Nonbenzenoid Cycloproparenes

Dieter Wege[a]

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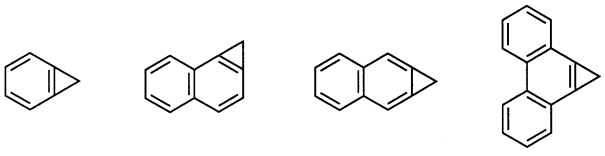
Despite the extensive literature on cycloproparenes, compounds possessing cyclopropa-fusion to functionalised benzenoid rings or to nonbenzenoid aromatic systems are rare. This review describes approaches to some of these novel systems. The cyclopropaquinones **29** and **30**, generated by bromodesilylation at −78 °C of precursors **47** and **70**, respectively, are too reactive to be isolated, but can be trapped as Diels–Alder adducts with furan. The high reactivity of **29** and **30** contrasts with the stability of quinones **24** and **26** in which the quinone moiety and cyclopropa-fusion are located in different rings. The cycloaddition methodology developed for the generation of **30** has been extended to the synthesis of favelanone (**98**), a natural product incorporating the cyclopropa[*b*]naphthalene-2,7-dione structural motif. While several six-membered heterocyclic cycloproparenes have been described, the synthesis of cyclopropafurans and cyclopropathiophenes poses significant challenges. There is tentative evidence for the generation of the cyclopropa[*c*]thiophene **160** by double dehydrobromination of **158**, but the photolysis of the pyrazolothiophene **166** yields only alkene **169** and none of the desired ring-closed product. In contrast, irradiation of the related pyrazolofuran **165** results in clean fragmentation to give the acetylenic enone **171**. The cyclopropatropone **201** has been prepared, and the derived hydroxytropylium ion **202** represents the first example of a cyclopropa-fused seven-membered aromatic ring system. Finally, while the synthesis of cyclopropazulenes remains to be achieved, the potentially useful precursor **230** has been obtained by a directed transannular aldol condensation.

1. Cycloproparenes

The fusion of a cyclopropene ring to an aromatic ring generates a family of theoretically interesting compounds known as cycloproparenes, exemplified by the parent member benzocyclopropene (**1**) and benzo-fused derivatives such as 1*H*-cyclopropa[*a*]naphthalene (**2**), 1*H*-cyclopropa[*b*]-naphthalene (**3**) and 1*H*-cyclopropa[*l*]phenanthrene (**4**) (Scheme 1). The chemistry of cycloproparenes has been reviewed extensively[1] and only those aspects that are relevant to the present Microreview are mentioned below. Much of the interest in the chemistry of cycloproparenes arises from the high reactivity of the three-membered ring and the geometrical and reactivity perturbations imposed upon the benzenoid ring as a result of the ring-fusion; hence this area has provided significant challenges for synthetic and computational chemists.[1] In general, benzenoid cycloproparenes are isolable compounds of moderate stability, although 1*H*-cyclopropa[*a*]naphthalene (**2**) is reported[2] to decompose on melting at 19−20 °C and 1*H*-cyclopropa[*l*]phenanthrene (**4**) could only be characterised spectroscopically at −60 °C and decomposes slowly even at this temperature.[3] The exceptional reactivity of **2**, and especially **4**, appears to be a consequence of the high double-bond character across the positions of cyclopropa-fusion, and this point is discussed further in Section 2.



1 **2** **3** **4**

Scheme 1. Some benzenoid cycloproparenes

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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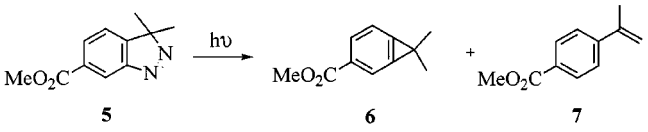
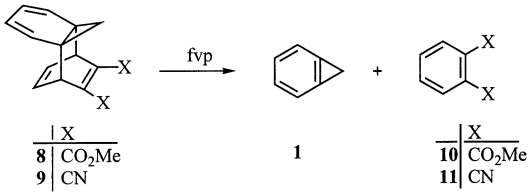
1.1. Synthesis of Cyclopropparenes

In 1964 Anet and Anet reported the isolation of the first cyclopropparene **6** together with the styrene **7** from the photolysis of methyl 3,3-dimethyl-3*H*-indazole-6-carboxylate (**5**) (Scheme 2).[4] Although this general route has been applied to the preparation of other cyclopropparenes,[1] it is somewhat limited due to the difficulty in obtaining the appropriate 3*H*-indazole precursor; however, it is of value for the preparation of certain heterocyclic cyclopropparenes as described in Section 3.



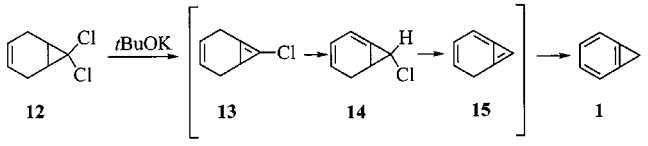
Scheme 2. Preparation of the first cyclopropparene **6**

The parent benzocyclopropene (**1**) was obtained shortly afterwards by Vogel and co-workers from the Alder−Rickert cleavage of the adducts **8** and **9** (Scheme 3).[5]



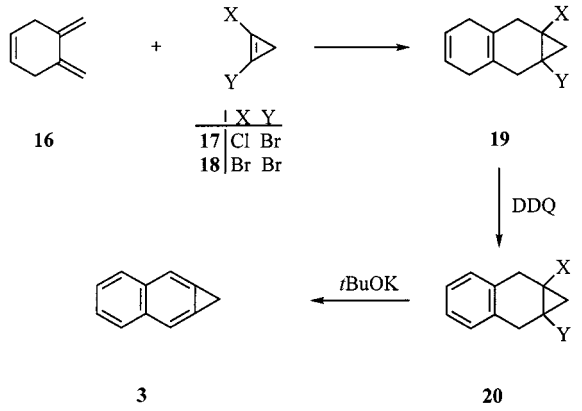
Scheme 3. Preparation of benzocyclopropene (**1**) by Alder−Rickert cleavage

Benzocyclopropene (**1**) became readily available from the interesting finding of Billups and co-workers[6] that dehydrochlorination of adduct **12**, derived from cyclohexa-1,4-diene and dichlorocarbene, delivers **1** in preparatively useful yields by the pathway[7] depicted in Scheme 4. This general method has been applied to the preparation of various benzo-fused analogues, although complications can occur in some instances due to accompanying ring-opening reactions.[1]



Scheme 4. The Billups dehydrochlorination route to benzocyclopropene (**1**)

A fourth relevant general route to cyclopropparenes involves the Diels−Alder addition of 1-bromo-2-chlorocyclopropene (**17**)[8] or 1,2-dibromocyclopropene (**18**)[9] to a diene, illustrated with **16** in Scheme 5. Subsequent dehydrogenation followed by dehydrohalogenation then provides the cyclopropparene. This approach has found considerable use in the preparation of polycyclic benzenoid cyclopropparenes.

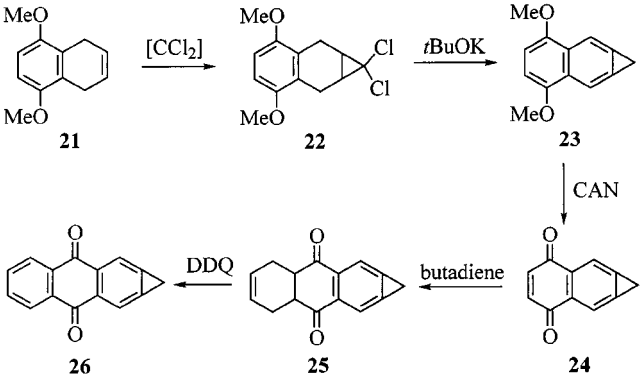


Scheme 5. Benzenoid cyclopropparenes from adducts of 1,2-dihalocyclopropenes and dienes

Despite the extensive literature on cyclopropparenes, very few cyclopropparenes possessing functionality in the cyclopropa-fused aryl ring have been reported.[1] The present review deals with one such class of compounds, namely cyclopropa-fused quinones. A second theme addresses some ring systems derived from cyclopropa-fusion to nonbenzenoid aromatic systems. This again is an area which so far has attracted only limited attention.

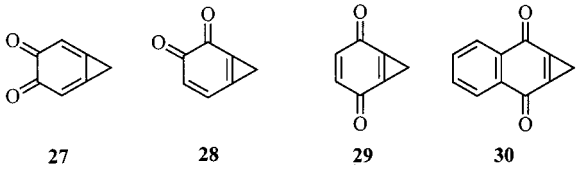
2. Cyclopropa-Fused Quinones

Two families of cyclopropa-fused quinones can be envisaged, those having the quinone moiety in the ring involved in cyclopropa-fusion, and those in which the quinone functionality and cyclopropa-fusion are located in different rings. With regard to the latter, Halton and co-workers have achieved the synthesis of 1*H*-cyclopropa[*b*]naphthalene-3,6-dione (**24**) by the route shown in Scheme 6.[10] The crystal structure of **24** shows the molecule to be almost planar with a 2.2° out-of-plane displacement of the three-membered ring, characteristic of other cyclopropparenes.[10b] Addition of butadiene to **24** followed by dehydrogenation provided the benzo-fused derivative 1*H*-cyclopropa[*b*]anthracene-3,8-dione (**26**).[11] Both **24** and **26** behave as normal cyclopropparenes in that they are isolable and possess moderate stability.



