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New processes for the synthesis of biologically relevant heterocycles*

Martin G. Banwell

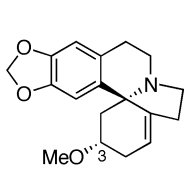
Research School of Chemistry, Institute of Advanced Studies,
The Australian National University, Canberra, ACT 0200, Australia

Abstract: This article describes the utility of certain readily accessible, ring-fused *gem*-dihalogenocyclopropanes as building blocks for the synthesis of heterocyclic and biologically active compounds.

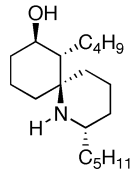
Keywords: alkaloids; allylic cations; dihalogenocyclopropane; electrocyclic ring-opening; nucleophilic trapping; radical addition/elimination.

INTRODUCTION

The natural products or natural product analogs **1–6** shown below exemplify the diverse range of heterocycles that can display interesting biological properties. Another common feature of these particular compounds is that, in our minds at least, they would appear to be accessible synthetically through the manipulation of certain readily available and ring-fused *gem*-dihalogenocyclopropanes. Accordingly, a brief discussion on the generation and chemical reactivity of these strained three-membered ring compounds is provided at this point [1].



1
(–)-Erythramine



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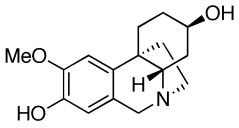
Perhydrohistrionicotoxin



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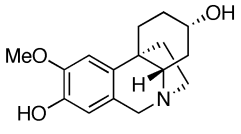
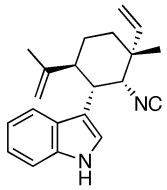
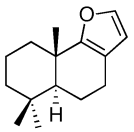


4
(–)-*epi*-Maritinamine



5
Hapalindole C



6
Pallescensin A

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gem-Dichloro- and *gem*-dibromo-cyclopropanes (**7**, Fig. 1) are generally prepared by the addition of dichloro- or dibromo-carbene to the corresponding olefin [1d]. Often this is achieved using the Mąkosza phase-transfer conditions [2] that involve treating a solution of the olefin and a quaternary ammonium salt such as triethylbenzylammonium chloride (the phase-transfer catalyst) in the relevant haloform with 50 % w/v aqueous sodium hydroxide. Highly effective variations on this approach include the application of ultrasonication techniques [3]. Whilst, on the face of it, such reaction conditions might seem rather harsh, and thus unattractive in terms of their application to the synthesis of complex organic molecules, surprisingly sensitive compounds readily survive these processes. For example, dichlorocarbene adds efficiently to the double bond of allylic acetates without any accompanying cleavage of the ester moiety [4]. This is because the concentration of hydroxide ion in the organic phase is very low indeed.

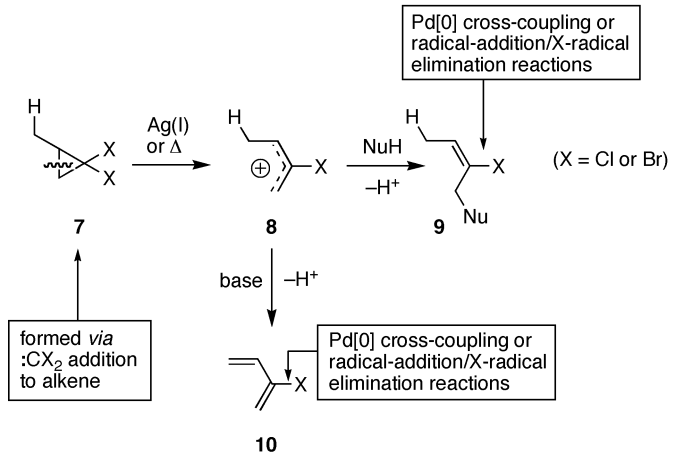
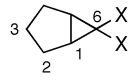


