Studies in Polyphenol Chemistry and Bioactivity. 3.[1,2] Stereocontrolled Synthesis of Epicatechin-4α,8-epicatechin, an Unnatural Isomer of the B-Type Procyanidins

Alan P. Kozikowski,* Werner Tückmantel,* and Youhong Hu

Georgetown University Medical Center, Drug Discovery Program, 3900 Reservoir Road NW, Washington, DC 20007

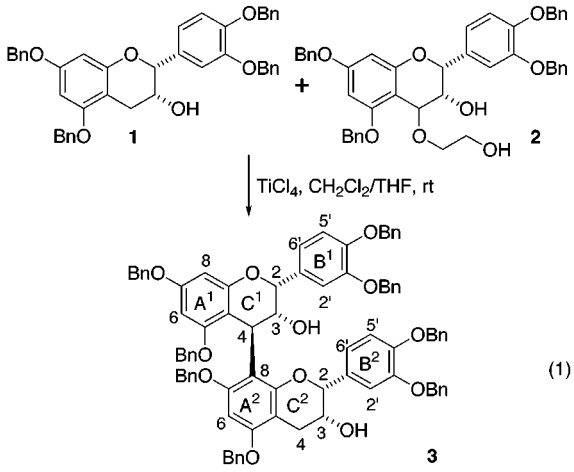
tueckmaw@giccs.georgetown.edu

Received October 10, 2000

Oligomeric procyanidins containing 4α-linked epicatechin units are rare in nature and have hitherto not been accessible through stereoselective synthesis. We report herein the preparation of the prototypical dimer, epicatechin-4α,8-epicatechin (**6**), by reaction of the protected 4-ketones **11a**,**b** with aryllithium reagents derived by halogen/metal exchange from the aryl bromides **26a**,**b**. Removal of the 4-hydroxyl group from the resulting tertiary benzylic alcohols **27a**,**b** was effected by tri-*n*-butyltin hydride and trifluoroacetic acid in a completely stereoselective manner, resulting in hydride delivery exclusively from the *β* face. If benzyl was chosen for protection of the 3-hydroxyls, all protective groups could subsequently be removed in a single step by hydrogenolysis. *tert*-Butyldimethylsilyl groups, on the other hand, permitted selective deprotection of the 3-hydroxyls in preparation for their subsequent acylation with tri-*O*-benzylgalloyl chloride. Only monogalloylation at the "bottom" 3-hydroxyl took place when **28c** was acylated under the previously reported conditions, reflecting the increased steric hindrance of the "top" 3-hydroxyl group in **28c** compared with its 4*β*,8-isomer **3**. The preparation of compounds **14** and **17** containing phloroglucinol trimethyl ether in the 4α and 4*β* linkages to epicatechin is also described. The 8-position of the bromine atom in **19**, previously conjectured in analogy to the structurally characterized tetramethyl ether **20**, was confirmed by transformation of both compounds into the common derivative **25**.

Introduction

Proanthocyanidins (nonhydrolyzable tannins) are of current interest because of their numerous biological activities, their widespread occurrence in foodstuffs, and their resulting relevance for human health.[1] As the starting point of a program directed at the synthesis of defined epicatechin oligomers for comparison with compounds isolated from cocoa, we have previously performed the $TiCl_4$-mediated alkylation of 5,7,3′,4′-tetra-*O*-benzyl-(−)-epicatechin (**1**) with 5,7,3′,4′-tetra-*O*-benzyl-4-(2-hydroxyethoxy)epicatechin (**2**) (eq 1).[1] Besides higher oligomers in yields rapidly decreasing with their molecular mass, a single dimeric product was obtained that was identified as the procyanidin B_2 derivative **3** by hydrogenolytic conversion to procyanidin B_2 and comparison of this material and its peracetate with isolates and preparations described in the literature. In the process of examining the relevant literature, it did not escape our attention that, until quite recently, the analytical methods employed for the assignment of interflavan bond regio- and stereochemistry in these compounds were not validated by an independent confirmation of the structure of any dimeric B-type proanthocyanidin.[1] The application of X-ray cystallography has been prevented by the poor crystallizability of proanthocyanidins and their derivatives. Assignments of



(1)

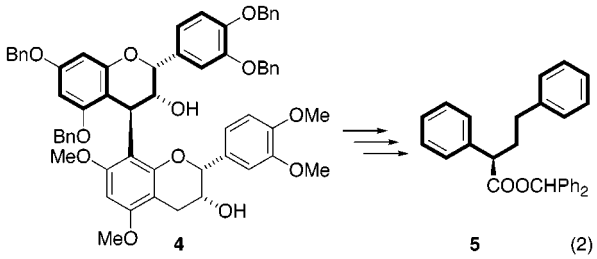
stereochemistry on the basis of ^{1}H NMR coupling constants and circular dichroism disregard the basic fact that the C rings are conformationally flexible. From a conservative point of view, postulates of specific conformations of flexible molecules, regardless of their source (intuitive or computational), cannot be considered a prudent approach to structure elucidation. Advances in synthetic methodology that have taken place after the isolation of numerous proanthocyanidins from natural sources have recently enabled us[2] to obtain a definitive proof of the previously conjectured 4*β* stereochemistry in procyanidin B_2. Thus, the differentially protected epicatechin dimer **4**, correlated with procyanidin B_2 through a common derivative, was subjected to a series of defunctionalization steps and finally degraded to (*R*)-(−)-

(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) Part 2: Kozikowski, A. P.; Tückmantel, W.; George, C. *J. Org. Chem.* **2000**, *65*, 5371.

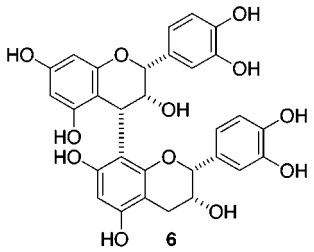
10.1021/jo001462y CCC: $20.00
Published on Web 01/31/2001

2,4-diphenylbutyric acid, isolated as its benzhydryl ester **5** (eq 2). The sole remaining asymmetric center in **5** is



directly derived from C-4 of the "top" epicatechin moiety in procyanidin B_2, and the sign of the optical rotation of **5**, the absolute configuration of which was established by X-ray crystallography, thus revealed the absolute configuration at C-4.[2]

In a parallel thrust, which is the subject of the present paper, we set out to prepare the alternative stereoisomer, now recognizable by default as epicatechin-4α,8-epicatechin (**6**). Literature reports of proanthocyanidins for which simultaneously a 2,3-cis and a 3,4-cis relationship of their C-ring substituents has been postulated are scarce,[3] and compound **6** has not (yet) been isolated from



natural sources. No stereoselective synthesis of any procyanidin containing a 4α-linked epicatechin unit has been reported to date. It is a plausible assumption that, in the course of the formation of the 4β,8-dimer **3**, the 2-aryl group and the 3-oxygen cooperate in directing the approach of the flavan nucleophile to the presumed carbocationic intermediate **7** toward its β-face (Figure 1).[4] The accessibility of the 4α-stereoisomer by merely modifying the reaction conditions or attaching protecting groups to one or both of the 3-hydroxyl groups was therefore deemed unlikely. We reasoned instead that a C4-carbocation **8** that has the "bottom" flavan unit already in place would analogously be attacked by a hydride nucleophile from its β-face, and the 4-flavanyl group would, therefore, be forced to occupy the α-face. The carbocation would be conveniently generated from a tertiary alcohol which in turn, as Weinges et al. have demonstrated earlier,[5] is accessible from an 8-lithiated building block and a 4-ketone.

Results

Preparation of Epicatechin-Phloroglucinol Dimers. Initially, a model study was conducted in which

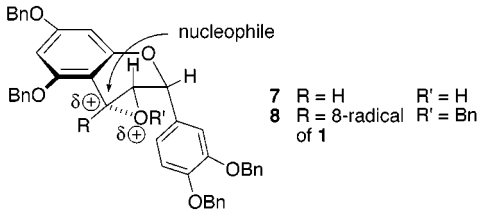
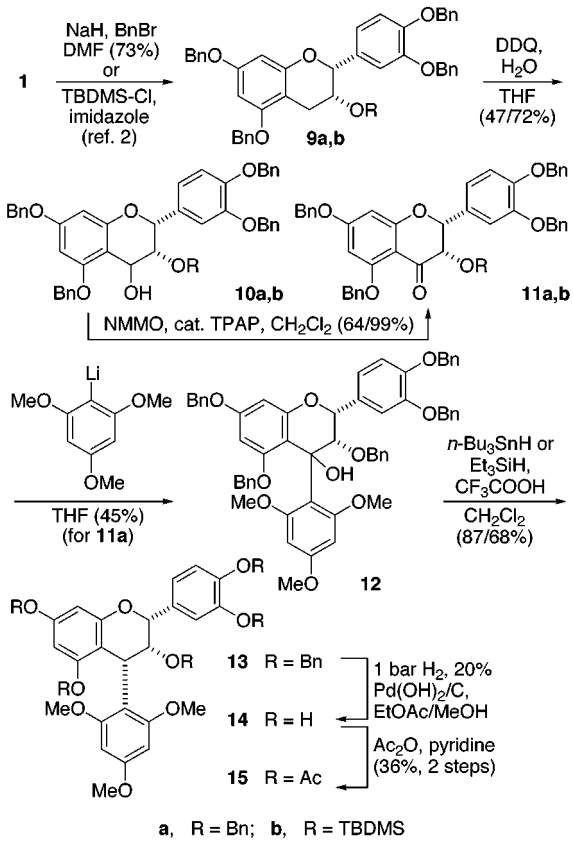


Figure 1. Model for the directing effect of the 2-aryl and 3-alkoxy substituents on the attack of nucleophiles at C-4

Scheme 1



phloroglucinol trimethyl ether was used as the "bottom" unit in place of another epicatechin moiety (Scheme 1). The free hydroxyl group in **1** was protected by benzylation or silylation[2] and the products **9a**,**b** oxidized with DDQ[6] in THF using water to capture the intermediate carbenium ion **7**. The resulting alcohols **10a**,**b** (presumably, but not with certainty, of 4β stereochemistry) were oxidized to the ketones **11a**,**b** using Ley's method.[7] Compound **11a** was reacted with 2,4,6-trimethoxyphenyllithium[8] to produce the tertiary alcohol **12** as a single stereoisomer. Steric hindrance exerted by the 2-substituent once more suggests that the incoming 4-aryl substituent should attack the carbonyl group from the β face. The hydrogenolytic deoxygenation at C-4 in a similar compound has been reported[5] to be very inefficient and was not taken into consideration by us. Instead, treat-

(3) (a) Foo, L. Y. *J. Chem. Soc., Chem. Commun.* **1986**, 236. (b) Foo, L. Y.; Karchesy, J. J. *Phytochemistry* **1989**, *28*, 3185. (c) Steynberg, P. J.; Steynberg, J. P.; Hemingway, R. W.; Ferreira, D.; McGraw, G. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2395.

(4) A reviewer suggested that instead the bulky 2-aryl group might occupy a pseudoequatorial position in the transition state and that the observed product stereochemistry could then result from a preferred pseudoaxial attack of the nucleophile. We do not have evidence for or against either possibility.

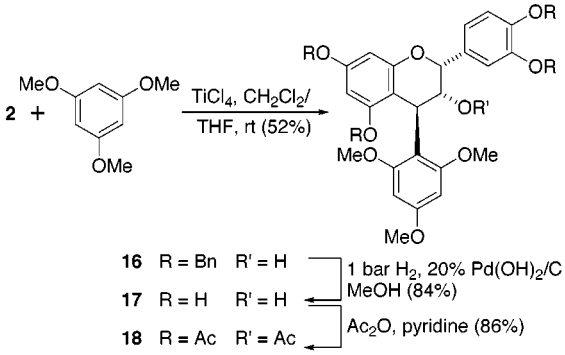
(5) Weinges, K.; Perner, J.; Marx, H.-D. *Chem. Ber.* **1970**, *103*, 2344.

(6) (a) Steenkamp, J. A.; Ferreira, D.; Roux, D. G. *Tetrahedron Lett.* **1985**, *26*, 3045. (b) Steenkamp, J. A.; Mouton, C. H. L.; Ferreira, D. *Tetrahedron* **1991**, *47*, 6705.

(7) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(8) Previously prepared by metalation of 1,3,5-trimethoxybenzene: (a) Van Koten, G.; Leusink, A. J.; Noltes, J. G. *J. Organomet. Chem.* **1975**, *85*, 105. (b) Kroth, H. J.; Schumann, H.; Kuivila, H. G.; Schaeffer, C. D.; Zuckerman, J. J. *J. Am. Chem. Soc.* **1975**, *97*, 1754.

