A Common Synthetic Route to the Pericarbonyl and Perimethylene Lignan Lactones Dimethyl Conidendrin and Dimethyl Retrodendrin

Ajay Gupta and Russell Rodrigo*

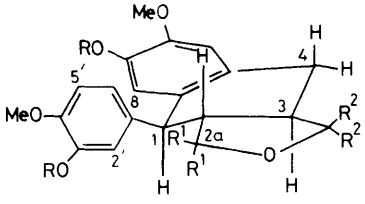
Guelph Waterloo Centre for Graduate Work in Chemistry, Department of Chemistry, University of Waterloo, Waterloo, Ontario N2L 3G1, Canada

An all *trans* 1-aryl-2-methoxycarbonyl tetralin-3-carboxylic acid synthesised in 32% overall yield can be converted, at will, to either dimethyl conidendrin or dimethyl retrodendrin in one step.

The 1-aryl tetralin lignan lactones, as well as their aromatic aryl naphthalide counterparts, occur naturally as the pericarbonyl (lactone carbonyl group vicinal to C-3) and perimethylene (lactone methylene group vicinal to C-3) variants.[1] The latter are more abundant, but α-conidendrin (**1**), the only pericarbonyl tetraline lactone, is well known[2] and widely distributed in nature. More recently, many lignan acetals related to (**1**) have also been isolated.[3] The control of relative stereochemistry in the synthesis of the antimitotic perimethylene lactone podophyllotoxin (**2**), has received much attention[4] and although α-conidendrin has been recently synthesised,[5] an efficient means of producing each regiochemical type of lactone, at will, from a single intermediate is a worthwhile objective that has not yet been achieved. Our interest in stereo- and regio-controlled lignan synthesis employing isobenzofurans *in situ*[6] has led to a rational solution of the problem and we illustrate it here with efficient syntheses of dimethyl α-conidendrin (**3**) (25%) and dimethyl retrodendrin (**4**) (24%).

The isobenzofuran precursor (**5**) was prepared in the usual way[7] from 6-bromoveratraldehyde dimethyl acetal and veratraldehyde (3,4-dimethoxybenzaldehyde). Treatment of (**5**) with dimethyl acetylene dicarboxylate and acetic acid on a steam bath for 0.5 h gave the crystalline adduct (**6**) of the isobenzofuran (**7**), in 74% yield (after recycling[7] the starting material in the mother liquor). Hydrogenation [Pd/charcoal, ethyl acetate, 50 psi (1 psi ≈ 6.9×10^3 Pa)] produced (**8**) (83% yield, m.p. 144—145 °C).

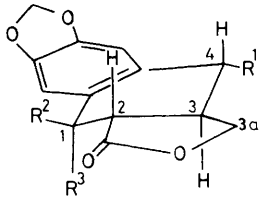
The bridging oxygen atom of (**8**) was removed by a two step procedure; first by hydrogenolysis with freshly prepared W-2 Raney Nickel to give (**9**) (m.p. 192—194 °C, 80%) with retention of stereochemistry at C-1 as expected,[6] and then by a second hydrogenolysis of the C-4 benzylic alcohol function as its trifluoroacetate (generated *in situ*[8]) to provide the all *cis*-tetralin diester (**10**) (m.p. 149—150 °C, 95% yield). The coupling constants of (**9**) ($J_{1,2}$ 6.0, $J_{2,3}$ 3.9, $J_{3,4}$ 13.5 Hz) compare very well[9] with those of a similar tetralin (**11**) as do the signals of H-8 at δ 6.38 and the high field C-2 axial ester methyl group at δ 3.32. The all *cis* deoxygenated product (**10**) ($J_{1,2}$ 6.2, $J_{2,3}$ 3.5 Hz, H-8 at 6.42 and C-2 CO_2Me at δ 3.33 was also much like (**12**), an intermediate in the synthesis of the lignan Lirionol;[9] these features define the 1,3-diequatorial-2-



