

Chemistry of spirodienones—A brief overview

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Received on May 26, 1994.

Abstract

Recent synthesis and novel reactions of spirodienones are briefly highlighted. The stereochemistry and the role of spirodienones in the biosynthesis of natural products are also discussed.

Key words: Biosynthesis, cycloaddition, oxidation, photoisomerisation, rearrangement, spirodienone, spironaphthalenone.

1. Introduction

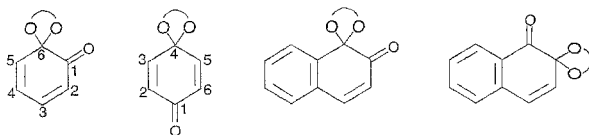
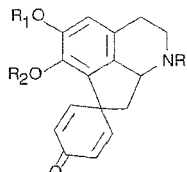
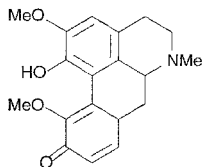
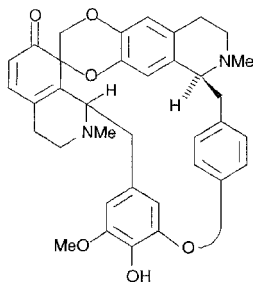
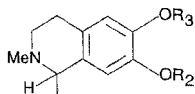
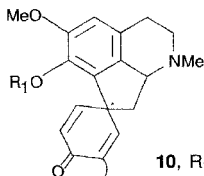
Spirodienones, a class of compounds which occur widely in nature and are considered important in biosynthetic pathways, have a fascinating chemistry. The term 'spirodienone' is used in this context to describe derivatives of cyclohexa-2,4- & 2,5-dienones **1** & **2** in which the carbon atoms 6 & 4, respectively, are spiro centers. Naphthalenones **3** and **4** form a special class of spirodienones, wherein one of the double bonds forms a part of the aromatic sextet.

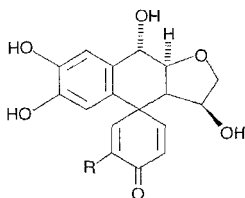
2. Occurrence

A number of proaporphinoid alkaloids exhibit spirodienone system. For example, proaporphine alkaloids like pronuciferine (**5**) from *Nelumbo nucifera*¹, crotonosine (**6**) from *Croton linearis*², N-carboxamidostepharine (**7**) from *Stephania venosa*³, homoaporphinoid alkaloid like kreysiginone (**8**) from *Kreysigia multiflora*⁴, proaporphine-benzylisoquinoline alkaloids like dielsine (**9**) from *Daphnandra dielsii*⁵, (+) valdivianine (**10**), (+) valdiberine (**11**), (+) patagonine (**12**) from Chilean species *Berberis valdiviana* and *Berberis empetrifolia*⁶ are found to have a common spirodienone moiety.

Anthrotaxin (**13**) and hydroxyanthrotaxin (**14**), the lignans isolated from *Anthrotaxis selaginoides* Don⁷, have the 2,5-dienone system. Eupodienone (**15**) isolated from the flowers of *Eupomatia laurina*⁸ also has the same spirodienone system.

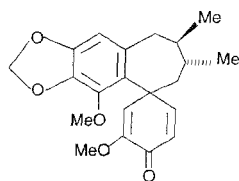
Discorhabdins B (**16**) and C (**17**) are cytotoxic pigments isolated from a New Zealand species of *latrunculia*^{9,10}. Both have the brominated 2,5-dienone system. Discorhabdins B containing sulphur atom in the ring is quite novel.

**1****2****3****4****5**, R₁=R₂=R=Me; Pronuciferine**6**, R₁=R=H; R₂=Me; Crotonosine**7**, R₁=R₂=Me; R=CONH₂; N-carboxamidostepharine**8**, Kreysiginone**9**, Dielsine**10**, R₁=H; R₂=R₃=Me; Valdivianine**11**, R₁=R₂=H; R₃=Me; Valdiberine**12**, R₁=R₃=Me; R₂=H; Patagonine

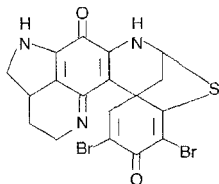


13, R=H; Anthrotaxin

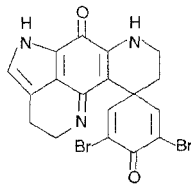
14, R=OH; Hydroxy Anthrotaxin



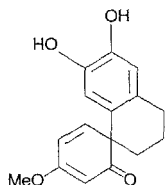
15, Eupodienone



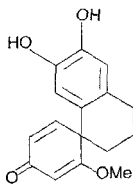
16, Discorhabdins B



17, Discorhabdins C



18, Spirobrousosin A

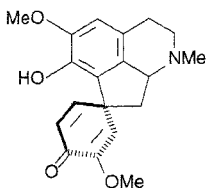


19, Spirobrousosin B

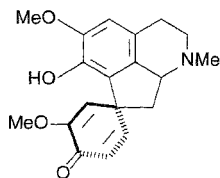
Some of the diarylpropanoid natural products like spirobrousosin A and B (**18** and **19**), isolated from the specimen of paper mulberry *Broussonetia papyrifera* that were infected by *Fusarium solani*, are found to have spirocyclohexadienone system¹¹.

3. Stereochemistry

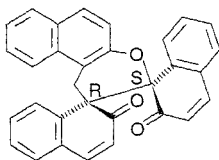
The spiro carbons of a spirodienone system are stereocenters and therefore can exist in two possible configurations (R and S). In some cases, both the forms of stereoisomers have been isolated from different species. For example, orientalinone (**20**) isolated from *Papaver orientale*¹²



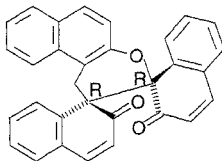
20, (R)-orientalinone



21, (S)-isorientalinone



22, RS-cis



23, RR-trans

has R configuration, while the iso-orientalinone (**21**), isolated from *Roemeria hybrida*¹³, has opposite S configuration. The dispiro-naphthalenones¹⁴ **22** and **23** formed in the reaction of bisnaphthol with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) have been shown to possess the RS and RR configurations, respectively.