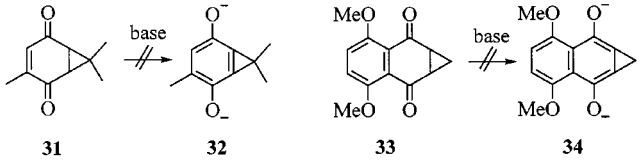
Scheme 6. Synthesis of cyclopropaquinones **24** and **26**

In the case of *o*- and *p*-benzoquinone, cyclopropa-fusion gives rise to three isomeric cyclopropabenzoquinones **27**–**29** (Scheme 7). It should be noted that in **28** and **29** methylene-bridging is across an essentially pure double bond, and in view of the properties observed for 1*H*-cyclopropa[*l*]phenanthrene (**4**), these isomers could well be expected to show enhanced reactivity over that normally expected for a benzenoid cycloproparene. Similar considerations apply to 1*H*-cycloprop[*b*]naphthalene-2,7-dione (**30**).



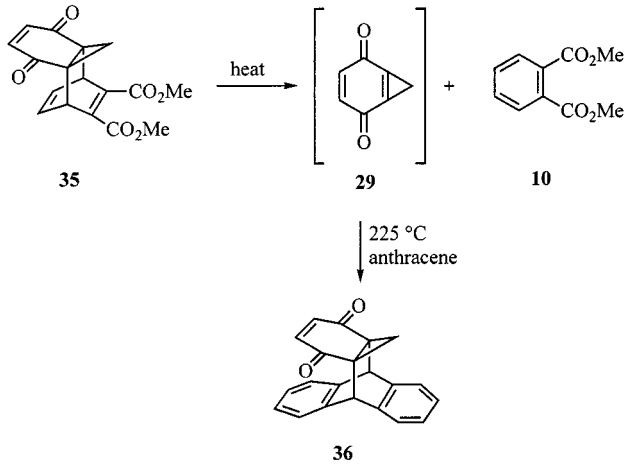
Scheme 7. Some cyclopropaquinones incorporating cyclopropa-fusion to the quinonoid ring

Only limited work pertaining to cyclopropaquinones such as **27**–**30** or their derivatives has been reported to date. In an interesting study which predates the pioneering paper of Anet and Anet,[4] Ullman and Buncel attempted to generate cyclopropa-fused hydroquinones and their dianions through enolisation of the bicyclo[4.1.0]hept-3-ene-2,5-dione derivatives **31** and **33** (Scheme 8).[12] Treatment of **31** with sodium ethoxide at −10 °C gave coloured decomposition products and did not lead to appreciable enolisation, as evidenced by the lack of deuterium incorporation after quenching with acidified D_2O. Reaction of the more stable naphthoquinone derivative **33** with CH_3ONa/CH_3OD or *t*BuOK/*t*BuOD at elevated temperatures gave no indication that the dianion **34** was formed, but suggested that deuterium incorporation at the bridgehead positions occurred by stepwise deuteration of the mono-anion derived from **33**. Attempts to intercept **34** as a dimethyl ether using methyl iodide were also unsuccessful. Clearly the hydroquinones resulting from protonation of **32** and **34** would have provided potentially useful precursors for the corresponding cyclopropaquinones, but an enolisation approach to such systems does not seem to be viable.



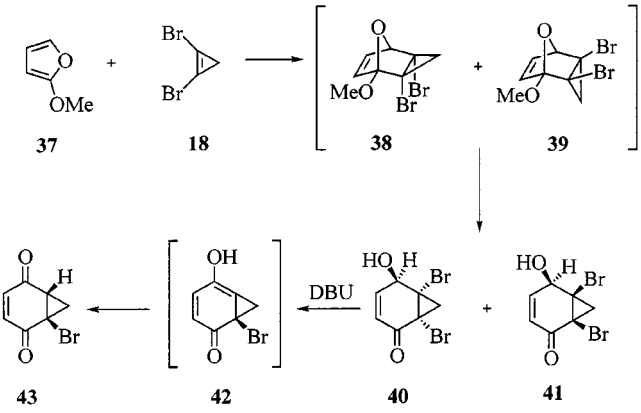
Scheme 8. Reluctance of the bicyclo[4.1.0]hept-3-ene-2,5-dione derivatives **31** and **33** to undergo double enolisation

In a more recent approach to the cyclopropaquinone **29**, Oda and co-workers examined the thermolysis of **35**, prepared by functional group manipulation of the adduct of 1,6-methano[10]annulene and dimethyl acetylenedicarboxylate (Scheme 9).[13] Flash vacuum pyrolysis of **35** gave dimethyl phthalate (**10**) as the only identifiable product; this is in marked contrast to **8** which provides the parent benzocyclopropene (**1**) under conditions of thermolysis (Scheme 3). The more reactive 1*H*-cyclopropa[*a*]naphthalene (**2**) has also been prepared by such a procedure.[2] However, thermolysis of **35** in molten anthracene at 255 °C did afford adduct **36** in 12% yield, providing evidence for the formation of **29** under these conditions.



Scheme 9. Trapping of cyclopropaquinone **29** at high temperature

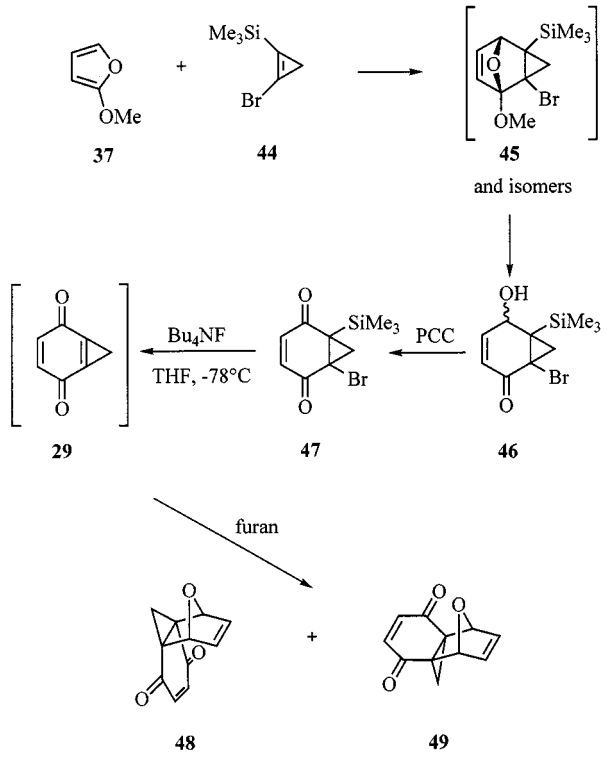
In order to probe further the reactivity and the feasibility of isolating the quinone **29**, we investigated its generation under milder conditions (Scheme 10).[14] Addition of 1,2-dibromocyclopropene (**18**) to 2-methoxyfuran (**37**) gave an inseparable mixture of the keto alcohols **40** and **41** in 50% yield. Brief treatment of the mixture with DBU gave the bromodione **43**, presumably via the enol **42**. Longer exposure of **40** and **41** or **43** to base failed to yield any recognisable products, even in the presence of furan as a potential trapping agent. Thus, if the target cyclopropaquinone **29** is formed under these conditions by further dehydrobromination of **43**, it appears to be consumed by secondary reactions.



Scheme 10. Bromodione **43** is not a suitable precursor for cyclopropaquinone **29**

The introduction of the final double bond into the bicyclic system of **29** under milder nonbasic conditions was carried out as outlined in Scheme 11.[14] 2-Methoxyfuran was treated with 1-bromo-2-trimethylsilylcyclopropene (**44**)[9] to give **46**, which on oxidation provided the dione **47**. Treatment of **47** with tetrabutylammonium fluoride in THF at −78 °C followed by conventional workup failed to give any recognisable product. However, in the presence of furan, adducts **48** and **49** were formed in a ratio of 4.5:1, and could be isolated in 49 and 12% yield, respectively, after

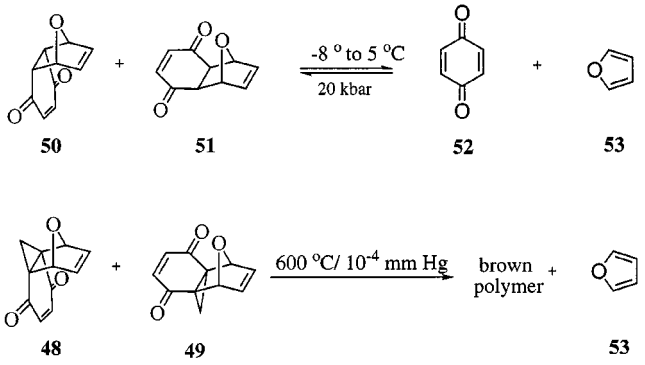
chromatography. Clearly the target cyclopropaquinone **29** is generated efficiently under these mild conditions, but does not survive normal workup.



