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Systematic synthesis of galloyl-substituted procyanidin B1 and B2, and their ability of DPPH radical scavenging activity and inhibitory activity of DNA polymerases☆

Akiko Saito,[a,*] Yoshiyuki Mizushina,[b,c] Hiroshi Ikawa,[b] Hiromi Yoshida,[b,c] Yuki Doi,[d] Akira Tanaka[e] and Noriyuki Nakajima[d,*]

[a]*Biotechnology Center, Toyama Prefecture, Kosugi, Toyama 939-0398, Japan*
[b]*Department of Nutritional Science, Kobe-Gakuin University, Nishi-ku, Kobe, Hyogo 651-2180, Japan*
[c]*High Technology Research Center, Kobe-Gakuin University, Nishi-ku, Kobe, Hyogo 651-2180, Japan*
[d]*Biotechnology Research Center, Toyama Prefectural University, Kosugi, Toyama 939-0398, Japan*
[e]*Department of Bioresources Science, College of Technology, Toyama Prefectural University, Kosugi, Toyama 939-0398, Japan*

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Abstract—Six galloyl-substituted procyanidin B1 and B2, 3-*O*-gallate, 3″-*O*-gallate, and 3,3″-di-*O*-gallate, were systematically synthesized with the condensation method using TMSOTf as a catalyst. Their ability of DPPH radical scavenging activity and DNA polymerase inhibitory activity were also investigated. The results indicated that the galloyl group of these compounds is very important for both activities. 3,3″-Di-*O*-gallate dimers acted as strong inhibitor against DNA polymerase α and β, whereas the desgalloyl and monogalloyl compounds did not exhibit any appreciable inhibitory activity against the DNA polymerase β.

1. Introduction

Among the polyphenols, gallates (galloesters) are known as one of the strongest bioactive compounds. Many research groups have reported the isolation and bioactivities of various types of gallates.[2,3] Proanthocyanidins, condensed tannins, and/or oligomeric flavonoids,[2,3] one of the polyphenol group, are naturally occurring plant metabolites widely available in fruits, vegetables, nuts, seeds, flowers, and bark. They react with one-electron oxidants, resulting in powerful antioxidant activity (free-radical scavenging activity).[4] Numerous galloyl-substituted flavan-3-ols and proanthocyanidins, oligomeric flavan-3-ols, have been also isolated from plants, and their strong bioactivities have recently received increasing attention. For example, epigallocatechin-3-gallate (EGCG), the major polyphenol in green tea which belongs to the flavan-3-ol group, has notably been the focus of intense research interest for its protective effect against a variety of cancer types, such as lung, prostate, and breast.[5] In more recent research, the receptor that mediates the anticancer activity of EGCG was identified.[6]

In the case of the galloyl procyanidin series, which has two hydroxyl groups on the B-ring, a number of isolation and biological research of gallate dimers have been reported; procyanidin B1 3-*O*-gallate (**5**),[7–15] B2-3-*O*-gallate (**9**),[12–19] B2-3″-*O*-gallate (**10**),[8,10,12–15,19–27] B2-3,3″-di-*O*-gallate (**11**),[7,8,10,12,14,16,18,21,23,28–31] B3-3-*O*-gallate,[32,33] B4-3″-*O*-gallate,[8,13,16,21] B5-3″-*O*-gallate,[34] B5-3,3″-di-*O*-gallate,[8,10,31] and B7-3-*O*-gallate.[13,35] Furthermore, many galloyl-substituted trimers and longer oligomers have been also reported. Although the structure-activity relationship (SAR) of these procyanidin gallates is most important, it has not been proved yet, because the presence of a large number of structurally similar isomers in the plants makes it very difficult to purify individual compounds and thus to supply extremely pure compounds necessary for biological assay. Another problem is that it is difficult to determine the structure of the oligomers by the NMR method because of spectra peak broadening. This phenomenon is

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☆See Ref. 1.
*Corresponding authors. Tel.: +81 766567500x568; fax: +81 766562498; e-mail: nori@pu-toyama.ac.jp

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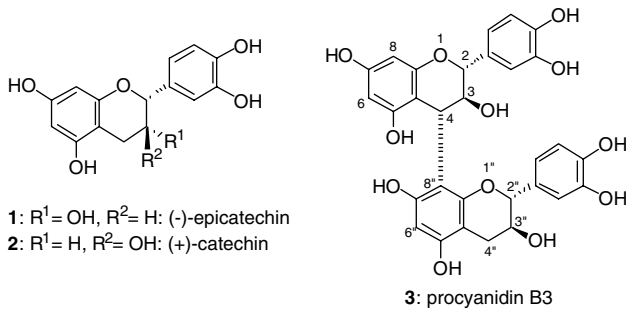


Figure 1. Structures of (−)-epicatechin (**1**), (+)-catechin (**2**), and procyanidin B3 (**3**).

frequently observed in the oligomers having epicatechin at the upper unit, for example, procyanidin B1 (**4**), B2 (**8**), and C1 (epicatechin trimer), and also the galloyl-substituted oligomers. Therefore, in most cases, the structure and constitutional unit of each oligomer are determined by the thiolysis method.[36] This peak broadening on the NMR spectra disappeared by acetylation of all hydroxy groups. On the other hand, the measurement of the NMR spectra at low temperature is effective to improve this peak broadening. Actually, Shoji et al.[37] reported characterization of some procyanidins which have an epicatechin moiety as an upper unit and are isolated from apple. In the low-temperature NMR method, the most appropriate temperature is required to be set for each compound. The measurement of the HMQC and HMBC spectra with this technique results in sharpened peaks of the spectra and a clear correlation between the proton signals and carbon signals.

Many reports on the isolation and semi-synthesis of procyanidin oligomers have been published thus far, but few studies concerning 3-*O*-substituted oligomers have appeared. We previously reported a stereoselective synthesis of procyanidin dimers[38] and trimers[1b,39] consisting of (−)-epicatechin (**1**) and (+)-catechin (**2**), and galloyl-substituted procyanidin B3 (Fig. 1).[1a] In this report, we undertook a systematic stereoselective synthesis of procyanidin B1/B2 derivatives substituted with a galloyl group at the C-3 and 3″ position (**5**–**7** and **9**–**11** in Fig. 2). The structure determination of each compound was accomplished by the low-temperature NMR method and after conversion into their peracetates. The bioactivities, that is, antioxidant activities on DPPH radical scavenging activity and inhibitory activity against DNA polymerases, of the synthesized procyanidin B1/B2 congeners (**4**–**11**) were investigated, and their results are described in detail.

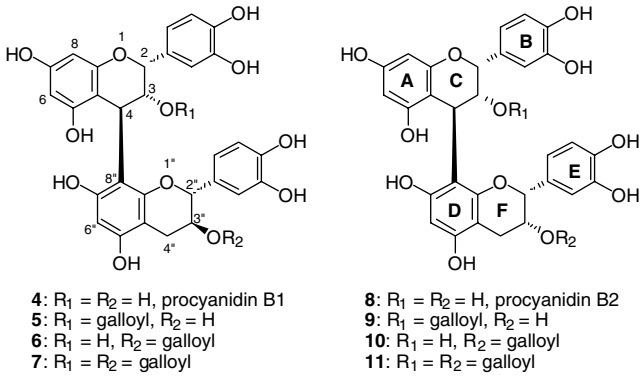


Figure 2. Structures of galloyl-substituted procyanidin B1 and procyanidin B2.

2. Results and discussion

2.1. Systematic stereoselective synthesis of six galloyl-substituted procyanidin B1 and B2

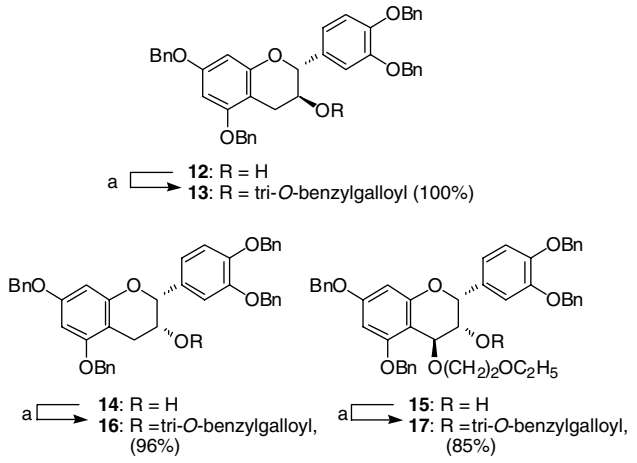
There have been numerous studies concerning the isolation and bioactivities of galloyl-substituted procyanidin oligomers. Bioactive abilities of these compounds, however, are poorly understood. As described above, to separate purely individual structural analogues from the plant is very difficult, because these compounds are present as mixtures containing a number of structurally related compounds, and the structure determination of these compounds is not easy. In 1999, Tückmantel et al.[40] reported a synthesis of procyanidin B2-3,3″-di-*O*-gallate and its bioactivities. In addition, the same group also reported the synthesis of 3,4-*cis* type procyanidin B2 and its galloyl derivatives.[41] Very recently,[1a] we reported an effective synthesis of procyanidin B3-3-*O*-gallate and B3-3,3″-di-*O*-gallate with a simple condensation method using TMSOTf as the catalyst, and also described their antioxidant activity and DNA polymerase inhibitory activities.

We report here a systematic synthesis of procyanidin B1 and B2 series including B1-3-*O*-gallate (**5**), B1-3″-*O*-gallate (**6**), B1-3,3″-di-*O*-gallate (**7**), B2-3-*O*-gallate (**9**), B2-3″-*O*-gallate (**10**), and B2-3,3″-*O*-gallate (**11**). This synthesis consists of a simple condensation between electrophiles and nucleophiles. We also describe the results of NMR measurement at low temperature. The NMR analysis of synthesized galloyl-substituted procyanidin dimers at room temperature is very difficult because of peak broadening.

Galloyl-substituted procyanidin dimers containing (−)-epicatechin at the upper part were synthesized based on our previously reported method. An electrophile having a 3-*O*-galloyl group and a nucleophile having a 3-*O*-galloyl group are condensed in the presence of TMSOTf (trimethylsilyl trifluoromethanesulfonate) as a catalyst in CH_2Cl_2 at an appropriate temperature.[42] The following deprotection yielded pure procyanidin dimers.

As shown in Scheme 1, nucleophile **12**, **14**, and electrophile **15** were esterified with tri-*O*-benzyl gallic acid by the DCC method to yield 3-*O*-galloyl catechin **13**, 3-*O*-galloyl epicatechin derivatives **16** and **17** in 100%,[1a] 85% and 96% yield, respectively.

At first, electrophile **17** was condensed with nucleophile **12** in the presence of TMSOTf to give undecabenzyl procyanidin B1 3-*O*-gallate **18** in 90% yield.[43] The stereochemistry was determined by NMR. The undecabenzyl procyanidin B1 3″-*O*-gallate **19** and pentadecabenzyl



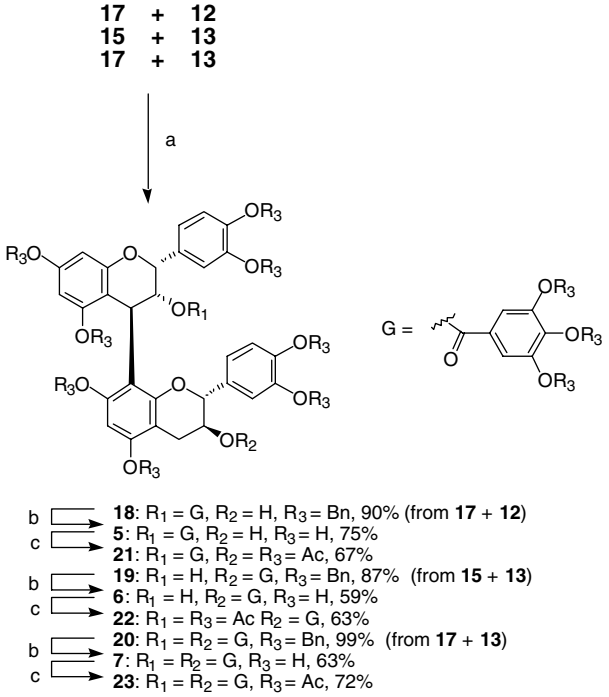
Scheme 1. Synthesis of tri-*O*-benzylgalloyl catechin (**13**) and tri-*O*-benzylgalloyl epicatechin derivatives (**16**) and (**17**). Reagents: (a) DCC, DMAP, CH_2Cl_2.

procyanidin B1 3,3″-di-*O*-gallate **20** were also obtained from the condensation between electrophile **15** and nucleophile **13**, electrophile **17**, and nucleophile **13** in 87% and 99% yields, respectively. The deprotection of all benzyl groups under hydrogenation conditions yielded procyanidin B1-3-*O*-gallate **5**, 3″-*O*-gallate **6**, and 3,3″-di-*O*-gallate **7** in 75%, 59%, and 63% yields, respectively. Acetylation of **5**, **6**, and **7** under the usual conditions afforded peracetates **21**, **22**, and **23** in 67%, 63%, and 72% yields, respectively. The structure confirmation of these compounds was accomplished by the NMR measurement at −40 °C for **5**, −30 °C for **6** and −40 °C for **7**. The procyanidin B1 3-*O*-gallate **5** is reported as a natural product isolated from rhubarb (Rhei Rhizoma).[7] The spectral data and optical rotation value of the synthetic **5** and its peracetate **21** were identical with those of the natural product.[7,9] The new compounds, procyanidin B1 3″-*O*-gallate **6** and its peracetate **22**, 3,3″-di-*O*-gallate **7** and its peracetate **23**, gave satisfactory NMR (^{1}H NMR, ^{13}C NMR), and FAB-MS data (Scheme 2).