Since the spirodienone moiety has a non-palindromic sequence of bonded atoms, a sense of directionality^{15,16} can be associated with it and this is observed in the calixenone type of molecules. This is known as cyclostereoisomerism. The directionality of the spirodienone moiety can be arbitrarily represented by a curved arrow in which the head and tail of the arrow represent the relative locations of the ether and the carbonyl moieties, respectively. The arbitrary convention used is shown in Fig. 1. For a single spirodienone moiety, different 'senses' of curved arrow (clock or anticlockwise) simply represent different views of the moiety, *i.e.*, the same moiety 'flipped over'. If two or more spirodienone moieties are present in the macrocycle, their relative sense (homo or heterodirectional) represent different constitutional isomers. For a bis(spirodienone) derivative of a calix[4]arene, two homodirectional arrows represent an alternate arrangement of enone and ether units of the spirodienone groups along the macrocycle while a tail to tail or head to head arrangement of arrows represents two cyclohexadienone rings attached to the same methylene groups.

4. Role in biosynthesis

Of greater significance than the natural occurrence of the spirodienones is the role which they play in the biosynthesis of several classes of natural compounds. In the biosynthesis of certain

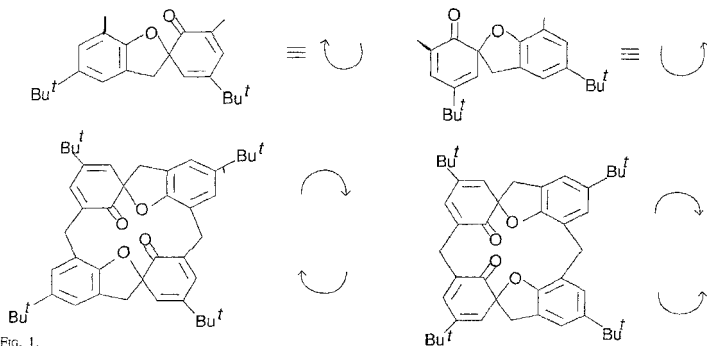
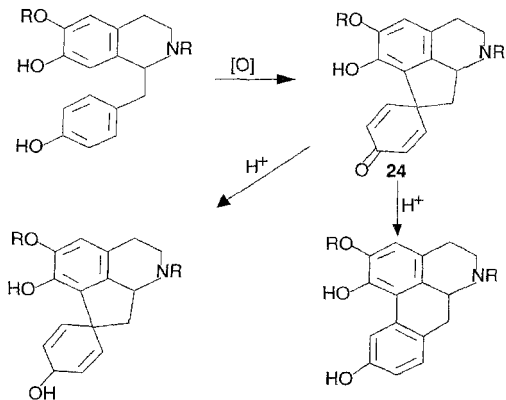


Fig. 1.

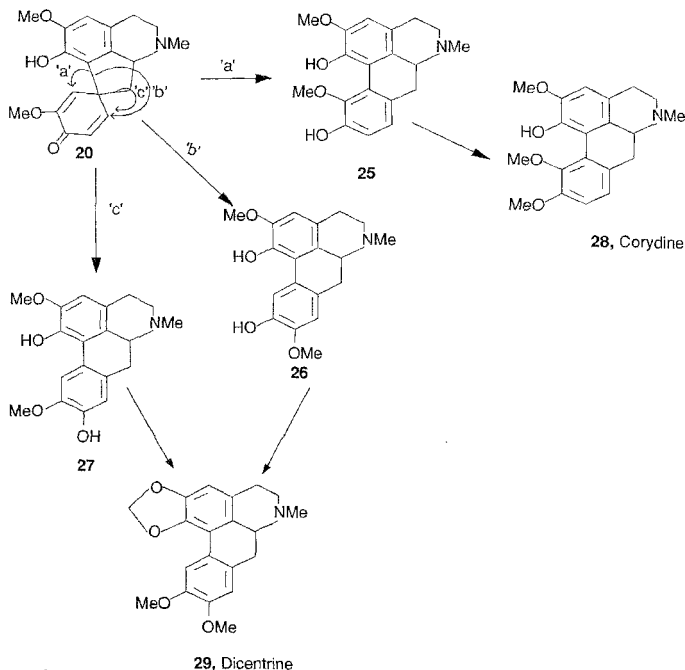
types of alkaloids, lignans, isoflavones, etc., spirodienones have been postulated as the intermediates.

In order to suggest a logical mechanistic pathway for the formation of aporphine alkaloids, Barton and Cohen¹⁷ have proposed the intermediacy of the dienone **24**, which could undergo an acid-catalysed dienone-phenol rearrangement. The above hypothesis received an overwhelming support with the isolation of a number of alkaloids having the skeleton **24** (Scheme 1). Formation of several aporphine alkaloids from spirodienones by the dienone-phenol rearrangement is well documented. For example, orientalinalone (**20**) can be transformed



SCHEME 1.

to aporphine skeletons¹⁸, **25**, **26** and **27** in three possible ways. These could then be converted into alkaloids corydine (**28**) and dicentrine (**29**) (Scheme 2).

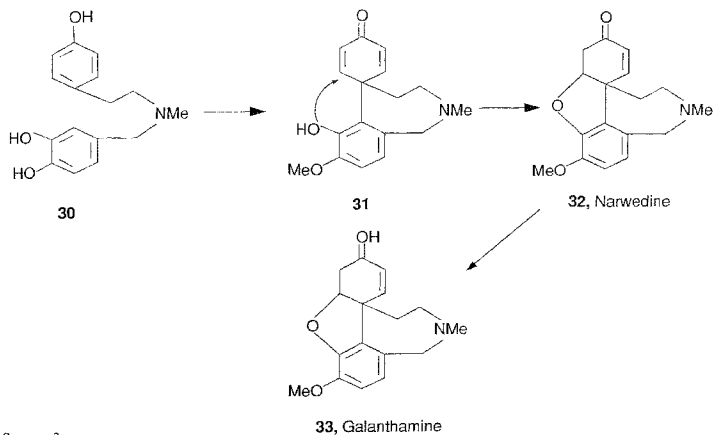


SCHEME 2.

