*Pure & Appl. Chem.*, Vol. 66, Nos 10/11, pp. 2053–2056, 1994.
Printed in Great Britain.


# Recent developments in the synthesis of drimane and lactarane sesquiterpenes

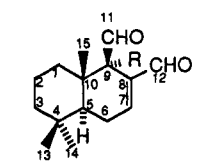
Ae. de Groot, B.J.M. Jansen, A.A. Verstegen-Haaksma, H.J. Swarts, R.V.A. Orru, G.A. Stork, and J.B.P.A. Wijnberg

Department of Organic Chemistry, Agricultural University, Dreijenplein 8, 6703 HB, Wageningen, The Netherlands. FAX 31 8370 84914

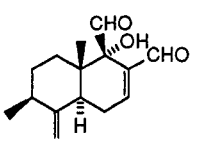
Abstract: Several new methods for the construction of ene-dialdehyde functionalities and for the regioselective annulation of butenolides were developed and applied in the synthesis of drimane and lactarane sesquiterpenes. Optically active drimanes were synthesised starting from S-(+)- and R-(-)-carvone. A new development in this approach starts with a conjugate addition of cyanide to the enone in carvone, followed by an annulation reaction.
Base-induced and directed reactions of substituted *trans* - perhydronaphthalene-1,4-diol monosulfonate esters in apolar solvents provide an effective route to *cis* - perhydroazulene systems. The rearrangement can be directed towards intramolecular ether formation. Based on this approach a total synthesis of lactaranes is under investigation.

The insect antifeedant properties of polygodial, warburganal and muzigadial are well known. These drimane sesquiterpenes all possess an ene-dialdehyde functionality, but also unsaturated lactones and furans are common structural elements in these class of compounds (1)(Fig. 1). The same structural features are present in lactarane sesquiterpenes (scheme 4).
Numerous syntheses of drimane sesquiterpenes have appeared within the last twenty years (2). In our laboratory a number of synthetic approaches towards several types of drimane and rearranged drimane sesquiterpenes were developed, starting from the decalones 7-10 (Fig. 1). Several new methods for the regioselective annulation of the required butenolides were discovered.

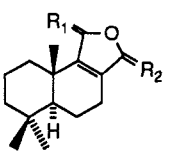
Figure 1



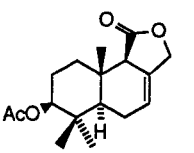
1 polygodial (R=H)
2 warburganal (R=OH)



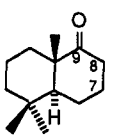
3 muzigadial



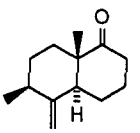
4 confertifolin ($R_2$=O)
5 isodrimenin ($R_1$=O)



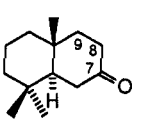
6 3β-acetoxydrimenin



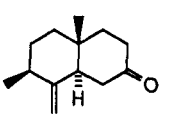
7



8



9

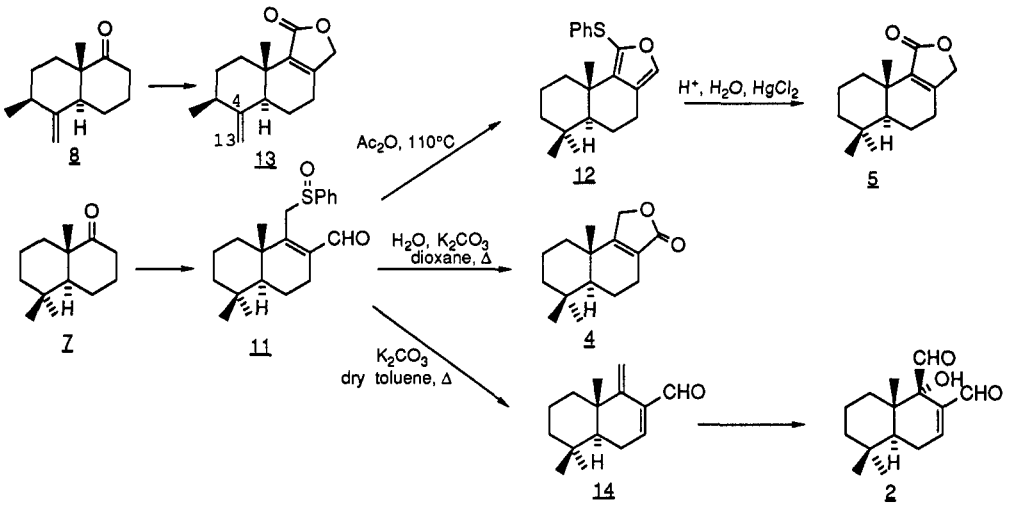


10

The decalin skeleton can be obtained via Robinson annulation of cyclohexanones followed by the necessary functional group transformations. The trimethyldecalone 7 was used for the synthesis of warburganal (3,4), isotadeonal (4), confertifolin (5,7), valdiviolide (5), euryfuran (5,6), and isodrimenin (5,7,8).
All these syntheses employ a formylation reaction at C-8 for the introduction of C-12. The conversion of 7 into its *n*-butylthiomethylene derivative, the addition of [(phenylthio)methyl]lithium, the mercuric chloride