Fig. 1

While *gem*-dihalogenocyclopropanes are highly strained species, they also have quite reasonable kinetic stability, meaning that they can be carried through even rather lengthy reaction sequences without misbehaving. Furthermore, the reactivity of these cyclopropanes is orthogonal to that of many other functional groups, meaning that they can be deployed in the synthesis of quite complex (polyfunctionalized) systems. Yet, at the appointed time and by exposure to the rather specific reaction conditions, particularly those involving silver(I) salts, these compounds can be induced to undergo heterolysis of one of the carbon-halogen bonds and so triggering an accompanying electrocyclic ring-cleavage reaction leading to the generation of the allylic cation **8** [5]. The fate of such cations depends upon the precise conditions under which they are generated. For example, in the presence of added nucleophiles (NuH) this species can be captured so as to deliver systems of the general type **9**. On the other hand, the generation of the cation **8** in the presence of base results in deprotonation and formation of the halogenated diene **10**. In an overall sense then, the two-step conversion of the starting, mono-functional olefin into the trifunctional systems **9** or **10** represents a high "value-adding" sequence that delivers products incorporating three orthogonal functional groups, including an alkenyl halide moiety that can engage in Pd[0]-catalyzed cross-coupling reactions [6] or in radical addition-(halogen)elimination processes (see below). Another noteworthy aspect of the conversion **8** → **9** or **10** is that it allows for the creation of highly substituted carbon–carbon double bonds of well-defined geometry, something that is often difficult to achieve by more conventional means [7].

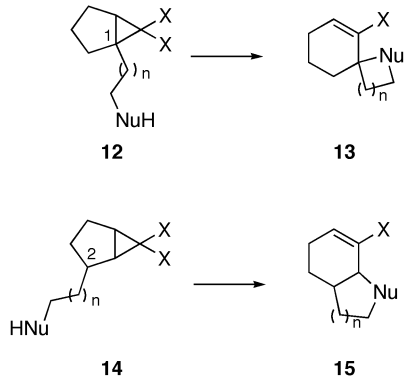
Our own interests in the processes defined above, which have only been exploited to a limited extent in chemical synthesis, have been focused on those variations where the nucleophilic species cap-

turing the allylic cation, **8**, is tethered to it [8]. In particular, we have become especially interested in cases involving ring-opening/nucleophilic trapping of the dibromo- and dichloro-carbene adducts of cyclopentene derivatives because such processes lead to the formation of various ring-fused cyclohexanes which are ubiquitous motifs encountered in natural products. Furthermore, the annulation of a three-membered ring to a five-membered one, as encountered in structure **11**, provides a system incorporating additional elements of strain and one that is, therefore, more readily engaged in the desired electrocyclic ring-opening process.



11

If one considers the 6,6-dihalobicyclo[3.1.0]hexane framework, **11**, there are four distinct sites within it (at C-1, C-2, C-3, and C-6) at which a tethered nucleophile could be attached and such that, upon opening of the three-membered ring and nucleophilic capture of the ensuing cation by this nucleophile, one of four distinct types of products could be obtained. Two of these four possibilities are shown in Scheme 1. Thus, when the nucleophile is attached through C-1 then the substrate, **12**, might be expected to engage in the proposed reaction sequence so as to generate a spirocyclic product of the general form **13**. On the other hand, when the substrate incorporates a nucleophile tethered through C-2, as seen in structure **14**, then this might be expected to deliver a ring-fused product of the general form **15**. As is illustrated in the following section, both of these processes have proven effective in delivering ring-fused compounds relevant to the synthesis of natural products.



