Benzodioxans by Oxidative Phenol Coupling. Synthesis of Silybin

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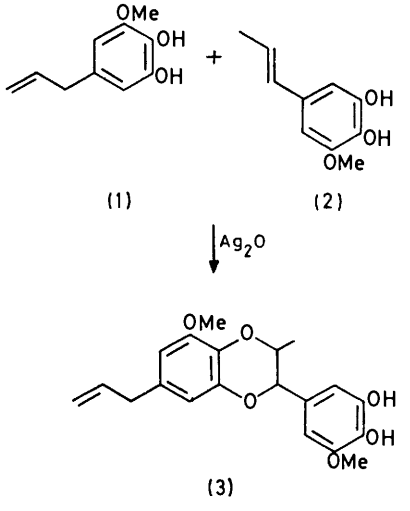
Oxidative coupling of substituted catechols with isoeugenol or coniferyl alcohol in the presence of silver oxide affords 2,3-*trans*-1,4-benzodioxans in good yield. The reaction is highly regioselective when the catechol bears an alkyl substituent, much less so in the case of an electrophilic one. A free-radical coupling mechanism is proposed. A one-step biomimetic synthesis in high yield of the natural flavanolignans silybin and isosilybin from 2*R*,3*R*-dihydroquercetin and coniferyl alcohol is reported.

RECENTLY two of us [1] reported on the synthesis of the natural benzodioxan (±)-eusiderin (3) by oxidative coupling of 5-allyl-3-methoxy- (1) and 3-methoxy-5-propenyl-catechol (2) with Ag_2O. The reaction proceeded in good yield (40%) and complete regioselectivity to give only *trans*-(3) (Scheme 1).



SCHEME 1

In order to explore further the synthetic potential and the regio- and stereo-selectivity of the reaction, we undertook a study of the oxidative coupling of a series of catechol derivatives with methoxypropenylphenols such as isoeugenol (5a) or coniferyl alcohol (5b). The reactions were performed in benzene containing another more polar solvent, ethyl acetate, methanol, or acetone, depending on the solubility of the reactants, with equimolar amounts of silver oxide, and were monitored by t.l.c. The products were isolated by chromatography. Only the expected benzodioxans were obtained, although the yields did not exceed 50%. With isoeugenol, variable amounts of the well-known oxidation product, dehydrodi-isoeugenol, were also produced. All the compounds have *trans*-configuration at C-2 and -3, as shown by the coupling constants in the n.m.r. spectra, which are *ca.* 8 Hz.[2]

Oxidative coupling of isoeugenol and coniferyl alcohol with 1,2-dihydroxybenzene was initially studied to test how viable the method was in this system. The expected benzodioxans (6a) and (6b) [3] were isolated in moderate yield (Scheme 2).

Reaction of 4-methylcatechol (4b) with isoeugenol produced only one benzodioxan (6c). It is very difficult to distinguish between the two possible regioisomers which could be formed in the reaction, due to the great similarity of their spectra.[4,5] Thus structure (6c) was assigned by comparison with a compound prepared by an unambiguous route. Such a synthesis has already been reported [6] and therefore (6c) was converted into its benzyl ether, which was compared with *both* synthetic isomers. Its structure is therefore securely assigned. The similar benzodioxan (6d), obtained from coniferyl alcohol and the same 4-methylcatechol, was again only one isomer, and its structure was confirmed by conversion into the methyl ether, which proved identical with an authentic sample.[6]

The same regioselectivity was obtained in the reaction between 4-allylcatechol (4c) and coniferyl alcohol, which gave (6f), containing only a small amount (t.l.c.) of what appeared later to be its regioisomer. The double bond in the side chain was shifted quantitatively with $PdCl_2$ to give (6g), which was treated with OsO_4 and $NaIO_4$. This oxidation afforded the aldehyde (6h), which was then methylated.

Comparison of this ether (t.l.c., i.r., and n.m.r.) with an authentic sample of the methyl compound synthesized unambiguously [6] indicated their identity. On the other hand, coupling of protocatechic aldehyde (4d) with coniferyl alcohol gave a mixture (*ca.* 3 : 7) of (6h) with its regioisomer (7a), which appeared slightly, but beyond any doubt, different from (6h) in its n.m.r., i.r., and t.l.c. behaviour. The availability of both isomeric aldehydes allowed us to identify the small amount of the regioisomer obtained in the reaction leading to (6f), which remained unchanged through the last steps of the oxidation sequence of (6f).

