Tetrahedron Letters No. 26, pp 2335 - 2338, 1978. 0040-4039/78/0622-2335$02.00/0
© Pergamon Press Ltd. Printed in Great Britain.

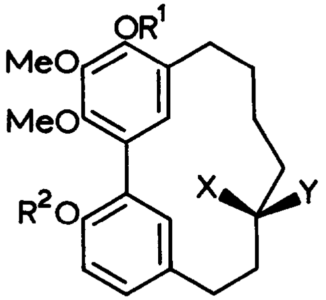
CYCLISATION OF 1,7-DIARYLHEPTANOIDS THROUGH OXIDATIVE, REDUCTIVE, AND PHOTOCHEMICAL RADICAL PROCESSES: TOTAL SYNTHESES OF THE m,m-BRIDGED BIARYLS MYRICANONE AND (±)-MYRICANOL, AND A RELATED DIARYL ETHER.

Donald A. Whiting* and Andrew F. Wood

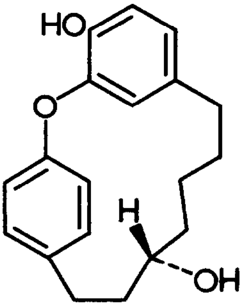
Chemistry Department, The University,
Nottingham, NG7 2RD.

(Received in UK 12 April 1978; accepted for publication 4 May 1978)

m,*m*-Bridged biaryls are rare in Nature, only four sources (higher plants) being known to us: *Ostrya japonica*[1] (asadanin and relatives), *Alnus japonica*[2] (alnusone and relatives), *Myrica gale*[3] (porson) and *Myrica nagi*[4] {the insect repellent myricanol (1a;R^1=R^2=H) and myricanone (1c;R^1=R^2=H)}. Biogenesis of these compounds plausibly involves *C*-*C* coupling of a 1,7-diarylheptanoid precursor,[2b,5] a number of which are known in Nature: the possibility of alternative *C*-*O* coupling has been recently indicated by the isolation of the diarylethers acerogenin A (2)[6] and galeon[7]. In the present work we set out to investigate the aryl-aryl cyclisation of appropriate 1,7-diarylheptanoids, with a view to synthesise the natural phenols (1a) and (1c). The required precursors, general type (5), were constructed by standard methods; thus the keto-acid (3), from the reaction of 1,2,3-trimethoxybenzene with succinic anhydride and aluminium chloride (condensation and *O*-demethylation) was converted to the 4-arylbutylbromide (4,R=$PhCH_2$). This bromide was used in a Grignard reaction (activated magnesium[8] was required) with *p*-benzyloxydihydrocinnamaldehyde to yield (5a;R^1=$PhCH_2$, R^2=R^3=H), readily oxidised to the corresponding ketone. The free phenols 5a and 5c (both R^1=R^2=R^3=H) were treated with various 1- and 2-electron oxidants; the cleanest reaction was observed with thallium (III) tris-trifluoroacetate which afforded, from (5c;R^1=R^2=R^3=H), a new ketone isomeric with myricanone (1c;R^1=R^2=H) for which structure (6) was indicated by ^{1}H.m.r. *C*-*O* Coupling was apparent from the presence of one O*H* and five Ar-*H* protons, comprising an AA'BB' system, and a single Ar-*H* at unusually high field, δ5.46; such a proton, inside the large ring and shielded by the neighbouring aryl, is characteristic of such ethers (*cf*. galeon[7], δ5.35, and acerogenin A (2), δ5.65). The electron impact fragmentation accords with



(1)

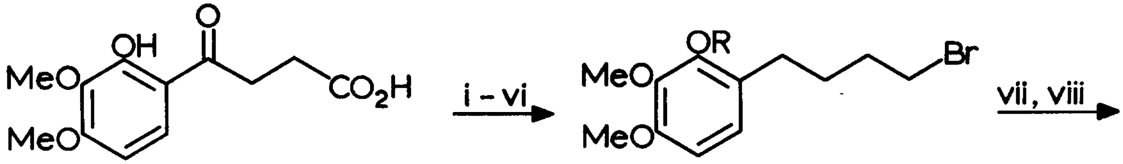


(2)

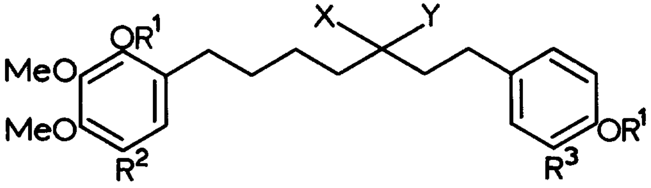
this formulation. Compound (6), a 14-oxa-[7,1]-metaparacyclophane, is the first example to be prepared synthetically, and the method should provide synthetic access to the naturally-occurring analogues.