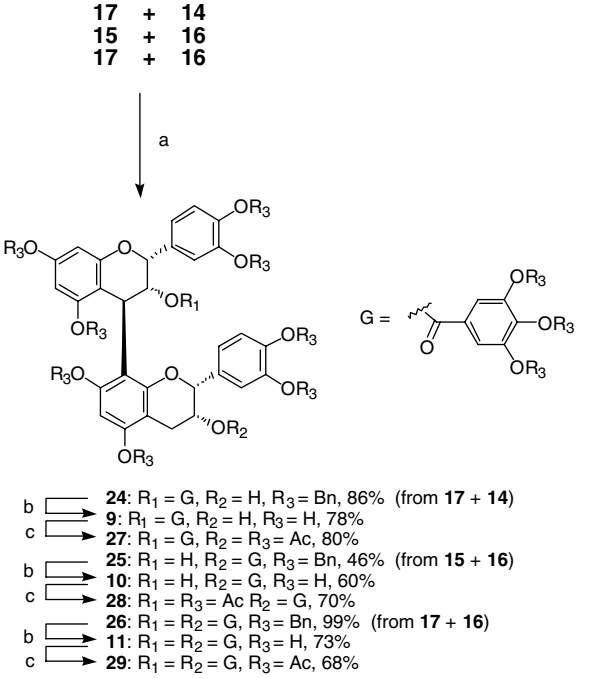
Similarly, the compounds belonging to the 3-*O*-galloyl-substituted procyanidin B2 series were synthesized as shown in Scheme 3. The electrophiles **15** and **17** were condensed with nucleophile **14** and **16** in the presence of TMSOTf to give procyanidin B2 derivatives **24**, **25**, and **26** in 86%, 46%, and 99% yields, respectively. Then the deprotection of these compounds yielded procyanidin B2-3-*O*-gallate **9** (78%), 3″-*O*-gallate **10** (60%), and 3,3″-di-*O*-gallate **11** (73%) and their peracetates **27**, **28**, and **29** were also synthesized in 80%, 70%, and 68% yield, respectively. The NMR measurements of **9**, **10**, and **11** were carried out at −40 °C, −30 °C and −50 °C, respectively. The obtained compounds **9**, **10**,[21] and **11**[7,21] are reported as a natural product and their spectral data and optical rotation value were identical with those of the natural product.

2.2. DPPH radical scavenging activity

Proanthocyanidins are known as strong antioxidants and radical scavengers as already described. In our previous paper,[1a] we investigated DPPH radical scavenging activity of procyanidin B3 series, (+)-catechin dimer, including galloyl-substituted compounds, and it became apparent that the galloyl moiety was not much effective for the radical scavenging activity.



Scheme 2. Synthesis of 3-*O*-galloyl-substituted procyanidin B1 series. Reagents: (a) TMSOTf, CH_2Cl_2; (b) $Pd(OH)_2$/C, H_2, THF/MeOH/H_2O; (c) Ac_2O, py, DMAP.



Scheme 3. Synthesis of 3-*O*-galloyl-substituted procyanidin B2 series. Reagents: (a) TMSOTf, CH_2Cl_2; (b) $Pd(OH)_2$/C, H_2, THF/MeOH/H_2O; (c) Ac_2O, py, DMAP.

Table 1. DPPH radical scavenging activity

Entry	Compound	SC_{50} (μM)
1	**4**	1.3
2	**5**	0.8
3	**6**	0.7
4	**7**	0.6
5	**8**	1.2
6	**9**	0.8
7	**10**	0.6
8	**11**	0.6
9	DL-α-Tocopherol	17

The SC_{50} values (concentration of 50% scavenging activity) of synthesized compounds (**4**–**11**) were 1.3, 0.8, 0.7, 0.6, 1.2, 0.8, 0.6, and 0.6 μM, respectively (Table 1). It appeared that the radical scavenging activity tended to keep even though the number of galloyl groups increased. As we described in a previous paper,[1a] the SC_{50} values of procyanidin B3, 3-*O*-galloyl procyanidin B3 and 3,3″-di-*O*-galloyl procyanidin B3 were 1.3, 3.2, and 1.1, respectively. As compared with the procyanidin B3 series, the galloyl group of the procyanidin B1/B2 series is effective for radical scavenging activity than that of the procyanidin B3 series.

2.3. Mammalian DNA polymerase inhibitory activities

Monomeric flavan-3-*O*-gallates, (−)-epicatechin-3-*O*-gallate, (−)-epigallocatechin-3-*O*-gallate, etc., that occur in green tea, are known as inhibitors of DNA and RNA polymerases,[45] and it was apparent that the galloyl group is essential for the inhibitory effect. As we described in a previous paper, flavan-3-ols without a galloyl group were not effective for this polymerase inhibitory activity.[1a] DNA polymerases, especially DNA polymerase α which is a DNA replicative polymerase,[46] are regarded as the target of some anticancer drugs because DNA polymerases play central roles in DNA replication which is indispensable for the proliferation of cancer cells. It is well known that DNA polymerase α is over-expressed in rapidly propagated cancer cells. These facts allowed us to expect galloyl-substituted procyanidin dimers to be effective inhibitors of DNA polymerases. In a previous paper, we described the ability of the procyanidin B3 series as DNA polymerase inhibitor. As the result, the IC_{50} values (concentration of 50% inhibitory activity) of procyanidin B3, 3-*O*-galloyl procyanidin B3 and 3,3″-di-*O*-galloyl procyanidin B3 were 36.4, 0.26, and 8.1 μM, respectively, for DNA polymerase α.[1a] However, the procyanidin B3 series were not effective for DNA polymerase β, a repair-related polymerase, at all.

Table 2 shows the IC_{50} values of compounds **4**–**11** against calf DNA polymerase α and rat DNA polymerase β. All procyanidin B1/B2 series compounds inhibit DNA polymerase α, and the activity tends to be stronger as the number of galloyl groups increases. Among procyanidin B1/B2 series compounds, di-gallates **7** and **11** are the strongest inhibitors of DNA polymerase α. Furthermore, these di-gallates **7** and **11** have also the ability to inhibit DNA polymerase β (entries 4 and 8); in contrast, des-gallates **4** and **8** and mono-gallates **5**, **6**, **9**, and **10** did not inhibit DNA polymerase β. This tendency is different from that of the procyanidin B3 series that we described in the previous report.[1a] These results suggest that the mode of inhibitory effect on DNA polymerases depends on the kind of the constitutional monomer units of procyanidin dimers, namely (−)-epicatechin (**1**) and (+)-catechin (**2**).

Table 2. IC_{50} values of enzymatic inhibition against mammalian DNA polymerase α and β

Entry	Compound	IC_{50} values (μM)	
		DNA polymerase α	DNA polymerase β
1	**4**	25.4	>500
2	**5**	0.72	>500
3	**6**	0.89	>500
4	**7**	0.23	89
5	**8**	24.0	>500
6	**9**	0.70	>500
7	**10**	0.85	>500
8	**11**	0.24	102

3. Conclusion

We synthesized six 3-*O*- and 3″-*O*-gallates of procyanidin B1/B2, **5**–**7** and **9**–**11**, with a simple systematic method whereby the nucleophile and electrophile derived from (−)-epicatechin **1** and (+)-catechin **2** were condensed in the presence of TMSOTf as a catalyst. Their ability of DPPH radical scavenging activity and DNA polymerase inhibitory activity were also investigated. The results indicated that the galloyl group of these compounds was very important for DNA polymerase inhibitory activity, which tended to be stronger as the number of galloyl groups increased. The 3,3″-di-*O*-gallate dimers acted as strong inhibitors for DNA polymerase α and specially for β. The corresponding des- and mono 3-*O*-gallates did not show any inhibitory effect. Furthermore, it is clear that the galloyl-substituted procyanidin B1/B2 series have stronger activity than the procyanidin B3 series.

4. Experimental

4.1. Synthesis

Optical rotation was measured with a Horiba SEPA-300 spectrometer. ^{1}H NMR spectra were measured with JEOL JNMLA400 spectrometer. MS spectra were recorded with a JEOL JMS-AX500 instrument. HPLC purification was carried out on a Mightysil® RP-18 GP column (Kanto Chemical Co. Inc, Japan; 250 × 20 mm, 5 mm) using the solvents (A) 0.05% CF_3CO_2H in CH_3CN and (B) 0.05% CF_3CO_2H in H_2O. Elution was done with a linear gradient 5–100% A in 40 min (flow rate, 4.0 mL/min).

4.1.1. (2*R*,3*R*)-5,7,3′,4′-Tetra-*O*-benzylflavan-3-yl (3″,4″,5″-tri-*O*-benzyl)gallate (16). To a solution of (2*R*,3*R*)-5,7,3′,4′-tetra-*O*-benzylflavan-3-ol **14** (497 mg, 0.76

mmol) and 3,4,5-tri-*O*-benzylgallic acid (670 mg, 1.52 mmol) in CH_2Cl_2 (60 mL) was added DCC (314 mg, 1.52 mmol) and DMAP (5.00 mg). After stirring for 12 h at rt, the reaction mixture was quenched with water, and extracted with CH_2Cl_2. The organic phase was washed with water and brine, and dried (Na_2SO_4). Filtration, concentration, and silica gel column chromatography (benzene/EtOAc, 20/1) afforded 780 mg of **16** (0.73 mmol, 96%) as a white solid. $[\alpha]_D^{23}$ −75.6 (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.43–7.18 (37H, m), 7.06 (1H, d, *J* = 1.7 Hz), 6.93 (1H, dd, *J* = 1.7, 8.3 Hz), 6.83 (1H, d, *J* = 8.3 Hz), 6.37 (1H, d, *J* = 2.2 Hz), 6.32 (1H, d, *J* = 2.2 Hz), 5.63–5.59 (1H, m), 5.08–4.99 (13H, m), 4.75 (1H, d, *J* = 11.7 Hz), 4.64 (1H, d, *J* = 11.7 Hz), 3.11 (1H, dd, *J* = 4.4, 17.8 Hz), 3.05 (1H, dd, *J* = 2.7, 17.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 164.9, 158.8, 156.0, 155.7, 152.3, 148.9, 148.8, 142.5, 137.4, 137.1, 137.0, 136.8, 136.5, 131.0, 128.6, 128.51 (x2), 128.49, 128.4, 128.32, 128.28, 128.1, 127.99, 127.96, 127.88, 127.86, 127.70, 127.66 (x2), 127.4, 127.3, 127.2 (x2), 124.9, 120.0, 114.7, 113.6, 109.0, 100.9, 94.6, 93.9, 77.6, 75.0, 71.2, 71.1, 70.9, 70.1, 69.9, 68.5, 26.1; IR (neat, cm^{-1}) 3090 (w), 3065 (m), 2936 (m), 2870 (m), 2361 (w), 2339 (w), 1952 (w), 1877 (w), 1811 (w), 1717 (s), 1618 (s), 1593 (s), 1498 (s), 1429 (s), 1373 (s), 1327 (s), 1143 (s), 1113 (s), 1028 (s), 910 (m), 860 (m), 812 (m), 752 (s); FAB-MS (*m*/*z*) 1097 (5.9), 1096 (15), 1095 ($[M+Na]^+$, 20), 1076 (6.5), 1075 (11), 1074 (25), 1073 ($[M+H]^+$, 29), 723 (27), 722 (27), 634 (49), 633 (100), 632 (100); FAB-HRMS calcd for $C_{71}H_{61}O_{10}$ $[M+H]^+$, 1073.4265; found: 1073.4215.

