic Synthesis*; Wiley-Interscience: New York, 1992.
(6) Wender, P. A.; Miller B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Eds., JAI Press: Greenwich, CT, 1993; Vol. 2, pp 27−67.
(7) Sertürner, F. W. A. (Trommsdorff's) *J. Pharmazie* **1805**, *13*, 234.
(8) Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1952**, *74*, 1109. Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1955**, *78*, 1380.
(9) Birch, P. J.; Hayward, N. J.; Rogers, H.; Hayes, A. G.; Naylor, A.; Scopes, D. I. C. In *New Leads in Opioid Research*; Van Ree, J. M., Mulder, A. H., Wiegant, V. M., Van Wimersma Greidanns, T. B., Eds.; Excepta Medica, Elsevier: Amsterdam, 1990; p 188.
(10) Chandler, M.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1984**, 322−323. Chandler, M. Unpublished results.
(11) Matthews, I. Ph.D. Thesis, University of Southampton, 1986.
(12) Spoors, P. G. Ph.D. Thesis, University of Southampton, 1989.
(13) Ellwood, C. W. Ph.D. Thesis, University of Southampton, 1989.
(14) Shell, A.; Parsons, P. J. Unpublished results.
(15) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030.
(16) Roush, W. R. *Comprehensive Organic Synthesis; Strategy and Efficiency in Modern Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 513.
(17) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261−6262.
(18) Parker, K. A.; Fokas, D. *J. Org. Chem.* **1994**, *59*, 3933−3938
(19) Fuchs, P. L.; Toth, J. E.; Hamman, P. R. *J. Org. Chem.* **1988**, *53*, 4694.
(20) Tyrrell, E. Ph.D. Thesis, University of Southampton, 1989.
(21) Parsons, P. J.; Angell, R.; Naylor, A.; Tyrell, E. *J. Chem. Soc., Chem. Commun.* **1993**, 366−367. Angell, R. Ph.D. Thesis, University of Reading, 1992.
(22) Cornell, A. Ph.D. Thesis, University of Reading, 1996.
(23) Morita, K.; Obayashi, M.; Ochiai, M. *Tetrahedron* **1967**, *23*, 2641. Lablanche-Combier, A.; Villaume, M. L. *Tetrahedron* **1968**, *24*, 6951. Winterfeldt, E.; Krohn, W.; Stracke, H.-U. *Chem. Ber.* **1969**, *102*, 2346.
(24) Grigg, R.; Armstrong, P.; Warnock, W. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1325. Grigg, R.; Armstrong, P.; Warnock, W. J.; Surendrakumar, S. *J. Chem. Soc., Chem. Commun.* **1987**, 1327. Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 10399.
(25) Carey, S. C.; Kishi, Y.; Aratani, M. *Tetrahedron Lett.*, **1985**, *26*, 5887.
(26) Stork, G.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 5875−5876.
(27) Sharpe, A. Ph.D. Thesis, University of Reading, 1995.
(28) Stork, G.; Dalfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872.
(29) Bayliss, A. B.; Hillman, M. E. G. P. 215513, 1972.
(30) Padwa, A.; Fryxell, G. E.; Gasdaska, J. R.; Vendatramanan, M. K.; Wong, G. S. K. *J. Org. Chem.* **1989**, *54*, 644. Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941.
(31) Barton, D. H. R. *Pure Appl. Chem.* **1968**, *16*, 1. Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170−177. Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051.
(32) Lathbury, D. C. Ph.D. Thesis, University of Southampton, 1982.
(33) Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81.
(34) Cloke, J. B. *J. Am. Chem. Soc.* **1929**, *51*, 1174.
(35) Borthwick, A. D.; Caddick, S.; Parsons, P. J. *Tetrahedron Lett.* **1990**, *31*, 6911−6914. Parsons, P. J.; Caddick, S. *Tetrahedron* **1994**, *50*, 13523−13532. Borthwick, A. D.; Caddick, S.; Parsons, P. J. *Tetrahedron* **1992**, *48*, 10655−10666. Caddick, S. Ph.D. Thesis, University of Southampton, 1989.
