Studies in Polyphenol Chemistry and Bioactivity. 2.[1] Establishment of Interflavan Linkage Regio- and Stereochemistry by Oxidative Degradation of an *O*-Alkylated Derivative of Procyanidin B_2 to (*R*)-(−)-2,4-Diphenylbutyric Acid

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The assignment of interflavan bond regio- and stereochemistry in oligomeric proanthocyanidins has in the past relied on empirical spectroscopic techniques which are influenced by the conformation of the C rings. Only recently was the 4,8-regiochemistry of procyanidin B_2 (**3b**) firmly established by 2-dimensional NMR methods. We describe herein the proof of 4β-stereochemistry in **3b** by oxidative degradation of the derivative **3d** bearing differential (*O*-benzyl and *O*-methyl) protecting groups in its "top" and "bottom" epicatechin moieties, to (*R*)-(−)-2,4-diphenylbutyric acid. The key elements of the degradative process are (1) removal of the C-3 alcohol functions through a modified Barton deoxygenation employing hypophosphorous acid as the reducing agent; (2) deprotection of the "top" unit by hydrogenolysis, followed by exhaustive aryl triflate formation with *N*,*N*-bis-(trifluoromethanesulfonyl)aniline and DBU in DMF; (3) hydrogenolytic deoxygenation of the "top" unit over Pearlman's catalyst with concomitant scission of the O−C2 bond; (4) selective oxidation of the "bottom" unit with $NaIO_4/RuCl_3$. The hitherto unreported absolute configuration of (−)-2,4-diphenylbutyric acid was established as *R* by X-ray crystal structure analysis of the (*R*)-(+)-α-methylbenzylamine salt. As a corollary, the selectivity of hydrogenolytic and solvolytic reactions of epicatechin-derived tetrasulfonates has been investigated.

Introduction

Proanthocyanidins (condensed or nonhydrolyzable tannins) constitute an important group of natural products.[1] Although crude preparations containing such compounds have been known for some time, the isolation and characterization of individual compounds had to await the arrival of modern chromatographic and spectroscopic techniques. As late as 1960, two equally wrong structures of the simple dimer, epicatechin-4β,8-epicatechin (**3b**, procyanidin B_2, or then referred to as leucocyanidin 1), were discussed which contained a supernumerary oxygen atom and a hemiacetal linkage between the two epicatechin units.[2] The accepted gross structures of dimeric proanthocyanidins were subsequently deduced by NMR spectroscopy[3] and by synthesis;[4] however, the assignment of interflavan bond regio- and stereochemistry proved to be a difficult task. The interflavan bond in procyanidin B_3 (catechin-4α,8-catechin) was located unequivocally by synthesis of a derivative from 8-bromo-5,7,3′,4′-tetra-*O*-methylcatechin,[4b] in which the position of the Br substituent was later established by X-ray crystallography.[5] In other cases, assignment of interflavan regiochemistry was undertaken on the basis of small chemical shift differences between 6-H of 4,8-linked units and 8-H of 4,6-linked units, as well as other empirical criteria for which there were neither firmly known structures as anchoring points nor compelling reasons why the observed parameters had to be influenced by the interflavan regiochemistry in the way they were postulated to be.[6] Only recently have the hypothesized interflavan regiochemistries for three more dimeric procyanidins and one trimer been confirmed by 2D-NMR techniques,[7] and the regiochemistry of procyanidin B_3 has been reconfirmed in the same manner.[8] In a different approach, NOE's were examined between the A[2] ring protons and the adjacent methoxyl protons in the methyl ether acetate derivatives of fisetinidol-4,6- and -4,8-catechin isomers (fisetinidol = 6-deoxycatechin).[9] It is our hope that such rational methods will in future be routinely utilized. Certainly, the fortuitous confirmation of previously conjectured structures should not be construed as a vindication of questionable empirical rules.

The stereochemical issue remains a challenge. Extensive use has been made of the coupling constant between

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(1) Part 1: Tückmantel, W.; Kozikowski, A. P.; Romanczyk, L. L., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 12073. See here for a general introduction of plant polyphenols, especially condensed tannins.
(2) Forsyth, W. G. C.; Roberts, J. B. *Biochem. J.* **1960**, *74*, 374.
(3) Geissman, T. A.; Dittmar, H. K. F. *Phytochemistry* **1965**, *4*, 359.
(4) (a) Creasy, L. L.; Swain, T. *Nature* **1965**, *208*, 151. (b) Weinges, K.; Perner, J.; Marx, H.-D. *Chem. Ber.* **1970**, *103*, 2344.
(5) Engel, D. W.; Hattingh, M.; Hundt, H. K. L.; Roux, D. G. *J. Chem. Soc., Chem. Commun.* **1978**, 695.
(6) The disturbing situation is reviewed in the Introductions of refs 7a and 8.
(7) (a) Balas, L.; Vercauteren, J. *Magn. Reson. Chem.* **1994**, *32*, 386. (b) Balas, L.; Vercauteren, J.; Laguerre, M. *Magn. Reson. Chem.* **1995**, *33*, 85. (c) Khan, M. L.; Haslam, E.; Williamson, M. P. *Magn. Reson. Chem.* **1997**, *35*, 854.
(8) De Bruyne, T.; Pieters, L. A. C.; Dommisse, R. A.; Kolodziej, H.; Wray, V.; Domke, T.; Vlietinck, A. J. *Phytochemistry* **1996**, *43*, 265.
(9) Steynberg, J. P.; Brandt, E. V.; Ferreira, D.; Helfer, C. A.; Mattice, W. L.; Gornik, D.; Hemingway, R. W. *Magn. Reson. Chem.* **1995**, *33*, 611.

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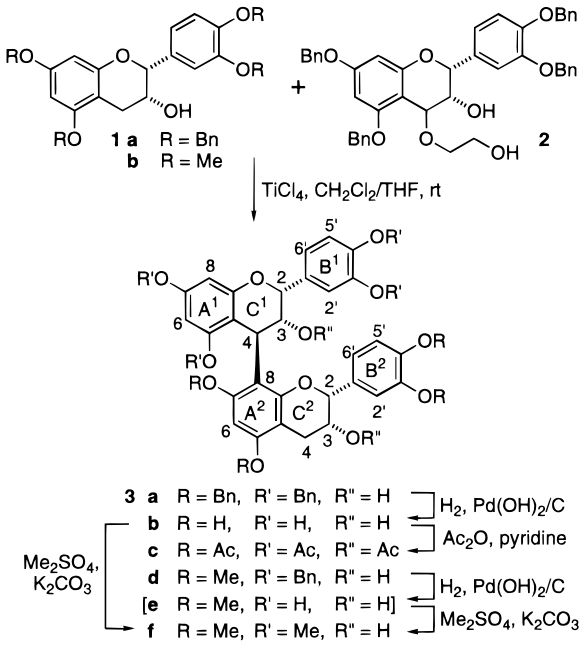
Scheme 1



the C-ring protons 3-H and 4-H. However, while large (approximately 8−10 Hz) values are indicative of a (nearly) trans-diaxial arrangement of the coupling protons, smaller values are inconclusive. Recourse to circular dichroism is usually made in such cases.[10] Circular dichroism, however, like $^1H-^1H$ coupling, is influenced by the C-ring conformation as well. It is thus not surprising that assignments based on this method have been documented that contradicted those obtained differently.[11] On a more fundamental level, any and all assumptions of preferred conformations, whether arrived at intuitively or through computation, must be rejected if a rigorous proof of structure is to be obtained.

We have recently described[1] the formation of a single dimeric product **3a** (Scheme 1) in the electrophilic substitution reaction between 5,7,3′,4′-tetra-*O*-benzylepicatechin (**1a**) and the 4-alkoxylated building block **2**, which upon hydrogenolysis and acetylation yielded the decaacetate **3c**, identical with deca-*O*-acetylprocyanidin B_2 as described by several sources. While the 4,8-position of the interflavan bond in the free polyphenol **3b** has previously been established by others,[7c] its stereochemistry could be only tentatively assigned as β in line with the literature tradition and mechanistic reasoning. An unequivocal determination of this point is long overdue, and the present paper describes our solution of the problem. As this investigation confirms the hitherto conjectured 4β stereochemistry, all formulas are depicted accordingly.

Strategy

Our attempts at obtaining crystalline derivatives of procyanidin B_2 have uniformly met with failure.[1] We therefore made recourse to the traditional approach of

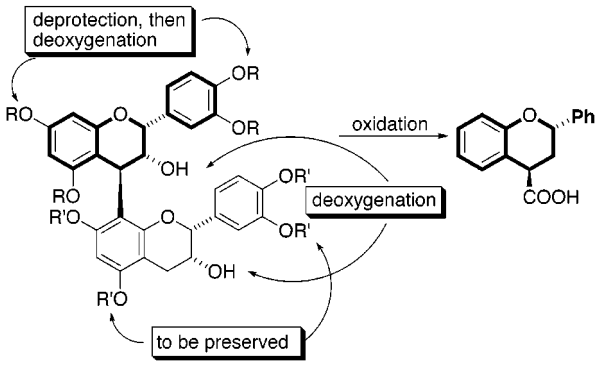
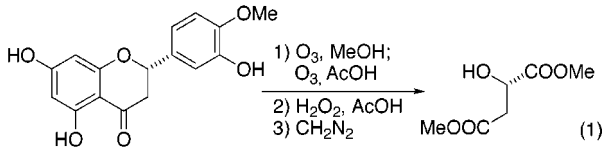


Figure 1. Strategy for the defunctionalization and oxidative degradation of a protected epicatechin dimer.

defunctionalizing and degrading the parent structure to a simpler compound that is either known or can be resynthesized from known compounds by stereochemically well-defined operations. For example, the absolute configuration of the flavonoid natural product, (−)-hesperetin, was established by ozonolysis, which resulted in the formation of L-malic acid isolated as its dimethyl ester (eq 1).[12]



The case at hand is more complex since degradation of all aromatic rings to carboxyl groups would destroy the asymmetric center at C-4 of ring C^1. Differentiation of rings A^1 and A^2 was therefore required with the aim of preserving ring A^1, and the final oxidation step would have to be conducted under carefully controlled conditions to achieve the required selectivity. Moreover, the presence of multiple ether functionality on all aromatic rings, which activates them toward oxidation, was deemed detrimental to the control of their oxidation and would furthermore complicate the structure of the degradation product. Last, initial removal of the C-3 alcoholic hydroxyls was also considered prudent, as these functions, too, increase structural complexity and additionally might participate in elimination reactions or undergo oxidation themselves depending on the oxidant and protecting group used. Deactivation of ring A^1 was envisaged by introduction of an electron-withdrawing substituent,[13] but it soon transpired in model studies (vide infra) that exhaustive derivatization of a dimeric procyanidin with substituents that permit a subsequent deoxygenation was difficult. As an alternative, differentiation between the two epicatechin units in the required sense could be achieved by maintaining the phenolic hydroxyl groups of the "bottom" unit in a suitably protected form while deoxygenating rings A^1 and B^1. The use of identical phenol protection for the A and B rings within each epicatechin unit, while inconsequential for

(10) (a) Barrett, M. W.; Klyne, W.; Scopes, P. M.; Fletcher, A. C.; Porter, L. J.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2375. (b) Botha, J. J.; Young, D. A.; Ferreira, D.; Roux, D. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1213.

(11) Hundt, A. F.; Burger, J. F. W.; Steynberg, J. P.; Steenkamp, J. A.; Ferreira, D. *Tetrahedron Lett.* **1990**, *31*, 5073 and references quoted therein.

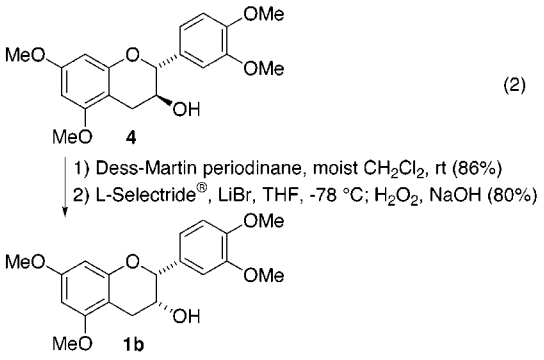
(12) Arakawa, H.; Nakazaki, M. *Liebigs Ann. Chem.* **1960**, *636*, 111. For similar examples, see: Arakawa, H.; Nakazaki, M. *Chem. Ind. (London)* **1959**, 671; Nakazaki, M. *Chem. Ind. (London)* **1962**, 1577; Goering, H. L.; Kimoto, W. I. *J. Am. Chem. Soc.* **1965**, *87*, 1748.

