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SYNTHESIS OF LIGNAN ARYLDIHYDRONAPHTHALENE LACTONES BY CYCLIZATION OF CINNAMYL ARYLPROPIOLATE ESTERS: REVISED STRUCTURE OF β-APOPOLYGAMATIN

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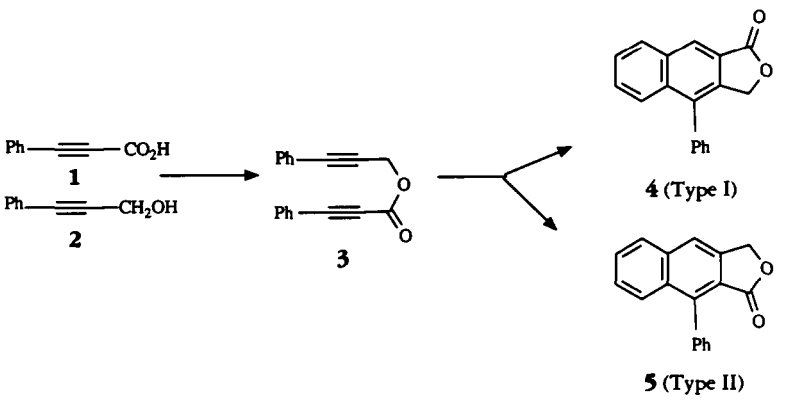
ABSTRACT.—Unlike arylpropargyl arylpropiolates (e.g., **3**) which yield, on heating in xylene, arylnaphthalene type I and type II lactones (**4** and **5**, respectively) in 1:1 ratio, cinnamyl arylpropiolates (e.g., **7**) on heating in DMF gave the aryldihydronaphthalene-2-carboxylic acid lactones (e.g., **8**) in excellent yield and regioselectivity. It is suggested that the aryldihydronaphthalene lactone product isolated from the tumor-inhibiting extract of *Polygala polygama* and previously named β-apopolygamatin [**17**] has in fact the structure 1-(3′,4′-methylenedioxyphenyl)-3-hydroxymethyl-7,8-dimethoxy-3,4-dihydro-2-naphthoic acid lactone [**18**].

An improved procedure for the synthesis of the arylnaphthalene lactone class of natural lignans, involving formation of arylpropargyl arylpropiolate esters and their cyclization, has recently been described (1). This is exemplified by reaction of the acid chloride of phenylpropiolic acid [**1**] with the solid-phase copolymer of 4-vinylpyridine (P4-VP), then with phenylpropargyl alcohol [**2**] to give the diynic ester **3**, which on heating in xylenes yielded quantitatively a 1:1 mixture of type I (**4**) and type II (**5**) lactones (Scheme 1).

We have now examined the preparation and cyclization of cinnamyl arylpropiolate esters under the same modified conditions with anticipation that, unlike the lack of regioselectivity shown on cyclization by the diynic esters, *trans*-enynic esters would yield predominantly the γ-apo type II lactones, e.g., **6** + **1**↦ **7**↦**8**. This followed from the pioneering studies of Klemm and coworkers (2–8) in which additional comment was made upon the capricious and difficult formation of enynic esters analogous to **7** (8). They noted that thermal cyclization in Ac_2O resulted in modest 20–40% yields (5) and that the effects of alternative solvents affected cyclization modal selectivity unpredictably (7).

Reaction of the solid-phase copolymer of P4-VP in CH_2Cl_2 with the acid chloride of phenylpropiolic acid [**1**], followed by addition of *trans*-cinnamyl alcohol [**6**] provided the cinnamyl phenylpropiolate ester **7** cleanly in 82% yield and is an evident improvement over the customary pyridine solvent method in which chlorine-bearing contaminants were produced (2). The reported cycliza-

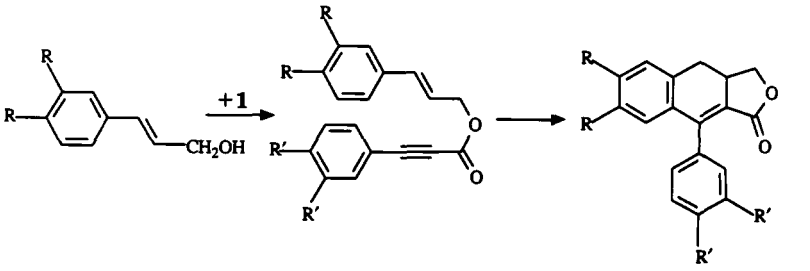


SCHEME 1.

