Tetrahedron Letters,Vol.25,No.10,pp 1099-1102,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF (±)-PHASEOLLIN; A PROTECTIVE SEQUENCE FOR CHROMEN DOUBLE BONDS

by Phillip Thomas and Donald A. Whiting*

(Chemistry Department, The University, Nottingham, NG7 2RD).

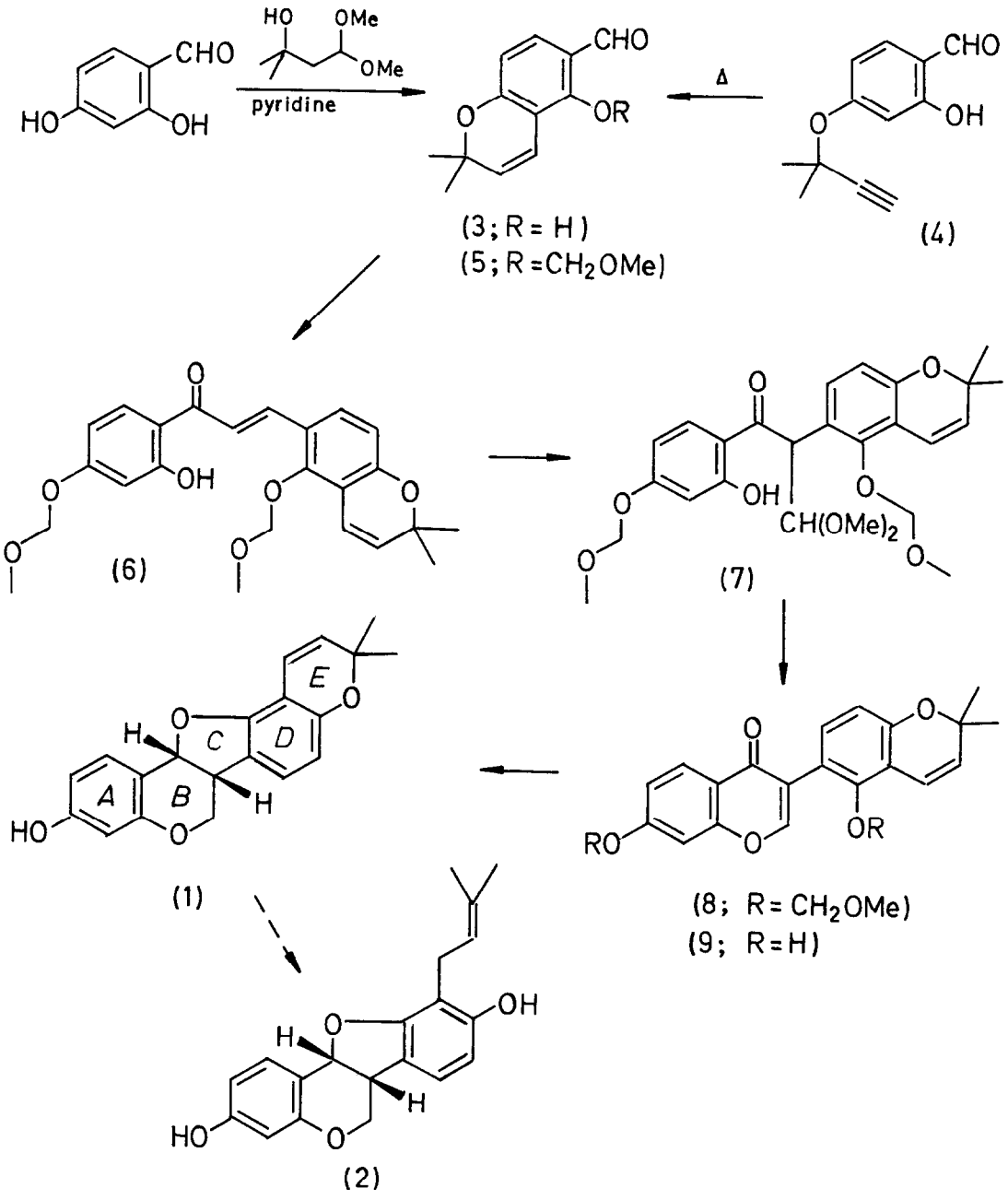
Summary (±)-Phaseollin, an important phytoalexin,has been synthesised, using as key step thallium III induced rearrangement of chromenochalcone (6) and proceeding via (8). The chromene double bond can be efficiently protected from thalliation by regioselective radical addition of thiophenol. An alternative route to phaseollin is given, through (12) → (14) → (1), with regeneration of the double bond by pyrolysis of the sulphoxide of (15).

Phaseollin (1) is a metabolite formed in response to fungal infection by certain members of the Leguminosae, and one of the first phytoalexins to be characterised.[1] It displays noteworthy antifungal[1c,2] antibacterial[2], and antiyeast[3] activities with MIC < 50 μg cm^{-3} for various microganisms. Phaseollidin[4] (2) was first found to occur with phaseollin in beans, and is also biologically active. Surprisingly, no synthesis of phaseollin has been reported, possibly since difficulties might be expected in applying available methodology to this compound.

