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LEUCOCYANIDIN: SYNTHESIS AND PROPERTIES OF (2*R*,3*S*,4*R*)-(+)-3,4,5,7,3′,4′-HEXAHYDROXYFLAVAN

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Key Word Index—Leucocyanidin; flavan-3, 4-diols; synthesis; polymerization; phytochemical significance.

Abstract—An isomer of leucocyanidin, (2*R*,3*S*,4*R*)-(+)-3,4,5,7,3′,4′-hexahydroxyflavan has been synthesized from (+)-taxifolin, isolated in its phenolic form, and characterized by ^{1}H and ^{13}C NMR, and formation of the 5,7,3′,4′-tetramethyl ether. Leucocyanidin readily polymerizes in acid solution to form a procyanidin polymer of high MW.

INTRODUCTION

Reports [1] of syntheses of leuco-cyanidin* or -pelargonidin, by reduction of the appropriate dihydroflavonol, led to a general acceptance of 3, 4, 5, 7, 3′,4′-hexahydroxyflavan as a probable natural product. For example, these reports were followed by several papers discussing the isolation of leucocyanidin from natural sources [3–12]. However, all this work, together with further syntheses of leucocyanidin [13, 14], suffered from a lack of convincing supporting spectroscopic evidence for a flavan-3, 4-diol constitution. The discovery of the dimeric, and oligomeric, nature of the majority of natural procyanidins in the late 1960s [15], and subsequent elaboration of their chemistry [15–18], has tended to de-emphasize this work in recent years, and subsequently led to some doubt [19] as to whether leucocyanidin exists as a natural product. In the meantime, however, the chemistry of 5,7,3′,4′-tetramethoxyflavan-3,4-diol was thoroughly explored, including the synthesis of two 2*R* enantiomers [20–22], and the four theoretically possible racemic diasteroisomers [23–25].

A recent report by Roux *et al.* [26] that a 2, 3-*trans*-4, 5, 7, 3′, 4′-pentamethoxyflavan-3-ol of undetermined stereochemistry at C-4 had been isolated from methylation of the product of direct $NaBH_4$ reduction of (+)-taxifolin (**1**) reawakened the possibility that leucocyanidin may be isolable in its phenolic form, and led us to re-investigate the above reduction.

*We follow the recommendation of Weinges *et al.* [2] that the name "leucocyanidin" be reserved for the flavan-3, 4-diol with a cyanidin oxygenation pattern, and "procyanidin" for a 4-*C*-substituted species.

†An MS of this compound has not been published. However, the observed fragmentation is, as expected, identical to 7, 8, 3′, 4′-tetramethoxyflavan-3, 4-diol [28] including the unusual ion at *m/z* 328 which we confirmed as $C_{19}H_{20}O_5$ by high resolution MS.

RESULTS AND DISCUSSION

Synthesis of leucocyanidin

Initial reductions of (+)-taxifolin (**1**) followed the procedure of Roux *et al.* [26]. Attempts to isolate leucocyanidin by direct evaporation of the EtOAc-soluble fraction led exclusively to polymerization, presumably catalyzed by residual HOAc. The work-up was modified so that the EtOAc was reduced to a small volume (10–20 ml) and applied to a column of Sephadex LH-20 and eluted with EtOH, which gave a 19% yield of leucocyanidin. Later experiments showed that the yield could be increased to over 60% by diluting the reaction mixture with water and adjusting the pH to 3–4 with HOAc.

The phenol (**2**) was dextrorotatory and shown to be the 3, 4-*trans* isomer from the ^{1}H NMR in d^6-acetone, which displayed the typical [27] large coupling constants associated with such stereochemistry ($J_{2,3}$ 9.9 Hz, $J_{3,4}$ 7.9 Hz). Furthermore, the chemical shifts of the heterocyclic ring carbon resonances in the ^{13}C NMR spectrum were very similar to those reported for the tetramethyl ether [17].

Methylation of the phenol with diazomethane gave 2, 3-*trans*-3, 4-*trans*-5, 7, 3′, 4′-tetramethoxyflavan-3, 4-diol (**3**) as the major product, together with a small amount of a pentamethyl ether (**4**). The constitution of the tetramethyl ether (**3**) was deduced from identical chromatographic, MS,† ^{1}H and ^{13}C NMR spectral properties to the known racemic tetramethyl ether [17, 25, 27, 28]. The tetramethyl ether (**3**) has a weakly positive optical rotation in chloroform at 578 nm and a negative ORD curve at shorter wavelengths. The major product from sodium borohydride reduction of (2*R*, 3*S*)-(+)-taxifolin (**1**) is therefore (2*R*, 3*S*, 4*R*)-(+)-3, 4, 5, 7, 3′, 4′-hexahydroxyflavan (**2**).