tion of ester **7** to give the dihydronaphthalene lactone **8** by heating in Ac_2O in 46% yield (2) has been confirmed (Scheme 2). The choice of solvent for this reaction is, however, significant. Whereas the diynic ester **3** was quantitatively cyclized to the naphthalene lactones **4** and **5** by heating in xylene, this solvent (and C_6H_6, toluene, and nitrobenzene) was surprisingly ineffective with the enynic ester **7**. In contrast, by heating ester **7** in DMF for 5 h, the expected dihydronaphthalene lactone **8** was obtained in 82% isolated yield. Accordingly, this solvent was chosen for cyclization of all cinnamyl arylpropiolate esters herein examined.

cyclization of the diynic analogues, which yielded both type I (naphthalene-3-carboxylic acid) and type II (naphthalene-2-carboxylic acid) lactones.

The diveratyl enynic ester **14**, prepared in analogous fashion from alcohol **9** and the propiolic acid **13**, gave on DMF cyclization the now anticipated lactones **15** and **16** in 8.5:1 ratio and in quantitative yield (Scheme 3). The ^{1}H-nmr spectra are particularly useful in distinguishing between 6,7- (e.g., **11** and **15**) and 7,8- (e.g., **12** and **16**) disubstituted aryldihydronaphthalenes. The pendent aryl ring markedly shields the H-8 proton of the former (singlet at δ ca. 6.4–6.6) and the 8-methoxyl



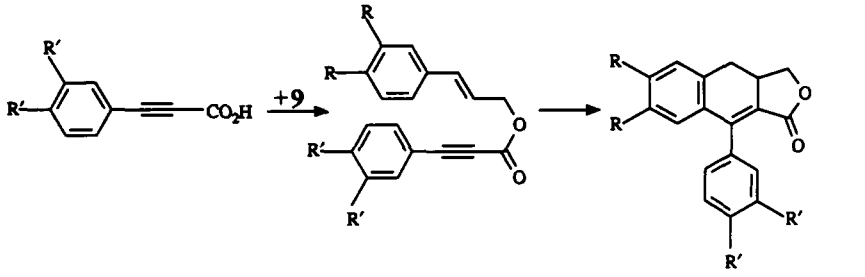
6 R=H **9** R=OMe **7** R=R'=H **10** R=OMe, R'=H **8** R=R'=H **11** R=OMe, R'=H

SCHEME 2.

Polymer-mediated esterification of phenylpropiolic acid [**1**] and *trans*-3,4-dimethoxycinnamyl alcohol [**9**] gave the cinnamyl phenylpropiolate **10** in over 90% yield. On heating in DMF, the ester underwent cyclization in excellent yield to give a mixture of two isomeric γ-lactones in ca. 4.25:1 isolated ratio. The major product (72% yield) gave empirical and spectroscopic data in excellent agreement with those reported for the 6,7-dimethoxy-3,4-dihydronaphth-2-oic acid lactone **11**, previously reported as the sole product (22% yield) from heating **10** in Ac_2O (3) (Scheme 2). The ^{1}H-nmr spectrum supported assignment of the 7,8-dimethoxy-3,4-dihydro-2-naphthoic acid structure **12** to the minor product. These experiments, therefore, contrasted significantly from

group (δ ca. 3.2) of the latter.

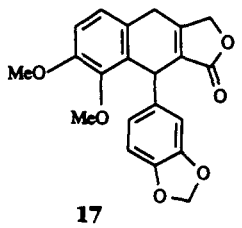
In phytochemical investigations of the tumor-inhibiting extract of *Polygala polygama* Walt. (Polygalaceae), Hokanson (9,10) isolated six lignans, of which one was an aryldihydronaphthalene lactone and for which, based upon analysis of spectrometric data, the name β-apopolygamatin and structure **17** were assigned. At about the same time, a compound with the same proposed structure was synthesized by an apparently unequivocal method (11). The poor correspondence in reported data for these compounds clearly indicates that they differ structurally; reappraisal of the ^{1}H-nmr spectrum of the *Polygala* product now suggests that it is better accommodated by the γ-apo isomeric structure **18**. This compound had previously been



