REACTIONS OF 2,6-DIARYL-3,7-DIOXABICYCLO[3.3.0]-OCTANE LIGNANS

Andrew Pelter* and Robert S. Ward

Chemistry Department, University of Swansea, Singleton Park,

Swansea SA2 8PP, U.K.

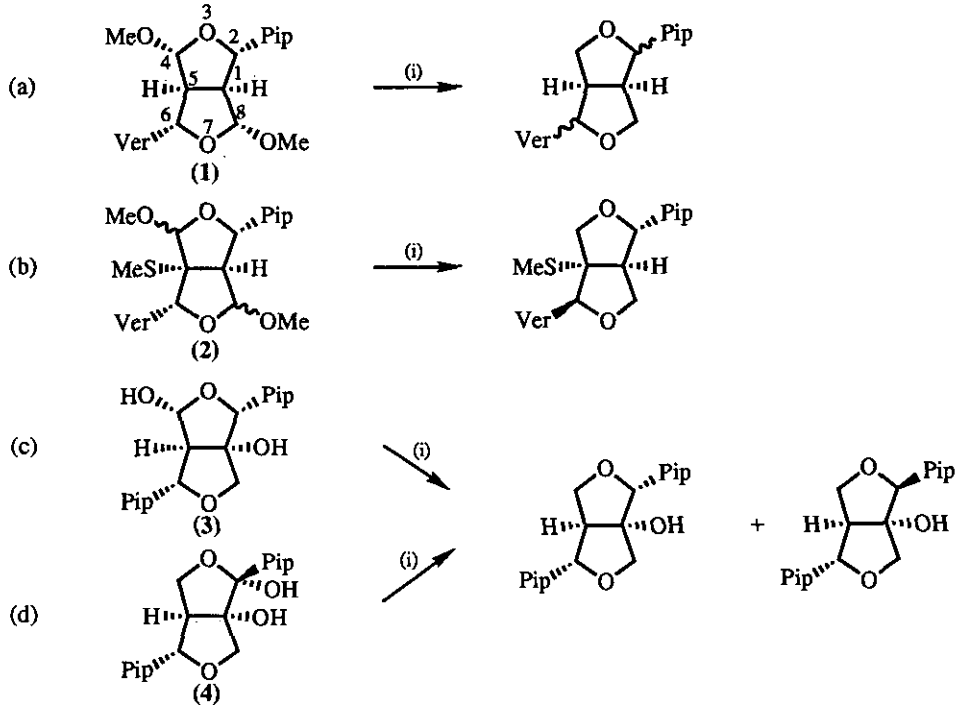
Abstract - Reactions of 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane lignans (furofurans) have been rationalised in terms of the production of stabilised carbocations. These may be produced by acid catalysed or oxidative reactions *dependant on the constitution of the lignan substrate.* The carbocations may then undergo rearrangements in the case of acid catalysed reactions or the rearrangement products may themselves be further oxidised. In the presence of triethylsilane the carbocations are reduced prior to rearrangement.

2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octanes (furofurans) are one of the largest groups of naturally occurring lignans.[1,2] Apart from the structure elucidation[1,3-7] and synthesis[8-11] of these compounds very little is known about their general chemical behaviour. In the last few years, we and colleagues have shown that they undergo a number of interesting reactions, several of which involve novel rearrangements.[11-16] The products include compounds with the parent 3,7-dioxabicyclo[3.3.0]octane ring system, aryltetralins, 3,6-dioxabicyclo[3.2.1]octanones, pyrones, tetrahydropyrans and a benzylidenebutyrolactone. In this paper we present a rationalisation of the outcome of these diverse reactions in terms of common *mechanistic pathways.*

The reactions in all cases involve carbocations generated either by acid alone[12] or in the presence of Et_3SiH[14,15] or by hydride abstraction by DDQ.[13,16]