An alternative synthesis of the tetramethyl ether (**3**), and (**6**), was achieved by reduction of (2*R*, 3*S*)-taxifolin tetramethyl ether (**5**). The properties of (**3**) were identical to the material obtained by methylation

of the phenol (**2**). Similarly the mp and specific rotation of (2*R*, 3*S*, 4*S*)-tetramethoxyflavan-3, 4-diol (**6**) were consistent with those reported by Brown *et al.* [20, 21] who synthesized the diol by $Pb(OAc)_4$ oxidation of (2*R*, 3*S*)-5, 7, 3′, 4′-tetramethoxyflavan-3-ol (**7**), and $LiAlH_4$ reduction of **5**.

The pentamethyl ether (**4**) was the same product (MS, ^{1}H NMR) as isolated by Roux *et al.* [26] from methylation of the reduction product of taxifolin (**1**). They [26] could not deduce the configuration at C-4, which was shown to be 4*R* in the current study as follows. Refluxing racemic 2, 3-*trans*-3, 4-*trans*-5, 7, 3′, 4′-tetramethoxyflavan-3, 4-diol with methanol in the presence of 1% acetic acid [25] resulted in complete solvolysis of the diol into a mixture of 3, 4-*cis* (**8**) and -*trans* (**4**) 3-hydroxy-4-methoxyflavans. As expected [25] the 3, 4-*cis* (**8**) isomer was the major product, the two isomers being readily distinguished by the lower magnitude of $J_{3,4}$ 3.5 Hz for the 3,4-*cis* isomer, compared with $J_{3,4}$ 5.7 Hz for the 3,4-*trans* isomer. The latter compound was identical (chromatographically, MS, ^{1}H NMR) to the earlier product (**4**) derived from methylation of the phenol (**2**). Roux *et al.* [26] had therefore isolated (2*R*, 3*S*, 4*R*)-4, 5, 7, 3′, 4′-pentamethoxyflavan-3-ol (**4**).

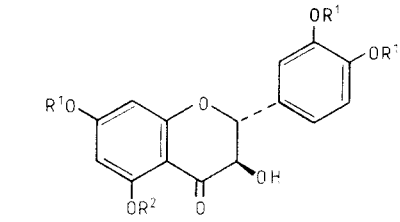
This work also showed that (**4**) must be formed by direct attack of diazomethane on the 4-hydroxyl function, which presumably is acidic enough for the reaction to proceed in moderate yield. The alternative mechanism would have been nucleophilic displacement by the solvent MeOH, which would favour the 3, 4-*cis* isomer.

Taxifolin tetramethyl ether

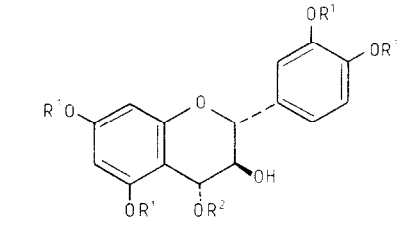
The current study also revealed that taxifolin tetramethyl ether, derived from (+)-taxifolin, has not been reported as chirally homogeneous material. Most earlier work relates to the racemic tetramethyl ether, usually synthesized by reaction of racemic taxifolin with dimethyl sulphate [23–25, 29–31]. Similar treatment of (2*R*, 3*S*)-taxifolin (**5**) causes racemization to a greater or lesser extent. Clark–Lewis and Korytnyk [32] obtained a tetramethyl ether with $[\alpha]_{589} - 23.4°$, Brown and McBride [21] obtained a value of −14°, while the method yielded a product with a rotation of −12.4° in our hands; Weinges [33] isolated a racemic tetramethyl ether. In contrast, methylation with diazomethane yielded a tetramethyl ether with $[\alpha]_{589} - 29.7°$.

It should also be noted that the mp of (2*R*, 3*S*)-taxifolin tetramethyl ether (**5**), 153–155°, is much lower than that reported by Clark–Lewis and Korytnyk [32], for the partly racemic tetramethyl ether. Melting points in the range 160–172° [23–25, 29–33] are apparently associated with racemic or partly racemic, material.