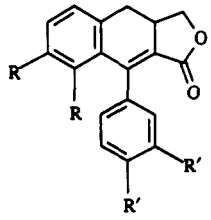
13 R′=OMe
21 R′=-OCH_2O-

14 R=R′=OMe
20 R=OMe, R′=-OCH_2O-

15 R=R′=OMe
19 R=OMe, R′=-OCH_2O-



17



12 R=OMe, R′=H
16 R=R′=OMe
18 R=OMe, R′=-OCH_2O-

SCHEME 3

obtained as a by-product in <5% yield in the synthesis of collinusin [**19**], a constituent of *Cleistanthus collinus* (Roxb.) Benth. & Hook. (12,13), by heating crude 3,4-dimethoxycinnamyl 3,4-methylenedioxyphenylpropiolate [**20**] in Ac_2O (14). We have now re-examined the cyclization of **20** under the improved conditions, and find that the major product, (±)-collinusin [**19**], is obtained in markedly increased yield (86%), but the yield of minor product **18** remained at 5%. Although an authentic specimen of the *Polygala* dihydronaphthalene lactone natural product was no longer available for direct comparison,[1] the excellent agreement in reported data (ir, ^{1}H nmr, uv) leaves little doubt that it has the structure 1-(3′,4′-methylenedioxyphenyl)-3-hydroxymethyl-7,8-dimethoxy-3,4-dihydro-2-naphthoic acid lactone [**18**].

[1]Personal communication from Dr. Gerard C. Hokanson, Warner-Lambert Company.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^{1}H-nmr spectra were determined in $CDCl_3$ solution with TMS as internal standard, using Varian EM390 and XL300 spectrometers. Cc was conducted on Si gel (Kieselgel 40, 70–239 mesh, EM Science) or neutral alumina (alumina Woelm, activity grade 1). Preparative tlc was conducted on Analtech Si gel GF (1000 microns, 20 × 20 cm). Petroleum ether (bp 20–40°) was from J.T. Baker. P4-VP-Reillex 425 (Reilly Tar and Chemical Corporation) was oven-dried at 125° to constant weight (ca. 24 h). Ester intermediates were prepared as described and subjected directly to cyclization without unrequired further purification; elemental analysis of minor isomeric cyclization products was not sought.

1-PHENYL-3-HYDROXYMETHYL-3,4-DIHYDRO-2-NAPHTHOIC ACID LACTONE [**8**].—Phenylpropiolic acid (0.72 g, 5 mmol) was added with stirring to freshly distilled thionyl chloride (5 ml) at room temperature until solution was complete (ca. 3 h), and excess thionyl chloride was removed by repeated addition of C_6H_6 and evaporation under reduced pressure. The residual acid chloride was dissolved in CH_2Cl_2 (10 ml) and added to a stirred suspension of P4-VP polymer (2 g) in CH_2Cl_2 (20 ml). After stirring for 15 min, *trans*-cinnamyl alcohol (0.33 g, 2.5 mmol) in CH_2Cl_2 (5 ml) was added dropwise over 5 min; the mixture was stirred overnight at room

temperature and filtered. Evaporation of the combined filtrate and CH_2Cl_2 washings gave a pale yellow oil, a solution of which in $CHCl_3$-petroleum ether (1:1) on filtration through a short plug of Si gel gave *trans*-cinnamyl phenylpropiolate [**7**] as a colorless oil (93% yield): ^{1}H nmr δ ($CDCl_3$) 4.82 (d, J = 6 Hz, CH_2), 6.36 (dt, J = 16, 6 Hz, H-α), 7.11–7.82 (m, ten ArH) and 8.05 (d, J = 16 Hz, H-β); ir ν ($CHCl_3$) 2240 (C≡C) and 1710 cm^{-1} (conjugated ester).