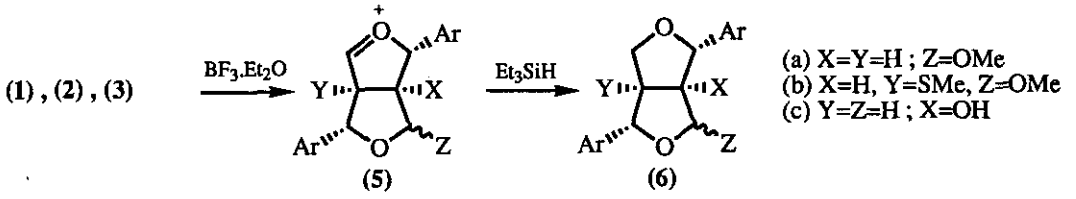
1. *Reactions not involving rearrangement*

Treatment of lignans (**1-4**) with triethylsilane and BF_3 results in reduction of the acetal and hemiacetal groups (Scheme 1).[11,15]



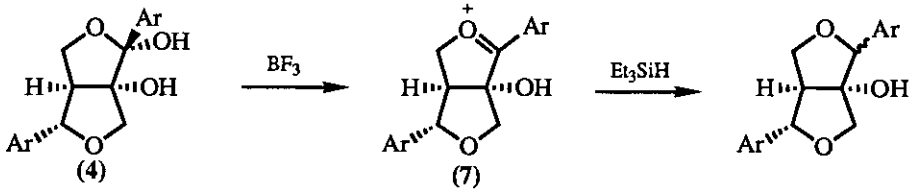
Scheme 1 (i) BF_3/Et_3SiH
Ver = 3,4-dimethoxyphenyl, Pip = 3,4-methylenedioxyphenyl

In cases (a)-(c) a highly favoured process gives the stabilised carbocation (**5**)which is then trapped by the reductant (Scheme 2). When Z=OMe, the process is repeated to finally reach **6**, Z=H, in all cases.



Scheme 2

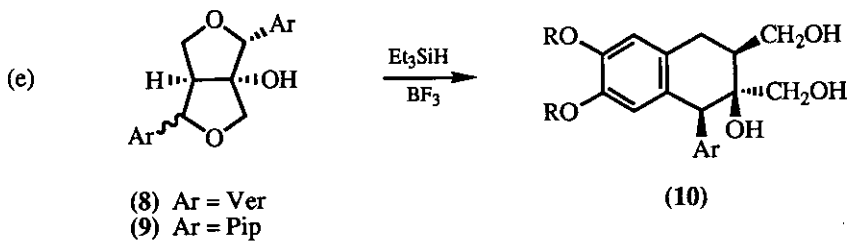
In case (d) there is a similar situation, as acid readily gives the stabilised carbocation (7) which is trapped by the reductant (Scheme 3).



Scheme 3

2. *Rearrangements to aryltetralins with retention of the overall carbon skeleton.*

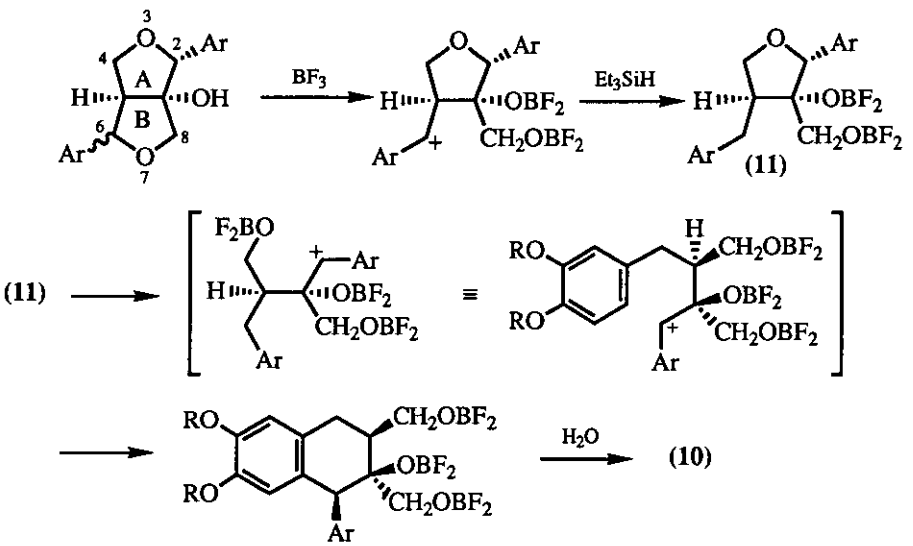
Gmelinol (8) and paulownin (9) each rearrange on treatment with triethylsilane and BF_3 to give an aryltetralin (10) (Scheme 4).[14,15]