4.1.2. (2*R*,3*R*,4*S*)-5,7,3′,4′-Tetra-*O*-benzyl-4-(2″-ethoxyethoxy)flavan-3-yl (3‴′,4‴′,5‴′-tri-*O*-benzyl)gallate (17). To a solution of (2*R*,3*R*,4*S*)-5,7,3′,4′-tetra-*O*-benzyl-4-(2″-ethoxyethoxy)flavan-3-ol **15** (481 mg, 0.65 mmol) and 3,4,5-tri-*O*-benzylgallic acid (574 mg, 1.30 mmol) in CH_2Cl_2 (80 mL) was added DCC (268 mg, 1.30 mmol) and DMAP (5.00 mg). After stirring 48 h at rt, the reaction mixture was quenched with water, and extracted with CH_2Cl_2. The organic phase was washed with water and brine, and dried (Na_2SO_4). Filtration, concentration, and silica gel column chromatography (benzene/EtOAc, 20/1) afforded 643 mg of **17** (0.55 mmol, 85%) as a colorless amorphous solid. $[\alpha]_D^{23}$ −48.7 (*c* 1.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.42–7.22 (37H, m), 7.08 (1H, d, *J* = 1.7 Hz), 6.98 (1H, dd, *J* = 1.7, 8.3 Hz), 6.83 (1H, d, *J* = 8.3 Hz), 6.35 (1H, d, *J* = 2.2 Hz), 6.31 (1H, d, *J* = 2.2 Hz), 5.41 (1H, dd, *J* = 0.9, 2.7 Hz), 5.35 (1H, br s), 5.12–4.95 (12H, m), 4.78 (1H, d, *J* = 11.5 Hz), 4.68 (1H, d, *J* = 11.5 Hz), 4.60 (1H, d, *J* = 2.7 Hz), 4.00 (1H, dt, *J* = 11.0, 5.3 Hz), 3.87 (1H, dt, *J* = 11.0, 4.4 Hz), 3.58 (2H, dd, *J* = 4.4, 5.3 Hz), 3.49 (2H, q, *J* = 7.0 Hz), 1.19 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 164.8, 160.5, 159.5, 156.4, 152.4, 152.3, 140.0, 148.9, 142.6, 137.4, 137.1, 137.0, 136.6 (x2), 136.4, 130.6, 128.54, 128.51, 128.45, 128.37, 128.30, 128.26, 128.1, 128.00, 127.98, 127.88, 127.69, 127.66, 127.60, 127.5, 127.40, 127.37, 127.2, 124.5, 120.3, 114.7, 113.9, 109.0, 102.2, 94.2, 94.0, 75.0, 74.0, 71.2, 71.1, 70.9, 70.2, 70.0, 69.9, 68.7, 69.3, 68.4, 66.4, 15.2; IR (neat, cm^{-1}) 3065 (w), 3032 (w), 2870 (w), 1717 (m), 1618 (s), 1592 (s), 1498 (m), 1429 (s), 1373 (m), 1330 (m), 1265 (m), 1215 (s), 1153 (s), 1167 (s), 1028 (m), 912 (w), 860 (w), 841 (w), 754 (m); FAB-MS (*m*/*z*) 1184 (5.0), 1183 ($[M + Na]^+$, 6.0), 1162 (3.1), 1161 ($[M + H]^+$, 6.4), 1160 (4.8), 783 (12), 782 (20), 722 (12), 721 (22), 720 (12), 633 (15), 632 (50), 631 (100); FAB-HRMS calcd for $C_{75}H_{69}O_{12}$ $[M + H]^+$, 1161.4789; found: 1161.4774.

4.1.3. [4,8]-2,3-*cis*-3,4-*trans*:2,3-*trans*-Octa-*O*-benzyl-(−)-epicatechin-(+)-catechin-3-*O*-(tri-*O*-benzyl)gallate (18). To a solution of **12** (172 mg, 0.27 mmol) and **17** (77 mg, 0.066 mmol) in CH_2Cl_2 (30 mL) was added dropwise TMSOTf (0.13 mL, 0.066 mmol, 0.5 M solution in CH_2Cl_2) at −10 °C. After stirring for 5 min, the pale yellow reaction mixture was quenched with satd sodium hydrogen carbonate. The aq solution was extracted with $CHCl_3$ and the organic phase was washed with water and brine, and dried (Na_2SO_4). Filtration, concentration, and preparative silica gel TLC purification (hexane/EtOAc, 2/1) afforded 93 mg (0.054 mmol, 90%) of **18** as a colorless amorphous solid: $[\alpha]_D^{25}$ −6.1 (*c* 0.72, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 0.83:0.17 mixture of rotational isomers) major isomer: 7.47–6.73 (51.46H, m), 6.56–6.53 (0.83H, m), 6.33 (0.83H, s), 6.09 (0.83H, d, *J* = 2.2 Hz), 5.67 (0.83H, d, *J* = 2.2 Hz), 5.64 (0.83H, br s), 5.61 (0.83H, br s), 5.20–4.50 (15.77H, m), 4.60 (0.83H, d, *J* = 12.2 Hz), 4.55 (0.83H, d, *J* = 12.2 Hz), 4.43 (0.83H, d, *J* = 11.7 Hz), 4.28 (0.83H, d, *J* = 11.7 Hz), 3.82 (0.83H, 6.5, 9.0, 9.8 Hz), 3.72 (0.83H, d, *J* = 9.0 Hz), 3.27 (0.83H, dd, *J* = 6.5, 17.0 Hz), 2.62 (0.83H, dd, *J* = 9.8, 17.0 Hz), 1.50 (0.83H, br OH); minor isomer: 7.47–6.73 (10.54H, m), 6.53–6.51 (0.17H, m), 6.37 (0.17H, br s), 6.23 (0.17H, br s), 6.21 (0.17H, br s), 5.47 (0.34H, br s), 5.20–4.23 (3.91H, m), 3.73–3.70 (0.34H, m), 3.18 (0.17H, dd, *J* = 5.9, 16.6 Hz), 2.78–2.62 (0.17H, m), 1.64 (0.17H, br, OH); ^{13}C NMR (100 MHz, $CDCl_3$, 0.83:0.17 mixture of rotational isomers) major isomer: 163.9, 158.1, 156.5, 156.2, 156.1, 155.8, 154.1, 152.1, 149.34, 149.26, 148.9, 148.8, 142.1, 137.6, 137.4, 137.2–137.1 (Cx8), 136.5 (x2), 132.0, 130.4, 128.6–127.1 (Cx27), 125.5 (x2), 120.6, 120.0, 114.6, 114.0, 113.4, 112.0, 110.3, 108.8, 104.8, 104.2, 93.5, 93.0, 91.5, 81.8, 77.2, 75.0, 72.8, 71.2 (x2), 70.9, 70.7, 70.6, 70.3, 70.0, 69.7, 69.3, 68.7, 33.7, 29.1; minor isomer: 163.6, 158.3, 157.5, 156.7, 156.1, 156.0, 153.2, 152.1, 149.0, 148.9, 148.53, 148.47, 142.1, 137.6, 137.4, 137.2–136.9 (Cx8), 136.6 (x2), 131.8, 130.9, 128.6–127.0 (Cx27), 125.3 (x2), 120.6, 120.2, 114.7, 114.2, 113.7, 112.0, 110.8, 108.6, 105.1, 103.2, 93.8, 93.3, 92.3, 81.6, 77.6, 75.1, 73.0, 71.3 (x2), 71.2, 71.0, 70.7, 70.1, 70.0, 69.9, 69.5, 68.2, 34.0, 28.0; IR (neat, cm^{-1}) 3065 (w), 3032 (w), 2900 (w), 1716 (m), 1593 (s), 1499 (s), 1429 (s), 1375 (m), 1327 (m), 1265 (m), 1215 (s), 1117 (s), 1028 (m), 910 (w), 852 (w), 808 (w), 752 (m), 696 (s); FAB-MS (*m*/*z*) 1746 (17), 1745 (30), 1744 ($[M + Na]^+$, 48), 1725 (37), 1724 (28), 1723 (18), 1722 ($[M + H]^+$, 73), 1283 (59), 1282 (98), 1281 (77), 1192 (53), 1191 (84), 1190 (100), 1099 (39), 1098 (37), 1071 (41); FAB-HRMS calcd for $C_{114}H_{97}O_{16}$ $[M + H]^+$, 1721.6777; found: 1721.6704.

4.1.4. [4,8]-2,3-*cis*-3,4-*trans*:2,3-*trans*-Octa-*O*-benzyl-(−)-epicatechin-(+)-catechin-3″-*O*-(tri-*O*-benzyl)gallate (19). To a solution of **13** (209 mg, 0.19 mmol) and **15** (36 mg, 0.049 mmol) in CH_2Cl_2 (30 mL) was added dropwise TMSOTf (0.098 mL, 0.049 mmol, 0.5 M solution in CH_2Cl_2) at −10 °C. After stirring for 5 min, the pale yellow reaction mixture was quenched with satd sodium hydrogen carbonate. The aq solution was extracted with $CHCl_3$ and the organic phase was washed with water and brine, and dried (Na_2SO_4). Filtration, concentration, and preparative silica gel column chromatography (hexane/EtOAc/$CHCl_3$, 8/1/9) afforded 73 mg of **19** (0.042 mmol, 87%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +106.3 (*c* 0.28, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 0.71:0.29 mixture of rotational isomers) major isomer: 7.46–6.95 (41.89H, m), 6.92 (0.71H, d, *J* = 8.3 Hz), 6.79 (0.71H, d, *J* = 1.7 Hz), 6.64 (0.71H, d, *J* = 8.3 Hz), 6.45 (0.71H, dd, *J* = 1.7, 8.3 Hz), 6.36 (0.71H, s), 6.04 (0.71H, d, *J* = 2.2 Hz), 5.54 (0.71H, d, *J* = 2.2 Hz), 5.44 (0.71H, br s), 5.12–4.74 (15.62H, m), 4.61 (0.71H, d, *J* = 11.0 Hz), 4.51 (0.71H, d, *J* = 11.0 Hz), 4.03 (0.71H, d, *J* = 9.7 Hz), 4.05–4.00 (0.71H, m), 3.48 (0.71H, dd, *J* = 6.9, 16.9 Hz), 2.72 (0.71H, dd, *J* = 9.3, 16.9 Hz), 1.76 (0.71H, d, *J* = 5.9 Hz); minor isomer: 7.46–6.84 (17.69H, m), 6.73 (0.29H, dd, *J* = 1.7, 8.3 Hz), 6.54 (0.29H, d, *J* = 8.3 Hz), 6.21 (0.29H, d, *J* = 2.2 Hz), 6.20 (0.29H, s), 6.04 (0.29H, d, *J* = 2.2 Hz), 5.31 (0.29H, br s), 5.23–5.14 (0.58H, m), 5.12–4.74 (6.09H, m), 4.61 (0.29H, d, *J* = 12.0 Hz), 4.38 (0.29H, d, *J* = 12.0 Hz), 3.95–3.91 (0.29H, m), 3.27 (0.29H, dd, *J* = 5.4, 16.6 Hz), 2.87 (0.29H, dd, *J* = 8.2, 16.6 Hz), 1.59 (0.29H, d, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 0.71:0.29 mixture of rotational isomers) major isomer: 164.8, 158.2, 157.0, 156.1, 155.9, 155.3, 154.4, 152.4, 149.19, 149.17, 148.8, 148.5, 142.4, 137.5, 137.43, 137.39, 137.29, 137.26, 137.18, 137.12, 37.07, 136.95, 136.6, 132.6, 130.8, 128.8–126.7 (Cx30), 125.0, 120.4, 119.7, 115.0, 114.0, 113.6, 112.0, 111.4, 109.0, 104.2, 103.6, 93.6, 93.0, 91.7, 79.1, 75.1, 72.3, 71.43, 71.39, 71.28, 71.16 (x2), 71.07, 70.6, 70.4, 70.1, 69.6, 69.1, 35.7, 27.7; minor isomer: 165.0, 158.4, 157.8, 157.1, 155.8, 155.6, 152.7, 152.5, 149.0, 148.83, 148.76, 148.6, 142.5, 137.39, 137.36, 137.24, 137.18, 137.15, 137.0, 136.91, 136.88, 136.6 (x2), 132.5, 131.0, 128.8–126.7 (Cx30), 125.1, 120.1, 119.9, 114.9, 114.4, 114.1, 112.9, 111.4, 109.0, 104.5, 102.1, 94.4, 93.3, 92.8, 78.6, 75.5, 71.9, 71.5, 71.35, 71.28, 71.16 (x2), 71.07, 70.96, 70.5, 70.0, 69.9, 69.6, 35.9, 24.6; IR (neat, cm^{-1}) 3090 (w), 3065 (w), 3032 (m), 2932 (w), 2870 (w), 1717 (m), 1593 (s), 1498 (s), 1454 (s), 1429 (s), 1379 (s), 1331 (s), 1263 (s), 1215 (s), 1119 (s), 1028 (s), 910 (w), 852 (w), 808 (w), 750 (s); FAB-MS (*m*/*z*) 1745 (23), 1744 ($[M + Na]^+$, 25), 1724 (33), 1723 (50) 1722 ($[M + H]^+$, 53), 1721 (39), 1283 (32), 1282 (43), 1174 (38), 1173 (49), 1172 (53), 631 (100); FAB-HRMS calcd for $C_{114}H_{97}O_{16}$ $[M + H]^+$, 1721.6777; found: 1721.6777.