37 **44** **45** **46** **47** **29** **48** **49**

Scheme 11. Generation and trapping of cyclopropaquinone **29** at −78 °C

In general, Diels−Alder adducts of furan undergo ready cycloreversion to their constituent components under mild conditions.[15] Thus, adducts **50** and **51** are formed from furan (**53**) and *p*-benzoquinone (**52**) only under conditions of high pressure, and the *endo*-adduct **50** dissociates within 1 h at −8 °C, while the *exo*-adduct **51** reverts within 12 h at 5 °C (Scheme 12).[16] In marked contrast, adducts **48** and **49** derived from furan and the cyclopropabenzoquinone **29** are stable in solution at and above room temperature. Furthermore, attempts to generate **29** by flash vacuum pyrolysis from **48** and **49** were unsuccessful. At temperatures up to 550 °C the adducts passed unchanged through the hot zone of the pyrolysis tube, while at 600 °C only a brown film formed at the exit zone, although furan was collected in the

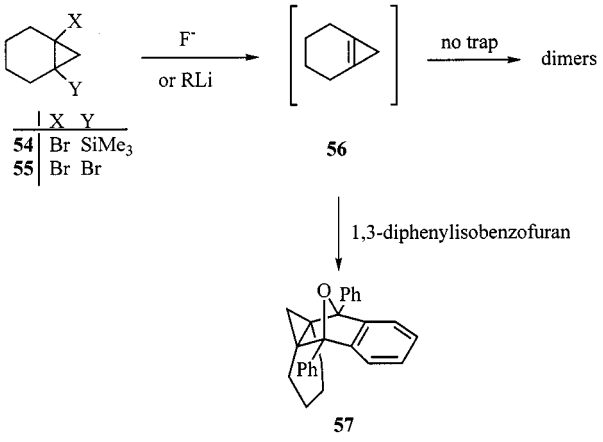


50 **51** **52** **53** **48** **49** **53**

Scheme 12. The remarkable thermal stability of cycloadducts **48** and **49**

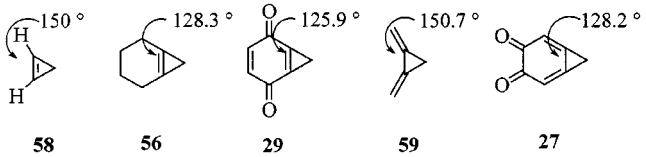
cold trap.[14] Thus adducts **48** and **49** exhibit a substantial activation barrier to cycloreversion compared to **50** and **51**, attributable to destabilisation of the cyclopropa-fused quinone **29** relative to benzoquinone (**52**) as a result of the high strain-energy contributed by the cyclopropene moiety of **29**.

The high reactivity of the cyclopropa-fused quinone **29** resembles that of bicyclo[4.1.0]hept-1(6)-ene (**56**) which was also found to be too reactive for spectroscopic characterisation, but could be trapped with 1,3-diphenylisobenzofuran to give adduct **57** (Scheme 13).[17] Calculations show that **56** is more strained than 1,2-dimethylcyclopropene by ca. 71 kJ mol^{-1} as a result of the large C=C−H bond angle (150°) observed in cyclopropene (**58**) being compressed to 128.3° in **56** as a consequence of bridging by the methylene chain (Scheme 14).[17] For the cyclopropaquinone **29**, Becke3LYP/6−31G* calculations reveal the analogous bond angle to be even smaller at 125.9° and the high reactivity of the cyclopropene double bond therefore is maintained in this structure despite the conjugation of the alkene linkage with the carbonyl groups.[14] These calculations also show that the cyclopropa-fused quinones **28** and **29** having the double bond across the positions of ring-fusion lie 78.7 and 58.6 KJ mol^{-1}, respectively, above the isomer **27** possessing a dimethylidenecyclopropene moiety, suggesting that **27** may be a potentially isolable compound. However, in **27** the internal bond angle of 128.2° is still compressed considerably from the value of 150.7° computed[18] for 1,2-dimethylidenecyclopropane (**59**).



56 **57**

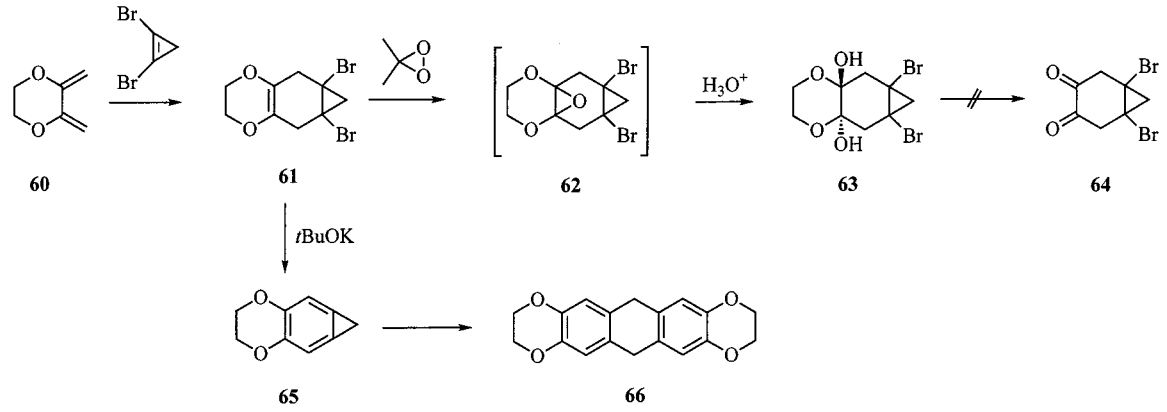
Scheme 13. The bridged cyclopropene **56** is a reactive alkene



58 **56** **29** **59** **27**

Scheme 14. Comparison of computed bond angles of some cyclopropene derivatives

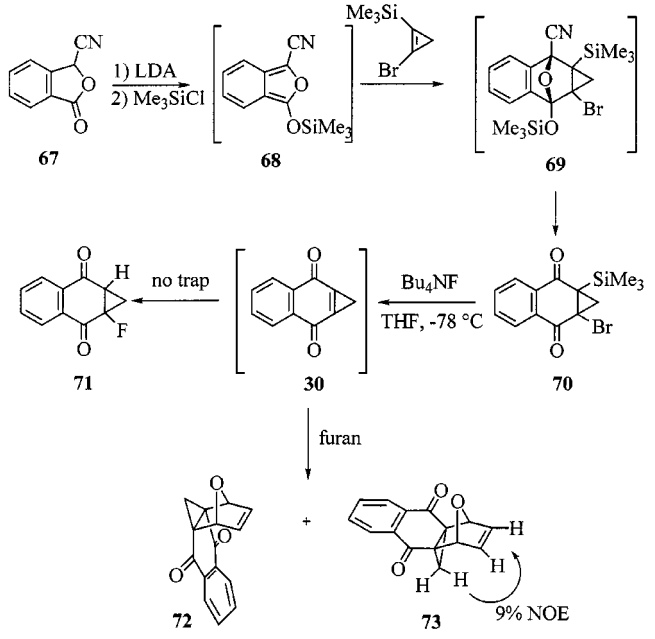
A preliminary approach to the cyclopropa-fused *o*-quinone **27** is shown in Scheme 15.[19] Adduct **61**, obtained from diene **60**[20] and 1,2-dibromocyclopropene (**18**), was epoxidised with dimethyldioxirane and the crude product treated with aqueous acid to give the crystalline bis-hemike-



Scheme 15. An unsuccessful approach to the cyclopropaquinone **27**

tal **63**, possessing only moderate stability. Attempts to liberate the dione **64** from **63** under a variety of conditions have so far been unsuccessful, complex reaction mixtures being obtained in all cases. Dehydrobromination of adduct **61** provided **65**, a rare example of an oxygenated cyclopropar-ene.[1] On standing or chromatographic manipulation, **65** dimerised to afford **66**; this behaviour is analogous to that observed for the related 3,8-dioxa-1*H*-cycloprop[*b*]anthracene system.[21]

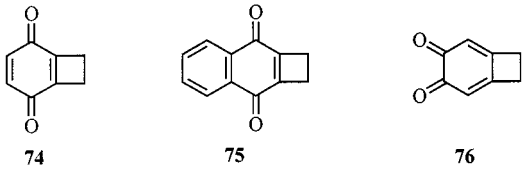
The generation and trapping of 1*H*-cyclopropa[*b*]naphthalene-2,7-dione (**30**), the benzo-fused derivative of **29**, was carried out as shown in Scheme 16.[14] The substituted isobenzofuran **68** was trapped with 1-bromo-2-trimethylsilylcyclopropene to give the dione **70** in 29% yield after hydrolytic workup and chromatography. Treatment of **70** with tetrabutylammonium fluoride in THF in the presence of furan afforded the adducts **72** and **73** in a ratio of 2:1 in 73% yield, indicating that **30** could be generated and intercepted in good yield. Configurational assignments of the adducts