The reaction of coniferyl alcohol with another catechol bearing an electron-withdrawing substituent, such as CO_2Et, gave again a mixture containing predominantly the isomer (7b) as shown by methylation, $LiAlH_4$ reduction, and comparison of the product with the methyl ether of the authentic isomeric diol (6e).

Even when both isomers are available, it is very difficult to distinguish between them on the basis of spectra.

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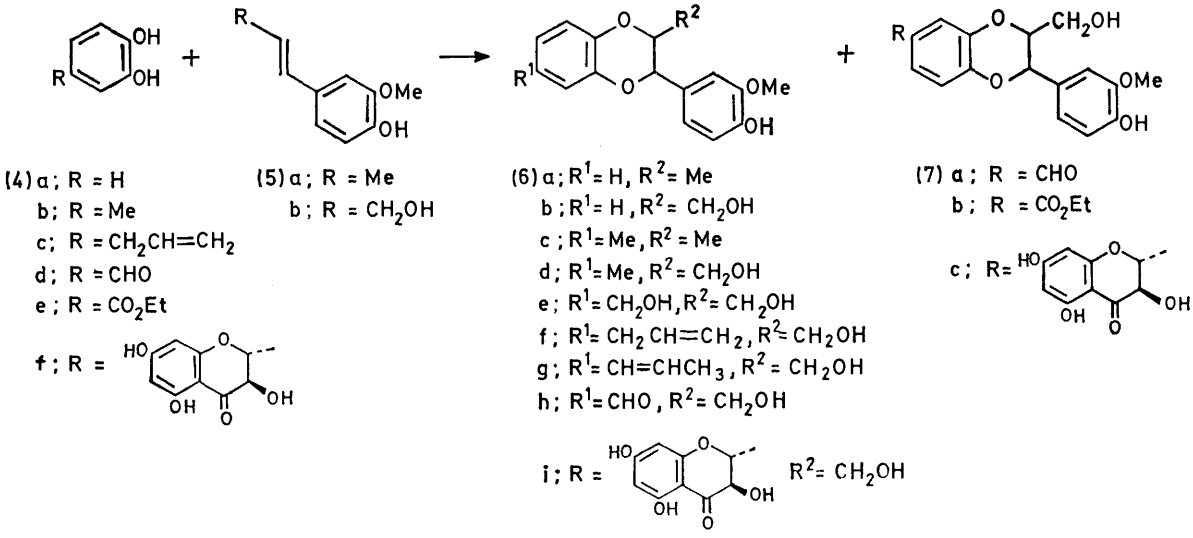
The only possible systematic difference is in the chemical shift of the proton adjacent to the aromatic substituent (say 3-H) in the benzodioxan ring, which appears at lower (higher) field when the electron-withdrawing (-donating) substituent is at position 7. This effect is observable for the two aldehydes (6h) and (7a) and for two other pairs of isomers.[7] Another difference is in the pattern of the signals for the aromatic protons, which is difficult to rationalize, however, due to overlapping of the signals.

Although only a few examples of substituents have been examined, due to the lack of suitable reference compounds, so far indispensable to assign the structures, it appears that the substituent on the catechol ring has a striking influence on the regioselectivity of the reaction. Changing from an electron-donating substituent such as methyl or allyl to a formyl or ethoxycarbonyl group induces a neat inversion of the regioselectivity. Yields are also much lower with electron-withdrawing substituents. Attempts at reaction using 4-chlorocatechol gave only small amounts of benzodioxans, not obtained in a pure state. Previously [1] we have suggested a free-radical coupling mechanism for the reaction (Scheme 3), where the first step is the well known intermolecular O–β coupling of two phenoxyl radicals.[8] Such a mechanism has already been suggested for the biosynthesis of silybin.[9]