Three efficient routes to the pterocarpan ring system cf. (1;A-D) are recognised, (i) annelation of chromens using o-hydroxy arylmercuric salts[5], (ii) via isoflavones, approached from deoxybenzoins, and (iii) via isoflavones, approached from chalcones[6]. In selecting a route to (1) it seemed preferable to introduce the dimethylchromen ring (E) at an early stage, to avoid problems of regioselectivity. In that case route (i) is not applicable since a mercurated chromen would presumably react with itself, and route (ii) employs deoxybenzoins, most readily prepared under acidic conditions which chromens do not survive. Route (iii) requires thallium (III) induced rearrangement of a chalcone e.g. (6). However thallium (III) nitrate reacts with chromen double bonds,[7,8a] leading to ring contraction and/or alkoxylation; a chromenochalcone has been successfully converted with thallic nitrate to a chromenoisoflavone in only few cases, with yields 55%[8b], 28%[8b], 33%[8b], 7%[8a] and unreported.[9]

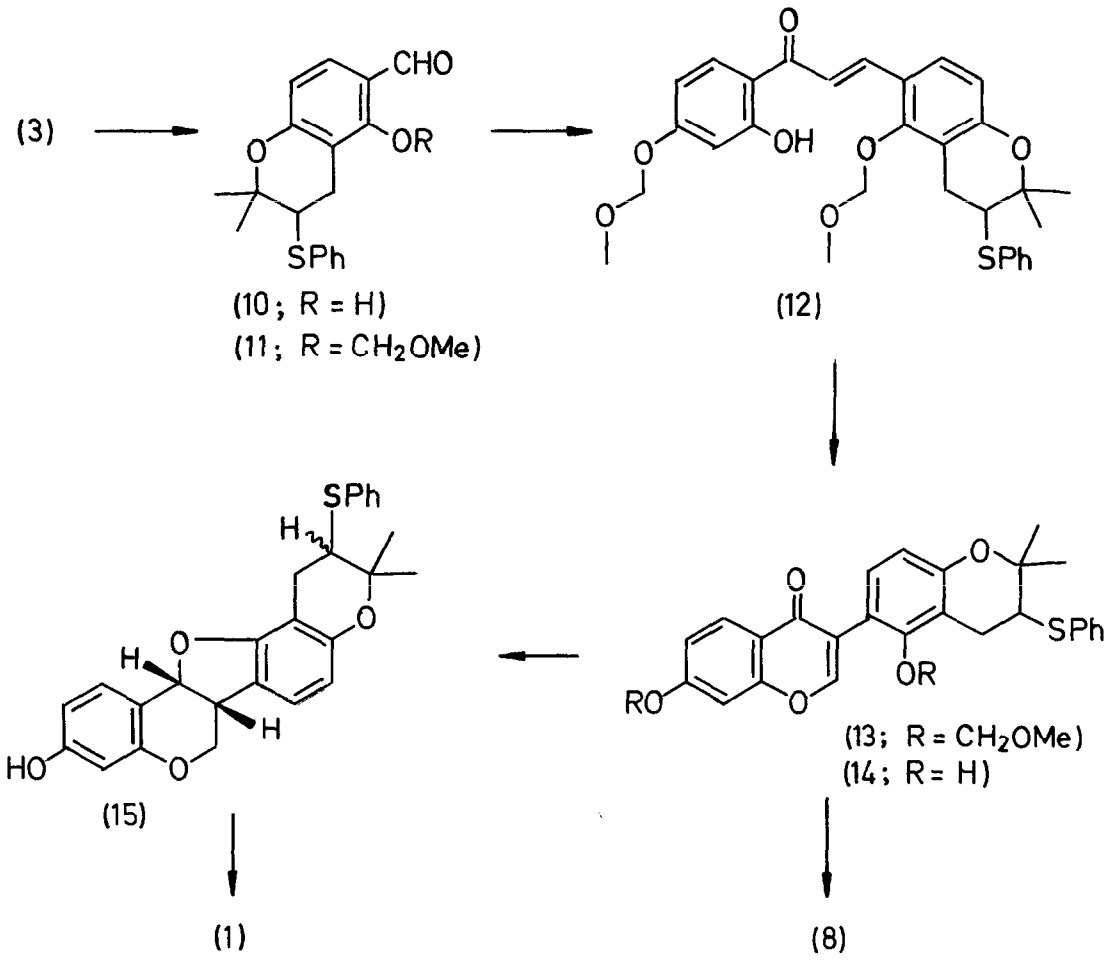
We set out to prepare chalcone (6) and examine the feasibility of its rearrangement to isoflavone (8); at the same time we aimed to develop a chalcone with a structural moiety which would be insensitive to thallium(III) oxidation and from which both a dimethylchromen and an o-3,3-dimethylbut-2-enyl unit could be generated.[10] We report here the synthesis of (±)-phaseollin, through both approaches.

