Anionic Cyclization of Phenols

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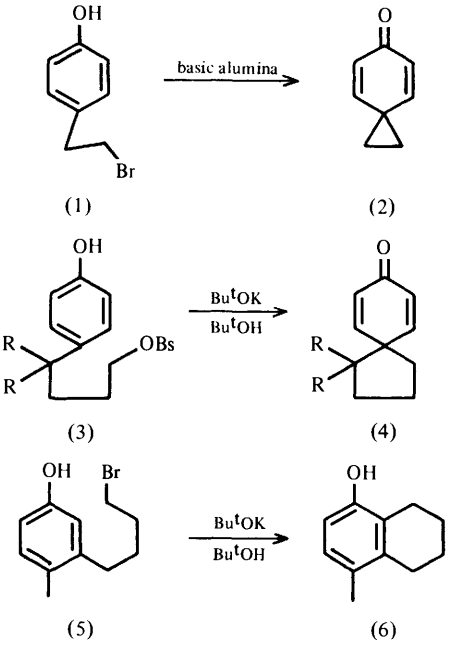
1 Introduction

This review is concerned with those cyclizations of phenols that are catalysed by base and in which a new carbon to carbon bond is formed. In 1957 Winstein and Baird[1] demonstrated that under basic conditions suitably substituted phenols undergo intramolecular geminal cyclization *via* participation of the neighbouring phenoxide ion group to form dienones, *e.g.* (2) and (4).[2-4] Since then this intramolecular reaction of phenolic compounds has been extensively studied from both mechanistic and synthetic standpoints. This reaction has been extended to the synthesis of fused products, *e.g.* (5)→(6)[5] and has been used to gain understanding



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[1] S. Winstein and R. Baird, *J. Am. Chem. Soc.*, 1957, **79**, 756.
[2] R. Baird and S. Winstein, *J. Am. Chem. Soc.*, 1957, **79**, 4238.
[3] R. Baird and S. Winstein, *J. Am. Chem. Soc.*, 1962, **84**, 788.
[4] R. Baird and S. Winstein, *J. Am. Chem. Soc.*, 1963, **85**, 567.
[5] M. S. Newman and A. B. Mekler, *J. Org. Chem.*, 1961, **26**, 336.

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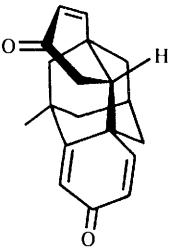

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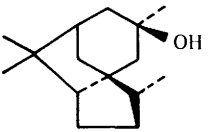

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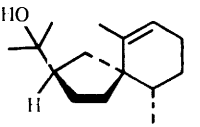

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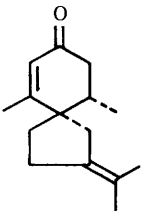

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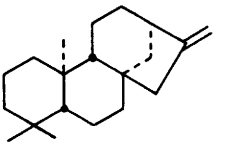

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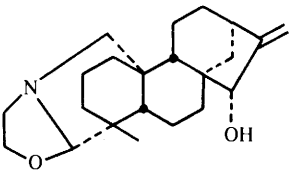

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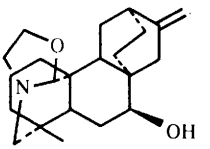

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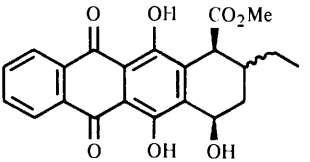

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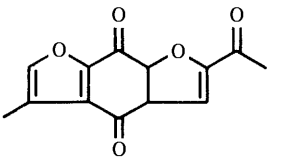

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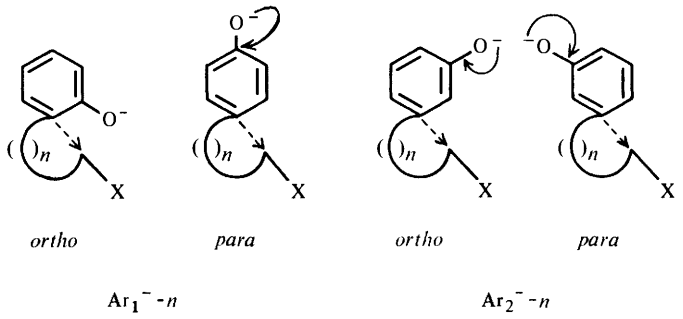
of *ortho–para*-alkylation ratios, reactivity of leaving groups, and the effect of the nature of the chain involved in the ring being formed. A review has covered aspects of these topics to a limited extent.[6]

Intramolecular alkylation of phenoxide ions has found widespread application to the synthesis of theoretically interesting compounds such as the tetracyclic dienone (7),[7] the adamantanoid dienones (8),[8] and the bridged bis-dienone (9),[8] as well as to the synthesis of natural products such as cedrol (10),[9,10] hinesol (11),[11] β-vetivone (12),[12] kaurene (13),[13] garryine (14),[14] atisine (15),[15] the anthracyclinone (16),[16] and conicaquinone (17).[17]

It is the purpose of this review to discuss the known intramolecular alkylations of phenoxide ions. Discussion will include base-catalysed cyclization reactions of phenolic epoxides, aldehydes, ketones, and related functional groups. An emphasis has been placed on their scope, limitations, and applications in natural product synthesis. Detailed mechanistic studies have not been undertaken in most systems.

2 Mechanism

Intramolecular alkylation of phenoxide ions are conveniently classified according to transition states:[4] $Ar_1^- - n$ and $Ar_2^- - n$ (Scheme 1). Ar^- denotes the participating (rate enhancing) phenoxide ion. The subscript, 1 or 2, refers to the position



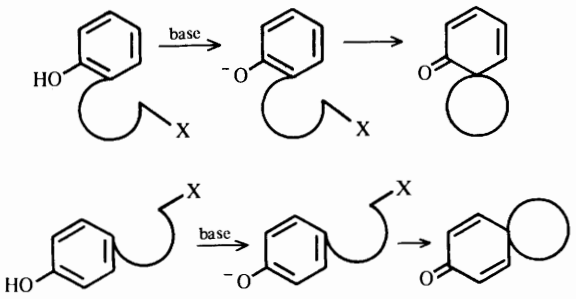
Scheme 1

of ring closure, and n to the size of the ring formed. Only one product is possible in the course of an $Ar_1^- - n$ cyclization, whereas two regio-isomers are possible in the course of $Ar_2^- - n$ cyclization. It should be noted that these symbols are used to

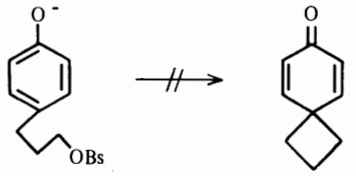
[6] B. Capon, *Quart. Rev.*, 1964, **18**, 45.
[7] A. P. Krapcho, *Synthesis*, 1974, 383.
[8] R. S. Atkinson and J. E. Miller, *J. Chem. Soc., Perkin Trans. 1*, 1979, 3017.
[9] E. J. Corey, N. N. Gikotra, and D. T. Mathew, *J. Am. Chem. Soc.*, 1969, **91**, 1557.
[10] T. G. Crandall and R. G. Lawton, *J. Am. Chem. Soc.*, 1969, **91**, 2127.
[11] J. A. Marshall and S. F. Brady, *J. Org. Chem.*, 1970, **35**, 4068.
[12] S. Torii, K. Uneyama, and K. Okamoto, *Bull. Soc. Chem. Jpn.*, 1978, **51**, 3590.
[13] S. Masamune, *J. Am. Chem. Soc.*, 1964, **86**, 289.
[14] S. Masamune, *J. Am. Chem. Soc.*, 1964, **86**, 290.
[15] S. Masamune, *J. Am. Chem. Soc.*, 1964, **86**, 291.
[16] K. Krohn, *J. Chem. Res. (S)*, 1978, 394.
[17] J. K. MacLeod, B. R. Worth, and R. J. Wells, *Aust. J. Chem.*, 1978, **31**, 1533.

describe the reaction throughout, although the mechanism frequently has not been established.

A. $Ar_1^- - n$ Cyclizations.—In $Ar_1^- - n$ cyclizations (Scheme 2), intramolecular displacement of the leaving group by the phenolate anion leads to spirodienones. This has been proved spectrophotometrically[1,4] and by product isolation.[1-4,8-12]



Scheme 2



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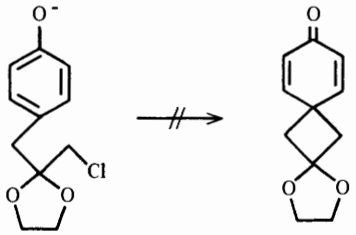

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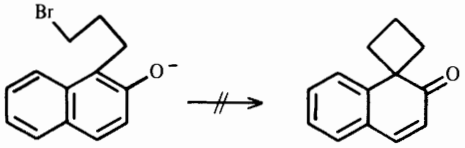
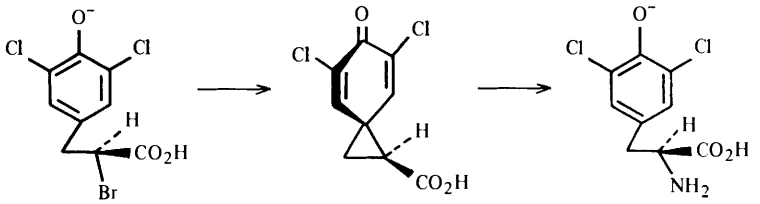


(22) (23)

Kinetic data which confirm $Ar_1^- - 3$ and $Ar_1^- - 5$ participation have been provided by Winstein and Baird.[1,4,6] le Noble and Gabrielsen[18] confirmed both the $Ar_1^- - 3$ and $Ar_1^- - 5$ mechanisms by studying the effect of pressure on the isopropanolysis of the phenols (1) and (3) under basic conditions. Phenoxide participation resulted in rate enhancements of 10^6 and 50, respectively. The small effect of hydrostatic pressure[18,19] on the rate constants of the solvolysis of (1) and (3) readily distinguished between these concerted processes and mechanisms involving carbo-cations. A detailed examination of phenoxide (18) led to the conclusion that $Ar_1^- - 4$ participation was ineffective compared to $Ar_1^- - 3$ and $Ar_1^- - 5$ processes. Other workers[20,21] investigating the phenoxides (20) and (22) arrived at the same conclusion as le Noble.[18]



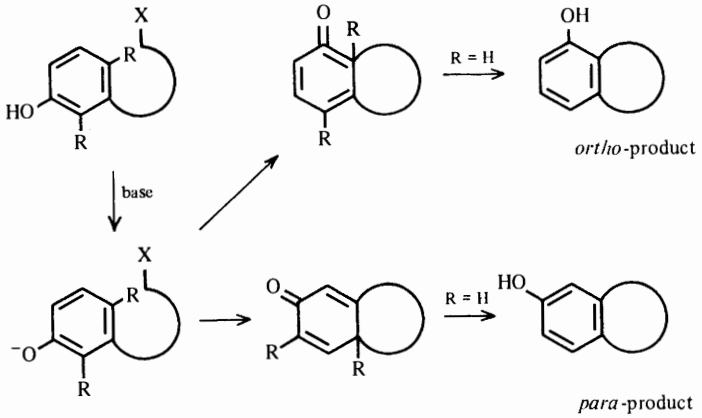
(24) (25) (26)

A stereochemical study also lent support to the $Ar_1^- - 3$ mechanism. Deaminative bromination, followed by amination, is a standard method of inverting the configuration of α-amino-acids.[22] However, when applied to 3,5-dichloro-L-tyrosine (26) net retention was observed.[23] Koga and co-workers[24] proved that amination of the intermediate (*S*)-(−)-α-bromo-β-phenylpropionic acid (24) with aqueous ammonium hydroxide occurred with complete retention of configuration. These results are consistent with an $Ar_1^- - 3$ mechanism and an intermediate spirodienone (25). A mechanism involving an α-lactone[25] was disproved in this instance.

B. $Ar_2^- - n$ Cyclizations.—In $Ar_2^- - n$ cyclization (Scheme 3), intramolecular displacement of a leaving group by phenolate anion participation at both the *ortho* and *para* ring-positions leads to dienone intermediates. These tautomerize spontaneously, under the reaction conditions, to the more stable phenols when R = H. Thus $Ar_2^- - n$ cyclization gives both *ortho* and *para* alkylation products.