(36) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303.
(37) Duff, P. Ph.D. Thesis, University of Reading, 1993.
(38) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900.
(39) Rawal, V. H.; Newton, R. C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, *55*, 5181−5183.
(40) Begley, M. J.; Murphy, J. A.; Room, S. J. *Tetrahedron Lett.* **1994**, *35*, 8679−8682.
(41) Brown, C. D. S.; Simpkins, N. S.; Clinch, K. *Tetrahedron Lett.* **1993**, *34*, 131−132.
(42) Willis, P. Ph.D. Thesis, University of Southampton, 1989.
(43) Parsons, P. J.; Willis, P. A.; Eyley, S. C. *J. Chem. Soc., Chem. Commun.* **1988**, 283. Parsons, P. J.; Willis, P.; Eyley, S. C. *Tetrahedron* **1992**, *48*, 9461−9472.
(44) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042−2044.
(45) Grigg, R.; Sridharan, V.; Sukirthalingam S. *Tetrahedron Lett.* **1991**, *32*, 3855−3858.
(46) Parsons, P. J.; Stefinovic, M.; Willis, P.; Meyer, F. (in part) *Synlett* **1992**, 864−866.
(47) de Meijere, A.; Meyer, F. E. *Synlett* **1991**, 777. de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411.
(48) Broka, C.; Chan, S.; Peterson, B. *J. Org. Chem.* **1988**, *53*, 1586.
(49) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888.
(50) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 791; *J. Am. Chem. Soc.* **1993**, *115*, 12491. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281. Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421−9438.
(51) Negishi, E.-I.; Sugihara, T.; Copéret, C.; Owczarczyk, Z.; Harring, L. S. *J. Am. Chem. Soc.* **1994**, *116*, 7923−7924.
(52) Cladingboel, D. E. Ph.D. Thesis, University of Southampton, 1990.
(53) Özlü, Y. Ph.D. Thesis, University of Southampton, 1993.
(54) Özlü, Y.; Cladingboel, D. E.; Parsons, P. J. *Synlett* **1993**, 357−358. Özlü, Y.; Cladingboel, D. E.; Parsons, P. J. *Tetrahedron* **1994**, *50*, 2183−2206.
(55) Jones, K.; Wilkinson, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1767.
(56) Jenkinson, J. Ph.D. Thesis, University of Southampton, 1991. Jenkinson, J.; Parsons, P. J.; Eyley, S. C. *Synlett* **1992**, 679−680.
(57) Penkett, C. S. Ph.D. Thesis, University of Reading, 1993. Parsons, P. J.; Penkett, C. S.; Cramp, M. C.; West, R. I.; Warrington, J.; Saraiva, M. C. *Synlett* **1995**, 507−509.
(58) Pattenden, G.; Hitchcock, S. A. *Tetrahedron Lett.* **1992**, *33*, 4843−4846; (corrigendum) *Tetrahedron Lett.* **1992**, *33*, 7448. ECTOC on-line conference, 1995 (http://www.ch.ic.ac.uk /ectoc/papers/ pattenden/). Pryde, D. W. Unpublished work, Nottingham University.
(59) Curran, D. P.; Chen, M. H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489−2490.
(60) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3720−3722.
(61) Beckwith, A. L. J.; Roberts, D. H.; Scheisser, C. H.; Wallner, A. *Tetrahedron Lett.* **1985**, *26*, 3349.
(62) Fraser-Reid, B.; Tsang, R. *J. Am. Chem. Soc.* **1986**, *108*, 2116−2117.
(63) Motherwell, W. B.; Harling, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1380.
(64) Kilburn, J. D.; Santagostino, M. *Tetrahedron Lett.* **1995**, *36*, 1365−1368.