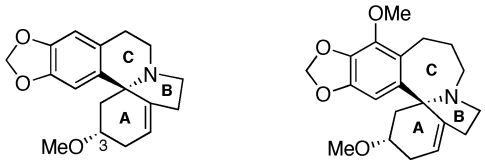
Scheme 1

SPECIFIC EXAMPLES OF THE USE OF *gem*-DIHALOCYCLOPROPANES IN THE SYNTHESIS OF BIOLOGICALLY RELEVANT HETEROCYCLES

Total synthesis of *ent*-erythramine

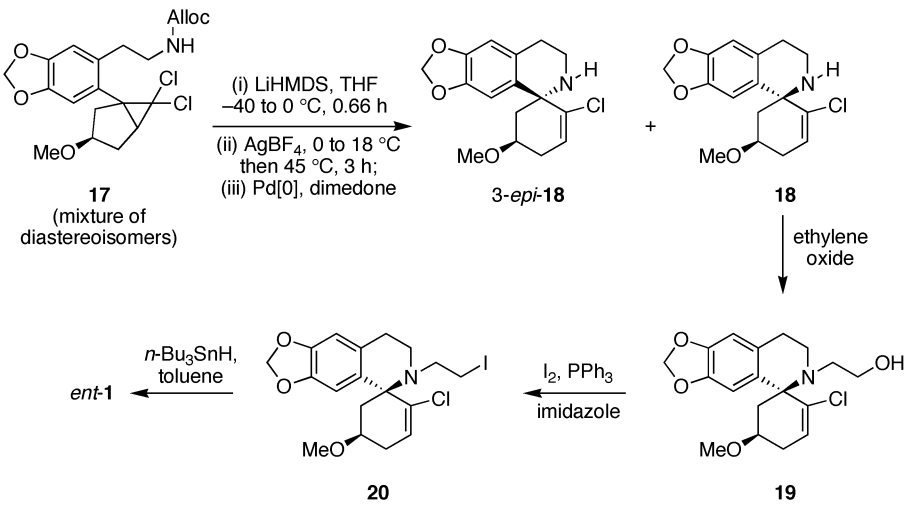
Some of our first attempts to exploit the spirocyclization processes defined in Scheme 1 for the purposes of natural products synthesis were concerned with assembling the heterocyclic frameworks of the alkaloids erythramine (**1**) and dyshomerythrine (**16**). The former natural product, which incorporates a six-membered C-ring, has been isolated from a variety of plant sources, including the seeds of *Erythrina sandwicensis* [9]. Like other members of the erythrina alkaloid family, erythramine displays a range of interesting biological activities, including curare-like action, hypnotic effects, cardiovascular

activity, and molluscicidal properties. Dyshomerythrine, which incorporates a seven-membered C-ring, has been isolated in significant quantities from *Lagarostrobos colensoi* (New Zealand silver pine) and displays useful activity against various agriculturally important insect pests [10].



1 **16**

Key elements of our ultimately successful synthesis of *ent*-erythramine (*ent*-**1**) are shown in Scheme 2 [11,12] and involved the spirocyclization of the *gem*-dichlorocyclopropane **17**, a compound that was readily prepared in enantiomerically pure form (but as a mixture of diastereoisomers) by chemoenzymatic means. Thus, successive treatment, at –40 to 0 °C, of a tetrahydrofuran (THF) solution of the latter material with lithium hexamethyldisilazide (LiHMDS) and reaction of the resulting conjugate base with silver tetrafluoroborate, at 0 to 45 °C, afforded a diastereoisomeric mixture of the expected spirocyclization products. When the deprotonation step was omitted, then the yields of these spirocyclization products dropped dramatically, presumably because of the reduced nucleophilicity of the carbamate nitrogen. Similarly, when the Boc-protected analog of compound **17** was employed, then almost no spirocyclization products were detected. This is attributed to the bulky Boc-group slowing the rate of interception of the intermediate allylic cation by the carbamate nitrogen. Subjection of the above-mentioned mixture of spirocyclization products to treatment with $Pd(PPh_3)_4$ and dimedone resulted in cleavage of the Alloc-group and thus affording a chromatographically separable mixture of the desired compound **18** (26 %) and its C-3 epimer, viz. 3-*epi*-**18** (30 %). Completion of the synthesis of erythramine from product **18** requires annulation of the B-ring through introduction of an ethylene bridge between nitrogen and the sp^2-hydridized carbon bearing the chlorine. To these ends, a methanolic solution of secondary amine **18** was treated, in a sealed tube, with excess ethylene oxide at 0 to 45 °C and the ensuing primary alcohol **19** (58 %) converted into the corresponding iodide **20** (75 %) using molecular iodine in the presence of triphenylphosphine and imidazole. Finally, treatment of compound