A solution of the ester **7** (100 mg) in DMF (5 ml) was heated under reflux (N_2 atmosphere) for 5 h. Et_2O (25 ml) was added to the cooled mixture, which was then extracted with 10% HCl (3 × 15 ml) and H_2O (3 × 15 ml). Evaporation of the dried organic phase gave a yellow oil (94 mg), a solution of which in $CHCl_3$ was filtered through Si gel to yield a colorless oil that crystallized from EtOH to give the lactone **8** in 82% yield: mp 194–195° [lit. (2) mp 194.5–195.5°], ^{1}H nmr δ ($CDCl_3$) 2.39–4.91 (complex m, five H) and 6.71–7.62 (complex m, nine ArH).

The ester was recovered unchanged after heating in C_6H_6, toluene, xylenes, and nitrobenzene for periods up to 48 h, but yielded the lactone **8** in 54% yield after heating with Ac_2O for 5 h.

FORMATION AND CYCLIZATION OF *trans*-3,4-DIMETHOXYCINNAMYL PHENYLPROPIOLATE [**10**].—Phenylpropiolic acid (5 mmol) and *trans*-3,4-dimethoxycinnamyl alcohol [**9**] (2.5 mmol) were reacted as in the above experiment to give *trans*-3,4-dimethoxycinnamyl phenylpropiolate [**10**] as a pale yellow oil (91% yield): ^{1}H nmr δ ($CDCl_3$) 3.78 (s, OMe), 3.81 (s, OMe), 4.81 (d, J = 6 Hz, CH_2), 6.41 (dt, J = 16, 6 Hz, H-α), 6.78–7.78 (m, eight ArH) and 7.84 (d, J = 16 Hz, H-β); ir 2232 (C≡C) and 1714 cm^{-1} (conjugated ester).

The ester **10** (100 mg) was heated under reflux in DMF (5 ml) and worked up as for **7** above. Elution of the Si gel column with petroleum ether-$CHCl_3$ gave 1-phenyl-3-hydroxymethyl-6,7-dimethoxy-3,4-dihydro-2-naphthoic acid lactone [**11**] as a colorless oil which crystallized from petroleum ether/$CHCl_3$ as needles (72 mg, 72% yield), mp 182–183° [lit. (3) mp 180–181°, 22% overall yield]; ^{1}H nmr δ ($CDCl_3$) 2.39–4.91 (complex m, five H), 3.59 (s, 7-OMe), 3.89 (s, 6-OMe), 6.44 (s, H-8), 6.75 (br s, H-5), 6.89–7.52 (m, five ArH); ir 1750 cm^{-1} (αβ-unsaturated γ-lactone). Continued column elution with $CHCl_3$ yielded 1-phenyl-3-hydroxymethyl-7,8-dimethoxy-3,4-dihydo-2-naphthoic acid lactone [**12**] as a yellow oil (17 mg, 17% yield); ^{1}H nmr δ ($CDCl_3$) 2.36–4.92 (complex m, five H), 3.13 (s, 8-OMe), 3.71 (s, 7-OMe), 6.76–7.56 (m, seven ArH); ir 1752 cm^{-1} (αβ-unsaturated γ-lactone).

FORMATION AND CYCLIZATION OF *trans*-3,4-DIMETHOXYCINNAMYL 3,4-DIMETHOXYPHENYLPROPIOLATE [**14**].—3,4-Dimethoxyphenylpropiolic acid [**13**] (0.64 g), thionyl chloride (5 ml), P4-VP resin (2 g), and 3,4-dimethoxycinnamyl alcohol [**9**] (0.30 g) were reacted as in above experiment. The yellow oil product (0.56 g) was chromatographed on neutral alumina, and elution with Et_2O-petroleum ether (1:1) yielded the ester **14** as a colorless oil (0.25 g, 41% yield); ^{1}H nmr δ ($CDCl_3$) 3.81 (s, OMe), 3.83 (s, OMe), 3.85 (s, OMe), 3.88 (s, OMe), 4.84 (d, J = 6 Hz, CH_2) and 6.01–7.34 (complex m, eight Ar and vinyl protons); ir 2223 (C≡C), 1714 (conjugated ester), 965 cm^{-1} (*trans*-alkene). Continued column elution with Et_2O gave unreacted alcohol **9** (0.15 g).