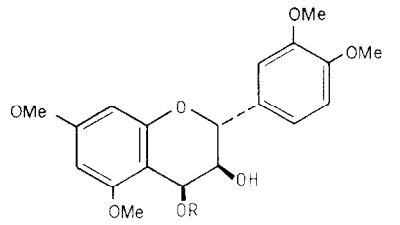
Evidence for the chiral homogeneity of the (+)-taxifolin (**1**) used in this study, and of the stereoselectivity [34] of the subsequent reduction, was obtained from formation of the heptamethyl ether of (2*R*, 3*S*, 4*R*)-4-(2, 4, 6-trihydroxyphenyl)-3, 5, 7, 3′, 4′-pentahydroxyflavan (**9**) from methylation of the product of reaction between phloroglucinol and the 4-carbocation from acid-catalysed decomposition of the reduced borate complex [26] of **1**. The optical



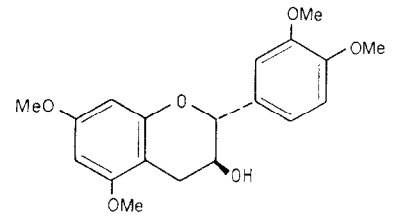
1 $R^1 = R^2 = H$
5 $R^1 = R^2 = Me$
11 $R^1 = Me, R^2 = H$



2 $R^1 = R^2 = H$
3 $R^1 = Me, R^2 = H$
4 $R^1 = R^2 = Me$



6 R = H
8 R = Me



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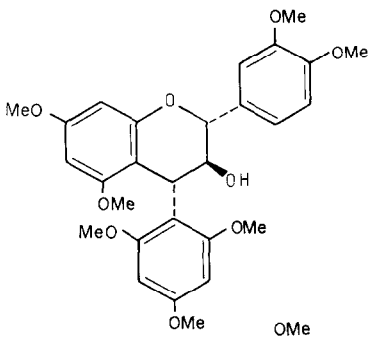
rotation of **9** agreed closely with material prepared by a similar condensation reaction between phloroglucinol and carbocation generated from a natural procyanidin polymer [17].

The 3, 4-*cis* isomer (**10**) was also formed, but in much lower relative yield than implied from the work of Roux *et al.* [26]. Further evidence for the 3, 4-*cis* configuration was obtained from the position of the heterocyclic ring carbon resonances in the ^{13}C NMR spectrum of **10**, where the chemical shift of C-2 at δ 78.2, compared with the position of C-2 of δ 82.5 in the spectrum of **9**, is consistent with a *pseudo*-axial phenyl substituent [17].

Is leucocyanidin a natural product?

As discussed earlier, the syntheses of leucocyanidin were followed by several reports of its isola-



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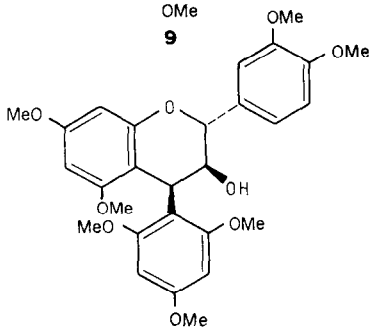

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tion from natural sources [3–12]. Of these, one report justifies further consideration, as the leucocyanidin from *Butea frondosa* gum was reported to have been synthesized from the reduction of taxifolin, and the natural and synthetic tetramethyl ethers found to be identical by mp and mmp [4]. We are now in a position to reappraise this work.

The natural *B. frondosa* leucocyanidin was reported to form a tetramethyl ether on reaction with diazomethane, which crystallized as prisms from methanol, mp 198–200°, $[\alpha]_{589} + 125.2°$ (in ethanol). Reduction of taxifolin tetramethyl ether was reported to produce the same compound, plus another isomer, needles, mp 171–172°.