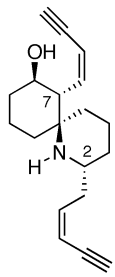
Scheme 2

21 with tri-*n*-butyltin hydride in toluene at 80 °C resulted in the formation of the target compound *ent*-**1** which was obtained in 89 % yield. This work constitutes the first total synthesis of erythramine in either enantiomerically pure or racemic form. Interestingly, applying the B-ring annulation protocol just described to the other spirocyclization product, viz. 3-*epi*-**18**, has allowed us to prepare 3-*epi*-erythramine [12].

Apart from the spirocyclization process that allows for the conversion **17** → **18**, the other notable feature of this synthesis is the final step (viz. **20** → *ent*-**1**) which is presumed to involve initial formation of a carbon-radical at that center bearing the iodine then 5-*exo*-trig-type cyclization of this species onto the chlorine-bearing terminus of the nearby alkene. The carbon-centered radical so-formed then loses a chlorine radical with the result that the original double bond is reinstated in a regiospecific manner. So, this C-radical addition/Cl-radical elimination sequence allows for (i) the ready replacement of a chlorine attached to an sp^2-hybridized by an sp^3-hybridized carbon (a conversion that can sometimes be difficult to achieve using organometallic methods) and (ii) the site-specific incorporation of a double bond at a ring-junction. As such, we believe this protocol has considerable synthetic utility. Indeed, we have recently deployed it in establishing a total synthesis of the non-natural enantiomer of the related montanine alkaloid brunsvigine [13]. Work is now underway to extend the results described in Scheme 2 so as to develop a total synthesis of dyshomerythrine (**16**).

Synthesis of the spirocyclic framework associated with the histrionicotoxins

The histrionicotoxins (HTXs) represent a series of alkaloids incorporating the 1-azaspiro[5.5]undecane ring system that have been isolated from, inter alia, arrow poison frogs of the genera *Dendrobates*, *Epipedobates*, and *Phyllobates* [14]. The parent member of the series is histrionicotoxin (**21**), and the others vary in the nature of the unsaturated side-chains attached to C-2 and C-7 of the spirocyclic core. The HTXs act as noncompetitive inhibitors of nicotinic receptors and also attack sodium- and potassium-ion channels. Consequently, they act as potent neurotoxins and have some potentially useful neurophysiological properties. Interestingly, perhydrohistrionicotoxin, **2**, the fully saturated derivative of compound **21**, displays similar biological properties. Accordingly, considerable effort has been devoted to the synthesis of both the natural product (**21**) and its less synthetically demanding derivative **2**. The extensive research in this area has been the subject of a recent and comprehensive review [14].