Scheme 16. Generation and trapping of the cyclopropaquinone **30**

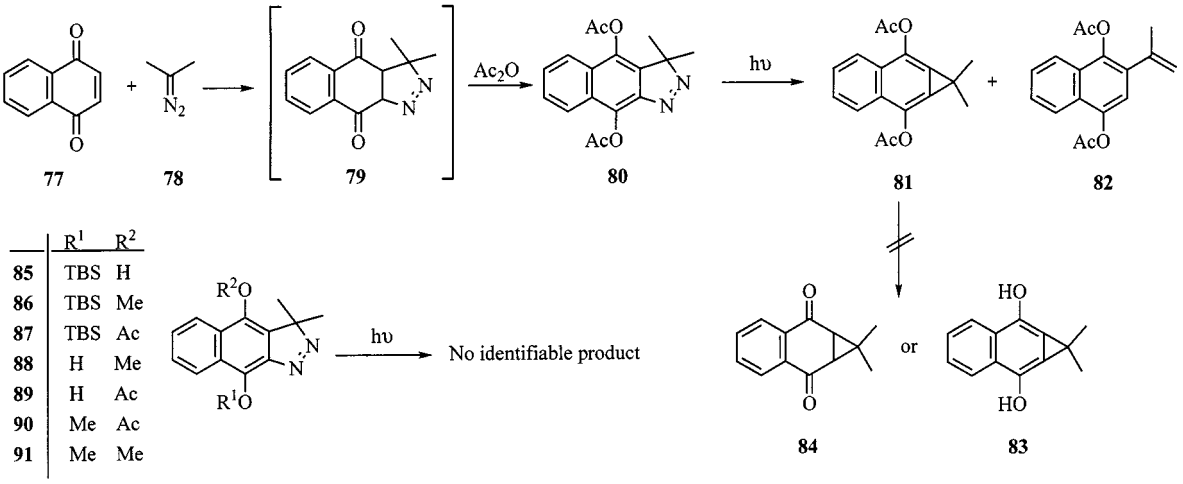
were possible through the observation of nuclear Overhauser effects, which, in turn, permitted assignment of the structures of the related adducts **48** and **49** encountered earlier (Scheme 11). In the absence of a trapping agent, the fluorodione **71** was isolated in 8% yield as the only product. This presumably arises by conjugate addition of the weakly nucleophilic fluoride ion to the reactive double bond of the cyclopropaquinone **30**.

The results summarised in Scheme 10, 11, 15, and 16 show that precursors to cyclopropa-fused quinones can be assembled rapidly through cycloaddition between either 1,2-dibromocyclopropene or 1-bromo-2-trimethylsilylcyclopropene and an appropriate diene. The quinones **29** and **30** are too reactive to be isolated, which is in marked contrast to the cyclobuta-fused quinones **74**,[22] **75**,[23] and **76**[24] (Scheme 17), all of which are isolable and stable compounds.



Scheme 17. Some stable cyclobuta-fused quinones

Kinetic stabilisation of cyclopropa-fused quinones should, in principle, be possible through the incorporation of bulky geminal substituents at the cyclopropene methylene group. This should hinder conjugate addition of the type found in the formation of the fluorodione **71**, and prevent an ene reaction, an observed reaction pathway for bicyclo[4.1.0]hept-1(6)-ene (**56**) in the absence of added trapping reagents.[17] An attempt to prepare 1,1-dimethyl-1*H*-cyclopropa[*b*]naphthalene-2,7-dione, the dimethyl derivative of **30**, is summarised in Scheme 18.[25] Addition of 2-diazopropane (**78**) to 1,4-naphthoquinone (**77**), followed by acetylation, afforded 4,9-diacetoxy-3,3-dimethyl-3*H*-benz[*f*]indazole (**80**) in 30% yield. Irradiation of **80** at 350 nm in ether at 0−5 °C led to rapid elimination of nitrogen. Careful chromatography using precooled solvents gave the alkene **82** (43%) together with the desired cyclopropa[*b*]-naphthalene **81** (32%), the latter being the first example of



Scheme 18. Photochemical route to the functionalised cycloproparene **81**

a hydroquinone derivative possessing the oxygen functionalities in a cyclopropa-fused ring.[26] Unfortunately, all attempts to isolate the hydroquinone **83** or its tautomer **84** by mild hydrolytic or reductive cleave of diacetate **81** have met with failure, complex mixtures being obtained in all cases.[25]

By suitable functional group manipulation of adduct **79** or diacetate **80**, we have also prepared the functionalised 3,3-dimethyl-3*H*-benz[*f*]indazoles **85−91.** However, irradiation of these derivatives failed to produce any recognisable products; compounds **85−87** gave unidentified decomposition products, while **88−91** were photochemically inert.[25]

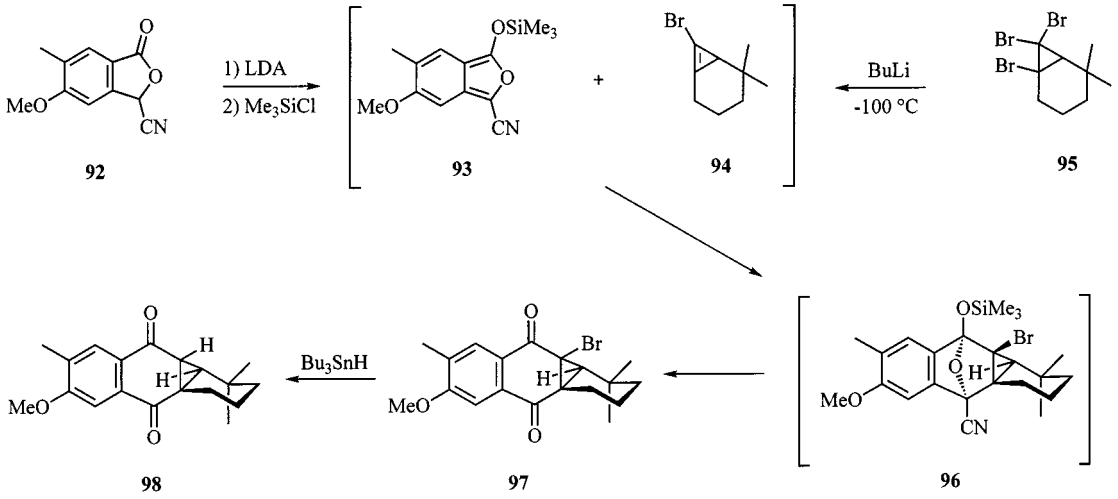
2.1. Favelanone, a Natural Product Containing the Cyclopropa[*b*]naphthalene-2,7-dione Ring System

During a screening of bioactive metabolites from the Brazilian plant Favela, *Cnidoscolus phyllacanthus* (Mart.) Pax et Hoffm., Nozoe and co-workers isolated a series of rearranged and modified abietane-type diterpenes including a dione they named (+)-favelanone, and to which they assigned structure **98** on the basis of spectroscopic evidence.[27] Favelanone is active against P-388 murine leukemia cells in vitro, and since its novel ring skeleton incorporates a cyclopropa[*b*]naphthalene-2,7-dione moiety, we carried out its synthesis using the methodology developed for the generation of the parent 1*H*-cyclopropa[*b*]naphthalene-2,7-dione (**30**).

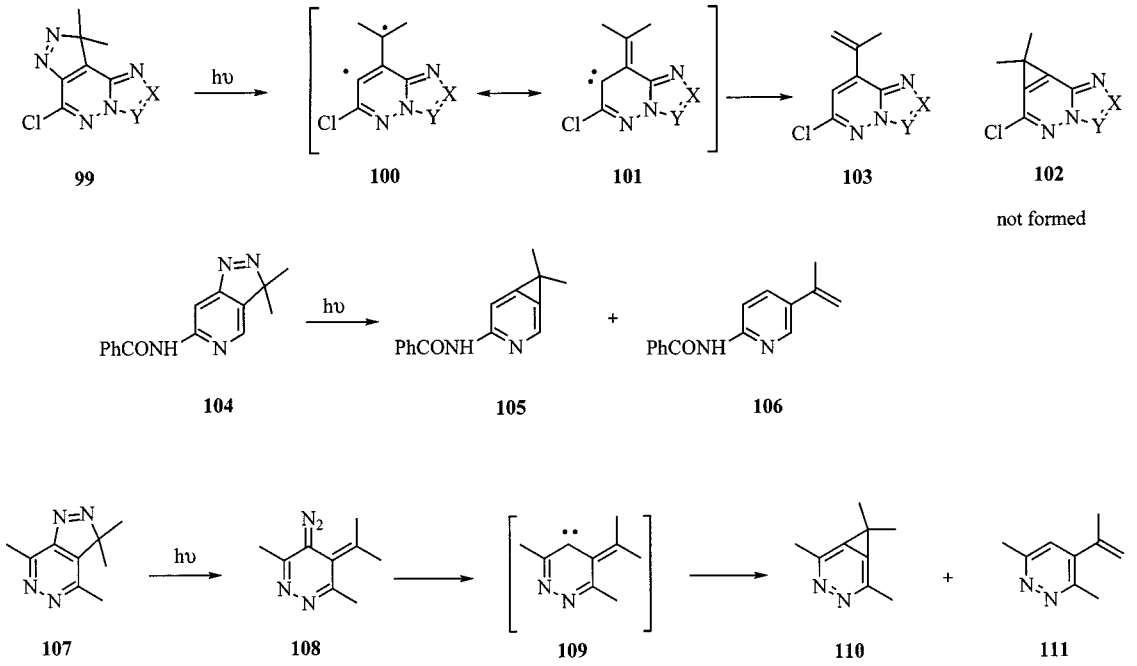
Addition of a solution of the isobenzofuran **93** to a solution of the bridged bromocyclopropene **94**, generated by debromination of **95** with butyllithium at −100 °C, gave, after hydrolytic workup, the dione **97** in 66% yield (Scheme 19).[28] The structure of **97** was established by 2D NMR measurements and confirmed that, as predicted, the cycloaddition of the push-pull isobenzofuran **93** and the polarised cyclopropene **94** occurred with high regioselectivity in the orientation shown. Debromination of **97** with tributylstannane then afforded (±)-favelanone, spectroscopically identical with the natural product.[28]