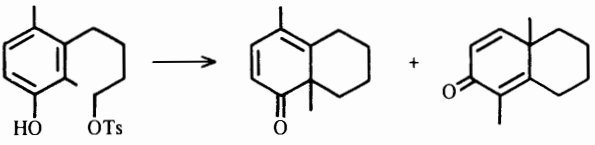
This mode of cyclization has not been investigated as extensively as $Ar_1^- - n$ cyclizations. The first two examples of $Ar_2^- - 6$ cyclization appeared in the same

[18] W. J. le Noble and B. Gabrielsen, *Tetrahedron Lett.*, 1971, 3417.
[19] W. J. le Noble and B. Gabrielsen, *Tetrahedron Lett.*, 1970, 45.
[20] S. Dorling and J. Harley-Mason, *Chem. Ind.*, 1959, 1551.
[21] W. S. Murphy and K. P. Raman, unpublished results.
[22] N. Izumiya, *Bull. Chem. Soc. Jpn.*, 1951, **72**, 26.
[23] W. K. Warburton, *J. Chem. Soc.*, 1961, 2651.
[24] K. Koga, T. M. Juang, and S. Yamada, *Chem. Pharm. Bull.*, 1978, **26**, 178.
[25] P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature*, 1950, **166**, 179.



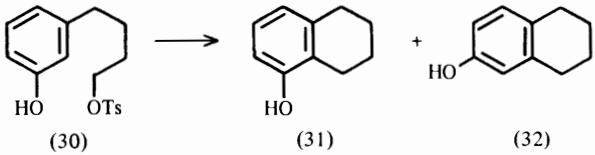
Scheme 3

year. Mandell[26] noted that the phenol (27) cyclized to give the two dienones (28) and (29) in the ratio 2 : 1. Only one product (6) was formed when the phenol (5) was treated with base.[5] Later, a kinetic investigation[27] of the cyclization of phenol



(27) (28) (29)

(30) revealed that it cyclized within 10 hours under reflux in t-butyl alcohol–tetrahydrofuran with potassium t-butoxide. The phenols (31) and (32) were formed in the ratio 3 : 1. The benzyl ether of (30) did not react under these conditions. A detailed study of the effect of pH on the rate of cyclization confirmed an $Ar_2^- - 6$ mechanism. The rate of cyclization increased 400-fold when the pH was increased from 8 to 12.

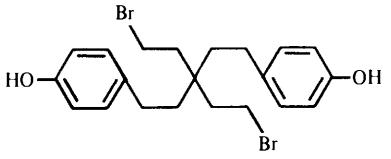


(30) (31) (32)

3 Synthetic Applications

Anionic cyclization of phenols, first reported by Winstein and Baird,[1-4] has been applied to the synthesis of a wide range of novel structures, for example, the spirodienones (7),[7] (9),[8] and (36).[7]

[26] L. Mandell, D. Caine, and G. E. Kilpatrick, *J. Am. Chem. Soc.*, 1961, **84**, 4457.
[27] P. G. Duggan and W. S. Murphy, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1054.



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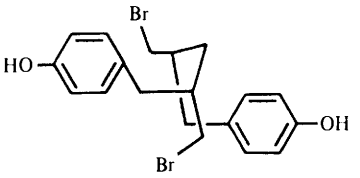

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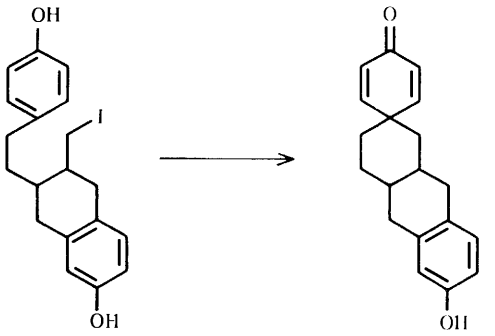
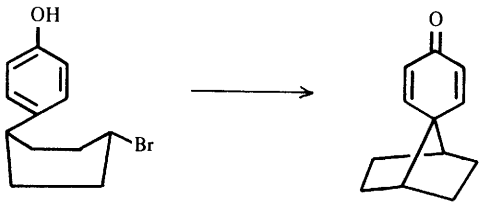


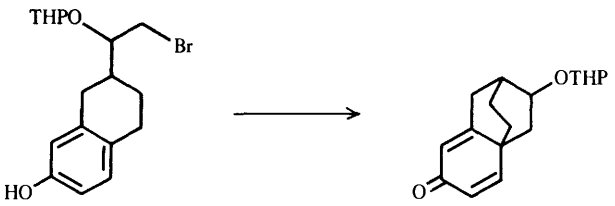
(35) (36)

This method has been used to generate compounds containing the bicyclo-[2.2.1]heptane system, *e.g.* (38),[28] and bicyclo[2.2.2]octane systems, *e.g.* (40).[29]



(37) (38)

[28] R. Barner, A. S. Dreiding, and H. Schmid, *Chem. Ind.*, 1958, 1437.
[29] D. J. Beames and L. M. Mander, *Aust. J. Chem.*, 1971, **24**, 343.



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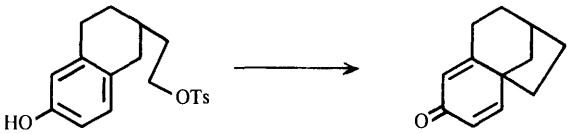

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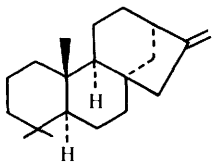
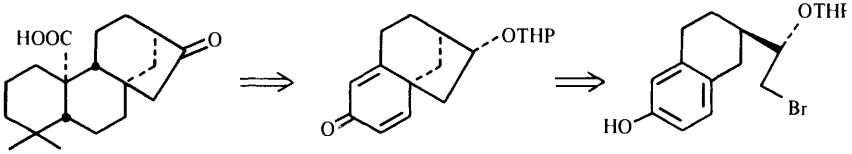
In search of a general route to natural products containing the bicyclo-[3.2.1]octane unit, *e.g.* phyllocladene (43), Masamune initiated an outstanding



(43)

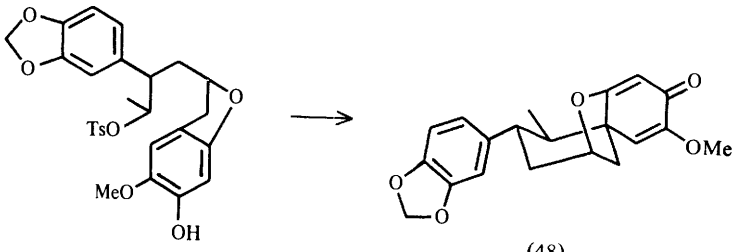
series of papers with a study of the base catalysed $Ar_1^- - 5$ cyclization of phenols (41)[30] which culminated in the formal synthesis of kaurene (13),[13] garryine (14),[14] and atisine (15).[15] The key intermediate leading to (13)—(15), *dl*-16-keto-10-carboxy-17,20-bisnorkaurane (44), was derived from (45) using standard methods. The latter was synthesized by an $Ar_1^- - 5$ cyclization of the phenol (46).



(44) (45) (46)

The neolignan, futoenone (48) was synthesized by Ogiso and his group[31,32] by a base catalysed $Ar_1^- - 6$ cyclization of the phenol (47).

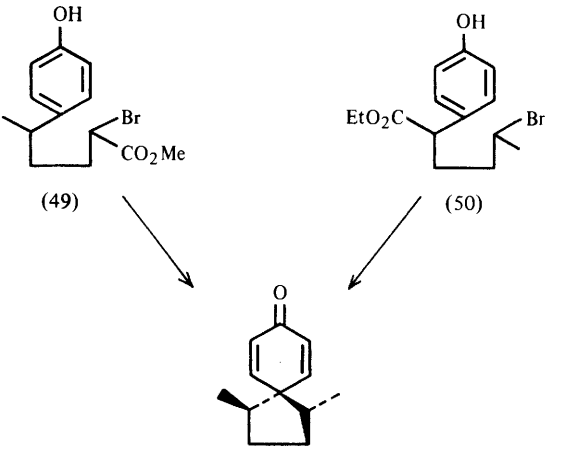
[30] S. Masamune, *J. Am. Chem. Soc.*, 1961, **83**, 1009.
[31] A. Ogiso, M. Kurabayashi, M. Mishima, and M. C. Woods, *Tetrahedron Lett.*, 1968, 2003.
[32] A. Ogiso, M. Kurabayashi, S. Takahashi, H. Mishima, and M. C. Woods, *Chem. Pharm. Bull.*, 1970, **18**, 105.



(47) (48)

Both Corey[9] and Lawton[10] and co-workers synthesized cedrol (10) from the common intermediate (51). Corey also synthesized cedrene (52) from this intermediate.

Marshall and Brady[11] used Masamune's dienone (53)[30] in the total synthesis of



(49) (50)

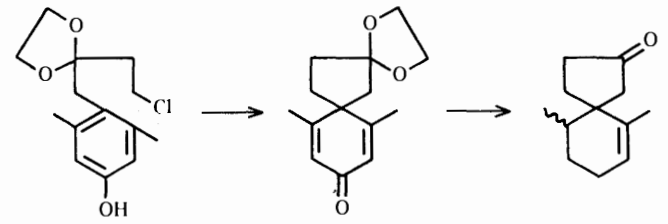
(51)

(10) (52)

(53) (11)

(±)-hinesol (11). They proved, for the first time, the relative stereochemistries of all chiral centres, in the course of their synthesis.

Ogiso and co-workers[33] prepared 6,10-dimethylspiro[4.5]dec-6-en-2-one (56), by utilizing Ar_1^--cyclization (54→55). It was intended to apply this mode of cyclization to the synthesis of spirosesquiterpenoids, *e.g.* hinesol (11) and β-vetivone (12). A related approach to β-vetivone was undertaken in the same year with the successful $Ar_1^- - 5$ cyclization of the phenol (57) to the spirodienone (58).[34] Torii and co-workers,[35] however, finally accomplished the synthesis of β-vetivone (12) using this approach by way of the spirodienone (60).



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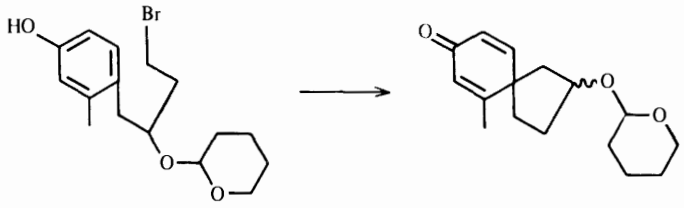

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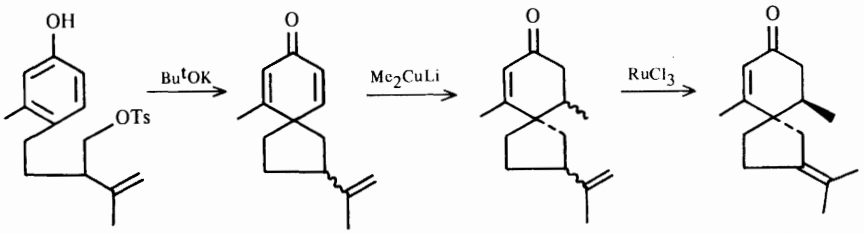
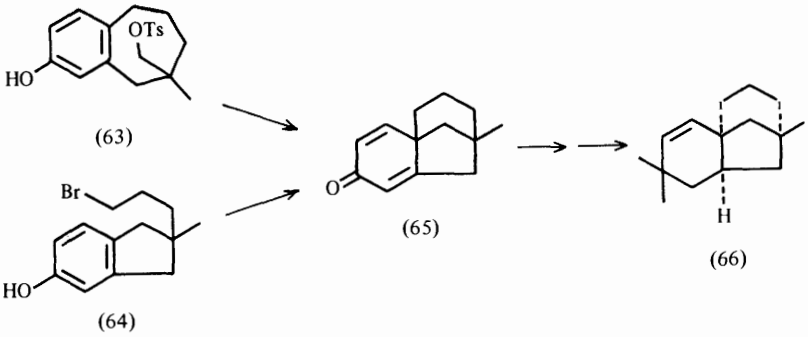
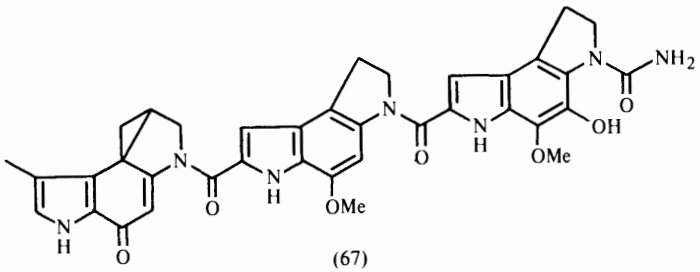


(59) (60) (61) (62) + (12)

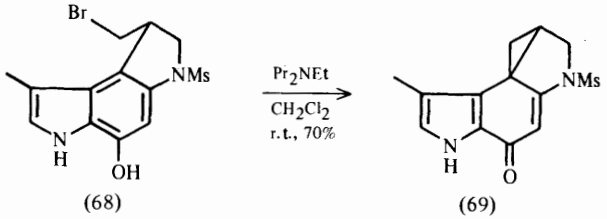
[33] A. Ogiso, M. Kurabayashi, H. Nagahori, and H. Mishima, *Chem. Pharm. Bull.*, 1970, **18**, 1283.
[34] P. C. Mukharji and P. K. Sen Gupta, *Chem. Ind.*, 1970, 533.
[35] S. Torii, K. Uneyama, and K. Okamoto, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 3590.