Scheme 2

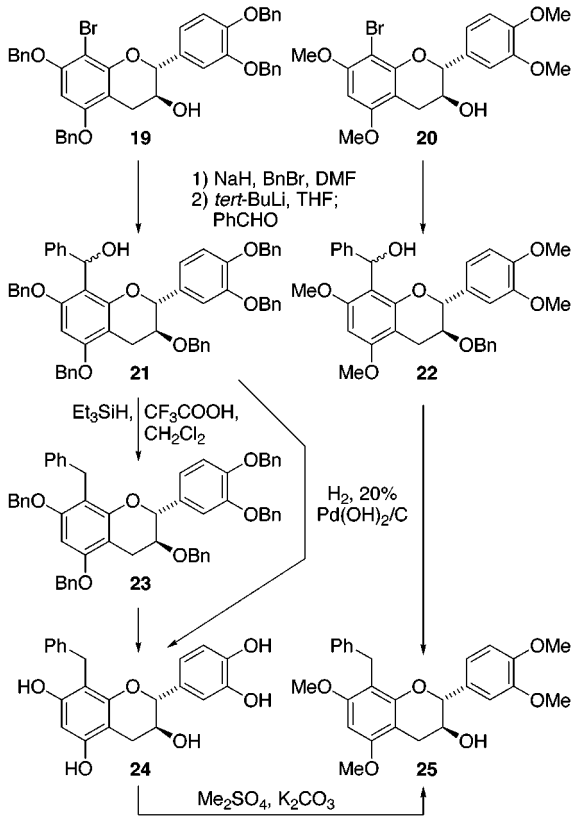


ment of **12** with Et_3SiH/CF_3COOH[9] gave the reduction product **13** as a single stereoisomer in 68% yield. Its 4α stereochemistry is assigned in analogy to that of the epicatechin dimer **6** discussed below on the basis of its mode of formation and its C-ring ^1H NMR coupling pattern. Significant loss of material is caused by a side reaction, elimination of water from the C3−C4 bond. Switching from Et_3SiH to the more reactive hydride source, *n*-Bu_3SnH, raised the yield to 87%. Hydrogenolysis and acetylation provided the pentaacetate **15**.

The $TiCl_4$-mediated condensation[10] between **2** and 1,3,5-trimethoxybenzene (Scheme 2) gave a single 4-arylepicatechin **16**. Its hydrogenolysis and subsequent acetylation resulted in a pentaacetate **18** different from **15**, to which 4β stereochemistry is assigned in analogy with **3**. Related preparations of catechin- and epicatechin-phloroglucinol condensation products involving different patterns of phenol protection have been reported previously.[3b,10−12] The parent heptaphenol is a natural product.[12]

Authentication of Bromide 19. We have thus identified conditions for the efficient removal of the 4-OH group and confirmed our hypothesis that this process generates an interflavan bond stereochemistry different from that obtained by electrophilic alkylation. To translate these results into an unequivocal synthesis of epicatechin-4α,8-epicatechin (**6**), it was essential to have certainty regarding the regiochemistry of the lithiated epicatechin derivative to be employed. We have previously reported the preparation of the required bromide **26c** from its C-3 epimer **19**.[1] 3-*O*-Protected derivatives of **19** have earlier been prepared by bromination of appropriate halogen-free catechin derivatives.[13] The postulated regiochemistry of those bromides was not commented upon by the earlier authors and appears to have been derived by analogy from that of the tetramethyl ether **20**, for which the 8-position of the Br substituent is known from an X-ray crystal structure analysis.[14] To dispel any possible doubt, **19** and **20** were both converted to the common derivative **25** (Scheme 3).

Scheme 3

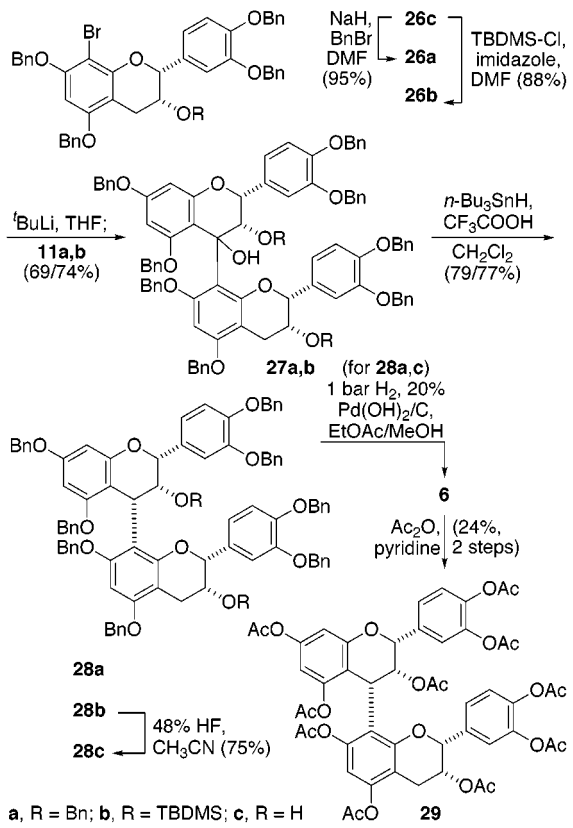


It is worth mentioning that our sample of 8-benzylcatechin (**24**) displays a melting point (212−213.5 °C) and an optical rotation substantially different from those reported.[15] On the other hand, the melting point of **24** in ref 15 (176 °C) is essentially identical with that reported in the patent literature (174−176 °C)[16] for 6-benzylcatechin. The melting point of our intermediate **23** (129.5−130 °C) matches reasonably well that reported by the patent authors for the same structure (133−134 °C).[17] It is then surprising that O-methylation of the mentioned literature sample of **24** has been reported[15] to yield compound **25** with a melting point essentially identical with and an optical rotation close to ours. An erroneous switching in ref 15 of the physical data of **24** but not of **25** with those of a sample of the 6-benzyl regioisomer would offer a likely explanation.

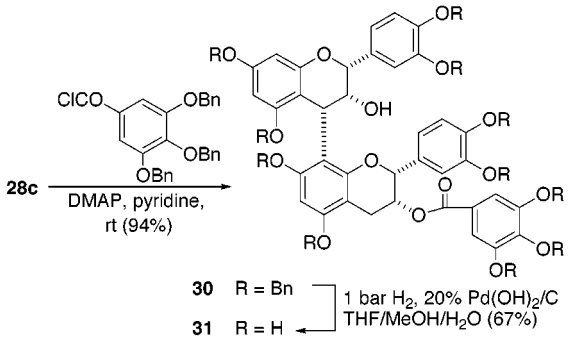
Synthesis of Epicatechin-4α,8-epicatechin (6). In preparation for the halogen−metal exchange, the 3-hydroxyl group in **26c** was protected by benzylation or silylation (Scheme 4). Subsequent treatment of the products **26a**,**b** with *tert*-butyllithium, followed by addition of the ketones **11a** (for **26a**) or **11b** (for **26b**), resulted in smooth formation of the biflavanoid tertiary alcohols **27a**,**b** as single isomers. Treatment of **27a** with Et_3SiH/CF_3COOH caused predominantly elimination, besides interflavan bond cleavage. If Et_3SiH was replaced with *n*-Bu_3SnH, smooth reduction of **27a**,**b** to the protected epicatechin dimers **28a**,**b** took place. Compound **28b** was readily desilylated to the diol **28c** with aqueous HF in CH_3CN, whereas *n*-Bu_4NF gave a complex mixture. The hydrogenolytic deprotection of **28a**,**c** was not as clean as in the 4β series. An analytically pure sample of **6** was

(9) Carey, F. A.; Tremper, H. S. *J. Org. Chem.* **1971**, *36*, 758.
(10) Kawamoto, H.; Nakatsubo, F.; Murakami, K. *J. Wood Chem. Technol.* **1989**, *9*, 35.
(11) (a) Geissman, T. A.; Yoshimura, N. N. *Tetrahedron Lett.* **1966**, 2669. (b) Jurd, L.; Lundin, R. *Tetrahedron* **1968**, *24*, 2653. (c) Botha, J. J.; Young, D. A.; Ferreira, D.; Roux, D. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1213.
(12) Kolodziej, H. *Tetrahedron Lett.* **1983**, *24*, 1825.
(13) Ballenegger, M. E.; Rimbault, C. G.; Albert, A. I.; Weith, A. J.; Courbat, P.; Tyson, R. G.; Palmer, D. R.; Thompson, D. G. *Eur. Pat.* 0096007, July 29, 1987 (Example Nos. 67−70); *Chem. Abstr.* **1984**, *100*, 209512w.
(14) Engel, D. W.; Hattingh, M.; Hundt, H. K. L.; Roux, D. G. *J. Chem. Soc., Chem. Commun.* **1978**, 695.
(15) Weinges, K.; Seiler, D. *Liebigs Ann. Chem.* **1968**, *714*, 193.
(16) Reference 13, Example No. 16.
(17) Reference 13, Example No. 17.

Scheme 4



Scheme 5



obtained only if aliphatic impurities were removed before the final lyophilization by extraction of the aqueous solution with toluene. Alternatively, the crude hydrogenolysis product was directly converted into its acetate **29**. Both compounds **6** and **29** were different by ^{1}H NMR spectroscopy from their 4β isomers. As the 4,8-position of their interflavan linkage is a necessary consequence of the structure of the starting material **26c**, compound **6** is unequivocally identified as the hitherto unknown epicatechin-4α,8-epicatechin.

Preparation of Gallic Acid Esters of 6. We were initially surprised to find that the galloylation of **28c** under the conditions described for its 4β isomer **3**[1] turned out a monoester (Scheme 5). In hindsight, this is not surprising as the C^1 ring hydroxyl group in **28c** is severely hindered by two vicinal, cis-oriented aryl substituents. This rationale hints at **30** as the structure of the major product. The same regiochemistry is suggested by the observation of COSY cross-peaks between the 4-H signals (narrow multiplets at δ 2.88 and 3.18 for the major and minor rotamer, respectively) of the C^2 ring and a narrow low-field multiplet (δ 5.39), indicating by its chemical shift that the vicinal 3-hydroxyl group should be acylated. 3-H of the C^1 ring, on the other hand, appears as a doublet of doublets at δ 4.25 for the major rotamer. As a note of caution, however, it should be kept in mind that signal assignments based on chemical shifts are problematic here because of the presence of multiple magnetically anisotropic functionality. An unequivocal synthesis of **30** and its regioisomer could be conceived starting from dimeric precursors bearing differential protecting groups at the 3-hydroxyls, available from the reaction of **11a** with the aryllithium derived from **26b**, and of **11b** with the aryllithium derived from **26a**, respectively. We did, however, not pursue this avenue as our target was the bisgallate. To our initial relief, inclusion of molecular sieves in the reaction mixture allowed further galloylation of the monogallate **30** to what appeared to be the di-3-*O*-galloyl derivative. The mechanism of action of the additive is not obvious; certainly, the large excess of acylating agent used renders a mere scavenging of adventitious moisture improbable. Surface catalysis is therefore likely to be involved. The supposed bisgallate upon hydrogenolysis yielded a mixture of two compounds (according to HPLC) both of which exhibited mass spectra in accordance with the desired di-3-*O*-galloyl derivative of **6**. Reexamination by HPLC of the protected precursor under different conditions subsequently revealed its inhomogeneity. The achieved separation was, however, inadequate for preparative purposes, and we abandoned our efforts toward the synthesis of the bisgallate.

Conclusion

A highly stereoselective synthesis of the hitherto inaccessible, unnatural procyanidin stereoisomer, epicatechin-4α,8-epicatechin (**6**), has been achieved. The preparation of higher 4,8-oligomers possessing α stereochemistry in some or all of its interflavan bonds should be possible by extending the previously reported electrophilic substitution process to the precursors **28a**−**c** or by subjecting bromides derived from these compounds or from compound **3** to the conditions of the present work.

Experimental Section

General Procedures. Pearlman's catalyst (20% Pd(OH)$_2$/C) was obtained from Aldrich and contained ≤50% H$_2$O. ^{1}H and ^{13}C NMR spectra were acquired at nominal frequencies of 300 and 75 MHz, respectively. ^{1}H 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). Combustion analyses: Micro-Analysis, Inc. (Wilmington, DE). Column chromatography (CC): Merck silica gel 60 Geduran (No. 110832-1), particle size 63-200 μm. TLC: Merck silica gel 60 F$_{254}$ (No. 5715-7), layer thickness 250 μm; visualization with alkaline KMnO$_4$ solution.

