Tetrahedron Letters,Vol.26,No.51,pp 6377-6380,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

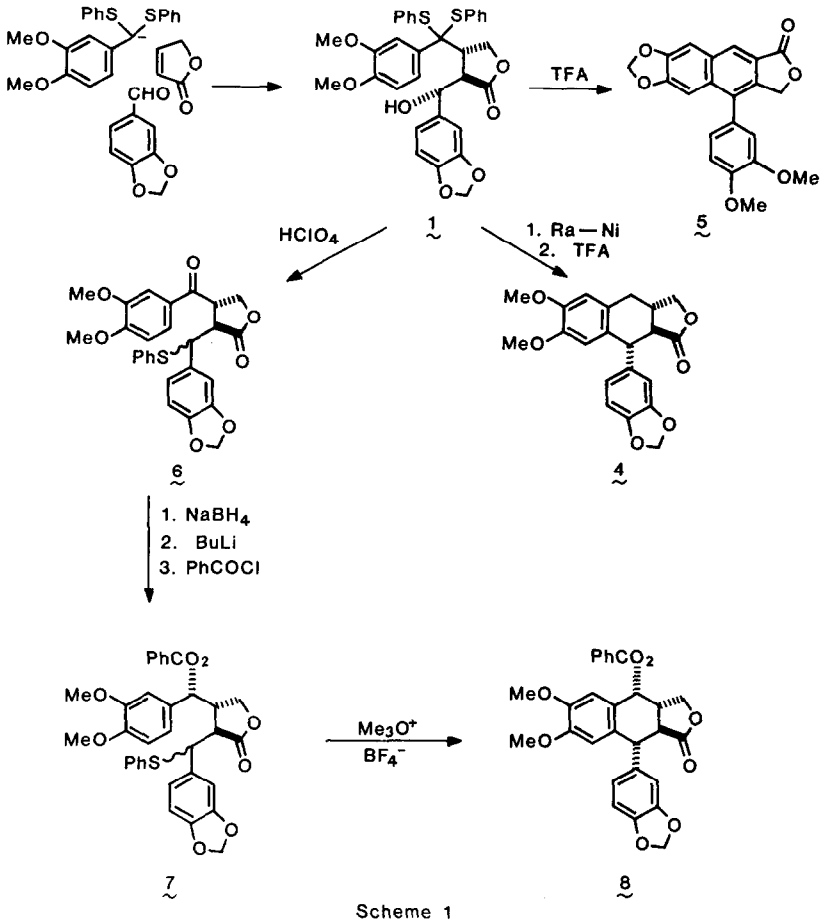
SYNTHESIS OF DEOXYISOPODOPHYLLOTOXIN AND EPIISOPODOPHYLLOTOXIN.

Andrew Pelter,[a*] Robert S. Ward,[a*] Martyn C. Pritchard[a] and I. Trevor Kay.[b]

[a]Chemistry Department, University College of Swansea, Singleton Park, Swansea SA2 8PP.
[b]I.C.I. Plant Protection Division, Jealott's Hill Research Station, Bracknell, Berkshire RG12 6EY.

Abstract. Cyclisation of the tandem conjugate addition products 1-3 by displacement of either the OH or SPh group provides a short efficient synthesis of lignan lactones including compounds of the clinically important podophyllotoxin series.

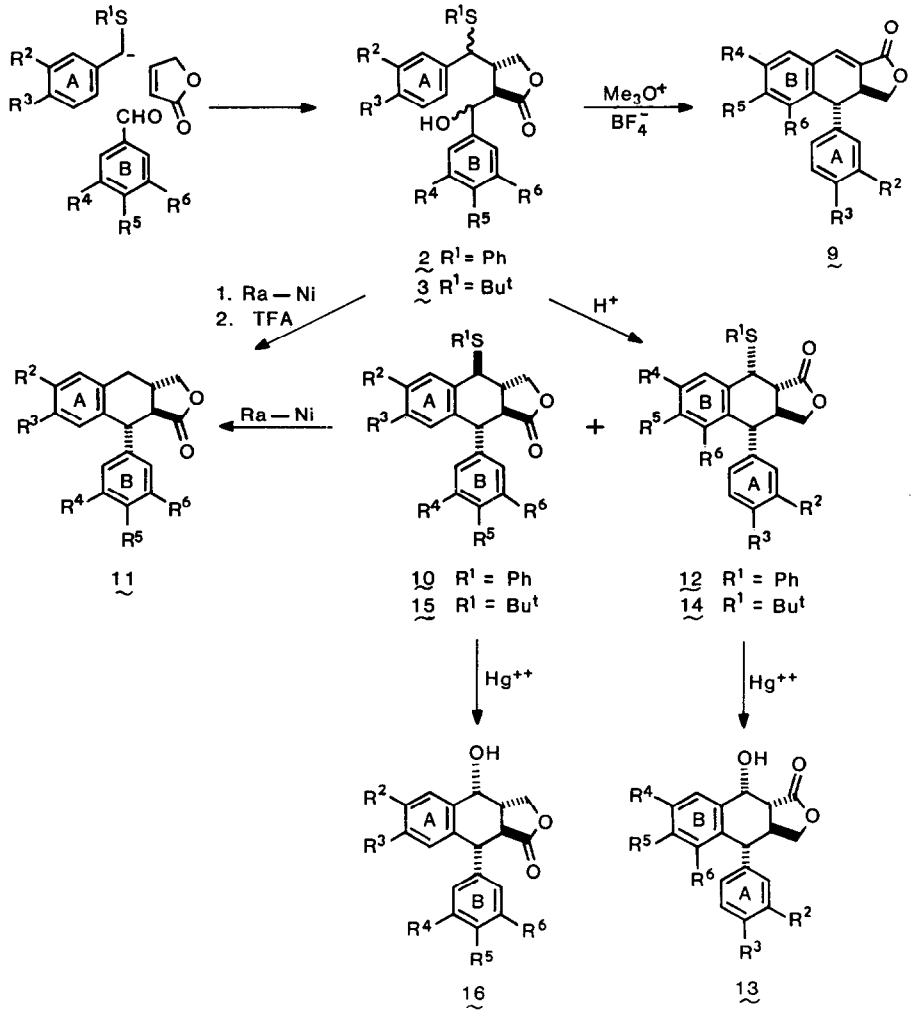
In continuation of our earlier studies[1] on the synthesis of lignan lactones we have now prepared a number of aryltetralin lactones including deoxyisopodophyllotoxin and epiisopodophyllotoxin by cyclisation of the tandem conjugate addition products 1-3. The benzylic alcohols 1-3 are readily prepared by conjugate addition of appropriate sulphur-stabilised carbanions to butenolide followed by trapping of the enolate anions so generated with an aromatic aldehyde.[2] Thus, the erythro isomer 1 (Scheme 1) was obtained in ca. 80% yield by reacting the carbanion derived from 3,4-dimethoxybenzaldehyde bis(phenylthio)acetal with butenolide and then with piperonal. Desulphurisation of 1 with Raney nickel followed by treatment with trifluroacetic acid (TFA) gave the aryltetralin 4 in 50% overall yield. However, treatment of 1 itself with TFA gave retrochinensin 5[4] in 60% yield, indicating that under these conditions the SPh group is the preferred leaving group. In contrast, treatment of 1 with conc. aqueous perchloric acid gave a quantitative yield of two epimeric rearrangement products 6. Direct cyclisation of 6 could not be achieved although after reduction of the deactivating ketone group followed by acylation, cyclisation could be accomplished to give the aryltetralin 8 in 30% yield.