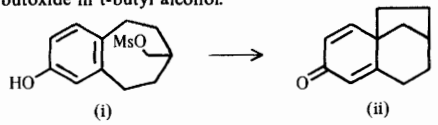
A recent synthesis of pseudoclovene-B (66) is of particular interest.[36] The dienone (65) was employed as the key intermediate. Initial attempts centred on the cyclization of the phenol (63). A low yield of (65) was observed. In contrast, cyclization of (64) was effective.*



The successful synthesis of the left-hand segment (69) of the anti-tumour agent CC-1065 (67) employed the $Ar_1^- - 3$ cyclization of the phenolic bromide (68) as the key step.[37] This is the first natural product synthesis which has employed an $Ar_1^- - 3$ reaction.

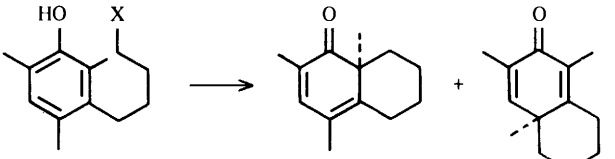


*Note added in proof: subsequent to the submission of the ms it was noted (J. D. McChesney and R. A. Swanson, *J. Org. Chem.*, 1982, **47**, 5201) that phenol (i) cyclized to dienone (ii) in 57% yield when heated with potassium t-butoxide in t-butyl alcohol.



[36] S. Chatterjee, A. Sarkar, and P. C. Dutta, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2914.
[37] W. Wierenga, *J. Am. Chem. Soc.*, 1981, **103**, 5621.

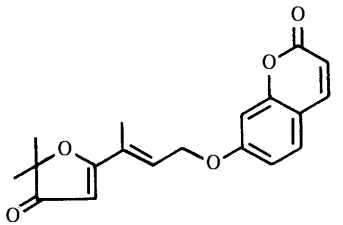
Asymmetric induction was observed[38] in the course of $Ar_2^- - 6$ cyclization of phenol (70) using the chiral (+)-camphor-10-sulphonate leaving group (X). The degree of induction depended on the solvent and the metal cation. A maximum of 19% e.e. was obtained for (71) and 13% e.e. for (72). The results were rationalized in terms of diastereomeric transition states involving a co-ordinated metal cation. The predominance of the (*S*)-enantiomer of both (71) and (72) meant that attack on the *ortho*- and *para*-positions of (70) occurred predominantly on one prochiral face of the phenoxide ring. Contrary to a recent claim,[39] this is the first example of asymmetric induction by a chiral leaving-group during nucleophilic substitution at a saturated carbon centre.



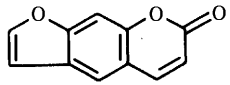
(+)-(70) (*S*)-(+)-(71) (*S*)-( )-(72)

Cyclization of phenoxyketones to benzofurans[40] were first observed some 50 years ago. Results were erratic[41] and the reaction unsatisfactory[42] until MacLeod and co-workers investigated the area in detail. They applied this cyclization to the synthesis of a wide range of benzofuranoid natural products.

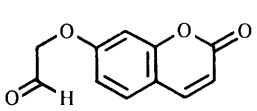
The naturally occurring coumarin geiparvarin (73) was found to generate the linear furocoumarin psoralene (74) when treated with aqueous base. The postulated intermediate (75) was synthesized by MacLeod[43] and when similarly treated,



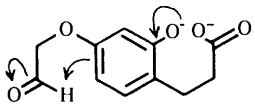
(73)



(74)



(75)

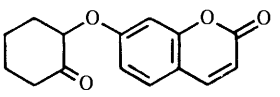


(76)

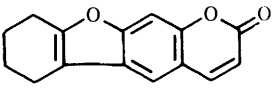
[38] P. G. Duggan and W. S. Murphy, *J. Chem. Soc., Perkin Trans. 1*, 1976, 634.
[39] J. M. Wilson and D. J. Cram, *J. Am. Chem. Soc.*, 1982, **104**, 881; see also *Chem. Eng. News*, 1982, Feb. 22, p. 34.
[40] J. K. MacLeod and B. R. Worth, *Tetrahedron Lett.*, 1972, 237.
[41] J. N. Ray, S. S. Silooja, and V. R. Vaid, *J. Chem. Soc.*, 1935, 813.
[42] R. C. Esse and B. E. Christensen, *J. Org. Chem.*, 1960, **25**, 1565.
[43] F. N. Lahey and J. K. MacLeod, *Aust. J. Chem.*, 1967, **20**, 1943.

was converted into psoralene. This conversion, considered to involve an $Ar_2^- - 5$ cyclization of the intermediate (76), was proved by analogy. Thus, when the monoacetonyl ether of resorcinol was treated with hot aqueous base, 6-hydroxy-3-methylbenzofuran was formed exclusively.[40] The $Ar_2^- - 5$ mechanism was further evidenced by the fact that the corresponding methyl ether did not react under these conditions.

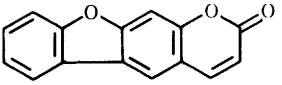
This strikingly facile and regiospecific reaction was then applied to synthesis. The dibenzofuran (79) was synthesized[40] by base-catalysed $Ar_2^- - 5$ cyclization of (77) followed by DDQ dehydrogenation.



(77)

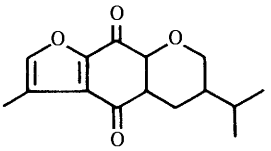


(78)

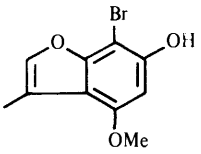


(79)

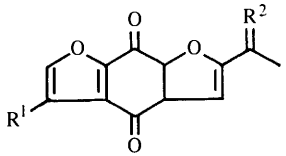
The structure (80), suggested for scabequinone, was confirmed by total synthesis[17] *via* the key intermediate (81). This intermediate was also used in the total synthesis of both cyperaquinone (82) and conicaquinone (17). The synthesis of the intermediate (81) involved the regiospecific $Ar_2^- - 5$ cyclization of the phloroglucinol derivative (84) to the benzofuran (85).



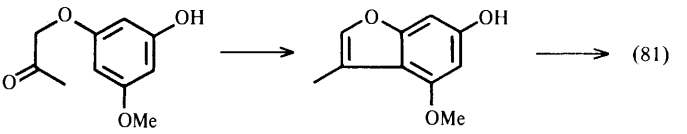
(80)



(81)

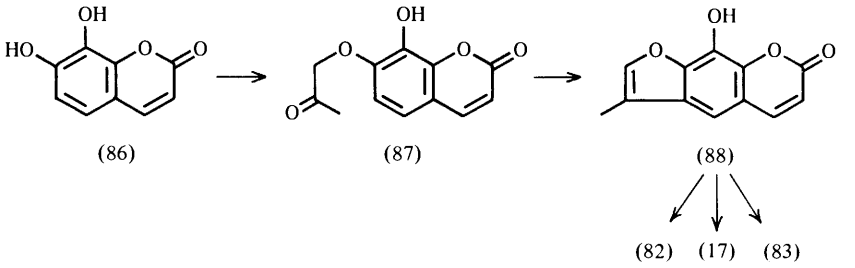


	R^1	R^2
(82)	Me	CH_2
(17)	Me	O
(83)	H	CH_2



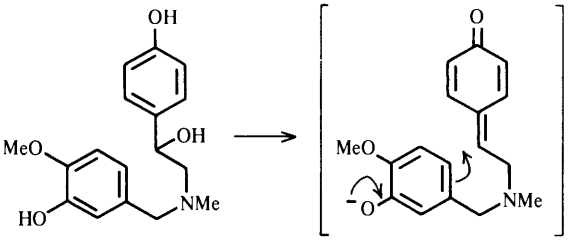
(84) (85)

An alternative synthesis of (82), (17), and (83) from daphnetin (86) was achieved.[44] The introduction of the furan ring was accomplished by $Ar_2^- - 5$ cyclization, (87)→(88).

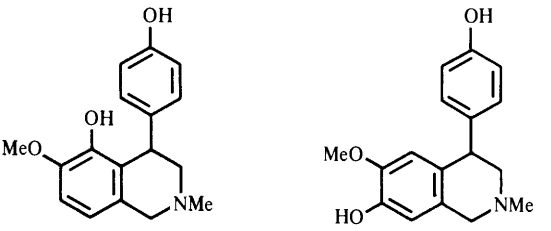


(86) (87) (88)

(82) (17) (83)



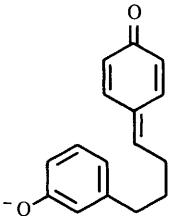
(89) (90)



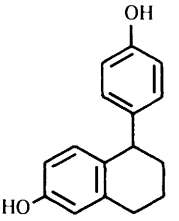
(92) (91)

[44] J. K. MacLeod, B. R. Worth, and R. J. Wells, *Aust. J. Chem.*, 1978, **31**, 1545.

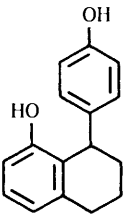
Phenoxide cyclizations have also been involved in a number of biomimetic syntheses and there is some evidence for their involvement in biosynthesis. A biogenetically patterned synthesis of (±)-cherryline (91), a unique Amaryllidaceae alkaloid, was completed by Schwartz and Scott.[45] The key cyclization step was considered to involve $Ar_2^- - 6$ phenoxide–quinone methide coupling. Thus, phenol (89) was converted into cherryline in 79% yield by refluxing in aqueous ammonium hydroxide. However, there remains some doubt about whether the cyclization was acid or base catalysed. This in part was due to the high reactivity of phenol (89). In addition, the fact that none of the regio-isomer (92) was detected must be compared with the phenoxide–quinone methide coupling of (93) where both the *ortho*- and *para*-cyclization products (94) and (95) were detected.[46]



(93)

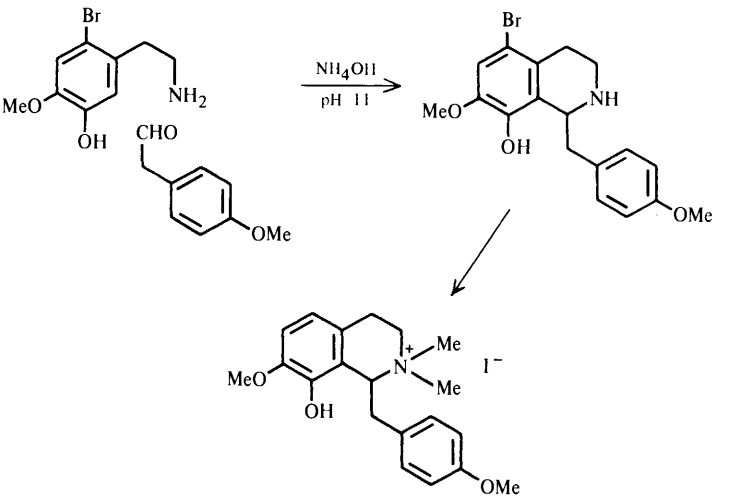


(94)



(95)

Anionic cyclization of phenols has also been applied to the synthesis of isoquinoline alkaloids, *e.g.* petaline (96).[47]



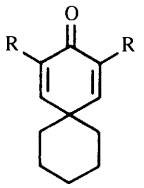
(96)

[45] M. A. Schwartz and S. W. Scott, *J. Org. Chem.*, 1971, **36**, 1827.
[46] W. S. Murphy and S. Wattanasin, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1567.
[47] T. Kametani, T. Kobari, K. Fukumoto, and M. Fujihara, *J. Chem. Soc.*, (*C*), 1971, 1796.