3,5,7,3′,4′-Penta-*O*-benzylepicatechin (9a). To a suspension of 180 mg (4.5 mmol) of NaH (60% in oil) in 10 mL of dry DMF was added at room temperature a solution of 2.60 g (4.00 mmol) of **1** in 10 mL of dry DMF. After 1 h, 0.56 mL (4.7 mmol) of BnBr was added. The mixture was stirred overnight, poured into ice−water, and extracted with 3 × 50 mL of CH$_2$Cl$_2$. The combined organic phases were washed with H$_2$O and brine, dried over MgSO$_4$, and evaporated. The residue was purified by CC (CH$_2$Cl$_2$/EtOAc/hexane 1:1:6) to give 2.20 g (74%) of the product as a colorless, amorphous solid: $[\alpha]_D$ −30.7, $[\alpha]_{546}$ −37.2 (*c* 6 gL^{-1}, EtOAc); ^{1}H NMR (CDCl$_3$) δ 7.48−7.25 (m, 20 H), 7.19 (s, 1 H), 7.17−7.12 (m, 3 H), 7.04−6.97 (m, 2 H), 6.91

(narrow ABq, 2 H), 6.27, 6.25 (ABq, 2 H, J = 2 Hz), 5.17 (s, 2 H), 5.05 (s, 2 H), 5.00 (s, 2 H), 4.98 (s, 2 H), 4.94 (s, 1 H), 4.44, 4.30 (ABq, 2 H, J = 12.5 Hz), 3.91 (narrow m, 1 H), 2.99, 2.77 (ABq, 2 H, J = 17 Hz, both parts d with J = 2.5, 4 Hz, respectively); ^{13}C NMR ($CDCl_3$) δ 158.59, 157.95, 155.56, 148.75, 148.33, 138.07, 137.37, 137.28, 137.07, 136.94, 132.20, 128.49, 128.45, 128.38, 128.32, 128.03, 127.87, 127.78, 127.67, 127.61, 127.57, 127.49, 127.32, 127.23, 127.17, 119.75, 114.69, 113.80, 101.45, 94.73, 93.73, 78.02, 72.55, 71.31, 71.14, 71.02, 70.03, 69.86, 24.47; IR (film) 1617, 1592, 1145, 1116, 735, 696 cm^{-1}. Anal. Calcd for $C_{50}H_{44}O_6$: C, 81.06; H, 5.99. Found: C, 81.19; H, 5.76.

3,5,7,3′,4′-Penta-*O*-benzyl-4-hydroxyepicatechin (10a). To a solution of 2.20 g (3.38 mmol) of **9a** in 20 mL of THF and 0.16 mL (8.9 mmol) of H_2O was added at room temperature 2.00 g (7.4 mmol) of DDQ. The mixture was stirred overnight, and then 0.91 g (7.4 mmol) of DMAP was added, stirring was continued for 5 min, and 20 g of silica gel was added. After evaporation, the residue was filtered over SiO_2 (EtOAc/hexane 1:4, then CH_2Cl_2/EtOAc/hexane 1:1:4) to give 1.05 g (47%) of the product as a white foam: $[\alpha]_D$ +6.6, $[\alpha]_{546}$ +7.2 (c 10 gL^{-1}, EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.50−7.28 (m, 20 H), 7.20−7.11 (m, 4 H), 7.04−6.92 (m, 4 H), 6.30 (narrow m, 2 H), 5.20 (s, 2 H), 5.09 (narrow ABq, 2 H), 5.06 (s, 2 H), 5.03 (s, 1 H), 5.01 (s, 2 H), 4.95 (narrow m, 1 H), 4.39, 4.25 (ABq, 2 H, J = 12 Hz), 3.70 (narrow m, 1 H), 2.41 (d, 1 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 160.32, 159.00, 156.09, 148.88, 148.39, 137.61, 137.38, 137.26, 136.64, 136.48, 131.58, 128.70, 128.59, 128.43, 128.38, 128.14, 128.06, 127.78, 127.63, 127.68, 127.54, 127.49, 127.35, 127.31, 127.28, 119.88, 114.82, 113.61, 104.77, 94.79, 94.06, 77.07, 74.83, 72.49, 71.34, 70.98, 70.20, 70.10, 61.10; IR (film) 1616, 1592, 1152, 1120, 736, 696 cm^{-1}. Anal. Calcd for $C_{50}H_{44}O_7$: C, 79.34; H, 5.86. Found: C, 79.91; H, 5.60.

5,7,3′,4′-Tetra-*O*-benzyl-3-*O*-(*tert*-butyldimethylsilyl)-4-hydroxyepicatechin (10b). To a solution of 1.52 g (1.98 mmol) of **9b** in 10 mL of THF and 0.10 mL (5.6 mmol) of H_2O was added at room temperature 1.34 g (5.9 mmol) of DDQ. The mixture was stirred overnight, and then 0.61 g (5.0 mmol) of DMAP was added, stirring was continued for 5 min, and 20 g of silica gel was added. After evaporation, the residue was filtered over SiO_2 (EtOAc/hexane 1:4) to give 1.12 g (72%) of the product as a white foam: $[\alpha]_D$ +2.0, $[\alpha]_{546}$ +2.2 (c 10 gL^{-1}, EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.49−7.22 (m, 20 H), 7.14 (d, 1 H, J = 2 Hz), 7.02, 6.95 (ABq, 2 H, J = 8.5 Hz, A part d with J = 1.5 Hz), 6.27, 6.25 (ABq, 2 H, J = 2.5 Hz), 5.17 (s, 4 H), 5.11 (narrow ABq, 2 H), 5.02 (s, 2 H), 5.00 (s, 1 H), 4.79 (d, 1 H, J = 2 Hz), 3.88 (dd, 1 H, J = 1, 2.5 Hz), 2.35 (s, 1 H), 0.70 (s, 9 H), −0.21 (s, 3 H), −0.45 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 160.11, 158.86, 156.27, 148.87, 148.26, 137.32, 137.28, 136.67, 132.20, 128.64, 128.57, 128.41, 128.38, 128.02, 127.99, 127.74, 127.66, 127.62, 127.46, 127.29, 127.09, 120.09, 115.25, 113.98, 104.63, 94.51, 93.67, 75.37, 71.66, 71.47, 71.28, 70.03, 64.18, 25.67, 17.98, −5.37, −5.51; IR (film) 1617, 1593, 1259, 1153, 1026, 835, 736, 697 cm^{-1}. Anal. Calcd for $C_{49}H_{52}O_7Si$: C, 75.35; H, 6.71. Found: C, 75.21; H, 6.65.

(2*R*,3*S*)-3,5,7,3′,4′-Pentakis(benzyloxy)flavan-4-one (11a). To a solution of 1.00 g (1.32 mmol) of **10a** in 8 mL of dry CH_2Cl_2 was added at room temperature 300 mg of 4 Å molecular sieves, 180 mg (1.54 mmol) of *N*-methylmorpholine *N*-oxide, and 58 mg (165 μmol) of tetra-*n*-propylammonium perruthenate. The reaction mixture was stirred overnight and evaporated, and the residue was purified by CC (EtOAc/CH_2Cl_2/hexane 1:1:10) to give 0.66 g (66%) of the ketone as a white foam: $[\alpha]_D$ −47.9, $[\alpha]_{546}$ −58.5 (c 10 gL^{-1}, EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.67−7.38 (m, 20 H), 7.27 (s, 1 H), 7.24−7.22 (m, 3 H), 7.12−7.10 (m, 2 H), 7.02 (m, 2 H), 6.33 (d, 1 H, J = 2.1 Hz), 6.29 (d, 1 H, J = 2.1 Hz), 5.34 (d, 1 H, J = 1.2 Hz), 5.26 (d, 2 H), 5.24 (s, 2 H), 5.14 (s, 2 H), 5.09 (s, 2 H), 4.78 (d, 1 H, J = 12.0 Hz), 4.50 (d, 1 H, J = 12.0 Hz), 3.85 (d, 1 H, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 187.59, 165.12, 164.53, 161.71, 149.06, 148.96, 137.37, 137.32, 137.30, 136.56, 135.89, 129.25, 128.85, 128.71, 128.63, 128.57, 128.49, 128.219, 128.154, 127.94, 127.91, 127.78, 127.72, 127.50, 127.37, 126.30, 120.29, 114.64, 114.08, 104.70, 95.47, 94.76, 80.96, 79.26, 72.30, 71.34, 71.22, 70.44; IR (film) 3031, 2870, 1673, 1606, 1572, 1512, 1454, 1269, 1165, 1120, 1025, 736, 696 cm^{-1}. Anal. Calcd for $C_{50}H_{42}O_7$: C, 79.56; H, 5.61. Found: C, 79.99; H, 5.31.

(2*R*,3*S*)-5,7,3′,4′-Tetra-*O*-benzyl-3-*O*-[(*tert*-butyldimethylsilyl)oxy]flavan-4-one (11b). To a solution of 0.39 g (0.50 mmol) of **10b** in 2 mL of dry CH_2Cl_2 was added at room temperature 100 mg of 4 Å molecular sieves, 60 mg (0.55 mmol) of *N*-methylmorpholine *N*-oxide, and 20 mg (55 μmol) of tetra-*n*-propylammonium perruthenate. The reaction mixture was stirred overnight and evaporated, and the residue was purified by CC (EtOAc/hexane 1:4) to give 0.38 g (99%) of the ketone as a white foam: $[\alpha]_D$ −32.5, $[\alpha]_{546}$ −39.2 (c 12 gL^{-1}, EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.52−7.26 (m, 20 H), 7.12 (br s, 1 H), 7.00, 6.94 (ABq, 2 H, J = 8.5 Hz, A part d with J = 1 Hz), 6.22, 6.18 (ABq, 2 H, J = 2 Hz), 5.25 (s, 1 H), 5.22−5.12 (m, 6 H), 5.05, 5.01 (ABq, 2 H, J = 11.5 Hz), 4.01 (d, 1 H, J = 1.5 Hz), 0.72 (s, 9 H), −0.11 (s, 3 H), −0.25 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 188.67, 164.60, 163.94, 161.18, 148.78, 148.73, 137.14, 136.53, 135.77, 129.59, 128.64, 128.46, 128.43, 128.40, 128.29, 127.78, 127.71, 127.62, 127.50, 127.38, 127.22, 126.41, 120.12, 114.90, 113.98, 104.51, 95.04, 94.32, 81.48, 75.10, 71.31, 71.28, 70.19, 70.14, 25.61, 18.12, −5.08, −5.37; IR (film) 1680, 1608, 1268, 1164, 1121, 736, 696 cm^{-1}. Anal. Calcd for $C_{49}H_{50}O_7Si$: C, 75.55; H, 6.47. Found: C, 75.67; H, 6.39.

3,5,7,3′,4′-Penta-*O*-benzyl-4-hydroxy-4-(2,4,6-trimethoxyphenyl)epicatechin (12). To a solution of 32 mg (130 μmol) of 1-bromo-2,4,6-trimethoxybenzene in 1 mL of dry THF was added at −78 °C 85 μL (145 μmol) of *t*-BuLi (1.7 M in pentane). After 1 h at −78 °C, a solution of 50 mg (66 μmol) of **11a** in 1 mL of dry THF was added. After another 3 h at −78 °C, 2 mL of aqueous NH_4Cl solution was added, and the product was extracted into 3 × 10 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated, and the residue was purified by CC (EtOAc/hexane 1:4) to give 25 mg (45%) of the product: $[\alpha]_D$ +22.7, $[\alpha]_{546}$ +27.2 (c 12 gL^{-1}, EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.48−7.26 (m, 15 H), 7.21−7.10 (m, 7 H), 7.08−7.03 (m, 2 H), 6.96−6.90 (m, 2 H), 6.81, 6.78 (ABq, 2 H, J = 8.5 Hz, B part br), 6.32 (d, 1 H, J = 2 Hz), 6.29−6.24 (m, 2 H), 6.05 (d, 1 H, J = 2.5 Hz), 5.15 (s, 2 H), 5.05 (s, 2 H), 5.04−4.80 (m, 6 H), 4.54 (d, 1 H, J = 12.5 Hz), 4.23 (s, 1 H), 3.83 (s, 3 H), 3.77 (s, 3 H), 3.21 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 160.27, 160.04, 159.28, 158.63, 158.44, 154.61, 148.65, 147.95, 138.78, 137.46, 137.40, 137.03, 136.88, 132.67, 128.47, 128.35, 128.28, 128.17, 128.08, 127.83, 127.77, 127.63, 127.53, 127.39, 127.29, 127.24, 126.99, 126.72, 119.51, 114.96, 114.61, 113.74, 111.39, 94.62, 94.27, 93.47, 92.20, 79.90, 76.13, 74.69, 74.52, 71.30, 70.95, 69.96, 69.86, 56.60, 56.00, 55.20; IR (film) 3535, 1605, 1590, 1151, 1117, 736, 697 cm^{-1}. Anal. Calcd for $C_{59}H_{54}O_{10}$: C, 76.77; H, 5.90. Found: C, 76.43; H, 5.48.