(8) Ar = Ver
(9) Ar = Pip

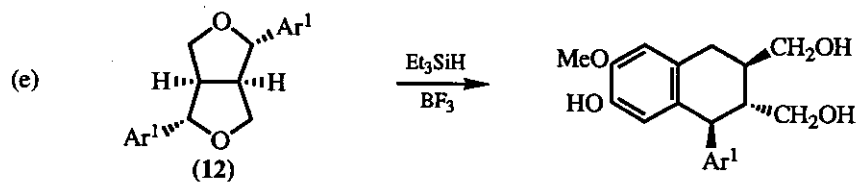
Scheme 4

This is envisaged as proceeding in two stages, as shown in Scheme 5. Ring B is cleaved preferentially next to the C-6 aryl group to give 11 probably as a boronated intermediate, by reduction of an intermediate carbocation. Ring A is then cleaved and intercepted by intramolecular attack by an activated aryl group.



Scheme 5

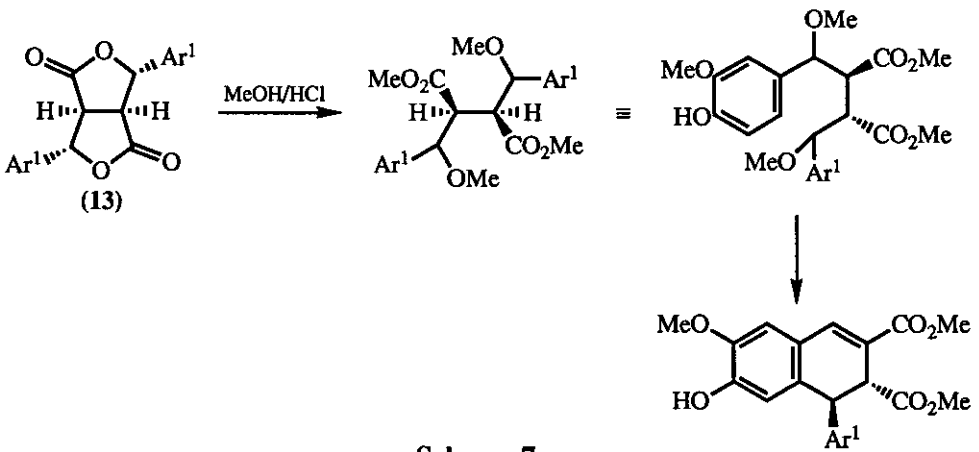
Pinoresinol (12), which lacks a tertiary hydroxyl group, behaves in a similar fashion (Scheme 6).[17]



Scheme 6

Ar^1 = 4-hydroxy-3-methoxyphenyl

In the literature there are many analogies for these acid catalysed rearrangements of tetrahydrofurfuryl lignans. An example involving a furofuran lactone (13) is shown in Scheme 7.[18,19]