4.1.5. [4,8]-2,3-*cis*-3,4-*trans*:2,3-*trans*-Octa-*O*-benzyl-(−)-epicatechin-(+)-catechin-3,3″-di-*O*-(tri-*O*-benzyl)gallate (20). To a solution of **13** (314 mg, 0.29 mmol) and **17** (85 mg, 0.073 mmol) in CH_2Cl_2 (40 mL) was added dropwise TMSOTf (0.15 mL, 0.073 mmol, 0.5 M solution in CH_2Cl_2) at −10 °C. After stirring for 5 min, the pale yellow reaction mixture was quenched with satd sodium hydrogen carbonate. The aq solution was extracted with $CHCl_3$ and the organic phase was washed with water and brine, and dried (Na_2SO_4). Filtration, concentration and preparative silica gel column chromatography (hexane/EtOAc/$CHCl_3$, 8/1/9) afforded a 155 mg of **20** (0.072 mmol, 99%) as a colorless amorphous: $[\alpha]_D^{25}$ +63.8 (*c* 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 0.74:0.26 mixture of rotational isomers) major isomer: 7.43–6.86 (56.24H, m), 6.86 (0.74H, d, *J* = 1.7 Hz), 6.78 (0.74H, d, *J* = 8.3 Hz), 6.66 (0.74H, d, *J* = 8.3 Hz), 6.49 (0.74H, dd, *J* = 1.7, 8.3 Hz), 6.36 (0.74H, s), 6.10 (0.74H, d, *J* = 2.2 Hz), 5.66–5.64 (2.22H, m), 5.21 (0.74H, ddd, *J* = 5.9, 9.2, 9.8 Hz), 5.11–4.67 (18.5H, m), 4.59 (0.74H, d, *J* = 11.5 Hz), 4.54 (0.74H, d, *J* = 11.5 Hz), 4.43 (0.74H, d, *J* = 12.0 Hz), 4.29 (0.74H, d, *J* = 12.0 Hz), 4.10 (0.74H, d, *J* = 9.8 Hz), 3.51 (0.74H, dd, *J* = 5.9, 15.9 Hz), 2.77 (0.74H, dd, *J* = 9.2, 15.9 Hz); minor isomer: 7.43–6.65 (20.54H, m), 6.42 (0.26H, dd, *J* = 1.7, 8.3 Hz), 6.26 (0.26H, d, *J* = 2.2 Hz), 6.25 (0.26H, s), 6.18 (0.26H, d, *J* = 2.2 Hz), 5.57 (0.26H, br s), 5.48 (0.26H, br s), 5.31–5.25 (0.26H, m), 5.21–5.17 (0.26H, m), 5.11–4.67 (7.02H, m), 4.48 (0.26H, d, *J* = 11.4 Hz), 4.37 (0.26H, d, *J* = 11.4 Hz), 3.18 (0.26H, dd, *J* = 4.9, 16.9 Hz), 2.99 (0.26H, dd, *J* = 7.0, 16.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: 164.8, 163.8, 158.1, 156.5, 156.22, 156.17, 155.9, 154.4, 152.4, 152.1, 149.28, 149.25, 148.8, 148.5, 142.5, 142.1, 137.6–136.4 (Cx17), 131.9, 130.8, 128.9–126.8 (Cx32), 125.2, 120.4, 120.1, 114.6, 114.1, 113.3, 111.8, 110.4, 109.0, 108.9, 104.6, 103.5, 93.5, 92.9, 91.6, 79.2, 77.2, 75.1, 74.9, 72.8, 71.6–69.2 (Cx11), 33.7, 27.7; minor isomer: 165.3, 164.1, 158.3, 157.5, 157.0, 156.2, 156.1, 156.0, 152.7, 152.5, 149.0, 148.7, 148.5, 148.4, 142.6, 142.1, 137.6–136.4 (Cx17), 131.7, 131.1, 128.9–126.8 (Cx32), 125.0, 120.0, 119.9, 114.4, 114.2, 113.8, 113.6, 110.8, 108.9, 108.7, 105.0, 102.2, 94.4, 93.3, 92.4, 78.3, 77.6, 75.14, 75.09, 73.0, 71.6–69.2 (Cx11), 33.9, 24.4; IR (neat, cm^{-1}) 3039 (w), 3065 (m), 3032 (m), 2934 (m), 2870 (m), 1954 (w), 1811 (w), 1717 (s), 1598 (s), 1498 (s), 1429 (s), 1373 (s), 1329 (s), 1265 (s), 1115 (s), 1028 (s), 910 (w), 852 (w), 808 (w), 752 (m); FAB-MS (*m*/*z*) 2169 (38), 2168 (43), 2166 ($[M + Na]^+$, 22), 2146 (33), 2145 (27), 2144 ($[M + H]^+$, 55), 1705 (70), 1704 (61), 1703 (86), 1702 (57), 1614 (63), 1613 (94), 1612 (100), 1174 (47), 1173 (29), 1172 (71), 1171 (87); FAB-HRMS calcd for $C_{142}H_{119}O_{20}$ $[M + H]^+$, 2143.8295; found: 2143.8262.

4.1.6. Procyanidin B1-3-*O*-gallate (5). A solution of **18** (90.0 mg, 0.052 mmol) in a mixture of THF/MeOH/H_2O (20/1/1, 22 mL) was hydrogenated over 20% $Pd(OH)_2$/C (5 mg) for 3 h at rt. Filtration and concentration afforded a pale brown solid, which was purified by Sephadex® LH-20 column chromatography (MeOH) and HPLC purification to give 28.6 mg of pure **5** (0.039 mmol, 75%) as a pale brown amorphous solid: $[\alpha]_D^{23}$ −18.9 (*c* 0.29, Me_2CO) {lit.[7] $[\alpha]_D^{31}$ −21.2 (*c* 1.00, Me_2CO)}; ^{1}H NMR (400 MHz, 10% D_2O in CD_3COCD_3, −40 °C, 0.57:0.43 mixture of rotational isomers) major isomer: 6.95–6.59 (3.42H, m), 6.87

(1.14H, s, 2′), 5.97 (0.57H, d, J = 2.2 Hz, 8), 5.94 (0.57H, s, 6″), 5.93 (0.57H, d, J = 2.2 Hz, 6), 5.91–5.46 (0.57H, m, 2), 5.47 (0.57H, br s, 3), 5.14 (0.57H, d, J = 3.0 Hz, 2″), 4.73 (0.57H, br s, 4), 4.33–4.27 (0.57H, m, 3″), 2.59 (0.57H, br d, J = 14.2 Hz, 4″), 2.27 (0.57H, br d, J = 14.2 Hz, 4″); minor isomer: 6.95–6.59 (2.58H, m), 6.87 (0.86H, s, 2′), 5.97 (0.43H, d, J = 2.2 Hz, 8), 5.94 (0.43H, s, 6″), 5.77 (0.43H, d, J = 2.2 Hz, 6), 5.91–5.46 (0.43H, m, 2), 5.51 (0.43H, br s, 3), 4.49 (0.43H, br s, 4), 4.44 (0.43H, d, J = 8.3 Hz, 2″), 3.95–3.87 (0.43H, m, 3″), 2.83 (0.43H, dd, J = 5.6, 16.1 Hz, 4″), 2.41 (0.43H, dd, J = 9.0, 16.1 Hz, 4″); ^{13}C NMR (100 MHz, 10% D_2O in CD_3COCD_3, mixture of rotational isomers) 82.1 (2″), 79.8 (2″), 75.0 (3), 73.4 (3), 67.8 (3″), 66.2 (3″), 33.2 (4), 28.8 (4″), 24.6 (4″); FAB-MS (*m*/*z*) 754 (30), 753 ([M + Na]$^+$, 45), 752 (41), 732 (28), 731 ([M + H]$^+$, 39), 730 (29), 561 (44), 560 (48), 483 (56), 482 (100), 414 (40), 413 (93); FAB-HRMS calcd for $C_{37}H_{31}O_{16}$ [M + H]$^+$, 731.1612; found: 731.1597.

4.1.7. Procyanidin B1-3″-*O*-gallate (6). A solution of benzylated **19** (75 mg, 0.044 mmol) in a mixture of THF/MeOH/H_2O (20/1/1, 22 mL) was hydrogenated over 20% $Pd(OH)_2$/C (5 mg) for 2 h at rt. Filtration and concentration afforded a pale brown solid, which was purified by Sephadex® LH-20 column chromatography (MeOH) and HPLC purification to give 19.2 mg of pure **6** (0.026 mmol, 59%) as a pale brown amorphous solid: $[\alpha]_D^{23}$ +108.0 (*c* 0.31, MeOH); ^{1}H NMR (400 MHz, −30 °C, 10% D_2O in CD_3COCD_3, 0.84:0.16 mixture of rotational isomers) major isomer: 7.02 (0.84H, d, J = 1.7 Hz), 7.01 (1.68H, s, 2′), 6.95 (0.84H, d, J = 1.7 Hz), 6.93 (0.84H, dd, J = 1.7, 8.3 Hz), 6.72 (0.84H, d, J = 8.3 Hz), 6.70 (0.84H, d, J = 8.3 Hz), 6.54 (0.84H, dd, J = 1.7, 8.3 Hz), 5.97 (0.84H, d, J = 2.2 Hz, 8), 5.92 (0.84H, s, 6″), 5.90 (0.84H, d, J = 2.2 Hz, 6), 5.36 (0.84H, ddd, J = 3.2, 4.2, 4.6 Hz, 3″), 5.29 (0.84H, d, J = 4.6 Hz, 2″), 5.11 (0.84H, br s, 2), 4.68 (0.84H, br s, 4), 3.87 (0.84H, br s, 3), 2.73 (0.84H, dd, J = 4.2, 15.3 Hz, 4″), 2.64 (0.84H, dd, J = 3.2, 15.3 Hz, 4″); minor isomer: 7.02–6.52 (0.96H, m), 7.01 (0.32H, s, 2′), 6.11 (0.16H, s, 6″), 5.86 (0.16H, d, J = 2.2 Hz, 8), 5.58 (0.16H, d, J = 2.2 Hz, 6), 5.38–5.29 (0.32H, m, 2 and 2″), 5.05–5.00 (0.16H, m, 3″), 4.53 (0.16H, br s, 4), 3.87 (0.16H, br s, 3), 2.80–2.60 (0.32H, m, 4″); ^{13}C NMR (100 MHz, −30 °C, 10% D_2O in CD_3COCD_3, 0.84:0.16 mixture of rotational isomers) major isomer: 111.2 (2′), 98.7 (6″), 97.2 (8), 95.3 (6), 79.8 (2″), 78.5 (2), 74.8 (3), 72.4 (3″), 38.4 (4), 25.6 (4″); minor isomer was not identified. FAB-MS (*m*/*z*) 754 (26), 753 ([M + Na]$^+$, 50), 752 (28), 732 (17), 731 ([M + H]$^+$, 51), 730 (39), 483 (73), 482 (100), 392 (100), 391 (100); FAB-HRMS calcd for $C_{37}H_{31}O_{16}$ [M + H]$^+$, 731.1612; found: 731.1608.

4.1.8. Procyanidin B1-3,3″di-*O*-digallate (7). A solution of **20** (120 mg, 0.056 mmol) in a mixture of THF/MeOH/H_2O (20/1/1, 22 mL) was hydrogenated over 20% $Pd(OH)_2$/C (5 mg) for 1.5 h at rt. Filtration and concentration afforded a pale brown solid, which was purified by Sephadex® LH-20 column chromatography (MeOH) and HPLC purification to give 30.6 mg of pure **7** (0.035 mmol, 63%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +65.6 (*c* 0.78, MeOH); ^{1}H NMR (400 MHz, 10% D_2O in CD_3COCD_3, −40 °C, 0.5:0.5 mixture of rotational isomers) 7.08 (1H, s, 2′), 6.97 (1H, s, 2′), 6.94 (1H, s, 2′), 6.90 (0.5H, d, J = 1.7 Hz), 6.87 (0.5H, d, J = 1.7 Hz), 6.84 (1H, s, 2′), 6.98–6.55 (5H, m), 6.12 (0.5H, s, 6″), 5.98–5.92 (1.5H, m, 6″, 6, 8), 5.90 (0.5H, d, J = 2.2 Hz, 8), 5.69 (0.5H, d, J = 2.2 Hz, 6), 5.90 (0.5H, br s, 2), 5.54 (0.5H, br s, 2), 5.48 (0.5H, br s, 3), 5.43–5.36 (0.5H, m, 3″), 5.35 (0.5H, d, J = 3.7 Hz, 2″), 5.14 (0.5H, br s, 3), 5.09–5.03 (0.5H, m, 3″), 4.80 (0.5H, br s, 4), 4.60 (0.5H, d, J = 4.7 Hz, 2″), 4.55 (0.5H, br s, 4), 2.76 (0.5H, br d, J = 13.6 Hz, 4″), 2.65–2.57 (1H, m, 4″), 2.55 (0.5H, br d, J = 13.6 Hz, 4″); ^{13}C NMR (100 MHz, 10% D_2O in CD_3COCD_3, 0.5:0.5 mixture of rotational isomers) 95.4 (6″), 94.3 (6″), 78.7 (2″), 77.7 (2″), 76.3 (2), 75.2 (2), 74.8 (3), 74.6 (3), 69.7 (3″), 69.6 (3″), 32.8 (4), 32.6 (4), 23.1 (4″), 23.0 (4″); FAB-MS (*m*/*z*) 906 (41), 905 ([M + Na]$^+$, 78), 904 (56), 883 ([M + H]$^+$, 23), 735 (26), 712 (31), 561 (42), 487 (60), 414 (65), 413 (100); FAB-HRMS calcd for $C_{44}H_{34}O_{20}Na$ [M + Na]$^+$, 905.1541; found: 905.1578.