3,5,7,3′,4′-Penta-*O*-benzyl-4α-(2,4,6-trimethoxyphenyl)-epicatechin (13). (a) Reduction with Et_3SiH/CF_3COOH. To a solution of 22 mg (24 μmol) of **12** in 1 mL of CH_2Cl_2 was added at room temperature 38 μL (0.24 mmol) of Et_3SiH and then 22 μL (0.29 mmol) of CF_3COOH. After 2 h, solid Na_2CO_3 was added. Filtration, evaporation, and purification by TLC (EtOAc/hexane 1:3) gave 15 mg (69%) of the product. **(b) Reduction with Bu_3SnH/CF_3COOH.** To a solution of 46 mg (50 μmol) of **12** in 1 mL of CH_2Cl_2 was added at room temperature 20 μL (74 μmol) of Bu_3SnH and then 75 μL of 1 M CF_3COOH/CH_2Cl_2. After 10 min, solid Na_2CO_3 was added. Filtration, evaporation, and purification by TLC (EtOAc/hexane 1:2) gave 39 mg (86%) of the product: $[\alpha]_D$ −29.0, $[\alpha]_{546}$ −43.7 (c 12 gL^{-1}, EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.48−7.25 (m, 16 H), 7.21−7.14 (m, 3 H), 7.06−6.97 (m, 4 H), 6.90 (d, 1 H, J = 8 Hz), 6.79−6.74 (m, 2 H), 6.66−6.61 (m, 2 H), 6.33 (d, 1 H, J = 2.5 Hz), 6.20 (d, 1 H, J = 2 Hz), 6.11 (d, 1 H, J = 2.5 Hz), 6.03 (d, 1 H, J = 2 Hz), 5.16 (s, 2 H), 5.05−4.97 (m, 3 H), 4.94−4.88 (m, 3 H), 4.77, 4.68 (ABq, 2 H, J = 11.5 Hz), 3.94 (d, 1 H, J = 6.5 Hz), 3.78 (s, 3 H), 3.69 (s, 3 H), 3.58, 3.49 (ABq, 2 H, J = 11 Hz), 3.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.04, 159.26, 158.17, 158.14, 157.44, 156.54, 148.97, 148.15, 138.04, 137.43, 137.39, 137.17, 137.01, 132.82, 128.51, 128.49, 128.39, 128.31, 127.88, 127.82, 127.68, 127.61, 127.55, 127.51, 127.42, 127.31, 127.12, 126.88, 126.84, 119.72, 114.94, 113.72, 110.80, 108.07, 94.99, 93.30, 92.22, 90.82, 79.98, 74.95, 71.45, 71.02, 69.97, 69.52, 56.21, 55.97, 55.25, 35.11; IR (film) 1605, 1590, 1151,

1113, 736, 697 cm^{-1}. Anal. Calcd for $C_{59}H_{54}O_9$: C, 78.12; H, 6.00. Found: C, 77.78; H, 5.89.

3,5,7,3′,4′-Penta-*O*-acetyl-4α-(2,4,6-trimethoxyphenyl)-epicatechin (15). To a solution of 100 mg (110 μmol) of **13** in 6 mL of MeOH/EtOAc 2:1 was added 20 mg of 20% $Pd(OH)_2$/C. The mixture was stirred under 1 bar of H_2 for 3 h, after which period TLC indicated completion of the reaction. The catalyst was filtered off and washed with MeOH. The solution was evaporated, and the residue was dried in vacuo and dissolved at room temperature in 4 mL of Ac_2O/pyridine. After being stirred overnight, the mixture was evaporated, 40 mL of CH_2Cl_2 was added, the phases were separated, and the organic phase was washed with 5 × 10 mL of H_2O and 10 mL of brine and dried over $MgSO_4$. The solution was evaporated, and the crude product was purified by TLC (EtOAc/hexane 1:1) to give 30 mg (41%) of the pentaacetate: $[\alpha]_D$ −38.8, $[\alpha]_{546}$ −48.0 (*c* 12 gL^{-1}, EtOAc); ^1H NMR ($CDCl_3$) δ 7.44 (d, 1 H, J = 2 Hz), 7.33, 7.18 (ABq, 2 H, J = 8.5 Hz, A part d with J = 2 Hz), 6.73, 6.44 (ABq, 2 H, J = 2.5 Hz), 6.11, 5.98 (ABq, 2 H, J = 2.5 Hz), 5.68 (d, 1 H, J = 5.5 Hz), 5.25 (s, 1 H), 5.00 (d, 1 H, J = 5.5 Hz), 3.88 (s, 3 H), 3.77 (s, 3 H), 3.36 (s, 3 H), 2.27 (s, 9 H), 1.58 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 169.57, 169.02, 168.07, 168.05, 167.74, 160.34, 160.00, 158.55, 155.37, 148.98, 148.46, 141.87, 141.54, 136.10, 124.18, 123.04, 121.77, 115.91, 108.74, 108.15, 105.86, 90.83, 90.17, 77.63, 68.46, 56.11, 55.38, 55.16, 33.78, 21.11, 20.63, 20.06, 19.77; IR (film) 1766, 1741, 1589, 1369, 1202, 1114 cm^{-1}. Anal. Calcd for $C_{34}H_{34}O_{14}$: C, 61.26; H, 5.14. Found: C, 61.08; H, 5.02.

5,7,3′,4′-Tetra-*O*-benzyl-4β-(2,4,6-trimethoxyphenyl)-epicatechin (16). To a solution of 28 mg (39 μmol) of **2** and 20 mg (0.12 mmol) of 1,3,5-trimethoxybenzene in 1 mL of CH_2Cl_2/THF 4:5 was added at room temperature 80 μL of $TiCl_4$ (1 M in CH_2Cl_2). After 2 h, 1 mL of saturated aqueous $NaHCO_3$ (1 mL) was added, the phases were separated, and the aqueous phase was extracted with 3 × 5 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated. Purification by CC (EtOAc/hexane 1:6) gave 17 mg (53%) of the product: $[\alpha]_D$ +101, $[\alpha]_{546}$ +123 (*c* 12.5 gL^{-1}, EtOAc); ^1H NMR ($CDCl_3$) δ 7.47−7.14 (m, 19 H), 7.00−6.90 (m, 4 H), 6.34 (s, 1 H), 6.20 (m, 2 H), 6.07 (s, 1 H), 5.28 (s, 1 H), 5.14 (s, 4 H), 5.06 (s, 2 H), 4.83 (s, 2 H), 4.75 (s, 1 H), 3.91 (d, 1 H, J = 4.Hz), 3.81 (s, 3 H), 3.73 (s, 3 H), 3.24 (s, 3 H), 1.76 (d, 1 H, J = 5 Hz); ^{13}C NMR ($CDCl_3$) δ 159.94, 159.88, 158.86, 158.25, 157.72, 155.60, 149.07, 148.41, 137.32, 137.27, 137.14, 132.45, 128.50, 128.41, 128.39, 128.01, 127.86, 127.73, 127.70, 127.59, 127.55, 127.26, 127.22, 126.75, 119.57, 115.13, 113.55, 111.82, 104.78, 94.20, 93.33, 92.63, 91.34, 75.63, 71.82, 71.41, 71.35, 70.06, 69.36, 56.25, 55.69, 55.25, 34.80; IR (film) 1603, 1266, 1149, 1122, 737, 697 cm^{-1}. Anal. Calcd for $C_{52}H_{48}O_9$: C, 76.45; H, 5.92. Found: C, 77.05; H, 5.57.

4β-(2,4,6-Trimethoxyphenyl)epicatechin (17). A solution of 17 mg (21 μmol) of **16** in 1 mL of MeOH was hydrogenated overnight at atmospheric pressure and room temperature over 1 mg of 20% $Pd(OH)_2$/C. The catalyst was filtered off and washed with MeOH. After evaporation, the crude product was purified by TLC (CH_2Cl_2/MeOH 10:1) to give 8 mg (84%) of a white solid: ^1H NMR (CD_3OD) δ 6.86 (d, 1 H, J = 1.5 Hz), 6.70, 6.63 (ABq, 2 H, J = 8 Hz, B part d with J = 1.5 Hz), 6.26 (br, 1 H), 6.13 (br, 1 H), 5.97, 5.86 (ABq, 2 H, J = 2.5 Hz), 5.02 (s, 1 H), 4.55 (s, 1H), 3.86 (br, 3 H), 3.77 (s, 3 H), 3.75 (s, 1 H); one OCH_3 signal concealed by the CD_2HOD signal at δ 3.30.

3,5,7,3′,4′-Penta-*O*-acetyl-4β-(2,4,6-trimethoxyphenyl)-epicatechin (18). A 64 mg (140 μmol) sample of **17** was dissolved in 1.5 mL of Ac_2O/pyridine 1:2, and the solution was stirred overnight at room temperature. After evaporation, 20 mL of CH_2Cl_2 was added, and the solution was washed with 5 × 5 mL of H_2O and 5 mL of brine, dried over $MgSO_4$, and evaporated. Purification by CC (EtOAc/hexane 2:1) gave 81 mg (87%) of the product: $[\alpha]_D$ +123, $[\alpha]_{546}$ +152 (*c* 8 gL^{-1}, EtOAc); ^1H NMR ($CDCl_3$) δ 7.30 (s, 1 H), 7.21, 7.13 (ABq, 2 H, J = 8.5 Hz, A part d with J = 1.5 Hz), 6.71, 6.44 (ABq, 2 H, J = 2 Hz), 6.18 (br s, 1 H), 6.02 (br s, 1 H), 5.48 (s, 1 H), 5.25 (s, 1 H), 4.58 (s, 1 H), 3.87 (br s, 3 H), 3.80 (s, 3 H), 3.31 (br s, 3 H), 2.28 (s, 3 H), 2.27 (s, 6 H), 1.88 (s, 3 H), 1.82 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.45, 169.13, 168.31, 168.15, 168.12, 160.81, 155.69, 148.95, 148.66, 141.84, 141.44, 136.91, 124.37, 122.92, 121.86, 113.79, 108.86, 108.47, 106.77, 92.39, 91.38, 74.41, 71.12, 55.93, 55.29, 32.73, 21.16, 20.76, 20.66, 20.03; IR (film) 1770, 1747, 1606, 1590, 1206, 1118 cm^{-1}.

3,5,7,3′,4′-Penta-*O*-benzyl-8-bromocatechin. To 0.23 g (5.8 mmol) of NaH (60% suspension in mineral oil) was added with stirring at room temperature under N_2 within 5 min 2.82 g (3.87 mmol) of **19**[1] in 8 mL of anhydrous DMF. After 10 min, 0.74 mL (6.2 mmol) of neat BnBr was added in 10 min with water cooling. The mixture was stirred at room temperature for 70 min and then cautiously hydrolyzed with 1 mL of water. Eighty milliliters of water was added, the product was extracted into 40 + 20 mL of toluene, and the combined organic phases were washed with 80 mL of water and evaporated. The residue was chromatographed on SiO_2; a forerun was removed with EtOAc/$CHCl_3$/hexane 1:2:17 and the product eluted with EtOAc/$CHCl_3$/hexane 1:9:10. Evaporation and drying in vacuo (rt, then 80 °C) yielded 3.13 g (99%) of the product as a colorless glass: $[\alpha]_D$ −15.7, $[\alpha]_{546}$ −18.8 (EtOAc, *c* 41.2 gL^{-1}); ^1H NMR ($CDCl_3$) δ 7.48−7.21 (m, 23 H), 7.10 (m, 2 H), 7.00 (s, 1 H), 6.91 (narrow ABq, 2 H), 6.22 (s, 1 H), 5.17 (s, 2 H), 5.10 (narrow ABq, 4 H), 4.99 (d, 1 H, J = 7 Hz), 4.97 (s, 2 H), 4.34, 4.22 (ABq, 2 H, J = 12 Hz), 3.72 (dt, 1 H, J = 5.5 Hz (d), 7 Hz (t)), 2.88, 2.73 (ABq, 2 H, J = 17.5 Hz, both parts d with J = 5.5, 7.5 Hz, respectively); ^{13}C NMR ($CDCl_3$) δ 156.14, 154.66, 151.23, 148.69, 148.62, 137.87, 137.28, 137.12, 136.71, 136.65, 131.88, 128.59, 128.55, 128.46, 128.42, 128.27, 128.01, 127.89, 127.77, 127.71, 127.63, 127.36, 127.24, 127.17, 127.03, 119.80, 114.78, 113.37, 104.00, 92.72, 79.71, 74.03, 71.49, 71.29, 71.26, 70.99, 70.23, 25.32; IR (film) 1605, 1580, 1513, 1126, 1097, 736, 696 cm^{-1}.