The latter compounds correspond well with the racemic diols, the 3,4-*trans* diol being prisms, mp range 205–207° and the 3, 4-*cis* isomer, needles, mp range 165–171°. In contrast, the optically pure diols both crystallize as needles, mp 189–190° for the 3, 4-*cis* isomer [21] and mp 167–168° for the 3, 4-*trans* isomer. Moreover, neither isomer is soluble in ethanol at the concentration stated by Ganguly and Seshadri [4] for the specific rotation of the natural diol. Furthermore, neither optically active diol has a rotation approaching the magnitude of the *Butea* compound. A further factor militates against the leucocyanidin constitution for Ganguly and Seshadri's [4] compound. Later work [17] established that the gum was a rich source of 2, 3-*cis* procyanidin units, so that the chance of finding a 2, 3-*trans* leucocyanidin seems unlikely on biosynthetic grounds. It therefore seems more plausible that these workers isolated a procyanidin dimer with a 2, 3-*cis* procyanidin unit, as the high positive rotation is consistent with such a constitution [36].

The question of whether or not leucocyanidin exists as a natural product therefore remains unresolved until unequivocal evidence is obtained. 'Cold trap' experiments failed to find evidence for such entities in a recent study [19]. However, the current demonstration that leucocyanidin is capable of existence, and characterization of its properties, may facilitate its isolation, or detection, in the future.

Leucocyanidin polymerization

As alluded to earlier, 2,3-*trans*-3,4-*trans*-leucocyanidin (**2**) readily polymerizes in the presence of even low concentrations of acid. Swain [37] stated: "Treatment with cold 2 N hydrochloric acid gave a white precipitate... soluble in alcohol, which appeared to be polymeric, since methylation and subsequent acetylation... gave a product having a molecular weight (1940) indicative of a tetramer or pentamer". Repetition of this experiment confirmed that leucocyanidin forms such a precipitate, and ^{13}C NMR revealed it to have a very similar spectrum to an all-2, 3-*trans* prodelphinidin polymer isolated from *Watsonia pyramidata* leaves [Foo, L. Y. and Porter, L. J., unpublished results] except for the absence of signals arising from the terminal flavan-3-ol unit in the latter spectrum, and the expected [18] differences due to B-ring oxidation pattern (see Fig. 1).

The specific rotation of the polymer at 578 nm was

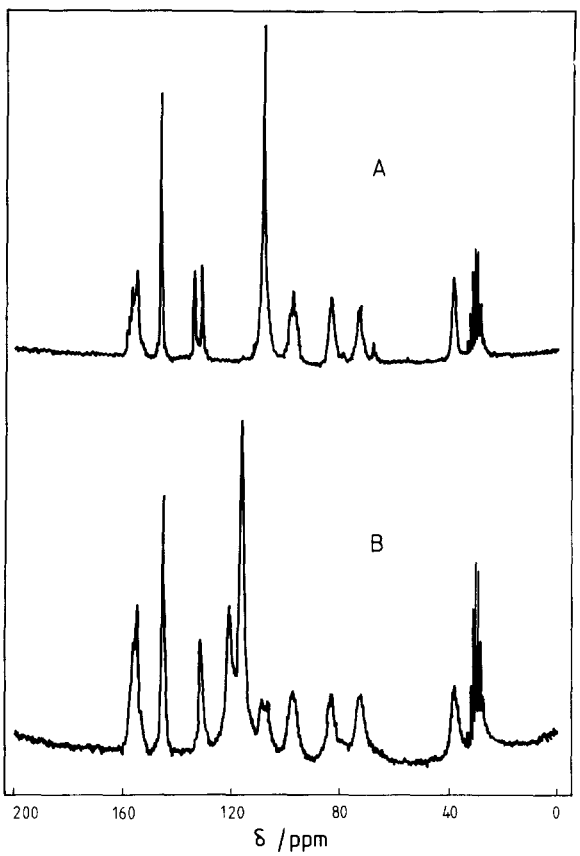

Fig. 1. ^{13}C NMR of 2, 3-*trans*-proanthocyanidin polymers. (A) *Watsonia pyramidata* tannin. (B) Synthetic polyleucocyanidin.

−331°, close to that predicted [18] for an all-2, 3-*trans* procyanidin or prodelphinidin polymer, −320°. Gel permeation chromatography [38] of the acetate derivative of the synthetic polymer showed that it had a very high number-average MW, $\bar{M}_n$ 5600 much higher than values observed for natural procyanidin polymers [18, 38, 39]. The magnitude of $\bar{M}_n$ is therefore too high for terminal flavan-3, 4-diol units to be observed [18], even though this is theoretically possible. It should be noted too, that in the absence of a chain-terminating flavan-3-ol unit, cyclic polymer species are possible in polymeric leucocyanidin.