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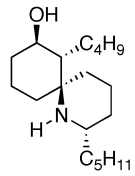
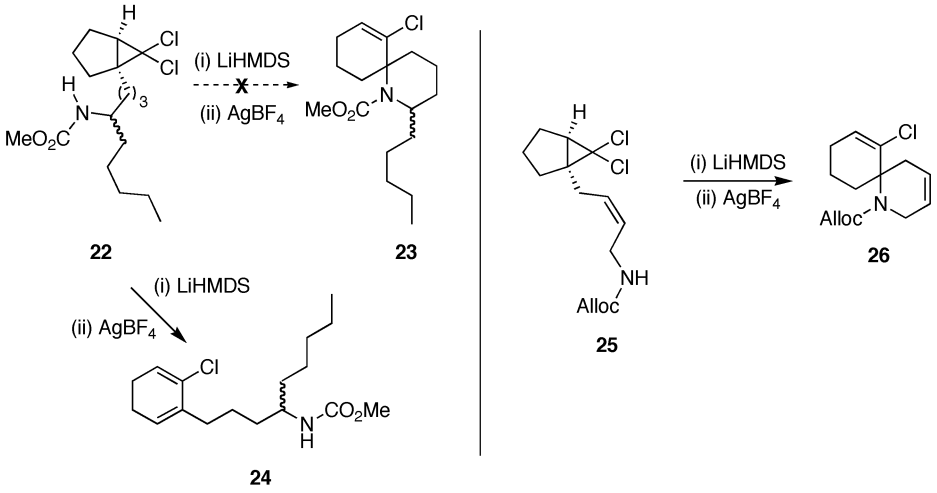


2

Our own interest in the area arose through the idea that the spirocyclic framework of the HTXs could be assembled in much the same way as was used to prepare the AC-ring substructure of erythramine. In a preliminary attempt to do so, the *gem*-dichlorocyclopropane **22** (Scheme 3), incorporating a carbamate-based nucleophile tethered through C-1, was prepared by more-or-less conventional means. However, upon exposure of this compound to LiHMDS then silver tetrafluoroborate none of the hoped-for spirocycle **23** was obtained [15]. Rather, diene **24** (50 %) proved to be the only isolable reaction product, and this presumably arises from deprotonation of the allylic cation formed upon elec-

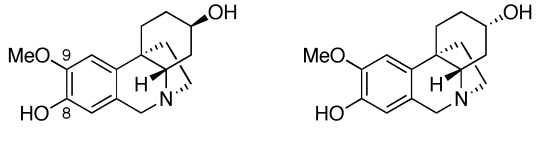
trocyclic ring-opening of substrate **22**. The lack of spirocyclization observed in this case, which stands in contrast to the successful process observed during the course of our synthesis of the erythrina alkaloids, may be attributed to the nonrigid nature of the tether linking the bicyclo[3.1.0]hexanyl and carbamate moieties to one another within substrate **22**. Accordingly, congener **25**, incorporating a rigidifying and *Z*-configured alkene residue within the side-chain, was prepared and subjected to the "usual" spirocyclization conditions [15]. As a result, the desired product, **26**, was now obtained, although only in 15 % yield. Clearly, then, much work remains to be done to optimize this spirocyclization process, but if this can be achieved then compounds such as **26** could be exploited in developing new routes to the HTXs. Certainly, other work within our group [16] leads us to believe that the nonhalogenated double-bond within dienes such as **26** can be removed selectively and efficiently.



Scheme 3

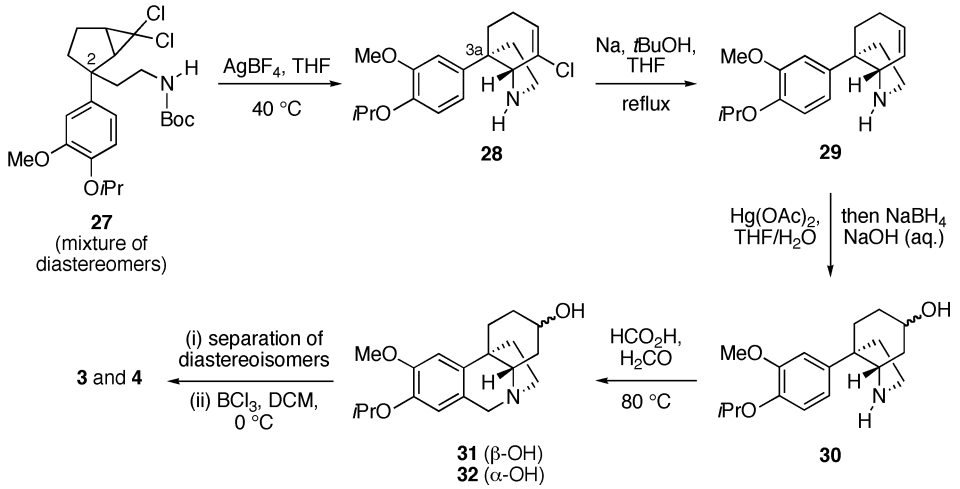
Total syntheses of the racemic modifications of the crinine alkaloids maritinamine and *epi*-maritinamine