3. Cyclopropa-Fused Heterocycles

The concept of cyclopropa-fusion to an aromatic heterocyclic ring system has been addressed only relatively recently in the history of cycloproparene chemistry.[1] The



Scheme 19. Synthesis of favelanone **98**

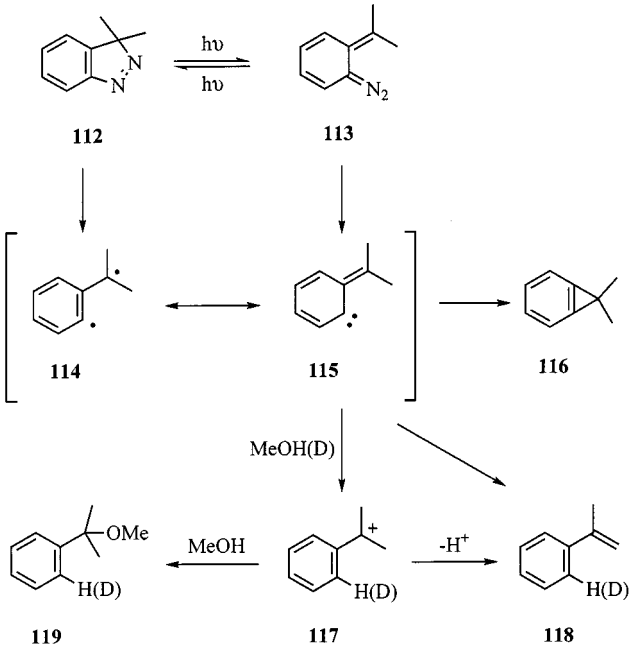


Scheme 20. Photochemical deazotization approaches to cyclopropahetarenenes

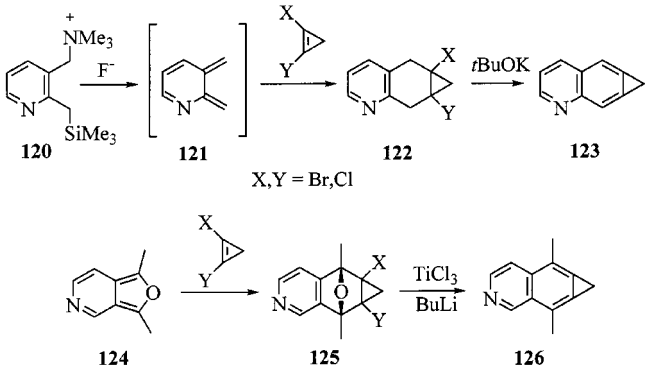
first reported attempt to prepare systems containing cyclopropa-fused six-membered heterocyclic rings involved irradiation of the pyrazolopyridazines **99** (X and Y are various combinations of CH and N).[29] In aprotic solvents only the alkenes **103**, derived by intramolecular hydrogen transfer in the intermediate diradical **100** or carbene **101**, were isolated, and the cycloproparenes **102** were not detected (Scheme 20). Shortly afterwards, the isolation of the first heterocyclic cycloproparene **105** was achieved by irradiation of the pyrazolopyridine **104**,[30] and this photodeazetation route has been extended to the preparation of the cyclopropapyridazine **110** (Scheme 20).[31] In the latter example, irradiation of precursor **107** in a matrix at 10 K provided evidence for the intermediacy of diazo compound **108** in the formation of alkene **111**, but not of cycloproparene **110**.[31]

The mechanistic details of the photodeazetation of some 3*H*-indazoles of relevance to the precursors in Scheme 20 have been probed in more detail by Kirmse and co-workers.[32] Thus, irradiation of **112** in methanol yielded the benzocyclopropene **116**, alkene **118** and ether **119** in a ratio of 28:45:27 (Scheme 21). Photolysis in MeOD afforded **119** with incorporation of 0.97 D and **118** with incorporation of 0.57 D, with the deuterium being located exclusively in the *ortho* position in both products. This suggests that the ether **119** is essentially completely derived by nucleophilic capture of the benzyl cation **117**, which is in turn generated by protonation (deuteration) of carbene **115**. The deuterated alkene **118** must arise by proton loss from cation **117**, while undeuterated **118** arises by intramolecular hydrogen transfer within **114** or **115**. This study shows that the intermediate formed on loss of nitrogen from indazole **112** possesses significant carbenoid character and undergoes protonation in protic solvents. The observation that methyl ethers are also formed in the photolysis of **99** (Scheme 20) in methanol[29] can be explained by a similar protonation pathway.

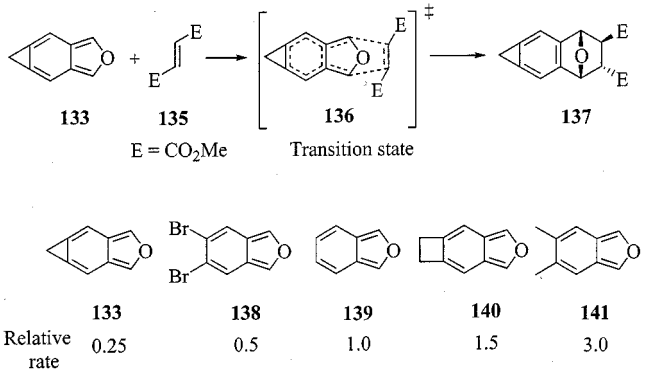
Cycloproparenes in which cyclopropa-fusion is to a six-membered ring adjacent to the heterocyclic moiety have been prepared by cycloaddition routes. The work of Müller and co-workers is summarised in Scheme 22 and used the trapping of the quinodimethane **121**[33] and the furo[*c*]pyridine **124**[34] with 1-bromo-2-chlorocyclopropene to generate the requisite precursors **122** and **125**, which were trans-



Scheme 21. Reaction pathways for the photochemical deazotization of indazole **112**



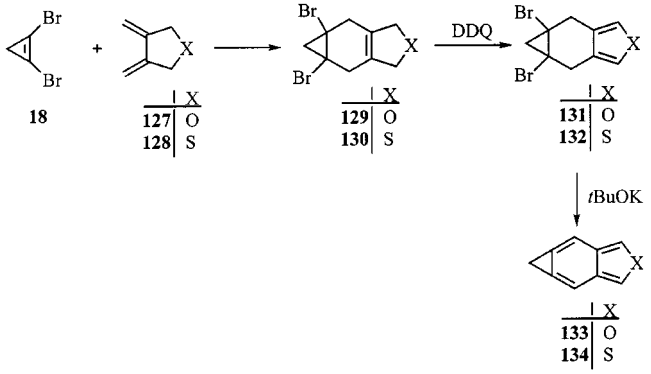
Scheme 22. Cyclopropahetarenes by cycloaddition chemistry



Scheme 24. Relative rates for the Diels–Alder addition of dimethyl fumarate to some isobenzofurans

formed by elimination into the cyclopropaquinoline **123** and the cyclopropaisoquinoline **126** respectively.

In view of our interest in the chemistry of isobenzofurans,[35] we prepared 5*H*-cyclopropa[*f*]isobenzofuran **133** and the related 5*H*-cyclopropa[*f*][2]benzothiophene **134** by the pathway shown in Scheme 23.[36] These compounds, and the related *gem*-difluoro derivatives,[37] possess reactivities similar to those of the parent isobenzofuran (IBF) and [2]benzothiophene.

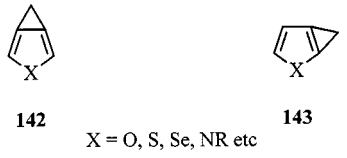


Scheme 23. Synthesis of 5*H*-cyclopropa[*f*]isobenzofuran **133** and 5*H*-cyclopropa[*f*][2]benzothiophene **134**

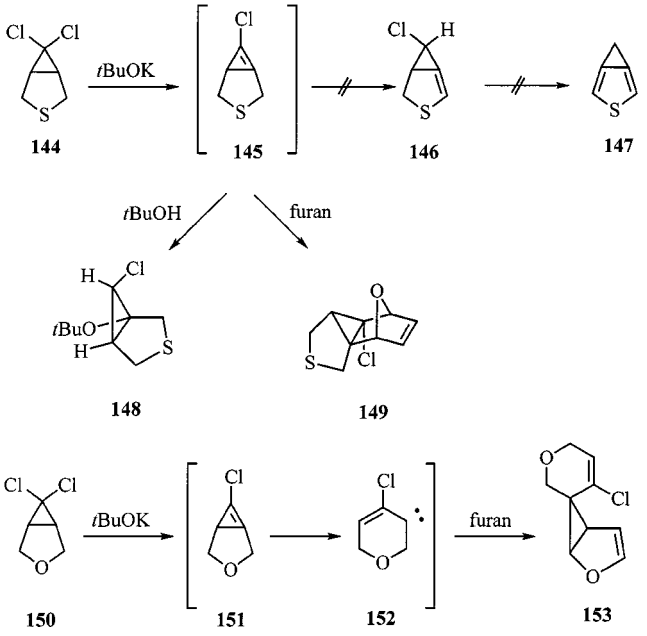
We were particularly interested in the effect of cyclopropa-fusion in **133** on the Diels–Alder reactivity of the isobenzofuran moiety in relation to the much-debated Mills–Nixon effect,[38] and accordingly measured the second-order rate constants for the addition of dimethyl fumarate (**135**) to **133** and **138–141**.[36] According to the concept of π-bond fixation or bond alternation in benzenoid systems (the Mills–Nixon effect), 5*H*-cyclopropa[*f*]isobenzofuran **133** should be substantially less reactive than the parent isobenzofuran **139** due to the reluctance of **133** to accept an increase in double bond character across the positions of ring-fusion in going from reactants to transition state **136** (Scheme 24). The absence of a substantial rate difference between **133** and **138–141** implies that π-bond fixation in the direction indicated for adduct **137** cannot be significant.[36]

