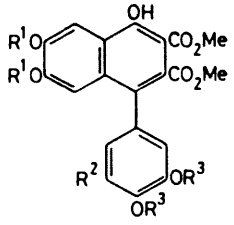
A Regiocontrolled Synthesis of Some Arylnaphthalide Lignans

By S. OSMUND DE SILVA, CAROLE ST. DENIS, and RUSSELL RODRIGO*

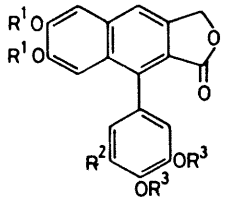
(Guelph-Waterloo Centre for Graduate Work in Chemistry, Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3GI)

Summary Three arylnaphthalide ligands are synthesised by regiocontrolled transformations of Diels–Alder adducts generated from dimethyl acetylenedicarboxylate and suitable isobenzofurans.

WE have recently described[1] a simple three-step procedure for the synthesis of several 4-hydroxy-1-arylnaphthalide lignans. Regioselective reduction of the 3-ester unit in the intermediate diester (**1**) was achieved in that instance by the use of borane, and attributed to prior reaction of the reagent with the 4-hydroxy-group. Many natural aryl-naphthalide lignans do not contain a 4-hydroxy-substituent however, and the lack of methods for regiocontrolled generation of each of the two possible phthalides (peri-methylene and pericarbonyl)[2] has been a perennial problem.[2] We now provide a general solution to part of this problem and illustrate it with a synthesis of three naphthalide lignans of the perimethylene type (**2a**—**c**).



(1)



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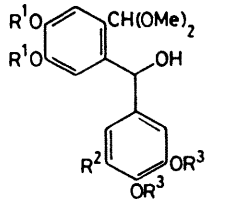
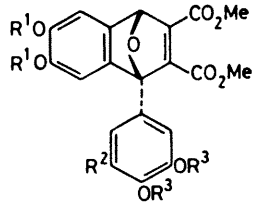
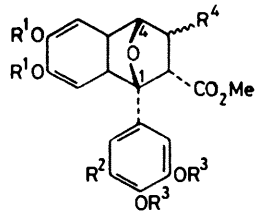


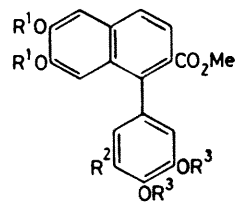
(3)



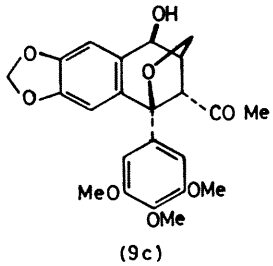
(4)



(5) R^4 = α-CO_2Me
(6) R^4 = β-CO_2Me
(7) R^4 = β-CH_2OH



(8)



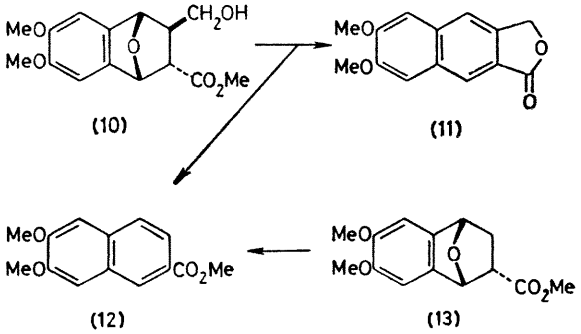
(9c)

a, R^1 = Me, R^2 = H, R^3R^3 = $-CH_2-$
b, R^1R^1 = R^3R^3 = $-CH_2-$, R^2 = H
c, R^1R^1 = $-CH_2-$, R^2 = OMe, R^3 = Me

The hydroxyacetal[1] (**3a**) upon brief treatment on a steam bath with an excess of acetylene dicarboxylate and a catalytic quantity of glacial acetic acid was converted into the bicyclo-adduct (**4a**) [64%, m.p. 182—183 °C, δ 3.72, 3.78, 3.85, 3.88 (s, 3H each), 6.02 (s, 3H, $-OCH_2O-$ and 4-H), and 6.72—7.30 (m, 5H), M^+ 440, ν($CHCl_3$) 1725 cm^{-1}] Catalytic hydrogenation (Pd/C, ethyl acetate, 50 lb in^{-2}) produced the *endo*-ester (**5a**) virtually quantitatively [m.p. 189 °C, δ 3.50, 3.52, 3.77, 3.84 (s, 3H each), 3.7—3.9 (2H, overlapped by OMe signals), 5.52 (d, 1H, $J_{3,4}$ 4.0 Hz), 5.98 (s, 2H), and 6.6—7.5 (m, 5H), M^+ 442, ν($CHCl_3$) 1735 cm^{-1}] which was selectively epimerised at C-3 when heated under reflux with sodium acetate in dry methanol[3] to yield (90%) the *trans*-ester (**6a**) as a foam which resisted crystallisation [δ 3.22, (d, 1H, 3-H, $J_{2,3}$ 4.5 Hz), 3.46, 3.77, 3.80, 3.90 (s, 3H each), 4.19 (d, 1H, 2-H, $J_{2,3}$ 4.5 Hz), 5.68 (s, 1H), 6.00 (s, 2H), 6.57 (s, 1H), and 6.8—7.4 (m, 4H), M^+ 442, ν($CHCl_3$) 1735 cm^{-1}] The appearance of the bridgehead proton (4-H) now as a singlet and the shift of one ester methoxy-signal downfield to δ 3.77 identified the site of epimerisation (C-3). Our investigations thus far of this remarkably selective process seem to suggest that prolonged treatment with sodium acetate–methanol might well provide the 2-epimer instead as the thermodynamic product in some bicyclo-systems and thereby delineate an unambiguous route to the pericarbonyl lactones.