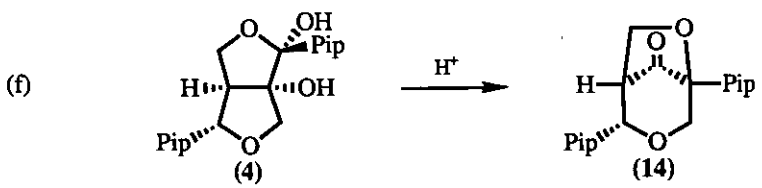


Scheme 7

3. *Rearrangements involving carbon-carbon bond migration*

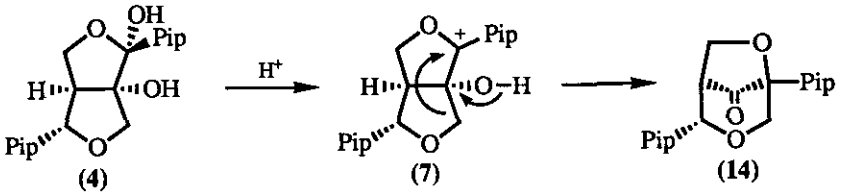
3.1 *Acid catalysed rearrangements.*

Arboreol (4) rearranges with acid to give gmelanone (14) (Scheme 8).[12] Since both compounds are natural products isolated from *Gmelina arborea*[3,20] this reaction represents a possible biomimetic transformation.



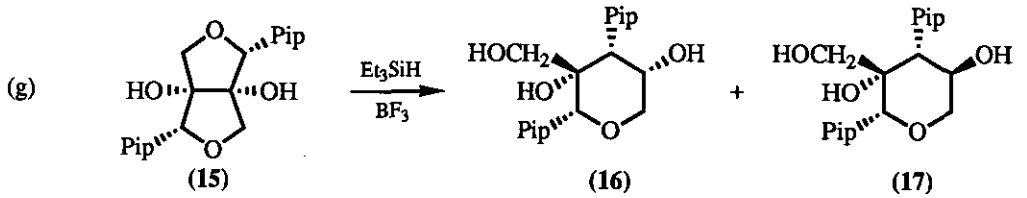
Scheme 8

The mechanism of this process is shown in Scheme 9. Once more the favoured carbocation (**7**) is produced, but in the absence of an hydride donor it undergoes migration of the primary alkyl group. This electronically unfavourable process occurs because migration of the secondary group would give a strained oxetane rather than a pyran.



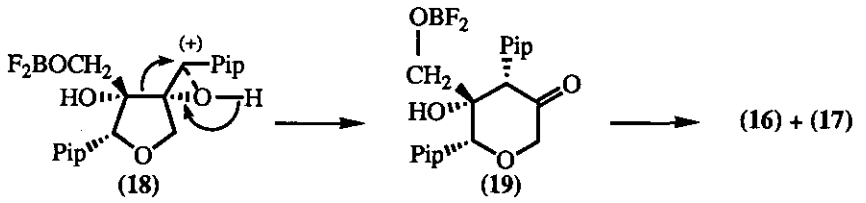
Scheme 9

In contrast, wodeshiol **15**[7,21] undergoes rearrangement on treatment with triethylsilane and BF_3 to give two epimeric tetrahydropyran derivatives (**16**) and (**17**) (Scheme 10).[15]



Scheme 10

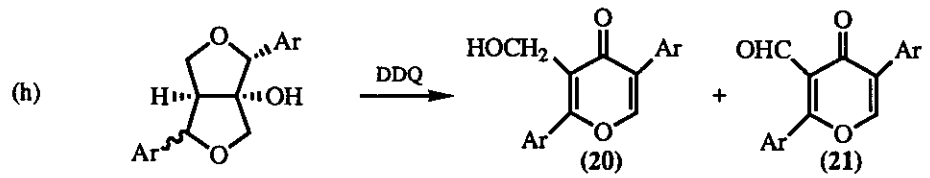
In this very symmetrical compound, ring cleavage can only give rise to **18**. There is now no steric barrier to migration of the tertiary alkyl group to give **19** which is reduced to give the products (**16**) and (**17**). The intermediate **18** may well have a bridged structure, with the C-1 hydroxyl group participating and maintaining the steric integrity of the carbocation (Scheme 11).