assisted hydrolysis of the adduct, and the subsequent oxidation to sulfoxide 11 is standard chemistry (8). The sulfoxide 11 is an important intermediate in the regioselective butenolide annulation procedures. This sulfoxide was prepared to achieve a higher oxidation level at C-11, however a Pummerer-type reaction of this sulfoxide by heating it in acetic acid anhydride at 110°C unexpectedly gives the formation of (phenylthio)furan 12. The hydrolysis of this furan results in the regioselective annulation of a butenolide to give 5. Starting from ketone 7 this series of transformations can be achieved in 35% overall yield (8). The rearranged drimane (+)-colorata-4(13),8-dienolide (13) (scheme 1) can be prepared using the same procedure, starting form *trans*-decalone 8 (9).
The reaction of sulfoxide 11 takes a different course when this compound is refluxed in dioxane in the presence of some water. To our surprise the butenolide 4 is obtained now, with the opposite regiochemistry, so with the carbonyl group at C-12 (scheme 1).

scheme 1

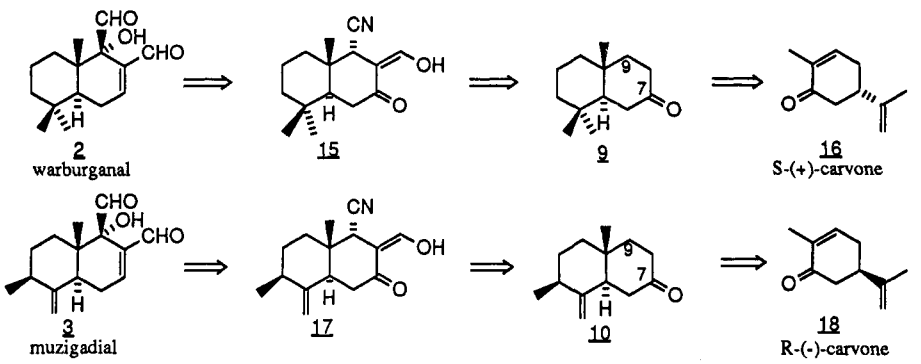



A higher oxidation state at C-11 can be achieved also *via* elimination of phenylsulfenic acid from this sulfoxide, which could be achieved in dry toluene at reflux temperature (10), followed by selective oxidation. It was shown by Goldsmith *et al.* (4) that selective osmylation and oxidation of the protected diene 14 to warburganal (2) can be performed in good yield (scheme 1).
Functional groups such as butenolides, furans, and unsaturated or hydroxylated dialdehydes, are not only found in drimane sesquiterpenes but they are also common in other classes of sesqui-, di-, and triterpenes like lactaranes, spongianes, and scalaranes, respectively. The developed methods can be applied in the total synthesis of these compounds as well.

Synthesis of drimanes from carvone

The total synthesis of polygodial, warburganal, muzigadial (11), and other drimanes has been achieved starting from the *trans*-decalones 7 and 8 with the carbonyl group at C-9 (9,11). In our laboratory a new approach was developed starting from the *trans*-decalones 9 and 10, with the carbonyl group at C-7 (12) (see scheme 2). These *trans*-decalones 9 and 10 are easily accessible and the carbonyl group is ideally located for the introduction of the necessary functional groups at C-8 and at C-9. Later on it can be used for the introduction of the $\Delta^{7,8}$ double bond. Moreover, these C-7 decalones can be prepared relatively easily in an enantiomerically pure form starting from S-(+)- or R-(-)-carvone (13).
Although the total synthesis of the natural enantiomers of the insect antifeedant drimanes proceeds with good yields of the individual reactions, the whole sequence takes 16 steps. S-(+)-Carvone is first reduced and annulated. Then the *gem* dimethyl groups are introduced, the chiral handle is removed and next the functionalized C-12 and C-11 moieties are introduced to obtain compound 15. Finally, a number of functional group transformations and an epimerization at C-9 lead to drimanes like 1 and 2 (scheme 2).