3,5,7,3′,4′-Penta-*O*-benzyl-8-(α-hydroxybenzyl)catechin (21). To a solution of 549 mg (670 μmol) of 3,5,7,3′,4′-penta-*O*-benzyl-8-bromocatechin in 6.7 mL of anhydrous THF was added dropwise with stirring at −78 °C under N_2 0.99 mL (1.68 mmol, 2.5 equiv) of *t*-BuLi (1.7 M in pentane). After 5 min, 136 μL (1.34 mmol, 2 equiv) of PhCHO in 1.3 mL of anhydrous THF was added dropwise in 3 min. After another 20 min, the cold bath was removed, 5 mL of H_2O was added, and the THF was evaporated. The product was extracted into 2 × 10 mL of EtOAc, and the combined organic phases were dried over $MgSO_4$ and evaporated. CC with EtOAc/hexane 1:4 (for forerun) then 1:3 gave, after evaporation and drying in vacuo, 397 mg (70%) of **21** as a yellowish glass: ^1H NMR ($CDCl_3$; ratio of diastereoisomers 5:4; MD = major, md = minor diastereoisomer) δ 7.50−7.13 (m, 28 H), 7.00 (m, 2 H), 6.92 (d, 1 H, MD, J = 1 Hz), 6.91, 6.86 (ABq, 2 H, MD, J = 8.5 Hz, B part d with J = 1 Hz), 6.84, 6.68 (ABq, 2 H, md, J = 8.5 Hz, B part d with J = 1.5 Hz), 6.77 (d, 1 H, md, J = 1 Hz), 6.33 (d, 1 H, md, J = 12 Hz), 6.26 (d, 1 H, MD, J = 11.5 Hz), 6.25 (s, 1 H, md), 6.23 (s, 1 H, MD), 5.18 (s, 2 H, MD), 5.17 (s, 2 H, md), 5.07−4.87 (m, 6 H), 4.80 (d, 1 H, md, J = 8 Hz), 4.70 (d, 1 H, MD, J = 8 Hz), 4.25, 4.06 (ABq, 2 H, MD, J = 12 Hz), 4.18, 4.01 (ABq, 2 H, md, J = 12 Hz), 4.10 (d, 1 H, MD + md, J = 12 Hz), 3.70 (dt, 1 H, MD, J = 5.5 Hz (d), 9 Hz (t)), 3.56 (dt, 1 H, md, J = 5.5 Hz (d), 9 Hz (t)), 3.08, 3.04, 2.70, 2.67 (2 ABq, 2 H, MD + md, J = 16.5 Hz, A parts d with J = 5.5 Hz, B parts d with J = 2 Hz); IR (film) 3544, 1603, 1513, 1499, 1454, 1264, 1211, 1121, 1023, 736, 697 cm^{-1}.

8-Bromo-5,7,3′,4′-tetra-*O*-methylcatechin (20).[5,14] To a solution of 2.62 g (7.56 mmol) of 5,7,3′,4′-tetra-*O*-methylcatechin[18] in 50 mL of anhydrous CH_2Cl_2 was added with stirring all at once at −45 °C 1.35 g (7.56 mmol) of NBS (recrystallized from water). The mixture was stirred for 100 min, during which time the bath temperature was allowed to rise to −9 °C. A solution of 0.5 g of $Na_2S_2O_3 \cdot 5H_2O$ in 20 mL of water was added, and the mixture was stirred vigorously at room temperature for 15 min. Fifty mL of 5% aqueous NaOH was added, the mixture was shaken in a separatory funnel, and the separated aqueous phase was back-extracted with 50 mL

(18) (a) Kostanecki, St. v.; Tambor, J. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 1867. (b) Mehta, P. P.; Whalley, W. B. *J. Chem. Soc.* **1963**, 5327.

of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated to yield 3.22 g (100%) of the product as a colorless solid. An aliquot was recrystallized from boiling EtOAc to furnish colorless needles: mp 165 °C if sample inserted at 160 °C and heated slowly, 172 °C if inserted at 164 °C and heated faster (discoloration sets in before melting, melt is blackish-red) (lit.[5] mp 174 °C, no mention of decomposition); $[\alpha]_D$ −96.3, $[\alpha]_{546}$ -116 ($CHCl_3$, *c* 20.3 gL^{-1}) (lit.[5] $[\alpha]_{578}$ −105.2 ($CHCl_3$, *c* 20 gL^{-1})); ^1H NMR[19] ($CDCl_3$) δ 7.01−6.94 (m, 2 H), 6.89 (d, 1 H, $J = 8$ Hz), 6.17 (s, 1 H), 4.09 (m, 1 H), 3.91, 3.89, 3.88, 3.84 (each s, 3 H), 2.99, 2.67 (ABq, 2 H, $J = 16.5$ Hz, both parts d with $J = 5$ and 8 Hz, respectively), 1.80 (d, 1 H, $J = 4$ Hz); ^{13}C NMR ($CDCl_3$, TMS) δ 157.46, 155.76, 151.46, 149.16, 149.04, 130.02, 119.01, 111.10, 109.62, 102.96, 91.25, 89.12, 81.64, 67.73, 56.49, 55.89, 55.60, 27.05; IR (KBr) 3430 (br), 1607, 1518, 1213, 1129, 1103, 1053, 1028, 791 cm^{-1}; MS *m/z* 426/424 (M^+, 11/11), 247/245 (96/100), 180, 165, 151.

3-*O*-Benzyl-8-bromo-5,7,3′,4′-tetra-*O*-methylcatechin.[15] To 48 mg (1.2 mmol) of NaH (60% suspension in mineral oil) was added with stirring at room temperature under N_2 342 mg (804 μmol) of **20** in 1.5 mL of anhydrous DMF. After 5 min, 0.15 mL (1.3 mmol) of neat BnBr was added (mild exotherm). The mixture was stirred at room temperature for 35 min, diluted with 1 mL of CH_2Cl_2, and directly chromatographed on SiO_2 with EtOAc/hexane 2:7 (forerun) and then 2:3. Evaporation and drying in vacuo yielded 393 mg (95%) of the benzyl ether as a colorless glass: ^1H NMR ($CDCl_3$) δ 7.31−7.22 (m, 3 H), 7.16−7.11 (m, 2 H), 6.98 (dd, 1 H, $J = 2$, 8.5 Hz), 6.93 (d, 1 H, $J = 2$ Hz), 6.87 (d, 1 H, $J = 8.5$ Hz), 6.14 (s, 1 H), 5.01 (d, 1 H, $J = 7$ Hz), 4.44, 4.33 (ABq, 2 H, $J = 12$ Hz), 3.89, 3.88, 3.82, 3.81 (each s, 3 H), 3.79 (dt, 1 H, $J = 5.5$ Hz (d), 7.5 Hz (t)), 2.97, 2.72 (ABq, 2 H, $J = 16.5$ Hz, both parts d with $J = 5.5$, 8 Hz, respectively); ^{13}C NMR ($CDCl_3$, TMS) δ 157.28, 155.72, 151.63, 148.76, 137.86, 131.18, 128.27, 127.76, 127.65, 119.02, 110.88, 109.98, 103.03, 91.28, 88.94, 79.87, 74.03, 71.38, 56.50, 55.91, 55.82, 55.57, 25.38; IR (film) 1606, 1518, 1464, 1130, 1101, 1027, 735 cm^{-1}; MS *m/z* 516/514 (M^+, 4/4), 270, 247/245, 241, 179 (100), 151, 91.

3-*O*-Benzyl-8-(α-hydroxybenzyl)-5,7,3′,4′-tetra-*O*-methylcatechin (22).[15] To a solution of 349 mg (677 μmol) of 3-*O*-benzyl-8-bromo-5,7,3′,4′-tetra-*O*-methylcatechin in 6.8 mL of anhydrous THF was added dropwise with stirring at −78 °C under N_2 1.55 mL (1.7 mmol, 2.5 equiv) of *t*-BuLi (1.1 M in pentane). After 5 min, 138 μL (1.35 mmol, 2 equiv) of PhCHO in 1.3 mL of anhydrous THF was added dropwise in 2 min. After another 20 min, the cold bath was removed, 5 mL of H_2O was added, and the THF was evaporated. The product was extracted into 3 × 10 mL of EtOAc, and the combined organic phases were dried over $MgSO_4$ and evaporated. CC with EtOAc/hexane 1:2 gave, after evaporation and drying in vacuo, in the sequence of their elution: 40 mg (13%) of the debromination product, 3-*O*-benzyl-5,7,3′,4′-tetra-*O*-methylcatechin; 71 mg (20%) of unreacted starting material; and 397 mg (70%) of **22** as a colorless glass: ^1H NMR ($CDCl_3$; ratio of diastereoisomers approximately 1:1) δ 7.34−7.12 (m, 8 H), 7.08−7.00 (m, 2 H), 6.91, 6.86 (ABq, 1 H, $J = 8.5$ Hz, A part d with $J = 2$ Hz), 6.79, 6.73 (ABq, 1 H, $J = 8.5$ Hz, B part d with $J = 2$ Hz), 6.79 (d, 0.5 H, $J = 2$ Hz), 6.66 (d, 0.5 H, $J = 2$ Hz), 6.26 (d, 0.5 H, $J = 12$ Hz), 6.21 (d, 0.5 H, $J = 11.5$ Hz), 6.16 (s, 0.5 H), 6.15 (s, 0.5 H), 4.80 (d, 0.5 H, $J = 8.5$ Hz), 4.72 (d, 0.5 H, $J = 8.5$ Hz), 4.37, 4.24 (ABq, 1 H, $J = 12$ Hz), 4.31, 4.17 (ABq, 1 H, $J = 12$ Hz), 4.22 (d, 0.5 H, $J = 11.5$ Hz), 4.13 (d, 0.5 H, $J = 12$ Hz), 3.91, 3.90, 3.85, 3.84, 3.81, 3.80, 3.73, 3.65 (each s, 1.5 H), 3.76 (dt, 0.5 H, $J = 5$ Hz (d), 8.5 Hz (t)), 3.62 (dt, 0.5 H, $J = 5$ Hz (d), 9 Hz (t)), 3.14 (t, 0.5 H, $J = 6$ Hz), 3.08 (t, 0.5 H, $J = 5.5$ Hz), 2.68 (d, 0.5 H, $J = 9.5$ Hz), 2.62 (d, 0.5 H, $J = 9.5$ Hz); ^{13}C NMR ($CDCl_3$, TMS) δ 157.53, 157.47, 156.53, 156.42, 152.65, 152.53, 148.83, 148.74, 145.29, 145.17, 137.85, 131.30, 130.94, 128.21, 127.79, 127.75, 127.69, 127.59, 126.32, 126.22, 125.71, 125.58, 119.75, 119.61, 111.41, 110.82, 110.62, 109.87, 109.79, 102.52, 102.48, 88.58, 88.51, 80.30, 80.26, 74.49, 74.15, 71.46, 71.30, 68.68, 68.08, 56.05, 55.95, 55.92, 55.73, 55.47, 26.46, 26.21; IR (film) 3542, 1611, 1517, 1463, 1454, 1262, 1206, 1127, 1028, 733, 699 cm^{-1}.