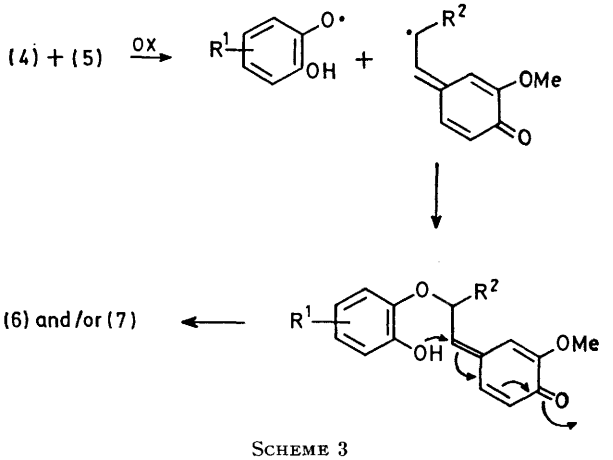
The yields and product distributions of the reaction are consistent with this hypothesis, as an alkyl substituent should make the oxidation of a *para* OH easier [10] and therefore induce a high regioselectivity. Conversely, an electrophilic substituent, with its opposite effect, could make the oxidation potential of the two OH groups more similar, with mixtures of regioisomers as a consequence. The possibility that the reaction is assisted by the formation of a silver complex with the olefinic double bond is not excluded, and probably warrants further investigation.

The synthetic potential of the reaction was explored in an attempt to synthesize silybin,[11] a naturally occurring benzodioxan which has interesting therapeutic applications.[12] After an extensive search for the correct experimental conditions, oxidation by silver oxide of equimolar amounts of 2*R*,3*R*-dihydroquercetin (4f) and coniferyl alcohol (5b) in benzene-acetone was found to give a mixture (78% yield) from which, by simple crystallization, pure silybin (6i) [13] could be obtained, identical with the natural product (t.l.c., h.p.l.c., and n.m.r., i.r., and c.d. spectra). Preparative t.l.c. of the crude mixture gave isosilybin (7c),[13] the regioisomer of silybin, also identical with the natural product. The ratio of the two products (6i) : (7c) was 57 : 43 (h.p.l.c.). This simple biomimetic synthesis is not only the first synthesis of natural silybin, but lends itself to the preparation of analogues. The long synthesis of racemic silybin reported by Mishima *et al.*,[14] performed before the conclusive establishment of the structure of silybin,[4] is in reality the synthesis of the regioisomer, isosilybin.

The ^{13}C n.m.r. spectra of both silybin and isosilybin

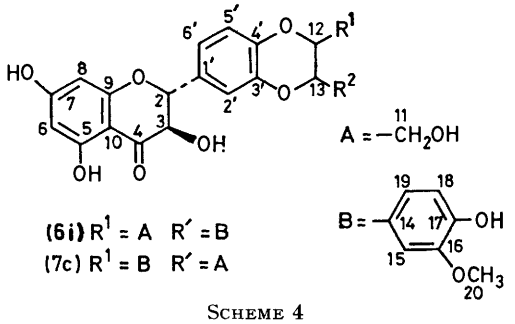


SCHEME 2



SCHEME 3

were measured in dimethyl sulphoxide (35 mg ml^{-1}) and all the signals assigned by single-frequency selective decoupling and comparison with model compounds [15] (Table).



SCHEME 4

EXPERIMENTAL

U.v. spectra were measured for solutions in 95% ethanol. N.m.r. spectra were recorded with Varian EM-390 or XL-100 instruments. Unless stated otherwise, column chromatography was performed with Merck silica gel 60 and t.l.c. with Merck HF_{154} silica gel.

The coupling reactions were performed on a 1—10 mmol scale, using, unless stated otherwise, equimolar amounts of the reactants and Ag_2O in benzene, with addition of AcOEt, acetone, or methanol at room temperature with magnetic stirring. The reactions were monitored by t.l.c. (hexane–AcOEt) and interrupted when one of the reagents was no longer detectable by t.l.c. The reaction mixture was then filtered and chromatographed through silica gel.

2-Methyl-3-(4-hydroxy-3-methoxyphenyl)-1,4-benzodioxan (6a).—Equimolar amounts of the reactants (5 mmol) in benzene (50 ml) and acetone (1 ml) were mixed and Ag_2O (5 mmol) was added after 30 min. Stirring for 1 h at 45° followed by filtration and chromatography gave (6a) (39%) as an oil, *m/e* 340, 272, 229, 197, and 164, $\lambda_{max.}$ 279 (ε 4 950) and 283sh nm (4 500), δ ($CDCl_3$) 1.15 (2-Me), 3.86 (OMe), 4.0—4.2 (2-H), 4.54 (*J* 8 Hz, 3-H), 5.77 (OH), and 6.8—7.0 (ArH).