(13) Bromination of **3a** with 1 equiv of NBS (compare ref 1) yielded mostly the monobromide bearing the substituent at C-8 of ring A^1, which could have been used as a starting material: Kozikowski, A. P.; Tückmantel, W., unpublished.

the goal at hand, was dictated by practical considerations. The resulting overall plan is summarized in Figure 1.

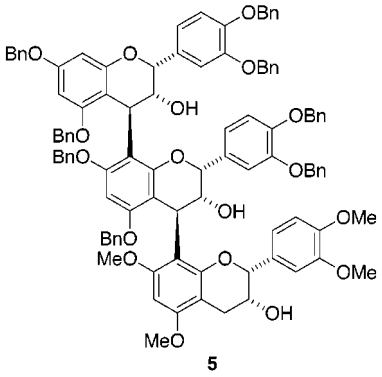
Results

Preparation of the Starting Material. Based on availability from the literature and our previous work, the obvious choice of phenol protecting groups was benzyl for the "top" and methyl for the "bottom" epicatechin moiety. (+)-Catechin was *O*-methylated[14] and the C-3 stereochemistry of the product **4** inverted by the same oxidation−reduction sequence as previously described in the *O*-benzyl series[1] to produce 5,7,3′,4′-tetra-*O*-methylepicatechin (**1b**) in good yield and purity (eq 2). Reaction



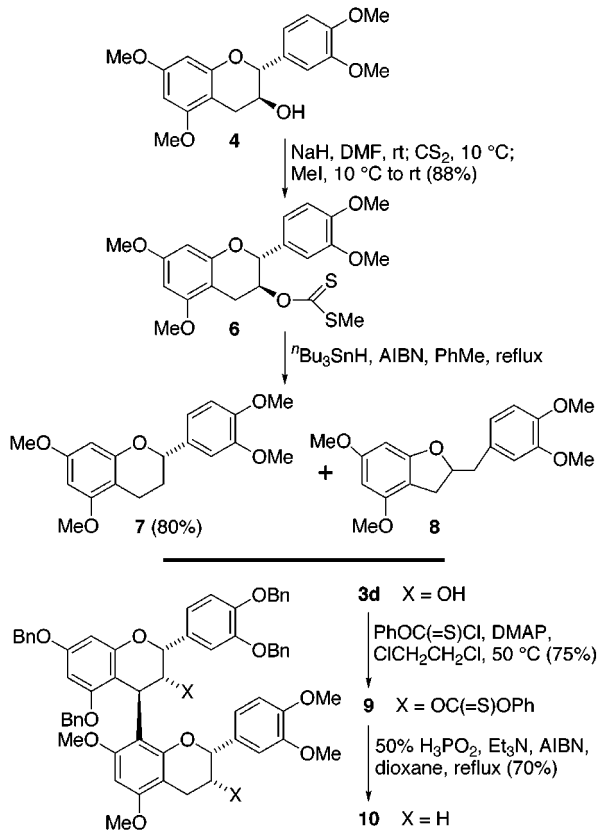
(2)

of **1b** with **2** mediated by $TiCl_4$[1,15] gave, after HPLC separation, a 67% yield of the desired "dimer" **3d** (Scheme 1) as a single isomer besides 14% of a "trimer", in all likelihood the isomer **5** with two 4β,8 interflavan linkages. We ascertained that **3d** and **3b** contain the same type of interflavan linkage by hydrogenolysis of **3d** to the partially deprotected compound **3e** which upon methylation furnished the same octa-*O*-methyl derivative **3f** as obtained by methylation of procyanidin B_2 (**3b**).[16]



Removal of the C-3 Hydroxyl Groups. Deoxygenation of **4** was effected by means of the Barton protocol[17] via xanthate **6**.[18] Preparation of the xanthate through the reported phase-transfer method (CS_2, MeI, *n*-Bu_4NBr, 50% aq NaOH/CH_2Cl_2, 7 °C to reflux)[18,19] gave an unacceptably low conversion. A far better yield was obtained

Scheme 2



with NaH, CS_2, and MeI in DMF, a solvent not commonly employed for this purpose (Scheme 2). *n*-Bu_3SnH/AIBN reduction of **6** gave the deoxygenated product **7** in the same yield as reported in the literature. However, product purification was complicated by the formation of several percent of an isomeric byproduct to which we assign structure **8** on the basis of its spectroscopic properties.[16] In the case of the "dimer" **3d**, thioacylation was performed efficiently with PhOC(S)Cl/DMAP.[20] The resulting ester **9** furnished the deoxygenation product **10** on treatment with *n*-Bu_3SnH/AIBN in only 54% yield. The byproducts when resubjected to the same conditions did not give additional **10** and may conceivably result from the contraction of one or both C rings in analogy to the formation of **8**. A 70% yield of **10** was subsequently realized by application of the more recently introduced reagent system, H_3PO_2/Et_3N/AIBN,[21] and the tin hydride variant was therefore not further examined. We note in passing that treatment of the crude product with alkaline H_2O_2 in the same manner as for the oxidation of organoboranes destroyed all foul-smelling S- or P-containing impurities and ensured a smooth hydrogenolysis in the subsequent step.

Phenol Deoxygenation. Model studies for this step were conducted on the silyl ether **14**, obtained from **1a** using a standard protocol (Scheme 3).[22] The benzyl groups were removed hydrogenolytically, and the intermediate **12** was carried on without purification. Complete mesylation of **12** succeeded readily with MsCl in pyri-

(14) Mehta, P. P.; Whalley, W. B. *J. Chem. Soc.* **1963**, 5327.
(15) Kawamoto, H.; Nakatsubo, F.; Murakami, K. *J. Wood Chem. Technol.* **1989**, *9*, 35.
(16) See Supporting Information for additional information concerning this point.
(17) Review: Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.
(18) Weinges, K.; Schick, H.; Zöllner, P. *Liebigs Ann. Chem.* **1992**, 293.
(19) This is apparently an adaptation of Lee, A. W. M.; Chan, W. H.; Wong, H. C.; Wong, M. S. *Synth. Commun.* **1989**, *19*, 547.
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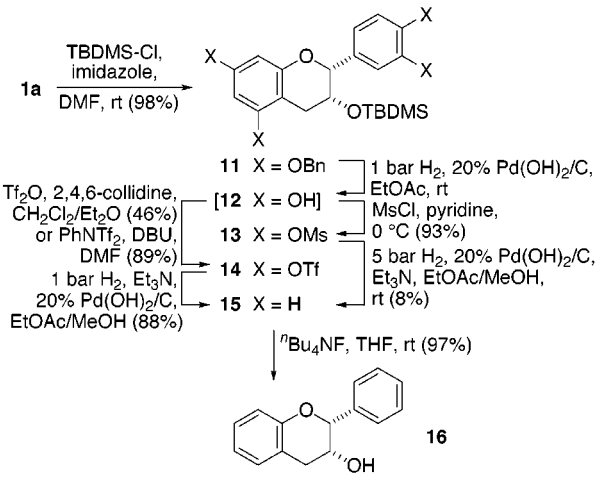
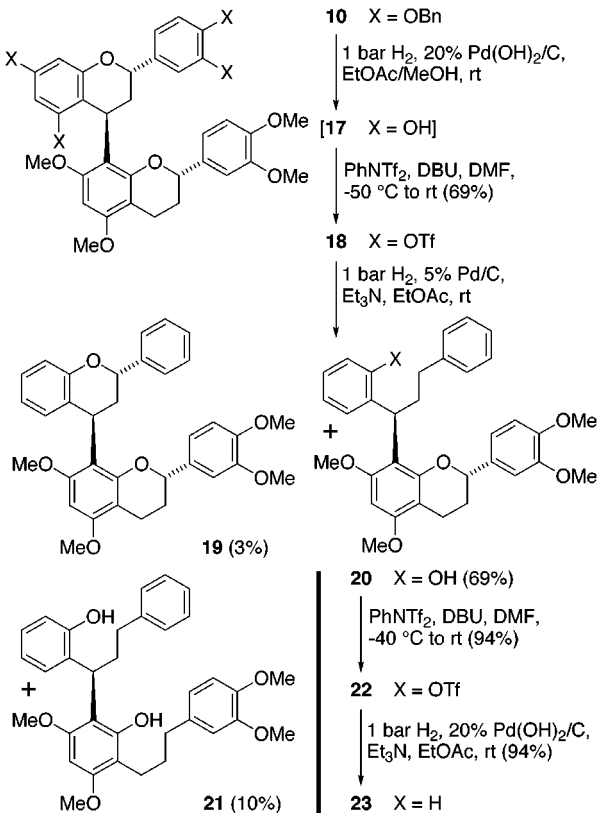
(22) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

Scheme 3



dine.[23] Hydrogenolysis of the tetramesylate **13** at 1 bar over Pd/C in the presence of Et_3N[24] was, unfortunately, extremely sluggish; use of the more active Pearlman's catalyst at 5 bar for 22 h resulted in the isolation of a mere 8% of the completely defunctionalized flavan **15** besides larger amounts of two dimesylates and several minor products.[16] Reports of the efficient hydrogenolysis of aryl nonaflates[25] and triflates[26] in the presence of a base prompted us to prepare the tetratriflate **14**. Initial experiments employing Tf_2O met with limited success.[16] Aryl triflates have also been prepared by reaction with *N*,*N*-bis(trifluoromethanesulfonyl)aniline of Li phenoxides[27] or of phenols in the presence of DMAP/Et_3N.[28] Combination of **12** with $PhNTf_2$ and DBU in DMF resulted in an exothermic reaction; under controlled conditions, **14** was isolated in 89% yield.[16] Hydrogenolysis of **14** in the presence of Et_3N proceeded efficiently at atmospheric pressure over Pearlman's catalyst. The product **15** underwent near-quantitative desilylation with *n*-Bu_4NF to the flavanol **16**, a compound which has previously been reported in racemic form.[29] Interestingly, protection of the alcoholic hydroxyl during sulfonylation is not necessary as demonstrated by the successful selective sulfonylation of the phenolic hydroxyls in (+)-catechin.[16] Application of these conditions to the bis(TBDMS) ether derived from **3a** by silylation and hydrogenolysis did, however, not result in the isolation of a defined octatriflate. We equally failed to effect formation of the octakis(1-phenyl-5-tetrazolyl) ether,[16] another type of derivative that has been employed for phenol deoxygenation.[30]

Scheme 4



At this point, we switched to the less-demanding strategy of deoxygenating only the "top" epicatechin moiety. Thus, the tetraphenol **17** was generated in situ from **10** and subjected to the preceding sulfonylation conditions. The tetratriflate **18** was formed in 69% yield (Scheme 4). This material upon hydrogenolysis as for **14** surprisingly yielded a mixture. By extending the reaction time, compound **20** was obtained as the major product in which, in addition to the intended deoxygenation, a hydrogenolytic scission of the C^1 ring has occurred. Although the crude reaction mixture contained several unidentified trace impurities, no significant amount of a product was detected in which the C^1 ring has survived and the C^2 ring has been opened. A minor product, however, was identified as **21** in which both C rings have been opened. While the C^1 and C^2 rings are a priori different, and the observed regioselective cleavage could thus result from differential access of the benzylic O−C2 bonds to the catalyst surface as a consequence of the overall geometry of the molecule, we also note that some degree of selectivity in favor of the hydrogenolytic cleavage of benzyl vs 4-methoxybenzyl and 3,4-dimethoxybenzyl ethers has previously been observed with Pd/C catalysts, and a good selectivity with Raney-Ni.[31] In a recent study, a more complex picture emerged in which, even though electron-donating substituents on a benzyl group increase and electron-withdrawing ones decrease the rate of hydrogenolysis of related ethers, a series of ethanediol dibenzyl ethers bearing either type of substituent on only one of the aromatic rings indiscriminately lose the unsubstituted benzyl group first,[32] a result

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(27) Peterson, G. A.; Kunng, F.-A.; McCallum, J. S.; Wulff, W. D. *Tetrahedron Lett.* **1987**, *28*, 1381.
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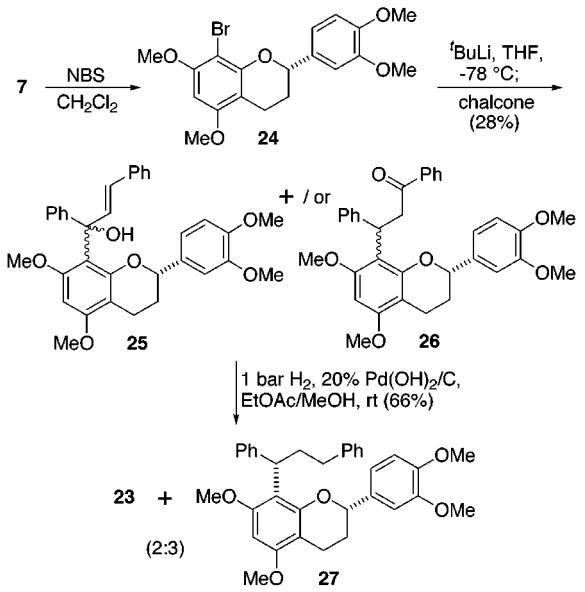
(30) (a) Musliner, W. J.; Gates, J. W. Jr. *J. Am. Chem. Soc.* **1966**, *88*, 4271. (b) Musliner, W. J.; Gates, J. W., Jr. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. VI, pp 150−152. (c) Hussey, B. J.; Johnstone, R. A. W.; Entwistle, I. D. *Tetrahedron* **1982**, *38*, 3775.
(31) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
(32) Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *63*, 4172.