4 Ring Size

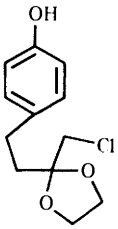
The case of cyclization and the extent of anchimeric assistance[6] by phenoxide depends on the size of the ring being formed and whether the reaction involves an $Ar_1^- - n$ or an $Ar_2^- - n$ transition state.

The anchimeric assistance[6] in $Ar_1^- - 3$ reactions is considerably greater than that in $Ar_1^- - 5$ reactions. Compound (97; R = H) has been obtained[48] only by

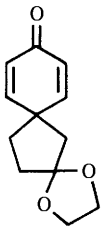


(97)

heating the potassium salt of 5-(*p*-hydroxyphenyl)pentyl bromide to 170 °C in t-butyl alcohol. This suggests that phenoxide participation in $Ar_1^- - 6$ reactions is weaker than in $Ar_1^- - 5$ reactions. However, anomalies exist. The dienone (97; R = Bu^t) was isolated in 98% yield by heating the anion of the corresponding tosylate in t-butyl alcohol at reflux temperature,[49] whereas the dienone (38) was obtained in 8% yield even though vigorous conditions were employed.



(98)

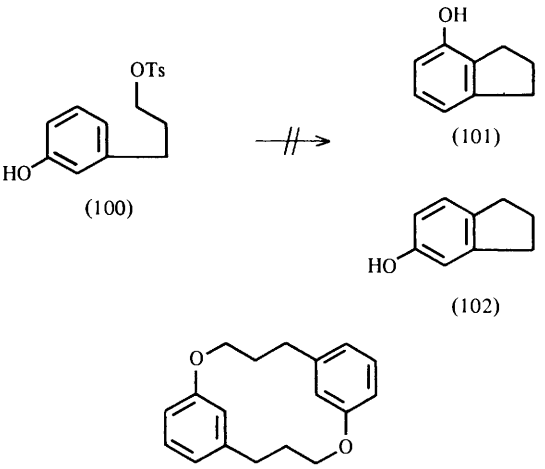


(99)

The dienone (99) has been prepared in 40% yield by heating (98) with potassium t-butoxide in t-butyl alcohol at 180 °C.[20] It is of particular note that no spirodienone was obtained when the higher and lower homologues of (98) were subjected to the above conditions.[20] Thus, although certain ambiguities still remain, it can be concluded from these results that the relative rates of ring closure in $Ar_1^- - n$ reactions decrease in the order $3 > 5 > 6 \gg 4$.

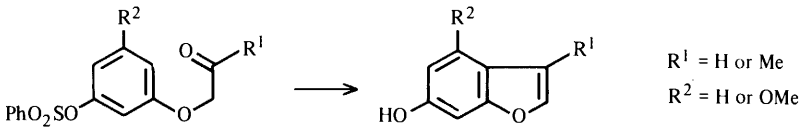
Phenol (100) was investigated as a model for $Ar_2^- - 5$ cyclization. Reactions were studied in a variety of bases and solvents at varying temperatures. Cyclization of (100), to give (101) or (102), was not observed.[27] The main product was the dimer (103). A polymer was also occasionally formed. Thus, $Ar_2^- - 5$ participation is an inefficient process with the result that intermolecular reactions compete success-

[48] A. S. Dreiding, *Helv. Chim. Acta*, 1957, **40**, 1812.
[49] J. D. McClure, *J. Org. Chem.*, 1962, **27**, 2365.



(100) (101) (102) (103)

fully. However, base catalysed Ar_2^- – 5 cyclization was observed[36] in the case of the phenol (63). The dienone (65) was formed in 11% yield. Although not rigorously proved, the mechanism was almost certainly an example of Ar_2^- – 5 cyclization. In the light of these results, the base catalysed Ar_2^- – 5 cyclization of the phenoxides derived from the aldehydes and ketones (104), extensively studied by MacLeod and co-workers[40] from a synthetic view-point (Section 3), are of particular note. In all cases, base catalysed intramolecular cyclization gave *para* products, in good yield under mild conditions. No products corresponding to the possible *ortho* cyclization were observed (see Section 8).



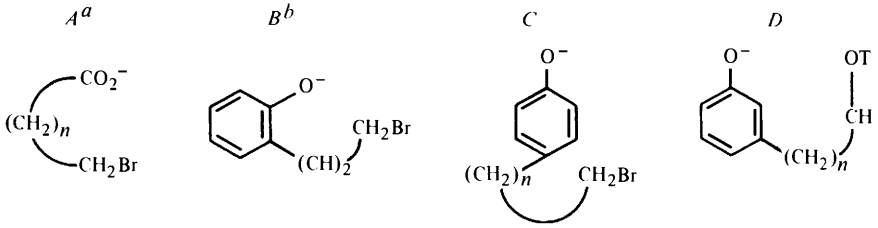
(104) (105)

It is clear from a comparison of the reactions of (30), (63), and (100) that the relative rates of ring closure in Ar_2^- – *n* reactions decrease in the order 6 > 5. Examples of Ar_2^- – 3, Ar_2^- – 4, and Ar_2^- – 7 are not known.

Kinetic data for Ar_1^- – *n* and Ar_2^- – *n* cyclizations are summarized in the Table (columns C and D) together with related anionic cyclizations for comparison (columns A and B). The ratio k_3/k_5 is normally greater than unity.[50] This is observed in Ar_1^- – *n* reactions and, in the Ar_1^- – 3 system, is due[51] to the overlap

[50] C. J. M. Stirling, *Angew. Chem., Int. Edn. Engl.*, 1968, **7**, 648.
[51] C. J. M. Stirling, *J. Chem. Educ.*, 1973, **50**, 844.

Table *Relative rates of cyclization by nucleophilic displacement reactions*



Ring Size	*Rel. rate* 50 °C	*Rel. rate* 50 °C	*Rel. rate* 25 °C	*Rel. rate*[e] 50 °C
3	21.7		~1100[c]	
4	2.4×10^4			
5	2.8×10^6	2.63×10^6	1.0[c]	slow[f,g]
6	2.6×10^4	1.32×10^5	< 1.0[d]	~0.7[g]

[a] C. Galli, G. Illuminati, L. Mandolini, and P. Tamborra, *J. Am. Chem. Soc.*, 1977, **99**, 2591. [b] G. Illuminati, L. Mandolini, and B. Masci, *J. Am. Chem. Soc.*, 1975, **97**, 4960. [c] S. Winstein and R. Baird, *J. Am. Chem. Soc.*, 1957, **79**, 756. [d] A. S. Dreiding, *Helv. Chim. Acta*, 1957, **40**, 1812. [e] Rates relative to those in column C. [f] S. Chatterjee, A. Sarkar, and P. C. Dutta, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2914. [g] P. G. Duggan and W. S. Murphy, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1054.

of the π-orbitals of the aryl ring and the distorted high *p*-character ring-bonds of the three-membered ring system which lowers the free energy of the transition state. The ratio k_5/k_6 is also usually greater than unity[50] (compare columns A, B, and C). It is of note that this is not the case in $Ar_2^- - n$ reactions. This contrast between $Ar_1^- - n$ and $Ar_2^- - n$ reactions is analogous to that observed by Heck and Winstein[52] during an investigation of the solvolysis of ω-phenylalkyl brosylates. They observed the following: $Ar_1 - 5 > Ar_1 - 6$ and $Ar_2 - 6 > Ar_2 - 5$. This comparison suggests that $Ar^- - n$ and $Ar - n$[53,54] reactions have transition states of similar geometry. Whereas a measure of the degree of phenyl participation has been determined in Ar_1 and Ar_2 reactions from the effects of ring substitution,[52] no comparable studies of phenoxide cyclizations have been undertaken.

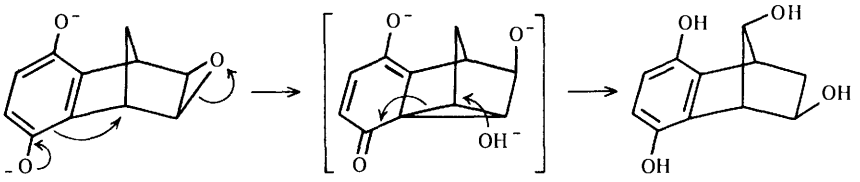
5 Leaving Groups; Electrophilic Centre

Developments of new leaving groups or new functional groups initiating cyclization are relatively few.[29] To date the only functional groups used successfully are sulphonates (OTs and OBs),[1,55] bromides,[9,10,30] iodides,[8,56] chlorides,[20] aldehydes,[40,57] and ketones.[40] The last two cases are in rather specific systems.[40,57]

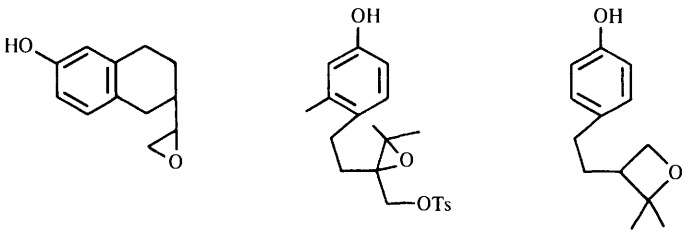
[52] R. Heck and S. Winstein, *J. Am. Chem. Soc.*, 1957, **79**, 3114.
[53] L. M. Jackman and V. R. Haddon, *J. Am. Chem. Soc.*, 1974, **96**, 5130.
[54] M. Gates, D. L. Frank, and W. C. von Felton, *J. Am. Chem. Soc.*, 1974, **96**, 5138.
[55] P. G. Duggan and W. S. Murphy, *Chem. Comm.*, 1972, 770.
[56] B. Rickborn and M. T. Wuesthoff, *J. Am. Chem. Soc.*, 1970, **92**, 6894.
[57] K. H. Bell, *Tetrahedron Lett.*, 1968, 3979.

Forcing conditions are normally required to effect the cyclization of chlorides.[20]

Interestingly, whereas cyclization involving $Ar_1^- - 3$ participation of the epoxide (106)[58] is observed, the others, (109)[13] and (110),[12] do not cyclize under similar basic conditions. However, these results may be attributed to stereoelectronic effects (see Section 6) and to the more effective aryl participation in $Ar_1^- - 3$ reactions than in $Ar_1^- - 4$ or $Ar_1^- - 5$ reactions.[6] The phenolic oxetane (111) is stable under basic conditions.[12]



(106) (107) (108)



(109) (110) (111)

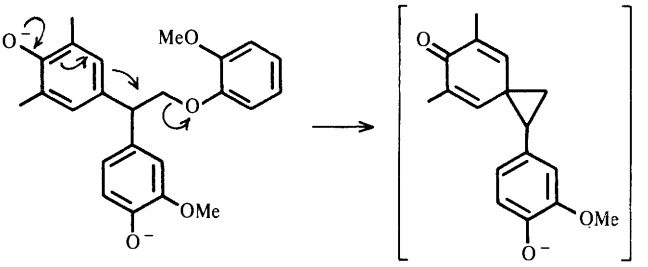
One example of $Ar_1^- - 3$ participation involving a phenoxide leaving-group has been observed[59] in aqueous base at 170 °C [(112)→(114)].