Conclusion

An isomer of leucocyanidin has been synthesized from (+)-taxifolin, and isolated in its phenolic form. The purified compound is quite stable, but is very sensitive to low concentrations of acid in solution, when it readily polymerizes through formation of a 4-carbocation. The compound therefore fits the predictions of Clark–Lewis very accurately, who stated [25]: "The considerable stabilization of the flavan 4-carbonium ion through electron release from the phloroglucinol ring implies that the 4-hydroxyl group will be particularly reactive in leucocyanidin flavan-3, 4-diols which, in consequence, will be especially difficult to handle. In addition there will be increased liability to polymeric condensation through electrophilic substitution by a 4-carbonium ion derived from one molecule into the phloroglucinol ring of a neighbouring molecule".

It may also be concluded that it is virtually certain that leucocyanidin has not yet been isolated from natural sources. The current study shows, however, that if leucocyanidin does exist in natural plant systems, it may, in principle, be isolated and characterized.

EXPERIMENTAL

Analytical separations by TLC were performed on Schleicher & Schull F1400 Cellulose and Merck 60F254 silica gel precoated plates (SiO_2 solvent, C_6H_6–Me_2CO, 4:1), and prep. TLC on Merck Kieselgel $PF_{254+366}$. Spots were visualized on cellulose by vanillin–HCl spray, and SiO_2 by UV illumination and $SnCl_4$–$SOCl_2$ fuming (for flavan-3, 4-diol methyl ethers). NMR measurements were performed on a Varian FT-80A instrument (^1H, 80 MHz; ^{13}C, 20 MHz), optical rotations on a Perkin–Elmer Model 241 spectropolarimeter, and MS on Kratos MS-30 (low-resolution) and MS-902 (high-resolution) instruments.

Taxifolin was obtained from Koch-Light {$[\alpha]_{578}^{25}$ + 47.9° (*c* 1.4 in Me_2CO–H_2O, 1:1)} and Fluka {$[\alpha]_{578}^{25}$ + 46.1° (*c* 0.8 in Me_2CO–H_2O, 1:1)}.

(2*R*,3*S*,4*R*)-(+)-3,4,5,7,3′,4′-*Hexahydroxyflavan* (**2**). Taxifolin (0.5 g) in EtOH (100 ml) was stirred with $NaBH_4$ (0.25 g), added in one lot, for 2 hr. The yellow solution was poured into H_2O (1000 ml) and the pH adjusted to 3–4 with HOAc. The solution was extracted with EtOAc (5 × 200 ml) and the combined extracts dried over Na_2SO_4–$NaHCO_3$. The EtOAc was evaporated *in vacuo* at <40° to 10–20 ml, and immediately added to a 2.5 × 30 cm column of Sephadex LH-20 pre-swollen in EtOH, the column was developed in EtOH and the eluant collected as 15-ml fractions. Leucocyanidin was eluted in fractions 20–30, minor isomer R_f (cellulose) 0.70 (water-saturated *s*-BuOH) 0.36 (6% HOAc) in the first two fractions, and the major isomer (**2**) in all fractions, R_f (cellulose) 0.73 (water-saturated *s*-BuOH) 0.72 (*t*-BuOH–HOAc–H_2O, 3:1:1) 0.48 (6% HOAc), yield 300–340 mg crude product. The major isomer was rechromatographed to produce the phenol (**2**), after Millipore filtration evapn of solvent, and drying *in vacuo* over P_2O_5, λ_{max} 278 nm (log ε 3.53 in MeOH–H_2O, 1:1, v/v):

$[\alpha]_{25°}^{\lambda}$	589	578	546	436
	+15.5	+16.0	+17.7	+25.0

(*c* 0.71 in MeOH–H_2O, 1:1, v/v).

^1H NMR (in d^6-acetone) δ 3.88 (*m*, H-3), δ 4.62 (*d*, *J* = 9.9 Hz, H-2), 5.00 (*d*, *J* = 7.9 Hz, H-4), 5.83 (*d*, *J* = 2.3 Hz, H-8), 5.97 (*d*, *J* = 2.3 Hz, H-6), 6.80 (*s*, H-2′), 6.81 (*s*, H-5′), 6.95 (*s*, H-6′). ^{13}C NMR (in d^6-acetone–H_2O, 1:1, v/v) δ 71.6 (C-4), 73.9 (C-3), 81.7 (C-2), 95.8 (C-8), 97.6 (C-6), 103.8 (C-4a), 116.2 (C-2′), 116.5 (C-5′), 121.1 (C-6′), 130.1 (C-1′), 145.4 (C-3′), 145.9 (C-4′), 156.6 (C-8a), 158.4 (C-5 or -7), 158.7 (C-5 or -7).