2-Hydroxymethyl-3-(4-hydroxy-3-methoxyphenyl)-1,4-benzodioxan (6b).—Silver oxide (30 mmol) was added to a solution of the reactants (8.8 mmol) in benzene–AcOEt (3 : 2 v/v) (150 ml) and the mixture stirred for 2 days. Filtration and chromatography with $CHCl_3$ gave (6b) (15%), m.p. 169—172°, identical (n.m.r. and mass spectra) with a sample reported elsewhere.[3]

3-(4-Hydroxy-3-methoxyphenyl)-2,6-dimethyl-1,4-benzodioxan (6c).—Compound (6c) was prepared in 48—50% yield from commercial isoeugenol (Merck) (4 mmol) or pure *cis*-isoeugenol, in benzene–MeOH (30 ml) (5 : 1 v/v), by stirring for 2 days, filtering and chromatographing with hexane–AcOEt (9 : 1, then 8 : 2). The product had m.p. 102—103° (from benzene), $\lambda_{max.}$ 282 nm (ε 7 500), δ ($CDCl_3$) 1.11 (2-Me), 2.24 (6-Me), 3.86 (OMe), 3.9—4.3 (2-H), 4.53 (*J* 8 Hz, 3-H), 5.78 (OH), and 6.6—7.0 (ArH). Reaction of (6c) with benzyl chloride and K_2CO_3 gave the benzyl ether, which was compared (i.r.) with an authentic sample [6] and with the isomeric 3-(4-benzyloxy-3-methoxyphenyl)-2,7-dimethyl-1,4-benzodioxan.[6]

3-(4-Hydroxy-3-methoxyphenyl)-2-hydroxymethyl-6-methyl-1,4-benzodioxan (6d).—Obtained in 50% yield by reaction in benzene at room temperature (4 mmol in 200 ml) and chromatography with hexane–AcOEt (2 : 1), compound (6d) had δ ($CDCl_3$) 2.26 (6-Me), 2.6—2.8 (AB of ABX, 2-CH_2OH), 3.90 (OMe), 4.1 (m, 2-H), 4.92 (*J* 8 Hz, 3-H), 5.8 (OH), and 6.6—7.0 (ArH). Acetylation of (6d) with Ac_2O and pyridine at room temperature gave the *diacetate*, m.p. 125—127° (from MeOH) (Found: C, 65.7; H, 5.65. $C_{21}H_{22}O_7$ requires C, 65.25; H, 5.75), $\lambda_{max.}$ 275sh (ε 5 500), 281 (6 350), and 287sh nm (3 850), *m/e* 386, 343, 283, and 222, δ (CD_3COCD_3) 1.94 (2-CH_2OAc), 2.20 (6-Me and 4′-OAc), 3.80 (OMe), 3.9—4.4 (2-H and 2-CH_2OAc), 4.97 (*J* 8 Hz, 3-H), and 6.7—7.4 (ArH). Methylation of (6d) with CH_3I and K_2CO_3 in acetone gave the monomethyl ether as an oil, *m/e* 316, 298, 283, and 257, $\lambda_{max.}$ 281 (ε 5 600) and 284 nm (5 600), δ ($CDCl_3$) 2.22 (6-Me), 3.4—3.8 (AB of ABX, CH_2OH), 3.93 (2 OMe), 4.0 (m, 2-H), 4.90 (*J* 8 Hz, 3-H), and 6.6—7.1 (ArH), superimposable on that of the authentic product obtained by hydrogenation with Pd–C of 2,6-dihydroxymethyl-3-(3,4-dimethoxyphenyl)-1,4-benzodioxan.[6]

6-Allyl-3-(4-hydroxy-3-methoxyphenyl)-2-hydroxymethyl-1,4-benzodioxan (6f).—Prepared in 50% yield by reaction in benzene–acetone (25 : 1) (5 mmol in 250 ml) for 20 h and chromatography with hexane–AcOEt (2 : 1), *compound* (6f) had m.p. 83° (from hexane–benzene) (Found: C, 69.25; H, 6.2. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.15), $\lambda_{max.}$ 282 (ε 7 350) and 227 nm (17 400), δ (CD_3COCD_3) 3.17 (*J* 6 Hz, 6-CH_2), 3.4—4.2 (3-H), 3.93 (OMe), 4.9—5.2 (2-H and =CH_2), 5.8—6.2 (m, =CH), and 6.6—7.1 (ArH).