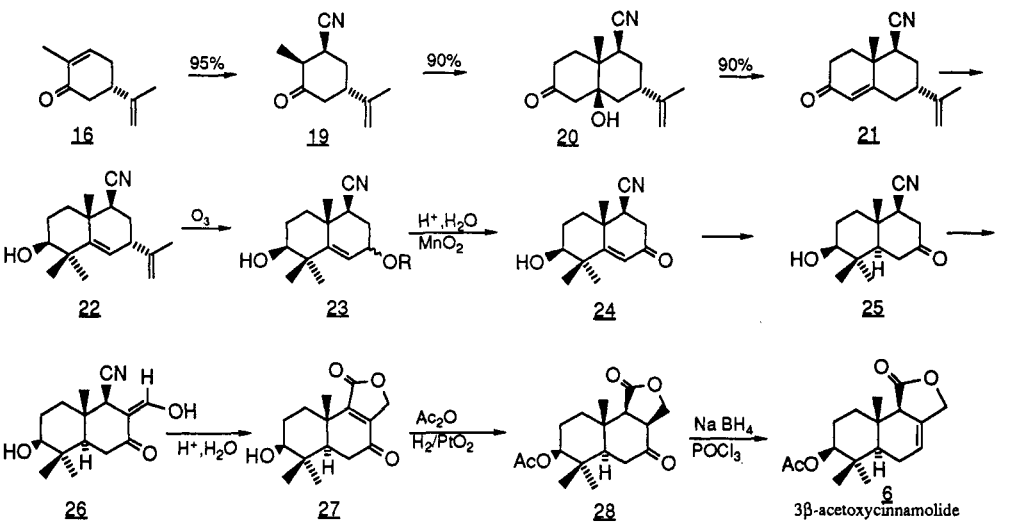
scheme 2




It seemed worthwhile to investigate a route where the introduction of the nitrile group (C-11) and the "reduction" of the double bond in S-(+)-carvone were combined in the first step of the sequence in the form of a conjugate addition. Then the annulation, the introduction of the *gem* dimethyl groups, the removal of the isopropenyl group and the introduction of C-12 could lead to compound 26 (scheme 3).

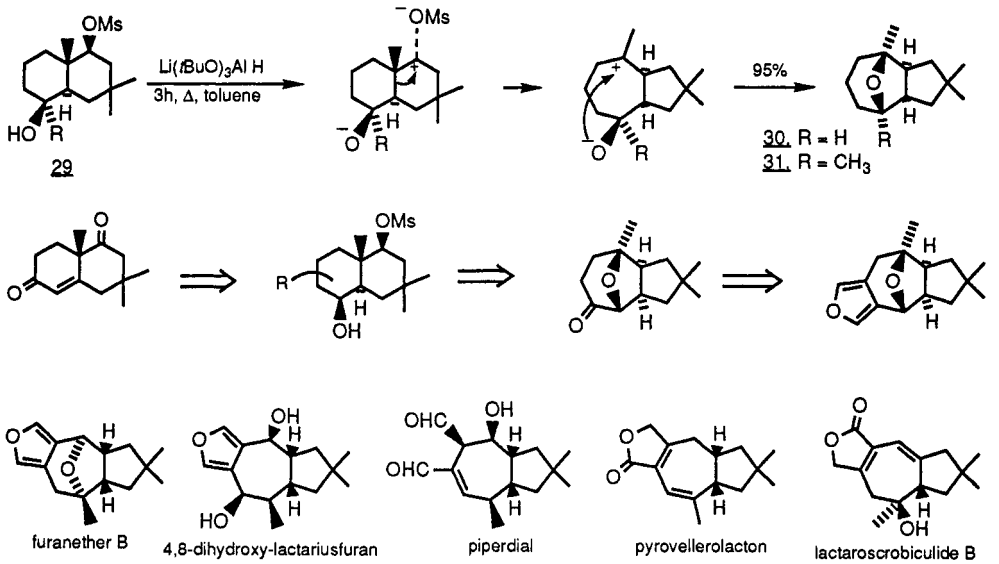
The investigation of a total synthesis of drimanes along these lines was strongly stimulated by the knowledge that the addition of cyanide to S-(+)-carvone yields selectively the adduct 19 which can be isolated by crystallization (14), and the discovery that the Robinson annulation of 19 with methyl vinyl ketone proceeds in an exceptionally high yield of 90% to give 20, which can be isolated also simply by crystallization. After dehydration of 20, the enone 21 is obtained in 77% overall yield from S-(+)-carvone in a series of simple reactions which can be performed on a large scale. Methylation of 21 followed by reduction gives the hydroxy nitrile 22 in high yield, without isomerization of the nitrile group (scheme 3). Ozonolysis followed by a Criegee rearrangement results in a mixture of the C-7 allylic alcohols and acetates 23. Mild hydrolysis followed by selective oxidation of the allylic alcohols gives the enone 24. The $\Delta^{5,6}$ conjugated double bond can be reduced either with lithium in ammonia or via catalytic reduction to give the *trans*-decalone 25. Next the aldehyde group is introduced at C-8 directly by formylation to give compound 26, no serious elimination or epimerization of the nitrile group is observed. Simple treatment of 26 with acid then gives the keto-lactone 27. The necessary functional group transformations in the final stage of the synthesis gives no problems (15) and a good yield of 3β-acetoxycinnamolide (6) is obtained.