(**1**) R = R^1 = H, R^2 + R^2 = O

(**3**) R = Me, R^1 = H, R^2 + R^2 = O

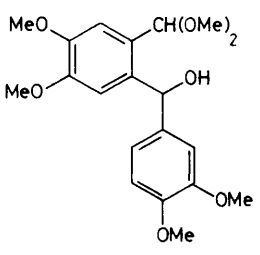
(**4**) R = Me, R^1 + R^1 = O, R^2 = H



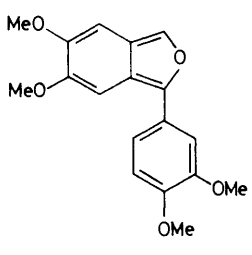
(**2**) R^1 = OH, R^2 = H, R^3 = Ar

(**16**) R^1 = H, R^2 = Ar, R^3 = H

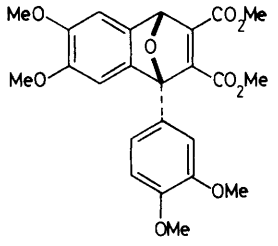
Ar = 3,4,5-Trimethoxyphenyl



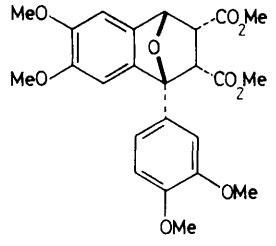
(**5**)



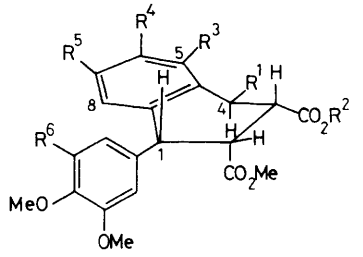
(**7**)



(**6**)



(**8**)



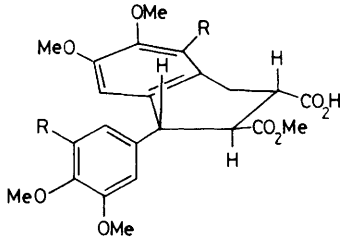
(**9**) R^1 = OH, R^2 = Me, R^3 = R^6 = H, R^4 = R^5 = OMe

(**10**) R^1 = R^3 = R^6 = H, R^2 = Me, R^4 = R^5 = OMe

(**11**) R^1 = OH, R^2 = Me, R^3 = H, R^4 + R^5 = OCH_2O, R^6 = OMe

(**12**) R^1 = H, R^2 = Me, R^3 = R^4 = R^5 = R^6 = OMe

(**13**) R^1 = R^2 = R^3 = R^6 = H, R^4 = R^5 = OMe



(**14**) R = H

(**15**) R = OMe

axial conformation of (**10**). Selective hydrolysis of the C-3 equatorial ester of (**10**) with dilute aqueous hydrochloric acid gave the expected acid (**13**) (m.p. 151—153 °C, 77% yield) with identical coupling constants and signals at 6.41 (H-8) and δ 3.36 (C2-CO_2Me). Epimerisation of the C-2 axial ester of this compound with methoxide in methanol produced the required all *trans*, all equatorial tetralin (**14**) (m.p. 176—178 °C, 95% yield, $J_{1,2}$ 11.0, $J_{2,3}$ 10.9, $J_{3,4ax}$ 11.9, $J_{3,4eq}$ 5.3 Hz) whose spectrum resembled[9] the ^{1}H n.m.r. spectral properties of (**15**) very closely.

This final synthetic intermediate (**14**), produced in seven steps and 32% overall yield from 6-bromoveratraldehyde dimethyl acetal with complete control of relative stereochemistry at C-1, C-2, and C-3, is also suitably differentiated at C-2 (ester) and C-3 (acid) for the production of either the pericarbonyl (**3**) or perimethylene (**4**) lignan lactones at will.