Scheme 5

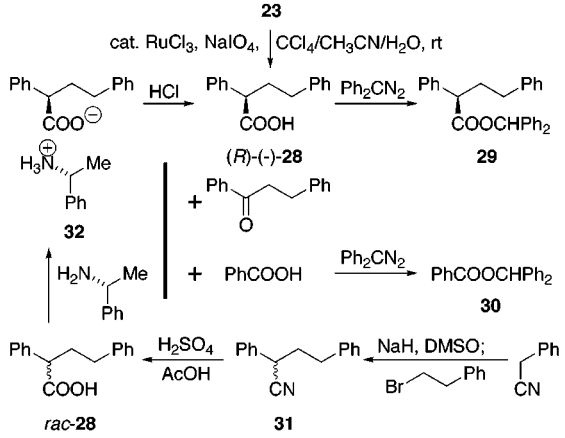


which was explained by preferred adsorption of the unsubstituted benzyl group and which parallels our present result. The fact that mono- or oligomeric 3-flavanols with their aromatic hydroxyl or alkoxyl groups in place do not readily suffer C-ring hydrogenolysis is the very foundation for the use of benzyl as a protecting group for this type of compounds. The absence of this reaction during the preparation of **15** suggests that the oxygen attached to C-3 also exerts a protecting effect on the O−C2 bond. O−C2 cleavage in flavanoids has previously been reported to occur by treatment with Na in NH_3 or EtOH[33] and with $NaBH_3CN/CF_3COOH$.[34] Under forcing conditions, oligomeric proanthocyanidins undergo more readily hydrogenolysis of the interflavan bond than of the O−C2 bond.[35]

It is likely that C ring hydrogenolysis could have been avoided under conditions of homogeneous catalysis.[26,27,36] From a practical point of view, however, **20** is more desirable for our purpose than compound **19** with an intact C^1 ring, since it contains solely the C-4 asymmetric center under scrutiny and is therefore immune from the objection affecting compound **19** that its degradation product may have epimerized under control of the C-2 asymmetric center during the reaction. The same fact reduces the determination of C-4 stereochemistry to a mere reading of an optical rotation. To get ready for the degradation step, we only needed to remove the hydroxyl group from **20** to form compound **23**, an operation which succeeded uneventfully using the same method as before via triflate **22**.

Oxidative Degradation. To procure sufficient material for the exploration of suitable oxidation conditions, the degradation substrate **23** was synthesized as a mixture with its epimer **27** from the bromide **24** which

Scheme 6



in turn was obtained quantitatively by NBS bromination[1] of **7** (Scheme 5). Halogen−lithium exchange followed by addition of chalcone gave a mixture of addition products the regio- and stereochemical nature of which we did not attempt to establish since either of the 1,2- and 1,4-adducts, **25** and **26**, would yield the same two epimeric products upon hydrogenolysis. This expectation was borne out; the product is a 2:3 mixture of **23** and **27** in which the "wrong" isomer **27** predominates. As a corollary, we note that this result constitutes independent evidence for the 4,8-regiochemistry in **3**, as long as one accepts the notion that deletion of the 3-hydroxyl in going from **4** to **7** will not change the regiochemistry of bromination from at least 98% 8-substitution to at least 98% 6-substitution.

The oxidation of phenyl to carboxyl is currently best performed with a large excess of $NaIO_4$ and a catalytic amount of $RuCl_3$ hydrate or RuO_2 hydrate in a two-phase solvent system composed of CCl_4, CH_3CN, and H_2O,[37] or with a related, ligand-containing catalyst in CH_3CN.[38] Under the latter conditions, *p*-methoxyphenyl groups have been reported to react more readily than phenyl groups. The oxidation of a phenyl group using $RuCl_3$ requires typically 1−2 d at room temperature. Compound **23** was subjected to the $RuCl_3$ reagent system and the oxidation stopped after 2 h at room temperature (Scheme 6). A product mixture was obtained which for the purpose of separation was esterified with diphenyldiazomethane.[39] Repeated chromatographic steps allowed the isolation of a small sample of levorotatory benzhydryl 2,4-diphenylbutyrate (**29**) besides 1,3-diphenyl-1-propanone and benzoic acid (isolated as its ester **30**).[16] Subjection of the independently synthesized 2:3 mixture of **23** and **27** to the same reaction conditions resulted in the isolation of a sample of benzhydryl 2,4-diphenylbutyrate which was enriched in the opposite enantiomer. This finding definitely precludes the remote possibility that epimerization might have occurred during the oxidation reaction under control by the additional asymmetric center in the still intact "bottom" epicatechin moiety, a notion which is a

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(39) Smith, L. I.; Howard, K. L. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, pp 351−352. A preliminary experiment indicated that the methyl ester of **28** is too volatile to be isolated without serious losses from the large solvent volumes present after HPLC purification.

priori unlikely since the asymmetric center of interest becomes subjected to potential enolization only after the A^2 ring has been destroyed and thereby the connection between the two centers severed. Furthermore, if enolization occurs, the highly reactive enol immediately undergoes further oxidation, resulting in the above-mentioned byproducts.

While the racemate resolution of **28** has been reported in the literature,[40] the absolute configuration of its enantiomers has not. We therefore prepared the nitrile **31**[41] by alkylation[42] of $PhCH_2CN$, and subsequent hydrolysis furnished the racemic acid **28**.[43] Recrystallization of the (*R*)-(+)-α-methylbenzylamine salt **32** effected racemate resolution and at the same time provided crystals suitable for X-ray structure analysis[44] which established that the (−)-acid has *R* configuration. Esterification of the free (*R*)-(−)-acid with Ph_2CN_2 gave a levorotatory benzhydryl ester **29**, as obtained above by degradation of **23**. It follows that compound **23** also has *R* configuration, and that the interflavan linkage in **3** has β stereochemistry.

Conclusion and Perspectives. The present paper provides the definitive proof that procyanidin B_2 possesses a 4β,8 interflavan bond. It also provides a case study demonstrating that traditional synthetic and degradative techniques, augmented by modern methodology, continue to have a role in the solution of analytical problems. In the course of this work, a procedure was developed which permits the exhaustive deoxygenation of a single flavanoid building block in a partially protected dimeric structure. Future efforts may lead to a more efficient technique which would also be applicable to free proanthocyanidin dimers or even larger oligomers, thus reducing the multitude of naturally occurring structures to a smaller number of reference compounds, the regio- and stereochemistry of which could be established in analogy to the present work.

Experimental Section

General Procedures. Chemicals: Anhydrous K_2CO_3 refers to material finely ground in a mortar and dried in an oil pump vacuum at 150 °C for 2−3 h. Pearlman's catalyst (20% $Pd(OH)_2/C$) was obtained from Aldrich and contained up to 50% H_2O. For others, see ref 1. ^1H, ^{13}C, and ^{19}F NMR spectra were acquired at nominal frequencies of 300, 75, and 282 MHz, respectively, in $CDCl_3$ unless specified otherwise. ^1H NMR spectra are referenced to internal TMS; ^{13}C NMR spectra to internal TMS if so marked, otherwise to the $CDCl_3$ signal (δ 77.00); ^{19}F NMR spectra to internal $CFCl_3$. Combustion analyses: Micro-Analysis, Inc. (Wilmington, DE). Column chromatography (CC): Merck silica gel 60 (No. 7734-7), particle size 63-200 μm. TLC: Merck silica gel 60 F_{254} (No. 7734-7), layer thickness 250 μm; visualization by UV light or with alkaline $KMnO_4$ solution. HPLC: column 1: Whatman Partisil 10, 500 × 9.4 mm, flow rate 5 mL/min; column 2: Whatman Partisil 10, 500 × 22 mm, flow rate 25 mL/min; UV detection at 280 nm for phenol and phenol ether chromophores, 260 nm for phenyl chromophores.

5,7,3′,4′-Tetra-*O*-methylcatechin (4).[14] A 24.7 g (85.1 mmol) sample of (+)-catechin was dried overnight in an oil pump vacuum at 90 °C, dissolved in 450 mL of acetone which had been freshly distilled over B_2O_3,[45] and added to 73 g (0.53 mol) of anhydrous K_2CO_3. After addition of 33 mL (0.35 mol) of Me_2SO_4, the mixture was agitated with an overhead stirrer and heated to reflux under N_2 for 6 h. After cooling, solids were removed by suction filtration over Celite and washed with 3 × 50 mL of acetone. The combined solutions were concentrated to approximately 250 mL, and then 500 mL of 1 N aq NaOH was added. Crystallization occurred readily. The precipitate was recovered by suction filtration, washed with 50 mL of H_2O, pressed dry, and recrystallized from 250 mL of MeOH (reflux to room temperature to 0 °C). Suction filtration, washing with 15 + 30 mL of cold (−20 °C) MeOH, and drying in vacuo gave 19.5 g of colorless needles. The acetone/NaOH aqueous phase of the initial crystallization was partially evaporated to remove acetone whereon additional product precipitated. This material was isolated by suction filtration, washed with plenty of water, and together with the mother liquor of the first recrystallization recrystallized from MeOH to yield another 3.1 g of **4**. Finally, CC of the evaporated mother liquor on SiO_2 with EtOAc/hexane 1:1 furnished another 0.8 g of **4** (total yield: 23.4 g, 79%): ^1H NMR δ 7.03−6.95 (m, 2 H), 6.89 (d, 1 H, J = 8 Hz), 6.14, 6.11 (ABq, 2 H, J = 2 Hz), 4.65 (d, 1 H, J = 8.5 Hz), 4.05 (m, 1 H), 3.89 (s, 6 H), 3.80 (m, 3 H), 3.75 (m, 3 H), 3.06, 2.58 (ABq, 2 H, J = 16.5 Hz, both parts d with J = 6 and 9 Hz, respectively), 1.80 (d, 1 H, J = 3.5 Hz); ^{13}C NMR ($CDCl_3$, TMS) δ 159.67, 158.69, 155.25, 149.30, 130.22, 119.91, 111.17, 109.91, 101.63, 92.96, 91.87, 81.75, 68.22, 55.93, 55.87, 55.46, 55.32, 27.62.