3,5,7,3′,4′-Penta-*O*-benzyl-8-benzylcatechin (23). To a solution of 363 mg (429 μmol) of **21** and 205 μL (1.28 mmol, 3 equiv) of Et_3SiH in 2.2 mL of anhydrous CH_2Cl_2 was added dropwise in 5 min with stirring and exclusion of moisture at 0 °C 0.33 mL (4.3 mmol, 10 equiv) of CF_3COOH. The orange-colored solution was stirred in the ice bath for 12 min. After addition of 5 mL of saturated aqueous $NaHCO_3$ solution, the phases were separated, and the aqueous phase was extracted with 2 × 5 mL of CH_2Cl_2. The evaporation residue of the combined organic phases was filtered over SiO_2 with EtOAc/hexane 1:4. Evaporation and drying in vacuo gave 332 mg of crude product, which remained contaminated by a $SiEt_3$-containing byproduct. Pure material was obtained by dissolution in 6 mL of hot ethyl acetate, addition of 6 mL of hexane, and crystallization at room temperature; a total of 313 mg (88%) of colorless, cotton-like crystals was obtained in three crops: mp 129.5−130 °C; $[\alpha]_D$ +8.2, $[\alpha]_{546}$ +9.7 (EtOAc, *c* 22.6 gL^{-1}); ^1H NMR ($CDCl_3$) δ 7.50−7.06 (m, 28 H), 7.02 (m, 2 H), 6.91 (overlapping, 1 H), 6.90, 6.84 (ABq, 2 H, $J = 8$ Hz, B part d with $J = 1.5$ Hz), 5.19 (s, 2 H), 5.02 (s, 2 H), 5.00 (s, 2 H), 5.00, 4.94 (ABq, 2 H, $J = 12.5$ Hz), 4.23, 4.07 (ABq, 2 H, $J = 11.5$ Hz), 4.02, 3.89 (ABq, 2 H, $J = 14$ Hz), 3.62 (dt, 1 H, $J = 5.5$ Hz (d), 8.5 Hz (t)), 3.03, 2.69 (ABq, 2 H, $J = 16.5$ Hz, both parts d with $J = 5.5$, 9 Hz, respectively); ^{13}C NMR ($CDCl_3$, TMS) δ 155.79, 155.49, 153.11, 148.72, 148.58, 142.33, 138.07, 137.35, 137.31, 137.20, 132.67, 128.82, 128.53, 128.45, 128.39, 128.17, 127.87, 127.85, 127.72, 127.67, 127.48, 127.35, 127.30, 127.19, 125.21, 120.46, 114.72, 113.46, 110.35, 102.63, 91.15, 79.89, 74.96, 71.58, 71.36, 70.88, 70.56, 70.10, 28.72, 26.36; IR (KBr) 1603, 1519, 1498, 1453, 1423, 1384, 1212, 1126, 733, 695 cm^{-1}. Anal. Calcd for $C_{57}H_{50}O_6$: C, 82.38; H, 6.06. Found: C, 82.22; H, 6.06.

8-Benzylcatechin (24) from 21. A solution of 242 mg (286 μmol) of **21** in a mixture of 7 mL of THF, 7 mL of MeOH, and 1 mL of water was stirred with 41 mg of 20% $Pd(OH)_2$/C under 1 bar of H_2 at room temperature for 4 h. After filtration from the catalyst, the dissolved product was adsorbed on 2 g of SiO_2 and chromatographed on SiO_2. A forerun was eluted with CH_2Cl_2/MeOH 10:1 and then the desired product with CH_2Cl_2/MeOH 6:1. Crystallization of the evaporated eluate was effected from a minimum volume of acetone by addition of water, yielding 30 mg (28%) of the product as an off-white solid: mp 212−213.5 °C; $[\alpha]_D$ −41.4, $[\alpha]_{546}$ −50.2 (MeOH, *c* 9.5 gL^{-1}); ^1H NMR (acetone-d_6) δ 8.00 (s, 1 H), 7.97 (s, 1 H), 7.85 (s, 2 H), 7.27 (d, 2 H, $J = 7$ Hz), 7.14 (t, 2 H, $J = 7.5$ Hz), 7.04 (t, 1 H, $J = 7$ Hz), 6.91 (d, 1 H, $J = 2$ Hz), 6.79, 6.73 (ABq, 2 H, $J = 8$ Hz, B part d with $J = 2$ Hz), 6.13 (s, 1 H), 4.56 (d, 1 H, $J = 8$ Hz), 4.00−3.87 (m, 2 H), 3.91, 3.80 (ABq, 2 H, $J = 14$ Hz), 2.96, 2.55 (ABq, 2 H, $J = 16$ Hz, both parts d with $J = 5.5$, 8.5 Hz, respectively), 2.88 (s, aliphat. OH + H_2O); ^{13}C NMR (acetone-d_6, TMS) δ 154.86, 154.82, 154.54, 145.64, 145.58, 143.65, 132.26, 129.63, 128.49, 125.80, 120.04, 115.67, 115.38, 107.50, 100.82, 96.02, 82.91, 68.47, 29.23; IR (Nujol) 1614, 1456, 1377, 1283, 1094, 1056 cm^{-1}; MS (EI) *m/z* 380 (M^+, 15), 229 (100), 152, 151, 124, 123.

8-Benzyl-5,7,3′,4′-tetra-*O*-methylcatechin (25).[15] **(a) From 24.** To 54 mg (0.39 mmol, 40 equiv) of anhydrous K_2CO_3 was added a solution of 3.7 mg (9.7 μmol) of **24** in 0.3 mL of anhydrous 3-pentanone followed by 34 μL (0.39 mmol) of Me_2SO_4 (*highly toxic; carcinogen!*). The mixture was stirred in a closed vial at 60 °C for 135 min. After cooling, residual Me_2SO_4 was destroyed by addition of 0.1 mL of concd aqueous NH_3 and stirring at room temperature for 40 min. The resulting mixture was directly filtered over SiO_2 with EtOAc/hexane 1:1 to give 4.7 mg of crude **25**. Preparative HPLC (Whatman Partisil 10, 500 × 9.4 mm, EtOAc/hexane 1:1, 5 mL/min, UV detection at 280 nm; t_R 18.4 min) yielded 3.1 mg (73%) of pure **25**, identical with the material prepared on the following route. (b) from **22**: A solution of 231 mg (426 μmol) of **22** in a mixture of 5 mL of EtOAc and 5 mL of MeOH was hydrogenated at 1 bar and room temperature over 113 mg of 50% $Pd(OH)_2$/C for 65 min. After filtration over cotton and evaporation, the residue was filtered over SiO_2 with EtOAc/hexane to yield

(19) Kiehlmann, E.; Tracey, A. S. *Can. J. Chem.* **1986**, *64*, 1998.

166 mg (89%) of **25** as a colorless glass. The analytical sample was obtained by crystallization from boiling EtOH and drying of the cotton-like crystals at 90 °C/oil pump vacuum: mp 136.5−138 °C (lit.[15] mp 136−137 °C); $[\alpha]_D$ −54.0, $[\alpha]_{546}$ −66.1 ($CHCl_3$, *c* 12.1 gL^{-1}) (lit.[15] $[\alpha]_{578}$ −46 ($Cl_2CHCHCl_2$, *c* 20 gL^{-1})); ^1H NMR ($CDCl_3$) δ 7.25−7.07 (m, 5 H), 6.90 (dd, 1 H, J = 2, 8 Hz), 6.86 (d, 1 H, J = 2 Hz), 6.85 (d, 1 H, J = 8 Hz), 6.17 (s, 1 H), 4.67 (d, 1 H, J = 8.5 Hz), 3.99, 3.87 (ABq, 2 H, J = 14.5 Hz), 3.95 (m, 1 H), 3.89 (s, 3 H), 3.84 (s, 6 H), 3.74 (s, 3 H), 3.07, 2.61 (ABq, 2 H, J = 16.5 Hz, both parts d with J = 5.5, 9.5 Hz, respectively); ^{13}C NMR ($CDCl_3$, TMS) δ 156.95, 156.63, 152.90, 149.15, 149.00, 130.72, 128.58, 127.87, 125.19, 119.64, 110.83, 109.54, 109.35, 101.72, 88.29, 81.46, 68.42, 55.91, 55.89, 55.75, 55.47, 28.43, 27.74; IR (film) 3490 (br), 1610, 1518, 1463, 1453, 1263, 1121, 1027, 910, 733 cm^{-1}; MS *m*/*z* 436 (M^+, 16), 257 (100), 180, 179, 165, 152, 151, 91.

3,5,7,3′,4′-Penta-*O*-benzyl-8-bromoepicatechin (26a). To a suspension of 29 mg (0.73 mmol) of NaH (60% in oil) in 2 mL of anhydrous DMF was added at room temperature 450 mg (617 μmol) of **26c**[1] in 3 mL of anhydrous DMF. After the mixture was stirred for 30 min, 90 μL (0.73 mmol) of BnBr and 20 mg (54 μmol) of *n*-Bu_4NI were added. The mixture was stirred overnight, poured into ice−water, and extracted with 3 × 50 mL of EtOAc. The combined organic phases were washed with 3 × 50 mL of water and 50 mL of brine, dried over $MgSO_4$, and evaporated. CC (EtOAc/hexane 1:2) gave 480 mg (95%) of the product: ^1H NMR ($CDCl_3$) δ 7.50−7.15 (m, 23 H), 6.99 (m, 2 H), 6.95, 6.90 (ABq, 2 H, J = 8.5 Hz, A part d with J = 1.5 Hz), 6.23 (s, 1 H), 5.19 (s, 2 H), 5.11 (s, 4 H), 4.97 (s, 2 H), 4.38, 4.29 (ABq, 2 H, J = 12.5 Hz), 3.97 (narrow m, 1 H), 2.95, 2.80 (ABq, 2 H, J = 17 Hz, both parts d with J = 3.5, 4.5 Hz, respectively); ^{13}C NMR δ 156.44, 154.62, 151.94, 148.65, 148.12, 137.92, 137.41, 137.26, 136.75, 136.71, 131.68, 119.15, 114.74, 113.29, 103.40, 93.11, 92.76, 78.06, 72.13, 71.32, 71.26, 71.21, 70.83, 70.22, 24.73; IR (film) 1605, 1580, 1177, 1125, 1095, 735, 697 cm^{-1}. Anal. Calcd for $C_{50}H_{43}BrO_6$: C, 73.26; H, 5.29. Found: C, 72.81; H, 5.12.

5,7,3′,4′-Tetra-*O*-benzyl-8-bromo-3-*O*-(*tert*-butyldimethylsilyl)epicatechin (26b). A solution of 180 mg (247 μmol) of **26c**,[1] 56 mg (0.37 mmol) of TBDMS-Cl, and 49 mg (0.72 mmol) of imidazole in 1 mL of anhydrous DMF was stirred at room temperature overnight. The mixture was poured into ice water and extracted with 3 × 20 mL of ether. The combined organic phases were washed with 3 × 20 mL of water and 20 mL of brine and dried over $MgSO_4$. Evaporation and CC (SiO_2, CH_2Cl_2/EtOAc/hexane 1:1:4) gave 187 mg (88%) of **26b** as a foam: ^1H NMR ($CDCl_3$) δ 7.49−7.27 (m, 20 H), 7.19 (d, 1 H, J = 1.5 Hz), 6.95, 6.89 (ABq, 1 H, J = 8.5 Hz, A part d with J = 1.5 Hz), 6.20 (s, 1 H), 5.15 (s, 4 H), 5.08 (s, 3 H), 4.99 (s, 2 H), 4.22 (m, 1 H), 2.89−2.73 (m, 2 H), 0.72 (s, 9 H), −0.16 (s, 3 H), −0.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.28, 154.40, 151.82, 148.60, 148.02, 137.37, 137.25, 136.81, 136.72, 132.19, 128.51, 128.48, 128.37, 128.35, 127.87, 127.79, 127.64, 127.61, 127.35, 127.22, 127.02, 127.00, 119.44, 114.96, 113.62, 103.48, 92.46, 79.18, 71.38, 71.13, 70.96, 70.16, 28.36, 25.63, −5.22, −5.26.