The crinine alkaloids maritinamine (**3**) and *epi*-maritinamine (**4**) have been isolated by Shamma and coworkers from *Sternbergia lutea* found in Turkey [17]. They differ from most other members of the crinine alkaloid class in that they possess a C-9-methoxy group and a C-8-hydroxy group rather than the usual (and less synthetically demanding) methylenedioxy unit spanning these positions. Because of such features, the limited amount of information available about their biological properties and the lack of synthetic routes to these compounds, we sought methods for their preparation.



The synthetic route that we ultimately established for preparing these compounds relied on the second of the two types of cyclization processes shown in Scheme 1 [18]. In particular, and as detailed in Scheme 4, the 6,6-dichlorobicyclo[3.1.0]hexane **27** incorporating the relevant aryl and β-aminoethyl residues at C-2 was prepared, in racemic form and as a 2:1 mixture of diastereoisomers, by relatively

conventional means. Subjection of this material to reaction with silver tetrafluoroborate in THF at 40 °C resulted in the consumption of both diastereoisomers, although at differing rates, and the formation of the C-3a arylated hexahydroindole **28** in 64 % yield. The conversion **27** → **28** clearly involves the predicted sequence of silver-ion-induced electrocyclic ring-opening of the three-membered ring and trapping of the resulting allylic cation by the pendant carbamate nitrogen. The loss of the Boc-group is presumed to occur after the cyclization event although, at the present time, we have no definitive evidence to support this proposed ordering of events. The facility with which this cyclization takes place, which contrasts with the difficulties encountered in effecting the conversion **17** → **18**, is attributed to the kinetic advantage associated with forming five-membered rings.



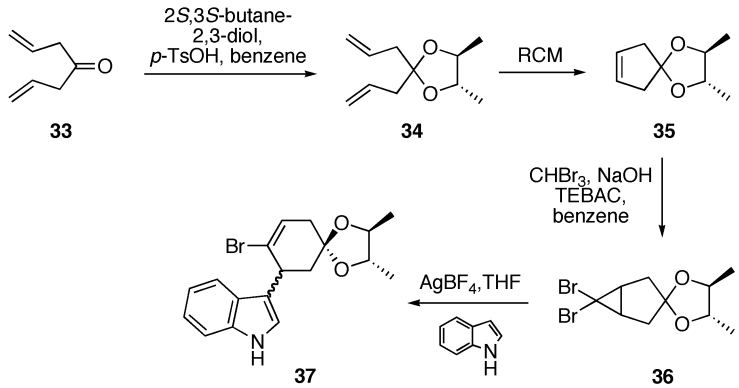
Scheme 4

Compound **28** participated smoothly in a Bouveault–Blanc reduction, thus providing its dechlorinated counterpart **29** (98 %). Following protocols established by Overman [19], the latter material was subjected to an oxy-mercuration/de-mercuration sequence that proceeded with excellent levels of regiochemical control but only modest levels of stereochemical control. As a consequence, a ca. 3:1 mixture of the two epimeric forms of compound **30** was obtained in a combined yield of 96 %. These epimers were then exposed to a combination of formic acid and formaldehyde so as to effect the required Pictet–Spengler reaction and thus affording, in racemic form, the chromatographically separable compounds **31** (72 %) and **32** (58 %). Independent subjection of each of products **31** and **32** to reaction with BCl_3 in dichloromethane at 0 °C then gave (±)-maritinamine (**3**) (83 %) and *epi*-maritinamine (**4**) (87 %), respectively.