Other electrophilic sites have been used in $Ar_2^- -$ type cyclizations. For example, the iminium group functions as electron sink in the base catalysed varient of the Pictet–Spengler reaction. Thus, epinephrine (115) reacts with either formaldehyde (R = H) or acetaldehyde (R = Me) under basic conditions.[60] In addition, both *ortho*- (119) (n = 1 or 2) and *para*-quinone methides (93) and (120)[46] as well as the benzyne (121)[61] undergo cyclization in basic conditions.

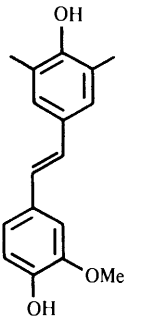
6 Stereoelectronic Factors

Stereoelectronic factors are particularly significant in cyclization at aromatic centres.[6,27] This is clear from a consideration of the probable transition states involved. In such reactions, perpendicular approach to the aromatic ring is considered common.[52] However, the actual angle depends on the extent of aryl participation.[52] In addition, strict S_N2 stereochemistry at the site of the leaving

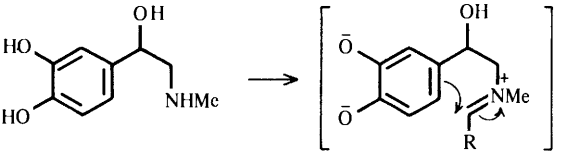
[58] J. Meinwald, H. Nozoki, and G. A. Wiley, *J. Am. Chem. Soc.*, 1957, **79**, 5579.
[59] J. Gierer and I. Pettersson, *Can. J. Chem.*, 1977, **55**, 593.
[60] H. A. Bates, *J. Org. Chem.*, 1981, **46**, 4931.
[61] D. H. Hey, J. A. Leonard, and C. W. Rees, *J. Chem. Soc.*, 1963, 5266.



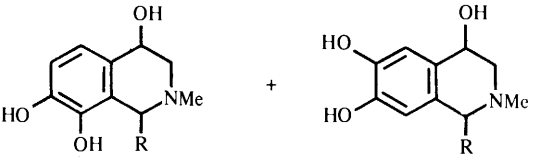
(112) (113)



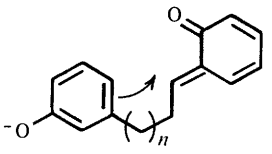
(114)



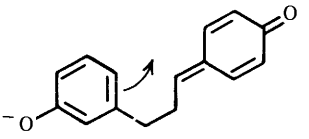
(115) (116)



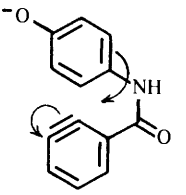
(117) (118)



(119)

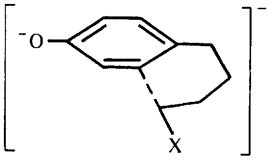


(120)

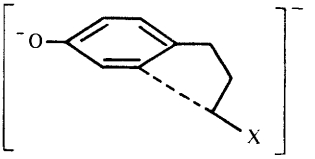


(121)

group is assumed. The transition states for $Ar_2^- - 6$ and $Ar_2^- - 5$ participation leading to *para*-alkylation of the phenolic sulphonates (30) and (100) can be represented by (122) and (123) respectively.[27] It is clear from inspection of models of these transition states that there is little, if any, strain in (122) but that the transition state (123) for the formation of a five-membered ring is highly strained. It

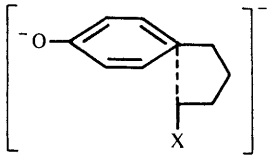


(122)

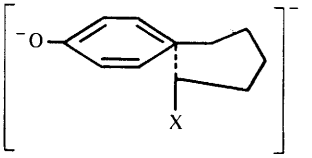


(123)

is of interest also that the transition state for $Ar_1^- - 5$ participation (124)[6] and $Ar_1^- - 6$ (125) are relatively strainless. It is probable that $Ar_1^- - 6$ cyclization is slower than $Ar_1^- - 5$ for entropy reasons.[6]

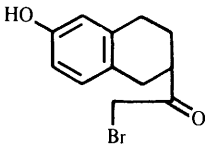


(124)

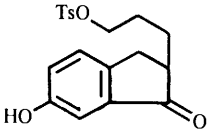


(125)

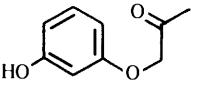
These stereoelectronic requirements can be used to explain the failure of the phenol (109),[13] (126),[13] and (127) to cyclize under basic conditions.



(126)



(127)

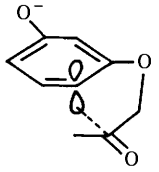


(128)

↓

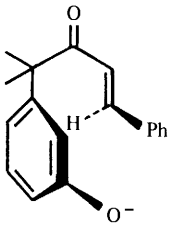
(33)

These considerations form a basis for understanding the facility with which the phenol (128) cyclizes under basic conditions. Applying the conclusions of Bürgi and co-workers[62] on the stereochemistry of reaction paths at carbonyl centres, a transition state (129) can be envisaged which is not as strained as (123). An alternative rationale for the difference in reactivity between (123) and (128) is that the S_N2 component in (123) makes more stereoelectronic demands than nucleophilic attack at the carbonyl centre in (129).



(129)

In order to explain the failure of the enone (130) to cyclize under basic conditions it was concluded[63] that the stereoelectronic requirements of the transition states were nucleophilic attack by the phenoxide ring along a trajectory such as that suggested by Bürgi[62] and Baldwin,[64] coupled with co-planarity of the enone functional group. From molecular models it was concluded that whereas this transition state was highly strained, higher homologues could cyclize, in the absence of over-riding entropy factors.[63]

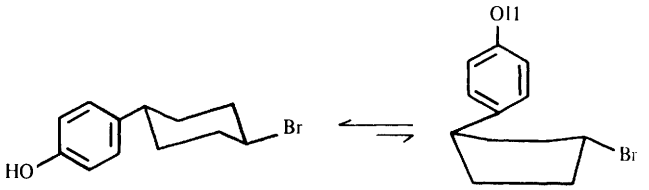


(130)

7 Steric Effects

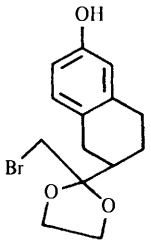
Subtle steric effects have frequently resulted in dramatic changes in yield. For example, the keto-phenol (126) failed[13] to cyclize whereas the corresponding phenol (41) was converted into dienone (42).[30] It is likely that entropy losses inhibited $Ar_1^- - 5$ cyclization of the *trans*-phenol (37) to the dienone (38).[28] The latter was formed in 8% yield.

[62] H. B. Bürgi, J. D. Dunitz, J. M. Lehn, and G. Wipff, *Tetrahedron*, 1974, **30**, 1563.
[63] W. S. Murphy and S. Wattanasin, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1555.
[64] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.

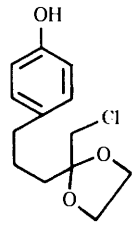


(37)

The ethylene dioxy-group when located α to the carbon bearing the leaving group confers neopentyl-like steric requirements and strongly represses reactivity. Attempts to cyclize phenol (131) failed.[13] Cyclization of (54) required pyrolysis with potassium t-butoxide.[20] Similar conditions were required to effect cyclization of phenol (98).[20] The homologous phenol (132) did not cyclize.[20] The steric requirements in this series, therefore, are very stringent.



(131)



(132)

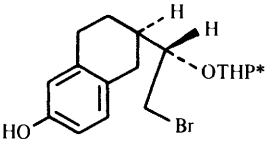
The *gem*-dimethyl effect, whereby the presence of a *gem*-dimethyl substituted carbon in the chain facilitates cyclization, has been discussed elsewhere.[6] Although steric in origin, no explanation is universally accepted.[65-67] This effect, however, does not appear to operate in $Ar_1^- - 5$ cyclizations. Thus the phenol (3; R = Me) cyclized in 25% yield[68] whereas the analogous phenol (3; R = H) cyclized in 50% yield. However, further study will be required to confirm this point.

It is well established that an oxygen heteroatom in a chain facilitates cyclization due to the absence of *gauche* interactions or transannular hydrogen repulsions.[69] The notable facility of the $Ar_2^- - 5$ cyclization of the keto-phenol (128)[40] is, at least in part, a result of this effect.

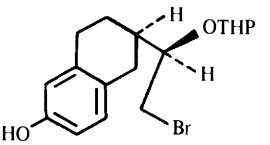
The bicyclic phenol (41) cyclized, under the conditions employed by Winstein and Baird, to the dienone (60) in 90% yield.[30] Masamune[30] considered that the efficiency of this reaction was due to an advantageous orientation of the carbon atom carrying the tosylate group and, in addition, that side reactions were

[65] M. Harfenist and E. Thom, *J. Org. Chem.*, 1972, **37**, 841.
[66] R. T. Borchardt and L. A. Cohen, *J. Am. Chem. Soc.*, 1972, **94**, 9175.
[67] R. T. Borchardt and L. A. Cohen, *J. Am. Chem. Soc.*, 1972, **94**, 9166.
[68] D. I. Schuster and W. V. Curran, *J. Org. Chem.*, 1970, **35**, 4192.
[69] B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 1980, **102**, 4743 and references therein.

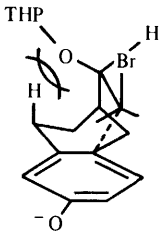
suppressed by the tertiary carbon atom C-6, a structural feature not present in phenols such as (3). However, the dienone (45) was not formed in high yield when phenol (46), as a mixture of diastereomers (α- and β-), was treated with potassium t-butoxide.[13] Phenol (46β) was recovered unchanged. Models (133) and (134) respectively, show that the ethereal oxygen atom of the uncyclized phenol (46β) in the transition state (133) interacts severely with a hydrogen atom at position-8. Failure of the ethylene glycolate (131) to cyclize[13] can be explained on the same basis.



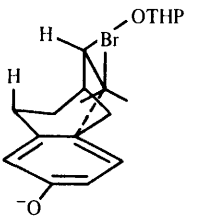
(46α)



(46β)

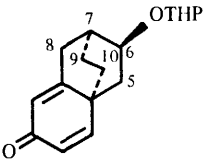


(133)

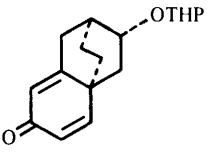


(134)

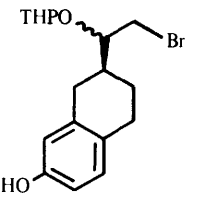
Beames and Mander[29] investigated the synthesis of the related dienones (135) and (136). In contrast, Ar_1^- – 6 cyclization of a 1 : 1 mixture of diastereomeric* phenols (137) gave a 3 : 1 mixture of dienone ethers (135) and (136) in 50% yield. The yield was not improved by variations in time, temperature, and solvent.



(135)



(136)

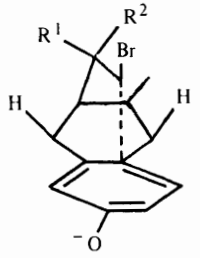


(137)

The transition state for Ar_1^- – 6 cyclization of the bromide mixture (137) requires both diastereomers (138) to have the side-chain ether substituent eclipsed with a ring methylene group. This interaction is intermediate in severity between

* Diastereoisomerism due to the tetrahydropyranyl (THP) group is not considered.

that for (46α) and (46β). The smaller yield of epimer (136) is due to the l important, but extra, 1,4-non-bonded interaction between the ether function a the *syn* C-10 hydrogen atom in the transition state leading to this isomer.[29]



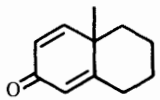
(138)

R^1	R^2		
OTHP	H	⟶	(135)
H	OTHP	⟶	(136)

8 *ortho–para* Ratio

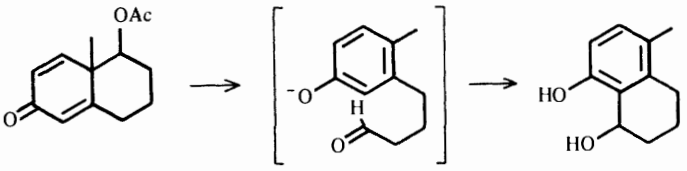
Discussion of the *ortho–para* ratio is applicable only to $Ar_2^- - n$ reactions. Of the two transition states, that leading to *para*-substitution is *a priori* favoured on steric grounds. Whereas simple Hückel theory predicts equal electron density on the *ortho* as on the *para* position, frontier electron density is higher at the *para* position.[70] That these theoretical predictions have had only limited success is to be expected since steric effects, the effect of solvent, metal cations, and temperature variations are also involved.