3,5,7,3′,4′-Penta-*O*-benzyl-4-hydroxyepicatechin-4,8-(penta-*O*-benzylepicatechin) (27a). To a solution of 200 mg (244 μmol) of **26a** in 1 mL of dry THF was added under N_2 at −78 °C 0.30 mL (0.51 mmol) of *tert*-BuLi (1.7 M in pentane). After stirring at −78 °C for 90 min, a solution of 120 mg (159 μmol) of **11a** in 1 mL of dry THF was added. After another 3 h at −78 °C, 2 mL of aqueous NH_4Cl was added, and the mixture was allowed to warm to room temperature and extracted with 3 × 20 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated, and the residue was chromatographed on SiO_2 (CH_2Cl_2/EtOAc/hexane 1:1:8) to give 165 mg (69%) of the product as a colorless foam: $[\alpha]_D$ −14.7, $[\alpha]_{546}$ −18.7 (*c* 10 gL^{-1}, EtOAc); ^1H NMR ($CDCl_3$; 2 rotamers, ratio 1:5.5) major rotamer (or overlapping multiplets of both rotamers) δ 7.47−6.84 (m, 52 H), 6.79−6.70 (m, 4 H), 6.44 (s, 1 H), 6.37 (dd, 1 H, J = 8, 1 Hz), 5.95, 5.71 (ABq, 2 H, J = 2 Hz), 5.44 (s, 1 H), 5.12 (s, 2 H), approximately 5.1−4.8 (m, 3 H), 5.08 (s, 2 H), 4.94 (s, 2 H), 4.85 (s, 2 H), 4.78, 4.73 (ABq, 2 H, J = 11.5 Hz), 4.61 (d, 1 H, J = 11.5 Hz), 4.61, 4.53 (ABq, 2 H, J = 11.5 Hz), 4.60 (d, 1 H, J = 12 Hz), 4.31 (d, 1 H, J = 12 Hz), 4.21 (s, 1 H), 4.16 (s, 1 H), 4.12 (d, 1 H, J = 12 Hz), 4.04 (d, 1 H, J = 12.5 Hz), 3.60 (d, 1 H, J = 2.5 Hz), 3.12, 2.68 (ABq, 2 H, J = 17.5 Hz, B part d with J = 4.5 Hz), minor rotamer (discernible signals) δ 6.14, 5.90 (ABq, 2 H, J = 2 Hz), 6.09 (s, 1 H), 3.90 (narrow m, 1 H), 3.15, 2.91 (ABq, 2 H, J = 17.5 Hz, both parts d with J = 2, 4 Hz, respectively); ^{13}C NMR ($CDCl_3$, major rotamer only) δ 158.15, 157.86, 157.23, 156.96, 154.30, 154.07, 149.01, 148.13, 148.10, 147.77, 138.90, 138.38, 137.59, 137.55, 137.47, 137.38, 137.35, 137.30, 137.08, 136.72, 133.07, 131.62, 128.62, 128.54, 128.39, 128.28, 128.24, 128.20, 128.14, 128.08, 128.00, 127.91, 127.76, 127.60, 127.48, 127.46, 127.22, 127.14, 127.07, 126.73, 126.99, 119.96, 119.80, 118.92, 114.74, 114.67, 113.67, 113.59, 113.44, 111.15, 102.28, 94.22, 93.84, 93.43, 81.34, 78.73, 76.30, 74.70, 74.56, 72.46, 72.19, 71.43, 71.01, 70.75, 69.91, 69.53, 69.38, 69.36, 25.56; IR (film) 3520 (br), 1592, 1511, 1267, 1118, 735, 696 cm^{-1}. Anal. Calcd for $C_{100}H_{86}O_{13}$: C, 80.30; H, 5.80. Found: C, 80.20; H, 5.66.

5,7,3′,4′-Tetra-*O*-benzyl-3-*O*-(*tert*-butyldimethylsilyl)-4-hydroxyepicatechin-4,8-[5,7,3′,4′-tetra-*O*-benzyl-3-*O*-(*tert*-butyldimethylsilyl)epicatechin] (27b). To a solution of 450 mg (533 μmol) of **26b** in 2 mL of dry THF was added under N_2 at −78 °C 0.64 mL (1.1 mmol) of *t*-BuLi (1.7 M in pentane). After the mixture was stirred at −78 °C for 60 min, a solution of 280 mg (359 μmol) of **11b** in 2 mL of dry THF was added. After another 3 h at −78 °C, 2 mL of aqueous NH_4Cl was added, and the mixture was allowed to warm to room temperature and extracted with 3 × 20 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated, and the residue was chromatographed on SiO_2 (CH_2Cl_2/EtOAc/hexane 1:1:10) to give 410 mg (74%) of the product as a colorless foam: $[\alpha]_D$ −9.2, $[\alpha]_{546}$ −11.6 (*c* 24 gL^{-1}, EtOAc); ^1H NMR ($CDCl_3$) δ 7.45−7.10 (m, 37 H), 7.07 (t, 2 H, J = 7.5 Hz), 6.95−6.84 (m, 4 H), 6.79 (t, 2 H, J = 8 Hz), 6.48 (d, 1 H, J = 8 Hz), 6.14 (s, 1 H), 5.95 (d, 1 H, J = 2 Hz), 5.65 (d, 1 H, J = 2 Hz), 5.43 (d, 1 H, J = 2.5 Hz), 5.32 (d, 1 H, J = 11.5 Hz), 5.12- approximately 4.8 (m, 9 H), 4.93, 4.85 (ABq, 2 H, J = 12 Hz), 4.80−4.70 (m, 3 H), 4.63, 4.41 (ABq, 2 H, J = 11 Hz), 4.61 (d, 1 H, J = 11.5 Hz), 4.09 (s, 1 H), 3.84 (br s, 1 H), 2.88, 2.79 (ABq, 2 H, J = 17 Hz, B part d with J = 4 Hz), 0.78 (s, 9 H), 0.70 (s, 9 H), −0.25 (s, 3 H), −0.27 (s, 3 H), −0.33 (s, 3 H), −0.46 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 158.46, 157.95, 157.32, 155.93, 154.14, 153.06, 148.42, 148.37, 147.71, 147.62, 137.72, 137.63, 137.61, 137.51, 137.35, 137.26, 137.21, 137.18, 133.41, 132.68, 128.56, 128.47, 128.33, 128.30, 128.28, 128.26, 128.21, 127.95, 127.64, 127.60, 127.51, 127.43, 127.26, 127.20, 127.12, 126.95, 119.99, 118.89, 115.46, 114.65, 114.54, 114.43, 113.63, 111.74, 103.42, 94.96, 94.31, 93.71, 79.37, 76.14, 75.40, 73.89, 72.79, 71.47, 71.31, 71.23, 70.15, 69.88, 69.62, 66.88, 29.90, 26.12, 25.76, 18.12, 16.98, −4.90, −5.03, −5.32, −5.40; IR (film) 1591, 1511, 1266, 1119, 1026, 835, 735, 696 cm^{-1}.

Penta-*O*-benzylepicatechin-4α,8-(penta-*O*-benzylepicatechin) (28a). To a solution of 70 mg (46.8 μmol) of **27a** in 1 mL of dry CH_2Cl_2 was added at 0 °C 20 μL (74 μmol) of *n*-Bu_3SnH followed by 71 μL of CF_3COOH (1 M in CH_2Cl_2). After 1 h, 1 g of solid Na_2CO_3 was added, and the solution was filtered and evaporated. The residue was chromatographed on SiO_2 (CH_2Cl_2/EtOAc/hexane 1:1:8) to give 55 mg (79%) of the product as a colorless foam: $[\alpha]_D$ −48.7, $[\alpha]_{546}$ −59.6 (*c* 25 gL^{-1}, EtOAc); ^1H NMR ($CDCl_3$; 2 rotamers, ratio 2.8:1; MR major, mr minor rotamer) δ 7.48−6.74 (m, 56 H), 6.62 (d, MR, 1 H, J = 8.5 Hz), 6.49 (br s, mr, 1 H), 6.28−6.04 (m, 3 H), 5.18−3.45 (series of m, 25 H), 3.14, 2.77 (ABq, MR, 2 H, J = 17 Hz, both parts d with J = 1, 4 Hz, respectively), 2.93, 2.54 (ABq, mr, 2 H, J = 17.5 Hz, B part d with J = 5 Hz); ^{13}C NMR ($CDCl_3$; low intensity signals of minor rotamer omitted) δ 158.04, 157.48, 156.79, 155.65, 152.93, 148.94, 148.76, 148.43, 148.10, 138.51, 138.34, 137.91, 137.47, 137.44, 137.39, 137.32, 137.24, 137.11, 132.98, 132.77, 128.57, 128.49, 128.47, 128.44, 128.38, 128.36, 128.28, 127.96, 127.75, 127.69, 127.61, 127.55, 127.50, 127.48, 127.38, 127.29, 127.27, 127.21, 127.17, 126.77, 119.77, 119.48, 114.51, 114.10, 113.83, 110.53, 108.29, 100.98, 94.96, 93.40, 92.31, 80.21, 78.13, 77.58, 75.06, 72.49, 71.39, 71.18, 71.11, 70.87, 70.70, 70.65, 70.03, 69.84, 69.60, 34.89, 24.89; IR (film) 1606, 1593, 1266, 1112, 734, 696 cm^{-1}. Anal. Calcd for $C_{100}H_{86}O_{12}$: C, 81.17; H, 5.86. Found: C, 80.89; H, 5.62.

5,7,3′,4′-Tetra-*O*-benzyl-3-*O*-(*tert*-butyldimethylsilyl)-epicatechin-4α,8-[5,7,3′,4′-tetra-*O*-benzyl-3-*O*-(*tert*-butyldimethylsilyl)epicatechin] (28b). To a solution of 240 mg (155 μmol) of **27b** in 1 mL of dry CH_2Cl_2 was added at 0 °C 50 μL (186 μmol) of *n*-Bu_3SnH followed by 154 μL of CF_3COOH (1 M in CH_2Cl_2). After 1 h, 1 g of solid Na_2CO_3 was added, and the solution was filtered and evaporated. The residue was chromatographed on SiO_2 (CH_2Cl_2/EtOAc/hexane 1:1:10) to give 181 mg (76%) of the product as a colorless foam: $[\alpha]_D$ −14.9, $[\alpha]_{546}$ −19.1 (*c* 15 gL^{-1}, EtOAc); ^1H NMR ($CDCl_3$) δ 7.49 (t, 4 H, *J* = 7 Hz), 7.44−7.15 (m, 34 H), 7.13 (s, 1 H), 7.09 (d, 1 H, *J* = 8.5 Hz), 6.97, 6.93 (ABq, 2 H, *J* = 8 Hz, B part br), 6.82, 6.61 (ABq, 2 H, *J* = 8 Hz, A part br), 6.77 (d, 2 H, *J* = 6.5 Hz), 6.08 (s, 1 H), 6.05, 5.93 (ABq, 2 H, *J* = 2 Hz), 5.22−5.00 (m, 12 H), 4.89 (s, 1 H), 4.80 (d, 1 H, *J* = 11.5 Hz), 4.74, 4.68 (ABq, 2 H, *J* = 11 Hz), 4.59, 4.48 (ABq, 2 H, *J* = 11 Hz), 4.43 (d, 1 H, *J* = 5.5 Hz), 4.34 (d, 1 H, partly overlapping), 4.31 (s, 1 H), 4.02 (br d, 1 H, *J* = 2 Hz), 2.97, 2.85 (ABq, 2 H, *J* = 17 Hz, B part d with *J* = 4.5 Hz), 0.71 (s, 9 H), 0.61 (s, 9 H), −0.32, −0.39, −0.89, −0.99 (each s, 3 H); ^{13}C NMR ($CDCl_3$) δ 157.92, 157.34, 157.25, 155.52, 153.63, 148.97, 148.95, 148.40, 147.99, 137.67, 137.47, 137.43, 137.39, 137.26, 137.24, 137.19, 137.14, 133.84, 133.46, 128.51, 128.45, 128.39, 128.34, 127.89, 127.79, 127.73, 127.66, 127.62, 127.59, 127.55, 127.46, 127.35, 127.33, 127.08, 127.03, 126.65, 126.55, 119.87, 119.72, 115.29, 115.15, 114.47, 114.32, 110.32, 108.59, 101.60, 94.91, 93.18, 91.38, 81.25, 78.79, 71.67, 71.61, 71.40, 71.35, 71.28, 69.90, 69.70, 69.46, 69.15, 67.56, 36.90, 29.57, 26.09, 25.81, 18.16, 17.96, −5.21, −5.24, −5.42, −6.22. Anal. Calcd for $C_{98}H_{102}O_{12}Si_2$: C, 77.03; H, 6.73. Found: C, 77.02; H, 6.63.