Scheme 11

3.2 *Oxidatively induced rearrangements.*

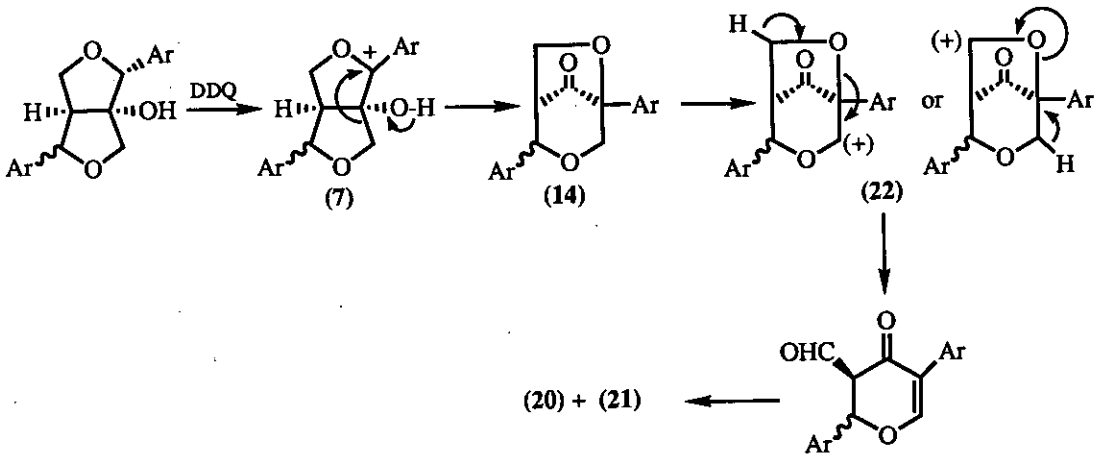
3.2.1 Gmelinol (**18**) and paulownin (**9**) react with DDQ in benzene to give pyrones (**20**) and (**21**) (Scheme 12).[13]



(**8**) Ar = Ver
(**9**) Ar = Pip

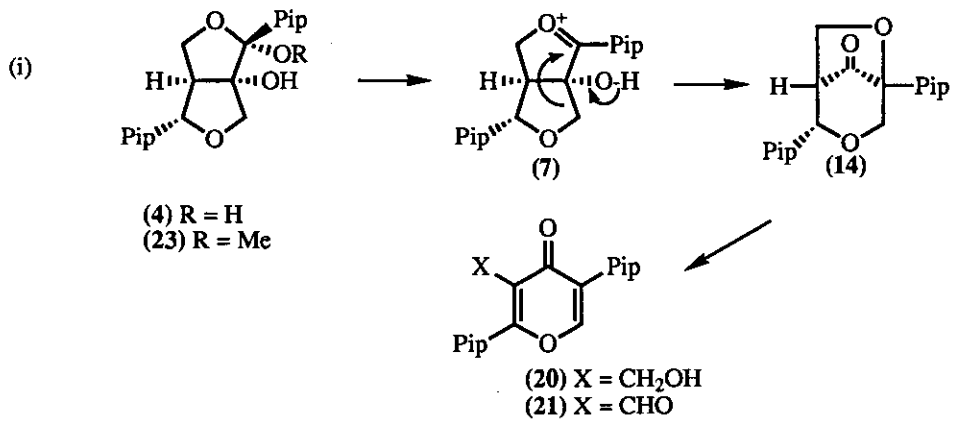
Scheme 12

In this case the intermediate (**7**) can be generated by hydride abstraction (Scheme 13). Although hydride can be abstracted from other positions, only the production of **22** can give simple ring cleavage and an irreversible reaction.



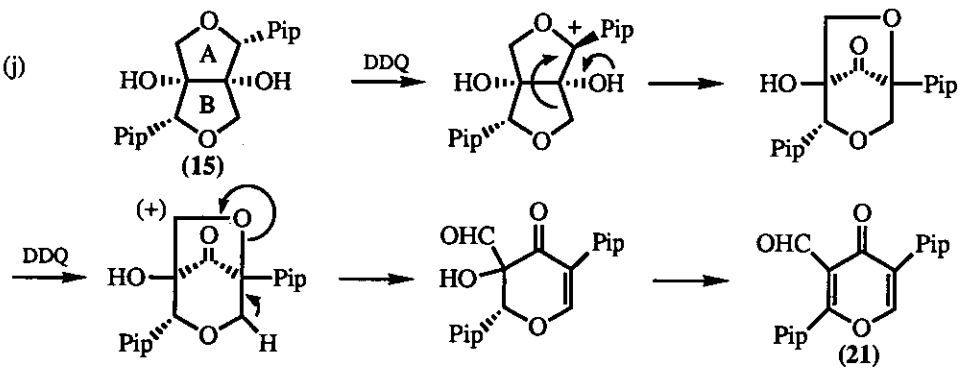
Scheme 13

3.2.2 Similar processes occur with arboreol (**4**) and methyl arboreol (**23**) (Scheme 14). In these cases the initial migration is not oxidatively induced but the subsequent irreversible steps are oxidative. This is strong evidence for the oxidative production of **7** proposed in Scheme 13.