3. Cyclopropa-Fusion to Five-Membered Heterocycles

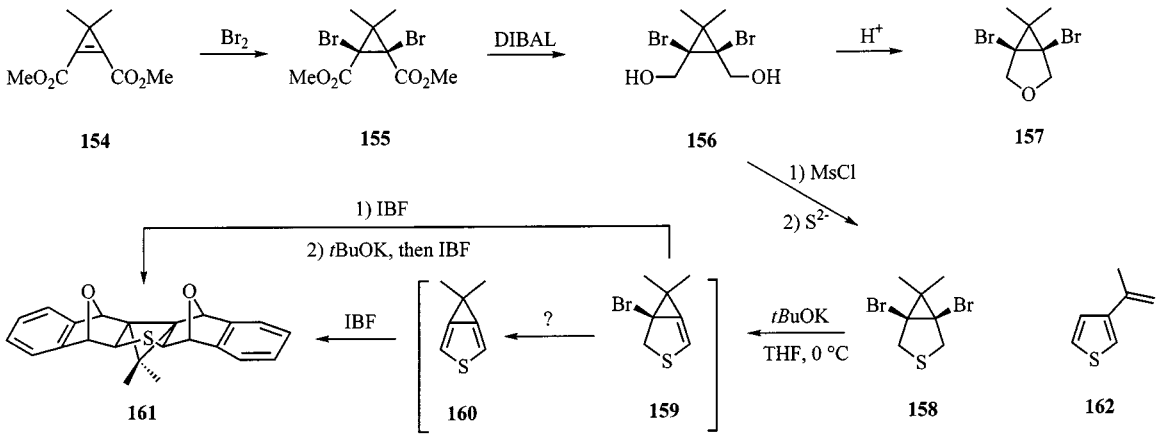
Fusion of the cyclopropene ring to a five-membered heterocyclic entity generates the *c*-fused and *b*-fused families of cyclopropahetarenes **142** and **143**, respectively (Scheme 25), which suffer from additional strain compared to benzenoid cycloproparenes due to the larger compression of the bond angles external to the three-membered rings. In addition, **143** has the methylene bridge across a bond of high π-character which should impart additional reactivity. We have examined several approaches to members of the cyclopropa[*c*]thiophene and cyclopropa[*c*]furan series.



Scheme 25. Cyclopropa-fusion to five-membered aromatic heterocycles



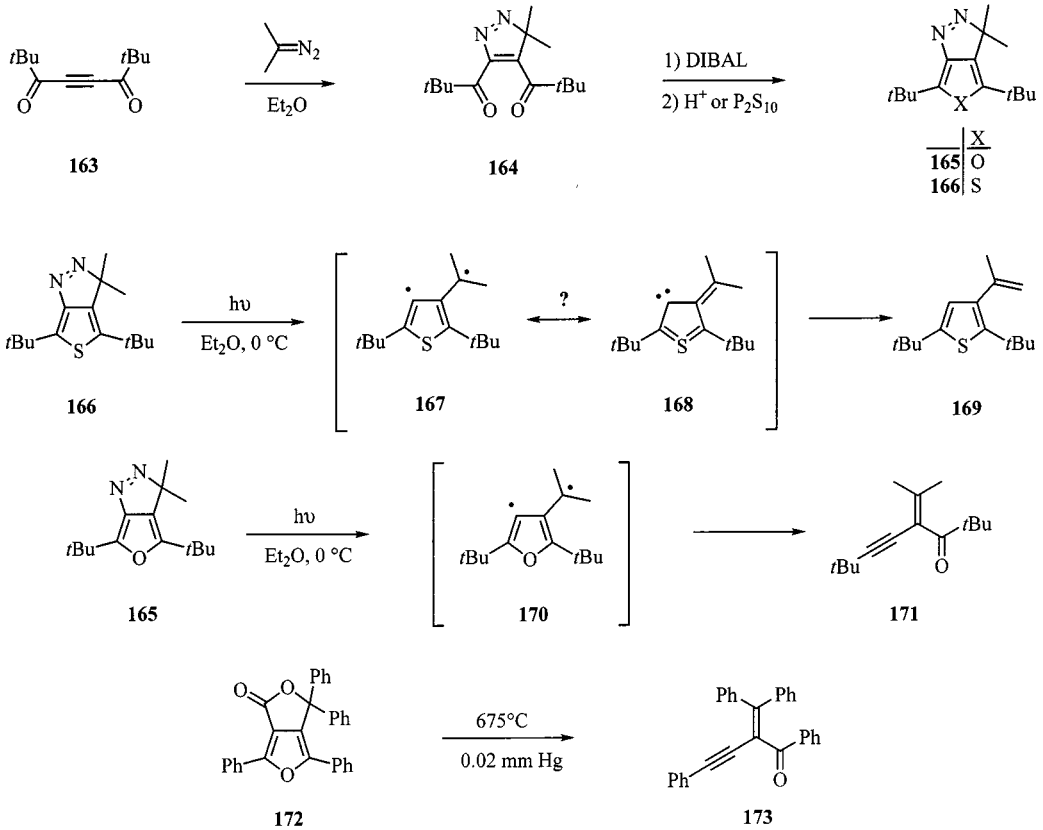
Scheme 26. Failure of the Billups protocol in an approach to a cyclopropa-fused thiophene and furan



Scheme 27. Tentative evidence for the generation of the cyclopropathiophene **160**

Dehydrochlorination of **144** using the Billups protocol for preparing benzocyclopropene generated the highly strained, bridged cyclopropene **145**, which was trapped by *tert*-butyl alcohol to give ether **148**, or by added furan to afford adduct **149**.[39a] Isomerisation to **146**, as required for a pathway which would deliver ultimately the cyclopropathiophene **147**, was not observed. Halton and co-workers found that, in the case of the dehydrochlorination of the furan analogue **150**, the initial product **151** could be intercepted with 1,3-diphenylisobenzofuran, but in the presence of the less-reactive diene furan, **151** rearranged to the carbene **152**, which was then trapped by furan to give adduct **153** (Scheme 26).[40]

In view of the failure of the putative intermediate **145** to undergo double bond isomerisation, we constructed a dihalide in which dehydrohalogenation could only occur in the desired sense (Scheme 27).[39a] Addition of bromine to the readily available diester **154**[41] gave the crystalline *cis*-dibromide **155** (50%) which was readily separated from the oily *trans* isomer. Reduction, followed by cyclisation, afforded the furan and thiophene derivatives **157** and **158**. In contrast to other tertiary bromides, which undergo rapid dehydrobromination with *t*BuOK in THF at −78 °C, **158** was consumed only slowly by this reagent at 0−10 °C and no characterisable product could be isolated by extractive workup. When the disappearance of dibromide **158** was



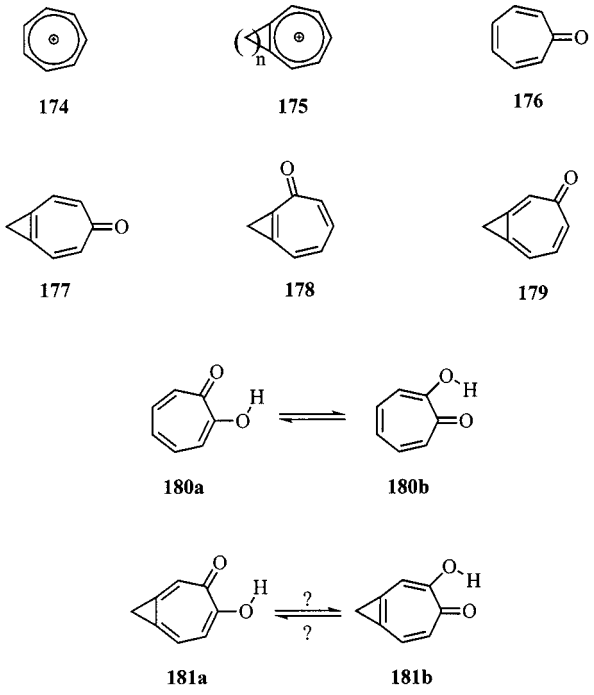
Scheme 28. Divergent photochemical behaviour of pyrazolothiophene **166** and pyrazolofuran **165**

monitored by gas chromatography-mass spectrometry in the presence of an internal standard, a product, which was tentatively formulated as the cyclopropathiophene **160** on the basis of its mass spectrum, was detected. This compound did not survive concentration of the solution extract and was shown not to be the isomeric alkene **162** (which could conceivably be generated from **158** by a circuitous elimination pathway). When the dehydrobromination was carried out in the presence of isobenzofuran, adduct **161** was obtained in 57% yield. At this stage we suspect that **161** arises from the trapping of alkene **159**, followed by a second elimination and cycloaddition, since **161** is not formed on addition of isobenzofuran to a solution containing (on the basis of mass spectrometric evidence) the thiophene **160**. Despite considerable effort, we have been unable to resolve this question further.[39b] However, it is evident that, because of its higher ring strain, **160** possesses substantially enhanced reactivity over benzocyclopropene or its *gem*-dimethyl-substituted derivative **116**, and appears to be too unstable to permit isolation under normal laboratory conditions.