(2*R*)-5,7,3′,4′-Tetramethoxyflavan-3-one. To 18.9 g (54.6 mmol) of **4** in 270 mL of anhydrous CH_2Cl_2 was added at room temperature all at once 27.8 g (65.5 mmol, 1.2 equiv) of Dess−Martin periodinane.[46] Approximately 20 mL of water-saturated CH_2Cl_2 was added dropwise within 70 min. TLC control (SiO_2, EtOAc/hexane 1:1) showed the absence of starting material. After another 10 min, 350 mL of saturated $NaHCO_3$ solution was added, followed by a solution of 14 g of $Na_2S_2O_3 \cdot 5H_2O$ in 140 mL of water. The phases were separated, and the aqueous phase was extracted with 20 mL of CH_2Cl_2. The combined organic phases were, without further treatment, filtered over SiO_2 with $CHCl_3$/EtOAc 9:1. The eluate was evaporated and dried in vacuo to obtain 16.2 g (86%) of the ketone as a cream-colored solid sufficiently pure to be used directly in the following step. An aliquot was further purified by recrystallization from CH_2Cl_2/hexane: mp 108 °C; $[\alpha]_D$ +27.7°, $[\alpha]_{546}$ +37.0° (EtOAc, *c* 11.5 g L^{-1}); ^1H NMR δ 6.93−6.87 (m, 2 H), 6.84 (d, 1 H, J = 8 Hz), 6.30, 6.18 (ABq, 2 H, J = 2 Hz), 5.28 (s, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.79 (s, 6 H), 3.60, 3.46 (ABq, 2 H, J = 21.5 Hz); ^{13}C NMR ($CDCl_3$, TMS) δ 205.22, 160.36, 157.96, 154.62, 149.18, 149.04, 127.46, 119.28, 111.02, 109.74, 101.45, 94.40, 93.10, 83.19, 55.84, 55.81, 55.50, 55.43, 33.59. Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.10; H, 5.88.

5,7,3′,4′-Tetra-*O*-methylepicatechin (1b). In a 1 L three-necked flask equipped with a magnetic stirrer, two dropping funnels, and a N_2 balloon, 21.5 g (248 mmol, 5.3 equiv) of anhydrous LiBr (dried at 150 °C in an oil pump vacuum for 1.8 h) was dissolved in 60 mL of anhydrous THF. The solution was cooled in an ice bath, and 61 mL (1.3 equiv) of a 1 M solution of lithium tri-*sec*-butylborohydride (L-Selectride) was added. The mixture was cooled in an acetone/CO_2 bath, and 16.15 g (46.9 mmol) of crude (2*R*)-5,7,3′,4′-tetramethoxyflavan-3-one in 240 mL of anhydrous THF was added dropwise within 80 min. Stirring was continued at −78 °C for 80 min. After removal of the cold bath, 220 mL of 2.5 M aqueous NaOH was

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(44) $C_{24}H_{27}NO_2$; M_r 361.47; colorless monoclinic rods; crystal size 0.54 × 0.16 × 0.09 mm^3; space group *C*2; *T* 293(2) K; a = 30.288(2) Å, b = 6.156(1) Å, c = 11.686(1) Å, β = 108.21(1)°; V = 2065.9(2) $Å^3$; Z = 4; D_{calcd} 1.162 gcm^{-3}; absorption coefficient 0.572 mm^{-1}; $F(000)$ = 776; data collection: 3.08° ≤ Θ ≤ 57.50°; 1884 independent reflections; $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.0316$, $wR2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2} = 0.0819$, $S = \{\Sigma[w(F_o^2 - F_c^2)^2]/(n-p)\}^{1/2} = 1.06$ [$I > 2\sigma(I)$]; $R1$ = 0.0347, $wR2$ = 0.0844, S = 1.06 (all data); GOF = 1.058; 254 refined parameters; maximum peak/hole in final ΔF map 0.089/−0.105 $eÅ^3$. See Supporting Information for further details.

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added (slowly at first until H_2 evolution abated). The flask was placed in a room temperature water bath, and a mixture of 55 mL of 35% aqueous H_2O_2 and 165 mL of EtOH was added dropwise within 70 min. Stirring in the water bath was continued overnight. A 300 mL amount of toluene was added, the phases were separated, and the organic phase was washed with 2 × 100 mL of brine. The combined aqueous phases were saturated with NaCl and extracted with 100 mL of EtOAc. The combined organic phases were dried over $MgSO_4$ and evaporated to leave a gellike mass. This material was dissolved in 100 mL of boiling MeOH and allowed to crystallize at room temperature and then in the freezer. The product was isolated by suction filtration, washed with 2 × 20 mL of cold (−20 °C) MeOH, and dried in vacuo to obtain 11.7 g (72%) of yellow crystals. The evaporated mother liquor was filtered over SiO_2 with EtOAc/hexane 1:1, the eluate evaporated, and the residue recrystallized from boiling EtOAc (rt, then freezer), to obtain an additional 1.4 g (9%) of **1b** as off-white crystals: $[\alpha]_D$ −62.8°, $[\alpha]_{546}$ −75.8° (acetone, *c* 15.5 g L^{-1}) (lit.[4b] $[\alpha]_{578}$ −61.0° ($CHCl_3$, *c* 20 g L^{-1})); ^1H NMR[47] δ 7.08 (s, 1 H), 7.05, 6.92 (ABq, 2 H, J = 8.5 Hz, A part d with J = 1.5 Hz), 6.20, 6.12 (ABq, 2 H, J = 2 Hz), 4.96 (s, 1 H), 4.28 (br s, 1 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 2.95, 2.89 (ABq, 2 H, J = 17.5 Hz, both parts d with J = 2 and 4 Hz, respectively), 1.76 (d, 1 H, J = 6 Hz); ^{13}C NMR ($CDCl_3$, TMS) δ 159.64, 159.23, 155.17, 149.09, 148.81, 130.81, 118.60, 111.15, 109.57, 100.22, 93.29, 92.16, 78.41, 66.41, 55.93, 55.43, 55.35, 28.09.

5,7,3′,4′-Tetra-*O*-benzylepicatechin-4*β*,8-(5,7,3′,4′-tetra-*O*-methylepicatechin) (3d) and 5,7,3′,4′-Tetra-*O*-benzylepicatechin-4*β*,8-(5,7,3′,4′-tetra-*O*-benzylepicatechin)-4*β*,8-(5,7,3′,4′-tetra-*O*-methylepicatechin) (5). A 1.88 g (2.64 mmol) amount of **2**[1] and 4.81 g (13.2 mmol, 5 equiv) of **1b** were dissolved in 24 mL of anhydrous THF and 30 mL of anhydrous CH_2Cl_2 and cooled in an ice bath. To this mixture was added dropwise in 5 min 5.3 mL of $TiCl_4$ (1 M in CH_2Cl_2; 2 equiv). The resulting dark red solution was stirred in the ice bath for 5 min and then at room temperature for 2.5 h. The reaction was terminated by addition of 40 mL of saturated aq $NaHCO_3$. Extraction with 2 × 20 mL of CH_2Cl_2 (filtration over Celite was necessary to achieve phase separation during the second extraction) was followed by drying over $MgSO_4$ and evaporation. The residue was chromatographed on SiO_2 with toluene/EtOAc mixtures as the eluent. With an initial solvent ratio of 5:2, 2.40 g of oligomers were eluted, and then with a ratio of 5:3, 3.72 g of unreacted **1b**. The "dimer" and "trimer" were separated by preparative HPLC (column 2, EtOAc/hexane 2:3, 26 mL/min) to give 1.75 g (67%) of **3d** (t_R 26.7 min) and 308 mg (14%) of **5** (t_R 32.7 min). Compound **3d**: colorless foam; $[\alpha]_D$ +30.4°, $[\alpha]_{546}$ +37.1° (EtOAc, *c* 9.1 gL^{-1}); ^1H NMR (selection; MR = major rotamer, mr = minor rotamer) δ 6.82 (d, J = 8.5 Hz, mr), 6.76 (s, 1 H, MR), 6.70, 6.52 (ABq, 2 H, MR, J = 8.5 Hz, B part somewhat br), 6.36 (d, 1 H, J = 2 Hz, mr), 6.24 (narrow m, 1 H, MR + mr), 6.11 (s, 1 H, mr), 6.00 (d, 1 H, MR, J = 2 Hz), 5.62 (d, 1 H, J = 1.5 Hz), 5.48 (s, 1 H, MR), 5.26 (s, 1 H, mr), 5.15 (s), 5.13 (s), 5.06 (s, 2 H, mr), 4.99 (s, 1 H, mr), 4.94 (s, 1 H, mr), 4.87 (s, 2 H, mr), 4.80 (s, 2 H, MR), 4.75 (s, 1 H, MR), 4.62, 4.40 (ABq, 2 H, mr, J = 11 Hz), 4.11 (1 H, MR), 4.02 (br d, 1 H, MR, J = 5 Hz), 3.98−3.88 (m), 3.88 (s, 3 H, MR), 3.83 (s, 6 H, mr), 3.81 (s, 3 H, MR), 3.78 (s, 3 H, mr), 3.73 (s, 3 H, MR), 3.63 (s, 3 H, MR), 3.25 (s, 3 H, mr), 3.06−2.80 (m, 2 H, MR + mr), 1.83 (d, 1 H, MR, J = 6 Hz), 1.75 (d, 1 H, mr, J = 5.5 Hz), 1.64 (d, 1 H, MR, J = 4.5 Hz), 1.38 (d, 1 H, mr, J = 5 Hz). Anal. Calcd for $C_{62}H_{58}O_{12}$: C, 74.83; H, 5.87. Found: C, 74.84; H, 5.74. Compound **5**: colorless foam; $[\alpha]_D$ +75.2°, $[\alpha]_{546}$ +91.9° (EtOAc, *c* 7.1 gL^{-1}); ^1H NMR (OCH_3 signals only) δ 3.87, 3.83, 3.78, 3.77, 3.18, 2.94. Anal. Calcd for $C_{105}H_{94}O_{18}$: C, 76.72; H, 5.76. Found: C, 77.00; H, 5.77.

5,7,3′,4′-Tetra-*O*-methylepicatechin-4*β*,8-(5,7,3′,4′-tetra-*O*-methylepicatechin) (3f).[48] (a) From **3d**: A solution of 21.3 mg (21.4 μmol) of **3d** in a mixture of 1 mL of EtOAc and 1 mL of MeOH was hydrogenated at 1 bar and room temperature over 22 mg of 20% $Pd(OH)_2$/C for 10 min. TLC (SiO_2, CH_2Cl_2/MeOH 11:1; R_f approximately 0.3) indicated the formation of a single product. The catalyst was removed by filtration over cotton and the solution evaporated. The residue was taken up in 1 mL of 3-pentanone, the solution was added to 127 mg (0.92 mmol, 43 equiv) of anhydrous K_2CO_3, and the first of four 22 μL portions (total: 0.93 mmol) of Me_2SO_4 was added. The mixture was stirred at 60 °C under N_2, and the remaining portions of Me_2SO_4 were added in 1 h intervals. After a final 1 h at 60 °C and cooling to room temperature, 0.2 mL of concd. aq NH_3 was added, and the mixture was stirred at room temperature for 30 min. Direct filtration over SiO_2 with EtOAc followed by evaporation and drying in vacuo gave 16 mg of crude product which was purified by preparative TLC (SiO_2, 200 × 200 × 0.25 mm, EtOAc/hexane 7:3) to yield 10.7 mg (72%) of **3f**.

(b) From **3b** by methylation with Me_2SO_4/K_2CO_3: A solution of 16.3 mg (28.2 μmol) of procyanidin B_2 (**3b**)[1] in 1 mL of 3-pentanone was added to 167 mg (1.2 mmol, 43 equiv) of anhydrous K_2CO_3, and the first of four 28.5 μL portions (total: 1.2 mmol) of Me_2SO_4 was added. The mixture was stirred at 60 °C under N_2, and the remaining portions of Me_2SO_4 were added in 1 h intervals. After a final 1 h at 60 °C and cooling to room temperature, 0.3 mL of concd aq NH_3 was added, and the mixture was stirred at room temperature for 30 min. Direct filtration over SiO_2 with EtOAc followed by evaporation and drying in vacuo gave 21 mg of crude product which was purified by preparative HPLC (column 1, EtOAc/hexane 7:3; t_R 21.7 min) to yield 7.9 mg (41%) of **3f** as a colorless film: ^1H NMR (two rotamers in an approximately 1:1 ratio) δ 7.23 (s, 0.5 H), 7.13−6.97 (m, 2.5 H), 6.93−6.83 (m, 2 H), 6.77, 6.58 (ABq, 1 H, J = 8 Hz), 6.28, 6.07, 5.82, 5.53 (each d, 0.5 H, J = 2 Hz), 6.25, 6.09, 5.47, 5.36, 5.12, 4.91, 4.66, 4.27 (each s, 0.5 H), 4.47 (br s, 0.5 H), 4.03−3.95 (m, 1.5 H), 3.87 (s, 10.5 H), 3.93, 3.90, 3.82, 3.81, 3.72, 3.61, 3.54, 3.40, 3.30 (each s, 1.5 H), 3.05, 2.95 (ABq, 1 H, J = 16 Hz, B part d with J = 3.5 Hz), 2.90 (m, 1 H), 1.82 (d, J = 5.5 Hz), 1.77−1.72 (m, 2 H), 1.65 (d, J = 4 Hz).