The phenol (70) cyclized at both the *ortho*- (71) and *para*- (72) positions in a ratio *ca.* 4 : 1.[38] Mandell[26] had noted that the disubstituted phenol (27) also cyclized with an *ortho* : *para* ratio 2 : 1, under basic conditions. When the *para*-position only was substituted, as in the case of phenol (5), only *ortho*-alkylation occurred.[5] None of the dienone (139) was detected. Similarly, only the phenol (142) was



(139)

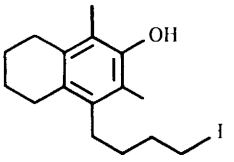
obtained when the dienone (140) was treated with methanolic sodium hydroxide.[71] A number of anomalies exist. For example, the *para*-dienone (144) was isolated in



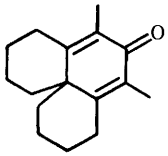
(140) (141) (142)

[70] I. Fleming, 'Frontier Orbitals and Organic Chemical Reactions', Wiley, London, 1976, p. 63.
[71] K. H. Bell, *Aust. J. Chem.*, 1972, **25**, 1117.

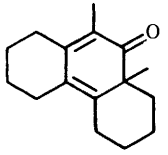
12% yield when the phenol (143) was treated with potassium t-butoxide. Apparently none of the *ortho*-dienone (145) was detected.[72]



(143)

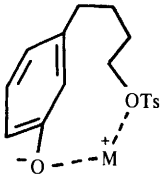


(144)



(145)

A detailed investigation of factors affecting the *ortho–para* ratio in the $Ar_2^- - 6$ cyclization of phenol (30) was reported.[73] Results were consistent with two transition states (146) and (147) leading respectively to *ortho*-alkylation (31) and



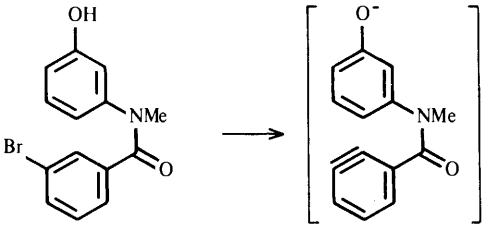
(146)

(147)

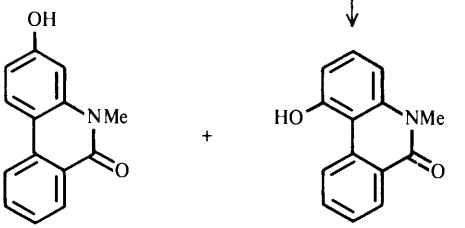
para-alkylation (32) products. Chelation of the metal cation facilitated charge transfer to the leaving group in the case of *ortho*-alkylation. Thus *ortho*-alkylation invariably predominated in solvents of low polarity. The percentage of *ortho*-alkylation decreased linearly with dielectric constant of the solvent in the order $Bu^tOH > Pr^iOH > EtOH > MeOH$ and reflected decreasing chelation of the metal cation. On the other hand, ion aggregation accelerated the relative rate of *para*-alkylation since charge transfer to the leaving group was facilitated by neighbouring metal cations in the ion cluster. Thus a lower *ortho–para* ratio was observed in toluene. The ionic radius of the metal, a measure of chelating ability, was inversely proportional to the *ortho–para* ratio. This ratio decreased in the order $Li^+ > Na^+ > K^+ > Bu_4^nN^+$. At higher temperatures, metal chelation was less effective. The *ortho–para* ratio was less than unity in methanol and in water at reflux temperatures.

These conclusions are consistent with the results of the investigation of the $Ar_2^- - 6$ cyclization of phenol (148).[61] This reaction, in which sodium amide in liquid ammonia was employed, involved a benzyne electrophilic centre (149). The phenolic products (150) and (151) were formed in a 1 : 1 ratio reflecting high solvent polarity and a low degree of metal cation complexation.

[72] W. L. Mock and K. A. Rumon, *J. Org. Chem.*, 1972, **37**, 400.
[73] P. G. Duggan and W. S. Murphy, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1291.

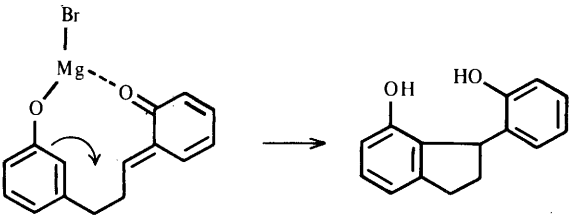


(148) (149)



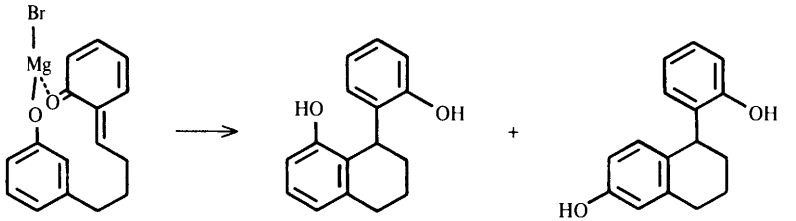
(151) (150)

A dramatic example of the effect of metal cation chelation was noted in the course of an investigation of the $Ar_2^- - 5$ and $Ar_2^- - 6$ cyclizations involving the *ortho*-quinone methides (152) and (154).[46] The phenoxide (152) cyclized exclusively at the *ortho*-position to give phenol (153). In the presence of 18-crown-6, (152) gave no



(152) (153)

cyclized products (see Section 3). The phenoxide (154) was less strongly chelated since both *para*- and *ortho*-cyclization occurred. The *ortho*–*para* ratio was 88 : 12.



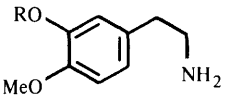
(154) (155) (156)

In the presence of 18-crown-6, (154) cyclized but the ratio of (155) to (156) changed to 38 : 62.

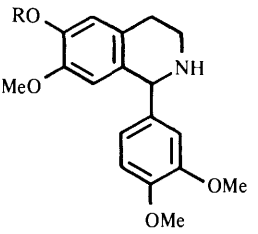
The cyclization of phenol (128),[40] one of the few known examples of $Ar_2^- - 5$, is deserving of further comment. A detailed mechanistic study was not undertaken by MacLeod,[40] although *para*-cyclization only was detected. No *ortho*-alkylation was detected. In this instance the ability of phenoxides to alkylate at the *para*-position is at least partially accentuated by the hardness of the carbonyl group.[74]

The *ortho*–*para* ratio (117) : (118) of the Pictet–Spengler cyclization[75,76] of (115) was pH dependent:[60] pH 1, $o:p = 3.97$; pH 9, $o:p = 34:66$. This effect is suggestive of two mechanisms—an $Ar_2 - 6$ cyclization at low pH and an $Ar_2^- - 6$ cyclization (116) at higher pH values.

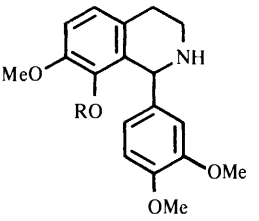
In the so-called phenol cyclizations, Kametani and co-workers[77] noted that the phenol (157; R = H) underwent *para*-cyclization with 3,4-dimethoxybenzaldehyde in the absence of acid to the isoquinoline (158; R = H). None of the *ortho*-isomer (159) was detected. However, when the ether (157; R = Me) was treated in the



(157)



(158)

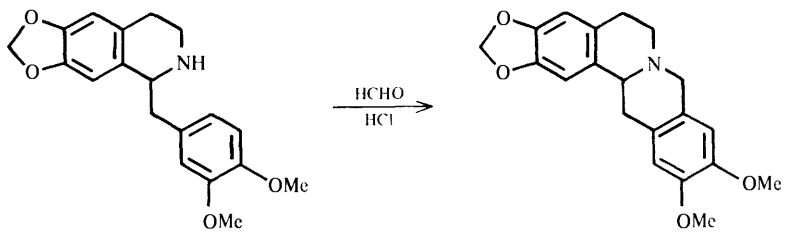


(159)

same way, no isoquinoline was formed. The corresponding Schiff's base only was isolated. Electron densities at the cyclization positions of (157; R = H) and (157; R = Me) were invoked as explanation.[77] In electrophilic substitution, it had been established that the hydroxyl is more activating than the hydroxy-group.[78]

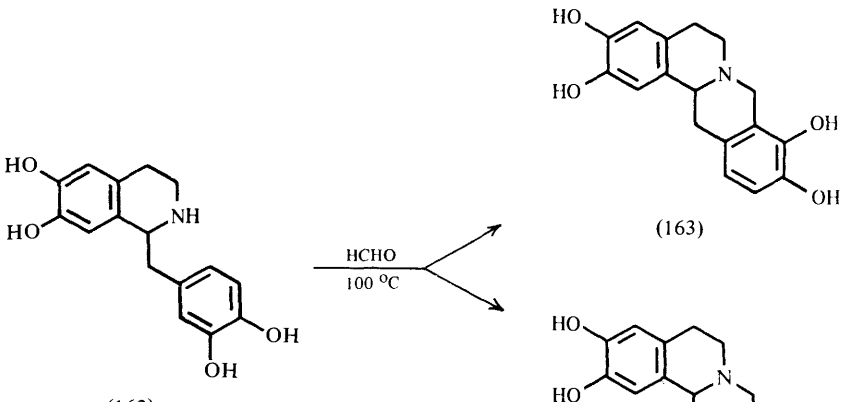
This effect is again highlighted by the comparison between the results of the following two reactions. In the reaction of 1-veratrylnorhydrohyrastinine (160) tetrahydro-ψ-berberine (161) was obtained exclusively.[79] However, it was subsequently noted[80] that treatment of tetrahydropapaveroline (162) with formaldehyde, afforded the *ortho*- (163) and *para*- (164) products in 1 : 1 ratio. It has been

[74] T.-L. Ho, *Chem. Rev.*, 1975, **75**, 1.
[75] W. M. Whaley and T. R. Govindachari, *Org. React.*, 1951, **8**, 151.
[76] T. Kametani, 'The Total Synthesis of Isoquinoline Alkaloids', ed. J. ApSimon, Wiley-Interscience, N.Y., 1977, **3**, p. 1.
[77] T. Kametani, K. Fukomoto, H. Agui, H. Yagi, K. Kigasawa, H. Sugahara, M. Hiiragi, T. Hayasaka, and H. Ishimaru, *J. Chem. Soc.* (*C*), 1968, 112.
[78] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry', Cornell University Press, Ithaca, N.Y., 1953, p. 70; P. B. D. de la Mara, O. M. H. el Dusouqui, T. G. Tillett, and M. Zeltner, *J. Chem. Soc.*, 1964, 5306; G. Chuchani, H. Diaz, and J. Zabicky, *J. Org. Chem.*, 1966, **31**, 1573; 2330.
[79] R. D. Haworth, W. H. Perkin, and J. Rankin, *J. Chem. Soc.*, 1924, **125**, 1686.
[80] E. Späth and E. Kruta, *Monatsh. Chem.*, 1928, **50**, 341.



(160) (161)

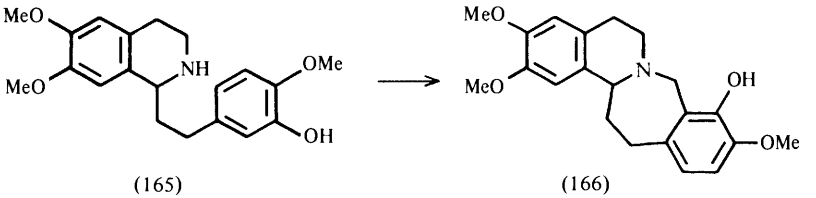
suggested[75] that the appropriate free hydroxy-group in the benzyl residue activated the *ortho*- and *para*-positions equally.