(2R, 3S, 4R)-5, 7, 3′, 4′-*tetramethoxyflavan*-3, 4-*diol* (**3**). The phenol (**2**) was dissolved in MeOH and treated with ethereal diazomethane to yield two major products from prep. TLC, the pentamethyl ether (**4**), R_f 0.46, and tetramethyl ether (**3**), R_f 0.18, which cochromatographed with authentic racemic 2,3-*trans*-3,4-*trans*-5,7,3′,4′-tetramethoxyflavan-3, 4-diol, and crystallized from MeOH as needles, mp 167–168°.

$[\alpha]_{25°}^{\lambda}$	589	578	546	436	365	313	302
	+0.9	+1.2	+0.9	−3.3	−27.6	−148	−192

(*c* 0.33 in $CHCl_3$),

$[\alpha]_{25°}^{\lambda}$	589	578	546	436	365
	−1.1	−1.4	−1.9	−6.9	−24.3

(*c* 0.72 in Me_2CO).

^1H NMR ($CDCl_3$): δ 3.77 (1 × OMe), 3.87 (1 × OMe), 3.89 (2 × OMe), 4.08 (1H, *q*, H-3), 4.69 (1H, *d*, *J* = 10.2 Hz), 5.00 (1H, *d*, *J* = 7.4 Hz), 6.11 (2H, AB*q*, H-6, H-8), 6.94 (1H, H-6′), 7.01 (2H, H-2′,-5′). ^{13}C NMR ($CDCl_3$) δ 70.5 (C-4), 73.6 (C-3), 80.9 (C-2), 93.0 (C-8), 93.9 (C-6), 105.9 (C-4a), 110.6 (C-2′), 111.4 (C-5′), 120.8 (C-6′), 149.5 (C-3′), 149.8 (C-4′), 156.0 (C-8a), 159.6 (C-7), 161.2 (C-5), MS (70 eV, 160°) *m/z* (rel. int.) 362.1369 (M^+, 11, calc. for $C_{19}H_{22}O_7$, 362.1364), 344 ($M^+ - H_2O$, 7) 328 (3) 316 (13), 183 (18), 180 (100), 165 (13), 151 (8), 95 (13). (Found: C, 63.2; H, 6.5. $C_{19}H_{22}O_7$ requires: C, 63.0; H, 6.1%.)

Synthesis of (2R, 3S, 4R)- *and* (2R, 3S, 4S)-5, 7, 3′, 4′-*tetramethoxyflavan*-3, 4-*diol from* (2R, 3S)-5, 7, 3′, 4′-*tetramethoxyflavan*-3-*ol*-4-*one*. Taxifolin (0.3 g) was dissolved in MeOH and reacted with ethereal diazomethane at 0° overnight. The solvent was removed *in vacuo* at 40° and the major products, the trimethyl ether (**11**) [R_f SiO_2, 0.55. MS (70 eV) *m/z* (rel. int.) 346 (M^+, 17), 317 (32), 180 (51), 179 (37), 178 (44), 167 (100), 151 (64), 121 (33)] and tetramethyl ether (**5**)—R_f SiO_2, 0.35—were separated by prep. TLC. The

tetramethyl ether was crystallized from MeOH or EtOH as plates, or EtOAc–C_6H_{14} as needles, mp 153–155°. MS (70 eV) *m/z* (rel. int.) 360 (M^+, 5), 331 (65), 193 (18), 181 (100), 167 (18), 151 (17).

$[\alpha]^{\lambda}_{25°}$	589	578	546	435	365
	−29.7	−31.7	−38.5	−102	−278

(*c* 0.70 in $CHCl_3$).

Taxifolin tetramethyl ether (0.43 g) was dissolved in MeOH (100 ml) and $NaBH_4$ (0.3 g) was added in one lot, and the soln stirred for 1 hr. The vol. was reduced to 10 ml (*in vacuo*, 40°) and water added (200 ml) and the soln extracted with Et_2O (3 × 100 ml). The soln was acidified (HOAc, 1 ml) and extracted again. The two Et_2O fractions were dried (Na_2SO_4), the 3, 4-*cis* isomer crystallizing as needles from the second fraction. Most of the 3, 4-*cis* isomer was removed from both fractions by crystallization from MeOH to give needles, mp 187–189° (lit. value [21] 189–190°), combined yield 0.22 g.