(65) Pattenden, G.; Mowbray, C. E. *Tetrahedron Lett.* **1993**, *34*, 127−30. Ellwood, C. W.; Pattenden, G. *Tetrahedron Lett.* **1991**, *32*, 1591−1594. Pattenden, G.; Hollingworth, G. J.; Schulz, D. J. *Aust. J. Chem.* **1995**, *48*, 381−399.
(66) Booker-Milburn, K. I.; Thompson, D. F. *Synlett* **1993**, 592−594.
(67) Penverne, M. Ph.D. Thesis, University of Reading, 1994. Parsons, P. J.; Penverne, M.; Pinto, I. L. *Synlett* **1994**, 721−722.
(68) Demircan, A. M.Sc. Thesis, University of Reading, 1995.
(69) Baldwin, J. E.; Adlington, R. M.; Robertson, J. *J. Chem. Soc., Chem. Commun.* **1988**, 1404.
(70) Dowd, P.; Zhang, W. *J. Org. Chem.* **1992**, *57*, 7163−7171.
(71) Cutting, I. Ph.D. Thesis, University of Southampton, **1983**. Cutting, I.; Parsons, P. J. *Tetrahedron Lett.* **1983**, *24*, 4463. Cutting, I.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1983**, 1209.
(72) Underwood, J. M. Ph.D. Thesis, University of Southampton, 1989.
(73) Pairaudeau, G.; Parsons, P. J.; Underwood, J. M. *J. Chem. Soc., Chem. Commun.* **1987**, 1718.
(74) Gray, M.; Ph.D. Thesis, University of Reading, **1993**. Gray, M.; Parsons, P. J. *Synlett*, **1991**, 729. Gray, M.; Parsons, P. J.; Neary, A. P. *Synlett* **1992**, 597−598. Gray, M.; Parsons, P. J.; Neary, A. *Synlett* **1993**, 281−282.
(75) Stefinovic, M.; Ph.D. Thesis, University of Reading, 1994. Parsons, P. J.; Stefinovic, M. *Synlett* **1993**, 931.
(76) Padwa, A.; Watterson, S. H.; Ni, Z. *J. Org. Chem.* **1994**, *59*, 3256−3258.
(77) Yoshii, E.; Hori, K.; Nomura, K.; Yamaguchi, K. *Synlett* **1995**, 568−570.
(78) Carmichael, W. W.; Biggs, D. F.; Gorham, P. R. *Science* **1975**, 187, 542.
(79) Parsons, P. J.; Camp, N. P.; Underwood, J. M.; Harvey, D. M. (in part) *J. Chem. Soc., Chem. Commun.* **1995**, 1461.
(80) Peterson, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539. Sardina, F. J.; Howard, M. H.; Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 4654.
(81) Fischer, M.-R.; Kirschning, A.; Michel, T.; Shaumann, E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 217−218.
(82) Achenbach, H.; Muhlenfeld, A.; Fauth, U.; Zahner, H. *Tetrahedron Lett.* **1985**, *26*, 6167−6170. Fauth, U.; Zahner, H.; Muhlenfeld, A.; Achenbach, H. *J. Antibiot.* **1986**, *39*, 1760−1764. Fauth, U.; Zahner, H.; Muhlenfeld, A.; Achenbach, H. DE 36 32, 168; Chem. Abstr. **1987**, *107* (5), 38121. Fauth, U.; Zahner, H.; Muhlenfeld, A.; Achenbach, H. *Ann. N. Y. Acad. Sci.* **1988**, *544*, 128−140.
(83) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897−5898. Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868−2877. Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48−61. Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479−485.
(84) Parsons, P. J.; Eshelby, J. J.; Sillars, N. C.; Crowley, P. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1497.
(85) Wender, P. A.; Sieburth, McN. S. *Tetrahedron Lett.* **1981**, *22*, 2471.
(86) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293−9294.

CR950023+