Concise assembly of the polycyclic frameworks associated with the hapalindole alkaloids

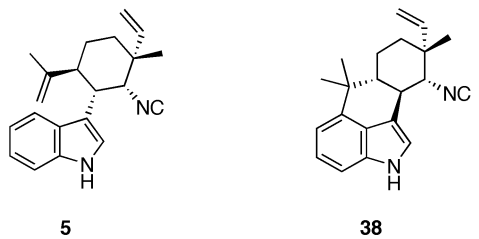
In each of the reaction sequences detailed above, nitrogen-centered nucleophiles have been used to trap the allylic cations arising from electrocyclic ring-opening of *gem*-dihalocyclopropanes. While Danheiser has described analogous chemistry involving oxygen-centered species [8], we are not aware of many examples of the trapping of such cations by carbon-centered nucleophiles, a situation that is perhaps surprising given the potential such processes offer for new modes of carbon–carbon bond formation. As a result, we have established a reaction sequence, shown in Scheme 5, that demonstrates the feasibility of effecting such conversions [20]. Thus, diallyl ketone (**33**) was converted into the cor-

responding ketal **34** under conditions defined by Dolbier et al. [21]. Subjection of the latter compound to ring-closing metathesis (RCM) using Grubbs' second-generation catalyst then afforded compound **35** in 76 % yield and so highlighting the utility of such protocols in generating new cyclopentenes capable of engaging in carbene addition reactions. Treatment of alkene **35** with bromoform in the presence of sodium hydroxide and the phase-transfer catalyst benzyltriethylammonium chloride then afforded the required 6,6-dibromobicyclo[3.1.0]hexane **36** in 87 % yield. Reaction of cyclopropane **36** with silver tetrafluoroborate in the presence of indole resulted in trapping of the intermediate cation by C-3 of this heterocycle and thus affording a 2:1 mixture of the diastereoisomeric forms of adduct **37** (59 % combined yield) that could be separated by high-performance liquid chromatography (HPLC) techniques.



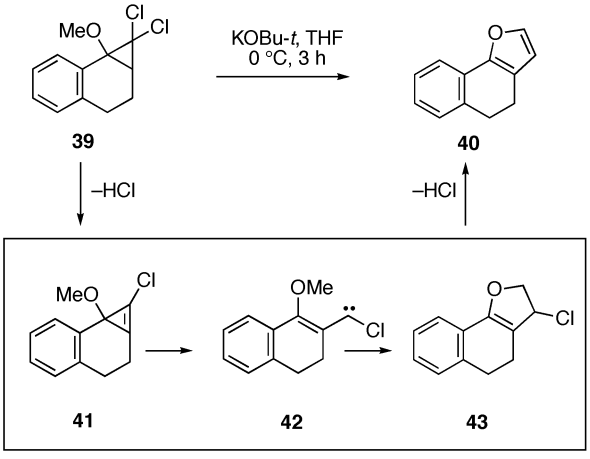
Scheme 5

Not only does this outcome demonstrate the capacity of such sequences to establish new carbon–carbon bonds but it also delivers a product that may be of value in natural products synthesis. In particular, compound **37** bears some significant structural resemblances to the indole alkaloids hapalindole C (**5**) and hapalindole J (**38**), compounds that have been isolated from cyanobacteria of the genus *Hapalosiphon* [22]. As a result of their notable antibacterial and antimycotic activity, these natural products have been attracting increasing attention and some very elegant syntheses of them have been reported in recent times [23].