$[\alpha]^{\lambda}_{25°}$	589	578	546	436	365	313	302
	+35.0	+37.0	+42.5	+81.1	+151	+320	+362

(*c* 0.30 in $CHCl_3$).

Lit. value $[\alpha]^{19}_{589}$ + 34° (*c* 2.27 in $CHCl_3$).

The mother-liquors were combined and the 3, 4-*cis* isomer (R_f 0.24) separated from the 3, 4-*trans* isomer (R_f 0.18), and the latter was crystallized from MeOH to give needles, mp 167–168°, undepressed when mixed with the 3, 4-*trans* isomer prepared by methylation of the phenol (**2**), yield 40 mg.

$[\alpha]^{\lambda}_{25°}$	589	578	546	436	365	313	302
	+1.2	+1.6	+1.9	−2.8	−29.5	−160	−192

(*c* 0.32 in $CHCl_3$).

Preparation of the racemic 3, 4-trans *and* -cis *isomers of* 2, 3-trans-*leucocyanidin tetramethyl ether.* (+)-Taxifolin was racemized by the method of Pew [40], and methylated by the procedure of Hergert *et al.* [29] to yield racemic taxifolin tetramethyl ether, needles from 95% EtOH, mp 174–176°, lit. value [33] 170–172°. The 2, 3-*trans*-3, 4-*trans* and -*cis* diols were prepared by $NaBH_4$ reduction of taxifolin tetramethyl ether by the method of ref. [24] to yield racemic (i) 2,3-*trans*-3,4-*trans*-5,7,3′,4′-tetramethoxyflavan-3,4-diol, stout rhombs from MeOH, mp 207–209° (lit. value [24] 205–207°) and (ii) 2,3-*trans*-3,4-*cis*-5,7,3′,4′-tetramethoxyflavan-3,4-diol, needles from MeOH mp 166–167° (lit. value [24] 165–167°).

Formation of the 4-*methoxy-isomers.* Racemic 2, 3-*trans*-3, 4-*trans*-5, 7, 3′, 4′-tetramethoxyflavan-3, 4-diol (0.12 g) was dissolved in MeOH (12 ml), HOAc (0.1 ml) added, and the reaction mixture refluxed overnight. TLC revealed complete conversion of the diol to two higher mobility products, which were separated by prep. TLC to yield (i) 2, 3-*trans*-3, 4-*cis*-4, 5, 7, 3′, 4′-pentamethoxyflavan-3, 4-diol (**8**), R_f 0.62, 50 mg of an amorphous solid, ^1H NMR ($CDCl_3$) δ 3.56 (3H, *s*, OMe), 3.75 (3H, *s*, OMe), 3.83 (3H, *s*, OMe), 3.88 (6H, *s*, 2 × OMe), 4.10 (1H, *m*, H-3), 4.68 (1H, *d*, *J* = 3.5 Hz, H-4), 4.96 (1H, *d*, *J* = 10.4 Hz, H-2), 6.10 (2H, AB*q*, H-6 and H-8), 6.9–7.0 (3H, H-2′, -5′ and -6′). MS (70 eV, 120°) *m/z* (rel. int.) 376 (M^+, 12), 344 (M^+ − MeOH, 19), 316 (M^+ − MeOH–H_2O, 75), 301, (22), 197 (100), 181 (22), 180 (26), 167 (27), 151 (23), 77 (12). (ii) 2,3-*trans*-3,4-*trans*-4,5,7,3′,4′-Pentamethoxyflavan-3-ol (**4**), R_f 0.46, co-chromatographed with the pentamethyl ether formed by methylation of the phenol (**2**), 14 mg of an amorphous solid, ^1H NMR ($CDCl_3$) δ 3.47 (3H, *s*, OMe), 3.74 (3H, *s*, OMe), 3.83 (3H, *s*, OMe), 3.87 (3H, *s*, OMe) 3.88 (3H, *s*, OMe), 4.20 (1H, *m*, H-3), 4.58 (1H, *J* = 5.7 Hz, H-4), 4.71 (1H, *d*, *J* = 8.8 Hz, H-2), 6.12 (2H, AB*q*, H-6 and -8), 6.9–7.0 (3H, H-2′, -5′ and -6′). MS (70 eV, 120°) 376 (M^+, 4), 344 (M^+ − MeOH, 6), 316 (M^+ − MeOH–H_2O, 15), 301 (8), 197 (100), 181 (20), 180 (35), 167 (35), 151 (25).