The ester **14** (100 mg) was heated under reflux in DMF (5 ml) under N_2 for 5 h. Workup as before and evaporation of the washed and dried Et_2O extract gave a residual brown oil (96 mg) that was subjected to preparative tlc by multiple development with hexane-EtOAc (8:2) to yield two products which were eluted with EtOAc. The major (slower moving, dark blue on uv irradiation) constituent crystallized from MeOH to give 1-(3′,4′-dimethoxyphenyl)-3-hydroxymethyl-6,7-dimethoxy-3,4-dihydro-2-naphthoic acid lactone [**15**] as yellow flakes (85 mg, 85% yield): mp 215–217° [lit. (15) mp 216–217°]; ^{1}H nmr δ ($CDCl_3$) 2.39–4.91 (complex m, five H), 3.66 (s, 7-OMe), 3.86 (s, 3′- or 4′-OMe), 3.95 (s, 6-OMe and 3′- or 4′-OMe), 6.58 (s, H-8), 6.80 (br s, H-5), 6.97 (m, H-2′ and H-5′) and 7.24 (m, H-6′); ir ($CHCl_3$) 1755 cm^{-1} (αβ-unsaturated γ-lactone). The minor (faster moving, dark blue on uv irradiation) constituent gave 1-(3′,4′-dimethoxyphenyl)-3-hydroxymethyl-7,8-dimethoxy-3,4-dihydro-2-naphthoic acid lactone [**16**] as a yellow oil (10 mg, 10%): ^{1}H nmr δ ($CDCl_3$) 2.37–4.92 (complex m, five H), 3.23 (s, 8-OMe), 3.69 (s, 7-OMe), 3.89 and 3.91 (two ring C OMe) and 6.69–7.13 (m, five ArH); ir ($CHCl_3$) 1752 cm^{-1} (αβ-unsaturated γ-lactone).

FORMATION AND CYCLIZATION OF *trans*-3,4-DIMETHOXYCINNAMYL 3,4-METHYLENEDIOXYPHENYLPROPIOLATE [**20**].—3,4-Methylenedioxyphenylpropiolic acid [**21**] (2.6 mmol), P4-VP resin (1.5 g), and 3,4-dimethoxycinnamyl alcohol [**9**] (2.6 mol) were reacted and worked up in the usual way. Chromatography on neutral alumina and elution with Et_2O-petroleum ether gave the ester [**20**] (14) as a golden yellow oil (89% yield): ^{1}H nmr δ ($CDCl_3$) 3.81 (s, OMe), 3.82 (s, OMe), 4.81 (d, J = 7 Hz, CH_2), 5.91 (s, OCH_2O), 6.12–7.29 (six Ar and two vinyl H); ir ($CHCl_3$) 2226 (C≡C), 1714 (conjugated ester), 963 cm^{-1} (*trans*-alkene).

The ester **20** (100 mg) was heated under reflux in DMF (5 ml) and worked up by preparative tlc as in the previous experiment by multiple development with petroleum ether-EtOAc (8:2).

The major fraction (slower moving, dark blue on uv irradiation) crystallized from Me_2CO-petroleum ether to yield 1-(3′,4′-methylenedioxyphenyl)-3-hydroxymethyl-6,7-dimethoxy-3,4-dihydro-2-naphthoic acid lactone [**19**] [(±)-collinusin] as a white solid (84 mg, 84% yield), mp 197–198° [lit. (12) mp 196–198°]; ^{1}H nmr δ ($CDCl_3$) 2.65–4.84 (complex m, five H), 3.68 (s, 7-OMe) 3.92 (s, 6-OMe), 5.97 (s, OCH_2O), 6.56 (s, H-8), 6.78–6.89 (m, four ArH); ir ($CHCl_3$) 1743 cm^{-1} (conjugated lactone).

The minor fraction (faster moving, dark blue on uv irradiation) crystallized from CH_2Cl_2-petroleum ether (bp 20–40°) to give 1-(3′,4′-methylenedioxyphenyl)-3-hydroxymethyl-7,8-dimethoxy-3,4-dihydro-2-naphthoic acid lactone [**18**] as a white solid (5 mg, 5% yield), mp 214–216° [lit. (14) mp 213–215°]; ^{1}H nmr δ ($CDCl_3$) 2.61–4.92 (complex m, five H), 3.23 (s, 8-OMe), 3.84 (s, 7-OMe), 5.96 (s, OCH_2O), 6.78–6.98 (m, five ArH); ir ($CHCl_3$) 1750 cm^{-1} (conjugated lactone).

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