Selective reduction of its C-2 ester group with lithium triethylborohydride, [4 equiv. tetrahydrofuran (THF), 0 °C, 2 h] followed by acidic work-up gave (±) dimethyl-α-conidendrin (**3**) (m.p. 166—168 °C, 77% yield) uncontaminated by the regioisomer (**4**). The dideuteriated analogue was also prepared using lithium triethylborodeuteride and was useful in the complete assignment of its ^{1}H n.m.r. spectrum.[3a]†

Reduction of the C-3 acid function of (**14**) on the other hand, was accomplished with borane–dimethyl sulphide in THF over 10 h (0—25 °C). The mixture was diluted with a little water and refluxed for 36 h with 3 drops of methane sulphonic acid to provide (±) dimethyl retrodendrin (**4**) (m.p. 187—189 °C, 74%) uncontaminated by any dimethyl conidendrin (**3**). The ^{1}H n.m.r. spectrum of (**4**) was very similar[7]‡ to that of (±) isodeoxypodophyllotoxin (**16**) and strikingly different from (**3**) in the absorption of the equatorial proton of the lactone methylene group [δ 4.22 in (**3**) but δ 4.51 in (**4**)]. The difference is a measure of shielding of this proton by the equatorial C-1 aryl group of (**3**).§

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† *Selected spectroscopic data* for (**3**); $\nu_{C=O}$ (KBr) 1775 cm^{-1}; *m/z* 384 (100, M^+), 269 (22, $M^+ - C_4H_4O_2$-OMe), δ (500 MHz, $CDCl_3$): 2.53 (m, 1H, H-2), 2.60 (m, 1H, H-3), 3.0 (dd, 1H, H-$4_{ax.}$), 3.22 (dd, 1H, H-4_{eq}), 3.60, 3.81, 3.89, 3.90 (s, 3H each, 4 × OMe), 3.93 (d, 1H, H-1), 4.04 (dd, 1H, H-$2a_{ax}$), 4.22 (dd, 1H, H-$2a_{eq}$), 6.32 (s, 1H, H-8), 6.57 (d, 1H, H-2′), 6.69 (s, 1H, H-5), 6.73 (dd, 1H, H-6′), 6.84 (d, 1H, H-5′): $J_{1,2}$ 10.56; $J_{2,3}$ 13.5; $J_{2,2a\ ax}$ 10.5; $J_{2,2a\ eq}$ 6.6; $J_{2a\ gem}$ 8.8; $J_{3,4ax}$ 11.7; $J_{3,4\ eq}$ 5.03; $J_{4\ gem}$ 16.1; $J_{5',6'}$ 8.2; $J_{2',6'}$ 1.8 Hz.

‡ *Selected spectroscopic data* for (**4**); $\nu_{C=O}$ (KBr) 1759 cm^{-1}; *m/z* 384 (100, M^+), 269 (13, $M^+ - C_4H_4O_2$-OMe), δ (500 MHz, $CDCl_3$): 2.48 (dd, 1H, H-2), 2.61 (m, 1H, H-3), 2.91 (dd, 1H, H-4_{ax}), 2.98 (dd, 1H, H-4_{eq}), 3.58, 3.81, 3.85, 3.86 (s, 3H each, 4 × OMe), 3.97 (dd, 1H, H-$3a_{ax}$), 4.10 (d, 1H, H-1), 4.51 (dd, 1H, H-$3a_{eq}$), 6.32 (s, 1H, H-8), 6.60 (s, 1H, H-5), 6.70 (d, 1H, H-2′), 6.77 (dd, 1H, H-6′), 6.81 (d, 1H, H-5′): $J_{1,2}$ 11.2; $J_{2,3}$ 13.6; $J_{3,3a\ ax}$ 10.6; $J_{3,3a\ eq}$ 6.7; $J_{3a\ gem}$ 8.6; $J_{3,4ax}$ 11.0; $J_{3,4eq}$ 4.9; $J_{4\ gem}$ 15.5; $J_{5',6'}$ 8.2; $J_{2',6'}$ 1.5 Hz.

§ Satisfactory analytical and spectral data were obtained for all compounds in this study. Full details will be published later.