The ^1H NMR and MS of this compound were identical to those of the pentamethyl ether isolated from methylation of the phenol (**2**).

(2R, 3S, 4R-)- *and* (2R, 3S, 4S)-4-(2, 4, 6-*trimethoxyphenyl*)-5,7,3′,4′-*tetramethoxyflavan*-3-*ol* (**9** *and* **10**). These compounds were synthesized from (+)-taxifolin and phloroglucinol as described in ref. [26], except that methylation was performed by reaction with Me_2SO_4–anhydrous K_2CO_3 to avoid formation of octamethyl ethers. The major 3, 4-*trans* (**9**) isomer had an ^1H NMR identical to that previously reported [26, 35], MS (70 eV), *m/z* (rel. int.) 512 (M^+, 19), 492 (28), 333 (72), 301 (100), 181 (20), 167 (27), 151 (33), $[\alpha]^{25}_{578}$ − 189° (*c* 0.19 in $CHCl_3$), lit. value −194° [17], mp 194–196° (lit. values 195–196° [26] and 196–197° [17]).* The minor 3, 4-*cis* isomer (**10**), an amorphous solid, $[\alpha]^{25}_{578}$ + 85.0° (*c* 0.13 in $CHCl_3$), MS (70 eV), *m/z* (rel. int.) 512 (M^+, 16), 493 (20), 333 (91), 317 (39), 315 (38), 301 (100), 181 (39), 167 (48), 151 (65). ^1H NMR ($CDCl_3$) δ 3.55 (3H, *s*, OMe), 3.77 (3H, *s*, OMe), 3.80 (6H, *s*, 2 × OMe), 3.86 (9H, *s*, 3 × OMe), 4.94 (1H, *d*, *J* = 5.8 Hz, H-4), 4.96 (1H, *d*, *J* = 9.7 Hz, H-2), 6.00 (1H, *d*, *J* = 2.3 Hz, H-8), 6.18 (3H, *br*, H-6, -3″ and -5″), 6.89, 6.95, 7.05 (3H, B-ring protons). ^{13}C NMR ($CDCl_3$) δ 32.2 (C-4), 71.8 (C-3), 78.2 (C-2), 91.4 (C-8), 92.8 (C-6), 92.9 (C-3″ and -5″; broad signal), 105.5 (C-4a), 109.7 (C-1″), 110.5 (C-2′), 111.1 (C-5′), 120.3 (C-6′), 132.1 (C-1″), 149.0 (C-3′, and -4′), 55.2, 55.3, 55.9, 56.0, 56.3 (OMe signals), 156.3, 158.2, 160.0 (C-5, -7, -8a, -2″, -4″, and -6″). The isomers were isolated in an approximate ratio of *trans* : *cis* of 20 : 1.

*Jurd and Lundin [35] made the racemic 3, 4-*trans* heptamethyl ether, mp 204°, as did Weinges *et al.* [41], mp 204–205°, who used taxifolin tetramethyl ether [41] racemized by methylation [33].

Synthesis of polymeric leucocyanidin. Leucocyanidin-borate complex was synthesized by the reduction of 1 g of (+)-taxifolin with 0.5 g of $NaBH_4$ in absolute EtOH (20 ml). After reaction the EtOH was evaporated off *in vacuo* at 40° and the resulting yellow solid dissolved in H_2O (20 ml) and the stirred solution acidified by dropwise addition of 2 N HCl. The resulting cream precipitate was collected by filtration and thoroughly washed with H_2O and dried *in vacuo* over NaOH and Si gel, yield 0.95 g, $[\alpha]_{578}^{25} - 331°$ (*c* 0.52 in MeOH–H_2O, 1:1). The polymer was readily soluble in Me_2CO–H_2O (1:1) and yielded cyanidin chloride on heating with EtOH–HCl. The polymer was acetylated with Ac_2O–pyridine, and the MW of the resulting acetate derivative was determined by GPC on a 1000 Å μStyragel column in THF [Foo, L. Y. and Porter, L. J., unpublished results].

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