(162) (163) (164)

An alternative explanation is feasible: Ar_2^- – 6 cyclization, wherein a reasonably high equilibrium concentration of phenoxide ($pK_a \sim 10$)[81] is provided by the amino-group ($pK_a \sim 10$)[81] even as it is transformed *via* the Schiff's base to tetrahydroisoquinoline. Although the *o* : *p* ratio is not always consistent with this mechanism, subtle effects do operate. For example, phenol cyclization[82] of tetrahydroisoquinoline (165) with formalin in hot ethanol was converted into the homoprotoberberine-type product (166) exclusively. This is the *ortho*-cyclization product.

[81] S. H. Pine, J. B. Hendrickson, D. J. Cram, and G. S. Hammond, 'Organic Chemistry', McGraw-Hill, Kogakusha, Tokyo, 1980, p. 200.
[82] T. Kametani, T. Terui, A. Ogino, and K. Kukumoto, *J. Chem. Soc.* (*C*), 1969, 874.



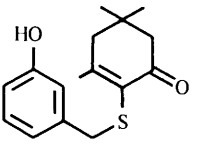
(165) (166)

Kametani and co-workers have used their theory to explain numerous other examples of phenol cyclization.[76,83] Whether or not these reactions are examples of $Ar_2^- - n$ cyclizations remains to be determined. The importance of reaction conditions on the Pictet-Spengler reaction has recently been highlighted by Cook and co-workers.[84] They found that yields in aprotic media were generally 300—400% better than those in aqueous acid.

9 Reactivity Considerations

External factors such as solvent, metal cation, and temperature, affect $Ar_1^- - n$ and $Ar_2^- - n$ cyclizations. Since they can be classified as intramolecular S_N2 reactions, their efficiency will also depend on the nucleophilicity of the phenoxide, the nature of the leaving group, and reactivity of the electrophilic centre. In addition, as discussed earlier, the nature of the chain[85] joining these two centres such as chain length, presence of an oxygen atom in the chain, and effect of *gem*-dimethylation, strongly affects the ease of cyclization.

Hydrogen–deuterium exchange under basic conditions was used to predict the ability of phenoxides to react with citral.[86] The basicity so determined was found to correlate with nucleophilicity. Only strongly nucleophilic phenoxides, such as the anion of resacetophenone, react with citral or related enones. It is therefore not surprising that enone (130) and (167) did not cyclize under basic conditions.

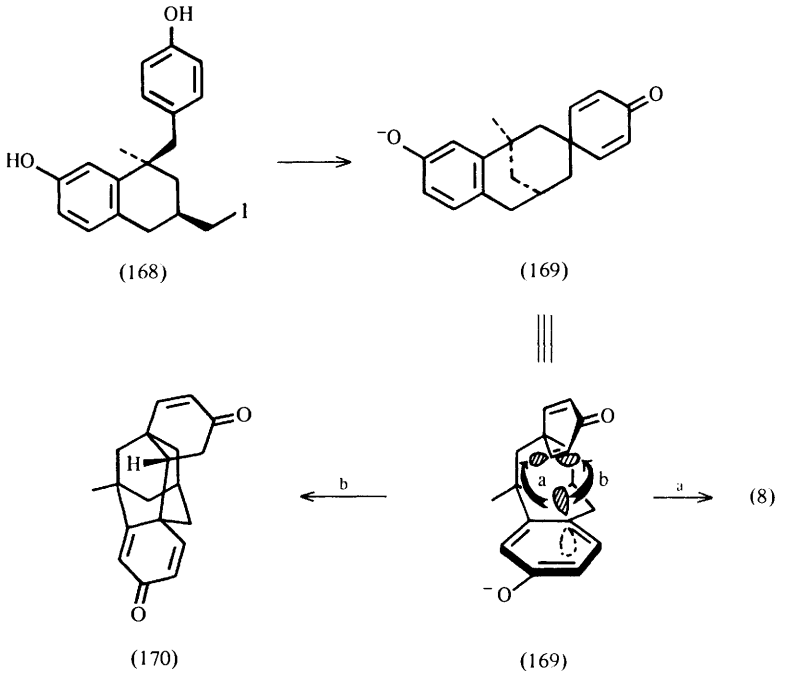


(167)

However, if forcing conditions are used then as Atkinson and Miller[8] noted, phenoxide–enone coupling may occur. They synthesized the dienone (169), required for this study, by an $Ar_2^- - 6$ cyclization of (168). Dienone (169) cyclized quantitatively to the adamantanoid dienone (170) when heated at 170 °C with

[83] T. Kametani and M. Ihara, *J. Chem. Soc., Perkin Trans. 1*, 1980, 629.
[84] D. Soerens, J. Sandrin, F. Ungemach, P. Mokry, G. S. Wu, E. Yamanaka, L. Hutchins, M. Di Pierro, and J. M. Cook, *J. Org. Chem.*, 1979, **44**, 535.
[85] M. A. Winnik, *Chem. Rev.*, 1981, **81**, 491.
[86] D. G. Clarke, L. Crombie, and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1007.

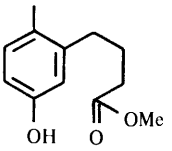
potassium t-butoxide for three hours. Although spectroscopically (8) and (170) could not be differentiated, Dreiding models indicated a clear preference for (8). It is of note that the stereoelectronic requirements clearly absent in the transition state (130) are fulfilled in (169). However, the vigorous conditions employed here were not applied to the enone (130).[63]



The *ortho*-quinone methides (152) and (154) cyclized *via* Ar_2^- – 5 and Ar_2^- – 6 modes respectively.[46] The success of these reactions is without doubt due to the inherently high reactivity of the quinone methide functionality.[87] However, without the assistance of Mg^{II} chelation, Ar_2^- – 5 cyclization failed whereas Ar_2^- – 6 occurred efficiently but with modified regiochemistry. The failure of (152) under these conditions again emphasizes the general reluctance of systems to undergo Ar_2^- – 5 cyclization.

Ester functional groups such as methoxy- and ethoxy-carbonyl are insufficiently electrophilic to permit Ar_2^- – 6 cyclizations. Thus the ester (171) was recovered unchanged after treatment with sodium methoxide.[5] The same result was observed with ester (172).[88] By comparison, the aldehyde function is sufficiently reactive. The aldehyde (141) cyclized smoothly under mildly basic conditions.[71]

[87] A. Zanarotti, *Tetrahedron Lett.*, 1982, 3815; 3963.
[88] W. S. Murphy and S. Wattanasin, unpublished results.



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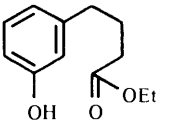
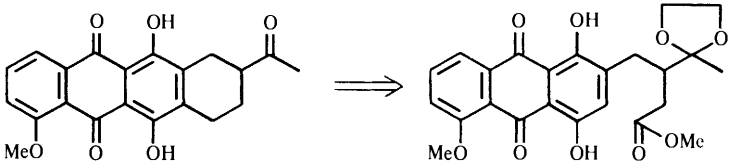


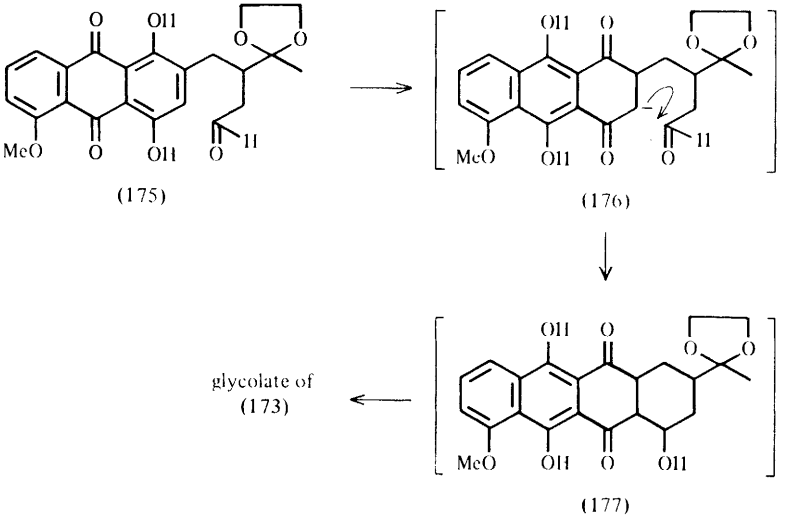
(172)

Sih and co-workers largely confirmed these observations in the course of their regiospecific synthesis of the anthracyclinone, adriamycinone (173) *via* base catalysed cyclizations.[89] Retrosynthetic analysis revealed (174) as a plausible precursor. However, the ester (174) resisted cyclization. This failure was attributed



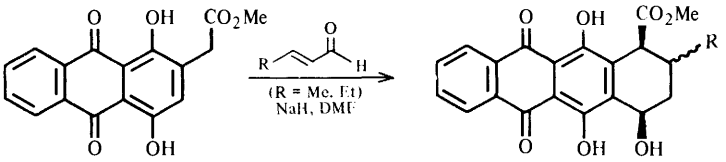
(173) (174)

to the electron-withdrawing property of the anthraquinone system. When the aldehyde (175), derived from (174), was treated with basic sodium dithionite, the ethylene ketal of adriamycinone was isolated in 53% yield. By analogy with his earlier results Sih suggested a mechanism which involved the leucoform (176). However, a reasonable alternative is base-catalysed Ar_2^- − 6 cyclization of (175).

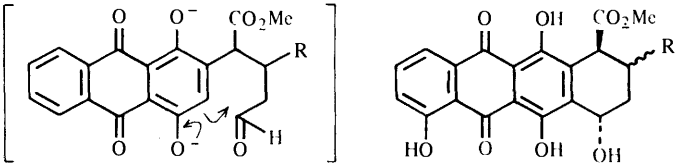


[89] F. Suzuki, S. Trenbeath, R. D. Gleim, and S. J. Sih, *J. Org. Chem.*, 1978, **43**, 4159.

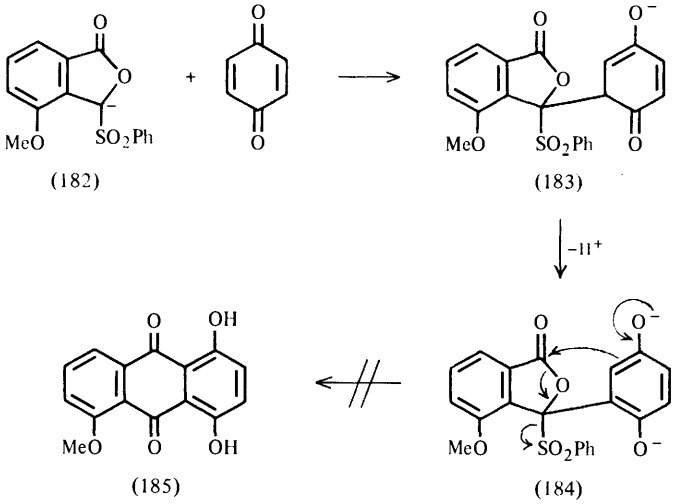
Support for this alternative mechanism is provided by the results of Krohn's[90] synthesis of 9-deoxyanthracyclinones. He isolated (179) as a mixture of epimers



after heating the ester (178) with enals under basic conditions. The intermediate (180), although not isolated, most reasonably cyclizes *via* an $Ar_2^- - 6$ mechanism. This methodology was extended to the synthesis of (±)-9-deoxy-ε-rhodomycinones (181).[90]

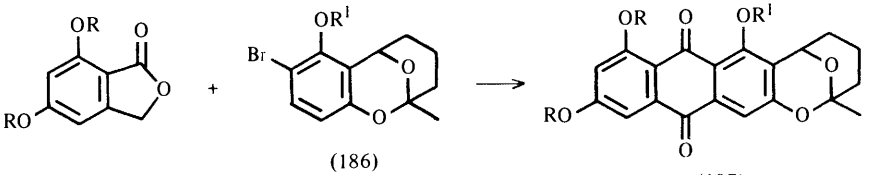


A reaction of the phthalide (182) and benzoquinone in the presence of base was attempted.[91] No anthraquinone (185) was formed. It was concluded that the phenolate (184)[92] derived from the Michael adduct (183) was insufficiently nucleo-



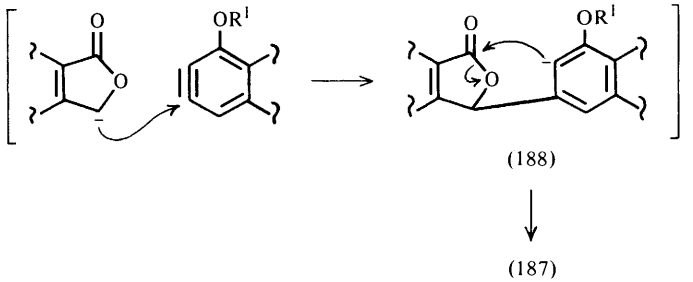
[90] K. Krohn, *J. Chem. Res. (S)*, 1979, 318.
[91] R. A. Russell and R. N. Warrener, *J. Chem. Soc., Chem. Commun.*, 1981, 108.
[92] W. Trueb and C. H. Eugster, *Helv. Chim. Acta*, 1972, **55**, 969.

philic. Two other factors, not considered by the authors,[91] also mitigated against the reaction (184)→(185), *i.e.* (a) an unfavourable $Ar_2^- - 5$ transition state, and (b) the low electrophilicity of the lactone functional group.