3-(4-Hydroxy-3-methoxyphenyl)-2-hydroxymethyl-6-propenyl-1,4-benzodioxan (6g).—Compound (6f) (2 g) was stirred for 24 h with a catalytic amount of $PdCl_2$ in methanol (80 ml). Filtration, evaporation, and crystallization from EtOH gave the product (6g) (1.8 g), m.p. 109—110°, $\lambda_{max.}$ 259 (ε 16 800), 266 (16 800), 287sh (8 300), and 302 nm (5 500), δ ($CDCl_3$) 1.82 (Me), 3.4—3.9 (2-CH_2OH), 3.88 (OMe), 4.0 (m, 2-H), 4.88 (*J* 8 Hz, 3-H), 6.0—6.5 (2 unsaturated H), and 6.8—7.0 (ArH).

3-(4-Hydroxy-3-methoxyphenyl)-2-hydroxymethyl-1,4-benzodioxan-6-carbaldehyde (6h).—To compound (6g) (100 mg) and OsO_4 (8 mg) in 10 ml dioxan was added over 10 h a solution of $NaIO_4$ (140 mg) in water (3 ml), and the mixture

^{13}C Chemical shift assignments for silybin (6i) and isosilybin (7c)

Carbon	(6i)	(7c)	Carbon	(6i)	(7c)	Carbon	(6i)	(7c)
4	197.48	197.43	1′	129.87	130.11	10	100.30	100.33
7	166.62	166.60	14	127.29	127.22	6	95.92	95.91
5	163.12	163.12	6′	121.12 [a]	120.68 [b]	8	94.87	94.90
9	162.27	162.24	19	120.33 [a]	120.24 [b]	2	82.42	82.39
16	147.44	147.39	2′	116.36	116.24	12	78.01	75.70
17	146.84	146.82	5′	116.16	116.24	13	75.72	77.89
4′	143.46	143.68	18	115.14	115.17	3	71.34	71.39
3′	143.07	142.72	15	111.51	111.56	11	60.09	60.05
						20	55.56	55.56

[a,b] Assignments can be interchanged.

stirred overnight. Treatment with brine and exhaustive extraction with AcOEt afforded (6h) as an oil, δ ($CDCl_3$) 3.5—4.0 (AB of ABX, CH_2OH), 3.90 (OMe), 4.0—4.1 (m, 2-H), 4.96 (*J* 8 Hz, 3-H), 6.9—7.5 (ArH), and 9.80 (CHO). Methylation with MeI and K_2CO_3 in acetone for 6 h at 40 °C, followed by preparative t.l.c. with $CHCl_3$–MeOH (30 : 1) gave the monomethyl ether, δ ($CDCl_3$) 3.5—3.9 (AB of ABX, CH_2OH), 3.91 (OMe), 4.0—4.3 (m, 2-H), 5.01 (*J* 8 Hz, 3-H), 6.9—7.5 (ArH), and 9.87 (CHO), which was compared by t.l.c. ($CHCl_3$–MeOH 30 : 1) with an authentic sample [6] (same R_F) and with the corresponding derivative of (7a), which has lower R_F.

2-(4-*Hydroxy*-3-*methoxyphenyl*)-3-*hydroxymethyl*)-1,4-*benzodioxan*-6-*carbaldehyde* (7a).—Coupling of the reagents (5 mmol) in benzene–MeOH (280 ml) (5 : 1) at room temperature for 30 min gave a 7 : 3 (n.m.r.) mixture (18%) of (7a) and (6h). Chromatography with hexane–AcOEt 3 : 2 gave a sample of (7a), δ ($CDCl_3$) 4.5—5.0 (CH_2OH), 3.90 (OMe), 4.0—4.1 (m, 3-H), 5.04 (*J* 8 Hz, 2-H), 6.8—7.5 (ArH), and 9.80 (CHO).