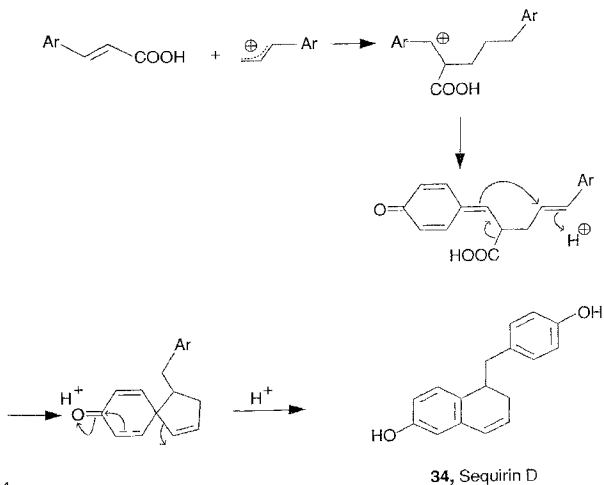
The biosynthesis of amaryllidaceae alkaloids like narwedine (**32**) and galanthamine (**33**) was shown to occur *via* the intermediacy¹⁹ of spirodienone **31**. This was proved beyond doubt by showing that triply labelled N,O-dimethylnorbelladine (**30**) was incorporated without breakdown into galanthamine (Scheme 3).

Lignans have attracted a number of biogenetic speculations. Birch and Liepa²⁰ suggested a biogenetic pathway for the norlignan sequirin-D **34**. The final dienone-phenol rearrangement seems plausible (Scheme 4).

Purpactin A (**37**), B (**35**) and C (**36**), possessing a skeleton similar to iso-grieseofulvin, have recently been identified from the cultures of *Penicillium purpurogenum* on the basis of

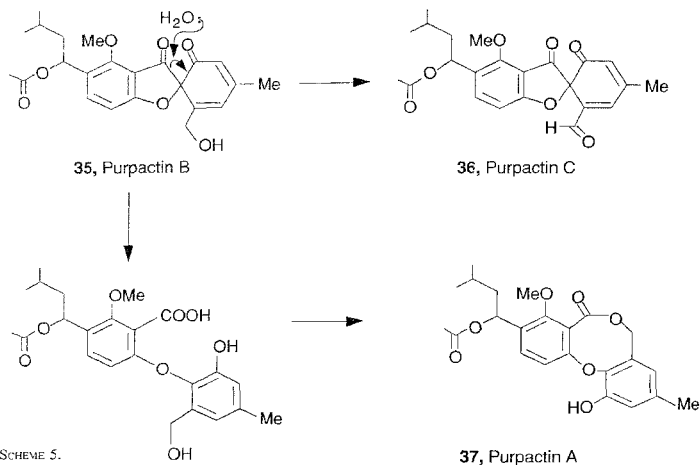


SCHEME 3.



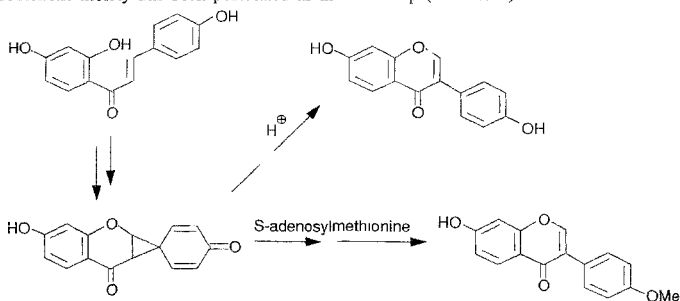
SCHEME 4.

their inhibition of acyl-CoA:cholesterol acyltransferase. It was demonstrated that **35** could be converted to **37** in aq. alcohol as shown below. This pathway could represent the true biosynthetic origin²¹ of purpactin A (**37**) (Scheme 5).



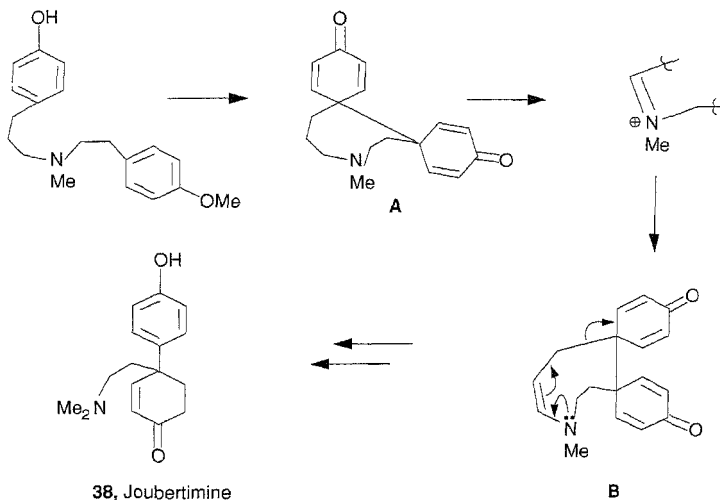
SCHEME 5.

In the biosynthesis of isoflavonoids, the rearrangement of an aryl group²² to form the 2,5-spirodienone moiety has been postulated as the first step (Scheme 6).



SCHEME 6.

The involvement of dispirointermediates²³ of type A and B has been invoked in the biosynthesis of scelletium alkaloids, for example, joubertimine (**38**) (Scheme 7).



SCHEME 7.

5. Synthesis of spirodienones

The presence of spirodienone moiety in a wide spectrum of families of natural products and its fascinating chemistry call for newer directions in the spirodienone synthesis.

There is a multitude of literature on the synthesis of dienones which can conveniently be classified as follows:

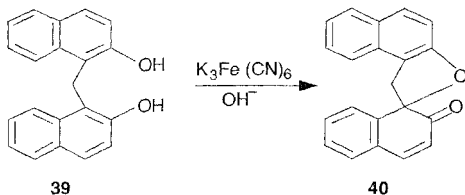
1. Phenolic oxidation
2. Quinone oxidation
3. Decomposition of the diazonium salts
4. Photochemical reaction
5. Anodic oxidation
6. Cycloaddition reaction
7. Miscellaneous

Only a few representative examples of each class, especially of recent origin, are discussed further.