(186) (187)

The base-catalysed phthalide–benzyne annulation reaction[93] has recently been used by Townsend[94] in a synthesis of (±)-averufin (187; R = R[1] = H). In contrast to the phenoxide (184) the intermediate (188) readily cyclized since it (a) is an aryl anion, (b) is highly nucleophilic, and (c) has quite different stereoelectronic requirements from a phenoxide anion, resulting in a transition state much less strained than the $Ar_2^- - 5$ (184).



(188)

(187)

10 Limitations

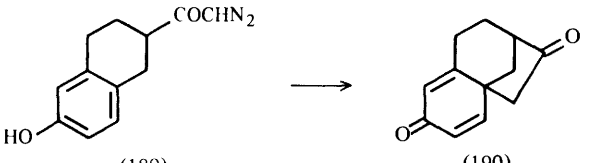
The principal limitation to $Ar_1^- - n$ cyclizations is steric factors. Forcing conditions are frequently used and presumably, required. Side reactions therefore, predominate on occasion.[28] $Ar_2^- - n$ cyclizations are limited both by ring size (Section 4) and reactivities of the substrate (Section 5).

Masamune[13] concluded from his investigation of the $Ar_1^- - 5$ cyclization of (46) that one diastereomer failed to react for steric reasons. Beames and Mander[29] probed these limitations in the course of their investigation of the $Ar_1^- - 6$ cyclization of the related system (39). However, they could not improve on Masamune's method. They concluded that steric interactions due to the presence of the ether substituent in the $Ar_1^- - 6$ cyclization of phenol (39) and similar substrates placed a severe restriction on the general utility of phenoxide cyclization for preparing compounds with an oxygenated bridge. In an attempt to solve this

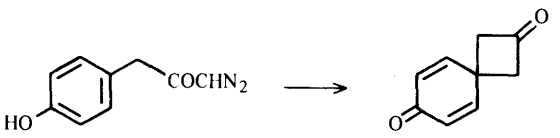
[93] D. J. Dodsworth, M.-P. Calcagno, E. U. Ehrmann, B. Devadas, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2120.

[94] C. A. Townsend, S. G. Davis, S. B. Christensen, J. C. Link, and C. P. Lewis, *J. Am. Chem. Soc.*, 1981, **103**, 6885.

problem they investigated the acid catalysed cyclization of phenolic diazoketones.[29] They were notably successful. Two examples are included here. The dienone (190) was formed in 100% yield.[95] The comparable $Ar_1^- - 5$ cyclization of phenol (126) failed.[13] The formation of the dienone (192)[96] is notable. All efforts to detect evidence for $Ar_1^- - 4$ cyclization have failed.[18,20,21,96]



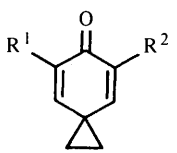
(189) (190)



(191) (192)

The conditions necessary for reaction are not predictable. Whereas it required[48] 170 °C to effect $Ar_1^- - 6$ cyclization to the dienone (97; R = H), the dienone (22; R = Bu^t) was obtained in 98% yield after heating with potassium t-butoxide in t-butyl alcohol at reflux temperature.[49]

Variable yields have been reported for spirodienones (193) synthesized *via* $Ar_1^- - 3$ cyclization. Although the yields appear to be affected by the nature of the double-bond substituents, in general they have not been optimized. In addition,



(193)

R^1	R^2	*Yield* (%)	*ref.*
Bu^t	Bu^t	81	97
C_6H_{11}	C_6H_{11}	50	97
Pr^i	Pr^i	59	97
Me	Bu^t	76	97
Me	Me	22	97
H	H	2–4	4, 98, 99

[95] D. J. Beames, T. R. Rose, and L. M. Mander, *Aust. J. Chem.*, 1974, **27**, 1269.
[96] D. J. Beames and L. N. Mander, *Aust. J. Chem.*, 1974, **27**, 1257.
[97] V. V. Ershov, I. S. Belostotskaya, and V. I. Volod'kina, *Zh. Org. Khim.*, 1967, **3**, 511.
[98] D. I. Schuster and C. J. Polowczyk, *J. Am. Chem. Soc.*, 1966, **88**, 1722.
[99] D. I. Schuster and I. S. Krull, *J. Am. Chem. Soc.*, 1966, **88**, 3456.

certain dienones are extremely reactive towards electrophilic and nucleophilic reagents.[4,100,101]

Spirodienones[102] *e.g.* (3; R = H and R = Me) have a strong tendency to rearrange to phenols in the presence of acid,[68] or thermally[56] in the course of distillation. These product characteristics may account for the low and variable yields. However, the successful $Ar_1^- - 3$ synthesis[37] of (69) by means of a trialkylamine catalyst at room temperature, promises more scope for this reaction.

The $Ar_2^- - 5$ transition state is highly strained and usually will not occur. Although $Ar_2^- - 6$ cyclizations occur readily, they are not regiospecific. Predominant *ortho*-alkylation is usually observed which contrasts with $Ar_2 - 6$ cyclization wherein *para*-alkylation occurs, frequently exclusively.[52] This inability to control the *o* : *p* ratio has limited the synthetic potential of $Ar_2^- - 6$ cyclizations. For this reason Mandell[26] did not pursue the $Ar_2^- - 6$ cyclization of phenol (27) route to the synthesis of santonin.

Aryl ring substituents deflect $Ar_2^- - 6$ cyclization to unsubstituted positions. Newman and Mekler[5] were therefore disappointed to find that none of the dienone (139), a potentially useful intermediate in terpenoid total synthesis,[11] was formed when the phenol (5) was treated with base.

11 Conclusions

Although the area of phenoxide cyclizations has been investigated in considerable detail, there is much scope for further development and application, particularly in the area of natural products synthesis. Base catalysis involves protecting groups and tolerance of substituents which differ from those used in the more common cationic processes. The S_N2 character of the reaction is implicitly more stereocontrolled than analogous cationic processes. With the exceptions of the cyclizations of (24),[24] (47),[31,32] and (70),[38] this aspect has not been fully appreciated.

Stereoelectronic requirements of $Ar_2^- - n$ cyclizations in particular require further elucidation. In addition, the steric requirements for the formation of rings with $n > 6$ has not been investigated.

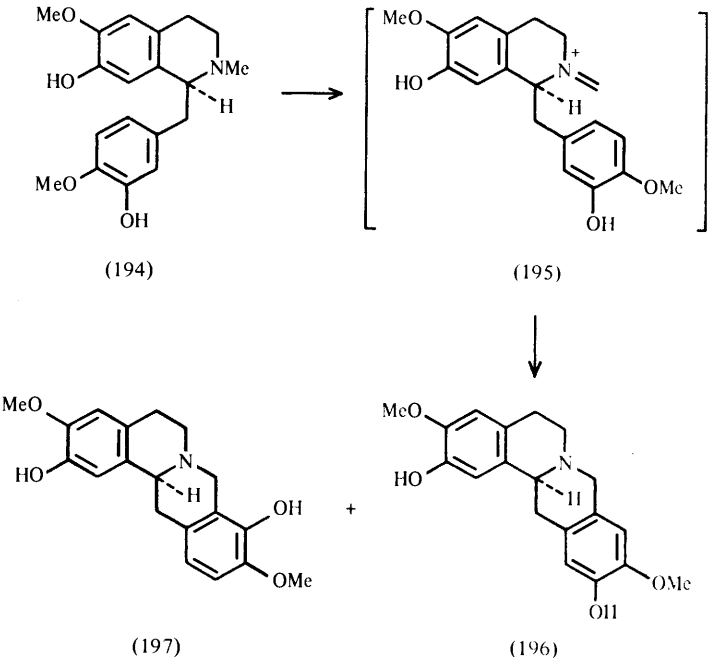
More recent developments, such as phenoxide–quinone methide coupling,[46] offer scope in the area of biomimetic syntheses, *e.g.* lignan total synthesis. The effect of metal cations leading to predominant *ortho*-cyclization[46,103] suggests an important alternative to cationic processes.

A number of areas remain to be developed such as the anionic Pictet–Spengler reaction,[60] intramolecular coupling of phenoxide with quinones,[104] quinone monoacetals,[91] and arynes,[61] in addition to phenoxide–radical coupling[105] and

[100] V. V. Ershov, I. S. Belostotskaya, and V. I. Volod'kina, *Izv. Akad. Nauk SSR, Ser. Khim.*, 1967, 930.
[101] V. V. Ershov, I. S. Belostotskaya, and V. I. Volod'kina, *Izv. Akad. Nauk SSR, Ser. Khim.*, 1966, 1496.
[102] R. S. Ward, *Chem. Br.*, 1973, 444.
[103] L. Bolzoni, G. Casiraghi, G. Casnati, and G. Sartori, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 684.
[104] H. Muzzo, U. V. Gizychi, U. I. Zahorszky, and D. Bormann, *Annalen*, 1964, **676**, 10.
[105] W. A. Waters, *J. Chem. Soc.* (*B*), 1971, 2026.

photochemically induced[106] phenoxide cyclizations. The importance of the nature of the leaving group and electrophilic centre needs to be stressed. For example, the low reactivity of common esters resulted in ineffective cyclization. More reactive esters coupled with appropriate metal cation chelation may lead to useful developments in the area of anthracyclone and tetracycline total synthesis.

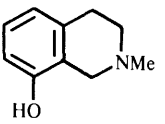
The possible involvement of phenoxide cyclization in biosynthetic pathways has not been investigated. Phenolic cyclization is the most frequently cited[107] mode of isoquinoline ring formation in the course of isoquinoline alkaloid biosynthesis. However, Kametani[108] showed that when (+)-reticuline (189) was incubated with rat liver microsomes under slightly basic conditions it was biotransformed *via* the iminium salt (195) into (−)-scoulerine (196) and (−)-coreximine (197), in the ratio 27 : 73, respectively. This ratio is suggestive of an Ar_2^- − 6 cyclization of (195). In addition, the ratio of isomeric alkaloids found together is, on occasion, more consistent with Ar_2^- − 6 cyclization. For example, longimammidine (198) and



[106] Z. Horii, Y. Nakashita, and C. Iwata, *Tetrahedron Lett.*, 1971, 1167; T. Kametani and Kohno, *Tetrahedron Lett.*, 1971, 3155.

[107] U. Weiss and J. M. Edwards, 'The Biosynthesis of Aromatic Compounds', Wiley, N.Y., 1980, p. 49; M. Luckner, 'Secondary Metabolism in Plants and Animals', Academic Press, N.Y., 1972, p. 321.

[108] T. Kametani, N. Kanaya, Y. Ohta, and M. Ihara, *Heterocycles*, 1980, **14**, 963.



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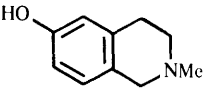

(199)

longimammosine (199) were isolated in a 1 : 1 ratio from the peyote cactus.[109] In the field of lignan biosynthesis[110] phenoxide–quinone methide coupling is a pathway which has yet to be investigated.

[109] R. L. Ranieri and J. L. McLaughlin, *J. Org. Chem.*, 1976, **41**, 319.
[110] A. J. Birch and A. J. Liepa, 'Chemistry of Lignans', ed. C.B.S. Rao, Andhra University Press, India, 1978, p. 316.