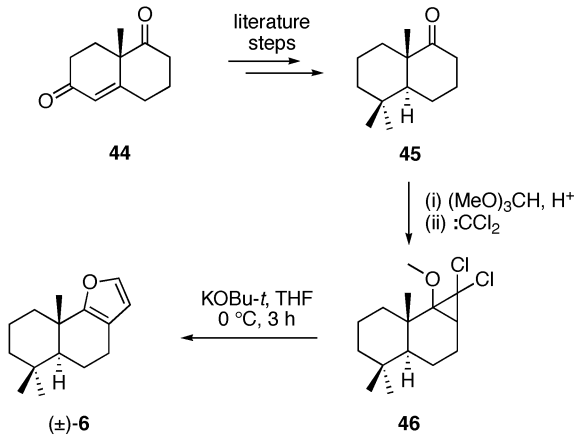
A new method for furanannulation: Application to a synthesis of the furanosesquiterpene pallescensin

In the course of a mechanistic investigation, we had occasion to prepare compound **39** and treat this with an excess of potassium *tert*-butoxide (Scheme 6). As a result, the annulated furan **40** was obtained in 56 % yield [24]. Based on proposals advanced by Müller and Pautex [25], it seems reasonable to suggest that this conversion proceeds via the initial base-promoted elimination of the elements of HCl from compound **39** and thus affording the ring-fused cyclopropene **41**. Species of this general type are known to rearrange to the corresponding vinyl carbene [26], and if such an event occurs in this instance then the resulting carbene **42** might be expected to undergo insertion into one of the C–H bonds of the adjacent methoxy group and thus affording the chlorodihydrofuran **43**. Dehydrohalogenation of this last species under the basic conditions employed would then afford the observed product **40**. Since the starting cyclopropane (**39**) was generated by conversion, under standard conditions, of α-tetralone into the corresponding methyl enol ether and addition of dichlorocarbene to the latter then, in an overall sense, the heterocycle **40** is formed as a result of the application of a three-step furannulation protocol to an enolizable ketone (viz. α-tetralone). Accordingly, we felt this sequence could represent a potentially versatile method for the production of furan-containing natural products.



Scheme 6

The furanosesquiterpene pallescensin A (**6**) is a marine natural product that has been isolated from the sponge *Disidea pallescens*, and it is likely to be biogenetically derived from a furanoid monocyclofarnesane precursor [27]. It has been suggested that the compound is involved in the defensive mechanisms employed by opisthobranch mollusks, which concentrate sponge metabolites in their skin and then release them when they come under attack [28]. A synthesis of the racemic modification of compound **6** that exploits the above-mentioned furannulation protocol is shown in Scheme 7 [24]. Thus, the readily available Wieland–Miescher ketone (**44**) was transformed, over nine steps using modifications of literature procedures [29], into the *gem*-dimethylated and enolizable ketone **45**. Conversion of the latter material into the corresponding methyl enol ether was achieved under standard conditions, and this was then subjected to reaction with dichlorocarbene that had been generated under the usual conditions. Treatment of the resulting carbene adduct **46** (obtained as an 11:8 mixture of diastereoisomers) with potassium *tert*-butoxide effected the final step of the furannulation protocol to give (±)-pallescensin [(±)-**6**] in 38 % yield.



Scheme 7

CONCLUSION

The reaction sequences detailed above should serve to highlight the value of certain *gem*-dihalogenocyclopropanes as building blocks in chemical synthesis, especially as this applies to the assembly of various heterocyclic natural products. In particular, the electrocyclic ring-opening of these three-membered ring compounds and the trapping of the ensuing allylic cation by various nucleophilic species create motifs that can be manipulated in a number of useful ways. A notable example involves the C-radical addition/halogen-radical elimination sequence (see Scheme 2) that can be applied to the haloalkenes formed upon ring-opening of the starting *gem*-dihalogenocyclopropanes. Work is continuing within our labs to extend the concepts defined here.

ACKNOWLEDGMENTS

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REFERENCES AND FOOTNOTES

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