2,4-Dihydroxybenzaldehyde was treated (Scheme 1) with 1,1-dimethoxy-3-



Scheme 1

hydroxy-3-methylbutane[11] in hot pyridine to form the formyl 2,2-dimethylchromen (3) regiospecifically. The propargyl ether (4) also gave (3) on heating, but formation of ether (4) from 2,4-dihydroxybenzaldehyde was inefficient. The methoxymethyl ether (5) was then condensed in base with the



Scheme 2

monomethoxymethyl ether of resacetophenone to provide the required chalcone (6). The oxidative rearrangement of chalcone (6) was executed with thallium (III) nitrate in methanol, and yielded acetal (7) in 23% yield (34% based on chalcone converted). Careful monitoring of the reaction was necessary. Treatment of acetal (7) with sodium methoxide gave isoflavone (8); deprotection to (9) was followed by reduction with sodium borohydride; ring C closed on acidification to yield (±)-phaseollin (1), 30% from (7), spectroscopically and chromatographically indistinguishable from a natural specimen.

Thus chalcone (6) reacts preferentially with thallium nitrate at the electron deficient double bond, but material is presumably lost in competitive reactions with the chromen double bond. To prevent such side reactions, chromen (3) was irradiated in the presence of thiophenol and diphenyldisulphide to yield the 3-phenylthiochroman (10), (63%), in a regiospecific manner (Scheme 2). The methoxymethyl derivative (11) was condensed with the

appropriate resacetophenone to provide chalcone (12). Thallium nitrate smoothly effected rearrangement of this chalcone to the corresponding acetal (53%), which was cyclised (83%) using methoxide to isoflavone (13). Deprotection, borohydride reduction and acid treatment completed the synthesis of pterocarpan (15), 33% from (13). The phaseollin target could be reached by oxidation of (13) to the corresponding sulphoxide (m-chloroperbenzoic acid); thermolysis (82%) in refluxing toluene then leads back into the route of Scheme 1 through isoflavone (8). Oxidation of (15) to sulphoxide level, and pyrolysis of the product, gives an alternative route to phaseollin. Since phaseollidin (2) has been prepared by lithium-ammonia reduction[12] of natural phaseollin, a synthetic route to (+)-phaseollidin is also opened.

References

1. (a) I.A.M. Cruickshank and D.R. Perrin. Life Sci., 1963, 2, 650; (b) D.R. Perrin, Tetrahedron Lett., 1964, 29; (c) J.L. Ingham in 'Phytoalexins', ed. J.A. Bailey and J.W. Mansfield, Blackie and Son Ltd., 1982, p.54.
2. (a) D.A. Smith in ref.1(c), p.218; (b) S.S. Gnanamanickam and J.W. Mansfield, Phytochem., 1981, 20, 997.
3. K. Nakanishi, J.Nat.Prod., 1982, 45, 15.
4. D.R. Perrin, C.P. Whittle, and T.J. Batterham, Tetrahedron Lett., 1972, 1673.
5. N. Inoue and H. Horino, J.Chem.Soc., Chem.Commun., 1976, 500.
6. (a) A. McKillop, B.P. Swann, and E.C. Taylor, Tetrahedron Lett., 1970, 5281; (b) L. Farkas, A. Gottsegen, M. Nógrádi, and S. Antus, J.Chem.Soc., Chem. Commun., 1972, 825; J.Chem.Soc., Perkin Trans.1, 1974, 305; (c) A. McKillop, Pure Appl.Chem., 1972, 43, 463.
7. M.J. Begley, S.E. Mohamed, N.A.R. Hatam, F. DeSouza, and D.A. Whiting, J.Chem.Soc., Perkin Trans.1, 1983, 883.
8. (a) S. Antus, A. Gottsegen, M. Nógrádi, and A. Gergely, Chem.Ber., 1979, 112, 3879; (b) S. Antus, L. Farkas, A. Gottsegen, Z. Kardos-Balogh, and M. Nógrádi, Chem.Ber., 1976, 109, 3811.
9. A. Gottsegen, S. Antus, P. Kolonits, M. Nógrádi, A. Lupi, G.D. Monache, M. Marta, and G.B.M. Bettolo, Gazz.Chim.Ital., 1981, 111, 121.
10. S.E. Mohamed, P. Thomas, and D.A. Whiting, J.Chem.Soc., Chem.Commun., 1983, 738.
11. (a) W.M. Bandaranayake, L. Crombie, and D.A. Whiting, J.Chem.Soc.(C), 1971, 811; (b) D.G. Clarke, L. Crombie, and D.A. Whiting, J.Chem.Soc., Perkin Trans.1., 1974, 1007.
12. P.M. Dewick and M.J. Steele, Phytochem., 1982, 21, 1599.

(Received in UK 16 January 1984)