scheme 3



Base-induced and -directed reaction of substituted *trans* - perhydronaphthalene-1,4-diol monosulfonate esters in apolar solvents is an effective route to *cis* - perhydroazulene systems (16). The dissociation of sulfonate ester can be induced by an electron donating alcoholate, even when it is located at a distance of four σ-bonds. The reactions of the substrates strongly depend on the regio- and stereochemistry of the alcoholate and sulfonate groups (17, 18). Rearrangement, regioselective elimination and homofragmentation are the observed reaction patterns. The reactions have been applied in the total syntheses of sesquiterpenes like 5-*epi* nardol (16) and alloapoaromadendrane-4β,10α- or -4α,10α-diol (19). The rearrangement can be directed towards intramolacular ether formation like 30 or 31, by the choice of the counter ion of the alcoholate (18). Based on this approach a total synthesis of lactaranes is under investigation (scheme 4).

scheme 4




REFERENCES

1. B.J.M. Jansen, and Ae. de Groot, *Natural Products Report*, **8**, 309 (1991).
2. B.J.M. Jansen, and Ae. de Groot, *Natural Products Report*, **8**, 319 (1991).
3. A.S. Kende, and T.J. Blacklock, *Tetrahedron Lett.*, **21**, 3113 (1980).
4. D.J. Goldsmith, and H.S. Kezar III, *Tetrahedron Lett.*, **21**, 3543 (1980).
5. S.V. Ley, and M. Mahon, *J. Chem. Soc. Perkin Trans I*, 1379 (1983).
6. B.J.M. Jansen, R.M. Peperzak and, Ae. de Groot, *Recl. Trav. Chim. (Pays-Bas)*, **106**, 549 (1987).
7. B.J.M. Jansen, R.M. Peperzak and, Ae. de Groot, *Recl. Trav. Chim. (Pays-Bas)*, **106**, 505 (1987).
8. Ae. de Groot, and B.J.M. Jansen, *J. Org. Chem.*, **49**, 2034 (1984).
9. Ae. de Groot, M.P. Broekhuysen, L.L. Doddema, M.C. Vollering, and J.M.M. Westerbeek, *Tetrahedron Lett.*, **23**, 4831 (1982).
10. Ae. de Groot, B.J.M. Jansen, J.T.A. Reuvers, and E.M. Tedjo, *Tetrahedron Lett.*, **22**, 4137 (1981).
11. M.P. Bosch, F. Camps, J. Coll, A. Guerrero, T. Tatsuoka, and J. Meinwald, *J. Org. Chem.*, **51**, 773 (1986).
12. B.J.M. Jansen, H.W.J.M. Sengers, H.J.T. Bos, and Ae. de Groot, *J. Org. Chem.*, **53**, 855 (1988).
13. B.J.M. Jansen, J.A. Kreuger, and Ae. de Groot, *Tetrahedron*, **45**, 1447 (1989).
14. C. Djerassi, R.A. Schneider, H. Vorbrueggen, and N.J. Allinger, *J. Org. Chem.*, **28**, 1632 (1963).
15. E. Wenkert and P.D. Strike, *J. Am. Chem. Soc.*, **86**, 2044 (1964).
16. J.B.P.A. Wijnberg, L.H.D. Jenniskens, G.A. Brunnekreef, and Ae. de Groot, *J. Org. Chem.*, **55**, 941 (1990).
17. R.V.A. Orru, J.B.P.A. Wijnberg, L.H.D. Jenniskens, and Ae. de Groot, *J. Org. Chem.* **58**, 1199 (1993).
18. R.V.A Orru, J.B.P.A. Wijnberg, C.T. Bouwman, and Ae. de Groot, *J. Org. Chem.* **59**, xxx, (1994).
19. L.H.D. Jenniskens, J.B.P.A. Wijnberg, and Ae. de Groot, *J. Org. Chem.*, **56**, 6585 (1991).