4.1.9. Peracetate of 5 (21). Procyanidin B1-3-*O*-gallate **5** (13.0 mg, 0.018 mmol) was acetylated with an excess of Ac_2O in pyridine as a solvent for 24 h. Water was added and the mixture was extracted with EtOAc and dried (Na_2SO_4). Filtration, concentration, and preparative silica gel TLC purification (hexane/EtOAc, 1/1.5) gave 15 mg of peracetate **21** (0.012 mmol, 67%) as a colorless amorphous solid: $[\alpha]_D^{25}$ +34.6 (*c* 0.24, MeOH), $[\alpha]_D^{25}$ +24.4 (*c* 0.24, $CHCl_3$); {lit.[7] $[\alpha]_D^{16}$ +20.0 (*c* 0.35, MeOH)}, ^{1}H NMR (400 MHz, $CDCl_3$, 0.91:0.09 mixture of rotational isomers) major isomer: 7.54 (1.82H, s, 2′), 7.29 (0.91H, dd, J = 1.7, 8.3 Hz), 7.28 (0.91H, d, J = 1.7 Hz), 7.43 (0.91H, d, J = 8.3 Hz), 7.10 (0.91H, d, J = 8.3 Hz), 6.96 (0.91H, dd, J = 1.7, 8.3 Hz), 6.90 (0.91H, d, J = 1.7 Hz), 6.70 (0.91H, s, 6″), 6.33 (0.91H, d, J = 2.2 Hz, 8), 6.05 (0.91H, d, J = 2.2 Hz, 6), 5.56 (0.91H, br s, 2), 5.41 (0.91H, t, J = 1.7 Hz, 3), 5.07 (0.91H, ddd, J = 6.6, 9.3, 9.8 Hz, 3″), 4.53 (0.91H, d, J = 2.0 Hz, 4), 4.36 (0.91H, d, J = 9.8 Hz, 2″), 3.23 (0.91H, dd, J = 6.6, 16.6 Hz, 4″), 2.57 (0.91H, dd, J = 9.3, 16.6 Hz, 4″), 2.38 (2.73H, s, Ac), 2.30 (2.73H, s, Ac), 2,28 (2.73H, s, Ac), 2.27 (2.73H, s, Ac), 2.26 (2.73H, s, Ac), 2.233 (2.73H, s, Ac), 2.224 (2.73H, s, Ac), 2.218 (5.46H, s, Acx2), 2,14 (2.73H, s, Ac), 1.87 (2.73H, s, Ac), 1.84 (2.73H, s, Ac); minor isomer: 7.41 (0.18H, s, 2′), 7.31–6.90 (0.54H, m), 6.79 (0.09H, d, J = 2.2 Hz, 8), 6.77 (0.09H, d, J = 2.2 Hz, 6), 6.62 (0.09H, s, 6″), 5.53 (0.09H, br s, 3), 5.36 (0.09H, br s, 2), 5.33–5.31 (0.09H, m, 2″), 5.25–5.20 (0.09H, m, 3″), 4.73 (0.09H, br s, 4), 3.03–2.97 (0.09H, m, 4″), 2.78–2.70 (0.09H, m, 4″), 2.30–2.05 (2.16H, m, Acx8), 2.17 (0.27H, s, Ac), 2.00 (0.27H, s, Ac), 1.93 (0.27H, s, Ac), 1.76 (0.27H, s, Ac); ^{13}C NMR (100 MHz, $CDCl_3$, 0.91:0.09 mixture of rotational isomers) major isomer: 169.74, 160.71, 169.0, 168.6, 168.3, 168.0, 167.9 (x3), 167.4, 166.2, 163.0, 155.3, 154.0, 149.3, 148.7, 147.90, 147.86, 143.3, 142.3, 142.0, 141.8, 141.7, 138.9, 135.8, 134.6, 127.4, 125.5, 124.5, 123.4, 123.2, 122.3, 122.2, 121.8, 116.7, 113.6, 111.3, 110.7 (6″), 108.9 (8), 107.1 (6), 78.2 (2″), 73.6 (2), 72.3 (3), 68.4 (3″), 34.2 (4), 27.1

(4″), 21.2, 21.1, 20.8, 20.7, 20.64, 20.63, 20.57, 20.46, 20.35, 20.1, 20.0; minor isomer was not identified. IR (neat, cm^{-1}) 3026 (w), 2936 (w), 2361 (w), 2844 (w), 1771 (s), 1618 (m), 1427 (m), 1371 (s), 1321 (m), 1206 (s), 1055 (m), 900 (m), 758 (m); FAB-MS (*m*/*z*) 1259 (44), 1258 (82), 1257 ($[M + Na]^+$, 100), 1236 (5.7), 1235 ($[M + H]^+$, 8.0), 896 (55), 895 (58), 620 (31), 619 (61); FAB-HRMS calcd for $C_{61}H_{54}O_{28}Na$ $[M + Na]^+$, 1257.2699; found: 1257.2656.

4.1.10. Peracetate of 6 (22). Procyanidin B1-3″-*O*-gallate **6** (8.0 mg, 0.011 mmol) was acetylated with an excess of Ac_2O in pyridine as a solvent for 24 h. Water was added and the mixture was extracted with EtOAc and dried (Na_2SO_4). Filtration, concentration, and preparative silica gel TLC purification (hexane–EtOAc = 1:1.5) gave 8.5 mg of peracetate **22** (0.0069 mmol, 63%) as a colorless amorphous solid: $[\alpha]_D^{25}$ +130.4 (*c* 0.23, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 0.91:0.09 mixture of rotational isomers) major isomer: 7.58 (1.82H, s, 2′), 7.30 (0.91H, d, $J = 1.7$ Hz), 7.26 (0.91H, dd, $J = 1.7$, 8.3 Hz), 7.17 (0.91H, d, $J = 8.3$ Hz), 7.07 (0.91H, d, $J = 8.3$ Hz), 6.97 (0.91H, d, $J = 1.7$ Hz), 6.95 (0.91H, dd, $J = 1.7$, 8.3 Hz), 6.70 (0.91H, s, 6″), 6.28 (0.91H, d, $J = 2.2$ Hz, 8), 6.00 (0.91H, d, $J = 2.2$ Hz, 6), 5.48 (0.91H, br s, 2), 5.23 (0.91H, ddd, $J = 6.6$, 9.0, 9.5 Hz, 3″), 5.16 (0.91H, t, $J = 1.7$ Hz, 3), 4.48 (0.91H, d, $J = 9.5$ Hz, 2″), 4.43 (0.91H, d, $J = 1.7$ Hz, 4), 3.32 (0.91H, dd, $J = 6.6$, 16.9 Hz, 4″), 2.66 (0.91H, dd, $J = 9.0$, 16.9 Hz, 4″), 2.36 (2.73H, s, Ac), 2.29 (2.73H, s, Ac), 2.28 (10.92H, s, Acx4), 2.27 (2.73H, s, Ac), 2.25 (2.73H, s, Ac), 2,.21 (2.73H, s, Ac), 2.09 (2.73H, s, Ac), 1.90 (2.73H, s, Ac), 1.86 (2.73H, s, Ac); minor isomer: 7.73 (0.18H, s, 2′), 7.31–6.94 (0.54H, m), 6.74 (0.09H, d, $J = 2.2$ Hz, 8), 6.69 (0.09H, d, $J = 2.2$ Hz, 6), 6.63 (0.09H, s, 6″), 5.36–5.30 (0.36H, m), 4.59 (0.09H, br s, 4), 3.22 (0.09H, dd, $J = 5.1$, 16.6 Hz, 4″), 2.90 (0.09H, dd, $J = 7.1$, 16.6 Hz, 4″), 2.36–1.86 (1.89H, m, Acx7), 2.26 (0.27H, s, Ac), 2.23 (0.27H, s, Ac), 1.93 (0.27H, s, Ac), 1.73 (0.27H, s, Ac), 1.62 (0.27H, s, Ac); ^{13}C NMR (100 MHz, $CDCl_3$, 0.91:0.09 mixture of rotational isomers) major isomer: 169.8, 169.1, 169.0, 168.3, 168.2, 168.1, 167.7, 167.5 (x2), 167.5, 166.3, 163.0, 155.5, 154.0, 149.3, 148.7, 148.0, 147.9, 143.3, 142.4, 141.94, 141.92, 141.7, 138.9, 136.4, 134.3, 127.6, 125.0, 124.5, 123.4, 123.1, 122.3, 122.1, 122.0, 117.1, 113.6, 111.4, 110.9 (6″), 108.6 (8), 107.3 (6), 78.2 (2″), 73.5 (2), 70.9 (3), 70.1 (3″), 34.0 (4), 27.2 (4″), 21.2, 21.0, 20.8, 20.72, 20.67, 20.62, 20.58 (x2), 20.4, 20.2, 20.0; minor isomer was not identified. IR (neat, cm^{-1}) 3026 (w), 2938 (w), 1771 (s), 1620 (w), 1599 (w), 1508 (w), 1429 (m), 1371 (m), 1325 (m), 1206 (s), 1128 (m), 1055 (m), 901 (w), 758 (m); FAB-MS (*m*/*z*) 1259 (34), 1258 (69), 1257 ($[M + Na]^+$, 100), 1235 ($[M + H]^+$, 15), 1132 (36), 1131 (47), 1090 (20), 1089 (22), 837 (21); FAB-HRMS calcd for $C_{61}H_{54}O_{28}Na$ $[M + Na]^+$, 1257.2699; found: 1257.2717.

4.1.11. Peracetate of 7 (23). Procyanidin B1-3,3″-di-*O*-gallate **7** (30.0 mg, 0.034 mmol) was acetylated with excess of Ac_2O in pyridine as a solvent for 24 h. Water was added and the mixture was extracted with EtOAc and dried (Na_2SO_4). Filtration, concentration and preparative silica gel TLC purification (hexane/EtOAc, 1/1.5) gave 36.0 mg of peracetate **23** (0.024 mmol, 72%) as a colorless amorphous solid: $[\alpha]_D^{22}$ +78.7 (*c* 0.68, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, a trace of rotational isomer was observed) major isomer: 7.59 (2H, s, 2′), 7.54 (2H, s, 2′), 7.31 (1H, dd, $J = 1.7$, 8.3 Hz), 7.30 (1H, d, $J = 1.7$ Hz), 7.15 (1H, d, $J = 8.3$ Hz), 7.07 (1H, d,$J = 8.3$ Hz), 7.00 (1H, d, $J = 1.7$ Hz), 6.97 (1H, dd, $J = 1.7$, 8.3 Hz), 6.73 (1H, s, 6″), 6.32 (1H, d, $J = 2.2$ Hz, 8), 6.06 (1H, d, $J = 2.2$ Hz, 6), 5.59 (1H, br s, 2), 5.42 (1H, t, $J = 1.7$ Hz, 3), 5.26 (1H, ddd, $J = 6.6$, 9.0, 9.8 Hz, 3″), 4.55 (1H, d, $J = 1.7$ Hz, 4), 4.51 (1H, d, $J = 9.8$ Hz, 2″), 3.34 (1H, dd, $J = 6.6$, 16.8 Hz, 4″), 2.67 (1H, dd, $J = 9.0$, 16.8 Hz, 4″), 2.39 (3H, s, Ac), 2.30 (3H, s, Ac), 2.29 (6H, s, Acx2), 2,27 (9H, s, Acx3), 2.26 (3H, s, Ac), 2.25 (3H, s, Ac), 2.23 (3H, s, Ac), 2.22 (3H, s, Ac), 2.20 (3H, s, Ac), 2.08 (3H, s, Ac), 1.88 (3H, s, Ac); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: 169.7, 169.0, 168.6, 168.3, 168.0, 167.8, 167.7, 167.53, 167.49, 167.41, 166.3, 166.2, 163.0, 162.9, 155.3, 153.9, 149.3, 148.8, 147.9, 147.8, 143.3 (x2), 142.3, 141.95, 141.90, 141.8, 138.91, 138.86, 135.8, 134.3, 127.5, 127.4, 125.2, 124.5, 123.4, 123.2, 122.3 (x2) (2′), 121.81, 121.76, 116.8, 113.5, 111.2, 110.9 (6″), 108.9 (8), 107.2 (6), 78.2 (2″), 73.6 (2), 72.2 (3), 69.9 (3″), 34.1 (4), 27.2 (4″), 21.2, 21.0, 20.74, 20.67, 20.60, 20.54, 20.50, 20.4, 20.3, 20.1 (x2), 19.9; IR (neat, cm^{-1}) 3073 (w), 2027 (m), 2940 (w), 1780 (s), 1728 (s), 1616 (m), 1595 (m), 1506 (m), 1429 (s), 1372 (s), 1825 (s), 1240 (s), 1055 (s), 970 (s), 901 (s), 854 (w), 821 (w), 758 (m); FAB-MS (*m*/*z*) 1494 (57), 1493 ($[M + Na]^+$, 100), 1492 (78), 1472 (9.6), 1471 ($[M + H]^+$, 12), 1133 (65), 1132 (87), 1131 (88), 1092 (45), 1091 (67), 1090 (62), 620 (45), 619 (69); FAB-HRMS calcd for $C_{72}H_{63}O_{34}$ $[M + H]^+$, 1471.3201; found: 1471.3230.