5.1. Phenolic oxidation

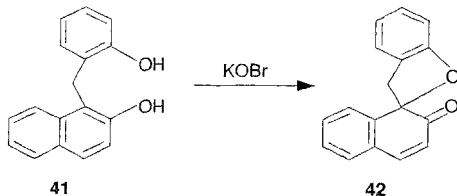
Spirodienones are usually formed in nature by the oxidative coupling of the phenolic precursors. Similar reactions can also be effected in laboratory by using reagents like

$K_3Fe(CN)_6$, $KOBr$, MnO_2 , etc. The history of phenolic oxidation to yield spirodienones can be traced back to the oxidation²⁴ of bis(2-hydroxy-1-naphthyl)methane (**39**) with $K_3Fe(CN)_6$ to yield the spiroketone **40** (Scheme 8).



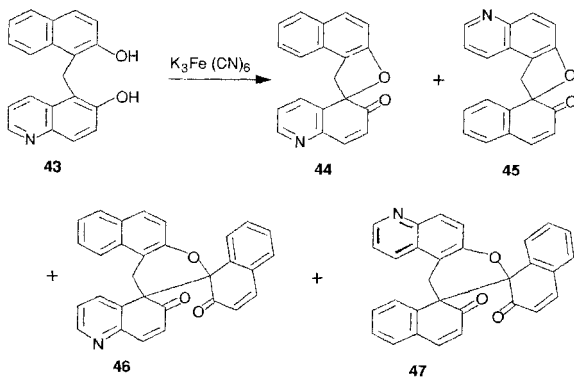
SCHEME 8.

Similar oxidation²⁵ of **41** with $KOBr$ or $K_3Fe(CN)_6$ gave exclusively **42** (Scheme 9).



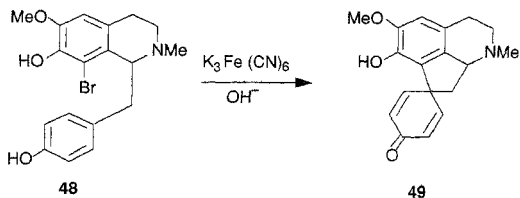
SCHEME 9.

1-[(6-Hydroxy-5-quinoliny)methane]-2-naphthol (**43**) on oxidation²⁶ with $K_3Fe(CN)_6$ gave the spirodienones **44** and **45**, and the dispiroketones **46** and **47** (Scheme 10).



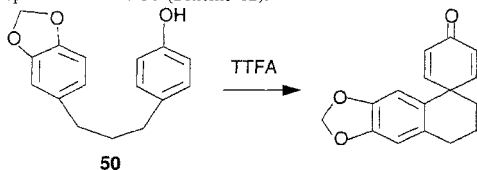
SCHEME 10.

The proaporphine alkaloid, glaziovine (**49**), was synthesised²⁷ by the oxidation of **48** with $K_3Fe(CN)_6$ (Scheme 11).



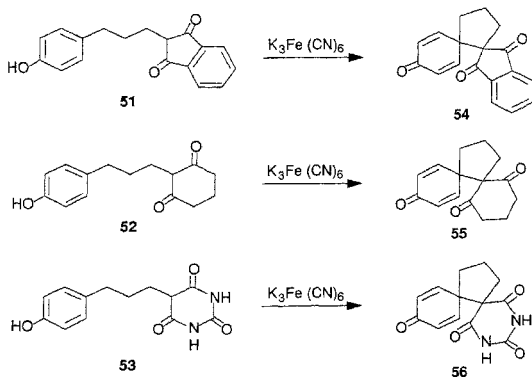
SCHEME 11

Thallium(III)trifluoroacetate (TTFA)²⁸, a two-electron oxidant, effects the spirocyclisation of the diaryl propane derivative **50** (Scheme 12).



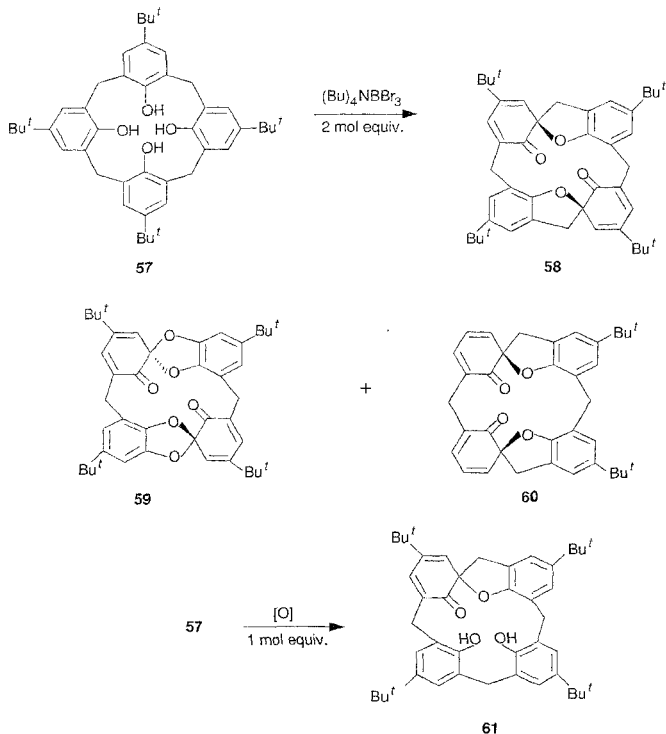
SCHEME 12.

Phenols bearing 3- or 4-carbon chains terminated by enolic or enolisable groups have been subjected to oxidation at alkaline pH using aq. $K_3Fe(CN)_6$ or potassium hexachloroiridate (K_2IrCl_6). Substrates in which the enolisable system is an indandione **51**, 1,3-cyclohexadione **52**, barbituric acid **53**, etc., undergo such oxidative cyclisations²⁹ (Scheme 13).



SCHEME 13.