5,7,3′,4′-Tetra-*O*-methyl-3-*O*-[[(methylthio)thiocarbonyl]-oxy]catechin (6).[18] To 1.84 g (5.31 mmol) of **4** in 5 mL of DMF was added all at once 0.25 g (6.4 mmol) of NaH (60% in oil). The mixture was stirred with a powerful magnetic stirrer at room temperature (mild exotherm) for 10 min while H_2 evolved, and then it was immersed in a +10 °C water bath, 0.48 mL (8.0 mmol) of CS_2 was added dropwise in 5 min, and stirring at +10 °C was continued for 10 min. To the resulting yellow to amber suspension was added dropwise in 5 min 0.50 mL (8.0 mmol) of MeI. Halfway through the addition, the stirrer stopped, and the mildly exothermic addition was continued without cooling to reduce viscosity. The reaction mixture remained pasty and soon hardened; it was left at room temperature for 20 min and then dissolved in 40 mL of H_2O and 60 mL of toluene. The phases were separated, and the aqueous phase was extracted with 20 mL of toluene. The combined organic phases were washed with 40 mL of H_2O and concentrated to 30 mL, and the residue was chromatographed on SiO_2 first with CH_2Cl_2/hexane 1:1 to remove a forerun and then with CH_2Cl_2/EtOAc 19:1 to elute the product. Mixed fractions with a nonpolar contaminant were resubjected to CC (SiO_2, EtOAc/CH_2Cl_2/hexane 1:7:12 for forerun, 1:19:0 for product), and all product-containing fractions were combined, evaporated, and dried in vacuo to yield 2.04 g (88%) of **6** as a yellowish solid: ^1H NMR δ 6.97−6.90 (m, 2 H), 6.83 (d, 1 H, J = 8 Hz), 6.19, 6.10 (ABq, 2 H, J = 2.5 Hz), approximately 6.16 (m, 1 H, overlapping), 5.26 (d, 1 H, J = 6.5 Hz), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.77 (s, 6 H), 3.04, 2.80 (ABq, 2 H, J = 17 Hz, both parts d with J = 5.5 and 6.5 Hz, respectively), 2.45 (s, 3 H); ^{13}C NMR δ 214.96, 159.82, 158.47, 154.66, 148.87,

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(48) This compound has been prepared previously but was characterized not as such but rather as its diacetate: Kolodziej, H. *Phytochemistry* **1986**, *25*, 1209. We omitted the acetylation as it offers no advantage in establishing the identity of the samples derived from **3b** and **3d**.

129.81, 119.02, 110.93, 109.37, 100.22, 92.90, 91.79, 77.69, 77.48, 55.78, 55.36, 55.29, 23.24, 18.88.

(2*S*)-5,7,3′,4′-Tetramethoxyflavan (7).[18] A stirred solution of 4.17 g (9.55 mmol) of intermediate **6** in 150 mL of anhydrous toluene was heated to reflux under N_2, and a solution of 10.3 mL (38.2 mmol) of $^nBu_3SnH$ and 0.31 g (1.9 mmol) of AIBN in 80 mL of anhydrous toluene was added dropwise through the reflux condenser over a period of 4.25 h. Reflux was continued for 4 h. The cooled reaction mixture was directly chromatographed on SiO_2. A forerun was eluted using toluene, and then a mixture of **7** and a slightly more polar impurity **8** using toluene/EtOAc (12:1). A late fraction containing mostly **8** was set aside for the isolation of this impurity (see Supporting Information); from the remaining mixture, **7** was isolated by further CC on SiO_2 with EtOAc/$CHCl_3$/hexane 1:7:12. Evaporation and drying in vacuo yielded 2.52 g (80%) of **7** as a colorless glass: ^{1}H NMR δ 7.00−6.85 (m, 3 H), 6.14, 6.08 (ABq, 2 H, J = 2.5 Hz), 4.91 (dd, 1 H, J = 2, 10.5 Hz), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 2.77, 2.64 (ABq, 2 H, J = 16.5 Hz, both parts dd with J = 2.5, 5.5 Hz and 6.5, 11.5 Hz, respectively), 2.17, 2.02 (ABq, 2 H, J = 13.5 Hz, both parts dt with J = 2.5 Hz (t), 6.5 Hz (d) and 5.5 Hz (d), 11 Hz (t), respectively); ^{13}C NMR δ 159.24, 158.47, 156.26, 148.96, 148.62, 134.16, 118.46, 110.97, 109.28, 103.22, 93.30, 91.28, 77.72, 55.85, 55.78, 55.32, 55.21, 29.45, 19.39.

(2*S*)-5,7,3′,4′-Tetrakis(benzyloxy)flavan-4*β*,8-[(2*S*)-5,7,3′,4′-tetramethoxyflavan] (10). To a solution of 519 mg (520 μmol) of **3d** and 254 mg (2.08 mmol, 4 equiv) of DMAP in 2 mL of 1,2-dichloroethane (HPLC grade, 0.002% H_2O) was added dropwise in 7 min with water cooling 252 μL (1.82 mmol, 3.5 equiv) of PhOC(S)Cl. The mixture was stirred in a resealable tube at room temperature for 1 h and then at 50 °C for 48 h. After addition of 20 mL of saturated aqueous $NaHCO_3$ and 50 mL of H_2O, the mixture was extracted with 50 + 10 mL of CH_2Cl_2, and the extract was dried over $MgSO_4$ and evaporated. CC (SiO_2, EtOAc/hexane 1:2; R_f approximately 0.35) gave, after evaporation and drying in vacuo, 494 mg (75%) of the bis[(phenoxy)thiocarbonyl] derivative **9** as a colorless glass: ^{1}H NMR (major rotamer only) δ 7.48−7.10 (m), 7.10−6.82 (m), 6.76 (d, 1 H, J = 8.5 Hz), 6.67, 6.51 (ABq, 2 H, J = 8.5 Hz, B part br), 6.29 (s, 1 H), 6.07 (s, 1 H), 5.88 (s, 1 H), 5.81 (s, 1 H), 5.64 (d, 1 H, J = 3.5 Hz), 5.52 (s, 1 H), 5.12 (s, 1 H), 5.07 (s, 2 H), 5.02 (s, 2 H), 4.88 (s, 2 H), 4.64, 4.45 (ABq, 2 H, J = 11.5 Hz), 4.24 (s, 1 H), 3.92 (s, 3 H), 3.81 (s, 3 H), 3.75 (s, 3 H), 3.52 (s, 3 H), 3.24, 3.02 (ABq, 2 H, J = 18.5 Hz, B part d with J = 4.5 Hz). To a solution of 532 mg (420 μmol) of **9** in 8.4 mL of anhydrous 1,4-dioxane (distilled over Na/benzophenone) were added at room temperature 1.46 mL (10.5 mmol, 25 equiv) of Et_3N and 0.88 mL (8.4 mmol, 20 equiv) of 50% (approximately 9.6 M) aq H_3PO_2. The mixture was stirred and heated under N_2 to gentle reflux, and a solution of 138 mg (0.84 mmol, 2 equiv) of AIBN in 2.1 mL of anhydrous 1,4-dioxane was added in 7 equal portions in 20 min intervals. Reflux was continued for 1 h, and then the mixture was cooled and without further treatment filtered over a short SiO_2 column with EtOAc/hexane 1:2. The evaporation residue (0.45 g) was taken up in 25 mL of THF, and to this solution were added sequentially 15 mL of EtOH, 10 mL of 2.5 M aq NaOH, and 2.5 mL of 35% aq H_2O_2. After stirring in an room temperature water bath for 4 h, another 2.5 mL of 35% aq H_2O_2 was added, and stirring was continued overnight. Partial evaporation was followed by addition of 10 mL of H_2O, extraction with 3 × 20 mL of EtOAc, and drying over $MgSO_4$. After evaporation, CC on SiO_2 with EtOAc/$CHCl_3$/hexane 1:12:7 yielded 286 mg (70%) of the product **10** which was sufficiently pure to be used in the subsequent step. The analytical sample was obtained by preparative HPLC (column 1, EtOAc/hexane 1:3; t_R 17.1 min): $[\alpha]_D$ +109°, $[\alpha]_{546}$ +132° (EtOAc, *c* 4.6 g L^{-1}); ^{1}H NMR δ 7.50−7.12 (m), 7.07−6.80 (m), 6.72 (d, J = 8.5 Hz), 6.67, 6.52 (ABq, J = 8.5 Hz), 6.60 (s), 6.30 (s), 6.21 (s), 6.18 (s), 6.09 (s), 6.00 (s), 5.51 (s), 5.33 (d, J = 11 Hz), 5.21 (d, J = 12 Hz), 5.17−5.07 (m), 5.04 (s), 4.91 (presumably one line of a partially concealed d), 4.87 (s), 4.81 (s), 4.69 (d, J = 5 Hz), 4.63, 4.49 (ABq, J = 11.5 Hz), 4.04 (d, J = 8 Hz), 3.87 (s), 3.83 (s), 3.81 (s), 3.75 (s), 3.73 (s), 3.64 (s), 3.61 (s), 3.26 (s), 2.91−2.75 (m), 2.75−2.56 (m), 2.30−1.82 (m), 1.80−1.63 (m); ^{13}C NMR ($CDCl_3$, TMS, excluding δ 129−126 region) δ 158.02, 157.73, 157.02, 156.87, 156.37, 156.25, 155.36, 153.39, 149.07, 149.01, 148.86, 148.42, 148.29, 148.23, 148.10, 137.61, 137.40, 137.32, 137.23, 136.18, 135.96, 135.00, 134.43, 119.66, 119.55, 118.03, 117.82, 115.62, 115.12, 114.48, 113.48, 113.34, 110.75, 110.24, 109.31, 108.84, 107.87, 107.50, 103.99, 103.95, 94.52, 93.75, 92.63, 92.31, 90.66, 88.02, 77.98, 74.84, 74.50, 71.40, 71.36, 70.06, 69.57, 69.51, 69.26, 56.89, 55.85, 55.74, 55.58, 55.49, 55.36, 38.97, 37.79, 30.56, 29.99, 26.60, 26.37, 20.33, 19.82. Anal. Calcd for $C_{62}H_{58}O_{10}$: C, 77.33; H, 6.07. Found: C, 77.33; H, 6.09.

5,7,3′,4′-Tetra-*O*-benzyl-3-*O*-(*tert*-butyldimethylsilyl)-epicatechin (11). A solution of 4.37 g (6.72 mmol) of **1a**, 0.69 g (10.1 mmol, 1.5 equiv) of imidazole, and 1.42 g (9.4 mmol, 1.4 equiv) of TBDMS-Cl in 6 mL of anhydrous DMF was stirred at room temperature in a closed flask for 19.5 h. Direct CC on SiO_2 with EtOAc/hexane 1:5, followed by evaporation and drying in vacuo gave 5.02 g (98%) of the silyl ether as a yellowish glass: ^{1}H NMR δ 7.47−7.25 (m, 20 H), 7.11 (s, 1 H), 6.94, 6.90 (ABq, 2 H, J = 1 Hz), 6.24, 6.22 (ABq, 2 H, J = 2 Hz), 5.15 (s, 2 H), 5.14 (narrow ABq, 2 H), 5.03 (s, 2 H), 5.02, 4.98 (ABq, 2 H, J = 11.5 Hz), 4.93 (s, 1 H), 4.18 (narrow m, 1 H), 2.86, 2.77 (ABq, 2 H, J = 17 Hz, both parts d with J = 4 Hz), 0.76 (s, 9 H), −0.15 (s, 3 H), −0.30 (s, 3 H); ^{13}C NMR ($CDCl_3$, TMS) δ 158.49, 157.85, 155.56, 148.69, 148.29, 137.39, 137.36, 137.25, 137.01, 132.75, 128.55, 128.49, 128.41, 127.93, 127.74, 127.69, 127.63, 127.47, 127.31, 127.07, 120.07, 115.03, 114.21, 101.66, 94.49, 93.45, 78.93, 71.47, 71.36, 70.08, 69.88, 67.48, 28.38, 25.78, 18.07, −5.09, −5.12. Anal. Calcd for $C_{49}H_{52}O_6Si$: C, 76.93; H, 6.85. Found: C, 77.17; H, 6.62.