4.1.12. [4,8]-2,3-*cis*-3,4-*trans*:2,3-*cis*-Octa-*O*-benzyl-(−)-epicatechin-(−)-epicatechin-3-*O*-(tri-*O*-benzyl)gallate (24). To a solution of **14** (179 mg, 0.28 mmol) and **17** (80 mg, 0.069 mmol) in CH_2Cl_2 (30 mL) was added dropwise TMSOTf (0.14 mL, 0.069 mmol, 0.5 M solution in CH_2Cl_2) at −40 °C. After stirring for 5 min, the pale yellow reaction mixture was quenched with satd sodium hydrogen carbonate. The aq solution was extracted with $CHCl_3$ and the organic phase was washed with water and brine, and dried (Na_2SO_4). Filtration, concentration, and preparative silica gel TLC purification (hexane/EtOAc, 2/1) afforded 102 mg of **24** (0.059 mmol, 86%) as a colorless oil: $[\alpha]_D^{25}$ −10.8 (*c* 0.52, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 0.71:0.29 mixture of rotational isomers) major isomer: 7.45–6.73 (44.02H, m), 6.48 (0.71H, dd, $J = 1.7$, 8.3 Hz), 6.32 (0.71H, s), 6.09 (0.71H, d, $J = 2.2$ Hz), 5.81 (0.71H, d, $J = 2.2$ Hz), 5.73 (0.71H, br s), 5.69 (0.71H, br s), 5.19–4.78 (13.49H, m), 5.60 (0.71H, d, $J = 11.4$ Hz), 4.49 (0.71H, d, $J = 11.4$ Hz), 4.40 (0.71H, d, $J = 11.7$ Hz), 4.29 (0.71H, d, $J = 11.7$ Hz), 4.14 (0.71H, br s), 4.95–4.92 (0.71H, m), 3.00 (0.71H, d, $J = 17.8$ Hz), 2.94 (0.71H, dd, $J = 4.7$, 17.8 Hz), 1.60–1.50 (0.71H, m, OH); minor isomer: 7.45–6.83 (17.98H, m), 5.43 (0.29H, m), 6.30–6.24 (0.87H, m), 5.57 (0.29H, br s), 5.45 (0.29H, br s), 5.19–4.27 (6.67H, m), 4.25–4.20 (0.29H, m), 4.20–4.15

(0.29H, m), 3.02–2.91 (0.58H, m), 1.60–1.50 (0.29H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 0.71:0.29 mixture of rotational isomers) major isomer: 163.9, 158.1, 156.8, 156.7, 156.1, 155.7, 154.5, 152.1, 149.3, 148.8, 148.6, 148.3, 142.1, 137.6, 137.38, 137.34, 137.29, 137.22 (x3), 137.19, 137.15 (x2), 136.6 (x2), 132.0, 131.3, 128.6–126.7 (Cx28), 125.3, 120.3, 118.9, 114.6, 114.5, 113.4, 112.5, 110.2, 108.9, 105.1, 102.2, 94.1, 93.1, 91.5, 79.1, 77.2, 75.0, 72.9, 71.3, 71.2, 70.8, 70.8, 70.5, 69.99, 69.95, 69.87, 69.2, 66.6, 33.7, 28.2; minor isomer: 163.7, 158.8, 158.3, 157.6, 156.7, 156.0, 155.3, 153.0, 149.1, 148.6, 148.5, 148.4, 142.2, 137.7, 137.4–137.2 (Cx6), 137.1, 137.0, 136.9, 136.6 (x2), 131.7, 131.4, 128.6–126.7 (Cx28), 125.1, 120.2, 119.4, 114.7, 114.2, 113.6, 113.2, 111.2, 108.7, 105.0, 102.0, 94.5, 93.4, 92.6, 78.3, 77.6, 75.3, 73.2, 71.4, 71.2, 71.1, 71.0, 70.7, 70.1, 70.04, 69.99, 69.6, 65.9, 34.0, 28.2; IR (neat, cm^{-1}) 3090 (w), 3065 (w), 3032 (m), 2930 (w), 2870 (w), 1954 (w), 1869 (w), 1181 (w), 1718 (m), 1593 (s), 1498 (s), 1429 (s), 1267 (s), 1215 (s), 1113 (s), 1028 (s), 910 (w), 852 (w), 754 (s), 696 (s); FAB-MS (*m*/*z*) 1746 (18), 1745 (26), 1744 ($[M + Na]^+$, 26), 1723 (17), 1722 ($[M + H]^+$, 19), 1284 (63), 1283 (42), 1192 (43), 1191 (92), 1190 (100), 993 (38), 992 (26), 859 (28), 858 (37), 857 (65); FAB-HRMS calcd for $C_{114}H_{97}O_{16}$ $[M + H]^+$, 1721.6777; found: 1721.6829.

4.1.13. [4,8]-2,3-*cis*-3,4-*trans*:2,3-*cis*-Octa-*O*-benzyl-(−)-epicatechin-(−)-epicatechin-3″-*O*-(tri-*O*-benzyl)gallate (25). To a solution of **16** (197 mg, 0.18 mmol) and **15** (34.0 mg, 0.046 mmol) in CH_2Cl_2 (30 mL) was added dropwise TMSOTf (0.092 mL, 0.046 mmol, 0.5 M solution in CH_2Cl_2) at −20 °C. After stirring for 5 min, the pale yellow reaction mixture was quenched with satd sodium hydrogen carbonate. The aq solution was extracted with $CHCl_3$ and the organic phase was washed with water and brine, and dried (Na_2SO_4). Filtration, concentration, and preparative silica gel TLC purification (hexane/EtOAc, 2/1) afforded 36 mg of **25** (0.021 mmol, 46%) as a colorless oil: $[\alpha]_D^{26}$ −17.3 (*c* 0.56, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$, 0.67:0.33 mixture of rotational isomers) major isomer: 7.45–6.54 (42.21H, m), 6.39 (0.67H, s), 6.03 (0.67H, d, *J* = 2.2 Hz), 5.65 (0.67H, d, *J* = 2.2 Hz), 5.60 (0.67H, br s), 5.39 (0.67H, d, *J* = 4.6 Hz), 5.13–4.75 (14.74H, m), 4.93–4.80 (0.67H, m), 4.60 (0.67H, d, *J* = 10.2 Hz), 4.50 (0.67H, d, *J* = 11.2 Hz), 4.47 (0.67H, d, *J* = 10.2 Hz), 4.21 (0.67H, br s), 4.14–4.05 (0.67H, m), 3.17 (0.67H, dd, *J* = 4.9, 18.8 Hz), 3.07 (0.67H, d, *J* = 18.8 Hz), 1.79 (0.67H, d, *J* = 5.1 Hz); minor isomer: 7.45–6.54 (20.13H, m), 6.21 (0.33H, s), 6.13 (0.33H, d, *J* = 2.2 Hz), 6.08 (0.33H, d, *J* = 2.2 Hz), 5.71–5.67 (0.33H, m), 5.25 (0.33H, br s), 5.17 (0.33H, br s), 5.13–4.75 (7.26H, m), 4.93–4.80 (0.33H, m), 4.63 (0.33H, d, *J* = 11.4 Hz), 4.34 (0.33H, d, *J* = 11.4 Hz), 4.14–4.05 (0.33H, m), 3.33–3.20 (0.66H, m), 1.84 (0.33H, d, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 0.67:0.33 mixture of rotational isomers) major isomer: 165.6, 158.1, 157.0, 156.13, 156.05, 155.2, 154.7, 152.5, 149.1, 148.8, 148.6, 148.4, 142.9, 137.38, 137.36, 137.33, 137.21, 137.15, 136.98, 136.95, 136.7, 136.5 (x2), 132.2, 130.7, 128.7–124.7 (Cx30), 119.9, 119.7, 119.6, 114.5, 114.0, 113.5, 113.0, 111,6, 109.6, 104.3, 102.4, 94.0, 93.1, 91.6, 78.0, 75.0, 72.5–68.3 (Cx12), 35.8, 26.7; minor isomer: 165.6, 158.1, 157.1, 158.4, 155.7, 155.4, 153.6, 152.0, 149.0, 148.8, 148.7, 148.5, 142.2, 137.5, 137.3, 137.23, 137.18, 137.12, 137.0, 136.84, 136.75, 136.49, 136.45, 132.4, 131.2, 128.7–124.7 (Cx30), 119.7, 119.6, 118.9, 115.0, 114.7, 114.0, 113.3, 11.3, 108.9, 104.7, 101.9, 94.7, 93.8, 92.3, 78.5, 75.7, 72.5–68.3 (Cx12), 37.0, 26.1; IR (neat, cm^{-1}) 3090 (w), 3065 (w), 3083 (m), 2932 (w), 2870 (w), 1710 (m), 1598 (s), 1498 (s), 1429 (s), 1383 (s), 1327 (s), 1267 (s), 1217 (s), 1119 (s), 1028 (s), 910 (w), 856 (w), 750 (s); FAB-MS (*m*/*z*) 1746 (19), 1745 (19), 1744 ($[M + Na]^+$, 20), 1724 (30), 1723 (50), 1722 ($[M + H]^+$, 57), 1721 (35), 1283 (32), 1282 (44), 1174 (30), 1173 (64), 1172 (62), 657 (100); FAB-HRMS calcd for $C_{114}H_{97}O_{16}$ $[M + H]^+$, 1721.6777; found: 1721.6752.

4.1.14. [4,8]-2,3-*cis*-3,4-*trans*:2,3-*cis*-Octa-*O*-benzyl-(−)-epicatechin-(−)-epicatechin-3,3″-di-*O*-(tri-*O*-benzyl)gallate (26). To a solution of **16** (140 mg, 0.13 mmol) and **17** (38 mg, 0.033 mmol) in CH_2Cl_2 (30 mL) was added dropwise TMSOTf (0.066 mL, 0.033 mmol, 0.5 M solution in CH_2Cl_2) at −20 °C. After stirring for 5 min, the pale yellow reaction mixture was quenched with satd sodium hydrogen carbonate. The aq solution was extracted with $CHCl_3$ and the organic phase was washed with water and brine, and dried (Na_2SO_4). Filtration, concentration, and preparative silica gel column chromatography (hexane/EtOAc/$CHCl_3$, 8/1/9) afforded 70 mg of **26** (0.033 mmol, 99%) as a colorless amorphous solid: $[\alpha]_D^{26}$ −50.3 (*c* 0.64, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 0.77:0.23 mixture of rotational isomers) major isomer: 7.47–6.57 (61.6H, m), 6.39 (0.77H, s), 6.10 (0.77H, d, *J* = 2.2 Hz), 5.80 (0.77H, br s), 5.73 (0.77H, d, *J* = 2.2 Hz), 5.72 (0.77H, br s), 5.49 (0.77H, d, *J* = 6.1 Hz), 5.11–4.36 (20.79H, m), 4.26 (0.77H, br s), 4.09 (0.77H, d, *J* = 12.0 Hz), 3.94 (0.77H, d, *J* = 12.0 Hz), 3.23 (0.77H, dd, *J* = 6.1, 18.5 Hz), 3.10 (0.77H, d, *J* = 18.5 Hz); minor isomer: 7.47–6.57 (18.17H, m), 6.28–6.10 (0.92H, m), 5.67 (0.23H, br s), 5.58 (0.23H, br), 5.37 (0.23H, br s), 5.19–4.10 (6.9H, m), 3.33 (0.23H, dd, *J* = 5.4, 18.8 Hz), 3.25 (0.23H, d, *J* = 18.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: 165.7, 163.9, 158.1, 156.6, 156.5, 156.2, 155.9, 154.8, 152.7, 152.1, 149.3, 149.0, 148.7, 148.3, 143.1, 142.2, 137.7–136.5 (Cx17), 131.6, 130.8, 128.7–127.0 (Cx31), 126.0, 125.7, 125.2, 120.1, 119.3, 114.1, 113.9, 113.1, 112.5, 109.7, 108.9, 104.8, 102.3, 94.0, 93.1, 91.5, 77.2, 75.0, 74.9, 72.9, 71.9–68.8 (Cx12), 33.8, 26.6; minor isomer: 165.5, 163.4, 158.3, 156.8, 156.7, 156.6, 156.9, 154.6, 152.7, 152.0, 149.2, 148.6, 148.5, 148.2, 142.1 (x2), 137.7–136.5 (Cx17), 131.5, 130.8, 128.7–126.8 (Cx31), 126.3, 125.0, 124.8, 119.8, 119.3, 114.6, 113.7, 113.4, 113.1, 110.7, 108.5, 105.0, 102.2, 94.8, 93.9, 91.9, 87.1, 75.5, 74.9, 73.0, 71.9–68.8 (Cx12), 35.2, 26.3; IR (neat, cm^{-1}) 3090 (w), 3065 (m), 3032 (m), 2934 (m), 2870 (m), 1869 (w), 1717 (s), 1598 (s), 1455 (s), 1429 (s), 1373 (s), 1327 (s), 1269 (s), 1198 (s), 1115 (s), 1028 (s), 910 (w), 858 (w), 810 (w), 752 (m); FAB-MS (*m*/*z*) 2167 (30), 2166 ($[M + Na]^+$, 54), 2145 (9.1), 2144 ($[M + H]^+$, 13), 1703 (73), 1702 (82), 1615 (40), 1614 (85), 1613 (89), 1162 (96), 1522 (52), 1521 (31), 1520 (75), 1174 (63), 1173

(28), 1172 (100); FAB-HRMS calcd for $C_{142}H_{119}O_{20}$ $[M + H]^+$, 2143.8295; found: 2143.8230.