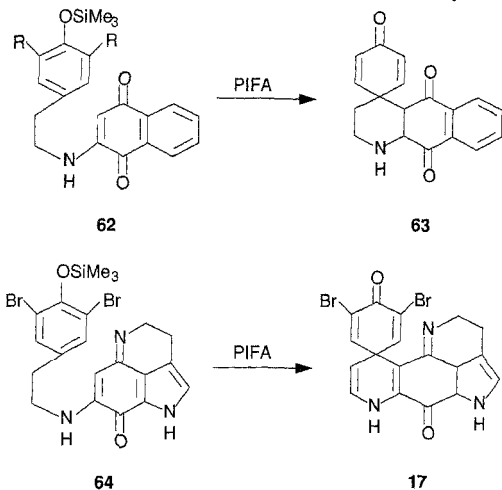
Calix[4]arenes (**57**) are macrocyclic compounds in which four phenolic and methylene units are arranged in an alternate fashion. Litwak *et al.*¹⁵ pointed out the structural similarity between calix[4]arenes and the bisnaphthols **39** and suggested the possibility of a similar oxidation to yield bis(spirodienone) of the type **58**, **59** and **60**. However, treatment of **57** with 1 equiv. of the oxidising agent gave the mono(spirodienone) **61** (Scheme 14).



SCHEME 14.

Hypervalent iodine–phenyliodine(III)bis(trifluoroacetate) (PIFA)–oxidation³⁰ of O-silylated phenols **62** bearing various types of aminoquinones at *p*-position in 2,2,2-trifluoroethanol gave azacarbocyclic spirodienones **63**. The final step in the total synthesis of discorhabdins

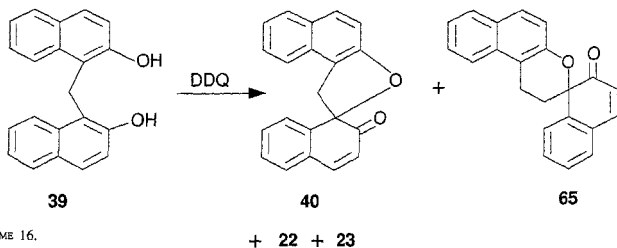
C (17) is the oxidative coupling of a preformed indoloquinone imine **64** by PIFA (Scheme 15).



SCHEME 15.

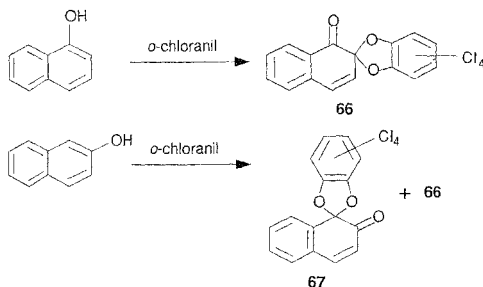
5.2. Quinone oxidation

Quinones with high oxidation potential are one of the most powerful oxidising agents. Oxidation¹⁴ of **39** with DDQ has been shown to give spiroketone **40**, quinone methide dimer **65** and the novel dispirodienones **22** and **23** (Scheme 16).



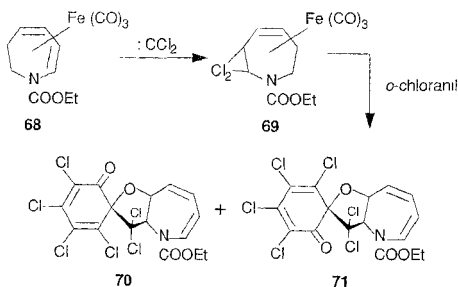
SCHEME 16.

Oxidation of 1-naphthol with *o*-chloranil³¹ gave spirodienone **66** while that of 2-naphthol gave **66** and **67** (Scheme 17).



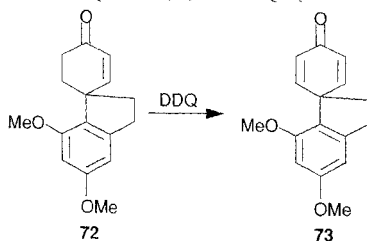
SCHEME 17

The reaction³² of tricarbonyl [N-methoxycarbonyl]-azepine iron (**68**) with excess of dichlorocarbene affords the derivative **69** which on oxidation with *o*-chloranil gives a mixture of spirodienones **70** and **71** (Scheme 18).

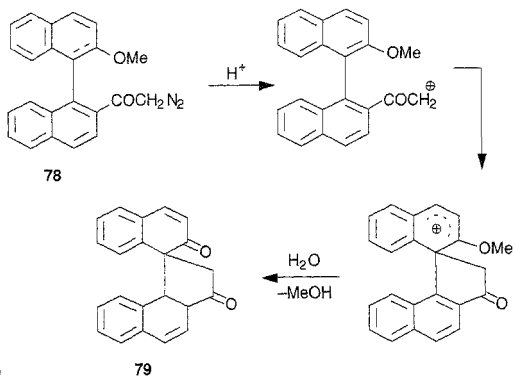


SCHEME 18.

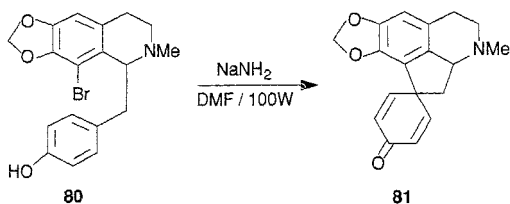
The spirodienone moiety in the cannabispirdienone (**73**) was synthesised by dehydrogenation of the precursor cannabispirenone (**72**) with DDQ³³ (Scheme 19).



SCHEME 19.

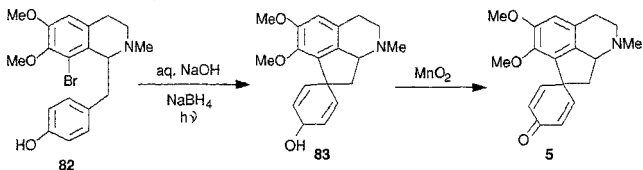


SCHEME 22.



SCHEME 23.

Irradiation³⁸ of **82** in aq. NaOH in the presence of NaBH₄ gave spirodienol **83**, which on oxidation with MnO₂ gave **5** (Scheme 24).