Very recently we have examined the photochemical extrusion of nitrogen from appropriate precursors as a potential route to cyclopropa[*c*]furans and cyclopropa[*c*]thiophenes.[42] Partial reduction of adduct **164** followed by treatment with either acid or P_2S_{10} gave the pyrazolo[*c*]furan **165** and pyrazolo[*c*]thiophene **166**, respectively (Scheme 28). Irradiation of **166** gave the alkene **169** (60%), while, under identical conditions, **165** provided the fragmentation product **171** (63%); in both cases, no NMR signals ascribable to the desired cyclopropahetarenes could be detected in the crude reaction mixtures. The formation of alkene **169** results from the usual intramolecular hydrogen-atom transfer process involving diradical **167**, but it should be noted that a carbene structure **168** can only be drawn in this system if one invokes nonclassical bonding of the sulfur atom.[43] Accordingly, the intermediate formed from the pyrazolofuran **165** must be depicted as the diradical **170** since tetravalency of O cannot be invoked. The fragmentation observed on irradiation of the furan derivative **165** is similar to that found in the flash vacuum pyrolysis of lactone **172** which delivers ketone **173**.[44] The cleavage of the pyrazolofuran **165** can be envisaged to occur via diradical **170**, although the concerted fragmentation of an excited state of **165** also is possible. The difference in behaviour between **166** and **165** can be rationalised in that formation of a carbon-oxygen π-bond is ca. 160 kcal mol^{-1} more exothermic than formation of a carbon-sulfur π-bond;[45] hence, the activation energy for cleavage of the furan ring is likely to be substantially lower.

4. Cyclopropa-Fused Seven-Membered Unsaturated Systems

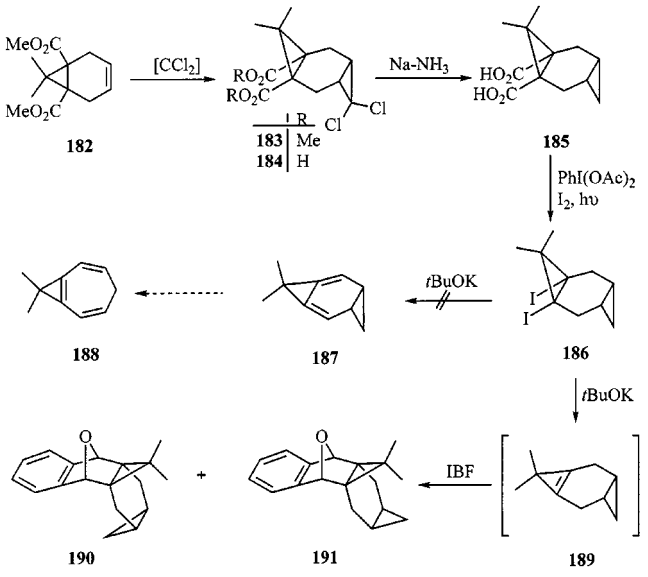
The tropylium ion **174** is a well-known aromatic ring system.[46–48] The smallest known 1,2-*n*-methylene-bridged tropylium ion is the cyclobuta-fused derivative **175**, (n = 2),[47] and in the context of nonbenzenoid cycloproparene chemistry, the generation of the cyclopropa-fused derivative **175** (n = 1) would be of obvious interest and significance. Although not formally aromatic, tropone (**176**) and α-tropolone (**180**) are usually considered together with **174** in discussions of the chemistry of nonbenzenoid aromatic systems.[48] Cyclopropa-fusion to **176** gives rise to three possible isomers **177–179**, two of which possess a high degree of cyclopropene character, and hence a reactivity comparison within this family would be informative. In the parent α-tropolone **180**, tautomerism in solution is rapid on the NMR time scale,[49] and since cyclopropa-fusion removes the structural degeneracy, it would be of interest to see, for example, whether tautomers **181a** and **181b** are separated by a substantial energy barrier (Scheme 29).



Scheme 29. Some cyclopropa-fused seven-membered unsaturated systems

Our work on approaches to such ring systems is summarised in Scheme 30 and 31.[50] Addition of dichlorocarbene to **182**, the adduct of dimethyl 2,2-dimethylcyclopropene-1,2-dicarboxylate and butadiene, afforded **183**, which was converted by functional group manipulation into diiodide **186**. Treatment of **186** with *t*BuOK gave no recognisable products and failed to deliver the desired cycloheptatriene derivative **188**, which would have functioned as a suitable precursor for a cyclopropa-fused tropylium ion. When the attempted dehydroiodination was carried out in the presence of the reactive diene isobenzofuran, adducts **190** and **191**, resulting from trapping of strained cyclopropene **189**, the product of deiodination rather than dehydroiodination, were unexpectedly isolated in 21% yield. We

attribute the formation of **189** to the rigid nature of the tricyclic ring system which prevents proper alignment of the C−H and C−I bonds necessary for the E2 pathway which would have provided **187** and hence **188**.

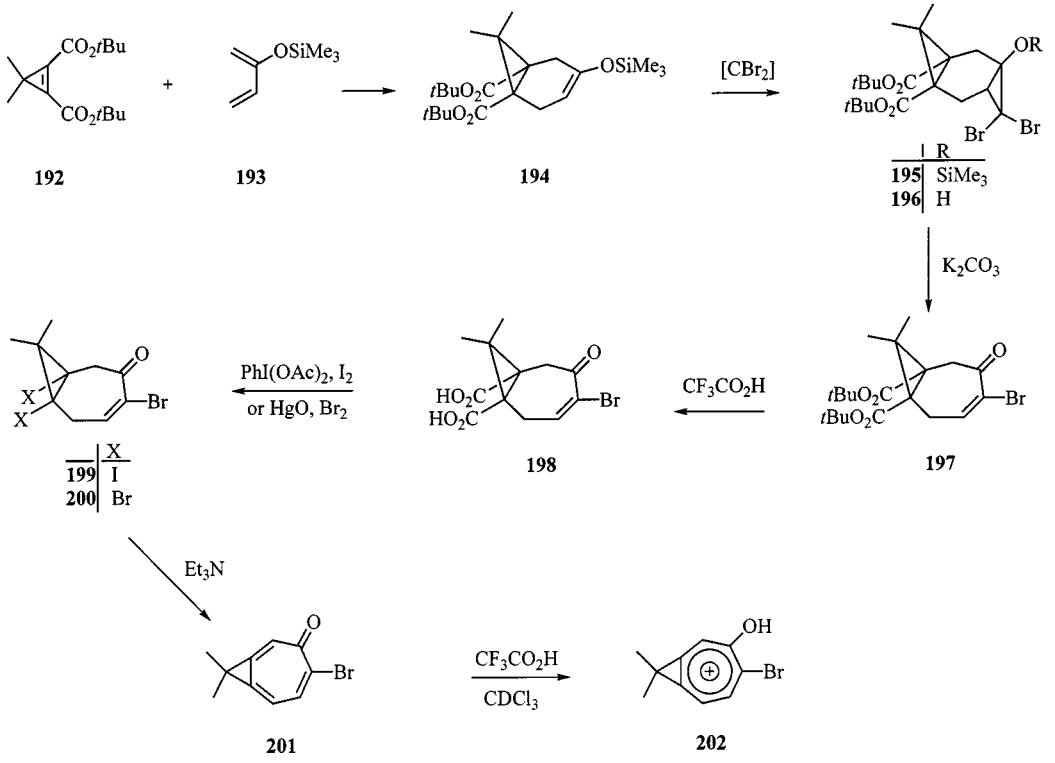


Scheme 30. Unexpected formation of cyclopropene **189** during the attempted dehydroiodination of **186**

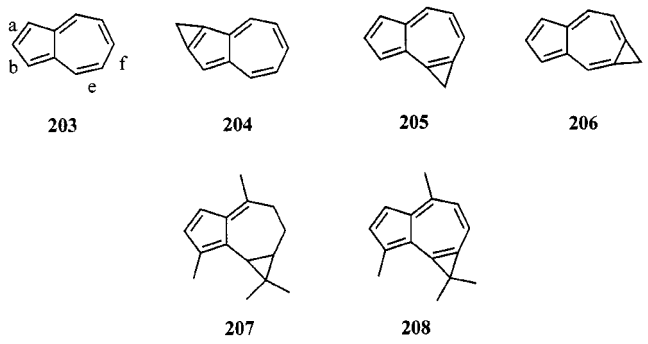
After considerable experimentation, the synthesis of a derivative of the cyclopropa-fused tropone **179** was achieved as outlined in Scheme 31. The key step involved ring-opening of the tricyclic cyclopropanol **196** to give the requisite bicyclic derivative **197**, which, after cleavage of the *tert*-butyl esters followed by halodecarboxylation, provided the dihalides **199** and **200**. Finally, treatment of diiodide **199** with Et_3N gave **201**, the first example of a cyclopropa-fused tropone. On protonation, **201** gave the hydroxytropylium ion **202** as evidenced by the downfield shift of all the ^1H NMR resonances.[50]

5. Cyclopropazulenes

The blue nonalternant hydrocarbon azulene **203** is interesting in that it possesses both a five- and seven-membered ring available for cyclopropa-fusion. Geometric factors should make **204** more strained than a benzenoid cycloproparene, but isomers **205** and **206** may well be stable and represent realistic targets for synthesis. The cycloprop[*e*]-azulene system of **205** is present in reduced form in many natural products of the aromadendrene family,[51] and it may be noted that the fulvene **207** has been isolated from a soft coral.[52] The introduction of two further double bonds into **207** would generate the aromatic cyclopropazulene **208**, and since azulenes have been isolated from natural sources,[53] we speculate that the cyclopropa-derivative **208** may possibly occur undetected in some marine or terrestrial organism. As such, it would represent the first naturally occurring cycloproparene (Scheme 32).