4.1.15. Procyanidin B2-3-*O*-gallate (9). A solution of **24** (100 mg, 0.058 mmol) in a mixture of THF/MeOH/H_2O (20/1/1, 22 mL) was hydrogenated over 20% $Pd(OH)_2$/C (5 mg) for 8 h at rt. Filtration and concentration afforded a pale brown solid, which was purified by Sephadex® LH-20 column chromatography (MeOH) and HPLC purification to give 32.8 mg of pure **9** (0.045 mmol, 78%) as a pale brown amorphous solid: $[\alpha]_D^{23}$ −34.4 (*c* 0.13, MeOH); ^{1}H NMR (400 MHz, 10% D_2O in CD_3COCD_3, −40 °C, 0.50:0.50 mixture of rotational isomers) 7.01–6.51 (6H, m), 6.97 (1H, s, 2′), 6.83 (1H, s, 2′), 6.15 (0.5H, s, 6″), 5.97 (0.5H, s, 6″), 5.97 (0.5H, d, *J* = 2.2 Hz), 5.94 (0.5H, d, *J* = 2.2 Hz), 5.79 (0.5H, d, *J* = 2.2 Hz), 5.76 (0.5H, d, *J* = 2.2 Hz), 5.67 (0.5H, br s, 2), 5.43 (0.5H, br s, 2), 5.36 (0.5H, br s, 3), 5.11 (0.5H, br s, 3), 5.05 (0.5H, br s, 2″), 4.68 (0.5H, br s, 4), 4.54 (0.5H, br s, 4), 4.45 (0.5H, br s, 2″), 4.35–4.25 (0.5H, m, 3″), 4.00–3.83 (0.5H, m, 3″), 2.81–2.70 (1H, m, 4″x2), 2.50–2.39 (1H, m, 4″x2); ^{13}C NMR (100 MHz, 10% D_2O in CD_3COCD_3, −40 °C, 0.50:0.50 mixture of rotational isomers) 79.6 (2″), 78.8 (2″), 767.0 (2), 75.6 (3), 75.1 (2), 73.6 (3), 66.7 (3″), 66.1 (3″), 34.5 (4), 34.1 (4), 28.2 (4″), 27.7 (4″); FAB-MS (*m*/*z*) 754 (35), 753 ($[M + Na]^+$, 100), 752 (54), 751 (31), 732 (12), 731 ($[M + H]^+$, 30), 561 (25), 560 (67); FAB-HRMS calcd for $C_{37}H_{31}O_{16}$ $[M + H]^+$, 731.1612; found: 731.1659.

4.1.16. Procyanidin B2-3″-*O*-gallate (10). A solution of benzylated **25** (135 mg, 0.078 mmol) in a mixture of THF/MeOH/H_2O (20/1/1, 22 mL) was hydrogenated over 20% $Pd(OH)_2$/C (5 mg) for 8 h at rt. Filtration and concentration afforded a pale brown solid, which was purified by Sephadex® LH-20 column chromatography (MeOH) and HPLC purification to give 41.7 mg of pure **10** (0.047 mmol, 60%) as a colorless amorphous solid: $[\alpha]_D^{25}$ −42.0 (*c* 0.12, Me_2CO) {lit.[21] $[\alpha]_D^{19}$ −45.8 (*c* 0.72, Me_2CO)}; ^{1}H NMR (400 MHz, 10% D_2O in CD_3COCD_3, −30 °C, 0.85:0.15 mixture of rotational isomers) major isomer: 7.14 (0.85H, d, *J* = 1.7 Hz), 7.05 (1.7H, s, 2′), 6.97 (0.85H, dd, *J* = 1.7, 8.3 Hz), 6.92 (0.85H, d, *J* = 1.7 Hz), 6.69 (0.85H, d, *J* = 8.3 Hz), 6.68 (0.85H, d, *J* = 8.3 Hz), 6.58 (0.85H, dd, *J* = 1.7, 8.3 Hz), 5.95 (0.85H, d, *J* = 2.2 Hz, 8), 5.91 (0.85H, s, 6″), 5.90 (0.85H, d, *J* = 2.2 Hz, 6), 5.50–5.46 (0.85H, m, 3″), 5.21 (0.85H, br s, 2″), 5.19 (0.85H, br s, 2), 4.82 (0.85H, br s, 4), 3.85 (0.85H, br s, 3), 3.01 (0.85H, dd, *J* = 4.4, 16.1 Hz, 4″), 2.85 (0.85H, d, *J* = 16.1 Hz, 4″); minor isomer: 7.16–6.55 (0.9H, m), 6.95 (0.3H, s, 2′), 6.13 (0.15H, s, 6″), 5.71 (0.15H, d, *J* = 2.2 Hz, 8), 5.60 (0.15H, d, *J* = 2.2 Hz, 6), 5.39–4.32 (0.6H, m), 3.56 (0.15H, br s, 3), 2.90–2.85 (0.15H, m, 4″), 2.77–2.70 (0.15H, m, 4″); ^{13}C NMR (100 MHz, 10% D_2O in CD_3COCD_3, −30 °C, 0.85:0.15 mixture of rotational isomers) major isomer: 118.4, 118.0, 115.1 (x2), 114.6, 113.9, 109.6 (2′), 96.0 (6″), 95.2 (8), 94.6 (6), 77.5 (2″), 76.2 (2), 73.8 (3), 69.2 (3″), 36.4 (4), 26.2 (4″); minor isomer was not identified. FAB-MS (*m*/*z*) 754 (19), 753 ($[M + Na]^+$, 20), 752 (20), 732 (17), 731 ($[M + H]^+$, 30), 730 (15), 641 (14), 639 (14), 414 (21), 413 (54), 392 (17), 391 (59), 361 (52), 360 (100); FAB-HRMS calcd for $C_{37}H_{31}O_{16}$ $[M + H]^+$, 731.1612; found: 731.1611.

4.1.17. Procyanidin B2-3,3″-di-*O*-gallate (11). A solution of **26** (61 mg, 0.028 mmol) in a mixture of THF/MeOH/H_2O (20/1/1, 22 mL) was hydrogenated over 20% $Pd(OH)_2$/C (3 mg) for 6 h at rt. Filtration and concentration afforded a pale brown solid, which was purified by Sephadex® LH-20 column chromatography (MeOH) and HPLC purification to give 18.1 mg of pure **11** (0.021 mmol, 73%) as a colorless amorphous solid: $[\alpha]_D^{25}$ −89.0° (*c* 0.15, 5% MeOH in Me_2CO, this sample was not completely soluble in acetone solution) {lit.[7] $[\alpha]_D^{31}$ −93.8 (*c* 1.00, Me_2CO), lit.[21] $[\alpha]_D^{22}$ −95.2 (*c* 1.10, Me_2CO), lit.[28] $[\alpha]_D^{24}$ −100.6 (*c* 1.00, Me_2CO)}; ^{1}H NMR (400 MHz, 10% D_2O in CD_3COCD_3, −50 °C, 0.50:0.50 mixture of rotational isomers) 7.04–6.35 (6H, m), 7.01 (1H, s, 2′), 6.99 (1H, s, 2′), 6.95 (1H, s, 2′), 6.78 (1H, s, 2′), 6.13 (0.5H, s, 6″), 5.94 (0.5H, s, 6″), 5.94 (0.5H, d, *J* = 2.2 Hz, 8), 5.58 (0.5H, d, *J* = 2.2 Hz, 6), 5.74 (0.5H, d, *J* = 2.2 Hz, 8), 5,68 (0.5H, br s, 2), 5.62 (0.5H, br s, 2), 5.56 (0.5H, d, *J* = 2.2 Hz, 6), 5.44 (0.5H, br s, 3″), 5.35 (0.5H, br s, 3), 5.27 (0.5H, br s, 2″), 5.27–5.20 (1H, m, 3 and 3″), 4.85 (0.5H, br s, 4), 4.63 (0.5H, br s, 2″), 4.57 (0.5H, br s, 4), 2.97 (0.5H, br s, *J* = 16.1 Hz, 4″), 2.88 (0.5H, br d, *J* = 16.5 Hz, 4″), 2.75 (0.5H, br d, *J* = 16.1 Hz, 4″), 2.66 (0.5H, br d, *J* = 16.5 Hz, 4″); ^{13}C NMR (100 MHz, 10% D_2O in CD_3COCD_3, −50 °C, 0.50:0.50 mixture of rotational isomers) 110.0–107.1 (2′x4), 96.3 (6″), 95.8 (6″), 94.7 (8x2), 94.6 (6x2), 77.1 (2″), 76.9 (2″), 75.9 (2), 75.2 (2), 74.9 (3), 73.4 (3), 69.2 (3″), 68.9 (3″), 33.7 (4), 33.2 (4), 26.4 (4″), 25.1 (4″); FAB-MS (*m*/*z*) 906 (17), 905 ($[M + Na]^+$, 34), 904 (24), 883 ($[M + H]^+$, 29), 712 (44), 460 (100); FAB-HRMS calcd for $C_{44}H_{35}O_{20}$ $[M + H]^+$, 883.1722; found: 883.1689.

4.1.18. Peracetate of 9 (27). Procyanidin B2 3-*O*-gallate **9** (5.2 mg, 0.0071 mmol) was acetylated with excess of Ac_2O in pyridine as a solvent for 24 h. Water was added and the mixture was extracted with EtOAc and dried (Na_2SO_4). Filtration, concentration, and preparative silica gel TLC purification (hexane/EtOAc, 1/1.5) gave 7.0 mg of peracetate **27** (0.057 mmol, 80%) as a colorless amorphous solid: $[\alpha]_D^{26}$ −11.3 (*c* 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 0.87:0.13 mixture of rotational isomers) major isomer: 7.56 (1.74H, s, 2′), 7.33 (0.87H, dd, *J* = 1.7, 8.3 Hz), 7.34–7.26 (0.87H, m), 7.17 (0.87H, d, *J* = 8.3 Hz), 7.04 (0.87H, d, *J* = 8.3 Hz), 7.04 (0.87H, d, *J* = 1.7 Hz), 6.90 (0.87H, dd, *J* = 1.7, 8.3 Hz), 6.68 (0.87H, s, 6″), 6.27 (0.87H, d, *J* = 2.2 Hz, 8), 6.05 (0.87H, d, *J* = 2.2 Hz, 6), 5.69 (0.87H, br s, 2), 5.45–5.43 (0.87H, m, 3), 5.12 (0.87H, d, *J* = 4.9 Hz, 3″), 4.58–4.56 (1.74H, m, 4, 2″), 2.95 (0.87H, dd, *J* = 4.9, 18.5 Hz, 4″), 2.87 (0.87H, d, *J* = 18.5 Hz, 4″), 2.40 (2.61H, s, Ac), 2.29 (2.61H, s, Ac), 2.28 (2.61H, s, Ac), 2,27 (5.22H, s, Acx2), 2.26 (2.61H, s, Ac), 2.24 (2.61H, s, Ac), 2.22 (2.61H, s, Ac), 2.18 (2.61H, s, Ac), 2.03 (2.61H, s, Ac), 2.01 (2.61H, s, Ac), 1.85 (2.61H, s, Ac); minor isomer: 7.34 (0.26H, s, 2′), 7.34–6.89 (0.78H, m), 6.82 (0.13H, d, *J* = 2.2 Hz, 8), 6.66 (0.13H,