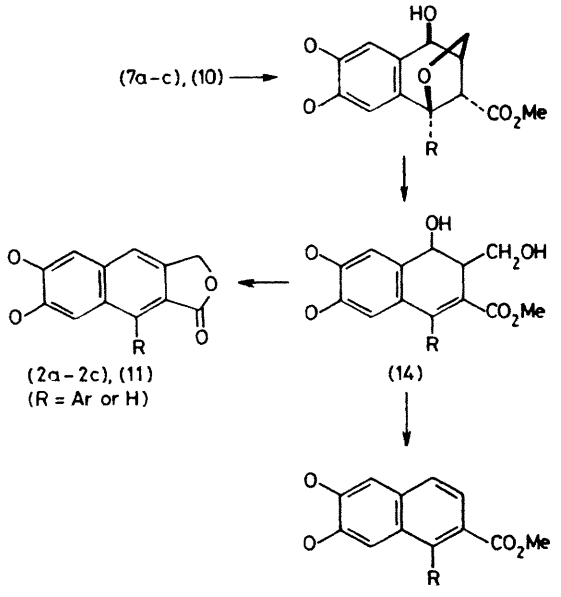
Regiospecific reduction of the *exo*-ester unit at C-3 was accomplished with lithium triethylborohydride in dry tetrahydrofuran to provide the crystalline alcohol (**7a**) [78%, m.p. 133 °C, δ 1.33 (t, 1H, exchanges with D_2O), 2.45 (t of d, 1H, $J_{2,3}$ 4, $J_{3,3a}$ 7.0 Hz), 3.50, 3·78, 3.92 (s, 3H each), 3.7—4.0 (m, 2H, overlapped by OMe signals), 5.28 (s, 1H), 6.00 (s, 2H), and 6.60—7.27 (m, 5H), M^+ 414, ν($CHCl_3$) 3500br and 1735 cm^{-1}] Aromatisation and lactonisation of (**7a**) (trifluoroacetic acid–methylene chloride, room temperature) produced a quantitative yield of two products in equal proportions. After separation by chromatography (silica) the slower-running component was identified as justicidin B (**2a**) by comparison of its properties with published data.[4] Taiwanin C[5] (**2b**) and dehydroanhydropicropodophyllin[6] (**2c**) were prepared similarly through intermediates (**3b**)—(**7b**) and (**3c**)—(**7c**), respectively. In every instance the second-faster-running component (**8a**—**c**) was found as a co-product of the final step.

The precursor (**7c**) was used to study the formation of this product (**8c**) [m.p. 168 °C, δ 3.63 (s, 3H), 3.83 (s, 3H), 3.95 (s, 6H), 6.03 (s, 2H), 6.50 (s, 2H), 6.95 (s, 1H), 7.16 (s, 1H), and 7.73 (2H, collapsed AB, J 8.5 Hz), ν($CHCl_3$) 1725 cm^{-1}]



(10) (11) (12) (13)

SCHEME 1



SCHEME 2

and to elucidate its structure in the following manner. When the reaction was followed by t.l.c. the initial formation of a third compound was revealed. This compound was isolated and identified[7] as the methyleneoxy-bridged isomer (**9c**) which was in turn converted into (**7c**) and (**8c**) with acid. Furthermore, the C-3a dideuterio analogue of (**7c**) when aromatised similarly with acid provided the doubly deuteriated phthalide (**2**), (**8c**) containing no deuterium, and formaldehyde.[8] Conclusive evidence for structures (**8a**—**c**) was obtained by repeating the reaction with a 1-de-aryl system (**10**) prepared similarly from the corresponding *trans*-ester.[9] Again two products, (**11**) and (**12**), were obtained and the latter was identical with a sample prepared independently from the bridged ester (**13**)[9] (Scheme 1).

Thus the acid-catalysed aromatisation of the bridged intermediates (**7a**—**c**) and (**10**) may be rationalised as in Scheme 2 with products (**8a**—**c**) and (**12**) arising from the cleavage of a 1,3-diol intermediate (**14**), a process not entirely without precedent.[10]

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