Scheme 14

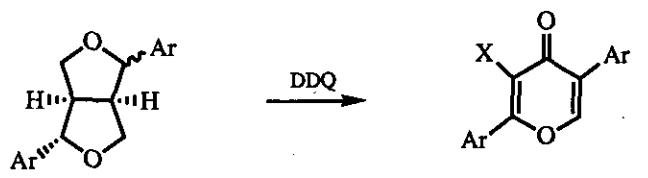
3.2.3 Wodeshiol (**15**) also gives rise to the same pyrone aldehyde (**21**) with DDQ (Scheme 15). In this case, as before, the primary alkyl group migrates because migration of the secondary alkyl group would once again give a strained oxetane.[16]



Scheme 15

3.2.4 Even when there are no bridgehead hydroxyl groups, oxidative pyrone formation occurs (Scheme 16). Thus sesamin (**24**) and epieudesmin (**25**) also give the pyrone products **20** and **21** with DDQ.[16]

(k)

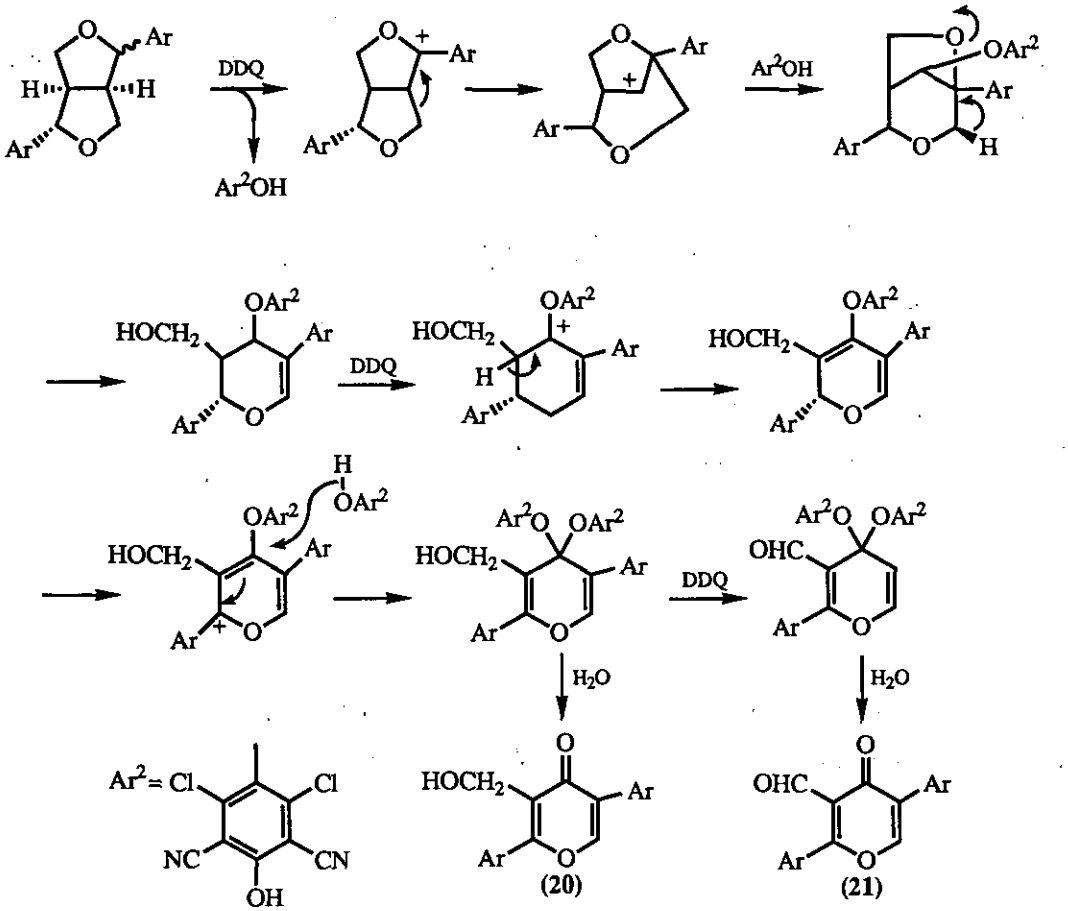


(24) Ar = Pip
(25) Ar = Ver

(20) X = CH_2OH
(21) X = CHO

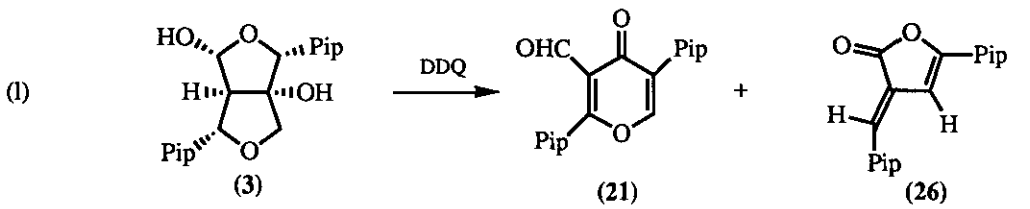
Scheme 16

The process here must necessarily be more circuitous than those previously giving **20** and **21**, as an extra oxygen must be introduced and this can come initially only from the quinone or its reduced phenol. One possible route is shown below (Scheme 17).