Since no products of C-C coupling were observed in oxidations, attention was turned to other ways of generating intermediates with radical character. Selective bromination of (5c;R^1=PhCH$_2$, R^2=R^3=H) gave the monobromide (5c;R^1=PhCH$_2$, R^2=Br, R^3=H); irradiation of the latter with 254nm light, in alkaline medium gave dibenzylmyricanone (1c;R^1=R^2=PhCH$_2$) (ca. 10%), identified by comparison with an authentic sample. Debenzylation yielded myricanone, thus completing a synthesis of the natural biphenyl. The photochemical process also provided a monobenzylmyricanone (1c;R^1,R^2=H,PhCH$_2$), photochemical benzyl ether cleavage having occurred. The acetate (5b;R^1=PhCH$_2$, R^2=Br, R^3=H) behaved similarly on irradiation.

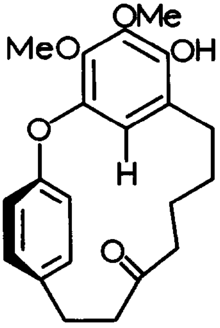
In another approach the bisiodides (5b,c; both R^1=PhCH$_2$, R^2= R^3 =I) were prepared in good yield by direct iodination of the appropriate diarylheptanoid, using iodine-silver trifluoroacetate. Treatment of either bisiodide with tetrakis (triphenylphosphine) Ni(O),[9] or tris(triphenylphosphine) Ni(O) generated in situ,[10] gave the corresponding biphenyls (±)-(1b;R^1=R^2=PhCH$_2$) and (1c;R^1=R^2=PhCH$_2$) authenticated by comparison with samples prepared from natural



(3) (4)



(5)



(6)

(a) $X = OH$, $Y = H$

(b) $X = OAc$, $Y = H$

(c) $X,Y = O=$

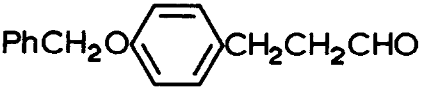
(i) Me_2SO_4, ^-OH; (ii) Pd, H^+

(iii) $PhCH_2Cl$, K_2CO_3; (iv) $LiAlH_4$

(v) TsCl; (vi) NaBr, Me_2CO

(vii) Mg(from $MgCl_2$, K), KI, THF

(viii)



myricanone. Removal of the protecting acetyl and benzyl functions as applicable then afforded (±)-myricanol and myricanone. Yields in the coupling stage were low (<u>ca</u>.10%), and de-iodinated diarylheptanoids were also recovered; this reflects the strain in the product (1a;$R^1=R^2=H$, contains a bent biphenyl unit[4]), and the crowding at the coupling sites. Better yields were obtained in the synthesis of alnusone[9] using a Ni(0) reagent (reported during progress of this work), but alnusone contains three sp^2 carbons in the heptane chain, reducing both angle strain and H-H steric interactions inside the ring, and has only unbuttressed *ortho*-functions adjacent to the biphenyl linkage.

References

1. M. Yasue, *J. Japan Wood Research Soc*., 1965, *11*, 146, 153, 202; M. Yasue and H. Imamura, *ibid*., 1966, *12*, 226, 231.
2. (a) M. Notnura, T. Tokoroyama, and T. Kubota, *J.C.S. Chem. Comm*., 1974, 65; (b) M. Notura and T. Tokoroyama, *ibid*., 1975, 316.
3. T. Anthonsen, G.B. Lorentzen, and K.E. Malterud, *Acta Chem. Scand*., 1975 *B29*, 529.
4. M.J. Begley, R.V.M. Campbell, L. Crombie, B. Tuck, and D.A. Whiting, *J. Chem. Soc., (C)*, 1971, 3634.
5. P.J. Roughley and D.A. Whiting, *J. Chem. Soc. Perkin I*, 1973, 2379.
6. M. Nagai, K. Kubo, M. Fujita, T. Inoue, and M. Matsuo, *J.C.S. Chem. Comm*., 1976, 338.
7. K.E. Malterud, T. Anthonsen, and J. Hjortas, *Tetrahedron Letters*, 1976, 3069.
8. R.D. Rieke and S.F. Bales, *J.C.S. Chem. Comm*., 1973, 879.
9. M.F. Semmelhack and L.S. Ryono, *J. Amer. Chem. Soc*., 1975, *97*, 3873.
10. A.S. Kende, L.S. Liebeskind and D.M. Braitach, *Tetrahedron Letters*, 1975, 3375.