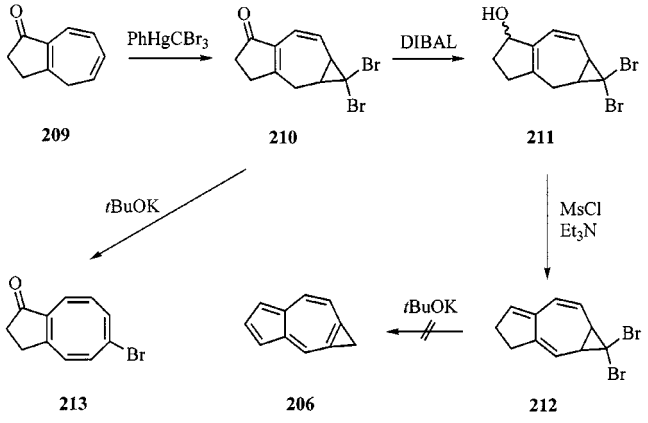


Scheme 31. Synthesis of the cyclopropa-fused tropone **201** and tropylium ion **202**



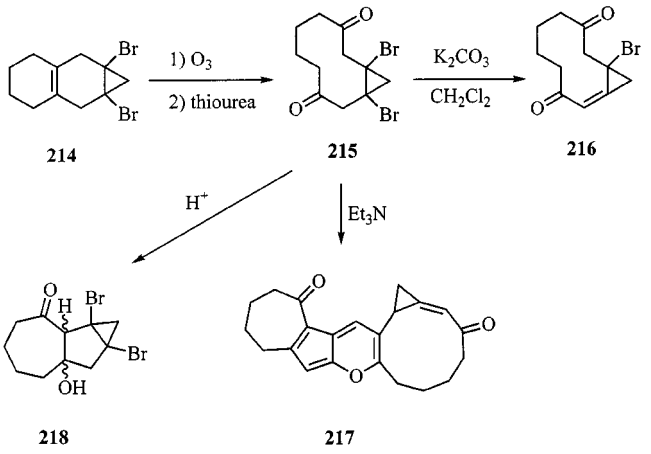
Scheme 32. Cyclopropazulenes

Some of our approaches to cyclopropazulenes are summarised in Scheme 33−36. Addition of dibromocarbene to trienone **209**[54] occurred selectively to give **210** possessing the requisite skeleton and correct number of double bond precursors for 1*H*-cycloprop[*f*]azulene **206**. Reduction of the carbonyl group followed by elimination gave the triene **212**. Disappointingly, this compound gave no recognisable product on treatment with *t*BuOK in THF at −78 °C. Consumption of starting material was accompanied by the formation of black insoluble material, and no azulenoid product was detected. Thus, as in the case of the heterocyclic derivatives **144** and **150** (Scheme 26), this system lacks the driving force for relocation of the initially-formed cyclopropene double bond as required by the Billups protocol (Scheme 4). Direct treatment of trienone **210** with *t*BuOK did not yield a hydroxycycloprop[*f*]azulene, but resulted in ring expansion to afford **213**.[55]

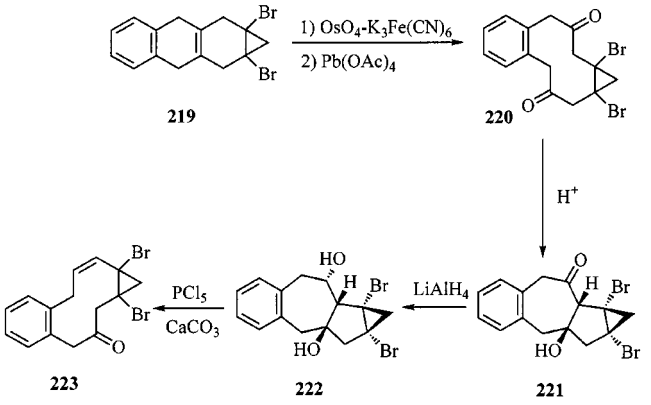


Scheme 33. Attempted synthesis of the cyclopropazulene **206**

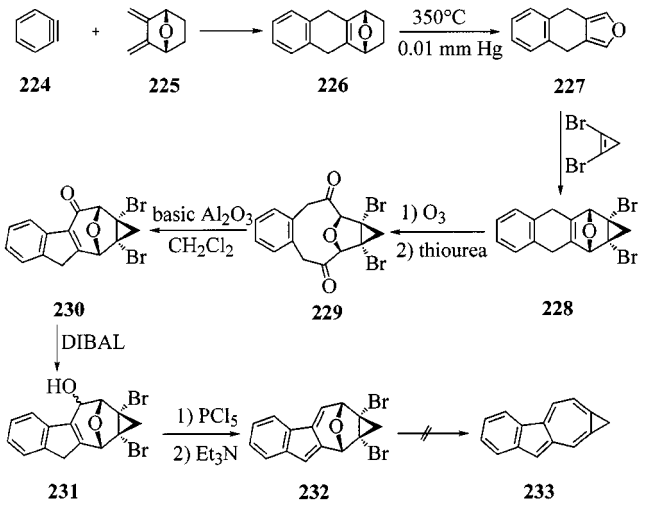
An approach in which the cyclopropazulene ring system was to be constructed through a transannular aldol condensation is shown in Scheme 34.[56] Careful ozonolysis of alkene **214** provided the sensitive, crystalline dione **215** which failed to give any recognisable product under a variety of basic aldol conditions.[57] The action of K_2CO_3 in CH_2Cl_2 did provide the enone **216**, while Et_3N in CH_2Cl_2 gave rise to the intensely coloured cyclopenta[*b*]pyran derivative **217** by a rather bizarre reaction pathway.[56] Under acidic conditions, dione **215** gave **218**, the "wrong" aldol product with regard to elaboration into the target 1*H*-cycloprop[*f*]azulene **206**.



Scheme 34. Some reactions of dibromodione **215**



Scheme 35. Benzannulation does not change the direction of acid-catalysed transannular aldol condensation



Scheme 36. Preparation of the advanced intermediate **232**

Similar studies were extended to the benzo-fused systems depicted in Scheme 35.[42] Here the relative stereochemistry of the aldol product **221** was established by X-ray crystallography.[58] Reduction of **221** gave a single diol **222**, which, on attempted conversion into a dichloride, underwent fragmentation to provide enone **223**.

Because our primary interest was in the preparation of a transannular aldol product in which the cyclopropane ring

was fused to the seven-membered ring, we adopted the blocking strategy shown in Scheme 36. Generation of 1,2-dibromocyclopropene in the presence of the furan **227** gave adduct **228** which was ozonised to provide dione **229**. Aldol condensation on basic alumina yielded the desired enone **230**, enolisation at the α-positions adjacent to the cyclopropane ring being prevented by the presence of the epoxy bridge. Reduction of the carbonyl group followed by chlorination and elimination yielded the benzofulvene derivative **232**. So far all attempts to generate the benzo-fused cyclopropazulene **233** by reductive elimination of the epoxy and dibromide functionalities of **232** have failed.[42] Müller and co-workers have also noted that the related elimination of **125** to give **126** using low-valent titanium (Scheme 22) fails in the parent system lacking bridgehead substituents.[34] Accordingly it may be necessary to incorporate substituents in the bridgehead positions of **232**.

Conclusions

Although the cyclopropaquinones **29** and **30** can be generated and trapped under mild conditions, they possess reactivity similar to that observed for the 1,2-bridged cyclopropene **56** and, as such, cannot be isolated. The methodology developed for the generation of the cyclopropanaphthoquinone **30** was applied to the synthesis of the novel metabolite favelanone **98**, illustrating that the concepts developed in the area of theoretically interesting molecules can be relevant to natural products chemistry. While six-membered cyclopropahetarenes are readily prepared using methodology developed for benzenoid cycloproparenes, the generation and identification of cyclopropafurans and cyclopropathiophenes remains a substantial challenge because of the higher ring strain within these systems. Further studies are also required to extend the family of cyclopropatropones, and the synthesis of cyclopropazulenes remains to be achieved. It is hoped that some of the results reported in this review will stimulate further endeavour in synthetic approaches to these and other nonbenzenoid cycloproparenes.

Acknowledgments

Early stages of our work were supported by a grant from the Australian Research Council. Thanks also go to the students whose names appear in the references for sharing in the excitement and occasional frustrations associated with these studies.

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