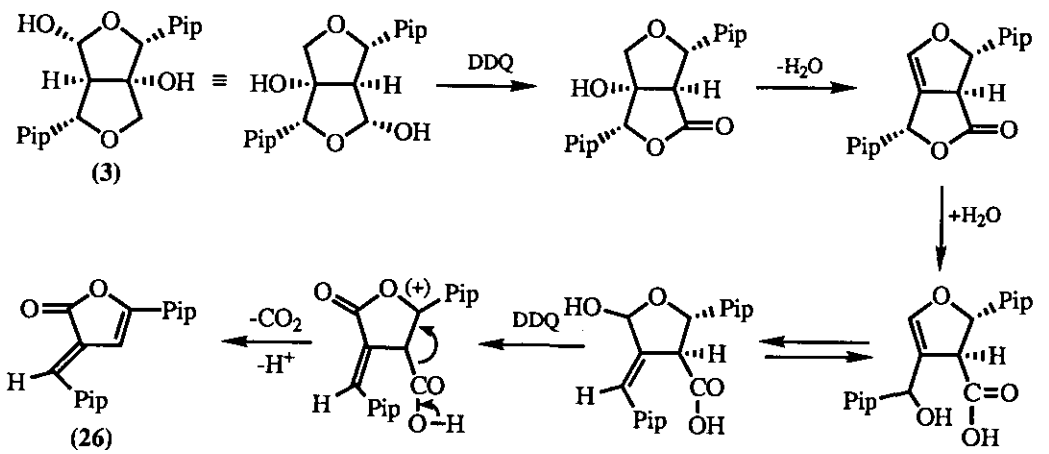
Scheme 17

3.2.5 A very interesting case is that of gummadiol (**3**).[5,22] In addition to pyrone (**21**) the piperonylidene butenolide (**26**) is isolated (Scheme 18).[13]



Scheme 18

We propose that this arises by a series of dehydrative and oxidative reactions as shown below (Scheme 19).



Scheme 19

Conclusion.

It is clear that a unity exists among these apparently diverse reactions. Stabilised carbocations are formed either by loss of an hydroxyl or methoxyl group or, alternatively, by hydride abstraction. The cations are then either reduced, undergo facile rearrangement or are attacked by appositely placed aromatic rings. Further reactions occur that depend on the external reagents and on the constitution of the initial products. The unique rearrangements to give pyrones are shown to fit in well with the characterised rearrangement to gmelanone.