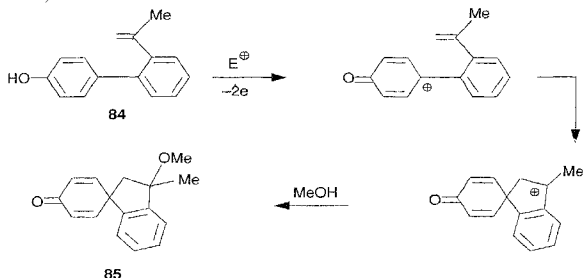


SCHEME 24.

5.5. Anodic oxidation

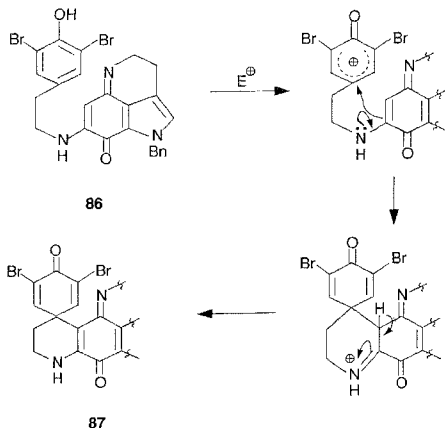
Anodic oxidation of oxygen and nitrogen-substituted aromatic systems often serve as a very useful method for preparing compounds not conveniently available *via* conventional chemistry.

Anodic oxidation³⁹ of 4-(2'-alkenylphenyl) phenols (**84**) in acetonitrile/MeOH affords spirodienones **85** arising from cyclisation of the olefinic side chain to the 4-position of the phenol and the reaction of resulting benzylic cation with MeOH. The most favourable condition for performing this anodic C–C bond-forming reaction involves anodic oxidation in slightly acidic media using a Pt anode, Pt cathode and current densities of about 1mA/cm² (Scheme 25).



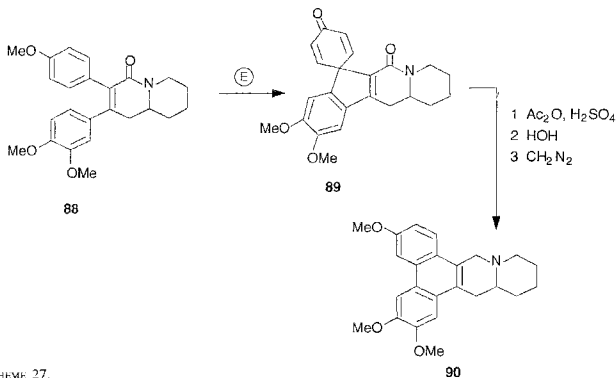
SCHEME 25

In the first total synthesis of discorhabdin C (**17**) the crucial phenolic oxidation of the appropriate phenol carrying no protection group was achieved by electrochemical methodology⁴⁰. Thus, anodic oxidation of **86** at a constant current (3mA) in CH₃CN, in the presence of LiClO₄ yielded N-benzyldiscorhabdin C (**87**) (Scheme 26).



SCHEME 26.

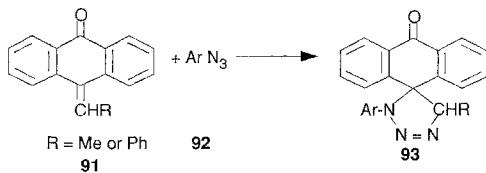
Anodic oxidation⁴¹ of the quinolizidine **88** gives the spirodienone **89**, which could be transformed to the alkaloid cryptoleurine (**90**) (Scheme 27).



SCHEME 27.

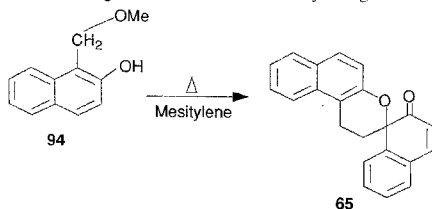
5.6. Cycloaddition reactions

Quinone methide **91** undergoes a 1,3-dipolar cycloaddition⁴² with the aryl azide **92** to give the corresponding spiroanthrotriazolines **93** (Scheme 28).



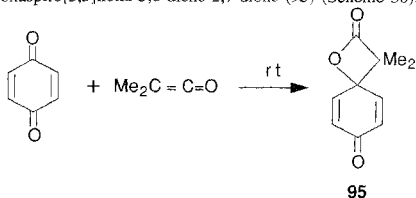
SCHEME 28.

Quinone methide dimer **65** is formed by the (4+2) cycloaddition reaction of two molecules of the quinone methide. Heating **94** under reflux in mesitylene gives **65** in 100% yield⁴³ (Scheme 29).



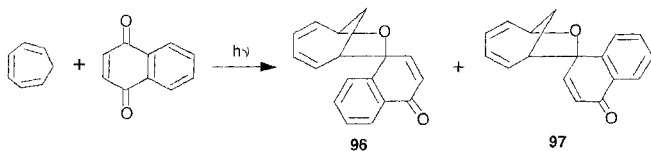
SCHEME 29.

Dimethylketene and *p*-benzoquinone reacted at room temp. in a (2+2)⁴⁴ fashion to give 3,3-dimethyl-1-oxaspiro[3,5]nona-5,8-diene-2,7-dione (**95**) (Scheme 30).



SCHEME 30.

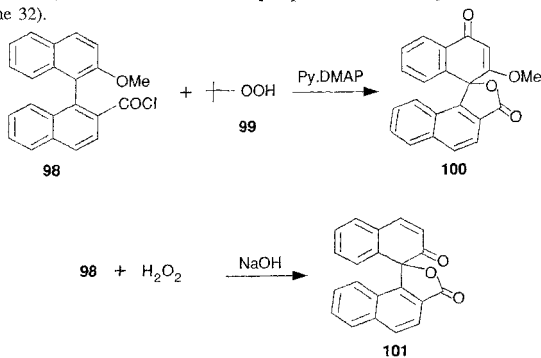
Photochemical reaction between cycloheptatriene and 1,4-naphthoquinone yielded the spirodienones **96** and **97** via a (6+2) cycloaddition reaction⁴⁵ (Scheme 31).



SCHEME 31.