3-*O*-(*tert*-Butyldimethylsilyl)-5,7,3′,4′-tetra-*O*-(methanesulfonyl)epicatechin (13). A solution of 188 mg (246 μmol) of **11** in 4 mL of EtOAc was hydrogenated at 1 bar over 34 mg of 20% $Pd(OH)_2$/C for 1 h. Filtration over cotton, evaporation, and drying in vacuo gave 109 mg of **12** as a colorless foam which was pure except for solvent residues: ^{1}H NMR ($CDCl_3$/CD_3OD 9:1, TMS) δ 8.69 (br s, 1 H), 8.63 (s, 1 H), 8.10 (br s, 1 H), 7.67 (br s, 1 H), 6.93 (d, 1 H, J = 1.5 Hz), 6.80, 6.76 (ABq, 2 H, J = 8 Hz, B part d with J = 1.5 Hz), 5.98, 5.94 (ABq, 2 H, J = 2 Hz), 4.88 (s, 1 H), 4.20 (narrow m, 1 H), 2.82, 2.69 (ABq, 2 H, J = 16 Hz, both parts d with J = 4.5 and 4 Hz, respectively), 0.77 (s, 9 H), −0.15 (s, 3 H), −0.20 (s, 3 H). The crude intermediate **12** was dissolved in 1 mL of anhydrous pyridine, and a solution of 0.15 mL (2.0 mmol) of $MeSO_2Cl$ in 0.5 mL of anhydrous pyridine was added dropwise with ice cooling and exclusion of moisture in 4 min. After standing at 0 °C for 71 h, 0.2 mL of water was added, and the mixture was allowed to stand for 10 min. Twenty milliliters of CH_2Cl_2 and 40 mL of 0.5 M aqueous H_3PO_4 were added, the phases were separated, and the aqueous phase was extracted with 10 mL of CH_2Cl_2. The combined organic phases were washed with 30 mL of water and 15 mL of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated. CC of the residue (SiO_2, EtOAc/hexane 3:2), evaporation, and drying in vacuo gave 163.5 mg (93%) of **13** as a colorless film: $[\alpha]_D$ −9.3°, $[\alpha]_{546}$ −12.2° (EtOAc, *c* 6.6 g L^{-1}); ^{1}H NMR δ 7.53 (s, 1 H), 7.51, 7.46 (ABq, 2 H, J = 8.5 Hz, B part d with J = 1.5 Hz), 6.92 (s, 2 H), 5.09 (s, 1 H), 4.29 (br s, 1 H), 3.253 (s, 3 H), 3.246 (s, 3 H), 3.238 (s, 3 H), 3.19 (s, 3 H), 3.10, 2.97 (ABq, 2 H, J = 17 Hz, both parts d with J = 3.5 and 3 Hz, respectively), 0.68 (s, 9 H), −0.10 (s, 3 H), −0.39 (s, 3 H); ^{13}C NMR ($CDCl_3$, TMS) δ 155.73, 148.20, 147.74, 140.85, 140.56, 139.27, 126.54, 123.91, 122.57, 113.75, 109.35, 108.97, 78.49, 66.00, 38.62, 38.46, 38.33, 37.60, 29.56, 25.51, 17.83, −5.11, −5.55. Anal. Calcd for $C_{25}H_{36}O_{14}S_4Si$: C, 41.89; H, 5.06. Found: C, 42.15; H, 4.90.

3-*O*-(*tert*-Butyldimethylsilyl)-5,7,3′,4′-tetra-*O*-(trifluoromethanesulfonyl)epicatechin (14). A solution of 67.6 mg (88.4 μmol) of **11** in 2 mL of EtOAc was hydrogenated at 1 bar over 20 mg of 20% $Pd(OH)_2$/C for 40 min. Filtration over cotton, evaporation, and drying in vacuo gave a residue of crude **12** which was dissolved in 0.5 mL of anhydrous DMF. After cooling to −45 °C and addition of 73 μL (0.49 mmol, 5.5 equiv) of DBU, a solution of 189 mg (0.53 mmol, 6 equiv) of *N*,*N*-bis-

(trifluoromethanesulfonyl)aniline was added dropwise in 2 min under N_2. The mixture was thawed to +5 °C within 80 min and then stirred at room temperature for 3.5 h. Direct CC on SiO_2 with EtOAc/hexane 1:5 followed by HPLC (column 2, EtOAc/hexane 1:9; t_R 19.6 min) gave 71.0 mg (89%) of **14** as a colorless oil: $[\alpha]_D$ −15.8°, $[\alpha]_{546}$ −19.7° (EtOAc, *c* 11.5 g L^{-1}); ^{1}H NMR δ 7.58 (narrow m, 3 H), 7.00, 6.90 (ABq, 2 H, J = 2 Hz), 5.19 (s, 1 H), 4.32 (br s, 1 H), 3.12, 3.00 (ABq, 2 H, J = 17 Hz, both parts d with J = 3.5 and 2.5 Hz, respectively), 0.66 (s, 3 H), −0.08 (s, 3 H), −0.44 (s, 3 H); ^{13}C NMR ($CDCl_3$, TMS) δ 155.86, 148.33, 148.00, 140.43, 140.15, 127.67, 123.59, 122.11, 118.76 (q, J = 320.5 Hz), 118.69 (q, J = 320.5 Hz), 116.62 (q, J = 320 Hz), 114.35, 110.10, 107.98, 78.73, 65.41, 29.51, 25.30, 17.72, −5.21, −5.83; ^{19}F NMR: δ 104.22, 103.70, 103.62, 103.46. Anal. Calcd for $C_{25}H_{24}O_{14}F_{12}S_4Si$: C, 32.19; H, 2.59. Found: C, 32.44; H, 2.41.

(2*R*,3*R*)-*cis*-3-[(*tert*-Butyldimethylsilyl)oxy]flavan (15). A solution of 1.75 g (1.88 mmol) of **14** and 1.3 mL (9.4 mmol, 5 equiv) of Et_3N in 10 mL of EtOAc and 30 mL of MeOH was hydrogenated at 1 bar over 131 mg of 20% $Pd(OH)_2$/C for 1 h. The solution was evaporated and the residue filtered over SiO_2 with EtOAc/hexane 1:15. Evaporation and drying in vacuo gave 563 mg (88%) of **15** as a colorless oil: $[\alpha]_D$ −46.0°, $[\alpha]_{546}$ −55.9° (EtOAc, *c* 10.0 g L^{-1}); ^{1}H NMR δ 7.46−7.25 (m, 5 H), 7.15 (t, 1 H, J = 7.5 Hz), 7.05 (d, 1 H, J = 7.5 Hz), 6.94 (d, 1 H, J = 8 Hz), 6.88 (t, 1 H, J = 7.5 Hz), 5.09 (s, 1 H), 4.26 (narrow m, 1 H), 3.14, 2.77 (ABq, 2 H, J = 3.5 and 4 Hz, respectively), 0.72 (s, 9 H), −0.16 (s, 3 H), −0.36 (s, 3 H); ^{13}C NMR δ 154.39, 139.17, 129.87, 127.83, 127.52, 127.34, 126.93, 120.39, 119.44, 116.23, 79.32, 67.55, 34.09, 25.64, 17.95, −5.23, −5.43.

(2*R*,3*R*)-*cis*-Flavan-3-ol (16). To a solution of 563 mg (1.65 mmol) of **15** in 5 mL of anhydrous THF was added 1.8 mL of *n*-Bu_4NF solution (1 M in THF). After 2 h at room temperature, 5 mL of water was added, the THF was evaporated in vacuo, and the product was extracted into 2 × 20 mL of ether. The combined organic phases were dried over $MgSO_4$ and evaporated, and the residue was chromatographed on SiO_2 with EtOAc/hexane 1:4. Finally, bulb-to-bulb distillation (oven 170 °C/0.65 Torr) gave 361 mg (97%) of **16** as a colorless, viscous oil: $[\alpha]_D$ −86.2°, $[\alpha]_{546}$ −104° (EtOAc, *c* 33.0 g L^{-1}); ^{1}H NMR δ 7.54−7.31 (m, 5 H), 7.15 (t, 1 H, J = 7.5 Hz), 7.10 (d, 1 H, J = 8 Hz), 6.96 (d, 1 H, J = 8 Hz), 6.92 (t, 1 H, J = 7 Hz), 5.09 (s, 1 H), 4.30 (br s, 1 H), 3.27, 2.97 (ABq, 2 H, J = 17 Hz, both parts d with J = 4 and 2 Hz, respectively), 1.79 (d, 1 H, J = 6.5 Hz); ^{13}C NMR δ 153.93, 138.17, 130.28, 128.52, 128.03, 127.56, 126.16, 121.25, 118.79, 116.66, 78.49, 66.61, 33.34. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.38; H, 6.22.

(2*S*)-5,7,3′,4′-Tetrakis[(trifluoromethanesulfonyl)oxy]-flavan-4*β*,8-[(2*S*)-5,7,3′,4′-tetramethoxyflavan] (18). A solution of 303 mg (314 μmol) of **10** in 14 mL each of EtOAc and MeOH was hydrogenated over 165 mg of 20% $Pd(OH)_2$/C at room temperature and 1 bar for 75 min. The catalyst was filtered off over cotton and rinsed with EtOAc. The solution was evaporated, taken up in 10 mL of toluene and again evaporated, and dried in vacuo to give 231 mg of crude **17**, which was characterized only by its ^{1}H NMR spectrum (CD_3OD, TMS): δ 7.05−6.75 (br, 3 H), 6.77 (d, 1 H, J = 1.5 Hz), 6.69, 6.60 (ABq, 2 H, J = 8 Hz, B part d with J = 2 Hz), 6.20 (br s, 1 H), 5.77 (br, 1 H), 5.12 (br d, 1 H, J = 9.5 Hz), 4.61 (br, 1 H), 3.80 (s, 6 H), 3.75 (s, 3 H), approximately 3.8−3.3 (very br, presumably containing one Me group and one C-ring H), 2.76−2.54 (m, 2 H), 2.16−2.00 (m, 2 H), 2.00−1.80 (m, 2 H); ore aromatic H too broad for detection or undergoing rapid H−D exchange. Intermediate **17** was taken up in 1.5 mL of anhydrous DMF, and the solution was cooled in an ice bath whereon 235 μL (1.57 mmol, 5 equiv) of DBU was added dropwise in 5 min. After cooling to −50 °C, a solution of 505 mg (1.41 mmol, 4.5 equiv) of $PhNTf_2$ in 2.5 mL of anhydrous DMF was added dropwise within 12 min at −45 to −50 °C. The temperature was allowed to rise to 0 °C over a period of 40 min. Stirring was further continued at 0 °C for 30 min and at room temperature for 70 min. The mixture was then directly filtered over SiO_2 with EtOAc/hexane 1:3 to give, after evaporation, 299 mg of crude triflate. This material was subjected to preparative HPLC (column 2, EtOAc/hexane 1:4; t_R 17.3 min), and the eluate was evaporated and dried in vacuo to yield 244 mg (69% over two steps) of **18** as a colorless glass: $[\alpha]_D$ +94.4°, $[\alpha]_{546}$ +115° (EtOAc, *c* 7.7 g L^{-1}); ^{1}H NMR δ 7.50 (s), 7.48 (s), 7.15−6.4 (br m), 6.25−5.95 (br m), 5.55−5.3 (br m), 5.0−4.75 (br m), 4.19 (br s), 3.89 (s), 3.87 (s), 3.62 (br s), 3.33 (br s), 2.95−2.75 (br m), 2.75−2.55 (br m), 2.27−2.07 (m), 1.97 (br s); ^{13}C NMR ($CDCl_3$, TMS) δ 157.92, 157.1 (br), 156.3 (br), 154.7 (br), 149.0 (br), 147.0 (br), 143.30, 140.40, 139.71, 134.7 (br), 133.1 (br), 127.08, 123.82, 121.52, 119.3 (br), 118.63 (q, 3 C, J_{C-F} = 319 Hz), 118.5 (br), 118.44 (q, 1 C, J_{C-F} = 319 Hz), 110.5 (br), 109.7 (br), 109.0 (br), 108.8 (br), 106.3 (br), 105.7 (br), 104.0 (br), 89.0 (br), 88.0 (br), 78.76, 74.0 (br), 55.88, 55.75, 55.46, 37.18, 30.0 (br), 29.5 (br), 26.70, 20.14; ^{19}F NMR δ 104.34 (br), 103.84 (br, sh), 103.80, 103.03 (br, sh), 102.95 (br).