Scheme 1

In an attempt to reduce the ease with which the SPh group was removed from 1 we next prepared the corresponding adducts 2a and 2b containing only one SPh group (Scheme 2). Both 2a and 2b were obtained as a mixture of isomers in 100% and 51% yield respectively. Treatment of 2a with Meerwein's reagent gave the dihydroretrochinensin 9a (40%), while treatment with TFA afforded cyclisation in the alternative manner to give the aryltetralin lactone 10a (61% + 16% of minor isomer), thus realising our objective[1] of inducing cyclisation by displacement of either the OH or SPh group leading selectively to either of the two series of lignan lactones. We believe that this methodology will be general, and will readily give rise to large numbers of similar compounds.

Desulphurisation of 2b followed by treatment with TFA gave deoxyisopodophyllotoxin 11b[5,6] in 60% overall yield. However, treatment of 2b itself with TFA gave only the retro-lactone 12b (58% + 8% of minor isomer), formed by displacement and rearrangement of the SPh group. The difference in the modes of cyclisation of 2a and 2b can be attributed in part to the poor stabilisation afforded to an adjacent carbocation by the 3,4,5-trimethoxyphenyl group, in turn due to the geometric disposition of the 4-methoxyl group.[7,8]



a $R^2 = R^3 = OMe$, $R^4R^5 = OCH_2O$, $R^6 = H$

b $R^2R^3 = OCH_2O$, $R^4 = R^5 = R^6 = OMe$

Scheme 2

Use of perchloric acid on 2b instead of TFA did in fact give a low yield (21%) of the required product 10b, in addition to the retro-lactone 12b. The SPh group of 12b could be readily replaced by OH by treatment with mercuric trifluoroacetate followed by aqueous work-up which gave the alcohol 13b in 62% yield.

Finally, in order to further reduce the leaving group ability of the SR group we prepared the Bu^tS analogue 3b. Treatment of 3b with perchloric acid gave, in addition to the retro-lactone 14b (43%) the required 4-substituted aryltetralin lactone 15b (47%), formed by displacement of the OH group. Treatment of 15b with Raney nickel gave once again deoxyisopodophyllotoxin 11b in quantitative yield, while treatment with mercuric trifluoroacetate gave epiisopodophyllotoxin 16b[9] in 60% yield.

Acknowledgement. We gratefully acknowledge financial support from the S.E.R.C. and Imperial Chemical Industries plc. We also thank Mr. M. R. Kipps (I.C.I. Plant Protection Division) and Dr. I. Sadler (Edinburgh University) for running and assisting with the interpretation of high field ^1H n.m.r. spectra, and Prof. E. Brown for providing a sample of deoxyisopodophyllotoxin for comparison purposes.

References.

1. A.Pelter, R.S.Ward, P.Satyanarayana and P.Collins, J.C.S.Perkin 1, 1983, 643.
2. For other examples of this strategy see R.S.Ward, Chem.Soc.Rev., 1982, 11, 102-6.
3. P.A.Ganeshpure and R.Stevenson, J.C.S.Perkin 1, 1981, 1681.
4. S.Ghosal and S.Banerjee, J.C.S.Chem.Comm., 1979, 165.
5. M.Kuhn and A. Von Wartburg, Helv.Chim.Acta, 1967, 50, 1546.
6. J.P.Robin, R.Dhal and E.Brown, Tetrahedron, 1982, 38, 3667.
7. W.J.Gensler, C.M.Samour, S.Y.Wang and F.Johnson, J.Am.Chem.Soc., 1960, 82, 1714.
8. W.S.Murphy and S.Wattanasin, J.C.S.Perkin 1, 1982, 271.
9. M.B.Glinski and T.Durst, Canad.J.Chem., 1983, 61, 573.

(Received in UK 4 October 1985)