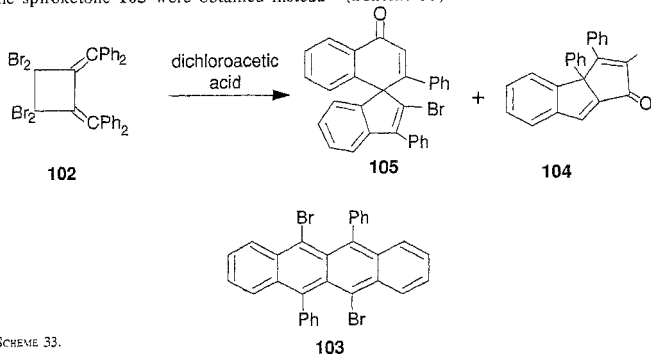
5.7. Miscellaneous

Reaction⁴⁶ of 2'-methoxy-1,1'-binaphthyl-2-carbonyl chloride (**98**) with the alkyl hydroperoxide **99** under Einhorn condition (**98** : **99**=1:1.1, DCM, Py-DMAP), gave the spiroactone **100**. On the other hand, the reaction of **98** with dihydroperoxide in NaOH gave the spiroactone **101** (Scheme 32).



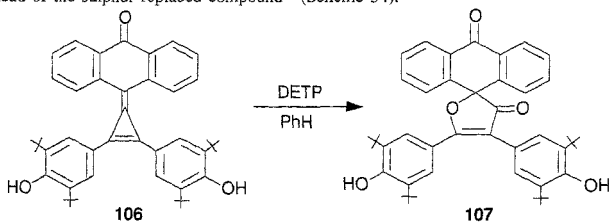
SCHEME 32.

In an attempt to obtain the substituted rubrene (**103**), 3,3,4,4-tetrabromo-1,2-bis(diphenylmethylene) cyclobutane (**102**) was heated in dichloroacetic acid. Surprisingly, **104** and the spiroketone **105** were obtained instead⁴⁷ (Scheme 33).



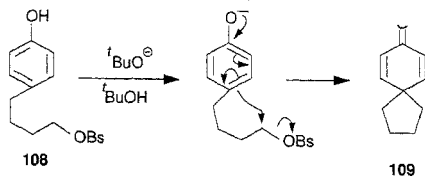
SCHEME 33.

In the reaction of **106** with DETP [diethylthiophosphate], a spiroanthrone **107** was obtained instead of the sulphur-replaced compound⁴⁸ (Scheme 34).



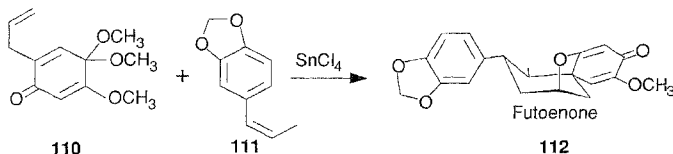
SCHEME 34.

Intramolecular alkylation⁴⁹ of phenols is a general method of synthesis of spirodienones. For example, a dilute solution of 4-(4-hydroxyphenyl)butylbrosylate (**108**) with a slight excess of KOBu^t gives the dienone **109** (Scheme 35).



SCHEME 35.

Futoenone (**112**), a neolignan, isolated from the Chinese herbal plant *Piper futokadsura* has a spiro-2,5-dienone skeleton. The spirodienone moiety of **112** was synthesised *via* the quinone ketal cycloaddition reaction between the quinone ketal **110** and isosafrole (**111**) in the presence of SnCl_4 ³⁰ (Scheme 36).

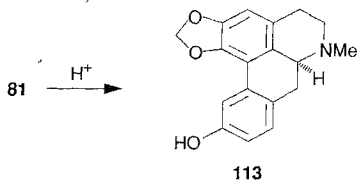


SCHEME 36.

6. Reactions of spironaphthalenones

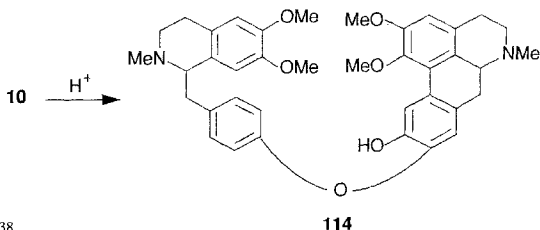
As mentioned earlier, spirodienones undergo a wide variety of bond-breaking and bond-making processes with many reagents and under various reaction conditions to give novel rearranged and stable products.

The most commonly observed rearrangement in spirodienones is the transformation of the dienone to phenol in the presence of an acid catalyst. As already mentioned, this also seems to be the most probable biogenetic pathway for the synthesis of aporphine alkaloids from the proaporphine alkaloids. For example, **81** can be transformed to mecambroline (**113**) in the presence of acid (Scheme 37).



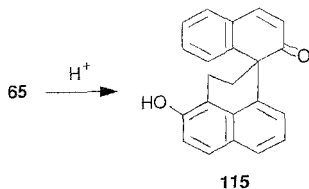
SCHEME 37.

The proaporphine benzyloquinoline alkaloid (+)-valdivianine (**10**) rearranges⁶ in dilute acid to give its aporphine benzylquinoline analogue **114** (Scheme 38).



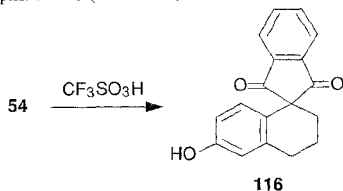
SCHEME 38.

Hot trifluoroacetic acid isomerises **65** to the phenolic phenalene derivative **115** via an acid-catalysed 3,3' sigmatropic rearrangement⁵¹ (Scheme 39).



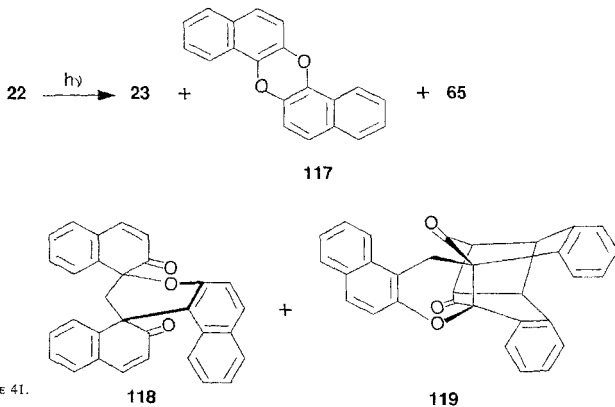
SCHEME 39.