(2*S*)-Flavan-4*β*,8-[(2*S*)-5,7,3′,4′-tetramethoxyflavan] (19), (2*S*)-8-[(1*R*)-1-(2-Hydroxyphenyl)-3-phenylpropyl]-5,7,3′,4′-tetramethoxyflavan (20), and (*R*)-3,5-Dimethoxy-2-[3-(3,4-dimethoxyphenyl)propyl]-6-[1-(2-hydroxyphenyl)-3-phenylpropyl]phenol (21). A solution of 228 mg (202 mmol) of **18** and 141 μL (1.01 mmol, 5 equiv) of Et_3N in 25 mL of EtOAc was hydrogenated over 150 mg of 5% Pd/C at room temperature and 1 bar for 2.5 h. TLC (SiO_2, EtOAc/hexane 1:3) showed spots for products **19** and **20** (R_f approximately 0.41 and 0.33, respectively) in approximately equal intensities. Another 150 mg of the catalyst was added, and the hydrogenation was continued for 6.5 h. At this point, TLC (as above) indicated that the product mixture consisted mostly of **20** besides small amounts of **19** and **21** (R_f approximately 0.22). The catalyst was filtered off over cotton, the solution was evaporated, and the residue was prepurified by filtration over SiO_2 with EtOAc/hexane 1:1 to yield 104 mg of a colorless film. This mixture was separated by preparative HPLC (column 2, EtOAc/hexane 1:3; t_R for **19**, **20**, and **21**: 17.5, 22.2, and 27.2 min, respectively). Evaporation of the fractions and drying in vacuo yielded 2.2 mg (3%) of **19**, 74.9 mg (69%) of **20**, and 10.7 mg (10%) of **21** as colorless oils. Compound **19**: ^{1}H NMR δ 7.36−7.18 (m, 6 H), 6.97 (t, 1 H, J = 7 Hz), 6.85−6.66 (m, 5 H), 6.13 (s, 1 H), 5.43 (dd, 1 H, J = 3.5, 7.5 Hz), 4.64 (br, 1 H), 4.59 (t, 1 H, J = 6 Hz), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.77 (s, 3 H), 3.56 (br, 3 H), 2.82, 2.66 (ABq, 2 H, J = 17 Hz, both parts dd with J = 2.5, 6 Hz and 6.5, 11.5 Hz, respectively), 2.50, 2.31 (ABq, 2 H, J = 13.5 Hz, A part dd with J = 3.5, 6.5 Hz, B part t with J = 7 Hz), 2.18, 1.94 (ABq, 2 H, J = 13.5 Hz, A part m, B part dt with J = 6.5 Hz (d), 11.5 Hz (t)). Compound **20**: $[\alpha]_D$ +48.2°, $[\alpha]_{546}$ +56.8° (EtOAc, *c* 9.6 g L^{-1}); ^{1}H NMR δ 7.27 (br, 1 H), 7.24−7.06 (m, 5 H), 7.03−6.86 (m, 4 H), 6.75 (dd, 1 H, J = 1, 8 Hz), 6.66 (br, 1 H), 6.12 (s, 1 H), 4.73 (br, 1 H), 4.43 (dd, 1 H, J = 6.5, 8.5 Hz), 3.92 (s, 3 H), 3.83 (br s, 3 H), 3.81 (s, 6 H), 2.87−2.36 (m, 6 H), 2.18−1.94 (m, 2 H); ^{13}C NMR δ 156.84, 154.64, 149.05, 148.80, 142.63, 128.91, 128.76, 128.42, 128.11, 126.73, 125.52, 119.23, 118.89, 115.49, 110.83, 110.44, 109.35, 55.89, 55.77, 55.38, 34.60, 33.15, 32.99, 29.45, 20.02. Compound **21**: $[\alpha]_D$ +53.4°, $[\alpha]_{546}$ +64.1° (EtOAc, *c* 5.2 g L^{-1}); ^{1}H NMR δ 7.54 (dd, 1 H, J = 1.5, 8 Hz), 7.28−7.06 (m, 6 H), 6.91 (dt, 1 H, J = 1 Hz (d), 7.5 Hz (t)), 6.83−6.70 (m, 4 H), 6.5 (br, 1 H), 6.12 (s, 1 H), 5.3 (br, 1 H), 6.50 (dd, 1 H, J = 5.5, 8.5 Hz), 3.85 (s, 3 H), 3.84 (s, 2 H), 3.78 (s, 3 H), 2.73−2.42 (m, 8 H), 1.77 (quint, 2 H, J = 7.5 Hz); ^{13}C NMR δ 157.34, 155.90, 154.45, 153.19, 148.75, 147.04, 142.37, 135.03, 128.66, 128.47, 128.22, 127.50 (with high-field shoulder), 125.68, 120.26, 120.17, 116.05, 111.64, 111.16, 110.78, 109.44, 88.72, 55.92, 55.81, 55.55, 35.16, 34.42, 33.45, 32.74, 30.66, 29.71, 22.45.

(2*S*)-8-[(1*R*)-1,3-Diphenylpropyl]-5,7,3′,4′-tetramethoxyflavan (23). To a solution of 74.9 mg (139 μmol) of intermediate **20** in 0.4 mL of anhydrous DMF was added with stirring at −40 °C under exclusion of moisture 42 μL (0.28 mmol) of DBU and then dropwise in 7 min a solution of 74 mg (0.21 mmol) of $PhNTf_2$ in 0.4 mL of DMF. The reaction mixture was allowed to reach 0 °C within 25 min and then stirred in an ice bath for 35 min and at room temperature for 1 h. After addition of 20 mL of half-saturated aq Na_2CO_3

solution, the mixture was extracted with 3 × 10 mL of EtOAc/hexane 1:1, and the combined organic phases were dried over $MgSO_4$. Filtration over SiO_2 with EtOAc/hexane 1:2, evaporation, and drying in vacuo gave 87.7 mg (94%) of the triflate **22** as a colorless glass which was used without further purification in the following step: ^{1}H NMR δ 7.45 (dd, 1 H, J = 1.5, 8 Hz), 7.24−7.06 (m, 7 H), 6.93 (dt, 1 H, J = 1 Hz (d), 7.5 Hz (t)), 6.87 (s, 1 H), 6.82 (s, 2 H), 6.12 (s, 1 H), 4.94 (dd, 1 H, J = 5.5, 8 Hz), 4.60 (dd, 1 H, J = 2, 10 Hz), 3.89 (s, 3 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.66 (s, 3 H), 2.79 (A part of an ABq, 1 H, J_{AB} = 17 Hz, dd with J = 2.5, 5.5 Hz), 2.67−2.50 (m, 4 H), 2.40−2.25 (m, 1 H), 2.12−1.90 (m, 2 H); ^{13}C NMR δ 156.98, 156.85, 154.94, 149.93, 148.53, 148.49, 142.78, 137.22, 134.46, 131.55, 128.35, 128.13, 126.98, 126.73, 125.51, 120.00, 118.69 (q [only 2 center lines observed], J = 319 Hz), 118.60, 110.72, 109.83, 109.21, 103.42, 87.63, 77.73, 55.89, 55.64, 55.54, 55.30, 34.44, 34.09, 29.65, 19.89. A solution of 87.7 mg (130 μmol) of **22** and 54 μL (0.39 mmol) of Et_3N in 9 mL of EtOAc was hydrogenated at 1 bar and room temperature over 72 mg of 5% Pd/C for 3 h. Completion of the reaction was established by HPLC (column 1, EtOAc/hexane 1:3; t_R 14.2 min (**23**), 15.4 min (**22**)). After filtration over a cotton plug and evaporation, the residue was filtered over SiO_2 with EtOAc/hexane 1:3 to furnish 64.1 mg (94%) of **23** as a colorless glass. The analytical sample was prepared by HPLC under the above conditions: $[\alpha]_D$ +21.1°, $[\alpha]_{546}$ +24.9° (EtOAc, c 6.5 g L^{-1}); ^{1}H NMR δ 7.30 (d, 2 H, J = 7.5 Hz), 7.23−7.01 (m, 8 H), 6.92−6.81 (m, 3 H), 6.12 (s, 1 H), 4.76 (d, 1 H, J = 10 Hz), 4.65 (dd, 1 H, J = 6, 8.5 Hz), 3.90 (s, 3 H), 3.82 (s, 3 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 2.80 (A part of an ABq, 1 H, J_{AB} = 17 Hz, dd with J = 1, 6 Hz), 2.71−2.49 (m, 4 H), 2.45−2.32 (m, 1 H), 2.20−2.09 (m, 1 H), 1.93 (ddt, 1 H, J = 6 Hz (d), 11.5 Hz (t), 13 Hz (d)); ^{13}C NMR δ 157.04, 156.45, 154.40, 148.86, 148.33, 145.69, 143.22, 134.74, 128.41, 128.14, 128.03, 127.55, 125.34, 125.05, 118.17, 112.74, 110.71, 109.11, 103.65, 88.33, 55.93, 55.89, 55.66, 55.30, 39.54, 34.84, 34.38, 29.73, 19.87.

(2*S*)-8-Bromo-5,7,3′,4′-tetramethoxyflavan (24). To a solution of 2.52 g (7.63 mmol) of **7** in 50 mL of anhydrous CH_2Cl_2 was added with stirring at −70 °C all at once 1.37 g (7.70 mmol) of recrystallized NBS. The mixture was stirred in the slowly thawing bath for 110 min, at which point the bath temperature was −16 °C. The cold bath was removed, and the mixture was stirred vigorously for 25 min with a solution of 0.5 g of $Na_2S_2O_3$•$5H_2O$ in 20 mL H_2O. The phases were separated, the aqueous phase was extracted with 5 mL of CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$. After concentration, the residue was filtered over SiO_2 with EtOAc/hexane 1:2. Evaporation and drying in vacuo gave 2.73 g (87%) of **24** as a colorless solid. This material was readily recrystallized from EtOAc/hexane but tenaciously held residual EtOAc even after drying in vacuo overnight at 70 °C, under which conditions the material turned pink: mp 145−148 °C (to form a red liquid; capillary inserted into bath at 136 °C; slow heating results in broader melting interval); ^{1}H NMR δ 7.07 (d, 1 H, J = 2 Hz), 6.97−6.87 (ABq, 2 H, J = 8.5 Hz, A part dd with J = 0.8, 2 Hz), 6.15 (s, 1 H), 5.11 (dd, 1 H, J = 2.5, 9.5 Hz), 3.90 (s, 6 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 2.74, 2.65 (ABq, 2 H, J = 17 Hz, both parts dd with J = 4, 6.5 Hz and 5.5, 10 Hz, respectively), 2.27, 1.99 (ABq, 2 H, J = 13.5 Hz, A part ddd with J = 2.5, 4, 6 Hz, B part dt with J = 6 Hz (d), 10 Hz (t)); ^{13}C NMR δ 157.17, 155.39, 152.42, 148.91, 148.32, 133.74, 117.69, 110.95, 109.07, 105.04, 91.75, 88.61, 77.49, 56.46, 55.89, 55.84, 55.55.