REFERENCES

1. A. Pelter and R. S. Ward, "Chemistry of Lignans" (ed. C. B. S. Rao), Andhra University Press, 1978, Chap. 7.
2. D. C. Ayres and J. K. Loike, "Lignans : Chemical, biological and clinical properties", Cambridge University Press, 1990.
3. A. S. R. Anjaneyulu, K. Jaganmohan Rao, V. Kameswara Rao, L. Ramachandra Row, C. Subrahmanyam, A. Pelter, and R. S. Ward, *Tetrahedron,* 1975, **31**, 1277.
4. A. Pelter, R. S. Ward, E. Venkata Rao, and K. V. Sastry, *Tetrahedron,* 1976, **32**, 2783.
5. A. S. R. Anjaneyulu, A. Madhusudhana Rao, V. Kameswara Rao, L. Ramachandra Row, A. Pelter, and R. S. Ward, *Tetrahedron,* 1977, **33**, 133.
6. A. Pelter, R. S. Ward, and C. Nishino, *Tetrahedron Lett.,* 1977, 4137.
7. A. S. R. Anjaneyulu, P. Atchuta Ramaiah, L. Ramachandra Row, R. Venkateswarlu, A. Pelter, and R. S. Ward, *Tetrahedron,* 1981, **37**, 3641.
8. R. S. Ward, *Chem. Soc. Rev.,* 1982, **11**, 75 and *Tetrahedron,* 1990, **46**, 5029.
9. A. Pelter, R. S. Ward, D. J. Watson, and I. R. Jack, *J. Chem. Soc., Perkin Trans. 1,* 1982, **183**.
10. A. Pelter, R. S. Ward, D. J. Watson, P. Collins, and I. T. Kay, *J. Chem. Soc., Perkin Trans. 1,* 1982, 175.
11. A. Pelter, R. S. Ward, P. Collins, R. Venkateswarlu, and I. T. Kay, *J. Chem. Soc., Perkin Trans. 1,* 1985, 587.
12. L. Ramachandra Row, R. Venkatewarlu, A. Pelter, and R. S. Ward, *Tetrahedron Lett.,* 1980, **21**, 2919.
13. R. S. Ward, A. Pelter, I. R. Jack, P. Satyanarayana, B. V. Gopala Rao, and P. Subrahmanyam, *Tetrahedron Lett.,* 1981, **22**, 4111.
14. A. Pelter, R. S. Ward, R. Venkateswarlu, and C. Kamakshi, *Tetrahedron,* 1989, **45**, 3451.
15. A. Pelter, R. S. Ward, R. Venkateswarlu, and C. Kamakshi, *Tetrahedron,* 1992, **48**, 7209.
16. P. Satyanarayana, P. Koteswara Rao, K. Sethuramu, K. N. Viswanathan, and S. Venkateswarlu, *Indian J. Chem.,* 1991, **30B**, 825.
17. A. Pelter, R. S. Ward, A. S. R. Anjaneyulu, R. Venkatewarlu, and C. Kamakshi, unpublished results.
18. N. J. Cartwright and R. D. Haworth, *J. Chem. Soc.,* 1944, 535.
19. R. Ahmed, M. Lehrer, and R. Stevenson, *Tetrahedron,* 1973, **29**, 3753.

20. L. Ramachandra Row, K. Jaganmohan Rao, V. Kameswara Rao, A. Pelter, and R. S. Ward, *J. Chem. Soc., Chem. Commun.*, 1974, 476.

21. A. S. R. Anjaneyulu, P. Atchuta Ramaiah, L. Ramachandra Row, A. Pelter, and R. S. Ward, *Tetrahedron Lett.*, 1975, 2961.

22. A. S. R. Anjaneyulu, A. Madhusudhana Rao, V. Kameswara Rao, L. Ramachandra Row, A. Pelter, and R. S. Ward, *Tetrahedron Lett.*, 1975, 1803.

Received, 18th May, 1993