The spirocyclic hexadienone **54** on reaction with trifluoroacetic acid rearranged²⁹ exclusively to the phenol **116** (Scheme 40).



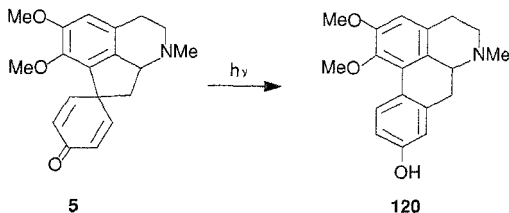
SCHEME 40.

Photolysis of spirodienones result in the formation of novel rearranged products. Irradiation of dispiroanthalene **22** affords a wide range of products **23**, **65**, **117**, **118** and **119** resulting from β -cleavage and intramolecular cycloaddition⁵² (Scheme 41).



SCHEME 41.

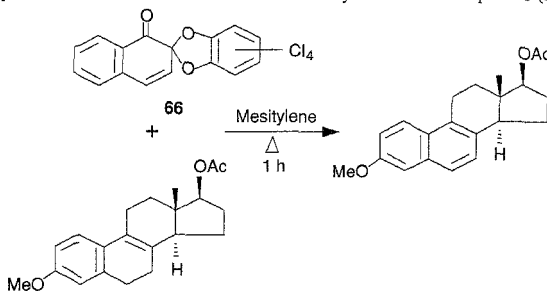
Proaporphine alkaloids undergo photochemical rearrangement to aporphine alkaloid. Thus, light-catalysed rearrangement⁵³ of pronuciferine (**5**) provides **120** (Scheme 42).



SCHEME 42.

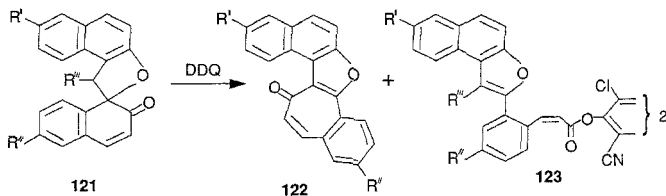
Spirodienones undergo a variety of thermolytic reactions. Pyrolysis of **22** or **23** gives dinaphthodioxins **117** and **65** through a novel C-C bond cleavage⁵⁴.

The pyrolytic cleavage of the bonds in the spirodienones **22**, **66** and **67** has been ingeniously used by Kasturi *et al*⁵⁵ for the aromatisation of dihydroaromatic compounds (Scheme 43).



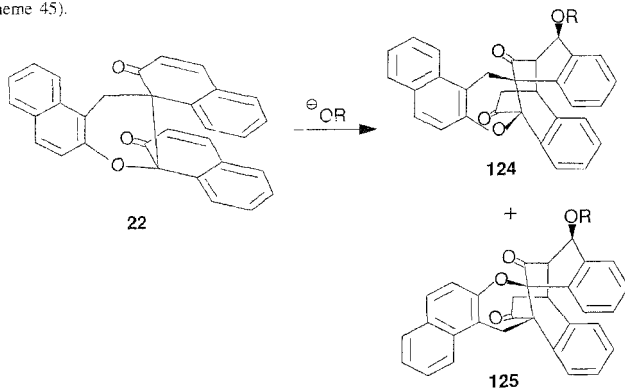
SCHEME 43.

Oxidation of spiroketones **121** with DDQ in dry benzene gave tropane derivatives **122** and the DDHQ esters **123** depending on the substitution at the 1'-position⁵⁶ (Scheme 44).



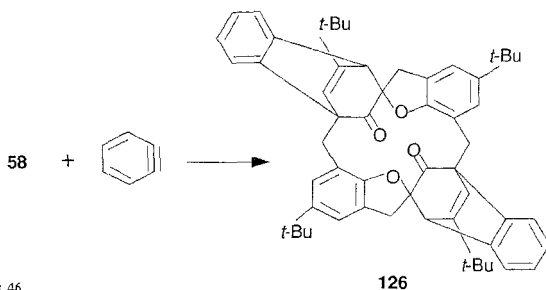
SCHEME 44.

The addition of **22** to a well-stirred solution of sodium alkoxide at room temperature resulted in the formation of diketones **124** and **125** via a tandem Michael addition reaction⁵⁷ (Scheme 45).



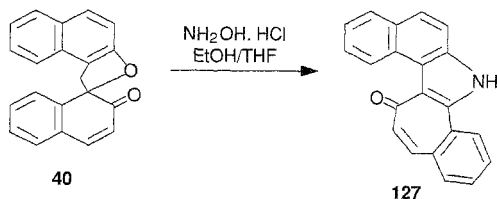
SCHEME 45.

The cyclohexadienone rings in **58** add a molecule of benzyne¹³ yielding the corresponding Diels-Alder adduct **126** (Scheme 46).



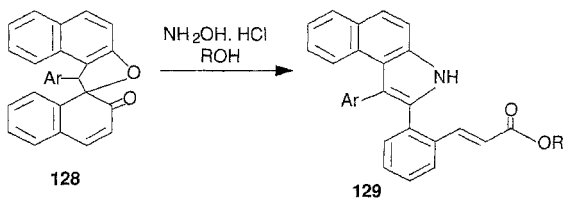
SCHEME 46.

Reaction of spironaphthalenone **40** with NH_2OH results in the formation of a novel pyrrolotropone **127**^{24,58,59}. The formation of this product has been shown to involve the intermediacy of a nitrene species resulting in an isopyrrole derivative. This further undergoes an 1,5-acyl migration to give the pyrrolotropone^{60,61} (Scheme 47).



SCHEME 47.

Under similar reaction conditions, 1'-substituted⁶¹ spiroketones **128** give the pyrroloesters **129** (Scheme 48).



SCHEME 48.

Acknowledgements

We thank the INSA and CSIR, New Delhi, for financial assistance.

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