Mixture of (2*S*)-8-[(1*R*)-1,3-Diphenylpropyl]-5,7,3′,4′-tetramethoxyflavan (23) and (2*S*)-8-[(1*S*)-1,3-Diphenylpropyl]-5,7,3′,4′-tetramethoxyflavan (27). To a solution of 1.59 g (3.89 mmol) of **24** (which has previously been evaporated with toluene to remove residual EtOAc) in 40 mL of anhydrous THF was added at −78 °C under N_2 with stirring over a period of 1.5 min 6.5 mL (11.0 mmol) of *t*-BuLi (1.7 M in pentane). The resulting yellow solution was stirred at −78 °C for 4 min, and then a solution of 1.13 g (5.45 mmol) of chalcone in 10 mL of anhydrous THF was added within 4 min, causing an initial color change to greenish-black and eventually to orange. The mixture was thawed to −10 °C over a period of 100 min. The cold bath was removed, 50 mL of water was added, and the THF was removed by partial evaporation. After extraction of the aqueous residue with 50 + 30 mL of EtOAc, the combined organic phases were dried over $MgSO_4$ and evaporated. The residue was chromatographed on SiO_2 with EtOAc/hexane mixtures (3:8 for unreacted chalcone and **7**, 2:3 for the desired intermediates). Evaporation of the respective fractions yielded 0.86 g (67%) of **7** and 0.57 g (28%) of the addition product (**25** and/or **26**) as a mixture of isomers. The crude intermediate was taken up in 24 mL of EtOAc/MeOH 1:1 and hydrogenated at 1 bar and room temperature over 0.29 g of 20% $Pd(OH)_2$/C for 6 h. After filtration over cotton and evaporation, the residue was chromatographed on SiO_2 with toluene/EtOAc 24:1, isolating the major, less-polar component of the product mixture. Evaporation and drying in vacuo yielded 367 mg (66%) of a mixture of **23** and **27** as a colorless glass in an isomer ratio of 2:3. The analytical sample was obtained by preparative HPLC (column 1, EtOAc/hexane 1:4; t_R 17.2 min, no separation of isomers under these conditions): ^{1}H NMR (selected signals of **27** only) δ 4.89 (dd, 1 H, J = 2, 10.5 Hz), 4.68 (dd, 1 H, J = 5.5, 8.5 Hz), 3.87 (s, 3 H), 3.81 (s, 3 H), 3.733 (s, 3 H), 3.729 (s, 3 H). Anal. Calcd for $C_{34}H_{36}O_5$: C, 77.84; H, 6.92. Found: C, 78.01; H, 6.85.

Oxidative Degradation of 23. To 64.1 mg (122 μmol) of **23** in 1.2 mL of anhydrous CCl_4, 1.2 mL of HPLC grade CH_3CN, and 1.8 mL of HPLC grade H_2O were added 0.52 g (2.4 mmol) of solid $NaIO_4$ and 5 mg (24 μmol if dry, but water content unknown) of $RuCl_3$•xH_2O. The mixture was stirred vigorously at room temperature for 2 h. After addition of 5 mL of 5% HCl, the products were extracted into 3 × 10 mL of CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$ and evaporated. The residue was taken up in 20 mL of ether and set aside at room temperature for 15 min to allow finely dispersed residual Ru compounds to coagulate, which were then removed by filtration over a cotton plug. After evaporation, the residue was taken up in 0.3 mL of THF, and 0.9 mL of MeOH was added followed by a solution of 63 mg (0.22 mmol) of diphenyldiazomethane in 0.3 mL of THF. This mixture was stirred at room temperature in the dark for 80 min, after which period the red color of the reagent was found to be completely discharged. Another 90 mg (0.46 mmol) of Ph_2CN_2 in 0.3 mL of THF was added, and the mixture was kept at room temperature in the dark for 64 h. The solvent was evaporated and the residue chromatographed on SiO_2 with CH_2Cl_2/hexane 1:1. The required degradation product eluted after several minor nonpolar byproducts as part of a band of R_f approximately 0.5−0.4 which appeared on TLC as a group of two closely spaced spots. This material (39.5 mg) was further fractionated by preparative TLC (SiO_2, two plates of dimensions 200 × 200 × 0.25 mm, EtOAc/hexane 1:15). The slower-moving of the two major bands was isolated (8.2 mg) and subjected to preparative HPLC (column 1; gradient of CH_2Cl_2 in hexane: 0−43 min, 25 to 50% CH_2Cl_2; 5.2 mL/min). A peak eluting at t_R 29.1 min on evaporation yielded 5.1 mg (10%) of (−)-**29** the ^{1}H NMR spectrum of which was identical with that of the authentic material prepared below; $[\alpha]_D$ −22°, $[\alpha]_{546}$ −27°, $[\alpha]_{435}$ −51° (c 2.4 g L^{-1}, EtOAc).

***rac*-2,4-Diphenylbutyronitrile (31).**[41] To a suspension of 2.12 g (53 mmol) of NaH (60% in oil) in 50 mL of anhydrous DMSO under N_2 was added dropwise with stirring and cooling (rt water bath) 5.8 mL (50 mmol) of $PhCH_2CN$ at such a rate that the internal temperature remained in the 25−30 °C range. The addition required 15 min. After another 10 min, 6.8 mL (50 mmol) of $PhCH_2CH_2Br$ was added at an internal temperature of 27−32 °C. This operation required 20 min. After another 30 min at room temperature, the solution was poured onto 90 g of ice, 200 mL of water was added, and the products were extracted into 3 × 100 mL of ether. The combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, and evaporated, and the residue was chromatographed on SiO_2 with EtOAc/hexane 1:25. The first-eluted product (0.88 g, 5%) was identified as 2-phenethyl-2,4-diphenylbutyronitrile based on its spectroscopic data. ^{1}H NMR δ 7.56−7.06 (m, 15 H), 2.87−2.73 (m, 2 H), 2.48−2.14 (m, 6 H); IR (film) 2236, 1603, 1495, 1454, 757, 701 cm^{-1}; MS m/z

325 (M^+, 6%), 234, 221, 105 (100%), 91. The major fraction was eluted subsequently and, after evaporation and drying in vacuo, yielded 6.41 g (58%) of **31** as an oil: ^{1}H NMR δ 7.44−7.16 (m, 10 H), 3.74 (dd, 1 H, J = 6, 9 Hz), 2.90−2.73 (m, 2 H), 2.35−2.10 (m, 2 H).

***rac*-2,4-Diphenylbutyric Acid ((±)-28).**[43] A mixture of 5.01 g (22.6 mmol) of **31**, 18 mL of AcOH, and 3 mL of 70% aq H_2SO_4 was refluxed with exclusion of moisture for 3 d. Volatiles were evaporated, 100 mL of ice−water was added, and the product was extracted into 3 × 30 mL of ether. After washing of the combined ether phases with 30 mL of ice−water, the product was extracted into a cold solution of 3.2 g (80 mmol) of NaOH in 60 mL of H_2O. The aqueous phase was washed with 30 mL of ether and then cooled by addition of ice and acidified with 7 mL of concd HCl. The product was extracted into 3 × 30 mL of ether, and the combined organic phases were dried over $MgSO_4$, evaporated, and briefly dried in vacuo to yield 5.49 g (101%) of *rac*-**28** as an amber oil. Bulb-to-bulb distillation (oven 165 °C/oil pump vacuum) gave a colorless oil which gradually solidified on standing: ^{1}H NMR δ 7.40−7.10 (m, 10 H), 3.56 (t, 1 H, J = 7.5 Hz), 2.58 (t, 2 H, J = 7.5 Hz), 2.49−2.35 (m, 1 H), 2.18−2.04 (m, 1 H).

(*R*)-α-Methylbenzylammonium (*R*)-2,4-Diphenylbutyrate (32).[40a] To a boiling solution of 1.94 g (8.07 mmol) of *rac*-**28** in 20 mL of MeOH was added 565 μL (4.44 mmol) of (*R*)-(+)-α-methylbenzylamine (Fluka, 99+%). No crystallization occurred at room temperature overnight; after 2 d at −20 °C, the mixture was found to have set to a compact solid. This material partially reliquefied on thawing, and subsequent suction filtration, washing with 5 mL of MeOH, and drying in vacuo yielded 607 mg of a colorless solid exhibiting $[\alpha]_{546}$ −12.2° (*c* 17.7 g L^{-1}, MeOH). A second crop of 513 mg was obtained by concentrating the mother liquor. Both crops together were recrystallized from 20 mL of MeOH (reflux to room temperature) to give 523 mg of a solid ($[\alpha]_{546}$ −14.5° (*c* 16.9 g L^{-1}, MeOH)). Another recrystallization from 12 mL of MeOH (reflux to room temperature) yielded 188 mg of a solid ($[\alpha]_{546}$ −14.3° (*c* 17.5 g L^{-1}, MeOH)). The constant optical rotation suggested that stereochemical purity had been achieved. However, when the mother liquor of this recrystallization was allowed to stand at room temperature for approximately 1 month during which period part of the solvent evaporated, long needles of substantial diameter were formed which exhibited $[\alpha]_D$ −13.2°, $[\alpha]_{546}$ −15.3° (*c* 17.2 g L^{-1}, MeOH). This material was used for X-ray structure analysis and for the preparation of (−)-**28**. ^{1}H NMR ($CDCl_3$/CD_3OD approximately 8:1) δ 7.40−7.12 (m, 15 H), 4.14 (q, 1 H, J = 6.5 Hz), 3.48 (t, 1 H, J = 7.5 Hz), 2.67−2.50 (m, 2 H), 2.44−2.31 (m, 1 H), 2.14−2.00 (m, 1 H), 1.46 (d, 3 H, J = 6.5 Hz).

(*R*)-(−)-2,4-Diphenylbutyric Acid ((−)-28).[40a] Part of the crystals of $[\alpha]_{546}$ −15.3° obtained above were shaken with 5 mL of 5% aq HCl and 5 mL of EtOAc, the phases were separated, and the aqueous phase was extracted with two more 5 mL portions of EtOAc. The combined organic phases were washed with 5 mL of 5% aq HCl, and the aqueous phase was back-extracted with 5 mL of EtOAc. Drying over $MgSO_4$, evaporation, and distillation as above yielded (−)-**28** as a colorless oil: $[\alpha]_D$ −56.8°, $[\alpha]_{546}$ −68.7° (*c* 24.9 g L^{-1}, $CHCl_3$) (lit.:[41] $[\alpha]_D$ +57° for an enantiomer of unknown absolute configuration (*c* "10%", $CHCl_3$)).

Benzhydryl (*R*)-2,4-Diphenylbutyrate ((−)-29). To a solution of 22.6 mg (94 μmol) of (−)-**28** in 0.3 mL of THF and 0.6 mL of MeOH was added a solution of 36.5 mg (188 μmol) of diphenyldiazomethane in 0.3 mL of THF. The mixture was stirred in a loosely stoppered flask at room temperature in the dark for 3 h. Initial purification was achieved by preparative TLC (SiO_2, two plates, 200 × 200 × 0.25 mm, EtOAc/hexane 1:15) which removed a close nonpolar zone. Subsequently, the product (39.2 mg) was subjected to preparative HPLC (column 1, EtOAc/hexane 1:19; t_R 11.4 min (impurity), 12.3 min (**29**)) to yield 29.1 mg of a colorless oil which, according to GC-MS, remained contaminated with Ph_2CO. Suitable HPLC conditions were later found for the removal of this contaminant (see above); in the present experiment, the material was taken up in 0.4 mL of anhydrous THF and reacted with 0.1 mL of BH_3·THF (1 M in THF) under N_2 at room temperature for 30 min. The reagent was then quenched by dropwise addition of a mixture of 0.1 mL of MeOH and 0.5 mL of THF, the mixture was evaporated, and the residue was chromatographed on SiO_2 with EtOAc/hexane 1:12 to furnish 22.0 mg (57%) of the pure oily ester: $[\alpha]_D$ −23.7°, $[\alpha]_{546}$ −28.9°, $[\alpha]_{435}$ −54.2° (*c* 5.2 g L^{-1}, EtOAc); ^{1}H NMR δ 7.37−7.13 (m, 16 H), 7.11−7.04 (m, 4 H), 6.83 (s, 1 H), 3.68 (t, 1 H, J = 7.5 Hz), 2.54 (t, 2 H, J = 7.5 Hz), 2.50−2.36 (m, 1 H), 2.19−2.06 (m, 1 H). Anal. Calcd for $C_{29}H_{26}O_2$: C, 85.68; H, 6.45. Found: C, 85.62; H, 6.30.

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Supporting Information Available: Methylation of **3b**; byproduct **8**; hydrogenolysis of mesylate **13**; formation and partial hydrogenolysis of triflate **14**; trifluoromethanesulfonylation of (+)-catechin; deoxygenation of **12** through its 1-phenyl-5-tetrazolyl derivative; byproducts isolated from the oxidative degradation of **23**/**27**; preparation of a bisgallate derived from **3e**; additional Experimental Section including (a) selected IR bands of (2*R*)-5,7,3′,4′-tetramethoxyflavan-3-one and compounds **3d**, **5**−**7**, **9**−**11**, **13**−**16**, **18**−**23**, **(**−**)-29**, and **31**; (b) selected MS peaks of (2*R*)-5,7,3′,4′-tetramethoxyflavan-3-one and compounds **1b**, **3f**, **7**, **12**, **15**, **16**, **19**−**24**, **(**−**)-29**, and **31**; (c) tables of atom coordinates, displacement parameters, bond lengths and angles, torsion angles, and hydrogen bonds for compound **32** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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