5,7,3′,4′-Tetra-*O*-benzylepicatechin-4α,8-(5,7,3′,4′-tetra-*O*-benzylepicatechin) (28c). To a solution of 130 mg (85 μmol) of **28b** in 1 mL of CH_3CN was added at 0 °C 50 μL of 48% aqueous HF. The mixture was stirred at room temperature for 8 h, 10 mL of EtOAc was added, and the solution was washed with 10 mL each of aqueous $NaHCO_3$, H_2O, and brine. After drying over $MgSO_4$ and evaporation, the residue was chromatographed on SiO_2 with CH_2Cl_2/EtOAc/hexane 1:1:5 to give 89 mg (81%) of the product as a foam: $[\alpha]_D$ −94.2, $[\alpha]_{546}$ −115 (*c* 9 gL^{-1}, EtOAc); ^1H NMR (selection; two rotamers, approximately 3:2, MR = major, mr = minor rotamer) δ 6.63 (d, 1 H, MR, *J* = 2 Hz), 6.35, 6.30 (ABq, 2 H, MR, *J* = 2 Hz), 6.05 (d, 1 H, mr, *J* = 1.5 Hz), 6.02 (s, 1 H, MR), 4.25 (dd, 1 H, MR, *J* = 5.5, 9.5 Hz), 4.16 (dd, 1 H, mr, *J* = 5, 9 Hz), 3.60 (d, 1 H, MR, *J* = 9.5 Hz), 3.24 (d, 1 H, mr, *J* = 9 Hz), 2.99, 2.87 (ABq, 2 H, mr, *J* = 17.5 Hz, B part overlapping), 2.85, 2.69 (ABq, 2 H, MR, *J* = 17.5 Hz, B part d with *J* = 5 Hz), 1.59 (d, 1 H, MR, *J* = 8 Hz), 1.39 (d, 1 H, mr, *J* = 5 Hz); ^{13}C NMR ($CDCl_3$) δ 159.03, 158.31, 158.14, 157.99, 157.02, 156.50, 156.29, 156.05, 155.94, 155.48, 153.38, 152.76, 149.1−148.4, 137.6−136.9, 136.55, 136.44, 132.07, 131.65, 130.51, 128.6−127.0, 120.49, 120.43, 119.42, 119.22, 115.0−114.2, 113.41, 113.30, 110.76, 110.29, 106.97, 106.30, 102.22, 101.40, 95.64, 95.03, 94.31, 93.98, 92.41, 91.98, 80.52, 79.84, 78.16, 77.88, 71.7−69.6, 66.07, 65.94, 35.89, 35.37, 28.84, 28.41. MS (API-ES, in MeOH/NH_4OH) *m*/*z* 1316.6 ($M + NH_4^+$; calcd for $^{13}C^{12}C_{85}H_{78}NO_{12}$ 1317.6), 1299.5 (M^+; calcd for $^{13}C^{12}C_{85}H_{74}O_{12}$ 1299.5), 967.4, 649.3 (M^{2+}). Anal. Calcd for $C_{86}H_{74}O_{12}$: C, 79.49; H, 5.74. Found: C, 79.59; H, 6.21.

Epicatechin-4α,8-epicatechin (6). A solution of 40 mg (31 μmol) of **28c** in 5 mL of MeOH/THF/water (20:20:1) was hydrogenated over 60 mg of 20% $Pd(OH)_2$/C at room temperature and 5 bar for 5 h. The catalyst was filtered off over Celite, the solids were washed with 10 mL of MeOH, and the solution was evaporated. The residue was taken up in HPLC-grade water, and the solution was washed with 5 mL of toluene to remove nonpolar impurities. The solution was evaporated again and then lyophilized from 5 mL of HPLC grade water to give 13 mg (73%) of **6** as a colorless, amorphous solid: $[\alpha]_D$ −38.6 (*c* 1.4 gL^{-1}, MeOH); ^1H NMR (CD_3OD, TMS; major rotamer only) δ 7.06 (d, 1 H, *J* = 1 Hz), 7.01 (d, 1 H, *J* = 1 Hz), 6.90−6.68 (m, 4 H), 5.99 (d, 1 H, *J* = 2 Hz), 5.92 (s, 1 H), 5.83 (d, 1 H, *J* = 2 Hz), 5.04 (d, 1 H, *J* = 4.5 Hz), 4.96 (s, 1 H), 4.94 (s, 1 H), 4.30 (d, 1 H, *J* = 4.5 Hz), 4.29 (br, 1 H), 2.95, 2.80 (ABq, 2 H, *J* = 17 Hz, both parts d with *J* = 1.5 Hz, respectively); ^{13}C NMR (CD_3OD, TMS; only signals listed which by their intensity appear to belong to the major rotamer) δ 157.78, 156.82, 156.69, 154.48, 146.04, 145.94, 145.82, 145.76, 132.32, 132.30, 129.56, 128.92, 128.82, 119.21, 115.97, 115.89, 115.24, 100.74, 97.62, 97.49, 96.60, 80.98, 79.98, 72.33, 66.98, 36.71, 29.68; MS (electrospray) *m*/*z* 1155.6 ($(2M)^+$; calcd for $C_{60}H_{52}O_{24}$: 1156.3), 577.3 (M^+; calcd for $C_{30}H_{26}O_{12}$: 578.1). Anal. Calcd for $C_{30}H_{26}O_{12}\cdot 3.4H_2O$: C, 56.32; H, 5.17. Found: C, 56.27; H, 4.82.

Penta-*O*-acetylepicatechin-4α,8-(penta-*O*-acetylepicatechin) (29). To a solution of 75 mg (51 μmol) of **28a** in 2 mL of MeOH and 1 mL of EtOAc was added 10 mg of 20% $Pd(OH)_2$/C. The mixture was stirred under 1 bar of H_2 for 10 h, filtered, and evaporated. The crude deprotected dimer **6** was dissolved in 3 mL of Ac_2O/pyridine 1:2, and the mixture was stirred overnight. After evaporation, 30 mL of EtOAc was added. The solution was washed with 5 × 20 mL of H_2O and 20 mL of brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on SiO_2 (EtOAc/hexane 2:1) to give 12 mg (24%) of the peracetate: $[\alpha]_D$ +10.0, $[\alpha]_{546}$ +11.3 (*c* 6 gL^{-1}, EtOAc); ^1H NMR ($CDCl_3$/benzene-d_6 1:1) δ 7.63 (s, 1 H), 7.44 (s, 1 H), 7.19 (s, 2 H), 7.13 (s, 2 H), 6.75, 6.64 (ABq, 2 H, *J* = 2 Hz), 6.62 (s, 1 H), 6.57 (s, 2 H), 5.85 (d, 1 H, *J* = 5.5 Hz), 5.24 (narrow m, 1 H), 5.13 (d, 1 H, *J* = 5.5 Hz), 5.01 (s, 1 H), 4.64 (s, 1 H), 2.91, 2.69 (ABq, 2 H, *J* = 17. Hz, both parts d with *J* = 2.5, 3.5 Hz, respectively), 2.023 (s, 3 H), 2.018 (s, 3 H), 1.97 (s, 3 H), 1.96 (s, 3 H), 1.94 (s, 3 H), 1.92 (s, 3 H), 1.82 (s, 3 H), 1.74 (s, 3 H), 1.70 (s, 3 H), 1.63 (s, 3 H); ^{13}C NMR ($CDCl_3$/benzene-d_6 1:1, TMS) δ 170.47, 169.45, 168.68, 168.31, 168.04, 167.95, 167.78, 167.73, 167.67, 167.25, 155.79, 152.11, 149.99, 149.50, 148.92, 148.26, 142.69, 142.62, 142.20, 141.99, 136.18, 136.10, 125.00, 124.64, 123.34, 123.17, 122.01, 114.72, 114.26, 109.67, 109.60, 108.74, 108.51, 77.96, 77.83, 67.80, 65.80, 34.60, 25.70, 20.63, 20.44, 20.42, 20.32, 20.31, 20.27, 20.20, 19.96; IR (film) 1770, 1746, 1621, 1595, 1371, 1207, 903, 734 cm^{-1}.

5,7,3′,4′-Tetra-*O*-benzylepicatechin-4α,8-[5,7,3′,4′-tetra-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)epicatechin] (30). To a suspension of 68 mg (154 μmol) of tri-*O*-benzylgallic acid[20] and 1 μL of DMF in 1 mL of anhydrous CH_2Cl_2 was added 15 μL (0.17 mmol) of oxalyl chloride. After stirring at room temperature for 2 h with exclusion of moisture, the resulting solution was evaporated and the residue dried in vacuo. A solution of 40 mg (31 μmol) of **28c** in 0.5 mL of anhydrous pyridine was added to the crude acid chloride, 24 mg (0.20 mmol) of DMAP was added, and the mixture was stirred at room temperature in a closed flask for 48 h. After addition of 20 μL of water, stirring at room temperature was continued for 2 h. Ten milliliters of 5% HCl was added, and the product was extracted into 3 × 5 mL of CH_2Cl_2. The organic phases were dried over $MgSO_4$ and concentrated, and the crude material was purified by CC on SiO_2 with EtOAc/hexane 1:4. Evaporation and drying in vacuo yielded 50 mg (94%) of the product: $[\alpha]_D$ −122, $[\alpha]_{546}$ −149 (EtOAc, *c* 12 gL^{-1}); ^1H NMR ($CDCl_3$; selection; two rotamers, approximately 3:1, MR = major, mr = minor rotamer) δ 6.54 (d, 1 H, MR, *J* = 8.5 Hz), 6.35 (d, 1 H, mr, *J* = 2 Hz), 6.08 (s, 1 H, mr), 5.39 (narrow m, 1 H, MR + mr), 5.18 (d, 1 H, MR, *J* = 5.5 Hz), 5.10 (d, 1 H, MR, *J* = 5 Hz), 4.30 (dd, 1 H, MR, *J* = 5.5, 9.5 Hz), 4.18 (s, 1 H, MR), 4.12 (dd, 1 H, mr, *J* = 4.5, 9.5 Hz), 3.58 (d, 1 H, MR, *J* = 9.5 Hz), 3.18 (narrow m, 2 H, mr), 3.10 (d, 1 H, mr, *J* = 9.5 Hz), 2.88 (narrow m, 2 H, MR); ^{13}C NMR ($CDCl_3$; weak signals of the minor rotamer omitted) δ 165.10, 158.14, 158.00, 157.06, 156.47, 155.59, 153.00, 152.33, 148.67, 148.63, 148.44, 142.43, 137.5−136.4, 132.04, 131.31, 128.6−127.0, 124.92, 119.97, 119.55, 114.53, 114.36, 114.29, 113.26, 110.85, 108.74, 107.03, 101.98, 95.03, 94.01, 91.80, 80.69, 74.94, 71.14, 71.10, 70.99, 70.77, 69.94, 68.28, 35.53, 26.13. Anal. Calcd for $C_{114}H_{96}O_{16}$: C, 79.51; H, 5.62. Found: C, 79.65; H, 5.38.

Epicatechin-4α,8-(3-*O*-galloylepicatechin) (31). A solution of 22 mg (13 μmol) of **30** in 4 mL of EtOAc/MeOH (1:1) was hydrogenated at 3.5 bar and room temperature over 33 mg of 20% $Pd(OH)_2$/C for 4.5 h. After filtration over cotton and

(20) Cavallito, C. J.; Buck, J. S. *J. Am. Chem. Soc.* **1943**, *65*, 2140.

evaporation, the residue was lyophilized from 2 mL of H_2O (HPLC grade) to give 6.3 mg (67%) of **31** as a colorless, amorphous solid: ^{1}H NMR ($CDCl_3$; selection; two rotamers, approximately 3:1, MR = major, mr = minor rotamer) δ 7.06 (d, 1 H, MR, J = 1.5 Hz), 7.0−6.65 (m), 6.54 (d, 1 H, mr, J = 8.5 Hz), 6.47 (d, 1 H, mr, J = 2 Hz), 6.20 (d, 1 H, mr, J = 2 Hz), 6.15 (s, 1 H, mr), 6.03 (dd, 1 H, mr, J = 2, 8.5 Hz), 5.99 (d, 1 H, mr, J = 2.5 Hz), 5.96 (d, 1 H, MR, J = 2 Hz), 5.93 (s, MR, 1 H), 5.82 (d, 1 H, MR, J = 2 Hz), 5.56 (narrow m, 1 H, MR + mr), 5.32 (narrow m, 1 H, mr), 5.18 (s, 1 H, MR), 5.08 (d, 1 H, MR, J = 5 Hz), 5.05 (d, 1 H, mr, J = 5 Hz), 4.28 (d, 1 H, MR, J = 5 Hz), 4.00 (d, 1 H, mr, J = 5 Hz), 3.07, 2.87 (ABq, 2 H, MR, J = 17.5 Hz, A part d with J = 4.5 Hz), 2.96, 2.80 (ABq, 2H, mr, partially overlapping with the preceding signal); MS (electrospray) m/z 729.2 (M^+; calcd for $C_{37}H_{30}O_{16}$: 730.2).

Acknowledgment. We are grateful to MARS, Incorporated, for funding of this work.

JO001462Y