d, $J = 2.2$ Hz, 6), 6.60 (0.13H, s, 6″), 5.62–5.58 (0.13H, m, 3″), 5.56–5.53 (0.26H, m, 2 and 3), 5.29 (0.13H, br s, 2″), 4.83 (0.13H, br s, 4), 3.11–3.04 (0.13H, m, 4″), 3.00–2.95 (0.13H, m, 4″), 2.40–1.85 (1.95H, m, Acx5), 2,31 (0.39H, s, Ac), 2.10 (0.39H, s, Ac), 2.08 (0.39H, s, Ac), 2.05 (0.39H, s, Ac), 1.97 (0.39H, s, Ac), 1.82 (0.39H, s, Ac), 1.80 (0.39H, s, Ac); ^{13}C NMR (100 MHz, $CDCl_3$, 0.87:0.13 mixture of rotational isomers) major isomer: 170.5, 170.0, 169.1, 168.6, 168.3, 168.1, 168.03, 167.98, 167.8, 167.4, 166.2, 163.0, 155.2, 154.2, 149.22, 149.16, 147.9, 147.8, 143.3, 142.1, 142.0, 141.9, 141.7, 138.9, 136.0, 134.5, 127.4, 125.2, 124.5, 123.5, 122.8, 122.5, 122.3 (2′), 121.9, 116.5, 111.7, 111.4, 110.3 (6″), 109.0 (8), 107.2 (6), 77.6 (2″), 73.8 (2), 72.4 (3), 66.8 (3″), 34.2 (4), 26.7 (4″), 21.3, 21.0, 20.9, 20.8, 20.7, 20.62, 20.59, 20.4, 20.3, 20.1, 19.9; the ^{13}C NMR of the minor isomer could not be assigned. IR (neat, cm^{-1}) 3027 (m), 2936 (w), 2855 (w), 2362 (w), 1734 (s), 1622 (m), 1597 (m), 1508 (m), 1429 (s), 1373 (s), 1321 (m), 1262 (s), 1227 (s), 1053 (s), 966 (w), 945 (w), 901 (m), 843 (w), 824 (m); FAB-MS (*m*/*z*) 1259 (32), 1258 (75), 1257 ($[M + Na]^+$, 100), 1236 (6.3), 1235 ($[M + H]^+$, 6.9), 896 (36), 895 (60); FAB-HRMS calcd for $C_{61}H_{54}O_{28}Na$ $[M + Na]^+$, 1257.2699; found: 1257.2679.

4.1.19. Peracetate of 10 (28). Procyanidin B2 3″-*O*-gallate **10** (6.8 mg, 9.3 μmol) was acetylated with excess of Ac_2O in pyridine as a solvent for 24 h. Water was added and the mixture was extracted with EtOAc and dried (Na_2SO_4). Filtration, concentration, and preparative silica gel TLC purification (hexane/EtOAc, 2/3) gave 8.0 mg of peracetate **28** (0.0065 mmol, 70%) as a colorless amorphous solid: $[\alpha]_D^{24}$ −36.6 (*c* 0.25, $CHCl_3$) {lit.[20] $[\alpha]_D^{20}$ −47 (*c* 0.07, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$, 0.85:0.15 mixture of rotational isomers) major isomer: 7.68 (1.7H, s, 2′), 7.40 (0.85H, d, $J = 1.7$ Hz), 7.20–7.17 (1.7H, m), 7.18 (0.85H, d, $J = 8.3$ Hz), 7.07 (0.85H, d, $J = 8.3$ Hz), 6.96 (0.85H, dd, $J = 1.7$, 8.3 Hz), 6.68 (0.85H, s, 6″), 6.24 (0.85H, d, $J = 2.2$ Hz, 8), 6.12 (0.85H, d, $J = 2.2$ Hz, 6), 5.59 (0.85H, br s, 2), 5.29–5.28 (0.85H, m, 3″), 5.23 (0.85H, dd, $J = 1.7$, 2.3 Hz, 3), 4.72 (0.85H, br s, 2″), 4.43 (0.85H, d, $J = 2.3$ Hz, 4), 3.05–3.02 (1.7H, m, 4″), 2.33 (2.55H, s, Ac), 2.29 (2.55H, s, Ac), 2.284 (2.55H, s, Ac), 2.279 (2.55H, s, Ac), 2.26 (2.55H, s, Ac), 2.25 (2.55H, s, Ac), 2.18 (2.55H, s, Ac), 2.19 (5.1H, s, Acx2), 2.04 (2.55H, s, Ac), 1.88 (2.55H, s, Ac), 1,67 (2.55H, s, Ac); minor isomer: 7.58 (0.3H, s, 2′), 7.31–7.17 (0.6H, m), 7.17 (0.15H, d, $J = 8.3$ Hz), 7.13 (0.15H, d, $J = 8.3$ Hz), 6.75 (0.15H, d, $J = 2.2$ Hz, 8), 6.68 (0.15H, d, $J = 2.2$ Hz, 6), 6.64 (0.15H, s, 6″), 5.66–5.63 (0.15H, m, 3″), 5.36 (0.15H, br s, 3), 5.30 (0.15H, br s, 2″), 5.28–5.27 (0.15H, m, 2), 4.69 (0.15H, br s, 4), 3.17–3.05 (0.3H, m, 4″), 2.33–2.04 (2.7H, m, Acx6), 2.32 (0.45H, s, Ac), 2.224 (0.45H, s, Ac), 2.221 (0.45H, s, Ac), 2.05 (0.45H, s, Ac), 1.70 (0.45H, s, Ac), 1.67 (0.45H, s, Ac); ^{13}C NMR (100 MHz, $CDCl_3$, 0.85:0.15 mixture of rotational isomers) major isomer: 169.7, 169.6, 169.3, 169.0, 168.4, 168.0, 167.9, 167.58, 167.56 (x2), 166.3, 164.0, 155.2, 154.1, 149.2, 149.0, 147.98, 147.96, 143.5 (x2), 142.0, 141.9, 141.8, 141.7, 136.6, 134.2, 127.6, 124.7, 124.5, 123.3, 123.1, 122.2, 122.1, 121.8, 116.8, 111.8, 111.6, 110.6, 108.7, 107.5, 77.2 (2″), 73.9 (2), 71.1 (3), 68.9 (3′), 34.0 (4), 26.5 (4″), 21.2, 20.8, 20.69, 20.68, 20.60, 20.58, 20.44 (x2), 20.38, 20.1, 19.9; the ^{13}C NMR of the minor isomer could not be assigned. IR (neat, cm^{-1}) 3027 (w), 1771 (s), 1597 (m), 1507 (m), 1429 (m), 1371 (s), 1321 (m), 1205 (s), 1236 (m), 1055 (m), 900 (m); FAB-MS (*m*/*z*) 1261 (31), 1259 (50), 1258 (100), 1257 ($[M + Na]^+$, 100), 1236 (23), 1235 ($[M + H]^+$, 23), 1133 (49), 1132 (69), 1131 (99), 1090 (51), 1089 (45); FAB-HRMS calcd for $C_{61}H_{54}O_{28}Na$ $[M + Na]^+$, 1257.2699; found: 1257.2736.

4.1.20. Peracetate of 11 (29). Procyanidin B2 3,3″-di-*O*-gallate **11** (4.0 mg, 4.5 μmol) was acetylated with excess of Ac_2O in pyridine as a solvent for 24 h. Water was added and the mixture was extracted with EtOAc and dried (Na_2SO_4). Filtration, concentration, and preparative silica gel TLC purification (hexane/EtOAc, 2/3) gave 4.5 mg of peracetate **29** (3.1 μmol, 68%) as a colorless amorphous solid: $[\alpha]_D^{25}$ −69.2 (*c* 0.25, $CHCl_3$) {lit.[7] $[\alpha]_D^{18}$ −62.9 (*c* 0.58, $CHCl_3$)}; ^{1}H NMR[7] (400 MHz, $CDCl_3$, 0.92:0.08 mixture of rotational isomers) major isomer: 7.72 (1.84H, s, 2′), 7.57 (1.84H, s, 2′), 7.34 (0.92H, d, $J = 1.7$ Hz), 7.25 (0.92H, dd, $J = 1.7$, 8.3 Hz), 7.20 (0.92H, d, $J = 1.7$ Hz), 7.18 (0.92H, d, $J = 8.3$ Hz), 7.06 (0.92H, d, $J = 8.3$ Hz), 6.97 (0.92H, dd, $J = 1.7$, 8.3 Hz), 6.69 (0.92H, s, 6″), 6.29 (0.92H, d, $J = 2.2$ Hz, 8), 6.21 (0.92H, d, $J = 2.2$ Hz, 6), 5.89 (0.92H, br s, 2), 5.55 (0.92H, dd, $J = 1.5$, 2.7 Hz, 3), 5.31–5.30 (0.92H, m, 3″), 4.77 (0.92H, br s, 2″), 4.50 (0.92H, d, $J = 2.7$ Hz, 4), 3.08–3.03 (1.84H, m, 4″), 2.33 (2.76H, s, Ac), 2.29 (2.76H, s, Ac), 2.28 (5.52H, s, Acx2), 2.27 (2.76H, s, Ac), 2.26 (2.76H, s, Ac), 2.25 (2.76H, s, Ac), 2.22 (2.76H, s, Ac), 2.19 (2.76H, s, Ac), 2.18 (2.76H, s, Ac), 2.13 (5.52H, s, Acx2), 2.04 (2.76H, s, Ac), 1.85 (2.76H, s, Ac); minor isomer: 7.52 (0.16H, s, 2′), 7.49 (0.16H, s, 2′), 7.36–6.96 (0.48H, m), 6.80 (0.08H, d, $J = 2.2$ Hz, 8), 6.71 (0.08H, d, $J = 2.2$ Hz, 6), 6.65 (0.08H, s, 6″), 5.69–5.67 (0.08H, m, 3″), 5.59–5.58 (0.08H, m, 3), 5.45 (0.08H, br s, 2), 5.36 (0.08H, br s, 2″), 4.86 (0.08H, br s, 4), 3.20–3.10 (0.16H, m, 4″), 2.32 (0.24H, s, Ac), 2.21 (0.24H, s, Ac), 2.20 (0.24H, s, Ac), 2.07 (0.24H, s, Ac), 1.76 (0.24H, s, Ac), 1.65 (0.24H, s, Ac), 2.33–1.81 (1.92H, m, Acx8); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: 169.5, 169.3, 168.7, 168.3, 167.92, 167.89, 167.84, 167.7, 167.6, 167.5, 166.3, 166.2, 164.0, 162.8, 155.0, 154.1, 149.3, 149.1, 148.0, 147.9, 143.5, 143.4, 142.09, 142.06, 141.8, 141.7, 138.97, 138.88, 136.0, 134.3, 127.6, 127.3, 124.7, 124.6, 123.6, 123.1, 122.4, 122.1, 122.0, 121.8, 116.4, 117.8, 111.5, 110.6 (6″), 109.2 (8), 107.5 (6), 77.6 (2″), 74.1 (2), 72.3 (3), 68.8 (3″), 34.2 (4), 29.7 (4″), 21.2, 21.0, 20.8, 20.70, 20.68, 20.6, 20.5, 20.4 (x2), 20.19, 20.16, 19.9; minor isomer was not identified. IR (neat, cm^{-1}) 3026 (m), 2928 (m), 1780 (s), 1725 (s), 1619 (m), 1597 (m), 1507 (m), 1429 (m), 1371 (m), 1321 (m), 1204 (s), 1055 (m), 901 (m), 760 (m); FAB-MS (*m*/*z*) 1495 (55), 1494 (77), 1493 ($[M + Na]^+$, 91), 1471 ($[M + H]^+$, 13), 1452 (31), 1451 (29), 1176 (26), 1175 (40), 1134 (42), 1133 (60), 1132 (69), 1131 (100), 1091 (29), 1090 (44), 1089 (73); FAB-HRMS calcd for $C_{72}H_{63}O_{34}$ $[M + H]^+$, 1471.3201; found: 1471.3173.

4.2. Measurement of DPPH radical scavenging activity

All of the assay samples were HPLC pure. DPPH radical scavenging activity was measured with the general DPPH method described in the previous paper.[1a]

4.3. DNA polymerase assays

All of the assay samples were HPLC pure. Inhibitory activity of calf DNA polymerase α (0.05 units) and rat DNA polymerase β (0.05 units) was measured with the general method described in the previous paper.[1a,47] One unit of DNA polymerase activity was defined as the amount of enzyme that catalyzed the incorporation of 1 nmol of deoxyribonucleotide triphosphates (i.e., dTTP) into synthetic template-primers (i.e., poly(d*A*)/oligo(d*T*)$^{12-18}$, *A*/*T* = 2/1) in 60 min at 37 °C under normal reaction conditions for each enzyme.

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