Ethyl 2-(4-*Hydroxy*-3-*methoxyphenyl*)-3-*hydroxymethyl*-1,4-*benzodioxan*-6-*carboxylate* (7b).—The reactants (5 mmol) in 250 ml benzene–AcOEt (2 : 3) (250 ml) were stirred with Ag_2O (12.5 mmol) for 2.5 h. Chromatography with $CHCl_3$ gave (7b), *m/e* 361 (*M* + 1, 22%), 360 (100), 342 (21), 193 (15), 180 (57), 162 (23), 161 (19), 137 (89), 124 (50), and 119 (14), δ ($CDCl_3$) 1.4 (t, OCH_2CH_3), 3.5—3.9 (m, CH_2OH), 3.9 (OMe), 4.0—4.2 (m, 3-H), 4.3 (q, OCH_2CH_3), 5.0 (*J* 7.5 Hz, 2-H), 6.8—7.1 (4 H, ArH), and 7.5—7.8 (2 H, ArH). Methylation of (7a) (67 mg) with CH_3I and K_2CO_3 in acetone gave the monomethyl ether (98%) as a yellow oil, δ ($CDCl_3$) 1.4 (OCH_2CH_3), 2.3 (OH), 3.6—3.9 (m, CH_2OH), 3.9 (2 OMe), 4.1 (m, 3-H), 4.4 (q, OCH_2CH_3), 5.1 (*J* 8 Hz, 2-H), 6.9—7.2 (4 H, ArH), and 7.5—7.8 (2 H, ArH). Addition of this product to solution of $LiAlH_4$ in THF at 0 °C and refluxing 2 h followed by addition of NH_4Cl and extraction with ether gave, after preparative t.l.c. with $CHCl_3$–MeOH (94 : 6), 2,6-*dihydroxymethyl*-3-(3,4-*dimethoxyphenyl*)-1,4-*benzodioxan* (2 mg), identified by its mass and n.m.r. spectra and comparison with an authentic sample,[6] and 2,7-*dihydroxymethyl*-3-(3,4-*dimethoxyphenyl*)-1,4-*benzodioxan* (15 mg), m.p. 161—171°, *m/e* 333 (*M* + 1, 19%), 332 (100), 314 (23), 255 (16), 194 (64), 176 (24), 151 (81), 138 (31), and 77 (15).

Reaction of 2*R*,3*R*-*Dihydroquercetin* (4f) *with Coniferyl Alcohol* (5b).—Compounds (4f) * (910 mg) and (5b) (540 mg) were dissolved in dry benzene–acetone (1 150 ml; 18 : 5 v/v). Ag_2O (1.5 g) was added and the suspension was stirred for 40 h at 55 °C until t.l.c. ($CHCl_3$–AcOEt–acetone, 18 : 1 : 1 v/v) showed no starting materials. The mixture was filtered, the solvent evaporated, and the oily residue chromatographed on silica gel (50 g) with chloroform–methanol (95 : 5) as eluant. The product (1.11 g) appeared by t.l.c. ($CHCl_3$–AcOEt–acetone–HCO_2H, 8 : 1 : 1 : 0.01) or h.p.l.c. (silica gel; CH_3CN–water) as a mixture of silybin (57%) and isosilybin (43%) [R_F(sil)/R_F(iso) 1.1]. Pure silybin (6i) was obtained by crystallization of the crude mixture with MeOH–water (9 : 1) and then AcOEt, δ (pyridine) 3.76 (OMe), 3.8—4.1 (CH_2OH), 4.15—4.35 (m, 2-H′), 4.95 (*J* 11 Hz, 3-H), 5.29 (*J* 8 Hz, 3′-H), 5.39 (*J* 11 Hz, 2-H), 6.30, 6.41 (2 d, each *J* 2 Hz, 6- and 8-H), and 7.0—7.5 (6 H, ArH), c.d. 330 (Δε +2.2), 295 (−8.8), and 255 nm (+1.7) (*c* 29 × 10^{-3}, dioxan). Preparative t.l.c. as above gave isosilybin (7c) m.p. 239—241° (from AcOEt), $[\alpha]_D^{20}$ +16.9 (*c* 0.15, acetone), $\lambda_{max.}$ 325 (ε 11 600) and 287.5 nm (19 800), δ (pyridine) 3.73 (OMe), 3.85—4.05 (CH_2OH), 4.2—4.3 (m, 2′-H), 4.92 (*J* 11 Hz, 3-H), 5.32 (*J* 8 Hz, 3′-H), 5.38 (*J* 11 Hz, 2-H), 6.35 and 6.43 (2 d, each *J* 2 Hz, 6- and 8-H), and 7.0—7.5 (6 H, ArH), c.d. 330 (Δε +2.2), 295 (−10.1), and 255 nm (+ 1.7) (*c* 39 × 10^{-3}, dioxan).

* Optical purity 68%.

[9/443 *Received*, 19*th March*, 1979]

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